Izhikevich Models For Hippocampal Neurons And Its Sub-Region CA3

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Abstract

Development of computational models of brain regions has always suffered a tradeoff between rendering computational efficiency by using simple models and capturing rich neuronal dynamics using detailed biophysical models. The development of Izhikevich neuron model in last decade has provided a way out of this predicament since it is both computationally efficient and biologically plausible. Present work is relevant to the ongoing hippocampal research. In this work, the Izhikevich neuron models have been produced for a total of 7 types of neurons in the hippocampus. The Izhikevich neuron parameters were tuned to reproduce the current-frequency profiles of these neurons, obtained from literature, using the genetic algorithm. Further, using the Izhikevich neurons of CA3, a network of CA3 has been constructed which is able to produce baseline activity of CA3 as observed in-vivo and therefore, qualifies as a reliable representation of the region. The network models of CA3 including both excitatory and inhibitory neurons use either biophysical neurons, lacking scalability or use Integrate and fire neurons which are not as biologically relevant. Development of the Izhikevich models of CA3 and DG neurons, and Izhikevich network model of CA3 comprising both excitatory and inhibitory neurons form the novelty of this work.

Keywords: Hippocampus; CA3; DG; Izhikevich neuron model

Introduction

Computational Neuroscience contributes to our understanding of brain in two major ways. One way is by analysis and careful observation of experimental data to provide hypotheses on principles behind brain functioning. Examples of this include Hodgkin-Huxley model of action potential generation. The other way is by building computational models based on experimental data combined with already established theoretical principles which can then be used to make predictions about the brain function. For example, the models of brain regions associated with epilepsy are being used to identify changes in these regions leading to seizures with an aim to provide better prognosis (Neymotin et al., 2011; Sanjay, Neymotin, & Krothapalli, 2015).

The present work falls in the second category. Izhikevich neuron models for seven different types of neurons in hippocampus have been produced, namely, Pyramidal cell, Basket cell, and Oriens Lacunosum Moleculare (OLM) cell of CA3 and Granule cell, Mossy cell, Basket cell, and Hilar Peforant-Path associated cell of Dentate Gyrus (DG). Except for the CA3 Pyramidal cell and DG Granule cell, there are no previous reports of Izhikevich neuron models of the neurons mentioned above. Moreover, using these neurons, a network model of CA3 has been constructed. Existing models of hippocampal sub-regions, specifically CA3, consist of biophysical neuron models or integrate and fire neuron models (de Almeida, Idiart, & Lisman, 2007; Sanjay et al., 2015). Biophysical models are computationally less efficient and thus, lack scalability while integrate and fire neurons do not capture all aspects of neuron dynamics. Izhikevich neuron model is a comparatively new model of a single neuron and is both computationally efficient and biologically plausible (Izhikevich, 2007). This encourages development of network models of brain regions using Izhikevich neurons. There are previous Izhikevich network models of CA3 but these models only include excitatory neurons (Dur-e-Ahmad et al., 2012).

This work is a part of a bigger objective that aims at building a whole-hippocampus model using Izhikevich neurons. By virtue of using these neurons, such a model would be both, computationally efficient as well as biologically relevant and can be used for in-silico investigations of the region.

Methods

Data

The intrinsic property data for DG neurons was obtained from Santhakumar, Aradi, and Soltesz (2005). This data for CA3 neurons was obtained by implementing biophysical models of these neurons provided by Neymotin et al. (2011) due to absence of direct availability of intrinsic property data for CA3 inhibitory neurons in this and other relevant research articles. The intrinsic property data of interest was

resting membrane potential, membrane capacitance, action potential threshold, action potential amplitude, maximum voltage undershoot during action potential refractory period, ionic conductance dynamics and current - frequency profile.

For the CA3 network, number ratio, synaptic parameters and connectivity of neurons was obtained from Neymotin et al. (2011).

Single Neuron Izhikevich Models

$$C_m \frac{dV}{dt} = k(V - V_r)(V - V_t) - u + I$$

$$\frac{du}{dt} = a(b(V - V_r) - u)$$

if, $V > V_{peak}$; $V \leftarrow c$ & $u \leftarrow d$

Here, C_m is membrane capacitance; V_r is resting membrane potential; V_t is voltage threshold; V_{peak} is the amplitude of the action potential; k is scaling factor; a is the time constant of slow current; b describes the amount of coupling between slow current and voltage fluctuations; c is voltage reset value; d describes the net amount of inward current that causes repolarization of membrane voltage; I is the external current.

The parameters V_{rest}, V_{thresh}, V_{peak}, and c can directly be obtained by looking at neuronal spikes. For DG, this data was directly available in Santhakumar et al. (2005) while for CA3 the spikes of a particular neuron were 'looked' at by implementing the biophysical neuron model of that particular neuron (Neymotin et al., 2011). Values of C_m for neurons of interest were directly available in the references mentioned above. A higher value of k was used when $V > V_t$ and a lower value was used when $V < V_t$ to get a reasonable spike shape. Values of these parameters are chosen to be closer to that of the ones used in Izhikevich models of other hippocampal neurons available in literature (Dur-e-Ahmad et al., 2012; Ferguson et al., 2014) since the shape of the spike was not the focus here.

The parameters a, b, d, and k_{low} were tuned using Genetic Algorithm (GA) to reproduce the f-I curves of the neurons of interest. GA from the optimization toolbox of MATLAB was used. To choose best GA settings for this problem, f-I curve was generated using a known set of Izhikevich neuron model parameters. With this as the 'desired curve', genetic algorithm was executed. The set of options chosen was the one that gave the parameters closest to the actual parameters. The objective function was taken as the Mean Squared Error (MSE) between the frequencies produced by Izhikevich model with a certain set of parameters and the desired frequencies for the input current range 0 to 1000 pA in steps of 1.

CA3 Network Model

The CA3 network was implemented in MATLAB by connecting the CA3 Izhikevich neurons. Various aspects of these connections like connectivity, synapses and connection weights are described in this section.

The in-degree of a neuron for each type of neuron in the network is shown in figure 2.The convergence (in-degree) to each neuron type is fixed but the divergence (out-degree) is selected randomly from a range such than convergence is not disturbed (Neymotin et al., 2011). For instance, any Basket cell receives input from exactly 50 other Pyramidal cells but any Pyramidal cell can synapse at any number of Basket cells determined by a random number in range 0 to (50 x number of Basket cells in the network).

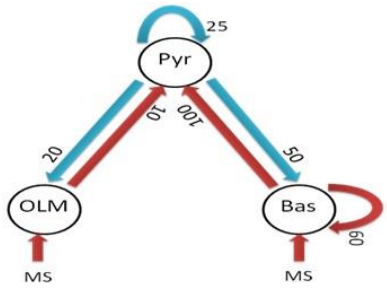

Figure 2: CA3 network connectivity; red – inhibition and blue – excitation; numbers on arrows show number of pre-synaptic cells that synapse on the post synaptic cells

Synaptic conductance was modeled as a double exponential mechanism. Synaptic parameters are given in table 3 (Neymotin et al., 2011).

Weight of a connection represents the number of synaptic channels at the synapse that connects the two neurons. The weights of the connections had not been fixed and were manually tuned to get the baseline activity.

Results

Single Neuron Models

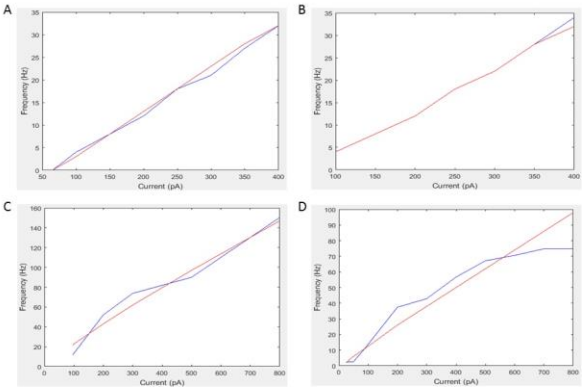

Figure 3: Current-frequency profiles of DG neurons; On x-axis is current (pA) and on y-axis is frequency of spiking (Hz); Blue curve – Desired current frequency profile and red curve – Izhikevich model generated current-frequency profile; A – Granule cell, MSE = 0.87; B – Mossy cell, MSE = 0.57; C – Basket cell, MSE = 76.16; D – HIPP cell, MSE = 83.2

The GA was run several times with a population size of 300, crossover fraction 0.7 and other settings at their default values. The best solution among these several solutions returned by GA was chosen. In some cases the chosen best solution was rheobase corrected and in some cases the parameters were manually changed in its neighborhood to get a better fit with the desired curve.

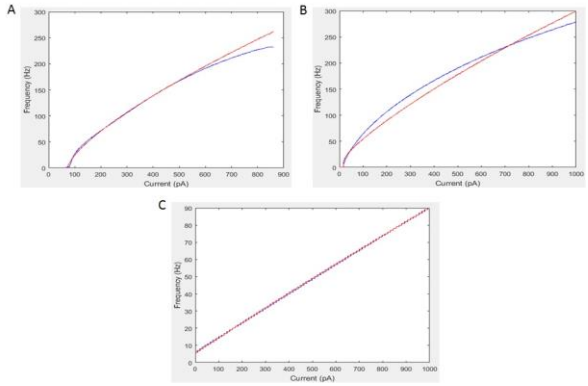

Figure 4: Current-frequency profiles of CA3 neurons; On x-axis is current (pA) and on y-axis is frequency of spiking (Hz); Blue curve – Desired current frequency profile and red curve – Izhikevich model generated current-frequency profile; A – Pyamidal cell, MSE = 84.9; B – Basket cell, MSE = 155.4; C – OLM cell, MSE = 0.25

Table 1: Izhikevich neuron model parameters for CA3 neurons

Parameters	Pyramidal	Basket	OLM
a (ms^{-1})	0.02	0.086	0.001
b (nS)	-7	-14.968	9.975
c (mV)	-78.5	-70	-71
d (pA)	15	17.629	19.999
k_{low} (nS/mV)	1.35	1.157	1.746
k_{high} (nS/mV)	5	14	10
V_{peak} (mV)	36	32.5	32
V_{thresh} (mV)	-45.3	-44	-44
V_{rest} (mV)	-65	-60	-60
C_m (pF)	62.83	100	100

Table 2: Izhikevich neuron model parameters for DG neurons

Parameters	Granule	Mossy	Basket	HIPP
a (ms^{-1})	0.0039	0.0011	0.014	0.004
b (nS)	-6	8.04	-3.673	-2
c (mV)	-75	-65	-65	-75
d (pA)	45	28.91	42.806	40.52
k_{low} (nS/mV)	1	4.3	0.102	0.01
k_{high} (nS/mV)	10	10	10	10
V_{peak} (mV)	80	88	78	90
V_{thresh} (mV)	-48.7	-52	-49	-50
V_{rest} (mV)	-70.4	-60	-60	-70
C_m (pF)	77	142.3	123.1	58.7

Figures 3 and 4 show the comparison between the desired current-frequency curve and the accepted Izhikevich model generated current-frequency curve for DG and CA3 neurons respectively along with the associated MSE. The parameters of the accepted Izhikevich model, chosen to represent each of the neuron types of interest are shown in tables 1 and 2.

CA3 Network Model

Various aspects of the network are as follows:

- Network has 800 pyramidal cells, 200 Basket cells and 200 OLM cells
- Synaptic reversal potentials: $E_{AMPA}=E_{NMDA}=0$ mV; $E_{GABA}=-80$ mV.
- Current injections to get baseline activity: Pyramidal=100 pA; Basket=0 pA; OLM = -75 pA
- Inhibitory inputs from Medial Septum (MS) to Basket and OLM cells with Gpeak = 1.6; Rise time = 20 ms; Decay time = 40 ms
- Synaptic delay of 2 ms to account for axonal propagation and neurotransmitter binding
- Synaptic parameters, connectivity and tuned weights of the connections are shown in table 3 and figure 2

Table 3: Properties of connections between neurons in CA3 network; Here P, B and O indicate Pyramidal, Basket and OLM neurons respectively

Type of connection	Synaptic parameters			Weight of the connection
	τ_r	τ_d	G_{peak}	
P→P (AMPA)	0.05	5.3	0.02	1
P→P (NMDA)	15	150	0.004	1
P→B (AMPA)	0.05	5.3	0.36	1.2
P→B (NMDA)	15	150	1.38	1.2
P→O (AMPA)	0.05	5.3	0.36	0.5
P→O(NMDA)	15	150	0.7	0.5
B→P (GABA)	0.07	9.1	0.72	0.5
B→B (GABA)	0.07	9.1	4.5	0.8
O→P (GABA)	0.2	20	72	1

In table 3, τ_r is the rise time in ms, τ_d is the decay time in ms and G_{peak} is maximum synaptic conductance in nS. Simulation of CA3 network with no external current is shown in figure 5.

The mean firing frequencies at baseline, that is, in absence of any external stimulus produced by CA3 network are comparable to the ones found in literature (Sanjay et al., 2015). This is shown in table 4.

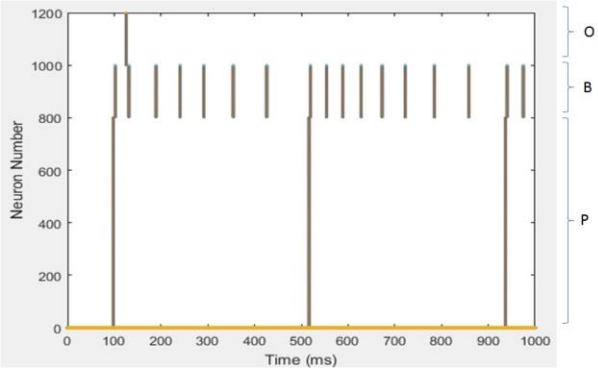

Figure 5: Simulation of CA3 network for 1000 ms with time-step 0.1 ms; On x-axis is time (ms) and on y-axis is neuron number; A dot in the plot indicates that neuron corresponding to y-coordinate of dot fired at the time point corresponding to x-coordinate; O – OLM neurons, B – Basket cells and P – Pyramidal cells

Table 4: Desired and network generated mean spiking frequencies of CA3 neurons at baseline

Neuron type	Desired Baseline Activity (Hz)	Network Baseline activity (Hz)
Pyramidal	2.36 +/- 0.024	3
Basket	16.05 +/- 0.15	17
OLM	0.96 +/- 0.027	1

Discussion & Conclusion

Single neuron Izhikevich models for seven types of neurons, spread across CA3 and DG have been produced by optimizing Izhikevich model parameters using genetic algorithm such that they produce desired current-frequency profiles. These models are able to closely capture the dynamics of aforementioned neurons reflected by reasonably low values of Mean Squared Error (MSE) of model generated current-frequency profiles with respect to desired profiles. However, availability of intrinsic property data for CA3 inhibitory neurons in future would provide a reliable means to cross-validate the models. Literature shows that there have been previous efforts to produce Izhikevich models for CA3 Pyramidal cell and DG Granule cell but this work is one of the first attempts to produce Izhikevich models for the other neuron types stated above. Izhikevich neuron models for these two neuron types have also been developed, as part of this wok, based on the data from same source as that for interneurons in order to minimize the error in the activity of network of a sub-region formed by connecting these neuron models.

Further, a network of the Izhikevich neuron models of CA3 neurons has been constructed using the data on the connectivity of these neurons, available in the literature. Currently available models of this region either consist of biophysical neurons or integrate and fire neurons (de Almeida et al., 2007; Sanjay et al., 2015). The ones with the Izhikevich neurons do not include inhibitory neurons (Dur-e-Ahmad et al., 2012). The fact that the CA3 network presented as a part of this work, consists of both inhibitory and excitatory Izhikevich neurons makes this network unique. This CA3 network shows the baseline activity that is comparable to the one observed in-vivo. This validates the network as a reliable representation of the CA3 sub-region and therefore, can be used for in-silico studies on CA3.

There are many avenues to build upon this work. The CA3 network can be made topographical by obtaining data on spatial arrangement of neurons in CA3 region. Further, DG neurons can be used to build a DG network. The network model of CA1 which is already available in literature (Ferguson et al., 2014) can then be integrated with CA3 and DG network models to form a whole-hippocampus Izhikevich neuron model.

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