Improvement of the Izhikevich model based on the rat basolateral amygdala and hippocampus neurons, and recognition of their possible firing patterns

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Highlights

1. Identification of the possible firing patterns following by the rat BLA and HIP
   neurons
2. Assigning a precise mathematical model to each recognized firing pattern of the
   BLA and HIP neurons
3. Parameters optimization of the Izhikevich model based on the HIP and BLA data
   applying a genetic algorithm
4. Improvement of the Izhikevich model accuracy in representing rat data firing
   patterns
5. Defining biological implication of changes in values of the Izhikevich model in
   the process of optimization

Plain Language Summery

One fundamental concept in understanding functions of different brain areas, how they
are connected to each other, and with which rate information transfers between the areas
is to recognize the firing pattern of neurons in those structures. These understandings
promotes the opportunity to more successfully treat relevant neural diseases in the sense
that firing pattern of neurons in abnormal areas should be brought back to the normal
firing activity. Additionally, identification of potential firing patterns for different
structures of the brain and allocating a mathematical model to them reduces a great
amount of complexity and implementation costs in simulation of neural networks, based
on the biological evidences. So, it is essential to identify the firing patterns that neurons
of different brain areas follow under normal and lesioned circumstances. On the other
hand, it is important to be able to model possible treatments for neural diseases in a
simulated sphere, as the first stage, and examine the effectiveness of them in a controlled condition before applying them to real world, to patients. In order to increase the accuracy of applied treatments, e.g. to return the abnormal firing activity of neurons to the normal one, the neural network should be built based on the real data and performed by a biologically plausible model. The Izhikevich model is one of the best neural models that can represent different firing patterns with a fairly simple formulation. In this study, we have identified the possible firing patterns following by the hippocampus (HIP) and basolateral amygdala (BLA) neurons as the primary goal. Second, in order to assign a mathematical model to each recognized firing pattern, the Izhikevich neural model have improved by optimizing its parameters for potential cases via genetic algorithm. In this algorithm, optimization tools such as crossover and mutation provide the basis for the generation of model parameters populations. The process of comparison in each iteration leads to the survival of better populations until achieving the optimum solution. Therefore, in future simulation of neural networks, applying the improved Izhikevich model for the possible firing patterns will increase the accuracy of modeling and reduce its complexity. This achievement along with greater understanding of firing activity of neurons under normal versus abnormal condition results in more accurate simulated treatments based on the biological data, and consequently real world treatments in the future efforts.

Abstract

Introduction: Identifying the potential firing patterns following by different brain regions under normal and abnormal conditions increases our understanding of what is happening in the level of neural interactions in the brain. On the other hand, it is important to be
capable of modeling the potential neural activities, in order to build precise artificial neural networks. The Izhikevich model is one of the simple biologically plausible models that is capable of capturing the most known firing patterns of neurons. This property makes the model efficient in simulating large-scale networks of neurons. Improving the Izhikevich model for adapting with the neuronal activity of rat brain with great accuracy would make the model effective for future neural network implementations.

**Methods:** Data sampling from two brain regions, the HIP and BLA, is performed by extracellular recordings of male Wistar rats and spike sorting is done using Plexon offline sorter. Further data analyses are done through NeuroExplorer and MATLAB software. In order to optimize the Izhikevich model parameters, the genetic algorithm is used.

**Results:** In the present study, the possible firing patterns of the real single neurons of the HIP and BLA are identified. Additionally, improvement of the Izhikevich model is achieved. As a result, the real neuronal spiking pattern of these regions neurons, and the corresponding cases of the Izhikevich neuron spiking pattern are adjusted with great accuracy.

**Conclusion:** This study is conducted to elevate our knowledge of neural interactions in different structures of the brain and accelerate the quality of future large scale neural networks simulations, as well as reducing the modeling complexity. This aim is achievable by performing the improved Izhikevich model, and inserting only the plausible firing patterns and eliminating unrealistic ones, as the results of this study.

**Keywords:** Izhikevich model; Firing pattern; Optimization; Genetic algorithm; Basolateral amygdala; Hippocampus.
1. Introduction

One of the pivotal components of the brain’s microscopic structure is a neuron cell. The importance of this concept has led to comprehensive researches to understand the mechanism behind neuronal activity. One of the major results is that unlike other body cells, neurons interact with each other by receiving and sending electric pulses or spikes. Each spike causes the release of neurotransmitters which results in changes in the activity of its neighboring neurons.

Spiking neural networks (SNNs) that are the third neural networks generation (Maass, 1997) have been developed to imitate the natural neural networks. Spiking neural networks follow the same trend as computational neuroscience. The ultimate goal of both is to realistically represent and configure the functionality of different brain areas. SNNs originated from the study of Hodgkin and Huxley (Hodgkin & Huxley, 1952) in 1952. The fundamental aim of SNNs is to encode all the information related to single spikes rather than just their firing rate (Maass & Bishop, 2001). Spiking neural networks have been used in large number of studies operating different applications. These approaches consist of regression and categorization (Hojjatinia, Lagoa, & Dabbene, 2019; Dreiseitl & Ohno-Machado, 2002; Hojjatinia & Lagoa, 2019), deep learning (Sutskever, Vinyals, & Le, 2014), pattern recognition (Taigman, Yang, Ranzato, & Wolf, 2014), and behavioral prediction (Shen & Bax, 2013; Lagoa, et al., 2017; Conroy et al., 2019). Moreover, spiking neural networks facilitate the understanding of human brain for researchers (Kuebler & Thivierge, 2014). Computational studies of SNN conducted by Maass and Schmitt (Maass, 1997; Maass, 1995a; Schmitt, 1998) have shown great efficiency of the third neural networks generation.
In each dynamical study, one critical issue is which model can describe spiking dynamics of the neuron more efficiently. Although the Hodgkin-Huxley model can greatly simulate the biological functioning of a neuron, it involves 12 equations consisting four differential equations, and three parameters to model the activity of one neuron (Johnson & Chartier, 2017). This complex modeling results in a very expensive implementation. Also, the Hodgkin-Huxley model fails to exhibit the all-or-nothing firing mechanism for action potential generation (Deng, 2017).

A popular model that represents a quite good compromise between computational efficiency and biologically realistic behaviors is the Izhikevich model (Izhikevich, 2003). This model is not only biologically plausible, similar to Hodgkin-Huxley model in this sense, but also it is as efficient as integrate-and fire model, computationally. The Izhikevich model is also capable of simulating large-scale spiking neurons in real time (Izhikevich, 2004). Therefore, in order to empower the neural interaction modeling based on real data, elevating the accuracy of the Izhikevich model in representing the neurons activity seems prominent. This will also result in increasing the application of Izhikevich model as an efficient model in implementation of functional neural networks. One of the techniques to improve this model and adapt it to the behavior of considering real neurons is to optimize its parameters.

Genetic algorithms have developed according to basic concepts in evolution and imitation of natural processes (Holland, 1975). These criteria consist of mutation, recombination, and assortment of populations in a synthetic environment. The substantial components required in developing genetic algorithms, introduced by Bremermann in 1962 (Bremermann, 1962). Deciphering complicated problems by applying evolutionary techniques consisting genetic algorithms increased the popularity of these algorithms in
the following years (Rechenberg, 1973; Schwefel, 1974). Genetic algorithm which is one of the most popular evolutionary algorithms are applicable in solving optimization problems with a complex fitness landscape (Kellerer, Pferschy, & Pisinger, 2004; Hojjatinia, Lagoa, & Dabbene, 2017).

Two leading parts of the brain are the amygdala and the hippocampus. The amygdala is an influential area in memory pattern formation based on emotions (Tovote, Fadok, & Luthi, 2015; LeDoux, 2000) as well as development of fear, anxiety and corresponded diseases (LeDoux, 2000; Beyenburg, Mitchell, Schmidt, Elger, & Reuber, 2005). The amygdala plays a pivotal role in creating organisms’ responses to their environment (Tovote, Fadok, & Luthi, 2015; Phelps & LeDoux, 2005). The hippocampus is one the major parts of the limbic system and important area in strengthening memories, spatial learning, and emotional reactions (El-Falougy & Benuska, 2006). Firing pattern identification of single neurons of these structures under brain’s normal activity can play an important role in differentiating the normal and abnormal patterns associated with them. Furthermore, the ability to represent the firing activity of these structures’ neurons with a mathematical model can conduct to better formulation and simulation of the problem and ultimately, more effective treatment for certain associated diseases.

Developing electrophysiological recording of single neurons activity provides a basis for exploring the structure of brain functions. However, the recorded signals are mostly contaminated by a high amount of background noise; noise from the recording system or the activity of distant neurons. Moreover, the recorded data is related to the activity of a number of neurons adjacent to the recording site (Lewicki, 1998). Analysis of neural recordings requires one of the complicated interpretation tools that is known as spike sorting.
Spike sorting is the process of isolating action potentials from the background activity which is considered as noise, extracting prominent spike features from the detected spike waveforms, and finally allocating spikes with same features to their originating neuron (Takekawa, Isomura, & Fukai, 2010; Rutishauser, Schuman, & Mamelak, 2006). This process can be done by an appropriate choice of clustering methods. Then, clusters of spikes can be used for further analysis and modeling.

In this study, one main objective is to identify the possible firing patterns that the neurons of the HIP and BLA follow under normal activity. Another noticeable following goal is to improve the Izhikevich model to make it more accurate in representing the firing activity of rat brain real data.

2. Methods

2.1. Experimental Implementation

Male Wistar rats were used to investigate neuronal electric signaling in the normal BLA and HIP. Each rat was housed in Animal Care Facility maintained at 23 ± 1°C on a 12:12 h light/dark cycle. Food and water supplied with no limitation. The experimental processes are implemented based on the Guidelines for the care and use of laboratory animals (National Institutes of Health Publication No. 80–23, revised 1996). All experiments were conducted in Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, according to terms and conditions of the Research and Ethics Committee of this institute.

2.2. Electrophysiological recording and data collection

Animals’ anesthesia was achieved using urethane with initial dose of 1.5 g/kg, intraperitoneally. Additional doses were given whenever needed to maintain surgical
anesthesia depth as checked by foot pinch and corneal reflex. To remove the potential pain, 0.1 ml buprenorphine was injected, subcutaneously. Conducting tracheotomy, rats were located in a stereotaxic instrument. Using a heating pad, the rat body temperature was maintained for the experiment duration. Electrophysiological recordings of the firing activity of neurons in the HIP and BLA were performed via an acute microelectrode with one channel. Each channel records the electric activity of a few neurons adjacent to it; the activity of farther neurons appeared as the background noise due to their low amplitude. The microelectrode was proceeded to the left BLA (AP: -2.52 mm and ML: -4.8 mm from the bregma, and DV: -8.4 mm from the surface of skull) and the left HIP (AP: -3 mm and ML: -1.8 mm from the bregma, and DV: -3 mm from the skull surface) according to the rat brain atlas (Paxinos & Watson, 2007). Signals were recorded using a data acquisition system, filtered between 300 and 10000 Hz, and sampled with the rate of 50 kHz. Each recording lasted for 1800 seconds.

2.3. Data Analysis

Recorded data from the electric activity of neurons were exported to and analyzed via an offline sorter software called Plexon (Plexon Inc., Dallas, TX). Spikes were detected through manual amplitude threshold discrimination. The threshold level discerns a trade-off between the missed spikes and the noise which may pass that level. The threshold was assigned based on the amplitudes distribution of background activity and spikes. Next, spike sorting was performed to cluster the electric activity of individual neurons, based on the first to third principle components, peak, valley, and other properties of signals. Principle component analysis (PCA) is one of the best linear spike feature extractors (Adamos, Kosmidis, & Theophilidis, 2008). Finally, spike clusters which represented a valid inter spike interval histogram (ISI) (Theodoridis &
Koutroumbas, 2009) were saved for further analysis. NeuroExplorer software (Nex Technologies, Colorado Springs, CO) was used to analyze the firing activity of clusters of neurons. The quality of sorted data was validated through auto-correlogram analysis. Auto-correlogram displays a single spike train against itself. Another tool that compares arrival times of spike trains is cross-correlogram. Through cross-correlogram, different identified clusters of spikes were explored to validate the exact number of neurons in each set of recorded data. Finally, the average firing rate histograms were generated and verified for all neurons, over the entire period of 1800 seconds. Then, validated clusters of spikes were exported to MATLAB software to be used for modeling. This software is also used to code our desirable genetic algorithm, Izhikevich model and depict the comparison figures of different firing patterns.

2.4. Izhikevich neuronal model

The two dimensional Izhikevich neuronal model (Izhikevich, 2003) is defined by three equations as follows:

\[ \dot{v} = 0.04v^2 + 5v + 140 - u + I \]  
\[ \dot{u} = a(bv - u) \]  
\[ \text{if } v \geq +30 \text{ mV, } v \leftarrow c, u \leftarrow u + d \]

Where variables \( v \) and \( u \) are the membrane potential of the neuron and membrane recovery variable, respectively. Activation of \( K^+ \) ionic currents and inactivation of \( Na^+ \) ionic currents can be represented by the variable \( u \). This variable supplies \( v \) with a negative feedback. Variable \( I \) represents the delivery of synaptic currents. Equation (3) activates when the amplitude of action potential reaches the threshold +30 mV. \( a, b, c, \) and \( d \) are dimensionless parameters of the model.
Differences in quantities of the Izhikevich model parameters result in the exhibition of various firing patterns that neurons may follow. The parameter $a$ traces the time scale of recovery variable $u$. Therefore, smaller amounts of $a$ represent slower recovery periods. The parameter $b$ describes the sensitivity of variable $u$ to oscillations in membrane potential $v$. Based on the values of this parameter, the resting potential is volatile between -70 and -60 mV (Izhikevich, 2003). The parameter $c$ depicts the after-spike reset value of the variable $v$ and has an amount between -50 and -65, in different patterns. Amount -65 determines deep voltage reset, the value -55 governs high voltage reset, and -50 represents moderate after-spike jump (Izhikevich, 2007). Parameter $d$ outlines the after-spike reset of the variable $u$. This parameter changes in a wider range. The higher values of $d$ represent greater amounts of after-spike jump of recovery variable $u$. Supplementary Fig. 1 summarizes the mentioned explanations related to the parameters in a visual standpoint.

In order to simulate 1 ms of the Izhikevich model, operation of only 13 floating point is required. This property makes the model very effective in simulating large-scale networks of neurons (Izhikevich, 2003). According to both points of view that are biological plausibility (number of features) and implementation cost (an approximate number of floating point operations), the Izhikevich model is fairly in desirable condition to be used. Therefore, the model efficiency in representing spiking behavior of rat brain neuron with great accuracy can fortify the model.

The Izhikevich model can exhibit all the firing patterns which are shown in supplementary Fig. 2. It illustrates the various spiking patterns of individual neurons, based on their response to the applied dc current (Izhikevich, 2010). The BLA and HIP neurons that have been used in this study follow neuronal behaviors similar to some of
these neuro-computational properties. The following properties are tonic spiking (Nessler & Bernhard, 2013), phasic spiking (Malsburg, 1999), mixed model (Connors & Gutnick, 1990), integrator, rebound spike, threshold variability (Izhikevich, 2003), depolarizing after-potentials (Malsburg, 1999), and inhibition-induced spiking (Izhikevich, 2003).

2.5. Genetic Algorithm

The genetic algorithm is one of the well-known evolutionary algorithms that employs the principle of best populations’ selection in each iteration for the whole process. This property provides the opportunity to select and generate individuals that are more adapted to the environment and remove the ones with less consistency. By repeating the same process for several generations and replacing undesirable populations by more adjustable ones, the algorithm evolves a population with optimal characteristics. Capability of genetic algorithm in operating with both continuous and discrete variables, as well as linear and nonlinear fitness functions makes this algorithm a great candidate in solving complicated optimization problems (Hassan, Cohanim, & Weck, 2004). A basic genetic algorithm procedure consists of the following key components (Goldberg, 1989; Pelikan, 2010):

- **Initialization**: genetic algorithms produce the initial population of solutions arbitrarily. This generation conducts based on a unique distribution of admissible solutions.

- **Selection**: over the course of each iteration, genetic algorithms select the more adjustable solutions from the existing set of populations. This process employs the more qualified solutions.

- **Variation**: two great tools recruited in genetic algorithms are crossover and mutations. Applying these tools to selected solutions in prior step, results in
generation of new solutions. Crossover is the process of recombining different subsections of promising solutions. Likewise, mutation applies instant alternation in integrated solutions.

- Replacement: in this step, next generation produces by replacing the primary solutions or some parts of them with the new desirable ones which are generated via crossover and mutation.

3. Results

As mentioned before, the parameters of the Izhikevich model have different values to exhibit different potential firing patterns of neurons. In this study, we optimized each set of parameters by modifying our optimization problem variables such as maximum number of iterations, crossover percentage, mutation rate, etc., in the performed genetic algorithm to minimize the associated error.

In this paper, recording data from two regions of the rat brain consists of the BLA and HIP under normal activity, spike sorting is done via Plexon Offline Sorter. The process resulted in three clusters of spikes for each region. Based on spike sorting criteria, each cluster represents the activity of one single neuron adjacent to the recording site. Afterward, we compared the firing patterns of the original Izhikevich model, model with optimized parameters $a$, $b$, $c$, and $d$, and the firing behavior of the mentioned regions real single neurons.

3.1. Parameters optimization and neural firing results

The main step after applying spike sorting was to recognize the firing patterns that each single neuron of the data was following. This way, we traced the activity of each neuron in a specific period of time and compared them with the known firing patterns.
Next step was to design a proper genetic algorithm to optimize corresponding cases of the Izhikevich model parameters. As mentioned before, in designing the proper genetic algorithm, the values of optimization problem variables were dependent on different cases of the Izhikevich neural pattern and data. So, in order to reach a customize genetic algorithm for each case, different tests were run with different variable amounts. The fitness criterion was the error minimization (mean square error) of the neural action potential difference between the Izhikevich and real neurons. As a case example, considering the designed genetic algorithm for tonic spiking pattern for the BLA neurons, the optimal crossover and mutation ratio are assigned 0.7 and 0.8, respectively. The algorithm terminated in 150 generations.

In this paper, we represent the results according to the potential firing patterns following by the detected single neurons. Other cases of Izhikevich pattern that were excluded from further consideration and explanations in this study, are the ones with considerable different spike timing or number of spikes in a given period of time. Some of these inconsistencies are shown in Fig. 2 (c) to (e) for the BLA and Fig. 3 (e) and (f) for the HIP.

We depicted comparison plots of possible firing patterns related to different clusters of the HIP and BLA, corresponding Izhikevich, and improved Izhikevich patterns in several figures. In all figures, the red/line curve is related to rat real neuron spiking, the black/dash curve is relevant to Izhikevich neuron and the blue/dash-dot curve is related to the improved Izhikevich neuron. As it can be seen, rat real neuron spiking plot and Izhikevich neuron plot are not matched in most of the cases. Therefore, the Izhikevich model needs to be improved for adjustments. It is clear that the initial jump in membrane
potential represented in a few figures is not a spike, but it is apparently a transient mode in firing activity of the neurons.

3.1.1. The BLA

The recording and analysis have been done on several rats and the results are desirably consistent. The outcomes of Izhikevich model parameter optimization for the BLA single neurons are shown in Fig. 1 and Fig. 2. According to figures, it is clear that real neurons of the BLA had a great adaptation with the improved Izhikevich neurons. Moreover, results represent that first cluster may follow a firing pattern of each of improved integrator, phasic spiking, depolarizing, rebound spiking, or threshold variability, as depicted in Fig. 1. The second and third clusters followed a firing pattern of the improved Izhikevich pattern for inhibition-induced spiking and tonic spiking, respectively. The activity pattern of these two clusters is depicted in Fig. 2 (a) and (b).

In Fig. 2 (c) to (e), we showed three neural behaviors that a real neuron of the BLA did not follow and compared them with either firing pattern of Izhikevich neuron or Izhikevich improved neuron. Mentioned firing behaviors consisted of mixed spiking, bistability, and spike frequency adaptation.

3.1.2. The HIP

Similar to the previous discussed region of the rat brain, the HIP neurons have greatly followed the improved Izhikevich pattern for each of the sorted clusters. The results can be seen in Fig. 3 (a) to (d). For all considered rats, the three single neurons extracted from data recording of this region had the firing pattern as follows: one cluster followed improved mixed or tonic spiking, the second cluster followed the improved inhibition-induced spiking, and the last one followed improved tonic spiking. Fig. 3 (e)
and (f) represented two firing activity which the HIP single neurons may not follow. These patterns are bistability and spike frequency adaptation.

4. Discussion

Several significant results are achieved based on the in vivo electrophysiological data in this study. First, the structure behind the firing patterns following by the single neurons of the rat BLA and HIP have identified. This finding increases our understanding of the behavior of different structures in the nervous system. Second, a precise mathematical model have assigned to each recognized firing pattern. This aim is achieved using one of the best neuronal spiking models for large scale simulations, Izhikevich model, due to its great trade-off between simplicity, computational feasibility, and biological plausibility. In order to reach the proper adjustable mathematical model for the BLA and HIP neurons, parameters of the Izhikevich model have optimized for all different possible cases, using genetic algorithm. This achievement increases the accuracy of the Izhikevich model in representing a mathematical model for real neurons of rat brain. These findings have a great impact in future modeling of networks of neurons consisting the BLA and HIP in which the unlikely firing patterns can be excluded from the consideration. Elimination of unrealistic firing patterns and performing the proper mathematical model for the probable ones will result in elevating the quality of neural networks simulations and reducing the complexity of the modeling. Finally, the biological implication of changes in values of the Izhikevich model in the process of optimization have defined.

As mentioned earlier, the Izhikevich model is capable of representing the firing pattern of most known types of cortical neurons according to changes in its parameters values. However, it fails to represent the neuronal firing pattern of some specified parts
of rat cortex such as the HIP and BLA with great accuracy. Shown by the real data in this study, one potential problem of the Izhikevich model is its after spike potential; the Izhikevich neuron potential returns to the amount of parameter \( c \), as it is shown in supplementary Fig. 1 (Izhikevich, 2003). Nevertheless, considered cases in current exploration did not follow this potential reset. In fact, they simply returned to their initial amount, as it can be seen in Fig. (1) to (3).

The Izhikevich model is a well-known spiking neuronal model that has been used in numerous Computational Neuroscience researches. Some of the studies that have been applied Izhikevich neural model are represented in the following. Zhao and colleagues have investigated the probability of detecting a weak electric field in neural networks with the presence of noise (Zhao et al., 2017). Lv and colleagues have implemented simultaneous simulations of brain networks based on the Izhikevich spiking model (Lv et al., 2014). Mizoguchi and coworkers have developed a silicon neuron circuit based on the Izhikevich neuron (Mizoguchi, Nagamatsu, Aihara, & Kohno, 2011). Nageswaran et al. have demonstrated an efficient, biologically realistic large-scale spiking neural model simulator considering Izhikevich spiking neuron (Nageswaran, et al., 2009).

As shown above, the Izhikevich neural model has been used in a variety of researches and is so applicable in neural network simulations. The popularity of this model in large scale simulations is because of its simplicity in implementation as well as its biological plausibility. This way, improving the model by increasing its accuracy in adjustment with brain real data spiking activity will result in outcome improvement of studies conducted based on this model. Improvements can be reflected in whether approaching a more realistic result or designing a more reliable neural networks. The necessity for model modification led us to investigate the potential techniques to improve
the Izhikevich model. To achieve this purpose, one of the best methods that is represented in this paper is to optimize the Izhikevich model parameters. This enhancement enables the model to adjust with rat cortex neuron spiking pattern with a great accuracy and promotes the efficiency of investigations based on the Izhikevich model.

Optimization is the process of improving a conception, based on the obtained information. In optimization problem the goal is to achieve the best solution, even with the presence of large amount of noise (Ravazzi et al., 2018, Hojjatinia,). This concept declares that there exist several solutions to the problem which each has a different value (Haupt & Haupt, 2004). Solutions should be determined by considering the situation and conditions. Optimization algorithms divide into six categories which some of them aim to minimize the cost. Although the minimum seeker algorithms are usually fast, they fail to distinguish the local minimum solutions from the global ones. In contrast, optimization algorithms such as genetic algorithm are more successful in achieving the global minimum, while decreasing the speed of process (Haupt & Haupt, 2004).

Sophisticated real-world problems and attempts to find appropriate solutions for them have led scientists to investigate natural phenomena and imitate them for years. Optimization algorithms have been developed based on the natural processes progressively in past decades (Michalewicz, 1996). Some outstanding algorithms such as evolutionary algorithms and the genetic algorithms perform intelligent searches in the massive space of solutions considering required statistical techniques. Natural approach followed by these algorithms results in achieving optimal solutions for natural phenomena such as spiking activity of neurons. This way, one of the best optimization algorithms, genetic algorithm is used in this inquiry.
To represent the effectiveness of genetic approach in optimizing the Izhikevich model parameters in a great way, we compared the firing pattern of model corresponded to optimized parameters with the firing pattern related to real data recorded from the BLA and HIP neurons. Modeling results have shown that rat real neurons activity and the improved Izhikevich pattern have a desirable adaptation.

The value of Izhikevich model parameters, before and after applying optimization is represented in table 1. As it can be seen, in all cases, one substantial point related to optimized parameters is that the values of parameters $d$ and $a$ have reinforced with a large rate. Other parameters have changed with a relatively slow rate, based on their spiking behavior. A larger amount of parameter $d$, which is the after-spike reset of the variable $u$, shows a larger after-spike jump of variable $u$ in behavior of the real single neurons. Additionally, larger values of parameter $a$ result in faster recovery of variable $u$. Greater values of the parameter $b$ represent stronger subthreshold fluctuations in neurons firing pattern, according to the values of the variables $u$ and $v$. The parameter $c$ has changed in range -65 to -50. Larger amounts of this parameter result in deep voltage reset. To sum up, according to this study, in vivo electrophysiological data recorded from the rat HIP and BLA represents larger after-spike jump of variable $u$, faster recovery of variable $u$, increasing or diminishing in low-threshold spiking dynamics, and deeper or shallower voltage reset, in comparison to the original Izhikevich neuron.

As an important result of this study, in future representation of the firing activity of rat HIP and BLA neurons under normal activity, one can use improved model with respect to the optimized values of Izhikevich neuronal model parameters. This will result in a great simplification in simulation of large-scale neural networks and development of hidden layers of them.
More importantly, our research is the first study investigating the possible firing patterns following by the rat HIP and BLA neurons under normal activity and anesthesia, from a mathematical point of view. Capability to assign a distinctive parametric model to each potential following firing pattern has a great implication in computational neuroscience and is a support for the concept that the form of distinctive firing patterns may play a role in representing the neuron’s function. Additionally, future networks modeling of spiking neurons based on the rat HIP and BLA neuronal activity can be performed by inserting only the possible firing patterns and excluding the cases that cannot be followed by the single neurons of these brain areas. The potential firing patterns of the BLA and HIP single neurons are represented in table 2.

Some of the irrelevant patterns which are not following by the HIP and BLA neurons are shown in Fig. 2 (c) to (e), Fig. 3 (e) and (f). In addition to these figures, there are also other firing patterns that are not compatible with the normal neural activity of the HIP and BLA under anesthesia. Potential reasons for the observed irrelevance are differences in spike timings, the number of spikes in a specific period of time, depolarization and repolarization timing and shape, either with or without applying improvement to the conducted model. We avoided further explanations regarded those patterns in this study.

To strengthen the validity of the achieved results, data recording has performed for several rats under anesthesia, and the whole analysis processes repeated for acquired data. The firing activity of all BLA and HIP neurons has compared; for the recorded data from each region, results were predominantly consistent.

Future researches may benefit from recording data from the BLA and HIP under the effect of drugs or in awake animals and investigate whether the Izhikevich model or
our modified model is capable of representing those neural activities. Also, it is noteworthy to explore the changes in possible firing patterns following by neurons under the effect of a special drug or awaking in comparison to the normal condition under anesthesia. Another interesting future study can be investigation of other optimization algorithms and compare their effectiveness in improving the Izhikevich model to efficiently represent the neural activity of different rat brain areas.

Compliance with ethical guidelines

All experiments were done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.
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Figure 1: The BLA first cluster firing patterns comparison. This figure depicts the comparison of the first cluster firing pattern of the rat BLA, possible firing patterns of the Izhikevich neuron, and the improved pattern, in distinct plots. The mentioned firing patterns are the integrator, phasic spiking, depolarizing after-potential, rebound spiking, and threshold variability.
Figure 2: Possible firing patterns of the BLA neurons. Plots (a) and (b) represent the comparison of the second and third cluster firing patterns of the rat BLA, possible firing patterns of the Izhikevich neuron, and the improved patterns. The second cluster may follow inhibition induced spiking and the third cluster may track tonic spiking. Plots (c) to (e) illustrate three possible firing patterns that may not be followed by the BLA neurons. In these plots, the comparison of second and third cluster firing pattern of the BLA, mixed spiking, bistability, and spike frequency adaptation from Izhikevich firing pattern, and improved ones are depicted.

Figure 3: Comparison of the HIP neurons firing patterns. Figure 3 (a) to (d) shows the comparison of the possible firing patterns of the rat HIP that are tonic spiking, mixed spiking, and inhibition induced spiking mode from Izhikevich firing pattern, and improved patterns. Figure 3 (e) and (f) represents unfollowed firing patterns that are bistability for the first cluster and spike frequency adaptation for the third cluster of the HIP neuron.

Supplementary Figures

Figure 1: Plots (a) and (b) represent the summery of Izhikevich parameters description; plot (a) shows the after-spike reset of the Izhikevich neuron, specifically. This figure is reproduced with permission from www.izhikevich.com.
Figure 2: Summary of the neuro-computational properties of biological spiking neurons. An electronic version of the figure and reproduction permissions are freely available at www.izhikevich.com.
Table 1: Comparison of the prior and posterior parameter values of Izhikevich neural model for various firing patterns under optimization.

| Firing Pattern   | Parameter status | Parameter $a$ | Parameter $b$ | Parameter $c$ | Parameter $d$ |
|------------------|-----------------|----------------|----------------|----------------|----------------|
| **Tonic spiking**| without optimization | 0.02 | 0.2 | $-65$ | 6 |
|                  | with optimization | 0.01877 | 0.26801 | $-66.3083$ | 12.46620 |
| **Mixed spiking**| without optimization | 0.02 | 0.2 | $-55$ | 4 |
|                  | with optimization | 0.037413 | 0.19586 | $-56.165$ | 10.82459 |
| **Integrator**   | without optimization | 0.02 | $-0.1$ | $-55$ | 6 |
|                  | with optimization | 0.1975 | $-0.1025$ | $-59.874$ | 12.16331 |
| **Depolarizing** | without optimization | 1 | 0.2 | $-60$ | $-21$ |
|                  | with optimization | 1.738625 | 0.165259 | $-67.823$ | $-4.4429$ |
| **Phasic spiking**| without optimization | 0.02 | 0.25 | $-65$ | 6 |
|                  | with optimization | 0.023135 | 0.24904 | $-67.904$ | 19.35829 |
| **Rebound spiking**| without optimization | 0.03 | 0.25 | $-60$ | 4 |
|                  | with optimization | 0.038877 | 0.25154 | $-64.0123$ | 11.09948 |
| **Threshold variability**| without optimization | 0.03 | 0.25 | $-60$ | 4 |
|                  | with optimization | 0.067733 | 0.251266 | $-62.2565$ | 13.03464 |
| **Inhibition-induced spiking**| without optimization | -0.02 | -1 | $-60$ | 8 |
|                  | with optimization | 0.0090563 | $-1.14721$ | $-62.0312$ | 16.2566 |

Table 2: Possible firing patterns following by the rat BLA and HIP neurons under normal activity and anesthesia.

| Firing Pattern         | Region   | Tonic spiking | Phasic spiking | Tonic bursting | Phasic bursting | Mixed mode | Spike freq. ad. | Class 1 excitable | Class 2 excitable | Spike latency | Subthreshold osi. | Resonator | Integrator | Rebound spike | Rebound burst | Threshold Var. | Bistability | DAP | Accommodation | Inhibition spike | Inhibition burst |
|------------------------|----------|---------------|----------------|----------------|----------------|------------|-----------------|-------------------|-------------------|---------------|-------------------|-----------|------------|---------------|--------------|----------------|-------------|-----|---------------|------------------|-----------------|
| **Tonic spiking**      | BLA      | +             | +              | -              | -              | -          | -               | -                 | -                 | +             | -                 | +         | +          | +             | +            | +             | +           | +   | -             | -                | -                |
|                        | Hippocampus | +            | -              | -              | -              | -          | -               | -                 | -                 | -             | -                 | +         | +          | +             | +            | +             | +           | +   | -             | -                | -                |