A Study of How Abnormalities of the CREB Protein Affect a Neuronal System and Its Signals: Modeling and Analysis Using Experimental Data

A. Emadi[1], *A. Abdi*[1,2]

1. Dept. of Electrical and Computer Engineering, New Jersey Institute of Technology, Newark, NJ, USA
2. Dept. of Biological Sciences, New Jersey Institute of Technology, Newark, NJ, USA
{ae378, ali.abdi}@njit.edu

***Abstract*— It is well understood that the CREB protein is highly involved in neuronal mechanisms underlying memory and learning in mammalian brain, and deficiencies in CREB activity can result in transition to certain pathological conditions. In this paper, we use some published experimental data, along with a neuronal system composed of the Izhikevich neuron model, to characterize how CREB abnormalities can alter neuronal signals and the system behavior. The abnormal data are extracted from intracellular recordings collected from the neurons of transgenic mice expressing VP16-CREB - a constitutively active form of CREB - whereas the normal data are obtained from the wild-type mice neurons. Upon estimating the neuron model parameters from the experimental data, we observe that the model exhibits good fit to both normal and abnormal data, for various synaptic input currents. To study the effect of CREB abnormalities on the considered neuronal system, we use the information theoretic redundancy parameter. It basically measures - for the system output neuron - the amount of spike count information overlap that exists between the states of the stimulus currents injected to the input neurons. Our analysis reveals a noticeable increase in the information redundancy, when CREB behaves abnormally. This finding motivates further exploration of the biological implications of the information redundancy in neuronal systems, and its use as a parameter to model abnormalities in CREB and perhaps other important transcription factors involved in learning and memory.**

Keywords*— *CREB, Izhikevich model, neuronal parameters estimation, information redundancy.

I. Introduction

Learning and memory are key functions of the cognitive human brain. CREB, a cAMP response element-binding protein (with cAMP denoting the cyclic adenosine monophosphate), is highly involved in learning and memory. Alterations and abnormalities such as its sustained activation can result in pathological conditions such as seizures and loss of neurons. Given its importance, targeting CREB and its pathway are of interest in therapeutic developments for several neurodegenerative disorders such as Alzheimer's disease and Huntington's disease [1].

Compared to the research efforts that study CREB as a molecule whose activity is regulated by a molecular network, e.g., [2], and focus on intraneuronal molecular interactions, in this paper our goal is to study and understand how CREB and its malfunction can affect a neuron and its action potential spike signals, as well as a system of such neurons.

Towards this goal, we use the experimental data given in Table 1 and Figure 1 of [1] that include both normal and abnormal CREB scenarios and the associated action potential signals, to estimate the parameters of a neuron model for both CREB scenarios. As we will see later in the paper, the model shows good fit to the experimental data. We then use an information theoretic parameter called redundancy [3], to model and study how the behavior of a neuronal system can change due to a deficiency in CREB activity. The use of information theoretic parameters and methods in neuroscience is advantageous for multiple reasons [3]. For example, they define and quantify how much information neuronal signals carry, they are model independent, they can be applied to various combinations of data, regardless of whether the relations among the data are linear or nonlinear, they are suitable for multivariate data modeling and analysis, and also can handle different types of data such as voltage, current, spike count and spike timing together.

The rest of the paper is organized as follows. Estimation of the parameters of the Izhikevich neuron model [4] using the measured data of [1] that reflect normal and abnormal CREB activities can be found in Section II, along with a comparison of the model results with the experimental data. The considered neuronal system is discussed in Section III, and its behavior is studied without and with the abnormality of CREB. The system behavior is further characterized using the redundancy parameter, and changes in this parameter due to the CREB deficiency are analyzed in Section III as well. Concluding remarks are provided in Section IV.

II. Calculation of Neuronal Parameters Using Experimental Data

Given the importance of CREB in learning and memory formation, CREB-related experimental data of [1] is used here to first compute several neuronal parameters for two different types of neurons: an abnormal neuron where

CREB exhibits abnormal activity, and a normal neuron. The abnormal neuronal data are intracellular measurements collected from neurons of transgenic mice expressing VP16-CREB, which is a constitutively active form of CREB, whereas the normal neuronal data are collected from neurons of wild-type mice. Both of the normal and abnormal experimental neuronal firing data sets include measured numbers of action potentials, in response to several different currents injected to the neurons [1]. Basically, when a neuron receives an electrical transmembrane current, its membrane potential changes according to the intensity of the input current. An action potential (AP) spike is generated when the neuron membrane potential reaches its apex upon receiving high enough input current injection [5][6]. And AP number is the number of spikes of the membrane potential, for a given injected current.

In this section, we use the experimental data to calculate the parameters of the Izhikevich model, which is widely used for modeling the dynamics of spiking neurons [4][5]. This allows to understand how the neuronal parameters vary, when comparing normal and abnormal neurons of wild-type and mutant mice, respectively. This is also important when studying a system of several neurons later in the paper.

In what follows, first a brief overview of the Izhikevich model is presented in Subsection A, followed by neuronal parameter calculations using the experimental data of normal and abnormal neurons in Subsections B and C, respectively.

A. The Izhikevich Neuron Model

This model is widely used by various groups of researchers and while it is computationally simple to implement, it incorporates certain biophysical aspects of more complex models and therefore is capable of reproducing different neuronal behaviors. The Izhikevich neuron model is composed of two ordinary differential equations [4][5]:

$$C\frac{dv(t)}{dt} = k(v(t)-v_r)(v(t)-v_{th}) - u(t) + I(t)\,, \quad (1)$$

$$\frac{du(t)}{dt} = a(b(v(t)-v_r) - u(t))\,, \quad (2)$$

$$u(0) = b\,v(0)\,, \quad (3)$$

where $v(t)$ is the neuron membrane potential, $u(t)$ is the membrane recovery variable and $I(t)$ represents the synaptic input. Furthermore, C is the membrane capacitance, v_r is the resting potential, v_{th} represents the instantaneous threshold potential, a is the recovery variable time scale, b reflects the recovery variable sensitivity, d refers to the after spike recovery variable reset, and c represents post action potential voltage reset value. Equations (1) and (2) need the following accompanying after-spike reset:

$$v(t) \geq v_{peak}\,, \quad \text{then} \begin{cases} v(t) \leftarrow c, \\ u(t) \leftarrow u(t) + d, \end{cases} \quad (4)$$

where v_{peak} is the spike cutoff voltage. The above equation shows how $v(t)$ and $u(t)$ are reset, if the membrane potential spike reaches its peak value.

When it comes to model parameter calculations in the next two subsections, the following equations are used [5]:

$$R_{in}^{-1} = b - k(v_r - v_{th})\,, \quad (5)$$

$$I_\infty(V) = -k(V-v_r)(V-v_{th}) + b(V-v_r)\,, \quad (6)$$

$$I_{rheo} = I_\infty(0.5(k^{-1}b + v_r + v_{th}))\,, \quad (7)$$

where R_{in}^{-1} is the inverse of the input resistance, $I_\infty(V)$ represents the steady state current-voltage relation, and I_{rheo} is the rheobase current defined as the minimum injected current for the neuron to fire. Equation (7) is obtained by noting that the maximum of $I_\infty(V)$ in Equation (6) can approximate the rheobase current [5]. We also have the following relation [5]:

$$\tau = R_{in}C\,, \quad (8)$$

where τ is the membrane time constant.

In the next two subsections, all the model parameters in Equations (1)-(4) are either directly taken from [1], or determined by substituting some of the measured parameters reported in [1] into Equations (5)-(8), or estimated from the measured data presented in [1].

B. Parameter Calculations for a Normal Neuron Using Experimental Data

All the numerical parameters for a normal neuron are presented in the second column of Table 1, obtained as explained at the end of the previous subsection, and specified in the footnotes of Table 1. The particular experimental data and parameters of [1] used here for a normal neuron are labeled as “Wild-type On” in [1].

The parameters *a* and *d* are estimated by minimizing the mean-squared-error (MSE) representing the difference between the number of spikes of the Izhikevich model, i.e., the measured number of APs in [1].

Comparison of the number of spikes of the model and the measured number of spikes for various synaptic input currents, as shown in Figure 1, indicates the suitability of the model and the calculated parameters.

Table 1. Model Parameters for *Normal* and *Abnormal* Neurons

Parameter	*Normal* Neuron	*Abnormal* Neuron
a	0.01 [3]	0.02 [3]
b	-0.205 [2]	-0.34 [2]
c	-57 mV [1]	-55 mV [1]
d	176 [3]	115 [3]
k	0.191 [2]	0.142 [2]
R_{in}	181 MΩ [1]	210 MΩ [1]
τ	25 ms [1]	21 ms [1]
C	138 pF [4]	100 pF [4]
v_r	-70 mV [1]	-70 mV [1]
v_{th}	-40 mV [1]	-34 mV [1]
v_{peak}	68 mV [1]	68 mV [1]
I_{rheo}	40 pA [1]	40 pA [1]

[1] Directly taken from [1]
[2] Calculated using Equations (5)-(7)
[3] Estimated from the measured data presented in [1]
[4] Calculated using Equation (8)

C. Parameter Calculations for an Abnormal Neuron Using Experimental Data

All the numerical parameters for an abnormal neuron are presented in the third column of Table 1. They are either directly taken from [1], or determined by substituting some of the measured parameters reported there into Equations (5)-(8), or estimated from the measured data (see the footnotes of Table 1). The specific experimental data and parameters used here for an abnormal neuron are labeled as "VP16-CREB^{high} On" in [1].

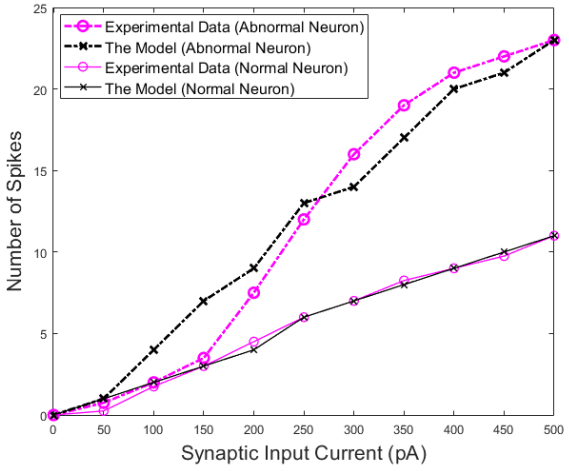

Figure 1. Number of spikes versus the synaptic input current in the *normal* and *abnormal* neurons.

Similarly to the normal neuron, a comparison of the number of spikes of the model and the abnormal neuron measured number of spikes for various synaptic input currents [1] is shown in Figure 1, generated by choosing a and d such that the MSE between the model and the data is minimized. The good fit of the model to the measurements demonstrates that the model and the calculated parameters reasonably represent the experimental data.

III. Neuronal System Analysis in the Presence of an Intraneuronal Molecular Abnormality

A. A Neuronal System

As discussed, and demonstrated previously, intraneuronal abnormalities such as constitutively active CREB can alter the spiking behavior of individual neurons. In this section, we consider a small neuronal system [3] to study how the intraneuronal abnormality of each neuron affects the interactions among neurons in a neuronal system. Here we consider a system of three neurons shown in Figure 2, where the excitatory neurons E1 and E2 drive the excitatory neuron E3. The neurons E1 and E2 receive the two separate stimulus currents A and B, that can have different levels of correlations. We have simulated this system using a neuroscience toolbox [3], as explained below.

Simulations are performed with a 0.1 ms time step. As Figure 2 shows, E1 and E2 receive two current pulses A and B, respectively, with equal durations of 500 ms and equal amplitudes of 500 pA. A pink noise is also simulated to represent membrane noise, with a noise power that is inversely related to the frequency. This noise results in spontaneous firings. The synaptic weight among the neurons is set at 100 pA [3]. Other parameters of the system are taken from Table 1, to simulate a normal or an abnormal system, respectively. The generated spikes by all the neurons and in response to various stimulus currents are shown in Figure 3A and Figure 3B, for normal and abnormal systems, respectively.

The increased number of spikes in Figure 3B for each neuron receiving a current pulse in the abnormal system is noteworthy, compared to Figure 3A that depicts the normal system. This is consistent with what we observe in the experimental results in Figure 1, i.e., a typically increased measured number of spikes for a given input current in an abnormal neuron, when compared to a normal neuron.

B. Analysis of the Redundancy in the Neuronal System

To gain further insight beyond visual differences among neuronal spike signals in normal and abnormal systems, we use an information theoretic parameter called redundancy [3].

Advantages of using information theoretic measures and parameters in neuroscience are already outlined in the Introduction section.

The redundancy quantity $R(X_1, X_2; Y)$ is the mutual information between the pair of input variables (X_1, X_2) and the output variable Y, with an additional minimization over X_1 and X_2 [3]. The redundancy parameter essentially specifies the minimum overlap in the amount of information which is redundantly provided by both X_1 and X_2 about each state of Y individually. In this paper and similarly to [3], X_1 and X_2 in $R(X_1, X_2; Y)$ represent the (ON/OFF) states of the two current stimuli A and B applied to the neurons E1 and E2, respectively, whereas Y represents the action potential spike count of the neuron E3. All these are graphically depicted in Figure 2 and Figure 3.

In Figure 4 we observe the information redundancy in the neuronal system of Figure 2 composed of three normal neurons, where the two neurons E1 and E2 receive the two current stimuli with various degrees of dependency, characterized by the parameter D. This parameter allocates the probabilities of $0.25+D$, $0.25-D$, $0.25-D$ and $0.25+D$, respectively, to the four states of the stimulus pair (A,B): (OFF,OFF), (ON,OFF), (OFF,ON) and (ON,ON) [3]. When $D=-0.25$, the anti-correlated case, the two stimuli take opposite states only. In the $D=0$ uncorrelated case, the two stimuli take all possible states with equal probabilities. Finally, if $D=0.25$, the correlated scenario, the two stimuli take exactly the same states.

As Figure 4a shows, the redundancy is mostly small for the anti-correlated, uncorrelated, and correlated

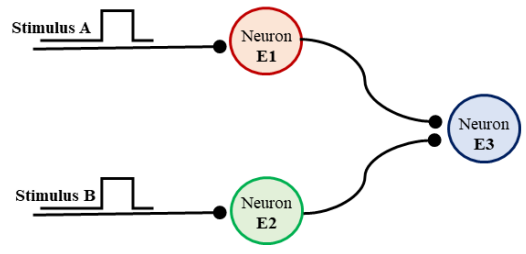

Figure 2. A system of three neurons where the two neurons E1 and E2 receive two stimulus currents A and B, respectively.

A)

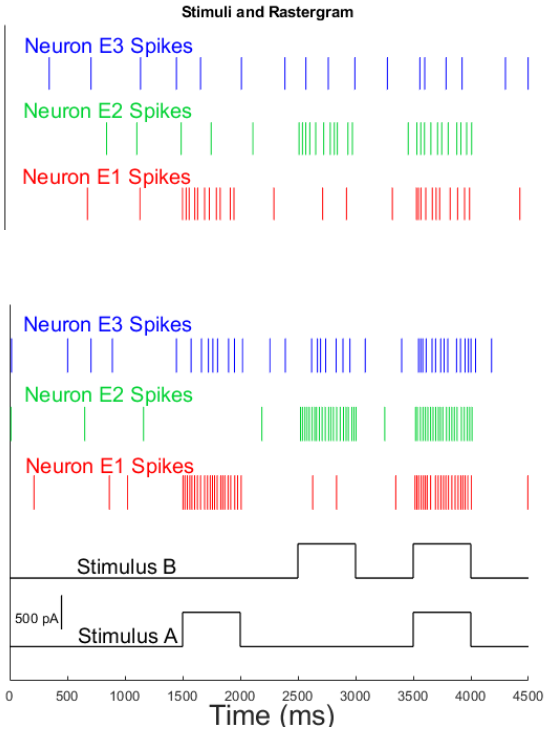

Figure 3. Spike rastergram of the neuronal system of Figure 2, together with the two stimulus currents: **A)** The three neurons are *normal*, **B)** The three neurons are *abnormal*.

stimulation scenarios in the normal neuronal system. This is persistently observed for other values of D, as shown in Figure 4b. The increase of the redundancy with D in Figure 4b is a reasonable trend, because as D increases, the states of the two stimuli are more likely to be the same. This means the overlap between the information individually provided by the two stimuli increases, i.e., more information redundancy in the system, when the two inputs become more correlated.

A comparison of the redundancy results of the abnormal neuronal system in Figure 5 with those of the normal system in Figure 4 reveals a noticeable increase in redundancy, especially for $D>0$. In other words, the amount of redundant information in the abnormal system is evidently increased. This is an interesting finding and encourages further research to understand the biological implications of the increased redundancy in an abnormal neuronal system where the neurons exhibit a memory-related intraneuronal molecular abnormality, i.e., a constitutively active form of the important transcription factor CREB.

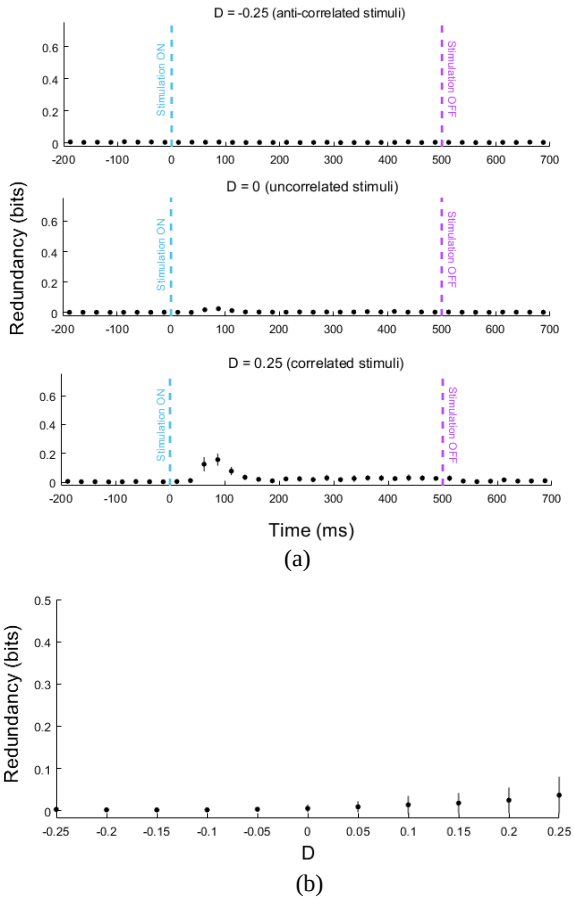

Figure 4. Information redundancy in the neuronal system of Figure 2 composed of three *normal* neurons, for different levels of correlation between the two stimuli: (a) Redundancy versus time, (b) Redundancy versus the correlation parameter *D*.

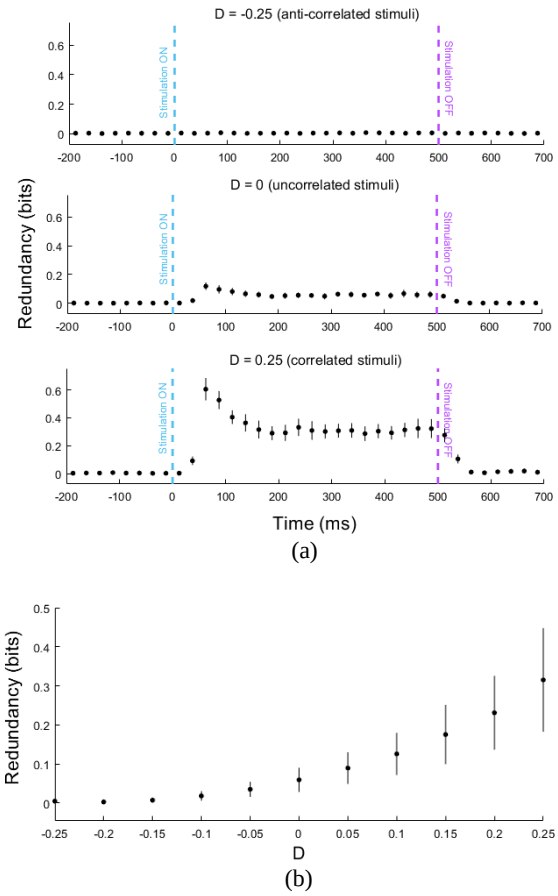

Figure 5. Information redundancy in the neuronal system of Figure 2 composed of three *abnormal* neurons, for different levels of correlation between the two stimuli: (a) Redundancy versus time, (b) Redundancy versus the correlation parameter *D*.

IV. Conclusion

Given the importance of the CREB protein in learning and memory, in this paper we have modeled and analyzed the effect of CREB deficiencies in a neural system. More specifically, first we have fitted a neuron model to some experimental data, by estimating the model parameters from the data. We have observed that the model accurately fits the data, for both normal and abnormal CREB scenarios. Then we have considered a system of few neurons where each neuron is characterized using the above model whose parameters are estimated from measured data. Consistent with the measured data, our simulations show an increased number of spikes for each neuron receiving a current pulse in the abnormal system.

Finally, we have computed the redundancy parameter in both normal and abnormal neuronal systems, for different correlation levels between the stimulus input currents. Our results indicate that the amount of redundant information in the abnormal system is increased, compared to the normal system. Therefore, one may conclude that perhaps the amount of information redundancy in a neuronal system can be used as a measure to model the departure of the system from its normal behavior, in the presence of an abnormality.

Further research using other datasets and other neuronal systems is needed to better understand the utility of the information redundancy concept in modeling the role of CREB or other important proteins and transcription factors that are involved in learning and memory.

The considered neuronal system in this paper is composed of three neurons. The small size of this system has allowed us to interpret the findings. One way of expanding this study is to apply it to other neuronal systems that have various combinations of excitatory and inhibitory neurons, similarly to those considered in [3].

The lessons learned from such analyses will pave the way for extending the work to much larger neuronal systems.

REFERENCES

[1] M. Lopez de Armentia, D. Jancic, R. Olivares, J. M. Alarcon, E. R. Kandel, and A. Barco, "cAMP response element-binding protein-mediated gene expression increases the intrinsic excitability of CA1 pyramidal neurons," *Journal of Neuroscience*, vol. 27, no. 50, pp. 13909-13918, 2007.

[2] A. Abdi, M. B. Tahoori and E. S. Emamian, "Fault diagnosis engineering of digital circuits can identify vulnerable molecules in complex cellular pathways," *Science Signaling*, vol. 1, no. 42, pp. 48-61, 2008.

[3] N. Timme and C. Lapish, "A tutorial for information theory in neuroscience," eNeuro, vol. 5, no. 3, e0052-18, 2018 (https://github.com/nmtimme/Neuroscience-Information-Theory-Toolbox).

[4] E. M. Izhikevich, "Simple model of spiking neurons," *IEEE Transactions on Neural Networks*, vol. 14, no. 6, pp. 1569-1572, 2003.

[5] E. M. Izhikevich, *Dynamical Systems in Neuroscience*. MIT Press, 2007.

[6] C. Börgers, *An Introduction to Modeling Neuronal Dynamics*. Berlin: Springer, 2017.