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

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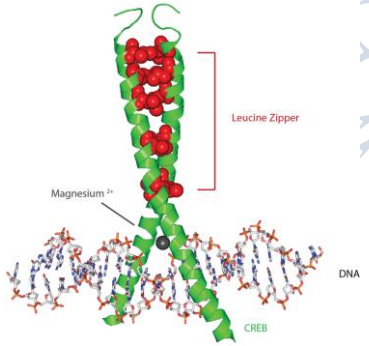
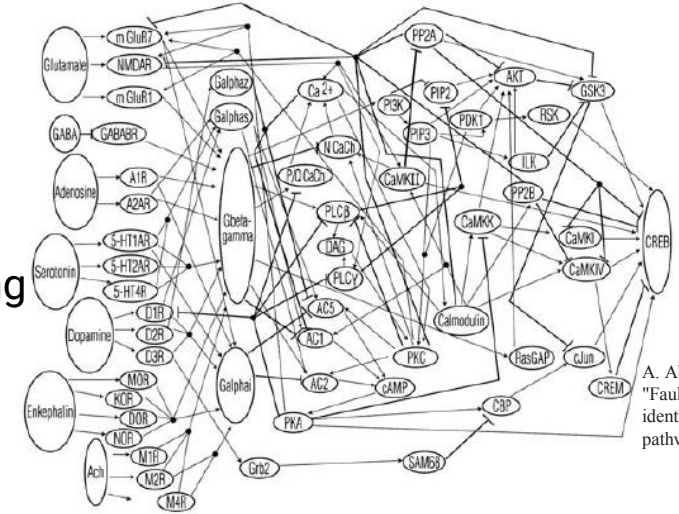
Introduction

- CREB, a cAMP response element-binding protein (with cAMP denoting the cyclic adenosine monophosphate), is highly involved in learning and memory.
- CREB protein is highly involved in neuronal mechanisms underlying memory and learning in mammalian brain.
- CREB is a molecule whose activity is regulated by a molecular network.
- For our recent study on CREB signaling network & neuronal spiking, see:



CREB. (2022, October 5). In *Wikipedia*. https://en.wikipedia.org/wiki/CREB



A. Abdi, M. Baradaran Tahoori, and E. S. Emamian. "Fault diagnosis engineering of digital circuits can identify vulnerable molecules in complex cellular pathways." *Science Signaling* 1.42, ra10-ra10, 2008.

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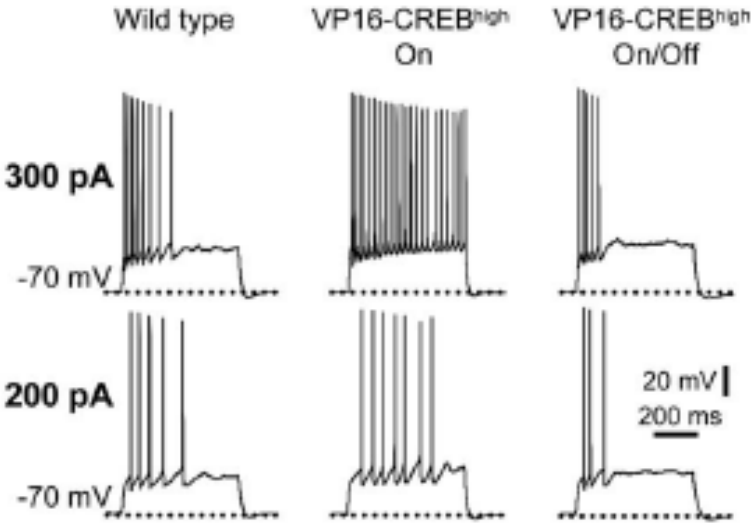
Introduction (cont.)

Here, we use some 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 experimental data include both normal and abnormal CREB scenarios and the associated action potential signals, to estimate the parameters of the neuron model for both CREB scenarios.



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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, p. 13909–13918, 2007.

Introduction (cont.)

- The use of information theoretic parameters and methods in neuroscience is advantageous for multiple reasons:
- 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.

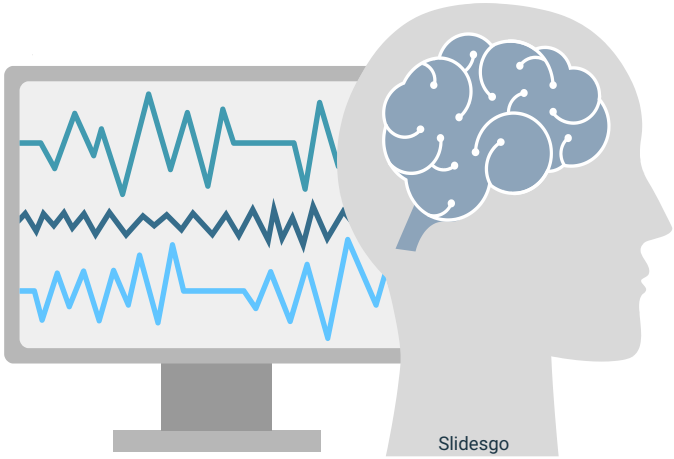
The Izhikevich Neuron Model

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

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

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

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



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The Izhikevich Neuron Model Parameters

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

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

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

$$\tau = R_{in}C$$

Slidesgo

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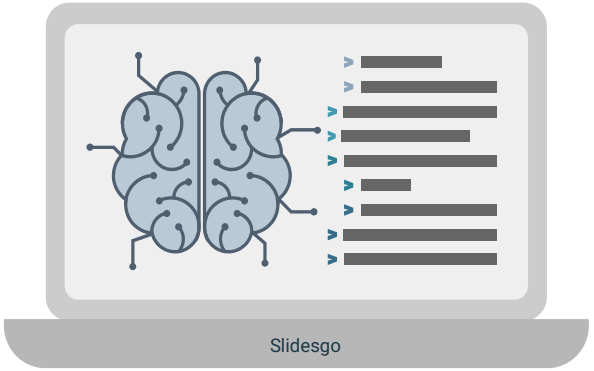
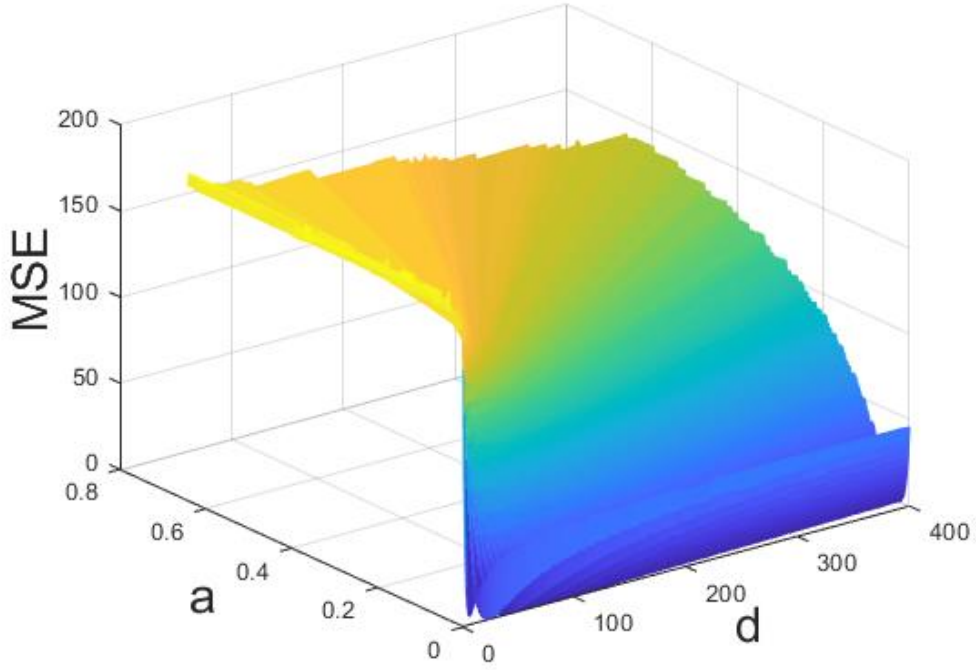
Parameter Calculations Using Experimental Data

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)



Estimation of the (a, d) Parameters for the Normal Neuron Using Numerical MMSE (Minimum Mean Squared Error)



Minimum MSE = 0.0625

(a, d) = (0.01, 176)

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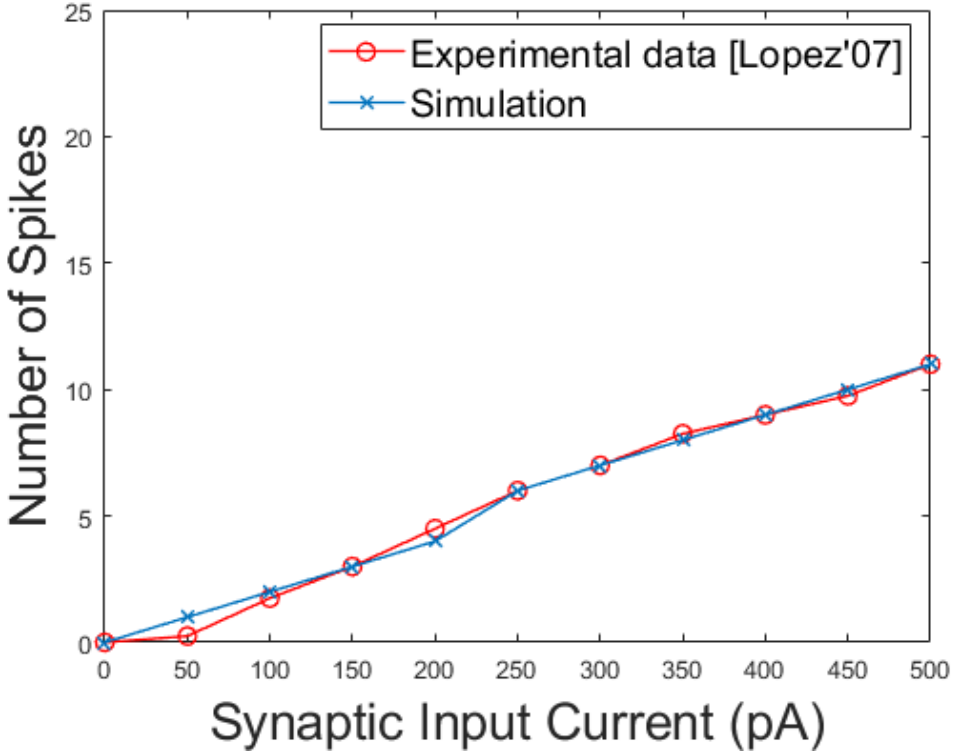
Number of Spikes vs. Synaptic Input Current in the Normal Neuron



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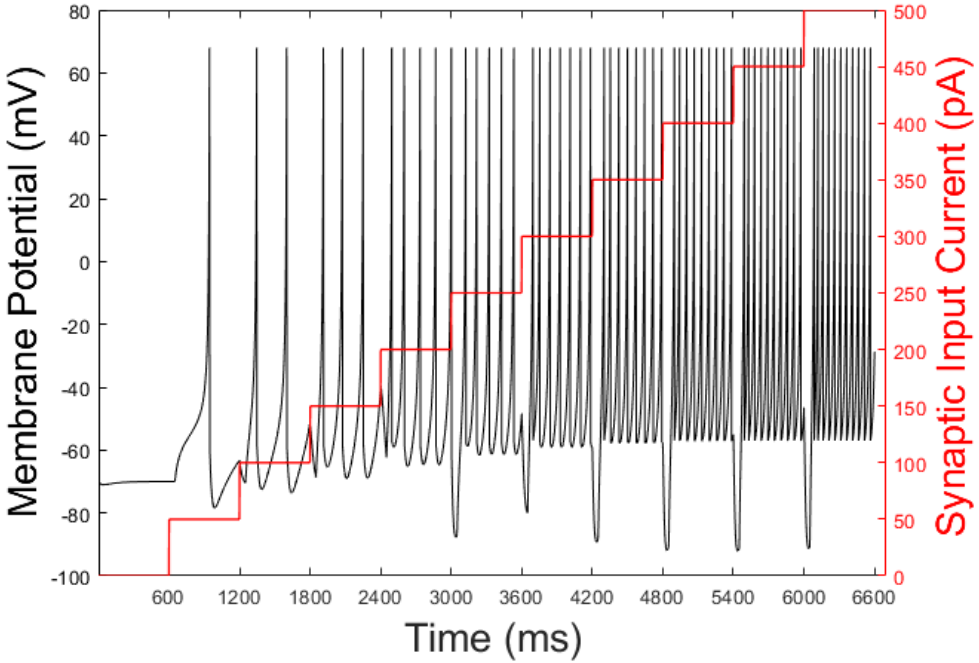
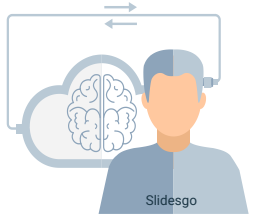
Membrane Potential of the Normal Neuron for Different Synaptic Input Currents vs. Time





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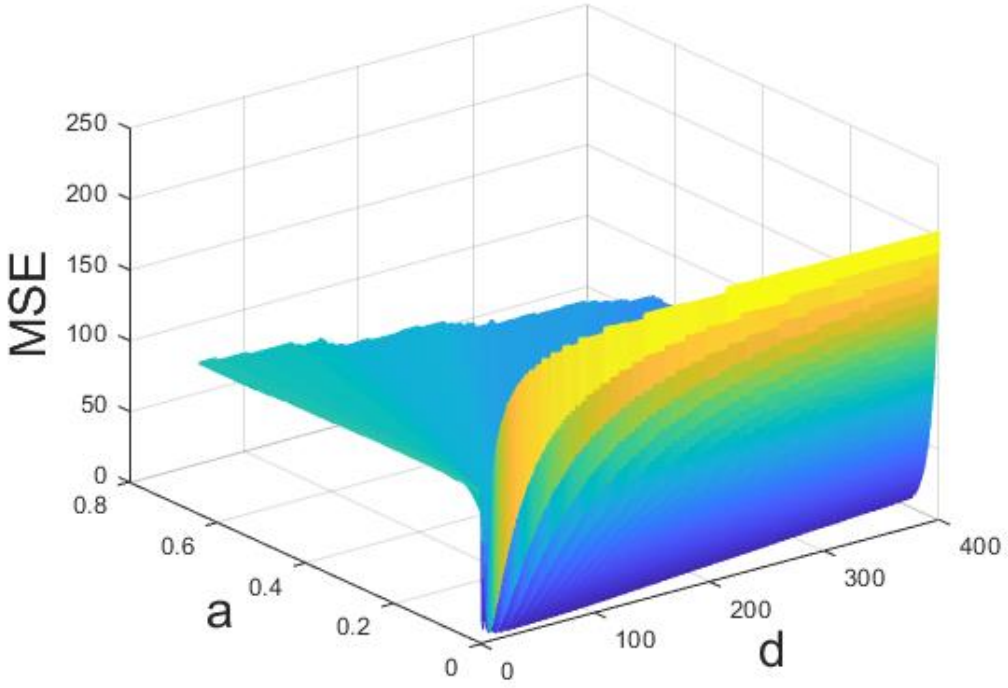
Estimation of the (a, d) Parameters for the Abnormal Neuron Using Numerical MMSE (Minimum Mean Squared Error)



Minimum MSE = 2.6

(a, d) = (0.02, 115)

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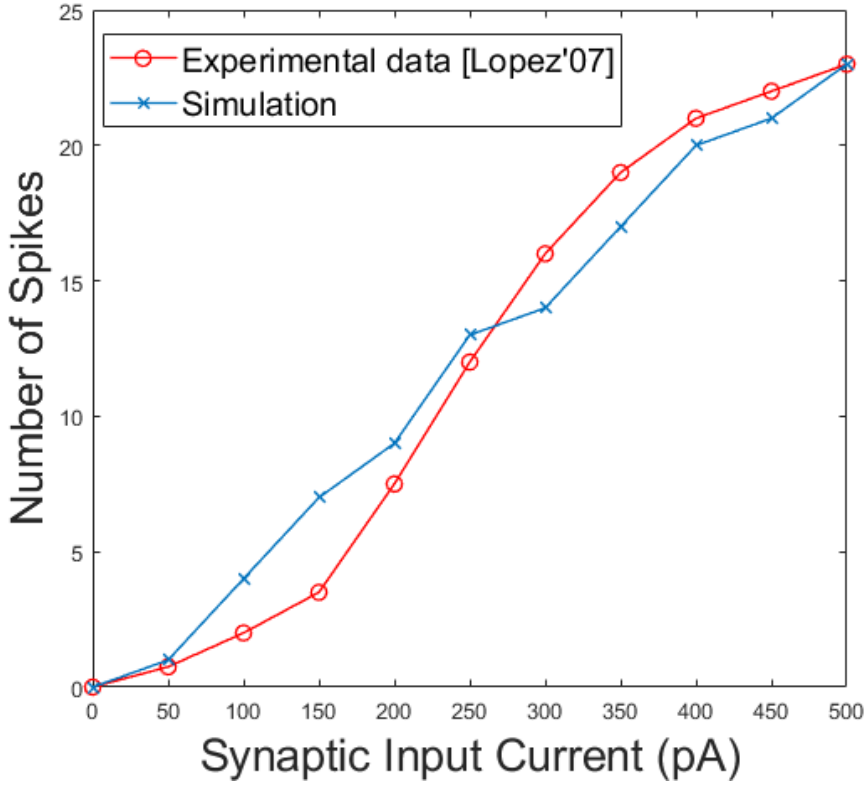
Number of Spikes vs. Synaptic Input Current in the Abnormal Neuron



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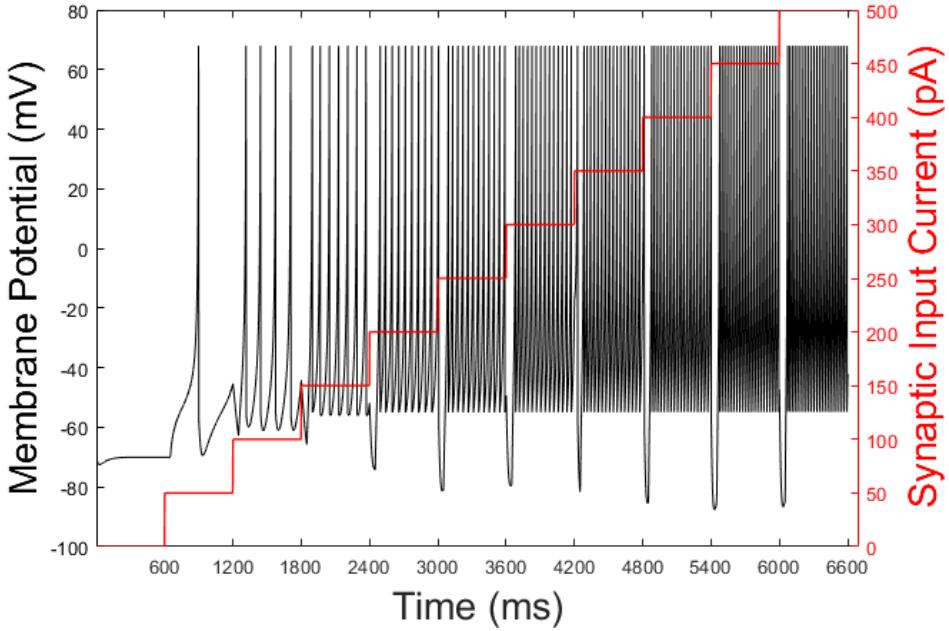
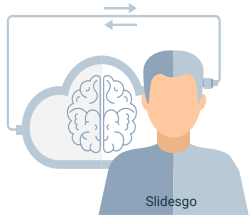
Membrane Potential of the Abnormal Neuron for Different Synaptic Input Currents vs. Time





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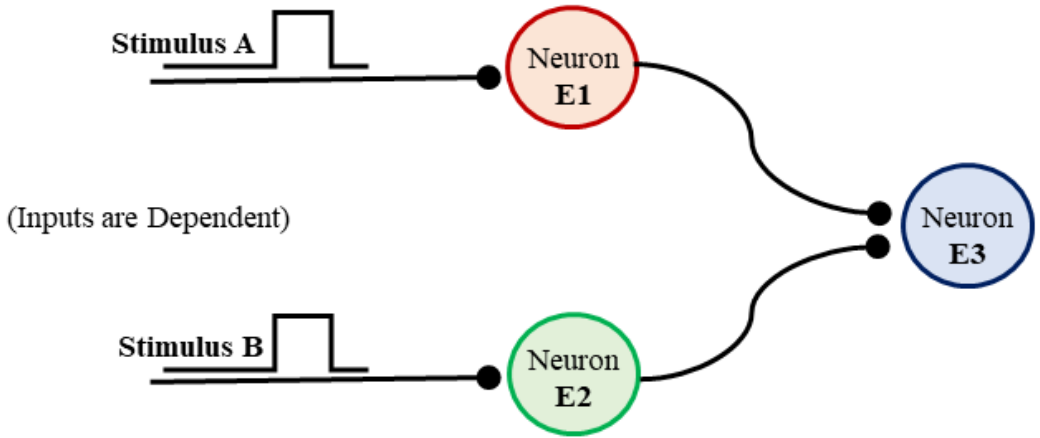
Our Neuronal System



Stimulus A	Stimulus B	Likelihood
ON	ON	0.25+D
ON	OFF	0.25-D
OFF	ON	0.25-D
OFF	OFF	0.25+D

D = -0.25 : Anti-Correlated
D = 0 : Uncorrelated
D = 0.25 : Correlated

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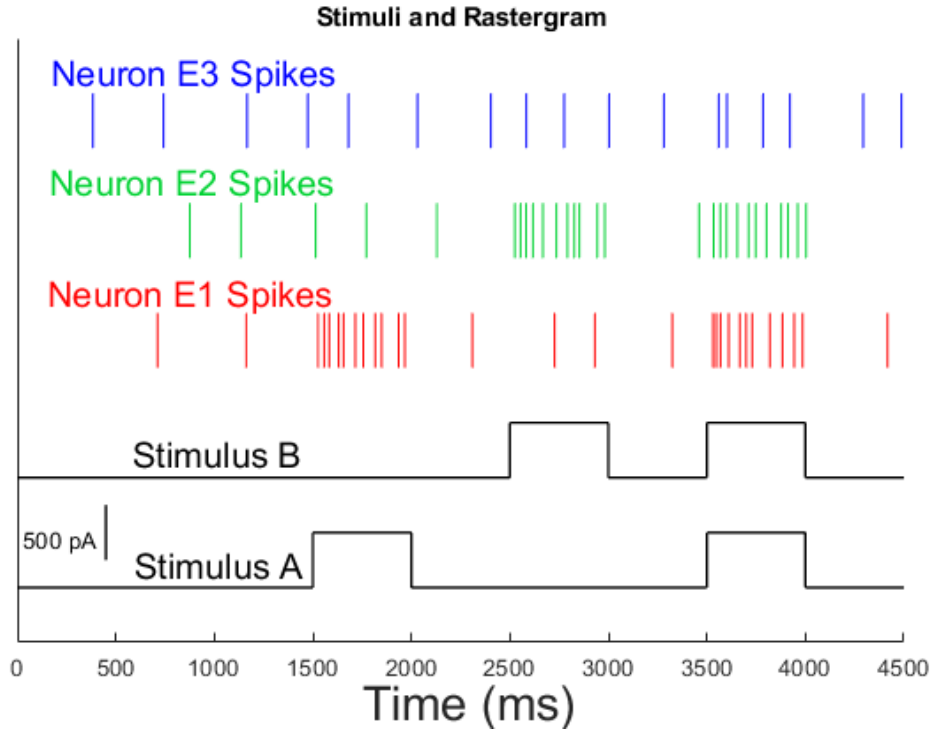
Spike Rastergram of the Neuronal System in the Normal Neuron



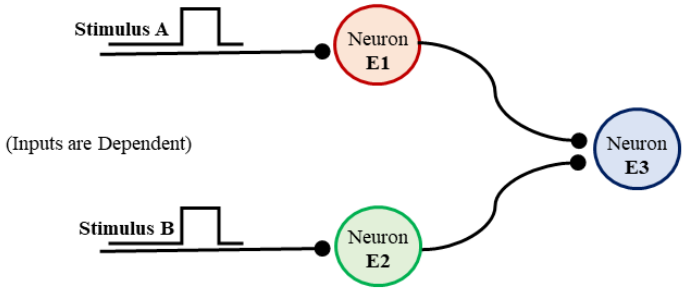
Simulated using the neuroscience toolbox of [3]

The Information Theoretic Parameter Redundancy *R*

- We use an information theoretic parameter called redundancy, to model and study how the behavior of a neuronal system can change due to a deficiency in CREB activity.

- The redundancy parameter $R(X_1,X_2;Y)$ essentially specifies the minimum overlap in the amount of information which is redundantly provided by both X_1 and X_2 variables about each state of the Y variable, individually.

- In simple terms, this redundancy parameter measures - for the output neuron - the amount of spike count information overlap that exists between the states of the stimulus currents injected to the input neurons.



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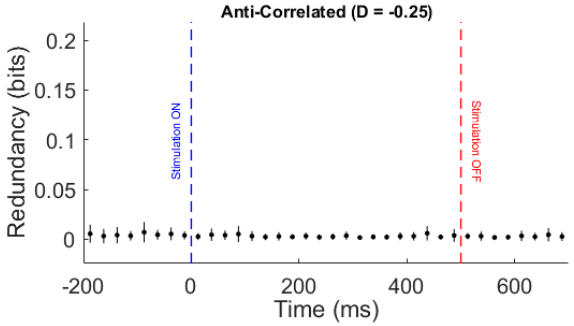
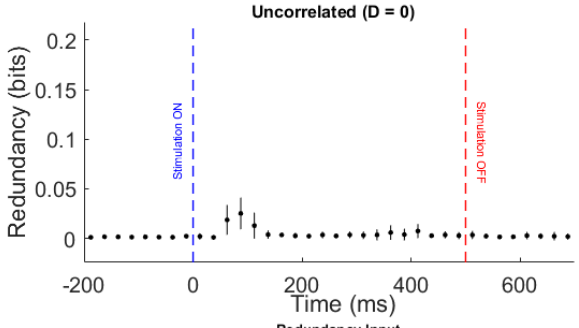
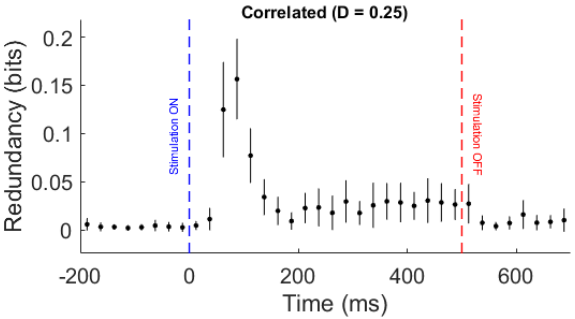
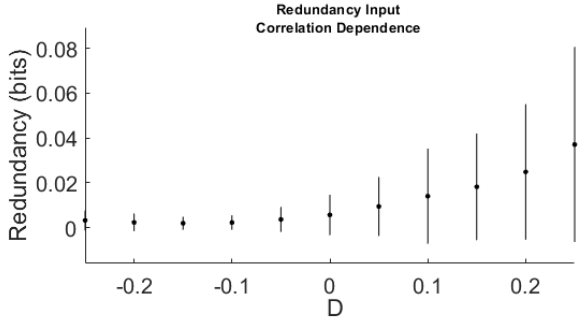
Redundancy for Different Correlation Values of Inputs in the Normal Neuron









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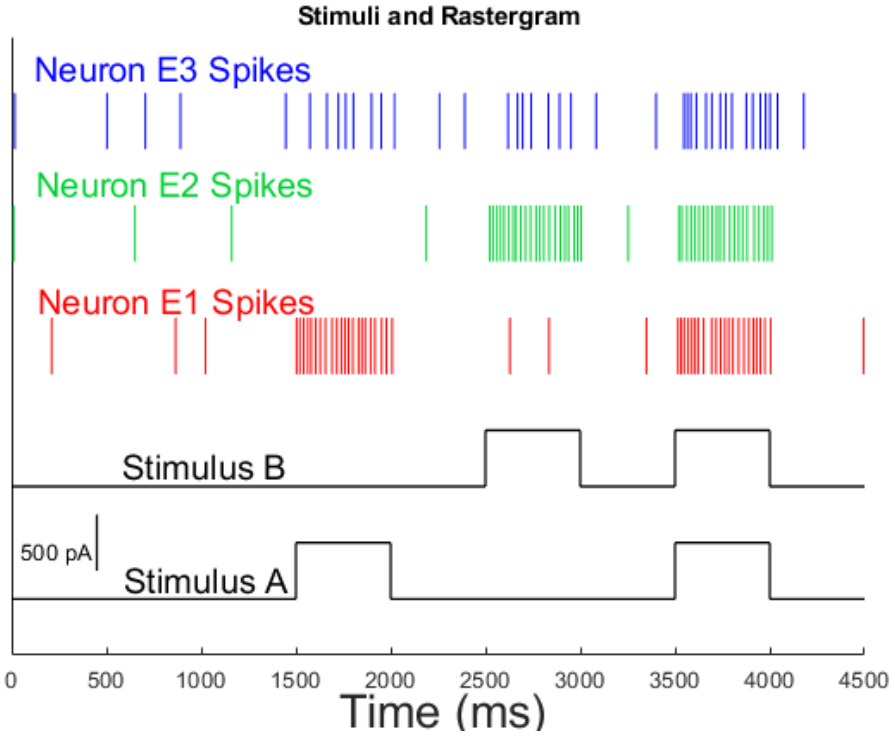
Spike Rastergram of the Neuronal System in the Abnormal Neuron



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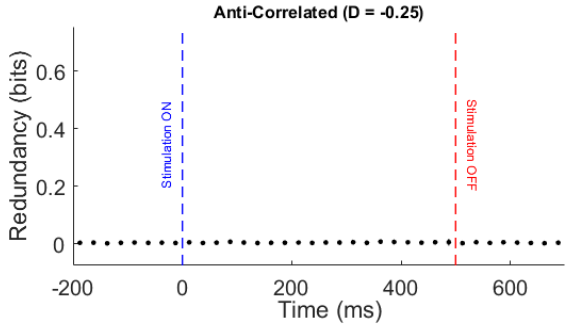

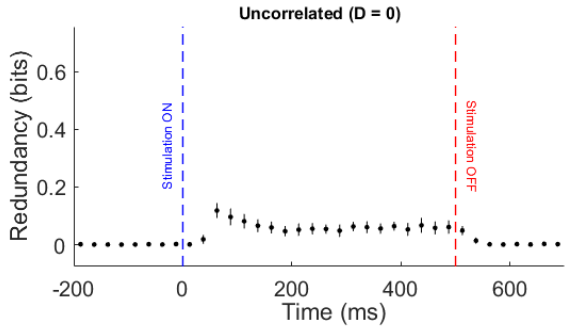

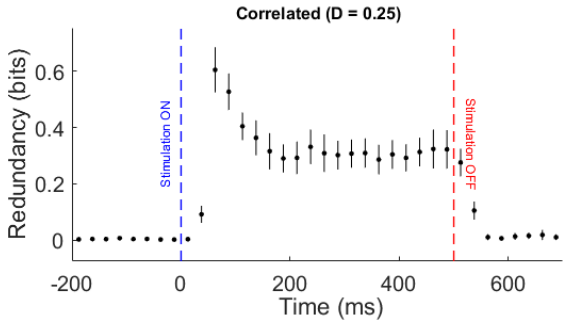

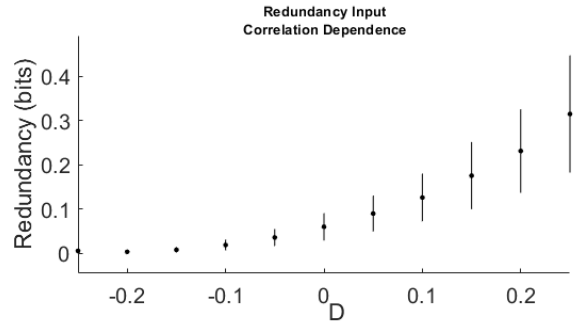

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Conclusion

- We have observed that the developed model accurately fits the data, for both normal and abnormal CREB scenarios.
- Consistent with the measured data, our simulations show an increased number of spikes for each neuron receiving a current pulse in the abnormal system.
- Our results indicate that the amount of redundant information in the abnormal system is increased, compared to the normal system.
- Therefore, 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.
- The lessons learned from such analyses can pave the way for extending the work to much larger neuronal systems.

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Thank You for Your Attention!

Any Questions?