

Computational Characteristic of Parvalbumin- and Cholecystokinin-containing Basket Cells, Regulated by Transcription Factor NPAS4

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Abstract

In neuro-circuits, the flow of information is regulated by a diverse population of inhibitory neurons. Previous studies(Bloodgood (2013), Lin (2008)) have shown that NPAS4, the activity-dependent transcription factor, regulates the number of inhibitory synapse and functions in the cell.

When information is travelling through the hippocampus, two kinds of perisomatic inhibitory interneurons, PV(Parvalbumin) basket cell and CCK(Cholecystokinin) basket cell, are recruited to transfer inhibition signals to the pyramidal cell(Freund (2012)). Previous experiments(Bartos (2012)) have shown that the output signaling properties of those two kinds of cells are different. While the output signal of PV basket cells is fast recruited, uniformed and with high frequency, that of CCK basket cells is slowly recruited, asynchronous, fluctuating and with less timed inhibitory output.

Our study focuses on modeling the whole mechanism of how NPAS4 affects the information flow in the hippocampus. Specifically, the genetic circuit approach is applied to model the recruitment of PV/CCK basket cells regulated by NPAS4. Meanwhile, the signal that is transferred inside the pyramidal cell(action potential spikes) is modeled by using the neural circuits.

As the result, we created a model which is able to recreate the spiking pattern of both basket cell by taking account of the interneural inhibition/excitation, as well as the regulation of NPAS4.

Keywords: Neuro-circuits, Inhibition Dynamics, Hippocampus, Computation, Parvalbumin-containing basket cells, Cholecystokinin-containing basket cells, NPAS4, Genetic-circuits

1 Introduction

The hippocampus(Figure 1.), an extension of the cerebral cortex and part of the limbic system in the brain, is known to play a major role in several key functions. These include spatial learning and awareness, navigation, episodic/event memory, and associational recollection. Damage to the hippocampus, such as that due to Alzheimer’s disease, results in memory loss and disorientation. The hippocampus is composed of three primary fields: the dentate gyrus, and the CA3 and CA1 pyrimadal cell fields. The flow of information is primarily unidirectional, as shown in Figure 2, with the entorhinal cortex as the interface between the hippocampus and the rest of the cerebral cortex.

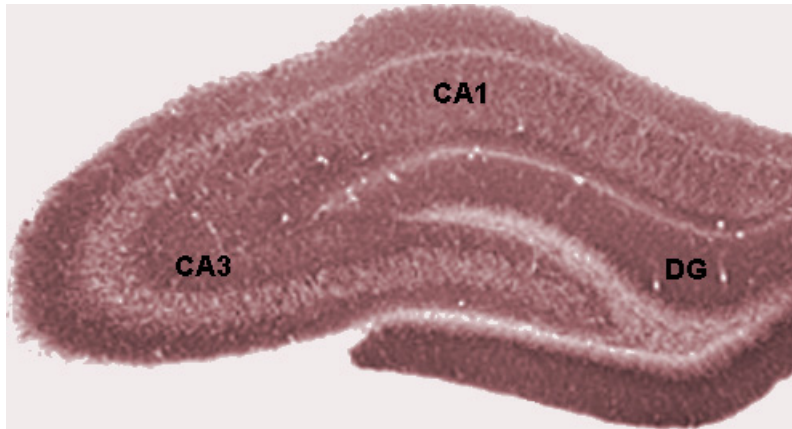


Figure 1: Different Regions in Hippocampus.

Within the CA1 region, the pyramidal cell field receives input from basket cells containing parvalbumin (PV) and cholecystokinin (CCK) (Figure 3.), and these cells are recruited by excitatory synaptic inputs from the pyramidal cells(Freund (2012)). Although PV and CCK basket cells are morphologically similar(Bartos (2012)), their synaptic regulation and effect on pyramidal cells is different. PV and CCK cells receive GABA-ergic inhibition, but CCK cells have double the GABA inhibition compared to PV cells. Additionally, both basket cells receive glutamatergic feed-forward excitation, but the CCK cells have one-third the amount of Glu excitation compared to PV cells. These and other minor differences result in different firing patterns between the two basket cell types. PV cells generate high-frequency trains of action potentials, discharge single action potentials phase-locked to fast network oscillations, and provide fast, stable and timed inhibitory output onto their target cells. In contrast, CCK cells discharge at moderate frequencies

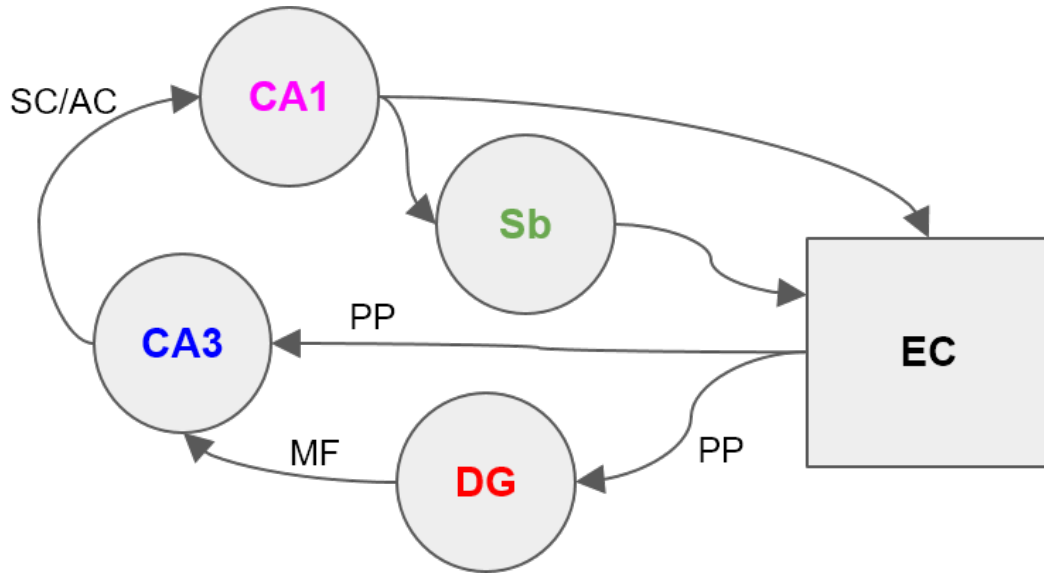


Figure 2: The hippocampal Network: The hippocampus forms a principally uni-directional network, with input from the entorhinal cortex (EC) that forms connections with the dentate gyrus (DG) and CA3 pyramidal neurons via the perforant path (PP). CA3 neurons also receive input from the DG via the mossy fibres (MF). They send axons to CA1 pyramidal cells via the Schaffer collateral pathway (SC), as well as to CA1 cells in the contralateral hippocampus via the associational commissural (AC) Pathway. CA1 neurons send axons to the subiculum (Sb) and the main hippocampal output back to the EC, forming a loop.

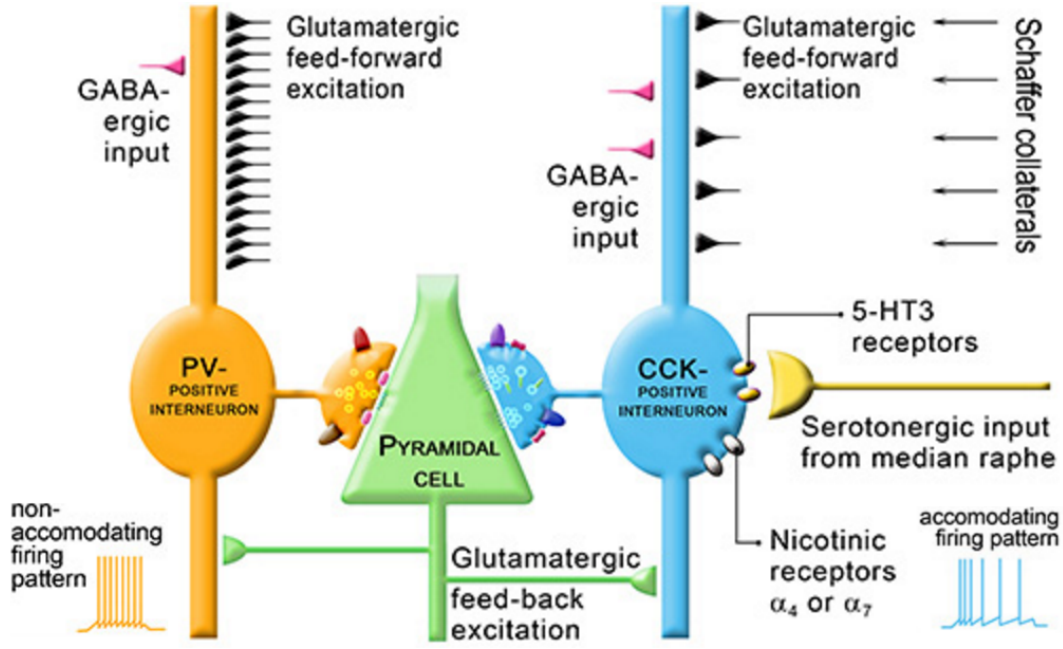


Figure 3: Two kind of basket cells(PV, CCK), with the piramidal cell in the CA1 region of Hippocampus.

with single action potentials weakly coupled to the phases of fast network oscillations and generate an asynchronous, fluctuating and less timed inhibitory output.

The dynamics of the pyramidal neurons, the PV and CCK basket cells, and other neuronal synaptic activity in the hippocampus are complex and regulated by various transcription factors. One of those transcription factors is NPAS4, which affects the excitatory and inhibitory balance in neural networks such as the hippocampus. The NPAS4 will be expressed when the neuron is stimulated by *KCl*(spikes generated)(Lin (2008)). When NPAS4 is expressed in excitatory neurons, it increases the number of binding inhibitory synapses. Similary, when NPAS4 is expressed in inhibitory neurons, it increases the effect of the binding excitatory synapses (Figure 4.)(Spiegel (2014)). The role of NPAS4 in the CA1 cell field of the hippocampus is a negative feedback loop: hippocampal neuronal activity induces the NPAS4 expression, while expression and activity of NPAS4 inhibits the neuronal activity. This interaction will be explored in the network models of this study.

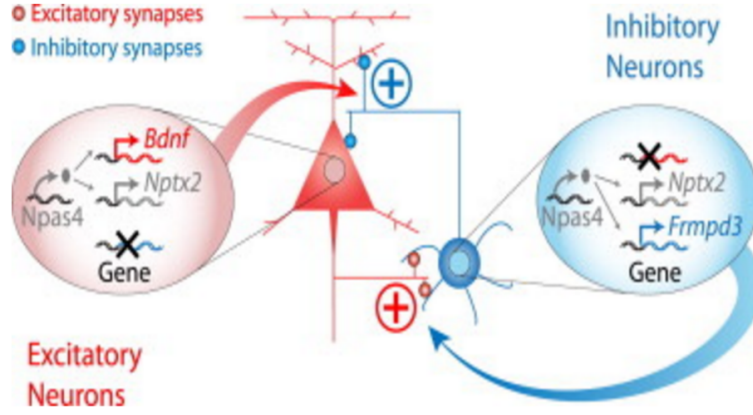


Figure 4: The function of transcriptional factor NPAS4

2 Methods

2.1 Manipulation of neuronal spiking patterns and interactions

2.1.1 Spiking pattern model

A model (Izhikevich (2003)) which could manipulate the spiking pattern is adopted. The formula are:

$$\begin{cases} \frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I \\ \frac{du}{dt} = a(bv - u) \end{cases}$$

if $v == 30mV$, then $v \leftarrow c, u \leftarrow u + d$ (update rule)

Where v is the membrane current and u is the recovery variable. Comparing to the classical Hodgkin-Huxley model(Hodgkin (1952)), the model is reduced into a dynamic system with two differential equations, one update rule and 5 parameters. Where the parameters are:

a :The time scale of the recovery variable u . Smaller values result in slower recovery, and so, lower spiking frequency;

b :The sensitivity of the recovery variable u to the subthreshold fluctuations of the membrane potential v . Changing the b value would mainly manipulate the shape of the spiking pattern as well as the threshold of generating spikes.

c : After spike reset potential.

d : Describes after-spike reset of the recovery variable u caused by slow high-threshold potassium

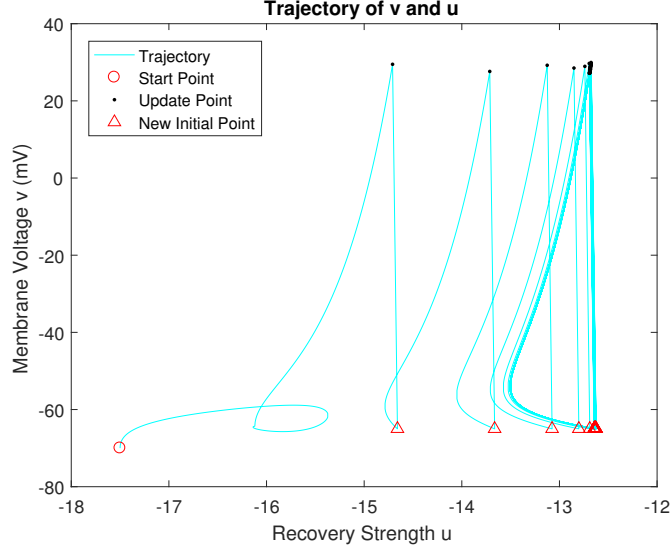


Figure 5: Trajectory of v vs. u when spikes are generated. Where $a_{pv} = 0.1, b_{pv} = 0.25, c_{pv} = -65, d_{pv} = 0.05$. With this group of parameter, the system would be unstable but reset to a resting point when the membrane voltage v reaches a certain value ($30mV$ is the plot), the reset procedure is showing as the straight trajectories from black dots to red triangles. In the end, the whole system is able to oscillate, which is shown as circles in the plot.

and sodium ion conductance, the lower the value is the faster the recovering will be;
 I : External current.

It is obvious that, by this model, the two differential equations are creating instability (which cause the membrane voltage leaving the resting potential), while the update rule would keep the system stable. In this case, the typical Hopf bifurcation in Hodgkin-Huxley model is actually shown as the bifurcation of unstable (Figure 5.) / stable (Figure 6.) with an update rule.

By adopting this model, we could create different spiking frequency for the two kinds of basket cells (Figure 7). While since CCK is having a irregularly slow spiking frequency, while the single neuron model is only able to generate regular pattern. The irregularity would be caused by the external surrounding, which would be introduced in the next section.

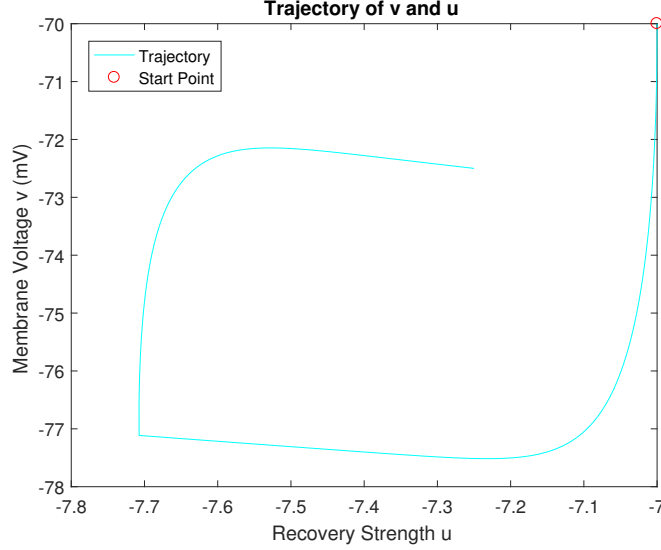


Figure 6: Trajectory of v vs. u when spikes are not generated. Where $a_{pv} = 0.1, b_{pv} = 0.1, c_{pv} = -65, d_{pv} = 0.05$, here the trajectory will reach a stable point($u = 7.3, v = -72mV$).

2.1.2 Synaptic current and interaction between neurons

According to the theory of synaptic inhibition(Koch (1999), Destexhe (1994)), when a spike is generated in the pre-synaptic neuron, an excitatory/inhibitory post synaptic current would be generated forward the post-synaptic neuron according to the synapse is excitatory or inhibitory. While the excitatory/inhibitory post synaptic current(EPSC/IPSC) is generated according to the conductance.

While according to the shape of the post synaptic current, we could simplify the model by linearizing it: from the time that spike is generated in the pre-synaptic neuron the EPSC will be a linear rise from 0 to $I_{syn,max}$ (fall from 0 to $-I_{syn,max}$ for IPSC) in a fixed time noted as t_{dock} , while after the absolute value of EPSC/IPSC reaches the maximum, it will start to fall to 0 in another fixed time period noted as t_{undock} .

By using this simplified format of the EPSC/IPSC, we are able to simulate the neuron interactions(Figure 9 and 10.).

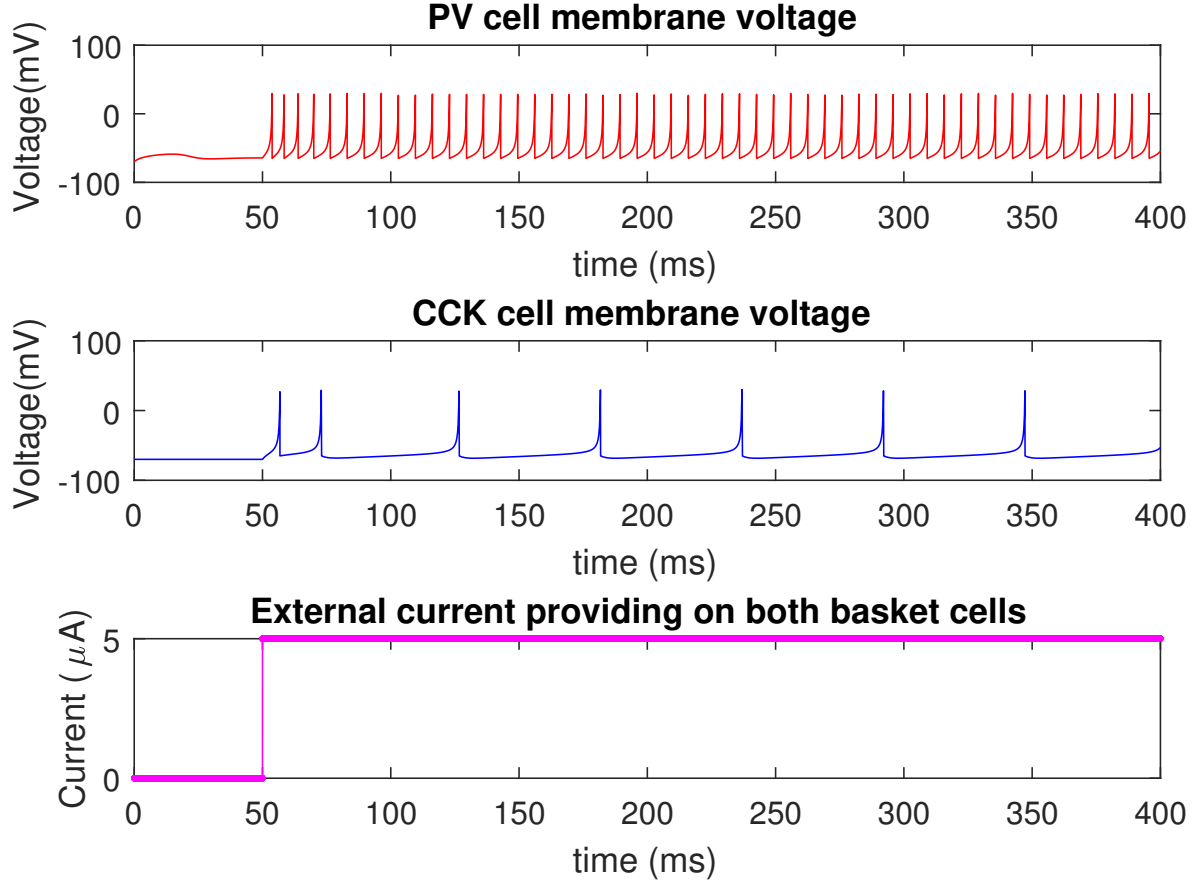


Figure 7: Simulation of PV/CCK basket cells' spiking patterns. Parameters for both basket cells: $a_{pv} = 0.1, b_{pv} = 0.25, c_{pv} = -65, d_{pv} = 0.05; a_{cck} = 0.02, b_{cck} = 0.2, c_{cck} = -65, d_{cck} = 2$; The external current on two basket cells are both $I_{ext} = 5\mu A$ after $50ms$.

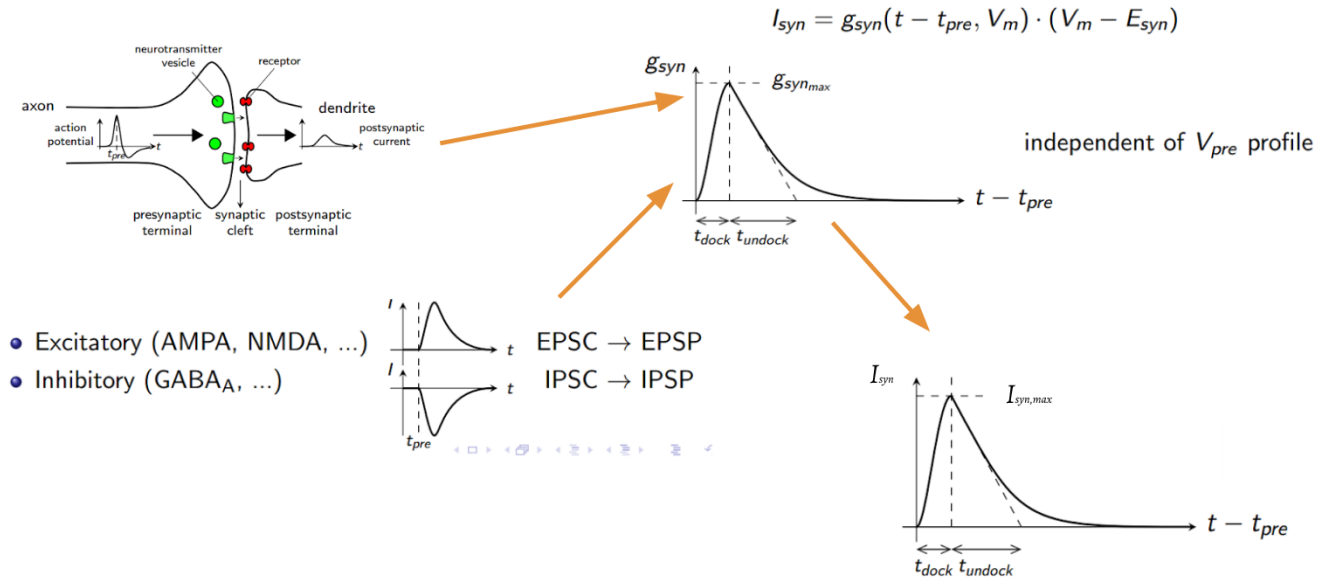


Figure 8: Simplification of modeling the synaptic effect

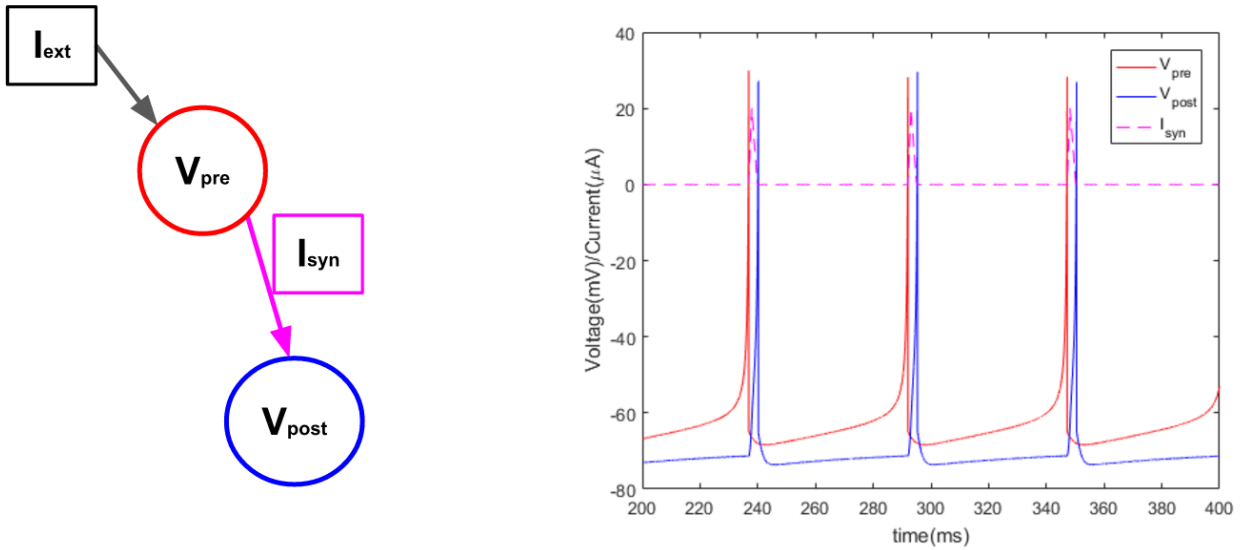


Figure 9: Excitatory effect from the pre-synaptic neuron(V_{pre}) to the post-synaptic neuron(V_{post}). In this scenario, only the pre-synaptic neuron receives the external current which is able to generate spikes(red solid line). With the excitatory synapse channel generating excitatory post synaptic current(magenta dash line), and stimulate the post-synaptic neuron(blue solid line).

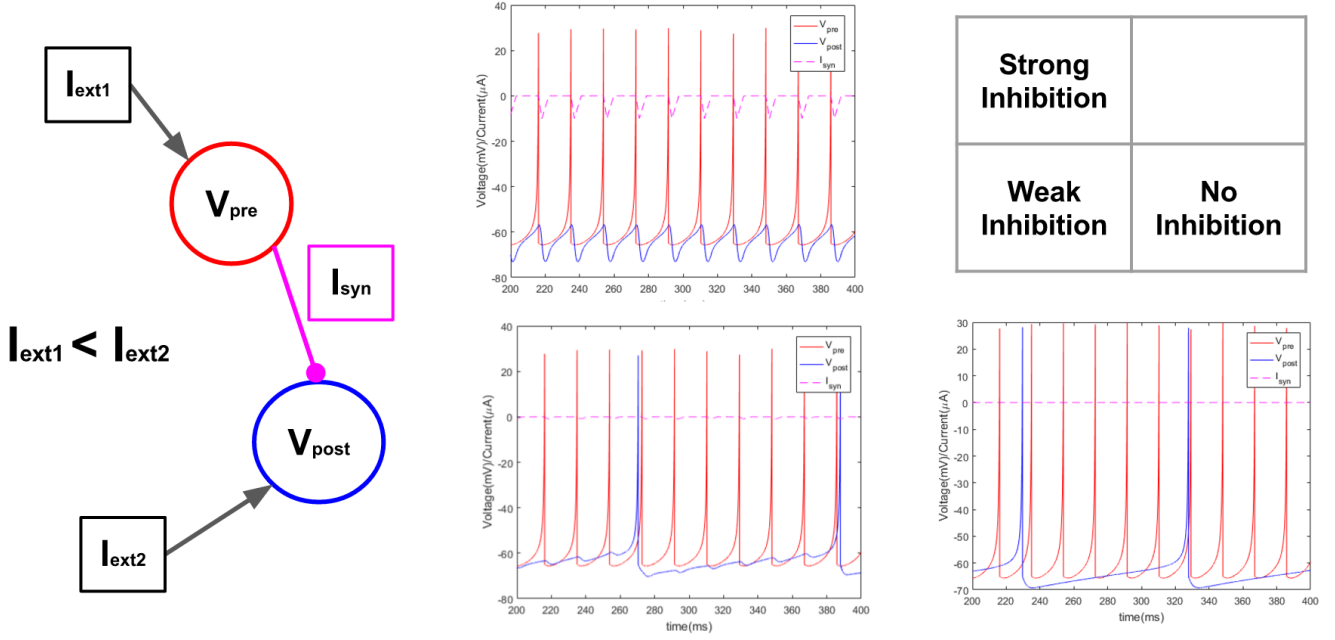


Figure 10: Inhibitory effect from the pre-synaptic neuron(V_{pre}) to the post-synaptic neuron(V_{post}). The external current providing on pre-synaptic neuron is larger than on post-synaptic current, while by varying the value of $I_{syn,max}$ would cause different strength of inhibition.

2.2 External Current provided on both basket cells.

2.2.1 Random Coupling neuronal network

The principle model is graphically presented as the brown circled part in Figure 11. In this model, we have an excitatory/inhibitory coupled network together with excitatory/inhibitory synapses for synaptic currents and NPAS4 expression for upper regulation. After a random external current is introduced, both excitatory and inhibitory neurons fire to affect the corresponding synapses. Under the regulation of NPAS4 expression, these synapses provide synaptic currents to the post-synaptic PV and CCK cells. On the other way around, the magnitude of the synaptic currents conversely affects the firing patterns of the excitatory/inhibitory neurons. The later further regulates the expression of NPAS4 transcription factor.

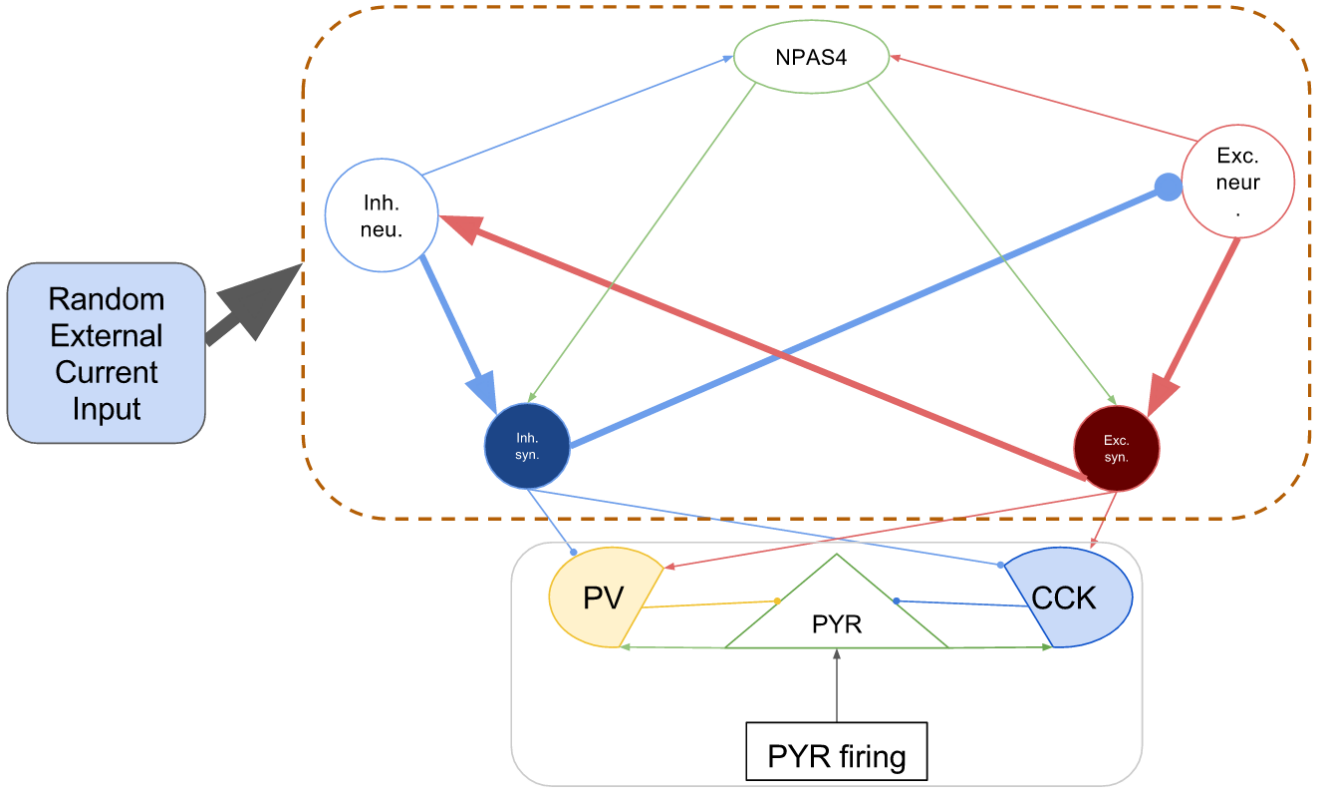


Figure 11: The random external current input provided by external neurons of the basket cells.

First, to construct an excitatory/inhibitory network, the random coupling model is applied. Random coupling describes the parallel interactions between the neurons to affect the general synaptic current (I_{sync}) provided to the post-synaptic cell. Here, we use a randomly generated matrix called Matrix of Synaptic Connection Strength (MSCS) to realize this random coupling. MSCS is a matrix of pairwise coupling between all the neurons in the network with columns as the neurons that exert the coupling influence and with rows as the neurons that receive the influence. If a neuron is excitatory, it will have positive connection strength on the other neurons ranging from 0 to 1. If a neuron is inhibitory, then it will have negative connection strength on the other neurons ranging from -1 to 0. A neuron will have a strength of 0 on its own. The connection strength of inhibitory neuron is usually larger than that of excitatory neuron on average (Izhikevich (2003)). For more clearance, Table ? provides a toy example of a 3-by-3 MSCS. This matrix represents a network formed by 2 excitatory neurons and 1 inhibitory neuron and is constructed in accordance to all the criterion mentioned above. With MSCS constructed, it can be applied into an existing algorithm (ref) to generate the resulting I_{syn} .

Table 1: Example of a 3-by-3 randomly couple neuron network

Post/Pre	N1(Excitatory)	N2(Excitatory)	N3 (Inhibitory)
N1(Excitatory)	0	0.4282	-0.6624
N2(Excitatory)	0.3354	0	-0.7662
N3 (Inhibitory)	0.2946	0.3614	0

To evaluate the effect of a random coupling neural network, two systems each with 900 excitatory neurons and 100 inhibitory neurons are constructed. With one system served as a control, the MSCS is applied to the other one. Figure ? shows the resulting firing neurons and I_{syn} generated from the two systems. The dotted map describes which neuron fires along time. The plots on the left are from the uncoupled neural network. We can see the neurons fire randomly and the resulting I_{syn} vibrates without any patterns. The plots on the right are from the randomly coupled neural network. When the neurons are randomly coupled, the resulting I_{syn} spikes periodically, showing the effect of random coupling.

We also investigate different neural networks by varying the numbers of coupled excitatory and inhibitory neurons. The results are presented in Figure 13. Figure 13 shows that as the ratio of the amount of excitatory neurons to inhibitory neurons decreases, the firing patterns become more randomized and the resulting I_{syn} becomes more asynchronous. As a result, different combinations of excitatory and inhibitory neurons can produce different I_{syn} s. We are able to use this property to model different types of cells like PV and CCK and to get cell-specific I_{syn} .

2.2.2 Adding NPAS4 Regulation

Next, the transcription factor NPAS4 regulation is integrated into the model. The general effect of NPAS4 regulation is illustrated in Figure 4. When NPAS4 is expressed in an excitatory neuron, it will increase the number of inhibitory synapses that bind to the host excitatory neuron. When NPAS4 is expressed in an inhibitory neuron, it will level up the effect of inhibitory synapses that

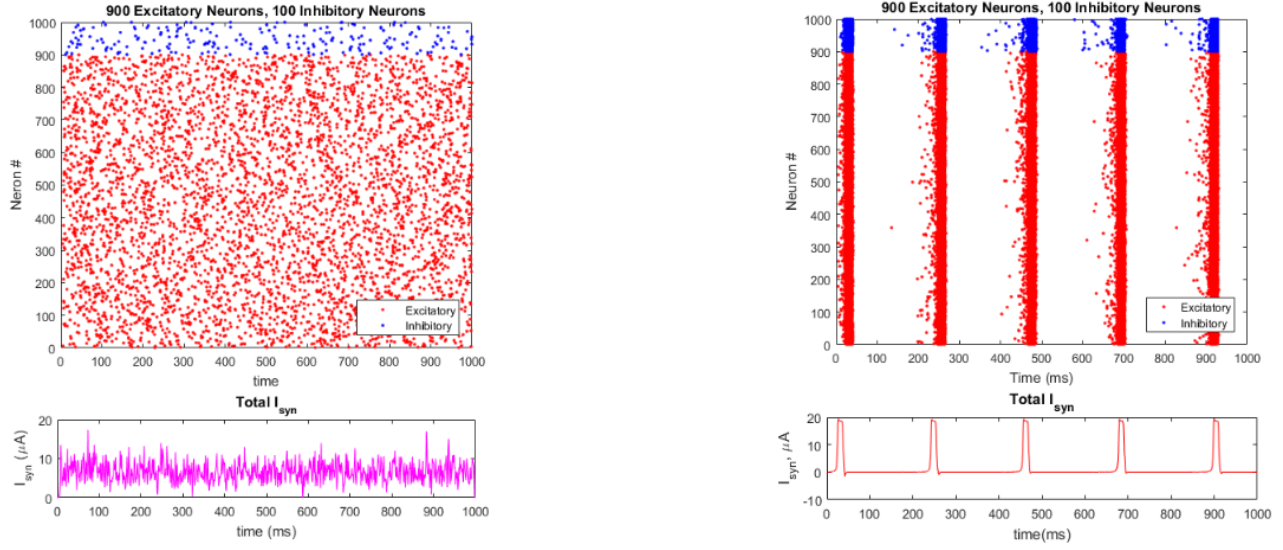


Figure 12: (Left)Control group without any coupling effect between neurons; (Right)Neuronal network with random coupling effect

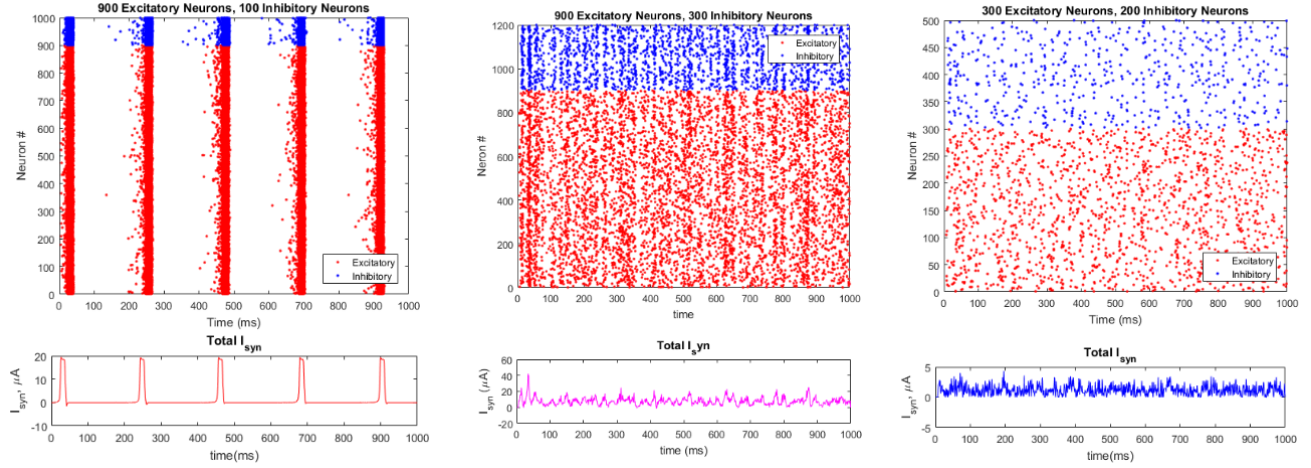


Figure 13: Comparison between the spike patterns and output currents of the neuronal network with different number of excitatory/inhibitory neurons

bind to the host inhibitory neuron. In our model, we realize NPAS4 regulation by modifying the Matrix of Synaptic Connection Strength. First, we set NAPS4 is expressed if and only if a neuron is fired (Lin (2008)). In the model, neurons are always checked if they are fired or not in every time step. If a fired neuron j is an inhibitory one, then in the connection strength matrix M ,

$M(i, j)$ will be incremented where i represents all the excitatory neurons. If a fired neuron k is an excitatory one, then $M(i, k)$ will be decremented where i represents all the inhibitory neurons here. For the other neuron m that is not fired, $M(i, m)$, where i represents all the neurons, will be reset to the initial value equal to where it is first randomly generated. As a result, the MSCS is updated in every time step based on the expression of NPAS4 and NPAS4 is further regulated by the firing of excitatory and inhibitory neurons.

Figure 14 shows a comparison between the two currents generated from a NPAS4 regulated system and a control system. While the non-regulated current generates organized spiking patterns, the NPAS4-regulated current keeps vibrating around a stable level. This little vibration of the current illustrates the balancing effect from the NPAS4 regulation.

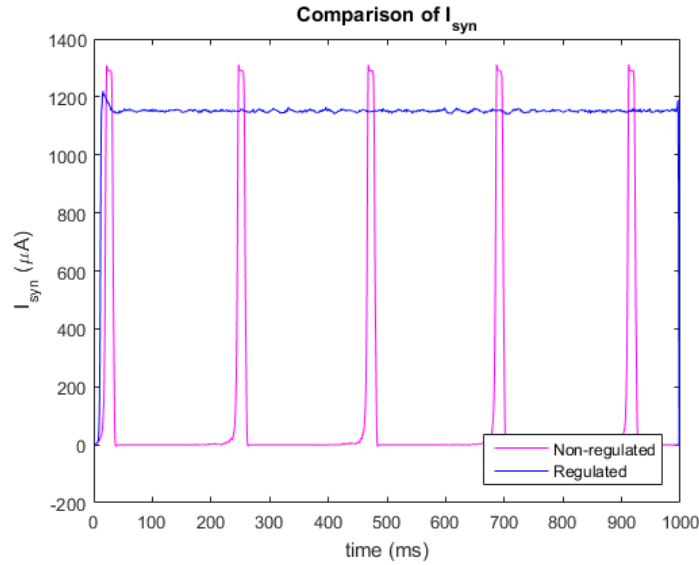


Figure 14: The effect of the NPAS4 regulation on random coupling neuronal network

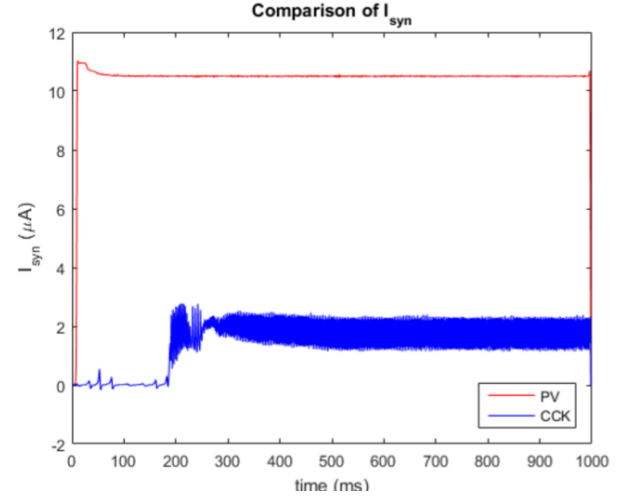
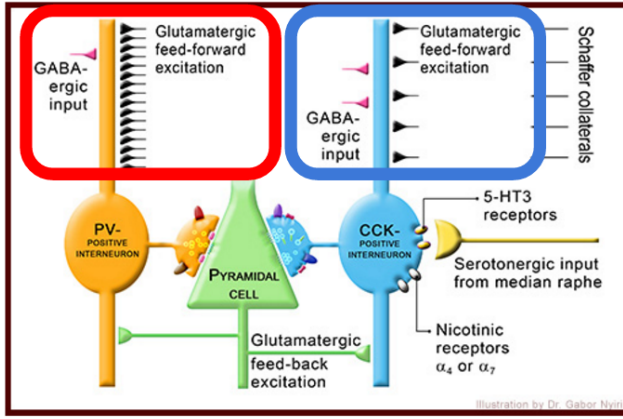


Figure 15: Synaptic current generated by the random coupling network serving as the external current on PV(Red)/CCK(Blue) basket cells

3 Results

3.1 External current providing on PV/CCK basket cells from random coupling neuronal network

According to the different amount of excitatory and inhibitory synapses binding on the PV/CCK basket cells, we generated the synaptic current by assigning the NPAS4 regulating random coupling neuronal network 1500 excitatory neurons, 100 inhibitory neurons on PV cell, while 500 excitatory, 200 inhibitory on CCK.

As the result, we got two different synaptic current serving as the external current providing on both basket cells(Figure 15). The current providing on PV cell is having a higher amplitude($11\mu A$ vs. $2\mu A$) and more stable than on CCK cell. Potentially, since the synaptic current providing on PV cell is more stable, PV cell will be able to generate spikes with more stable frequency. This is close to the result of the experimental studies that external current providing on PV cell is around 7 times as large as on CCK cell(ref.).

After generating the synaptic current, the whole schematic of the model(shown in Figure. 16) could be simplified into the one shown in figure.

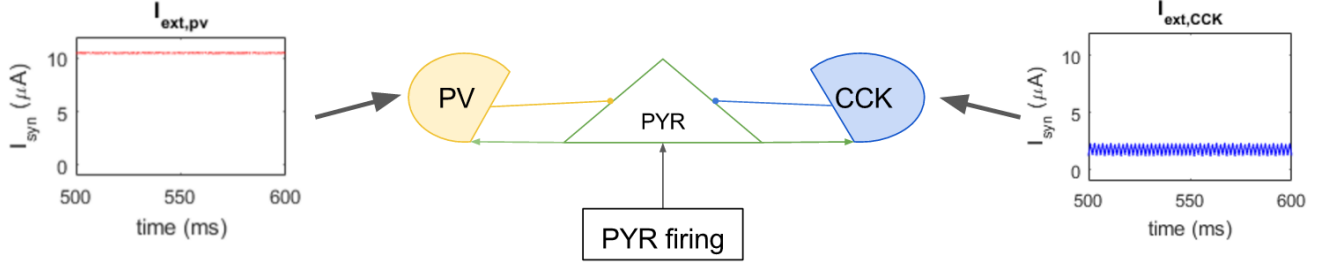


Figure 16: Simplified schematic of the model after working out the synaptic current providing on the two basket cells.

3.2 The spikes generated in PV/CCK basket cells

As shown in Figure 17, after generating the synaptic current providing on both basket cells, we added a stable external current on the pyramidal cell. As the result, we are able to generate the spiking patterns of CCK(red) basket cell, PV(blue) basket cell, and pyramidal(green) cell. The firing pattern matches the observation in the paper(ref.) saying that the PV cell is generating non-accommodating spiking pattern while CCK is generating accommodating spiking pattern.

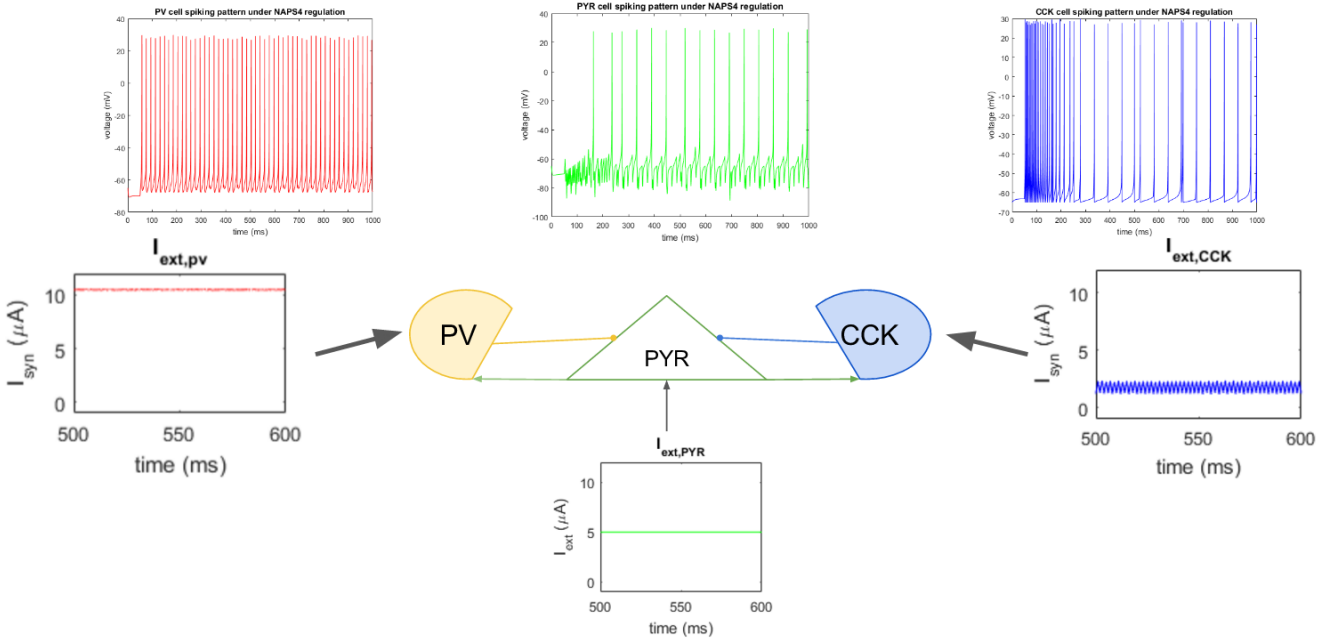


Figure 17: The spikes in PV/CCK basket cells and in pyramidal cell.

4 Conclusion

In this study, a model which could qualitatively recreate the spiking pattern in PV cell and CCK basket cell is built. Moreover, by using the random coupling neuronal network model, the model gives an explanation of how the transcription factor NPAS4 affect neural activity.

The model creates a good fundamental structure for studying the perisomatic neural activity in a micro scale. Based on our study, more biological factors such as the neuron structure, dendrite dynamics, complexity of different ion channels could be taken account.

SUPPLEMENTAL MATERIALS

The whole model is written with Matlab,in the compressed folder 'BENG260_Proj.zip'.

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