

BUCHIN¹ ANATOLY, RIEUBLAND² SARAH, ROTH² ARND, HAUSSER² MICHAEL AND GUTKIN³ BORIS

¹Ioffe Institute of Physics, Saint-Petersburg

²Ecole Normale Supérieure, Group of Neural Theory, Paris

³University College London, Wolfson institute for biomedical research,
anat.buchin@gmail.com

BISTABILITY AND INVERSE STOCHASTIC RESONANCE OF PURKINJE CELLS

Experimental data reveal the bimodal behavior of Purkinje cells which could be characterized by firing-rate hysteresis in response to ramp current. We propose an adaptive Exponential Integrate-and-Fire neuron (aEIF) model to explain this bimodality. Another phenomenon found in Purkinje cells, inhibition by noise stimuli, so-called Inverse Stochastic Resonance (ISR) is also explained in terms of aEIF model by switching between quiescent and spiking states of a neuron. We have found the tuning parameters for the external stimuli that will preferably switch the neuron between these states. We propose that this switching is directly linked to the switching between quiescent and spiking state of Purkinje neurons revealing definitively their bistability.

Keywords: purkinje cell, bistability, noise, inverse stochastic resonance, hysteresis

INTRODUCTION

Cerebellum is an important part of the nervous system it's involved in motor control of precise movements, maintaining of the sense of balance and simple motor learning. The Purkinje cells possess inhibitory GABA-synapses and their axons is the main projection from cerebellar cortex to its deep structures. These neurons are also one of the biggest cells in the nervous system therefore they are a good model for cellular neuroscience.

Theoretical models of spiking neurons show that neurons may exhibit the stochastic resonance, i.e. enhance the excitability in response to noise current injections [1, 2]. Meanwhile it has been shown theoretically that conductance-based spiking neuron models as Hodgkin-Huxley may be inhibited by noise injections when stimulus parameters such as noise amplitude and mean are in a specific range [3].

It's known that Purkinje cells may demonstrate pauses in spike generation *in vivo* in awake cat brain [4]. This implies the existence of two states: active, when the neuron spikes and passive when the cell is at rest.

We have found experimentally that Purkinje cell in response to ramp current stimulation show the firing-rate hysteresis. When the stimulus goes up and down, there are different spike frequencies. The presence of hysteresis in Purkinje cell implies the existence of two stable states or bimodality. The model of Exponential Integrate-and-Fire neuron (aEIF) is used to explain this phenomenon. We show that the geometry of phase plane defines the intensity and direction of switching between different states of the system. We measure the hysteresis range in a neuron and approximate it with aEIF model. We show that inhibition of Purkinje cell by noise injection, so-called Inverse Stochastic Resonance (ISR) is directly linked to its bimodal behavior.

EXPERIMENTAL RESULTS

Electrophysiological recordings have been done on the slices of mice Cerebellum. The potential $V(t)$ has been recorded in the current clamp mode, Fig. 1. In order to prevent the spontaneous firing the neurons were additionally depolarized with the constant step current from -200 to -400pA.

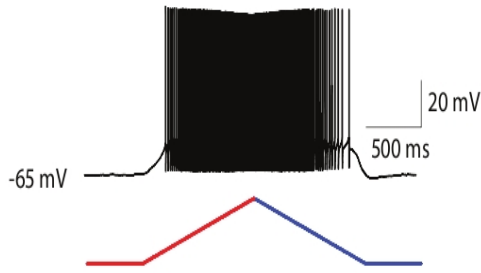


Fig. 1 Stimulation of the Purkinje cell by current ramp.

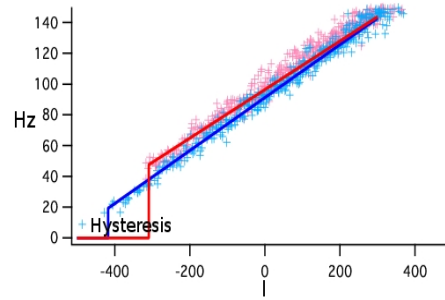


Fig. 2 The instantaneous firing-rate of the same cell.

On the Fig. 2 is shown the firing-rate of the Purkinje neuron in response to current ramp injection, Fig. 1. One can see different number of spikes and different moments of spike initiation during the up-stroke and down-stroke of the stimulus. To measure this firing-rate hysteresis we have calculated the instantaneous frequency of spikes for the upstroke and downstroke of ramp, Fig. 2. In order to estimate the hysteresis range we measured the difference between spike initiation moments. The instantaneous f-I curve of the neuron has an abrupt beginning of spike generation during the gradual increase of the input current therefore we can see that this Purkinje neuron possesses type II excitability [5]. Because we assume that the neuron has the same parameters during the upstroke and downstroke of the stimulus, this firing-rate hysteresis implies that the system has two states that we can see during ramp injection.

Each neuron *in vivo* receives a huge amount of inputs on the dendritic tree that are summarized. One of the simplest experimental model of this physiological input is an injection of the complex stimuli into the soma. In our experiment the Purkinje cells were stimulated to mimic dendritic input by noise-like stimuli that was generated as an Ornstein-Uhlenbeck process:

$$\tau_s \frac{dI}{dt} = -I + \tau_s \sigma \zeta(t)$$

where $\zeta(t)$ denotes the white Gaussian noise $\langle \xi(t) \rangle = 0$, $\tau_s = 3\text{ms}$ is the correlation time, σ is the noise amplitude. Each stimuli generated resembles the superposition of noise current with zero mean and constant step of negative hyperpolarising current.

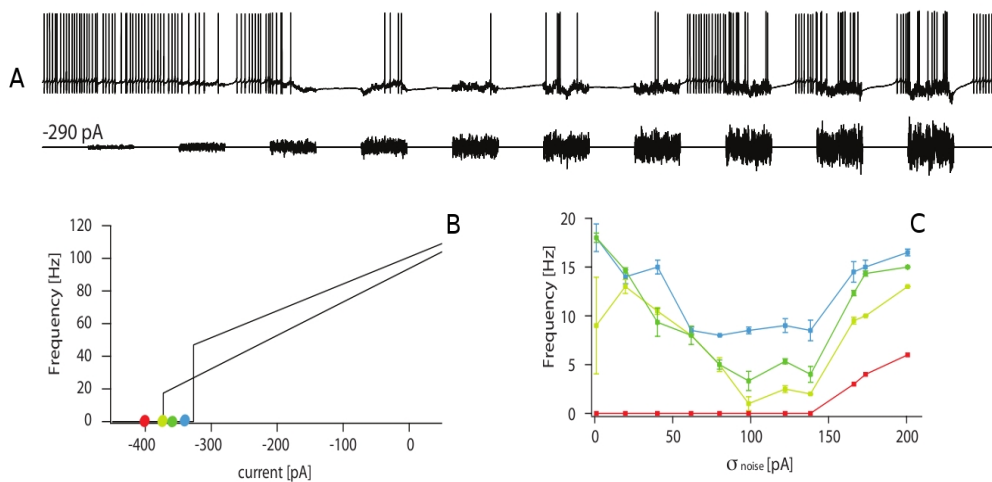


Fig. 3 A – the response of a neuron to the stimulus with increasing amplitude. Each noise stimuli is separated by 1 sec of rest, i.e. 1 sec of constant current injection. B – hysteresis of instantaneous firing-rate of the same neuron when stimulating by current ramp. C – averaged frequency of a neuron in response to noise injections as in A. Different colors correspond to different mean of the stimuli on B, error-bars represent the standard error.

The Purkinje cell that posses the firing-rate rate hysteresis in response to current ramp injection, Fig. 3B, has the non-linear response to the stimulation by noise stimulus, Fig. 3A, C. One can see that by injecting the noise current with the mean in the hysteresis range, Fig. 3B, we can see effective inhibition of spiking of the Purkinje cell. It can be seen in the form of the averaged firing-rate, Fig. 3B. If the mean of noise stimulus is out of the hysteresis range, red marker in Fig. 3B, then it has just linear effect on the averaged firing-rate, Fig. 3C.

Thus if the input stimulus is tuned to its mean and amplitude in the hysteresis range, it will significantly inhibit the activity of the single neuron. In the opposite case the firing-rate of a neuron has just linear relationship in response to the stimulus amplitude.

THE MODEL OF NEURON

There are many mathematical models of a single neuron that describe it's spiking activity. The most common are conductance-based models of Hodgkin-Huxley type. They approximate the dynamics of ionic channels and biophysics of spike generation in many details. But despite it's biophysical plausibility their mathematical form is quite complex that is why they are not amenable to explicit analysis. Therefore in some cases more simple non-linear models with reach dynamical behavior can be used for analysis [6].

One of these models is an adaptive Exponential Integrate-and-Fire neuron [7] that is used in the present work.

$$C \frac{dV}{dt} = -g_l(V - V_l) + g_l \Delta_T e^{\frac{V - V^T}{\Delta}} - w + I \quad (1)$$

$$\tau_w \frac{dw}{dt} = a(V - V_l) - w \quad (2)$$

$$\text{if } V > V_{spike} \text{ then } V = V_{reset} \ \& \ w = w + b$$

Variable $V(t)$ correspond to the membrane potential, $w(t)$ is the adaptation variable that models both spike-triggered and subthreshold adaptation. Each time when potential crosses the threshold V^T it grows because of the exponential term in eq. (1). This models fast upstroke of the membrane potential during the spike initiation. Once potential crosses the conditional threshold $V_{spike} = 0$, it is reset to V_{reset} and adaptation variable increases by b .

In the subthreshold regime when parameter I is relatively small, two focus exist in the model: stable and unstable. These focuses correspond to the intersection between null-clines. On the bifurcation diagram, Fig. 4, they conform to two branches of solutions. When I is gradually increasing these branches meet and annihilate in the bifurcation point.

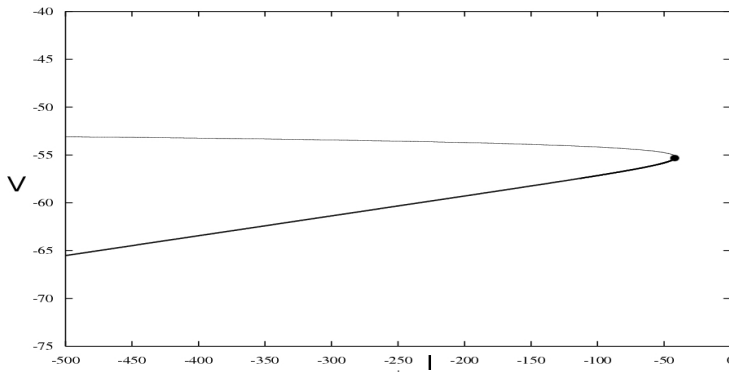


Fig. 4 Bifurcation diagram of aEIF model in subthreshold mode. Top and bottom branches correspond to unstable and stable focuses.

The bifurcation type is defined by parameters of the model [8]. In our case the model possess the Andronov-Hopf bifurcation and has type II excitability as a consequence. Therefore the

f-I curve is characterized by an abrupt beginning as in the Purkinje cell when stimulating by constant current steps.

Parameters of the model:

$$C=217\text{pF} \quad , \quad \tau_m=4.5\text{ms} \quad , \quad V_l=-55.144\text{mV} \quad V^T=-56.252\text{mV} \quad , \quad \Delta_T=0.77\text{mV} \quad , \\ a=35.4\text{nS} \quad \tau_w=11.2\text{ms} \quad , \quad b=495\text{pA} \quad .$$

MODEL OF HYSTERESIS AND INVERSE STOCHASTIC RESONANCE

We have fitted parameters for aEIF model using dynamic I-V method [9] in order to reproduce maximally the electrophysiological behavior of a single cell. All the following numerical experiments are shown for the typical Purkinje cell.

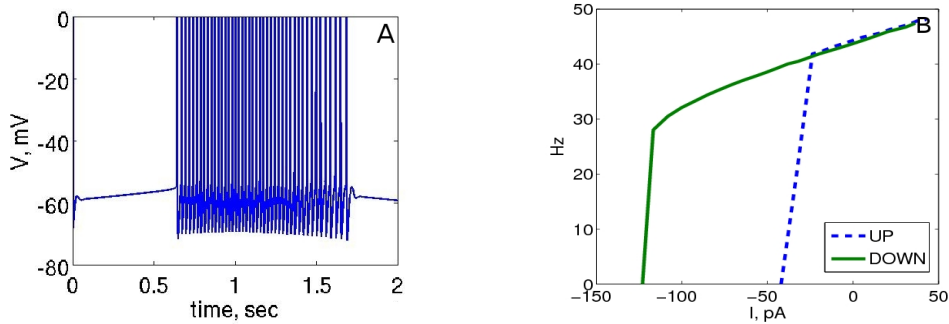


Fig. 5. A – the response of the single neuron to the stimulation by ramp current as in the experiment, Fig. 1. B – the instantaneous firing-rate when the stimulus goes up (dotted line) and down (solid line).

When the model neuron is stimulated by ramp current, Fig. 5A, one can see different start of the firing-rate curve during upstroke and downstroke of the stimuli, Fig. 5B. At given parameters the model possess hysteresis as in the experiment, Fig. 1. It demonstrates such behavior because of the adaptation variable $w(t)$. Its is changing at each spike and it also changes because of the coupling with $V(t)$, eq. 2. Thereby during the first and last spike the system is in different states that leads to hysteresis.

When the symmetrical current ramp is present to the system, one can calculate the instantaneous firing-rate. Difference between the moments of spike initiation during the upstroke and downstroke of the stimulus corresponds to the hysteresis range, Fig. 5 B.

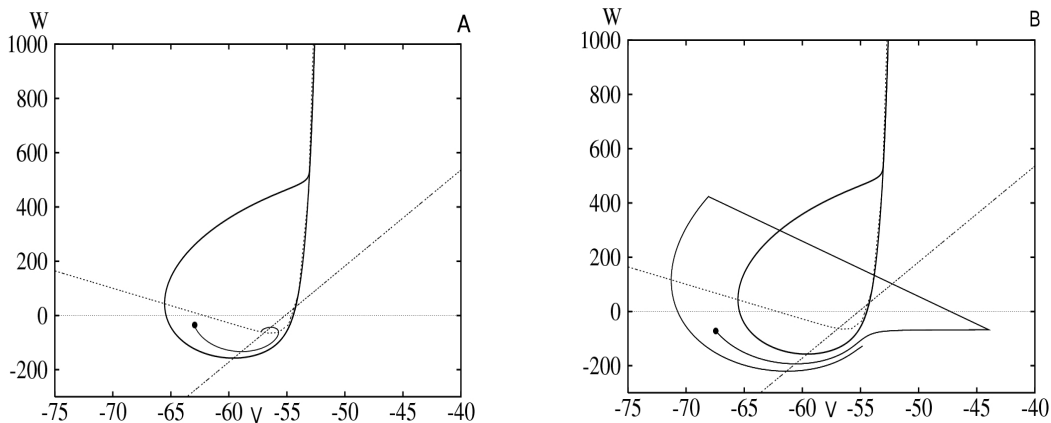


Fig. 6 Phase portrait of the system, eq. (1-2) when stimulating by constant current $I=-100\text{pA}$. A – trajectory moving to stable focus, B – trajectory of the limit cycle. Black dots denote the initial conditions. Dashed lines correspond to null-clines. The the drop-like area is the basin of attraction of the stable fixed point, resting state. The rest of the plane is the area of spike generation.

On Fig. 6 is depicted the phase plane of the system in the range of hysteresis. In that case the

phase plane consist of three sets. The area inside the drop-like set correspond to the basin of attraction of the stable focus. Once the trajectory moves over this set, it goes to the stable focus, that corresponds to rest state. All solutions outside the drop-like set are the limit cycles. When the system is in this set, it is continuously spiking. Both stable solutions are separated by the separatrix, the boundary of the drop-like set, that is an unstable solution.

Because of the shape of the phase plane one can see that two stable solutions may exist at the same parameters of the model. One solution corresponds to tonic spiking, another to the resting state. Thereby when two null-clines, eq. (1-2) intersect in two points, the model is bistable. If null-clines do not intersect that corresponds to the large values of the input current I , then each solution is a limit cycle.

Hysteresis in the model is explained by existence of different solutions at the same parameters or bistability. When stimulating by current ramp with increasing amplitude the solution of the system becomes unstable throw Andronov-Hopf bifurcation when $I \approx -48 \text{ pA}$, Fig. 4. After this point, there is no intersection between the null-clines and therefore all solutions correspond to tonic spiking. When stimulating by decreasing current ramp, the trajectory becomes unstable once the solution crosses the basin of attraction of the stable fixed point, Fig. 6B. During the limit cycle the system is gradually moving therefore we don't know exactly where the trajectory crosses the attraction basin. But we suppose that it happen when the trajectory and basin of attraction are maximally close to each other, $V \sim V^T$ Fig. 6B.

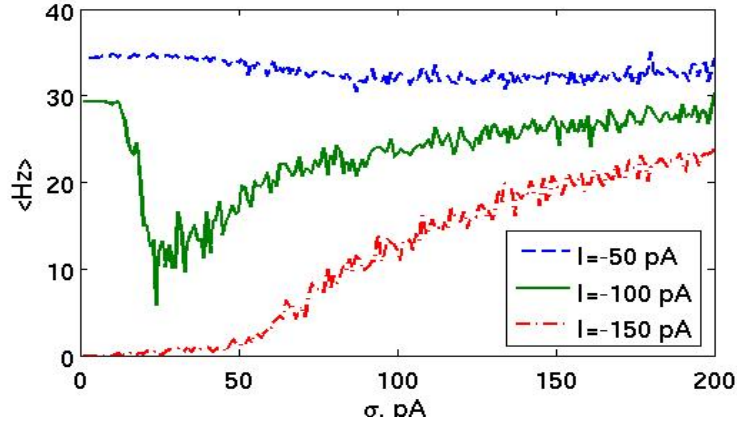


Fig. 7. The averaged firing-rate of the model in response to the stimulation by complex stimuli with increasing amplitude (details in text). Each line corresponds to the mean of the stimuli.

When noise is present in the dynamical system, there are no precise methods of estimation of the shape of the phase space. But if the amplitude of the stimuli is small enough, one can use the analysis for the stationary case. Therefore when the noise amplitude is small we use the phase plane analysis of unperturbed system.

On Fig. 7 is shown the averaged firing-rate response of the model when stimulating by noisy current with constant mean and amplitude. In each point the model has been integrated 10 times during 1 sec., then the number of spikes were averaged. In that way we get the numerical estimation of the bistability region. One can see that when the mean of the stimuli is in the bistability region, $I = -100 \text{ pA}$, Fig. 5B, we can see the effective inhibition of spike generation, Fig.7. It happen because at this parameter the trajectory of the system is maximally close to the basin of attraction of the stable fixed point. In that case noise at given amplitude will effectively move the system to the rest state. We call this phenomenon of noise inhibition the Inverse Stochastic Resonance (ISR) in opposite to stochastic resonance when the system is more excited the more amplitude of noise is present.

When the mean of the stimuli is out of the bistability range, dotted and line-dotted lines, Fig. 7, we can't see the effective inhibition of spike generation. When the mean is large, negative and

behind the bistability range, it leads to intersection between the basin of attraction of the stable fixed point and line $V_{reset} = -68$. It leads to crossing between the trajectory and basin of attraction after the spike and correspondingly will move the system to the stable fixed point.

Therefore when $I = -150$ pA and noise amplitude isn't high enough one can see the characteristic delay of spike generation till $\sigma \approx -50$ pA. When $I = -50$ pA, the signal is also out of the bistability range, Fig. 5B. In that case the basin of attraction of the stable fixed point is too small. Then the basin and trajectory of spiking are too far from each other, therefore it leads to the absence of inhibition.

The tuned noisy stimuli can effectively inhibit the activity of a single neuron. Herewith, the intensity of switching highly depends on the mean of the stimuli. This effect can take place only at low amplitudes of the stimuli because too strong input will fully control the activity of a neuron. In that way the ISR phenomena exist only when the external stimuli is tuned in amplitude and mean from the bistability region.

CONCLUSION

Hysteresis and inhibition of Purkinje neurons by noise stimuli or ISR is explained in terms of aEIF model. In the bistability range that is defined by mean of the stimuli two stable solutions coexist at fixed parameters. One solution corresponds to tonic spiking another to the resting state of a neuron. When the input stimuli resembles noise, there is an amplitude that will preferentially switch the neuron to the resting state. It is the reason of inhibition by noise or ISR phenomenon.

In that way, the bimodality and ISR found in the Purkinje neurons can be explained by properties of aEIF neuron model. We propose that this switching between spiking and quiescent state is directly linked to the bistability of Purkinje cells *in vivo*.

REFERENCES

- [1] Ermentrout G.B., Galan R.F., Urban N.N., Reliability, Synchrony and noise // Trends in Neuroscience. 2008. P. 428-434.
- [2] Mainen Z.F., Sejnowsky T.J.. Reliability of spike timing in Neocortical neurons // Science. New series. 1995. Vol. 268. No. 5216. P. 1503-1506.
- [3] Gutkin B., Tuckwell H.C., Jost J., Inhibition and modulation of rhythmic neural spiking by noise // Physical Review. 2009. E 80, 031907.
- [4] Yartsev M.M, Givon-Mayo R., Maller M., Donchin O., Pausing Purkinje cells of the awake cat // Frontiers in system Neuroscience. 2009. Vol. 3, article 2.
- [5] Izhikevich E.M., Dynamical Systems in Neuroscience. The Geometry of Excitability and Bursting // The MIT Press. 2007.
- [6] Izhikevich E.M., Which model to use for cortical spiking neurons? // IEEE Trans. On neural networks (special issue on temporal coding). 2004.
- [7] Toboul J., Bifurcation analysis of a general class of non-linear integrate-and-fire neurons // INRIA. 2007. Rapport du recherche n 1.
- [8] Toboul J., Brette R., Dynamics and bifurcations of the adaptive exponential integrate-and-fire model // Biological cybernetics. 2008. P. 319-334.
- [9] Badel L., Lefort S., Brette R., Petersen C.C.H., Gerstner W., Richardson J.E., Dynamic I-V curves and reliable predictions of naturalistic pyramidal-neuron voltage traces // Journal of Neurophysiology. 2008. P. 656 — 666.