Role of hyperpolarization-activated conductances in the auditory brainstem

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1 Abstract

This study examines the possible functional role of two hyperpolarization-activated conductances in the interaural intensity difference detector lateral superior olive. Inputs of these neurons are transformed into an output, which provides a firing-rate code for a certain interaural intensity difference range. The I_h conductance's effect is partly masked by the inwardly rectifying outward K^+ current's effect. Since resting potential, input resistance, membrane time constant, as well as synaptic release probability are all affected by the pharmacological agents used in vitro experiments, it is not easy to dissect out the role of these conductances. We therefore used computer simulations to investigate this issue. The interplay between the two hyperpolarization activated conductances, first-spike latency, f-I function, input resistance and the width of the dynamic firing regime were examined .

2 Introduction

The lateral superior olive (LSO) is the first nucleus in the ascending auditory pathway that is specialized for interaural sound-intensity difference (IID) detection. LSO is tonotopically organized and azimuthal location is encoded by the position along the isofrequency LSO column, where LSO cell firing first goes to zero. IID detection involves detecting differences in the amplitude and relative timing of synaptic inputs at stimulus onset. The frequency as well as the onset response (for lower frequencies and for moving sound sources) during both depolarization and hyperpolarization is likely to be important. Two hyperpolarization activated conductances were reported recently in these neurons [1]. One is the slowly activating I_h, the other is the very fast inwardly rectifying K^+ conductance. Here we demonstrate and characterize further the possible functional significance of the interplay between these currents in the rate-coding IID detector neurons.

3 Model

We constructed a simple point neuron to investigate the effect of the two hyperpolarization activated conductances. With this simplified model, we studied the influence of these two currents on the onset spike, firing frequency, rebound spiking property, input resistance change, and the interplay between the two conductances. We used the formulations for the point neuron found in Cclamp of Huguenard and McCormick (1994), based on their previous data [2]. We used the two hyperpolarization activated and two spike generating active conductances. Due to the lack of the description of channel kinetics in the literature for these active conductances from the LSO chopper neurons, we used kinetics from a thalamic neuron for the I_h channel. [2]. For the inwardly rectifying conductance, we used channel description from the study by Wessel at al. [3]. This channel is assumed to be voltage dependent, but not time dependent, since it acts quickly, the authors assumed the time dependence to be negligible. The model of the voltage-dependent sodium and potassium channels is borrowed from Connor at all [7]. A voltage-dependent scaling factor on the potassium channel activation time constant is borrowed from Shapiro and Lenherr, in order to adjust the maximum value of the firing rate [4]. Simulations were performed on SUN Ultra-4 station, running Linux operating system, and using XPP simulation software. The differential equations were solved with a 4th order Runge-Kutta method, with a step size 0.05 msec. For the bifurcation analysis the the AUTO part of XPP was used. The current balance equation is given by:

$$C\frac{dV}{dt} = -G_{Na}(V - E_{Na}) - G_K(V - E_K) - G_h(V - E_h) - G_{inw}(V - E_K) - I_{leak} + I_{inj} \tag{1}$$

Where $G_{Na}, G_K, G_h, G_{inw}$ are sodium, potassium, Ih and inwardly rectifying conductances, respectively, t is time in milliseconds, V is a membrane potential in millivolts, C is total capacitance. The gating variables are described for sodium, potassium and Ih conductances by the Hodgkin-Huxley formalism:

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x \tag{2}$$

Where x is m,n,h,p gating variables.

$$G_{Na} = \overline{g_{Na}} m^3 h \tag{3}$$

$$G_k = \overline{g_K} n^4 \tag{4}$$

$$G_h = \overline{g_h} p \tag{5}$$

$$I_{leak} = \overline{g_{leak}}(V - E_{leak}) \tag{6}$$

The detailed descriptions for α-s, and β-s are not given here. The inwardly rectifier K^+ current is supposed to act quickly, thus its time dependency is neglected [3].

$$G_{inw} = \overline{g_{inw}} \frac{1}{1 + \exp((V - V_{1/2})/\gamma)} \tag{7}$$

The following parameters are used: $C_m = 290pF, E_h = -43mV, E_K = -80mV, E_{Na} = 45mV, g_{leak} = 7nS, g_{Na} = 60nS, g_K = 20nS, V_{1/2} = -65mV$,$\gamma$=6,

4 Results

We examined questions that can not be addressed experimentally with our point neuron. The dynamic interplay between the two hyperpolarization activated conductances defines the first spike latency, the resting membrane potential, the input resistance and the duration of the spiking regime. Though the rest state of our neuron model is near a Hopf bifurcation, the neuron fires in a certain frequency range, and can not fire with arbitrary low firing frequences, these channel kinetics allowed us to have wide dynamical range and physiologically still plausible low firing frequences. (LSO neurons are spontanously active in vivo). We changed the conductances of these channels, and examined 4 basic situations. If we did not add any hyperpolarization activated conductances, (fig 1.A, D curve), we have a large input resistance. The fixed point looses its stability via a Hopf bifurcation, and an unstable periodic solution emerges with small amplitude. When the injected current increases further, stable periodic solution follows and the neuron fires. As we increase injected current magnitude even more, the amplitude of the oscillation decreases, the frequency of the stable periodic solution increases until it disappears, and we have again a stable fixed point solution. When we have both of the hyperpolarization activated currents (fig 1.A, B curve), we have a shallow I-V curve in the hyperpolarized direction, the input resistance is decreased by both of the conductances. The stable fixed point looses stability, and an unstable large amplitude periodic solution emerges. Increasing further the injected current, we get stable periodic solution. This solution becomes unstable in a very narrow parameter regime, and periodic solution vanishes, and a fixed point appears. The amplitude of the unstable periodic solutions has a plateau period. Also if we add both conductances, the inwardly rectifying conductance partly masks the I_h induced sag, and decreases the hyperpolarization which follows the depolarizing prepulse. When I_h conductance was added alone (fig 1A, A curve) figure, the input resistance was low, but due to the depolarization mediated by the outward current, the cell gets closer to threshold. It looses stability via a Hopf bifurcation, after a small amplitude unstable periodic

solution a large amplitude stable solution starts. The frequency changes continuously. This conductance gets the neuron closer to threshold, and the first spike latency decreases. The I_h conductance is responsible for the sag feature, and for the depolarized, hyperpolarized membrane potential after prepulse current injection. Finally we added only the inwardly rectifying instantaneous conductance (fig 1.A, C curve). The input resistance is low and the cell is hyperpolarized by the outward conductance. When the injected current is increased, the solution looses stability, and the membrane potential jumps to a higher value. Decreasing the bifurcation parameter from higher values, the membrane potential looses stability, and after a narrow parameter range a periodic unstable solution occurs, and the membrane potential jumps to lower values. In that case the whole spike generating mechanism is canceled, and the cell reaches a stable more depolarized value without spiking. We demonstrated, that the inwardly rectifying channel can be responsible for nonmonotonous I-V relationship (fig 3). In a certain parameter regime (as a function of the total conductance of the inwardly rectifying channel) the current causes a hump in the I-V relationship and in slope resistance.

The qualitative analysis of the special points in two dimensions (injected current and the conductances of the two currents) shows, that the width and the location of spiking regime is defined by the two conductances. The Ih conductance increase moves the first Hopf bifurcation to the left. The point, where the stable periodic solution vanishes is not influenced by the I_h total conductance. Again, this is due to the I_h deactivation. The inwardly rectifying conductance moves the first Hopf bifurcation to the right, and makes the spiking regime narrower.

Since these cells are regarded to be rate coders, we examined their frequency responses. On adding the I_h conductance (fig 1B, A), the first spike latency decreased, the firing rate curve is shifted to the left at lower frequencies in comparison with the case, where there are no hyperpolarization activated conductances added (fig 1B, D). At higher frequencies, due to the I_h deactivation, the shift decreases. Low amplitude unstable periodic solution increases by adding I_h conductance. The ratio between the two conductances determines, whether the frequency curve is shifted to the left, or to the right. (Fig 1B, B) is the situation, where we added both conductances. In this case the curve is shifted to the right. Interestingly the periodic solution here is unstable for wider parameter regime, and the amplitude of the oscillation has a plateau regime, while the frequency increases. The unstable solutions become stable, but before vanishing, there is an unstable solution again at a narrow parameter regime. If only inwardly rectifying conductance is added, due to the nonmonotonicity of the I-V relationship mediated by this conductance, there is no stable periodic solution, unstable periodic solution occurs in a narrow parameter regime, with decreasing frequency. (Fig 1B, C)

5 Discussion

Accuracy of rate coding could be "hard wired" by setting the two hyperpolarization activated conductances during development along isofrequency LSO lines, thus neurons with differently expressed hyperpolarization activated conductances could be serially arranged according to threshold [5]. Excitability is able to change dynamically due to the slow I_h conductance, and change in kinetics of these conductances by neuromodulators provides a mechanism for further plasticity in the threshold setting on slower timescales [6].

Consistent with the result of Adam at al, the spike count versus prepulse voltage function is nonmonotonic, meaning that if the cell membrane potential is held at different potential levels for a while, and then depolarizing current is applied, the maximum spike number is achieved with prepulse potentials between 60 - 40 mV region [1]. The excitability is decreased in both directions. The I_h current is a possible candidate for explaining part of this phenomenon, because due to depolarization induced deactivation the excitability is decreased. The inwardly rectifying conductance could contribute to the same phenomenon by causing nonmonotonicity in the I-V relationship on the dendrites, and thus causing voltage dependent nonmonotonous membrane time constant change.

6 Conclusion

We demonstrated, that activation of the I_h conductance by hyperpolarization causes depolarized RMP, and shortens the first spike latency. Though the input resistance decreases and the slope of the I-V curve is shallower, due to the depolarization the cell gets closer to threshold. In time dependent cases, when the hyperpolarization is followed by depolarization (due to moving sound sources, or due to the inhibitory spontaneous activity), the activated Ih conductance is partly responsible for rebound spike property. Due to the slow deactivation, the cell's excitability is increased after the hyperpolarized time period. However after depolarization, the cell's excitability is decreased, since that conductance is partly activated at resting potential and depolarization causes deactivation. Inwardly rectifying current partly masks the Ih channel's effect to hyperpolarizing direction, by clamping the cell to the equilibrium potential of potassium, and by decreasing the input resistance further. This K^+ current hyperpolarizes the RMP, induces an increase in the first spike latency, the spike threshold is reached later and decreases the input resistance. The amplitude of the synaptic events' is therefore decreased by this conductance [9], [10]. Both the duration of the firing regime, and the position of the IID/firing regime is affected by the two hyperpolarization activated conductances. Effects of the two hyperpolarization activated conductances in a model, where the rest potential is near a saddle-node bifurcation, and the cell is able to exhibit arbitrary low frequencies requires further studies. Also whether similar qualitative change occurs due to the nonmonotonicity caused by the inwardly rectifying outward current is an other interesting question to answer.

6.1 1.A figure legend

Bifurcation analysis of our point neuron membrane potential, the bifurcation parameter is the injected current. We examined 4 basic situations. The point neuron without, with both, just with the I_h, or just with the inwardly rectifying K^+ conductance: Fig 1.D,B,A,C respectively. Injected current is between the -10 - 90 pA range. The bifurcation parameter is I, the injected current in pA. The bifurcation variable is membrane potential in mV. The two hyperpolarization activated conductances are the following, all the values are in nS. Open circle and thin line are unstable periodic solution and unstable fix points respectively, while dots and thick lines are stable periodic solution and stable fix points respectively.

1: g_h=0, g_{inw}=0, in case of D; 2: g_h=20 g_{inw}=5, in case of B; 3: g_h=50 g_{inw}=0, in case of A;

4: g_h=0 g_{inw}=10, in case of C,

6.2 1.B figure legend

Frequency values of periodic solutions at the same situations as the fig 3.A bifurcation analysis. Open circles are the frequency values, which belong to unstable periodic solutions, and dots denote the frequency values of the stable periodic solution.

6.3 2. figure legend

Qualitative analysis on the change of special points in two dimensional parameter space. On the top figure we examined the special points in the I_h total conductance-injected current two dimensional space. At the bottom the inwardly rectifying total conductance-injected current space was plotted.

6.4 3. figure legend

Nonmonotonous I-V relationship mediated by the inwardly rectifying conductance. The I-V relationship is examined as a function of the total conductance of the inwardly rectifying current.

7 Acknowledgements

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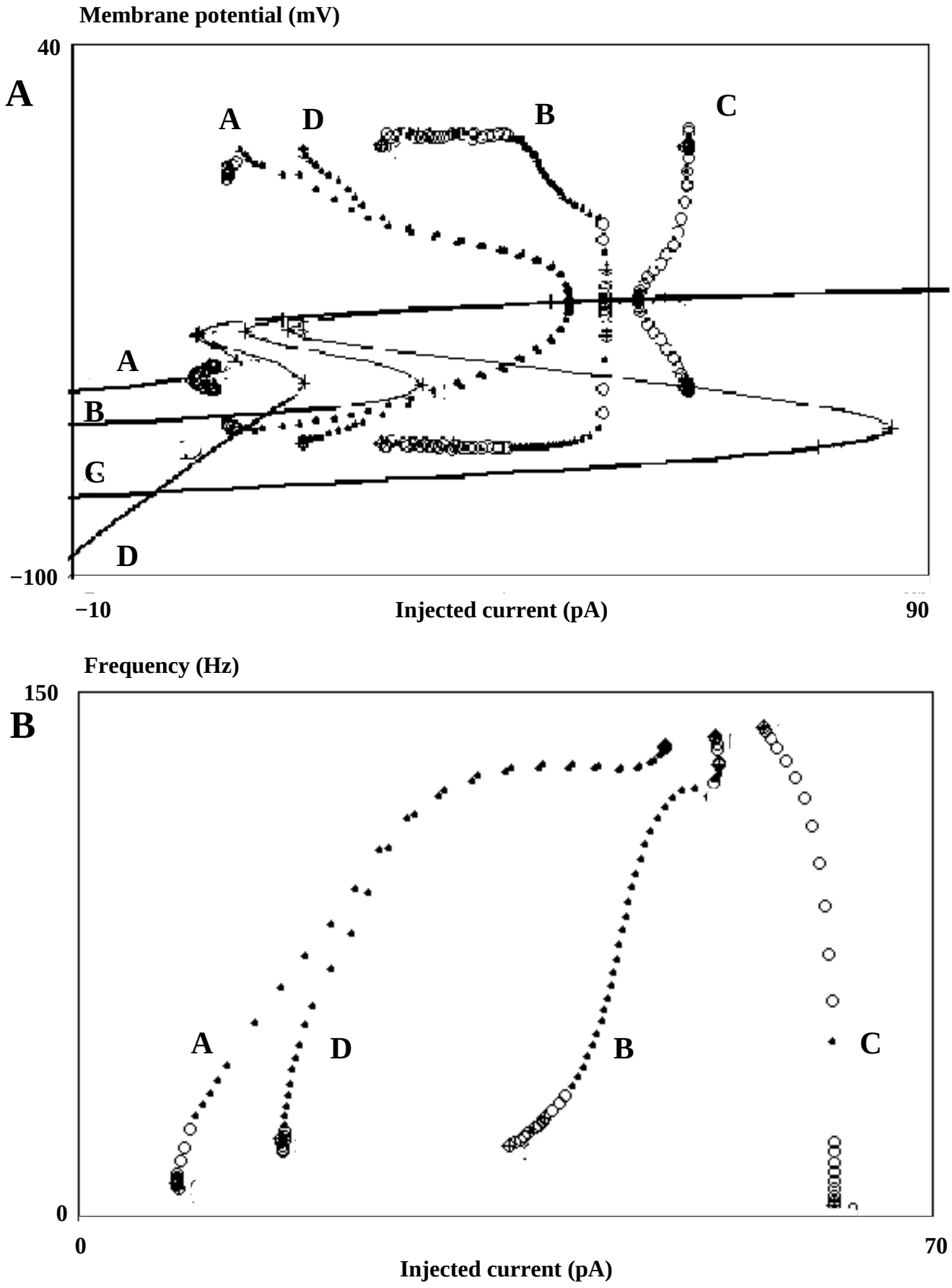
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Injected current (pA)
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Frequency (Hz)
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C
0
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70
Injected current (pA)

Figure 1:

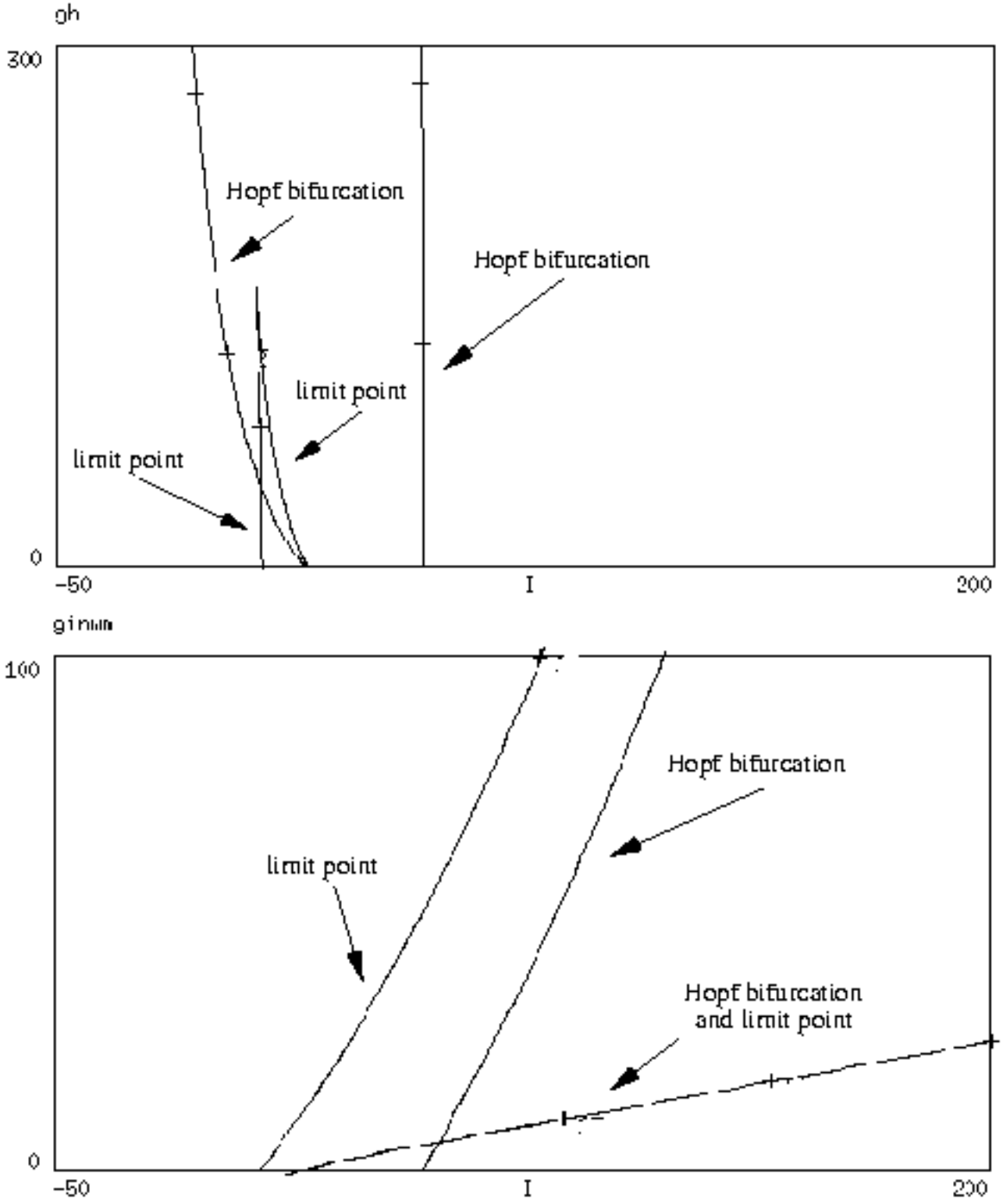
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Figure 2:

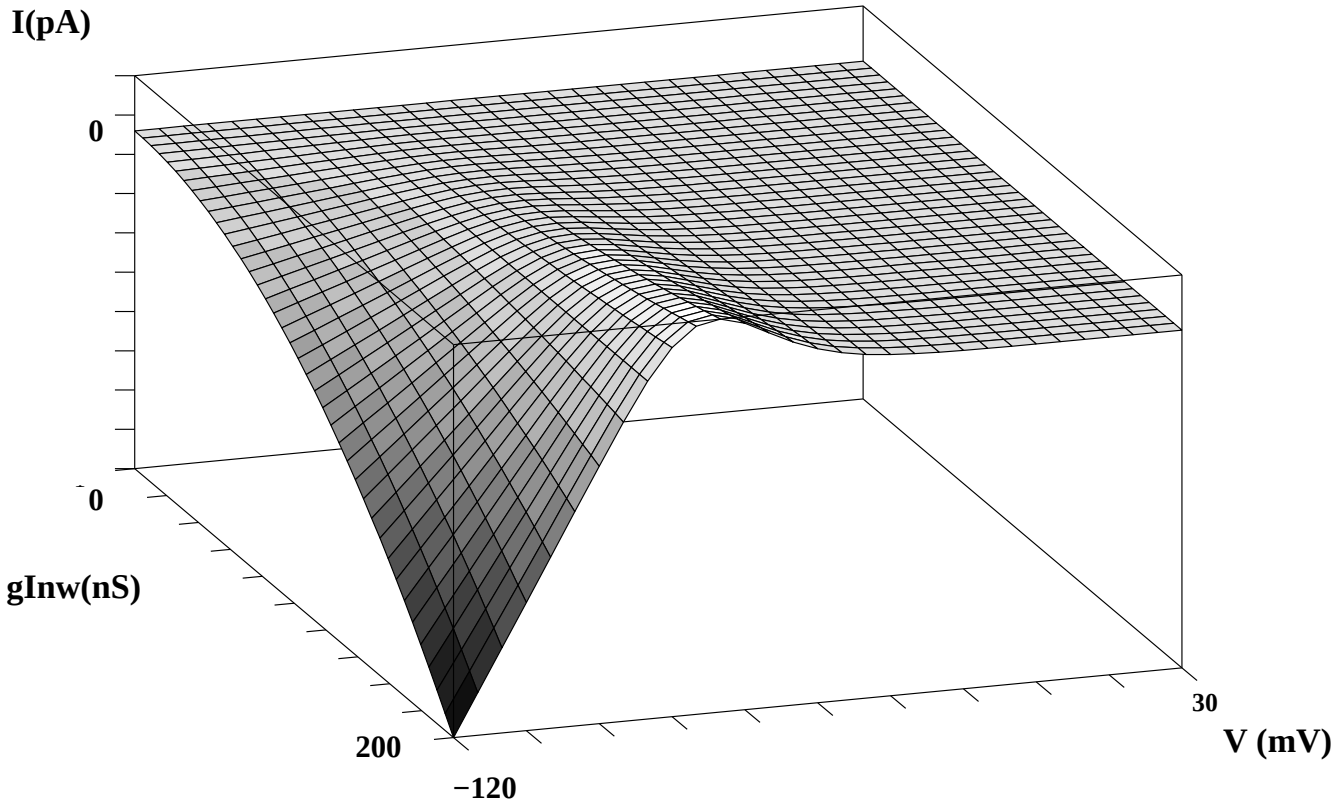

Figure 3: