A Simulation-Based Study of Dorsal Cochlear Nucleus Pyramidal Cell Firing Patterns

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ABSTRACT

A two-variable integrate and fire model is presented to study the role of transient outward potassium currents in producing temporal aspects of dorsal cochlear nucleus (DCN) pyramidal cells with different profiles namely the chopper, the pauser and the buildup. This conductance based model is a reduced version of KM-LIF model (Meng & Rinzel, 2010) which captures qualitative firing features of a detailed physiological model (Kanold & Manis, 2000). For our development we benefit from transient potassium currents properties i.e. fast activation and slow inactivation to generate long latency before start of firing. We compare our minimal model outputs in response to a hyperpolarizing stimulus fallowed by a depolarizing one with the data of KM-LIF model. The results conform well to the KM-LIF model with lower complexity.

1. Introduction

Dorsal cochlear nucleus neurons represent different kinds of firing patterns in response to auditory nerve stimulation (Godfrey et al. 1975; Pfeiffer1966; Rhode et al. 1983; Rhode & Smith 1986; Manis 1990; Goldberg & Brownell 2003; Street & Manis 2007). A fast transient potassium current, I_{kif}, in DCN neurons was suggested as the main factor of producing different firing patterns (Kanold & Manis 1999). The role of I_{kif} in producing such patterns was proved by a detailed ten-variable physiological model, Km model (Kanold & Manis 2000) and Later on by a reduced version of it, Km-LIF model (Meng & Rinzel 2010). The latter model confirmed the matter by isolating the primary biophysical mechanism on a three variable model.

The importance of transient potassium currents in causing various firing behaviors have been investigated by several researchers (Connor & Stevens 1971; Byrne 1980; Av-Ron 1994; Rush & Rinzel 1995; Kanold & Manis 1999; Rothman & Manis 2003). These currents mostly activate fast and inactivate slowly. The slow inactivation can cause long latencies before firing. Based on previous findings (Kanold & Manis 2000 & 2005; Meng & Rinzel 2010), applying a hyperpolarizing stimulus followed by a depolarizing one leads to long delays at start of firing. The reason is that pre hyperpolarization increases inactivation gate variables of potassium currents, and then depolarization maximizes activation gate variables. This provides enough transient potassium currents to re-polarize the membrane and not to allow membrane voltage increases, thus limits the spike

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generation mechanism. While inactivation variable decreases slowly, potassium current inactivates again and spiking is started.

For our development, we started with a reduced conductance based integrate and fire model (Meng & Rinzel 2010) and minimized it in the way that the model with minimum state variables could still represent the desired features coming next. Minimal models for their least complexity can be really useful in large-scale simulations, although they may not be able to explain all physiological aspects of a neuron. Instead, a detailed physiological model, including all neuron currents and ion channel dynamics, may justify lots of neural events but the complex dynamics makes trouble in large scale simulations.

In this study our main concerns are different firing patterns of dorsal cochlear neurons. There are three basic firing patterns related to DCN neurons listed as chopper, pauser and buildup. Consecutive spiking without a delay is called chopper pattern but spiking after a long delay is called pauser pattern. If the delay happens after the first spike, and it lengthens the first interspike interval, the firing pattern is called pauser.

During this study we generated all above patterns with our suggesting minimal model. The results compares well with those of KM-LIF & KM models (Meng & Rinzel 2010; Kanold & Manis, 2000). As mentioned in the reference (Meng & Rinzel 2010), the simulated firing properties of these models match well with both in vivo and in vitro responses (Kanold and Manis 2001; Rhode et al. 1983), thus in this article we just compare our minimal model responses with those of KM-LIF model.

2. Methods

To generate different firing patterns of DCN neurons, we started with the five-variable integrate and fire model developed by Meng and Rinzel (2010), then we made our own modifications. This conductance based model contains four currents including a transient sodium current, I_{Na}, fast and slow inactivating transient potassium currents, I_{kif} and I_{kis}, and finally a leak current, I_L. The membrane voltage equation of this model is:

$$C\frac{dv}{dt} = I_{stimulus} - g_{Na}m_{Na,\infty}(v-E_{Na}) - g_{Kif}m_f{}^4h_f(v-E_K) + g_{Kis}m_s{}^4h_s(v-E_K) - g_L(v-E_L)$$

Where g_{Na}, g_{Kif}, g_{Kis} and g_L represent ionic conductance's of the above currents and E_K, E_L and show sodium, potassium and leakage Nernst potentials respectively. For all the currents, activation gate variables are referred as m while those variables for inactivation are defined by h. Five state variables of the model are: membrane voltage, v, fast and slow inactivating potassium currents (I_{Kif} and I_{Kis}) gating variables, m_f, h_f, m_s and h_s. The detailed model dynamics has been given in the appendix A.

Time constants of these gating variables are shown in fig.1a &b. Comparing to activations, inactivation time constants are too long, which confirms fast activation and slow inactivation of I_{Kif} and I_{Kis}. Provided that transient potassium currents activate fast, the activation variables can be approximated by their steady state values. In other words m_f, m_s dynamics can be substituted by $m_{f,\infty}$, $m_{s,\infty}$, thus two state variables are reduced.

Fig 2.a shows inactivation kinetics of fast and slow transient potassium currents over time. By applying a transformation on inactivation gate of I_{Kif}, it coincides fairly well with that of I_{Kis}. We obtained by simulation the relation between both variables: $h_f(t)$, $h_s(t)$. Fig 2.b shows the transformed $h_f(t)$ coincident with $h_s(t)$. The relation between these two gating variables can be demonstrated by the following formula:

$$h_s = \sqrt[10]{h_f} + 0.6694h_f(0) - 0.6904$$

where $h_f(o)$ defines the initialization for h_f. Hence, h_s dynamics is estimated by h_f, resulting one more variable reduction. By this preparation, we developed our own model with the remaining two variables: v, h_f. the membrane voltage equation is described by:

$$C\frac{dv}{dt} = I_{stimulus} - g_{Na}m_{Na,\infty}(v-E_{Na}) - gK(v-E_K) - g_L(v-E_L)\ gK = g_{Kif}m_{f,\infty}{}^4h_f + g_{Kis}m_{s,\infty}{}^4(\sqrt[10]{h_f} - 0.16)$$

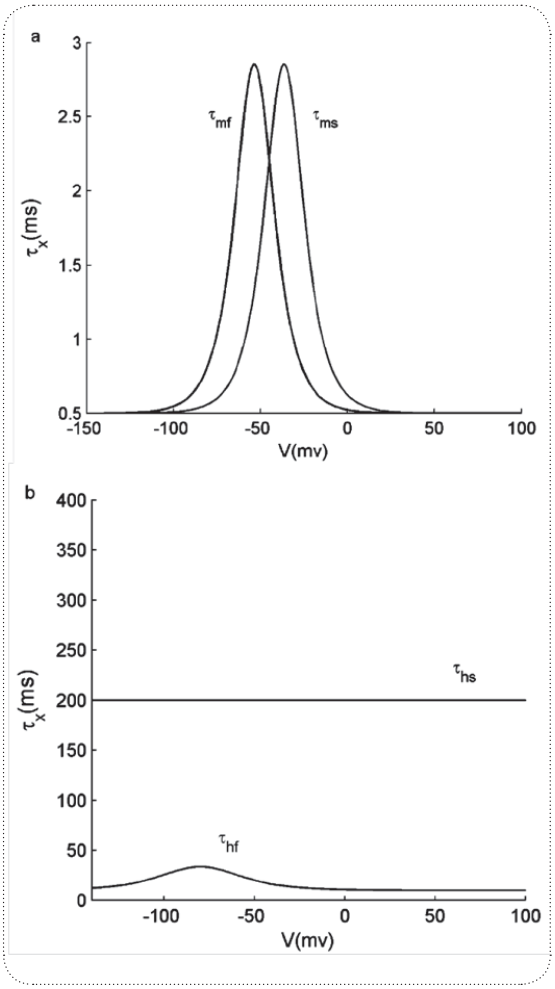

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Figure 1. transient potassium currents activation gate time constants versus voltage (a) inactivation gate time constants versus voltage (b) according to KM and KM-LIF models (Kanold &Manis, 2000; Meng&Rinzel, 2010). Different time scales in (a) and (b) show distinct difference in rate of activation and inactivation e.g 50 ms against 3 ms.

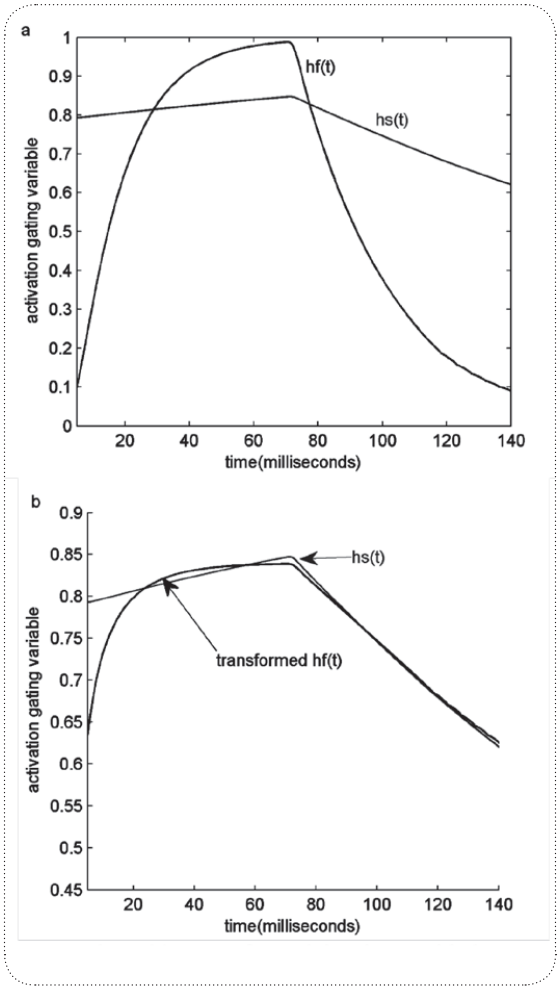

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Figure 2. hf and hs versus time (a) transformed hf along with hs versus time (b) good matching exist for transformed hf and hs after passing first 20 milliseconds of model running

all parameters are identical with those of KM and KM-LIF models (Kanold & Manis 2000; Meng & Rinzel 2010).

The detailed equations describing model dynamics are represented in appendix B.

A big difference between our methodology and what is utilized by (Meng & Rinzel, 2010) is that we assume potassium currents activate instantaneously. For this assumption we may miss the first leading spike in the same situation with KM-LIF model. The reason is that applying a depolarization after a hyperpolarizing stimulus not only deinactivates I_{Kis}, I_{Kif} immediately, but also activates I_{Na} infinitely fast since I_{Na} activation variable has also been replaced by its steady state value. It means that I_{Na} tends to depolarize the membrane and arise a spike and at the same time I_{Kis}, I_{Kif} repolarize the membrane and thus a balanced state is provided. In KM-LIF model, I_{Kis}, I_{Kif} activation time scales are assumed fast but finite, so at the exact time of applying the depolarization, I_{Na} activates and since I_{Kis}, I_{Kif} have not been activated yet, the net membrane inward current depolarizes the membrane and a leading spike arises. By I_{Kis}, I_{Kif} activation, a balanced state between all membrane currents appears showing a delay in spiking. When they inactivate again, contiguous spiking is started.

Since we ignored h_f, h_s dynamics and used their steady state values instead, we can not benefit from above hypothesis. This is the reason why we calculate I_{Na} one step before calculation of potassium currents. Next, we compare the difference between these currents in each step. If the difference increases regarding to previous steps, it means that I_{Na} has had a sudden increase and the membrane depolarization has been started. Interestingly, voltage changes over time, dv/dt can show this difference since it is sum of all the membrane currents. Thus, we measure dv/dt in each step, if it reaches a threshold, say 20; we amplify it in order to highlight the effect of depolarization before activation of potassium currents. The problem of lacking first spike is solved by this assumption. In Fig.3 you can see voltage changes versus time. An obvious change is seen at around 70th millisecond after running the model, exactly at the moment we applied the depolarization.

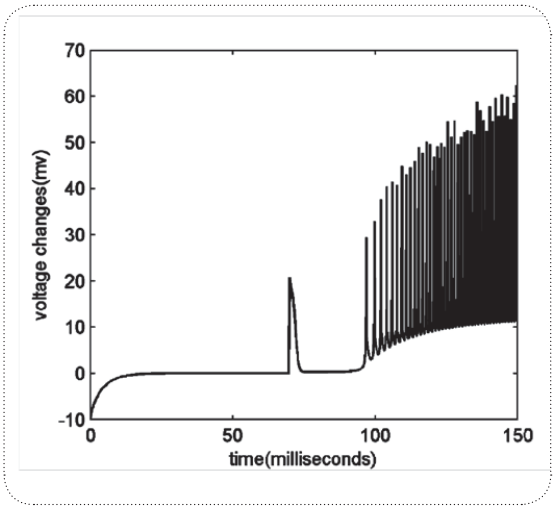

Figure 3. voltage changes over time. A great increase in amplitude is seen at time of applying depolarization.

Whenever the membrane voltage reaches to a threshold voltage, say 0 mili-volts, an action potential arises and we reset the voltage to -65 mili-volts.

All the simulations are performed using MATLAB 2008, and Euler method with step size equal to 0.01 is used for solving differential equations. Calculations were double checked by step size of 0.001 but the results were rather the same. During this study, our main concern was generating three different firing patterns of DCN neurons.

3. Results

Different firing patterns obtained from the model in response to a hyperpolarization followed by a depolarizing stimulus, show a good correspondence with three firing patterns of DCN pyramidal cells. In figure.4 firing patterns of our minimal model is compared with those of KM-LIF model under applying similar stimuli. Fig.4 (a1-a3) exhibit KM-LIF model responses to step stimuli with hyperpolarizing amplitudes of -80, -147 and -200 pA during 50 milliseconds and a post depolarization with amplitude of 130 pA. Chopper, pauser and buildup patterns are obtained, respectively. In Fig.4 (b1-b3) same patterns are generated by applying step stimuli with hyperpolarizing amplitudes of -80, -130 and -200 pA during 70 milliseconds and a post depolarization with amplitude of 130 pA to the minimal model. Applied step stimuli to the models are shown in Fig 4(a4, b4).

The resulting firing patterns match well with the DCN pyramidal cells firing patterns. In their study, Meng and Rinzel (2010) demonstrated that the delay before spiking or after the first spike is related to transient potassium currents and can be controlled by them. In fact these currents are inactivated at rest. If the membrane voltage decreases, e.g. a hyperpolarizing current applies, inactivation gating variables, h_f , h_s increases. Then, with some depolarizing current, I_{Kif}, I_{Kis} activate fast and in balance with other membrane currents make a long delay. Since I_{Kif}, I_{Kis} inactivations are slow, this delay lasts until inactivation variables, h_f, h_s , fall below a specific point. Then they inactivate again and regular firing is started. Stronger or longer hyperpolarizations leads to more deinactivation of I_{Kif}, I_{Kis}.

In Fig.5 we show the dependency of first spike latency, FSL, and first inter-spike interval, FISI, to the strength of pre hyperpolarization. Our results match well with the data of KM-LIF model. This figure shows the FISI and FSL duration versus pre hyperpolarization. When prehyperpolarized voltage is weak, these values are low since there is no delay or latency, but stronger hyperpolarization causes these values change suddenly. Fig.5 (a1-a3) shows the dependency of FISI and FSL extracted from KM-LIF model to the pre hyperpolarized voltage while following depolarizing currents are 70, 120, 160, respectively. In Fig.5 (b1- b3), the minimal model FSL and FISI dependency to preset voltage is also shown when depolarizing currents are 100, 150, 200. When hyperpolarization is weak, all the figures show chopper pattern but when hyperpolarization is stronger, depend on the depolarizing current, the firing pattern change into pauser or build-up.

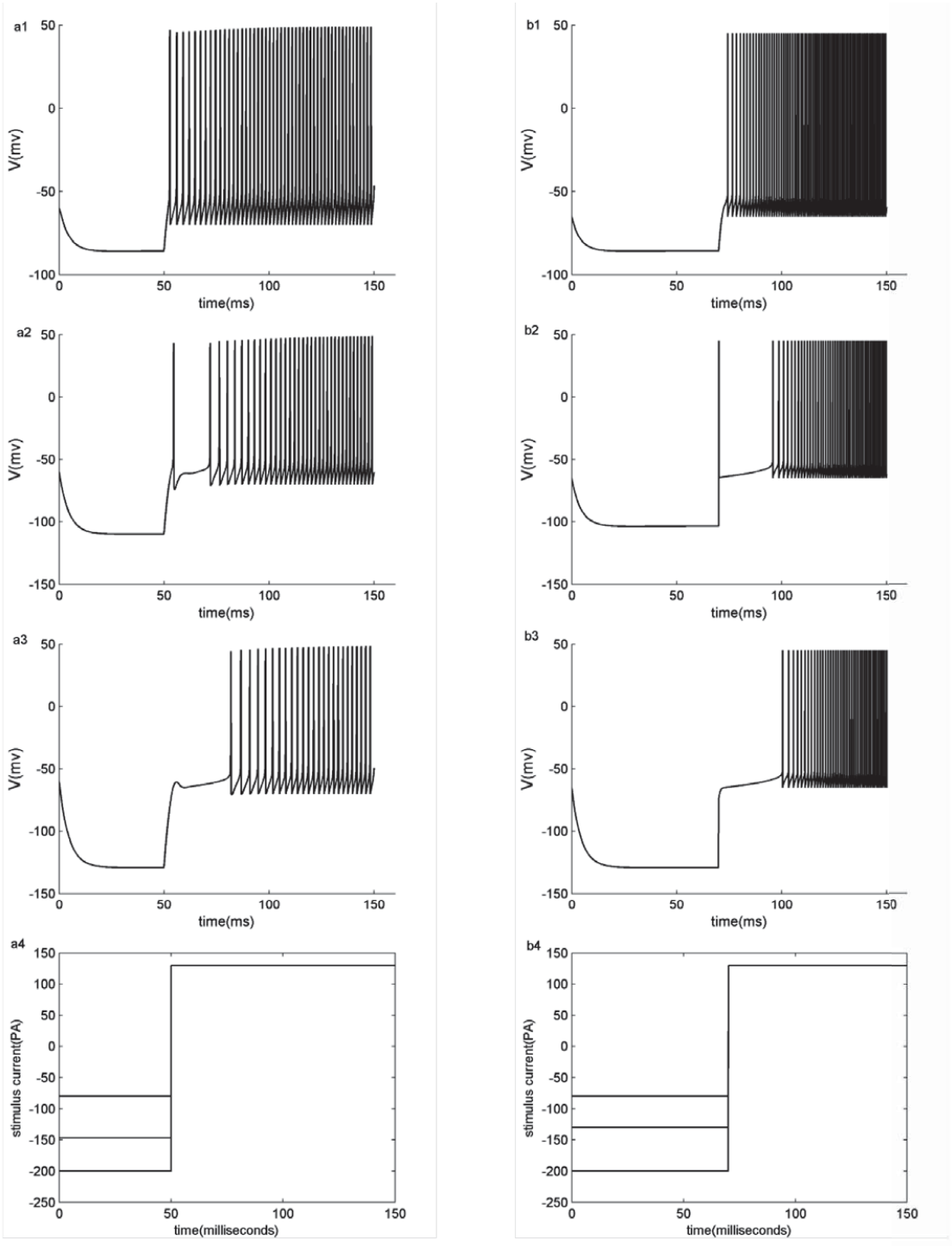

Figure 4. Different firing patterns of KM-LIF model(a1-a3) and firing patterns of the minimal model(b1-b3) in response to three different levels of hyperpolarizing currents followed by a depolarization (a4, b4) chopper pattern is generated by applying -80 pA hyperpolarizing current(a1,b1) pauser pattern is generated by applying -147 pA hyperpolarizing to KM-LIF model and -130 pA to the minimal model(a2, b2) and buildup pattern is generated by applying -200 pA hyperpolarizing current(a3, b3). Different levels of hyperpolarization applied to both models are all preceding a 130 pA depolarizing current (a4, b4).

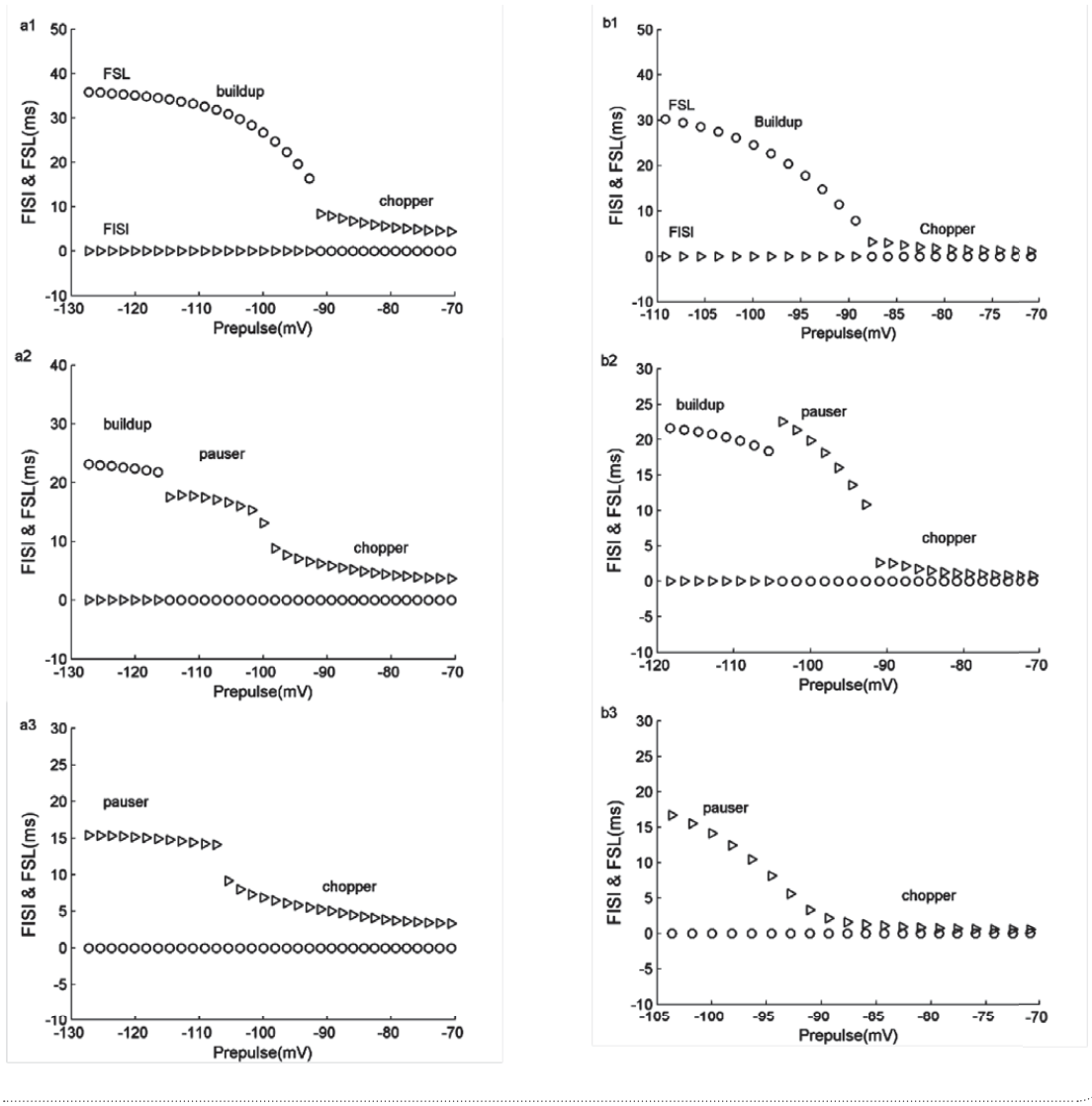

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Figure 5. FISI and FSL of KM-LIF model versus hyperpolarizations prior to different depolarizing currents: 70, 120,160 (a1-a3). FSL and FISI of the minimal model versus hyperpolarizations prior to different depolarizing currents: 100, 150, 200 (b1-b3). Sudden change in FISI and FSL represents pattern changing. Circles represent FSLs and triangles show FISIs.

Fig.6.a shows I_{Kif}, inactivation variable changes over the time. The more it hyperpolarizes, the more h_f increases.

Fig.6b exhibits the effect of depolarizing current, I0 on h_f changes. Each point represents the value of h_f during a spike. If we look into h_f decreasing path from right to left for a specific I0, we can see the distance between two adjacent spots is large at the beginning. While we approach to the left, the distance becomes smaller, i.e. h_f rarely changes among two adjacent spikes, presenting fast spiking. For the currents less than 20 pA, no spike fires unless h_f decreases to very low values because such current can hardly depolarize the membrane and arise a spike, so a long delay happens and buildup pattern forms. If the current increases more than 300 pA, no matter what pre hyperpolarization is the model fires continuously and generates chopper pattern. Large number of spots on the left side of the figure confirms that. When the current value is between 15 to 300 pA, depend on h_f initialization, pauser pattern or chopper may occur. This trend can also explain sudden changes

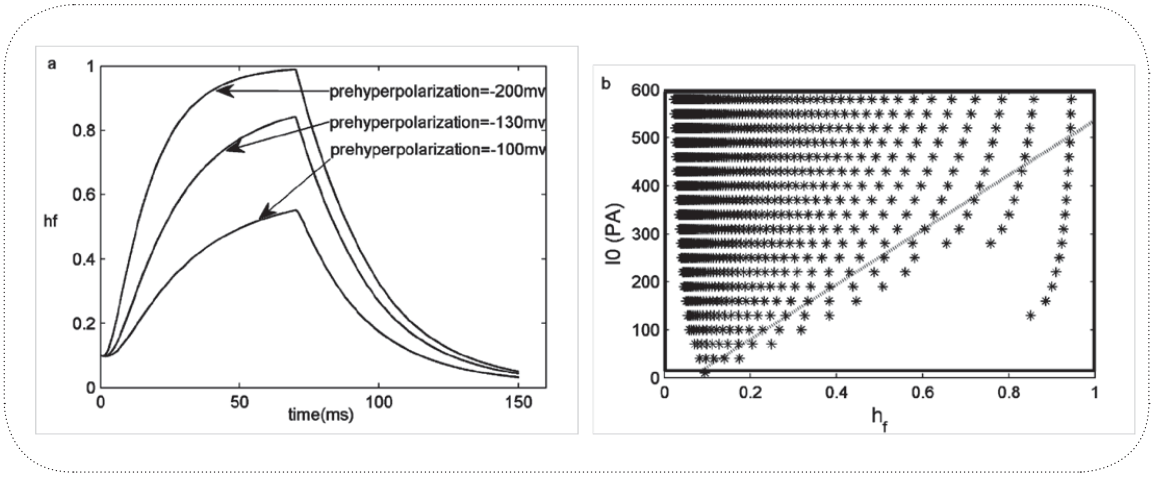

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Figure 6. Changes of hf over time (a). By applying stronger pre hyperpolarization, hf approaches the maximum, and more IKif deinactivates. The relation of hf changes with depolarizing current (b). Each point shows the value of hf during a spike. For a specified depolarizing current, hf starts from a value near 1, and then decreases gradually. When hf decreases enough, fast spiking is started. Large number of spots in the left triangle represents large number of spikes.

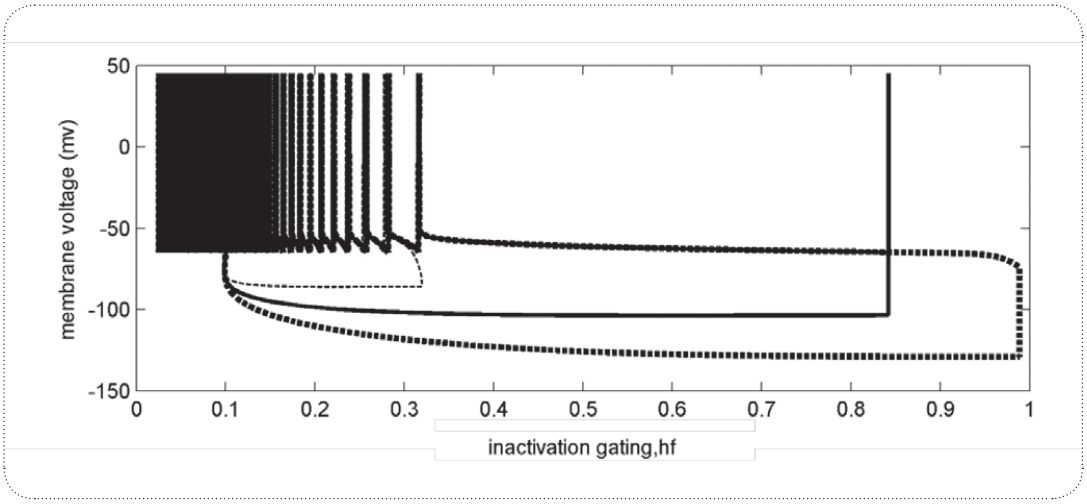

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Figure 7. three responses with different initialization versus hf. Different firing patterns is related to the value of hf at depolarization time. Low hf results in chopper pattern (thin dashed trend) but larger values result in pauser and buildup patterns (solid black and thick dashed trends).

of FSL and FISI in figure 5. When h_f starts from the right triangle, delay of spiking is high, thus FSL or FISI is rather high, but if h_f starts from left triangle, firing continues regularly and thus FISI and FSL would be low.

Fig7 shows three different responses of the minimal model versus h_f changes. The initialization for all responses is (h_f=0.1,v =-65) representing the rest conditions. Start from this point, the trends move forward to the direction of h_f increase. This forward movement goes on where hyperpolarization stops, and then by applying a depolarization, membrane voltage increases. Depend on the value of h_f, different firing patterns may occur. An example of weak pre hyperpolarization in this figure brings h_f to about 0.3. This value is not enough to deinactivate I_{Kif}, so applying depolarization increases membrane voltage and spiking starts with no delay -chopper pattern (thin dashed trend). When pre hyperpolarization is stronger, h_f increases more, e.g. goes to 0.85 or 0.98 in this figure. Depend on how much I_{Kif}

deinactivates, a leading spike may fire or not. However, we would have a long delay before h_t returns to low values. Then regular spiking starts - pauser or buildup pattern (solid black and thick dashed trends respectively)

4. Discussion

In this study, a minimal model of two variables has been presented for simulation of DCN pyramidal cells firing profiles. This model uses fast activation and slow inactivation properties of the transient potassium currents to generate different patterns. The responses conform well to the firing profiles of KM-LIF model and thus of DCN neurons.

The stimuli applied to this model have a hyperpolarizing part followed by a depolarizing part. Depend on the value of stimulus in each part; the model represents the following behaviors:

1) If the hyperpolarization is low and depolarization is high, the model would start firing regularly. This firing pattern is called chopper.

2) If the hyperpolarization is rather high and depolarization is also high, a leading spike may occur and after a long delay the model will start firing continuously. This firing pattern is called pauser.

3) If the hyperpolarization is too high and depolarization is rather low, the firing pattern would fire after a long latency. This pattern is called buildup.

Appendix A:

The equations describing KM-LIF model dynamics are as follows:

$$C\frac{dv}{dt} = I_{stimulus} - g_{Na}m_{Na,\infty}(v-E_{Na}) - g_{Klf}m_f^{\,4}h_f(v-E_K) + g_{Kls}m_s^{\,4}h_s(v-E_K) - g_L(v-E_L)$$

$$\frac{dm_f}{dt} = \frac{m_{f,\infty}(v)-m_f}{\tau_{mf}(v)}$$

$$\frac{dh_f}{dt} = \frac{h_{f,\infty}(v)-h_f}{\tau_{hf}(v)}$$

$$\frac{dh_s}{dt} = \frac{h_{s,\infty}(v)-h_s}{\tau_{hs}(v)}$$

$$m_{Na,\infty} = \frac{1}{1+\exp(-\frac{v_{mNa,1/2}-v}{k_{mNa}})}$$

$$m_{f,\infty} = \frac{1}{1+\exp(-\frac{v_{mf,1/2}-v}{k_{mf}})}$$

$$h_{f,\infty} = \frac{1}{1+\exp(-\frac{v_{hf,1/2}-v}{k_{hf}})}$$

$$m_{s,\infty} = \frac{1}{1+\exp(-\frac{v_{ms,1/2}-v}{k_{ms}})}$$

$$h_{s,\infty} = \frac{1}{1+\exp(-\frac{v_{hs,1/2}-v}{k_{hs}})}$$

$$\tau_{mf}(v) = \frac{1}{0.15\exp(\frac{v+87}{10}) + 0.3\exp(-\frac{v+57}{10}) + 0.5}$$

$$\tau_{hf}(v) = \frac{1}{0.15\exp(\frac{v+87}{20}) + 0.03\exp(-\frac{v+87}{20}) + 10}$$

$$\tau_{hs}(v) = 200$$

In this model, the parameters default values are as:

$$v_{1/2,mNa} = -38,\ v_{1/2,mf} - 53,\ v_{1/2,ms} = -40.9,\ v_{1/2,hf} = -89.6 \text{ و } v_{1/2,hs} = -38.4$$
$$k_{mNa} = -3,\ k_{mf} = -25.8,\ k_{ms} = -23.7,\ k_{hf} = 6.5,\ k_{hs} = 9$$
$$g_{Na} = 350, g_{Kif} = 450, g_{Kis} = 40, g_L = 2.8$$

Appendix B

The equations describing the minimal two-variable model dynamics are as follows:

$$C\frac{dv}{dt} = I_{stimulus} - g_{Na} m_{Na,\infty}(v - E_{Na}) - gK(v - E_K) - g_L(v - E_L)$$
$$gK = g_{Kif} m_{f,\infty}{}^4 h_f + g_{Kis} m_{s,\infty}{}^4 (\sqrt[10]{h_f} - 0.16)$$

$$\frac{dh_f}{dt} = \frac{h_{f,\infty}(v) - h_f}{\tau_{hf}(v)}$$
$$m_{Na,\infty} = \frac{1}{1 + \exp(-\frac{v_{mNa,1/2} - v}{k_{mNa}})}$$
$$m_{f,\infty} = \frac{1}{1 + \exp(-\frac{v_{mf,1/2} - v}{k_{mf}})}$$
$$m_{s,\infty} = \frac{1}{1 + \exp(-\frac{v_{ms,1/2} - v}{k_{ms}})}$$

Where all parameters are identical with those of KM-LIF model in appendix A.

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