Phasic, tonic, and mixed mode firing of an auditory neuron model – bifurcation analysis

Ramana Dodla* and John Rinzel*†

*Center for Neural Science, New York University, New York, NY 10003

†Courant Institute of Mathematical Sciences, New York University, New York, NY 10012

Abstract

Temporal processing, such as coincidence detection, on sub-msec time scales by auditory brain stem neurons is enhanced by a low-threshold potassium current (I_{KLT}). I_{KLT} also helps to make the neurons (e.g. in the medial superior olive, MSO) fire phasically rather than tonically. In response to a step of current (I_{app}) MSO cells typically fire a single spike at stimulus onset but not tonically for the maintained current or for a slow ramp of I_{app}. We have studied the response properties of an HH-like model [Rothman et al., 1993] that incorporates an I_{KLT}. The model shows phasic behavior over a large range of parameters. But for reduced I_{KLT} strength tonic firing is elicited by an adequate step of I_{app}. Curiously, the model does not fire if I_{app} is very slowly ramped through this entire range of I_{app}. The behavior is explained by using bifurcation theory: the rest state is stable for all I_{app} but there is a coexistent limit cycle for some I_{app} range. This mixed mode behavior leads to spike patterns that appear bursty (with high CV) when the model is driven periodically in the presence of noise. [Support contributed by: NIH/NIMH MH62595-01]

1 Introduction

Low threshold potassium currents (I_{KLT}) are believed to play an important role in sound localization mechanisms, such as coincidence detection, and firing properties of auditory neurons in the medial superior olive (MSO) [Rothman et al., 1993, Brand et al., 2002, Svirskis et al., 2002, Rothman and Manis, 2002]. Most MSO neurons fire phasically, just one or a few action potentials in response to a current step. Blocking I_{KLT} can lead to repetitive firing (e.g., [Svirskis et al., 2002]). Here we study an MSO neuronal model consisting of sodium, potassium, and a low-threshold potassium current using bifurcation analysis, and we show that depending on the strength of I_{KLT} the membrane exhibits one of three principally distinct firing modes: a pure phasic mode, where the membrane responds to a depolarizing current step with one or a few spikes at the onset but eventually settles to a stable steady voltage; a pure tonic mode, where the membrane fires repetitively in response to a step of positive current or a slow ramp of current; and a mixed mode, where the membrane fires tonically in response to a current step, but does not fire repetitively if the current is slowly ramped upward. The model's pure tonic firing behavior is characterized by a linear instability of the steady state, and existence of a stable limit cycle that is borne out of subcritical Hopf bifurcation; this occurs at enhanced values of sodium and potassium peak conductances and reduced G_{KLT} (peak conductance of I_{KLT}). The mixed mode firing state is associated with the existence of an isola (an isolated branch of periodic solutions coexistent with a stable steady state), occurring at smaller G_{KLT} values. The pure phasic firing mode is characterized by a linearly stable steady state being the only attractor.

Coincidence detecting neurons receive frequency modulated stochastic inputs. As a first step in understanding the role of the three firing modes in determining the response properties of the cell under such a stochastic stimulus, we next study the cell's behavior at different G_{KLT} values by presenting it with an excitatory synaptic current that included a deterministic component with a fixed stimulus frequency and a small random background component. At large G_{KLT} values when the model shows a stable rest state alone, the firing of the cell is strongly locked to the driving frequency. As G_{KLT} is lowered, integration becomes less precise and more temporal summation of inputs occurs, thus the firing rate increases above the driving frequency. As G_{KLT} begins to fall in the isola region, the residency time of the cell in the rest state increases and the firing resembles bursting, random switching between phases of spiking and not spiking. First we present the model equations in the next section followed by a summary of the results.

2 Methods

The model studied here incorporates three voltage dependent Hodgkin-Huxley like gating currents: sodium (I_{Na}), delayed rectifier (I_K), and a low-threshold potassium (I_{KLT}) current. This model was earlier constructed by [Rothman et al., 1993] for a theoretical study of the experimental finding in bushy cells of ventral cochlear nucleus. The membrane potential evolves according to:

$$C_m \frac{dV}{dt} = I_{app} - I_{Na} - I_K - I_{KLT} - I_L - I_{syn}, \tag{1}$$

where C_m is the membrane capacitance(= 23 pF), and I_{app} is the externally applied steady current. $I_{Na} = G_{Na} m^2 h(V - E_{Na})$, $I_K = G_K n(V - E_K)$, $I_{KLT} = G_{KLT} w(V - E_K)$, $I_L = G_L(V - E_L)$, and $I_{syn} = [10(t'/0.3)\exp(1 - t'/0.3) + \eta(t)](V - E_{exc})$. m, n, and w are the activation variables of Na^+, K^+, and KLT. h is the inactivation variable of Na^+. The gating variables evolve according to $dx/dt = \alpha_x(1 - x) - \beta_x x$, $x = m, h, n$, and w. We refer to [Rothman et al., 1993] for the functional forms of α_x and β_x. The reversal potentials are $E_{Na} = 55$ mV, $E_K = -77$ mV, $E_L = 2.8$ mV, and $E_{exc} = -10$ mV. The peak conductances, when not varied in the bifurcation diagrams, are $G_{Na} = 985.2$ nS, $G_K = 173.3$ nS, $G_{KLT} = 86.6$ mV, and $G_L = 5.2$ mV. The three firing patterns presented in Fig. 1 are studied for steps and ramps of I_{app}. The bifurcation diagrams shown in Fig. 2 are studied as a continuous function of I_{app}. Synaptic current is used only in Fig. 3 where $I_{app} = 0$. The arrival times t' in the alpha-function are determined by a periodic stimulus with a frequency of 100 Hz. $\eta(t)$ is a subthreshold, random noise.

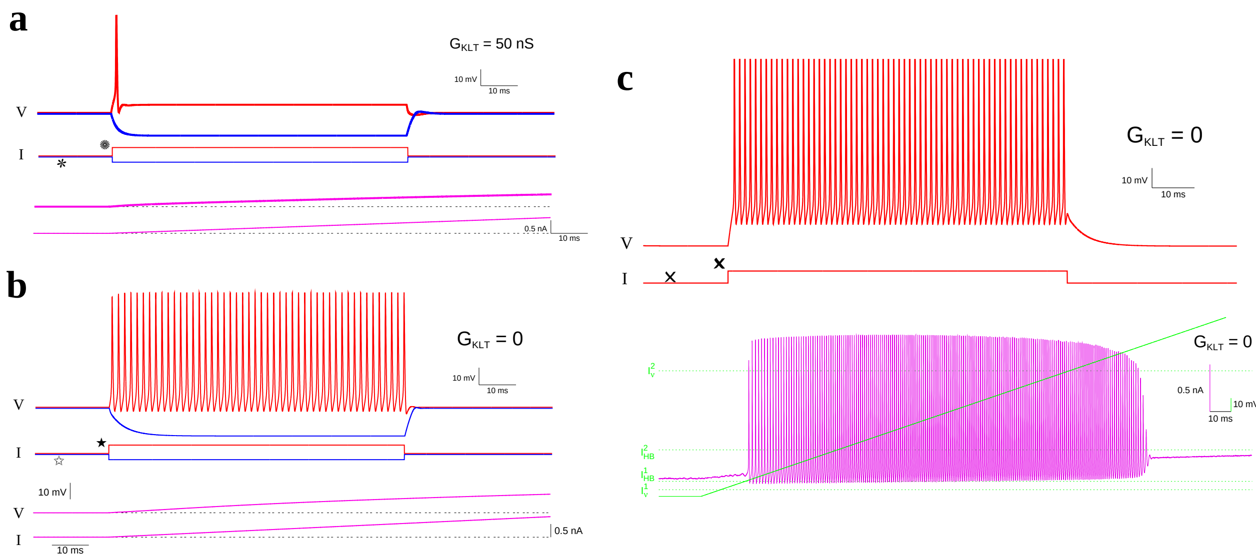

Figure 1: (a) Phasic mode. Voltage response of the membrane for a step and ramp of current. (b) Mixed mode. Voltage response for a step of current yielding repetitive firing, and no repetitive firing for a slow ramp of current. (c) Tonic mode. Repetitive firing for both step of current and ramp of current. For (a) and (b) $G_{Na} = 985.2$ nS, and $G_K = 173.3$ nS (control case). For (c) $G_{Na} = 3000$ nS, and $G_K = 250$ nS (enhanced case).

3 Results

Figure 1 displays the three kinds of firing patterns exhibited by the model. Fig. 1a shows the voltage response for a step of positive, and negative currents. A single spike is evoked at the onset of the positive step of current. (The negative step of current hyperpolarizes the membrane, and upon releasing the current, the present model does not evoke the classical postinhibitory rebound.) On the contrary, a slow ramp of current evokes no spike. This is the behavior of a cell in "phasic mode" of firing. When the low-threshold potassium (G_{KLT}) is blocked (Fig. 1b), the cell shows mixed-mode behavior. It can fire tonically or phasically depending on the kind of input current: For a positive step of current the cell fires repetitively, where as for a slow ramp of current, it fails to evoke a spike. With G_{KLT} blocked an enhancement of sodium and potassium conductances can lead the cell to a pure tonic mode (Fig. 1c), where the cell fires repetitively for both a step of positive current as well as for a slow ramp of current.

We explain these different firing modes as a function of the applied current using bifurcation analysis, first when G_{KLT} is blocked. Then we will present the full phase diagram in the plane of applied current and G_{KLT}. First note that evoking one or more spikes in response to a step of current is a transient phenomenon of the model equations, and finding linear stability of the eventual steady state determines the stability of the phasic mode of firing. Figure 2a shows this steady state as a function of I_{app}, and this state is stable (SFP) for all applied currents. It also shows a stable (SPO) and an unstable periodic orbit (UPO) for applied currents between -0.1 nA and 0.2 nA in the form of an isola, an orbit that is disjoined from the steady state branch. For applied currents

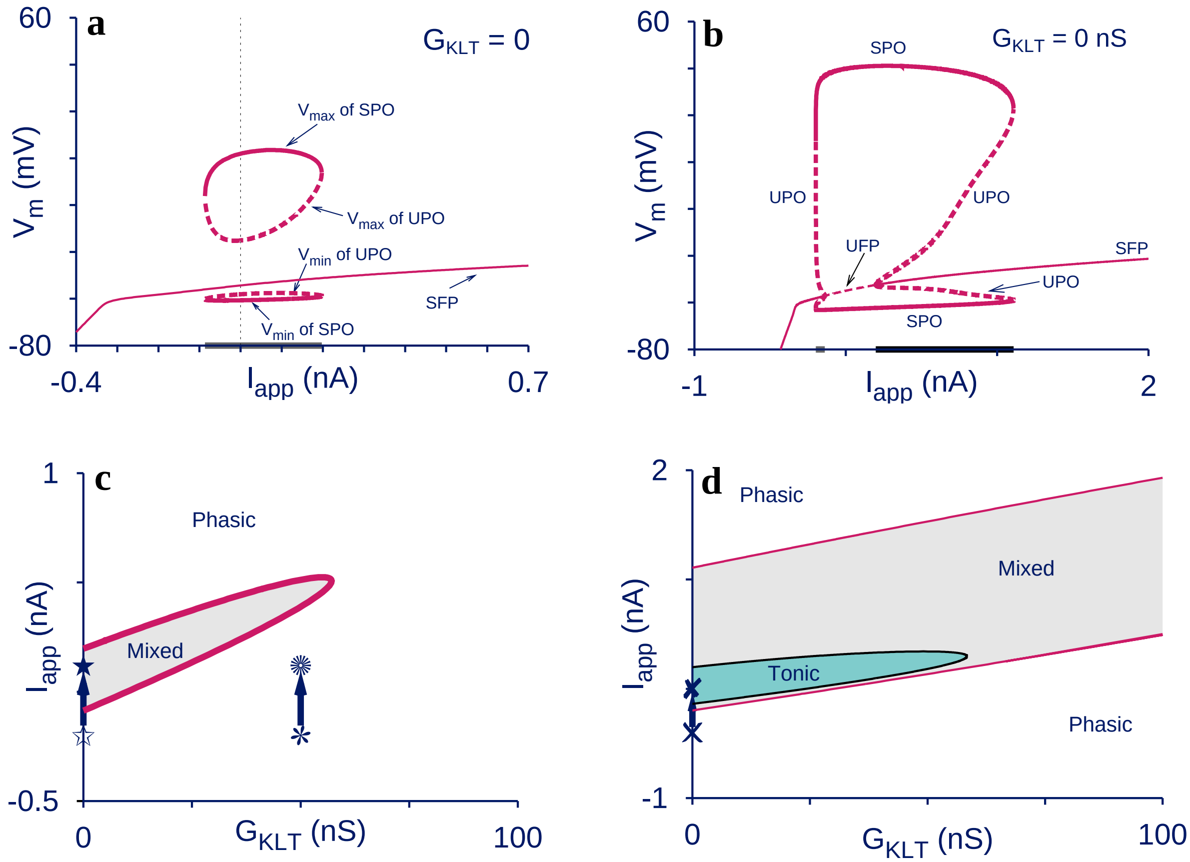

Figure 2: (a) Bifurcation diagram showing stable fixed point for all I_{app}, and isola for small values (control case); corresponds to Fig. 1b. (b) Bifurcation diagram showing subcritical Hopf bifurcation (enhanced case); corresponds to pure tonic case of Fig. 1c. (c) Phase diagram under control case in (G_{KLT}, I_{app}) plane exhibiting phasic and mixed modes. Symbols and arrows correspond to current steps in Figs. 1a,b. (d) Phase diagram under enhanced case exhibiting phasic, tonic, and mixed modes. Symbols and arrow correspond to current steps in Fig. 1c.

that fall inside the isola region, the cell can show either repetitive firing with a frequency equal to that of the stable periodic orbit, or it can show phasic firing, depending on the current's history. If I_{app} is increased in a slow ramp from a value that falls outside the isola region to a value that is inside, the cell's voltage slowly depolarizes (perhaps with an onset spike), showing phasic behavior. On the other hand, if the current is given as a step, the cell can fire repetitively.

For enhanced values of sodium and potassium currents (Fig. 2b), the bifurcation diagram reveals the underlying subcritical bifurcations along the fixed point branch seen in Fig. 2a. In addition to the coexistence regions of stable fixed point and stable periodic orbits that we saw in Fig. 2a, we also have a purely tonic state where the fixed point is unstable (UFP) and the periodic orbit is stable. For I_{app} falling in this region, the cell can only fire repetitively (pure tonic state). These two figures so far showed the bifurcations as a function of I_{app} when G_{KLT} is blocked. Figure 2c (for control levels of sodium and

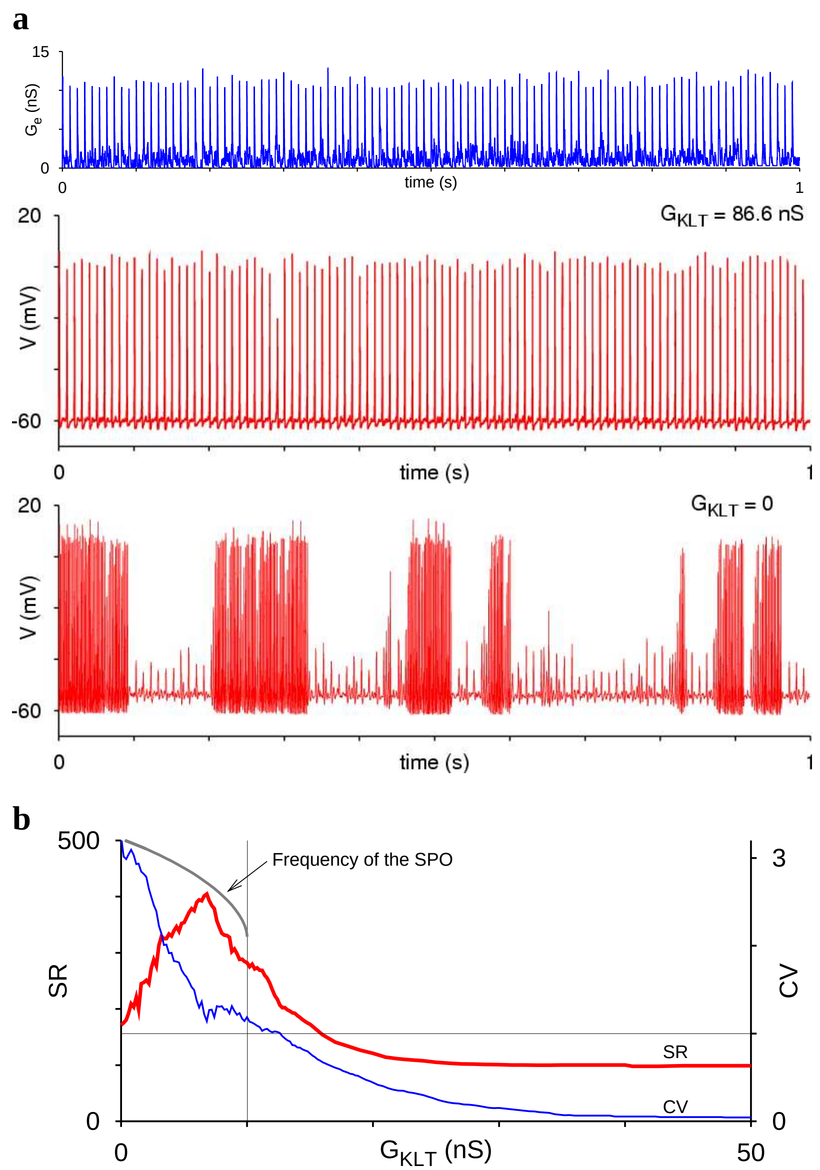

Figure 3: (a) Top: A 100 Hz alpha-function (with a peak value of 10 and time constant of 0.3 ms) synaptic conductance with an over-riding noise applied to the membrane. Middle: Membrane response in the phasic mode with frequency locking to the synaptic input. Bottom: Membrane response in the mixed mode showing bursty behavior with long residency times in the rest state. (b) Spike rate (SR) and coefficient of variation (CV) as a function of G_{KLT}. The vertical line separates the G_{KLT} parameter regime of mixed mode (left side) from the phasic mode (right side). The frequency of the stable periodic orbit (SPO) in the mixed mode is also shown.

potassium currents), and Fig. 2d (for enhanced values) display the full phase diagrams for the two bifurcation diagrams shown, respectively, in Fig. 2a and Fig. 2b.

So far we have seen that by an appropriate choice of G_{KLT} the membrane can exhibit three kinds of firing modes. We now explore the effect of a periodic excitatory synaptic input (that has a high frequency overriding noise) on the spike rate and coefficient of variation as we vary G_{KLT} in such a way that a transition is made between phasic and mixed modes. The upper record in Fig. 3a shows the synaptic conductance applied to the membrane in the absence of any steady currents. The second and third records show, respectively, the membrane responses in the phasic and mixed modes. Figure 3b shows the spike rate (SR) and coefficient of variation (CV) as a function of G_{KLT}. The residency time of the membrane in the rest state has increased in the isola region (smaller G_{KLT}). This time, however, also changes with the noise term $\eta(t)$ that we have introduced in the synaptic term. Within the numerical accuracy, the CV is below 1 when G_{KLT} is in the phasic mode, and it is above 1 when G_{KLT} begins to fall in the isola region.

4 Conclusions

We have shown that an MSO neuronal model exhibits three distinct firing modes for externally applied currents: pure phasic, pure tonic, and mixed modes. The bifurcation analysis reveals that an isola exists for weak G_{KLT} and the corresponding periodic orbit can merge with the stable fixed point in a subcritical Hopf bifurcation at enhanced values of sodium and potassium conductances. For adequate G_{KLT} usually phasic mode prevails. As G_{KLT} is lowered, or blocked, mixed and pure tonic modes can be reached. In the mixed mode regime the cell responds to periodic excitatory synapse with a firing pattern that resembles random bursting making the residency time of the cell in the rest state longer.

The present results may have interesting implications in the coincidence detection mechanism. Recently this model was used to study the experimental findings of coincidence detection in gerbils by [Brand et al., 2002]. Their choice of G_{KLT} was 86.6 nS, and the cell, according to our present results, was in phasic mode. As a future study, we are planning to explore the parameter regime that shows the other two firing modes.

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