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Influence of subthreshold nonlinearities on signal-to-noise ratio and timing precision for small signals in neurons: minimal model analysis

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Abstract

Subthreshold voltage- and time-dependent conductances can subserve different roles in signal integration and action potential generation. Here, we use minimal models to demonstrate how a non-inactivating low-threshold outward current (I_{KLT}) can enhance the precision of small-signal integration. Our integrate-and-fire models have only a few biophysical parameters, enabling a parametric study of I_{KLT} 's effects. I_{KLT} increases the signal-to-noise ratio (SNR) for firing when a subthreshold 'signal' EPSP is delivered in the presence of weak random input. The increased SNR is due to the suppression of spontaneous firings to random input. In accordance, SNR grows as the EPSP amplitude increases. SNR also grows as the unitary synaptic current's time constant increases, leading to more effective suppression of spontaneous activity. Spike-triggered reverse correlation of the injected current indicates that, to reach spike threshold, a cell with I_{KLT} requires a briefer time course of injected current. Consistent with this narrowed integration time window, I_{KLT} enhances phase-locking, measured as vector strength, to a weak noisy and periodically modulated stimulus. Thus subthreshold negative feedback mediated by I_{KLT} enhances temporal processing. An alternative suppression mechanism is voltage- and time-dependent inactivation of a low-threshold inward current. This feature in an integrate-and-fire model also shows SNR enhancement, in comparison with a case when the inward current is non-inactivating. Small-signal detection can be significantly improved in noisy neuronal systems by subthreshold negative feedback, serving to suppress false positives.

1. Introduction

Neurons possess multiple voltage-dependent channels, which define their functional response properties by participating in the integration of synaptic input (Llinas 1988). Some mixtures of currents render cells suitable for rate coding by enabling them to vary their firing rate smoothly as stimulus intensity varies. In other cases where temporal coding and spike timing matter a cell might have currents that assist in fast resetting after a spike (Softky and Koch 1993, Wang *et al* 1998) or that enhance responsiveness to sudden changes but not to slow changes in the stimulus, i.e. that make the cell fire phasically. For example, in the auditory system, where temporal precision is important at peripheral stages (Trussell 1999), many cell types have phasic firing properties. Spherical bushy cells and octopus cells in the cochlear nucleus and medial superior olive (MSO) neurons (and their homologues in the avian system) respond only with a single spike to a current step stimulus (Oertel 1983, Carr and Konishi 1990, Reyes *et al* 1996). This phasic firing behaviour has been attributed to a fast-activating potassium current, I_{KLT} (Manis and Marx 1991, Reyes *et al* 1994, Smith 1995, Bal and Oertel 2001), that turns on below the spike threshold. Inputs that are faster

than the activation rate of I_{KLT} can lead to a spike but slower inputs will be filtered out, suppressed by I_{KLT} ; this current endows the neuron with high-pass filter properties. Other examples of neural systems where phasic firing depends on potassium currents that are recruitable at modest depolarization include trigeminal sensory-motor (DelNegro and Chandler 1997) and even squid giant axon which does not typically fire in tonic mode (Clay 1998). Here, we take the auditory examples as motivational for exploring the effects of I_{KLT} and more generally of fast subthreshold negative feedback on integration of synaptic inputs.

Exactly how phasic firing relates to temporally precise integration is unclear. It has been seen in experimental and modelling studies that I_{KLT} enhances the ability of auditory neurons to synchronize (phase lock) to sinusoidal stimuli (Rothman and Young 1996, Reyes *et al* 1996, Cai *et al* 2000). Moreover, coincidence detection, that subserves an important role in sound localization, is degraded at the cellular level if I_{KLT} is blocked (Reyes *et al* 1996). While such studies of input/output properties have usually considered strong suprathreshold stimuli it seems natural to ask how a current like I_{KLT} , that activates below the spike threshold, influences the integration and detection of subthreshold stimuli. This is particularly relevant in sensory systems where in early stages of processing there is a high level of spontaneous firing which would lead to significant background random synaptic input in target neurons. For example, in the absence of a sound stimulus the random firing in the auditory nerve can reach rates of several hundred hertz (Lieberman 1978, 1982). One wonders how the phasic firing property or I_{KLT} might deal with this noisy background in neurons that seem specialized for precision in phase-locking, coincidence detection or temporal processing generally. It is possible that in these sensory systems noise can play a facilitatory role in small-signal detection as reported in many natural and artificial systems (Wiesenfeld and Moss 1995, Bezrukov and Vodyanoy 1995).

We recently explored these issues for MSO neurons both experimentally (gerbil, *in vitro*) and computationally with a Hodgkin-Huxley model that included I_{KLT} (Svirskis *et al* 2002). We presented our neurons and models with an identified weak excitatory 'signal' synaptic input in the presence of background noisy input. The presence of I_{KLT} significantly increased the signal-to-noise ratio (SNR), defined as the ratio of increased probability to fire in the presence of the 'signal' EPSP and the probability of firing spontaneously. I_{KLT} also improved phase-locking, using vector strength as a measure of quality. The essential mechanism for I_{KLT} 's effects is that it strongly reduces the rate of spontaneous firings—it filters out some of the summated but not exactly coincident weak random inputs that might have led to a 'spurious' spike. On the other hand, due to time-dependent activation of I_{KLT} , it still allows a fast coincident subthreshold 'signal' aided by noise to break through and possibly cause the cell to fire. Thus, I_{KLT} only mildly influences the response to weak fast signals if its activation time constant is of the same order as the decay time constant of an excitatory postsynaptic current (EPSC).

Here, we demonstrate and extend the generality of our findings by formulating and analysing computationally minimal models, of the leaky integrate-and-fire (LIF) type, that exhibit similar characteristics. We show the improvement in SNR and phase-locking, as well as in coincidence detection, by incorporating a qualitative analogue of I_{KLT} into an LIF model. This idealization, with only a few biophysical parameters, enables us to identify key parameters needed to observe the improvement of small-signal integration. Further reaching for generality, we consider another LIF model with an instantaneously activating subthreshold inward current that inactivates on a fast timescale. This model also shows an improved SNR when compared with the case when inactivation is removed. Our results suggest that a general mechanism of subthreshold dynamic negative feedback is responsible for improvement of weak-signal integration by suppressing false positives.

2. Model formulation and methods

We use a single-compartment leaky integrate-and-fire neuron model with a time-dependent piecewise-linear, membrane current–voltage (I – V) relation. Such time-dependent models were used previously to study response properties of nonlinear neuronal models (Svirskis *et al* 1998, Baginskas *et al* 1999). The membrane potential (deviation from rest) V and activation variable n for the low-threshold outward current I_{KLT} satisfy the following equations:

$$CdV/dt = -G_m V - G_{KLT} n (V - V_{Th-KLT}) + I(t) / A_{cell},$$

$$dn/dt = \alpha_n(V)(1 - n) - \beta_n(V)n,$$

where G_m and G_{KLT} are the membrane conductances for leakage and I_{KLT} ; $I(t)$ is the stimulus current, and A_{cell} is the model cell's area. To model the activation of I_{KLT} the net slope of the membrane's I – V changed with time due to the dynamics of the gating variable n (see figure 1(A)). For this we used $\alpha_n(V) = \alpha_0 H(V - V_{Th-KLT})$ and $\beta_n(V) = \beta_0 [1 - H(V - V_{Th-KLT})]$, where $H(x)$ denotes the Heaviside step function: $H=1$ for $x \geq 0$ and $H=0$ otherwise. With $1/\alpha_0 = \tau_{KLT} = 2$ ms, the slope of the I – V characteristic increased with an exponential time constant τ_{KLT} toward a maximum of $G_m + G_{KLT}$ when the membrane potential exceeded $V_{Th-KLT} = 7.5$ mV. With β_0 large the slope returned to its initial value essentially instantaneously if the potential dropped below V_{Th-KLT} , i.e. for implementation we set $n = 0$ instantaneously when V dropped below V_{Th-KLT} . In simulations $G_{KLT} = 3G_m$ for the LIF- I_{KLT} model and the same calculations were repeated for comparison in the LIF model, where $G_{KLT} = 0$.

To simulate an inactivating inward current (figure 4(A)), we used a similar model but with two separate thresholds, $V_{Th-Inw} = 7.5$ mV for very fast activation and $V_{Th-Inact} = 2.5$ mV for the inactivation variable h :

$$CdV/dt = -G_m V + G_{Inw} m_\infty(V) h (V - V_{Th-Inw}) + I(t) / A_{cell},$$

$$dh/dt = \alpha_h(V)(1 - h) - \beta_h(V)h,$$

where G_{Inw} is the maximal conductance for the inward current; V_{Th-Inw} is the threshold for fast activation of the inward current; $m_\infty(V) = H(V - V_{Th-Inw})$ represents instantaneous and sharp activation of the inward current. To implement the inactivation we used $\alpha_h(V) = \alpha_{h0} [1 - H(V - V_{Th-Inact})]$ and $\beta_h(V) = \beta_{h0} H(V - V_{Th-Inact})$. With $1/\beta_{h0} = \tau_{inact} = 2$ ms the net slope of the I – V relation exponentially approaches the value G_m . For large α_{h0} the deinactivation is instantaneous if the potential value becomes less than $V_{Th-Inact}$. In all simulations $G_{Inw} = 3G_m$. For comparison we also did simulations without inactivation by setting $V_{Th-Inact}$ equal to the spike threshold, V_{Th} .

To simulate firing, an exponentially decaying conductance for outward current was activated when the membrane potential exceeded V_{Th} : $I_{AHP} = G_{AHP} \exp[-(t - t_0)/\tau_{AHP}] (V - V_K)$, where G_{AHP} is the maximal conductance of the outward current (we set $G_{AHP} = G_m$), t_0 is the time of the threshold crossing, $\tau_{AHP} = 5$ ms; $V_K = -30$ mV is the reversal potential for this current I_{AHP} . The activated conductance was added to any that remained from the

previous threshold crossing. Our treatment of the post-spike phase is different from the classical LIF model with resetting of V to rest (see the discussion).

The area of the compartment, A_{cell} was $10^4 \mu\text{m}^2$; G_m was $5 \times 10^{-3} \text{ nS } \mu\text{m}^{-2}$; specific capacitance, C , was $10^{-5} \text{ nF } \mu\text{m}^{-2}$ with the resulting membrane time constant of 2 ms. Numerical integration of the model equations with stochastic input was performed with a fixed step-size implicit first-order strong scheme (Kloeden and Platen 1992). This scheme is similar to the Crank–Nicholson (trapezoidal) integration scheme (Press *et al* 1992) used for the deterministic case. The integration time step was 50 μs .

Two types of stimulus were used. A single subthreshold 'signal' EPSC that decayed exponentially with time constant, τ_s , of 1 ms was used to represent the coincidence of several weak unitary EPSCs. The signal was delivered in the midst of random unitary inputs, repeating each 30 ms. The random inputs were modelled as a continuous stochastic process (Svirskis and Rinzel 2000) with the mean equal to zero. The parameters were chosen to represent independent Poisson trains with the same rate of random smaller (on average) transient EPSCs and IPSCs with decay time constants equal to τ_s , with the total rate equal to 10 kHz and with the exponentially distributed amplitude having the mean, a , equal to 0.02 nA. Such mean amplitudes led to 1 mV mean amplitude for individual synaptic potential transients in the LIF model. The random input generated membrane potential fluctuations with standard deviation, σ_v , of 7.5 mV in the LIF model. The resulting spontaneous firing rate was between several and several tens of hertz, in agreement with *in vivo* auditory studies of MSO neurons (Goldberg and Brown 1969). The amplitude for the 'signal' EPSC led to a peak voltage, A , of 10 mV for the LIF model. Each time moment when the membrane potential crossed $V_{Th} = 15 \text{ mV}$ was marked as a spike event for later analysis. Thousands of events were gathered for computing post-stimulus time histograms, PSTHs.

For studying the model's phase-locking properties we used a stimulus that consisted of random PSCs with a periodically modulated delivery rate (figure 3(A)). The probability, p , for a PSC to occur in the time interval $dt = 0.05 \text{ ms}$ was equal to $dtR(M(\sin(2\pi[t-D]/T) - 1) + 1)$ if it was greater than zero and $p = 0$ otherwise. Here, R was a maximal rate, M modulation depth, T period and D delay. R was equal to 5 and 2 kHz for excitation and inhibition, respectively; $M = 2$; $D = 0.5 T$ for inhibition. The PSCs had exponentially distributed random amplitudes with the mean $a = 0.05 \text{ nA}$ leading to the mean amplitude of PSPs, a_{PSB} , of 2.5 mV in the LIF model. Several thousand events were collected for computing a post-stimulus time histogram (PSTH) and vector strength (Goldberg and Brown 1969), which was calculated as $VS = (\langle \cos(2\pi t_j/T) \rangle^2 + \langle \sin(2\pi t_j/T) \rangle^2)^{1/2}$, where t_j is the time of the j th threshold crossing, and $\langle \cdot \rangle$ indicates the average over j .

3. Results

We used an enhancement of the usual LIF model to explore how a dynamic subthreshold outward current, I_{KLT} , influences the integration of small subthreshold signals in the presence of noise. Our idealized representation of I_{KLT} involves a time-dependent piecewise linear rectification of the membrane's I – V relation (figure 1(A)). For a subthreshold current step the model responds with an overshoot before settling to a lower potential after I_{KLT} activates (figure 1(B)). For a range of current steps above some threshold level, I_0 , our enhanced LIF-KLT model fires phasically, only a single spike, because I_{KLT} , once fully activated, prevents V from reaching the threshold level (figure 1(B)). The model fires tonically if the stimulus exceeds this range and is not too strong. Notice the afterhyperpolarization following a spike (dashed arrow in figure 1(B)); it is the result of using I_{AHP} to restore the membrane potential to subthreshold levels rather than the classical method for LIF of resetting V to some prescribed level. This mechanism fails for extremely

strong steady I , but that does not concern us since we operate in a reasonable range of stimuli.

Next, we explored how I_{KLT} influences the integration of a subthreshold EPSP in the presence of continuous random input simulated as a continuous stochastic process. We used the post-stimulus time histogram, PSTH, to characterize changes in firing probability in a given time bin during the injection of a 'signal' EPSC. The amplitude of the 'signal' EPSP was 10 mV in the LIF model if no noise was added (figure 1(C), lower panel). Consequently, such a 'signal' cannot be detected by a noiseless system; however, the addition of random input not only allows the detection but also causes spontaneous firing. The presence of noise also makes the system sensitive to the 'signal' onset from its very beginning.

The probability of firing increases just after the 'signal' onset (figure 1(C)). Also, the peak probability of firing in response to the signal in the presence of noise occurs before the peak of the 'signal' EPSP (figure 1(C)). Both of these phenomena are due to the dependence of the probability of crossing the threshold level on the rate of change of membrane potential. In general, the probability of firing is given by (Bunimovich 1951, Svirskis and Rinzel 2000)

$$f_1 = \int_0^\infty w_1(V', V_{th}) V' dV',$$

where $V' = dV/dt$, and w_1 is the joint probability density for the membrane potential and its rate. The 'signal' EPSP changes both the mean membrane potential and the mean rate. At the onset of the 'signal' EPSP, there is no change in mean membrane potential; however, the mean rate of potential change has a positive value due to the current injection, which increases the probability of crossing V_{Th} due to fluctuations when V is just subthreshold. The influence of V' on firing can also explain why the peak firing probability takes place before the peak of the 'signal' EPSP occurs. At the peak of the small 'signal' EPSP the mean potential reaches a maximum; consequently, the mean rate for membrane potential is equal to zero, thereby reducing the probability for membrane potential fluctuations to cause a threshold crossing when V is near V_{Th} . Thus, for a small 'signal' EPSP the probability to fire peaks at the time when both of these factors in the integrand have non-zero values maximizing the firing probability, f_1 .

To quantify how well the system can detect the 'signal' EPSC we used a ratio between increased probability of firing at a particular time in the presence of the 'signal' EPSP and the probability of firing spontaneously. This ratio can be thought of as an SNR, because it defines the quality of detection. As can be seen in figure 1(C), the presence of I_{KLT} reduces the spontaneous firing rate several-fold, but decreases the response probability to a 'signal' EPSP by only 10%. Consequently, the SNR increases several-fold (figure 1(C), inset). When the activation of the outward current was made twice as fast, i.e. τ_{KLT} was changed from 2 to 1 ms, the amplitude of the SNR remained almost the same, because the spontaneous rate together with the response to the 'signal' EPSP were reduced proportionally. However, the PSTH is narrower due to faster activation of the outward current. The effect of I_{KLT} on SNR is similar to the effect of a high-pass filter. Spontaneous membrane fluctuations approach the threshold with different rates, and activation of I_{KLT} prevents the slowest fluctuations from reaching the threshold potential. The 'signal' EPSP increases the rate and reduces the time for the activation of I_{KLT} ; thus, the probability of reaching the threshold increases.

The dynamic nature of the conductance for I_{KLT} suggests that dynamics of the input preceding the threshold level crossing should be changed. We used the reverse correlation

(spike-triggered averaging) method (Bryant and Segundo 1976, Mainen and Sejnowski 1995) to compute the mean input current preceding the crossing. The inclusion of I_{KLT} in the model makes the mean spike-triggering input current faster (figure 1(D)), presumably reducing the amount of I_{KLT} conductance that is activated. If the activation time constant τ_{KLT} was changed from 2 to 1 ms, the mean current became even faster. This faster current led us to expect better temporal precision and phase-locking in the integration of periodically modulated inputs (see below).

The SNR depends on parameters that describe the strength of inputs. We varied the amplitude of the 'signal' EPSC, A , as a continuous control parameter, for two different strengths of random fluctuations, and observed how the peak value of SNR changed. As one expects, larger A increases the probability of firing in response to greater signal strength and hence yields a larger SNR (figure 2(A)). However, the difference between the LIF and LIF-KLT models is particularly large in the case of weaker fluctuations. When σ_v was equal to $0.5 V_{Th}$, the SNR increased very strongly. For random input that causes the standard deviation of membrane potential, σ_v , to be equal to the threshold level (the 15 mV case), SNR was increased only modestly. Thus, in the case of very strong noise the effect of I_{KLT} is weaker because membrane potential fluctuations can cross the threshold level with high rate of change, and I_{KLT} has little time to activate. For weak noise, the membrane potential on average reaches the threshold level more gradually, i.e. with a slower rate of change. Consequently, the I_{KLT} conductance can become larger and more effectively suppress spontaneous firing.

In the model, I_{KLT} activates with a certain time constant, fast but not instantaneously, so that the temporal properties of the input are important. In the context of our characterization of weak-signal detection, we varied the values of the synaptic decay time constant, τ_s , and the membrane time constant, τ_m , to explore their effect on SNR in the LIF and LIF-KLT models. In order to focus primarily on the effect of the time course, we scaled the mean amplitude of the random PSCs, a , and that of the 'signal' EPSC, A , so that σ_v and the peak of the EPSP in response to 'signal' were constant and equal to 7.5 and 10 mV, respectively. As can be seen in figure 2(B), neither time constant has much effect on SNR in the LIF model. The same is true for the membrane time constant in the case of the LIF-KLT model; however, increasing the synaptic time constant, τ_s , augmented the SNR steeply. Apparently, this effect is due to the τ_s role in smoothing the synaptic input (Svirskis and Rinzel 2000). The smoother input causes slower membrane potential fluctuations, and, consequently, stronger activation of I_{KLT} that strengthens suppression of the spontaneous firing rate.

Above, we studied how I_{KLT} influences the detection of a weak signal in the presence of stationary noise. Next, we explored how I_{KLT} influences the cell's ability to integrate random input with a time dependent rate. A simple example of such an input is a periodically modulated Poisson train. The time course of the instantaneous rate of Poisson arrivals of EPSCs and IPSCs is seen in figure 3(A) (top). We looked at the neuron's ability to synchronize (phase-lock) to such a noisy time-dependent stimulus.

The response (period histogram, lower panel) shows approximate, not exact, phase locking because the stimulus is subthreshold and noisy. Due to the input's small amplitude, the cell responds less than once for ten periods of the stimulus. The effect of I_{KLT} is to tighten the phase-locking, eliminating some of the firings at non-desirable phases (i.e., some of the 'false positives'), and therefore yields a higher vector strength, VS, than the control case of LIF, although it also reduces the response strength. Another way to view the increased precision in phase-locking due to I_{KLT} is in the interspike interval (ISI) histograms (figure 3(B)). One sees, first of all, that the ISIs are distributed over a much broader range than the 2 ms stimulus period due to the low response rate; there can be many skipped cycles between

firings. Actually, on average, the cell is firing at frequencies of 35 and 20 Hz in the two cases (figure 3(D)), i.e. on average, once per 14 and 25 cycles, respectively. But for LIF-KLT (figure 3(B), lower panel) the fine structure of the individual cycles is stronger compared to the case of LIF (top) (Engel *et al* 2001).

For all the modulation frequencies that we tested, the presence of I_{KLT} improves phase-locking, as measured by VS (figure 3(C)). When I_{KLT} activation was made faster, VS became even stronger. Making I_{KLT} even faster however does not lead to unlimited improvement of phase-locked output. If the outward current is too fast, then too many spikes are eliminated; higher precision is gained at the expense of net throughput. This, as well as the generally decreasing throughput as modulation frequency increases, is seen in figure 3(D). The strength of phase-locking was dependent on the strength of the input (figure 3(E)). When the mean amplitude, a_{PSP} , of synaptic potentials increases, VS decreases for the model with I_{KLT} and the difference between LIF and LIF-KLT models is reduced as well. This can be explained by activation of I_{KLT} by random EPSPs. For small amplitudes, only EPSPs occurring near the phase of the maximum rate can reach the threshold, while others are suppressed by I_{KLT} . For larger mean amplitudes, additional EPSPs can cause firing even if these inputs are not occurring at the peak of the modulated input rate. Some of these inputs can overcome the activation of I_{KLT} , reducing VS while increasing the average number of spikes per stimulus period, rotation number (figure 3(E), inset).

Synaptic and membrane time constants influence the VS in predictable ways for the LIF and LIF-KLT models. When these time constants increase, fluctuations of the membrane potential become smoother due to the slower decay of synaptic potentials (Svirskis and Rinzel 2000). Such increased smoothness of random membrane potential fluctuations reduces temporal precision of signal integration, and, consequently, decreases VS (figure 3(F)). Because the smoothness of the membrane potential fluctuations is a critical feature in determining synchronization, VS is also reduced in the LIF-KLT model, despite the fact that a slower synaptic time constant allows stronger suppression of false positives and higher SNR for a single 'signal' EPSP.

The increase of SNR due to the dynamic outward current can be thought of as resulting from negative feedback. From this more general point of view, one would expect that turning off (inactivating) a subthreshold inward current should also increase SNR when compared with the case of no inactivation of the inward current. To demonstrate this we included an instantaneously activating inward current that could inactivate or not with a time constant $\tau_{inact} = 2$ ms into our control LIF model, creating a dynamic negative slope in the membrane's $I-V$ relation (figure 4(A)). When the inactivation threshold, $V_{Th-Inact}$, is lower than the threshold for the instantaneous activation of the inward current, V_{Th-Inw} (figure 4(A)), such a model has qualitatively similar response properties to the previous model, LIF-KLT: it generates overshoots in response to subthreshold current step stimuli and fires only once for some range of suprathreshold inputs (figure 4(B)).

In this model the effective threshold for firing became lower than in the LIF model. In the case of the non-inactivating inward current such a lowered threshold increases the probability of firing in response to any inputs. But inactivation of the inward current only allows fast inputs to take advantage of this lowered threshold. Accordingly, SNR is increased in the model when inactivation is operative as compared to the case when inactivation is disallowed (figure 4(C)). However, SNR was smaller than in the LIF-KLT model (compare figure 1(C)). In contrast to the outward current in the LIF-KLT model, inward current does not suppress but strengthens spontaneous firing; thus, if we include I_{KLT} , SNR increases further (figure 4(C)). The mean input current (from reverse correlation analysis) preceding the threshold crossing is also much faster for the model with the

inactivating inward current. Notice also that the mean input current drops from its peak value as t approaches zero. This is merely a consequence of the fact that as V approaches close to threshold the intrinsic regenerative inward current is activated and therefore less synaptic input current is needed to trigger the spike. Of course the peak value of this current is greater for the case with inactivation, since there is less inward current available.

4. Discussion

We have studied the integration of small noisy signals in a minimal LIF model as influenced by the addition of a voltage- and time-dependent outward current that activates below the spiking threshold. The formulation leads to a piecewise-linear membrane current-voltage relation. The dynamic outward current increased SNR for weak subthreshold signals in the presence of noise. This effect was more pronounced for moderate noise strength and for slower synaptic time constants. The presence of I_{KLT} improved phase-locking (larger VS) to a weak periodically modulated random stimulus for all frequencies. The difference in VS between the LIF models, with and without I_{KLT} , was largest for the weakest stimulus. The LIF model with an inactivating subthreshold inward current showed similar response patterns and increased SNR, suggesting that a general mechanism of subthreshold negative feedback is responsible for the effects described.

Small-signal integration aided by noise was extensively studied previously in various artificial and natural systems (Wiesenfeld and Moss 1995, Bezrukov and Vodyanoy 1997). It is well known that noise can help in signal detection, and some optimal strength of noise can maximize SNR, the effect being called stochastic resonance (McNamara and Wiesenfeld 1989, Collins *et al* 1995). Similar effects of noise were observed in neural systems as well (Longtin and Chialvo 1998, Douglass *et al* 1993, Russell *et al* 1999). In these studies the main emphasis was placed on the strength of noise. In our work, we tried to explore how time-dependent potential-sensitive currents influence small signal integration aided by noise. We did not investigate here *per se* whether a particular noise strength maximizes SNR, but rather we compared the performance of the LIF model with that of the enhanced LIF-KLT model. We showed that the effects of SNR increase are present for different noise strengths (figure 3(A)). Although it may be that some optimal noise strength can maximize the effects of negative feedback, this remains to be explored in future studies. In our previous work using a conductance-based spiking model (Svirskis *et al* 2002) we saw that the probability of firing in response to the 'signal' EPSC decreased for low and high levels of noise.

On the other hand, numerous *in vitro* studies have considered the effects of low-threshold outward currents in auditory neurons (Reyes *et al* 1996, Cai *et al* 2000, Rothman and Young 1996, Rothman *et al* 1993), typically focusing on strong suprathreshold stimuli. Such strong stimuli are thought to be similar to those used in *in vivo* studies where it is important to gather as much data as possible in the shortest time. Usually, the effect of subthreshold conductances is attributed to a reduction of the membrane time constant (Oertel 1983, Manis and Marx 1991) which makes postsynaptic potentials decay very fast and filters out small signals. The increased conductance is very important for precise integration of strong inputs, which can overcome such membrane leakiness and still trigger the cell to fire. However, as shown in our work here, the voltage sensitivity and dynamic nature of the subthreshold current are major factors for improvement of integration for small subthreshold signals, that cannot be detected without noise.

Previously, we studied experimentally (gerbil, *in vitro* slice preparation) how SNR and phase-locking are affected by low-threshold potassium currents in MSO neurons (Svirskis *et al* 2002), finding results similar to those in this paper. We also showed there using a Hodgkin-Huxley type model that a low-threshold potassium conductance, based on

experimentally defined parameters, could account for the effects observed. In this work, we used the LIF model enhanced with a time-dependent piecewise-linear membrane current–voltage relation and showed that its response properties were qualitatively similar to those recorded experimentally and seen in a model with Hodgkin–Huxley type conductances (Svirskis *et al* 2002). This means that the minimal model captures a number of the essential firing and membrane properties of phasic auditory neurons.

Moreover, the minimal model indicates that the low threshold and the gating dynamics for I_{KLT} activation are the major properties responsible for the improvement of weak-signal integration. Reducing the activation time constant for I_{KLT} leads to more precise small-signal detection (figure 1(C)) and improves phase-locking (figure 3(C)). However, the strength of the response to the signal is reduced (figures 1(C) and 3(D)). This suggests that the activation cannot be made very fast or instantaneous; thus, the dynamic properties of the current are important. On the other hand, if activation is too slow, then the effect of reducing spontaneous activity would be weaker, since only fluctuations slower than the activation timescale can be effectively prevented from reaching the spike threshold (figure 2(B)).

Our LIF-KLT model fires phasically over a range of steady stimulating current I that is just suprathreshold for the LIF model to fire tonically. This phasic property is due to the combined effects of I_{KLT} and I_{AHP} dynamics. Our outward current I_{KLT} deactivates instantaneously. Thus, if the post-spike membrane potential falls below V_{Th-KLT} the neuronal model 'forgets' about the previous activation of I_{KLT} . In such a case the possibility of phasic firing would depend on the amount and speed of afterhyperpolarization following a V_{Th} crossing. Only if the recovery from a strong I_{AHP} is sufficiently slow could I_{KLT} re-activate enough to preclude another spike. Notice, in our simulations (figure 1(B)), that the afterhyperpolarization was not so large as to completely deactivate I_{KLT} after a firing. So, the phasic firing seen in figure 1(B) is due to residual I_{KLT} after the first spike. If the amplitude of I_{AHP} were somewhat larger and the post-spike V were pushed below V_{Th-KLT} the model neuron would fire tonically if the recovery from I_{AHP} is not too slow. Correspondingly, an LIF model in which V is reset to rest after a spike would also fire tonically, if I_{KLT} were implemented with instantaneous deactivation. We ignored the kinetics of I_{KLT} deactivation in order to make our model as simple as possible to show the effect of enhanced SNR and demonstrate the basic firing properties of MSO neurons.

For comparison purposes, we also did some simulations with the classical LIF model, with resetting of V to rest after a spike, and saw the same effect of SNR enhancement by I_{KLT} (not shown). For low firing rates and small noisy signals, whether or not the neuron fires phasically or tonically does not influence the integration taking place just before threshold crossing. Long interspike intervals ensure that the effects of conductances activated by threshold crossings decay before the next spike event. On the other hand, delayed kinetics of I_{KLT} deactivation would further enhance SNR because spontaneous firing would be reduced even more strongly by such longer-lived outward current.

Apart from the effects of a low-threshold outward current, we also explored weak-signal integration in an LIF model that includes an inactivating inward current. It is interesting that such a minimal model also shows phasic firing behaviour. The model's response properties are similar to those observed experimentally in older animals (P15–17), where phasic firing in response to a current step stimulus persists even after I_{KLT} is blocked with DTX (Svirskis *et al* 2002). It was suggested that inactivation of sodium channels could be responsible for such firing patterns. Since the presence of inactivation increased SNR, it is probable that sodium channels together with I_{KLT} participate in the integration of small signals in MSO neurons. Indeed, when both nonlinearities are added to the LIF model the spontaneous activity is reduced very strongly, but without reducing response to the 'signal' EPSP (figure

4(C)). This feature of integration could be very important for neurons, since the absolute response strength defines the smallness of signals that are detectable. It is notable that in this example with an inactivating inward current we find that SNR improvement comes from a decreased membrane conductance, in contrast to I_{KLT} 's contribution that increases conductance.

Summarizing, we have explored the integration of weak signals in the presence of noise in LIF models enhanced with voltage- and time-dependent subthreshold negative feedback. We have shown that subthreshold dynamic negative feedback in the form of an activating outward current or an inactivating inward current improves small-and-noisy-signal detection.

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Figure 1.

Model properties and response to noisy stimulus. (A) Membrane I - V plot illustrating time- and potential-dependent outward current I_{KLT} . V_{Th} indicates the spike threshold, in this case for generation of I_{AHP} . V_{Th-KLT} indicates the threshold for activating I_{KLT} ; the conductance for I_{KLT} approaches its maximal value exponentially (dotted arrow). I_0 indicates the current value needed to trigger firing in the LIF model. (B) Firing properties of the model when the current steps (duration 100 ms, initial amplitude 0.3 nA and change of the amplitude 0.3 nA) were injected. The arrow indicates overshoot due to slightly delayed activation of I_{KLT} . The dotted arrow indicates the afterhyperpolarization generated after the voltage crosses the spike threshold. (C) PSTH in response to the subthreshold 'signal' EPSP in the presence of random input. Note that the probability of firing decays much faster than the EPSP (lower plot). I_{KLT} increases SNR (inset), while faster activation (but not too fast) of I_{KLT} additionally improves temporal precision. (D) Spike-triggered reverse correlation shows that spike generation in the presence of I_{KLT} requires on average faster developing net depolarizing input current with larger peak value.

Figure 2.

Dependence of SNR on model and stimulus parameters. (A) SNR (peak value) as a function of EPSP 'signal' amplitude, A , with and without I_{KLT} . Two cases are compared, with different strengths of random input that cause membrane fluctuations with two different standard deviations, σ_v . Note that SNR is more sensitive to the amplitude when membrane fluctuations are smaller. σ_v was calculated for the LIF model. The light dotted vertical line denotes control parameter values (as used in figure 1). (B) SNR as a function of membrane or synaptic current time constant. SNR for the LIF model without I_{KLT} depends very weakly on both parameters. For the model with I_{KLT} , increases in the synaptic current time constant lead to larger SNR.

Figure 3.

Response statistics to 500 Hz periodically modulated Poisson input. (A) Period histogram of the stimulus (top) and response (bottom). The presence of I_{KLT} sharpens the synchronization, but also reduces the mean firing rate. Note that because the stimulus is weak firings are infrequent (about one in 25 cycles). (B) Histograms of interspike intervals, ISIs. (C) Vector strength versus period of the stimulus. The presence of I_{KLT} in the model increases the tightness of phase-locking. The faster kinetics of the current enhances vector strength even more. The light dotted vertical line (here, and in panels (D) and (E)) denotes control parameter values (as used in figure 1). (D) The rate of firing increases with the stimulus period. (E) Vector strength decreases as a function of the mean synaptic potential amplitude. Note that the difference in phase-locking precision between the LIF models with and without I_{KLT} is decreasing for stronger inputs. The inset shows rotation number, the average number of spikes per stimulus period, versus the mean synaptic potential amplitude. (F) Vector strength decreases with increasing membrane or synaptic current time constant. For the model with I_{KLT} the decrease of VS is more gradual with a decrease of time constants.

Figure 4.

Response properties of the model with inactivating inward current. (A) Membrane I - V plot illustrating time- and potential-dependent current. V_{Th} indicates the spike threshold, in this case for generation of I_{AHP} . V_{Th-Inw} indicates the threshold for the activation (exponential in time) of inward current (dotted arrow). $V_{Th-Inact}$ indicates the threshold for the inactivation. (B) Firing properties of the model. The arrow indicates overshoot due to inactivation of the inward current. The dotted arrow points to the afterhyperpolarization generated after the voltage crosses the spike threshold. (C) PSTH in response to the subthreshold 'signal' EPSP in the presence of random input. Inactivation of inward current increases SNR (inset). Addition of I_{KLT} suppresses spontaneous firing and increases SNR even more (inset). (D) Spike-triggered reverse correlation shows that the presence of inactivation of inward current requires faster development of input current to reach the spike threshold.