Using computer simulations to determine the limitations of dynamic clamp stimuli applied at the soma in mimicking distributed conductance sources

Authors: Risa Lin and Dieter Jaeger

Supplemental Materials

Detailed Description of Channel kinetics

All channel conductances G_j are modeled based on the Hodgkin & Huxley (1952) formalism and calculated as the product of a maximum conductance g_j and voltage or calcium dependent activation and inactivation variables m, h and z:

$$G_j = \bar{g}_j m^p h^q \quad \text{or} \quad G_j = \bar{g}_j z \qquad \text{(A1)}$$

The temporal evolution of all activation and inactivation variables x = {m, h, z} is determined by their steady state values x_∞ and their time constants τ_x:

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x} \qquad \text{(A2)}$$

For all voltage gated channels, the voltage dependences of the steady state activation and inactivation variables $x_\infty = \{m_\infty, h_\infty\}$ are represented by Boltzmann functions:

$$x_\infty = \frac{1}{1 + \exp\left(\frac{V - V_h}{k}\right)} \qquad \text{(A3)}$$

Where indicated, the time constants for activation and inactivation are described by:

$$\tau_x = \frac{A}{\exp\left(\frac{V-B}{C}\right)+\exp\left(\frac{V-D}{E}\right)} + F \qquad \text{(A4)}$$

All equations are for 32 ˚C.

Fast sodium current NaF

$$I_{NaF} = \overline{g}_{NaF}\, m^3 h\, s(V - E_{Na})$$

with E_{Na} = 71 mV.

Activation m: V_h = −35 mV, k = −7.3 mV. The activation time constant is voltage independent and given by τ_m = 0.025 ms.

Inactivation h: V_h = −32 mV, k = 5.9 mV. The inactivation time constant τ_h also follows equation (A4), with A = 25 ms, B = 23.3 mV, C = −29 mV, D = −51 mV, E = 9 mV and F = 0.3 ms.

Slow Inactivation s: The inactivation variable is described by:

$$s_\infty = s_{\min}\frac{1-s_{\min}}{1+\exp\left(\frac{V-V_0}{k_s}\right)}$$

where s_{min} = 0.50, V_0 = −40 mV, and k_s = 5.4 mV. The slow inactivation time constant is described by:

$$\tau_s = \tau_{s_{\min}} + \frac{\tau_{s_{\max}} - \tau_{s_{\min}}}{\exp\left(\frac{V_0-V}{k_1}\right)+\exp\left(\frac{V-V_0}{k_2}\right)}$$

Where τ_{smin} = 70 ms, τ_{smax} = 1 s, V0 = −40 mV, k_1 = 18.3 mV, and k_2 = 10 mV.

Persistent sodium current NaP

$$I_{NaP} = \bar{g}_{NaP}\, m^3 h\,(V - E_{Na})$$

with E_{Na} = 71 mV.

Activation m: V_h = −65 mV, k = -4.1 mV. The activation time constant is voltage independent and given by τ_m = 0.3 ms.

Inactivation h: V_h = −75 mV, k = 5 mV. The inactivation time constant is described by:

$$\tau_h = \frac{1750\,ms}{1+\exp\left(\frac{V+60\,mV}{-8\,mV}\right)} + 250\,ms$$

High voltage activated calcium current CaHVA

The current through high voltage activated calcium channels is modeled by the Goldman-Hodgkin-Katz equation:

$$I_{CaHVA} = \bar{p}_{CaHVA}\, m^3\, \frac{z^2F^2V}{RT}\, \frac{[Ca^{2+}]_i - [Ca^{2+}]_o \exp\left(\frac{-zFV}{RT}\right)}{1-\exp\left(\frac{-zFV}{RT}\right)}$$

where p_{CaHVA} is the maximum Ca^{2+} permeability, z = 2 is the valency of Ca^{2+}, R = 8.3145 J K^{-1} mol^{-1} is the gas constant, F = 96480 C mol^{-1} is the Faraday constant and T is the thermodynamic temperature in K. The voltage dependence of the activation variable m is

described by a Boltzmann function (equation A3) with V_h = −24.5 mV and k = −9 mV, and the activation time constant is given by:

$$\tau_m = \frac{1\,ms}{31.746\left(\exp\left(\frac{V-5mV}{-13.89mV}\right)+1\right)^{-1} + 3.97\times10^{-4}\,mV^{-1}\left(V+8.9mV\right)\left(\exp\left(\frac{V+8.9mV}{5mV}\right)-1\right)^{-1}}$$

Low voltage activated calcium current CaLVA

$$I_{CaLVA} = \bar{g}_{CaLVA}\, m^2 h\,(V - E_{Ca})$$

with E_{Ca} = 139 mV.

Activation m: V_h = −56 mV, k = −6.2 mV. The activation time constant τ_m is described by equation (A4) with A = 0.333 ms, B = −131 mV, C = −16.7 mV, D = −15.8 mV, E = 18.2 mV and F = 0.204 ms.

Inactivation h: V_h = -80 mV, k = 4 mV. The inactivation time constant is given by

$$\tau_h = 0.333\,ms\exp\left(\frac{V+466mV}{66mV}\right) \qquad \text{for } V < -81\text{mV}$$

$$\tau_h = 0.333\,ms\exp\left(\frac{V+21mV}{-10.5mV}\right)+9.32\,ms \qquad \text{for } V \geq -81\text{ mV}$$

Tonic non-specific cation current TNC

This is a mixed cation current with a with a reversal potential E_{TNC} = −35 mV and a voltage independent conductance:

$$I_{TNC} = \bar{g}_{TNC}\,(V - E_{TNC})$$

HCN current

$$I_h = \bar{g}_h \, m^2 \, (V - E_h)$$

with $E_h = -45$ mV.

Activation m: $V_h = -80$ mV, $k = 5$ mV, $\tau_m = 400$ ms.

Fast delayed rectifier fKdr

$$I_{fKdr} = \bar{g}_{fKdr} \, m^4 \, (V - E_K)$$

with $E_K = -90$ mV.

Activation m: $V_h = -30$ mV, $k = -7.8$ mV, τ_m given by equation (A4) with A = 13.9 ms, B = −30 mV, C = 12 mV, D = -30 mV, E = −13 mV, F = 0.1 ms.

Slow delayed rectifier sKdr

$$I_{sKdr} = \bar{g}_{sKdr} \, m^4 \, (V - E_K)$$

with $E_K = -90$ mV.

Activation m: $V_h = -40$ mV, $k = -9.1$ mV, τ_m given by equation (A4) with A = 14.95 ms, B = −40 mV, C = 21.74 mV, D = −40 mV, E = −13.91 mV, F = 0.05 ms.

Small conductance calcium dependent potassium current Sk

$$I_{Sk} = \bar{g}_{Sk}\, z\,(V - E_K)$$

with E_K = -90 mV.

The calcium dependent activation variable z is given by:

$$z_\infty = \frac{[Ca^{2+}]^4}{[Ca^{2+}]^4 + (3\times 10^{-4} mM)^4}$$

The calcium dependence of the activation time constant is described by:

$$\tau_z = \begin{cases} 60ms - 11.2\times 10^3\ ms\ mM^{-1}[Ca^{2+}] & for \quad [Ca^{2+}] < 0.005mM \\ 4ms & for \quad [Ca^{2+}] \geq 0.005mM \end{cases}$$

Calcium concentration

We assume that the Sk channel is selectively activated by calcium ions that enter the cell through CaHVA channels, and calculate the effective calcium concentrations using a simple phenomenological model:

$$\frac{d[Ca^{2+}]}{dt} = BI_{CaHVA} - \frac{[Ca^{2+}] - [Ca^{2+}]_{base}}{\tau_{Ca^{2+}}}$$

where $[Ca^{2+}]_{base}$ = 50 nM is the baseline calcium concentration, τ_{Ca2+} = 70 ms is the decay time constant and $B = k_{Ca2+}/v_{shell}$ is a free parameter that scales inversely with the volume of a hypothetical submembrane shell with a thickness of 200 nm. Tuning the model

resulted in $k_{Ca2+} = 3.45 \times 10^{-7}$ mol C^{-1} in the soma and $k_{Ca2+} = 1.04 \times 10^{-6}$ mol C^{-1} in the dendritic compartments.

Detailed Description of Synaptic Properties

All synaptic conductances are described with double-exponential functions:

$$G_{syn}(t) = \frac{A\, g_{\max}}{\tau_{decay} - \tau_{rise}} \left(\exp(-t/\tau_{decay}) - \exp(-t/\tau_{rise})\right)$$

where g_{max} is the maximum synaptic conductance, τ_{rise} and τ_{decay} are the rise and decay time constants, respectively, and A is a normalization factor chosen so that $G_{syn}(t)$ reaches a maximum value of g_{max}.

The total excitatory synaptic current comprises AMPA, fast NMDA and slow NMDA components and is given by:

$$I_{ex}(t) = \left(G_{AMPA}(t) + f_{fNMDA}(V)\, G_{fNMDA}(t) + f_{sNMDA}(V)\, G_{sNMDA}(t)\right)(V - E_{ex})$$

where E_{ex} is the excitatory reversal potential and f_{fNMDA} and f_{sNMDA} are factors describing the voltage dependence of the fast and slow NMDA conductances:

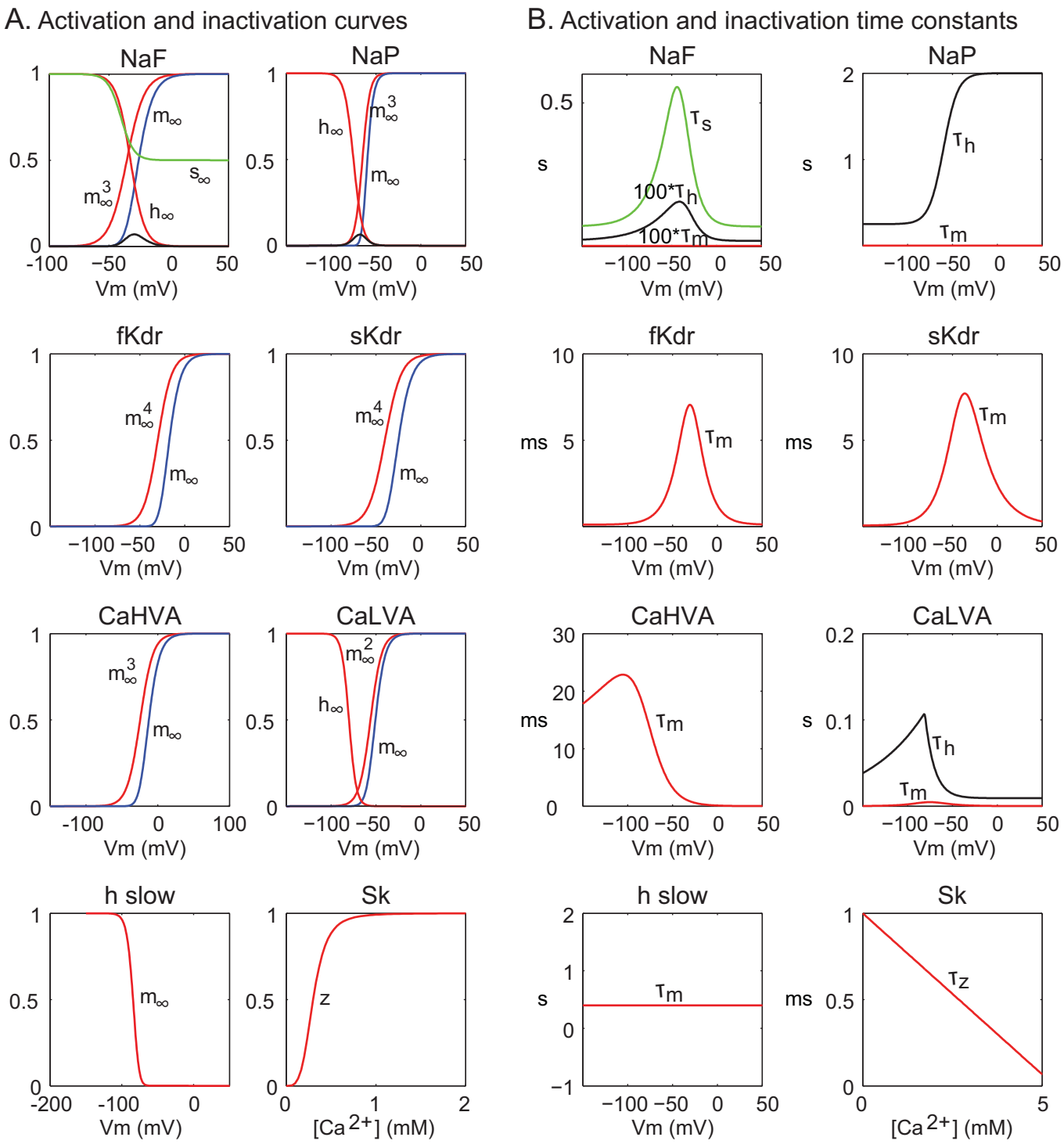
$$f(V) = \frac{1}{1 + p_1 \exp(-p_2\, V)}$$

The parameters p_1 and p_2 are set to 0.002 and 0.109 mV^{-1} for the fast NMDA component and to 0.25 and 0.057 mV^{-1} for the slow NMDA component. The rise and decay time

constants are 0.5 ms and 7.1 ms for AMPA, 5 ms and 20.2 ms for fast NMDA, and 5 ms and 136.4 ms for slow NMDA.

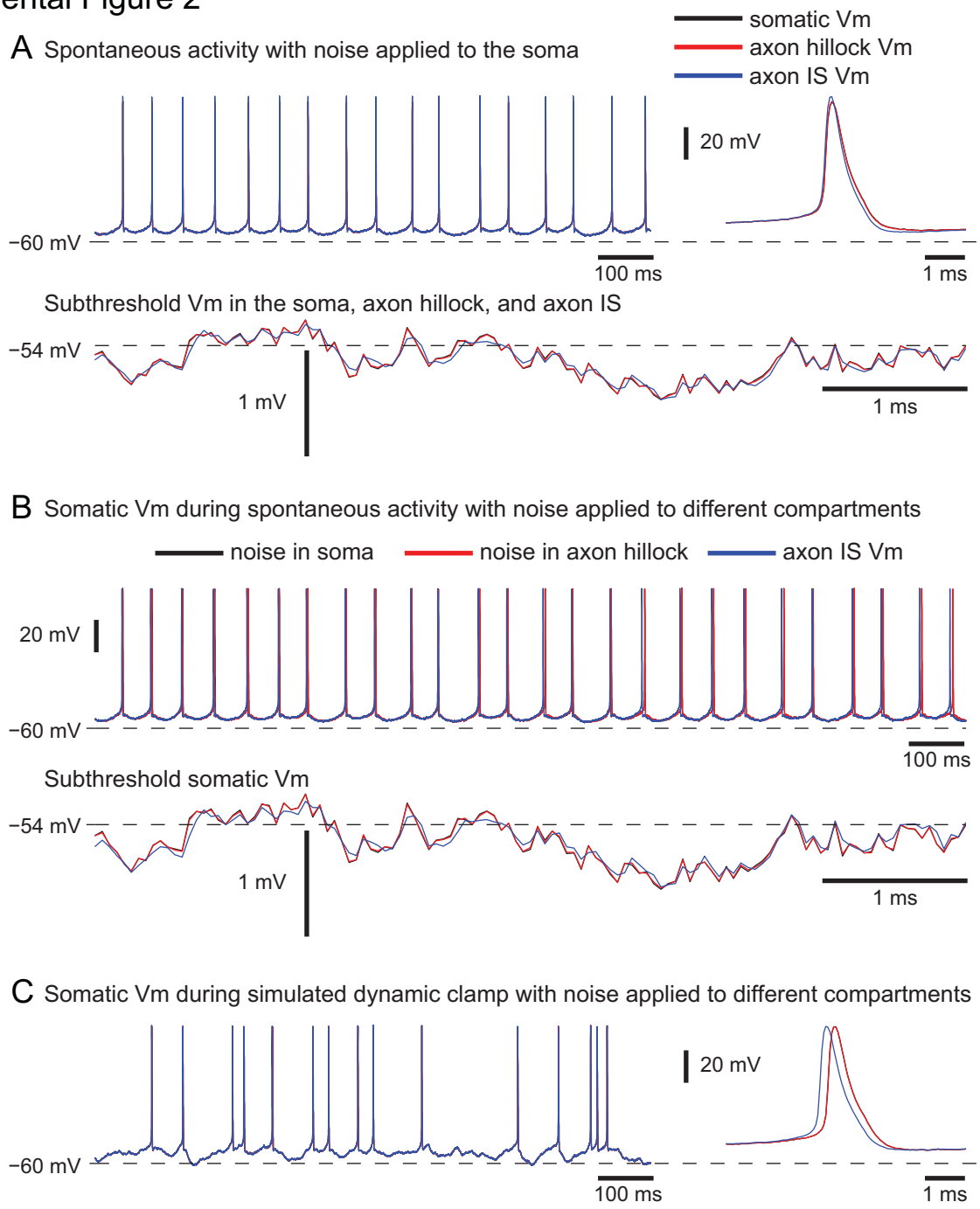
The GABAergic inhibitory synaptic current $I_{in}(t) = G_{GABA}(t)(V - E_{GABA})$ has rise and decay time constants of 0.93 ms and 13.6 ms. $E_{ex\ and}\ E_{GABA}$ were initially set to 0mV and −70mV, respectively. Since the original recordings were not corrected for a junction potential of 10mV during dynamic clamp, the reversal potentials of the synapses in the model were shifted downward by 10mV. They were then further shifted by the difference in the mean value of the subthreshold membrane potential between the slice recordings (−49.4 ± 3.0 mV) and the model (−53.8 ± 1.83 mV). These values were calculated after removing a window of 3ms before and after the peak of each action potential. The final values for $E_{ex\ and}\ E_{GABA}$ were −14.4mV and −84.4mV. The result of these manipulations was that the amplitude of total synaptic current generated in the model was comparable to the current injected by dynamic clamp in the experiments for a given input condition

Supplemental Figure 1



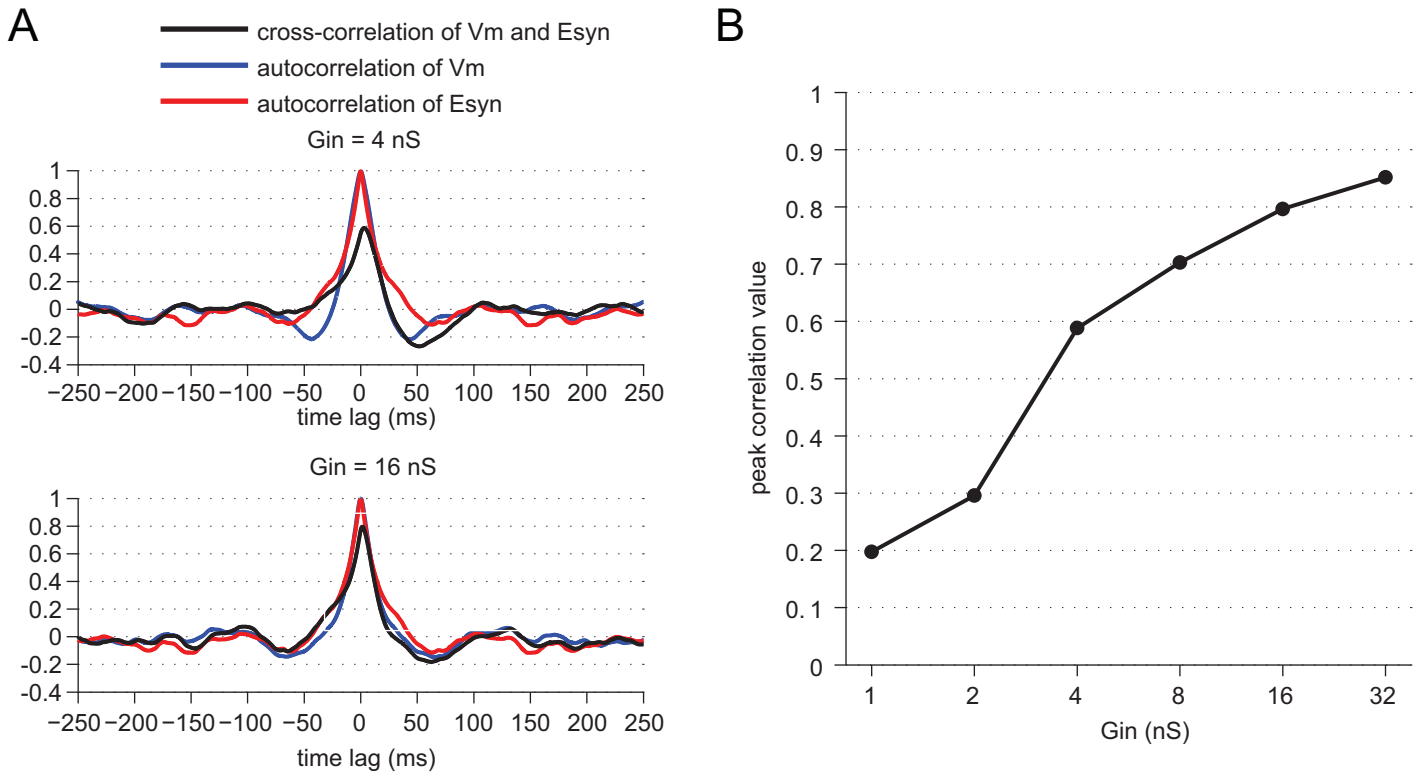
Supplemental Figure 1: A) Steady-state voltage and calcium dependencies of activation and inactivation for the membrane conductances. B) Voltage and calcium dependencies of activation and inactivation time constants.

Supplemental Figure 2



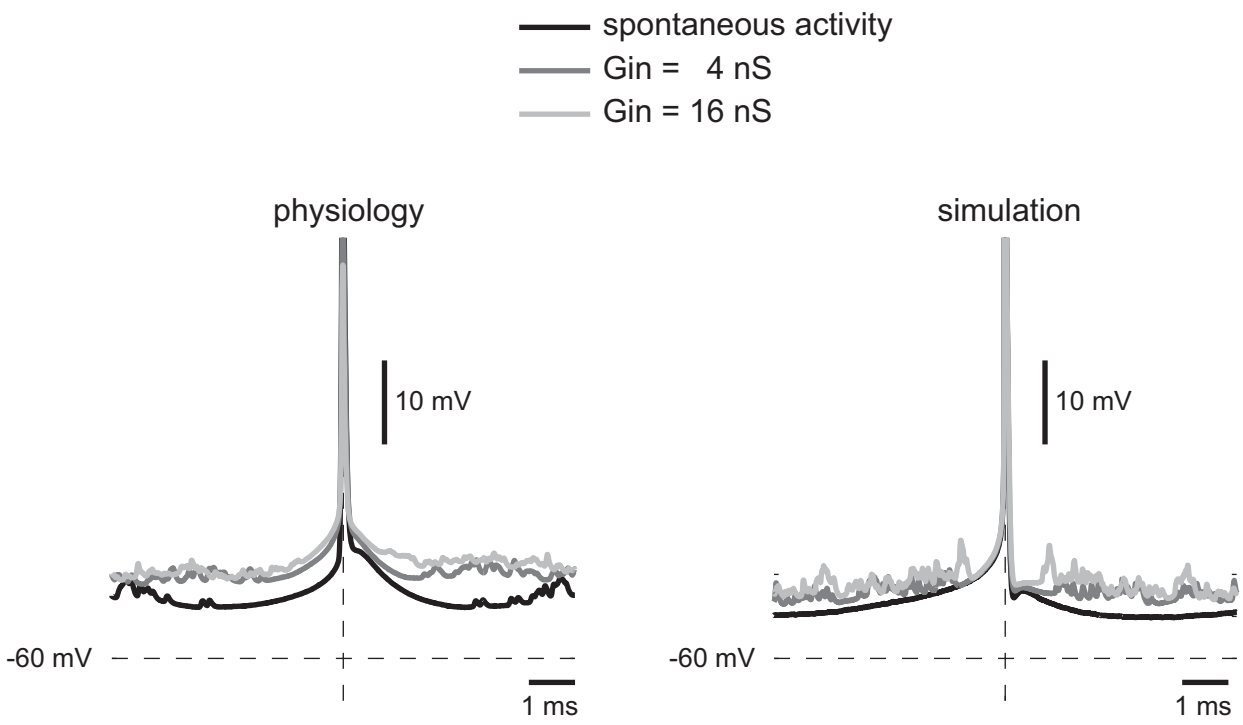
Supplemental Figure 2: A) When noise is applied to the soma of the model during spontaneous activity, there is very little attenuation of the spike and subthreshold noise fluctuations from the soma to the axon initial segment (IS). B) Simulations were also performed in which the the same noise was applied instead to the axon hillock or the axon IS. During spontaneous activity, there is initially no significant difference in spike timing, but small differences in how spikes were generated in the IS eventually accumulated and led to diverging spike times after long simulation times. The subthreshold noise fluctuations in Vm are nearly indistinguishable from those in (A), which can be explained by the electrotonically close proximity of the axon IS to the soma in the model. C) During simulated dynamic clamp, the output spike pattern remained the same when the noise was applied to different compartments, and differences in spike times were always less than 1 ms.

Supplemental Figure 3



Supplemental Figure 3: The subthreshold membrane potential was obtained by removing spikes from the recordings of the membrane potential and replacing it with a straight line connecting the endpoints of a +/- 3ms window around each detected spike time. A) The cross-correlation between the subthreshold membrane potential and the combined synaptic reversal potential, Esyn, was computed using an unbiased estimation method (black). The cross-correlation shows a strong positive central peak. The autocorrelations of the subthreshold membrane potential (blue) and Esyn (red) explain the strong negative correlation in the major side lobes at +/- 50ms lag. B) The magnitude of the central peak in the cross-correlogram increased as the average level of synaptic input was increased showing that the subthreshold membrane potential was increasingly controlled by the trajectory of the synaptic input conductance. Data is shown for simulations in which inhibitory synapses and excitation applied as a constant conductance were localized in the soma only to simulate dynamic clamp as in Figure 3C.

Supplemental Figure 4



Supplemental Figure 4: The average spike waveform was computed from recordings of a biological neuron (left) and the model neuron (right) spiking spontaneously and under dynamic clamp with a mean inhibitory conductance of 4 nS or 16 nS. At an increased mean inhibitory conductance of 16 nS, the shunting effect of inhibition was increased such that both in the dynamic clamp data and in the model the spike AHPs were almost completely suppressed. There is a difference of 1-2 mV in the AHP for these two levels of inhibitory conductance for both the biological neuron and the model.