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Supporting Material

An Integrated Model of Electrical Spiking, Bursting, and Calcium Oscillations in GnRH Neurons

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A Model Description and Parameter Values

The following definitions for the functions and parameter values are the same in both the spatial and simplified models, except where indicated. Thus, in what follows, C and C_e should be interpreted as $C(r,t)$ and $C_e(r,t)$ for the spatial model. Table 1 gives the standard set of parameters values used in the present study. The calcium flux densities are given by:

$$j_{\text{in}} = -\alpha I_{\text{Ca}} = -\alpha(I_{\text{CaL}} + I_{\text{SOC}} + \gamma I_{\text{NSC}}) \tag{1}$$

$$j_{\text{out}} = \frac{\nu_{\text{p}} C^2}{C^2 + K_{\text{p}}^2} + \frac{\nu_{\text{n}} C^4}{C^4 + K_{\text{n}}^4} \tag{2}$$

$$j_{\text{ref}} = \frac{\nu_{\text{e}} C^2}{C^2 + K_{\text{e}}^2} \tag{3}$$

$$j_{\text{rel}} = (L + PO_{\text{I}})(C_e - C). \tag{4}$$

Calcium entry at the plasma membrane is obtained by scaling the whole-cell current, I_{Ca} by $\alpha = (2FA_{\text{cell}})^{-1}$ (4.12e^{-3} μM μm ms^{-1} pA^{-1}) to yield the per unit area flux required by the boundary condition of the spatial model. The parameter γ (0.3) accounts for the fractional calcium conductance of the I_{NSC} channel as in LeBeau et al. (1). The ν_{x} and K_{x}, where x=p, n, and e are the maximal pump rates, and the Ca^{2+} levels at which half-maximal activation is reached, respectively, for the PMCAs, NCXs, and SERCAs (ν_{e}=1.3 μM pL ms^{-1}; (in μm μM ms^{-1}): ν_{n}=0.13 (0.4 in the simplified model), ν_{p}=0.04; (in μM): K_{e}=0.2, K_{n}=1, K_{p}=0.1).

The calcium release from stores is the sum of a leak and flux through the IP_3R channel, with flux rates L and P (0.0021 and 15 pL ms^{-1}, respectively). Following Li and Rinzel (2), the open probability of the IP_3R channel (O_{I}) depends on cytosolic [Ca^{2+}] and the inactivation variable h_{i} and is parameterized by IP_3 concentration (I) as follows:

$$O_{\text{I}} = \left(\frac{I}{I + K_{\text{i}}}\right)^3 \left(\frac{C}{C + K_{\text{ca}}}\right)^3 h_{\text{i}}^3. \tag{5}$$

where K_{i}=0.1 μM and K_{ca}=0.4 μM. The rate of change of the variable h_{i} at a given radius depends on the local cytosolic [Ca^{2+}] at that radius as follows:

$$\tau_{\text{hi}} \frac{dh_{\text{i}}}{dt} = (K_{\text{d}} - (C + K_{\text{d}})h_{\text{i}}), \tag{6}$$

where $K_{\rm d}$=0.4 μM and $\tau_{\rm hi}$, the time constant of IP_3R channel inactivation, is 2 μM ms for the biphasic response. Qualitatively similar results can be obtained by replacing $h_{\rm i}$ by its quasi-steady state value $K_{\rm d}/(C+K_{\rm d})$, thus reducing the number of variables by one.

The voltage gated ionic currents are given by:

$$I_{\rm Na} = g_{\rm Na} m_\infty^3 h (V - E_{\rm Na}) \tag{7}$$

$$I_{\rm CaL} = g_{\rm CaL} a^2 (V - E_{\rm Ca}) \tag{8}$$

$$I_{\rm K} = g_{\rm K} n^4 (V - E_{\rm K}) \tag{9}$$

$$I_{\rm ir} = g_{\rm ir} b_\infty (V - E_{\rm K}) \tag{10}$$

where the activation variable m for $I_{\rm Na}$ is assumed to be fast and takes its equilibrium value, m_∞. The whole cell conductances are (in nS): $g_{\rm Na}$=11, $g_{\rm CaL}$=1.2, $g_{\rm K}$=25, and $g_{\rm ir}$=1. The three gating variables $q \equiv h, a$, and n are governed by

$$\tau_{\rm q} \frac{dq}{dt} = q_\infty - q. \tag{11}$$

The $q_\infty(V)$ have the form $q_\infty = q_{\rm max}/(1+exp((V_{\rm m}-V_{\rm q})/k_{\rm q})) + q_{\rm min}$, with $s=-1$ for m_∞, a_∞ and n_∞, $s=1$ for h_∞ and b_∞, and $q_{\rm max}$ and $q_{\rm min}$ are 1 and 0 respectively for all gating variables except b, which takes the values 0.8 and 0.2 respectively. Except for Fig. 8, the parameter values for the $q_\infty(V)$ are identical for the generation of all results presented (in mV): $V_{\rm m}$=-43, $V_{\rm h}$=-55, $V_{\rm a}$=-29, $V_{\rm n}$=-27, $V_{\rm b}$=-80, $k_{\rm m}$=6, $k_{\rm h}$=6, $k_{\rm a}$=10, $k_{\rm n}$=15, and $k_{\rm b}$=12.

The $\tau_{\rm q}(V)$ have the form $\tau_{\rm q} = \overline{\tau_{\rm q}}/(exp((V_{\rm m}-V_{\rm q})/k_{\tau_{\rm q}}) + z exp(-z(V_{\rm m}-V_{\rm q})/k_{\tau_{\rm q}}))$, with $z=2$ for $\tau_{\rm h}$, and $z=1$ for $\tau_{\rm a}$, and $\tau_{\rm n}$. The parameter values for the $\tau_{\rm q}(V)$ are identical for generation of all results presented (in ms): $\overline{\tau_{\rm h}}$=150, $\overline{\tau_{\rm a}}$=10, and $\overline{\tau_{\rm n}}$=40; (in mV): $V_{\tau_{\rm h}}$=-65, $V_{\tau_{\rm a}}$=-29, $V_{\tau_{\rm n}}$=-33, $k_{\tau_{\rm h}}$=15, $k_{\tau_{\rm a}}$=25, and $k_{\tau_{\rm n}}$=23.

We use a Hill function to parameterize the activation of the NSC current by cAMP:

$$I_{\rm NSC} = g_{\rm NSC} \frac{A^2}{K_{\rm NSC}^2 + A^2} (V_{\rm m} - E_{\rm NSC}) \tag{12}$$

where $g_{\rm NSC}$=0.3 nS is the whole cell conductance, A is the cytosolic cAMP concentration in μM, $K_{\rm NSC}$=2 μM is the cAMP concentration at which $I_{\rm NSC}$ is half maximally activated, and $E_{\rm NSC}$=72 mV is the Nernst potential based on the fractional conductance of Ca^{2+} and Na^{+}, given as $E_{\rm NSC} = E_{\rm Na} + \gamma(E_{\rm Ca} - E_{\rm Na})$. We assume that $I_{\rm NSC}$ is activated is a Hill function of

cAMP to model effect of adenylyl cyclase activity on PM excitability, although here cAMP is a parameter and the activation due to cAMP is constant. A few candidates for the effector of the adenylyl cyclase pathway on membrane excitability exist, including CNG channels and HCN channels (3, 4), the cAMP activated Cl^- channel CFTR (5), or the phosphorylation of other ion channels by PKA (6, 7). The hill coefficient of 2 is not critical for any of the model behavior present, but is inspired from the cAMP dependence of CNG channels (8).

The calcium-activated potassium current is given by

$$I_{\mathrm{SK}} = g_{\mathrm{SK}} \frac{C_{\mathrm{R}}^8}{C_{\mathrm{R}}^8 + K_{\mathrm{SK}}^8}(V - E_{\mathrm{K}}), \tag{13}$$

where $\mathrm{C_R}$ is the $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$ at the cell membrane, given by either $C(R)$ in the spatial model or its approximation C_{R} in the simplified model. g_{SK}=1.5 nS is the whole cell conductance, and K_{SK}=1 μM is the $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$ at which $\mathrm{I_{SK}}$ is half maximally activated.

The store operated current is inhibited by high ER calcium, and is given by

$$I_{\mathrm{SOC}} = g_{\mathrm{SOC}} \frac{K_{\mathrm{SOC}}^4}{K_{\mathrm{SOC}}^4 + C_{\mathrm{eR}}^4}(V_{\mathrm{m}} - E_{\mathrm{Ca}}) \tag{14}$$

where $\mathrm{C_{eR}}$ is the $[\mathrm{Ca}^{2+}]_{\mathrm{ER}}$ near the cell membrane in the spatial model, or just the whole cell value of $[\mathrm{Ca}^{2+}]_{\mathrm{ER}}$ in the simplified model. g_{SOC}=0.03 nS is the whole cell conductance, and K_{SOC}=100 μM is the $[\mathrm{Ca}^{2+}]_{\mathrm{ER}}$ at which $\mathrm{I_{SOC}}$ is half maximally activated, and the Hill coefficient comes from Luik et al. (9).

Numerical Methods. By assuming spherical symmetry, we are able to use the transformations of variables $U = rC$ and $W = rC_e$ to rewrite the PDE system with just one spatial dimension, the radius from the center of the cell. This system is then discretized in space with a second order central difference approximation and integrated using the ode15s routine as implemented in MATLAB® (2007b, The MathWorks, Natick, MA). We used 50 spatial grid points to produce the results below; there was no qualitative changes when the number of grid points was reduced to 25. Code for both the spatial and simplified model in MatLab are available upon request. Code for the simplified model is also available for XPP.

Parameter	Symbol	Value
basal [cAMP]	A	0.7 μM
basal [IP_3]	I	0.01 μM
Cell Radius	R	10 μm
Cell Area	A_{cell} ($4\pi R^2$)	1257 μm^2
Cell Volume	V_{cell} ($4/3\pi R^3$ $1e^{-3}$)	4.19 pL
Cytoplasmic Volume	V_{cyt} (0.85 V_{cell})	3.56 pL
ER Volume	V_{ER} (0.15 V_{cell})	0.63 pL
Surface Area to Volume Ratio	β ($A_{\text{cell}}/V_{\text{cyt}}$)	0.35 μm^{-1}
Membrane Capacitance	C_{m}	14 pF
K^+, Na^+, Ca^{2+} Reversal Potentials	E_{K}, E_{Na}, E_{Ca}	-80, 60, 100 mV

Table 1: Table of some standard parameter values used in the model.

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