Ca^{2+} Diffusion within the Presynaptic Terminal

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Special Topic: Modeling and Simulation in Science, Engineering, and Economics

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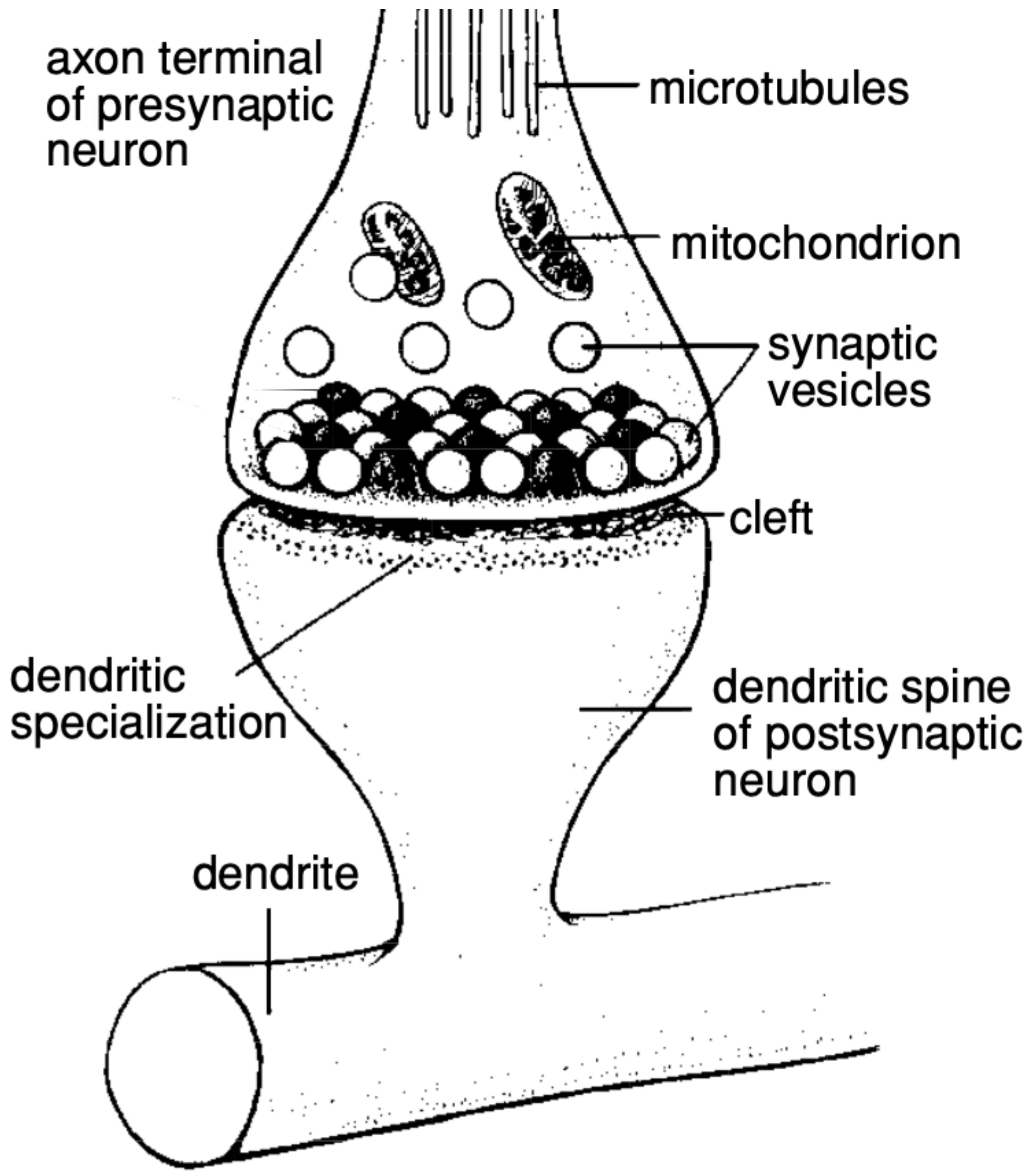
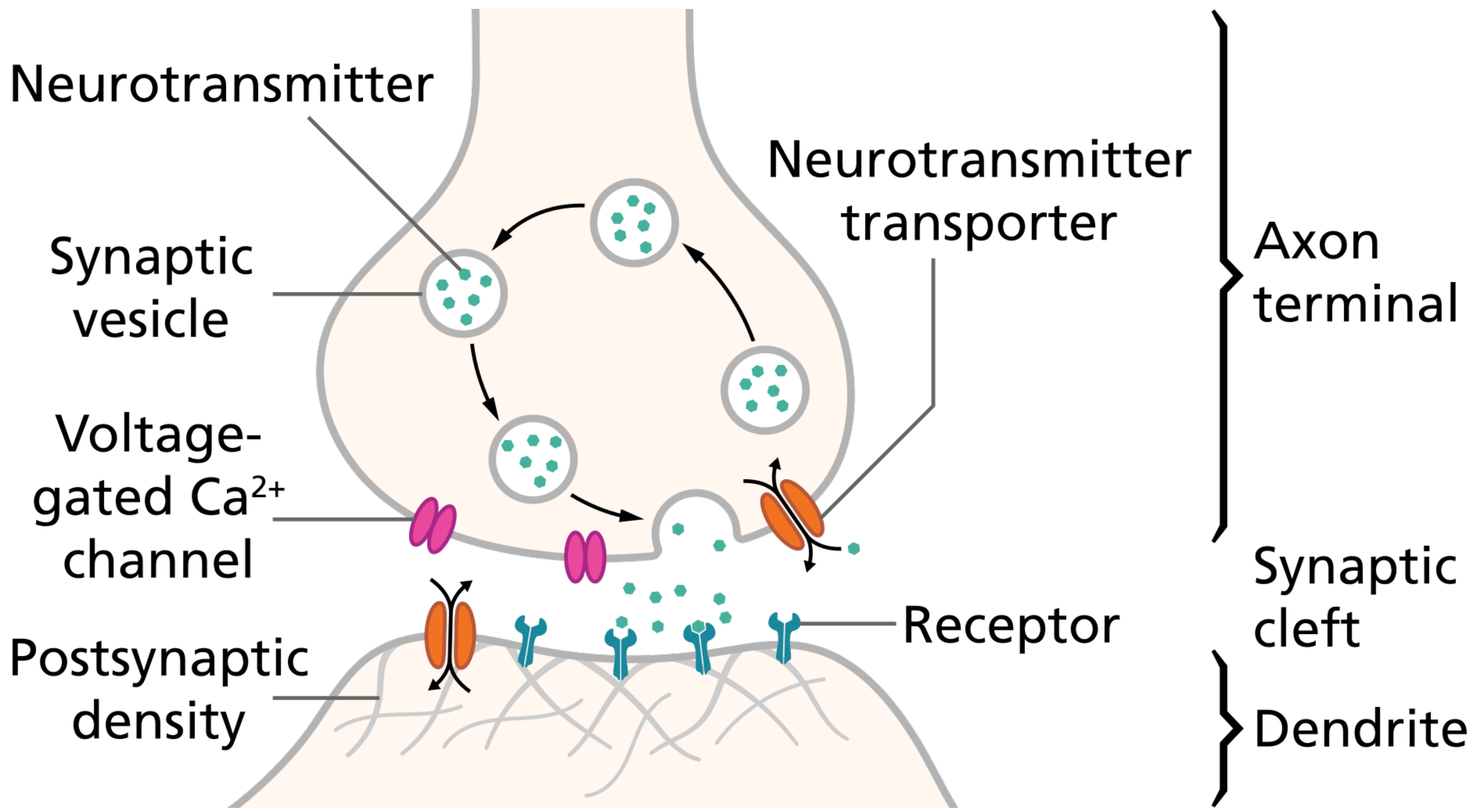
Synaptic Transmission



Dayan & Abbott, *Theoretical Neuroscience,* 2001.

Excitatory synapses onto cortical pyramidal cells form on dendritic spines.



SciStyle

- Channels with bound neurotransmitter can open.
- Transmitter action is terminated by enzymatic degradation, uptake into presynaptic terminal, and diffusion out of the cleft.

Events in the Synaptic Cleft

- Release of transmitter:

$$\rightarrow T$$

- Binding of transmitter to receptor and subsequent channel opening:

$$T + R \rightarrow_{\kappa_R} TR \;{}_{\beta_R}\!\leftrightarrow_{\alpha_R} (TR)*$$

- Enzymatic degradation of receptor:

$$T + E \rightarrow_{\kappa_E} TE \rightarrow_{\alpha_E} E$$

Presynaptic Ca^{2+} Channel

- Llinas, et al., 1976: S-shaped relationship between presynaptic potential and Ca^{2+} current and a linear relationship between Ca^{2+} current and postsynaptic potential.

$$i_{\text{Ca}} = (2q)\frac{aD}{\ell}\left(\frac{2qv}{kT}\right)\frac{[\text{Ca}^{2+}]_{\text{in}}\exp\left(\frac{2qv}{kT}\right) - [\text{Ca}^{2+}]_{\text{out}}}{\exp\left(\frac{2qv}{kT}\right) - 1}, \; f_{\text{Ca}} = -\frac{i_{\text{Ca}}}{2q}$$

- $[\text{Ca}^{2+}]_{\text{in}} \approx 0$: Ca^{2+} is actively pumped out of the cell, pumped into intracellular organelles, and heavily buffered.
- Ca^{2+} gating: 5 independent subunits

$$S \underset{\beta_s^0}{\overset{\alpha_s^0 \exp\left(\frac{qv}{kT}\right)}{\rightleftharpoons}} S^*$$

Ca^{2+} Diffusion within the Presynaptic Terminal

- Simon & Llinas, 1985: Release involves fusion of the vesicle membrane and the cell membrane.
- Vesicle release site is close to the Ca^{2+} channel (half space with plane boundary)
  - Ca^{2+} profile rapidly achieves a steady state; Local Concentration.
- **Spherically symmetric solution** to the steady-state diffusion problem.
  - Flux through an arbitrary hemisphere at radius r = flux through the channel.

$$f_{\mathrm{Ca}} = 2\pi r^2 J_{\mathrm{Ca}} = -2\pi r^2 D \frac{\partial[\mathrm{Ca}^{2+}]}{\partial r}, \ [\mathrm{Ca}^{2+}] = \int_r^\infty \frac{f_{\mathrm{Ca}}}{D 2\pi (r')^2} dr' = \frac{f_{\mathrm{Ca}}}{D 2\pi r}.$$

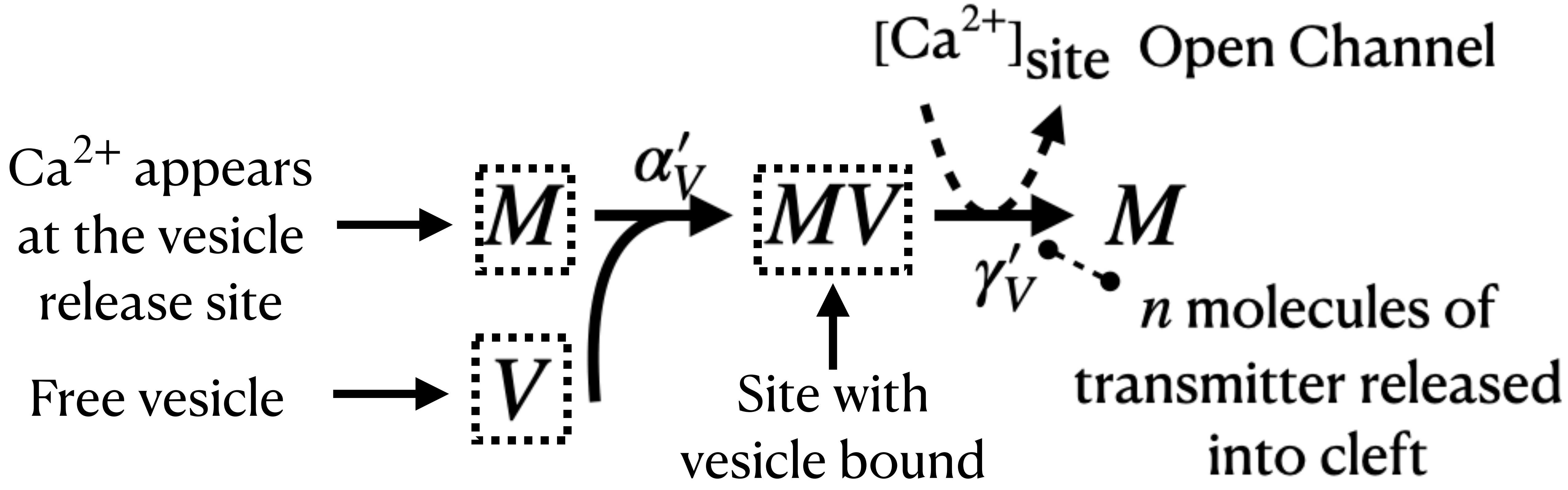
Open

$$[\mathrm{Ca}^{2+}]_{\mathrm{site}} = [\mathrm{Ca}^{2+}]_{\mathrm{out}} \cdot \underbrace{\boxed{\frac{a}{2\pi r_0 \ell}}}_{\text{Dimensionless geometric parameter}} \frac{\boxed{\left(\frac{2qv}{kT}\right)}}{\exp\left(\frac{2qv}{kT}\right) - 1}.$$

Dimensionless membrane potential parameter

Dimensionless geometric parameter

Release of Vesicles from the Presynaptic Terminal



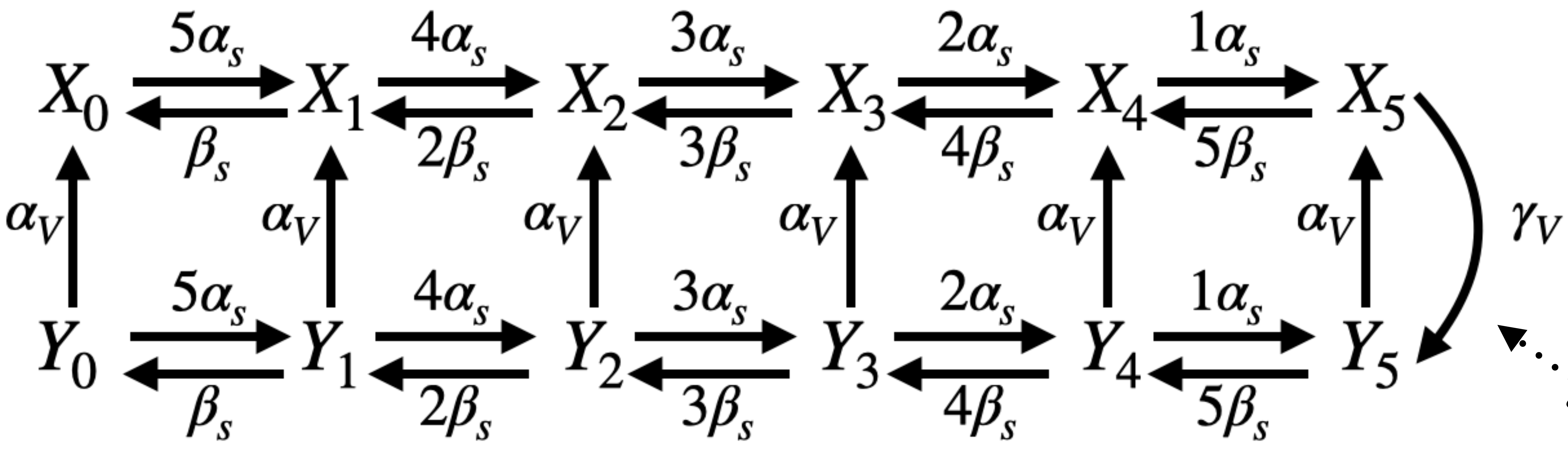
Hyperparameters

$$\alpha_V = \alpha'_V[V]$$

$$\gamma_V = \gamma'_V[\mathrm{Ca}^{2+}]^{OpenChannel}_{site}$$

$$X_k = S_{5-k}S^*_k MV$$

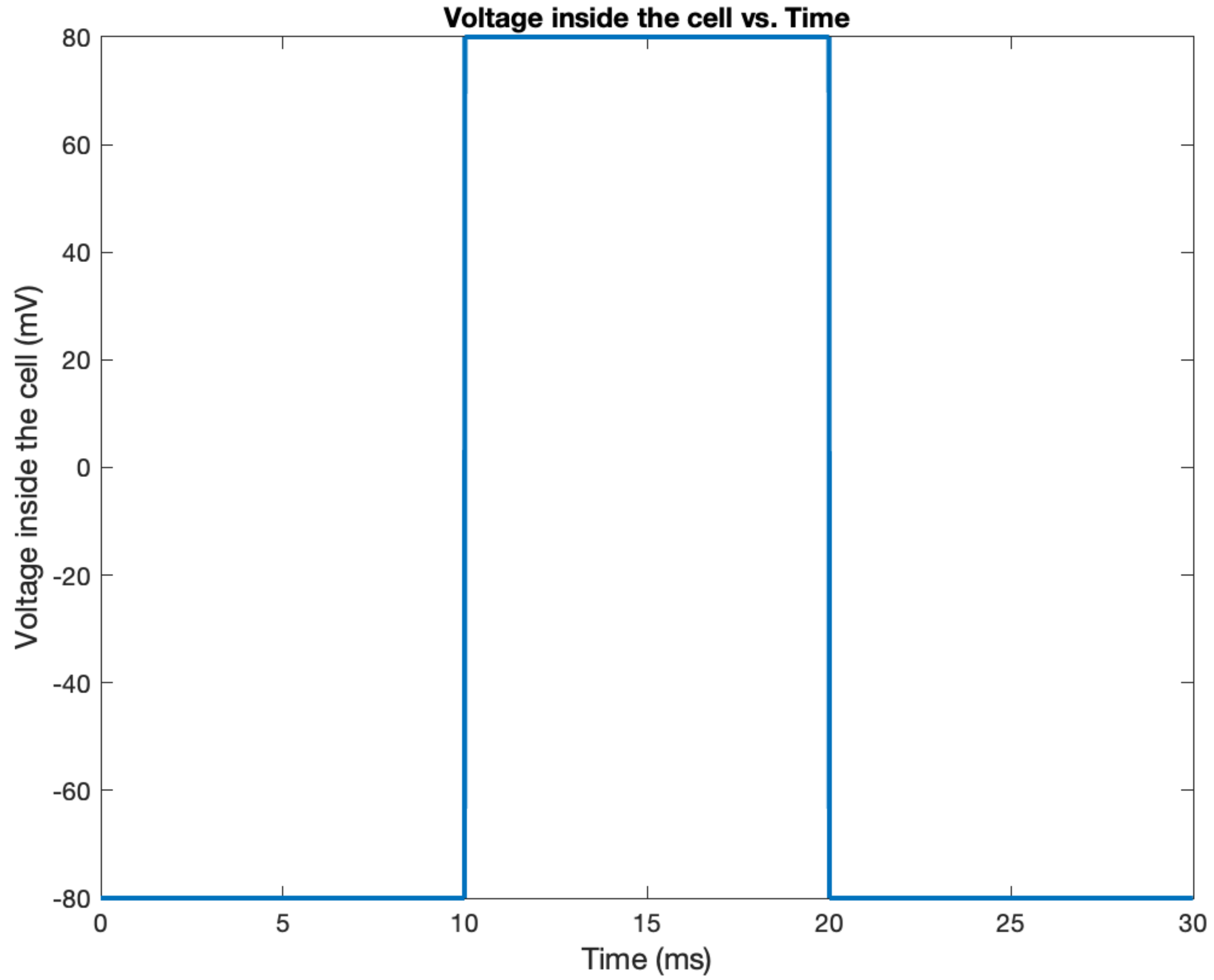
$$Y_k = S_{5-k}S^*_k M$$

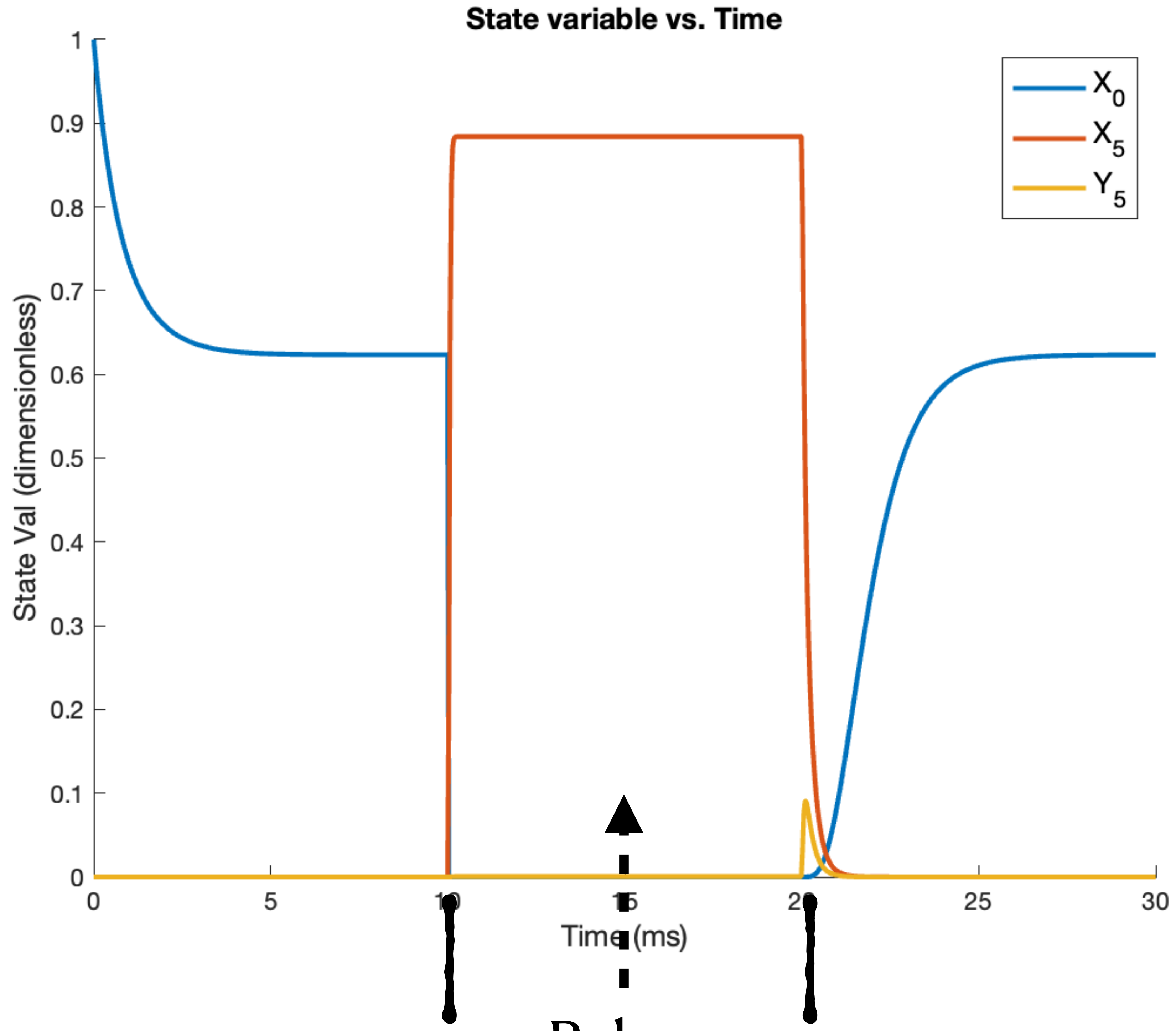


"Open Probability"

Voltage Clamp

- Rectangular function, $V_1 \rightarrow V_2 \rightarrow V_1$

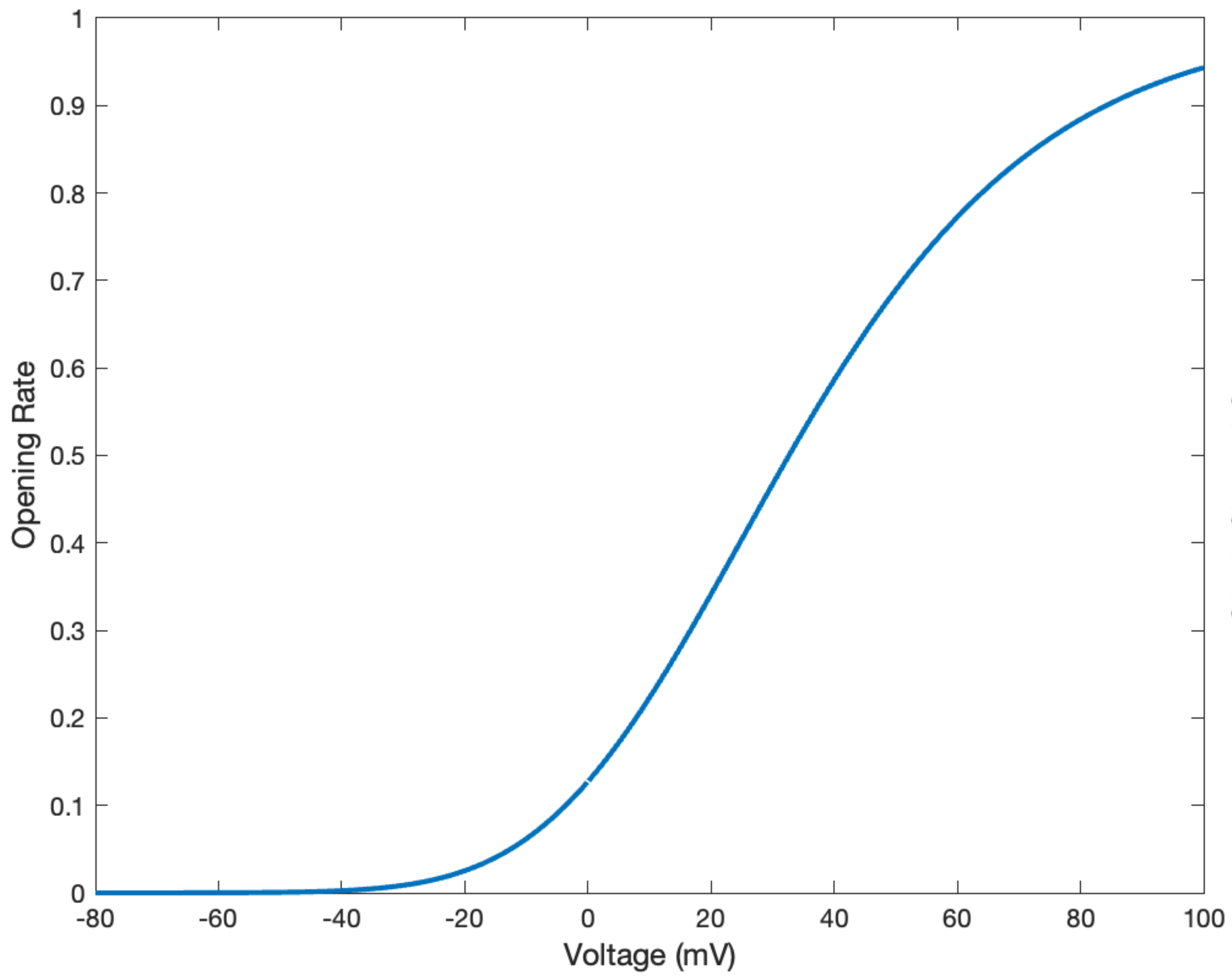




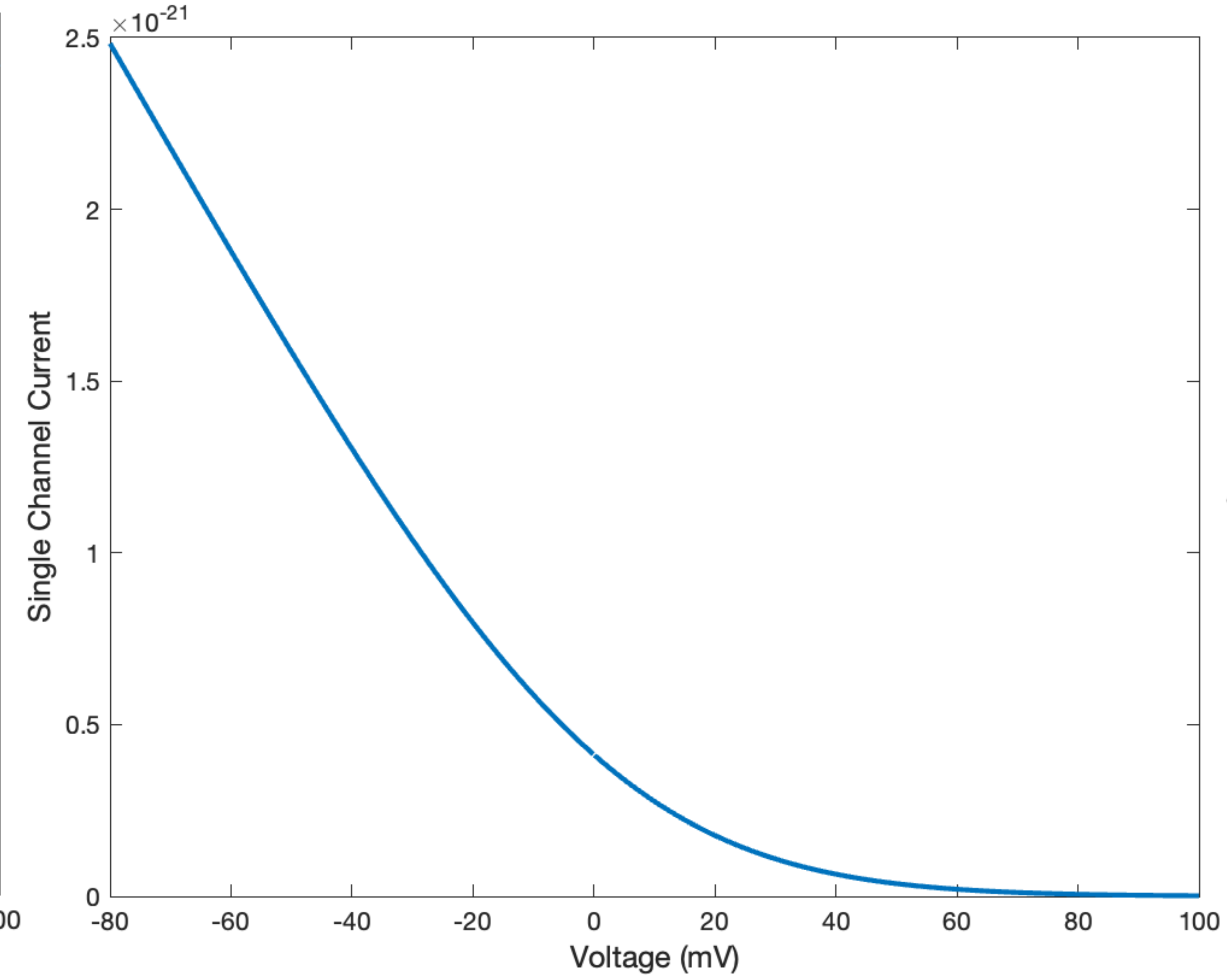
× Release

Ca^{2+} is negligible at such high membrane potential

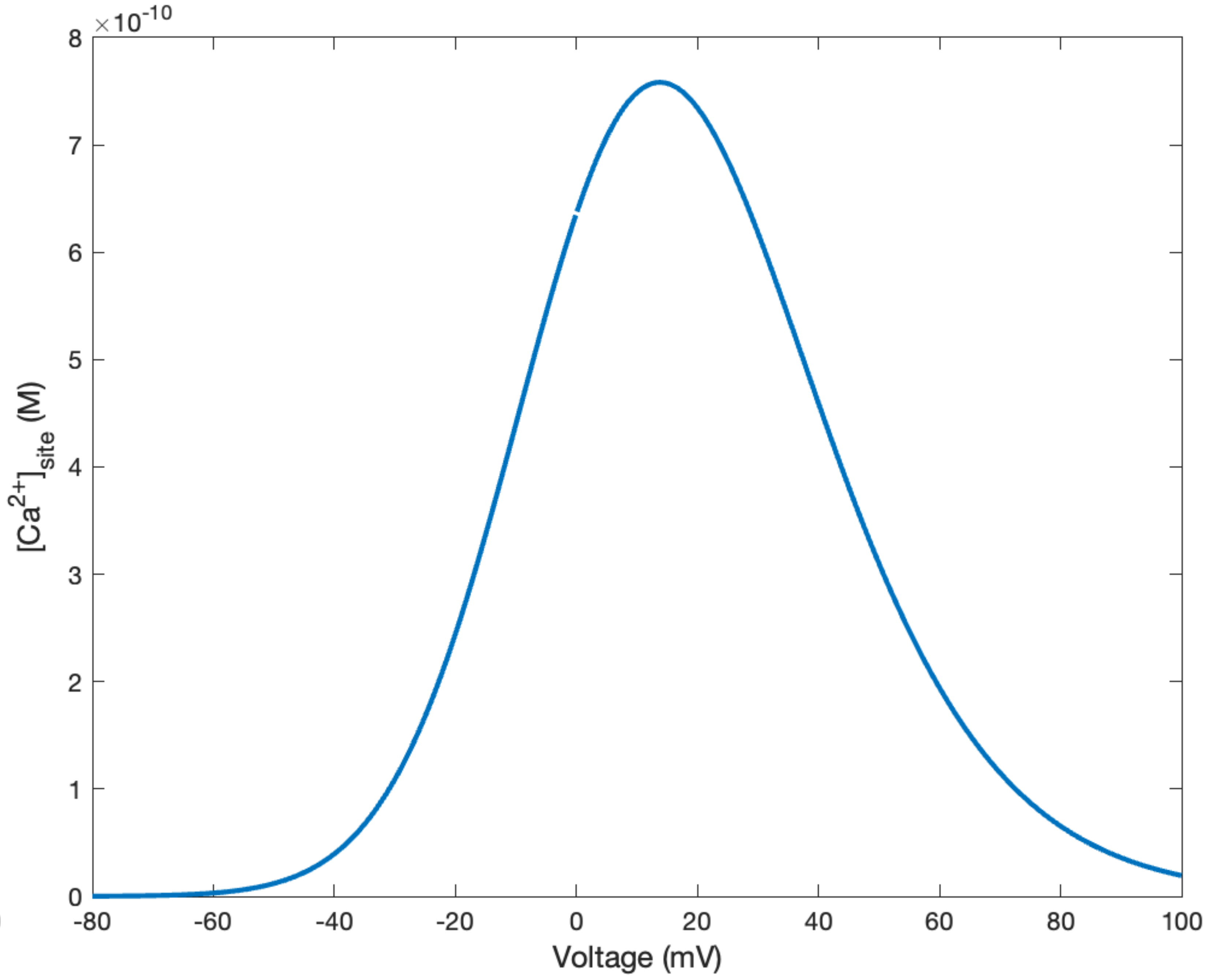
Results



Opening Rate



Single Channel Current



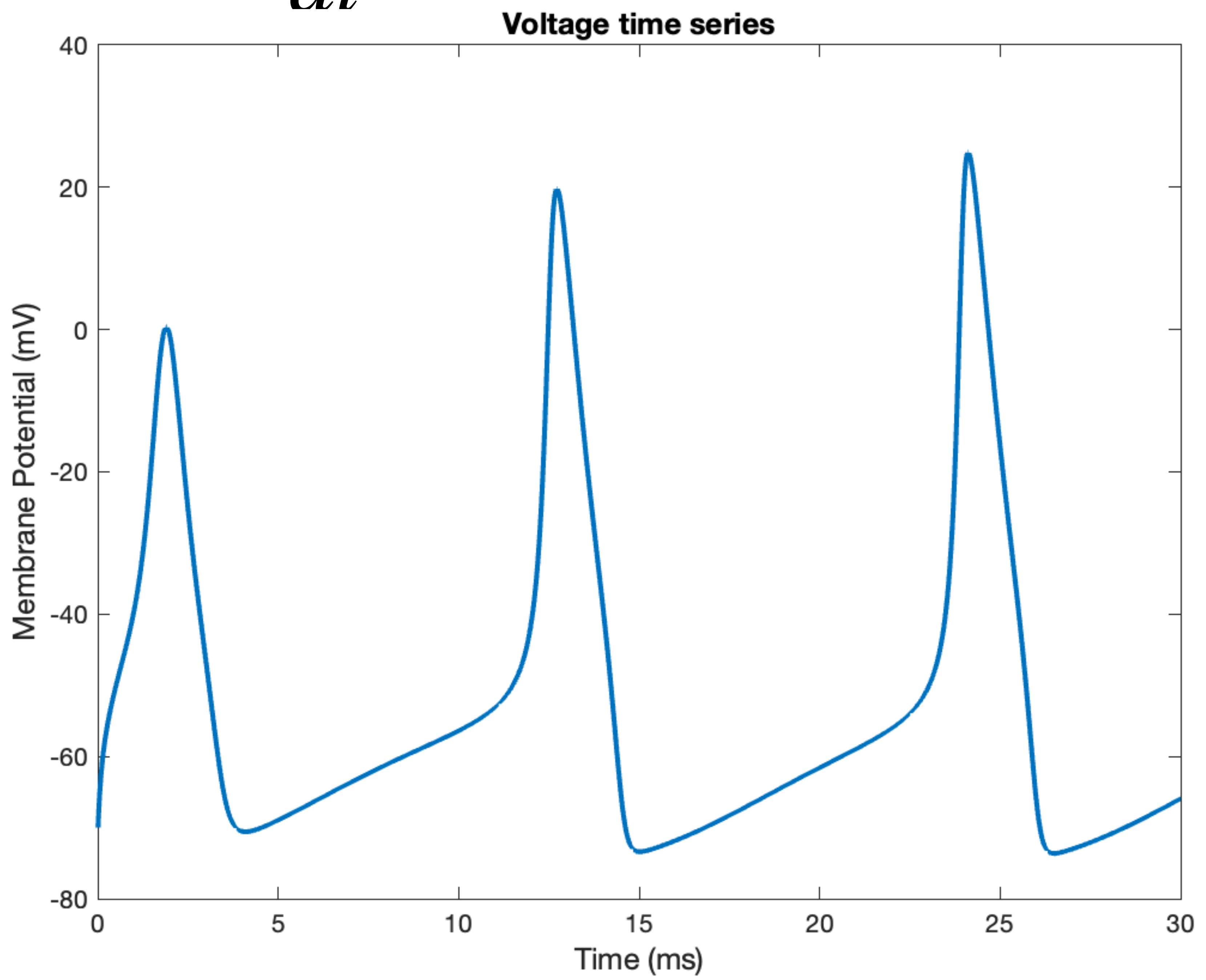
Total $[Ca^{2+}]_{site}$

Steady state Ca^{2+} current

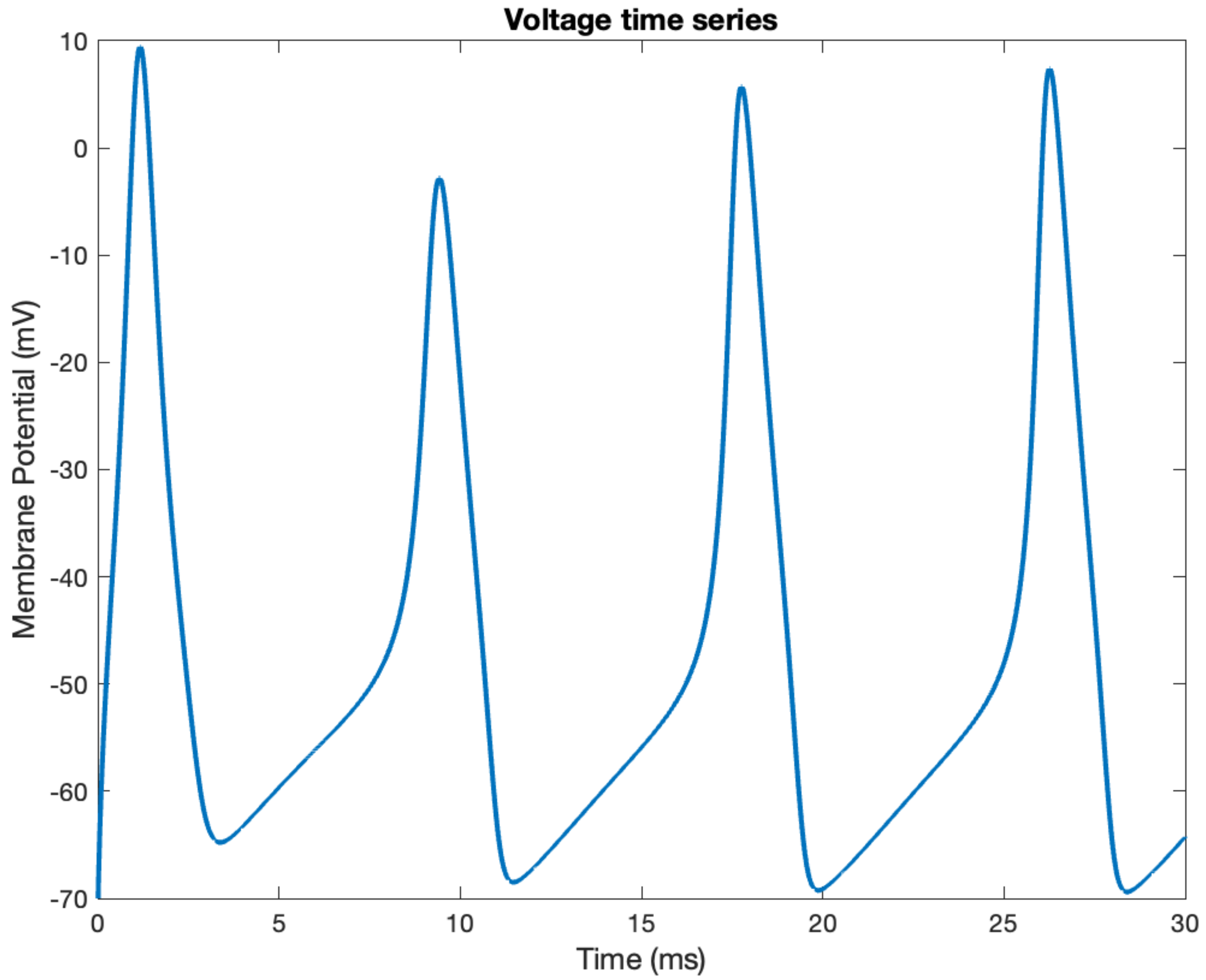
Hodgkin-Huxley Formalism of Action Potential

- Action potential is produced by an interplay of voltage-gated Na^+ and K^+ ion currents.
- Activation/Inactivation gating variable m, n, h.

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K) + I_{app}\,.$$

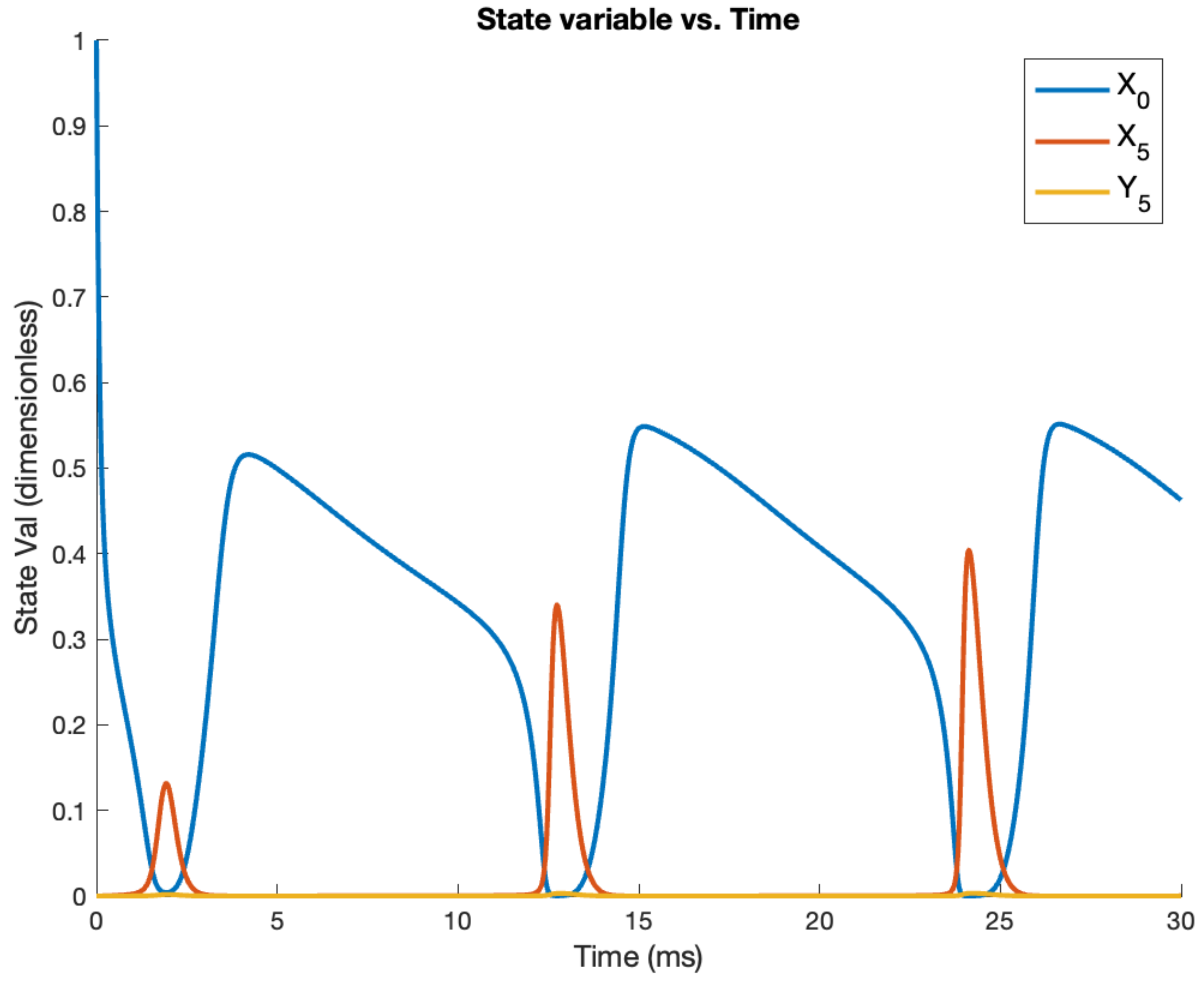


$I_{inj} = 20nA$

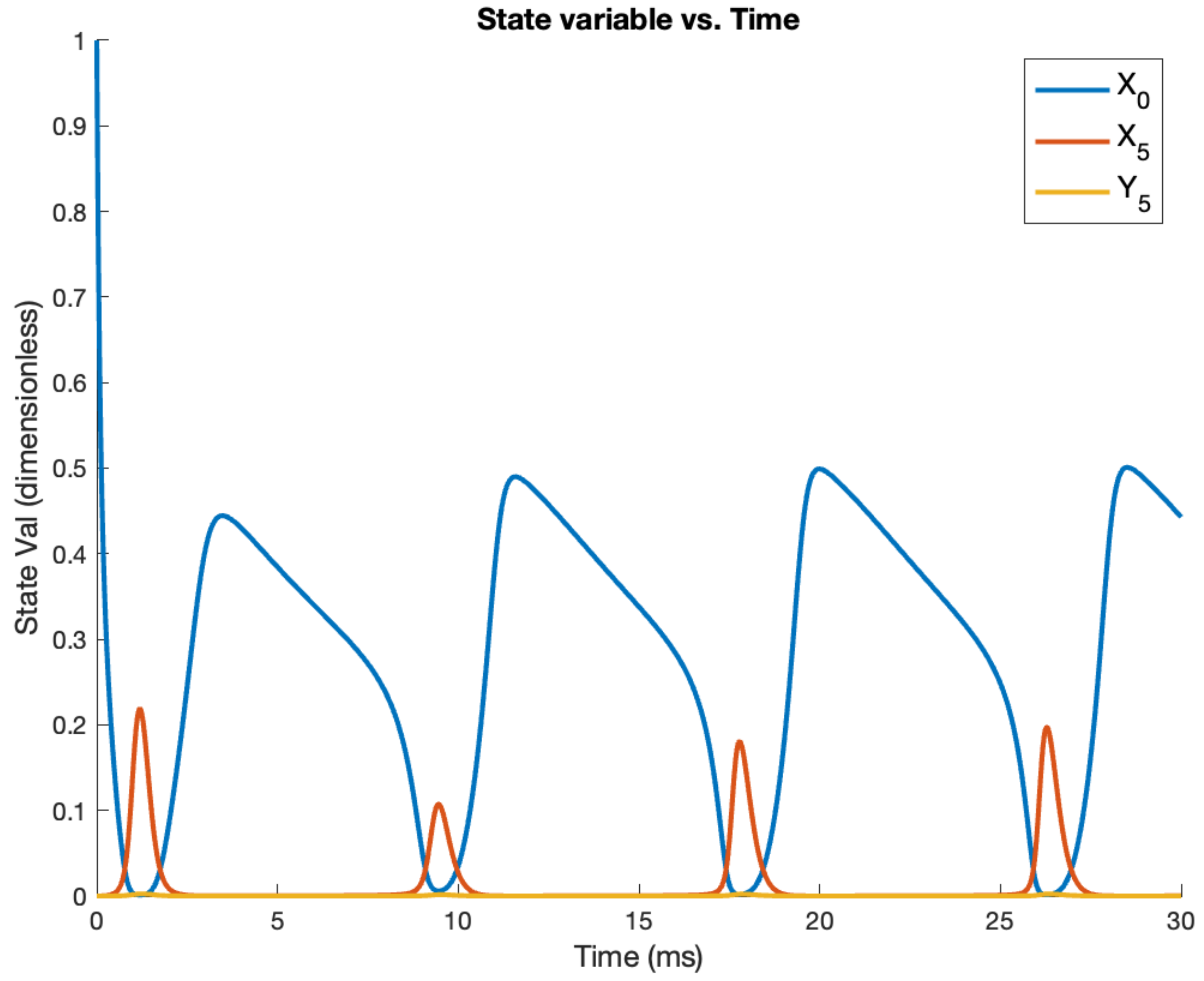


$I_{inj} = 50nA$

States Dynamics



$I_{inj} = 20nA$



$I_{inj} = 50nA$

Summary

- Model the presynaptic Ca^{2+} channel and diffusion (and vesicle release) within the presynaptic terminal during on-transient and off-transient.
- Membrane potential is formulated either by rectangular function or Hodgkin-Huxley model.
- Captures and reproduces most salient features of Ca^{2+} channel and diffusion described in Peskin's 2000 notes *Mathematical Aspects of Neurophysiology.*