Modeling Action Potentials

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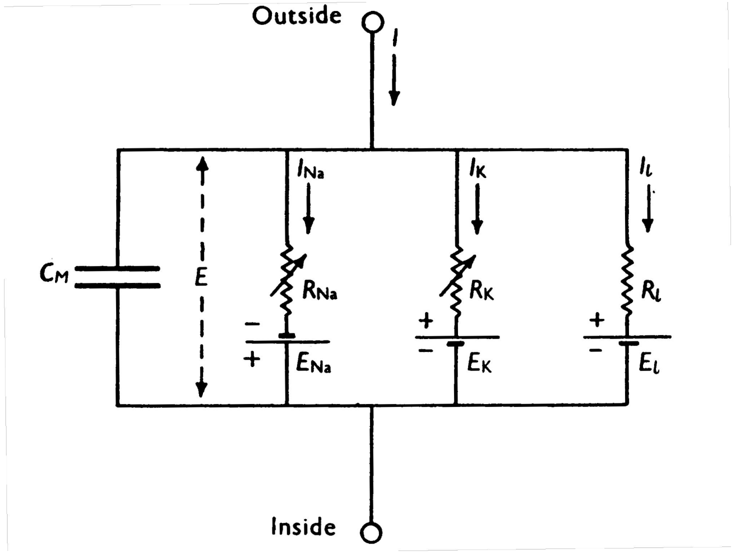
Problem Statement & Motivation

Hodgkin Huxley Model: Describe the propagation of action potentials along neurons focusing on *conductance, current,* and *voltage*.

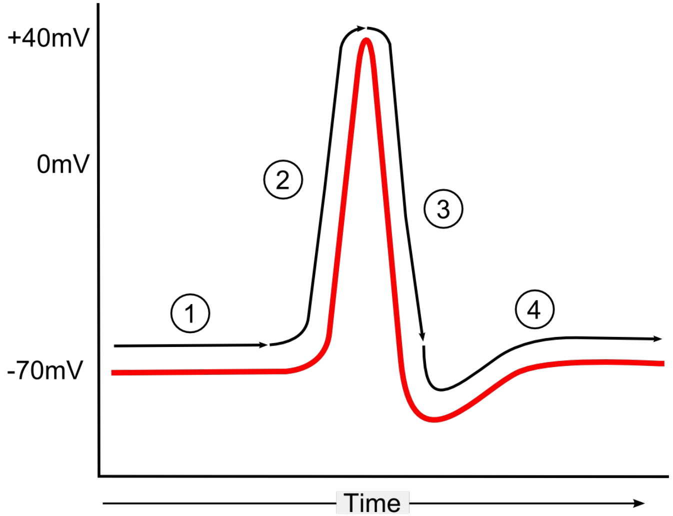
Goal:

- Model Action Potentials via Simulink using the Hodgkin Huxley model
  - Recreate an action potential with focus on the dynamics of sodium and potassium voltage gated channels
  - Expand upon it with the dynamics of sodium/potassium ion pumps
- Variations to ion concentrations and effects on AP
  - Cross check with literature



Background Information

- Action Potential can be seen as an explosion of electrical activity where the cell membrane rapidly rises (depolarization) and falls (repolarization)
    - Depolarization
        - Na ions influx into the cell with rapid opening of the Na voltage gated ion channels
    - Peak + Repolarization
        - Na ions flow in but voltage gated ion channels begin to deactivate
        - K ions flow out of cell from slow activation of K voltage gated ion channels
- Channels eventually reach steady state



Describe the control system and its component in relevant physical detail.

Control system defined to be the Hodgkin Huxley equations

Sodium channels:	Potassium channels:
- *m particles* = activation - *h particles* = deactivation	- *n particles* = activation

Determine sodium, potassium, and leak channel conductance → current calculation for Hodgkin Huxley model

**Equations listed on next slide*

Sodium Equations

$$I_M = C_M \frac{dV_m}{dt} + (V_M - V_{Na})G_{Na} + (V_M - V_K)G_K + (V_M - V_L)G_L$$

$$V_{Na} = \frac{kT}{q}\left(\frac{1}{[Na]_o} + \frac{1}{[Na]_i}\right)\frac{1}{V}\frac{I_M}{F} \rightarrow \textit{assuming non constant reverse potential}$$

$$G_{Na} = G_{Na,max} m^3 h$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

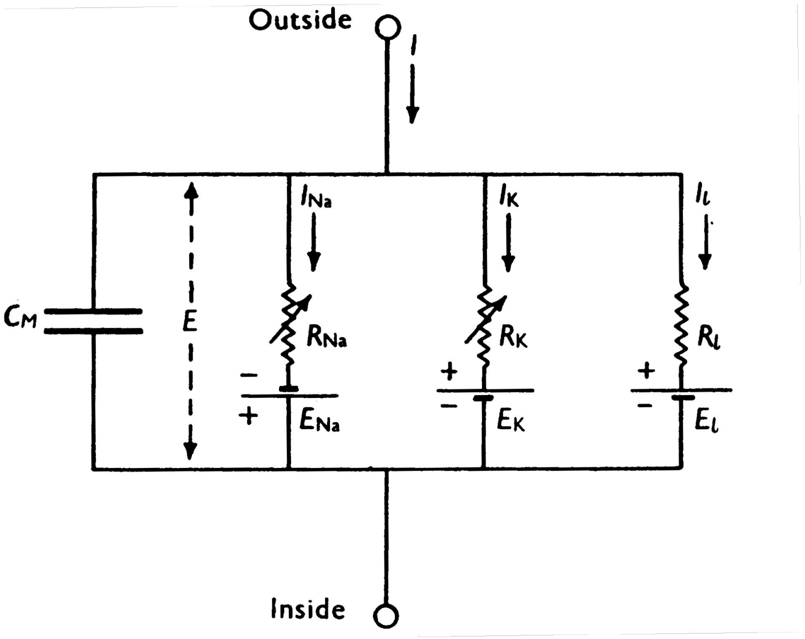
$$\alpha_h = \frac{0.07}{e^{0.05V'}}$$

$$\beta_h = \frac{1}{e^{(3-0.1V')} + 1}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$

$$\alpha_m = \frac{2.5 - 0.1V'}{e^{(2.5-0.1V')} - 1}$$

$$\beta_m = \frac{4}{e^{\left(\frac{V'}{18}\right)}}$$



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$$\beta_h = \frac{1}{e^{(3-0.1V')} + 1}$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$$

Potassium Equations & Constants

$$I_M = C_M \frac{dV_m}{dt} + (V_M - V_{Na})G_{Na} + (V_M - V_K)G_K + (V_M - V_L)G_L$$

$$V_K = \frac{kT}{q}\left(\frac{1}{[K]_o} + \frac{1}{[K]_i}\right)\frac{1}{V}\frac{I_M}{F} \rightarrow \textit{assuming non constant reverse potential}$$

$$G_K = G_{K,max}n^4$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$

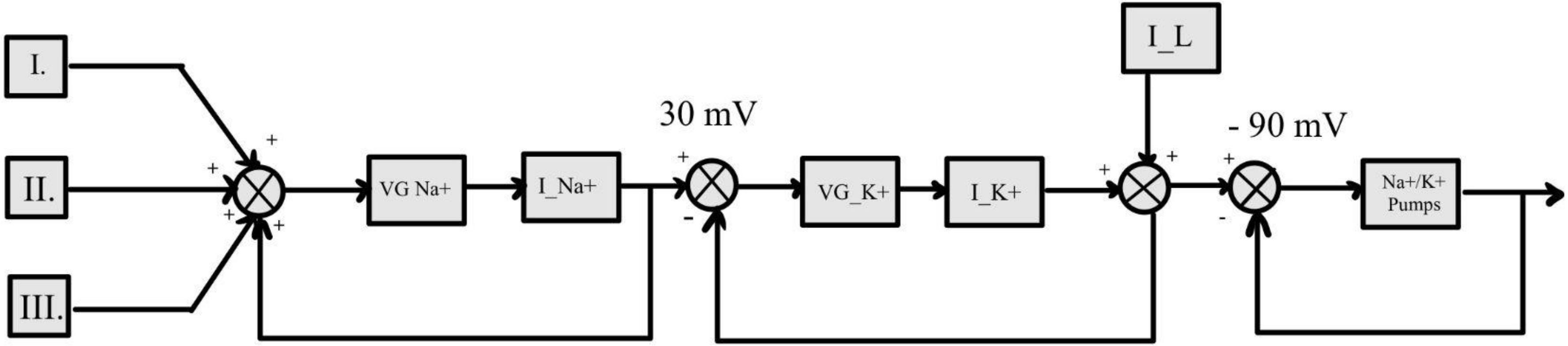
$$\alpha_n = \frac{0.1 - 0.01V'}{e^{(1-0.1V')} - 1}$$

$$\beta_n = \frac{0.125}{e^{0.0125V'}}$$

Constant Variable	Numerical Value	Units
$V_{Initial}$	0	mV
$V_{Resting}$	-70	mV
E_{Na}	115	mV
E_K	-12	mV
E_{Leak}	10.613	mV
C_M	1	$\mu F/cm^2$
G_{Na}	0.3	mS/cm^2
G_K	120	mS/cm^2
G_{Leak}	36	mS/cm^2

** values obtained via literature

Block diagram in time domain



Transfer Function of Biosystem

$$Im = Cm\left(\frac{dVm}{dt}\right) + (Vm - Vna)Gna + (Vm - Vk)Gk + (Vm - Vl)Gl$$

$$L(Im(s)) + Gna * L(Vna(s)) + Gk * L(Vk(s)) = L(Vm(s)) * [SCm + Gna + Gk + Gl] - \frac{GlVl}{s} \quad (1)$$

$$L(Vna(s)) = L(Im(s)) * (\frac{KT}{qv})(\frac{1}{[Na]i} + \frac{1}{[Na]o}) \quad (2)$$

$$L(Vk(s)) = L(Im(s)) * (\frac{KT}{qv})(\frac{1}{[K]i} + \frac{1}{[K]o}) \quad (3)$$

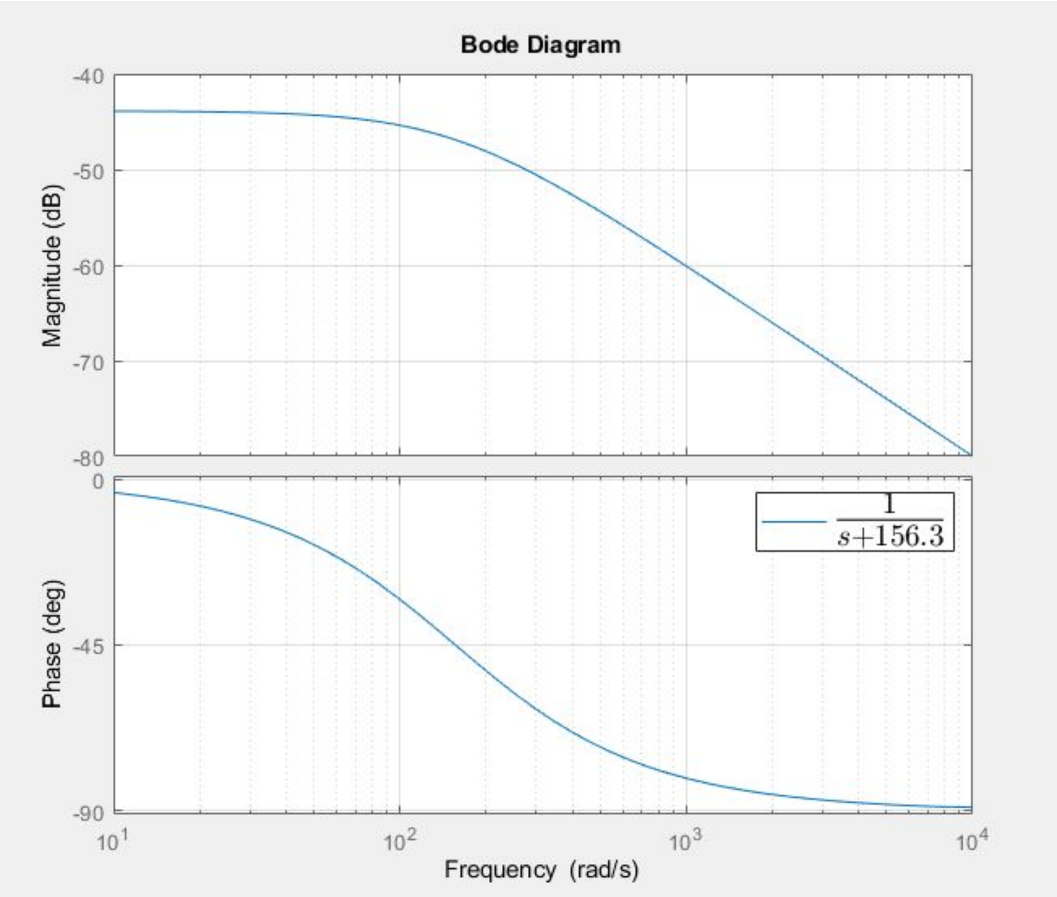
Plugging equations 2, 3 into equation 1 yields the transfer function,

$$H(jw) = \frac{L(Vm(s))}{L(Im(s))} = \frac{1 + \left(\frac{KT}{qF}\right)\left[\frac{1}{[Na]o} + \frac{1}{[Na]i} + \frac{1}{[K]o} + \frac{1}{[K]i}\right]}{SCm + Gna + Gk + Gl}$$

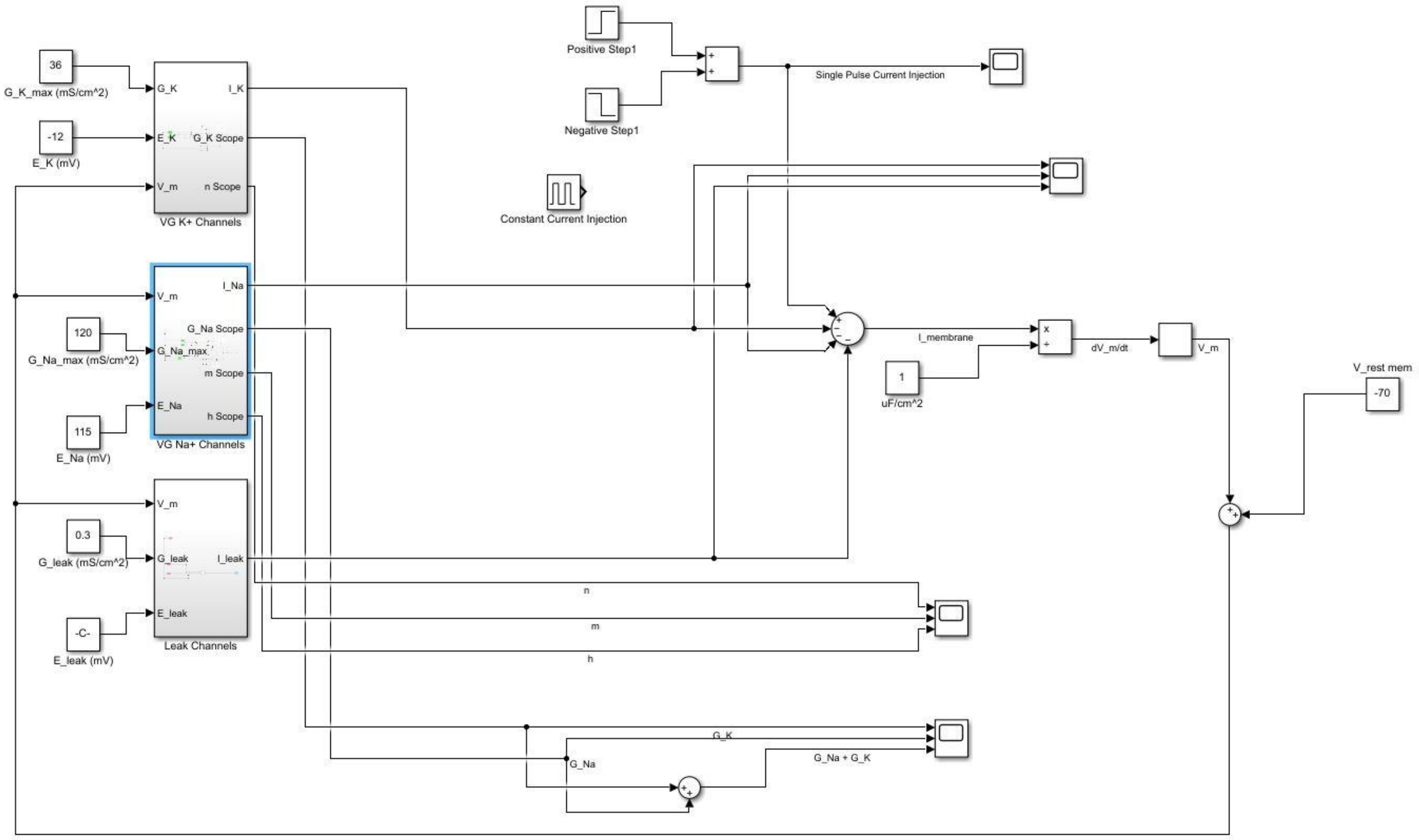
Pole at; $s = -\frac{Gna+Gk+Gl}{Cm}$

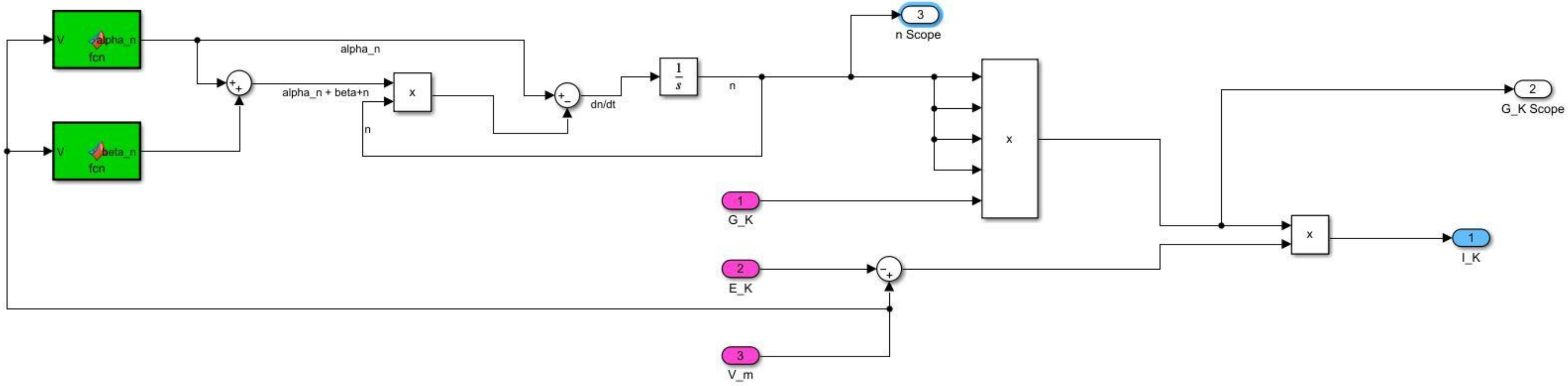
This is stable as the pole will always be less than 0 as these conductance will be positive

Bode Plot of the Biosystem



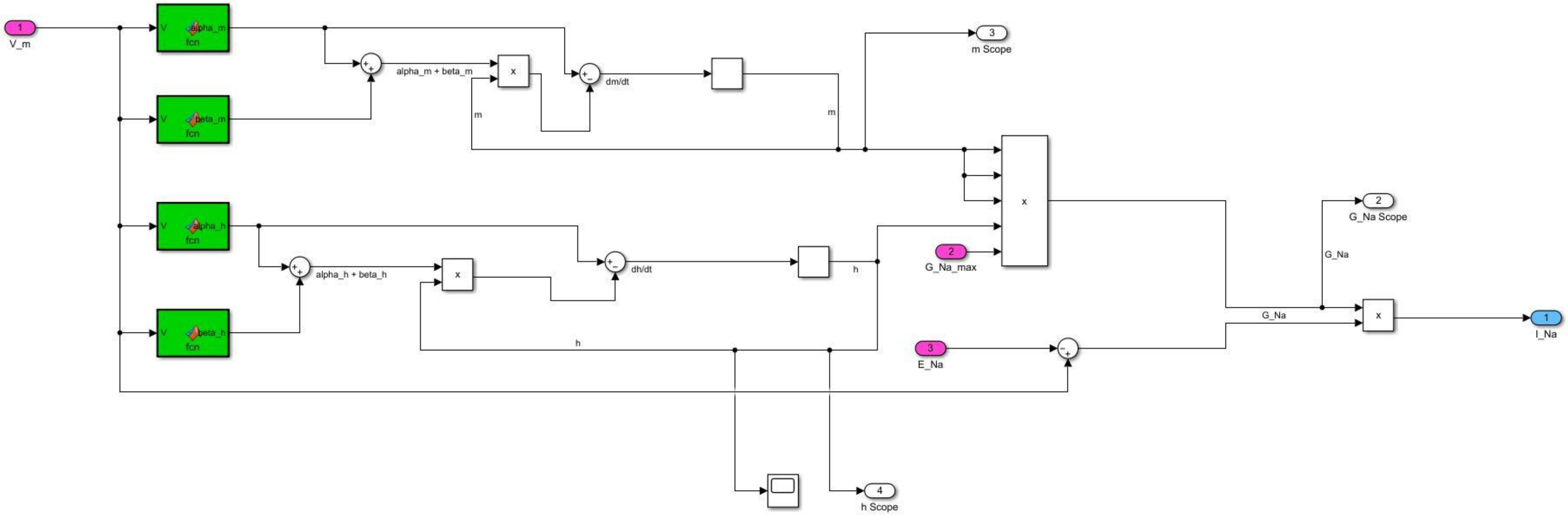
SIMULINK of Voltage Gated Ion Channels for Na+/K+





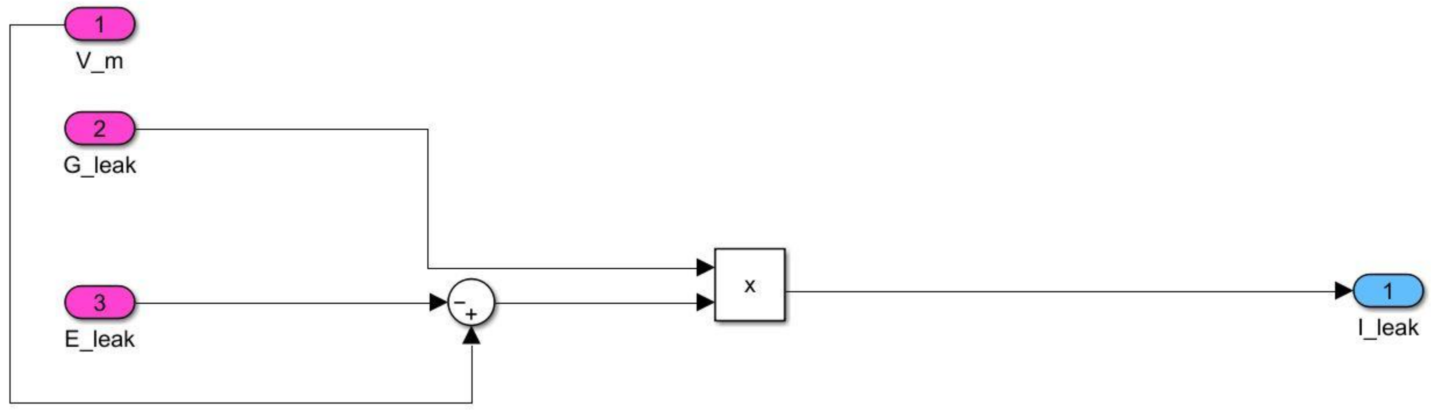
Subsystem 1: Voltage-gated Potassium Channels.

- Dependent on gating variables n and membrane voltage (V_m)
- $\boldsymbol{\alpha}_n$ and β_n are voltage-dependent variables which represent the transfer rate coefficients of gating channels from closed to opened state ($\boldsymbol{\alpha}_n$) and opened to closed state (β_n).
- Output is the current of potassium



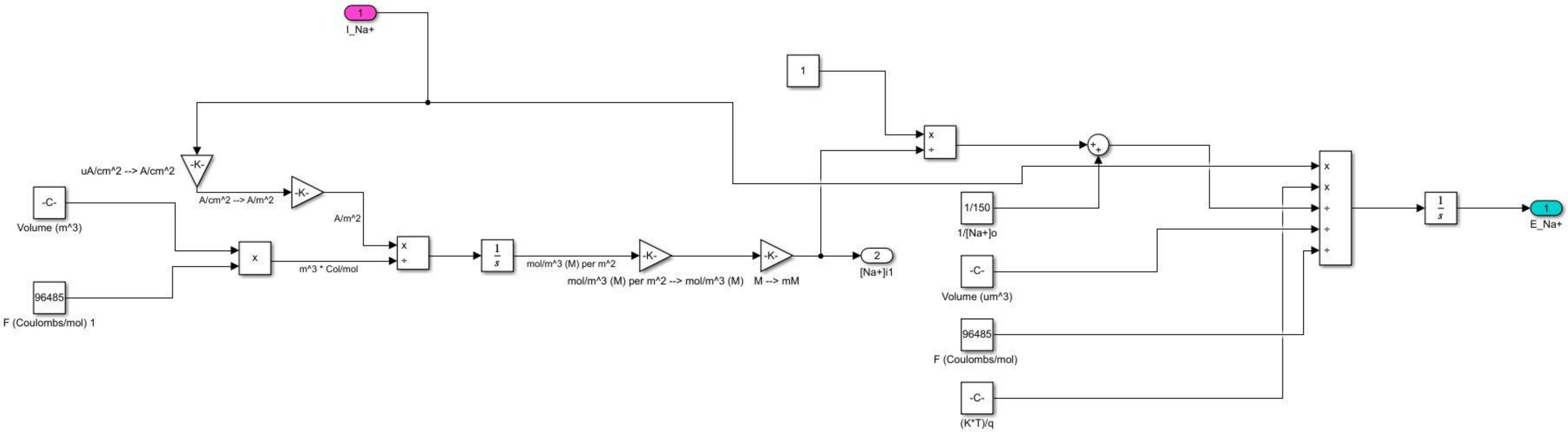
Subsystem 2: Voltage-gated Sodium Channels.

- Dependent on gating variables m & h and membrane voltage (V_m)
- $\boldsymbol{\alpha}_{m,h}$ and $\boldsymbol{\beta}_{m,h}$ are also voltage-dependent variables which represent the transfer rate coefficients of gating channels from closed to opened state ($\boldsymbol{\alpha}_n$) and opened to closed state ($\boldsymbol{\beta}_n$).
- Output is the current of sodium

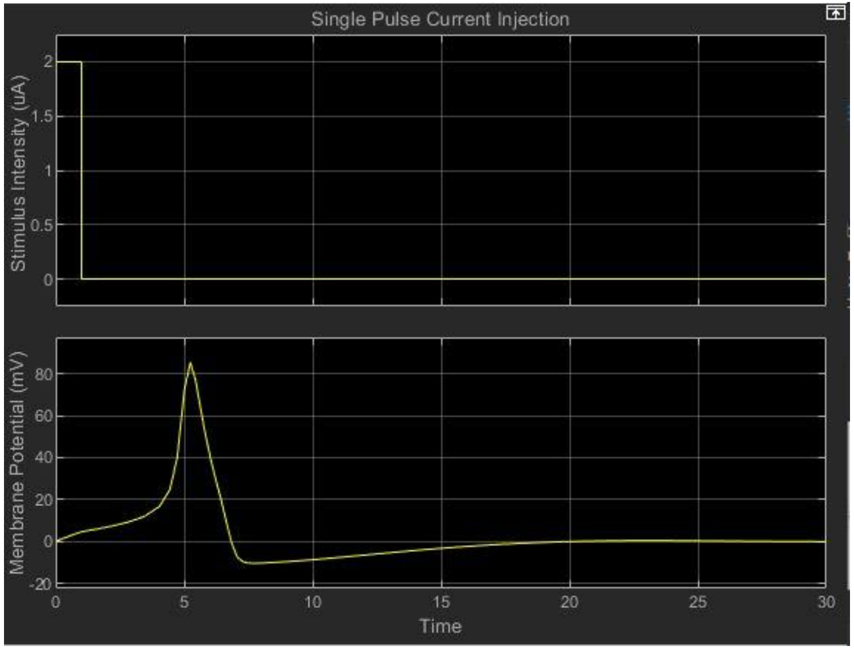


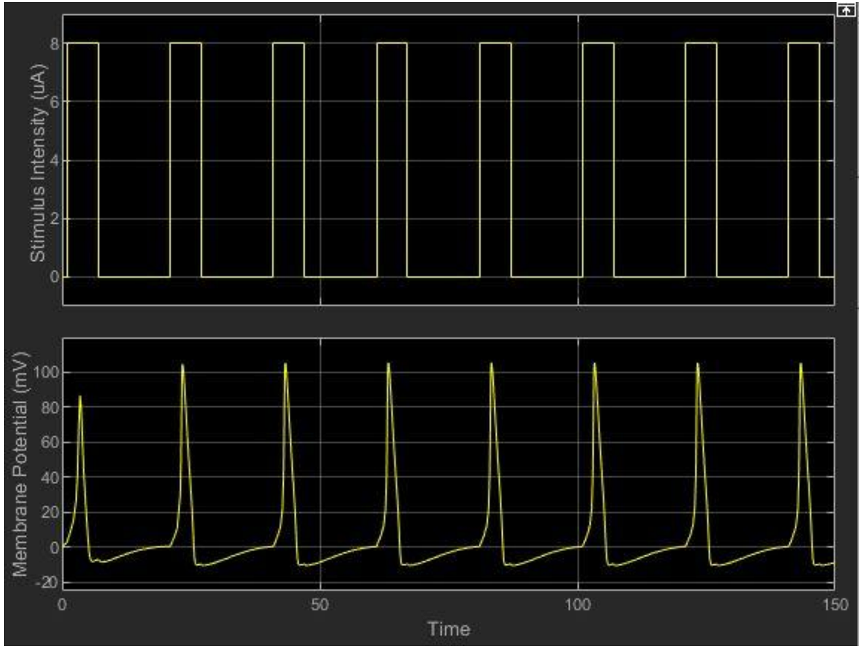
Subsystem 3: Leak Channels

- Independent from voltage and any gating variables since they open and close randomly
- Output is the leak current
- Leak channels is important in terms of restoring the resting membrane potential since it serves as a feedback mechanism, allowing K+ to flow back into the cell.



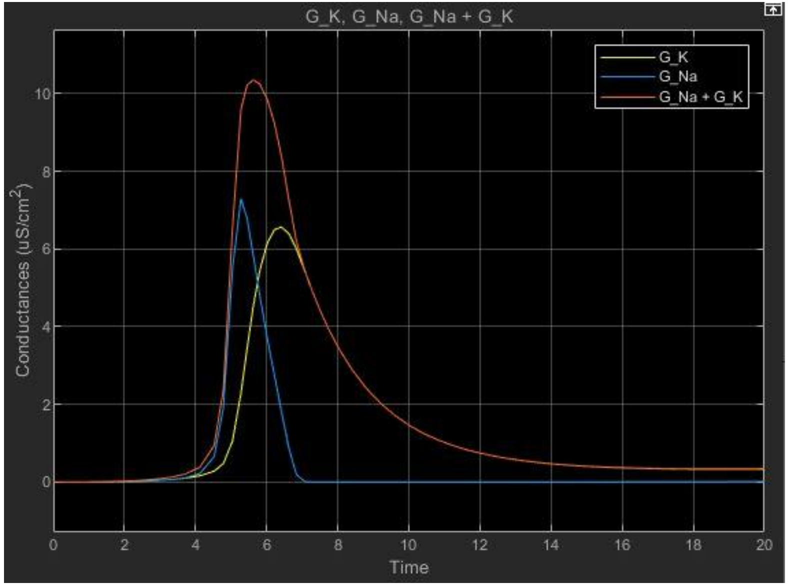
- This model was made in order to model the dynamic of ion pumps
- Dynamics of ion pumps affect the ion's reverse potentials, making the reverse potential a function of intracellular and extracellular ion concentrations

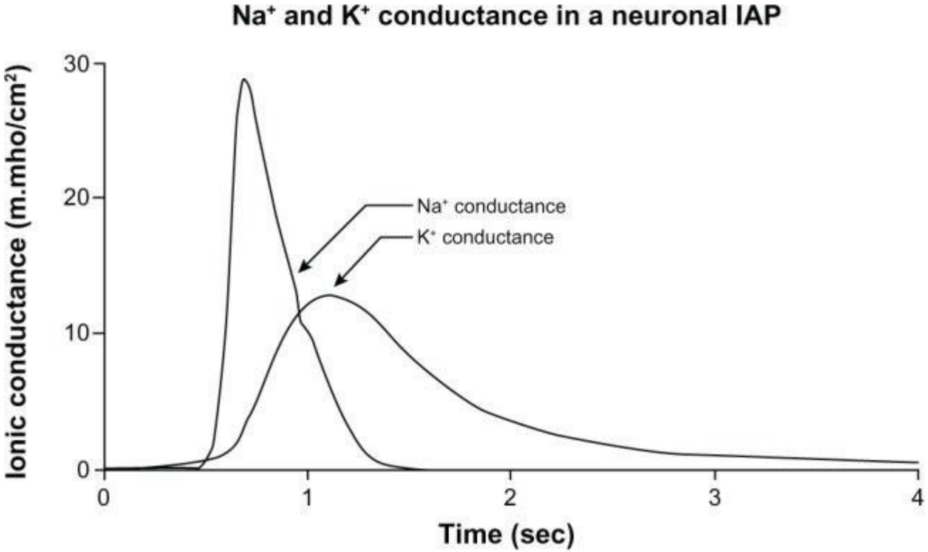




I. Response of model with a single pulse of current with magnitude of 2 uA

II. Response of model with a wave of current with magnitude of 8 uA at 53.3 Hz





III. Our plot displays the conductances of Na+, K+ and the total conductance. Left plot exhibits similarities to the plot from literature. The difference in magnitude of conductance of K+ could be due to differences in I.C (when deriving for the gating variables).

Comparison of Biosystem Simulink with Physiological Phenomenon

Physiological Observations

- Know AP stays between E_Na and E_K from previous courses
    - During repolarization, the cell membrane potential approaches but never equates E_K due to slight resting permeability to Na ions
    - Similarly for depolarization, the cell membrane potential approaches but never equates nor surpasses the E_Na due to permeability to K ions

Simulink

- AP starts at 0 mV instead of the normal -70 mV
- AP follows same depolarization→ repolarization → hyperpolarization curve

Errors That May Be Present in Model

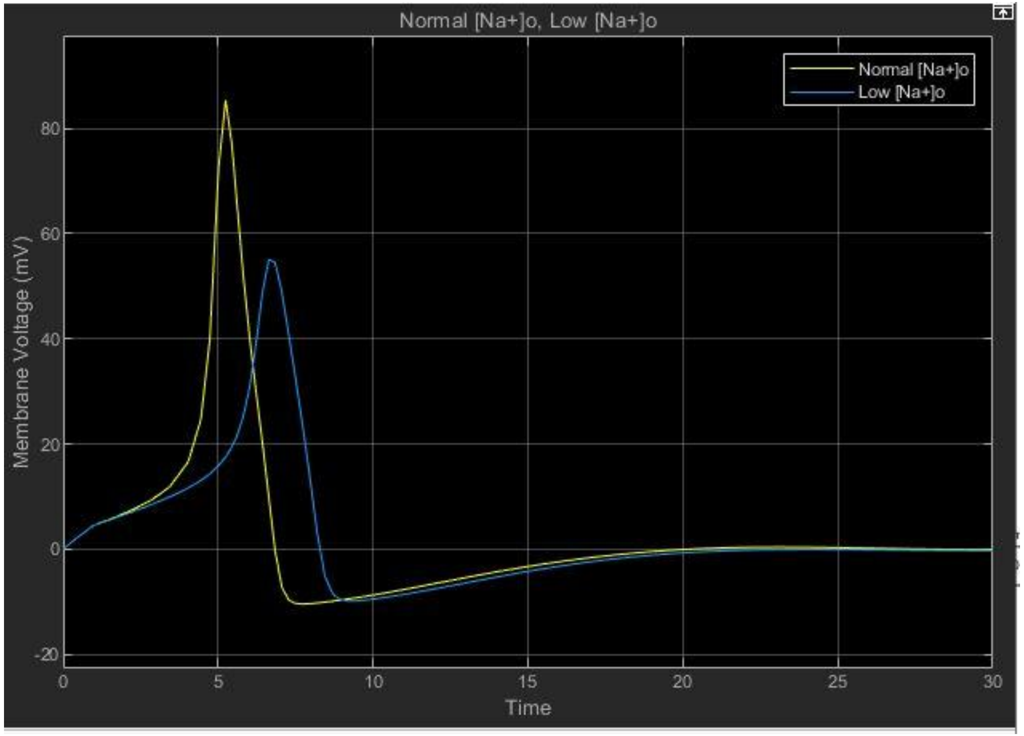
- Equations
  - When calculating, the G_L (aka conductance of leak channels) is assumed to be constant
  - For volume of an ion channel, it is approximated as shape of truncated cone
- Hodgkin Huxley Model
  - Gated variables vary significantly across literature and are approximated equations
    - Three *m particles* required to activate sodium channels
    - One *h particle* required to deactivate sodium channels
    - Four *n particles* required to activate potassium channel
- Biology
  - Threshold allowing for AP to occur assumed to be constant
  - Resting membrane potential is constant
  - Volume of channel is approximated as a truncated cone

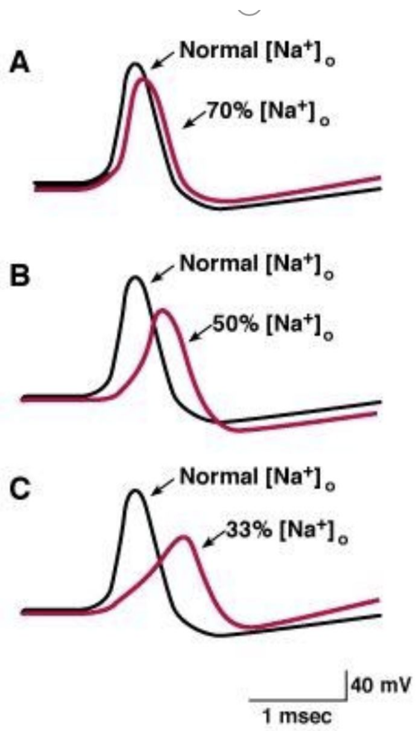
- Simulink
  - Voltage starts at 0 mV instead of the actual -65 mV
    - Unable to shift plot to match literature

Applications into a Clinical Syndrome

- Studying how low sodium concentration may influence action potentials
    - EX: Sodium gated voltage channel NavCHs
        - Genetic disorders → Mutations and/or polymorphisms
        - Channel prone to closing due to slow inactivation of D3-D4 linker (channel protein on cytoplasmic membrane)
- Hypothesis:
    - Low sodium concentration = Decrease in resting membrane potential and E_Na
        - According to Nernst
        - Backed by literature

Model this via Simulink by introducing a higher/lower ion concentrations





IV. Simulink system at normal vs lowered extracellular Na concentrations. Left plot exhibits similarities to the plot from literature. The difference in magnitude of membrane voltage could be due to errors in Simulink.

Improvements + Conclusion

- Model generated trend of AP with different voltage values
- Decreased sodium concentration → lowered action potential voltage values
  - Cross checked both with literature
- System is stable

Future Improvements:

- Accurately model the ion pumps and incorporate it into the main AP model to see the dynamics and cooperation of different subsystems
  - Work to get a more accurate AP model

Thank you!