Modelling Transients in  ction Potentials

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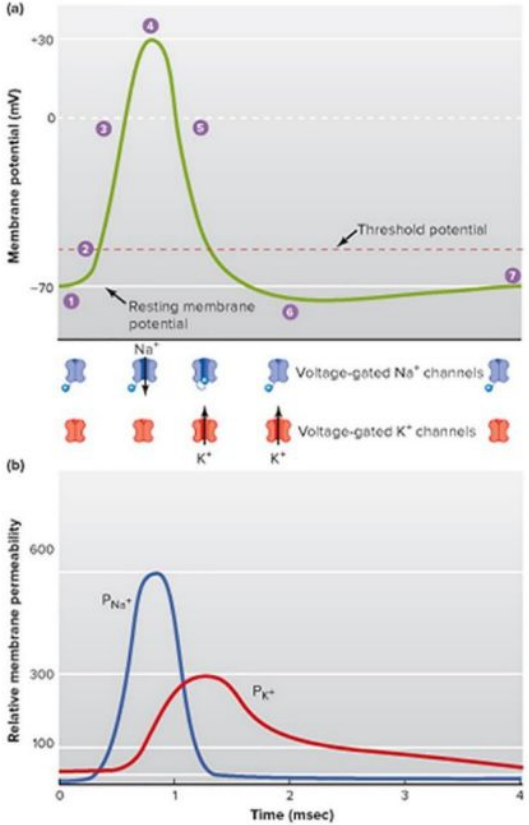
Background [1,5]

- Neuron is the functional unit of nervous system
  - Afferent neuron: Information into CNS (brain & spine) from peripheral endings
  - Efferent neuron: Information out of CNS to effector cells (glands, muscles, neurons)
  - Interneurons: integrators and signal changers, only inside the CNS
- Neurons rely on chemical and electrical stimuli to relay information
  - We'll be focusing on the modelling of the chemical stimuli
- Glial cells in CNS:
  - Astrocytes: regulate composition of extracellular fluid in CNS by removing potassium ions and neurotransmitters around synapses
    - Potassium relevant for action potential propagation
- Resting membrane potential: -40 to -90 mV
  - Changes in potential due to movement of ions
- Graded potentials produced from ligand-gated ion channels and mechanically gated ion channels serve as initiating stimulus for action potential
- Voltage-gated ion channels give membrane ability to undergo action potentials

Background [1,5]

- Calculation of resting membrane potential using:
  - Goldman-Hodgin-Katz (GHK) equation
    - $$E = \frac{RT}{F} \ln \frac{P_K[K_o^+] + P_{Na}[Na_o^+] + P_{Cl}[Cl_i^-]}{P_K[K_i^+] + P_{Na}[Na_i^+] + P_{Cl}[Cl_i^-]}$$
    - T=temperature, n=valence, R=gas constant, F = Faraday's constant
- Na^+/K^+- ATPase pump sets up concentration gradients
  - Greater flux of K^+ out of cell than Na^+ into cell due to greater permeability (leak channels) for K^+
    - Negative membrane (resting potential) develops
    - Na^+ has low permeability but large electrochemical gradient
  - Local membrane brought to threshold voltage by depolarizing stimulus
  - Current through voltage gated Na^+ channels rapidly depolarizes membrane, causing more Na^+ channels to open
  - Inactivation of Na^+ channels, delayed opening of K^+ channels halts membrane depolarization
  - Outward current through open voltage-gated K^+ channels repolarizes membrane back to negative potential
  - Na^+ channels go from inactivated to closed state
  - K^+ channels close, returning membrane potential to resting value.

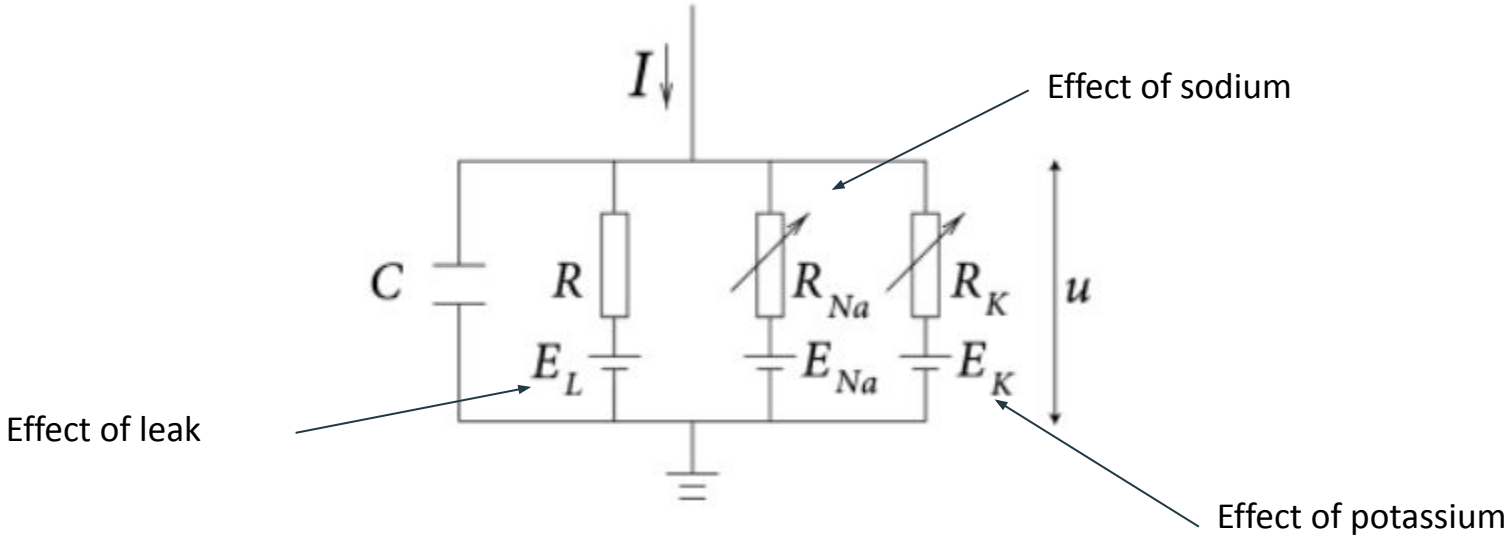


Clinical Relevance [6]

- Early epilepsy is clinical symptom of patients with CDKL5-deficiency disorder
  - Whole-cell patch-clamp recordings revealed higher action potential firing rate and lower rehobase in CDD organoids, indicating increased neuronal excitability
  - Dysfunction of voltage-gated ion channels in CDD neurons that leads to hyperexcitability
  - Higher Na^+ and K^+ current densities and negative shift in Na^+ channel activation
- The above is observed in Rett syndrome patients as well
- Change in current densities and channel activation affects excitation and firing rate
  - This could be a modelled in a complex system in Simulink

Hodgkin-Huxley Model[3,4]

- Cell membranes can be modeled as a capacitor in parallel with an ionic current.
  - Hodgkin-Huxley: current is split up by charged molecules (sodium, potassium, and chlorine)
  - Model based on the propagation of an electrical signal along a squid giant axon

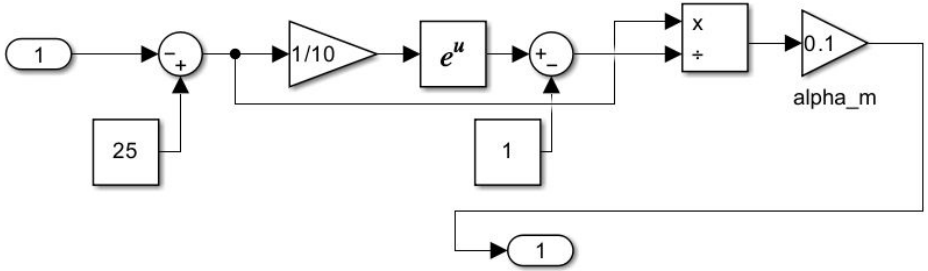


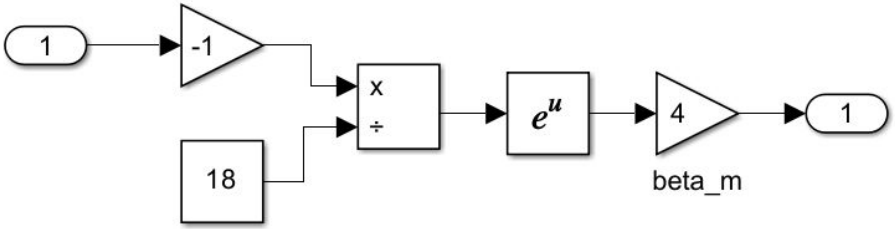
Hodgkin-Huxley Model (Part 2)[3,4]

- Let m^3h represent the effects of sodium conductance, n^4 be the effects of potassium conductance.
  - α and β are numerical values depending on the voltage potential
  - g values are constants with respect to each ion

$$C_m \frac{dv}{dt} = -\bar{g}_K n^4 (v - v_K) - \bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_L (v - v_L)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$





$$\alpha_m = 0.1\,\frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1},$$

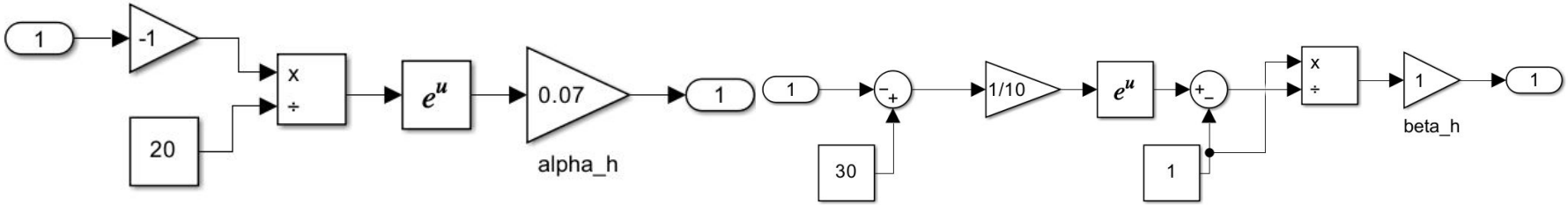
$$\beta_m = 4\,\exp\left(\frac{-v}{18}\right),$$

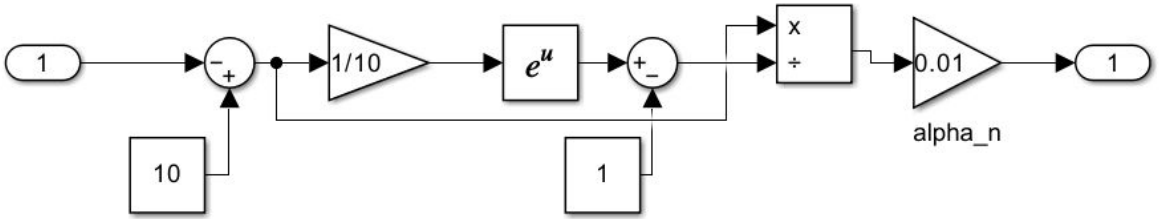
$$\alpha_h = 0.07\,\exp\left(\frac{-v}{20}\right),$$

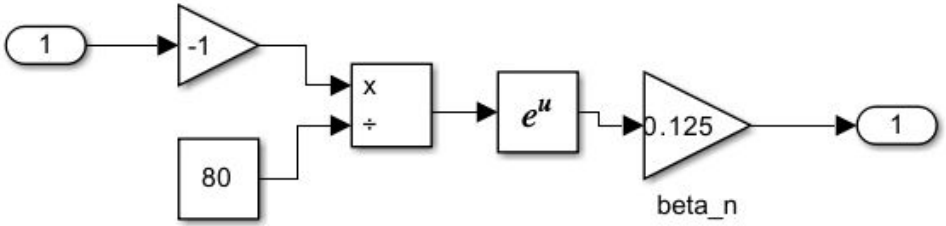
$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1},$$

$$\alpha_n = 0.01\,\frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1},$$

$$\beta_n = 0.125\,\exp\left(\frac{-v}{80}\right).$$







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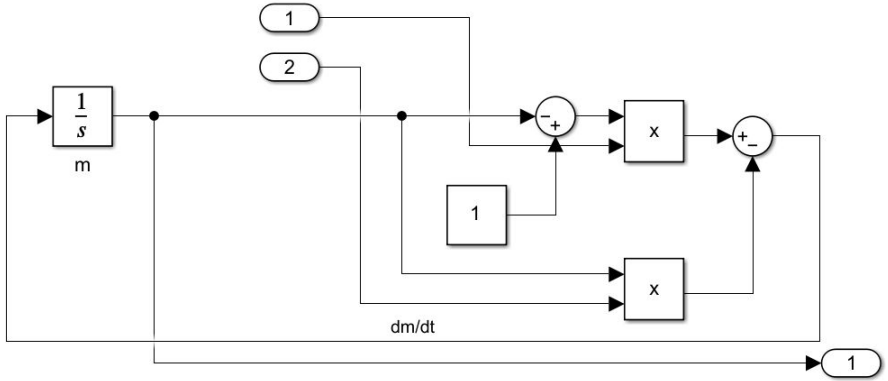
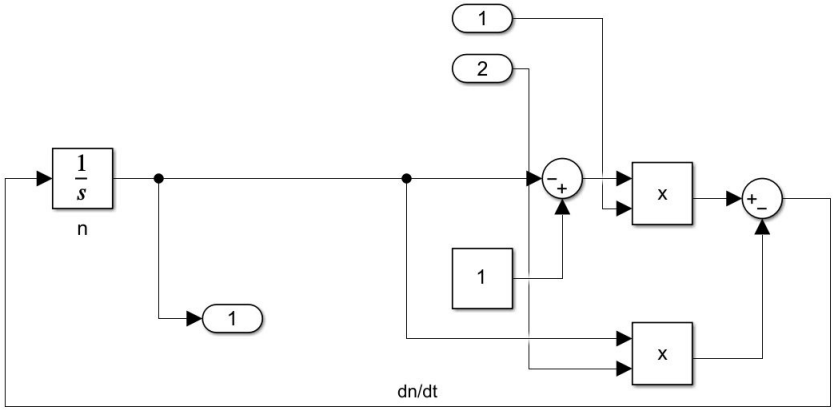
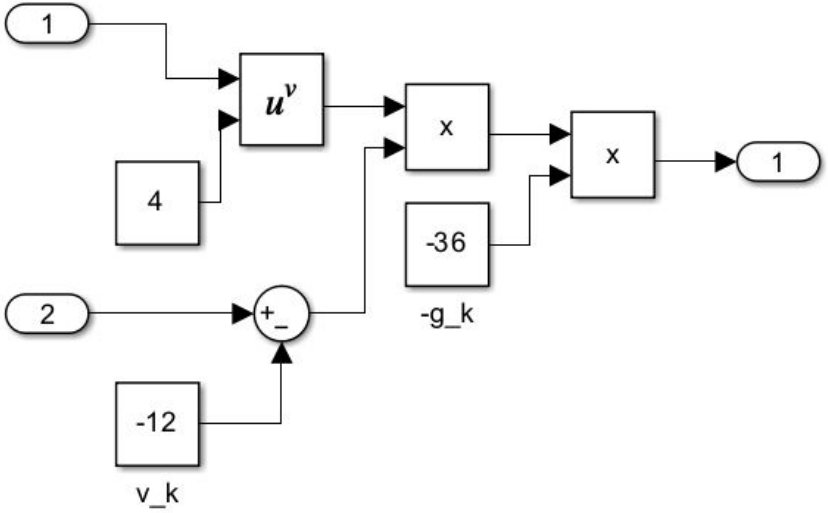
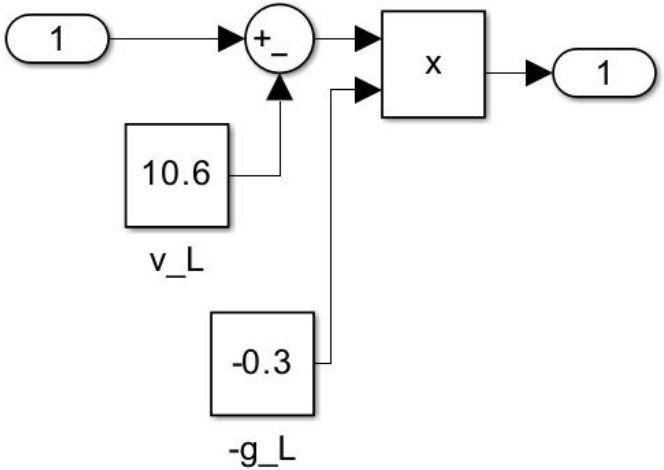
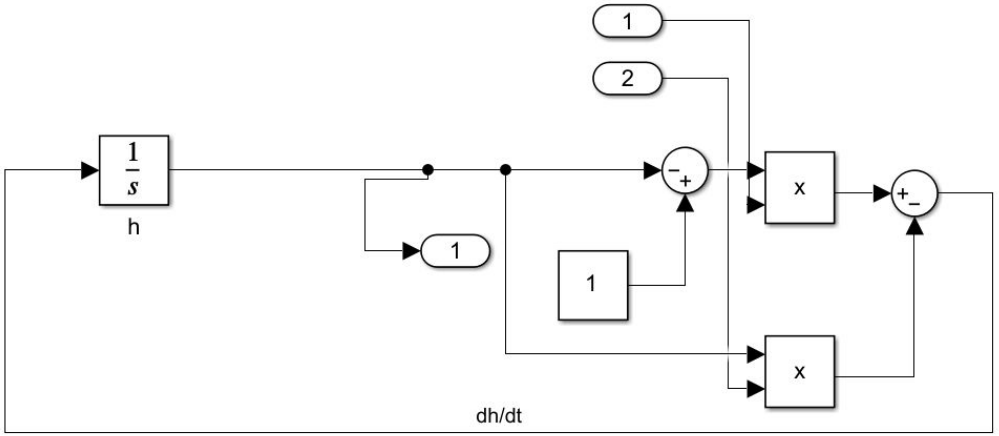
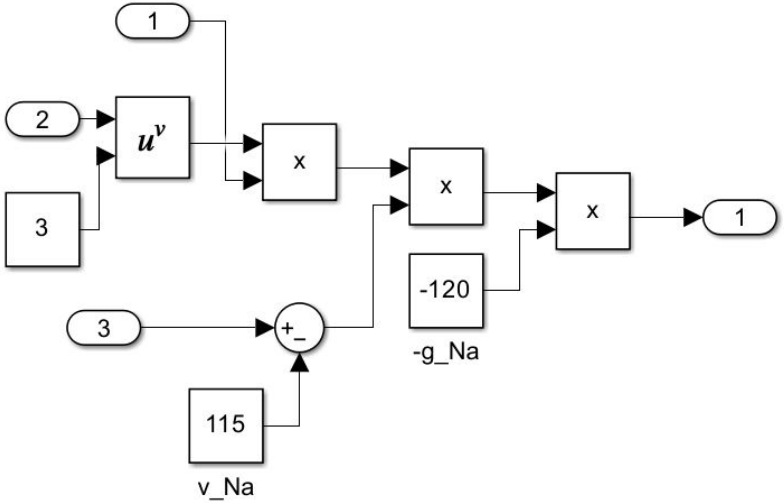

1
2
$\frac{1}{s}$
m
1
x
x
dm/dt
1

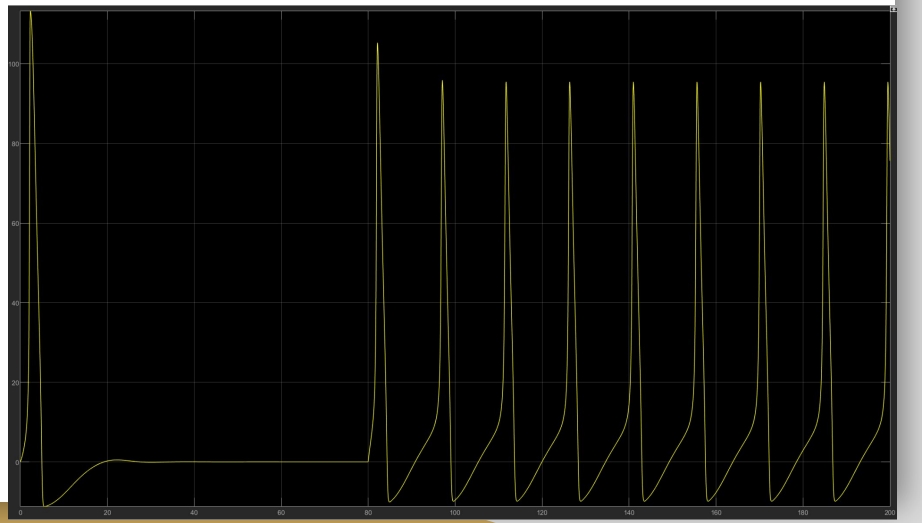

1
2
$\frac{1}{s}$
n
1
1
x
x
dn/dt


1
u^v
4
x
x
1
-36
-g_k
2
-12
v_k

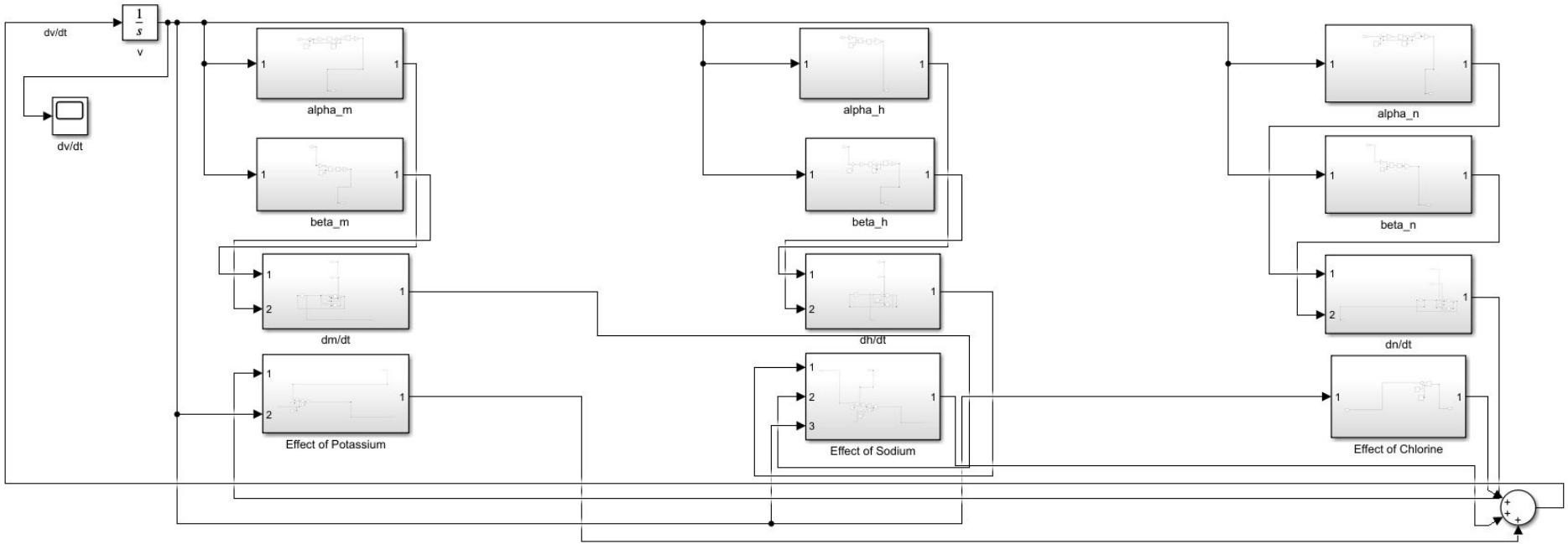

1
10.6
v_L
x
1
-0.3
-g_L


1
2
1/s
h
1
1
x
x
dh/dt


1
2
u^v
3
x
x
x
1
-120
-g_Na
3
115
v_Na



Hodgkin-Huxley Applied



Izhikevich Model[2]

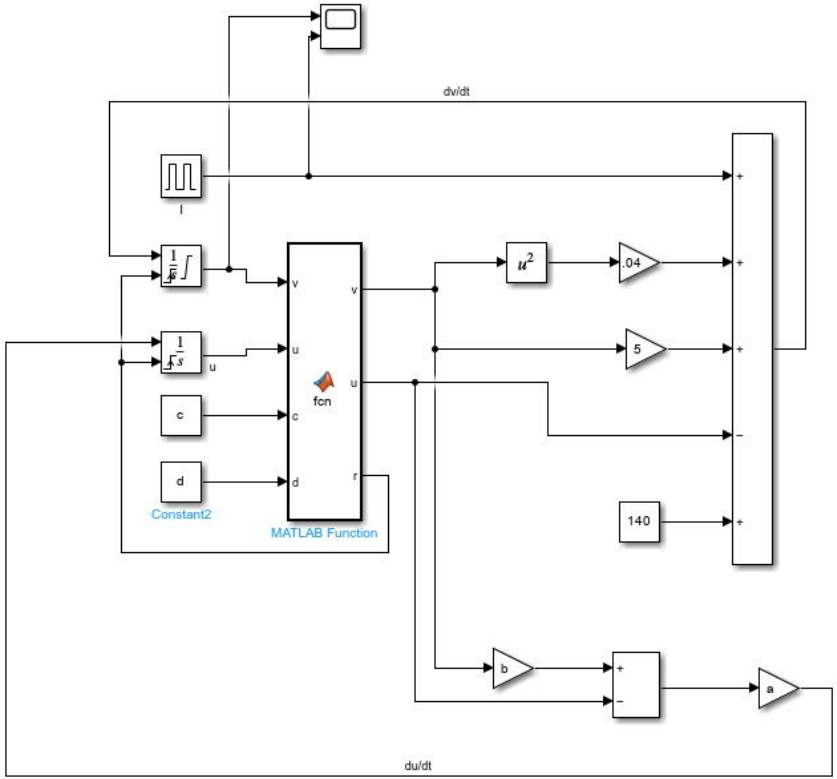
- Designed to reproduce the spiking and bursting behavior of known types of cortical neurons.
  - Combines the biologically plausibility of Hodgkin–Huxley-type dynamics and the computational efficiency of integrate-and-fire neurons.
  - Modelled using a 2D system of ODEs

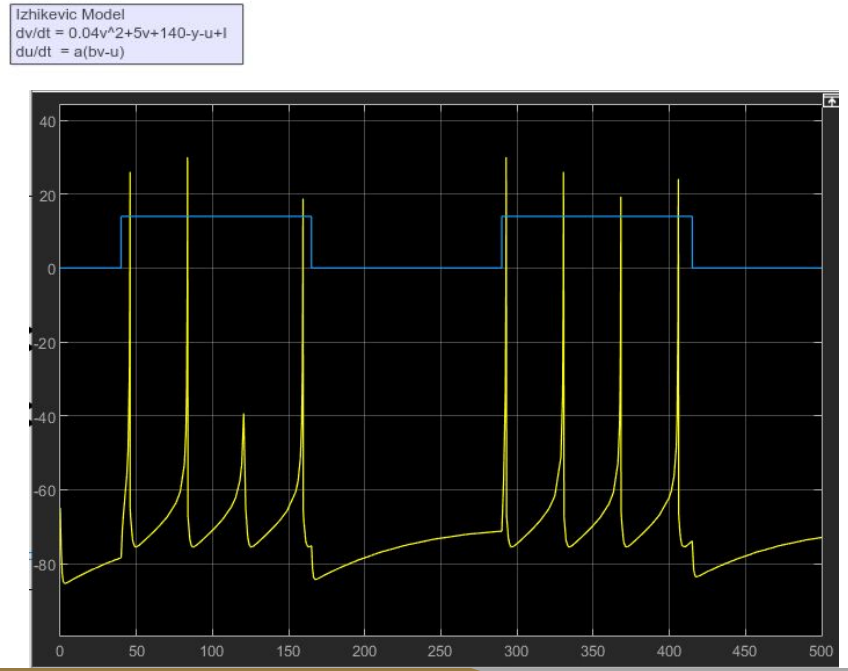
- This model allows for the recreation of complex neuronal behaviour
  - Simplest canonical model of the Hodgkin Huxley class of models

$$v' = 0.04v^2 + 5v + 140 - u + I$$
$$u' = a(bv - u)$$

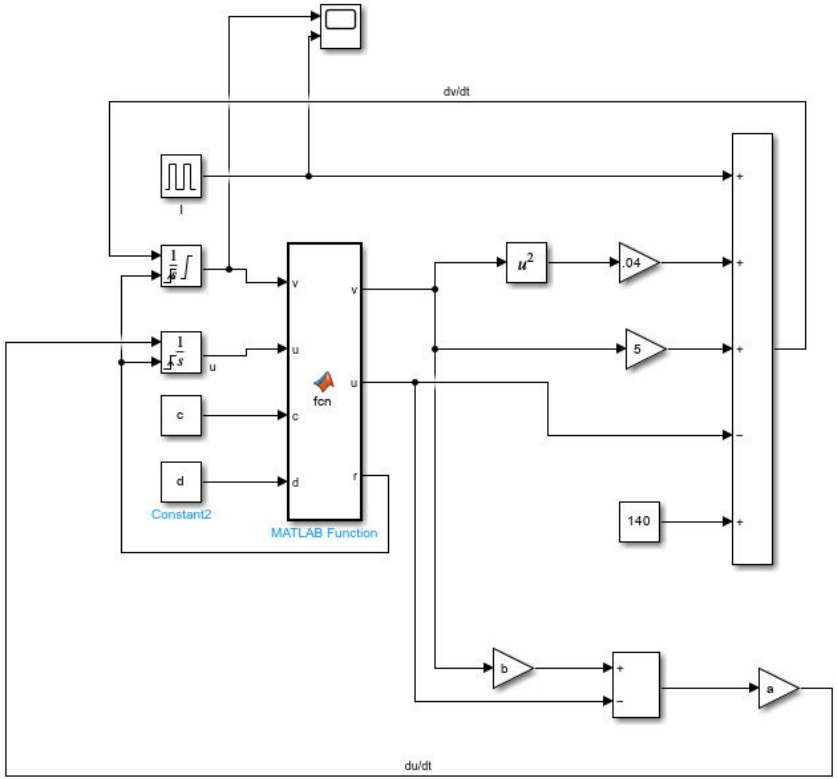
$$\text{if } v \geq 30\ \text{mV, then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d. \end{cases}$$

Izhikevich Model - Individual Spiking [2]

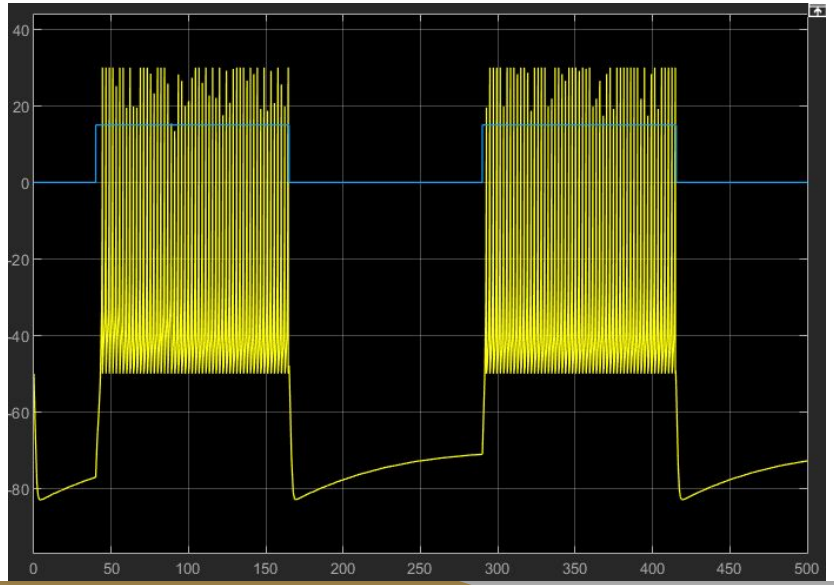




Izhikevich Model - Bursting [2]



Izhikevic Model
dv/dt = 0.04v^2+5v+140-y-u+I
du/dt = a(bv-u)



Future Directions

- Our models simulate action potentials looking at the basic ions during “normal” physiological behavior and cell signaling
- In truth, neuronal signaling is far more complex, and includes glutamatergic signaling and GABAergic signaling
    - In graduate level neuroengineering and study, this could be modelled more in depth
    - Requires more subsystems
- As indicated by clinical relevance slide:
    - Voltage gated and ligand gated channels can be affected by genetic mutations and disorders
    - Leads to different conditions for depolarization and repolarization
    - Can play with initial conditions more
    - With biosensors or some more patient specific data, the model can be adapted
- We would want to additionally analyze perturbations in the model to identify potential treatment pipelines

Acknowledgements

- We would like to thank Dr. Cauwenberghs for his guidance and lectures throughout the quarter

References

[1] Cauwenberghs, G. Lecture 7 Notes: *Origins of biopotentials. Excitable Cells. Nernst and resting potentials. Action Potentials* . 2022 Jan.

[2] Izhikevich EM. Simple model of spiking neurons. IEEE Trans Neural Netw. 2003;14(6):1569-72. doi: 10.1109/TNN.2003.820440. PMID: 18244602.

[3] Keener, James P., and Sneyd Alfred James Robert. *Mathematical Physiology*. Springer, 1998.

[4] Nelson ME(2011) Electrophysiological models of neural processing. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 3: 74-92.

[5] Widmaier, Eric, et al. *Vander's Human Physiology*. McGraw-Hill, 2014.

[6] Wu W, Yao H, Negraes PD, Wang J, Trujillo CA, de Souza JS, Muotri AR, Haddad GG. Neuronal hyperexcitability and ion channel dysfunction in CDKL5-deficiency patient iPSC-derived cortical organoids. Neurobiol Dis. 2022 Nov;174:105882. doi: 10.1016/j.nbd.2022.105882. Epub 2022 Oct 3. PMID: 36202289.