- Hodgkin and Huxley model -

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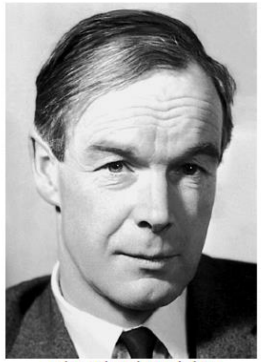
Importance of Hodgkin & Huxley model

- They understood;
  - The basis of neuronal communication: the electrical signal.
  - How this electrical signal is generated and propagated: both under passive and active current flow.
- They mathematically described and ***predicted*** the behaviour of these electrical signals.
  - The predictions were not verifiable at the time.
  - Ultimately verified after decades when the tools got available.

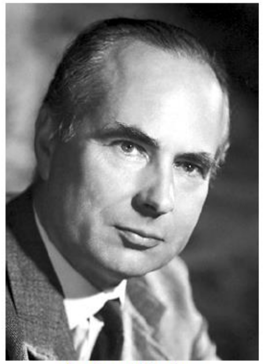
Hodgkin & Huxley

- Allan Lloyd Hodgkin
  - 1914-1998
  - Oxfordshire
  - Trinity College, Cambridge
- Andrew Fielding Huxley
  - 1917-2012
  - London
  - Trinity College, Cambridge

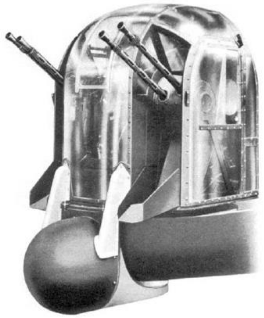
- Hodgkin & Huxley partnership
  - 1935-1939
    - The Voltage Clamp (on a frog)
  - 1939-1945
    - World war II
  - 1946-1952
    - The Hodgkin-Huxley Model
  - 1952-1957
    - Sliding filament theory of muscle contraction
  - 1963
    - Nobel prize in physiology or medicine
  - 1978-1984 & 1984-1990
    - Masters of Trinity College



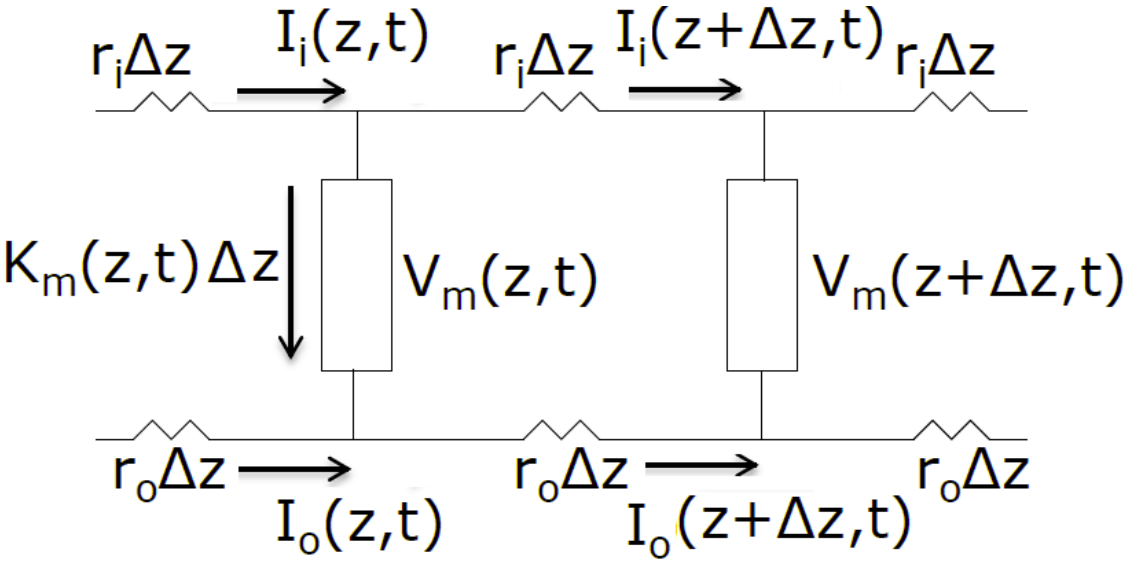
Alan Lloyd Hodgkin



Andrew Huxley



Core-conductor model

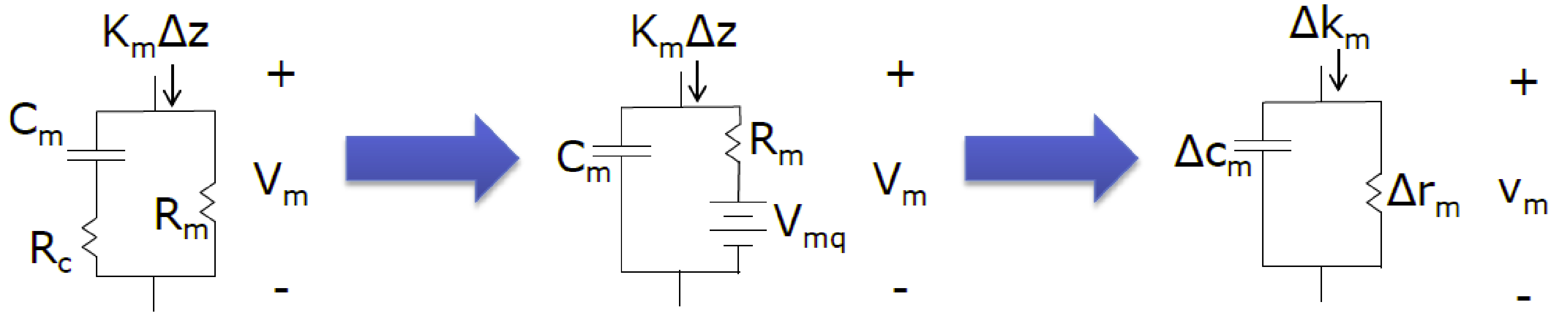


- An infinitesimal segment along the $\hat{z}$ direction Δz

$$\frac{\partial^2 V_m(z,t)}{\partial z^2} = (r_o + r_i) K_m(z,t) - r_o K_e(z,t)$$

Cable model

Cable model | Total variables | Incremental variables

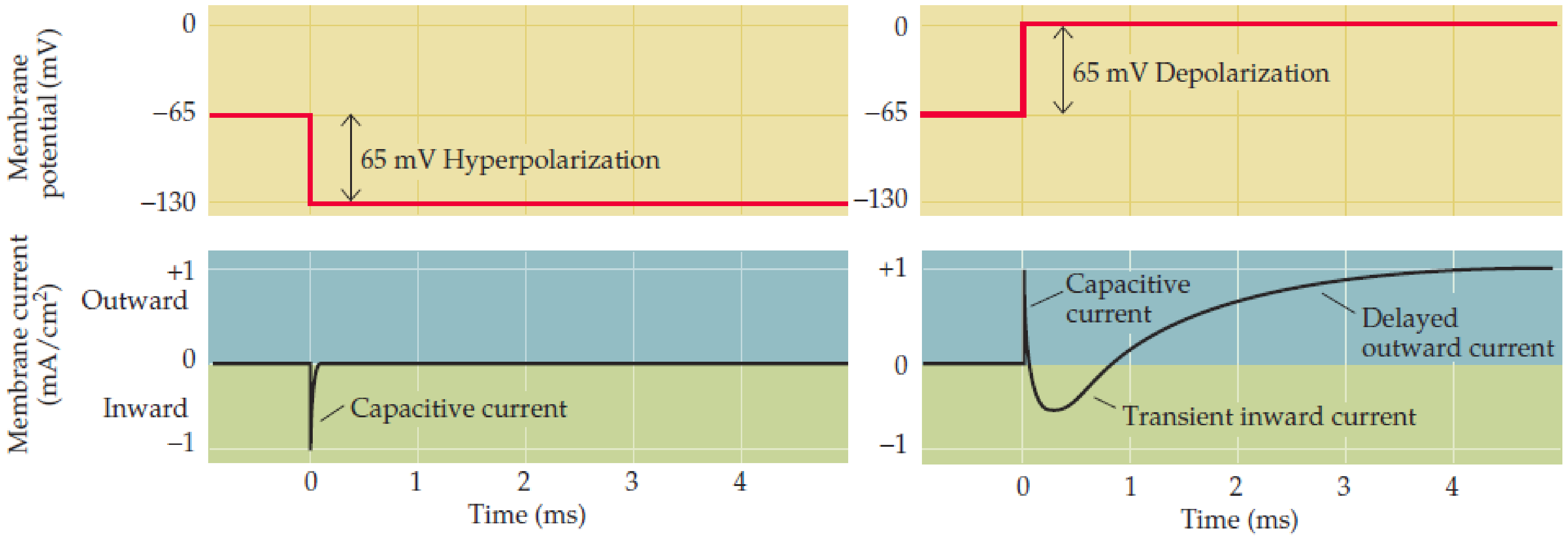


$$\frac{\partial^2 v_m(z,t)}{\partial z^2} = (r_o + r_i)\left(g_m v_m(z,t) + c_m \frac{\partial v_m}{\partial t}\right) - r_o k_e(z,t)$$

- Solution:

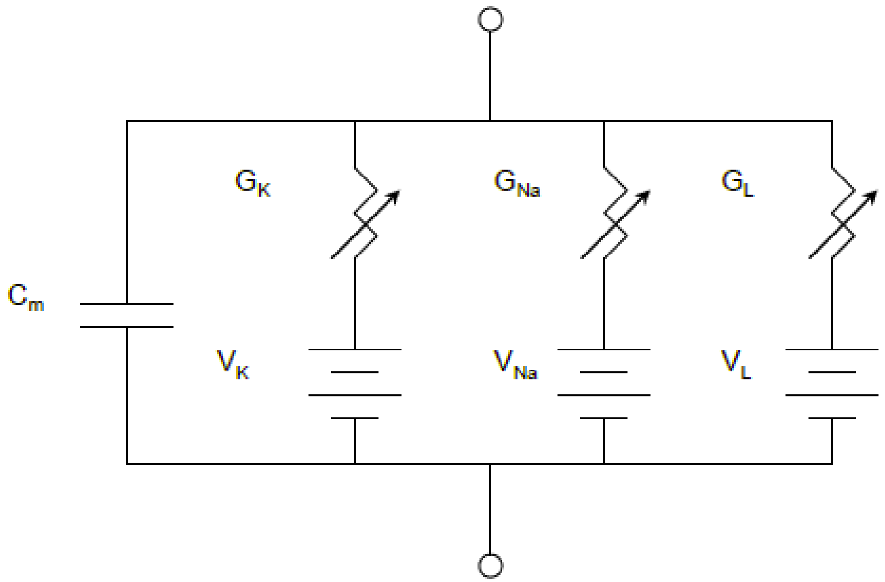
$$v_m(z,t) = \frac{\frac{\lambda r_o Q_e}{\tau}}{\sqrt{4\pi\left(t/\tau\right)}} e^{\left(z/\lambda\right)^2/\left(4t/\tau\right)} e^{-t/\tau}$$

Voltage-dependent ionic currents



- H&H experiment
  - Depolarization induces a capacitive current followed by a
    - Inward current → Na^+ flow
    - Outward current → K^+ flow
      - Persistent due to constant depolarization current

Modelling voltage-dependent ionic conductances

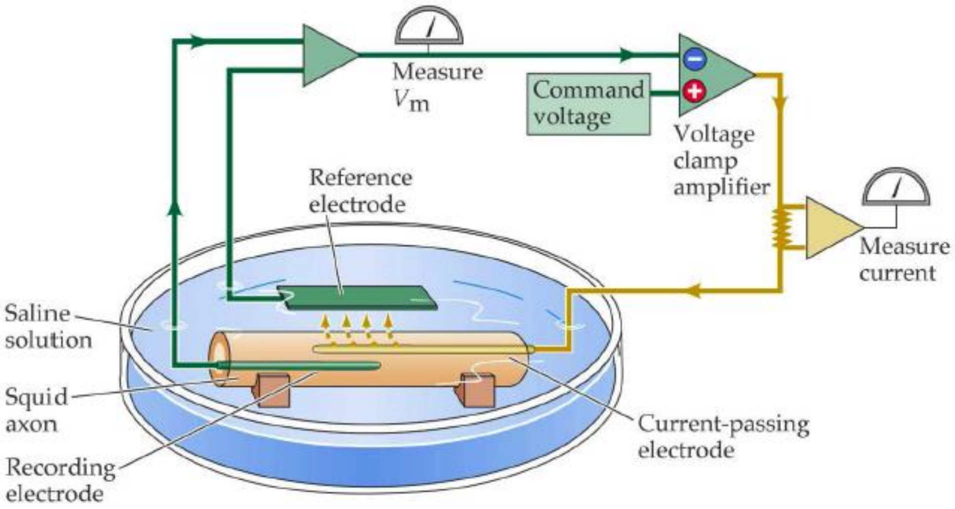


- Separate conductances for Na^+, K^+ and leakage channels (Ca^{2+}, Cl^-)
- Conductances are variables of
  - Time
  - Membrane voltage (which is a function of temperature and other variables)

Finding H&H model parameters

- Voltage clamp
  - Short-circuit the membrane across axial distance (z)
  - No variation w.r.t. time and distance

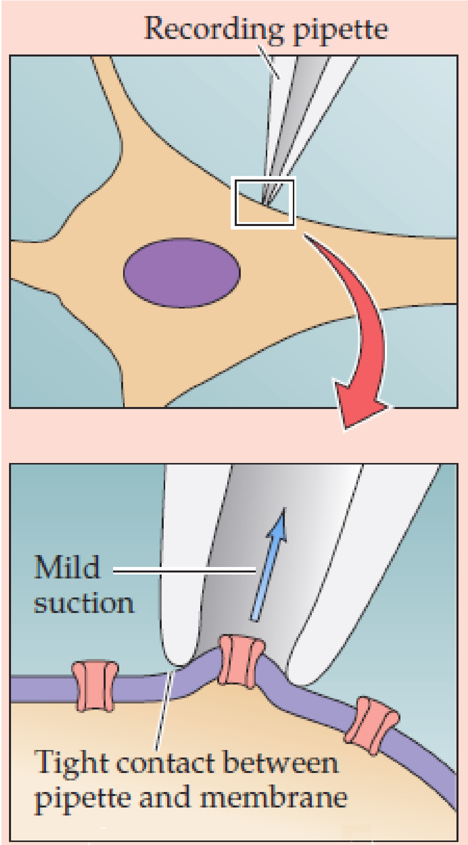
$$\cancelto{0}{\frac{\partial^2 v_m(z,t)}{\partial z^2}} = (r_o + r_i)\left(g_m v_m(z,t) + c_m \cancelto{0}{\frac{\partial v_m}{\partial t}}\right) - r_o k_e(z,t)$$



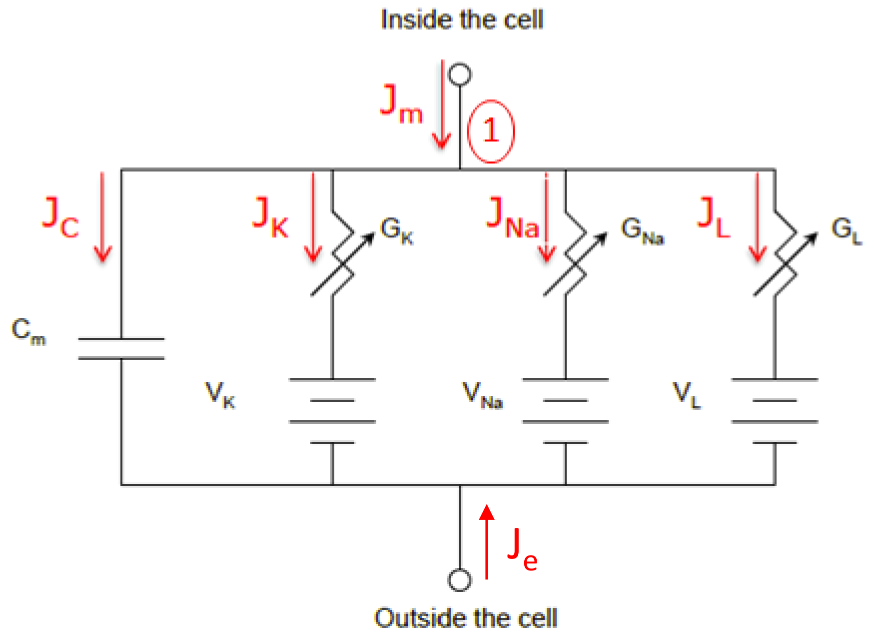
Finding H&H model parameters

- Patch clamp
  - To isolate individual/small populations of ionic channels
  - Used neurotoxins to deactivate specific ion channels
  - Determine currents caused by remaining specific ions

Na channel inhibitors	Tetrodotoxin
K channel inhibitors	Tetraethylammonium
Cl, Ca channel inhibitors	Chlorotoxin, Conotoxin
Inhibitors of synaptic vesicle release	Botulinum toxin, tetanus toxin
Blood brain barrier inhibitors	Aluminium, mercury
Cytoskeleton interference	Arsenic, ammonia
Ca-mediated cytotoxicity	Lead
Multiple effects	Ethanol



- Consider ionic current densities



$$J_c = C_m \frac{\partial V_m}{\partial t} \qquad J_{Na^+} = G_{Na^+}\left(V_m - V_{Na^+}\right)$$

$$J_{K^+} = G_{K^+}\left(V_m - V_{K^+}\right) \qquad J_L = G_L\left(V_m - V_L\right)$$

Derivation of the H&H equation

- From KCL at node 1

$$J_m = J_C + J_{K^+} + J_{Na^+} + J_L - J_e$$

$$J_m = C_m \frac{\partial V_m}{\partial t} + G_{K^+}(V_m - V_{K^+}) + G_{Na^+}(V_m - V_{Na^+}) + G_L(V_m - V_L) - J_e$$

- Recall core-conductor equation

$$\frac{\partial^2 \mathrm{V_m}(\mathrm{z,t})}{\partial \mathrm{z}^2} = (\mathrm{r_o} + \mathrm{r_i})\mathrm{K_m}(\mathrm{z,t}) - \mathrm{r_o}\mathrm{K_e}(\mathrm{z,t})$$

- Converting *K* to *J*

$$K(z,t) = 2\pi a J(z,t)$$

Derivation of the H&H equation

- Then, the core-conductor becomes:

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m(z,t)}{\partial z^2} + \frac{r_o}{(r_o + r_i)} J_e(z,t) = J_m(z,t)$$

- Substituting J_m back to KCL equation

$$\boxed{\begin{aligned} &\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m(z,t)}{\partial z^2} = \\ &C_m \frac{\partial V_m}{\partial t} + G_{K^+}(V_m - V_{K^+}) + G_{Na^+}(V_m - V_{Na^+}) + G_L(V_m - V_L) - \left(1 + \frac{r_o}{(r_o + r_i)}\right) J_e(z,t) \end{aligned}}$$

- G_{K+} and G_{Na+} are functions of V_m and t
- G_L does not depend on V_m and t

Ionic conductances

- Applying voltage and patch clamps, isolate:

$$G_{K^+}(V_m,t) = \overline{G_K} n^4 (V_m,t)$$

$$G_{Na^+}(V_m,t) = \overline{G_{Na}} m^3 (V_m,t) h(V_m,t)$$

- Where $\overline{G_K}$ is a constant
- n, m and h are in the form of:

$$x(V_m,t) = X_\infty - (X_\infty - X_0)e^{-t/\tau}$$

  - whereX_0 and X_∞ are values of x at present and at infinite time
  - And $\tau = \dfrac{1}{\alpha + \beta} \quad \alpha = f_1(V_m), \quad \beta = f_2(V_m)$

Ionic conductances

- Experimentally H&H found that;

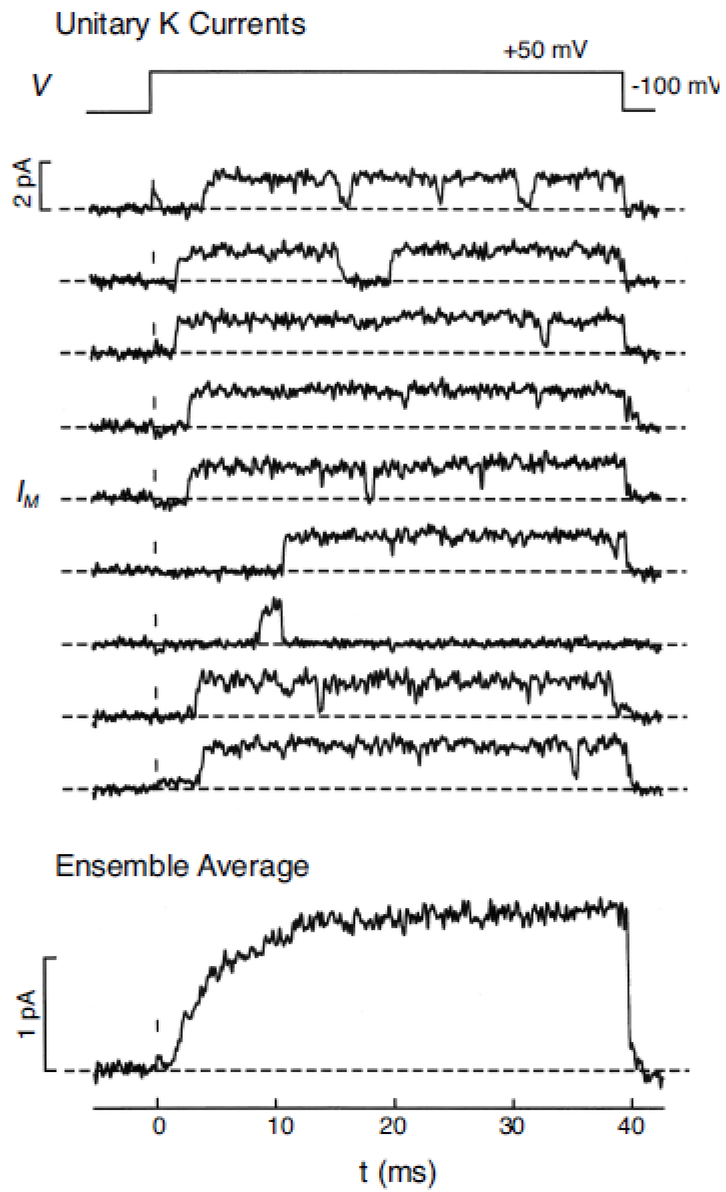
$$\tau_{n,m,h} = \frac{1}{\alpha_{n,m,h}(V_m) + \beta_{n,m,h}(V_m)}$$

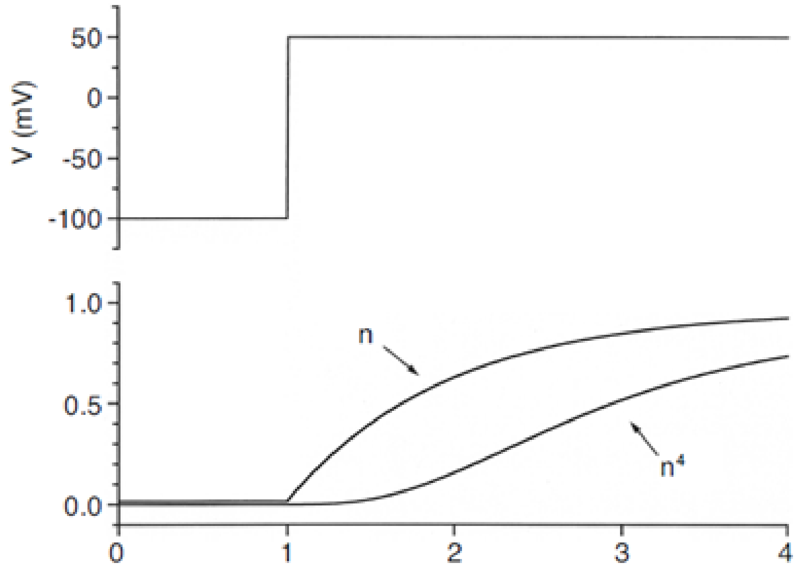
Where

$$\alpha_n(V_m) = \frac{0.01(V_m - 10)}{\exp\left(\frac{V_m - 10}{10}\right) - 1} \qquad \alpha_m(V_m) = \frac{0.1(V_m - 25)}{\exp\left(\frac{V_m - 25}{10}\right) - 1} \qquad \alpha_h(V_m) = 0.07\exp\left(\frac{V_m}{20}\right)$$

$$\beta_n(V_m) = 0.125\exp\left(\frac{V_m}{80}\right) \qquad \beta_m(V_m) = 4\exp\left(\frac{V_m}{18}\right) \qquad \beta_h(V_m) = \frac{1}{\exp\left(\frac{V_m - 30}{10}\right) + 1}$$

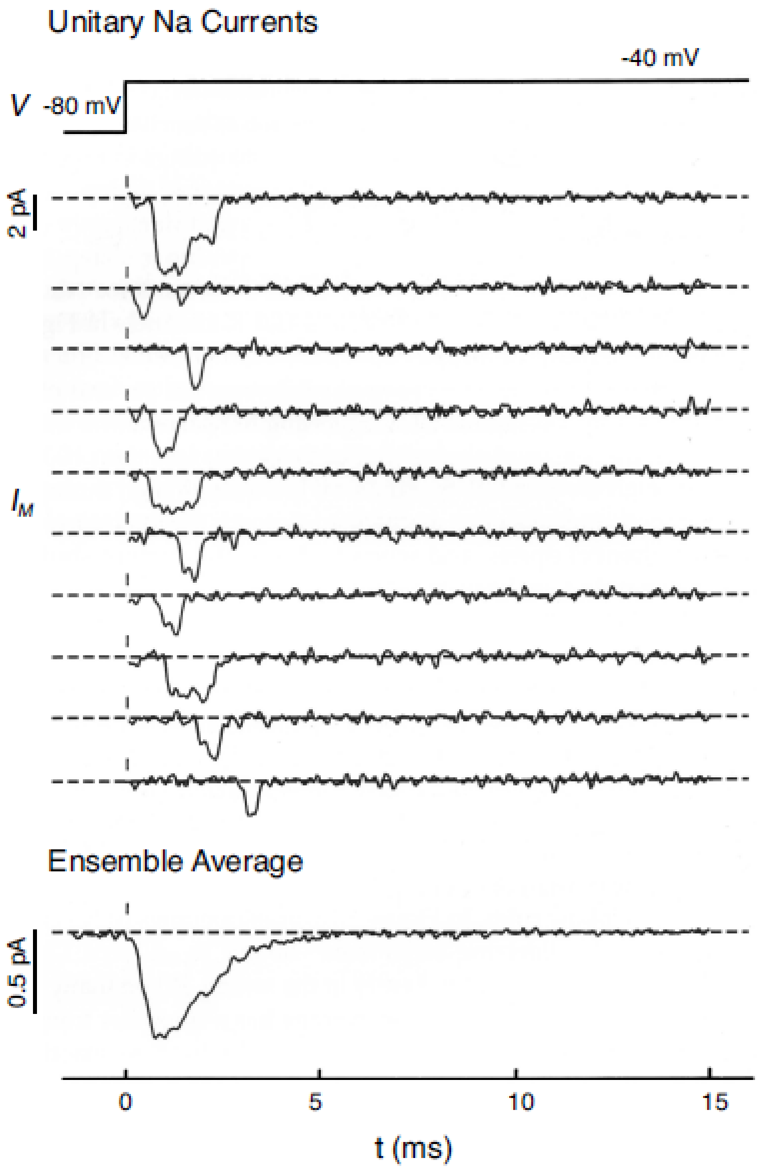
Ionic conductances

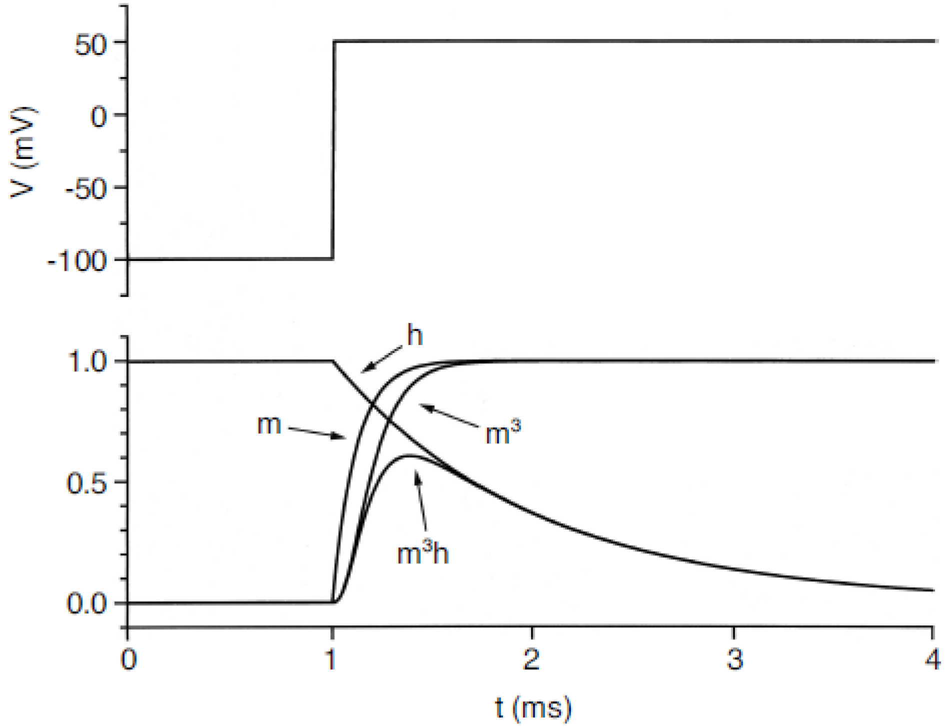




$$G_{K^+}(V_m, t) = \overline{G_K} n^4 (V_m, t)$$

Ionic conductances





$$G_{Na^+}(V_m, t) = \overline{G_{Na}} m^3(V_m, t) h(V_m, t)$$

Ionic conductances

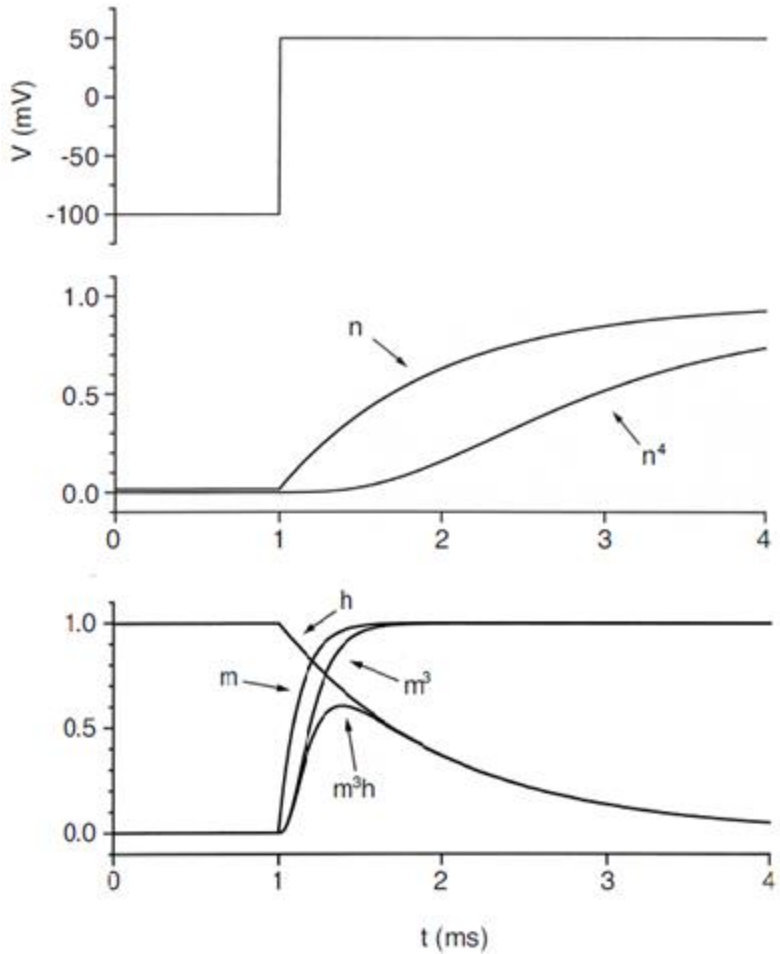
- Typical values of constants associated with the H&H equation

$$\overline{G_{Na^+}} = 120\, mS\ cm^{-2}, \overline{G_{K^+}} = 36\, mS\ cm^{-2}, \overline{G_L} = 0.3\, mS\ cm^{-2}$$

$$V_{Na^+} = 55\, mV, V_{K^+} = -72\, mV, V_L = -49.4\, mV, C = 1\mu F cm^{-2}$$

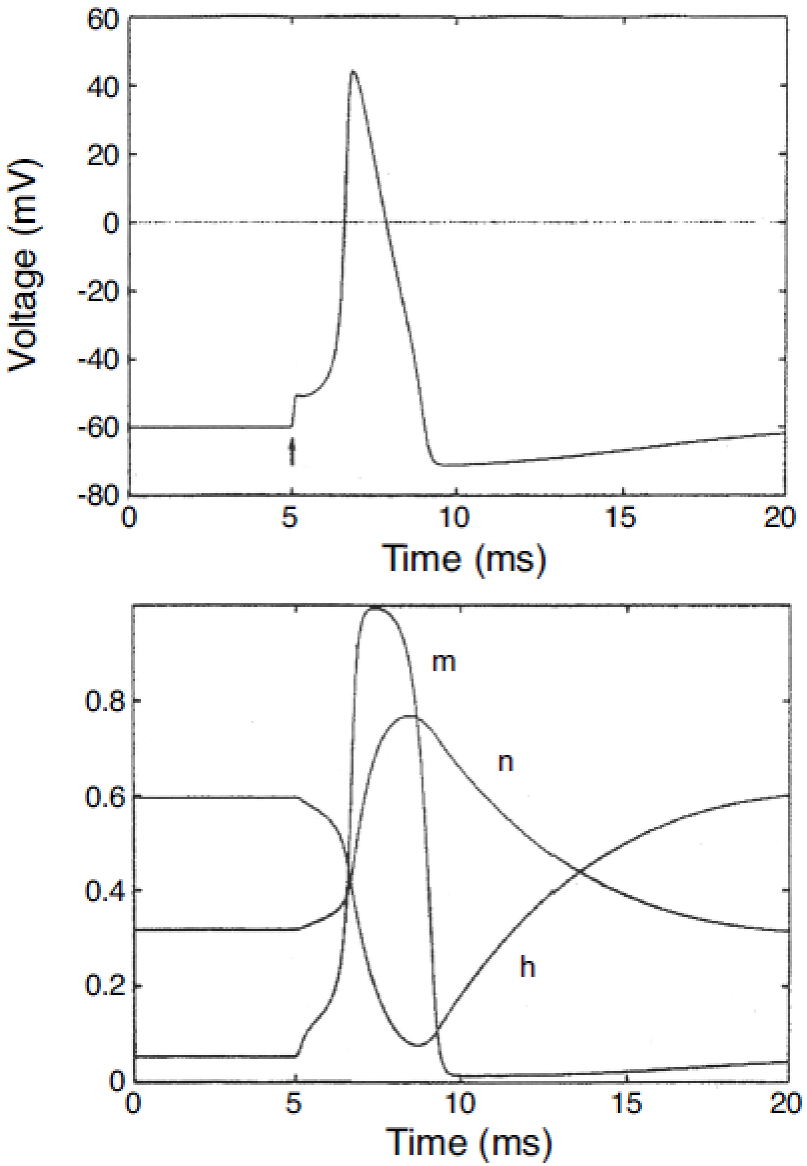
Graphical summary of the H&H equation

- Hodgkin & Huxley
- Voltage-dependent ionic currents
- Clamping methods
- Hodgkin & Huxley model
- Ionic conductances
- Model predictions
- Applications



$$G_{K^+}(V_m,t) = \overline{G_K}\, n^4(V_m,t)$$

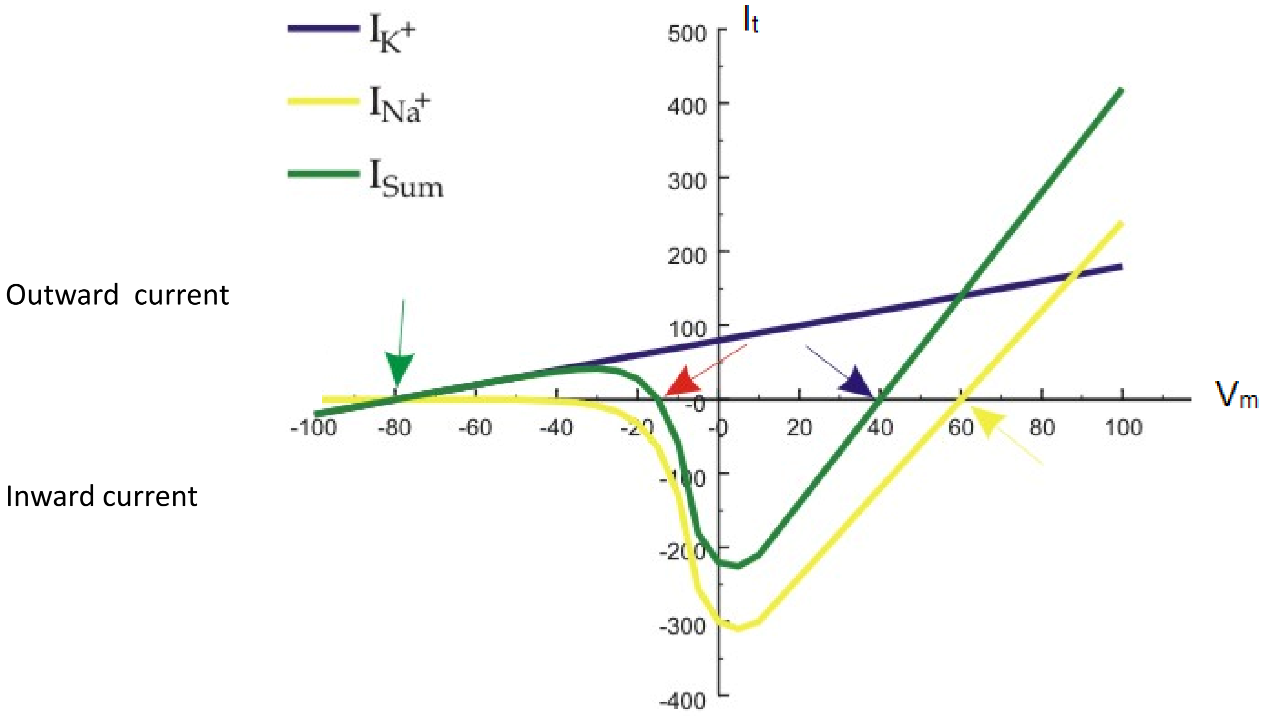
$$G_{Na^+}(V_m,t) = \overline{G_{Na}}\, m^3(V_m,t)\, h(V_m,t)$$



H&H model predictions for unknown stimuli

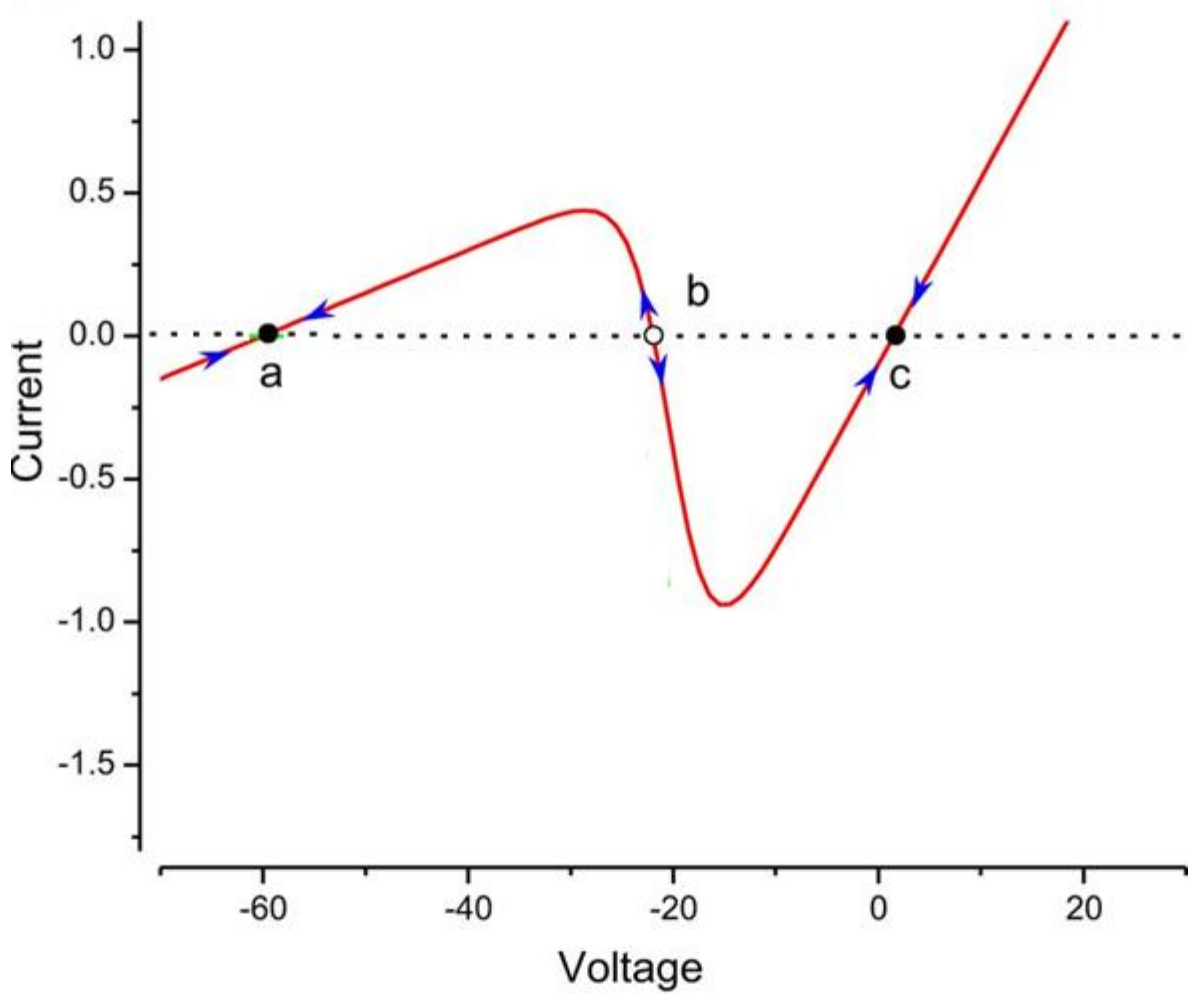
- The importance of H&H model is due to the accurate prediction it could make on neuronal behaviour.
- Stimulations are made by varying $k_e(z,t)$
- Predictions:
  1. Equilibrium points
  2. Frequency coding
  3. Refractory periods
  4. Spatio-temporal integration
  5. Accommodation
  6. Anode-break excitation
  7. Subthreshold oscillations
  8. Temperature dependence

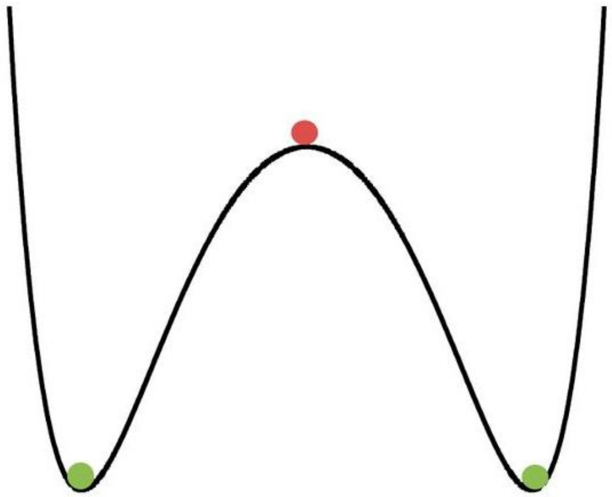
Prediction 1: Equilibrium points



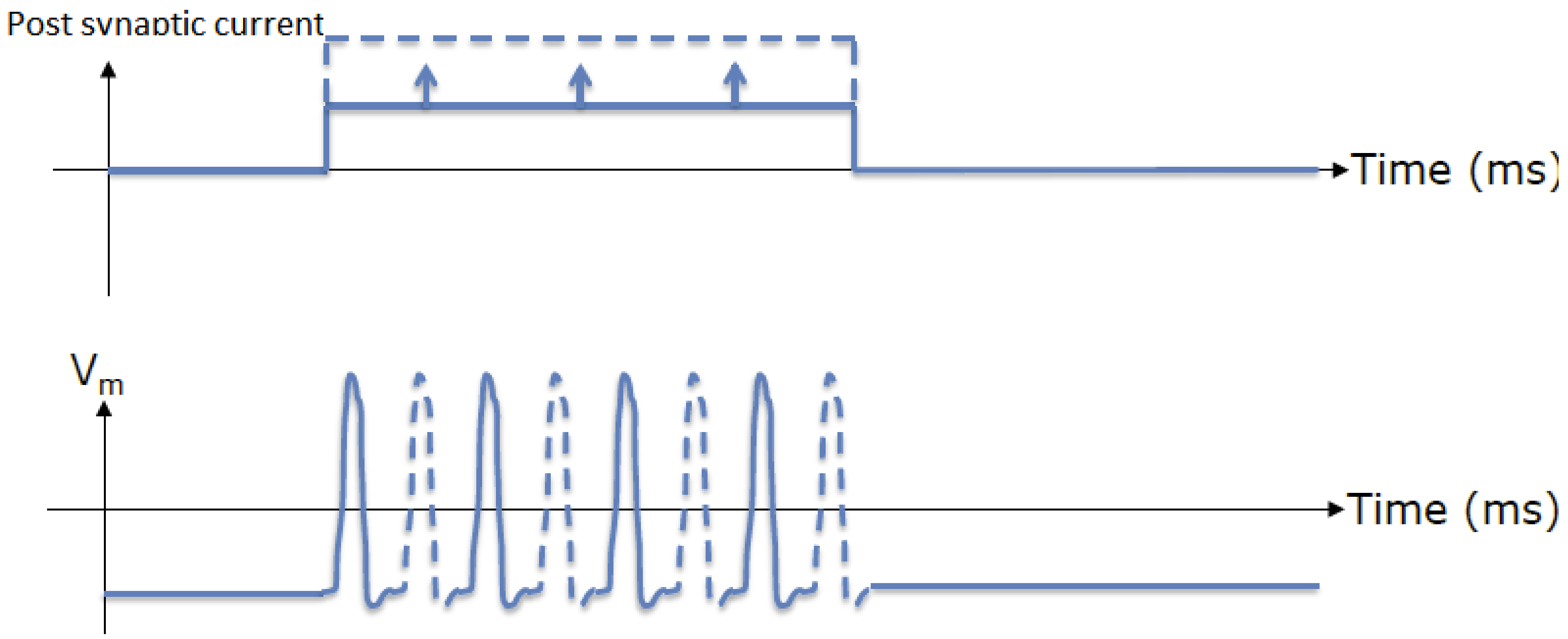
- Stable points
  - -80 mV: resting membrane potential for K^+
    - Small perturbations of V_m from this point will cause K^+ currents flow and return back to resting potential
  - +40 mV: peak membrane potential
    - Small perturbations of V_m from this point will cause K^+ and Na^+ currents flow and return back to the peak potential
- Unstable point
  - -15 mV: threshold voltage
    - Dominated by voltage gated Na^+ currents

Prediction 1: Equilibrium points





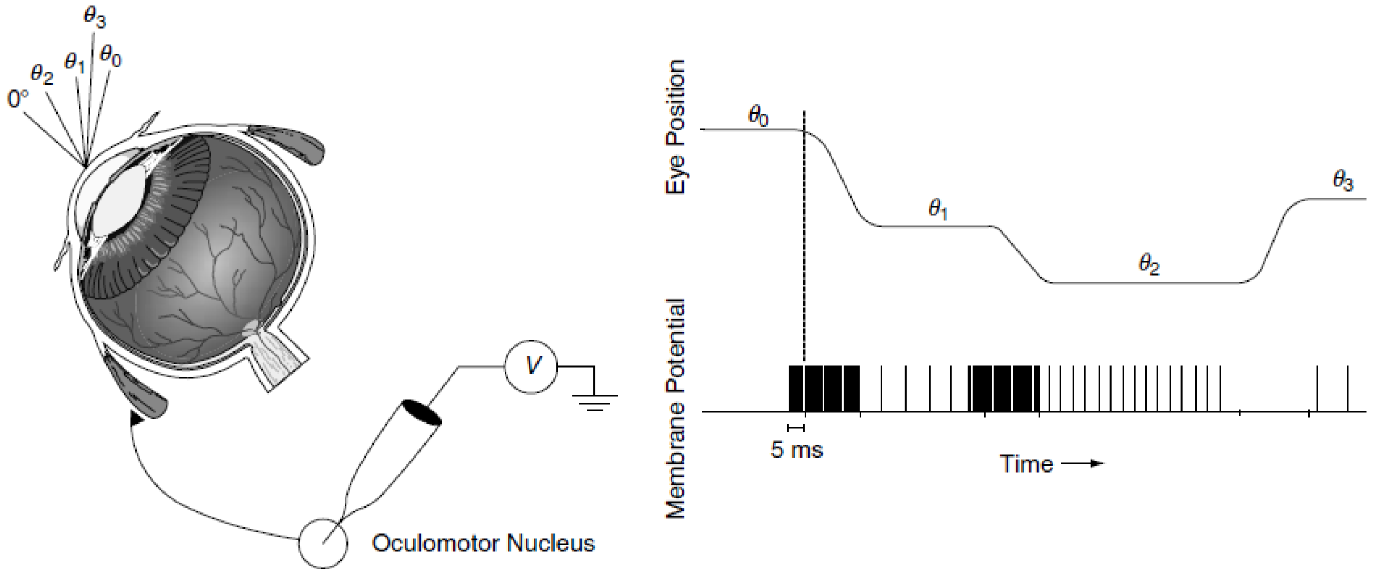
Prediction 2: Frequency coding

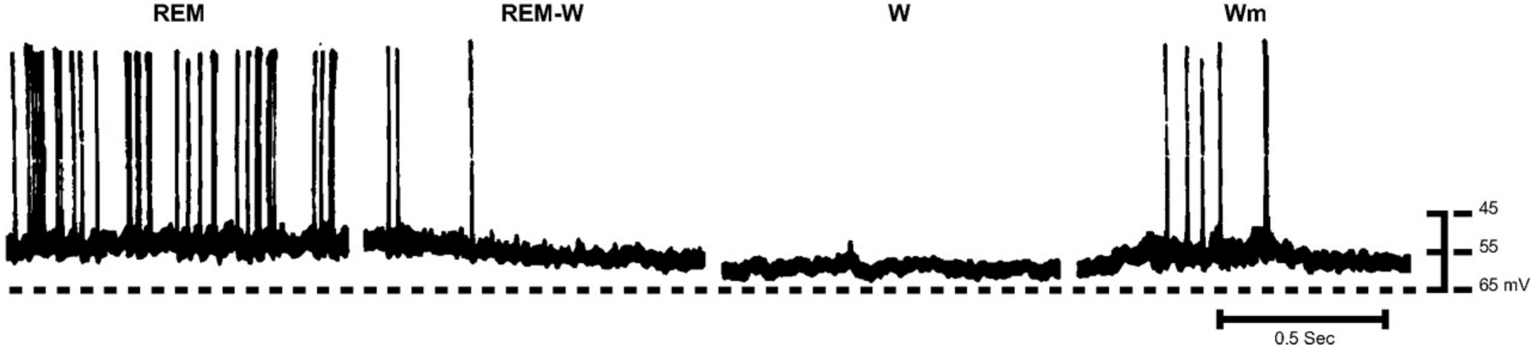


- PSPs are amplitude modulated.
- APs are all or nothing (not amplitude modulated)
  - Can detect light from no light (visual sensory neurons)
  - How to detect bright light from dim light?
- For a given short excitatory PSC, the rate of firing APs change (frequency coded).
  - Limited by only absolute refractory period.

Prediction 2: Frequency coding

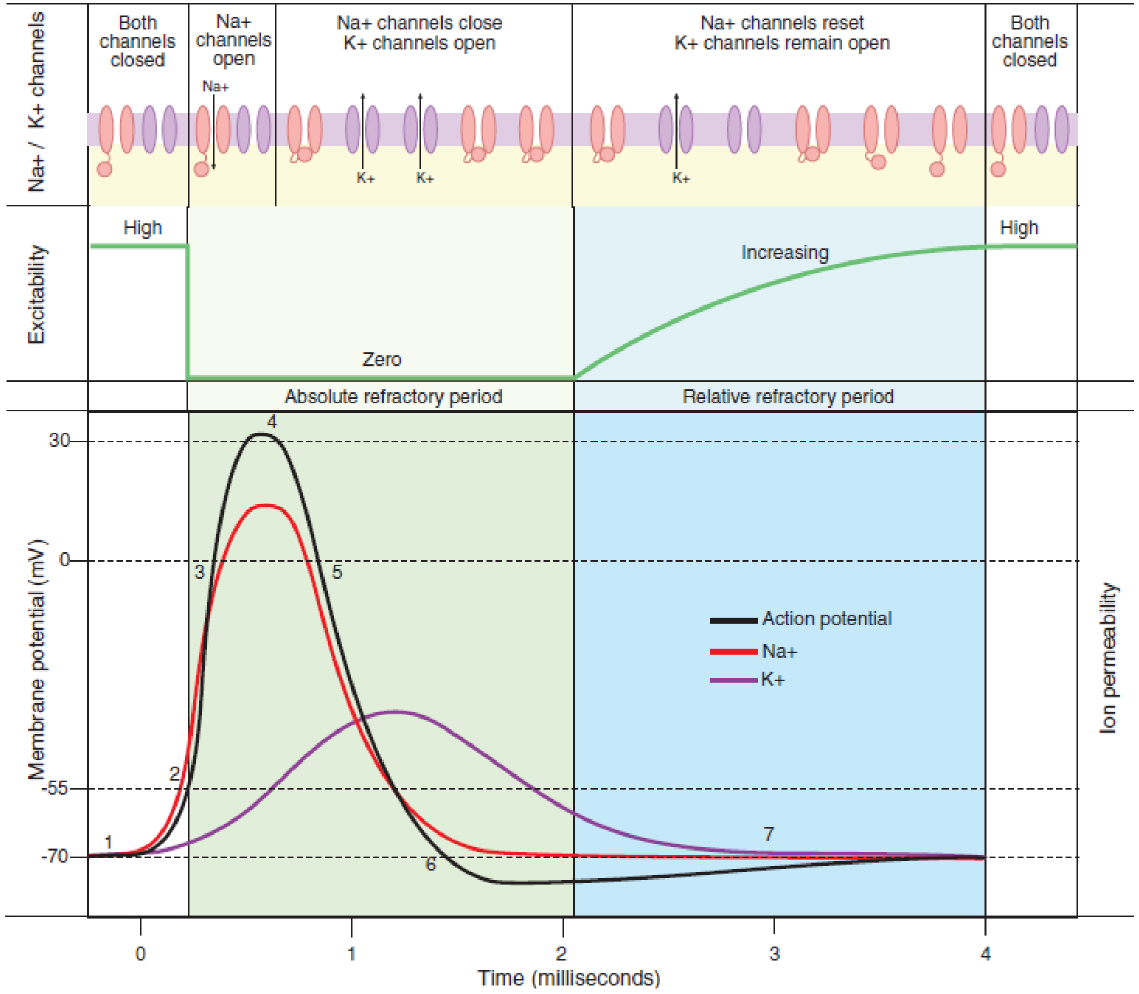
Rate of APs





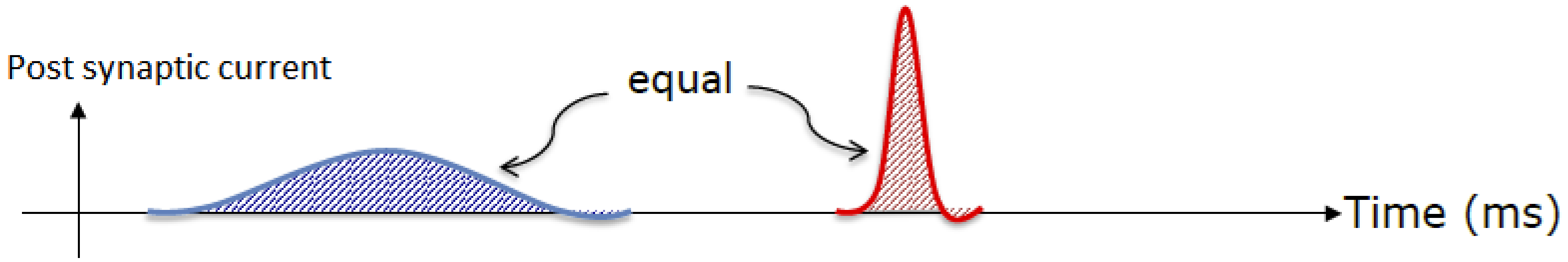
REM: Rapid Eye Movement W: Wake m: movement

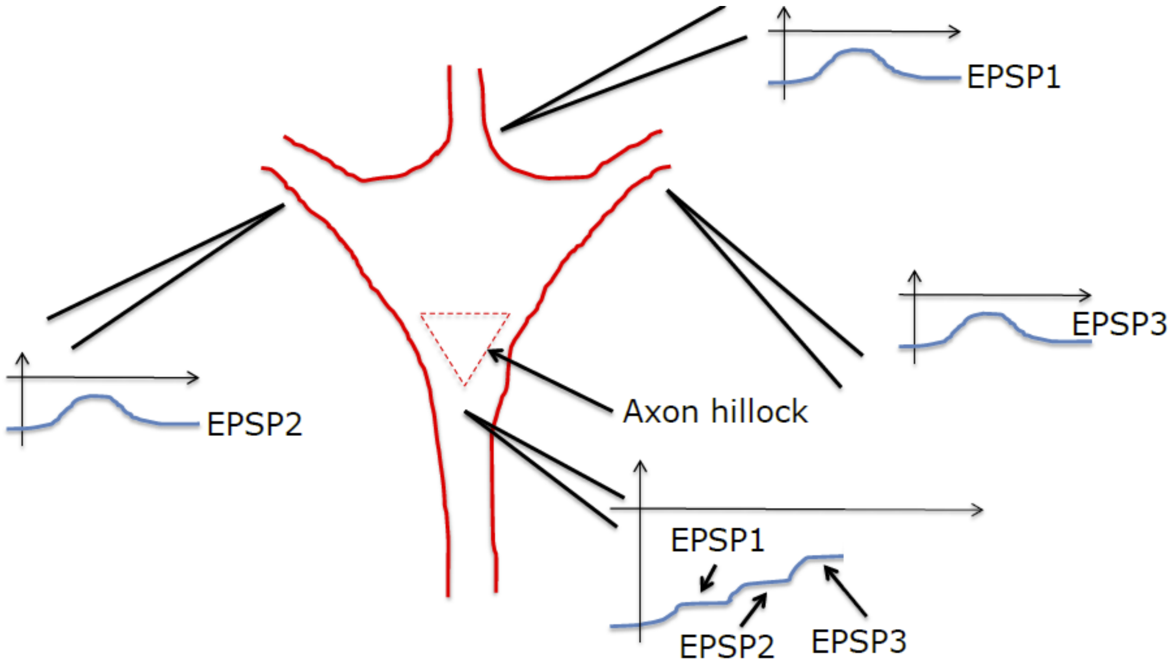
Prediction 3: Refractory periods



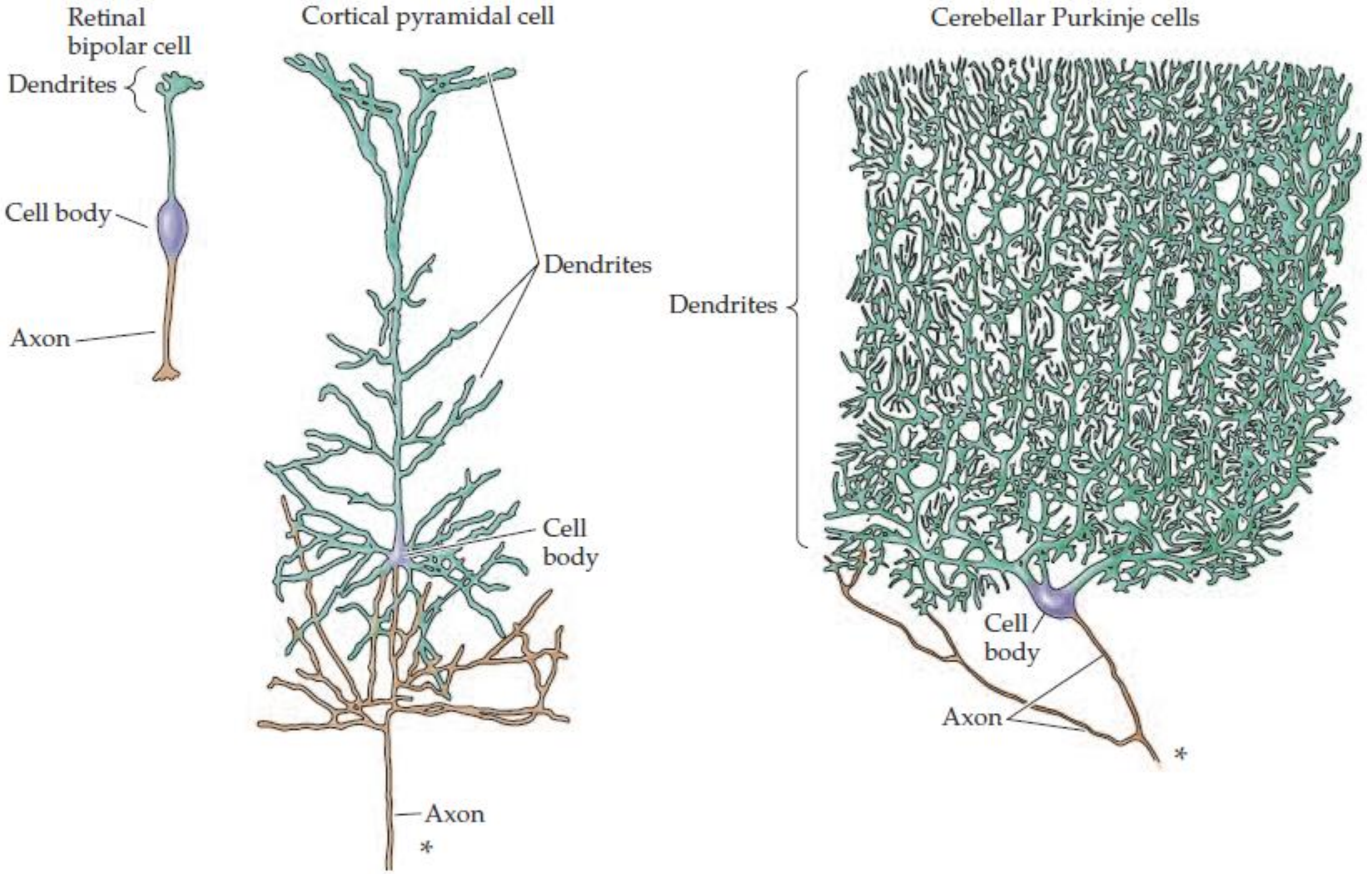
- Information in neurons are frequency coded. However, it’s not a linear frequency coding due to these two refractory periods.

Prediction 4: Spatio-temporal integration



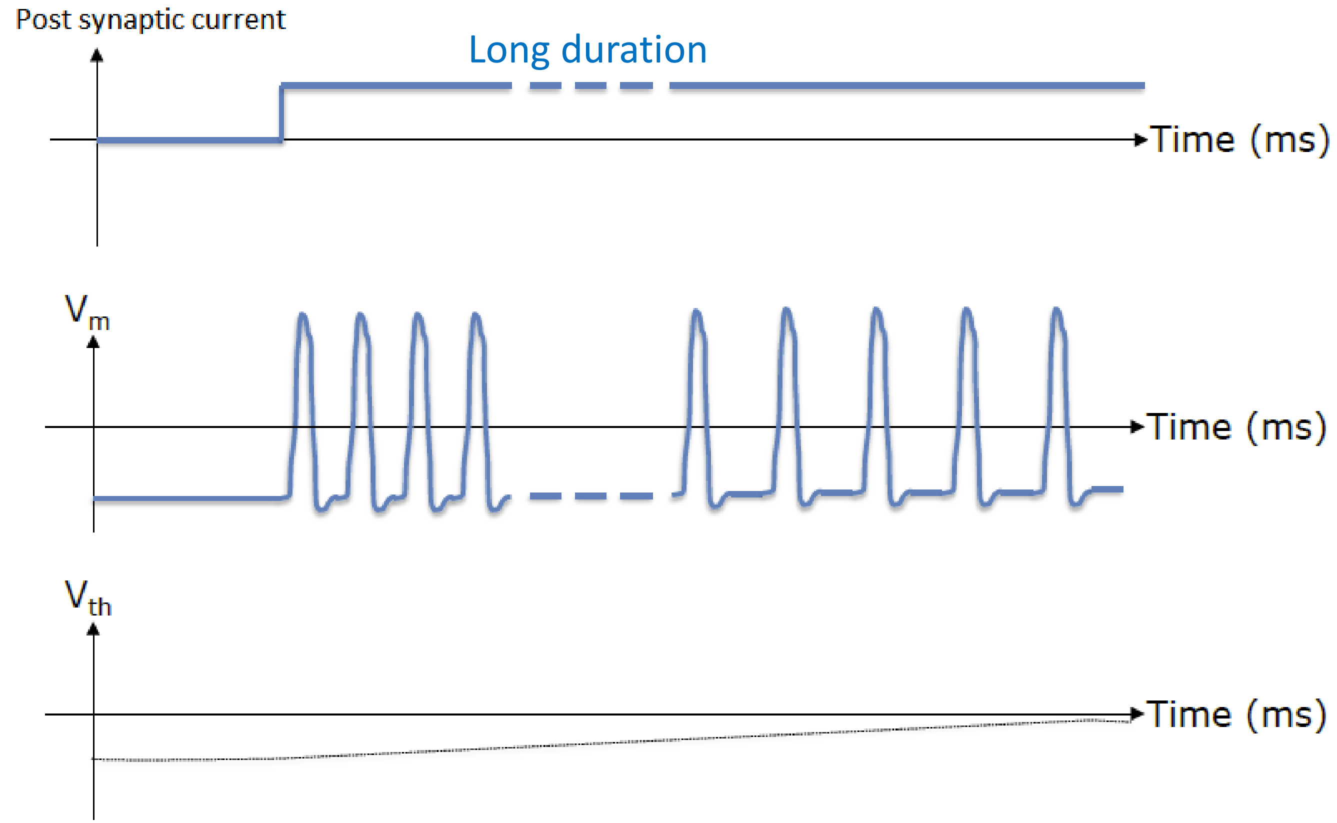


Prediction 4: Spatio-temporal integration



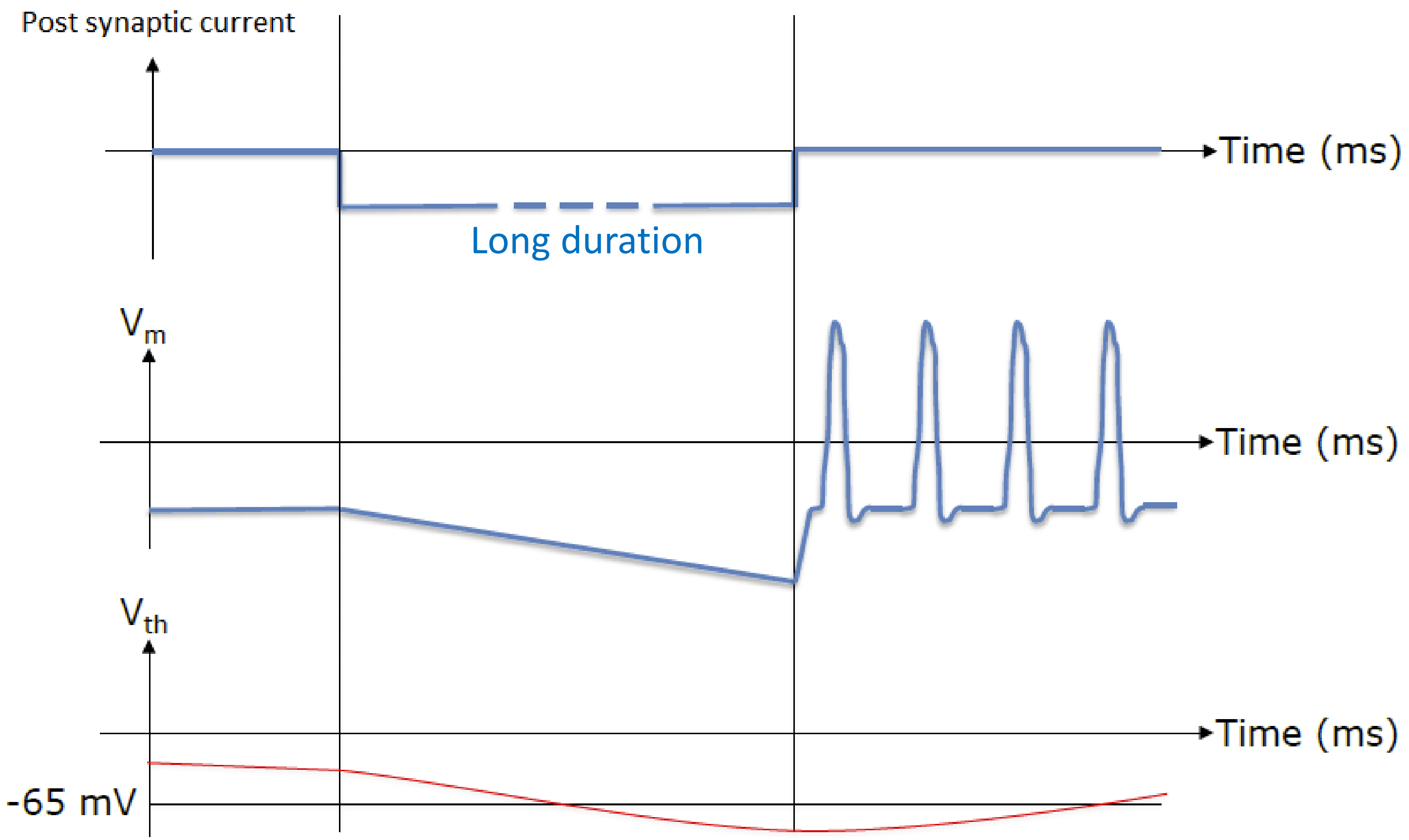
- Explains complex processors of the brain
  - Retinal bipolar cells: limited information of a rod/corn cell
  - Cortical pyramidal cells: wider sensory information processing (EEG)
  - Cerebellar Purkinje cells: more complex smooth motor coordination activity

Prediction 5: Accommodation



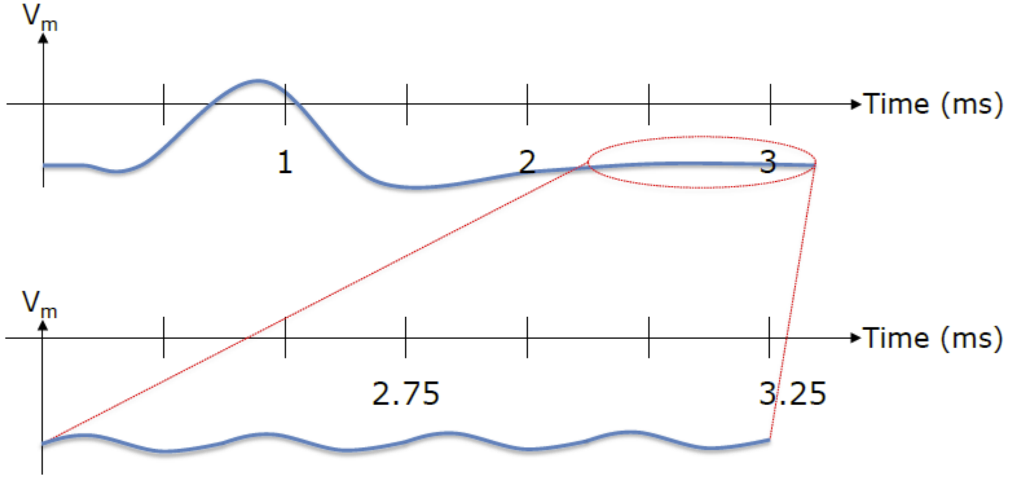
- Desensitise for long duration constant stimuli.
- In other words, neurons are sensitive to change
  - Hearing: silent room a/c on/off
  - Visual: edges are visible than constant colour/intensity spaces
  - Smell: adaptation

Prediction 6: Anode-break excitation

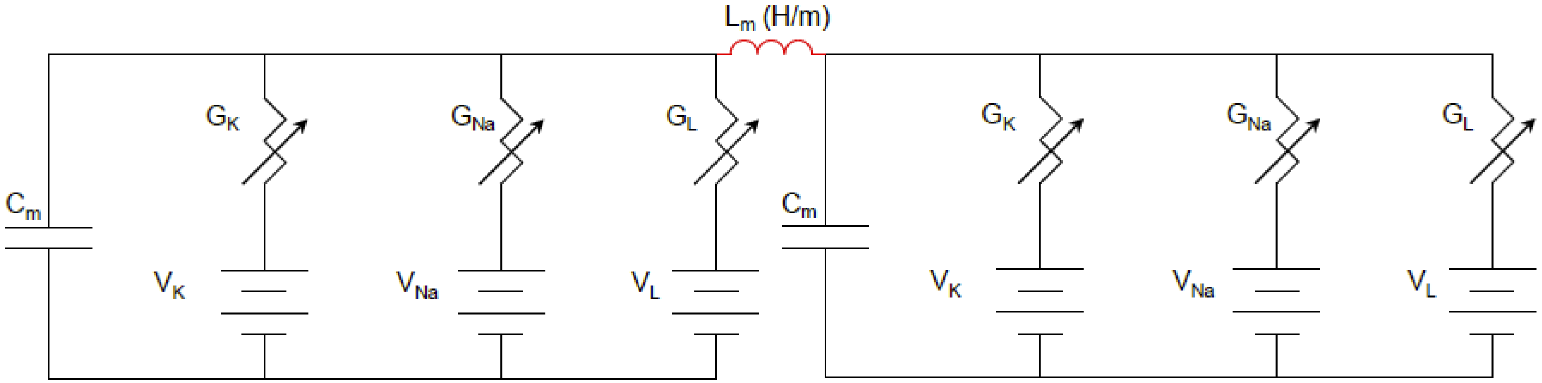


- Neurons will fire to an inhibitory post synaptic potential!
  - As a result of reducing the threshold voltage
- Essential for rhythm generator circuits in the brain.

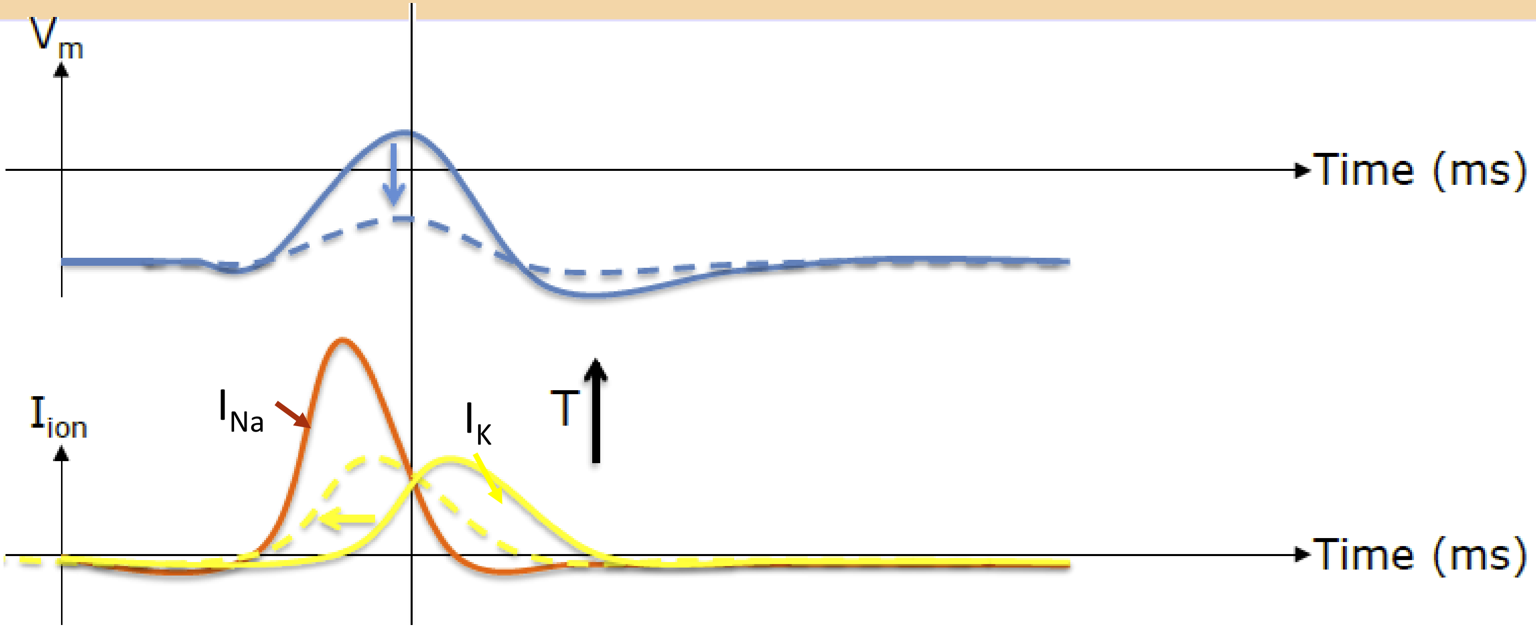
Prediction 7: Subthreshold oscillations



- This oscillatory behaviour could be modelled with the resonant behaviour of an inductor between two infinitesimal segments.
- Even though H&H model predicted this behaviour, it was not practically measured at the time.
- This could be electrical resonance or intracellular communication???



Prediction 8: Temperature dependence



- I_{Na} – transient inward current
- I_K – delayed outward current
  - This delay in opening K^+ channels is caused by the temperature
- Nernst potential is temperature dependent

$$E_{mV} = \frac{RT}{zF}\ln\left(\frac{concentration\ outside}{concentration\ inside}\right)$$

- Membrane potential (V_m) is a function of the Nernst potential.
- The delay reduces as the temperature $\boxed{\uparrow}$ causing the amplitude of the AP to be reduced.
- If the maximum amplitude falls below the V_{th}, AP will not generate at the next Ranvier node. (purpose of the cell communication is lost)
- Giant squid experiments were done in 20^0 C but AP could not be seen at 37^0 C (typical temperature of mammalian cells).
- It is found out anatomically, density of K^+ channels is much less in mammalian cells than in cold blooded animals.