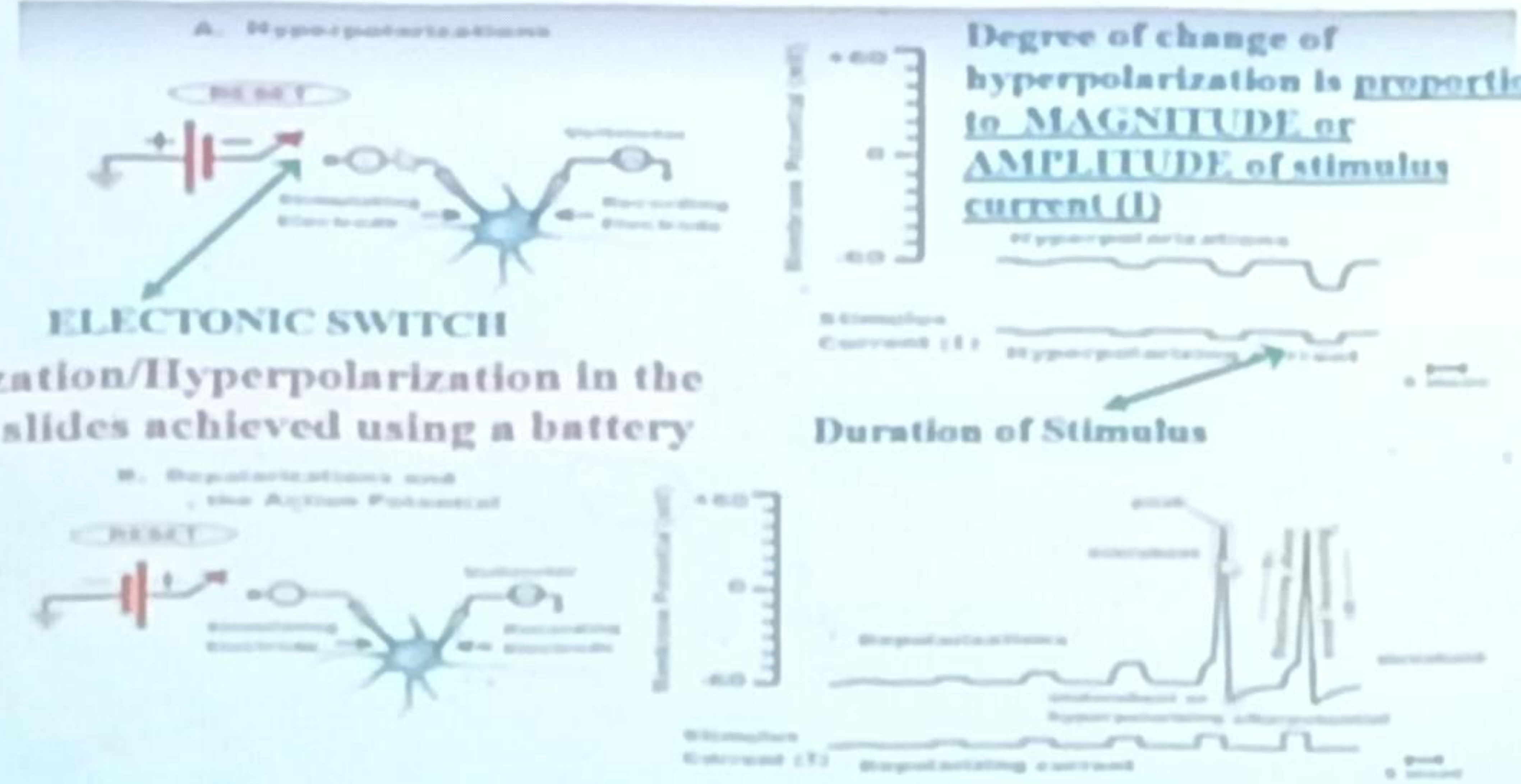
Action Potential (Electrical Viewpoint)



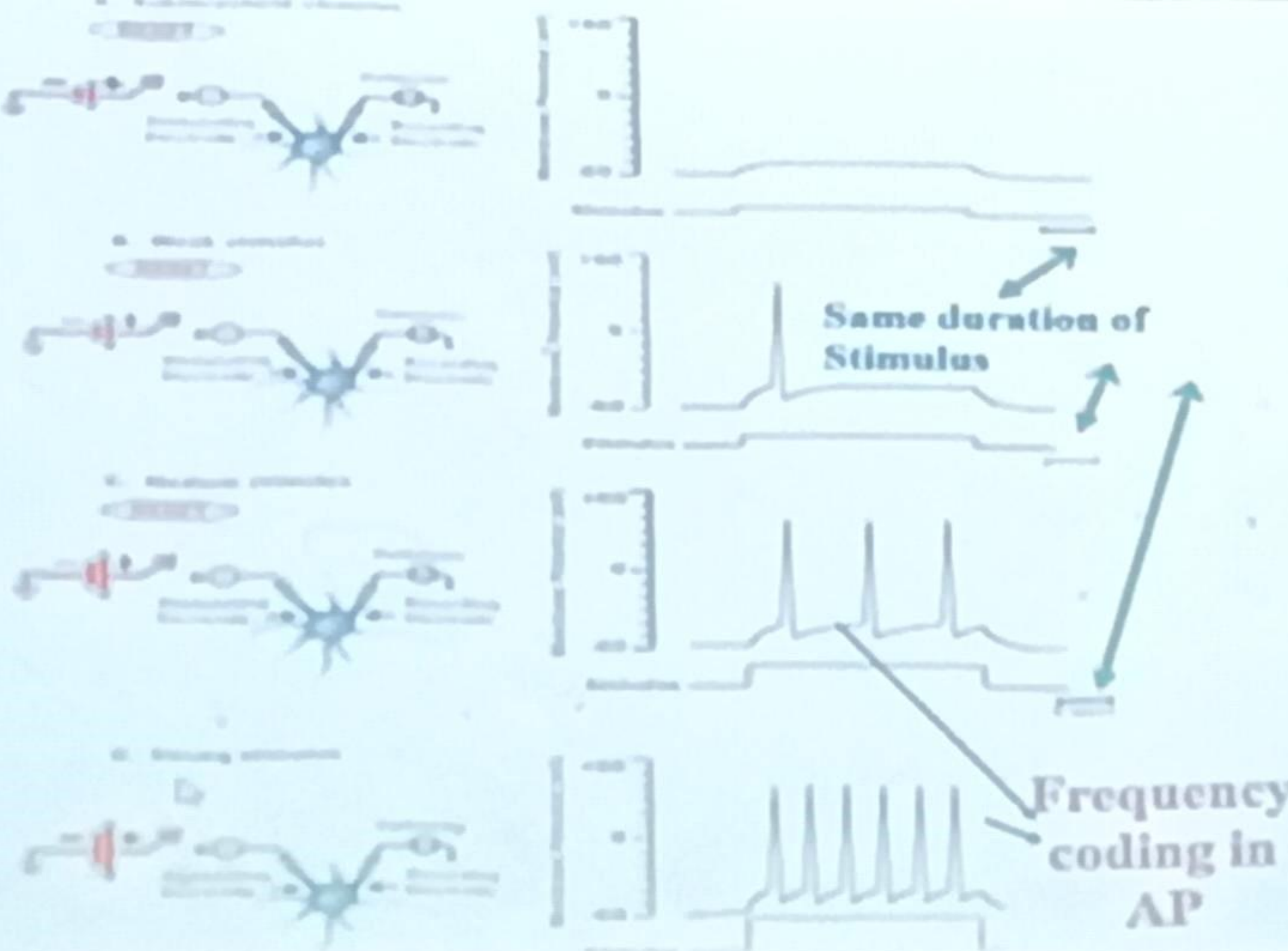
Degree of change of hyperpolarization is proportional to MAGNITUDE or AMPLITUDE of stimulus current (I)

ELECTONIC SWITCH

Depolarization/Hyperpolarization in the previous slides achieved using a battery

Duration of Stimulus

Depolarizing current is responsible for action potential evoking.

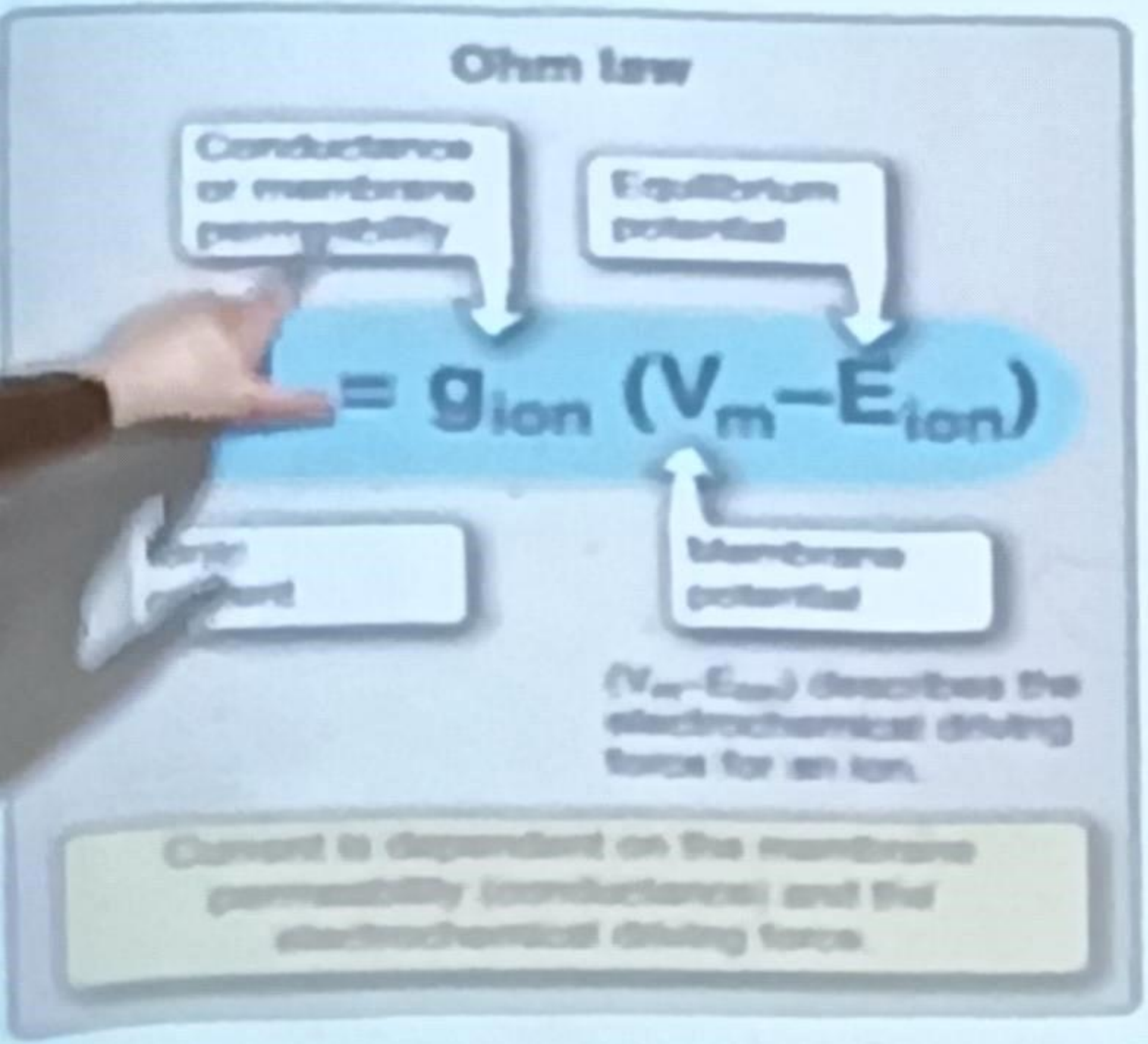

Same duration of Stimulus
Frequency coding in AP

Tutorial-2 (Tomorrow)- PLEASE BRING LAPTOPS

ANY CONCERNS, EMAIL TA and ME

Ohms Law

Current Flow (Action Potential) in Axon Depends on ?



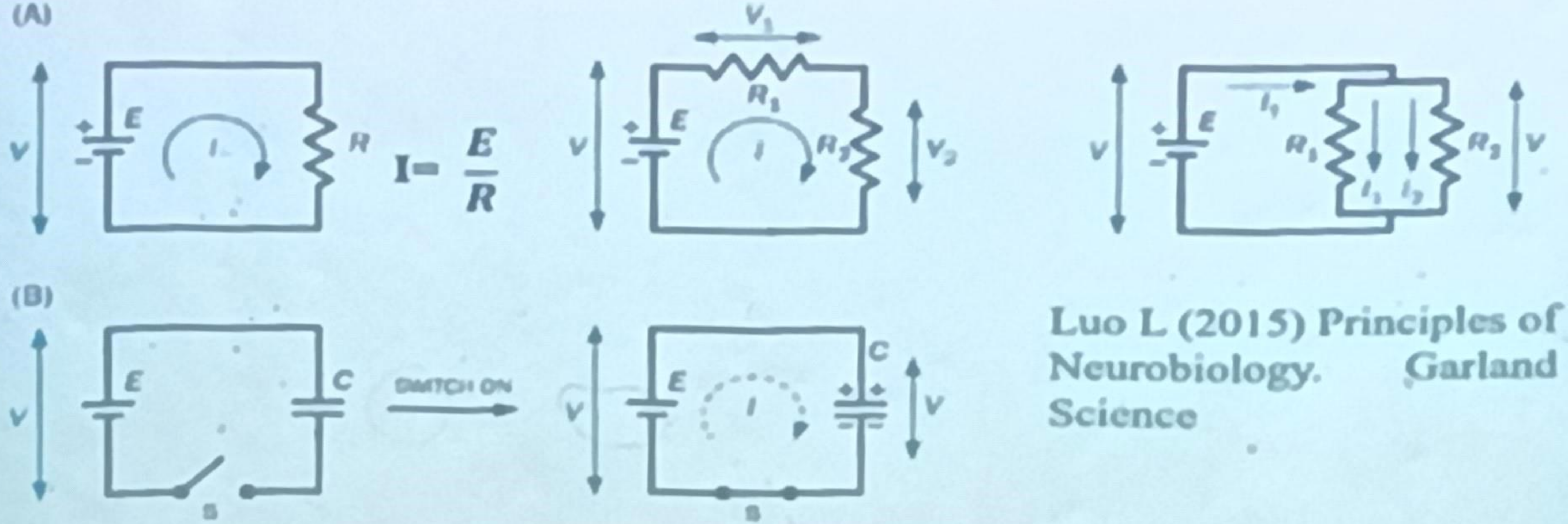
Ohms Law

Content from book: Neuroscience by Claudia Krebs

Introduction to Hodgkin Huxley Model

ng Ohms law/Electrical Circuit Theory
(R,C and RC)

Neuronal Plasma membrane or Biological membrane as Electrical circuits



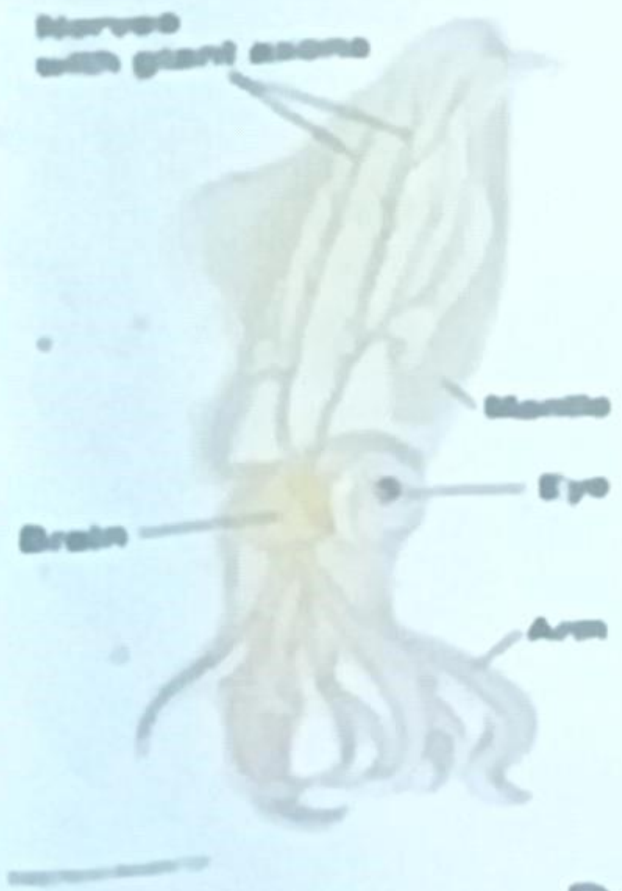
Luo L (2015) Principles of Neurobiology. Garland Science

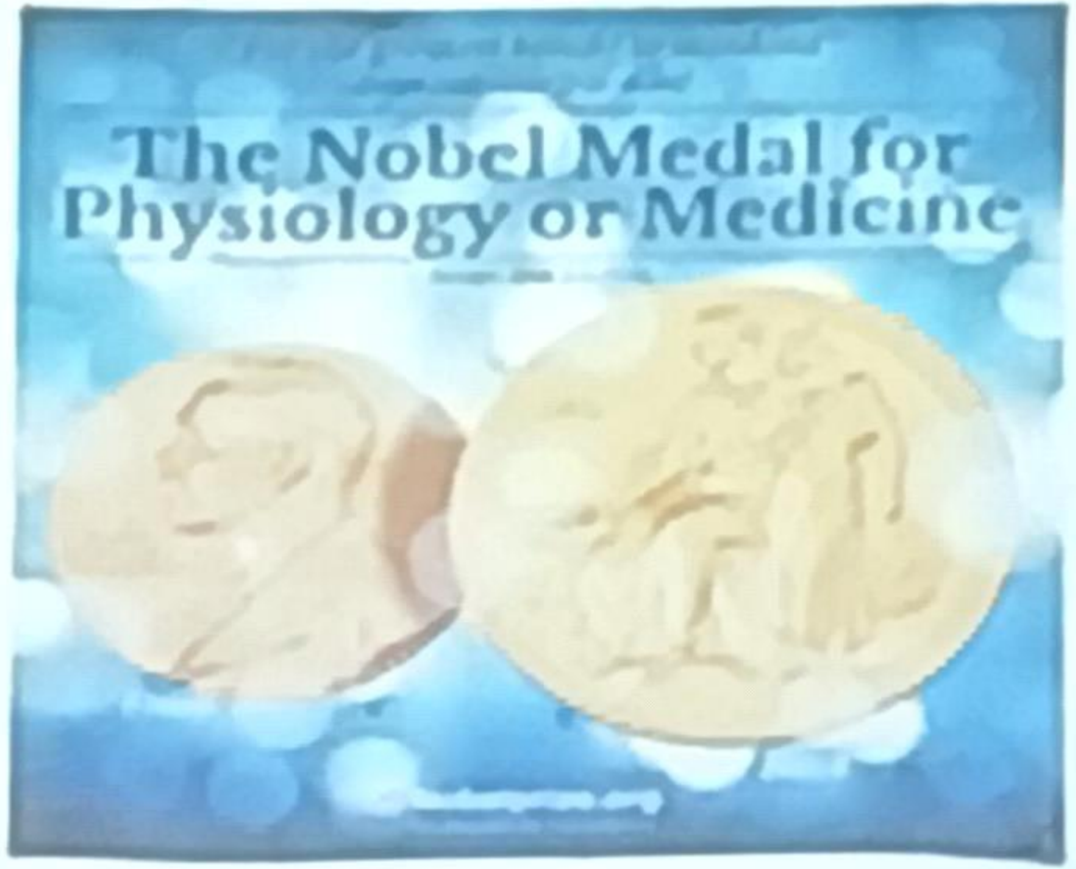
Initially there is no charge across the Capacitor and it needs time (Current is biggest)

Over time capacitor gets charged and creates voltage same as battery E and current is zero

Neuron and Capacitor Link

Hodgkin Huxley (HH) Model





- Developed in 1952 using the squid axon, which is quite large
- Model was developed, tested and refined before the use of computers (!)
- Awarded the 1963 Nobel Prize in Physiology/Medicine
- Remains the most widely used model for the action potential

Breakthrough of HH Model

- The breakthrough of Hodgkin and Huxley was that they succeeded to measure how the cell membrane voltage or current can be modeled and represented as electrical circuits

Hodgkin and Huxley, Journal of Physiology, 1952

Applications of Hodgkin Huxley Model

- Mathematical modeling can reveal mechanisms long before they can be observed directly.

- Framework for studying and analyzing ion channel kinetics.

Hodgkin and Huxley, Journal of Physiology, 1952

Why Study HH model, Applications

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN and A. F. HUXLEY

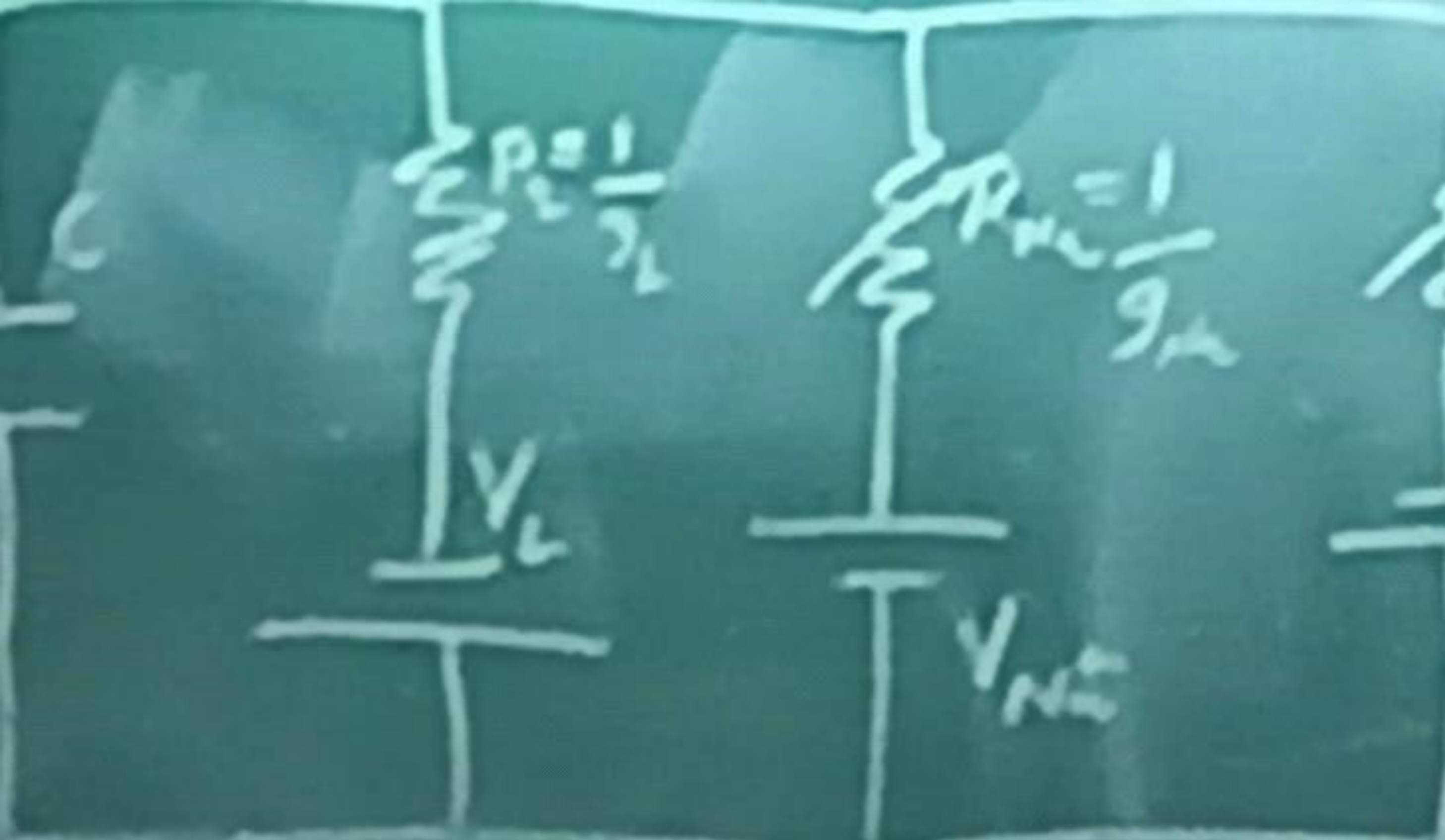
From the Physiological Laboratory, University of Cambridge

What is Hodgkin Huxley Model?

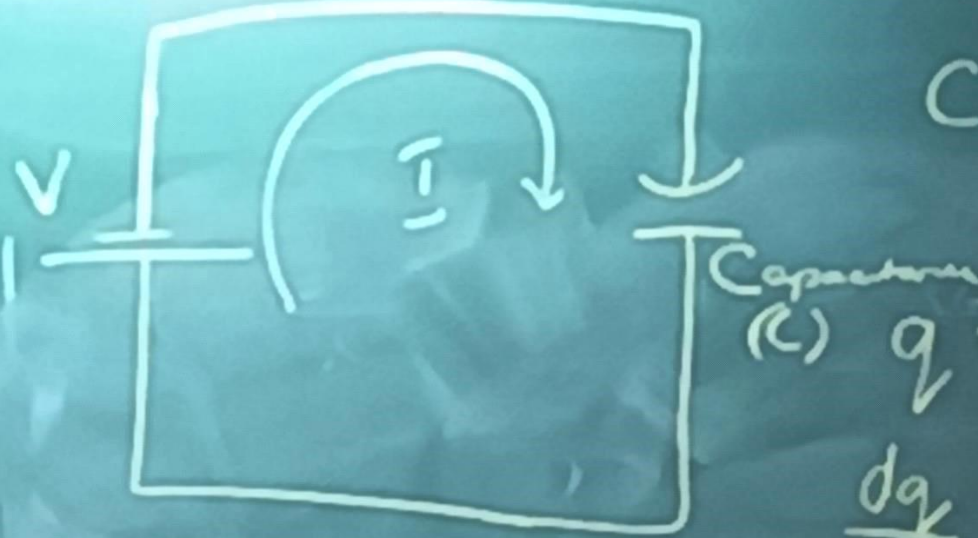
(23426 citations on Google scholar)

Nobel Prize in Physiology or Medicine, 1963

Lets Derive the HH Model



C
R_L = 1/g_L
V_L
R_Na = 1/g_Na
V_Na

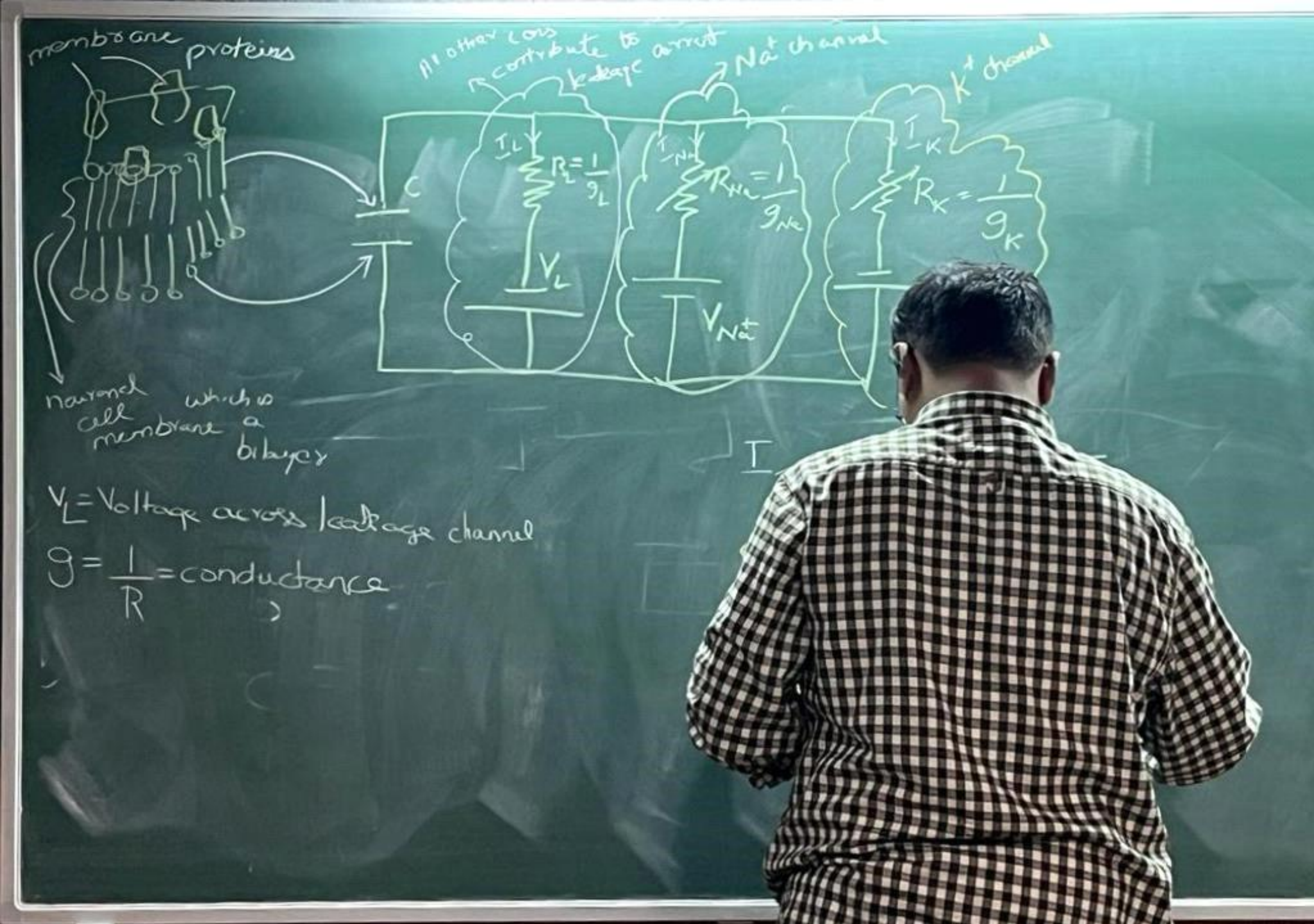


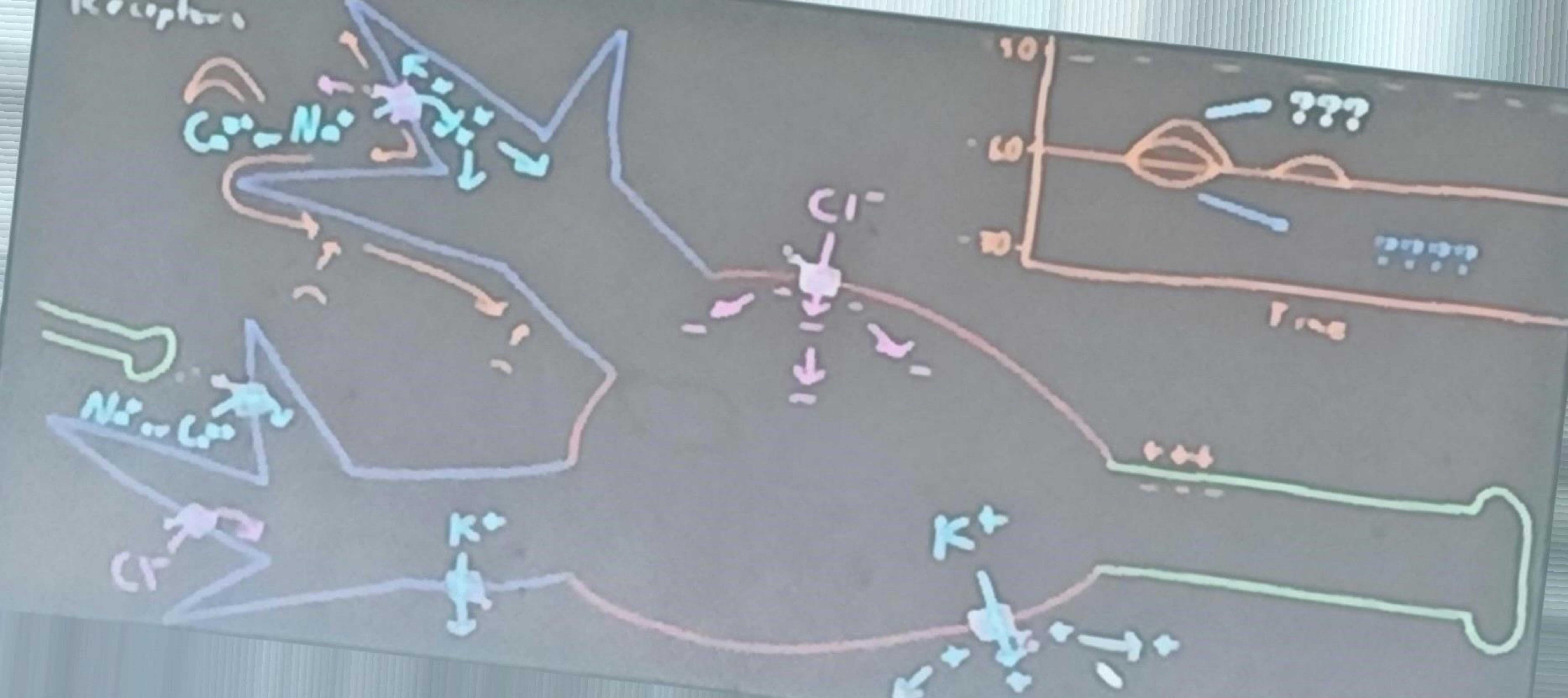
$$C = \frac{q}{V} = \frac{\text{charge}}{\text{voltage}}$$

$$q = CV$$

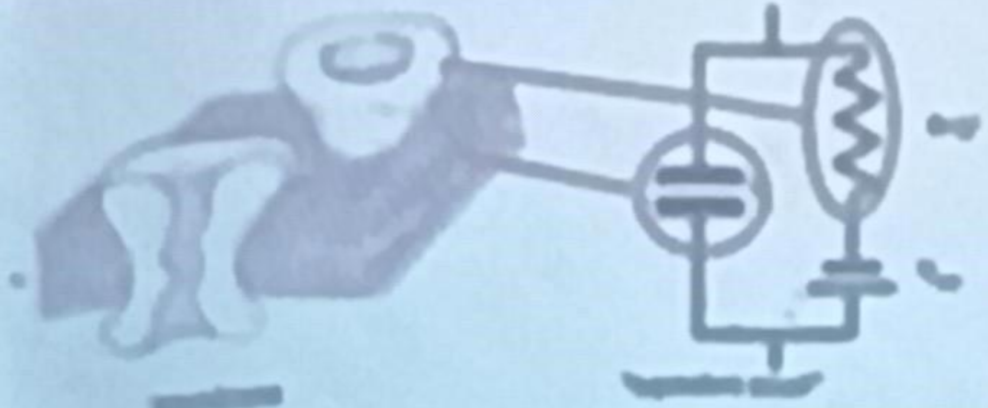
$$\frac{dq}{dt} = C\frac{dv}{dt}$$

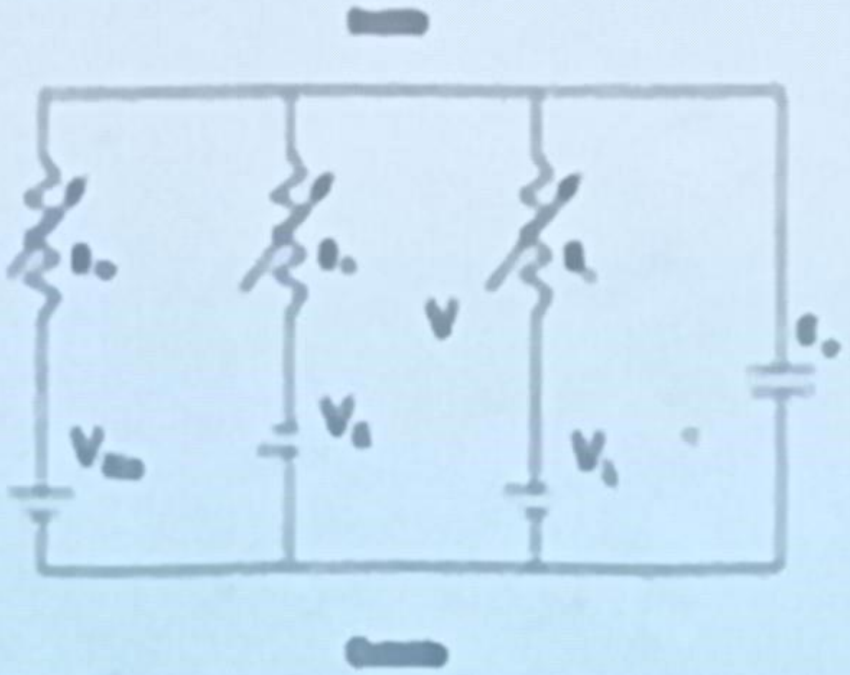
$$I_c = C\frac{dv}{dt}$$


membrane proteins
All other ions contribute to leakage current
Na^+ channel
K^+ channel
C
I_L
$R_L = \frac{1}{g_L}$
V_L
I_{Na}
$R_{Na} = \frac{1}{g_{Na}}$
V_{Na^+}
I_K
$R_K = \frac{1}{g_K}$
neuronal cell membrane which is a bilayer
V_L = Voltage across leakage channel
$g = \frac{1}{R}$ = conductance
I


Ca²⁺ - Na⁺
Na⁺ or Ca²⁺
Cl⁻
Cl⁻
K⁺
K⁺
???
Time

Full equations for electric circuit model





Hodgkin Huxley (HH) Model

$$I_{TOT} = I_K + I_{Na} + I_L$$

$$I_{Na}(V,t) = (V_{Na} - V)\,g_{Na}(V,t)$$

$$I_K(V,t) = (V_K - V)\,g_K(V,t)$$

$$I_L(V,t) = (V_L - V)\,g_L$$

$$I_{TOT} = \frac{dQ}{dt} = C\frac{dV}{dt}$$

Basic form of conductances:

$g = g_{max} * f(V, t)$

f is the fraction of channels open, which depends on V and t

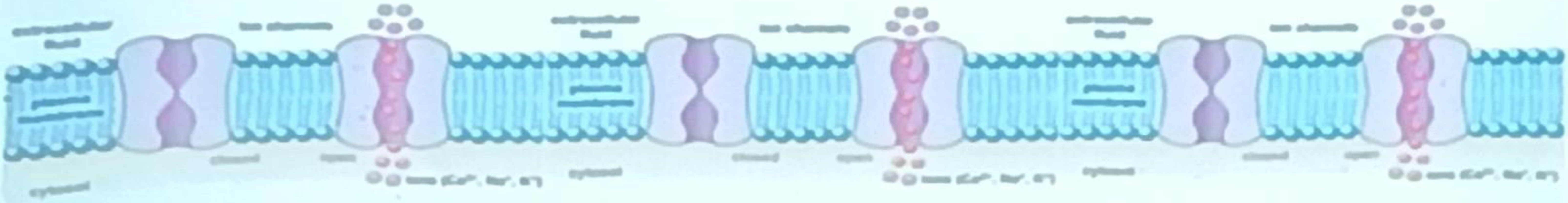
$$I_{TOT} = C\frac{dV}{dt} = (V_K - V)g_K(V,t) + (V_{Na} - V)g_{Na}(V,t) + (V_L - V)g_L$$

Hodgkin Huxley Model

- *Semi permeable membrane* acts as a capacitor
- Each channel type (Na^+, K^+) is represented/characterized by a *resistor*
- *Nernst potential* generated by differences in ion is represented by battery. E_L is leakage voltage for Cl^- and other ions
- Specific batteries since Nernst potential is different for each ion type.
- If input current $I(t)$ is injected into the neuron cell it charges the capacitor or leaks through the channels in cell membrane.

Hodgkin and Huxley, Journal of Physiology, 1952

Key concept : gating variable Hodgkin Huxley (HH) Model



Rate coefficients

$$\underset{\text{Portion of closed channels}}{1-f} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \underset{\text{Portion of open channels}}{f}$$

$$\frac{df}{dt} = \alpha_f(1-f) - \beta_f f$$

f = Gating varjable

f : fraction of open channels
a.k.a. the gating variable
(depends on V and t)

α : rate at which closed channels open (depends on V)

β : rate at which open channels close (depends on V)

Note: The f gating variable will be called n, m and h for the three types of gating: K activation, Na activation, and Na inactivation

Potassium current (activation)

$$g_K(V,t)$$

Maximum conductivity with all gates open ($n = 1$)

We can write an expression for the conductivity of this ion as

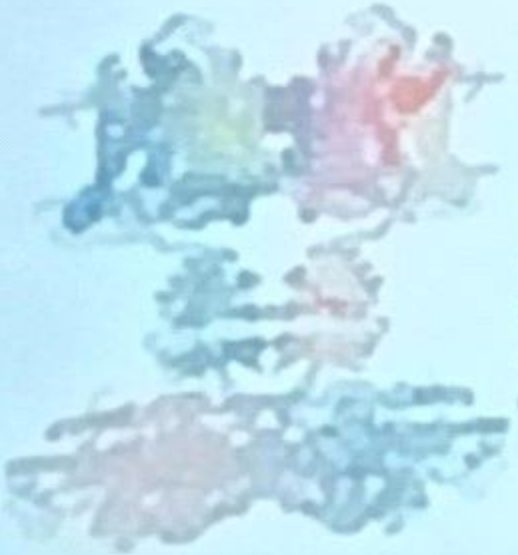
$$g_K = \bar{g}_K \, n^4(V,t)$$

Four activation gates result in fourth power for gating variable n

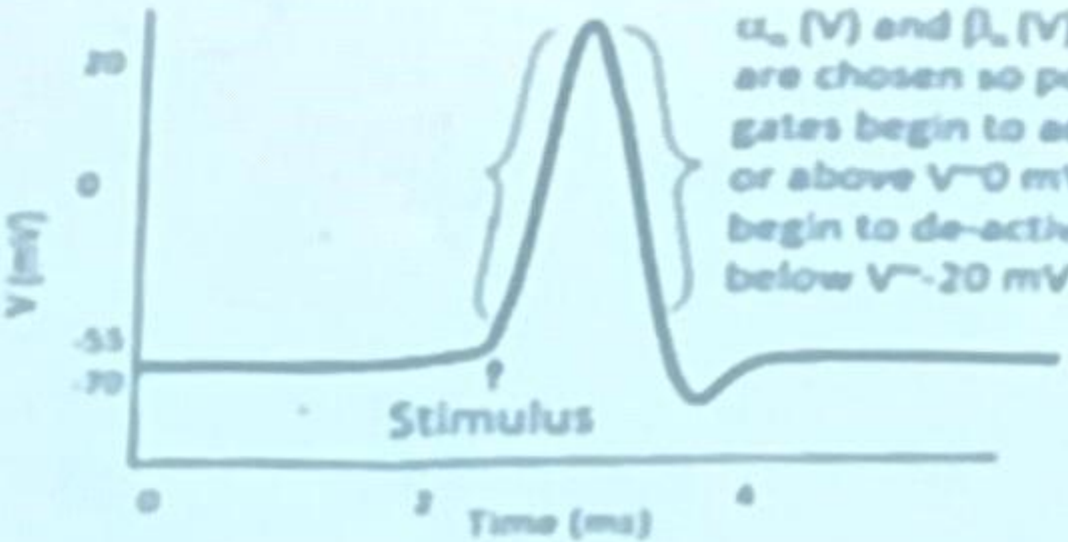
And then assume a simple first order kinetic behavior of the gating variable n

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

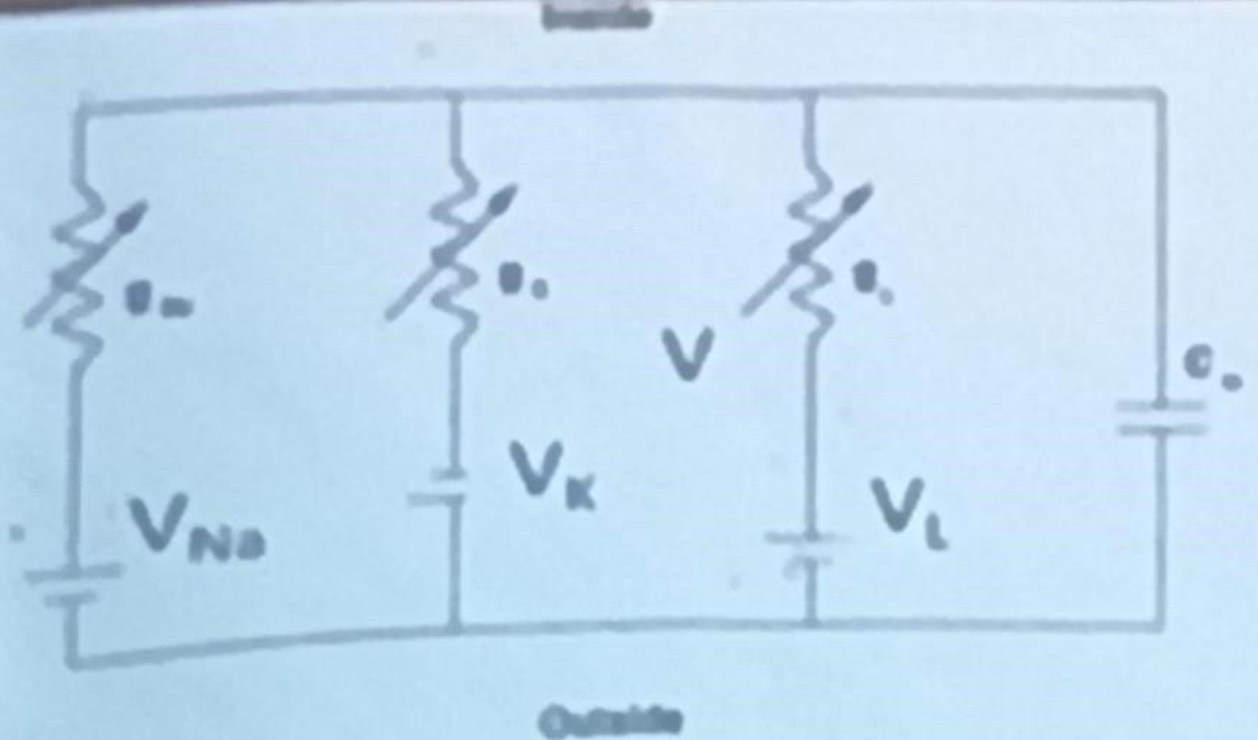
(same as previous slide, with f now called n)



Potassium gate protein with 4 identical tetramers in a ring shape (resulting in the 4[th] power of n, as all gates must be open for ion to pass)



$\alpha_n(V)$ and $\beta_n(V)$ are chosen so potassium gates begin to activate at or above V~0 mV and begin to de-activate at or below V~-20 mV



Entire Hodgkin Huxley (HH) Model

$$I_{TOT} = C\frac{dV}{dt} = (V_K - V)g_K(V,t) + (V_{Na} - V)g_{Na}(V,t) + (V_L - V)g_L$$

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

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

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

$$g_K(V,t) = \overline{g}_K\,(n(V,t))^4$$

$$g_{Na}(V,t) = \overline{g}_{Na}\,(m(V,t))^3\,h(V,t)$$

$$g_L = \overline{g}_L$$

The three α and β functions are chosen so that the channel gates open at the observed membrane potentials and with the appropriate speed for a particular type of neuron

Parameters C, V_K, V_{Na}, V_L, $\overline{g}_K$, $\overline{g}_{Na}$, $\overline{g}_L$ are derived from experimental measurements

Ion channels-related diseases

Ion channels-related diseases

Neuronal disorders like Epilepsy, Alzheimer's disease, Parkinson's disease, Schizophrenia may result from dysfunction of voltage-gated sodium, potassium and calcium channels

D[illegible] Dworakowska, Acta Biochim Pol. 2000