# Signal processing in nervous system
# - Hodgkin-Huxley model

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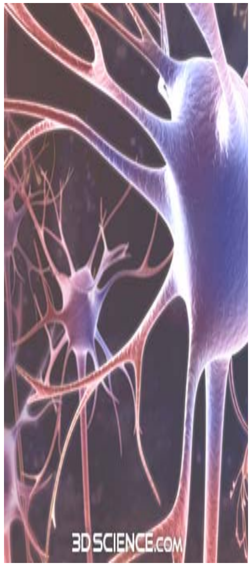
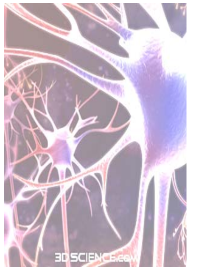
Seminar

"Gute Ideen in der theoretischen Biologie / Systembiologie"

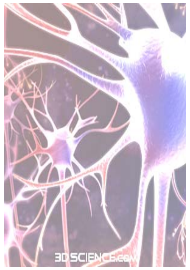


# Signal processing in nervous system



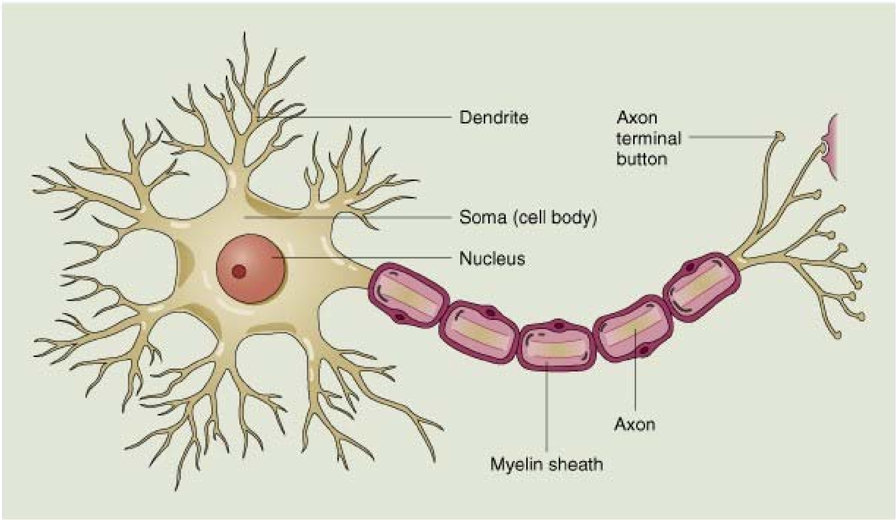

- Nerve cell and Action Potential
  - Structure of neurons
  - Generation of action potential
- Hodgkin-Huxley model
  - Voltage clamp experiment
  - Action potential as a biophysical model
  - Action potential as mathematic model
  - Dynamic behaviour of Hodgkin Huxley modeled neuron

# Nerve cell and action potential



- **nervous system**
  - collects information
  - processes information
  - elicits responses to the information

- **human brain**
  - about 100 billion neurons
  - highly connected

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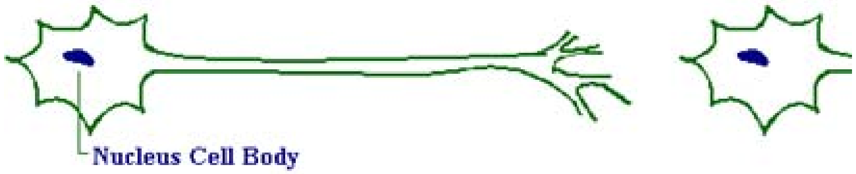
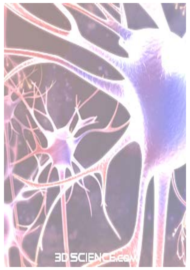
- **neuronal cells**
  - cell body (soma)
  - dendrites : → receive chemical messages from other neuronal cells
  - axon : → transmitting an electro-chemical signal to other neurons
  - axon foot → transformation from electro-chemical into a chemical message

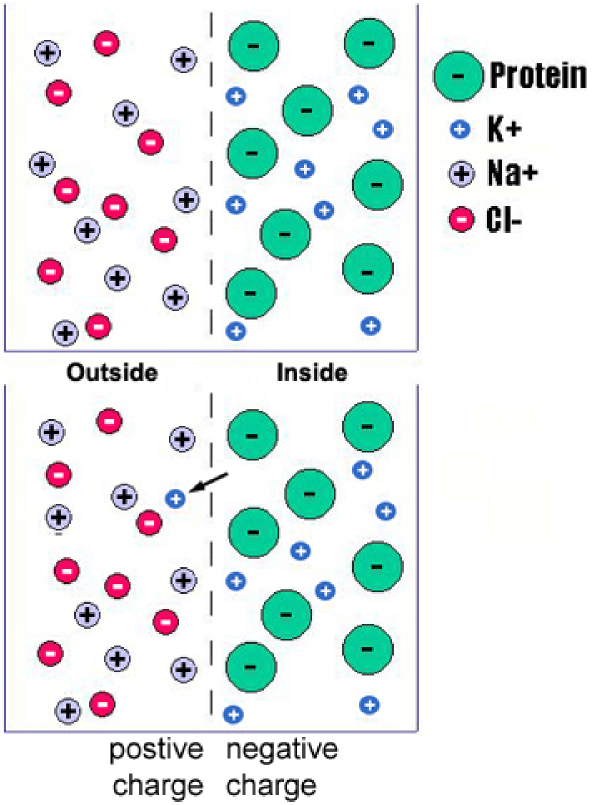



http://peer.tamu.edu/curriculum_modules/OrganSystems/module_5/Images/ImpulseAnimation/Nervous_anim.gif

# Nerve cell and action potential

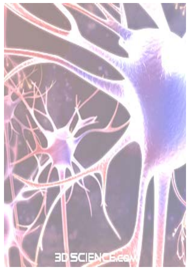


- **nerve Signals**
  - changes in membrane voltage
  - ion movements through membrane
- **membrane potential**
  - Different charges on both sides
  - Resting membrane: negative
    - Inside (cytoplasm): negative
    - Outside (extracellular): positive
  - Resting potential of -70 mV :
    - transmit no electric signal
    - Steady-state (concentration)
- **stimuli by chemical transmitter or electric signal**
  - influence the balance of ions between inside and outside
  - Response to stimuli: All-or-none principle
    - Stimulus threshold: -55 mV
    - < threshold → nothing happens
    - > threshold → generation of Action Potential

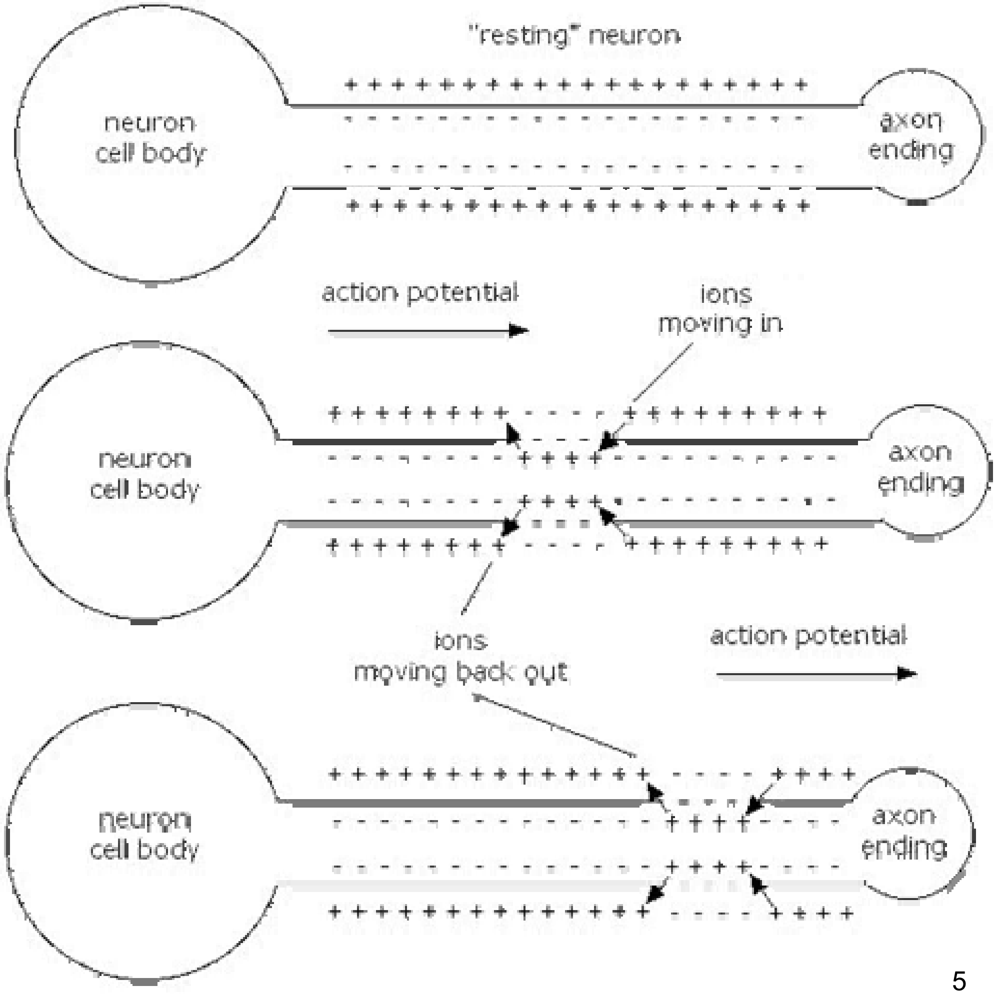



http://www.colorado.edu/kines/Class/IPHY3430-200/image/figure3a.jpg

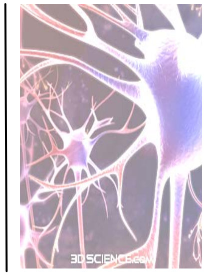
# Action potential



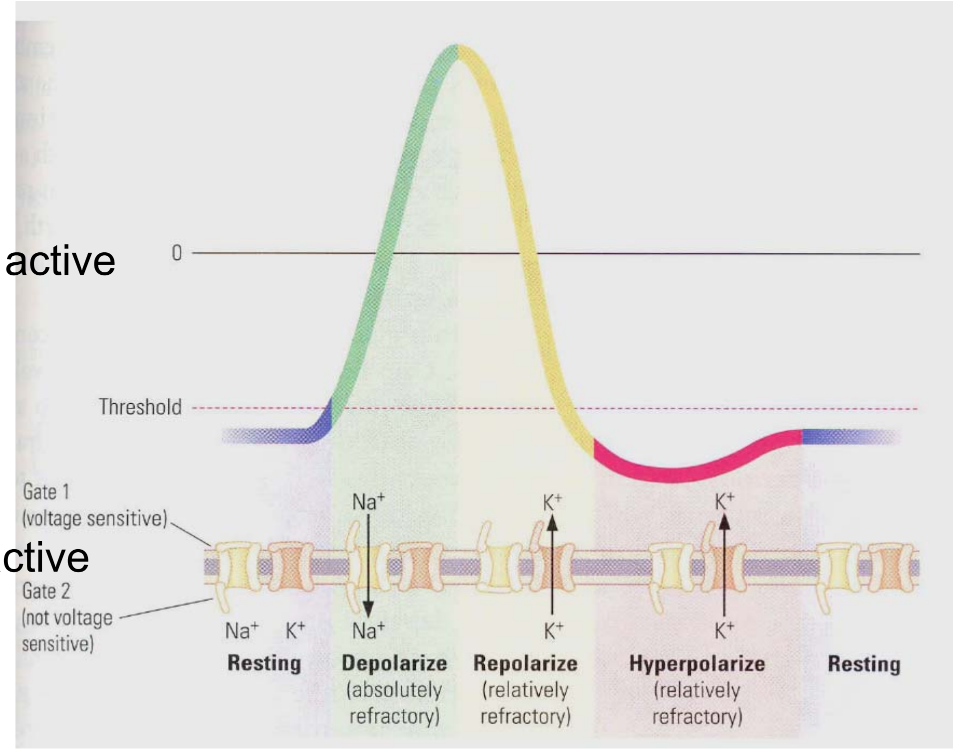
- action potential
  - rapid changes in membrane potential
  - Change from positive to negative and back
- Nerve Impulse
  - Move of action potential at axon



# Action potential (AP) - Phases



- Resting (-70 mV)
  - Steady state
  - Ion conductance for $Na^+$ very low
- Depolarization (+50 mV)
  - Voltage dependant Ion channel for $Na^+$ active
  - High $Na^+$-influx
- Repolarization
  - $Na^+$ Channel closed
  - Voltage-dependant ion channel for $K^+$ active
- Hyperpolarization (-85mV)
  - More $K^+$ outside
  - Refractory period : no fire possible
  - $Na^+/K^+$ pump restores to -70 mV
- Resting → again steady state



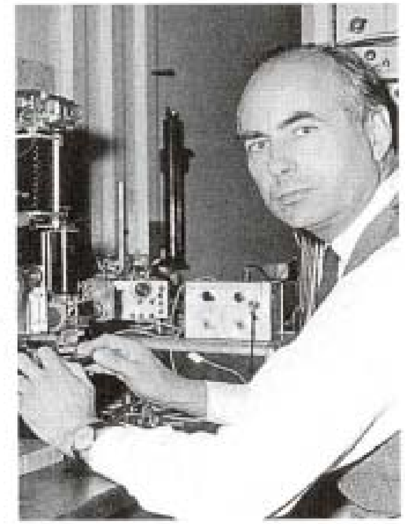



http://www.kyb.tuebingen.mpg.de/bs/people/felix/UniPsy_VL_BioKog_WS05-06.htm

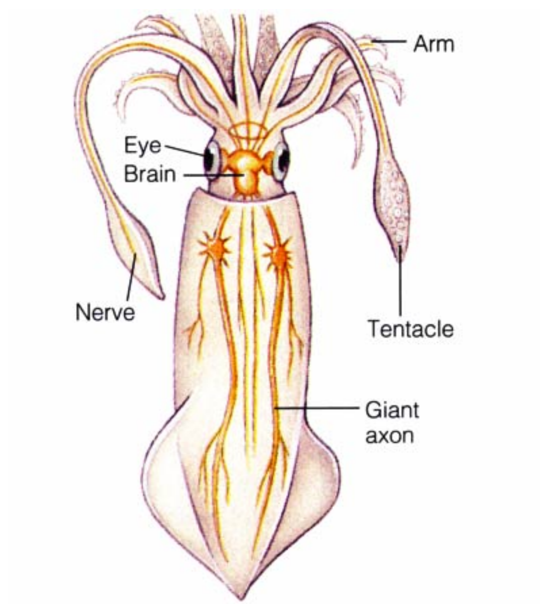
# Hodgkin-Huxley Model

- developed in 1952 by Alan Lloyd Hodgkin and Andrew Huxley
- 1963 Nobel Prize
- Characterizes the initiation and propagation of the neuronal signals in giant axons of squids
- describing the dynamic behaviour of channel kinetics.
- mathematical model
  → explains the experimental results
- prediction of stimuli response possible

A.L. Hodgkin



A.F. Huxley

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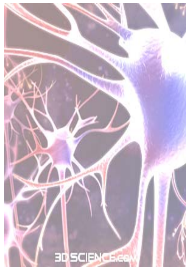
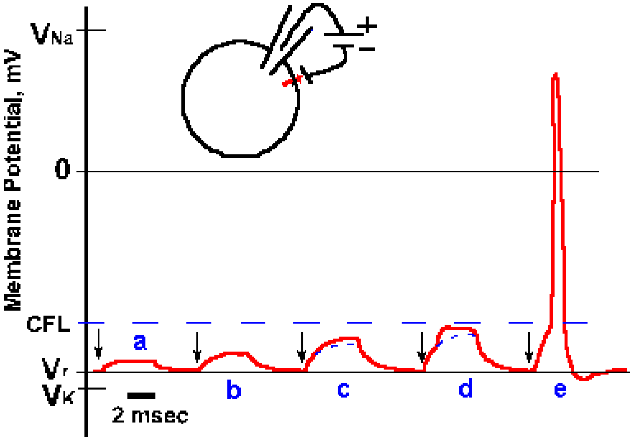
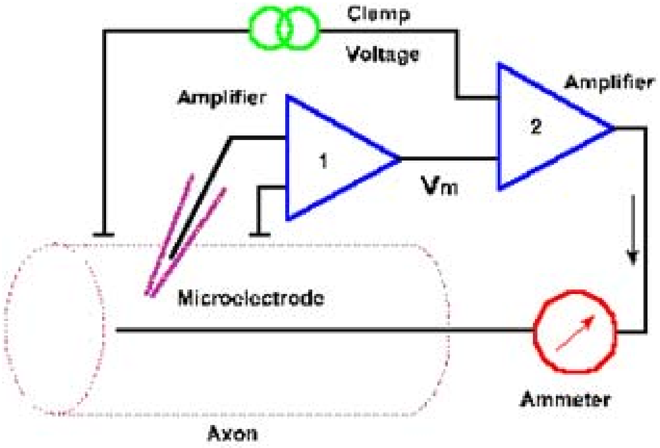
# HH model – voltage clamp experiment

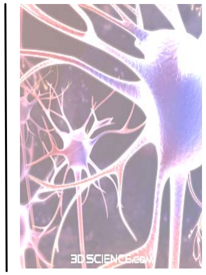


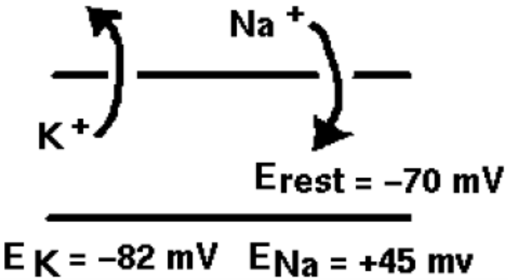

- Measurement of membrane voltage $V_m$
  - Intracellular micropipette electrode
  - Electrode in extra cellular fluid
- Possible to control $V_m$ → extern Current
  - |1> : compare between $V_m$ and $V_{clamp}$
- CFL = critical firing level
- Generation of AP in squid axon
- Only measurement of potential changes
- Could not measure influx / efflux currents



# HH model – equilibrium potential & conductance






**Equilibrium potential: E**

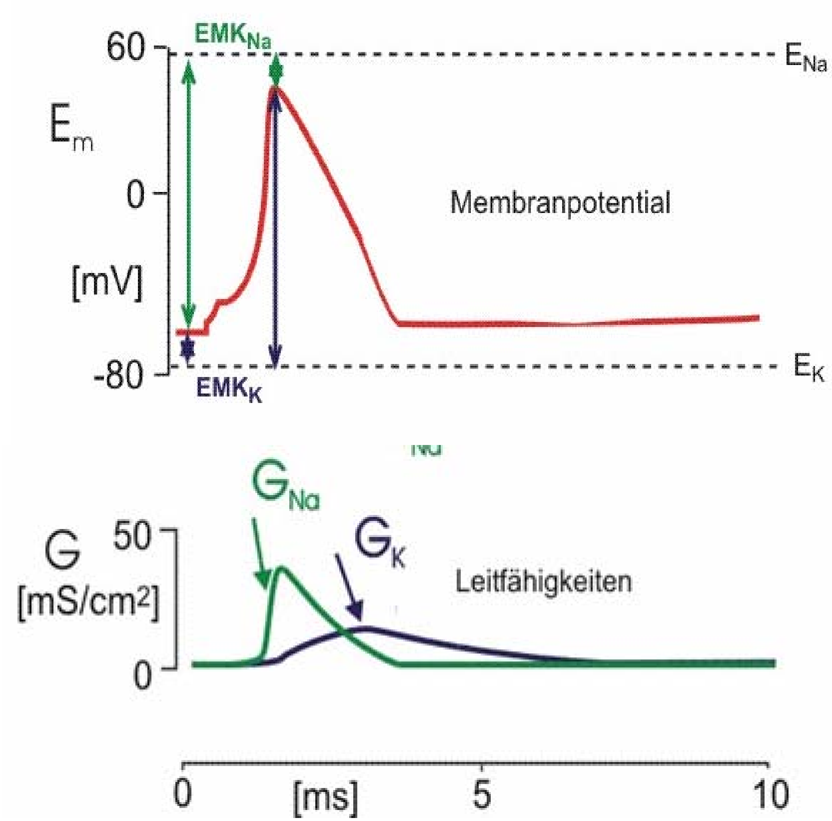
- $E_{Na}$
  - Na+ conc. outside higher than inside
  - Passive Influx → equilibrium potential = +45 mV
- $E_K$
  - K+ conc. inside higher than outside
  - Passive efflux → equilibrium potential = -82 mV
- Na/K-ion pump
  - compensate passive currents of K+ / Na+
  - equilibrium potential Erest = -70 mV

**Action Potential → changes in ionic conductance**

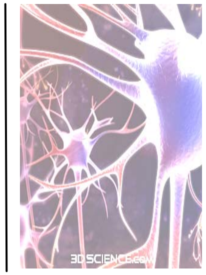
- ↑ conductance = ↑ ion current
- ↓ conductance = ↓ ion current

**Electric Conductance : g**

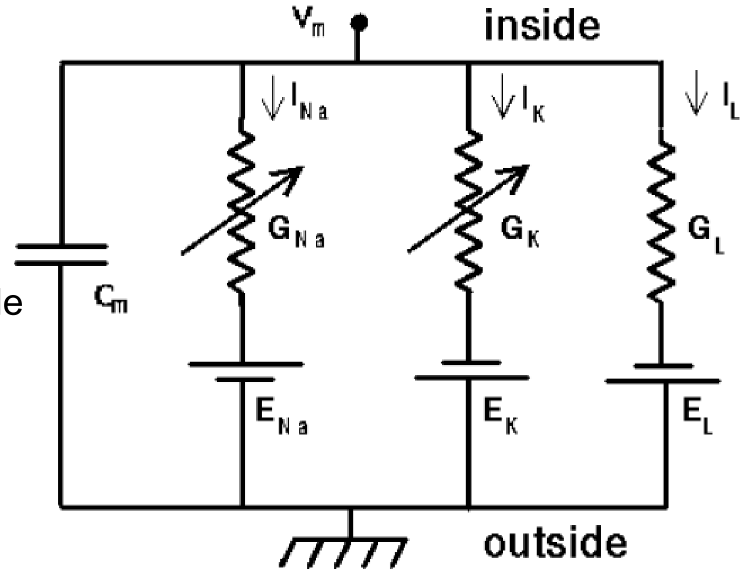
- gNa = inward Na+ -influx
- gK = outward K+ -efflux
- gL = for other ions (Cl-, …) ; L = leakage

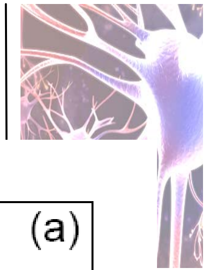


# HH model – equivalent electric model

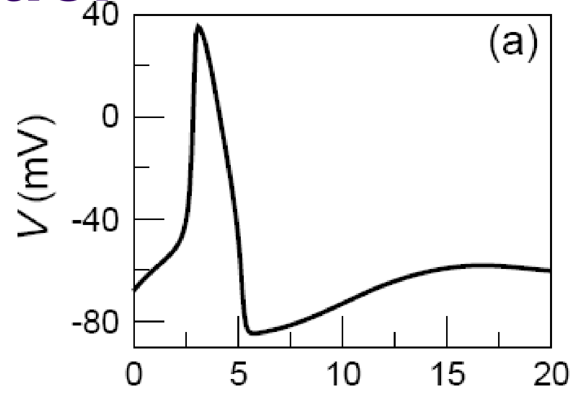


- Each component of an excitable cell has a biophysical analog.
- Cm - membrane capacitance
  - Separation of ions through membrane
  - Discharging = influx currents
  - Charging = efflux currents
- Vm – membrane potential
  - Electric potential difference between inside and outside
- $G_{Na}$ ,$G_K$ , $G_L$
  - Different conductance values
  - Voltage dependant
- $E_{Na}$, $E_K$, $E_L$
  - Electrochemical gradient →driving the flow of ions
  - Represented by batteries (E)
- $I_{Na}$, $I_K$, $I_L$
  - ion current through ion channels
  - Flow because of different  ion concentration

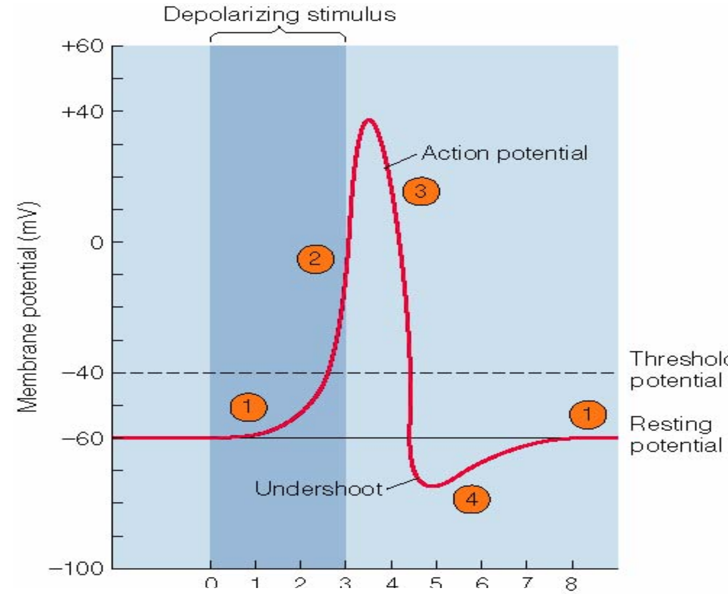




# HH model – mathematic model




- approximates the electrical features of excitable cells very well
- A set of nonlinear ordinary differential equations
- $C_m = \frac{q}{V}$ *q = charge density on both sides of the membrane*
- $I_{Ion} = -\frac{dq}{dt}$ *"-" → loss of charge*
- $I_{Ion} = \sum_{\text{ion species } i} I_i$ *Ions : K+, Na+, Leakage (Cl-)*
- → $C_m \frac{dV}{dt} + I_{Ion} = 0$




$$\dot{V}_m = -\frac{1}{C_m}\left(\sum_i I_i\right),$$ time derivative of the potential across the membrane is proportional to the sum of the currents

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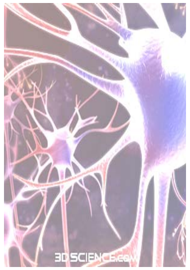
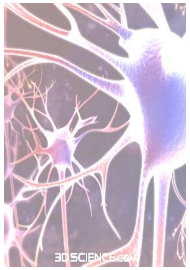
# HH model – ionic currents



- **following assumptions:**
- Ionic currents obey Ohm's law : R = U / I
  - I = g * V
- Driving force for current: $(V - V_i)$.
  - Difference between the V and Vi
  - V = Vm and Vi for each ion → $E_{Na}$, $E_K$, $E_L$
  - $V_i$ = Nernstian equilibrium potential of corresponding ion species
    - $$V_i = \frac{RT}{F} \ln \frac{c_i(\text{outside})}{c_i(\text{inside})}$$
- Combination yields: $C_m \frac{dV}{dt} + I_{Ion} = 0$ & $I_i = g_i(V - V_i)$.

→ $$C_m \frac{dV}{dt} + \sum_i g_i(V - V_i) = 0$$

# HH model – gating variables



- For every ion species: $I_i = g_i(V - V_i)$

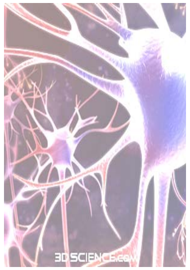
$$I_{Na} = g_{Na} \cdot (V - E_{Na}) \quad \rightarrow \quad I_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h \cdot (V - E_{Na})$$

$$I_K = g_K \cdot (V - E_K) \quad \rightarrow \quad I_K = \bar{g}_K \cdot n^4 \cdot (V - E_K)$$

$$I_L = g_L \cdot (V - E_L) \quad \rightarrow \quad g_L = \text{const.}$$

- gating-variables :
  - Probabilistic Dynamic of ion channels
  - Fraction of open channels
  - Exp data → m, n, h

# HH model – gating variables

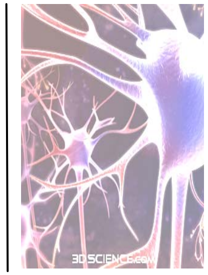



- Gating variables:
  - Time-dependant
  - With exponential functions ($a_m(V)$, $ß_m(V)$, …)
  - Parameter adjusted with exp. data

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

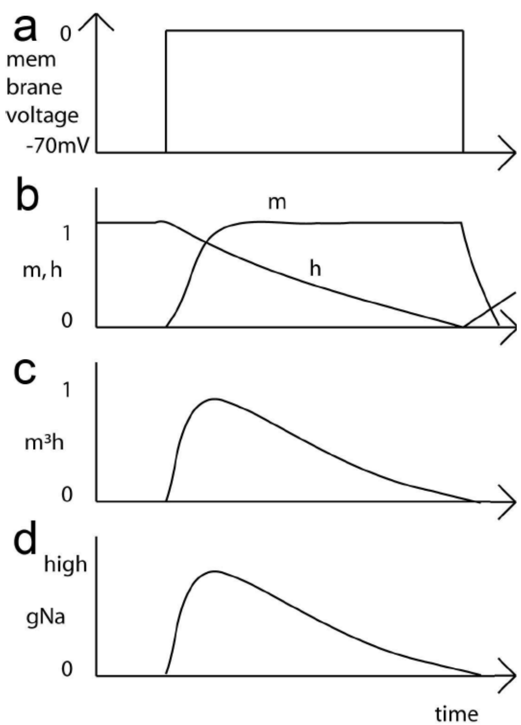
$$\frac{dm}{dt} = \alpha_m(V) \cdot (1 - m) - \beta_m(V) \cdot m$$

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

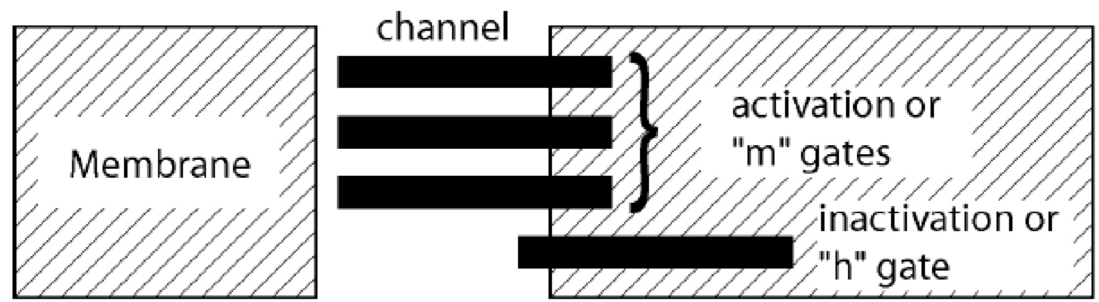


# HH model – gating variables for Na⁺

- Postulated gating var. → structure properties of ion channels

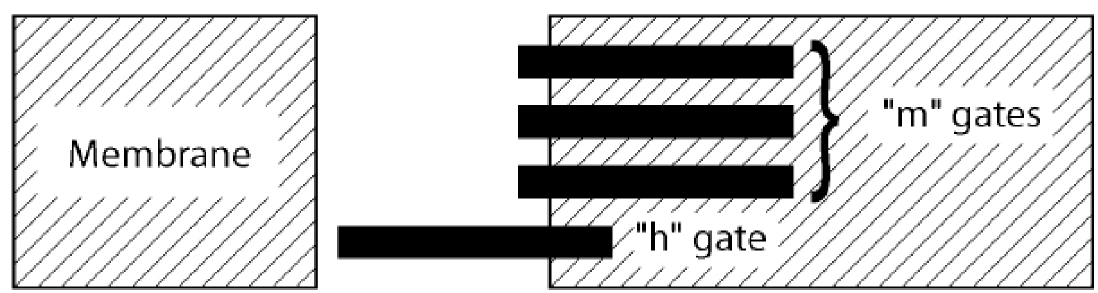



Resting (polarized) membrane

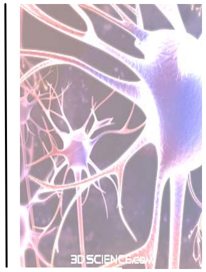



$$I_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h \cdot (V - E_{Na})$$

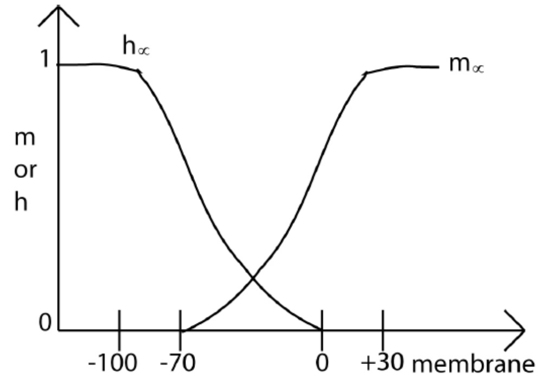
Depolarized for long time

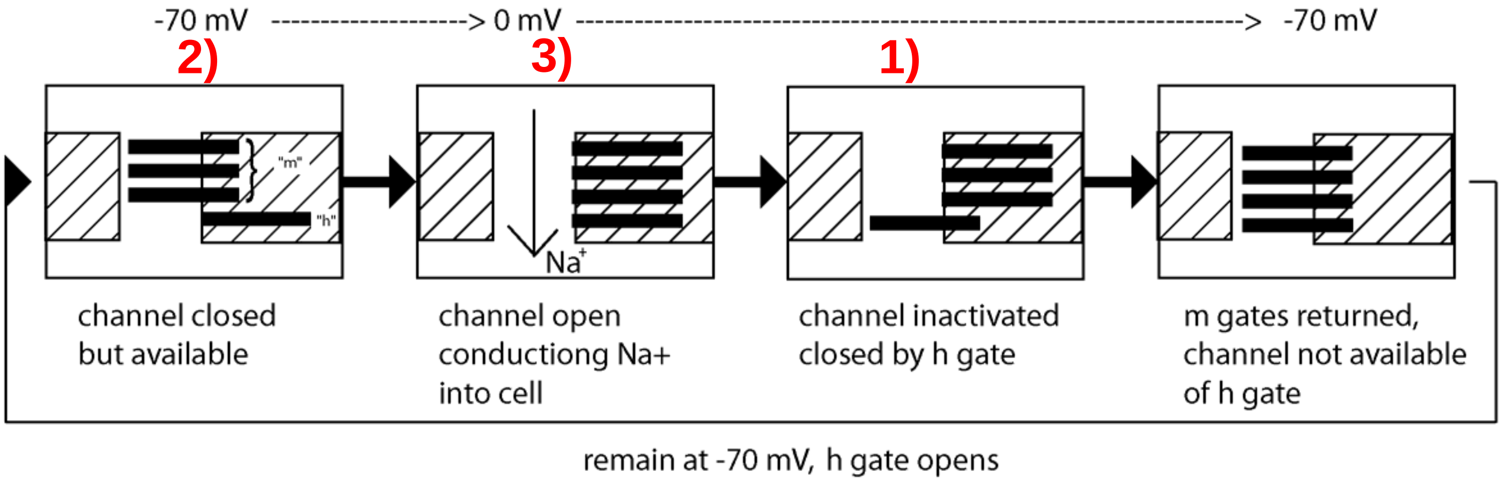


# HH model – gating variables for $Na^+$

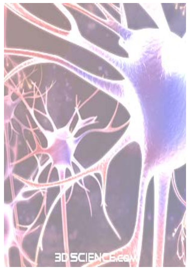


- 1) Closed (inactive / not available)
- 2) Closed (active / available)
- 3) Open (active)



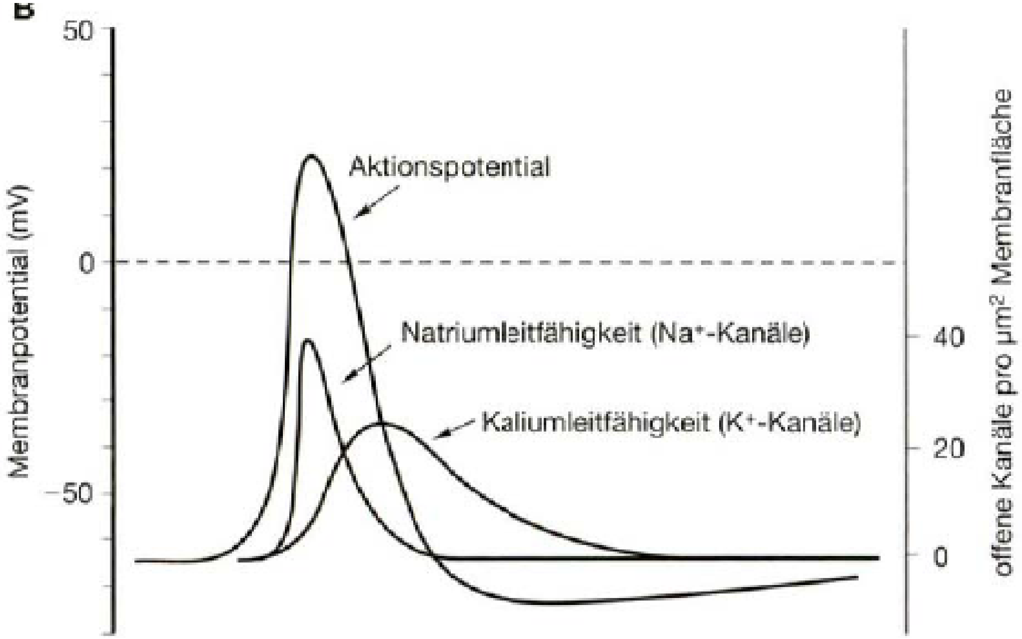



# HH model – gating variable for K⁺

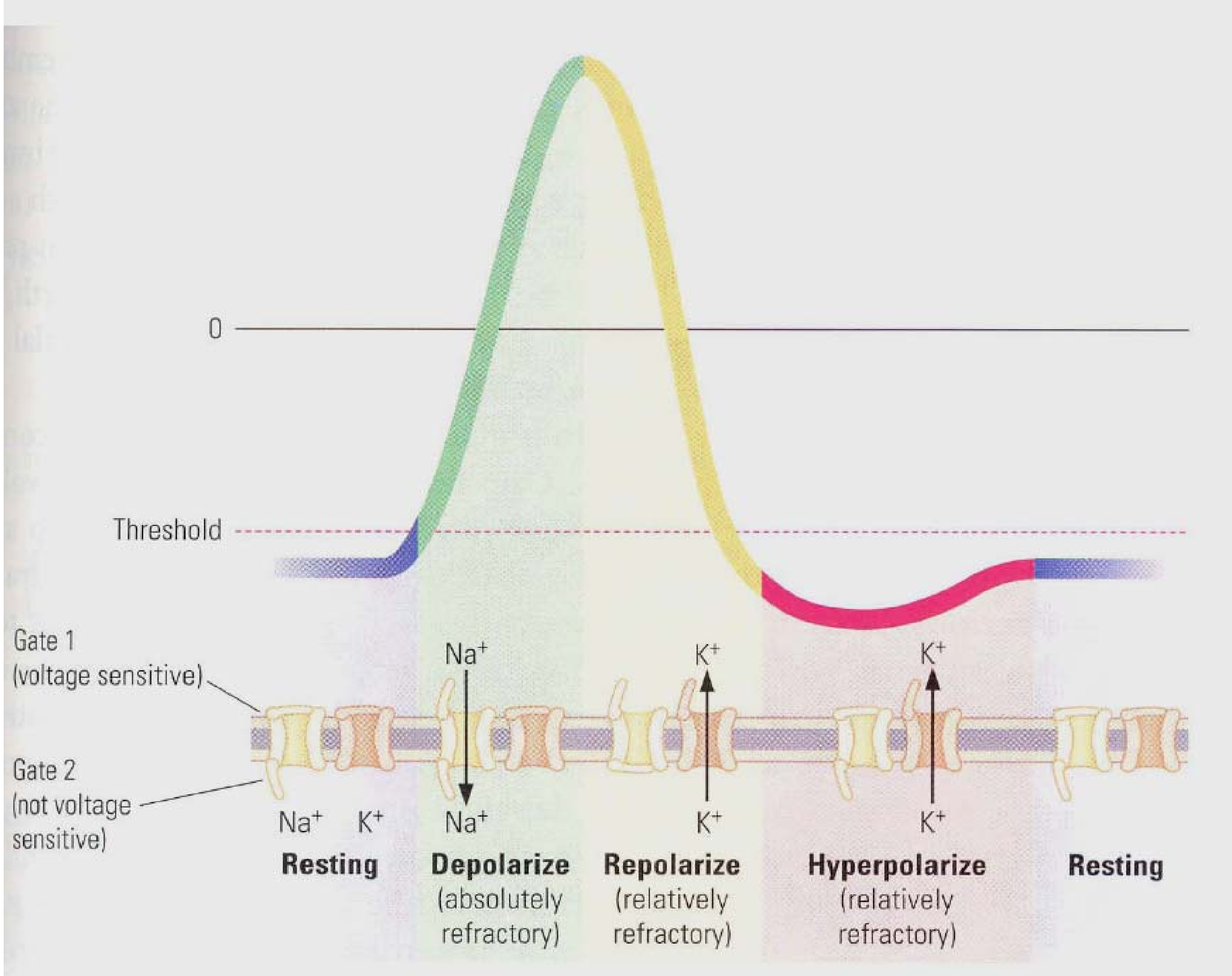


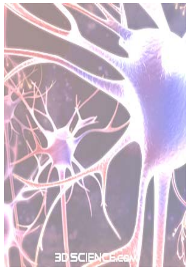
- Independet gating of 4 channel-subunits
- n = fraction of subunits in active status
- ↑ Voltage → n gates open
- No gate for inactivation
- Time delay

$$I_K = \bar{g}_K \cdot n^4 \cdot (V - E_K)$$

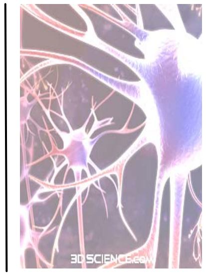


# HH model – generation of action potential

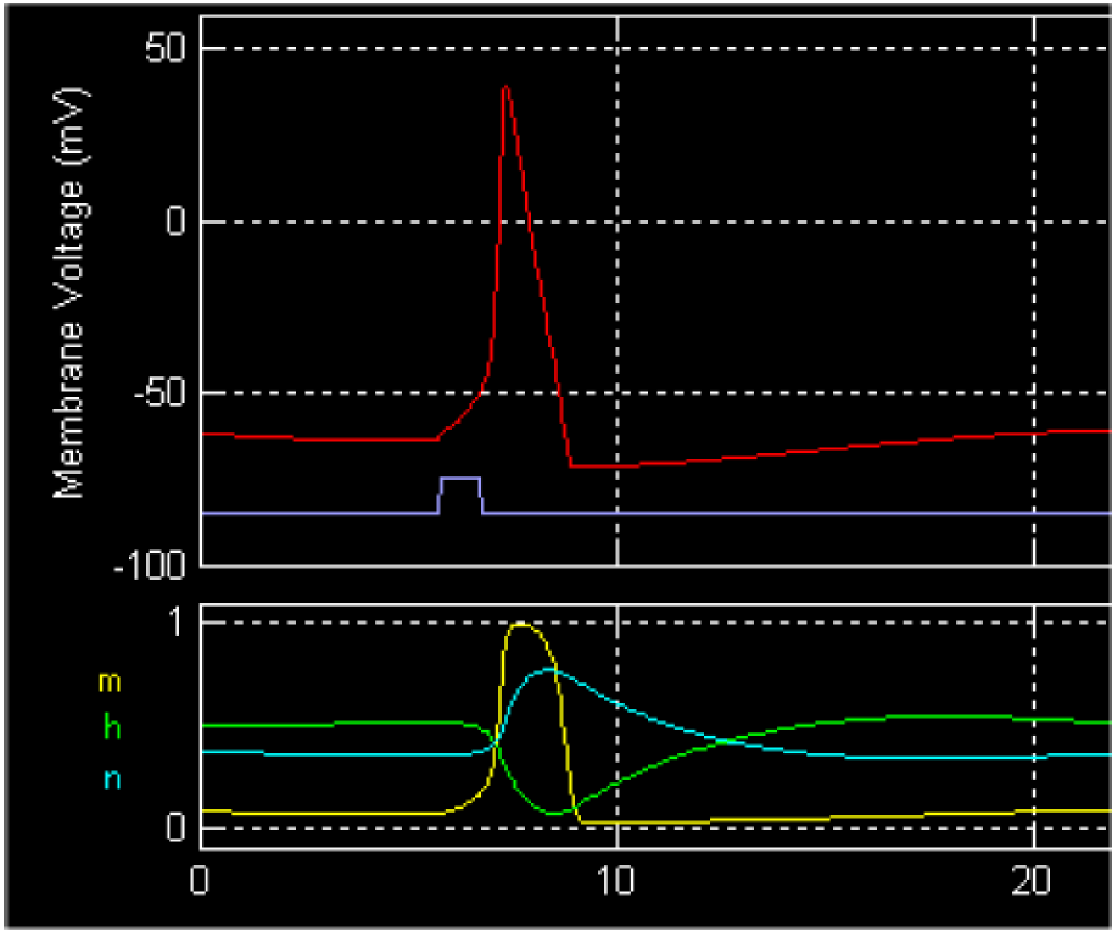


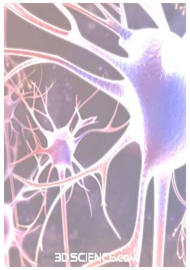
# HH model – dynamic behaviour



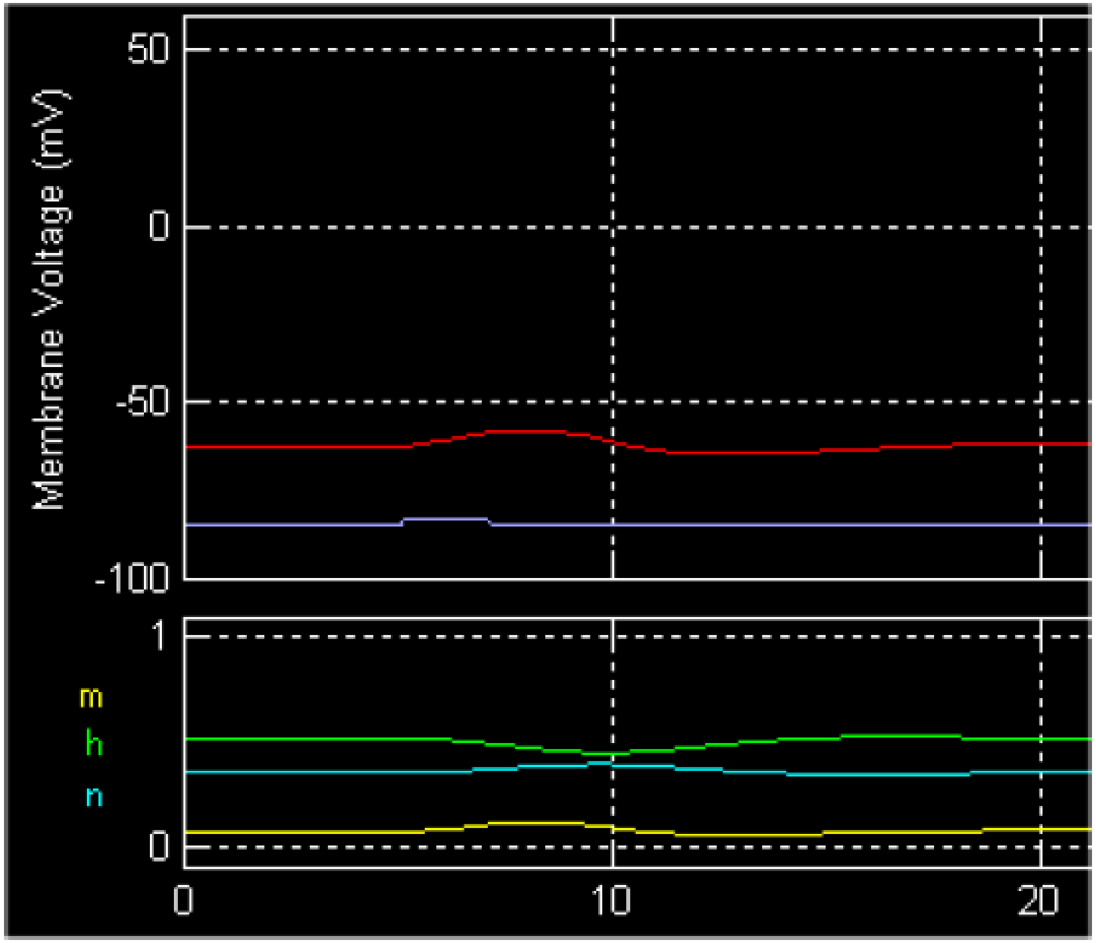
- Stimulus of neuron > threshold
- Action potential



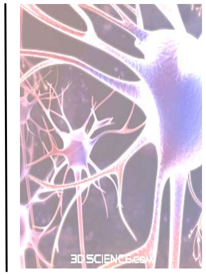
# HH model – dynamic behaviour



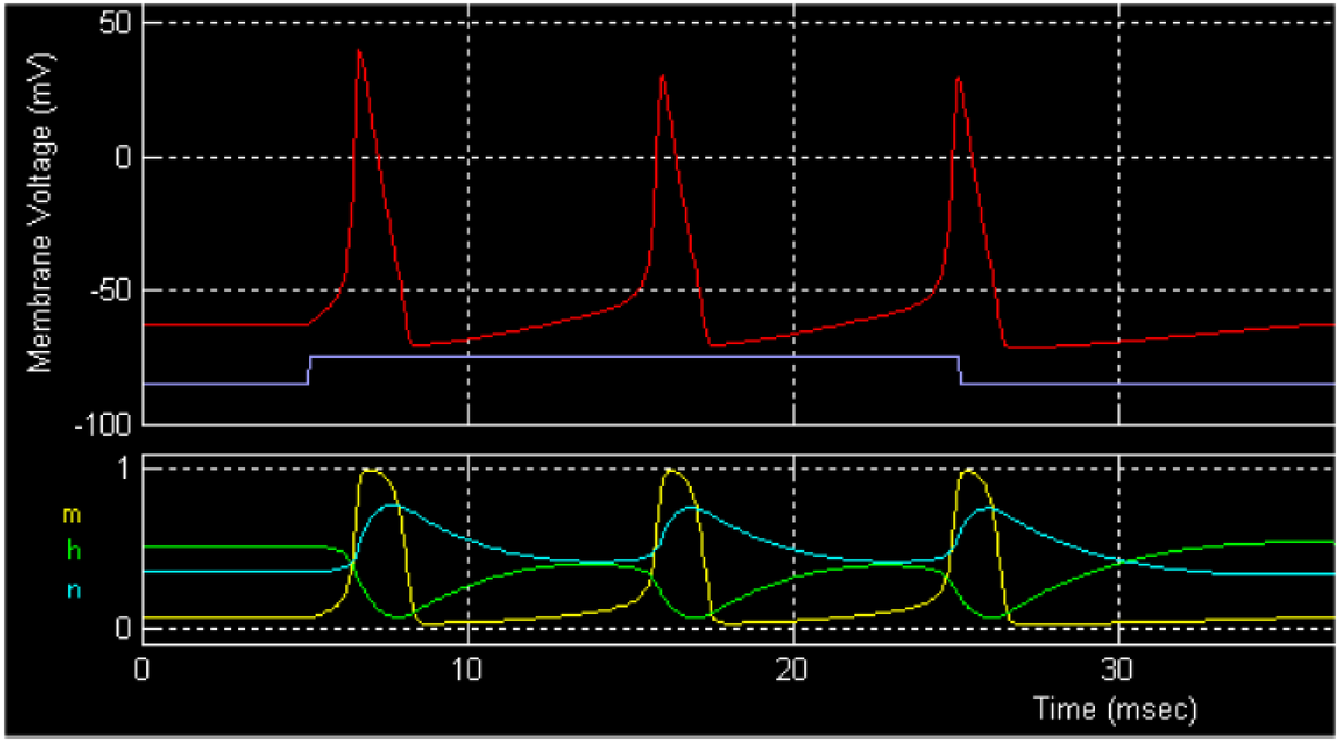
- Stimulus of neuron < threshold
- No action potential



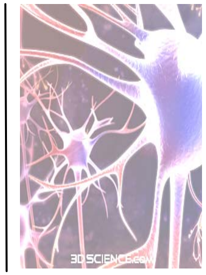
# HH model – dynamic behaviour



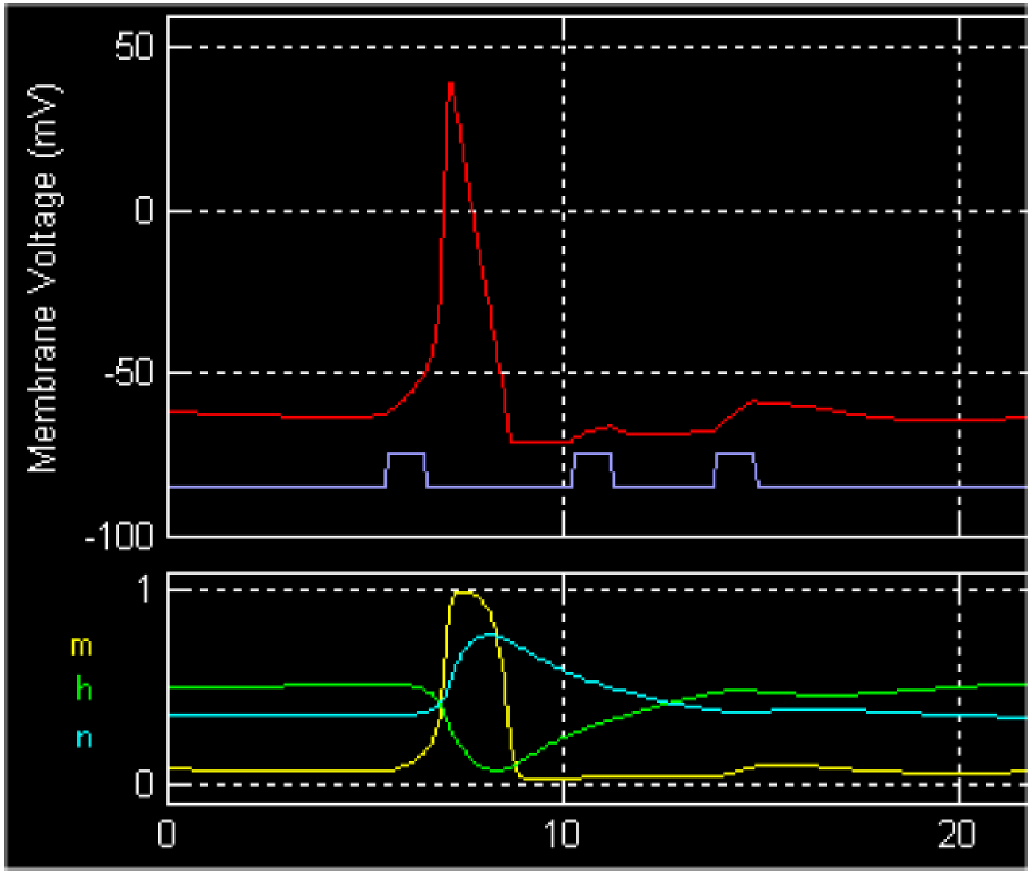
- Continuous stimulus
- Repeating sequence of APs



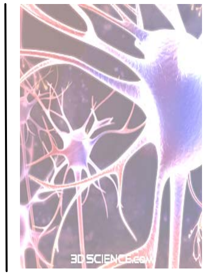
# HH model – dynamic behaviour



- 2nd stimulus during refectory phase
- h = very slow
- $Na^+$ channel still closed
- n = very high
- High K+ efflux
- No AP possible



# HH model - simplification



- HH :
  - too complex
  - not analytic solvable, only numerical
  - system of four non-linear differential equations: $V_m$, *n, m, h*
  - Reduction necessary

- simplification

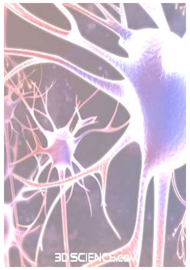
1) *m* is replaced by its steady-state value
2) and *h* are replaced by a new variable *w*
3) *a* and *b* are constants
4) *n* does not exist (K+)

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

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

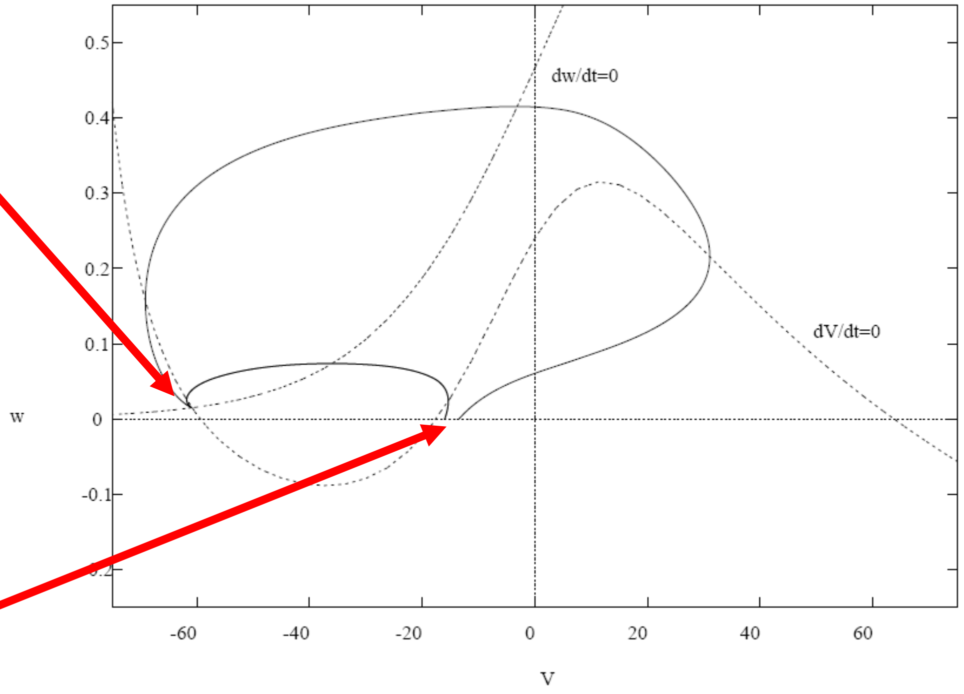
$$\frac{dn}{dt} = \alpha_n(V) \cdot (1 - n) - \beta_n(V) \cdot n$$

- Reduced to a system of 2 variables
  - $V_m$ (potential ) and *w (V)*

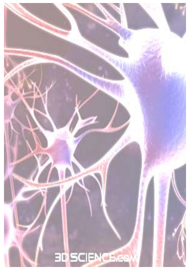


# HH model - simplification

- Steady state:
  - Intersection of nullclines
  - *dV/dt* = 0 and *dw/dt* = 0
  - $E_{res}t$ = -60 mV
- small disturbance
  - Relaxation of potential
- Action Potential
  - Narrow threshold for generation
  - All-or-nothing

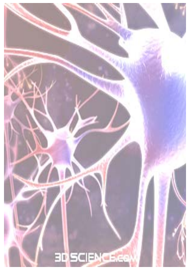


# HH model - summary



- HH model describes initiation and propagation if action potentials
- Approximate the electrical characteristics of excitable cells
- Ion channels kinetics are described with gating variables
- Stimuli responses are predictable
- For model analysis → reduction of HH model is needed

# Quellen





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