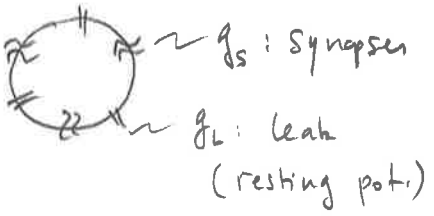
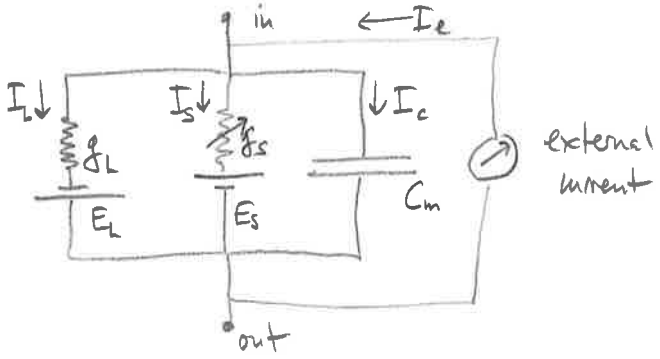
ACTION POTENTIAL

Recap: A simple model of electrical properties of neurons:



- Single compartment (isopotential)
- Selective ion-channels
  ↳ drive V towards reversal pot. (E) for that channel type

Equivalent electrical circuit:

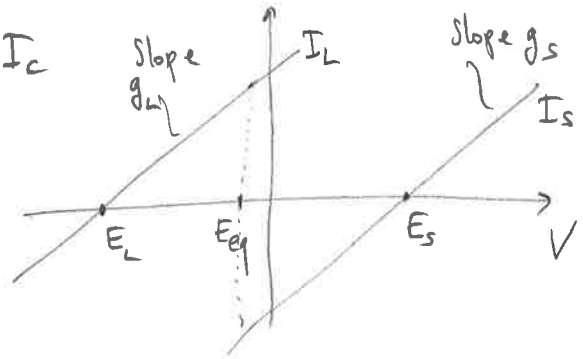


 : variable conductance g_s
↓
depends on presence of neurotransmitter

Charge conservation: $I_e = I_L + I_s + I_c$

Ohm's law: $I_L = g_L \cdot (V - E_L)$

$I_s = g_s \cdot (V - E_s)$



@ Equilibrium: $I_c = 0$

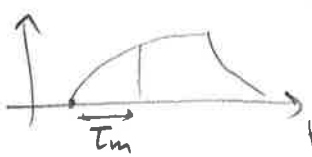
$$I_e = g_L \cdot (V - E_L) + g_s \cdot (V - E_s)$$

$$(g_L + g_s) \cdot V = I_e + g_L E_L + g_s E_s$$

$$\boxed{V_{eq} = \frac{I_e}{g_L + g_s} + \frac{g_L E_L + g_s E_s}{g_L + g_s}}$$

- Synapse closed: $g_s \ll g_L \Rightarrow V_{eq} \simeq E_L$
- Synapse open: $g_s \gg g_L \Rightarrow V_{eq} \simeq E_s$

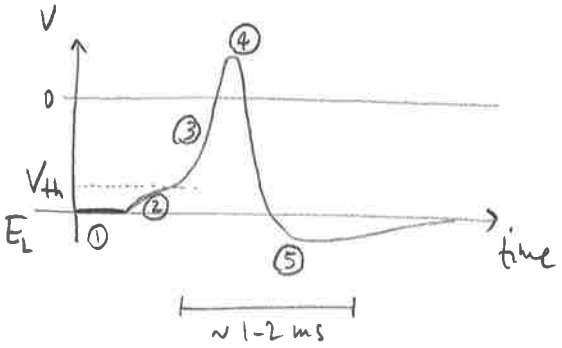
not @ equilibrium



as in previous lecture...

Action potential

- occurs in axons
- all-or-none, i.e. stereotyped (If $I_e \uparrow \Rightarrow$ AP initiated sooner, but same shape → non-linear, unlike passive mem.)
- travels down the axon
  (if initiated close to soma, i.e. in axon initial segment)



① @ rest $V = E_L$
② current injected $I_e \rightarrow V(t)$ = exponential
③ fast depolarization if $V > V_{th}$
④ Overshoot ($V > 0$)
⑤ Repolarization & undershoot ($V < E_L$)

GOAL: Explain the above observations with the RC-circuit formalism

→ Nobel prize in Medicine & Physiology
Alan Hodgkin and Andrew Huxley

Everything they did: was before the existence of ion-channels was even known!

Questions:
- why is AP all-or-none?
- why does it have the shape above?
- why generated only in axon?

Answer: $g = g(V,t)$ i.e. Voltage dependent channels that occur only in the axon

What could be happening? We saw: channels open → pull V towards E

→ Hypothesis:
- rising phase of AP: $g_{Na} \uparrow$ or $g_{Ca} \uparrow$
- decaying phase of AP: $g_{Na} \downarrow$ or $g_{Ca} \downarrow$ or $g_K \uparrow$ or $g_{Cl} \uparrow$

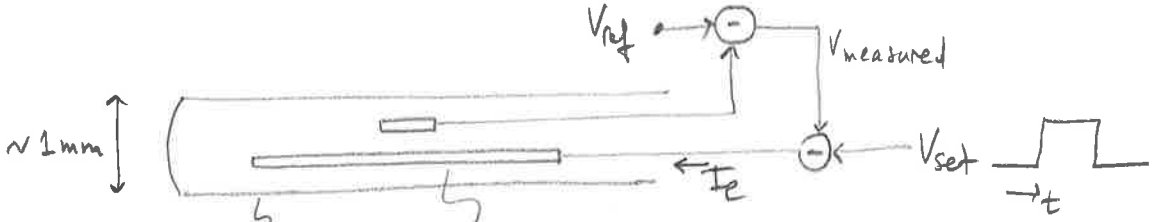
} as function of V!

→ To test it: need to measure $g_{Na}, g_K, \dots$

Solution: use IV-relation: measure I_{Na}, I_K for different V
then infer g_{Na}, g_K

achieved with new technique: Voltage clamp

- **Voltage clamp** (& space clamp): A new technique invented by Hodgkin & Huxley
  - fast feedback system to fix V and measure I
  - Makes the axon isopotential → not traveling AP (but same mechanism)



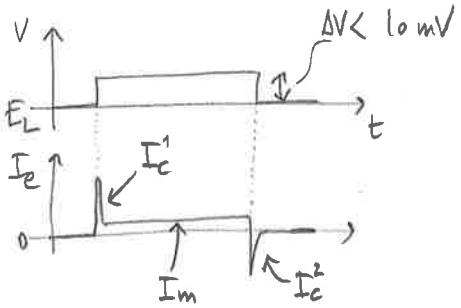
Before: inject I_e → measure V

Here: Set V → measure I_e required to keep $V_{measured} = V_{set}$

- **Voltage-clamp experiment**

Small V

passive / linear membrane



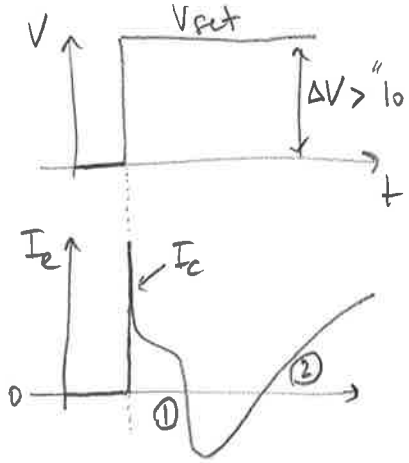
I_c^1: depolarize membrane (add + charge to inside)

I_m: compensate for leak current I_L ($V \neq E_L \Rightarrow$ cell wants to go back to E_L)

I_c^2 Repolarize membrane i.e. remove charge added in I_c^1

large V

active / non-linear membrane



①: cell wants to depolarize → need to inject negative I_e to keep $V = V_{set}$

②: cells wants to hyperpolarize → need to inject positive I_e to keep $V = V_{set}$

Hypothesis: ① I_{Na}, $E_{Na} \simeq +50$ mV

② I_k, $E_k \simeq -80$ mV

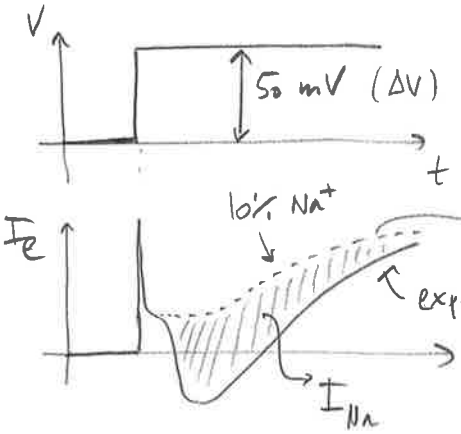
Note: No direct comparison of $I_e(t)$ in voltage clamp exps & AP shape because here V = fixed V_{set}.

- Test the nature of the currents

(i) Hodgkin & Huxley : did it by removing Na concentration gradients

ie. : replace extracellular medium with a solution that has 10% Na^+ compared to seawater

↳ eliminates I_{Na} for $\Delta V \simeq +50$ mV



$= I_{10\% Na}$ for $\Delta V = 50$ mV

↓

- get $I_{Na} = I_{seawater} - I_K$
- repeat for many V_{set} (ie. ΔV) ⇒ get $I_{Na}(V)$ & $I_K(V)$
- get $g_{Na}(V)$ & $g_K(V)$ with $I_{Na} = g_{Na} \cdot (V - E_{Na})$ & $I_K = g_K \cdot (V - E_K)$

(ii) Later : people removed intracellular K^+

⇒ confirmed I_K & Hodgkin and Huxley predictions

(iii) Later : Pharmacology : - TTX : poison in Puffer fish

↳ eliminates I_{Na}

- TEA

↳ eliminates I_K

⇒ **see slides** for $g_{Na}(V,t)$ & $g_K(V,t)$

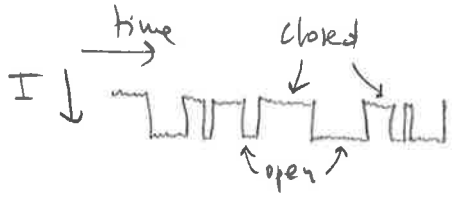
g_{Na} : - fast activation
- fast inactivation

g_K : - slow activation
- no inactivation

- How to capture V & t dependence of g_{Na} & g_K?

2 possibilities: (i) Single channels have variable (analog) permeability
(ii) Single channels are either open or closed (digital)

Today we know: (ii) is correct

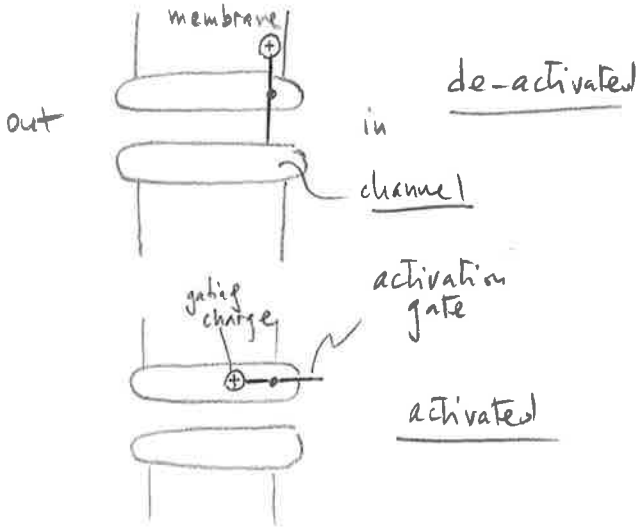


Patch clamp: Nobel prize Med/Phys. 1991
Erwin Neher & Bert Sakmann
↳ Allows recordings of current I through single channels

→ Hodgkin & Huxley: "inferred" it from their voltage clamp data

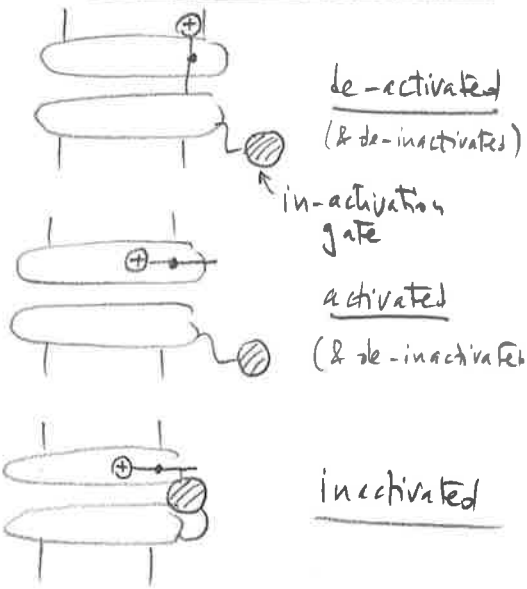
- Two types of V-dependent Conductances:

Persistent Conductance



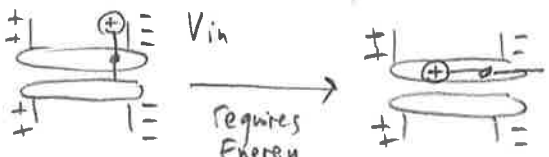
Example: g_K (in AP)

Transient Conductance



Example: g_{Na} (in AP)

Note: @ rest



to test if Vin ↑ ⇒ Voltage dependent

- Hodgkin & Huxley formalism: used for active conductances in general

$$g_i = \bar{g}_i \cdot p_i$$

g_i: overall conductance of channels of type i

$\bar{g}_i$: maximal conductance (if all open)

p_i: probability open (or fraction open)

- Persistent conductances

Assume: k {independent / identical} events are necessary to open a single channel

$\Rightarrow P = n^k$

Hodgkin & Huxley: $g_{K^+} = \bar{g}_{K^+} \cdot P_{K^+}$, $P_K = n^4 = \underbrace{n}_{\text{first}} \cdot n \cdot n \cdot \underbrace{n}_{\text{fourth}}$ ← 4 subunits

} 4 subunits in the channel need to open

n: gating / activation variable

= probability of subunit gate being open } Voltage & time dependent

k: number of subunits in each channel

→ fitted to data → resulted in correct prediction for K^+ channels!

How to derive (V,t)-dependence of n?

(i) time-dependence: Assume closed → open & open → closed transitions such that:

$$\underbrace{\Delta n}_{\substack{\text{change in}\\ \text{fraction open}\\ \text{channels in } \Delta t}} = \underbrace{\alpha_n(V)}_{\substack{\text{rate of}\\ \text{opening}}} \cdot \underbrace{(1-n)}_{\substack{\text{fraction}\\ \text{closed}}} \cdot \underbrace{\Delta t}_{\text{time}} - \underbrace{\beta_n(V)}_{\substack{\text{rate of}\\ \text{closing}}} \cdot \underbrace{n}_{\substack{\text{fraction}\\ \text{open}}} \cdot \Delta t$$

closed → open: $\Delta n > 0$; open → closed: $\Delta n < 0$

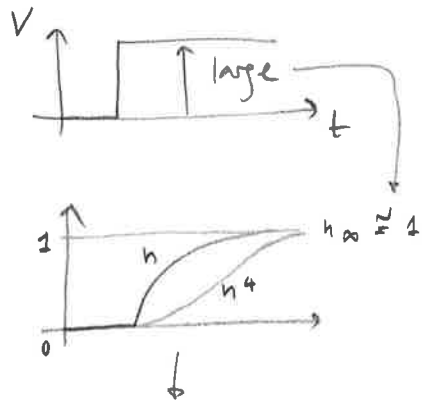
$\Delta t \to 0$

$$\Rightarrow \boxed{\frac{dn}{dt} = \alpha_n(V)\,(1-n(t)) - \beta_n(V)\cdot n(t)}$$ α_n, β_n not time-dependent

$$\Rightarrow \boxed{\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n}$$

with: $\tau_n(V) = \dfrac{1}{\alpha_n(V)+\beta_n(V)}$ } faster transitions ↓ faster change in n

$n_\infty(V) = \dfrac{\alpha_n(V)}{\alpha_n(V)+\beta_n(V)}$ } between 0 and 1



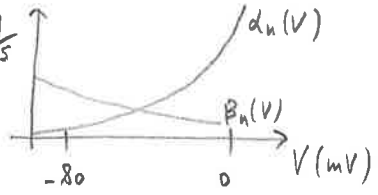
n^4 better fit to $g_k(V,t)$ curves!

see slides

(ii) Voltage-dependence of : $\alpha_n(V) = ?$ $\beta_n(V) = ?$

In practice : $\alpha_n(V)$ & $\beta_n(V)$ are fit to the data (i.e. $g_K(V,t)$)

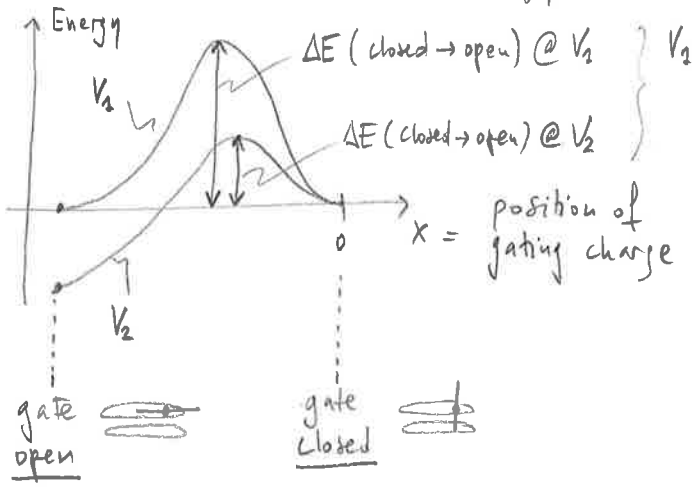
Fits :



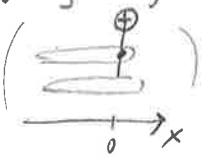
→ $\alpha_n(V)$, $\beta_n(V)$ approximately exponentials

Why? Consider Energy barriers that need to be overcome by the gating charge:

Putative (Voltage-dependent) energy barrier for the gating charge:



V_1 & V_2 : potential inside the cell.
$0 > V_2 > V_1$



In this case :

$$\alpha_n(V) \cong A_\alpha \cdot e^{-\frac{E_\alpha}{k_B T}}$$

$$\beta_n(V) \cong A_\beta \cdot e^{-\frac{E_\beta}{k_B T}}$$

Similar derivation as for Nernst Eq. factor: $e^{-\frac{\Delta E}{k_B T}}$

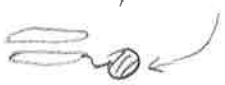
- Transient conductances

Similar, but include inactivation:

$$P_{Na} = m^3 \cdot h$$

(m^3: activation variable; h: inactivation variable)

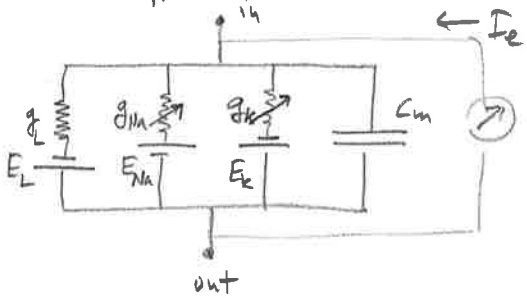
h = Probability that channel is not blocked by inactivation gate



See slides for :
- $m_\infty, h_\infty, n_\infty$ & τ_m, τ_h, τ_n & $m(t), h(t), n(t)$
- m : fast , h, n : slow
- m & h have opposite V-dependence

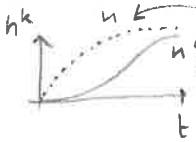
Full Hodgkin & Huxley model :

with $g_{Na}(V,t)$ & $g_K(V,t)$ from above



Model parameters are fit to $g_{Na}(V,t)$ & $g_k(V,t)$ (from voltage clamp)

e.g.: g_k



→ evidence for $k=4$ Subunits !

Some model parameters:

$\bar{g}_L = 0.003\ mS/mm^2$ $\quad E_L = -54\ mV$

$\bar{g}_k = 0.036\ mS/mm^2$ $\quad E_k = -77\ mV$

$\bar{g}_{Na} = 1.2\ mS/mm^2$ $\quad E_{Na} = +50\ mV$

Siemens = $\frac{1}{Ohm}$

Model predictions:

(a) AP-Shape: see simulations of HH-Model (Slides)

(b) AP-Threshold V_{th}

Note: $n_\infty, m_\infty, h_\infty$ all >0 for $V = E_L$ $(= V_{rest})$

i.e. g_{Na} already open @ rest.

Why no AP @ rest? bec. I_L & I_k are larger than I_{Na} for $V < V_{th}$

@ V_{th}: $|I_L + I_k| = |I_{Na}|$

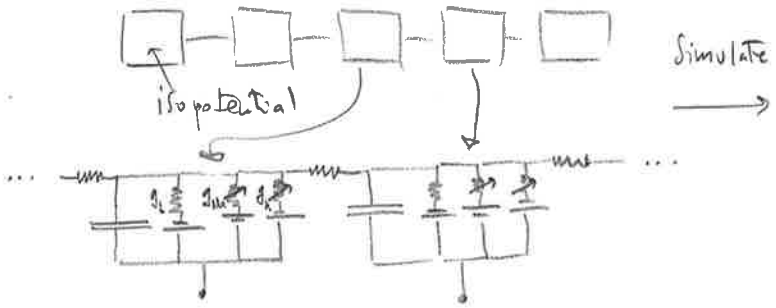
(c) Refractory period: harder to generate AP immediately after AP

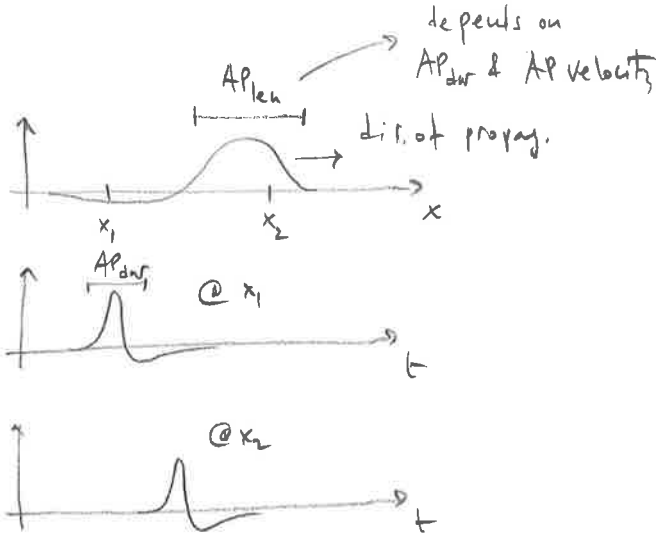
↳ requires larger current injection.

↳ Reason: g_k still activated, g_{Na} still inactivated

(d) AP-propagation in unmyelinated axon

Simulate with multicompartment model:



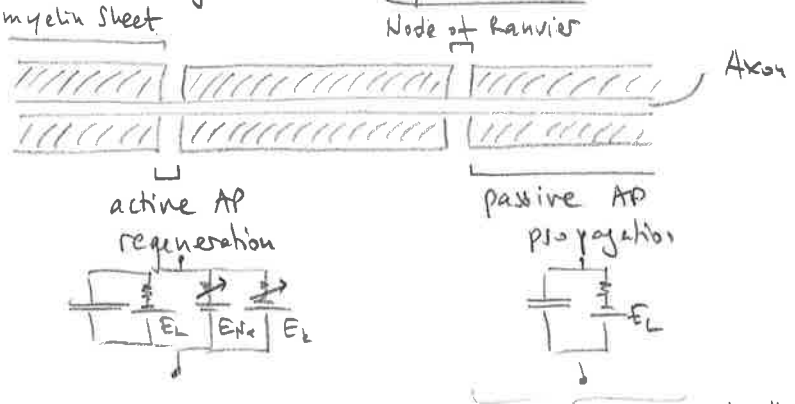


AP velocity $v_{AP} = 0.5\ m/s = 0.5\ mm/ms$ (un-myelinated axon)

AP dur $\simeq 2\ ms$

$AP_{len} \simeq 1\ mm$

(e) AP-propagation in myelinated axon



bec. of myelin: – small capacitance
– large resistance

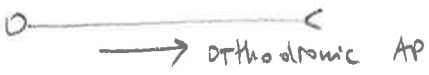
overall: compared to no myelin:
- faster AP propagation
- smaller current
- faster v_{AP} increase with axon radius

(f) AP-propagates in 1-direction along axon

Either direction is possible (in principle)

Reason: refractory period: g_{Na} still inactivated in the wake of AP

Soma

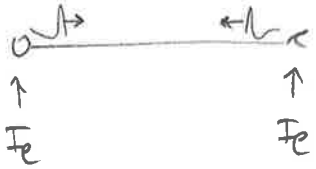


→ orthodromic AP

← antidromic AP

↳ does not usually happen in the brain

Antidromic AP can be generated artificially



Collision experiment: simultaneous APs generated in orthodromic & antidromic directions

⇒ the 2 APs annihilate in the middle (i.e.: neither AP makes it to the other end)

(g) AP not reflected @ axon terminal (i.e. @ the end of the cable)

↳ Reason: refractory period, (as in (f))

(h) AP does not usually propagate in dendrites. Because $g_{Na}(V)$ is missing

However: in a few cell types $g_{Na}(V)$ is present also in dendrites

⇒ not sufficient to trigger AP, but can propagate AP from soma into dendrite to some extent: axonal backpropagation

(i) Number of pores in K^+ channel: verified much later with structural studies