How conductance(s) affect the response of a neuron

Rodrigo FO Pena

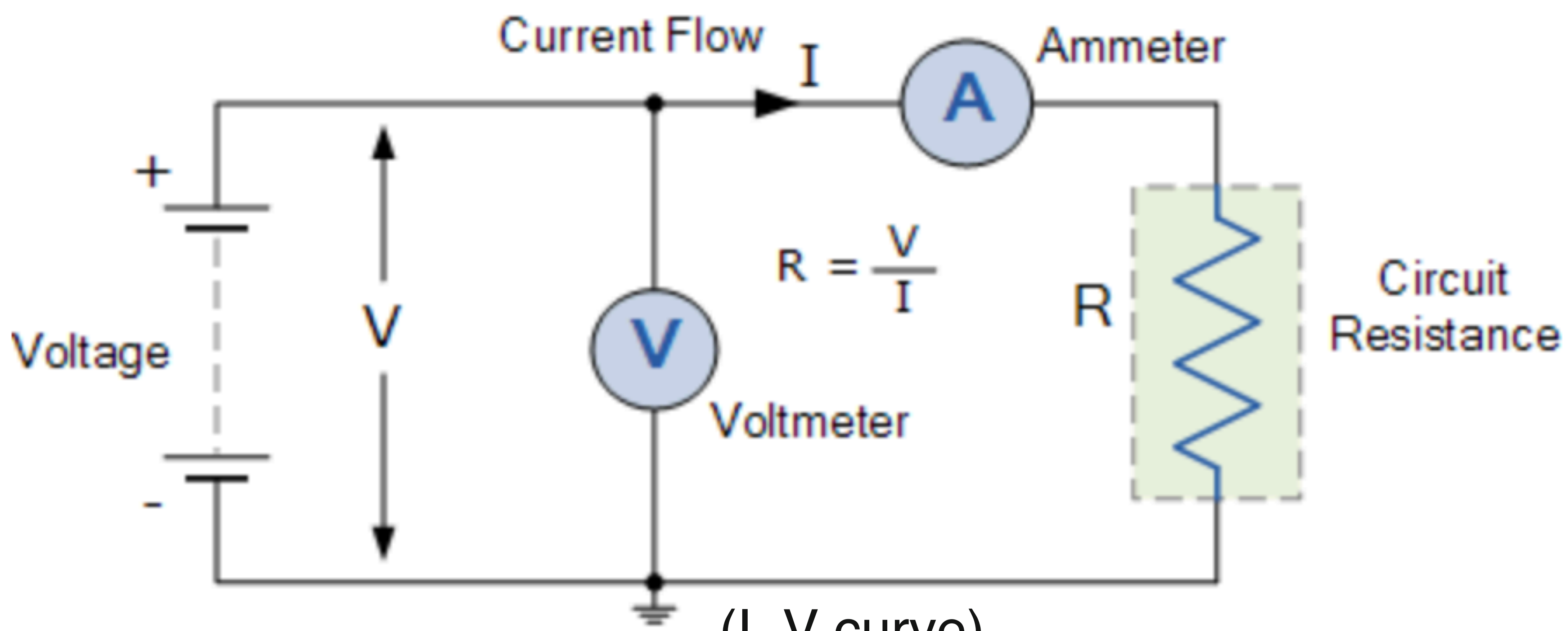
Lab SisNe Members

NeuroMat SimLab

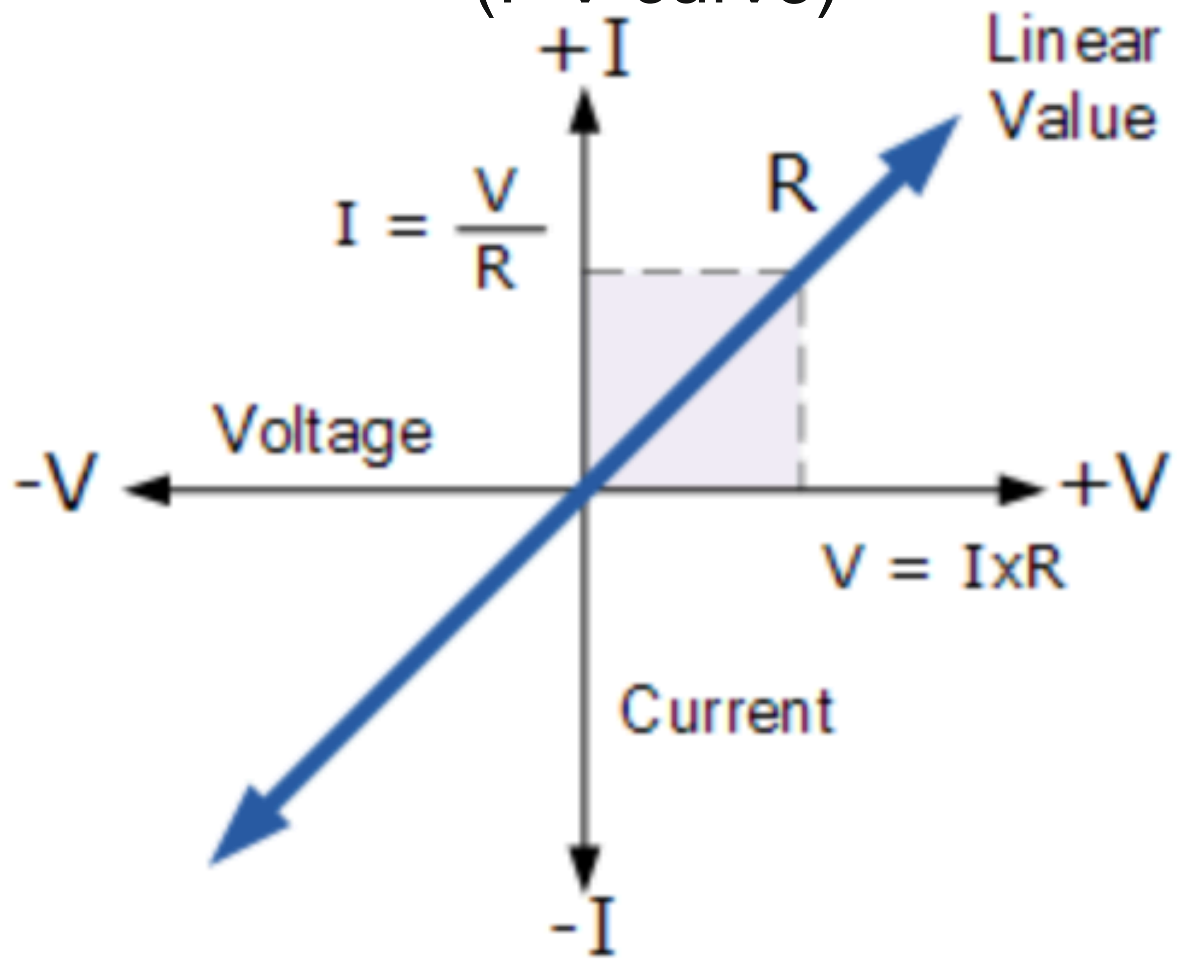
Outline

- Definitions;
- Negative slope conductance;
- Zero slope conductance;
- Resonance and derivative conductance;

Ohm’s law and IV relationships



(I–V curve)



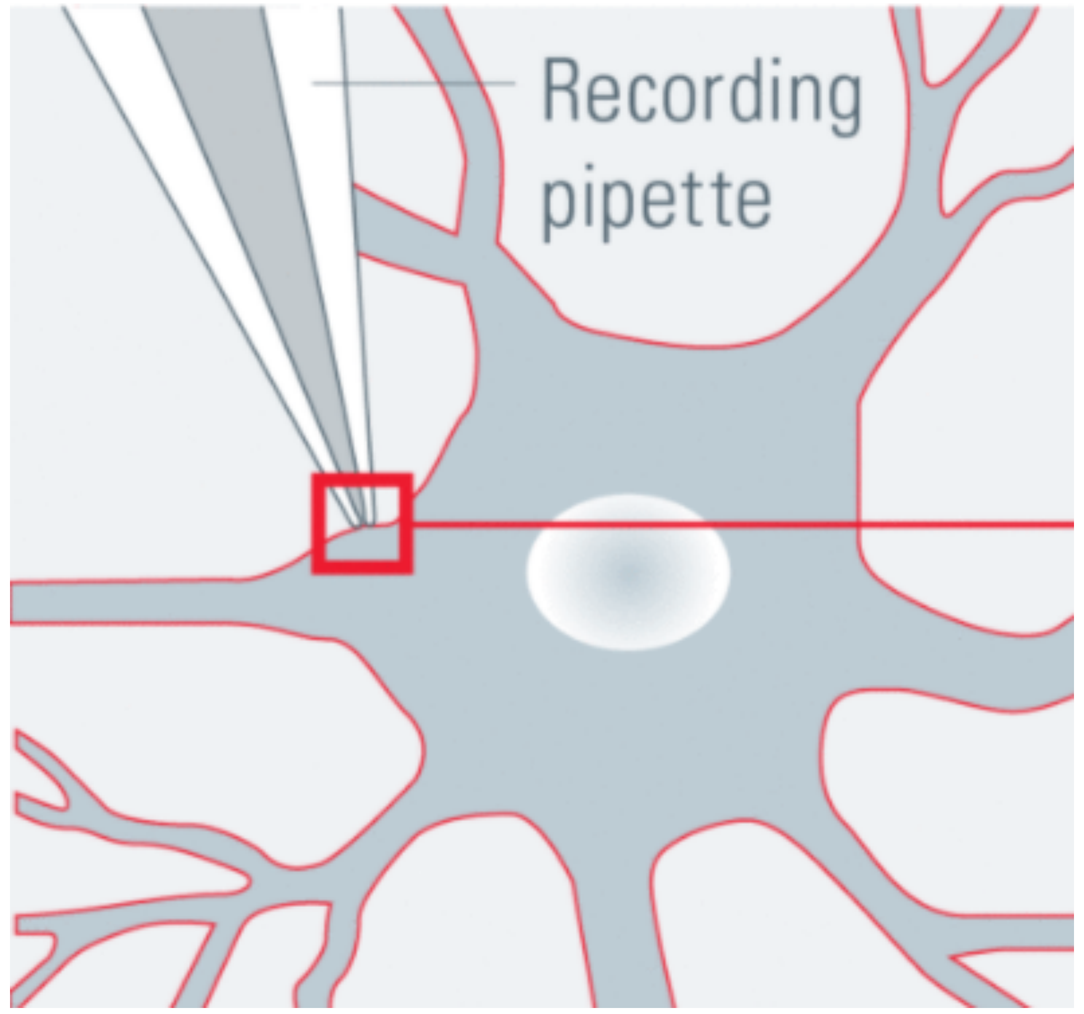
- Ohmic leak currents have a linear I-V relationship
- They produce a positive slope conductance

Conductance

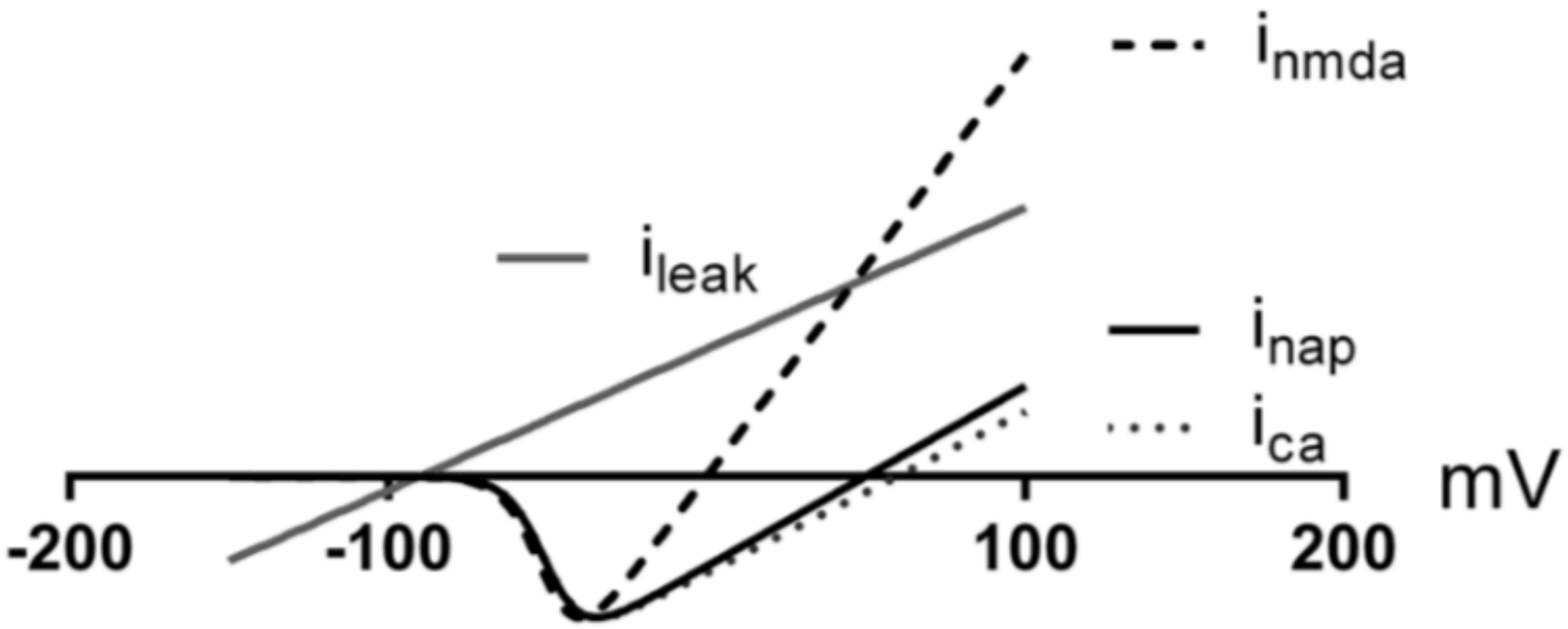
$$G = \frac{I}{V}$$

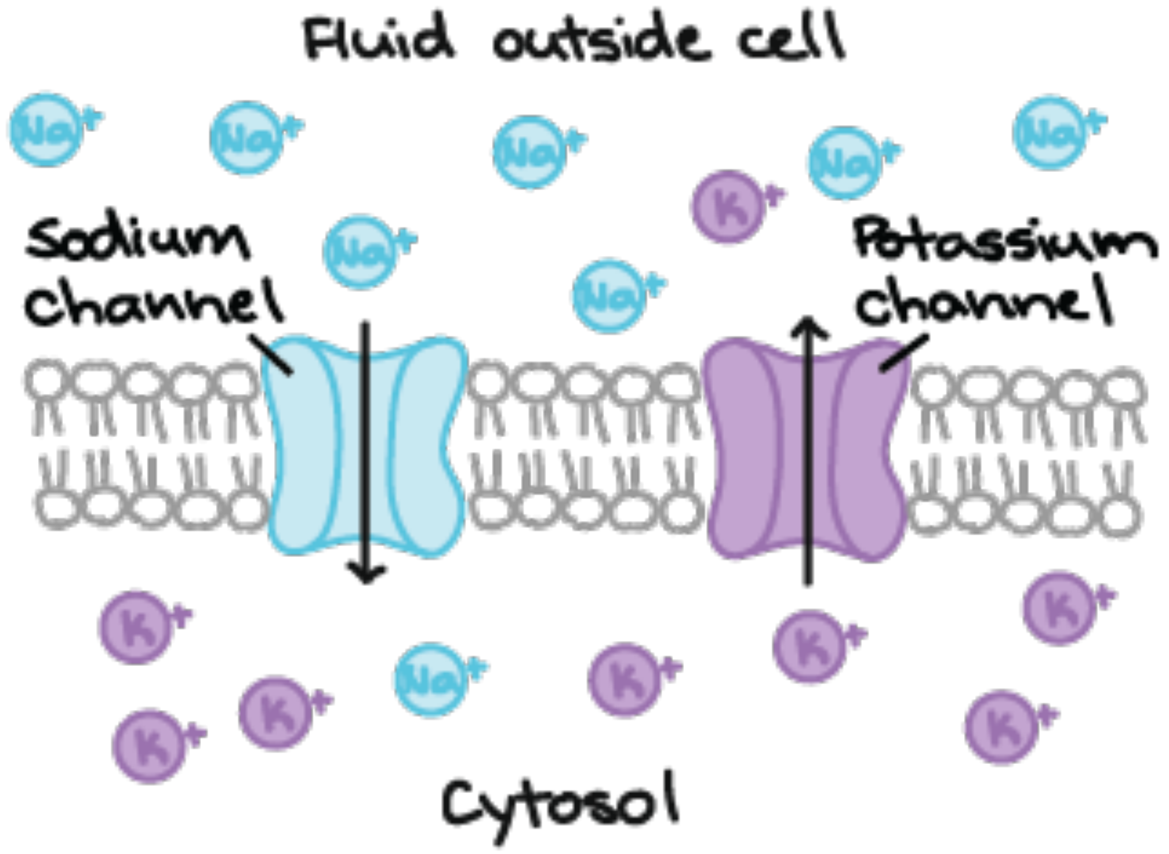
ionic currents follow ohm's law?

However, voltage-gated channels present **nonlinear** I–V relationships



Patch-clamp





Ceballos et al., Biophys Rev (2017) 9:827–834

Some definitions

- Membrane conductance (slope conductance)

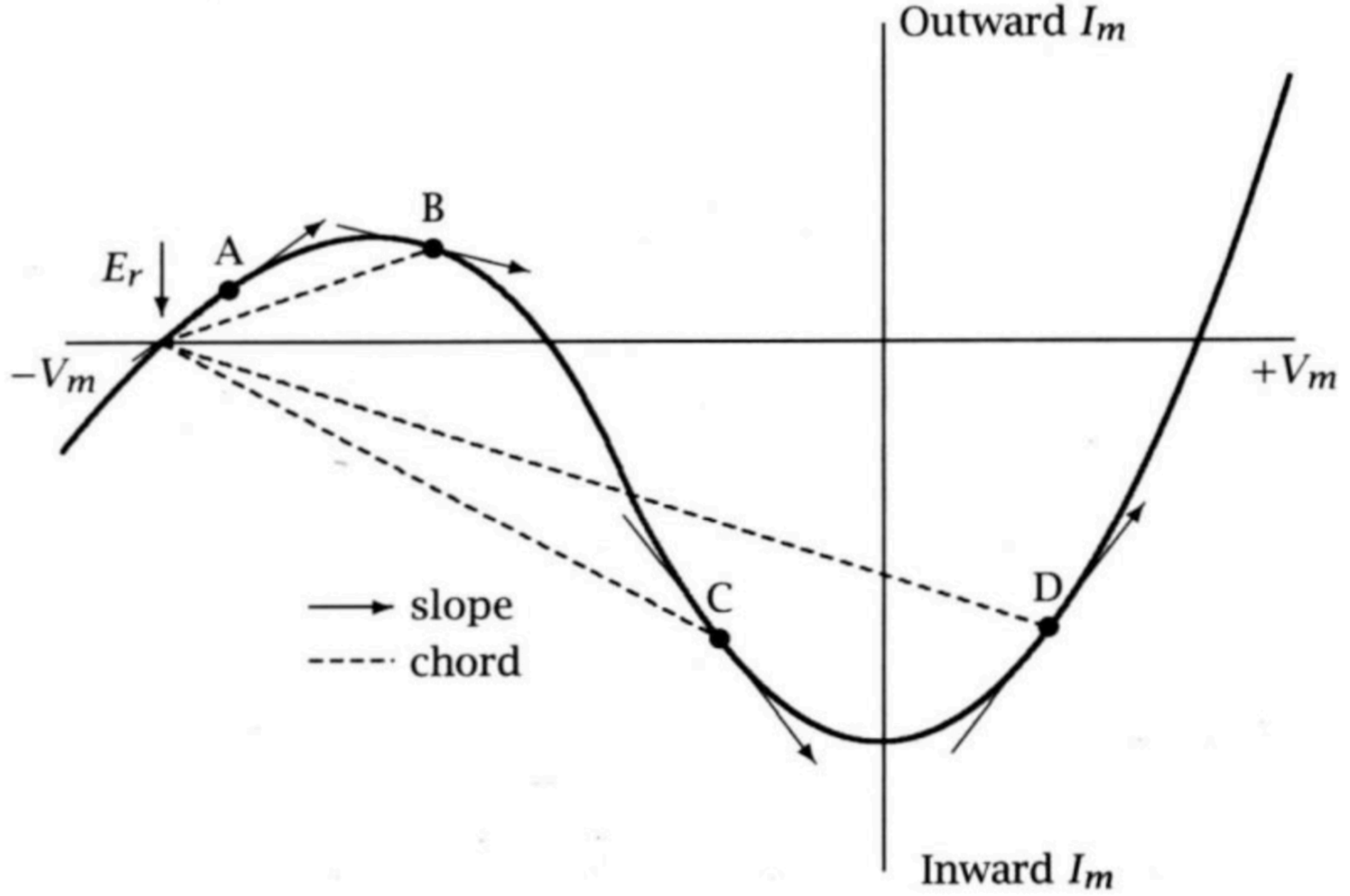
$$G_m = \frac{dI}{dV}$$

infinitesimal or **differential** definition of conductance in the steady state

- Chord conductance

$$g^{chord} = \frac{I(V_m) - I(E_{rev})}{V_m - E_{rev}}$$

ratio of the total **current** flowing at any *V*m relative to the **resting potential**



Szabolcs Káli, presentation at Peter Pazmany Catholic University 10/27/2010

- At linear case (**only**) both slope and chord conductance are equal to g_m at any potential

$$I_m = g_m(V_m - E_r)$$

- Membrane resistance (slope resistance; input resistance)

→ Inverse of the membrane conductance

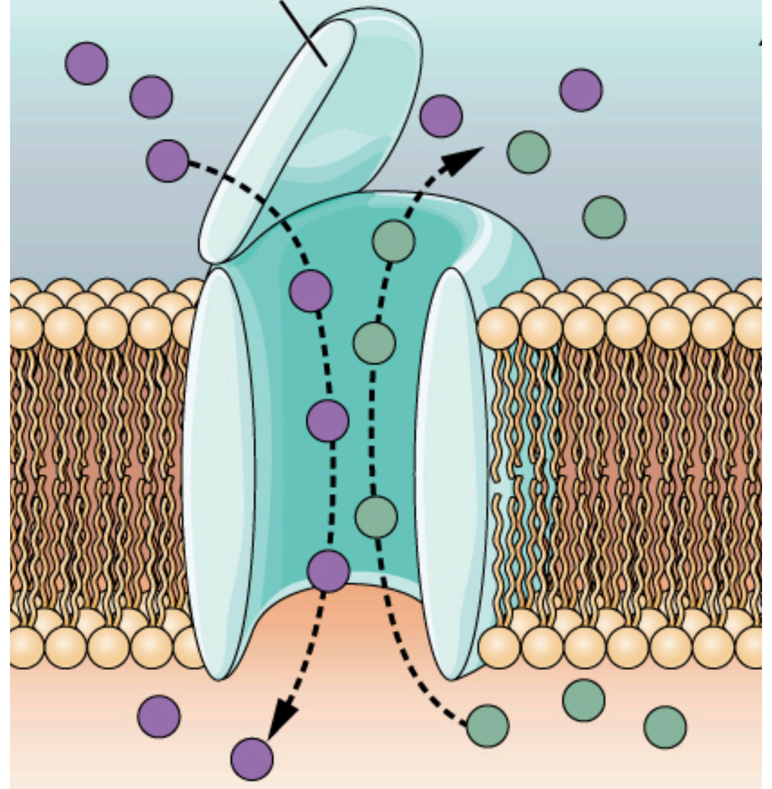
(or R_{in})

$$R_m = \frac{1}{G_m}$$

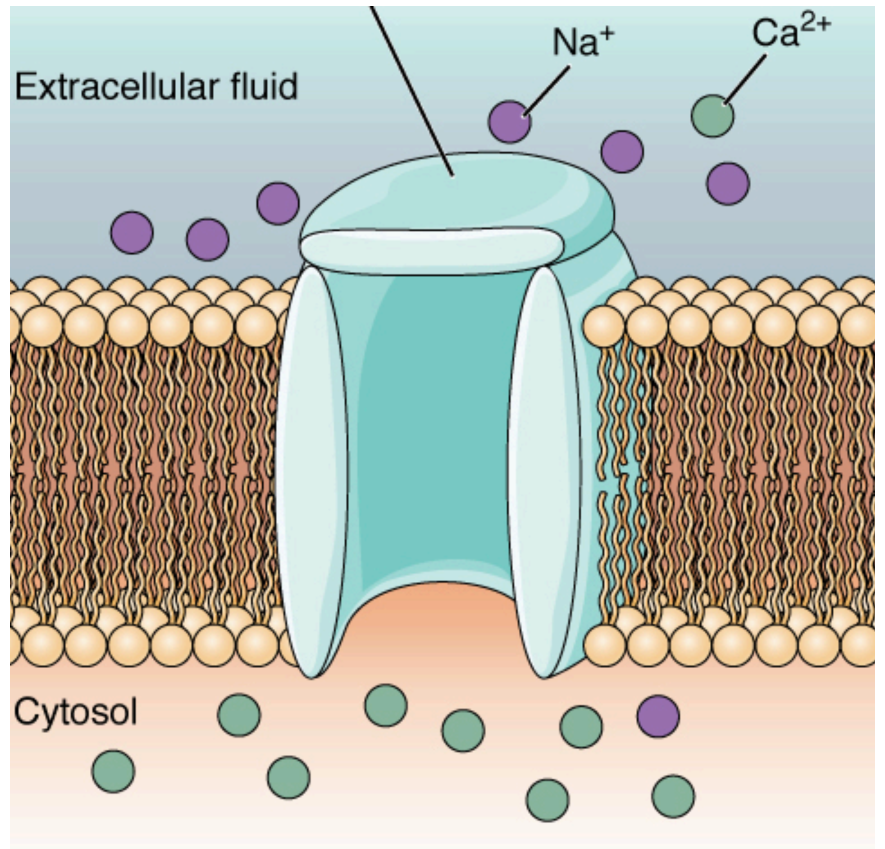
input resistance

extent to which membrane **channels are open**

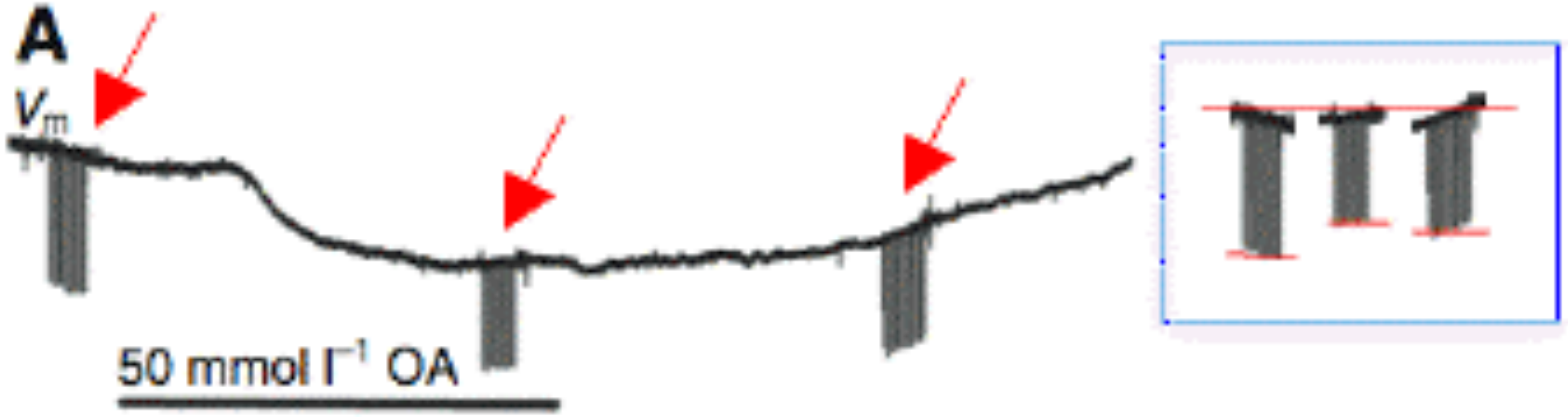
- **low** resistance (high conductance) implies **open channels**
  - charge leaks out across membrane



- **high** resistance implies **closed channels**
  - few charge leaks out across membrane



Steven Telleen



octopamine (OA)

open channels

lower input resistance

Tschuluun, N, WM Hall, and B Mulloney (2009).

[*J. Exp. Biol.* 212: 3605-3611.]()

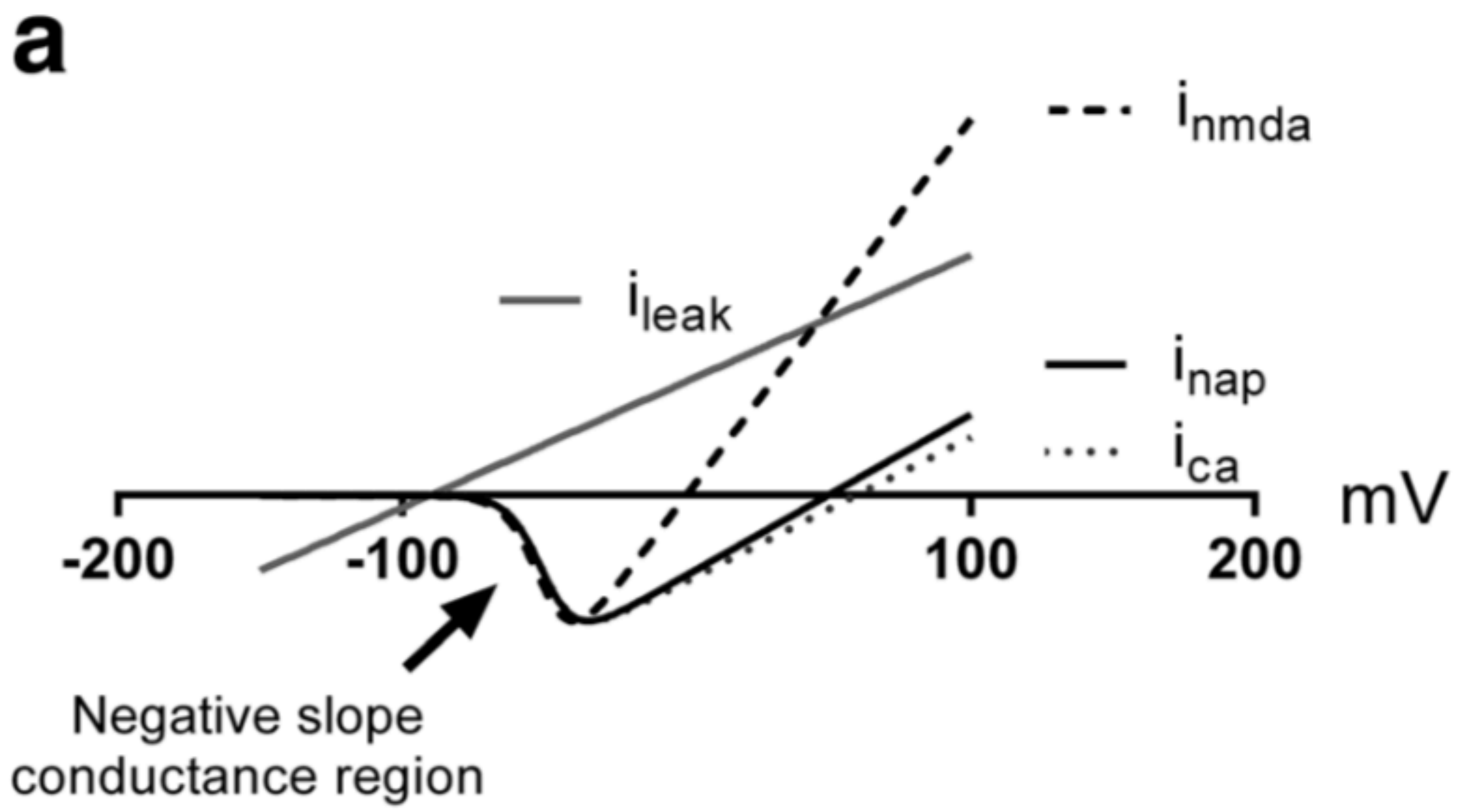
- Time constant

For a single ***RC*** **compartment** or an **infinite, homogeneous cable**

$$\tau_m = R_m C = \frac{C}{G_m}$$

- **opening** of the channels **increases** ionic **permeability**
- which **decreases membrane resistance** R_m.
- and so does the **time constant** τ_m.

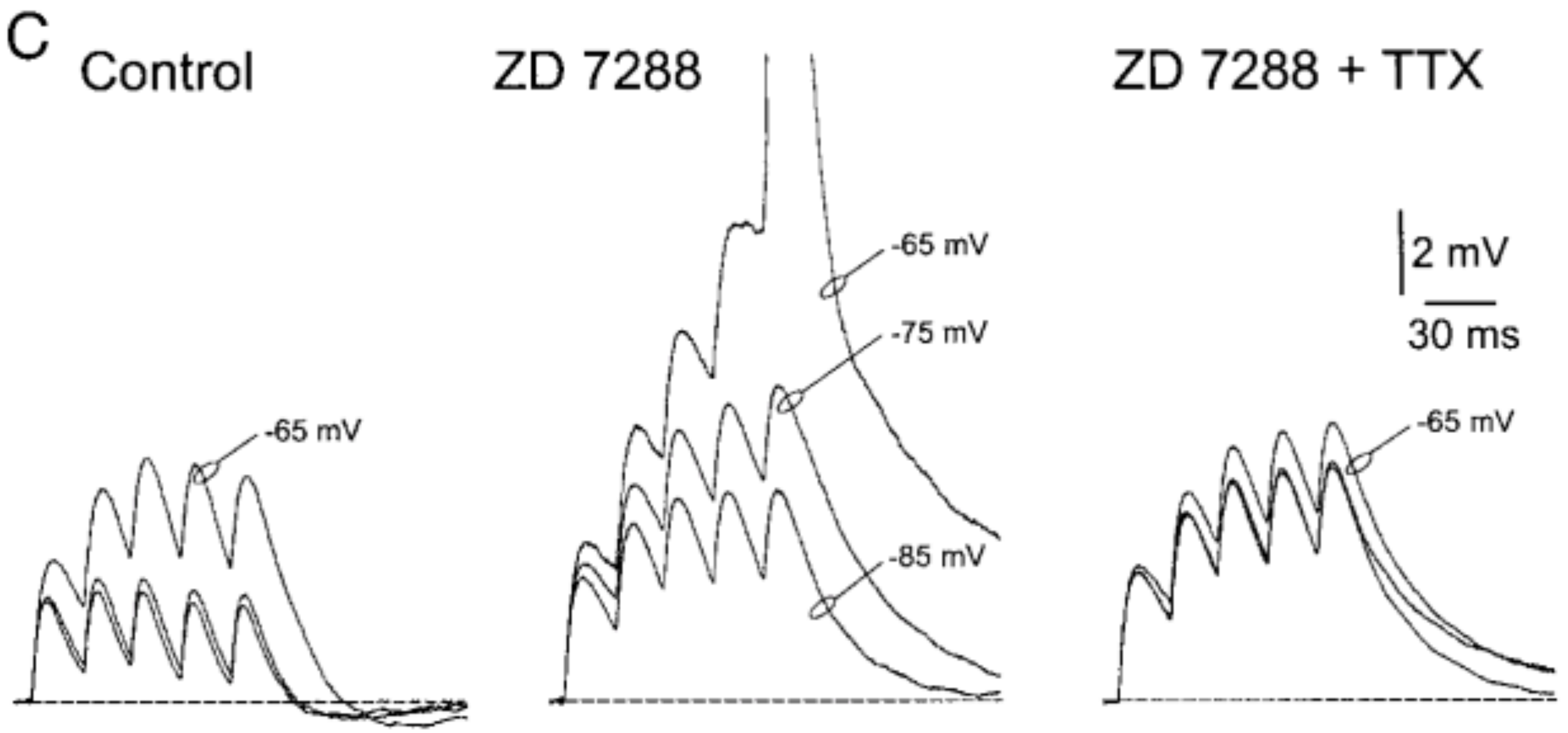
An example: Persistent sodium (I_{NaP})



- I_{NaP} **increases** R_{in} and τ_m in its **negative slope** conductance region (known);
- **relationship** of the negative conductance with these effects **has not been determined**;
- **amplitude** and **duration** of excitatory post synaptic potentials (EPSPs) are **voltage dependent**.

Ceballos et al., Biophys Rev (2017) 9:827–834

An example: Persistent sodium (I_{NaP})



Williams et al., J. Neurophysiol. (2020) *83*(5), 3177-3182.

- EPSPs arriving closer to threshold are amplified;
- **I_h** has the opposite effect: **shortens** the duration of EPSPs;
- why opposite effects on EPSP-time-course prolongation?

Investigation

Model:

$$I = \bar{g}_{\mathrm{NaP}} A^{\infty}_{\mathrm{NaP}}(V)(V - E_{\mathrm{Na}}) + \bar{g}_L(V - E_L)$$

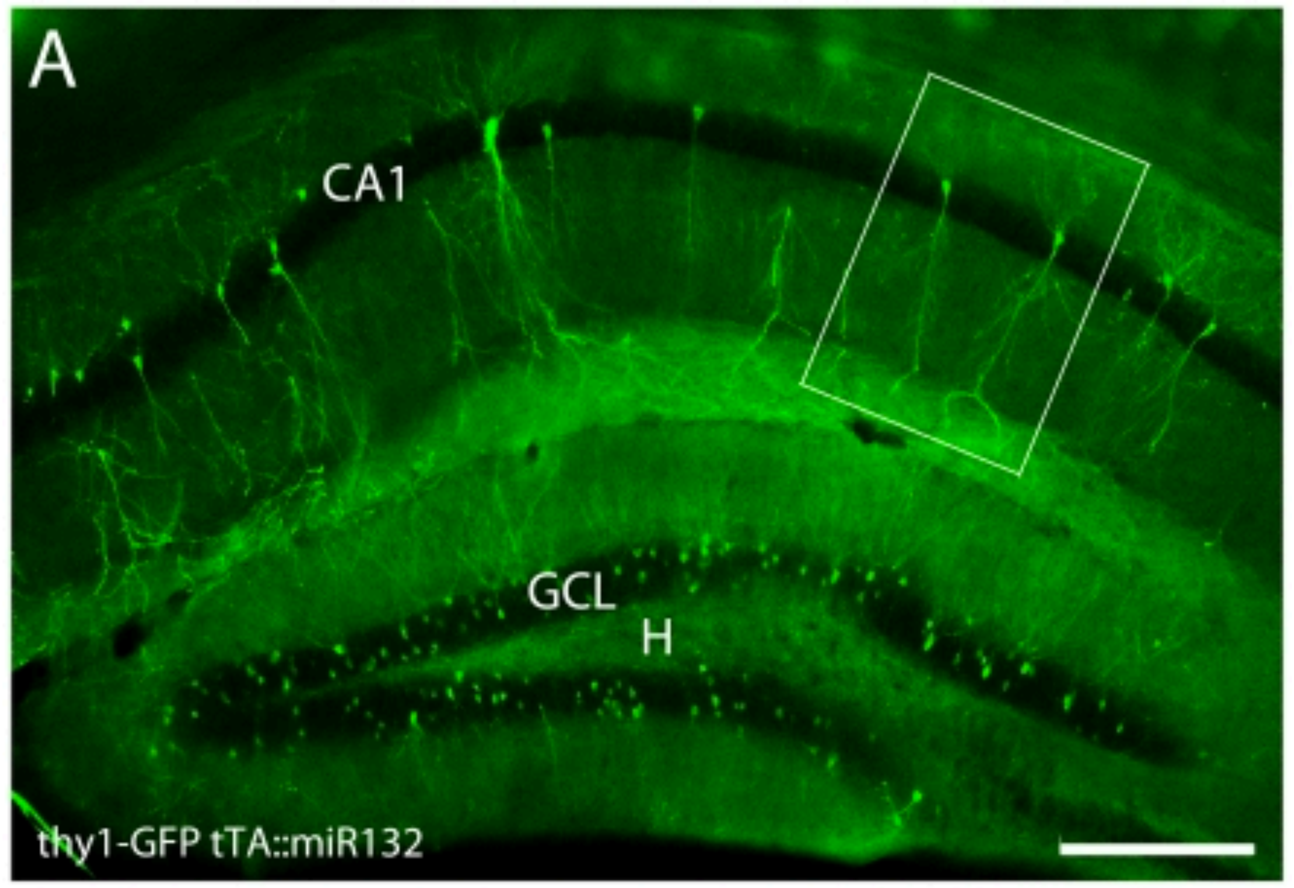
Experiment:

Hippocampal slices and electrophysiology

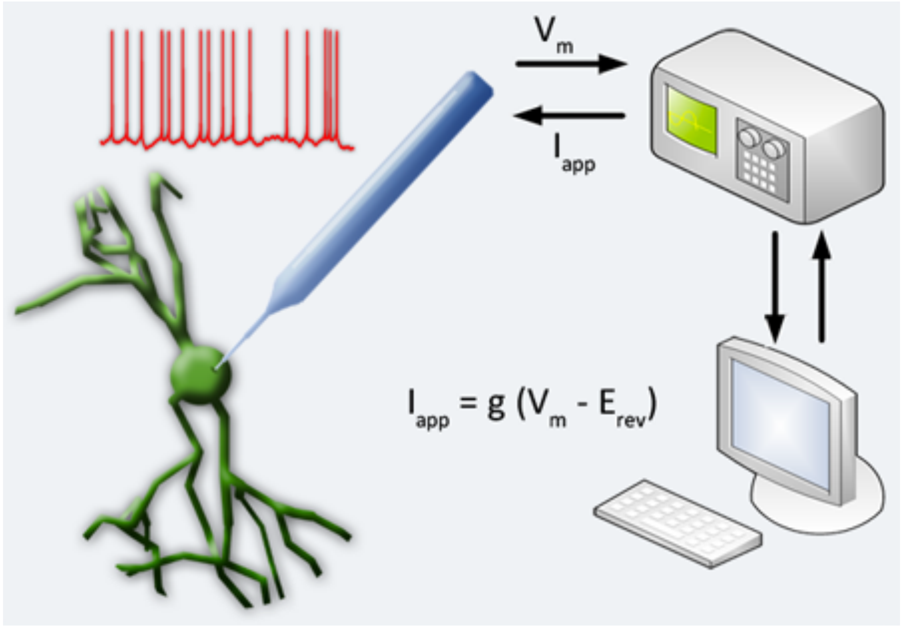
CA1 Pyramidal cells

Dynamic-clamp

Artificial *I*NaP injected in neurons bathed in TTX.



Hansen et al. (2010)



rtxi.org/

Opening the Persistent sodium (I_{NaP})

$$G_{\mathrm{NaP}}(V_{ss}) = \frac{dI_{\mathrm{NaP}}}{dV_{ss}} \quad = \bar{g}_{\mathrm{NaP}} A_{\mathrm{NaP}}^{\infty} + \bar{g}_{\mathrm{NaP}}(V - E_{\mathrm{Na}}) \frac{dA_{\mathrm{NaP}}^{\infty}}{dV_{ss}}$$

$$G_{\mathrm{NaP}} \quad = g_{\mathrm{NaP}} + G_{\mathrm{NaP}}^{\mathrm{Der}}$$

Slope = chord + derivative

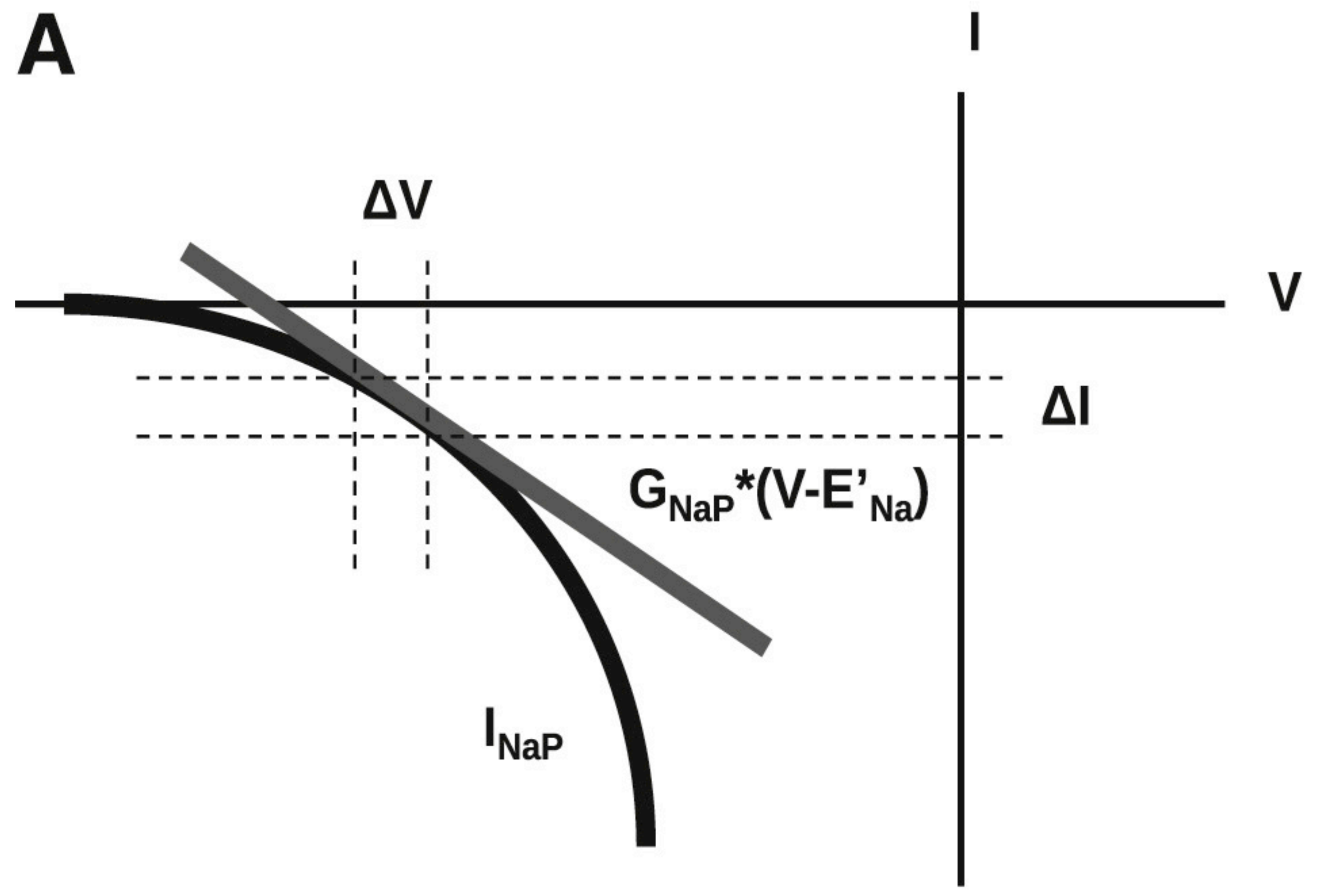
→ I_{NaP} is fast

$\tau_{\mathrm{NaP}} << \tau_{\mathrm{m}}$

steady-state slope conductance (G_{NaP}) **equals** its **instantaneous** slope conductance

It is possible to rewrite *I* as a linear current with a slope conductance equal to G_{NaP}

$$I_{\mathrm{NaP}} = G_{\mathrm{NaP}}(V - E_{\mathrm{Na}})$$



Ceballos et al., Biophys J (2017) 113:2207-17

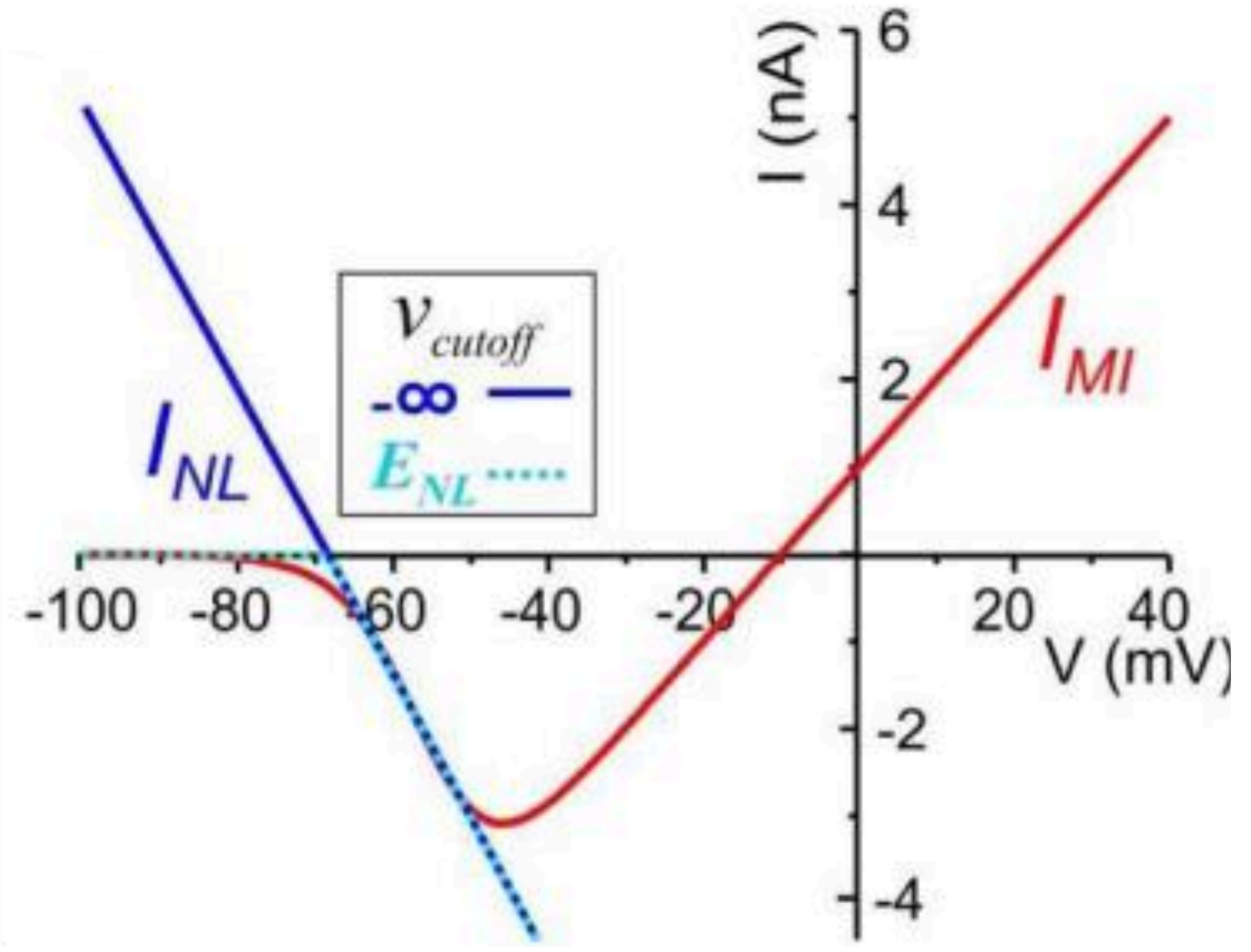
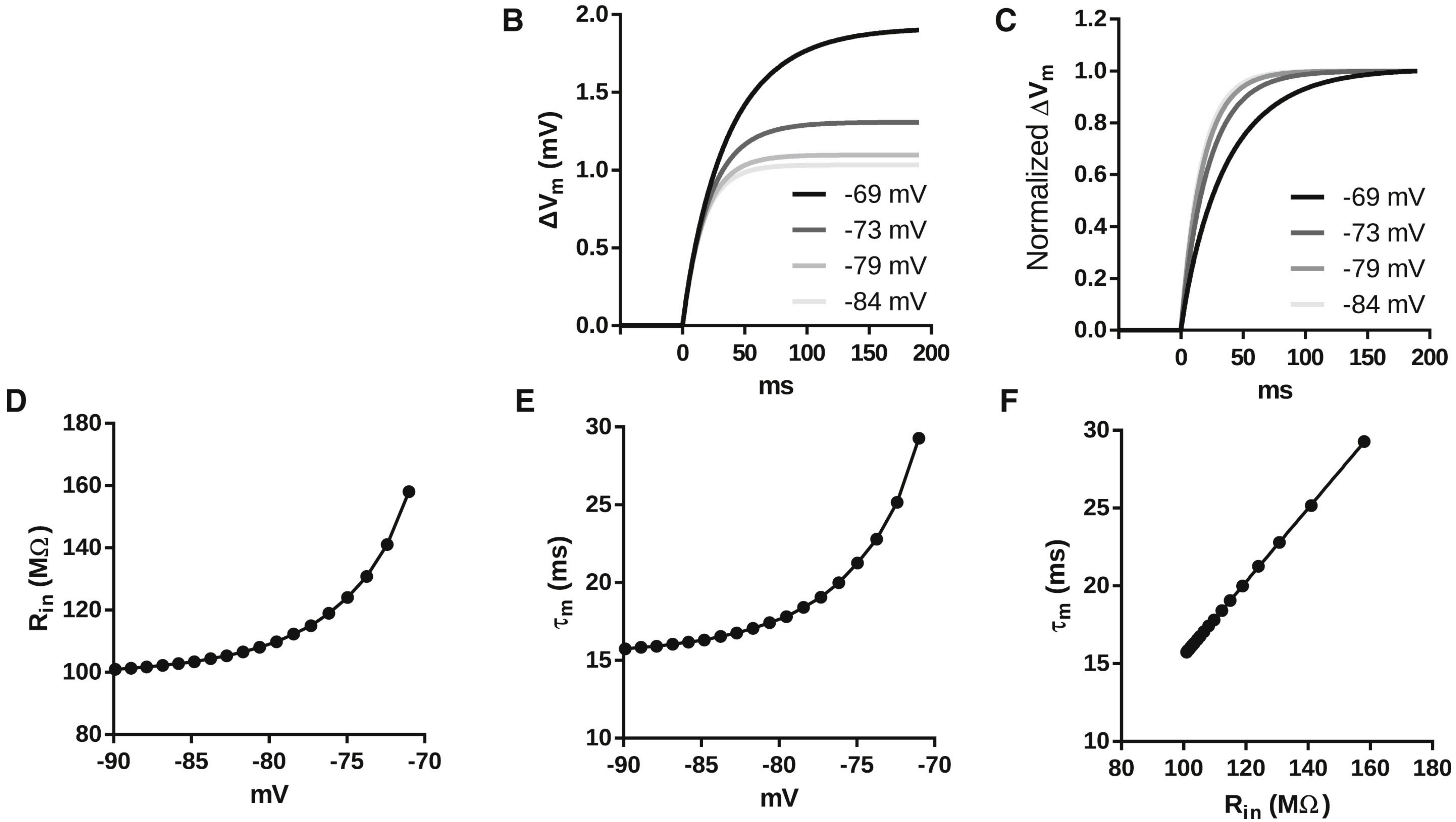


Fig 2 from Bose, A., Golowasch, J., Guan, Y., & Nadim, F. (2014). *J Comput Neurosci*, *37*(2), 229–242.

→ The negative slope conductance of I_{NaP} predicts an increase in τ_{m} by increasing R_{in}

response to a current of 10 pA



Ceballos et al., Biophys J (2017) 113:2207-17

just as for a purely passive membrane where $\tau_{\mathrm{m}} = C_{\mathrm{m}}R_{\mathrm{in}}$

$$G_T = G_{\mathrm{NaP}} + \bar{g}_L$$

If negative, G_T decreases and Rin increases

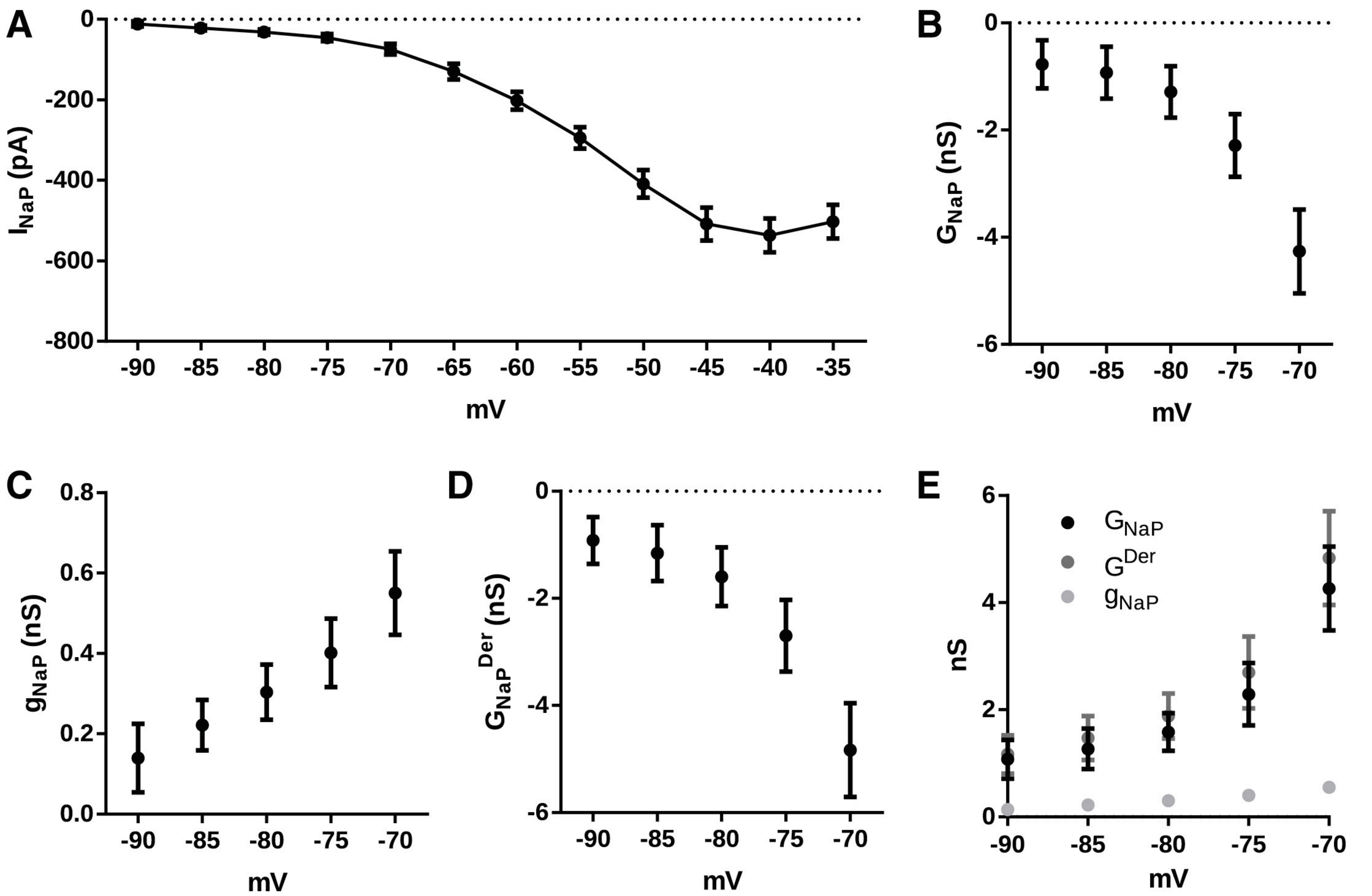
→ G_{NaP} is composed mainly by its derivative conductance

$$G_{\mathrm{NaP}} = g_{\mathrm{NaP}} + G_{\mathrm{NaP}}^{\mathrm{Der}}$$

Slope = chord + derivative

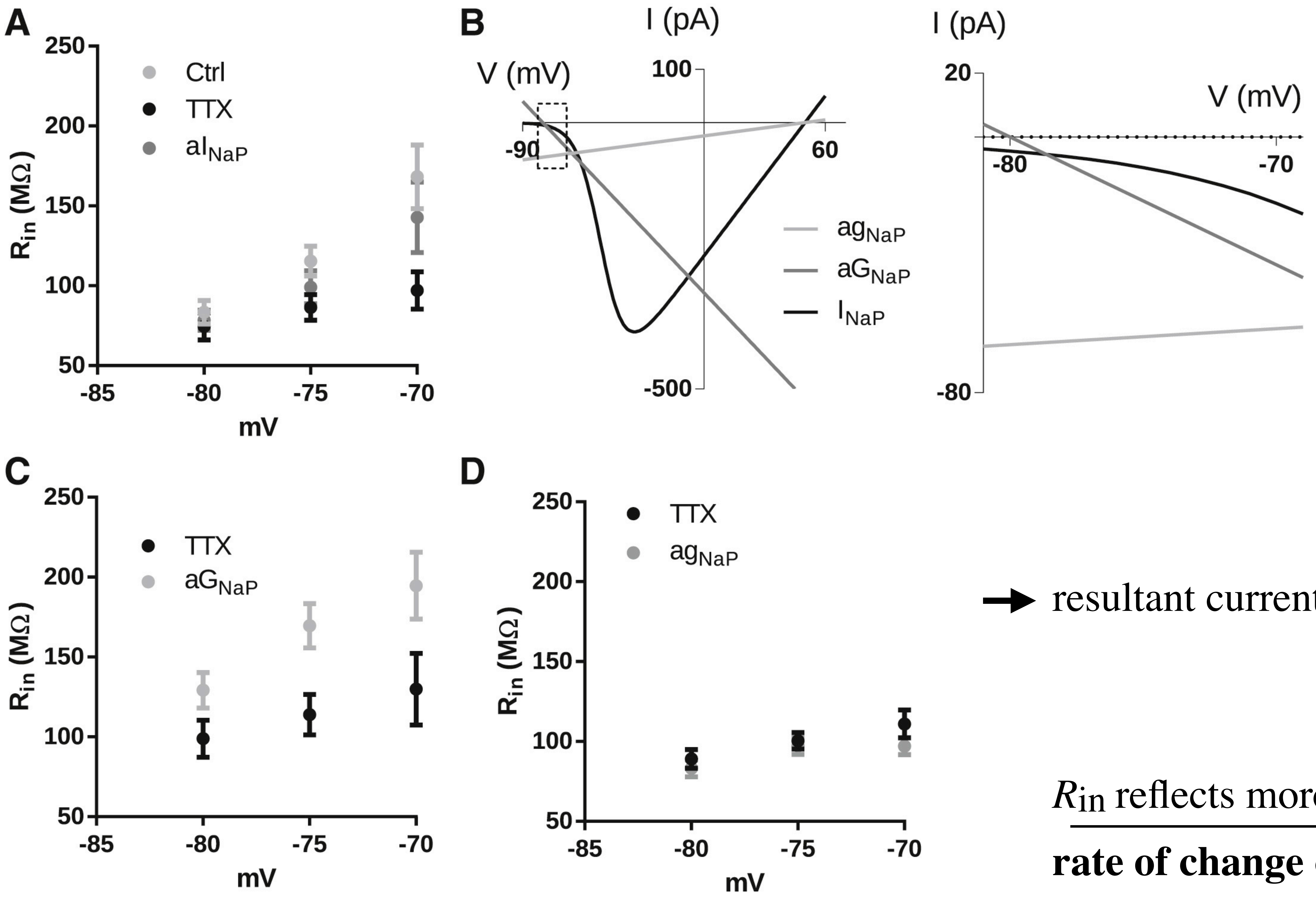
If **slope** conductance is **negative:**

- **derivative** conductance must be **negative**
- and **bigger** than the chord conductance (positive)



Ceballos et al., Biophys J (2017) 113:2207-17

→ The negative slope conductance of I_{NaP} is sufficient to increase R_{in} (dynamic clamp)



Ceballos et al., Biophys J (2017) 113:2207-17

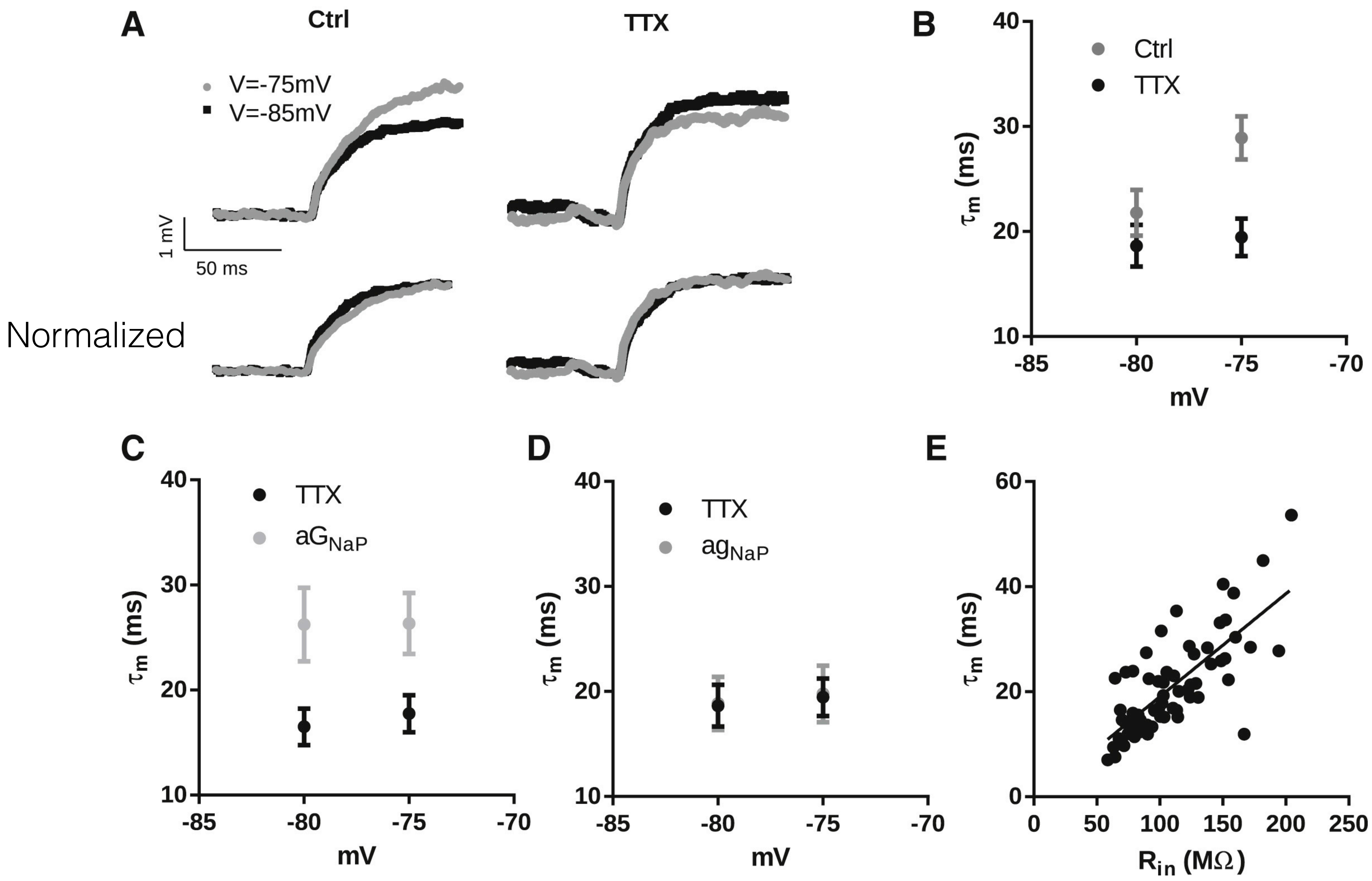
ag$_{NaP}$ = artificial positive
aG_{NaP} = artificial negative

→ resultant current of **ag$_{NaP}$ is bigger** than the resultant current of **aG$_{NaP}$**

R_{in} reflects more

rate of change of the currents (**slope conductances**) than **absolute value** (**instantaneous currents**).

→ The membrane time constant is voltage dependent and is determined by the voltage dependence of R_{in}



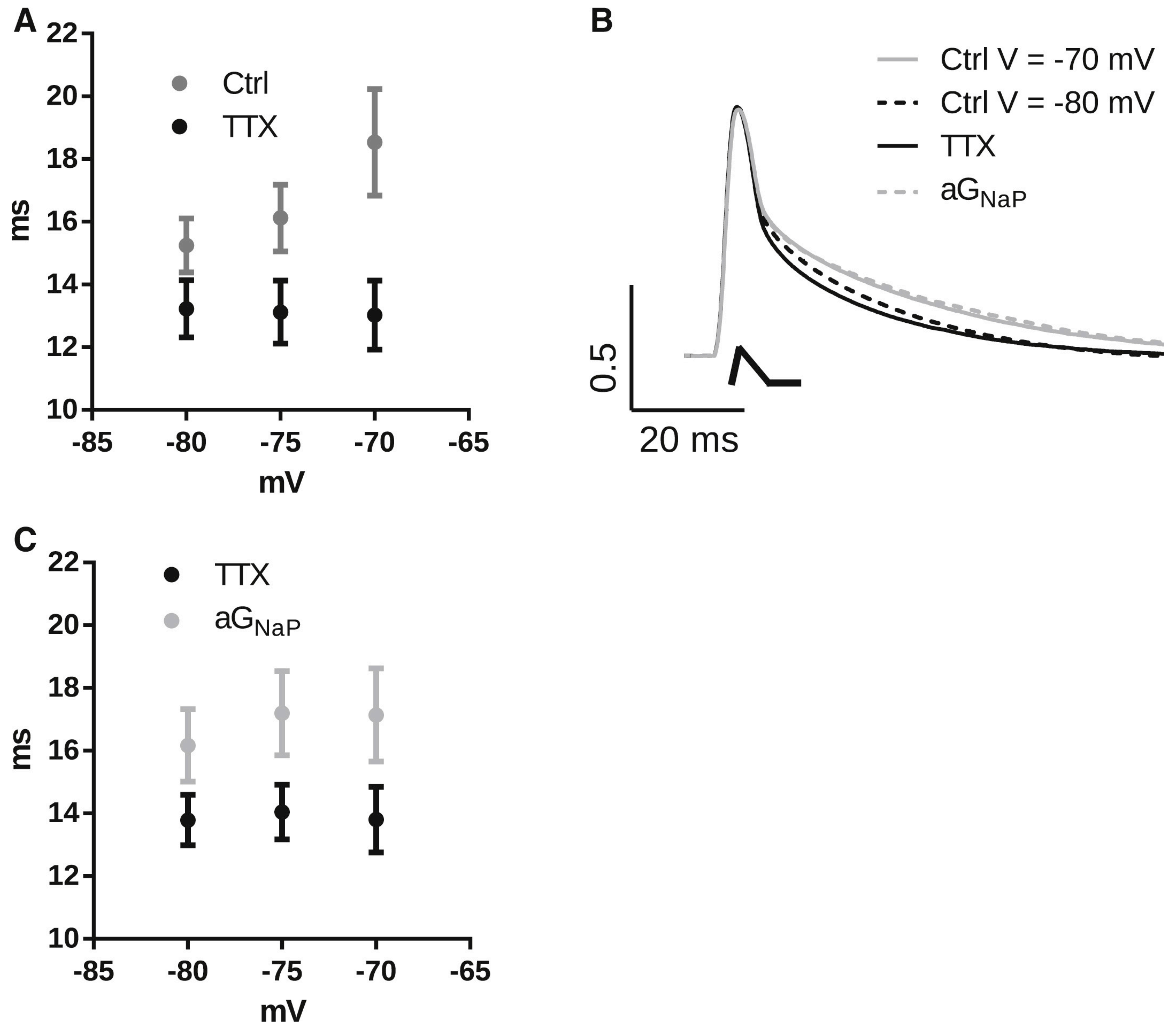
The relationship $\tau_m = CR_{in}$ holds in the presence of I_{NaP}.

Ceballos et al., Biophys J (2017) 113:2207-17

→ The negative slope conductance amplifies EPSPs

Area

Area



Inside the negative slope conductance region

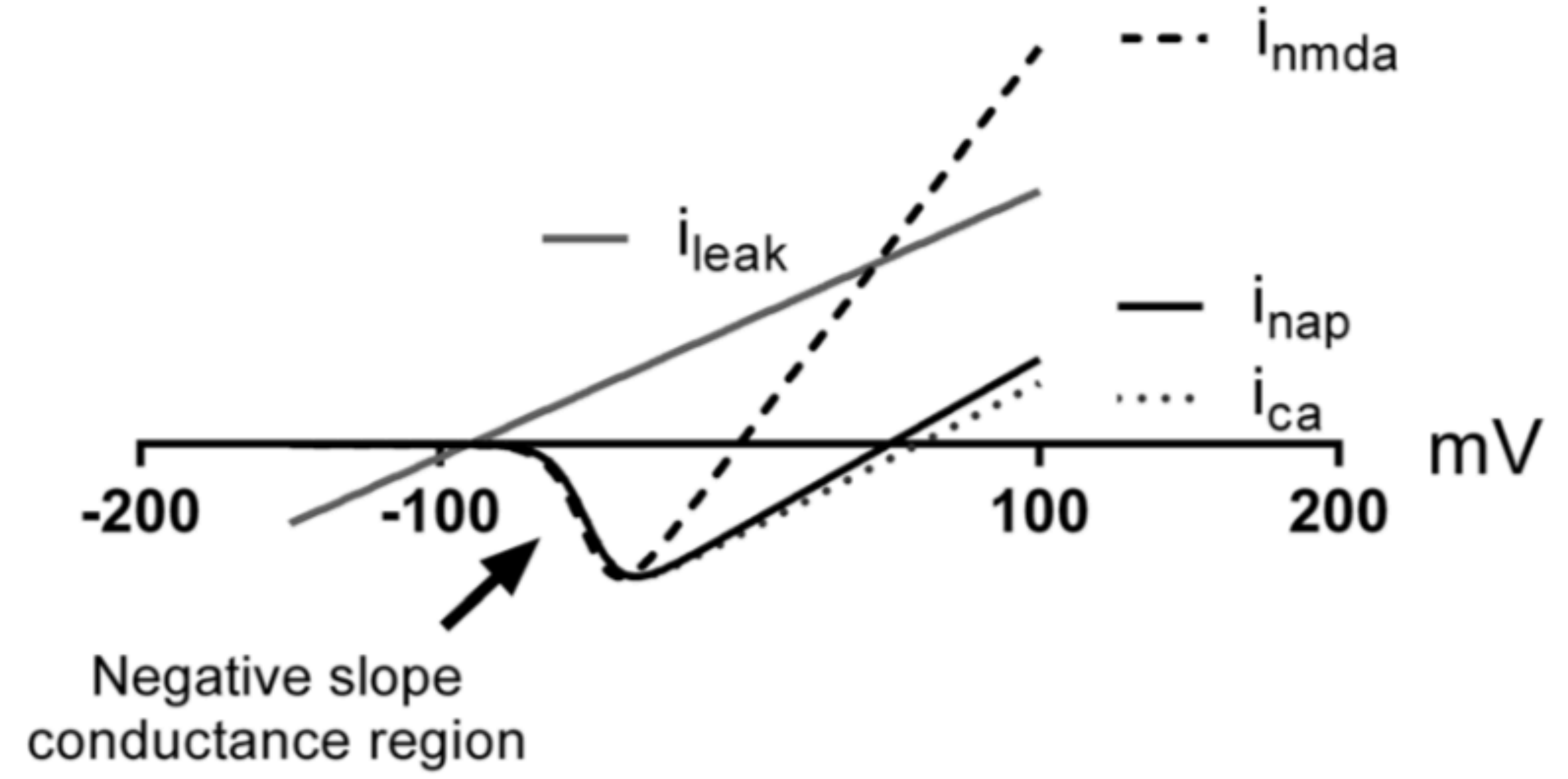
Ceballos et al., Biophys J (2017) 113:2207-17

Summary (so far)

- $\mathbf{I_{NaP}}$ **increases** the **amplitude** and prolongs the **decay time** of subthreshold EPSPs;
- **negative slope** conductance **increases** R_{in} and τ_{m};
- These results resolve an apparent paradox :
  - block of I_{NaP} (TTX) was observed to decrease R_{in} and shorten τ_{m}.
  - Contrary to the idea that closed channels imply high R_{in}

These concepts can be extended to **other ionic currents** that present negative slope conductance regions

- voltage- dependent Ca^{2+} channels,
- NMDA receptors,
- inward rectifier potassium currents.



See references for those within the review:

Biophys Rev (2017) 9:827–834
DOI 10.1007/s12551-017-0300-8

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REVIEW

The role of negative conductances in neuronal subthreshold properties and synaptic integration

Cesar C. Ceballos [1,2] · Antonio C. Roque [2] · Ricardo M. Leão [1]

Zero slope conductance

- When negative slope conductance **opposes** positive slope conductances of other currents

- Theoretical and experimental studies show that **zero slope** conductance **imply an infinite τ_m**

    - Non-decaying EPSPs.

$$G_m = \frac{dI}{dV}$$

$$\tau_m = R_m C = \frac{C}{G_m}$$

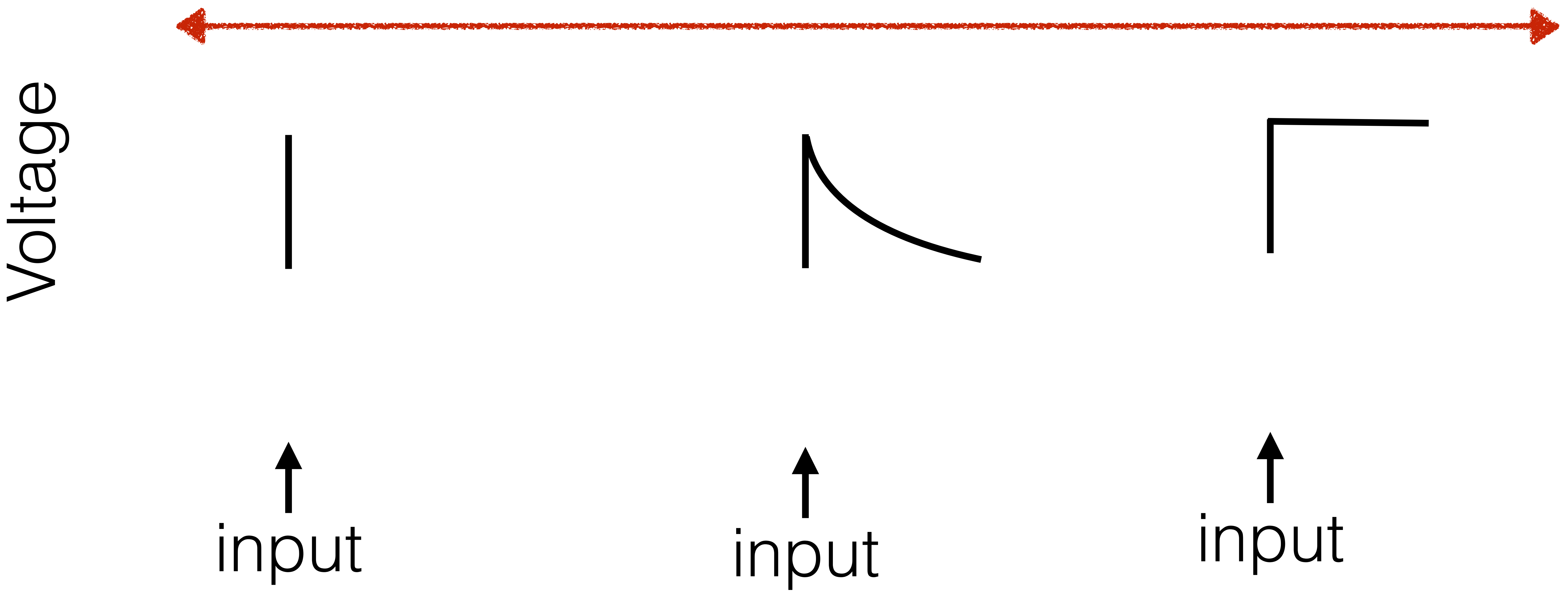
Coincident detectors vs. **Integrators**

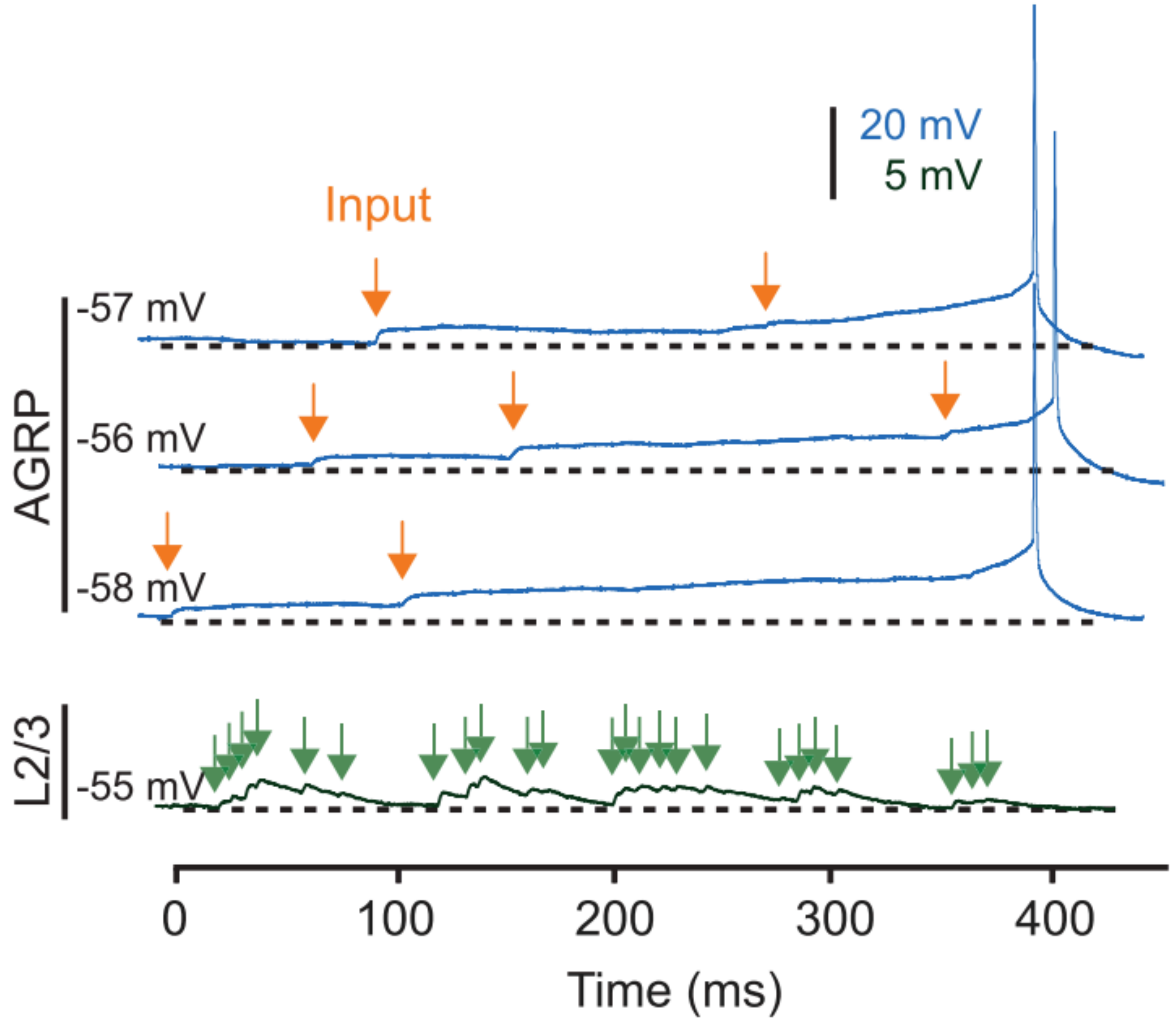
$\tau_m \to 0$ | τ_m | $\tau_m \to \infty$

coincident detectors

Perfect integrator

(e.g. hypothalamic neurons)



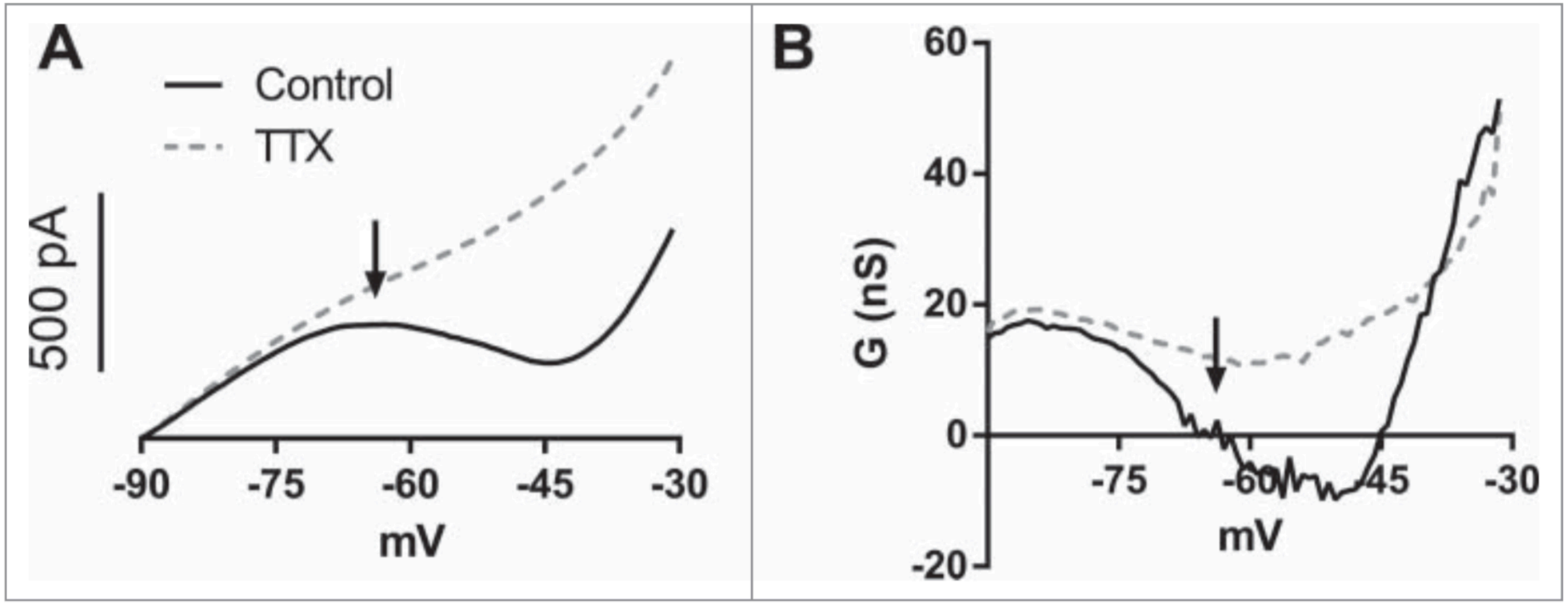


Branco, Tiago, et al. *Cell* 165.7 (2016): 1749-1761.

No report of **non-decaying subthreshold EPSPs in CA1** pyramidal neurons although a region of **zero slope** conductance

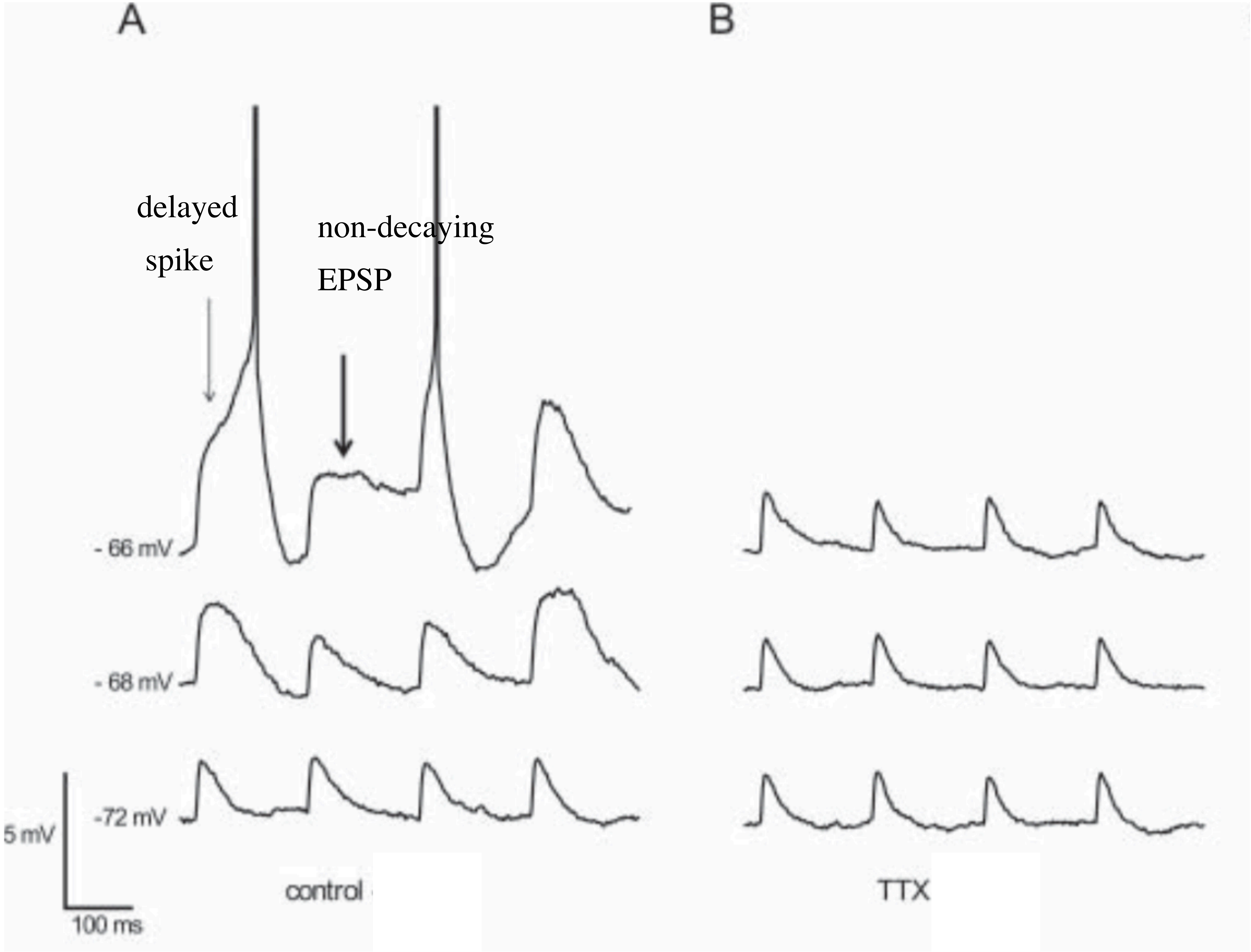
CA1 pyramidal cells have a suprathreshold zero slope conductance region

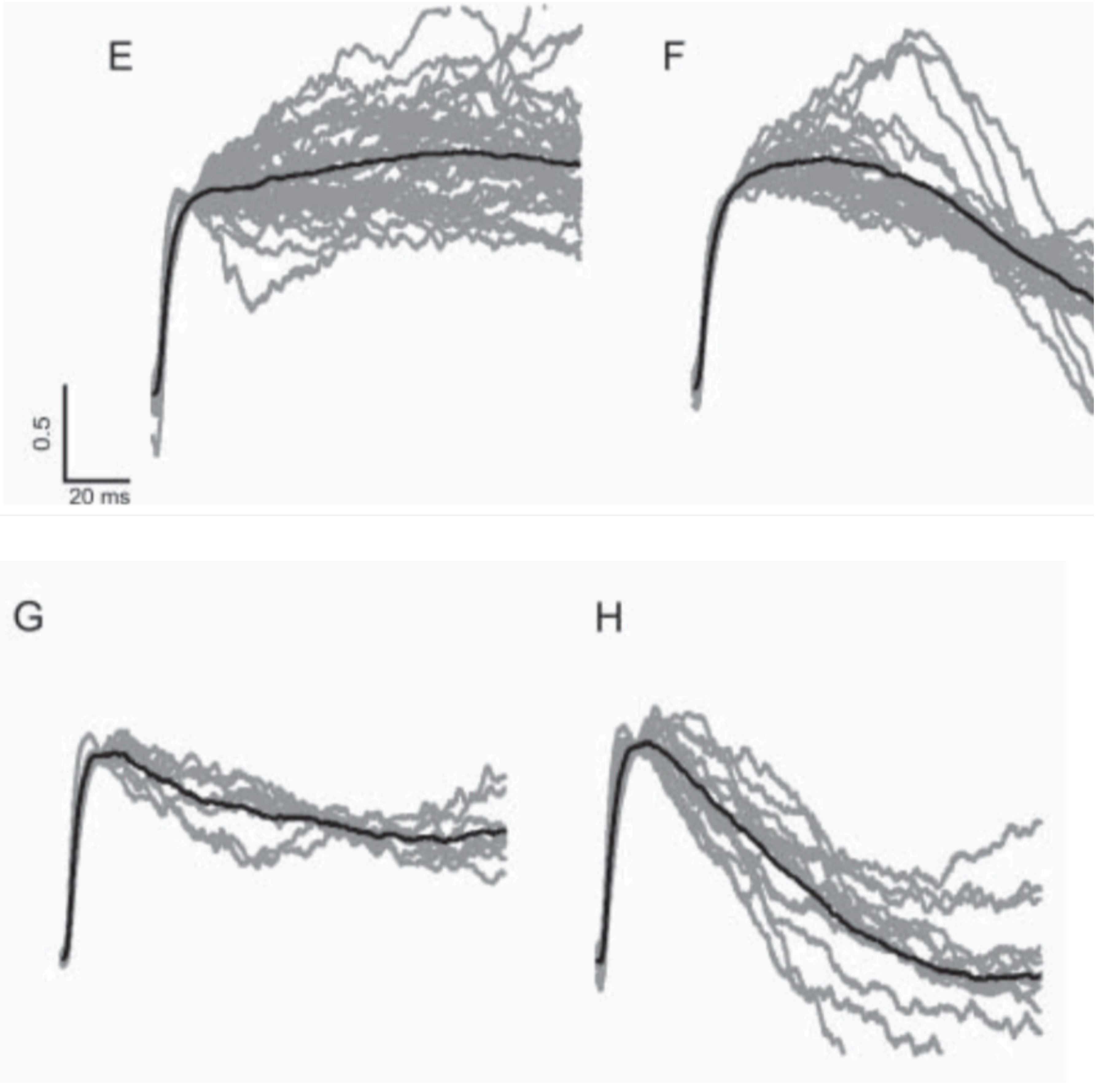
Mean slow ramps (15 mV/s)
recorded in voltage-clamp



Ceballos, Pena, Roque and Leão (2018), Channels, 12:1, 81-88

- After TTX: **only positive slope** conductance remains,
- **negative** and **zero** slope conductance regions are mainly generated by I_{NaP}.





Ceballos, Pena, Roque and Leão (2018), Channels, 12:1, 81-88

Summary (so far)

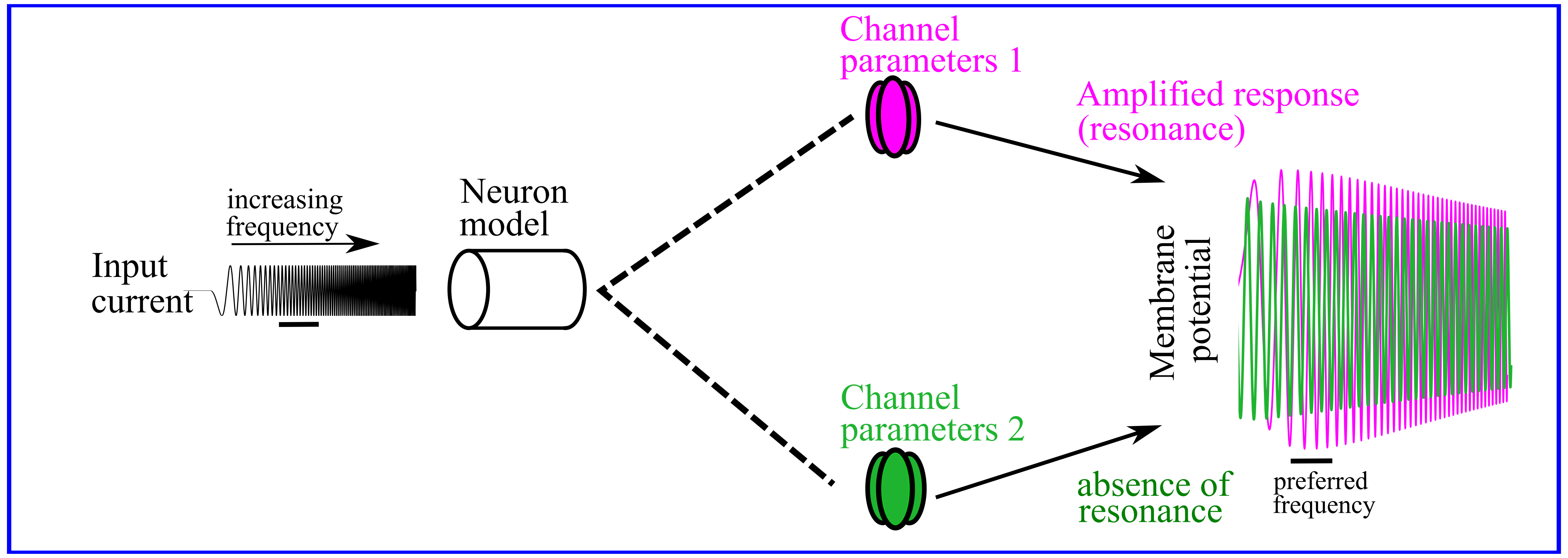
Zero slope conductance:

To our knowledge: **first study showing non-decaying EPSPs** in a neuron that is **not a perfect integrator;**

Non-decaying EPSPs and delayed spikes may exist in neurons with **zero slope conductance**.

Resonance and derivative conductance

- ***I*$_h$** is responsible for **resonance** in several neuron types;



- there is **no resonance** for membrane potentials too **depolarized** or too **hyperpolarized** or for very fast currents;
- Currents are voltage-dependent;

We found out that

- **Derivative conductance** together with **time constant** changes the **frequency-dependent response** of a neuron to the
- Resonance frequency only exists if G^{Der} exists.

Model of CA1 pyramidal cells of the hippocampus

$$C\frac{dV}{dt} = -I_h - I_L + I(t),$$

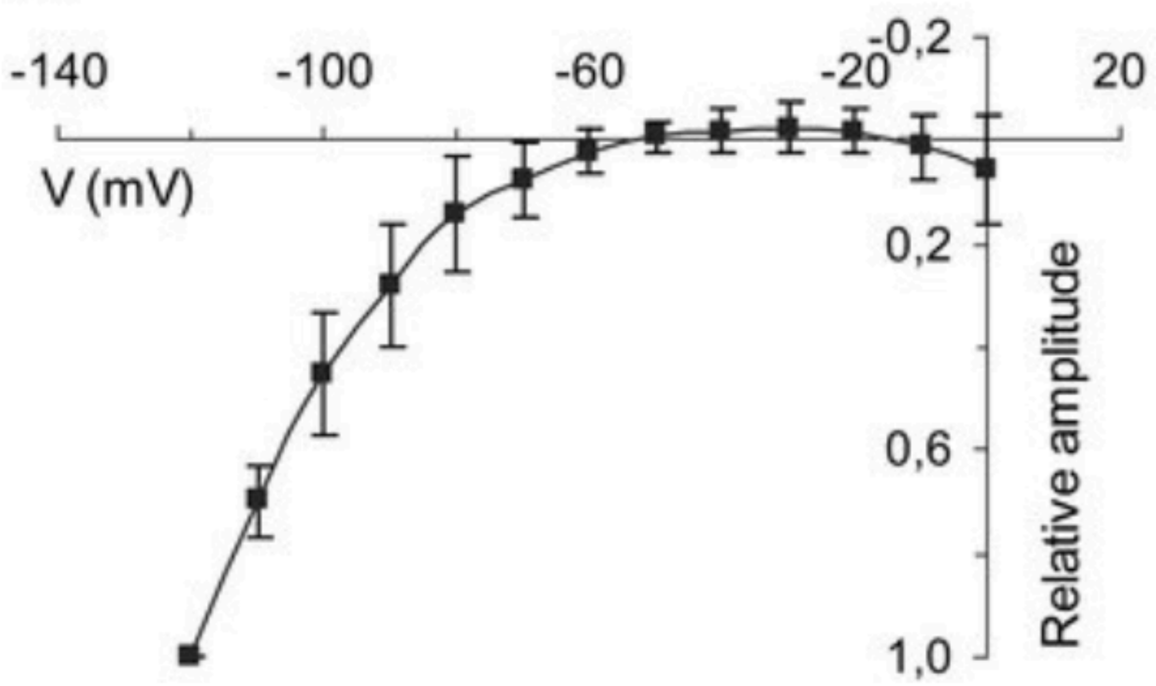
$$I_h = \bar{g}_h A_h(V,t)(V - E_h),$$

$$\frac{dA_h(V,t)}{dt} = \frac{A_h^\infty(V) - A_h(V,t)}{\tau_h},$$

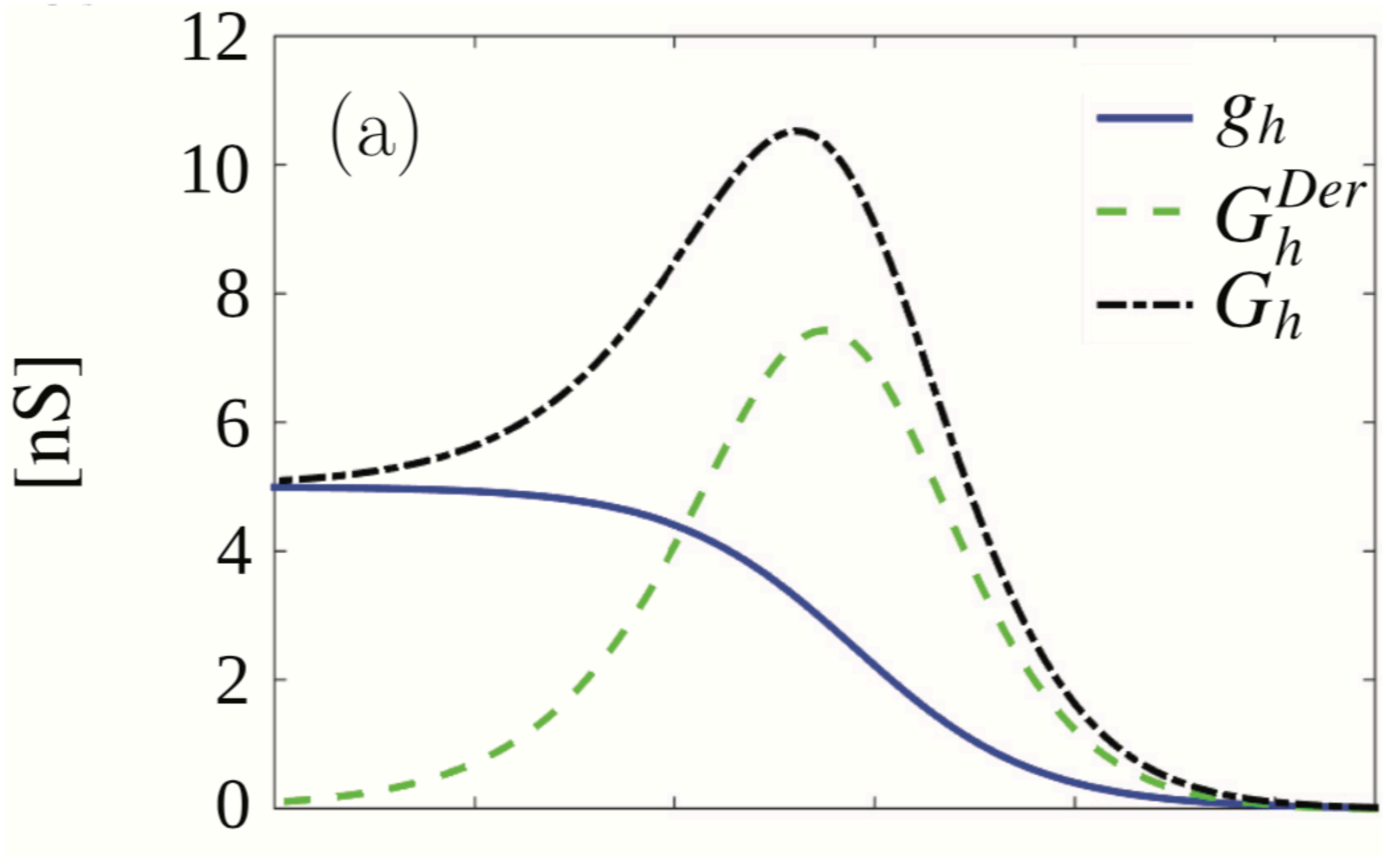
$$A_h^\infty = \frac{1}{1+\exp\left(\frac{V-V_{1/2}}{k}\right)},$$

The I_h slope conductance (G_h), i.e., the slope of the steady- state IV plot

$$G_h = \frac{dI_h}{dV} = \underbrace{\bar{g}_h A_h^\infty}_{\text{chord}} + \underbrace{\bar{g}_h(V - E_h)\frac{dA_h^\infty}{dV}}_{\text{derivative}}$$



Stöhr et al., J Neurosci (2009) 29:6809-18



Pena, Ceballos, Lima, and Roque, Phys Rev E **97**, 042408 (2018)

→ Existence of resonance and its voltage dependency

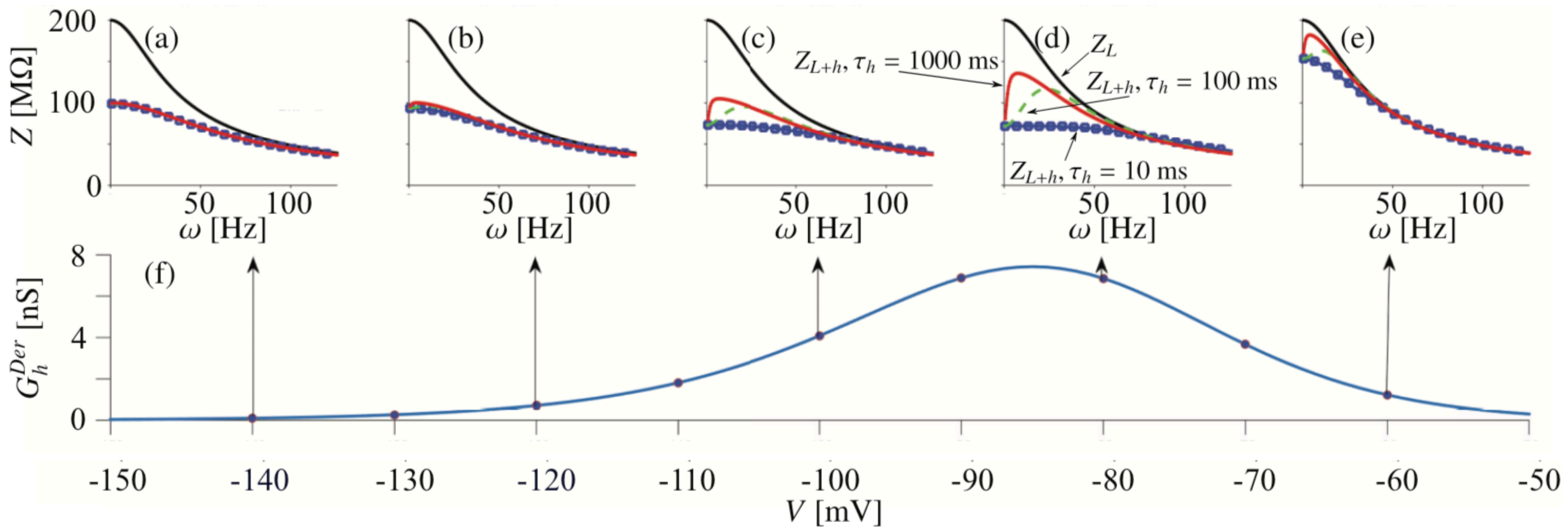
$$\omega_{\text{res}} = \frac{\sqrt{\frac{\sqrt{\tau_h(D+B\tau_h)}}{C} - 1}}{\tau_h}.$$

$$D = 2G_h^{\text{Der}}C$$

$$B = 2G_h^{\text{Der}}(g_L + g_h) + (G_h^{\text{Der}})^2$$

There is resonance only when ω_{res} is real

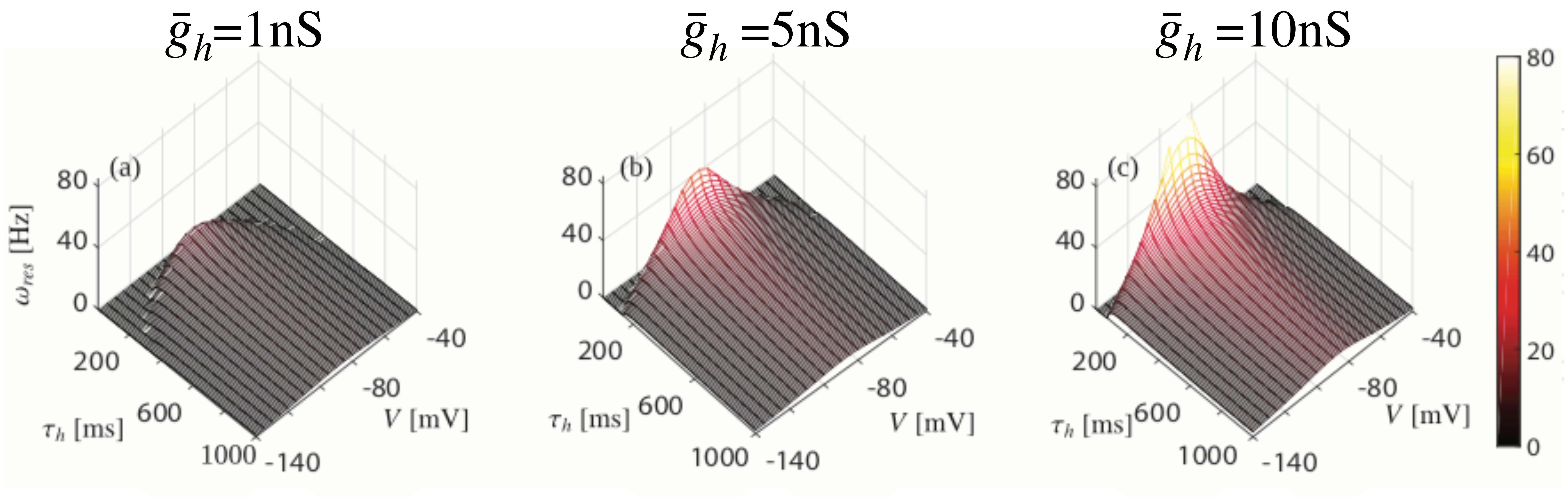
$\tau_h(D + B\tau_h) > C^2$



→ If $G^{Der} = 0$ there is **no resonance**,

since $\omega_{res} = \dfrac{\sqrt{-1}}{\tau_h}$.

- **nonzero** G^{Der} means that the activation variable A_h is able to **vary**.
- **Existence of resonance** requires a **variation** of A_h **in time**.
- **Chord** conductance g_h **influences** resonance
- But, **major responsible** is the **derivative conductance** G^{Der}



Resonance frequency resembles the voltage-dependent behavior of **G**[**Der**].

Summary

- **Chord conductance** is appropriate for characterizing the **ionic permeability**;

- **Slope conductance** reflects an electric property directly affecting the membrane **input resistance**;

- Interplay between the **derivative conductance** and the **current kinetics** determines the existence of the **resonance** and the resonance frequency.

- **Hutcheon et al., (2000)** classified the voltage dependent currents in two categories: amplifying and resonant currents.

- **Amplifying currents** (e.g. I_{NaP}) exhibit **negative slope** conductance meanwhile **resonant currents** (e.g. I_h) **only exhibit positive slope** conductance, affecting the membrane input resistance differentially.

References

Concept of negative resistance

https://en.wikipedia.org/wiki/Negative_resistance

Biophysical Journal
Article

Biophysical Society

A Negative Slope Conductance of the Persistent Sodium Current Prolongs Subthreshold Depolarizations

Cesar C. Ceballos,[1,2] Antonio C. Roque,[2,*] and Ricardo M. Leão[1,*]
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REVIEW

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CHANNELS, 2018
VOL. 12, NO. 1, 81–88
https://doi.org/10.1080/19336950.2018.1433940

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RESEARCH PAPER

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Non-Decaying postsynaptics potentials and delayed spikes in hippocampal pyramidal neurons generated by a zero slope conductance created by the persistent Na^+ current

Cesar C. Ceballos[a,b], Rodrigo F. O. Pena[b], Antônio C. Roque[b] and Ricardo M. Leão[a]

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PHYSICAL REVIEW E **97**, 042408 (2018)

Interplay of activation kinetics and the derivative conductance determines resonance properties of neurons

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(Received 9 December 2017; published 10 April 2018)