On the relation between neuronal size and extracellular spike amplitude and its consequence on extracellular recordings interpretation

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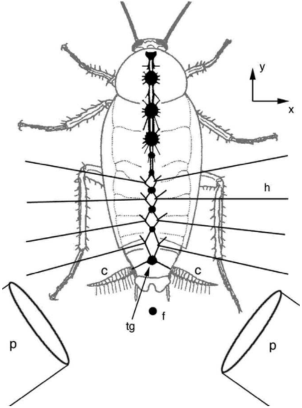
Where are we ?

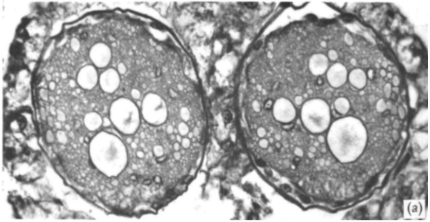
Something you already know

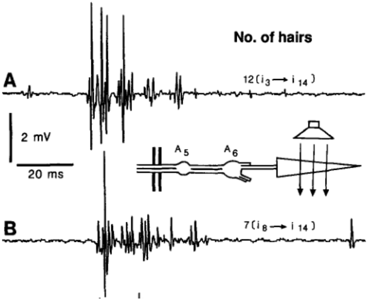
Relation between neurite size and extracellular spike amplitude

Potential consequences

Large neurites are easy to record from







Left, Rinberg and Davidowitz (2002); top, Spira et al (1969); bottom, Hamon et al (1990).

My own experience with the insect olfactory system

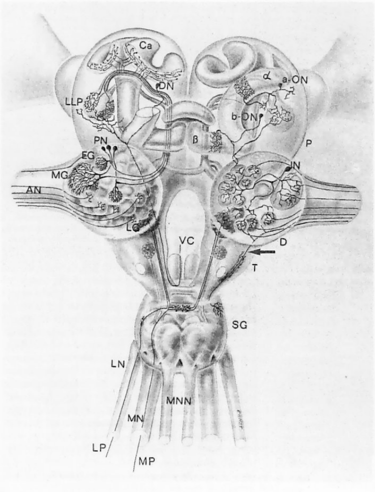
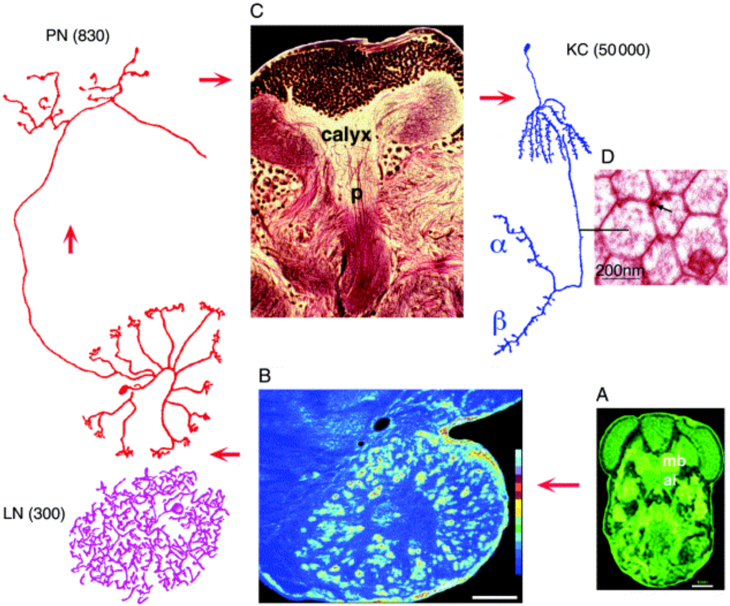
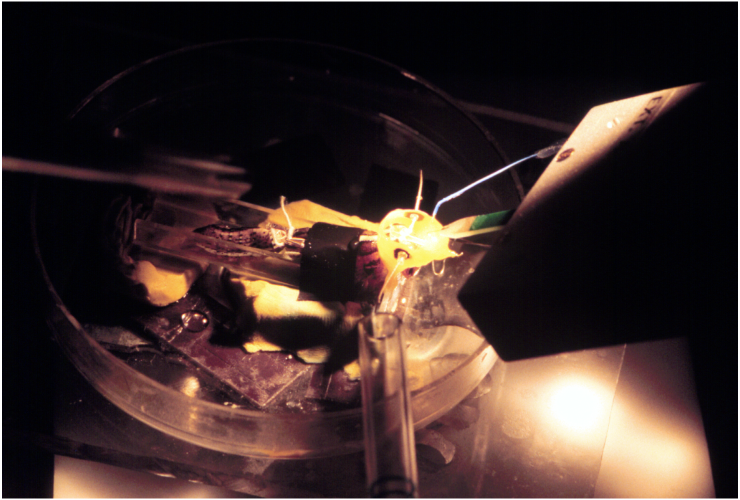


Fig. 4. Semidiagrammatic representation of the brain of an adult male *Periplaneta americana* with identified neuron types (optic lobes omitted). *AN* antennal nerve; *a(b)-ON* α (β)-lobe output neuron; *Ca* calyx of corpus pedunculatum; *D* deutocerebrum; *DN* descending neuron; *EG* glomerulus with cineole-sensitive projection neuron; *IN* local interneuron; *LG* lobus glomeratus; *LLP* lobus lateralis protocerebralis; *LN* labial nerve; *LP* sensory nerve of labial palp; *MG* macroglomerulus; *MN* maxillary nerve; *MNN* mandibular nerve; *MP* sensory nerve of maxillary palp; *P* protocerebrum; *SG* suboesophageal ganglion; *T* tritocerebrum; *VC* ventral cord; α α-lobe; β β-lobe of corpus pedunculatum. Arrow points to descending receptor axons from the antennal nerve. (After data of Ernst et al. 1977; Esslen 1982; Ernst and Boeckh 1983; Hösl, unpublished)

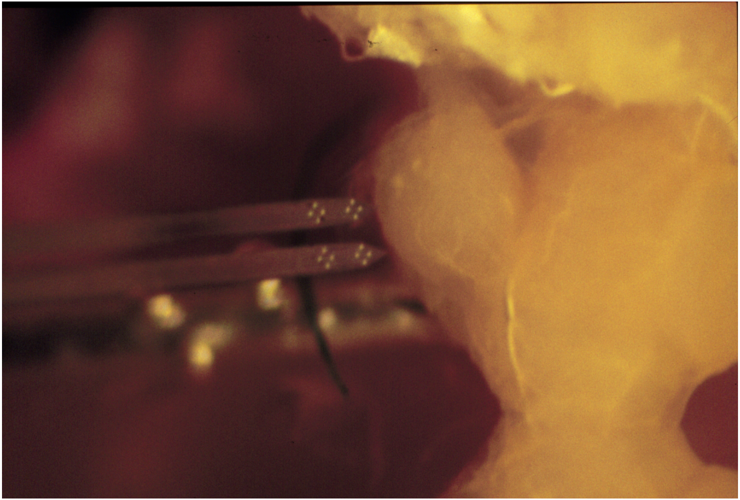
Fig. 4 of Boeckh and Ernst (1987): cockroach, *Periplaneta americana*.



Laurent (1996): locust, *Schistocerca americana*.

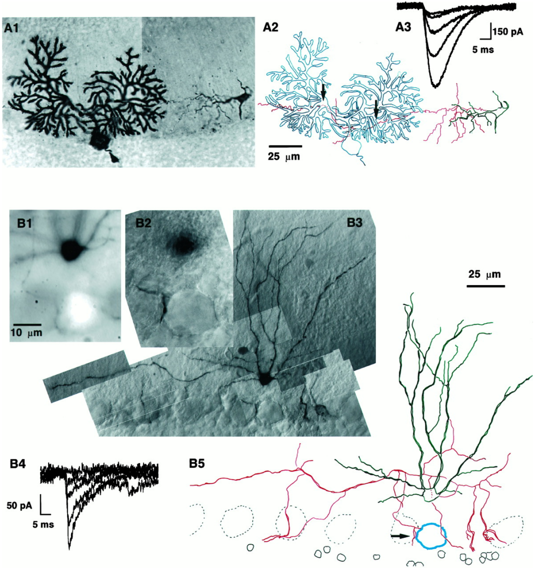


Pouzat, Mazor, Laurent: locust, *Schistocerca americana*.



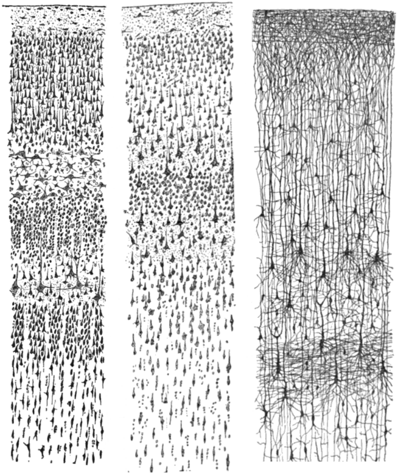
Pouzat, Mazor, Laurent: locust, *Schistocerca americana*.

My experience with the cerebellar cortex



Pouzat and Hestrin (1997): rat.

Consequence for neo-cortical recordings



Ramon y Cajal
(`https://en.wikipedia.org/wiki/Cerebral_cortex`).

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"Fundamental" equation

A (point) current source of intensity I_0 (measured in Ampere) generates an electrostatic potential Φ_e (measured in Volt) at a distance r (assumed null at ∞) given by:

$$\Phi_e = \frac{1}{4\pi\sigma_e}\frac{I_0}{r} \, ,$$

where σ_e is the conductivity of the extracellular medium assumed uniform (measured in Siemens / m).

Sources with spatial extension

When the source is distributed with a current *density* $i_m(x)$, where x is the position along the cable, we have:

$$\Phi_e = \frac{1}{4\pi\sigma_e} \int_N \frac{i_m(x)}{r(x)} dx \,,$$

where the integral is computed over the neuron's "skeleton".

Relation between membrane potential derivative and membrane current

Following Rall (1977) and Plonsey and Barr (2007), we consider of tiny neurite portion of radius a and length Δx.
If the intracellular potential $\Phi_i(x,t)$ at one end is not identical to the one at the other end, $\Phi_i(x+\Delta x,t)$, then Ohm's law implies that we will observe an axial current with intensity:

$$I_i(x,t) = -\pi a^2 \sigma_i \frac{\Phi_i(x+\Delta x,t) - \Phi_i(x,t)}{\Delta x} \approx -\pi a^2 \sigma_i \frac{\partial \Phi_i(x,t)}{\partial x} ,$$

where σ_i is the intracellular conductivity and where currents are positive if they go towards increasing x values.

If the axial current $I_i(x,t)$ at the "entrance" is not identical to the one at the "exit", $I_i(x+\Delta x, t)$, then charge conservation implies that the difference must go through the membrane. Since membrane current density $i_m(x,t)$ is positive in the outward direction we get:

$$I_i(x+\Delta x, t) - I_i(x,t) = -\Delta x\, i_m(x,t) \quad \text{or} \quad \frac{\partial I_i(x,t)}{\partial x} = -i_m(x,t)\,,$$

A combination with the previous equation leads to:

$$i_m(x,t) = \pi a^2 \sigma_i \frac{\partial^2 \Phi_i(x,t)}{\partial x^2}\,.$$

Then considering that the potential gradient outside the cable is much smaller than inside we get:

$$i_m(x,t) = -\pi a^2 \sigma_i \frac{\partial^2 V_m(x,t)}{\partial x^2},$$

where $V_m = \Phi_e - \Phi_i$ is the transmembrane potential (difference). The extracellular potential for an extended source can the be written:

$$\Phi_e = -\frac{a^2\sigma_i}{4\sigma_e}\int_N \frac{1}{r(x)} \frac{\partial^2 V_m(x,t)}{\partial x^2}\, dx\,.$$

Do not conclude from that that the extracellular potential is proportional to the cross-section of the neurite.

Velocity effect

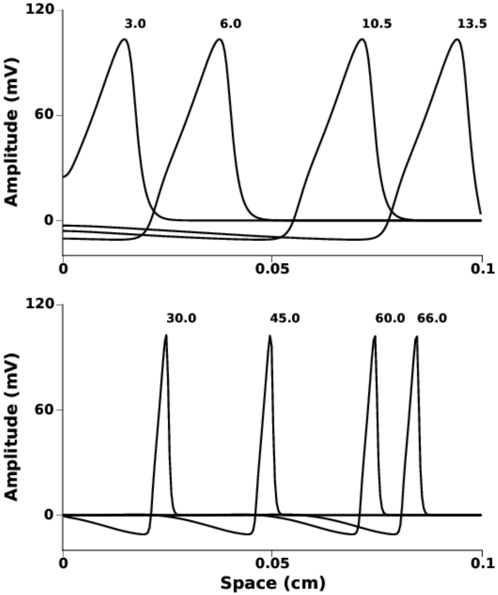
We are going to consider two neurites able to sustain action potentials with the same voltage-dependent channels densities, the same membrane properties and whose only difference is their radius. Now, is the fourth opus of their monumental series, Hodgkin and Huxley (1952) did not solve what are now called the H & H equations (involving a PDE) but found the shape and the speed of a traveling wave solution of their equations (involving only) ODEs:

$$V_m(x,t) = V_m(0, t - x/\theta)\,.$$

They showed thereby that conduction speed, θ, and axon / neurite diameter are related by:

$$\frac{\theta^2}{a\,\sigma_i} = K\,,$$

where K is a constant.



Top, $a = 10\mu m$; bottom $a = 0.5\mu m$. Numerical solution of H & H. Ordinate origin is resting potential. Show the film!

This leads to:

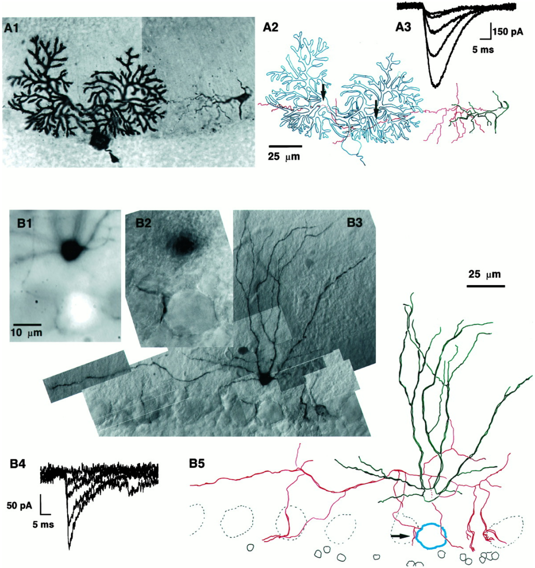
$$\frac{\partial^2 V_m(x,t)}{\partial x^2} = \frac{1}{\theta^2}\frac{\partial^2 V_m(x,t)}{\partial t^2},$$

And by substitution to:

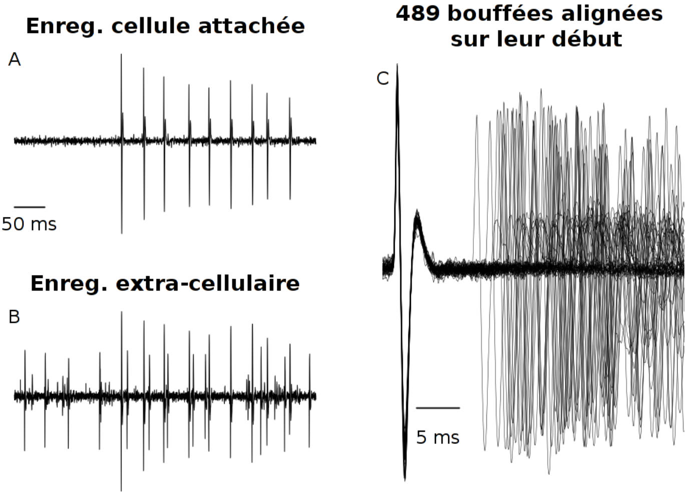
$$\Phi_e(a, V_m) = -\frac{a}{K\sigma_e}\int_L \frac{1}{r(x)}\,\frac{\partial^2 V_m(x,t)}{\partial t^2}\,dx\,.$$

The extracellular potential amplitude of a traveling spike is proportional to the neurite diameter.

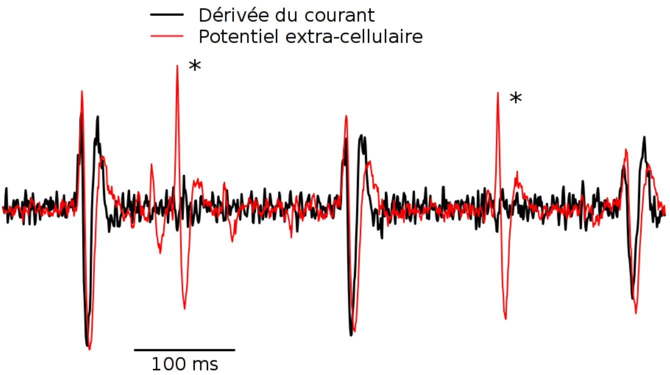
An empirical test of the second time derivative dependence



Pouzat and Hestrin (1997): rat.



Simultaneous extracellular and cell-attached recordings from Purkinje cells in the rat cerebellar cortex. Delescluse and Pouzat (2006). Data available on https://zenodo.org/record/15228.



Black, first time derivative of the cell-attached current (identical to the second time derivative of the membrane potential); red, the extracellular potential.

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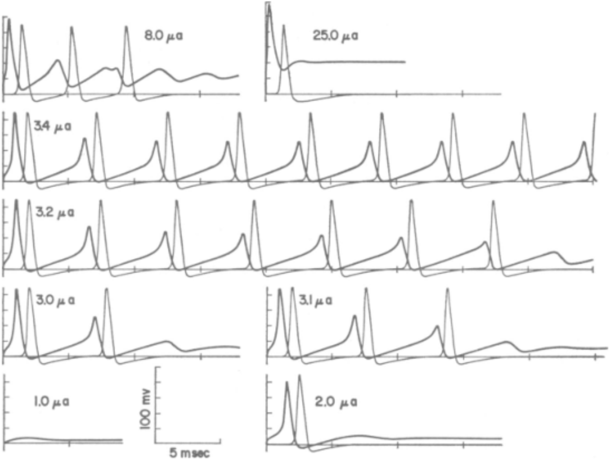
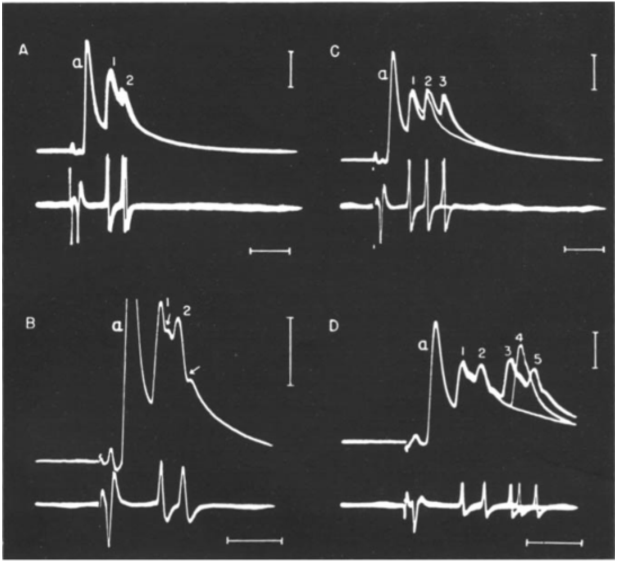
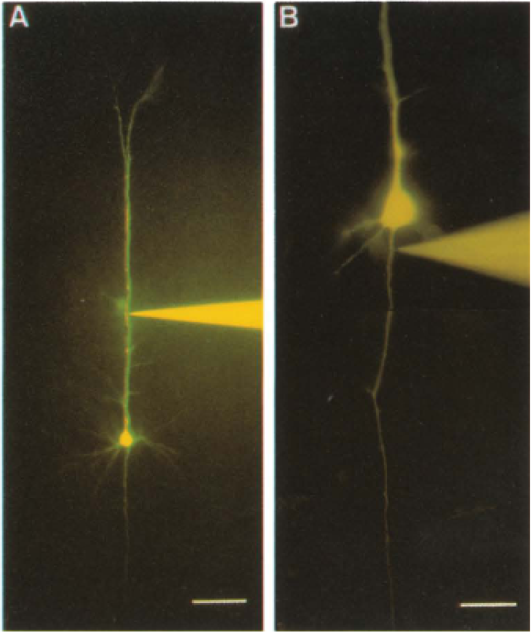


FIGURE 5 Response of the continuous axon to a steady stimulus of various intensities showing time course of the membrane potential V at $x = 0$ (heavy lines) and at $x = 2$ cm (lighter lines).

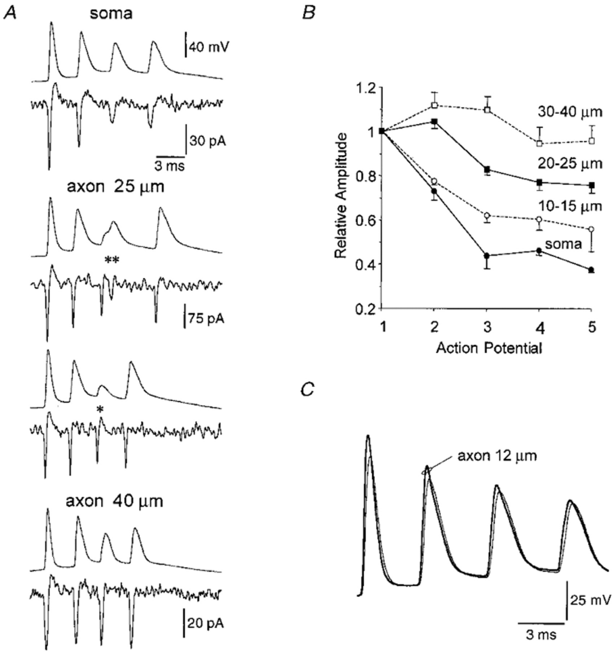
Cooley and Dodge (1966). First numerical solution of the H & H equations.



Eyzaguirre and Kuffler (1955), Lobster stretch receptor.



Stuart and Sakmann (2009).



Williams and Stuart (1999).

Conclusions

- Extracellular recording from regions with neurons having different "sizes", like the neo-cortex, results in a biased sampling of the neuronal populations.
- The amplitude of the extracellular potential generated by a traveling spike is proportional to the neurite diameter.
- Since what goes on in the soma is not necessarily what goes on in the axon and since the extracellular potential is dominated by what goes on in the former, we might get wrong output estimations from extracellular recordings.

Thank you!

I want to thank:

- Christine, Patricia, Francine, Bruno and Matthieu for organizing this wonderful workshop.
- The SynchNeuro ANR project.
- Patricia, Antonio and Maureen, for giving me the opportunity to sort out the relationship between diameter and extracellular spike amplitude.
- You, for listening.