

Engineering Nanopipettes for Probing Neuronal Communication at the Nanoscale

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Summary:

Nanopipettes offer a geometrically matched interface to the nanoscale structures where neuronal communication occurs, but their use as probes is limited by fundamental physical and chemical constraints. We investigate how the nanopipette–neuron interface, including probe geometry, electrolyte composition, and electrical coupling, determines both access and signal fidelity. Through controlled impalement experiments and systematic variation of recording conditions, we identify key trade-offs that govern successful measurements at this scale.

Keywords: Nanopore, Cell-Cell Communication, Neuroscience

Neuronal communication is governed by ionic and molecular events occurring at spatial scales of tens to hundreds of nanometres, yet most experimental techniques interface with neurons at substantially larger dimensions. This mismatch limits direct access to the subcellular processes that shape signal propagation and synaptic transmission. Nanopipettes offer a geometrically compatible probe for these domains, but their practical use is constrained by the interplay between probe geometry, electrical impedance, and ionic composition at the nanoscale interface.

Axons provide a particularly clear example of this limitation. Rather than acting as passive transmission cables, they are now understood to be active, spatially heterogeneous structures in which local ion channel distributions shape spike generation, propagation dynamics, and synaptic output [1]. However, the sub micrometre diameters of most central axons place them beyond the reach of conventional patch-clamp techniques, leaving the ionic mechanisms underlying their computational role largely inaccessible.

Here, we evaluate the use of glass nanopipettes with submicron tip diameters as probes for neuronal communication. Using controlled membrane impalement experiments, we investigate how nanoscale probe geometry, electrolyte composition, and seal formation influence access and signal fidelity. In this regime, recordings are fundamentally shaped by the electrical

properties of the probe, such as high access resistance, stray capacitance, and the small dimensions of the recorded structure impose bandwidth limitations and distort fast voltage signals. Attempts to reduce electrode impedance, for example through high-concentration electrolytes, introduce additional trade-offs by altering ionic gradients and generating junction potentials that can perturb the system under study. As a result, the recorded signal reflects not only the underlying membrane dynamics but also the constraints imposed by the measurement interface and the geometry of the neuronal compartment. In addition, nanopipettes are prone to clogging by membrane fragments or adsorbed biomolecules, leading to progressive changes in resistance and signal quality. We therefore explore surface functionalization and coating strategies to stabilize the pipette interface and improve recording reproducibility.

To systematically explore these constraints, we combine experiments with electrical modelling of the nanopipette–neuron interface. The model (Fig. 1) is used to map how variations in pipette resistance, capacitance, seal quality, and axonal geometry [2] influence the amplitude, shape, and interpretability of recorded signals, thereby defining the parameter space in which meaningful measurements are possible.

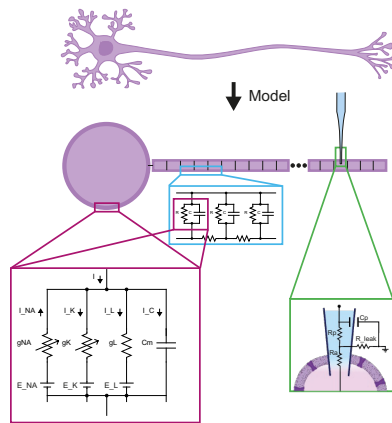


Fig. 1. Electrical model of the pipette-neuron interface.

In parallel, we develop Polydimethylsiloxane (PDMS) microstructures [3] to constrain axonal growth and define accessible geometries for targeted probing. By guiding neuronal connectivity and restricting the spatial location of axons and synapses, these platforms provide a controlled

framework for reproducible nanopipette access at subcellular sites. Together, this approach establishes practical design constraints for nanopipette-based sensing and advances the ability to probe neuronal communication at the nanoscale.

References

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