Comment on “Detection, Stimulation, and Inhibition of Neuronal Signals with High-Density Nanowire Transistor Arrays”

Patolsky et al. (Reports, 25 August 2006, p. 1100) used silicon nanowires to record action potentials in rat neuronal axons and found increases in conductance of about 85 nanosiemens. We point out that the data correspond to voltage changes of about −85 mV on the nanowires and that conceivable mechanisms of axon-nanowire interaction lead to signals that are opposite in sign or smaller by orders of magnitude.

Patolsky et al. described how they stimulated, recorded, and modified action potentials (AP) in dendrites and axons of rat neurons using p-type silicon nanowires (NW) (1, 2). As discussed below, we have concerns about the sign and amplitude of the recordings they reported.

The recordings were presented as changes of NW conductance, with an average increase of 85 nS [figure S3 in (1)]. The authors emphasized the proportionality of changes in NW conductance and intracellular (IC) potential “because the relative potential at the outer membrane becomes more negative and then more positive (opposite to the measured IC potential)” (2). They pointed out that the typical active junction area for devices is “three orders of magnitude smaller than microfabricated electrodes and planar FETs [field-effect transistors].” No value was presented for the extracellular potential, and no explanation was given for why a small size is advantageous.

Here, we describe a voltage calibration of the data and then try to explain the data by various mechanisms.

NWs work similar to electrolyte-oxide-semiconductor (EOS) FETs (1, 3). A voltage change \(\Delta V_{\text{NW}}\) along their length \(L = 2.6\) to 3 \(\mu\)m induces a conductance change \(\Delta G_{\text{NW}}/V_{\text{NW}} = -\mu_p C_{\text{NW}}/L\) that is \(-3.7\) to \(-4.3\) nS/mV for \(C_{\text{NW}} = 2.8\times10^{-10}\) F/m and \(\mu_p = 400\) cm²/Vs.

That value can be verified from the experimental pH effect \(\Delta G_{\text{NW}}/\Delta pH = 100\pm20\) nS/pH (2). Assuming a Nernstian sensitivity \(-59\) mV/pH of the surface potential, we obtain \(-1.7\) mV. With a sub-Nernstian sensitivity of \(-30\) mV/pH, common for silicon dioxide (4), we get \(-3.3\) mS/mV.

An axon with a diameter \(d_{\text{axon}} = 0.6\) to 1 \(\mu\)m affects only a fraction of the NW (1). The local voltage change \(\Delta V_j\) yields a conductance change \(\Delta G_{\text{NW}}/\Delta V_j = (d_{\text{axon}}/L)\Delta G_{\text{NW}}/V_{\text{NW}}\) that is around \(-1\) nS/mV. Thus, recordings of +85 nS correspond to voltage changes of about −85 mV.

This value is rather large compared with recordings using microperipettes (5), microfabricated metal electrodes (6), or planar transistors (7). For example, beneath the soma of individual rat neurons (E19), EOSFETs recorded about ±300 µV after 1 to 2 weeks in serum-free medium on oxidized silicon with polylysine, culture conditions similar to those in (1).

To explain their data, Patolsky et al. (1) used a circuit with a seal resistance between NW and axon, a membrane capacitance, and a leakage conductance [figure S10 in (1)]. They estimated an increase in NW conductance of 13 to 47 nS after 1 to 2 weeks in serum-free medium on oxidized silicon with polylysine, culture conditions similar to those in (1).

For a dominating capacitive current, \(\Delta V_j\) would be the first derivative of the AP (8), apparently incompatible with the data. If the seal resistance were extremely high, because the NW touches the lipid bilayer of the axon, the change of the IC voltage \(\Delta V_M = +100\) mV would act by a field effect across a bilayer/oxide stack with a positive voltage change \(\Delta V_j = \Delta V_M C_{\text{OX}}/(C_{\text{CM}} + C_{\text{OX}})\) on the NW due to the serial capacitances of membrane and oxide (9). The NW conductance would decrease, opposite to the data. For a dominating capacitive current, \(\Delta V_j\) would not mirror the IC signal (10). Let us assume that the NW forms a linear junction on the axon with a width \(d_J = 20\) nm, given by the diameter of the NW, and a sheet resistance \(r_J\). The balance of current (8) is described by \(-r_J d_J^2 \Delta V_j\) with a conductance \(g_{\text{OX}}^{\text{NW}}\) and a reversal voltage \(V_0^{\text{NW}}\). For boundary conditions \(\Delta V_j = 0\) at the edges, \(\Delta V_j\) is expressed by hyperbolic functions. With \(d_J = d_J \sqrt{g_{\text{OX}}^{\text{NW}}/r_J/4}\), the average is \(\langle \Delta V_j \rangle = (V_M - V_0^{\text{NW}})(1 - d_J/\tanh d_J)\) and \(\langle \Delta V_j \rangle \approx (V_M - V_0^{\text{NW}})g_{\text{OX}}^{\text{NW}}d_J^2/12\) for small signals. During an AP, the Na conductance may rise to \(g_{\text{Na}}^{\text{NW}} = 50\) mS/cm² at a driving force \(V_M - V_0^{\text{Na}} \approx -50\) mV. When we use \(r_J = 10\) MΩ/square for rat neurons on oxidized silicon with polylysine (11), we obtain \(\langle \Delta V_j \rangle \approx -8\) nV. Alternatively, we assume that a linear junction is formed between axon and substrate of a width \(d_J = 0.6\) µm, given by the diameter of the junction, and the NW as an embedded probe. We get \(\langle \Delta V_j \rangle \approx -7\) µV. In both configurations, the estimated signals are far smaller that the −85 mV reported in (1). Tens of millivolts could only be obtained with sheet resistances of 50,000 GΩ and 30 GΩ, respectively. In such junctions, ion currents would be suppressed and a signal generation by Na current would cease.

Two further remarks on the Na current mechanism may be helpful. First, for comparison, we consider a circular junction as it was used to describe the coupling of transistors to axon stumps of leech neurons and somata of rat neurons (7, 10). The average signal is \(\langle \Delta V_j \rangle = (V_M - V_0^{\text{Na}})g_{\text{OX}}^{\text{NW}}d_J^2/32\) (12). For a typical diameter \(d_J = 17\) µm (7, 10) and other parameters as above, we obtain \(\langle \Delta V_j \rangle \approx 2.3\) mV in good agreement with observed recordings in the millivolt range (7, 10). Unlike the soma/transistor junction, the NW/axon and axon/substrate junctions are much smaller. Consequently, as the signals scale with the squared diameter of the junction, the expected signals in NW/axon or axon/substrate junctions are smaller by orders of magnitude. Second, the estimated amplitude of −7 µV for axon/substrate junctions is an upper limit for a rather high Na conductance as it may occur in mature rat neurons (3 to 4 weeks in culture). Younger neurons (1 to 2 weeks old) exhibit a lower expression of Na channels. Accordingly, the observed amplitudes were about −300 µV in soma/transistor junctions, compared with −3 mV for mature neurons (7). Considering the short culture time (4 to 8 days) in (1), the expected amplitudes are lower than −7 µV, and the discrepancy to the reported −85 mV becomes even larger.

As further alternatives, we consider two electrostatic models: (i) When ion channels open, gating charges are displaced across the membrane. A NW within the Debye length of the electrolyte may be affected by a field effect. The gating kinetics during an AP are well known (13). A change of NW conductance that matches the AP is impossible. (ii) An increase of NW conductance can be caused by a drop of the negative surface potential on silicon dioxide (4), as it may be induced by a dissociation of protons (4) or other cations. A change of −85 mV implies an increase by three pH units at a sensitivity of −30 mV/pH. Generally, proton channels open for outward current, thus lowering the extracellular pH (14). Further, gating of proton channels and proton binding to silicon dioxide (15) are slow, such that ion binding would not follow an AP.

As the mechanisms discussed so far fail to explain the data in (1), one might resort to an unknown “nanoscale” process involving NW/axon interactions on a molecular level. As the electrical...

Department of Membrane and Neurophysics, Max Planck Institute for Biochemistry, D-82152 Martinsried/Munich, Germany.

*To whom correspondence should be addressed. E-mail: fromherz@biochem.mpg.de
effects of neurons (ion current, gating charges) rely on single protein molecules, their inherent stochastic dynamics would inevitably translate to a stochastic modulation of NW conductance, in contrast to the reported smooth modulation. To explain the data, a “nanoscale” mechanism would have to mediate the deterministic AP to a deterministic change of NW conductance without introducing stochastic effects. It cannot rely on a small number of molecules. Effects of macroscopic parameters, however, have been shown above to be incompatible with the data.

In conclusion, on the basis of common neurophysiology, surface science, and semiconductor physics, we are not able to find a physical rationale for the sign and amplitude of the NW recordings described by Patolsky et al. (1).

References
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Editor's Summary

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