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

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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 millivolts on the nanowire 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).” They pointed out that the typical active junction area for devices is “three orders of magnitude smaller than micro-fabricated 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 ΔV_{NW} along their length $L = 2.6$ to $3 \mu\text{m}$ induces a conductance change $\Delta G_{NW}/\Delta V_{NW} = -\mu_p C_{NW}/L$ that is -3.7 to -4.3 nS/mV for $C_{NW} = 2.8 \cdot 10^{-10}$ F/m and $\mu_p = 400$ cm²/Vs. That value can be verified from the experimental pH effect $\Delta G_{NW}/\Delta \text{pH} \approx 100 \pm 20$ nS/pH (2). Assuming a Nernstian sensitivity -59 mV/pH of the surface potential, we obtain -1.7 nS/mV. With a sub-Nernstian sensitivity of -30 mV/pH, common for silicon dioxide (4), we get -3.3 nS/mV.

An axon with a diameter $d_{axon} = 0.6$ to $1 \mu\text{m}$ affects only a fraction of the NW (1). The local voltage change ΔV_J yields a conductance change $\Delta G_{NW}/\Delta V_J = (d_{axon}/L) \cdot \Delta G_{NW}/\Delta V_{NW}$ 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 micropipettes (5), microfabricated metal electrodes (6), or planar transistors (7). For example, beneath the soma of individual rat neurons (E19), EOSFETs recorded about $\pm 300 \mu\text{V}$ 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 (μS is obviously a typing error) but did not explain how they arrived at that value. If membrane leakage dominates, the inward current in the resting state would be lowered during the AP. There would be a positive ΔV_J proportional to the AP (8). The NW conductance would decrease, opposite to the data. For a dominating capacitive current, ΔV_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 $\Delta V_J = \Delta V_M c_M / (c_M + c_{OX})$ on the NW due to the serial capacitances of membrane and oxide (9). The NW conductance would decrease, opposite to the data in (1).

A negative ΔV_J could be induced by a sodium inward current that flows along the seal resistance. We estimated its amplitude, even though the signal 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 $-r_J^{-1} d^2 \Delta V_J / dx^2 = g_{JM}^{Na} (V_M - V_0^{Na} - \Delta V_J)$ with a conductance g_{JM}^{Na} and a reversal voltage V_0^{Na} . For boundary conditions $\Delta V_J = 0$ at the edges, ΔV_J is expressed by hyperbolic functions. With $\tilde{d}_J = d_J \sqrt{g_{JM}^{Na} r_J / 4}$, the average is $\langle \Delta V_J \rangle = (V_M - V_0^{Na}) (1 - \tanh \tilde{d}_J / \tilde{d}_J)$ and $\langle \Delta V_J \rangle \approx (V_M - V_0^{Na}) g_{JM}^{Na} r_J d_J^2 / 12$ for small sig-

nals. During an AP, the Na conductance may rise to $g_{JM}^{Na} = 50$ mS/cm² at a driving force $V_M - V_0^{Na} \approx -50$ mV. When we use $r_J = 10$ M Ω /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 $d_J = 0.6 \mu\text{m}$, given by the diameter of the junction, and the NW as an embedded probe. We get $\langle \Delta V_J \rangle \approx -7 \mu\text{V}$. In both configurations, the estimated signals are far smaller than the -85 mV reported in (1). Tens of millivolts could only be obtained with sheet resistances of 50,000 G Ω and 30 G Ω , 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 $\langle \Delta V_J \rangle \approx (V_M - V_0^{Na}) g_{JM}^{Na} r_J d_J^2 / 32$ (12). For a typical diameter $d_J = 17 \mu\text{m}$ (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 $-7 \mu\text{V}$ 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 $-300 \mu\text{V}$ 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 $-7 \mu\text{V}$, 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

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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).

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