Nyquist Noise of Cell Adhesion Detected in a Neuron-Silicon Transistor

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Interfacing of nerve cells and field-effect transistors is determined by current flow along the electrical resistance of the cell-chip junction. We study the thermal noise of the junction by measuring the fluctuations of extracellular voltage with a low-noise transistor. We find a spectral power density of 5×10^{-14} V^2/Hz and interpret it as Nyquist noise of the cell-chip junction with a resistance of 3 MOhm. The thermal noise allows us to elucidate the properties of cell adhesion and it sets a thermodynamical limit for the signal-to-noise ratio of neuroelectronic interfacing.

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Direct electrical interfacing of semiconductors and nerve cells is the physical basis for a systematic development of hybrid neuroelectronic devices, such as neurocomputers and neuroprostheses. Excited nerve cells and field-effect transistors are coupled by a dissipative mechanism: ionic current through the adherent cell membrane flows along the electrical resistance of a narrow layer of electrolyte between cell and chip and gives rise to an extracellular voltage on the open gate oxide of the transistor [1]. The resistance in the area of cell adhesion determines the amplitude of the recorded extracellular voltage. That resistance, however, is also an intrinsic source of thermal voltage noise [2,3]. This aspect has two interesting implications: (i) on the engineering side, the noise of adhesion may set a thermodynamical limit for the signal-to-noise ratio of extracellular recording of neuronal excitation. (ii) On the analytical side, the noise of adhesion may provide an excellent tool to elucidate the nature of cell-chip adhesion without perturbing the system.

In the present Letter, we study the voltage fluctuations in the adhesion area of nerve cells from rat brain which are cultured on oxidized silicon. As a probe, an electrolyte-oxide-silicon field-effect transistor is used as sketched in Fig. 1(a). It consists of an open gate between source and drain contacts and is insulated from the electrolyte by 10 nm silicon dioxide. A local change of voltage in the electrolyte layer between cell and chip gives rise to a modulation of source-drain current. Because of a buried channel configuration, the transistor has a particularly low $1/f$ noise [4]. The gate with a dimension of $6\ \mu m \times 7\ \mu m$ is small enough to be completely covered by a mammalian nerve cell, but large enough to avoid a dominance of the $1/f$ noise that increases with decreasing gate area.

Prior to cell culture, the chip surface is cleaned with a detergent (5% Tickopur R36 at 80 °C, Stamm/Berlin), sterilized with 70% ethanol for 1 h and coated with poly-L-lysine (150.000 kD, adsorbed from 0.1 mg/ml solution in water). Nerve cells are dissociated from the hippocampus of embryonal rats (ED 19) and cultured on the chip for 10 to 12 days at 37 °C in neurobasal medium supplemented with B27 and glutamax I [4,5]. After contacting the bath electrolyte with a Ag/AgCl electrode, the working points of the transistors are adjusted by bias voltages between bulk silicon/source and bath ($V_{gs} \approx -0.3$ V) and between source and drain ($V_{ds} \approx -0.5$ V). Immediately before a measurement, the source-drain currents are carefully cali-

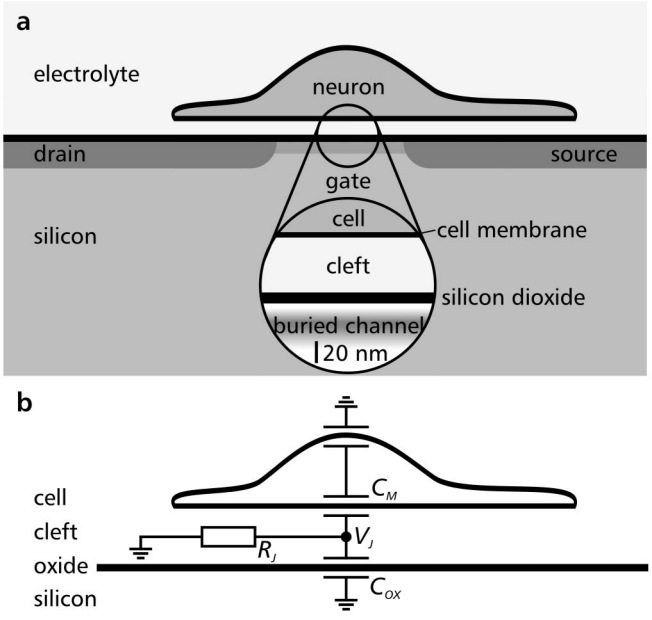

FIG. 1. Nerve cell on silicon chip in electrolyte. (a) Schematic cross section of a cell on a field-effect transistor. The gate oxide is exposed to the electrolyte beneath the cell, allowing the transistor to record the extracellular voltage in the cleft between cell and chip. The diameter of the adhesion area is about 30 μm; the cleft has a width of about 50 nm (see inset, drawn to scale). (b) Equivalent circuit of one-compartment model to describe the thermal noise of cell adhesion with extracellular voltage V_J, seal resistance R_J, and capacitances C_{OX} and C_M of the oxide and of the attached cell membrane.

brated in terms of a change of extracellular voltage by applying defined voltage steps to the bath electrode.

Figure 2(a) shows a nerve cell grown on a linear array of transistors with transistors No. 4 and 5 being completely covered by the cell body. In Fig. 2(b), the extracellular voltage of eight transistors is depicted for a bandwidth of 1 Hz to 10 kHz. The biphasic signals at the end of three traces are caused by spontaneous excitation of the nerve cell as discussed previously [4]. The voltage noise of the transistors which are beneath the cell body is significantly enhanced compared to the noise of the transistors that are not covered. We also recorded the noise after removing the cell by rinsing the chip with a jet of water (data not shown). In that case, the enhancement disappears and all transistors exhibit a similar noise record.

We sample the transistor signals in periods without neuronal excitation for 2 minutes at a rate of 1 M Samples/s to make use of the full 100 kHz bandwidth of the amplifier. The spectral power density of the voltage noise is plotted in Fig. 3 for the covered transistor No. 5 as well as for the same transistor after removing the cell. Apparently, the cell enhances the power density over a wide range of frequencies.

The intrinsic noise of the open transistor exhibits a typical $1/f$ power spectrum in the frequency range up to 10 kHz. The power density of gate-referred voltage is determined by the density of electronic traps n_T at the oxide-silicon interface with a tunnel distance λ_T [6,7] according to Eq. (1) with area A_g and oxide capacitance c_{OX} of the gate (thermal energy $k_B T$, elementary charge e_0).

$$S_{V_g}(f) = \frac{k_B T e_0^2 \lambda_T n_T}{A_g c_{\mathrm{ox}}^2} \frac{1}{f}. \quad (1)$$

For $A_g = 42\ \mu\mathrm{m}^2$ and $c_{\mathrm{OX}} = 0.3\ \mu\mathrm{F/cm}^2$ of the 10 nm gate oxide with a tunnel distance $\lambda_T = 0.1$ nm [7], we obtain $n_T = 3 \times 10^{17}\ \mathrm{eV}^{-1}\,\mathrm{cm}^{-3}$ which is in a typical range for low-noise field-effect transistors. Above 30 kHz, the noise of the open transistor is frequency independent. The power density of gate-referred voltage is determined by the thermal noise of the transistor channel [8] according to Eq. (2) with a channel conductance g_d at vanishing source-drain voltage and a transconductance g_m.

$$S_{V_g} = \frac{4 k_B T\ g_d}{g_m^2}. \quad (2)$$

For uncorrelated noise sources, the total noise power density of a system is the sum of the individual power densities. Thus, we obtain the additional noise which is due to cell adhesion by subtracting the power spectra of covered and open transistor. The result is shown in Fig. 4. We find a white spectrum of the voltage noise up to a frequency of 60 kHz with a power density $S_V = 5 \times 10^{-14}\ \mathrm{V}^2/\mathrm{Hz}$. At low frequencies, the adhesion noise is below the $1/f$ noise of the transistor, whereas it exceeds the transistor noise above 2 kHz as illustrated in Fig. 4.

We reproducibly observe power densities of the adhesion noise in a range of $3\text{–}6 \times 10^{-14}\ \mathrm{V}^2/\mathrm{Hz}$ if the cell completely covers the transistor gate, with the exact value depending on the particular adhesion geometry.

In principle, various kinds of fluctuations may contribute to the voltage noise in cell adhesion: (i) the Ohmic resistance of the electrolyte between attached membrane and substrate together with the capacitance of the cell-chip contact may exhibit a Nyquist-type voltage noise [3]. (ii) Ion channels in the attached cell membrane may statistically open and close and generate current fluctuations [9]. With the Ohmic resistance of the cell-chip contact they

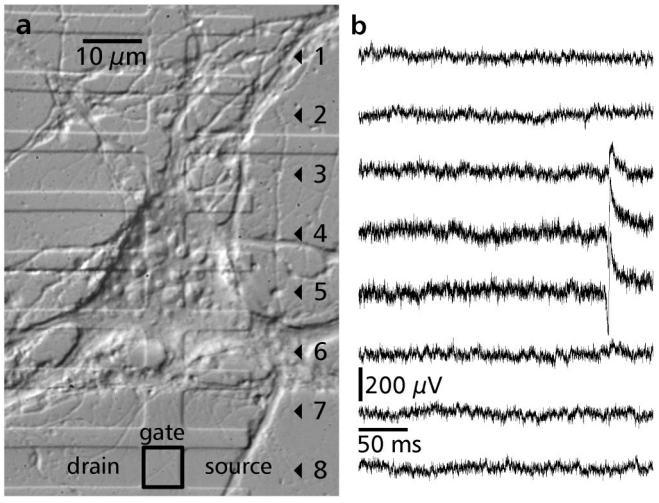

FIG. 2. Noise of extracellular voltage due to cell adhesion. (a) Differential interference contrast micrograph of nerve cell from rat on linear array of electrolyte-oxide-silicon field-effect transistors. The elements of a selected transistor are indicated at the bottom. The cell body completely covers the transistors No. 4 and 5. (b) Extracellular voltage recorded by the transistors within a bandwidth of 1 Hz to 10 kHz. The transistors beneath the cell body exhibit an enhanced noise. Near the end of the traces, the transistors No. 3, 4, and 5 record spontaneous neuronal excitation.

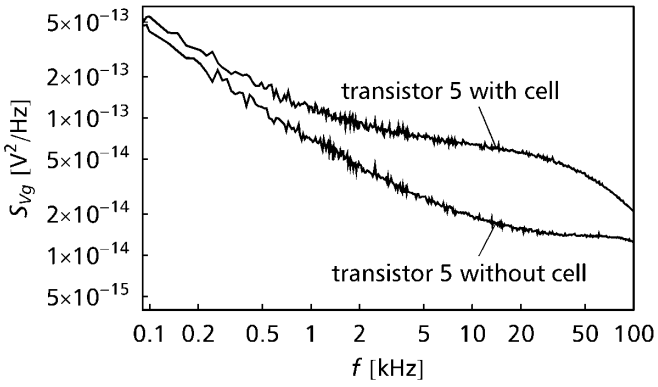

FIG. 3. Spectral power densities of voltage noise for electrolyte-oxide-semiconductor field-effect transistor 5 of Fig. 2(a) with and without nerve cell on the gate.

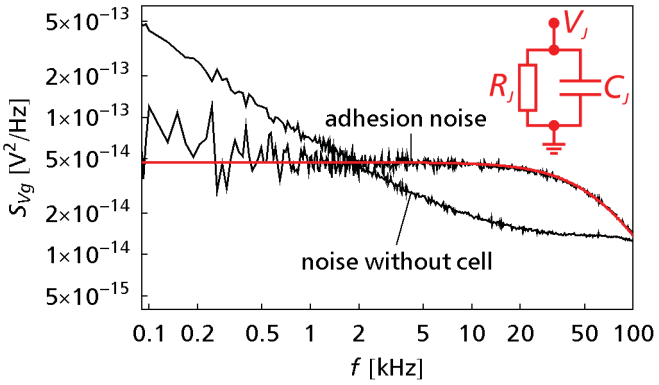

FIG. 4 (color). Spectral power density of voltage noise caused by cell adhesion. The net noise of cell adhesion is obtained by subtracting the noise spectra of transistor No. 5 with and without nerve cell. It is fitted with a Lorentzian (red line) for an *RC* circuit (red insert) according to Eq. (3). For comparison the noise spectrum of transistor No. 5 without cell is plotted. At frequencies above 2 kHz, the noise of cell adhesion exceeds the transistor noise and is the dominant noise source of the system.

would give rise to a noise of extracellular voltage. (iii) The attached membrane may undergo mechanical fluctuations that are driven by thermal excitation [10] or by active membrane processes [11]. These deformations may give rise to hydrodynamic flow in the electrolyte layer [12] that could create a fluctuating streaming potential at the negatively charged oxide surface.

For an evaluation of the data in terms of a Nyquist-type noise, we describe the cell-chip junction by an equivalent circuit [13] as shown in Fig. 1(b) with a resistance R_J and a capacitance $C_J = C_{\mathrm{OX}} + C_M$ of oxide and membrane. Using the concomitant Lorentzian power spectrum of Eq. (3), we are able to fit the plateau of the experimental spectrum in Fig. 4 with $R_J = 2.9\ \mathrm{M\Omega}$ and its corner frequency with a time constant $R_J C_J = 2.5\ \mu\mathrm{s}$ at $C_J = 0.85$ pF, respectively.

$$S_V(f) = \frac{4k_B T R_J}{1 + (2\pi f R_J C_J)^2}. \qquad (3)$$

We introduce specific capacitances of membrane and oxide $c_M \approx 1\ \mu\mathrm{F/cm^2}$ and $c_{\mathrm{OX}} = 0.3\ \mu\mathrm{F/cm^2}$. Using the relation $C_J = (c_M + c_{\mathrm{OX}})A_{J,\mathrm{eff}}$, we obtain an effective area $A_{J,\mathrm{eff}} = 65\ \mu\mathrm{m^2}$ of the cell-chip contact. That value is similar to the area $A_g = 42\ \mu\mathrm{m^2}$ of the gate, but far smaller than the estimated area $A_{\mathrm{cell}} = 700\ \mu\mathrm{m^2}$ of cell adhesion. Thus within the limitations of a circuit model, the data are compatible with a localized noise detection by the transistor. With respect to an interpretation of the resistance $R_J = 2.9\ \mathrm{M\Omega}$, we assume for sake of simplicity circular shapes of gate and cell adhesion with radii a_g and a_{cell}. In that case the resistance from gate to bath is $R_J = (r_J/2\pi)\ln(a_{\mathrm{cell}}/a_g)$ with the sheet resistance r_J of the electrolyte layer. With $A_g = 42\ \mu\mathrm{m^2}$ and $A_{\mathrm{cell}} = 700\ \mu\mathrm{m^2}$, we obtain $r_J = 13\ \mathrm{M\Omega}$ per square. This value is in good agreement with a dissipative measurement where capacitive current is applied from a chip and the resulting voltage in the cell-chip junction is observed [14].

In the geometry of cell adhesion, fluctuations of ion current in the attached cell membrane together with the resistance of the narrow layer of electrolyte may give rise to a Lorentzian power spectrum of extracellular voltage noise. However, the corner frequency would be in a range of 0.1 to 1 kHz due to the slow dynamics of ion channels [9]. There is no indication in the data for such a contribution. The average fraction of open channels may be too low at the resting potential of a nerve cell.

Mechanical fluctuations of adherent membranes may couple to hydrodynamic flow in the narrow layer of electrolyte [12]. However, mechanical fluctuations with large amplitudes in adhesion are reported only for pure lipid membranes with low elastic bending modulus [10], but not for living cells with a far higher elastic modulus of their plasma membrane. We see no indication in the data for a contribution of mechanical fluctuations to the voltage noise.

The observed spectrum of voltage noise recorded in a neuron-transistor system can be quantitatively interpreted in terms of a Nyquist-type noise. The experiment demonstrates that thermal noise can be used as a probe for the electrical properties of cell adhesion. In comparison to other methods [13–15], the approach does not require a perturbation of the cells, e.g., staining with a dye or contacting with a pipette, nor any external stimulation.

The thermal noise of cell adhesion is generic for neuroelectronic interfacing, as the resistance of adhesion is a prerequisite for an extracellular voltage to arise from neuronal excitation. It sets a thermodynamical limit for the signal-to-noise ratio of extracellular recording. Of course, that limit is independent of the method of voltage measurement, such as transistors, planar metal electrodes [16], or voltage sensitive dyes [14]. In our system, the adhesion noise exceeds the transistor noise above 2 kHz (Fig. 4). For short extracellular voltage spikes, which are as short as 0.15 ms for mature rat neurons [4], cell adhesion dominates the total noise in the relevant frequency range, and the limit of extracellular recording is reached.

A more detailed characterization of the adhesion noise may be achieved by measuring the voltage fluctuations as a function of position and by applying theories that account for the two-dimensional nature of adhesion. The recording and analysis of voltage noise may be applied not only for cell adhesion, but also for other contacts of organic films and solids in electrolyte, such as supported lipid membranes without or with membrane proteins.

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