

Silicon-on-Insulator Based Thin-Film Resistor for Chemical and Biological Sensor Applications

Michael G. Nikolaidis,^[a] Stephan Rauschenbach,^[a] Sebastian Lubner,^[b] Karin Buchholz,^[b] Marc Tornow,^[b] Gerhard Abstreiter,^[b] and Andreas R. Bausch*^[a]

Efficient detection of specific or nonspecific interactions at solid–liquid interfaces is becoming increasingly important for a wide variety of applications and technologies, which range from industrial and biomedical applications to basic research.^[1, 2] The most prominent example of applications in basic research is the label-free detection of biomolecular interactions. There is growing need for new detection schemes, as the common fluorescent labeling techniques are limiting the applicability of DNA or protein arrays.^[3] Increasingly sophisticated techniques are being developed to provide versatile techniques for label-free detection methods.^[4, 5] The main requirement for new technologies is the highly sensitive and specific detection of molecules. At the same time, for the applicability of the technique towards screening of biomolecular interactions, the potential of simultaneous parallel detection is mandatory. Several different approaches have been developed to address these requirements. For the electrical detection of molecular interactions, physical principles of field-effect transistors are used in most cases: Variations of the surface potential induce changes in the charge carrier concentration and thus in the conductivity of the semiconductor. The most extensively studied technique to date is the technology of ion-sensitive field-effect transistors (ISFETs), which have been shown to be versatile tools for detecting chemical and enzymatic reactions.^[6] The direct electrical detection of cell signaling was realized with recently developed semiconductor chips.^[7, 8] The capacitive detection of inversion layers in silicon structures has successfully been used to monitor the hybridization of DNA molecules.^[9] A similar approach with a biofunctionalized, porous silicon electrolyte–insulator–semiconductor (EIS) structure as a sensing device was used to detect biomolecules, such as penicillin, with a sensitivity down to 10 nM.^[10]

Here, we present a device based on silicon-on-insulator (SOI) substrates that enables the detection of changes of electrolyte concentrations and of small numbers of charged biomolecules. In the SOI substrates the conducting layer is limited to a thin surface layer, covered by a thin native oxide layer. Hence, the conductivity of this thin conductive layer is strongly dependent on variations of the surface potential and the distribution of the surface states, which results in variations of the space charge

region. We utilized a four-point resistance measurement in a hallbar geometry to determine the conductivity of the sensing layer. A variation of the salt concentration of the electrolyte could be detected over five magnitudes and an excellent agreement with the Grahame equation was found. The unspecific adsorption of poly-L-lysine was detectable at concentrations of 1 nM (80 ng mL⁻¹). The measurements showed that variations of surface charges of 0.01 e⁻ per nm², or one electronic charge per 100 nm², could be detected by the device.

For the experiments, commercially available SOI wafers (ELTRAN, Canon) were used. The silicon layer in these wafers was 30 nm thick and was slightly doped with boron (10¹⁶ cm⁻³). To control the concentration of charge carriers in this layer, a voltage was applied to the backgate of the substrate. For some experiments, this upper silicon layer was overgrown by molecular beam epitaxy (MBE) with a 50 nm thick, single crystalline layer of doped silicon. The p-doping concentration of boron was 10¹⁸ cm⁻³ or 10¹⁹ cm⁻³. A sketch of the SOI device is given in Figure 1. In the subsequent steps, the silicon layer was patterned

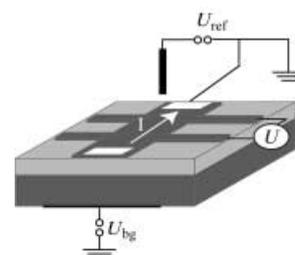


Figure 1. Sketch of the SOI device used to measure the changes in surface potential. A constant current was applied between the source and drain contacts of the hallbar. The measured voltage drop between two adjacent contacts directly yields the area normalized sheet resistance. A Ag/AgCl reference electrode was used to control the potential of the electrolyte solution above the device. The SOI layer sequence, from top to bottom is: 2–3 nm natural Si oxide (not shown), optional 50 nm MBE regrown p-doped Si on top of 30 nm low-doped Si (dark gray, sensing layer), 200 nm buried oxide (light gray), 675 μm Si handle wafer (dark gray).

using standard lithographic methods and wet chemical mesa-etching in a mixture of HF and H₂NO₃ for 60 to 90 s, depending on the dopant concentration. The obtained hallbar-like structure was chosen to miniaturize the sensitive area and to separate the ohmic contacts from the electrolyte solution, while allowing four-point resistance measurements at the same time. After exposing the surface for 30 s to HF vapor, to remove the native oxide, 50 nm thick Al contacts were deposited in a thermal evaporation chamber at 5 × 10⁻⁶ mbar. The metal contacts were annealed in a mixture of H₂/N₂ for 2 s at atmospheric pressure and at a temperature of 250 °C, which resulted in ohmic contacts with satisfying low contact resistance. Figure 2 shows an optical micrograph of a processed active hallbar together with a picture of the complete sensing device.

A current was applied between the source and drain contacts of the hallbar (in Figure 2 left and right) and the voltage drop

[a] Prof. A. R. Bausch, M. G. Nikolaides, S. Rauschenbach
Lehrstuhl für Biophysik – E22
Technische Universität München, 85747 Garching (Germany)
E-mail: abausch@ph.tum.de

[b] S. Lubner, K. Buchholz, Dr. M. Tornow, Prof. G. Abstreiter
Walter-Schottky-Institut
Technische Universität München, 85747 Garching (Germany)

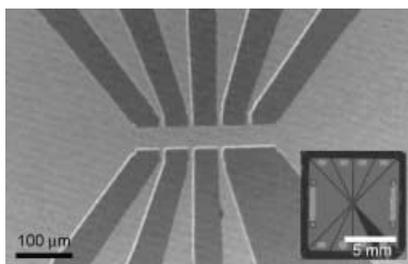


Figure 2. Optical micrograph of the sensing device. Bright regions indicate conducting silicon, insulating silicon dioxide appears dark. The dimensions of the active hallbar in the middle are $240\ \mu\text{m} \times 80\ \mu\text{m}$. The inset shows the complete chip with the sensing area in the middle and the metal contacts at the outer part of the chip. For the electrolyte measurements, a flow chamber was put on top of the chip, limiting the contact of liquids to the active hallbar structure.

was measured between two adjacent contacts. The current was varied to determine the current–voltage characteristics, which were found to be linear. A linear fit was applied, yielding the resistivity of the conducting layer. In order to relate the sheet resistance to the potential at the oxide surface, calibration measurements in a buffer solution with an Ag/AgCl reference electrode were carried out. The surface potential and the voltage of the reference electrode add linearly to the total applied voltage at the oxide/electrolyte interface. Thus, the relation between the square resistance (R_{square}) and the potential of the reference electrode is the same as the relation between surface potential and the square resistance, except for a constant offset originating from the potential drop at the solid/liquid junction of the electrode. Additionally, the dependence of the sheet resistance from an applied backgate voltage V_{bg} was determined, yielding the working point of the device. The backgate voltage with the highest $dR_{\text{square}}/dV_{\text{bg}}$ was chosen to get the highest possible sensitivity.

The surface potential of a solid substrate in contact with an electrolyte solution has been well-studied and is best described by the Grahame equation.^[11] The charge density of the silicon oxide surface depends primarily on the pH value of the electrolyte solution. A variation of the surface charge due to the complexation of alkali ions at the surface will strongly depend on the nature of the oxide. This has been discussed very actively in the literature, and different models have been used to explain the mechanism of surface complexation of alkali ions.^[12,13]

The potential at a surface with a constant charge density is controlled by the salt concentration of the electrolyte solution. Hence, any change in salt concentration will alter the surface potential. In our setup, a specially designed fluid cell allowed the rapid exchange of the solutions at the solid interface by turbulent flow conditions.

As can be seen in Figure 3, changes of the electrolyte concentration were easily detected by the SOI device. The surface charge density of the device was kept constant by controlling the pH (6.4) of the solution tightly. In the example shown, we used KCl solutions, buffered with 10 mM phosphate buffer (PB). The Grahame equation for the dependence of the surface potential on the concentration of a 1:1 electrolyte, such

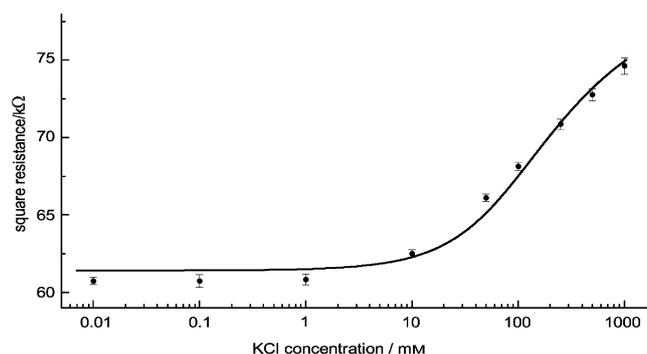


Figure 3. The exchange of the buffer solutions with varying salt concentration (KCl) resulted in variations of the sheet resistance. The experimental data (solid symbols) are in very good agreement with theoretical curve (solid line) after Equation 1, using calibration measurements as described in the text. The error bars were determined by calculating the standard deviation of the sheet resistance over 15 min. The total change in resistance can be related to a change in surface potential of $\Delta\psi = 50\ \text{mV}$ by the calibration measurements. Specific alkali ion adsorption was neglected in the fit.

as KCl, in the presence of an additional amount of divalent ions and the surface charge density σ is given by Equation (1)

$$\sigma = \sqrt{8\epsilon\epsilon_0 kT} \sinh\left(\frac{e\psi_0}{2kT}\right) \sqrt{[n_0] + [d_0] \left(2 + e \frac{e\psi_0}{kT}\right)} \quad (1)$$

where $[n_0]$ is the bulk concentration of monovalent ions, $[d_0]$ is the bulk concentration of the divalent ions far away from the surface, e is the elementary charge, ϵ is the dielectric constant of water, ϵ_0 is the vacuum dielectric constant, k is Boltzmann constant, T is the temperature, and ψ_0 is the potential at the surface. The calibration measurements enabled us to fit the inversion of Equation (1) directly to the experimental data, using only the surface charge density σ and the dissociation of the divalent HPO_4^{2-} buffer ions $[d_0]$ as fit parameters (Figure 3).

The theoretical curve corresponds to a surface charge density of $0.036\ \text{C m}^{-2}$ and a dissociation of the divalent buffer ions of 30%; both are in good agreement with the literature values.^[14,15]

The resistance measured with our device is a superposition of the contributions by the diffuse double layer and is partly due to the specific adsorption of alkali ions. An average response of 10 mV per decade of alkali ion concentration could be incorporated into Equation (1) by a linear term and the data could still be fitted, changing the surface charge density from $0.036\ \text{C m}^{-2}$ to $0.023\ \text{C m}^{-2}$. Our measurements do not enable us to distinguish between the two contributions.

The sensors capability to detect variations of the surface charge density was studied by adding increasing amounts of the positively charged polypeptide poly-L-lysine to the buffer solution. In order to test the sensitivity of the sensor in physiological buffers, an electrolyte concentration of 500 mM was used (10 mM phosphate buffer plus 490 mM KCl). These measurements were done with a sensor that was not overgrown by MBE. The working point was chosen at a backgate voltage of +16 V. This positive bias of the substrate with respect to the electrolyte also reduced the drift of the signal due to diffusion of alkali ions into the oxide.^[16] Figure 4 shows the change in

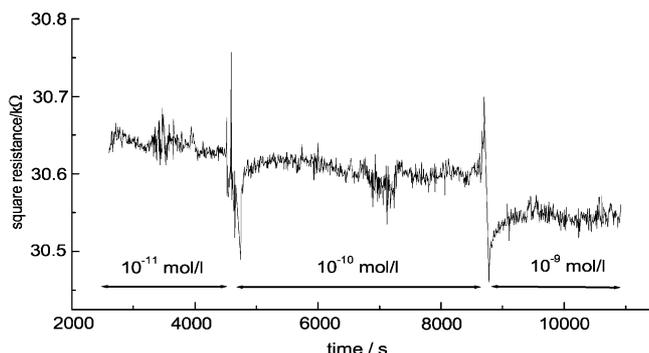


Figure 4. Change of square resistance for different poly-L-lysine concentrations in 490 mM KCl solution buffered with phosphate buffer. For 0.1 nM, no change was recorded, whereas for 1 nM, a clear decrease of the resistance was obtained. A linear drift of the device, which could be caused by the diffusion of ions into the oxide layers, was subtracted.

resistance after exposure to different poly-L-lysine concentrations.

Injection of a solution of 0.1 nM poly-L-lysine into the fluidic chamber was not detectable, whereas a solution of 1 nM poly-L-lysine (80 ng mL⁻¹) resulted in a clear change in the conductance. Additional injection of buffer solution did not alter the measured conductivity, which indicates the stability of the adsorbed poly-L-lysine layer. The calibration measurement can be used to relate the observed jump in resistance of $\Delta R = 100 \Omega$ to a change in the surface potential of $\Delta\psi = 2.2$ mV. Using the Grahame equation, this computes to a charge density of around $0.025 e^- \text{ nm}^{-2}$, neglecting screening effects in the electrolyte solution and assuming that the charge sits directly at the native oxide surface. The typical signal-to-noise ratio would already allow the detection of resistance changes of 50Ω per square or $0.01 e^- \text{ nm}^{-2}$. Using a rough estimate of an average diameter of 3–5 nm for a typical biomolecule such as a protein, this would mean that the SOI device is able to detect approximately between 0.3 and 0.8 net charges, in physiological solutions, per molecule. When used as a sensor for specific molecular bindings, a passivation of the interface with linker molecules will be necessary. This biofunctionalization will help to reduce the drift of the signal and will also eliminate the sensor response towards the ion concentration of the electrolyte.

In conclusion, we have shown that an SOI device can be used to detect changes of the surface potential caused by changes in the electrolyte concentration and also to detect changes in the surface charge density. The high surface sensitivity of the device can be attributed to the surface near quasi-two-dimensional electron gas (2DEG) of the SOI. The ability to detect an average charge variation of $1 e^-$ per 100 nm^{-2} is promising for the detection of specific interactions of charged molecules such as DNA or proteins in future experiments. Standard SOI technology allows the structuring of the sensitive area; this can not only be used to decrease the sensitive area but also to parallelize the detection scheme. The former and the high sensitivity could enable the detection of single molecules, the latter will result in applicability to biomedical research.

Acknowledgements

The authors thank E. Sackmann for many fruitful discussions and continuous support. The MBE regrowth of the SOI substrates by K. Brunner and H. Riedl is gratefully acknowledged. We also thank V. Lehmann for many discussions. The support of the Fonds der Chemie and the Leonhard Lorenz Stiftung is gratefully acknowledged. The project was supported in part by the Deutsche Forschungsgemeinschaft (SFB563, B1) and by Fujitsu Labs Europe. M.G.N. was supported by the "Studienstiftung des deutschen Volkes".

Keywords: Grahame equation · interfaces · lysine · sensors · silicon-on-insulator substrates · surface potentials

- [1] International Human Genome Sequencing Consortium, *Nature* **2001**, *409*, 860–921.
- [2] P. A. Fodor, *Science* **1997**, *277*, 393–395.
- [3] J. Wang, *Nucleic Acids Res.* **2000**, *28*, 3011–3016.
- [4] E. B. Cooper, J. Fritz, G. Wiegand, P. Wagner, S. R. Manalis, *Appl. Phys. Lett.* **2001**, *79*, 3875–3877.
- [5] Y. Cui, Q. Wei, H. Park, C. M. Lieber, *Science* **2001**, *293*, 1289–1292.
- [6] P. Bergveld, *Sens. Actuators B* **2003**, *88*, 1–20.
- [7] A. Offenhäuser, W. Knoll, *Trends Biotechnol.* **2001**, *19*, 62–66.
- [8] G. Zeck, P. Fromherz, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 10457–10462.
- [9] J. Fritz, E. B. Cooper, S. Gaudet, P. K. Sorger, S. R. Manalis, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 14142–14146.
- [10] M. J. Schöning, H. Lüth, *Phys. Stat. Sol. A* **2001**, *185*, 65–77.
- [11] J. N. Israelchvili, *Intermolecular and Surface forces*, **1985**, Academic Press, London.
- [12] L. Bousse, N. F. De Rooij, P. Bergveld, *Surf. Sci.* **1983**, *135*, 479–496.
- [13] K. F. Hayes, G. Redden, W. Ela, J. O. Leckie, *J. Coll. Int. Sci.*, **1991**, *142*, 448–469.
- [14] J. Sonnefeld, M. Löbbus, W. Vogelsberger, *Colloids Sur.* **2001**, *195*, 215–225.
- [15] P. Atkins, J. De Paula, *Physical Chemistry*, 7th ed., **2002**, Oxford University Press, Oxford.
- [16] M. Rentschler, P. Fromherz, *Langmuir* **1998**, *14*, 547–551.

Received: April 14, 2003 [Z 785]