Sensing glucose concentrations at GHz frequencies with a fully embedded Biomicro-electromechanical system (BioMEMS)

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The progressive scaling in semiconductor technology allows for advanced miniaturization of intelligent systems like implantable biosensors for low-molecular weight analytes. A most relevant application would be the monitoring of glucose in diabetic patients, since no commercial solution is available yet for the continuous and drift-free monitoring of blood sugar levels. We report on a biosensor chip that operates via the binding competition of glucose and dextran to concanavalin A. The sensor is prepared as a fully embedded micro-electromechanical system and operates at GHz frequencies. Glucose concentrations derive from the assay viscosity as determined by the deflection of a 50 nm TiN actuator beam excited by quasi-electrostatic attraction. The GHz detection scheme does not rely on the resonant oscillation of the actuator and safely operates in fluidic environments. This property favorably combines with additional characteristics—(i) measurement times of less than a second, (ii) usage of biocompatible TiN for bio-milieu exposed parts, and (iii) small volume of less than 1 mm³—to qualify the sensor chip as key component in a continuous glucose monitor for the interstitial tissue. © 2013 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution 3.0 Unported License. [<http://dx.doi.org/10.1063/1.4811351>]

I. INTRODUCTION

Microelectronics is increasingly recognized as a unique technology platform for biomedical devices due to its functional performance on the meso- and nanoscale, at the dimensions of which most physiological processes are operative. Applications appear promising in the field of intelligent biosensors, where it enables the monolithic integration of sensing devices with intelligent functions like detection, signal analysis, electrical stimulation, data transmission, etc., in a single microchip.^{1–3} In particular, low-cost implants for monitoring metabolites in the human body are strongly requested by medical diagnostics, with D-glucose representing the most important one. According to WHO, about 346×10^6 patients worldwide suffer from diabetes,⁴ i.e., are subjected to persistent deviations from glucose concentrations c_g that normally should lie between 3.6 and 6.1 mM. Practically, all commercially available sensors operate by enzymatic principles, where glucose is converted to gluconic acid and H₂O₂ and the detection of the latter is performed electrochemically. The technique has reached the highest degree of maturity among all biosensors in form of test-strips.⁵ It operates reliably, however, only outside the body, since the growth of body tissue on an implant affects the influx of reactants and typically causes a drift of $c_g(t)$ transients.

It has recently been succeeded to control the drift by measuring glucose and O₂ concomitantly and correcting the

first signal with the latter.⁶ Another approach is offered by affinity assays^{7,8} that make use of the reversible affinity binding between the analyte and a receptor and for which drift-free glucose monitoring has been demonstrated.⁹ Their function does not rely on the chemical reaction of glucose, but exploits its reversible binding to a receptor. Affinity assays may exhibit an unrivaled specificity since the molecular recognition is performed by a receptor evolutionary adapted to the analyte. The plant lectin concanavalin A (ConA, 237 amino acids, 26.5 kDa) turned out to be well suited, if the binding to glucose competes with that to a polysaccharide like dextran or sephadex.¹⁰

In previous affinity sensors, the binding of ConA to glucose has been transformed into variations of light intensity.^{7,11–13} However, other spectral ranges of electromagnetic radiation may equally apply, when physical constraints are obeyed like minimization of ionic drift and absorption. An interesting alternative is offered by GHz frequencies. The latter became accessible to the dominating CMOS (complementary metal-oxide-semiconductor) technology since the late 1990s in accordance with Dennard's scaling rules¹⁴ or—from a more general perspective—Moore's law,¹⁵ when first MOSFETs in the GHz range were introduced.¹⁶ The dielectric constant $\epsilon(\omega)$ of aqueous protein solutions exhibits an absorption minimum in the few GHz range, which is limited at low frequencies by the absorption of proteins (maximum at some 100 MHz) and at high frequencies by the absorption of water (maximum near 17 GHz for 37 °C).¹⁷ Also the drift of solved ions is small in this frequency range since ionic mobilities in water (on the order of $10^{-8} \text{ m}^2 \text{ V}^{-1} \text{ s}^{-1} = 10 \text{ nm}^2 \text{ GHz V}^{-1}$ (Ref. 18)) allow

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for nanometer-sized oscillations only, instead of screening electrical fields as observed at lower frequencies.¹⁹ Here, we present, to the best knowledge of the authors, the first micro-electromechanical system (MEMS)-based affinity assay operating with GHz frequencies for continuous glucose monitoring. It will be shown that the fundamental problem of mechanical biosensors to operate in fluid environments is conveniently solved by the approach.

II. BIOMEMS FOR GHz FREQUENCIES

The sensing concept examined in this work is schematically shown in Figure 1. A cavity filled with sensoric fluid containing ConA and dextran is used for this purpose. The cavity is separated from the tissue by a semipermeable membrane (not shown), the cut-off of which allows for the passage of glucose, but not of macromolecules. ConA molecules with one saccharide binding site per monomer configure into tetramers at physiological pH values²⁰ yielding a cross-linking between macromolecules into a highly viscous gel-like phase. Dextran is partially displaced from the active ConA sites upon adding glucose, which translates into a change of viscosity η . Depending on glucose concentration, the viscosity may vary between 1–100 mPa·s for appropriate concentrations of ConA and dextran.²¹ The fundamental approach for determining $\eta(c_g)$ is based on moving an actuator in the sensoric fluid and measuring its velocity. The figure shows a single clamped actuator beam that is subjected to a deflection z_{max} at its free end, which is caused by electrically charging the beam and attracting it to the ground plate.

The fundamental problem of CMOS applications in implantable biosensors relates to the interface design that couples the assay to the integrated circuit.^{22–24} The problem was solved here by implementing the electrodes from titanium nitride. TiN is a well-established material in semiconductor technology for suppressing diffusion and improving electrical contacts. Most advantageous is the high stability of TiN against bio-corrosion.^{25–27} Only recently, it has been shown that suspended TiN beams can be prepared from the back-end-of-line (BEoL) stack and may not only apply for the preparation of actuators in nanoelectromechanical systems (NEMS).^{28,29} Instead, also the compensation of residual stress gradients has been succeeded allowing for the fabrication of microelectromechanical systems with TiN actuators.³⁰

Due to the large Young's modulus of TiN of about 500 GPa,³¹ the actuator beam has to be prepared with a

FIG. 1. MEMS concept and schematic operation: a cavity is filled with macromolecular receptors (small red spheres) and polymeric ligands (blue spheres) exhibiting a high viscosity. Insertion of monomeric analyte causes a partial unbinding of macromolecules and the viscosity to decrease. A clamped beam is electrostatically attracted to the ground plate, from the velocity of which the viscosity and analyte concentration derives.

FIG. 2. (a) Scanning electron micrographs of (unfilled) MEMS with bendable beam in form of an X-shaped actuator. (b) The elastic spring in the middle of the sensor MEMS is implemented as double-U. (c) The beam is close and connected for the reference MEMS. Thighs of the spring are bent upward due to residual stress gradients within the TiN layer.

thickness of only 50 nm, when sufficiently large deflections shall be achieved by a voltage of 3.5 V obtainable in 0.25 μ m CMOS circuits.³⁰ Figure 2 displays a SEM picture of the BioMEMS prepared with SiO₂ side walls, while the upper surface is covered by a 400 nm passivation of siliconoxynitride. In contrast to the conceptual sketch shown in Figure 1, the actuator was realized as an X-shaped four-fold clamped beam. Viscosity can be measured with signals from two cavities that differ by using a bendable and a locked actuator. The elastic element is formed by an open double U in the first case, which is close and connected in the latter one.

During a single measurement, the deflection of the beam is registered through a capacitance change ΔC that is translated into a frequency variation Δf . For this purpose, the sensor and reference MEMS are each electronically integrated in a ring oscillator circuit (ROC), see Figure 3. It is composed of an uneven number of inverters, i.e., three in the case considered here, each of which is constituted from a *p*- and

FIG. 3. Equivalent circuit of the affinity BioMEMS: the supplied DC voltage pulse V_{dd} is converted to HF by two ring oscillator circuits composed of inverters I_1, I_3 . The actuator-ground-plate configurations act as capacitances with parallel and serial resistances (shaded areas). In the conductive body fluid, they are accounted for by resistive and capacitive parts (described by σ and ϵ) that both vary during the movement of the beam (R_b). Sensing and reference circuit are symmetric except for C'_1 that may externally be adjusted in the reference circuit by V_{ctrl} .

n -channel MOSFET. The ROC frequency f_0 is determined by the time constants for recharging the channel capacitance of the constituting MOSFETs and thus by their dimensions and design parameters.³² Both MEMS are given by R and C components in an equivalent circuit with their capacitances deriving from the fluid dielectric constant $\epsilon_0\epsilon_r$ and the geometry of the beam-ground-plate configuration that can be approximated by a parallel plate capacitor $C = \epsilon_0\epsilon_r A/d$.

The basic idea for the measurement is that the ROC frequency f_0 is varied through the capacitance change $\Delta C = \epsilon_0\epsilon_r A/\Delta d$ caused by the deflection Δd of the actuator beam. For the configuration depicted in Figure 2, for instance, the capacitance C starts from 770 fF as calculated for water and $\epsilon_r = 70$ for the undeflected actuator to increasingly higher values the closer the beam approaches the ground plate. Depending on viscosity η of the surrounding medium, it takes the time t_{sw} until the beam reaches a defined position z_{max} . The quantity t_{sw} thus inversely scales with viscosity η . Channel lengths L and widths W of the MOSFETs are devised such that a ROC frequency of $f_0 = 3.2$ GHz is obtained. That is the frequency, by which the voltage supplied to the actuator beams is oscillating, while the ground plate is subjected to a DC voltage $V_{dd}/2$, see Figure 4(a). A word on nomenclature should be added: the chip comprises actuatoric (TiN beam) and sensoric elements (ROC with beam-groundplate-capacitance and phase-frequency-detector (PFD)) that it may equally be denoted as transducer; in order to be specific, however, the

FIG. 4. (a) During operation, the high-frequency oscillating voltages of the ROCs appear like an average or effective voltage V_{eff} attracting the beam to the ground plate. (b) Frequency transients after switching on V_{dd} . The deflection of the actuator beam decreases the beam-ground-plate capacitance causing the frequency $f_s(t)$ in the sensor ROC to increase, while $f_r(t)$ remains constant, since the rigid actuator cannot bend. Viscosity η derives from the time t_{sw} it takes for the sensing actuator to reach its final position adjusted by V_{ctrl} .

TiN beam and the full chip are denoted in this work as actuator and sensor chip, respectively.

It has to be emphasized that the actuator is not mechanically oscillating with GHz frequencies. Rather its resonance frequency defined by beam geometry and material would fall in the few 10 MHz range. In contrast to other mechanical biosensors,^{33,34} the beam deflection here operates in the regime of aperiodic damping. It may thus be avoided to take out the BioMEMS from the analyte-containing liquid in order to raise sensor sensitivity as required in other devices.^{35,36} Instead of being impaired by viscous damping, the sensor transforms damping into the sought viscosity signal. The effect relies on the high frequency voltage supplied to the actuator, which appears as quasi-static force to the mechanical system. A voltage supply of $V_{dd} = 3$ V, for instance, results in a quasi-static voltage V_{eff} of 0.8 V, by which the actuator is attracted to the ground plate. Switching on the power supply thus induces a beam bending and, simultaneously, the frequency in the sensor MEMS circuit increases, $df_s(t)/dt > 0$. Frequency remains constant, however, in the reference ROC. Figure 4(b) schematically shows the transients in both circuits, where $f_s(t)$ is seen to vary until attaining the level of f_r . At this point, the voltage supply is switched off and this time represents the switching time t_{sw} .

Utilization of the reference MEMS has the advantage that variable effects upon the fluid state like unsteady electrolyte concentrations can be compensated to a large extent. The comparison of frequencies in the measuring and the reference circuit is performed in a PFD³² causing the V_{dd} supply to be blocked by a logic gate for $f_s = f_r$. Both frequencies are inserted into three frequency dividers before they reach the phase-frequency-detector (PDF) leading to an 8-fold reduction of 3.2 GHz frequencies into the 400 MHz range. The precise value of the reference frequency f_r may be adjusted via an external voltage V_{ctrl} in order to deal with fabrication scatter of the many different sensor chips prepared on a full wafer. V_{ctrl} drives a variable capacitance C_1' , which operates in parallel to the reference MEMS such that f_r may be adjusted on every sensor chip individually. The full transformation cascade of the sensor signal is depicted in Figure 5(a).

The viscosity of biomolecular solutions exhibit pronounced temperature dependencies, which has been investigated in detail for ConA-dextran mixtures.^{21,37} Although, temperature is regulated rather constant in the human body, it appeared useful to measure it in addition to viscosity in order to correct for possible variations. A temperature sensor operating as a band gap reference³⁸ was thus included.

Unconventionally, sensor cavity and actuator were prepared from the BEoL stack, in which AlCu layers are sandwiched between Ti/TiN layers. The preparation was performed with a cost effective SGB25V technology.³⁹ The ground plate of the cavity was formed by the lowest metal layer M1, while the actuator was prepared from metal 3 (M3) causing a vertical distance between both of 2.5 μ m. BioMEMS with X-, Y-, and I- shaped actuators were prepared.³⁰ Additionally, deposition of the thin bottom TiN layer was thoroughly optimized, in order to adjust the residual stress gradients as they are usually introduced during thin film growth (see Appendix).⁴⁰ Figure 5(b) displays the

FIG. 5. (a) Sensor transformation cascade: The analyte concentration c_g determines the viscosity η , which transforms in beam deflection $z(t)$ associated with capacitance $C(t)$ and frequency tuning $f(t)$ in the ROC; frequency equality in both circuits finally switches off the voltage after t_{sw} . (b) Optical micrograph of the sensor chip showing MEMS cavities, ROCs, frequency dividers, PFD, and octagon-shaped bond pads.

BioMEMS chip containing the components mentioned and having a footprint of 1.3×0.36 mm only.

III. MODELING OF CRITICAL PARAMETERS

Finite-element simulations were applied for estimating critical parameters and spatial field distributions in the MEMS cavity during operation. Figure 6(a) displays the electrical fields in the vicinity of an X-shaped beam for $V_{eff} = 0.8$ V. The surrounding medium has been modeled by normal saline at 37 °C.⁴¹ Moreover, thermal constants of pure water were applied that differ only little from those of saline.⁴² It can be recognized that the field reaches maximum values close to 3.2×10^5 V m⁻¹. Field amplitudes will even increase upon beam deflection, yielding values close to 10^6 V m⁻¹ for $z_{max} = 1$ μm, for instance. Also electrical current densities were determined and found to attain maxima on

FIG. 6. Finite element simulations for a quarter of reference MEMS cavity with an undeflected beam at $V_{eff} = 0.8$ V. (a) The electric fields attain maximum values of some 10^5 V m⁻¹, but are generally smaller due to electrical currents flowing from the beam to the ground plate. (b) Temperature distribution in isotonic saline. Ideal heat conduction via TiN ground plate and SiO₂ cavity walls are assumed by fixing them to 37 °C.

the order of 10^6 A m⁻². An important goal of our work was therefore to investigate whether the macromolecules would suffer an activity loss or tolerate the high field strengths and current densities.

In addition, Figure 6(b) displays the stationary temperature distribution that is formed within a few ms after switching on. The heating is mainly caused by Ohmic losses of the current through the TiN beam and the liquid, but is also due to dielectric losses within the latter. It may be recognized that the maximum temperature arises close to the beam anchor points and attains 13 °C at most, but is significantly smaller in the rest of the volume (see Appendix). Investigations addressing the stability of ConA were also performed within this work showing that lectin-dextran mixtures retained their activity when stored for several days at 60 °C. It was thus not assumed that the heating temperatures would cause a decline of ConA activity. We had to consider, however, how the temperature dependence of viscosity would affect the measurement precision. In order to ensure moderate operation temperatures, the sensor chip was hooked to a cooling body of some mm³ volume to sufficiently dilute the heat produced during one measurement cycle.

IV. PERFORMANCE OF THE BIOMEMS

Investigations of *in vitro* operation of the sensor chips were performed by immersing them in different test liquids. For this purpose, test chips with additional probes into the microelectronic circuit were also fabricated (see Appendix). The additional contacts allowed for monitoring frequencies f_s and f_r after frequency division and before entering the PFD; moreover, the test chip circuit caused no switching-off of V_{dd} , when $f_s = f_r$. Figure 7(a) displays the concomitant monitoring of beam deflection and frequency change for the BioMEMS flooded with normal saline that was monitored by a laser Doppler vibrometer.³⁰ For beam deflections up to about 2 μm, the frequency in the measurement circuit is seen to steadily increase.

In addition, frequency transients of both $f_s(t)$ and $f_r(t)$ could simultaneously be measured in this set-up and are

FIG. 7. Measurement results from viscosimeter chips in liquids. (a) Deflection and reference frequency vary upon applying V_{dd} to the MEMS device. (b) Frequency transients $f(t)$ as taken with a test structure, in which $f_s = f_r$ did not cause V_{dd} to be switched off. Transients are shown after signals passed the frequency dividers.

given in Figure 7(b). It can clearly be seen that the signals follow the expected course as given in Figure 4(b): while the frequency remains nearly unchanged in the reference circuit, it continuously increases in the sensing circuit, because the bending of the beam and the capacitance continuously increase too. All variations are observed to occur on a time scale of ms, which is determined by the viscosity of water or normal saline used here. Both frequencies f_s and f_r coincide at about 1.9 ms and follow the same trend for about 1 ms, where they diverge again. The non-punctual equality is understood from the crosstalk on the microchip, which causes both frequencies to collapse on approaching. The frequencies diverge again for too large a difference, which occurs at about 3.1 ms. The first coincidence was set as the switching point, at the time t_{sw} of which the beam has attained its final position and V_{dd} is switched off.

Verification of sensor chip functionality was performed by immersing them in sensoric liquid containing ConA, dextran, and glucose as shown in Figure 8(a) by measured t_{sw} data. Switching times were found in the 70–150 ms range, which is significantly higher than in normal saline due to the higher viscosities of sensoric liquids. Time constants

associated with the sensor transfer to another solution are seen from the figure to lie in the range of minutes. These values are caused by the comparatively large measuring volumes of about 1 ml and the small effective diffusion coefficient of glucose in the sensoric liquid due to repeated formation and dissociation of affinity bonds to ConA tetramers. Time constants will substantially diminish in a glucose sensor system, in which the sensoric liquid is confined to a much smaller volume and separated from the tissue by a semipermeable membrane. It can also be seen from Figure 8(a) that data points exhibit a large spreading for different glucose concentrations showing also an excellent signal-to-noise ratio. For selected sensor chips, measurements were performed over weeks showing constant signal outputs and no activity drop of ConA. The reproducibility of a certain t_{sw} value was on the order of a few % for constant c_g and temperature T . This represents a remarkably high precision, since the active volume beneath the MEMS actuator encompasses a volume of about 5.4 pL and the number of participating macromolecules is on the order of a few 10^9 only.

V. DISCUSSION AND CONCLUSIONS

It is evident from the data that a temperature calibration is required for practical applications of the sensor chip. For this purpose, data as measured in Figure 8(a) were plotted in a (c_g, t_{sw}) diagram, see Figure 8(b). The $t_{sw}(c_g)$ functions for $T = 30, 35$, and 40°C are seen to follow the model function

$$t_{sw} = k_1 \exp(-c_g/k_2) + k_3 \quad (1)$$

with high precision. In this equation, k_3 stands for the switching time for infinite c_g , when all active ConA sites are saturated with glucose and the viscosity is essentially determined by the shape of ConA tetramers and dextran molecules. For vanishing glucose concentrations, on the other hand, the viscosity is governed by maximally cross linked macromolecules described by coefficients $k_1 + k_3$.

The set of coefficients k_i , $i = 1, 3$, are given in Table I together with their estimated standard deviations derived from non-linear data regressions. Also the fitting coefficients describing their temperature dependence are listed. Whereas k_1 and k_2 were precisely accounted for by linear regressions, $k_i = k_{i0} + k_{i1}T$, the coefficient k_3 could be described by an Andrade form of temperature-dependence, $k_3 = k_{30} \exp(k_{31}/T) + k_{32}$, in accordance with results on other bio-macromolecules.^{43,44} It can be concluded that the monitoring of glucose requires a preceding determination of coefficients $k_i(T)$, in the temperature range of interest. With their knowledge, glucose levels are derived by converting to $c_g = k_2 \ln(k_1/(t_{sw} - k_3))$ for any measured (T, t_{sw}) data pair.

Measurement errors then derive from the estimated standard deviations of coefficients k_{ij} , which also holds for employing the sensor chip as a microviscosimeter. Generally, the precision of viscosity measurements is decisively determined from the precision, by which the temperature of the fluid can be controlled. The main advantage of the device presented here for the determination of viscosity is due to the small volume that becomes accessible and which is less than two

FIG. 8. Switching times t_{sw} (a) as measured with a sensor chip immersed in sensoric liquids of varying c_g and T and (b) as a function of both parameters allowing for sensor calibration and determination of c_g from measured t_{sw} and T data.

TABLE I. Sensor calibration coefficients were derived for the particular sensor system yielding the results shown in Figure 4(d). (Top) $k_i(T)$ for 30, 35, and 40 °C. (Bottom) k_{i0} and k_{i1} for $k_i = k_{i0} + k_{i1} \cdot T$, for $i = 1, 2$, as well as k_{30} , k_{31} and k_{32} for the expansion $k_3 = k_{30} \exp(k_{31}/T) + k_{32}$. Numbers in parenthesis give the standard deviation of the last significant digit.

$T / ^\circ\text{C}$	k_1	k_2	k_3
30	88.2 ms	3.58 mM	97.7 ms
35	67.0 ms	3.94 mM	85.9 ms
40	47.5 ms	4.31 mM	78.5 ms
k_{ij}	k_{ij}	k_{2j}	k_{3j}
k_{i0}	210(3) ms	1.39(2) mM	1875 ms
k_{i1}	-4.1(1) ms/°C	0.073(1) mM/°C	6.94 °C
k_{i2}	...	...	73.1 ms

orders of magnitude lower than in conventional mechanical viscosimeters.

Before applying the sensor MEMS in a medical implant, however, one has to consider its biocompatibility. For this purpose, the stability of sensor chips in biomilieu has been investigated under *in vitro* and *in vivo* conditions in a recent study.²⁷ The highest degradation of all exposed layers was found in human tissue for the SiON passivation to amount to 50 nm per month. This would allow an operational life time of several months, but additional measures may be taken to improve the biostability like compacting and thickening the passivation or covering it by more biocompatible layers.

Next to the sensor chip, the components of a perspective sensor implant based on the presented BioMEMS chip would furthermore encompass a microcontroller, a battery, an antenna, and a radio module.⁴⁵ Moreover, the biochemical assay has to be separated from the body fluid by a semi-permeable membrane as has already been demonstrated for a minimally invasive sensor system.⁴⁶ Based on the power consumption of the sensor chip, $I \approx 0.35$ mA at 3 V and $\langle t_{sw} \rangle_{av} \approx 150$ ms, a charge capacity of 0.4 mAh can be calculated to be required, when 300 measurements should be performed per day or one every 5 min. This capacity may be delivered by Li-MnO₂ batteries achieving energy densities in the 1 Wh cm⁻³ range⁴⁷ and which are technically well established for use in cardiac pacemakers. A battery capacity of 100 mAh having a volume of 0.3 cm³ would suffice to provide the energy for a safe sensor operation over several months.⁴⁸ An implant with outer dimensions in the cm range may thus be fabricated on the basis of the sensor chip introduced here. This would enable a large progress in diabetes diagnostic and therapy, if the functionality demonstrated in the laboratory can be transferred to *in vivo* operation.

It should be emphasized that the BioMEMS operation has not only been demonstrated in a proof-of-principle laboratory set-up; rather operability was shown for some 100 devices during the last two years. This became possible due to device preparation with established semiconductor technology. This fact also represents an important presupposition for future low-cost mass production of the presented sensor chips.

Summarizing, a glucose BioMEMS microchip has been presented demonstrating the solution of various problems of *in vivo* biosensors: first, the operation of an affinity assay in the so far unexploited GHz frequency range was shown, paving the

way to continuous data monitoring in fluidic environments. In addition, the stability of the bio-interface was provided by preparing actuators from corrosion-resistant TiN of the backend-of-line stack in a CMOS/BiCMOS technology. The fully embedded BioMEMS was successfully shown to continuously monitor glucose concentrations by affinity viscosimetry. Sensor chips operated for weeks *in vitro* without deactivating the lectin, although the latter was subjected to electrical fields and current densities on the order of 10⁵ V m⁻¹ and 10⁶ A m⁻². The example convincingly demonstrates the potentials of bio-electronic systems for medical applications, in which the functionalities of biomolecules and microelectronics synergistically combine.

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APPENDIX: EXPERIMENTAL DETAILS

1. Preparation of sensor chips

Microelectronic circuits with fully embedded BioMEMS were fabricated in the certified CMOS/BiCMOS pilot line of IHP in the framework of multi project wafer (MPW) shuttles that are run on a regular basis for in- and external customers (<http://www.ihp-ffo.de/en/services>). 200 mm CZ Si wafer with a thickness of 750 μm and 0.5 Ωm resistivity served as starting material. The preparation was performed with a cost effective SGB25V technology, exhibiting a 4-level metallisation (Al0.5wt%Cu), 0.25 μm half pitch and encompassing 22 lithographic masks and about 500 process steps that were executed within 2½ months. Two modifications of backend processes were required to integrate the micromechanical part in the standard flow:

- (1) In the actuator region, which is exposed during operation to the sensoric liquid, the top TiN and AlCu of the M3 stack was removed, in order to circumvent AlCu corrosion by the high concentration of electrolyte in the human body.
- (2) A special wet-etching process with high selectivity to TiN was developed to open the cavity of the microsystem in the insulator stack down to the M1 ground plate.

In order to prevent static friction (stiction) of the actuator to the ground plate, the last etch step was followed by a critical point drying process using supercritical CO₂ (Tousimis Research, USA).

Octagon-shaped bond pads (80 μm width) were used for electrically contacting the chip. On one hand, sensor chips S3 with three bond pads for supply voltage V_{dd} , control voltage V_{ctrl} , and Ground were prepared. On the other hand, test circuits T8 with additional bond pads for circuit diagnostics were fabricated.

The bandgap reference circuit for temperature measurements was built up from CMOS bipolar transistors that converted the temperature interval 0–100 °C into an electrical current I_T from 136 to 195 μA and exhibiting a foot print of $90 \times 30 \mu\text{m}^2$.

2. Finite element simulations

Finite element simulations were carried out with a commercial software package (COMSOL MULTIPHYSICS). The thickness of the actuator and its height above the ground plate were set to 50 nm and 2.5 μm, respectively, in accordance with the geometrical layout. The cavity was assumed to extend further 10 μm above the actuator. Calculations could be restricted to the asymmetric unit of the cavity of $30 \times 75 \mu\text{m}$ by exploiting the two perpendicular mirror planes of the full BioMEMS ($60 \times 150 \mu\text{m}$). Neither beam deflections nor geometrical details of the actuator like slits and spring opening were considered in order to constrain the model to its main physical features. The number of tetrahedral elements and degrees of freedom could then be limited to the order of some 10^4 .

A conductivity of $1.18 \times 10^6 \text{ S m}^{-1}$ was assumed for the actuator that derived from the sheet resistance of $17 \Omega \text{ sq}^{-1}$ as determined for the TiN layer. The effective medium in the cavity was modeled by salt water of T of 37 °C and salinity S of 0.9 wt. %. For the dielectric function $\varepsilon = \varepsilon' - i\varepsilon''$ and the complex conductivity $\sigma = \omega\varepsilon_0\varepsilon''$ (ε_0 permittivity of vacuum), however, the data for saline with $S = 0.9$ had to be applied.

The basic approach followed here was that the complex high-frequency operation with $\omega = 2\pi f$ and $f = 3.2 \text{ GHz}$ could reliably be modeled by assuming an effective DC voltage $V_{eff} = 0.8 \text{ V}$ to act between beam and ground plate. Comsol modules emdc and htgh then applied for stationary simulations of the electrical field $E(x)$ and temperature distribution $T(x)$ by inserting appropriate material constants. The actually active high frequency was considered by setting the values $\varepsilon(\omega) = 71.1 - i19.1$ as valid at $f = 3.2 \text{ GHz}$, $T = 37 \text{ °C}$, and $S = 0.9\%$ for the medium's dielectric constant, yielding an effective conductivity of $\sigma = (\sigma'^2 + \sigma''^2)^{1/2} = 13.1 \text{ S m}^{-1}$. Field distributions $E(x)$ and derived quantities as current densities were determined under these constraints compare Figure 6(a). Temperature distributions $T(x)$ were simulated by confining the walls of the cavity to 37 °C. The dielectric heating was obtained from $P = \omega\varepsilon_0\varepsilon''|E|^2$ in all cavity volumes containing saline, see Figure 6(b).

The results obtained for the stationary state will remain basically unchanged when switching to a transient modeling of the system. An increased E field will, of course, be

obtained for the deflected beam: the highest values will occur for some ms in the middle of the beam shortly before switching off V_{dd} , where z_{max} values close to $1 \mu\text{m}$ may lead to electrical field amplitudes close to 10^6 V m^{-1} . Also the simulated temperature distribution will not change fundamentally with beam deflection: only the transition from T_{max} to $T = 37 \text{ °C}$ at the ground plate becomes steeper causing an increase of the temperature gradient, but not of the maximum temperature within the medium.

3. Testing solutions

Fluids of different viscosity were prepared for electrical tests of the sensor chips. Starting point was a standard electrolyte solution that was prepared on the basis of normal saline (140 mmol/l NaCl) by adding CaCl₂ (1 mmol/l), MnSO₄ (1 mmol/l, all from Roth GmbH), 0.1 wt. % NaN₃ and buffering with Tris-HCl to pH = 7.4. Sensoric liquid was prepared by the addition of dextran (7 wt. %, T2000), concanavalin A (0.7 wt. %, type IV), and α -D-glucose (96%, all from Sigma-Aldrich) of different concentrations c_g (0, 2, 4, 6, 8, 10, 15, and 20 mmol/l). Generally, deionised water ($\rho \geq 18 \text{ M}\Omega \text{ cm}^{-1}$) was used.

4. Electrical characterization

Measurements were either performed with full wafers or fragments from cutting a wafer to some cm² large pieces. Bond pads were contacted with microwave testing probes (Picoprobe by GGB Industries) of a manual 200 mm prober system (Wentworth Labs) in the first case and through Al wire bonding ($\phi 50 \mu\text{m}$) in the latter. Fluids were measured in a “test-tube-on-a-chip” configuration by gluing glass cylinders ($\phi_o 5, \phi_i 4$, height 5 mm) to the wafer surface such that MEMS structures were flooded while the bond pads remained outside and had no contact with the fluid. Frequency transients of T8 test structures were measured with this set-up by introducing the signals of sensor and reference MEMS after frequency division into a 7 GHz signal source analyzer (Aegilent E5052B).

In addition, sensor chips were connected to a flex cable (PI with Cu wires) by flip chip bonding with Au stud bumps being embedded in a non-conductive adhesive. Sensor chips could then be safely immersed into test solutions without subjecting voltage-carrying parts to corrosion by the electrolyte. Switching times were determined in this configuration by subjecting the chip to V_{dd} voltage pulses and reading t_{sw} from an oscilloscope.

Moreover, a dedicated system board was developed for tests of the implantable system and used here, where V_{dd} pulses are regularly applied to the sensor chip. The board is equipped with a programmable microcontroller (Texas Instruments 16 bit MSP430) and a commercial front end chip (Zarlink ZL70321) operating in the 403 MHz band approved for the medical implant communication standard (MICS). The data given in Figure 8(a) were measured by immersing an S3 sensor chip with a single band actuator (I shape) in thermostatically controlled (Labnet) testing tubes containing about 1 ml sensoric liquid.

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