System integration of a silicone-encapsulated glucose monitor implant

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Abstract

An intelligent sensor implant for continuous glucose monitoring is presented as intended for use in the human interstitial. The sensor operates by the principle of affinity viscosimetry, by which glucose concentrations are determined with a microelectromechanical system (MEMS) measuring the glucose-dependent viscosity of a concanavalinA-dextran assay. Data transmission is performed in the 403MHz band as approved for medical implant communication services (MICS). The sensor system is encapsulated in silicone to enable a sufficient hermiticity for time spans of weeks and months. *In vitro* testing revealed no corrosion of system components for a period of months.

1 Introduction

The number of patients suffering from *Diabetes mellitus* is continuously increasing worldwide and in particular in the industrialized countries [1]. The enhanced blood glucose level causes a number of secondary diseases that may impose severe health impairments and loss of live quality. Next to hyperglycemia also hypoglycemia is considered as threatening by insulin-applying patients. It may be caused by too high insulin doses and is associated with states of unconsciousness. Hyperglycemic states thus often tolerated – with consequences as mentioned above.

Today, the monitoring of blood sugar levels is mainly performed by test stripes that allow the amperometric determination of glucose concentrations c_g by the enzymatic reaction of glucose to gluconolacton and H_2O_2 [2]. Measurements, however, are performed with insufficient frequencies because of the required self-injury.

A more advantageous method would be a continuously measuring sensor implant that determines c_g in regular intervals and that would transmit glucose concentration transients $c_g(t)$ to an extracorporeal receiver like a mobile phone. The interstitial tissue is generally considered as an appropriate position for such perspective implants, since c_g values are observed to correlate with those in blood [3].

Next to the sensing element, a biosensor implant has to encompass a radio module and antenna for data transmission as well as a microcontroller (µC) for regulating the measurement program, data transmission and data storage. In addition, energy has to be supplied to the aforementioned components and the system has to be shielded hermetically against body fluid, in particular against the formation of water precipitations on device surfaces.

The large number of laws and prescriptions to be obeyed during the development of implants represent a particular difficulty. Among other aspects, the sterilizability of the system has to be provided, resulting in severe constraints with respect to the integration of temperature- or radiation-sensitive components or with respect to designing the integration flow.

In this work, the components and the technical integration of a biosensor implant that shall allow for the continuous monitoring of blood sugar levels *in vivo* will be presented [4]. It has been endeavored to rely on technical modules already established in implantology whenever possible.

1.1 Glucose sensing by affinity assays

The sensoric principle used in the system was not the enzymatic conversion of glucose by GOd or GDH, but its reversible binding to a chemical receptor, i.e. by using an affinity assay [5, 6]. The approach appears advantageous, since it is independent from oxygen concentration, the diffusion of which will be modulated by the unavoidable body reaction [7]. The covering of the implant in the body environment was often observed to cause erroneous drifts of c_g data.

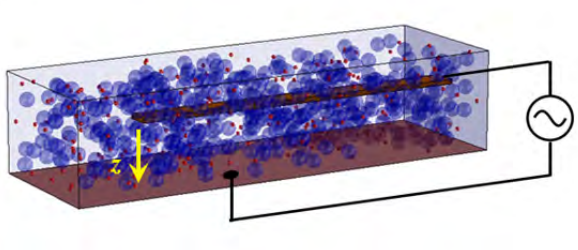

Image 1 Principle of affinity viscosimetry based on a microelectromechanical system (MEMS), see [8].

A viscosimetric variant of affinity assays was applied in the system presented here, i.e. variable glucose concentrations c_g are transformed into variations of viscosity η. For this purpose, the competing binding reaction of glucose and its polymer dextran to the plant lectin Concanavalin A (ConA, 26.5 kDa, 237 amino acids [9]) is exploited.

Under physiological pH conditions ConA forms tetramers with four binding sites for glycosyl residues that may cause a high viscosity in ConA-dextran mixtures due to a high degree of cross linking between macromolecules [6].

The viscosity is lowered by the presence of free glucose causing a de-linking of the macromolecular network by also occupying the active binding sites of ConA. A microelectromechanical system (MEMS) can be applied to determine the viscosity of the assay, compare Image 1.
A sensor chip has been designed and fabricated by virtue of microelectronics technology that makes use of a mechanically bendable beam. The viscosity follows from the velocity by which the beam can be moved within the assay [10]. Beam bending is operated in a quasi-electrostatic actuation scheme, i.e. the high-frequency applied is on the order of 3.2 GHz and far beyond any mechanical resonance frequency. The beam is fabricated from conductive TiN and configured as a deformable electrode of a capacitor, such that the deformation z transforms in a change of capacity C.
The capacity is followed by connecting it to a ring oscillator circuit (ROC) and monitoring its resonance frequency f. The time is determined until the beam reaches a defined position, where the sensor chip is switched off. The switching time t_{sw} then is as a measure for viscosity and glucose concentration c_g within the assay.

1.2 Biocompatibility

Appropriate materials were to be selected and a number of optimizations were to be performed in order to establish the operability of microchip and sensor system within the human body. MEMS electrodes were prepared from titanium nitride TiN that is well established in CMOS technologies and was shown to be sufficiently biostable in previous investigations [11, 12]. Also the surface passivation of microchips from SiON and the flanks of MEMS cavities from SiO_2 showed no measurable degradation or degradation rates incompatible with a sensor life time of months, both *in vitro* and *in vivo* [13].
The impermeable enclosure of implanted electronics may be ensured for long lifetimes by metallic cases only [14]. However, for systems that operate in the body for a few weeks or month only, polymers may also be considered. Silicone that was shown in previous investigations to fulfill these requirements was selected for the casing of the implant presented here [15].

2 Methods

2.1 Chip preparation and integration

Preparation of sensor chips was performed in the IHP pilot line in the framework of multi project wafer (MPW) shuttles [16]. 200 mm CZ Si wafer with 750 µm thickness and 0.5 Ωm resistivity served as starting material. SGB25V technology was applied, exhibiting a 4-level metallization (M1-M4) and encompassing 22 lithographic masks and about 500 process steps [17]. The sensor cavity was fabricated from the back-end-of-line stack, in which Al layers are covered by Ti/TiN layers from above and below. The ground plate of the cavity and beam were made of M1 and M3, respectively, resulting in a distance between both of

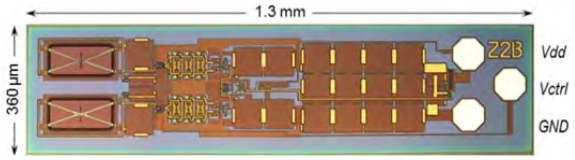

Image 2 Sensor chip with fully embedded BioMEMS [8].

2.5 µm [18]. Image 2 shows a photograph of the sensor chip with X-shaped beams in the measurement and reference cavity (top and bottom left).
MEMS cavities had to be etched in a post clean room process; sensor chips were populated with stud bumps, separated by an IR laser process [19] and finally bonded to flexible boards for connecting with the system board.
Sensor chips with flex cables had to be integrated into a cooling body, which were also fabricated from CZ-Si. This integration was necessary, since the amount of heat dissipated during one measurement was on the order of a few 10 mJ, which may denature ConA when not properly conveyed. The cooling body had the additional functionality to hold the affinity assay, in which the MEMS beam was to follow viscosity variations. It also served as a carrier for the semipermeable membrane to separate the sensoric fluid from the interstitial [20]. Probes with sensor chips were filled with ConA and dextran containing fluid, sealed and made available to be integrated into the implant.

2.2 Energy supply

The operation scenario of the implant envisions the determination of one c_g value every five minutes. With this approach, health-critical deviations from the normal concentration range will become predictable sufficiently early. 288 measurement data will show up every day corresponding to an increase of data point density of about two orders of magnitude when compared to conventional test stripe technique. About 26 J will be required per day, when an energy consumption of 20 mJ per measurement is assumed. Moreover, five data transmission cycles shall be allowed per day consuming additional 70 mJ [21].
Cardiac pacemaker and defibrillators often make use of Li-MnO_2 batteries exhibiting energy densities in the range of 1 Wh cm^{-3}. The 3.2 V battery LiS 3150M (Litronik) with 1200 mAh was applied here with a shape of an elongated D, lateral extensions of 31 × 27 mm and a height of 5 mm [22]. It is evident from comparing the data with the dimensionality of the sensor chip (Image 2) that the battery represents the size-determining component of the full system.

2.3 Design of the system board

A printed circuit board (PCB) was designed having the same D shape as the battery in order to integrate both into the system in a sandwich configuration. The MSP430 µC (Texas Instruments) uses a ZL70321 (Microsemi, previously Zarlink) [23] radio as uplink to send and receive data in the 402-405 MHz MICS band [24]. A voltage regulator stabilizes the battery voltage and a current-to-frequency (I/F) converter transforms the analog sensor current into

the frequency domain, where it can be measured very accurately by the µC. The sensor current is used to charge a reference capacitor with a very low temperature coefficient. As soon as a preset trip voltage is reached, the capacitor is discharged and the process starts again. The output of the I/F converter is a digital signal with a frequency dependent on the sensor current.
Following this approach was necessary, because the low current from the sensor chip cannot be measured directly with the µC's analog to digital converter. Amplifying and converting such low currents to voltages by standard operational amplifiers was not suitable here, because of the constraints defined by power supply, conversion speed and resolution, immunity against electrical interference and temperature effects.

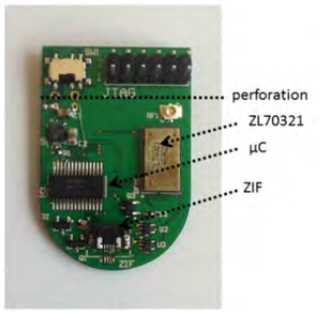

Image 3 System board with microcontroller, radio module and connectors to sensor chip, antenna and programming device; the latter is cut-off prior to integration along the perforation line; width of the device is 27 mm.

The tradeoff between accuracy and measurement time can be adjusted by varying the observation time of the frequency. A reference timer in the µC is driven with a reference clock. Its operation is gated by a selectable number of I/F cycles. Therefore, the measurement resolution can be increased simply by increasing the observation time.
A reference frequency of 8 MHz clocks a counter up to 65535 within 8.2 ms, allowing to achieve a resolution of 16 Bit. Setting a gate time of 1ms will yield a resolution of 13 bit (8191) accordingly. Gating of the reference timer is done via a second counter. It counts edges of the input frequency asynchronously to the system clock. The reference timer is stopped after a preset number of edges and its value is saved for further processing. This approach provides several degrees of freedom to optimize the system's performance, battery life, resolution etc. which would not be possible with fixed analog amplifier setups.
Additionally, several discrete devices for signal conditioning and an impedance network for the antenna [25] were installed on the PCB. Next to the parts to be integrated into the implant the PCB accomodated an additional JTAG connector for µC programming. This board area is separated by a perforation and might be cut-off after successful tests of the µC program, see Image 3.

2.4 Configuring the full system

System components were arranged in a stacked configuration. The sensor probe occupies the top-most position allowing the sensor window to directly view into the surrounding tissue. Also the antenna resides on the top-most level. Distance holders are inserted above and below the PCB in order to enable the starting integration of the PCB-battery stack. Distance holders were constructed with open areas to enable a complete space filling of the implant with silicone, s. Image 4.
Silicone grouting started with processing the sandwich consisting of PCB, battery and lower distance holder. The assembly was rinsed with isopropanol, cleaned in a cleaning solution, rinsed with deionized water and dried. The implants were put in a solution of adhesion promoter to increase the adhesion of Parylene C on the surfaces. Afterwards, they were rinsed with isopropanol and dried again. Parylene C was deposited in a Parylene coater (Para Tech LabTop3000) with an intended thickness of 10 µm. Subsequently, the sensor and antenna were mounted on the battery-PCB sandwich together with the upper distance holder.

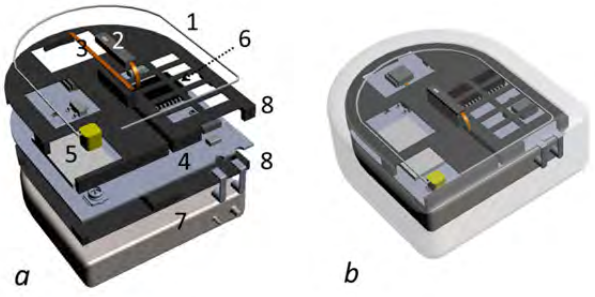

Image 4 ***a*** Explosion scheme of the sensor implant encompassing the antenna 1, sensor probe 2, flex cable 3, system board 4 with frontend chip 5 and microcontroller 6, battery 7 and distance holders 8. ***b*** Implant design as integrated in a transparent silicon housing.

Prior to silicone encapsulation the sensor window was protected by Kapton tape. For increasing the adhesion of polydimethylsiloxane (PDMS) on the Parylene C coating a plasma activation of the upper and the lower surface was performed in the low pressure plasma system NANO-HF-PC (diener electronic). In order to further improve the adhesion, the implant was pretreated with silicone primer Nusil MED1-161. Specially designed and produced distance holders made of silicone were glued on the surfaces of the implant to guarantee a defined thickness of the PDMS coating and subsequently cross-linked at 50°C.
For encapsulation of the whole assembly, the implant was positioned in a specially designed casting box which was placed in a vacuum-tight case. The whole assembly was installed in a vacuum caster ULC 5/01 (SLM Solutions GmbH) and the casting box was filled with liquid silicone Nusil MED-6015 by pressure difference technique. The casting box was removed from the case and tempered at 50 °C for PDMS crosslinking. After releasing the encapsulated implant from the casting box, the protecting Kapton tape was stripped from the top of the sensor after scratching the edge with a scalpel. For aligning the surface to the edge region of the sensor silicon body, silicone glue Nusil MED-1000 was applied near the side of the silicon body until there are no more sharp edges. Finally, the silicone glue was cross-linked again at 50°C.

3 Results

A set of implants were integrated, for which a successive transition from dummy components to operating ones was performed. The transparency of silicone turned out to be very useful for corrosion tests, since it allowed an optical inspection of possible defects. However, neither gas inclusions nor water precipates on device surfaces could be detected in any of the buildup systems. Image 5 shows the top and bottom side of one of the integrated systems with fully operational components.

Image 5 Silicone-encapsulated glucose monitor implant from **left** top-front and **right** bottom-rear perspectives; dimensions of the device are 38.6 × 49.3 × 15.5 mm [26].

Fully integrated systems were subjected to corrosion tests by storing them for longer times in isotonous saline. Image 6 shows photographs of an implant that was treated for more than six months. Only a small brown clouding may be recognized at the end of the antenna, which was realized, however, directly after the grouting process and may thus not be considered as a corrosion effect.

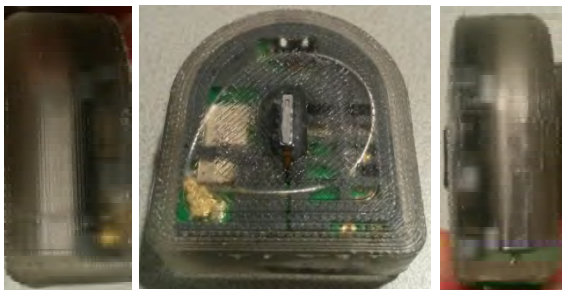

Image 6 Sensor implant after 233 days in isotonous saline, **(left)** left side **(middle)** top view and **(right)** right side.

4 Conclusions

The system integration of an implantable biosensor was shown, which determines glucose concentrations with a fully embedded BioMEMS according to the principle of affinity viscosimetry. Energy supply was provided by a Li-MnO_2 battery well established in cardio implants as data were transmitted in the MICS band. The full system was encapsulated in silicone which allowed to expose only the sensor window to the surrounding tissue. No corrosions effect or defunctionalization of sensor components could be detected after *in vitro* testing the implants on a time scale of months.

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