Biocompatible packaging solutions for implantable electronic systems for medical applications

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Abstract
Our biocompatible packaging concept for implantable electronic systems combines biocompatibility, hermeticity and extreme miniaturization. In a first phase, all chips are encapsulated in order to realize a bi-directional diffusion barrier preventing body fluids to leach into the package causing corrosion, and preventing IC materials such as Cu to diffuse into the body, causing various adverse effects. Various clean room materials are tested with respect to their suitability as encapsulation material. In a second phase of the packaging process, all chips of the final device should be electrically connected, applying a biocompatible metallization scheme using eg. gold or platinum. Device assembly is the final packaging step, during which all system components will be interconnected. To provide sufficient mechanical support, all these components are embedded using a biocompatible elastomer such as PDMS.

INTRODUCTION
Traditionally an implantable electronic device such as a pacemaker is packaged in a rigid titanium (Ti) box to ensure hermetic and biocompatible packaging of the microelectronic device. Unfortunately, this Ti box is often much larger compared to the electronics inside, hence a larger insertion wound is needed during implantation. Moreover, the Ti-box is a rigid package, which is in strong contrast with the soft tissue. Both the size and the rigidity of the Ti package might result in a pronounced Foreign Body Reaction (FBR), a clear infection risk upon implantation, and adverse effects such as irritation of surrounding tissue during device use.

To decrease the problems listed above, the miniaturization technologies in packaging of microelectronics should be extended towards packaging of implanted medical devices, resulting in smaller implants. Additionally, by selecting proper materials, the final package can be made soft and biomimetic, resulting in a comfortable implantable device, causing limited FBR and adverse effects.

NOVEL IMPLANTABLE PACKAGING CONCEPT
Our implantable package concept is illustrated in Fig. 1. In the first phase, individual dies are encapsulated by top and bottom capping layers which should provide an excellent hermetical enclosure for each die. To avoid any influence of possible pinholes, the encapsulation consists of more than one layer. Obviously the capping layers should be biocompatible, which means that the material should not cause harm to the body. Biocompatibility is a contextual concept, depending on duration and type of body contact, and on implant location, more stringent demands are

Fig. 1. Proposed miniaturized implantable packaging. (1) all chips are individually encapsulated by insulating and conductive diffusion barriers using a wafer level process; (2) biocompatible chip interconnect and embedding of multiple chips using a flexible polymer such as polyimide; (3) final system assembly including biocompatible metallization and embedding in a soft biomimetic polymer.
imposed on the material to avoid any harm to the patient. Furthermore, the die encapsulation layers and electrodes (see Fig. 1, Phase 1) should also form a bi-directional diffusion barrier: no body fluid should leach into the device and harmful IC materials such as Copper (Cu) should not diffuse into the body tissue.

In a second phase of the packaging process, all chips of the final device should be electrically connected. Gold (Au) or platinum (Pt) metallization is interesting for implants, due to the excellent biocompatibility and corrosion resistance. A disadvantage is their high cost; hence attention needs to be paid at a cost-effective deposition/patterning technique.

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**PHASE 1: DIE ENCAPSULATION**

Standard IC processing is used for chip fabrication, followed by a dedicated wafer level post process for this biocompatible and hermetic chip encapsulation. A brief description is given below, for more info see [1]. Thinned dies with sloped edges are encapsulated by a stack of standard clean room materials, as indicated in Fig. 2. Both insulating and conductive materials are needed. Related to the processing sequence, all top layers should be deposited at 400°C max, while for the bottom layers 200°C is the limit. It is a challenge to obtain good step coverage using these lower temperatures, but after some process optimization very good results are obtained (Fig. 3).

**Fig. 2**: Cross-section of an encapsulated chip showing the various encapsulation layers.

**Fig. 3**: A dedicated deposition process for SiO₂ results in a die encapsulation with excellent step coverage.

**DIE ENCAPSULATION MATERIALS: GENERAL CONSIDERATIONS**

Two series of materials are investigated:

(a) **insulating materials**: SiO₂ (Ox) and Si₃N₄ (N), deposited at a medium (M) or low (L) temperature of 400°C or 200°C (further called OxM, NM, and OxL, NL).

(b) **conductive materials**: well-known clean room materials with interesting barrier properties are: titanium (Ti), Ti-nitride (TiN), tantalum (Ta) and Ta-nitride (TaN) [2-4].

The capping materials need to have various properties:

1. suitable biocompatibility
2. excellent bi-directional diffusion barrier
3. good stability in biofluids

(1) Suitable biocompatibility

Biocompatibility tests will investigate if a material causes harm to the body, a first and very important test is the so-called 'cytotoxicity test'. We investigate cytotoxicity according to the ISO 10993-5 standard regarding biocompatibility, using both co-culture and immersion tests using primary cells such as cardiomyocytes (Fig. 4). After 5 days cell culture, the cell viability is calculated (viability: amount of healthy cells divided by total amount of cells). The cell condition is made visible by 'live/dead cell assays': fluorescent dyes will color healthy cells green and dead cells red. For more test details see [5].

As an example, the cytotoxicity results for the oxide and nitride layers are shown in Fig. 5. Cell viability should not differ more than 10% from the control result. We proved that all our insulating and conducting materials are non-cytotoxic.
(2) Tests on bidirectional diffusion barrier properties
Two types of tests are needed for diffusion characterisation of barrier layer: (a) test of diffusion of Cu through the barrier layer, done by Cu sensitive cell cultures and (b) evaluation of fluid leaching through the barrier layer, done by Cu corrosion tests during/after submersion.
For these tests, we typically use 100nm thick layers of the material under test. For later encapsulation, the thickness of the materials will be adjusted to obtain good diffusion barrier properties.

Diffusion of harmful IC materials into the tissue is tested by immersing Cu layers encapsulated by 100nm of the material under test, followed by a 5-day primary cell culture (See Fig. 4 for test protocol, more details in [5]). For the insulating materials, results are plotted in Fig.5. The films deposited at 400°C (OxM and NM) have better barrier properties to stop copper diffusion. For the conductors, Ti and TaN performed well, while TiN and Ta are weaker in stopping diffusion.

To ensure that a good diffusion barrier is obtained, we will always use stacks of conductive materials such as Ti/TiN and SiO_2/Si_3N_4. The optimum layer thickness is dependent on the implantation duration and site in the body.

(3) Test of interaction of materials with biofluids
Essential is also to investigate the bio-stability of the encapsulating materials when immersed for a long time in various types of bio-fluids (saline, cell culture medium, ...). Since immersion times might be unpractical long, accelerated tests should be considered (see further).

(4) Accelerated diffusion test and bio-stability test
Diffusion evaluation based on cell co-culture tests is typically limited to a duration of 5-6 days, longer tests will result in cell death due to overpopulation or aging of the medium. This short test period is in contrast with the use of long term implants, i.e. a cochlear implant will remain 50 years or longer in the body. Hence accelerated diffusion testing is essential. For electronics, such tests are typically done using elevated temperatures. Diffusion and corresponding Mean Time To Failure (MTTF) are related to time and temperature, as expressed in the well known Arrhenius equation [6]:

\[ \text{MTTF} = A \exp \left( -\frac{E_a}{kT} \right) \]

With: \( A \): pre-exponential constant \( E_a \): activation energy \( T \): temperature in Kelvin \( k \): Boltzmann’s constant

Performing cell cultures at elevated temperatures is out of question: above 45-50°C proteins of the cells and in the medium start to denaturize, resulting in cell death. Elution tests at elevated temperatures can be used to evaluate Cu diffusion. We test typically at 70°C (high temperature elution conditions according to USP standard). After the elution period, the biofluid will be analyzed, to detect very small traces of Cu. We developed a sensitive Cu detection technique in house, based on TXRF analysis [5].

Also for long term bio-stability tests, these accelerated test procedures are an interesting alternative. Obviously, certain material/biofluid reactions might occur only at temperatures > 37°C, hence when an interaction is observed at 70°C, a real time test at 37°C has to be performed too, to check the validity of the 70°C test result.

Accelerated biostability tests on the insulating and conductive materials revealed surprising results. We found that the nitride layer slowly dissolves in water based solutions, the dissolution rate is low and dependent on the nitride deposition process. For long term implants, even a low dissolution rate is unacceptable, hence an extra capping layer is essential to prevent direct contact between nitride and the biofluids. Silicon-carbide (SiC) proved to have a much higher biostability and will be used as an extra capping layer.

Also for the conductive materials, long term biostability problems were observed in some biofluids such as DMEM. Also here an extra capping layer is applied to protect the conductive materials from direct contact with biofluids. Platinum will be used; since this material is not compatible with CMOS processing, it will be applied after all clean room processing. More info can be found in [7].

Corrosion tests
We fabricated a corrosion test device to investigate the encapsulation of phase 1. The device is carrying long copper interconnects on chip, using the encapsulation processes as mentioned before and illustrated in Fig.6. Extra electrodes, the weakest point regarding corrosion, are added to the Cu interconnects to create a worst case scenario for corrosion. The Cu interconnects have varying line widths (500nm to 50µm). For electrode fabrication, the contact pads are covered with 15nm Ta, 40nm TaN and 50nm Pt. Passive accelerated tests proved no corrosion occurs (no visible corrosion, no Cu resistance change) after a 4-week

![Cardiomyocytes viability after 5-day co-culture test](image-url)
incubation at 70°C, which corresponds to ~ 8 months stability against corrosion at 37°C. In active tests, the device is immersed in a biofluid (PBS) except for the main contact pads at which 1 mA AC or DC current is applied. Meanwhile the voltage across the device is monitored. So far the devices have proven to be corrosion-free for 2 weeks. Longer term and accelerated active tests are ongoing.

**Interconnects**

For the interconnects between various components in phase 2 and 3 of the packaging, various requirements should be combined such as excellent biocompatibility and bio-stability, low impedance, good mechanical properties and cost. Very interesting materials for these interconnects are Pt and Au. Since these packaging phases will take place outside the clean room, Pt and Au can be used. These noble metals are expensive, hence a cost effective deposition technique should be applied. We are currently developing a selective Pt plating technique, which will be compared with the more conventional lift-off technique for Pt patterning.

**Encapsulation in polymers.**

In phase 2 of the packaging procedure, all chips are encapsulated in a polymer. For many years, imec developed a Ultra-Thin-Chip-Package (UTCP) process. The metallization used for standard UTCP is still copper; as described above a new Pt metallization technique is under development, this will enable the fabrication of a Pt-based thin chip package. In phase 3 of the packaging sequence, all components are assembled, interconnected and embedded in a flexible biocompatible elastomer. At the sensor location, this elastomer embedding should be adjusted in order to enable high sensitivity of the sensor. For electrodes for example, the elastomer should have a window to allow direct contact between electrode and tissue. In case of a pressure sensor, the elastomer should be locally very thin, in order to realize hermeticity without losing sensor functionality, as shown in Fig. 7. This medical device –an implant measuring the bladder pressure- is encapsulated using Silastic MDX4-4210, a biomedical grade silicone from Dow Corning [8]. This device is still fabricated using conventional Copper metallization. In vitro cytotoxicity tests are performed in accordance with the ISO 10993-1 guidelines, showing that the applied silicone encapsulation functions as a good seal for at least 8 days [9]. As explained before, a superior Pt-based metallization scheme for implants is under development, which will make the packaging approach suitable for long term implants.

**CONCLUSIONS**

A miniaturized, biocompatible packaging method is proposed, resulting in a small, soft and comfortable implantable package. For phase 1 of this packaging concept various common insulating and conductive clean room materials are tested with respect to their suitability as biocompatible and biostable barrier layers. To realize a biocompatible metallization in phase 2 and 3, a Pt deposition technique is under development. Die embedding in polyimide and global system embedding in elastomers is explored, although the Cu metallization currently applied has still to be replaced by Pt metallization for biocompatibility.

**REFERENCES**