

Implantable autonomous drug synthesis and delivery system

Promotors :

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IMEC : Chris Van Hoof

Imec strategy :

The proposed PhD research fits in the long-term edge activities of the Smart Implants programme, which for the technology focuses on flexible / stretchable & 3D type of packaging, highly integrated and small form factor systems.

Short description of the PhD subject :

In the current society there is a growing demand for automated, patient tailored drug delivery systems. A relevant example is the delivery of insulin for diabetes patients. Insulin supply is necessary when the blood glucose level is above a certain threshold level. This insulin is normally delivered by injection. An implantable system which monitors the glucose level and actuates insulin release when necessary would mean a huge increase of comfort for the diabetes patient. A still more visionary version of such a system would be one, where the drug (in the diabetes case: the insulin) would be synthesized in the implant itself. This would have the big advantage that the insulin "reservoir" would not have to be "refilled" from the outside at regular intervals. It is precisely the aim of the proposed PhD project to perform research in the direction of such an autonomous drug synthesis and delivery system. It is clear that this development requires a multidisciplinary approach; therefore the thesis is promoted by groups from the UGent Engineering as well as Pharmacy faculty.

The base of the developments will be the technologies for compact flexible electronic circuitry, including embedded components and flexible ultrathin chip packages (UTCP)¹, combined with technologies for compliant (elastic) biocompatible circuits², as developed at CMST. The group is currently expanding the development of these technologies towards (bio)medical applications, especially in co-operation with other IMEC groups. As an example CMST is actively participating in IMEC's starting "Smart Implants" programme.

For the realisation of the drug delivery system as described above, the development of a number of innovative and generic technology building blocks is necessary. These developments are planned in the first period of the PhD work. As the final goal is long-term implantation, biocompatible silicone materials (PDMS = poly-dimethyl siloxane) will be chosen as carrier and interconnection substrate for the sensors, actuators and accompanying electronics, as these soft conformable materials offer the maximum comfort to the user and also allow integration with living cells, which will synthesize the drug.

¹ J. Vanfleteren, W. Christiaens, "Method for Embedding Dies", US patent application, #US2007/0134849 A1, June 14, 2007

² J. Vanfleteren, D. Brosteaux, F. Axisa "Methods for embedding of conducting material and devices resulting from the methods", US patent application, #US2006/0231288 A1, October 19, 2006; EP patent application EP 1 746 869 A1, January 24, 2007.

The technology blocks to be developed include :

- Microfluidic channels in PDMS: the PhD student will be able to start from preliminary results, obtained in another running IMEC supported PhD subject³, and will have common developments with this subject, but it is expected that also specific developments will be necessary. Possibilities for microfluidic channel formation in PDMS include moulding and laser structuring. Different ways to produce the moulds will be investigated, including precision machining, photolithography, etc.
- Development of electro-osmotic flow unit for drug release: electro-osmotic flow (EOF) is the motion of ions in a solvent environment through very narrow channels, where an applied potential across the channels cause the ion migration. It has been proven that electro-osmosis in PDMS microchannels is possible⁴. The basic stretchable electronics technology of CMST offers the possibility to develop a highly integrated elastic EOF actuator unit. EOF will be used for transportation and release of the drug in the body.
- Sensor integration: as the ambition is to develop a closed loop system a suitable sensor (e.g. a glucose sensor for diabetes application) must be selected and integrated. A number of glucose sensors have been developed by other groups, most of them for external or minimal invasive use, some of them implantable^{5,6}. It is not the intention to develop new sensors in this PhD, but to start from an existing available sensor. It is expected that such a sensor will have to be adapted if it has to be long-term implantable and integrated with the rest of the system. Therefore two options will be considered :
 - Adaptation of an existing sensor to an long-term implantable version
 - Use of a separate existing non- or minimally invasive sensor and wireless communication between the sensor and the (implanted) drug delivery system (back-up solution if adaptation of the sensor proves to be difficult).
- Development of implantable drug synthesis unit: the aim is to create a compartment, in which cells are cultured, with these cells synthesizing the drug. In a human body, insulin is produced in significant quantities only in beta cells in the pancreas. It is the intention to use these type of cells in the PhD work. A compartment will be constructed in which the secreting cells are confined, however with possibility of interaction with the outside environment, which is necessary for 3 reasons :
 - Oxygen/nutrient supply for the synthesizing cells
 - Harvesting of the produced insulin
 - Monitoring and control of the cell population

The intention is to ensure oxygen/nutrient supply and insulin harvesting through the integration of a microporous membrane, allowing to pass these substances, but blocking the cells. It will be tried to monitor cell population through electrical (capacitive) measurements. Therefore stretchable electrodes must be integrated in the system. These electrodes will then also be used for controlling the cell population. By applying appropriate electrical signals cell population will either be stimulated or decreased. Study of the influence of the electrical signals on the cell population growth or decrease is an important aspect in this development. Also ways will have to be found to monitor insulin production rate.

³ Rik Verplancke : “Generische MID technologie voor biosensoren”, started November 2007.

⁴ N. Bao et al., *J. of Chromatography A*, 1099 (2005) 203–206

⁵ N. Tubiana-Rufi et al., *Diabetes & Metabolism* 33 (2007) 415–420

⁶ N. Henninger et al., *Biosensors and Bioelectronics* 23 (2007) 26–34

The developments will result in 2 demonstrators :

- The phase 1 demonstrator will be an autonomous drug delivery system with an integrated or external glucose sensor, electro-osmotic flow unit, and insuline compartment with external refill
- The phase 2 demonstrator will additionally include the drug synthesis unit.

In the design special attention will be paid to low power consumption, and wireless communication integration. The developments and experiments will be done mainly in vitro. At the end of the thesis some in-vivo experiments might be foreseen (e.g. on mouse model), but this will at least require that the developed systems can be made sufficiently small.