Healthy Aims – Development of Implantable Microsystems Medical Devices
MPMD 2004, St. Paul, Minnesota

S.B.Dunkerton
TWI Ltd/Medical Devices Faraday Partnership, Cambridge, UK

D.Hodgins, MBE
ETB Ltd, Codicote, Herts., UK

Abstract

Currently there are very few implanted, microsystems medical devices available for citizens in the EU and worldwide, despite the fact that end user requirements are clearly present. There are various reasons for this, including the fact that most micro-structures, micro-sensors and micro-actuators are not developed for medical applications and there are few materials available for long term implantation in the human body.

In December 2003, an EU programme, Healthy Aims, was launched to address these and other issues. This arose from the European microsystems network, NEXUS Medical Devices Group and led to a 26 partner team from 9 countries participating in this ambitious and cross disciplinary project. The range of technologies and target products are as follows:

- RF communications suitable for implanting into the human body
- Implantable power sources
- Biocompatible materials
- Micro-electrodes to connect the power source to nerves
- Micro-assembly techniques for 3D, flexible structures requiring coating with biomaterials
- Sensors and actuators to fit inside the body.

These technologies are being targeted at a range of clinical requirements to meet devices ranging from cochlear and eye implants, to pressure sensors and Functional Electrical Stimulation (FES).

Introduction

There has been considerable growth in microsystem technology in recent years, with good commercial examples found within the automotive, telecommunications and environmental sectors but surprisingly little so far in the medical device area. The factors holding back this sector, despite large potential benefits include:

- Limited materials available that are suitable for encapsulation and implantation in the human body.
- No long life implantable batteries (rechargeable or otherwise).
- Packaging and interconnect systems have not been developed for flexible 2D and 3D micro-structures.
- Data rates and power for in and out of body communications are limited.
- Micro-structures, micro-sensors and micro-actuators are yet to be developed for medical implant applications.

Clinical:
- The system concepts developed by clinicians often cannot be produced due to lack of resources/access to the relevant technology providers.

Commercial:
- The perceived volumes are often low for different applications and hence are not of interest to large organisations.
- The time to market due to clinical trials and regulatory approval is long, which puts off large organisations and makes investment risky for SMEs and their financial supporters.
- The regulatory procedure for obtaining approvals requires the highest quality standards within all organisations involved in the development of the product and is extremely labour intensive. Furthermore, it is often prohibitively expensive, particularly for SMEs.
- The risk is high.

Looking at the available products today, most focus on applications relating to the heart and blood system, for example pacemakers. This is because research activities including clinical research has been well funded in this area, and the potential market is fairly large. As a result, the main players are large organisations.

There are also a few other implants available including a cochlear implant for the profoundly deaf, and a bladder
stimulator for people with no bladder control. More recently 2 types of artificial urethral sphincters for people with manual dexterity have become available, and most recently a simple 2 channel functional electrical stimulator (FES) implant for ‘Dropped Foot’ sufferers has come on the market. In Europe, these are mostly produced by SMEs, and have demonstrated that smaller high-risk niche markets can be successfully addressed by SMEs.

By examining the market potential, clinical need and available technical resource, the European microsystems network, NEXUS, undertook a roadmapping exercise which led onto the development of a major EU consortium to develop new implantable products utilising advanced generic technologies. This programme, named Healthy Aims, includes 26 partners across 9 countries and started on 1st December 2003. The programme size is 26meuro and will run for 4 years.

**Programme Structure**

The range of interests within implantable devices are diverse, but all have a central theme of being electrically driven and focused on the nervous system. As a result, the programme was structured with technology leads and product leads, to enable generic technologies to be developed but with a specific range of end products being targeted, Fig. 1. The core technologies were defined as:

- RF Communications suitable for implanting into the human.
- Implantable power source.
- Biocompatible materials.
- Micro-electrodes to connect the power source to the nerves.
- Micro-assembly techniques for 3D, flexible structures requiring coating with biomaterials.
- Sensors and actuators to fit inside the body or on the body.

The products chosen were:

- Cochlear (enhancement over existing high cost, low resolution system)
- Retina implant and glaucoma sensor
- FES for upper and lower limbs (enhancement over simple 2 channel ‘Dropped Foot’)
- Artificial intra-urethral sphincter
- Sphincter sensor
- Intracranial pressure sensor for long term implant (>10 years)

The consortium was developed to address the entire project needs from basic research through to clinical trials and subsequent regulation approvals. Complementary skills in the core technologies were included to ensure that the products did not focus on using one technology but would develop a range of methodologies using knowledge from a number of key research areas.

**Technology Development**

The programme will address core technologies that are seen to advance the status of microsystems, by targeting miniaturisation, higher reliability and reduced size alternative power systems, as are required for small scale active medical implants.

**Communication**

Certain current medical devices require some level of communication with the outside world, but the datasets are relatively low and an external antenna is used to collect data from the internal device. Within this programme a Body Area Network (BAN) is to be developed that will miniaturise the system such that an internal antenna is employed with low power RF electronics, all packaged in a sealed system for implantation within the body. This device will then communicate high data rates (500 kbps) to base stations that can be up to 3m away. Under development are a microcontroller to manage an RF transceiver, an antenna to be within the device and associated electronics. Such a system is planned to be applicable to many of the devices under development within the overall programme.

**Power sources**

The requirement for a miniature, high density, long life, secondary (rechargeable) power source is common to a range of microsystems, including the medical devices of this work. Implantable devices for medical applications impose other difficulties, namely: prevention of any form of failure mode over a 10 year life, high energy density (in excess of 150mWh/cc), and non standard forms, e.g. cylindrical.

Battery fuel cells and biofuel cells will be explored in this project, the first to extend current aerospace state-of-the-art
and the latter to develop completely new systems using the bodies own natural sources as a means of generating on-
going power. The current power limit of biofuel cells is 2.7µW mm⁻², and the target power output is 100µW mm⁻².

On the conventional power source route, lithium battery technology is being explored to enable miniaturisation whilst achieving the power level needed over a long life. Within biofuel cells, a concept study has compared power capabilities with alternative systems such as mechanical generators, thermal generators and galvanic cells. The biofuel cell remains superior in terms of continuous output, longevity, minimally invasive implantability and biocompatibility. Within this category, there are three options:

- Direct fuel cells – long life, amenable to sterilisation and biocompatible
- Enzymatic fuel cells – high reactant specificity allowing a simple, one-compartment design
- Microbial fuel cells – superior longevity (self-generating), but need to consider infective nature of the micro-organisms.

It has been agreed that early work will focus on a direct glucose/oxygen fuel cell with improved power output.

Biocompatible materials
Coating materials currently available for Microsystems devices are limited. Polymeric coatings already qualified for in vivo use may not be functionally ideal or compatible with the objectives of maximum functionality and compliant properties within a package of minimum size. This drive for compactness is expected to lead to the development of new and improved materials and surface treatments to enable the combination of biocompatibility and increased functionality.

Materials and coatings to provide the encapsulation of electronic devices, together with thin flexible coatings or compatible surface modifications, need to be compatible with both the body environment but also the processing conditions needed in the manufacture of the entire system.

Strategies to develop such materials will be based on new and upcoming materials, and will also include methods to reduce formation of fibrous material, avoidance of undesired film growth and routes for drug delivery.

Other biomaterials are also being developed specifically to enhance the electrical conductivity at the electrode/nerve interface.

Micro-assembly techniques
Many of the devices and technologies to be developed in this work include non-silicon technology, although some silicon based devices are involved. The complexity of achieving enhanced functionalisation within minimum size packages, requires advanced assembly technologies, based on 2, 2.5 and 3D architectures. At the interconnect level, functional density is targeted to be twice that available today, with I/O pitch on active devices reaching a level of <40µm through modified wire bond and flip chip techniques, and interconnection on biocompatible rigid and flexible substrates increasing to 200 cm/cm². 3D chip scale packaging techniques will be extended to be applicable to medical devices. Wherever possible, existing methods will be employed but adapted for these specialist applications, to ease transfer to production applications.

Micro-electrodes
To stimulate the nerves for functional electrical stimulation (FES), micro-electrodes are needed that can interface effectively with targeted nerves and be integrated into a true microsystem. Although technology is available, it has so far been difficult to integrate effectively into medical Microsystems because of the increased number and density of the electrodes. This work is covering a range of technologies that include thin flexible polymers containing coated micro-electrodes and on thinning silicon electrodes to thicknesses of 25-30µm. In all cases, means of maximising surface area to improve contact with the nerves will be determined.

For this new generation of active devices, it is necessary to incorporate multiplexing electronics near the electrodes, which must be protected from ingress of moisture. Also, the tissue environment in which the device is to be implanted must be protected from leaching of the cytotoxins inherent in the electronic components.

To date, work has determined the focus to be on topographical changes to encourage/discourage cell adhesion and the use of chemical and biomolecular routes to influence patterns of cell growth and differentiated function.

Sensors and actuators
Essential components of any microsystem are the sensors and actuators. To date, most of the focus has been on silicon based sensors for low cost, high volume automotive applications. The result is that the space envelope and power requirement is generally much too large for applications where size and power are real issues. For instance, motion measuring of human limbs requires 6 degrees of freedom, without restricting movement.

A range of sensors or actuators are under investigation in this project, including:
- 3-axis gyro and 3-axis accelerometer combined in an inertial measuring unit for human body motion.
- Pressure sensor for medical diagnostics.

Complex algorithms and signal processing will also be developed during the project to enable the motion sensors to be used as a trigger for the FES application.

Product Applications

Cochlear implant
All current cochlear implants consist of a relatively large stimulator implanted into the mastoid bone behind the ear, and have a lead connection to the passive electrodes at the stimulation site, Fig. 2. There is a
strong drive to reduce the size of the implant so that the complete system can be placed in the cochlea, apart from the power source and the communication antenna. This should allow for quicker and less traumatic implantation, and assist the plan to implant such devices in younger infants who would otherwise be susceptible to the anesthetic. Miniaturisation and improved hearing performance are key targets: the available size is just 1.5mm and currently devices attach to just 22 nerve endings when there are 15,000 nerves connecting the cochlea to the brain.

Retina implant and glaucoma sensor
For the first time in human medical history, there is strong evidence that certain blind populations and those suffering from blinding diseases worldwide, will gain or regain visual perception aided by a new level of artificial vision. The technique known as Learning Retina Implant System, will substitute the signal processing function of a healthy retina. This will consist of a device implanted onto the retina of the eye (stimulator), a signal and energy transmission system connecting wirelessly to the retina device and to an external signal processing unit located on a pair of spectacles. Additional electronics modules may also be used to optimise individual vision. Particular requirements are for micro-electrodes with specificity for the retina application and biocompatibility to enable implantation over a 7 year period (initially). Communication via a Body Area Network will enable transfer of data to local and remote (medical centres) areas.

To help combat glaucoma, a soft contact lens will be developed with in-built pressure sensing to enable measurement of pressure within the eye, and give early detection of disease development. Similar technologies as identified above are needed for this device.

Functional Electrical Stimulation (FES)
FES can produce and control the movement of otherwise paralysed limbs. Various devices already exist for this purpose but they are relatively straightforward in concept and design, giving limited choice to clinicians and patients. This project is targeted to develop an integrated modular stimulator system, with up to 12 stimulating channels and 4 recording channels. Ultimately these will be capable of stimulating both upper and lower extremities. The innovation needed includes miniaturisation, improved encapsulation, improved stimulation patterns/control algorithms, better sensors and wireless communication with an external controller. The longer term goal is for an implanted power source, rechargeable via an external inductive loop.

Sphincter sensor
Failure of sphincters (human valves) to open and close correctly can cause distress and lead to longer term health problems. The goal in this phase of the work is to develop a microsystem close proximity sensor to measure valve performance. Initially a device will be designed for the oesophagus, and will comprise a micro-fabricated electrode array on a flexible substrate, micro-connections to a multiplexor and a micro-fabricated receiver coil. This will be coated in a suitable biomaterial for placing in the body, and will be activated externally. The flexibility is critical in this application, as insertion will be through the nose.

Artificial intra-urethral sphincter
The present day solution for intractable urinary incontinence is generally a simple catheter that drains into a bag. Advances in this field have been extremely limited over the last 50 years, despite the fact that over 50% of the aging population suffer from this. This project will endeavour to combine Microsystems technology with biomaterials to produce an artificial sphincter that will effectively replace the natural sphincter that has stopped functioning. This will help enable people to lead normal lives without tubes and bags attached to the body.

Intra-cranial pressure sensor (>10 year life)
For certain head injuries or disease, conventional implants include shunts to allow pressure release on the brain and stents to unblock aneurysms. In both cases, it is not currently possible to determine if these implants are operating successfully, and failure in the worst case can lead to instant death. A means of monitoring performance by measurement of local pressure provides a route to identify an on-set of failure allowing time for recovery. This work package aims to develop a highly miniaturised (<1mm²), pure capacitive absolute pressure sensor chip. Critical features are: stability, low electrical and thermally induced mechanical drift and low temperature dependency.

Programme Outputs
This programme has been designed with active involvement from academics, industrialists and clinicians to enable development of fundamental
understanding, generic technology development, prototype application studies and early stage clinical trials. It has a high involvement of small enterprises that will actively pursue specific products following completion of the work, to ensure benefit is returned to the end-user (patients) as early as possible. It is an ambitious programme and one of the first of its kind supported in Europe. To the knowledge of the participants, it is unique in taking application design concepts, building them into prototypes and undertaking early clinical work, to demonstrate the benefits to clinicians and patients, as well as significantly extending the state-of-the-art of microsystem technology such that early exploitation in the medical sector becomes feasible. This has been achieved by involving clinical experts with academics, research groups and medical end user manufacturers in one project. This true multi-disciplined approach is essential if the medical sector is to take full advantage of the latest state-of-the-art in Microsystems, nanotechnology and biomaterials.

Summary and Conclusions

This ambitious 26 partner programme will develop a range of microsystems technologies that, when integrated, can contribute to the application of a range of new implantable medical devices. Exploitation will be through the specific devices themselves, but the generic technologies will be applicable across other microsystems applications, particularly those involving non-silicon technology.

The work to date has helped verify the approach and has confirmed the various prototype product devices, such that better definition of the specifications the technologies have to meet has been determined.

This project will extend the usage of microsystem and nanotechnology in the medical sector, thus ultimately improving the quality of life for citizens across Europe. Moreover, combining the medical products with a local body area network the medical devices can become ‘intelligent systems’ without the need of patient intervention. This project will help develop the concept of ‘Ambient Intelligence’ for people suffering with medical conditions that require treatment in order to help the citizen lead a normal life.

Acknowledgements

The authors first wish to thank the European Commission for their financial support of this programme, and also acknowledge the support of all partners in their approval to publish this paper and in their ongoing commitment to the development of complementary technologies and products.

Important addresses

Sue Dunkerton, TWI Ltd, Granta Park, Gt Abington, Cambridge, CB1 6AL, UK
Tel. 44 1223 891162
Email: sue.dunkerton@twi.co.uk

Diana Hodgins, ETB Ltd, Codicote Innovation Centre, St Albans Road, Codicote, Hertfordshire, SG4 8WH, UK
Tel. 44 1438 822822
Email: DMH@etb.co.uk