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TOPICAL REVIEW

Microsystem technologies for implantable applications

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Abstract

Microsystem technologies (MST) have become the basis of a large industry. The advantages of MST compared to other technologies provide opportunities for application in implantable biomedical devices. This paper presents a general and broad literature review of MST for implantable applications focused on the technical domain. A classification scheme is introduced to order the examples, basic technological building blocks relevant for implantable applications are described and finally a case study on the role of microsystems for one clinical condition is presented. We observe that the microfabricated parts span a wide range for implantable applications in various clinical areas. There are 94 active and 67 commercial 'end items' out of a total of 142. End item refers to the total concept, of which the microsystem may only be a part. From the 105 active end items 18 (13% of total number of end items) are classified as products. From these 18 products, there are only two for chronic use. The number of active end items in clinical, animal and proto phase for chronic use is 17, 13 and 20, respectively. The average year of first publication of chronic end items that are still in the animal or clinical phase is 1994 ($n = 7$) and 1993 ($n = 11$), respectively. The major technology–market combinations are sensors for cardiovascular, drug delivery for drug delivery and electrodes for neurology and ophthalmology. Together these form 51% of all end items. Pressure sensors form the majority of sensors and there is just one product (considered to be an implantable microsystem) in the neurological area. Micro-machined ceramic packages, glass sealed packages and polymer encapsulations are used. Glass to metal seals are used for feedthroughs. Interconnection techniques such as flip chip, wirebonding or conductive epoxy as used in the semiconductor packaging and assembly industry are also used for manufacturing of implantable devices. Coatings are polymers or metal. As an alternative to implantable primary batteries, rechargeable batteries were introduced or concepts in which energy is provided from the outside based on inductive coupling. Long-term developments aiming at autonomous power are, for example, based on electrostatic conversion of mechanical vibrations. Communication with the implantable device is usually done using an inductive link. A large range of materials commonly used in microfabrication are also used for implantable microsystems.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Microsystem technologies have become the basis of a large industry with total sales of MST manufacturers exceeding US$5B, continuous growth for the past 10 years and main applications in automotive and communication markets. Pioneered in the early 1970s [1], the field was firmly established in the early 1980s with the first mass produced micro-machined pressure sensor, international conference and review paper. There has been an increasing number of publications in MST journals with the keyword 'medical' taking off from a rather constant (low) level around 1985. The advantages of MST compared to other technologies provide opportunities for application in implantable biomedical devices. Developments in these devices are driven by the desire to better mimic normal physiology and to improve the quantity and quality of life. Major healthcare challenges such as the aging population, patient centered care and affordable costs can be well addressed by MST [2–5].

According to the literature, MST offer opportunities ranging from extending human functions [6] to using it as a disruptive technology with enormous commercial potential [7]. The advantages of MST for biomedical applications are small size [1, 2, 4, 5, 7–11], low weight [1, 8, 10, 11], high reliability [1, 8, 12], low power [7, 8, 11, 12], low cost [1, 2, 7–9, 11, 12], superior functionality or performance [1, 2, 4, 7, 9–12] and MST can be combined with biotechnology and molecular biology [13]. In other words, MST provide unique opportunities and will have major impact on domains including medicine [1, 3, 4, 9, 14].

Products made with microtechnology now exist in all phases of the development cycle, including volume manufacturing, and they are being used in lots of medical applications that are on the market already [15]. There are numerous examples of microsystem technologies for biomedical applications in almost all areas of medicine including diagnostics and monitoring [5, 7, 8, 14], drug delivery [8, 14, 16], neurology [3, 7, 14], surgery [8, 14, 15], audiology [8] and cardiology [7, 8].

There are also many challenges for (microfabricated) biomedical devices including reliability [2, 8, 17], packaging [1, 2, 4, 7, 18, 19], bio-compatibility and -stability [1, 7, 9, 17–20], the absence of a mass market driver [1, 4, 7] and long development times [1, 4, 21].

The opportunities sketched above have led us to the idea to perform a literature review of MST for implantable applications in order to investigate what is the reality and what is the promise. A number of excellent literature reviews exist focusing on specific technological categories or clinical areas [14, 22–30]. This paper provides a general and broad overview of implantable MST as reported in the literature. It is focused on the technical domain but it is not a comprehensive guide on 'how to design and manufacture an implantable microsystem'; it does not provide a detailed clinical background and it is not a business analysis. The overview ends with a table were all applications are classified and a description of the observations that can be made from this table. To deal with the enormous amount of technical aspects of microsystems for a variety of applications and still stay within the scope of a review paper, we have chosen the following approach. The key technological concepts for specific applications have been summarized as briefly as possible in the body text of section 2. Technological aspects common to a complete class of microsystems are presented in general terms at the start of each section dealing with that class (see table 1). Basic technological building blocks relevant for all implantable applications of microsystems are described in a separate section (section 3, see table 1). Finally we present a case study of one clinical condition and describe the role that microsystems play in treating that disease (section 4).

2. Overview of implantable microsystems

An implantable medical device is considered any device that is intended to function inside the body for some time, meaning that we include short term use (further defined in section 2.7). The literature gives various definitions of what a microsystem is [1, 4, 31]. In this paper, a microsystem is loosely defined as a device that contains at least one part that is made using IC-like fabrication technology with dimensions in the order of micrometers. The aim of this section is to give a global overview of which microsystems are being used and how they are clinically applied. The focus is on the microfabricated part of the total microsystem. Therefore the information presented in this section is grouped according to corresponding types of microfabricated parts. The focus is also on implantable microsystems not enclosed by a hermetic metal can, although these will be briefly mentioned. An effort is made to explain the clinical need for these microsystems in just one line and to place the solution being presented in historical context. At the end of this section a summary and overall analysis of the information is provided.

2.1. Sensors

Implantable microfabricated sensors are, for example, used to facilitate diagnosis or to provide a means to generate closed loop control of therapy. The following subsections are grouped per sensor type. Some products or concepts use multiple sensors at the same time. These are presented in section 2.1.4.

The most common type among pressure sensors is made using surface micromachining processes. A suspended thin mechanical membrane is created by etching a sacrificial layer. Membrane deflection caused by environmental pressure variations can be transduced with the help of piezoresistors on the high strain areas of the membrane or conductors on both sides of the gap and appropriate electronic circuitry. Complementary metal oxide semiconductor CMOS (CMOS) compatible micromachining processes allow integration of read out circuitry close to the sensor. Operating pressure ranges can be tuned towards the desired range by changing layer thickness and diameter. Accelerometers have a suspended mass that moves relative to its mechanical support by external acceleration. The same transducer versions as for pressure sensors (capacitive or piezoresistive) are used. Both bulk micromachining in combination with wafer bonding and surface micromachining techniques are used to manufacture accelerometers. The use of these two types of sensors for implantable applications can leverage the knowledge acquired by the microelectromechanical system

Table 1. MST class and part are used as the section headings in section 2 and form the main structure of this section. Electrical is short for electrical stimulation and sensing, drug delivery includes gene delivery and MOEMS = microoptoelectromechanical systems. Technological aspects that are specific for a complete MST class (Specific technology) are described at the start of each section. Technologies that are relevant for all MST classes (Building blocks) are presented in general terms in section 3. This means we group the building block information per row.

	MST class and part					
	Sensors	Electrical	Drug delivery	MOEMS	Ultrasound	Other
Specific technology						
Sensors	V					
Electrical		V				
Drug delivery			V			
MOEMS				V		
Ultrasound					V	
Other						V
Building blocks						
Processing	V	V	V	V	V	V
Packaging	V	V	V	V	V	V
Communication	V	V	V	V	V	V
Power	V	V	V	V	V	V
Materials	V	V	V	V	V	V

(MEMS) industry from the high volume markets that exist today (millions of MEMS pressure- and acceleration-sensors are sold each year for non-implantable applications). A variety of other less common sensors will be described. Power consumption, size, sensitivity, specificity, accuracy and stability are important design parameters for most implantable applications of sensors.

2.1.1. Pressure sensors.

2.1.1.1. Intra-ocular pressure sensors. Long-term (continuous) intra-ocular pressure (IOP) measurements offer new perspectives for patients suffering from glaucoma. Glaucoma is the loss of vision due to the damage of the optic nerve for which elevated IOP is one of the risk factors. An implantable miniature pressure transensor was proposed in 1967 [32] followed by a miniature pressure sensor system intended to fit in an artificial lens in 1990 [33]. In 1998 an intraocular pressure sensor consisting of a coil on flex, flip chip pressure sensor and IC embedded in a lens was introduced [11, 34]. Such a system is currently being commercialized. Another principle is to use a distributed parallel-resonant inductive-capacitive circuit, with a pressure-dependent resonance frequency. The high Q inductor is deposited by electrodeposition of copper on a micromachined chip incorporating a pressure-sensitive diaphragm [35].

2.1.1.2. Intra-cranial pressure sensors. Patients suffering from head injury or diseases such as chronic hydrocephalus, brain tumors or abscesses may show an increase in intra-cranial pressure (ICP). Continuous measurement using a wireless implanted system offers the advantage of increased mobility over catheter-based systems [36], can reduce the mortality risk of intensive care patients [37] and allows us to monitor the ICP of patients after surgery to treat obstructive hydrocephalus [38]. In 1979 several patients were implanted with a differential pressure sensor incorporated with a shunt valve system using a resonant circuit in the sensor and a radio frequency detector outside the body for telemetry [39]. Eleven years later the same system was used to determine the quantitative relationship between changes in body position and ventricular fluid pressure in normal subjects and subjects with shunts [38]. In 1983 a long-term monitoring technique was presented [40]. A one-chip implanted device with micro coil operating through inductive coupling for both powering and read/write operation was used with success to read intra-cranial pressure values in 1988 [41].

In 1995 an implantable telemetric endo system (ITES) was developed by an interdisciplinary consortium of industrial and non-industrial partners [42]. Further developments used surface micromachined polysilicon membranes for capacitive absolute pressure detection and monolithic integrated circuitry. The sensor system was tested *in vitro* in 0.9% NaCl solution, showing excellent results compared to a commercially available reference sensor [37]. Eggers *et al* [43] made an argument for a non-integrated approach, using a surface micro-machined capacitive absolute pressure sensor fabricated in an eight-mask metal oxide semiconductor (MOS)-like process and two low-power application specific integrated circuits (ASICs) for capacitance change read-out and telemetric data and energy transmission. They used flip-chip mounting on a flexible substrate. The same system is also proposed for intraocular pressure [44]. In 1997 a fully implantable CMOS compatible pressure and temperature sensor on flex with ASIC with on chip coil for telemetry protected with silicone was made based on prior experience with catheter versions. This system used a switch between the sampling rates in order to capture special signal components in an emergency situation [36, 45].

An implantable telemetric pressure sensor system for long-term monitoring of therapeutic implants is currently being developed in the framework of the European project Healthy Aims [46]. One of the clinical application areas mentioned is the measurement of ICP. Other applications include measurement of IOP (see above) and monitoring pressure outside an aortic stent-graft placed to exclude aneurysms from blood flow (see below). The implanted part of the system consists of a measuring head made of a pressure

sensor and an interface IC connected to a telemetry unit by a conducting lead. The telemetry unit contains a transponder chip, a micro-controller and an antenna coil [47]. An ICP system using a miniature strain gauge pressure sensor mounted in a titanium case at the tip of a 100 cm flexible nylon tube is commercially available [48] and was clinically evaluated in 1998 [49].

2.1.1.3. Cardio vascular pressure sensors. The heart pumps blood through the body's vascular system and blood pressure at various anatomical positions contains clinically relevant information. Pressure proximal and distal to an occlusion can be measured to quantify its severity in terms of flow reserve [50]. It is also measured before and after a balloon catheter operation [51]. Pulmonary wedge pressure measured downstream of a temporarily occluded pulmonary artery is used to monitor patients with heart failure. This section starts by describing microfabricated pressure sensors on catheters that have been proposed or developed to address these temporary needs and then progresses to examples of microsystems for continuous monitoring of cardiovascular pressure as found in the literature.

Microfabricated pressure sensors on catheters offer advantages over fluid filled catheters with external transducers and are used on a regular basis in the clinic or for animal research [52]. They do not suffer from catheter whip, limited frequency response and resonance and due to their small size they can reach small places while yielding pressure readings comparable to reference sensors. In 1973 a patent was issued describing miniature strain gauges for measuring pressure variations at the tip of a catheter [53]. Other patents describe the use of piezo-resistive material [54], a differential pressure measurement [55] and a miniature catheter tip measurement device with a pressure sensor of 0.4 mm × 0.9 mm × 0.15 mm (width × length × height) that is determining the total diameter [56]. This company is currently making pressure-conductance catheters used for mouse experiments. Another company produces conductance catheters with pressure sensors. The transducer consists of a miniature strain gauge pressure sensor mounted in a titanium case at the tip of a 100 cm flexible nylon tube [49]. Two multiplexed pressure sensors operated via two wires for differential pressure measurements were presented in 1992. A hermetic cavity is made using anodic bonding of silicon to a glass substrate and a dissolved wafer process. Conductors pass into the cavity through a recessed area that is later sealed with plasma enhanced chemical vapor deposition (PECVD) of silicon nitride or oxide. CMOS circuitry is mounted in a recessed area in the glass and connected to the diaphragm using wirebonding [57]. An integrated circuit (IC) piezo resistive pressure sensor mounted on the tip of a catheter was already proposed by this group in 1973 [58]. A reference to a capacitive pressure sensor dates from 1980 [59]. A guide wire with a pressure sensor at the tip also exists that uses a tiny 100 μm × 150 μm × 1300 μm chip incorporating a piezo resistor attached to the side of a thin surface micromachined membrane that hermetically seals a cavity in which a vacuum exists. The membrane deflects under pressure, causing stress in the piezo material. The change in resistance is measured using a wheatstone bridge. A passive piezo resistor is provided to compensate for temperature effects [51, 60]. The same group describes a tip pressure catheter using an optical technique to detect a resonance frequency which is changed by the pressure [51, 61] or using a cantilever that moves due to the pressure, thus changing the amount of reflected light [62]. Drawbacks are in the optical connections and production packaging limitations [51]. Another company describes an optical pressure sensor that is based on detecting a pressure sensitive interference pattern in a cavity with a photo detector [63]. Since everything is happening in the tip there is no need for special measures to correct for influences of catheter bending [64, 65]. Capacitive pressure sensors have a high pressure sensitivity, low temperature drift but need onsite detection electronics if capacitance is very small [51]. A surface micro-machined capacitive pressure sensor (0.7 mm × 5 mm) on a 1 mm catheter is described in [11]. It has a 120 μm membrane with 1 μm gap, on board amplification and pulse width modulated output at a power consumption of 5 mW. This pressure sensor has already been described for an invasive measurement of blood pressure in 1990 [66] and for use on a catheter in 1991 [67]. In that same year another catheter-tip capacitive pressure sensor was presented [68]. The size of this sensor is 0.7 mm × 3.5 mm × 0.8 mm and the spacing between the capacitor electrodes is 1.0 μm. A capacitance detection IC is placed close to the diaphragm and only two wires are needed for the sensor. Eight years earlier the same group was presenting work on buried piezo resistors for catheter tip and side wall biomedical applications [69, 70]. Very recently they have developed a fiber-optic Fabry–Perot interferometric pressure sensor 125 μm in diameter and a detection system [71]. This same principle is used by another company and dates from 1993 [72, 73]. The sensor has two optical fibers polished perpendicular to the transmission line and coated with a thin layer to form the mirrors placed at a distance from each other to form the cavity. This yields a precise, stable, fast and inexpensive sensor.

Continuous monitoring of pressure for cardiovascular applications using wireless implantable microsystems offers additional opportunities for better therapies and increased quality of life for a number of conditions that are presented below.

2.1.1.3.1. *Coronary artery disease.* Atherosclerosis is the forming of plaques inside arteries which can lead to the reduction or obstruction of blood flow, ultimately causing chest pain, myocardial infarction (MI), arrhythmias and/or heart failure if this happens in the coronary arteries of the heart. A stent can be placed in the occluded area via percutaneous technique (coronary angioplasty). Researchers have proposed to use pressure sensors on stents to be able to monitor restenosis of the stent (reoccurrence of occlusion after the procedure) [74]. The backbone of this stent is fabricated from a 50 μm thick stainless steel foil using micro-electro-discharge forming two 50 nH coils, coupled to two micromachined capacitive pressure sensors. Each coil-capacitor (LC) circuit can be wirelessly probed. The use of a permanently implanted pressure sensor for ambulatory left atrial pressure monitoring may detect heart failure and help confirm successful revascularization [75]. This device is also used to optimize therapy for heart failure ([76], see below). To improve the recovery of damaged heart muscle, the circulation

of patients arriving in the emergency room with an acute MI is sometimes temporarily assisted by a catheter-based cardiac assist device. There is a need for pump control, for example to detect correct placement or obstruction, that can be provided by a pressure sensor. One cardiac assist device has a pump head with sensors using an integrated full bridge piezo resistive pressure sensor [77]. The same company has a completely implantable version that also incorporates pressure sensors.

2.1.1.3.2. *Heart failure.* When the heart muscle weakens due to prior infarction or muscle disease, the heart loses part of its capacity to pump blood, leading to an enlarged heart, which causes symptoms such as fatigue and shortness of breath. A permanently implanted pressure sensor may function as a means of optimizing a cardiac resynchronization/defibrillator system [76]. Frequent, noninvasive, monitoring of pulmonary artery diastolic pressure (PADP) may provide necessary direction for therapy in ambulatory patients with heart failure [78]. Implantable hemodynamic monitoring using right heart pressures provides diagnostic, therapeutic and prognostic information that may have a significant impact on health care delivery in congestive heart failure (CHF) [79].

One implantable hemodynamic monitoring system contains a power source, integrated circuitry, a piezoelectric activity sensor and a radiofrequency transmission coil hermetically sealed in a titanium can. A modified pacemaker lead containing an absolute capacitive pressure sensor is positioned in the right ventricular outflow tract, requiring correction for ambient atmospheric pressures [79]. First experiments using this system to measure the maximum rate of rise of right ventricular pressure for rate adaptive pacemakers were reported in 1992 [80] followed by clinical studies for heart failure [79, 81–83].

A fully implantable device that can sense direct left atrial pressure, core temperature and intra-cardiac electrocardiogram using external radio-frequency power via a telemetry coil has the sensor placed across the inter-atrial septum. The sensor device has been tested in animal models with good evidence that it is impervious to full thickness tissue coverage, still delivering accurate left atrial pressure signals [76].

A permanent implantable device placed percutaneously in the right pulmonary artery via the internal jugular vein for the noninvasive monitoring of PADP is used in a clinical setting for HF therapy as well. Using ultrasonic signals, it generates the PADP waveforms on a desktop system [78]. This device is also being used for abdominal aortic aneurysm (AAA) sac pressure monitoring ([84], see below). A major challenge for all sensors placed in the left side of the circulation is that blood clots may develop on their surface that, when released, may cause stroke.

2.1.1.3.3. *Aneurysm.* An aneurysm is a bulging of a weakened vessel wall. The success of AAA repair by placing a stent graft is expressed in terms of AAA sac shrinkage, most probably caused by excluding the sac from the systemic pressure [84]. The noninvasive detection of sac pressure may allow a change in the current follow-up strategy [85]. Currently lifelong monitoring typically using computed tomography (CT) scans is indicated [86]. A miniaturized pressure monitoring device ($3 \times 9 \times 1.5$ mm) using an ultrasound-based system that allows for pressure measurements in a noninvasive, transcutaneous fashion was implanted in an animal model and yielded almost identical results compared to catheter-based pressure readings. The efficacy of identifying pressure changes in an excluded aneurysm sac with endoleaks was demonstrated [85]. The implant contains a piezoelectric membrane that energizes a capacitor when actuated by ultrasound waves from a hand-held probe. Once charged, a transducer within the device measures ambient pressure and then generates an ultrasound signal that is relayed to the hand-held probe. First human clinical experience with this device was reported in the same year [87] and work is continuing [84]. In an alternative concept an external magnetic loop puts a signal on an implanted loop containing coil and microfabricated pressure sensitive capacitor using RF energy. The change in capacitance can be read out on the external side as a change in resonance frequency [86]. The device has recently been approved by the Food and Drug Administration for acute implantation [88].

2.1.1.3.4. *Hypertension, arrhythmias.* Permanent recordings of intravascular pressure may also improve the diagnosis and treatment of hypertension or might be used to detect pulse rate and amplitude for assessing the hemodynamic effects of arrhythmia. The pressure gradient between two positions at different depths in the myocardium is very well correlated with ventricular pressure under various cardiac rhythms, preventing the need to measure inside the left circulation [89].

A completely implantable, tined silicone capsule [90] containing a telemetric sensor chip and a ferrite coil to be anchored in a branch of a vessel is currently under investigation [91]. The sensor chip uses a surface micro-machined capacitive pressure sensor [66]—also mentioned above for temporary use on catheters—that can be designed to operate at a specific pressure range by adapting the diameter of the membrane. The read-out electronics are integrated on the same chip using a standard CMOS process. The chip contains an additional temperature sensor, readout and calibration electronics, a micro-controller-based digital unit and an RF-transponder front end [34].

In 1990 a miniaturized capacitive pressure sensor has been developed for implantation in the human heart. The pressure signal modulates the current in the power line resulting in a two-wire approach, with low output impedance, in total absence of any direct current (DC) components. The device is mounted in a needle extending a certain length off a base plate under an angle for reaching a specific depth inside the myocardium [89].

2.1.1.4. Pressure sensors for urology. Urodynamic investigations to diagnose urinary problems involve interventions in the bladder and simultaneous measurements. Typically these are catheter-based tools that use miniature pressure sensors at the tip. Totally implantable pressure measurement systems would enable measurements under close to normal life circumstances for the patients [92, 93]. In 1984 such a device has been proposed. A thick film substrate serves as a carrier and interconnecting device for the components. The entire circuit is protected with a micro-machined ceramic

package, with a removable container for the disposable battery. The system can transmit pressure data over at least 4 m, with an autonomy of half a week [92, 94, 95]. A pressure sensitive telemetry device consisting of a pressure sensor, an amplifier and a voltage controlled oscillator (VCO) has also been reported. The device was able to transmit pulses of radio waves which pulsing rate is a function of the pressure [93]. In 1987 a closed loop control of the unstable bladder has been proposed. It relies on a biofeedback system, which makes use of the bladder pressure as a parameter for functional stimulation. The key element consists of an implantable bladder pressure telemetry device that relies on a radio frequency (RF) power link. To close the biofeedback system, an independent programmable stimulator has been developed that is triggered by the pressure data [96]. The combination of microfabricated sensors and actuators to form a closed loop control system is currently still under investigation. An artificial sphincter and sphincter sensor is being developed in the European project Healthy Aims [97].

2.1.1.5. Pressure sensors for other applications. A small pill shaped bio-telemeter to be used for monitoring the health of a fetus during and after *in utero* fetal surgery was presented in 1998. The fully implantable, miniaturized sensing device is linked to a remote receiver through a wireless radio frequency link. It is small enough to be introduced to the uterine cavity through a 10 mm trocar during endoscopic fetal surgery [98]. Solid-state-pressure-sensor-catheters are also used in gastroenterology for measurements in the gastro intestinal tract (GIT). Another GIT application uses a stimulus sensitive hydrogel at the core of a sensor to measure the partial pressure of carbon dioxide in the stomach for patients with gastrointestinal ischemia. Briefly, CO_2 goes through a membrane, mixes with an electrolyte and changes the pH causing the hydrogel to swell/crimp which changes the pressure that is measured by a pressure sensor [99, 100].

A miniaturized micro structured measurement cell covered by a semi-permeable diaphragm to be implanted micro invasively into the anterior chamber of the eye has been proposed as a glucose sensor. Osmotic pressure within this cell depends on the intraocular glucose concentration and is translated into the deformation of the diaphragm which is measured using white light interferometry [101]. In a similar sort of concept a thin membrane is deflected using a glucose-sensitive hydrogel which exhibits swelling when immersed in a glucose-containing solution [102].

2.1.2. Acceleration sensor. Many modern pacemakers contain accelerometers that monitor the activity of the patient and adapt the pacing rate accordingly [103]. One company has developed an accelerometer in the tip of a lead [104]. Another device uses an accelerometer and telemetry system for the detection of hip prosthesis loosening by vibration analysis [105]. The same group already used accelerometers for injectable animal monitoring in 1993 [106].

2.1.3. Amperometric sensors. An amperometric principle (measuring current) is, for example, used to measure glucose. Glucose oxidase (GOx) is immobilized in some way on a microfabricated electrode. GOx is an enzyme (a catalyst in biological systems) that facilitates the oxidation of glucose. This reaction produces hydrogen peroxide that takes part in the corresponding reduction reaction at another electrode. Micromachined electrodes have the advantages of low cost, mass production, fast response time and high reliability. However, the output current is very low because of the small size and it is difficult to immobilize GOx on the electrode surface. Therefore the main technological challenges of these sensors are in the charge transfer mechanism, the GOx immobilization using various methods (glutaraldehyde cross linking, bovine serum albumin cross linking, electro polymerization, sol–gel) or self-assembling mono-layers and electrode material issues (Au, Pt, carbon). The largest portion of these sensors is for use outside the body. We present here implantable devices that use microfabrication to add functionality to amperometric glucose sensors with microelectrodes. One group presents a surface micromachined needle-shaped structure for *in situ* glucose monitoring. The Ti/Pt and Ag/AgCl electrodes are located at the tip of the needle. The needle shape and windows in the cells are created using wet and dry etching [107]. Others have used cleanroom processing techniques to mass-produce flexible, electroenzymatic glucose sensors designed for implantation in subcutaneous tissue for continuous glucose monitoring [108]. Currently this system is market released and feasibility studies of a combination with insulin pump therapy are being performed [109].

2.1.4. Other sensors. Under this heading we will present flow-, ac conductance-, magnetic-, strain-, force- and other sensors for a variety of clinical applications.

Measurement of blood flow can be relevant for the diagnosis of cardiovascular disease, for monitoring restenosis in stents [110] or for optimizing settings of pacemakers. Some techniques for measuring flow are based on the differential hot film anemometer. One implementation of this principle uses a bulk micromachined 5 μm thick membrane with two temperature sensitive diodes and polysilicon heating resistor [11]. Another one proposes the use of distributed thermistor thin film on a catheter to measure flow [111]. A flow sensor based on a microoptomechanical principle is described in [112]. The position of a micro-machined part that is packaged between two glass wafers is dependent on the flow and is measured by a light emitting diode (LED) and a photodiode on opposite sides of the two glass plates. It uses a 30 μm thick silicon on insulator (SOI) layer with 3 μm oxide where the carrier layer is completely etched away. An electromagnetic principle to detect wrong probe placement by an unbalance in flow is presented in [113]. An electric field is measured perpendicular to the flow and a magnetic field created by a dual magnet setup. For flow based on the Doppler effect using micro-machined ultrasound transducers, see section 2.4.

Alternating current (ac) conductance can be correlated to the hematocrit value of the blood and can be measured with a four-point measurement from Pt electrodes made using a lift-off technique [11].

Magnetic sensors are used to facilitate navigation during clinical procedures. One such system has a three-dimensional (3D) magnetic sensor on a catheter [114, 115].

Strain sensors are used in dental care and orthopedics to monitor the status of implants. A low power miniaturized

autonomous datalogger capable of measuring, compensating and processing 18 different strain gauges simultaneously is presented in [116]. Hip and knee joint prosthesis are modified to enclose strain gauges and electronics [117].

Force sensors are used in minimally invasive robotic surgery. One sensor is based on a flexible titanium structure fabricated using electrodischarge machining of which the deformations are measured through reflective measurements with three optical fibers. It has a range of 2.5 N in the axial direction and 1.7 N in the radial direction [118]. The addition of MEMS tactile sensors on tools for minimal invasive surgery is described in [119].

Information from multiple sensors located on the tip of a catheter generates more data that will be available to the doctor to improve diagnosis, monitor the procedure and assess the effectiveness of therapy during minimal invasive transvenous cardiological or neurological procedures [120]. Measuring pressure, flow and temperature at the same time assists in diagnosing small vessel disease [121]. A multiple parameter blood sensor for simultaneous pressure, flow and oxygen saturation is presented in [18, 120]. The pressure sensor has a 4 μm thick polysilicon membrane with polysilicon piezoresistive readout; the flow velocity sensor has a polysilicon heater with aluminum-polysilicon thermopiles on either side and the oxygen saturation sensor uses two stacked diodes with the top one being sensitive to 660 nm and 800 nm and the bottom one only to 800 nm. Another catheter tip chip measures pressure, flow and temperature simultaneously. Pressure is measured using piezo resistive elements on a flexible membrane. Flow is measured using the hot wire method or temperature dillution. Temperature is measured using the temperature sensitivity of the piezo resistor [121]. Another contribution describes a silicon chip with a pressure and a temperature sensor with a total catheter size of about 1.5 to 2 mm diameter [4].

There are a number of other examples involving other types of sensors that are made using microfabrication technology. One research project is developing miniscule subcutaneous sensors which can be used to monitor, for example, the function of the heart or prosthetic joints over long periods of time [122]. Others are aiming at the development of an implantable glucose sensor [123, 124].

Finally there are some implantable applications of sensors for continuous long-term animal monitoring that we would like to mention. One company has a whole range of products for animal use (blood pressure, heart rate, electro-cardiogram (ECG), electro-encephalogram (EEG) and activity) and also a human clinical division. [125]. A European research project yielded a device that monitors heart sounds. The electronics are housed in a polyallomer tube (dimensions 75 mm $\times$ 17 mm) including a piezoelectric sensor [126]. Even though storing an identification number is not really sensing something, we mention two chronically implantable radio frequency identification devices (RFID) chips for animal use. One consists of a passive chip and antenna sealed in an inert glass capsule implanted under the skin and only activated when the scanner is placed over it [127] and the other is implanted using an injection pistol [128].

2.2. *Electrical stimulation and sensing*

A large portion of implantable clinical applications of microsystem technology deals with electrical stimulation and/or sensing and has a long history starting in the 1950s [25]. Examples of current devices and therapies are cardiac pacemakers, cardiac resynchronization devices, implantable cardioverter defibrillators, cochlear stimulators, neurological pulse generators for spinal, deep brain or sacral nerve stimulation [129, 130] and there are options for other clinical areas [131]. Generally speaking, an electrical stimulus is generated by an implantable pulse generator (IPG) and electrically conducted to an electrode positioned at the therapy delivery site.

This section provides a general overview of the various electrical stimulation/sensing devices using microfabricated electrodes including complete stimulators made using microsystem technologies (microstimulators) for implantable applications. The term microelectrode is also used for single electrodes with a diameter in the order of 1 μm made of glass or etched metal needles applied for intra-cellular potential recordings. In this paper we only consider microelectrodes made using IC-like fabrication technologies, offering the advantages of exact electrode positions, small size, multiple electrodes, improved electrode tissue interface and active circuitry [131–134] that can lead to adaptable therapy [135].

Microelectrodes are made on a flat substrate with thin film techniques (2D array), plating (electroplating or electroless) creating 2.5D or with combinations of various processing steps to create poles with the possibility of having multiple electrodes along the length of each pole (3D array). The electrode materials are Pt/Au/Ir/Ir-oxide/Ag/TiNi/C. These materials have optimum charge transfer properties for electrical stimulation in combination with electrochemical properties that lead to long-term stability. There are several concepts in which the electrodes are made on top of electronic circuitry providing some form of intelligence (multiplexing/current sources). The substrates can be thinned or processed to the extent that they become flexible, or can be made of a flexible material from the start.

2.2.1. Microelectrodes for opthalmic applications. In some diseases of the eye such as retina pigmentosa or age related macula degeneration, only the rods and cones that transform incoming light into electrical signals are affected while the optic nerve fibers are still intact. Electrical stimulation of the nerve cells in the retina [136, 137], in order to generate visual sensation in these patients, is being investigated by several groups. In general terms, the stimulation pattern is either based on wirelessly received information generated by a camera system, data processing algorithm and transmitter unit or directly received from photosensitive elements attached to the electrodes. Other approaches use electrical stimulation of the optical nerve or in the visual part of the cortex [138]

2.2.1.1. Epiretinal stimulation. In this case electrodes are place in contact with the ganglion cells that are located at the inner surface of the retina. An intraocular prosthesis that could electrically stimulate the inner retina to provide vision has been postulated in 1994 [139]. Since then this system has gone through animal [140] and human testing [141]. It

consists of an implantable stimulator and a 4 × 4 array of 460 μm diameter platinum discs positioned on the retina. The implantable part of another system consists out of a coil on flex with decoder IC and stimulation IC with electrodes [11, 19, 34, 142]. This work started in 1995 [143] and has been extensively tested in animals [144]. The authors involved in the above projects have published the actor component of the retina implant stimulator, which is a flexible active silicon multielectrode used for electrostimulation of the retinal ganglion cells [142]. A similar system is being developed in the context of the European project Healthy Aims [145]. First acute human trials with part of the system are being done [146]. In 1996 another group reported on stimulation of ganglion cells using conventional electrodes or a neural prosthesis [147]. The retina is electrically stimulated using iridium oxide electrodes on a flexible substrate [148].

2.2.1.2. Subretinal stimulation. In this case electrodes are placed under the surface of the retina and receive their signals from photosensitive elements. Subretinal electrical stimulation of the rabbit retina with a bipolar strip electrode consisting of two pieces of Au foil on both sides of a polymer foil was reported in 1997 [149]. The same authors are involved in a company that makes an 'artificial silicon retina', a microchip with 5000 solar cells that stimulates remaining functional retinal cells [150, 151] which is currently in clinical trial [152]. The feasibility of a similar concept investigated by another group is presented in 1999 [153]. The long-term stability and biocompatibility of the subretinal implants have been studied extensively [153–155] using wired prototypes and a silicon-based micro-photodiode array that closely resembled the design and composition of the final prosthesis [156]. Three-dimensional microfabrication substrate-integrated microelectrodes show an improved charge transfer capacity [157]. This group has also published a survey of subretinally implanted microphotodiode arrays [158] and visual prostheses in general [159].

2.2.1.3. Optical nerve stimulation. Visual information received in the eye is transmitted in electrical form through the optical nerve to the visual cortex. Appropriately encoded electrical stimulation of the optical nerve could restore vision in blind patients. A first system was implanted in 1998 [160] and patients are still being followed [161]. It is experimentally determined which stimulus causes which phosphenes, and this information is used to transform images into a stimulation pattern.

2.2.1.4. Visual cortex stimulation. Electrical stimulation of the medial occipital cortex can produce visual sensations [138]. One system includes a video camera, external signal processing equipment and a brain implant that gives blind people with totally non-functional retinas the ability to have some kind of vision [162, 163]. Research into an array of penetrating electrodes that can form the basis of a visual prosthesis centered around electrical stimulation of the visual cortex was reported in 1988 and is ongoing [164–166]. The system is also being used for chronic recording of the neuronal activity in the visual cortex [167, 168]. These studies can aid in the development of implantable electrical stimulation systems to restore vision [168]. The evolution of the electrode array manufacturing and design is extensively described in the literature [165, 169–171]. Another group uses an array of 38 microelectrodes spaced 500 μm apart [172]. Yet another group uses a miniaturized visual implant containing a microelectrode array [173–175].

2.2.2. Microelectrodes for auditory applications. Along similar principles as applied in the ophthalmic case described above, electrical stimulation can restore 'hearing' in patients who have an intact nervous system but irreversible conduction hearing loss like damaged hair cells in the inner ear. Electrical stimulation of the auditory nerve can be applied in the cochlear nerve in the inner ear, in the midbrain or in the brain [176].

The use of microfabrication for better field distribution, using addressable electrodes and well-timed electrical pulses for field steering, can improve the therapeutic effect [177]. Microtechnologies for this application are being investigated in the context of a European project [178, 179]. Topics include active electrodes for implantation in the cochlea, polyimide- and integrated silicon based electrodes for implantation in the modiolis nerve bundle and microconnectors and microelectrodes [176, 178]. An example from another group is an entirely flexible microelectrode array (40 mm long, 4 μm thick) that is made using a boron/ethylenediamine-pyrocatechol (EDP) approach designed for insertion into the cochlea. The shape and position can be monitored by sensors on the probe [133].

2.2.3. Microelectrodes to restore motor function. Restoration of motor function in paralyzed limbs due to damaged nerve fibers may be realized by electrical stimulation. Recording of signals from nerves may be used as feedback or input to form neuroprosthetic devices [180].

There are many examples of restoring motor function by electrical stimulation that are not using microelectrodes but that do use microfabrication techniques in other parts of the implant [181–186]. Most of these have a history of over 25 years. In 1991 an injectable microstimulator contained in a hermetically sealed glass capsule receiving power and command signals by inductive coupling for use at neuromuscular sites was described [187–189]. In the same year another group performed a study with a 45 μm thick tip-shaped silicon substrate containing twelve platinum electrode sites (10 μm × 50 μm and 50 μm distance) with a Si_3N_4 insulating layer [190]. Four years later a 3D multi-electrode array manufactured using a sawing procedure in combination with a reactive ion etching (RIE) process was presented. A flip-chip technique to connect the array to (de)multiplexing circuitry, in which current sources and buffer amplifiers are also integrated, is being studied [191]. Later, a two-dimensional 24-channel array using 25 μm diameter NiCr wires was used to achieve the desired level of redundancy [192].

A microstimulator that can be implanted through a gauge-10 hypodermic needle was developed in 1996. It uses a glass silicon anodic bond and polysilicon feedthroughs [193–196]. The same microelectrode arrays that have been described above for visual cortex stimulation and recording have been proposed as a means to enable patients with severe neuromuscular disease to more effectively interact with

their environment [166, 180, 197]. Another group describes platinum electrodes fabricated with a lift-off technique on a 5 μm polyimide carrier to be placed around a nerve. A top layer of polyimide is deposited for mechanical support and isolation, the electrode areas are opened by RIE [198]. Mutiplexer circuitry is connected to the electrodes using a specially developed interconnect technique to reduce the number of cables needed to address the electrodes [10, 13, 17, 131, 199]. Special electrode designs using similar fabrication techniques are intended to promote nervous regeneration through holes in the structure [13, 200]. More recently, the development of an all plastic implant including electronics and conductors for improved flexibility has been presented [200, 201]. Another implantable microstimulator system for neuromuscular stimulation is described in [202, 203]. In 1987 an implantable stimulator packaged in a ceramic cylinder for long-term muscle stimulation was reported [204, 205].

2.2.4. Microelectrodes for brain research. Penetrating neuro probes for recording of brain activity offer the advantage that signals can be collected from within the brain. The examples mentioned in this section are mainly used to study the functioning of the brain at a fundamental level. They enable discovering correlations between electrical activity in the central nervous system and externally applied psychophysical stimuli [206, 207]. Mostly, the long-term outcome of this fundamental research is targeted towards a specific clinical application. For example, brain activity during a developing epileptic seizure was measured inside the brain before it was measurable on the surface [22] and its use for closed-loop control of neural prostheses was studied [208]. Although they are aimed at these applications, we feel that the concepts presented here fit best under this heading of brain research. There are several ways to fabricate such electrical probing devices using micro technology. One example uses a silicon carrier (3 mm $\times$ 50 μm $\times$ 15 μm) that supports an array of polysilicon or tantalum thin-film conductors. Silicon nitride and silicon dioxide are used to define the electrode openings. The process allows inclusion of circuitry for signal amplification and multiplexing [208]. More recently this group presented silicon ribbon cables for implantable neural probes [209]. Another multiple electrode probe is produced by means of thin-film techniques. Silicon dioxide and silicon nitride are used as the insulation layer. Gold, platinum or silver that can be chlorodized at the surface are used for recording [22]. Others have proposed to treat chronic pain in a closed-loop scheme of electrical recording and stimulation in the brain. The probe substrate structure is obtained from a thinned silicon wafer. Each recording probe has ten TiW/Au recording sites [207]. Yet another penetrating neural probe for neuro biological research has 16 iridium electrodes on each tip that are made in three phases using a combination of dry and wet etching [132]. One implant has three shanks with five recording sites (20 μm $\times$ 20 μm) and two via holes (40 μm $\times$ 40 μm) to promote tissue attachment on each shank. The electrodes have a 5–10 μm thick silicon backbone layer at the tip that is rigid enough to penetrate the pia and a 1 mm flexible segment without a silicon backbone layer [210, 211]. A multifunctional probe allowing both electrical and chemical recording and stimulation for fundamental brain research is being developed in the context of a European project [212]. Another example is the use of a three-dimensional array of microneedles that penetrates the outer skin layer for electroencephalography. The spikes are etched in silicon by deep reactive ion etching and are subsequently covered with a silver–silverchloride (Ag–AgCl) double layer [213]. A device that allows the stimulation electrodes to be configured and thereby reduces side effects for deep brain stimulation is under investigation by another group [214].

2.3. Micromachined drug and gene delivery devices

Drugs can improve the life of patients for a wide range of clinical conditions and can be administered in a number of ways. Microsystems are aiming at improving the control over the release of the drug at the appropriate time and site and in appropriate dosage. We distinguish four different sorts of microsystems in this area: implantable pumps, smart pills, micro porous materials and microneedles (considering skin penetration as implantable).

The basic ingredients of a membrane type of pump are a fluid inlet, a pumping chamber and a fluid outlet. The volume of the pumping chamber is controlled by a deflectable membrane. One stroke of the membrane moves a controlled volume of fluid. Valves on the in- and out-let ensure flow in the correct direction. Important design characteristics for the delivery of substances to the body are accuracy, resolution, safety and control. Therefore additional features on such pumps are integrated-pressure sensors, -flow restrictors and -fluid filters [215].

One completely microfabricated pump opens the way to the implantation of the pump at various anatomical positions [216, 217]. Another company is progressing towards the first market introduction of a micro pump [218]. Implantable biosensors and micropumps also work together as a closed loop control system for personal pharmaceutical delivery [219]. Other pumps contain micromachined parts or sensors for pump control.

An ingestible capsule that signals a remote receiver and releases a dosage of medicament when triggered is described in [220]. A similar concept is a micro pill containing drug reservoirs and microelectronics for the controlled release of the drug using wireless technology [221, 222]. Another variation of this concept is the timed release of single doses from within a large array of dose reservoirs [223].

Some drug delivery concepts are based on porous materials or nanoporous membranes [216]. There are also various examples of microneedles being used for transdermal drug delivery. [124, 216, 224, 225]. One concept includes pumping, liquid storage, liquid dosing and anti clogging measures [226–228].

Microneedles have also been used for transdermal gene delivery. One technique is based on a set of oscillating solid microneedles driven by a modified tattooing device that results in plasmid DNA delivery directly to the target cells. This technique is more efficient than single injection and particle-mediated gene transfer [229]. Arrays of silicon projections ranging in height from 50 to 200 μm have been fabricated using isotropic potassium hydroxide etch techniques on 1 cm^2 microchips. When these micro structures were placed in

contact with DNA solution and then moved laterally over the skin they were able to breach the skin barrier [230]. There is one example of a stent with micro needles covered with a nanoporous layer that contains the therapeutic agent such as DNA. The needles are designed to penetrate the internal elastic lamina of a vessel leading to an effective delivery. The translamina stent has been successfully deployed *in vivo* in rabbit femoral arteries [27].

2.4. Micromachined ultrasound transducers

Micromachined ultrasound transducers are used to measure flow based on the Doppler effect [110] or provide images based on echos [231–233] for vascular or endoscopic [234] applications. The implantable ultrasound transducers mentioned here are designed to fit on a tool in the shape of a catheter or guidewire for use in transvenous or minimally invasive procedures. Individual element dimensions in the order of micrometers are achieved with 'non-standard' microfabrication techniques out of bulk lead zirconium titanate (PZT) material, and are needed to fit the transducers on the implant tools. More recently, capacitive micromachined ultrasound transducers (cMUT) were introduced manufactured by means of surface micromachining, offering the advantage of higher integration levels for improved quality.

cMUT consist of a sealed cavity beneath a membrane with electrodes on both sides of the membrane. An electrostatic force between the plates of the capacitor causes the membrane to vibrate and emit acoustic energy. A 16 × 16 cMUT array that fits through a 5 mm lumen is proposed for two-dimensional (2D) real-time volumetric imaging in [234]. The silicon substrate on which the cMUT are made can also be thinned down and bent [235]. Another group has used cMUT for forward looking intravascular ultrasound [232, 236, 237].

The devices based on PZT all realize a large number of interconnects in a small space. One group creates the transducers on a flexible circuit that is rolled up to fit into a 1.2 mm diameter guide wire which puts very high requirements on flip chip, chip thinning, dicing accuracy and number of interconnects [238]. Likewise, a 112 channel two-dimensional array constructed on a six-layer flexible polyimide interconnect circuit is mounted on a catheter with 2.33 mm outside diameter [239, 240] or a 1 mm diameter intravascular probe involving a bended flex circuit with connections to a multiplexer and cable [233].

2.5. Microoptoelectromechanical systems (MOEMS)

Endoscopes are used to visualize the interior of a hollow organ or to provide vision during minimally invasive surgery. Endoscopy started with the use of rigid tubes with fixed lenses until the 1970s. Multicore fiber optics enabled flexible endoscopes in the 1980s [4]. Further miniaturization led to the development of endoscopes with a video camera at the distal end [241]. Microsystem technology can further enhance the functionality of next generation endoscopes. Examples are a diagnostic endo laser scanner with optical components realized using lithographic methods and microscanning mirrors to avoid the spectral limitations of conventional image guides [242], a miniature endoscopic confocal optical scanning microscope with a scanning head including an electrostatic 2D MEMS scanner [243] and an optical coherence tomography endoscope based on a microelectromechanical mirror [244].

Endoscopy can be uncomfortable for the patient, has to be done in the hospital and does not allow optimal view in difficult areas of the anatomy. A capsule endoscope attempts to address these limitations. Two examples of capsule endoscopes are a camera pill containing an optical lens, CMOS imager, battery and radio transmitter that travels through the GIT while sending video images out and an intracorporeal videoprobe that uses a CMOS camera and micro-mechanical tilting mechanism [245–247].

A glucose sensor for implantation in the subcutaneous tissue of the human body is being investigated. The optical characteristics of glucose in the near infrared spectrum are used for concentration measurement by absorbance of fluid in a microfabricated chamber [248]. Finally there is a miniature implantable telescope with two glass fabricated micro lenses that can project a magnified image over a large area of the retina [249, 250].

2.6. Other microsystem devices for implantable applications

Micro actuators are used for making smart catheters for minimally invasive (transvascular) procedures. They involve the use of 3D lithography, electronics and shape memory [251], distributed microactuators made of shape memory alloys [26, 252] and a catheter that can be heated locally via distributed electrical contacts [253].

Micro-machined cutting tools have sharper edges then conventional needles and can be combined with ultrasonic energy or sensors [254, 255]. They can be used when very fine and precise surgery is needed, for example in ophthalmology [254, 256]. One device consists of two silicon ultrasonic horns bonded with a channel along the length to form a needle [254]. Later devices are silicon needles with integrated piezoresistive pressure sensors fabricated using bulk micromachining technology and bonded PZT-4 plates for ultrasonic energy [255, 256].

Nano- or microstructured surface topologies may provoke a desired tissue response in urological, cardiological or orthopedical implants [257–259]. Likewise, nano reinforced materials might have suitable properties for neural or orthopedic prosthetic devices [260].

A subset of microfabricated scaffolds used for tissue engineering is made implantable by using biodegradable material. Several types of polymers have been described. Closed micro fluidic channels at the capillary size-scale have been manufactured of poly-lactic-co-glycolic acid using a micro molding process. The process is high resolution, fast, inexpensive, reproducible and scalable [261]. Likewise, microstructures with simple fluidic channels have been fabricated of poly-(ε-caprolactone-dl-lactide) tetraacrylate using a fast and flexible soft-lithography process. Microstructures down to 50 μm suitable for liver reconstructs were fabricated [262]. Polyglycerol sebacate is another biocompatible and biodegradable elastomer that can be used as a material for fabricating microfluidic vascular scaffolds or nerve guides. Three-dimensional structures are created from this material by a micromolding process in combination with multilayer bonding. Controlling the

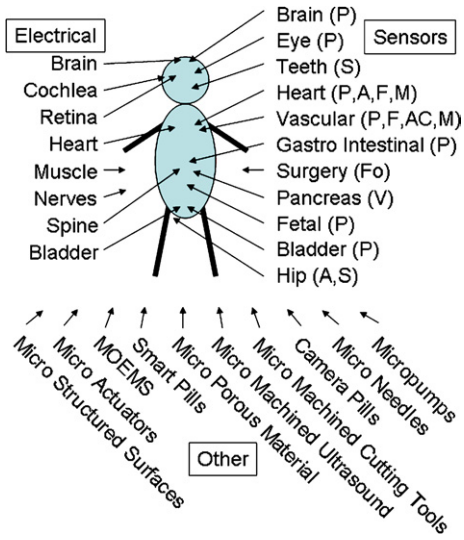

Figure 1. Microsystem technologies for implantable applications. Electrical means MST for electrical stimulation and sensing and includes micro stimulators. Sensors: P = Pressure, A = Acceleration, Fl = Flow, AC = AC conductance, M = Magnetic, S = Strain, Fo = Force, M = Multiple, V = Viscosity. Other is the collection of other types of MST. MOEMS = micro opto electro mechanical system.

cellular microenvironment (concentration of oxygen, fluid shear forces) within scaffolds is critical for eliciting desirable biological responses such as proliferation, migration and maturation. The scaffold is suitable for incorporating multiple cell types and integration with existing biomaterial systems and technologies for tissue-specific applications [263]. There is one company that uses nanostructured porous silicon as a biodegradable material, which can be easily micromachined in the form of scaffolds [264].

A system for continuous glucose monitoring during dialysis involves a microneedle array to sample interstitial fluid and an electrochemical enzyme-based glucose sensor. The microneedles contain an integrated porous polysilicon dialysis membrane that separates the interstitial fluid from dialysis fluid, which is pumped through the microneedles. Glucose can diffuse through this membrane into the system. The glucose sensor involved in this system is an integrated enzyme-based microsystem fabricated on wafer-level using in-device immobilization which is located outside the body [265].

2.7. Summary of implantable microsystems

In the previous sections, a wide range of microsystems for implantable applications has been presented with a focus on its micro part. As a first observation we can state that a large range of microsystems is being used or investigated. We have presented a variety of sensors, numerous microelectrodes, drug delivery devices, micro-machined ultrasound transducers, MOEMS, micro actuators, surgical tools and micro surface topology (figure 1). In figures 2 and 3 respectively graphical overviews of microsystems for chronic and acute/temporary implantable applications are shown.

To further analyze the information we have classified each 'end item' on a number of aspects. By end item we mean the total 'product'. We have introduced this term because the microsystem is frequently just a part of a product. We say 'product' because the end item can have various status (see below).

End items are categorized by

1. MST class and -part
   - Class according to paragraph headings used in this section (E = Electrical, S = Sensor, D = Drug delivery, M = MOEMS, U = Ultrasound, O = Other).
   - Part to further specify detail per class.
2. Duration of implant
   - Transient (<1 day, TR); Temporary (1 day < duration < 30 days, TE); Chronic (>30 days, CH).
3. Type of organization
   - Academic (A);Commercial (C).
4. Status of end item
   - Idea (ID); Proto (OTO); Animal (AN); Clinical (CL); Product (ODU).
5. Clinical Field
   - Animal (An), Auditory (Aud), Cardiology (Car), Dentology (Dent), Drugdelivery (Drug), Endocrinology (Endo), Fetal (Fetal), Gastroenterology (Gastro), Neurology (Neuro), Oncology (Onco), Ophthalmology (Oph), Orthopedics (Orth), Surgery (Surg), Tissue Engineering (Tis), Urology (Uro) and Various (Var).
6. Activity
   - Active (A) if publication or webpage update in year 2000 or later, Passive (P) otherwise.

Classification is based on the references mentioned in this paper; fields are filled out as unknown if it is not clear how to classify based on the available information. As with every classification, there is never a perfect match for all; therefore there is always a category 'Other'. There are many examples of end items that are being realized in the context of government funded programs. We have classified these as commercial if there is an industrial partner driving the application and as academic otherwise. Besides the classifications, the name of the end item, name of the organization, reference to the internet address and year/author of the oldest and most recent paper are given. Note that we only mention a couple of implantable microfabricated parts contained in a 'classic' hermetically sealed metal casing. An overview is given in table 2.

Although there are more then 140 microsystems for implantable applications listed in table 2 we do not claim that this overview is complete. Nevertheless we will make some observations based on these data. In figures 4 and 5, the distributions of the publication dates of the references that have been included in table 2 are examined. Thirty-three percent (15 of 45) of the end items with both most recent and oldest reference originate from the year 2000 or later. Thirty-two percent of the end items have both a most recent and oldest reference. Tables 3–6 provide various ways of ordering the

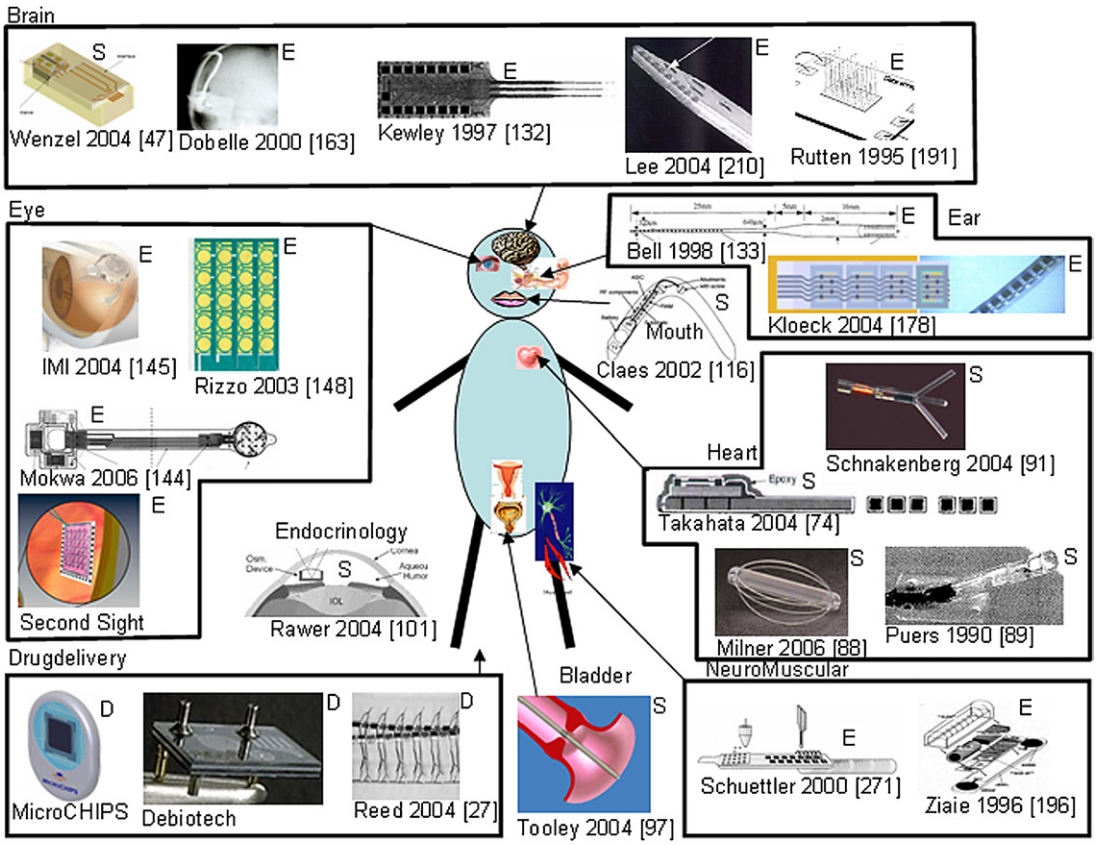

Figure 2. Graphical impression of microsystems for chronic implantable applications. The capital letter next to the figure refers to the main section in which this example is described in the text. S = Sensors in section 2.1; E = Electrical stimulation and sensing in section 2.2; D = micromachined drug and gene delivery devices in section 2.3; U = micromachined ultrasound transducers in section 2.4; M = microoptoelectro mechanical systems in section 2.5 and O = Microsystem technologies for other implantable applications in section 2.6. The figures are grouped per anatomical location as indicated by the black lines, text and arrow towards the graphical representation in the center which can be used to locate the applicable subsection in the text. The text under each figure provides reference to the original source. All graphics are reprinted with kind permission of both the publisher and the authors. When taken from a publication the last name of the first author, the year of publication and the reference number (between square brackets [ ]) are given below the graphic. The reference number refers to the numerically ordered reference list at the end of this paper in which full details of the source publication can be found. The year of publication is also the year of copyright. When taken from the internet the name of the organization is given below the graphic. The complete internet address is given in the overview table 2 (see below). [89, 91, 116, 132, 133, 191, 210] copyright by Elsevier. [74, 196] copyright by IEEE. Photo credit for Second Sight: Doheny Eye Institute/USC. [148] copyright by the Association for Research in Vision and Ophthalmology.

data using the classification scheme. Further commenting on the numbers is done in the table captions.

3. Overview of basic technological building blocks

In this section the information will be restructured in the form of the underlying technical blocks needed to produce the end items:

- Processing
- Packaging
- Communication
- Power
- Materials.

To treat these building blocks in detail would take a separate review paper for each of them. Therefore, the aim of this section is to provide a general overview of what type of technologies are used, regardless of the classification as presented above. Figure 6 provides a schematic representation of an implantable system.

3.1. Processing

In this section, microfabrication processes that form the basic manufacturing technologies used to produce the end items reviewed in this paper are briefly described. Surface micromachining involving thin layer deposition, sacrificial layer etching, photolithographic patterning and etching are used. Processes compatible with CMOS allow integration with electronic circuitry. Bulk micro-machining involving both dry and wet etching of silicon, and stacking of wafers is shown. Some devices use soft materials made using polymer micro-machining technologies such as micro molding or hot embossing. Laser micro-machining is used to drill holes or cut material. Sometimes 'non-traditional' fabrication processes coming from disciplines such as chemistry or biology are used, for example, for amperometric sensors or coatings. Many of the papers referenced in this review contain details of the micro processing steps used to manufacture the design. A number of introductory texts on microfabrication technologies exist, for example [31, 266, 267].

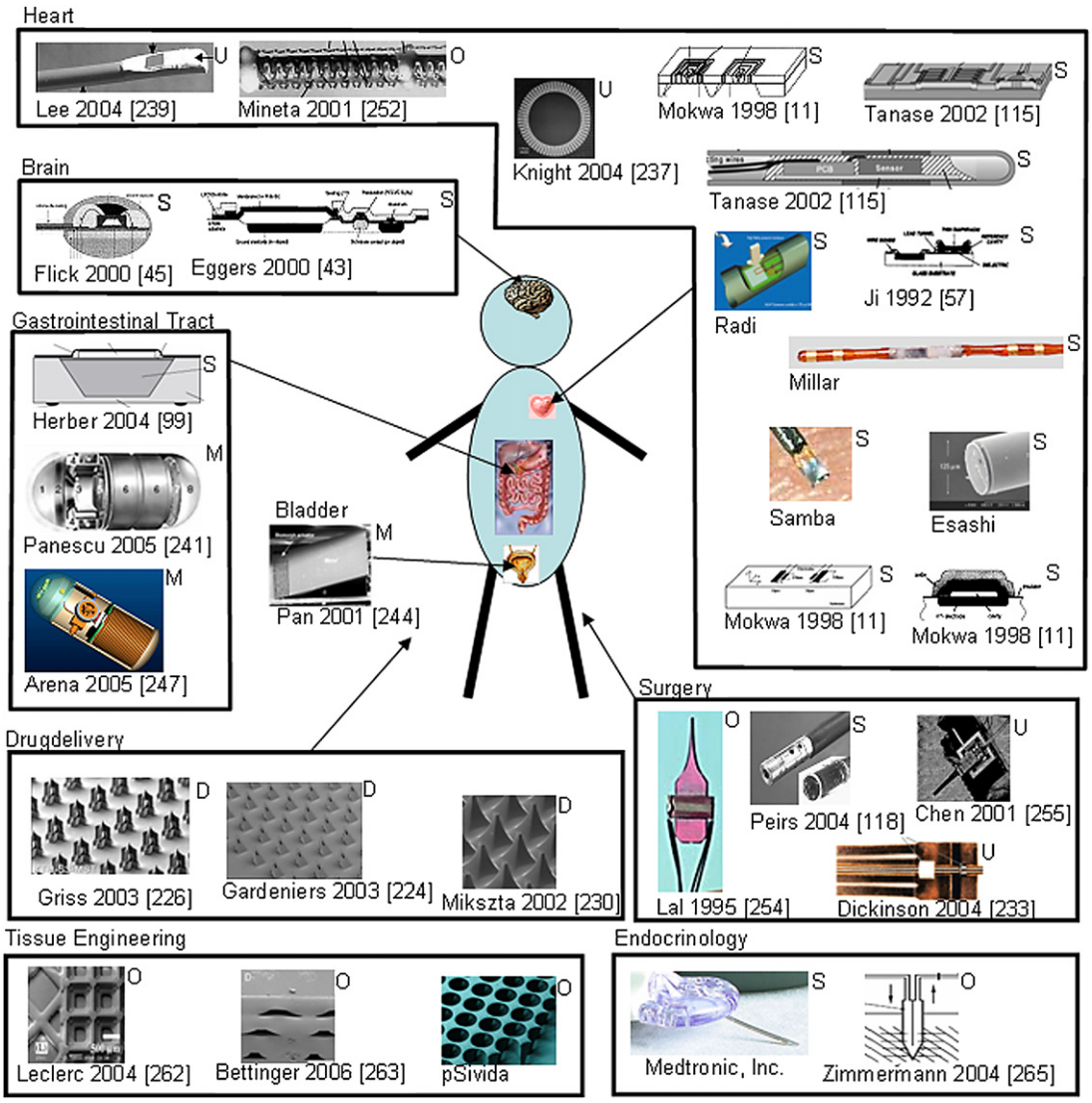

Figure 3. Graphical impression of microsystems for acute and temporary applications. The capital letter next to the figure refers to the main section in which this example is described in the text. S = Sensors in section 2.1; E = Electrical stimulation and sensing in section 2.2; D = micromachined drug and gene delivery devices in section 2.3; U = micromachined ultrasound transducers in section 2.4; M = microoptoelectromechanical systems in section 2.5 and O = Micro system technologies for other implantable applications in section 2.6. The figures are grouped per anatomical location as indicated by the black lines, text and arrow towards the graphical representation in the center which can be used to locate the applicable subsection in the text. The text under each figure provides reference to the original source. All graphics are reprinted with kind permission of both the publisher and the authors. When taken from a publication the last name of the first author, the year of publication and the reference number (between square brackets [ ]) are given below the graphic. The reference number refers to the numerically ordered reference list at the end of this paper in which full details of the source publication can be found. The year of publication is also the year of copyright. When taken from internet the name of the organization is given below the graphic. The complete internet address is given in the overview table 2 (see below). [99, 115, 118, 252, 262, 265] copyright by Elsevier. [43, 45, 57] copyright by IEEE. [247] copyright by IOS Press. [233] copyright by IOP Publishing Ltd. [263] copyright by Wiley-VCH. [230] copyright by Macmillan Publishers Ltd.

3.2. Packaging

This section deals with the packaging for implantable applications. The body is (fortunately) a very hostile environment for foreign bodies that enter it, due to our active immune system. Delicate parts of microsystems are therefore often protected by a hermetic package, traditionally a metal casing. Electrical communication with the outside of a hermetic cavity is possible by means of hermetic feedthroughs. Electrical conductors and interconnections outside a hermetic cavity will have to be biostable. Coatings used to improve the properties of the implant can be seen as a special way of packaging.

3.2.1. Hermetic protection, electrical-feedthrough, -interconnect and -conductors. We will focus on presenting the examples found in the literature of electrical interconnects outside a hermetic cavity (if there is one) and on how electrical signals are fed into the hermetic cavity (feedthroughs) assuming that once inside the hermetic cavity packaging can

Table 2. Overview of end items with classification and additional information. End item refers to the total product. Organization is the main organization that is driving the development. Part is an abbreviated indication of the actual microsystem part of the end item. In this column ac cond = alternating current conductance, CMUT = capacitive micromachined ultrasound transducer, PZT = lead zirconium titanate and the remaining abbreviations should be self apparent. Dur. is the duration of implant (transient (<1 day, TR); temporary (1 day < duration < 30 days, TE); chronic (>30 days, CH)). Type is the type of organization (Academic (A); Commercial (C)). Stat. is the development status of the end item (Idea (ID); Proto (OTO); Animal (AN); Clinical (CL); Product (ODU)). Clin. is the clinical field of application (Animal (An), Auditory (Aud), Cardiology (Car), Dentology (Dent), Drug delivery (Drug), Endocrinology (Endo), Fetal, Gastroenterology (Gastro), Neurology (Neuro), Oncology (Onco), Ophthalmology (Oph), Orthopedics (Orth), Surgery (Surg), Tissue Engineering (Tis), Urology (Uro) and Various (Var)). Act. is the activity (Active (A) if most recent reference published in year 2000 or later or on the internet, Passive (P) otherwise). Then the publishing year and first author of the most recent reference followed by the publishing year and first author of the oldest reference (if applicable). Full references can be found in the reference list of this paper. The final column contains a reference to the internet. Rows are first ordered per MST class: Sensors; Electrical Stimulation and Sensing; Micromachined drug and gene delivery devices; Micromachined ultrasound transducers; Microoptoelectromechanical systems and other microsystem devices for implantable applications that correspond to the major sections in this section. Rows are then ordered alphabetically on Part, Activity and Duration.

End item	Organization	Part	Dur.	Type	Stat.	Clin.	Act.	Year	Author	Year	Author	Internet
Sensors												
Hematocrit sensor	RWTH Aachen	AC Cond.	TR	A	OTO	Car	P	1998	Mokwa			iwe1.rwth-aachen.de
Hip prosthesis loosening	Leuven, Katholic University	Accelero.	CH	A	AN	Orth	A	2000	Puers			esat.kuleuven.be/micas
Accelerometer	Sorin Biomedica	Accelero.	CH	C	ODU	Car	P	1998	Langenfeld			elamedical.com
Injectible AN Monitor	Leuven, Katholic University	Accelero.	CH	A	OTO	An	P	1997	Puers	1993	Vergrote	esat.kuleuven.be/micas
CGMS	Medtronic, Inc.	Ampero.	TE	C	ODU	Endo	A	2006	Mastro.	1992	Johnson	medtronic.com
Needle glucose sensor	Electr. Telecom. Res. Inst.	Ampero.	TE	A	OTO	Endo	P	1999	Kim			cadvax.etri.re.kr
Flow catheter	Verimetra	Flow	TR	C	AN	Car	A					verimetra.com
Flow sensor on catheter	Millar	Flow	TR	C	ID	Car	P	1979	Millar			millarinstruments.com
Flow sensor on catheter	RWTH Aachen	Flow	TR	A	OTO	Car	P	1998	Mokwa			iwe1.rwth-aachen.de
Force sensor	Leuven, Katholic University	Force	TR	A	OTO	Surg	A	2004	Peirs			esat.kuleuven.be/micas
3D cath. nav. sys.	Delft University of Technology	Magnetic	TR	A	OTO	Car	A	2003	Tanase	2002	Tanase	http://ei.et.tudelft.nl
Pressure, temp and flow	Radi	Other	TR	C	ID	Car	A	2001	Smith			radi.se
Multiple parameter sensor	Delft University of Technology	Other	TR	A	OTO	Var	A	2000	Goosen	2000	Goosen	http://ei.et.tudelft.nl
MEMS tactile sensors	Verimetra	Other	TE	C	OTO	Surg	A	2003	Rebello			verimetra.com
Bloodglucose	Thera Sense	Other	TE	C	ID	Endo	A	2005	Heller			http://abbottdiabetescare.com
Implantable CO2 sensor	Twente, Technical University	Other	TE	A	CL	Gastro	A	2004	Herber	2003	Herber	mesaplus.utwente.nl
Wireless TULE	Tampere University Tech	Other	CH	A	OTO	Car	A	2004	Riistama			cs.uta.fi/hci/wtpc/groups.html
Animal monitor	Transoma	Other	CH	C	ODU	An	P	1997	Gelzer			datasci.com
Transdermal ECG monitor	Tras-os-Montes Alto Douto	Other	CH	A	AN	An	P	1997	Torres-Pereira			utad.pt
PV catheter	CDLeykom	Pressure	TR	C	ODU	Car	A					cdleycom.com
Pressure catheter	Millar	Pressure	TR	C	ODU	Car	A	1999	Millar	1973	Millar	millarinstruments.com
PressureWire, Piezo	Radi, KTH	Pressure	TR	C	ODU	Car	A					radi.se
Pressure catheter	Samba	Pressure	TR	C	ODU	Car	A	2001	Engstrom			samba.se
Catheter	Unisensor	Pressure	TR	C	ODU	Var	A					unisensor.ch
Catheter (optical)	Radi	Pressure	TR	C	ODU	Car	A	2000	Stemme	1993	Tenerz	radi.se
Bladder pressure	Wisconsin, Universityof -Madison	Pressure	TR	A	CL	Uro	A	2002	Siwapornsathain			wisc.edu
Catheter (Fabrit Perot)	Tohoku University	Pressure	TR	A	AN	Car	A	2005	Kentaro			mems.mech.tohoku.ac.jp
Impella	Abiomed/ Impella	Pressure	TE	C	ODU	Car	A	2006	Siess			abiomed.com
ICP, catheter based	Codman Neurosciences	Pressure	TE	C	ODU	Neuro	A					codman.com
ICP	SICAN / TU Berlin	Pressure	TE	C	OTO	Neuro	A	2000	Flick			tu-berlin.de
ICP telemetric (ITES)	Bremen University	Pressure	TE	C	AN	Neuro	A	2000	Eggers	1995	Zacheja	imsas.uni-bremen.de/
IOP, telemetric (ITES)	Bremen University	Pressure	TE	C	AN	Oph	A	2000	Marschner			imsas.uni-bremen.de/
IOP Sensor	Mesotec	Pressure	CH	C	CL	Oph	A	1998	Mokwa			mesotec.de

Table 2. (Continued.)

End Item	Organization	Part	Dur.	Type	Stat.	Clin.	Act.	Year	Author	Year	Author	Internet
Sensors (Continued.)												
HeartPod	Savacor	Pressure	CH	C	CL	Car	A	2005	Walton			savacor.com
Pressure Sensor	CardioMEMS	Pressure	CH	C	ODU	Car	A	2005	Allen			cardiomems.com
ICP Sensor	Campus Micro Tech.	Pressure	CH	C	OTO	Neuro	A					campus-micro-technologies.com
Remon AAA	Remon	Pressure	CH	C	CL	Car	A	2006	Ellozy	2004	Milner	remonmedical.com
Remon CHF	Remon	Pressure	CH	C	CL	Car	A	2006	Parikh			remonmedical.com
Chronicle	Medtronic, Inc.	Pressure	CH	C	CL	Car	A	2006	Braunsch.	1992	Bennett	medtronic.com
HeartPod	Savacor	Pressure	CH	C	CL	Car	A	2006	Ritzema-Carter			savacor.com
Stent	Michigan, University of	Pressure	CH	A	OTO	Car	A	2004	Takahata			eecs.umich.edu
IOP	Leuven, Katholic University	Pressure	CH	A	OTO	Oph	A	2000	Puers			esat.kuleuven.be/micas
Occular glucose sensor	Karlsruhe, University	Pressure	CH	A	OTO	Endo	A	2004	Rawer			itiv.uni-karlsruhe.de
Glucose sensitive hydrogel	Illinois Urbana-Champaign	Pressure	CH	A	OTO	Endo	A	2005	Mariserla			mse.uiuc.edu
Multiplexed catheter	Michigan, University of	Pressure	TR	A	OTO	Car	P	1992	Ji	1973	Sauman	eecs.umich.edu
Pressure catheter	RWTH Aachen	Pressure	TR	A	OTO	Car	P	1998	Mokwa	1990	Kandler	iwe1.rwth-aachen.de
Catheter (capacitive)	Tohoku University	Pressure	TR	A	OTO	Car	P	1990	Esashi			mems.mech.tohoku.ac.jp
Catheter (Piezo)	Tohoku University	Pressure	TR	A	OTO	Car	P	1982	Esashi			mems.mech.tohoku.ac.jp
Bladder pressure	Leuven, Katholic University	Pressure	TE	A	OTO	Uro	P	1987	Sansen	1984	Sansen	esat.kuleuven.be/micas
Valve and sensor	Healthy Aims	Pressure	CH	C	OTO	Uro	P	2004	Tooley			healthyaims.org
Fetal Monitor	NASA	Pressure	CH	A	OTO	Fetal	P	1998	Mundt			nasa.gov/centers/ames
Telesensor	Radionics	Pressure	CH	C	CL	Neuro	P	1990	Chapman	1979	Cosman	http://hms.harvard.edu
ICP Sensor	Texas Instruments	Pressure	CH	C	OTO	Neuro	P	1988	Talamonti			ti.com
'Swimmer'	RWTH Aachen	Pressure	CH	A	AN	Car	P	2001	Mokwa	1990	Kandler	iwe1.rwth-aachen.de
Pressure Sensor	Leuven, Katholic University	Pressure	CH	A	OTO	Car	P	1990	Puers			esat.kuleuven.be/micas
Pressure monitoring	Uppsala Institute of Tech.	Pressure	CH	A	OTO	Oph	P	1990	Backlund			uu.se
IOP	Smith-Kettlewell Ins.	Pressure	CH	A	AN	Oph	P	1967	Collins			ski.org
Dental Implant	Leuven, Katholic University	Strain	CH	A	ID	Dent	A	2002	Claes			esat.kuleuven.be/micas
Prosthesis, electronics	Stanmore Orthop. Hosp.	Strain	CH	A	OTO	Orth	A	2003	Canham			rnoh-stanmore.org.uk
Glucose Sensor	Sensile Medical	Viscosity	CH	C	OTO	Endo	A					sensile-medical.com
Electrical stimulation and sensing												
Electrodes	Royal Institute of Tech.	Electr.	CH	A	CL	Neuro	A	2001	Griss			s3.kth.se/mst
Penetrating Neural Probe	Michigan, University of	Electr.	CH	A	CL	Neuro	A	2004	Lisby	1985	Najafi	eecs.umich.edu
Retina stim photodiodes	Tuebingen, University	Electr.	CH	C	CL	Oph	A	2005	Sachs	1997	Zrenner	eye-chip.com
Artificial Silicon Retina	Second Sight	Electr.	CH	C	CL	Oph	A	2005	Weiland	1994	Humayun	2-sight.com
Configurable stimulation	Medtrode	Electr.	CH	C	OTO	Neuro	A	2004	Capaldi			medtrode.com
Artificial Silicon Retina	Optobionics	Electr.	CH	C	CL	Oph	A	2004	Chow	1993	Chow	optobionics.com
Brain implant	Artificial Ophthalmology	Electr.	CH	C	CL	Oph	A	2000	Dobelle	1974	Dobelle	artificialvision.com
Neuroprobes	Imec	Electr.	CH	C	ID	Neuro	A	2006	Neves			neuroprobes.org
Smart Electrode	Cochlear	Electr.	CH	C	ID	Aud	A	2006	Humbeeck			healthyaims.org
Neuroprobe	Cochlear	Electr.	CH	C	OTO	Aud	A	2006	Humbeeck			healthyaims.org

Table 2. (Continued.)

End Item	Organization	Part	Dur.	Type	Stat.	Clin.	Act.	Year	Author	Year	Author	Internet
Electrical Stimulation and Sensing (Continued.)												
Intra-occular Stimulation	IMI	Electr.	CH	C	OTO	Oph	A	2005	Hornig			intmedimplants.com
Polymer neural probes	Foster Miller	Electr.	CH	C	OTO	Neuro	A	2005	Farrel			foster-miller.com
Smart Electrode	IBMT	Electr.	CH	A	AN	Neuro	A	2006	Koch	1995	Stieglitz	ibmt.fraunhofer.de
EPI-RET	RWTH Aachen	Electr.	CH	A	AN	Oph	A	2006	Mokwa	1995	Eckmiller	iwe1.rwth-aachen.de
Micro intra-cortical probe	Arizona State University	Electr.	CH	A	AN	Neuro	A	2004	Lee			asu.edu
Visual Neurostimulator	Montreal, Ecole Polytech.	Electr.	CH	A	AN	Oph	A	2004	Trepanier	1996	Harvey	polystim.ca/
MeCFES	Polytechnico di Milano	Electr.	CH	A	CL	Neuro	A	2001	Thorsen			cbi.polimi.it
Optical Nerve	Leuven, Universite Cath.	Electr.	CH	A	CL	Oph	A	2006	Delbeke	1998	Veraart	md.ucl.ac.be/gren
Retina stimulation	Harvard Medical School	Electr.	CH	A	CL	Oph	A	2003	Rizzo			meei.harvard.edu
Drop Foot Stimulator	FineTech Medical	Electr.	CH	C	CL	Neuro	P	2004	Spensley	2002	van der Aa	salisburyfes.com
Freehand	NeuroControl Corp	Electr.	CH	C	ODU	Neuro	P	1995	Scott			neurocontrol.com
Cochlea stimulation	Michigan, University of	Electr.	CH	A	AN	Aud	P	1997	Bell			eecs.umich.edu
Penetrating Neural Probes	Case Western Reserve University	Electr.	CH	A	AN	Neuro	P	1986	Prohaska			cwru.edu
Neurology prostheses	MRC	Electr.	CH	A	CL	Neuro	P	1994	Perkin	1979	Brindley	mrc.ac.uk
Intracortical stimulation	Nat.Ins.Neur.Disorders	Electr.	CH	A	CL	Oph	P	1996	Schmidt			ninds.nih.gov
Neural Microprobe	Leuven, Katholic University	Electr.	CH	A	OTO	Neuro	P	1991	Peeters			esat.kuleuven.be/micas
Electrical Stimulator	Montreal, Ecole Polytech.	Electr.	CH	A	OTO	Neuro	P	1999	Arabi	1997	Arabi	polystim.ca/
Utah Electrode Array	Utah, University of	Needles	CH	A	AN	Neuro	A	2005	Patterson	1993	Nordhausen	ece.utah.edu
Utah Electrode Array	Utah, University of	Needles	CH	A	AN	Neuro	A	2005	Patterson	1998	Rousche	ece.utah.edu
Utah Electrode Array	Utah, University of	Needles	CH	A	AN	Oph	A	2003	Normann	1988	Campbell	ece.utah.edu
3D multi electrode array	Twente, Technical University	Needles	CH	A	AN	Neuro	P	1999	Smit	1991	Rutten	bmti.utwente.nl
Penetrating neural probes	Stanford, University	Needles	CH	A	AN	Neuro	P	1997	Kewley			http://cis.stanford.edu
Bion micro stimulator	Alfred Mann Foundation	Stim.	CH	C	CL	Neuro	A	2005	Baker	1991	Loeb	http://ami.usc.edu
Microstimulator	Michigan, University of	Stim.	CH	A	AN	Neuro	A	2004	Dokmeci	1996	Ziaie	wimserc.org
Implantable Stimulator	Leuven, Katholic University	Stim.	CH	A	AN	Neuro	P	1991	Callewaert	1987	Callewaert	esat.kuleuven.be/micas
Micromachined drug and gene delivery devices												
Drug delivery system	ChipRX	Drugdel.	CH	C	OTO	Drug	A	2003	Deo			chiprx.com
Micropump	Sarcos	Drugdel.	CH	C	OTO	Drug	A					sarcos.com
SimpleChoice	SpectRX	Drugdel.	TE	C	ODU	Drug	A					spectrx.com
Enterion	Pharmaceutical Profiles	Drugdel.	TE	C	ODU	Drug	A	2005	Clewlow	2004	Clewlow	enterion.co.uk
Porous silicon	PSimedica	Drugdel.	TE	C	OTO	Drug	A					psimedica.co.uk
Transdermal Interfaces	Royal Institute of Tech.	Drugdel.	TE	A	OTO	Drug	A	2005	Roxhed	2003	Griss	s3.kth.se/mst
Implantable Pump	Codman Neurosciences	Drugdel.	CH	C	OTO	Drug	A					codmanjnj.com
Array of drug reservoirs	MicroCHIPS	Drugdel.	CH	C	AN	Drug	A	2006	Presscot			mchips.com
Nanoporous drug delivery	Debiotech	Drugdel.	CH	C	ID	Drug	A	2003	Maillefer			debiotech.ch
Mircomachined pump	Debiotech	Drugdel.	CH	C	OTO	Drug	A	2003	Maillefer	1998	Leung Ki	debiotech.ch
Ingestible capsule	GastroTarget Corp.	Drugdel.	TE	C	ID	Gastro	P	1994	Schentag			
Transdermal drug delivery	Debiotech/KTH	Needles	TE	C	OTO	Drug	A	2003	Maillefer			debiotech.ch

Table 2. (Continued.)

End Item	Organization	Part	Dur.	Type	Stat.	Clin.	Act.	Year	Author	Year	Author	Internet
Micromachined drug and gene delivery devices (Continued.)												
Microtrans	BioValve	Needles	TE	C	ODU	Drug	A					biovalve.com
Micro needles	Micronit	Needles	TE	C	OTO	Drug	A	2003	Gardeniers	2002	Gardeniers	micronit.com
Microneedles stent	Virginia, University of	Needles	CH	A	AN	Car	A	2004	Reed			http://bme.virginia.edu
Microenhancer	BD Technologies	Needles	TR	C	AN	Gene	A	2002	Mikszta			bd.com
Microseeding	Brigham Hospital Boston	Needles	TR	A	AN	Gene	P	1998	Eriksson			brighamandwomens.org
Micromachined ultrasound transducers												
Ultrasound	Sensant, Stanford	CMUT	TR	C	ODU	Onco	A	2003	Wong	2002	Johnson	sensant.com
Ultrasound	Georgia Tech	CMUT	TR	A	OTO	Car	A	2005	Degertekin	2002	Knight	me.gatech.edu
CardioQTM	Deltex	PZT	TR	C	ODU	Car	A					deltexmedical.com
Flowire	Volcano	PZT	TR	C	ODU	Car	A	2000	Schulze-Clewing			volcano.com
Ultrasound	Duke University	PZT	TR	A	AN	Car	A	2004	Lee	2000	Light	bme.duke.edu
Ultrasound	Imperial College	PZT	TR	A	CL	Surg	A	2004	Dickinson			imperial.ac.uk/biomedeng
Microoptoelectromechanical systems												
Conf. Opt. Scan. Micr.	Olympus	MOEMS	TR	C	OTO	Var	A	2005	Murakami			olympus.co.jp/en/
Camera Pill	Given Imaging	MOEMS	TE	C	ODU	Gastro	A	2005	Panescu			givenimaging.com/
Endoscope	Pittsburgh, University of	MOEMS	TE	A	AN	Onco	A	2001	Pan			engr.pitt.edu/bioengineering
Flow Sensor	IZM, Fraunhofer	MOEMS	TE	A	OTO	Fetal	A	2003	Keoschkerjan			izm-m.fraunhofer.de/
Implantable telescope	Opthalmic Technologies	MOEMS	CH	C	CL	Oph	A	2004	Lane	2002	Peli	visioncareinc.net
BioInfoMicro Interface	Brown University	MOEMS	CH	A	OTO	Neuro	A	2005	Anderson			brown.edu
Near IR glucose sensor	Iowa University	MOEMS	CH	A	OTO	Endo	A	2006	Kanukurthy			ece.engineering.uiowa.edu
IVP	IMS-CHIPS	MOEMS	TR	A	OTO	Gastro	P	2005	Arena	2000	Neidlinger	http://ivp.ims-chips.de/
DELAS	Laser- und Medizin Tech	MOEMS	TR	C	OTO	Surg	P	1997	Schutz			lmtb.de
Other Microsystem devices for implantable applications												
Smart Catheters	Tohoku University	Actuators	TR	A	OTO	Var	A	2001	Mineta			mems.mech.tohoku.ac.jp
Smart Catheters	Delft University of Technology	Actuators	TR	A	OTO	Var	A	2005	Langelaar			dimes.tudelft.nl
Smart Catheters	Sarcos	Actuators	TE	C	OTO	Var	A					sarcos.com/medicalproj.html
Micro Surgical Tools	Wisconsin, University -Madison	Cutting	TR	A	OTO	Surg	A	2001	Chen	2001	Son	wisc.edu
Cutting Tools	Berkeley, University of California	Cutting	TE	A	OTO	Surg	P	1995	Lal			berkeley.edu/
Stent with nanobumps	Purdue University	Bumps	CH	A	OTO	Car	A	2005	Palin	2003	Thalpa	purdue.edu
Polymer with nano tubes	Purdue University	Nanotubes	CH	A	OTO	Var	A	2004	Webster			purdue.edu
Microdialysis	Berkeley, University of California	Needles	TE	A	OTO	Endo	A	2004	Zimmerman			me.berkeley.edu
RFID	Verichip	Other	CH	C	AN	An	A					adsx.com
AN Identification	Destron Fearing	Other	CH	C	ODU	An	A					destronfearing.com
Biodegr. Scaffold	MIT	Scaffold	TE	A	OTO	Tis	A	2002	King			mit.edu
Biodegr. Scaffold	Inst. Industr. Science Tokyo	Scaffold	TE	A	OTO	Tis	A	2004	Leclerc			iis.u-tokyo.ac.jp
Biodegr. Scaffold	Charles Stark Draper Lab	Scaffold	TE	A	OTO	Tis	A	2006	Bettinger			draper.com/business/biomed
BioSilicon	pSivida	Scaffold	TE	C	OTO	Tis	A					psivida.com

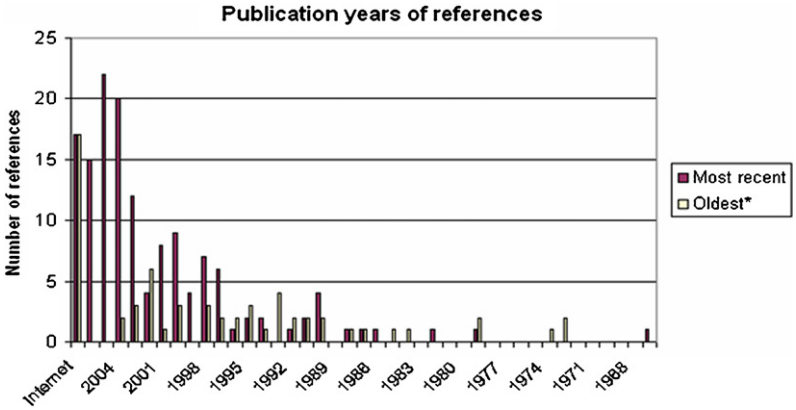

Figure 4. Number of references per year of publication for all end items mentioned in table 2. Purple bars are the most recent publications. Yellow are the oldest publications (*excluding end items that only have a most recent reference). Internet references are placed in a separate category since no additional investigations into the publishing date was done.

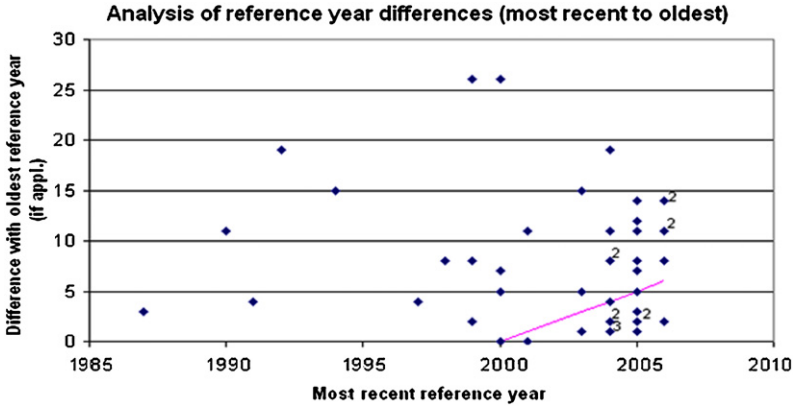

Figure 5. Difference between most recent and oldest references as a function of most recent reference year (only those references that have most recent and oldest reference). The small numbers next to a data point (number is placed at upper right corner of data point) indicate doubles or triple. End items below or on the purple line are from the year 2000 or more recent. End items above the purple line are from 1999 or earlier. In formula Diff = Yrec – Yco, where Diff is the difference between oldest and most recent, Yrec is the most recent year of publication and Yco is the desired 'cut off' year. In this case Yco = 2000.

be achieved. We start with describing how hermitic protection is realized.

Hermetic housings are traditionally made of titanium, tantalum, niobium [268] or stainless steel. Micro-machined ceramic packages [92, 94, 95, 204, 205] glass sealed packages [127] and polymer encapsulations [116, 126] are also used. One package uses a glass silicon anodic bond which has a mean time to failure of 177 years at 37 °C, estimated from saline soak tests [193–196].

Glass to metal seals made of sodium free borosilicate glass are used for feedthroughs [268]. Interconnection techniques used in the semiconductor packaging and assembly industry are also used for manufacturing implantable devices [233, 238, 239]. Flip chip is frequently used [10, 11, 98] with Au–Au thermo compression bonding [269] on a flex circuit [34, 43, 145] or on top of a MEMS chip [175]. Wirebonding on flex with globtop [36] or on printed circuit board (PCB) with two component glue for isolation [99, 100, 270] has also been applied. A hybrid interconnect technique based on ball wedge bonding that survives 4 years in saline solution and 10 months implantation in rats has been developed [10, 17, 131, 271]. A three-dimensional chip scale package based on an ultra violet (UV) curable polymer with integrated conductors is under investigation [272]. Conductive glue has also been proposed [74].

In general, dc potential on conductors should be avoided [20] or hermetically sealed [268], because of the risk of failure due to electrochemical corrosion or the creation of conductive pathways when salt crystals form (dendrite growth). To minimize this risk, metal parts should not differ in electrochemical contact voltage, alloys are to be avoided and welding is preferred [268]. Corrosion products should have low solvability and corrosion should be controlled also by the shape of the design [4]. One concept uses liquid crystal polymer films with metal traces on top of it [273] and another one silicon ribon cables [209].

3.2.2. Coatings. Coatings are used to improve the interface of the implant with the body organs [274]. Criteria for an excellent coating are the edge covering, peel resistance and integrity of the regular coating film [37]. Polymer is the most common coating material with silicone rubber probably being number one [11, 34, 37, 45, 56, 90, 275, 276]. The implant can be completely injection molded in this substrate [90]. Other

Table 3. Number of end items as a function of duration of implant (Transient (<1 day, TR); Temporary (1 day < duration < 30 days, TE); Chronic (>30 days, CH)); as a function of status of development of the end item (Idea (ID); Proto (OTO); Animal (AN); Clinical (CL); Product (ODU)); as a function of activity (Active (A) if most recent reference published in year 2000 or later or on the internet, Passive (P) otherwise) and as a function of the type of organization (Academic (A);Commercial (C)). There are 142 end items in total of which 105 are active (20 + 20 + 6 + 18 + 41) and 70 are commercial (7 + 12 + 2 + 5 + 2 + 18 + 3 + 18 + 3). The majority of passive end items (25 of 37) have a status of prototype or animal research and are created by academic types of organizations. From the 105 active end items, 18 (13% of the total number of end items) are classified as products, all made by commercial types of organizations, as is to be expected for products. Note also that from these 18 products, there are only two for chronic use. There is still considerable potential for chronic implantable microsystem products to come, judged by the number of active end items in animal, clinical and proto phase in this category (13, 17 and 20, respectively). However the path from academic research to commercialization, clinical trials and market introduction of chronically implantable products is long (more than 12 to 13 years) as indicated by the average year of first publication of end items that are still in the animal or clinical phase (1994 $n = 7$ and 1993 $n = 11$, respectively).

	AN						CL							ID						ODU					OTO						
	A			P			A			P				A			P			A		P			A			P			
Duration	A	C	A To	A	P To	AN To	A	C	A To	A	C	P To	CL To	A	C	A To	C	P To	ID To	C	A To	C	P To	ODU To	A	C	A To	C	P To	OTO To	Grand To
CH	10	3	13	8	8	21	5	12	17	2	2	4	21	1	3	4			4	2	2	3	3	5	10	10	20	6	2	8	28	79
TE	1	2	3			3	1		1				1		1	1	1	1	2	7	7			7	6	7	13	3		3	16	29
TR	2	2	4	1	1	5	2		2				2		1	1	1	1	2	9	9			9	7	1	8	7	1	8	16	34
Total	13	7	20	9	9	29	8	12	20	2	2	4	24	1	5	6	2	2	8	18	18	3	3	21	23	18	41	16	3	19	60	142

Table 4. Classical technology-market matrix with MST Class on the vertical axis and Clinical Field on the horizontal axis (Animal (An), Auditory (Aud), Cardiology (Car), Dentology (Dent), Drugdelivery (Drug), Endocrinology (Endo), Fetal, Gastroenterology (Gastro), Neurology (Neuro), Oncology (Onco), Ophthalmology (Oph), Orthopedics (Orth), Surgery (Surg), Tissue Engineering (Tis), Urology (Uro) and Various (Var)). The table entries are the number of end items. The major technology market combinations are sensors for cardiovascular, drug delivery for drug delivery and electrodes for neurology and ophthalmology. Together these form 51% of all end items. Sensors for cardiovascular are further detailed in table 5 and electrodes for neurology are further detailed in table 6.

Class	An	Aud	Car	Dent	Drug	Endo	Fetal	Gastro	Neuro	Onco	Oph	Orth	Surg	Uro	Var	Gene	Tis	Total
Drugdelivery			1		13			1								2		17
Electrodes		3							21		11							35
MOEMS						1	1	2	1	1	1		1		1			9
Other	2		1			1							2		4		4	14
Sensor	3		28	1		6	1	1	7		5	2	2	3	2			61
Ultrasound			4							1			1					6
Total	5	3	34	1	13	8	2	4	29	2	17	2	6	3	7	2	4	142

Table 5. Sensors for cardiovascular application as a function of status and duration for all types of organizations (academic and commercial) and activities (active and passive). On the vertical axis the type of sensor is classified. On the horizontal axis the status of development (Idea (ID); Proto (OTO); Animal (AN); Clinical (CL); Product (ODU)) and the duration of implant (1 day < duration < 30 days, TE); Chronic (>30 days, CH)) are classified. The table entries are the number of end items. From this table it can be seen that the majority of cardiovascular pressure sensors are pressure sensors (20 of 28). A relatively large portion of the pressure sensors are product (7 of 20, or 35%). Most of these cardiovascular pressure sensors products are for transient use (5 of 7, or 71%).

	AN			CL		ID		ODU				OTO			
Part	CH	TR	AN To	CH	CL To	TR	ID To	CH	TE	TR	ODU To	CH	TR	OTO To	Total
AC Conductance													1	1	1
Accelerometer								1			1				1
Flow		1	1			1	1						1	1	3
Magnetic													1	1	1
Other						1	1					1		1	2
Pressure	1	1	2	5	5			1	1	5	7	2	4	6	20
Total	1	2	3	5	5	2	2	2	1	5	8	3	7	10	28

Table 6. Electrical stimulation and sensing for neurological applications (involving implantable microsystems) as a function of status and duration for all types (academic and commercial) and activities (active and passive). On the vertical axis the main MST part of the end item is classified. On the horizontal axis the status of development (Idea (ID); Proto (OTO); Animal (AN); Clinical (CL); Product (ODU)) and the duration of implant (1 day < duration < 30 days, TE); Chronic (>30 days, CH)) are classified. The table entries are the numbers of end items. From this table it can be seen that there is just one product (considered to be an implantable microsystem) in the neurological area. It can also be seen that all applications are for chronic use and that the majority has to do with microfabricated electrodes (14 of 21, or 67%).

Part	AN CH	AN Total	CL CH	CL Total	ID CH	ID Total	ODU CH	ODU Total	OTO CH	OTO Total	Total
Electrodes	3	3	5	5	1	1	1	1	4	4	14
Needles	4	4									4
Stimulator	2	2	1	1							3
Total	9	9	6	6	1	1	1	1	4	4	21

polymer coatings are parylene [74, 131], epoxy [10] or others [192, 277]. Electrografting yields highly covering, highly versatile polymer coatings especially on complex shapes [278]. A polymer coating can also be used to promote cell growth [19, 127].

Other coating materials are metal coatings [279], ultrananocrystalline diamond prepared by plasma chemical vapor deposition [280], calcium phosphate deposited by pulsed laser ablation [281] or hydroxyapatite (HA)-TiO_2 created by micro-arc oxidation of a predeposited HA layer on titanium [282]. This last one is primarily used to improve osseointegration of the implant with hard tissue (bone). Surface (topology) modifications can also provoke the desired response of the body [1, 283].

3.3. Power

For implantable products that have physical connection to the outside world, power consumption is generally not a problem since an 'unlimited' supply can be accessed. Autonomous implants that operate on a primary battery need to have sufficient longevity. Especially for chronic implants this places an important requirement on the power consumption of the device. Since device functions are steadily progressing and since size should be kept as small as possible, much development effort has been invested in implantable batteries. Recently, implantable devices with rechargeable batteries [284, 285] were introduced. The examples that will be briefly presented in this section are ongoing (long term) developments aiming at autonomous power and concepts in which energy is provided from the outside.

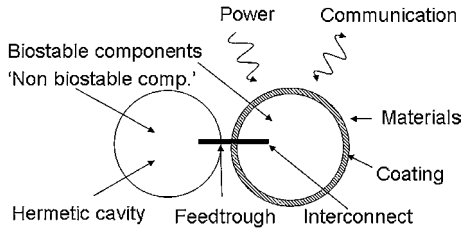

Figure 6. Schematic representation of technological aspects of an implantable (micro)system.

Inductive coupling uses changing electro magnetic fields outside the body that are picked up by an implant inside the body [11, 34]. Pick up coils can be micro machined on chip [36, 43] or on flex [276]. The coupling range is limited [10]. To overcome this problem, a distributed implant system connected via cables powered via a central coil that is close under the skin has been proposed [13]. Efficiency can also be improved by a self-tuning system [286, 287].

Autonomous power could be delivered by electrostatic conversion of mechanical vibrations. A capacitance change due to external vibrations causes current to flow and has generated 0.2 uW [288]. Thousands of thermocouples on chip have been developed for an implantable biothermal battery [289]. The use of ultrasound at 1.7 Mhz with PZT discs has been described in [290]. Implantable bio fuel cells are also being investigated [291]. Other concepts use solar energy or pressure variations [292].

3.4. Communication

Most of the time, communication with the implantable device is desirable to either receive data concerning the device status or patient condition or to send data to the device to (re)program it. Most of the time this is done using an inductive link, which is sometimes also used for transmitting power (see 3.3) [19, 98, 127, 173, 277]. Advances in RF engineering have enabled detection from deep within the lossy medium of the body [86]. Thick magnetic materials on silicon support higher magnetic flux for higher power density and longer coupling distance [293].

Entirely passive circuits that can be wirelessly probed to detect a property that changes value in response to, for example, flow have been described [74]. Others describe a special protocol which enables both powering and signal transfer to be done via two leads only [207]. An optical telemetry link to transmit data to an external controller is also an option [202].

3.5. Materials

The choice of materials for implantable applications is limited by both biostability and biocompatibility requirements. With biostability we mean that the material must withstand the attacks of the body. With biocompatibility we mean that the material must not cause any unwanted reactions by the body. A list of biocompatible and biostable materials does not exist, since the mechanisms involved depend on many details, such as material processing, shape, finish, post treatment and impurities but also on the place and duration of use. Nevertheless we feel that it makes sense to present the various materials that have been described in the literature on implantable microsystems. The materials include silicon [7, 18, 154], silicon dioxide [18, 51, 133, 154], silicon nitride [18, 51, 133], silicon carbide [294], titanium nitride [154], poly-silicon [193–196], parylene [74, 131], epoxy [10, 74, 131], polyimide [3, 10, 13, 17, 131], polyester [3], silicon rubber [3, 9, 131], gold [131], platinum [20, 25, 131], iridium [20, 25, 131], titanium [3, 7, 18], tantalum [133], stainless steel [74] and shape memory alloys [3].

While it is beyond the scope of this paper to fully discuss material properties and issues here, we will briefly describe material aspects relating to their use in implantable applications. Silicon can be made in a very pure form which is good for high reliability applications of silicon micro mechanical systems due to stable mechanical properties. Apart from material properties this has to do with the highly developed infrastructure related to silicon microfabrication processes. In addition, silicon is the dominant material for IC manufacturing, offering the opportunity for MEMS IC integration, often leading to superior characteristics. Silicon carbide, for example, is ideal for application in harsh environments (such as the human body) because of its high chemical resistance. Silicon dioxide is a very effective insulator and is often used in combination with silicon nitride for its ability to prevent impurity diffusion and ionic contamination. Many of the metals described are used as electrical interface to the body; see section 2.2 for a brief discussion. Titanium is the preferred material for hermetic housings of chronically implantable devices because it is in the passive region of the electrochemical anodic polarization curve (it forms an oxide so fast that it protects the metal from further corrosion). The same is true for stainless steel which is commonly used as a conductor in non-hermetic environments for chronic implantable applications. Polymers are soft and flexible which minimizes the chance of damage to the body and they are advantageous for applications in which the device has to be able to adapt itself to the shape of the human anatomy. Polyimide is often used because of its low moisture uptake and because of its well-developed fabrication processes.

4. Implantable microsystems: a case study

Since a general and broad overview is per definition very general and broad, we would like to present one small case study which shows in more detail the successful role that microsystems can play in a clinical setting. This case study is presented in the form of (1) what the physiology of the clinical condition is and how it can be treated and (2) how microsystems play a role (historical perspective and outlook). Sick sinus syndrome is selected because this is a disease which uses implantable microsystems as therapy of choice.

4.1. Sick sinus syndrome

During exercise the metabolic need of the body rises. Part of this increased need can be met by upregulating the supply of oxygen. This is done by increasing cardiac output (CO, amount of blood that is pumped through the circulation expressed in liters per minute) and/or the amount of oxygen that is taken from the arterial blood. The cardiac output is the

product of heart rate (HR) and stroke volume (SV, volume of blood pumped per heartbeat) that both can be increased. In total the body has the ability to increase the oxygen supply by a factor of approximately 20 compared to the resting state (HR × 3.3; SV × 1.7 and oxygen uptake × 3.5).

Heart rate is determined by the sinus node. The cardiac cells in the sinus node function as a natural pacemaker, initiating an electrical activation wave that is conducted over the heart and results in contraction of the heart muscle. While other heart cells have a constant membrane potential as a function of time when at rest, the cells in the sinus node depolarize spontaneously at a certain rate, until a threshold voltage is reached that triggers the rapid depolarization of the cell that initiates an action potential. The depolarization rate of the sinus cells (and thus the heart rate) is regulated by adrenaline and under direct control by the nervous system.

People with sick sinus syndrome have a degenerated sinus node that no longer responds properly to the control mechanisms that dictate its depolarization rate. That is, the heart beats at an inappropriately low rate. Therefore these people are limited in the amount of exercise they can perform since they only have change in stroke volume and oxygen uptake left to adapt the oxygen supply.

4.2. Implantable microsystems for sick sinus syndrome

Electrical stimulation by an implanted electrode in contact with heart cells can also initiate electrical activation followed by mechanical contraction. Therefore, sick sinus syndrome can be well treated with an implantable pulse generator (IPG) if there is a way to determine at which rate it must pace. The literature of rate adaptive pacing starts around 1978. Until that time, there were only fixed rate pacemakers that started in 1958 with the first fully implantable battery operated fixed rate pacemaker [295]. Of course, in patients requiring a pacemaker because of atrio-ventricular block who have maintained normal sinus node function, the natural atrial rate, originating in the sinus node, is the best initiator of the optimal ventricular pacing rate. Several ways have been described to control heart rate in patients with sick sinus syndrome based on measuring a property that is a measure for the actual metabolic need. Examples are the QT interval in the cardiac electrogram [296], the pH [297], oxygen saturation [298, 299], activity [103, 300], right ventricular pressure [80], respiratory frequency [301] and temperature [302]. Oxygen saturation is sensed on the basis of colorimetric principles. The sensor contains a light sensitive photodiode that detects reflected light alternatively emitted from an infrared (IR)- or red (R)-LED also contained in the sensor. Each LED emits until a predefined amount of light energy is collected by the photodiode. The oxygen saturation is calculated from the ratio between the two ON times and two calibration constants that come with the sensor [299]. The first tests have been performed with an external system [298]. Patient activity causes pressure waves in the body that result in bending of the metal shield of the implanted device. A piezoelectric sensor mounted on the inside of the shield transforms this bending into an electrical signal and together with appropriate algorithms can be used for rate response [103]. First experiments with pressure sensors were using an externally closed loop. A signal proportional to the rate of change of the right ventricular pressure (dP/dt) was generated by a piezoelectric bender sensor positioned on the inside of a deformable portion of a hermetically sealed capsule located on the distal end of a lead [80]. Temperature is measured with a thermistor incorporated in the tip of a lead [302]. In the end, most modern pacemakers today use acceleration sensors for rate control because they are relatively simple (it does not have to interface with the outside) and because they can provide appropriate rate response. These sensors are typically micro-machined accelerometers, present in the majority of the about 500 000 pacemakers that are implanted worldwide each year.

There is some room to improve the exercise performance of patients with sick sinus syndrome by finding more advanced ways to control the heart rate for maximum metabolic demand, but the impact on daily life would not be very great. The main emphasis of developments that are building on the use of sensors as described above is in other areas than heart rate control. It is in automatic programming of devices and expanding it to other clinical areas such as detection of unstable arrhythmias [303] or heart failure management [79].

5. Discussion

This section highlights the perspectives and challenges of microsystems related to the areas reviewed. Power consumption, size, sensitivity, specificity, accuracy and stability are important design parameters for most implantable applications of sensors. Since many sensors have to interface to the environment in order to function, and since the body is an active system trying to control this interface, achieving the requirements on these aspects is often challenging especially for chronic implantation. The clinical advantages are driving the efforts aimed at overcoming these challenges: relevant information is made available on a continuous basis, quality of life can be increased, patient compliance is guaranteed, diagnosis is quantified or even enabled (no prior means to perform the diagnosis), therapy is improved for example by adapting the therapy according to the sensors input (close loop system), disease status can be continuously monitored, implantation procedure can be facilitated and sensors based on an implantable microsystem have improved performance compared to existing technology.

Microelectrodes made using IC-like fabrication technologies offer the advantages of exact electrode positions, small size, multiple electrodes, improved electrode tissue interface and active circuitry. The main challenges are in optimizing the charge transfer properties needed for electrical stimulation in combination with electrochemical properties that lead to long-term stability. For wireless applications the transmission speed is sometimes a limitation. Flexible electrodes offer advantages compared to the (generally) more rigid silicon structures in certain applications. Microelectrodes can provide improved therapy due to the ability to better target electrical stimulation energy to a specific region. It can be more challenging to determine which region this is then to provide the hardware to do it.

Important design characteristics for the delivery of substances to the body are accuracy, resolution, safety and control which can be realized by micro-machined components with order of magnitude improvements compared

to conventional technology. Transdermal gene delivery using microfabricated structures is more efficient than single injection and particle-mediated gene transfer. The use of microneedles designed to penetrate diffusion barriers for DNA material leads to a more effective delivery. Miniaturized imaging tools enabled by micro-machined components are used in minimal access surgery which greatly reduces the impact of the treatment on the patient and allows improved diagnosis on the basis of superior or completely new images. Micro actuators are being developed for making smart catheters to expand the applicability of minimally invasive (transvascular) procedures. Smart micro-machined cutting tools with sharper edges than conventional needles could be used when very fine and precise surgery is needed. Tissue response to implants can be modified by surface topology in the micrometer range, and high-resolution, fast, inexpensive, reproducible and scalable microfabricated biodegradable scaffolds are being investigated for *in vivo* tissue engineering of capillary structures or liver reconstructs.

In general, the perspectives that microsystems for implantable applications have to offer are low cost, small size, low weight, high reliability, low power and superior functionality or performance. Microsystems can be combined with biotechnology and molecular biology. The reliability requirements are at the same time also a challenge, since new technologies generally present new failure mechanisms. The realization of low cost can also be difficult in practice due to the lack of real mass volumes (in the order of millions) in many implantable applications. Other challenges include long development times, packaging and bio-compatibility and -stability. Success factors of new products depend on more then technical characteristics alone.

6. Summary

We have provided a general and broad overview of microsystems for implantable applications as found in the literature. The focus has been on implantable microfabricated parts not contained in 'classic' hermetically sealed metal casings, including transient and temporary use. Although this paper lists more then 140 examples, we do not claim that this overview is complete. As a first observation we can state that a large range of microsystems is being used or investigated. We have presented sensors, microelectrodes, drug and gene delivery devices, micro-machined ultrasound transducers, MOEMS, micro actuators, surgical tools, micro surface topology, microfabricated bio-degradable scaffolds and others. These microsystems find application in a wide range of clinical areas including cardiology, neurology, ophthalmology, orthopedics, drug delivery (for various clinical areas), surgery, endocrinology, tissue engineering etcetera.

To further analyze the information, we have introduced a classification scheme consisting of MST-class and -part, duration of implant, type of organization, status of end item, clinical field and activity. Besides the classifications, the name of the end item, the name of the organization, reference to the internet address and year/author of the oldest and most recent paper are given. Classification is based on the information available to the authors. There are 105 active and 70 commercial end items from a total of 142. The majority of the 37 passive end items (25 of 37) are prototypes or animal research devices created by academic organizations. From the 105 active end items, 18 (13% of total number of end items) are classified as products, all made by commercial organizations. Note also that from these 18 products, there are only two for chronic use. There is still considerable potential for permanent implantable microsystem products to come, judged by the number of end items in the clinical- (17), animal- (13) and proto- (20) phase in this category. The path from academic research to commercialization, clinical trials and market introduction of permanently implantable products is long, however, as indicated by the average year of first publication of end items that are still in the animal- (1994, $n = 7$) or clinical- (1993, $n = 11$) phase. The major technology-market combinations are sensors for cardiovascular, drug delivery for drug delivery and electrodes for neurology and ophthalmology. Together these form 51% of all end items. The majority of sensors are pressure sensors and there is just one product (considered to be an implantable microsystem) in the neurological area.

A general overview of packaging, communication, power and materials—the major underlying technical blocks needed to produce end items—has been provided regardless of the classification. Hermetic housings are traditionally made from titanium, tantalum or niobium. Micro-machined ceramic packages, glass sealed packages and polymer encapsulations are also used. Glass to metal seals are used for feedthroughs. Interconnection techniques such as flip chip, wirebonding or conductive epoxy as used in the semiconductor packaging and assembly industry are also applied for manufacturing implantable devices. Coatings are used to improve the interface of the implant with the body organs with polymers or metal as coating material. Longevity for chronic implants not connected by wires to the outside places an important requirement on the power consumption of the device. Since device functions are steadily progressing and size should be kept as small as possible, much development effort is put in implantable batteries. As an alternative, rechargeable batteries were introduced or concepts in which energy is provided from the outside based on inductive coupling. Long-term developments aiming at autonomous power are, for example, based on electrostatic conversion of mechanical vibrations. Most of the time, communication with the implantable device is desirable to either receive data concerning the device status or patient condition or to send data to the device to (re)program it. This is usually done through an inductive link although optical means also have been reported. Entirely passive circuits that can be wirelessly probed to communicate information from inside to outside the body have been described. The choice of materials for implantable applications is limited by both biostability and biocompatibility requirements. A list of biocompatible and biostable materials does not exist, since the mechanisms involved depend on many details, such as material processing, shape, finish, post treatment and impurities but also on the place and duration of use. There is a large range of materials commonly used in microfabrication used for implantable microsystems including silicon, polymers and metals.

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