WIRELESS IMPLANTABLE MICROSYSTEMS: Creating a Revolution in Health Care

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ABSTRACT

The first integrated silicon sensors based on microelectronic technology were developed in the 1960s for medical applications. Today, they have evolved into integrated microsystems combining micropower circuits, wireless interfaces, sensors, wafer-level packaging, and energy-scavenging power sources. Catheter-tip pressure sensors have grown into smart cardiovascular stents and 1mm^3 wireless devices for treating glaucoma. Neural interfaces are launching revolutionary advances in neuroscience and in prostheses for deafness, blindness, epilepsy, Parkinson's disease, and other disorders. This paper examines the factors that limited the development of implantable microsystems in the past and continuing challenges for the future. Such devices are poised at last to provide important breakthroughs in health care.

INTRODUCTION

Since the birth of the planar process for integrated circuits in the early 1960s, microelectronics has seen phenomenal growth, and driven by scaling it has revolutionized many aspects of society. However, its impact on health care has been muted, and very few implantable devices have been successfully commercialized. This is surprising, because the microelectronics programs at many leading universities began by working on medical devices. It was evident very early that the small sizes facilitated by lithography would be important in developing minimally-invasive devices for diagnosing, and perhaps even treating, a variety of physiological conditions.

Some of the first work on silicon image sensors was done to develop a reading aid for the blind at Stanford University [1], and by the late 1960s work was also underway there on implantable Doppler microsystems for arterial blood flow and for cardiac imaging [2,3]. The first projects to develop micromachined silicon sensors began at Stanford in 1966, exploiting the silicon etching work then underway for air-isolated integrated circuits at Bell Telephone Laboratories [4]. In the over forty years since those first devices were produced, a wide variety of biomedical sensors have been reported. Pacemakers have developed into sophisticated programmable microsystems whose outputs can be conditioned on levels of exertion, improving the quality of life for millions, but except for the electrodes such systems reside entirely within a welded titanium package. Progress using sensors directly exposed to the body has been slow, partly because technology had to evolve to a level suitable for commercialization and partly because the sensor was only part of the problem. To solve the entire problem, and thus permit commercialization, full systems were required. It is only the recent emergence of microsystems, combining low-power integrated circuits, wireless connectivity, and advanced sensors that the revolution in health care originally envisioned has finally begun to occur.

EARLY BEGINNINGS

The first work on selectively-etched ("micromachined") silicon sensors was under the direction of Professor James B. Angell and had the goal of realizing multi-site microprobes for

single-unit recording in the central nervous system (CNS) [5]. These devices were tested acutely in animals (Fig. 1) and by 1970 were also being used to stimulate phosphenes in human visual cortex as a basis for a visual prosthesis. The devices were successful but with nothing to shape the silicon substrate except isotropic etching, they did not yet have the yield needed to supply them in quantity to the biomedical community. Nevertheless, the etching technology demonstrated led to funding from NASA to develop catheter-tip pressure sensors for use within the chambers of the heart [6]. This led to the first silicon pressure sensors with a built-in thick rim to absorb packaging stresses (Fig. 2). By this time, anisotropic etching technology was available but in spite of using $60\mu\text{m}$ -thick silicon wafers with self-terminating V-grooves for die separation, it was hard to form the $5\mu\text{m}$ -thick diaphragms reproducibly with no etch-stop. The yield difficulties with the probes and pressure sensors underscored the importance of having a process consistent with high-yield and high throughput. Packaging challenges also emphasized the importance of minimizing lead count when dealing with very small implantable devices as well as the difficulties of calibration. The pressure work led to a second project with NASA-Ames to build a wafer-level gas analyzer based on chromatography [7]. Unlike the neural probes and pressure sensors, this was a *system* and not just a device.

Fig. 1: Diagram and photograph of a micromachined neural probe (1969) along with a neural spike recorded in response to a tone burst in cat auditory cortex [5].

The goal of the micro gas chromatography (μGC) work was a light-weight low-power wafer-level device for the 1975 Viking Mars Lander, although applications in health care were also envisioned. The original plan for this system, shown in Fig. 3, included a gas sampling system, a spiral separation column, and a thermal-conductivity-based gas detector along with signal processing and temperature control circuitry. By 1972, $100\mu\text{m}$ -diameter column channels had been formed, had been capped using anodic silicon-glass bonding, and had yielded the first separations, but the available valve technology was not yet adequate. Work continued on the μGC through most of the 1970s at Stanford [8] and would form a basis for the re-emergence of microfluidics more than a decade later.

Fig. 2: A 1.6mm-diameter catheter-tip pressure sensor fabricated with a thick silicon rim using anisotropic etching (1971) together with pressure from the left ventricle of a dog [6].

Fig. 3: Design for a wafer-scale gas chromatograph (1971).

In 1974, Fig. 4 was drawn to describe a possible wireless implantable pressure sensor. Powered by a galvanic cell formed with the body electrolyte, on-chip CMOS circuitry would charge an MOS capacitor and would form an oscillator whose frequency would be set by the sensing capacitor. Once every cycle, the oscillator would trigger a switch that would rapidly dump the stored MOS charge through an on-chip antenna, generating a current spike that could be detected externally. The technology was not ready to support for this kind of system, but the ideas were there.

These early projects defined a number of problems that silicon sensors had to overcome to be applied successfully in-vivo. First, it is important to be able to produce devices that are reproducible enough to support animal trials and can be used by physiologists and others not skilled in the art. Enough devices must be provided to establish their efficacy. Second, technology must be developed that permit high yield and high performance. Third, packaging must exist that will be well tolerated by the body and will to protect the device from it. Fourth, in any implant leads are a major concern, and the fewer the better. And fifth, it is important to solve the entire problem, not just a piece of it. It is not enough to provide a single device. An entire *system* must be

Fig. 4: Design for a self-powered wireless pressure sensor (1974). The ideas were there but the technology was not.

provided, including the transducer, the signal processing, the package, and a suitable communication link.

The 1970s focused on technology development, and a variety of other sensors emerged. The 1980s focused on devices, including flowmeters, gas sensors, and accelerometers. They saw the birth of surface micromachining [8], efforts to understand stress in deposited films, and the first chemical-vapor-deposited (CVD) sealed vacuum cavities. The first sensor conferences and journals began [9] and major funding developed for microelectromechanical systems (MEMS). In the 1990s, deep reactive ion etching (DRIE) entered the scene, and MEMS proliferated into subfields, including bio-MEMS. Today, wireless integrated microsystems are re-uniting portions of the field with mainstream microelectronics, driven by the needs of portable instrumentation and by a search for new frontiers that will drive the industry in the “more than Moore” era.

WIRELESS IMPLANTABLE MICROSYSTEMS

The convergence of advanced sensor technology with very low power circuits and wireless connectivity is enabling implantable devices to finally emerge. Hermetic packaging is an integral part of such systems along with a suitable power supply. The end of the scaling paradigm that has driven microelectronics for the last forty years is also driving many companies to search for interdisciplinary partnerships that can generate new high-volume high-margin products in areas such as health care, now a national priority. To assess some of the ways that wireless implantable microsystems are solving problems in health care and what the continuing challenges are, it is appropriate to look at the original devices targeted at Stanford and where they are today.

Neural Interfaces

During the past decade, neural interfaces have emerged as one of the hottest topics in bioengineering. The goal is to use multipoint recording and stimulation to better understand the CNS at the circuit/system level and serve as a basis for neural prostheses. To understand neural networks, it is important to be able to record simultaneously from dozens or even hundreds of cells, and in order to explore changes over time (learning) it is important to do so over periods from weeks to months. For use in neural prostheses, it is important to do so over years and decades.

A variety of high-density penetrating microprobes for use in CNS have been reported [10-12]. Boron etch-stops, deep dry etching (DRIE), and silicon-on-insulator (SOI) technology have made acute probe fabrication a solved problem. Such devices are now commercially available and have been used by hundreds of investigators worldwide to better understand the brain. Planar probes can be microassembled [13] to form 3D arrays (Fig. 5), permitting, in principal, every cell within a 1mm³ block of tissue to

be monitored. Circuitry has been integrated with such probes for site selection, signal amplification, multiplexing, self-test, and stimulus generation.

Fig. 5: A 64-site four-probe microassembled 3D electrode array with site spacings of $200\mu\text{m}$ [20].

Much of the interest in neural interfaces is due to the success of cochlear implants and deep brain stimulation (DBS). Over 150,000 cochlear prostheses have been implanted worldwide, allowing many profoundly deaf individuals to function normally in a hearing world, and deep brain stimulation has been remarkably successful in suppressing the tremor associated with Parkinson's disease with and more than 50,000 implanted to date. When the electrodes are correctly positioned in the subthalamic nucleus, tremor can be completely masked with few, if any, side effects. The biggest barrier preventing the realization of dense recording arrays, for example for capturing control signals from the motor cortex to help paralyzed individuals, is the tissue reaction around the implanted devices. Electrode arrays placed in-vivo are recognized as foreign bodies and are slowly encapsulated by astrocytes/glia. While this encapsulation is typically only a few microns thick, it can degrade recording performance over weeks or

Fig. 6: A first-generation wireless neural microsystem, shown before packaging on a U.S. penny. A recording of neural activity is also shown as wirelessly recovered from the external system.

months. This may be exacerbated by probe size and/or micro-motion of the probe with respect to the brain. As probe size is scaled down to cellular dimensions, dramatic reductions in tissue reaction have been observed [14].

In order to succeed in neuroscience and neural prostheses, complete neural microsystems will also be required, including embedded signal amplification, multiplexing, spike recognition,

power, and a bidirectional data interface. Such systems are beginning to appear. For example, a digital spike detector chip has been reported [15] that computes per-channel means and standard deviations and allows the user to set biphasic thresholds around these baselines. The $2\text{mm} \times 3\text{mm}$ chip digitizes 32 multiplexed inputs at 2.56Mbps, outputs a 5b quantization of spikes above and below threshold, operates at 1.2mW from 3V, and saves about 10x in typical output bandwidth. Figure 6 shows a first-generation wireless neural microsystem [16] along with an externally reconstructed spike train. Other processors are also in development. Neural microsystems will soon allow new progress in understanding the brain and in overcoming many of its disorders.

Pressure Sensors

While piezoresistive bridges have remained the approach of choice for many pressure sensing applications, in the early 80s they were joined by capacitive devices, which offer easier diaphragm formation, lower temperature sensitivity, broader dynamic range, and lower power but require a vacuum-sealed reference cavity and on-chip readout circuitry. Many pressure sensors have been developed for cardiovascular catheters [17], with some realized in widths of $350\mu\text{m}$ or less for use on guide wires within the coronary arteries of the heart. Wireless capacitive devices have also been formed on stents to allow pressure/flow sensing in the carotid arteries [18] but are not yet small enough for the coronaries. Efforts to reduce their size are being aided by the dramatic power reductions being achieved in subthreshold circuits. Figure 7 shows an intraocular pressure sensor for the improved treatment of glaucoma [19]. The system contains a microcontroller, an energy-scavenging (solar) power system, an UWB wireless link, and a capacitive pressure sensor, all realized in a parylene-covered glass capsule 1mm^3 in size. The system wakes up and takes a data point every fifteen minutes, stores the data, and then returns to sleep mode. Once every day or so, it can be optically triggered to transfer its data to the external world. The system is made possible by the extremely low power of the embedded processor [20] (30pW standby, 300nW active). Pressure sensors combined with wireless interfaces and embedded electronics are forming microsystems that will significantly advance health care.

Fig. 7: Diagram of a 1mm^3 intraocular microsystem with a close up of several pressure sensors and a full system prototype on a U.S. penny.

Chromatographic Gas Analysis and Microfluidics

Very little additional work on μ GCs or microfluidics was reported until the late 90s; however, the last decade has seen significant efforts on μ GCs, including work at Sandia and at the University of Michigan [21]. This work has shown that silicon-based preconcentrators, separation columns, and detectors can separate numerous analytes in seconds to tens of seconds with detection limits less than 1ppb. The very small size and low mass of such systems makes them very low power and able to be temperature programmed at relatively high speed to improve selectivity and avoid co-elutions. Figure 8 shows a preconcentrator, 25cm-long column, and chemiresistive detector on an Apple "Shuffle" MP3 player, representing the expected size of an eventual system. Micro-GC-based gas analyzers have already demonstrated the ability to detect biomarkers in breath for lung cancer and tuberculosis. Microfluidics has emerged as a field in its own right with a variety of DNA analyzers, cell capture and cancer drug screening devices, and other structures poised to significantly aid in the diagnosis and treatment of serious diseases.

CONCLUSIONS

The development of implantable devices for use in health care has been underway for at least four decades, but is only now emerging to make important impacts. Driven by spectacular successes in pacemakers, cochlear implants, and DBS, work on neural interfaces, active stents, intraocular monitors, and other microsystems is underway. There are many challenges ahead, but if past successes are any indicator, the resulting devices may work better than we even dream possible.

Fig. 8: A microfluidic gas analyzer on an Apple "Shuffle" MP3 player along with a column separation of alkanes C_5 - C_8 .

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REFERENCES

- [1] J. S. Brugler, J. D. Meindl, J. D. Plummer, P. J. Salsbury, and W. T. Young, "Integrated Electronics for a Reading Aid for the Blind," *IEEE JSSC*, 4, pp. 304-311, Dec 1969.
- [2] R. Gill and J. D. Meindl, "Low-Power Integrated Circuits for an Implantable Pulsed Doppler Ultrasonic Blood Flowmeter," *IEEE JSSC*, 10, pp. 464-471, December 1975.
- [3] J. D. Plummer, J. D. Meindl, and M. G. Maginness, "An Ultrasonic Imaging System for Real-time Cardiac Imaging," *IEEE Int. Sol.-St. Circuits Conf.*, pp. 162-163, February 1974.
- [4] M. P. Lepselter, "Beam-Lead Technology," *Bell System Technical Journal*, 45, pp. 233-254, February 1966.
- [5] K. D. Wise, J. B. Angell, and A. Starr, "An Integrated Circuit Approach to Extracellular Microelectrodes," *IEEE Int. Conf. on Med. and Biological Engr.*, Chicago, 1969.
- [6] Samaun, K. D. Wise, and J. B. Angell, "An IC Piezoresistive Pressure Sensor for Biomedical Instrumentation," *IEEE Trans. BME.*, 20, pp. 101-109, March 1973.
- [7] S. C. Terry, J. H. Jerman, and J. B. Angell, "A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer," *IEEE Trans. ED*, 26, pp. 1880-1886, December 1979.
- [8] R. T. Howe and R. S. Muller, "Resonant-Microbridge Vapor Sensor," *IEEE Trans. ED*, 33, pp. 499-506, April 1986.
- [9] S. Middelhoek, "The Past, Present, and Future of Transducer R&D," *Sensors and Actuators, A*, pp. 2-23, 2000.
- [10] K. Najafi and K. D. Wise, "An Implantable Multielectrode Array with On-Chip Signal Processing," *IEEE JSSC*, pp. 1035-1045, December 1986.
- [11] K. C. Cheung, K. Djupsund, Y. Dan, and L. P. Lee, "Implantable Multichannel Electrode Array Based on SOI Technology," *IEEE JMEMS*, 12, pp. 179-184, April 2003.
- [12] R. A. Normann, "Microfabricated Electrode Arrays for Restoring Lost Sensory and Motor Functions," *IEEE Int. Conf. on Solid-St. Sensors, Actuators, and Microsystems*, pp. 959-962, June 2003.
- [13] G. E. Perlin and K. D. Wise, "A Compact for Three-Dimensional Neural Microelectrode Arrays," *IEEE EMBS Conf.*, Vancouver, BC, pp. 5806-5809, August 2008.
- [14] J. L. Skousen, et al., "Reducing Surface Area while Maintaining Implant Penetrating Profile Lowers the Brain Foreign Body Response to Chronically-Implanted Planar Silicon Microelectrode Arrays," in J. Schouenborg, ed., *Progress in Brain Research*, vol. 194, Elsevier, 2011.
- [15] R. H. Olsson, III, and K. D. Wise, "A Three-Dimensional Neural Recording Microsystem with Implantable Data Compression Circuitry," *IEEE JSSC*, 40, pp. 2796-2804, December 2005.
- [16] A. M. Sodagar, K. D. Wise, and K. Najafi, "A Fully-Integrated Mixed-Signal Neural Processing Module for Implantable Multi-Channel Cortical Recording," *IEEE Trans. BME*, 54, pp. 1075-1088, July 2007.
- [17] J. Ji, S. T. Cho, Y. Zhang, K. Najafi, and K. D. Wise, "An Ultraminiature CMOS Pressure Sensor for a Multiplexed Cardiovascular Catheter," *IEEE Trans. ED*, 39, pp. 2260-2267, October 1992.
- [18] A. DeHennis and K. D. Wise, "A Fully-Integrated Multi-Site Pressure Sensor For Wireless Arterial Flow Characterization," *IEEE JMEMS*, pp. 678-685, June 2006.
- [19] R. M. Haque and K. D. Wise, "An Intraocular Pressure Sensor based on a Glass Reflow Process," *Solid-State Sensor, Actuator, and Microsystems Workshop*, Hilton Head, S. C., June 2010.
- [20] M. Seok, S. Hanson, Y.-S. Lin, Z. Foo, D. Kim, Y. Lee, N. Liu, D. Sylvester, and D. Blaauw, "The Phoenix Processor: A 30pW Platform for Sensor Applications," *IEEE Symp. on VLSI Circuits*, pp. 188-189, 2008.
- [21] E. T. Zellers, et al., "An Integrated Micro-Analytical System for Complex Vapor Mixtures," *Int. Conf. on Solid-St. Sensors, Actuators, and Microsys.*, Lyon, France, pp. 1491-1496, June 2007.