Chapter 19
Digital Health and Bio-Medical Packaging

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Abstract This chapter reviews the healthcare trends and implications, as well as electronic packaging applications in implantable devices, pacing leads, bio-medical sensors, and point-of-care sensors. Each presents unique opportunities and challenges for electronic packaging and materials.

Keywords Implantable devices · bio-medical sensors · leads · point of care · packaging

19.1 Introduction

The revolution in personal computers and cell phones that has driven the telecommunication and semiconductor industries has resulted in ever more powerful consumer-friendly products. At the same time, however, the products have become commodities with low margins and ever higher investments required to stay competitive. This has left manufacturers looking for new markets to drive growth and profits.

At the same time, the population is aging and there is an increasing demand for better medical therapies. A variety of medical devices have been proposed to meet this need and, since medical devices have typically commanded high margins, many of the biggest players in the electronics field have set up digital health divisions. Medical devices, however, pose new challenges in terms of electronic packaging and materials. In addition, the industry presents high barrier of entry for new entrants, such as long regulatory approval time, high quality and reliability demands, liability and patient safety considerations. Medical devices are usually manufactured in small volume, which reduces the cost effectiveness of high-volume manufacturing processes that provides significant leverage for the large electronic companies. There are also significant

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market development challenges to raise awareness of both patients and physicians about medical devices due to the many alternatives available, such as medications and minimally invasive therapies.

19.2 Healthcare Trends – Opportunities/Challenges on Medical Devices and Electronic Packaging

19.2.1 Healthcare Trend and Key Drivers

Healthcare will see significant changes in the next decade due to a variety of drivers, including economic pressure, demographic changes, patient-centered care, IT and technology advances. Healthcare is facing enormous and unprecedented cost pressure. Medicare faces bankruptcy in 10 years, even if the reimbursement is reduced by 10% each year. The population is aging with the baby boomers moving into their golden ages. While improvements in medical care have allowed people to live longer, that longevity also means people will develop and live with additional chronic conditions requiring medical management. It is also expected that the delivery of care will change from hospital-centered care to patient-centered care. Patients will take a more active role in managing their own health and move the point of care to their homes.

19.2.2 Implications of Healthcare Trends on the Opportunities/ Challenges of Electronic Packaging

Each of the key drivers in healthcare trends presents opportunities and challenges for the electronic packaging and materials.

19.2.2.1 Economic Pressure

The reimbursements for medical devices have been on a steady decline in an attempt to reduce healthcare cost. This puts downward pricing pressure on device manufacturers who must reduce costs and improve efficiency. As patients start to cover more of the cost of their medical care out of their own pockets, they also demand therapies and devices with better quality and lower cost.

19.2.2.2 Demographic Changes

Many patients are facing co-morbidities as they age. Some are managed by a number of different physicians each with a specialty such as general practitioners, internal medicine, cardiology, nephrology, and endocrinology. Treating one condition, however, may prove ineffective unless the other conditions (co-morbidities) are also monitored and treated. Unfortunately, there may be

little to no communication among the various specialists. New technologies must be developed that can measure all of the information necessary to manage these patients and communicate it to the managing physicians.

19.2.2.3 Patient-Centered Care

Patients will be more involved and empowered in managing their own health. The slow shift to consumer-driven, patient-centered healthcare will make meeting patient needs a critical success factor. Miniaturization is a top requirement for patients who would prefer minimum interference to their daily life. For the same reason, patients do not want to be concerned with the interaction of their devices with their environment, therefore demanding the devices to be MRI (Magnetic Resonance Imaging) safe and electromagnetic compatible. The globalization and diversification of the patient population also made customization increasingly important to satisfy the needs of various cultures and geographies.

Most implantable devices are battery-powered. Battery longevity is an important concern for the patients. When the battery is depleted, not only do patients have to pay for a replacement device, they often have to undergo the surgical procedures again to take out the existing device and put in the new one. This increases patient cost, inconvenience, and potential risks of infection. Therefore, an ongoing challenge is to increase battery capacity, reduce energy consumption, while simultaneously decreasing the size of the implantable device.

The aging baby boomer population will put high demand in hospital availability and compete for the limited clinician time. Patients are also less tolerant of driving for hours for a routine follow-up. Therefore remote patient management is being embraced by both clinicians and patients alike.

19.2.2.4 Information Technology Advances

The advance in information technology is driving the paradigm shift in medical information management. Seventy percentage of hospitals are making progress in establishing Electronic Health Records. The technology advance will allow increase in patient data collection. On the other hand, information overload and medical staff shortage lead clinicians to demand actionable information. This put increasing demands on data storage and processing capabilities.

19.3 External Packaging of Implantable Medical Devices

19.3.1 Biological Hermeticity

External packaging of implantable medical devices serves as a biological barrier between the body and sensitive electronics, helps absorb mechanical forces applied to the device, and also may serve some key electronic functionality for

a variety of therapies. Any object placed inside the body for medical purposes must meet strict controls and undergo rigorous testing to ensure that the packaging is biocompatible. The accepted definition of biocompatibility was stated by David Williams in 1987: Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application [1]. Examples of undesirable responses include cytotoxicity (toxic to cells), mutagenicity and/or chromosomal aberrations, sensitization (allergic response), pyrogenicity (fever producing), or hemolysis (red blood cell damage). Fortunately, in spite of this list of potentially adverse bio-responses to implants, there are a number of widely tested and approved materials used extensively throughout the device industry for the external packaging of implantable medical devices. The external construction of most implantable pulse generators (IPGs) such pacemakers, neurostimulators, drug pumps, implantable cardioverter defibrillators (ICDs) used in chronic medical implants are constructed of relatively common, non-exotic materials such as titanium metal for the "cans" and polyurethane or silicone compounds and adhesives for interface headers. These materials have been the primary components in external device packaging for decades and are backed by literally billions of patient hours in the field with a high degree of reliability and demonstrated biocompatibility. Biocompatibility of implantable leads have additional challenges which will be described in Section 19.4.

Occasionally, patients with sensitivities or allergies to various metals can be provided with custom devices (usually plated with gold) in order to reduce or eliminate any allergic type reactions to devices. While general metal allergies are not uncommon, it is rare for any implantable medical device to require such special coatings.

Some medical applications, such as device leads, focus a great deal of energy on pursuing new materials that are more robust and tolerant of the biological interaction, but most device "cans" are relatively happy with the current state of affairs. Some new technologies on the horizon that will impact external packaging include investigations into different surface coatings to reduce the chance of infection. New implantable medical electronics that rely on novel materials as sensor components will have to demonstrate adequate safety and biocompatibility before they will be approved for use.

19.3.2 Electrical Compatibility

Another primary function of the external packaging is to work with the device's circuitry to keep the sensitive electronics safe from a myriad of external electrical and magnetic sources of interference. Several decades ago, the first few generations of internally implanted pacemakers had the electronics encapsulated in a polymeric material without the benefit of a metal can to act as a Faraday shield around the device. This could possibly lead to device interference as those who remember once ubiquitous signs warning pacemaker patients

of the presence of microwave ovens can attest. These warnings of microwaves are now relics of the past, due primarily to the metallic can and the design of electronic input circuitry that serves as a gateway for both bio-signal sensing and transmission of therapies to patients. Several standards exist that prescribe the level of immunity to electrical and magnetic fields that an implantable medical device, especially one providing life-sustaining therapy, is required to exhibit. These include EN45502-2-1 (for low power devices), EN45502-2-2 (for high power devices), and CD ANSI/AAMI PC69 standards. These standards define test methods, criteria for device performance during and after exposure, and rationale for testing devices to certain frequency ranges of electro-magnetic radiation at certain power levels.

Low frequency ($f \leq 450$ MHz) emitters and power level requirements are typically those encountered in radio and television transmission, electronic article surveillance gates, RFID systems, some wireless services, and some medical procedures (e.g. diathermy, RF ablation, etc.). Testing at intermediate frequencies (450 MHz $\leq f \leq 3$ GHz) is centered around technologies that include cell phones and some radio systems. This range of frequencies has seen explosive growth in the last decade or so and will continue to evolve new modulation schemes and applications that devices will need to withstand. At very high frequencies ($f > 3$ GHz) such as microwave radiation, there are few requirements due to the understanding that both the limited sources and the natural protection of the device electronics afforded by both the device can and the body provide ample immunity to these radiators.

New technologies and gadgets are constantly being introduced into the marketplace, so the effort required to characterize and catalog these emitters is rapidly changing. Medical device manufacturers are constantly asked about potential device interference due to new sources such as hybrid car engines, portable music systems (e.g. iPods), video game systems with wireless transmitters, etc. The device construction (packaging and input circuit design) requires that the external interference does not change the therapeutic behavior of the device or adversely interact with the device in a way that places a patient at risk. This includes safe device operation, maintenance of device settings and programming, and safe therapy delivery to the patient during the specified interference exposure levels.

19.3.3 Mechanical Requirements

Mechanical requirements for device reliability are also strongly dependent upon the external construction of the device and the packaging used inside the can to protect the sensitive electronics. Requirements exist that outline the use conditions (temperature, vibration, shock, etc.) and performance criteria during device transportation, storage, and handling. Once the device is implanted, the external packaging is expected to protect the device from scenarios such as cyclic

loadingconditions (repeated muscular motion forces on the device), atmospheric pressure changes (from high altitude commercial aircraft to scuba diving), and mechanical shock (blunt trauma). Again, existing standards such as EN45502-2-1 and -2 prescribe minimum requirements, but do not force adherence to any particular design methods or practice.

Additional mechanical requirements exist for the connector block that acts as the interface between the implantable device and leads that connect the device to the appropriate organ or tissue. It is important for the connector to maintain mechanical integrity under both implant (e.g. lead insertion) and chronic implant conditions (e.g. cyclic loading) in order to keep a viable pathway between the leads and the electronics that drive them.

19.3.4 Electrical Pathway

Electrically, the external packaging of the device may become part of the electrical circuit formed between the device and the human body. In many pacing applications, the device can be programmed to act as an electrode that completes a circuit with one or more lead electrodes. This configuration can be found in some pacing applications (so called unipolar pacing) or bio-impedance measurements such as those made across the thoracic cavity between the lead tips and the device implanted in the pectoral region of the chest (see Fig. 19.1).

In high power defibrillation therapies found on ICDs, the device may become an integral portion of the circuit that permits more efficient delivery of high

Fig. 19.1 Electrical pathway formed between the device can and a lead

energy from the lead defibrillation electrodes across the cardiac muscle into the can. Without the can in the defibrillation circuit, it would require a great deal more energy and/or different, and possibly less comfortable, device and lead configurations within the body in order to shunt the energy across the heart to stop a life-threatening arrhythmia.

19.3.5 Internal Packaging

Inside an implantable medical device, the electronics and packaging look surprisingly similar to off-the-shelf consumer electronic devices. While the earliest pacemakers were extremely simple in their design, requiring only a power source and a few transistors to provide a stable series of electrical output pulses to stimulate cardiac tissue, modern pacemakers provide a wide array of functions including on-board microprocessors for signal processing and therapy optimization, wireless telemetry for communication to the outside world, and diagnostic data storage. These additional features support the crucial sensing and pacing functions of the device as well as additional high voltage therapies included in ICD products. Figure 19.2 shows an implantable pacemaker

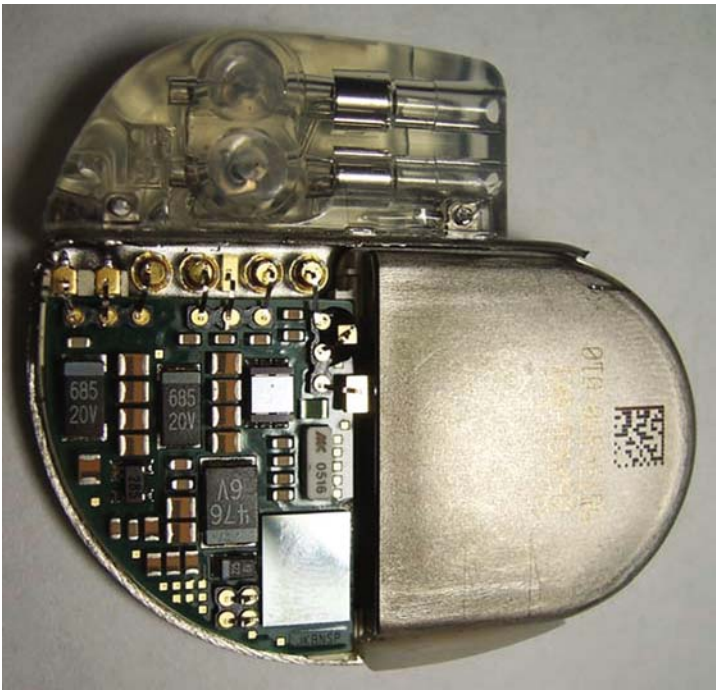


Fig. 19.2 Internal view of a pacemaker (Medtronic EnRhythm Model P1501DR)

(Medtronic EnRhythm Model P1501DR) with one half of the shield removed to show internal components including ICs, discrete components, electrical feedthroughs, and a battery.

The range of signals required to perform all of these functions is quite varied and provides a source of challenges for both the electronic circuitry and the packaging that pulls all that functionality together. Figure 19.3 illustrates a view of signal amplitude and pulse width (proxy for frequency) characteristics for several basic functions of an ICD product. Sensing, important to the optimal operation of a device, must be sensitive to cardiac signals with typical amplitudes between 0.5 and 30 mV and frequencies <100 Hz. Similar sensing requirements are also required for non-cardiac devices such as neurostimulators. This crucial sensing must be performed in the presence of pacing signals (0.5–5 V amplitudes with 0.1–1 ms pulse widths are typical).

Occasionally, high voltage defibrillation therapies are needed to terminate life threatening tachyarrhythmias. These therapies can generate high energy (8–35 J) output pulses with voltage amplitudes of several hundreds of volts and ~100 ms pulse durations. Because of this wide variation of applications: from low amplitude sensing requirements, pacing therapies, high voltage defibrillation therapies, on-board microprocessor and memory functions, and telemetry frequencies in the 100's of kHz for close (order cm) range up to 100's of MHz for distance (order meters) telemetry applications all coupled with aggressive power management techniques, there is not really any single integrated circuit (IC) technology that adequately and simultaneously addresses these requirements while maintaining sufficient noise immunity for proper sensing. These conflicting requirements and technological capabilities limit the ability of system design to accommodate all of the functions on a single piece of silicon, and typical designs will select the best IC technology for the given performance, power, and reliability requirements. While many circuit techniques, including highly tuned filtering and blanking periods, are applied in order to minimize the impact of these signals on the sensing capabilities of the device, packaging plays a critical role in permitting these various functions to be interconnected with each other

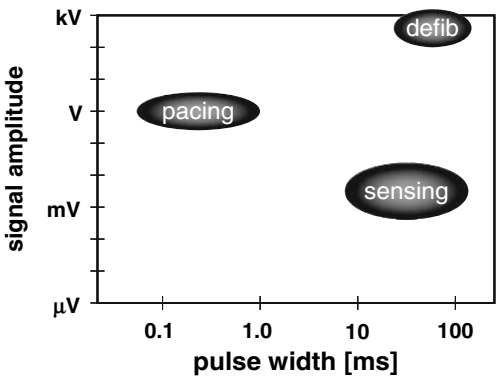


Fig. 19.3 Approximate ranges of signal amplitude and pulse widths sensed and provided by an ICD

while also maintaining proper noise immunity, especially to the delicate sensing function of the device.

One important aspect of electronic packaging that is worth mentioning is the relatively benign thermal environment encountered in implantable medical products once placed inside the body. The device is held at a relatively constant 37°C body temperature throughout its implant lifetime. In addition, designs that place a premium on extremely low power consumption (<100 microWatts dissipation typical) keeps component and package heating to an absolute minimum throughout the vast majority of a product's lifetime. Thermal heating that occurs during high voltage defibrillation therapy is kept under design control and only constitutes a very small fraction of time in a typical device application. Both baseline temperatures and thermal gradients in the electronic packaging and not typically high reliability risk items for ICs in these products.

The primary components of an implantable medical device include a battery, an electronic assembly with a populated circuit board, large capacitors (for high voltage therapy applications), telemetry antennae, sensors (such as motion and magnetic field), and additional connectors. On the electronic assembly, the circuit board is comprised of both discrete electronic components and ICs. The ICs themselves are packaged in a variety of form factors, including well known flip chip and stacked die assembly processes in modern devices. One drive in the industry is the continued reduction in device size for cosmetic purposes, patient comfort, and optimal device implant location selection. These requirements place continuous pressure on both the external and internal packaging considerations. Figure 19.4 shows the evolution in ICD device volumes over the last decade and a half.

Pacemaker products do not require the larger capacitors for high energy defibrillation therapy nor the high rate battery designs to support it, so they are significantly smaller in volume than their ICD cousins by roughly a factor of three. Reduction in ICD device volume is clearly evident since the first models

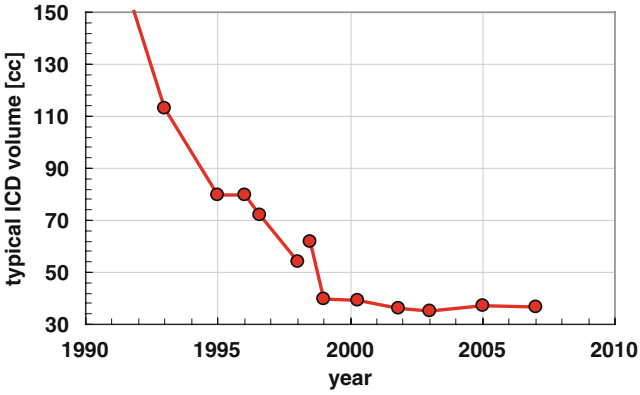


Fig. 19.4 Evolution of typical ICD volume vs. year

introduced circa 1990, but has not been a consistent device requirement. Typically, increases in device volume or periods of relative constant device size (from the late 1990s to day) are driven by addition of new features and technologies into devices that consume some of the natural decrease in product volume that would occur if device performance stayed constant. Some of these new features over the past few years include a trend towards higher defibrillation energies (~35 J today) which may require modifications to batteries and high voltage capacitors, addition of distance telemetry to enable longer range device to receiver communications, greater computational functionality, or larger batteries to support longer device lifetimes between replacements. In addition to traditional device configurations, new implantable monitors and therapeutic devices are continuously driving device size reduction in order to reach new locations within the body and simplify implantation procedures away from surgery towards more benign approaches such as direct injection through a needle. Research into new and improved design techniques, material advances, therapy optimization, and packaging technologies will all contribute to reductions in device volumes in the upcoming years.

19.3.6 Soft Errors and Single Event Upsets

Because of the aggressive power management and moderate computational burden used in implantable medical devices, there is a strong push towards running ICs at extremely low voltages in order to save power. These operating modes can lead to exacerbated sensitivity to soft-errors from alpha particles, thermal neutrons, and energetic neutrons from cosmic radiation. Our understanding of the physics of soft errors and their impact on integrated circuit technology is certainly not new, but very high reliability requirements in life-sustaining devices lead to a variety of safety features incorporated into them. In order to minimize the power, area, and computational burden of these features (such as error correcting codes, redundancy, data integrity checking, etc.) it is highly desirable to utilize packaging materials and technologies that minimize the potential impact of alpha particle induced upsets by maintaining high levels of purity in materials and cleanliness in processing and manufacturing. Cleaner end product packaging reduces the burden and necessity of additional safety features in the product.

19.4 Leads in Medical Devices

19.4.1 Overview of Leads

Pacing leads are the “wires” that carry the electricity from the pacemaker or ICD to the heart. Pacemaker leads are implanted through a vein in the chest and

fixated inside the heart. There is usually one lead put in the right ventricle, another positioned in the right atrium and in heart failure patients another lead may be inserted into the coronary sinus and positioned over the left ventricle. Defibrillator leads are typically inserted into the right ventricle.

Once inside the heart the lead must be fixated to the muscle. Fixation is either active (traumatic fixation), such as an extendible/retractable helical electrode [2] or passive (atraumatic) such as a tine [3] shown in Fig. 19.5. The lead bodies are compliant and flex with each beat of the heart. A heart rate of 60 beats per minute corresponds to flexing the lead approximately 32 million times per year.

Like implantable pulse generators, the leads must be both biocompatible and biostable. Factors that affect the biocompatibility of the pacing lead would include: materials, lead design or shape, implant location, skill of the implanter and the ability of material/device to resist degradation within the body (biostability). The biocompatibility of the materials and the lead must be assessed prior to use in people. Testing is performed per guidelines and test methods outlined in ISO 10997. These tests evaluate hemocompatibility, pyrogenicity, acute and chronic toxicity, sensitization and carcinogenicity. The leads are also implanted in animals to assess both long term biocompatibility and biostability.

The lead and the materials that comprise the lead must withstand the chemical and mechanical environment within the body. The humoral (bulk) environment within the body consists of water, electrolytes (e.g., Na^+, K^+, Ca^{+2}, Mg^{+2}, Cl^-, HPO_4^{-2}, SO_4^{-2}, HCO_3^-), proteins, fatty acids, lactic acid, uric acid, creatinine, bilirubin, bile salts, glucose, urea and many more. Additionally a pacing lead or any implanted device must deal with the inflammatory or foreign body response. Once implanted a cascade of reactions start that result in the pacing lead being covered with a layer or layers of foreign body giant cells and/or macrophages and a fibrotic capsule composed primarily of collagen containing phagocytic cells and fibroblasts [4]. The cellular component of the foreign body reaction can have a significant effect on the biostability of the materials in the pacing lead. These cells can release number of enzymes and oxidants to destroy the foreign body (pacing lead). The compounds that seem to have the greatest effect on biostability appear to be the oxidants (H_2O_2, O_2^-, OH) and hydrolytic enzymes.

Fig. 19.5 Lead with active fixation extendible/retractable helix and a tined lead

Pacing leads are comprised of a connector that plugs into a pulse generator, electrical conductor or conductors that carry charge to the pacing site, insulation that isolates the conductors and electrodes.

19.4.2 Lead Connector

Lead connection is often looked at as trivial; however, improper insertion of the lead into the pulse generator connector is one of the leading causes for reoperation. Lead connectors were not always standardized between the manufacturers. Several unique connector designs were introduced in the early 1980s. This meant the lead from one manufacturer could not be directly inserted into the pulse generator from another manufacturer without an adapter. In the mid 1980s, a joint IEC/ISO International Pacemaker Standards Working Group defined a formal international standard for lead connectors, IS-1 shown in Fig. 19.6.

However, this standard only defines connections for unipolar and bipolar brady pacing lead designs. The development of the implantable cardioverter defibrillators (ICD's) brought about the standardized DF-1 connection for high voltage lead connectors. Today, the pacing companies are working toward a new connector standard, IS-4, that would allow a reduced size lead connector with multiple connections. As one looks toward the future, there is opportunity to design connectors that eliminate the problems associated with improper insertion and allow the multiple connections that will be needed for multiple electrodes and sensors on the lead.

19.4.3 Conductors

There are two types of conductors used in pacing leads: coils and cables shown in Fig. 19.7. The coil was first suggested in 1961 by Dr. William Chardack and greatly reduced conductor fracture [5]. The original wire used in coils was

Fig. 19.6 IS-1 Lead Connector

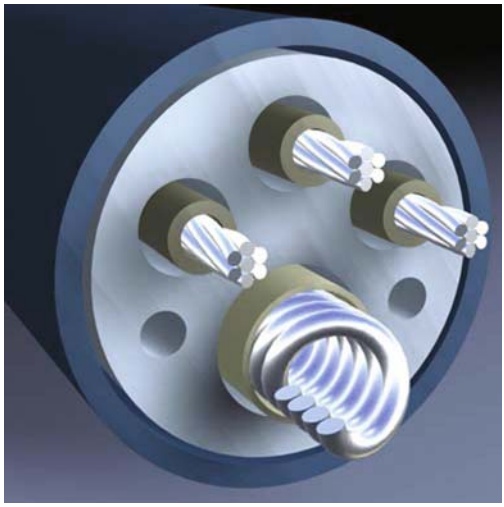


Fig. 19.7 Cross section of a defibrillator lead body showing cable and coil conductors, tubing insulating the conductors, multi-lumen tubing separating the conductors and a protective tube over the multi-lumen tubing

stainless steel which occasionally corroded. Platinum and platinum alloys were used to reduce concerns with corrosion but were very expensive and still fractured. These materials were eventually replaced by the super alloy, MP35N. MP35N has both excellent corrosion properties and mechanical properties making it ideal for use in coils. MP35N coils were improved by using multiple smaller diameter wires. The use of multiple smaller diameter wires allowed the electrical resistance to drop and improved the flex life of the coil. To further reduce the electrical resistance, the drawn filled tube (DFT) was used. In the DFT wire the core of the MP35N wire was replaced with silver which dramatically reduced resistance. The corrosion resistant MP35N on the outside of the wire protected the silver from corroding.

Cables were implemented to further reduce electrical resistance in defibrillator leads. Cables are comprised of many strands of pure MP35N or silver cored MP35N wire. However, both coils and cables are still susceptible to fatigue and fracture within the body. Additionally, it is known that cobalt corrosion byproducts from the MP35N can catalyze the degradation of polyurethanes and other materials used for pacing lead insulation.

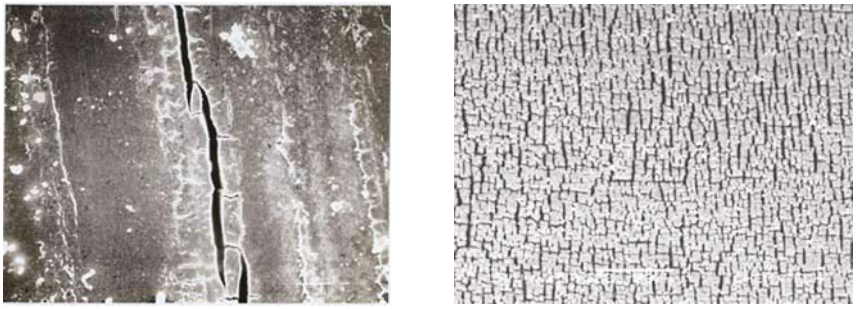
19.4.4 Insulation

Teflon, or polyethylene was used as insulation in early leads. Bonding concerns made Teflon difficult to use in manufacturing, so it was abandoned. The use of polyethylene insulation was stopped because it makes stiff leads which increases the possibility of perforating the heart, and is not biostable [6, 7]. Polyester polyurethanes were tried because of their excellent mechanical properties, but

were stopped because they are subject to rapid degradation in water. Silicone rubber became the material of choice for insulation because it was nontoxic, chemically inert and biostable. Silicone rubber has low tear strength and had to be used with thicker walls to minimize mechanical damage. Silicone rubber also has a high coefficient of friction in blood which made it difficult to pass two leads in the same vein. As a result, dual chamber pacing did not realize its full potential in the 1970s. In the early 1980s polyether polyurethane began to be used as lead insulation. Polyether polyurethane is hydrolytically stable unlike the polyester polyurethane, stronger mechanically than silicone and is slippery when wetted with blood. The increased mechanical properties allowed the insulation thickness to be downsized. The smaller size combined with lubricious surface in blood made it easy to place two leads in one vein making dual chamber pacing a practical therapy.

Unfortunately, the softer polyether polyurethanes were discovered to be subject to two previously unknown failure mechanisms, metal ion oxidation (MIO) and environmental stress cracking (ESC) [8, 9, 10] shown in Fig 19.8 (a) and (b). Pacemaker lead manufacturers have learned how to design around these failure mechanisms to produce excellent longevities [11].

High performance silicone rubbers have replaced the early silicone rubbers and allowed the insulation wall thickness to be reduced. Additionally, surface treatments were developed to make silicone rubber more lubricious and easier to implant. Thus, today, silicone rubber leads can be made substantially smaller and easier to use, but still not as small and tough as polyurethane leads. Silicone rubber, while chemically inert, still has failure mechanisms, including susceptibility to mechanical damage. Silicone rubber insulation failure due to compressive creep (cold flow) or wear is a concern in multiple lead implants. Thus, it is probably correct to say that at the present time, there is no optimum insulation material. Manufacturers continue to research new, biostable polymers for insulation.



(a) (b)

Fig. 19.8 (**a**) MIO breach in inner insulation and (**b**) ESC in outer insulation

19.4.5 Electrodes

Early transvenous leads were relatively large diameter (12 French, 0.156") as were the electrodes. The large electrode size had low pacing impedance which resulted in high current drain and shorter pacemaker longevity. Early work by Irnich showed that the theoretically optimum (spherical) electrode for stimulation was about 0.7 to 1 mm in radius, corresponding to the thickness of the connective tissue that forms around it [12]. The next generation of pacing electrodes was smaller which increased impedance and reduced battery current drain, however, the smaller size also increased the impedance associated with sensing (source impedance) [13]. Mismatch between the input impedance of the pulse generator's sensing circuit (too low) and the source impedance (too high) can result in signal attenuation and sensing failure. This drove electrode size to the 6 to 12 mm^2 size range in order to optimize impedance and minimize signal attenuation.

In the late 1970s, the totally porous and porous surface electrode were introduced [14, 15]. These structures produced high pacing impedance because of their small size (defined by the electrode's radius), but their increased surface area from the porosity resulted in much lower source impedance. Thus, porous electrodes provided better sensing than polished electrodes. An added benefit was that the pores facilitated tissue ingrowth, which aided fixation (Fig. 19.9a, b, and c).

In 1979, the carbon electrode was introduced with microporous surface structure [16]. The microporosity further improved the performance of the electrodes and different coating began to be added to increase the interfacial surface area. These coatings are used today and include platinum black, titanium nitride [17] and iridium oxide [18].

The steroid-eluting electrode was introduced by Stokes in 1982 [19]. The steroid was combined with silicone to form a plug which was positioned inside the electrode shank behind the porous tip (Fig. 19.10). This electrode technology combined porosity and microporosity with a glucocorticosteroid resulting

(a) (b) (c)

Fig. 19.9 Sintered, porous, titanium nitride coated electrode (**a**) and scanning electron microscope photographs at 2500X (**b**) and 20,000X (**c**) magnification, respectfully

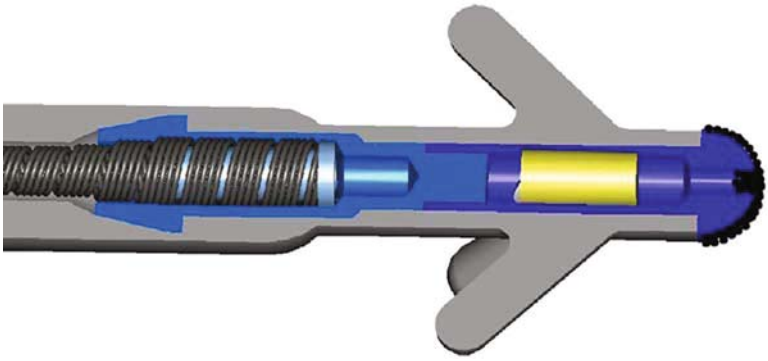


Fig. 19.10 Cross section of steroid eluting electrode

in minimal to no threshold rise as a function of implant time [20, 21]. The steroid mitigates the foreign body response at the electrode tip, preventing threshold rise that would occur in its absence [22]. The addition of the steroid not only prevented threshold rise it significantly reduced exit block. Exit block is a phenomenon where pacing thresholds continue to rise beyond the ability of the pacemaker to capture the heart.

Electrode materials used in early transthoracic temporary pacemakers included tantalum, silver plated copper and stainless steels [23]. Stainless steel was used in the early 1960s for implantable electrodes, but gave way to more corrosion-resistant materials. Platinum, platinum alloys, and Elgiloy became the materials of choice for the vast majority of permanent leads. However the current density, which governs corrosion, was high enough to cause the Elgiloy to corrode. The issues with current flow were partially solved by coupling a capacitor between the output terminals of constant voltage generators. "Capacitively coupled" generators limit current output below that required for significant corrosion.

Other materials with better corrosion resistance have been studied extensively. Both titanium and tantalum are excellent electrode materials [24, 25]. Under controlled conditions, oxides of varying structures are grown on their surfaces. These oxides are stable in the body, even when charged. Titanium oxide electrodes have been used successfully for over 25 years in Europe [26, 27]. The only negative aspect of titanium is its poor radiopacity, which makes implant more difficult because the tip does not show up on X-ray.

Leads are available with a bewildering array of electrode designs, fixation mechanisms, conductor configurations, insulation materials, etc. As technology progresses over the sixth decade of cardiac pacing, lead reliability will improve and the evolution will continue at a remarkable pace. New conductor and insulation technologies are needed that will eliminate the major device failure mechanisms (such as ESC, MIO, creep, wear, crush, fracture). New electrode materials will be developed that allow drug elution as well as improve

the electrical performance of the lead. Meanwhile, the lead may look like a simple wire, but in many ways, it is far more complex than the pulse generator.

19.5 Implantable Biomedical Sensors

19.5.1 Overview of Implantable Sensors

The previous two sections contained overviews of the advances and opportunities for chronically implanted pacemakers, defibrillators and leads that are used to correct problems with the rhythm of the heart. Recently, medical devices have been demonstrated that are intended to manage or correct numerous other medical conditions either through the use of closed-loop implanted systems or by providing important information to the managing physician who can change drug therapies or order procedures. In these systems, one of the key components is a sensor that measures the physiologic variable of interest. The specific requirements of the sensor are determined by the variable to be measured, the environment in which the sensor is to be used, the accuracy of the sensed signal, and the lifetime of the device.

The applications for these sensors are extremely varied. For example, sensors that are intended to help diagnose problems in the digestive system may be swallowed or placed in a specific position that is prone to extremely high levels of moisture and acidity. These sensors are only expected to last a few days before they are passed through the system. Sensors that are placed under the skin or into the head, cardiovascular system, or eyes of people in order to manage or correct the effects of chronic diseases are expected to operate flawlessly for years. Some applications for these sensors include the management of diabetes, hypertension, heart failure and blindness. Chronically implanted sensors have also been used as a method to diagnose an infrequent but problematic condition or provide an early warning for the onset of a condition for which a patient is at risk. Diagnosing the cause of fainting is an example of the former condition while providing an early warning for the start of a stroke or heart attack is an example of the latter. Another application for implanted sensors consists of devices that are intended to monitor the status of another implanted medical device such as an artificial cervical disc or a prosthetic hip or knee joint. These sensors are used to measure the stresses on the device or determine if excessive wear is occurring.

In the remainder of this section, different sensors will be described including their key requirements.

19.5.2 Sensors for Gastrointestinal Diagnosis

The Bravo^{TM} pH Monitoring System from Medtronic (Minneapolis, MN) is shown in Fig. 19.11. This system is used to measure the pH level in the esophagus

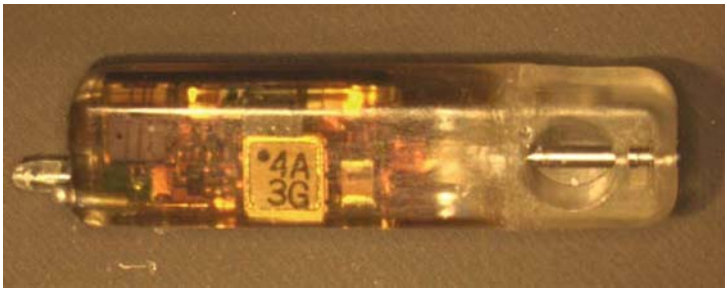


Fig. 19.11 Photograph of the Bravo esophageal pH sensor for the diagnosis of gastroesophageal reflux disease

of patients who are suspected of having gastroesophageal reflux disease [28]. The Bravo sensing capsule is approximately 2.5 × 0.6 × 0.5 cc and contains a pH sensor, electronic circuitry, a radio transmitter, and a battery. Unlike pacemakers and defibrillators that have a titanium can for the external packaging, the Bravo circuitry is potted in epoxy, leaving only the electrodes for the pH sensor exposed. The choice of epoxy rather than titanium permits the telemetry to operate over a few meters of distance and keeps the cost of the device low.

The Bravo sensor capsule is positioned in the esophagus just above the entry into the stomach using a specially designed catheter. The sensor is attached to the wall of the esophagus using a metal pin and the catheter is removed. The sensor then transmits the pH sensor reading to a nearby receiver every few seconds for 24 to 48 hours.

The sensor must survive in an extremely hostile environment of high humidity and acidity. The selected epoxy encapsulation is thick enough to prevent moisture from reaching the circuitry while also providing a durable, low-cost protective layer for the circuits.

A second device with a similar operating environment is the PillCam from Given Imaging, Ltd (Yoqneam, Israel). The device is 11 mm × 26 mm and weigh less than 4 grams. It is swallowed and, while moving through the stomach and small intestines, takes and transmits two images per second for approximately eight hours. The result is more than 50,000 images. The application is to detect polyps, cancer, or causes of bleeding and anemia inside of the small intestine. The capsule contains a camera, lights, RF transmitter and batteries. A unique requirement for the PillCam packaging is that it must accommodate the optical functions of the device. The capsule has a clear end that allows the internal lights to illuminate the lining of the small intestine and the image to be focused on the camera.

19.5.3 Implantable Pressure Sensors

The measurement of pressure is used to diagnose and manage a number of serious medical conditions including heart failure, glaucoma, and hydrocephalous.

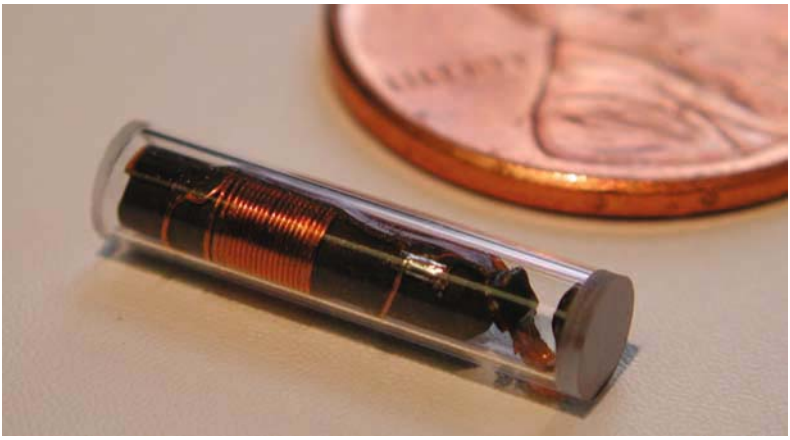


Fig. 19.12 Photograph of the wireless pressure sensor capsule for the measurement of intracardiac pressures (Courtesy of ISSYS)

A number of companies are developing pressure sensors for chronic implantation to manage these conditions. ISSYS (Ypsilanti, MI USA) is developing a two-part system consisting of an implantable, batteryless, sensor shown in Fig. 19.12 and a companion hand-held reader. The implantable sensor module contains a silicon MEMS (MicroElectroMechanical System) pressure sensor along with custom electronics and a telemetry antenna. The pressure sensor is powered and interrogated using an RF signal from the external reader. The reader transmits power to the sensor and the sensed pressure is in turn transmitted back using inductive magnetic telemetry.

The sensor is intended to be implanted in the left atrium of the patient's heart for the management of heart failure [29]. This also drives a number of requirements for the packaging of the device. First, the device is expected to last more than 10 years. Therefore, the package must be impervious to moisture. Second, the device must be safe. Therefore it must be made using biocompatible materials and cannot cause clots to form that might break off and cause a stroke. Finally, the package must allow the RF energy to easily couple to the internal antenna. ISSYS has chosen to use a glass capsule that is sealed to a silicon MEMS pressure sensor. A non-thrombogenic coating is applied to glass to prevent the formation of clots.

Mesotec (Hanover Germany) is developing an implantable pressure sensor to measure Intraocular Pressure (IOP) in the eye of a patient with glaucoma [30]. The pressure sensor is a single silicon IC that contains an integrated pressure sensor as well as the recovery circuitry and RF telemetry. The sensor IC is sealed inside an annular silicone ring, called the mesoRing, as shown in Fig. 19.13. The selection of the polymer and the sealing process are critical to the proper operation of this device. Not only must the polymer protect the circuitry but it must also not

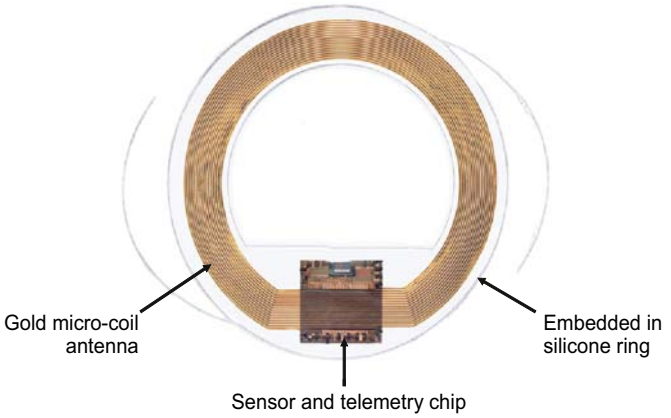


Fig. 19.13 Photograph of the mesoRing telemetric Intraocular Pressure Sensor implant (courtesy of Mesotec)

swell or cause a force to be applied to the surface of the pressure sensor that would produce an offset.

The ring also contains a foldable gold micro coil connected to the IC. Similar to the ISSYS design, power delivery and communication are accomplished through RF inductive coupling to an external reader. The mesoRing is approximately 1 cm across and is implanted during the eye surgery to replace a diseased lens.

Pressure sensors are also in development to monitor chronic diseases like heart failure. One such device is the Chronicle ® Implantable Hemodynamic Monitor from Medtronic (Minneapolis, MN USA). As shown in Fig. 19.14 the Chronicle system consists of an implanted pacemaker-sized monitor and a pressure-sensing lead placed in the right side of the heart. The cardiac pressures are measured continuously and stored in the device. The data are then intermittently transmitted by the patient to a secure website accessible by treating clinicians [31].

The pressure sensor is the small capsule that is approximately 3 cm from the distal tip of the lead. The Chronicle pressure sensor capsule consists of a titanium housing that has been machined to have a thin diaphragm in one section. This diaphragm is one plate of a capacitor and deflects due to cardiac pressure to produce a change in the capacitance. This pressure-dependant capacitance controls the output of an IC inside of the capsule. Therefore, the titanium housing provides not only protection for the internal circuitry, but the machined diaphragm is the pressure sensitive element. Because the pressure sensor is on a lead that is placed in the heart, the construction must be very robust to repeated loading. It should be expected that the lead will flex tens of millions of times during the life of the patient.

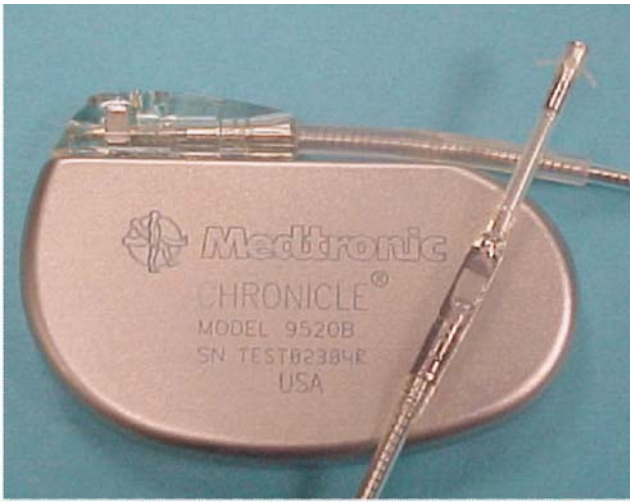


Fig. 19.14 Photograph of the Chronicle Implantable Hemodynamic Monitor and pressure sensor on the lead

St. Jude Medical (St. Paul, MN) and Transoma Medical (St. Paul, MN) are each developing pressure sensors that are to be placed in the heart. Although there are differences between these devices and the Chronicle in terms of sensor design and position of implant, the requirements for the package to be robust, hermetic, and mechanically stable are common.

19.5.4 Implantable Sensors for the Blind

An exciting application of sensors in ophthalmic applications is the design and manufacture of implantable medical devices to aid in vision improvement. Optobionics (Naperville, IL USA) is developing the Artificial Silicon Retina™ (ASR) microchip to restore some sight to patients who have been blinded by retinitis pigmentosa or age-related macular degeneration [32]. In these patients, the retinal cells are damaged but the underlying nerves are still intact. The system is designed to stimulate the damaged retinal cells, allowing them to send visual signals again to the brain. The ASR microchip is a silicon chip 2 mm in diameter and 25 microns thick, which is surgically implanted under the retina. It contains an array of approximately 5,000 "microphotodiodes," each with its own stimulating electrode. These microphotodiodes are designed to convert the light energy focused on them by the lens of the eye into impulses that stimulate the remaining functional cells of the retina.

Alternative approaches to returning sight to the blind are being investigated at other institutions. The Doheny Eye Institute and the Intraocular Retinal

Prosthesis Group at the University of Southern California [33] is using a small external camera to generate an image which is transmitted to a system surgically implanted in the eye. The implanted components contains electronic circuitry that receives the transmitted signal, converts it into a set of electrical impulses and an array of electrodes that deliver the impulses to the nerves of the eye. Ultimately, the desire is to place the camera in the eye as well.

In all of the vision applications, the materials and packaging for the implanted portion of the system must simultaneously meet a number of requirements. Because there is a need to keep the devices thin, the outer coating of the device must be thin as well. These layers must protect the underlying electronic components from the fluids in the eye but must also be biocompatible and prevent irritation, even after years of implantation. Polymer coatings such as silicone or deposited layers such as diamond-like coatings are being investigated.

19.5.5 Implanted Sensors for Orthopedics and Spine

Sensors implanted in orthopedic and spinal devices are new being investigated to provide accurate information on the mechanical stresses and wear of the implanted systems. In these application, great care must be taken to protect the sensors from being crushed by the large forced generated by the motion of the joints as well as to design a package that will not leak after millions of cycles. MicroStrain (Williston, VT USA) has built an investigational, full artificial knee replacement that can wirelessly report digital, 3 dimensional torque and force data back to computers [34, 35]. The sensing system was enclosed in a custom titanium alloy total knee replacement. The unit includes all of the electronics and is hermetically sealed using laser welding. Piezoelectric transducers sense the local strain in the titanium, and the wireless sensor sends the data to an external antenna. The system itself must be mechanically robust enough to withstand millions of knee movements. The information gained from this device can be used to develop design improvements, refine surgical instrumentation, guide postoperative physical therapy and potentially detect the individual activities that would overload the implant.

19.5.6 Implanted Glucose Sensors

Biochemical sensors are an area of active research. The search for a long-lived, continuous glucose sensor for the management of diabetes has been underway for decades [36] but the magic device still remains elusive. At the time of this writing, there are two companies, Medtronic, Inc. [37] and Dexcom, Inc. (San Diego, CA) that have FDA-approved continuous glucose sensors. These are not the dream design of a small sensor capsule that is inserted under the skin and accurately measures glucose levels for years. Instead, these are devices for which

the sensing element contains electrochemical electrodes coated with a glucose converting enzyme. The electrodes are printed onto a long, thin polymer film. The electrodes are inserted through the skin and remain in place for three to seven days before they are replaced. A small transmitter is connected to the external end of the sensing electrode. The electronics in the transmitter measures the glucose value regularly and sends the information to a nearby receiver.

Dexcom has also reported on their progress to build a fully implanted monitor [38]. The first version of the sensor that was implanted in humans consisted of an electrochemical sensor packaged in a small, cylindrical device about the size and shape of an AA battery. The package also contains a battery, circuit board, microprocessor, and radio-transmitter. One further feature of the sensor was a multilayered membrane that coated the sensor and was intended to control the body's natural response to form a fibrous tissue layer around the sensor. This layer must be avoided because it would prevent the diffusion of glucose to the sensor surface, resulting in erroneous glucose readings. These sensors have been implanted in patients for up to three months.

Sensors for Medicine and Science (Germantown, MD) is developing an implantable sensor which relies on fluorescence to measure glucose concentration under the skin. A drawing of the sensor is shown in Fig. 19.15. The sensor capsule contains an LED to excite the fluorophores in the indicator layer, optical detectors to measure both the LED emission and the fluorescence, and circuitry to drive and control the optoelectronic components. The implanted capsule also has circuitry to harvest energy from an RF signal from an external monitor.

Implanted biomedical sensors are an area of active research and technical development although only a handful have been commercially released to date due to the difficulty of simultaneously achieving accuracy, stability, and biocompatibility in an extremely small package. The requirement for better information

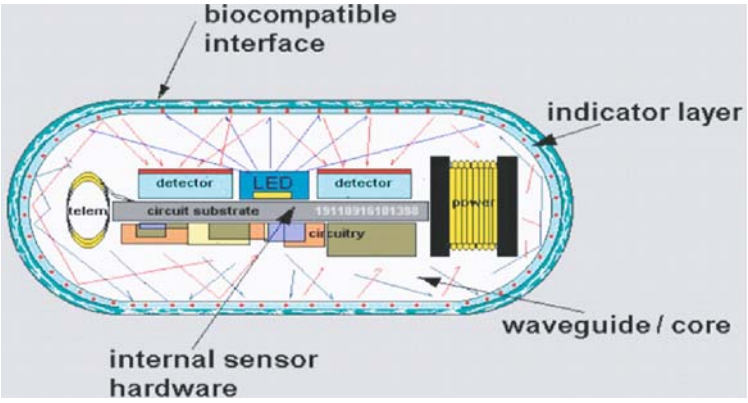


Fig. 19.15 Drawing of a fluorescence-based implantable glucose sensor capsule (courtesy of Sensors for Medicine and Science)

on patient health as an enabler of lower cost healthcare combined with the number of organizations that are now moving into this area will result in a number of devices being released in the near future.

19.6 Chip-Based Point of Care Sensors: Opportunities and Challenges

19.6.1 Introduction

Point-of-care biosensors can have a wide and profound impact on diagnosis and management of disease. Point-of-care biosensors can be used at the bedside, at the doctor's office, or at home. The need for such sensors and devices has been on the rise due to an increased need to detect targets of disease for a more efficient management of disease and also for the increased need to manage the disease at the individual level. The fact that we are witnessing the largest ever aging population in the US in the coming decades, very high costs of health care, and widespread AIDs epidemic in much of the underdeveloped part of the world, point of care biosensors are urgently needed to help tackle these complex issues. These sensors need to be cheap, disposable and one-time-use and sensitive and be able to detect the target biological entities such as cells, bacteria, viruses, proteins, DNA, or small molecules.

Currently, only a few examples of point of care sensors are available in the market. The pregnancy test and the blood glucose monitoring are perhaps the two most common examples of tests which can be purchased over the counter, are easy to use, and provide critical information needed by the user. Two additional examples include the cholesterol test and the iSTAT/Abbott cartridges for detection of blood gases, ions, and most recently cardiac markers. Many more opportunities exist in making such point-of-care sensors more pervasive, especially if microfluidics, micro and nanotechnology and lab-on-a-chip technologies are employed in the development and realization of these sensors.

19.6.2 Microsystems, BioMEMS, and BioChips

The point-of-care biosensors available over the counter today are limited to proteins, enzymes, or small molecules (as in the case of the iSTAT or the Cholesterol tests). Many more opportunities exist for the detection of cells, microorganisms, viruses, proteins, DNA, and small molecules. The recent technological advances in top–down silicon nanotechnology and development of microfluidic devices present themselves with new opportunities for small, sensitive, one time use, point of care diagnostic biochip sensors capable of rapid and highly accurate analysis of samples of body fluid. Micro and nanofabrication

techniques have enabled researchers to produce very small-scale sensors. In general, the small size of sensors not only improves their sensitivity and also enables formation of arrays. Moreover, micro-electro-mechanical-systems (MEMS), micro-fluidics and nanotechnology also offer fabrication of sensors that have the capability of detecting biological entities, possibly without using any labels.

The use of micro and nano-scale detection technologies is justified by, (i) reducing the sensor element to the scale of the target species and hence providing a higher sensitivity, (ii) reduced reagent volumes and associated costs, (iii) reduced time to result due to small volumes resulting in higher effective concentrations, and (iv) amenability of portability and miniaturization of the entire system. Monitoring of cancer biomarkers from serum or blood, detection of viruses or bacteria from blood or urine, detection and counting of CD4+ white blood cells, and detection of presence of live cells from drinking water, are only some of the examples of possible applications. The actual sensing modalities could include electrical methods and all its derivatives, mechanical sensing, or optical sensing (Bashir, et al. 2004). The sources of sample for diagnostic applications can include saliva, blood, or urine, with blood being the richest repository of information about the individual's state of health (Toner and Irimia, 2005). In addition to body fluids, other samples such as water and other fluids used industrial microbiology and pharmaceutical manufacturing, and fluids from extracts of food samples also compose a large market segment for such point-of-care or point-of-test sensors. Figure 19.16 shows the steps to be performed for point-of-care sensors sample analysis. The target fluid is to be metered and injected into a device. Depending on the target entity to be detected, the sample might have to be processed, i.e. target entities separated from other entities in the sample. Such sample preparation and analyte extraction or concentration is needed to increase the signal to noise ratio and to be able to detect minute quantities of the target. Then the target entity is detected and the results need to be displayed in the reader or the data analysis system. The model here is that of a disposable cartridge/sensor and a reusable reader/system.

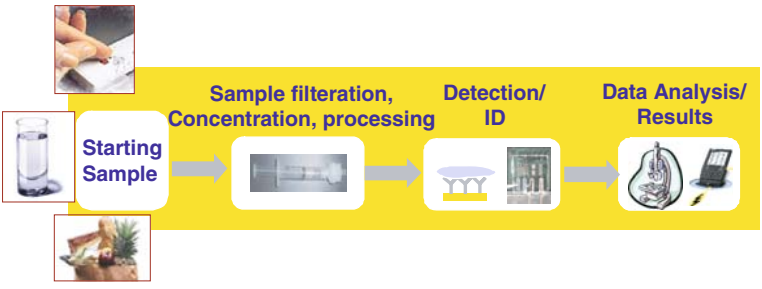


Fig. 19.16 Overview of steps to be performed in a point of care biochip sensor

19.6.3 Sensor Technology Platform

Microfluidic devices can handle fluids in the range of few tens of hundreds of microlitres depending on the device architecture and the application. Depending on the target analyte, the possible technology elements in such a biochip sensor are shown in Fig. 19.17. Some means to dispense and transport the sample are needed. The sample might have to be filtered to separate cells from serum, for example, or separate viruses and bacteria from blood cells. Further sorting or separation might be done using charge or pH based separation, or by the use of electrophoresis or dielectrophoresis. Then the target entities might have to be captured using surface receptors that bind to antibodies to achieve specific capture. Once the target cells are captured, in some cases, the cells might have to be grown and cultured to either increase their number, e.g. for the case of detection of live bacteria, or for detection of proteins secreted by growing cells. Then the cells might need to be lysed to analyze the cellular contents using bio-molecular identification techniques. These techniques could be label free, for example, using electrical (impedance, electrochemical, or field effect) or mechanical sensors (micro or nano-cantilever). Optical detection with fluorescence labels or other techniques such chemiluminescence or bioluminescence can be used with integrated photo-detectors (in the system/reader). Not all modules have to be used for all applications and the order could also be switched around depending on the target analyte and entity. Figure 19.18 shows images from literature of BioMEMS and microfluidic devices that are being developed in academia or industry.

Mechanical detection for biochemical entities and reactions has more recently been used through the use of micro- and nano-scale cantilever sensors on a chip. These cantilever sensors (diving board type structures) can be used in

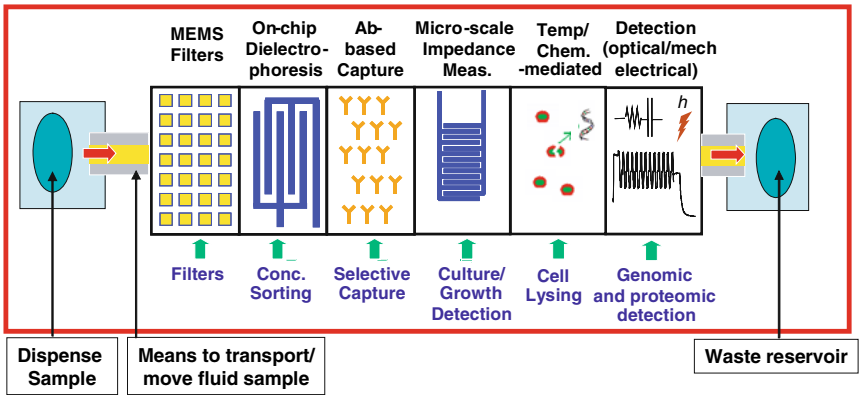


Fig. 19.17 Overview of a possible technology platform for on-chip detection of microorganisms or cells from fluids. Not all modules might be needed and the sequence of modules can be rearranged based on the type of assay needed

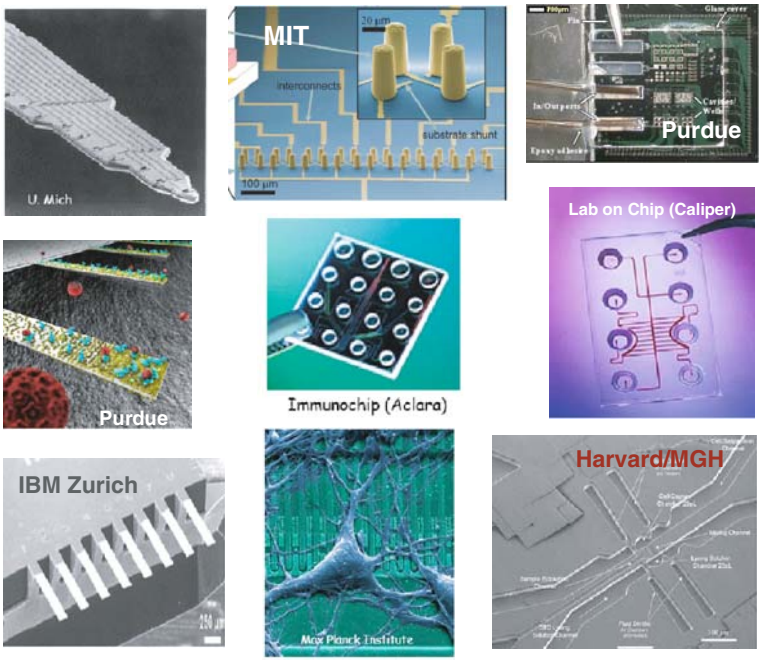


Fig. 19.18 Various biochip sensors and lab on chip devices from literature

two modes, namely stress sensing and mass sensing. In the stress sensing mode, the bio-chemical reaction is performed selectively on one side of the cantilever. A change in surface free energy results in a change in surface stress, which results in measurable bending of the cantilever. Thus, label-free detection of biomolecular binding can be performed. The bending of the cantilever can then be measured using optical means (laser reflecting from the cantilever surface into a quad position detector, like in an AFM) or electrical means (piezo-resistor incorporated at the fixed edge of the cantilever). In the mass sensing mode, the cantilever is excited mechanically so that it vibrates at its resonant frequency (using external drive or the ambient noise, for example). The resonant frequency is measured using electrical or optical means, and compared to the resonant frequency of the cantilever once a biological entity is captured. The change in mass can be detected by detection of shift in resonant frequency, assuming the spring constant does not change. The quality factor is decreased with increased damping, for example in a fluid, and hence the minimum detectable mass is much higher in damped mediums as compared to low-damped mediums.

Electrical or electrochemical detection techniques have also been used quite commonly in Biochips and BioMEMS sensors. These techniques can be amenable to portability and miniaturization, when compared to optical detection techniques, however, recent advances in integration optical components on a chip can also produce smaller integrated devices. Electrochemical biosensors

include three basic types; (i) amperometric biosensors, which involves the electric current associated with the electrons involved in redox processes, (ii) potentiometric biosensors, which measure a change in potential at electrodes due to ions or chemical reactions at an electrode (such as an ion Sensitive FET), and (iii) conductometric biosensors, which measure conductance changes associated with changes in the overall ionic medium between the two electrodes. There are more reports on potentiometric and amperometric sensors, specially, due to the established field of electrochemistry, and many of these sensors have been used as the micro and nano-scale.

Optical detection techniques are perhaps the most common due to their prevalent use in biology and life-sciences. There is a very significant amount of literature on BioMEMS devices with optical detection. Optical detection techniques can be generally based on Fluorescence or Chemiluminescence. Fluorescence detection techniques are based on fluorescent markers that emit light at specific wavelengths and the presence and enhancement, or reduction (as in Fluorescence Resonance Energy Transfer) in optical signal can indicate a binding reaction. The detectors include photodiodes or CCD elements which are integrated in the readers so that the cost of the disposables are minimized as much as possible.

19.6.4 Bio-Chip Packaging Issues and Challenges

The packaging of biochips and lab-on-chips poses significant challenges as compared to micro-electronic device packaging. Such devices need to possibly have all or some of these interfaces [41]; (i) electrical interface, for the case of electromechanical detection, (ii) optical interfaces, for fluorescence or other means of optical detection to reaction regions in the chip, (iii) fluidic interfaces, for possibly transferring fluid from the cartridge to the chip itself, and (iv) mechanical interfaces, for applying pressure to move and pushing the fluids in the chip, for example. The co-existence of these multiple interfaces makes the packaging issues more complex than other device or sensor packages. In addition, the cost needs to be low enough for these devices to be used in throw-away one-time-use applications. Figure 19.19 shows drawn schematic of such sensor layouts, and Fig. 19.20 shows a concept schematic of packaging system for such micro-fluidic biochip sensors.

The design criteria and the performance specifications for any of these devices could include any or all of these considerations below [41]. (i) The package should eliminate manual handling and connection of individual fluidic ports, (ii) The package and sensor itself should be designed such that a failure more in one does not compromise the other, (iii) If the devices is to be used a one-time-use sensor, the package must also protect the sensor from the environment till the device is used, and subsequent to use, the package and device must hold all fluids used during the test and prevent any contamination to the environment, (iv) The package should be able to handle the desired pressure

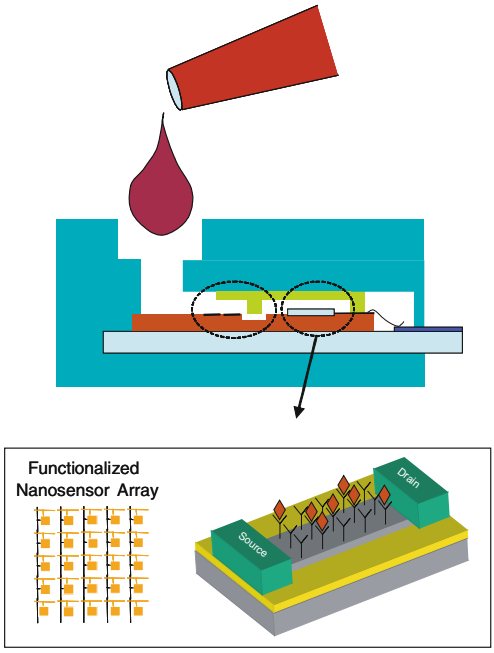


Fig. 19.19 Drawn schematic of cartridges for integrated biochips for point-of-care testing. The integrated sensor is shown to be a field effect transistor sensor but could also include other types of sensors

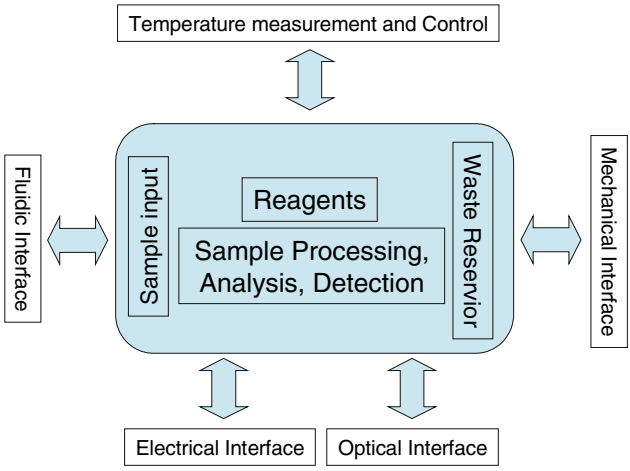


Fig. 19.20 Schematic of packaging requirements for integrated lab-on-chip and microfluidic biochip sensors

ranges for movement of fluids inside the biochip sensor, (v) Any or all of the interface schemes mentioned above must be designed in the package, (vi) The package and the biochip must not contaminate or degrade the biological entity of interest under test, (vii) The package and biochip must not be permeable to

gases or fluids for them to leak to the environment, (viii) The fluidic interface must be reliable and robust, (ix) The materials used for building the package needs to be sterilized before the introduction of the sample to be tested. These are only some of the requirements, and depending on the specific test and assay under development, the requirements might be increased or decreased from the above list.

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