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Microelectromechanical Systems and Nephrology: The Next Frontier in Renal Replacement Technology

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Abstract

Microelectromechanical systems (MEMS) is playing a prominent role in the development of many new and innovative biomedical devices, but remains a relatively underutilized technology in nephrology. The future landscape of clinical medicine and research will only see further expansion of MEMS based technologies in device designs and applications. The enthusiasm stems from the ability to create small-scale device features with high precision in a cost effective manner. MEMS also offers the possibility to integrate multiple components into a single device. The adoption of MEMS has the potential to revolutionize how nephrologists manage kidney disease by improving the delivery of renal replacement therapies and enhancing the monitoring of physiologic parameters. To introduce nephrologists to MEMS, this review will first define relevant terms and describe the basic processes used to fabricate MEMS devices. Next, a survey of MEMS devices being developed for various biomedical applications will be illustrated with current examples. Finally, MEMS technology specific to nephrology will be highlighted and future applications will be examined. The adoption of MEMS offers novel avenues to improve the care of kidney disease patients and assist nephrologists in clinical practice. This review will serve as an introduction for nephrologists to the exciting world of MEMS.

Keywords

microelectromechanical systems; MEMS; microsystems; microdevices; microfluidics; pressure sensors; point of care testing; drug delivery; lab on a chip; bioartificial kidney

Introduction

Since the advent of renal replacement therapy, nephrology has remained at the interface between clinical medicine and engineering. The life-sustaining treatment of millions of

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patients worldwide with hemodialysis[1] is a testament to the successful interplay between nephrology and engineering. To maintain this crucial relationship, this review will introduce nephrologists to the innovative realm of microelectromechanical systems (MEMS). The term MEMS originally referred to the use of fabrication techniques borrowed from the microelectronics industry for the manufacturing of miniaturized devices with integrated mechanical and electrical systems.[2] These devices were micro-sensors and micro-actuators that had feature sizes on the order of a few microns (one millionth of a meter). However, over the past two decades, the term MEMS has broadened considerably to encompass not only mechanical and electronic microdevices, but also includes integrated fluidics, optics, and biochemical systems. The fabrication techniques have also evolved significantly from those that were originally developed for silicon semiconductor production to now include molding, embossing, and printing techniques used with polymer and gel materials. The broadened definition of MEMS has resulted in a variety of terms such as microsystems, microdevices, and micromachines that are often used interchangeably with MEMS.[2] Therefore, MEMS now represents a generalized term that refers to devices with miniaturized features based on modified techniques adapted from the microelectronics industry.

MEMS currently permeates our everyday life from airbag accelerometers to ink jet printers and is emerging in prominence for use in biomedical devices and diagnostics.[2-4] The push for cost-effective technologies that can improve the delivery and management of healthcare has resulted in growing excitement for MEMS technology.[4] There have been new developments in a vast array of innovative MEMS devices such as implantable biosensors and monitors, novel drug delivery devices, rapid point-of-care-testing, and all encompassing lab-on-a-chip devices.[2,4-6] Despite the recent strides made in the use of MEMS, the technology remains a relatively untapped tool in nephrology. Given that nephrologists already comfortably manipulate complex mechanical, fluidic systems for renal replacement, it is only natural to incorporate MEMS technology to better diagnose, monitor, and improve the care of kidney disease patients. The goal of this review will be to first introduce basic MEMS fabrication techniques and materials currently utilized by researchers and industry. This will be followed by examples of current biomedical devices and research employing MEMS technology with an emphasis on devices near or at the clinical stage of development. Finally, this review will explore recent and future applications of MEMS in nephrology.

Background

Silicon ushered in the semiconductor revolution and created a robust base of processing and manufacturing for the microelectronics industry. These techniques inspired the development of innovative new devices and techniques utilized in MEMS today. The attraction of MEMS based technology for use in biomedical devices can be attributed to several inherent advantages summarized here. 1) Small feature size- the typical size scale for MEMS ranges between 1-100 microns, but given the broad definition it has been used to describe device features as small as a few nanometers (one billionth of a meter) to as large as a centimeter. This permits the design of devices amenable for significant miniaturization even with complex components and systems. Additionally, smaller scale devices make implantation a feasible goal. 2) High precision- despite the extraordinary small feature sizes, MEMS enables the geometry and layout of features to be reliably reproduced. This is accomplished while still maintaining precise control of feature sizes at the micron and nanometer level. The high level of precision allows for unprecedented control of device specifications. 3) System integration- multiple components can be incorporated together in a single device such as fluidic channels, mechanical actuators, and optical sensors. The incorporation of microelectronics also enables signal processing, communication, and feedback loops that result in an “intelligent” device. MEMS, therefore, allows for a variety of functions to be easily integrated into a single device. 4) Cost effective- batch fabrication allows for the

concurrent manufacturing of thousands of components leading to significantly reduced per unit cost. This allows MEMS technology to compete commercially against traditional manufacturing techniques. Therefore, the advantages of MEMS technology as detailed above make it a natural fit for the development of various biomedical applications.

Fabrication

The fabrication of MEMS devices is a step-wise approach that has been utilized for decades in the semiconductor industry and illustrated in Figure 1. The process is extremely sensitive to environmental factors especially dust; therefore all work is performed in a *cleanroom* that has precise temperature, humidity, airflow, and particulate controls. The fabrication process typically begins with a silicon substrate that has been sliced into circular disk shapes, each referred to as a *wafer*. Then a thin-film (i.e. inorganic: silicon dioxide, silicon nitride, polycrystalline silicon or metal: aluminum, copper, tungsten) is deposited on top of the silicon substrate, which will form the basis for the device features. The thin-film layer of silicon, polysilicon, or oxide can also be altered or *doped* with impurities (boron, phosphorus) to change the properties of the layer. A *photoresist*, an ultra-violet light sensitive polymer material, is then layered onto the thin-film. This prepares the surface for a process termed *photolithography*, a technique analogous to photographic film development. The desired design is patterned onto a *photomask* using computer-aided software and transferred to the wafer using a lithography tool such as an *aligner* or *stepper*. Ultraviolet light is shone through the photomask and exposes the light sensitive photoresist. Next, the exposed photoresist is developed and the underlying patterned thin-film layer is revealed. The newly exposed regions of the thin-film layer are chemically or physically *etched* away, while the covered thin-film is protected by the overlying photoresist. Finally, the remaining photoresist is removed and the desired design is revealed. The process is iterated multiple times (thin-film deposition, photoresist, photolithography, then chemical etching) until creation of the final product. This basic methodology forms the basis for MEMS device fabrication.

Bulk Micromachining & Wafer Bonding

The term *bulk micromachining* refers to the process of directly sculpting or *etching* away the silicon substrate to create the desired microstructure and is depicted in Figure 2.[7] The technique has been used extensively to create micromechanical elements such as: beams, membranes, nozzles and plates with commercial success.[3,7] This process is made possible by anisotropic etching, which allows for the removal of silicon in selective planes due to the chemicals' preferential reaction in specific crystalline planes or directions.[8-10] In contrast, isotropic etching chemicals non-selectively remove silicon in all directions equally. The combination of etch masks and thin-film etch stops can protect specific regions from being removed and create even more complex features.[7] Bulk micromachining techniques have allowed for the creation of high aspect ratio features and are used for a variety of applications such as pressure sensors and ink-jet printer nozzles.

To craft three-dimensional structures and complex architectures, two or more microstructures can be joined via a process called *wafer bonding*.[11] The technique can be used to attach two silicon substrates together as well as silicon to glass. The bonding process either involves applying high voltage and pressure to the substrates (electrostatic bonding) or via high temperatures (fusion bonding). The process of wafer bonding can also be used to create packaging around a MEMS device or for encapsulation.

Surface Micromachining

Surface micromachining is another important technique that enables movable structures and layered design.[12,13] As opposed to bulk micromachining, surface micromachining utilizes the silicon wafer as a foundation on which to build up structural elements. The process is shown in Figure 3 and involves growing a patterned *sacrificial layer* on top of the silicon substrate. Next, a structural layer (i.e. polysilicon) is deposited over the sacrificial layer according to the designed pattern. The sacrificial layer is then etched away leaving behind the structural layer, which is now anchored to the underlying silicon substrate. The method can be repeated to build multiple structural layers for intricate designs with small feature sizes and movable parts.[14-16]

Soft Lithography, Micromolding, and Embossing

The term “soft” material is used to describe polymers and gels that are used as an alternative to silicon, especially in biomedical applications. Soft materials can be used with photolithography, molds, stamps, and embossing techniques to create *micropatterned* structures with polymers and gels.[17-19] The advantages of using these techniques include mechanical flexibility, durability, low cost, convenience, ability for rapid prototyping, and improved biocompatibility.[3,17,20-22] Soft lithography patterns the surface of a substrate using photolithography and etching techniques to create a negative of the final device. Then a polymer, most often polydimethylsiloxane (PDMS), is poured over the surface, cured, and peeled off to create a solid cast.

Micromolding is a procedure that creates a master mold for either the injection of polymers or as a template for embossing, shown in Figure 4. During micromolding, a silicon wafer is coated with a metallic layer and then patterned with photoresist. A second metallic layer is deposited around the photoresist and when the photoresist is removed it leaves behind a patterned cavity. The cavity can then be injected with a polymer to produce the micromolded device or can be used to *emboss* the design onto a polymer substrate. These basic techniques have popularized soft materials as a simple alternative to traditional silicon based fabrication and will likely continue to increase in popularity for biomedical device applications given the techniques' versatility and biocompatibility

Examples of Mems Technology

The era of MEMS has fostered an increasing number of products, devices, and applications utilizing MEMS technology. The area of MEMS academic research is even more robust with entire scientific journals dedicated to the development of MEMS technology (i.e. *Journal of Micromechanics & Microengineering, Journal of Microelectromechanical Systems, Lab-on-a-Chip, Microfluidics and Nanofluidics, and Biomedical Microdevices*). Given the overwhelming breadth and depth of the field, this review will only survey a representative selection of biomedical devices with a particular emphasis on devices at or near clinical use that have relevance to nephrology. This review is not intended to be a comprehensive examination of all MEMS devices and research currently being pursued.

Pressure Sensors

The use of MEMS to develop miniature pressure sensors capable of accurate in-vivo monitoring has been a long-standing objective with exciting recent progress in the field.[23,24] The general principle behind a MEMS pressure sensor is the use of a mechanical element (i.e. cantilever, diaphragm) that is deformed in response to an external pressure change. The deformation is then converted to a signal that is read as a pressure. The signal is usually either a change in piezoresistivity, an alteration in electrical resistivity, or a change in capacitance, an alteration in electrical storage, when a mechanical stress is applied.

Additionally, some devices use a fiber-optic sensor that measures changes in light reflected back from the deflected membrane. Currently, the majority of pressure sensors used in clinical practice are catheter based and require that the device be attached to an external monitor. However, recent devices now incorporate wireless technology for a fully implantable design. This next section will explore in-vivo pressure sensor technology.

Vascular Pressure Sensors—Current invasive pressure monitoring within the vascular system is largely limited to the intensive care unit and are catheter based. An arterial line is used for accurate and continuous monitoring of blood pressure especially in hemodynamically unstable patients.[25,26] The arterial system is connected to a column of fluid that transmits the pressure to an external transducer. The transducer consists of a flexible diaphragm that converts the pressure wave into an electrical signal. Similarly, central venous pressure measurements also use a catheter-based sensor with a calibrated water column to determine the pressure within the vena cava. The central pressure in turn allows for an estimation of the patient's volume status. Finally, a pulmonary artery catheter is used to measure filling pressures or “wedge pressure” within the left atrium. When the balloon catheter is introduced into a small pulmonary artery and inflated the pulsations are transduced into a waveform. The waveform is interpreted as a pressure tracing. These current catheter-based methods all require the patient to be hospitalized with close monitoring and tethered to an external monitor.

Two products are currently being tested for heart failure management and utilize a pressure sensor attached to a lead similar in concept to a pacemaker or Implantable Cardioverter Defibrillator (ICD) lead. The Chronicle by Medtronic (Minneapolis, MN) has a pacemaker size generator with a lead that measures right ventricular pressure as a surrogate for pulmonary artery diastolic pressure.[27,28] The device was evaluated in the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) a multicenter, prospective, randomized control trial of 274 patients with NYHA Class III and IV heart failure [29]. Unfortunately, the study had a non-significant 21% reduction in heart failure events and subsequently was not FDA approved. An ongoing trial with similar design, REDUCEhf (Reducing Events In Patients with Heart Failure), is testing the Chronicle's hemodynamic monitoring system that has been incorporated into an ICD device.[30] A similar lead based device is the HeartPOD made by St. Jude Medical Inc. (St. Paul, MN). The HeartPOD sensor lead is, however, placed in the left atrial septum and measures left atrial pressures.[31,32] The signal is transmitted via a coil antenna that is placed subcutaneously in the abdomen. In the HOMEOSTASIS trial (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure) the HeartPOD was implanted in 40 patients and followed for a median of 25 months. The results were encouraging with no device related complications and improvements in left arterial pressures, ejection fraction, NYHA Class and reduction in loop diuretics with guided therapy.[33] Additionally, there was a significant reduction in event free survival. The Left Atrial Presure Monitoring to Optimize Heart Failure (LAPTOP-HF)I is currently underway and will further evaluate these promising results.

The next generation of vascular pressure sensors being developed is fully implantable and wireless, which allows for improved patient mobility and remote monitoring. The EndoSure wireless pressure sensor by CardioMEMS (Atlanta, GA) is one such device that uses a capacitance-based sensor. The CardioMEMS device has first successfully used to measured intrasac pressures following endovascular repair of abdominal and thoracic aortic aneurysms.[34,35] The pressure sensor measures 30 × 5 × 1.5mm and has a nitinol wire basket surrounding the sensor to center it within the vessel. The implantable device consists of two flexible plates arranged as a capacitor along with a microcoil, which together comprise a resonant circuit with a characteristic frequency. As the pressure changes, the position of the

plates are altered and causes a shift in the resonant frequency, which is detected via an external antenna. The antenna interrogates the implanted sensor for its resonant frequency and translates it to a real-time pressure waveform. The detection of the resonant frequency by an external antenna means that no internal battery is required and pressures can be monitored long-term in real-time. In-vivo testing has shown that the sensor remains stable without recalibration and is able to function for several years with a resolution of 1mmHg.[35]

The APEX trial (Acute Pressure Measurement to Confirm Aneurysm Sac EXclusion) was a prospective, multicenter trial using the EndoSure sensor to detect intraoperative endoleaks and evaluate the safety and efficacy of the device.[35] The trial enrolled a total of 90 patients with 76 whom ultimately were eligible for implantation. The study compared the EndoSure pressure sensor to angiography for their ability to detect endoleaks after endovascular repair. The EndoSure device had an overall sensitivity and specificity of 0.94 and 0.8, respectively in identifying type I and III endoleaks. There were two unrelated deaths and no adverse events at 30 days. The study will continue to follow these patients for 5 years to determine if surveillance monitoring with the EndoSure pressure sensor will be beneficial in long-term patient outcomes.

The CardioMEMS sensor, shown in Figure 5, was also used clinically to monitor pulmonary artery pressures in patients with congestive heart failure (CHF).[36] The CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) was a randomized, multicenter controlled trial to evaluate whether use of the CardioMEMS pressure sensor could reduce the rate of heart failure related hospitalizations at 6 months.[37] The pressure sensor was implanted in 270 patients with New York Heart Association (NYHA) Class III. Daily pulmonary artery pressure readings from the CardioMEMS sensor was used in conjunction with standard of care to assisted clinicians in volume status management. The control group consisted of 280 patients who received standard of care only. At 6 months, the study reported a reduction in hospital admissions with a rate of 32% versus 44% between the CardioMEMS group and the control group, respectively. Additionally, there was an overall 37% reduction in heart failure related hospitalizations at a mean follow-up time of 15 months when the CardioMEMS sensor was used.[37] These exciting initial studies demonstrate how MEMS devices can successfully assist clinicians in improving patient care and monitoring.

The capacitance pressure sensor concept has also been developed by a number of different companies for in-vivo pressure monitoring. Campus Micro Technologies has developed a similar capacitance based pressure-sensing device with an array design using surface micromachining techniques.[38] The capacitive pressure sensor measures 0.8 × 2 × 0.5mm and the sensing membrane is constructed from a layer of polysilicon. The array uses 16 capacitive pressure sensors and has a resolution of 1mmHg. The device is being developed to monitor post aneurysm repair[24] and long-term monitoring of intracranial pressure[39] in conditions such as traumatic brain injury and hydrocephalus.

An important aspect of implantable sensors is wireless communication that can efficiently relay the pressure signal to a display that a clinician or patient can easily read. NASA's Glenn Research Center developed radio frequency technology to transmit pressure signals from an implantable pressure sensor to a hand held device. The sensor used a spiral chip antenna that allows for contact-less powering and telemetry.[40] The capacitance sensor consisted of a tri-layer diaphragm fabricated from silicon dioxide and silicon nitride.[41] The technology has been further adapted by Endotronix (Peoria, IL) and is being developed for use in cardiac monitoring, shown in Figure 6. The device is currently being tested for congestive heart failure applications.

Integrated Sensing Systems (ISSYS), Inc. (Ypsilanti MI) uses similar capacitance pressure sensing for their implantable device. The sensor employs a battery-less, wireless, magnetic telemetry with an external readout unit. The device has been tested in canines for continuous, real-time pressure waveforms with an accuracy of <1mmHg. However, the communication distance of the device is limited to <4cm and has yet to receive approval in humans.[42]

An alternative to capacitance based pressure sensors is utilizing piezoelectricity, which is the generation of electric charge in a material when a mechanical stress is applied. ImPressure (Remon Medical Technology, now Boston Scientific, Natick, MA) has used this property for the development of a piezoelectric based sensor seen in Figure 7. The device uses a piezoelectric membrane and acoustic waves to power and transmit a signal via a hand-held probe for pressure measurements.[4,24] The device is encased in titanium and measures 15 × 3 × 2.4mm. The implantable sensor has been used to monitor abdominal aortic aneurysms post-endovascular repair [43] and showed good concordance between intraoperative catheter pressure readings and device readings. The ImPressure sensor has also been used to monitor heart failure patients.[34,44-46] The PAPIRUS (Pulmonary Artery Pressure by Implantable device Responding to Ultrasonic Signal) II trial was a phase I study with 31 patients with NYHA class III-IV heart failure.[47] The device was implanted into the right pulmonary artery for monitoring of volume status. There were no device or implantation related adverse events noted at 6 months post-implantation. The study also had 23 patients obtain home pressure readings using a simple hand-held unit and achieved a median compliance of 86%. The next stage of evaluation for the device will reportedly entail a randomized trial that will evaluate the utility of home monitoring for the long-term management of heart failure patients.

Endovascular and cardiac pressure monitoring has advanced significantly with several promising devices in clinical trials showing that real-time pressure monitoring coupled with clinical management can improve patient care. MEMS technology has enabled smaller and more accurate devices to be implanted for long-term management. The use of these MEMS based pressure sensors will likely continue to increase as safety and efficacy are shown for these initial devices.

Intracranial Pressure Monitoring—Intracranial pressure measurements are an important parameter in patients following traumatic brain injuries[48] and conditions such as hydrocephalus and idiopathic intracranial hypertension. Currently, the two most common methods to measure intracranial pressure use either intraventricular catheters or intraparenchymal devices. Both of these devices, however, are wired and require in hospital monitoring. The intraventricular catheter is considered the “gold standard” for measurement and is surgically placed into the lateral ventricle. The device uses a fluid filled manometer and an external transducer to measure pressure. The advantage of the intraventricular catheter is that it allows for drainage of cerebral spinal fluid, infusion of medications in addition to the monitoring of intracranial pressure. However, they do incur a higher risk of both hemorrhage and infection, especially following prolonged use.[48]

Intraparenchymal pressure sensors have micro-transducers at the tip of the catheter and are placed directly into the brain parenchyma. They are easily placed and have a lower risk of hemorrhage and infection compared to intraventricular devices.[49] The Camino ICP sensors (Integra Life Sciences, Plainsboro, NJ) are the most widely used and measures pressure via a fiber optic transducer. The amount of light that is reflected back from a diaphragm is detected and translated into a pressure measurement. The Codman microsensor (Johnson and Johnson, New Brunswick, NJ) and Neurovent-P (Raumedic AG, Münchberg, Germany) uses a piezoresistive sensor at the tip to measure intracranial pressure changes. The main

disadvantage of intraparenchymal systems compared to intraventricular catheters is the inability to therapeutically drain CSF to treat elevated ICP. Additionally, intraparenchymal systems are more susceptible to drifting pressure readings leading to inaccuracies over time.[50]

Current intracranial pressure monitoring systems tether patients to the bedside, but newer devices aim to develop wireless intracranial pressure monitors. As described in the previous sections, both Campus Micro Technologies and Integrated Sensing Systems (ISSYS) have adapted their capacitance pressure sensors for use in ICP monitoring applications.[39,51] The Campus Micro Technology system reports to have ultra-low power consumption without the need for an internal battery.[39] The device is implanted either in the ventricle or brain parenchyma and intended for long-term monitoring. The ICP measurements are collected transcutaneously by an external device and aimed to provide non-invasive home monitoring.

The Neurovent P-tel (Raumedic AG, Münchberg, Germany) is an implantable piezoresistive device used to measure ICP long term and can potentially be used at home (Figure 8).[52-54] The sensor is placed in the brain parenchyma and the telemetric transducer is implanted between the galea and calveria. The telemetric reader is placed over intact skin and collects the pressure readings. Initial clinical testing was conducted on 10 patients who underwent implantation and monitoring for 2-24 weeks. Three out of the ten patients underwent surgical intervention for elevated ICP pressure reading with normalization following surgery. These preliminary studies showed that the system could be used for ICP monitoring with the benefit of home monitoring.

A novel ICP monitoring device couples optics with mechanical sensing with the use of Near-infrared Fluorescent-based Optomechanical (NiFO) pressure sensor.[55] The NiFO sensor is a long hollow tube that is implanted into the brain. The key feature is the set of quantum dot micro-pillars, tiny nanoscale particles that emit light at specific frequencies upon excitation that are patterned on a silicon nitride membrane. The membrane moves in response to changes in intracranial pressure and the micro-pillars move in conjunction. The incoming light excites the quantum dots and they emit light at 705nm and 800nm. Depending on their relative positions the quantum dots will emit at different intensities. The ratio of the intensities are detected and read out as a pressure. In-vitro tests showed that the senor could detect pressures within a clinically relevant range (0-40mmHg) and had a maximum error of 15%. The advantages of the quantum dot micro-pillar design is that it is fully implantable, smaller than comparative MEMS ICP monitoring devices and is MRI compatible. However, the device has only undergone in-vitro testing with plans for future in-vivo validation studies. ICP monitoring is well suited for MEMS based devices given the size constraints of the skull and the ability to track continuous pressure reading in patients.

Intraocular Pressure Sensors—The 24-hour, continuous intraocular pressure monitoring of glaucoma patients was extremely challenging until a novel approach was developed by Leonardi et al.,[56] and commercialized by Sensimed (Lausanne, Switzerland). The concept takes advantage of the correlation between intraocular pressure and corneal curvature.[57,58] The device, depicted in Figure 9, consists of a disposable soft silicone contact lenses with an embedded microfabricated platinum-titanium strain gauge.[59] The strain gauges measure the circumferential changes of the cornea and an integrated microprocessor sends a signal[56,59-61] via a gold film loop antenna. The thickness of the strain gauges is 7μm and the overall thickness of the device is less then 600μm. The power and data are transmitted wirelessly via a patch periorbital external antenna. A study of 40 patients with glaucoma was conducted to assess safety, tolerability, and reproducibility.[60] There were complaints of mild blurred vision (82%), conjunctival hyperemia (80%) and superficial punctate keratitis (15%), but was well tolerated overall. Additionally, two 24-hour pressure

measurements collected one week apart showed fair to s good reproducibility.[60] The development of a pressure sensing contact lens depicts an example of how microsensors can be efficiently incorporated into already well-established devices to expand their functionality.

Lab on a Chip

Point of care testing (POCT) allows for the capability of diagnosing and monitoring patients in a single condensed device that previously would have required a large clinical laboratory to accomplish. Central to these devices is microfluidics, the ability to handle small quantities of liquid. One of the most commercially successful POCT devices is the glucose test strip, which uses techniques in advanced circuit board printing for manufacturing. Briefly, oxidoreductases (i.e. glucose oxidize, glucose dehydrogenate, glucose dye oxidoreductase) located on the test strip oxidize glucose to gluconolactone.[62] The electrons from glucose are then transferred to a mediator molecule that converts the mediator to its reduced form. The mediator then transfers its electrons to an indicator molecule for photochemical or electrochemical detection. The use of glucose test strips has allowed patients to closely monitor their blood sugar in a convenient and self-reliant way. The glucose test strip is an early example of simple fluidic handling in POCT devices and has laid the foundation for more complex POCT devices.

Several companies have developed hand-held POCT devices for small molecule detection, and they were recently reviewed by Chin et al.[63] Alere (Waltham, MA) is a diagnostic device company with a broad range of POCT devices.[64] They have also acquired several companies including BioSite and Epocal that had FDA approved POCT devices on the market. The Triage Meter (BioSite), seen In Figure 10A, uses microfluidics test strips with microtextured surfaces driven by capillary forces. The disposable strips, however, cannot handle finger-stick blood samples and require EDTA anticoagulated whole blood or plasma. The device is able to measure cardiac biomarkers troponin I, B-type natriuretic peptide and creatine kinase MB. They have also developed a strip for the measurement neutrophil gelatinase-associated lipocalin in acute kidney injury diagnosis. The strips use an immunoassay that conjugates a fluorescently tagged antibody to the analyte.[4] The complex is captured within the diagnostic zone, fluorescence is detected and a measurement is made. Another Alere product, epoc Blood Analysis System (Epocal), is able to test nine analytes on a single SmartCard (sodium, potassium, calcium, glucose, hematocrit, lactate, pH, pCO_2, and pO_2). [65] The card contains microporous elements that have been deposited with patterned electrodes for electrochemical detection. The epoc device (Figure 10B) also has the capability to communicate wirelessly and can interface with laboratory information systems.

The iSTAT (Abbott Laboratories, Abbott Park, IL) is a popular hand-held POCT device with single-use cartridges for the measurement of various clinical tests (Figure 11).[66] The iSTAT can detect a broad range of small molecules from only 2-3 drops of blood. The clinical tests include a full chemistry panel, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and ionized calcium. Additionally, depending on the cartridge the iSTAT can also measure lactate, blood gases, hemoglobin, coagulation, and cardiac biomarkers (troponin I, creatinine kinase MB, and B-type natriuretic peptide). The disposable cartridge contains an array of thin-film electrodes that have been microfabricated onto a silicon chip.[67,68] Depending on the small molecule being detected the electrodes are either coated with specific enzymes or ionophores. For example, urea is detect by hydrolyzing urea to ammonium by urease and then measuring the ammonium ion by an ion-selective electrode. On the other hand, sodium, potassium, and chloride are measured by direct ion-selective potentiometry.

Soft lithography techniques have also been used as a method to form the microcapillary system vital to many POCT devices. Gervais et al. has developed a lateral flow immunoassay microfluidics device that uses polydimethylsiloxane (PDMS) patterned with capture antibodies to detect C-reactive protein.[69] The patterned PDMS is incorporated onto a silicon microfluidics chip that is driven by capillary forces for a one-step assay design. The final signal is detected by measuring the fluorescence in the PDMS reaction chamber within the microchip. The device required only 5μl of human serum to detect 1ng/ml of CRP in 14 minutes.

Small scale handling of nanoliter quantities of fluid is a key component of miniaturized MEMS devices. Microfluidics large scale integration (mLSI) is a technology that allows for thousands of integrated mechanical valves to be fabricated for automated, multiplex assays that can be run in parallel. Quake and colleagues have applied mLSI to numerous applications with great success including single cell analysis [70], genetic analysis [71,72], amino acid analysis [73], and high throughput screening.[74,75] The core of this technology is soft lithography techniques with PDMS to create hundreds to thousands of novel and innovative mechanical valves integrated on a chip. The monolithic mechanical valve is produced by replica molding PDMS and bonding a control channel and flow channel together to form a membrane (Figure 12). Depending on the orientation of the control channel as pressure within the channel increases the membrane will either push up or push down, occluding the liquid within the flow channel. Thus, by systematically actuating each valve at specific intervals complex fluid handling can be achieved. The process is then scaled to control hundreds to thousands of valves, which allows for multiplexing, parallelization, and serial processing for numerous multifaceted biologic applications.[76,77]

Microarrays were initially developed for genomics studies by spatially encoding hundreds to thousands oligonucleotides on a single chip, which allowed for multiplex analysis of DNA samples based on their complementary sequence. The microarray concept has further been adopted for the study and screening of proteins including tumor markers, cytokines, CRP and hepatitis C.[78] Fan et al. has developed a microfluidics device using soft lithography techniques with PDMS for multiplex analysis of proteins including PSA and 11 cytokines in cancer patients.[79] The microchip is able to separate plasma from whole blood using branched microchannels that preferentially allow plasma to flow into the microchannels, while blood cells remain in the low resistance primary channel. The microchannels are each individually coded with an array of single-stranded DNA that provides a barcode for the identification of the proteins. The device has 13-20 parallel channels each with different DNA oligomers. The setup was able to detect a variety of proteins from a single finger prick amount of whole blood within 10 minutes.[79] The ability for multiplex protein identification has been combined with microfluidics systems for the development of miniaturized POCT applications.[80]

The lab on a chip concept integrates the functions of a clinical laboratory and shrinks it down to a single chip. This allows for small quantities of sample and reagents to be consumed with more efficient analysis times. The compactness, ability to multiplex, and low fabrication costs make lab on a chip devices ideal for rapid medical diagnosis. These devices have the potential to allow for true bedside medicine with the power of advanced biologic assays at the clinician's fingertip.

Drug Delivery Systems

Improved drug delivery systems are an ideal niche for MEMS devices where highly precise miniaturized devices need to provide an accurate and convenient avenue of delivery. Deep Reactive Ion Etching (DRIE) is a method of anisotropic etching that allows for deep features with high aspect ratios. This method has been used to develop microneedles for intradermal

drug delivery. By using DRIE techniques Micronjet Needles (NanoPass Technologies, Nes Ziona, Israel) have developed pyramid shaped microneedles that are sharp and robust enough to penetrate skin effectively. (Figure 13). The needles themselves are between 450-600μm and enable the delivery of any molecule including vaccines and proteins. The microneedles have been used for various drug delivery applications including vaccine administration and have shown equivalent immunization using 1/5th of the dose and on occasion improving the vaccine's immunogenicity compared to standard delivery of full dose vaccine..[81,82] Another approach uses DRIE and anisotropic etching to create hollow microneedles with side-holes to prevent blockage and allow for a sharper tip for skin insertion. [83,84] The Nanoject (Figure 14) side-hole needles by Debiotech are being used in conjunction with their MEMS insulin delivery system. Veleritas, Inc (Bridgewater, NJ) are also using an array of microneedles for transdermal delivery of insulin. The fabrication uses a polymer mold and seed layer that is then electroplated with nickel. The mold is selectively etched away to reveal the microneedle array.[85,86] These tiny needles offer a unique method for MEMS technology to allow for controlled delivery of medications with minimal tissue damage and limited pain associated with injections.

Another important aspect of drug delivery devices is the transfer of medications from a drug reservoir to the patient by accurate and reliable micropumps. Debiotech S.A. (Lausanne, Switzerland) has developed a nanopump (Figure 15) for insulin delivery in patients with diabetes.[4,87] The design is a volumetric pump with a membrane that compresses the drug reservoir via a piezoelectric actuator.[88,89] The pump consists of a micromachined pump structure on a silicon wafer that is bonded between two glass layers. The piezoelectric actuator is a separate unit, which allows the pumping membrane and reservoir to be disposable. The micropump is able to achieve flow rates up to 2ml/min with a stroke volume of 160nl.[89] The Debiotech JewelPUMP is the company's initial insulin delivery device that uses a patch-pump design. The device weighs about 25 grams that contains 500 units of insulin for up to 7 days of use.[90] The device is able to delivery 0.02 units of insulin within 5% accuracy and has been tested in 35 diabetic patients. The JewelPUMP is still in clinical trials and is not yet commercially available.

Ocular delivery of medications is amenable to MEMS technology given the need for a miniature delivery system within the eye. Replenish, Inc. (Pasadena, CA) has developed an implantable ocular drug pump, the MicroPump (Figure 16), that can be programmed to dispenses nanoliter quantities of drug and easily refillable after prolonged use. The MicroPump uses MEMS fabrication for both the pump and cannula chip design. The device has two interdigitated platinum electrodes immersed in an electrolyte solution that produces oxygen and hydrogen gas after a current or voltage is applied.[91] The gas formation increases the pressure in a sealed reservoir that pushes the drug out of the cannula and into the eye. The feasibility of the device was tested ex-vivo in enucleated porcine eyes.

The ability for scheduled and controlled delivery of drugs is an important pharmacologic aspect of medication dosing. The MicroCHIPS, Inc. (Waltham, MA) uses a silicon substrate with an array of drug filled micro-reservoirs that are sealed with a titanium and platinum membrane (Figure 17). When a timed electrical current is applied to the sealed membrane, it disintegrates and releases the drug.[92-95] The device was first implanted in 8 osteoporotic women for the delivery of human parathyroid hormone fragment for 4 months with programmed release daily for 20 days.[96] The drug release of the device had similar pharmacokinetics as multiple injections of the medication, but displayed less variation and was well tolerated. The study was also able to show that daily release via the device was able to promote bone formation.

A diffusion based approach to drug delivery incorporates a silicon nanopore membrane with pores that are near the hydrodynamic diameter of the drug.[97] This allows for zero order diffusion of solutes based on the tunable width of the nanopores.[98] The process allows for pores ranging between 7-50nm. Surface micromachining forms the nanochannels within a thin film layer and are exposed by etching away the bulk silicon from the bottom. Theses membranes from (currently defunct) iMedd, Inc. (Columbus, OH) were fitted into a cylindrical titanium casing that also serves as the drug reservoir (Figure 18). The device was loaded with radiolabeled bovine serum albumin and implanted subcutaneously into rats and showed prolonged levels for 7 weeks in the blood.[98] A similar diffusion based device uses nanochannels formed between two silicon substrates that are bonded together and releases interferon alpha-2b locally for the treatment of melanoma.[99] The study was able to show zero order kinetics and the drug remained functionally active following release onto host immune cells and melanoma cell lines in-vitro. The controlled release of drugs by implantable MEMS devices provides a steady, reliable, and convenient new method of drug delivery.

Mems in Nephrology

The rising number of MEMS based medical devices being developed illustrates the utility of high precision and integrated micro-systems in medical applications. The field of nephrology offers many potential applications for MEMS technology that can be closely integrated in daily practice. This review will examine the burgeoning use of MEMS in nephrology and will also explore new potential points of interface. To illustrate how a kidney disease patient's care might be integrated with MEMS technology now and in the future, this review will follow a patient though the course of their disease.

> A 54-year-old male with history of diabetes and hypertension who lives alone was brought into the emergency room by his daughter after being found confused at home. The patient is unable to provide any further history. His daughter reports that he had been complaining of worsening knee pain over the last several months. He takes lisinopril for his blood pressure and on examine he is confused. His labs are significant for a creatinine of 2.4mg/dL (baseline 1.2 mg/dL) and a bland urine sediment.

POCT for AKI

Often times the etiology of acute kidney injury can be difficult to ascertain, especially in the absence of clear history or obvious inciting event. The search for a kidney “troponin” has been an elusive holy grail for nephrologists for many years. However, more and more it appears that a panel of various kidney biomarkers will have greater clinical benefit and may help differentiate between various causes of kidney injury rather than relying on a single biomarker.[100] The multiplex testing of AKI biomarkers is time sensitive and therefore an ideal candidate for point of care testing devices. Currently, there are commercially available POTC testing devices for creatinine and urea[101,102], but they still rely on current biomarkers that have limited value due to their delayed rise following injury and rapid turn around time of most clinical laboratories. The use of immunoassays or microarrays for future blood and urinary biomarkers can be integrated with microfluidics devices for rapid point of care testing in the emergency room or clinic. The miniaturized lab-on-a-chip device offers the benefit of small sample quantities, rapid results, and ease of use. The biomarker panel could help the on-call nephrologists diagnosis the etiology of acute kidney injury when standard evaluation still leaves in doubt whether the injury is pre-renal, acute tubular necrosis, medication toxicity, glomerular process or some other insult. Currently, Alere markets the Afinion ACR to measure urinary albumin creatinine ratios and the Triage NGAL test for the measurement of neutrophil gelatinase-associated lipocalin in acute kidney injury. As

additional microdevices are developed, they could easily be integrated into the overall work flow and could become as standard a part of AKI consult evaluation as urinalysis and urine microscopy is today.

> The patient is found to have septic arthritis in his knee and treated with antibiotics. As the patient's confusion improves he states that he has been taking NSAIDs for his knee pain. The patient's AKI was likely secondary to medications (NSAID & lisinopril), dehydration, and infection. He eventually recovers from his episode of AKI. However, over the next several years the patient's renal function slowly declines due to poorly controlled diabetes and HTN. After a discussion with the patient, he opts for in-center hemodialysis and is referred to vascular surgery for fistula placement in preparation for hemodialysis.

Vascular Access

Vascular access plays a crucial role in the lifetime of any ESRD patient and maintaining a well functioning fistula is a task requiring extreme vigilance. There have been several strategies for surveillance of stenosis and prevention of thrombosis in vascular access, including intra-access blood flow monitoring, static dialysis venous pressure, and duplex ultrasound.[103] The shortcomings of these methods are the reliance on imagining techniques and the inability for continuous monitoring. The development of a “smart” vascular access that is able to monitor continuous, real-time flow measurements and transmit the data to a clinician provides a means for proactive monitoring and intervention. Cheong et al. have designed a MEMS based pressure sensor for monitoring blood flow in prosthetic vascular grafts.[104] The implantable device uses a silicon nanowire sensor with tunable piezoresistivity to monitor blood flow illustrated in Figure 19. The MEMS fabricated device uses a stack of silicon nitride and silicon oxide layers to form a membrane and a nanowire serves as the sensing element. The sensor can be embedded within the vascular graft for monitoring. The resolution of the monitor was 0.176mmHg with a total pressure sensor area of 0.064mm^2. The pressure readings are then transmitted wirelessly to an external hand-held device. The prototype device has only been evaluated with bench-top experiments, and is yet to be studied in-vivo. Additionally, previously described implantable vascular pressure sensors being developed for cardiovascular pressure monitoring is a logical extension of their applications to vascular graft monitoring. While the size, pressure range and correlation to stenosis will need to be further refined, the overall principle remains the same.

> 6 months later the patient has symptoms of uremia and is initiated on thrice weekly in-center hemodialysis. His dry weight is targeted at 62kg, but he is frequently unable to achieve his ultrafiltration target secondary to cramping. Additionally, his Kt/V is 1.4 although his treatments are often ended prematurely due to cramping.

Monitoring Hemodialysis

The current standard of monthly labs to assess dialysis adequacy does not allow for the evaluation of each dialysis treatment or the ability to make prescription changes real time. Sant et al. has described the fabrication of an electrochemical microsensor for on-line monitoring of urea during hemodialysis.[105] The sensor detects the pH change following enzymatic hydrolysis of urea by urease. The sensor is fabricated on a silicon wafer and the enzymatic reaction is integrated onto the chip using ink jet printing techniques. The chips measured 2.1 × 1.6mm and the entire device was tested for continuous monitoring of urea using artificial dialysis conditions in-vitro. The monitoring of urea concentrations correlated well with standard laboratory testing and showed overall good sensitivity during testing. The authors envision a disposable, mass fabricated urea microsensor that will allow for simple and accurate on-line urea monitoring.

Volume status monitoring of hemodialysis patients is another crucial element of hemodialysis care. The current use of dry weight for ultrafiltration goals are inevitability prone to fluctuations, error, and does not reliably measure intra-vascular fluid volume. Clinical trials using CardioMEMS implantable pressure sensor, previously described, has shown promising clinical benefit in CHF patients. The device could similarly be implanted into hemodialysis patients and ultrafiltration goals could be titrated based on pulmonary artery pressures in addition to standard parameters. Additionally, Endotronix, Remon, and Integrated Sensing Systems (ISSYS) have similar implantable MEMS based pressure sensors for CHF monitoring that could also be utilized in ESRD patients as well.

> The patient reports being depressed due to his lack of independence and diminished quality of life. He complains that because of his three times a week dialysis schedule he is unable to meet his friends and no longer as active as he used to be.

Portable Dialysis

There have been several recent advancements in membrane technology that aim to improve the independence of ESRD patients on dialysis. One such solution improves portable renal replacement system by taking advantage of regenerated dialysate with sorbent-based cartridges that allow patients the freedom of mobility during treatment. The Wearable Artificial Kidney (WAK) by Gura et al. and XCorporeal (Los Angeles, CA) in pilot studies with ESRD patients has already demonstrated the feasibility of solute clearance, including middle molecules, and effective ultrafiltration using a wearable hemodialysis device (Figure 20).[106-110] AWAK Technologies (Singapore) using similar sorbent cartridge technologies is developing a wearable portable peritoneal dialysis device that regenerates the spent dialysate thus limiting the number of large volume exchanges (Figure 21).[111,112]

Another unique design for wearable dialysis is being developed by Leonard et al. and uses “membraneless” dialysis by incorporating a microfluidics system that uses fluid-to-fluid contact for clearance and ultrafiltration.[113,114] The key component of the device is a fluid ‘sheath’ layer that comes into concurrent contact with blood. Solutes in the blood diffuse into the sheath layer, which then resembles blood plasma. The sheath layer is diafiltrated using a conventional dialysis membrane for clearance and ultrafiltration. The resulting hyperosmotic protein containing sheath fluid is recirculated back into the blood. In this way, blood is never in contact with the artificial dialysis membrane and allows for improved biocompatibility. The device is being optimized to limit cells within the sheathing layer. The system is also being developed for an ultrafiltration only mode that would allow ESRD patients to maintain their dry weight between dialysis treatments.

Home Dialysis Plus (Sunnyvale, CA) is developing a microscale dialyzer and water treatment system for home dialysis applications using technology licensed from Oregon State University.[115] The technology uses micro-energy and chemical systems (MECS) to create microfluidics devices with highly parallel arrays of microchannels.[116] The microchannels have a high surface area to volume ratio that shortens the diffusion distances and provides high rates of heat and mass transfer. This in turn reduces the fluid volume needed during hemodialysis and allows for a more compact and efficient system. Home Dialysis Plus has also licensed inkjet technology from Hewlett Packard (Palo Alto, CA) that will be used to accurately proportion and mix concentrated dialysate and water all in real time.[117] The small, portable system does not need advance preparation and is designed to provide dialysis ready water immediately from any tap water source. The Home Dialysis Plus system is targeted for home dialysis use or as a portable system anywhere with access to tap water.

The Draper Laboratory (Cambridge, MA) has patented a MEMS device for the filtration of small molecules using an array of microchannels.[118] The device is constructed using micromolding techniques and is comprised of two polymer substrates that sandwich a semi-permeable membrane. The first polymer substrate functions as the blood layer with an inlet that serially branches into an array of microchannels (5-100μm in height) and forms a microvascular network. The network then converges back to form the outlet. The second polymer substrate is a fluidic chamber (100-900μm in width and height) that contains dialysate and flows in a countercurrent direction to the blood layer. A semi-permeable membrane separates the two polymer substrates allowing for diffusion and convection of small molecules. The envisioned device will have multiple bilayer units stacked upon each other for increased efficacy.

These portable systems have the potential to improve the convenience, mobility, and quality of life for ESRD patients. One important aspect of portable renal replacement devices is the need for miniaturization, while not sacrificing clinical efficacy. MEMS technology promises to solve these often competing design constraints. The use of MEMS micropumps to circulate blood and dialysate would further streamline these portable devices. However, a limitation to using MEMS micropumps in these devices is the high resistance to flow from the use of standard dialyzer membranes and sorbent cartridges. Therefore, new membrane technologies with high permeability will need to be explored and is examined in the following section.

> The patient has been on hemodialysis for 5 years and has been listed for renal transplant during this time. He receives news that a cadaveric kidney has become available and undergoes an uncomplicated deceased-donor transplant.

MEMS and Transplant

The realm of renal transplant offers numerous opportunities where MEMS technology can be utilized for improved pre and post transplant management. Cadaveric renal transplant can occur at unpredictable times with incomplete workups and delays can significantly affect the viability of the organ. The use of lab-on-a-chip technologies offers a high throughout, rapid method of expedited screening for potential mismatches or complications with compatibility between the donor and recipient. Additionally, a similar approach could be utilized post-transplant for screening of donor specific antibodies in allograft rejection or point of care monitoring of immunosuppressant drug levels. The use of MEMS technology for rapid, point-of-care analysis could allow prompt results without the necessity of a large specialized clinical laboratory.

Drug delivery is another avenue where MEMS can be utilized in both transplant and non-transplant patients. Patients with chronic kidney disease and ESRD on renal replacement therapy require numerous medications that can be both cumbersome and burdensome to patients. The use of microneedles and MEMS based drug delivery devices could allow for simple and reliable method of medication administration. While transplant patients have the added concern for infection, MEMS drug delivery devices would provide a logical application for this patient population given their complex immunosuppression regimens that require vigilant monitoring.

> Ten years post-transplant the patient's allograft function slowly declines. An allograft biopsy shows chronic rejection and his graft eventually fails. The patient is reinitiated on in-center hemodialysis. Over the next several years he develops worsening phosphorus and PTH values despite phosphate binders, active vitamin D and dietary compliance. Additionally, his hypertension regimen has needed to be titrated up due to pre-treatment hypertension, but frequently becomes hypotensive during treatment. He continues to deteriorate clinically.

Bioartificial Kidney

The mounting evidence that slower and longer hemodialysis confers improved outcomes requires a paradigm shift in how hemodialysis treatment is delivered in the United States. While this shift would require enormous infrastructural and economic changes to modify existing hemodialysis delivery, MEMS technology is already being utilized to change this paradigm. Our group has pioneered the use of silicon nanopore membranes as a novel hemofilter for use in a bioartificial kidney (Figure 22).[119-124] The silicon nanopore membranes are fabricated using innovative MEMS techniques (Figure 23) that create uniform slit pores with much higher hydraulic permeability (coefficient of ultrafiltration, K_{UF}) than circular pores.[125] The fabrication process also permits pore sizes as small as 5nm with less than 1% variability.[121] Current hemodialysis membranes exhibit a wide distribution of pore sizes and shapes that leads to variable solute retention, but MEMS fabrication allows each pore to have the exact same size and geometry. These attributes allow the silicon nanopore membranes to selectively filter solutes based on molecular weight while excluding larger macromolecules such as albumin. The selectivity of silicon nanopore membranes was demonstrated using various globular proteins [121] as well as $ß_2$-microgloulin.[126] Additionally, the membranes showed stable hemofiltration for over 90 hours in-vitro with anti-coagulated blood showing the viability for long-term blood exposure. The bioartificial kidney will recapitulate the function of the native kidney and consists of a two-part system with the first segment acting as the glomerulus and is comprised of the silicon nanopore membranes. The membrane will provide a filtration rate of 30ml/min owing to the very high hydraulic permeability that furthermore negates the need for an internal pump. The miniaturization permitted by MEMS technology allows for a total surface area of $0.1m^2$, roughly the size of a deck of cards. The second segment of the device will be a cellular bioreactor seeded with renal epithelial cells that will function to reabsorb water and electrolytes as well as providing the metabolic and endocrine activity of native kidneys. The bioartificial kidney is made possible by MEMS technology, which allows for a new membrane with performance specifications hitherto impossible with polymers.

Conclusions

The advancements made in the silicon microelectronics industry have readily been adopted by the biological research and medical device community. These novel techniques have further been adapted to form an entirely new field of research, MEMS, that continues to innovate and push the boundaries of size and scale. There have been exciting developments that incorporate MEMS technology with clinical medicine especially in regards to pressure sensor technology and has allowed for improved care of vascular and CHF patients. The implantation of these devices has not usurped clinical judgment, but instead enhances the clinician's understanding of the patient's physiology that leads to better care. The development of point-of-care testing and microarray technology are aimed to replace inefficient and labor intensive laboratory testing with a rapid, multiplex analysis that can be performed easily by the clinician or patient at the bedside. Finally, novel drug delivery mechanisms utilizing micropumps and microneedles hold the promise of reliable, simple, and convenient methods of medication administration for a whole host of patients. Therefore, MEMS based medical devices will only grow further as continued research and development will improve existing systems and introduce innovative new devices.

Nephrology is a discipline based on the principles of fluid mechanics and mass transport. The development of renal replacement therapy is evidence of the technological advancements that are possible with close collaboration between engineering and clinical medicine. The challenge is to continue to innovate and improve the management of kidney disease patients using technology to solve known problems. The incorporation of blood flow

sensors into vascular grafts is an excellent example of how MEMS technology can help further understand blood flow patterns in vascular access and monitoring for graft deterioration. MEMS technology is also being utilized to improve dialysis membrane technology by creating a compact, high permeability membrane that is suitable for use in an artificial kidney. The ability to recapitulate the function of the native kidney via MEMS technology will provide an alternative to transplantation given the scarcity of organ procurement. While there are a few examples of MEMS devices in nephrology, the landscape is still rather vacant compared to other disciplines. This provides exciting opportunities for new areas of advancement and application. Nephrology is an ideal field for MEMS technology to be further cultivated as nephrologists already comfortably navigate complex mechanical, fluidic systems on a daily basis. Therefore, MEMS will likely continue to permeate into nephrology with new devices and applications, and it will be essential that nephrologists remain informed and updated on this innovative technology.

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Clinical Summary

- MEMS fabrication techniques permit the production of integrated systems with extremely small feature sizes, high precision, and cost-effective manufacturing.
- MEMS devices are currently being explored in numerous clinical disciplines for implantable pressure monitoring, point of care testing, and drug delivery.
- MEMS technology can improve the care of kidney disease patients by advancing physiologic monitoring and innovating renal replacement therapies.

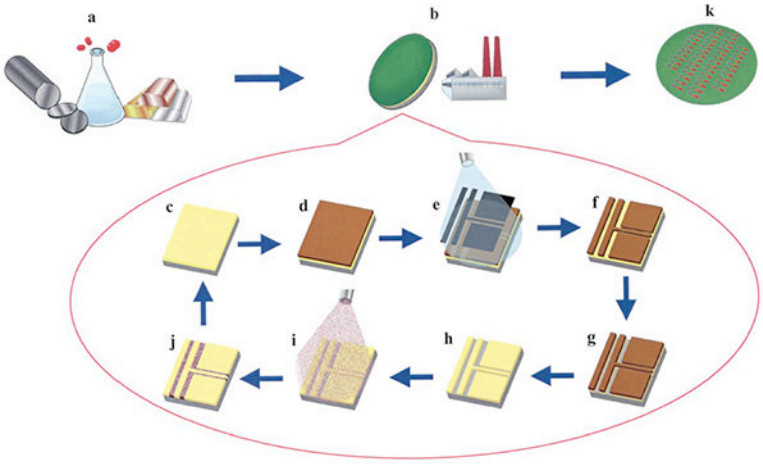

Figure 1.

Graphic illustration of the major processing steps in MEMS fabrication. Raw materials-Si wafers, ultrapure chemical reagents, and highly purified metals (a) – are gathered and processed inside a cleanroom (b). The fabrication is based on repeated cycles of the process sequences, shown in (c) through (j). Typical process includes the growth of SiO_2 on the Si wafer (c); deposition of thin films of photosensitive polymer (photoresist) (d), which is subsequently patterned by exposing it to ultraviolet light through a photomask (e); development of the exposed photoresist, which are those areas of the photoresist that are exposed to light, become soluble, and are washed away in the developing solution (f), reproducing the pattern from the photomask in the photoresist and selectively exposing the underlying SiO_2; etching of the exposed SiO_2 by wet chemicals or plasma to expose the surface of the underlying Si wafer (g) and subsequent removal of the photoresist (h); doping of the exposed wafer surface to change the electrical characteristics (i); the SiO_2 removed to leave behind a doped region of the wafer. The cycle is repeated with additional photomasks until the MEMS fabrication process is complete (k). *Reprinted with permission.*[2]

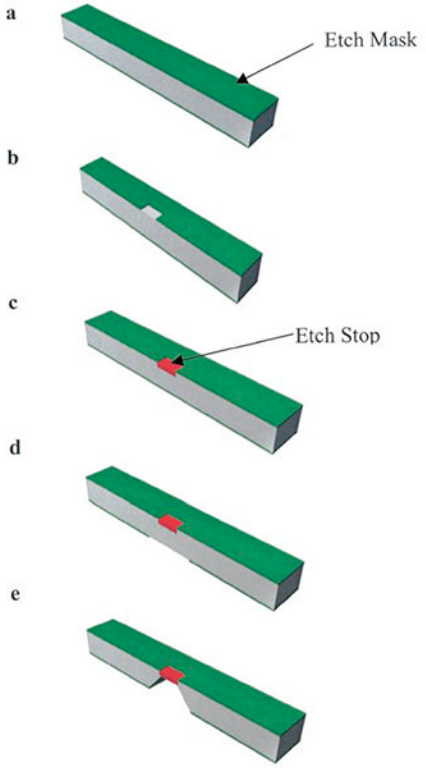

Figure 2.
Schematic depiction of bulk micromachining of a diaphragm. Etch masks are those areas with a deposited material and patterned to protect the underlying Si during etching. Etch stops are those regions in which the Si has been doped so that it does not etch. (a) silicon nitride is deposited onto the Si wafer. (b) the nitride film on the tope side of the wafer is patterned by photolithography and etching to define the etch stop region in the Si wafer. (c) the exposed Si is doped with boron, which chemically modifies the Si to prevent its itching. (d) the nitride on the bottom side of the wafer is patterned to expose a region of Si to be etched. (e) the Si wafer is anisotropically etched in a potassium hydroxide solution. The potassium hydroxide etches through the Si and stops at the etch stop. *Reprinted with permission.*[2]

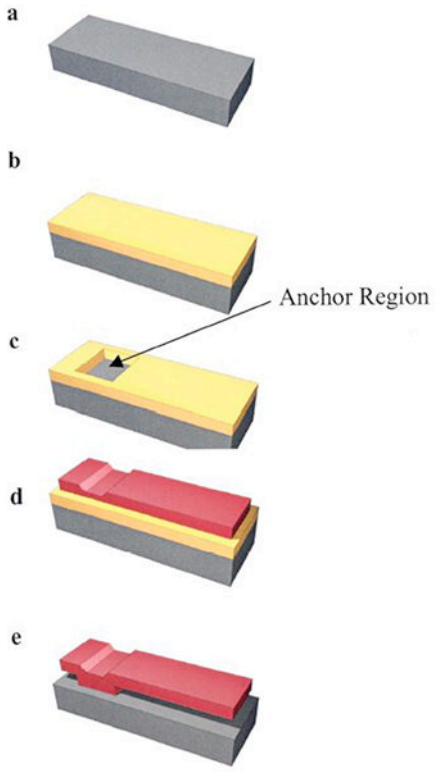

Figure 3.
Schematic depiction of surface micromachining of a cantilever beam. (a) blank section of Si wafer. (b) SiO_2 is grown on the wafer. (c) a well is patterned in the SiO_2 by photolithography and etching to expose the underlying Si. (d) polycrystalline silicon is deposited and patterned on the wafer. (e) the cantilever is released by etching all the SiO_2 with acid but does not etch the Si wafer or polycrystalline silicon. *Reprinted with permission.*[2]

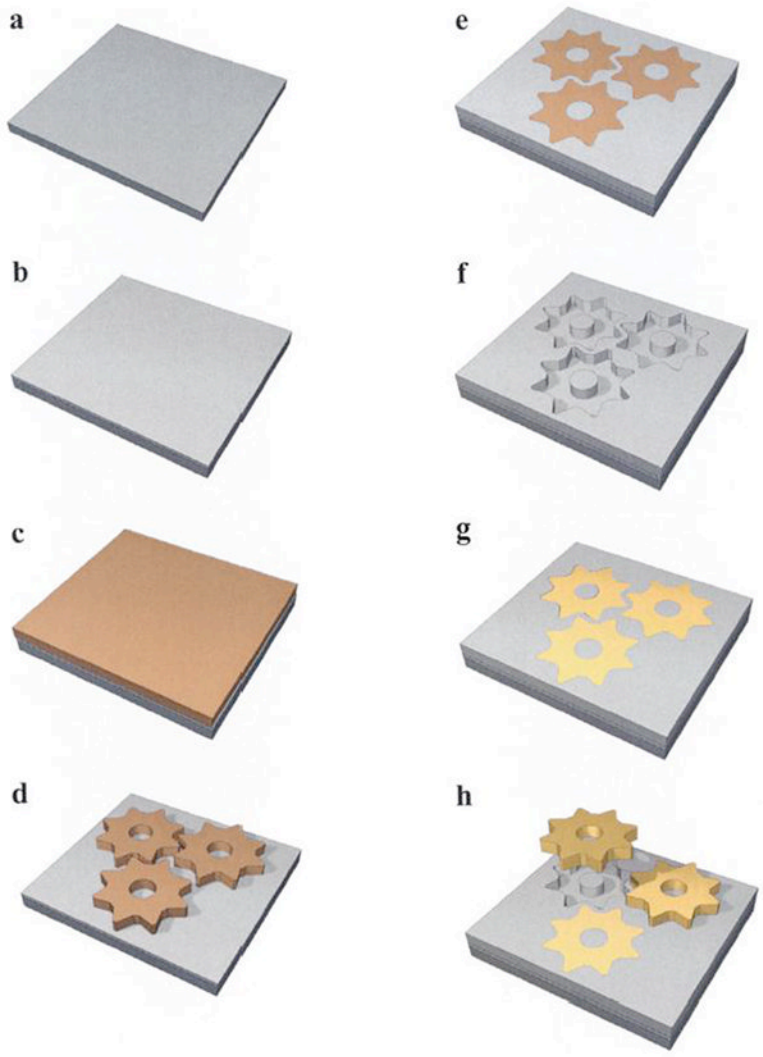

Figure 4.
Schematic depiction of the Micromolding of gears. (a) blank Si wafer. (b) deposition of a metallic seed layer for subsequent plating step. (c) coating of the wafer with photoresist. (d) patterning of photoresist. (e) plating of metal in all areas not covered by photoresist. (f) photoresist is dissolved, leaving a metallic insertion mold. (g) plastic injection molding. (h) plastic gears are ejected. *Reprinted with permission.*[2]

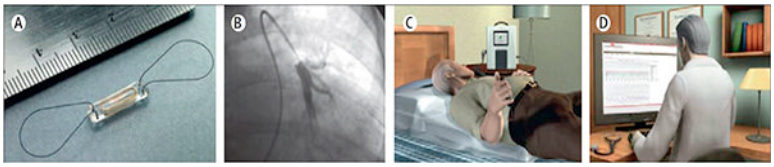

Figure 5.
(A) CardioMEMS sensor. (B) Transcatheter is implanted into a distal branch of the descending pulmonary artery. (C) Patient is instructed to take daily pressure readings from home using the home electronics. (D) Information transmitted from the monitoring system to the database is immediately available to the investigator for review. *Reprinted with permission.*[37]

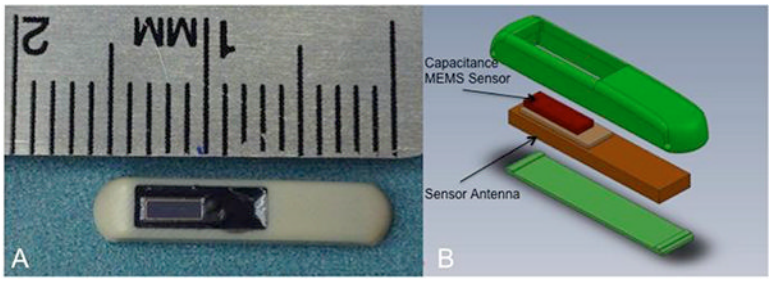

Figure 6.
Endotronix MEMS sensor (A). Schematic drawing of the Endotronix sensor within a biocompatible housing shown in green (B). *Courtesy of Endotronix, Inc.*

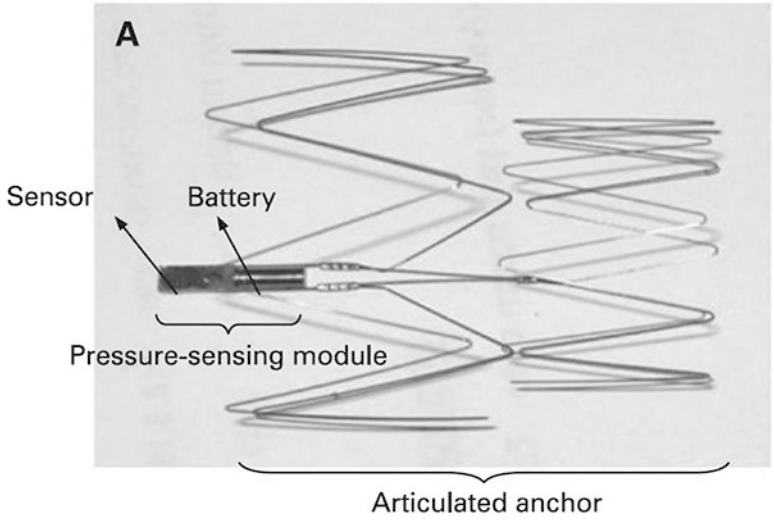

Figure 7.
Remon ImPressure pressure monitoring system showing the pulmonary artery implant. Reprinted with permission.[47] *Photos courtesy of Boston Scientific Corporation or its affiliates. Opinions expressed herein are those of the authors and not of Boston Scientific*

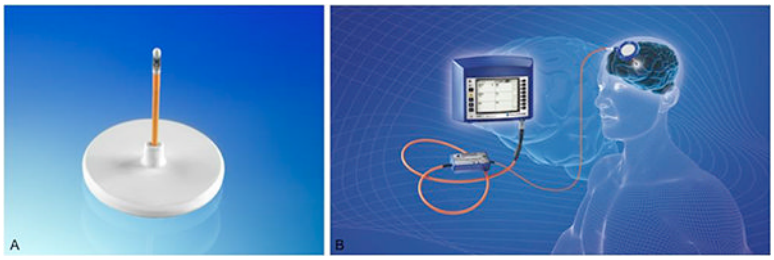

Figure 8.
Neurovent P-tel: (A) implantable piezoresistive ICP monitoring sensor. (B) A telemetric reader is placed over intact skin and collects intracranial pressure readings. *Copyright Raumedic, Inc.*

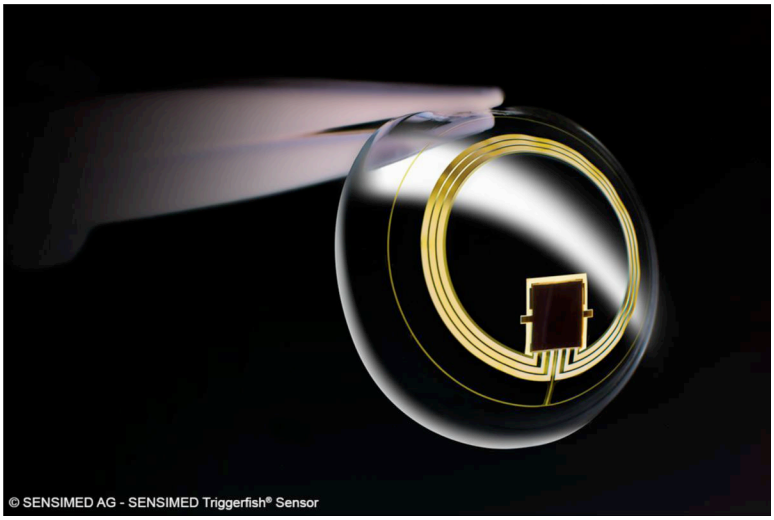

Figure 9.
Sensimed Triggerfish sensor for continuous non-invasive monitoring of intraocular pressure. *Courtesy of Sensimed AG.*

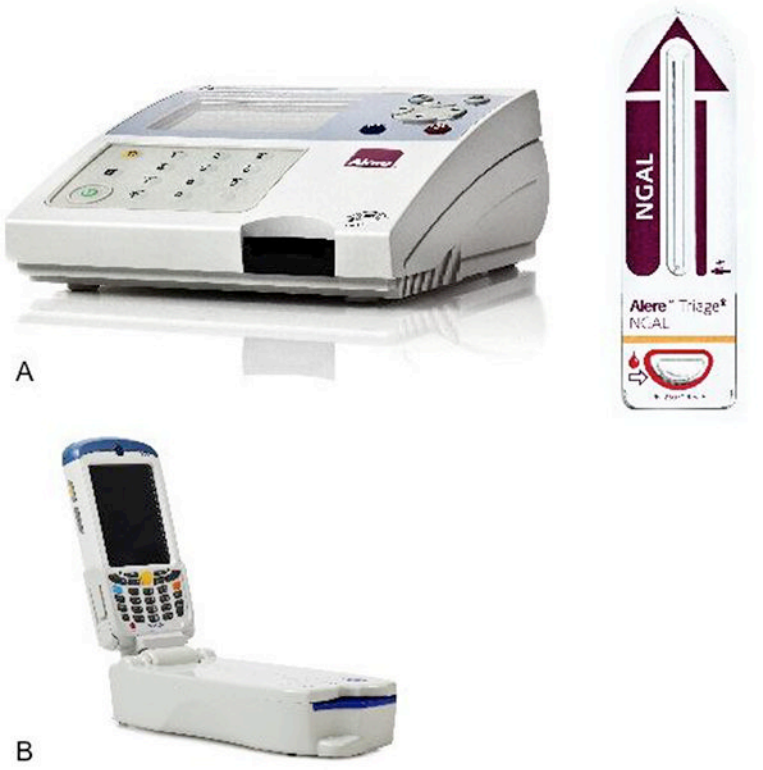

Figure 10.
Hand-held POCT Devices. (A) Alere Triage MeterPro and Alere Triage NGAL test for the early risk detection of acute kidney injury. Courtesy of Alere. (B) Alere epoc Blood Analysis System. *Courtesy of Alere*.

Figure 11.
iSTAT cartridge and handheld system. *Courtesy of Abbot Laboratories.*

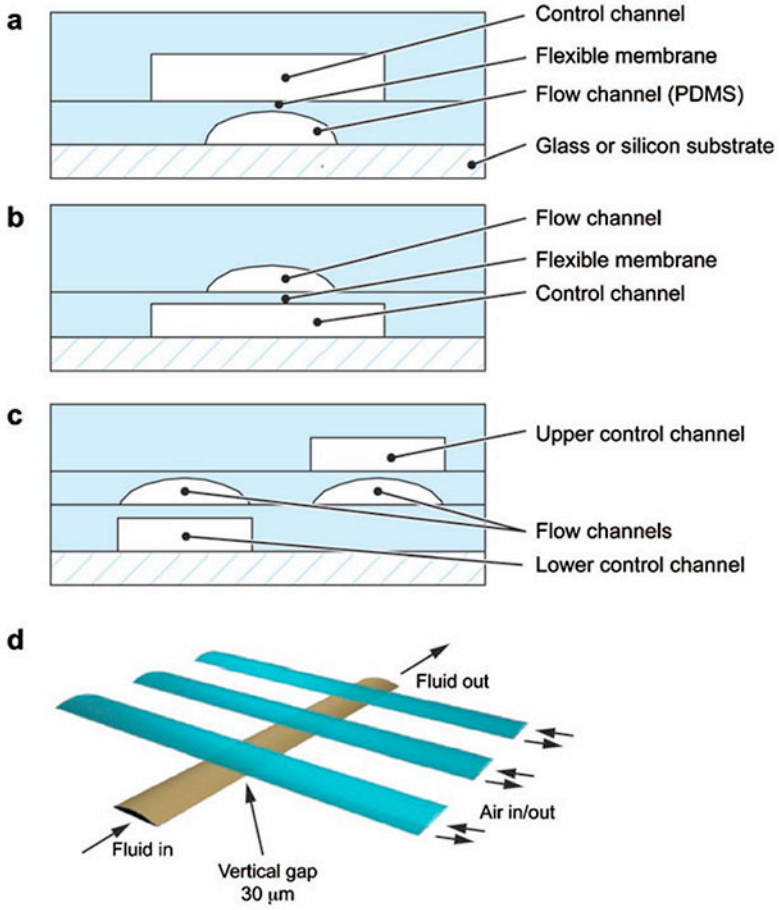

Figure 12.

(a) A two-layer PDMS push-down microfluidics valve. An elastomeric membrane is formed where the flow channel is positioned orthogonal to the control channel directly above. Fluid flow is out of the page. (b) A two-layer PDM push-up microfluidics valve. (c) A three-layer device with both push-up and push-down valves. (d) Schematic of a linear peristaltic pump using three membrane valves in a series. *Reprinted with permission.*[76]

Figure 13.
Micronjet Needles (NanoPass Technologies). A Single-use 450μm microneedle device for intradermal delivery. The device can be used with standard syringes to inject drugs, proteins or vaccines directly into the skin. *Courtesy of NanoPass Technologies, Inc.*

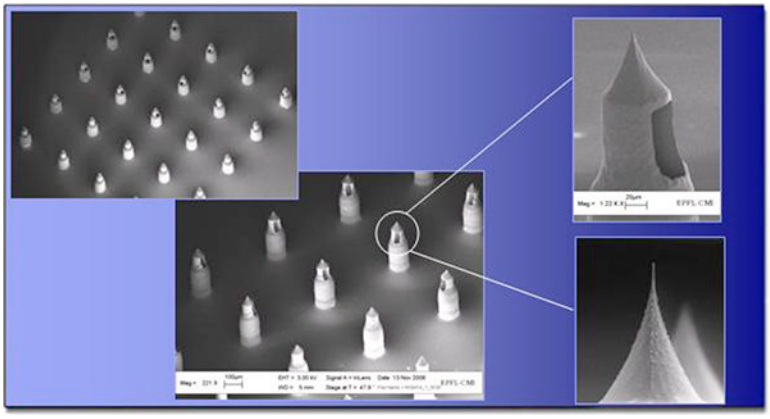

Figure 14.
Debiotech Nanoject Device with side-holed microneedles. *Courtesy of Debiotech.*

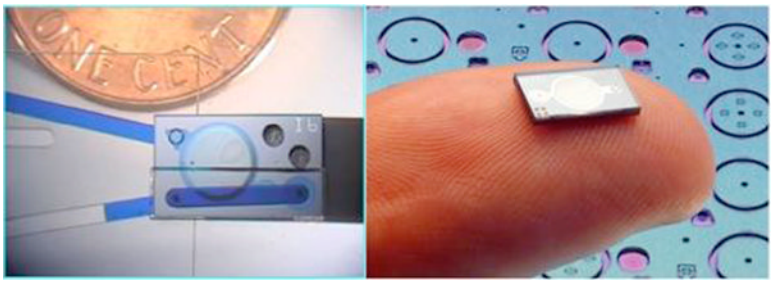

Figure 15.
Debiotech Nanopump- Volumetric membrane pump for drug delivery using a piezoelectric actuator. *Courtesy of Debiotech.*

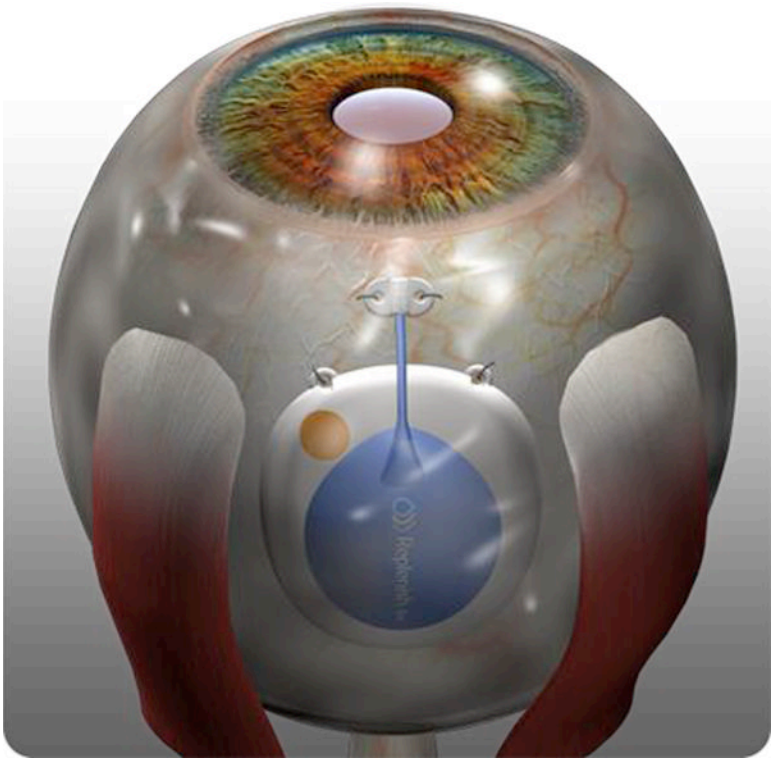

Figure 16.
Replenish Inc. Intra-ocular drug delivery pump. *Sourced from* www.replenishinc.com

Figure 17.
MicroCHIPS Drug delivery device. *Courtesy of MicroCHIPS, Inc.*

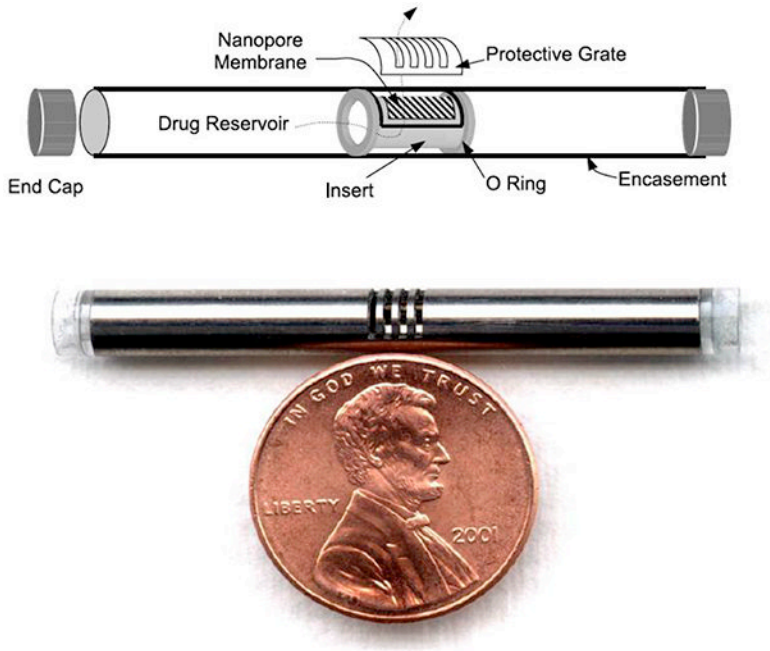

Figure 18.

Implanted device fitted with nanopore membranes. (Top) Drawing illustrating key features of the device. The dashed arrows represents a possible diffusion path of a drug molecular held within the device reservoir. (Bottom) Photograph of prototype implant device illustrating its size in relation to a U.S. 1 cent piece. *Reprinted with permission.*[98]

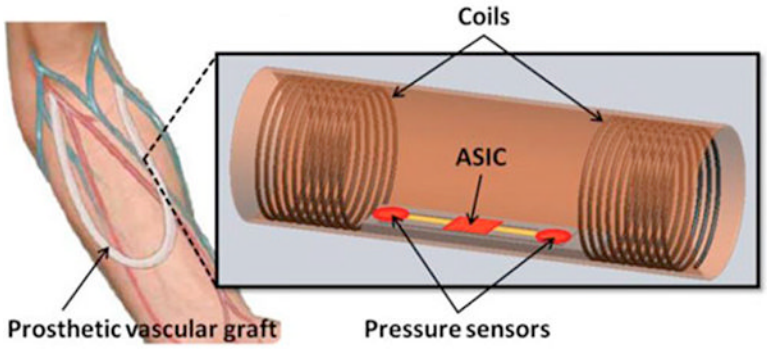

Figure 19.
Wireless implantable blood flow sensor microsystem. The microsystem measures the blood flow rate inside prosthetic vascular grafts to detect graft degradation. *Reprinted with permission.*[104]

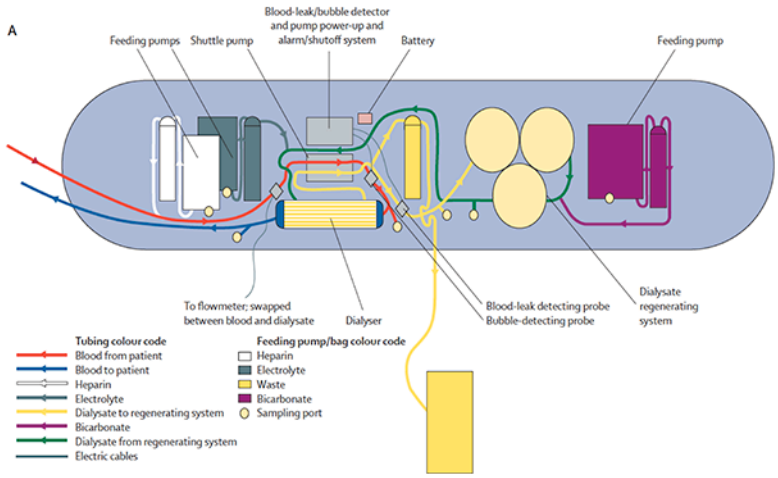

Figure 20.

Schematic of the Wearable Artificial Kidney. The circuit consists of two basic sections: the blood compartment in which the arterial line (red) supplies blood to the dialyzer and then returns blood to the patient (blue line), and the dialysate compartment, where fresh dialysate enters the dialyzer and then exists to a series of sorbent canisters, where it is regenerated, and bicarbonate added. *Reprinted with permission.*[106]

Figure 21.
Automated Wearable Artificial Kidney (AWAK) is a portable peritoneal dialysis system using sorbent cartridges to regenerate spent dialysate. *Sourced from* www.awak.com

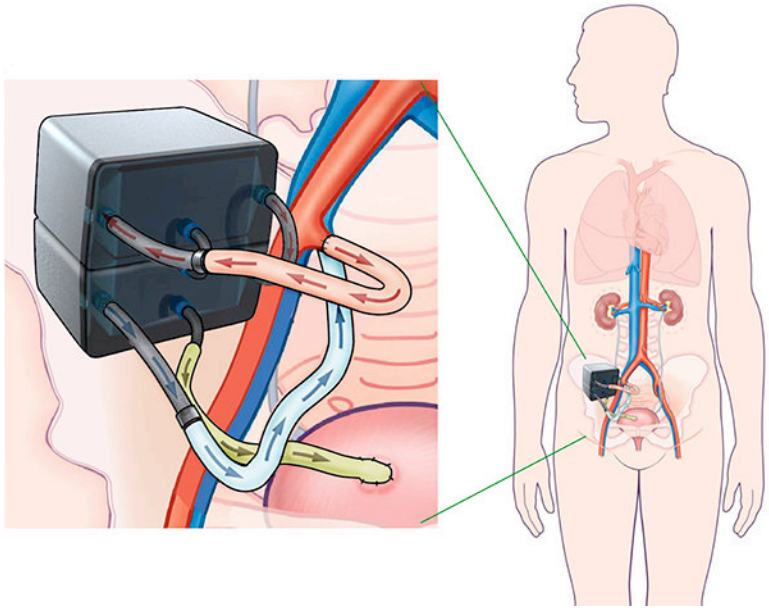

Figure 22.
Schematic drawing of the implantable bioartificial kidney. The figure shows the vascular anastamoses and urinary conduit for the device.

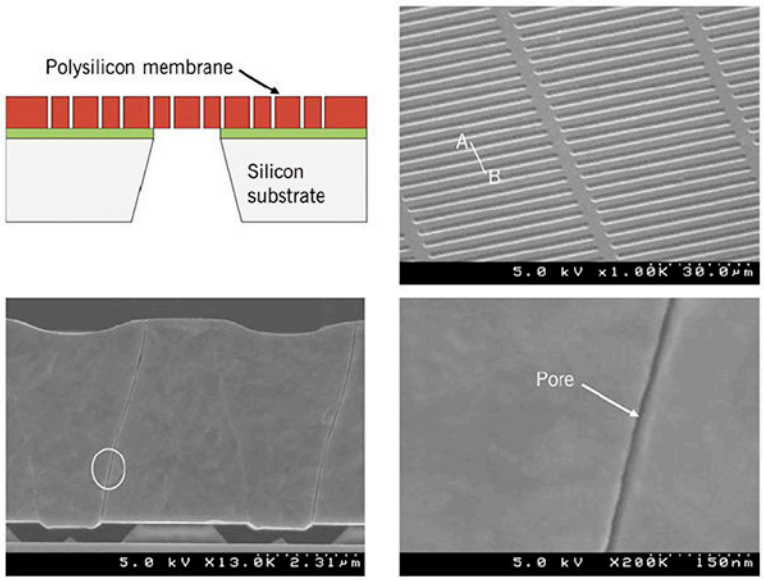

Figure 23.

Nanopore membrane fabricated using silicon MEMS technology. *Top left:* Cross-section of membrane illustrating various structural layers (not to scale). Pores (exaggerated) are formed in the polysilicon diaphragm, which is supported by an underlying silicon substrate. *Top right:* SEM image of membrane showing uniformly spaced array of slit pores. *Bottom left:* SEM image showing membrane cross-section and non-tortuous pore geometry. *Bottom right:* SEM image showing close-up of 9nm slight pore and smooth surface characteristics. *Reprinted with permission.*[121]