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# Therapeutic BioMEMS Overview

## Primary Knowledge (OK)

### Instructor Guide

#### Notes to Instructor

This Primary Knowledge unit provides introductory material on various Microelectromechanical Systems (MEMS) that are being designed or currently being used for therapeutics. This PK and its related activity and assessment are part of the *Therapeutic BioMEMS Overview Learning Module*:

- Knowledge Probe (KP - Pre-test)
- Therapeutic BioMEMS Overview PK
- Marketing a Therapeutic BioMEMS Activity
- Final Assessment

#### Description and Estimated Time to Complete

*This learning module is an overview of BioMEMS that are currently being used or tested as therapeutic devices for patients. As an activity you will study a particular therapeutic BioMEMS and develop a marketing brochure for doctors and patients. Review this primary knowledge unit prior to completing the activity.*

In medicine, therapeutics is the process of caring for the patient in a comprehensive manner. Therapeutics includes preventing disease as well as managing disease or disease specific problems. Microtechnology and MEMS (microelectromechanical systems) have revolutionized and will continue to revolutionize therapeutic medicine as more technological advances are made. Some micro-sized devices are already being offered commercially and many more are being tested. This unit provides an overview of how microtechnology has been incorporated into a variety of therapeutic applications.

#### Estimated Time to Complete

Allow approximately 15 minutes to review.

## Introduction

Therapeutic bioMEMS can be used to manage a disease by placing a device in vitro (externally), in vivo (internally) or by using a combination of both. In vitro devices gather and process information. In vivo devices more easily detect changes in a disease. Combination devices detect, monitor and manage disease. Some of the devices already on the market and being tested at the human stage include

- drug delivery systems,
- devices for invasive surgeries, and
- artificial retinal prosthesis.

This figure shows a prototype of a MEMS-based array that is placed onto the retina of a blind patient. The array generates electrical impulses that are carried through the optic nerve to the brain. Recently trials have shown that this device, working with external components, enable a blind person limited sight, but more on that later. Because of its biomedical application, this device is considered bioMEMS.

This unit discusses MEMS and bioMEMS devices that are currently on the market and that are being tested for commercial use.



*Prototype of a Retina Implant  
[Photo by Randy Montoya. Courtesy of  
Sandia National Laboratories]*

## Learning Module Objectives

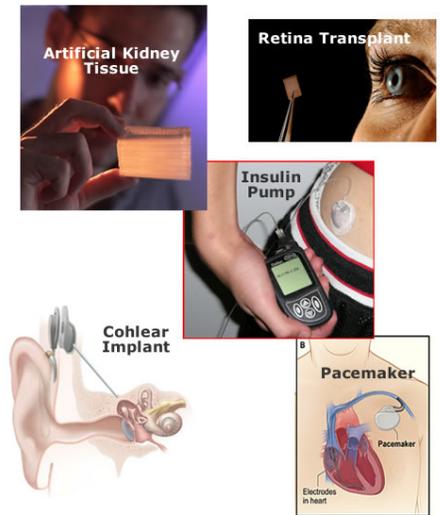
- Explain why microtechnology is advantageous for therapeutics.
- Describe a therapeutic bioMEMS device and explain how it works.
- List and define the areas of medicine that could benefit from microtechnology.

## The Possibilities

The possibilities for bioMEMS therapeutic applications for healthcare are numerous. Such applications include

- minimal invasive surgery,
- drug delivery,
- treatment of cardiovascular diseases, diabetes and cancers,
- applications in neurology, ophthalmology, audiology, and
- applications in dermabrasion and tissue engineering.

Therapeutic bioMEMS devices already exist for many of these applications. One of the most successful applications has been for disease control in diabetes.



### *BioMEMS Therapeutic Applications*

## Therapeutics for Diabetes: The Disease

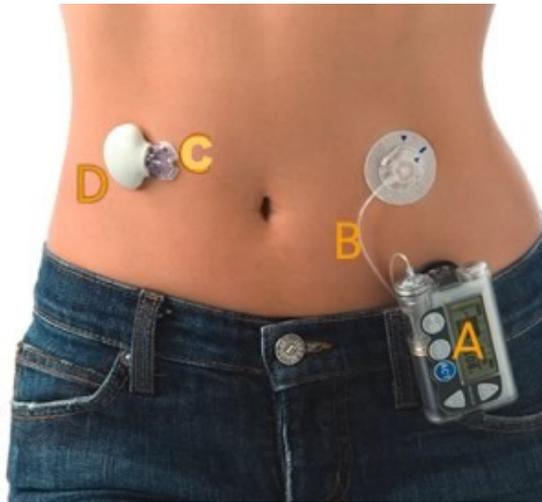
According to the [American Diabetes Association](#), 30.3 million Americans (9.4% of the population) had diabetes (Type 1 or Type 2) in 2015. Of those 30.3 million, 1.25 million are children and adults with Type 1. Each year, 1.5 million American are diagnosed. Globally, the [World Health Organization \(WHO\)](#) reports 422 million people with diabetes in 2014, up from 108 million in 1980. WHO predicts that diabetes will be the seventh leading cause of death worldwide in 2030.<sup>1</sup> The American Diabetes Association already shows it as the seventh leading cause of death in the United States in 2015. The statistics are based on “diagnosed” patients. There are still an estimated 7 million plus undiagnosed patients in the U.S. alone.

Type 1 diabetes, often referred to as juvenile diabetes, is an autoimmune disease resulting in the destruction of the beta cells in the pancreas. This destruction prevents the production of insulin or production of enough insulin. Type 2 diabetes, once known as adult-onset diabetes, is a chronic condition that affects the way the body metabolizes sugar (glucose). Again, the pancreas may not produce enough insulin or the body does not know what to do with the insulin produced.

Over 28 percent of all diabetics in the United States use insulin to control their disease. This means over eight million Americans. The therapeutic technology for treating diabetes has been a twice daily prick to determine glucose concentration and twice daily shot to administer the insulin. This is especially hard on the young patients and patients in remote or low income areas. Compliance to this regimen is a major problem, especially for juvenile diabetics. A lack of compliance causes hypoglycemic events (a drop in blood glucose) to go undetected.

Undetected hypoglycemic events can also occur during sleep and during the day if the patient develops hypoglycemia unawareness. These undetected events can lead to seizures and loss of consciousness. They also increase the risk of diabetic eye disease, and kidney and nerve damage.

## Therapeutics for Diabetes: The Solution



*MiniMed Paradigm[R] 522 insulin pump, with MiniLink™ transmitter and infusion set.  
[Printed with permission from Medtronic Diabetes]*

Most of the current products for diabetics either continuously monitor glucose levels or deliver insulin. However, there are a few newer products on the market that can do both – monitor and deliver insulin.

One of these products is the MiniMed Paradigm® 522 insulin pump, with MiniLink™ transmitter and infusion set pictured above:

- (A) an external pump and computer
- (B) a soft cannula that delivers the insulin
- (C) an interstitial glucose sensor
- (D) a wireless radio device that communicates with the pump.

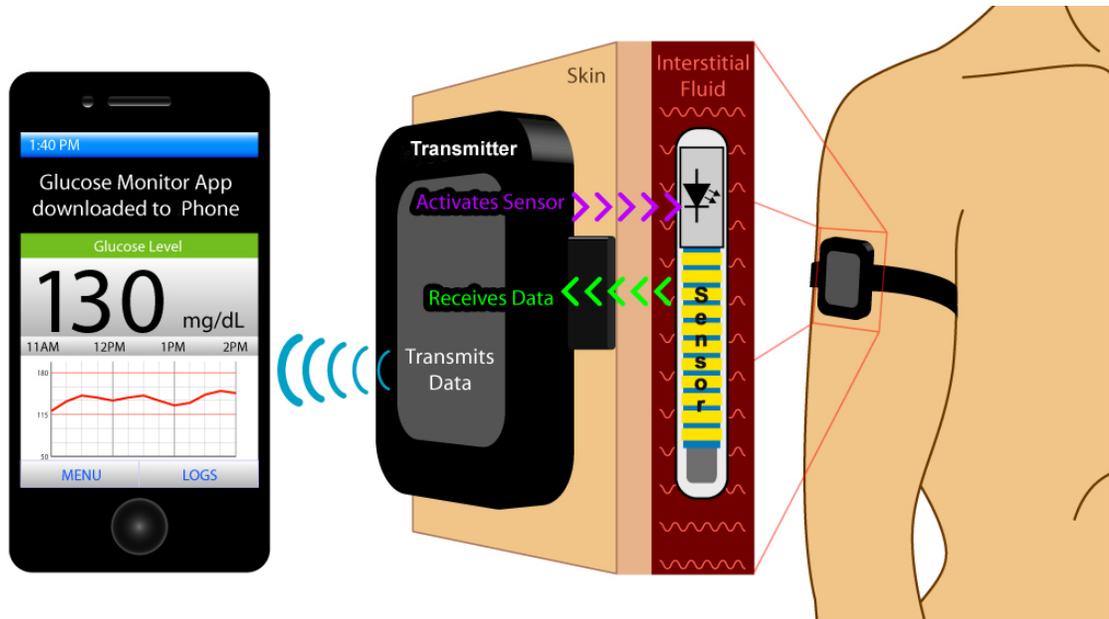
The sensor (C) is placed subcutaneously (under the skin). It continuously measures glucose levels in the interstitial fluid, the fluid between body tissues. The sensor transmits its measurements in real time via radiofrequency to the wireless radio device (D). This device sends the readings to the computer (A) which determines the amount of insulin needed. The pump (in A) administers that amount into the patient via the cannula (B). The MiniMed Paradigm® also stores all the data (A). This data can be downloaded, providing valuable information to the patient and physician for improved disease management.

This device has become smaller, more accurate and more efficient over the past five years due to the continuous developments in microtechnology. Visit the Medtronics website (<https://www.medtronicdiabetes.com/home>) to see the latest and greatest in continuous glucose monitoring.

## The Senseonic Continuous Glucose Monitor (CGM)

Senseonic, a privately held medical device company is currently in the process of developing and testing a biocompatible CGM that contains a sensor that can be implanted under the skin where it measures glucose in the interstitial fluid for up to six months. “Encased in a biocompatible material, the Sensor utilizes a unique fluorescent, glucose indicating polymer. A light emitting diode (LED) embedded in the Sensor excites the polymer, and the polymer then rapidly signals changes in glucose concentration via a change in light output.”

Below is a graphical representation of how this Senseonics CGM works. A transmitter worn on the upper arm wirelessly activates the LED in the Sensor which turns the Sensor on. The transmitter reads changes (data) in the LED’s output which varies based on the glucose concentration. The transmitter sends the data to the patient’s smartphone or computer via Bluetooth. All of this is “done autonomously and independently without any prompting by the user.”<sup>11</sup>



In February of 2013 Senseonics received an ISO certification that allowed for “the design, development, manufacturing, servicing and distribution of active implantable glucose sensors and accessories for continuous glucose monitoring”.<sup>12</sup> As of June 2014, Senseonics announced that it had “raised an additional \$20 million of private equity financing” toward the continued development and testing of this device in both Europe and the United States.<sup>13</sup>

## Other Therapeutic Drug Delivery Applications

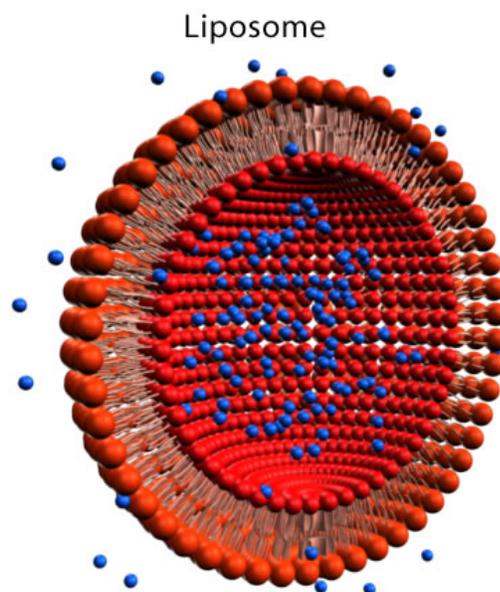
Currently, medications are administered topically, sublingually, orally, nasally, subcutaneously, intramuscularly, intravenously, intrathecally, rectally, vaginally, and by perfusion to arteries and target organs via catheters. Microdevices that use biomolecules as drug delivery components could decrease the necessity for many of these routes. These devices could allow for controlled drug delivery directly to the targeted tissue or organ, bypassing metabolic processing by the liver and other organs.

### Vesicle for Drug Delivery

An example of such a bioMEMS device is the liposome vesicle (cavity) shown in the graphic. Liposomes are closed bilayer phospholipid systems ranging from 1 to 250  $\mu\text{m}$  in diameter and with nano-sized cavities. The cavity is filled with a drug or combination of drugs (blue). Several of these drug filled vesicles can be injected into the bloodstream and "guided" to the target tissue where they are either absorbed or adsorbed by the tissue. Once there, the drug migrates through the membrane and into the tissue, destroying or neutralizing the diseased tissue.

There have been numerous clinical trials to test the efficacy of liposome vesicles for the delivery of "anti-cancer, anti-fungal and antibiotic drugs, the delivery of gene medicines, and the delivery of anesthetics and anti-inflammatory drugs. A number of liposomes (lipidic nanoparticles) are on the market, and many more are in the pipeline."<sup>2</sup>

*Biomolecular Drug Delivery  
Liposome vesicle with drug inside (blue)*



## **Advantages of bioMEMS for Drug Delivery**

Advantages of bioMEMS devices for drug delivery include

- controlled release,
- reliable dosing,
- targeted therapy,
- precise delivery, and
- automated or semi-automated feedback control.

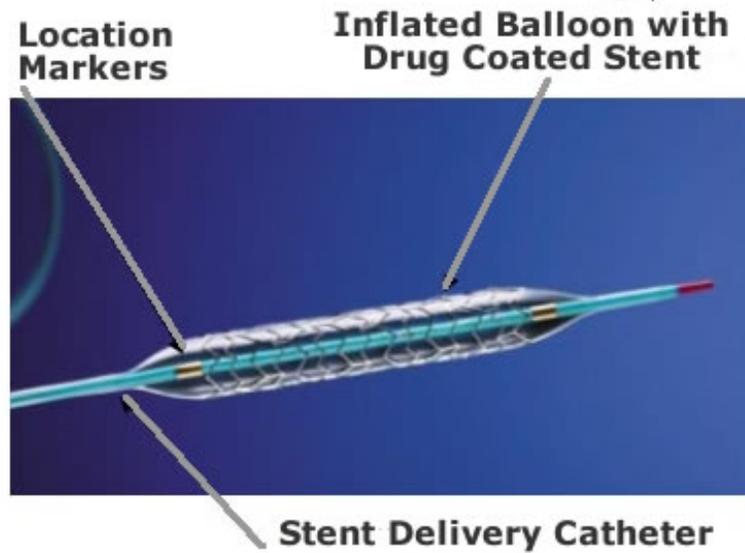
Medications that could be administered by implanted bioMEMS include analgesics, insulin, cancer drugs, antibiotics, and radiation sources (antitumor treatment). Various transdermal systems (patches) using reservoir gels have been developed for precise and timed delivery of nitroglycerin, hormones, scopolamine, and other drugs where gradual release is required.

## **Designing a Drug Delivery Device**

The parameters that must be considered when designing drug delivery systems are dose, frequency, duration, toxicity, drug interaction, allergies, and oscillatory behavior of the drug in the body. In addition, therapy for a given disease may change over time as the disease state of the patient changes or as new therapies become available. This requires that the device be easy to remove or for it to be easy to change out the drug in the existing device. Some bioMEMS devices may need to be able to degrade and be discharged by the body's systems.

Examples of bioMEMS drug delivery systems that are currently being used or investigated incorporate components that are environmentally sensitive hydrogels, electro-active polymers (EAPs), piezoelectric devices and microspheres. Many of these devices are being investigated as targets controlled drug delivery devices or TCDD.

## Nanopore Coated Stents



*Drug-eluting Stent by Taxus [Image provided by the FDA]*

Another example of bioMEMS drug delivery currently on the market is the nanopore drug delivery coating system associated with stents (devices inserted into obstructed arteries). These stents are referred to as drug-eluting stents. The picture shows the TAXUS Express2 Paclitaxel-Eluting Coronary Stent System.

The stent coating is a medication that is slowly released (eluted) to decrease restenosis (tissue growth in the artery lining that decreases the diameter of the opening in the stent). Restenosis increases the possibility of re-blockage and thus, another procedure. The practice of using drug-eluting stents should lead to a decrease in repeat procedures and minimization of cost-intensive bypass surgery.

For more information on drug delivery systems, review the following article:

*“Biomedical microelectromechanical systems (BioMEMS): Revolution in drug delivery and analytical techniques”*. Saudi Pham J. 2016 Jan; 24(1): 1-20. <http://bit.ly/2wcOfxt>

## **Minimal Invasive Surgery (MIS)**

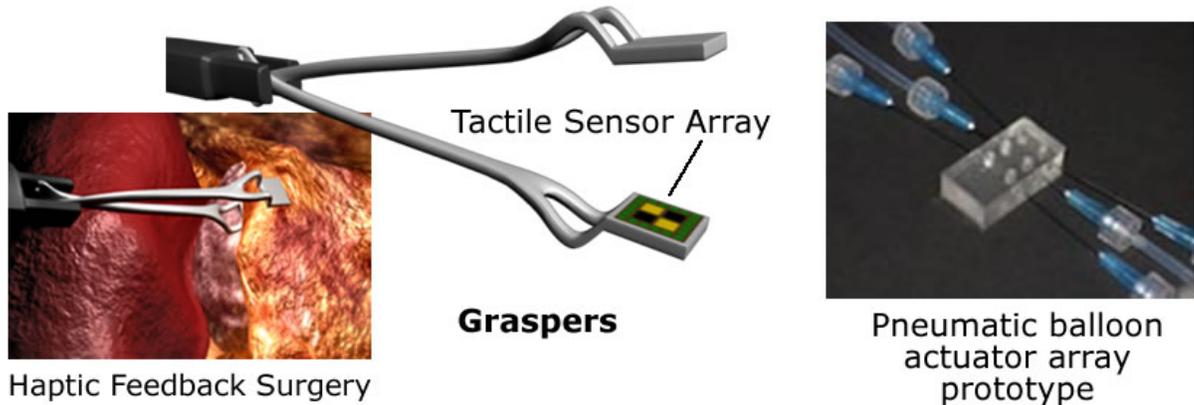
Minimal Invasive Surgery (MIS) is the process of accomplishing a surgical task with the least amount of intrusion and harm to the patient. Typically, there is

- less postoperative pain,
- shorter hospital stays,
- quicker recoveries, and
- less scarring.

A bioMEMS device currently used for MIS is a micro-sized robot. Robot-assisted minimally invasive surgery offers improved range of motion over standard laparoscopic techniques. The da Vinci S MIS is one of the most advanced surgical robots on the market. "The robot looks a little like an octopus with four arms – one arm holds the camera and three working arms hold surgical instruments." (ExpressNews, UofA)<sup>5</sup>. In reality, the da Vinci is not really a robotic system because it still requires human interface. During surgery, the movements of the surgeon are transmitted electrically to mechanical arms where there are seven degrees of freedom – “three for translation, three for rotation, and one for grasping.” Since approved by the FDA, “the da Vinci Surgical System has been installed in about 2,000 hospital in the United States.”<sup>6</sup>

Unfortunately, MIS robots (including the da Vinci) are characterized by a total loss of haptic (sense of touch) feedback, requiring surgeons to rely solely on visual clues. Visual information is sufficient for many procedures, however, it is often challenging to cauterize tissues and apply appropriate force to sutures without tactile information. MEMS devices with haptic feedback could enable expansion of robotic surgery to procedures that are difficult to perform without a sense of touch.

## Haptic Feedback for MIS



*Haptic Feedback Graspers with tactile sensor array (left images)  
Pneumatic Balloon Actuator Array Prototype (right image - Printed with permission of UCLA)*

The development of a pneumatic balloon-based haptic feedback system is currently underway at the Center for Advanced Surgical and Interventional Technology (CASIT) at UCLA. Mounted on the end of the surgical tool (the grasper) is a force sensor array with several sensing points (see simulated graphics above). Each point (transducer) of the sensor array detects the force applied to the patient's tissue at the distal end of the robotic grasper. These force measurements translate to proportional pressures that are sent to a joystick in the surgeon's hand. The surgeon "feels" the change in pressure and adjusts as needed.<sup>7</sup>

This system is currently under development for use with the da Vinci robotic surgical system at CASIT. It can also be scaled for other robotic or prosthetic applications.

## Artificial Retinal Prosthesis

Another bioMEMS device being tested is the artificial retinal prosthesis called the Argus™ Retinal Stimulation System. This was developed through a collaborative effort called the Artificial Retina Project: ([ArtificialRetina.energy.gov](http://ArtificialRetina.energy.gov)).

This project is a collaboration between several institutions:

- Doheny Eye Institute at the University of Southern California
- Department of Energy (Argonne National Laboratory)
- Lawrence Livermore National Laboratory
- Brookhaven National Laboratory
- Oak Ridge National Laboratory
- Los Alamos National Laboratory
- Sandia National Laboratories
- University of California, Santa Cruz
- Second Sight Medical Products Inc.



*Prototype of a Retina Implant*

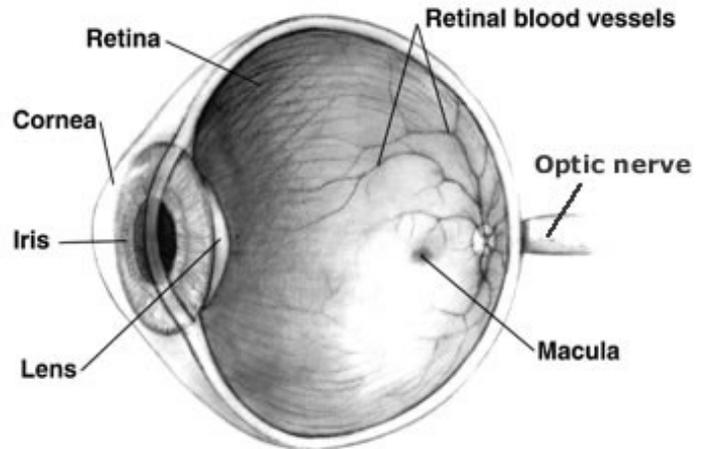
*[Photo by Randy Montoya. Courtesy of Sandia National Laboratories]*

This collaboration has produced a series of retinal prosthesis that consist of an artificial retina implanted onto or beneath the retina of a human eye (see picture of prototype). In the initial testing phase, six patients received the retina prosthesis. As a result of the prosthesis, each of these previously blind patients has been able to distinguish and identify objects and motion. (D.M. Deupree, The Macula Center)

## How Does the Eye Work?

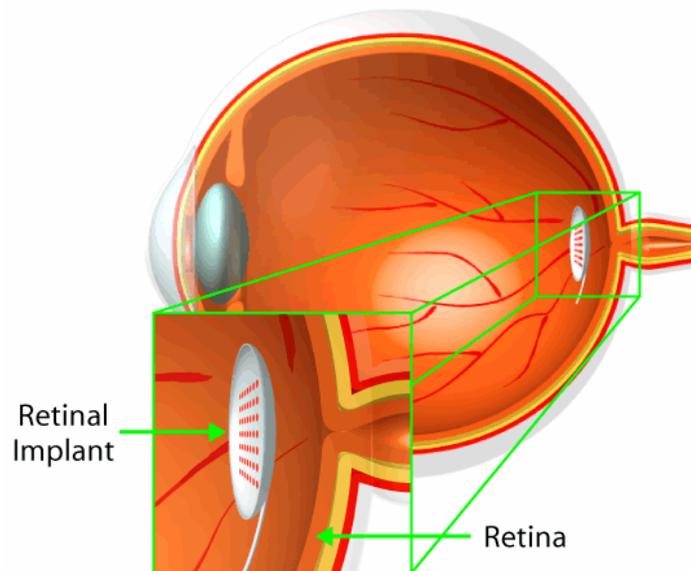
As with any bioMEMS device, it is important to fully understand how the biological device works. Let's take a quick look at how the human eye works before discussing how an artificial retina works.

Normal vision occurs when light enters the eye through the cornea then the lens. The lens focuses the light on the retina, the inner-most lining of the eyeball. The retina contains photoreceptor cells which convert the light to electric impulses. These impulses travel into the optic nerve then to the brain where the information is processed.



*Human Eye*  
[Image courtesy of the National Eye Institute]

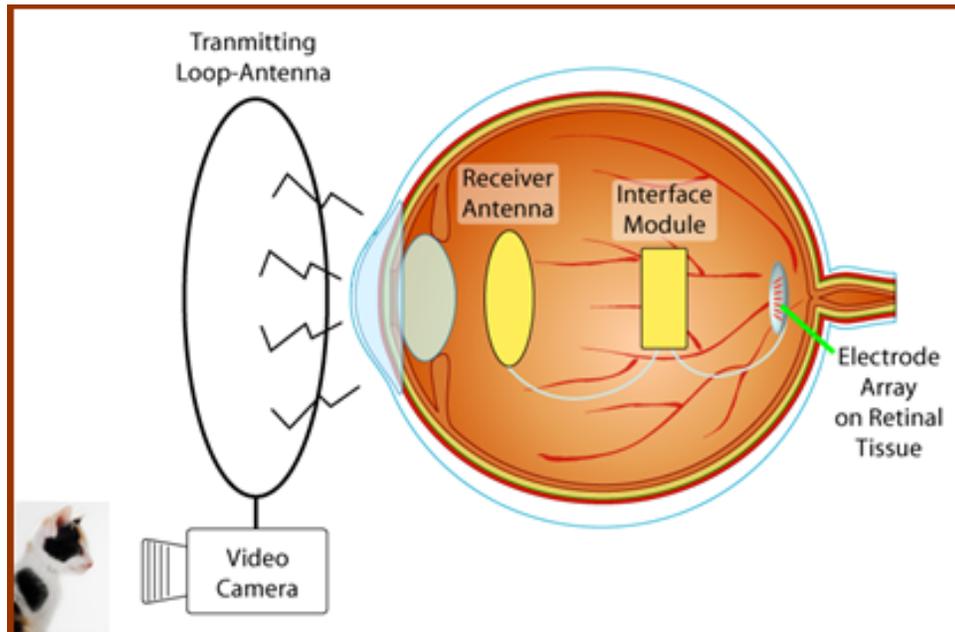
## Artificial Retina – What is it?



*Artificial Retinal Implant*

In retinal diseases, such as age-related macular degeneration and retinitis pigmentosa, the photoreceptor cells in the retina are destroyed. An artificial retina is designed to bypass these cells and transmit signals directly to the optic nerve. The artificial retina is an electrode studded array placed on or beneath the surface of the retina. The electrode array is designed to perform the tasks of the destroyed photoreceptor cells by converting light to electric impulses. Just like in a working eye, these electric impulses travel to the neurons below the retina and to the optic nerve then to the brain.

## Restoring Sight In Vivo



*Artificial Retina MEMS - image to brain*

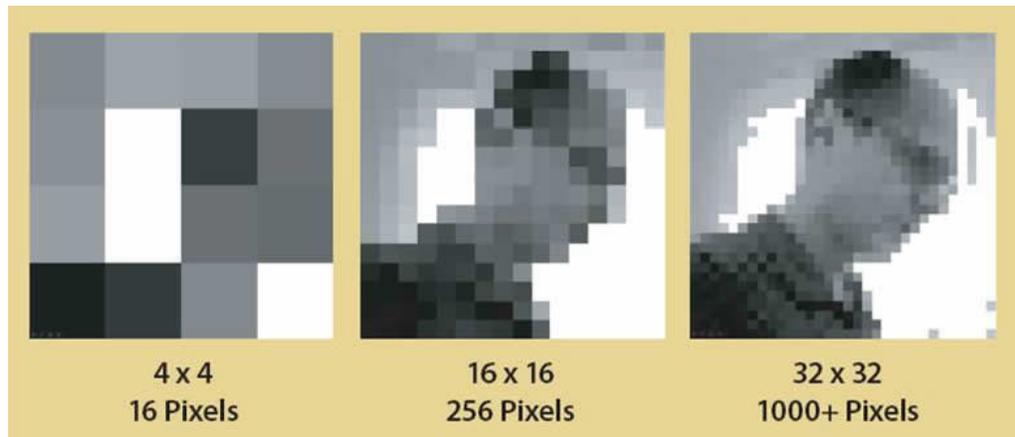
The Artificial Retina MEMS consists of a camera, microprocessor, transmitter, receiver, interface module and the artificial retina (electrode array).

The graphic of the retina MEMS shows the imaging camera at bottom (usually situated on or in the frame of glasses).

- The camera captures an image and sends the information to the microprocessor (in the glasses frame or on the belt).
- The microprocessor converts the data to an optical signal and transmits it via the transmitter to the receiver antenna on the eye.
- The antenna transmits the signal via cable to the electrode array tacked to the retina.
- The optical signal stimulates the array to emit electrical pulses in the working retinal neurons.
- These pulses travel through the optic nerve to the brain, which perceives patterns of light and dark spots corresponding to the electrodes stimulated.

Patients have to learn to interpret the visual patterns produced.

## What does the patient see?



*Images produced by the artificial retina prosthesis*

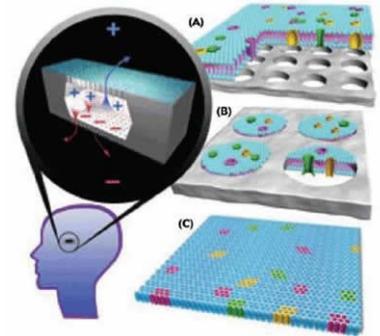
*[Images generated by the DOE-funded Artificial Retinal Implant Vision Simulator devised and developed by Dr. Wolfgang Fink and Mark Tarbell at the Visual and Autonomous Exploration Systems Research Laboratory, California Institute of Technology. Printed with permission.]*

These images show what a patient with retinal devices should see. Increasing the number of electrodes in the retina array results in more visual perceptions and higher resolution vision. In 2007 six patients were successfully implanted with the first prototype Model 1 device or Argus I™. Argus I™ contained 16 electrodes (16 pixels - left picture). The Argus II™ (60 pixels) is currently being tested and as of June 2012 it had been implanted into 32 people. With Argus I, it took patients about 15 seconds to recognize objects. That time was significantly improved with the Argus II with an object recognition time of 2 to 3 seconds.<sup>10</sup> The success of the Argus II clinical trials has led to the approval of the Argus II for clinical and commercial use in both Europe (March 2011) and the United States (February 2013).

The Argus III prototype currently has 200+ pixels with a goal of 1000+ pixels (right picture) for the Argus 4.<sup>10</sup> The ultimate goal for this device is to enable facial recognition and large-print reading vision, using materials that will last for a lifetime.

## Powering the artificial retina<sup>8</sup>

Artificial retina MEMS are powered by a wireless battery pack worn on the person's belt. However, Sandia National Laboratories is working on a battery that can be implanted in the person's head.



*Battery Pack for Artificial Retina system  
[Courtesy of Sandia National Laboratories]*

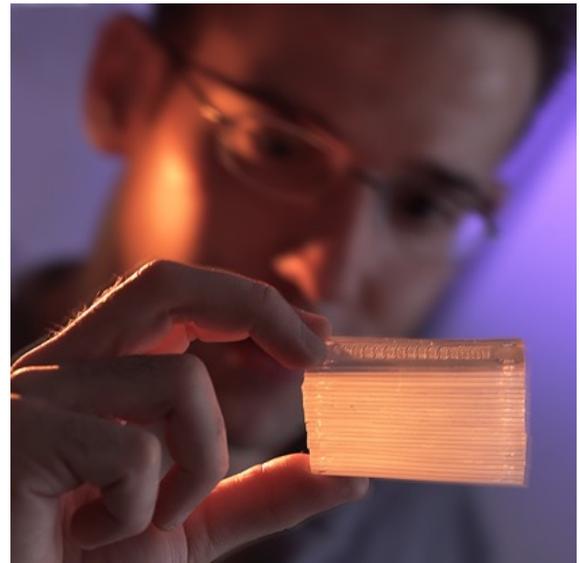
## Other Retinal Devices

Other artificial retina MEMS projects are under way in the United States and worldwide (Germany, Japan, Ireland, Australia, Korea, China, and Belgium). This same technology is also being examined for applications in neurological disorders such as memory loss due to stroke or dementia.

## Tissue Engineering (CIMIT)<sup>9</sup>

Almost ninety-thousand Americans are waiting for a new organ. These patients live with the knowledge that a transplant could save their lives, but understand there is a good chance they will die because of a donor shortage. On average, there are only three thousand livers for thirty thousand patients annually. For patients waiting for a kidney, dialysis offers some mechanical support; however, a quarter of them will not survive the wait. BioMEMS innovation is addressing this problem.

The CIMIT tissue engineering program is working to develop a kidney dialysis unit that can be worn around the waist. CIMIT is also working on MEMS that can build complex organs such as kidneys, livers, and replacement tissue. This is possible because the micro-scale of MEMS enables the replication of the internal network of capillaries and vessels that bring blood and oxygen to living growing tissue. The picture shows a prototype of an artificial kidney based on MEMS technology.



*Artificial Kidney  
[© The Charles Stark Draper Laboratory, Inc. All rights reserved. Reprinted with permission.]*

*In 2014 the area of tissue engineering was still in the research phase but making advancements. For a more recent and interesting read check out the article “Building cyborg tissues: Bioengineering meets nanoelectronics”. Tom Ulrich. August 30, 2012 <http://on.bchil.org/2vDJdGH>*

## Summary

The therapeutic MEMS and bioMEMS presented in this unit are the tip of the iceberg and as of this writing, many have already advanced to the next generation while new products have been developed and approved for commercialization. Quick research on Therapeutic BioMEMS will yield a host of references.

The majority of therapeutic MEMS are a combination of external and internal components. In many cases they are larger than micro or nano-sized MEMS. However, some of these devices are already being fabricated into micro-sized and even nano-sized components with fewer or no macro-sized parts. Eventually, many of these devices will become totally in vivo (no external parts), allowing patients to be more mobile and more independent.

Who knows? We might develop a therapeutic bioMEMS that could be placed internally to monitor for the first signs of a disease. This would enable treatment of the disease immediately or at least let the person know that the disease is present, thus preventing the disease from manifesting itself. The possibilities are endless.

## **Food For Thought**

What are some current and future applications for therapeutic MEMS and bioMEMS?

What are the advantages of bioMEMS drug delivery systems compared to the current macro-systems?

## **Glossary of Key Terms**

Audiology: Treatment of hearing disorders

da Vinci Surgical System: A device commonly used for laparoscopies. It consists of a surgeon's console, a patient-side cart with four interactive robotic arms, the high-performance InSite® Vision System and proprietary EndoWrist® Instruments.

Dermabrasion: "Refinishes" the skin's top layers through a method of controlled surgical scraping. It is used to give the skin a smoother appearance. It can also be used to treat pre-cancerous spots.

Haptic feedback: Kinesthetic or force feedback that is generally used to convey something about the physical characteristics of the space in which a user is operating.

Hypoglycemia unawareness: When diabetic patients are no longer aware of low blood sugar events because stress hormones are no longer being produced in response to low blood sugar. The event becomes asymptomatic and goes undetected until more dire side-effects, such as seizures or loss of consciousness are realized.

Intramuscularly: Administration of a drug into a muscle.

Intrathecaly: An injection of a drug into the spinal canal. Typically the drug has to be specially made because it cannot contain any preservatives or other potentially harmful inactive ingredients.

Juvenile diabetes or Type 1: An autoimmune disease resulting in the destruction of the beta cells in the pancreas that produces insulin.

Laparoscopy: A group of operations performed with the aid of a camera placed in the abdomen.

Neurology: Treatment of the nervous system including the brain.

Ophthalmology: Treatment of eye injuries and diseases.

Oscillatory behavior: Variation of drug concentration in the body.

Stents: Mechanical devices inserted into an obstructed vessel in order to return circulation. Once inserted, the stent is expanded and left in place.

Sublingually: Administration of a drug by placing it under the tongue.

Tissue engineering: Engineering of tissues to treat defective cells such as in burn patients and diabetics.

Topically: Administration of a drug by putting it on the skin.

Transdermal: Controlled delivery of drugs by placing a patch (containing the drug) on the skin.

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<http://www.who.int/mediacentre/factsheets/fs312/en/>
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- 15 “Tissue Engineering and Regenerative Medicine”. *Science Education*. National Institute of Biomedical Imaging and Bioengineering. NIH. <http://bit.ly/2iCwxyS>

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*This Learning Module was developed in conjunction with Bio-Link, a National Science Foundation Advanced Technological Education (ATE) Center for Biotechnology @ [www.bio-link.org](http://www.bio-link.org).*