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Building An Electrochemical Contact Lens Biosensor

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Abstract
This review discusses the convergence of several research and engineering fields working to design and integrate electrochemical biosensing units into contact lenses. Tear fluid contains a wide variety of biochemical information about both ocular and systemic environments. By measuring biomarkers and their concentrations, it is possible to determine whether certain disease states are present. Emerging biosensor technology, most notably materials constructed at the nano scale, are showing incredible precision in the identification and quantification of individual molecules. Miniature, integrated biosensing units, which require energy self-sufficiency and wireless operation, consist of a few fundamental electronic components. The major systems discussed in this work include: energy, circuits and communication. Publicly documented contact lens prototypes provide an idea of how far the field has come and what challenges lie ahead. The projected clinical impact of real-time, continuous tear fluid monitoring is immense. It is vital that the eye care field remains keenly aware of the efforts underway and active in the conversation going forward.

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BUILDING AN ELECTROCHEMICAL CONTACT LENS BIOSENSOR

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CRAIG JORDAN

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MASTER OF SCIENCE IN VISION SCIENCE PROGRAM
PACIFIC UNIVERSITY COLLEGE OF OPTOMETRY, 2016

ABSTRACT

This review discusses the convergence of several research and engineering fields working to design and integrate electrochemical biosensing units into contact lenses. Tear fluid contains a wide variety of biochemical information about both ocular and systemic environments. By measuring biomarkers and their concentrations, it is possible to determine whether certain disease states are present. Emerging biosensor technology, most notably materials constructed at the nano scale, are showing incredible precision in the identification and quantification of individual molecules. Miniature, integrated biosensing units, which require energy self-sufficiency and wireless operation, consist of a few fundamental electronic components. The major systems discussed in this work include: energy, circuits and communication. Publicly documented contact lens prototypes provide an idea of how far the field has come and what challenges lie ahead. The projected clinical impact of real-time, continuous tear fluid monitoring is immense. It is vital that the eye care field remains keenly aware of the efforts underway and active in the conversation going forward.

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INTRODUCTION

In 1967, the first biosensor was created for the purpose of measuring glucose levels in liquid samples.[1,2] It contained the immobilized enzyme glucose oxidase on the surface of an oxygen electrode, which broke glucose into electrons and inert byproducts.[2] The electrode measured electron flow and the supporting sensor unit calculated concentration proportional to the current produced.[2] Two years later, in 1969, the Apollo Guidance Computer safely landed the Apollo 11 spacecraft on the moon. The revolutionary command module controlled the ship's trajectory and velocity as several dozen computers in Houston tracked and communicated with it from Earth. Today, the average smartphone has more computing power than all of the Apollo spacecraft combined.[3] Developments in technology over the last several decades have not only revolutionized the way we interact with the world, but are changing the way we understand and interact with our own biology.

Contact lenses have historically been used for the correction of refractive error. Approximately 125 million individuals worldwide, more than 30 million of them Americans, wear contact lenses.[4,5] Researchers and engineers from diverse fields are working to embed contact lenses with electronic systems. Using biosensors to measure the contents of tear fluid has become one of the more intriguing applications. One approach uses materials embedded with optically active polymers to indicate the presence of certain molecules.[6] The other method and subject of this work uses integrated electrochemical sensors in lenses to measure the biochemistry of tear fluid. The final goal being the identification and quantification of tear contents for the purpose of diagnosis and management of disease.

This work is intended to provide the health care community with a physiological and technological foundation for understanding the developments being made in the field of electrochemical contact lens biosensors.

DIAGNOSTIC POTENTIAL OF TEAR FLUID

Blood has historically been the principal diagnostic fluid used to examine health and disease. It is responsible for transporting nutrients and waste to and from all of the major tissues in the body. Collecting blood is relatively invasive and in the case of individuals with diabetes, must be done multiple times each day.[7] Tear fluid has been examined as a potential diagnostic fluid for several decades. Advances in diagnostic technology, aided by new sample preparation techniques, have revealed more biological information and complexity in tear fluid than was previously suspected.

Tear fluid is produced by a number of tissue types in the ocular environment and serves many important functions including: protection, lubrication, nutrition source and refractive surface.[8] The three distinguishable layers are lipid (outermost), aqueous (central layer) and mucin (associated with corneal epithelium). The lipid layer is primarily responsible for providing a smooth, airtight barrier that slows the evaporation of aqueous fluid.[9] The aqueous layer carries the bulk of nutrition and enzymatic protection and is made of water (98% by volume), proteins, electrolytes and other small molecules.[10] The mucin layer creates a junction and physical barrier to protect corneal epithelial cells.[11]

Tear Production

The main and accessory lacrimal glands, meibomian glands and conjunctival goblet cells make the majority of tear fluid.[12] Some contents diffuse into tear fluid through the cornea and conjunctiva vessels, as well as after cellular damage.[12] Meibomian glands in the upper and lower tarsal plates of the lids produce a majority of the lipid layer.[13] The long, tubular glands are

apocrine in nature, meaning that portions of their apical epithelial cells are pinched off and rupture into the gland lumen.[9] Meibomian secretion occurs passively as the eyelids are closed and the glands are squeezed by the tarsal plates.[9] There is evidence that a percentage of lipids in tear fluid may come from the conjunctiva, cornea and lacrimal glands.[14] Mucins come in two forms: major gel-forming and membrane-associated. Major gel-forming mucins are produced by goblet cells of conjunctiva, while membrane-associated mucins are expressed by lacrimal gland, corneal and conjunctival epithelial cells.[11]

The main and accessory lacrimal glands produce the majority of aqueous tear fluid.[13] The main lacrimal gland is innervated primarily by parasympathetic fibers and is responsible for reflex, basal and emotional tearing.[9,13] Reflex tearing is stimulated when the conjunctiva or cornea is irritated by chemical, thermal, mechanical or light stimuli.[9] The main and accessory glands provide the majority of basal tearing, but as much as 25% of basal tear fluid comes from the conjunctiva.[15] The conjunctiva is constantly secreting or absorbing water and ions to maintain optimum physiological conditions.[15]

There have been a number of studies showing a large range in measured basal tear volume, but 5-10μL is an accepted value for healthy individuals.[9] Basal tear secretion rate is measured at roughly 1.2μL/minute or 1.2mL/day, while reflex tearing can increase the rate by 50-100 times.[9,15] When the eyes are closed reflex tearing and turnover rates decrease, while serum protein leakage increases.[12] Tear turnover rate is estimated at 16-40% per minute.[9,17] The majority of fluid is drained into the upper and lower puncta, evaporated or absorbed back into the cornea and conjunctiva.[9] Normal evaporation is estimated at 0.1μL/min, but can jump to 1.7μL/min with a deficient lipid layer.[15] Normal tear thickness has been measured to be roughly

3μm using laser interferometry and measurements taken over time can be used to calculate tear evaporation rates.[16]

Tear Measurement

Tear fluid has historically been difficult to collect and measure because of its small volume. Several collection techniques have been used, including: capillary tubes, Schirmer strips, liquid eye flushing and absorbent materials.[12] Literature shows that the collection technique used and the type of tearing measured have a large influence on the concentration and even presence of certain molecules.[15] For example, glucose concentration is highest when reflex tears are collected after the conjunctiva has been mechanically irritated.[15] Glucose concentration is lowest when non-stimulated basal tear are collected.[15] Capillary tubes are proving to be a reliable and minimally contaminating collection method. Many feel that they should be the standard for future studies.[12]

Several molecular analysis techniques have been used to measure the presence or concentration of target molecules. These include polyacrylamide gel electrophoresis, high performance liquid chromatography, mass spectrometry, PCR, immunoblotting and ELISA.[8,18,19] These methods are often enhanced by additional sample preparation techniques that aim to improve sensitivity and selectivity.[19] New generation mass spectrometers combined with liquid crystal techniques are greatly enhanced precision.[8] Most of the tests commercially available are restrictive to clinical practice due to cost, speed, sample size, and/or false positive/negative reliability.[20]

Biochemical Composition

Tear fluid contains of unique mixture biomolecules, each serving a number of functions. Published research shows that there is great effort underway toward compiling a comprehensive catalog of tear contents and the relation to blood chemistry.

Component	Tear concentration	Blood concentration
Na+	120-165mM	130-145mM
K+	20-42mM	3.5-5mM
Ca2+	0.4-1.1mM	2.0-2.6mM
Mg2+	0.5-0.9mM	0.7-1.1mM
Cl-	118-135mM	95-125mM
HCO3-	20-26mM	24-30mM
Glucose	0.1-0.6mM	4.0-6.0mM
Urea	3.0-6.0mM	3.3-6.5mM
Lactate	2- 5 mM	0.5-0.8mM
Pyruvate	0.05-0.35mM	0.1-0.2mM
Ascorbate	0.008-0.04mM	0.04-0.06mM
Total Protein	~ 7 g/L	~ 70 g/L

Table 1: Comparison of the concentration of biochemical components in tears and blood.[55]

Proteins

Roughly 500 proteins have been identified in tear fluid, most of them being synthesized in the ocular environment.[18] There are four proteins, all excreted by the lacrimal glands, that makeup the vast majority of total protein concentration: lysozyme, lactoferrin, lipocalin and sIgA.[9] Lysozyme alone, having strong gram-positive bacteriolytic properties, is 30-40% of total

proteins.[21] Lactoferrin prevents hydroxyl radicals and makes iron unavailable for bacterial growth.[9,21] Lipocalin is known for having lipid-binding properties and also sequesters iron from bacteria.[9] sIgA is part of the body's defense from HSV, EBV, HIV, adenovirus, Streptococcus epidermidis and Chlamydia trachomatis.[13]

The significant proteins that leach through conjunctival capillaries include albumin (osmotic pressure), IgG (blood-born immunity) and transferrin (iron transport).[21] The lacrimal gland has been shown to secrete several important proteins including: IgM (higher in allergic conjunctivitis), IgE, serotonin, epidermal growth factor, angiotensin, macrophage inflammatory protein and lacritin.[13] Several antimicrobial peptides are expressed from corneal and conjunctival epithelial cells to protect the ocular environment from foreign organisms.[19] The total protein concentration in tear fluid is 6-11mg/mL, compared to 60-80mg/mL for blood.[12,22] It is thought that the production of protein fluctuates with water production in order to keep concentrations steady.[9]

Electrolytes and Metabolites

Electrolytes in tear fluid include sodium, potassium, calcium, magnesium, chloride, phosphate and bicarbonate.[13] Metabolites include amino acids, urea, ascorbate, glucose, and lactate. Around 90 metabolites have been classified and their concentrations can reveal the physiological condition of ocular surface cells.[12] Ascorbate, which comes from the corneas and lacrimal glands, is very important in controlling superoxide radicals on the ocular surface.[24] Free radicals come from cellular metabolism and photochemical reactions.[24]

Using glucose as an example, a concomitant correlation has been measured between tear

and blood glucose levels.[7] Carbohydrate loads, ingested orally, show increased tear glucose concentration with about a 10-minute delay behind blood glucose levels.[23] Tear glucose levels alone have been shown to determine whether a subject is diabetic.[7] Non-diabetic subjects have tear glucose concentrations ranging from 0 to 65mg/dL, while subjects with diabetes mellitus on average have higher levels, reaching 84mg/dL.[15]

Lipids and Mucins

The lipid layer is made of wax esters, cholesterols, phospholipids, triglycerides, free fatty acids, polar lipids, and neutral diesters.[12] Over 150 unique lipids have been identified, most of which come from the meibomian glands. Wax esters and cholesterol esters are responsible for creating the air resistant top layer of tear film.[9] The mucin layer is made of several types of glycoproteins, which are either secreted into the aqueous or associated with cell membranes.[13] Most mucins are made of more than 50% carbohydrates.[9]

Other molecules

Several systemic drugs have been identified in tear fluid including: phenobarbital, carbamazepine, methotrexate, acetaminophen, ampicillin, rifampicin and cytosine arabinose.[9] Their pathways into tear fluid are not fully understood, but lipid soluble drugs are often measured at concentrations similar to serum levels.[9]

Disease States

Biomarkers in tear fluid have been linked to several ocular conditions including

evaporative keratoconjuntivitis sicca, meibomian gland disease, Sjogren syndrome, blepharitis, androgen deficiency and lacrimal gland dysfunction.[8] It is suggested that the balance between oxidative reactions in tear fluid plays a key role in maintaining ocular health.[18] Oxidative stress, which can be measured by the presence of several enzymes and byproducts, has been linked to cataracts, AMD and glaucoma.[24] Superoxide dismutase, one of the major systemic antioxidant enzymes, was found in tear fluid.[24] Lipid peroxidation can also be observed through the marker malondialdehyde (MDA).[24]

Dry eye is known to cause increased inflammation and osmolarity in tear fluid. The concentration of certain meibomian lipids changes significantly in individuals with dry eye.[8] Dry eyes have lower concentrations of carnitine, an important molecule for fatty acid transport.[12] Several immune mediators have been linked to dry eye disease. Higher IL-Ra and IL-8 levels are strongly correlated with corneal inflammation and epithelial defect staining.[25] Some biomarkers have been identified that might be used to indicate the extent of ocular rosacea.[8] Free fatty acids, cholesterol and wax ester levels are greatly altered in blepharitis.[12]

Analysis of cytokine and chemokine levels can discriminate between different allergic pathologies.[12] Conditions such as vernal keratoconjuntivitis and atopic keratoconjuntivitis show increased levels of IgE, an antibody that signals mast cells to release histamine.[12] VKC shows up to 130 times higher Eosinophil Cationic Protein (ECP) concentrations, while MMP-1 and MMP-9 greatly increase as well.[12] Keratoconus displays elevated levels of IL-6, TNF-a, MMP-1 and MMP-9.[12] The ratio of lysozyme to IgA increases in thyroid eye disease.[8]

In non-proliferative diabetic retinopathy, T-cell Stimulating Protein A (TSPA) decreases, while lysozyme and apolipoprotein AI increase.[8,26] In proliferative diabetic retinopathy, nerve

growth factor (NGF), zinc a2-glycoprotein and lactoferrin increase.[19,26] Lacryglobin, which is associated with cancer of the colon, breasts, prostate, lungs and ovaries, has been found in tear samples.[8] Researchers state that it is possible to identify breast cancer by evaluating tear proteins alone.[12,19]

INTEGRATED BIOSENSOR UNITS

An electrochemical biosensor is defined as a compact analytical unit incorporating a biologically derived recognition component associated with an electrochemical transducer.[2] The components at the heart of contact lens biosensors can be put into 4 categories: biosensing elements, power circuits, communication circuits, and supporting components.

Biosensing, or recognition, components are often biomolecules that mimic parts of living systems.[20,27] They typically include receptors, enzymes, antibodies, nucleic acids and other biologically active proteins.[2,28] Receptors, for example, are embedded into electrically conductive materials whose electrical properties change when target molecules bind.[27,29] A transducer is used to convert the output current into a signal that is interpreted by an external computation device.[30] Biosensing in a simple, homogeneous fluid is relatively easy. When a sensor is placed in a complex solution, such as blood or tear fluid, false receptor binding and saturation of recognition components can significantly skew measured values.[31]

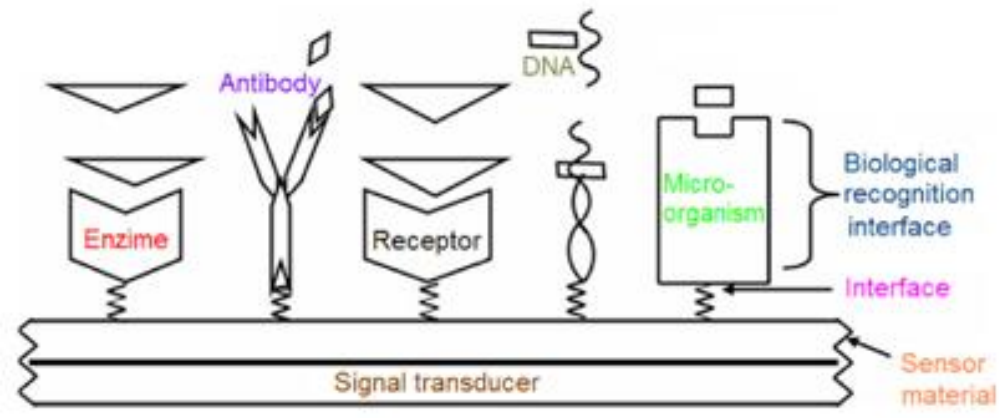


Figure 1: Recognition components of a biosensor.[27]

Emerging Sensor Materials

A revolution in biosensing has been fueled by research and development in the field of nanotechnology. Nanotechnology generally refers to processes or materials that are controllable below the scale of 100 nanometers.[32] The average human hair is around 60,000-80,000 nanometers wide[33]. Using bottom up or atom-by-atom construction techniques allows engineers to design sensor materials with optimum specificity and sensitivity in mind.[20,34] Some of the other benefits include increased surface-to-volume ratio, lower energy consumption and lower long-term costs.[34]

Graphene and its derivatives, carbon nanotubes and nanowires, are the main areas of research being explored for advanced biosensor materials. Graphene is a two-dimensional sheet of carbon atoms bonded together in a hexagonal pattern.[35] Carbon nanotubes are graphene sheets rolled into tube form, while carbon nanowires are solid rods of carbon molecules.[35] Carbon in these forms becomes extremely conductive and energy efficient.[35] Enzymes and antibodies can be embedded into carbon nanomaterial to form incredibly dense biosensor recognition elements.[36] Embedding nanomaterials with DNA, cells, and organelles is also being explored.[36,37] The 'doped' materials act as electrical gates, altering the sensor circuit when target molecules are bound.[27,32] Even though nanomaterials have different electrical properties when compared to conventional materials, signal transduction can be measured in nearly the same way.[27,29] Because of the immensely small size of nanotubes and nanowires, an almost endless combination of detection elements can be integrated into single sensor units.[20] Carbon nanotube films have been demonstrated on soft plastics, showing that flexible soft contact lens applications are possible in the future.[32]

Providing Energy

Current micro sensor units do not require large amounts of energy to operate, due to their small size and periodic operation.[38] Even so, one of the biggest challenges facing engineers in the field of contact lens electronics is energy self-sufficiency while the device is being worn.

The transmission and communication of data consumes a majority of the power in micro-sensor units.[39] In the last 15 years, battery technology has tripled in energy density and many research groups have demonstrated flexible lithium ion platforms.[40,41] Batteries will likely only be needed in early generations of biosensing lenses.[41,42] The power provided is inherently linked to volume and size requirements of contact lenses do not allow significant energy densities.[42]

Energy Harvesting

Energy harvesting at the micro scale has supplemented or replaced batteries in many small devices. The human body and surrounding environment are sources of relatively large amounts of energy, which can be collected and converted into electrical current.[39] For example, heat from the wrist has been used to power watches.[41] Nanomaterials are being used to further optimize and reduce the size of micro harvesting systems even further.[41] The micro harvesting methods being explored include thermal, kinetic, biofuel, solar, and electromagnetic.[41] It is important to keep in mind that current micro harvesting technology doesn't produce the peak currents needed for wireless communication, meaning that early contact lens units might rely on batteries or super-capacitors to operate independently throughout the day.[41] Super-capacitors,

which are solid-state devices, have been proposed as an alternative to batteries for energy storage.[42]

Thermal

Micro-scale thermal harvesters or thermocouples can convert small amounts of thermal energy into electricity.[43] Thermal harvesters are solid-state units that use temperature differences between two unique metals to generate electrical flow.[44] Electrons are naturally propelled from hot to cold and the current produced is proportional to temperature difference, known as the Seebeck coefficient.[44] Thermocouples can be linked in series or parallel to increase power output.[45]

The front of the eye has an average temperature of 32–34°C (~90-93°F) when open and is constantly emitting thermal energy to the environment.[46] A temperature difference of 1.5K (2.7°F) has been shown to produce 300mV, which is enough to power early contact lens prototypes.[43,46] Some thermocouples have been demonstrated as small as 100μm.[43]

Thermal energy has also been used to power individual wireless nodes of electroencephalograms (EEG).[44] The units produce and use power up to a few milliwatts, which is enough to power an electrode and processing unit.[44]

Kinetic

As the eye moves throughout the day, there kinetic energy that can be converted into electrical current using piezoelectric technology.[39] Piezoelectric transducers, getting their name from the Greek word for “pressure”, use special capacitors that deform easily under mechanical

stress.[41] The stress creates a flow of electrons and electrical current is produced.[41] Some units have been demonstrated down to 1mm in size.[41] Nanowires are being researched as piezoelectric transducers, which promise to reduce size and increase efficiency even further.[38]

Biofuel

Biofuel is readily available in the tear film in the form of glucose and ascorbate.[47,48] One example of a micro biofuel cell uses glucose oxidase, similar to the glucose sensors previously discussed, to generate electrons from the breakdown of glucose.[47] The current and voltage produced increase with larger concentrations of glucose.[47] Early examples of glucose harvester use living enzymes which breakdown over time, but have been shown to produce power for up to one month.[38] Glucose can also be abiotically catalyzed with noble metals and activated carbon to reduce enzyme breakdown.[45] Ascorbate is also being explored as a source of biofuel. Early work shows that it can be abiotically oxidized and produce enough power for early prototype glucose-sensing contact lenses.[48]

Solar

Solar cells, also known as photovoltaic cells, create electricity by converting captured photons into electrons. State-of-the-art micro-scale photovoltaic harvesters show almost the same power density as full-scale cells.[41] Outdoor illumination provides more energy than any other micro-harvesting sources, while typical indoor lighting provides 10-100uW/cm^2. [41] For context, 90uW is enough to power a wireless pulse oxymeter sensor.[41]

Solar harvesting efficiency is being improved by artificially reproducing the fundamental steps in photosynthesis. One early example is based on the light-harvesting biomolecules found in phototropic bacteria.[45] Infrared radiation is also being used to power implanted cardiac pacemakers.[45] The devices can be powered for 24 hours after 17 minutes of exposure.[45]

Electromagnetic

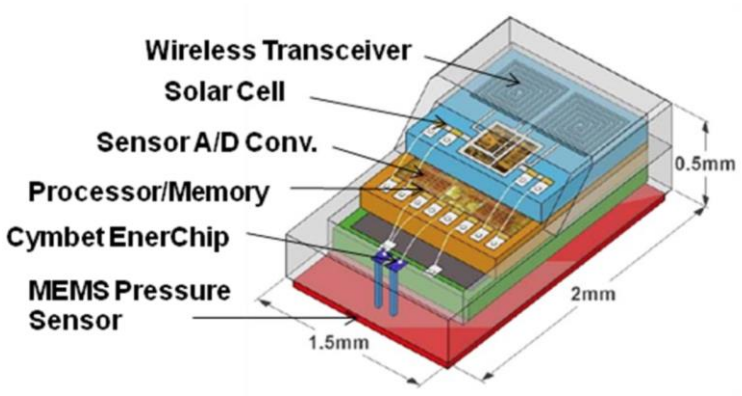
Electromagnetic radiation is all around the modern world in the form of telecommunication devices. Radio frequency waves, also known as RF, can be harvested from the environment and converted into electrical current.[49] While ambient RF energy is quite constant, the density of waves is relatively low and not likely useable for small devices with small antennas.[41] By using dedicated RF sources, harvesting units have been reliably powered at a distance of a few meters.[49] An example unit sends waves at 906MHz with a power of 2-3 watts.[41] A chip in a harvesting unit converts the waves into 15mW of energy at 30cm, with power decreasing significantly as distance increases.[41]

Some implantable devices use near-field inductive coupling for both power transfer and communication.[49] Studies show that short (5 second) exposures to RF do not significantly heat biological tissue, demonstrating that the technology could eventually replace batteries in biomedical applications.[49]

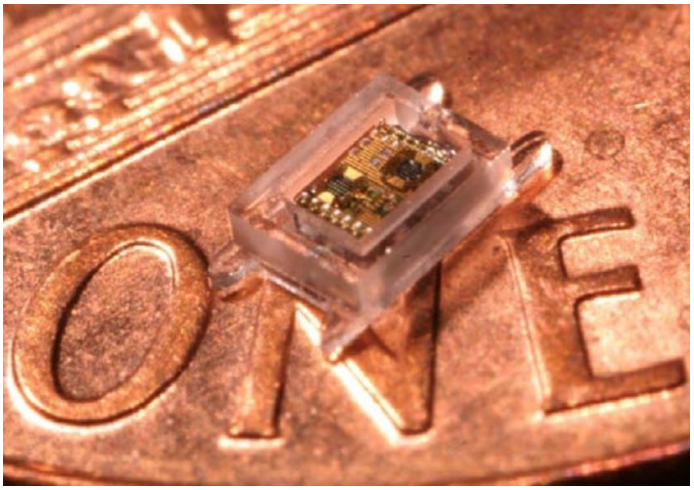
Hybrid

Power and efficiency can be increased dramatically by combining multiple harvester methodologies.[39] Hybrid examples under investigation include piezoelectric/biofuel and

piezoelectric/solar cells.[38,39] Not all harvesting sources produce the same kind (AC vs. DC) and amount of current. Thermoelectric, solar and biofuel cells produce DC current, while piezoelectric and RF cells produce AC current.[41] Power management circuits are required to convert and store energy, while providing steady output for sensing and communication components.[39,41] These chips have been demonstrated to the millimeter scale.[42]



Figures 2: Schematic integrated sensor with solar cell.[56]



Figures 2 and 3: Integrated sensor with solar cell.[56]

Wireless Communication and Integrated Circuits

Wireless micro sensor units currently use radio frequency technology to communicate with external devices.[46] The ocular environment is not covered by thick tissue, so radio communication is relatively unhindered.[46] integrated sensor units have dedicated communication chips to convert electrical current output from sensors into radio waves.[46] The waves sent from the chips deviate from a standard frequency, for example 900MHz, in proportion to current from the sensors.[46] An external receiver analyzes the frequency spectrum and converts the data into concentration values.[46] These communication chips have been constructed and operated on the scale of a few millimeters.[46]

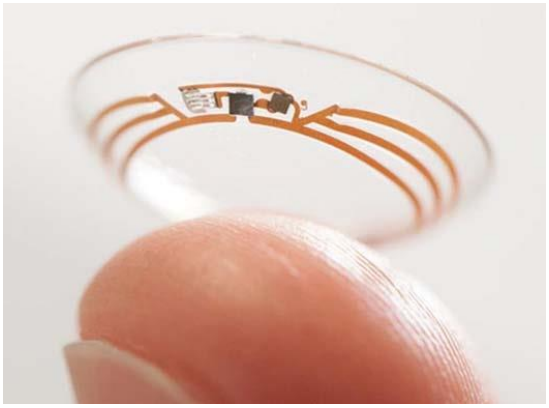
The use of nanomaterials is also being explored to reduce the size and energy consumption of communication chips.[50] Proposed units will continue to use electromagnetic radiation to transmit data, but utilize different frequency bands.[50]

An integrated circuit at the heart of the biosensor unit is required to facilitate information movement between the sensor and communication components. Fully integrated chips have been demonstrated as small as 0.6 mm × 0.6 mm, with a thickness of 200 μm.[46] Large advances in circuit technology are producing circuit hardware with the elasticity of rubber bands.[51] Transparent, flexible electronic circuits are currently being used in many biomedical applications.[52] Carbon nanotubes are being investigated as circuit and transistor materials, promising not only smaller size but also immensely faster electron transfer and computation speed.[50]

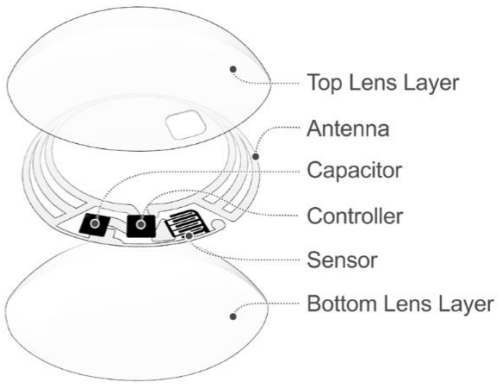
Public Prototypes

There are several academic research groups whose prototyping work is leading to integrated electrochemical contact lenses biosensors. One group in Japan has constructed a biosensor using the glucose oxidase on the surface of a polydimethylsiloxane (PDMS) contact lens.[23] Although it does not yet operate wirelessly, it has been used to measure tear glucose in-situ on a rabbit eye.[23]

The most advanced example comes from a group at the University of Washington. They integrated a wireless glucose sensor unit onto a rigid contact lens platform. The device consists of two differential glucose sensor modules, a sensor read-out circuit, an antenna, a telecommunication circuit, and imbedded interconnects. It has shown linear output in glucose concentrations of 0–2 mM, which covers the normal tear range of 0.1–0.6 mM.[46] The telecommunication circuit receives wireless power from and transmits data to a dedicated external RF unit at a distance of several centimeters.[46] This technology is currently being developed further by Google and Novartis.[57] The physical parameters of modern contact lens materials are being investigated to determine their compatibility with integrated sensor units.[53]



Figures 4: Glucose sensing contact lens prototype designed by Google.[57]



Figures 5: Schematic glucose sensing contact lens prototype designed by Google.[57]

DISCUSSION

There are many challenges that lie ahead for the emerging field of electrochemical contact lens biosensors. One of the biggest tasks will be compiling and normalizing tear fluid data. Future studies should compare the tear compositions of a large number of healthy and unhealthy individuals, as well as differences based on age and gender. For example, the aging lacrimal gland is known to undergo fibrosis, resulting in a change in the quantity and composition of fluid excreted.[9] Studies should adopt universal tear sampling techniques to ensure data is reliable and repeatable. One confounding factor that might prove the above tear data compilation to be difficult is the complex and open nature of the ocular environment. Unlike blood, which is in a closed system, tear fluid is potentially contaminated by whatever environment the eye is exposed to. This can be overcome, but immense precision and calibration will be required.

It will also be important to continue studying how contact lens wear affects the biochemistry in the ocular environment. Mechanical irritation during initial contact lens wear is known to affect basal tear rates and solute concentrations, but values stabilize after periods of adaptation.[15] Some studies have also shown that contact lens wear increases tear evaporation.[25] Biocompatibility is another important topic that needs to be explored. Many researchers have been examining the effects of electrical circuits being in close proximity to biological tissue.[54]

While research and development into fields like nanotechnology are certainly advancing biosensing and microelectronics, progress will likely come in incremental steps. Early examples of contact lens sensors will be relatively rudimentary in the information they provide. Glucose measurement will likely be the first application to reach the clinic. Other early units might

monitor the osmolarity or oxidation balance in the ocular environment. Technology is certainly the limiting factor and open collaboration between researchers and engineers is critical for the field to flourish. As large corporations begin to develop and commercialize these technologies, market potential and return on investment might be the main driving forces going forward.

Tear fluid is a rich and complex substance that contains a wealth of information about both ocular and systemic environments. As understanding of tear physiology expands and technology becomes less of a limiting factor, the conversation going forward should be enhanced by clinicians who fit and prescribe contact lenses. They are uniquely able to understand and interact with the individuals behind the lenses.

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A yearlong fellowship to design and build a prototype biosensor unit measuring mock tear fluid. Data was relayed wirelessly to a tablet computer using open source hardware and software. Collaboration included faculty in Biochemistry, Computer Science, Physics and Business departments.