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FM Continuous Monitoring of Intraocular Pressure, an Engineering Perspective

Adrian E. Rendon-Nava, Alejandro Díaz-Méndez and Luis Nino-de-Rivera

Abstract

This chapter discusses the problem of continuously monitoring intraocular pressure (IOP) from an engineering perspective. It is aimed to all public in general although we think that medical staff and engineers may benefit the most from it. Although equations are included for engineers to get a glimpse of how the system works, this chapter does not go into great detail in mathematics and physics to make it understandable to medical staff. It provides though references for engineers who wish to get a better understanding of key subjects tackled in this chapter. The chapter is organized as follows: Section 1 introduces intraocular pressure (IOP) and need for its continuous monitoring. Section 2 describes the most recent efforts to develop a continuous IOP monitoring system. Section 3 shows what medical and engineering considerations must be taken into account to effectively measure IOP. Section 4 deals with health issues due to tissue warming and how to prevent them. Section 5 explains how an implant can be fabricated using either passive electronic components or active ones. Finally, Section 6 explains how the pressure sensor and the electronic circuits can be integrated.

Keywords: biomedical implants, IOP monitoring, magnetic coupling, wireless coupling, wireless power transmission

1. Introduction

Before we can begin to talk about intraocular pressure (IOP) continuous monitoring, let us have a look at some key facts according to the World Health Organization (WHO) [1]:

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There are 285 million people estimated to be visually impaired worldwide, of which 246 million have low vision.

About 90% of the visually impaired people globally live in low-income environments.

Eighty per cent of all visual impairment can be prevented or cured.

Among the three major causes globally that cause visual impairment is glaucoma. Glaucoma can be understood as a group of ocular diseases mainly associated with a rise in intraocular pressure. All these groups of diseases have in common the progressive injury to the optic nerve [2]. If glaucoma is left untreated, it can cause total blindness.

The problem with diseases such as glaucoma is that they present no symptoms, so trying to diagnose it without previously measuring the IOP becomes a real challenge. Actual methods for IOP measurement involve the use of medical equipment called tonometers. Tonometers measure IOP over the cornea but in some cases, where the hardness of the cornea is above normal standards, important measurement errors can be produced which do not allow a correct IOP estimation.

There are nowadays other indirect methods that have been under research in the last years such as multifocal electroretinography to know the effects of IOP rising [3]. Nevertheless, with available tonometry and electroretinography techniques, it is not possible to take measurements during normal activities of the patient such as the sleep cycle, stage where IOP can be increased in a significant manner. In order to take an IOP measurement with tonometry or multifocal electroretinography methods, the measurement must be taken by qualified personnel which implies that the patient has to be in the hospital facilities.

The development of sensors with the capacity of measuring IOP inside the eyeball is of paramount importance in order to know with all precision not only intraocular pressure values but also IOP variations in daily activities of the patients.

A new measurement instrument is needed that allows medical staff to study the aetiology of diseases such as glaucoma, that is, to provide with a new tool which will enable to know if there is a cause-effect relationship between daily activities of patients and IOP variations in real time.

Fortunately, we are at a point where technology has evolved in such a way that biomedical implants wirelessly powered are now a reality.

2. State of the art

There have been many efforts in different parts of the world over time to build an IOP monitoring system. In this section, we only present a few researches to give the reader a broad idea of what has been done in terms of IOP monitoring systems but references [4–8] are included in case the reader wants to know more about researches not mentioned in this chapter.
Between the first researches carried out, there is the one done by Tufte et al. when in 1962 in Honeywell, they developed piezoresistive sensors with silicon membranes [9].

In 2000, Mokwa, Schnakenberg and collaborators proposed the design and fabrication of an implantable intraocular system for continuous IOP measurement through OPHTAL project [10]. The system consisted of a pressure sensor connected to the integrated circuits altogether in an artificial contact lens. Three prototypes were fabricated. The last one is shown in Figure 1.

![Third pressure sensor prototype.](image1)

Humayun and collaborators proposed in 2008 a prototype sensor to measure IOP [11]. Two sensor designs were fabricated, one with a variable capacitor and the other one with a variable capacitor and a variable inductor (Figure 2).

The pressure sensor response showed a high sensitivity (>7000 ppm/mmHg) in both designs, confirming a resolution of less than 1 mmHg for biomedical applications. The authors also conducted a 6-month study in animals to verify the implant bio-stability in vivo and no surgical or post-operation complications were found.
In 2011, Melki and collaborators published a study with the purpose of determining the biocompatibility of an IOP sensor in rabbits and comparing IOP measurements from the sensor with other IOP sensor devices [12]. Figure 3 shows the photograph of the sensor encapsulated in a silicon rubber.

The intraocular sensor was implanted in six New Zealand white rabbits. The upper part of the sensor contains the Application-Specific Integrated Circuit (ASIC). The external diameter of the coil was of 11.3 mm, the inner diameter was of 7 mm and the thickness was of 0.9 mm.
The animals were observed and examined in intervals of up to 25 months after surgery. From the obtained results, it was found that the sensor had acceptable tolerance by the eye of the rabbit since no evidence of significant inflammation or scar formation was observed in *in vivo* tests. The measurements made with pneumotonometry, tonometry and with the sensor resulted in standard deviations of 2.70, 3.35 and 0.81 mmHg, respectively.

3. Merging medicine and engineering

As seen in the previous section, all efforts to build a continuous IOP monitoring system proposed a wireless power transmission method. This obeys to the fact that having a battery inside the eye to power the biomedical implant can be both bulky and most importantly health threatening to the patient due to the hazardous chemicals it contains.

If we are to develop a continuous IOP monitoring system, we need to approach the problem with a multidisciplinary focus.

3.1. Medical considerations

The human eyeball measures approximately 2.5 cm in diameter so there is a restriction in terms of the maximum area that the implant can have to be successfully implanted in the patient. Among medical factors that come into play for implanting a continuous IOP monitoring system are the following:

- The location of the implant must not interfere with the vision and movement of the eye.
- Surgery should be as less invasive as possible.
- Implant design must be such that it allows the physician to implant the monitoring system in the shortest time possible.

3.1.1. Electromagnetic radiation

At frequencies between 10 MHz and 30 GHz, organic tissue warming is the major effect in electromagnetic energy absorption and temperature increases of more than 1 or 2°C can have adverse health effects [13].

A great number of physiological effects have been observed in cellular studies and with animals when electromagnetic energy is absorbed in levels that cause an increment in body temperature of more than 1 or 2°C [14]. These effects include alterations in neural and neuromuscular functions, increased permeability of the blood-brain barrier, ocular damage, changes in the immune system associated with stress, haematological changes, reproductive changes and changes in cell morphology.

Experimental data available indicate that human exposition in a resting position to electromagnetic fields for 30 min, which produce a specific absorption rate (SAR) in the whole body of 1–4 W kg⁻¹, will result in an increase of temperature of less than 1°C. Exposition to electro-
magnetic fields more intense producing SAR values of more than 4 W kg\(^{-1}\) may overwhelm the thermoregulatory capacity of the body and produce warming tissue harmful levels. Table 1 shows basic restrictions for exposure to time-varying electric and magnetic fields for frequencies up to 10 GHz.

<table>
<thead>
<tr>
<th>Nature of the exposition</th>
<th>Frequency range</th>
<th>Current density for head and trunk (mA·m(^{-2}) (rms))</th>
<th>SAR average for the whole body (W·kg(^{-1}))</th>
<th>Localized SAR (head and trunk) (W·kg(^{-1}))</th>
<th>Localized SAR (limbs) (W·kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational exposure</td>
<td>Up to 1 Hz</td>
<td>40</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1–4 Hz</td>
<td>40/f</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>4 Hz to 1 kHz</td>
<td>10</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1–100 kHz</td>
<td>f/100</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>100 kHz to 10 MHz</td>
<td>f/100</td>
<td>0.4</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>10 MHz to 10 GHz</td>
<td>--</td>
<td>0.4</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>General public exposure</td>
<td>Up to 1 Hz</td>
<td>8</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1–4 Hz</td>
<td>8/f</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>4 Hz to 1 kHz</td>
<td>2</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1–100 kHz</td>
<td>f/500</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>100 kHz to 10 MHz</td>
<td>f/500</td>
<td>0.08</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>10 MHz to 10 GHz</td>
<td>--</td>
<td>0.08</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Basic restrictions for time-varying electric and magnetic fields exposition for frequencies up to 10 GHz.

3.2. Engineering considerations

Regarding technological restrictions for the localization of the implant, we can find the following:

- The implant must have the maximum area possible.
- The implant should be placed as near as possible from the exterior of the body.

Both of the previous considerations are based on the fact that the implant needs to maximize power transfer and magnetic coupling.

IOP measurement requires the size of the implant not to be so large neither so bulky so it can be implanted into the eye of the patient without causing any discomfort. This is the reason why several IOP monitoring systems are based on radiofrequency identification (RFID) technology [15].

Given that power consumption is a key factor in IOP monitoring system design, we may classify electronic implants based on their power consumption briefly as described below.
3.2.1. Active electronic implant

An active electronic implant will have active electronic components such as diodes and transistors. By using active electronic components, there is the drawback of higher power consumption. On the other hand, by using transistors and diodes the electronic implant would have the advantage of having more precise and reliable pressure measurements.

3.2.2. Passive electronic implant

The passive option consists of having pure passive electronic components (resistors, capacitors and inductors). The main advantage of this proposal is that power demand would be much lower than its active counterpart so a possible health risk in the patient due to tissue warming is greatly reduced.

Both types of implants will be discussed in more detail in Section 5.

4. Health issues due to tissue warming

A vital requirement when designing electronic implants is to limit temperature increment of the implant in order to prevent damaging organic tissue. In general, temperature variation in a body can be described by a partial differential equation of heat conduction which expresses the variation in the temperature of a body with respect of time, but in order for this equation to be used in human tissue, Pennes incorporated a few extra terms into the partial differential heat conduction equation to describe the warming effect of basal metabolism and the influence of blood in temperature regulation of tissue [16]. Pennes bio-heat equation can be written as follows:

\[
C \rho \frac{dT}{dt} = \nabla \cdot (K \nabla T) + A - B(T - T_b)
\]

where \(A\) is the heat production rate due to metabolic processes per volume unit, \(B\) is the perfusion constant and \(T_b\) is the blood temperature (it is assumed as a constant at \(T_b = 37^\circ\text{C}\)).

The bio-heat equation may be applied to human tissue without any external sources of heat. For our case of study, however, the temperature increase in human tissue is also caused by power dissipation of the electronic implant and by electromagnetic radiation coming from the external device that will be supplying wireless power to the implant.

4.1. Joule heating

When considering an electronic implant inside the human body, power dissipation by electronic circuitry has to be considered. Assuming that heat dissipation per volume unit of an implant is \(P_i\) this can be incorporated in the bio-heat equation as a source of heat and is expressed as
\[ P_i = V_i \cdot I_i \] (2)

where \( V_i \) is the biasing voltage of the electronic circuitry and \( I_i \) is the total electric current circulating through the implant.

### 4.2. Electromagnetic energy contribution

If a biological tissue is exposed to electromagnetic radiation, the electric field \( E \) and the magnetic field \( H \) penetrate the tissue causing it to warm up due to electromagnetic deposit. On the other hand, SAR is the specific absorption rate and it is defined as the differential with respect of time, of the increment of dissipated energy by a material. The SAR is related with the magnitude of the electric field \( |E| \) so, once we know the electric field distribution in the tissue, we can obtain the SAR from which we can obtain the generated heat per volume unit per time unit to include the term to the bio-heat equation.

In order to have a complete bio-heat equation, we need to include Joule heating and electromagnetic energy contribution. The complete bio-heat equation can be expressed as

\[
C_p \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) + A - B(T - T_b) + \rho \text{SAR} + P_i
\]

(3)

Eq. (3) needs to be solved for each particular case of study to know how many degrees of temperature will the tissue increase caused by the implant. For the graphic shown in Figure 4, Eq. (3) was solved using Matlab software. Figure 4 shows a graphic of how an electronic implant heats the tissue of the sclera when exposed to an electromagnetic energy radiation and joule heating. Details of the implant design and characteristics are shown in Table 2.

![Figure 4](image_url)

*Figure 4. Warming graphic of the sclera. Exposition time: 60 s.*
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of turns</td>
<td>18</td>
</tr>
<tr>
<td>Metal thickness</td>
<td>0.035 mm</td>
</tr>
<tr>
<td>Inner radius</td>
<td>1 mm</td>
</tr>
<tr>
<td>Outer radius</td>
<td>10 mm</td>
</tr>
<tr>
<td>Width of metal tracks</td>
<td>0.25 mm</td>
</tr>
<tr>
<td>Distance between tracks</td>
<td>0.25 mm</td>
</tr>
<tr>
<td>Resistance</td>
<td>150 Ω</td>
</tr>
<tr>
<td>Inductance</td>
<td>7.84 µH</td>
</tr>
<tr>
<td>Quality factor (Q)</td>
<td>3.28</td>
</tr>
</tbody>
</table>

Table 2. Proposed electrical parameters for the simulated reader coil.

5. Implant fabrication with passive and active electronic circuits

As stated in Section 3, we can classify electronic implants based on the nature of their components. Next, we describe both options.

5.1. Passive RLC implant

For this kind of approach, an Resistive Inductive Capacitive (RLC) passive circuit is proposed as an IOP sensor like the one shown in Figure 5. The capacitor would be a variable capacitor, sensitive to variations in pressure.

![Electric diagram of the circuit proposed as an IOP sensor.](image)
The resonance frequency of the RLC circuit shown in Figure 5 is given by Eq. (4) where we can note that if the value of capacitance varies, the resonance frequency of the circuit will change too.

\[ f = \frac{1}{2\pi\sqrt{L_s C_s}} \]  

(4)

From electromagnetic theory, we know that if we place two inductors close enough and we make a time-varying electric current circulate through one of the coils, it will induce a voltage in the other coil. This is the principle by which wireless energy transfer is done. Figure 6 shows a Maxwell-Wien circuit which could act as the external device in charge of both delivering power to the implant and reading data from it.

![Figure 6. Maxwell-Wien bridge circuit coupled with the coil from the implant.](image)

The implant is shown inside the dotted lines. If the RLC circuit in the implant formed by \( R_s \), \( L_s \) and \( C_s \) is placed near the inductor \( L_x \), a magnetic coupling will be created. By being \( L_s \) and \( L_x \) coupled, a change in the capacitance of \( C_s \) will change the value of the resonance frequency of the RLC circuit of the sensor which will in turn modify the impedance of \( L_x \) coil.

Eq. (5) shows how the impedance of the external device coil will vary by being coupled with the coil of the implant [17].
where $f$ is the resonance frequency of the external device, $k$ is the coupling factor between both coils, $Q$ is given by

$$Q = \frac{2\pi f_0 L_s}{R_s}$$

(6)

And $f_0$ is the resonance frequency of the implant described previously in Eq. (4).

The main disadvantage for this approach is the lack of precision and accuracy in the measurements. If we were to obtain precise and accurate measurements with a very small error, then both coils would have to be at the exact same place each time a measurement is to be taken. We could assume that the implant is always fixed so in order to make this kind of approach to work properly, the system design must be done to ensure that the coils will remain in the same position for each measurement and no misalignment will occur.

Another important issue to be noted is the transmission medium between coils. So far, we have considered air as the transmission medium between coils. Much more realistic calculations and simulations may be performed if organic tissue is considered as the transmission medium [18].

5.2. Electronic implant using transistors

Designing an electronic implant using transistors needs special care since they require a much larger amount of power compared to passive RLC implants. Electronic circuit design must be done in such a way that warming of the tissue does not exceed 1°C to avoid organic tissue damage. Tissue warming is the main disadvantage of designing electronic implants using transistors. On the other hand, they are very precise and accurate since measurements depend only on having enough power available in the implant rather than if the coils are misaligned or not.

The active electronic circuit for the implant can be divided into three sub-modules, which are reviewed below.

5.2.1. Rectifier and regulator circuit

As mentioned in Section 5.1, a time-varying electric current circulating through one coil will induce a time-varying voltage in the other coil. Biasing in electronic circuits, however, requires...
a direct current (DC) voltage so that is when the rectifier and the regulator circuits come into play.

5.2.1.1. Rectifier circuit

A rectifier circuit changes an alternating current into a direct current. It has a small error though, since at the output the voltage has a little ripple. Figure 7 shows a full-wave rectifier with P-type metal-oxide semiconductor (PMOS) transistors.

![Figure 7. PMOS rectifier circuit.](image)

5.2.1.2. Regulator circuit

To get rid of the small ripple at the output of the rectifier, a regulator circuit is often added. The aim of the regulator is to deliver a stable power supply voltage for proper operation of the rest of the circuits in the implant. It has a minimum voltage needed at the input below which it will not deliver a constant voltage. If the input voltage is, on the other hand, greater than the minimum, then the regulator will output a constant voltage. This is the circuit responsible for making active electronic implants independent of coils distance. If the distance between coils is enough for the regulator to provide an output, it will provide a steady voltage regardless of how close the coils are. If on the contrary, the distance between coils is not close enough, then the voltage regulator simply will not provide any voltage at all. Figure 8 depicts a Complementary Metal-Oxide Semiconductor (CMOS) topology for a voltage regulator circuit.
5.2.2. Signal-conditioning circuit

Once we have a stable DC voltage, we can move on to the next sub-module of the implant. If the sensor is in charge of transforming an analogue physical signal into an electric variable, the signal-conditioning circuit has the task of taking the analogue electric signal and manipulate it in such a way that it meets the requirements for the next stage in the system. For our case, the next stage would be the transmission circuit.

Figure 8. Topology of a voltage regulator. Taken with permission from [19].

Figure 9. Cross-coupled LC VCO topology.

There are many electric circuit designs that can be used as a signal-conditioning circuit. Here, we take a brief look at a voltage-controlled oscillator (VCO) [20]. As seen in Section 2, most
pressure sensors are variable capacitors which change their value of capacitance according to a change in pressure. On the other hand, a VCO is an oscillator with an oscillating frequency that depends on the value of its capacitor. If we connect the pressure sensor with the VCO, then we would have a signal-conditioning circuit for IOP monitoring. In Figure 9, a cross-coupled LC VCO topology is shown.

5.2.3. Transmission circuit

The transmission circuit sub-module takes the conditioned signal and transmits it back to the external device. A power amplifier (PA) circuit can achieve the latter. Since we are discussing circuits for an electronic implant, it would be desirable to have a low-power amplifier to deal with the transmission. There are many PAs from where we can choose; there are linear amplifiers (Classes A, B and AB) or switched-mode amplifiers (Classes E and F). In Figure 10, a class E PA is shown. Switched-mode amplifiers have a higher efficiency than linear ones (50–70% in the case of linear vs. a theoretical 100% in switched-mode amplifiers). Chapter 5 in [21] has a deeper explanation in power amplifiers for biomedical implants.

![Class E power amplifier](image)

Figure 10. Class E power amplifier. Taken with permission from [22].

6. Sensor and circuit integration

At this point, the reader may ask: Why do we even need this section since at present, sensors and electronic circuits can be fabricated on the same substrate? And the answer is: Because it depends on what type of application we want to develop.

It is true that nowadays it is possible to fabricate sensors and circuits in the same substrate. The inconvenience with actual fabrication processes is that they use a rigid silicon wafer as a substrate. For many applications, this is enough, but for biomedical applications this approach is not useful. That is why in Section 2 all proposals that have active circuits in their designs (such as the one shown in Figure 3) tend to divide the fabrication process of the implant.
one hand, they fabricate the coil in a flexible substrate such as parylene, silicone rubber or polyimide so the implant can adapt to the curved surface of the eye. On the other hand, all electronic circuitry and in general all IOP sensors too are fabricated in a rigid silicon wafer. The final step involves connecting the coil with the sensor and the electronic circuits.

The main drawback from this approach is the potential damage that the silicon wafer can cause to the tissue of the eye. Fortunately, there has been a significant advance in terms of electronic circuit fabrication on a flexible substrate. In Figure 11, an electronic circuit fabrication process with Carbon Nanotubes (CNT) on a flexible substrate and photographs of the final chip are shown.

![Figure 11](image-url)

**Figure 11.** Circuit fabrication process on a flexible substrate. (a) Fabrication process of flexible InGaZnO-CNT CMOS logic circuits. Photographs of flexible CMOS circuits under (b) bending by hand and (c) rolling over a glass bar (~2.6-mm radius). (d) Atomic Force Microscopy (AFM) image of CNT network film for p-type thin-film Transistors (TFT). (e) FEM simulation plot modelling the strain distribution in the InGaZnO channel region under bending ($r = 2.6$ mm). Taken with permission from [23].

7. Summary

In this chapter, we presented an overview of how an electronic implant can be designed. We showed what has been done in this area over the years and we pointed to a major medical concern that is tissue warming when it comes to implanting the IOP sensor into a patient.
From an engineering perspective and despite the tremendous advance that has been made in this area, there are still key issues that must be tackled in the years to come such as power efficiency in wireless power transfer. Another aspect, not less important, is the possibility to have electronic circuits fabricated in the same flexible substrate along with the pressure sensor. This is an area of recent creation that has though an immense growth potential. Microelectronic devices fabricated in a flexible substrate can have applications not only in intraocular pressure monitoring but in many other biomedical applications. And these circuits can not only have biomedical applications demand but also in other numerous engineering fields such as energy harvesting, domotics and wearable technology (clothing and accessories).

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