Inductively Powered Implant for Monitoring and Application of Telemetric Metronomic Photodynamic Therapy

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***Abstract*— Photodynamic therapy (PDT) is an emerging treatment for numerous types of cancer. The main advantages of PDT compared to radiotherapy are its potential selectivity and the fact that it does not produce cumulative damage to tissue. Currently, light delivery and monitoring are normally achieved by mean of optical fibres. In this paper we describe ongoing work on a telemetric PDT delivery and monitoring system. By using implantable PDT instrumentation in place of fibres, long-term treatment while targeting organs deep inside the body becomes possible. The system reported is meant for experiments in small size laboratory animals. It consists of three main parts: the optodes, which deliver and monitor the treatment; a central unit, which communicates with the outside and manages the available power; and a base station, which acts as an interface between the implant and the operator. The optode consists of a chip-form light source and photodiodes, integrated in a single silicon die. This paper presents the details of the optode design and fabrication. First measurements characterising the devices have been performed are they are presented and discussed.**

***Index Terms*— Photodynamic Therapy, Inductive Transcutaneous Link, Microfabricated Optodes**

I. Introduction

PHOTODYNAMIC therapy (PDT) is an emerging treatment for numerous cancers in the head and neck, bile duct, bladder, esophagus bladder and in the skin. It has also been developed for a range of non-malignant conditions such as psoriasis and atherosclerosis [1]. The principle of PDT is as follows. The patient receives a dose of photosensitiser that localizes at the tumor because of its selective uptake by cancerous tissue. When the photosensitiser is irradiated with light of the appropriate wavelength in the presence of oxygen it produces singlet oxygen. This leads to the destruction of tumoral tissue in the following ways: by direct damage to the tumor, by the destruction of the vasculature of the tumor, by activation of the immune system or by a combination of the three [2].

The main advantage of PDT compared to radiotherapy is its selectivity. The tumor has selective uptake for the photosensitiser and the light can be targeted to a specific volume. The complexity of the biological mechanisms by which oxygen, photosensitiser and light lead to the destruction of cancer cells makes the dosimetry of PDT very difficult. In order to successfully determine the actual PDT dose, monitoring the three parameters of the treatment is essential.

Until now, PDT has used external photonic instrumentation. In most cases, sources and detectors are coupled to optical fibres, used in this way both to measure and to deliver light. One can imagine that this instrumentation is bulky and inconvenient, especially if several treatment sessions are necessary, or if the volume of interest is not readily accessible. This is the case for metronomic PDT, where the patient receives several times a much smaller dose instead of one large dose in a single session [3]. Metronomic PDT has the advantage that less healthy tissue is damaged.

A telemetric light source will be very useful for this purpose. Advantages of PDT with an implant versus fibres are that the implant can stay in the body for long-term treatment and that it can be used for organs deep in the body.

A. Requirements for the system

The main purpose of the system is the delivery of light to a specific volume of tissue. The light source should be controlled from outside the body. The number of sources should be moderately large, in this way the targeted volume can be illuminated in a controllable and well-defined manner. The secondary application is monitoring the treatment. This consists of monitoring the fluence rate, the level of photosensitiser and the oxygen level. This data has to be available for the physician supervising the treatment.

The system is meant for long term operation, meaning more than 6 months, thus battery operation is not desirable and the implant should be externally powered. Furthermore, the implant should be packaged in a biocompatible way. The system should be modular in a way that is can be adapted to different types of PDT and different volumes.

The system consist of three main parts, the optodes which deliver and monitor the treatment, a central unit which communicates and manages the power and a base station which acts as an interface between the system and the operator at the outside. This paper describes the development of the optode device.

II. Methods

Fig. 1 shows a schematic diagram of the full telemetric system. Two main elements are visible in the proposed concept, namely the external unit and the implant. The external unit should take care of inductively powering the implant and communicating with it. The implant includes communication electronics to exchange data digitally with the external unit and a digital control unit. This unit is in charge of multiple optodes, which are combinations of light sources and detectors with suitable signal conditioning and readout electronics. The telemetry units are currently being developed, while in this paper we will focus on the design and fabrication of the optodes.

The optodes have two main functions: to activate the photosensitiser and to monitor the treatment. In order to fulfil their first task, the optodes need to deliver a controllable amount of

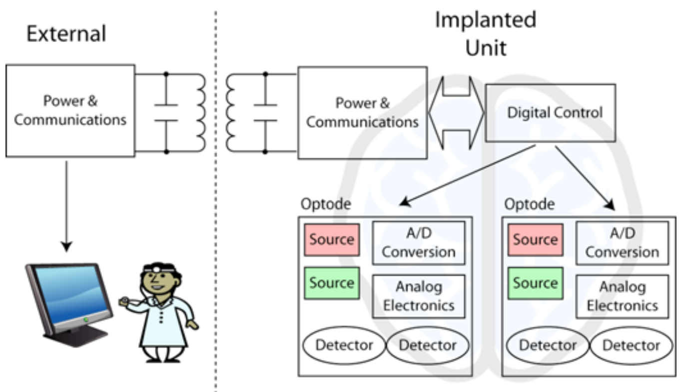

Fig. 1. Impression of the telemetric PDT system

light in the activation wavelength region of the photosensitiser. This is achieved with Light Emiting Diodes (LEDs). These are available in a large variety of wavelengths, can the deliver an optical power of around 5mW, can be obtained in chip form, and are moderately power efficient light sources.

As stated earlier, three ingredients are necessary for PDT: light, photosensitiser and oxygen. These have to be monitored. The first quantity can be estimated from the fluence rate. The reflected fluence can be easily measured by a set of photo detectors. The radiated fluence is known, and by fitting a model of light propagation in tissue, an estimation can be made on the fluence rate absorbed by the tissue.

The second quantity is the amount of photosensitiser. A property of many photosensitisers of interest is that they are fluorescent. This means that the photosensitiser can be promoted by photons with a specific wavelength to an excited state, and after a certain amount of time it will fall back to its ground state, radiating a photon. These radiated photons are an indication of the amount of photosensitiser and can easily be measured by a photo detector after the source is switched off. A drawback of this is that the surrounding tissue will influence the measurement.

The last quantity is the oxygen level. This parameter is the most difficult to measure. Differential Pathlength Spectroscopy (DPS) has been developed to this end by Amelink et al.[4]. This method uses the difference in spectrum of two fibers. One of the fibers delivers white light and detects the reflected spectrum, the other one detects only the reflected spectrum. By combining the information coming from both spectra, we can isolate the properties of the volume just before the first fibre. From the optical properties of this region an indication of oxygen level can be calculated [4].

For implementation of DPS a rather large amount of sources is needed. Several sources with a very small bandwidth (1 to 2 nm) might be used, but this poses important integration challenge. Quantum dots could be used to achieve this by producing different wavelengths at the same time, especially when combined with filters on the detector. Another option is to place a fluorescent dye on the optode which can be activated by a LED and which radiates a broad-band spectrum. With this last option a spectral detector is also needed.

A schematic view of a possible optode is given in figure 2. In this paper we present a first optode design, in which the electronics are not yet integrated. The optode is made of a silicon wafer as a carrier for the LEDs and as a substrate for the photodiodes. Four different types are made with different configurations on the amount of LEDs and photodiodes. The photodiode was designed using the DIMES 02 bipolar process. In order to dimension the photodiode, several steps have been taken. In the first place, an estimation on how much optical power would be available at the photodiode was calculated. The light distribution generated by a 5mW light source was simulated using Monte Carlo software [5]. This type of

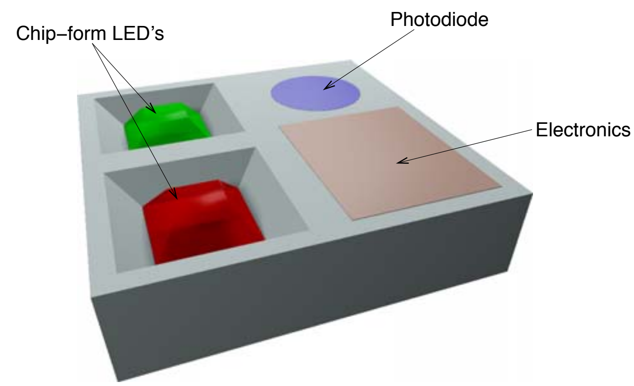

Fig. 2. Impression of the optode

software computes an approximation of the Radiative Transfer Equation (RTE) by tracking the paths of a large number of photons.

The photodiode was constructed with the junction between the p-substrate and an N-epi layer. The contacts were made with a deep P implantation, a highly doped P implantation and a highly doped N implantation. To determine a good size for the photodiodes the expression for the photocurrent (I_{photo}) was used (equation 1).

$$I_{photo} = qA\frac{P_{photo}\lambda}{hc}\eta \qquad (1)$$

In this equation, $q=1.602\ 10^{-19}\ C$ is the charge of the electron, A is the area of the photodiode, P_{photo} is the optical power incident per unit of area, λ is the wavelength of the incident light, $h=6.626\ 10^{-34}\ J\cdot s$ is Planck's constant, η is the quantum efficiency of the device and $c=2.998\ 10^{8}\ m/s$ is the speed of light in vacuum.

The expected quantum efficiency was estimated and the results of the simulation were used to get an indication of the photocurrent for several sizes of the photodiode. A photodiode of 160*160 um was chosen. After these considerations the spectral response of the photodiode was determined by calculating the space charge width using equation 2 and the parameters from DIMES 02 [6].

$$W = \left(\frac{2\in_s\left(V_{bi}+V_R\right)}{e}\left[\frac{N_a+N_d}{N_aN_d}\right]\right)^{1/2} \qquad (2)$$

In this equation, W corresponds to the width of the space-charge region, V_{bi} is the built in potential of the diode, $e=1.602\ 10^{-19}\ C$ is the charge of the electron, V_R is the reverse voltage applied to the diode, N_a is the concentration of acceptor impurities in the p-side and N_d is the concentration of donor impurities in the n-side of the junction.

With this result and the absorption coefficients of silicon from Green et al [7] the photocurrent due to absorption within the depletion region is calculated. There are several photodiodes on the wafer with spacings from the source ranging from 300μm to 1200μm can be measured enabling DPS measurements. All the diodes have the same dimensions.

For the sources LEDs are integrated on the optode. LEDs are not manufactured on the substrate because silicon is not a suitable material in this wavelength range. We chose to use LED chips, which are available in the small sizes (<300μm) and wavelengths (500-670nm) that we require.

These chips have a bottom and a front contact. We decided to put the LED in a hole covered with metal. This ensures that no direct light will be delivered to the photodiodes and provides the LED with a back contact. This back-contact is fixed to the LED's contact pad with a conductive glue. The front contact will be connected with a bond wire and passivated using a biocompatible polymer.

The hole is made by means of the following processing steps. First the rest of the wafer is passivated using Silicon Nitride. After that the wafer is patterned and the holes are etched in TMAH. The walls of the pits resulting from the etching in the TMAH bath are tilted with 54.7 degrees, thus the holes in the corresponding mask are 640μm×640μm to get the desired space to mount the LEDs. After this step the second metal is deposited using lift off. With lift off a larger variety of metals can be used, which is useful for the through wafer contacts.

The LED's are mounted by hand. Because the mounting of the LED is done after processing in the clean-room, it is possible to install different LED's on different substrates, which gives flexibility in choosing the photosensitiser and the measurement setup. An optode can for example be equipped with a LED with a short wavelength, which is capable of exciting the fluorescence of the photosensitiser in order to measure its concentration. Another option is just to equip it with a LED for activating the photosensitiser.

A flexible backplane will connect the optodes with the rest of the instrumentation. The contacts from the optode are ideally made using through wafer interconnects and conductive glue. The top metal will be a layer of TiN and Al. From the back of the wafer a hole is etched using RIE, stopping on the metal. After that, copper is grown from the TiN seed layer. This technique is still experimental; therefore, also bond pads are made on the front side of the wafer. In this way the device can be used separately of the through-wafer interconnect technology. The bond wires needed in that case will need to be passivated by means of a biocompatible polymer.

III. RESULTS

A Monte Carlo simulation has been made to determine how much optical power is available at different distances from a 5 mW source. The simulation used the input parameters given in table 1. These are parameters which are characteristic of brain tissue. The reflection of a 5mW source at several distances from the source are simulated with different thickness of a transparent layer between the optode and the brain tissue, simulating the effect of a passivation or packaging layer. The results are plotted in figure 3. We see that the effect of a transparent layer has a significant effect on the distribution of light within tissue.

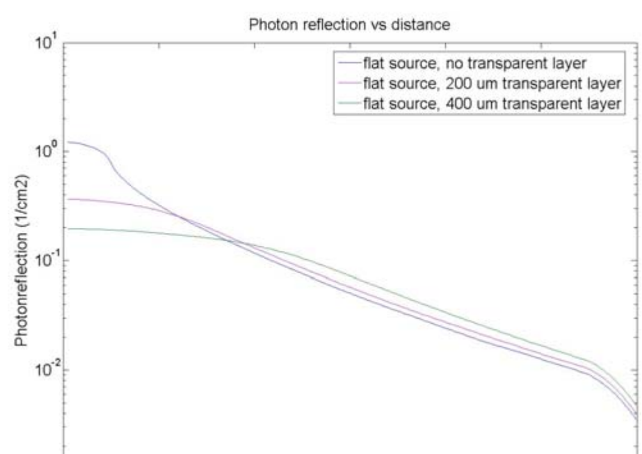

Fig. 3. Photon reflection versus distance from source.

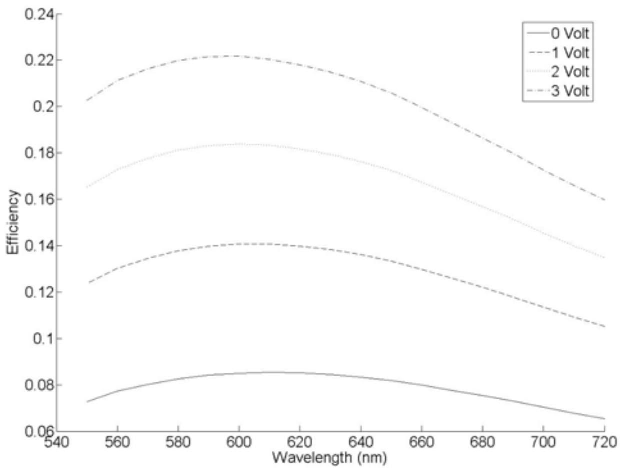

Fig. 4: Calculated spectral efficiency of photodiode

The spectral response, calculated according to the method mentioned above, is reproduced in figure 4. The spectral response was computed for several reverse voltages. We see that an increase in reverse voltage leads to higher quantum efficiencies and a shift in the sensitivity peak towards shorter wavelengths. This is a product of the expansion of the space-charge region.

A photo of an optode during manufacture, just before the deposition of the second metal, can be seen in figure 5. The

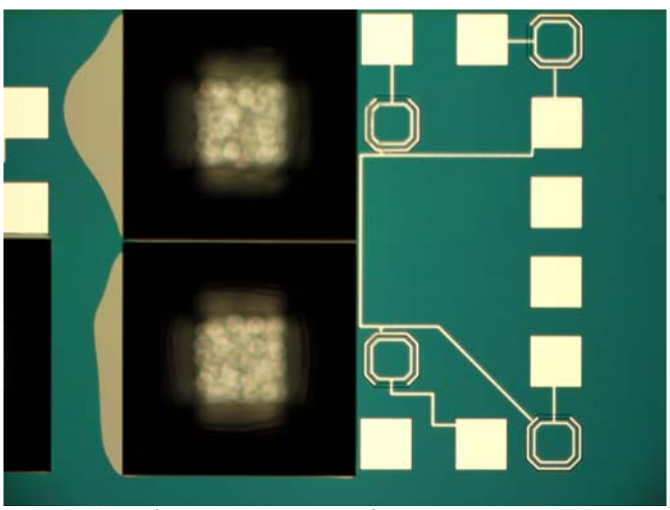

Fig.5. Photo of the optode during manufacturing.

holes for the LED's are visible, with the bottom out of focus due to the large difference in altitude. The four photodiodes can be seen as the octagonal structures interconnected by the first metal.

The first measurements on the photodiodes resulted in the IV characteristic which are given by figure 6. From the slope of the forward polarisation a series resistance of 6 ohms can be derived.

IV. Conclusions

The process for manufacturing the optodes using a standard bipolar process and some micro-machining steps has been

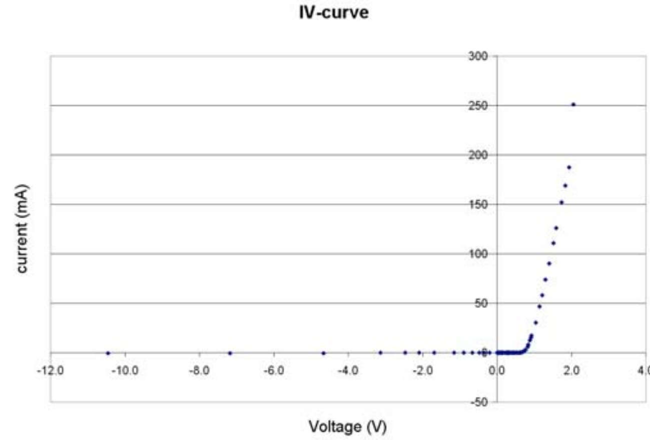

Fig.6. IV characteristic of the photodiode

succssful. The first measurements on the devices look promising and the LEDs can be placed in the hole. This means that the proposed implementation is feasible. The simulations give an idea about the performance of the photodiodes. Although the efficiency of the photodiodes is not very high, it is expected that it is enough for the envisaged application. The next step is characterizing the photodiodes optically. After that, the rest of the telemetric system has to be implemented and the resulting implants will be tested *in vitro* and *in vivo*.

In the future, the whole system can be integrated and optimized, with more signal-conditioning and read-out electronics being included in the optode. Also, extra features like a separate way to measure oxygen levels will enhance the clinical value of this type of photonic implant.

TABLE I
Input for Monte Carlo Simulations

	Transparent Layer	Brain Tissue*
Absorption Coefficient (1/cm)	0	1.5
Scattering Coefficient (1/cm)	0	400
G	1	0.9
Refractive Index	1.8	1.37
Thickness	0.00-0.04	15e8

* From Biomedical photonics handbook [8]

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