

Telemetric Photonic Implant for Metronomic Photodynamic Therapy of Glioblastoma

Eduardo Margallo-Balbás, Johan G. Kaptein, D. Tanase, Floor van Zaane, Dominic J. Robinson, Grégory Pandraud, Patrick J. French and Henricus J.C.M. Sterenberg

Abstract— Photodynamic therapy (PDT) is a developing cancer treatment modality based on the activation of a drug using light. Under illumination, the drug destroys the tumoral cells in the neighbouring area. Among the advantages of this technique are its low side-effects, the locality of its effects and the non-cumulative nature of its damage to surrounding tissue. PDT is promising for glioblastoma multiforme, a common and aggressive form of brain cancer. However, it is believed that its benefits could be maximised if it is administered in a low-dose regime during extended periods of time (metronomic PDT). The main challenge then is the need for implantable instrumentation. An inductively powered photonic implant has been developed, which is able to deliver the excitation light and monitor the treatment. The implant is built around a microfabricated optode which includes up to two light sources and four photodiodes. The optode can also use one of the PN junctions as a temperature sensor.

Index Terms—Photodynamic Therapy, Glioma, Biomedical Telemetry, Biomedical Applications of Optical Radiation, Optical Transducers

I. INTRODUCTION

PHOTODYNAMIC Therapy (PDT) is an upcoming treatment modality which is being successfully applied to several types of cancer [1]. Its operation involves the interaction between three elements: tissue oxygen, a photosensitising drug and light of the adequate wavelength for activation. PDT has many advantages in terms of treatment specificity, cost and post-operative recovery [2].

Specificity is achieved firstly through the controllable local activation that can be obtained through the tailoring of the light fluence distribution to the treatment volume. It is also possible to apply the photosensitiser locally in the treatment area. Finally, tumoral tissue will take up larger concentrations of photosensitiser due to its accelerated metabolism [1].

Under irradiation, the photosensitiser will be promoted to an excited single state. From there, it makes a transition

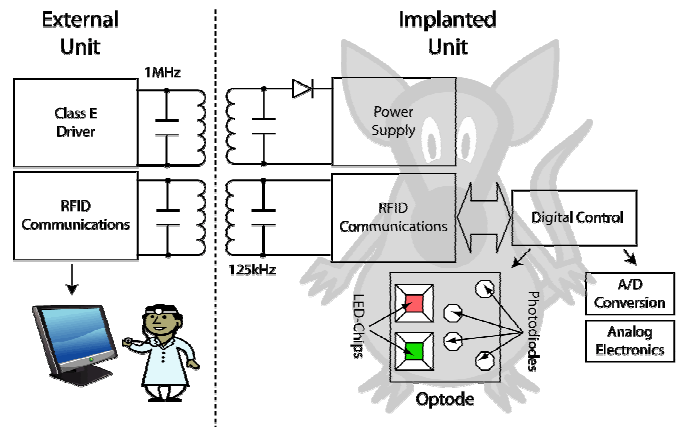


Fig. 1. Schematic of the total PDT system.

(intersystem crossing) to a triplet state with a longer lifetime. In this state it is able to interact with ground state oxygen (triplet) and take it to its respective singlet state. This last species (singlet oxygen) is very aggressive and will react with any nearby bio-molecule, causing cell damage and eventually destroying the cells in the treatment area.

Up to now, PDT has been applied mainly for situations where physical access to the target tissue is relatively easy. This is the case for cancers of skin or mucosa. In the cases where the target volume is not directly accessible, as for inner organs, delivery by means of needles has been performed. In these cases, as well as in the cases where PDT is delivered in combination with surgery, treatment administration patterns are seriously limited; in fact, only a single delivery session is possible most of the times. These limitations are clearly related to the instrumentation used for the administration and monitoring of PDT, which is to date mainly based on optical fibres [2].

However, there is much complexity in the interplay between electromagnetic radiation, drug and oxygen that is required to produce the desired therapeutic effect. Especially if the biological host response is considered, it becomes apparent the actual effects of PDT can vary in important ways depending on the specific therapeutic conditions. This implies that the choice of administration patterns for the photosensitiser and the light dosage can have a major impact on the final outcome of the treatment.

This is the case for glioblastoma multiforme (GBM), which is the most common form of brain tumor, being responsible for

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E. Margallo-Balbás, J.G. Kaptein, D. Tanase, G. Pandraud and P.J. French are with the Electronic Instrumentation Lab, Faculty of Electrical Engineering, Mathematics and Computer Science, TU Delft, The Netherlands (phone: +31-152-76-8432; fax: +31-152-76-85755; e-mail: e.margallo@tudelft.nl).

F. van Zaane, D.J. Robinson and H.J.C.M. Sterenberg are with the Dept. of Radiation Oncology, Erasmus MC, The Netherlands (e-mail: d.robinson@erasmusmc.nl).

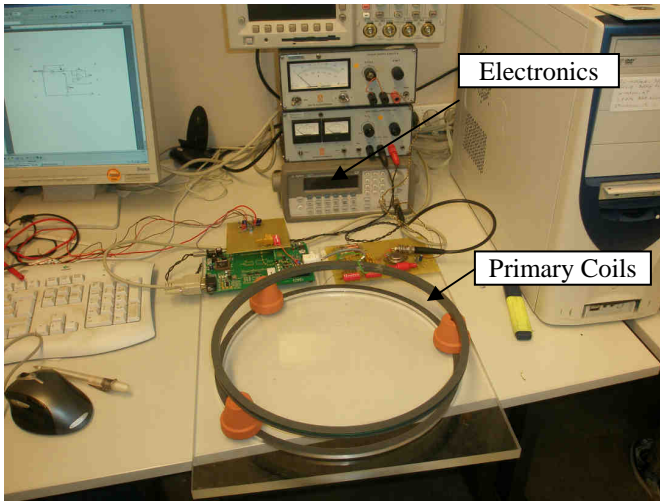


Fig. 2. External unit, showing the two primary coils used for communications and power transfer.

more than half of all cases of brain cancer [3]. The incidence of GBM is not extremely high (reportedly 3.55 cases per 100.000 people per year), but no effective treatments exist and survival rates after two years are known to be very low (3.3%). More dramatically, little success has been achieved by means of standard therapy options, based on combinations of surgery, chemotherapy and radiotherapy. In this sense, new ideas for treatment are very much needed.

It has been strongly argued that metronomic PDT, in which light delivery is performed over extended periods of time, can provide therapeutical advantages as compared to single dose PDT for the case of GBM [4]. However, as mentioned before, limited access to the intracranial cavity makes PDT delivery quite involved.

It appears clearly, thus, that instrumentation is an important bottleneck for the case of PDT applied to GBM, but also in a wide range of other applications. In this sense, being able to deliver and monitor PDT without the need for a percutaneous link is expected to be a major step forward in the expansion of this therapy.

Some advances have been reported in the literature towards smaller, more portable instrumentation, with light delivery systems for small animals having been described [5]. Although these devices are an important step towards clinical metronomic PDT, as they can be used to administer the treatment over some days, the reported approach still has some limitations. In the first place, the volume of the battery and the fiber-coupled components prevents full implantation, therefore excluding truly long term operation. Secondly, the battery limits the total light dose that can be delivered. Last, the number of sources and detectors is restricted by the size of the individually packaged components.

In order to overcome some of the limitations, a fully implantable metronomic PDT system has been designed and manufactured. In contrast with fibre based systems, a solid state optode containing a hybrid assembly of sources on a silicon chip including detectors is used. Power transfer and communications are achieved by means of an inductive link.

The goal of this device is to serve as a platform for experiments on metronomic PDT of glioblastoma in small animal models.

II. METHODS

The system is composed of two units as depicted in Fig. 1. One of them is meant to be implanted, while the other one is external to the animal and takes care of interfacing with the user program running on the computer. The external unit provides the operator in charge of controlling and evaluating the parameters of the PDT treatment with user-friendly commands and indicators. This unit is shown in Fig 2.

A. Inductive Link

Two pairs of coils have been used, simplifying the design and minimising interference between the powering field and the communications signals. The system has to be tuned to resonance depending on the environment of the coils, but this tuning has proved to be stable. This setup allows for a working circular area with a diameter of 30cm for the animal experiments. The coils in the implant are constructed using Litz wire to minimise power loss and therefore heat dissipation within the animal body.

Power is coupled from the external unit into the implant by means of an oscillating magnetic field, which induces an alternating current in the pickup coil of the implant. The values chosen for the power part of the inductive link were obtained following the design methodology described by Kendir et al [6]. The primary power coil is driven by a class E amplifier excited with a square wave working around 1MHz.

The communications are managed by means of a commercial RFID solution (Atmel U3280) working at 125kHz. Messages are transmitted serially to the implant, encoded in the amplitude of the field generated by the primary communications coil. Information coming back from the implant is conveyed by means of load keying at the secondary

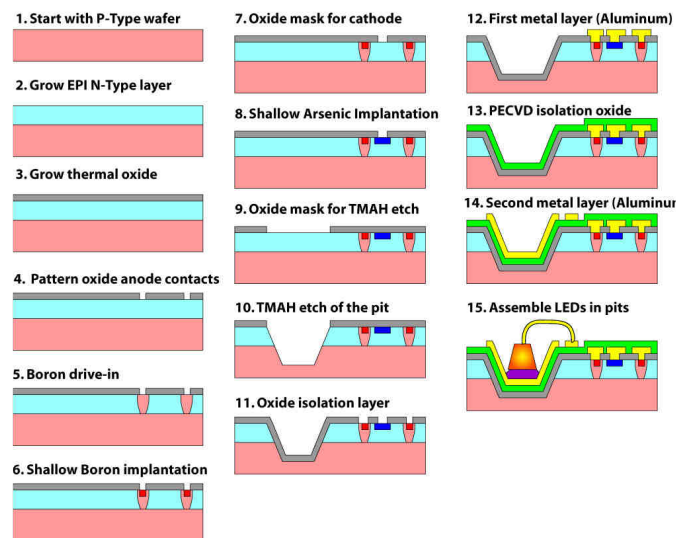


Fig. 3. Overview of the steps involved in the manufacturing process of the optodes

communications coil.

B. Solid-state Optode

Optodes are a combination of optical sources and light detectors. In the case of this paper, the optode is implemented using a hybrid assembly of III-V LEDs onto a silicon substrate. This silicon substrate has a micromachined cavity to accommodate the source and shape the light beam. Furthermore, it includes a set of photodiodes that are able to monitor the light distribution around the source. These measurements could be used to obtain an estimation of the optical properties of the tissue in front of the optode and the dose being delivered, actually providing an approximation to in situ dosimetry during treatment [7].

The photodiodes can also, with suitable readout electronics, be used to make measurements of fluorescence. These measurements could enable monitoring of the concentration of photosensitizer in the tissue. The PN junction forming the photodiodes can also be used as a PTAT temperature sensor (Proportional To Absolute Temperature). Knowing the local temperature at the optode can be interesting for monitoring the biological process, but it can also be used to prevent thermal damage to tissue due to heat dissipation coming from the light source.

The optodes were produced using a custom process at the DIMES facility of TU Delft. The photodiodes are obtained in a first series of steps adapted from a broader bipolar process. An overview of the steps in this process can be seen in Fig. 3. An n-type arsenic doped epitaxial silicon layer ($N_D=10^{16}/\text{cm}^3$) is grown on a standard boron doped p-type wafer. It is important to control the parameters of this layer ($t=2.8\mu\text{m}$) in order to determine the spectral response of the detector, as the junction formed between the epitaxial layer and substrate defines the photodiode. The device has been designed to have maximum sensitivity at a wavelength of 625nm. Thermal oxide serves as a masking layer to define boron-doped regions ($9.2\Omega/\square$) that ensure a high quality contact to the substrate. Shallow implantation of arsenic ($5 \cdot 10^{15}$ ions/ cm^2) and boron ($5 \cdot 10^{15}$ ions/ cm^2) is used to produce highly doped contact windows on the diode surface, that guarantee an ohmic contact between the metal layers and the cathode and anode regions.

The remaining steps in the fabrication involve the interconnections and the micromachining of the pits that will accommodate the solid-state light sources. First, a 365nm TEOS silicon oxide layer is deposited, which serves as a mask for TMAH etching of the pits. The dimensions of the pit openings are $500 \times 500 \mu\text{m}^2$ and their depth is $265 \mu\text{m}$. This size is appropriate to accommodate most LED chips available in the market. The TEOS oxide layer is also used for isolation purposes. Therefore, openings are made at those locations where contact with the cathode or anode regions is desired and then the first metal (aluminum) is deposited and patterned.

A new layer of TEOS silicon oxide is grown to separate the first and second metal layers, and windows are opened at the spots where interconnection between both layers is desired. The second metal is evaporated and defined by means of a lift-

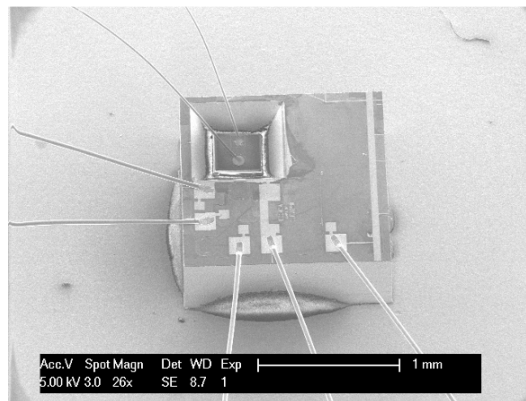


Fig. 4. Scanning Electron Microscope picture of the optode assembled on a standard carrier for testing.

off process. Square cavities are then produced to accommodate the chip-form LEDs. Up to two chip-form LEDs are hand-mounted in the cavities with electrically conductive glue, which means that two wavelengths can be emitted. The final manufactured devices measure $1.2 \times 1.2 \times 0.5 \text{mm}^3$.

C. Implant Electronics and Biocompatible Packaging

The implant unit that has been constructed is composed of a single optode. The driving electronics are built around it using discrete components and take care of signal amplification, A/D conversion, device control and power management. The electronics and the optode are mounted on a flexible substrate composed of adhesiveless polyimide. The electronics, together with the communications and power coils have been encapsulated in medical grade silicone for biocompatibility (Applied silicone LSR-10), while a biocompatible clear epoxy (EPOTEK-301) has been used to protect the optode.

III. RESULTS

A. Inductive Link

With the current electronics, electrical power up to 4W can be dissipated into the primary coil, which translates into an available power of around 8mW, as for the worst-case scenario (center of the coil) the power coupling efficiency is around

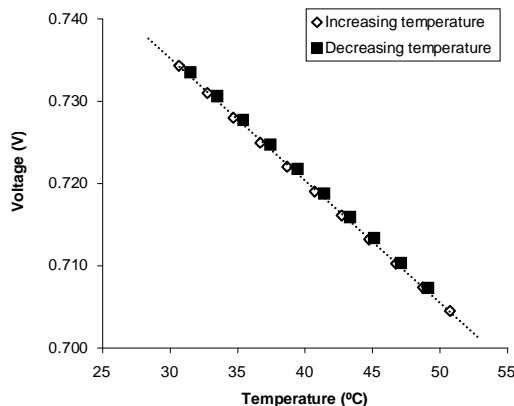


Fig. 5. Calibration curve for the PN junctions of the optode working as PTAT temperature sensors

0.2%. The implant has a maximum power consumption of 14mW if all the sources are simultaneously activated. In order to adjust the available power to the dissipated power and to provide a buffer in case of power link loss, a supercapacitor of 0.3F is used. This gives an autonomy of several tens of seconds at full power dissipation without any field applied.

B. Solid-state Optode

Fig. 4 displays a picture of the optode acquired using a scanning electron microscope. A LED mounted in the micromachined cavity is visible. The photodiodes are not clearly distinguishable in the picture because of the low contrast between their electrodes and the background.

The device has been successfully tested electrically and optically. The photodiodes present a shunt resistance that is lower than expected, but this has not been a problem for CW measurements. The behaviour of the photodiodes as PTAT temperature sensors has been demonstrated. The calibration curve obtained in a temperature controlled oven is shown in Fig. 5. A temperature coefficient of 1.493mV/K was found, which corresponds to a temperature resolution 0.71K with the readout electronics currently used (10bits ADC, 1.1V input range).

C. Encapsulation and packaging

Fig. 6 is a photograph of the implant electronics including the two secondary coils for communications and powering, after encapsulation in biocompatible silicone. Fig. 7 shows a detail picture of the optode mounted on the flexible substrate. The chip has been glued to the board and wire bonded. Biocompatible epoxy has been applied around the resulting chip and potted in a cylinder shape with a diameter of 3mm, providing a robust encapsulation for the device.

IV. DISCUSSION

This paper reports the design and fabrication of a telemetric light delivery and monitoring system for advancing metronomic PDT of glioblastoma. By making use of solid state optodes combining sources and detectors, the need for

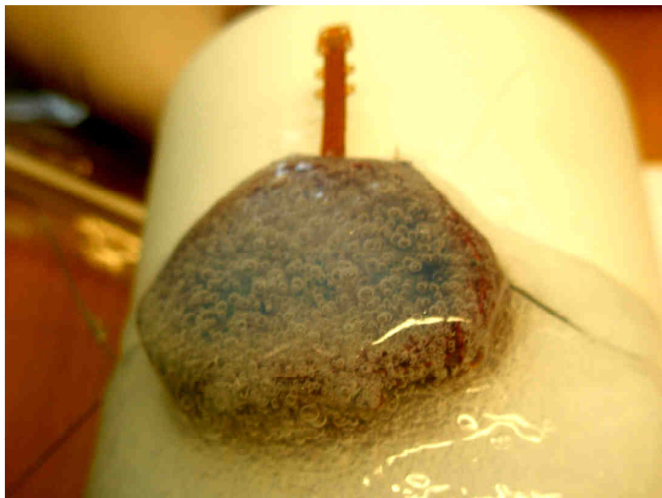


Fig. 6. Implant after encapsulation of the electronics in biocompatible silicone.

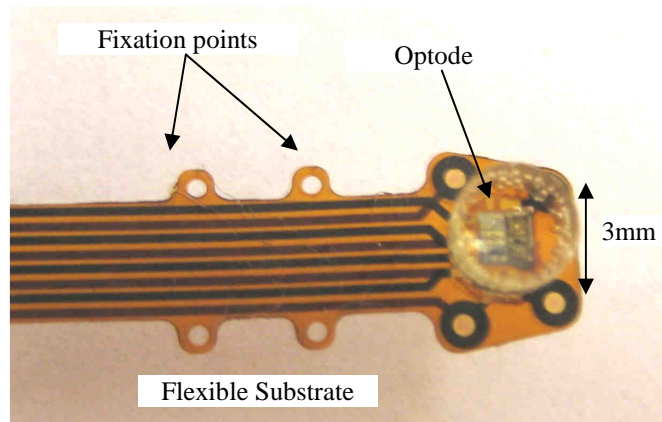


Fig. 7. Close-up picture of the optode mounted on the flexible substrate and encapsulated in biocompatible epoxy

percutaneous access during treatment disappears. This enables the evaluation and optimisation of metronomic PDT in an animal model over long periods of time. It is the first time to the best of our knowledge that this approach to PDT instrumentation has been pursued. Animal experiments are planned for the coming months.

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