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2nd year Internship report :
Combining carbon fiber and photoelectric dye for nerve fabrication

by

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Summary

2 Glossary

Photoelectric dye : Organic compound composed of aromatic cycles called chromophore able to absorb light photons and excite an electron resulting in electrical current generation. These chemicals are often found in organic solar cells.

OUReP : The Okayama University Retinal Prosthesis, shortened in OUReP, is the artificial implant developed since 2003 by Pr. Mastuo and Pr. Uchida research team it is composed of a thin film of polyethylene with a photoelectric dye layer bounded on.

Biocompatibility: The capability of materials to coexist with living tissues or organisms without causing harm or initiate a reaction from the immune system.

Conductive Bio-polymer: Synthetic and biocompatible macromolecules possessing highly delocalized π-conjugated backbone structures and configurable side chains.

Nerve Conduit: is an artificial means of guiding axonal regrowth to facilitate nerve regeneration and is one of several clinical treatments for nerve injuries.

Nerve Scaffold: Porous material used alongside nerve conduit to guide and support neural fibers during nerve regeneration

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3 Introduction

Okayama university is a comprehensive public university of Japan founded in 1870 and composed of 13,000 students and 1,700 faculty members spread over 11 faculties. Over the past ten years, the university has been expanding its international profile by taking part in common projects with overseas laboratories or by hosting international students joining laboratories for summer internships. The work presented in this report was achieved in such context from June to August 2022.
Designing implantable health system devices requires to combine knowledge from several major fields of science, from biology to physics going by material science to insure the final product fulfill all requirements in term of bio-compatibility, durability and efficiency. The research team of Okayama University led by Pr. MATSUO and Pr. UCHIDA has taken up on such challenge since 2003 by developing a unique type of retinal prosthesis, the Okayama University Retinal Prosthesis (also called OUReP). The principle of operation of OUReP is based a chemical reaction of a photoelectric dye with light making the system fully autonomous and easy to install into the eyes as a medical device. The current OUReP device aims to treat photoreceptor cells diseases such as Retinitis Pigmentosa[2], a genetic disease causing the degradation of cones and rods until blindness, 1 people out of 4000 is affected by this disease. Clinical trial of the device on humans are aimed to begin in the near future. This internship work is part of a new project aiming to develop a device extending the OUReP technology to be able to cure diseases that impacts other cells of the optic chain such as the ganglion cells that can be affected by glaucoma for example. Glaucoma is the second biggest source of blindness in the world, 64 millions of people suffers from it. The project being at the forefront of innovation and in its early steps, no studies or article have been conducted or published to show what should be the characteristics of such system, from the dimensions to the materials used as well as its effect on the neuron cells.

This report aims to present the work achieved in that way during a 3 months internship, from a state of art study for the choice of materials to a numerical simulation for the excitation of neurons cells membrane.

The report content is the following: a brief anatomy description of the optic nerve, a literature review to identify the materials commonly used in nervous tissue regeneration engineering. Finally, their possible use in artificial nerve manufacturing is discussed from electrical modeling using COMSOL Multiphysics . The main objectives of the modeling process was to model the evolution of potential in the neuron's membrane after external stimulation. This would help to understand whether it would be possible to activate neurons using an artificial nerve combined with the light sensitive technology developed by the research team.

4 Reviewing the state of art of nervous tissues engineering

4.1 Anatomy

4.1.1 Optic nerve

The Cranial Nerve II mostly known as the optic nerve is the nerve responsible for transmitting the electrical pulses, generated initially by the photo-receptor cells as a response to a light stimulus and conducted to the visual cortex located in the back of the brain as shown in figure 1. The optic nerve is about 4cm in length and 4 mm in width at its widest, it is also composed of 1,2 million nervous fibers. As figure 1 shows, the route taken through the cranium is complex and it could represent a challenge to successfully deploy an artificial nerve following the exact same path. In order to overcome such issue, the possibility to proceed by an extra cranial way was investigated in the past. [3].

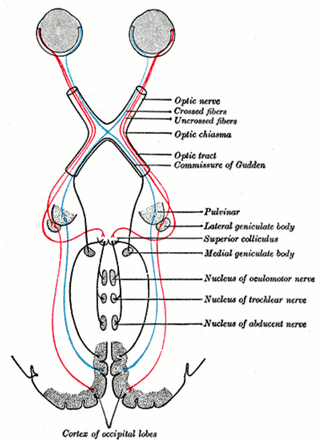


Figure 1: Schematic representation of the optic nerve, Source: Wikipedia

4.1.2 Neurons

In the optic neural chain, the neurons are the final receiver of the electrical pulses. Thus, they are the cells which the artificial nerve should transmit the photo-generated signal.
The activation of neurons is achieved by creating a difference of potential between the outside and the inside of the cell. Usually this activation is achieved by the ions contained in the extracellular medium such a sodium or potassium but this activation can also be triggered by external stimulation. Neurons have a resting membrane potential of about $-70mV$, if this potential is depolarized by external stimulus and exceeds the threshold potential (usually around $-50/-55mV$) action potential will be elicited in the neuron [4] and transmitted to the other neurons connected. Figure 2 shows the theoretical response of a neuron.

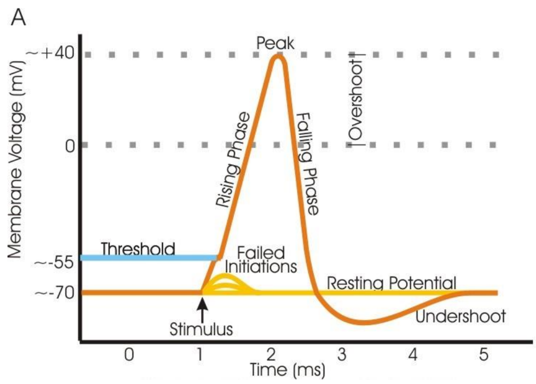


Figure 2: Theoretical electric response of a Neuron to a stimulus *Artwork by Synaptidude at en.wikipedia - From en:Image:Action potential vert.png; Modified version of older Image:Action potential reloaded.jpg., CC BY-SA 3.0, Link for full size*

The preceding researches allowed for determining requirements for the initial design of an artificial optic nerve: its size needs to approach the one of the natural optic nerve, the device needs to be resistant enough to handle the installation procedure and it also needs to create a difference of potential big enough to activate neurons. The basic understanding of this requirements simplifies the task of finding suitable materials as they provide a frame of properties to look for in research articles : bio-compatibility, electrical properties (conductivity, relative permittivity).

4.2 Materials

The field of artificial nerve engineering is still in its early development. Hence, there is not plethora of published articles describing attempts in designing such devices. In order to find materials suitable for the system envisioned by the research team, it was important to determine fields that were similar and would provide interesting information. Most of the current studies on nervous tissues engineering concentrates on nerves regeneration with the use of temporary artificial devices like scaffolds [5][6] or nerve conduits[7]. Articles reporting the developments of these systems allowed to identify commonly used bio-compatible materials. Reports from research teams trying to manufacture implantable electrodes [8] provided useful information as the theoretical principle between an implantable electrode and an artificial nerve is expected to be similar. Finally, review articles that focused on a unique material are also an interesting source of information as they summarize the current knowledge and also gave insights about the possible future usage, occasionally artificial nerves design was indeed mentioned [9] [10]

4.2.1 Conductive bio-polymers

Conductive bio-polymers are the most studied materials for nervous applications because they often offer a naturally high bio-compatibility which makes them suitable for long-term implantation. Their electrical conductivity comes from their specific chemical structure made of alternating single and double carbon bonds. this property can be enhanced by doping the polymer with Lewis acid for p-type doping and Lewis base for n-type doping [11]. 3 families of polymers have been identified as the most studied and promising ones.[12] : Polypyrrole (PPy), Polyaniline (PANI) and Poly(3,4-ethylenedioxythiophene) (PEDOT) fig 3.

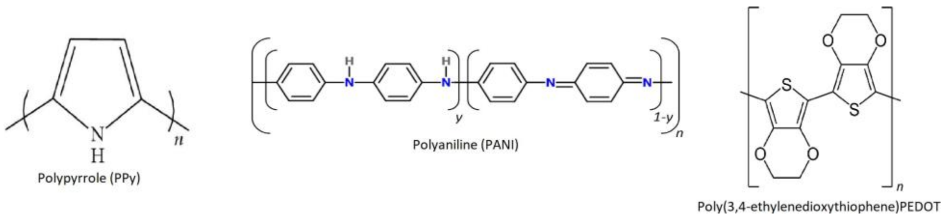


Figure 3: Most studied conductive bio-polymers

The main weakness of these polymers is they are brittle which makes their processing into large objects quite difficult but researches have shown that using a non conductive but mechanically strong co-polymers could resolve these issues.[10][13] Most of the conductive bio-polymers are not bio-degradable which in the case of artificial nerve conception is an interesting property. [14]

Polyaniline is an non-biodegradable bio-polymer commonly used in nerve conduits. [15] Its implantation usually provoke a inflammatory response [10] and can lose its conductivity at physiological pH values [11] making it non-adapted for this project.

PPy molecules are often used as coating for preexisting fibers as polypyrrole cannot be processed into long fiber on its own because of its brittleness. For exeample PPy was binded to silk films to obtain a conductive and mechanically robust material. [13]. Older studies have shown to was possible to coat polypyrrole on silk fibroin or cotton fibers and obtain conductive fibers [16]. The cytoxicity of PPy was investigated in [17] and showed that various doped Polypyrrole molecules showed no cytoxicity.

PEDOT is a well known material in the solar cell industry as its association with polystyrene sulfonate (PEDOT:PSS) is one of the key materials in organic solar cells. The final conductivity of the polymer can vary depending on the dopant used (from about $10.2 S/m$ for PEDOT:PSS to $6.5\ 10^4 S/m$ for $PEDOT : ClO_4$). PEDOT have also been studied as a promising material for neural applications [18] and bio-implantable electrodes by coating it to silk fibers [8] or to metal wires [11]. Biocompatibility of PEDOT has been demonstrated both *in vitro* and *in vivo* with a variety of dopants [11][19], however the impact of long term implantation (>12 weeks) was never reported.

The table 1 summarizes the main devices made using the 3 bio-polymers, its final shape, the intended usage and the measured conductivity.

Bio-polymer	Shape	Coated on	Usage	σ (S/m)	Reference
Polypyrrole	Film	Silk fibers	Scaffold	1	[13]
PPy	Fiber	Silk/Cotton fibers	Not disclosed	0.8	[16]
PPy	amorphous	Hyaluronic acid hydrogel	Drug delivery	0.73	[6]
Polyaniline	Fiber	microtube	Nerve conduit	3	[15]
PEDOT:PSS	Fiber	Silk fiber	Electrode	10.2	[8]
$PEDOT : ClO_4$	Fiber	Platinium	Electrode	6.5×10^4	[11]

Table 1: The main identified conductive bio-polymers and their usage in studies

4.2.2 Carbon fiber

Carbon fiber is an versatile material, studied in a large variety of research field, tissue engineering included. Carbon fiber have been used for bone graft [20] or for creating scaffold allowing cell growth [21]. Different types of carbon fiber exists with different properties associated, The Japan Carbon Fiber Manufacturers Association[22] list 2 different types of fiber depending on the raw material used :

- PAN type fibers, obtained from carbonization of Polyacrylonitrile, mostly used for structural material composites in aerospace and industrial field.
- Pitch type fibers, obtained from carbonization of oil/coal pitch precursor they shows high elastic modulus and are commonly used in in high stiffness components and various uses as utilizing high thermal conductivity and / or electric conductivity

All carbon fibers can be heat treated in order to enhance its electrical conductivity with values that can reach $7.04 \times 10^5 S/m$ for Pitch type fibers. [23]. Usually the conductivity obtained with PAN type fiber is lower, about $10^2 S/m$ [24] The combined mechanical and electrical properties of carbon fiber make it a good candidate to be used as the conductive part of an artificial nerve. Studies also showed that carbon fibers showed little to no cytotoxicity [20]
However it was not possible to find many articles detailing the use of carbon fiber in nerve regeneration attempts or tissue engineering. Most of the time carbon nanotubes (CNT) appears to be preferred by researchers, this could be explained by the fact that CNT are smaller than carbon fibers offering more possibilities to create small complex organisation such as the yarn detailled in [25].

4.2.3 Insulation

As the artificial nerve device, when implanted, will be surrounded by the body's conductive fluids, it is essential to use an insulation layer to make sure the generated signal can be carried to the neurons. In the natural optic nerve, the insulation layer corresponds to the axon's membrane. Since no article studied the implantation of a complete artificial nerve, it is difficult to identity materials that could be suitable in this precise context.
However, the OUReP device developed by the research team uses polyethylene as an insulating film onto which photoelectric dye is coupled. The experience gathered during OUReP development makes of the high density polyethylene (HDPE) a coherent material to choose for the insulation layer. The research team also showed that HDPE demonstrates good biocompatibility [26]. Hence only this material will be used as an insulator during the simulation step.

5 Simulation

5.1 About COMSOL Multiphysics

COMSOL Multiphysics is a finite element analysis, solver and multiphysics simulation software developed since 1986. It allows conventional physics-based user interfaces and coupled systems of partial differential equations (PDEs). The software provides a variety of modules containing predefined physics equations for Electromagnetic to Chemical engineering by Fluid flow and Heat Transfer.

5.2 Model design

The objective of this modelling is to implement the difference of potential generated by the photoelectric dye between each tip of the artificial nerve device and check if this difference can excite neurons membrane

under various parameters. Designing an accurate model of such biological system from scratch can be a lengthy process to insures accuracy of the results. Choice was made to find pre-exisiting models and implement them in a final model representing a simplification of the real situation. This was motivated by the short time the software was available, 1 month trial licence provided by KESCO, Japanese distributor of COMSOL Multiphysics, to the research team.
The simplification is that the extracellular medium is supposed to be located only at the interface between the tip of the artificial nerve and the neurons meanwhile in reality this medium would surround the artificial nerve too.
In order to optimize the simulation, the chosen geometry follows 2D-axisymmetry which mean that only one plan needs to be drawn and the software will extend the study to a 3D cylindric model . The final geometry is made of 4 domains and 3 interfaces 4:

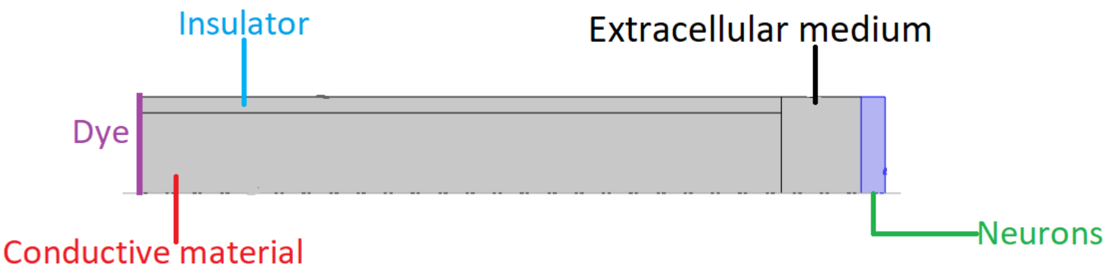


Figure 4: Representation of the model in COMSOL Multiphysics

5.2.1 Domains

The 4 domains are the following :

- Conductive material, part of the artificial nerve made of the materials described in 2.
- Insulator, coated onto the conductive material, made of high density polyethylene.
- Extracellular medium, represents the physiological liquid surrounding the cells it has a relatively high concentration of ions that can activate the cell's membrane.
- Neurons, the target cells of the artificial nerve device

The modelling relies on one major hypothesis : A drift current is generated by the separation of the dipoles formed on the photoelectric dye.
In each of these domains the physics used is the electric current from the AC/DC module, this module solves the Maxwell's equation and the conservation of current law equation locally within the declared materials and with set boundary conditions. The global equation solved is the following :

$$\nabla \cdot \mathbf{J} = 0 \tag{1}$$

With $\mathbf{J}$ the current density.

$$\begin{aligned} \mathbf{J} &= \sigma \mathbf{E} + \frac{\delta \mathbf{D}}{\delta t} + \mathbf{J}_e \\ \mathbf{E} &= -\nabla V \\ \mathbf{D} &= \epsilon_0 \epsilon_r \mathbf{E} \end{aligned} \tag{2}$$

Where σ is the electrical conductivity, $\mathbf{E}$ the electric field, $\mathbf{J}_e$ is an external current density generated at interfaces (in A/m^2) and $\frac{\delta D}{\delta t}$ is the displacement current.
The conductive materials that will be investigated during the simulation are summarized in table 2

Material	Conductivity (S/m)	Relative permittivity	Reference
Carbon fiber (PAN type)	10^2	≈ 4500	[24]
Carbon fiber (Pitch type)	7.04×10^5	≈ 4500	[23]
PPy/Silk	0.8	4.31	[16]
PEDOT:PSS / Silk	10	≈ 200	[8]
Polyethylene	10^{-15}	2.3	embedded in Comsol

Table 2: Conductivity and relative permittivity of the materials investigated

The values of relative permittivity for the composite materials was computed using the parallel model described in [27]

5.2.2 Boundary conditions

Dye Layer The photoelectric dye behavior was approximated by a square function of constant amplitude. The tested values for the amplitude are chosen from measurement achieved by the research team using Kelvin probe force microscopy [28]. The tested values are enclosed between 0 and 550 mV 11

Ganglion cell membrane The source used for the modelling of the ganglion cell membrane was an article [1] and a related Powerpoint presentation used during the COMSOL Conference in Milan in 2009. This model simulated the membrane reaction of the axon of a cell when an electrical stimulation was coming from the inside of the cell (the axoplasm). The model was recreated following the step described in the article and then modified so the stimulation comes from the extracellular medium. The first equation implemented was the current conservation equation :

$$J_{\mathrm{eq}} = \sigma_{\mathrm{m}} \frac{V_2 - V_1}{d_{\mathrm{m}}} + J_{\mathrm{e}} + C_{\mathrm{m}} \frac{\delta(V_2 - V_1)}{\delta t} \tag{3}$$

With σ_{m} the conductivity of the membrane, d_{m} its thickness and C_{m} its capacitance their values can be found in table 4. $V_2 - V_1$ corresponds to the membrane voltage with V_2 the potential outside of the cell and V_1 the potential inside.

J_{e} is an external current corresponding to the current generated by the ions going on each side of the membrane. It is defined by : .

$$\mathbf{J}_{\mathrm{e}} = \sum \begin{cases} 0 & \text{out of the membrane} \\ G_{\mathrm{i}} \times E_{\mathrm{i}} & \text{at the membrane} \end{cases} [1]. \tag{4}$$

G_{i} corresponds to the conductance per unit are of the ion i channel and E_{i}, to the Nernst voltage associated with the concentration of ions i. The values of G and E for each ions impacting the neurons are summarized in table 3

Ions	$G_0(S/m^2)$	E (mV)
Na	1200	55
K	360	-72
others (leak)	3	-49.387

Table 3: Conductance per unit area and Nernst Voltage of the ions crossing the neuron membrane. [1]

In order to recreate the ionic channels and implement their impact on the variation of the potential, another set of equations is locally implemented at the interface, each one of them corresponds to one ionic channels and are solving for the variables m, n and h [1] :

$$
\begin{aligned}
G_{Na} &= G_{Namax} * m^3 * h \\
G_K &= G_{Kmax} * n^4 \\
\frac{dx}{dt} &= \alpha_x * (1 - x) - \beta_x * x
\end{aligned} \tag{5}
$$

with $x \in \{m, n, h\}$, the values of α_x and β_x can be found in table 4

These equation are solved in COMSOL by the PDE packet : weak form on boundaries, which allows to enter the the previous equations and solve them by multiplying the expression by a test function.

$$test(x) \times \left(\frac{dx}{dt} - \alpha_x * (1 - x) + \beta_x * x\right) \tag{6}$$

All the parameters extracted from [1] and used in the implementation are summarized in table 4

C_m	$0.01[F.m^{-2}]$
d_m	5[nm]
G_m	$G_{Na} + G_K + G_l$
σ_m	$G_m * d_m$
ϵ_m	5.65
α_m	$1000\frac{2.5 - 0.1V'}{e^{(2.5-0.1V')} - 1}$
β_m	$1000\frac{4}{e^{V'/18}}$
α_n	$1000\frac{0.1 - 0.01V'}{e^{(1-0.1V')} - 1}$
β_n	$1000\frac{0.125}{e^{0.0125V'}}$
α_h	$1000\frac{0.07}{e^{0.05V'}}$
β_h	$1000\frac{1}{e^{(3-0.1V')} + 1}$

Table 4: main parameters used for membrane activation modeling, $V' = V_m - V_{sta}$, the resting value [mV]

The resulting simulated membrane displayed convincing shape of the evolution of the transmembrane potential as a function of time but some features were quite unrealistic (cf 5.4)

Between the nerve and the extracellular medium This interface is the transition between the artificial nerve and the extracellular medium. It is expected that, at this interface the electrons and ions accumulate on each side. the change of the nature of the charge carriers between the materials is called an electrical double layer, it can be described as a compact layers of opposite charges formed at the electrolyte/artificial nerve interfaces, this result to a voltage drop and a capacitive effect that can be modelled as a Neumann boundary condition [29] :

$$\mathbf{J}_{0electrolyte} \cdot \vec{n} = \sigma^{\star}_{electrolyte} \vec{\nabla} V^{\star}_0 \cdot \vec{n} = iC_{EDL}\Delta V_{EDL} \tag{7}$$

With $\sigma^{\star}_{electrolyte}$ the conductivity of the electrolyte, $V_0^{\star}$ the potential applied potential. C_{EDL} is the EDL capacitance and $\Delta V_{EDL} = V_{AN} - V$ the voltage drop in the EDL, V_{AN} the potential applied at the Artificial nerve and V, the potential at the EDL/bulk interface.

The value of the EDL capacitance varies depending of a multitude of parameters from the materials used or from the interface. The article [30] provided an expression to approximate the Electrical Double Layer capacitance value for the case of carbon materials by assimilating the situation to a parallel plate capacitor :

$$C_{EDL} = \frac{\epsilon_0 * \epsilon_r}{d} \tag{8}$$

With ϵ_0 the vacuum permittivity, ϵ_r the relative permittivity of the ionic liquid and d the thickness of the EDL which was estimated to be around 1 nm. [31]

5.3 Studies

5.3.1 Insulation layer thickness

Motivation The objective of this first study is to study the impact of the insulation layer deposited around the conductive material on the transmembrane voltage. This study aims to provide the research team an estimation of the thickness of insulation to use when manufacturing a prototype in the future.

Method In order to study the effect of changing the thickness of the insulation layer, a measure metric was created the insulation thickness proportion called R, The total thickness of the system is set to 4mm to match the maximum width of the optic nerve. By modifying the value of R and computing the study under constant stimulation and using the same conductive material (Carbon fibers PAN-Type), it was possible to evaluate the importance of the thickness of the insulation layer.

Results Initial computation showed that as long as the value of R is constant, the thickness of the system can be increased without changes in the membrane response. Several values of R were investigated, from R=1 corresponding to a device made exclusively of polyethylene to R=0,1, Figure 5 show the outcome of the study for R=1, 0,4, 0,3 and 0,2. As expected when the nerve is entirely made of polyethylene (R=1) the membrane is not activated, For values of R between 0.9 to 0.4, the shape of the evolution of the transmembrane voltage can be interpreted as a failed initiations of the membrane activation. From 0.4 to 0.3, the shape of the membrane response is a smoothed square function which cannot be interpreted otherwise than an inaccuracy from the model.
Finally, the transmembrane voltage evolution matches the real evolution when the value of R is between 0.25 and 0.15 which corresponds to a thickness of insulation between 1 mm and 0,6 mm. In the following studies the value of R was set to R =0,2 as this is a value within the interval showing the most realistic response to the stimulation.

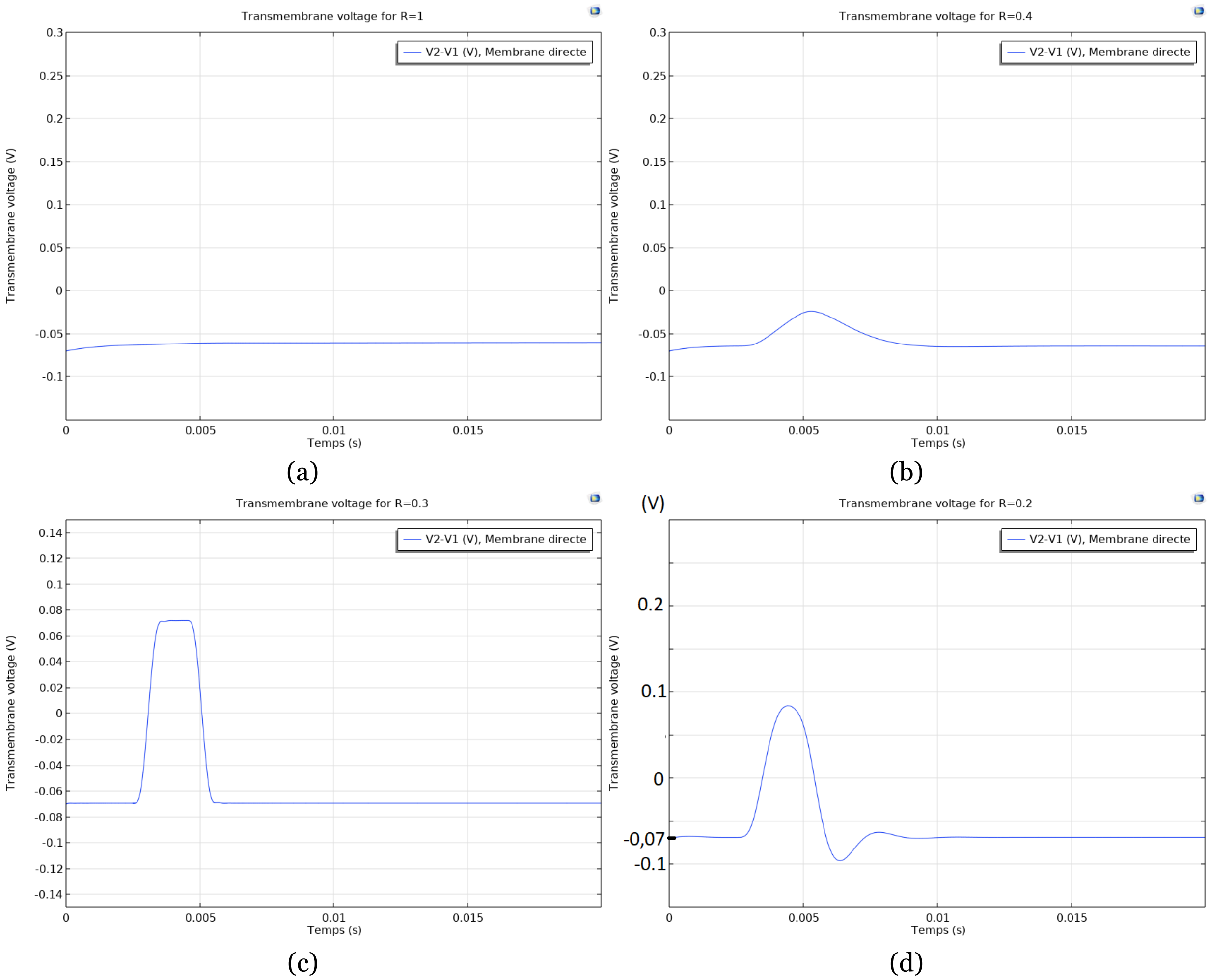


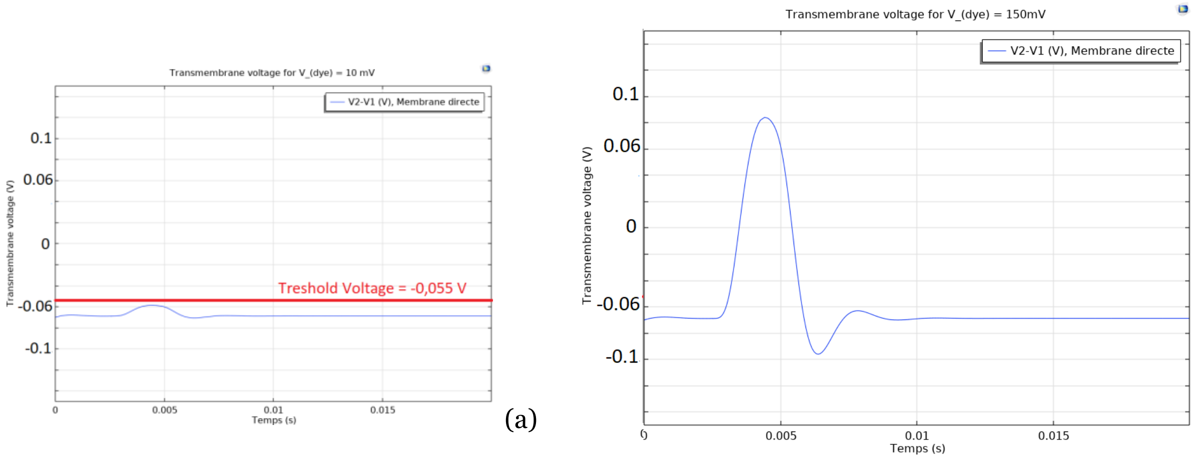
Figure 5: Outcomes of the simulation when studying the impact of insulation layer thickness (a) R=1, (b) R=0.4, (c) R=0.3 and (d) R=0.2

5.3.2 Stimulation potential

Motivation: The artificial nerve relies on photoelectric dye to generate the stimulation that is propagated to the neurons through the conductive material, the interval of tested values for the photogenerated potential has been measured using Kelvin Probe Force Microscopy [28], this interval is $V_{dye} \in [0; 550] mV$. This study investigates the minimal potential value needed to obtain a reaction of the membrane, allowing to justify the use of this specific photoelectric dye.

Method: As discussed in 5.2.2 the photoelectric dye layer is modelled as an square function of amplitude V_{dye}, the principle of this study is then to test if for amplitudes contained in the interval measured by the research team the cell membrane is activated.

Results: The outcomes of the study demonstrated that all amplitudes values superior to 20 mV were able to iniate membrane activation as the value of the potential was superior of the treshold potential (-55 mV) . Hence the choice of the photoelectric dye used in OUReP is coherent in the case of an artificial nerve. The device could allow people to sense light at intensity higher than 1500 U.A (or about 15 Lux) Figure 11 shows the outcomes for a value inferior to 20 mV and for 150mV which corresponds to the potential generated by the light under usual light intensity in classrooms.



(a) (b)

Figure 6: Outcomes of the simulation when studying the impact of the value of the photogenerated potential with V_{dye} equal to (a) 10mV and (b) 150mV

5.3.3 Studying the distance of implantation

Motivation : Contrary to the biological optic nerve, the artificial nerve will probably not be connected to the neurons. Thus, studying the impact of the implantation distance between the neurons and the tip of the artificial nerve present an interest for future experiments and implantation.

Method: All the results obtained in the previous studies are implemented and combined, the insulation thickness ratio is set to 0.2, the stimulation potential is set to 150 mV and the material chosed is the PAN-Type Carbon fiber. The dimensions are simply modified in the geometry parameters of COMSOL. The only degree of freedom in this study is the distance between the nerve and the cells (ie the thickness of extracellular medium called h), different values of h have been tested from 1mm to 25µm .

Results: For h = 500µm, the membrane's response is the one expected but when increasing or reducing the distance between the artificial nerve and the cells, the amplitude of the membrane's response respectfully increases or decrease and even change its shape drastically to a square function when the distance value reaches 325µm. Trying to lower the distance below 25µm created convergence issues within the model which prevented the study on smaller distances. The maximum distance between the nerve and the cells still allowing membrane's activation appears to be 1mm which appears to be quite unrealistic. Such drastic changes of the signal shape and the fact that the signal appears to be able to still activate the cell's membrane even if the extracellular medium thickness is big are probably caused by the simplified model who is designed to not have any electric losses on the sides of the nerve.

(a) (b)

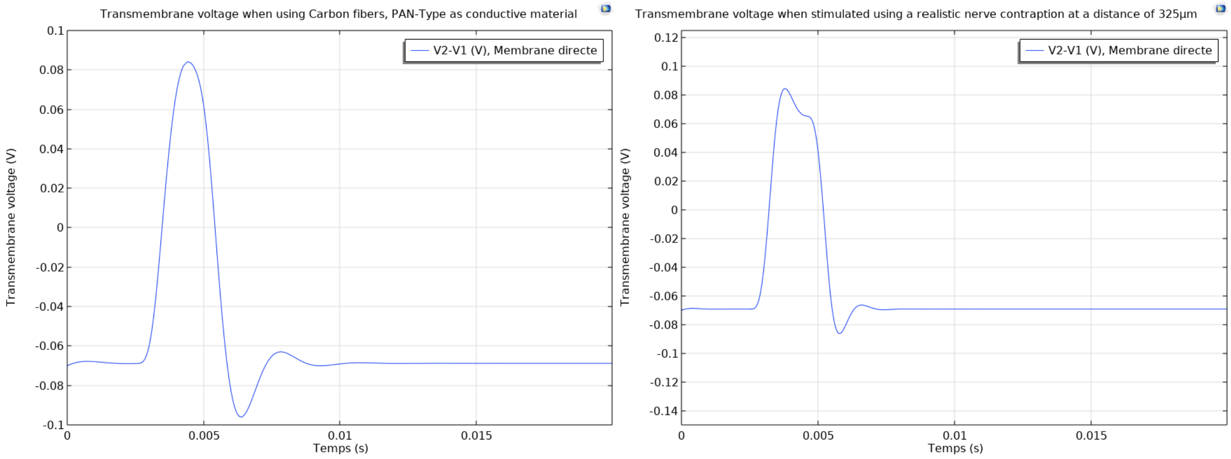


Figure 7: Outcomes of the simulation when modifying the distance between the artificial nerve and the cells, (a) h= 500µm and (b) h= 325µm

5.3.4 Changing the conductive materials

Motivation: This study aimed to investigate the materials selected after the literature review by checking if each material be used to initiate the membrane's response by propagating the dye stimulation and observe the difference in the transmembrane voltage evolution.

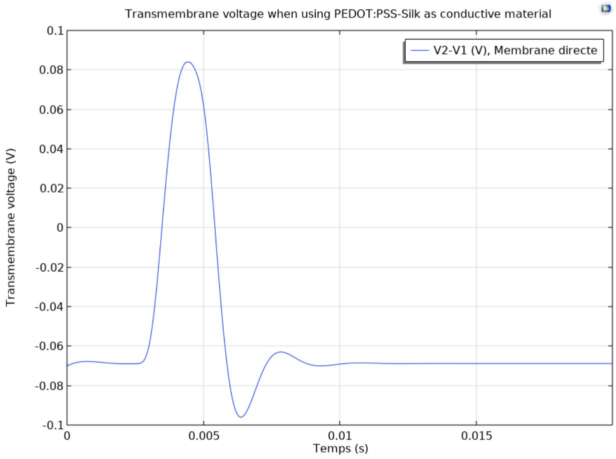
Method: In COMSOL Multiphysics, the materials can be implemented and swapped easily, the principle of this study is to compare the outcome and evolution of the transmembrane voltage for each materials implemented with a stimulation amplitude set to 150 mV.

Results: The results of this study showed in figure 8 shows neither of the three materials tested displayed a difference in the membrane's response. There is 2 possible ways to explain the absence of difference in the membrane reaction when using different conductive materials :

1. The conductive material does not impact the membrane reaction as much as the extracellular medium does. As long as a drift current, generated and propagated by the conductive material, the ions contained in the extracellular medium will convey the stimulation and excite the cell membrane. Per the values studied, any conductive material whose conductivity is in the range of $\sigma \in [2 \times 10^{-2}; 7 \times 10^{5}] S/m$ could activate the cell's membranes.

2. The geometry and the boundary conditions are too simple to accurately model such complex situation and the choice made, due to the time limitations, to only use simple electrical properties was not pertinent to fully recreate the situation. As a result, the model implemented approximates the electrical double layer as a simple capacitor which only uses the properties of the extracellular medium. The absence of difference when changing the conductive materials is explained by the facts that their properties are not taken into account. However, despite the efforts to find articles, in the literature, providing formulas that could be adapted and implemented into the model to reduce the approximations made around the EDL no example of formulas taking conductive material into account could be found.

Since this study could not provide a way to choose the conductive material based on its electrical properties. The conductive material must be chosen for its bio-compatibility and also for it simplicity to manufacture or find on the market. With these criteria the Carbon fiber appears to be the most promising material to use in further studies.



(a)

Figure 8: Outcome of the simulation when changing the conductive material to PEDOT:PSS coated on silk fibers, Polypyrrole coated on silk fibers and Carbon Fibers PAN-Type

5.4 Model's limitations

As the model was implemented in a short period of time, there is still limitation in its computation. Issues comes from the implementation of the cell membrane whose behavior does not fully correspond to the real behavior of the neuron cell's membrane.
For example in real membrane the maximum amplitude of the peak is limited to 0.04 V meanwhile the maximum value in the case of the modelled membrane is around the initial value au V_{dye} (cf figure 9)

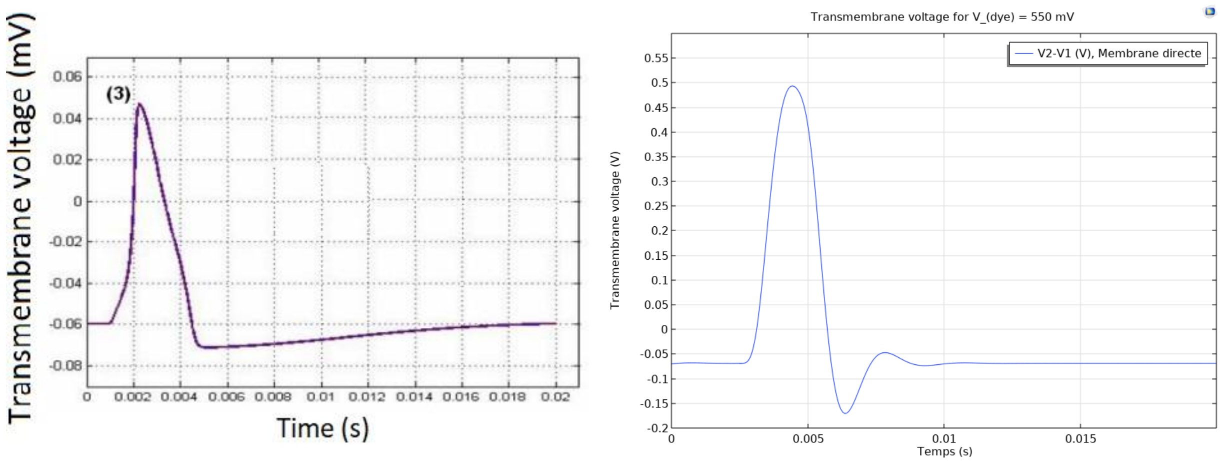


Figure 9: Non realistic behavior of the membrane model high intensity, on the left the expected results [1], on the right the obtained results for $V_{\text{dye}} = 550mV$

Another example can be seen when comparing the behavior of the real membrane and the modelled membrane to long stimulation (>10ms). A real membrane will react by activating multiple times within the time of the stimulation, meanwhile the modelled membrane plateaus at the peak value before going back to the resting potential, this major difference is shown in figure 10.

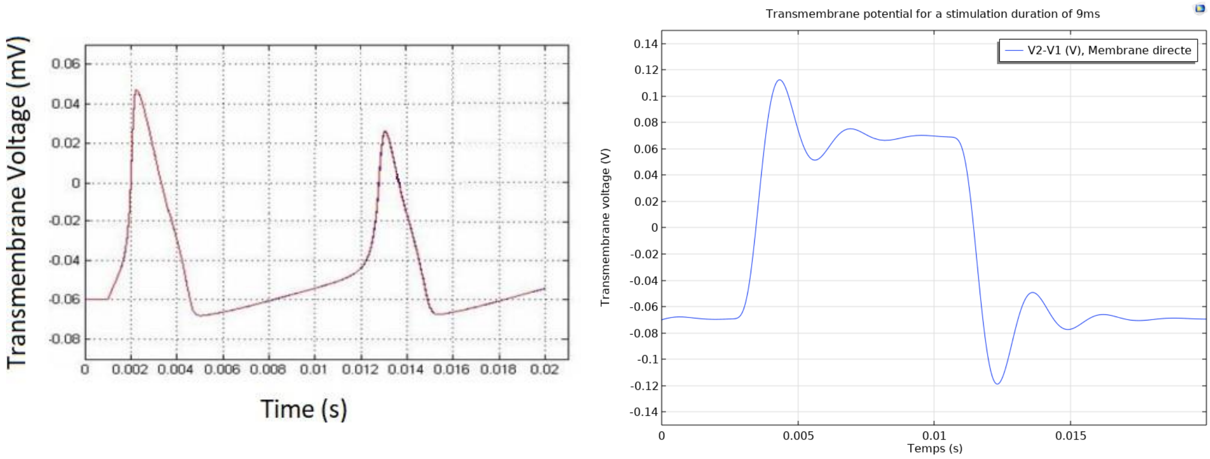


Figure 10: Non realistic behavior of the membrane model under long stimulation, on the left the expected results [1], on the right the obtained results

The limitations linked to the membrane model are the result of an incomplete recreation of the model described in [1]. However this implementation was done with little to no support material to recreate the model, only the article [1]. The article, published in 2009, describes the implementation in an older version of COMSOL Multiphysics. Also it does not state important parameters to use, the initial values of the variables (m,n and h) used for the activation of the ionic channels for example. This lack of documentation is one of the reason why the implementation of the membrane model is not completely accurate but still demonstrates good qualitative evolution of the potential over time for short stimulation (<10ms).

5.5 Future developments

From the results obtained with the modelling several insights can be provided to the research team for the future development of the project :

- Check the generation of drift current from the dye into a conductive material :
  As the existence of the drift current is the main hypothesis behind the modelling, it is necessary to check the generation of the drift current when the photoelectric dye is connected to a conductive material. A first step would be to deposit a layer of photoelectric dye on a metallic sheet and measure the current generated by light irradiation.
- Improve or create a more complex model of the device to verify the finding presented in this report.
- Manufacture a prototype of the artificial nerve device using PAN-Type Carbon fiber as this appears to be the most promising material.
- this report focused on studying the electrical properties of the nerve system, the mechanical strength and the durability of the system for implantation still needs to be addressed.

6 Complementary work : OUReP Light evoked surface potential

This part of the report is dedicated to a complementary work achieved during the internship regarding the phenomena responsible for the surface potential generation of OUReP.

The photoelectric dye NK-5962 (2-[2-[4-(dibutylamino)phenyl] ethenyl]-3-carboxymethylbenzothiazolium bromide) provided by Hayashibara, Okayama, Japan is the main component of the retinal prosthesis developped by Pr. Mastuo and Pr. Uchida research team. When light reaches the device, the photons are absorbed by the chromophore part of dye molecules and an electron is excited from the highest occupied molecular orbit (HOMO) to the lowest un-occupied molecular orbital (LUMO). as the molecules are binded on the polyethylene film which is an insulator, the electron is supposed to stay in the molecule forming an electrostatic dipole with the hole created by its excitation, their bounding by Coulomb force is also known as an exciton. This dipole generates a dipole field that aligns with the field generated on the others dye molecules due to the binding with the insulator. This multiplicity of aligned dipole fields generates a difference of potential between the excited state and the ground state of the molecule. This difference of potential can be measured using Kelvin Probe Force Microscopy which is used to measure the work functions of sample by scanning its surface. The light-evoked surface potential genrerated by OUReP has been measured using the Kelvin probe system SKP05050 and the surface photovoltage spectroscopy module SPS040 developed by KP Technology.

6.1 Finding the source of the non linear behavior

One of the measurements conducted by the research team consisted on studying the evolution of the light-evoked surface potential in function of the light intensity, the resulting graph is shown in figure 11.

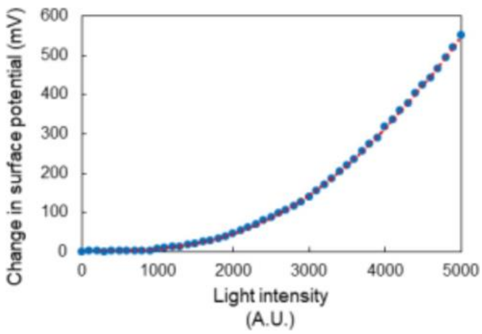


Figure 11: Light evoked surface electric potential as a function of light intensity

The light-evoked surface voltage follows a non linear variation which was unexpected by the research team. Understanding the physics behind this evolution is important for the research team as it is essential to be able to explain every aspects of the operation of a device when trying to obtain approval from health agencies. One objective of this internship was then to discuss with Pr. Takarabe, professor emeritus and expert in semi-conductors to find explanations behind this non-linear behavior.
It was decided to contact Dr. Ian Baikie, founder of KP Technology, for advice, he had conducted measurement on OUReP for the research team in the past and is an expert on the Kelvin Probe measurement, he provided a list of possible steps to follow to understand the relationship between the Light intensity and the Light evoked surface potential. The complete list of advice can be found in Appendix 8.1. One of the step mentionned the calibration of the light source as a way to be able to change the X-axis unit from arbitrary units to something more meaningful.

6.1.1 Light calibration and graphics modification

On the figure 11 the unit corresponding to the light intensity is "Arbitrary Unit" corresponding to the values shown on the front panel of the light generator. The people working at Tokyo Instrument, Inc, the Japanese distributor of KP Technology systems, kindly conducted the measurement of the power emitted by the light source as a function of the arbitrary values and sent the corresponding graph. By using this new data and making the assumptions that all the power emitted was absorbed at the surface of OUReP it was possible to modify the previous graph to show the relation between the surface power and the surface voltage shown in figure 12. This modification allowed to show there is a linear relationship between the the surface voltage and the absorbed power. Measurements will be conducted by the research team to obtain accurate measurements of the absorbed power.

6.2 Proposing experiments to understand the physics behind the light evoked surface potential generation behavior

During the discussion with Pr. Takarabe, 2 hypothesis emerged to explain the behavior of the surface potential generation.

6.2.1 Hypothesis 1: Donor-Acceptor Polarization(Linear Optical Process)

The first hypothesis supposes that the polarization of the photoelectric dye layer is proportional to the number of molecules contained but is also supposes that the light power absorbed by the dye is also

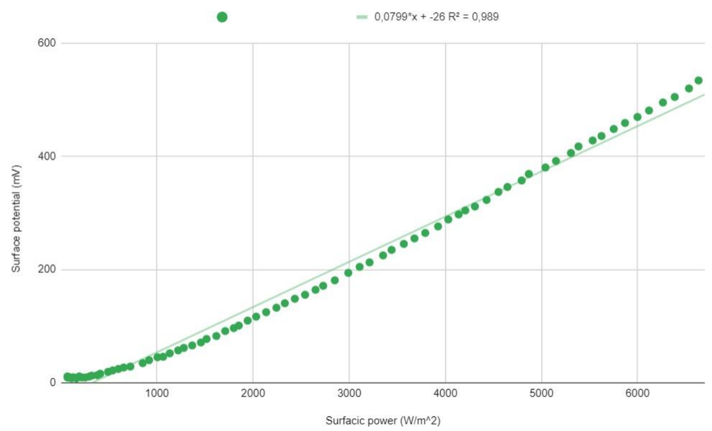


Figure 12: Light evoked surface potential (mV) as a function of absorbed power (W/m^2)

proportional to the number of molecules N. Summarized mathematically :

$$\rho_{\text{layer}} = N \times \rho_{\text{molecules}}$$
and,
$$P_{\text{absorbed}} \propto N \tag{9}$$
Thus,
$$\rho_{\text{layer}} \propto P_{\text{absorbed}} \times \rho_{\text{molecules}}$$

In the previous equations ρ_{layer} corresponds to the total polarization of the device (ie the surface voltage measured), ρ_{molecule} the polarization of a single dye molecule and P_{absorbed} the surfacic power absorbed by OUReP.

6.2.2 Hypothesis 2: Optical Rectification Effect (Non-linear Optical Process)

This hypothesis supposes that the polarization of the photoelectric layer can be expressed as a non linear function depending on the electric field E :

$$\rho_{\text{layer}} = \chi_1 E + \chi_2 E^2 + \chi_3 E^3 + \ldots \tag{10}$$

Since the electric field can be written : $E = E_0 \times cos(\omega t) \longrightarrow E^2 = \frac{E_0}{2} + E_0^2 \times cos(2\omega t)$.
The term $\frac{E_0}{2}$ is the continuous part of the signal and corresponds to the value measured with the Kelvin probe, it is called the Optical rectification. With this hypothesis the reason behind the fact that the polarization measured by the Kelvin Probe is linear to the power of the light source comes from the fact that E^2 is proportional to the Power absorbed.

6.2.3 Proposed experiment :

Since the second hypothesis supposes that the polarization is polynomial function of the electric field with each order that can be measured by different methods. Thus, a way to check this hypothesis would be to measure the other components of the polarization. According to the article [32], the non linear refractive index of the tested material is proportional to the real part of the coefficient χ_3 and the nonlinear absorption is proportional to its imaginary part. So one way to assess the existence of the nonlinearity would be to measure the nonlinear refractive index and nonlinear absorption, thus, measuring the value of χ_3.The article [32] provides a detailed protocol followed to make such measurement on gold nanoparticules samples, using an optic measurement method called Z-scan.
The first hypothesis could be tested by measuring the light induced potential on OUReP samples with various number of dye molecules under constant light intensity. This experiment was previously conducted by the research team but with a small number of samples [33]. Increasing the number of sample could allow to show more directly the relationship between the number of dye molecules and the light evoked surface potential.

7 Conclusion

The main objective of this 3 months internship among Pr. MATSUO and Pr. UCHIDA research team was to evaluate the necessary characteristics required in an artificial nerve system to be able to propagate the difference of potential created by the photoelectric dye and activate neurons cells. Thus, allowing the brain to process the signal and partially restore patient's impaired vision. Using electrical modelling of such system allowed to study a large variety of parameters without the need of manufacturing prototypes. Hence, it was possible to check that the measured values for the light evoked surface potential in the photoelectric dye were enough to activate the neurons when the potential value is superior to 20mV. It was also possible to study important parameters for future prototype development and testing such as the insulation layer's thickness or the distance between the tip of the artificial nerve and the neurons. Studying the use of diverse conductive materials lead to believe that the conductive material should be chosen firstly for its biocompatibility and its availability as a standard material on the market. When taking these parameters into account the most promising material appears to be the carbon fiber. However, the designed model is simplified situation from the real one as there was a strong time limitation over the use of COMSOL Multiphysics. This simplification lead to inaccuracies in the outcomes of the studies. For the future development of the project, since the results obtained during this work cannot be considered as absolute proofs of the behavior of the artificial nerve system after implantation but rather be interpreted as a positive insight to pursue further research by reevaluating the model developed to make it suit the real situation better or by manufacturing a first prototype using carbon fiber as the conductive material and polyethylene as the insulator to measure the real characteristics of the system and begin *in vitro* studies.

Overall this internship was the opportunity to experience the research team operates in an international context and to confront myself to a very interdisciplinary subject as this project involved chemistry, physics, biology and mathematics applied to modelling.

Abstract

Study for developing artificial nerve prosthesis is under-represented in the research field of reparation of impaired nerve function, where priority has been given to nerve regeneration. During this 3 month internship among Pr. Matsuo and Pr. Uchida research team in Okayama University in Japan, the possibility to combine the photoelectric dye, already in use for the OUReP device, with a conductive material was investigated. First by summarizing the recent findings in nerve tissue engineering using conductive bio-polymers. Then by modelling an artificial nerve system electrical properties in COMSOL Multiphysics it was possible to study the ability of the system to activate a cell membrane model depending of various parameters such as the conductive material used or the dimensions of the system. The outcomes of this studies allowed to check that the values of potential generated by the photoelectric dye allowed neurons membrane activation, to find that the optimal thickness of insulation to use was between 15% to 25% of the total thickness. Finally studying various conductive materials showed no difference in the membrane response, indicating either that the model implemented was not set up accurately or that every conductive materials could be used and the main characteristic should be the biocompatibility, making the carbon fiber as the most promising material for further investigation.

Résumé

Durant ce stage de 3 mois au sein de l'équipe de recherche de l'Université d'Okayama dirigée par Pr. MATSUO and Pr. UCHIDA, la possibilité de combiner une teinture photoelectrique avec un matériau conducteur pour former un nerf optique artificiel a été étudiée. Après une étude de l'état de l'art, divers matériaux conducteurs ont été sélectionnés. Leurs propriétés électriques ont été implémentées au sein d'un modèle du système grâce au logiciel COMSOL Multiphysics, permettant d'évaluer l'impact de divers paramètres. Ainsi il a été possible de montrer que les cellules nerveuses pouvaient être activées par toute stimulation électrique supérieure à 20 mV, justifiant la cohérence du choix de cette teinture photoelectrique. l'épaisseur d'isolation électrique en polyethylène offre une réaction idéale lorsqu'elle représente entre 15% et 25% de l'épaisseur totale. Enfin l'emploi de différents matériaux conducteurs n'a pas démontré de différences dans le comportement de la membrane cellulaire, suggérant que une mauvaise implémentation du modèle ou alors que le matériaux conducteur doit principalement être sélectionné pour sa biocompatibilité. Ce constant fait de la fibre de carbon un candidat prometteur pour de futures études.

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8 Appendix

8.1 Transcription of the Advice provided by email by Dr. Ian Baikie

From iain@kelvinprobe.com :

1. To characterise the SPS040 light output as a function of intensity. This could be white light or another wavelength selected by the SPS040 LVF. Useful devices are a power meter (such as Thorlabs) or a calibrated spectrometer. I am an honorary Professor at St Andrews University in Scotland. A physics PhD whom my company sponsors has done the power meter calibration and, if I put you in touch, he may share his report on the power meter data. He will be using the same equipment as you, the relative change in light output is likely to be similar.

2. With this data you could make a good characterisation of the light source and the number of photon emitted.

3. The lamp output could also be monitored on a photodiode too.

4. The lamp emission will depend upon the filament temperature, so we do not expect it to be linear.

5. The photons impinge on the artificial retina, some will be adsorbed, some reflected, some transmitted and some scattered (RATS). Make a gestimate or use measured optical properties of the artificial retina. Make a gestimate of the number of carriers generated (see below).

6. You will need a model of photo adsorption and voltage generation. Probably best to start with a semiconductor model; SPS data will show if there is a clear band-gap, if so, work with wavelengths below band-gap.

7. If we assume that the adsorption is across a semiconductor then we can use the already derived formulas: for example pn junction or single sided semiconductors. It is important to note that we are not seeking a current as in the case of a photodetector,r but a voltage derivation, as in the case of a fermi-level shift, often terms Vs.

8. The fermi-level shift occurs because the absorbed light creates mobile charge carriers that disturbs the electrical balance within the artificial retina and this displaces the fermi-level. The fermi-level represents an equilibrium situation. You should consider the dark situation, the effect of the initial photons and the saturated condition. This is the key figure that will allow other readers to understand your work.

9. The relationship between shift of fermi-level and voltage is exponential, i.e. non-linear. This is the prime reason we do not necessarily expect a linear relationship.

10. I suggest you purchase a Si solar cell, ground one side and monitor the change the surface potential with illumination. Plot the surface potential change versus log light intensity- look for a straight line relationship.

11. Now move to the artificial retinal and see if it is similar or different. Review the data and discuss it.