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Design and manufacture of flexible implantable and energy autonomous neuroelectronic devices

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Neurodegenerative diseases are increasing with the aging of the population. One such neurodegenerative disease is age-related macular degeneration (AMD). The photoreceptors in the center of the retina degenerate and die, which results in vision loss. The French National Authority for Health (HAS) has estimated that AMD will increase by 50% within 20 years and double in 30 [1]. This disease will then affect more than one million people in France.

Medical implants are designed to compensate human body failures, like retinal implants, which aim at restoring the visual capacities of AMD patients. The Institute of Electronics, Microelectronics and Nanotechnology (IEMN) and Axorus, a startup founded in 2019, are collaborating on a retinal implant prototype. IEMN developed and patented an electronic circuit which mimics the electrical signal of a biological neuron. Axorus has integrated this “artificial neuron” into an implant. It is an array of (nearly) identical circuits on a silicon substrate.

The implant will be placed under the retina in order to replace the photoreceptors. Photodiodes connected to the artificial neurons will detect light and act both as sensor and power supply (light is the energy source). The artificial neurons then generate an electrical signal that is transmitted to the healthy cells of the retina. This signal contains the visual information that will be transmitted to the visual cortex. Axorus is currently conducting *ex vivo* excitation tests on blind rat retinas using signals produced by the implant.

To ensure the autonomy of AMD patients, a visual prosthesis must at minimum grant a visual acuity of 2/20 and a visual field of 30°. Regarding the state of the art, two major contributions are made by the works of Prof. Daniel Palanker (Stanford University, USA) and Prof. Diego Ghezzi (EPFL, Switzerland).

Daniel Palanker and Pixium Vision are collaborating on the “Prima” visual prosthesis [2][3]. Today, it is the most advanced retinal implant, currently in clinical trials. To maximize visual acuity, the Palanker’s group chose to use CMOS technology and made a silicon array of coupled photodiodes and electrodes, which is thinned to favor the insertion of the implant and the adhesion of the cells in the retina. The advantages of a silicon substrate are the efficient conversion of light into electric energy (integration of CMOS-photodiodes), the possibility to integrate and connect directly electronic circuits and energy sources to the implant for neural stimulation and a good compatibility with existing microfabrication and manufacturing equipment. In its current state, the implant offers a low visual field, around 10° and measures 2 mm across.

The group led by Diego Ghezzi, develops the prototype called “POLYRETINA”. It offers a visual field greater than 40° (and a diameter greater than 10 mm) [4][5]. It has successfully stimulated retinal cells *in vitro*. POLYRETINA is made of hyper flexible polydimethylsiloxane (PDMS). The implant is foldable and can fit small surgical incisions. The restored visual acuity is for now lower than 1/20 (threshold of legal blindness and acuity restored by the Prima implant).

In view of these results, the two materials (silicon & PDMS) are interesting as substrates for different reasons. On the one hand, flexible materials are very promising for biocompatible implants [6] but new microfabrication processes must be developed to integrate neuro-stimulation interfaces with innovative

substrates (non-silicon). On the other hand, as illustrated above, silicon substrates have many advantages but their rigidity limits their adaptation in the body.

In the frame of this thesis, we want a thin, bendable silicon substrate, that follows the shape of the eye, bendable for easy insertion, and a large implant size to provide a maximum visual field. Our aim is to push the limits of substrate thinning. To preserve the circuit properties, the implant only needs a thin layer of silicon, between 0.1 and 0.2 μm [7], but to be able to handle the implant without breaking it, one objective of this thesis work is to reach a thickness of 10 μm . At this thickness, the silicon should be bendable. The thinning of the implant involves the development of a process using DRIE (Deep Reactive Ion Etching) technology. In addition, a flexible substrate will be added on the back side as a support, to avoid breakage and keep the mechanical (bending) properties of silicon.

AMD and visual prosthetics are not the only application that could benefit from an implant based on the artificial neuron. In some applications like nerve stimulation to cure hemiplegia or urinary disorders, the implant may not be easily powered by light. In the case where photovoltaic energy is not usable, it is necessary to develop another power source. In this thesis, we also aim to select an energy source that will be able to store and provide enough energy to stimulate biological neurons. The energy source will also have to be biocompatible, so that it can be integrated into a retinal implant, or a medical implant intended for another use in a part of the body other than the eye.

We are currently considering several energy sources like RF waves, β -voltaic batteries, ultrasound sources and biofuel batteries [8][9] :

- RF harvesters exploits the ambient RF waves which are the Wi-Fi and the GSM [10]. These waves are highly present in our environment and works on RF technologies are advanced. Thus, developing this type of device seems possible but it is necessary to determine if the power collected will be sufficient to supply the implant with the constraints of size and implantation area.
- β -voltaic batteries use common radioactive components such as tritium or nickel 63, which emit β -rays (high-energy, high-speed electrons), and convert them into electrical energy [11]. These batteries should produce enough power for neuroelectronic implants (not just retinal implants), their longevity largely exceeds 10 years and there does not seem to be any physical barrier to miniaturization. However, studies must be conducted to design this type of device, especially for the miniaturization, which can be expensive and time-consuming.
- Ultrasonic batteries use transducers to emit ultrasound and store energy [12]. This allows for remote battery charging and does not require the source to be attached to the implant. However, ultrasounds can have negative effects on the human body.
- Biofuel batteries are batteries powered by biochemical substances: sugars, bacteria, plants [13]. They are usually biocompatible. The enzymes used are selective but are, for now, not very stable: they denature over time and last only a few months in the best cases.

Within the framework of this thesis, several approaches will be explored in order to design and manufacture compliant and energetically autonomous implants. Two major questions will be studied. First, the flexible nature of the implant and thus the possibility of being more easily implanted in patients, while maintaining its electronic properties. Second, the energy balance of the device has to be defined in order to choose and develop innovative solutions in terms of power supply and autonomy.

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