



Simulating the cortical activity evoked by artificial retinal implants

Teva Andréoletti

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ÉCOLE NATIONALE SUPÉRIEURE DE L'ÉLECTRONIQUE
ET DE SES APPLICATIONS

Simulating the cortical activity evoked by artificial retinal implants

By

Teva ANDRÉOLETTI

Supervisors:

M. Bruno CESSAC

INRIA Sophia Antipolis

M. Frédéric CHAVANE

INT Marseille

M. Nicolas SIMOND

ENSEA Cergy

March-August 2019, 3^e année - option EIB (2018-2019 - Promo 2019)



2004 Route des Lucioles,
06902 Valbonne



Faculté de Médecine,
27 Boulevard Jean Moulin,
13005 Marseille



6 Avenue du Ponceau,
95000 Cergy

ABSTRACT

This study was carried out as part of the third year of study at ENSEA, and more specifically as the final year project of the engineer school.

This is a continuation of my internship from the previous year, the objective of which was to better understand the activity evoked by stimulation of the retina with implanted retinal prostheses used to partially restore sight in blind patients suffering from retinal degeneration.

Currently, the BIOVISION team at Inria is designing a retina simulator, called MACULAR, aiming at reproducing the retina response to stimulation in normal (stimulation by light) and pathological conditions (electric stimulation by prostheses).

The goal of this internship is to integrate the model I worked on last year in MACULAR.

The internship has been done in collaboration between Bruno Cessac (Biovision, INRIA, Sophia-Antipolis) and Frédéric Chavane (INT, CNRS, Marseille).

Keywords

Neurosciences, low vision, retina, visual cortex, retinal prostheses, modeling, simulation.

RÉSUMÉ

Cette étude s'est déroulée au cours de la troisième année d'étude de l'ENSEA, et plus précisément en tant que projet de fin d'étude (PFE) d'école d'ingénieur.

Il s'agit de la continuation de mon stage de l'année précédente, dont l'objectif était de mieux comprendre l'activité évoquée par la stimulation de la rétine par des prothèses rétiniennes utilisées pour restaurer partiellement la vue chez des patients aveugles atteints de dégénérescence rétinienne.

Présentement, l'équipe Biovision de l'Inria conçoit un simulateur de rétine, appelé MACULAR, visant à reproduire la réponse rétinienne à la stimulation en conditions normales (stimulation par la lumière) et pathologiques (stimulation électrique par prothèses).

Le but de ce stage est d'intégrer le modèle sur lequel j'ai travaillé l'année dernière à MACULAR.

Le stage a été réalisé en collaboration entre Bruno Cessac (Biovision, INRIA, Sophia-Antipolis) et Frédéric Chavane (INT, CNRS, Marseille).

Mots-clés

Neurosciences, basse vision, rétine, cortex visuel, prothèses rétiniennes, modélisation, simulation.

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I would also like to thank the entire Experimentation and Development Department team, whose help was particularly valuable in moving this complex project forward. Working with them has been a particularly enriching experience.

I would like to particularly thank Bruno Cessac, Frédéric Chavane and Sébastien Roux for allowing me to do these internships. The passion they have for their job and the enthusiasm they show when they talk about it are among the main reasons why I have enjoyed working on this subject so much.

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GENERAL INTRODUCTION

Context

In an aging society like the French one, diseases like AMD (Age-related Macular Degeneration) are increasingly present and require treatment. Because visual impairment is such a major global health issue, research in this area is essential.

With over 280 millions of people living with a visual impairment due to pathologies of the retina, scientific interest in understanding how those diseases impact on the visual system has increased in the last years. Although the majority of these impairments are preventable or curable (such as the cataract, which is a clouding of the lens in the eye leading to a decrease in vision), retinal degeneration disorders had no cure until recently.

With this in mind, one of the objectives of the BIOVISION team at INRIA and the NeOpTo team at INT Marseille is to improve prosthetic vision through cortical imaging and computational science.

Indeed, the increase of our knowledge in this field is one of the factors which, at the same level as the development of new technologies, will bring progress in the adaptation of fundamental research to tools that improve the sight of visually impaired people.

The project

The visual system consists of many elements, all of which interpret the coded information from visible light in order to reconstruct our environment. The light enters through the eye and is projected onto its fundus, called the retina. The retina converts this light into variations of electric potential in neurons using a mechanism called phototransduction. At the output of the retina these variations of electric potential are converted into sequences of action potentials (spike trains). This signal is then transmitted through the optic nerve to the thalamus in the brain, one of known main functions is to relay sensory signals to the visual cortex. Descriptions

of the major elements of visual recognition will be given in Part I.

However, several factors can affect the functioning of the visual system. Among them, many pathologies of the retina. Some of these degenerations, such as *Macular Degeneration* and *Retinitis Pigmentosa*, may lead to blindness. Nevertheless, new techniques have begun to be used to partly compensate these disorders (chapter 3).

Among those techniques, retinal implants are electronic devices attached to the retina that substitute to defective cells in order to partially restore vision. The principle is as follows: images acquired by a "camera + processor" system are encoded and sent as pulses to a matrix of electrodes. It then stimulates the still functional cells of the retina in order to reproduce a luminous impression. Unfortunately, these prostheses have several limitations that will be discuss later (see subsection 3.2.4).

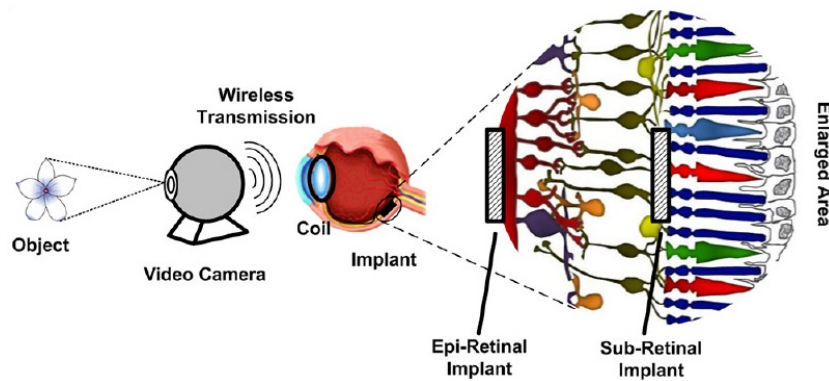


Figure 1 – Chain of function of retinal prostheses. Two types of retinal electrical implant (epiretinal or subretinal) are shown on the enlarged area (*Source: Journal of ophthalmic & vision research website*)

Among those limitations, it is difficult to target specific cells in the retina because of the larger electrode size. When an electrical pulse is sent to the visual cortex, what is called a *phosphene* is observed. This is a luminous activation point in the visual field that corresponds to the spatial location of the pulse. However, recent results in F. Chavane team on local stimulation of the retina showed evoked phosphene that are up to 10 times larger than what was expected from the activity evoked by visual stimuli, leading to a severe loss of visual resolution [1].

This observed spread of evoked cortical activity is presumably due to four effects: (i) an electric diffusion at the interface implant-retina; (ii) a spread of electric activity induced by the activation of retinal cells axons near the implant; (iii) an electric diffusion in the visual cortex and (iv) the optical diffusion of the signal registered by optical imaging.

In order to help understand the origin of the observed diffusion, a simulation model was developed by F. Chavane (see Part II). First, the retinal activation is

modeled to take into account the diffusion effects (i) and (ii). In a second step, the diffusion effects (iii) and (iv) are applied to the activation profile obtained after retino-cortical transformation. This model aims to quantify these four diffusive effects and more especially to analyse the role played by the retina's network (diffusive effect (ii)) in the spread of activity, by comparing the results of the model with the experimental results.

Thus, the subject of my first internship, last year, was to reuse this model in order to find the results already obtained while modifying the program to optimize it; then finally to improve it in order to be able to compare the result obtained with experimental data. Moreover, this preliminary study was carried out on the rat but retinal prostheses are a priori implanted in humans. The interest was then to adapt the model for animals closer to humans such as the monkey.

The goal of my final year project

Currently, the BIOVISION team at Inria is designing a retina simulator, called MACULAR, aiming at reproducing the retina response to stimulation in normal (stimulation by light) and pathological conditions (electric stimulation by prostheses).

The goal of the present internship is to integrate the model I worked on last year in MACULAR.

This report is divided into four parts, starting with an introductory part giving a short description of the working environments related to this internship: the INRIA Sophia Antipolis and INT Marseille laboratories. Then, the first part presents the visual system as a whole and more specifically the retina. The second is presenting the project as a whole, including a description of my study topic from the previous year. Finally, the last chapter will present the results obtained this year and the prospects they open up.

Please note that since the study context has not changed since my previous internship, several parts of my previous report have been reused.

Presentation of the INRIA and of
the Institut des Neurosciences de la
Timone (INT)

This internship, a collaboration between INRIA and INT, allowed me to learn more about these two institutions. If the majority of the internship took place on the INRIA site, my few visits to INT Marseille gave me the opportunity to really see the differences that can exist between two environment of work with the same purpose: Research.

INRIA

INRIA, Institut National de Recherche en Informatique et en Automatique, is a French institution dedicated to computational sciences which was created in 1967. There are 8 research centers in France, with more than 180 project-teams, in the following fields :

- Applied Mathematics, Computation and Simulation;
- Algorithmics, Programming, Software and Architecture;
- Networks, Systems and Services, Distributed Computing;
- Perception, Cognition and Interaction;
- Digital Health, Biology and Earth.



Figure 2 – Map of the INRIA research centers (*Source: conf-ng.jres.org / JRES 2015 "Le centre de services d'Inria et ses outils"*).

The Inria Sophia Antipolis - Méditerranée research center

Since 1983, the Inria Sophia Antipolis - Méditerranée research center, with its research teams based in Nice-Sophia Antipolis, Montpellier, Bologna (Italy) and Athens (Greece), is one of the major players in the European research area.

The center has not only research-oriented objectives but also entrepreneurial ones. It has 33 research teams, and 25 start-ups have been created in its incubator since 2005. This makes it possible to industrialize products from research prototypes, while disseminating the know-how acquired at the institute.

Nearly half of the research teams are mixed with one or more partners (the University of Côte d'Azur, CNRS, etc.). Nevertheless it does not stop there, since it also has many international partnerships. Moreover, organisms such as the ANR (The French National Research Agency) and the ERC (European Research Council) are really important since they help public research organisations, universities and even private companies by funding projects in all fields of science - for both basic and applied research.

The BIOVISION team

Among the 29 teams that are located in the Sophia-Antipolis center, my internship was affiliated to the BIOVISION team created in 2017.

Its theme is *Computational Neuroscience and Medicine* and the acronym means: "*Biologically plausible Integrative mOdelS of the Visual system : towards synergIstic Solutions for visually-Impaired people and artificial visiON*".

People with vision loss due to retina impairments either have a certain degree of vision loss, low vision or even blindness.

The purpose of the BIOVISION team is to better understand biological vision through fundamental research as well as innovative technological developments in order to develop tools that will enable people with visual impairments to regain sufficient vision for their daily lives.

Website : <https://team.inria.fr/biovision>

The Experimentation and Development Department

The Experimentation and Development Department (SED - Service d'Expérimentation et de Développement) is an Inria service composed of engineers whose mission is to assist the laboratory teams in the development of their software. This service is organized in the form of a one to three-week coding sprint during which engineers

work in collaboration with team members in order to set up tools that enable them to respond to their needs.

During this internship, I had the opportunity to participate in two coding sprints. In particular, it showed me the importance of the following skills:

- Synthesis and explanation of a work in progress: it is imperative to be able to present your project in a concise and understandable way to people external to the project who are not necessarily familiar with the subject area (in our case, neuroscience and vision).
- Description of a problem and listing of the requirements that must be met: accurately defining the objectives that we want to achieve is what will allow engineers to provide us with more precise advice.

C++ language training for beginners

During my two internships, I was able to see the importance given to trainings at INRIA. For instance, many training offers are proposed by email and the opportunity is given to team members to participate in summer schools according to the team budget.

For instance, this year I had the opportunity to participate in a one-week C++ language course for beginners. Even though I had already been working on the project for three months, this short training allowed me to get back to the basics of the C++ language in order to better resume my work on the MACULAR platform, which is particularly complex.

As I had never done C++ before this internship, I thought that the difficulties I experienced at the beginning came from my lack of knowledge of the language. However after this training, I noticed the significant similarity to Java that I studied in my second year at ENSEA. I therefore realized that my difficulties came from the complexity of the project I was working on.

INT

The INT, Institut de Neurosciences de la Timone, is a French institution dedicated to computational sciences which was created in 2011. It is a research unit of the University of Aix-Marseille and CNRS (National Center for Scientific Research). The CNRS is the largest governmental research organisation in France and the largest fundamental science agency in Europe.

In order to bridge the gap between fundamental and clinical research, INT conducts world-class research in fundamental neuroscience, from the cellular to the cognitive level.

The main thematic axes to which the institute devotes itself deal with the understanding of the dynamics of motor control (spinal and cortical systems), the perception systems (audition, vision) and the behavioral regulation systems (emotion, motivation).

Moreover, the institute hosts eleven research teams and has six technological platforms such as the molecular and cellular neurosciences platform or the in vivo and in vitro neuronal photon imaging platform.

The presence of these technological platforms in the same building makes it possible to handle a wide variety of interdisciplinary projects in the following fields:

- Neurophysiology;
- Cellular, Cognitive and Behavioural Neurosciences;
- Photonic Neuroimaging.

Website : <http://www.int.univ-amu.fr/>

The NeOpTo team

The NeOpTo team, headed by F. Chavane, aims at elucidating the neural computations that underlies active vision. Even if vision is a major sensory input that guides our actions, helps us perceive our environment and conduct cognitive tasks, the visual inputs that reach the brain represent a computational challenge due to their complexity and dynamics. To investigate the functioning of the visual system, the NeOpTo team combines multiple expertises involving behavioral studies in both humans and monkeys, ophthalmologic clinical approaches and electrophysiological and real-time optical imaging studies in behaving monkeys.

Part I

Fundations

Chapter 1

The visual system

This chapter gives an overview of the structure of the visual system. In Section 1.1, the visual pathway is described. Sections 1.2 to 4.1 focus on the description of each part of the visual system.

1.1 The visual pathway

The visual system is the set of organs involved in the processing of visual information, from the eye to the visual cortex. A diagram of the visual pathway is given in the Figure 1.1. It is a detailed diagram that gives not only the main elements responsible for visual recognition, but also the evolution of the visual field projection from the retina to the visual cortex via the thalamus. This diagram has been very useful in understanding the visual system.

Light penetrates the eye and passes through it to the photosensitive cells of the retina on which the inverted image of the visual field is projected. The photons are then converted into electrical signals and transmitted to the brain by the optic nerve to the visual cortex, for interpretation.

1.2 The anatomy of the eye

Light enters the eye through the cornea, through the pupil and then through the lens. Accommodation corresponds to the lens shape change and is controlled by the ciliary muscle. It allows to change the focus position of the lens.

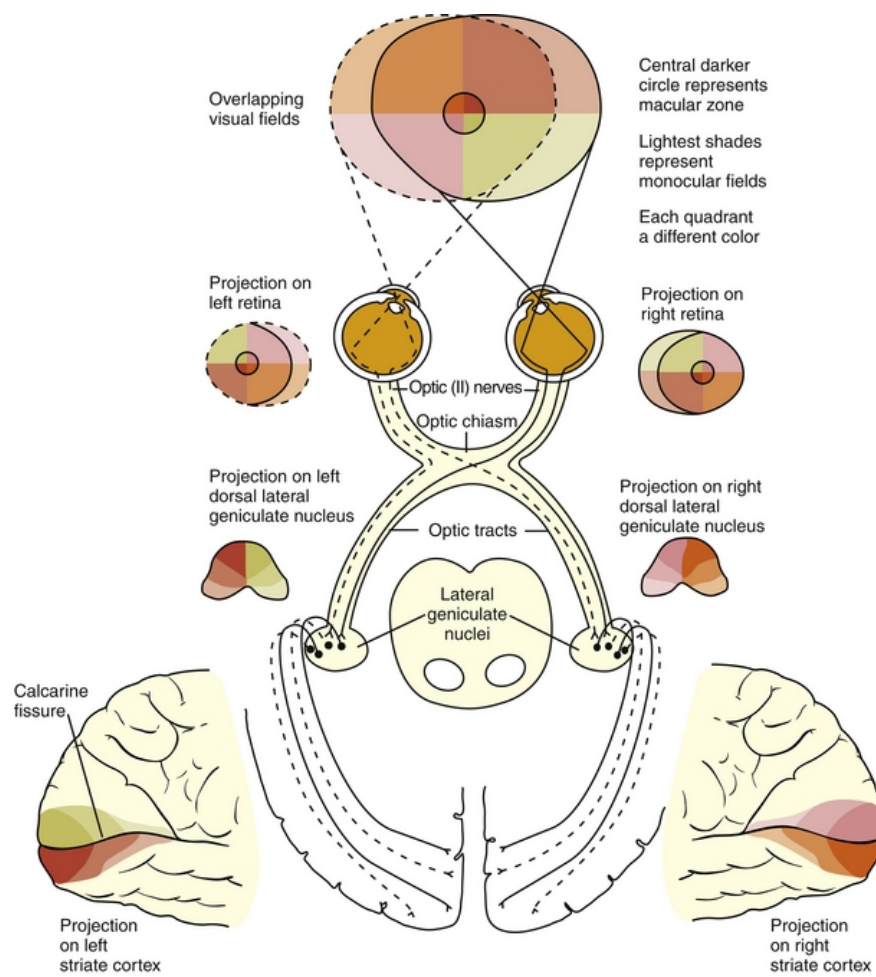


Figure 1.1 – Diagram of the visual pathway (Source: <https://basicmedicalkey.com/>).

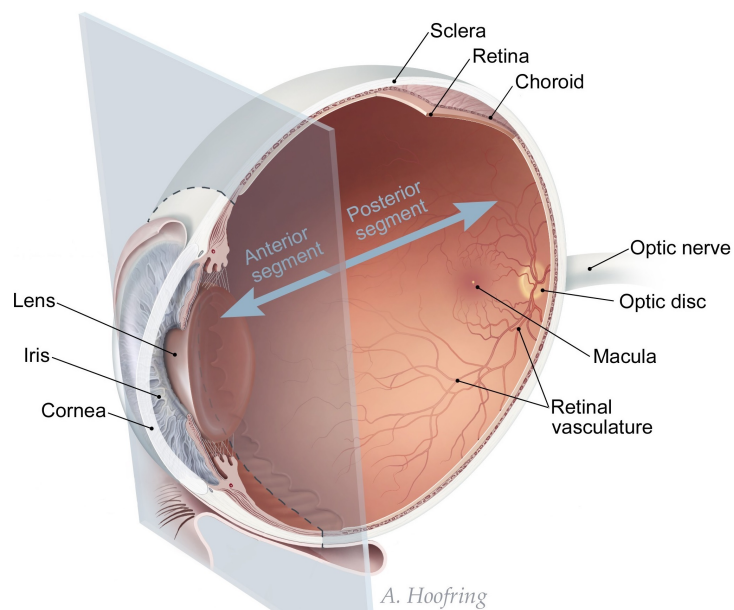


Figure 1.2 – Eye structure diagram (Source: NIH Medical Arts).

1.3 From the optic nerve to the visual cortex

The optic nerve corresponds to the axons of the ganglion cells that constitute the last layer of the retina, which will be described in chapter 2. The two optic nerves then meet at the level of the optical chiasma which reconstructs the visual field and separates it into two parts. Indeed, the left part is treated by the right hemisphere of the visual cortex and vice versa (see Figure 1.1).

The continuation of the optic nerves after chiasma is called the optic tract. For each hemisphere, visual information is distributed to nuclei that have different roles. However, nearly 90% of the axons of the optic nerve move towards the lateral geniculate body of the thalamus.

Some examples among these nuclei:

- the lateral geniculate body (LGN). Located in the thalamus, it sends information that will be analyzed by the visual cortex;
- the suprachiasmatic nucleus (SCN). Located in the hypothalamus, this nucleus contains the biological clock allowing to synchronize the awakening/sleep cycle according to the presence or absence of light;
- the superior colliculus. Its role is to direct sensory receptors from the head to objects of interest.

The nerve fibres that connect the lateral geniculate nucleus to the visual cortex are called optical radiations. An optical radiation lesion leads to partial or total loss of vision in the hemisphere concerned (anopia).

Finally, visual information is processed in the visual cortex which is the largest system in the human brain. It performs low level treatments (orientation, contours) but also high level treatments (shapes, movements).

Chapter 2

Anatomy and physiology of the retina

In this chapter, the main properties of the retina are summarized: its organization but also its signal processing within the visual system. In Section 2.1, an overview of its anatomical structure is given. And in Sections 2.2 and 2.3, we focus on the description of each type of retinal cells as well as their function.

2.1 The anatomical structure of the retina

The retina is the sensitive organ of vision and is located at the back of the eye attached to Retinal Pigment Epithelium (RPE) under the choroid. The retinal pigment epithelium is the pigmented cell layer that bring nutrients and oxygen from the choroid to the photoreceptor cells, and supplies, recycles, and detoxifies products involved with the phototransduction process. The choroid is the vascular layer of the eye filled with blood vessels that nourish the retina.

It has three specific areas (see Figure 1.2):

- the macula : central region of the retina, located close to the optical axis of the eye;
- The fovea : central region of the macula which corresponds to the highest density of cone-type photoreceptors. This is where visual acuity is at its peak;
- the optic disc : region of optic nerve emergence without photoreceptors.

The retina is a complex multi-layered structure that converts light into electrical signals and performs the first stages of image processing in vision. It is composed

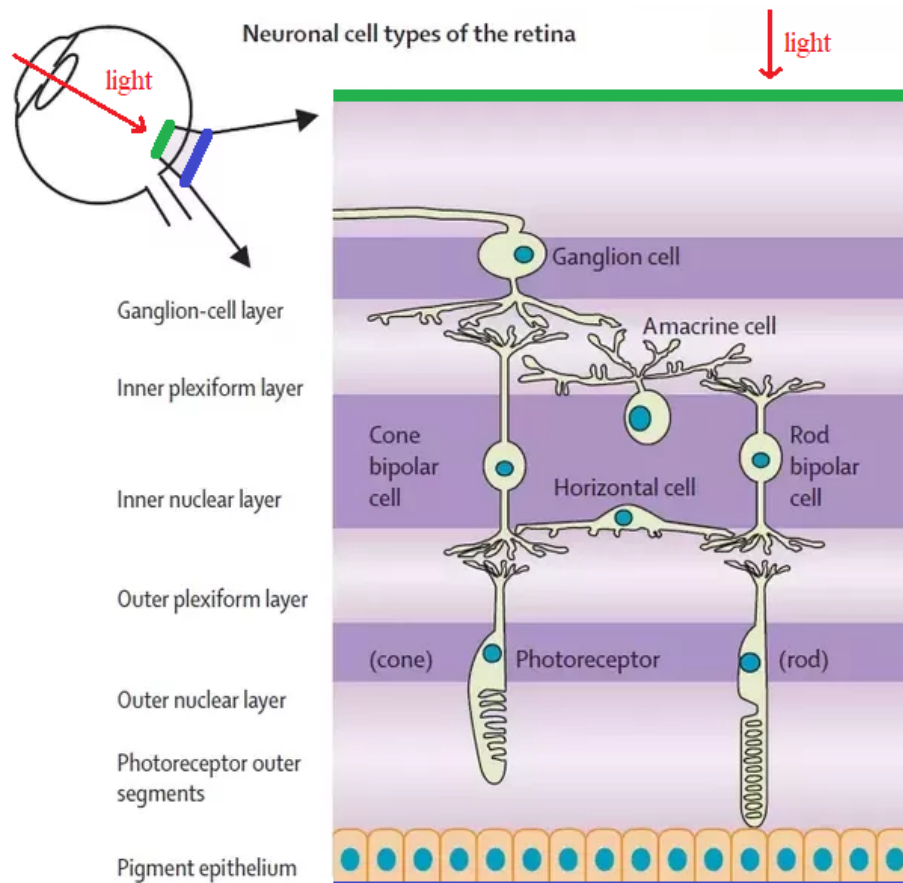


Figure 2.1 – Structure of the retina (Hartong et al. 2006).

of six classes of cells (ganglion, amacrine, bipolar, horizontal, photoreceptors and Müller glial cells), three nuclear layers and two synaptic layers.

The nuclear layers are:

- the Outer nuclear layer (ONL) : photoreceptors (rods and cones);
- Inner nuclear layer (INL): horizontal cells, bipolar cells, amacrine cells;
- Ganglion cell layer (GCL) : ganglion cells (output cells, axons form the optic nerve), displaced amacrine cells;
- The retina is also composed of Müller glial cells that ensure both homeostasis (the tendency of organisms to regulate themselves and maintain their internal environment in a stable state) of tissues and the protection of neurons.

The synaptic layers are:

- Outer plexiform layer (OPL) : synaptic contacts between photoreceptors, horizontal and bipolar cells;

- Inner plexiform layer (IPL) : synaptic connections between bipolar, amacrine and ganglion cells. IPL is divided into On and Off layer.

2.2 Feedforward connectivity

2.2.1 Photoreceptors

In the retina, only photoreceptors are sensitive to light. There are three types of them:

- The rods: about 120 million in the human retina [10], they are located outside the foveal zone. Rods are low-light receptors responsible for scotopic (night) vision. They do not mediate color vision, and have a low spatial acuity;
- The cones: most of them are located in the fovea centralis, they are about 6 million in the human retina [10]. Cones high-light receptors responsible of photopic (daylight) vision. They ensure color vision and are responsible for high spatial acuity;
- The intrinsically photosensitive retinal ganglion cells (ipRGCs) are the third and rarest type of photoreceptor. Unlike the other two types of photoreceptors that show rapid hyperpolarization in response to a light stimulus, ipRGCs have a very slow response curve to light stimuli, allowing them to integrate information over a long period of time. Their role is therefore more dedicated to reporting the overall level of light intensity rather than transmitting detailed information about the visual image.

2.2.2 Phototransduction

The retina has the capacity of converting photons in variations of electric potential. Phototransduction provides an enormous signal amplification system and consists of several stages:

- A photon is captured by a visual pigment molecule, called opsins (rhodopsins in the case of the rods);
- The activation of a molecule induces a cascade of chemical reactions whose multiplicative factor is huge. Indeed, for one activated rhodopsin molecule, there are about 800 transducin molecules and 4 800 activated cGMP molecules participating to the enzyme cascade;

- It then causes the closure of about 200 Na⁺ channels (representing 2% of all channels of a rod) that induces a significant variation of the photoreceptor membrane potential.

Therefore, to sum up, one single photon triggers a variation of about 1mV in the photoreception membrane.

It is interesting to do an analogy between phototransduction (biological system) and photomultiplier (electronic system). The photomultiplier is a photon detection device in the form of an electron tube containing a photocathode, several dynodes (electrodes) and an anode. Under the action of light, electrons are ejected from the photocathode by photoelectric effect followed by a multiplier effect. These detectors multiply the current produced by incident light by as much as 100 million times. However, unlike the biological system, this one requires a greater consumption of energy to impose the tensions of the various components. Indeed, each dynode is held at a more positive potential (by about 100 Volts) than the preceding one.

In contrast, photoreceptors, and more generally retinal cells, handle voltages of order mV and currents of nA.

2.2.3 Bipolar cells

Bipolar cells are so-named because they have a central body with two extensions (axons). They transmit signals from photoreceptors or horizontal cells directly or indirectly to ganglion cells (via amacrine cells).

A bipolar cell is synaptically connected to nearly 100 photoreceptors grasping the light from a local region of a visual scene. As a consequence, the bipolar cell will respond electrically (variation of its membrane potential) to the light pattern occurring in this region. This leads to the notion of receptive fields explained in Figure 2.2.

Moreover, unlike most neurons in the retina, bipolar cells communicate through graduated potentials, rather than action potentials (spikes). Depending on the stimulus, the graduated potentials can be depolarizing (OFF) or hyperpolarizing (ON), while the action potentials always lead to depolarization of the membrane and inversion of the membrane potential. However, the main difference is that graduated potential are equivalent to analogic computation while spikes are equivalent to binary computation.

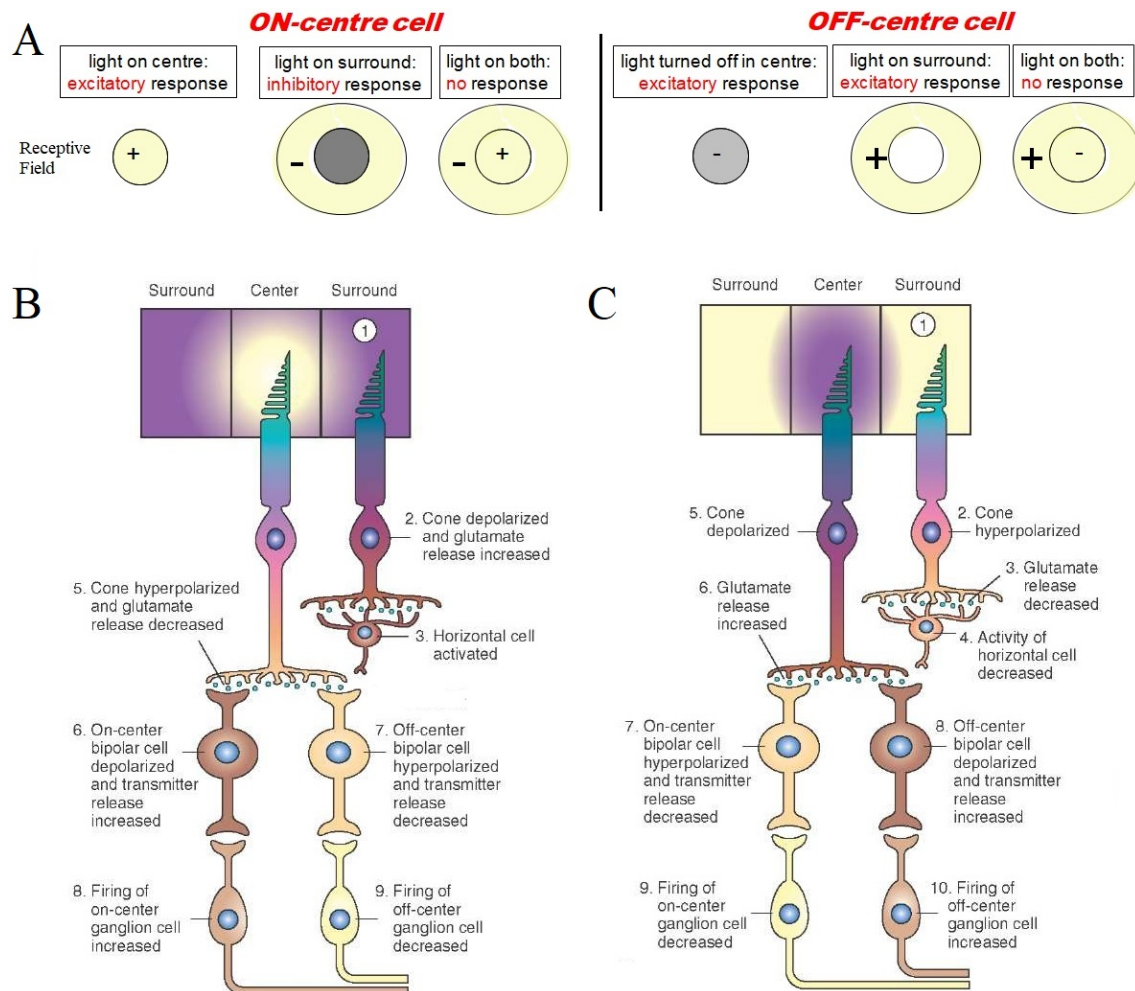


Figure 2.2 – Responses of retinal bipolar and ganglion cells to darkness and illumination in centre-surround receptive fields (*Source: <http://what-when-how.com/neuroscience/>*). (A) ON and OFF type center-surround cells (*Source: Evelyne Sernagor, lecture on the retina, september 2015*). (B) Changes in the electrical activity of the photoreceptor and on-center and off-center bipolar and ganglion cells when the photoreceptor receptive field surround is in the dark. (C) Changes in the electrical activity of the photoreceptor and on-center and off-center bipolar and ganglion cells when the photoreceptor receptive field surround is illuminated.

2.2.4 Ganglion cells

Retinal Ganglion Cells (RGC) are at the final stage of retina encoding. They are the ones that emit spikes (via their axons which constitute the optic nerve) to the visual cortex, via the thalamus (LGN). Spikes consist of stereotyped mechanisms which are initiated by excitatory presynaptic potentials, causing the membrane potential to rapidly increased and then decrease. There are about 1.2 to 1.5 million retinal ganglion cells in the human retina. With about 125 million photoreceptors per retina, on average each retinal ganglion cell receives inputs via bipolar cells from about 100 rods and cones. However, these numbers vary greatly among individuals and as a function of retinal location. In the fovea, a single ganglion cell communicate with a few number of photoreceptors, while in the extreme periphery, a single ganglion cell receive information from many thousands of photoreceptors. Like bipolar cells, RGN can also be of ON or OFF type. They are also diversified in terms of receptive fields (notion described in Figure 2.2) which can be roughly divided in 3 groups:

- Magnocellular (M-retinal ganglion cells) have relatively large center-surround receptive fields, are color insensitive, and are most sensitive to movement of visual stimuli;
- Parvocellular (P-retinal ganglion cells) have relatively small center-surround receptive fields, are color sensitive, and are well suited for detecting contrasts that form the basis for shape discrimination;
- Koniocellular behave like P-retinal ganglion cells, have the smallest concentric receptive fields, have stronger color sensitivity than P-retinal ganglion cells, and are well suited for detecting colors that aid in shape discrimination.

2.3 Lateral connectivity

2.3.1 Horizontal cells

The horizontal cells are laterally connected to several cones, rods and bipolar neurons. Their role is to inhibit the activity of surrounding cells. This selective suppression of certain nerve signals is called lateral inhibition and its general role is to increase the acuity of a sensory signal by suppressing the signal of less illuminated photoreceptors.

It results in the center-surround architecture presented in Figure 2.2: When the centre field of a bipolar cell is illuminated, there is a hyperpolarization of center photoreceptors. Less illuminated photoreceptors in the surround field cause the

hyperpolarization of horizontal cells, which by releasing neurotransmitters ¹ trigger the depolarization of the surround photoreceptors.

2.3.2 Amacrine cells

The morphology of amacrine cells is very diverse and they use an impressive number of neurotransmitters. Their cellular bodies are all located in the inner nuclear layer (INL) and their synaptic endings in the inner plexiform layer (IPL). By connecting bipolar and ganglionic neurons, they form an indirect alternative route between them. Amacrine cells seem to have many functions, most of which are still unknown, but some specific functions can be outlined [7]:

- Form an indirect alternative route between retinal ganglion cells and bipolar cells in the IPL;
- Create functional subunits within the receptive fields of many ganglion cells;
- Contribute to vertical communication within the retinal layers;
- Through their connections with other retinal cells at synapses and release of neurotransmitters, they contribute to the detection of directional motion. They also modulate light adaptation and circadian rhythm, and control high sensitivity in scotopic vision through connections with rod and cone bipolar cells;
- They also contribute to differential motion detection. [8]

¹As a reminder, neurotransmitters are chemical messengers that transmits signals across a chemical synapse from one neuron to another.

Chapter 3

Retinal degeneration and treatments

3.1 Retinal diseases

There are many retinal diseases that can affect any part of the retina, and most of them cause visual symptoms. If left untreated, some retinal diseases can cause severe vision loss or blindness. Depending on the disease and the patient's condition, there are treatments that aim to stop or slow the disease or even partially restore vision. We will focus here on diseases that have received treatment in terms of gene therapy, cell transplantation and retinal prostheses.

3.1.1 Retinal degeneration (rhodopsin mutation)

Retinal degeneration is the deterioration of the retina caused by the progressive and eventual death of the cells in the retina. People with retinal degeneration may have the following symptoms: visual impairment such as the development of black spots in the field of vision for example, night blindness, retinal detachment, sensitivity to light, tunnel vision and loss of peripheral vision until complete loss of vision.

3.1.2 Retinitis Pigmentosa (rod-cones dystrophy)

Among degenerative diseases of the retina, retinitis pigmentosa (RP) is one of the most common diseases. RP is a group of hereditary diseases that cause retinal degeneration. In most cases, the rods are affected first, affecting peripheral and night vision. As the disease progresses and the cones are affected, there is a decrease in visual acuity, colour perception and central vision.

To be more precise, it is a disease that results from harmful changes in genes that carry the instructions for making proteins that are needed in photoreceptors. Three scenarios can result in damage to photoreceptors [7]:



Figure 3.1 – Visual perception of a person with retinitis pigmentosa.

- The cell's functioning is limited by the severity of gene mutations that cannot then produce the required protein;
- Some mutations produce a protein that is toxic to the cell.;
- Finally, other mutations lead to an abnormal protein that does not function properly.

3.1.3 Macular degeneration

Also called Age-related Macular Degeneration (AMD), it affects older people and results in the distortion and loss of vision in the center of the visual field (see Figure 3.2). In the Western world where population is aged, it is the most common retinal disease because it is the leading cause of blindness and visual impairment in the elderly [7].

It occurs in two forms:

- In the "dry" form, there is gradual degradation of the photosensitive cells in the macula and the supporting tissue under the macula. These changes cause vision loss at several points in the center of the visual field;
- In the "wet" form, abnormal blood vessels grow underneath the retina. These vessels can leak fluid and blood, which can cause swelling and damage to the macula. Unlike the dry macular degeneration, damage can be rapid and severe.

While this disease does not lead to total blindness, it does result in distorted vision with loss of contrast sensitivity. For example, a grid of straight lines appears wavy at its center; contours are less sharp and shadows and colors less vivid (Figure 3.2).

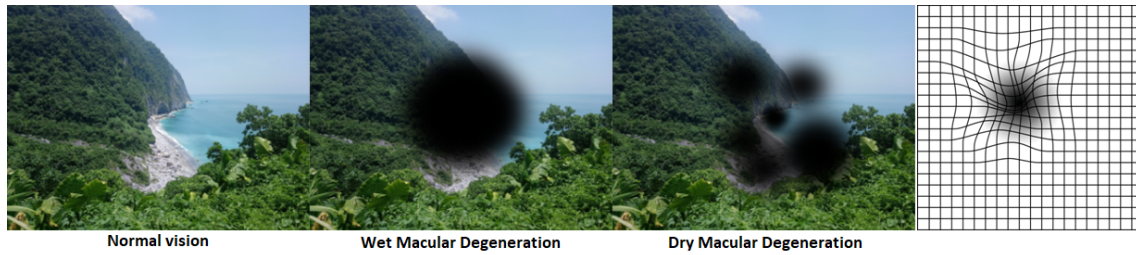


Figure 3.2 – Visual perception of a person with macular degeneration, and visual perception of a grid. AMD results in distorted vision with loss of contrast sensitivity. For example, a grid of straight lines appears wavy at its center; contours are less sharp and shadows and colors less vivid (Source: <https://www.allaboutvision.com/conditions/amd.htm>).

3.2 Retinal therapy

Today, retinal therapies are essential to stop retinal diseases and even partially restore vision to near-normal acuity. Currently, techniques such as electrical prostheses, for instance, make it possible to partially restore sight to blind people. The patient can then read large letters or catch objects. Their daily lives are therefore greatly improved, for example by being able to move around or climb stairs.

3.2.1 Genes therapy and stem cells transplant

Gene and cell therapies have the potential to prevent, halt, or reverse diseases of the retina in patients with currently incurable blinding conditions.

The gene therapy apply only for very specific diseases involving a few genes mutations. Its goal is to virally supplement retinal cells expressing mutant genes with healthy forms of the gene. It thus allows the repair and proper functioning of retinal photoreceptor cells in response to the instructions associated with the healthy gene inserted via a virus vector (tools commonly used by molecular biologists to deliver genetic material into cells [Wikipédia]). Likely, gene therapy may preserve remaining healthy retinal cells but it fails to repair the damage in already diseased photoreceptor cells [7].

For its part, stem cells transplantation is currently investigated with the objective of repairing the damage caused by the loss of photoreceptors. Since the inner part of the retina is left intact by the photoreceptors degeneration, replacement by stem cell could be efficient. Indeed, to contribute to the retinotopic map, the new cells need to make the right synaptic connections with the inner layer of the retina.

3.2.2 Retinal prostheses

Even if retinal degenerative diseases leave the retina unable to sense light, there are still neurons remaining in the retina (bipolar and ganglion cells) that can be electrically activated on the base of established techniques for nerve stimulation.

For this, there are currently two types of retinal prostheses: electrical and optogenetic prostheses.

3.2.3 Optogenetic prostheses

These new generation prostheses are based on the photosensitization of neurons (Wikipédia). In other words, it involves genetic modification of nerve cells so that they become sensitive to certain wavelengths. Photosensitization is obtained by injecting a viral vector allowing the production of specific cells in a target zone of the retina. This method is very recent and is still under development (first human trial in 2016), but it is expected to restore vision to near normal acuity [7].

3.2.4 Electrical prostheses

The retinal prosthesis is composed of three elements (see Figure 3.3): a camera that converts photons into digital data, an electronic microcircuit (which transforms the camera information into an electrical signal and produces stimulus current) and a matrix of microscopic electrodes (implanted in the eye in contact with the retina, it directly delivers coded information to the inner layers of the retina).

As a reminder, when the photoreceptors of the retina are defective or even inoperative, the biochemical processes that convert photons into action potentials are no longer effective. The purpose of implanting an electrical prosthesis is therefore to replace these chemical processes and directly send coded information to the inner layers of the retina, by electrically stimulating ganglions cells.

There are two types of electrical prostheses: epiretinal or subretinal implants.

Note however that it is the electrons that carry the charge in the metals, whereas in the body, it is the ions. In addition, living systems have been able to perform highly sophisticated cognitive tasks with minimal energy consumption, unlike electronic systems. Indeed, even if each unit works slowly, the whole system is massively parallel.

The difference in the nature of these two components imposes two problems :

- The Joule effect: The implantation of a prosthesis must necessarily take into account this very restrictive effect. The amount of information sent cannot

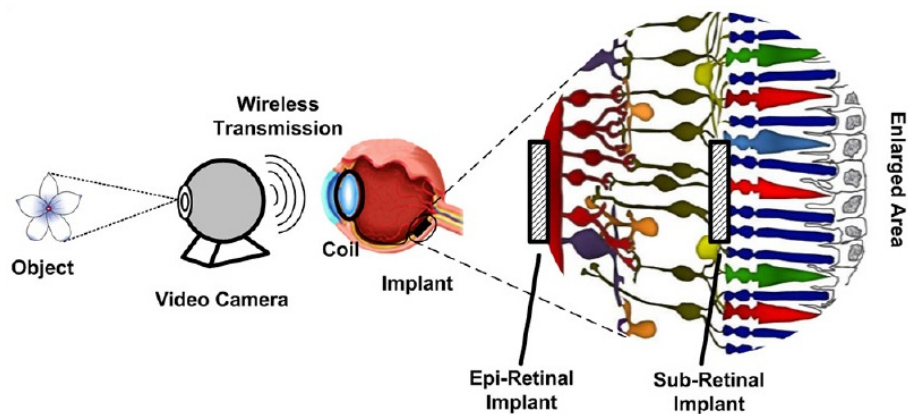


Figure 3.3 – Chain of function of retinal prostheses. Two types of retinal electrical implant (epiretinal or subretinal) are shown on the enlarged area (*Source: Journal of ophthalmic & vision research website*)

be too significant due to heating of the electrode, which may burn the eye or cause pain. The dangerous effects of a rise in temperature imposed by the Joule effect limit therefore the sending of information;

- The electronic prosthesis and the retina are not perfectly touching each other. The aqueous system at the back of the eye forms an interface between the two systems, which causes the electrical signal to diffuse.

Electrical prostheses have several additional limitation such as:

- the electrodes are larger than the retinal cells, making it difficult to target individual cells;
- Electrical stimulus can excite but not inhibit neurons;
- Since electronic retinal prostheses are implanted, the device lifespan must be as long as possible while ensuring that they do not cause functional loss to surrounding tissues.

Finally, although retinal prostheses have many limitations, they still make partial vision restoration possible in blind people which is an important progress. They can read big letters, catch objects and even climb stairs. However, this technology is still poorly mastered and only a few companies are manufacturing retinal implant, such as the French company Pixium Vision and the American company Second Sight Medical Products.

Chapter 4

Physiological model of the neural processing of visual information

The visual cortex, mainly occupying the occipital lobe of the brain, is responsible for processing visual information.

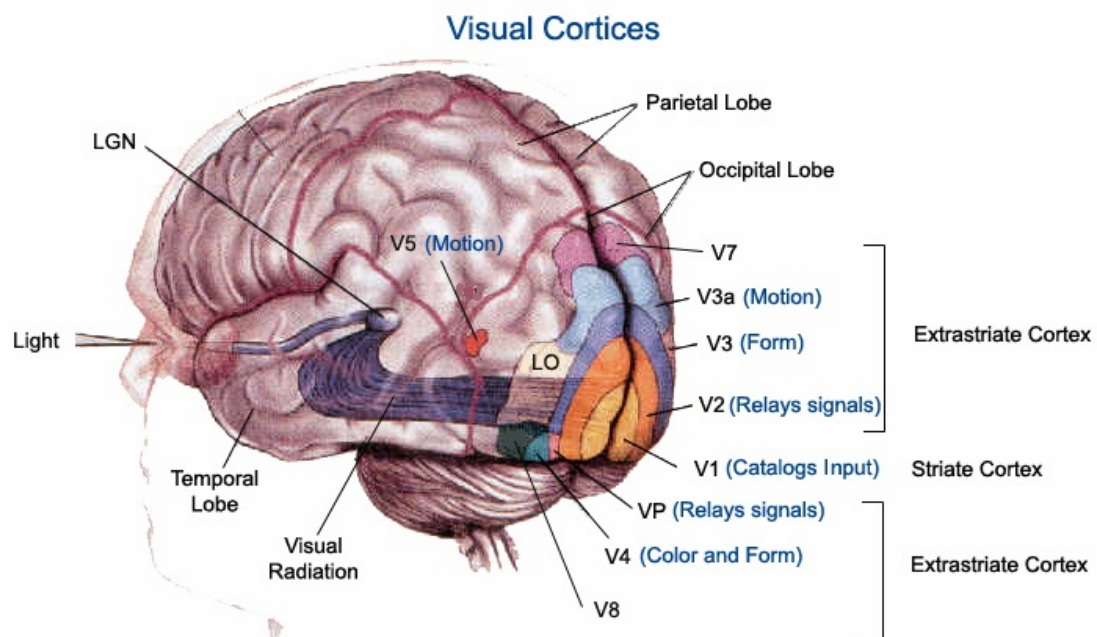


Figure 4.1 – Diagram of the visual cortices (Source: <http://www.galileiani.it/rubriche-galileiane/ma-cosa-sogna-un-cieco-e-un-feto/>).

Among the visual areas we distinguish:

- the primary visual cortex or area V1 which is the best understood part of the visual cortex and the part on which our model will focus;
- the extrastriate areas which correspond to all visual areas other than V1 (i.e. V2, V3, VP, V4, MT...).

4.1 The visual cortices

The visual cortex is divided into 5 distinct zones, V1-V5.

The primary visual cortex or V1 is the first to receive and process information. Its specificity is to process information about static and moving objects, but also in pattern recognition.

After a first processing in this area, the visual neural spikes are directed towards the secondary visual cortex or V2, which performs further interpretation. V2 then projects itself towards the other zones which make it possible to identify the colours (V4), the movement (V3a and V5), the forms (V3 and V4), etc.

Each of these areas is subdivided and constantly and simultaneously exchanges messages with at least 20 other areas of the brain that process visual information. It is this massively parallel processing that allows a global visual perception of our environment.

4.2 Retinotopy

Retinotopy refers to the spatial organization of neural responses in V1 to visual stimuli. In other words, it is a bijective correspondence between an illuminated area of the retina and an area of neurons in the cortex; it is a mapping of the retina in the cortex.

This mapping is however very difficult to express in an analytical way for the following reasons [14]:

- It is non-linear;
- Because the retina is a hemispheric plane, it is expressed from polar coordinates;
- It varies from one animal to another.

In order to obtain a mapping of the retina, different areas of the visual field are illuminated one after the other. The observation by optical imaging of the activated area in the cortex then indicates the position of the corresponding zones.

Scientists are therefore led to extrapolate experimental results in order to obtain a model of the retinotopy, by averaging the maps obtained for a set of animals.

Studies on the retinotopies of the rat [6] and of the monkey ([14],[15]) proved how different visual perception can be between two animals.

Retinotopy of the rat

The analytical form of the retinotopic map is not known for the rat. Thus, F. Chavane and S. Roux used the same methodology as [6] to express the retinotopic map. Because of its complexity, two simplifications were then made:

- Since the rat has no fovea, the cortical position is determined by the distance of the point in the retina from the optic disc;
- In order to simplify the numerical calculations, Frédéric Chavane's model uses cartesian coordinates. The coordinates of the cortical position can be determined independently according to decreasing functions of the form $\frac{1}{ax + b}$ and $\frac{1}{cy + d}$, with x and y the horizontal and vertical distances from the optic disc.

The experiment is conducted by splitting the left rat's visual field into several zones (Figure 4.2A). Each area is then illuminated to observe the associated cortical activity in the right hemisphere of the visual cortex. A mapping of the retina in the visual cortex is then obtained by averaging data from several rats (Figure 4.2B).

It should be noted that these experiments are complex to set up [6] because it requires surgery. A median incision is made to expose the surface of the skull. A part of the skull covering the right primary visual cortex is then thinned to translucent. Performing this procedure instead of a craniotomy (surgical operation in which a bone flap is temporarily removed from the skull to access the brain [Wikipedia]) provides sufficient image quality while preserving the integrity of the intracranial environment.

In addition, the experiments are conducted on several rats, which requires a certain amount of preparation and measurement time.

4.3 The importance of "reciprocal" connections between areas of the visual cortex

Finally, there is a effective way to prove the complexity of the visual system : optical illusions. When processing visual information, there may be conflict between cells that respond to the same stimuli (e.g. contours) but with different abilities. The reciprocal connections that allow information to flow in both directions between different areas of the visual cortex are then essential. An example of this type of conflict is given by the Kanizsa triangle.

In this visual illusion, a normal observer perceives a white triangle superimposed on a triangle with a black outline. It has been shown (von der Heydt and Peterhans

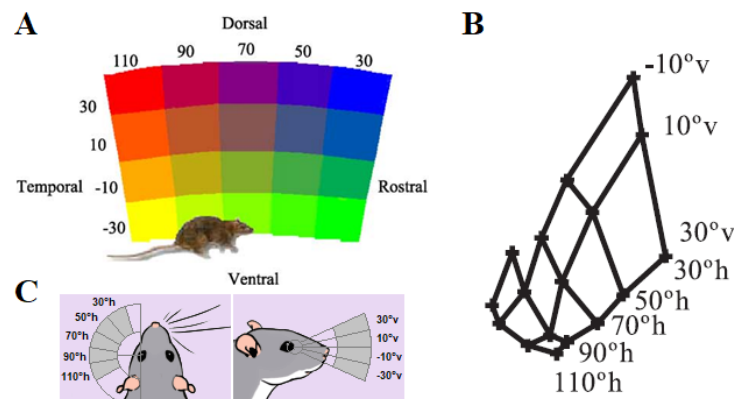


Figure 4.2 – (A) Color code of the visual field location of the stimuli [6]. (B) Representation of the rat visual field projection and the centres of activity onto primary visual cortex according to the average retinotopic map across rats [6]. (C) This figure, from my own, shows the representation as I understood it of the visual field on which the light stimuli will appear

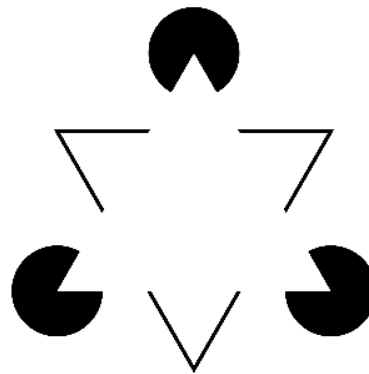


Figure 4.3 – The optical illusion of the Kanizsa triangle [Wikipedia].

1989) that shape-sensitive cells of the V1 area do not react when looking at the figure and do not detect the absent line. This is because the majority of cells in V1 are simple cells with a single receptive field. In contrast, the cells in area V2 are more complex because they respond to the summation of several receptive fields which are integrated from many simple cells [12]. So, even though V1 and V2 cells respond to the same visual cues such as the orientation of edges and lines, they will not give the same interpretation of the same information.

For the Kanizsa triangle, V2 cells interpretation infer the presence of a "line" instead of the non-existent white contour. There is then harmonization of the results of the treatments carried out by the two areas thanks to the reciprocal connections between them, which makes it possible to carry out a visual construction of the two triangles.

Part II

Study topics and description of the model

Chapter 5

Study project of my first internship

Recent advances in neuroscience and microelectronics offer the prospect of partially restoring the vision of blind patients using retinal prostheses (chapter 3). However, because this area of research is at an early stage, devices have several limitations and some main concepts are still not well known. Especially, the way an electric stimulation activates the visual cortex is poorly understood.

5.1 State of the art

Equipped with retinal implants, patients - totally blind - recover visual perceptions in the form of phosphenes. At present, unfortunately, the perceived light signals are not accurate enough to restore a sufficient level of vision so that they have a minimum of autonomy on a daily basis.

In order to understand the resolution limits of the image generated by the prosthesis, a vast experiment on the rat was conducted at INT Marseille by F. Chavane's team. The objective of this study was to compare the visual system response of a rodent with natural visual stimuli and stimuli produced by the prosthesis, with the aim of optimizing retinal implants.

For the experimentation [1], F. Chavane et al. used subretinal Micro Electrode Arrays (MEAs) manufactured at the CEA-LETI (Pham et al., 2013) (Grenoble, France). These planar MEAs of 1 and 1.2 mm diameter comprise respectively 9 and 17 ($50\text{ }\mu\text{m}$ radius) electrodes. As for the model, we assumed that an implant size 30 would represent a whole MEA stimulation (wMEA), and an implant size 5 would represent a single electrode stimulation (SE).

The results show that V1 is activated at the appropriate position and with amplitudes comparable to those obtained under natural conditions. Unfortunately, the activation zones are too large and too elongated compared to the result obtained for

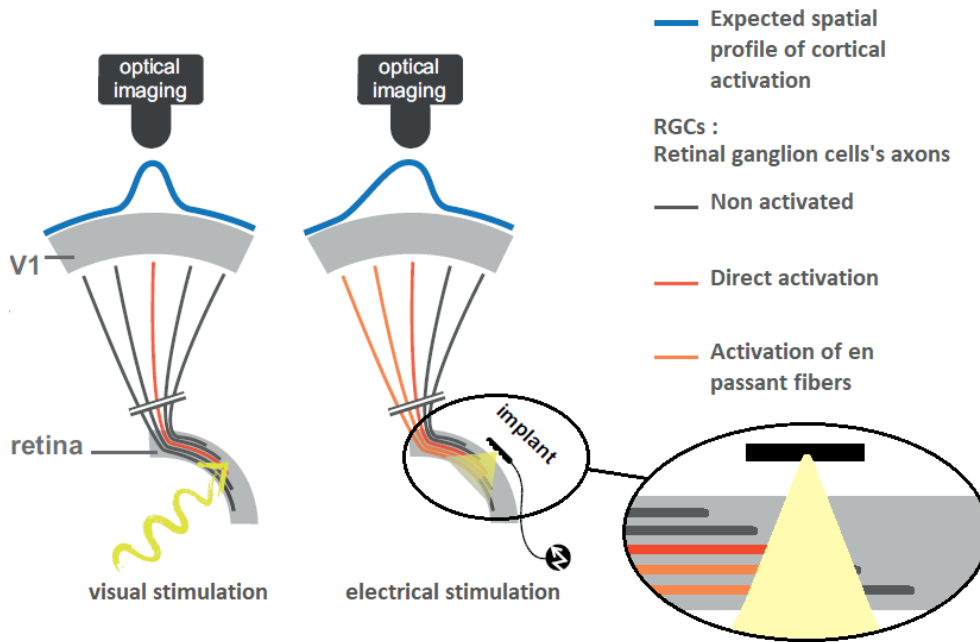


Figure 5.1 – Schematic view of the experimental setup with the camera and the visual pathway from the retina to V1 activated with normal visual stimuli (left) or with sub-retinal electrical stimulation using a MEA (right). With normal vision, we observe the activation of a single ganglion cell (red line). On the other hand, cell activation is different in the case of sub-retinal implant stimulation. In this case, the targeted ganglion cell is not the only one activated. Because of the diffusion of the stimulation current, the axons of neighbouring ganglion cells are also activated (orange lines). The received signal is then perceived as the activation of a larger area. This is why the shape of the cortical profile is more expanded (blue line). Note that the current represented by the light yellow triangle decreases over the distance. *Source: [1] with addition of zoomed figure.*

a visual stimulus.

This deformation may be due to the four diffusion phenomena described in the next Section. The interest of a better knowledge of the intensity of influence of each parameter is to offer the necessary material to optimize retinal implants.

5.2 A model of retino-cortical activation by electric stimulation

5.2.1 Effects to consider

Four effects may be responsible for the extent of artificially evoked cortical activity:

- 1) an electric diffusion at the interface made by the complex electrode-retinal tissue;
- 2) an electric diffusion in the visual cortex;
- 3) the optical diffusion of the signal registered by optical imaging;

- 4) a spread of electric activity induced by the direct activation of retinal cells axons away from their somata (see Figure 5.1).

If the first three effects can be described by standard diffusion equations, the effect due to axons "en passant" activation is asymmetric and complex. The different intensities of these effects should also be taken into account in order to provide a reliable model.

As shown in Figure 5.1, the cortical profile is symmetric for visual stimulation and asymmetric for electrical stimulation if axons "en passant" are activated.

5.2.2 Steps and characteristics of the simulation model

In [1], a 2D simulation model of cortical activity evoked by artificial retinal implants was implemented by F. Chavane and his collaborators. The final objective of this modeling is to be able to characterise each diffusive effect independently. This will then make it possible to estimate the intensity of each of them by comparing the experimental results with those obtained for a set of parameters.

This section is also included in the Appendix B as a reminder of the model and equations as part of the MACULAR documentation which will be used by the team to continue this study.

First step - Model of the retinal activation

A functional model was designed to predict the spatial characteristics of retinal activation triggered by electrical stimulation. The retinal plane is represented by a two-dimensional matrix of dimension N :

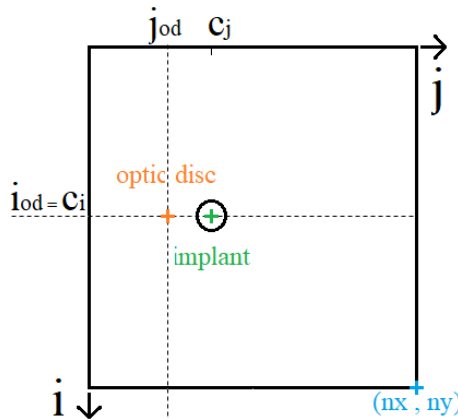


Diagram of the matrix representing the retinal plane.

To predict the profile of retinal activation (its level, shape and size), two electric diffusion components, that extend beyond the electrode surface, were introduced:

- An isotropic Gaussian diffusion (G): corresponding to the first effect presented in subsection 5.2.1;
- A non-linear diffusion due to the passing activation (EP) of ganglion cell axons;

These diffusions are calculated in response to a stimulation of a given size and location in the retinal space.

The first contribution to retinal activation is the isotropic 'direct' activation induced by implant stimulation which was modeled as a 'flat-top' Gaussian that can be expressed as follows:

$$IsoA(i, j) = \begin{cases} 1, & \text{if } \sqrt{(i - c_i)^2 + (j - c_j)^2} < s_z \\ e^{-\frac{(i - c_i)^2 + (j - c_j)^2}{2 \times (\sigma \times s_z)^2}}, & \text{if } \sqrt{(i - c_i)^2 + (j - c_j)^2} \geq s_z, \end{cases} \quad (5.1)$$

Where (i, j) and (c_i, c_j) are the position in space and the position of the implant respectively, s_z the size of the electrode and σ the standard deviation of the Gaussian related to the spatial isotropic diffusion extending beyond the electrode.

The other contribution to retinal activation is anisotropic "en passant" recruitment of ganglion cell axons. It was modeled as a shadow cone activation that results from the isotropic "direct" activation. Its expression is the following:

$$EP(i, j) = Att(i, j) \times Sig(i, j) \times Cone(i, j) \quad (5.2)$$

As written, its computation results from the multiplication of three functions:

- $Cone$: cone-like activation modeled as an angular Gaussian activation. It represents the exponential decay of the quantity of activated ganglion axons "en passant" as a function of the angle to the horizontal axis (maximum horizontally);
- Sig : sigmoid function centered on the position of the optic disc;
- Att : general attenuation of the activation centered on the position of the implant.

Their expressions have been obtained empirically:

$$\begin{cases} Att(i,j) = e^{-\frac{\left(\sqrt{(i-c_i)^2 + (j-c_j)^2} - s_z\right)^2}{2(N/2)^2}} \\ Sig(i,j) = \frac{1}{1 + \frac{dOD - (c_j - j_{od})}{s_z/4}} \\ Cone(i,j) = e^{-\frac{ConeAng^2}{2 \times \sigma^2}}, \quad \text{if } j > j_{od} \end{cases} \quad (5.3)$$

With

- N is the size of the matrix representing the retinal plane;
- (i_{od}, j_{od}) is the position of the optic disk;
- $dOD(i, j) = \sqrt{(i - i_{od})^2 + (j - j_{od})^2}$ is the distance to the optic disk;
- $ConeAng = |atan2(i - i_{od}, j - j_{od})| / angleDisk$ is the normalized angle used in the calculation of the activation cone;
- $angleDisk = 2 \times asin(\frac{s_z/2}{dOD})$ is the angle formed by the tangents to the implant passing through the optic disc.

In the original model [1], the calculation of "angleDisk" was: $angleDisk = 2 * asin(s_z/dOD)$. However, as shown in Figure B.1, the calculation must be done according to the radius and not the diameter of the implant. The computation (section 7.2) takes this change into account.

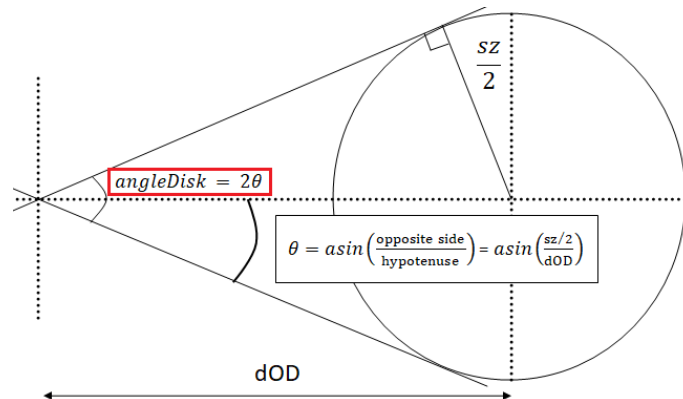


Figure 5.2 – Explanatory diagram of angleDisk calculation.

In our computation, $N = n_x = n_y$ is 400, σ is 1, (i_{od}, j_{od}) is (200,100), (c_i, c_j) is (200, 150), s_z varies between 3 and 30 pixels, and α between 0.1 and 1. Finally, these

two activations (isotropic "direct" activation and anisotropic "en passant" recruitment of ganglion cell axons) are combined with different ratio $\alpha \in [0,1]$ (contribution for the axons "en passant") via a weighted sum, :

$$retinian_activation = IsoA + \alpha \times EP \quad (5.4)$$

Second step - Model of the cortical activation

Since the retinocortical transform has no analytical expression for the rat, F. Chavane and S. Roux had to determine its shape by experimentation. As a reminder, retinotopy is obtained by stimulating a set of areas of the retina until a map is obtained in the visual cortex. By studying the data, they were able to define a bijective function whose form approximates the expected result.

This transform applies to the coordinates of a point independently according to the following expression:

$$RCT : \begin{cases} Retina \rightarrow Cortex \\ (i, j) \mapsto (\frac{1}{ai + b}, \frac{1}{cj + d}) \end{cases} \quad (5.5)$$

where a, b, c, d is the set of values selected by matching the function results with the rat retinotopy.

The implementation of this geometrical transform produces a correspondence between the coordinates of the retinal space and the cortical space. It remains then to interpolate the image representing the retinal activation.

Finally, the effects relative to the diffusion in the visual cortex and due to optical imaging do not have mathematical expressions. In the computation, they will be implemented as a smoothing effect on the cortical activation. In our case, the image will be blurred using a normalized box filter.

Chapter 6

Presentation of the project of the present internship

6.1 Presentation of the platform MACULAR

The BIOVISION team at Inria is currently designing a retina simulator, called MACULAR, aiming at reproducing the retina response to stimulation in normal (stimulation by light) and pathological conditions (electric stimulation by prostheses).

Experiments in the field of neuroscience require considerable resources and are complex to carry out. The objective of developing such a platform is therefore to assist biologists and neuroscientists in their work.

A first use case scenario is the prediction of results. Once the simulation model has been validated by different protocols, in particular by comparison with experimental data, it would then be possible to simulate results without the need for real experiments, thus saving considerable time and experimental resources.

To give another example of the simulator possible uses, one of the features currently under development is the implementation of a model of a circuit for object motion sensitivity [8]. This work is currently being carried out by the PhD student Evgenia Kartsaki. The main focus of her thesis is to investigate how specific classes of retinal neurons (ganglion and amacrine cells) contribute to the encoding of visual scenes.

Thanks to MACULAR, it is therefore possible to emulate normal and impaired retinal function (from single-cell to large-scale level) and to mimic specific pathologies or pharmacologically induced impairments. It is also able to handle different visual processing circuits and allows us to visualise responses to visual scenes (video input) [8].

Many features could be added to MACULAR to make it more efficient and to add more use cases, which is why the scientific scope of this tool is so important.

6.2 The objectives and prospects of the internship

The model developed by Roux et al.[1] aims to study the phenomenon of expansion of cortical activity between visual and prosthetic stimulation for a single electrode. However, retinal prostheses integrate hundreds of electrodes and there is no computational study yet about the effect of the simultaneous activation of several electrodes reproducing the shape of an object while integrating the non-linear diffusion effects. The goal is now to integrate and develop the model for a single electrode into a multi-electrode model and integrate it as a new feature of MACULAR.

The interest of this study lies in the multitude of possible uses of its results, for example:

- Compare the simulation results of electrical stimulation by retinal prosthesis with normal vision, which will show which criteria should be optimized (resolution, size of the field of view, calculation speed with respect to dynamic movement, etc.).
- Predict the results of experiments such as those carried out at INT Marseille, for example. Indeed, carrying out experiments of this type requires structures and the follow-up of complex and precise protocols. Once the simulation model has been validated by using real data as a comparison, this tool could be very useful both from a material and a time saving point of view.

Part III

Results

This part summarizes the work I did during this internship

The first step of the project was to transcribe the Matlab code by F. Chavane et al. [1] in C++ in the MACULAR platform.

The program is divided into two main parts, starting with the model for a single electrode. It results in a set of four activation profiles: direct activation by electrode, activation due to the passing activation of ganglion cell axons, retinal profile and cortical profile.

After checking that the transcribed program works, the objective was to model a whole prosthesis. Thus, the second part runs the model for a single electrode in a loop depending on the number of electrodes composing the prosthesis. It also results in a set of four activation profiles which are the sum of the corresponding profiles of all electrodes.

Finally, I worked on the possibility of applying intensity levels to the matrix of electrodes in order to reproduce complex grayscale images.

Indeed, the final objective is to be able to load a prosthesis design and an input image or video at best, and obtain the simulated retinal and cortical activity profiles.

Chapter 7

Transcription from Matlab to C++ and familiarization with the platform

7.1 From Matlab to C++

7.1.1 The coding sprint sessions

During this internship, I had the opportunity to participate in two coding sprints. During one to two weeks, team members that work on the project gather with the engineers from the Experimentation and Development Department.

Milestones are defined and ranked in order of importance for completion, followed by the distribution of tasks among participants of the coding sprint.

In addition, it was also possible to receive their advice and assistance even outside the coding sprint sessions, by using GitLab. GitLab is defined as a DevOps platform (development and operations). It is a *set of software development practices that combines software development and information-technology operations* (definition source: Wikipedia). This service includes various functionalities such as project planning, source code management, monitoring and even provides issue-tracking and a wiki.

7.1.2 Difficulties encountered and adaptation of the code

Even though I started my internship two weeks before the first coding sprint, I didn't know the platform yet. Having never worked on a project of this scale, and with a language I wasn't familiar with, there were many difficulties on which the engineers assisted me. Their help was particularly valuable to me in order to create as quickly as possible a basic structure in which to incorporate my transcription of the Matlab code.

Due to the differences between Matlab and C++/OpenCV, it was necessary to adapt the implementation of the retino-cortical transform in order to obtain results as close as possible to the original results. Figure 7.1 and 7.2 shows the differences between the result from MACULAR and the one from Matlab.

After a pixel-to-pixel comparison, there are only significant differences between the results, at the retino-cortical transform level. These are due to the non-existence of a C++ function equivalent to the Matlab function "fitgeotrans". It was therefore decided to use the OpenCV "cv::remap" function. However, while both functions use the source and destination point maps as arguments, the distortion of the resulting image is not the same.

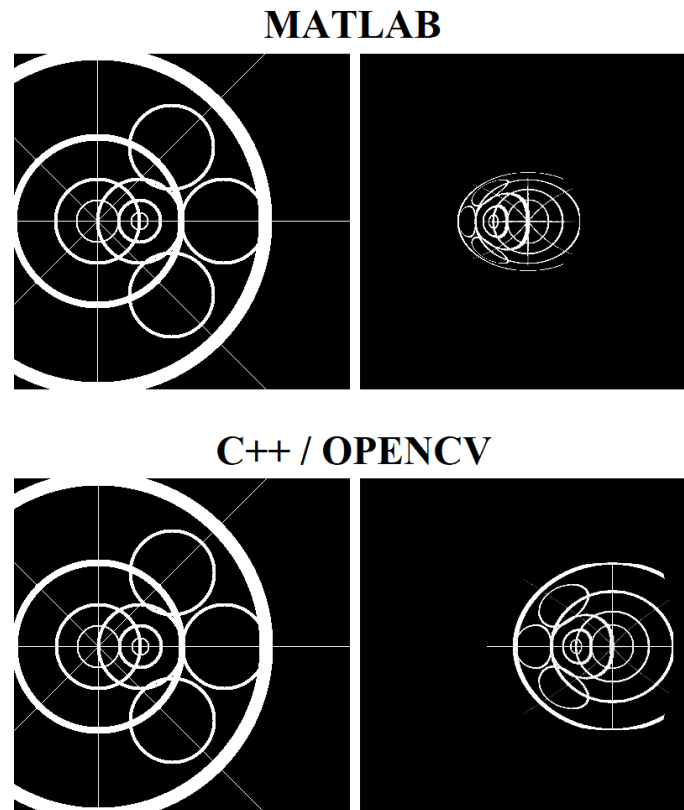


Figure 7.1 – Comparison between Matlab and MACULAR results: retino-cortical transformation applied to a calibration mire. First row: Matlab (using the function "fitgeotrans" to compute the retino-cortical transform); second row: MACULAR (C++/OpenCV; using the function "cv::remap" to compute the retino-cortical transform). The first column represents the calibration mire in the retinal plane. The second columns gives the results from MACULAR of the cortical activation profiles.

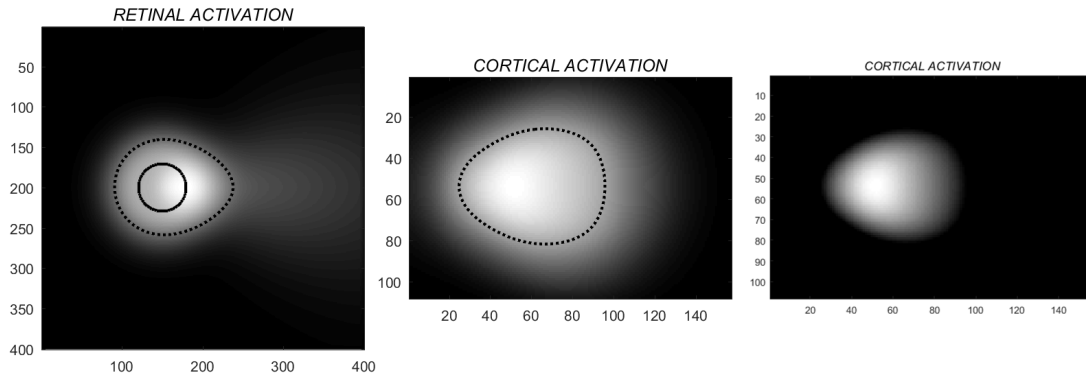
Note here that the distortion of the image is more important in the case of the Matlab result. Indeed, the circles of the MACULAR result should shrink more as the pixels move away from the optical disc, with a slightly different factor depending on the horizontal or vertical axis. However, it is not known yet by our biologist

partners what should be the correct form.

Thus, since the difference between the results was not significant enough, it was decided to continue the study using this implementation.

However, further research must be conducted in order to find the implementation that is most accurate to the expected result.

MATLAB



C++ / OPENCV

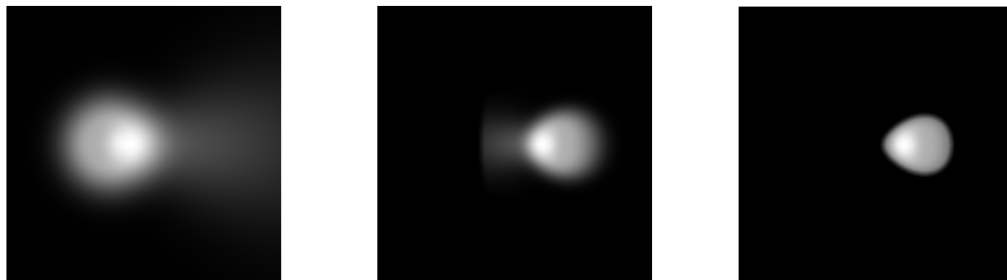


Figure 7.2 – Comparison between Matlab and MACULAR results: retino-cortical transformation applied to a retinal profile.

First row: result with Matlab where the dotted outline represents the activation area above a certain threshold. Second row: MACULAR (C++/OpenCV). Left: retinal profile, Middle: cortical profile, right: cortical profile on which an activation threshold has been applied in order to facilitate the comparison of activities. All results obtained from MACULAR correspond to matrices of size 400x400.

Note that the inversion along the vertical axis between the retinal and cortical profiles is due to rat retinotopy.

7.2 The results of the model

7.2.1 Model for a single electrode

After implementation of the model and running in MACULAR, the result is as shown in Figure 7.3

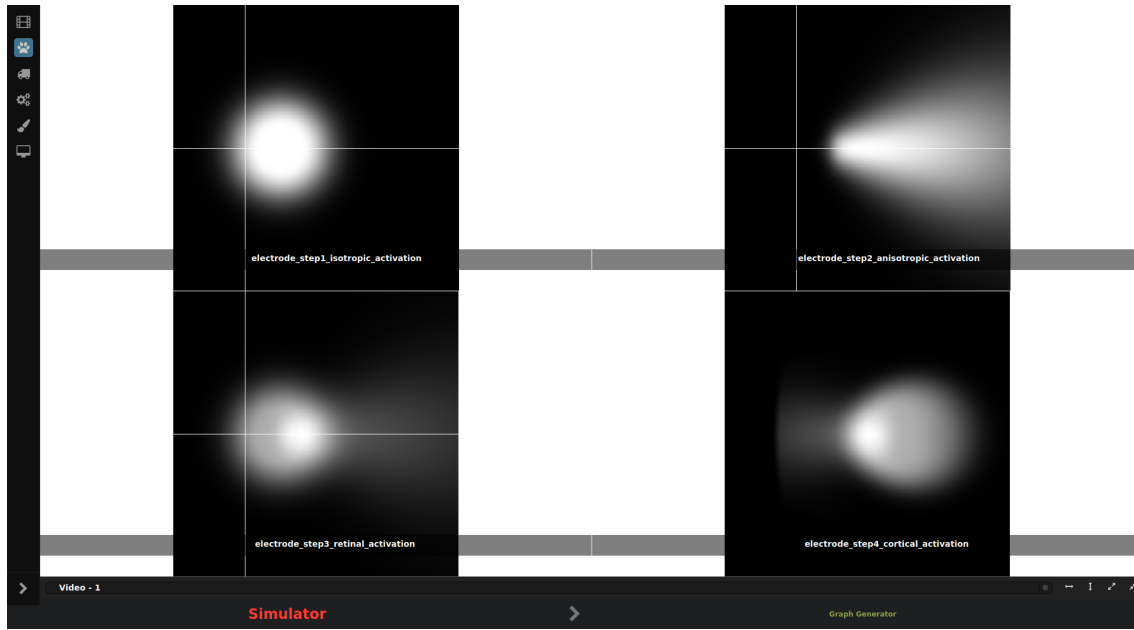


Figure 7.3 – Result obtained in MACULAR. The four steps of the model are displayed : the isotropic "direct" activation (left-top), the anisotropic activation due to "en passant" recruitment of ganglion cell axons (right-top), the retinal activation (left-bottom) and the cortical activation (right-bottom). Note that a zoom has been made on the cortical profile compared to Figure 7.2 for a better visualization.

As shown in Figure 7.3 the four steps of the model are displayed in MACULAR: the isotropic "direct" activation (left-top), the anisotropic activation due to "en passant" recruitment of ganglion cell axons (right-top), the retinal activation (left-bottom) and the cortical activation (right-bottom). Due to the axons "en passant" recruitment, it is observed that the retinal and cortical activation profiles are expanded while it wouldn't be in the case of a stimulation by light.

The display of the model results in the Graphical User Interface (GUI) was one of the major difficulties I encountered. Because I was not familiar enough with all the files on the platform, I had to call on the engineers several times in order to progress in my work.

For instance, in order to link my model (whose results were already validated) to the GUI, it was necessary to link the menu of parameters that the user uses for each simulation to the parameters defined in the .cpp file in which the model is implemented.

However, even after this link was established, the result that was displayed was still not the one expected (see Figure 7.4). After discussion with the Experimentation and Development Department team, it turned out that it was due to a conflict in the definition of default values between the GUI menu and the .cpp file in which the model is implemented.

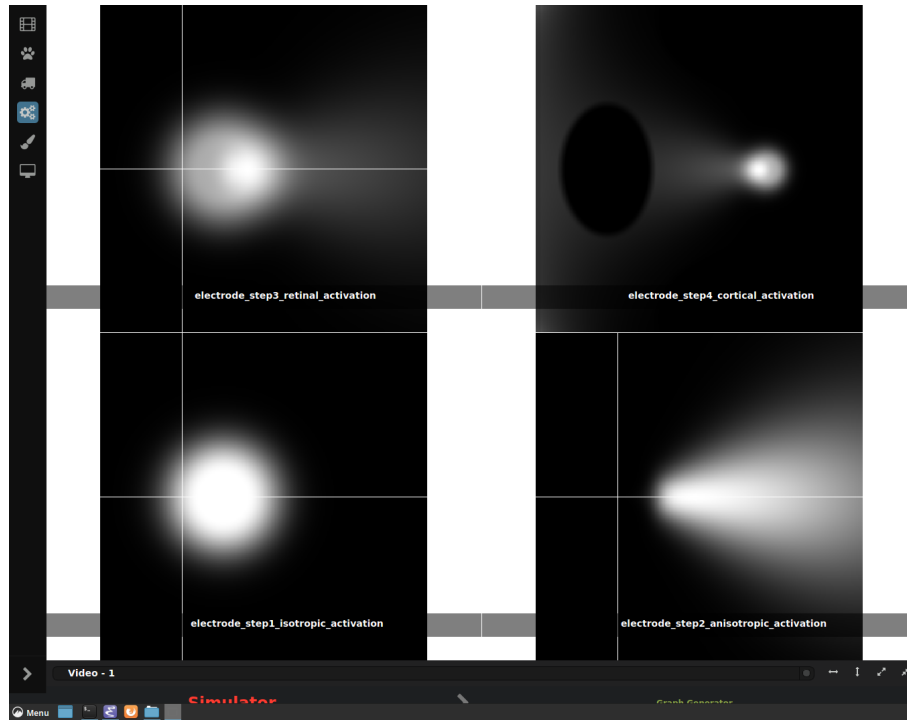


Figure 7.4 – Partially incorrect result (only the cortical activation profile) obtained in MACULAR due to a conflict in the definition of default values between the GUI menu and the .cpp file in which the model is implemented. It can also be observed that the order of the four images is not the same as in Figure 7.3. This issue is due to the chosen type for the output and still needs to be fixed. Indeed, at each opening of the GUI of MACULAR, the order of the output images will change.

This problem, whose solution was so simple, made me realize the importance of teamwork on such a project. Indeed, the problem solving on the small-scale development of the model I realized last year on Matlab did not require a strong targeted expertise. By contrast, adding my work to a global platform is much more complex and requires a real knowledge and understanding of the language and material on which the work is done.

Hence the importance of working with INRIA’s Experimentation and Development Department.

7.2.2 Generalization towards a whole prosthesis

Result with the original default values

Since one of the objectives is to be able to use this functionality of MACULAR to predict experimental results, it is necessary to generalize the implementation of the model to a matrix of electrodes. This would then make it possible to carry out more complex simulations, even equivalent to real experiments carried out in laboratories such as INT Marseille.

In order to do so, a new method has been implemented as the main one, and follows the following steps:

- Creation of a vector of the positions of each electrode. The function used to calculate this vector takes into arguments the central position of the prosthesis as well as the total number and spacing of the electrodes.
- Application of the model to each electrode. This step is performed by applying the model to each pair of coordinates calculated in the previous step and returns an output containing four matrices.
- The method finally returns four matrices, which correspond to the sum of the activations for each electrode.

This method ends up giving the following result (Figure 7.5) for a 6x6-matrix of electrodes:

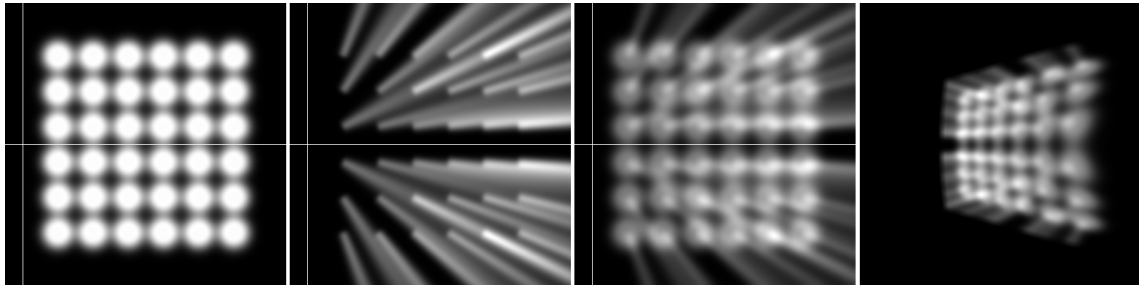


Figure 7.5 – Result obtained for a 6x6-matrix of electrodes.

For a better visualization, the electrodes have been spaced apart. In a more realistic representation of a prosthesis, the distances between the electrodes are smaller and the electrode activations overlap due to diffusion.

Consequently, the implementation of the model must be reviewed in order to take into account with more precision the real scale. Both in terms of the design of the prosthesis, the size of the retinal plane or the placement of the prosthesis on it.

Tests on the two parameters responsible for the diffusions.

After discussion with Frédéric Chavane of the INT Marseille, the interest of testing the influence of the two parameters responsible for the diffusions was raised. Indeed, it seemed to him that the diffusion produced by the recruitment of axons en passant was not sufficiently important. On the Figure 7.5, this is noticeable by the non-overlapping of conical activations and more particularly at the level of the central horizontal axis around which a black band is formed.

The two parameters whose influence must be studied are as follows:

- Related to direct isotropic diffusion by the implant: the Gaussian standard deviation modelling the diffusion.
- Related to anisotropic diffusion due to axons en passant recruitment: the Gaussian standard deviation modelling diffusion (which is the same as for the isotropic diffusion) and the recruitment ratio of axons en passant.

Several series of tests were carried out using a cross-shaped input.

Influence of the Gaussian standard deviation on diffusion

Two series of tests were carried out for this case:

- Ratio axons en passant = 0.0 and Gaussian standard deviation = variable between 0.1 and 6.0.
- Ratio axons en passant = 1.0 and Gaussian standard deviation = variable between 1.0 and 6.0.

Even if the results with a standard deviation of less than 4 are unlikely according to Frédéric Chavane, performing the series of tests from a value close to zero makes it possible to better observe the evolution of the result as a function of the variation of the parameter.

In the case where the anisotropic activation due to the recruitment of the ganglion cells axons "en passant" is not taken into account (see Figure 7.8), a deterioration in shape is observed for a standard deviation of more than 4.5.

Therefore, in the second set, the test for the value 0.1 was replaced by 3.5, in order to get another result closer to the more likely values. In the case of the maximum ratio (see Figure 7.9), there is a sharpening effect of the expected shape.

As a result of these observations, it seems that the ratio has less influence on the clearness of the shape than the standard deviation.

Influence of the ratio of axons en passant recruitment

Two series of tests were carried out for this case:

- Ratio axons en passant = variable between 0.0 and 1.0 and Gaussian standard deviation = 3.0;
- Ratio axons en passant = variable between 0.0 and 1.0 and Gaussian standard deviation = 4.5;

Unlike the standard deviation, the observation of the Figure 7.10 and 7.11 does not reveal a strong influence of the ratio of axons en passant activation. However, it seems that for a high ratio, the result for a high standard deviation is more sharp than for a low ratio. Indeed, we can observe a better distinction of the cross shape when the ratio is high.

7.2.3 Activation levels as an add-on to the basic model

In order to be able to reproduce a real image, it is necessary to be able to apply activation levels to the electrodes. These levels correspond to the intensities delivered by the electrodes, here simplified as values within the interval $[0.0, 1.0]$.

Currently, these coefficients are calculated using a Matlab code. However, the goal is to implement this computation into MACULAR. Indeed, the objective is to be able to load an input image from the GUI and calculate its decomposition into intensity levels directly in the implementation of MACULAR.

This computation follows the next steps: An input image is divided according to the number of electrodes forming the prosthesis. For each part, the average of the pixel values is computed and normalized. A text file is created as an output and contains all activation levels as a row vector.

Figure 7.6 gives an example of result for 5 and 10 electrodes.

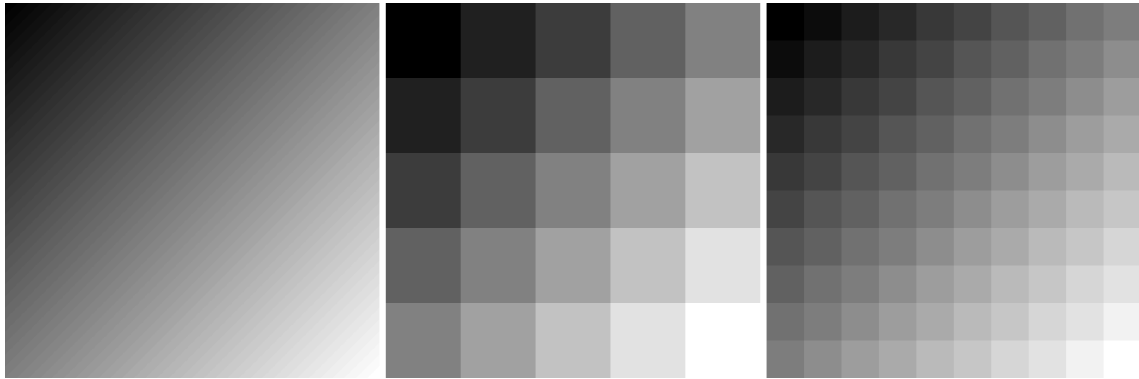


Figure 7.6 – Creation of the text file containing all the activation levels as a row-vector. For example, in the case of a 5x5-electrode matrix (middle image) the approximate output vector is as follows:

output = [0.11, 0.22, 0.33, 0.45, 0.56, 0.22, 0.33, 0.45, 0.56, 0.67, 0.33, 0.45, 0.56, 0.67, 0.78, 0.45, 0.56, 0.67, 0.78, 0.89, 0.56, 0.67, 0.78, 0.89, 1].

Result with MACULAR in the case of a complex picture

In order to obtain the results shown in Figure 7.7, the intensity vector was loaded from a text file external to the code.

The next step is therefore to add the Matlab image processing code to MACULAR in order to load (in the GUI) an input image and obtain the vector of activation levels afterwards directly used in the rest of the computation.

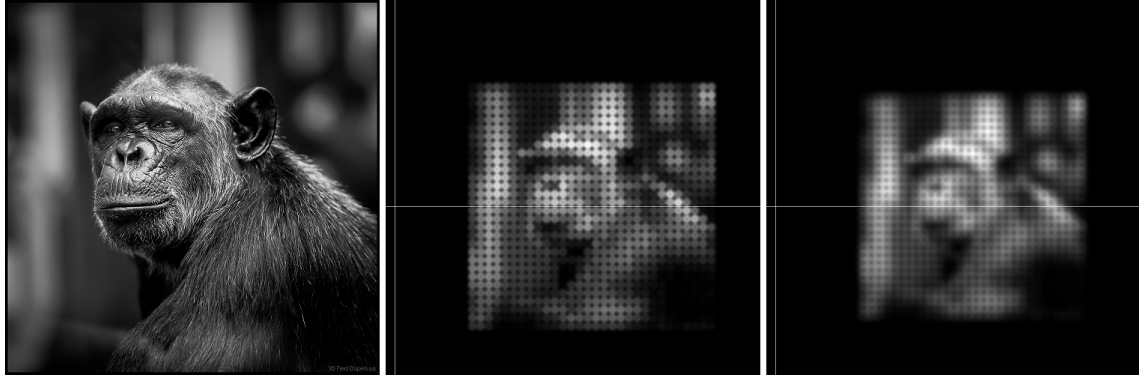


Figure 7.7 – Example in the case of a picture of a monkey as input. Left: original picture. Middle: Isotropic "direct" activation obtained with MACULAR with 30x30 electrodes of 5 pixels size and 22 pixels spacing. Right: Isotropic "direct" activation obtained with MACULAR with 30x30 electrodes of 7 pixels size and 20 pixels spacing.

Test of the variation of the Gaussian standard deviation a complex image (with ratio = 1.0)

In order to show the importance of the parameters previously studied, and more particularly the importance of the Gaussian standard deviation, two results were generated with a complex input image. For both results, the ratio of axons en passant activation is equal to 1.0 while the Gaussian standard deviation takes the values 1.0 and 3.0.

By comparing the Figure 7.12 and 7.13, it can be noticed that, in the case of complex shapes without high contrast, it becomes difficult to distinguish the shapes when the Gaussian standard deviation is high.

It will therefore be necessary in a subsequent study to define their values more precisely in order to obtain results as close as possible to the actual data.

Note that the scale at which these tests are performed still needs to be defined more precisely. A more accurate interpretation of these results can only be made once the dimensions of the objects have been confirmed.

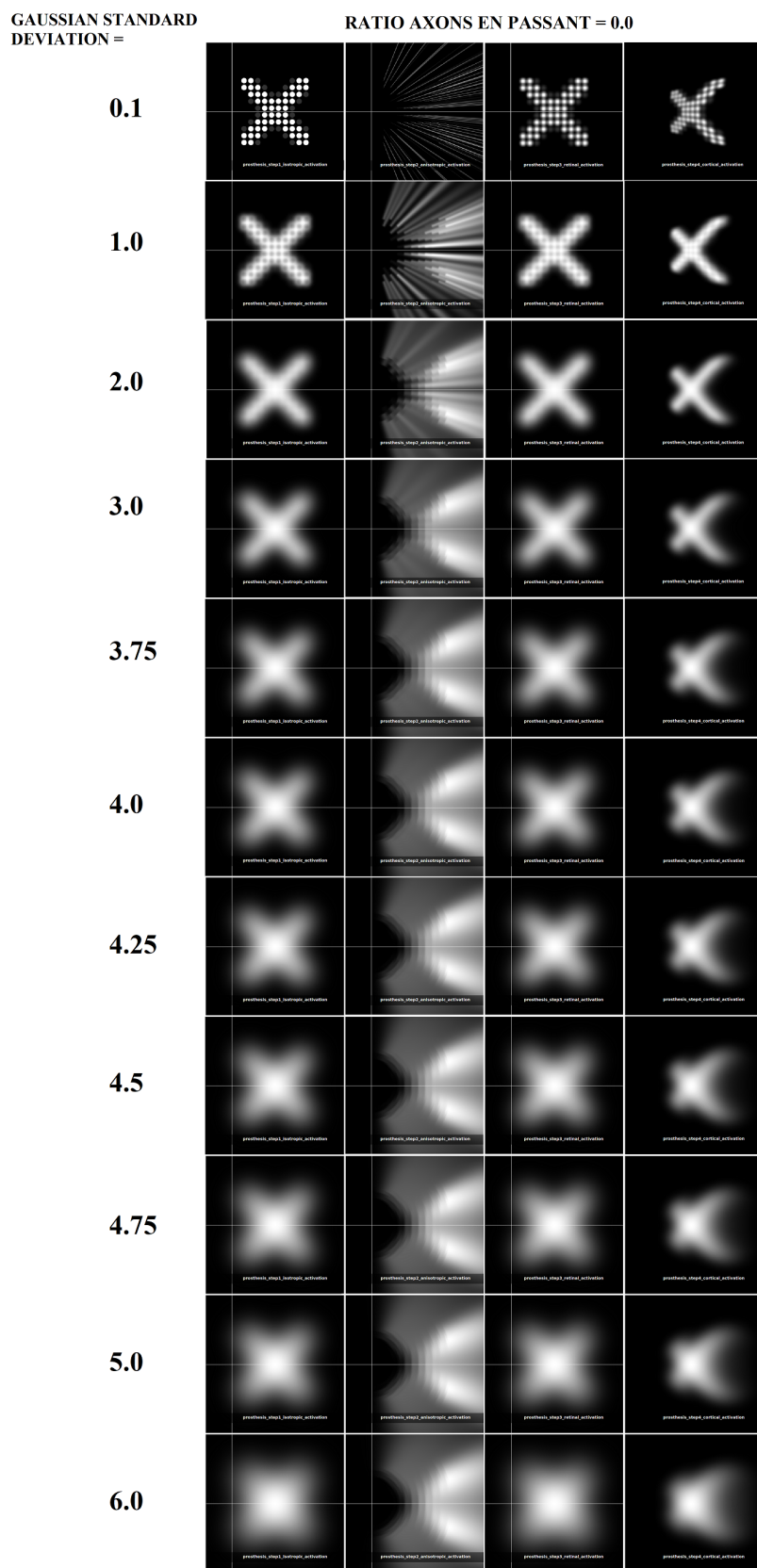


Figure 7.8 – Result obtained for a 10x10-matrix of electrodes with: ratio of axons en passant activation = 0.0 and Gaussian standard deviation = variable between 0.1 and 6.0.

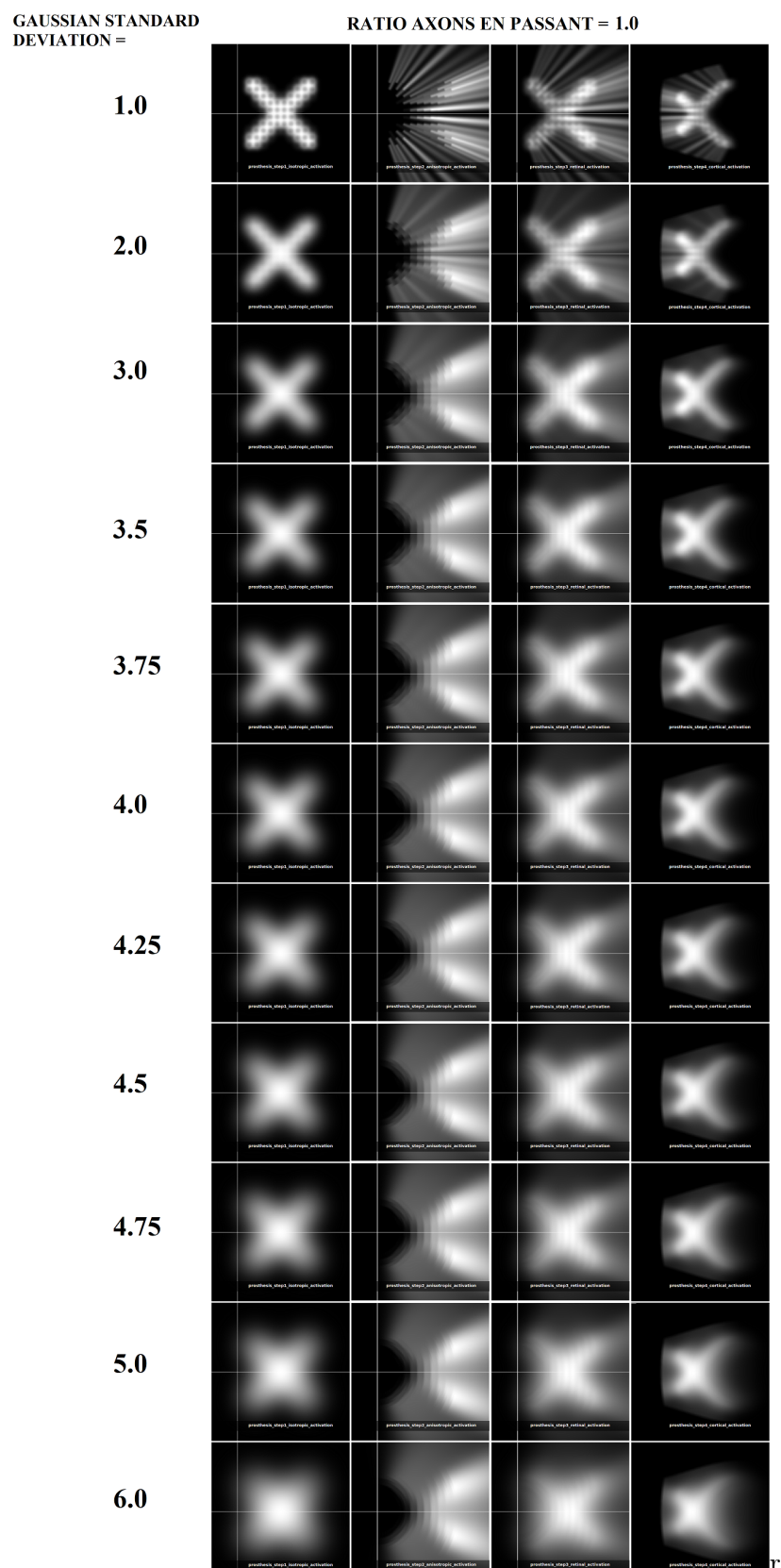


Figure 7.9 – Result obtained for a 10x10-matrix of electrodes with : ratio of axons en passant activation = 1.0 and Gaussian standard deviation = variable between 1.0 and 6.0.

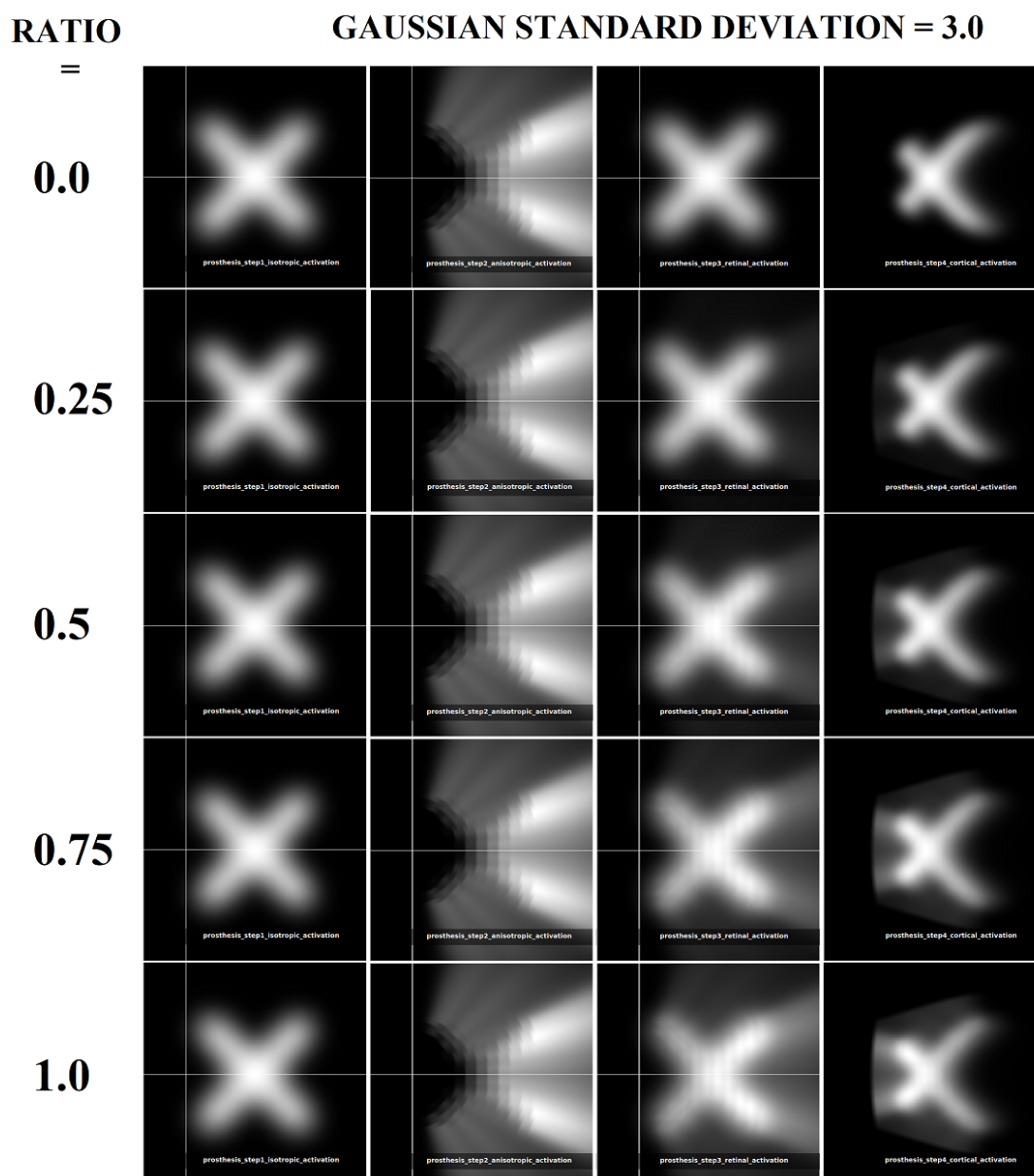


Figure 7.10 – Result obtained for a 10x10-matrix of electrodes with: ratio of axons en passant activation = variable between 0.0 and 1.0 and Gaussian standard deviation = 3.0.

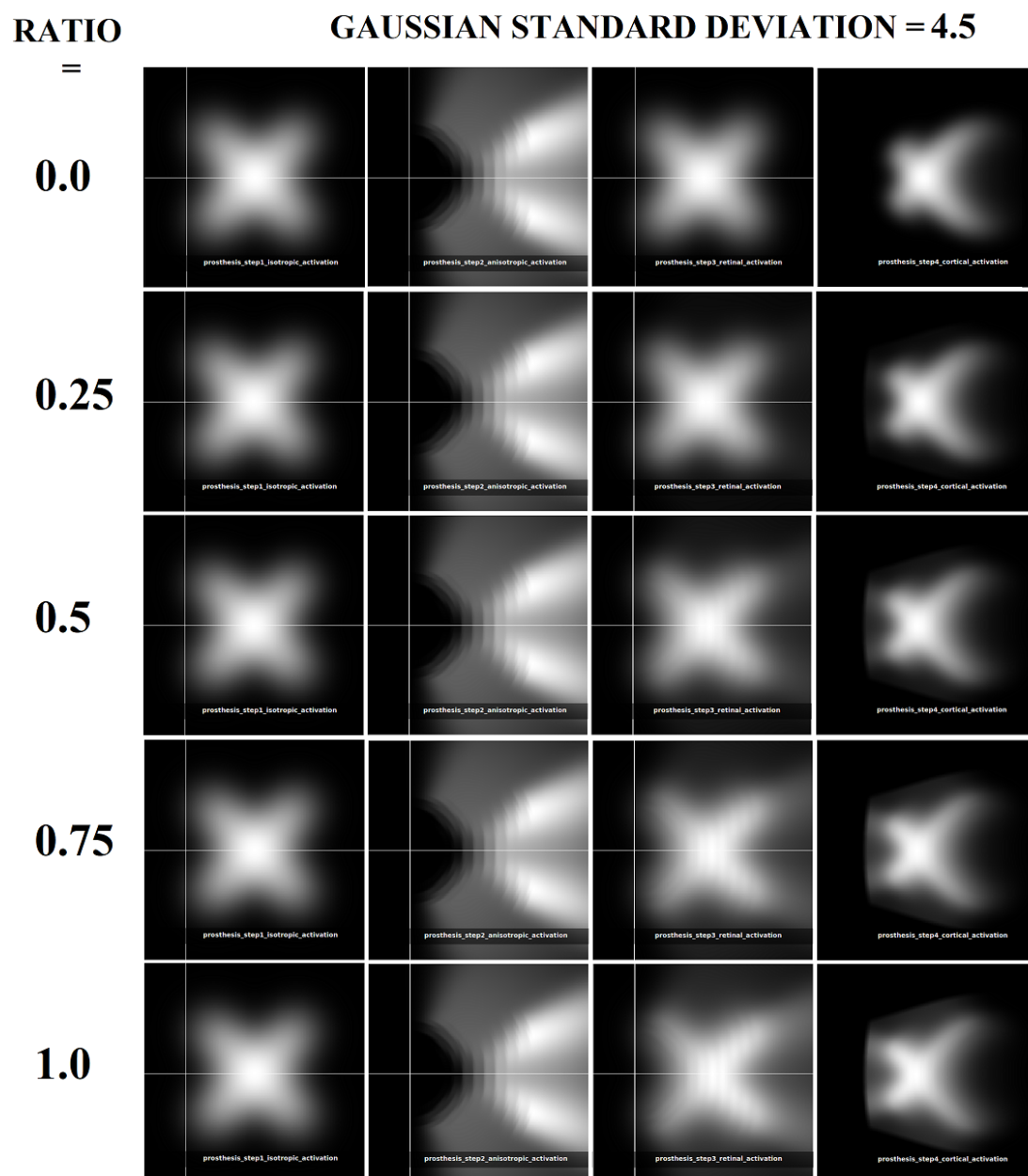


Figure 7.11 – Result obtained for a 10x10-matrix of electrodes with: ratio of axons en passant activation = variable between 0.0 and 1.0 and Gaussian standard deviation = 4.5.

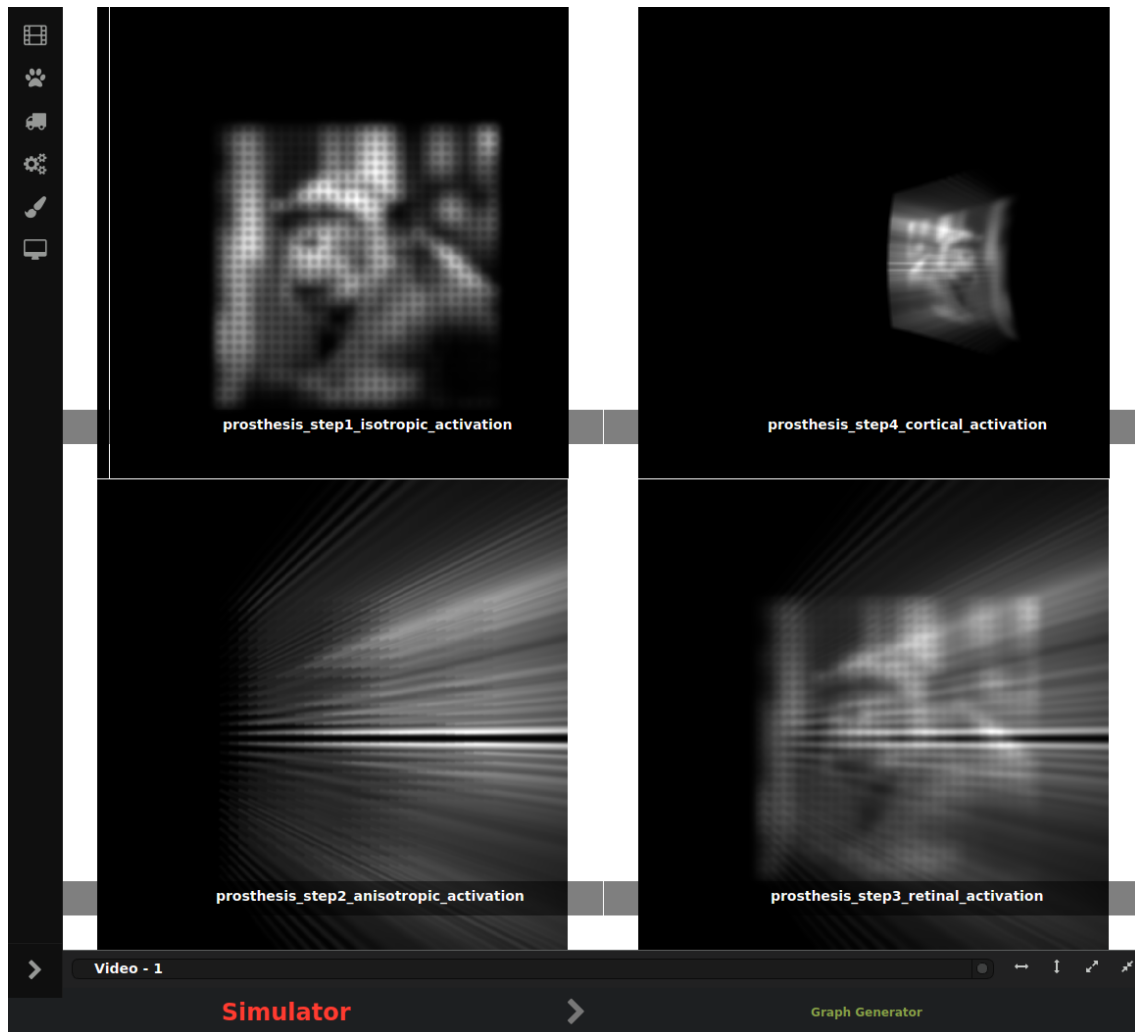


Figure 7.12 – Result obtained for a 10x10-matrix of electrodes (monkey picture as input) with: ratio of axons en passant activation = 1.0 and Gaussian standard deviation = 1.0.

Due to the too low value of the standard deviation, the bands representing the anisotropic activations, due to recruitment of axons en passant, are too distinguishable. In this case, where no electrode is located on the horizontal axis, a wide black band can be observed.

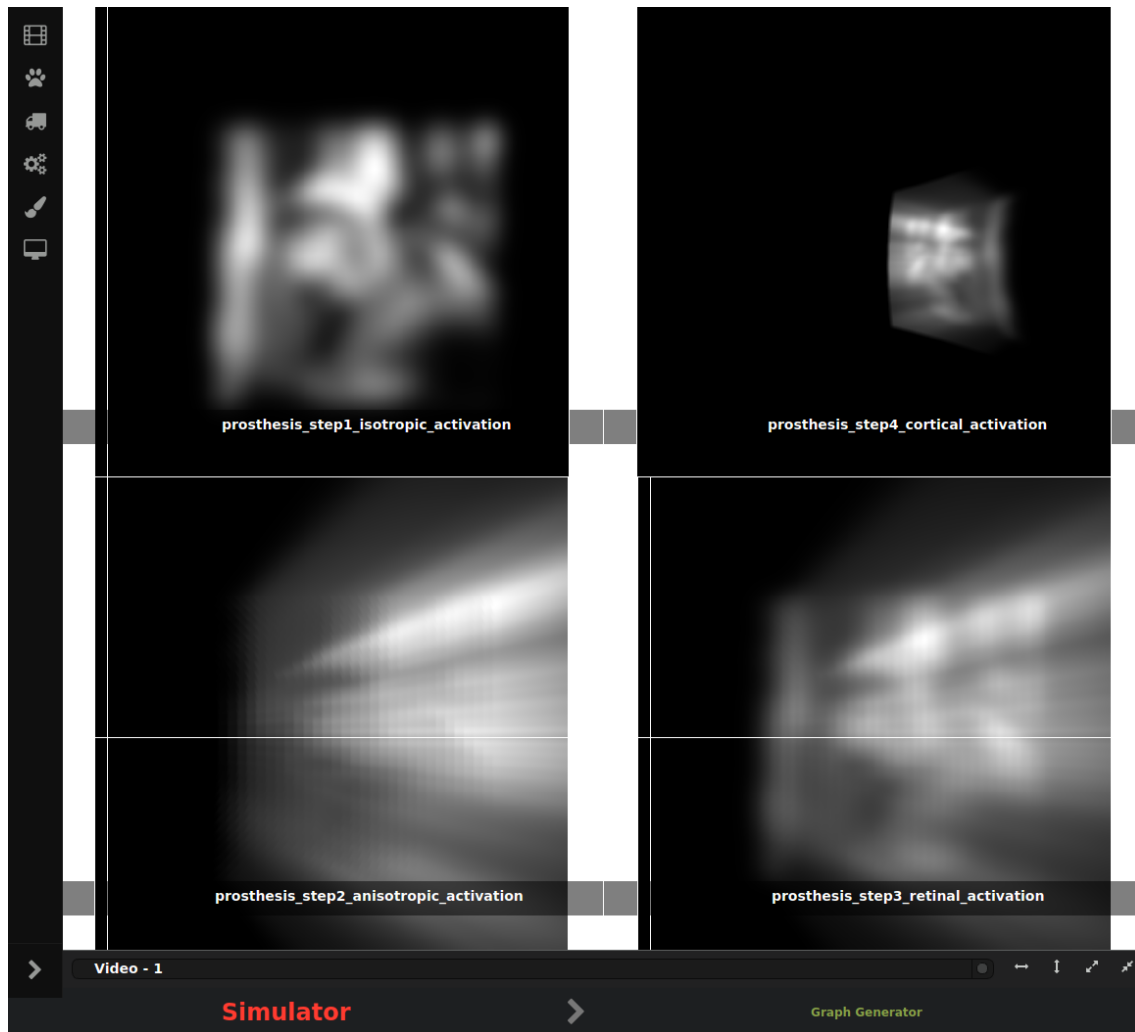


Figure 7.13 – Result obtained for a 10x10-matrix of electrodes (monkey picture as input) with: ratio of axons en passant activation = 1.0 and Gaussian standard deviation = 3.0.

With a high standard deviation, bands representing the anisotropic activations, due to recruitment of axons en passant, are no longer distinguished from each other.

Chapter 8

Ongoing work and prospects

8.1 Be able to process an image from the MACULAR GUI

While the results shown in Figure 7.7 were obtained by using a loaded vector of intensity levels, the interest is to add the calculation of this vector directly in the implementation of the model in MACULAR.

Thus, the next step is to add the Matlab image processing code currently used in MACULAR in order to load (from the GUI) an input image and obtain the final results without any external computation.

8.2 Protocol on how to obtain a dynamic result

It would be of particular interest to make a new topic of study on the possibility of adding a dynamic dimension to the model.

To do this, the objective would be to implement the time response of an electrode to an activation:

- Choice of prosthesis design (shape, spacing and electrode size);
- Measurement of the response of each electrode at the maximum value;
- Response profile model (average over all electrodes);
- Sampling of the standard profile chosen for dynamic activation (a sample corresponds to an intensity level for electrode activation);

- For each sample, calculation of the response to the model implemented in MACULAR according to the corresponding intensity;
- As a reminder, it was decided during this internship that the intensities allow to give the final activation profile according to the following formula:

$$\text{response} = \text{activation level} * \text{electrode response for the maximum intensity}$$

- When displayed in the GUI, the result to a fixed input image is displayed as a video. Each frame of the video corresponds to a sample, i.e. a level of activation intensity. In case there is more than one electrode, the calculation time for a frame will be increased.

The work of Pascale Pham [1] could also be used in order to choose the shape of the intensity signal with more accuracy. Indeed, it has been shown that the wave shape of the stimulation current needs to be adapted in order to obtain the expected responses of retinal cells.

8.3 Parallel computing

In the current implementation, many loops are used. For example, to obtain the results of a multi-electrode prosthesis, a loop is made to obtain the results for each electrode.

However, it would be interesting to optimize the implementation by parallelizing the calculations whose elements are independent (as in the example given). Thus, when a response to a video or a dynamic response is desired, the computation time will be reduced.

In conclusion, many improvements can be made to this project to optimize it or increase its multi-functionality in terms of possible uses.

GENERAL CONCLUSION

The prospects of the study

Although improvements mentioned during the internship could not be developed, the results obtained are satisfactory. Indeed, even if it is still necessary to optimize the calculation times by parallelling and to implement in MACULAR the Matlab code used to calculate of the intensity levels of the electrodes of the prosthesis, the project in its current state already gives first results of a great interest. MACULAR aims to help neurobiologists predict results before experiments. Thus, despite the uncertainties regarding the realism of the results obtained, they remain based on a configurable mathematical model. Its realism can therefore be studied by comparing simulation results with experimental results.

Therefore, the main interest of this project is that it opens up many opportunities for further studies. For instance:

- Add a configurable model to obtain the retinal response from an input image, depending on the chosen animal model (human included). The image would be placed in a space corresponding to the animal's visual field, which would allow the retina's response to be obtained with greater accuracy.
- Use the work of Ayzenshtat et al. (2012) and Schira et al. (2010) on monkeys to change the retinotopy (retino-cortical transformation) of the rat by the monkey one. This would allow a result closer to the one for humans. And predictions of experimental results could be done.
- Design of a software to create a prosthesis model file (not connected with the MACULAR platform). This file would contain information such as the shape of the prosthesis, its size, the number and spacing of the electrodes composing it, and even their characteristics. This would allow biologists to create a realistic model of the prostheses they use in their experiments and use it in MACULAR to predict experimental results that can be adapted to their own protocol. In this case, it would be necessary to add a functionality to MACULAR allowing to load and use this file.

The benefits of the internship

This internship was a collaboration between two research centers, thus allowing me to discover two different work places linked by research. My work environment during this period allowed me to be in contact with people with different professional backgrounds (researchers, PhD students, engineers...), which led me to think more

about my own career path. Moreover, being in an international environment has not only allowed me to acquire new scientific knowledge, but also to practice my English.

In terms of computer skills, I was able to learn how to code with C++. Even though I already had C and Java basic skills from ENSEA, I was not familiar with C++ and I had never worked on a major project like this before. The main difficulty I encountered was not so much in terms of my lack of C++ programming, but more in terms of working on a project that had been under development for some time and of which I was not familiar to MACULAR architecture. Incorporating my work into the platform was therefore a real challenge for me.

Last year was a real opportunity for me to learn more about how I like to work. While I appreciate the autonomy and creativity involved in working in the field of Research, I also realized the difficulty of defining its own milestones to be achieved and the delay that there could sometimes be before obtaining satisfactory results. While I came to the same conclusions this year, I also realized much more clearly that it was difficult for me to ask for help. Since my programming skills are not as advanced as those of the engineers on the Experimentation and Development Department team, I often did not understand part of the platform code and did not know how to adapt my code to their architecture. This helped me to work on my communication skills when I need assistance.

Finally, I was given the opportunity to think about continuing on a thesis on a subject of my choice. This reflection allowed me to realize my uncertainties about my professional motivations and the direction I want to give to my life. I therefore decided that there would still be time to do a thesis after living a few years in the "real world" when I have decided with certainty that I want to work in the Research field.

What I mean by this is that, for the time being, my main objective will be to form my own opinion of the world of work at the international level. I therefore plan to do a V.I.E. within the next five years or why not participate in international volunteer missions. Since I want the international to be an important aspect of my life, I have decided to use it to find my vocation.

Appendix A

Poster for 1st NeuroMod meeting

During my two internships, I also had the opportunity to attend two meetings.

Entitled C@UCA until this year, the University Côte d’Azur core program “Cognitive systems, normality and pathology of the human brain and computational neuroscience” is the first thematic institute of the Université Côte d’Azur and is now the NeuroMod Institute.

I attended this meeting last year. It is a very interesting experience as it allowed me to learn more about the research currently being carried out in the field concerned.

Unfortunately, I was not able to participate this year, but I still had the chance to make a poster about my work so that it could be presented.

A more precise description of the NeuroMod Institute can be found on their website: <http://univ-cotedazur.fr/en/index/projet-structurant/neuromod>

Appendix B

Documentation for MACULAR platform - Reproducing the retinal and cortical responses to stimulation in pathological conditions (electric stimulation by prostheses).

B.1 The context

This documentation deals with the simulation of retinal prosthesis stimulation, whose model is based on the work carried out by Roux et al. (eLife 2016). The implementation of this model in the MACULAR platform was based on the original Matlab code created by Frédéric Chavane (NeOpTo Team leader, INT Marseille). However, the original model only concerned one electrode. It was therefore necessary to adapt it to obtain the response of a stimulation by a matrix of electrodes.

B.1.1 The model of Roux et al. (eLife 2016)

First step - Model of the retinal activation

A functional model was designed to predict the spatial characteristics of retinal activation triggered by electrical stimulation. The retinal plane is represented by a two-dimensional matrix of dimension N :

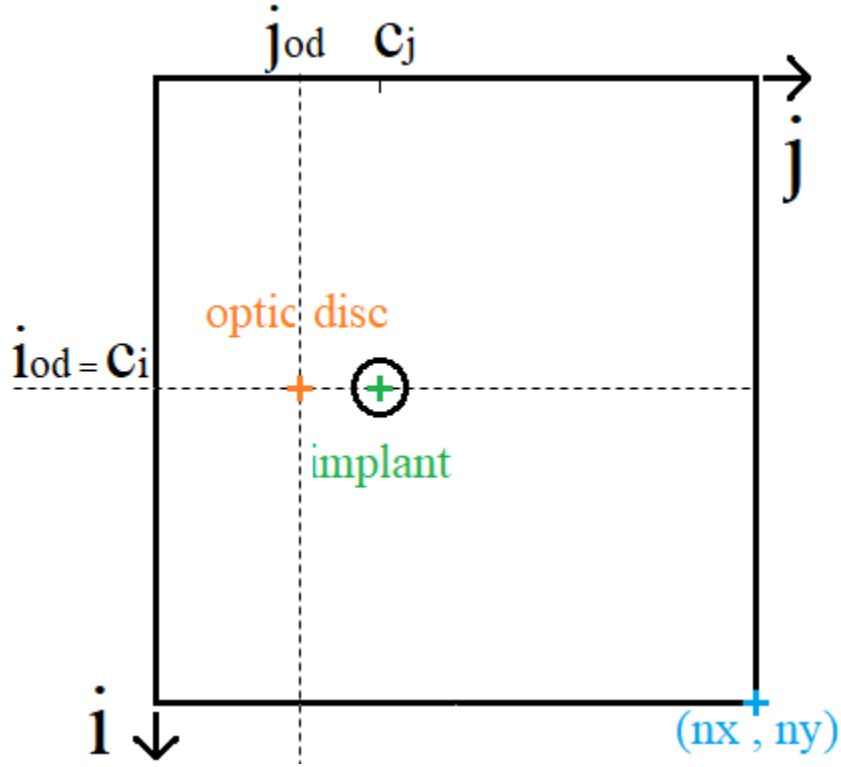


Diagram of the matrix representing the retinal plane.

To predict the profile of retinal activation (its level, shape and size), two different activity diffusions, that extend beyond the electrode surface, were introduced:

- An isotropic Gaussian diffusion (G) corresponding to the electric diffusion at the interface separating the electrode and the retinal tissue;
- A diffusion due to the passing activation (EP) of ganglion cell axons (a spread of electric activity induced by the direct activation of retinal cells axons away from their somas);

These diffusions are calculated in response to a stimulation of a given size and location in the retinal space.

The first contribution to retinal activation is the isotropic 'direct' activation induced by electrode stimulation which was modeled as a 'flat-top' Gaussian that can be expressed as follows:

$$IsoA(i, j) = \begin{cases} 1, & \text{if } \sqrt{(i - c_i)^2 + (j - c_j)^2} < s_z \\ e^{-\frac{(i - c_i)^2 + (j - c_j)^2}{2 \times (\sigma \times s_z)^2}}, & \text{if } \sqrt{(i - c_i)^2 + (j - c_j)^2} \geq s_z, \end{cases} \quad (B.1)$$

Where (i,j) and (c_i,c_j) are the position in space and the position of the electrode respectively, s_z the size of the electrode and σ the spatial isotropic diffusion extending beyond the electrode.

The other contribution to retinal activation is anisotropic "en passant" recruitment of ganglion cell axons. It was modeled as a shadow cone activation that results from the isotropic "direct" activation. Its expression is the following:

$$EP(i,j) = Att(i,j) \times Sig(i,j) \times Cone(i,j) \quad (B.2)$$

As written, the computation results from the multiplication of three functions:

- *Cone* : cone-like activation modeled as an angular Gaussian activation. It represents the exponential decay of the quantity of activated ganglion axons "en passant" as a function of the angle to the horizontal axis (maximum horizontally);
- *Sig* : sigmoid function centered on the position of the optic disc;
- *Att*: general attenuation of the activation centered around the position of the electrode.

Their expressions have been obtained empirically:

$$\begin{cases} Att(i,j) = e^{-\frac{\left(\sqrt{(i-c_i)^2 + (j-c_j)^2} - s_z\right)^2}{2(N/2)^2}} \\ Sig(i,j) = \frac{1}{1 + \frac{dOD - (c_j - j_{od})}{s_z/4}} \\ Cone(i,j) = e^{-\frac{ConeAng^2}{2 \times \sigma^2}}, \quad \text{if } j > j_{od} \end{cases} \quad (B.3)$$

With

- N is the size of the matrix representing the square retinal plane;
- (i_{od},j_{od}) is the position of the optic disk;
- $dOD(i,j) = \sqrt{(i-i_{od})^2 + (j-j_{od})^2}$ is the distance to the optic disk;
- $ConeAng = |atan2(i-i_{od}, j-j_{od})| / angleDisk$ is the normalized angle used in the calculation of the activation cone;

- $angleDisk = 2 \times asin(\frac{s_z/2}{dOD})$ is the angle formed by the tangents to the electrode passing through the optic disc.

In the original model, the calculation of "angleDisk" was: $angleDisk = 2 \times asin(s_z/dOD)$. However, as shown in Figure B.1, the calculation must be done according to the radius and not the diameter of the electrode. The computation takes this change into account.

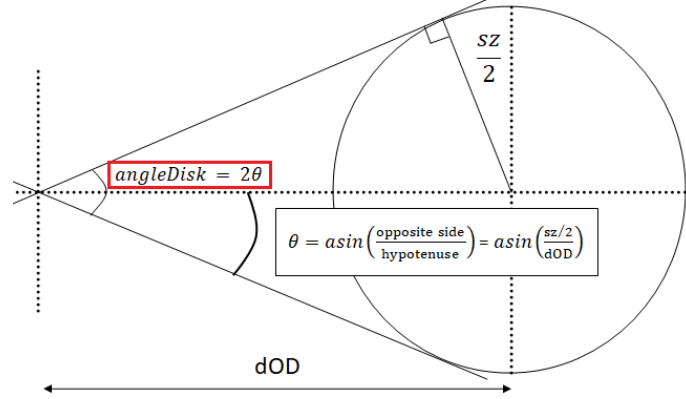


Figure B.1 – Explanatory diagram of angleDisk calculation.

In the original matlab computation, $N = n_x = n_y$ is 400, σ is 1, (i_{od}, j_{od}) is (200,100), (c_i, c_j) is (200, 150), s_z varies between 3 and 30 pixels, and α between 0.1 and 1. Finally, these two activations (isotropic "direct" activation and anisotropic "en passant" recruitment of ganglion cell axons) are combined with different ratio α (contribution for the axons "en passant") via a weighted sum:

$$retinian_activation = IsoA + \alpha \times EP \quad (B.4)$$

Second step - Model of the cortical activation

Since the retino-cortical transform has no analytical expression for the rat, F. Chavane and S. Roux had to determine its shape by experimentation. As a reminder, retinotopy is obtained by stimulating a set of areas of the retina until a map is obtained in the visual cortex. By studying the data, they were able to define a bijective function whose form approximates the expected result.

This transform applies to the coordinates of a point independently according to the following expression:

$$RCT : \begin{cases} Retina \rightarrow Cortex \\ (i, j) \mapsto (\frac{1}{ai + b}, \frac{1}{cj + d}) \end{cases} \quad (B.5)$$

where a, b, c, d is the set of values selected by matching the function results with the rat retinotopy.

The implementation of this geometrical transform produces a correspondence between the coordinates of the retinal space and the cortical space. The remaining task will then be to interpolate the image representing the retinal activation.

Finally, the effects relative to the diffusion in the visual cortex and due to optical imaging do not have mathematical expressions. In the computation, they will be represented by a smoothing effect on the cortical activation.

B.1.2 Summary list of parameters

The units of the parameters are to be confirmed.

The parameters related to the prosthesis

Name	Label	Doc	Default	Unit value
electrode_number	Number of electrodes per side	Number of electrodes per side is equal to the square root of the total number of electrodes.	1	no unit
electrode_size	Size of electrodes	Size of electrodes in μm .	30	μm (pixel for now)
electrode_spacing	Spacing between electrodes	Spacing between the centres of electrodes in pixel (for now), positive or zero.	35	μm (pixel for now)
activation_levels	Intensity levels of electrodes	Activation levels of electrodes, between 0 and 1.	1.0	ratio without unit

The parameters of model by Roux et al.

Related to the retinal activation profile

Name	Label	Doc	Default value	Unit
vert_matrix_size	Vertical size of the retinal plane	Vertical size of the retinal plane	400	pixels
hori_matrix_size	Horizontal size of the retinal plane	Horizontal size of the retinal plane	400	pixels
vert_optic_disc	V-position of the optic disc	Vertical position of the optic nerve head.	200	pixels
hori_optic_disc	H-position of the optic disc	Horizontal position of the optic nerve head.	25	pixels
vert_prosthesis	V-position of the prosthesis	Vertical position of the prosthesis centre.	200	pixels
hori_prosthesis	H-position of the prosthesis	Horizontal position of the prosthesis centre.	200	pixels
sigmoid_baseline	Sigmoid baseline	Baseline of the sigmoid.	0.0	mA
sigmoid_amplitude	Sigmoid amplitude	Amplitude of the sigmoid.	1.0	mA
isotropic_spread_deviation	Isotropic spread	Isotropic spread, represents the current diffusion from the direct activation.	1.0	N/A
anisotropic_spread_deviation	Anisotropic spread	Anisotropic spread, represents the current diffusion in relation to the axons en passant activation.	1	N/A
ep_ratio	Axons en passant ratio	Contribution of the activation of the axons en passant.	0.5	ratio without unit
retinal_smoothing_criteria	Retinal smoothing	Smoothing criteria applied to the retinal activation profile.	10	N/A

Related to the cortical activation profile

Name	Label	Doc	Default value	Unit
cortical_smoothing_criteria	Cortical smoothing	Smoothing criteria applied to the cortical activation profile.	10	
v_magnification_rat_1	Vertical magnification rat 1	First parameter of the vertical magnification (retino-cortical transform of the rat)).	-0.008	N/A
v_magnification_rat_2	Vertical magnification rat 2	Second parameter of the vertical magnification (retino-cortical transform of the rat).	3.0	N/A
h_magnification_rat_1	Horizontal magnification rat 1	First parameter of the horizontal magnification (retino-cortical transform of the rat).	-0.007	N/A
h_magnification_rat_2	Horizontal magnification rat 2	Second parameter of the horizontal magnification (retino-cortical transform of the rat).	3.0	N/A

B.2 How to use MACULAR to simulate the stimulation by retinal prosthesis

B.2.1 User - The protocol when using the GUI of MACULAR

This section gives the different steps to follow after opening MACULAR in order to obtain the results in the case of a simulation by prosthesis stimulation.



Figure B.2 – Opening of MACULAR.

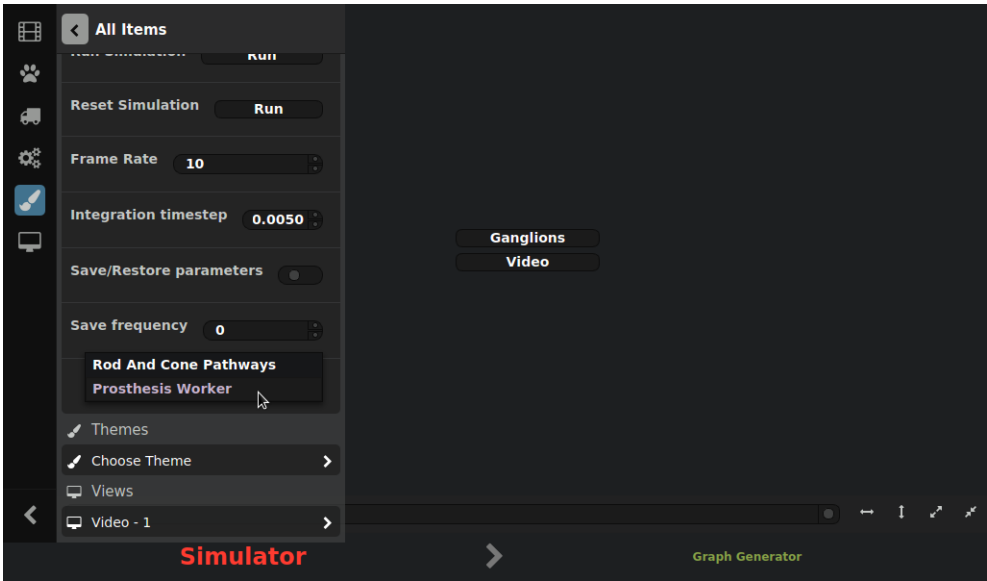


Figure B.3 – Selection of the worker between the simulation using Virtual Retina and simulation of the prosthesis stimulation.

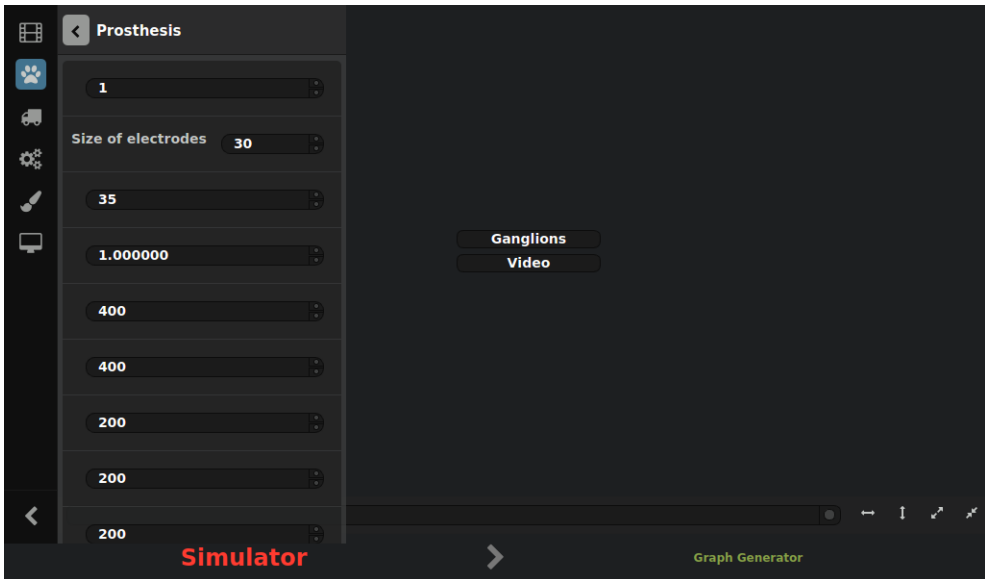


Figure B.4 – List of parameter values.

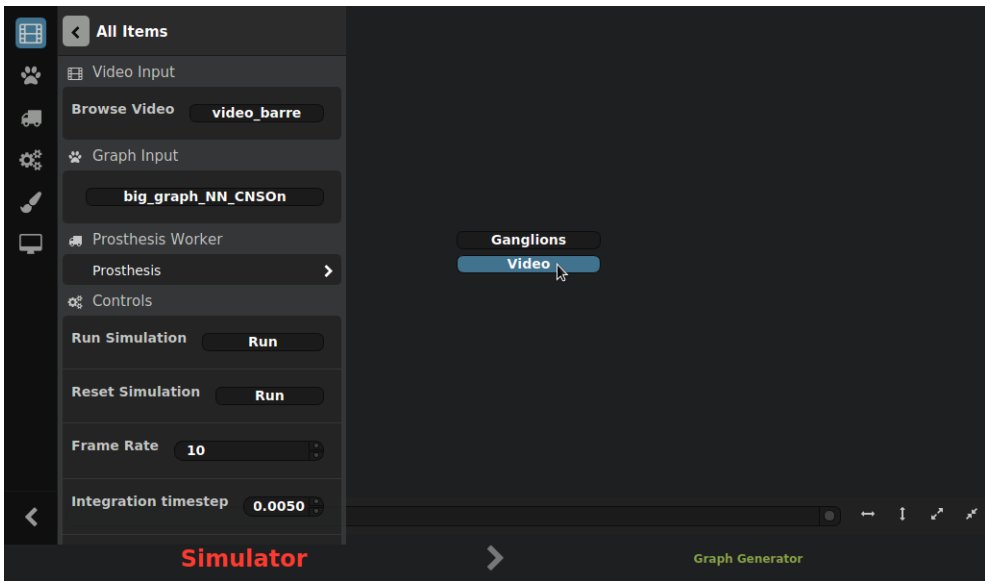


Figure B.5 – Opening of the display windows.

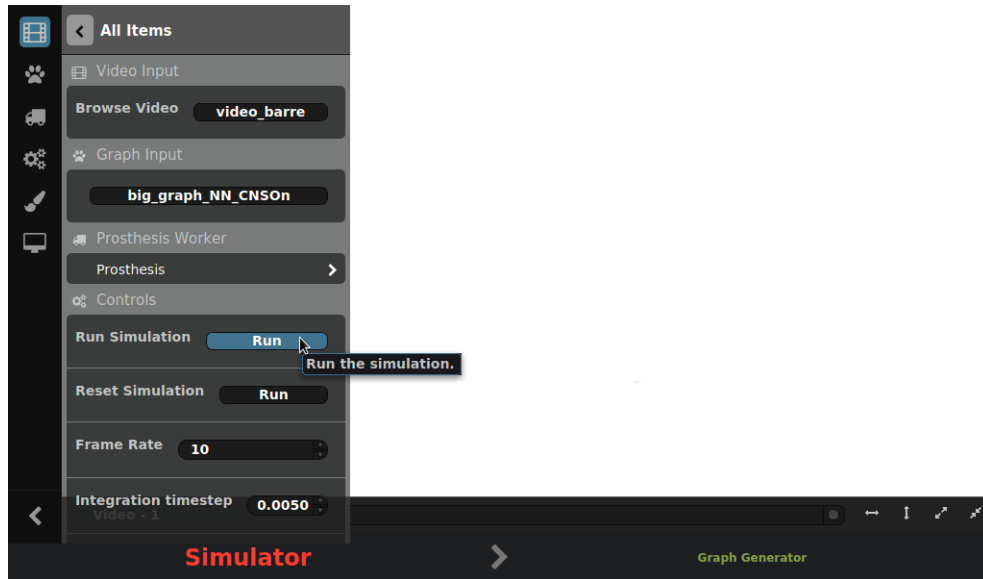


Figure B.6 – Starting macular run.

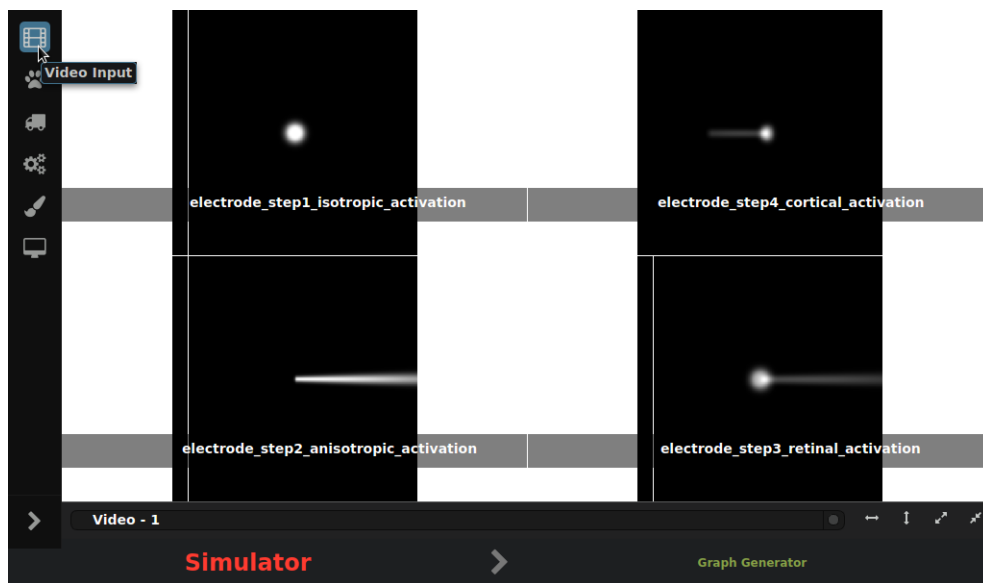


Figure B.7 – Results displayed when running macular.

B.2.2 Development - General structure overview

Diagram of the links between the MACULAR files related to macularProsthesisInput.cpp and macularProsthesisWorker.cpp. In particular, to show (by arrows for example) in which order the files are called, etc. To be discussed with the Experimentation and Development Department if it is possible to represent it correctly or if it is better to write an explanatory text (with the risk for it to be too complicated to understand).

B.2.3 Development - Explanation of the implementation of the model

Description of the project files

- *macularProsthesisInput.cpp*
Contains the implementation of the model by Roux et al. (eLife 2016).
- *macularProsthesisWorker.cpp*
Makes the link between the GUI and macular ProsthesisInput.cpp
- *macularProsthesisInputTest.cpp*
Tests the results of macularProsthesisInput.cpp. Creates images in the build directory, to directly view the effects of the value of a parameter.

Methods & functions in *macularProsthesisInput.cpp*

- *double wrapToPi(double theta)*
Returns the value of the input angle in the interval $[-\pi, \pi]$.
- *cv::Mat retinoCorticalTransform(cv::Mat)*
Returns the input image after applying the retino-cortical transformation given in section B.1.1
- *vector< vector<int> > matrixElecPos(int vert_prosthesis, int hori_prosthesis, int electrode_number, int electrode_spacing)*

Returns the matrix of the position of each electrode of the prosthesis. There are four input parameters: the number and spacing of electrodes, and the position of the prosthesis (considering that this position as the geometric center of the prosthesis). The position of each electrode will then be calculated with respect to this central point by applying the following formulas (see Figure B.8):

- $vertical_position = elec_nb_row \times electrode_spacing - central_position + vert_prosthesis$
- $horizontal_position = elec_nb_col \times electrode_spacing - central_position + hori_prosthesis$
- with $central_position = (electrode_spacing \times (electrode_number - 1)) / 2$

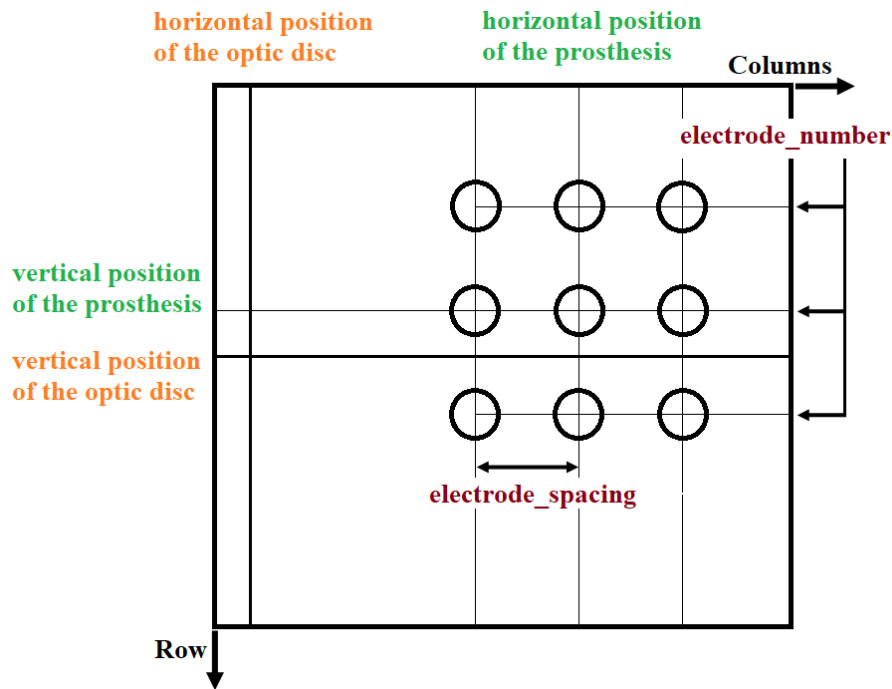


Figure B.8 – Explanatory diagram of the positions of electrodes calculation.

- *vector<double> intensityLevels(string shape)*
Returns the vector of intensity levels to be applied to electrodes. A more detailed description is given in subsection 7.2.3.
- *void electrodeProfile(int v_elec, int h_elec)*
Returns the activation profile of one electrode. The input parameters correspond to the position coordinates of the electrode.
- *void prosthesisProfile(void)*
Returns the activation profile of the prosthesis. It is the sum of the activations of each electrode weighted by their respective intensity level.

Outputs:

- *QHash<QString, cv::Mat> output_to_one_electrode*
Contains the four activation profiles for an electrode: direct activation by the electrode, activation due to the passing activation of ganglion cell axons, retinal activation profile and cortical activation profile.
- *QHash<QString, cv::Mat> output*
Contains the four activation profiles for the whole prosthesis (sum of all electrodes profiles).

Appendix C

Auto-évaluation - Synthèse compétences

Ce document a pour objectif de donner une auto-évaluation dans le cadre de ce stage selon un référentiel défini par l'ENSEA et classé en 8 compétences. Le référentiel de travail initial a été celui des recommandations de la Commission du Titre d'Ingénieur établies en 2016 et sera fourni à titre indicatif en police réduite sous chaque intitulé de compétence.

Notez qu'il s'agit d'une évolution de compétences sur l'ensemble de ma scolarité. C'est donc le fait de ce développement continu et du fait d'avoir acquis ces compétences au fur et à mesure qui m'a permis de réaliser mon stage sereinement.

Connaissances techniques et scientifiques

- *Connaissance et compréhension d'un large champ de sciences fondamentales et capacité d'analyse et de synthèse qui leur est associée.*
- *Maîtrise des méthodes et des outils de l'ingénieur : identification, modélisation et résolution de problèmes même non familiers et incomplètement définis, utilisation des outils informatiques, analyse et conception de systèmes.*

Si la plupart de mes connaissances sur le sujet sont le résultat des recherches que j'ai effectuées pour mon stage de 2ème année ou lors de mon échange en Italie (domaine Biomédical avec spécialisation dans les Neurosciences), le domaine de la Recherche nécessite une constante mise à jour de nos connaissances sur les dernières avancées dans celui-ci. Par exemple, en participant à des conférences ou en lisant des revues scientifiques. En effet, puisque de nouvelles informations sont partagées chaque jour, il est essentiel de se tenir informé de l'avancée au niveau international et ce dans le cas où un travail déjà réalisé puisse contribuer à améliorer sa propre recherche.

Sur le plan technique, ce stage m'a permis de découvrir un langage de programmation avec lequel je n'étais jusqu'ici pas familière. Je me suis notamment rendue compte de la facilité grandissante d'adaptation à un nouveau langage au fur et à mesure de mes participations à des projets différents. De plus, le travail en collaboration avec l'équipe d'ingénieurs du Service d'Expérimentation et de Développement m'a fait découvrir la méthode agile de travail ; et ce, grâce aux deux coding sprint auxquels j'ai participé.

Cependant, ma capacité à adapter ma façon de travailler ou celle de rassembler et utiliser des connaissances nouvelles n'est pas seulement due à ce stage. Elle a en effet évolué sur l'ensemble des projets que j'ai réalisés au cours de ma scolarité, aussi bien lors de ma formation à l'ENSEA qu'au cours du temps d'étude et d'apprentissage par stage dans le milieu universitaire.

Conception de systèmes complexes

- *Capacité à concevoir, concrétiser, tester et valider des solutions, des méthodes, produits, systèmes et services innovants.*

Bien que je n'ai jamais effectué de stage en entreprise mais seulement en laboratoire (en laboratoire universitaire en première année, et en laboratoire de recherche ces deux dernières années), le développement de la plateforme de simulation MACULAR m'a permis de développer mes compétences dans la réalisation de produits, puisque sa visée est d'être utilisable par des biologistes, neuroscientifiques ou scientifiques du domaine de la vision.

Maîtrise des TIC & Aptitude à mobiliser des ressources variées

- *Capacité à trouver l'information pertinente, à l'évaluer et à l'exploiter, compétence informationnelle.*
- *Aptitude à mobiliser les ressources d'un champ scientifique et technique spécifique.*

Rappelons tout d'abord la définition des TIC, Technologies de l'Information et de la Communication : il s'agit de *l'ensemble des techniques et des équipements informatiques permettant de communiquer à distance par voie électronique* (source : Larousse).

Dans le cadre de la recherche, la maîtrise des TIC et l'aptitude à mobiliser des ressources variées font, d'après moi, partie d'un tout.

En effet, il s'agit avant tout de la capacité à rassembler et analyser des informations en utilisant un ensemble de bases de données différentes et de sources variées.

Au cours de mes stages, différentes sources se sont avérées des plus utiles pour rassembler les éléments nécessaires à mon travail, ou simplement pour m'informer des avancées réalisées dans les domaines associés : assister à des conférences, lecture de revues scientifiques ou de thèses, recherche dans des documentations en ligne (par exemple, pour la librairie OpenCV ou sur le site internet de Matlab) et même accès à la bibliothèque et aux supports d'information papiers du centre Sophia-Antipolis.

Il est à noter qu'avec l'importance grandissante donnée aux technologies, cette compétence de mobilisation des ressources, notamment avec les TIC, est désormais développée dès le collège. Seule l'échelle à laquelle elle est utilisée change d'un projet à l'autre. Il s'agit donc plutôt d'apprendre à s'adapter à toute échelle de travail et par la suite de développer son esprit critique et sa capacité à faire le tri dans les informations, ce qui est également possible par échange avec les autres membres de l'équipe.

Capacité d'adaptation et relationnelle, leadership

- *Capacité à s'insérer dans la vie professionnelle, à s'intégrer dans une organisation, à l'animer et à la faire évoluer : exercice de la responsabilité, esprit d'équipe, engagement et leadership, management de projets, maîtrise d'ouvrage, communication avec des spécialistes comme avec des non-spécialistes.*
- *Capacité à se connaître, à s'autoévaluer, à gérer ses compétences notamment dans une perspective de formation tout au long de la vie, à opérer ses choix professionnels.*

Un des aspects que j'ai le plus apprécié au cours de mes deux stages a été de m'intégrer non seulement dans une équipe et dans un projet mais également de confronter ma vision du monde à celle des nombreuses personnes dont j'ai croisé la route. Ce stage m'a permis de revoir mes attentes aussi bien au niveau professionnel qu'au niveau personnel.

En apprenant à évoluer en tant que groupe, j'ai également réalisé une évolution sur le plan personnel. Lorsque mon tuteur de stage m'a proposé de continuer en thèse, il s'est agit d'une véritable remise en question du projet professionnel que je suivais jusqu'alors.

Discuter des expériences vécues par les membres de mon équipe m'a donné matière à réflexion et m'a permis de mettre en relief ce qui avait pour moi le plus d'importance en termes de priorité. Ainsi, alors que j'ai commencé mon stage dans une confusion totale vis-à-vis de ce que je souhaitais faire après mon diplôme, mes nombreux échanges et questionnements réalisés tout au long du stage ont été d'une réelle aide afin de réapprendre à me connaître et revoir mes objectifs de vie.

Aptitude à l'innovation et à la recherche

- *Capacité à effectuer des activités de recherche, fondamentale ou appliquée, à mettre en place des dispositifs expérimentaux, à s'ouvrir à la pratique du travail collaboratif.*
- *Capacité à entreprendre et innover, dans le cadre de projets personnels ou par l'initiative et l'implication au sein de l'entreprise dans des projets entrepreneuriaux.*

S'agissant d'un projet de recherche sur lequel j'ai travaillé deux années de suite, il m'a été donné d'apprendre à travailler dans ce domaine particulier dont les enjeux ne sont pas les mêmes que dans l'industrie.

Travailler dans le domaine de la Recherche a été une véritable opportunité d'en apprendre davantage sur la façon dont j'aime travailler. L'année dernière, je me suis rendu compte de la difficulté à définir ses propres jalons à atteindre et du délai qu'il peut parfois y avoir avant d'obtenir des résultats satisfaisants. J'ai malgré tout apprécié l'autonomie et la créativité qu'implique le travail dans le domaine de la recherche. Bien que j'en sois arrivée aux mêmes conclusions cette année, j'ai aussi réalisé beaucoup plus clairement qu'il était difficile pour moi de demander de l'aide. Travailler en équipe avec les ingénieurs du SED m'a donc permis de travailler sur ce manque de compétence.

J'ai également eu l'occasion de constater la dimension plus proche de l'entrepreneuriat à l'INRIA en discutant avec les deux ingénieurs de l'équipe qui travaillaient sur un projet à visée commerciale.

Pour finir, la remise en question de mes projets me fait envisager non plus de chercher un travail en tant que salarié mais pourquoi pas de viser l'auto-entrepreneuriat.

Enjeux de l'entreprise, connaissance sociétale, ouverture culturelle

- *Aptitude à prendre en compte les enjeux de l'entreprise : dimension économique, respect de la qualité, compétitivité et productivité, exigences commerciales, intelligence économique.*
- *Aptitude à prendre en compte les enjeux des relations au travail, d'éthique, de responsabilité, de sécurité et de santé au travail.*
- *Aptitude à prendre en compte les enjeux environnementaux, notamment par application des principes du développement durable.*

S'agissant d'un projet d'équipe, chacun contribue au projet global et il est donc important d'en comprendre les enjeux afin de mieux communiquer et répondre aux exigences attendues pour le produit final.

L'objectif principal de ce projet est d'offrir un outil aux scientifiques travaillant dans le domaine de la recherche lié à la vision.

Le développement de ce simulateur a de nombreuses applications potentielles, notamment sur le domaine éthique. En effet, l'optique finale est de pouvoir obtenir des résultats sans avoir la nécessité de réaliser des expérimentations et tests sur animaux (humains inclus). En effet, une fois les modèles de simulation optimisés et réalisés à partir de données expérimentales, ils pourront être utilisés pour prédire des résultats sans perte de temps ou de moyens. Le but est donc de diminuer l'utilisation de matériel et d'animaux en remplaçant les tests effectués en laboratoires d'expérimentation par des simulations.

Pour finir, l'importance de l'environnement se retrouve par des gestes simples à mettre en place, comme par exemple en évitant d'imprimer des documents ou bien encore avec l'installation de nouvelles machines à cafés permettant d'utiliser sa propre tasse.

Aptitude à l'international

- *Aptitude à travailler en contexte international : maîtrise d'une ou plusieurs langues étrangères et ouverture culturelle associée, capacité d'adaptation aux contextes internationaux.*

Si je suis toujours incertaine de la voie professionnelle que je souhaite suivre, je suis au moins sûre de l'importance que je veux donner à l'international dans ma vie. Il s'agit en effet de l'aspect que j'ai veillé à développer le plus possible au cours de ma scolarité; et ce, aussi bien par mon adhésion dès la première année à l'association RII puis INO, que par mon stage de première année à Taïwan et finalement par mon échange Erasmus en Italie. L'international était donc un critère qui m' a décidé à faire mon stage à l'INRIA.

Au cours de mes deux stages, j'ai donc eu la chance de travailler dans une équipe internationale dont les membres étaient : Chilien, Mexicaine, Marocaine, Grecque, Taïwanaise, Américaine-Polonaise et Allemande ... En comptant également les autres équipes, le centre rassemble une véritable palette de nationalités. Même si mes deux derniers stages ont été effectués en France, il s'est agit d'une totale immersion dans un environnement international ; ce qui m'a permis d'améliorer mon anglais bien plus qu'au cours de mon stage à Taïwan (puisque que je l'avais réalisé avec deux autres élèves de l'ENSEA avec qui je parlais plus souvent français qu'anglais).

Ce contexte permet aussi de discuter de sujets comme l'actualité mondiale en échangeant différents points de vue, et en permettant de développer son esprit critique tout en s'informant.

De plus, le domaine de la Recherche a pour avantage d'utiliser en grande majorité la langue internationale afin partager les résultats d'études (articles, conférences, ...). Cela rend le rassemblement d'informations sur les avancées dans le domaine bien plus simples à faire. Malgré tout, si j'ai nettement vu mon évolution dans cette compétence au cours de mon premier stage, elle a été moins importante au cours de cette année.

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