Extracellular Electrical Stimulation of Retinal Ganglion Cells

by

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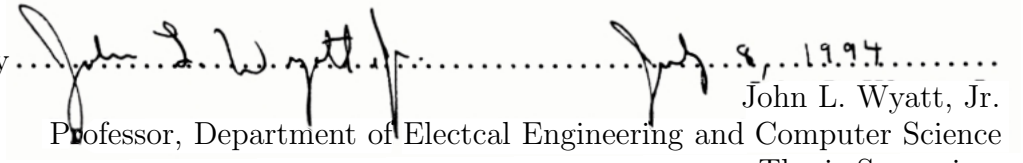
Certified by .....  .....
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Abstract

The research conducted for this thesis was part of an overall effort to develop a retinal prosthesis to aid blind patients suffering from disease of the photoreceptors. We hope to restore vision to such patients by implanting a device which electrically stimulates the healthy cells of the inner retina. Preliminary experiments indicate that the threshold amounts of current required to stimulate retinal ganglion cell bodies and axons typically fall within the same range. We believe that stimulation of ganglion cell axons will hinder our ability to elicit phosphenes of discernible resolution in implanted patients. For this reason, current research efforts are directed in part at finding a way to stimulate retinal ganglion cell bodies without exciting the axons which overlie them at the innermost layer of the retina.

The goal of this thesis is to design a stimulating electrode which employs a novel geometry to selectively stimulate retinal ganglion cell bodies. Discussions of the retina and of the retinal prosthesis are provided at the outset of the thesis. Simple models of nerve cells are then constructed and analyzed both to guide the design process and also to develop a general understanding of electrical stimulation. Analysis leads to the specification of a new experimental electrode and a description of how it was constructed. A description of preliminary experiments which were conducted to test the electrode follows. Due to a number of unresolved experimental issues, experimental results were inconclusive. Suggestions for further study are made in the concluding chapter of the thesis.

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Contents

Chapter 1

Introduction

The research conducted for this thesis was part of an overall effort to develop a retinal prosthesis to aid blind patients suffering from disease of the photoreceptors. Millions of people worldwide are affected by two such diseases, retinitis pigmentosa (RP) and age-related macular degeneration (AMD) [3, 40, 65]. Preliminary evidence suggests that while these diseases result in degeneration of the outer retina, inner retinal elements may remain healthy to some degree [60]. Furthermore, it has long been known that visual sensations (*phosphenes*) are created when the retinal cells of healthy subjects are stimulated electrically [6, 23, 37]. In light of these two facts, we hope to restore vision to patients suffering from RP and AMD by implanting a device which electrically stimulates the healthy cells of the inner retina. Lending support to our approach is a more recent study which demonstrated that phosphenes could be elicited in a patient with RP [25].

1.1 Thesis problem

Preliminary experiments have been conducted to characterize the response of rabbit retinal ganglion cells to electrical stimulation *in vitro*. Results to date indicate that the threshold amounts of current required to stimulate ganglion cell bodies and axons typically fall within the same range [26, 64]. We believe that stimulation of ganglion cell axons will hinder our ability to elicit phosphenes of discernible resolution in implanted patients. For this reason, current research efforts are directed in part at finding a way to stimulate retinal ganglion cell bodies without exciting the axons which overlie them at the innermost layer of the retina.

The goal of this thesis is to design a stimulating electrode which employs a novel geometry to selectively stimulate retinal ganglion cell bodies. All stimulating electrodes used in previous experiments have had radially-symmetric geometries. For this reason, the current investigation focuses on non-radially-symmetric electrodes.

1.2 Thesis outline

The body of the thesis is divided into four chapters. Chapter 2 provides a discussion of the retina and of the retinal prosthesis. This chapter is intended to broaden the reader's understanding the thesis problem described above. We will attempt to solve the thesis problem through a combination of theoretical and experimental approaches. The theory of extracellular electrical stimulation of nerve cells is discussed in Chapter 3. Simple models

of nerve cells are constructed and analyzed in this chapter to guide the design process and also to broaden our general understanding of electrical stimulation. The design and construction of an experimental stimulating electrode are covered in Chapter 4. A model for numerically predicting the electric fields produced by the electrode is presented at the end of the chapter. Chapter 5 describes preliminary experiments which were conducted to test the electrodes. Due to a number of unresolved experimental issues which are described in the final section of the chapter, experimental results were inconclusive. Suggestions for improved experimental methods are made in the concluding chapter of the thesis.

Chapter 2

The Retina and the Retinal Implant

The essence of the thesis can be clarified by a general description of the retina and of the retinal implant. The chapter is divided into three sections. The first section deals in a general way with the anatomy and physiology of the normal retina. Where appropriate, known correlations between retinal structure and function will be given. The second section provides the motivation for and a functional description of the retinal implant. In addition, two design issues relevant to this work will be discussed. The third section of the chapter is devoted to one of the many lines of research towards the development of a successful retinal prosthesis, electrical stimulation of retinal cells. A review of the literature in this area will lead to a more complete formulation of the thesis problem.

2.1 Overview of retinal anatomy and physiology

The retina is a delicate tissue that lines the back of the interior of the eye (Figure 2-1). The retina (*ret*) resides between the choroid (*ch*) and vitreous (*vitr*). From a functional viewpoint, the retina lies at the front end of the visual system. Light enters through the eye and is transduced at the retina to neural signals. These signals propagate through the retina and incite a number of processing operations, some of which will be discussed below. The signals are then conducted from the retina to the visual areas of the brain via the optic nerve (Figure 2-2).

2.1.1 Cross-sectional view of the retina

A cross-sectional view of the retina, suggested by the dashed box in Figure 2-1, reveals a multi-layered cellular organization. A common feature among vertebrates is the interposition of two synaptic layers between three cellular layers [14]. This feature is evident in layers (4) through (8) of Figure 2-3. There are six basic classes of retinal neurons [14]. These are photoreceptors, horizontal cells, bipolar cells, amacrine cells, interplexiform cells[1], and gan-

[1]It has been argued that interplexiform cells should in fact be classified as amacrine cells [62], reducing the number of classes to five. I have arbitrarily chosen to include the interplexiform cell as a distinct class, as in [14].

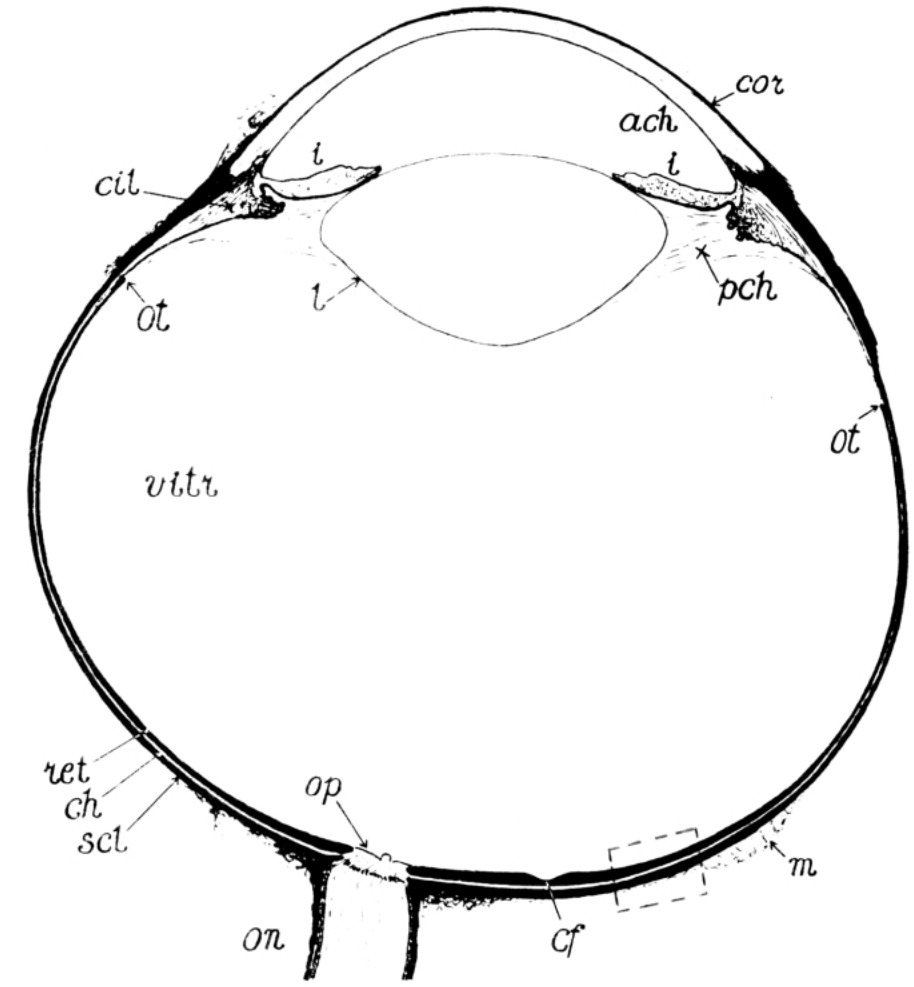

Figure 2-1: View of a horizontal section through the right eye of a Rhesus Macaque (*macaca mulatta*). From Polyak [42]. Abbreviations - *scl:* sclera; *ch:* choroid membrane; *ret:* retina; *on:* optic nerve; *op:* optic papilla, or disc; *cor* cornea; *cil:* ciliary body; *i:* iris; *l:* lens; *ach:* anterior chamber; *pch:* posterior chamber; *vitr:* vitreal chamber; *ot:* ora terminalis; *cf:* central fovea; *m:* extrinsic muscle.

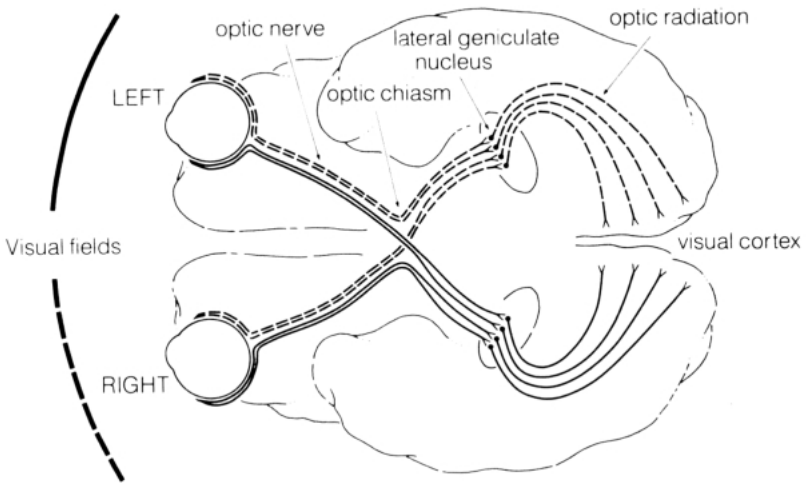

Figure 2-2: Diagram of the visual pathways in primates viewed from the underside of the brain. From Dowling [14].

glion cells. Each type of neuron will be briefly discussed below[2]. In addition to neurons, the retina also contains *glial cells*. These cells do not have axons or conduct action potentials [32], but may be responsible for a variety of physiological functions [63]. One such cell, the Müller cell, is considered first.

Müller cells

The dominant type of glial cell in the retina is the Müller cell. These cells and their processes fill most of the space between neural elements in the retina, leaving extracellular gaps about 20nm wide. The nuclei of Müller cells reside in the inner plexiform layer (see layer 6c) and the cell bodies extend vertically through the retina, spanning the distance between the outer and inner limiting membranes. Also, Müller cells have large *endfoot* regions which extend downwards through the optic nerve fiber layer as triangular or conical structures that form the inner limiting membrane. While Müller cells are integral to the functioning of the retina, they are not in the direct line of signal flow from the outer to the inner retina [49]. On the other hand, the cells appear to be the main contributor to the electroretinogram b-wave. The model for b-wave generation in Müller cells posits two potassium current sinks along the cell's length, one in the outer plexiform layer and one in the inner plexiform layer, and a source of potassium current at the cell's endfoot region.

[2]The better part of the material presented in the remainder of this section and in section 2.1.2 is derived from [14], [42], and [62]. Unless otherwise noted, the information presented applies specifically to primate retinas.