### 2.3.1 Previous work

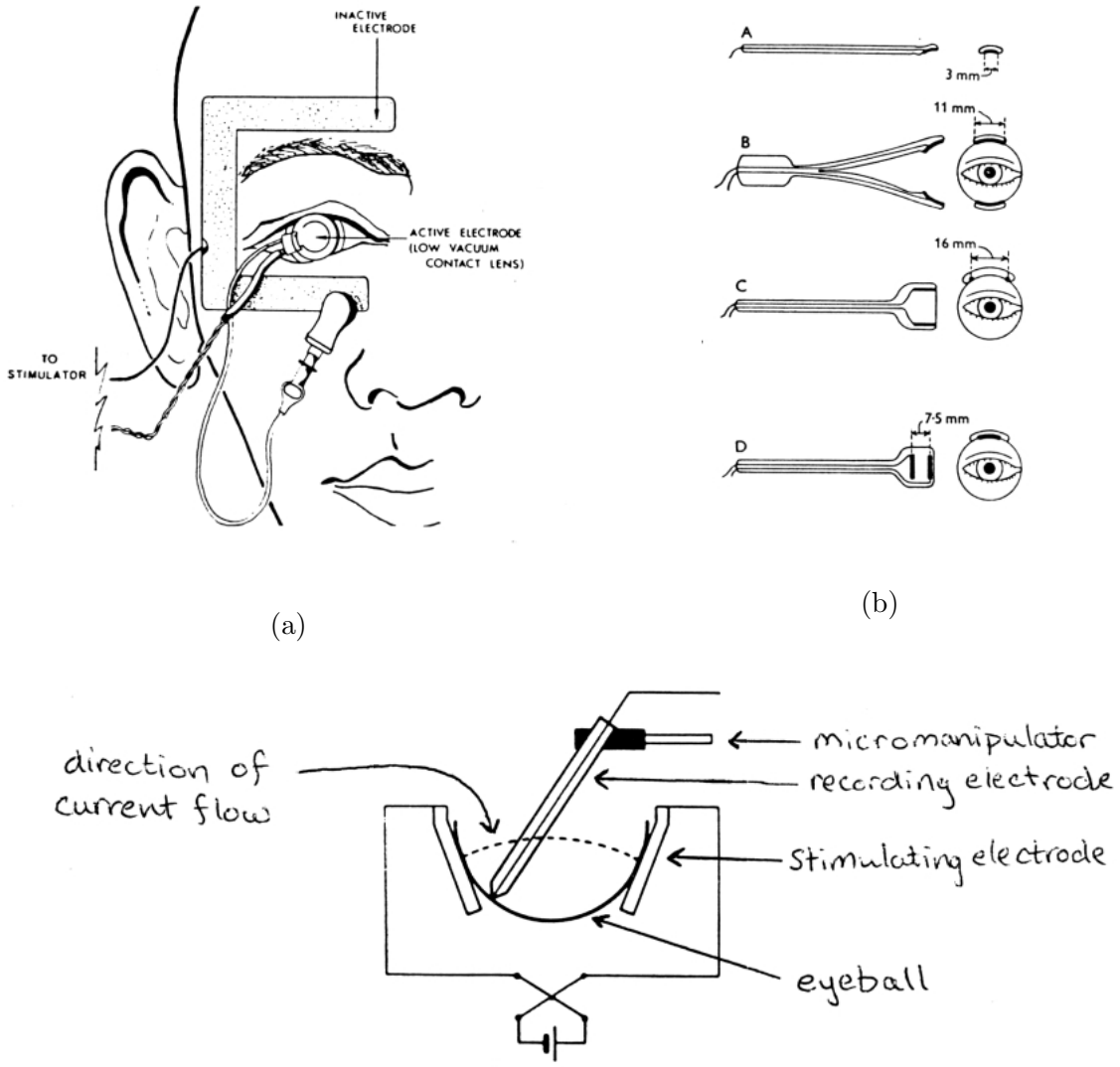
The literature to date on electrical stimulation of retinal cells reveals a substantial and diverse body of work. An overview of the work is provided below, followed by a summary of the work which is of greatest relevance to this thesis.

#### Overview

A number of investigators have employed electrical techniques to study aspects of visual system function [10, 11, 13, 18, 19, 20, 35, 36, 37, 39]. These studies were often motivated by the fact that, from a functional point of view, electrical stimulation represents a novel mode of input to the visual system. For example, while visible light necessarily enters the system at the photoreceptor level, electrical currents might act on any of the retinal neurons and possibly on cortical neurons as well. Related studies were devoted explicitly to determining where electrical inputs occur [6, 23, 29, 30, 43, 44]. Since a cell which has been excited by an electrical stimulus will in turn excite other cells through conventional neural pathways, some care must be used when describing the nature of cellular responses. The cells at which such responses originate are said to be stimulated *directly*. A third line of inquiry concerns electrical stimulation of the inner retinal surface elements [2, 24, 25, 26, 38, 64]. These studies have been conducted in efforts to characterize retinal responses to stimulation by an implanted device such as the one depicted in Figure 2-8.

The methods used in the electrical stimulation studies vary considerably. Stimuli were usually delivered using one of three basic configurations. In the first configuration, electrical currents were channeled into the retinas of subjects through electrodes which had been placed outside of the eye (Figure 2-10) [6, 18, 19, 20, 23, 37, 43, 44]. This configuration was the least invasive of the three and was used in many cases on alert human subjects. The second configuration, which has been used to produce current flow perpendicular to the retinal surface, places one electrode inside of the eye and the other outside [10, 11, 29, 30, 35, 36, 39]. For *in vitro* studies, the extraocular electrode was placed off to one side of the eyecup, as depicted in Figure 2-11a. For *in vivo* studies, the extraocular electrode was placed directly behind the eye. In the third configuration, either a monopolar [2, 26, 64] or bipolar [2, 13, 24, 25, 26, 38] electrode was placed at the inner margin of the retina. Stimulating currents delivered using this configuration were thought to be concentrated at the retina's inner surface. An example of this configuration is shown in Figure 2-11b.

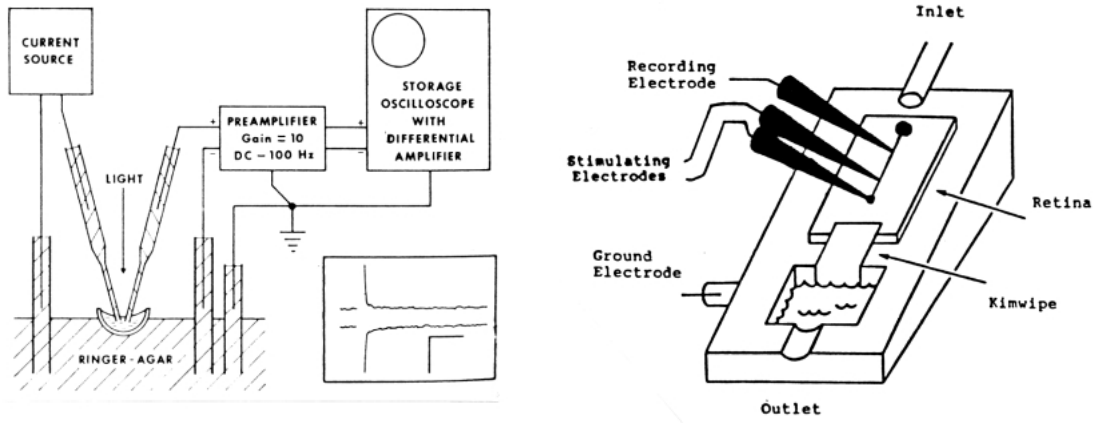
Visual system responses to electrical stimulation were measured in several ways. Some investigators have used visual sensations called *phosphenes*, which may be elicited by delivering electricity to points on the body located inside of or near the eyes, to gauge the effect of stimuli [6, 23, 25, 37]. Central to the phosphene studies is the use of human subjects who can describe the sensation and be easily trained to detect it. A perhaps more flexible and objective method which has been used by other investigators involves recording bioelectrical potentials at the surface of the scalp or cortex in response to electrical stimuli [11, 13, 38, 43, 44]. Brain potentials, however, indicate the gross behavior of a population of neurons and reveal little about interactions at the cellular level. Responses of individual nerve cells have been recorded by a third group of investigators through the use of microelectrodes [10, 18, 19, 20, 26, 35, 36, 64]. Less common forms of visual system response which have been recorded include intraocular potentials in an eyecup preparation [29, 30], potentials at the inner retinal surface [24], intraretinal potentials [39], and potentials at the optic nerve [2].




(a) (b)

(c)

Figure 2-10: Configurations for electrical stimuli delivered outside of the eye. (a) One pole of the electrode is mounted on a contact lens and placed against the cornea, while the other contacts a large area around the eye. From Potts *et. al.* [44]; (b) Several types of electrodes designed to be placed under the eyelids, against the conjunctiva. From Brindley [6]; (c) Schematic of silver-silver chloride wires placed on opposite sides of the cat eyeball *in vivo*. From Granit [20].




(a) (b)

Figure 2-11: Configurations for electrical stimuli delivered (a) transretinally and (b) to the inner surface of the retina. (a) Current flows between an electrode pole placed in the vitreal cavity of a frog eyecup and an extraocular pole. From Knighton [29]; (b) Current flows between the two poles at the inner surface of the retina. From Jensen [26].

**Summary of relevant work**

The site of origin of electrically evoked visual system responses appears to depend strongly on the stimulus configuration used. While transretinal currents seem to stimulate the photoreceptors directly [29], currents applied to the outside of the eye as in Figure 2-10a were thought to stimulate elements proximal to the photoreceptors [43]. Furthermore, while currents applied to the retinal surface stimulate ganglion cell axons directly [2, 26], currents applied using the electrodes of Figure 2-10b do not [6]. In order to avoid ambiguities in the mode of action of applied currents, we will focus on those studies in which electrical stimuli were concentrated at the inner retinal surface [2, 13, 24, 25, 26, 38, 64], as will be those delivered by the retinal implant.

Even within this smaller group of studies, substantial variations in experimental methods are found. In general, three types of stimulating electrodes were used. Bipolar electrodes, illustrated schematically in Figures 2-12a and 2-12b, create more concentrated or *focal* patterns of stimulus current than the monopolar type shown in Figure 2-12c. Also, two distinct types of stimulus waveforms were used. Biphasic waveforms such as those depicted in Figure 2-13b produce less damage to neural tissue and to electrodes than monophasic waveforms such as those of Figure 2-13a [24]. Finally, neural responses were measured either from individual ganglion cells, from a population of cells at the inner retinal surface, from the optic nerve, from the cortex, or in the form of phosphenes. A summary of stimulus and recording parameters used in the studies relevant to this work is provided in Table 2.1.

In spite of the diversity of methods used, two general themes emerge from the studies summarized in Table 2.1. First, all concluded that neural responses to stimulation originated at the inner retina. In such cases, ganglion cells may have been stimulated either directly or as an indirect result of amacrine or bipolar cell stimulation. This result provides support for

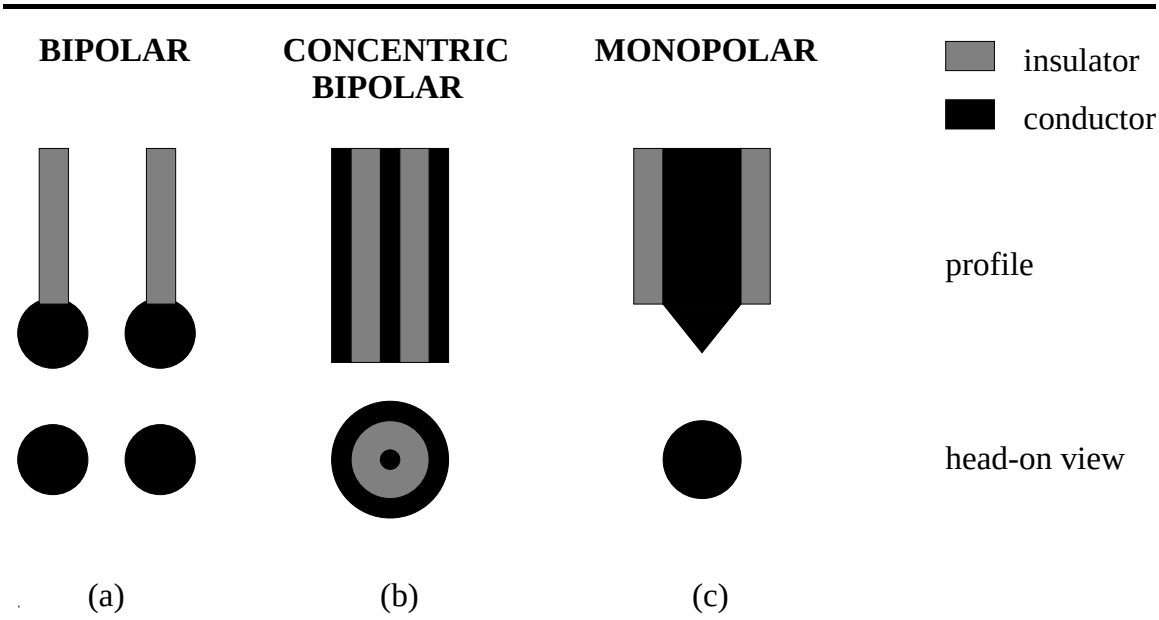



Figure 2-12: Schematic diagram of electrodes used for stimulation of the inner retina. (a) Bipolar electrodes; (b) Concentric bipolar electrodes; (c) monopolar electrode. Electrodes are not drawn to scale.

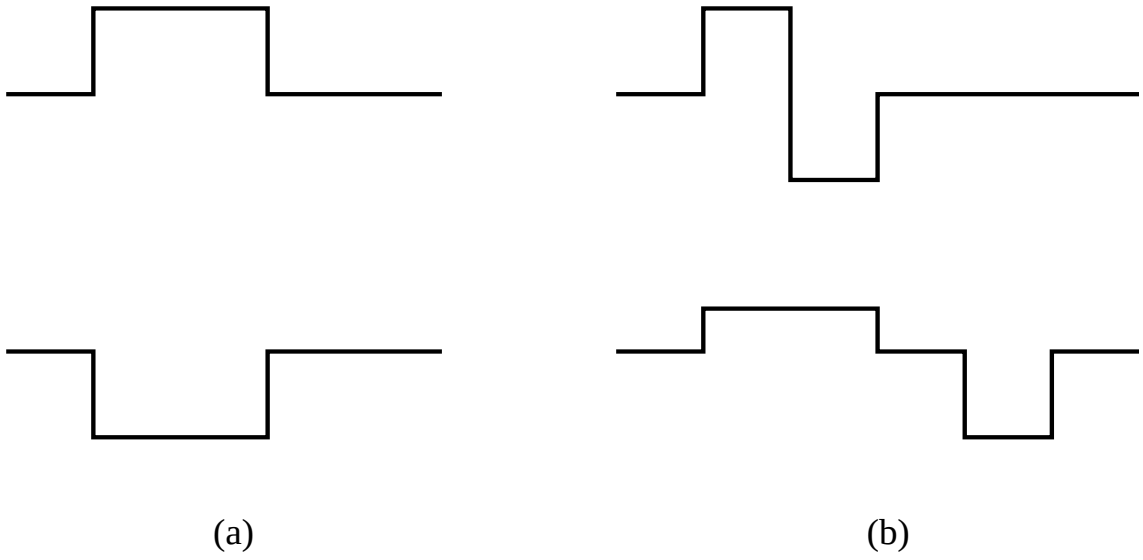



Figure 2-13: Examples of monophasic (a) and biphasic stimulus waveforms. These waveforms represent voltages or currents established across the two poles of a bipolar electrode, or between a monopolar electrode and a return pole which is very far away.

| Author(s) | Electrode Type | Stimulus Waveform | Stimulus Duration | Stimulus Amplitude | Recording Site |
|---|---|---|---|---|---|
| Benjamin *et. al.* [2] | bipolar | mono- and biphasic | 400$\mu$s per phase | up to 2mA | optic nerve |
| Doty & Grimm [13] | bipolar | monophasic | 0.1ms or 1ms | 1V to 15V | cortex |
| Humayun *et. al.* [25] | bipolar | monophasic | 75$\mu$s | up to 100$\mu$A | phosphene |
| Humayun *et. al.* [24] | bipolar | biphasic | 75$\mu$s per phase | 50-300$\mu$A (half phase) | retinal surface |
| Narayanan*et. al.* [38] | bipolar | biphasic | 400$\mu$s or 700$\mu$s total | 30-600$\mu$A | cortex |
| Jensen [26] | concentric bipolar | monophasic | 200$\mu$s | 0.4-400$\mu$A | single cell |
| Wyatt *et. al.* [64] | monopolar | monophasic | 20-500$\mu$s | 8-24$\mu$A | single cell |

Table 2.1: Summary of stimulus and recording parameters which successfully evoked visual system responses when electrodes were placed against the inner retinal surface.

the basic premise of the retinal implant work, that an array of surface-residing stimulating electrodes such as that depicted in Figure 2-8 may be used to stimulate inner retinal cells. Second, cells close to the stimulating electrode were more likely to be stimulated than cells further away. This supports the notion (presented in section 2.2.2) that intelligible visual perceptions might be created by stimulating the patient's inner retinal cells in a pixel-like fashion. To create the impression of a square, for example, stimulating current might be delivered to a subset of the implant electrodes bordering the square. This situation is depicted schematically in Figure 2-9. If a suitable amount of current is applied, ganglion cell bodies in the vicinity of each electrode will be stimulated either directly or indirectly. Because ganglion cells have restricted receptive fields centered approximately over their cell bodies [31, 26], the resulting perception might correspond to the pattern of stimulating electrodes used. That is, the patient might see spots of light bordering a square.

However, the electrodes might also be stimulating ganglion cell axons, which overlie the cell bodies at the innermost portion of the retina (see Figure 2-3). Were this the case, we hypothesize that the the brain would interpret incoming nerve messages from the stimulated axons as if they had originated at their peripherally located cell bodies. As depicted in Figure 2-9, we might expect the resulting sensation to be "referred back" to a more diffuse portion of the visual field than originally expected, corresponding to the receptive fields of the more peripheral cell bodies.

To determine the likelihood of this phenomena, a series of experiments were conducted to compare the threshold amounts of current needed to stimulate ganglion cell bodies and axons. When a stimulating electrode was placed over the center of a ganglion cell's receptive field, measurements were believed to represent thresholds for stimulating ganglion cell bodies, whereas when the electrode was positioned between the receptive field center and the optic disk, measurements were taken to represent axon thresholds. In these experiments,

cell body and axon thresholds typically fell within the same range [26, 64]. It would appear from this result that ganglion cell bodies and axons in the vicinity of a stimulating electrode are equally likely to be excited.

### 2.3.2 Thesis problem revisited

The above discussion suggests that a more careful approach must be taken to extracellular stimulation of retinal cells if the retinal implant is to be used to produce well-defined phosphenes. In order to achieve this goal, we believe it will be necessary to selectively stimulate retinal ganglion cells at or near the cell body without affecting the overlying axons. It is evident from Table 2.1 that a number of stimulation parameters might be varied in order to achieve selective stimulation. This thesis attempts to address the problem through the design of a novel, non-radially symmetric electrode geometry.