junctions with On-center cone bipolars [62].

It has been argued that the On-center and Off-center ganglion cells operate within two distinct and independent information processing channels[54]. Three lines of evidence support this claim. First, the dendrites of the On-center and Off-center ganglion cells stratify in different sublayers of the inner plexiform layer. Within these sublayers, it has been shown that the On-center and Off-center dendrites are each regularly arrayed so as to provide complete coverage of the retina [62]. In theory, either type of cell should be able to respond to light falling anywhere on the retina. Second, studies with the neurotransmitter analogue 2-amino-4-phosphonobutyrate (APB) have shown that blockage of On-center cone bipolar cells does not interfere with normal Off-center responses [54]. This fact indicates that center/surround antagonism is produced independently in the two channels, rather than through their interaction with one another. The third line of evidence comes from behavioral studies with APB. Under photopic conditions (where the cones are most active) intra-ocular APB injections in experimental animals led to difficulty in detecting bright-spot illumination, but did not effect performance in detection of dark spots [54]. Since only the ON channel is blocked by APB, these results are in agreement with the notion that the ON channel is sensitive to incremental light stimuli, while the OFF channel is sensitive to decremental stimuli.

The color-opponent and broad-band channels

Another classification scheme for ganglion cells has emerged from studies of chromatic responses. Color-opponent cells have small, color-specific receptive fields, while broad-band cells have large, color-insensitive fields. These two types of cells differ in several additional respects as well. The color-opponent ganglion cells have β morphology (see section 2.1.1), project their medium conduction velocity axons to the four parvocellular layers of the lateral geniculate nucleus of the thalamus (LGN), and respond to illumination of retina in a sustained fashion. The broad-band cells have α morphology, project their fast conduction velocity axons to the two magnocellular layers of the LGN, and respond transiently to visual stimuli [55].

Like the On-center and Off-center cells, both types of cells have antagonistic center/surround receptive field organization. A color-opponent cell might respond preferentially to illumination of its receptive field center with red light, for example, while a broad-band cell would respond identically to center illumination of various visible frequencies. The surround of color-opponent cells is not color-specific, so that in both cases, center responses would be reduced by any illumination of the surround.

The origins of the antagonistic center/surround receptive field organization were considered above in the discussion of the On and Off information processing channels. The underlying anatomy responsible for color-opponent responses is now considered. Recall from the discussion of photoreceptors (section 2.1.1) that the cones are sensitive to the different wavelengths of the visual light spectrum. Humans and many other species have three types of cones, which absorb maximally in the red, green and blue regions of the spectrum [14]. In the fovea, it is believed that midget ganglion cells connect via midget bipolar cells to a single cone [62]. This singular connection is probably responsible for color-specific receptive field centers of the color-opponent cells. The color-insensitive surrounds of the color-opponent cells are likely to receive input from all three cone types [55].

The characteristics of the color-opponent and broad-band ganglion cells lead us to think of them as parts of two distinct and independent information processing channels, much

as in the case of the On-center and Off-center cells. The color-opponent channel plays a central role in color vision and perception of fine spatial detail, while the broad-band channel is concerned with mainly with perception of motion, low-contrast stimuli, and night vision when only the rods are active [55]. It must be noted that the color-opponent and broad-band channels, while distinct from one another, are not distinct from the On and Off channels. In the midget system of the primate central retina, for example, there are On and Off systems for each of the three cone types [54]. Under these functional schemes, an On-center, broad-band cell would respond transiently to illumination of its receptive field center, unlike the "ON cell" of Figure 2-6.

Other ganglion cell groupings

X and Y

From studies of the cat retina comes a retinal ganglion cell classification scheme known as X/Y. The X/Y distinction was originally made on the basis of the cells' responses to changes in luminance across their receptive fields. While cells of both types exhibit On-center and Off-center responses, they differ substantially when a sinewave grating is overlayed such that the transition between bright and dark bars is centered over the receptive field. Since the two sides of the receptive field receive equal and opposite amounts of light, the net luminance across the field is zero. An X cell does not respond to this type of stimulus, and is considered to be "linear" because its lack of response reflects the (zero) sum of the light intensities. By contrast, a Y cell responds in a transient fashion to the same stimulus, and is therefore described as "nonlinear".

Substantial parallels exist between the cat Y and X cells and the broad-band and color-opponent cells, respectively. The receptive field centers of the Y cells generally larger than those of the X cells. Like the broad-band cells, the Y cells have the fastest conduction velocity. Like the midget cells of the primate retina, the cat X cells are relatively frequently encountered in the central area. Y cells have α morphology as do the broad-band cells, and the X cells have β morphology as do the color-opponent cells. Furthermore, Y cells have transient or *phasic* responses, while X cells have sustained or *tonic* responses.

Direction-sensitive cells

Many of the On-Off ganglion cells found in rabbit, turtle and other retinas show direction-sensitive or DS responses. These cells respond most strongly to spots of light moving through their receptive fields in a particular direction, the *preferred* direction, and either don't respond to or are inhibited by a spot moving in the opposite or *null* direction [14]. It has been suggested that DS responses are the result of an asymmetric wiring at the level of amacrine cell dendrites which includes a time delay between excitatory and inhibitory inputs to ganglion cells [62].

Spatial processing, temporal processing, and the plexiform layers

In section 2.1.1, it was suggested that ganglion cell responses strongly reflect two distinct types of input. Ganglion cells responding in a sustained fashion and having antagonistic center/surround receptive field organization are thought to receive their input primarily from bipolar cells. The bipolar cells receive their input from the outer plexiform layer, and are concerned primarily with spatial relationships. Ganglion cells responding in a transient fashion to the onset and cessation of light (On-Off) are thought to receive input primarily

from the amacrine cells. Amacrine cells receive their input from the inner plexiform layer, and are concerned primarily with temporal relationships. Thus, there appear to be two basic types of information processing carried out in the retina, a spatial type performed in the outer plexiform layer and a temporal type performed in the inner plexiform layer [14].

Not all ganglion cells fit neatly into one of these categories. An On-center Y cell, for example, has antagonistic center/surround receptive field organization, but responds transiently to illumination of its receptive field center. In the present scheme, these cells might be conceived of as reflecting a combination of outer plexiform and inner plexiform layer processing. Other cells such the DS cells are not so easily explained. DS cells perform a spatial and temporal analysis which is thought to be carried out entirely within the inner plexiform layer by amacrine cells.

2.2 The retinal implant

This section provides the motivation for and a description of an epi-retinal prosthesis which is being developed to aid patients suffering from certain forms of blindness. The background material provided in the previous section will explain both the causes of certain forms of blindness and also how the prosthesis is designed to aid such patients.

2.2.1 Motivation

The retinal implant targets patients who develop blindness secondary to loss of outer retinal function from diseases such as *retinitis pigmentosa* (RP) and *age-related macular degeneration* (AMD). Retinitis pigmentosa is a group of diseases caused by gene abnormalities on one of several chromosomes. About 1 in 4000 develop this hereditary disorder which affects an estimated 1.5 million worldwide. Early symptoms of RP include impaired adaptation to light, night blindness, and difficulty with the mid-peripheral visual field. Eventually, visual loss extends to the central and far-peripheral regions [3, 40]. Well over a million people worldwide are affected each year by a second disease, age-related macular degeneration [49]. At least 10% of the U.S. population in the 65-75 age group have lost some central vision from AMD, and the incidence rises in the older age groups [65]. As the world population ages due to improvements in health care, these numbers are bound to increase. Blindness associated with AMD is attributed to degeneration of the photoreceptors, which might be a secondary result of prior degenerative changes in the retinal pigment epithelium. AMD strikes the macula and therefore impairs the regions of highest visual acuity [65].

A third circumstance which may lead to loss of outer retinal function is infrared laser photocoagulation. Using a diode semiconductor laser delivering energy in the 810nm range, it was found that mild burns could be obtained in rabbit eyes which damaged the outer retina and choroid, but spared the inner retinal cells [5, 57].

Only photoreceptors transduce light (section 2.1.1). A patient who suffers the loss of photoreceptor function will not be able to see because his/her retina can no longer perform this transduction. Would it be possible to perform light transduction artificially, and then introduce the artificially generated visual signals into a healthy region of the visual system?

It is well known that responses can be elicited from living nerve cells through the application of an electric current. Furthermore, semiconductor devices which transduce optical signals to electrical signals are readily available. Based on these two facts, we believe that the answer to the above question - at least from a *functional* point of view - is "yes". The task of artificial light transduction is conceived of as channeling optical signals through an

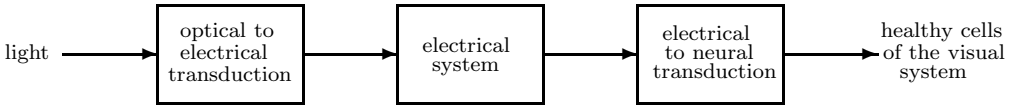

Figure 2-7: Block diagram of an artificial light transduction system.

electrical system which stimulates visual system nerve cells. A block diagram representation of such a system is illustrated in Figure 2-7.

2.2.2 Description and selected design issues

The retinal implant is currently being developed to accomplish the functions outlined in Figure 2-7. Light from the visual field will be transduced to electrical signals outside of the eye, perhaps by a device which has been mounted on a pair of spectacles (see Figure 2-8). The first stage of the electrical system will transmit information about the visual field to a second stage which has been surgically implanted inside the eye, against the inner margin of the retina. There, the second stage of the electrical system will drive an array of stimulating electrodes, thus providing the electrical to neural transduction.

The choices that have been made to arrive at the current design will not be discussed in this thesis. However, two significant design issues regarding the choice of retinal cells as the stimulation site will be raised. The first regards the health of the retinal cells in the diseases RP and AMD. Nervous system cells may die in the absence of synaptic input through a process known as *transneuronal degeneration*. The horizontal, bipolar, amacrine, interplexiform, and ganglion cells of a retina which has lost photoreceptor function probably receive little or no synaptic input, making them susceptible to this degenerative process. Of particular concern is the health of the ganglion cells. Since the ganglion cells provide the retina's output through their axons, it will be impossible to perform a successful electrical to neural transduction within the retina if these cells degenerate. There is some evidence to support that live ganglion cells may still be found in retinas which have lost photoreceptor function. In a histological study where ganglion cell counts in retinas with RP were compared with those of healthy retinas, it was found that RP patients retain on the order of 50% to 75% of the normal number of cells[60]. This study indicates that ganglion cells are present, albeit in subnormal quantities, in retinas with RP. A second study indicates that the cells are alive and functioning: alert patients with end-stage RP described having sensations of light when current was injected through a bipolar electrode located near the inner retinal surface [25]. As a final note, there appear to be no specific reports describing damage to the ganglion cell layer in the so-called "standard" form of AMD [49].

The second important design issue concerns the psychophysical effects of electrical stimulation of retinal cells. What will a patient perceive when the cells of his/her retina are stimulated? Recall from section 2.1.3 that, due its restricted receptive field, each cell is concerned with a restricted part of the visual scene. We hypothesize that when a retinal cell is stimulated electrically, the brain will perceive that light was present in the part of

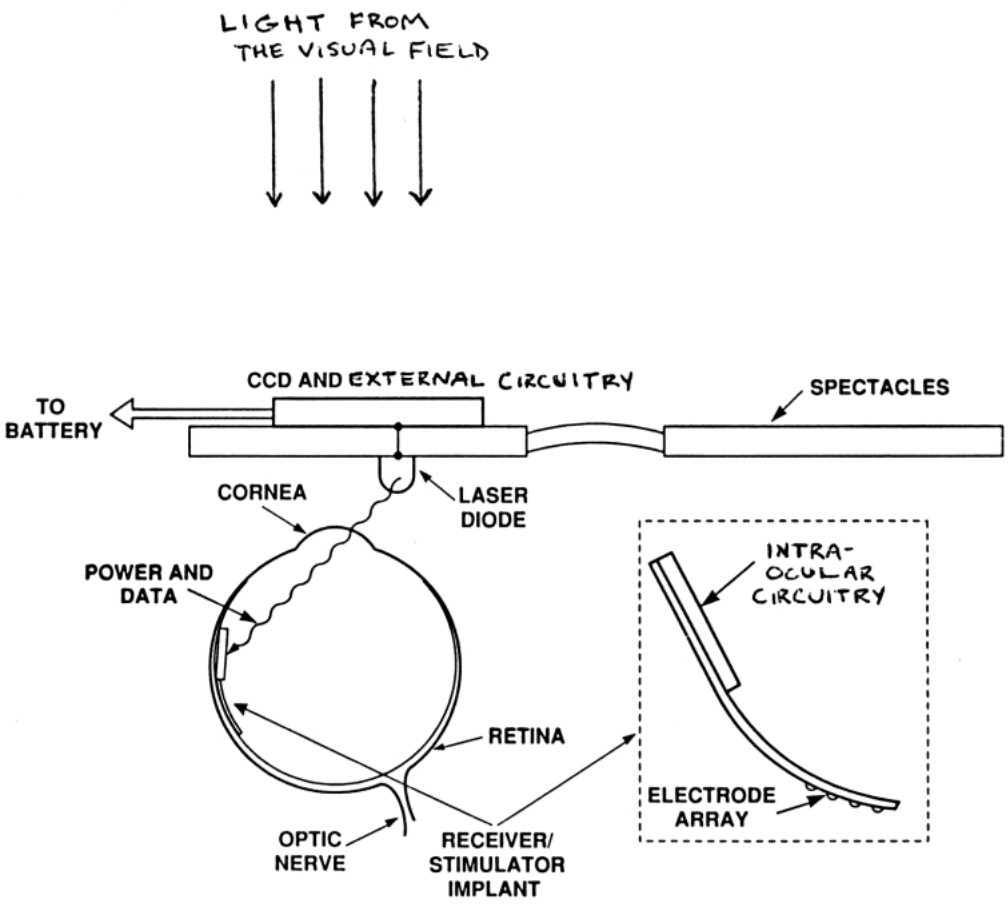

Figure 2-8: Schematic diagram of the retinal implant system. Incoming light is transduced to electricity by a charge-coupled device (CCD) located outside of the eye. Information about the visual field is transmitted into the eye by a laser diode. Inside the eye, the laser diode signals are decoded by a circuit which drives an array of stimulating electrodes.

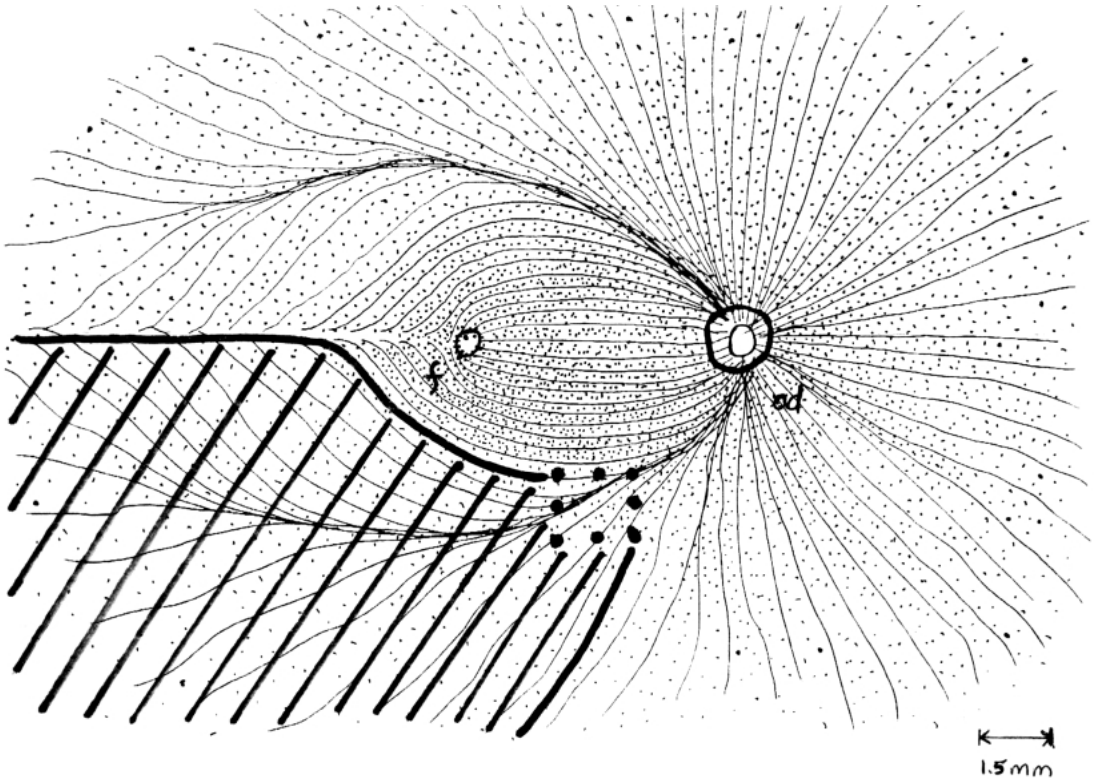

Figure 2-9: To create the impression of a square, we will try to stimulate cells along the borders of the square using a subset of the implant electrodes (large dots). If more peripheral cells are stimulated as well (shaded area), the resulting perception may considerably distorted.

the visual field with which that cell is concerned. Furthermore, if another cell some small distance away from the first cell is stimulated, there should be a corresponding shift in the location of the perceived light. Based on these hypotheses, we hope to create intelligible visual perceptions by using a regularly arrayed group of electrodes to stimulate retinal cells in a pixel-like fashion. For example, if the patient is to perceive a square, we will try to stimulate cells along the borders of an imaginary square which has been projected onto the retinal surface (see Figure 2-9). As we will see below, a substantial challenge to this approach has arisen.

2.3 Electrical stimulation of retinal cells

The development of a successful retinal prosthesis entails several lines of inquiry spanning a broad range of research interests. This thesis is concerned with the electrical to neural transduction depicted in Figure 2-7, which will be accomplished through electrical stimulation of the retinal cells. A review of the work which has been done in this area will help to both motivate and formulate the central problem of the thesis.