Review

Review of Epiretinal Protheses Technologies

Zilong Liang *

Posted Date: 24 October 2024

doi: 10.20944/preprints202410.1697.v1

Keywords: Epiretinal protheses; Electronic devices; Array of microelectronics; Signal processing algorithm; Retinal cells

Review

Review of Epiretinal Protheses Technologies

Zilong Liang

School of Electronics and Computer Science, University of Southampton, University Road, Southampton, SO17 1BJ, United Kingdom; zl42n22@soton.ac.uk

Abstract: Electronic devices called epiretinal prosthesis are used to restore vision in patients with age-related macular degeneration (AMD) and retinitis pigmentosa (RP), two degenerative retinal illnesses. It functions by stimulating the retina's surviving cells, which then excite the brain to receive visual information from the retina. Epiretinal prosthesis have the flexibility of electrode placement, which enables them to target particular regions of the retina. Furthermore, it enables a high level of spatial resolution, enhancing visual quality. For the purpose of activating retinal cells, it transforms visual input into electrical signals. In general, epiretinal prosthesis are a potential method for helping people with degenerative retinal illnesses regain their vision. Ongoing research aims to increase the effectiveness and safety of these devices.

Keywords: epiretinal protheses; electronic devices; array of microelectronics; signal processing algorithm; retinal cells

---

1. Introduction

The optics, the retina, the optic nerve, the visual cortex, or other brain regions involved in the processing of vision can all experience injury, leading to blindness [1]. Since they have been used extensively for many years, medical implants today play a significant part in replacing or enhancing the performance of each major bodily system to maintain a high quality of life [2]. The retinal Implant is one of medical implant technologies to focus on visual diseases. The goal of retinal implant technology is to help people with retinal illnesses including retinitis pigmentosa (RP) and age-related macular degeneration (AMD) regain their vision [3].

Retinal electrical stimulation can be achieved by placing epiretinal, subretinal or suprachoroidal stimulating electrode arrays [4]. Epiretinal prostheses have a greater therapeutic potential than subretinal prostheses due to the downstream nature of their placement [5]. It is important to note that each type of prosthetic has its own advantages and limitations, and the choice of prosthetic type should depend on the individual condition and needs of the patient. This report mainly introduces the technology of epiretinal protheses.

The contribution of this report is to provide an overview of the principles behind epiretinal protheses, with a focus on the role of neurons and electronics in restoring vision. Furthermore, advantages and disadvantages of epiretinal protheses are discussed in section III and IV where the suggestions are proposed for existing limitations. What is more, the report also illustrates various clinical applications of epiretinal protheses and analyse them in section V, and the progress of new technologies of epiretinal protheses is also discussed in it. Finally, the report's conclusion will include a summary of the main issues and a look at the potential future applications of epiretinal protheses.

2. Principles of Epireinal Protheses

2.1. Principle of Retinal Projection

Before introducing the principle of epiretinal protheses, the principle for retinal projection should be illustrated. Millions of photoreceptor cells in the retina transform incoming light into electrical signals, which are subsequently sent from the optic nerve to the brain. The photoreceptor cells' signals are set up in such a way that the spatial and temporal details of the visual scene are retained. A number of specialised neuronal circuits in the brain analyse these signals as they travel through the optic nerve in order to extract and integrate various visual scene elements like colour, shape, and motion. These circuits eventually meet in the visual cortex, where additional processing and integration take place to produce a perceptual experience of the visual scene.

2.2. Principle of Retinal Protheses

Photoreceptor cell death is a defining characteristic of retinal disorders[5]. Retinal implants work by stimulating the healthy nerve cells that are still there to take the place of the damaged or dead cells. Photoreceptors and retinal ganglion cells are the two different types of nerve cells in the retina. Light detection and electrical signal conversion are carried out by photoreceptors. Retinal ganglion cells then communicate these to the brain.

In order to send visual signals from a camera to the retina's surviving cells for transmission to the brain, implants will be affixed to the retina [6]. The purpose of retinal implants is to directly stimulate the remaining neural circuitry in the retina to produce visual perceptions by bypassing damaged photoreceptor cells. According to the precise design of the implant, this is often accomplished by implanting an array of microelectrodes either beneath or on top of the retina. The microelectrodes are then linked to an external camera, which records visual data and sends it wirelessly to the implant. The remaining neuronal circuitry in the retina is then stimulated by the implant's conversion of the visual data into electrical impulses, which enables the brain to experience visual images. An electrode array and an electronic enclosure make up the implanted unit. Power and signal data are transmitted from the secondary coil across the eye wall to the intraocular electrode array, which in this instance is fastened to the epiretinal surface using a retinal tack [7].Platinum disc electrodes are arranged in a square pattern in the electrode array [8]. The electrodes of a retina implant are the neural interface because they deliver electric energy to the retina [9]. Neuroprostheses that use electrode arrays to stimulate or record brain activity, such as retinal implants, are extremely dependent on the design of the electrode arrays. The goal of electrode array design is to provide an array with the ability to selectively target particular groups of neurons while causing the least amount of tissue damage possible.

The presence of viable cells in the inner retina is required for a retinal prosthesis [10]. That is because the retinal prosthetic depends on the remaining retinal cells to transmit visual signals to the brain. If the inner retinal cells are not viable or are damaged, the retinal prosthesis cannot effectively transmit visual signals to the brain.

2.3. Electrode Array Design of Epiretinal Protheses

Although this report mainly describe epiretinal protheses, subretinal protheses should be also simply illustrated for a better comparison. Epiretinal and subretinal electrode array designs are the two basic strategies used in retinal implants [9]. Subretinal electrodes are positioned between the retina's underlying retinal pigment epithelium and photoreceptor cells beneath the retina. The remaining functional photoreceptor cells can now be directly stimulated by the electrodes, stimulating them to send visual information to the remaining retinal cells and ultimately the brain.

Epiretinal electrodes are positioned on the retina's surface in the ganglion cell layer, the retina's deepest layer, to generate phosphenes [2]. To concurrently stimulate several spots on the retina, these electrodes are often set up in a grid pattern. The electrodes are attached to a tiny stimulator—a type of implanted electronic device—that is positioned close to the eye.

The microelectrode array is attached to the surface of the retina using adhesive. The advantage of this technique is that revision of device placement and explantation can be less complex, while the surgical approach and field are more familiar to surgeons performing routine vitreoretinal surgery [11]. However, gluing the microelectrode array to the retinal surface has potential disadvantages. For example, it can damage the retina and possibly cause the device to detach or shift over time.

The success of epiretinal prostheses depends on the electrode array's design. The array is made up of a grid of electrodes that are adhered directly to the retina's surface. The typical material for electrodes is platinum, which has a low resistance and is biocompatible. The visual field's resolution and coverage depend on the electrodes' size and spacing. Depending on the particular device, the array can contain anywhere between a few and several hundred electrodes. The electrodes are coupled to a flexible circuit that is mounted to the back of the eye and linked to an outside device, such as a camera or computer. By stimulating the retinal cells and generating visual sensations in the brain, the electrodes are fed electrical signals by the device. To ensure that the electrodes on the retina are activating the proper retinal cells and generating a functional visual image, they must be positioned with exactitude.

2.4. Epiretinal Stimulation

By sending current through electrodes arranged in an array implanted on the retinal surface, an epiretinal prosthesis restores artificial eyesight to patients who have lost it due to photoreceptor illnesses such as RP [12]. Epiretinal stimulation relies on the application of electrical current to the outermost layer of the retina using a microelectrode array placed on the inner retinal surface. The array typically comprises of many electrodes that can be individually or collectively operated to selectively activate various retinal areas. The electrodes' electrical current depolarizes the retinal neurons, which triggers the start of visual impulses that go up the optic nerve to the brain. However, in order to stimulate the retina at high enough stimulus frequencies [13] for useful visual perception, vision prosthesis devices need hundreds or even thousands of electrodes [14]. To solve it, parallel stimulation was proposed by a research team led by Miganoosh Abramian [15]. The fundamental objective of epiretinal stimulation is to excite the remaining retinal neurons while avoiding the injured photoreceptors to partially restore visual function.

A prerequisite for electrical stimulation was the charge balance of the stimulating pulse. Electrode corrosion and tissue injury could result from the net charge used to activate the tissue [16]. The quantity of charge during a cathode phase and energy consumption of each electrical stimulation waveform were computed as follows [17]:

$$E = \int_0^{PW} I^2(t)Z(t)dt = dt * \sum_{n=0}^{N} I_N^2 Z_n \tag{1}$$

$$Q = \int_0^{T_c} I(t)dt = dt * \sum_{n=0}^{N} I_n \tag{2}$$

where PW denotes the pulse waveform's duration. The energising current is I. Z is equivalent to 1 kΩ and represents the load impedance. The time step of discretizations is denoted by dt. In the pulse waveform's duration, there are N discretizations. The cathode phase's duration is T_c [18].

2.5. System of Epiretinal Protheses

The epiretinal prosthesis system typically consists of an intraocular and extraocular component [19] and is based on a flexible construction with stimulating electrodes fixed to the retina [20]. The extraocular component consists of a transmitter, a retina encoder, an artificial neural network (CMOS image sensor for acquisition of visual images), and several ganglion layers of the retina [20]. The neural network transforms the visual images into stimulation electrode control signals [21]. The remaining retinal cells are stimulated as the electrical signals are transmitted to them; these cells subsequently communicate vision information to the brain via the optic nerve. There are many different types of visual experiences that can be produced by varying the stimulation patterns provided by the microelectrode array, including spots of light, lines, and forms.

3. Advantages and Disadvantages of Epireinal Protheses

3.1. Advantages of Epiretinal Protheses

Epiretinal and subretinal prostheses have their advantages [22]. As a result, the choice of which type of prosthesis to use relies on the unique requirements and conditions of the patient, and the benefits and drawbacks of each type of implant should be carefully considered. This report mainly illustrate the epiretinal protheses, so various advantages for it are listed below.

3.1.1. Precise Stimulation

Epiretinal prostheses have more control over stimulation because of the electrodes' close proximity to the remaining retinal cells, which leads to more precise stimulation and better visual acuity. However, it is crucial to remember that while though precise stimulation is a considerable benefit, there may be other aspects that have an impact on the general effectiveness and safety of epiretinal prostheses and should also be taken into account. For instance, in order to guarantee the best results for patients, it may be necessary to closely monitor the possibility of tissue injury or electrical interference.

3.1.2. High Resolution

Epiretinal prostheses have higher electrode densities, which allow for more precise activation of the remaining retinal cells, resulting in improved visual acuity and spatial resolution. Epiretinal prosthesis have a higher density of electrodes than subretinal prostheses, which enhances visual perception and spatial resolution. It is important to keep in mind, though, that the precise level of resolution and visual perception attained by epiretinal prostheses depends on a number of factors, including the number and placement of electrodes, the quality of the signal processing algorithms, and individual patient response variations. Subretinal prostheses also have advantages of their own, including a reduced risk of retinal injury during implantation and the potential for enhanced preservation of residual retinal function. Therefore, choosing the appropriate prosthesis type necessitates a comprehensive assessment of both the distinctive demands of each patient and the distinctive qualities of each device.

3.1.3. Flecibility in Electrode Placement

The electrode array can be positioned and oriented specifically for each patient's unique retinal structure, which might vary substantially between patients, by placing it directly on the retina's surface. This makes it possible to apply stimulation in a more focused and customised manner, which may lead to better visual outcomes. Subretinal prostheses, on the other hand, need for the electrodes to be positioned below the retina, which restricts the flexibility of electrode placement and might lead to a less exact stimulation pattern.

3.2. Disadvantages of Epireinal Protheses

3.2.1. Stimulation Artifact

There may be stimulation artefact that impairs vision because of how close the electrodes are to the remaining retinal cells. Stimulation artefacts are electrical reactions that can happen as a result of the electrical stimulation supplied by the electrodes but are unexpected or undesirable. These artefacts can degrade the quality of visual perception and obstruct the electrical signals that are supposed to function.

Utilising cutting-edge signal processing methods to eliminate or reduce the impact of stimulation artefacts is one possible answer to this issue. This would entail creating algorithms that can reliably differentiate between intended and accidental electrical inputs, and then modify the stimulation parameters as necessary. Another strategy may be to select electrode components or layouts that reduce the likelihood of stimulation artefacts. The possibility of stimulation artefacts, for instance, may be decreased with the use of electrodes with smaller surface areas or more focused stimulation.

3.2.2. Limited Number of ELectrodes

Due to the physical area available on the retina's surface, epiretinal prosthesis can only accommodate a certain number of electrodes. The size of the sclerotomy, the surgical incision in the eye used to access the retina, and the spacing between electrodes must be sufficient to prevent electrical crosstalk between neighbouring electrodes, serve as limits on the size of the electrode array. The complexity of the hardware and software needed to regulate an increasing number of electrodes can also rise, which can increase the device's overall size and weight.

Epiretinal prostheses' small number of electrodes can make it difficult to achieve high levels of visual acuity. However, there might be ways to fix this issue. One option might be to create electrode arrays that are more compactly packed, which would enable placement of more electrodes on the retina while keeping the electrode array's size constant.

Investigating the use of multi-electrode stimulation techniques could be another option. These approaches could increase the number of distinct stimulation locations and possibly enhance the resolution of the ensuing visual impression. Furthermore, improvements in image processing and signal analysis techniques may help to extract more information from the few electrodes, thus enhancing visual experience even with fewer electrodes.

3.2.3. Power Consumption

To stimulate the remaining retinal cells, epiretinal prosthesis need a lot of power, which can reduce their battery life and raise the possibility of device failure. The need for a high voltage and current to stimulate the remaining retinal cells accounts for the epiretinal prostheses' high power consumption. Since the impedance between the electrode and the tissue can demand more power to achieve the appropriate amount of stimulation, the electrode-tissue contact also adds to power usage. The device's stimulation patterns can also have an impact on power usage because more complicated patterns demand more energy to generate. Patients may find it cumbersome and expensive to often change or recharge their batteries, and the possibility of device failure owing to power problems may reduce the device's overall efficacy.

The problem of power consumption in epiretinal prostheses has a number of potential solutions. One strategy is to create stimulation methods and electrode materials that use less energy to produce the necessary amount of retinal stimulation. Increasing the effectiveness of the device's power management system is another strategy that can result in a longer battery life and more dependable performance. Furthermore, the adoption of energy-harvesting or wireless charging technologies, such as ERIRET3 system [23], may offer a more practical and long-lasting power source for the gadget. Finally, patient engagement and education can help manage power consumption by motivating patients to keep track of their battery usage and conserve energy by adjusting their lifestyle and device settings.

3.3. Comparison with Subretinal Protheses

Table 1 shows a comparison between epiretinal protheses and subretinal protheses. The detail of the table is from the reference [24]. It is apparent that subretinal prosthesis appear to have an advantage in terms of attachment, following eye movements, and full implantation even if both epiretinal and subretinal prostheses have advantages and downsides. Epiretinal prosthesis, on the other hand, provide greater processing flexibility and maintain peripheral visual processing. The final prosthesis will depend on the patient's unique requirements and the medical staff's experience.

Table 1. Comparison between Epiretinal Protheses and Subretinal Protheses.

	Epiretinal	**Subretinal**
Population of blind patients concerned	RP, AMD	RP, AMD
Surgical complications	least serious	least setious
Attachment (mechanical stability)	difficult	easy
Visuotopic stimulation	easy	easy
Preserves peripheral visual processing	YES	YES
Follows eye movements	NO	YES
Fully implantable	NO	YES
Processing flexibility	YES	possible
Large scale integration	difficult	easy

doi:10.20944/preprints202410.1697.v1

4. Clinical Applications of Epireinal Protheses

Patients with retinal degenerative illnesses such RP and AMD have proven that epiretinal prosthesis are helpful in recovering some visual function. The retinal periphery, also known as the entire retina outside the macula, is where Leber congenital amaurosis (LCA), RP, and AMD begin. These conditions affect the entire retina outside the macula [25].

4.1. Restoring Vision in Patients with End-Stage Reinal Degeneration

Patients with advanced retinal degeneration may benefit from epiretinal prosthesis to stimulate their remaining viable retinal cells. Some visual abilities, such the capacity to recognise objects and detect light, may be restored as a result. The details of principles are illustrated in section II.

The extent of the remaining retinal cells' degeneration and their health play a role in how well epiretinal prosthesis restore visual function, therefore it's vital to keep this in mind. The device's accessibility to patients in some areas may be hampered by the fact that the implantation surgery and its use necessitate significant resources, knowledge, and training.

Despite these drawbacks, the possibility of improving patients' end-stage retinal degeneration patients' quality of life significantly by recovering some degree of visual function is noteworthy. The technology may evolve and improve further as a result of the ongoing study and development in this field, becoming more accessible and useful to patients.

4.2. Improving Visual Function in Patients with Low Vision

By activating the retinal cells that are still alive, epiretinal prosthesis have the potential to enhance visual function in people with limited vision. The prosthesis can make up for the loss of function brought on by the degeneration of the photoreceptor cells by stimulating these cells electrically. As a result, visual field, contrast sensitivity, and sharpness may all improve.

It is crucial to remember that the degree of improvement may differ from patient to patient and might not be as noticeable as in people with advanced retinal degeneration. Epiretinal prosthesis are a type of assistive technology that can help people with visual impairment, not a cure for the underlying ailment that is causing retinal degeneration. This is a crucial point to keep in mind.

Notwithstanding these drawbacks, patients with impaired vision brought on by retinal degeneration may benefit substantially from the possible enhancement in visual function offered by epiretinal prostheses, enabling them to carry out everyday tasks more easily and independently.

4.3. Enhancing Prothetic Vision in Patients with Retinal Implants

To improve prosthetic vision, epiretinal prosthesis can be combined with subretinal or suprachoroidal prostheses. This may involve enhancing the visual perception's clarity and resolution as well as broadening the visual field. Subretinal and suprachoroidal prosthesis excite the cells below the surface of the retina, whereas epiretinal prostheses activate the cells on the retina's surface. The visual field can be increased by stimulating a wider portion of the retina by combining several types of prosthesis. The sharpness and quality of the visual percept may also be improved as a result of the increased number and dispersion of electrodes. According to electrical principles, ocular prostheses work by precisely and carefully applying electrical current to the retinal cells that are still alive to produce a visual perception.

The necessity for exact coordination and communication between the various types of prosthesis is one of the major difficulties when adopting a combination of epiretinal, subretinal, and suprachoroidal prostheses. To make sure that the patient receives a coherent visual image and that the visual percept is properly integrated, each form of prosthesis must synchronise the electrical stimulation it offers.

The possibility of electrical interference between the various prosthetic types is another difficulty and can restrict the advantages of the combined method by lowering the quality of the visual perception.

The creation of sophisticated algorithms and control systems that can coordinate the electrical stimulation delivered by each type of prosthesis, as well as the use of shielding and other methods to minimise electrical interference, could be potential answers to these problems. The functionality and design of each type of prosthesis may also be improved as a result of continuous research and development, which could further increase their usability and efficacy when combined.

4.4. New Clinical Technologies of Epiretinal Protheses Are Implemented from Research to Clinic

Epiretinal prosthesis are an example of a new clinical technology that must go through a difficult implementation process before being used in actual clinical settings. Usually, it involves a number of steps, such as preclinical research, clinical trials, regulatory approval, and post-market monitoring.

To establish the safety and effectiveness of the technology, preclinical research is the process of conducting fundamental studies in animal models. Testing the device's electrical characteristics, biocompatibility of the materials utilised, and efficiency in stimulating retinal cells are all part of this process.

The clinical trial phase starts once the preclinical stage is finished. The device is tested on humans at this stage to determine its safety and effectiveness. This entails identifying individuals who have the particular ailment that the gadget is meant to treat and assessing how well the technology works to restore visual function.

If the clinical trial outcomes are encouraging, regulatory approval is requested from appointing agencies like the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). The device must be approved by presenting proof of its efficacy and safety as well as proof that it complies with all legal requirements.

Once the gadget has received regulatory approval, it can be made available for clinical usage. The device's long-term security and efficacy must still be monitored during post-market surveillance, though. This entails gathering information from users of the technology and informing regulatory authorities of any negative outcomes.

In conclusion, the process of moving epiretinal prostheses from the laboratory to the clinic is one that requires extensive testing and regulatory approval. But it's important to make sure that these medical devices are beneficial to patients' quality of life and are both safe and efficient for them.

5. Conclusion

Patients with retinal degenerative illnesses such retinitis pigmentosa and age-related macular degeneration have seen improvement in their visual function thanks to epiretinal prosthesis. The future of epiretinal prosthesis appears promising as technology develops, with possible improvements in a number of areas.

The creation of fully implantable epiretinal prosthesis may be one area for progress. At the moment, epiretinal prosthesis necessitate the placement of a receiver and processing unit outside of the eye, which might be burdensome for patients. Patients would not have to lug around extra parts and may feel more at ease and mobile if the gadgets were made totally implanted.

The incorporation of epiretinal prosthesis with other technologies, like as artificial intelligence (AI) and virtual reality (VR), could be another field for development. AI may improve epiretinal prosthetics' ability to comprehend images, enabling more accurate and focused activation of retinal cells. Patients could benefit from real-time visual feedback in VR to help them navigate their surroundings more efficiently.

Furthermore, improvements in materials science may result in the creation of epiretinal prosthesis that are more resilient and biocompatible, lowering the possibility of problems and extending the useful life of the implants.

In general, epiretinal prosthesis have a promising future thanks to advances in materials science, the possibility of fully implantable devices, and integration with AI and VR. Patients with retinal

doi:10.20944/preprints202410.1697.v1

degenerative illnesses may see considerable improvements in their quality of life as a result of these breakthroughs.

References

1. Zrenner, E. Will Retinal Implants Restore Vision? *Science* **2002**, *295*, 1022–1025. Publisher: American Association for the Advancement of Science, doi:10.1126/science.1067996.
2. Zhou, D., D. Microsensors and microbiosensors for retinal implants. *Frontiers in Bioscience* **2005**, *10*, 166. doi:10.2741/1518.
3. Lim, L.S.; Mitchell, P.; Seddon, J.M.; Holz, F.G.; Wong, T.Y. Age-related macular degeneration. *Lancet (London, England)* **2012**, *379*, 1728–1738. doi:10.1016/S0140-6736(12)60282-7.
4. Lewis, P.M.; Ackland, H.M.; Lowery, A.J.; Rosenfeld, J.V. Restoration of vision in blind individuals using bionic devices: A review with a focus on cortical visual prostheses. *Brain Research* **2015**, *1595*, 51–73. doi:10.1016/j.brainres.2014.11.020.
5. Farnum, A.; Pelled, G. New Vision for Visual Prostheses. *Frontiers in Neuroscience* **2020**, *14*.
6. Chader, G.J. CHAPTER 20 - Degenerative Retinopathies. In *Ocular Therapeutics*; Yorio, T.; Clark, A.F.; Wax, M.B., Eds.; Academic Press: London, 2008; pp. 443–472. doi:10.1016/B978-012370585-3.50022-4.
7. Humayun, M.S.; Rowley, A.P.; Whalen, J.J.; Weiland, J.D.; Tanguay, A.R. E - The Development of a Retinal Prosthesis: A Significant Biomaterials Challenge. In *Biomaterials Science (Third Edition)*; Ratner, B.D.; Hoffman, A.S.; Schoen, F.J.; Lemons, J.E., Eds.; Academic Press, 2013; pp. 946–957. doi:10.1016/B978-0-08-087780-8.00081-4.
8. Margalit, E.; Maia, M.; Weiland, J.D.; Greenberg, R.J.; Fujii, G.Y.; Torres, G.; Piyathaisere, D.V.; O'Hearn, T.M.; Liu, W.; Lazzi, G.; Dagnelie, G.; Scribner, D.A.; de Juan, E.; Humayun, M.S. Retinal Prosthesis for the Blind. *Survey of Ophthalmology* **2002**, *47*, 335–356. doi:10.1016/S0039-6257(02)00311-9.
9. Hornig, R.; Velikay-Parel, M. 15 - Retina implants. In *Implantable Sensor Systems for Medical Applications*; Inmann, A.; Hodgins, D., Eds.; Woodhead Publishing Series in Biomaterials, Woodhead Publishing, 2013; pp. 469–496. doi:10.1533/9780857096289.3.469.
10. Weiland, J.D.; Liu, W.; Humayun, M.S. Retinal Prosthesis. *Annual Review of Biomedical Engineering* **2005**, *7*, 361–401. _eprint: https://doi.org/10.1146/annurev.bioeng.7.060804.100435, doi:10.1146/annurev.bioeng.7.060804.100435.
11. Bloch, E.; Luo, Y.; da Cruz, L. Advances in retinal prosthesis systems. *Therapeutic Advances in Ophthalmology* **2019**, *11*, 2515841418817501. doi:10.1177/2515841418817501.
12. Fan, V.H.; Grosberg, L.E.; Madugula, S.S.; Hottowy, P.; Dabrowski, W.; Sher, A.; Litke, A.M.; Chichilnisky, E. Epiretinal stimulation with local returns enhances selectivity at cellular resolution. *Journal of neural engineering* **2019**, *16*, 025001. doi:10.1088/1741-2552/aaeef1.
13. Humayun, M.S.; de Juan Jr., E.; Weiland, J.D.; Dagnelie, G.; Katona, S.; Greenberg, R.; Suzuki, S. Pattern electrical stimulation of the human retina. *Vision Research* **1999**, *39*, 2569–2576. doi:10.1016/S0042-6989(99)00052-8.
14. Cha, K.; Horch, K.; Normann, R.A. Simulation of a phosphene-based visual field: Visual acuity in a pixelized vision system. *Annals of Biomedical Engineering* **1992**, *20*, 439–449. doi:10.1007/BF02368135.
15. Abramian, M.; Lovell, N.H.; Morley, J.W.; Suaning, G.J.; Dokos, S. Activation of retinal ganglion cells following epiretinal electrical stimulation with hexagonally arranged bipolar electrodes. *Journal of Neural Engineering* **2011**, *8*, 035004. doi:10.1088/1741-2560/8/3/035004.
16. Chun, H.; Yang, Y.; Lehmann, T. Safety ensuring retinal prosthesis with precise charge balance and low power consumption. *IEEE transactions on biomedical circuits and systems* **2014**, *8*, 108–118. doi:10.1109/TBCAS.2013.2257171.
17. Foutz, T.; McIntyre, C. Evaluation of novel stimulus waveforms for deep brain stimulation. *Journal of neural engineering* **2010**, *7*, 066008. doi:10.1088/1741-2560/7/6/066008.
18. Wu, J.; Jin, M.; Qiao, Q. Modeling electrical stimulation of retinal ganglion cell with optimizing additive noises for reducing threshold and energy consumption. *BioMedical Engineering OnLine* **2017**, *16*, 38. doi:10.1186/s12938-017-0333-z.
19. Zou, Y.; Shi, G.; Jin, Y.; Zheng, Y. Extraocular image processing for retinal prosthesis based on DSP. 2009 4th IEEE International Conference on Nano/Micro Engineered and Molecular Systems. IEEE, 2009, pp. 563–566.
20. Mokwa, W. MEMS technologies for epiretinal stimulation of the retina. *Journal of Micromechanics and Microengineering* **2004**, *14*, S12. doi:10.1088/0960-1317/14/9/002.

21. Schwarz, M.; Ewe, L.; Hauschild, R.; Hosticka, B.J.; Huppertz, J.; Kolnsberg, S.; Mokwa, W.; Trieu, H.K. Single chip CMOS imagers and flexible microelectronic stimulators for a retina implant system. *Sensors and Actuators A: Physical* **2000**, *83*, 40–46. doi:10.1016/S0924-4247(00)00290-9.
22. Kien, T.T.; Maul, T.; Bargiela, A. A REVIEW OF RETINAL PROSTHESIS APPROACHES. *International Journal of Modern Physics: Conference Series* **2012**, *09*, 209–231. doi:10.1142/S2010194512005272.
23. Klauke, S.; Goertz, M.; Rein, S.; Hoehl, D.; Thomas, U.; Eckhorn, R.; Bremmer, F.; Wachtler, T. Stimulation with a Wireless Intraocular Epiretinal Implant Elicits Visual Percepts in Blind Humans. *Investigative Ophthalmology & Visual Science* **2011**, *52*, 449–455. doi:10.1167/iovs.09-4410.
24. Perez Fornos, A. Minimum requirements for a retinal prosthesis to restore useful vision. PhD thesis, University of Geneva, 2006.
25. Roska, B.; Sahel, J.A. Restoring vision. *Nature* **2018**, *557*, 359–367. Number: 7705 Publisher: Nature Publishing Group, doi:10.1038/s41586-018-0076-4.