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14. ABSTRACT Ocular trauma or laser injury can result in loss of sight due to damage of photoreceptors. Similarly, retinal degeneration leads to a gradual loss of photoreceptors and associated visual impairment. In these conditions, the inner retinal neurons are preserved to a large extent, and visual perception can be restored by electrical stimulation of the remaining retinal network. We developed photovoltaic replacement of photoreceptors, which directly converts light into pulsed electric current in each pixel, stimulating the nearby inner retinal neurons. Clinical trial with such implants having 100um pixels confirmed feasibility of such approach and demonstrated that spatial resolution closely matches the pixel pitch (20/420). For a wide-spread acceptance of this technology, prosthetic visual acuity should exceed 20/100, which requires pixels smaller than 25um. We are developing and testing a novel 3-dimensional electro-neural interface to significantly decrease the stimulation threshold and reduce the pixel size down to 10-20um.					
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Introduction

Ocular trauma can result in traumatic retinopathy associated with the loss of sight due to damage of photoreceptors. Similarly, retinal degenerative diseases result in a gradual loss of photoreceptors and associated visual impairment. In these conditions, the inner retinal neurons are preserved to a large extent, and therefore visual perception can be restored by electrical stimulation of the remaining retinal network.

Photovoltaic subretinal prosthesis directly converts light into pulsed electric current in each pixel, stimulating the nearby neurons. Visual information is projected onto the retina from video glasses using pulsed near-infrared light. Wireless design of these arrays allows scalability to thousands of pixels, and combined with the ease of implantation, offers a promising approach to restoration of sight in patients blinded by retinal trauma or degeneration. Clinical trial with such implants (PRIMA) having 100 μm pixels started in 2018, and the results already confirmed that patients perceive visual patterns, including letters and numbers, with spatial resolution very close to the theoretical limit for this pixel size (20/400).

To further advance this remarkably successful technology toward highly functional restoration of sight pixel size should be decreased. For reading and face recognition, prosthetic visual acuity should, at least, exceed the threshold of legal blindness (20/200), which requires pixels smaller than 50 μm in size. For a wide-spread acceptance in patients with the loss of central vision, acuity of prosthetic vision should exceed 20/100, which requires pixels smaller than 25 μm . We are developing novel 3-dimensional electrodes to significantly decrease the stimulation threshold and enable reducing the pixel size down to 10-20 μm , which geometrically correspond to visual acuity of 20/40 - 20/80, respectively. If successful, this technology can be rapidly transferred to our industrial partner Pixium Vision for clinical testing.

Keywords

Retinal prosthesis, photovoltaic, retinal degeneration, traumatic retinopathy, restoration of sight.

Major goals of the project

Specific aims, subtasks and milestones	Timeline, quarters	% complete
Specific Aim 1 Develop mock-up honeycomb arrays with pixels of 20, 30 and 40µm in width to study retinal migration into the implants in-vivo.		
Subtask 1 Submit documents to ACURO.	Q4, 2019	100
Milestone: Obtain ACURO approval.		
Subtask 2 a) Develop inactive 3-D arrays with honeycomb-shaped walls surrounding each pixel. b) Study retinal migration into such cavities, including the optimal height of the walls for targeting neurons in the inner nuclear layer. We expect to use 5-10 animals per group, so with 4 implant heights about 20-40 animals will be required in this set of experiments.	Q4 2019- Q3 2021	100 30
Milestone: Established optimal height of the honeycomb walls and minimum width of the pixels.		
Subtask 3 Using immunohistochemistry, analyze distribution of the neural and glial cells in the honeycombs of various dimensions. We expect to use 5-10 animals per group, so with 4 implant heights about 20-40 animals will be required in this set of experiments.	Q2 2020 – Q2 2021	20
Milestone: Established optimal geometry of the honeycomb arrays for single-cell resolution. We expect to use about 20-40 animals (5-10 animals per group, two embedding methods, two heights of the honeycomb wells).		
Specific Aim 2 Model, design and manufacture photovoltaic arrays with optimal geometry of the honeycombs and electrodes.		
Subtask 1 Add polymer honeycomb walls to our current flat photovoltaic arrays with 40µm pixels, using multiphoton polymerization (Nanoscribe).	Q3 2019 – Q3 2020	50
Subtask 2 a) Map electric fields in front of these photovoltaic arrays to validate the computational model of electric field in COMSOL. b) Optimize the computational model of the network-mediated retinal stimulation by comparing to in-vivo stimulation thresholds measured with flat implants. c) Using computational modeling of electric field and retinal stimulation, optimize the sizes of the active and return electrodes for lowest stimulation threshold.	Q2 2020 – Q2 2021 Q2 2020 – Q2 2021 Q2 2020 – Q2 2021	40 30 30
Milestone: Design of the honeycomb array is optimized, and electrical requirements for stimulation specified.		
Subtask 3		

c) Manufacture photovoltaic arrays with optimal electrodes configuration.	Q3 2020 – Q3 2021	
Milestone: Active photovoltaic arrays are manufactured.		
Specific Aim 3 Test stimulation thresholds, spatial resolution and dynamic range of prosthetic vision using VEP measurements in-vivo.		
Subtask 1 Implant photovoltaic arrays with honeycombs of various pixel sizes as well as transcranial screws for VEP recordings. Measure full-field stimulation thresholds and dynamic range of VEP response as a function of light intensity and pulse duration.	Q2 2021 – Q4 2021	
Subtask 2 Using alternating gratings, measure spatial resolution of the retinal response to honeycomb implants with various pixel sizes. With 4 pixel sizes (40, 30, 20 and $\sim 10\mu\text{m}$), we expect about 40 animals being used in these measurements. The same animals will be used for the stimulation thresholds, dynamic range and acuity measurements.	Q2 2021 – Q4 2021	
Milestone: Simulation thresholds and spatial resolution of prosthetic vision in rats based on honeycomb arrays is measured.		

Accomplishments

Retinal degenerative diseases lead to blindness due to loss of the “image capturing” photoreceptors, while neurons in the “image-processing” inner retinal cells survive to a large extent [1]. Information can be reintroduced into the visual system by photovoltaic subretinal implants which convert incident light into electric current and stimulate neurons in the inner nuclear layer (INL). Pixels on the implant functionally replace the natural photoreceptors, with many critical signal-processing features of the retina preserved [2]. To provide sufficient light intensity for photovoltaic stimulation while avoiding visual perception by the remaining photoreceptors, images captured by a camera are projected onto the retina from augmented-reality glasses using pulsed near-infrared (NIR, 880nm) light [3], and the thickness of the implant - $30\mu\text{m}$,

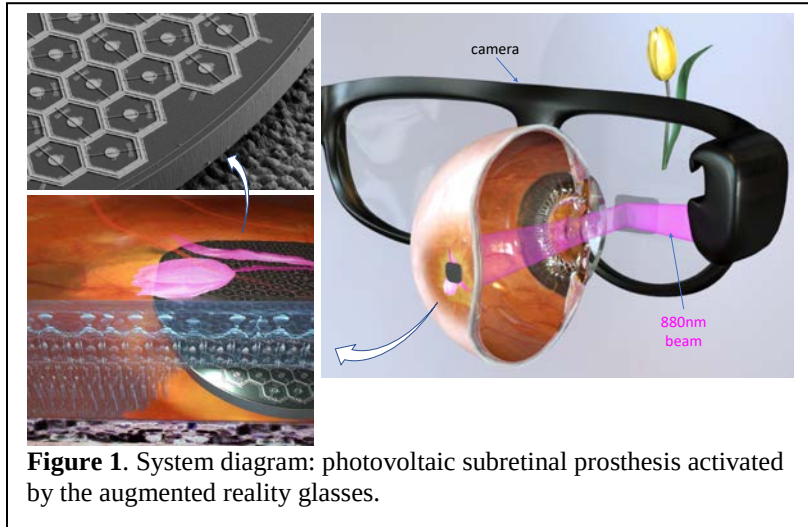


Figure 1. System diagram: photovoltaic subretinal prosthesis activated by the augmented reality glasses.

is chosen to balance the absorption of NIR light and the integrity of the retinal anatomy (Figure 1). This design avoids the use of bulky electronics and wiring, thereby greatly reducing the surgical complexity and enabling scaling the number of photovoltaic pixels to thousands.

Prosthetic visual acuity is fundamentally limited by the pixel size. With photovoltaic subretinal implants containing pixels of $100\mu\text{m}$ in size, patients blinded by geographic atrophy

demonstrated prosthetic acuity up to 20/460, which is only 10% lower than the sampling limit of the pixel size (20/420) [4]. In animal studies, implants with hexagonal pixels of 55 μm in pitch were implanted under the degenerate retina in rats, and the animals showed cortical response to alternating grating of 48 μm -wide stripes [5], matching the distance between adjacent lines in the hexagonal grid. Such resolution, if translated to human retina, exceeds the standard of legal blindness - 20/200. For a broad acceptance of this technology in clinical practice, we aim at visual acuity exceeding 20/100, which requires pixels smaller than 25 μm .

To ensure sufficient light-to-current conversion with limited photosensitive area of smaller pixels, we fabricated photodiodes with vertical p-n junctions. The responsivity of the photodiodes was 0.51A/W with 880nm NIR light for all pixel sizes: 55, 40, 30 and 20 μm , corresponding to an internal quantum efficiency of 85%. With proper design of anti-reflection coating on the front surface and reflective titanium coating on the back of the implants, we achieved an external quantum efficiency of over 70%, independent of pixel size (Figure 2).

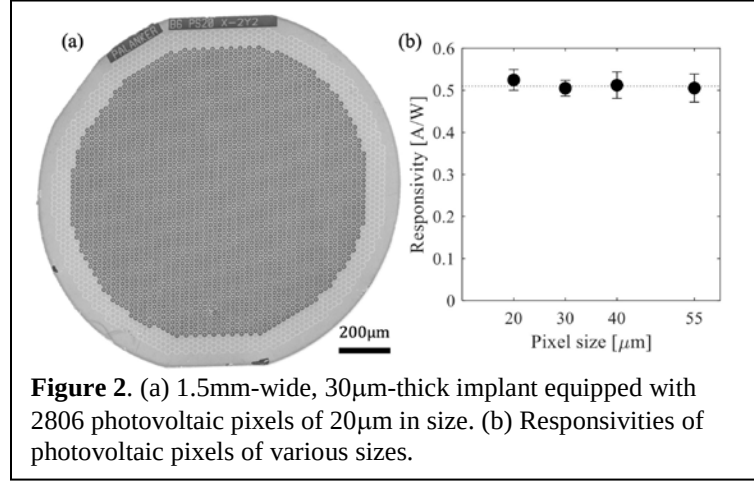


Figure 2. (a) 1.5mm-wide, 30 μm -thick implant equipped with 2806 photovoltaic pixels of 20 μm in size. (b) Responsivities of photovoltaic pixels of various sizes.

Even bigger challenge with small pixels is the efficacy of neural stimulation with spatial selectivity, which requires (1) vertical penetration of the electric field elicited by the implant into the INL, and (2) minimal lateral crosstalk between neighboring pixels. With planar configuration of electrodes, these two goals cannot be achieved simultaneously for pixel sizes smaller than the desired penetration depth of electric field, because lateral confinement also limits the vertical span in any conservative and solenoidal vector field. As a result of shallow penetration of electric field, with planar pixels smaller than 40 μm , the stimulation threshold exceeds the capacity of even the sputtered iridium oxide film, which is the state-of-the-art electrode material for neural stimulation [6].

To address this problem, we developed a novel honeycomb configuration of the electrode array with vertical walls surrounding each pixel, and the cavities between walls are filled with neurons in the INL due to retinal migration [6]. Such geometry decouples the penetration depth of electric field from the pixel size by vertically aligning the electric current along the axons of bipolar cells, thereby maximizing the efficiency of electrical stimulation, and blocking the crosstalk by the insulating walls. Simulation

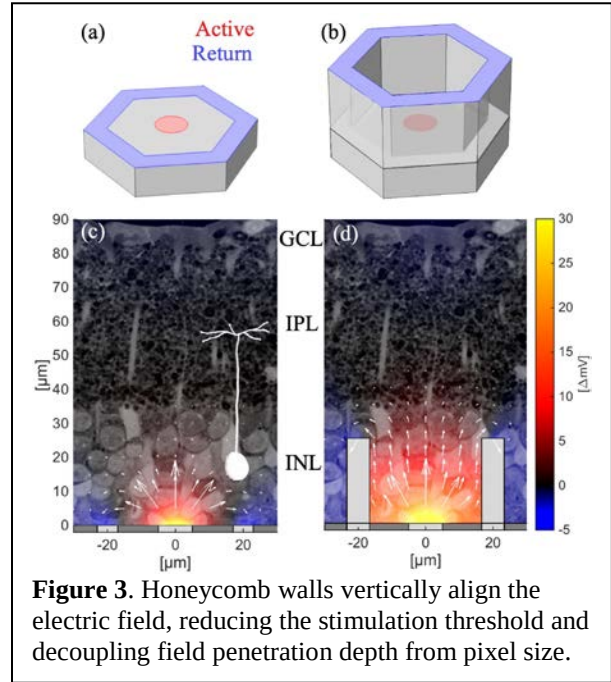


Figure 3. Honeycomb walls vertically align the electric field, reducing the stimulation threshold and decoupling field penetration depth from pixel size.

demonstrated that honeycomb structures drastically reduce the stimulation threshold compared with planar configurations (up to 33 folds for 20 μ m pixels), while the spatial contrast was fully retained (Figure 3) [6].

We built inactive devices with honeycomb walls to confirm the retinal migration into the 3D structures, the integrity of the retinal anatomy, and the minimal immune response to the implants. Using two-photon polymerization, we also fabricated polymer honeycomb walls on top of active implants with 40 and 20 μ m pixels (Figure 4). We are currently evaluating the performance of such implants in animals, as well as developing the process of fabricating the return electrodes on top of the walls, in order to even better confine the electric field laterally than with the polymer structures. With 20 μ m pixels, visual acuity may reach 20/80, which would provide very meaningful restoration of sight not only for patients completely blinded by Retinitis Pigmentosa, but also for patients who lost central vision due to age-related macular degeneration.

To better understand the dynamics of the charge injection from electrodes to electrolyte and redistribution of current over time, we studied these phenomena experimentally and developed computational models [7,8], which will be used in optimization of the retinal implant.

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8. Harmonic-Balance Circuit Analysis for Electro-Neural Interfaces. Z.C. Chen, B. Wang, D. Palanker. *J. Neural Eng.* 17: 035001 (2020).

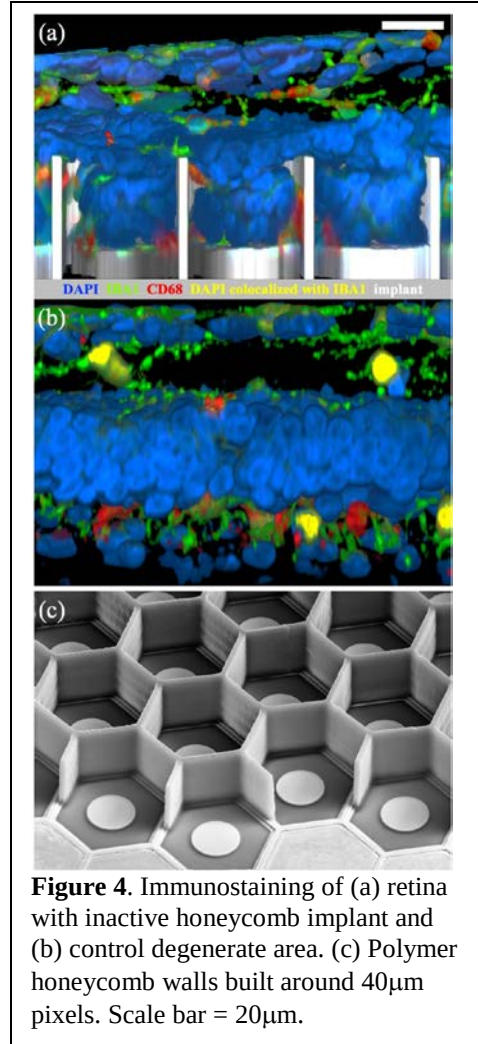


Figure 4. Immunostaining of (a) retina with inactive honeycomb implant and (b) control degenerate area. (c) Polymer honeycomb walls built around 40 μ m pixels. Scale bar = 20 μ m.

Impact

Shear forces inflicted by explosion or head impact may result in traumatic retinopathy due to damage of the photoreceptors, leading to irreversible loss of sight. Similarly, retinal degeneration leads to gradual loss of photoreceptors and associated visual impairment. In these conditions, the inner retinal neurons that process the visual signals and relay them to the brain are relatively well preserved. Photovoltaic replacement of the lost photoreceptors offers a very promising approach to restoration of sight due to its high resolution, wireless nature of the implants, small size, modularity and ease of implantation. We continue advancing this technology according to the SOW. If successful, we expect the current implants to provide visual acuity exceeding 20/100.

Products

Dissemination of the Results

Peer-reviewed publications

1. On Optimal Coupling of the ‘Electronic Photoreceptors’ into the Degenerate Retina. P. Werginz, B. Wang, Z.C. Chen, and D. Palanker. J. Neural Eng. 17: 045008 (2020).
2. Harmonic-Balance Circuit Analysis for Electro-Neural Interfaces. Z.C. Chen, B. Wang, D. Palanker. J. Neural Eng. 17: 035001 (2020).
3. Photovoltaic Restoration of Central Vision in Atrophic Age-Related Macular Degeneration D. Palanker, Y. Le Mer, S. Mohand-Said, M.M.K. Muqit, J.A. Sahel. Ophthalmology, 127:1097-1104 (2020).
4. Current Distribution on Capacitive Electrode-Electrolyte Interfaces. Z. Chen, L. Ryzhik, and D. Palanker. Phys. Rev. Applied 13, 014004 (2020).

Conference presentations

1. Photovoltaic Replacement of Photoreceptors in Geographic Atrophy. Daniel Palanker, Symposium on Retinal Prosthetics, May 2020.
2. Photovoltaic Restoration of Sight in Atrophic Macular Degeneration. Baylor College of Medicine, Houston, TX, August 2020.

Participants & other Collaborating Organizations

Organization Name: Stanford University

Location of Organization: Hansen Experimental Physics Laboratory,
452 Lomita Mall, Astrophysics Building,
Room S05 & S04, Stanford, CA 94305-4085

1. Prof. Daniel Palanker

Name:	Daniel Palanker
Project Role:	PI
Nearest person month worked:	1.8 CM
Contribution to Project:	Directs the project, evaluates the results, writes the reports and publications.

2. Ms. Valentina Zuckerman

Name:	Valentina Zuckerman
Project Role:	Sr. Research Associate
Nearest person month worked:	2.8 CM
Contribution to Project:	Works on animal protocols and handling, tissue processing and immunohistochemistry.

3. Mr. Tong Ling

Name:	Tong Ling
Project Role:	Postdoc
Nearest person month worked:	8.0 CM
Contribution to Project:	Works on optical and electronic system for in-vivo evaluation of the photovoltaic arrays.

4. Ms. Roopa Dalal

Name:	Roopa Dalal
Project Role:	Research Associate (Histologist)
Nearest person month worked:	1.0 CM
Contribution to Project:	Works on tissue fixation, embedding, histological sectioning, staining and microphotography.

5. Mr. Zhijie Chen

Name:	Zhijie (Charles) Chen
Project Role:	Graduate Student
Nearest person month worked:	6.0 CM
Contribution to Project:	Works on design and fabrication of the photovoltaic arrays.

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To ensure full consideration, applications must be received by June 30, 2019. However, applications will be reviewed as they are received. Early submission is highly encouraged.



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On optimal coupling of the ‘electronic photoreceptors’ into the degenerate retina

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Keywords: bipolar cell, ribbon synapse, neural stimulation, retinal prosthesis, electro-neural interface

Supplementary material for this article is available [online](#)

Abstract

Objective. To restore sight in atrophic age-related macular degeneration, the lost photoreceptors can be replaced with electronic implants, which replicate their two major functions: (1) converting light into an electric signal, and (2) transferring visual information to the secondary neurons in the retinal neural network—the bipolar cells (BC). We study the selectivity of BC activation by subretinal implants and dynamics of their response to pulsatile waveforms in order to optimize the electrical stimulation scheme such that retinal signal processing with ‘electronic photoreceptors’ remains as close to natural as possible. **Approach.** A multicompartamental model of a BC was implemented to simulate responses of the voltage-gated calcium channels and subsequent synaptic vesicle release under continuous and pulsatile stimuli. We compared the predicted response under various frequencies, pulse durations, and alternating gratings to the corresponding experimental measurements. In addition, electric field was computed for various electrode configurations in a 3-d finite element model to assess the stimulation selectivity via spatial confinement of the field. **Main results.** The modeled BC-mediated retinal responses were, in general, in good agreement with previously published experimental results. Kinetics of the calcium pumps and of the neurotransmitter release in ribbon synapses, which underpin the BC’s temporal filtering and rectifying functions, allow mimicking the natural BC response with high frequency pulsatile stimulation, thereby preserving features of the retinal signal processing, such as flicker fusion, adaptation to static stimuli and non-linear summation of subunits in receptive field. Selectivity of the BC stimulation while avoiding direct activation of the downstream neurons (amacrine and ganglion cells—RGCs) is improved with local return electrodes. **Significance.** If the retinal neural network is preserved to a large extent in age-related macular degeneration, selective stimulation of BCs with proper spatial and temporal modulation of the extracellular electric field may retain many features of the natural retinal signal processing and hence allow highly functional restoration of sight.

1. Introduction

Phototransduction in photoreceptors (PRs) converts light into changes of the cell’s membrane potential, which then alters the release rate of the neurotransmitter glutamate into synapses of the secondary neurons—the bipolar cells (BCs). This affects the BC’s membrane potential, which defines the

release rate of glutamate into synapses of the tertiary retinal neurons—the ganglion cells (RGCs). This input, in turn, modifies the RGC’s membrane potential, which governs its spiking rate—the visual signals subsequently propagate to the brain via the optic nerve. Synapses between PRs and BCs are regulated by inhibitory horizontal cells (HCs), while synapses between BCs and RGCs—by amacrine cells

(ACs). Signal processing by the retinal neural network defines the way images on the retina are encoded in spiking patterns of the two dozen types of RGCs (Baden *et al* 2016).

In atrophic (dry) form of age-related macular degeneration (AMD), PRs gradually disappear in the central macula, but the inner retinal cells survive to a large extent (Kim *et al* 2002), albeit with some alterations (Jones *et al* 2016). To restore sight in the area of geographic atrophy, we replace the lost photoreceptors with photovoltaic pixels, which convert light into electric current to stimulate the secondary neurons in the retina (Lorach *et al* 2015a, Palanker *et al* 2020). These ‘electronic photoreceptors’ replace the two main functions of the natural photoreceptors: (1) the light-to-current conversion, corresponding to the function of the photoreceptor outer segment, and (2) conveying the visual information to secondary neurons by the generated extracellular electric field—an electronic substitute of a synapse. In this paper, we discuss the possibilities and limitations of proper coupling of these ‘electronic photoreceptors’ into the retinal neural network in order to preserve the remaining signal processing to the maximum extent possible.

Selective stimulation of bipolar cells without direct activation of the downstream neurons, the amacrine and ganglion cells, can be achieved by utilizing the differences in cellular shape and location as well as ion channels expressed in various types of retinal neurons. For this purpose, we model the electric field with various configurations of subretinal electrodes as well as the response of BCs and RGCs to pulsed electrical stimulation and compare it to experimental measurements.

Since conductivity in metals and semiconductors is electronic, while in liquids it is ionic, transfer of the electric current from an electrode to an electrolyte can be mediated by either the double layer capacitance or by electrochemical reactions. To avoid irreversible electrochemistry, which may lead to electrode erosion and/or tissue damage, the applied current should be pulsed and charge balanced. On the other hand, to provide steady visual percepts under pulsed illumination, the pulse repetition rate should exceed the frequency of flicker fusion. We discuss the cellular machinery responsible for the signal processing in BCs—the voltage-sensitive ion channels, calcium pumps and ribbon synapses—and demonstrate that many of its functions are largely preserved under pulsed electrical stimulation. In particular, we show how the temporal filtering and non-linearity of the ribbon synapses between BCs and RGCs retain the functions of flicker fusion and adaptation under electrical stimulation.

We review the consequences of selective activation of BCs and experimental evidence of preservation of multiple features of the natural signal processing with a subretinal prosthesis, including antagonistic

center-surround organization of receptive fields and non-linear summation of its subunits, as well as limitations on selectivity in the activation of the ON and OFF pathways in the retina.

This paper consists of three parts: (1) First, we describe the computational models for electrical activation of BCs and RGCs, and assess the selectivity of BC stimulation by a point source of electric current; (2) Then we show that better spatial confinement of the electric field can further increase selectivity of the BC activation; (3) Finally, we compare the temporal response of BCs under pulsatile stimulation to that with a continuous stimulus and discuss the cellular mechanisms and consequences of flicker fusion.

2. Methods

2.1. Modeling the extracellular potential

To compare the computed stimulation thresholds with experimental measurements performed using a micro-pipette electrode for stimulation (Boinagrov *et al* 2014), we modeled the extracellular potential for a point source placed in the outer plexiform layer (OPL), as shown in figure 1(A). The extracellular potential distribution (V_e) generated by an ideal point source electrode in homogenous medium was modeled as $V_e = \frac{I_{stim} * \rho_{ext}}{4 * \pi * r}$, with I_{stim} being the applied current, $\rho_{ext} = 1000 \Omega \text{ cm}$ being the resistivity of the surrounding medium (the retina (Werginz and Rattay 2016)), and r being the Euclidean distance from the electrode to each cellular compartment (see below).

To simulate responses of BCs and RGCs to extracellular electrical stimulation, we developed multicompartmental models of BCs and RGCs with realistic anatomy. Current flow along the intracellular space as well as across the cell membrane is simulated by a network of compartments with given electrical properties (Rall 1964, Rattay 1999). Figure 1(B) shows the electric circuit of a multicompartmental model, the change of membrane potential (dV_n) at each time step was described by

$$\frac{dV_n}{dt} = \left[-I_{ion,n} + \frac{V_{n-1} - V_n}{\frac{R_{n-1}}{2} + \frac{R_n}{2}} + \frac{V_{n+1} - V_n}{\frac{R_{n+1}}{2} + \frac{R_n}{2}} + \dots \right. \\ \left. + \frac{V_{e,n-1} - V_{e,n}}{\frac{R_{n-1}}{2} + \frac{R_n}{2}} + \frac{V_{e,n+1} - V_{e,n}}{\frac{R_{n+1}}{2} + \frac{R_n}{2}} + \dots \right] * \frac{1}{C_n}$$

with I_{ion} being the ionic current across the membrane which was computed by the dynamics of Fohlmeister (Fohlmeister *et al* 2010) for RGCs and a simplified membrane model for BCs (see below). Currents between neighboring compartments were dependent on each compartment’s intracellular resistance (R) and the rate of change of membrane potential was dependent on the membrane capacitance (C). The influence of extracellular electrical stimulation (V_e) was coupled into the model via the activating function (Rattay 1999). The dots in the equation indicate

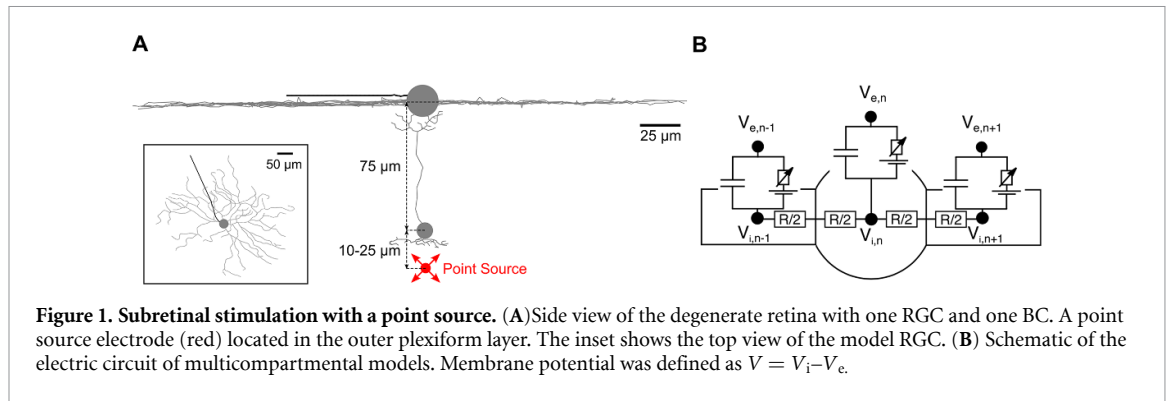


Table 1. Ion channel densities on the membrane of the model RGC. Values are based on Fohlmeister *et al* (Fohlmeister *et al* 2010) with minor modifications. All values are given in mS/cm^2 .

	Dendrites	Soma	Soma-AIS	AIS	Axon
g_{Na}	50	70	175	350	100
g_{K}	35	35	90	175	50
g_{Ca}	1	0.75	0.75	0.75	0.75
$g_{\text{K,Ca}}$	0.11	0.05	0.05	0.05	0.25
g_{L}	0.5	0.5	0.5	0.5	0.5

the possibility of more than two neighboring compartments.

2.2. Ganglion cell model

RGC membrane dynamics were modeled as previously presented by Fohlmeister *et al* (Fohlmeister *et al* 2010) as this model was shown to capture the main characteristics of the RGC responses observed in intracellular stimulation experiments. The ion channel densities are listed in table 1 for the five different sections along the neuron: dendrites, soma, axon hillock (soma-AIS), axon initial segment (AIS), and the axon. Intracellular resistivity was set to $143.2 \Omega \text{ cm}$ and specific membrane capacitance to $1 \mu\text{F cm}^{-2}$. The cell morphology of a traced mouse ON- α sustained RGC (Raghuram *et al* 2019), shown in figure 1(A), consisted of 2182 compartments, with the compartment length ranging from 3 to 5 μm .

2.3. Bipolar cell model

The simplified bipolar cell model has been adjusted from a previous study (Werginz and Rattay 2016). In brief, the 2-d morphology of a rat ON bipolar cell has been extracted from the literature (Euler and Wässle 1995, Encke *et al* 2013) and has been converted into a realistic 3-d multicompartmental model (figure 1(A)). We used an anatomical reconstruction of a rat BC (in comparison to the mouse RGC) as we are not aware of detailed reconstructions of mouse BCs. However, results presented in this study are not dependent on detailed morphological features which were also shown to be similar between mouse and rat retina (Ghosh *et al* 2004).

A linear leak current was assumed to be distributed over the whole neural membrane, and a calcium

Table 2. Ion channel densities on the membrane of the model BC. All values are given in mS/cm^2 .

	Dendrites	Soma	Axon	Terminals
g_{Ca}	0	0	0	0.5
g_{L}	0.5	0.5	0.5	0.5

L-type channel was localized to synaptic terminals only. Ionic current densities at the n^{th} compartment were described by the following set of equations:

$$i_{\text{ion},n} = i_{\text{CaL},n} + i_{\text{L},n}, \text{ with}$$

$$i_{\text{CaL},n} = g_{\text{Ca},n} * m_n^2 * h_n * (V_n - E_{\text{Ca},n})$$

$$i_{\text{L},n} = g_{\text{L},n} * (V_n - E_{\text{L}})$$

Ion channel densities of the calcium ($g_{\text{Ca},n}$) and leak channel ($g_{\text{L},n}$) for the four different sections (dendrites, soma, axon, axon terminals) are listed in table 2. The leak reversal potential (E_{L}) as well as the resting membrane potential were assumed to be -60 mV (Walston *et al* 2018), while the reversal potential for calcium ($E_{\text{Ca},n}$) was computed as a Nernst potential based on the intracellular calcium concentration $[\text{Ca}]_i$:

$$E_{\text{Ca},n} = 10^3 * \frac{R * T}{2 * F} * \ln \frac{[\text{Ca}]_e}{[\text{Ca}]_i,n}$$

with the gas constant $R = 8.31 \text{ J/K}^{\circ}\text{mol}$, temperature $T = 296.15 \text{ K}$, Faraday's constant $F = 9.6485 * 10^4 \text{ C mol}^{-1}$, the intracellular calcium concentration $[\text{Ca}]_i,n$ (see below for calculation) and the extracellular calcium concentration $[\text{Ca}]_e = 1800 \mu\text{M}$.

Intracellular resistivity was set to $130 \Omega \text{ cm}$, specific membrane capacitance to $1 \mu\text{F cm}^{-2}$. The L-type calcium channel model presented previously (Werginz *et al* 2015) was adjusted to account for slightly slower activation kinetics. Gating variables m and h were defined by the following equations:

$$\frac{dm}{dt} = \alpha_m * (1 - m) - \beta_m * m, \text{ with}$$

$$\alpha_m = \frac{0.21 * (V + 5)}{1 - \exp(-\frac{V + 5}{10.5})} \text{ and } \beta_m = 0.02 * \exp(-\frac{12 - V}{12})$$

$$\frac{dh}{dt} = \frac{h_{\infty} - h}{\tau_h}, \text{ with } h_{\infty} = \frac{1}{1 + \exp\left(\frac{V + 55}{66.4}\right)} \text{ and } \tau_h = 292 \text{ ms}$$

Dependence of the intracellular calcium concentration ($[Ca]_{i,n}$) on influx of calcium ions through the calcium channel and on passive extrusion was defined as following:

$$\frac{d[Ca]_{i,n}}{dt} = -\frac{i_{Ca,n}}{2 * F * d} - \frac{[Ca]_{i,n} - [Ca]_{res}}{\tau}$$

with the depth at which $[Ca]_{i,n}$ was determined $d = 50$ nm, the residual calcium level $[Ca]_{res} = 0.1 \mu\text{M}$, and the time constant of the extrusion process $\tau = 50$ ms.

2.4. Synaptic release model

Release of neurotransmitter-filled vesicles from the ribbon synapses was modeled similarly to a previously published model (Sikora *et al* 2005), with the release rate dependent on the intracellular calcium concentration in BC terminals as well as on the current vesicle filling state of each synapse. In brief, vesicles can be released from two separate vesicle pools: (1) a fast pool, which represents vesicles already primed for release, and (2) a slow pool with vesicles that are not readily releasable. The mathematical framework to compute vesicle release has been adapted from Sikora *et al* (Sikora *et al* 2005). The model converts intracellular calcium concentration in BC terminals to an instantaneous release rate. This vesicle release rate is further applied independently and stochastically to each release site of the synaptic ribbon. We slightly modified the original model by using the intracellular calcium concentration at only one depth (50 nm) for both vesicle pools. We compared the release model against data from a previous study showing strong transient release emptying the fast pool within 20 ms, followed by sustained steady-state release of approximately 0.5 vesicles/ms/terminal when the BC was depolarized from -60 to -10 mV (Singer and Diamond 2006). A manual fitting procedure was performed to match experimental data. The best fit was obtained by slowing the calcium-dependent rate constant for the fast pool down by a factor of 20 and for the slow pool by a factor of 800 (in comparison to (Sikora *et al* 2005)). Each synaptic terminal ($n = 8$) was equipped with 10 ribbon synapses, resulting in a total number of 80 synapses per BC. 6 release sites with 5 rows of vesicles were defined at each synapse, resulting in a total number of 30 releasable vesicles per synapse. Vesicles could be refilled to the synapse at a time constant of 1 s, except otherwise noted, similar to experimental results (Singer and Diamond 2006).

All models were solved in Matlab (Mathworks) using a custom written implicit (backward) Euler solver. Time step was set to 0.025 ms. Since we compared modeled results primarily to data obtained in ex-vivo experiments at room temperature, model temperature was set to 23°C in all simulations.

2.5. Modeling the electric field

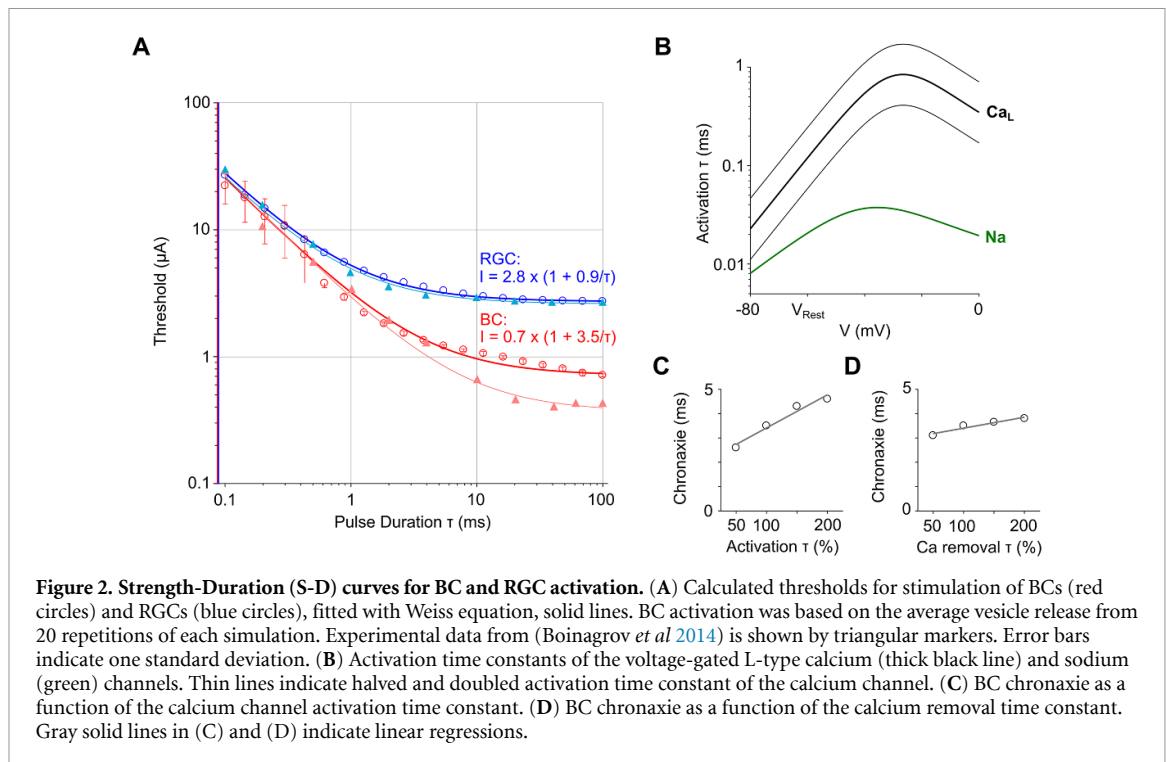
In addition, we calculated the electric field in an electrolyte using a 3-d finite element model of complete arrays of approximately 1000 pixels in COMSOL Multiphysics 5.4. The electrostatics module was implemented to solve Poisson's equation for electrical conduction, assuming a steady-state electric current of $0.2 \mu\text{A}$, close to the stimulation threshold with $40 \mu\text{m}$ pixels (Flores *et al* 2019). To illustrate the differences in field confinement among various pixel designs, we computed the electric field potential distribution for four distinct geometric configurations of the active (anodic) and return (cathodic) electrodes: flat monopolar (common return at the edge of the chip) and 3 bipolar (local returns surrounding each pixel)—flat, pillar and honeycomb (figure 3). All modeled arrays are 1.5 mm in diameter, $30 \mu\text{m}$ thick, and consist of $40 \mu\text{m}$ hexagonal pixels with an active electrode of $16 \mu\text{m}$ in diameter. In bipolar pixels (flat and 3-D) the return electrode was $4 \mu\text{m}$ in width, surrounding each active electrode in a hexagonal array. Pillar electrodes were $10 \mu\text{m}$ in height, and honeycombs were $25 \mu\text{m}$ in height, as described in our previous publications (Flores *et al* 2019, Ho *et al* 2019).

The thickness of the degenerate retina was assumed to be $100 \mu\text{m}$, and the resistivity of the medium in that layer was assumed to be equal to that of the retina: $1000 \Omega \text{ cm}$ (Werginz and Rattay 2016), while above it—that of the vitreous: $90 \Omega \text{ cm}$ (Oksala and Lehtinen 1959). To model the steady state behavior, constant current density is injected from active electrodes and collected on return electrodes (Chen *et al* 2020). The array of pixels is enclosed in a 1 cm^3 cubic volume, where the peripheral sides of the cube are defined as the ground. The initial values are set such that the total current injected from active electrodes is equal to the current collected at designated return electrodes. The bounding box is much larger than the implant modeled, so the gradient of electric potential at the boundary is negligible. Source of and sink of electric current are assumed to be confined to the electrode array, as in photovoltaic implants, and therefore the electric potential on active electrodes is above, and on return electrodes is below the ground level during the pulse.

3. Results

3.1. Factors shaping the chronaxies in BCs

To compare our modeling results to measurements performed with a micro-pipette electrode (Boinagrov *et al* 2014), we simulated BC and RGC responses to extracellular stimulation defined by a point source electrode located in the outer plexiform layer (OPL, electrode $15 \mu\text{m}$ from BC soma) and applied monophasic, anodic stimulation (figure 1(A)). Threshold for RGC activation during the anodic phase of the pulse was defined as the minimum stimulus amplitude that elicited an action potential that propagated



as far as the distal axon ($\sim 950 \mu\text{m}$ from soma) within 3 ms after the pulse offset. Indirect RGC responses are mediated by synaptic activity in BC terminals, which is driven by elevated intracellular calcium concentration ($[\text{Ca}]_i$) and subsequent vesicle release. The BC threshold was defined as a release of 3 vesicles from the synapse. Since the cathodic phase of the charge-balanced pulse in photovoltaic stimulation lasts several times longer than the anodic phase, with accordingly lower amplitude (Boinagrov *et al* 2016), and stimulation threshold during the cathodic phase is about 4 times higher than in the anodic phase (Boinagrov *et al* 2014), we did not consider the cathodic phase in retinal stimulation here.

The computed Strength-Duration (S-D) curves for RGCs (blue) and BCs (red) in the range of pulse durations from 0.1 to 100 ms are shown in figure 2(A). The simulated thresholds for RGCs matched the experimental values very closely (blue). Since the vesicles release is a stochastic process, the BC model required multiple runs for each pulse duration to compute an average number of released vesicles. Figure 2(A) (red) shows the S-D curve for 20 repetitions of the BC activation. As in earlier experimental measurements (Boinagrov *et al* 2014), BC thresholds decreased monotonically with increasing pulse duration up to a rheobase, and could be well-fit by Weiss equation (Weiss 1901). Modeling confirmed much longer chronaxie for BCs ($>3 \text{ ms}$) than RGCs ($<1 \text{ ms}$), and therefore longer pulses can preferentially activate BCs over RGCs.

Simulated BC thresholds matched the experimental data well for short pulse durations (0.1–2 ms), but did not decrease as much at longer pulses

(figure 2(A)). Consequently, the rheobase in simulations was not as low as in experimental data (0.7 vs. $0.4 \mu\text{A}$). BC thresholds (including the rheobase) could be lowered by (1) increasing the extracellular resistivity of the surrounding medium, (2) increasing the calcium channel density on BC terminals, or (3) lowering the threshold criterion. However, these modifications affect the whole curve in the same way, i.e. a better fit at long pulse durations results in underestimation for short pulses. The S-D curve with BC activation defined by elevated $[\text{Ca}]_i$ did not fit the Weiss equation as well as that based on the vesicles release, and was even lower at pulse durations below 1 ms (see figure S1) (available online at stacks.iop.org/JNE/17/045008/mmedia).

In order to initiate an action potential in RGCs, voltage-gated sodium channels should open during depolarization and remain open long enough for the membrane potential to rise to the threshold value. This opening occurs in tens of microseconds (figure 2(B), green), which results in the observed sharp onset of spikes. On the other hand, RGC responses mediated by the retinal network require synaptic input from the stimulated BCs. This activity is driven by the voltage-gated calcium channels located in the pre-synaptic terminals of BCs. Calcium channels are about 1–2 orders of magnitude slower than the sodium channels—their opening time constant is around 1 ms (figure 2(B), black).

To assess the effect of various model parameters on chronaxie for BC activation, we first modified the activation time constant of the calcium channel (figure 2(B)). Chronaxie extracted from the computed S-D curves increased linearly with the

activation time constant (figure 2(C)). Similarly, the calcium removal time constant, which determines the passive extrusion of $[Ca]_i$ from the intracellular space also affected chronaxie for BC activation in a linear fashion (figure 2(D)), i.e. slower removal of $[Ca]_i$ increased the chronaxie. However, the effect of the Ca extrusion rate on chronaxie was much smaller than that of the Ca channel activation time. On the other hand, neither the threshold criteria for BC activation nor the calcium channel density on BC terminals affected the chronaxie since the resulting S-D curves just shifted along the threshold (vertical) axis without changing their curvature (not shown).

3.2. Effect of the local return electrode on shaping the electric field

Since the cell cytoplasm is much more conductive than the cell membrane, upon application of an electric field (current) in the surrounding medium, the cell quickly polarizes by redistributing electric charges along its membrane. Since cations are attracted to the anode (area of higher potential) and anions—to the cathode (lower potential), the cell polarizes such that the negative membrane potential on its anodic side increases (membrane is hyperpolarized), while on the cathodic side, it decreases (membrane is depolarized). With the anode located in the OPL, the soma and dendritic parts become hyperpolarized, while the axonal portion of the BC becomes depolarized. Opening of the voltage-sensitive Ca ion channels in axonal terminals of the BC in response to depolarization consequently triggers the release of synaptic vesicles (as reviewed in (Wan and Heidelberger 2011)).

To assess how the shape of the electric field affects the BC stimulation threshold, we compared membrane polarization obtained with a point source to that observed in a uniform electric field that had the same total voltage drop between the top and bottom (z-dimension) of the BC (figure S2(A)). This comparison demonstrated that the uniform field created slightly (by about 25%, range 18%–31%) larger depolarization of the axonal terminals, both of which scale linearly with electric field (figures S2(B)–(C)). Therefore, BC membrane polarization can be estimated for various field shapes by just the voltage step between its top and bottom boundary.

To provide selective stimulation of BCs while avoiding activation of the downstream neurons—ACs and RGCs, the electric potential should rapidly drop across the INL. As shown in figures 3(A)–(B), activation of a single monopolar pixel (with a distant return electrode) generates an electric potential which declines across the retina with a rate similar to that in a bipolar pixel (where a local return electrode surrounds an active electrode). However, when many pixels are activated simultaneously, electric fields from monopolar electrodes add up, resulting in a much slower decline in the potential across the retina. Such a deep penetrating field provides

much lower selectivity in activation of BCs vs. ACs, which are located in the top (inner) strata of INL (Balasubramanian and Gan, 2014), than with bipolar pixels (figures 3(C)–(D)). In addition, since the electric potential in front of the monopolar array increases with the number of activated pixels, perceptual brightness of the image will depend on its sparsity. Local return electrodes in bipolar pixels isolate their electric fields from the neighbors, and hence the perceptual brightness should not depend on the image sparsity.

However, as we demonstrated earlier (Flores *et al* 2019), retinal stimulation thresholds with flat bipolar pixels below 40 μm in width exceed the charge density limit even for SIROF electrodes. To overcome this limitation, two 3-dimensional configurations have been proposed: pillar electrodes (Ho *et al* 2019) and honeycomb arrays (Flores *et al* 2019). Both approaches utilize the phenomenon of cellular migration in the subretinal space, when the cell somas in the INL fill the space provided in the subretinal implant over a few weeks post implantation. As a result, pillar (active) electrodes penetrate into the middle of INL, which helps reduce the stimulation threshold (Ho *et al* 2019). However, as the maximum electric potential is shifted closer to the top of INL, the discrimination between BCs and ACs is likely weakened. With honeycomb arrays, the penetration of electric field into the INL is also increased via elevating the return electrode, but the maximum potential is located at the bottom, which likely provides better selectivity. Other advantages of the honeycomb arrays in size scalability and in contrast are described in the previous publication (Flores *et al* 2019).

3.3. BC response to high frequency stimulation—the low-pass filtering

Membrane depolarization in BC synaptic terminals in response to repetitive pulsed stimuli (monophasic, anodic pulses at 4 ms and 4 μA from a point source in the OPL, see Methods) is shown in figure 4(A). Responses to each pulse at frequencies ranging from 2 to 50 Hz did not change since the cell can be readily de- and re-polarized by the applied electric field with a time constant of about 0.2 ms (figure 4(A), inset). Subsequently, membrane depolarization led to opening of the voltage-sensitive calcium channels in the synaptic terminals, which resulted in an inward calcium current (not shown) leading to increased calcium concentration $[Ca]_i$ (figure 4(B)). Since upon opening of the Ca channels the ions can only flow into the cell (due to the voltage and concentration difference), the cell acts as a rectifier—converting the AC stimulus into the pulsatile inward current. After the pulse, calcium channels close and ions are removed from the intracellular space by ion pumps with a time constant of 50 ms. At low frequencies (<5 Hz), the inter-pulse interval was long enough to let $[Ca]_i$ return to its resting state before the next stimulus.

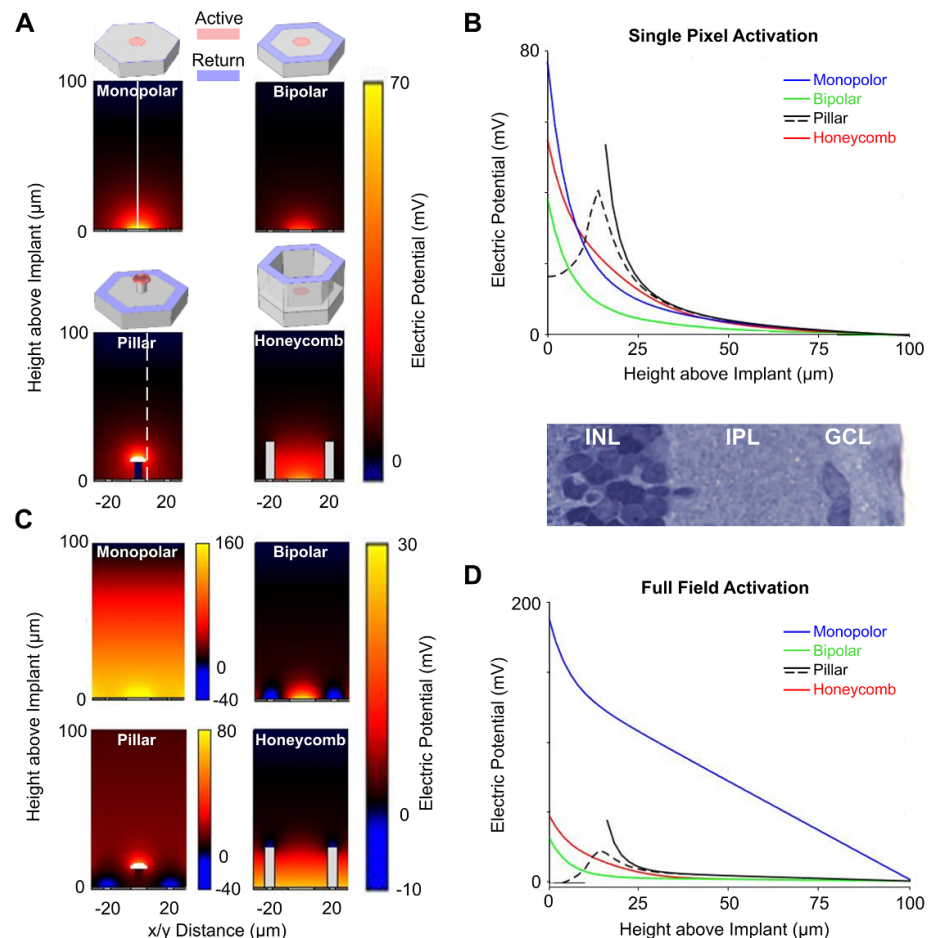


Figure 3. Electric potential in the retina with various electrode configurations. (A) Electric potential in the medium of $1000\ \Omega\ \text{cm}$ resistivity, generated by $0.2\ \mu\text{A}$ of current flowing from the active electrode in steady state, when a single pixel is activated in the array. The active electrode is shown in red, and the return—in blue. (B) Electric potential as a function of z-distance on axis (solid vertical line in (A)) or slightly off axis (dashed vertical line in (A)) of the pixel. (C) Electric potential in the medium when all pixels in the array are activated by the same current ($0.2\ \mu\text{A}$) simultaneously. (D) Corresponding electric potential as a function of z-distance on axis of the pixel. Rat retinal histology is shown to scale with the plots in (B) and (D); INL: inner nuclear layer, IPL: inner plexiform layer, GCL: ganglion cell layer. All potentials are calculated relative to the medium above the retina (Height above Implant = $100\ \mu\text{m}$).

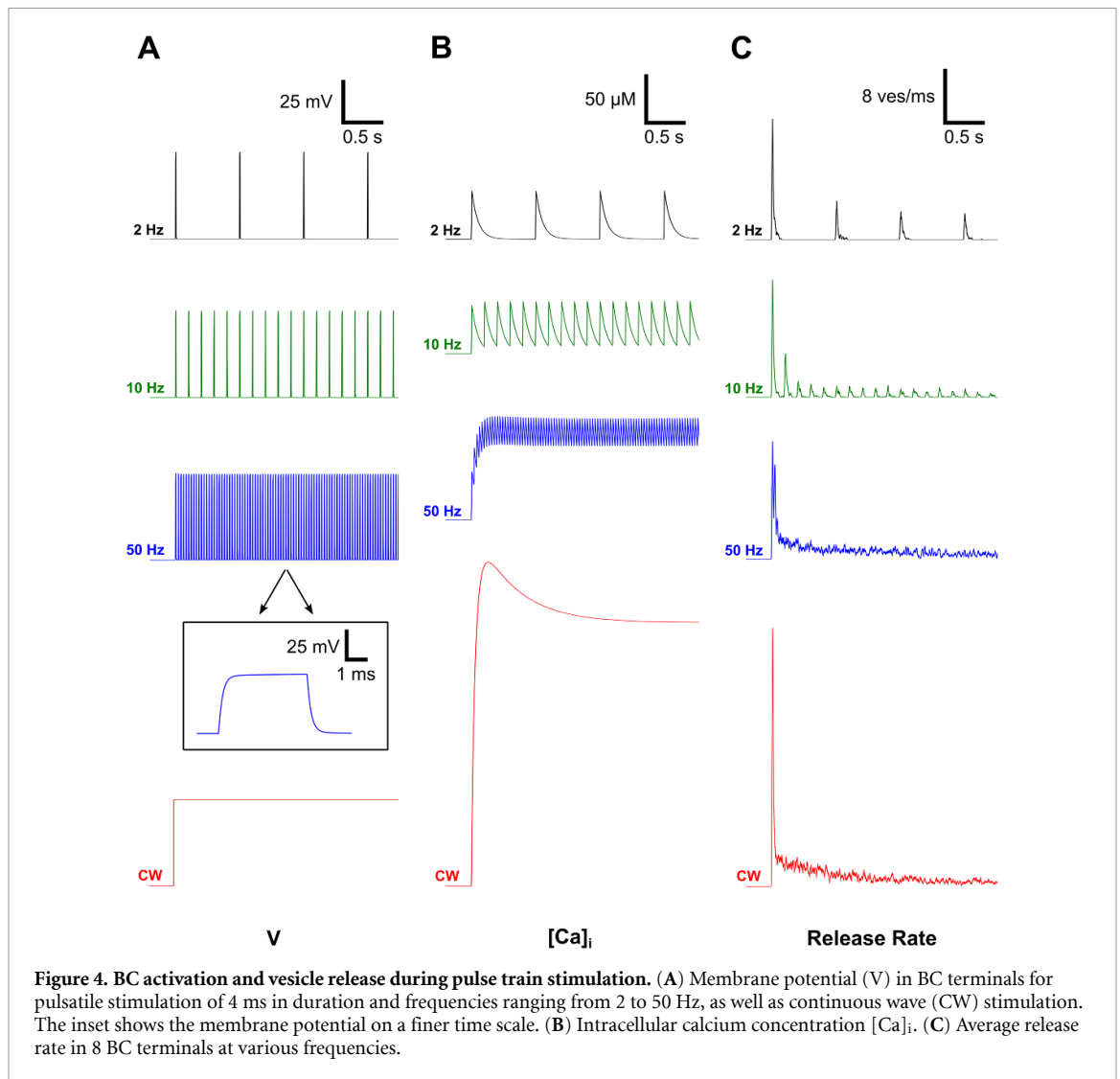
Higher pulse rates (10–100 Hz), on the other hand, led to an elevated level of $[\text{Ca}]_i$ even between the pulses. Therefore, the amplitude of the oscillation in $[\text{Ca}]_i$ concentration at steady state decreased with increasing frequency, while the constantly elevated level increased (figures 4(B) and 5(A)). Such a low-pass filtering in BCs may be partially responsible for the flicker fusion phenomenon—diminished perception of pulsation with increasing frequency of the flash stimuli. The other part of such filtering occurs in synaptic transmission, as described in the next section.

3.4. Synaptic kinetics results in high-pass and low-pass filtering of the BC output

Increased $[\text{Ca}]_i$ drives the release of the neurotransmitter-filled vesicles from ribbon synapses in BC terminals in a biphasic manner, with a fast transient release phase followed by a sustained release at lower rate (Singer and Diamond 2003, Oesch

and Diamond 2011). Since availability of the readily releasable vesicles decreases after the first transient release, the following pulses have attenuated amplitude, and this attenuation increases with the pulse frequency (figure 4(C)). To better understand the kinetics of the vesicle release, we plotted the average vesicle occupancy of 80 synapses over the initial 2 s of the stimulus (figure 5(B)). The average filling state decreased from about 80% at 10 Hz to lower levels as the stimulation frequency increased to 50 and 100 Hz—closer to the level of continuous stimulation (red).

Figure 5(C) demonstrates that the peak release rate, i.e. the maximum release rate during the whole stimulus, starts increasing with frequency above 50 Hz due to summation of a few pulses within the rapid release phase of the ribbon synapse. We also characterized responses based on the oscillatory release rate which was defined as the difference between the maximum release rate and the minimum



release rate during each pulse. The oscillatory release rate in steady-state monotonically decreases with frequency, as shown in figure 5(C) (dash green line). On the other hand, the average release rate decreases with frequency up to about 20 Hz, and then stabilizes on a constant level, as shown by a solid green line in figure 5(C). Integrating the difference between the transient and steady-state release rate over time provides the total number of vesicles released in response to a step function illustrated in figure 4(C). As shown in figure 5(C), this value increases with frequency as well.

Assuming that the RGC firing rate is proportional to synaptic input in pulsed stimulation, we can compare predictions of our model to experimental data. Figure 5(D) depicts the population-averaged RGCs firing rate as a function of the stimulation frequency in two experiments: degenerate rat retina (Royal College of Surgeons (RCS) rats) stimulated by a subretinal prosthesis and normal retina (Long Evans rats) stimulated by visible light (Lorach *et al* 2015a), together with the vesicle release rate in steady state from the current model. Results of our model show that the declining response

with increasing frequency is similar to the decrease observed in the degenerate retina, while in normal retina, the response declines much faster. The matching rate of this decrease between our model and degenerate retina suggests that bipolar cells are the main temporal filter in this case (Ca accumulation and vesicle release from BC terminals). The faster decline in normal retina indicates that photoreceptors (phototransduction and ribbon synapse) represent another temporal low-pass filter, on top of the filter by bipolar cells, which matches the previous direct measurements of the photoreceptors response (Pandarinath *et al* 2010).

Another important aspect of the BC response is the effect of pulse duration on vesicle release. Figure 6(A) shows the vesicle release rate in response to 4 μ A stimulation with different pulse durations, when the carrier frequency was fixed at 2 Hz. Maximum steady-state response amplitude gradually increased with longer pulses and plateaued around ~7-10 ms, depending on stimulus amplitude (figure 6(B)). A similar trend was observed in measurements of the RGC firing rate in rat retina stimulated subretinally

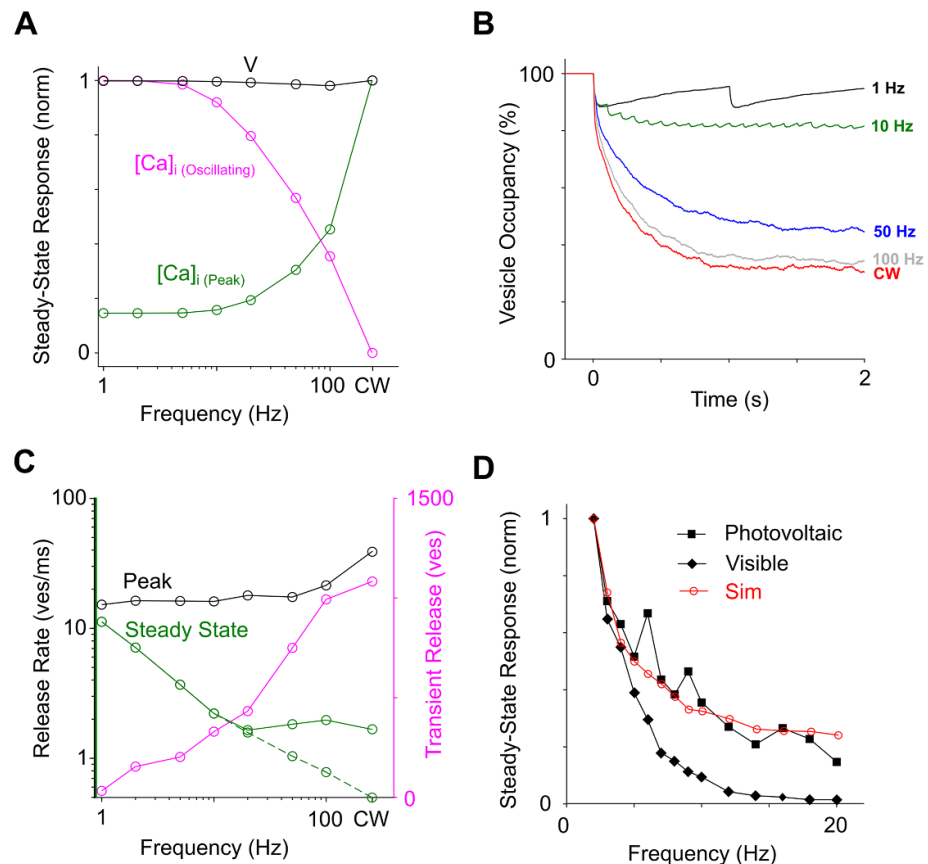


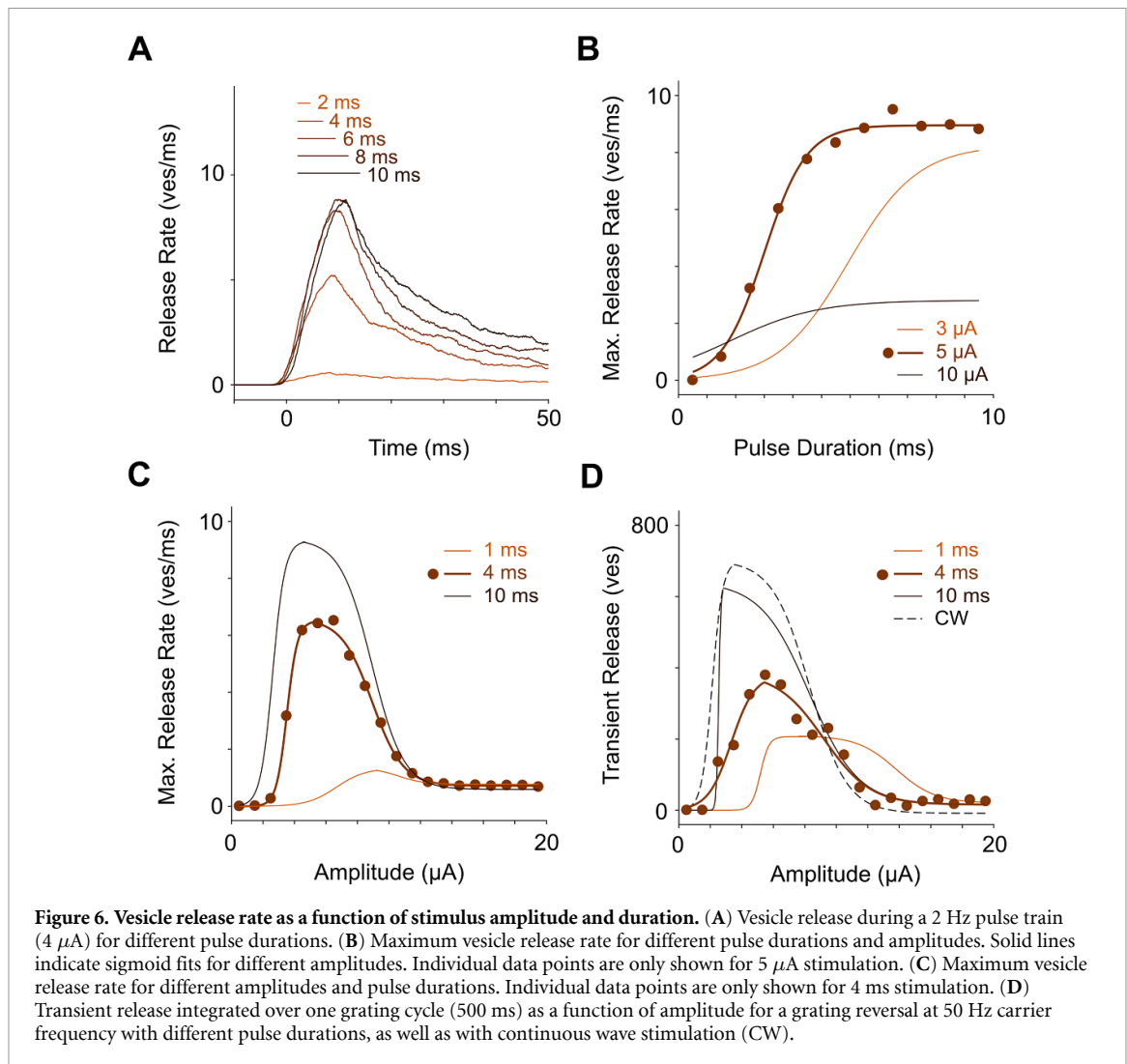
Figure 5. Ca concentration and vesicles release characteristics during pulse train stimulation. (A) Peak V (black), peak $[Ca]_i$ (dark green) and the amplitude of oscillation of $[Ca]_i$ (magenta) for different stimulus frequencies as well as continuous wave stimulation (CW). (B) Vesicle occupancy over time for 1, 10, 50 and 100 Hz as well as CW. Data is averaged over 80 ribbon synapses. (C) Peak release rate (black), steady-state release rate (green) and number of released vesicles within one second (magenta) for pulsatile (1–100 Hz) and CW stimulation. Release rate for each pulse in steady state was measured as a mean value (solid green line) and as an oscillatory value (dashed green line). (D) Vesicles release rate (red, same data as figure 3(C) green dash line) compared to the RGC firing rate measured ex-vivo during photovoltaic stimulation of degenerate retina (black squares) and visible light stimulation of normal retina (black diamonds) from (Lorach *et al* 2015a).

ex-vivo (Mathieson *et al* 2012) as well as with visually evoked potentials measured in rats *in-vivo* (Lorach *et al* 2015b). As described previously (Werginz and Rattay 2016), increase in the stimulus amplitude initially leads to increased BC response, but then above certain threshold, the response starts decreasing (figure 6(C)). Such an upper threshold is expected when the membrane potential exceeds the reversal potential of calcium, which is in the range of 20–100 mV, depending on $[Ca]_i$ (Werginz and Rattay 2016). Such non-monotonic responses also vary with pulse duration, as shown in figure 6(C). At very strong stimuli ($>15 \mu A$), the maximum release rate reached the same level for all amplitudes and pulse durations—approximately 10% of the maximum level.

In summary, the modeled response of the BC to pulsatile electrical stimulation was generally in good agreement with the previously published experimental results. The model suggests that kinetics of the calcium channels together with the vesicle release dynamics in ribbon synapses capture the BC response characteristics observed in experiments with degenerate rat retina.

3.5. BC response to alternating gratings

Retinal (and cortical) response to alternating gratings is a well-established test of resolution and contrast sensitivity in animals (Harnois *et al* 1984) and in human infants (Dobson and Teller 1978, Sokol 1978). The grating period (or contrast) is decreased until the RGC (or cortical) response to the grating reversal vanishes into the noise. We used this test with natural and prosthetic vision ex-vivo (Lorach *et al* 2015b) and *in-vivo* (Ho *et al* 2019) in rats and demonstrated that the spatial resolution of prosthetic vision can match the pixel pitch (Lorach *et al* 2015b, Ho *et al* 2019). In rats, the resolvable grating stripe width in these measurements is about 10 times smaller than the average size of receptive field (20 μm vs. 200 μm). If BC responses would just linearly reproduce the illumination intensity and sum-up into the RGC, there would be no response to alternation since the average intensity over the receptive field much larger than the stripe width does not change much. What enables the RGC response in this case is adaptation—decrease of the response to a constant stimulus over time. Such a transient response to a step



in continuous illumination (mimicking normal vision, albeit without the low-pass filtering by photoreceptors) is shown in the bottom row of figure 4(C). Transiency of the BC response is due to faster initial release of the vesicles from the primed pool, compared to sustained release from the slower pool. To model this effect, we summed the output from two distinct BCs into an RGC, as has been proposed by Demb *et al* (Demb *et al* 2001).

In the grating reversal paradigm, shown in figures 7(A)–(B), the total release rate is higher upon the grating reversal for each half-a-cycle, and it declines after that until the next reversal. Such compound signal explains the typically observed frequency doubling during stimulation with alternating gratings (Demb *et al* 2001, Lorach *et al* 2015a). The grating reversal is detectable until such oscillations decrease below the noise level, when stripes become smaller than the BC sub-units.

With electrical stimulation, we apply pulsed stimuli, and in order to prevent strong image flickering, which may interfere with the perception of the grating reversal, we operate at frequencies sufficiently high for flicker fusion. Patients with a subretinal implant

could still see a little bit of flicker at 30 Hz, and no flicker at all at 60 Hz (Palanker *et al* 2020). In rats we typically operate at 40 Hz *in-vivo* (Ho *et al* 2019), while we limited the rep. rate to 20 Hz *ex-vivo*, due to the lower retinal temperature used to slow its metabolic demand. In this simulation, gratings were reversed at 1 Hz and a 20, 50 and 100 Hz carrier with 4 ms pulses was used (figures 7(c)–(F)). Each BC generated synaptic output when the pulsed electric field was applied to the corresponding BC, i.e. under the bright grating stripe but not under the dark stripe. Responses to the 20 Hz carrier showed transients at each grating reversal and each individual pulse led to a smaller transient release (figure 7(D)). With higher carrier frequencies, the response to the grating reversal became closer to that under continuous illumination (figure 7(B)). Like the responses with a continuous stimulus, responses with 50 and 100 Hz carrier are stronger right after the grating reversal, and decrease over time until the next reversal (figures 7(E)–(F)). At carrier frequency much below 20 Hz, there would be no significant attenuation of the pulse response, and hence such paradigm would not work for the grating acuity test.

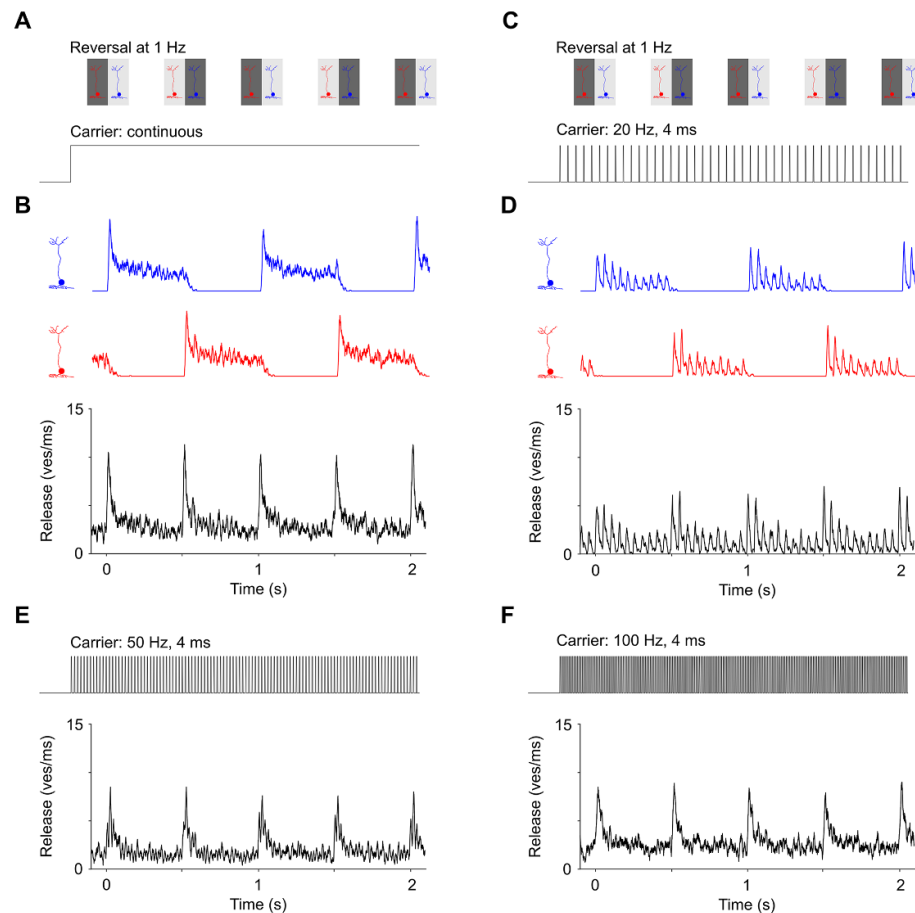


Figure 7. BC response to alternating grating stimulation. (A) Diagram illustrating stimulation with gratings alternating at 1 Hz (top row), when two different BCs correspond to the bright and dark stripes of the grating. (B) Responses from the two BCs (red and blue) are combined to simulate summation of the synaptic inputs in RGC (black). (C)–(F) Similar as (A)–(B) but for pulsatile electrical stimulation. The underlying carrier frequency was 20 (D), 50 (E) and 100 Hz (F) with 4 ms stimulus duration (bottom row in (C) and top row in (E)–(F)). All simulations were computed with an accelerated refill time constant of 0.5 s.

Transient vesicle release in response to the grating reversal increased with the stimulus strength and then declined, when the stimulus amplitude exceeded the upper threshold, as shown in figure 6(D) for 50 Hz carrier frequency and grating reversal at 1 Hz. Both, the lower and upper stimulation thresholds decreased with increasing pulse duration, as shown in figure 6(D) for 1, 4, 10 ms and CW stimulation.

4. Discussion

Photoreceptors operate within about 8–10 orders of magnitude in luminance, with this range divided between rods specializing in scotopic, and cones—in photopic vision. Their response to increasing brightness follows a sigmoidal curve, with about 2 orders of magnitude in the center of the range providing a nearly linear rise, and saturating towards zero on the lower end and towards maximum on the higher end. Photoreceptors adjust their amplification mechanisms (together with the pupillary response) such that their response curve centers around the average brightness level. In retinal prosthetics, this function is performed by the camera which adapts to the ambient

illumination, so that the brightness of the images projected onto the photovoltaic pixels matches their dynamic range for retinal stimulation.

As shown in figure 6, dynamic range of the BC response to electrical stimulation (from the stimulation threshold to saturation) is much narrower than the natural 2 orders of magnitude (Pelli and Bex 2013). This is likely to result in reduced temporal contrast sensitivity of prosthetic vision, as was observed ex-vivo and *in-vivo* (Ho *et al* 2018).

Horizontal cells (HCs), wired to the terminals of photoreceptors, inhibit the photoreceptors' output into BCs based on the average luminance level within their receptive fields (antagonistic center-surround) and thereby enhance the spatial contrast. Upon demise of photoreceptors in retinal degeneration, HCs become disconnected from the retinal circuit, so their function should also be performed externally—by contrast enhancement between the camera and the stimulating array.

To preserve the remaining retinal signal processing as much as possible when the lost photoreceptors are replaced with photovoltaic pixels, they should be coupled into the secondary retinal neurons

in a manner that is (1) spatially selective, and (2) retain temporal dynamics similar to natural vision.

4.1. Spatial selectivity

Spatial selectivity of electrical stimulation can be enhanced either by providing local return electrodes around each pixel to confine the electric field, or by sequential activation of the pixels so that their electric fields do not add up and hence the electrical crosstalk is reduced. Temporal multiplexing is limited by the ratio of the frame duration to pulse duration. For example, with a frame rate of 33 Hz and pulse duration of 10 ms, only 3 groups of electrodes can be activated sequentially. Since penetration depth of the electric field generated by a flat bipolar pixel is similar to its radius, pixels smaller than 40 μm cannot effectively stimulate the whole INL (Ho *et al* 2019). Pillar electrodes can center the electric field in the middle of the INL (figure 3), but this decreases the selectivity between stimulation of BCs and ACs, located in the top strata of INL and (some) displaced into the ganglion cell layer. Honeycomb implants provide optimal balance between the lateral confinement of the electric field and axial selectivity between the top and bottom of the INL (figure 3). With honeycombs, the penetration depth of the electric field is decoupled from pixel width, meaning that this geometry is scalable down to cellular sizes.

4.2. Temporal filtering and rectification in BCs

Naturally, photoreceptors provide a continuous influx of glutamate into BCs, modulated by light intensity. In electrical stimulation, the applied stimuli should be pulsed and biphasic due to the requirement of charge balance. To make the effect of pulsed stimulation on the retinal network as close to that of a continuous stimulus as possible, we operate at frequencies above the flicker fusion. Since the resting membrane potential is negative, cells respond to an alternating current as rectifiers—they only allow cations inflow when ion channels open during depolarization, and the ion concentration is restored after the stimulus by ion pumps and leakage currents. Patch clamp experiments demonstrated pulsatile depolarizing response to extracellular electrical stimulation in retinal BCs (Walston *et al* 2018) accompanied by the glutamate release from their axonal terminals (Margalit and Thoreson 2006).

Due to the relatively slow pump-out of Ca from BCs, its intracellular concentration under high frequency stimulation increases, and the amplitude of inter-pulse oscillations decreases, which represents one aspect of the low-pass temporal filtering, as shown in figure 4(B). Decreasing amplitude of the BC response with increasing frequency of pulsatile extracellular electrical stimulation has been observed in direct patch clamp recordings (Walston *et al* 2018). The second phase of temporal filtering in BCs occurs due to specific vesicle release dynamics

in the ribbon synapses. When the readily available pool of vesicles is exhausted after the initial rapid response, the sustained rate becomes much lower and its dynamics is much slower (the transient response is $\sim 50\times$ larger than the sustained response, figure 4(C) and (Singer and Diamond 2006)). Therefore, with increasing stimulation frequency, the release rate dynamics becomes more and more similar to that observed with continuous illumination, as shown in figure 4(C). Such temporal filtering represents not only flicker fusion, but also adaptation to a static input (response to a constant stimulus diminishes over time (Suh and Baccus 2014)). Photoreceptors also represent low-pass temporal filtering, and therefore flicker fusion in healthy retina occurs faster than in degenerate retina, as shown in figure 5(D). For this reason, we operate typically at 40 Hz in rodents *in-vivo*, and human patients with photovoltaic implants reported that they see much less flickering at 30 Hz than at 10 Hz, and no flickering at all at 60 Hz (Palanker *et al* 2020).

Another important aspect of the ribbon synapse is the rectifying nonlinearity, which arises from the fact that the vesicle release cannot be negative. Thus, the vesicle release rate initially shoots up upon a rapid increase in membrane potential and then drops to a much lower sustained rate, but does not turn negative during the falling edge of the voltage pulse. Such temporal filtering and rectification enable the non-linear summation of inputs from multiple bipolar cells (sub-units) into an RGC, which explains the response to alternating gratings with the stripe width much smaller than the average size of its receptive field, as shown in figure 7, and measured experimentally in (Lorach *et al* 2015a).

The physiological properties of the ribbon synapses contribute to multiple aspects of retinal neural computations (reviewed in (Lagnado and Schmitz 2015)), and preservation of their response dynamics under high frequency electrical stimulation should retain these aspects of the natural signal processing. In addition to flicker fusion, adaptation to static images and non-linear summation of sub-units (Lorach *et al* 2015a), we see preservation of several other important aspects of the retinal signal processing, likely due to properly functioning amacrine cells. One preserved feature is the antagonistic center-surround organization of the RGC receptive fields in prosthetic vision (Ho *et al* 2018) and the other—inhibitory responses of OFF RGCs (figure 3 in (Ho *et al* 2019)).

4.3. Limitations of selectivity and their potential consequences

One potential limitation of the ‘electronic photoreceptors’ is the indiscriminate activation of ON- and OFF-cone BCs. In *ex-vivo* recordings, we see much fewer OFF-responding RGCs than ON, unlike in natural vision in rats, where the split is close to equal (Ho *et al* 2018). In addition, patients with our implants

(PRIMA, Pixium Vision) report perceptions faithfully representing the polarity of the visual stimuli, such as bright letters on dark background (Palanker *et al* 2020). One reason why indiscriminate stimulation of the ON and OFF BCs elicits correct visual percepts may be the role of rod BCs. In natural day vision, rod BCs are mostly saturated and do not play a major role in modulating the RGC firing rate. Electronic photoreceptors however, likely stimulate rod and cone BCs to the same extent. Since there are only ON-rod BCs, which are coupled into the cone pathway by enhancing the ON and inhibiting the OFF signals, they correctly represent the contrast of the excitatory input into BCs. Another reason could be the much higher spontaneous firing rate of the OFF RGCs than ON in degenerate retina (Sekirnjak *et al* 2011). With the same number of elicited spikes, the signal-to-noise ratio in the quiet ON pathway will be much higher than that in the noisy OFF RGCs, and hence the ON responses may perceptually dominate.

Another important factor for selective stimulation of single BC subtypes might be the distribution of different subclasses of calcium channels in BC terminals. Here, we modeled a calcium L-type channel as it has been shown to be driving vesicle release from BC terminals (reviewed in (Wan and Heidelberger 2011)). Another class—the T-type calcium channels—has also been found in BCs and are involved in neurotransmitter release (Pan *et al* 2001). In contrast to L-type, the T-type channels are characterized by lower activation thresholds and slower dynamics. Therefore, retinal implants could use lower current to activate BCs expressing T-type channels, which would allow selective stimulation of these BC types over others. Also, the larger activation time constants of T-type channels would slow down BC responses, thereby increasing chronaxie and improving selectivity of BCs activation over RGCs even further. Therefore, BC chronaxies presented in figure 2(A) should be considered as a lower bound. Since little is known about the distribution of different types of calcium channels in BCs, this issue requires further exploration.

Lastly, the whole concept of electronic replacement of the lost photoreceptors in atrophic AMD relies on the assumption of preservation of the inner retinal cells and circuits to a large extent. Even though the first clinical results with this approach are very encouraging (Palanker *et al* 2020), the extent of the retinal preservation, as well as the effect of retinal migration into the honeycomb-shaped implants remains to be verified experimentally.

4.4. Model limitations

In this study we assumed the retinal resistivity to be $1000\ \Omega\ \text{cm}$, which is in the mid-range of the previously reported values (Karwoski *et al* 1985, Greenberg *et al* 1999, Kasi *et al* 2011). The good agreement between the computed and experimentally measured

RGC thresholds (figure 2(A)) adds support to the assumed retinal resistivity.

Simulated BC S-D curves had lower chronaxies than observed in experiments (~ 3.5 vs. 7 ms in (Boinagrov *et al* 2014)). Thresholds matched well for short pulse durations, however, for pulses longer than 2 ms, the simulated and experimental data diverged (figure 2(A)). By adjusting the model parameters, such as extracellular resistivity, calcium channel density as well as the threshold criterion, the rheobase can be matched. However, such modifications would only shift the S-D curve along the vertical axis, but will not change the chronaxie values. The mismatch of chronaxie might be related to post-synaptic processing on RGCs, which is not included in the present model. Post-synaptic glutamate receptors, as well as the dendritic ion channels, shape the BC input and affect the RGC spiking, and therefore can extend the corresponding chronaxies. Furthermore, since RGCs are also depolarized to some extent during BC stimulation, such sub-threshold activation might lower the BC-mediated thresholds.

Multiple mechanisms are involved in pumping calcium ions out of the intracellular space, and many aspects of these processes are still not very well understood. Here, we modeled extrusion of calcium from the intracellular space with a single time constant of 50 ms. This value is smaller than the hundreds of milliseconds time constants observed with calcium indicators (Burrone *et al* 2002). Since the latter have fast onset but a slow decaying phase of the response signal (Stringer and Pachitariu 2019), these observations result in overestimation of the Ca extrusion time constant. Direct whole-cell recordings in neurons yielded $[\text{Ca}]_i$ decay times in the range of tens of milliseconds (Dittman and Regehr 1998).

Recently, it has been reported that BCs can initiate calcium-driven spikes in response to electrical stimulation of the retina (Walston *et al* 2018). Since the origin as well as kinetics of these calcium spikes are still not fully understood, we did not model them in the present study. The reported transient depolarizations had an amplitude of only 10 – 20 mV, which might not be enough to trigger substantial synaptic release. However, measurements in (Walston *et al* 2018) were performed at the soma, whereas calcium spikes are thought to be initiated within the axon (terminals) of BCs. It will be interesting to learn in the future the potential effect of calcium spikes on the performance of subretinal prostheses.

5. Conclusions

The modeled BC-mediated retinal responses were in general in good agreement with previously published experimental results. Kinetics of the calcium pumps and of the neurotransmitter release from ribbon synapses, which underpin the BC's temporal filtering and rectifying functions, allow mimicking the natural BC

response to continuous visual stimuli using high frequency pulsatile electrical stimulation. Such replacement preserves many features of the natural retinal signal processing such as flicker fusion, adaptation to static stimuli and non-linear summation of subunits in the RGC receptive field. Selectivity of the BC stimulation while avoiding direct activation of the downstream neurons is further improved using local return electrodes. Selective stimulation of BCs using proper spatial and temporal modulation of the electric field may allow highly functional restoration of sight.

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PAPER

Harmonic-balance circuit analysis for electro-neural interfaces

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PAPER

Harmonic-balance circuit analysis for electro-neural interfaces

Zhijie Charles Chen^{1,2,5} , Bing-Yi Wang^{3,2} and Daniel Palanker^{4,2} ¹ Department of Electrical Engineering, Stanford University, Stanford, CA, United States of America² Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, United States of America³ Department of Physics, Stanford University, Stanford, CA, United States of America⁴ Department of Ophthalmology, Stanford University, Stanford, CA, United States of America⁵ Author to whom any correspondence should be addressed.E-mail: zcchen@stanford.edu**Keywords:** neural stimulation, electro-neural interface, charge injection capacity, harmonic-balance analysis, electrochemical impedance spectrum, photovoltaic neural stimulation**Abstract**

Objective. Avoidance of the adverse electrochemical reactions at the electrode-electrolyte interface defines the voltage safety window and limits the charge injection capacity (CIC) of an electrode material. For an electrode that is not ideally capacitive, the CIC depends on the waveform of the stimulus. We study the modeling of the charge injection dynamics to optimize the waveforms for efficient neural stimulation within the electrochemical safety limits. **Approach.** The charge injection dynamics at the electrode-electrolyte interface is typically characterized by the electrochemical impedance spectrum, and is often approximated by discrete-element circuit models. We compare the modeling of the complete circuit, including a non-linear driver such as a photodiode, based on the harmonic-balance (HB) analysis with the analysis based on various discrete-element approximations. To validate the modeling results, we performed experiments with iridium-oxide electrodes driven by a current source with diodes in parallel, which mimics a photovoltaic circuit. **Main results.** Application of HB analysis based on a full impedance spectrum eliminates the complication of finding the discrete-element circuit model in traditional approaches. HB-based results agree with the experimental data better than the discrete-element circuit. HB technique can be applied not only to demonstrate the circuit response to periodic stimulation, but also to describe the initial transient behavior when a burst waveform is applied. **Significance.** HB-based circuit analysis accurately describes the dynamics of electrode-electrolyte interfaces and driving circuits for all pulsing schemes. This allows optimizing the stimulus waveform to maximize the CIC, based on the impedance spectrum alone.

1. Introduction

Electrical stimulation of neurons requires injection of a sufficient amount of charge through the electrode-electrolyte interface. The stimulation threshold depends on various factors, including the electrode geometry [1, 2], proximity to the neurons [3, 4], the pulse waveform [2, 5], the pulse duration [6, 7], and the repetition rate [2, 8]. When too much charge is injected, the potential drop across the electrode-electrolyte interface would rise beyond the safety window, enabling adverse electrochemical reactions, such as water electrolysis, which may result in damage to the electrode material and biological tissues. The charge injection capacity (CIC) of an electrode is

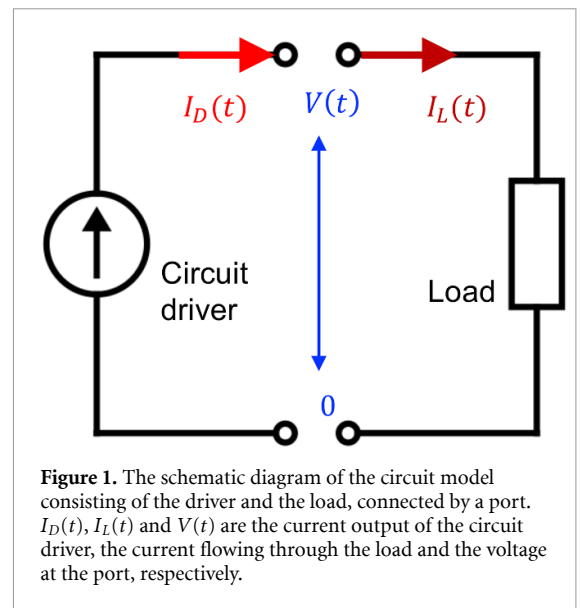
defined as the maximum amount of charge that can be injected in one pulse without driving the electrode-electrolyte interface beyond the safety window [9]. For the efficacy of neural stimulation, bio-compatible electrode materials with large CIC are desirable. Iridium oxides (IrOx) [10–15], platinum black (Pt-Black) [16] and poly(3,4-ethylene-dioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) [8, 17–19] are some common materials used as neural electrodes for this reason.

The CIC is related to the material capacitance and is affected by the impedance spectrum over a frequency range corresponding to the applied stimulus waveform [12, 20]. Very often, however, the impedance is reported only at one specific frequency,

1 kHz, for example [21], or even not reported at all [8, 14, 15, 18, 19]. Since highly capacitive materials are usually porous and often involve reversible electrochemical reactions, the electro-electrolyte interface is not ideally capacitive. Therefore, dynamics of the charge injection and the CIC depend on the applied waveform. For example, the impedance spectrum of sputtered iridium oxide film (SIROF) shows phase characteristics of the transmission lines, due to the pore resistance and the mass-transfer limitation associated with its porous structure [12, 22]. Hence, the CIC was found to vary with pulse duration [23]. Therefore, materials cannot be characterized by a single CIC value, but should rather be described in a more comprehensive manner, taking into account the impedance spectrum and the waveform of stimulus.

Traditionally, electrode-electrolyte interfaces are described by circuit models with discrete elements, the values of which are fit to the impedance spectrum. Solving the differential equations corresponding to such circuits should describe the resulting charge injection dynamics [24–26]. However, as we will show in section 3.2, depending on the applied waveform, various discrete-element approximations to the impedance spectrum may result in highly variable outcomes. An accurate representation of the impedance spectrum typically involves constant phase elements (CPEs) [27], the dynamics of which needs to be modeled in frequency domain through the Laplace transform [28], causing extra complications and often incompatible with non-linear circuit elements, such as diodes, for example.

In this paper, we propose a framework to describe the circuit response without the need to fit an equivalent discrete-element circuit model. If the circuit is driven by controlled current or voltage, directly applying the impedance spectrum in frequency domain yields the corresponding voltage or current response. In cases where neither current nor voltage is directly controlled, we use harmonic-balance (HB) analysis to solve for the response when the circuit driver is non-linear. For example, photovoltaic retinal prosthesis is driven by photodiodes, which have non-linear relationship between the voltage and the current [11]. The results of our modeling are validated by comparing with the actual experimental measurements and with the time-domain solutions of the discrete-element circuit approximation. Since the wireless photovoltaic prosthesis is inaccessible to direct measurements *in vivo*, we developed an experimental technique to mimic the prosthetic circuit without using light. The proposed framework offers a powerful tool for optimizing the design of electro-neural interfaces in general, and predicts, among other useful metrics, the CIC under any stimulation waveform for any electrode material.



2. Methods

2.1. Circuit modeling

The circuit for neural stimulation generally consists of two parts: the circuit driver and the load, as shown in figure 1. The circuit driver is a controlled power source, while the load comprises an electrochemical cell and other power consuming circuit components. These two parts are connected at a port. The output current of the circuit driver is a function of time t , denoted by $I_D(t)$. Similarly, $I_L(t)$ represents the current flowing through the load, and $V(t)$ the voltage at the port. The polarities of I_D , I_L and V are defined as in figure 1. By Kirchhoff's laws, for all t , we have

$$I_D(t) = I_L(t). \quad (1)$$

The load is typically a lumped circuit, which we assume to be linear. By the Butler-Volmer model, an electrochemical cell can be linearized within a relatively small window of overpotential, and the non-linear Tafel behavior outside this window is associated with high rate of Faradaic reactions [29], which usually should be avoided in neural stimulation. Furthermore, electrochemical impedance spectroscopy (EIS) is only meaningful for electrode-electrolyte interfaces with linear circuit behavior, and as a result, most discrete-element circuits used to model neural electrodes assume linearity. The circuit driver, however, may have non-linear current-voltage ($i-v$) relationship, especially when neither the current nor the voltage output of the circuit driver is directly controlled. For example, for photovoltaic retinal prosthesis, only the light intensity projected onto the photodiodes is directly controlled, and the $i-v$ relationship of the photodiodes is exponential [24].

2.1.1. Directly controlled driver of current or voltage

For a circuit driven by controlled $I_D(t)$ or $V(t)$, we can calculate the steady-state response of the load to

periodic stimulus directly from the impedance spectrum. Let impedance $Z(\omega) : \mathbb{R} \mapsto \mathbb{C}$, as a function of frequency ω , be the impedance spectrum of the load, and $\mathcal{F}$ be the Fourier transform. I_D , equivalently, I_L , and V are related by

$$I_D = \mathcal{F}^{-1}[(\mathcal{F}V)/Z] = SV. \quad (2)$$

(2) is a linear transform from function V to function I_D , which we denote with the linear operator S . Since the impedance is typically nonzero and finite, S is invertible. Therefore, given a stimulus waveform $I_D(t)$ or $V(t)$, we can calculate the corresponding response of $V(t)$ or $I_L(t)$. [28] proposes a similar approach to study the responses of electrochemical cells in frequency domain, but this method still involves equivalent circuits to calculate the Laplace transform for transient behavior. Our approach avoids the complication of finding an equivalent circuit, and can also be applied to describe the transient behaviour in the non-periodic stimulus, as shown in section 2.1.3. Note that the DC impedance $Z(0)$ is not measured in the standard EIS, and can be determined separately via chronoamperometry or methods alike. However, in neural stimulation, charge should be balanced, and therefore the DC current should be zero.

2.1.2. Nonlinear circuit driver

When neither $I_D(t)$ nor $V(t)$ is directly controlled, we can rely on the $i-v$ relationship G of the driver at each time step:

$$I_D(t) = G(V(t), t). \quad (3)$$

To vary the current, the $i-v$ relationship of the circuit driver must change with time, and hence G is a function of both V and t , which may be non-linear, such as the $i-v$ curve of a photodiode illuminated by a pulsed laser. An example of such G is given in section 2.2.1. Knowing G , we can study the steady-state response following the principles of HB analysis - comparing the current responses of the linear and the non-linear parts of the circuit, and numerically minimizing the difference between the two responses [30, 31]. The solution is found if and only if the two responses match exactly, which is required by Kirchhoff's current law (KCL). Kirchhoff's voltage law (KVL) is hardwired in the definition of V .

Today, the Newton-Raphson method is the most common approach in HB analysis [30, 31] but its implementation requires proprietary software or custom coding. Since the HB problem can be formulated as an optimization, any optimization method can be used to match the responses. To demonstrate the ease of implementation, we use an off-the-shelf optimization tool in MATLAB to find the solution. Our demonstration code is available online at [32].

For any given $V(t)$, the nominal $\tilde{I}_L(t)$ is given by (2):

$$\tilde{I}_L = SV, \quad (4)$$

and the nominal $\tilde{I}_D(t)$ is given by (3). Note that $\tilde{I}_L(t)$ and $\tilde{I}_D(t)$ have no physical meanings, because generally $\tilde{I}_L(t) \neq \tilde{I}_D(t)$, which violates (1). We can define the difference between $\tilde{I}_L$ and $\tilde{I}_D$ as an operator acting on V :

$$QV := SV - G(V, t). \quad (5)$$

The true voltage response at the port, V^* , is obtained if and only if $\|QV^*\|^2 = 0$. We perform optimization on $\|QV\|^2$ to find V^* :

$$V^* = \arg \min_V \|QV\|^2. \quad (6)$$

We prove in the Appendix that $\min_V \|QV\|^2 = 0$ and the solution $V^*(t)$ is unique, if $G(V)$ is monotonically non-increasing. The monotonicity is a realistic premise, because higher voltage at the port counteracts the current output.

2.1.3. Transient behavior

HB analysis only provides the steady-state solution of circuits under periodic stimuli [30, 31]. However, the several initial pulses may show transient behavior uncaptured in the steady-state solution, especially when they are monophasic capacitor-coupled. For example, in [24], the initial pulses are not charge-balanced, and the response to them is quite different from the steady state.

The general approach to study the transient behavior of an electrode-electrolyte interface is using the Laplace transform without assuming periodicity, which involves finding its equivalent circuit [28]. Here, we convert the transient behavior into a virtually periodic one by padding the waveform with an additional discharging phase and a checking phase. To calculate the initial pulses between $t = 0$ and $t = T_0$, we insert a discharging phase of length $T_1 - T_0$ after T_0 and a checking phase of length $T_2 - T_1$ after T_1 , as illustrated in figure 2.

In the discharging phase, we keep $V(t)$ constant at the resting voltage V_0 of the load, and allow any amount of current to flow through the driver. In the checking phase, the circuit driver has the resting $i-v$ relationship $G_0(V)$ to verify the load has sufficiently discharged. The circuit driver is resting before the current injection begins, during which its $i-v$ relationship G does not change with time, and we define $G_0(V)$ as $G(V, t)$ before all stimulations. Hence, G_0 is a function of only V but not t . For the circuit driver, we have

$$\tilde{I}_D(t) = \begin{cases} G(V(t), t), & \text{if } 0 \leq t < T_0, \\ \tilde{I}_L(t), & \text{if } T_0 \leq t < T_1, \\ G_0(V(t)), & \text{if } T_1 \leq t < T_2. \end{cases} \quad (7)$$



Figure 2. Schematic diagram of the augmented period consisting of the initial pulses, the discharging phase and the checking phase.

For this scheme to work properly, $T_1 - T_0$ should be at least several times longer than the time constants of the electrode relaxation and charge redistribution calculated in [33]. To verify the efficacy of the discharging phase, the deviation of $V(t)$ from V_0 in the checking phase should be negligible compared to its average magnitude between 0 and T_0 :

$$\max_{t \in [T_1, T_2]} |V(t) - V_0| \ll \overline{|V(t) - V_0|}_{t \in [0, T_0]}. \quad (8)$$

2.2. Experimental validation

2.2.1. Circuit driver

The circuit of a photovoltaic retinal prosthesis described in [11] can be driven by shining light on photodiodes. However, quantitative analysis of such circuit requires precise measurement of the irradiant power on each photodiode and their light-to-current conversion. To simplify such experiments, we use a current source in parallel with the same photodiode in the dark, which exhibits an identical $i-v$ curve, and therefore allows driving the circuit in an equivalent way as using light.

By equation (1) of [24], I_D , the output current of the photodiode, equals the short-circuit photocurrent I_{photon} minus the forward current of the diode in dark under the output voltage V :

$$I_D(V) = I_{\text{photon}} - I_{\text{forward}}(V), \quad (9)$$

and $I_{\text{forward}}(V)$ can be approximated by the exponential relationship

$$I_{\text{forward}}(V) = I_0 \left(\exp \left(\frac{Ve}{nk_B T} \right) - 1 \right), \quad (10)$$

where I_0 is the scale current, e is the elementary charge, n is the diode ideality factor, k_B is the Boltzmann constant and T is the temperature. Note that we did not explicitly use (10) to calculate I_{forward} , but rather interpolate current from measured dark $i-v$ curve of the photodiode. The dataset of the $i-v$ curve is available at [32].

By (9), the current source and the shaded photodiode D_p combined in parallel are equivalent to the photodiode in light, as shown in the red dashed box in figure 3. The ON and OFF status of the current source correspond to turning the light on and off, respectively. Because of the limited precision of the current source, we cannot set the OFF current

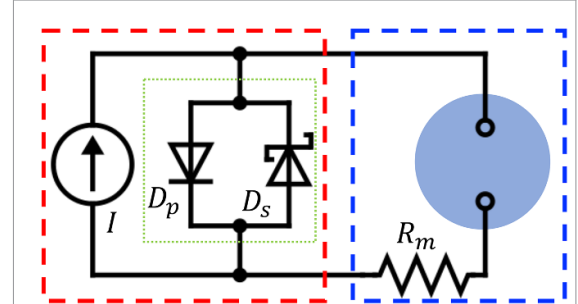


Figure 3. The circuit diagram of the experiment, consisting of the current source, the photodiode D_p , the Schottky diode D_s , the electrochemical cell (blue circle) and the monitor resistor R_m . The circuit driver and the load are noted by the red and the blue dashed boxes, respectively.

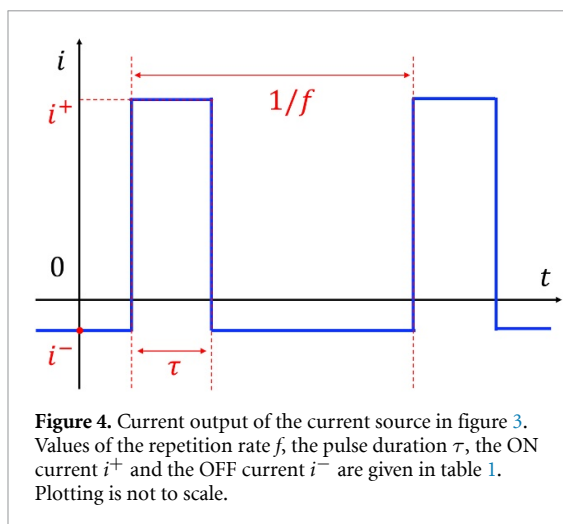
to be strictly zero between pulses. To prevent random drift of $V(t)$ due to charge accumulation, a Schottky diode D_s is connected in parallel with D_p in opposite polarity, and a negative current i^- that is much smaller in amplitude than the stimulating current i^+ is applied between pulses. In the resting state, $V \approx -0.1$ V, which is the turn-on voltage of D_s . The circuit is designed to function when $V \geq 0$, and D_s has no effect on the circuit in this range. We applied Stimulus 1 and Stimulus 2 to the current source, whose features are summarized in figure 4 and table 1. Together, the $i-v$ relationship of the circuit driver is given by

$$G(V, t) = \begin{cases} i^+ - I_{\text{forward},p}(V), & \text{for } t \text{ during pulses } (V \geq 0), \\ i^- - I_{\text{forward},p}(V), & \text{for } t \text{ between pulses and } V \geq 0, \\ i^- + I_{\text{forward},s}(-V), & \text{for } t \text{ between pulses and } V \leq 0. \end{cases} \quad (11)$$

$I_{\text{forward},p}(V)$ and $I_{\text{forward},s}(V)$ are the $i-v$ relationship of D_p and D_s , respectively.

2.2.2. Electrochemical cell

We use an electrochemical cell of the 2-electrode setup. The working and the counter electrodes are a pair of 80 μm -diameter platinum disks coated with 400 nm of SIROF, spaced 250 μm apart center-to-center on an insulating planar substrate. The electrolyte is a cell-culture medium made of 89% of DMEM/F12 base solution, 10% of fetal



bovine serum and 1% of Penicillin($10,000 \text{ U ml}^{-1}$)-Streptomycin(10 mg ml^{-1}) in volume. The experiment is conducted at 37°C . A resistor $R_m = 5.10 \text{ k}\Omega$ is connected in series with the electrochemical cell to monitor the current. The complete circuit is illustrated in figure 3.

To check linearity of the electrochemical cell, we first measured the impedance spectra at different voltage biases and with different perturbation amplitudes. The EIS was performed with a Gamry's Interface 1010 E potentiostat using the 2-electrode setup, with the working and counter electrodes being the pair of SIROF-coated disks mentioned above. Impedance was measured at 121 sampling frequencies (20 points per decade) between 0.1 Hz and 100 kHz. We then applied Stimulus 1 and Stimulus 2 and recorded the current (I_L) and the voltage (V) of the load. Next, we used HB analysis to calculate I_L and V directly from the impedance spectrum, and compare with the experimental measurements. For comparison, we also fit the discrete-element circuit models to the impedance spectrum and solve the corresponding differential equations for I_L and V in time domain.

3. Results

3.1. Validation of linearity by EIS

To validate that the electrochemical cell can be treated as a linear system, we performed EIS at 10 different voltage biases, evenly spaced by 0.1 V from -0.2 V to 0.7 V , with perturbation of 10 mV root-mean-square (RMS). We also measured the impedance spectrum at 0.3 V bias with 100 mV-RMS perturbation. All the spectra, plotted in figure 5(a), match each other very well, confirming linearity of the electrochemical cell. The DC impedance $Z(0)$ is determined to be $962 \text{ M}\Omega$ by chronoamperometry.

3.2. Discrete-element circuit models

A widely used equivalent circuit model of the electrode-electrolyte interface, the Randles circuit, typically includes the constant phase elements (CPEs)

Table 1. Parameters of the periodic waveform output by the current source. f , τ , i^+ and i^- are defined in figure 4.

	f (Hz)	τ (ms)	i^+ (μA)	i^- (nA)
Stimulus 1	2	50	2.679	-51.2
Stimulus 2	30	10	9.72	-255.7

Table 2. Fit values of the discrete components from the impedance spectrum.

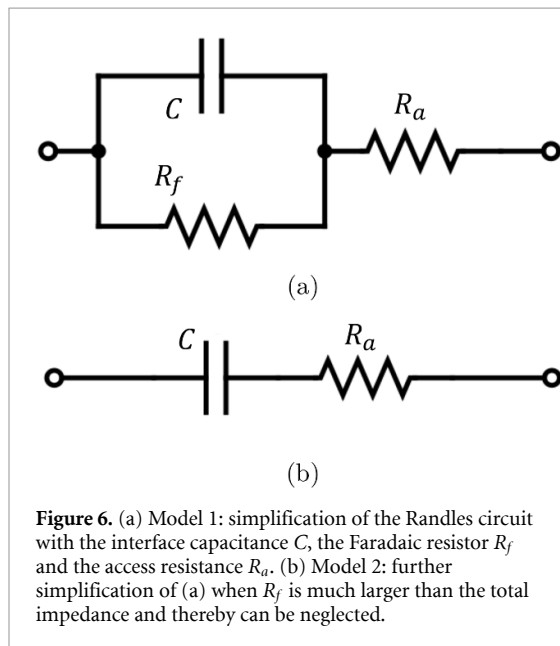
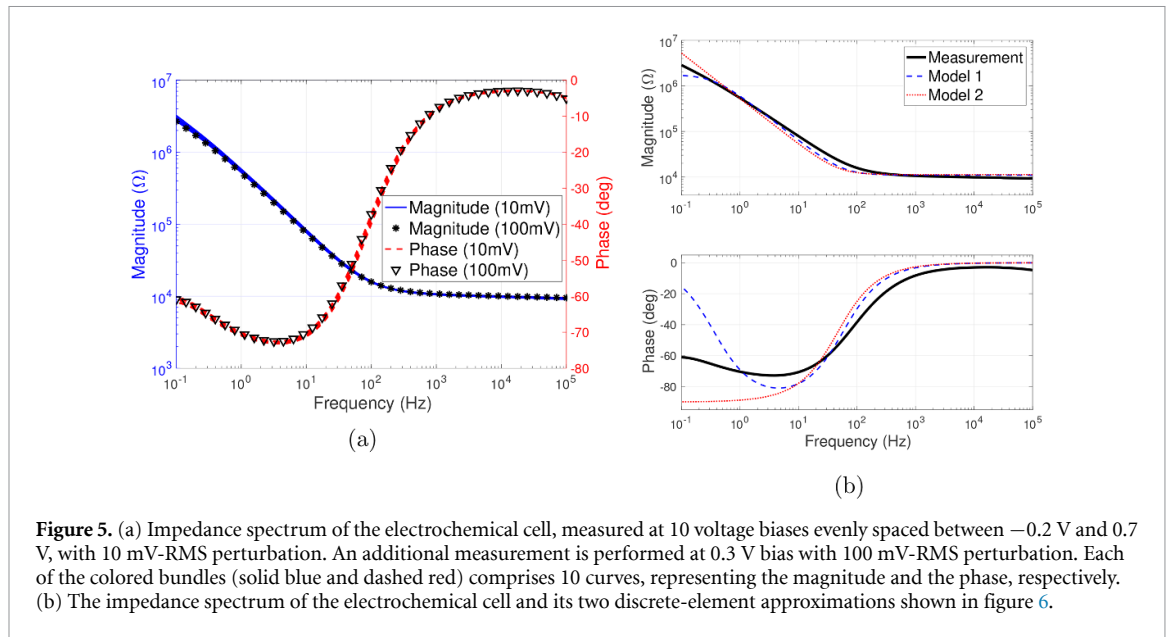
	R_a ($\text{k}\Omega$)	R_f ($\text{M}\Omega$)	C (nF)
Model 1	11.00	1.746	252.7
Model 2	11.30	$+\infty$	302.7

[29], the dynamics of which is given in frequency domain. However, since modeling involving a non-linear circuit driver is more convenient in time domain, a simplification of the Randles circuit, comprising only capacitors and resistors [24, 25, 34] is usually applied. Figure 6(a) shows one possible simplification consisting of the interface capacitor C , the Faradaic resistor R_f and the access resistor R_a (Model 1). Sometimes, R_f is neglected and the circuit further simplifies as illustrated in figure 6(b) (Model 2) [26]. Generally, we need two sets of lumped circuits to model the working and the counter electrodes, respectively. However, since we use symmetric working and counter electrodes, only one set of the circuit is needed in each model. We averaged all the 10 mV-RMS impedance spectra in figure 5(a), and fit the two circuit models to the mean spectrum using the method of least squares on the relative error, which is described in section 3.3.2.3 of [27]. The spectra of the fit circuits are plotted in figure 5(b), and the values of the discrete elements are shown in table 2.

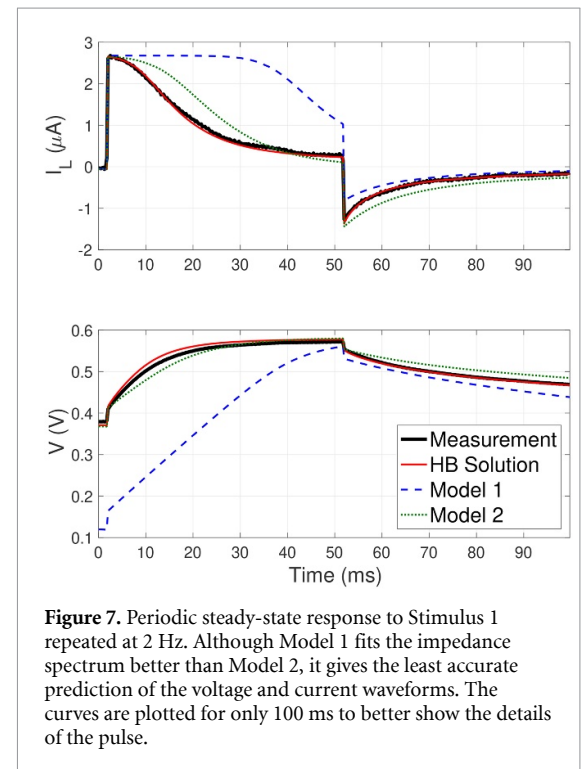
The periodic steady-state response to Stimulus 1 with Model 1 and Model 2 can be calculated by solving the differential equations in time domain using Mathematica 11. As shown in figure 7, the two models produce very different results. Since Model 2 is a special case of Model 1 where R_f is constrained at ∞ , Model 1 fits the impedance spectrum better than Model 2. However, the response calculated with Model 2 is more accurate than that with Model 1.

3.3. HB analysis for steady-state response to periodic stimulus

To find the steady-state circuit response to a periodic stimulus, we implement the optimization in (6) with the built-in non-linear least square solver (lsqnonlin) in MATLAB (R2017a). As shown in figure 7, the steady-state response to Stimulus 1 matches the experimental result better than both models in section 3.2. The response is calculated in 0.25 ms steps, yielding 2000 sampling points per period of 500 ms.



Stimulus 2 is repeated at a higher frequency of 30 Hz. Measurement and modeling were performed with another working electrode of the same geometry and material, whose impedance spectrum closely resembles that of the electrode used for Stimulus 1. We calculated the periodic steady-state response to Stimulus 2 in 50 μ s steps (666 sampling points per period of 33.3 ms). The optimization converges in eight iterations for both stimuli. Figure 8 depicts the final result plotted with the starting values of $V(t)$ and $I_L(t)$, and the two intermediate iterations of the optimization. For comparison, we also calculated the response of Model 1 to Stimulus 2 using the time-domain method in section 3.2, as shown in figure 8. The time-domain solution is significantly improved at higher stimulation frequencies (Stimulus 2, 30 Hz) compared with lower frequencies (Stimulus 1, 2 Hz),



because the impedance spectrum of Model 1 fits the EIS measurement better in frequency range higher than approximately 30 Hz, although the HB solution still matches the measurement better.

3.4. HB analysis for transient behavior

Following the scheme outlined in section 2.1.3, we model the first 115 ms of the response to Stimulus 2, which includes the four initial pulses. According to figure 5 in [33], the relaxation time for SIROF electrodes of the same geometry is around 10 ms. Therefore, we design the discharging and the checking

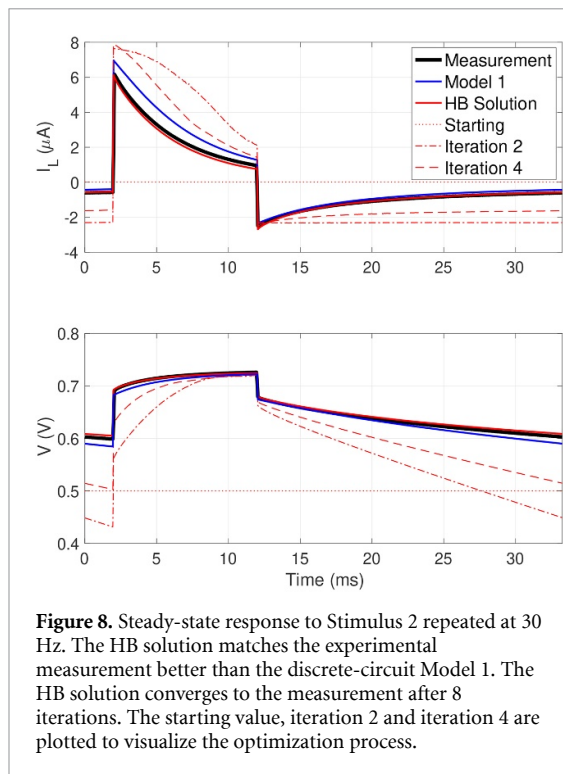


Figure 8. Steady-state response to Stimulus 2 repeated at 30 Hz. The HB solution matches the experimental measurement better than the discrete-circuit Model 1. The HB solution converges to the measurement after 8 iterations. The starting value, iteration 2 and iteration 4 are plotted to visualize the optimization process.

phases to be 60 ms and 15 ms, respectively. The transient response based on HB analysis, calculated in 50 μ s steps (3800 sampling points per augmented period of 190 ms) with convergence after 10 iterations, is plotted in figure 9, and it matches the experimental measurement well. The last pulse in this sequence is already fairly close to the periodic steady-state response to Stimulus 2, shown in figure 8.

4. Discussion

Successful design of electro-neural interfaces requires comprehensive understanding of the electrode response to given current or voltage stimuli. Only under the assumption that the electrode is ideally polarizable could the electrode-electrolyte interface be treated as a simple capacitor and CIC has a fixed value. In reality, an electrode material usually exhibits more complex impedance spectrum than what can be represented by a simple RC series. One reason for this complexity is that materials capable of storing large amount of charge usually have porous surfaces [20], and some even allow diffusion into the bulk of the electrode [27]. Dynamics of the charge transfer to distributed double layer or redox sites leads to a phase element characteristic of a transmission line in the impedance spectrum [12, 22, 27, 29], and therefore, the CIC becomes waveform-specific. Hence, a computational framework for proper modeling of the electrode-electrolyte interface is nontrivial and important.

One way to model the electrode response is by fitting a discrete-circuit model, comprising capacitors

and resistors, to the impedance spectrum, and solving the differential equations in time domain. However, we have demonstrated that the solutions are highly susceptible to small variations in the discrete-element approximations widely used in engineering of electro-neural interfaces. Figure 5(b) shows that both discrete-element models approximate the impedance spectrum well in most of the frequency range, except for the low-frequency end. Model 1 includes the Faradaic resistor to improve the fitting, but the self-discharge of the electrodes between pulses is overestimated as a result. Calculation of the response to Stimulus 1 repeated at 2 Hz with Model 1 shows much higher CIC than in reality. Model 2 does not capture the electrode discharge mechanism, but predicts the response better, even though it approximates the spectrum worse than Model 1. The effect of the Faradaic resistor is so prominent because the stimulation period is comparable to the RC time constant of the self-discharge loop (R_f and C). Although the specific discrete-circuit model predicts the response better with stimuli repeated at higher frequency (30 Hz), this itself illustrates the problem that a match between the discrete-element circuit model and experiment varies with the stimulus shape. With more resistors and capacitors, one can build models that better approximate the full spectrum using phasor analysis [35]. A more accurate approximation usually requires CPEs [12, 27–29], and there are established tools to generate discrete-element models for different physical processes that induce the CPEs, which typically takes 1 to 1.5 circuit lumps per frequency decade to yield a good fit [36]. However, rather than incrementally improving the accuracy of the approximation, a better approach is to directly apply the impedance spectrum without any approximations. Even though the equivalent circuit models are useful for mechanistic description of various processes in electrochemistry, they may not be the most efficient approach for electro-neural engineering.

Some electro-neural interfaces are driven by non-linear power sources, such as photodiodes [11] or phototransistors [15]. The proposed HB technique enables computational analysis of circuits with non-linear elements. By minimizing the difference between the responses of the linear load and the non-linear circuit driver, the true solution is found if and only if the difference vanishes. HB analysis is adopted because of the convenience to incorporate distributed components described in frequency domain [30]. We show that if the circuit driver has a non-increasing $i-v$ relationship, the optimization is guaranteed to converge to the unique true solution. Note that our separation of the circuit into the driver and the load is nominal, only for the convenience of discussion. If the load has non-linear components, it can be lumped with the non-linear part of the circuit driver to keep the nominal load linear.

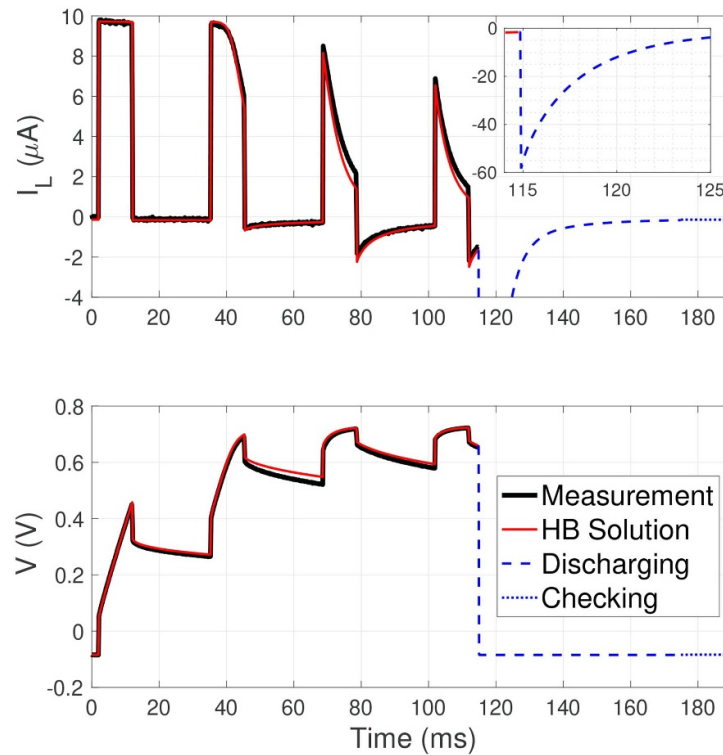


Figure 9. Transient response to Stimulus 2 in the first 115 ms, featuring the first four pulses. The discharging and the checking phases are 60 ms and 15 ms, respectively. The inset of the current (top) panel shows the spike in the discharging phase between 115 ms and 125 ms, which is truncated in the main plot.

The efficient optimization-based HB technique is enabled by advances in optimization research and the growing power of computers. Many optimization algorithms are shown to converge linearly (the distance to the solution decreases exponentially with the number of iterations, i.e. $\|\epsilon_{n+1}\| \leq \beta \|\epsilon_n\|$, where ϵ_n is the distance to the true solution after the n^{th} iteration and β is a constant such that $0 < \beta < 1$), some even quadratically ($\|\epsilon_{n+1}\| \leq \beta \|\epsilon_n\|^2$) [37]. Modeling the electro-electrolyte interfaces is a small-scale problem compared with typical applications of HB analysis in radio-frequency circuit design, so an off-the-shelf optimization tool can solve the system efficiently. The runtime of the optimization varies from a few seconds (Stimulus 2, 666 sampling points) to about a minute (the transient modeling, 3800 sampling points) on a laptop computer (3.1 GHz dual-core CPU, 8 GB of memory). We demonstrated the baseline capability of HB analysis using a simple implementation, and the computational efficiency can be further improved with more sophisticated algorithms. For example, modern HB software uses the Newton-Raphson method, which is a powerful algorithm for finding zeros of non-linear multivariate functions [31]. In addition, a variety of highly efficient algorithms are developed for convex optimization [38], although the specific optimization in (6) is not convex. The comparison of different numerical methods is beyond the scope of this paper.

Standard HB analysis can only be applied to periodic waveforms, i.e. it assumes a steady state when repetitive pulsing is applied [30, 31]. We adapted the HB technique to model the transient behavior in the beginning of a long burst of pulses by virtually augmenting the period with the discharging and the checking phases. This adaptation is possible when the electrode-electrolyte interface takes only several cycles before it reaches the steady state, as is the case of typical neural stimulation settings. We demonstrated that the computational workload of the optimization is manageable on a laptop computer, if the number of sampling points in a period is on the order of a few thousands. If the ramp-up would include hundreds or thousands of cycles, as in typical radio-frequency circuits, our adaptation would be computationally inefficient. It also would be inefficient if the pulse duration is very short compared to the period since most sampling points would fall in the inter-pulse intervals the details of which are not of particular interest. Similarly, our adaption is not applicable to the case when the discharge time of the electrode is much longer than the transient behavior.

We developed an experimental technique that enables testing the characteristics of photovoltaic electro-neural interfaces without using light. The observation that a current source and a shaded photodiode in parallel mimic the $i-v$ relationship of the illuminated photodiode greatly simplifies the experiments, which would otherwise require optical setup

with precise measurements of the irradiant power on the diode and the light-to-current conversion efficiency.

The framework we proposed requires the electrode-electrolyte interface to be linear within the relevant voltage range. Linearity is also the underlying premise of using EIS to characterize the electrode. We verified the linearity on SIROF electrodes by performing the EIS at different voltage biases (-0.2 V to 0.7 V) and different perturbation amplitudes (10 mV and 100 mV). To avoid excessive Faradaic reactions in neural stimulation, the electrochemical overpotential is usually limited to a relatively small range, where the electrode-electrolyte interface exhibits linear behavior.

For neural stimulation, even if electrodes are in close contact with tissue, vast majority of electric current flows through the extracellular medium between the electrode and the neurons rather than through the cell membrane, as evidenced by much lower seal resistance (≈ 50 M Ω) than the membrane resistance (≈ 20 G Ω) [39]. Therefore, changes in the cell membrane conductivity due to opening and closing of the voltage-gated ion channels are unlikely to significantly affect the tissue impedance. However, at the onset of stimulation, biological tissue may also respond by gradual changes of its impedance due to change in the metabolic activity, which may affect the osmotic balance, affecting cellular volume, shape and hence the tissue impedance. In extreme stimulation conditions, exceeding the safety limits, tissue might be damaged by electroporation or pH changes, and hence will change its impedance very significantly. Nevertheless, under safe chronic stimulation, tissue properties are expected to be stable and hence maintain linearity of the electrode-electrolyte interface.

In the future, this computational method could be extended to cover the case when the impedance spectrum is piece-wise linear, for example, corresponding to different Faradaic reactions within different voltage ranges.

5. Conclusions

We established a computational framework to study electro-neural interfaces and the associated electrical circuit dynamics. To model the steady state under periodic stimulus, we directly apply the impedance spectrum to the stimulus in frequency domain. If non-linear components are involved, we implement HB analysis using a rapidly converging optimization. By adding the discharging and the checking phases in a period, the HB technique is also adapted to study the transient behavior in the beginning of a burst of pulses. We demonstrate that the HB optimization is computationally tractable on a laptop computer, and guaranteed to converge to a unique solution if the circuit driver has a non-increasing $i-v$

relationship. Comparing the computational results to the experimental measurements, we show superiority of the HB method over the discrete-element circuit approximations.

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Appendix

Here we show the existence of a unique solution V^* to the optimization (6), such that

$$\|QV^*\|^2 = 0, \quad (A1)$$

if $\|QV\| \rightarrow +\infty$ when $\|V\| \rightarrow +\infty$, and $G(V, t)$ is monotonically non-increasing in V for all t .

Proof. First, we show the existence of such V^* , by proving

$$\min_V \|QV\|^2 = 0. \quad (A2)$$

Because $\|QV\| \rightarrow +\infty$ when $\|V\| \rightarrow +\infty$ and $\|QV\|^2 \geq 0$, $\|QV\|^2$ has a minimum. We now show that all extrema of $\|QV\|^2$ are 0. Suppose $\|QV\|^2$ is an extremum at V_0 . By the Karush-Kuhn-Tucker conditions,

$$\langle Q[V_0] | \delta Q \rangle = \langle Q[V_0] | \int \frac{\delta Q[V_0]}{\delta V}(t) \delta V(t) dt \rangle = 0 \quad (A3)$$

for any variational δV . By equation (5),

$$\int \frac{\delta Q[V_0]}{\delta V}(t) \delta V(t) dt = \left(\mathbf{s} - \frac{\partial G}{\partial V} \right) \delta V. \quad (A4)$$

Therefore, we have

$$\langle Q[V_0] | \left(\mathbf{s} - \frac{\partial G}{\partial V} \right) Q[V_0] \rangle = 0. \quad (A5)$$

The net power consumption of the load is positive, so by definition, for all $V \neq 0$, $\langle V | \mathbf{s} V \rangle > 0$. Because $\frac{\partial G}{\partial V}$ is non-positive, we also have:

$$\langle V | \left(\mathbf{s} - \frac{\partial G}{\partial V} \right) V \rangle > 0, \quad (A6)$$

for all $V \neq 0$, which implies

$$\mathbf{Q}[V_0] = 0. \quad (\text{A7})$$

Therefore, $\|\mathbf{Q}V\|^2$ has at least one minimum at V_0 , and all extrema of $\|\mathbf{Q}V\|^2$, including V_0 , are 0.

Next, we show the uniqueness of the minimum. We prove, by contradiction, a stronger claim that $\mathbf{Q}V$ is injective, from which the uniqueness directly results. Assume there exist V_1 and V_2 , such that $\mathbf{Q}[V_1] = \mathbf{Q}[V_2]$ but $V_1 \neq V_2$. We define a function $P: [0, 1] \mapsto \mathbb{R}$ by

$$P(x) := \langle V_1 - V_2 | \mathbf{Q}[xV_1 + (1-x)V_2] \rangle. \quad (\text{A8})$$

By (A6), we have:

$$\begin{aligned} P(1) - P(0) &= \int_0^1 P'(x) dx \\ &= \int_0^1 \langle V_1 - V_2 | \left(\mathbf{S} - \frac{\partial \mathbf{G}}{\partial V} \right) (V_1 - V_2) \rangle dx > 0. \end{aligned} \quad (\text{A9})$$

However, we also have

$$\begin{aligned} P(1) &= \langle V_1 - V_2 | \mathbf{Q}[V_1] \rangle \\ &= \langle V_1 - V_2 | \mathbf{Q}[V_2] \rangle = P(0), \end{aligned} \quad (\text{A10})$$

which is a contradiction, and it follows that $\mathbf{Q}V$ is injective. Therefore, $\|\mathbf{Q}V^*\|^2 = 0$ is the unique minimum of (6). $\square$

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Photovoltaic Restoration of Central Vision in Atrophic Age-Related Macular Degeneration

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Purpose: Loss of photoreceptors in atrophic age-related macular degeneration results in severe visual impairment, although some peripheral vision is retained. To restore central vision without compromising the residual peripheral field, we developed a wireless photovoltaic retinal implant (PRIMA; Pixium Vision, Paris, France) in which pixels convert images projected from video glasses using near-infrared light into electric current to stimulate the nearby inner retinal neurons.

Design: We carried out a first-in-human clinical trial to test the safety and efficacy of the prosthesis in patients with geographic atrophy (ClinicalTrials.gov identifier, NCT03333954).

Participants: Five patients with geographic atrophy zone of at least 3 optic disc diameters, no foveal light perception, and best-corrected visual acuity of 20/400 to 20/1000 in the worse-seeing study eye.

Methods: The 2-mm wide, 30- μ m thick chip, containing 378 pixels (each 100 μ m in diameter), was implanted subretinally in the area of atrophy (absolute scotoma).

Main Outcome Measures: Anatomic outcomes were assessed with fundus photography and OCT for up to 12 months of follow-up. Prosthetic vision was assessed by mapping light perception, bar orientation, letter recognition, and Landolt C acuity.

Results: In all patients, the prosthesis was implanted successfully under the macula, although in 2 patients, it was implanted in unintended locations: within the choroid and off center by 2 mm. All 5 patients could perceive white-yellow prosthetic visual patterns with adjustable brightness in the previous scotomata. The 3 with optimal placement of the implant demonstrated prosthetic acuity of 20/460 to 20/550, and the patient with the off-center implant demonstrated 20/800 acuity. Residual natural acuity did not decrease after implantation in any patient.

Conclusions: Implantation of the PRIMA did not decrease the residual natural acuity, and it restored visual sensitivity in the former scotoma in each of the 5 patients. In 3 patients with the proper placement of the chip, prosthetic visual acuity was only 10% to 30% less than the level expected from the pixel pitch (20/420). Therefore, the use of optical or electronic magnification in the glasses as well as smaller pixels in future implants may improve visual acuity even further. *Ophthalmology* 2020;127:1097-1104 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



Supplemental material available at www.aaojournal.org.

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss, affecting more than 8.7% of the population worldwide; the number of affected persons is projected to reach 196 million by 2020.¹ Advanced forms of AMD (neovascularization and geographic atrophy) are associated with severe visual impairment, and their prevalence dramatically increases with age: from 1.5% in the United States population older than 40 years to more than 15% in the population older than 80 years.²

Geographic atrophy, which occurs at an advanced stage of the disease, results in gradual loss of photoreceptors in the central macula (which is responsible for high-resolution vision) and severely impairs reading and face recognition. Low-resolution peripheral vision is retained in this condition, necessitating the use of eccentric fixation. Therefore, the goal of any treatment strategy should be to provide

functional central vision without jeopardizing the surrounding retina.

Although photoreceptors in retinal degeneration are lost, the inner retinal neurons survive to a large extent.³⁻⁵ Electronic retinal prostheses are designed to reintroduce visual information into the degenerate retina by electrical stimulation of the remaining neurons. Current strategies involve placing electrode arrays either subretinally, to stimulate the first layer of neurons above the photoreceptor cells (mainly bipolar cells in the inner nuclear layer⁶⁻⁸), or epiretinally, to target the retinal ganglion cells.^{9,10} The epiretinal implant (ARGUS II; Second Sight Inc, Sylmar, CA) currently approved for patients blinded by inherited retinal degeneration (retinitis pigmentosa [RP]) has 60 electrodes (200 μ m in diameter, 575 μ m pitch)¹¹ that are relatively distant (on average, approximately 180 μ m)

from the target retinal ganglion cells.¹² Patients using this system have been reported to have low visual acuity, of 20/1260 or worse.¹³ In addition to activation of proximal neurons, this implant stimulates the axons of remote retinal ganglion cells passing underneath the electrodes, causing distorted visual percepts.¹⁴

Preclinical studies in rodents demonstrated that stimulation of bipolar cells via subretinal implants results in a network-mediated retinal response that preserves many features of normal vision: flicker fusion at high frequencies (>20 Hz)^{15,16} and adaptation to static images,¹⁷ “on” and “off” responses to increments and decrements in light with antagonistic center-surround organization,¹⁸ and nonlinear summation of the inputs from bipolar cells into ganglion cells’ receptive fields (so-called subunits),¹⁶ essential for high spatial resolution.

A subretinal implant, the Alpha IMS/AMS (Retina Implant AG, Reutlingen, Germany), having up to 1600 pixels, each of 70 μm in width, was tested in patients blinded by RP. Of 44 trial participants, visual acuity using Landolt C was measurable in 6 patients, ranging from 20/2000 to 20/546 (2 patients).^{19,20} None of the trials’ participants achieved an acuity approaching the theoretical limit of resolution of the pixel array, approximately 20/280. This could be because of the monopolar design of this implant, in which active electrodes share a common remote return electrode, an arrangement that may result in strong so-called cross-talk between neighboring electrodes, and thus may limit spatial contrast.²¹ It is also possible that the highly remodeled retinal neural network in advanced stages of RP²² degrades the attainable prosthetic acuity in such patients.

Both of these implants are powered via a transscleral cable inserted in complex surgical procedures that is associated with postoperative complications^{13,19} that may affect residual peripheral vision, an especially important concern for patients with AMD.

We developed a wireless prosthesis in which photovoltaic pixels directly convert projected light patterns into local electric current.^{8,16} It is 2 mm in width (corresponding to approximately 7° of the visual angle in a human eye), 30 μm in thickness, with 378 pixels, each of which is 100 μm in diameter (PRIMA [Pixium Vision, Paris, France]; Fig 1). Images captured by the camera are processed and projected onto the retina from video glasses using near-infrared (880 nm) light to avoid photophobic and phototoxic effects of bright illumination.²³ Current flowing through the retina between the local active and return electrodes stimulates the nearby inner retinal neurons,⁸ which then pass the responses to ganglion cells, thereby harnessing some of the residual retinal signal processing.^{16,18,24} To avoid irreversible electrochemical reactions at the electrode–electrolyte interface, stimulation is charge balanced, and hence it is pulsed with alternating polarity.²⁵ For continuous perception under pulsed illumination, we apply sufficiently high frequencies to enable flicker fusion. Preclinical studies in rodents demonstrated retinal adaptation to frequencies exceeding 20 Hz under network-mediated stimulation.^{16,26} Localization of the electric field is achieved by providing active and return electrodes in each pixel.¹⁶ In preclinical testing in rodents, such photovoltaic arrays with

pixels of 75 μm and 55 μm in width provided grating visual acuity (alternating light and dark stripes) matching the pixel density.^{16,26} Preclinical testing of the PRIMA implants having 100- μm pixels in nonhuman primates demonstrated similar stimulation thresholds to those observed in rodents and perceptual responses (saccadic movement) down to a single pixel activation.²⁷

Methods

Patients

The aim of this first-in-human feasibility study of the PRIMA implant (ClinicalTrials.gov identifier, NCT03333954) was to test safety and functionality of this device in 5 patients with AMD. The study adhered to the tenets of the Declaration of Helsinki and received ethics committee approval from the Comité de Protection des Personnes Ile de France II and the Agence Nationale de Sécurité du Médicament et des Produits de Santé. Study participants were older than 60 years and had advanced dry AMD with an atrophic zone of at least 3 optic disc diameters and best-corrected visual acuity of 20/400 or worse in the worse-seeing study eye; no foveal light perception (absolute scotoma), but visual perception in the periphery, with preferred retinal locus determined by microperimetry; absence of photoreceptors and presence of the inner retina in the atrophic area as confirmed by OCT; and absence of choroidal neovascularization verified by retinal angiography. All other ocular and general pathologic features that could contribute to the low visual acuity were excluded. Patients provided written informed consent to participate in the study.

Surgery

Surgical procedures were performed in the Fondation Ophtalmologique A. de Rothschild (Paris, France) under local or general anesthesia. The study eye was prepared for surgery with antiseptic solution. Complete 23-gauge vitrectomy and removal of the posterior hyaloid was performed. The macula was detached with a subretinal injection of balanced salt solution via a 42-gauge needle inserted at a position away from the preferred retinal locus to avoid damage to the residual useful vision. A retinotomy (of approximately 2.5 mm) was performed at the margin of the atrophic area with vertical scissors, and if not totally detached by the balanced salt solution injection, the neural retina was dissected from the underlying atrophic pigment epithelium with a subretinal pick or spatula. A 2.4-mm sclerotomy then was created for intraocular implant delivery. The implant was inserted under the neural retina using silicone-coated forceps and placed near the target location under the retina. The implant then was guided to the desired central location by application of soft touch over the retina. Perfluorocarbon liquid was injected over the posterior pole to stabilize the implant and then removed via fluid-to-air exchange. Intraoperative OCT was used to verify retinal flattening, and the air was exchanged with a tamponade agent, either silicone oil or gas. In patients 1, 2, and 3, the air was exchanged with silicone oil (which was removed under local anesthesia 1 month later), and in patients 4 and 5, the air was exchanged with gas (hexafluoroethane and sulfur hexafluoride, respectively), and the 2.4-mm sclerotomy was closed.

After surgery, the patients were prescribed the usual postoperative topical treatment with a combination of dexamethasone and tobramycin eye drops 3 times daily for 4 weeks. Patients 4 and 5, who received an air–gas exchange, received 250 mg of acetazolamide 1 and 6 hours after surgery and assumed a prone position for 12 hours after surgery.

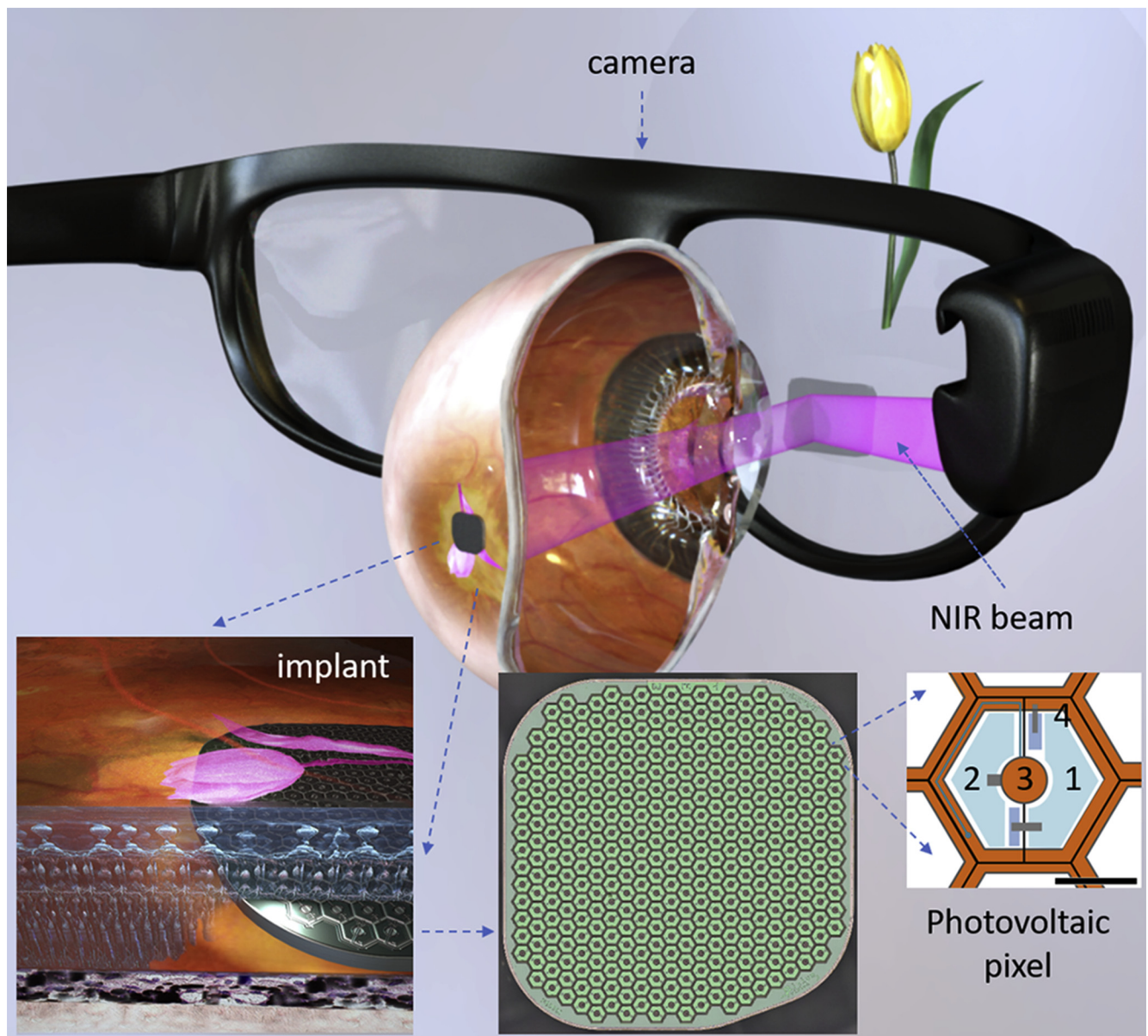


Figure 1. System diagram showing the photovoltaic retinal prosthesis, including the camera integrated into augmented reality–like video glasses, with the processed image projected onto the retina using pulsed near-infrared (NIR) light. Subretinal wireless photovoltaic array converts pulsed light into pulsed electric current in each pixel to stimulate the adjacent inner retinal neurons. Each pixel includes 2 diodes (1 and 2), connected in series between the active (3) and return (4) electrodes. Scale bar = 50 μm .

Assessment of Prosthetic Vision

The patients' rehabilitation and visual function assessment were carried out at the Clinical Investigation Center of Quinze-Vingts National Eye Hospital (Paris, France). To assess prosthetic vision independently of remaining natural vision, we made use of opaque video glasses with a Digital Mirror Display in front of the operated eye (Fig 2). The projected images cover a field of 5.1 mm (17°) on the retina, with resolution of 10.5 μm . Maximum peak retinal irradiance was 3 mW/mm^2 , well within the thermal safety limits for chronic use of near-infrared light.²⁸ Brightness of the percept was controlled by pulse duration of between 0.7 and 9.8 ms, in 0.7-ms steps. The glasses also included a miniature video camera, allowing patients to see a video stream of the visual scene

captured by the camera (Fig 2). Alternatively, the system can project computer-generated images into the eye. The camera captured a visual field of $50^\circ \times 40^\circ$, but only the central one third of the image was projected onto the retina to match the 17° field of view of the display. Thus, the angular magnification of the system was 1:1, that is, no optical or electronic zoom was used for acuity measurements or letter recognition.

Visual acuity was assessed using a computer-generated Landolt C chart in 4 different orientations (gap at the top, bottom, right, or left), so that a random response corresponds to 25% accuracy. The minimum optotype size was defined as the proper symbol recognition with at least 62.5% accuracy. To minimize the number of presentations, the study was conducted similarly to the Freiburg vision test.²⁹

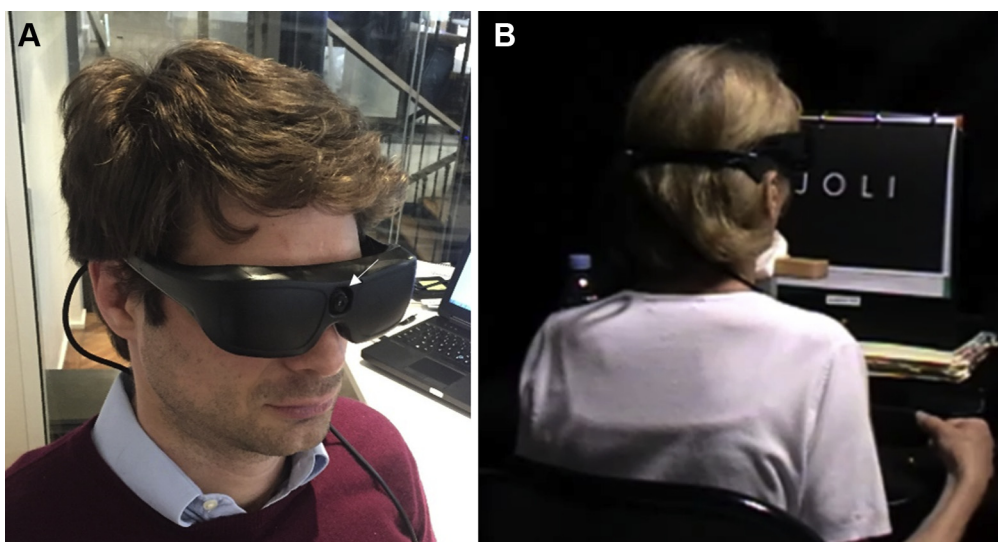


Figure 2. A, Photograph showing the opaque video glasses with an integrated camera (white arrow) used in the feasibility study. B, Photograph showing letter recognition and reading tests with one of the patients, using the camera mode.

For the letter recognition test, the alphabet was split into 3 groups of increasing difficulty, as applied previously in assessment of prosthetic vision:³⁰ set A comprised L, T, E, F, J, H, I, and U; set B comprised A, Z, Q, V, N, W, O, C, D, and M; and set C comprised K, R, G, X, B, Y, S, and P. The overall methodology of the test (forced-choice, closed-set, with 4 repetitions of each letter) also matched the previous study,³⁰ except that we used smaller letters of 2.8 cm at a distance of 30 cm.

Results

Following screening of the patient database at the Rothchild Foundation and Quinze-Vingts National Eye Hospital, those who met the inclusion criteria were invited to participate. The first patient was enrolled on November 13, 2017, and the last patient was enrolled on May 25, 2018. The 12-month examinations were completed on June 14, 2019.

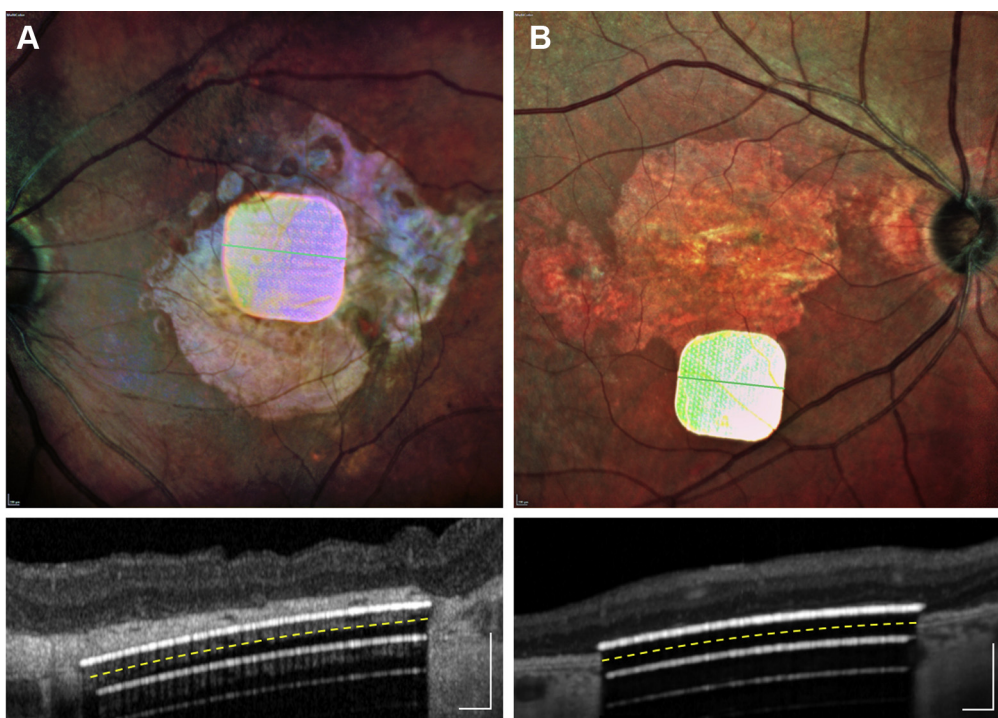


Figure 3. Fundus photographs and OCT images obtained along the green line, with 2 implants in unintended locations: (A) in the choroid in patient 1 and (B) in the periphery of the macula in patient 4. Yellow dashed line indicates the back side of the implant. White lines underneath the implant are the OCT reflections. Images were obtained during the 6-week to 6-month postoperative visits. Scale bars = 200 μ m.

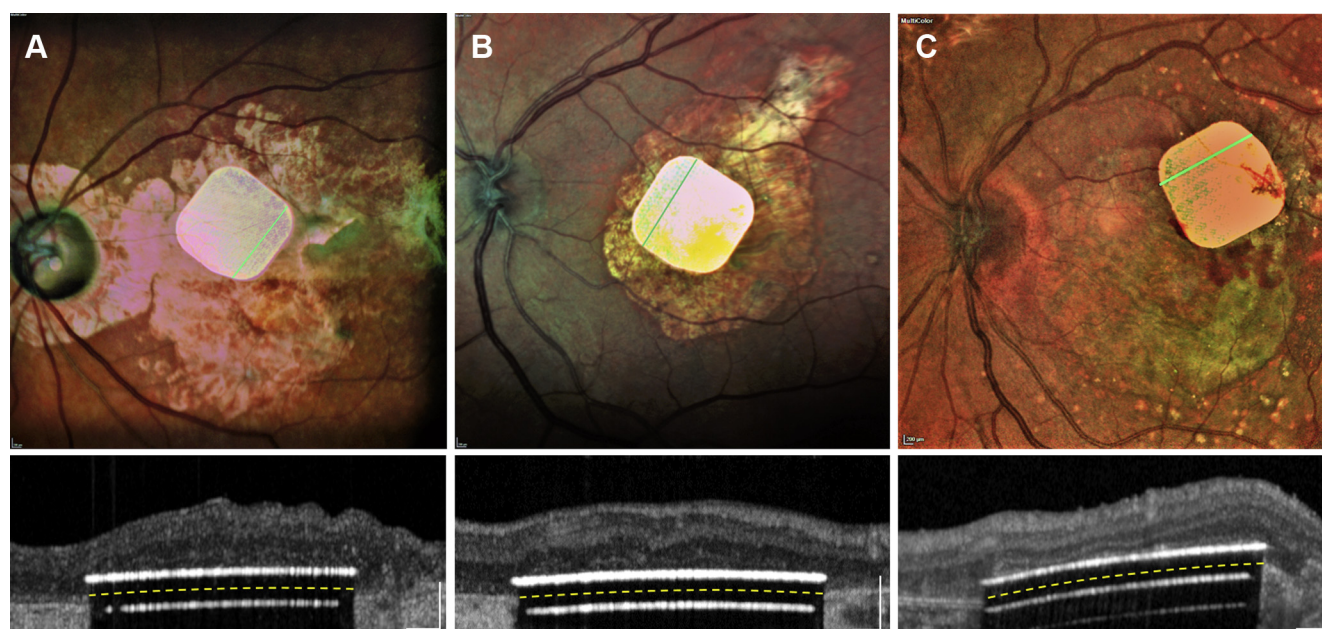


Figure 4. Fundus photographs and OCT images with 3 implants in intended locations: (A) patient 2, (B) patient 3, and (C) patient 5. Images were obtained during the 6-week to 6-month postoperative visits.

Surgical Placement of Implant

Patient 1, who underwent surgery under local anesthesia, moved when the implant was held by forceps under the retina, provoking inadvertent insertion of the chip into the choroid, accompanied by bleeding from the choroid that was evacuated partially during surgery. The blood resolved within 6 months, but an OCT image obtained at 6 months (Fig 3A) demonstrated that the chip was separated from the inner nuclear layer by a hyperreflective layer of approximately 70 μm in thickness. This layer could be a choroid, scar tissue that formed above the chip in response to choroidal injury, or both. For all other patients (patients 2–5), surgery was performed under general anesthesia.

In 2 other patients, focal subretinal bleeding occurred from the retinal vessels at the retinotomy site, remaining at a distance from the implant and resolving within a few weeks. One patient with a gas exchange (patient 4) moved his head from the prone position immediately after surgery, before the retina had fully re-adhered. As a result, the chip shifted by approximately 2 mm from its initial location in the center of the geographic atrophy area, although it remained in the scotoma (Fig 3B). The same patient did not take the prescribed medication (250 mg acetazolamide) after surgery, resulting in acute increase of intraocular pressure. This was treated successfully with intravenous acetazolamide, followed by β -blocker eyedrops for 1 week. In patients 2, 3, and 5, the implant remained stable, in a central location, and in close proximity to the inner retina (Fig 4). The mean surgical time for all 5 implantations was 2 hours and 4 minutes, ranging from 1 hour and 57 minutes to 2 hours and 10 minutes.

Over the 12 months after surgery, the implants remained in the same location under the retina. To assess the effect of separation between electrodes and neurons on visual acuity and stimulation threshold, we measured the average distance between the chip and the bottom of the inner nuclear layer in each patient at 3, 6, and 12 months after surgery (Table 1). In patients with subretinal placement of the implant (patients 2–5), the average distance between the inner nuclear layer and implant was 35 to 39 μm at 12 months.

Natural Vision

Residual natural visual acuity in the treated eye did not decrease in any patient during the follow-up period (Table 1). In fact, it improved slightly in patients 1, 3, 4, and 5. This could be either the result of neurotrophic benefit of the subretinal surgery or of the electrical stimulation,³¹ or a result of the vision rehabilitation training, which has the potential to improve preferred eccentric fixation.

Prosthetic Vision

In each patient, we first determined the perceptual threshold in terms of pulse duration using a 16-pixels-wide circular spot at a 10-Hz repetition rate, presented for up to 20 seconds at 3 mW/mm^2 irradiance (Table 1). Thresholds were determined with adaptive Best PEST (Parameter Estimation by Sequential Testing) procedure³² of 15 to 20 repetitions. A strength-duration curve also was measured in each patient, from which the chronaxie and rheobase were computed. All patients described the percepts as bright white-yellow phosphenes inside the scotoma. At maximum pulse duration (9.8 ms), each patient described the percept as being as bright as a desk reading lamp. When we increased pulse frequency from 3 to 10 Hz, all patients reported that percepts were more persistent. Flickering decreased further when the frequency was increased to 30 Hz and disappeared completely at 60 Hz. When tested in the dark, the patients sometimes could see the 880-nm radiation as a faint red light in the periphery. Therefore, during vision tests, all patients were asked about the color of percepts to ensure that only the white-yellow percepts were considered. Stimulation thresholds and perceptual brightness remained stable during the follow-up of the study.

In the visual field test (Octopus 900; Haag-Streit, Koniz, Switzerland) at 6 and 12 months, all 5 patients reported light perception in the atrophic zone, elicited by the implant when the system was turned on, and no perception when the system was turned off. At the 12-month test, patient 5 reported also sometimes

Table 1. Residual Natural Vision, Anatomic, and Functional Outcomes with the Implant

Test	Patient No.				
	1	2	3	4	5
Residual peripheral vision					
Preoperative eccentric natural acuity in the study eye	20/400 (1.3 logMAR)	20/800 (1.6 logMAR)	20/1000 (1.7 logMAR)	20/500 (1.4 logMAR)	20/500 (1.4 logMAR)
Postoperative eccentric natural acuity in the study eye (12 mos)	20/320 (1.2 logMAR)	20/800 (1.6 logMAR)	20/800 (1.6 logMAR)	20/400 (1.3 logMAR)	20/400 (1.3 logMAR)
Implant location					
Implant location in the macula	Intrachoroidal	Central subretinal	Central subretinal	Off-center subretinal	Central subretinal
Average distance from implant to bottom of INL (μm)					
3 mos	127	34	43	37	51
6 mos	103	28	35	38	39
12 mos	138	39	39	35	37
Perceptual stimulation thresholds					
Chronaxie (ms)	NA	2.5	2.3	2.2	2.1
Rheobase (mW/mm^2)	NA	1.0	0.4	1.4	0.5
Threshold pulse duration (ms) for 3 mW/mm^2	2.1	0.8	0.7	1.0	0.8
Central vision					
Natural central visual perception	None	None	None	None	None
Prosthetic bar orientation, % correct (95% CI)	28 (20–40)	96 (93–98)	96 (93–98)	94 (86–98)	88 (75–95)
Prosthetic minimum bar width on retina, pixels (% correct), (95% CI)	2 (90), (55–100)	1 (100), (69–100)	1 (70), (35–93)	1 (50), (19–82)	1 (80), (44–97)
Prosthetic central acuity	Light perception	20/550 (1.44 logMAR)	20/500 (1.4 logMAR)	20/800 (1.6 logMAR)	20/460 (1.37 logMAR)
Minimum Landolt C gap (pixels)		1.3	1.2	1.9	1.1

CI = confidence interval; INL = inner nuclear layer; logMAR = logarithm of the minimum angle of resolution.

experiencing a phantom visual perception not elicited by visual or electrical stimulation³³ when the device was turned off.

Tests with the computer-generated images defined the minimum width of a visible bar to be 1 pixel for patients 2 through 5, with the population average of identification of $75 \pm 20\%$ ($P = 0.002$; 95% confidence interval, 59%–87%), and 2 pixels for patient 1, with 90% identification ($P = 0.021$; 95% confidence interval, 55%–100%). In the forced-choice bar orientation test (vertical, horizontal, and 2 diagonals in opposing directions), patients 2, 3, 4, and 5 achieved $93.5 \pm 3.8\%$ accuracy. Patient 1, in whom the implant was placed in the choroid, identified the correct orientation with 28% accuracy, consistent with no improvement when using prosthetic vision (Table 1). Patients described the bars presented in various orientations as straight lines or elongated objects, demonstrating correct retinotopy of perception.

The 3 patients with optimal placement of the implant (patients 2, 3, and 5) demonstrated visual acuity with the Landolt C chart in the range of 20/460 to 20/550 (1.37–1.44 logarithm of the minimum angle of resolution) within 12 months, which is 10% to 30% less than the theoretical resolution limit (Nyquist sampling limit) for this pixel size (20/420, assuming 10° of the visual angle corresponds to 288 μm on the retina³⁴). Patient 4 demonstrated prosthetic acuity of 20/800 (1.6 logarithm of the minimum angle of resolution), whereas patient 1 could not resolve letters or optotypes of any size (Table 1). The population average prosthetic logarithm of the minimum angle of resolution acuity was 1.45 ± 0.10 , with the 95% confidence interval of 1.29 to 1.62, calculated based on t distribution.

We asked patient 2 to recognize letters of 2.8 cm in height positioned 30 cm away from the face. This patient identified group A letters with 88% accuracy and 8-second median

response time, group B letters with 80% accuracy and 7-second median response time, and group C letters with 75% accuracy and 11-second median response time. Letter recognition did not involve the head scanning, but rather, just the eye scanning of the image (Video 1, available at www.aaojournal.org). This patient was able to read words, as illustrated in the same video. As a control, when the system was turned off, the patient had no visual perception because the opaque glasses used in these tests blocked the residual natural vision (Video 2, available at www.aaojournal.org).

Discussion

The wireless nature of the PRIMA implant greatly simplifies the surgical procedures compared with the wired retinal prostheses. All the procedures in PRIMA surgery can be performed within 2 hours, as opposed to approximately 4 hours with the Argus II¹³ and 6 to 8 hours with the Alpha IMS.¹⁹ The most challenging part of the surgery is to separate the retina from retinal pigment epithelium–choroid in atrophic macula, which often requires not only subretinal injection of fluid, but also careful delamination with a spatula. Implant release from the forceps in the intended location under the retina also is not trivial. To simplify this step in the procedure, we developed an injector of the implant, which will be used in future trials. To avoid potential movement of patients in a wrong moment, as occurred with patient 1, we

recommend performing the surgery under general anesthesia, if possible, or to ask patients to keep steady at critical moments. Patient compliance regarding the prone head position after the gas exchange procedure is essential, because otherwise the implant can shift from the original location before complete retinal reattachment, as was seen with patient 4.

Spatial resolution in patterned retinal stimulation depends not only on the pixel size, but also on the distance between electrodes and target neurons.³⁵ Ideally, for localized and efficient stimulation, it should not exceed the pixel radius. In patients 2 through 5, the distance between the inner nuclear layer and the implant was approximately 35 to 39 μm , smaller than the 50- μm radius of the current pixels (Table 1). However, in patient 1, it exceeded 100 μm , which may explain the suboptimal performance of this patient.

From preclinical studies in rodents, we knew that many features of the retinal signal processing are preserved with subretinal prosthetics, such as flicker fusion at high frequencies,^{15,16} on and off responses with antagonistic center surround,¹⁸ and nonlinear summation of the inputs from bipolar cells into ganglion cells' receptive fields.¹⁶ However, we did not know what the actual human perception with such prosthesis would be. One of the most striking aspects of these clinical observations is that perception of prosthetic vision was remarkably natural, that is, as soon as patients learned how to use the video glasses, the prosthetic line patterns appeared in a correct shape right away, without scanning. Despite the likely indiscriminate electrical activation of multiple cell types in the inner retina (on and off, for example), our patients reported correct form perception of bright patterns (lines, letters, etc.) on a dark background. This may indicate that either the excitatory pathways dominate the perception, or that the brain filters out conflicting inputs and correctly interprets the images even when the signal encoding deviates from natural.

One reason for better and more consistent performance of the patients in the current trial compared with previous trials with a subretinal implant may be patient selection: AMD patients may have much better-preserved inner retina in the relatively small central scotoma than at the end stage of RP, associated with a long-lasting and nearly complete loss of photoreceptors in the entire retina. Animal studies of the retinal remodeling in inherited retinal degeneration indicate that massive retinal reorganization occurs only when nearly all the photoreceptors are gone,^{22,36} a situation that does not occur in AMD patients.

In summary, within the limits of a small study, we demonstrated that submacular implantation of a wireless photovoltaic array in patients with geographic atrophy is feasible, that the implant is stable over time, and that it did not decrease the eccentric natural acuity. All 4 patients with subretinal placement of the chip achieved letter acuity. In 3 patients with central chip placement, prosthetic acuity was only 10% to 30% less than the sampling limit for the current pixel size. The use of optical or electronic magnification in future glasses or implants with smaller pixels may improve the prosthetic visual acuity further. As the next step, we will test the transparent (augmented reality) glasses to allow simultaneous use of the prosthetic central and natural

peripheral vision, which should improve the benefit of the PRIMA system in daily living.

Acknowledgments

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AMD = age-related macular degeneration; RP = retinitis pigmentosa.

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Current Distribution on Capacitive Electrode-Electrolyte Interfaces

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The distribution of electric current on an electrode surface in an electrolyte varies with time due to charge accumulation at a capacitive interface, as well as due to the electrode kinetics and concentration polarization in the medium. Initially, the potential at the electrode-electrolyte interface is uniform, resulting in a nonuniform current distribution due to the uneven ohmic drop of the potential in the medium. Over time, however, the nonuniform current density causes a spatially varying rate of the charge accumulation at the interface, breaking down its equipotentiality. We develop an analytical model to describe such a transition at a capacitive interface when the current is below the mass-transfer limitation and demonstrate that the steady distribution of the current is achieved when the current density is proportional to the capacitance per unit area, which leads to a linear voltage ramp at the electrode. More specific results regarding the dynamics of this transition are provided for a disk electrode, along with an experimental validation of the theoretical result. These findings may be of importance for many electrochemical applications and, in particular, for proper design of the electroneural interfaces.

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I. INTRODUCTION

The dynamics of charge transfer across electrode-electrolyte interfaces is of great importance in electrochemistry in general and for many applications, including batteries, electroplating, electrolysis, chemical sensors and, in particular, bioelectronics. The distribution of current and voltage across such an interface is governed by multiple mechanisms, including the concentration polarization of the reactants in the medium, the kinetics of the electrode reactions, the ohmic drop in the bulk of the electrolyte, and charging of the electric double layer. The effects of the concentration polarization are modeled by the Warburg impedance, which is only significant at high current density, when the reactant concentration is considerably affected by the mass-transfer limitation [1,2]. The electrode kinetics is associated with faradaic electrochemical reactions and modeled by the charge-transfer resistance varying with voltage, which is considered linear at a lower current density according to the Butler-Volmer model [1,2]. The access resistance—the ohmic drop in the medium—is determined only by the electrode geometry and electrolyte conductivity. The electric double layer is modeled as a capacitance, where the Helmholtz plane in the electrolyte serves as the “plate” on the electrolyte side

of this capacitive interface [3]. The double-layer capacitance is typically on the order of $10\text{--}20\text{ }\mu\text{F}/\text{cm}^2$ for inert materials including carbon [4], platinum [5], and gold [6]. Additionally, some materials can exhibit a range of quasi-continuous oxidation states, enabling reversible storage of a much larger amount of charge than in a typical double-layer capacitance, and therefore known as pseudocapacitance [7–9]. Together, the double-layer capacitance and the pseudocapacitance are often called the supercapacitance [10].

Newman [11] calculated the primary current distribution at the interface of an equipotential (EP) disk electrode. It has been pointed out that both the electrode kinetics and the mass-transfer limitation result in secondary current distributions being more uniform than the primary one [12,13]. When the ohmic drop in the medium is the dominant part of the impedance, the calculation of the access resistance based on the EP boundary condition from Ref. [11] is broadly used [14–17]. The transient charge redistribution within the double layer on a disk electrode made of the same material has been described for controlled potential [18] and for controlled current [19], respectively. The frequency dispersion of such interfaces has been studied in Ref. [20].

However, there has been no theory describing the current distribution on electrodes of all geometries or with multiple surface materials. Such a theory is of interest in

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many electrochemical applications involving capacitive-coupling electrodes and especially for neural stimulation, where various geometries and materials are used in different applications. For neural-stimulation electrodes, the distribution of the electric current affects the stimulation thresholds and tissue safety and extra care should be taken to avoid irreversible electrochemical reactions. Therefore, materials of large charge storage capacity are often used to minimize the voltage swing and to ensure that the charge transfer is fully reversible, i.e., pseudocapacitive.

In this study we demonstrate, for any electrode geometry, that in the absence of the concentration polarization, the steady-state current distribution is achieved when the current density is proportional to the surface capacitance per unit area (PCD), where the boundary condition is not necessarily EP and the electrode potential converges to a linear ramp. For an electrode made of the same material, PCD implies a uniform current density (UCD). Initially, current begins to flow at a nonuniform density from the EP surface, but over time the uneven charge accumulation at the Helmholtz plane, as well as that in the pseudocapacitance, begins to affect the voltage drop across the double layer. Such uneven potential at the Helmholtz plane rearranges the electric field in the electrolyte and hence redistributes the current density, until the system reaches the PCD steady state.

Note that we model the possibly changing equilibrium potential of the associated electrochemical reactions by the pseudocapacitance, while Refs. [18,19] assumed constant reaction potentials. Therefore, in their notion, the steady state was resistive and unrelated to the surface capacitance. More recent studies [3,21] have assumed ideally polarizable disk electrodes—with no faradaic reactions—and have described the transition from the primary current distribution to the steady state using finite-element models, yielding only numerical solutions. However, without analytical description, fitting the numerical results to the RC approximations provides only a limited understanding of the transition, let alone that such finite-element models are usually intractable for an arbitrary electrode geometry. Nevertheless, the results have been widely adopted in practical applications [22–25].

The general model in this paper presents the transition from the initial current distribution to PCD for any electrode geometry and material composition, while considering the effects of the supercapacitance, the electrode kinetics, and the ohmic drop. We develop a framework to study capacitive interfaces with sinusoidal waveforms, chronoamperometry (controlled potential), or chronopotentiometry (controlled current), using the bra-ket notation. We demonstrate the application of this framework to a disk electrode, which agrees with the previous analytical results. We also demonstrate validation of some of these results experimentally.

II. THE SYSTEM MODEL

Typically, an equivalent-circuit model of the electrode-electrolyte interface with supercapacitance includes the double-layer capacitance C_d , the pseudocapacitance C_p , the faradaic leakage resistance R_f , the charge-transfer resistance R_{ct} , the Warburg impedance Z_w , and the access resistance R_a [1,26], as shown in Fig. 1(a). The complex Warburg impedance has a constant angle of $-\pi/4$, which is a result of the phase delay between the current and the concentration polarization, stemming from the diffusion of reactants. It is a special case of a constant phase element (CPE). In more complicated models, more than one CPE may be included, the detailed mechanisms of which often remain unclear [27].

We are interested in the conditions in which the current density is below the mass-transfer limitation and hence Z_w is insignificant. The limiting current density is given by Eq. (28) of Ref. [12] for a disk electrode. We also assume negligible faradaic leakage. The charge transfer across the interface in this case is governed by the distributed capacitance and the charge-transfer resistance at the interface and by the ohmic drop in the medium. Thereby, our circuit can be simplified to that shown in Fig. 1(b). The model studied in Ref. [3] is a special case when $C_p = 0$ and the one in Refs. [18] and [19] is when $C_p \rightarrow +\infty$.

For an extended electrode, the capacitance, the charge-transfer resistance, and the access resistance are

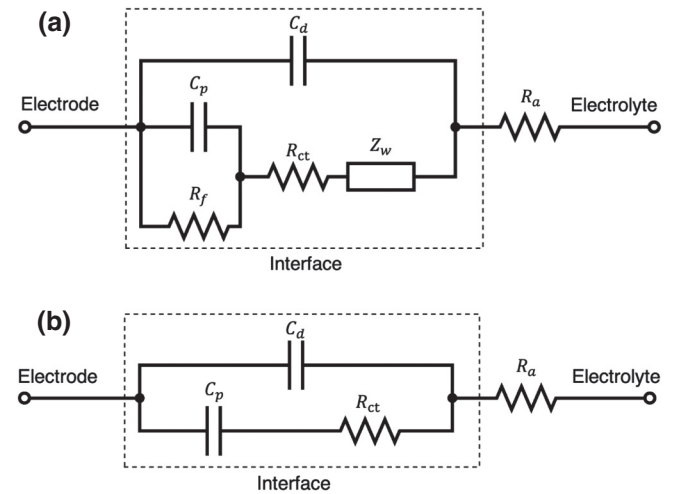


FIG. 1. Diagrams of the equivalent-circuit models of the electrode-electrolyte interface. The other electrodes of the electrochemical cell are omitted for simplicity. (a) A complete circuit model with pseudocapacitance includes the double-layer capacitor C_d , the pseudocapacitance C_p , the faradaic leakage resistance R_f , the charge-transfer resistance R_{ct} , the Warburg resistance Z_w , and the access resistance R_a . (b) When the contributions to the total impedance from R_f and Z_w are negligible, the circuit model can be simplified. To model an ideally polarizable electrode, let $C_p = 0$.

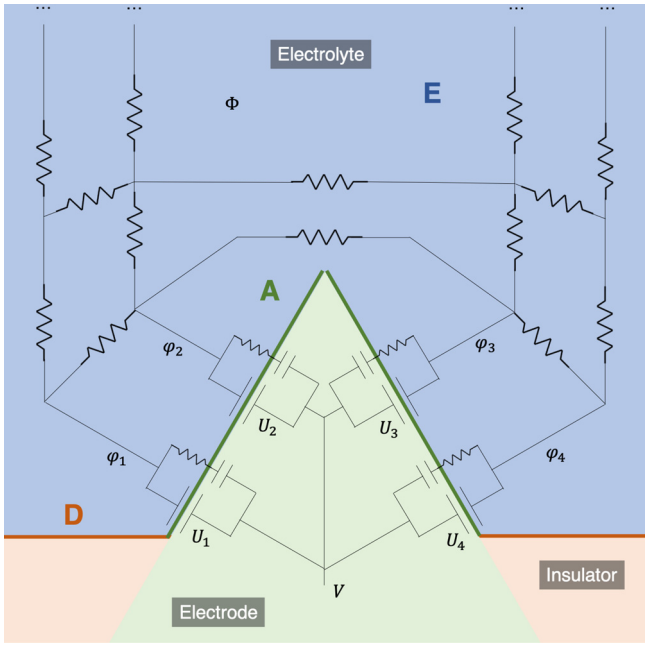


FIG. 2. A schematic illustration of the system, overlaid with the discretized version of the circuit diagram. The boundary of the electrolyte E consists of the insulating surface D and the electrode-electrolyte interface A . The electrode has the same potential V throughout its bulk but the potential drop U across the interface is generally a function of the location. Therefore, the potential in E just next to A is also a spatially varying function φ . Different locations at A have different access resistance to a return electrode at infinity.

distributed, as illustrated in Fig. 2. Each location on the interface is approximated by a discrete circuit in Fig. 1(b). Although illustrated with discrete components, our mathematical treatment makes no explicit discretization. Note that we only study half of the electrochemical cell, assuming that the current is collected on a large counter electrode infinitely far away.

In Fig. 2, E denotes the subset of the three-dimensional (3D) space occupied by the electrolyte. Its boundary with the electrode is denoted by A and has an insulating surface, denoted by D . $A \cup D = \partial E \subset E$. Let $\Phi(\mathbf{r}, t)$ denote the potential distribution in E as a function of both the spatial variable $\mathbf{r}$ and time t . We choose $\Phi(\infty) = 0$ and define φ as the two-dimensional restriction of Φ on A :

$$\varphi(\mathbf{r}, t) := \Phi(\mathbf{r}, t), \quad \mathbf{r} \in A. \quad (1)$$

The electrode is EP in its bulk, the potential of which as a function of time is denoted as $V(t)$. A nonuniform potential drop across the surface, which also varies with time, is denoted by $U(\mathbf{r}, t)$:

$$\varphi(\mathbf{r}, t) + U(\mathbf{r}, t) = V(t). \quad (2)$$

U is the voltage across C_d and we denote the potential drop across C_p by $U_p(\mathbf{r}, t)$. Let $C_p(\mathbf{r})$ and $C_d(\mathbf{r})$ be the pseudocapacitance and the double-layer capacitance per unit area on A , respectively. $R_{ct}(\mathbf{r})$ is the charge-transfer resistance times the unit area on A . Typically, the pseudocapacitance is much larger than the double-layer capacitance [10]. For an area in which no electrochemical reactions take place, we may set $C_d = 0$, $R_{ct} = 0$, and C_p the double-layer capacitance, so that $C_p(\mathbf{r}) \gg C_d(\mathbf{r})$ for $\forall \mathbf{r} \in A$.

In E , the current density is

$$\mathbf{i}(\mathbf{r}, t) := -\frac{1}{\rho} \nabla \Phi(\mathbf{r}, t), \quad (3)$$

where ρ is the resistivity of the electrolyte. On D , insulation implies zero normal current:

$$\mathbf{i}(\mathbf{r}) \cdot \mathbf{n}(\mathbf{r}) = 0, \quad \mathbf{r} \in D, \quad (4)$$

where the unitary $\mathbf{n}(\mathbf{r})$ is normal to the surface at $\mathbf{r}$ pointing to the electrolyte side. We choose the direction of $\mathbf{n}(\mathbf{r})$ as positive for current flow and define the normal current density on A :

$$i(\mathbf{r}, t) := \mathbf{i}(\mathbf{r}, t) \cdot \mathbf{n}(\mathbf{r}), \quad \mathbf{r} \in A. \quad (5)$$

Only the normal current component contributes to the charge accumulation on A . Conceptually, we may divide i into two components: the faradaic component i_a (the C_p - R_{ct} path) and i_b that charges the double layer (the C_d path). By definition,

$$i_a(\mathbf{r}, t) + i_b(\mathbf{r}, t) = i(\mathbf{r}, t). \quad (6)$$

i_a drives the voltage of the pseudocapacitance by

$$i_a(\mathbf{r}, t) = C_p(\mathbf{r}) \dot{U}_p(\mathbf{r}, t), \quad (7)$$

and, similarly, for i_b we have

$$i_b(\mathbf{r}, t) = C_d(\mathbf{r}) \dot{U}(\mathbf{r}, t). \quad (8)$$

The two current paths have the same potential drop:

$$R_{ct}(\mathbf{r}) i_a(\mathbf{r}, t) + U_p(\mathbf{r}, t) = U(\mathbf{r}, t). \quad (9)$$

The potential Φ satisfies the Laplace's equation:

$$\Delta \Phi = 0, \quad (10)$$

with the boundary conditions (1), (4), and $\Phi(\infty) \rightarrow 0$ as $\text{dist}(\mathbf{r}, A) \rightarrow +\infty$. Given the boundary condition φ , the potential Φ is fully determined and thus so is i . As Eq. (10) and all its boundary conditions are linear, there is a linear

mapping from φ to i , which we denote as a linear operator $\hat{\mathbf{S}}$:

$$\hat{\mathbf{S}}\varphi = i. \quad (11)$$

Because of the uniqueness of the electric field, $\hat{\mathbf{S}}$ is reversible. Define $\hat{\mathbf{R}}_a := \hat{\mathbf{S}}^{-1}$. Combine Eqs. (2), (6), (8), and (11), so that Eq. (6) gives

$$i_a = \hat{\mathbf{S}}\varphi - C_d(V' - \dot{\varphi}). \quad (12)$$

We take the derivative of Eq. (9) and use Eqs. (2) and (7):

$$R_{ct}\dot{i}_a + C_p^{-1}i_a = V' - \dot{\varphi}. \quad (13)$$

Combine Eqs. (12) and (13):

$$\begin{aligned} \hat{\mathbf{R}}_a R_{ct} C_p C_d \ddot{\varphi} + \left[\hat{\mathbf{R}}_a C_d + (\hat{\mathbf{R}}_a + R_{ct}) C_p \right] \dot{\varphi} + \varphi \\ = \hat{\mathbf{R}}_a R_{ct} C_p C_d V'' + \hat{\mathbf{R}}_a (C_d + C_p) V'. \end{aligned} \quad (14)$$

At the steady state of current distribution, by Eq. (11), φ no longer changes with time:

$$\ddot{\varphi} = \dot{\varphi} = 0. \quad (15)$$

Thus at steady state we have

$$i(\mathbf{r}) = \hat{\mathbf{S}}\varphi = R_{ct} C_p C_d V''(t) + (C_d + C_p) V'(t). \quad (16)$$

In Eq. (16), the left-hand side is time independent, implying that there is a constant v so that

$$R_{ct} \frac{C_p C_d}{C_d + C_p} V'' + V' = v. \quad (17)$$

Therefore, V' converges to v with time constant $R_{ct} C_p C_d / (C_d + C_p)$, which may vary in space. The “steady” steady state has $V'' = 0$ and yields

$$i(\mathbf{r}) = [C_d(\mathbf{r}) + C_p(\mathbf{r})] v. \quad (18)$$

Because v is constant in space, at steady state the (normal) current density on the electrode surface is proportional to the capacitance per unit area. Note that a capacitive interface requires $v \neq 0$ for nonzero steady states of current distribution.

By Eq. (14), the characteristic polynomial of the system is

$$p(x) = x^2 \hat{\mathbf{R}}_a R_{ct} C_p C_d + x \left[\hat{\mathbf{R}}_a C_d + (\hat{\mathbf{R}}_a + R_{ct}) C_p \right] + \hat{\mathbf{I}}, \quad (19)$$

where $\hat{\mathbf{I}}$ is the identity operator. As proven in Appendix A,

the operator $\hat{\mathbf{S}}$ is positive definite and so is $\hat{\mathbf{R}}_a$. R_{ct} and C_d are positive functions. Since $C_p \gg C_d$, the coefficient of the first-order term of Eq. (19) is dominated by C_p . Therefore, we may perturb the term $\hat{\mathbf{R}}_a C_d$ by its magnitude to make the system more tractable. We define a perturbation operator

$$\hat{\mathbf{P}} := -\hat{\mathbf{R}}_a (\hat{\mathbf{R}}_a + R_{ct})^{-1}, \quad (20)$$

the operator norm of which is bounded by 1. We perturb $p(x)$:

$$\tilde{p}(x) \approx \tilde{p}(x) := p(x) + x \hat{\mathbf{R}}_a C_d \hat{\mathbf{P}}. \quad (21)$$

Let $\hat{\mathbf{T}}_a = (\hat{\mathbf{R}}_a + R_{ct}) C_p$, and $\hat{\mathbf{T}}_b = \hat{\mathbf{R}}_a R_{ct} C_d (\hat{\mathbf{R}}_a + R_{ct})^{-1}$. We have

$$\tilde{p}(x) = (x \hat{\mathbf{T}}_b + \hat{\mathbf{I}}) (x \hat{\mathbf{T}}_a + \hat{\mathbf{I}}). \quad (22)$$

From Eq. (22), we know that the system has two sets of characteristic times, $\{\tau_a\}$ and $\{\tau_b\}$, corresponding to the eigenvalues of $\hat{\mathbf{T}}_a$ and $\hat{\mathbf{T}}_b$, respectively. Let $\{\Upsilon_a\}$ and $\{\Upsilon_b\}$ be the normalized (dimensionless) eigenfunctions of $\hat{\mathbf{T}}_a$ and $\hat{\mathbf{T}}_b^\dagger$, respectively. Each of the eigenfunctions corresponds to a eigenmode of φ , which is a potential distribution on A that elicits a current such that φ changes proportionally to itself. As mentioned, $\hat{\mathbf{R}}_a$ is positive definite, so $\{\tau_a\}$ and $\{\tau_b\}$ are positive. Furthermore, if the surface is uniform, namely R_{ct} , C_p and C_d are constant, $\hat{\mathbf{T}}_a$ and $\hat{\mathbf{T}}_b$ are positive definite, and thus the eigenmodes are orthogonal within each set. Because $C_p \gg C_d$, $\{\tau_a\}$ are much larger than $\{\tau_b\}$. Thus, $\max\{\tau_a\}$ is the dominant time constant and $\{\varphi_b\}$ decay much faster than $\{\varphi_a\}$. Different eigenmodes of the same operator have different time constants because of the shape of the eigenmodes. Intuitively, if a eigenmode oscillates more rapidly in space, more charge transfers across small distances, having lower resistance and hence happening faster. $\hat{\mathbf{T}}_a$ may also have very small eigenvalues close to 0 but the magnitudes of the corresponding eigenmodes are very small as well. This is because the eigenmodes, which rapidly oscillate in space, usually do not correlate with the shape of the total potential distribution. We will show an example of this in Sec. IV.

III. RESPONSES TO TYPICAL STIMULI

With the model developed in Sec. II, we study the system responses to three typical stimuli in electrochemical measurements: sinusoidal waveforms in Sec. III A, chronoamperometry (controlled potential method) in Sec. III B, and chronopotentiometry (controlled current

method) in Sec. III C. With the approximation of Eq. (21), Eq. (14) becomes

$$\begin{aligned} & (\hat{\mathbf{T}}_b \partial_t + \hat{\mathbf{I}}) (\hat{\mathbf{T}}_a \partial_t + \hat{\mathbf{I}}) \varphi \\ &= \left[(\hat{\mathbf{T}}_b \partial_t + \hat{\mathbf{I}}) (\hat{\mathbf{T}}_a \partial_t + \hat{\mathbf{I}}) - R_{ct} C_p \partial_t - \hat{\mathbf{I}} \right] V. \end{aligned} \quad (23)$$

A. Sinusoidal waveforms

A sinusoidal waveform is applied to the electrode: $V(t) = V_0 e^{j\omega t}$, where j is the imaginary unit. Use of the time-domain Fourier transform in Eq. (23) yields

$$\begin{aligned} \varphi &= (j\omega \hat{\mathbf{T}}_a + \hat{\mathbf{I}})^{-1} (j\omega \hat{\mathbf{T}}_b + \hat{\mathbf{I}})^{-1} \\ &\times \left[-\omega^2 \hat{\mathbf{T}}_b \hat{\mathbf{T}}_a + j\omega \hat{\mathbf{R}}_a (C_p + C_d) \right] V_0 e^{j\omega t}. \end{aligned} \quad (24)$$

It is not possible to solve Eq. (24) explicitly without assuming a specific electrode configuration but we can estimate the impedance,

$$\begin{aligned} \hat{\mathbf{Z}} &= V i^{-1} = \left[-\omega^2 \hat{\mathbf{T}}_b \hat{\mathbf{T}}_a + j\omega \hat{\mathbf{R}}_a (C_p + C_d) \right]^{-1} \\ &\times (j\omega \hat{\mathbf{T}}_b + \hat{\mathbf{I}}) (j\omega \hat{\mathbf{T}}_a + \hat{\mathbf{I}}) \hat{\mathbf{R}}_a, \end{aligned} \quad (25)$$

at the extremes of the frequency ω .

We now use $\|\cdot\|$ to denote the Hilbert-Schmidt norm. As explained in Sec. II, $\|\hat{\mathbf{T}}_a\| \gg \|\hat{\mathbf{T}}_b\|$. In order of magnitude, $\|\hat{\mathbf{R}}_a (C_p + C_d)\|$ is close to $\|\hat{\mathbf{T}}_a\|$.

When $\omega \|\hat{\mathbf{T}}_b\| \gg 1$, $\hat{\mathbf{Z}} \approx \hat{\mathbf{R}}_a$ and we have

$$\varphi = V, \quad (26a)$$

$$i = \hat{\mathbf{S}} V. \quad (26b)$$

We see from Eq. (26a) that at high frequencies the interface is equipotential and from Eq. (26b) that the current is changing in phase with voltage and the access resistance associated with the EP boundary condition is measured.

When $\omega \|\hat{\mathbf{T}}_a\| \ll 1$, $\hat{\mathbf{Z}} \approx [j\omega (C_p + C_d)]^{-1}$ and we have

$$\varphi = j\omega \hat{\mathbf{R}}_a (C_p + C_d) V, \quad (27a)$$

$$i = j\omega (C_p + C_d) V. \quad (27b)$$

We see from Eq. (27a) that at low frequencies, the interface is not equipotential and from Eq. (27b) that the current is shifted by 90° and is proportional to the total surface capacitance $C_p + C_d$.

Now, if $\omega \|\hat{\mathbf{T}}_a\| \gg 1$ but $\omega \|\hat{\mathbf{T}}_b\| \ll 1$, we have

$$\hat{\mathbf{Z}} \approx C_p^{-1} \hat{\mathbf{S}} (\hat{\mathbf{R}}_a + R_{ct}) C_p \hat{\mathbf{R}}_a. \quad (28)$$

Equation (28) is more intuitive when R_{ct} and C_p are uniform, which gives $\hat{\mathbf{Z}} = \hat{\mathbf{R}}_a + R_{ct}$. Similar to high frequencies, at middle frequencies, the boundary is equipotential and the current is in phase with the voltage. The impedance is the sum of the access resistance and the charge-transfer resistance.

B. Chronoamperometric response

To study the transient behavior, we focus on the eigenmodes with long characteristic times and assume that all eigenmodes of $\hat{\mathbf{T}}_b$ decay infinitely fast. Explicitly, we assume $\hat{\mathbf{T}}_b \partial_t + \hat{\mathbf{I}} \approx \hat{\mathbf{I}}$ and Eq. (23) becomes:

$$\hat{\mathbf{T}}_a \dot{\varphi} + \varphi = \hat{\mathbf{R}}_a C_p \dot{V}. \quad (29)$$

Without loss of generality, we assume that $U_p(\mathbf{r}, 0) = U(\mathbf{r}, 0) = 0$, and $V(t) = 0$ when $t \leq 0$. We take $V(t)$ of the form $V(t) = V_0 + vt$ for $t > 0$. Since $U_p(t)$ must be continuous, we have

$$(R_{ct} + \hat{\mathbf{R}}_a) i(\mathbf{r}, 0^+) = V(0^+). \quad (30)$$

At steady state, we have $\dot{\varphi} = 0$. Together, we have

$$\varphi(0^+, \mathbf{r}) = \hat{\mathbf{R}}_a i(\mathbf{r}, 0) = \hat{\mathbf{R}}_a (R_{ct} + \hat{\mathbf{R}}_a)^{-1} V_0, \quad (31a)$$

$$\varphi(\infty, \mathbf{r}) = \hat{\mathbf{R}}_a C_p(\mathbf{r}) v. \quad (31b)$$

Let $\Upsilon_{a,l}$ be the l th normalized eigenfunction of $\hat{\mathbf{T}}_a$, corresponding to the eigenvalue τ_l . We expand φ in the basis $\{\Upsilon_a\}$, with the coefficients $\{\varphi_l\}$. If C_p is uniform, $\{\Upsilon_a\}$ is orthonormal and the expansion is straightforward:

$$\varphi_l(t) = \langle \Upsilon_{a,l}(\mathbf{r}) | \varphi(\mathbf{r}, t) \rangle. \quad (32)$$

For the more general case when C_p is not uniform, we perform the Gram-Schmidt orthogonalization to $\{\Upsilon_a\}$ with a coefficient matrix $\mathbf{G}$:

$$\begin{bmatrix} \tilde{\Upsilon}_{a,1} \\ \tilde{\Upsilon}_{a,2} \\ \tilde{\Upsilon}_{a,3} \\ \vdots \end{bmatrix} = \mathbf{G} \begin{bmatrix} \Upsilon_{a,1} \\ \Upsilon_{a,2} \\ \Upsilon_{a,3} \\ \vdots \end{bmatrix} = \begin{bmatrix} 1 & & & \\ g_{21} & g_{22} & & \\ g_{31} & g_{32} & g_{33} & \\ \dots & \dots & \dots & \ddots \end{bmatrix} \begin{bmatrix} \Upsilon_{a,1} \\ \Upsilon_{a,2} \\ \Upsilon_{a,3} \\ \vdots \end{bmatrix}, \quad (33)$$

such that $\{\tilde{\Upsilon}_a\}$ is orthonormal. We have

$$\begin{bmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \\ \vdots \end{bmatrix} = \mathbf{G}^\top \begin{bmatrix} \langle \tilde{\Upsilon}_{a,1} | \varphi \rangle \\ \langle \tilde{\Upsilon}_{a,2} | \varphi \rangle \\ \langle \tilde{\Upsilon}_{a,3} | \varphi \rangle \\ \vdots \end{bmatrix}. \quad (34)$$

By the principle of superposition, we have

$$\begin{aligned} i(\mathbf{r}, t) &= \hat{\mathbf{S}}\varphi(\mathbf{r}, t) \\ &= C_p(\mathbf{r})v + \hat{\mathbf{S}} \sum_l (\varphi_l(0) - \varphi_l(\infty)) \Upsilon_l(\mathbf{r}) e^{-t/\tau_l}. \end{aligned} \quad (35)$$

The solution consists of a steady-state component $C_p(\mathbf{r})v$, which is PCD, and a transient component consisting of eigenmodes $\{\varphi_l \Upsilon_l(\mathbf{r})\}$ that exponentially decay at the rates τ_l . We call such transient behavior the EP-PCD transition (or EP-UCD when the interface material is uniform), the longest characteristic time of which corresponds to the largest eigenvalue of $\hat{\mathbf{T}}_a$:

$$\tau_{\max} = \lambda_{\max}(\hat{\mathbf{T}}_a). \quad (36)$$

C. Chronopotentiometric response

With controlled total current, Eq. (29) still holds but the solution is not the superposition of exponentially decaying eigenmodes, since $\dot{V}$ is no longer constant in time. Without loss of generality, we assume that $U_p(\mathbf{r}, 0) = U(\mathbf{r}, 0) = 0$ and the total current $I_{\text{tot}}(t) = 0$ when $t \leq 0$. We take $I_{\text{tot}}(t) = I_0$ for $t > 0$. Denote the current coefficient of the l th eigenmode by u_l :

$$u_l = \int_A \hat{\mathbf{S}} \Upsilon_{a,l} dS, \quad (37)$$

so that $\varphi_l u_l$ is the net current of $\varphi_l \Upsilon_{a,l}$. We expand $\hat{\mathbf{R}}_a C_p$ in basis $\{\Upsilon_a\}$ with coefficients $\{v_l\}$:

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ \vdots \end{bmatrix} = \mathbf{G}^\top \begin{bmatrix} \langle \tilde{\Upsilon}_{a,1} | \hat{\mathbf{R}}_a C_p \rangle \\ \langle \tilde{\Upsilon}_{a,2} | \hat{\mathbf{R}}_a C_p \rangle \\ \langle \tilde{\Upsilon}_{a,3} | \hat{\mathbf{R}}_a C_p \rangle \\ \vdots \end{bmatrix}, \quad (38)$$

so that $\dot{V} v_l$ is the $\Upsilon_{a,l}$ component of $\hat{\mathbf{R}}_a C_p \dot{V}$.

For the initial and the steady-state conditions, Eqs. (30) and (31) still hold. We combine Eqs. (31a) and (34) and

$V(0^+)$ is given by V_0 in

$$\begin{bmatrix} u_1 \\ u_2 \\ u_3 \\ \vdots \end{bmatrix}^\top \mathbf{G}^\top \begin{bmatrix} \langle \tilde{\Upsilon}_{a,1} | \hat{\mathbf{R}}_a (R_{\text{ct}} + \hat{\mathbf{R}}_a)^{-1} 1 \rangle \\ \langle \tilde{\Upsilon}_{a,2} | \hat{\mathbf{R}}_a (R_{\text{ct}} + \hat{\mathbf{R}}_a)^{-1} 1 \rangle \\ \langle \tilde{\Upsilon}_{a,3} | \hat{\mathbf{R}}_a (R_{\text{ct}} + \hat{\mathbf{R}}_a)^{-1} 1 \rangle \\ \vdots \end{bmatrix} V_0 = I_0. \quad (39)$$

We can thereby determine $\{\varphi_l(0^+)\}$.

The total current does not change, so we have

$$\sum_l \dot{\varphi}_l u_l = 0. \quad (40)$$

In basis $\{\Upsilon_a\}$, Eq. (29) becomes

$$\tau_l \dot{\varphi}_l \Upsilon_{a,l} + \varphi_l \Upsilon_{a,l} = \dot{V} v_l \Upsilon_{a,l}, \quad \forall l. \quad (41)$$

Let $\mathbf{y}$ be a vector of variables,

$$\mathbf{y}^\top = [V \ \varphi_1 \ \varphi_2 \ \varphi_3 \ \dots], \quad (42)$$

and let $\mathbf{\Gamma}$ be a matrix of coefficients,

$$\mathbf{\Gamma} = \begin{bmatrix} 0 & u_1 & u_2 & u_3 & \dots \\ v_1 & -\tau_1 & & & \\ v_2 & & -\tau_2 & & \\ v_3 & & & -\tau_3 & \\ \vdots & & & & \ddots \end{bmatrix}. \quad (43)$$

We combine Eqs. (40) and (41) and have

$$\mathbf{\Gamma} \dot{\mathbf{y}} = \begin{bmatrix} 0 & \\ & \mathbf{I} \end{bmatrix} \mathbf{y}. \quad (44)$$

$\mathbf{\Gamma}$ has full rank and solving for the transient behavior with controlled current becomes a standard problem of a homogeneous linear dynamic system, as in Eq. (44).

IV. SOLUTION FOR A DISK ELECTRODE

We now consider a disk electrode placed at the center of an insulating plane, with electrolyte filling the half-space above the plane. For simplicity of mathematical forms, from here on we assume uniform surface material, with constant R_{ct} , C_p , and C_d . The majority of the theoretical derivation has been done in Ref. [18], with the assumption of a constant electrochemical reaction potential ($C_p \rightarrow \infty$). As a demonstration of our more intuitive framework developed in Secs. II and III B, we apply it to this problem in Sec. IV A, and then compare the results with experimental measurements in Sec. IV B.

A. Theoretical derivation

We consider a disk electrode of radius a . As defined in Sec. II, R_p , C_p , and C_d are uniform. In Cartesian coordinates, we have $E = \{(x, y, z \geq 0)\}$, $A = \{(x, y, 0) : \sqrt{x^2 + y^2} \leq a\}$, and $D = \{(x, y, 0) : \sqrt{x^2 + y^2} > a\}$. Following Ref. [11], we will use the elliptic coordinate system (ξ, η) . The Laplace's equation in elliptic coordinates is

$$\Delta \Phi(\xi, \eta) = \partial_\xi [(1 + \xi^2) \partial_\xi \Phi] + \partial_\eta [(1 - \eta^2) \partial_\eta \Phi] = 0, \quad (45)$$

with the boundary conditions

$$\Phi(0, \eta) = \psi(\eta), \quad (46a)$$

$$\Phi(\infty, \eta) = 0, \quad (46b)$$

$$\left. \frac{\partial}{\partial z} \Phi(\xi, 0) \right|_{\xi > 0} = 0. \quad (46c)$$

We note that

$$\partial_z|_{r \leq a, z=0} = \frac{1}{a\eta} \partial_\xi, \quad (47a)$$

$$\partial_z|_{r > a, z=0} = \frac{1}{a} \partial_\eta. \quad (47b)$$

By Ref. [12], the solution to Eq. (45) is

$$\Phi(\xi, \eta) = \sum_{l=0}^{\infty} k_l X_l(\xi) P_{2l}(\eta), \quad (48)$$

where $l \in \mathbb{N}$, k_l are constant coefficients, P_{2l} is the $2l$ th Legendre polynomial of the first kind and $X_l(\xi)$ is the solution to

$$[(1 + \xi^2) X']' - 2l(2l + 1)X = 0. \quad (49)$$

We normalize P_{2l} , so that $\tilde{P}_{2l} := \sqrt{4l + 1} P_{2l}$ form an orthonormal basis of functions in $\{f \in C^\infty : [0, 1] \rightarrow \mathbb{R}, f'(0) = 0\}$. k_l in Eq. (48) are chosen so that $\Phi(0, \eta)$ matches a given $\varphi(\eta)$. With $X_l(0) = 1$, Eq. (48) becomes

$$\Phi(\xi, \eta) = \sum_{l=0}^{\infty} |\tilde{P}_{2l}\rangle X_l(\xi) \langle \tilde{P}_{2l} | \varphi \rangle. \quad (50)$$

By the definition of $\hat{\mathbf{S}}$ in Eq. (11),

$$\hat{\mathbf{S}}\varphi(\eta) = i(\eta) = -\frac{1}{\rho} \partial_z \Phi(0, \eta) \Big|_{r \leq a}. \quad (51)$$

By Eq. (47), we then have

$$\hat{\mathbf{S}} = -\frac{1}{\rho a \eta} \sum_{l=0}^{\infty} |\tilde{P}_{2l}\rangle X'_l(0) \langle \tilde{P}_{2l} |. \quad (52)$$

Equation [18] of Ref. [12] gives, without derivation, that

$$X'_l(0) = -\frac{2}{\pi} \left[\frac{(2l)!!}{(2l-1)!!} \right]^2. \quad (53)$$

A detailed derivation is provided in Sec. 6.9 of Ref. [28]. Appendix B provides the derivation in a more rigorous manner and proves the monotonicity of $X(\xi)$. Intuitively, this shows that potential distribution is monotonic along each hyperbolic line in the elliptic coordinates.

Therefore, the operator $\hat{\mathbf{S}}$ has the form

$$\hat{\mathbf{S}} = \frac{2}{\pi \rho a} \eta^{-1} \sum_{l=0}^{\infty} |\tilde{P}_{2l}\rangle \left[\frac{(2l)!!}{(2l-1)!!} \right]^2 \langle \tilde{P}_{2l} |. \quad (54)$$

Since R_{ct} and C_p are uniform, we now use these two notations as scalars. $\hat{\mathbf{T}}_a$ becomes

$$\hat{\mathbf{T}}_a = C_p (\hat{\mathbf{S}}^{-1} + R_{ct} \hat{\mathbf{I}}), \quad (55)$$

which shares the same eigenspace with $\hat{\mathbf{S}}$. We define a dimensionless operator

$$\hat{\mathbf{A}} := \eta^{-1} \sum_{l=0}^{\infty} |\tilde{P}_{2l}\rangle \left[\frac{(2l)!!}{(2l-1)!!} \right]^2 \langle \tilde{P}_{2l} |, \quad (56a)$$

so that $\hat{\mathbf{S}} = (2/\pi \rho a) \hat{\mathbf{A}}$. We have

$$\tau_a = \frac{\pi \rho a C_p}{2\lambda(\hat{\mathbf{A}})} + R_{ct} C_p. \quad (57)$$

As $|\eta| \leq 1$, the smallest eigenvalue of $\hat{\mathbf{A}}$ can then be estimated as $\lambda_{\min}(\hat{\mathbf{A}}) \geq 1$ and

$$\max\{\tau_a\} \leq \left(\frac{\pi \rho a}{2} + R_{ct} \right) C_p. \quad (58)$$

The numerically computed first four eigenfunctions of $\hat{\mathbf{A}}$, together with their respective eigenvalues, are shown in Fig. 3. It turns out that the smallest eigenvalue of $\hat{\mathbf{A}}$ is about 1.8, which gives

$$\max\{\tau_a\} = (0.864 \rho a + R_{ct}) C_p. \quad (59)$$

Note the similarity between Φ and the electrostatic potential of a charged disk. Specifically, if a flat disk in free space has charge density $\sigma(r) = 2\varepsilon_0 \rho i(r)$, then Φ is also the potential distribution around the charged disk. With UCD, the potential at the center of the disk electrode is

$$\varphi(r=0) = \int_0^a \frac{2\pi r \times 2\varepsilon_0 \rho i}{4\pi \varepsilon_0 r} dr = \rho a i. \quad (60)$$

Although the access resistance is not well defined with UCD, since the electrode surface is not equipotential, we

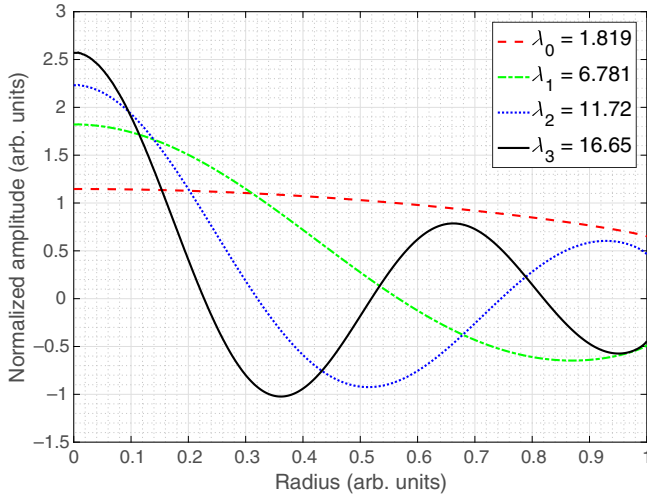


FIG. 3. The first four eigenfunctions and their respective eigenvalues of the operator $\hat{A}$, in the cylindrical coordinate r . Each eigenfunction, which is also an eigenmode of $\hat{T}_a$, evolves with a time constant determined by the corresponding eigenvalue of $\hat{T}_a$. The smallest eigenvalue of $\hat{A}$ is 1.819, corresponding to the largest time constant $(0.864\rho a + R_{ct})C_p$, dominates the overall transition.

can define an effective access resistance as the potential at the center of the electrode divided by the total current:

$$R_{a,\text{eff}} = \frac{\rho a i}{\pi a^2 i} = \frac{\rho}{\pi a}. \quad (61)$$

This value is higher than the widely accepted access resistance value $\rho/(4a)$ of an equipotential disk electrode [11]. There are different definitions of the effective access resistance. For example, [29] defines $R_{a,\text{eff}}$ as the average of φ divided by the total current. We choose our definition because the center of the electrode surface is the most typical point to sample when measuring potential in the electrolyte.

To illustrate the dynamics of the current redistribution in chronoamperometry, let ρ and νC_p , defined in Sec. III B, as well as the radius a , be unitary and let $R_{ct} = 0$. To keep the total current the same at the initial state and at the steady state, we will choose $V_0 = \pi\rho\eta Ca/4$. The resulting evolution of the current density and the potential distribution on a disk electrode over time are shown in Fig. 4 and also as a video in the Supplemental Material [31].

B. Experimental validation

To experimentally verify whether the dynamics of the total current on a capacitive electrode-electrolyte interface matches the solution described by Eq. (35), we perform chronoamperometric measurements. From here on, all potentials are referred to the Ag-AgCl electrode, unless noted otherwise. In order to sustain higher current within the relatively small voltage window, we use

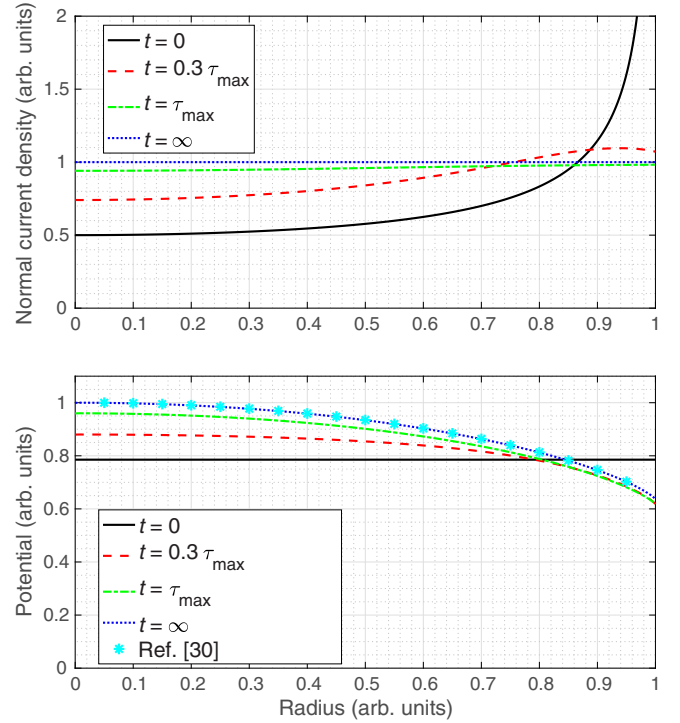


FIG. 4. Top panel: the current density on a disk electrode at four different time points. Here, τ_{max} is the time constant of the slowest decaying eigenmode, $0.864\rho a C_p$. Bottom panel: the electric potential on a disk electrode at the same time points as in the top panel. The cyan asterisks are the analytical solution to the electrostatic potential of a uniformly charged disk given by Ref. [30], which is mathematically equivalent to the potential distribution under the UCD boundary condition.

an electrode coated with a sputtered iridium oxide film (SIROF)—a material known for its large charge-injection capacity (CIC) [32]. The continuous iridium valency of SIROF between 0 and 0.8 V [33], together with its porous surface [34], enables a large capacitance.

We use an electrochemical cell of the three-electrode configuration. The working electrode is an 80- μm -diameter platinum disk coated with 400 nm of SIROF. The electrode is treated with 4% NaClO solution and plasma cleaning, following the protocol of Ref. [35] (Secs. 2.15 and 3.3). A large ($>1\text{ cm}^2$) platinum grid is used as the counter electrode. The reference is an Ag-AgCl electrode in 3M KCl solution. The electrolyte is six-time-diluted phosphate-buffered saline (PBS) solution, the resistivity of which is 353 $\Omega\text{ cm}$, measured with an electrical-conductivity meter.

First, we validate that the electrode kinetics are invariant within the potential range and that concentration polarization is not the dominating factor in the electrode impedance. As shown in Fig. 5, the black solid line in the top panel represents a voltage step. The corresponding total current is shown by the black solid line of the

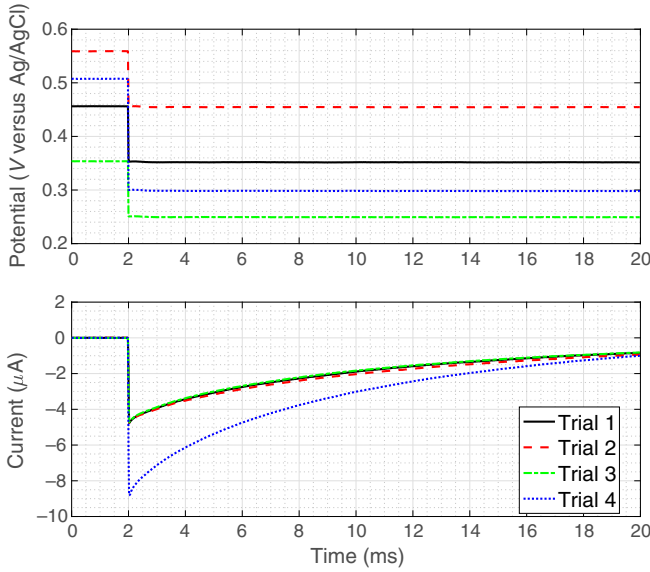


FIG. 5. Validation that the electrode kinetics is invariant within the potential range and that the concentration polarization is negligible at the selected settings. A curve in the top panel and the curve of the same style in the bottom panel represent the voltage and current measured, respectively. Trial 1 is the baseline. Trials 2 and 3 show that the electrode kinetics is varying with the potential, while trial 4 shows linear scaling with the amplitude of the voltage step, indicating that the concentration polarization has no effect on the circuit.

bottom panel (trial 1). To show that the electrode kinetics is not varying with potential, we offset the voltage pulse up and down by 100 mV (trials 2 and 3) and observe that the current does not change. To check whether the concentration polarization affects the current amplitude, we scale the voltage pulse by a factor of 2. The current nearly doubles as well, indicating that the concentration polarization is negligible, since the concentration overpotential does not scale linearly with the current density.

We observe very small charge-transfer resistance on this electrode, which allows us to neglect the effect of R_{ct} and combine C_p and C_d into one supercapacitance, C_s . To confirm this, we perform electrochemical impedance spectroscopy (EIS) and use the Levenberg-Marquardt method to fit the Bode plot to the circuit diagram in Fig. 6(a). The measurement and the fitting curves are plotted in Fig. 6(b). From the fitting, $R_{ct} + R_a = 22.3 \text{ k}\Omega$, within the 2% error range of the EP access resistance predicted by $\rho/(4a) = 22.0 \text{ k}\Omega$. Per the discussion in Sec. III A, we confirm that R_{ct} is negligible. We also find that $C_s = 8.52 \text{ mF/cm}^2$ from the fitting.

A voltage waveform including a step and a ramp, with $V_0 = -100 \text{ mV}$ and $v = -3.24 \text{ V/s}$, as defined in Sec. III B, is applied to the SIROF electrode (top panel in Fig. 4). Note that this waveform is different from the one used in Fig. 4 and hence the total current at the initial

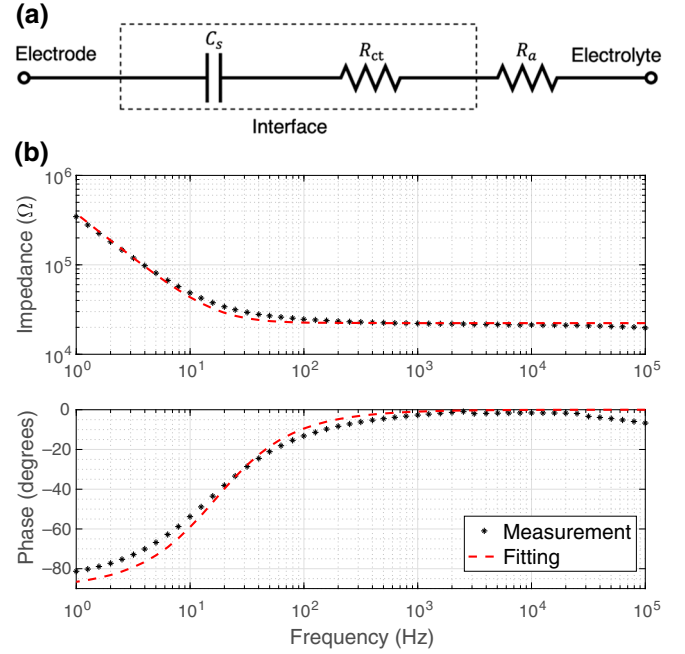


FIG. 6. (a) The circuit diagram of the fitting model. (b) The EIS Bode plot of the 80- μm -diameter SIROF disk electrode.

and the steady states is not the same either. The resulting current waveform is shown in the same panel.

One competing theory is that the surface instantly exchanges charge laterally, so the charge accumulation in the capacitor is uniform and the interface is always EP. This is the assumption behind the RC fitting in Refs. [3], [17], and [21]. To compare the experimental results with the predictions of the constant-EP theory and of the EP-UCD transition, the time derivative of the total current is calculated and plotted for both models and the measurement. The EP-UCD prediction is from Eq. (35), while the constant-EP prediction is a simple RC process. As can be seen in the bottom panel of Fig. 7, the measurement matches our theory rather than the constant-EP assumption.

V. DISCUSSION

A highly conductive electrode is always equipotential in its bulk but this equipotentiality is often confused with the surface layer of electrolyte at the interface, which is the boundary typically modeled as the Helmholtz plane. Electrode kinetics and concentration polarization are the two mechanisms previously considered to cause uniform secondary current distribution. Another important mechanism is the charge accumulation on the interface, which is often underappreciated in applications since it is not reflected in the initial current distribution. Previously, this effect has only been modeled for disk electrodes of uniform surfaces, assuming constant reaction potentials [18,19] or no electrochemical reactions [3,21].

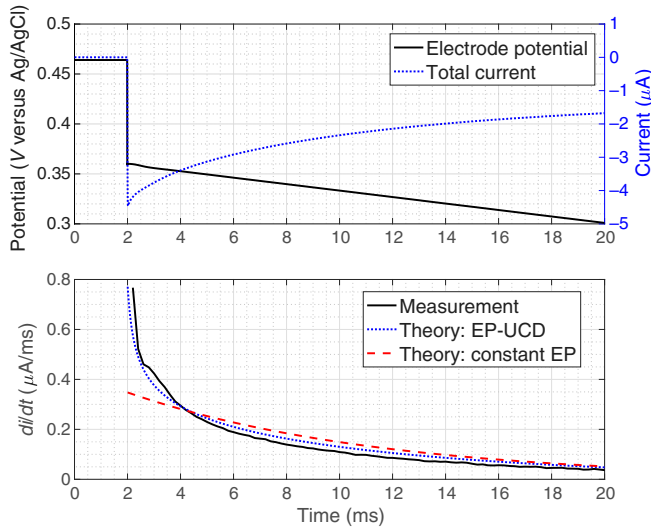


FIG. 7. Top panel: the voltage waveform applied to the SIROF electrode and the measured current. Bottom panel: the time derivative of the current from the measurement and the theoretical predictions calculated with two different theories: EP-UCD transition and constant EP.

As we show in Sec. II, for any geometry and any combination of surface materials, the current density eventually reaches the PCD steady state (or a UCD if the capacitance per unit area is the same over the whole electrode). Redistribution of the current from the initial nonuniform spread at an equipotential state is driven by the uneven charge accumulation at the capacitive interface until it reaches the PCD, when the potential of all parts of the interface rises at the same rate. This transition is described by the superposition of exponentially decaying eigenmodes, each of which has a different time constant. Each eigenmode is a surface potential distribution that elicits the circuit response to change itself proportionally. The shorter the time constant is, the faster the eigenmode decays. For a disk electrode of radius a and with uniform surface capacitance C , the dominant (longest) time constant is $0.864\rho Ca$, only 10% larger than the simple RC time constant $\tau_{EP} = \pi\rho Ca/4 = 0.785\rho Ca$, where the EP access resistance $R_{EP} = \rho/(4a)$ is assumed. In earlier finite-element modeling [3], the total current was fitted to one simple RC process, resulting in an 8.7% increment of the time constant compared to τ_{EP} , which roughly matches our result. Strictly speaking, there are two sets of eigenmodes and time constants, dominated by the pseudocapacitance C_p and the double-layer capacitance C_d , respectively. However, since the latter is faster than the former, when studying the transient behavior, we consider the latter to be instant, with a negligible effect on the circuit behavior. This requires $C_p \gg C_d$ everywhere, which may not be true if a surface consists of both electrochemically active parts and inert parts, but we can avoid this subtlety by choosing, nominally, $C_d = 0$,

$R_{ct} = 0$, and C_p , the double-layer capacitance. Empirically, the inverse time constants of different eigenmodes are separated almost evenly, which is equivalent to an asymptotic approximation conjectured by Troesch and Troesch [36] in a solution of a problem in fluid dynamics and confirmed computationally up to the 200th time constant [28].

It is important to note that the measurements of the access resistance using EIS correspond to the high end of the frequency range. At frequencies exceeding the inverse time constants of the current redistribution, the interface remains practically equipotential. Therefore, the access resistance measured in EIS is associated with the EP boundary condition. In the middle of the frequency range, we should see the sum of the EP access resistance and the charge transfer resistance, if C_p and C_d are separated sufficiently far apart.

Under the constant-EP boundary condition, the current in response to a voltage step with a ramp is a simple exponential decay to the steady state, with a RC time constant. Distinguishing this curve from a plot corresponding to our theory is not easy, since the dominant time constant is only slightly longer than in the constant-EP theory and the magnitude of the slowest eigenmode is the largest. Therefore, the bottom panel in Fig. 7 compares the time derivative of the total current. Since the constant-EP theory has only one decaying mode, while the EP-UCD transition has infinitely many and much faster decaying eigenmodes, the total current decreases faster at the beginning of the pulse, as can be seen in the plot.

At steady state, the PCD boundary condition enables control of the current distribution on various parts of the interface by selecting electrode materials of different capacitance per unit area. For example, if a part of the Au electrode is coated with SIROF and the pulse duration exceeds the characteristic EP-PCD transition time, the current will flow primarily through the SIROF area, while the Au surface will be practically passive, since its capacitance is about 1000 times smaller than that of SIROF. This effect was discovered in Ref. [37] but only analyzed using a discrete-circuit approximation. The phenomenon of PCD greatly simplifies the 3D electrode fabrication by electroplating: the side walls of the Au-electroplated electrode do not have to be coated with an insulator. They can remain exposed to the liquid since the SIROF on top of these walls will collect the vast majority of the current [38–40]. Similarly, the leads to high-capacitance electrodes—for example, the electrodes used in Ref. [41]—do not have to be well insulated from the medium as long as their capacitance is much smaller than that of the target electrode.

An understanding of the distribution of the electric field in the medium is particularly important for proper design of the electroneural interfaces. For example, if the pulse duration is significantly shorter than the EP-PCD transition time, the electric current will flow primarily from the

electrode edges. This will result in a highly enhanced electric field in these areas, which may stimulate and even damage the nearby cells much more than the average current density calculated by dividing the total current by the total electrode area [42]. The edge effect can be effectively avoided if the electrode capacitance is selected such that the characteristic transition time is below the intended pulse duration. In addition, the electrode capacitance can be gradually reduced toward the edges, for example, by decreasing the SIROF thickness using partial shadowing techniques.

VI. CONCLUSIONS

We provide an analytical solution describing the dynamics of the current redistribution on capacitive electrode-electrolyte interfaces and validate our theory experimentally. We demonstrate that the current and voltage redistribute over time from the initial nonuniform spread to the steady state, where the current density at the surface is proportional to the capacitance per unit area. This transition can be described as a superposition of the exponentially decaying eigenmodes. The slowest and dominant eigenmode of a disk electrode has a time constant similar to the RC time constant of the electrode. We also note that since the EIS-based measurements of the access resistance are performed at high frequencies, they correspond to an equipotential boundary condition, which is different from the access resistance at low frequencies. To avoid the strong edge effects on large electrodes, the capacitance of the electrode material should be selected so that the EP-PCD transition time does not significantly exceed the intended pulse duration.

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APPENDIX A

Here, we show that the operator $\hat{\mathbf{S}}$ defined in Eq. (11) is positive definite.

Proof. Let Φ and Ψ be two nonzero potential distributions in E and define

$$\phi_0(\mathbf{r}) := \Phi(\mathbf{r}), \quad \mathbf{r} \in A, \quad (\text{A1a})$$

$$\phi_1(\mathbf{r}) := \Phi(\mathbf{r}), \quad \mathbf{r} \in D, \quad (\text{A1b})$$

with similar definitions for ψ_0 and ψ_1 . By Eqs. (4) and (5),

$$\nabla \Phi(\mathbf{r}) \cdot \mathbf{n}(\mathbf{r}) = 0, \quad \mathbf{r} \in D, \quad (\text{A2a})$$

$$\nabla \Phi(\mathbf{r}) \cdot \mathbf{n}(\mathbf{r}) = -\rho \hat{\mathbf{S}}\phi_0, \quad \mathbf{r} \in A. \quad (\text{A2b})$$

We may now write

$$\begin{aligned} \langle \psi_0, \hat{\mathbf{S}}\phi_0 \rangle &= \int_A \psi_0 (\hat{\mathbf{S}}\phi_0) dS \\ &= -\frac{1}{\rho} \int_A \Psi \nabla \Phi \cdot \mathbf{n} dS = -\frac{1}{\rho} \int_{A \cup D} \Psi \nabla \Phi \cdot \mathbf{n} dS. \end{aligned} \quad (\text{A3})$$

The last equality above uses Eq. (A2a). By the divergence theorem and Eq. (10), we now have

$$\begin{aligned} - \int_{A \cup D} \Psi \nabla \Phi \cdot \mathbf{n} dS &= \int_E \nabla (\Psi \nabla \Phi) dV \\ &= \int_E \nabla \Psi \cdot \nabla \Phi dV + \int_E \Psi \Delta \Phi dV \\ &= \int_E \nabla \Psi \cdot \nabla \Phi dV; \end{aligned} \quad (\text{A4})$$

thus

$$\langle \psi_0, \hat{\mathbf{S}}\phi_0 \rangle = \frac{1}{\rho} \int_E \nabla \Psi \cdot \nabla \Phi dV. \quad (\text{A5})$$

It follows that $\hat{\mathbf{S}}$ is Hermitian, which is the result of the Lorentz reciprocity. Furthermore, as

$$\int_E \|\nabla \Phi\|^2 dV > 0, \quad (\text{A6})$$

we have

$$\langle \phi_0, \hat{\mathbf{S}}\phi_0 \rangle > 0, \quad \forall \phi_0 \neq 0, \quad (\text{A7})$$

and it follows that $\hat{\mathbf{S}}$ is positive definite.

APPENDIX B

The general solution to Eq. (49) is

$$X_l(\xi) = c_1 P_{2l}(j\xi) + c_2 Q_{2l}(j\xi), \quad (\text{B1})$$

where $j = \sqrt{-1}$, $c_1, c_2 \in \mathbb{C}$ are coefficients and Q_{2l} is the $2l$ th Legendre polynomial of the second kind. The

boundary conditions are

$$X(0) = 1, \quad (\text{B2a})$$

$$X(+\infty) = 0. \quad (\text{B2b})$$

As $Q_{2l}(0) = 0$, by Eq. (B2a) we have $c_1 = 1/P_{2l}(0)$. By Eq. (12.216) in Ref. [43], we also have

$$Q_{2l}(z) = \frac{P_{2l}(z)}{2} \ln \frac{1+z}{1-z} + R_{2l-1}(z), \quad (\text{B3})$$

where R_{2l-1} is a polynomial of degree $(2l-1)$ with only odd-order terms; thus

$$X_l(\xi) = \frac{P_{2l}(j\xi)}{P_{2l}(0)} + c_2 (jP_{2l}(j\xi) \arctan \xi + R_{2l-1}(j\xi)) \quad (\text{B4a})$$

$$= \left(\frac{1}{P_{2l}(0)} + jc_2 \arctan \xi \right) P_{2l}(j\xi) + c_2 R_{2l-1}(j\xi). \quad (\text{B4b})$$

Using Eq. (B2b), we conclude that

$$\lim_{\xi \rightarrow +\infty} \left(\frac{1}{P_{2l}(0)} + jc_2 \arctan \xi \right) = 0 \quad (\text{B5})$$

and

$$c_2 = \frac{2j}{\pi P_{2l}(0)}. \quad (\text{B6})$$

By Theorem 1 below, a solution satisfying Eq. (B2) exists and it must be of the form

$$X_l(\xi) = \frac{1}{P_{2l}(0)} \left(P_{2l}(j\xi) + \frac{2j}{\pi} Q_{2l}(j\xi) \right). \quad (\text{B7})$$

Now, because $P'_{2l}(0) = 0$, it follows that

$$X'_l(0) = \frac{2j}{\pi P_{2l}(0)} \frac{d}{d\xi} Q_{2l}(j\xi) \Big|_{\xi=0} \quad (\text{B8a})$$

$$= -\frac{2}{\pi P_{2l}(0)} Q'_{2l}(0) \quad (\text{B8b})$$

$$= -\frac{2}{\pi} \frac{1}{\frac{(-1)^l (2l-1)!!}{(2l)!!}} \frac{(-1)^l (2l)!!}{(2l-1)!!} \quad (\text{B8c})$$

$$= -\frac{2}{\pi} \left[\frac{(2l)!!}{(2l-1)!!} \right]^2. \quad (\text{B8d})$$

Theorem 1: A monotonically decreasing solution to Eq. (49) satisfying the boundary conditions (B2) exists.

Proof. When $l = 0$, $X_l(\xi) = 1 - (2/\pi) \arctan \xi$ is a valid solution, so we assume that $l \geq 1$.

Let X_n be a sequence of solutions to Eq. (49), defined on $0 \leq \xi \leq n$, with the boundary conditions

$$X_n(0) = 1, \quad (\text{B9a})$$

$$X_n(n) = 0. \quad (\text{B9b})$$

Choosing $c_1 = 1/P_{2l}(0)$ and $c_2 = -P_{2l}(in)/Q_{2l}(in)$ gives an explicit form for X_n .

We claim that X_n monotonically decreases in $(0, n)$ and prove this by contradiction.

Indeed, Eq. (49) gives

$$(1 + \xi^2)X''(\xi) + 2\xi X'(\xi) = 2l(l+1)X(\xi). \quad (\text{B10})$$

If X_n is not monotonic, there exists a local extremum $\xi_0 \in (0, n)$ such that $X'_n(\xi_0) = 0$. We see from Eq. (B10) that $X''_n(\xi_0)$ has the same sign as $X_n(\xi_0)$. Thus, if $X_n(\xi_0) > 0$, then ξ_0 is a local minimum. Therefore, there exists a local maximum $\xi_1 \in (\xi_0, n)$ such that $X_n(\xi_1) > 0$. However, at ξ_1 , which is also an extremum, $X''_n(\xi_1)$ and $X_n(\xi_1)$ have different signs, which is a contradiction. Similarly, assuming that $X_n(\xi_0) < 0$ leads to a contradiction as well. Therefore, X_n monotonically decreases in $(0, n)$.

We also claim that $X_n(\xi)$ is increasing in n ; that is, if $m > n$, then $X_m(\xi) \geq X_n(\xi)$ for $0 \leq \xi \leq n$. Indeed, monotonicity of $X_m(\xi)$ in ξ implies that $X_m(n) > 0$; thus $Z = X_m(\xi) - X_n(\xi)$ satisfies Eq. (49) with $Z(0) = 0$ and $Z(n) > 0$. By the same argument, Z cannot attain a negative minimum; thus $Z(\xi) > 0$ for all $0 < \xi < n$. Therefore, the limit

$$X_l = \lim_{n \rightarrow +\infty} X_n, \quad (\text{B11})$$

exists and $X_l \geq 0$ is monotonically decreasing. We claim that

$$\lim_{\xi \rightarrow +\infty} X_l(\xi) = 0 \quad (\text{B12})$$

and prove this by contradiction.

Assume that there exists $\epsilon > 0$ such that $X_l(\xi) \geq \epsilon$ for all $\xi \geq 0$. The integral of the left side of Eq. (49) yields

$$\int_0^t [(1 + \xi^2)X'_l]' d\xi = (1 + t^2)X'_l(t) - X'_l(0) \leq -X'_l(0). \quad (\text{B13})$$

The integral of the right side of Eq. (49) yields

$$\int_0^t 2l(l+1)X_l(\xi) d\xi \geq 2l(l+1)\epsilon t. \quad (\text{B14})$$

As $t \rightarrow +\infty$, we have $2l(l+1)\epsilon t > -X'_l(0)$, which is a contradiction, and Eq. (B12) follows.

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