Title:

Spike-triggered average electrical stimuli as input filters for bionic vision – a perspective.

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D.R. drafted the manuscript. All authors contributed equally to the final text and figures.

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DR has received surplus equipment on loan and minor support for supplies from Retina Implant AG. EZ is Advisor to Retina Implant AG, stock holder and co-inventor of patents held by this company. However, Retina Implant AG had no influence on the planning and execution of the work presented here.

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Abstract:

Bionic retinal implants are gaining acceptance in the treatment of blindness from degenerative diseases including retinitis pigmentosa and macular degeneration. A current obstacle to the improved performance of such implants is the difficulty of comparing the results of disparate experiments. Another obstacle is the current difficulty in selectively activating the many different retinal ganglion cell types that are used as separate pathways for visual information to the brain. To address these obstacles, we propose a modelling framework based on white noise stimulation and reverse correlation.

In this perspective, we first outline early developments in visual retinal physiology leading up to the implementation of white noise stimuli and spike-triggered averaging. We then review recent efforts to adapt the white noise method for electrical stimulation of the retina and some of the nuances of this approach. Based on such white noise methods, we describe a modelling framework whereby the effect of any arbitrary electrical stimulus on a ganglion cell's neural code can be better understood. This framework should additionally disentangle the effects of stimulation on photoreceptor, bipolar cell and retinal ganglion cell – ultimately supporting selective stimulation of specific ganglion cell types for a more nuanced bionic retinal implant. Finally, we point to upcoming considerations in this rapidly developing domain of research.

Introduction:

Overview

Retinal degenerations like retinitis pigmentosa and macular degeneration cause blindness worldwide. They are characterized by dysfunctional photoreceptors leading to the impairment of light detection in the retina. One approach to restore vision for such degeneration is a retinal prosthetic implant. The electrical stimulation provided by such devices elicit neuronal activity from the retina, perceived by the brain as visual objects called phosphenes.

According to the placement of the electrode array of the device, there are three main categories of retinal implant (Zrenner 2013). Epiretinal implants are placed on the retinal ganglion cell (RGC) nerve fiber layer within the vitreous space (Weitz et al. 2015). Subretinal implants are placed between the retina and the retinal pigment epithelium (Zrenner 2013). Finally, suprachoroidal implants are placed between the choroid and sclera near the external surface of the eye (Bareket et al. 2017).

It is well-established that each of the main categories of retinal implant have the potential to activate RGCs directly (direct activation) or via activation of retinal network elements preceding the RGCs (indirect activation) (Weiland et al. 2016). Yet, even now, controlling which network elements are activated remains an active domain of research. It is our belief that a better understanding of retinal activation can be achieved through a spike-triggered average (STA)-based modelling framework that we present following the *Introduction*. In this framework, the three neuron classes in the vertical (serial) pathway of the retina (photoreceptor, bipolar cell, and RGC) each have a characteristic filter that they apply to incoming electrical input; and this electrical input filter is passed down the pathway, eventually resulting in RGC action potentials (spikes). The electrical input filter is a formal model of a cell's sensitivity to electrical stimuli. It can be estimated by calculating the average stimulus preceding a response (the spike-triggered average). Functionally, by convolving the input filter with the stimulus, one can estimate how much a cell should be excited by any arbitrary stimulus. Throughout this work we will be careful to distinguish between the neuronal classes of the retina (photoreceptor, horizontal, bipolar, amacrine, and ganglion cells) and types that are found within each of these classes (e.g. ON, OFF, starburst, etc.).

To provide the proper context for our modelling proposal, we outline the historical development of visual neuron characterization. This culminates with an overview of Gaussian white noise visual methods of characterization. Having reviewed visual characterization methods, we use this foundation as a springboard to discuss electrical noise characterization. We then exhaustively review recent attempts at adapting such methods to electrical stimulation of the retina for bionic vision. (For a related treatment of electrical stimulation modeling, we recommend (Halupka 2017)). We next address specifics of electrical noise stimulation such as subthreshold and suprathreshold stimulation modes and how spike burst responses can be addressed in white noise electrical stimulation.

In addition to understanding how each of the main retinal neuron classes (photoreceptor, bipolar cell, and RGC) respond to electrical stimulation, an important open question remaining is ‘How does each of the many cell types (e.g. ON vs. OFF) within each class differentially respond to electrical stimulation?’ Therefore, in addition to reviewing response characterization and white noise methods in retinal electrostimulation, we also review early work on that question with an emphasis on how the electrical input filter of different cell types within a class can help identify stimuli that selectively activate chosen cell types.

Finally, we conclude with a discussion of how current methods can be elaborated, the implications of so-called ‘subthreshold’ electrical noise stimulation on bionic vision, and challenges one may encounter with the proposed modelling framework that arise from considerations of the neural code of the retina.

Islands of Knowledge

Although it is not obvious, our current understanding of how neural tissue responds to electrical stimulation is actually broken into a number of knowledge islands that only loosely communicate. These island nations are divided by their individual currencies and the uncertain exchange factors between them. On one island, the currency may be voltage, on another, it may be charge, and on others, it may be spatial or time derivatives or integrals of either of these. Examples include current (the time derivative of charge), charge density, current density, voltage curvature, etc. It is customary, therefore, to use simple conversion factors to compare between these different domains. For example, to calculate the current delivered by a voltage pulse, one might simply divide voltage by the impedance of the electrode. To calculate the charge delivered by a current pulse, one might simply integrate current across time. But such simplified conversions (yes, we are also guilty – [see (Jalligampala et al. 2017)]) critically overlook considerations of how neural tissue sensitivity to any of these values can be nonstationary across time or space. Likewise, in practice the current produced by an electrode will not necessarily scale as a linear function of voltage (see (Cogan 2008)). For example, if one researcher were to stimulate with a very low current, but over a very long time duration, activation of the neuron might not be achieved despite the integral of the current summing to the ‘threshold charge’ (one which results in a neural response) as determined by another researcher. As another example of flawed conversion, while impedance is normally reported in units of Ohms, allowing us to matter-of-factly substitute it into the familiar $V=IR$ equation, the reality is that the single impedance value is only really valid at the cycling frequency at which it was measured. This reflects that, for a square wave voltage pulse, the combined effect of the resistive and capacitive components of the experimental system will be a distorted current pulse. For more accurate predictions of the current associated with a voltage, electrochemical impedance spectroscopy can be used (Cogan 2008), but even this measure fails to capture the effect on impedance from the recent voltage history. Even the common conversion trick of discussing ‘peak’ or ‘plateau’ currents misses the fact that the biological system is integrating across the entire stimulus waveform.

To reconcile these disparate knowledge domains, we propose a modelling framework in which the system filter is estimated using white noise and spike-triggered averaging of the time varying charge passed into the neural tissue. We focus on this charge because, in our experience, this stimulus value most closely correlates to the transmembrane voltage that determines a neuron's response. By expressing neuronal excitation in terms of the instantaneous charge integrated in a leaky fashion by the neuron's filter, we believe that a universal definition of threshold can be achieved. The result will be that disparate experimental paradigms will all arrive at the same definition of what constitutes a threshold stimulus – regardless of stimulus waveform shape. [See *A Modelling Framework for Retinal Electrostimulation*]

Retinal Activation has Many Mechanisms

When the retina is stimulated as in a retinal prosthesis, spikes can be elicited from retinal ganglion cells (RGCs) through multiple mechanisms. The simplest mechanism is 'direct stimulation' of the RGC that activates its spike initiating zone (a high-density band of voltage-gated ion channels in the axon initial segment, AIS) (Wollner & Catterall 1986; Boiko et al. 2003; Fried et al. 2009; Jeng et al. 2011; Werginz et al. 2014). Within the category of direct stimulation are included both 1) an extracellular voltage gradient along the cell, inducing an intracellular current through the RGC dendrites, soma, and axon, thus leading to accumulation of positive ions within the AIS that activates the voltage-gated cation channels underlying the action potential, and 2) the creation of a localized hyperpolarization of the extracellular space adjacent to a segment of membrane with such cation channels (axon, AIS, or even somatic or dendritic segments), thus effectively depolarizing the transmembrane. Within this latter mechanism is the local depolarization of a distal segment of the axon (beyond the AIS) creating a bidirectional action potential – as when passing axons of distal RGCs in the nerve fiber layer are stimulated (Greenberg et al. 1999; Nanduri et al. 2008; Nanduri et al. 2012; Weitz et al. 2015; Rizzo et al. 2003; Werginz et al. 2014; Chen et al. 2009; Grumet et al. 2000; Jensen et al. 2003).

In contrast, 'indirect stimulation' of RGCs is produced by activation of an upstream member of the retinal network that is then propagated to the RGCs through synaptic communication. Bipolar cells (BCs) and photoreceptors (PRs) are the network elements most susceptible to such activation because of their elongated architecture along the voltage gradient, although it may still be possible to directly activate the other elements of the retinal network – amacrine cells, horizontal cells, or even the Müller glial cells [but see (Tsai et al. 2011)]. In network stimulation, the more likely mechanism of neuronal activation is the first one described for direct RGC stimulation where a voltage gradient across the retina induces an inverted voltage gradient within the neuron – ultimately depolarizing the presynaptic membrane to activate voltage-gated cation (primarily calcium) channels. However, with the miniaturization of electrodes, it may also someday be possible to locally depolarize the presynaptic membranes of the retinal network in the absence of a large transretinal electrical field. A primary goal of this paper, recognizing these many interacting mechanisms involved in electrical stimulation of the retina, is **to lay out a conceptual framework to better understand how activation of the various retinal elements converges in the retinal ganglion cell to give rise to spike patterns that carry all retinal information into the visual centers of the brain.**

Tickling the Retina

Recently, our group and another in parallel have shown that the integration of sequences of subthreshold pulses can produce RGC spikes (Sekhar et al. 2016; Ho et al. 2018). We have termed this 'tickling the retina' to draw attention to this underappreciated approach and the accompanying need for a model of how it works. The main advantage of tickling the retina is that probing electrical responsiveness of the retina in the context of ongoing stimulation better mimics the *in situ* environment of clinical retinal prostheses. Furthermore, we believe that the integration of ongoing

stimulation can provide leverage to activate defined RGC types with greater selectivity than can be achieved with single suprathreshold pulses.

We demonstrate here that reverse correlation techniques can shed light on many active themes in the realm of retinal prosthetics. In particular, the technique of using spike-triggered averaging of a RGC's responses to a (noise) sequence of randomized electrical stimulus amplitudes has recently yielded promising results in this domain (Freeman, Rizzo, et al. 2010; Sekhar et al. 2017; Sekhar et al. 2016; Ho et al. 2018; Maturana et al. 2018). A detailed review of these and related studies is provided in *Electrical Noise Stimulation*.

A Modelling Framework for Retinal Electrostimulation

Suprathreshold electrical stimulation of the retina has been described using a diverse array of methods and metrics (Sekirnjak et al. 2006). Example metrics include charge (Humayun et al. 1999), voltage (Zrenner 2002), current (the time derivative of charge (Jensen 2003)), charge density (Rizzo 2003), current density (Eickenscheidt et al. 2012), voltage curvature (Eickenscheidt & Zeck 2014), etc. (these are the *Islands of Knowledge* mentioned before). It is customary, therefore, to use simple conversion factors to compare between these different domains, but with the inherent shortcomings discussed in the *Introduction: Islands of Knowledge*. To reconcile these disparate windows into retinal electrostimulation, and to do so in the context of retinal network stimulation, we propose measuring the composite retinal filter using white noise and spike-triggered averaging of the time-varying charge that is passed into the neural tissue. It is this charge that is carried by the current through the tissue; and it is the ongoing flow of this charge which establishes and maintains the voltage gradients across the retina which, in turn, depolarize the voltage-activated membranes of the retinal neurons. Thus, electrical stimulation of the retina can be understood in terms of its effect on the retinal encoding of spikes that are provided as the retina's only output to the rest of the brain. With such a common currency, what have previously been mutually irreconcilable lines of research will be unified within a single framework.

Because typical prosthetic stimulation of the retina generates an electrical field spanning the thickness of the retina, all retinal neurons have the opportunity to respond depending on the spatio-temporal contrast along the field. Therefore, we propose that the electrical input filter of the retinal network during such stimulation is best understood as the combination, through the feedforward synaptic pathway of the retina, of electrical input filters from each element of the retinal circuit (**Figure 1**). This composite filter is then passed through a nonlinear function for generation of RGC spiking responses. In this modelling framework, photoreceptors (PRs), bipolar cells (BCs), and RGCs each have their own electrical input filter for extracellular stimulation (**Fig. 1b**). The convolution of these filters with the electrical stimulus yields the generator signal for each cell (**Fig 1d**). However, for BCs, this generator signal must then be combined with that of the PR – but altered slightly by synaptic transmission to mimic feedforward input from PR to BC. This compound BC generator signal is then modified further as it is synaptically transmitted to the RGC and combined with that neuron's electrical generator signal to produce the compound generator signal of the RGC. Ultimately, the compound RGC generator signal is subjected to a spiking nonlinearity to produce the spike train that is used for generating the STA [e.g.(Paninski et al. 2007)]. Thus, with careful experimental design, we believe it will be possible to measure an electrical input filter from the RGC that reflects the filtering properties of not only the RGC but also the BC and PR (**Fig 1c**).

The linear system modelling framework that we propose for electrical stimulation is similar to many previous visual models [e.g. (Wohrer & Kornprobst 2009)], and estimates the duration and shape of the retinal circuit's memory for past charge delivery, thus capturing its temporal filtering behavior. It has the advantage of being empirically based on easily recorded spiking responses and the actual flow of charge through the tissue rather than the suspected charge or the command signal of the stimulator. In terms of converting stimulation levels and threshold values between different studies, the modelling framework we propose will allow all researchers to talk about stimulation thresholds in the same units – that is to say '**integrated charge**'. The instantaneous integrated charge of any arbitrary stimulus can simply be calculated as the convolution of the temporal stimulus charge sequence and the compound linear filter described here.

Visual Response Characterization

The Receptive Field

For any sensory neuron, there is a circumscribed region of sensory space over which the neuron is responsive to stimulation (**Fig. 2**). This region is termed the receptive field (RF). In visual neuroscience, the RF was first probed with punctate stimuli by luminaries such as Adrian and Matthews (Adrian & Matthews 1927), Hartline (Hartline 1938), Granit (Granit 1946), Barlow (Barlow 1953), Kuffler (Kuffler 1953), Hubel and Wiesel (Hubel & Wiesel 1961), and Rodieck (Rodieck 1965). Such 'hand-mapping' was highly valuable in establishing a foundation for understanding how visual neurons integrate stimulation both across the RF and across time. Over the spatial extent of the RF, neurons typically vary in sensitivity, with sensitivity highest in the center of the RF, and smoothly falling off to the RF periphery (**Fig. 2d,e**). Moreover, due to lateral inhibition in visual networks, the RF typically has a center/surround structure in which stimuli that activate the center region inhibit the surround and *vice versa*. The consequence is to enhance local contrast, thus sharpening the spatial selectivity of the neuron. Across time, most sensory neurons act as leaky integrators over their RF. A leaky integrator is a circuit element that accumulates the effects of input stimuli over recent time, but slowly leaks this integrated input over time such that the influence of previous stimuli completely vanishes if enough time has passed (**Fig. 2c**). Accordingly, it is useful to think of the RF of a visual neuron as applying a complex space-time filter to the visual stimulus (Rodieck 1965). For example, for some RGCs, the spatial RF evolves over time, imparting a selectivity to the neuron for stimulus frequency (Moore et al. 2013). Building on this concept of visual neurons as spatiotemporal filters, later researchers shifted to systematically characterizing their responses to sine wave stimuli that occupy well-defined spatiotemporal frequency bands of the stimulus space (Enroth-Cugell & Robson 1966). By combining a neuron's sensitivity to different frequencies, one can build a linear model of the neuron's filter in a given stimulus dimension (Shapley & Lennie 1985; Brodie et al. 1978). This systematic sine-wave stimulation and accompanying formal modeling laid the conceptual groundwork for white noise methods.

White Noise Stimulation and the STA

Building on the success of sine wave-based linear models, spike-triggered averaging has been used to understand the filtering properties of visual neurons in both the spatial and temporal domains for many decades (Marmarelis & Naka 1973c; Marmarelis & Naka 1973b; Marmarelis & Naka 1973a; Marmarelis & Naka 1972; Korenberg & Hunter 1986; Ringach & Shapley 2004; Sharpee 2013). In generating the spike-triggered average (STA), the stimuli that precede each neuronal spike are averaged together to yield an estimate of the input filter for that neuron. Tightly coupled to spike-triggered averaging has been the presentation of *Gaussian white noise* stimuli. Here, the term 'white'

indicates that the distribution of frequency amplitudes (e.g. across the temporal domain) is relatively flat, in analogy to the photon frequency distribution of white light. This is achieved by sampling the amplitude values (e.g. brightness) randomly from a Gaussian distribution at regular intervals across the stimulus domain (e.g. time). Such white stimuli are often also referred to as ‘noise’ stimuli, in analogy to their resemblance to a noisy audio signal – reflecting the fact that the power-balanced frequencies are uncorrelated in their phases. For visual stimulation, such a Gaussian white noise stimulus can be sampled simultaneously across multiple orthogonal stimulus domains such as time, space, and color (Devries & Baylor 1997; Chichilnisky 2001). In contrast to earlier sine wave experiments this process can be much more efficient, as the entire frequency space can be probed simultaneously with a single noise stimulus rather than sequentially with multiple different sine waves.

Binary Noise and Noise Stimulus Design

We address the binary noise case here because it is particularly useful in understanding important nuances of noise stimulus design. A common special case of the Gaussian noise stimulus is binary noise. At first glance, this would seem to be a contradiction in that Gaussian and binary distributions are mutually exclusive. However, the central limit theorem demonstrates that if enough binary samples are integrated by a system, the distribution of integrated values approaches a Gaussian distribution (as shown in **Fig. 3c**, left plots). This points to an important consideration in the design of any noise stimulus for spike-triggered averaging. Specifically, it is important not only to consider the distribution of stimulus amplitudes but also the expected filter shape of the neuron as well as the filter size relative to the stimulus sampling resolution. This point is elaborated for the spatial domain in **Figure 3**. In matching the stimulus to the neuronal filter, a balance must be struck. On the one hand, it is desirable to generate a wide range of neuronal excitation levels so that the input/output function of stimulus vs. response can be sampled densely – especially the degree of nonlinearity in this function. The prediction of how much a stimulus should excite a neuron based on a linear convolution of that stimulus with the neuron’s filter is called the ‘generator signal’ (Chichilnisky 2001). The generator signal can be loosely interpreted as a prediction of the non-spiking membrane potential of the neuron, as is typically measured with patch-clamp recordings. Mathematically, the expression of this generator signal is equivalent to a dimensionality reduction whereby the multiple stimulus dimensions are reduced to a single dimension corresponding to the predicted excitation level of the cell. On the other hand, competing with the need for high-density sampling is the need for the stimulus frequencies to be sampled with enough power that the filter shape can be determined with sufficient resolution. **Figure 3d** demonstrates how the power at which stimulus frequencies are sampled decreases as more frequencies are sampled. Beyond a threshold power, the neuron will not respond to the stimulus frequencies. To elaborate, if the match between the stimulus presentation density and the neuronal filter is such that only one stimulus element influences the response at each time point (**Fig. 3b, upper plot**), the generator signal distribution remains the same as the original stimulus distribution (**Fig. 3c, upper pair of plots**). Additionally, only low-frequency stimuli (relative to the RF size) can be presented (**Fig. 3d, lavender lines**). In contrast, if the stimulus is designed such that the filter integrates across too many stimuli, the generator signal distribution becomes much narrower around the stimulus mean (**Fig. 3c, lower pair of plots**) and, although many frequencies are sampled, the sampling power at all frequencies falls below the threshold detection level (**Fig. 3d, cyan lines**). Therefore, it is critically important that a noise stimulus is designed such that both the generator signal and sampled frequencies span a wide range of values at a sampling density that is useful for the question at hand. In the examples in **Figure 3c**, the top plot for the Gaussian stimulus and the middle plot for the binary

stimulus provide the best sampling of the filter nonlinearity. This tradeoff between stimulus power and sampling density is a crucial, but often neglected consideration in the design of noise stimuli.

Electrical Noise Stimulation

In analogy to the success of *visual* noise stimulation, multiple groups have sought to develop a method of delivering noise-based *electrical* stimulation to the retina. In doing so, the typical goal is that temporal filters can be estimated for prosthetic stimulation of the retina. The earliest electrical noise stimulation we have identified in the visual prosthesis literature was by Ryu *et al.* [(Ryu *et al.* 2009), and revisited in (Ryu *et al.* 2017)], although the use of noise in auditory electrostimulation predates this by more than two decades (Morse & Evans 1996; Motz & Rattay 1986). Curiously, while noise stimulation was used to examine the fidelity of the current amplitude encoding in the spike train, the data does not appear to have been used to calculate the electrical input filter via STA. At stimulation rates of 1-10 Hz, it is possible that temporal integration across subsequent pulses was rare and that only single-pulse activation was observed.

In a more relevant study by Freeman *et al.* (Freeman, Rizzo, *et al.* 2010), electrical current was modulated by a binary noise sequence from a nearby epiretinal stimulating electrode during cell-attached patch-clamp recordings of RGCs. For both spiking responses and the membrane voltage, reverse-correlation kernels (electrical input filters) were calculated, yielding a biphasic waveform with a peak latency of 25 ms and a likely preferred frequency around 5-10 Hz. Although promising, we are unaware of any work following up on this first demonstration of STAs relevant to prosthetic vision.

A few years later, Lorach *et al.* (Lorach *et al.* 2015) delivered a ‘sparse’ spatio-temporal binary noise stimulus to their subretinal electrode while recording ganglion cell spike trains. Sparse refers to sequential stimulation at single points in the stimulation space, in contrast to simultaneous stimulation at all points. They reported maps of the spatial and temporal sensitivity profiles that they termed an electrical receptive field (eRF). To create these maps, only one of the 142 electrodes were stimulated at a time, at a refresh rate of 2 Hz. Because of this low rate and sparse design, we consider this method to be more analogous to the visual hand mapping discussed earlier rather than the noise-based STA method, since a rate of 2 Hz appears insufficient for multiple pulses to be integrated by the temporal filters of the retina that have been subsequently reported. In this paper, the temporal response pattern was reported, but this pattern is best identified as an ‘impulse response’, in contrast to the related but distinct ‘temporal filter’ that is typically produced from noise stimulation. A common mistake is to assume that the impulse response and temporal filter are identical, however, this equivalence is only true in a purely linear system (unlike the nonlinear retina). The most important distinction here is that the impulse response only provides temporal information about the spiking response pattern after the activation threshold has been crossed. In contrast, the input filter estimated from noise stimulation better reflects the generator signal leading up to a spiking event. These two time series, the impulse response and the temporal filter, are only identical if the relationship between generator signal and response is perfectly linear (Bracewell 1986). Interestingly, the spacing of electrodes (70 μm pitch) is appropriately matched to the spatial eRF to allow true noise mapping – had the authors activated multiple pixels at a time as in their more recent paper (Ho *et al.* 2018). Based on these earlier methods, however, only points in the receptive field which can independently activate the cell were mapped. With non-sparse Gaussian noise mapping – even at a stimulation frequency of 2 Hz, one could expect such methods to yield a full mapping of the excitatory and inhibitory eRF regions.

Shortly following the Lorach *et al.* work, Maturana *et al.* (Maturana *et al.* 2016) extensively examined Gaussian white noise estimation of the spatial eRF. They too stimulated at a frequency too low to probe the temporal filter (10 Hz). Although their electrodes were subretinal, they primarily examined direct RGC stimulation. They found that weighting pulse amplitudes across 2, or 3 electrodes in proportion to the eRF was more efficient than naïvely weighting all effective electrodes equally. Furthermore, they found the same 1, 2, or 3 effective electrodes for both cathodic-first and anodic-first biphasic pulses. Using spike-triggered covariance (STC) analysis, they found that the STA estimate of the spatial eRF was typically sufficient to explain how RGCs responded to direct stimulation by combinations of electrode, and that higher order interactions between electrodes played little role in RGC responsiveness. Importantly, the STC analysis revealed that simple STAs, while often correct, had weak amplitudes due to the antagonistic effects of similarly effective cathodic-first and anodic-first biphasic pulses in the STA calculation process. A recent study that similarly examined the eRF can be found in (Esler *et al.* 2018), demonstrating how these methods are being quickly adopted by the research community. Interestingly, this study showed that the types of linear models described here are good approximations for much more complex biophysical models of retinal electrical stimulation.

More recently, our group (Sekhar *et al.* 2016; Sekhar *et al.* 2017) and another (Ho *et al.* 2018) have finally been successful in measuring temporal electrical input filters from network-based stimulation of RGCs. We first reported this success in 2016 when we stimulated the mouse retina epiretinally with 1 ms, cathodic, voltage-controlled pulses delivered at a rate of 25 Hz and with an amplitude distribution largely falling below single pulse activation thresholds (**Fig. 4**). We found that the electrical input filters of many retinal ganglion cells had a strong negative deflection with peak latencies typically in the range of 100 to 400 ms (**Fig. 4c**). Mathematically, the STA can be thought of as a vector in stimulus space pointing from the center of the original stimulus distribution towards the center of the spike-associated stimulus ensemble (**Fig. 4d**) (Schwartz *et al.* 2006). By plotting the probability that stimuli of a given generator signal range will elicit a spike, the nonlinearity relating generator signal to neuronal response can be estimated (**Fig. 4e,f**). Examining the stimulation frequency for pulse trains, we found that 10 Hz seldom yielded useful filters. In contrast, 50 Hz stimulation produced very smooth filters; however, because of the lower temporal contrast of the stimulus (as discussed for spatial resolution in **Fig. 3**), such fine resolution stimulation drove fewer spikes – requiring longer recording times to yield enough data for STAs. Accordingly, we settled on 25 Hz pulse trains as an optimal frequency to provide smooth STAs in a reasonably short recording time. Likewise, we compared 20% vs. 35% contrast in the Gaussian distribution of pulse amplitudes and found that, while both contrasts produced useful filters, the higher contrast drove higher firing rates. We next examined the STAs of degenerated mouse retinas and found them to be drastically altered relative to healthy retinas. We concluded that the healthy filters are likely the result of photoreceptor (PR) stimulation being passed on through the retinal network to the RGC and therefore, the electrical input filter measured under these conditions primarily reflects the filter of PRs. Complementary to these experiments, Ho *et al.* (Ho *et al.* 2018) used a subretinal electrode array to stimulate the rat retina with a spatiotemporal binary noise sequence at a refresh rate of 20 Hz. Both their study and ours found filters with peak sensitivities in the 2-10 Hz range, although our filters tended to have slower onset latencies and longer durations. Based on these frequencies as well as the effects of degeneration and PR transmission blockade, they agreed with our conclusion that the filters are primarily the result of PR stimulation transmitted to RGCs via the retinal network. We suspect, however, that given the higher frequency, multiphasic filters they sometimes reported that PR-mediated stimulation may have combined with bipolar cell (BC) stimulation for some cells (see *Modelling Retinal Electrostimulation*). We also suspect that some of the

filters reported in the Ho *et al.* study resulted from single suprathreshold pulse activation rather than the integration of multiple pulses (as discussed in the next section). This supposition is based on their fast onset latencies, short peak latencies, and narrow widths – although the Nyquist limit of 20 Hz stimulation (10 Hz) makes it difficult to be certain.

Finally, in a paper published by Maturana *et al.* (Maturana et al. 2018), synaptic blockers were used to distinguish direct and indirect activation by a space-time varying electrical noise stimulation. While their previous discovery - that the spatial eRF characterizes well the linear interactions of multiple electrodes - holds true for direct stimulation, indirect stimulation appears to involve more nonlinear interactions. By stimulating at rates of 10, 20, and 30 Hz, they reinforce that rates higher than 10 Hz are necessary to accurately detect electrical input filter components arising from network activation.

‘Subthreshold’ Stimulation

Our use of electrical white noise confirmed our suspicion that stimulation of the network to activate RGCs can function through two distinct mechanisms (**Figure 5**). On the one hand, Single pulse amplitudes that are strong enough can activate the network by themselves (**Fig. 5a**). On the other hand, analogous to the integration of subthreshold postsynaptic potentials that is a basic principle of neuroscience, a series of ‘subthreshold’ electrical pulses can be integrated by the network to achieve activation (**Fig. 5a,b**). It is this latter mechanism that we have termed ‘tickling the retina’ and that has proven useful in understanding the electrical input filter. Appreciation of these two mechanisms requires a reevaluation of the concept of the electrical stimulation threshold. Traditionally, single pulses have been delivered while some aspect of the pulse (amplitude, duration, shape, interphase interval, etc.) was varied to determine the value beyond which reliable stimulation can be achieved. This value is then termed the threshold. However, recognizing that neurons can integrate multiple *subthreshold* stimuli across time, such a simple concept of threshold becomes muddled. In the *Modelling Retinal Electrostimulation* section we introduce the concept of an integrated charge threshold to delineate between these two mechanisms of electrical activation.

In examining our electrical STAs, we found evidence in some RGCs that single pulse activation and multi-pulse, integrative activation might be combined into a single STA (**Fig. 5a, d**). While integrative activation tended to have a peak latency above 50 ms, the single pulse activation had latencies closer to 20 ms (**Figure 5c**). To validate this observation, we plotted the firing rate of the RGC during the 40 ms interval following each pulse against the amplitude of that pulse (**Fig. 5a,b**). As suspected, RGCs with a contribution from single pulse activation showed a strong increase in firing rate approaching the high end of our stimulus pulse amplitude distribution (**Figure 5a**). In contrast, RGCs with no contribution from single pulse activation did not show such a firing rate increase (**Fig. 5b**). In order to better represent the integrative electrical input filter, we subsequently nullified the first time sample in the STA by setting it to the mean stimulus value, thus discarding the contribution of single pulse activation (within 40 ms latency of each pulse).

Conveniently, the plot of firing rate vs. pulse amplitude relates directly to earlier studies of the voltage amplitude threshold for single pulses (**Figure 6**). Beyond this relationship, however, calculating the single pulse amplitude threshold from noise stimulation has two advantages. First, because long recovery periods are not interleaved between successive pulses, the resolution with which voltage amplitudes can be probed is much higher for a fixed recording time, providing for a much more detailed voltage-response curve than in traditional studies (Jalligampala et al. 2017). Second, by measuring the voltage-response function in the context of ongoing electrical stimulation, the adaptive phenomenon

of desensitization (Weiland et al. 2016) is held constant and the adaptation state of the retina is better matched to that of real-world prosthetic stimulation (Hosseinzadeh et al. 2018). It will be informative to compare such white-noise generated stimulus-response curves to those generated under traditional methods in the same experiment. In doing so, we expect to better understand the role of adaptation (visual and electrical) in altering the sensitivity and gain of RGC coding in response to electrical stimulation.

Spike Burst Correction

In our indirect stimulation experiments, we have found that RGCs respond to noise stimulation with both individual (tonic) spikes and bursts of multiple spikes in short succession. The fraction of spikes that occur in a burst appears to vary across the RGC population but is expected to be somewhat stereotyped within each of the many RGC types (Wong et al. 2012). By examining the time intervals before and after each spike, we were able to classify each spike as either a tonic spike or for bursts, a first spike, intra-burst spike, or last spike (**Figure 7a,b**). When electrical stimulation triggers a burst of spikes, the undesired effect will be to smear out the STA across time. This is because the latency between the triggering stimulus and each of the spikes in the burst increases for later spikes. This poses a problem when the STA is being used to understand the average stimulus that drives an RGC to respond. Accordingly, we have described a method of correcting for temporal smear in the STA caused by bursts (Sekhar et al. 2016). The result is the first spike-triggered average (fSTA). In such burst correction, the first spike of each burst is identified. Then the contribution of the stimulus preceding that burst is weighted by the number of spikes in the burst to reflect the reality that stronger stimuli tend to produce bursts with more spikes in them. While burst correction had little effect for some RGCs (**Fig. 7c**), we found that others exhibited notable changes in the shape and timing of their STAs (**Fig. 7d,e**). So far, we have found little difference between STAs calculated with only corrected burst responses vs. those calculated with only tonic spikes, suggesting that one can consider tonic spikes to be bursts of only one spike. However, more work is needed to fully explore how tonic and burst spikes in the retina may encode distinct information about electrical stimulation CITE.

Type-specific Retinal Stimulation

The neurons of the retina can be divided into five primary cellular *classes* (photoreceptor, horizontal, bipolar, amacrine, and ganglion), each of which incorporates numerous *types* and subtypes (Masland 2011; Baden et al. 2016; Franke et al. 2017). Within the feedforward pathway of PR to BC to RGC, it has been shown that temporal filtering for electrical stimulation becomes progressively higher in preferred frequency (Freeman, Eddington, et al. 2010; Twyford & Fried 2016).

Of particular interest are the many types of retinal ganglion cells which differ from each other due to their individual cellular physiologies as well as their pattern of inputs from the retinal network (Baden et al. 2016). Of key interest, Wong *et al.* (Wong et al. 2012) showed a diversity of electrical responses in RGCs due to their intrinsic physiological properties. With the inclusion of the diversity of network connections that is known to exist, it is reasonable to hope that many RGC types will have key electrical stimulation patterns that can selectively activate them without strongly activating other RGC types. As an early foray into this domain, both we and Ho *et al.* (Ho et al. 2018) have demonstrated that the electrical input filters for visual ON and OFF RGCs tend to be mirror reflections of one another, likely due to dominant activation of photoreceptors (**Fig. 8**). This result reflects earlier work by Freeman *et al.* (Freeman, Eddington, et al. 2010). In that study, they used a similar systems modeling approach to ours, but with the presentation of current-controlled sinusoids with varying temporal frequencies – sampling just one frequency at a time in contrast to white noise stimulation. Their strategy echoes

early developments in visual response characterization using sinusoids. They found that visual ON cells tended to respond during the anodal phase of a slow (5 Hz) sine wave while OFF cells responded during the cathodal phase. Other recent contributions to growing evidence of cell-type selective stimulation include (Twyford & Fried 2016; Guo et al. 2014; Im & Fried 2016; Goetz et al. 2015; Im et al. 2018; Guo et al. 2018; Qin et al. 2017).

It remains unclear whether the differential filters found in healthy retina will be reflected in degenerate retina. Likewise, it remains unknown whether the different RGC types will each have a unique filter. Nevertheless, as noise stimulation methods become more refined and our ability to functionally discriminate RGCs improves (see (Baden et al. 2016)) we expect that further differences in electrical input filter shapes (spatial and/or temporal) that correlate with functional RGC type will be revealed. In doing so, we expect that methods will be derived that allow bionic retinal implants to selectively address the different visual information channels of the retina, and thus provide a more nuanced visual percept for implant patients (Barriga-Rivera et al. 2017). Indeed, the diversity of electrical spatiotemporal receptive fields recently described in (Maturana et al. 2018) provides strong support for such optimism.

Another domain of controversy for the electrical filters that have been recently described is the upper limit they may place on the maximal possible stimulation frequency. With electrical filters on the order of 500 to 1000 ms in duration, a reasonable expectation is that discrete stimulation may only be possible at rates around 1 Hz. However, a relevant detail that remains unknown is whether integration of electrical stimulation resets after a response. If there is no reset, then continuous stimulation could achieve much higher rates than discrete stimulation. Also unknown is the filter duration for bipolar cell-mediated activation of RGCs. While photoreceptors seem to have the long filters described thus far, bipolar cells are expected to have notably shorter filters that could support higher stimulation rates.

Discussion and Future Directions:

Multidimensional Sampling

As with visual noise, electrical noise has the ability to more efficiently sample from the potential stimulus space (**Fig. 9**). In the method we developed, we only explored the amplitude dimension as a proof-of-principle (Sekhar et al. 2016). Nevertheless, even this dimension was sampled more efficiently than in more traditional methods (see **Fig. 6**). In contrast, the binary noise stimulus used in Freeman *et al.* (Freeman, Rizzo, et al. 2010) better sampled the duration space, but at the expense of the amplitude dimension. In the future, researchers should strive to develop stimulation and recording methods that will allow multiple dimensions to be probed simultaneously.

In contrast to our focus on stimulus dimensionality in time, many other researchers have examined the spatial dimension of the eRF with noise stimuli (Maturana et al. 2016; Halupka 2017; Halupka et al. 2017; Lorach et al. 2015). The use of noise stimuli allows powerful computational methods like the STA, spike-triggered covariance (STC), and linear-nonlinear-linear modeling (Halupka et al. 2017) to be used. Nevertheless, more traditional hand-mapping styles of estimating the eRF have also been used by a number of researchers recently (Sim et al. 2014; Jepson et al. 2014; Eickenscheidt et al. 2012; Stett et al. 2000; Stett et al. 2007; Stutzki et al. 2016). Combining spatial and temporal noise mapping has proven to be a difficult task, however two reports this year demonstrate that such multidimensional eRF mapping is possible (Ho et al. 2018; Maturana et al. 2018). By incorporating the spatial dimensions into noise stimulation, even more refined methods of RGC type-specific stimulation may be discovered.

In contrast to asking about the underlying spatial eRF, many researchers have pursued electrical field shaping strategies to understand how multiple simultaneously activated electrodes can be weighted to best direct stimulation to a chosen neuron (Savage et al. 2012; Matteucci et al. 2013; Dumm et al. 2014; Spencer et al. 2018). Beyond considering combinations of stimulating electrode, field shaping also considers the role of return electrode in determining the path taken by current flow. In modern neuroprosthetics, field shaping (including current steering and current focusing) is a relatively new field of discussion that has been more extensively pursued for cochlear implants (Bonham & Litvak 2008). The field shaping concept considers the overlap of individual electrical fields from several electrodes and their influence on the overall electric field. It is applied either to focus the current in order to excite a narrowing region in tissue or to redirect the pulses for excitation in different regions of the tissue (Dumm et al. 2014). It is reasonable to expect that field shaping techniques might support cell-specific stimulation above and beyond that achievable by tailoring stimulation to the characteristic eSTRFs of selected RGC types. Furthermore, it appears that in a fully 3D structure like the LGN or optic nerve, such multielectrode approaches will be necessary. However, related work to date in the optic nerve (Yan et al. 2016) indicates that percepts are much more likely to involve nonlinear interactions between electrodes when visual space is represented in a disorganized 3D structure – requiring much more sophisticated modeling. In such cases, deep learning, *in silico*, neural networks may be the best approach (McIntosh et al. 2016).

Stimulation Thresholds

We have used the term ‘subthreshold’ pulses here to indicate single pulses that cannot independently drive responses. Nevertheless, by presenting a sequence of pulses that are integrated by the neuron to elicit a response, the neuron is driven above its threshold for activation. Thus, the sequence of subthreshold pulses can be considered to be a suprathreshold stimulus. We are not the first to make this observation that spreading stimulation out over extended time can reduce the stimulus amplitude necessary to elicit a response (Sekirnjak et al. 2006; Boinagrov et al. 2010; Johnson et al. 2004; Eickenscheidt et al. 2012; Ye et al. 2008; Grumet et al. 2000; Goo et al. 2011; Samba et al. 2015). In fact, this relationship underlies the classic strength-duration curve. However, we do differ slightly from the traditional understanding of the strength-duration relationship embodied in the Weiss and Lapicque equations (Rabinovitch et al. 2016). In our approach, we seek to explicitly model the leakiness of integration through a finite temporal filter [e.g. (Horsager et al. 2009)]. It is this leakiness that results in the asymptotic minimal stimulation threshold for arbitrarily long pulses (rheobase). We feel that shifting from thinking in terms of a single threshold charge with an asymptotic rheobase to thinking in terms of a threshold of the generator signal (integrated charge) for a neuron modeled with a finite temporal filter will prove more useful in characterizing the set of stimuli that are expected to drive a response from the retina.

Fading

An outstanding problem in artificial vision is fading – in which phosphenes tend to disappear with repeated stimulation at a constant level. The strength and speed of fading is proportional to the stimulation frequency. Perceptual fading has been reported in some Argus II subjects (Fornos et al. 2010; Stronks et al. 2013) and as well in Alpha-IMS subjects (Zrenner et al. 2011; Stingl et al. 2013). The latter patients overcame fading using relatively low stimulation rates of 1 to 20 bursts per second, but at the cost of visibly blinking percepts.

While it appears that fading has a strong cortical contribution, the desensitization of electrical responses in the retina due to repetitive stimulation has been investigated as one target to minimize

fading. A common misconception of retinal desensitization is that pulse trains eliminate electrical responses. In contrast, most reports of desensitization point to a marked reduction, but not elimination of electrical responses (Freeman & Fried 2011; Jensen & Rizzo 2007; Ryu et al. 2009). Perhaps surprisingly, the subthreshold white noise stimulus we presented yielded robust, ongoing responses, despite being presented at a frequency of 25 Hz that is typically expected to induce strong desensitization. Likewise, others have confirmed that robust responses persist at high frequencies as long as the pulse amplitudes are modulated over time (Maturana et al. 2018; Ho et al. 2018). Desensitization typically compares pulse train responses to a single isolated pulse response (an atypical stimulation pattern for bionic vision applications). We suspect that the robust responses we and others have observed at high stimulation rates reflect the encoding of stimulation changes in the context of a saturated desensitization mechanism. In effect, this amounts to stimulating within the context of a fixed electrical adaptation state – the absence of which compounds typical studies on desensitization. Furthermore, we speculate that the use of primarily subthreshold pulses in such a sequence may further reduce the effects of desensitization. Whether low-amplitude pulse modulation can drive visual perception without engaging cortical fading remains an outstanding question of great interest.

Neural Coding

An interesting yet unresolved issue, not only in retinal prosthetics but also in neuroscience at large, is the relative importance of firing rate vs. the precise timing and pattern of individual spikes – rate coding vs. temporal coding [Freeman *et al.* 2011]. Prostheses which target the retinal network (indirect RGC stimulation) tend to incorporate a presumption that the natural pattern of spikes generated by complex interactions in the network may be necessary for visual perception – a temporal code (Im et al. 2018; Lee et al. 2013; Im & Fried 2015). In contrast, in direct stimulation some investigators emphasize firing rate while others emphasize the temporal spiking pattern (Ryu et al. 2011; Fried et al. 2006). While indirect stimulation has the problem that precise control of the firing rate and pattern is difficult, direct stimulation necessitates an explicit model of visual encoding to employ temporal coding [e.g. (Fried et al. 2006)]. Accordingly, because the spiking response to electrical stimulation could be encoded in both bursts and tonic spikes, it is important to consider such coding in calculating STAs. Here, we have briefly presented a method developed to account for the influence of burst coding on the STA. As more is learned about temporal coding in the retina, further modifications to the STA method may become necessary. An open question is whether burst spikes and tonic spikes convey distinct information about electrical stimulation of the retina.

Oscillations

Related to bursts, a common spiking pattern seen in degenerated retinas is subthreshold membrane oscillations which strongly bias the timing of both tonic spikes and bursts toward the peak of the oscillation. Recent work has demonstrated that electrical stimulation can shift the phase of these oscillations, entraining subsequent burst cycles (Goo et al. 2015; Haselier et al. 2017). With respect to STAs, this poses a particular problem in that both the first volley of spikes driven by the electrical stimulus and subsequent entrained cycles will be reflected in the STA. Accordingly, we have seen evidence of such oscillations in the rd10 mouse retina (Sekhar et al. 2017). In order to better depict the average stimulus that drives responses in the rd10 retina, it will be necessary to develop a method to separate contributions of the stimulus shape and the ongoing oscillations from the STA.

Building the Model

Throughout this work, we have referred to a proposed modelling framework rather than an explicit model. This is because many of the important details of models falling within this framework may vary

from model to model. Furthermore, many of the details for implementation of such models remain uncertain. In **Figure 1**, we indicate that electrically-stimulated PR signals are passed synaptically to the BC where they are combined with electrical stimulation signals intrinsic to the BC. A similar process happens from BC to RGC. Nevertheless, we have remained agnostic as to how exactly these signals are combined. The relationship between depolarization and neurotransmitter release will entail a certain degree of nonlinearity owing to physiological limitations. Due to processes like consumption of the readily releasable pool of vesicles, this nonlinearity might have multiple kinetic parameters. Within the BC and RGC, it is unclear how direct stimulation and synaptic inputs will be weighted relative to one another. Additionally, it is unclear whether the two signals (BC electrical generator signal and PR synaptic input for BC; RGC generator signal and BC synaptic input for RGC) will be summed linearly or not.

Beyond refining the details of the proposed framework, we expect that a number of elaborations may be necessary. As noted in **Figure 5**, retinal neurons can be stimulated through at least two distinct mechanisms. Traditionally, a single short stimulus greater than the threshold can be used to drive spikes at short latency from stimulus onset. Complementarily, if the stimulus is more subtle, an extended stimulus waveform that matches the electrical input filter can elicit a response. In the framework presented, we have assumed that all instantaneous stimuli are subthreshold and that only the integrative mechanism is engaged. This is useful since single pulse activation could complicate input filter estimation and obscure the fast filter of direct RGC stimulation and possibly even the BC indirect filter, depending on stimulus design. Another potential elaboration may be the need to incorporate higher order stimulus-response correlations. While the STA is a good estimate of the first order stimulus-response relationship, higher order interactions are well documented for visual stimulation. Yet another elaboration that may be necessary is the incorporation of a spike history feedback term. It is well known that the Poisson distribution is an imperfect model for RGC spike train statistics. By incorporating a feedback term, effects like the refractory period, network inhibition, and post-inhibitory rebound can be reflected in the modeled spike train (Pillow et al. 2005).

As implied above, it will be useful to continue to develop noise stimuli beyond the temporal noise our group has examined. Other groups have had recent success in combining both time and space. A continuing constraint however is achieving sufficient resolution in each dimension for full characterization of the spatiotemporal receptive field. Spatially, there is currently a limit on the order of 50 μm pitch for electrode spacing. An obstacle in the temporal domain is the need to record neural signals in the presence of electrical stimulation artifacts. While we would love to present our noise stimulus at 1 kHz rather than the 25 Hz we used, such high stimulation rates would obliterate the neural signal with artifacts. However, based on the temporal filtering expected for the primary cells of the retina (1-100 Hz), it may be possible to design a band-pass filtered noise stimulus that is effectively continuous in time – thus reducing artifact amplitudes enough to preserve the neural signals.

Finally, as explicit models are developed within this framework, it will become necessary to implement iterative model fitting. While we have presented the STA as an estimate of the electrical input filter, and the generator signal-firing rate curve as an estimate of the nonlinearity, these functions are only good first approximations. By simultaneously fitting these two functions as well as the synaptic parameters, spiking history feedback function, and possibly higher order stimulus-response correlation functions, the various elements of the model should come into sharper focus. Toward that end, a strong stimulus-response correlation is important. To date, we have found that our methods produce only modest correlations. By stimulating more strongly, while remaining within the subthreshold,

integrative domain, it should be possible to drive more reliable responses that are still useful for the modeling described above.

Conclusions

Investigations of the retina's response to electrical stimulation have advanced significantly in the past twenty years. Recently, a growing body of work has sought to apply linear systems analysis to this domain. Of particular interest is the use of white noise stimuli to characterize the linear filtering behavior of the retina to electrical stimulation. We have proposed a modelling framework for such research that we hope may address ongoing challenges in bionic vision. By expressing stimulation of the retina in terms of integrated charge – taking into account the leaky memory of retinal neurons – a more useful understanding of the stimulation may be realized. Furthermore, by carefully measuring the spatio-temporal filtering properties of individual retinal ganglion cells, we expect that stimuli can be identified to selectively activate each of the approximately thirty different RGC types. Finally, modeling the temporal integration of the retina should enable the use of lower amplitude stimuli that minimize retinal desensitization and reduce perceptual fading of bionic visual percepts. Ultimately, the linear systems framework is hypothesized to facilitate substantially improved bionic vision for future recipients of retinal prostheses.

Legends

Figure 1: Three-stage filter

(A) Proposed modelling framework for how direct electrical noise stimulation of photoreceptor (PR), bipolar cell (BC), and retinal ganglion cell (RGC) may be combined to yield ganglion cell spiking responses. (B, left) In the proposed model, the PR, BC, and RGC filters are each shifted such that their peak latencies match the typical RGC spiking latencies for each source [100, 15, and 2 ms respectively; (Boinagrov et al. 2014)]. (right) The corresponding power spectrums show peaks at 5, 25 and 100 Hz, respectively [(Freeman, Eddington, et al. 2010); but see also (Twyford & Fried 2016)]. (C) The three time-shifted filters are combined to yield the compound filter that would be measured from the RGC as a STA. (D) The generator signals resulting from presenting a noise sequence to each cell as well as the net RGC generator signal created by summing all shifted signals as described in A. Vertical axes in B, C, and D are in arbitrary units.

Figure 2: Spatiotemporal receptive fields.

Antagonistic center and surround mechanisms contribute to the retinal ganglion cell visual receptive field in space for ON (A) and OFF (B) cells. Center and surround mechanisms combine in both time (C) with the surround delayed relative to the center, and in space (D, E) with the surround coextensive with the center. The net effect is a sensitivity profile in both time and space (C and E combined) termed the spatiotemporal receptive field (STRF). [Modified from (Rathbun 2009), Fig 1.3.]

Figure 3: Matching stimulus and receptive field sampling density.

(**A**) Binary (**top**) and Gaussian (**bottom**) stimulus amplitude distributions and example stimulus frames for a 16 x 16-check spatial layout. (With such stimuli, instead of 'pixel' the term 'check' is often used in analogy to a checkerboard in order to discriminate between stimulus elements and pixels of the visual display device.) For each video frame of a time-varying stimulus, the brightness of each check is drawn independently from either the binary or the Gaussian distribution. (**B**) Relationship of the neuronal receptive field (RF) size to the stimulus with either one (**top**), a few (**middle**), or many (**bottom**) checks being integrated by the RF. (**C**) Generator signal sampling distributions (arbitrary units) produced by the stimulus/RF combinations shown in **B**. In each pair of plots, sampling distributions for binary (**left**) and Gaussian (**right**) stimuli are shown. Bar colors correspond to the stimulus distributions in **A**; plot borders correspond to the stimulus/RF pairings of **B**; the underlying stimulus/response nonlinearity of the cell is the dotted red line with sampled points indicated by red dots, and the threshold indicated in maroon. Left y axis corresponds to bar heights, right y axis corresponds to the nonlinearity. (**D**) Spatial frequency power spectrum of the RF-filtered stimulus relative to the Nyquist frequency of the stimulus. Black points indicate the frequencies that can be sampled for any given RF/stimulus pairing. The three pairings of **B** are indicated with lavender, blue, and cyan lines. Threshold of the cell is shown in maroon.

Figure 4: Spike-triggered Averaging

(A) Stimulus segment (**top**) containing a random pulse amplitude sequence of 1 ms pulses at 25 Hz with accompanying high-pass filtered voltage recording (**middle**) and spike train rastergram (**bottom**). An example pulse sequence and its associated spike are highlighted in red. Pulse amplitudes were drawn randomly with replacement from a Gaussian distribution shown at **right** in blue. Dotted lines mark mean and SD voltages. **(B)** Sample pulse amplitude sequences of the 7 spikes from **A**. **(C)** Average pulse modulation sequence preceding all spikes (blue) overlaid with individual sequences that best matched the STA (black) and the significant kernel used for calculating the generator signal (red). **(D)** Scatterplot of the first and second principal component amplitudes for all stimulus waveforms (blue points) with waveforms preceding spikes overlaid in red. Insets show the principal components overlaid with the STA. **(E)** Generator signal was calculated by convolving stimulus sequences with the STA kernel. Generator signal distributions for all stimuli (black), for spike-associated stimuli (blue) and for spike count weighted spike-associated stimuli (red) are overlaid. **(F)** The spike generation nonlinearity derived from **E**. For high signal values low sample size leads to uncertain firing probability estimates. [Modified from (Sekhar et al. 2016), Fig. 1]

Figure 5: Two Stimulation Modes – single pulse and pulse integration

(A) For two example cells, the firing rate within 40 ms of a pulse is plotted against the amplitude of that pulse to yield a voltage-response curve (**left**), demonstrating the threshold for single pulse activation via network stimulation. The STA for each cell is shown in blue at **right**. (B) As in A, but for two RGCs that do not respond to single pulse stimulation. Note the red point in each of the 4 STAs. The RGCs in A exhibit notable single pulse activation in the first time point to the left of 0 in their STAs while the RGCs in B do not. (C) Distribution of first STA deflection latencies when STAs are not corrected for single-pulse activation. (D) Overlay of pulse modulation waveforms with (red) and without (black) single pulse activation for another sample cell. [Modified from (Sekhar et al. 2017), S2]

Figure 6: Measuring threshold from noise stimulation

Overlay of voltage-response curves for: 1) a single RGC (dotted, red) and 2) a large population (solid, black) using traditional methods (1 ms pulses presented at 5 s intervals, 20 repetitions each, response integration window: 10–100 ms, [per (Jalligampala et al. 2017)]) as well as for 3) a single cell using white noise (thick, red). Inset is to scale on the voltage axis and demonstrates the amplitude of the STA relative to the voltage-response curve for the cell stimulated with white noise (thick red line). White noise stimulus distribution from Fig. 3 is replotted below for context. [Modified from (Sekhar et al. 2016), Fig. 3]

Figure 7: Burst Correction:

(A) Classification of RGC spikes: all spikes within 100 ms of each other were considered burst spikes, while remaining spikes were singleton (tonic) spikes. Burst spikes were classified as either first, last, or intraburst spikes. To correct STA calculations for burst responses, the first spike of each burst was weighted according to the number of spikes in the burst. (B) A plot of following interspike interval (ISI) against preceding ISI for every spike of an RGC reveals these 4 spike categories. (C-E) Uncorrected (blue) and burst corrected (red) STAs for three example cells showing the range of effects for burst correction. Shaded regions mark negative deflections for each STA. [Modified from (Sekhar et al. 2016), Fig. 2]

Figure 8: Correspondence of visual and electrical responses.

(A) responses of example ON (red) and OFF (blue) RGCs to on/off flashing stimulation. (B) Visual input filters (STAs) for these cells calculated from full-field, 10 Hz, Gaussian visual noise stimulation. (C) Electrical input filters (STAs) of the same cells calculated from 25 Hz, cathodic, Gaussian noise electrical stimulation as described above. (D) Latencies of the upward and downward electrical input filter deflections for a population of cells. Some cells have monophasic filters while others are biphasic (schematic inserts). [Modified from (Sekhar et al. 2017) Fig. 3, 5, first appeared in (Rathbun & Hosseinzadeh 2017), Fig. 4]

Figure 9: Noise samples stimulus space

Electrical stimuli are drawn from a high-dimensional space of parameters. Three such parameters for a train of pulses are amplitude, duration, and interpulse interval. White noise stimuli, however, draw randomly from this parameter space. [Modified from (Rathbun & Hosseinzadeh 2017), Fig. 2]

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