

Parallel Cone Bipolar to On- β Ganglion Cell Pathways in the Cat Retina: Spatial Responses, Spatial Aliasing and Spatial Variance

Bennett Levitan* and Gershon Buchsbaum

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Department of Bioengineering
School of Engineering and Applied Science
University of Pennsylvania
220 South 33rd St.
Philadelphia, PA 19104-6392
Phone: (215) 898-5767
E-mail: gershon@eniac.seas.upenn.edu

* Corresponding author

Present address is
Santa Fe Institute
1399 Hyde Park Road
Santa Fe, NM 87501
Phone: (505) 984-8800
Fax: (505) 982-0565
E-mail: levitan@santafe.edu

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Abstract

An important issue in understanding the retina is finding candidate functional roles for different cell pathways and the details of their anatomy and physiology. We consider various spatial properties of the three main cone pathways: cone bipolar cell, on- β ganglion cell pathways in the cat retina and possible roles for the particulars of their anatomy. The cone bipolar cells in these

pathways have distinct morphologies and modest differences in their convergence, divergence, densities and synaptic weighting; and it is unclear whether the pathways differ in their spatial properties or in some other manner. Since differences in spatial processing of cells are best studied on a system-wide level, we developed the multirate filter-based method of retinal modeling, a technique for relating the anatomy of multiple cell layers to its systemic effects. We demonstrate: (i) Despite the anatomic distinctions between the three main cone bipolar cell pathways, their spatial responses are essentially identical; (ii) Despite the spatial averaging in the pathways, there is essentially no filtering of the non-aliasing signal components after the cone layer; (iii) Instead, this averaging combined with prefiltering by the eye's optics and cone gap junctions prevents spatial aliasing; and (iv) The averaging and prefiltering combined allow cell responses to be similar despite significant cell-to-cell anatomic differences.

1. Introduction

Retinal anatomic and neurophysiologic research provides a wealth of details on the fine architecture of retinal circuitry. These details include cell densities, fine distinctions between cell types, shape and form of dendritic trees, convergence and divergence between cells, and details of synaptic contacts [1, 2, 3, 4, 5, 6, 7, 8]. Many of the well-mapped cell-to-cell connections can be analyzed on an individual basis. However, issues such as spatial aliasing, variation in responses of cells of the same type, and changes in the content of the image signal through multiple cell layers depend on system-wide collective properties. These issues can not be studied on a cell-to-cell basis because array-wide spatial operations and properties are not always easily inferred from individual cell anatomy and physiology.

In this paper, we examine several system-wide operations as a signal passes through the three main cone bipolar cell and on-axis ganglion cell pathways in the cat retina. We chose these pathways since their anatomy and physiology are known in great detail. The goal is to explore candidate functional roles for the different pathways and for the particulars of their anatomy. The cone bipolar cells in these pathways have distinct morphologies and modest differences in their convergence, divergence, densities and synaptic weighting; and it is unclear whether the pathways differ in their spatial properties or in some other manner. In an earlier paper, we showed that spatial aliasing is prevented in the cat cone bipolar cell (CBb1) and on-axis ganglion cell pathway by the optics of the eye, cone-cone gap junctions and other sources of spatial

blurring before the cones in combination with synaptic and dendritic weighting between cell layers [9]. To relate cell-to-cell anatomy to its systemic effects for this study, we de-veloped the multirate filter method of retinal modeling [9, 10], which we also use in this work. We briefly review the multirate method here.

Multirate filtering is a branch of signal processing that concerns manipulating signals of different sampling rates. The basic multirate retinal model is defined for cells of class A with density d_A presynaptic to cells of class B with density d_B . Signals s_A and s_B correspond to the arrays of A and B cells respectively, where the sampling period of each signal equals the nearest neighbor distance of the corresponding array. At a single adaptive state, the cells we model sum their inputs linearly [11, 12, 13] and can be simulated by convolving s_A with the appropriate filter. However, since s_A and s_B are at different sampling rates, multirate filtering is necessary. The basic multirate operations required are upsampling and downsampling [14, 15]. An L-fold upsampler inserts $L-1$ zero-valued samples between adjacent samples along each axis in a signal and decreases the signal's sampling period by a factor of L. An M-fold downsampler removes $M-1$ out of every M samples along each axis in a signal and increases the signal's sampling period by a factor of M. These operations are used as shown in Fig. 1 to form the basic multirate model. The filter h models the synaptic and dendritic weighting. Without the appropriate filtering, the resamplers may induce aliasing [14, 15]. Depending on the characteristics of s_A and s_B , s_A will show aliasing or be aliasing-free.

This basic multirate model can model any synapse by appropriate choice of L, M and h.. For a two-dimensional array of cells,

$$C = \frac{d_A}{d_B} \quad (1)$$

where anatomic convergence C is the average number of A cells to synapse upon a single B cell and anatomic divergence D is the average number of B cells a single A cell synapses upon [9, 16]. L and M are set to the smallest integers that satisfy (1).

The weighting in the retina is characterized by a synaptic weighting function (swf) and a dendritic weighting function (dwf) [17]. For an A cell synapsing at location (x, \hat{y}) relative to the center of a B cell's dendritic tree, $swf(x, \hat{y})$ is the average number of synapses between the B cell and the A cell, and $dwf(x, \hat{y})$ is the average change in voltage in the B cell soma induced by a unit injection of current from the A cell. h is proportional to both functions:

$$h = \frac{swf(x, \hat{y}) \cdot dwf(x, \hat{y})}{d_A} \quad (2)$$

where T_x is the presynaptic array sampling period and K is a gain factor [9]. The number of non-zero value samples in h , N_h , is set so model convergence and divergence match the anatomy:

$$\text{and } \quad , \quad (3)$$

where C_m and D_m are the convergence and divergence in the model. Typically, we use circular shapes for the filters as defined by

The system in Fig. 1, in which the upsampler, filter and downsampler operate separately, is known as the direct-form filter implementation. The more intricate implementation which combines these operations and corresponds to the anatomy is the space-varying filter implementation [9]. It uses different filters at different spatial locations, because the samples of h and g are not always aligned [14, 15]. There are L_2 space-varying filters with different numbers, locations and values of weights, corresponding to dendritic trees with variable convergence, branching pattern and number of synapses. There are on average C_m samples in the filters whose weight values are selected from the weights of direct-form filter h [9, 14].

To maintain the same zero-frequency gain in all the space-varying filters, it is sometimes necessary to rescale them so that the sum of the coefficients in each filter is the same [9]. This problem arises whenever cells of the same type receive different numbers of synapses [18]. Rescaling corresponds to changes in K or in small modifications to the dwf and results in abrupt changes in direct-form filter height [Fig. 3]. However, these changes only reflect the different scaling factors for each space-varying filter and do not change their shapes.

With the multirate method, we model and study the cone f1 cone bipolar cell f1 on- $\$$ ganglion cell pathways in the cat retina. In Section 2, we design the multirate model, paying special attention to the derivation of model parameters from the known anatomy. Since some anatomic parameters needed in the model have not been measured, we had to make some assumptions. In Section 3, we describe various tests that demonstrate the validity of these assumptions. Finally, in Section 4, we calculate the responses of cells in the model and examine the issues of spatial aliasing, changes in the frequency content of the image signal through multiple cell layers, and variation in responses of cells of the same type.

2. Designing the cone f1 CBb1, 2, 3 f1 on- $\$$ cell systems model

Four types of cone bipolar cells, CBb1 - CBb4, transmit signals from cones to on- $\$$ ganglion cells [1]. We model the pathways involving bipolars CBb1 - CBb3 at 1° eccentricity [Fig. 2]. These three cell types contribute 97% of the bipolar cell input to on- $\$$ cells and essentially can be

regarded as their bipolar cell input. Amacrine cell synapses are also an integral part of the on- β cell circuit, but they are not addressed by our model.

The three cone bipolar cell pathways operate in parallel [Fig. 2]. Each synapse is modeled using the multirate structure described above and in [9, 10]. The model's input is the output of the cone array (icone). In our analysis, we set icone to either an arbitrary test signal or the cones' response to an impulse of light. Since this response has not been measured directly, we use the cone response computed in [17], shown in Fig. 9(f). This response is the "optics-to-cone" impulse response or "prefilter," indicating the spatial impulse response of all processing that occurs from the cornea through and including the cone pedicles, e.g., the optics, cone aperture, cone-cone gap junctions, A and B horizontal cells, etc. [9]. iCBb1, iCBb2 and iCBb3 are the three cone bipolar cell images. The model's output is the on- β cell array's signal (ion- β), formed from a weighted sum of the outputs of the three cone bipolar cell pathways, $i\beta_1$, $i\beta_2$, and $i\beta_3$. $i\beta_1 - i\beta_3$ do not correspond to cells but are useful signals that we use below. The filters represent synaptic and dendritic weighting when cells are at a constant adaptive state and not near saturation.

The densities for the cells are listed in Tab. 1. Table 2 lists the anatomic convergences (C), divergences (D), C/D ratios and density ratios of the six synapses. Typically only a few cells are available to calculate anatomic properties, and several properties we use below have large variances. However, in the tables, we list anatomic values at the precision given in their original reports. We use their full precision to demonstrate the high degree of matching possible between multirate models and retinal anatomy.

Because the three pathways in the model act on the same input array and merge to form the same output array, they each must undergo the same overall change in sampling rate [14, 15].

Thus, the resampling factors M and L have the additional anatomic constraint of

$$. \quad (4)$$

We select resampling factors subject to this constraint [Tab. 3]. Except where otherwise indicated, we refer to the resampling factors as M and L without subscripts, using the context to identify the synapse. We demonstrate the derivation in detail for three synapses and summarize the calculations for the others.

2.1. Cone $iCBb1$ synapse

In [9], we derived a model for this synapse in which $L = 1$ and $M = 2$ (Fig. 2, top, left-hand side). To achieve complete tiling, we alternated between two filters: , which

has five weights arranged in a plus-shape (+), and \hat{w}_+ , which has five weights arranged in a cross-shape (\hat{w}_+). These filters yield $C_m = 5.0$ and $D_m = 1.25$ [Eqn. (3)], matching the anatomic convergence of 5.1 and divergence of 1.2 [Tab. 2].

Since CBb1 - CBb3 are narrow field bipolar cells and are likely isoelectric, we set their dwf's to a constant. The properties we examine are independent of this constant, so without loss of generality we arbitrarily set the dwf to one. Below, we estimate swf's for the cone fi CBb2 and cone fi CBb3 synapses using available anatomic data, but the analogous data is unavailable for the cone fi CBb1 synapse. Using the CBb2 and CBb3 estimates, we assume an average of 5.4 synaptic contacts between one cone and one CBb1. Some evidence favoring this average comes from Figs. 1 and 2 in [2] which show a range of 4 to 7 contacts/cone to cone bipolar cells of uncertain type. Data on several cell types suggests that the number of contacts/cone lessens with the cone's distance from the center of a dendritic tree [3, 4, 5]. With this data, we estimate a swf of 7 contacts from the center cone and 5 contacts each from the four distant cones, giving an average of 5.4 synapses/cone. Using Eqn. (2), the resulting filters are

$$\hat{w}_+ = K \left(\frac{r}{r_0} \right)^2 \quad (5)$$

where K is set to 0.037 to give a unit zero-frequency gain.

2.2. CBb1 fi on- $\$$ cell synapse

Because the measured C/D ratio and density ratio differ significantly for this synapse [Tab. 2], the model can not be set to match both parts of Eqn. (1). We set the model to match the generally more reliable density measurements. This decision yields $M\hat{E} = \hat{E}16$, $L\hat{E} = \hat{E}9$ and $R_{\text{circ}} = 13.35$, which define a filter with $C_m = 6.93$ (anatomic range 6 - 7) and $D_m = 2.19$ (anatomic measurement of 3). These values also permit complete tiling of the CBb1 array.

Smith and Sterling argue that electrotonic decay along on- $\$$ cell dendrites at 1° eccentricity is insignificant, and therefore the dwf for this synapse is constant [17]. We set the dwf to one. The swf is not known in detail, but several anatomic measurements constrain it: i) CBb1's near the middle of the on-b cell dendritic tree give many (12-33) contacts [6], ii) CBb1's near the edge of the tree give few (3-4) contacts [6], and iii) CBb1's presynaptic to an on- $\$$ cell make on average a total of 81 contacts with the cell [7]. The largest value of 33 corresponds to the peak of the swf. The distance from the center of the on- $\$$ cell dendritic tree to the most distant dendrite tip is about 20 mm [6]. Assuming a Gaussian swf, we set

$$\hat{w}_+ = K e^{-r^2/r_0^2} \quad (6)$$

where radius r is in mm. Equation (3) gives CBb1's that average 33 or fewer contacts at the center

of an on- ϕ cell and about 3 contacts at 20 μ m radius. The average total number of CBb1 contacts to one on- ϕ cell in the model is 83.0 [10], close to the anatomic value of 81 [7].

To derive the filter, we substitute (3), $L_{CBb1} = 9$, $T_x = T_{CBb1} = 12.8$ μ m, and our dwf of 1 into (2) to give

$$\dots (7)$$

To set gain K, we note that the bipolars CBb1, CBb2 and CBb3 are weighted in the ratio of 4:2:1 in their number of contacts to the on- ϕ array [7]. The sum of their signals form the on- ϕ signal. To maintain a unit zero-frequency gain in on- ϕ cell output, we set K to $4 / (4 + 2 + 1)$ times the value that would give the output of the CBb1 fi on- ϕ filter alone a unit zero-frequency gain, giving $K = 8.5 \times 10^{-5}$. As explained in the Introduction, multirate filters based on anatomy usually require rescaling of their coefficients to maintain a constant zero-frequency response in all output samples.

The rescaled version of this filter is shown in Fig. 3(a).

2.3. Cone fi CBb2 synapse

For the cone fi CBb2 synapse (Fig. 2, middle, left-hand side), Eqn. (1) gives $M = 32$ and $L = 13$. No circular filter can completely tile the presynaptic array yet also match the anatomic convergence and divergence of 6 and 1 respectively. To achieve complete tiling, we added samples to the circular filter until it was large enough for complete tiling. The resulting filter shape is essentially square and has $C_m = 6.09$ and $D_m = 1.01$ [Fig. 4(a)] [10].

Since CBb2 is a narrow field bipolar cell, we use a constant dwf. To estimate the swf, we note that cone pedicles have invaginations, called triads, where bipolar cells insert dendritic processes to receive cone synapses [19]. These synapses are of three morphological types: flat, invaginating and semi-invaginating [20, 21]. CBb2's and CBb4's form fully-invaginating synapses in triads while CBb1's form semi-invaginating ones [1]. Though CBb3 synapses are of unknown type, since CBb3's are morphologically more similar to CBb2's and CBb4's than to CBb1's, we regard them as invaginating also. To estimate the swf, we equate the number of locations for invaginating synapses with the number of invaginating processes that CBb2, CBb3 and CBb4 cells provide.

Cones have on average 17 triads, and each triad has one invaginating synapse [22]. Thus, the number of spots for fully-invaginating processes/mm² is $(d_{\text{cone}} \times \text{cones/mm}^2) (17 \text{ triads/cone}) (1 \text{ spot for an invaginating synapse/triad}) = 24,200 \times 17 = 411,400$. Defining S_i as the average number of invaginating processes provided by one CBbi, the number of fully-invaginating

processes/mm² is given by $d_{CBb2} S_2 + d_{CBb3} S_3 + d_{CBb4} S_4 = 4,000 S_2 + 4,400 S_3 + 4,300 S_4$. Since cone bipolar cells gather synapses from every cone above their dendritic trees, we assume that S_i is proportional to the average area of the dendritic tree for CBb_i . The radii of CBb_2 and CBb_4 dendritic trees are both about 8.5 mm [1]. CBb_3 dendritic tree radii are not known, but since CBb_3 is also a narrow field bipolar cell, we consider their radii approximately the same and set $S = S_2 = S_3 = S_4$. Equating the number of invaginating processes with the number of places for them gives $S = 32.39$ as the average total number of synaptic contacts from cones to each of CBb_2 , CBb_3 and CBb_4 cells. For an invaginating bipolar cell in [2], we counted a total number of 31 contacts from cones, a value close to our estimate here.

Dividing 32.39 synapses/ CBb_2 by the convergence of 6 cones/ CBb_2 gives 5.4 CBb_2 synapses/cone. This number is well-within the 4 - 7 range we counted in [2]; and we set the swf's peak to 7. The Gaussian that gives an average total of 32.39 synaptic contacts to CBb_2 cells is

$$(8)$$

where r is in mm. Substituting (5), $L_{cone} = 13$, $T_x = T_{cone} = 6.428$ mm and $d_{wf} = 1$ into (2) gives the direct-form filter

$$(9)$$

$K = 1.82 \cdot 10^{-4}$ for unit zero-frequency gain. Fig. 3(b) shows the rescaled version of this filter.

2.4. Other synapses

The remaining three synapses in the model are defined similarly. Their parameters are listed in Tab. 3. The d_{wf} 's for the CBb_2 fi on- $\$$ and CBb_3 fi on- $\$$ synapses are identical to that of the CBb_3 fi on- $\$$, as all three use the same dendritic tree. The cone fi CBb_3 d_{wf} is also set to one as it is a narrow field cell. The swf's and filters are derived as follows:

CBb_2 cells presynaptic to an on- $\$$ cell give on average a total of 42 synaptic contacts, while the number of contacts between CBb_2 cells and on- $\$$ cells varies from 1 to 18 [7]. No Gaussian curve can give an average of 42 contacts yet have a peak of 18 and reach 1 at R_{circ} , so we tried curves of the form $p(1 - r^q/s)$, where p , q and s are constants. One such curve that fit our constraints is , which, by Eqn. (2), yields direct-form filter

$$(10)$$

$swf_{cone} CBb_3$ is identical to $swf_{cone} CBb_2$. As for $h_{cone} CBb_2$, a circular filter with the correct convergence does not completely tile the presynaptic cone layer. The modified filter shape in Fig. 4(b) provides the correct convergence and complete tiling. Using Eqn. (2), the filter is

$$(11)$$

Finally, CBb3 cells give on average a total of 21 contacts to on- $\$$ cells with a range of 2 to 21 contacts per CBb3. The Gaussian swf that matches these constraints is which yields a direct-form filter of

(12)

where again a non-circular shape is required for complete tiling. The K's listed in Tab. 3 for hCBb2fion- $\$$ and hCBb3fion- $\$$ are set to give zero-frequency responses of 2 / 7 and 1 / 7 respectively to maintain unit zero-frequency gain in ion- $\$$ (subsection 2.2).

2.5. Cell densities in the model

Throughout the model, the M/L ratios are essentially equal to the density ratios. Differences are of little consequence, because of anatomic variability within a species and measurement error. However, because there is not an exact match, the model densities are not identical to those of the anatomy. Setting $d_{\text{cone}} = 24,200/\text{mm}^2$ and using the resampling factors defined above, Eqn.

(1) gives the model densities, sampling periods and Nyquist rates listed in Tab. 4.

3. Testing the model

In designing the swf's from the limited data available, we made assumptions about their shapes and heights. We also made the common assumption of rectangular sampling. Despite the enforced match of the model to the anatomy, there are potential incompatibilities between them. To test the assumptions and the correspondence between model and anatomy, we show that anatomic and physiologic properties of the cat retina compared well with their equivalents in the model.

(i) Distribution of total number of cone bipolar cell synapses to on- $\$$ cells

From the three on- $\$$ cells examined in [7], the total numbers of synaptic contacts from

CBb1's and CBb2's to on- $\$$ cells appear to stay within small ranges. An on- $\$$ cell receives 81 ± 12

CBb1 contacts and 42 ± 3 CBb2 contacts. The number of CBb3 contacts is more variable and has

been observed at 9, 26 and 27 with an average of 21. Similar measurements in the model show

the total number of model CBb1 contacts averages 83 and varies from 74 to 88. Model CBb2

contacts average 42.1 and vary from 38 to 48, model CBb3 contacts average 24.5 and vary from

22 to 27. There is a good match between model and anatomy in the ranges of total number of

contacts for CBb1's and CBb2's. The results for CBb3's match less well, primarily because of the

influence of one on- $\$$ cell in [7] which received only 9 CBb3 contacts.

(ii) Synaptic contributions of different cone bipolar cells to on- $\$$ cells

While the total number of bipolar cell contacts to on- $\$$ cells stays in a limited range, the

number of contacts from individual bipolar cells is quite variable [7]. Another test of our swf's is

whether the model demonstrates this variability. For the on- $\$$ cells in [7], we calculated the average percent of total CBb1 contacts given by that CBb1 which makes the most contacts. We repeated this calculation for those CBb1's giving the second-most, third-most and fourth-most contacts, then made the same calculations for CBb2's, CBb3's and the model. The test results show a very good match between model and anatomy for both percent contributions as well as the percentage that the first four bipolar cells make of the total number of bipolar cell contacts [Tab. 5].

(iii) Coverage factors

Detailed reconstructions demonstrate the degree to which the dendritic trees of adjacent cells of the same type tangentially overlap [4, 7]. This overlap is typically quantified with the coverage factor, the product of dendritic tree area and cell density. Coverage factors for the cone bipolars are all approximately one, meaning that on average each cone contacts only one cone bipolar cell of each type [4]. We calculate an anatomic on- $\$$ cell coverage factor of 2.2, using a dendritic tree radius of 19.5 μ m [6]. As shown in Tab. 6, with the exception of CBb1, there is a good match between these coverage factors and the corresponding values in the model. We are uncertain why CBb1 is an exception.

A graphic demonstration of this difference in coverage factors between cone bipolars and on- $\$$ cells is shown in Fig. 5. The trees of adjacent model CBb1's do not intermesh, while the trees of adjacent model on- $\$$ cells overlap significantly. Tangential photos of the corresponding cells in the cat retina show similar degrees of overlap [4, 7, 8].

(iv) Total convergence and divergence

In the model, the overall convergence from cones to on- $\$$ cells averages 38.8 and ranges from 34 to 45, the overall model divergence averages 3.07 and ranges from 1 to 5. Signals from these cones travel through between 4 - 9 CBb1's, 4 - 6 CBb2's, and 2 - 4 CBb3's en-route to one model on- $\$$ cell, giving a range of 10 - 19 model cone bipolar cells synapsing upon a model on- $\$$ cell. From retina serial reconstructions, up to 37 cones converge via 14 - 17 bipolar cells onto one on- $\$$ cell [7]. The range of 14 - 17 is very likely an underestimate since only three on- $\$$ cells are included. Though more reconstructions are necessary to make a statistically significant comparison, the overall model convergence is consistent with the anatomic observations.

(v) On- $\$$ cell frequency response

By setting α to the estimate of the response of cones to an impulse of light, the optics-to-cone response or prefilter, we can compute spatial frequency responses for the other arrays in the

model. The model's on- $\$$ array response to this input matches an estimate of the cat retina's 1° eccentricity on- $\$$ cell frequency response (calculated from [14]), though they diverge somewhat beyond their peaks [Fig. 6].

4. Analyzing the model

4.1. Spatial similarities in the three bipolar cell paths

Because the three types of cone bipolar cells have distinctly different morphology [1], we expect there to be important differences in their functions. However, they differ little in convergence, divergence, dendritic tree size and density, so the spatial component of their responses should be similar. It is not known whether their post-synaptic receptors differ.

Calculations based on anatomic reconstructions show very similar impulse responses for a few CBb1 and CBb2 cells [7]. We find similar results in general for the three bipolar cell paths here.

For comparative purposes, we characterize the model impulse responses in terms of their best-fitting difference of Gaussians (DOG) curve given by

$$(13)$$

where r is radius, k_c and r_c define the center Gaussian, and k_s and r_s define the surround Gaussian.

This model is often used to describe both individual ganglion cell responses and system level responses of ganglion cell pathways [17, 23, 24, 25, 26].

Figure 7 shows the frequency do-main responses of the three bipolar cell images (iCBb1, iCBb2, iCBb3) and their on- $\$$ contributions (i $\$$ 1, i $\$$ 2, i $\$$ 3) when i_{cone} is set to the optics-to-cone response.

For purposes of comparison, the curves are normalized to have a maximum value of one. The

center-surround nature of i_{cone} is propagated through all subsequent arrays in the model. All

responses are well fit by the DOG curves whose parameters are given in Tab. 7.

The three bipolar

cell responses differ slightly in detail above 3 cycles/degree, but are essentially the same. The

bipolar cell paths are slightly more diverse in their on- $\$$ response

contributions. Some of the

difference for frequencies above about 2 cycles/degree is caused by aliasing of i $\$$ 2, and i $\$$ 3

(discussed in subsection 4.2). This similarity of the different bipolar cells' responses argues in

favor of differences between the three classes of cone bipolar cells being in a domain other than

spatial processing, such as their temporal response, degree of adaptation, or the range of light

levels to which they respond linearly [7].

4.2. Aliasing analysis of bipolar cell pathways

Throughout the model, because the signal propagates in the direction of decreasing cell

density [Tab. 4], there is the potential for spatial aliasing. To prevent this aliasing, the filters must

remove high frequencies from the signal in one array before they can alias in the next array. In particular, multirate filtering theory shows that direct-form filters in systems like Fig. 1 must attenuate components above the filter's Nyquist frequency/ $\max(M, \hat{E}L)$ to prevent aliasing (Technically, two similar artifacts can occur, aliasing and imaging; but we will not distinguish between them here) [14, 15].

The magnitudes of discrete time Fourier transforms (DTFT's [27]) of some direct-form filters from the model are shown in Fig. 8. The DTFT's are mostly rotationally symmetric, and we show only their cross-sections. The vertical lines show the cutoffs required to prevent aliasing. Solid lines show the original filters and the dashed lines show the rescaled filters. As can be seen, rescaling has negligible effect on the filters below the cutoffs. While these filters are low-pass, they pass with significant magnitude frequency components above their cutoffs. The same is true for all filters in the model. The main anatomic reason that the filters are not sufficiently low-pass is that their dendritic trees have small convergences [9].

We characterize the degree of aliasing with frequency response functions, shown in Figs. 9(a) and 9(b) for the CBB2 pathway with no prefiltering. The dashed lines show the response of CBB2's and on-S cells to frequencies below their Nyquist frequencies, 6.95 and 4.81 cycles/degree respectively. Components of higher frequencies are aliased into the 0 to Nyquist frequency baseband; the solid line shows the dashed line response plus the aliasing. As indicated by the large differences between the dashed and solid lines, ICBb2 and IS2 show considerable aliasing. The situation is even worse for IS2 as much of the CBB2 signal acting as input to the second stage consists of aliasing from the first stage. Results are essentially identical for the S1 [9] and S3 pathways. Thus, high frequency components in the input can alias in all stages and introduce spurious frequencies. While irregular sampling in the retina [1, 5] would cause this aliasing to manifest partly as low frequency sinusoids and partly as broadband noise [28, 29, 30], both types of artifacts lead to significant degradation of the signal [28].

By changing the input to reflect prefiltering by the cat's visual system, we demonstrate how the prefilter mitigates this aliasing. We first examine the effects of the cat's optics alone, whose frequency response is shown in Fig. 9(c) [31, 32]. As compared to the responses with no prefiltering, the optics remove about 2/3 of the aliasing [Figs. 9(d) - 9(e)]. To include all the prefiltering in the cat retina, we set the model's input to the optics-to-cone prefilter [Fig. 9(f)]. For ICBb2

and I^2 , the differences between the dashed and solid lines are small and the aliasing is essentially removed [9(g) and 9(h)]. We consider the slight amount of aliasing that remains insignificant because the aliasing forms a near insignificant part of the on- S output and is likely at or barely above the level of neural noise. Thus, the combination of synaptic weighting along the bipolar cell pathways along with the attenuation of high frequencies done before or at the cone level just barely prevents aliasing that would otherwise corrupt cone bipolar cell and on-b cell signals. Neither the prefilter nor the synaptic weighting alone is sufficient to prevent aliasing. We found the same type of results for the CBb1 [9] and CBb3 pathways.

4.3. Changes in cell responses through cone bipolar cell cascade

We have shown that the synaptic weightings and convergences form low-pass filters which remove the aliasing frequency components. In this subsection, we examine whether this averaging serves only to prevent spatial aliasing or also changes the signal by altering the non-aliasing frequencies. We address this issue by comparing successive outputs in the model.

The center of the model's bipolar cell responses are essentially identical to that of the cone response. The centers of the on- S contributions are slightly wider than the centers of the corresponding bipolar cell responses [shown for the CBb2 pathway in Fig. 10(a)]. This result is similar to the overall cone to on- S cell change over the CBb1 pathway found for one on- S cell [17]. In the frequency domain, the downslope drops slightly from bipolar cells to on- S cells [Fig. 10(b)]. (The apparent increase in magnitude of i^2 above 3.5 cycles/degree is due to aliasing, not to increased baseband response [see section 4.2].)

Changes can also be seen in the difference-of-Gaussians fits to the outputs (Tab. 7). The radius of the center Gaussian r_c increases slightly from the cone image to the cone bipolar cell images and increases somewhat more from the bipolar cell images to the on- S component images. Changes in the radius of the surround Gaussian r_s are not reliable, since changes on the order of ± 10 have little effect on the difference-of-Gaussians curve when $r_s \gg 130$. With the exception of the cone bipolar cell synapse, k_s increases in each bipolar cell pathway in each stage. These changes indicate a slight widening of the center as the surround deepens, as shown in Fig. 10.

4.4. Prefiltering lessens differences in on- S cell responses caused by anatomic variation

In the retina, the shapes of dendritic trees and the synaptic weighting between cells are quite

variable [1, 2, 7]. This variability can cause cells of the same class exposed to the identical visual stimulus to respond differently, a property known as spatial-variance. Spatial-variance can be problematic, as identifying objects is made more difficult if they appear differently at different locations in an image. Some authors have proposed methods whereby the visual cortex adjusts for the spatial-variance in the retina [33, 34]. Others have suggested that the cat optics so blur differences in the CBb1 pathway caused by different synaptic weighting that the differences are of no consequence [6]. In this subsection, we show that both prefiltering and the averaging of signals through cell convergence and synaptic weighting together remove much of the spatial-variance of the bipolar cell pathways.

Spatial-variance in the model is caused by having L2 different space-varying filters for a synapse. Space-varying filters are analogous to dendritic trees. Since the filters have the same envelope for their weights, their DTFT's are of similar form; and rescaling insures that each space-varying filter has the same zero-frequency gain. The differences between the space-varying filters become significant for frequencies above about 3 cycles/degree, which we show for the CBb2 pathway in Fig. 11(a). Spatial-variance in the model is even more apparent in the space-domain. An impulse placed at location $icone(0,0)$ gives output $iS2$ with one non-zero sample. If the impulse is moved two cone samples over to $icone(0,2)$, $iS2$ has two non-zero samples. Depending on where the input impulse is, between one and five samples in $iS1$, $iS2$, and $iS3$ will be non-zero. In addition, the non-zero samples will be arranged in different patterns and often will have different values.

Analyzing the model indicates that optics-to-cone prefiltering significantly lessens spatial variance. The prefilter frequency response is plotted with a dashed line in Fig. 11(a). Differences between the cone filter CBb2 space-varying filters are small for frequencies passed by the prefilter, and the cone filter CBb2 frequency responses are essentially identical [Fig. 11(b)]. Similar effects occur in the CBb2 filter stage and the CBb1 and CBb3 pathways, though to a lesser extent for the second stage in the CBb3 pathway. Even if the samples in the model were irregularly placed, as in the retina, prefiltering would lessen spatial-variance, as the low-pass components of the different cells' responses are not much altered by small displacement of samples.

In the space-domain, prefiltering has the effect of widening the impulse responses, thereby lessening the relative differences between responses to stimuli at different locations. The

prefiltered responses to impulses at different locations also all fit the same best-fitting DOG [Fig. 12]. However, the values of the non-zero samples still vary with the location of the impulse. This remaining spatial-variance occurs because prefiltering does not correct for phase differences between the space-varying filters. Phase differences would occur even in a highly ordered array of cells with identical filters in every location, because the input to the retina is a continuous image and can be displaced by distances smaller than any sampling period.

5. Discussion

In this paper, we examined several spatial properties of the cat cone bipolar cell pathways using a multirate filter-based model to relate cell-to-cell anatomy to its systemic effects. Model parameters were matched to known anatomic data as much as possible, and several tests indicated that our assumptions for unknown information were reasonable. We showed that

(i) Despite the anatomic distinctions between the three pathways, there are no significant differences in their spatial responses; (ii) Despite the averaging of information over several presynaptic cells in the pathways, there is negligible low-pass filtering of the signal after the cone layer; (iii) Instead, this averaging combined with prefiltering by the eye's optics and cone gap junctions just prevents aliasing that would otherwise corrupt retina outputs; (iv) The prefiltering lessens spatial-variance caused by variation in dendritic tree shapes and synapse distribution; and (v) Some spatial variance must remain since prefiltering can not correct for phase differences in the synaptic weighting of different dendritic trees. Additionally, the model suggests detailed spatial patterns and weighting for synaptic contacts between cells. These calculations can be considered predictions for the properties of dendritic trees not yet measured.

That the three cone bipolar cell pathways show no differences in their spatial responses is not too surprising; as the bipolar cells in the different pathways are not very different in convergence, divergence or dendritic tree size. The differences between pathways may be in their temporal responses, degree of adaptation to a signal or in the range of light levels to which they respond without saturation. They may also differ in their post-synaptic receptors, though this is presently unknown. However, it is surprising that, in low-pass filtering the signal, the weighting between the three cell layers seems to only remove those frequency components that alias. Lower frequencies are essentially unchanged. Our calculations suggest that the cat visual system is maintaining the highest fidelity signal it can given the constraint of decreasing cell array densities.

One means by which the retina could lessen spatial variance is to rigidly control the placement of every dendritic branch and synapse during development, producing as identical dendritic trees and patterns of synapses as possible. Our analysis shows that the frequency response magnitudes for the space-varying filters differ considerably in frequencies close to their Nyquist frequencies, but these frequencies are attenuated by retinal prefiltering, giving frequency magnitude plots that are essentially identical [Fig. 11] . The low-frequency responses are based more on the shape of the weighting function than the exact locations of the weights, while the high frequency responses depend more critically on the locations. Thus prefiltering may be a means by which the developing retina can reduce spatial-variance yet still avoid tightly controlling the exact location and number of synapses. The dendritic trees need the same shape to their weighting function and approximately the same convergence, but they can vary significantly in the placement and values of these weights.

It is instructive to compare the multirate modeling technique to cable models. Cable models are concerned with quantifying the effects of electrotonic decay along cable representations of neurons [35, 36, 37] . They are amenable to a form of analytic solution, but are often simulated using a compartmental model with complex nonlinear elements such as voltage-gated channels that have no easy analytic representation. The models are typically composed of hundreds to many thousands of electrically coupled elements, each of which corresponds to a neuron or to anatomic components of a neuron such as a soma or a dendritic tree segment. The elements are defined using membrane resistance, membrane capacitance, element volume, and several other detailed anatomic properties. The geometry of the model is based on both the morphology of individual cells and the anatomy of cell circuits. Because of the detailed element descriptions, their number, and the intricate connections between them, cable models can give exquisitely detailed information on the responses of individual cells, the effects of cell morphological details and the spatiotemporal responses of cells to complex inputs. However, because of this level of detail, cable models are notoriously computationally intensive. The influences of constraints such as convergence or a membrane resistance are also not immediately apparent in cable models, and typically variations of a model must be run repeatedly for the effects of a given parameter to be apparent.

The multirate model is much less detailed than cable models, assumes linear responses,

and uses primarily anatomic circuit anatomy and little cell morphology information. As a result, the multirate model does not give cell morphology effects or temporal responses. However, multirate models can be simulated instantly and easily yield analytic results such as the input/output relation of a cascade of cell arrays. Additionally, the influence of anatomic parameters are easily seen from the analytic descriptions, such as the precise degree of low-pass filtering caused by a given convergence or synaptic weighting function. Thus, the two kinds of models are complementary: Multirate models are generalized to a whole cell array and are amenable to an analytical approach, but use several approximations of the anatomic details. Cable models consider minute local anatomic details but are limited in size because of computational complexity. Cable models may be more advantageous for studying local single cell effects and complex networks on nonlinearly-processing neurons while multirate models can better handle cell array characteristics. Extensions of the multirate model such as non-linear filters and spatiotemporal filters will help bridge the gap between these approaches.

Cable models by Smith et. al. of a few cells in the cat cone bipolar pathways yield spatial responses for CBb1 cells and the CBb1 contribution very similar to ours [37]. This similarity likely results from the two models being based on the same raw anatomic data. However, the similarity also suggests that the spatial response results are robust to the particular modeling method used and that the anatomic data is complete enough to constrain disparate modeling approaches.

Certain limitations of the model with respect to the types of calculations we perform should be kept in mind: (i) The filters are linear and do not incorporate adaptation to the signal. If the dendritic weighting or gain K change with the light level, the spatial aliasing analysis will alter. (ii) The degree of variability of the space-varying filters is highly dependent on the choice of M and L . However, we have informally observed that the results of our analysis do not change significantly for most choice of M and L when M/L is kept approximately constant. The exception is when L approaches 1, and there no longer is any space-varying filter variation. (iii) Our spatial variance estimates should be considered to show a low bound on the spatial variance, as other factors such as irregular cone placement can also contribute to this variance. The variance from these other factors may not be so well attenuated. (iv) There may be additional connections between the cells

in the model that can alter the results. For example, recent work found inhibitory synapses from horizontal cells to bipolar cells in primates and in lower vertebrates. Light microscopy suggests that similar synapses may exist in the cat [38]. Our model does not include these synapses. Since cat horizontal cells have a spatial cut-off frequency in the 0.4 - 1.5 cycle/degree range [39], their effect would likely be to additionally attenuate the on- β cell signal below 1.5 cycle/degree. One benefit of such inhibition is attenuation of the minimal aliasing remaining in iCBb2, iCBb3, i β 2 and i β 3.

The rescaling of the direct-form filters in the model is required to maintain a constant zero-frequency (dc) gain. Rescaling may actually be a physiologic requirement when cells that differ in anatomic details are required to have the same zero-frequency response. A situation like this is reported in [16] where primate midget ganglion cells are shown to belong to two classes, each receiving a different number of cone synapses. The two cell classes are predicted to have different postsynaptic gains, equivalent to the rescaling in our model. Despite this effect, rescaling does not influence the shapes of the space-varying filter impulse responses [Fig. 8]. Each space-varying filter is simply multiplied by a coefficient, generally not far from one, so they all give the same zero-frequency response. Equivalent anatomic changes might be to have small differences in terminal branch geometry, postsynaptic cell body sizes, or dendritic branch diameters of different postsynaptic cells so each cell responds with the same membrane voltage to a given light level, a very reasonable scenario for retinal anatomy.

Fundamental to the multirate approach is the assumption that a synaptic weighting function can represent synaptic weighting well. swf's in the model had an assumed Gaussian or polynomial shape which was set based on measured or estimated maximum and minimum values and measured total number of contacts between two cell classes. Despite the continuous and gently-sloping functions used, synaptic weights for individual dendritic trees had irregular surfaces reminiscent of those observed in the retina [7]. The percentage contributions of different cone bipolar cells to on- β cells showed the same distribution as in the retina; and, for CBb1 and CBb2 cells, the total number of bipolar cell synapses to on- β cells varied over ranges that agreed with the small anatomic ranges. Thus, the swf's yielded patterns of synapses that showed both the constancy and irregularity of synapse patterns seen in the anatomy.

For the cells we model, we have observed that swf functions should (i) be strictly

descending from the origin, (ii) be at least approximately circularly symmetric, (iii) be set to the correct anatomically measured values at the origin and the periphery, and (iv) have the volume under its surface set to give dendritic trees with the correct average number of contacts. We noticed no significant differences between the Gaussian and polynomial filters. If the number of synaptic contacts is based on the amount of dendritic tree available to synapse upon beneath a given presynaptic cell, further from the center of the tree, where there are fewer spots/unit volume for synapses, the number of contacts from a presynaptic cell should decrease. We hypothesize that the swf concept works because of sufficient regularity within a cell class in the reduction of dendritic tree contact volume with distance from the center of the tree.

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FIGURES

Fig. 1. Systems level representation of basic multirate model. L and M indicate L -fold upsampling and M -fold downsampling respectively. H is a linear filter representing the synaptic and dendritic weighting.

Fig. 2. Systems-level representation of the cone bipolar CBb1, CBb2 and CBb3 pathways included in the model. Each box represents synaptic and den-dritic weighting. As shown explicitly for the cone fi CBb1 case, each box indicates the multi-rate structure shown in Fig. 1. Variables in parentheses are the names of the corresponding signals in the model. Anatomic details for these pathways are listed in Tabs. 1 and 2.

Fig. 3. Space domain plots of two of the rescaled direct-form filters in the model. (a) rescaled H_1 ; (b) rescaled H_2 .

Fig. 4. Shapes of direct-form filters needed for complete tiling of presynaptic layers. The points show the virtual signal after the upsampler in Fig. 1 and are a mixture of samples from the presynaptic array and the zero samples added by the upsampler. u_1 and u_2 are the axes of the filters. For the filters to completely tile the presynaptic array, they must make contact with every point shown. The heavy circles in the corners are the outputs in the postsynaptic array. The solid and dotted lines show the intersection of four quarters of the circular, direct-form filters that compute these outputs. The empty points indicate the

samples not contacted by any of the filters. The shaded region shows a new, larger shape for the filters that achieve complete tiling while maintaining the correct convergence. (a)

hcone fi CBb2; (b) hcone fi CBb3; (c) hCBb3 fion- ϕ .

Fig. 3. Intermeshing of space-varying filters in model. (a) Sixteen space-varying filters from the cone fi CBb3 synapse model. Large circles indicate the CBb3 samples, filled diamonds indicate the cone samples they contact. Contacts are shown by the lines. The offset of the diamonds from the circles reflects the different alignments between samples in arrays of different densities. Filters do not make contact with samples within the space occupied by adjacent filters. Some filters share cones in their peripheries.

(b) Sixteen space-varying filters from the CBb1 fion- ϕ synapse model. Large circles indicate the on- ϕ cell samples, filled diamonds indicate the CBb1 samples they contact. Filters either share CBb1 samples on their peripheries or overlap by reaching for samples within the space occupied by adjacent filters.

Fig. 6. Normalized spatial frequency response of cat on- ϕ cells. The solid line shows the spatial frequency response of the on- ϕ array in the model when the cone input image is prefiltered with the cat optics-to-cone impulse response. The dashed line shows the cat's response at 1° eccentricity based on calculations in [17].

Fig. 7. Normalized cross-sections of frequency domain responses of arrays in model with optics-to-cone prefiltering (solid line - CBb1 pathway, dashed line - CBb2 pathway, dotted - CBb3 pathway). (a) ICBb1, ICBb2 and ICBb3, ; (b) Ib1, Ib2 and Ib3.

Fig. 8. Cross-sections of discrete time Fourier transforms (DTFT's) of two direct-form filters in the model and their rescaled versions. The frequency axes are in units of normalized radian frequency and extend from zero to the Nyquist frequency for each filter. The vertical lines show the cutoffs required to prevent aliasing. The solid lines show the original filter, the dashed lines show the rescaled filters. (a) HCBb1 fion- ϕ and rescaled

HCBb1 fion- ϕ ; (b) Hcone fi CBb2 and rescaled Hcone fi CBb2.

Fig. 9. Normalized spatial frequency response functions and aliasing for CBb2 pathway with (i) no prefiltering, (ii) prefiltering by the cat eye's optics only and (iii) optics-to-cone prefiltering. Each response is normalized so that the maximum frequency response with no aliasing equals unity. Frequency axes f are in cycles/degree. For each plot, f extends to the Nyquist frequency for that cell array. The dashed line shows the response to input

frequency components up to the Nyquist frequency. The solid lines show the dashed response plus the aliasing. (a) ICBb2 with no prefiltering; (b) Ib2 with no prefiltering; (c) Cone response with only the cat's optics prefiltering (3 mm pupil) [31, 32]. (d) ICBb2 with optics prefiltering; (e) Ib2 with optics prefiltering; (f) Cone response (optics-to-cone prefilter) at 1° based on computations in [17]. (g) ICBb2 with optics-to-cone prefiltering; (h) Ib2 with optics-to-cone prefiltering.

Fig. 10. Successive normalized outputs in model for three bipolar cell pathways with optics-to-cone prefiltering. (a) Space-domain plots of icone (solid line), iCBb2 (dashed line) and ib2 (dotted line); (b) Frequency-domain plots of same responses as in (a).

Fig. 11. Influence of prefiltering on degree of variation in cone fi CBB2 space-varying filters. (a)

Cross-sections of spatial frequency responses of the 169 space-varying filters when there is no prefiltering. Significant differences in their responses start at about 3 cycles/degree.

The dashed curve is the optics-to-cone spatial frequency response. (b) Spatial frequency responses with prefiltering. Differences between responses are highly attenuated.

Fig. 12. Influence of prefiltering on spatial-variance of ib2 outputs. The plot shows superimposed x-axis space-domain responses to prefiltered impulses at different locations in icone ('s - Response to impulse centered at (0,0) in icone, +'s - (4,1) response, *'s - (2,2) response).

The solid line is the best DOG fit to the response to the impulse at (0,0). The same curve fits all three responses.

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TABLE 1. ANATOMIC DENSITIES OF CELLS MODELED

Cell Class	Density (mm ⁻²) a
Cones	24,200
CBb1	6,100
CBb2	4,000
CBb3	4,400
On-§	1,860

a Ref. 1.

TABLE 2. ANATOMIC PROPERTIES FOR CONE fi
CBb1,2 AND 3 fi ON-§ CELL SYNAPSES AT 1° ECCENTRICITY

Synapse	Convergence a-c	Divergence a-c	C/D ratio	Density
Cone fi CBb1	5.1 ± 1.0		1.2	4.25 3.97
Cone fi CBb2	6 ± 1,2	1		6 6.05
Cone fi CBb3	6 d	1 d		6 5.50
CBb1 fi on-§	6 - 7	3	2 - 2.33	3.28
CBb2 fi on-§	4 - 5	2	2 - 2.5	2.15
CBb3 fi on-§	2 - 4	1 - 3	0.67 - 4	2.37

a Ref. 4.

b Ref. 6.

c Ref. 7.

d Values estimated by comparison with CBb2 pathway.

TABLE 3. FILTER AND RESAMPLING PARAMETERS IN THE MULTIRATE MODEL

Synapse	L	M	Rcirc	K	No. of Non-zero Weights	Cm	Dm
Cone fi CBb1 +		1	2	1	0.037	5	5.00 1.25
Cone fi CBb1 ´		1	2	-	0.037	5	5.00 1.25
CBb1 fi on-§		9	16	13.35	8.495	10 ⁻⁵	561 6.93
2.19							
Cone fi CBb2		13	32	-	1.820	10 ⁻⁴	1029 6.09
1.005							
CBb2 fi on-§		9	13	10.5	8.386	10 ⁻⁵	349 4.31
2.07							
Cone fi CBb3		7	16	(9.5)	7.985	10 ⁻⁴	301 6.14
1.18							

CBb3 fi on-§	9	14	(9.0)	7.312	10 ⁻⁵	265	3.27
1.35							

TABLE 4. DENSITIES, SAMPLING PERIODS AND NYQUIST FREQUENCIES FOR CELL ARRAYS IN THE MULTIRATE MODEL

Cell Class	Density (mm ⁻²)	Sampling Period (mm)	Nyquist Frequency (cycles/degree)
Cones	24,200	6.428	17.1
CBb1	6,050	12.856	8.56
CBb2	3,994	15.823	6.95
CBb3	4,632	14.693	7.49
On-§	1,914	22.858	4.81

TABLE 5. PERCENTAGE OF TOTAL NUMBER OF BIPOLAR CELL SYNAPSES TO ON-§ CELLS CONTRIBUTED BY INDIVIDUAL CONE BIPOLAR CELLS - RANKED BY PERCENTAGE a

on-§ Contribution	CBb1 fi on-§		CBb2 fi on-§		CBb3 fi	
	Anatomy	Model	Anatomy	Model	Anatomy	Model
1st largest	37.5	33.1	35.8	39.1	60.3	59.0
2nd largest	21.3	22.6	27.0	29.0	28.6	26.0
3rd largest	17.2	15.6	22.9	18.7	-	10.5
4th largest	12.4	12.3	8.3	11.7	-	4.4
Total	88.4	83.5	94.0	98.6	88.9	85.0 b

a All anatomic measurements from Ref. [7] .

b Total includes only contributions from 1st and 2nd largest contributors as two on-§ cells had only two CBb3's synapsing upon them [7] .

TABLE 6. COVERAGE FACTORS IN CAT RETINA AND MODEL

Cell Class	Coverage Factor	
	Anatomy a	Model
CBb1	1	1.26
CBb2	1	0.95
CBb3	1	1.11
On-§	2.2	2.19

a - All anatomic measurements from Ref. [4] .

TABLE 7. CENTER-SURROUND FITS TO OUTPUTS
OF CONE fi BIPOLAR CELL fi ON- $\$$ CELL MODEL a

Cell array	kc	rc (mm)	ks	rs (mm)
Cone	1.0	25.00	0.0320	133.0
CBb1	1.0	25.61	0.0307	143.8
CBb2	1.0	25.79	0.0375	125.9
CBb3	1.0	25.89	0.0357	128.5
$\$1$	1.0	28.62	0.0519	112.2
$\$2$	1.0	28.92	0.0453	126.0
$\$3$	1.0	27.64	0.0495	108.0
on- $\$$	1.0	28.53	0.0491	115.7

a Fits are normalized to kc = 1.