Modelling Functional Wiring and Processing from Retinal Bipolar to Ganglion Cells

David A. Klindt*, Cornelius Schröder*, Anna Vlasits, Katrin Franke, Philipp Berens & Thomas Euler

Abstract. Although the processing of visual information in the retina has been studied in detail, the underlying functional connectivity is not yet completely understood. While many specific circuits are well-characterized (e.g. the rod photoreceptor pathway), a comprehensive picture of how these microcircuits work together to form the retinal network is still lacking. Furthermore, connectomic information, which could help dissect the functional underpinnings of the retina, is not yet fully leveraged. The integration of different datasets and data sources to (computational) models is a key challenge to elucidate the processing of visual information in the retina. A step towards a comprehensive understanding of the retinal network was made in a recent publication [1], which suggests a biophysically-constrained bipolar and amacrine cell network model (BCN model) of light processing in the mouse inner retina, enabling *in silico* experiments. Here, we extended this model to predict the responses of previously characterized mouse retinal ganglion cell (RGC) types to full-field light stimulation [2]. Specifically, we tested how bipolar cell glutamate release can be combined in an additional linear nonlinear model to predict RGC output (BCN-LN). We show that recordings of full-field stimulation combined with mechanistically detailed modelling allowed us to predict connectivity between cell types, as well as to investigate the role of inhibitory feedback and feedforward AC modulation. In summary, this work shows how a machine-learning approach informed by biological structures can produce interpretable and accurate predictions about neural connectivity and circuit functions, thus explaining the hierarchical emergence of functional RGC diversity.

Additional Details. We restricted the connection weights in our model to be positive, reflecting the fact that direct BC input to RGCs is excitatory, obtaining a sparse connectivity matrix between all BC and RGC types. Comparing this matrix to published connectomics and functional connectivity data revealed a number of well-matching circuits [3] (Fig. 1b). Moreover, by translating the weights into stratification depths in the retina's inner synaptic layer (inner plexiform layer; [4]), we found that RGC input weights yielded predictions of dendritic stratifications that were largely consistent with EM data [3]. Where connectomics data is not available or functional circuits are not yet anatomically identified, we were able to make predictions about putative RGC connectivity.

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Next, we examined the contribution of ACs in two ways: (i) As a baseline model, we stripped the BCN-LN model from the feedback AC modulation, which shaped the BC output, resulting in a linear-nonlinear release model [1] with the additional linear-nonlinear block (LNR-LN model). (ii) We added an additional pathway of feedforward AC modulation that can simulate direct inhibitory AC inputs to RGCs (BCN-AC-LN model). We found that the baseline LNR-LN model performed worse (Fig. 1e). Importantly, its predictions can be tested experimentally by pharmacologically blocking different populations of ACs as in [4], allowing to investigate the contribution of specific AC circuits in more detail. For the extended BCN-AC-LN model, the additional AC pathway increased model performance as expected. However, while some cells were better predicted with feedforward AC inhibition (e.g. JAM-B cells, Fig. 1d), others were already well predicted with excitatory BC input only (e.g. On mini alpha, Fig. 1d). Thus, we can use this approach to differentiate the importance of feedforward AC inhibition across RGC types for spatially homogeneous stimuli. These predictions can be validated by looking at well-studied microcircuits of RGCs that are known to depend heavily on AC modulation (e.g. W3 cells, direction-selective RGCs). Future steps include testing experimental predictions (pharmacology, connectivity, AC circuitry), as well as extending the approach to spatial processing to study spatio-temporal computations, like e.g. for motion direction-selective RGC types.

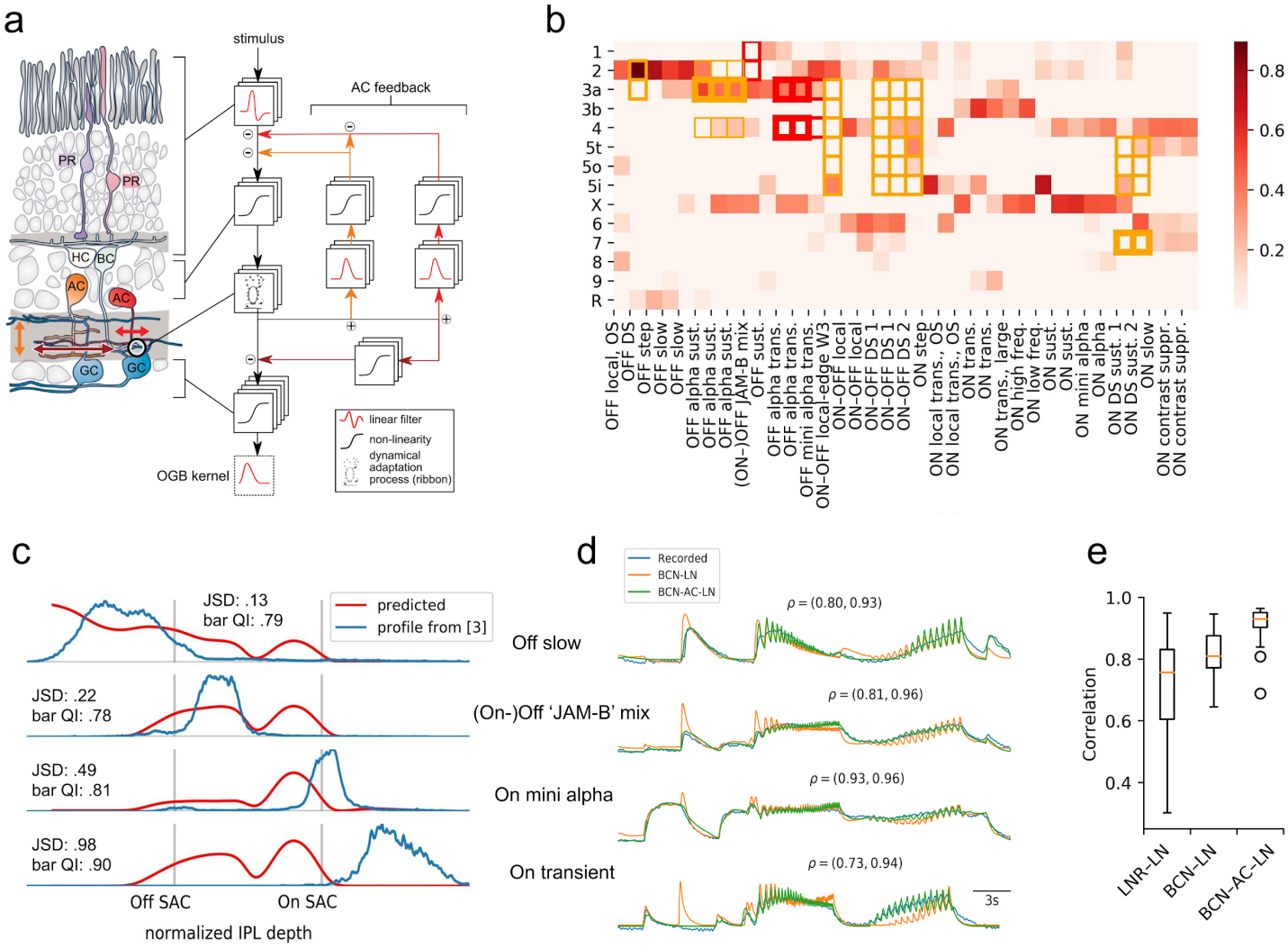

Figure 1. a) Schematic retinal circuit and translation into a computational network model. The BCN [1] model is extended by a LN model accounting for the processing in RGCs. Optionally, a feedforward AC pathway acting directly on RGCs is included (dark red) (BCN-AC-LN model). **b)** Learned BC-to-RGC connectivity matrix. Red/orange squares indicate certain/probable connections described in the literature, with linewidth indicating connectivity strength (strong/unknown/weak). **c)** Comparison of stratification profiles for four example RGC types (selected to showcase both good and bad matches). Jensen-Shannon divergence (JSD) measures the match of the stratification and the bar quality index (QI) the response reliability for a moving bar stimulus (see [2] for details). **d)** Model predictions for the cell types in c). **e)** Performance comparison for the LNR-LN baseline model, the BCN-LN and the best performing BCN-AC-LN model, with additional feedforward AC inhibition.

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