Mechanisms underlying the formation of beta retinal ganglion cell mosaics

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Introduction

Beta retinal ganglion cells (RGCs) are labelled ON-centre or OFF-centre, depending on their response to light (Fig. 1). Cell bodies of each type form a semi-regular pattern, termed "retinal mosaics". We do not yet know how the mosaics of ON- and OFF-centre cells emerge during development:

- A population of undifferentiated beta cells may divide into two types during development through heterotypic interactions, possibly mediated by activity.
- The two types of cell may develop independently of each other.

Previous statistical approaches are based on testing for *statistical independence* between ON and OFF cells. This is not scientifically relevant when both types of neuron are located in the same layer, since the constraint that two neurons cannot then occupy the same (x,y)-location rules out independence *a priori*.

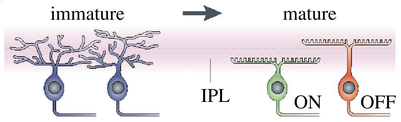

Figure 1: *Development of stratification in beta RGCs (drawing from Wong & Ghosh, 2002). Stratification reflects functional class.*

Approach: we fit models of the joint spatial pattern which respect the constraint that no two neurons can be separated by less than their soma diameter. If model replicates real maps without requiring heterotypic interactions, this might suggest heterotypic interactions do not occur during development.

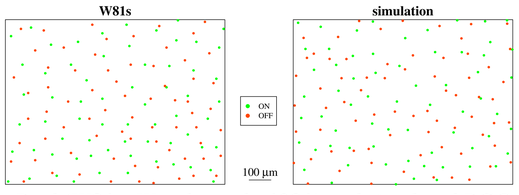

Figure 2: *Real (W81s; Wässle et al., 1981) and simulated RGC mosaics.*

Methods

- d_{min} model (Galli-Resta et al., 1997) adapted to bivariate case (Fig. 3). Size of homotypic exclusion zones drawn from a Normal distribution (mean ± s.d.); heterotypic exclusion zone fixed at soma diameter.
- Model parameters varied to find best fit to real maps (M623 and W81s) for:
  1. $L(t)$ — mean (scaled) number of cells within distance t of a cell. L functions are cumulative versions of DRP (Rodieck, 1991).
  2. regularity index — mean/s.d. of the distance to nearest-neighbour.
  3. fraction of 1^{st}, 2^{nd}, 3^{rd}, or all, nearest neighbours of opposite type.

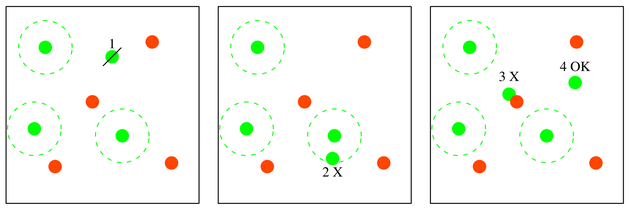

Figure 3: *Bivariate d_{min} model. On and off-centre cells are initially located randomly throughout the array. All cells are then moved within the array according to the following procedure. A cell is selected (1) and repositioned randomly (e.g. at 4) avoiding homotypic exclusion zones (dotted circles; 2) and smaller heterotypic zones (solid red circles, which are cell bodies of opposite type; 3). One sweep consists of moving all cells in the array once. Cells are moved for many sweeps to allow the patterns to stabilise.*

Results

Both fields could be replicated by bivariate d_{min} model (Table 1; Fig. 2, 4, 5). DRP to right shows equivalent DRP for an L function.

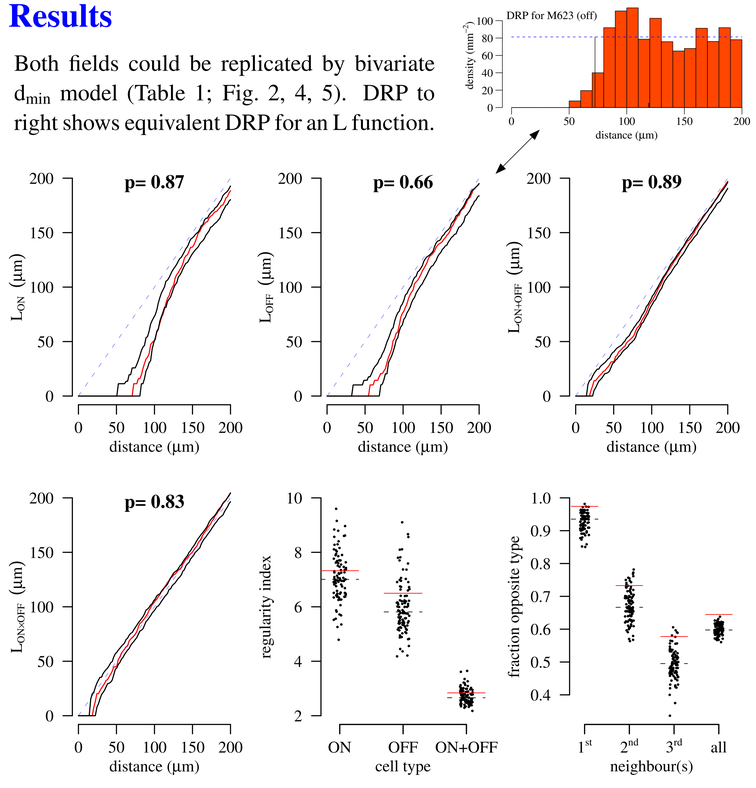

Figure 4: *Results for field M623. Red lines indicate experimental data; black lines indicate envelope from 99 simulations. Dashed blue lines indicate the expectation of L for a Poisson pattern. In strip charts, each black dot indicates one simulation, and dotted black line indicates median.*

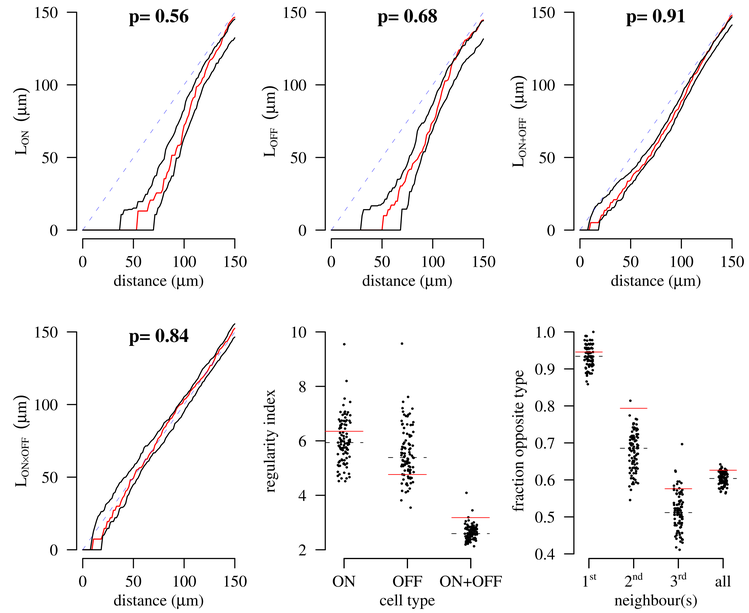

Figure 5: *Results for field W81s (same format as Fig. 4).*

field	# ON	# OFF	d_{ON}	d_{OFF}	soma
W81s	65	70	$116 \pm 20\,\mu$m	$130 \pm 25\,\mu$m	$9\,\mu$m
M623	74	82	$100 \pm 13\,\mu$m	$90 \pm 15\,\mu$m	$15\,\mu$m

Table 1: *Best-fit parameters of the d_{min} model to the two datasets. d_{ON} and d_{OFF}: mean ± s.d. of homotypic exclusion zones; soma: diameter of heterotypic exclusion zone.*

Conclusions

- Beta RGC maps can be simulated with limited interactions between the two mosaics. Heterotypic interactions are limited to preventing somal overlap.
- Confirms general principle that mosaics are *functionally independent* of each other (Rockhill et al., 2000).
- Previous model suggested fixed dependency between two mosaics (Zhan & Troy, 2000); may be by-product of model implementation.
- Functional implications of independence in arrays?
- Caveats: model works with adult maps (ignoring developmental processes, such as cell death). Limited data sets (n=2). Interactions between dendritic refinement and soma positioning unknown.

Acknowledgements: Wellcome Trust (SJE) and NIH EY06669 (JBT). Thanks to Heinz Wässle for providing map W81s.