A Mechanistic Model of the Interaction Between Blue Cones and Blue Cone Bipolar Cells in Macaque Retina

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Internship Report

August 26, 2008

EPSRC Engineering and Physical Sciences Research Council

1. Background
2. Model
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   - Step 2, differentiation of blue cones
   - Step 3, generation of blue cone bipolars
   - Step 4, formation of synaptic contacts
   - Step 5, blue cone bipolar migration
   - How to assess the output?
3. Results
   - 'Optimal' parameters
   - Dendrite length, migration and synapses
   - Density recovery profiles (DRP)
   - K functions
4. Conclusions

The eye and the retina

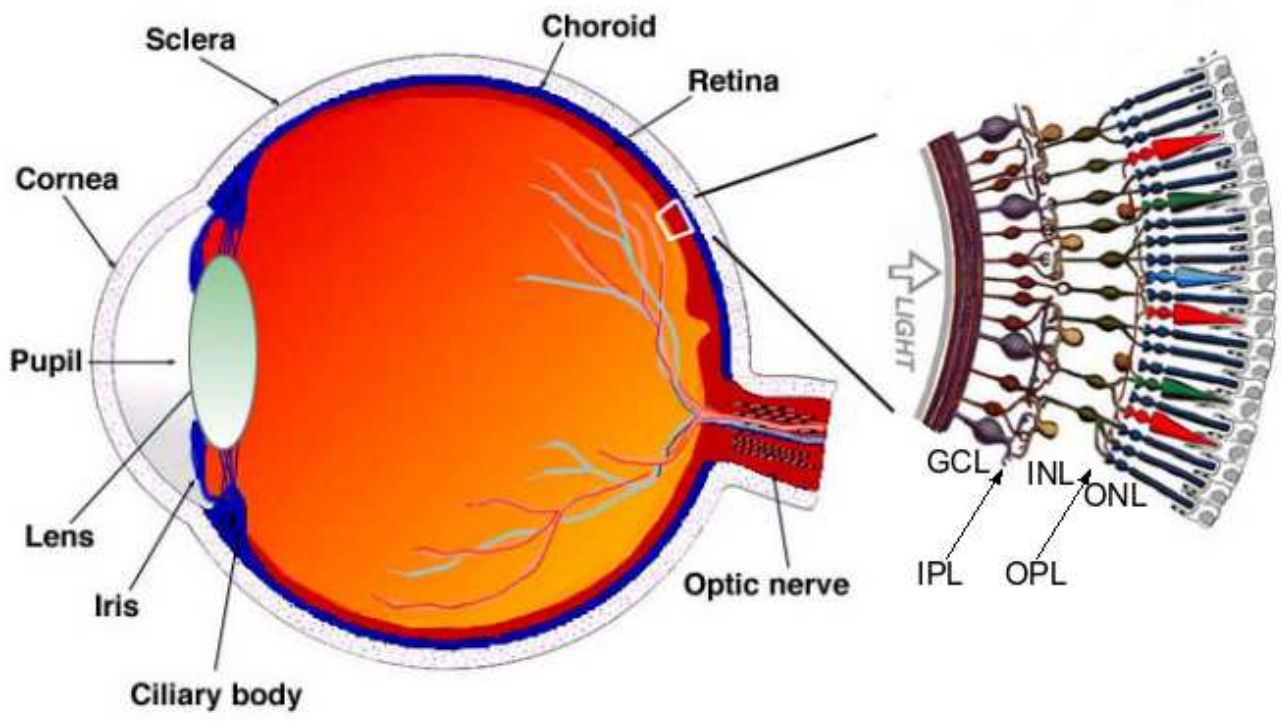


Figure: From Webvision, http://webvision.med.utah.edu/sretina.html. The labelling of the retinal layers is my adaptation.

Mosaics, a prominent feature of many retinal cell types

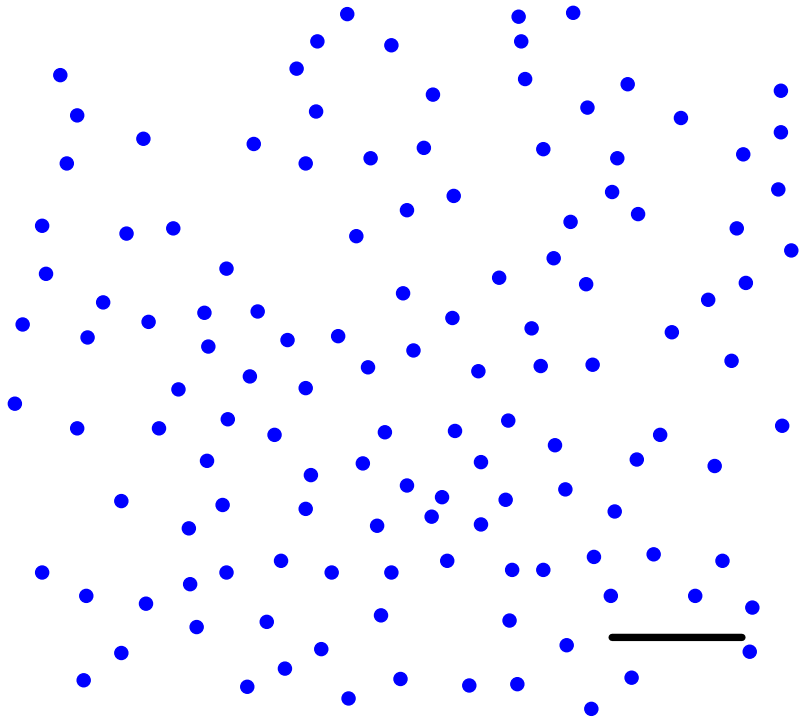


Figure: An example of a retinal mosaic, in this case blue cones (BC) from macaque monkey. Scale bar is 100 µm.

Are the mosaics of different cell types correlated?

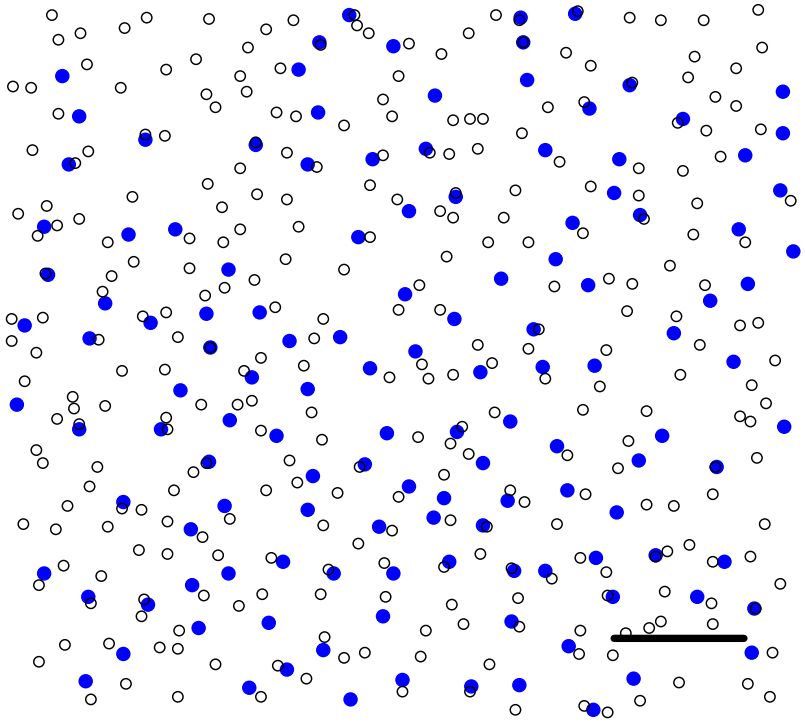


Figure: Data from macaque monkey. BCs (filled blue circles) and blue cone bipolars (BCBP) (open circles). The two mosaics are spatially correlated, but it is hard to see by eye. Scale bar is 100 µm.

Aims of project

- Develop a *mechanistic* model for the interaction between BCs and BCBPs in macaque.
- Generate BC and BCBP mosaics based on a simple statistical model.
- Simulate mechanistic model based on generated BCs and BCBPs.
- Fit parameters.
- Compare model output with real data (five macaque fields).

Outline of retinal model

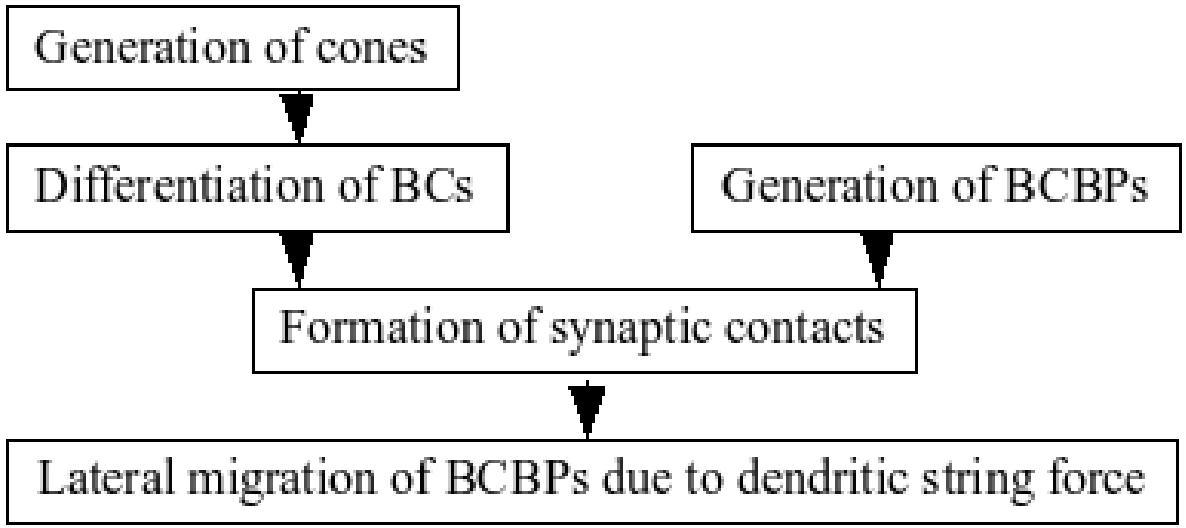


Figure: An arrow from A to B indicates that A precedes B in retinal development. Only the last step is mechanistic. Emphasis lies on this.

Step 1, generation of cones

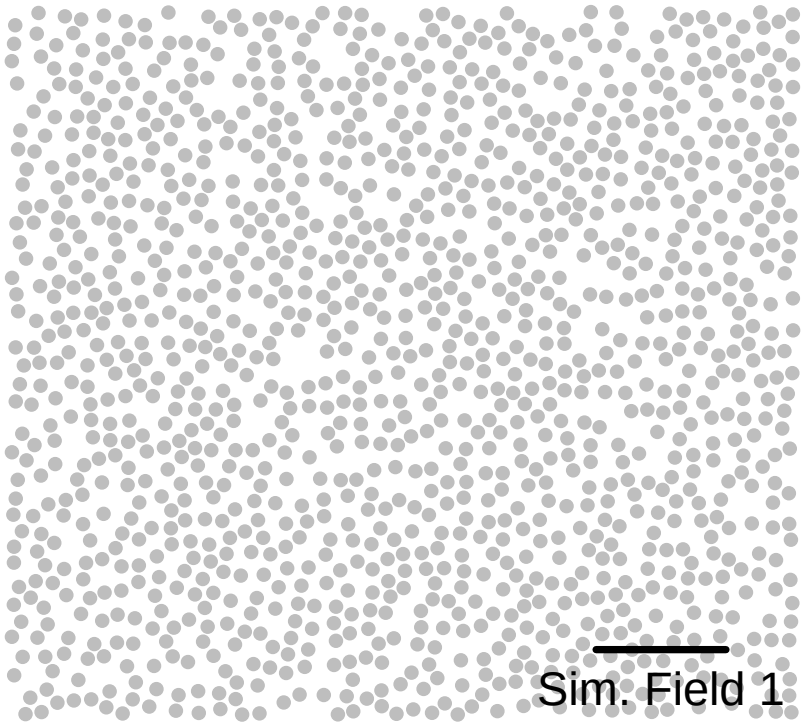


Figure: Cone mosaic before differentiation into BCs and other cone types. Scale bar is 100 µm.

Step 2, differentiation of blue cones

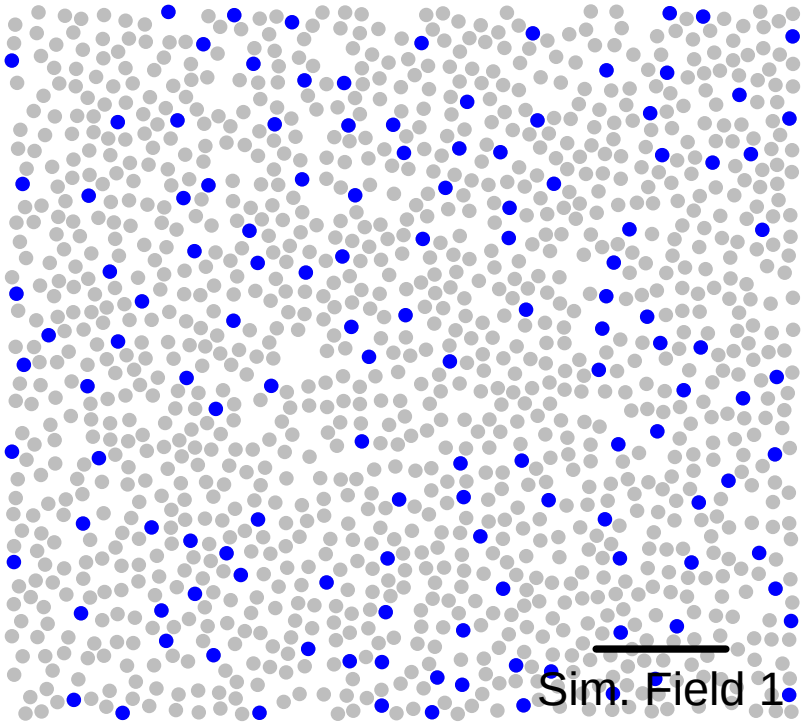


Figure: BC differentiation. Scale bar is 100 µm.

Step 3, generation of BCBPs

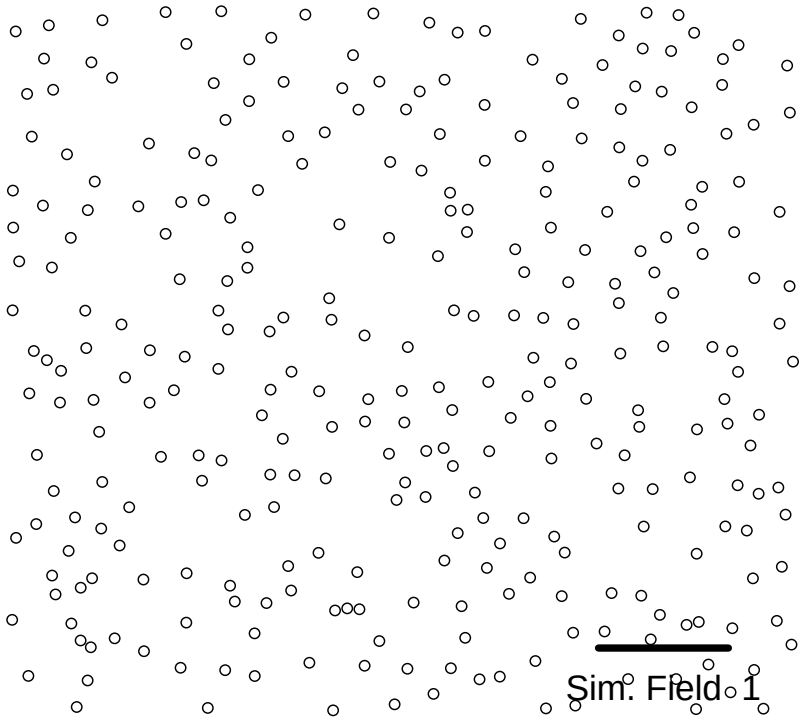


Figure: BCBP generation. Scale bar is 100 µm.

Step 4, formation of synaptic contacts

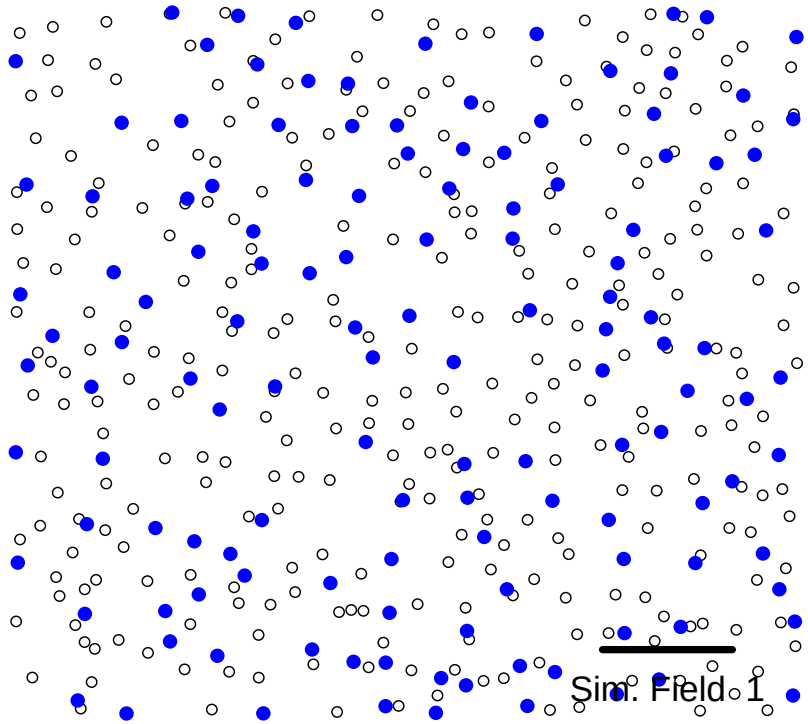


Figure: BCs and BCBPs *before* they form synaptic contacts. Scale bar is 100 µm.

Step 4, formation of synaptic contacts (cont.)

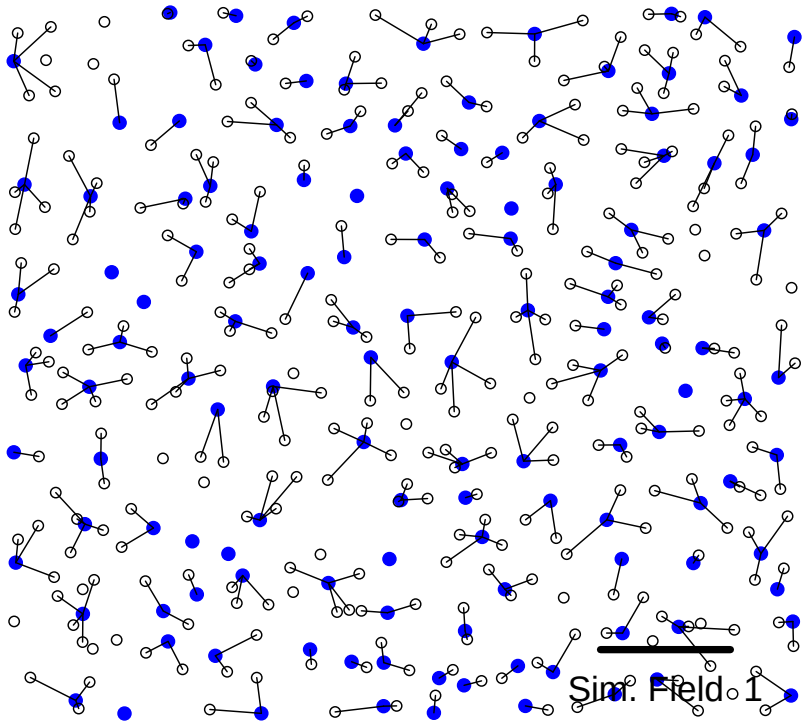
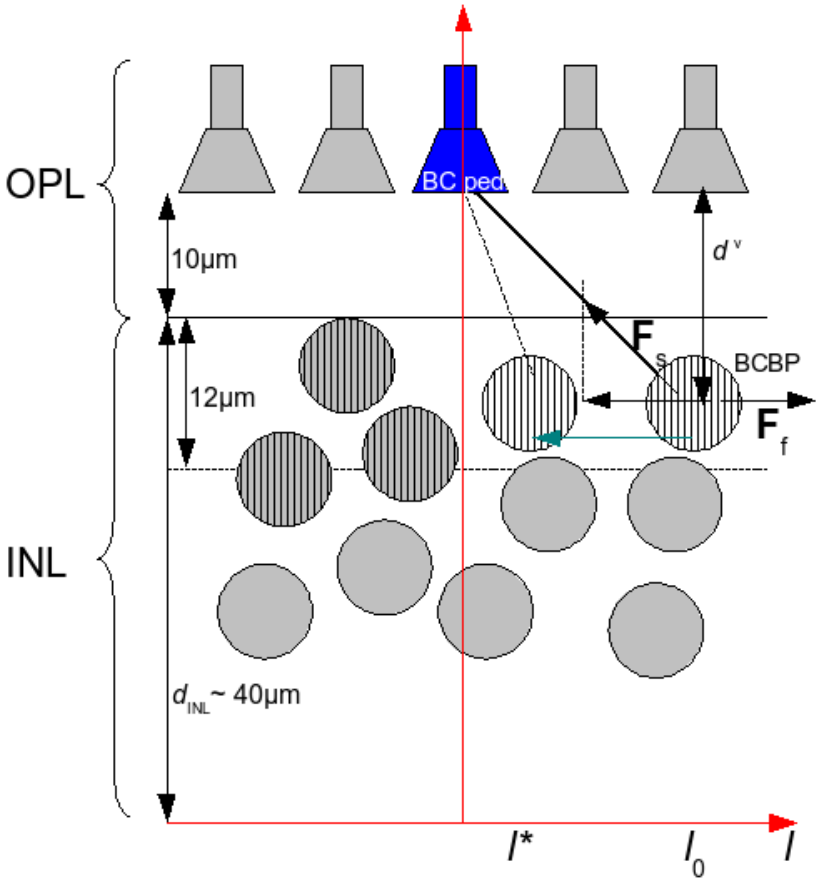


Figure: BCs and BCBPs *after* they have formed synaptic contacts. A few BCBPs don't form contacts. Scale bar is 100 µm.

Step 5, how the BCBPs can migrate, focus of project



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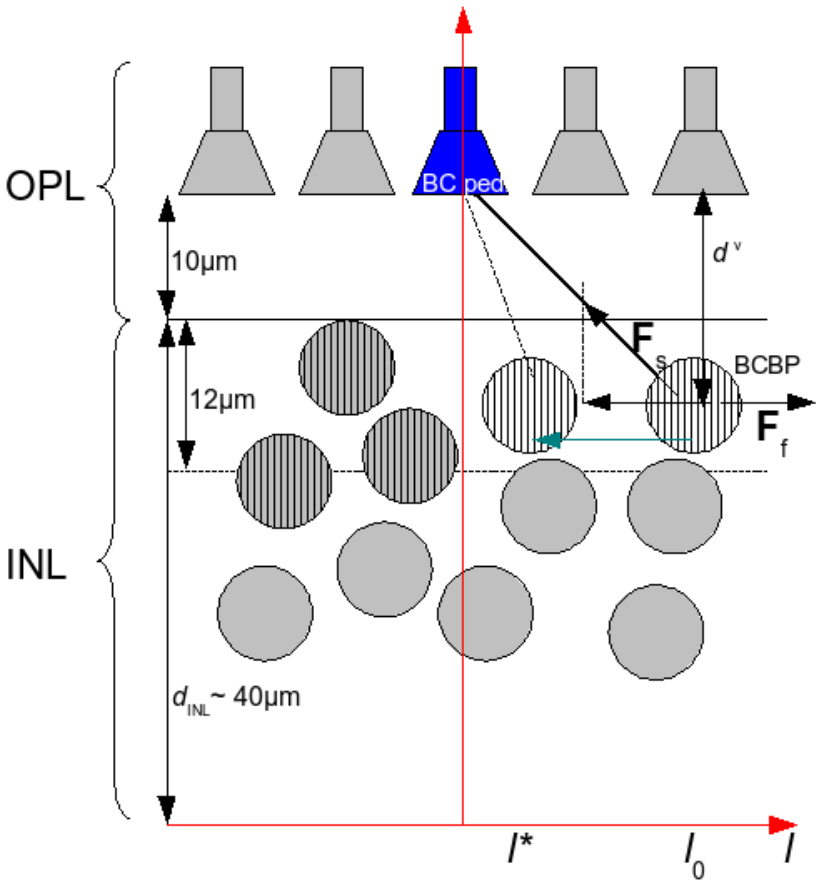


$$l_i^* = \frac{2F_{(f/s),i}\sqrt{l_{0,i}^2 + (d_i^v)^2} - \left(\left(F_{(f/s),i}\right)^2 + 1\right) l_{0,i}}{1 - \left(F_{(f/s),i}\right)^2}.$$

Step 5, after migration

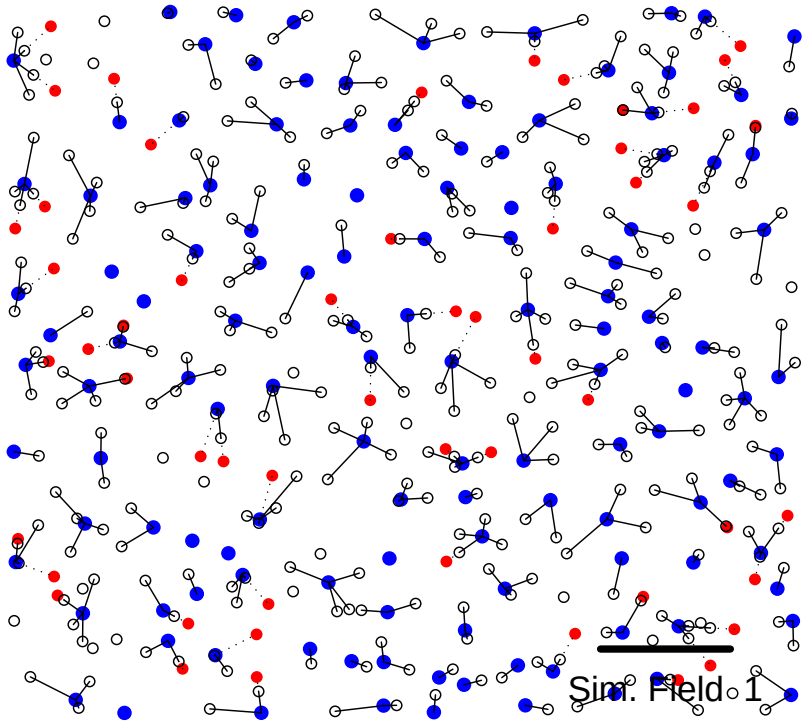
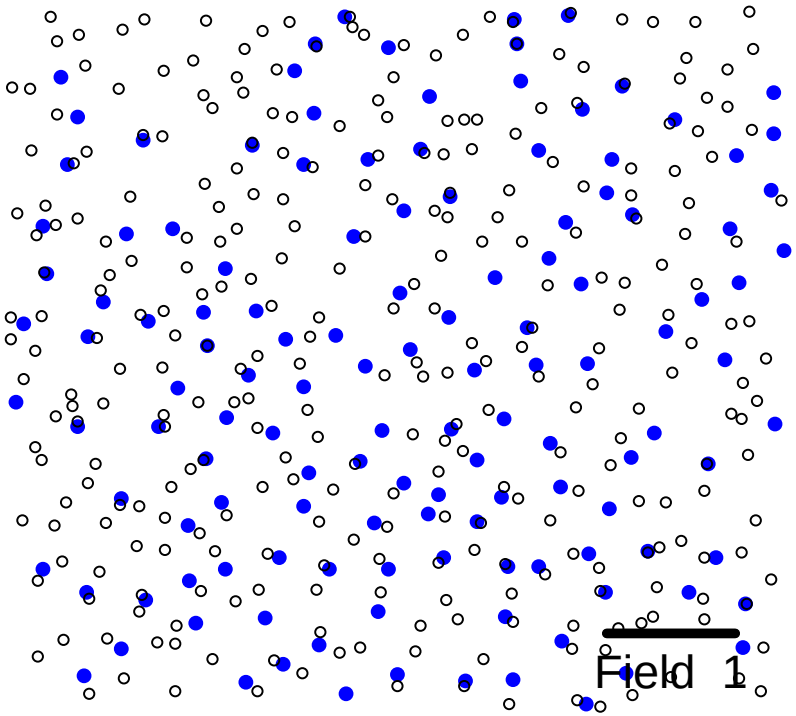
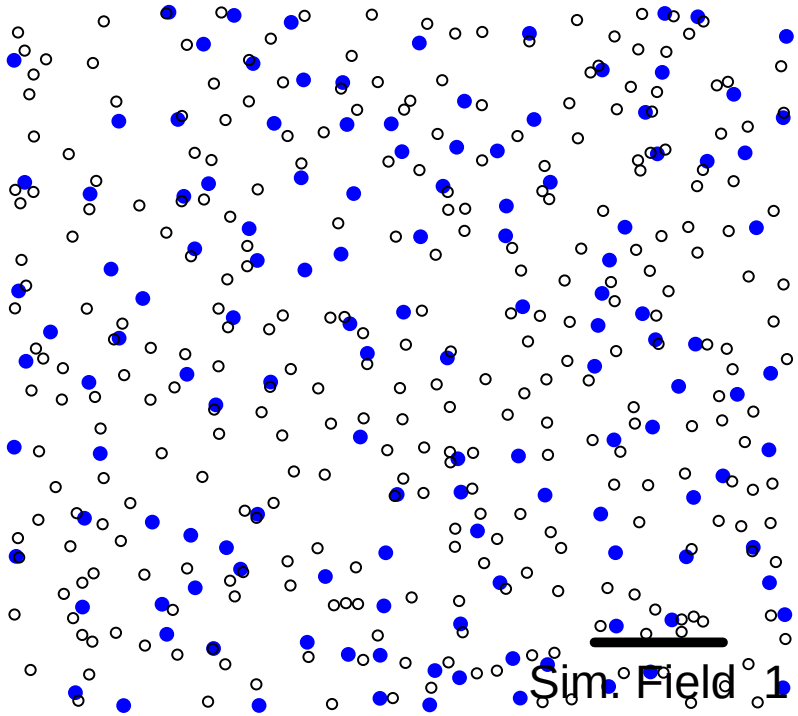


Figure: BCs and BCBPs *after* BCBPs have migrated. Scale bar is 100 µm.

Does the simulated data look like the real data?





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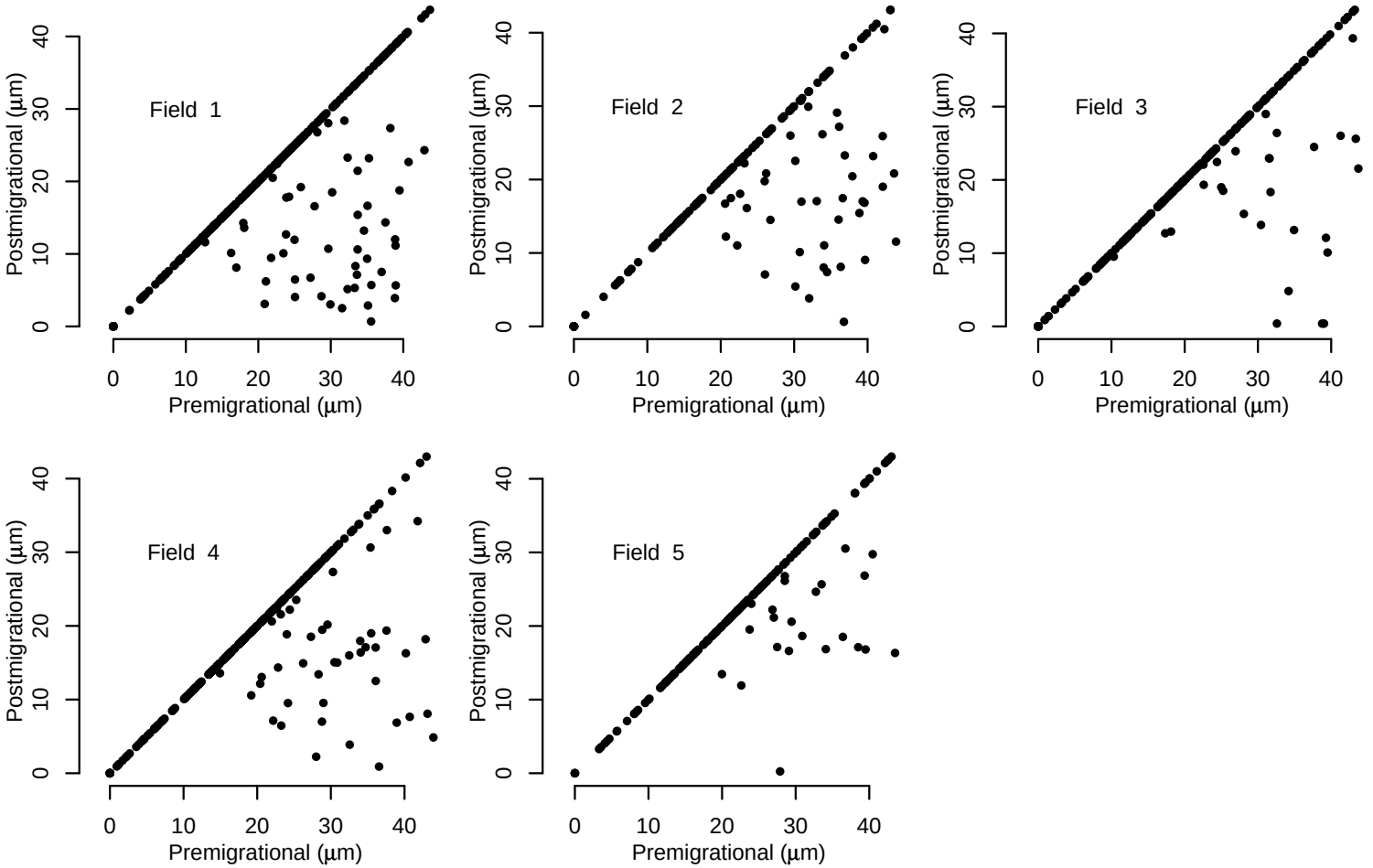
- Steps 2-5 were simulated 99 times to reduce variability in results and to enable calculation of Monte Carlo p values.
- Appropriate statistics and methods for analysis of output were chosen, among those were:
  - Dendrite length and migration distance.
  - Proportion of BCBPs that migrate.
  - Number of synapses.
  - Density recovery profiles.
  - K functions.

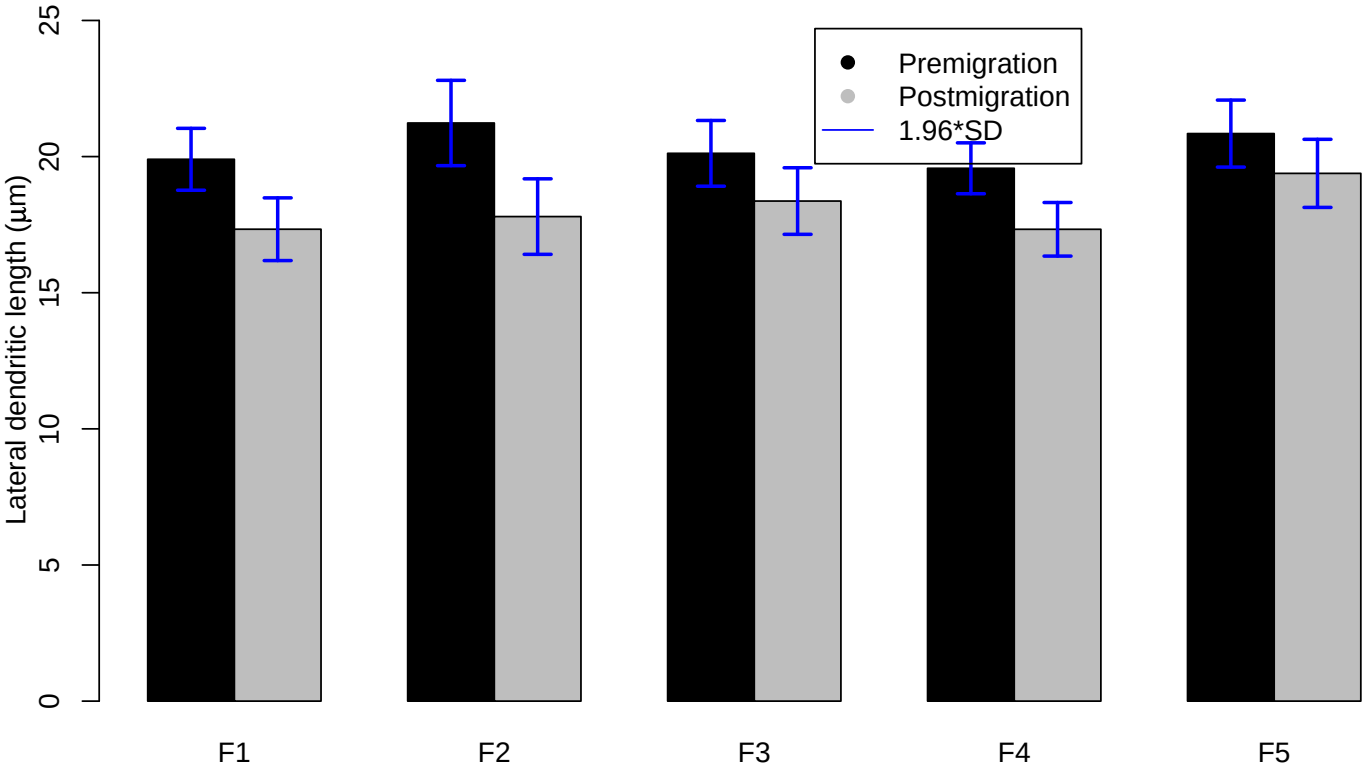
'Optimal' parameters

	Monkey 1				
	Field 1	Field 2	Field 3	Field 4	Field 5
Mean BC excl. zone, μ_{BC} (µm)	30	38	28	30	37
SD of BC excl. zone, σ_{BC} (µm)	6	5.5	3	6	7
BC truncation, d_{BC}^{min} (µm)	13	32	18	18	23
Mean BCBP excl. zone, μ_{BCBP} (µm)	18	18	18	19	22
SD of BCBP excl. zone, σ_{BCBP} (µm)	5	6	5	3	7
BCBP truncation, d_{BCBP}^{min} (µm)	8	7	5	5	3
Mean rel. friction/string force, $\mu_{f/s}$	0.75	0.90	0.82	0.84	0.97

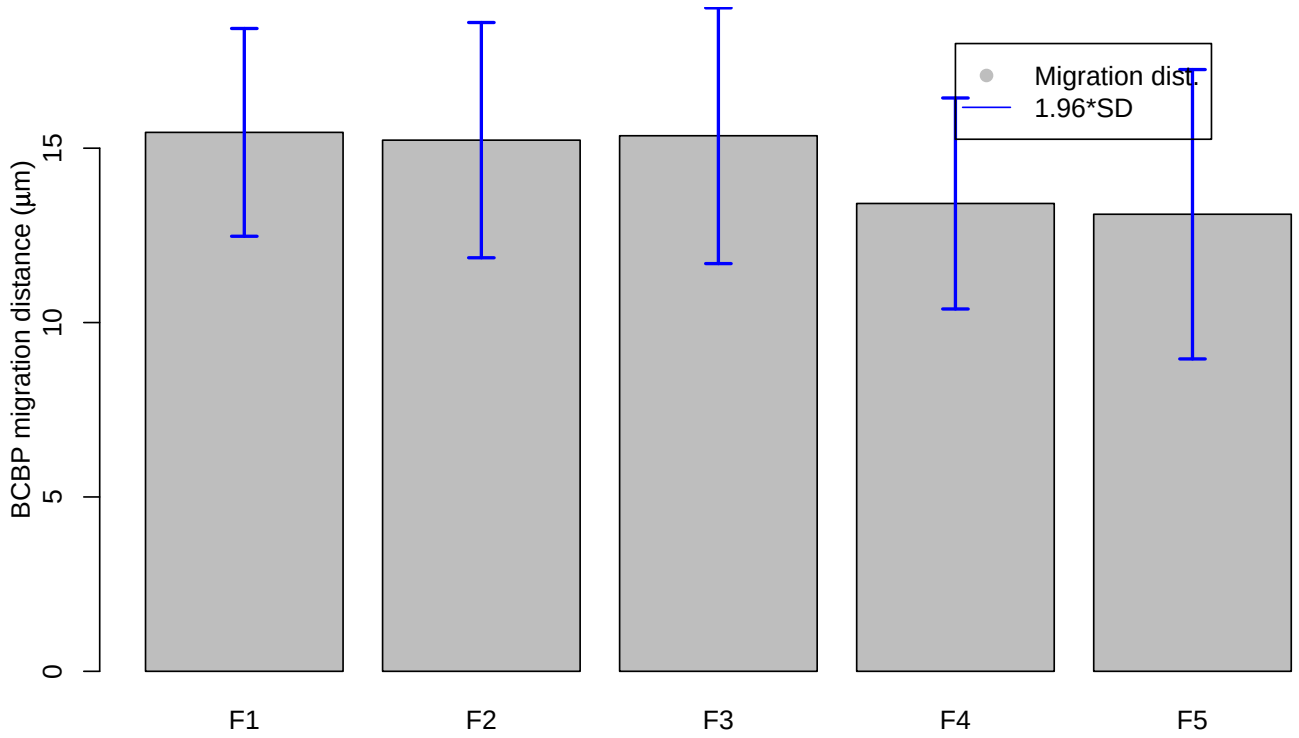
Dendrite length, all BCBPs, one simulation



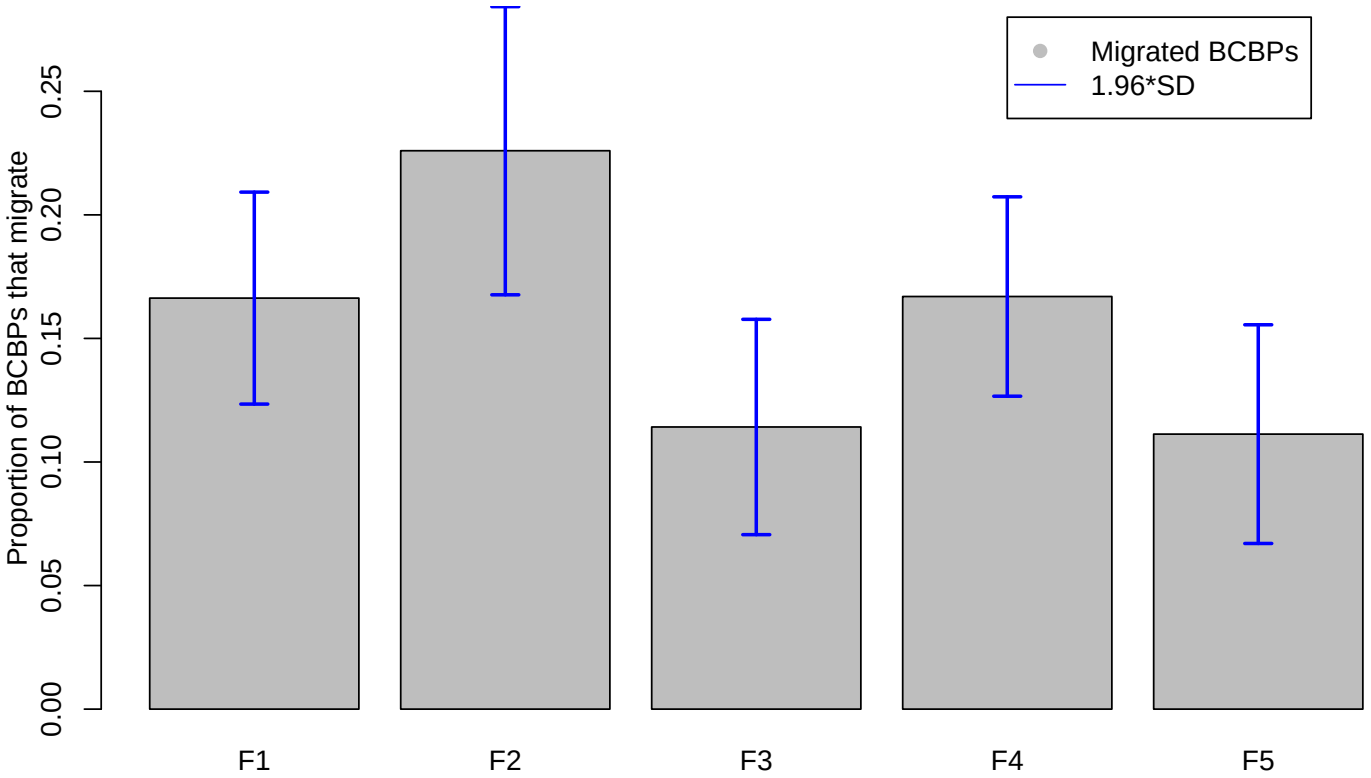
Dendrite length, all BCBPs, 99 simulations



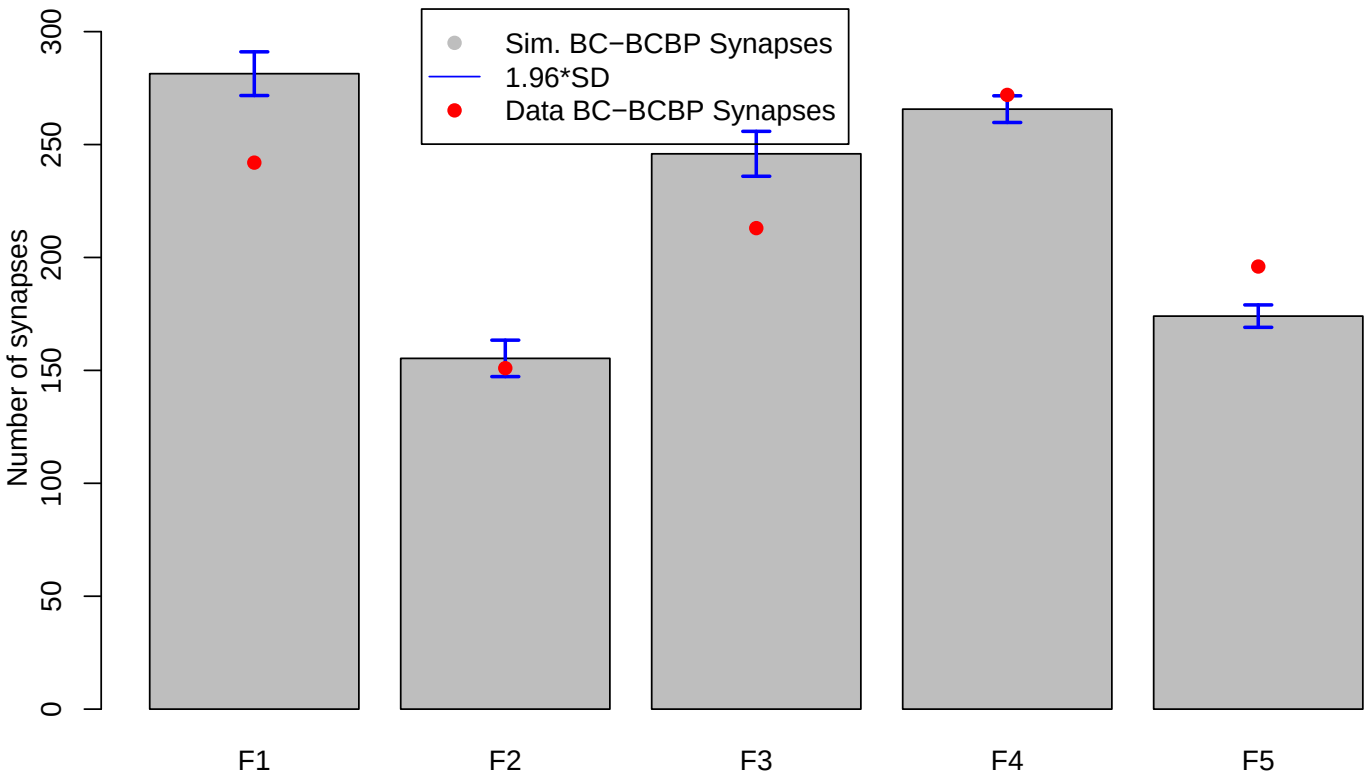
Migration distance, only migrating BCBPs, a biological prediction



Proportion of BCBPs that migrate, another prediction



Number of synapses, yet another prediction



Density recovery profile (DRP)

How can we analyse the mosaics of BCs and BCBPs and their interactions?

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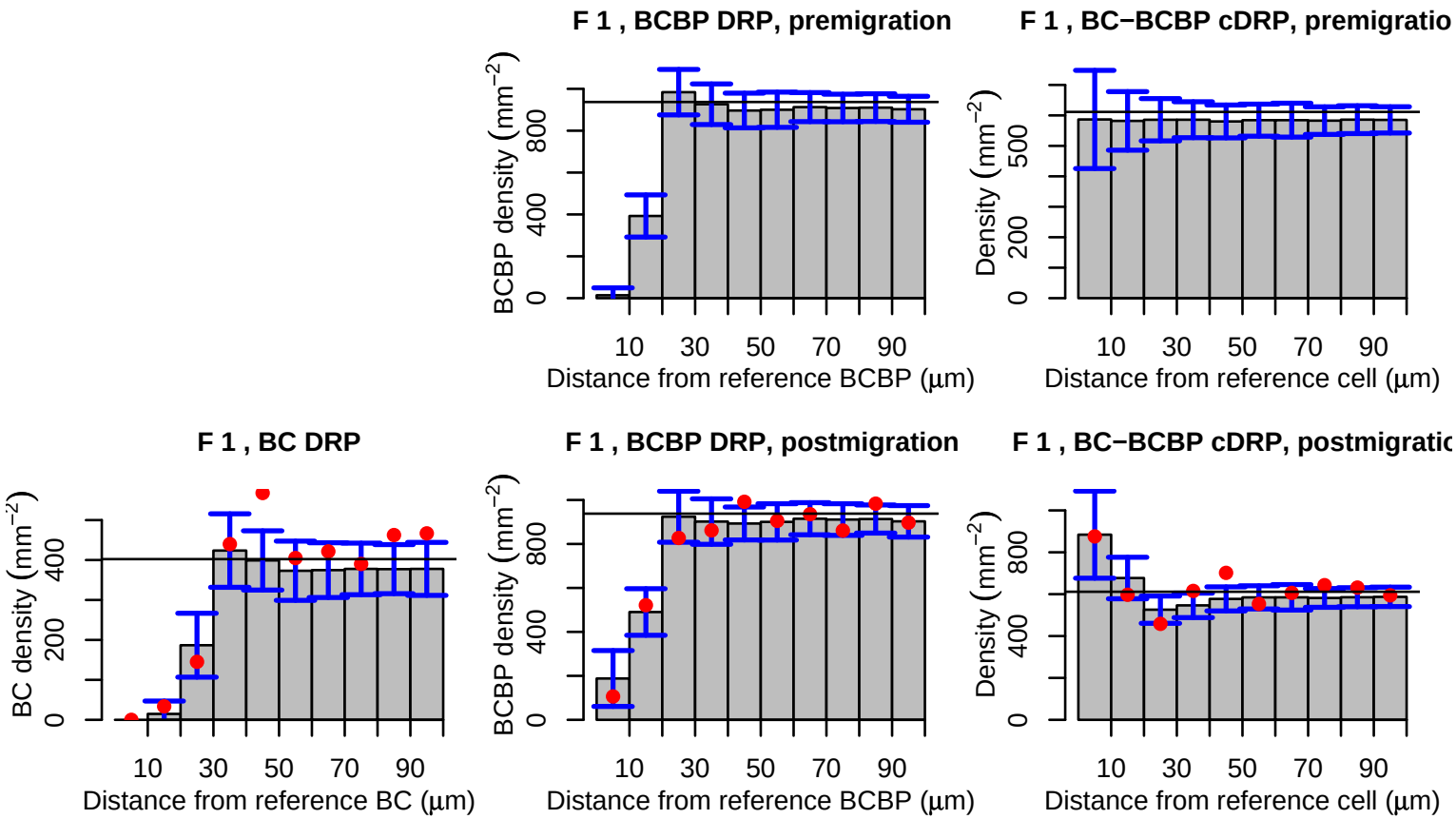
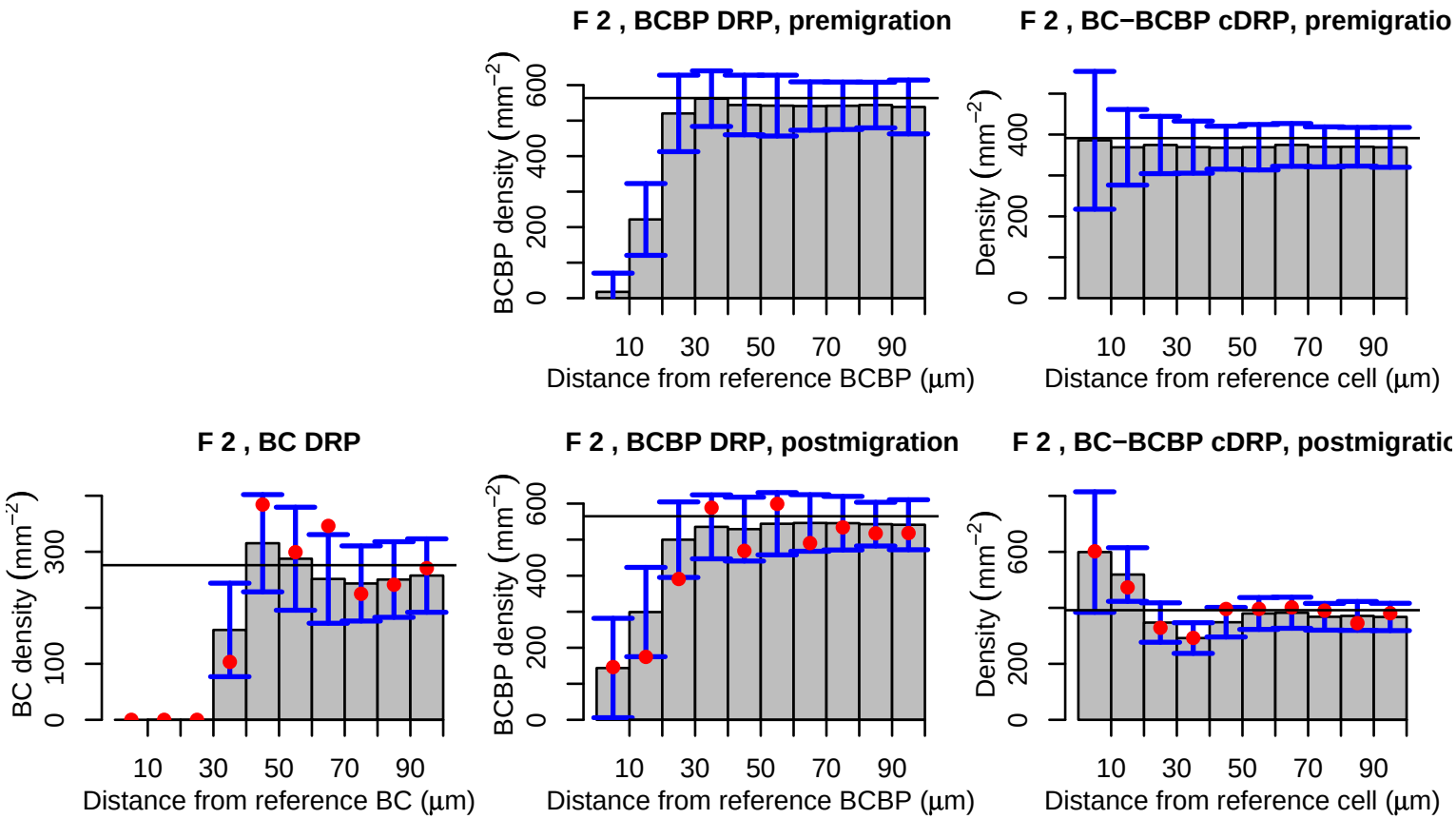
How can we analyse the mosaics of BCs and BCBPs and their interactions?

- Consider one reference point from population i and ask how many points from population j are at a distance between l and $l + \delta l$. Convert into density.
- Do this for all such reference points. This gives a density function, called a *DRP*.
- If $i = j$, we are analysing one population and a dip in the beginning of the (auto) DRP indicates a mosaic structure.
- If $i \neq j$, we are analysing two populations and a nonflat (cross) DRP indicates correlation.

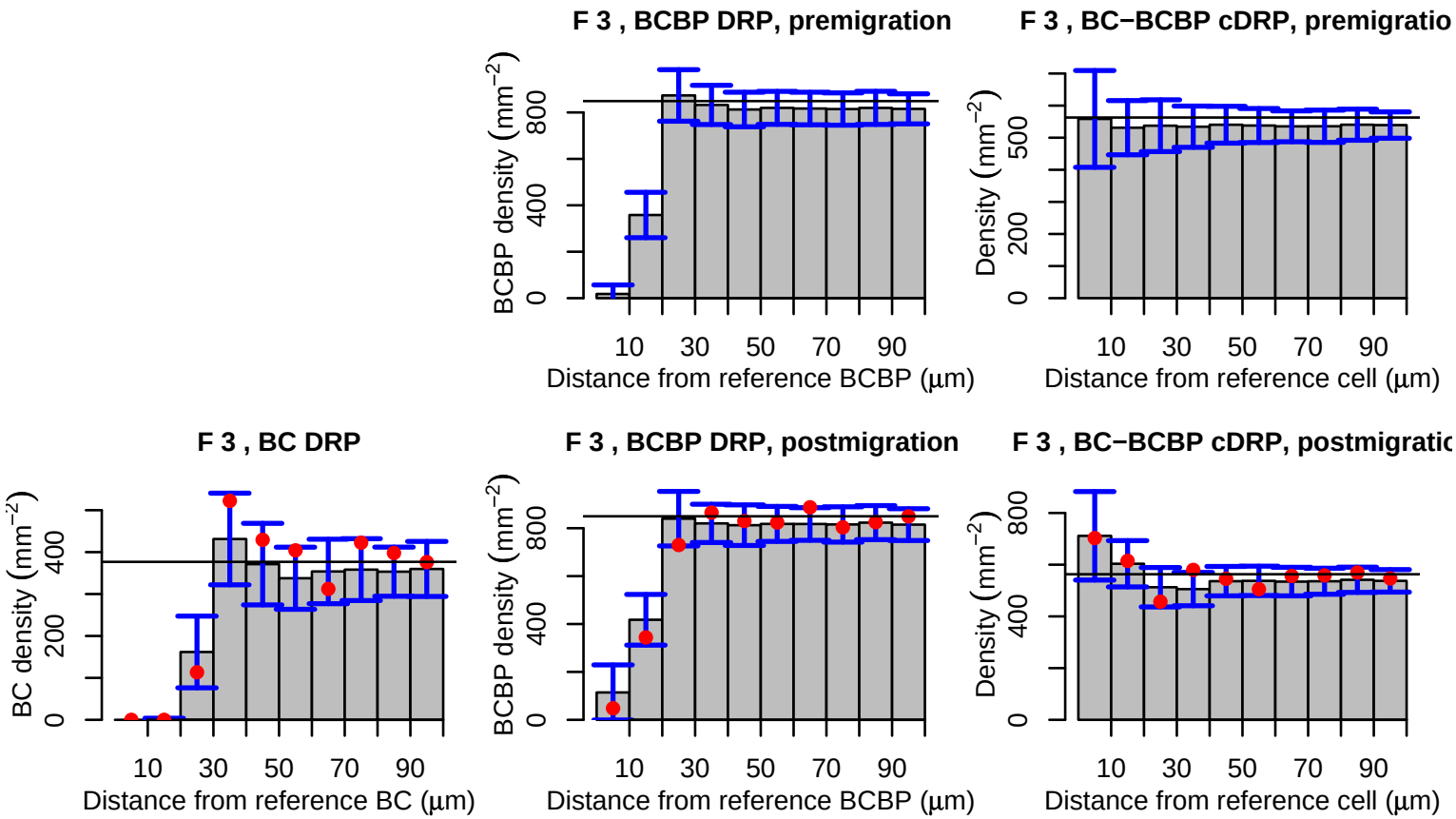
DRP, field 1


F 1 , BCBP DRP, premigration
BCBP density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference BCBP (µm)
F 1 , BC−BCBP cDRP, premigratio
Density (mm^{-2})
0
200
500
10
30
50
70
90
Distance from reference cell (µm)
F 1 , BC DRP
BC density (mm^{-2})
0
200
400
10
30
50
70
90
Distance from reference BC (µm)
F 1 , BCBP DRP, postmigration
BCBP density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference BCBP (µm)
F 1 , BC−BCBP cDRP, postmigratic
Density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference cell (µm)

DRP, field 2


F 2 , BCBP DRP, premigration
BCBP density (mm^{-2})
0 200 400 600
10 30 50 70 90
Distance from reference BCBP (µm)
F 2 , BC−BCBP cDRP, premigratio
Density (mm^{-2})
0 200 400
10 30 50 70 90
Distance from reference cell (µm)
F 2 , BC DRP
BC density (mm^{-2})
0 100 300
10 30 50 70 90
Distance from reference BC (µm)
F 2 , BCBP DRP, postmigration
BCBP density (mm^{-2})
0 200 400 600
10 30 50 70 90
Distance from reference BCBP (µm)
F 2 , BC−BCBP cDRP, postmigratic
Density (mm^{-2})
0 200 600
10 30 50 70 90
Distance from reference cell (µm)

DRP, field 3


F 3 , BCBP DRP, premigration
BCBP density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference BCBP (µm)
F 3 , BC−BCBP cDRP, premigratio
Density (mm^{-2})
0
200
500
10
30
50
70
90
Distance from reference cell (µm)
F 3 , BC DRP
BC density (mm^{-2})
0
200
400
10
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70
90
Distance from reference BC (µm)
F 3 , BCBP DRP, postmigration
BCBP density (mm^{-2})
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400
800
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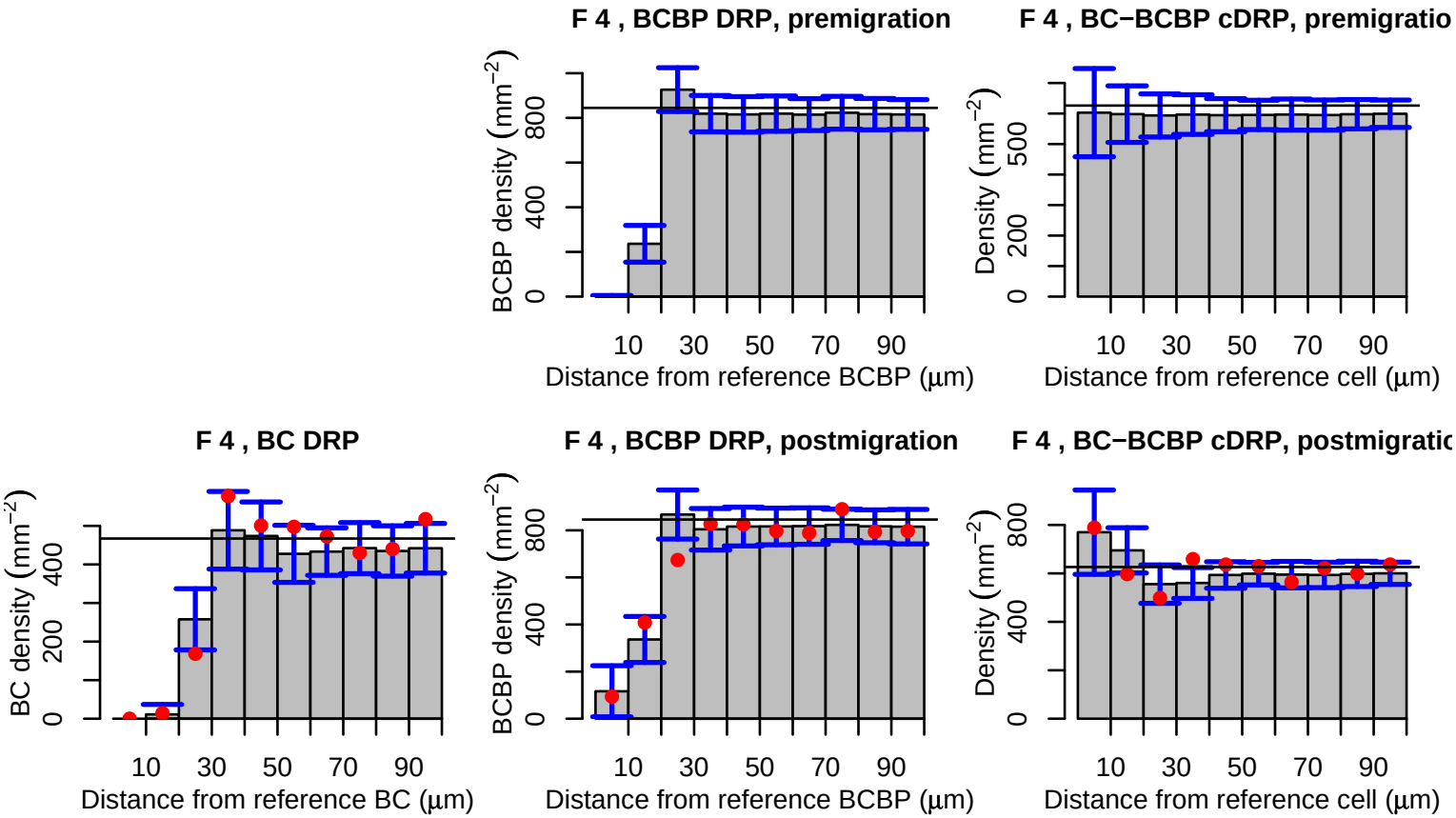
30
50
70
90
Distance from reference BCBP (µm)
F 3 , BC−BCBP cDRP, postmigratic
Density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference cell (µm)

DRP, field 4


F 4 , BCBP DRP, premigration
BCBP density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference BCBP (µm)
F 4 , BC−BCBP cDRP, premigratio
Density (mm^{-2})
0
200
500
10
30
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Distance from reference cell (µm)
F 4 , BC DRP
BC density (mm^{-2})
0
200
400
10
30
50
70
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Distance from reference BC (µm)
F 4 , BCBP DRP, postmigration
BCBP density (mm^{-2})
0
400
800
10
30
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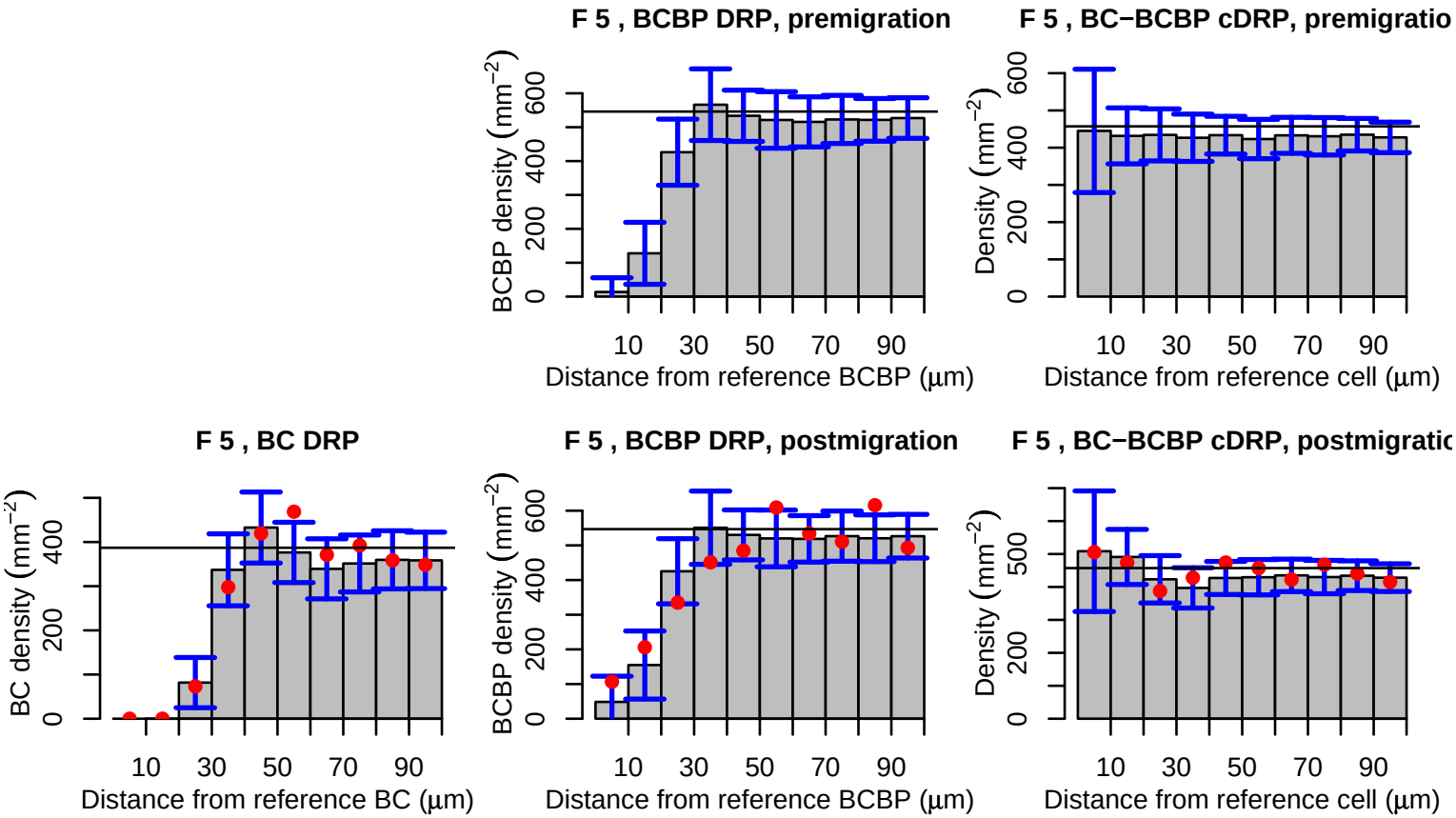
Distance from reference BCBP (µm)
F 4 , BC−BCBP cDRP, postmigratic
Density (mm^{-2})
0
400
800
10
30
50
70
90
Distance from reference cell (µm)

DRP, field 5


F 5 , BCBP DRP, premigration
BCBP density (mm^{-2})
0 200 400 600
10 30 50 70 90
Distance from reference BCBP (µm)
F 5 , BC−BCBP cDRP, premigratio
Density (mm^{-2})
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Distance from reference cell (µm)
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K functions

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- Idea: look at a circular area (with radius t) around a given reference point and count the points; and compare with what would be expected under complete randomness.
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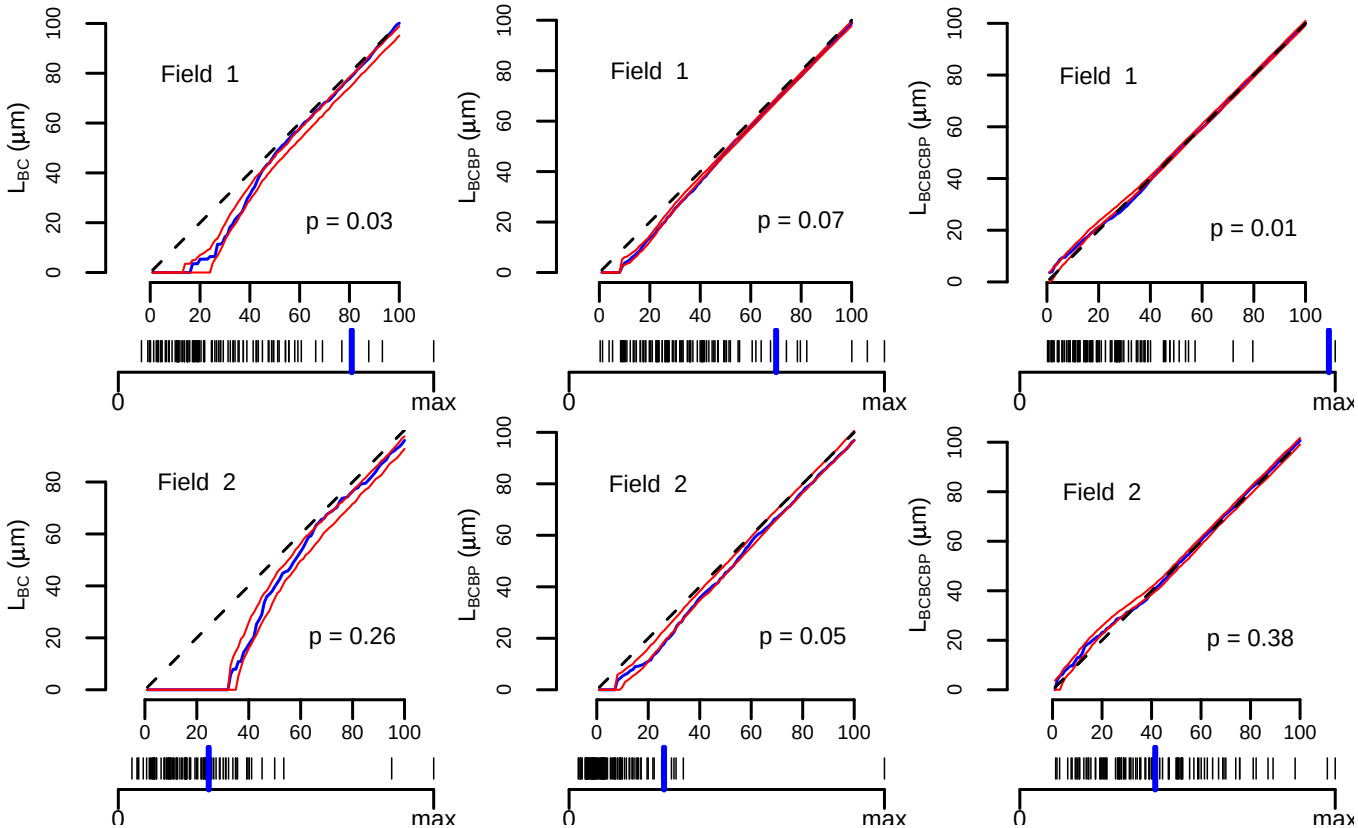
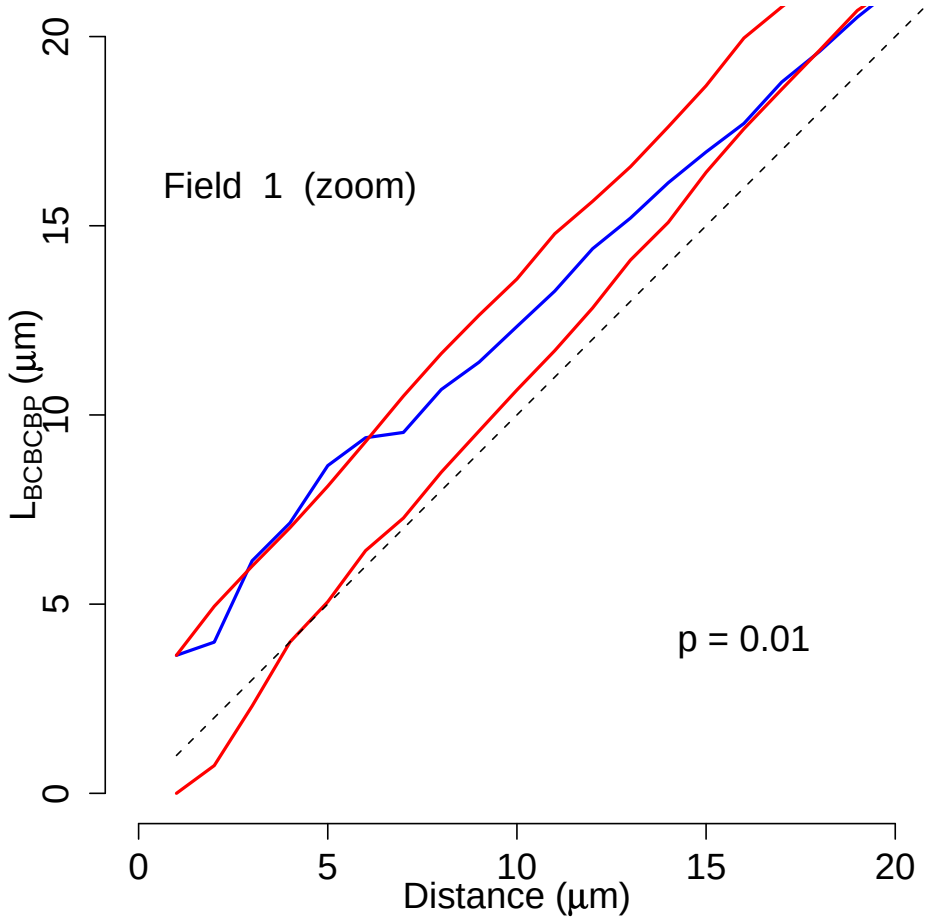
- Inference: we have one K function for the real data and 99 for the simulations. Why don't we measure how far each of these 100 K functions is from the 99 others and see if the data K function stands out or not.

L functions, fields 1 and 2



L function, $L_{BC,BCBP}$ field 1



All K function p values

Field	p_{BC}	p_{BCBP}	$p_{BC,BCBP}$
1	0.03	0.07	0.01
2	0.26	0.05	0.38
3	0.00	0.07	0.59
4	0.24	0.05	0.03
5	0.38	0.04	0.07

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- Future work: measurements of neuronal forces (Guck's lab) and further developments of theoretical models.

Acknowledgements

- N. Kouyama (Tokyo Women's Medical University) and D. W. Marshak (The University of Texas Medical School) for providing the data.
- Dr. Stephen J. Eglen for being my supervisor.
- EPSRC for financial support.

EPSRC Engineering and Physical Sciences Research Council