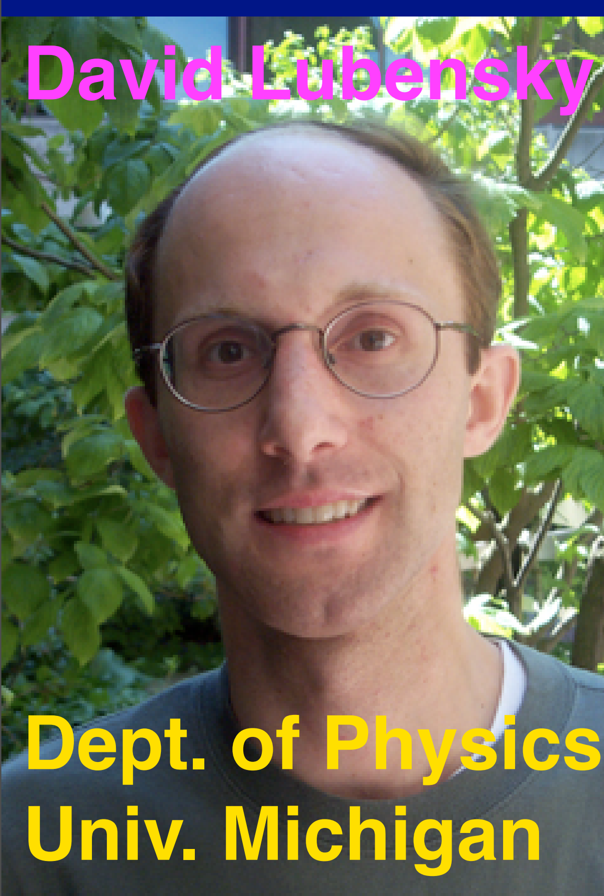
Patterning Neurogenesis: A dynamical model of Drosophila eye development

Nick Baker
Genetics Dept,
Albert Einstein
Coll of Med

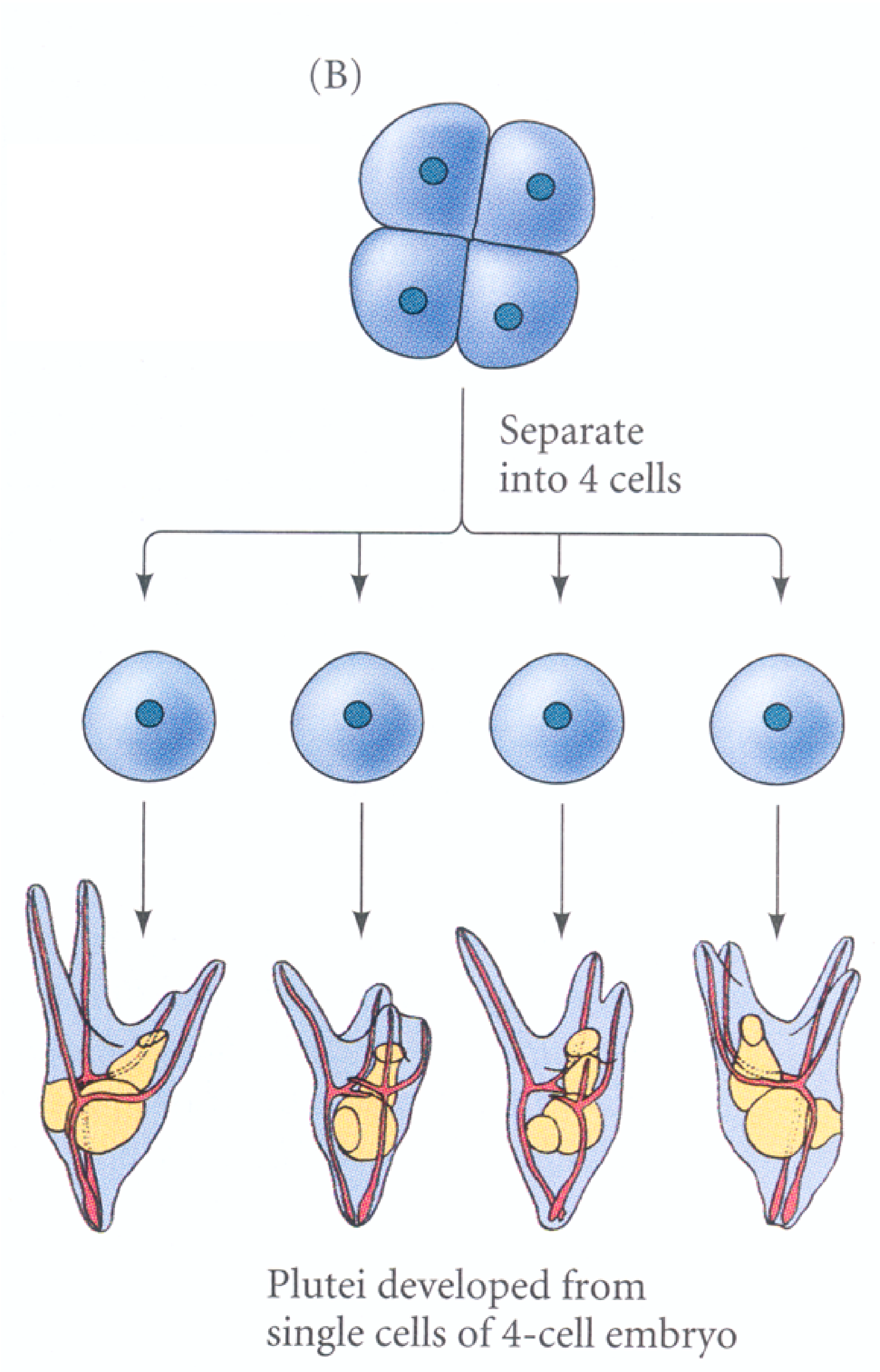


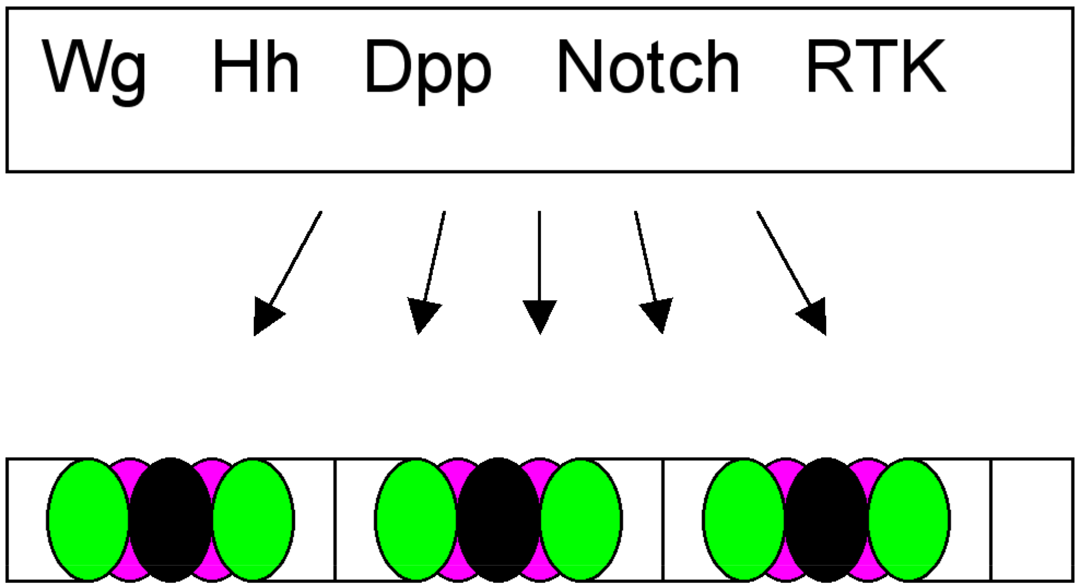
David Lubensky
Dept. of Physics
Univ. Michigan

Matthew Pennington
Biophysics Program, Univ. Michigan

Boris Shraiman
KITP
UC Santa Barbara

Cell-cell communication in development and growth

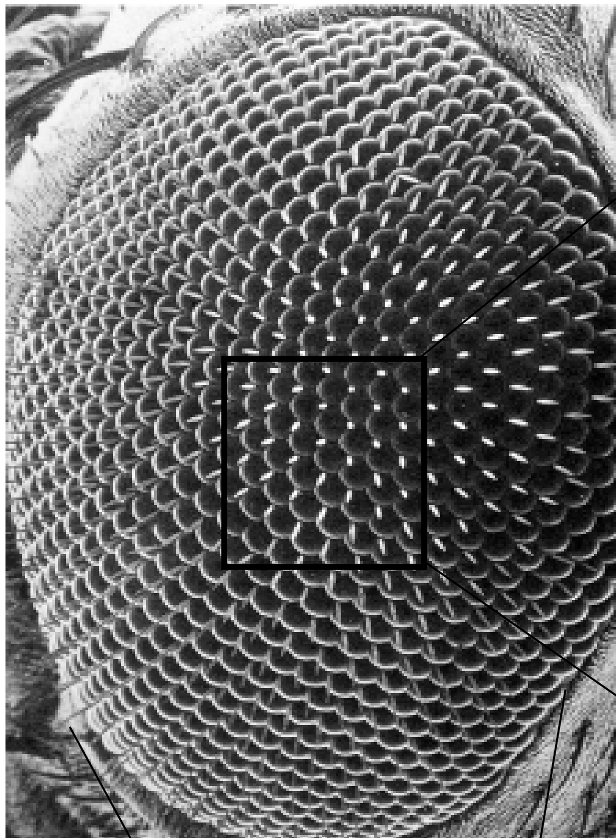




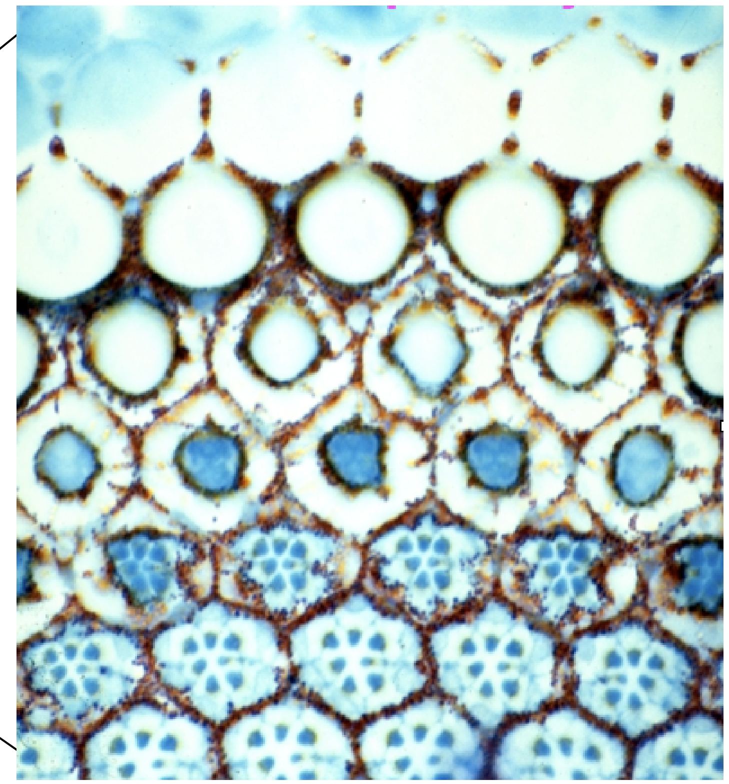
Driesch, 1892

Drosophila melanogaster and compound eye development

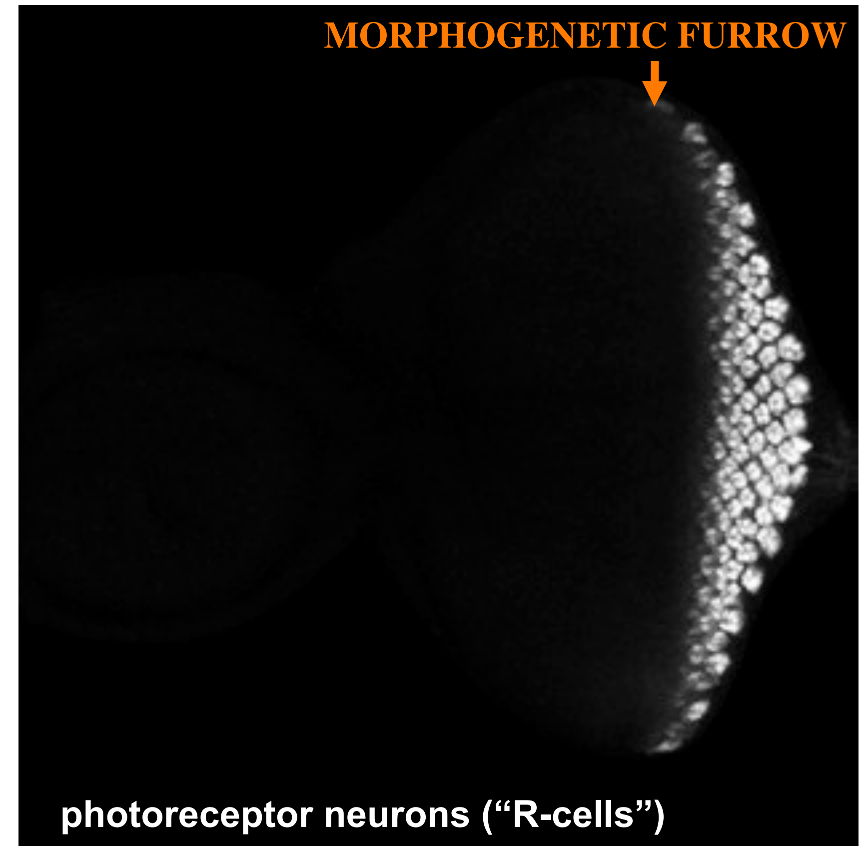
accessible, developmentally-staged neurogenesis



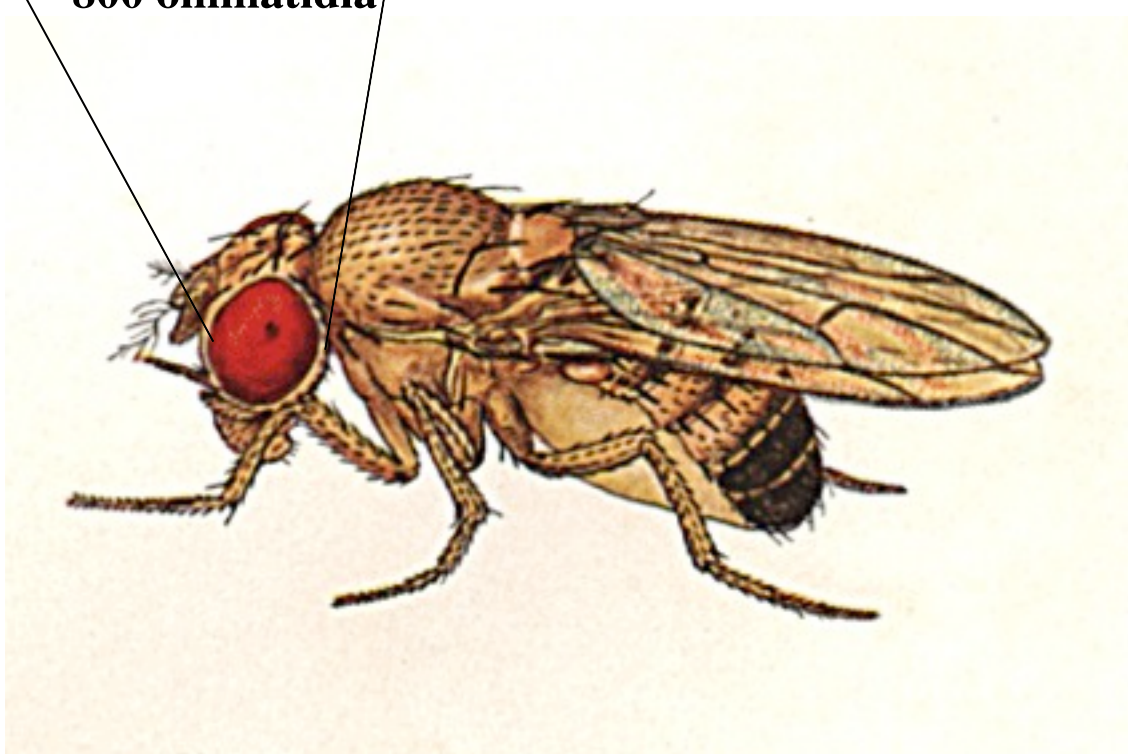
~800 ommatidia



Cell diversity and reproducibility



Wave of differentiation crosses the retina in two days



Talk based on:

Lubensky et al 2011
PNAS **108**: 11145-11150

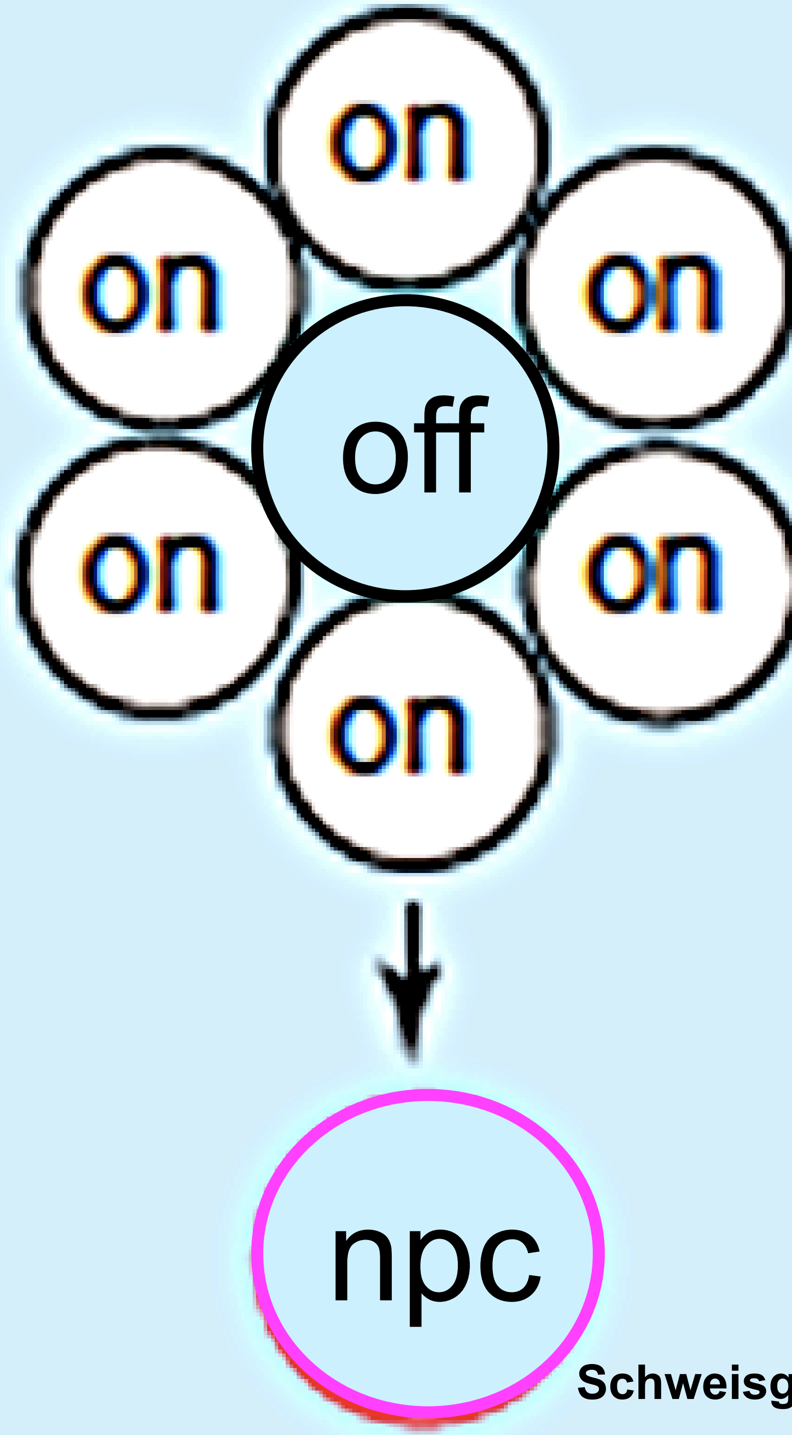
Pennington & Lubensky 2010
Eur Phys J E Soft Matter **33**:129-148

R-cell specification has been thought to follow the proneural plan

Step 1: neurogenic epithelium defined by proneural bHLH gene transcription

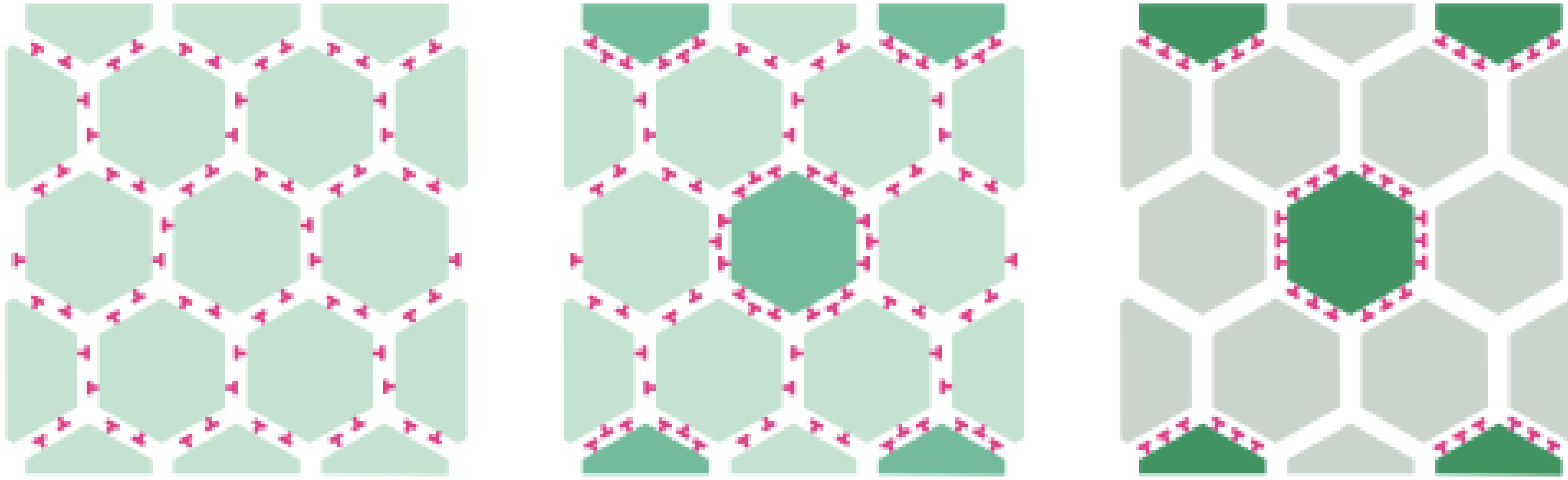
Step 2: competitive cell interactions lead to Notch activation inmost proneural cells

Step 3: single cells sustain proneural gene transcription to differentiate as neural precursor cells

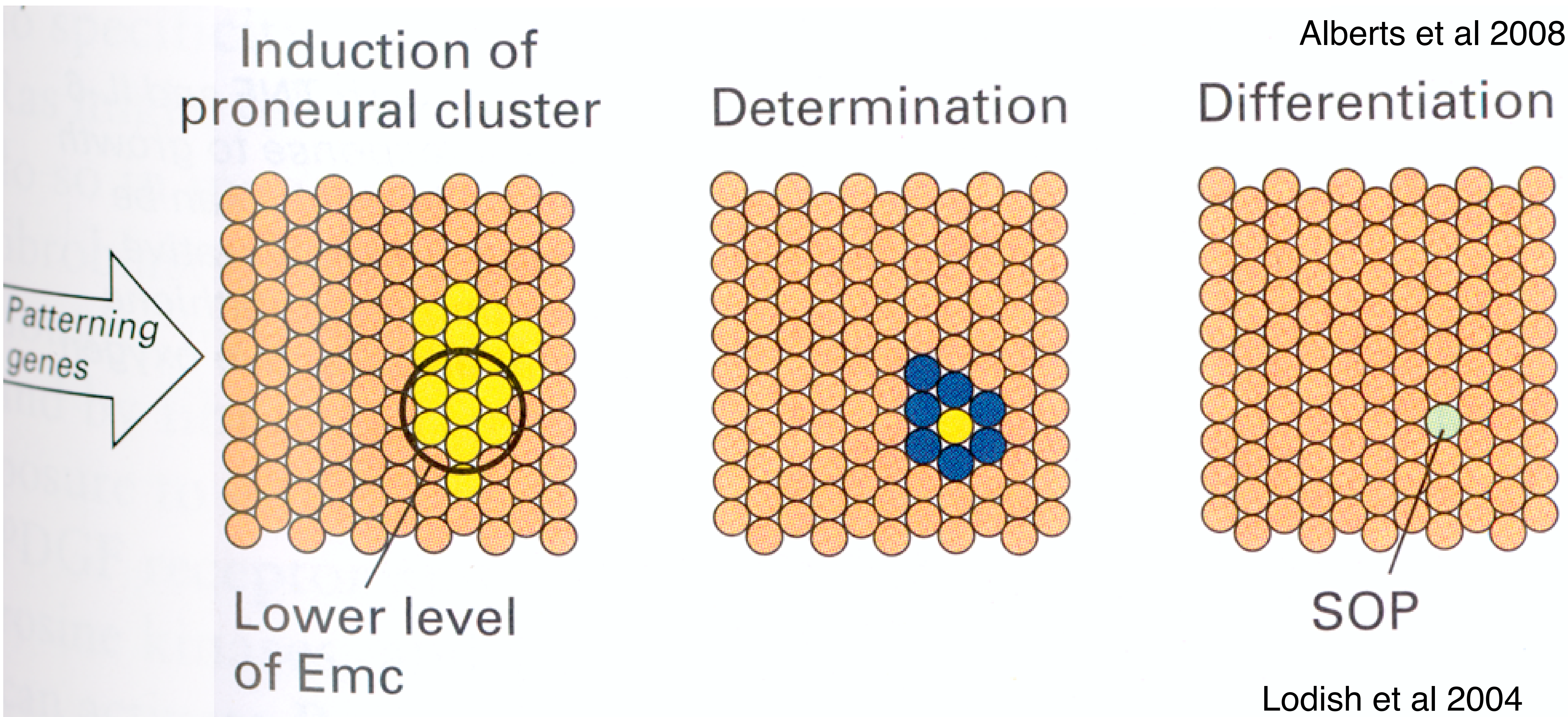


Makes precise pattern in several steps; can regulate in response to damage

Textbook model: Interaction within equivalence groups

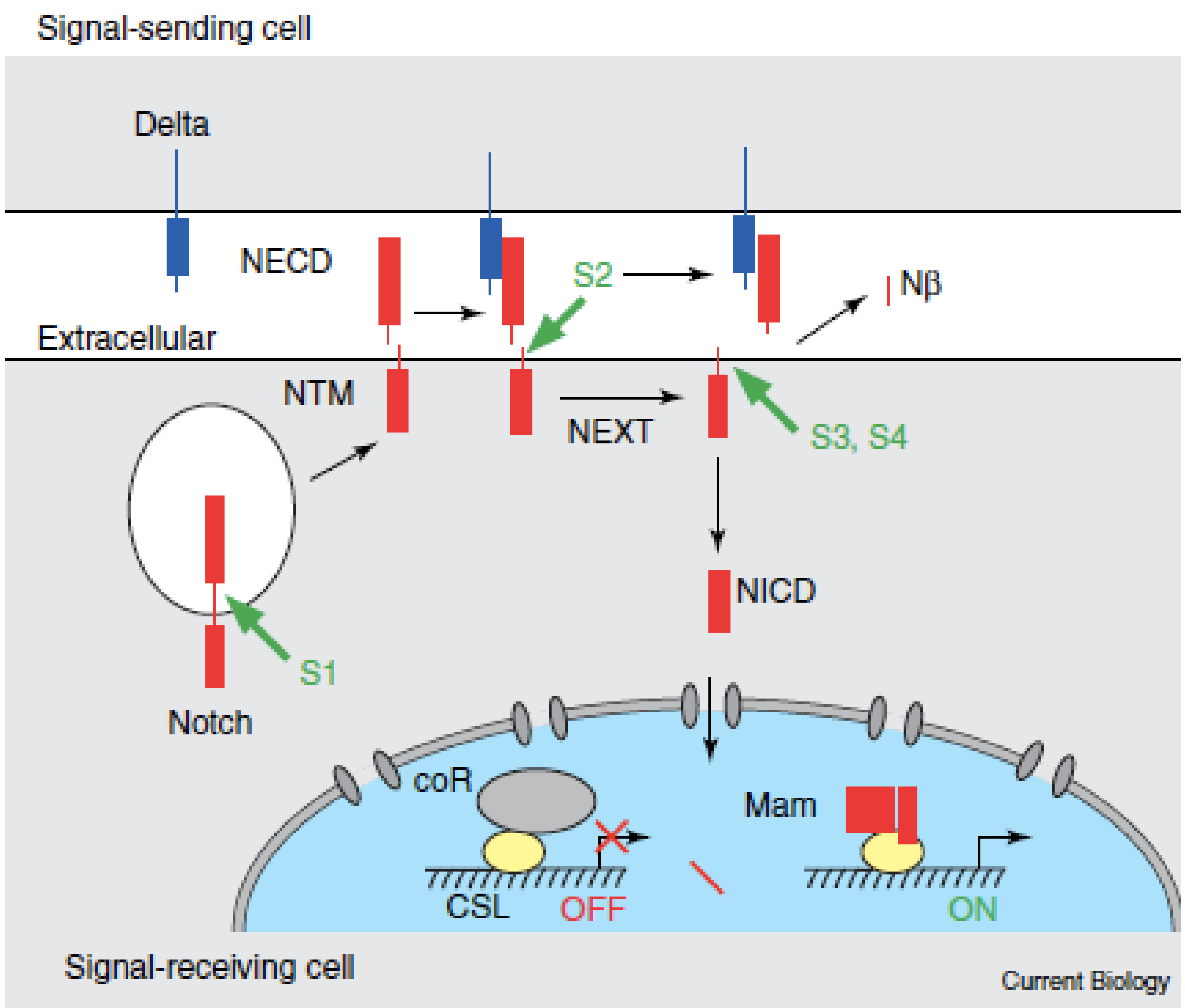


Alberts et al 2008



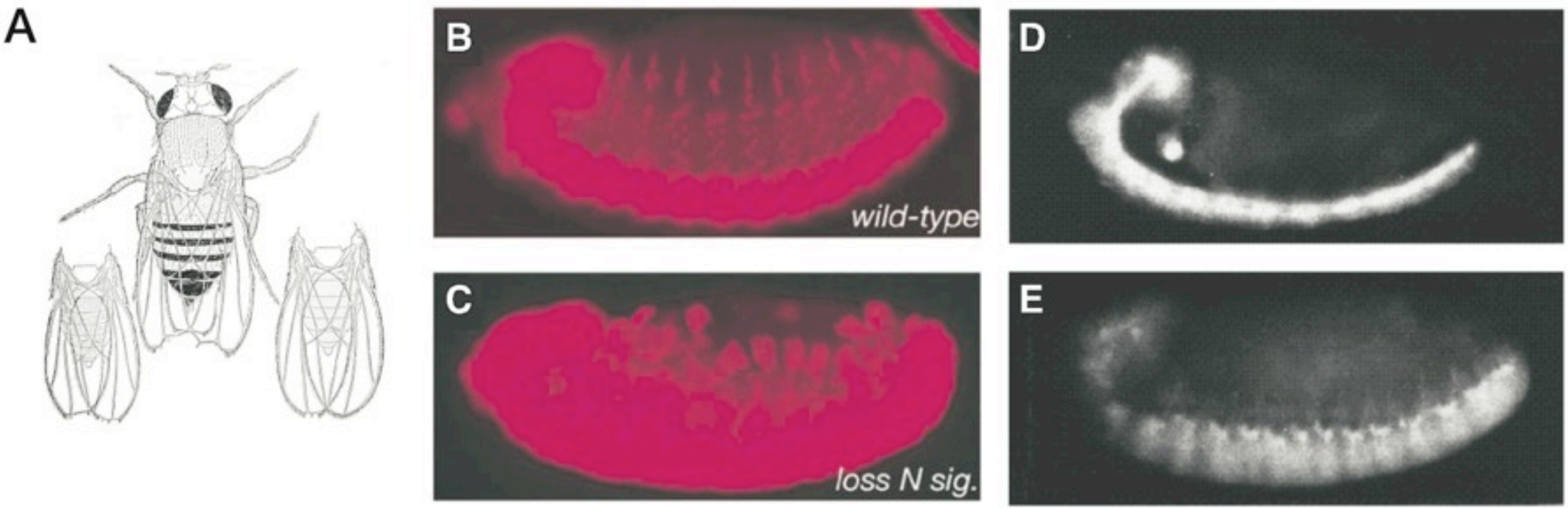
Lodish et al 2004

Notch encodes a large transmembrane receptor for cell-cell signaling. Its ligand Delta is also a large transmembrane protein



Schweisguth (2004)

Cell fate choices dependent on Notch signaling



See also Poulson, D.F
J Exp Zool 83:271-325(1940)

Lateral inhibition restricts and defines the extent of neurogenesis

Step 1: neurogenic epithelium defined by proneural bHLH gene transcription

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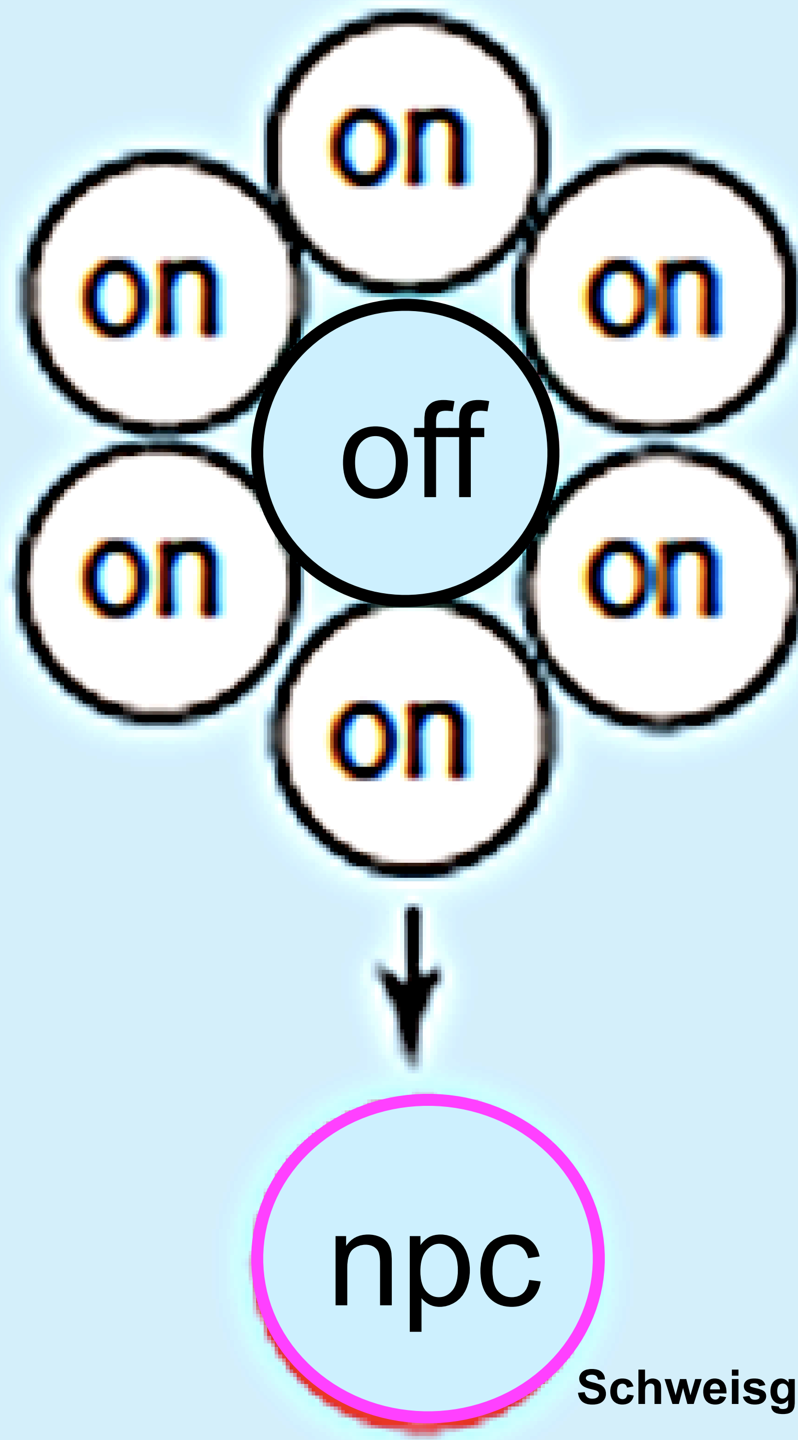

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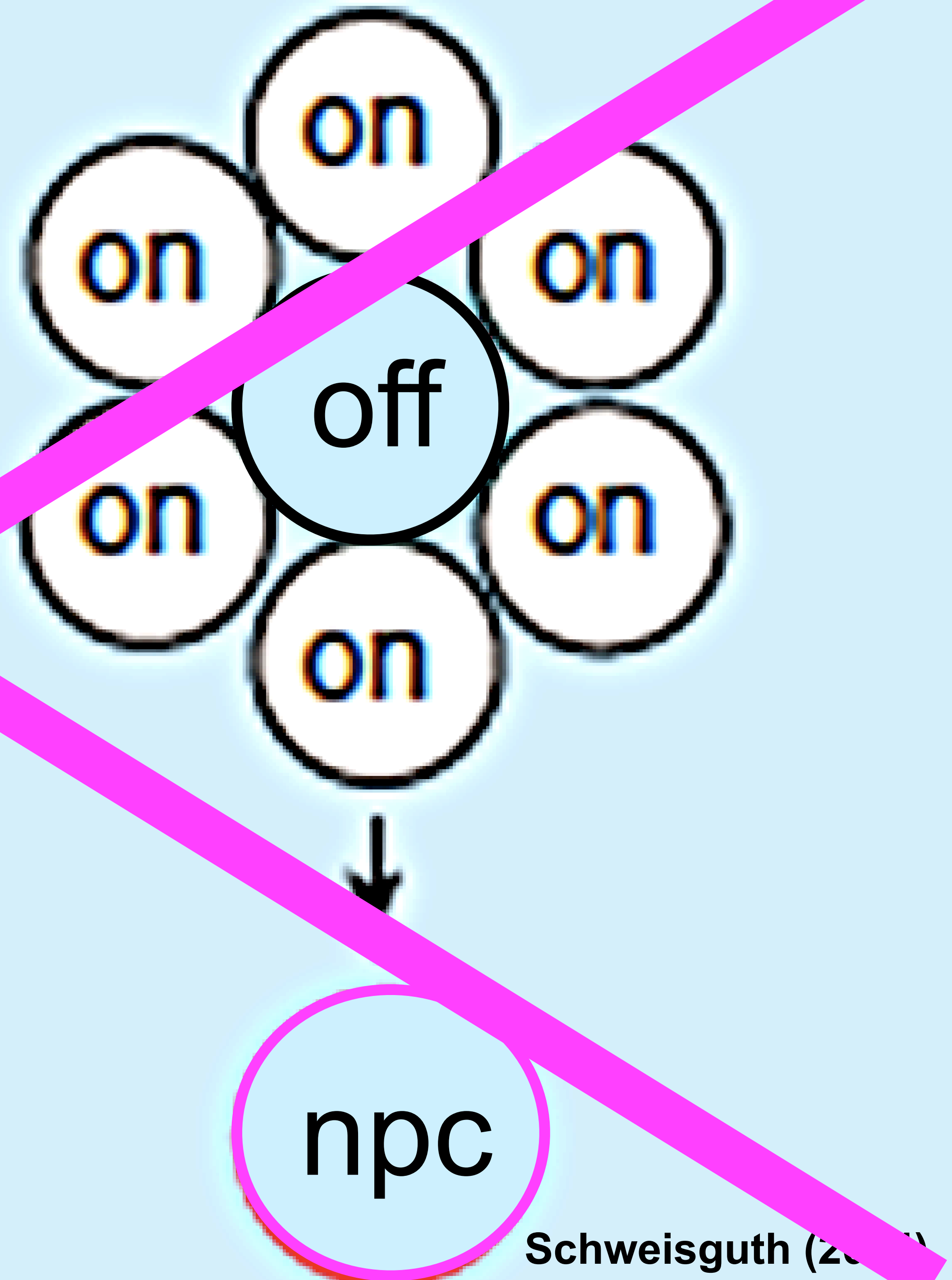
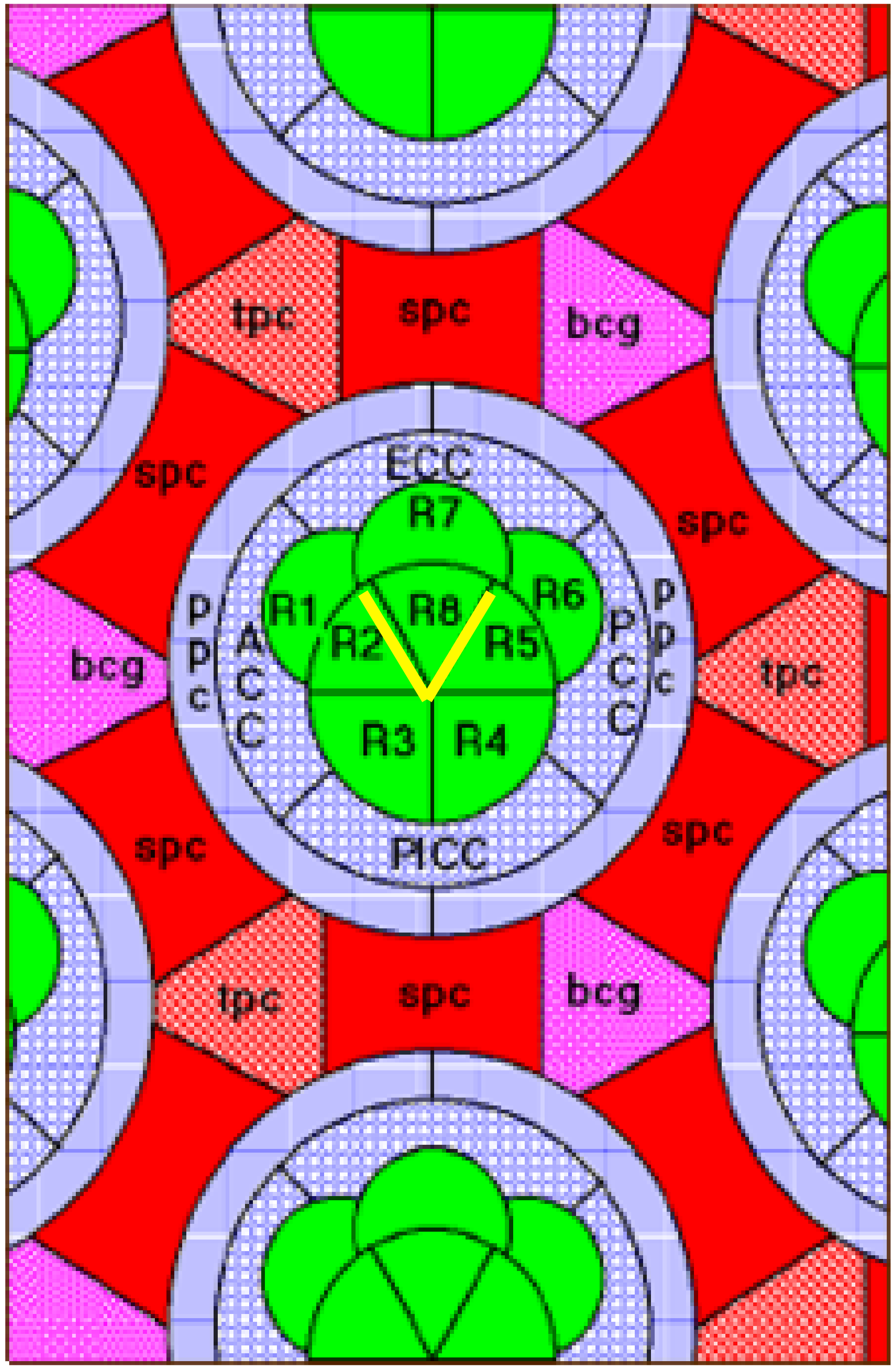
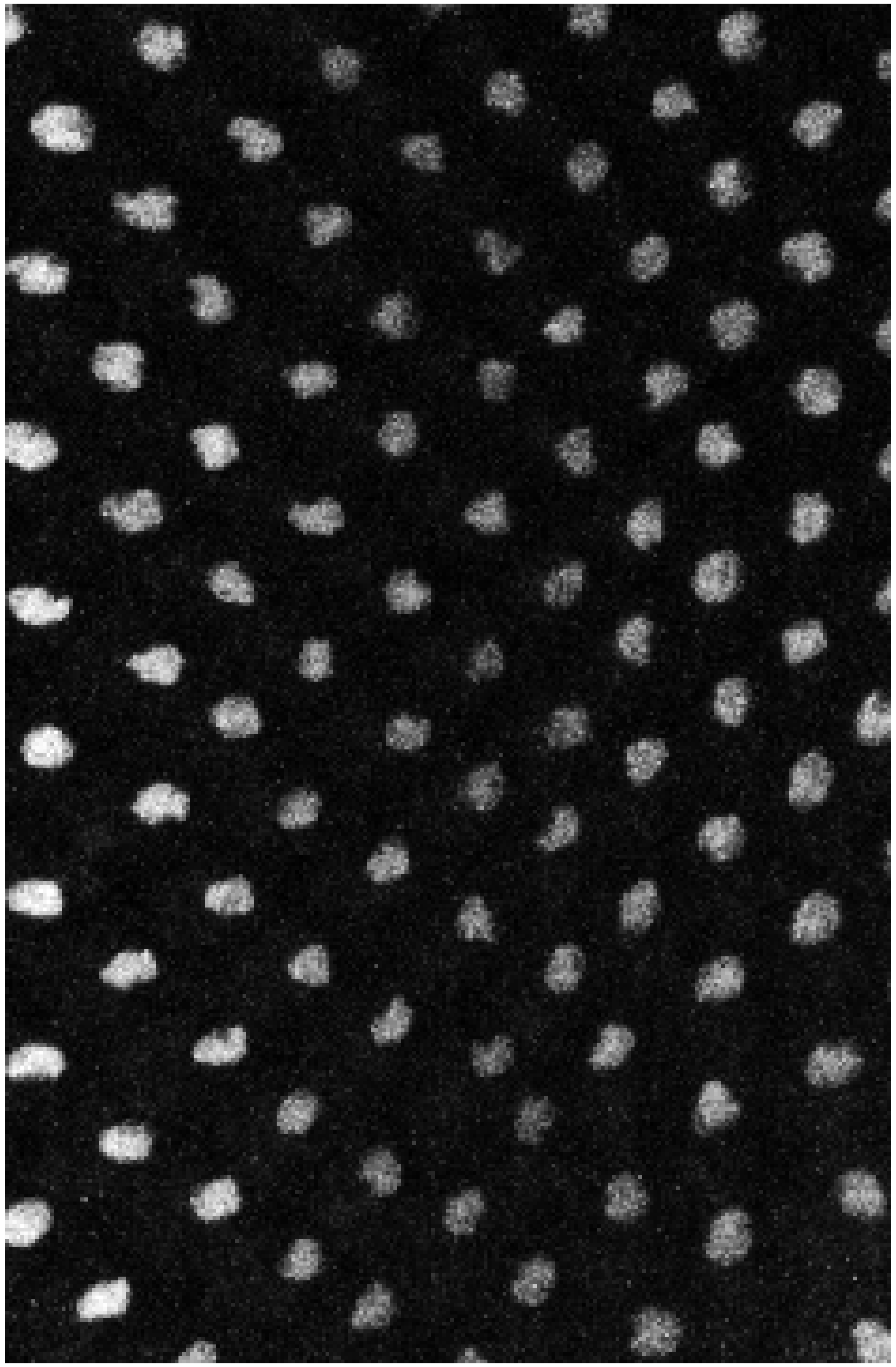


Makes precise pattern in several steps; can regulate in response to damage

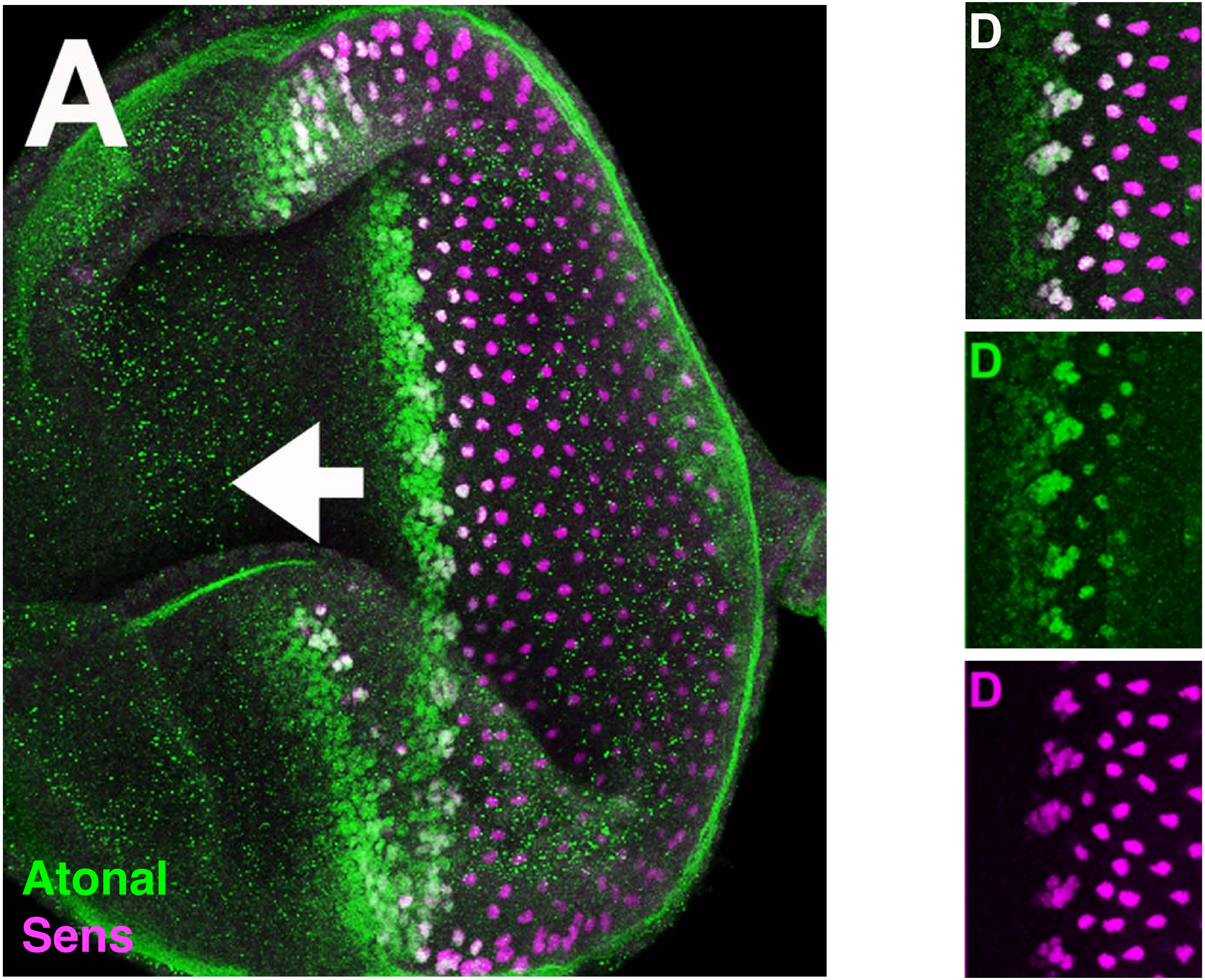
Eye develops around the R8 cell pattern



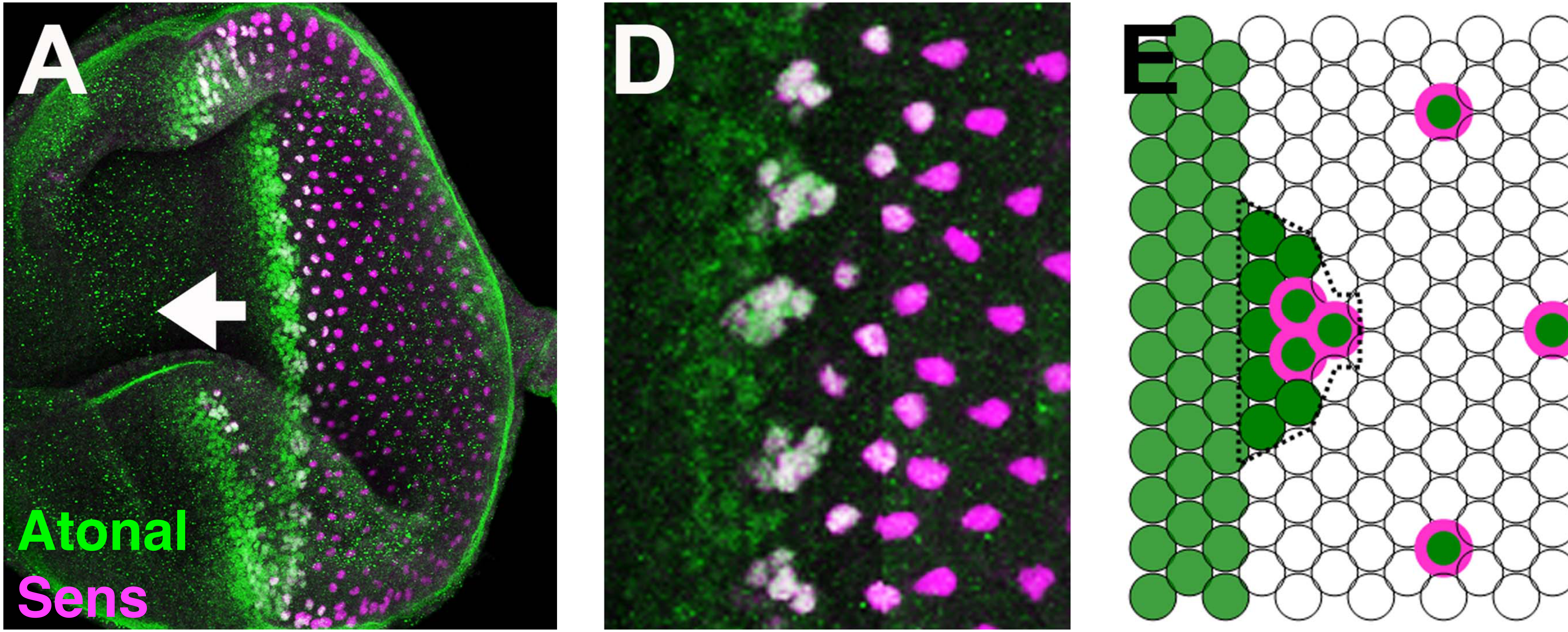
retinal organization

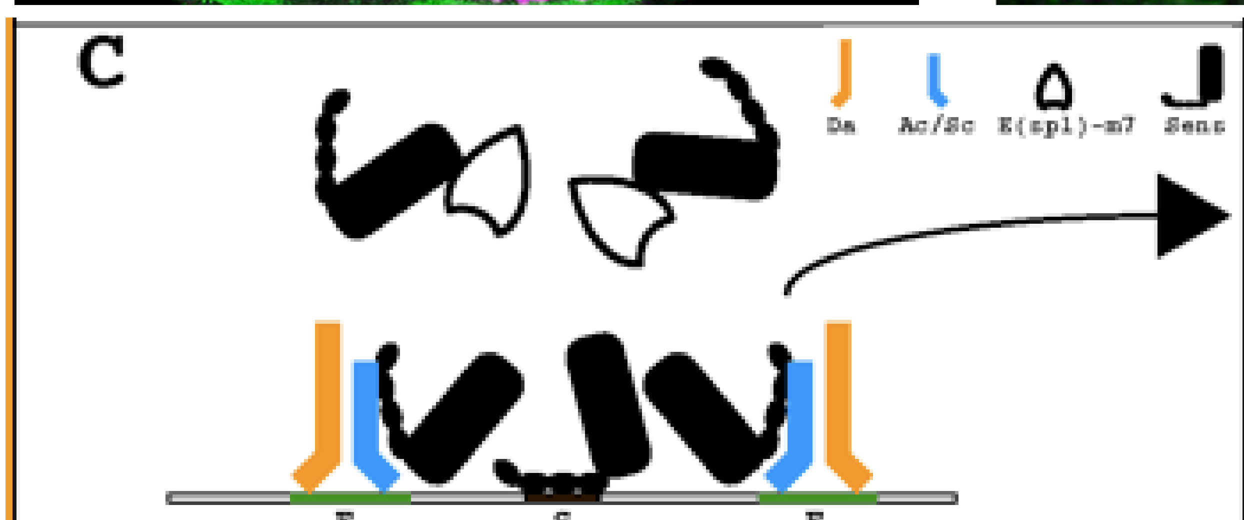


nuclear Senseless protein


A
Atonal
Sens
D
D
D

Atonal and its target/partner Senseless specify R8 cells



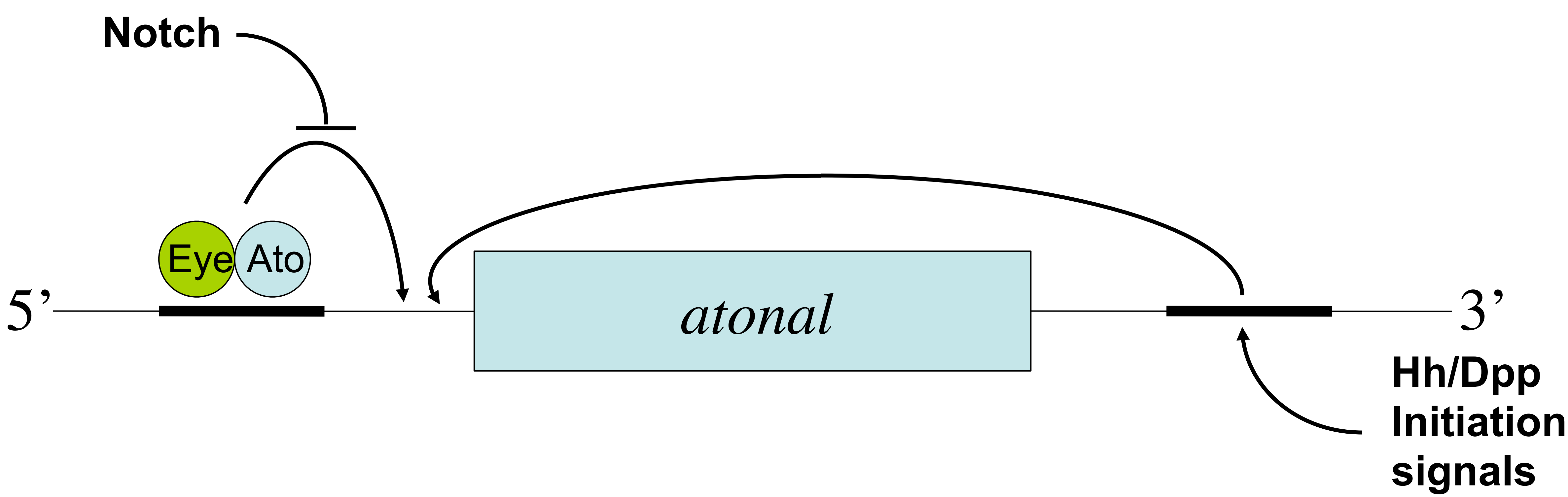


Acar et al., *Development* **133** 1979 (2006)

Fig. 8. A model for the dual role of Sens Zn fingers in the transcriptional regulation of proneural target genes. E rep

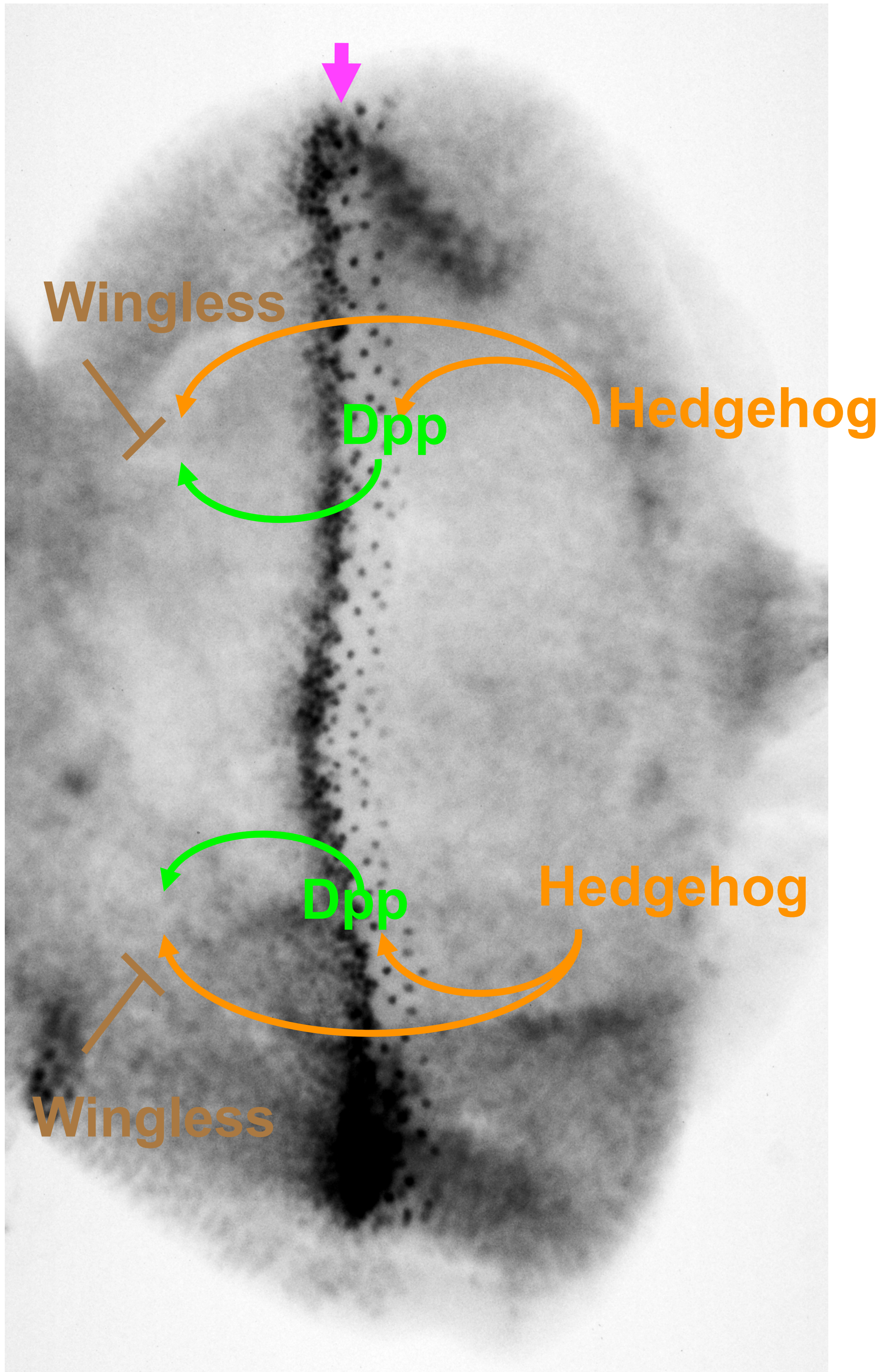
Atonal is the bHLH protein
Senseless is a Zn-finger protein

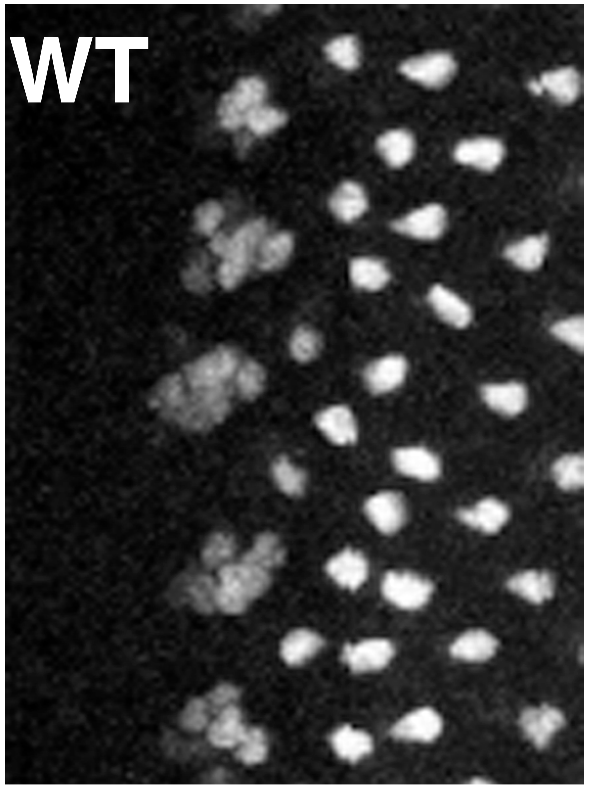
Scheme for progressive atonal regulation during R8 determination

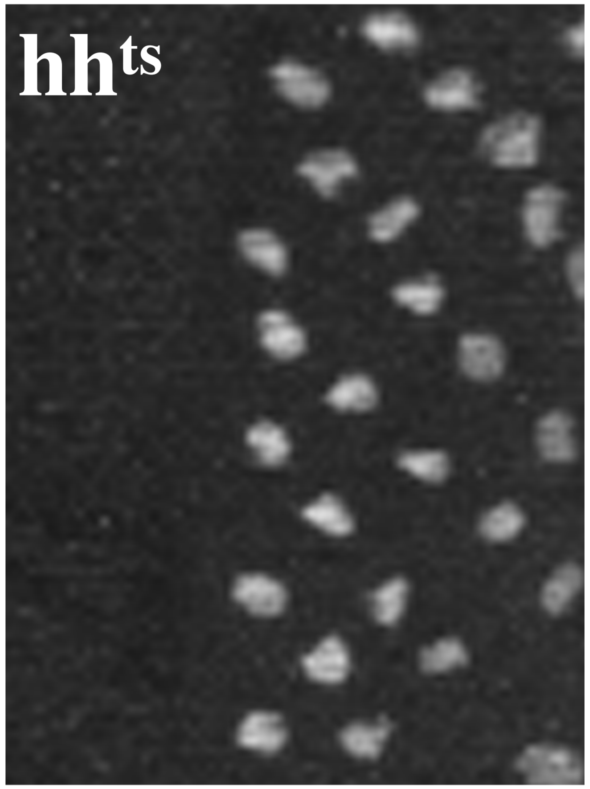


Adapted from Baker, N.E. *Dev Cell* **7** 632-4 (2004)

+ve and -ve signals that regulate Atonal







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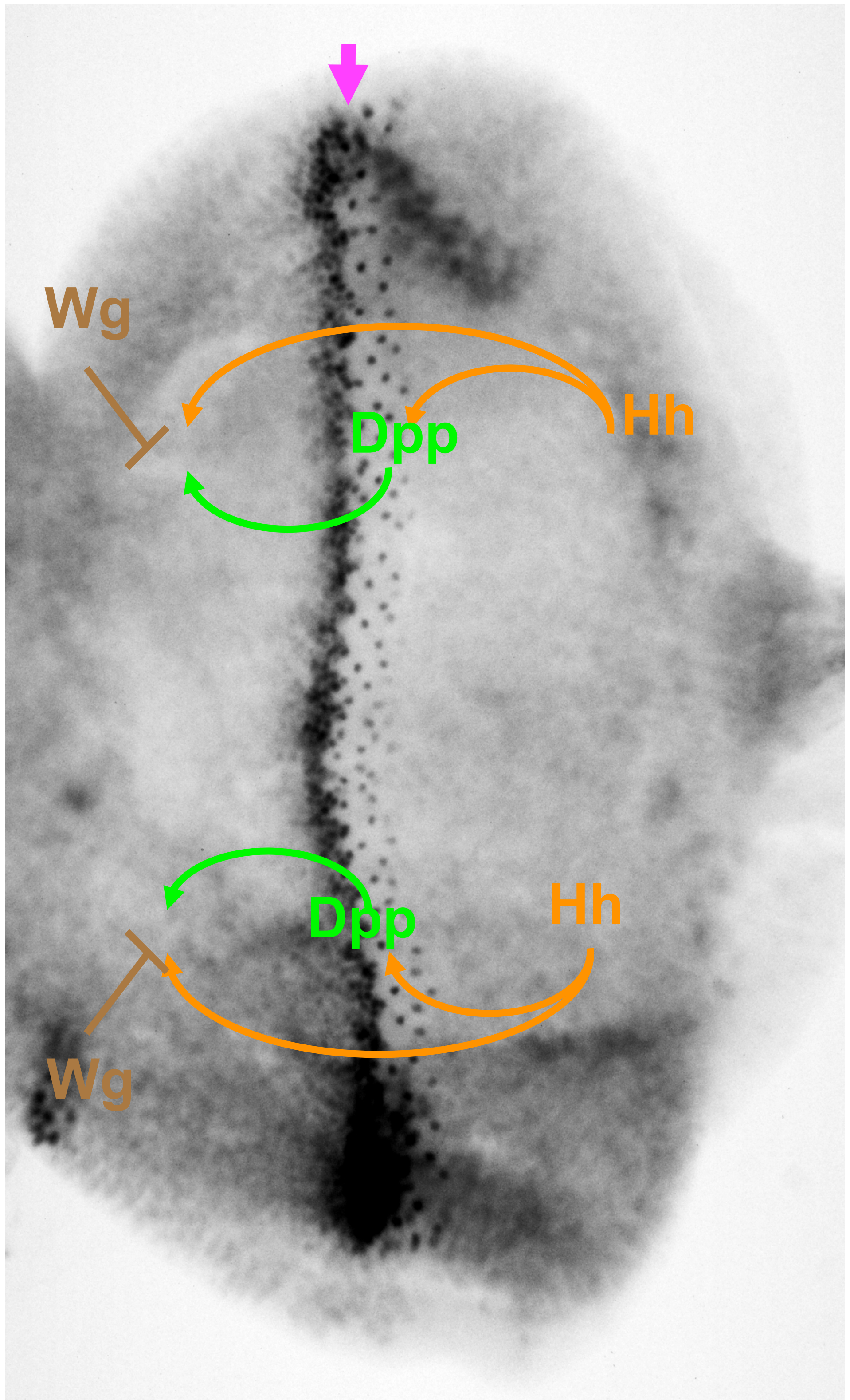
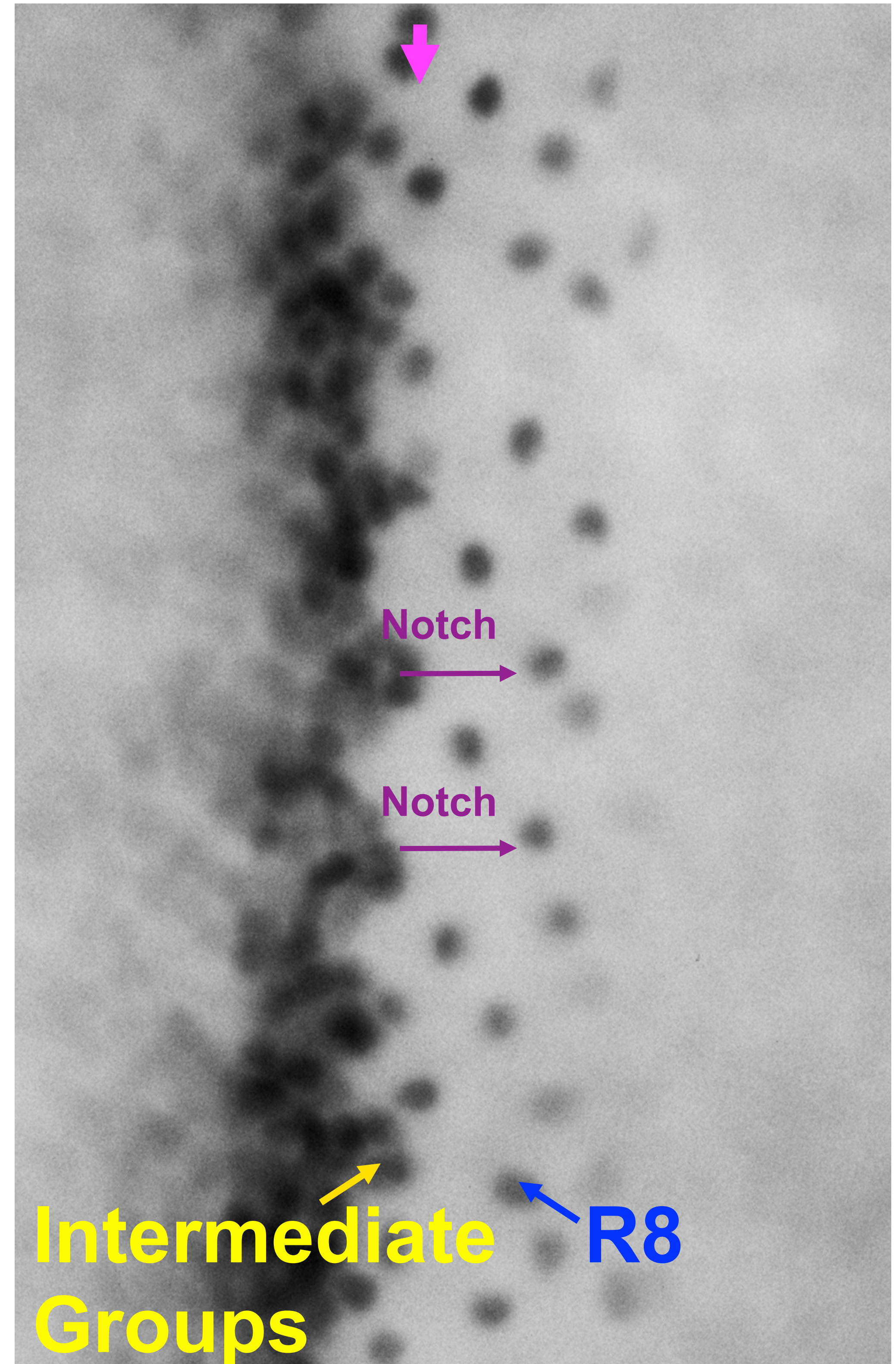
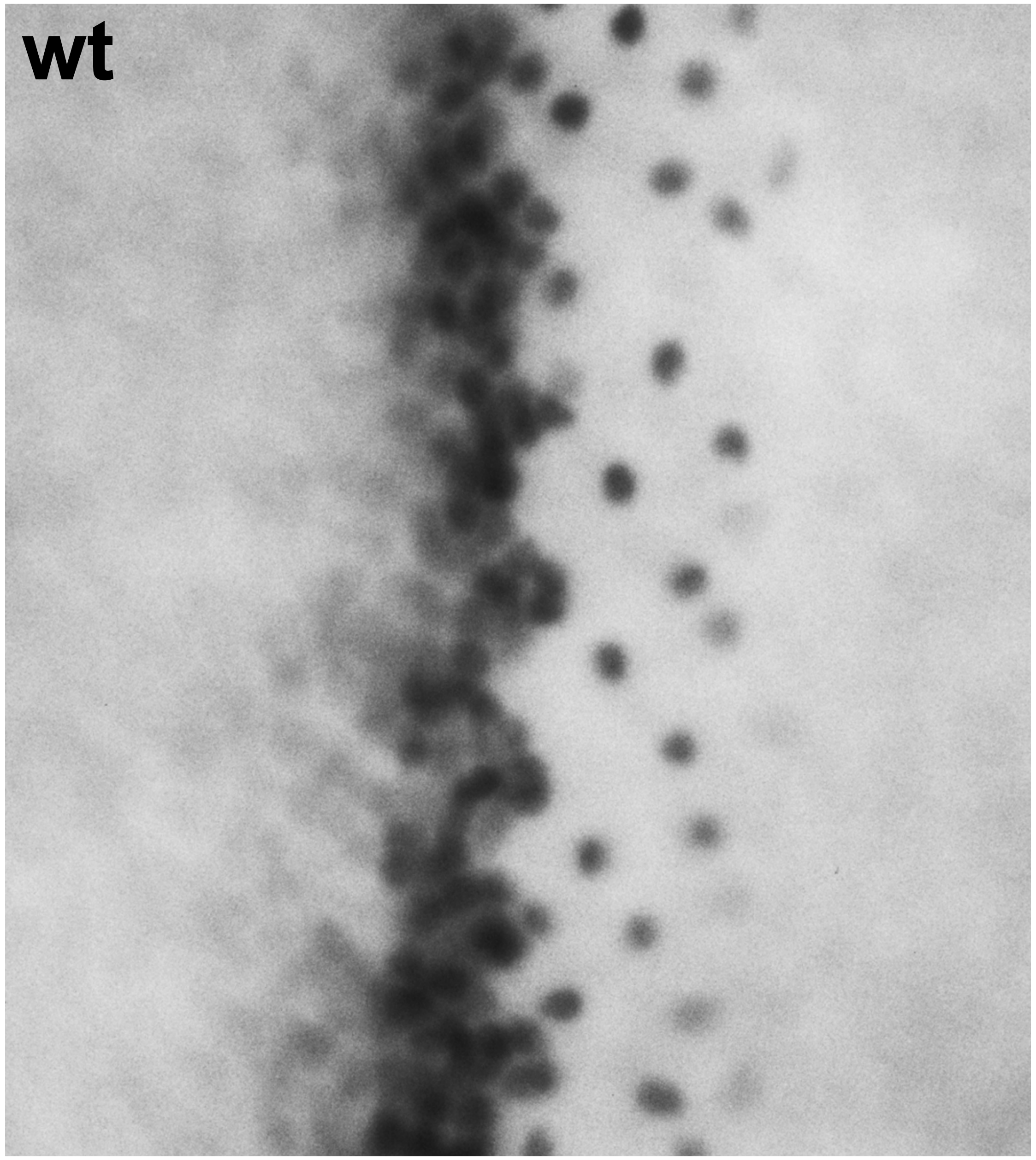
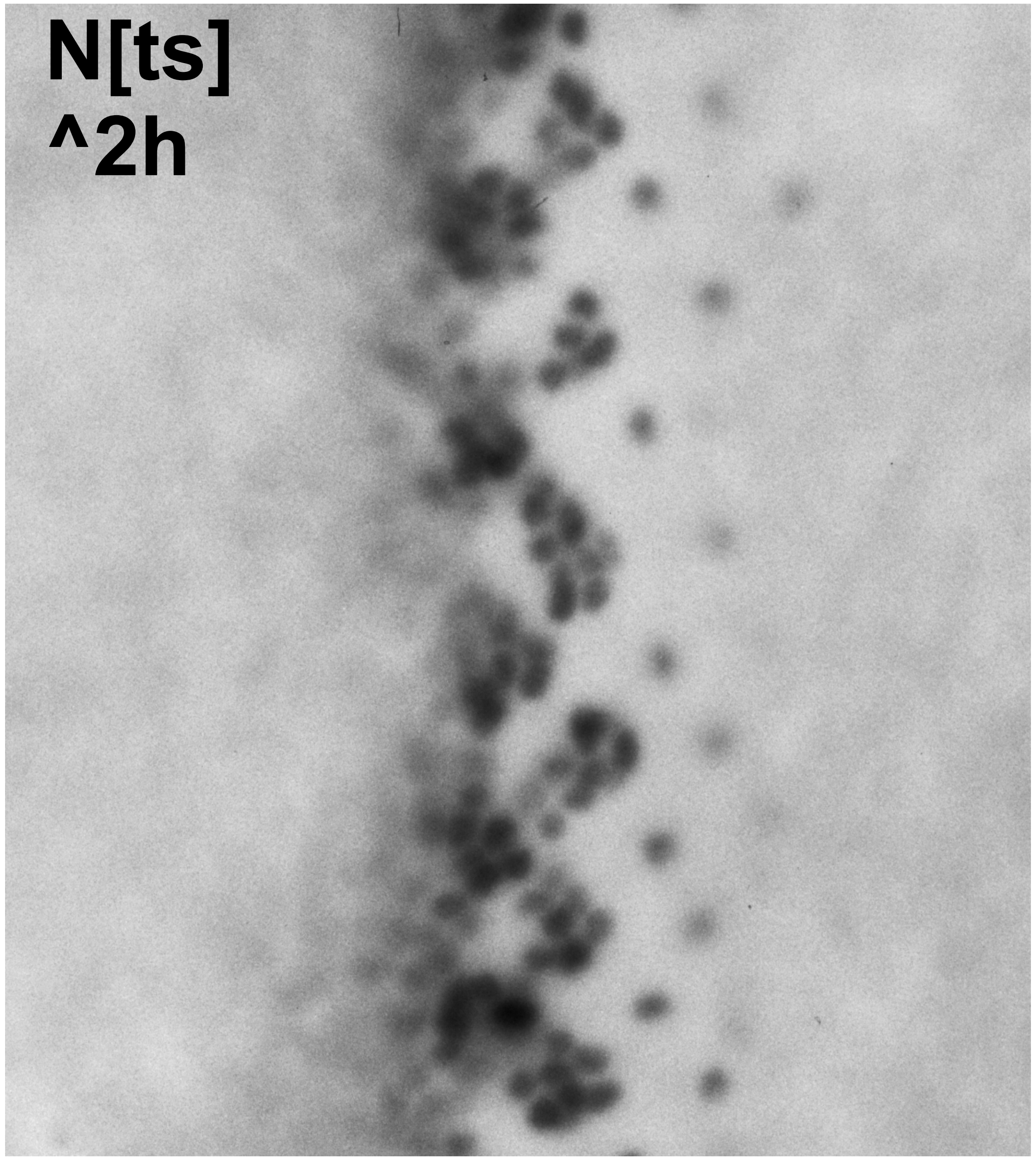




Heberlein et al *Cell* **75** 913-926 (1993); Ma et al., *Cell* **75** 927-938 (1993)-Ma et al., *Development* **121** 2279-2289 (1995); Treisman & Rubin *Development* **75** 3519-3527(1995) Baker *Curr Biol* **6** 1290-1301 (1996)

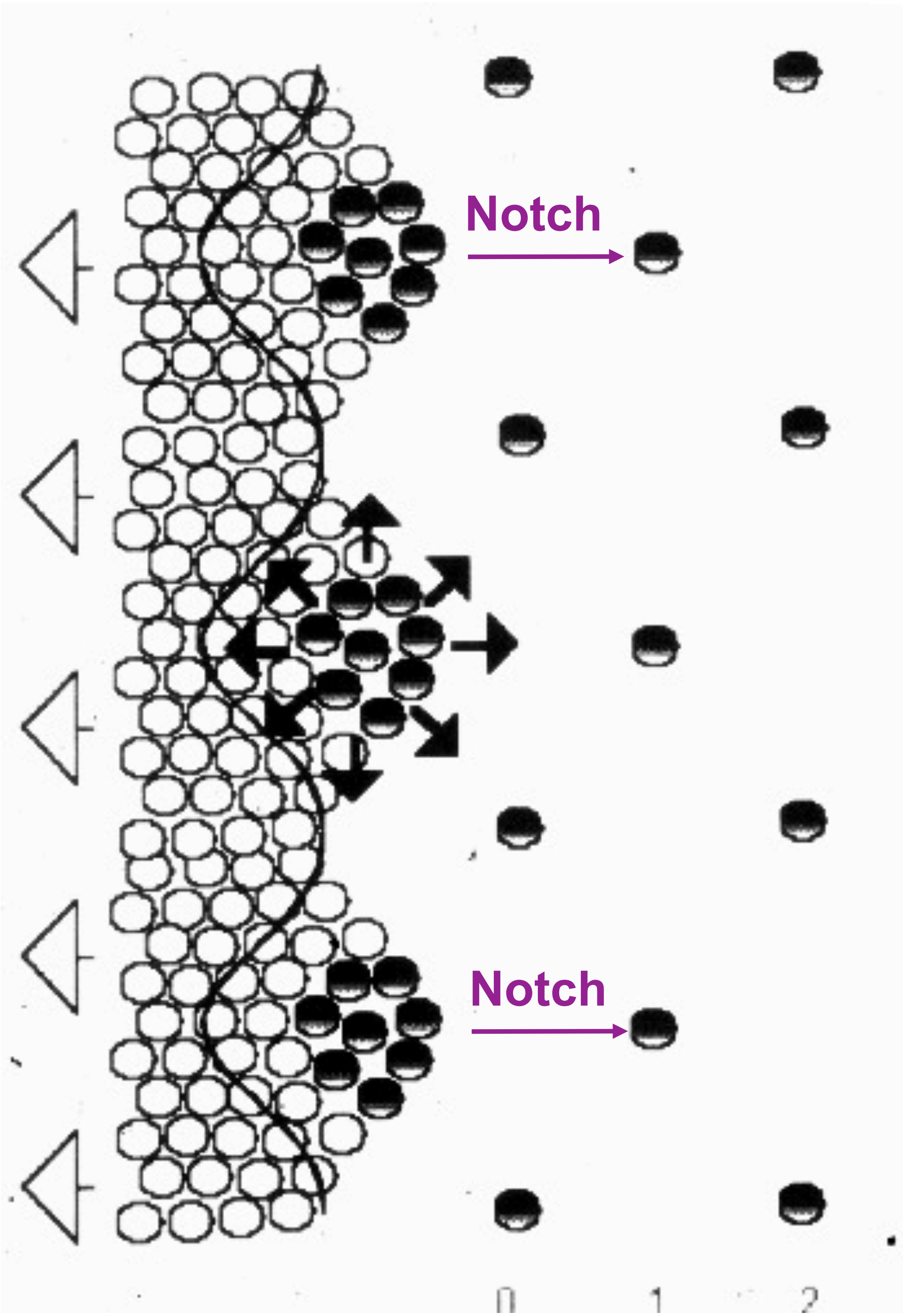
Notch resolves Proneural Clusters

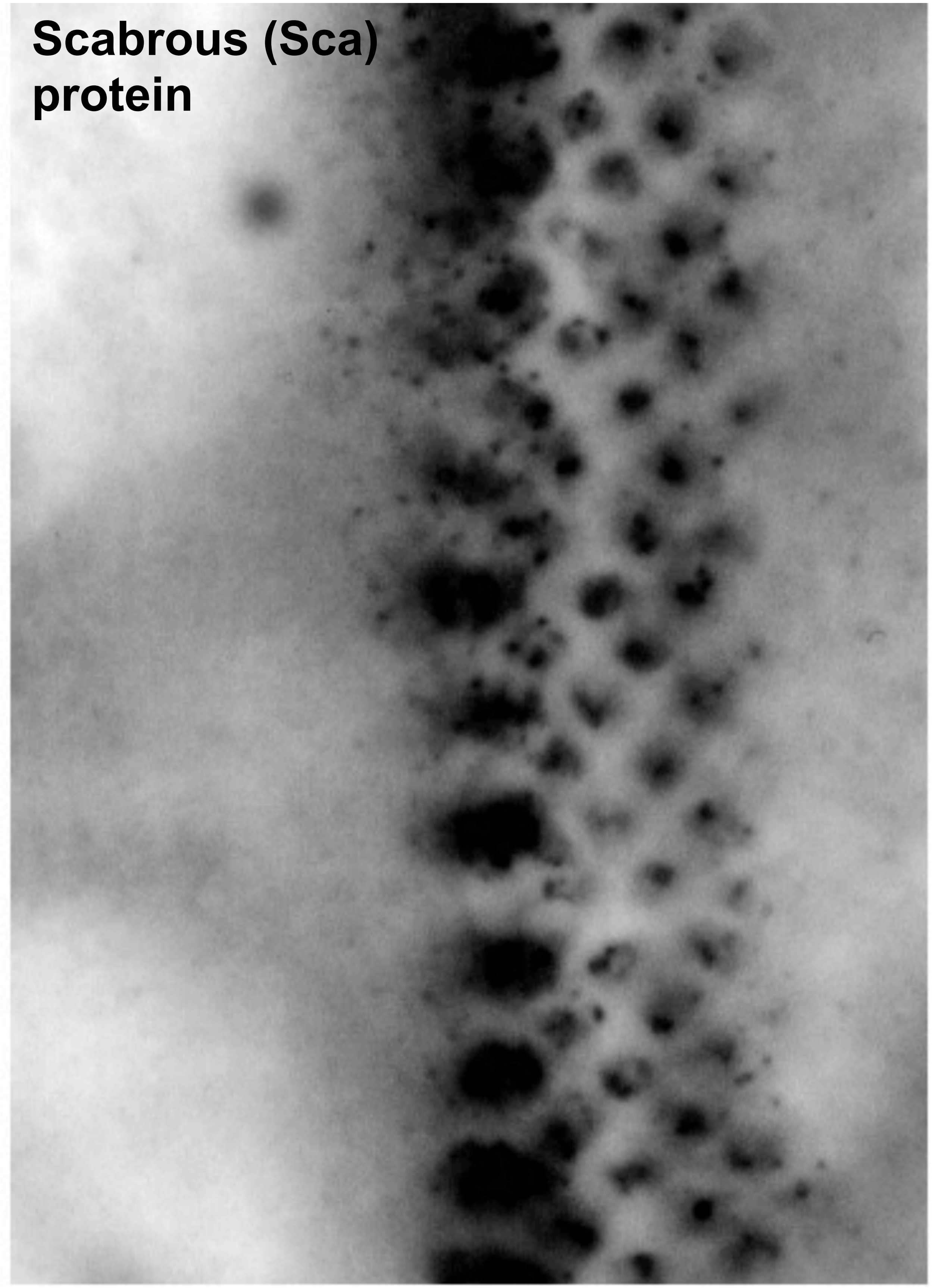




Baker, et al (1996)

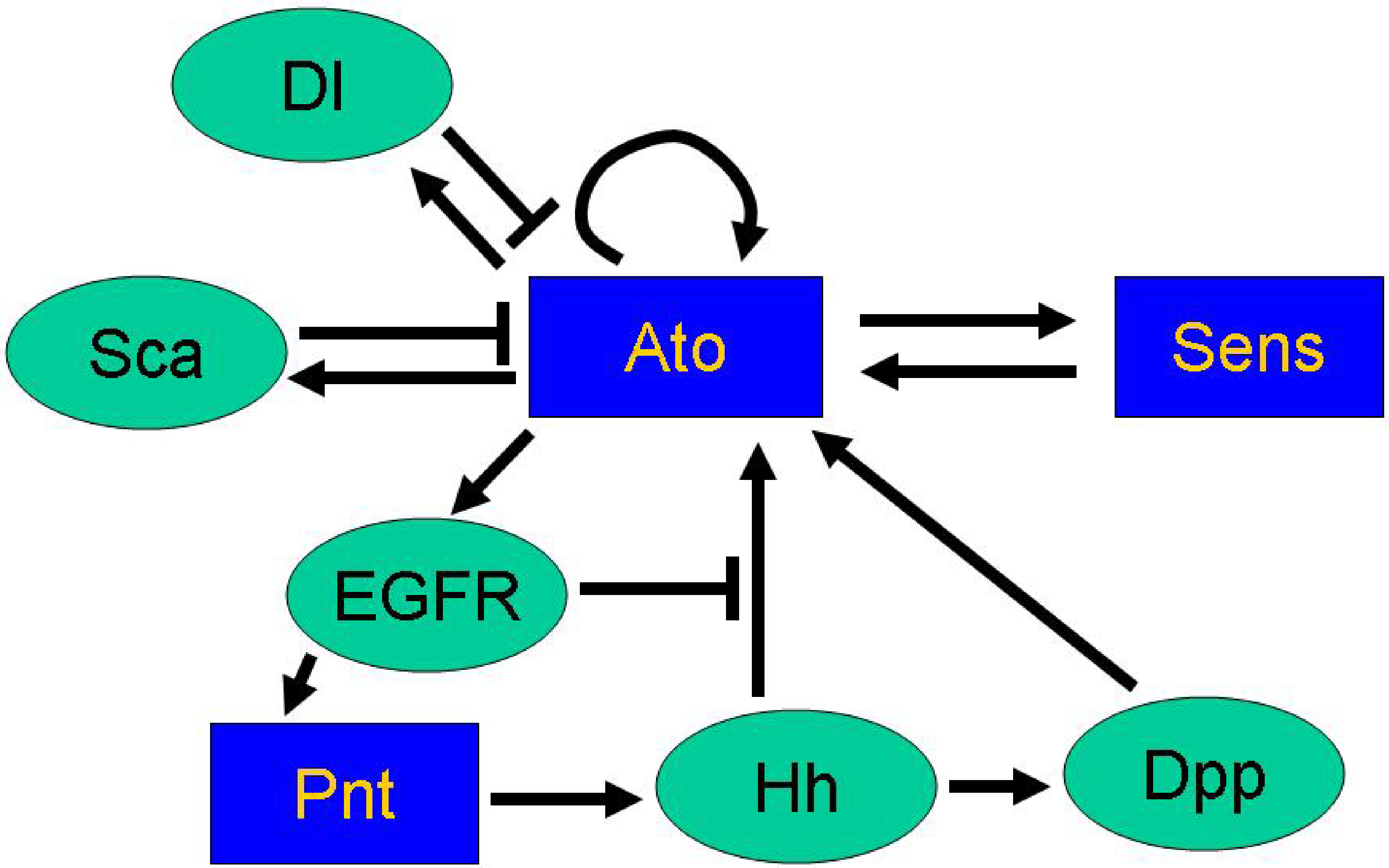
Does Scabrous protein space the intermediate groups?





Network regulating the proneural gene Atonal

1. All the regulation proceeds through various feedback loops centered on Atonal



A) Reported interactions regulating the expression of Ato in the morphogenetic furrow. Pointed arrows, activation; blunt arrows, inhibition. Green ellipses, non-autonomous signals; blue boxes, transcription factors acting cell-autonomously

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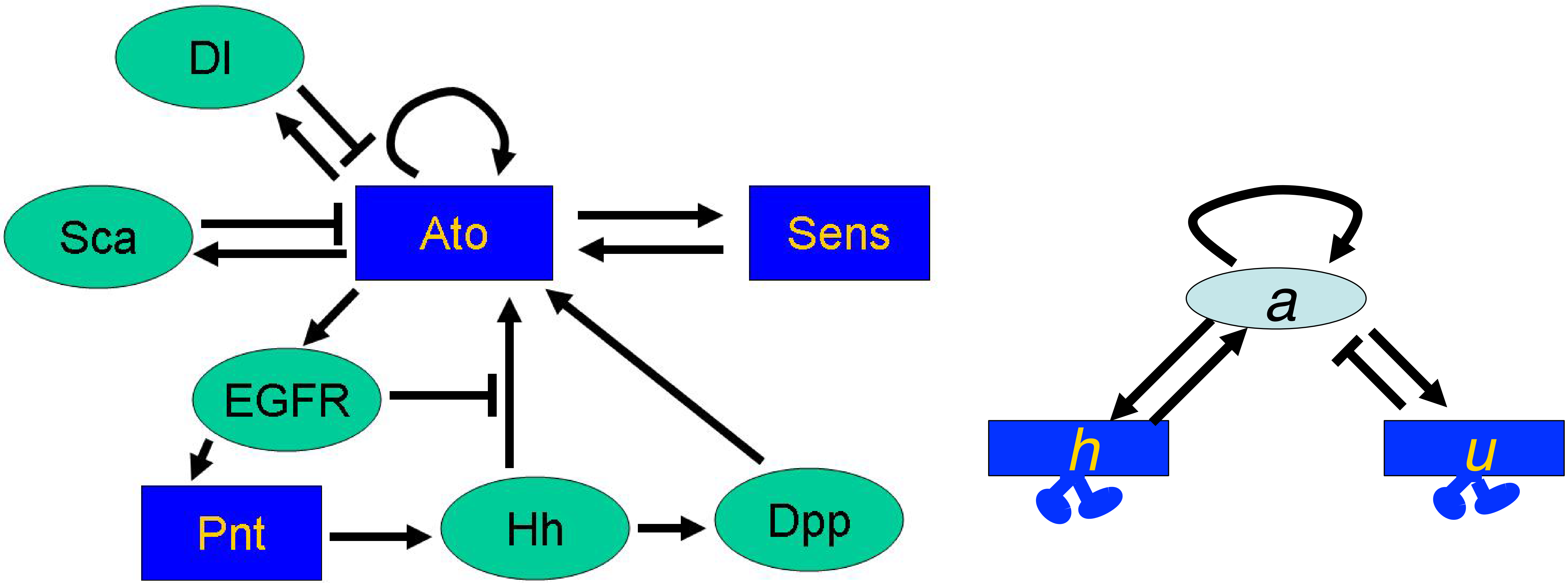

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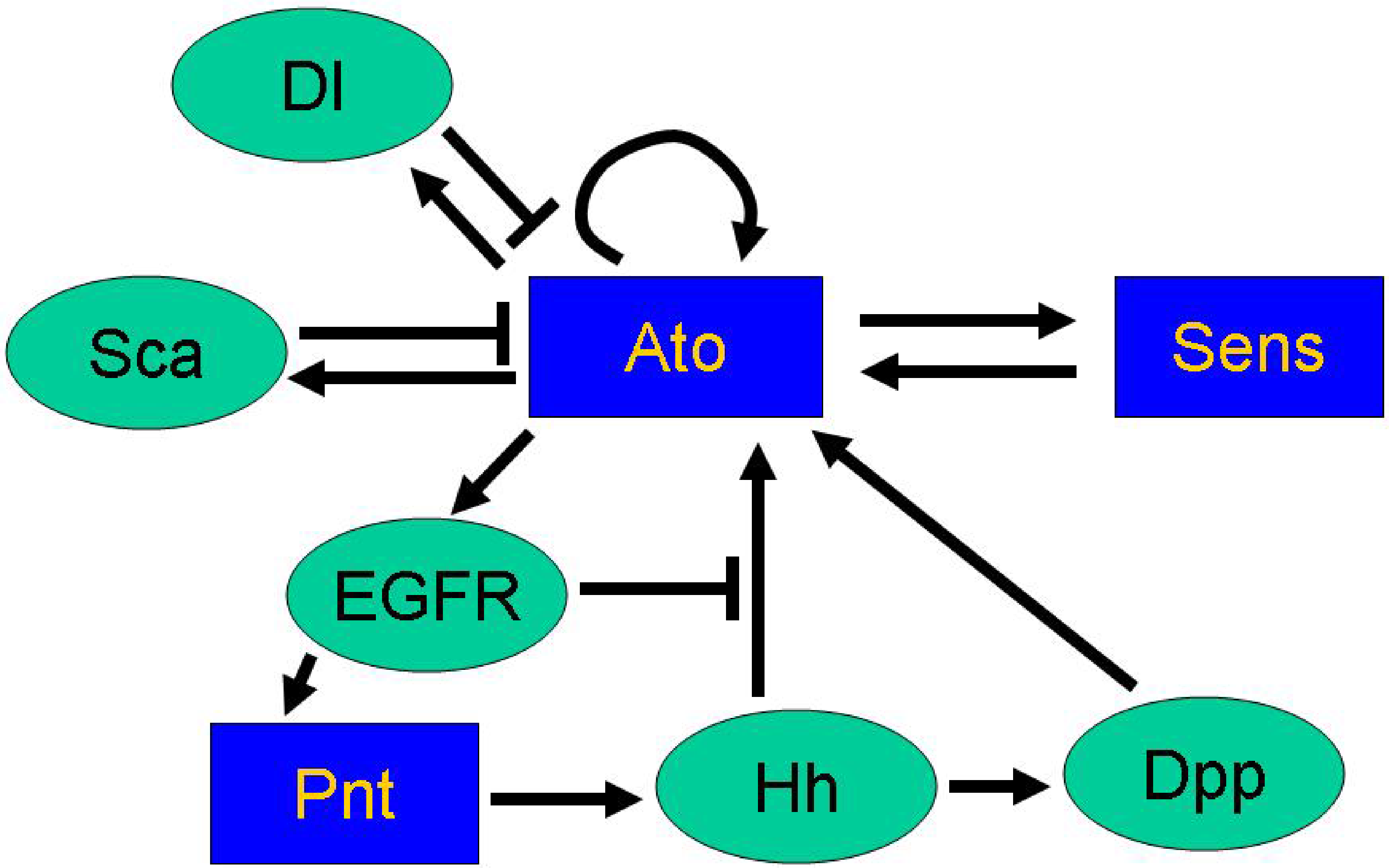
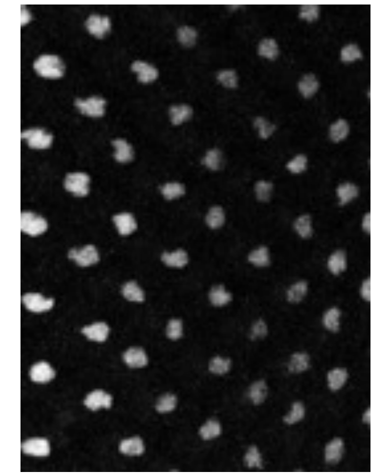
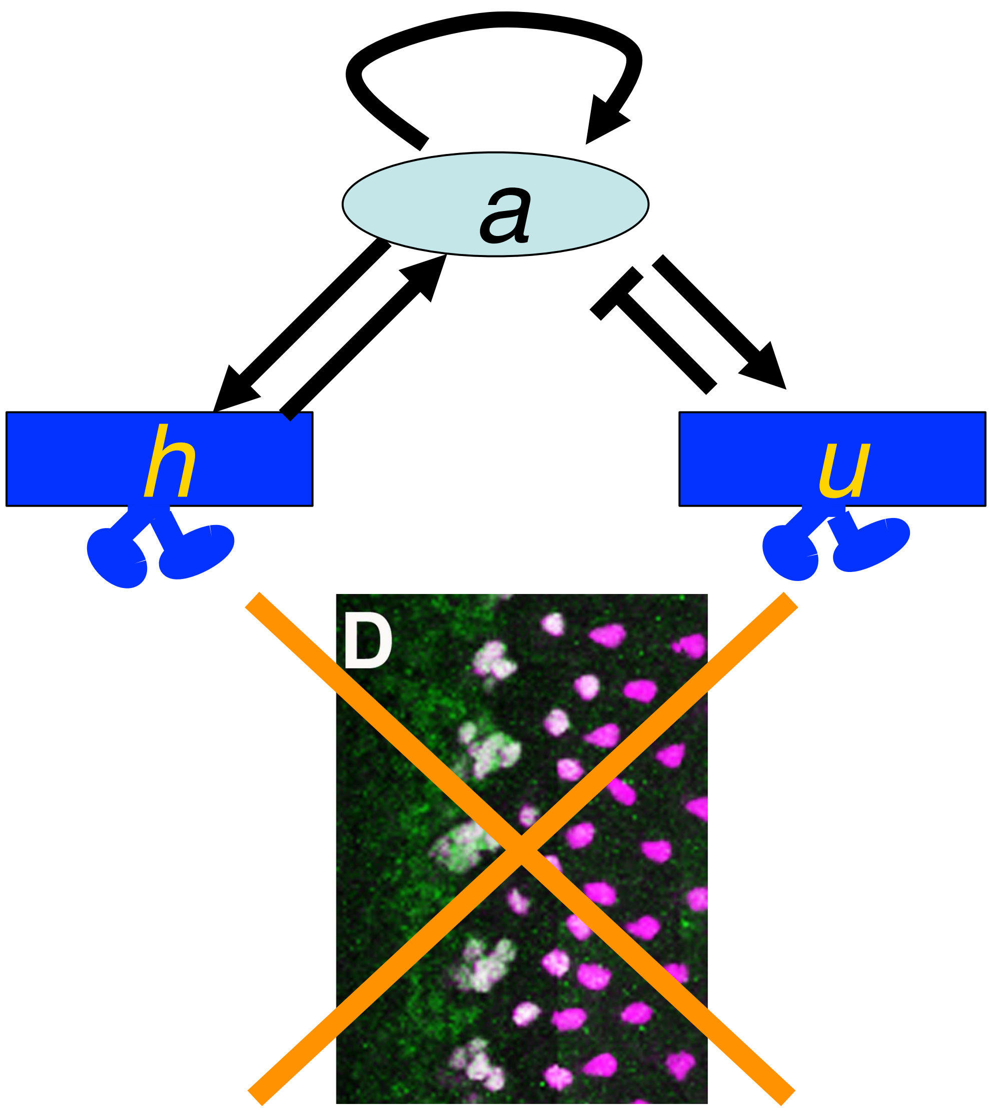
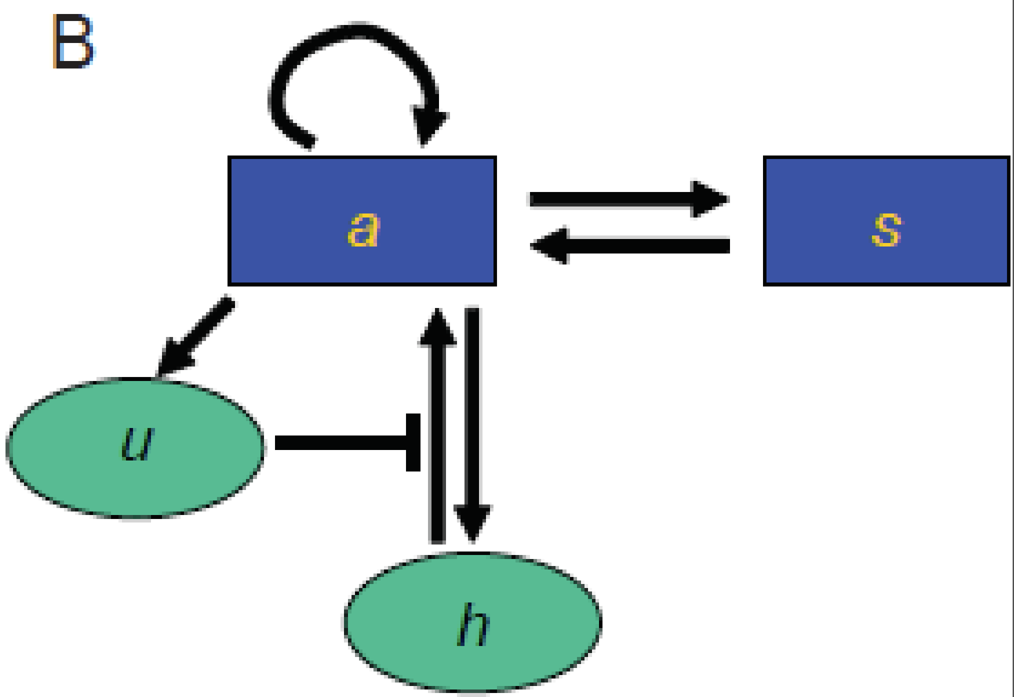






4-component model



Lubensky et al 2011
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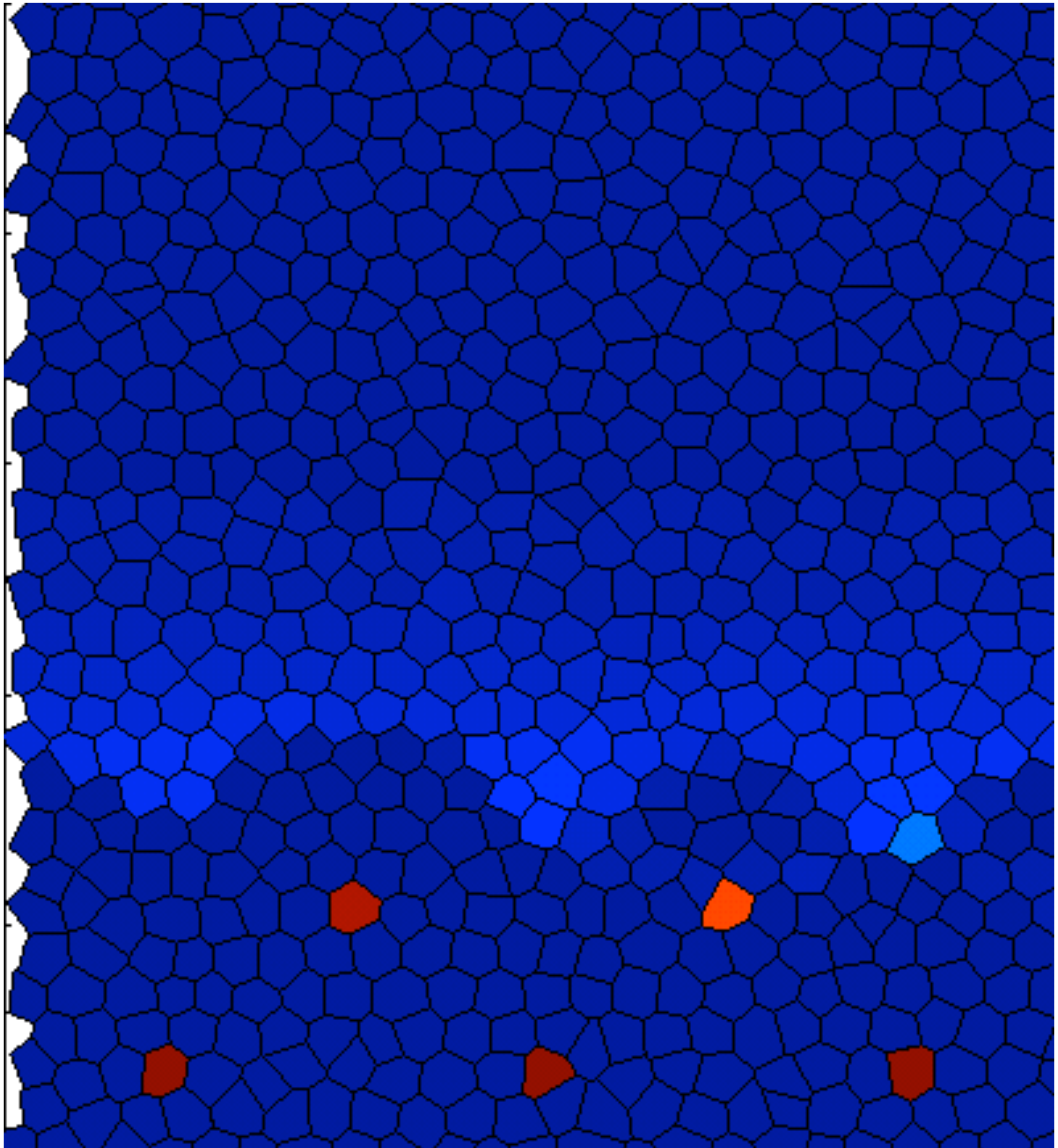

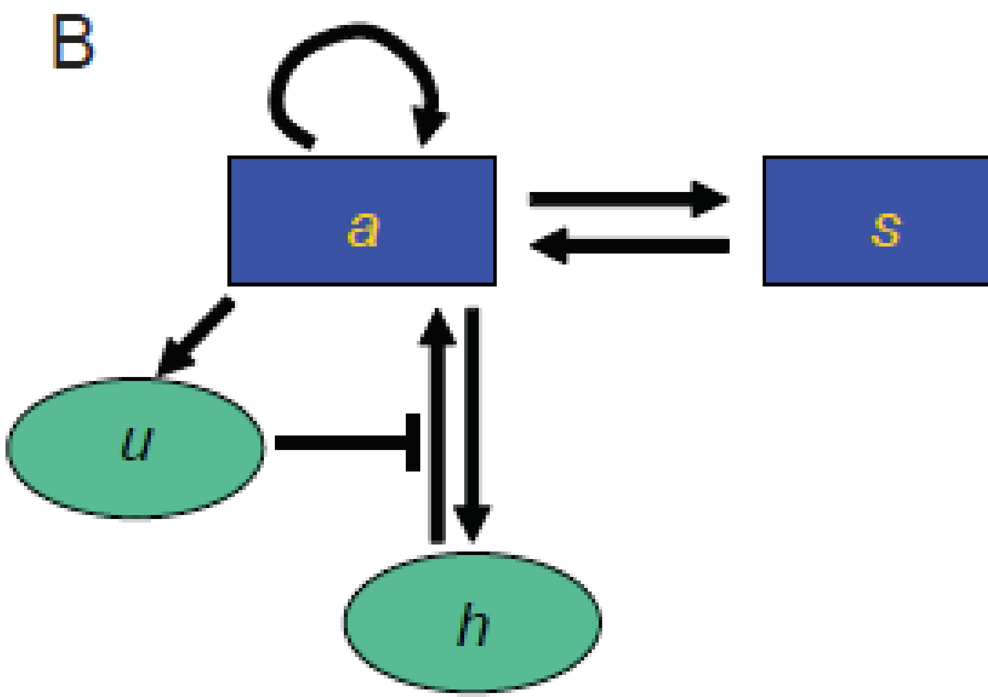

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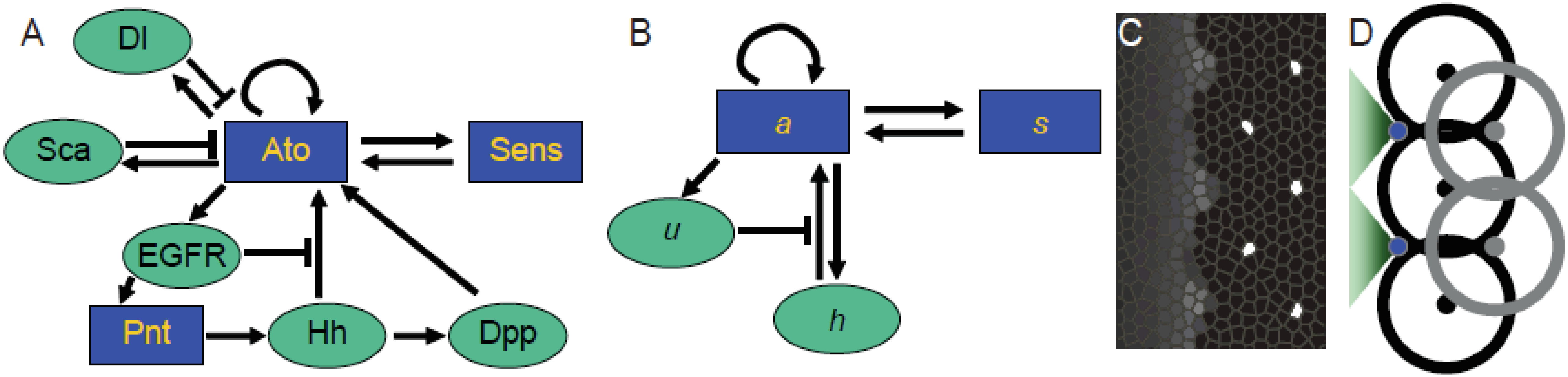
4 component model can mimic observed gene expression



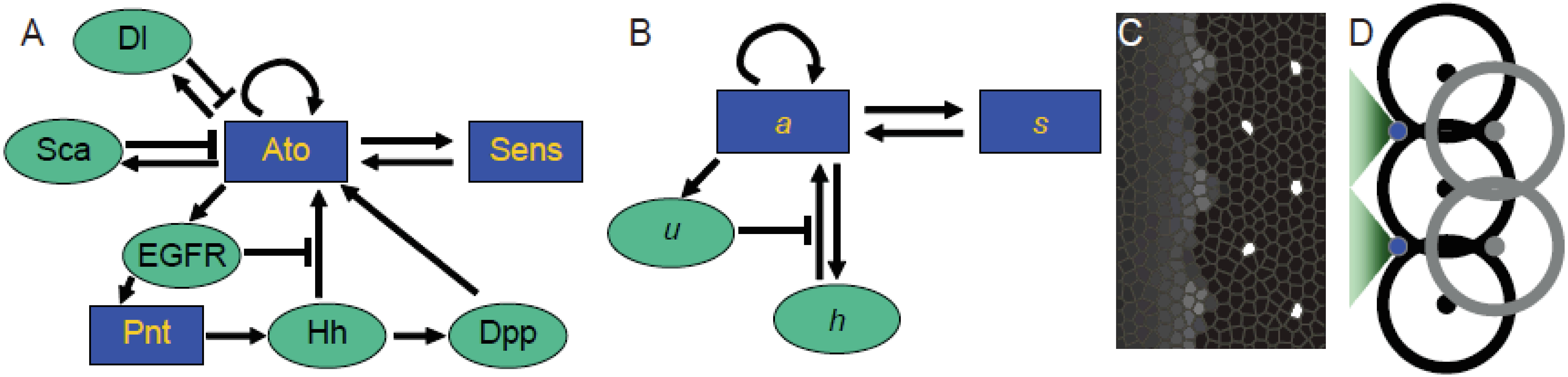
$$\frac{\partial a_j}{\partial t} = f_{n_a}\left(\frac{a_j}{A_a}\right) - a_j + F f_{m_s}\left(\frac{s_j}{S}\right) + G f_{m_h}\left(\frac{h_j}{H}\right)\left[1 - f_{m_u}\left(\frac{u_j}{U}\right)\right] \quad [1]$$

$$T_s \frac{\partial s_j}{\partial t} = f_{n_s}\left(\frac{a_j}{A_s}\right) - s_j \quad [2]$$

$$T_h \frac{\partial h_j}{\partial t} = f_{n_h}\left(\frac{a_j}{A_h}\right) - h_j + D_h \Delta(h_j) \quad [3]$$

$$T_u \frac{\partial u_j}{\partial t} = f_{n_u}\left(\frac{a_j}{A_u}\right) - u_j + D_h \Delta(u_j). \quad [4]$$

The model creates the R8 spacing pattern through a novel mechanism



- *h* longer-ranged than *u*
- (*u* typically of the order of 1 cell diameter)
- *u* highly cooperative but high threshold
- *h* changes more slowly than *a* and *s*
- *u* responds faster than the *a*-*s* feedback loop

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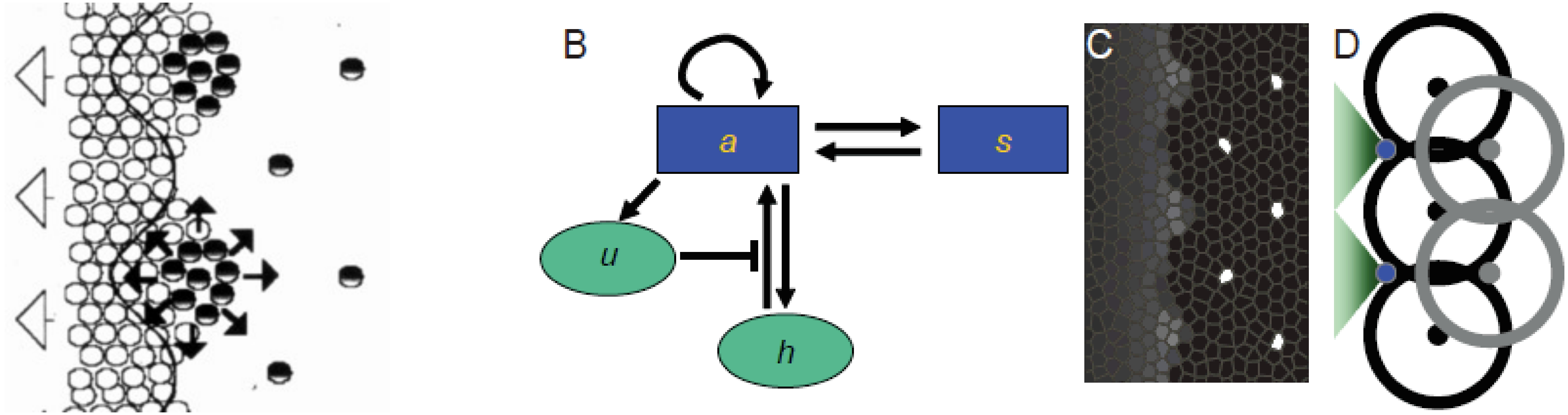
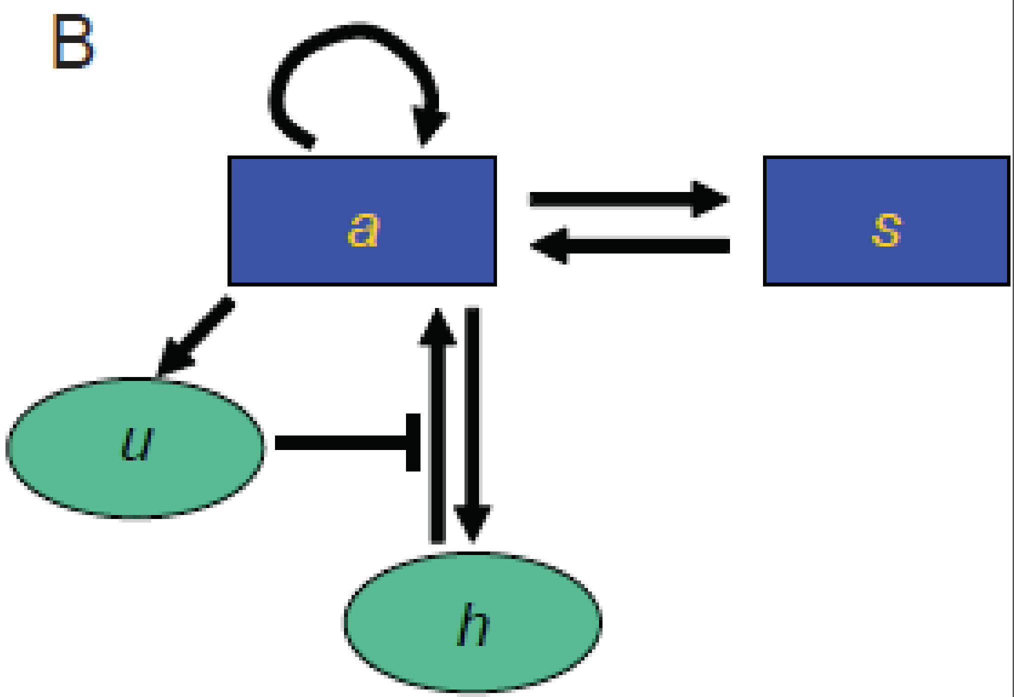
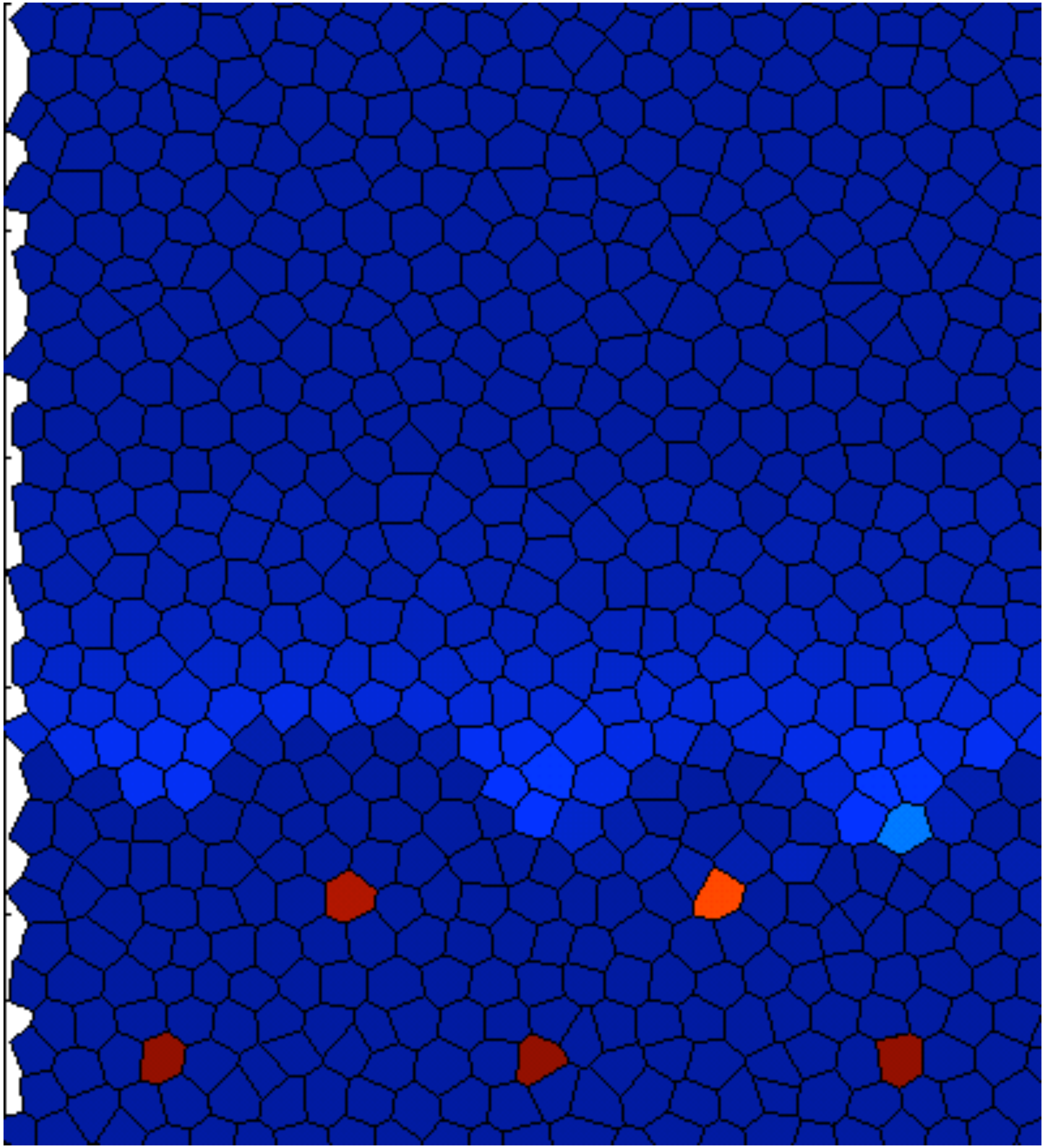


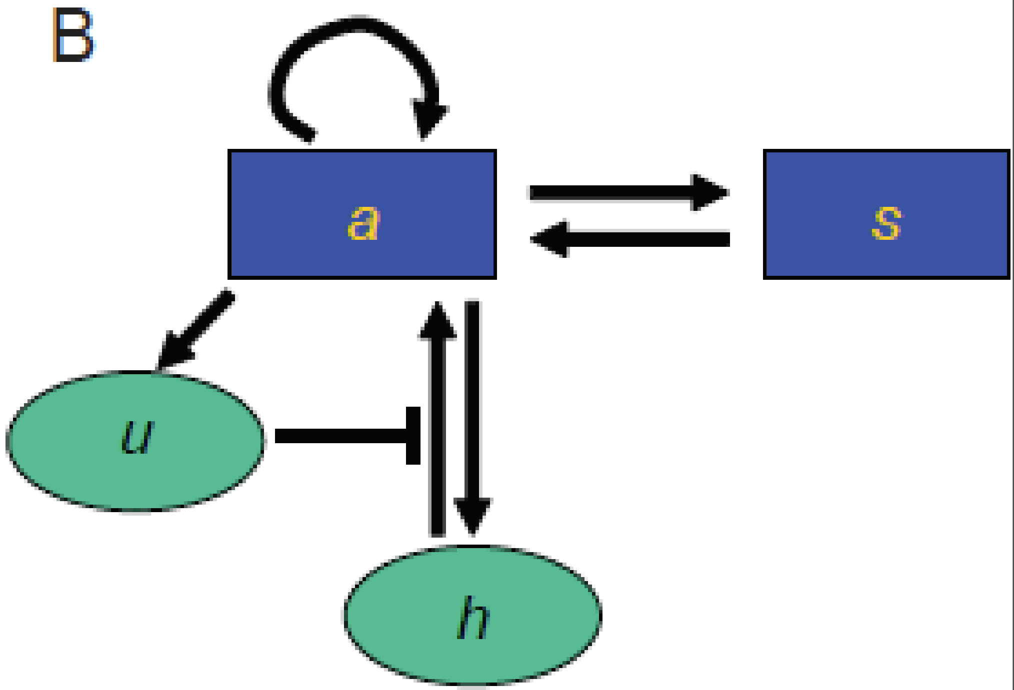
- each R8 defines an inhibitory region where *a* is restrained
- as *h* spreads anteriorly and builds up, it first reaches threshold in the most posterior cells that are not inhibited
- the delay in *a*, and *u* ramping up in these future R8 cells allows *h* to start affecting other cells
- these cells, which form a larger and less regularly-shaped group due to their distance from the previous column, are the IG's
- IG's will *always* be suppressed by the R8 that already has a head start
- there is no instability or Turing mechanism

4-component model



4-component model





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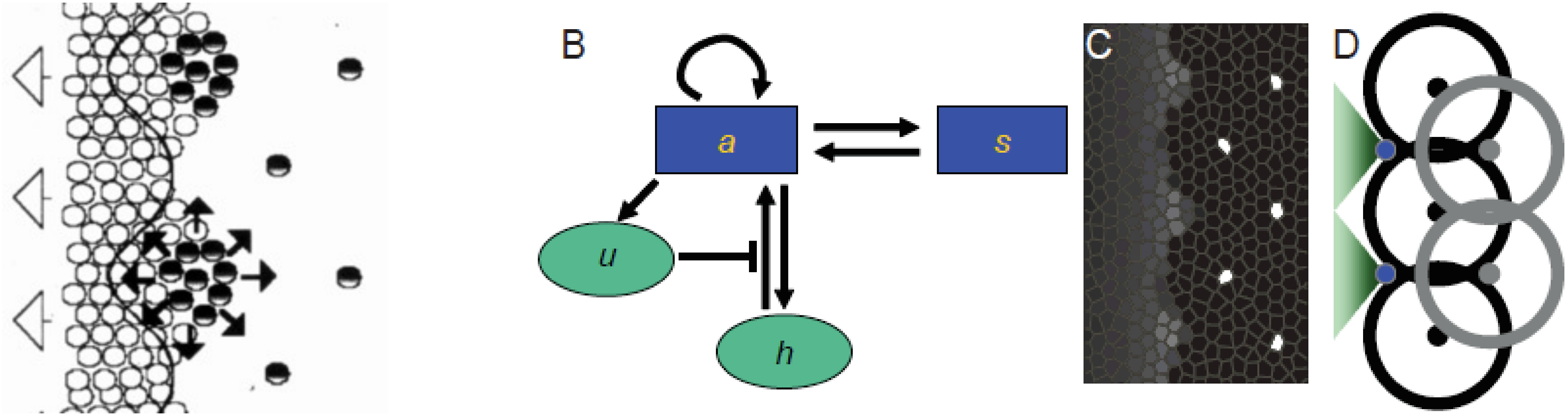
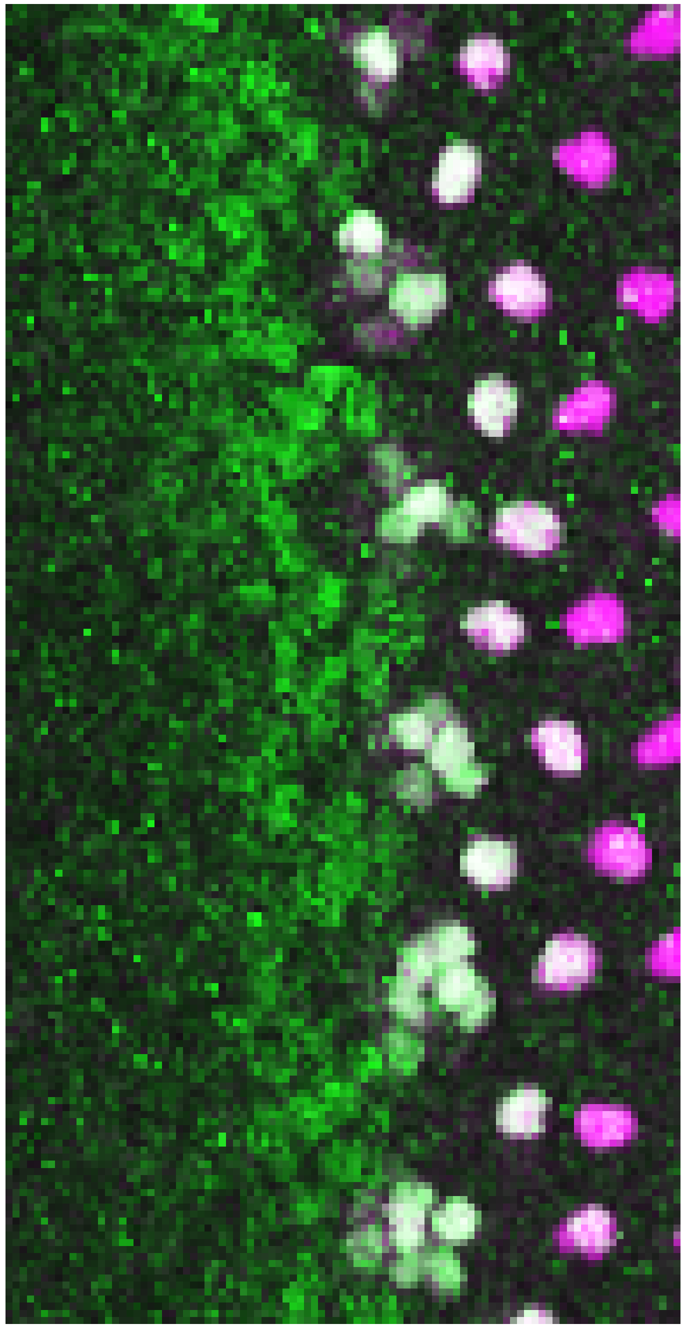


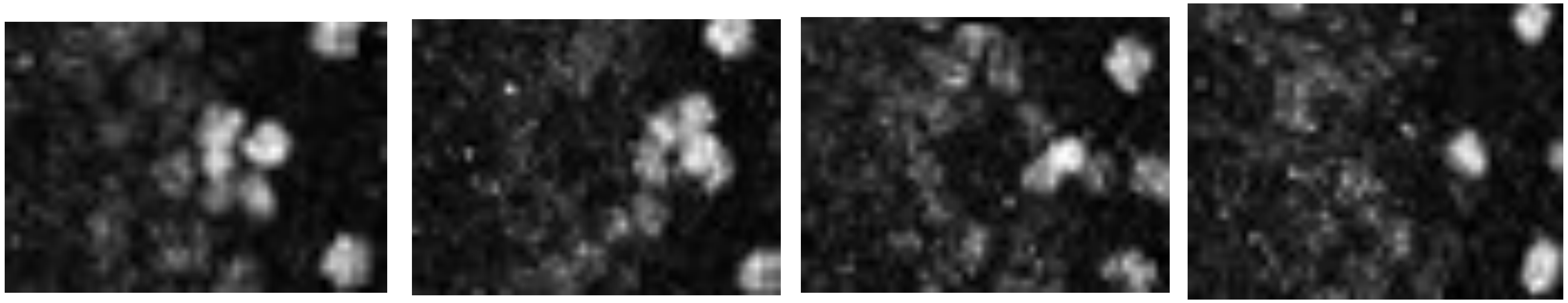
When is a model right?

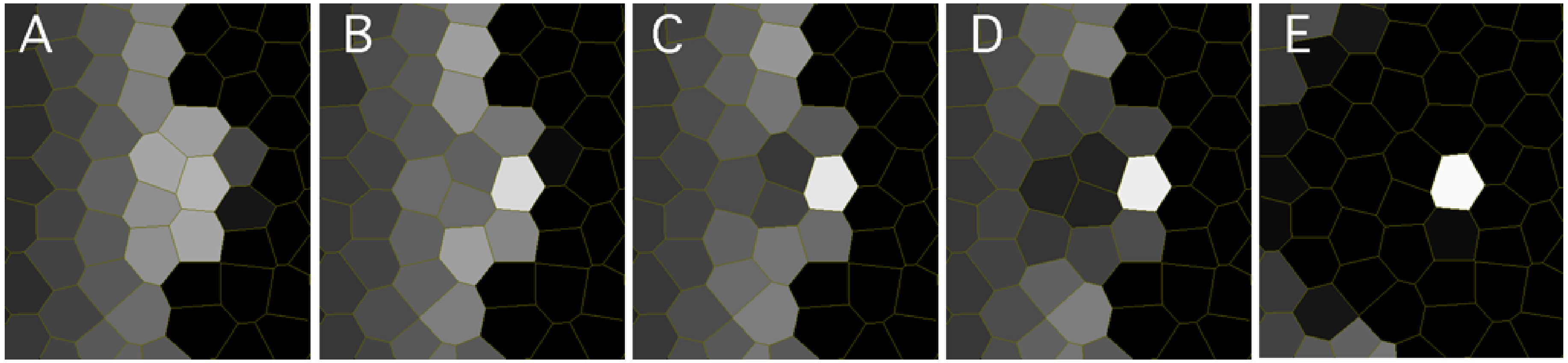
a) When some definitive experiment validates a prediction not made by other models

b) When it is too useful not to be adopted

IG’s usually resolve via similar intermediates to a posterior R8 cell

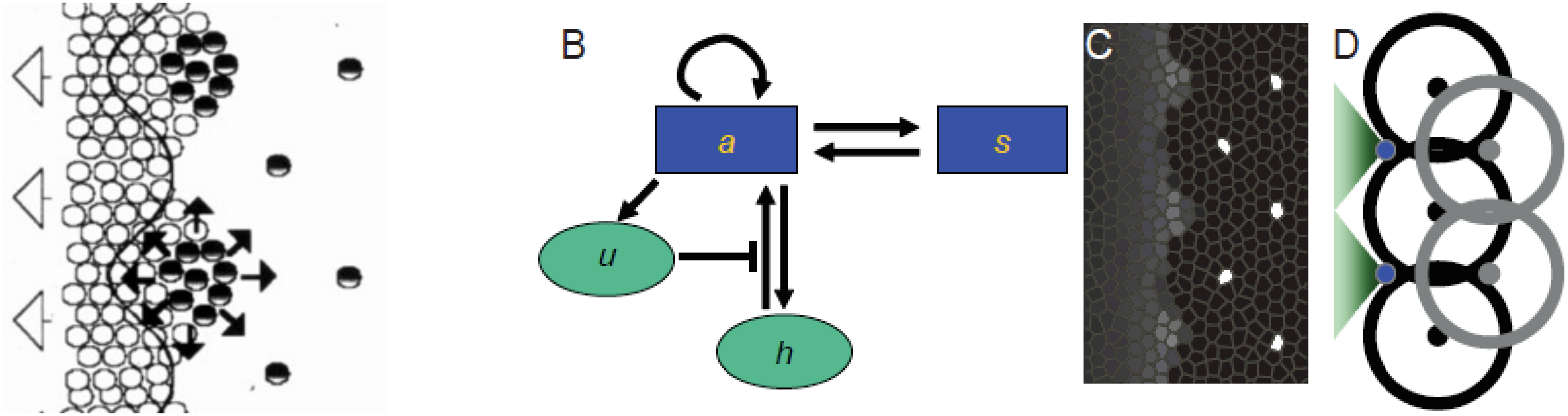






Neural precursors arise from particular locations in many other proneural regions. This is attributed to asymmetric prepatterns. In the eye, this prepattern is already explicit in our simple model.

The model creates the R8 spacing pattern through a novel mechanism

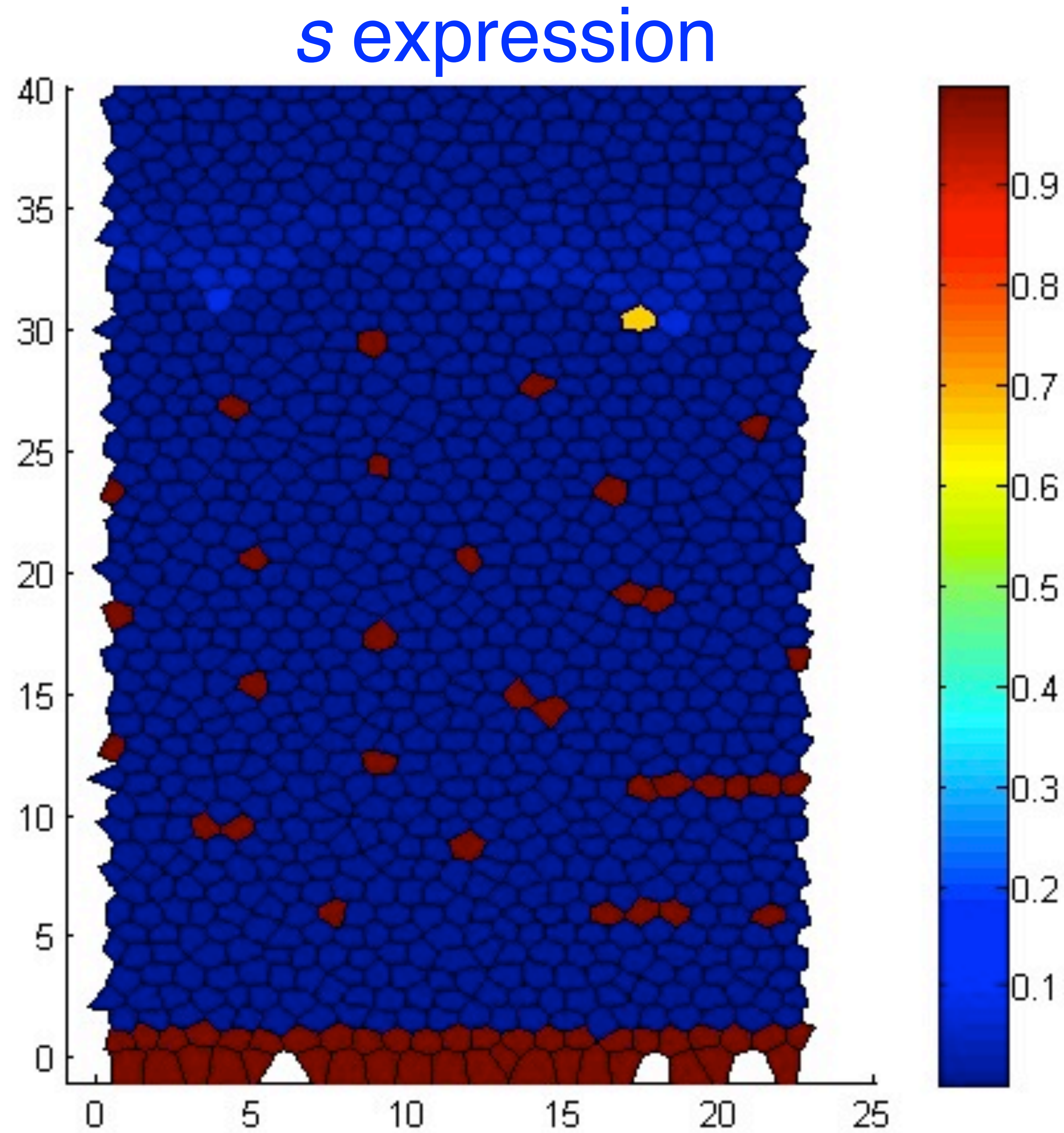


When is a model right?

a) When some definitive experiment validates a prediction not made by other models: the model predicts that the R8 pattern is related to a stripe.

b) When it is too useful not to be adopted

Model requires a patterned template



Changing parameters cannot replace template requirement but can give stable stripes instead

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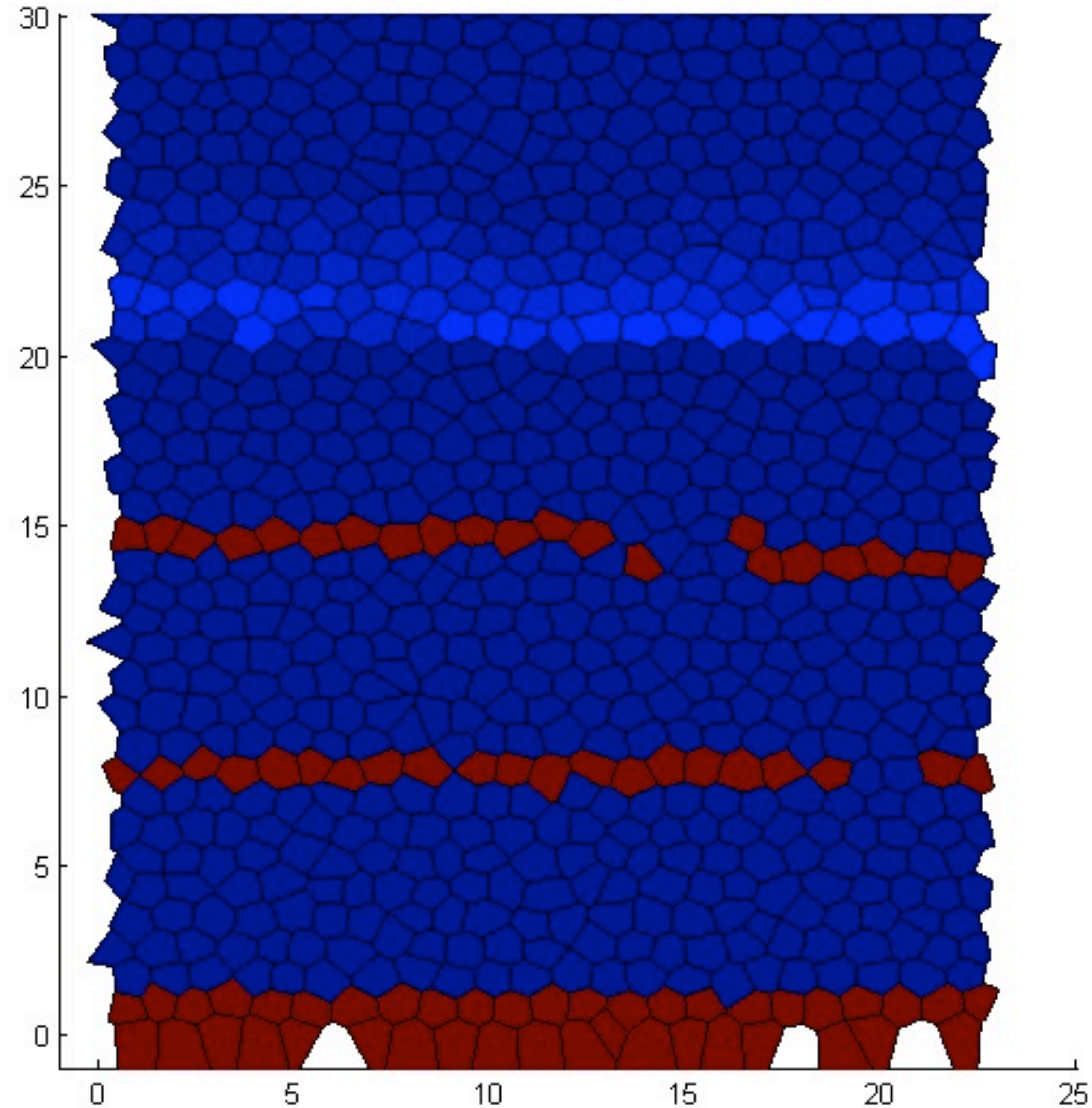
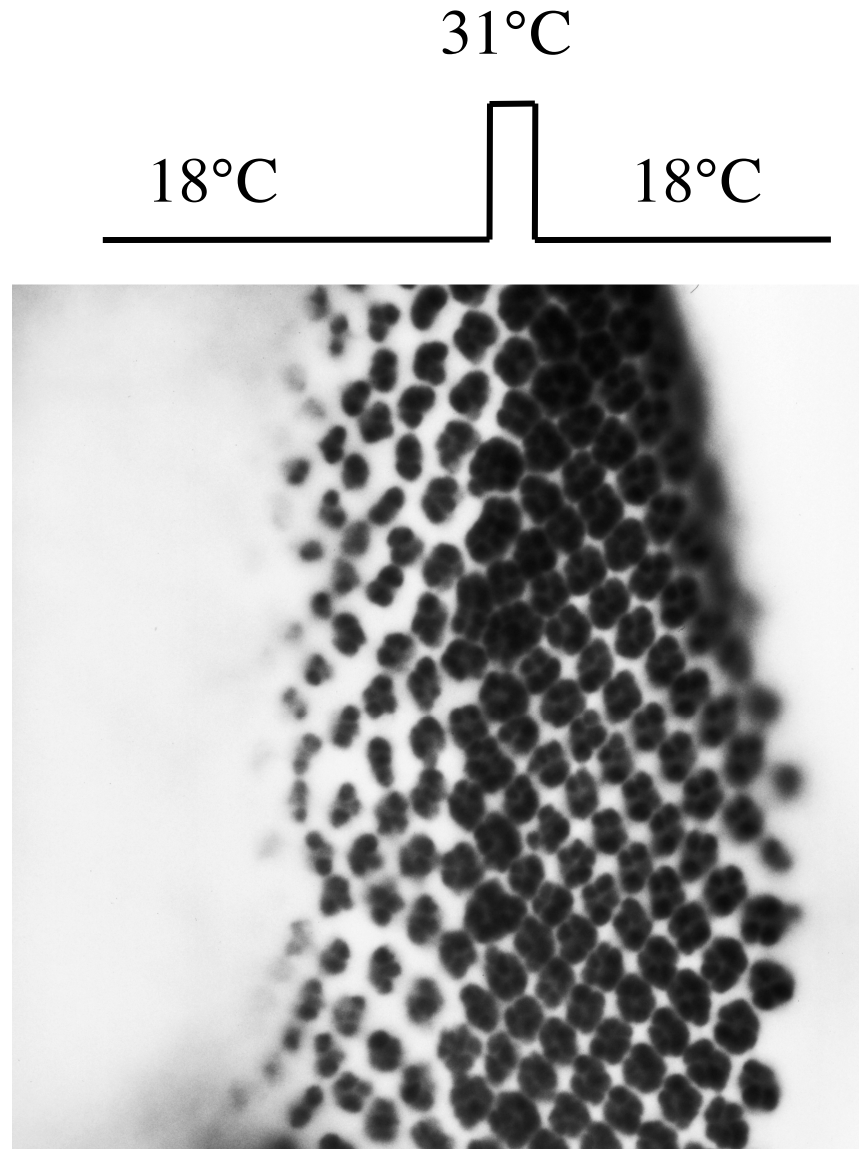


The real eye also cannot make a normal pattern once the pattern is perturbed…

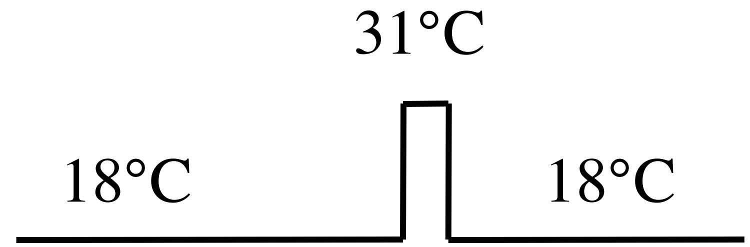
Wild type

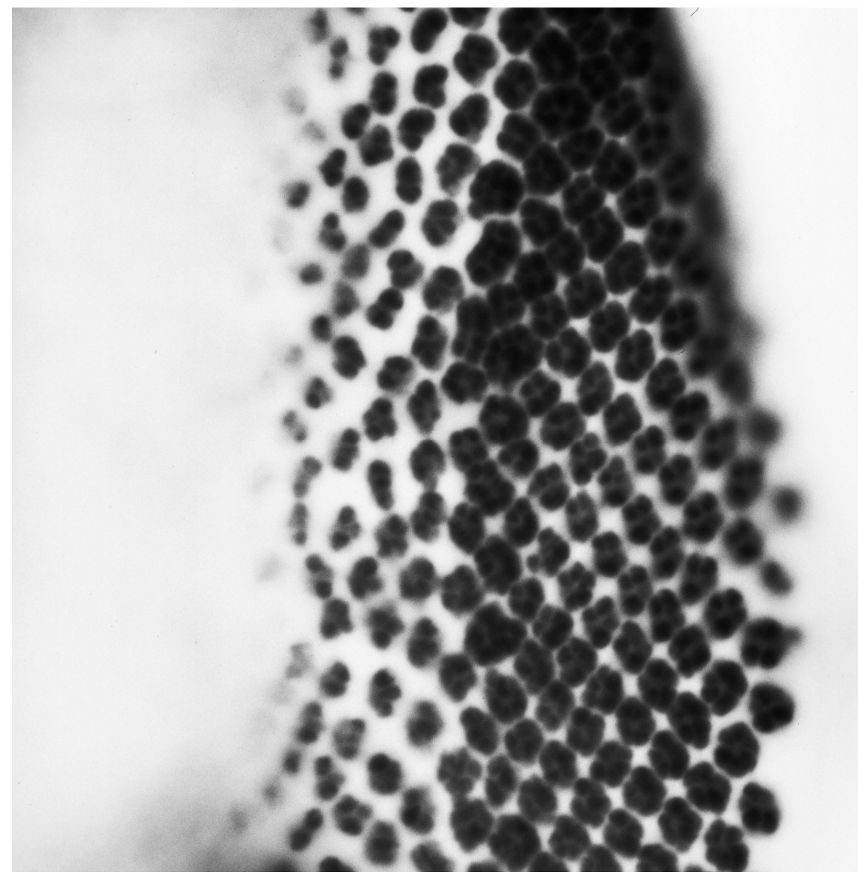


N[ts]

Baker et al (1996)

The eye cannot make a normal pattern after perturbation…
but a *scabrous* mutant can make stripes after perturbation





Wild type

N[ts]

N[ts]
sca

N. Baker, unpublished

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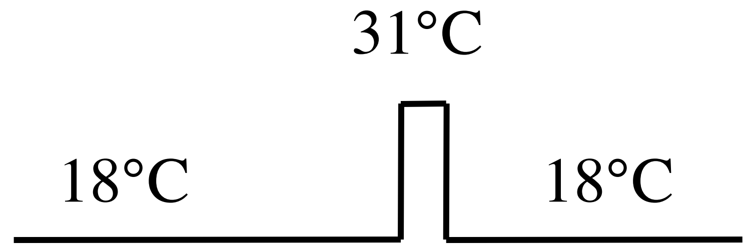

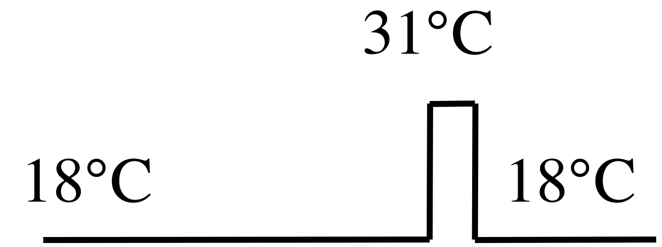

Wild type

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N. Baker, unpublished

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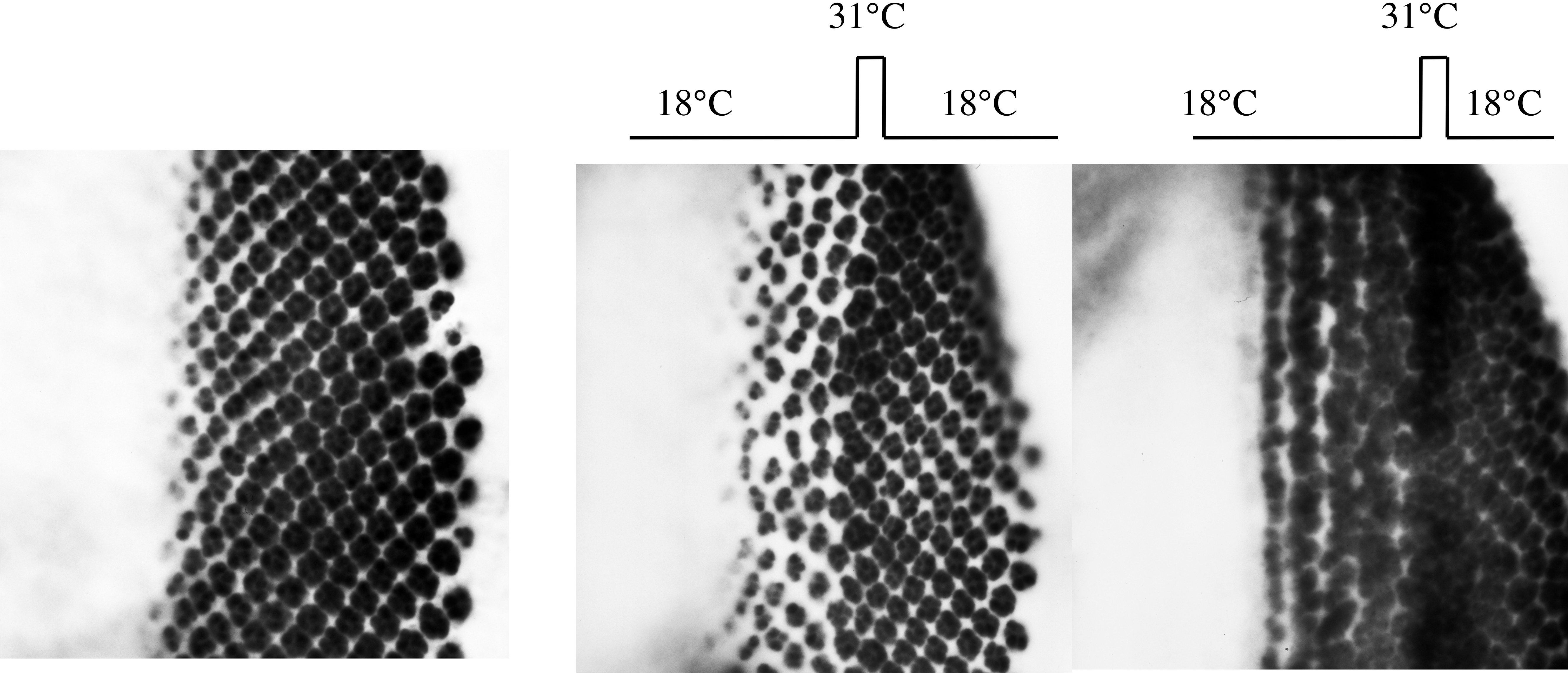


Wild type

N[ts]

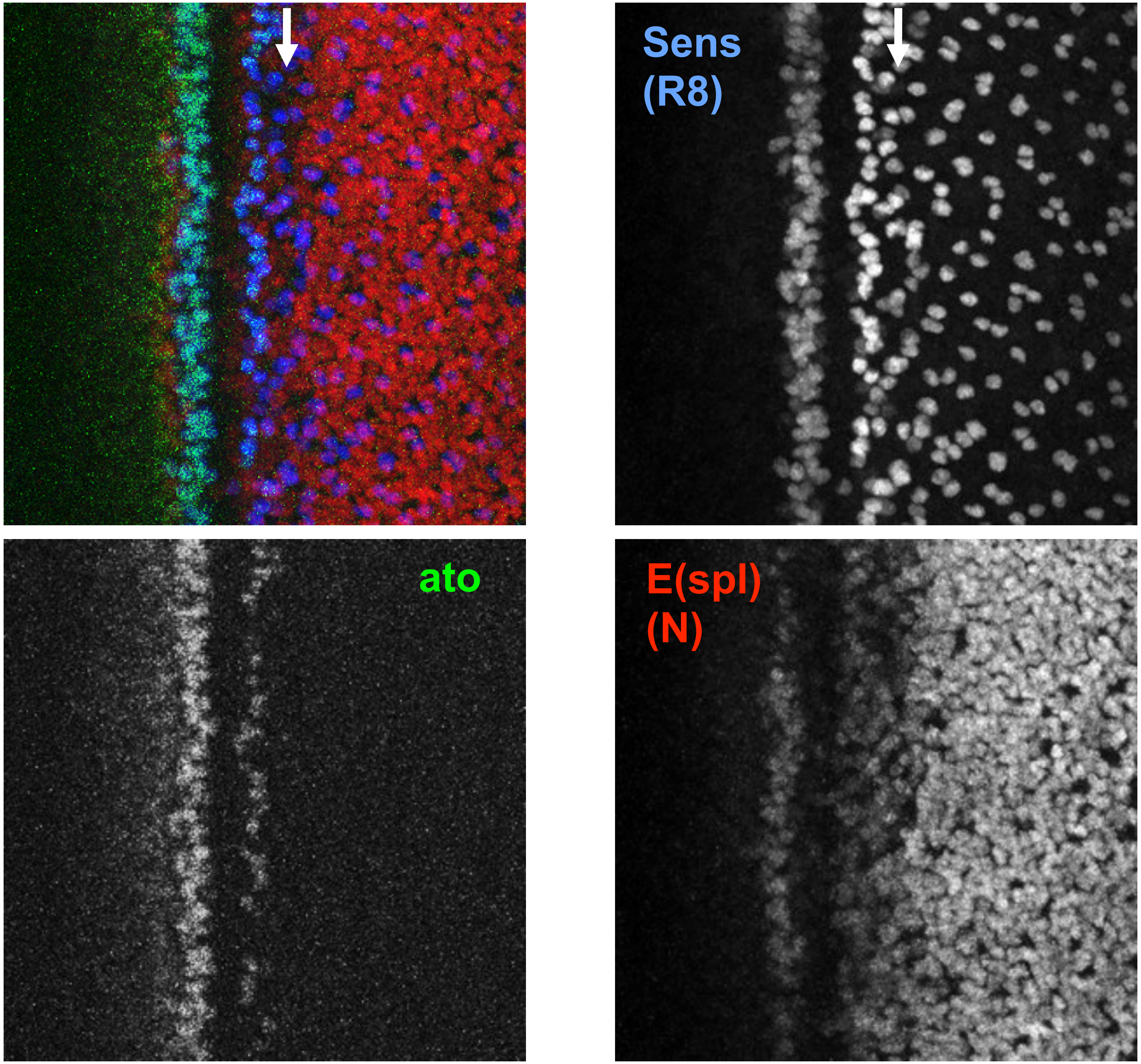
N[ts]
sca

N. Baker, unpublished

The perturbed scabrous pattern

Alternating stripes of Notch signaling and Atonal expression

N[ts], sca
2h at 31°



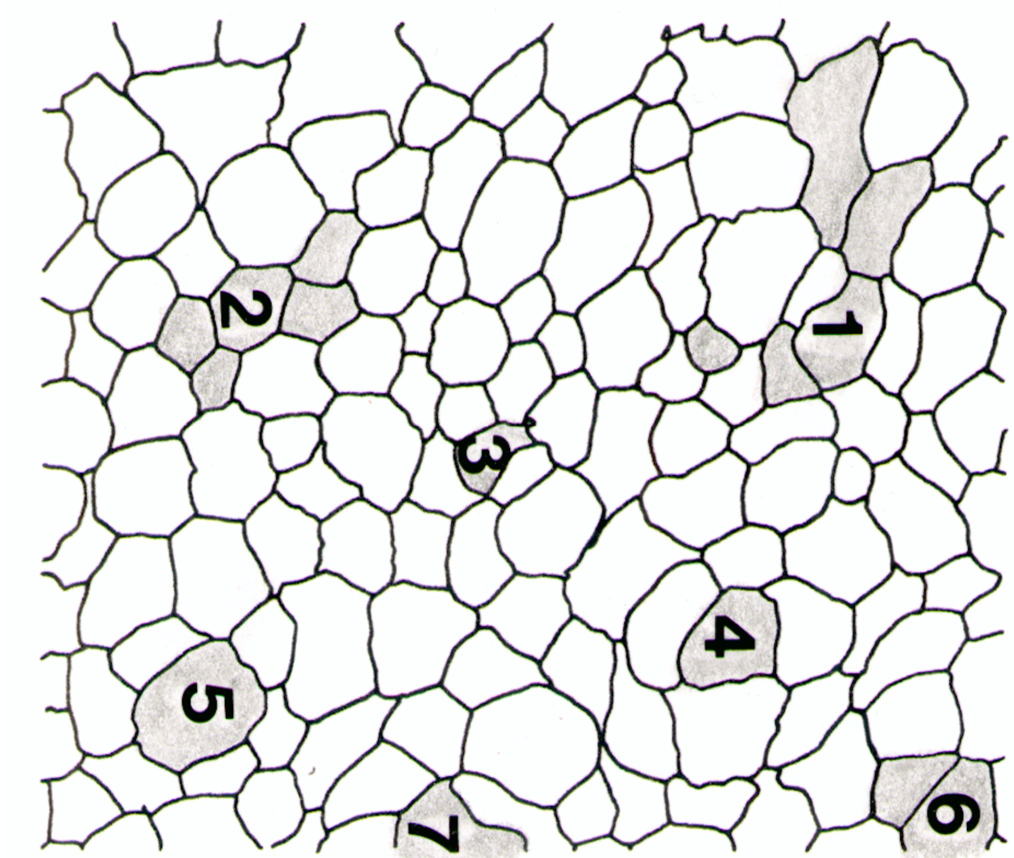
N. Baker
unpublished

When the template is uniform, why shouldn't there be a stripe of R8's?

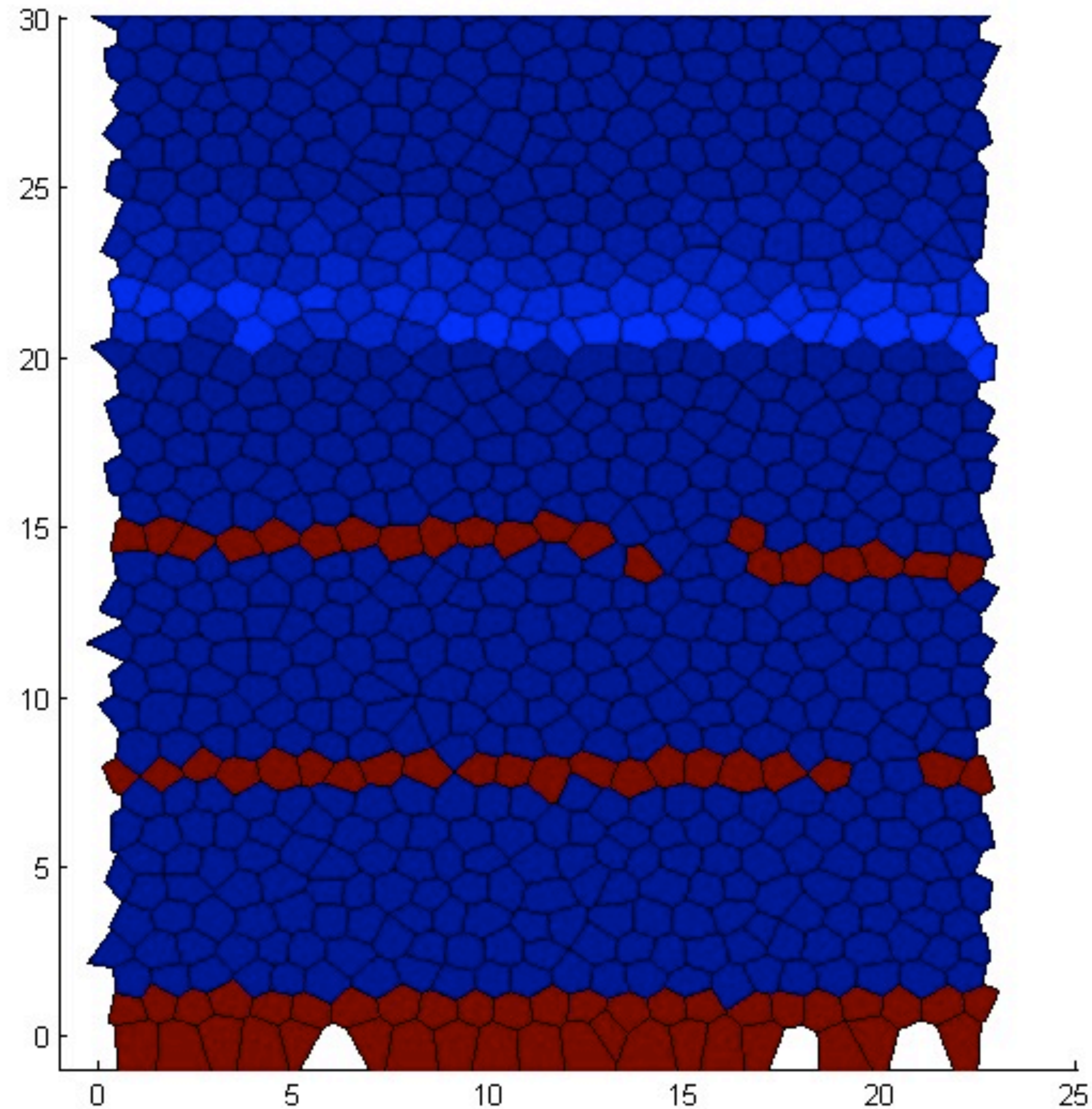
Stripe-breaking occurs with a fixed range of *u* properties.

The irregular cellular lattice also contributes to stripe-breaking

Some R8 twins occur even in the best parameter sets



When the template is uniform, why shouldn't there be a stripe of R8's?



Stripe-breaking occurs with a fixed range of *u* properties.

The irregular cellular lattice also contributes to stripe-breaking

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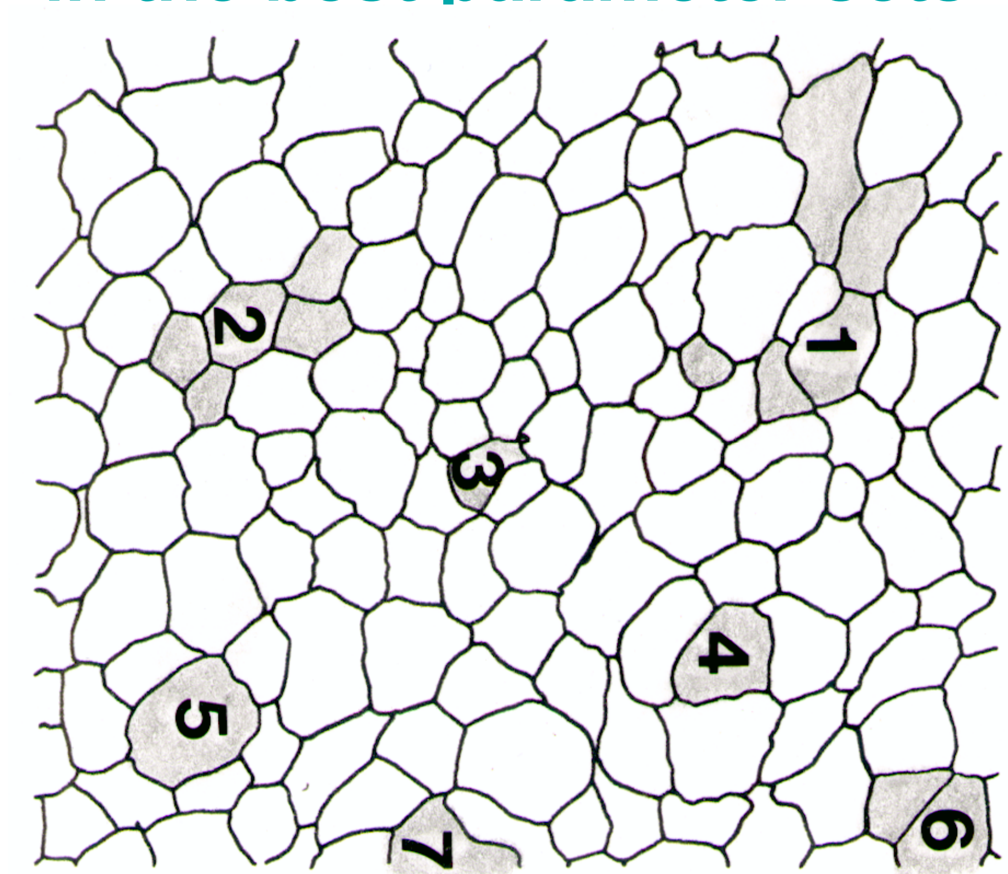

Do *u* parameters that fail to break stripes model the *sca* mutant?

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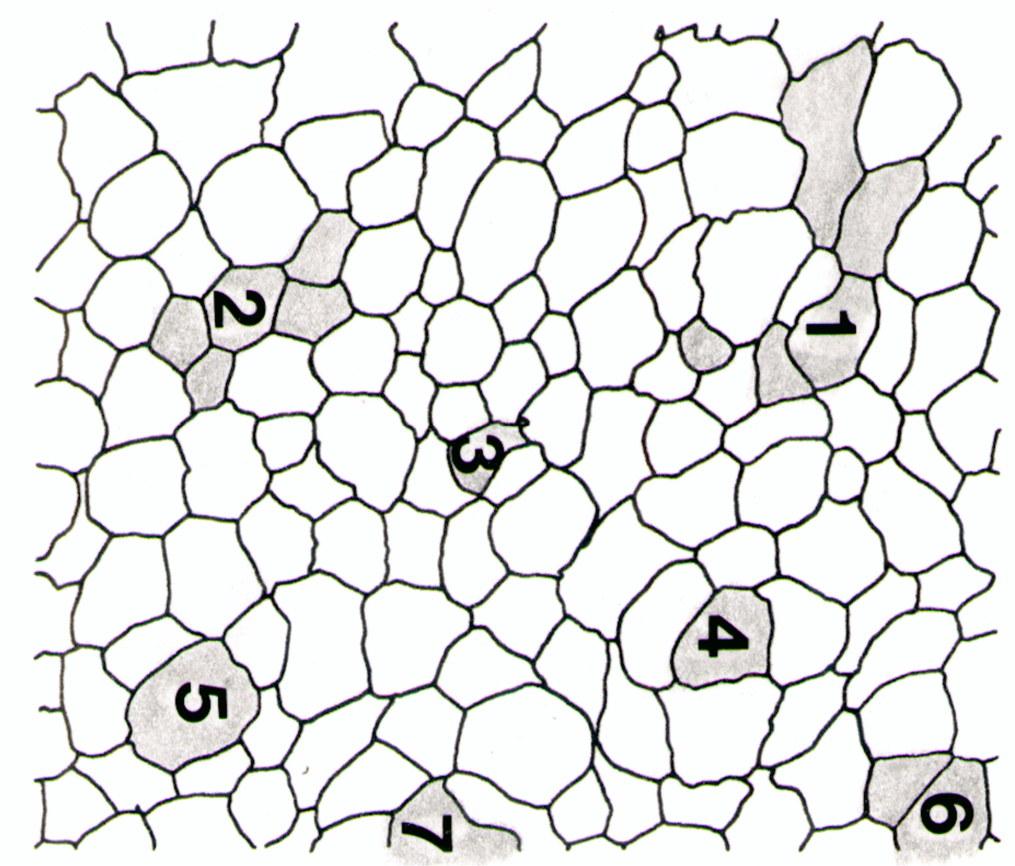

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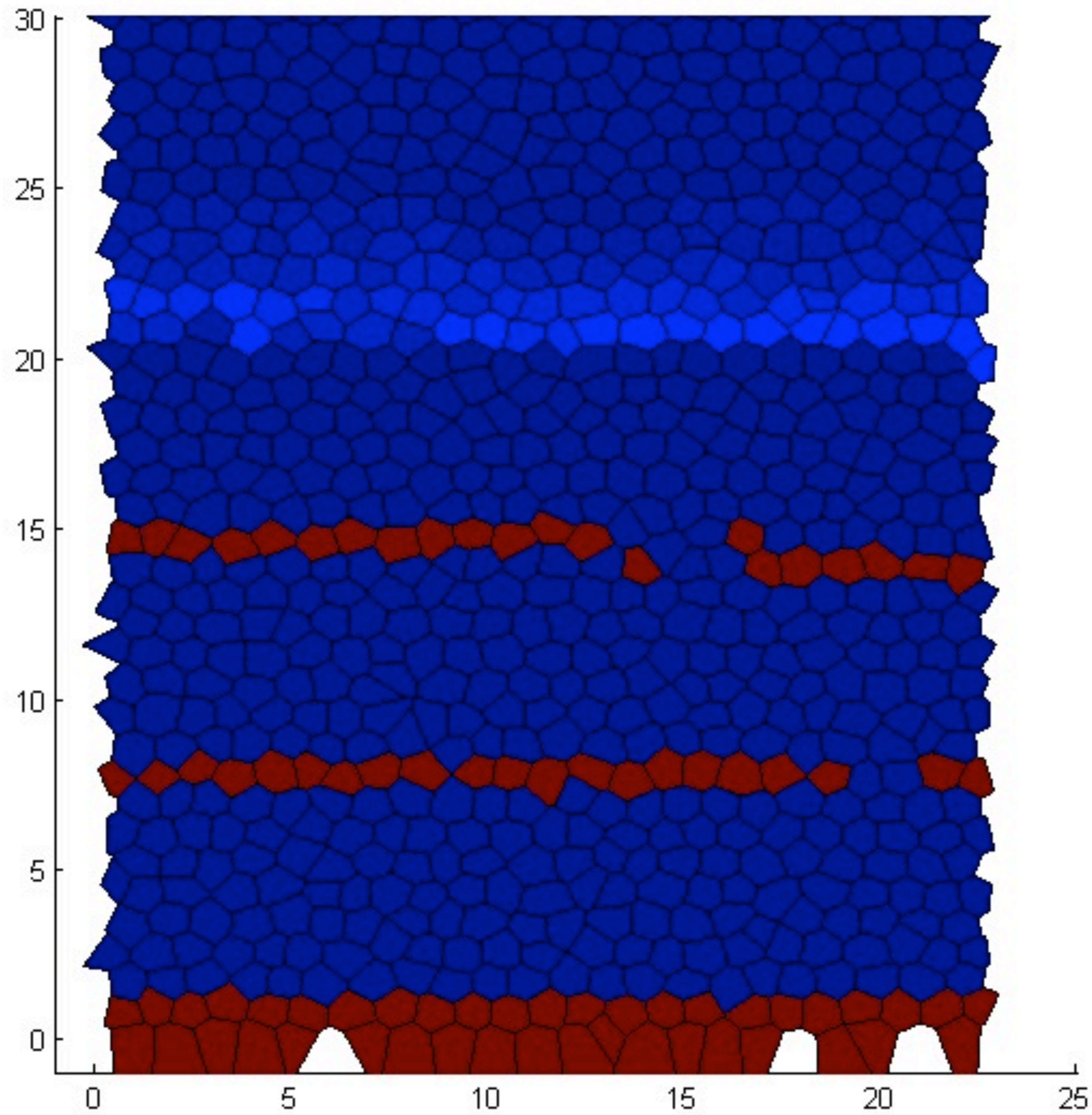

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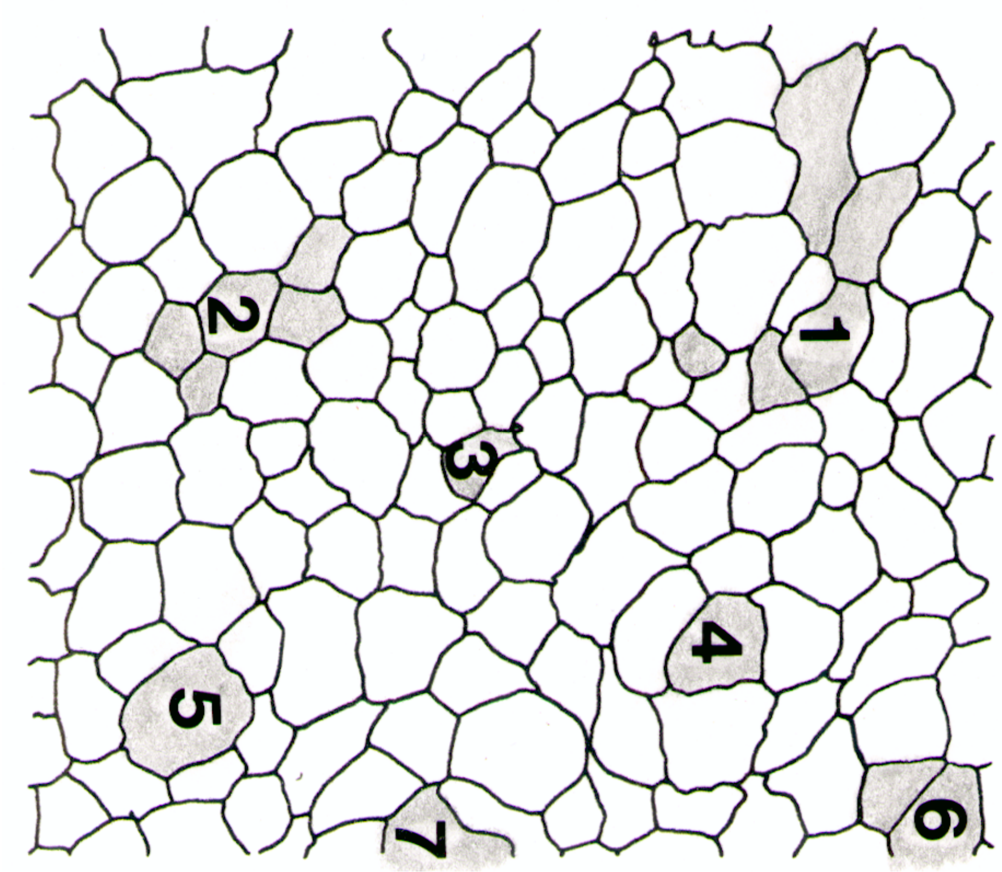
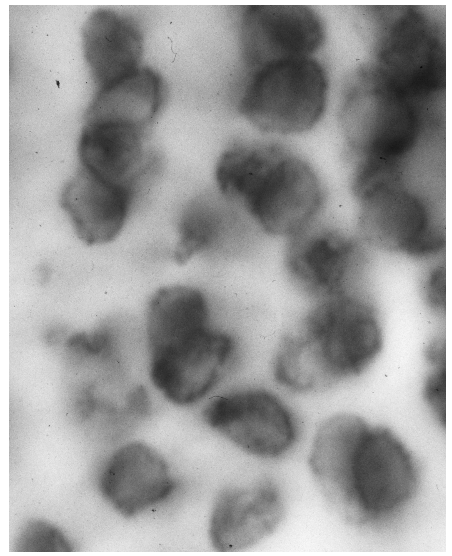
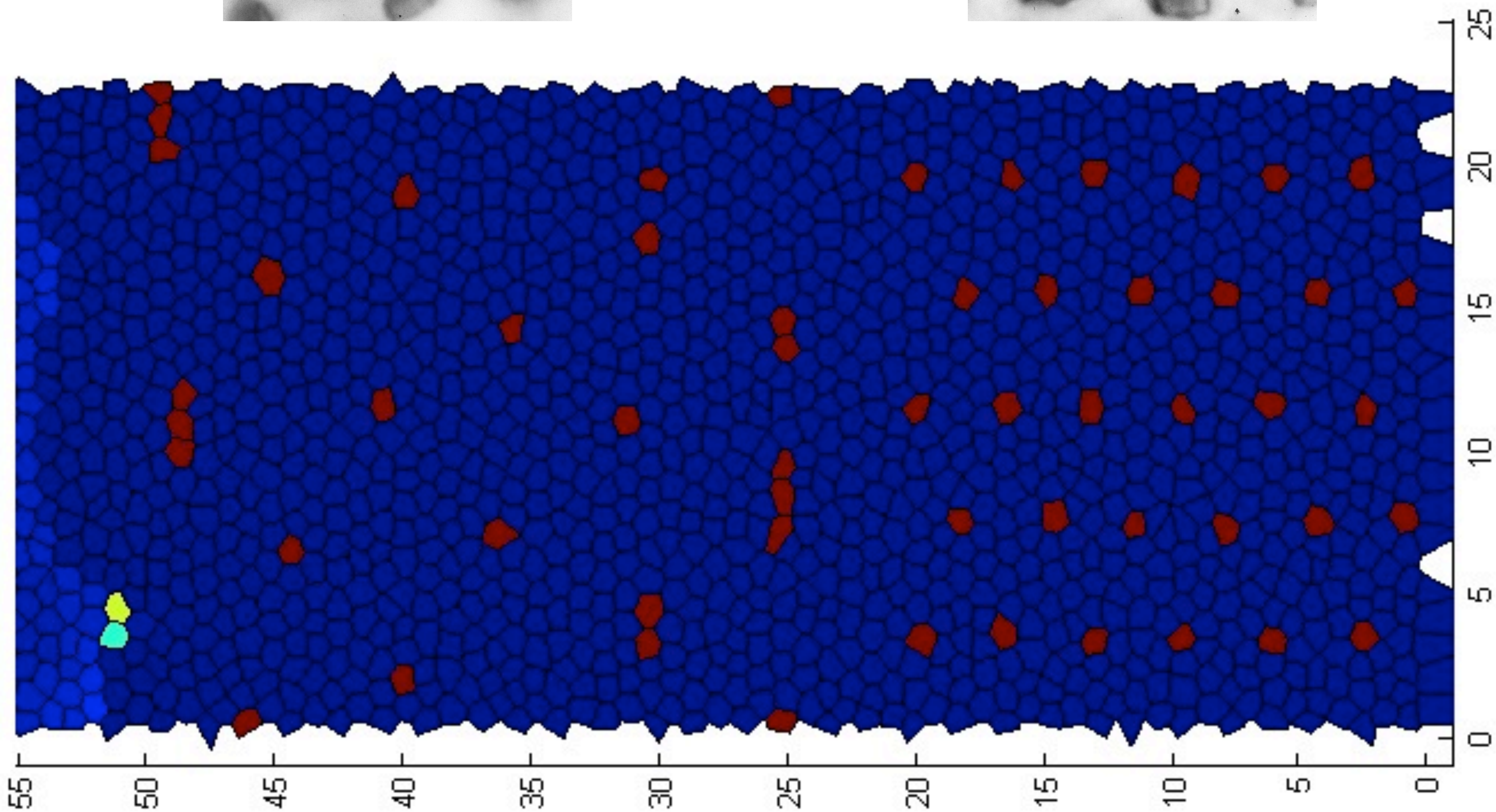


Slower “*u*” predicts the *sca* mutant phenotype



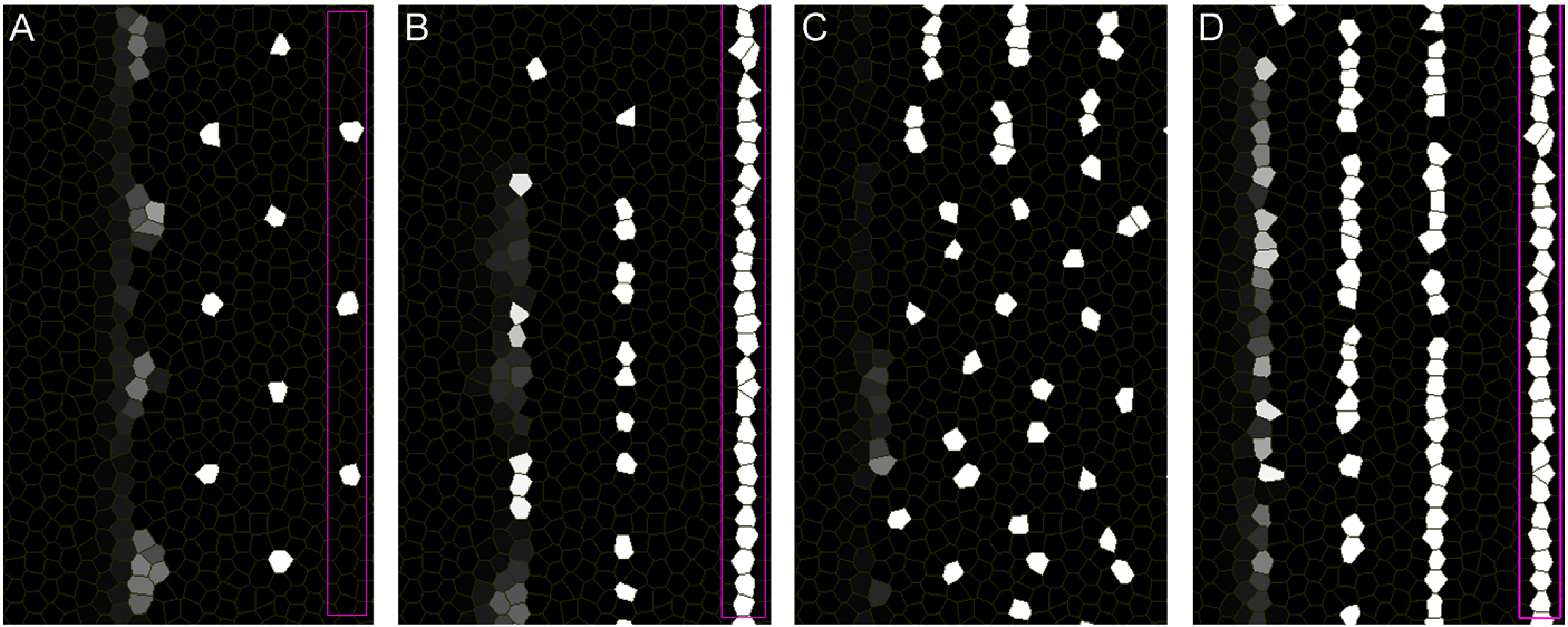
sca
mutant

wt



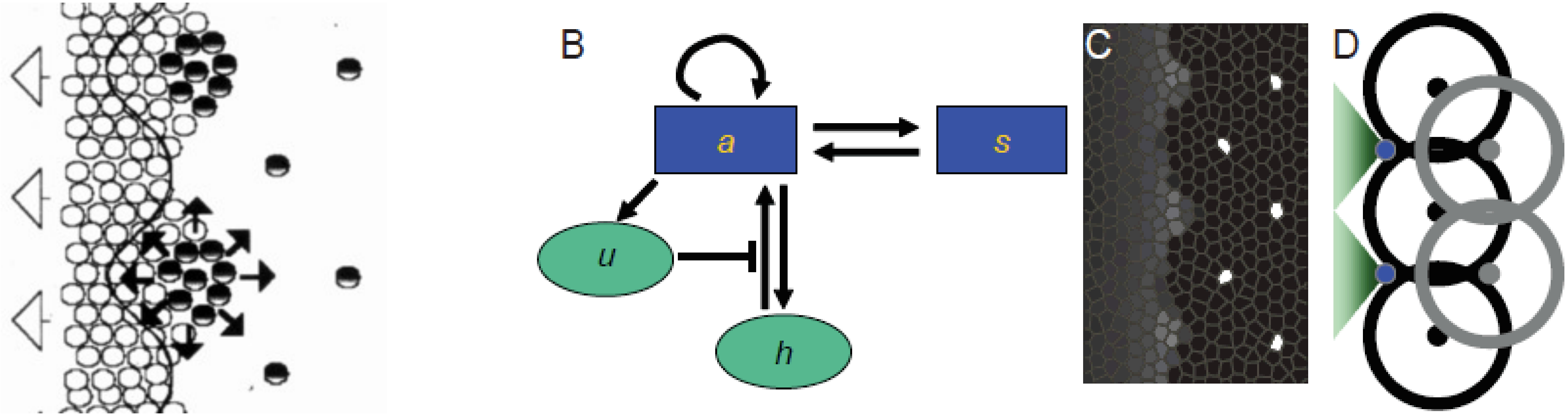
The model predicts multiple patterns from each parameter set (=genotype)

Normal | uniform template | slow u | both



Wild type | transient N^{ts} | *sca* | transient N^{ts} & *sca*

The model creates the R8 spacing pattern through a novel mechanism



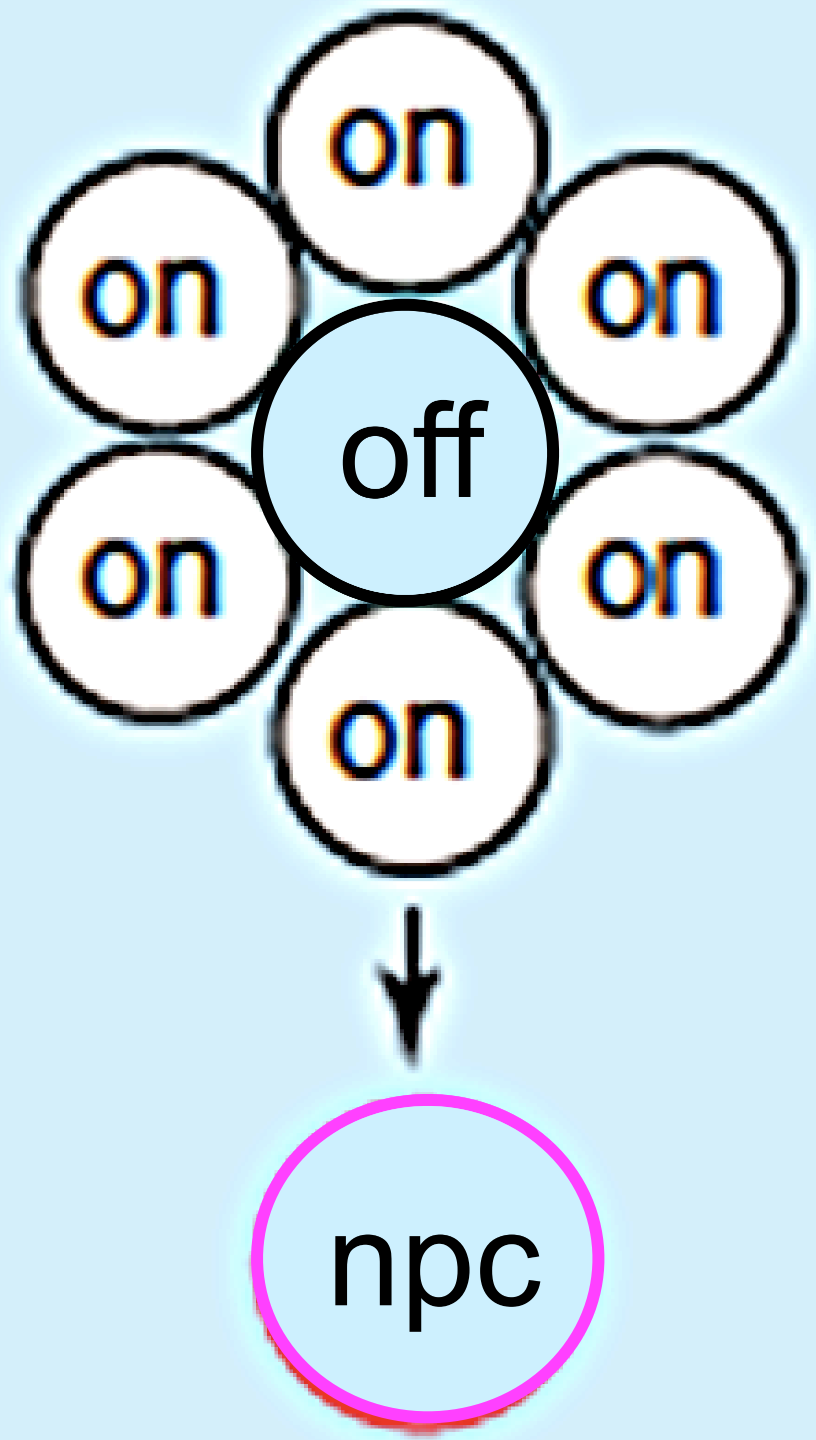
- each R8 defines an inhibitory region where *a* is restrained
- as *h* spreads anteriorly and builds up, it first reaches threshold in the most posterior cells that are not inhibited
- the delay in *a*, and *u* ramping up in these future R8 cells allows *h* to start affecting other cells
- these cells, which form a larger and less regularly-shaped group due to their distance from the previous column, are the IG's
- IG's will *always* be suppressed by the R8 that already has a head start
- there is no instability or Turing mechanism

Lateral inhibition restricts and defines the extent of neurogenesis

Step 1: neurogenic epithelium defined by proneural bHLH gene transcription

Step 2: competitive cell interactions lead to Notch activation in most proneural cells

Step 3: single cells sustain proneural gene transcription to differentiate as neural precursor cells



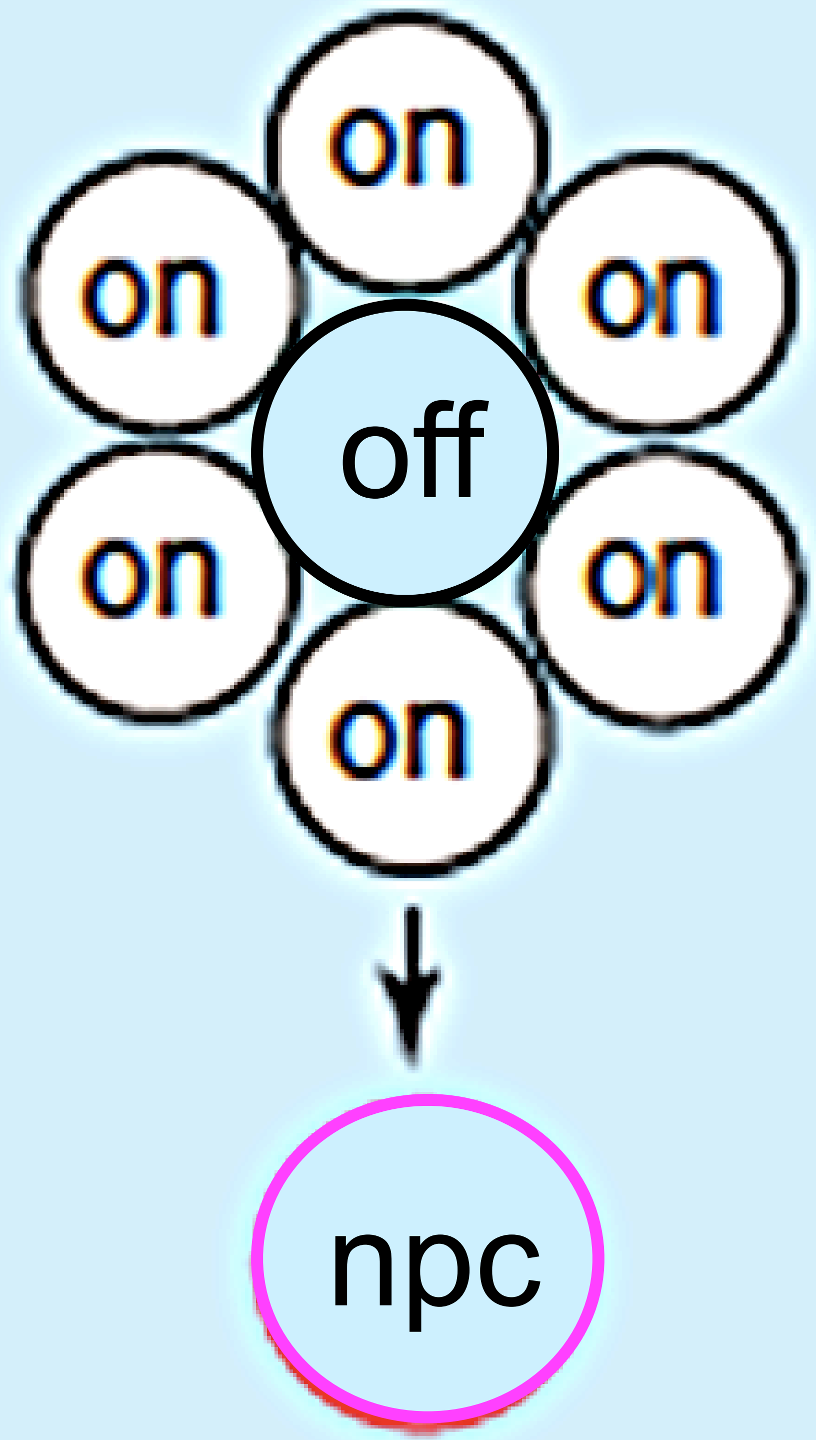
Schweisguth (2004)

Lateral inhibition restricts and defines the extent of neurogenesis

1. Neural cell chosen first, not by amplifying instability but by a template-dependent switch

2. Proneural group is a side-effect of neural cell selection, not its precursor

3. NO interactions within the proneural group selecting the neural cell



Schweisguth (2004)

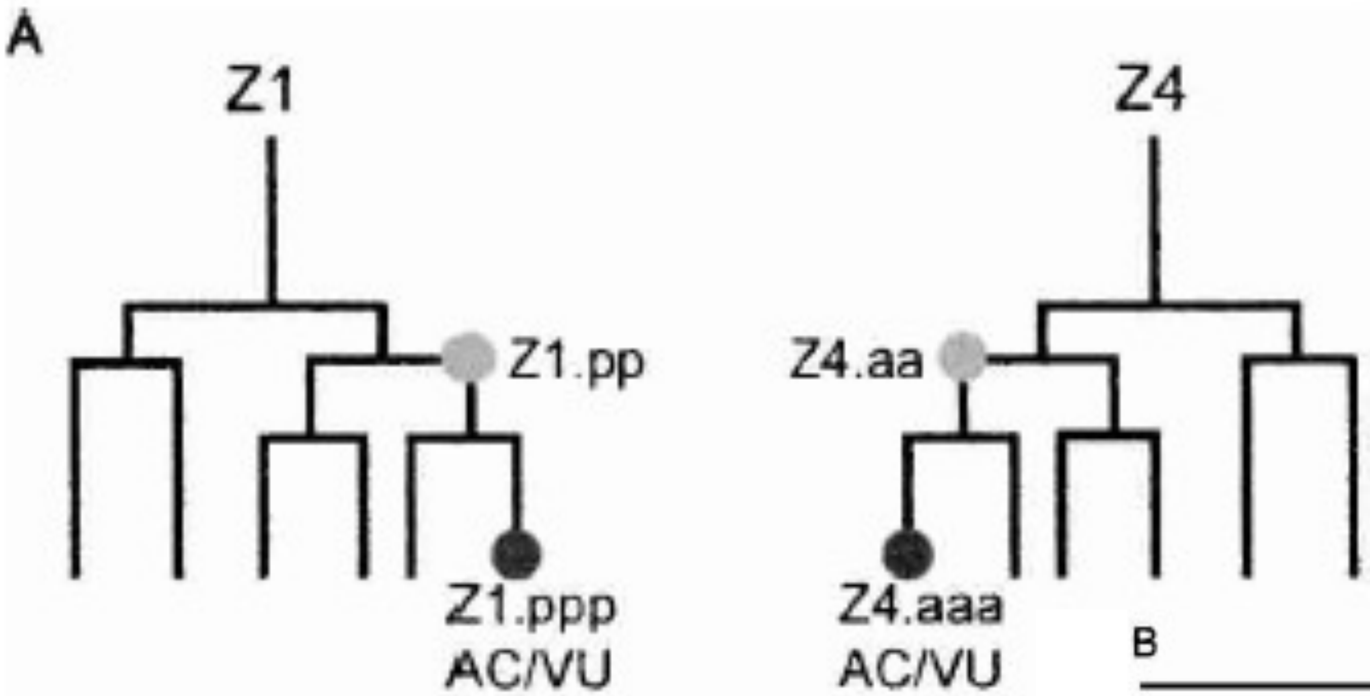
Further questions?

- What are the effects of noise on this system?
- What are the effects of retinal geometry?
- Does the Sca protein affect the speed of Notch signaling?
- Are there dynamic predictions that can be confirmed by live images?
- Does the model predict the persistence/repair of pattern defects?
- Does this mechanism have robustness or other properties that justify its use?
- Is our new view applicable to other proneural regions, or other equivalence groups? How would one test this?

Cell fate specification by Lin-12(Notch) in the AC/VU equivalence group is largely predetermined

Karp and Greenwald

A



B

First born cell	Fate of First-born cell	Time between births (min)
Z1.ppp	VU	7
Z1.ppp	VU	15
Z1.ppp	VU	27
Z1.ppp	VU	60
Z1.ppp	VU	75
Z1.ppp	VU	115
Z4.aaa	VU	2
Z4.aaa	VU	12
Z4.aaa	VU	15
Z4.aaa	VU	25
Z4.aaa	VU	25
Z4.aaa	AC	40
Z4.aaa	VU	75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NIGMS
Research to Prevent Blindness
NSF, NIH & Burroughs Wellcome via KITP