Genetic network of R8 neuron specification in the Fly Eye

Nick Baker
Department of Molecular Genetics
Albert Einstein College of Medicine

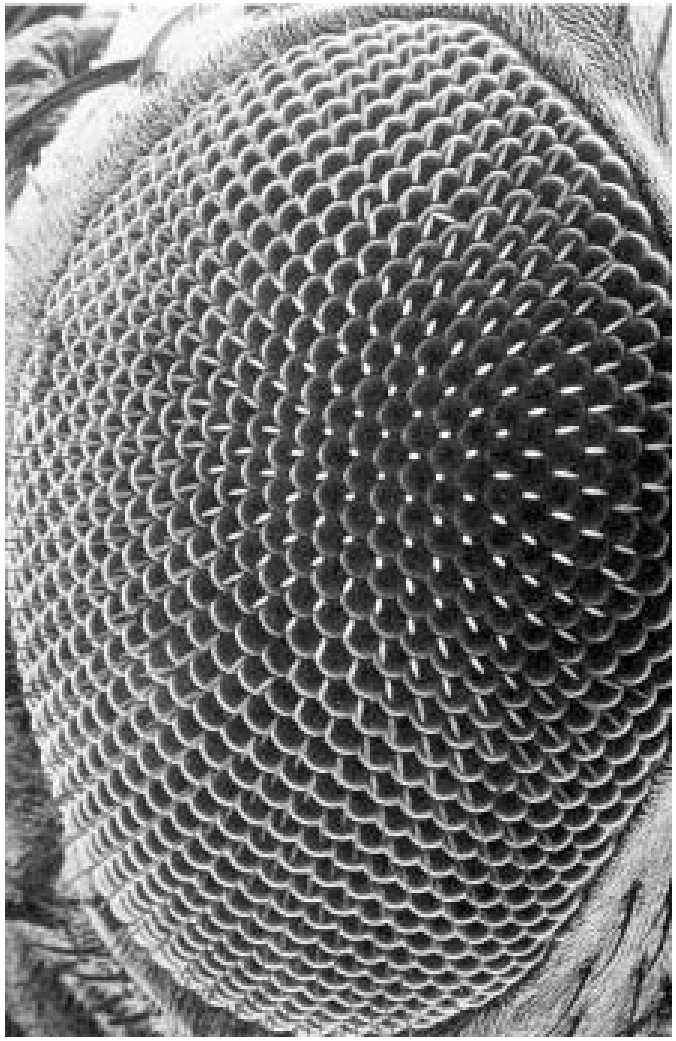
The R8 race: Computational modeling of pattern formation in the *Drosophila* eye imaginal disc

David Lubensky
Department of Physics
University of Michigan

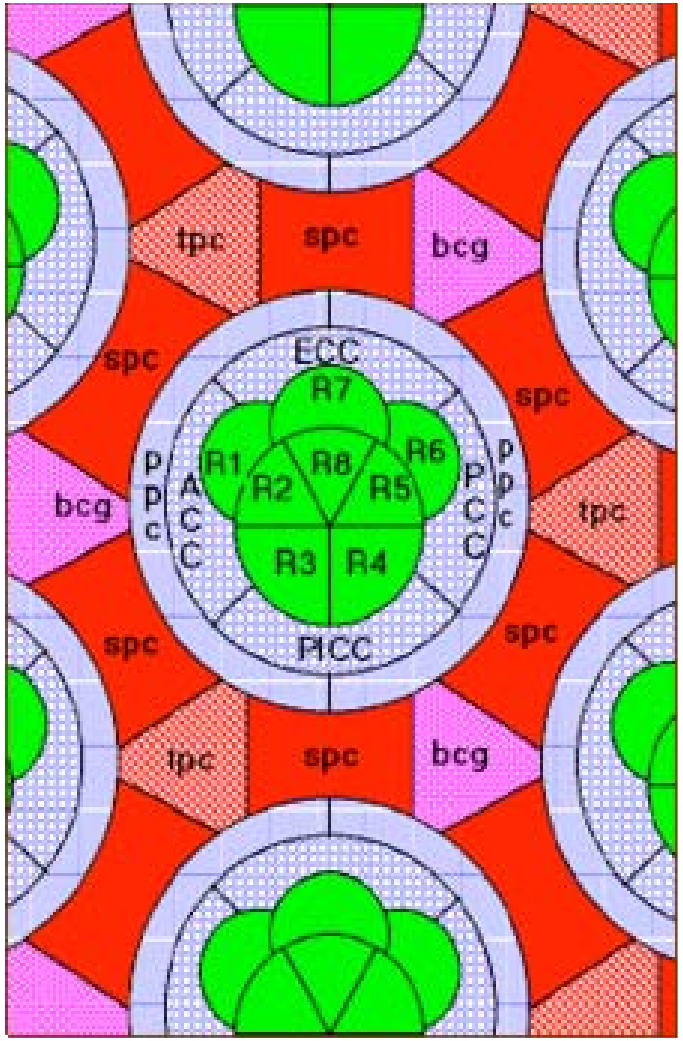
KITP 03/05/08

The *Drosophila* compound eye

N. Baker Albert Einstein College of Medicine, NY

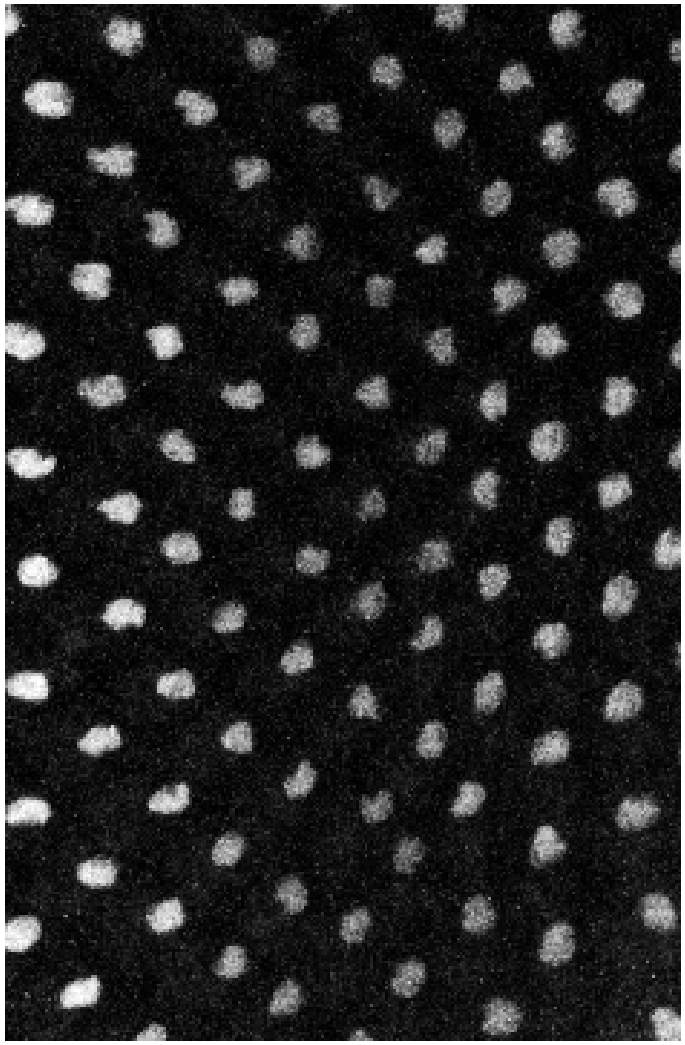


Scanning EM

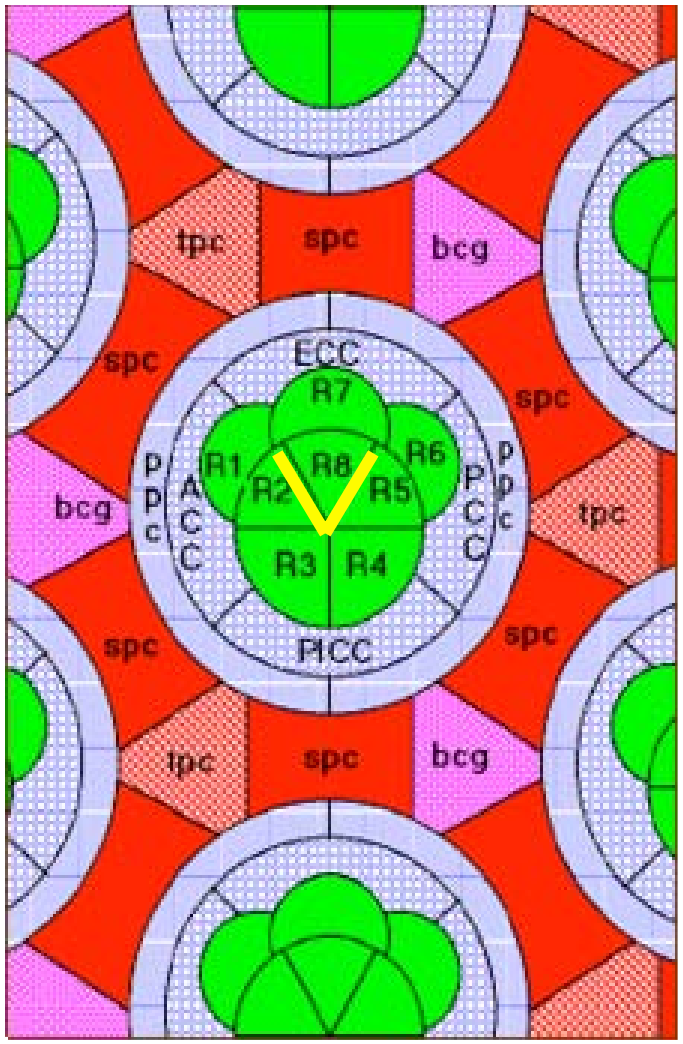


retinal organization

Eye develops around the R8 cell pattern

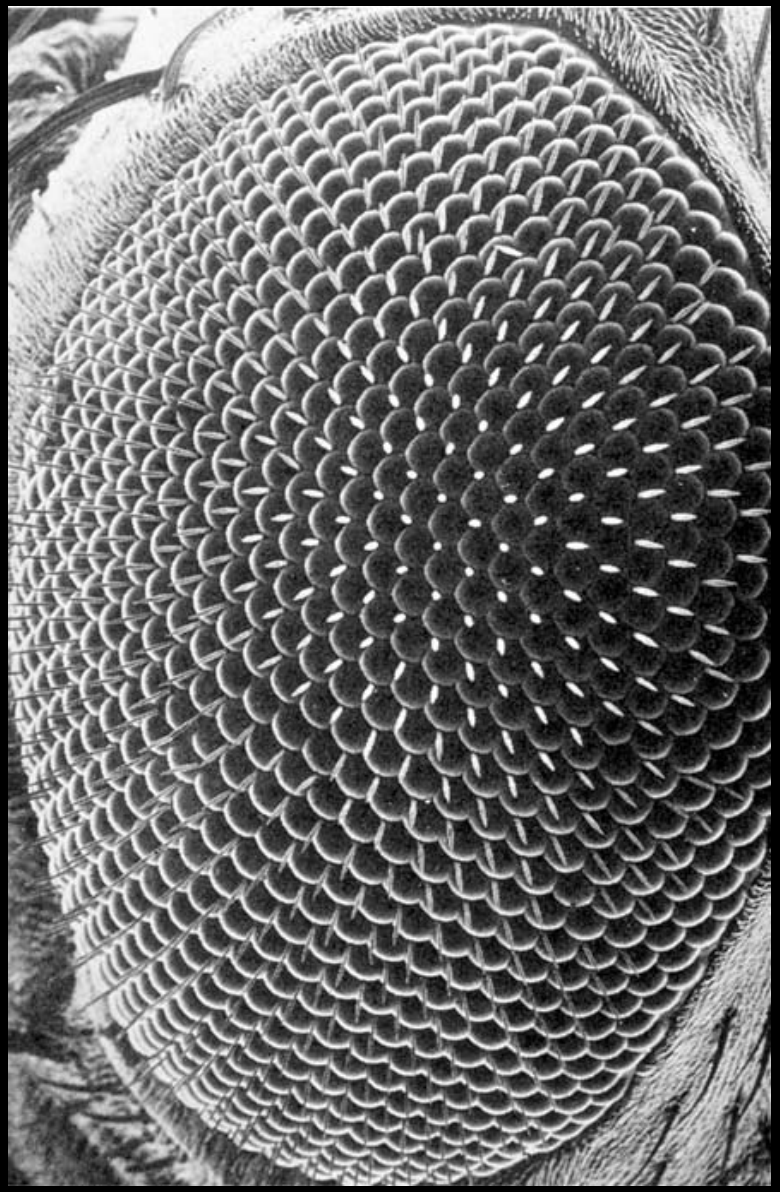


nuclear Senseless protein

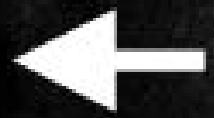


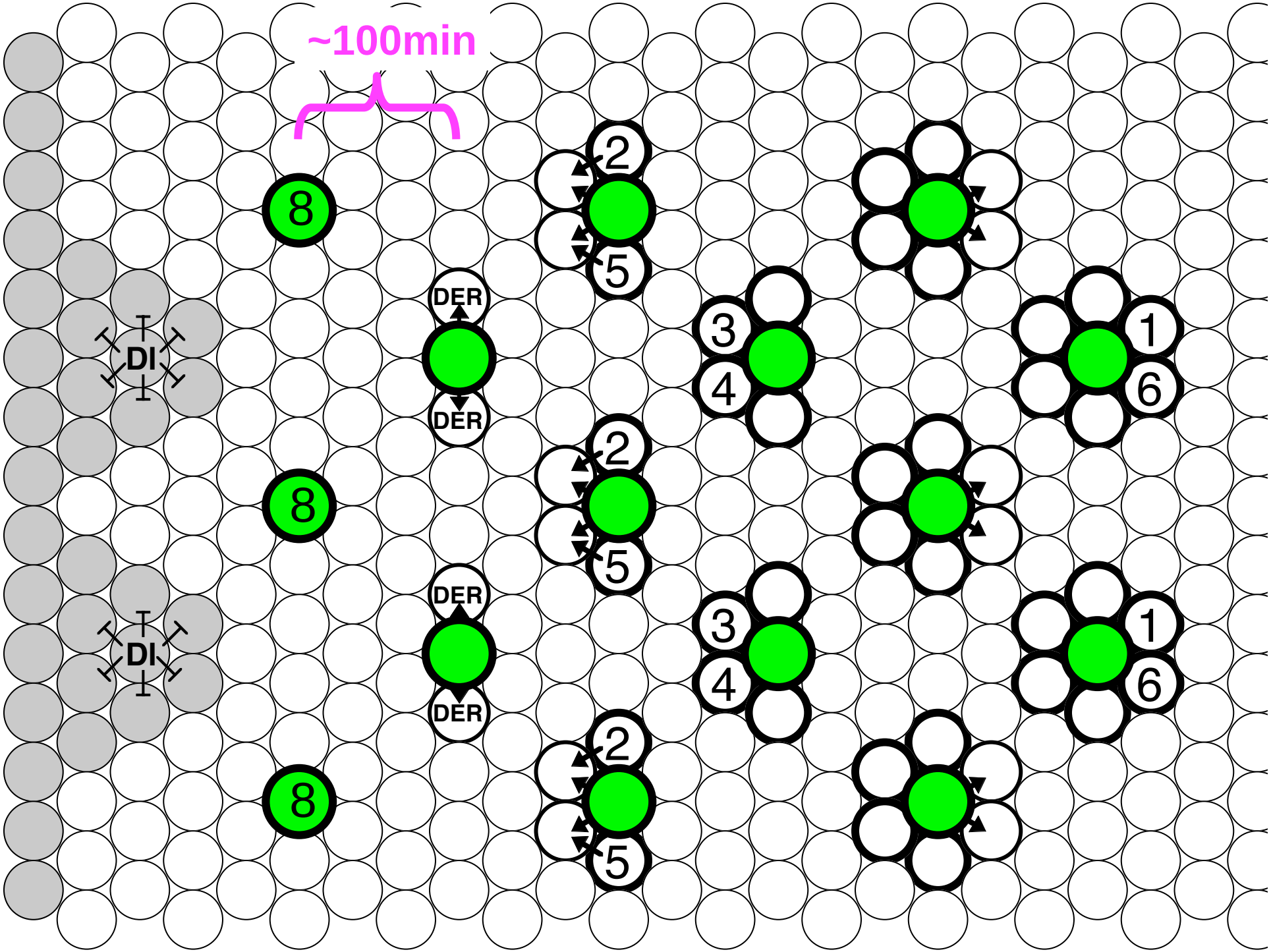
retinal organization

Patterning occurs in the Morphogenetic Furrow



no division
no death
little movement?
transient apical
constriction

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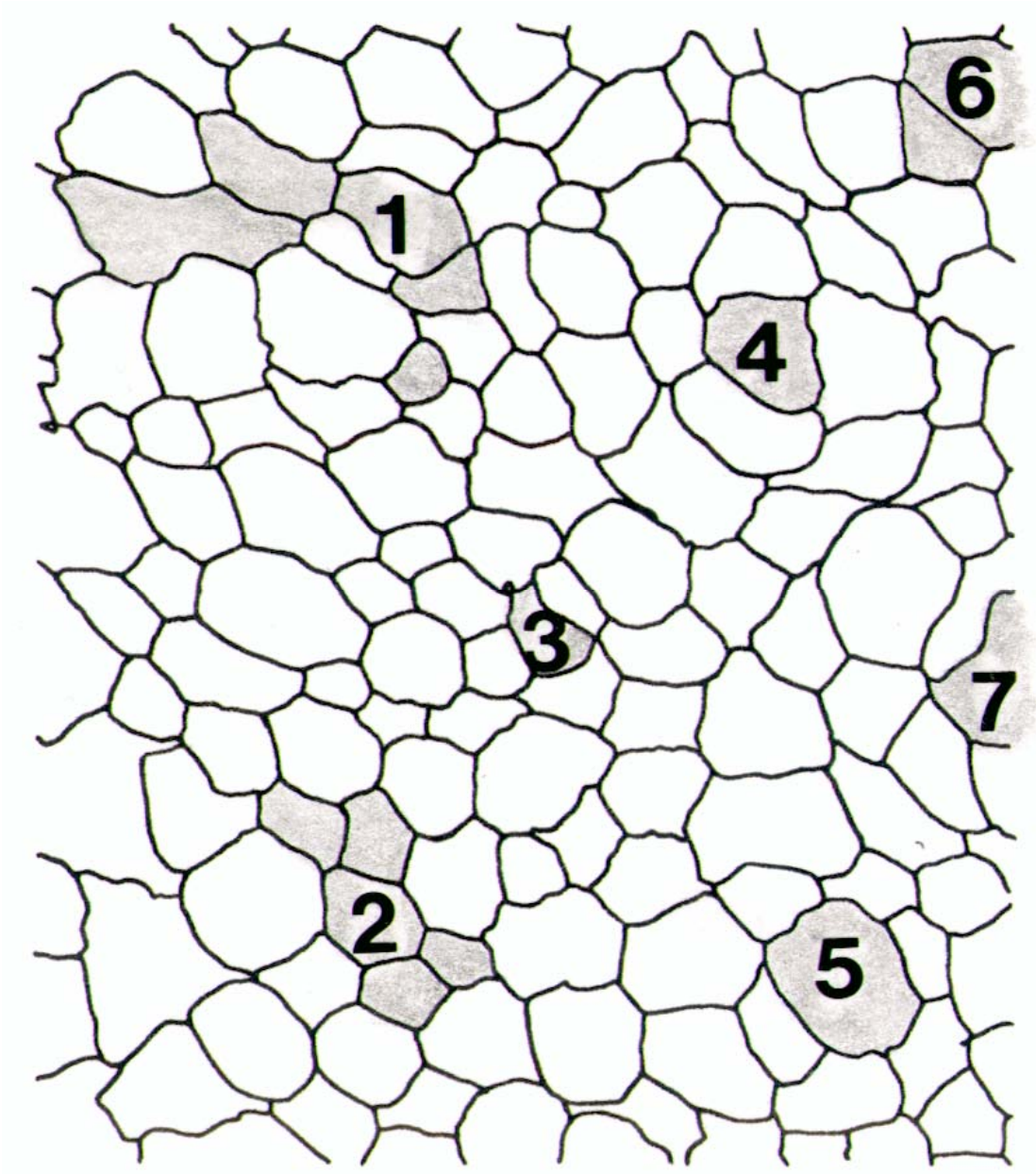
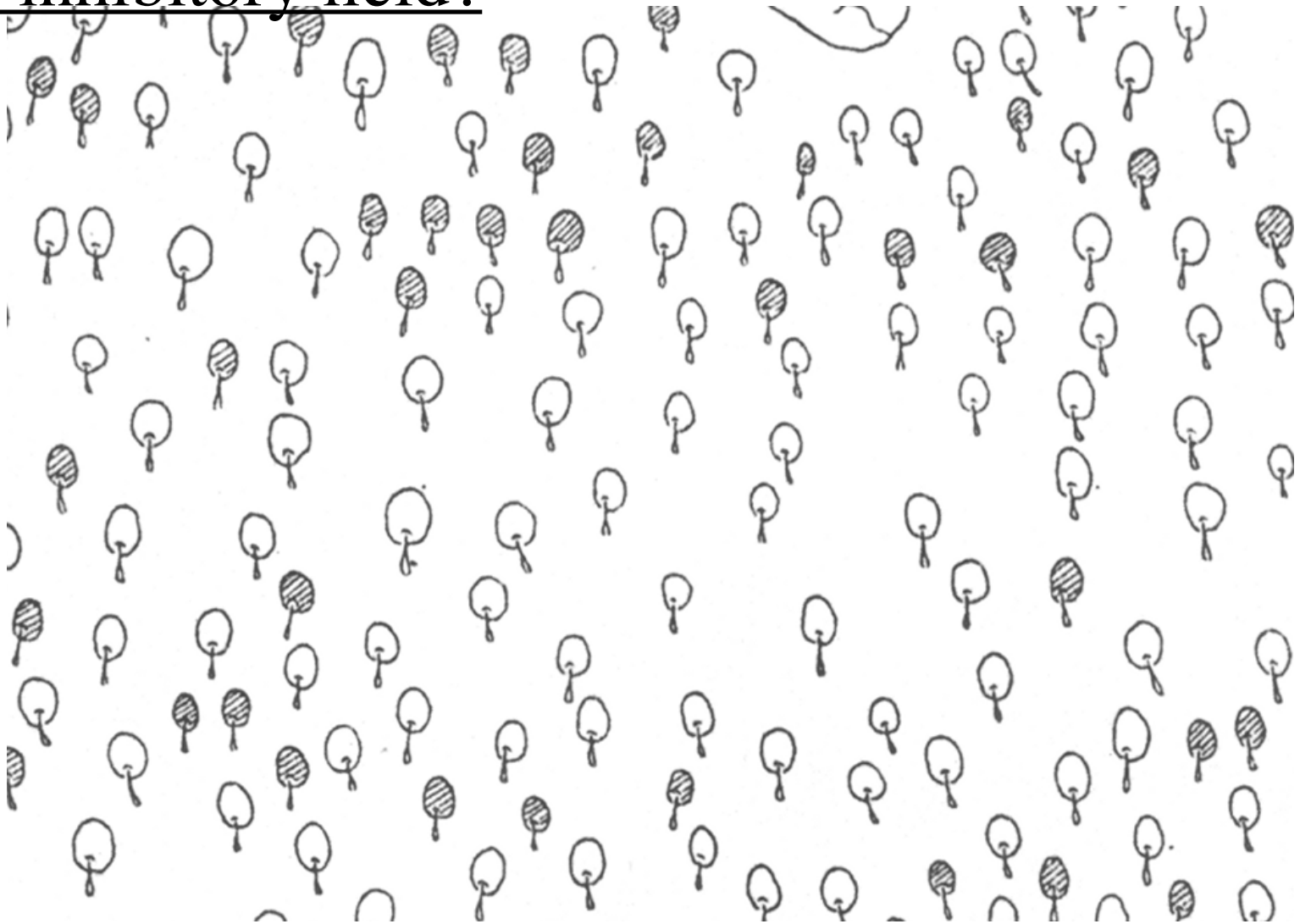


Baker & Zitron *Mech Dev* **49** 173-89 (1995)

New sensory organs intercalating between old ones; An inhibitory field?



Wigglesworth, V.B. *J exp Zool* **17** 180-220 (1940)

Reaction-diffusion systems that pattern spontaneously

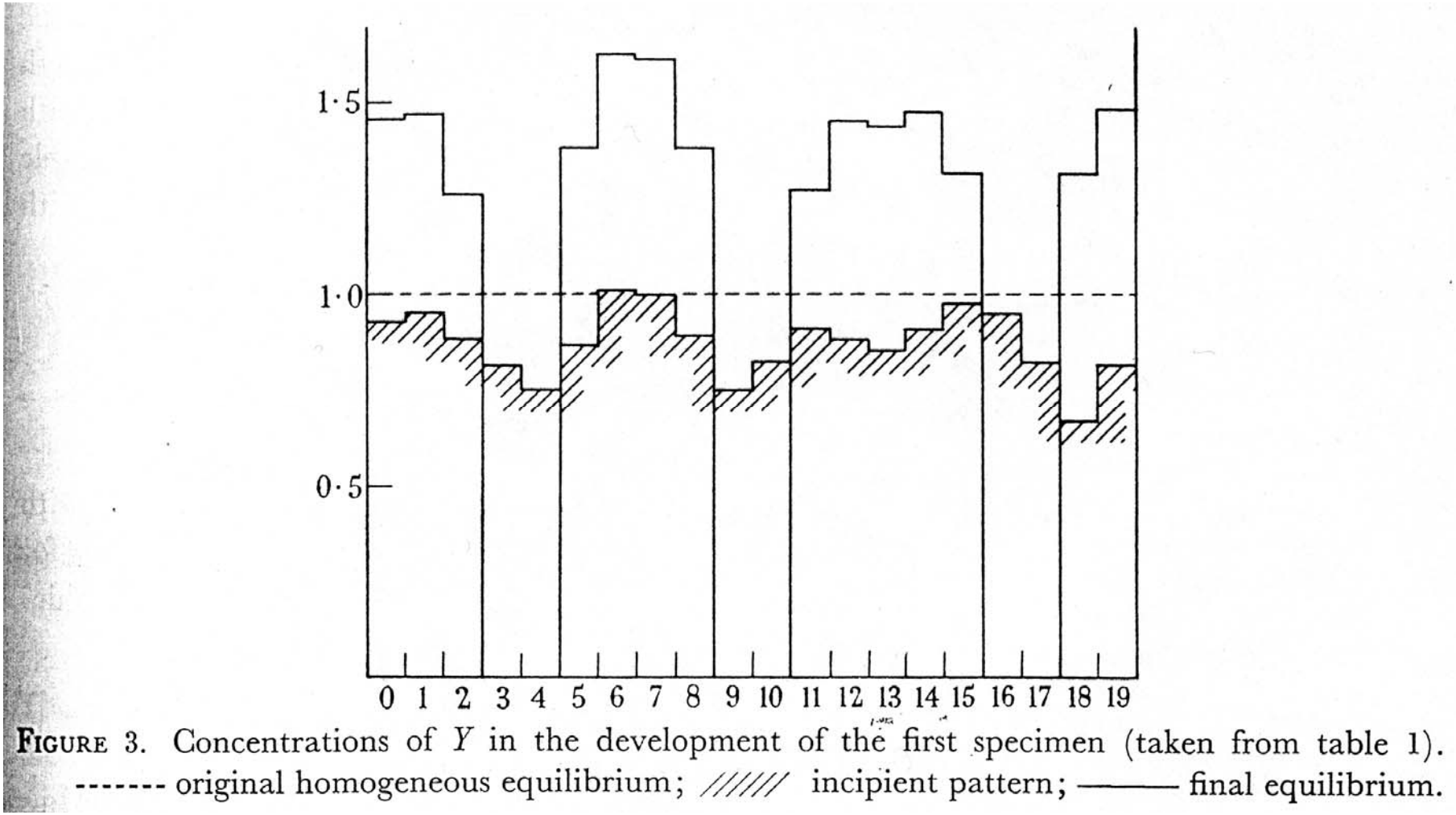


FIGURE 3. Concentrations of Y in the development of the first specimen (taken from table 1). ------- original homogeneous equilibrium; ////// incipient pattern; ——— final equilibrium.

Turing, A.M. *Phil Trans Roy Soc Lon* **237** 37-72 (1952)

David Lubensky's talk will describe a model

Novel features:

1. This hexagonal pattern is a modified form of a stripe pattern
2. The cellularity of the epithelium contributes to the patterning
3. Model revises our view of the proneural mechanism

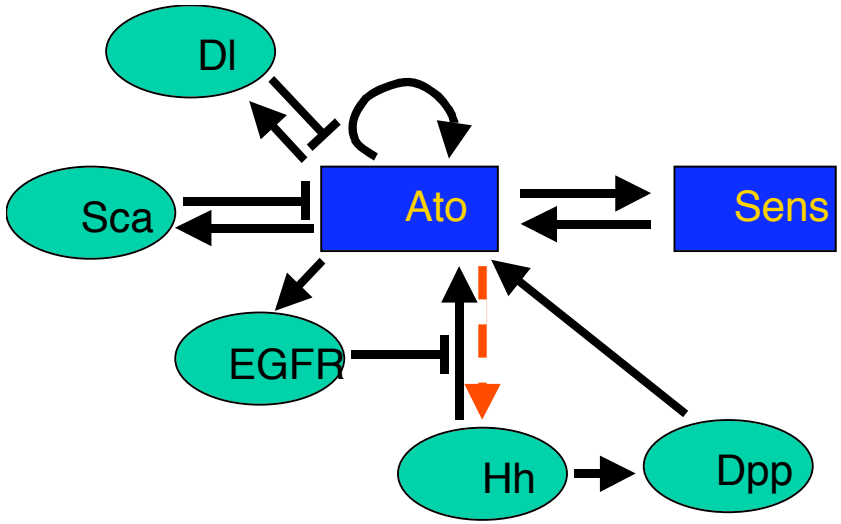


Figure 2a **Some genetic interactions controlling the R8 markers *ato* and *sens*. Pointed arrows, activation, blunt arrows, repression; the red dotted arrow indicates particuarly indirect and delayed activation (see text). Blue boxes, transcription factors; green ellipses, intercellular signaling molecules. Note the presence of 3 different negative feedback loops. EGFR works by blocking Hh-mediated activation**cite Nick**. The precise mode of action of the other two inhibitors is not known, though there is some evidence that Dl acts later than Sca or EGFR.**

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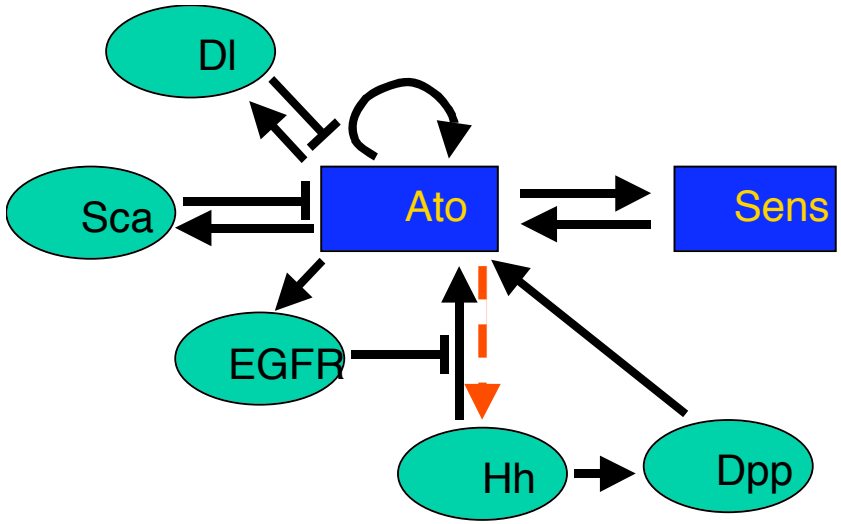

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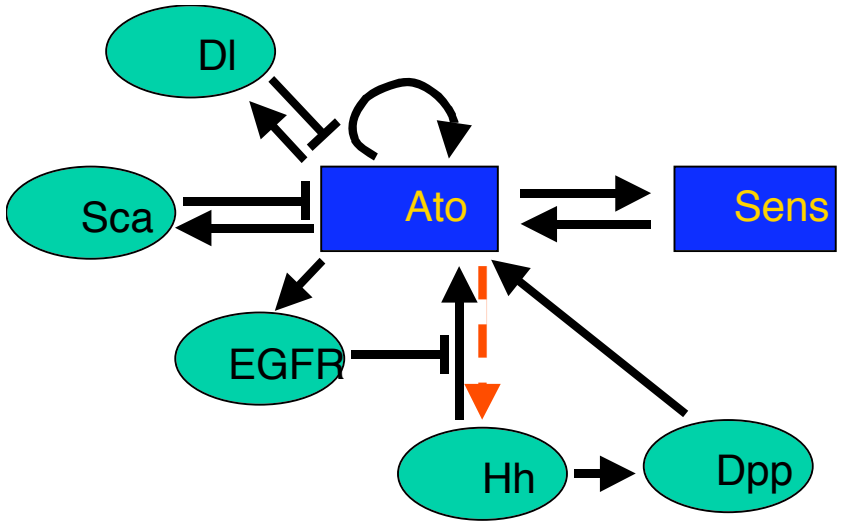

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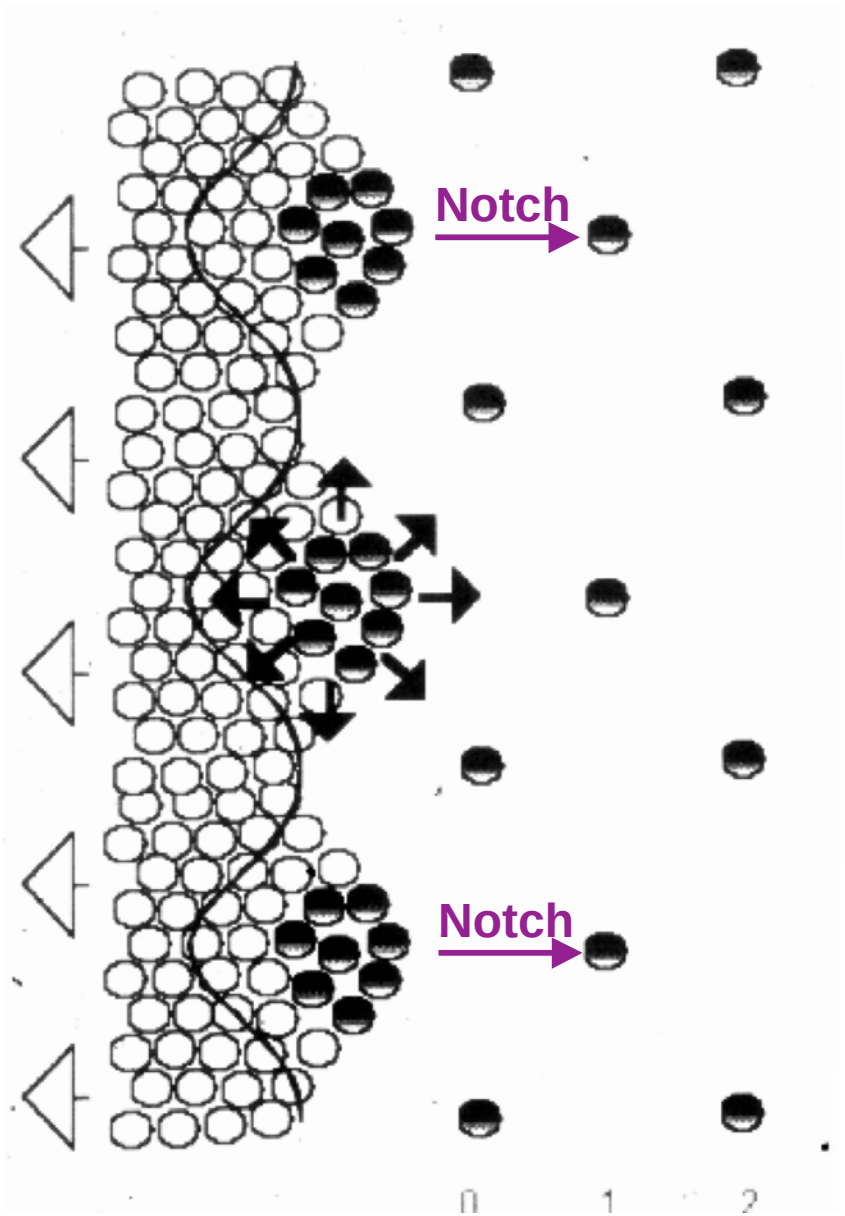
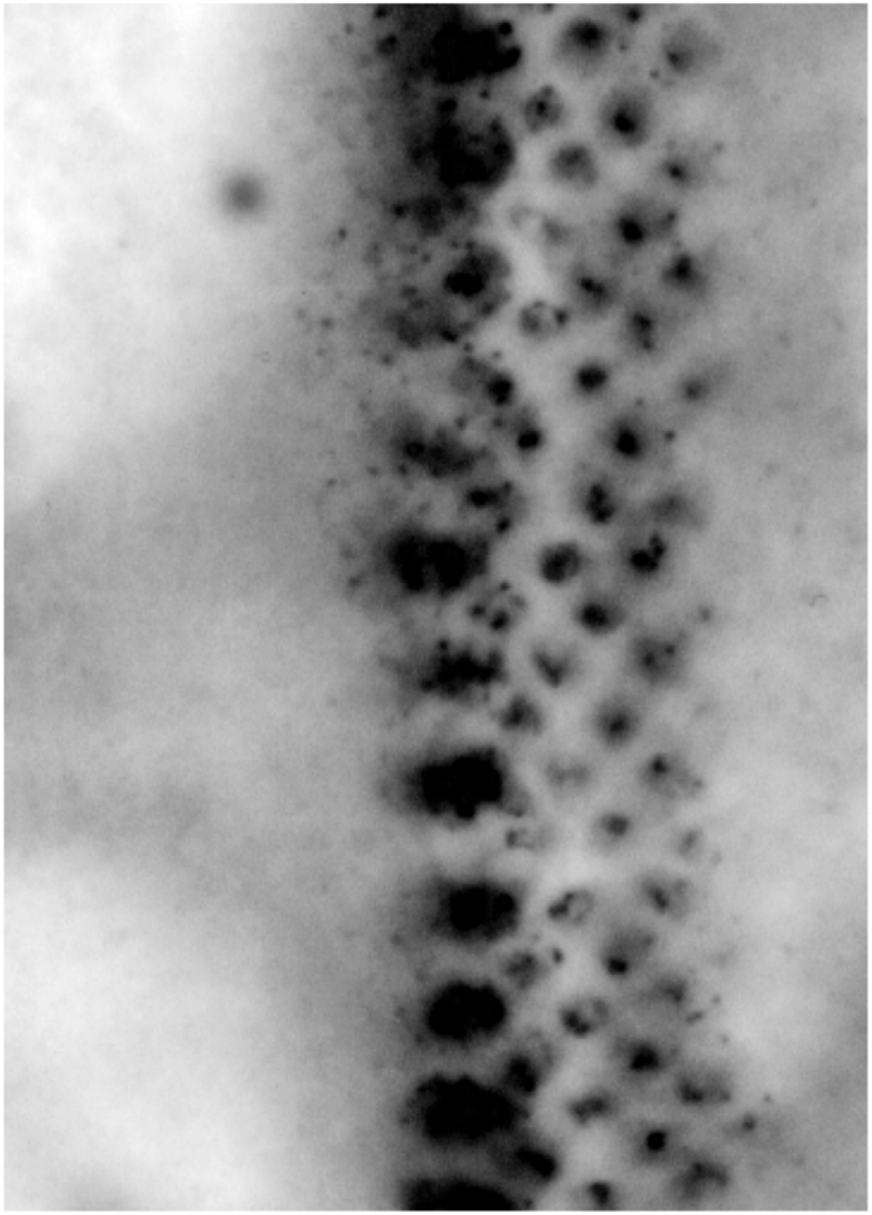
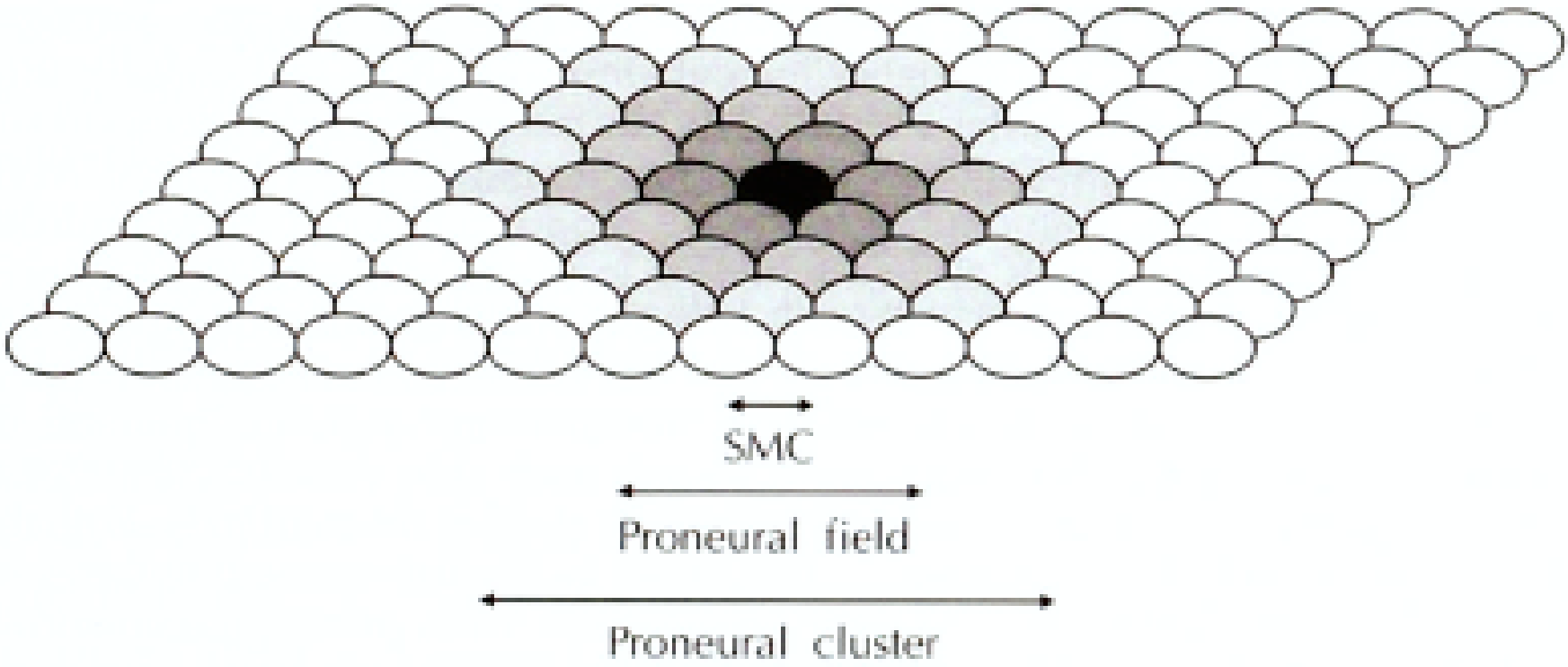
Secreted Scabrous protein is dynamically expressed during R8 specification





Baker et al *Science* **250** 1370-7 (1990); Mlodzik et al *Genes Dev* **4** 1848-61 (1990)

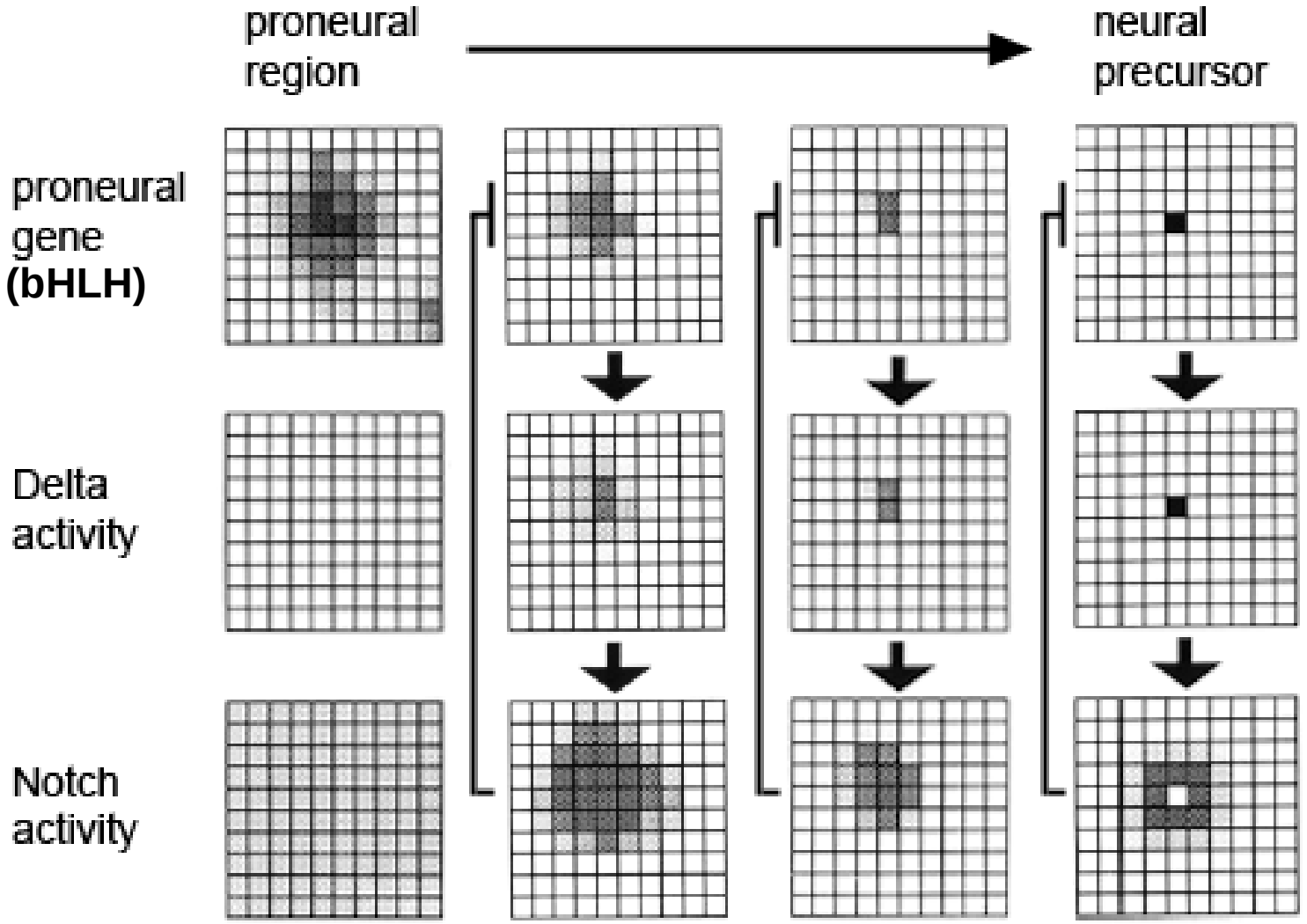
Proneural model for neural cell specification



Proneural groups:

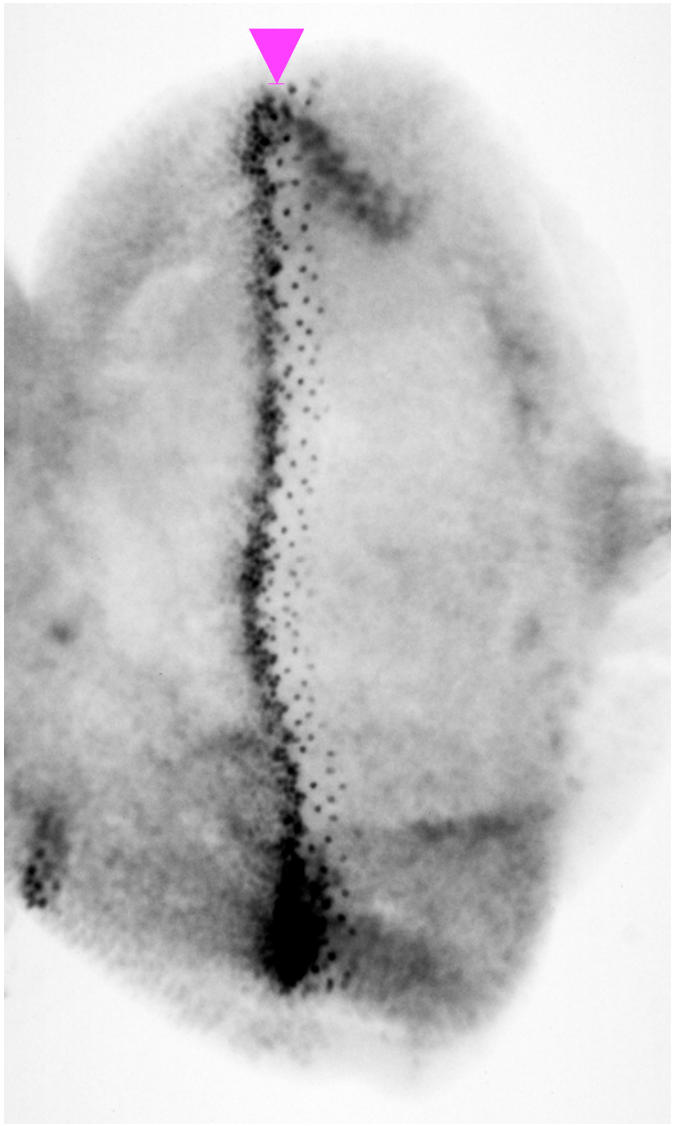
1. Provide regulation in the event of damage;
2. Achieve precise patterns in successive steps

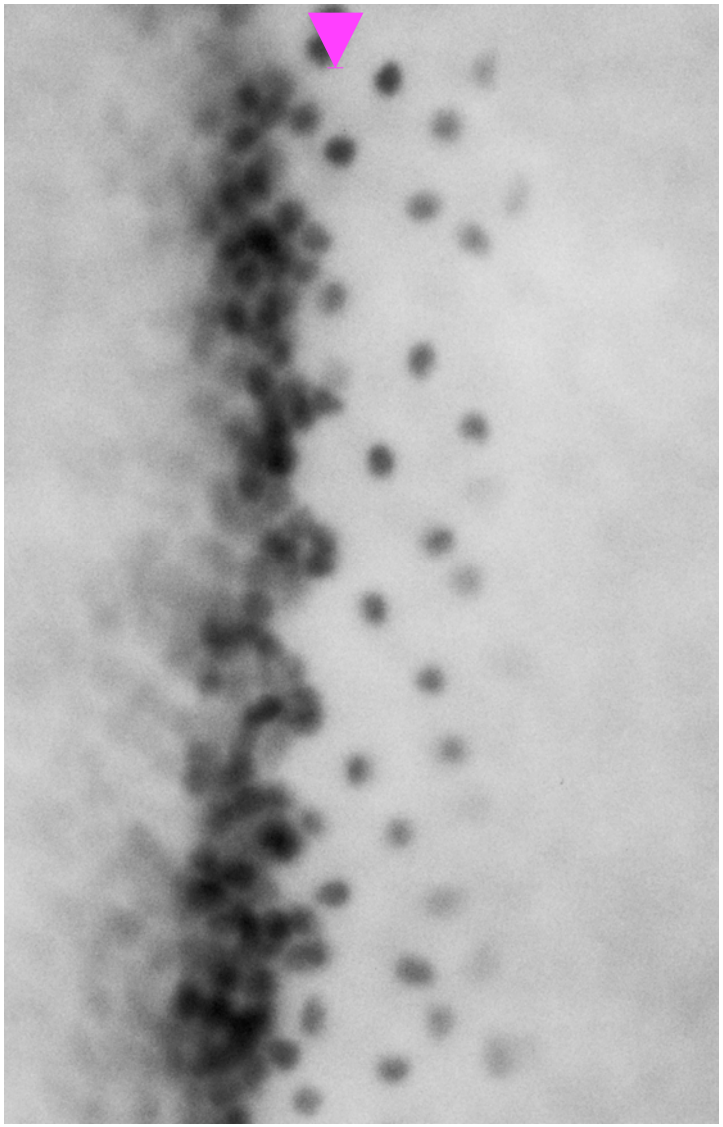
Scheme for proneural region development



Adapted from: Ghysen, A, Dambly-Chaudiere, C, Jan, LY & Jan, Y-N *Genes Dev* **7** 723-733 (1993)

Atonal is the proneural protein for R8 cells





Jarman et al., *Nature* **369** 398-400 (1994); Jarman et al., *Development* **121** 2019-2030 (1995)

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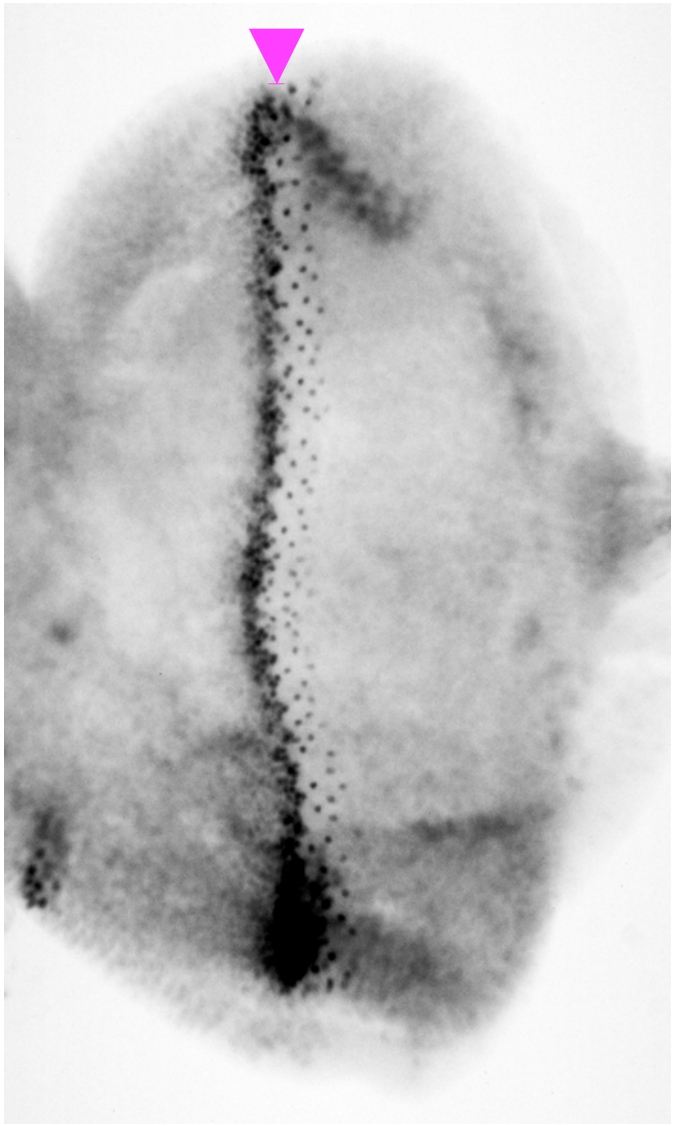

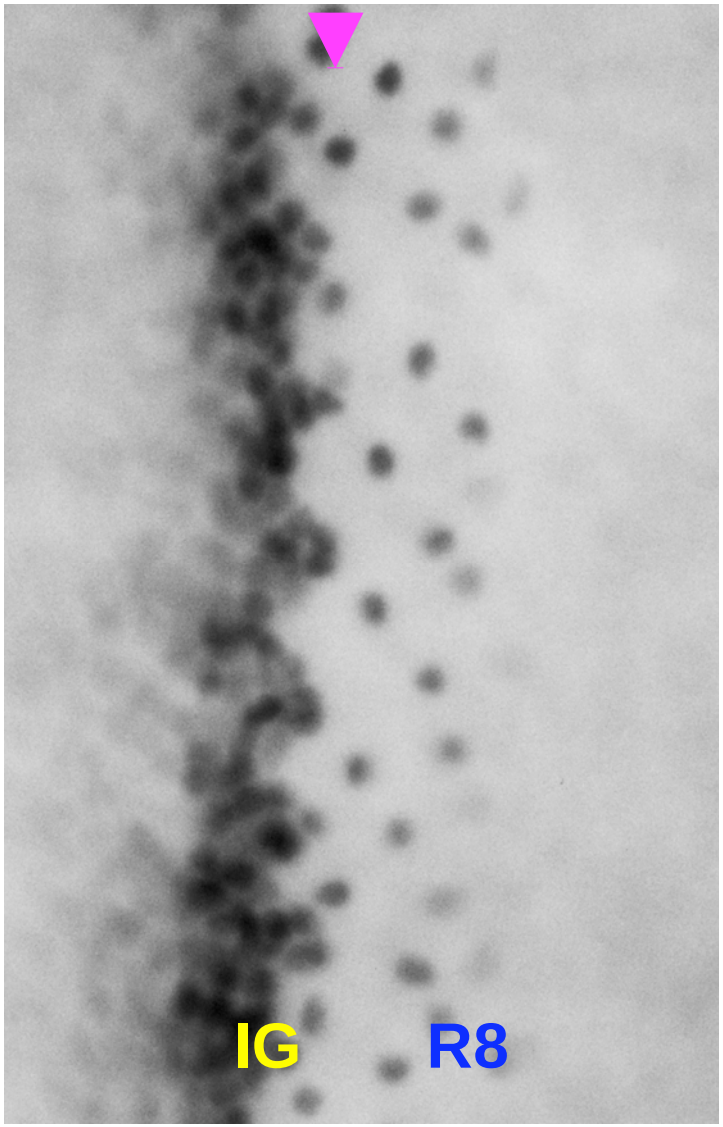

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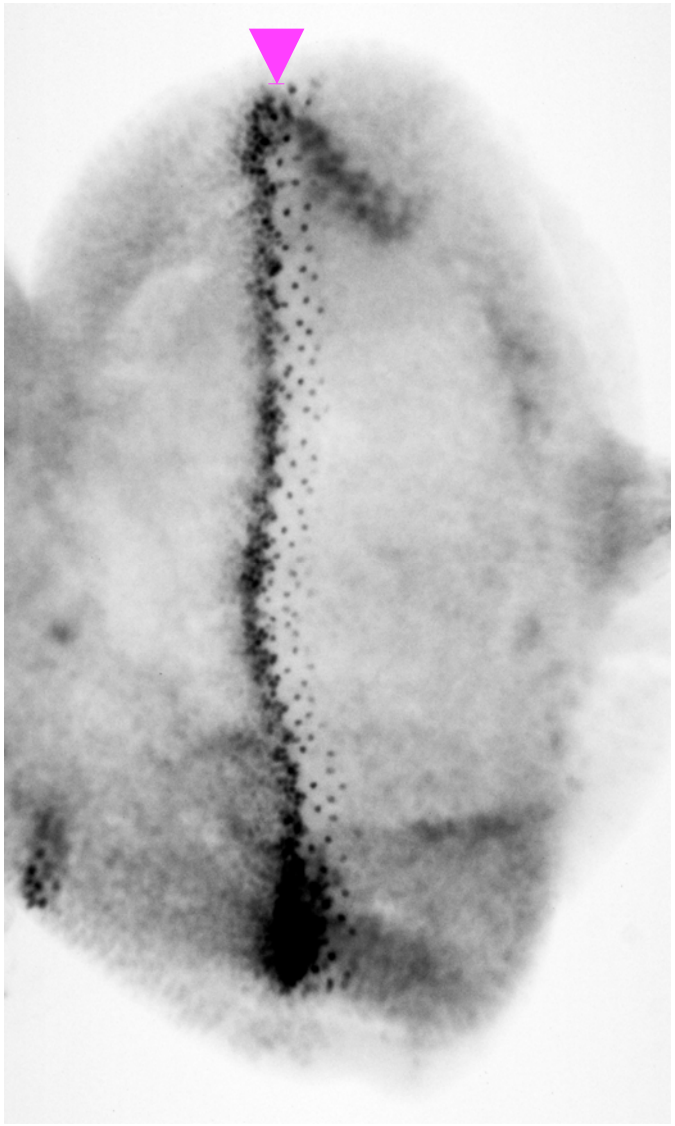

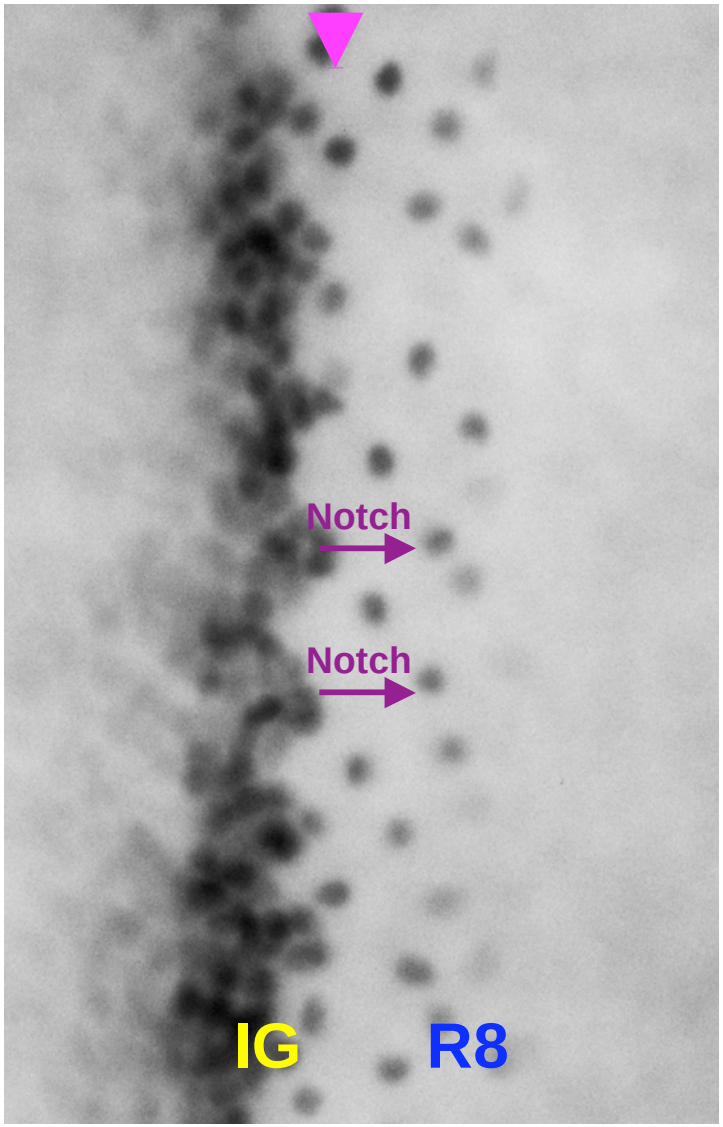

Baker, NE, Yu, S-Y, & Han, D *Curr Biol* **6** 1290-1301 (1996)

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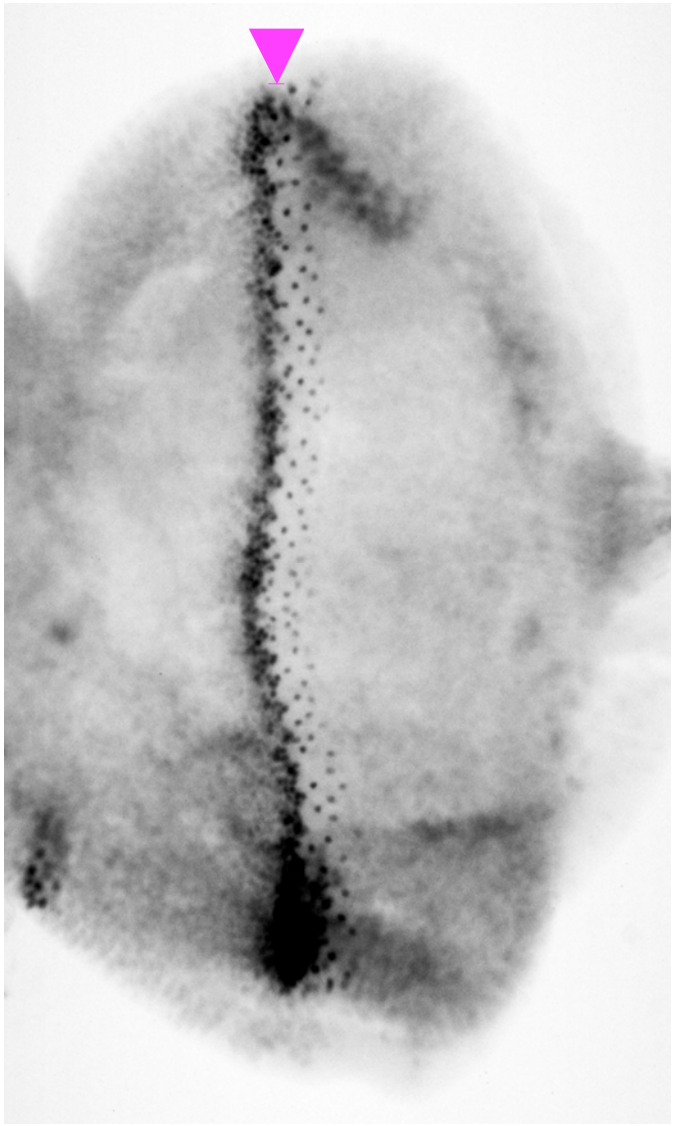

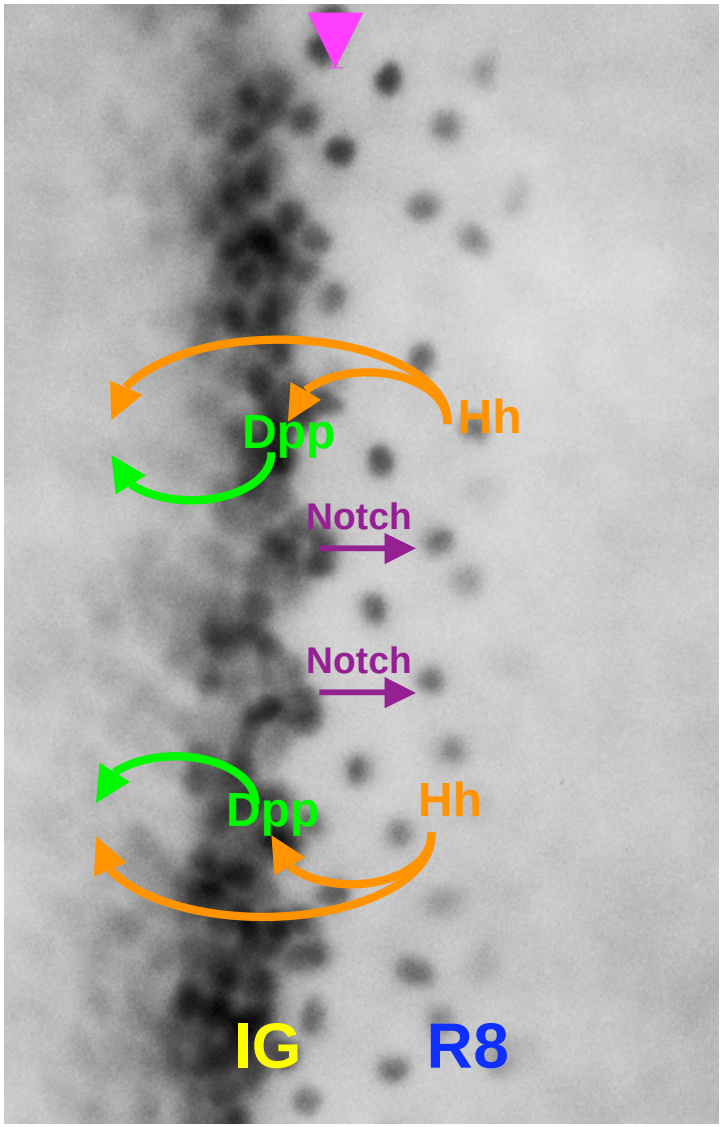

Heberlein et al *Cell* **75** 913-926 (1993); Ma et al., *Cell* **75** 927-938 (1993)

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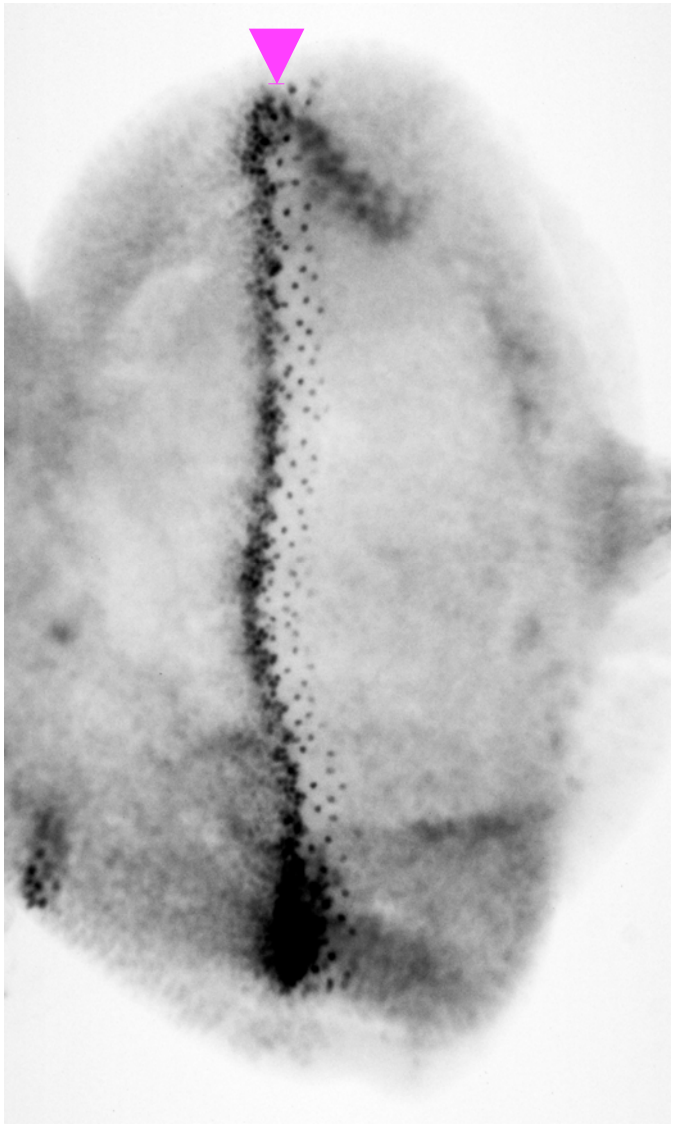

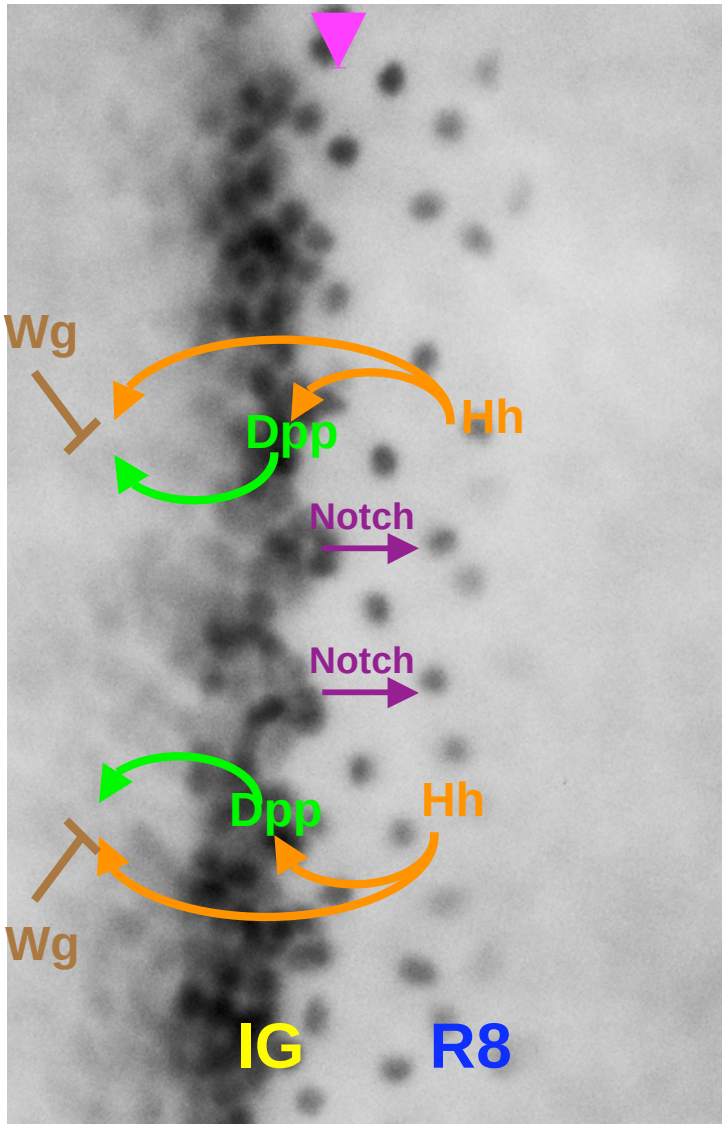

Ma et al., *Development* **121** 2279-2289 (1995); Treisman & Rubin *Development* **75** 3519-3527(1995)

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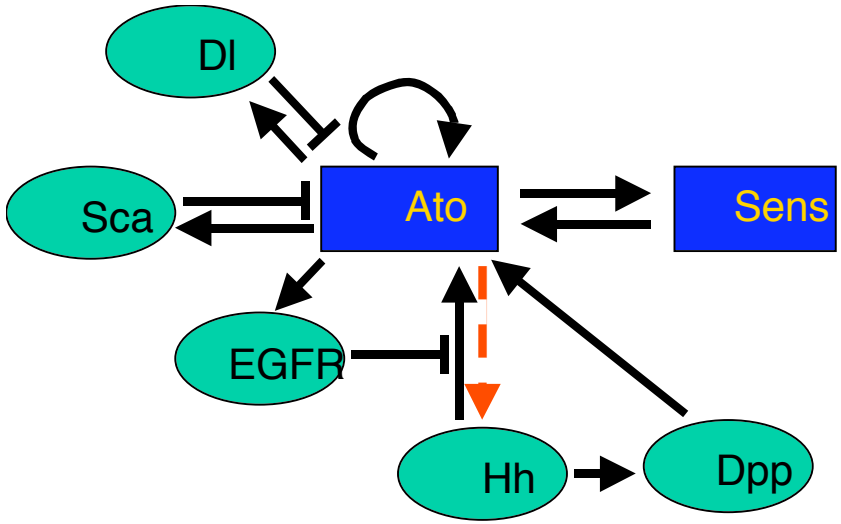

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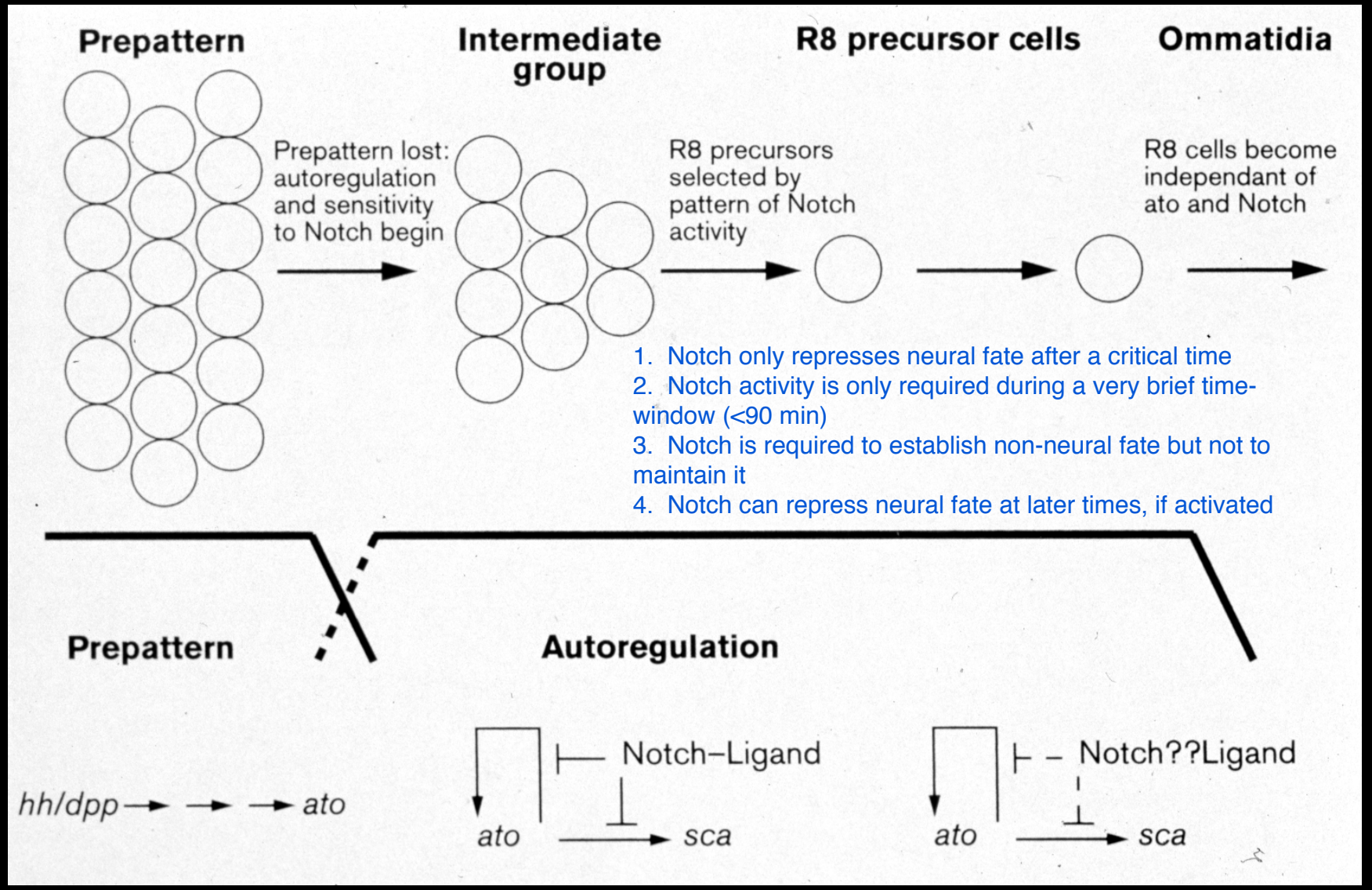
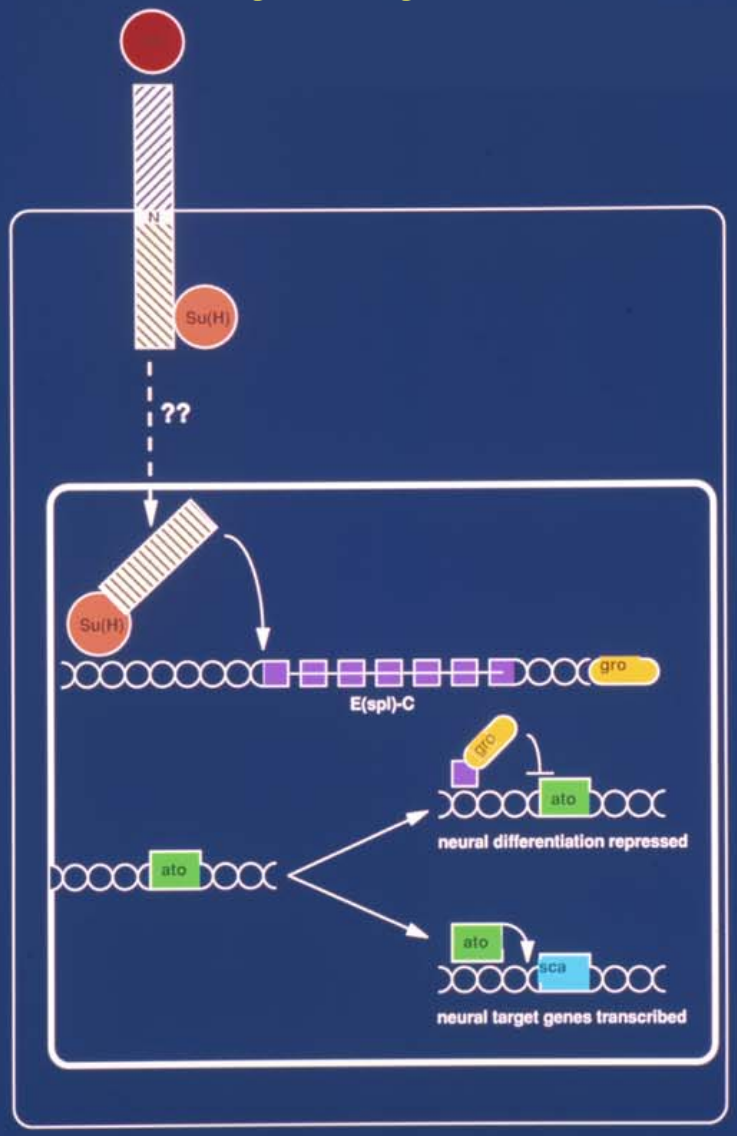
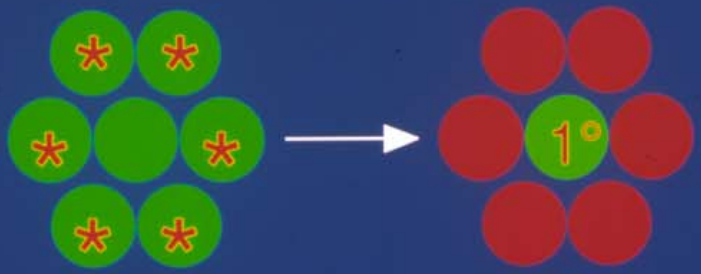
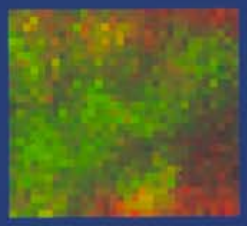
Atonal, lateral inhibition and R8 cell fate

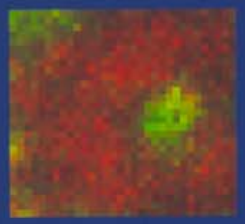


Notch signaling: Lateral inhibition from homogenous protein distributions









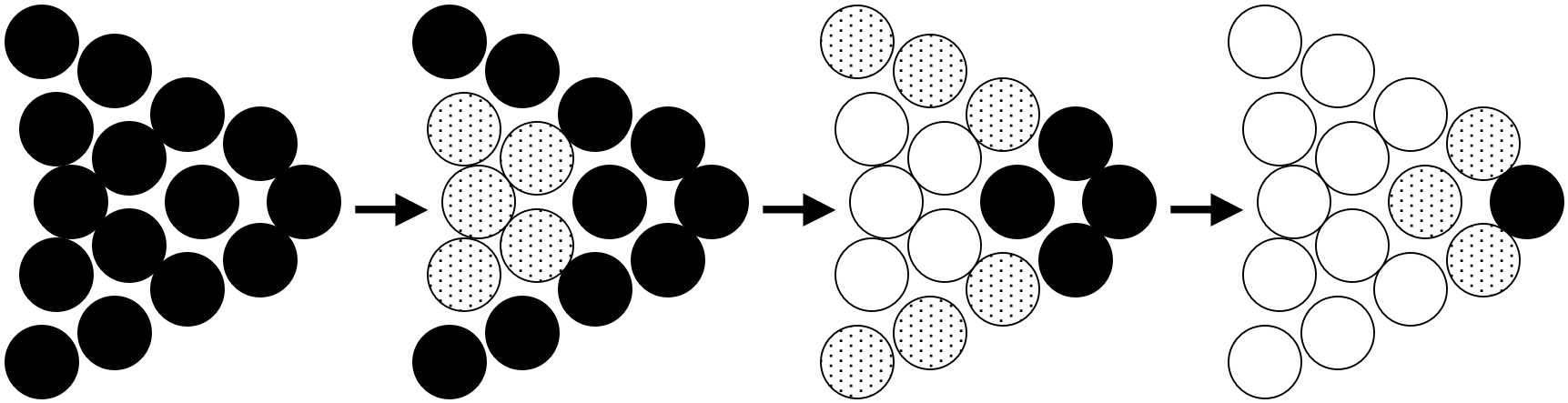
atonal - green

E(spl) mδ - red

N

Dl

Notch resolves the intermediate group asymmetrically

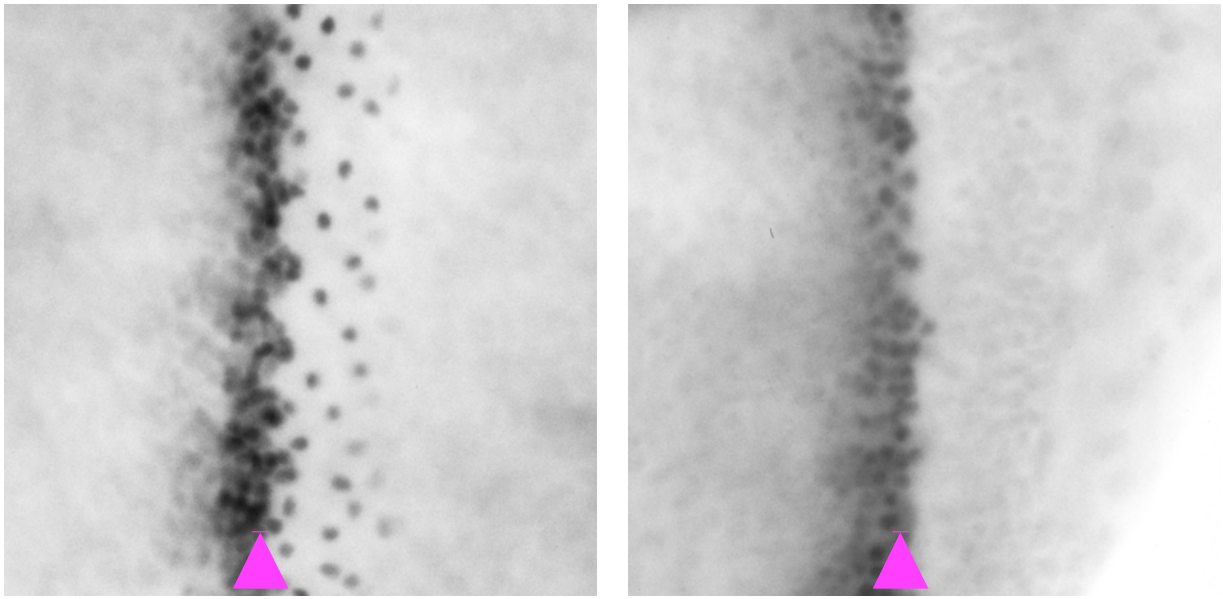


This occurs over ~90 minutes.
Notch signaling is required for ~20-50 minutes during this time
Repression of Atonal is irreversible and not maintained by Notch
Notch *can* repress Atonal at later times, but not earlier times

Establishment and maintenance of *ato* expression

wild type

*ato*1/*ato*1



init main

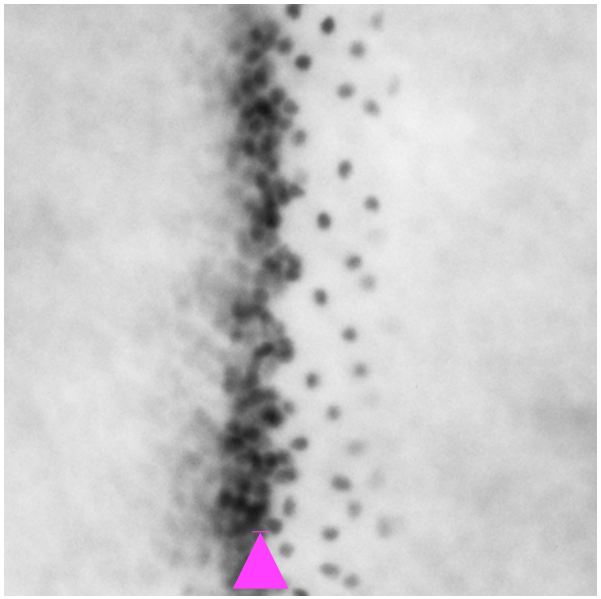
Jarman et al., *Development* **121** 2019-2030 (1995); Sun et al., *Development* **125** 3731-40 (1998)

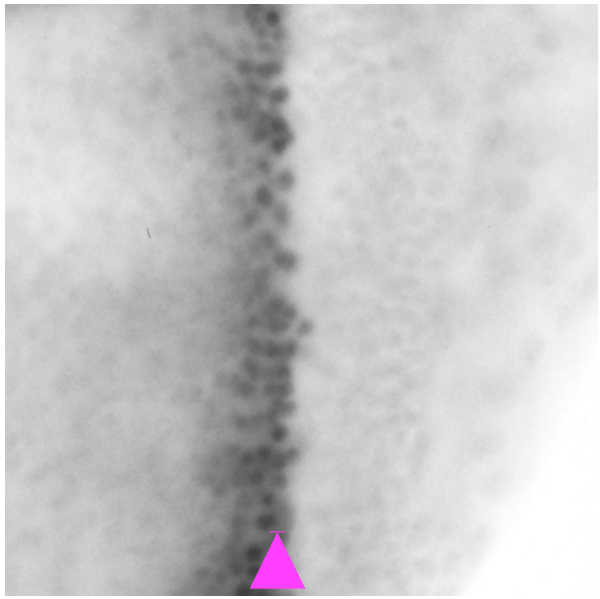
Notch has most effect on the maintenance of *ato* expression

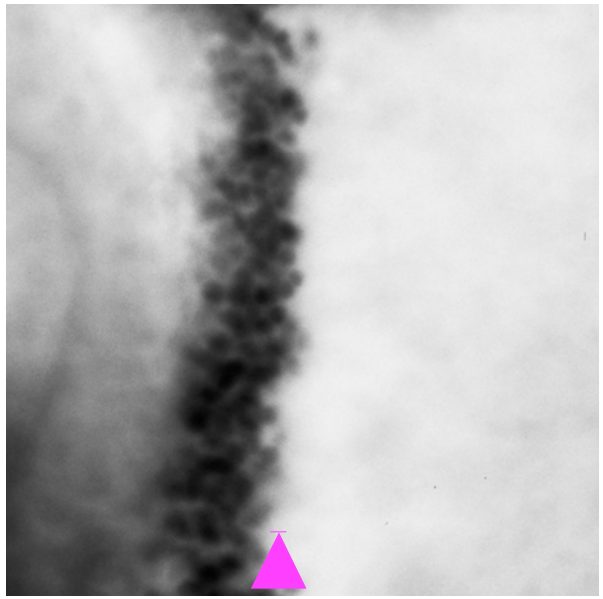
wild type

*ato*1/*ato*1

N{act}







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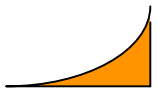
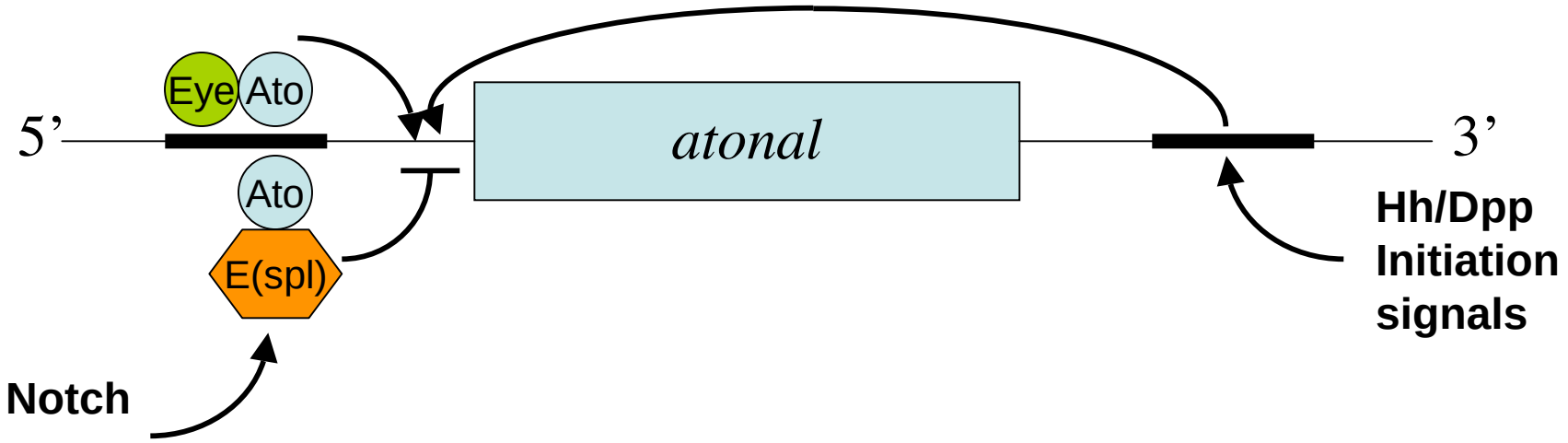


Baker, NE, Yu, S-Y, & Han, D *Curr Biol* **6** 1290-1301 (1996)

Scheme for progressive atonal regulation during R8 determination



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

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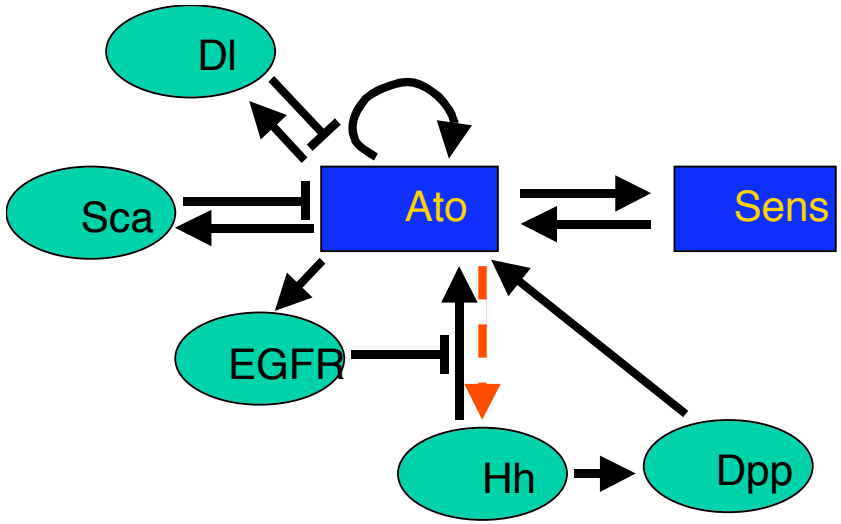

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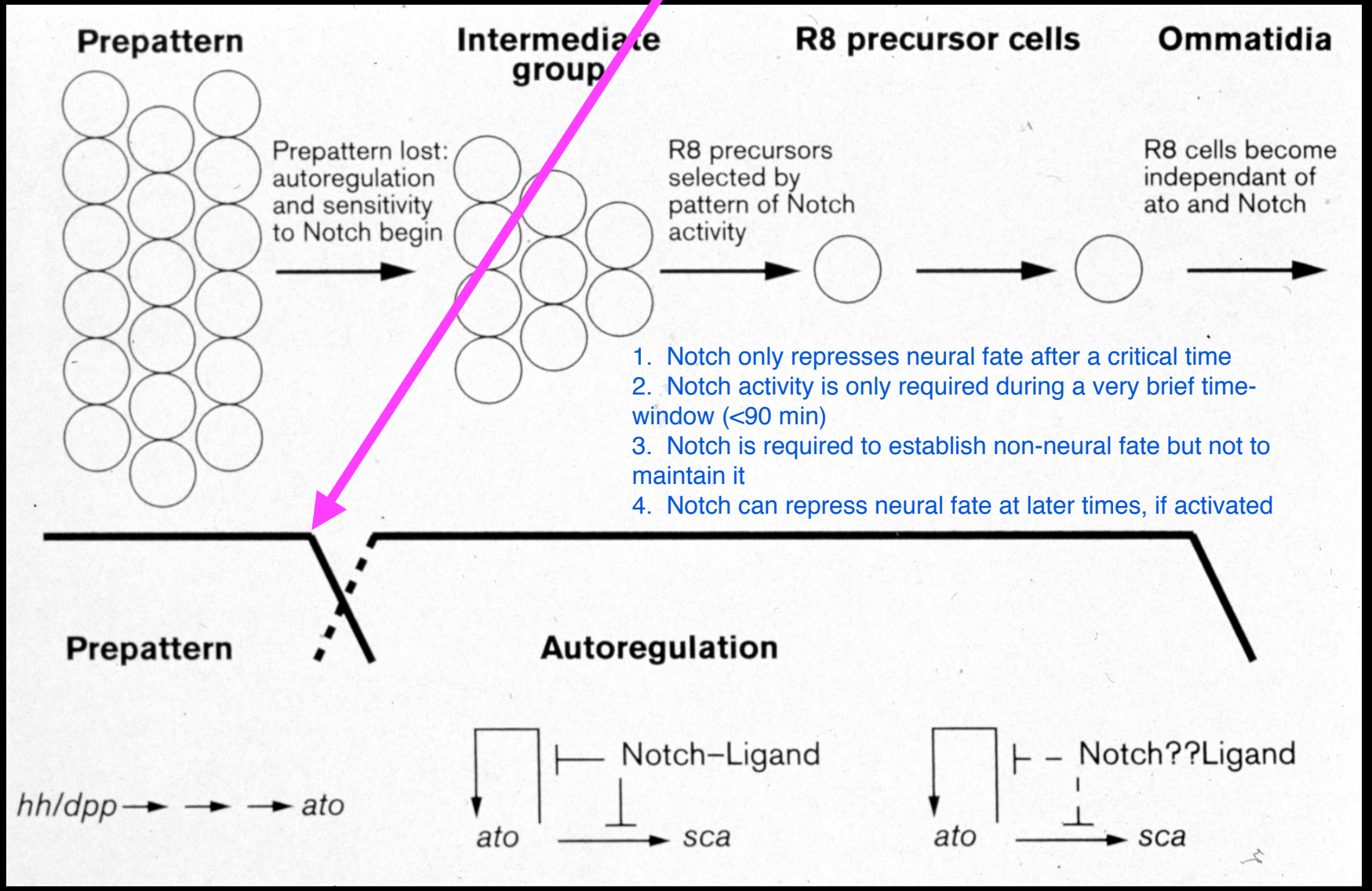
Why does Hh not keep turning *atonal* on?



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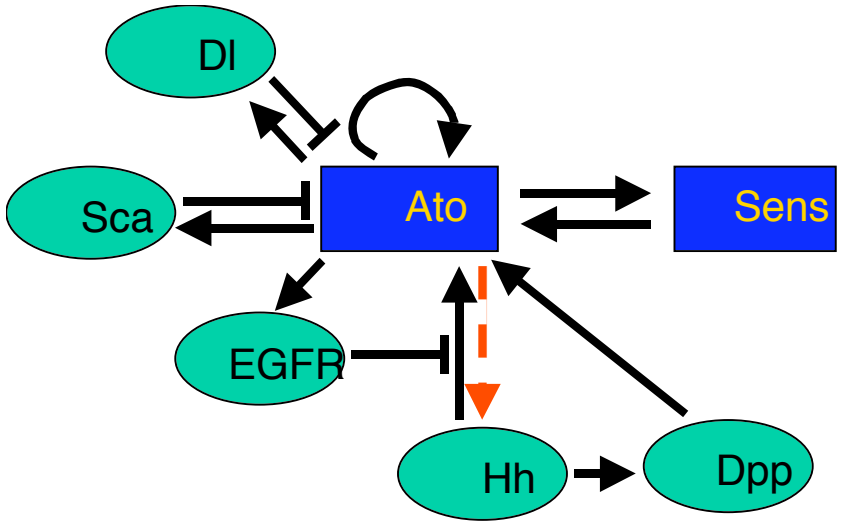

Figure 2a **Some genetic interactions controlling the R8 markers *ato* and *sens*. Pointed arrows, activation, blunt arrows, repression; the red dotted arrow indicates particularly indirect and delayed activation (see text). Blue boxes, transcription factors; green ellipses, intercellular signaling molecules. Note the presence of 3 different negative feedback loops. EGFR works by blocking Hh-mediated activation**cite Nick**. The precise mode of action of the other two inhibitors is not known, though there is some evidence that Dl acts later than Sca or EGFR.**

Nick Baker's talk:

1. The proneural process, Atonal, and eye development
2. Repression of Ato by Notch and Delta
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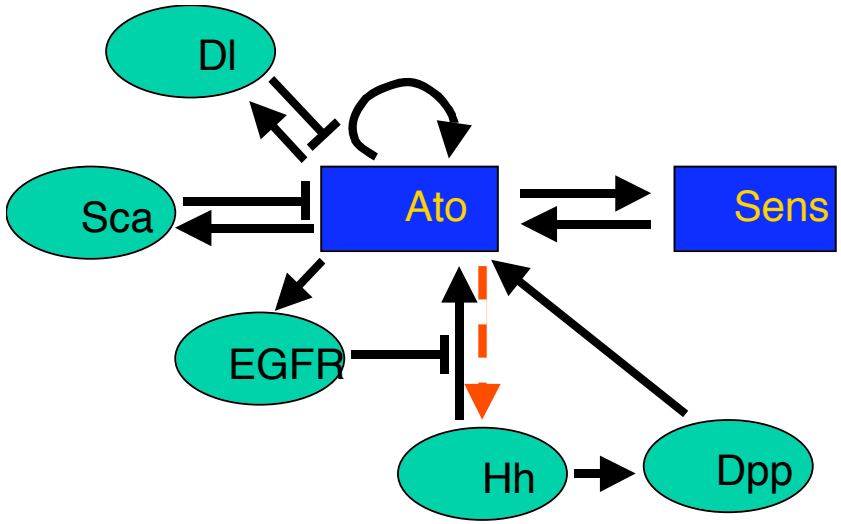

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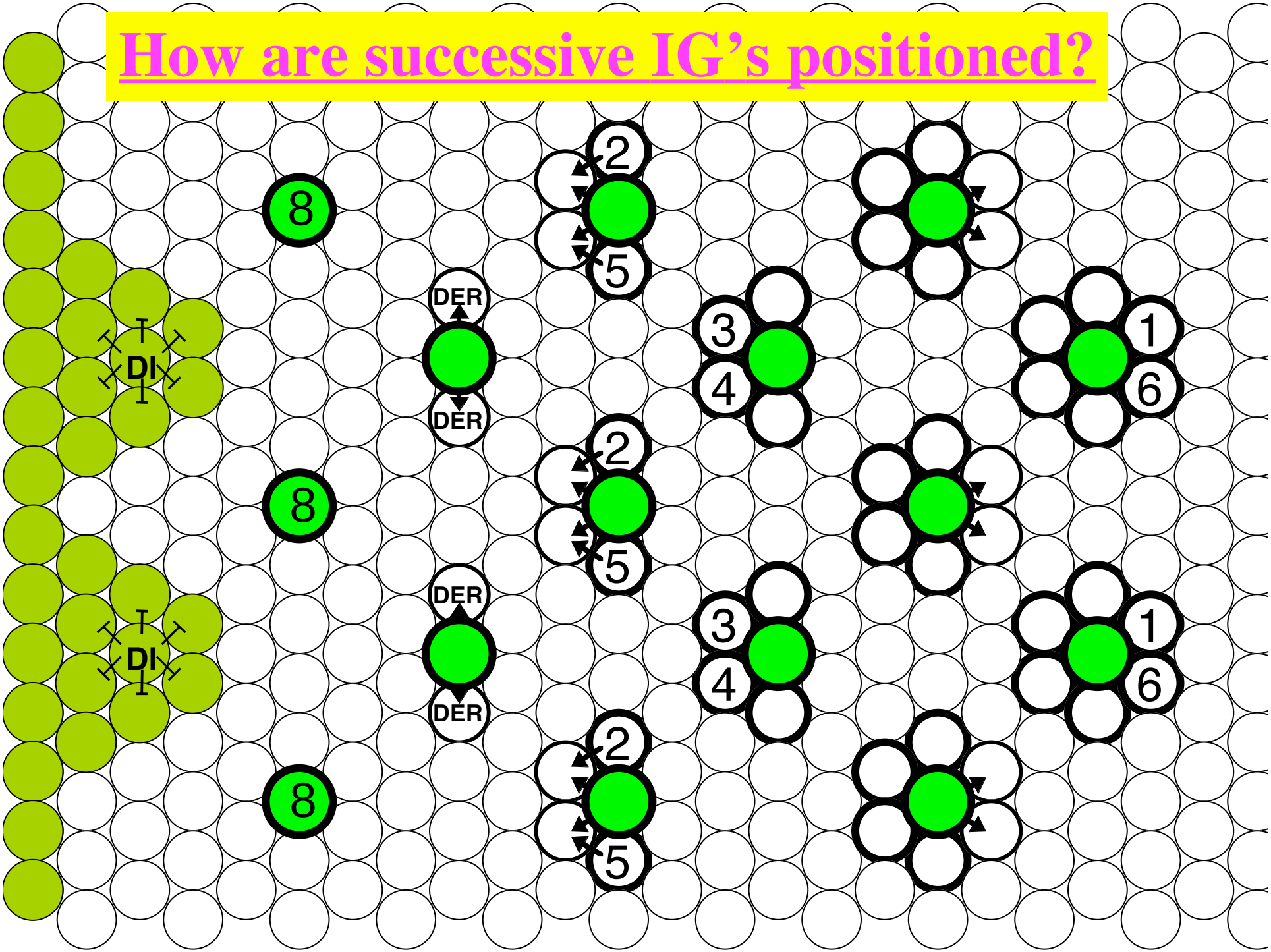
How are successive IG's positioned?

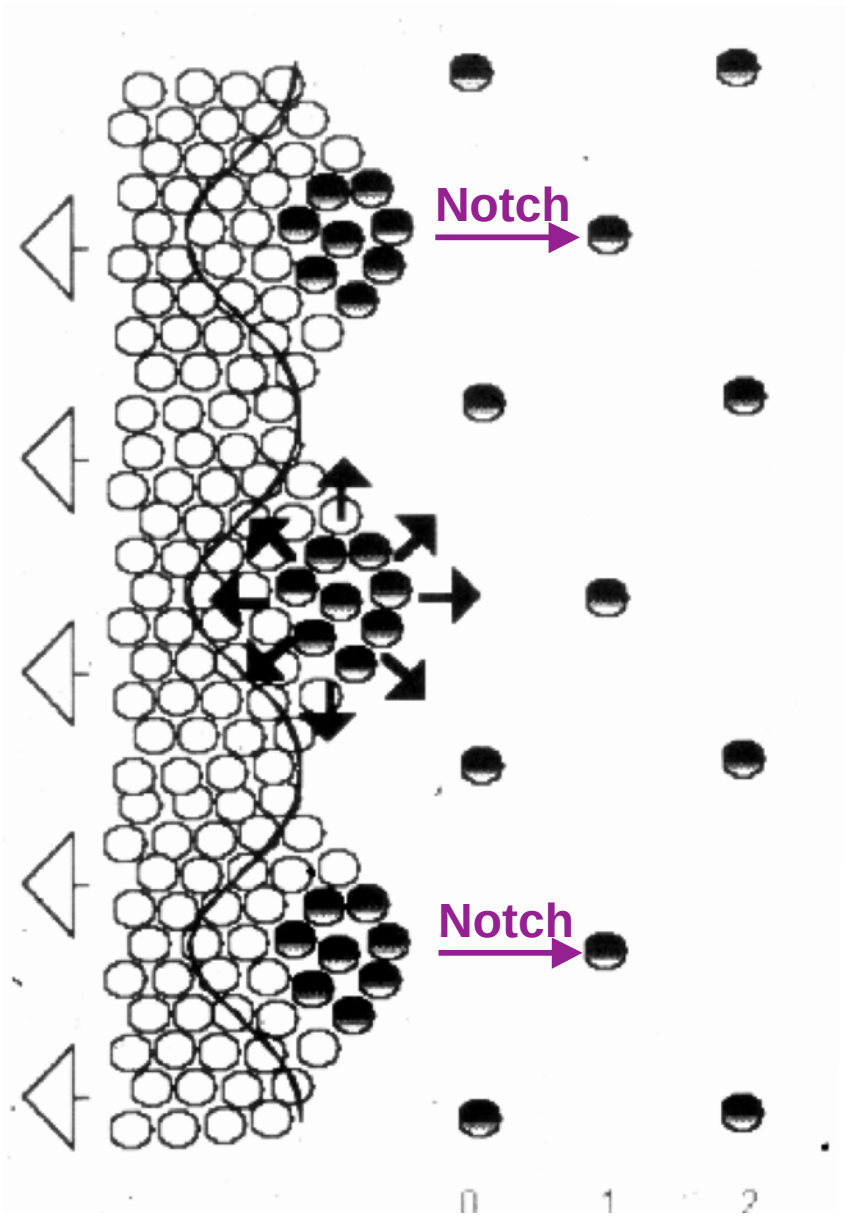


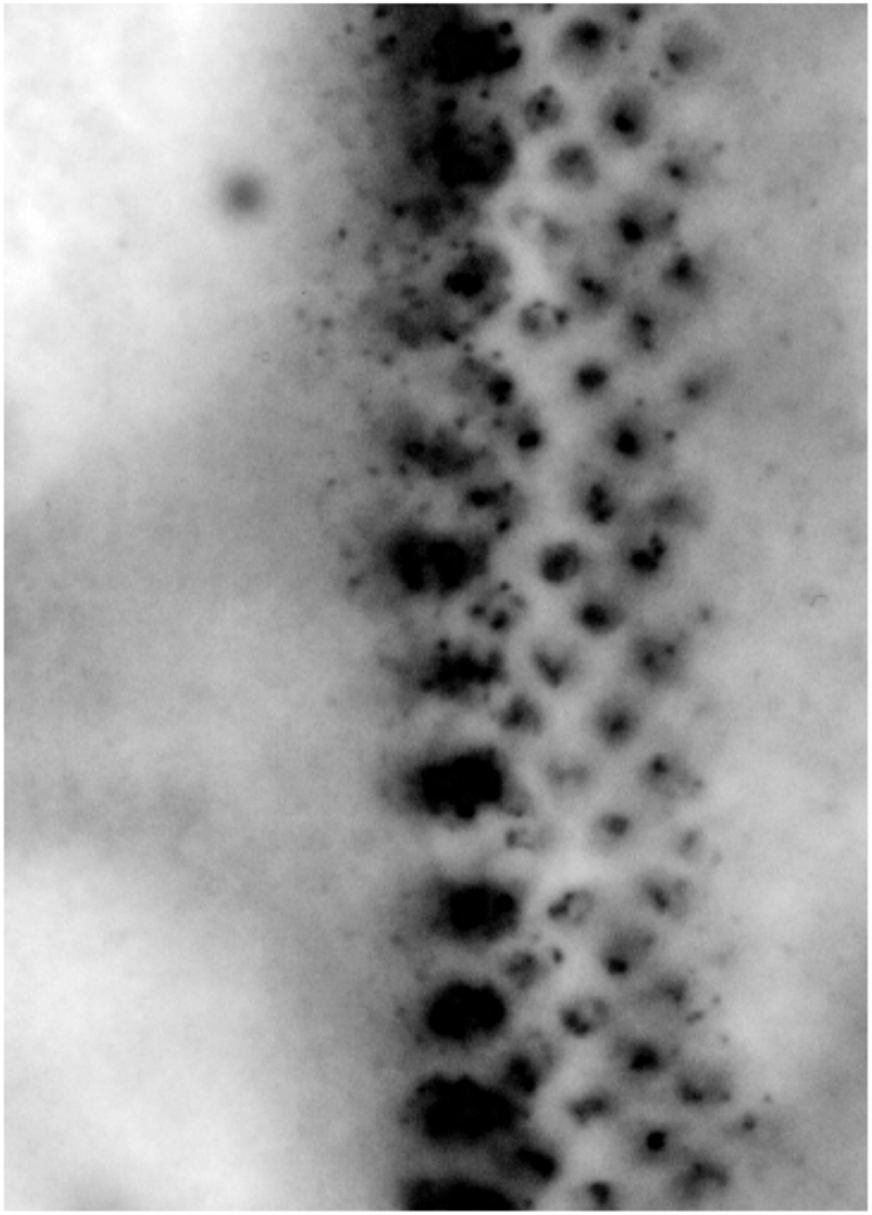
Experimental evidence for templating

1. Phenotype for *sca* mutant
2. Longterm effect of transient loss of Notch
3. Longterm effect of transient activated Notch

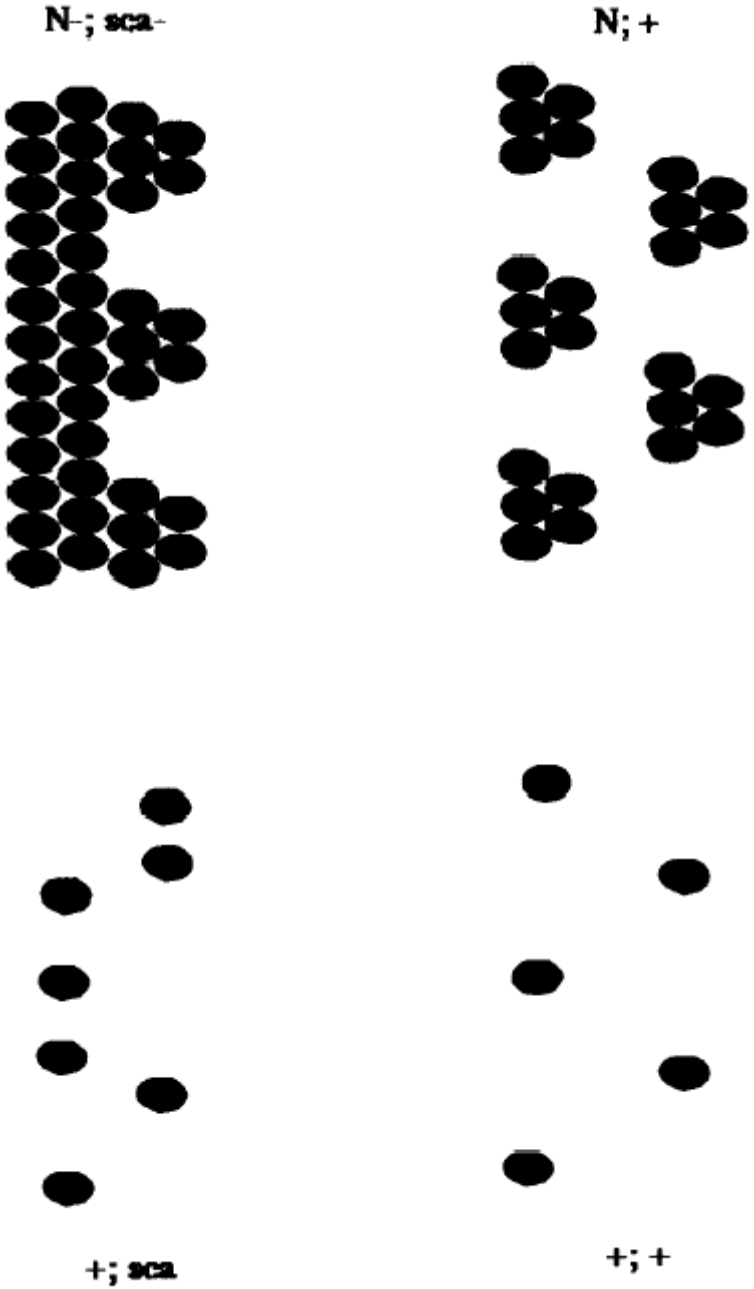
Baker et al *Science* **250** 1370-7 (1990); Baker, NE, Yu, S-Y, & Han, D *Curr Biol* **6** 1290-1301 (1996)

Secreted Scabrous protein is dynamically expressed during R8 specification



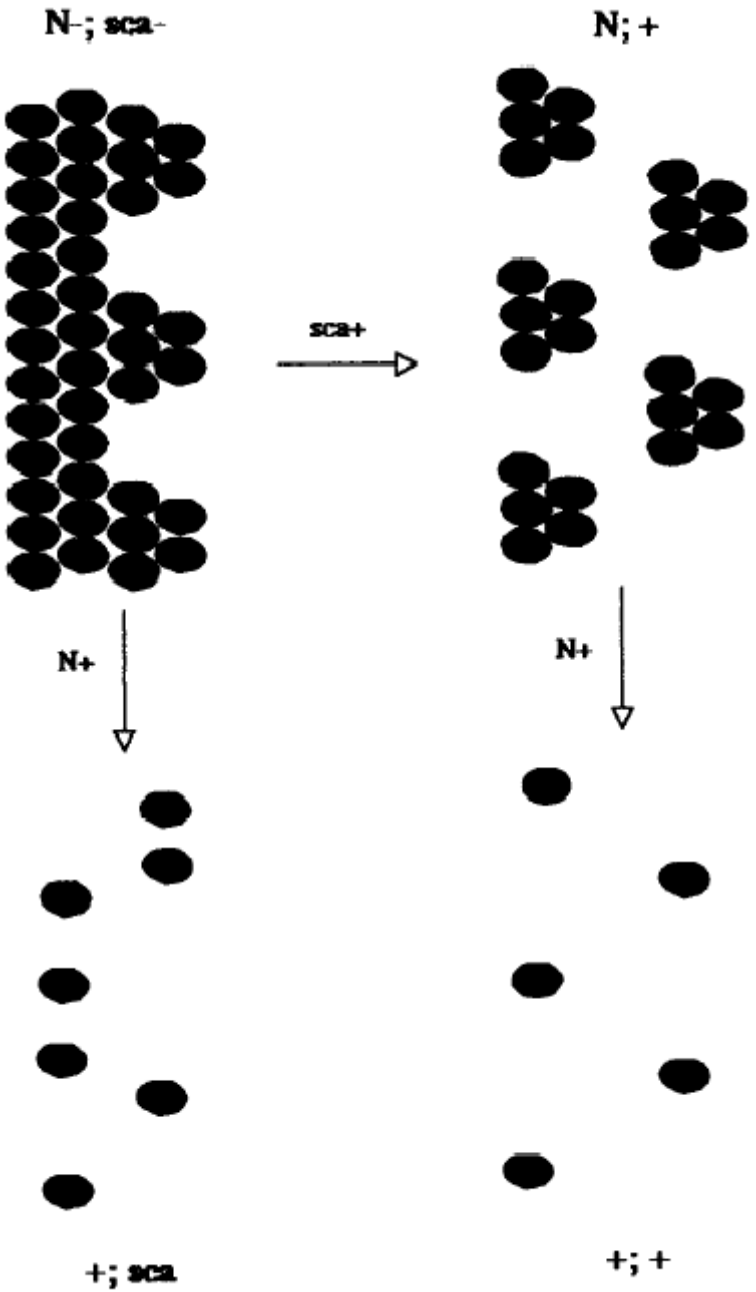


Baker et al *Science* **250** 1370-7 (1990); Mlodzik et al *Genes Dev* **4** 1848-61 (1990)



Two-step model for making an R8-cell array

Baker & Zitron
Mech Dev **49** 173-89 (1995)



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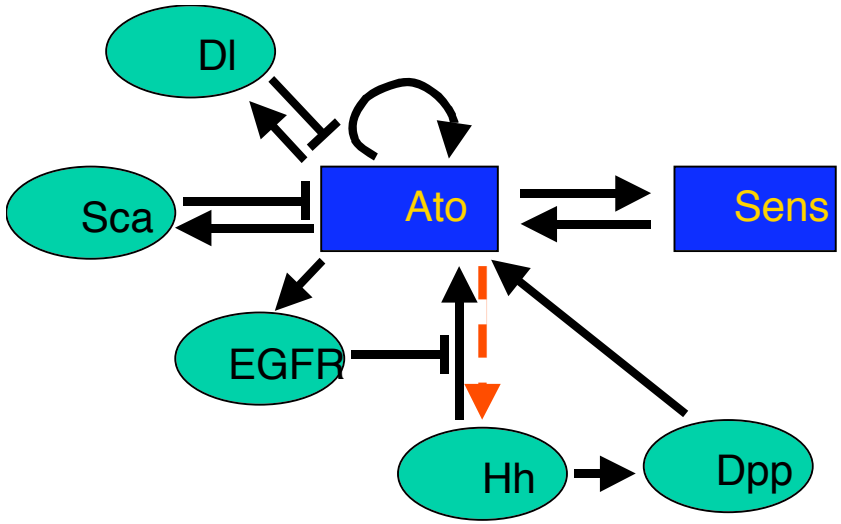

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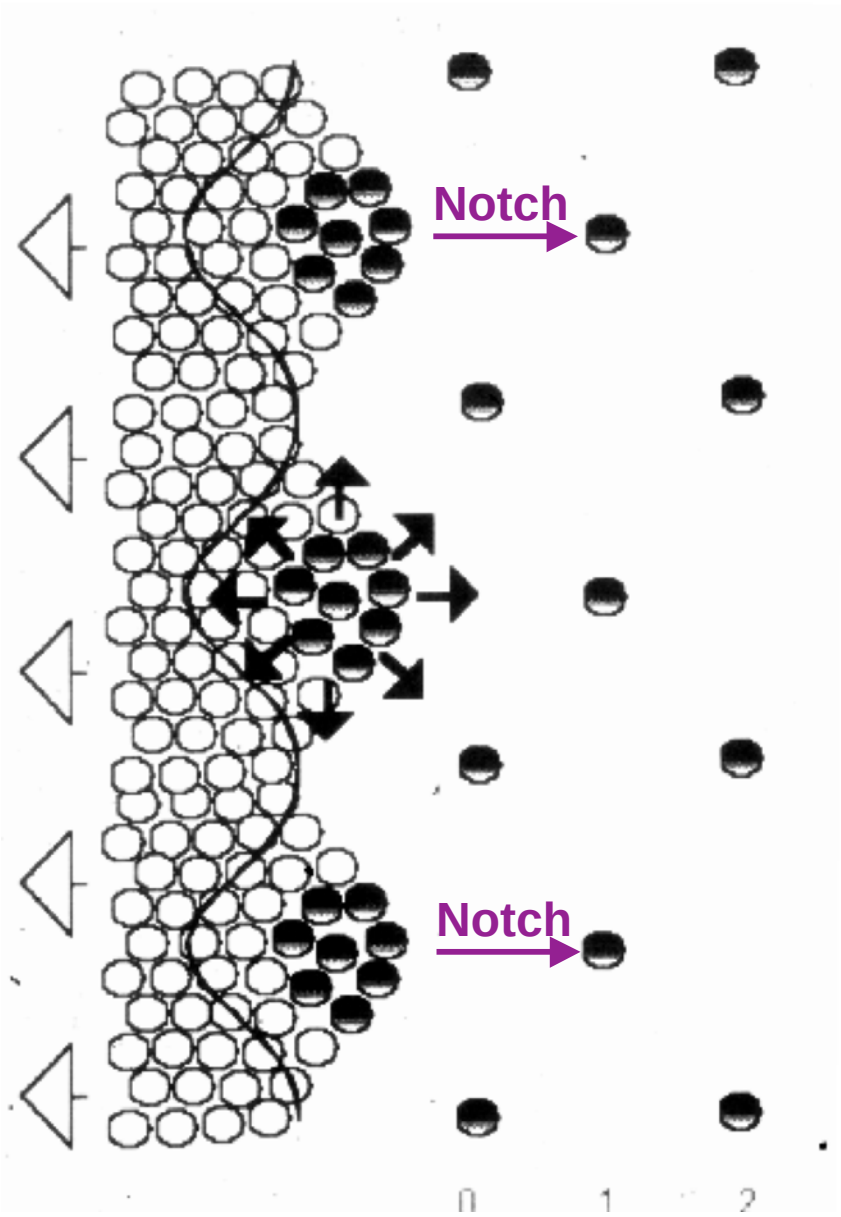
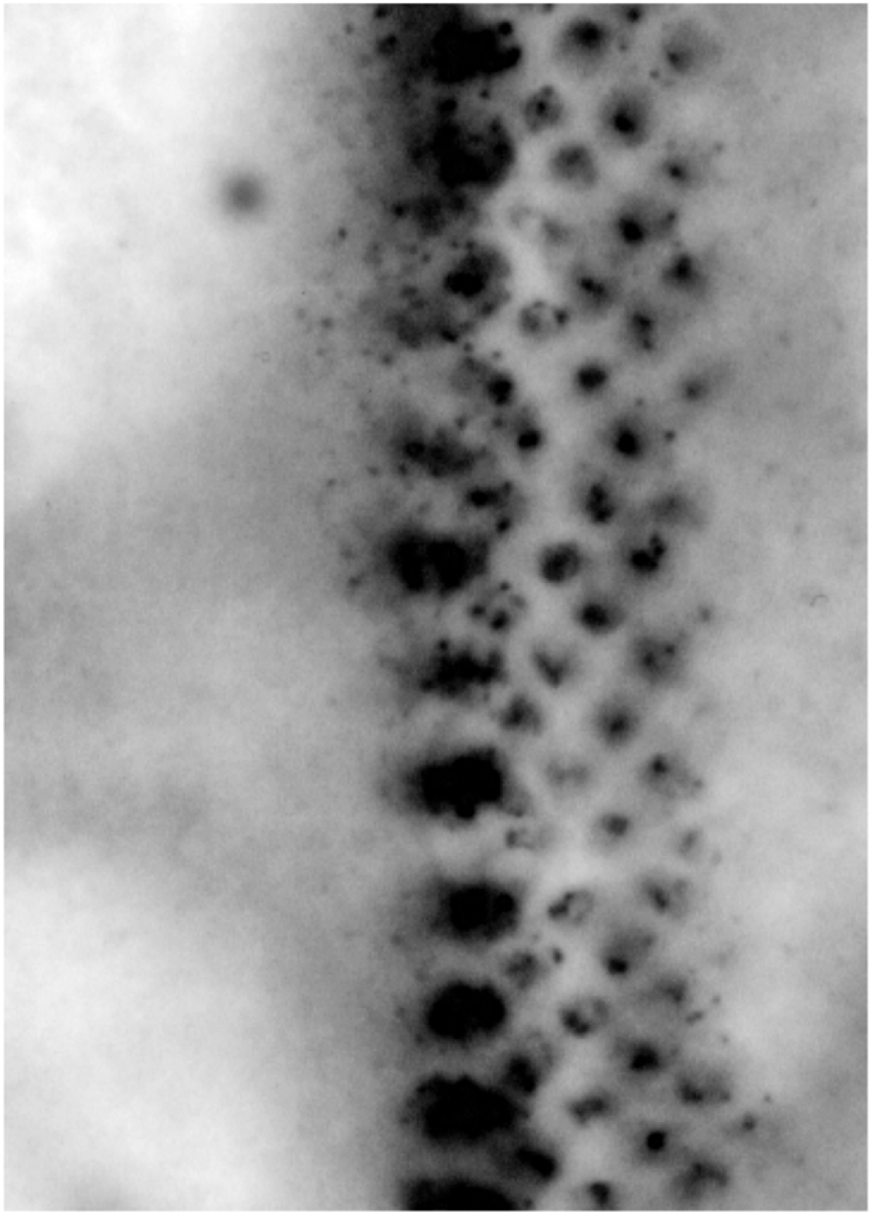
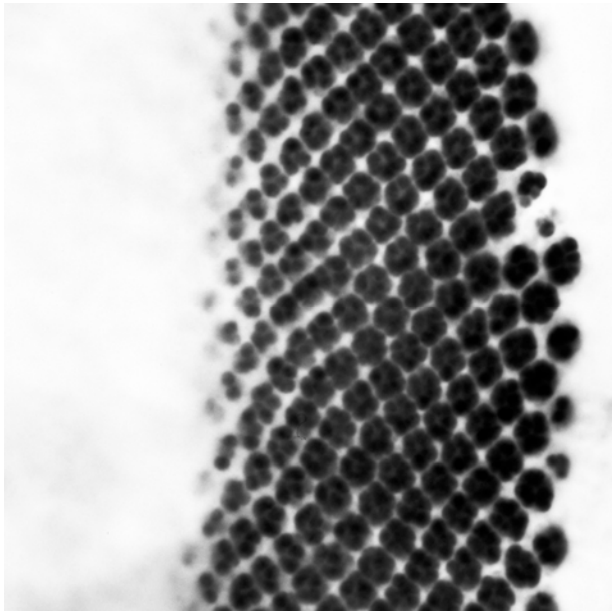
Does Scabrous protein space the intermediate groups?



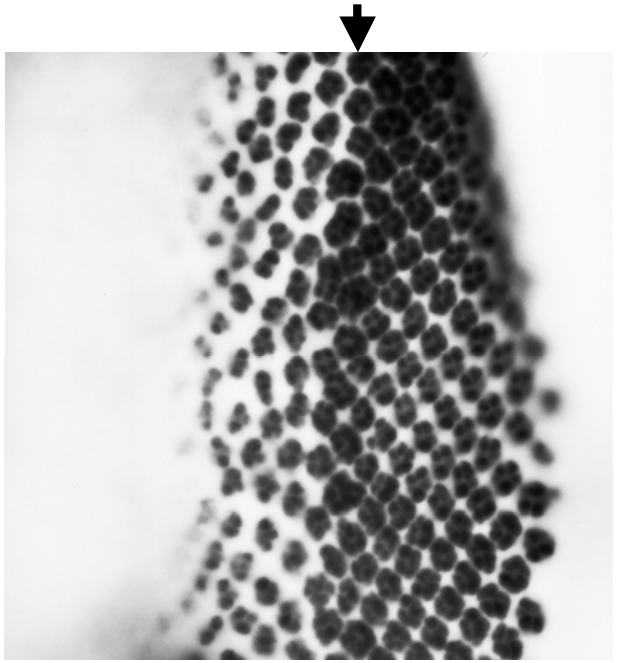


Hypothesis

abnormal templating initiates the persistent effects of perturbation



Wild type



N[ts]

N. Baker, unpublished

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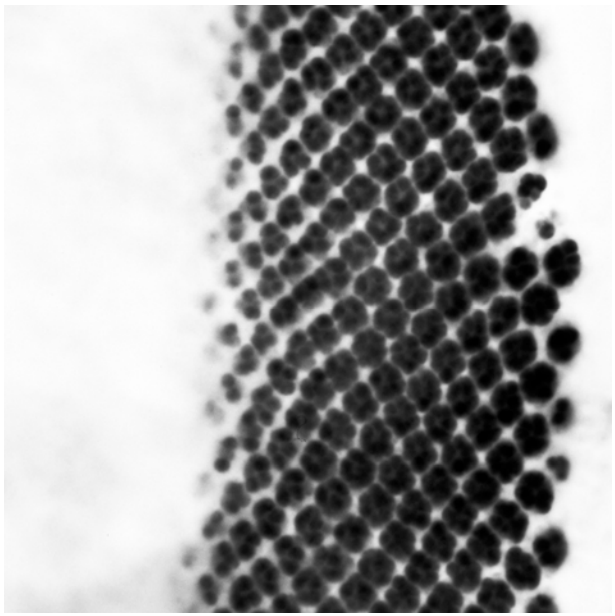
Question: how much template information is transmitted by Scabrous?



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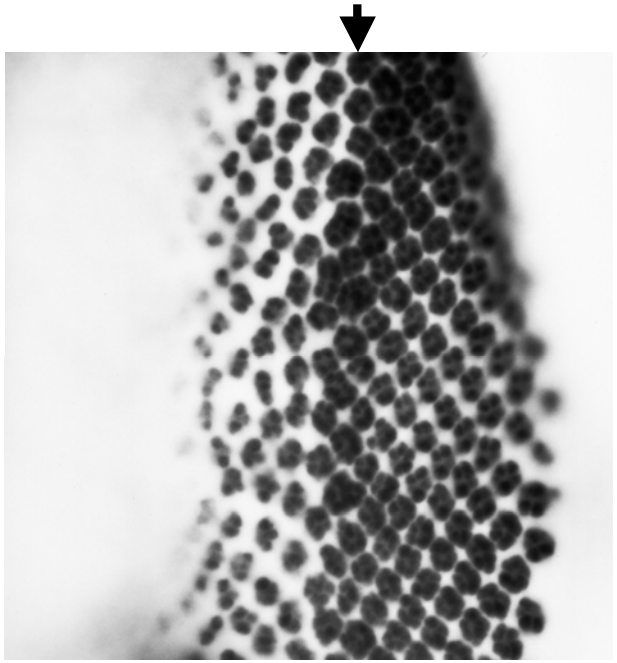

N[ts]

N. Baker, unpublished

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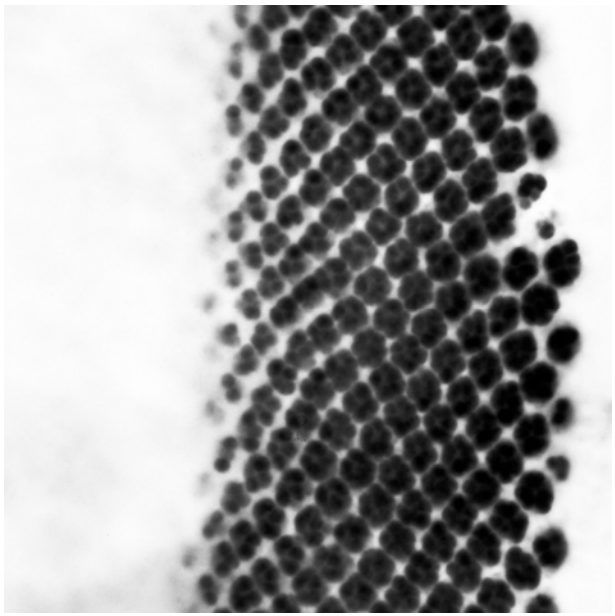
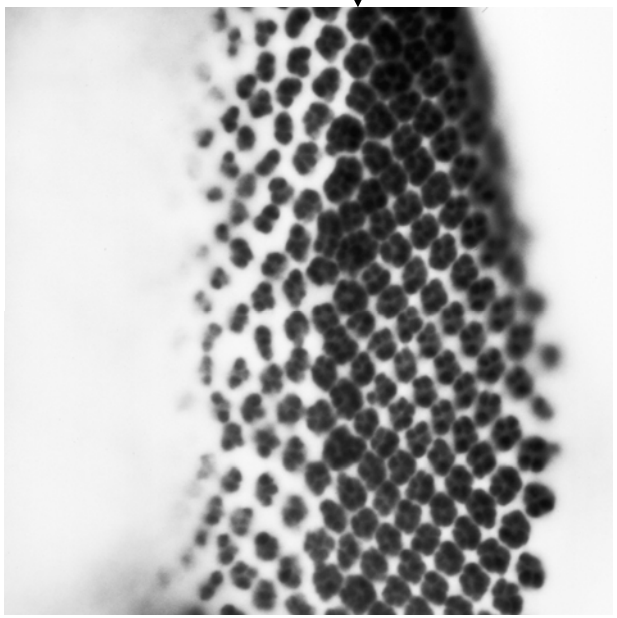
Expect that the *sca* gene might be required for the persistent effects





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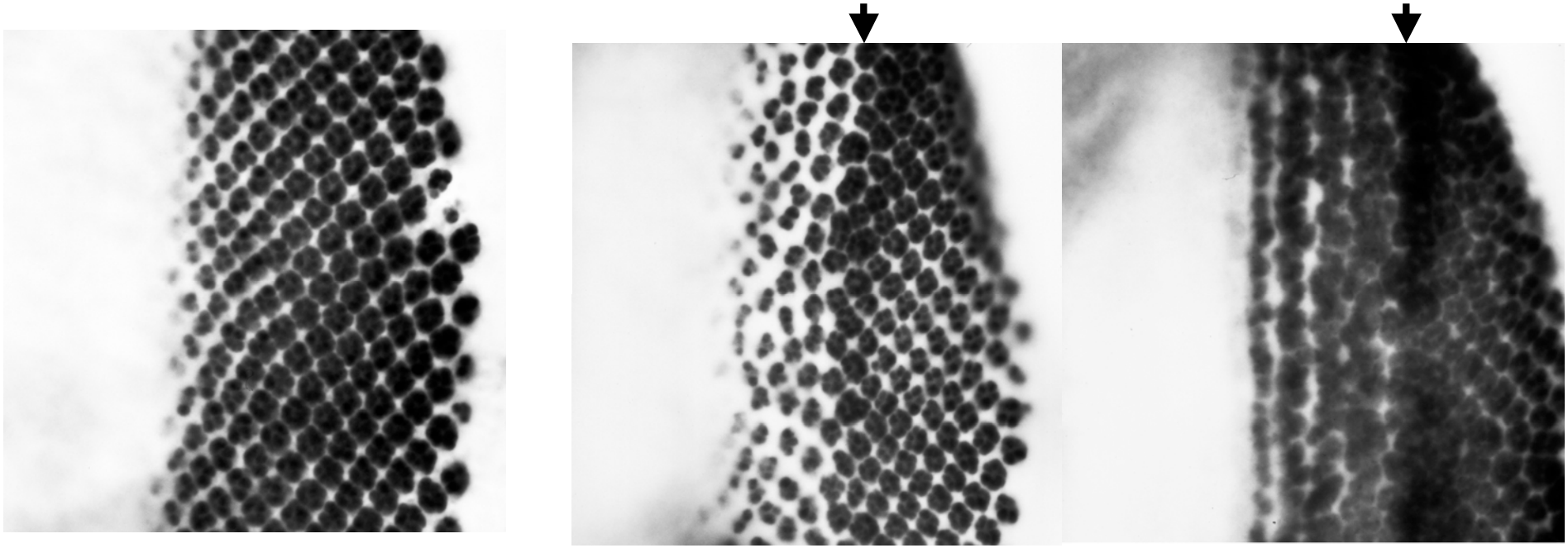
N. Baker, unpublished

Surprise!

A *scabrous* mutant disc switches to a striped pattern when perturbed



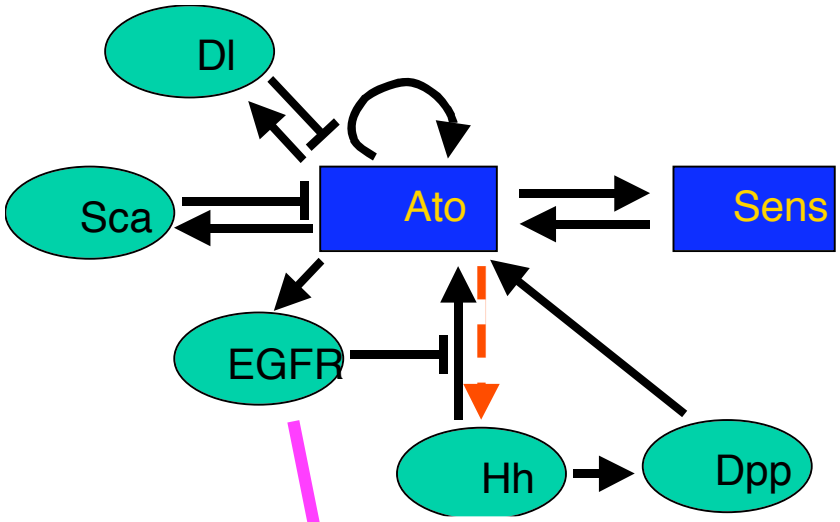
Wild type

N[ts]

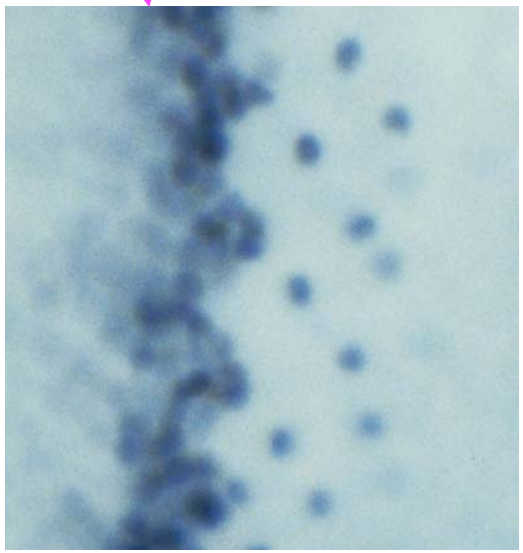
N[ts]
in sca

N. Baker, unpublished

Can a model of normal development predict the perturbed *scabrous* pattern?



1. **This spacing pattern is a modified form of a stripe pattern**
2. **The cellularity of the epithelium contributes to the patterning**
3. **Model revises the proneural process**



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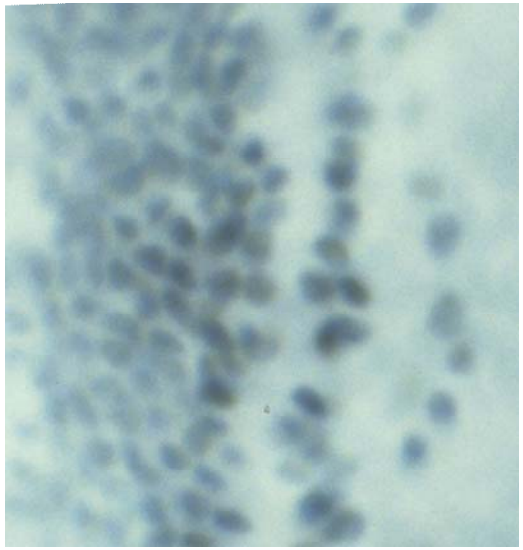

Albert Einstein College of Medicine, July 2006

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