Elementary networks for pattern formation in early development

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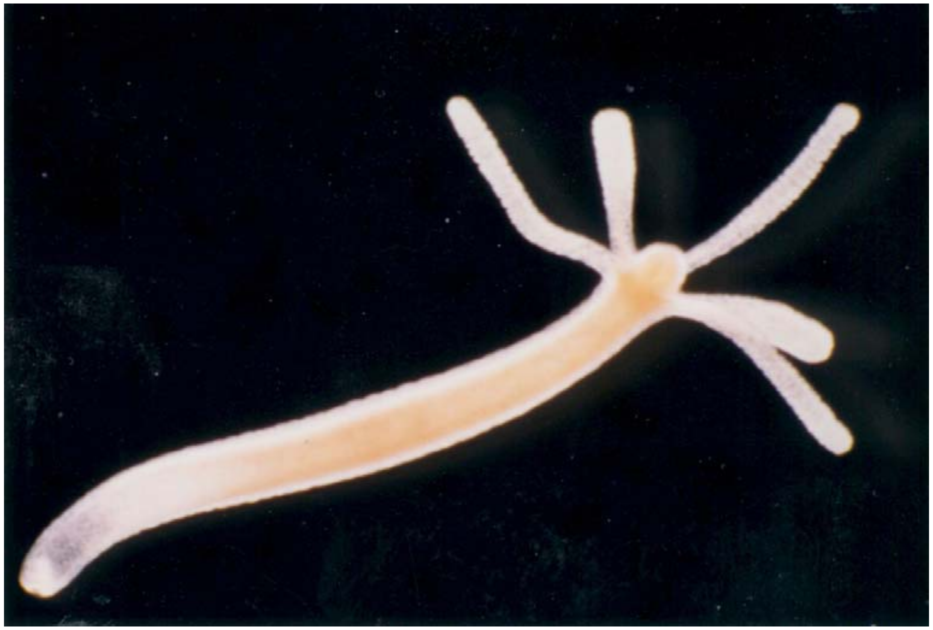
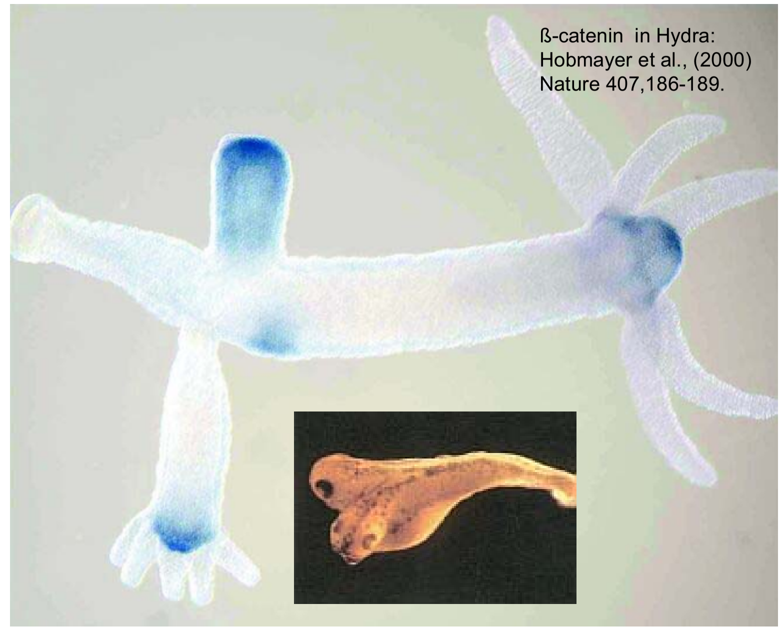
Complementary approach:

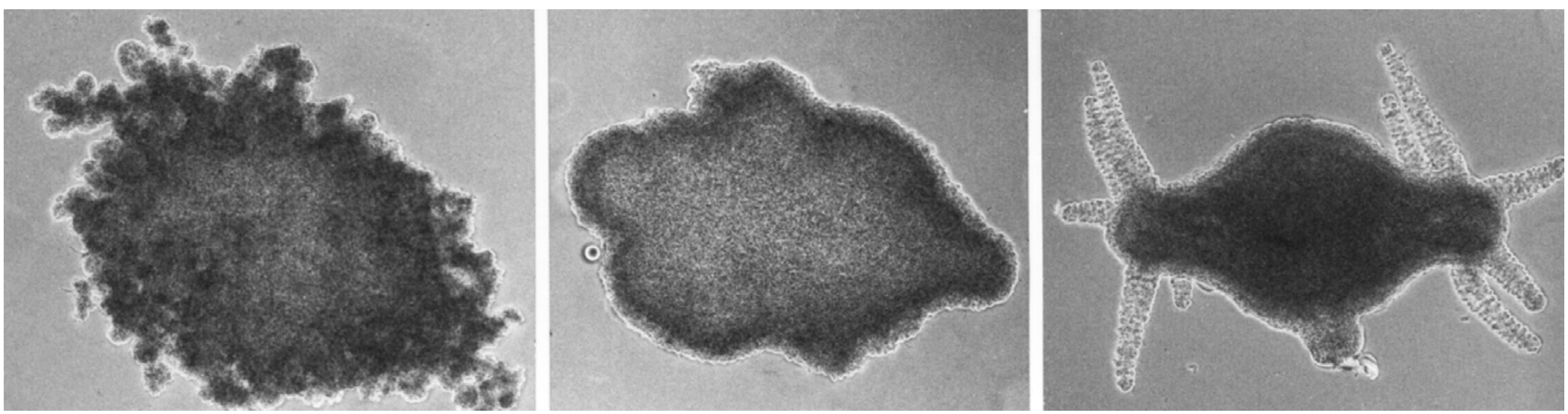
Minimal models: what is required at least

An ancestral axis: pattern formation in hydra



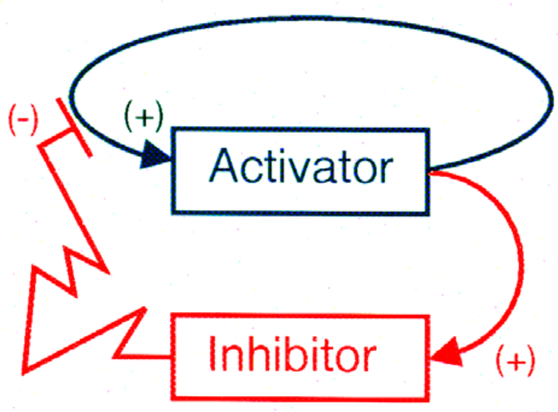


ß-catenin in Hydra:
Hobmayer et al., (2000)
Nature 407,186-189.



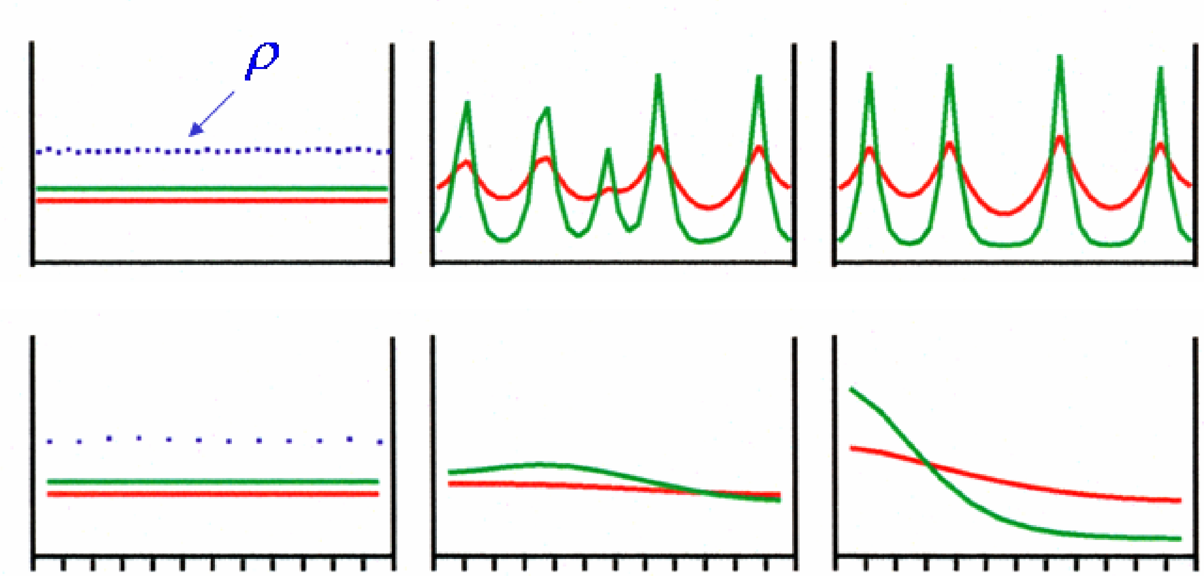
Gierer A., Berking S., Bode H., David C.N., Flick K., Hansmann G., Schaller H. and Trenkner E. (1972). Regeneration of hydra from reaggregated cells. Nature New Biology 239, 98-101. Figure: Holstein-group

Pattern formation requires local self-enhancement and long range inhibition (with Alfred Gierer, 1972)



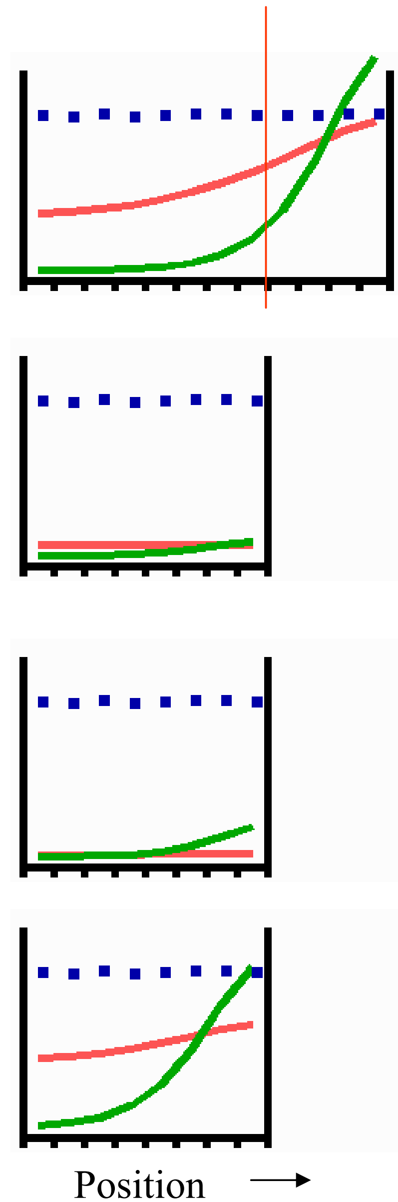
$$\frac{\partial a}{\partial t} = \rho \frac{a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_a$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} + \rho_h$$

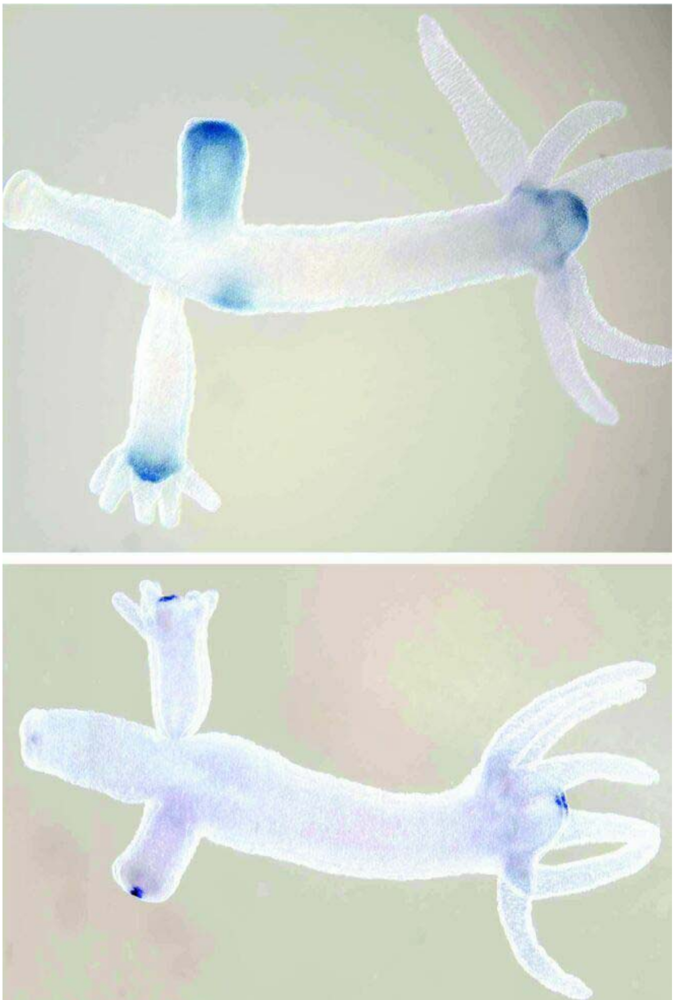


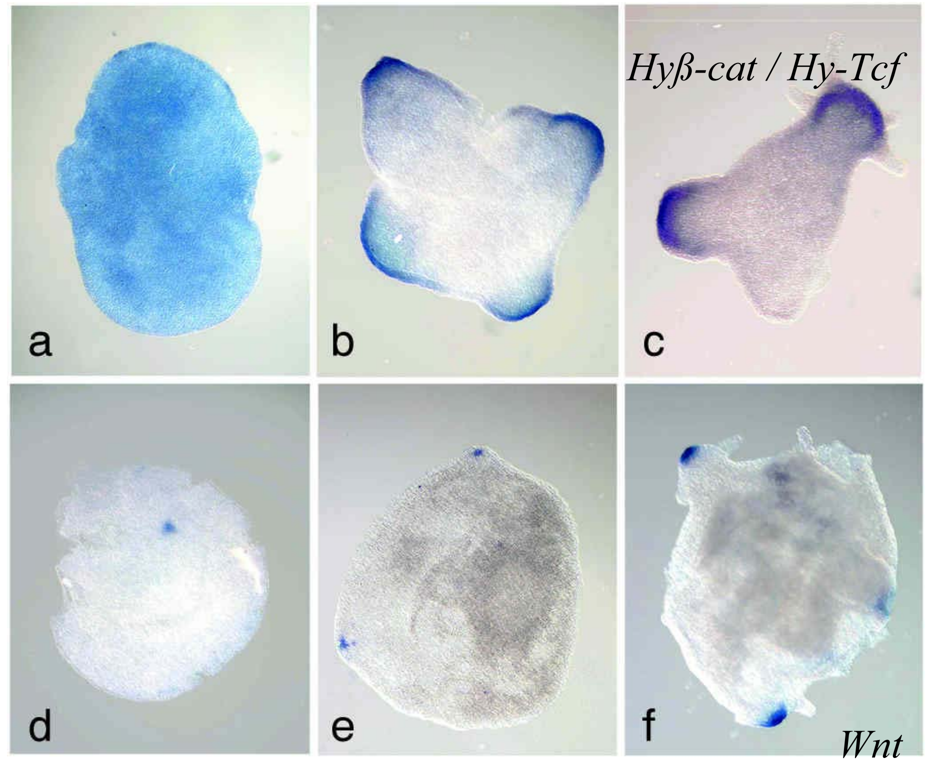
Kybernetik 12, 30-39 (1972) ;
(on our web-site)

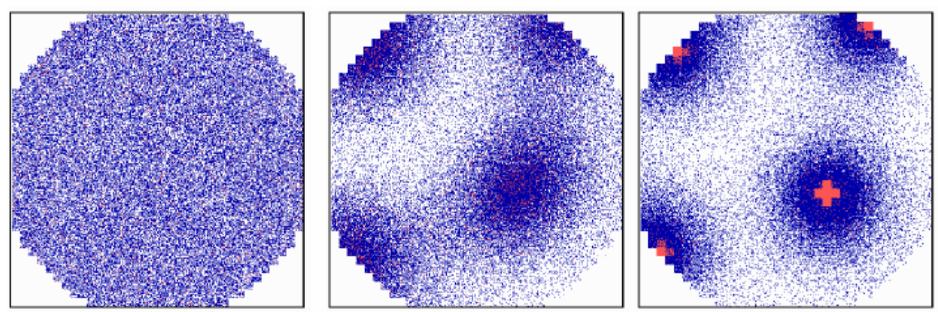
Regeneration of a graded distribution: inhibitor decays, a new activation is triggered



HyTcf and *HyWnt* in aggregates

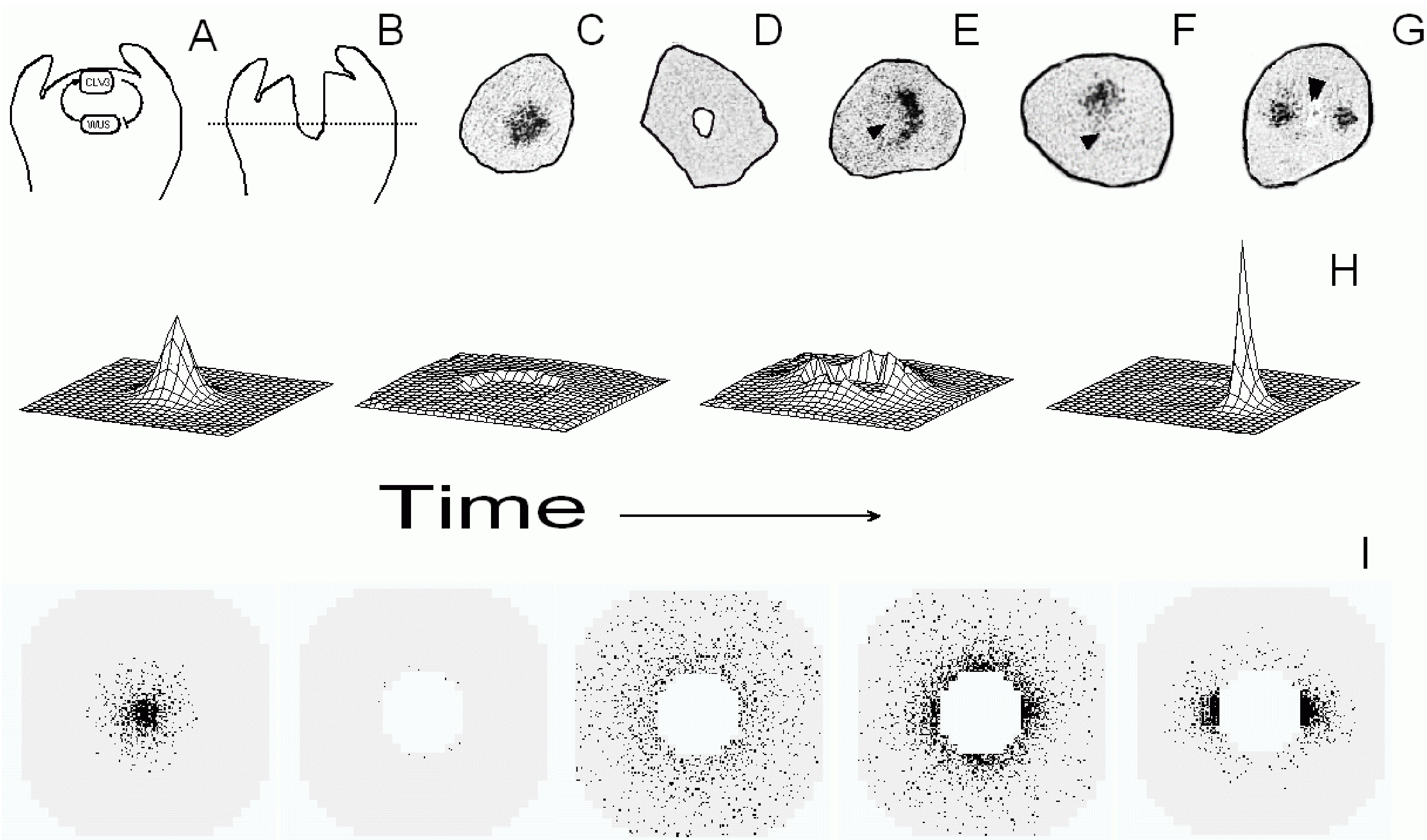






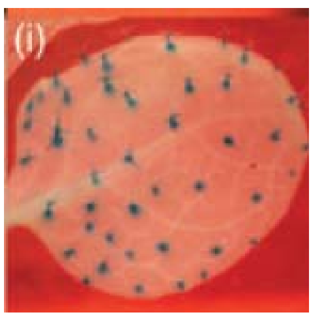
Hobmayer et al.: 2000
Nature 407, 186-189 (2000)

After laser ablation of the plant organizing region (Wuschel) one or two organizing regions regenerate



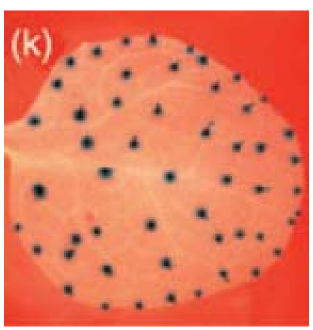
A-G after Reinhardt et al., (2003) Development 132, 15-26

…If the range of the inhibitor is smaller than the field size: periodic patterns



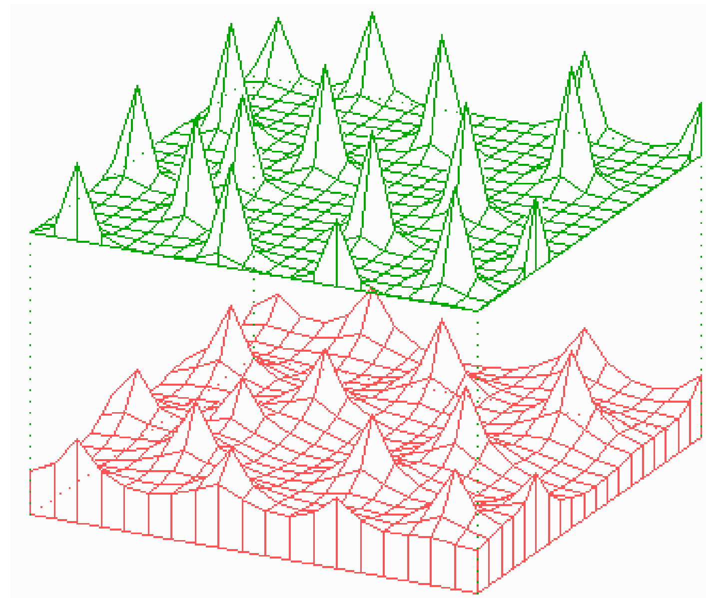
Prediction: Activator and Inhibitor are produced at the same position

An aktivator *(GL2)*



an Inhibitor *(try)*

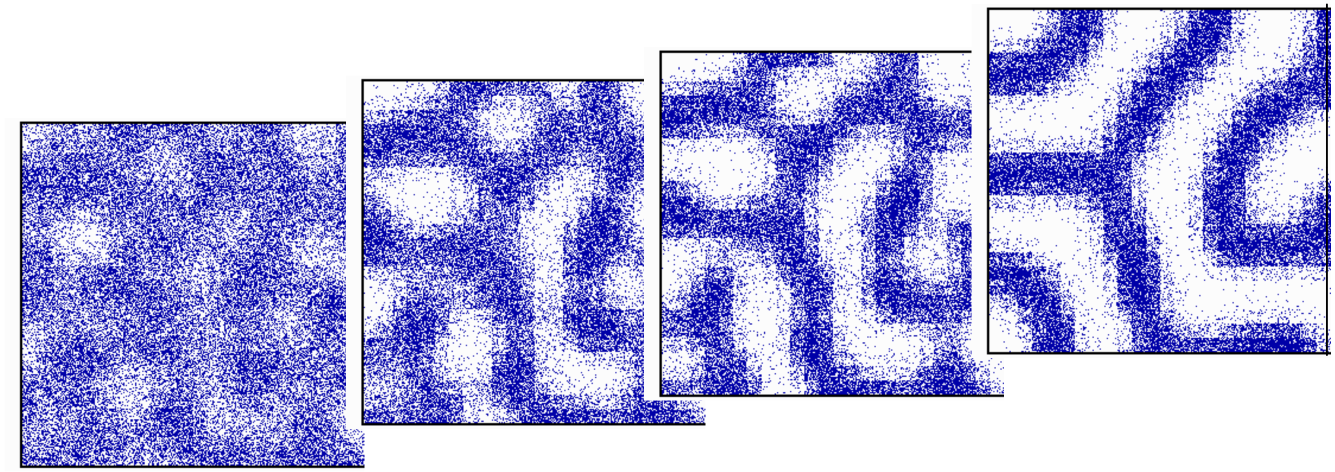
From: Esch et al, Plant J. 40, 860, 2004

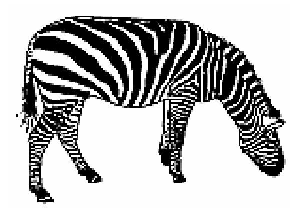


$$\frac{\partial a}{\partial t} = \rho \frac{a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_a$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} + \rho_h$$

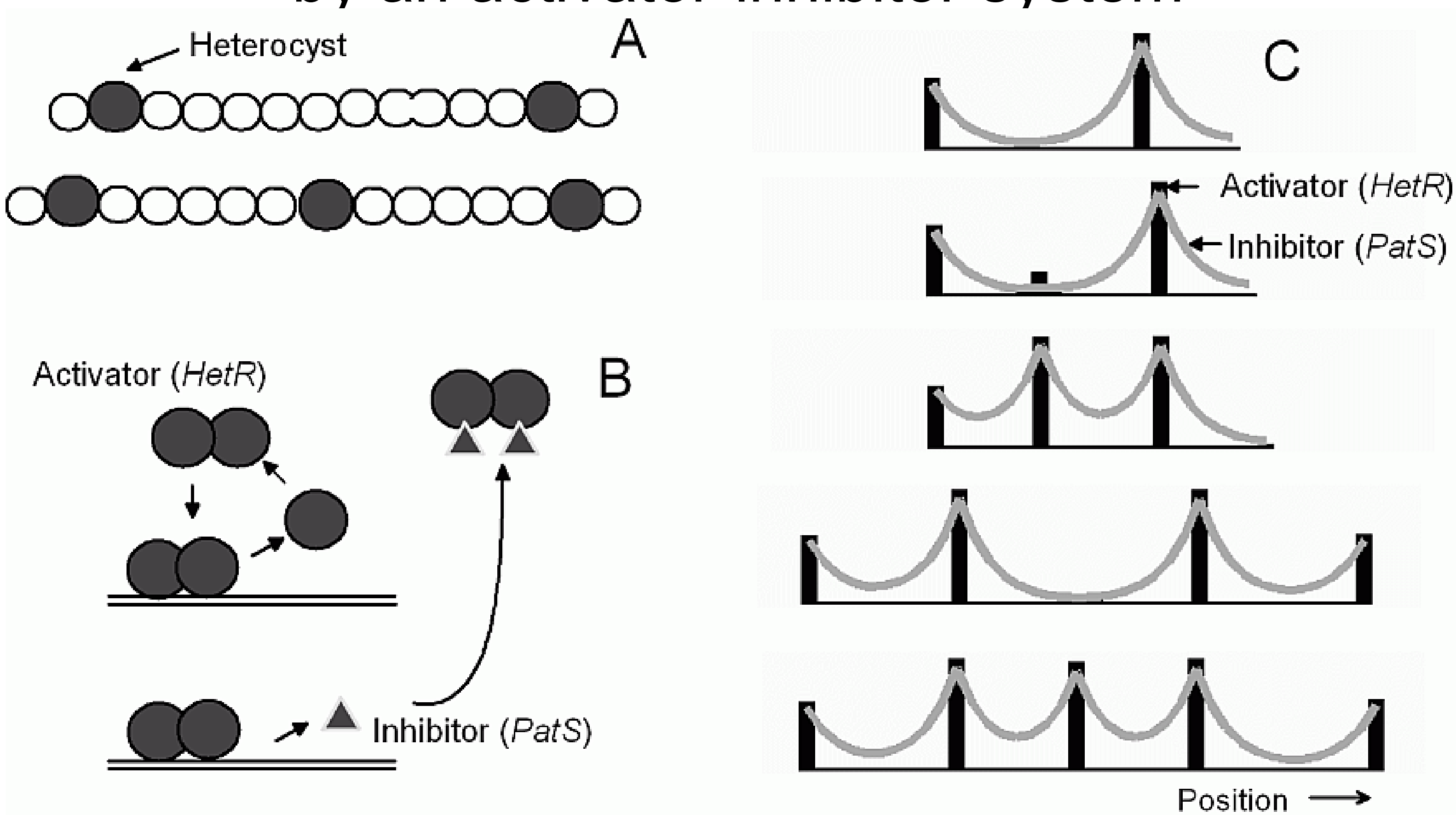
Saturation of the autocatalysis: stripe formation





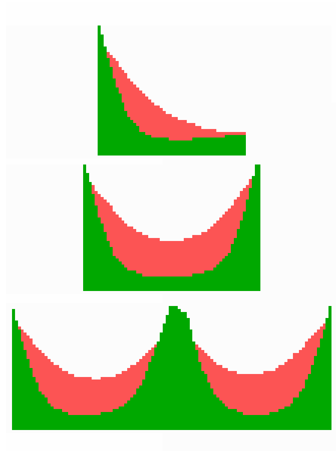
$$\frac{\partial a}{\partial t} = \frac{s\,a^2}{b\,(1+s_a\,a^2)} - \ldots.$$

Heterocyst formation in Anabaena: new Nitrogen-fixating cells are initiated during growth by an activator-inhibitor system



Activator: HetR, a DNA-binding molecules that forms dimers (Nonlinearity!(
Inhibitor: PatS, a 13-17 AA polypeptide, binds to HetR, abolishes its DNA binding

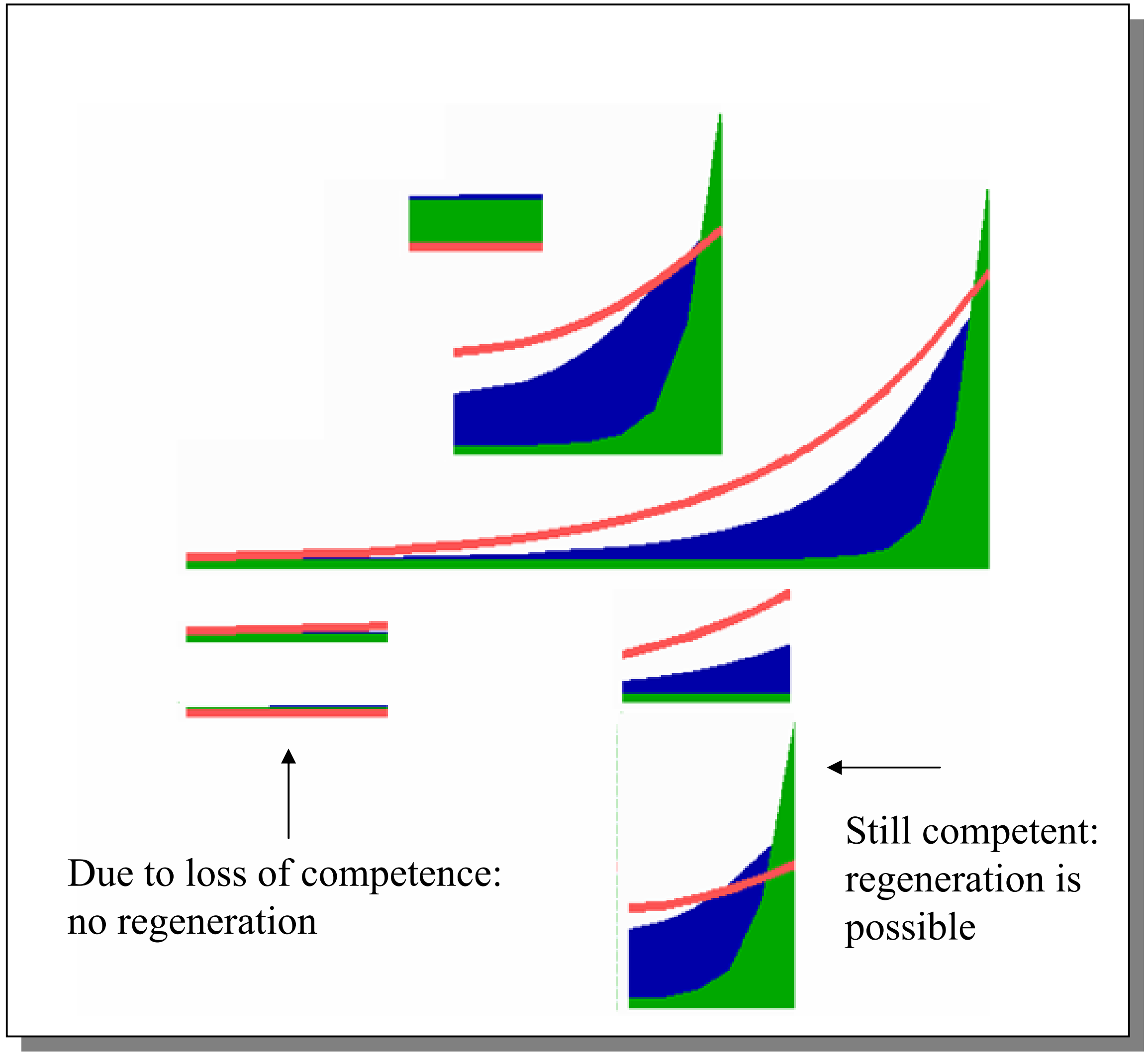
The wavelength problem: how to avoid multiple peaks during outgrowth?



$$\frac{\partial a}{\partial t} = \frac{\rho a^2}{h} - \ldots$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \ldots$$

$$\frac{\partial \rho}{\partial t} = c a - \gamma \rho \ldots$$



Solution: feedback of the organizer on the competence

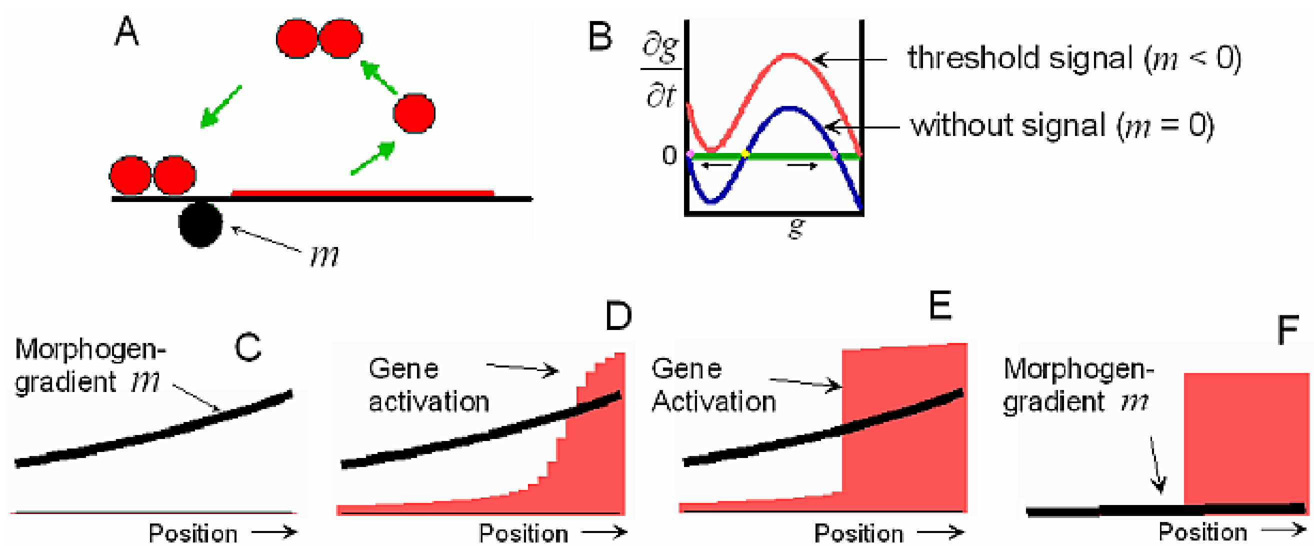
Thus:

Pattern formation requires local self-enhancement and long-range inhibition

Next:

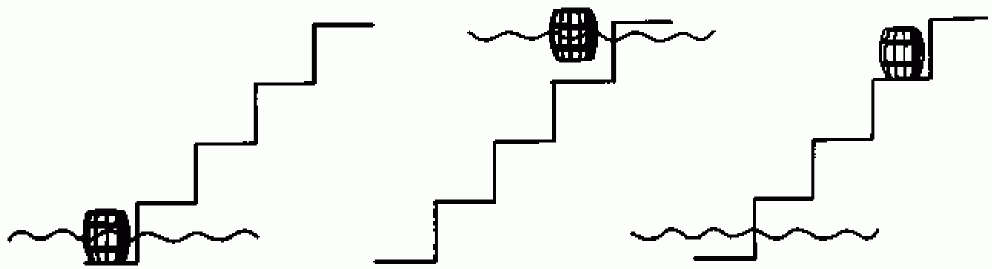
How to achieve stable gene activation?

Gene activation requires autoregulatory genes



Differentiation 6, 117-123 (1976)

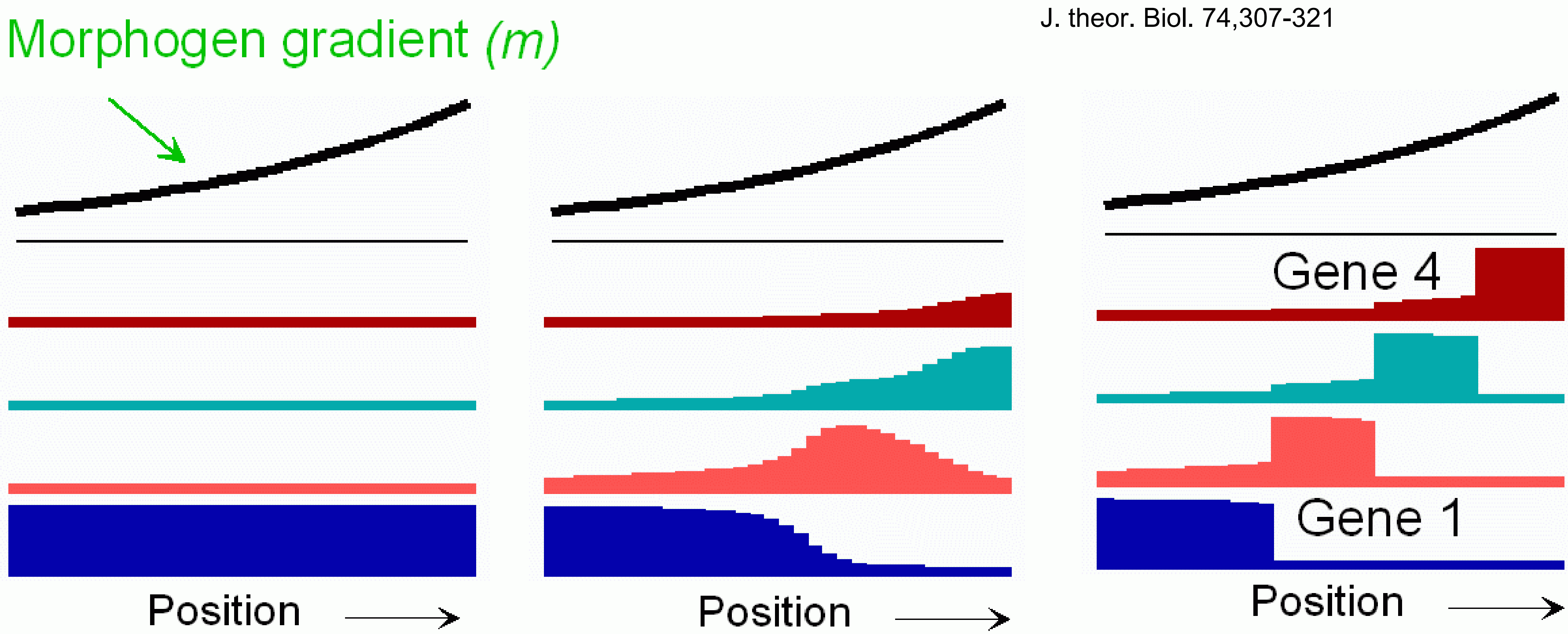
Space-dependent activation of several genes by a morphogen gradient: step-wise promotion



$$\frac{\partial g_i}{\partial t} = \frac{c_i g_i^2 + b_i g_{i-1} m}{\sum_{i=1}^{n} c_i g_i^2} - r_i g_i$$

with $c_{i+1} > c_i$

J. theor. Biol. 74,307-321



Thus:

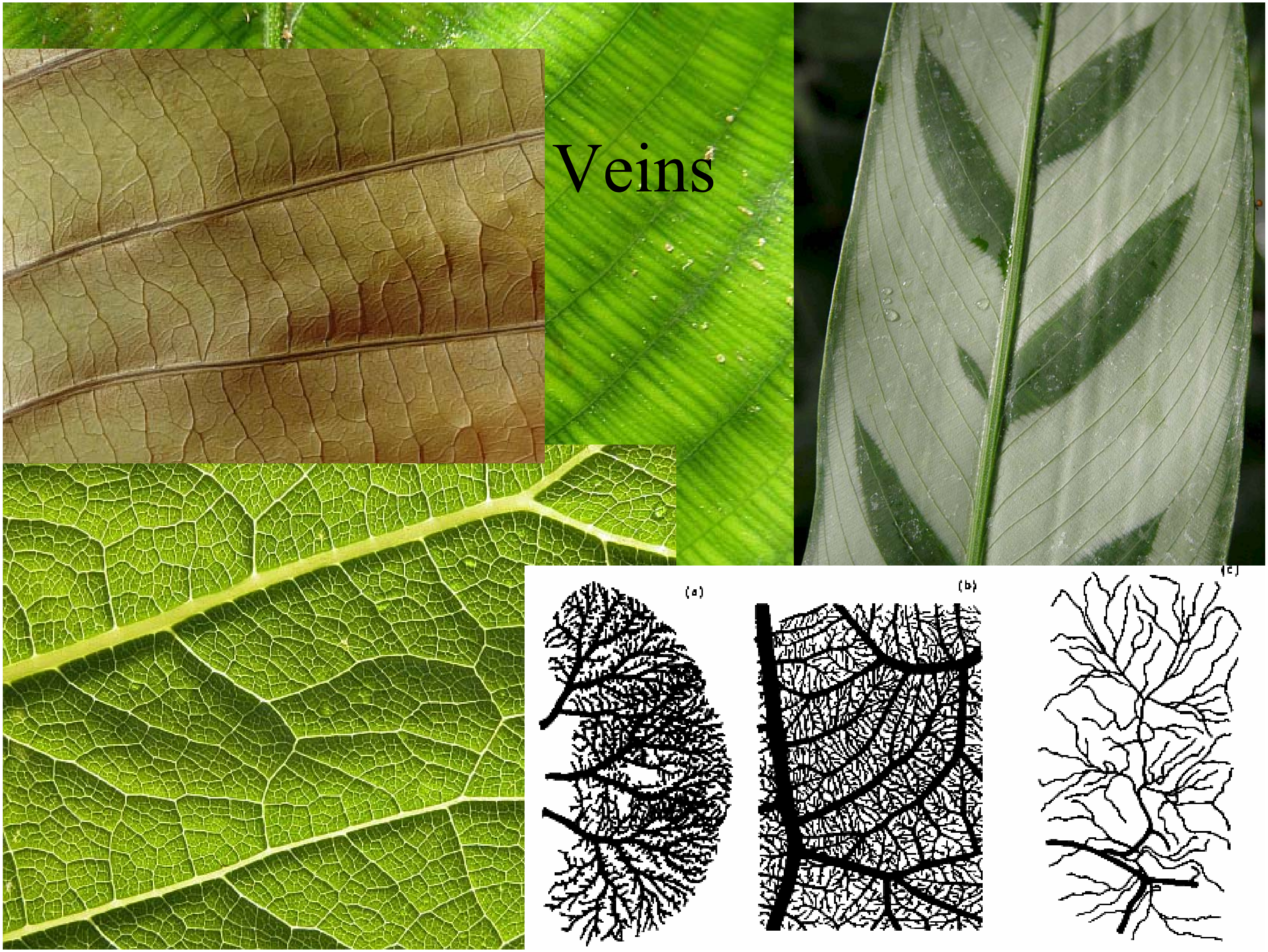
Stable gene activation requires an autoregulatory feedback of a gene product on its own gene

Competition between alternative genes leads to unequivocal decisions

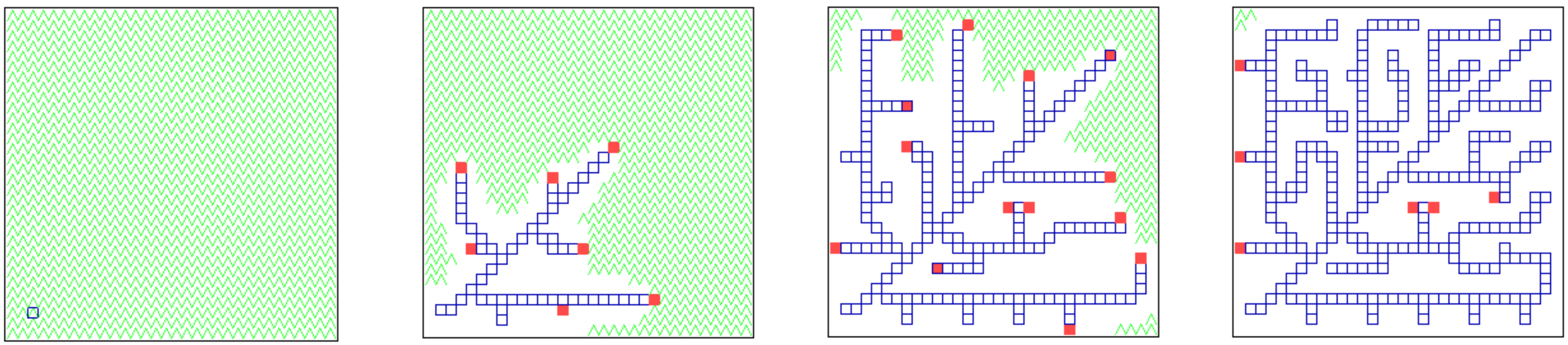
‘Promotion’

Next:

How to achieve branched structures

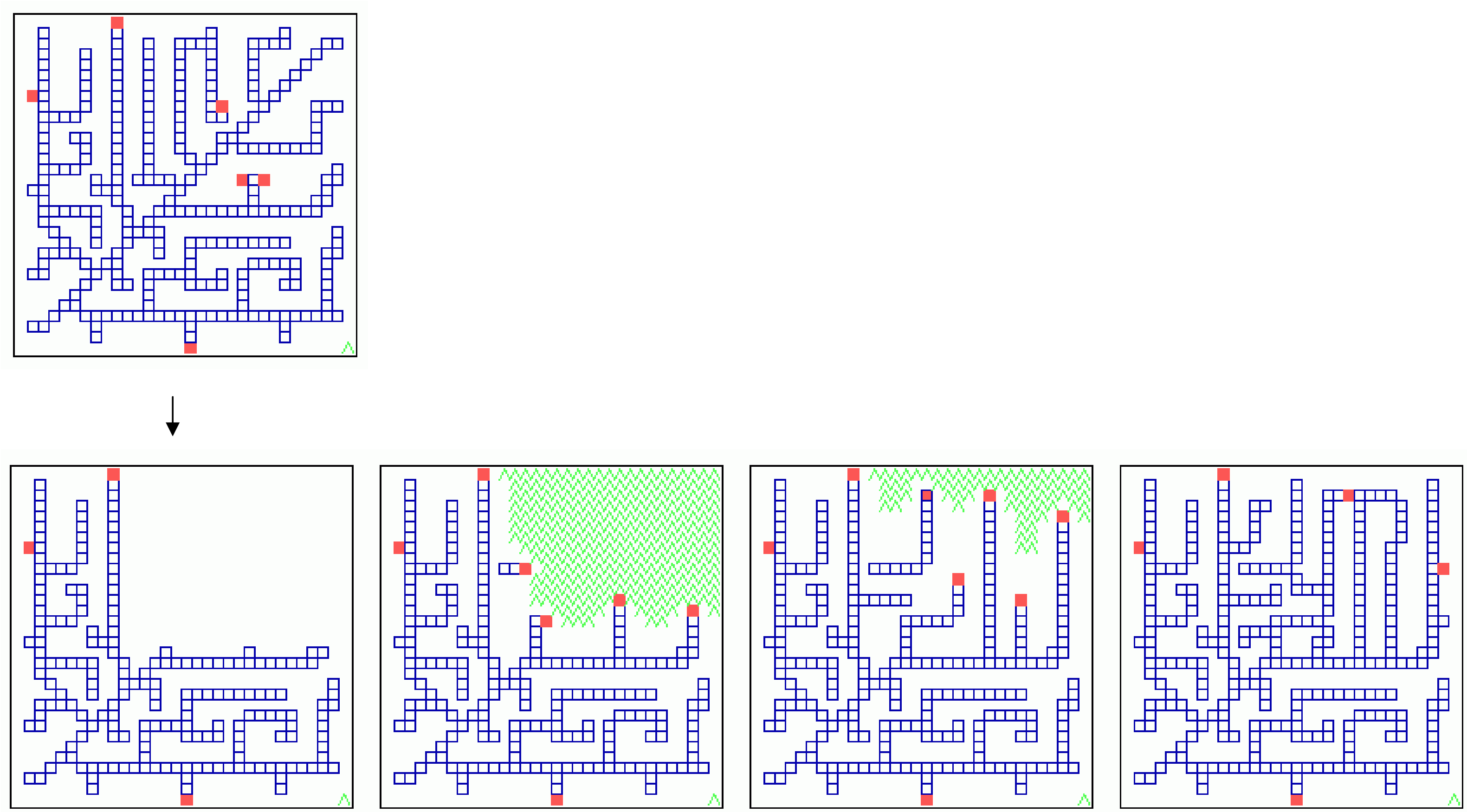

Veins
(a)
(b)
(c)

Formation of a netlike structure: a trace behind a shifting signal



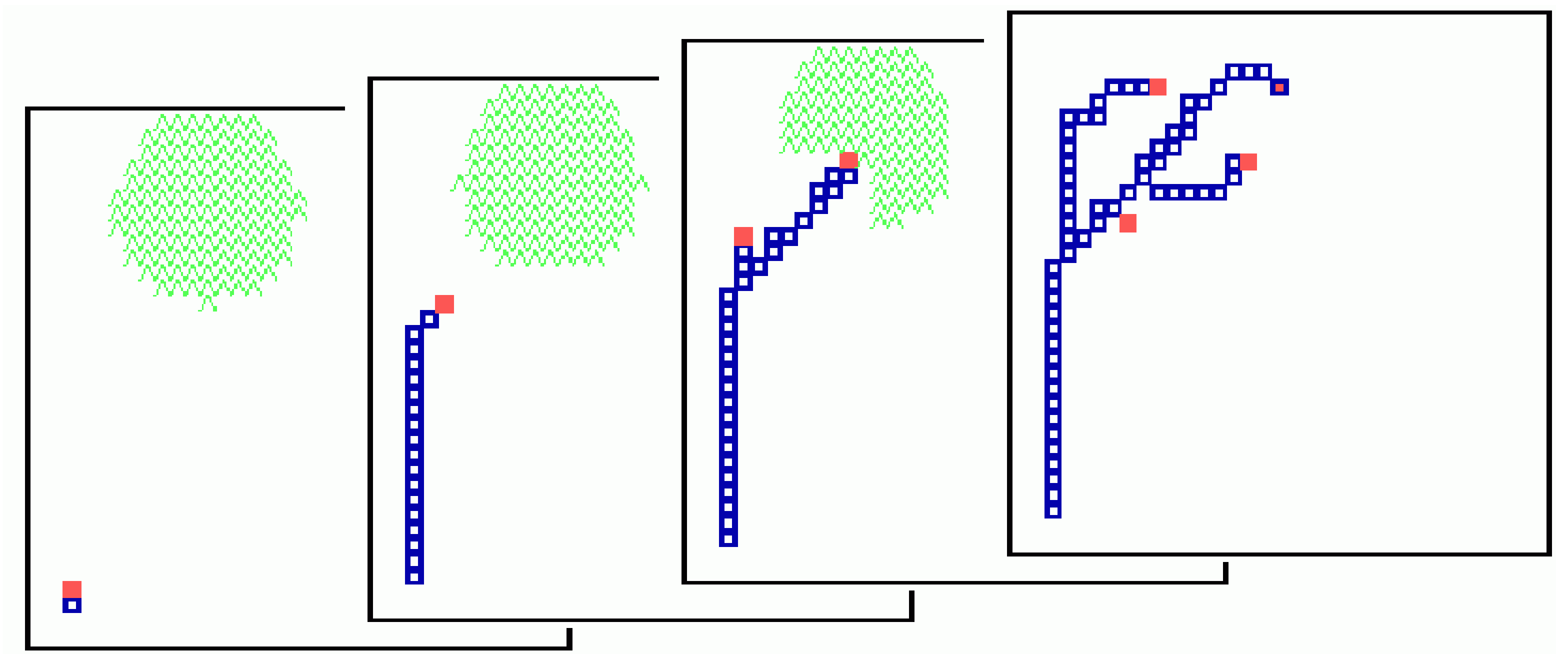
Differentiation 6, 117-123 (1976)

Regeneration of a net-like structure



Differentaiation 6, 117-123 (1976)

Elongation towards a target area



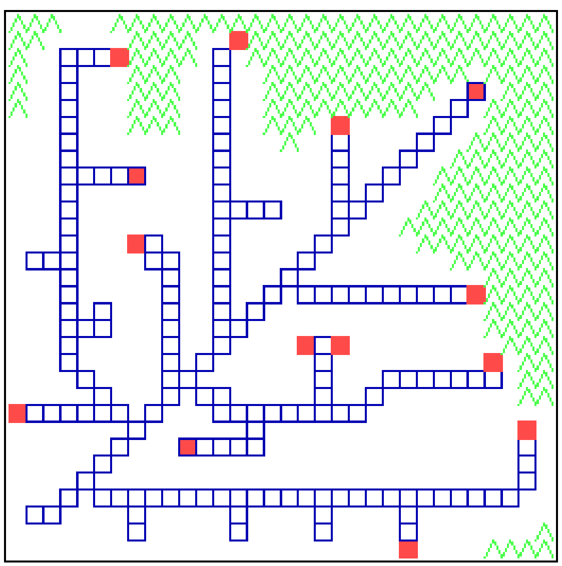
J. Cell Sci. 112, 2867-2874 (1999)
Differentiation 6, 117-123 (1976)

Thus, for net-like structures we need:

1. A signal that determines at which position the filament should be elongated or where to initiate a new branch (e.g., an activator-inhibitor system)

2. The filaments remove something (auxin, NGF, oxygen deficiency)

3. A irreversible determination that makes the filament different from the remaining cells



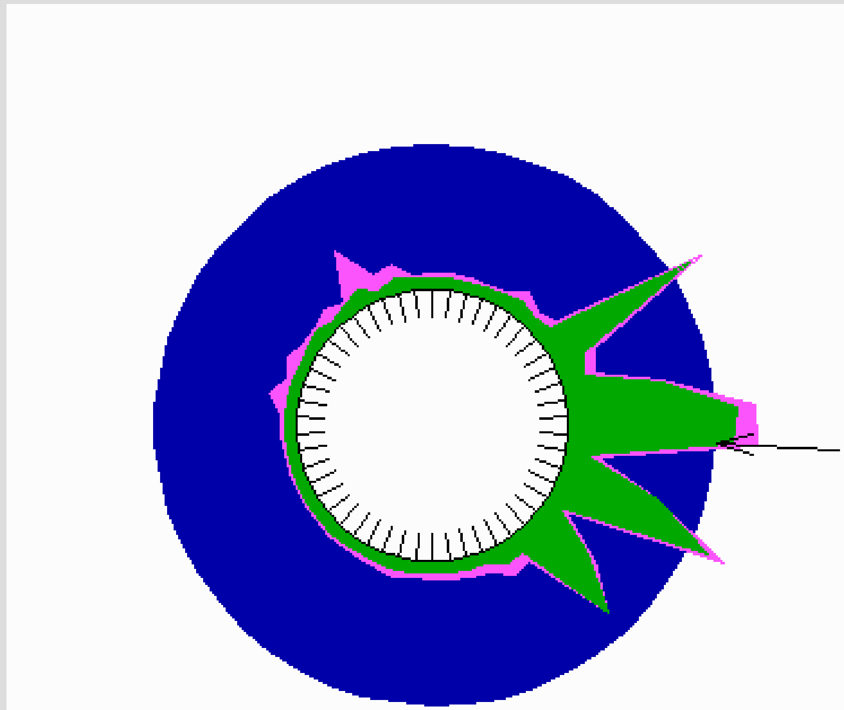
$$\frac{\partial a}{\partial t} = \frac{sca^2}{b} - r_a a + D_a \Delta_a + b_a d$$

$$\frac{\partial b}{\partial t} = sca^2 - r_b b + D_b \Delta b + b_b d$$

$$\frac{\partial c}{\partial t} = b_c - r_c c - c_c c \quad d + D_c \Delta c$$

$$\frac{\partial d}{\partial t} = \frac{r_d \quad d^2}{1 + s_d d} - r_d d + b_d a$$

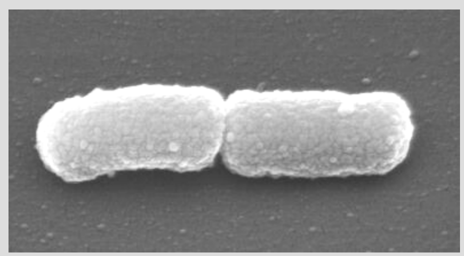
Permanent sensitivity is achieved by generation of local signals and their subsequent local destabilization



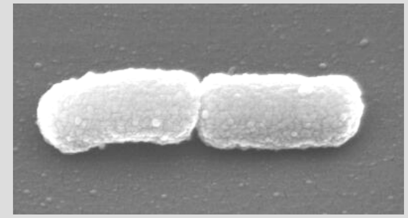
(separation of inhibition in time and inhibition in space)

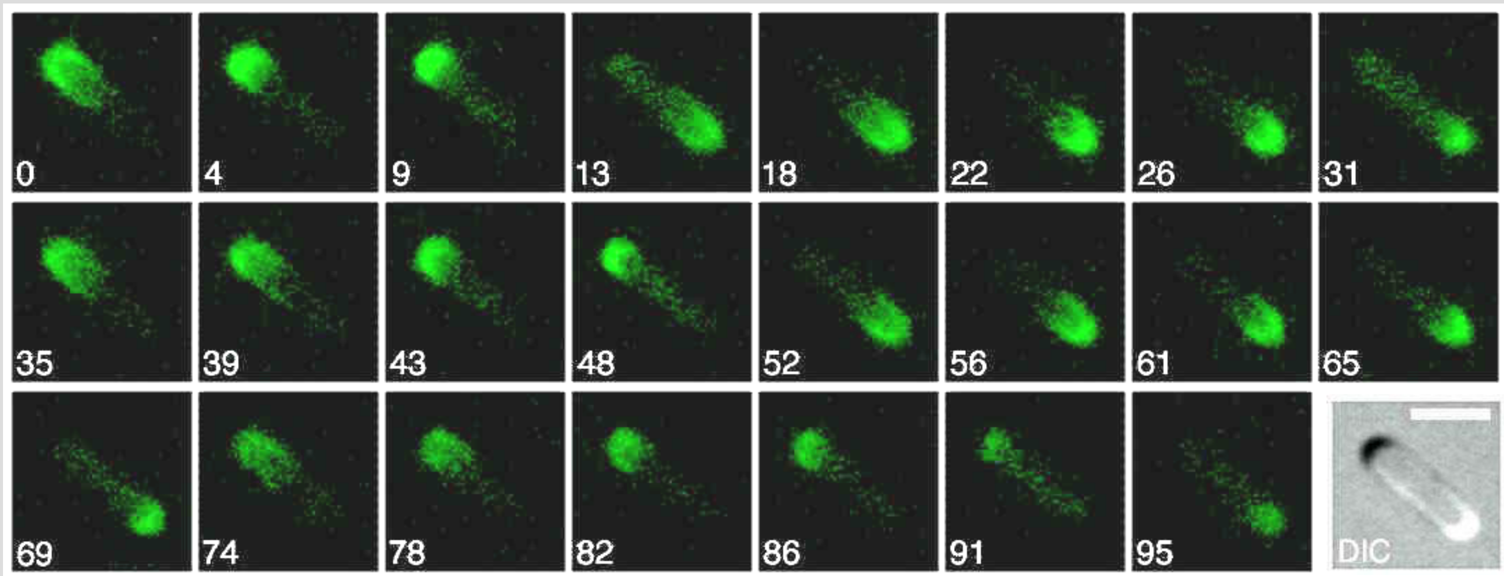
J. Cell Sci. (1999) 112, 2867-2874

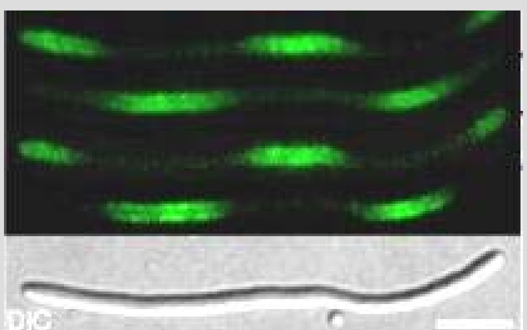
The use of local destabilization and waves in intracellular pattern formation: Center finding in E.coli



Oscillation of *MinD* out of phase

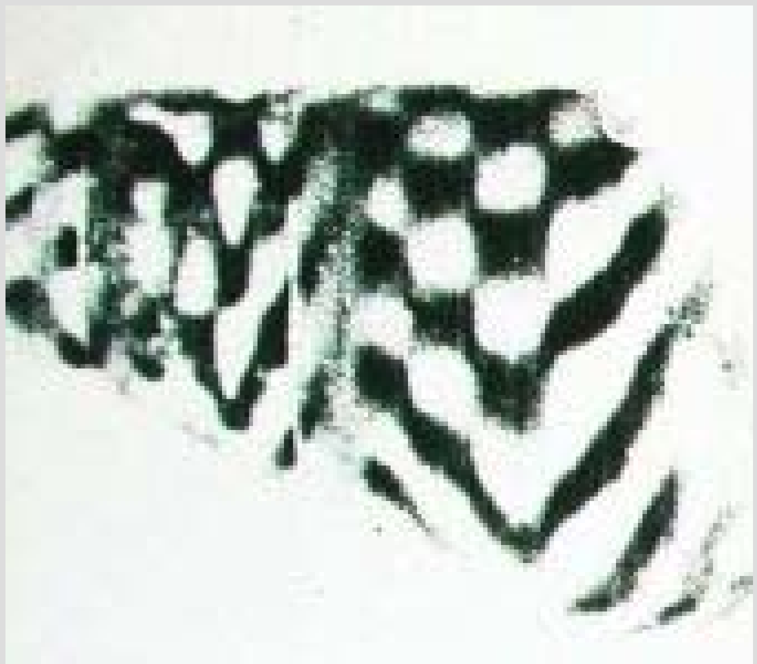


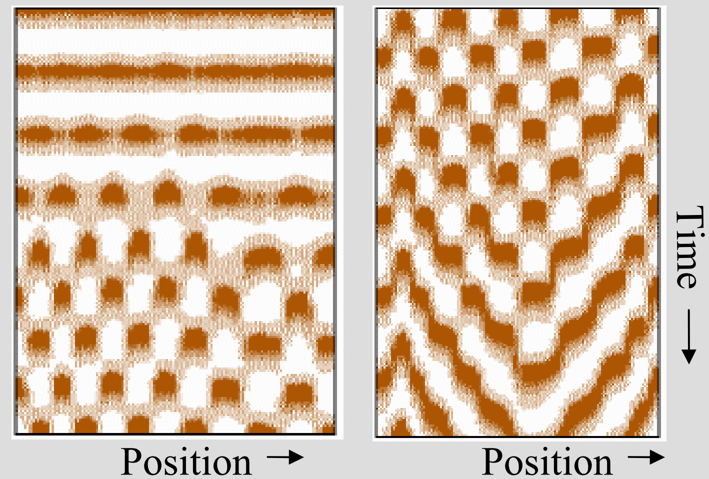




Raskin and de Boer (1999):
J. Bacteriology 181,6419-6424

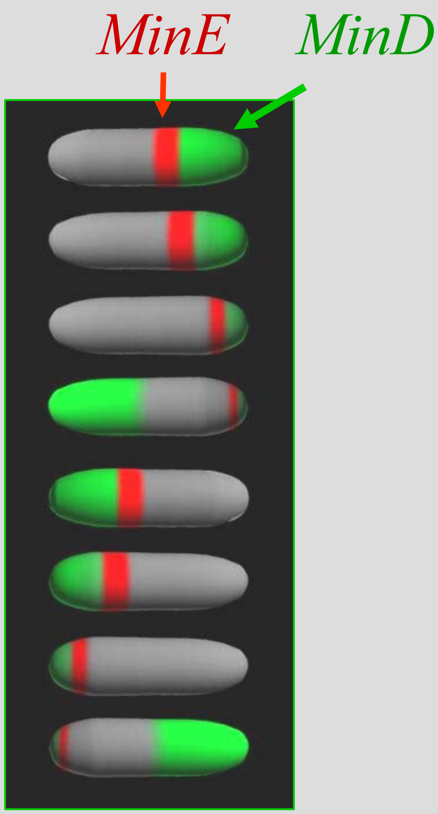
The key: oscillations in counter phase are generated by destabilizations of recently formed peaks

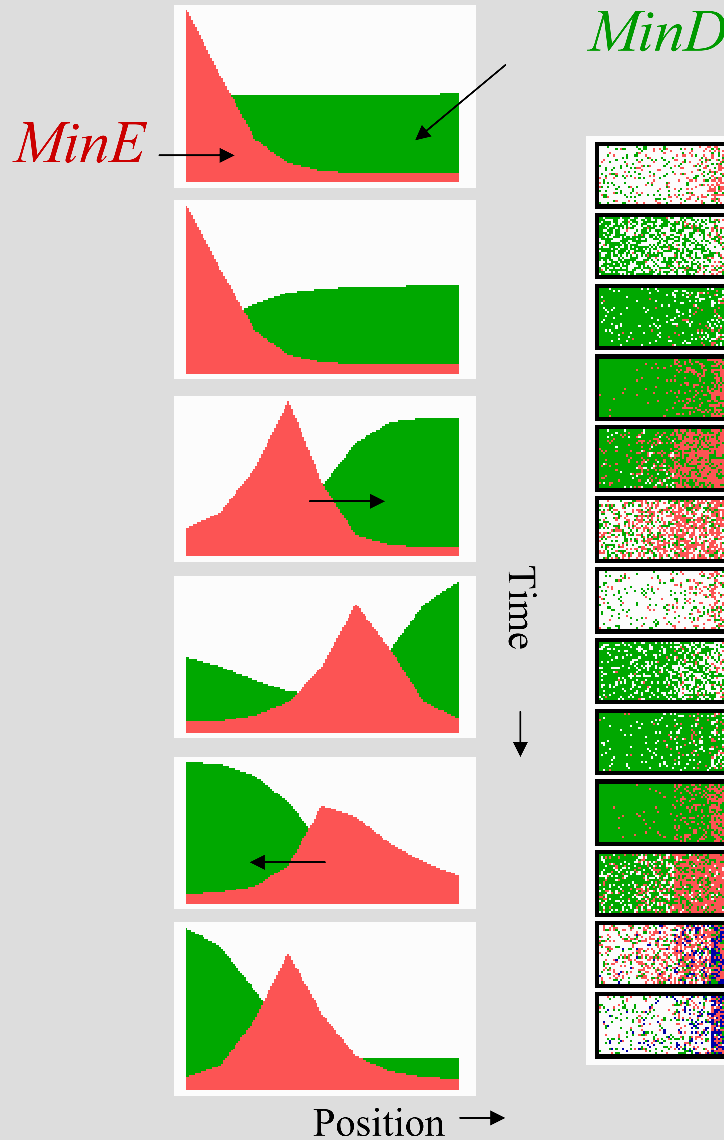


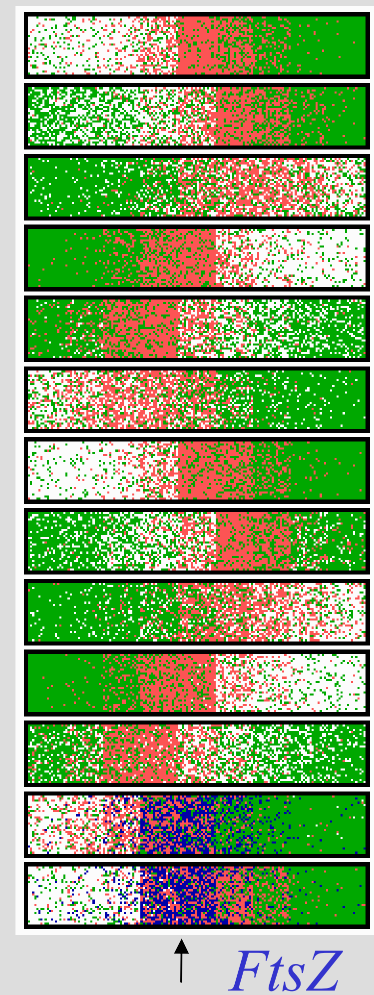


Meinhardt and Klingler (1987)
J. theor. Biol 126, 63-69
H.M., Algorithmic Beauty of Sea Shells
(Springer-Verlag, 1995 / 2003)

MinD pole-to-pole oscillation by MinE removal







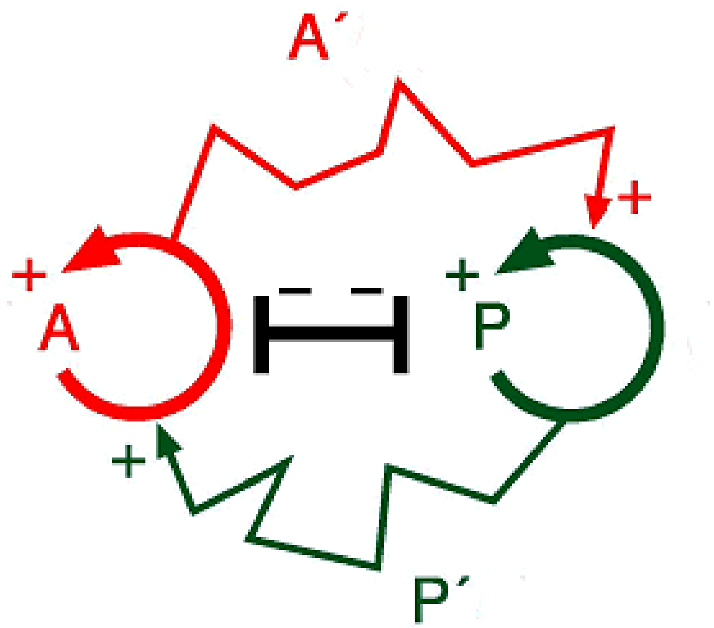
Meinhardt and de Boer (2001). PNAS 98,14202-14207

Next: **Segmentation:**

Mutual activation of structures that locally exclude each other

Mutual long range activation of locally exclusive cell states: Segmentation as example

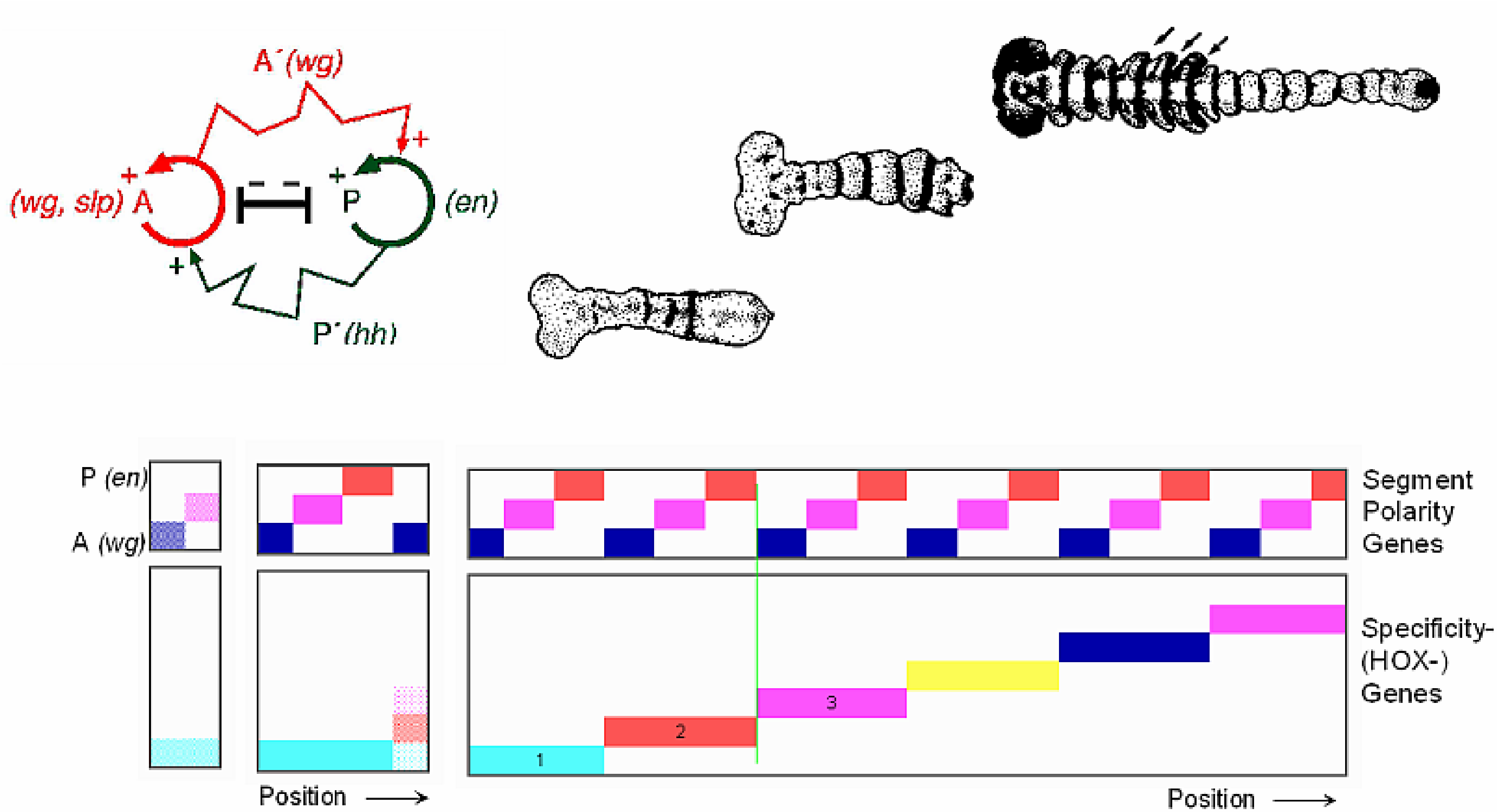
after N. Patel



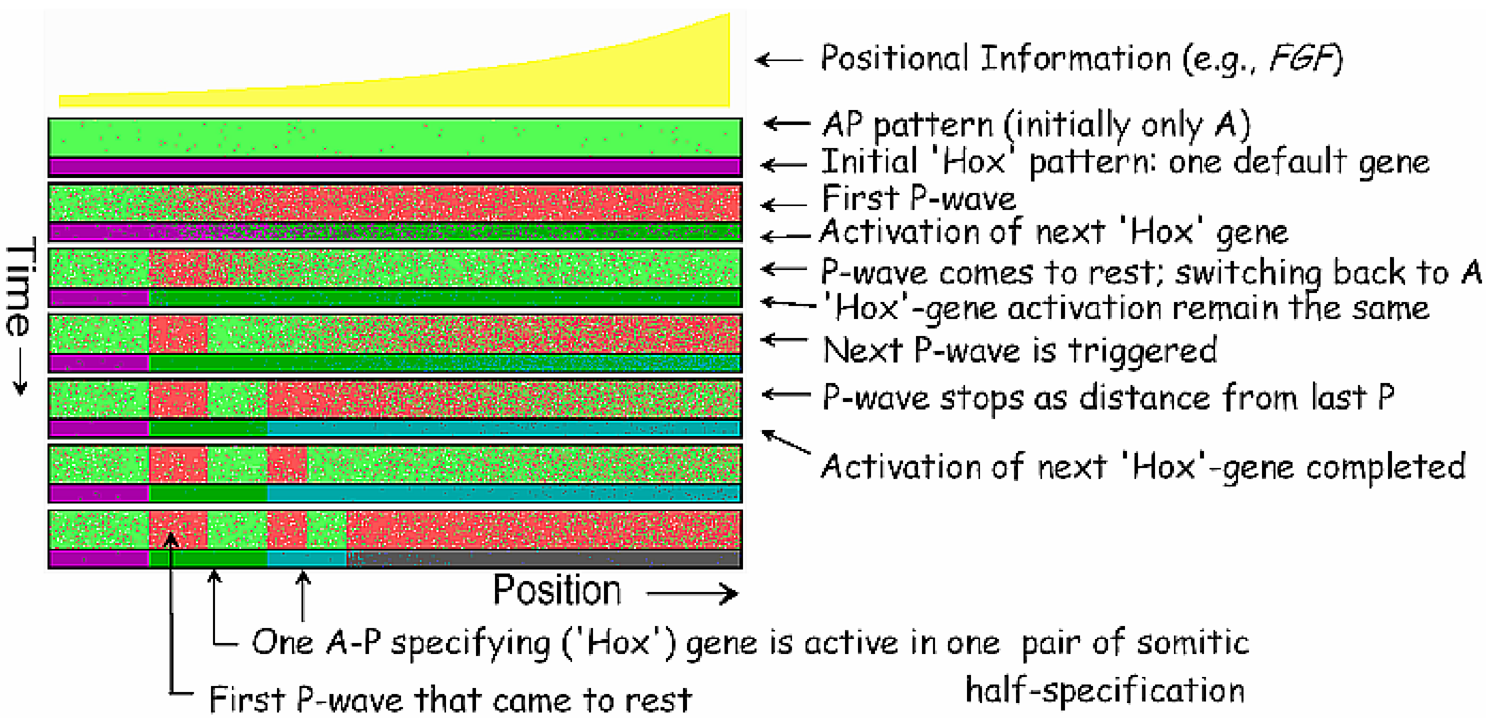
$$\frac{\partial a}{\partial t} = \frac{cs_p a^2}{r} - \alpha a + D_g \frac{\partial^2 a}{\partial x^2} + \rho_0$$
$$\frac{\partial p}{\partial t} = \frac{cs_a p^2}{r} - \alpha p + D_g \frac{\partial^2 g_2}{\partial x^2} + \rho_0$$
$$\frac{\partial s_a}{\partial t} = \gamma(a - s_a) + D_s \frac{\partial^2 s_a}{\partial x^2} + \rho_1$$
$$\frac{\partial s_p}{\partial t} = \gamma(p - s_p) + D_s \frac{\partial^2 s_p}{\partial x^2} + \rho_1$$
$$\frac{\partial r}{\partial t} = cs_p a^2 + cs_a p^2 - \beta r \left[+ D_r \frac{\partial^r}{\partial x^2} \right]$$

Meinhardt and Gierer (1980) J. theor. Biol., **85**, 429-450

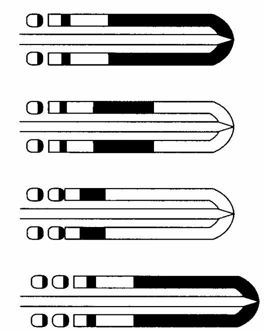
Segmentation: Mutual long range activation of locally exclusive cell states generates a periodic structure; oscillation at the posterior pole allows a counting in the gene level



Somite formation: a sequential conversion of a periodic pattern in time into a periodic pattern in space; correctly predicted: waves move from posterior towards anterior and form anterior and posterior half-somites



Models of Biological Pattern Formation,
Academic Press, 1982 (available on our website)



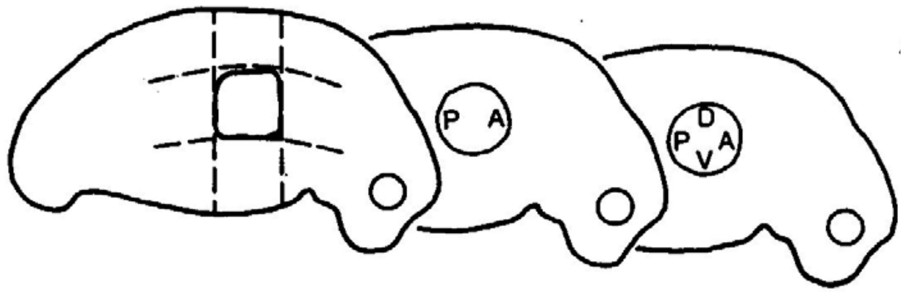
Oscillation of *c-hairy1* in the chick
Palmeirim et al. (1997). Cell 91, 639-648

Next:

Initiation of legs, wings…

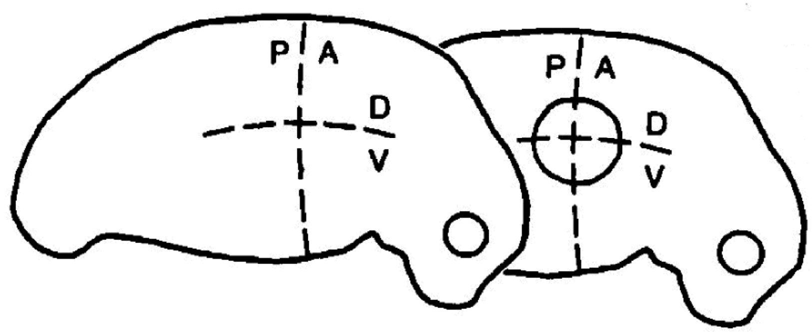
Intersection of boundaries become the new organizing regions

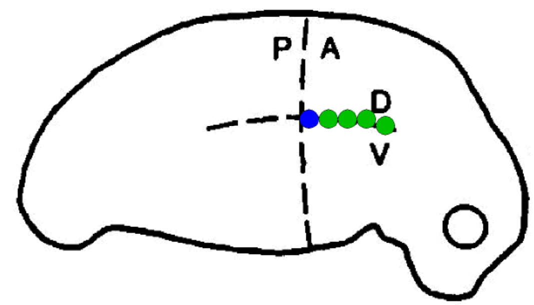
Initiation of legs and wings



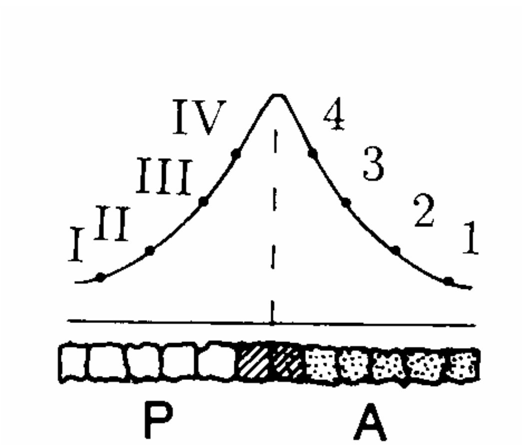
Conventional view: (G. Harrison, 1918)
Homogeneous limb field that becomes subsequently subdivided

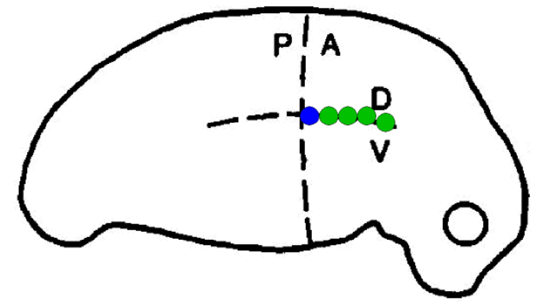
Proposal (1980,1983):
Differentiation borders first

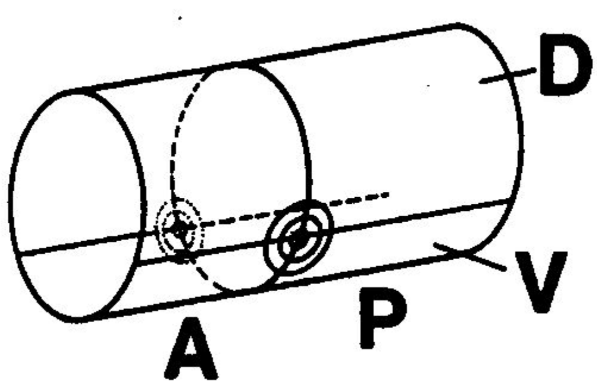


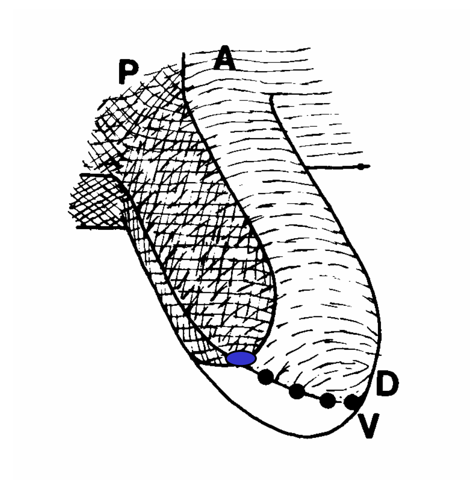


Vertebrate limb: only the anterior part is used





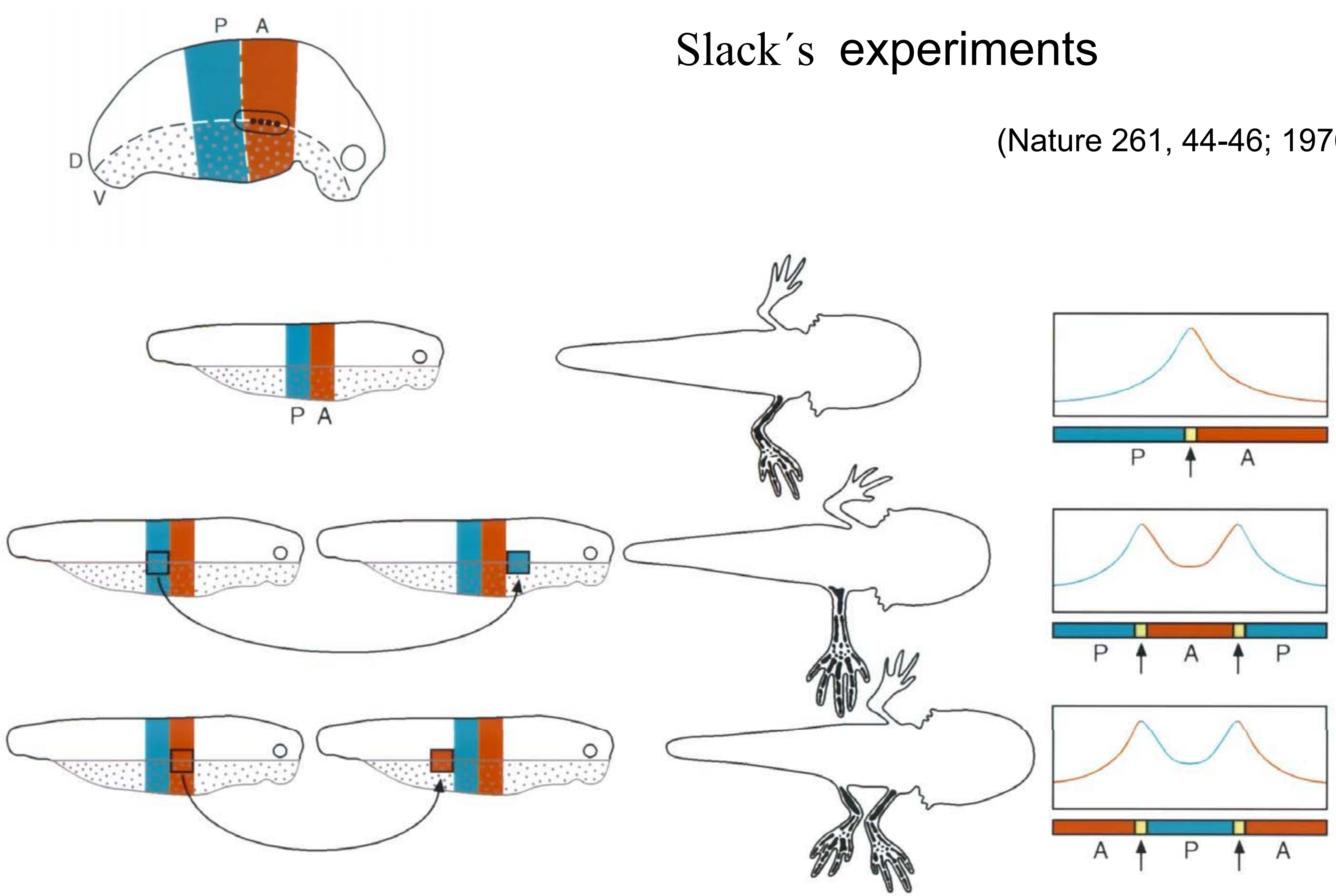




H.M. (1983) A boundary model for pattern formation in vertebrate limbs.J. Embryol. exp. Morphol.; 76,115-137

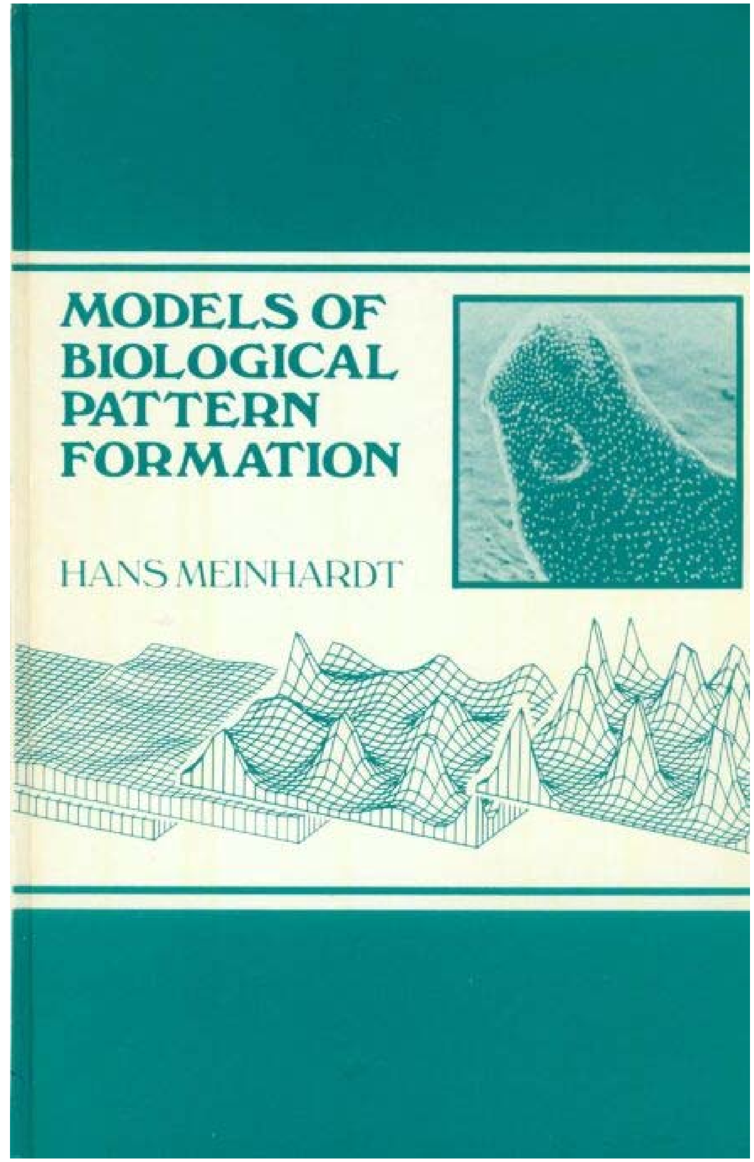
Slack´s experiments

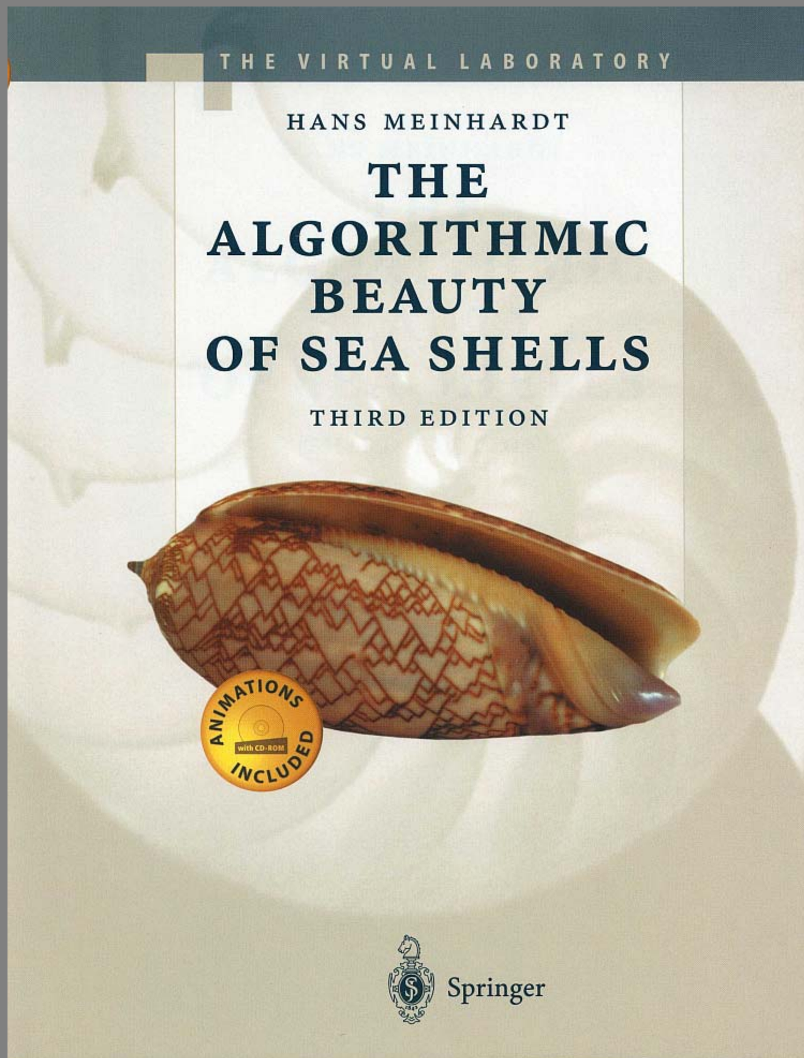
(Nature 261, 44-46; 1976)



Model: A boundary model for pattern formation in vertebrate limbs
J. Embryol. exp. Morphol. 76,115-137 (1983)

Academic Press (1982);
available at
http://www.eb.tuebingen.mpg.de/meinhardt

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