Physics of multicellular systems 2022

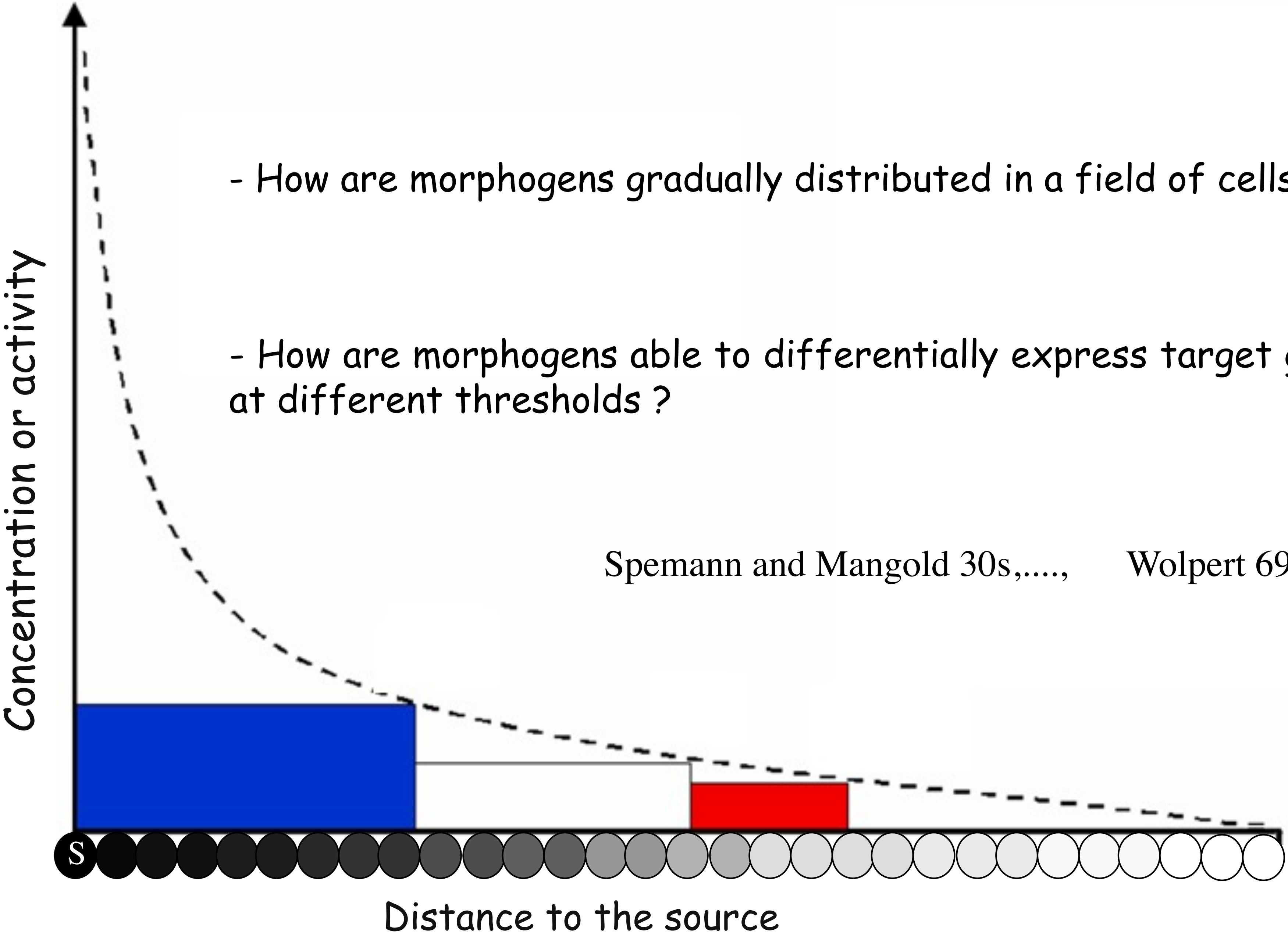
Lecture 2
Positional information and tissue patterning

Gradients and the french flag model

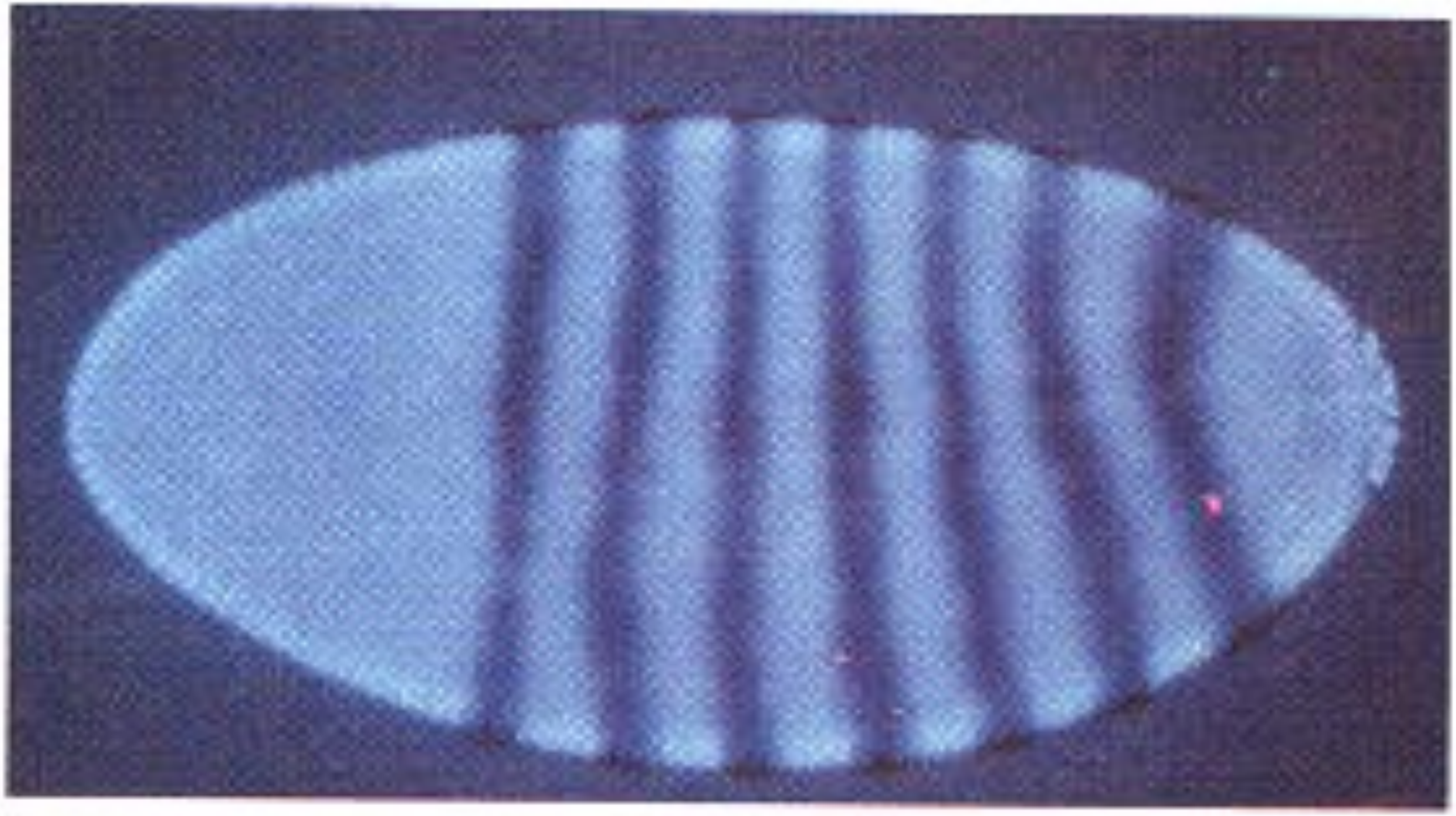
- How are morphogens gradually distributed in a field of cells ?

- How are morphogens able to differentially express target genes at different thresholds ?

Spemann and Mangold 30s,...., Wolpert 69,....

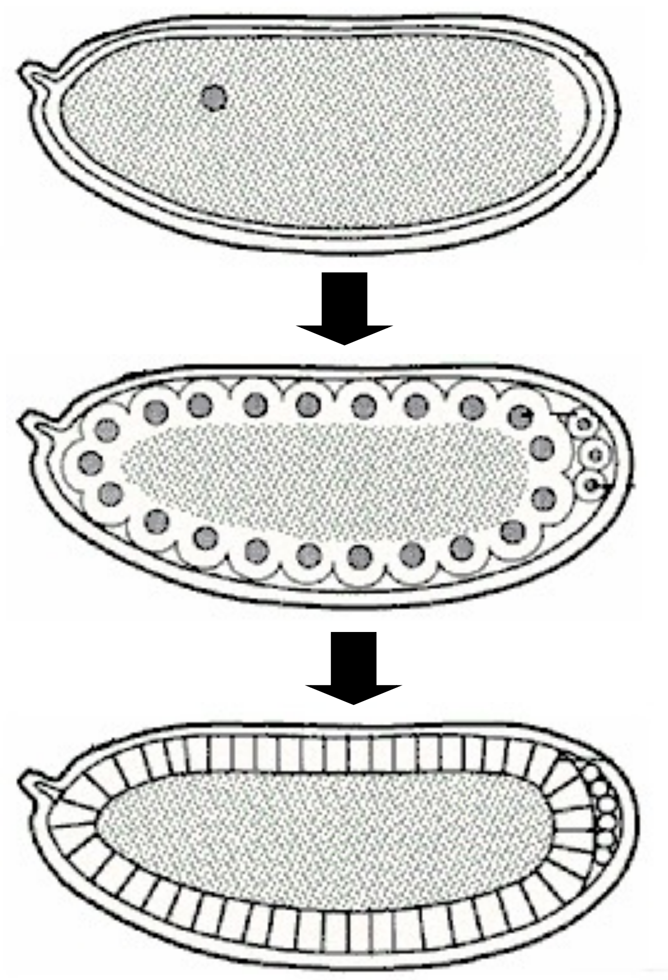


Drosophila embryo



Nüsslein-Volhard and Wieschaus, 1980;....

The early development of the *drosophila* embryo occurs in a syncytium



Early syncytium :

. cycle-1 to cycle-8 (~ 70 mn)

. No transcription

Syncytial blastoderm :

. cycle-9 to cycle-13 (~ 70 mn)

. Transcription of the zygotic genome

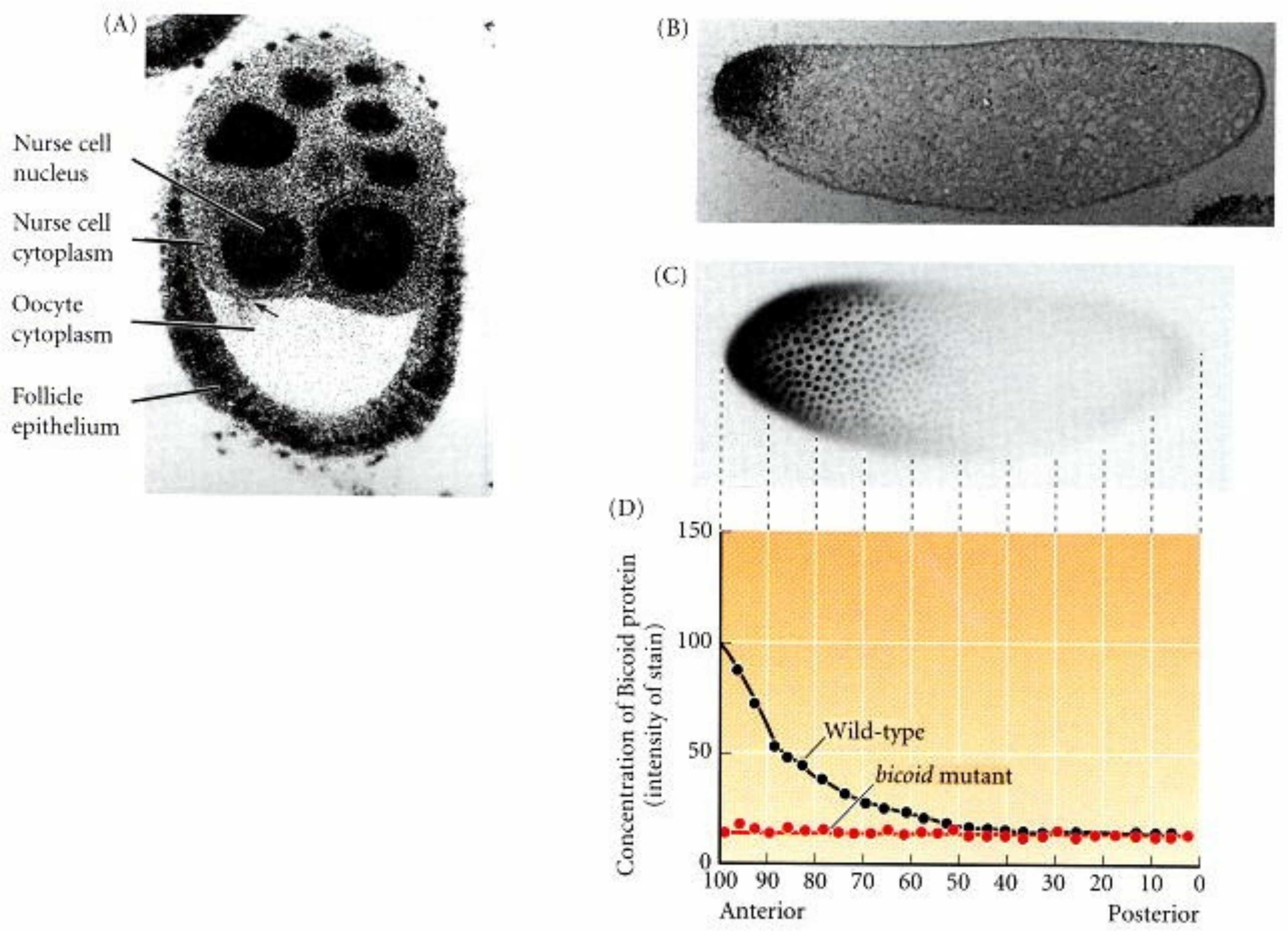
Cellular blastoderm :

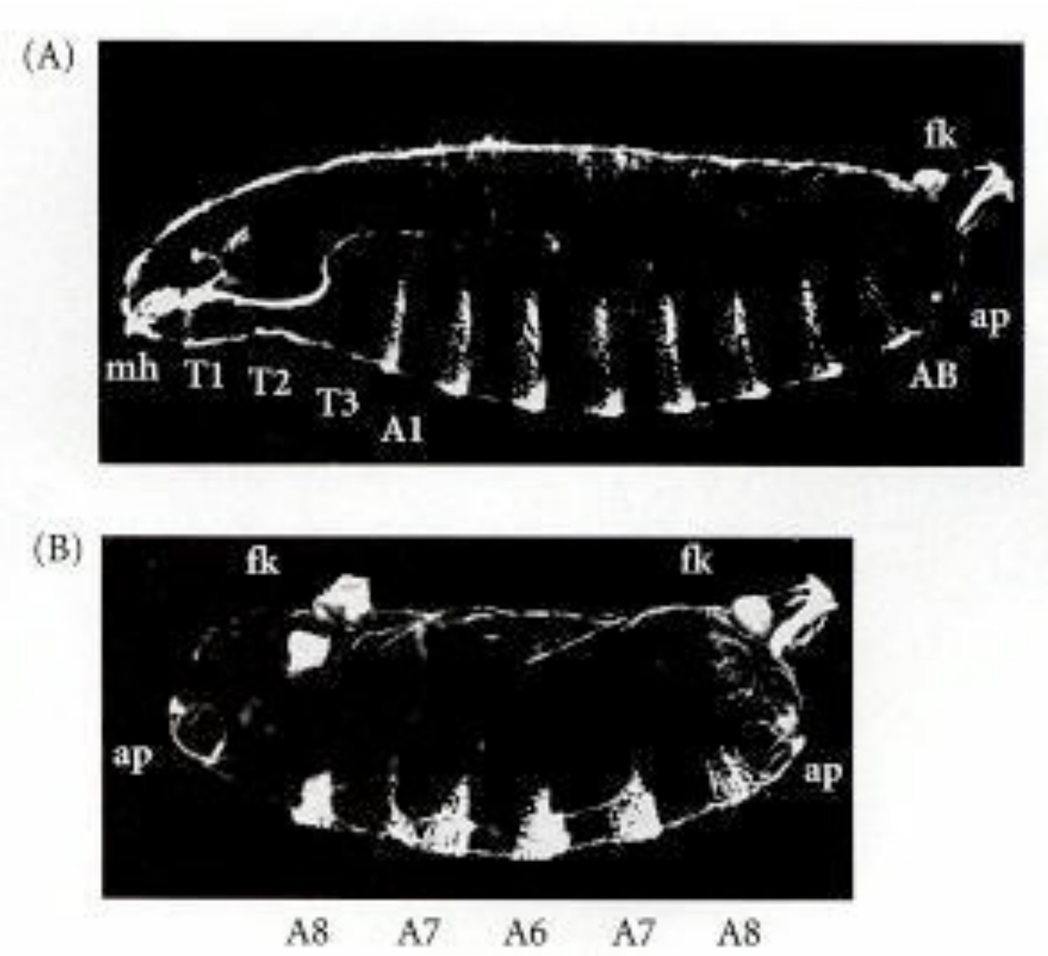
. cycle-14 (> 60 mn)

. Cellularisation

N Dostatni, Curie

The bicoid gradient





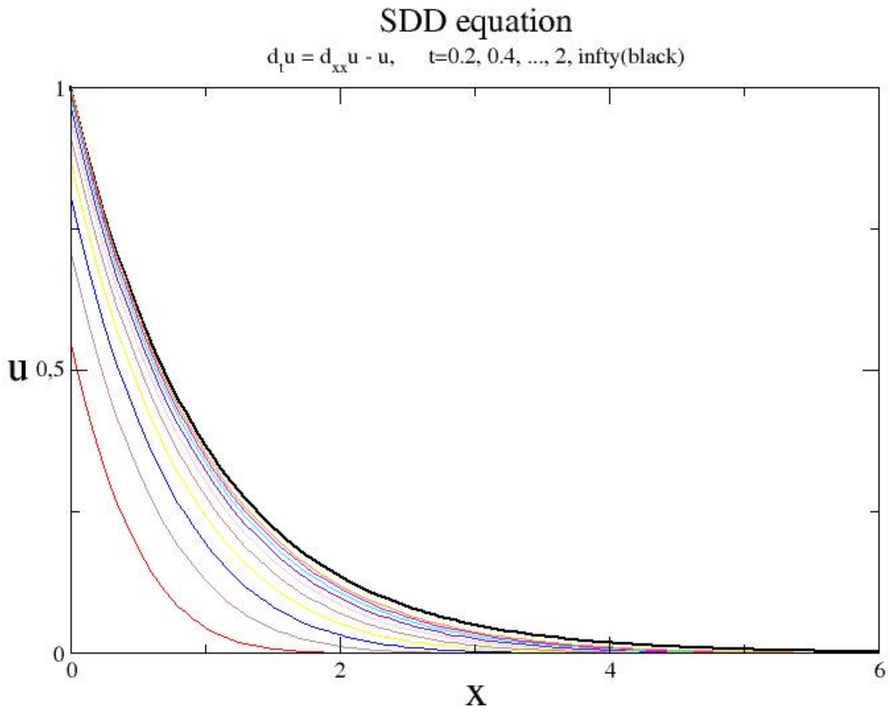
Wild-type cuticle patterns

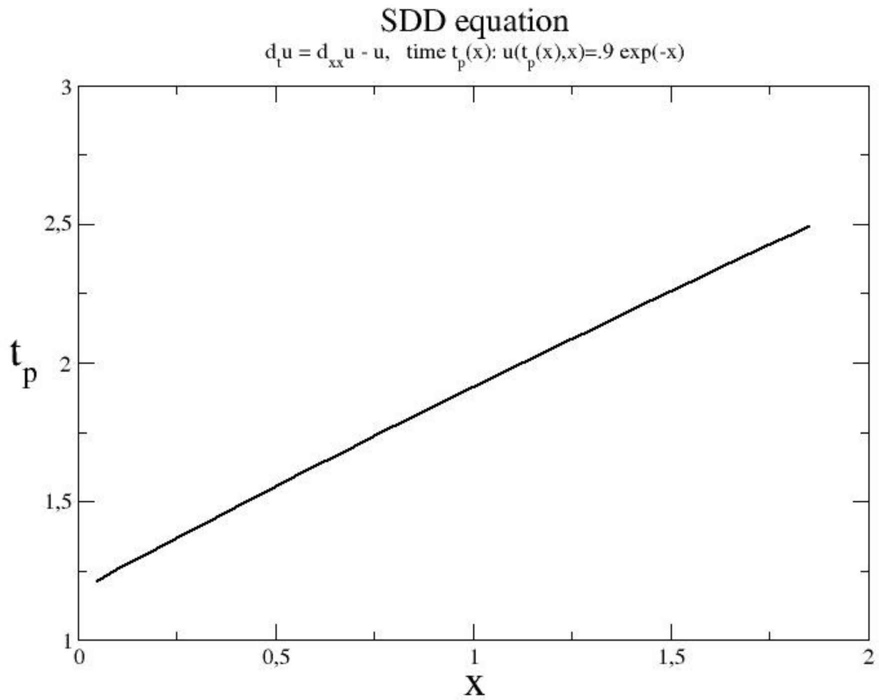
Bicoid mutant

Driever, Nusslein-Vollhardt, Cell (1988)

Positional information from a morphogen gradient

Source-Diffusion-Decay: form of the gradient and time to establish it





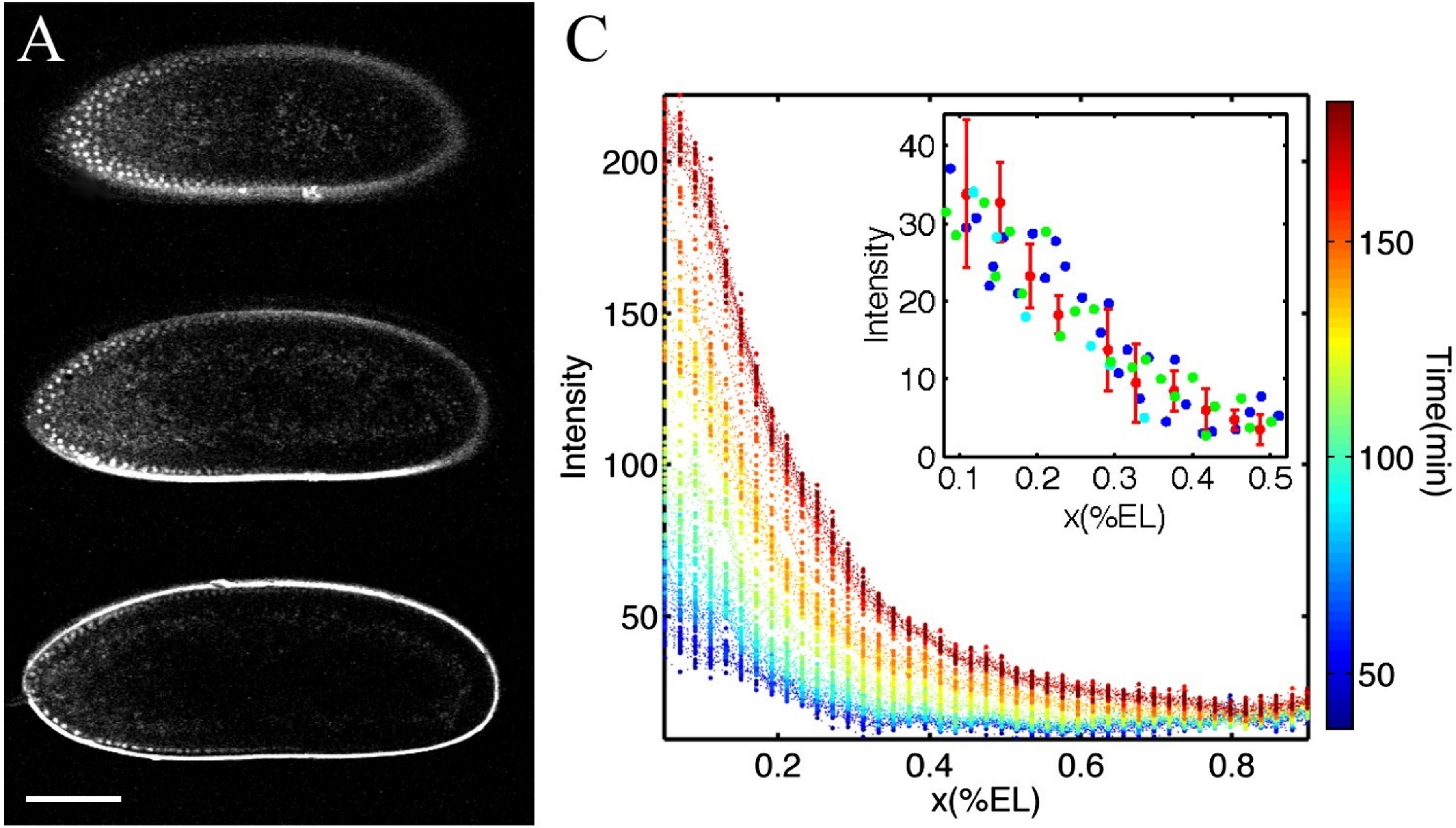
Diffusion length: $\ell = \sqrt{D/\delta}$

$D \simeq 7\mu\mathrm{m}^2/\mathrm{s},\ \delta \simeq 30\,\mathrm{min}^{-1}$

$\ell \simeq 100\mu\mathrm{m}$ (embryo $\simeq 500\mu$m)

$(D\delta)^{-1} \simeq 16\,\mathrm{s}/\mu\mathrm{m}$

Precision measurements of the Bicoid(-GFP) gradient dynamics



T. Gregor et al, Cell 130 (2007)

Time to read the gradient

Classic analysis of Berg and Purcell (Biophys J, 1977)

Basic argument:

Incoming flux J of molecules at concentration c
for a perfect absorbing sphere of radius a : $J=4\pi acD$

Mean number of molecules impinging on a time T : $\langle N(T)\rangle = 4\pi acDT$

Fluctuations of N(T) (independent events) : $\Delta N(T)=N(T)^{1/2}$

In order to measure c with precision δc one has to wait $\delta c/c= N(T)^{-1/2} =(4\pi acDT)^{-1/2}$

Many studies since then (see Aquino et al, J Stat Phys 2016, for a short review).

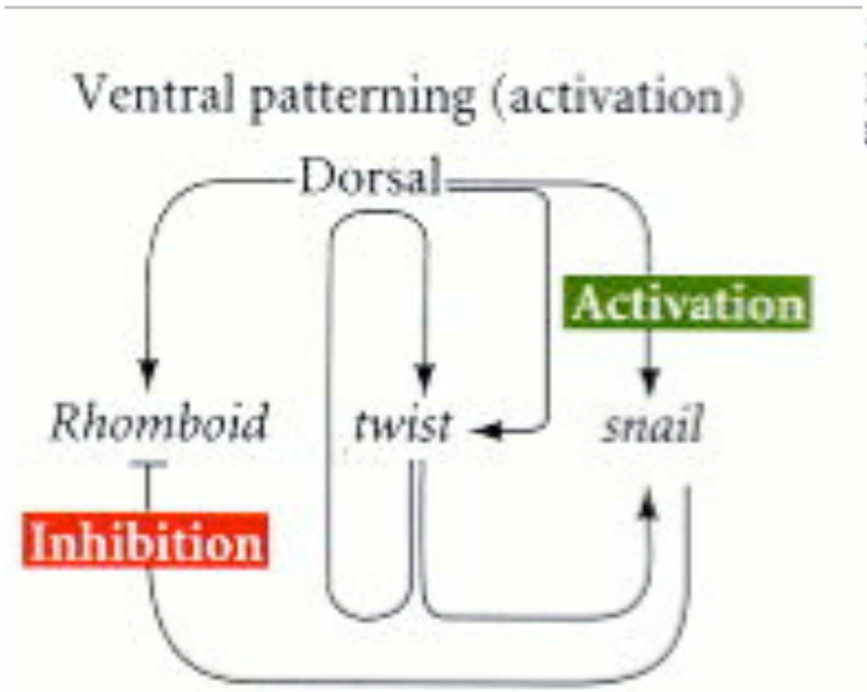
Application to the fly (Gregor et al, 2007; Porcher et al, 2010; ...)

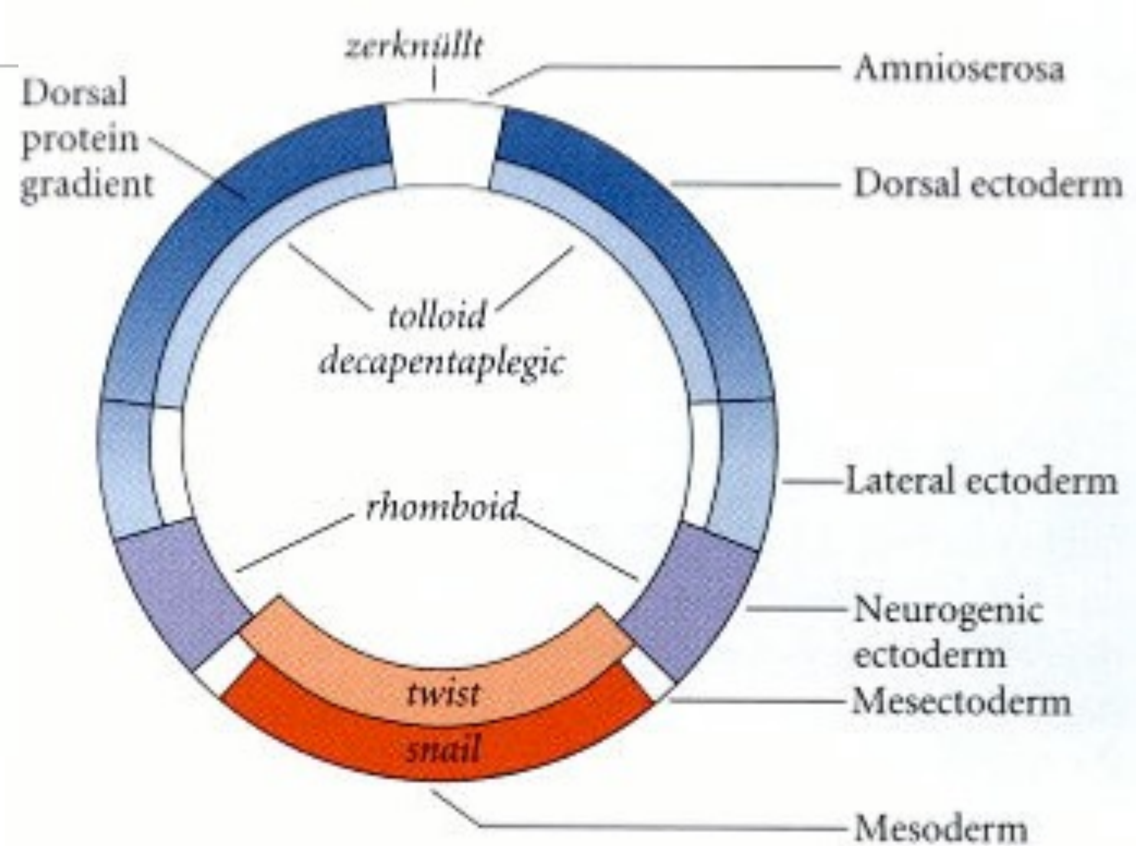
$\delta c/c= 0.1$, $c=10nM=5/\mu m^3$, $D = 7\mu m^2/s$, $a=3nm$ => $T>$ qq mins

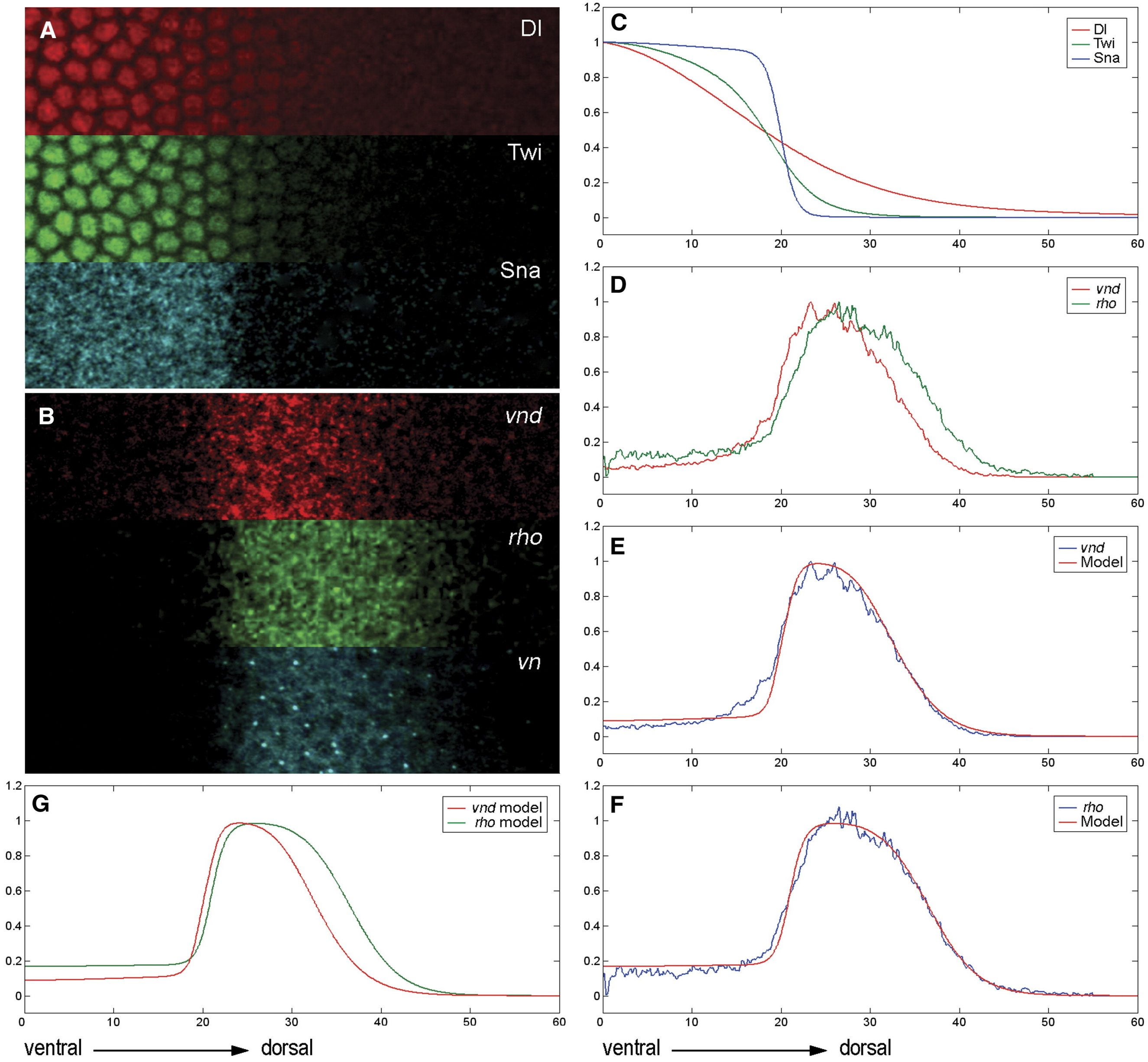
Can do better by not considering fixed time but average decision time :
Desponds et al, eLife (2020)

Pattern formation in a positional gradient

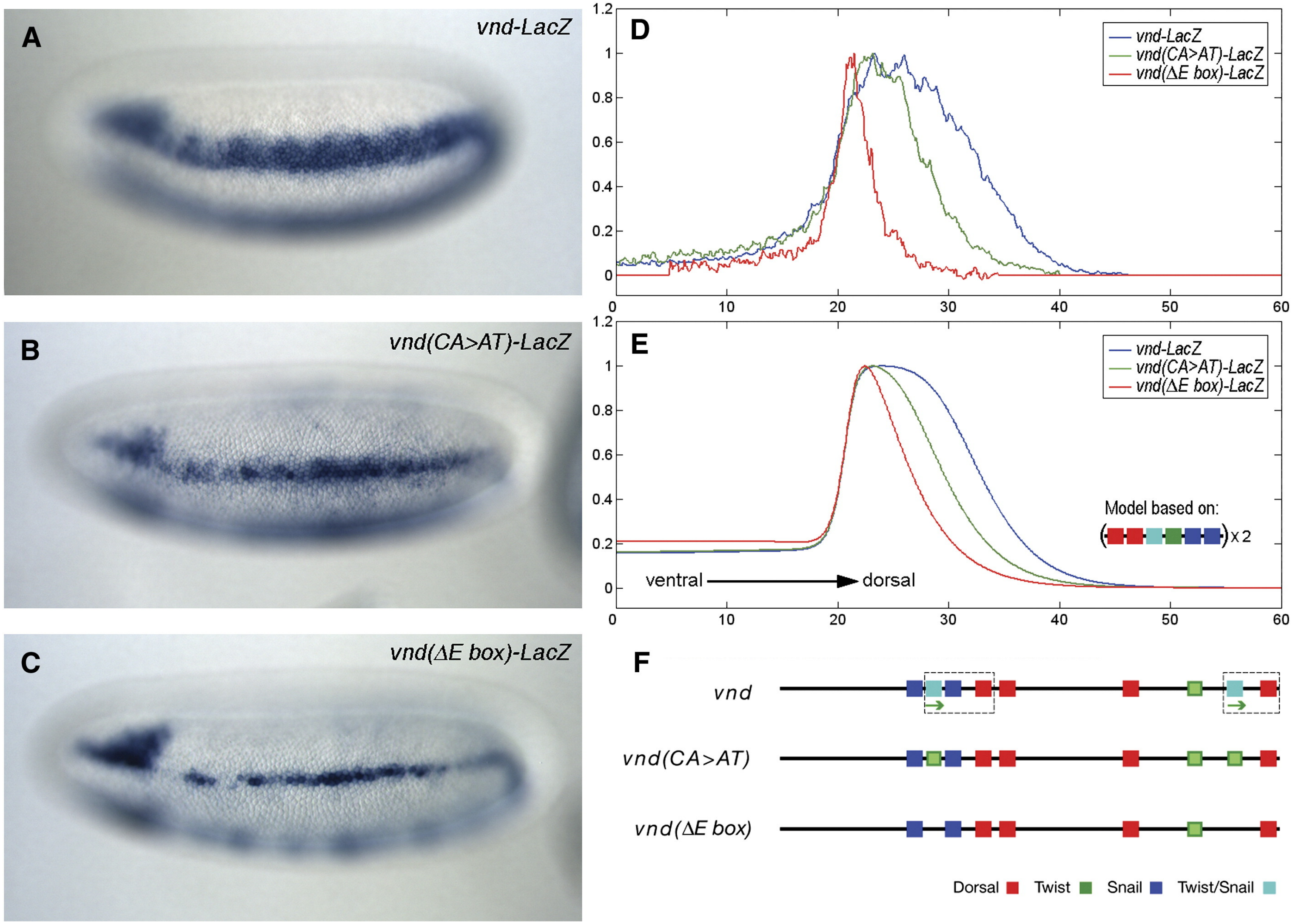
Drosophila : embryonic dorso-ventral patterning







R Zinzen, K Senger, M Levine and D Papatsenko, Curr. Biol. 16, 1358 (2006)



The vnd band becomes narrower

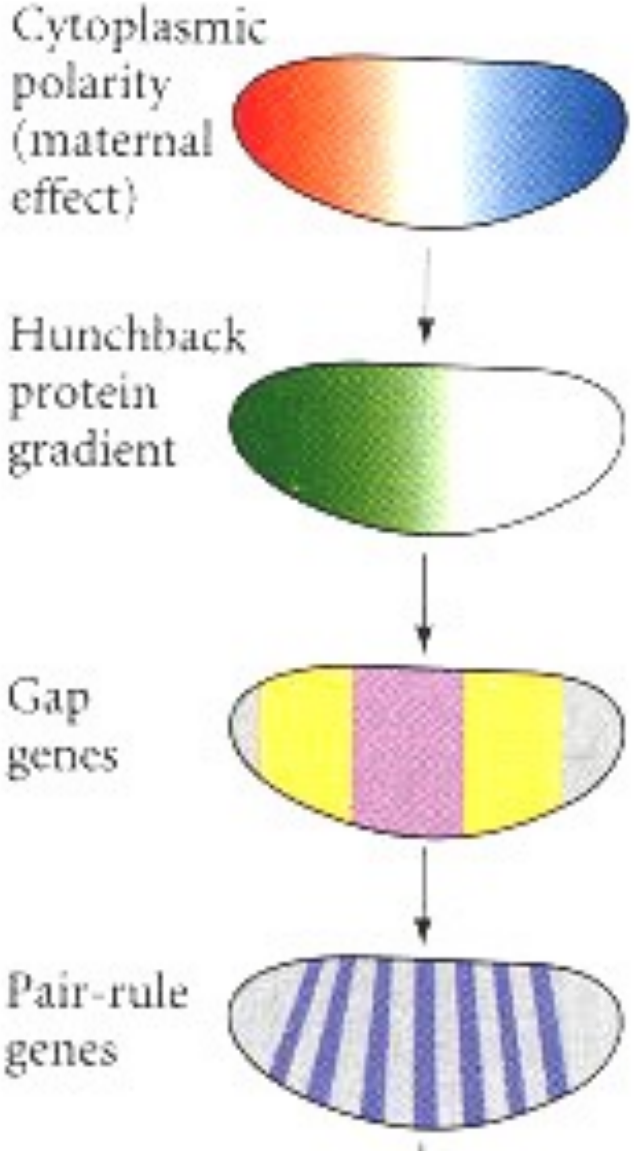
upon

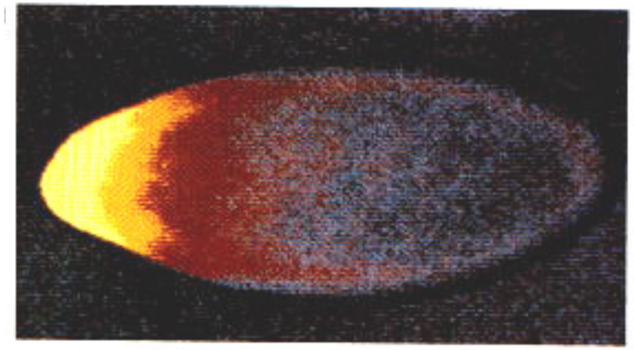
reduction of Twist activation

After mutation, higher concentration of activator needed for active transcription i.e. activation starts more ventrally.

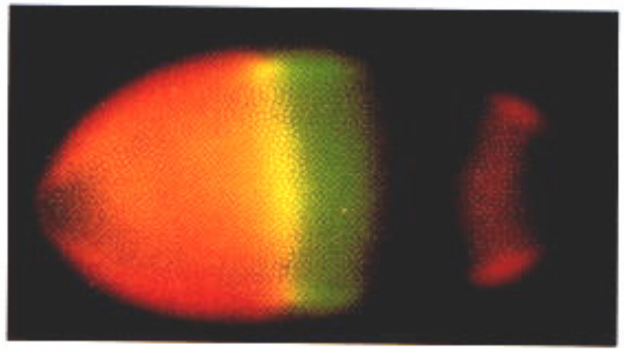
R Zinzen, K Senger, M Levine and D Papatsenko, Curr. Biol. 16, 1358 (2006)

Drosophila embryonic A-P segmentation

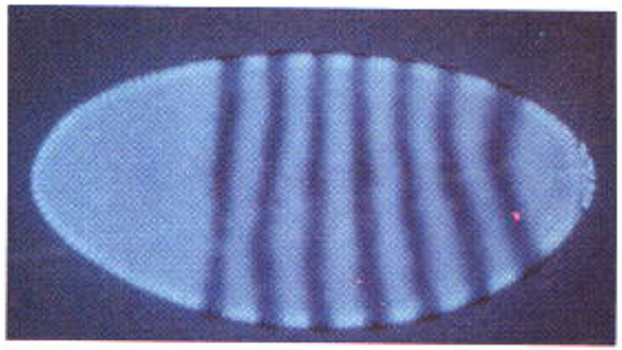




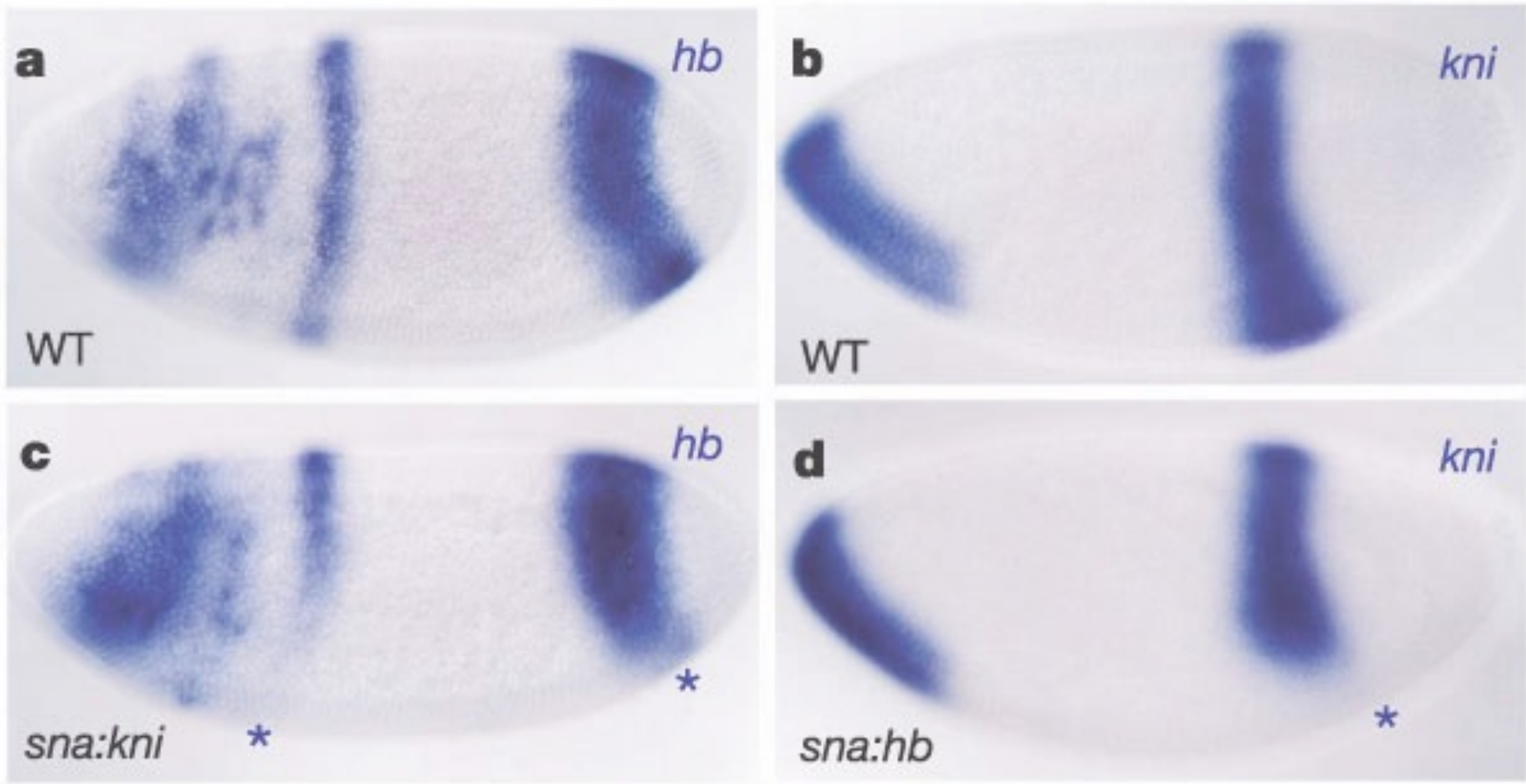
Bicoid gradient



Gap genes



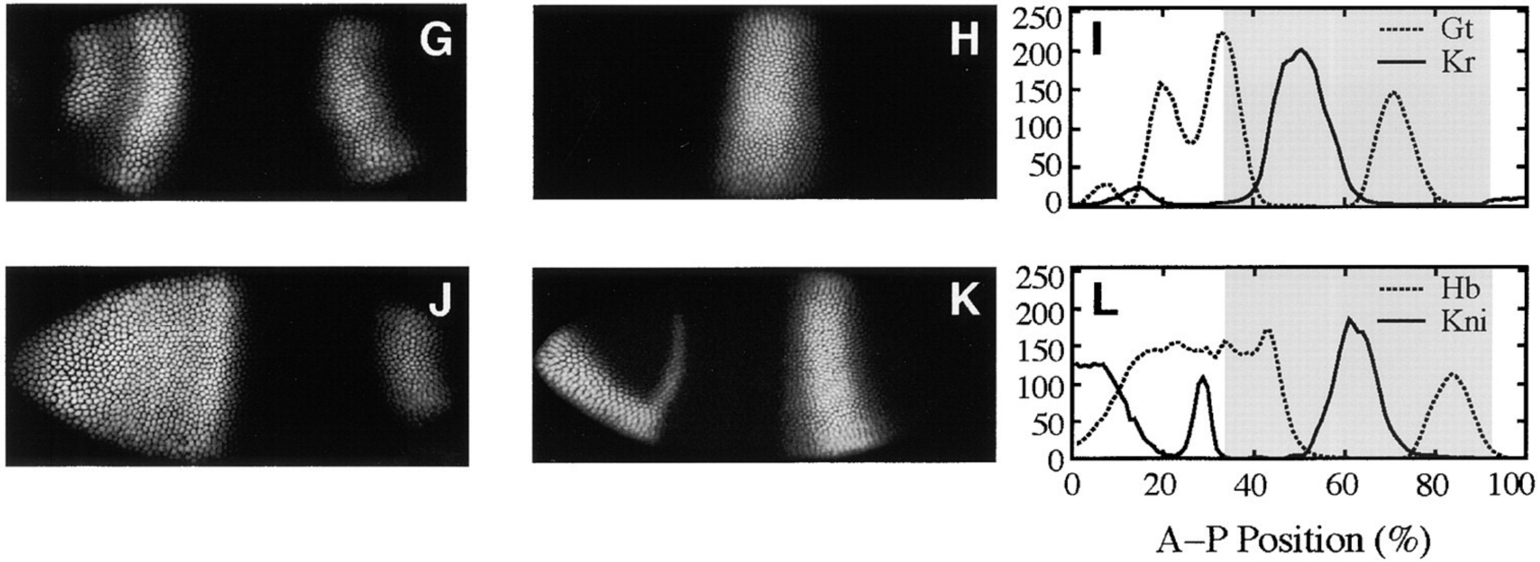
Mutual repression between Hb and Kni.



D. E. Clyde,…, S. Small Nature 426, 849-853 (2003)

Gap gene functional interactions in the embryo central region

Jaeger J et al. Genetics 2004;167:1721-1737

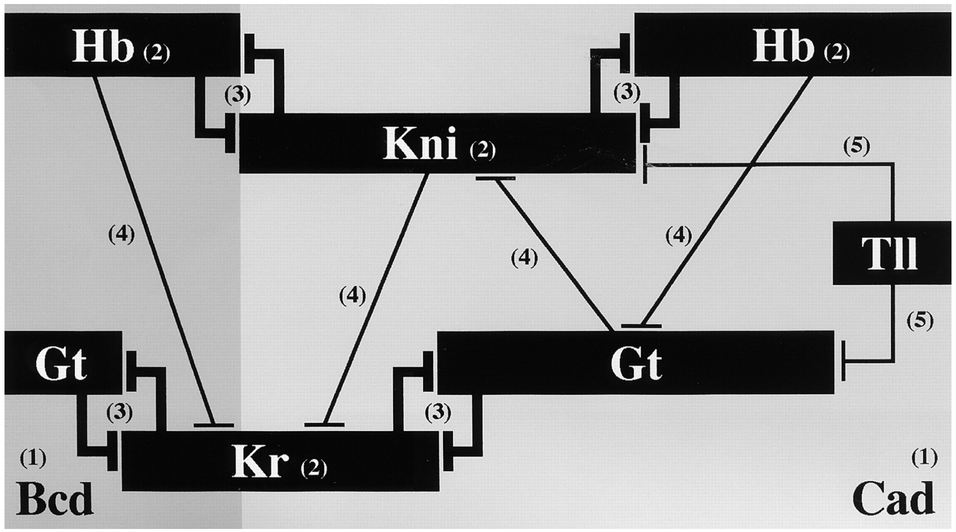


General features:

-activation by bcd and cad
(gradients)

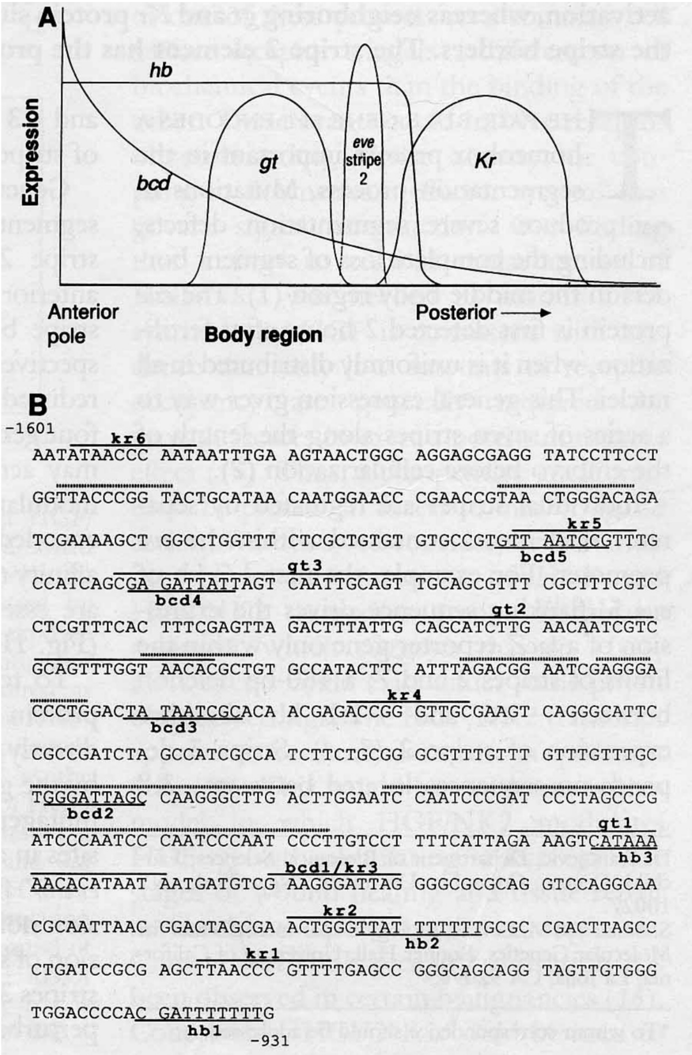
-auto-activation

-strong mutual repression of Hb/Kni and Gt/Kr

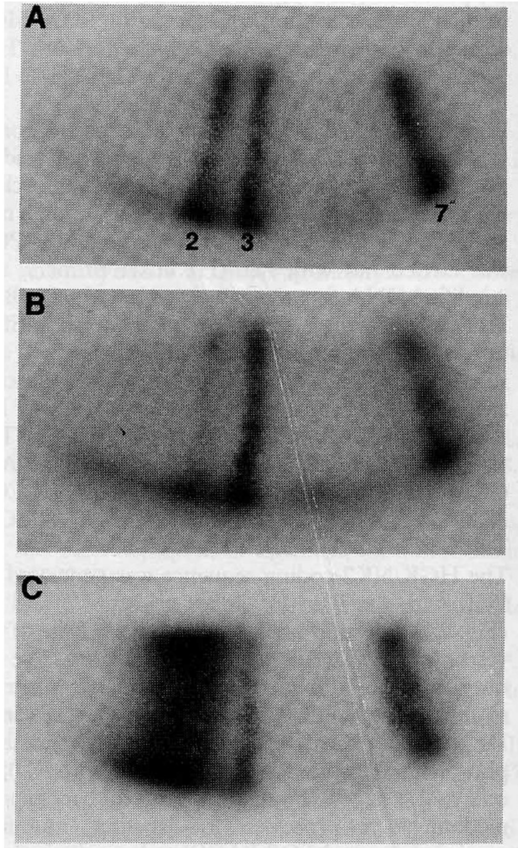


Pair-rule gene stripes are specified one by one : the *eve* case.

3 enhancers for single stripes 1, 2, 5
2 enhancers for pairs of stripe 3+7, 4+6



eve2
enhancer



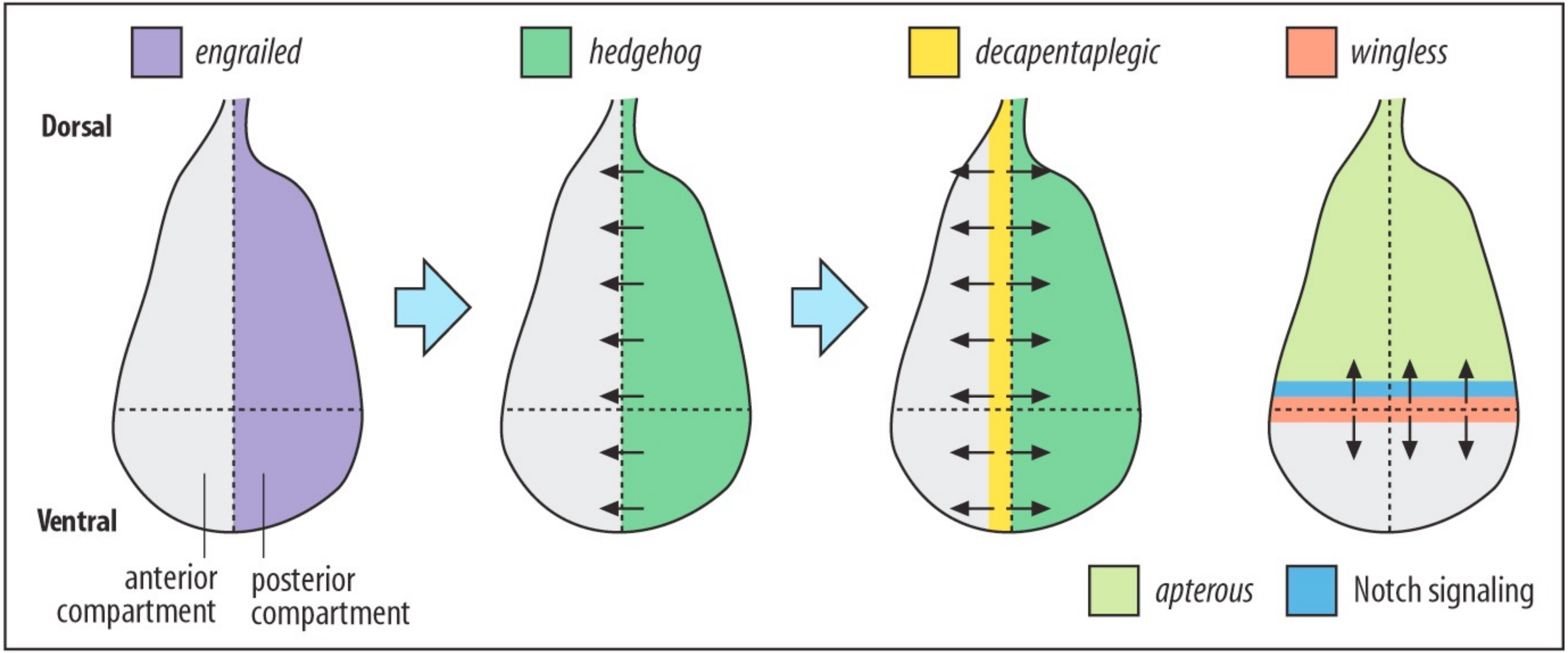
Mutations :

bcd1-kr +
bcd2 sites

gt1+gt2+
gt3 sites

D Stajonevic, S. Small, M Levine, Science (1991)

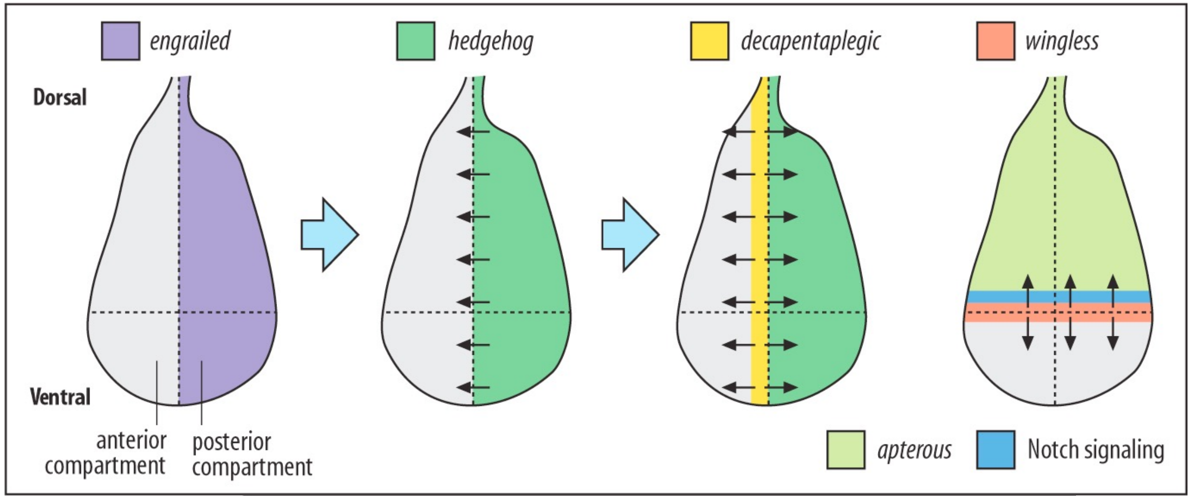
Patterning the wing disc

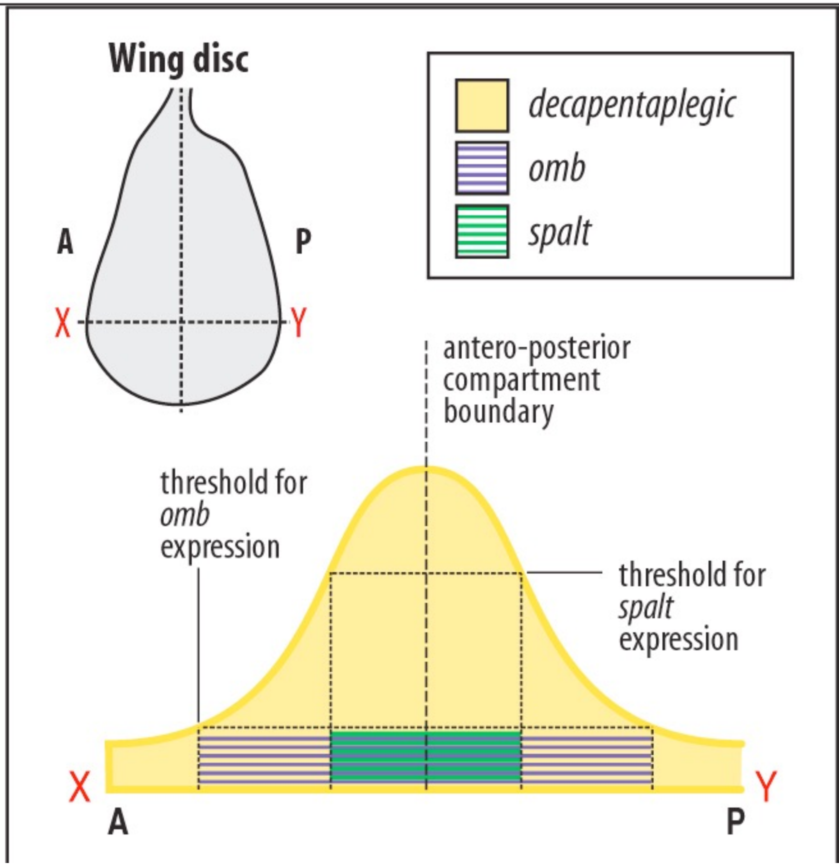


-Engrailed inherited from previous patterning
-Posterior Engrailed active cells express hh
-Anterior Engrailed-negative responsive to hh signalling
-Expression of Dpp at the anterior boundary (responsive cells+signals)

B. E. Staveley

Patterning the wing disc





B. E. Staveley

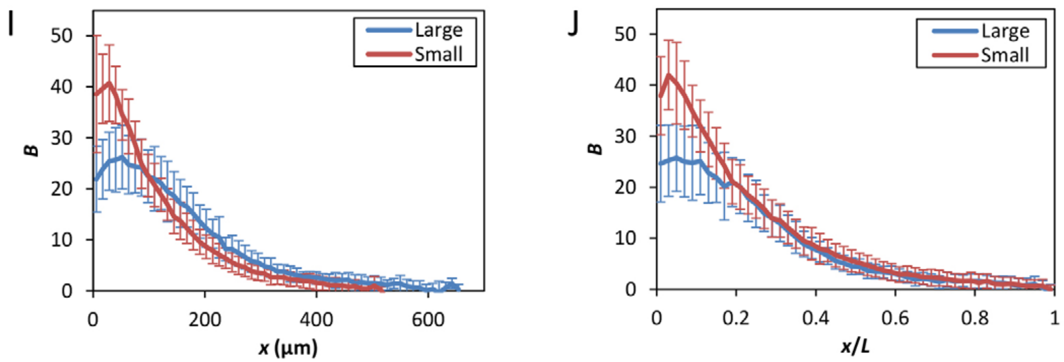
Different organisms : how can the gradient scale with size?

Question : the diffusion depends on molecular parameters.
How can it be adapted to the size of an organism?

Different species : possible adaptation of the degradation rate by evolution.
but how to buffer environmental fluctuations?

Kinetic constants (production and degradation rates
depend on factors on the size of the organism : **expander E**

<u>Simple illustrative example</u>
Size s
E produced at a constant rate, degraded everywhere $E/E_0 \sim (s_0/s)$,
If $\delta=\delta_0 (E/E_0)^p$ then, $l=(D/\delta)^{1/2} \sim =(D/\delta_0)^{1/2} (s/s_0)^{p/2}$,
scaling with size L with e.g. $s\sim L^2$ and p=1, s~L and p=2



Scaling in large (626 mm) and small (507mm) fly embryo
Cheung et al, dev. (2011,2014)

Reviews: Ben-Zvi, Barkai (2011), Umulis, Othmer (2013)

Patterning and growth control by membrane-tethered Wingless

Cyrille Alexandre[1]*, Alberto Baena-Lopez[1]* & Jean-Paul Vincent[1]

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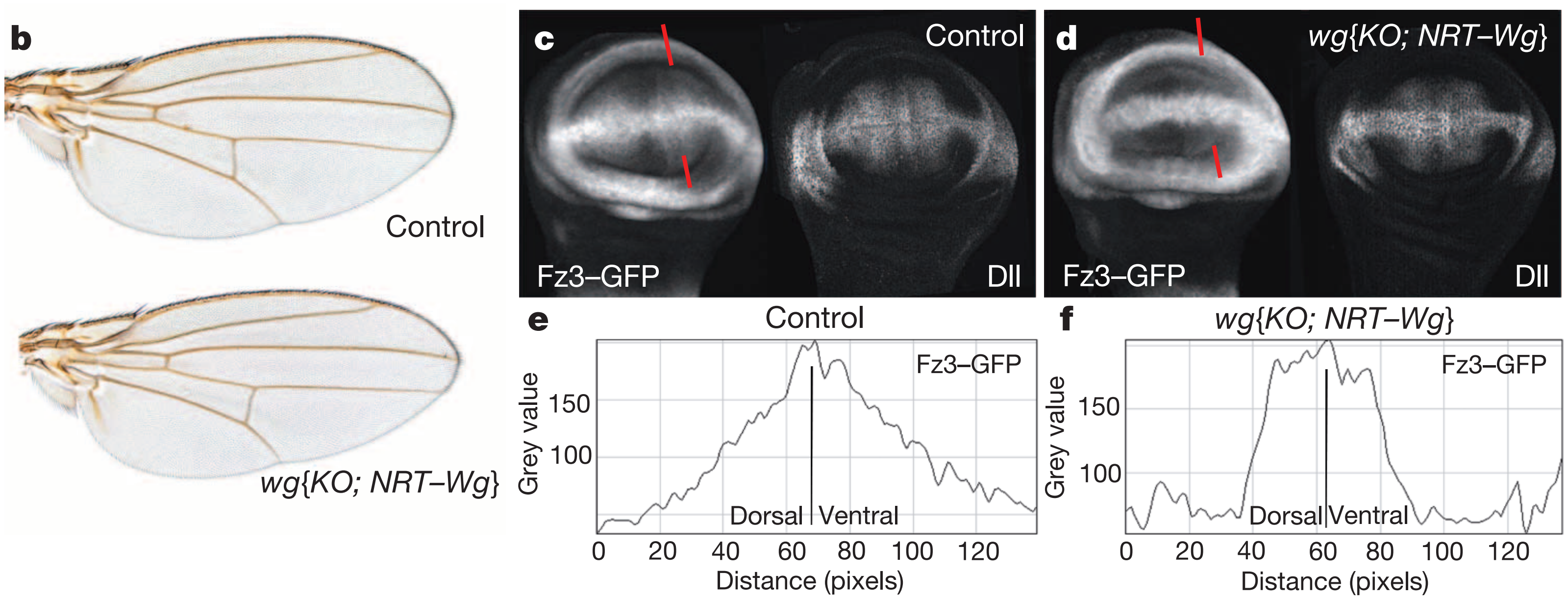
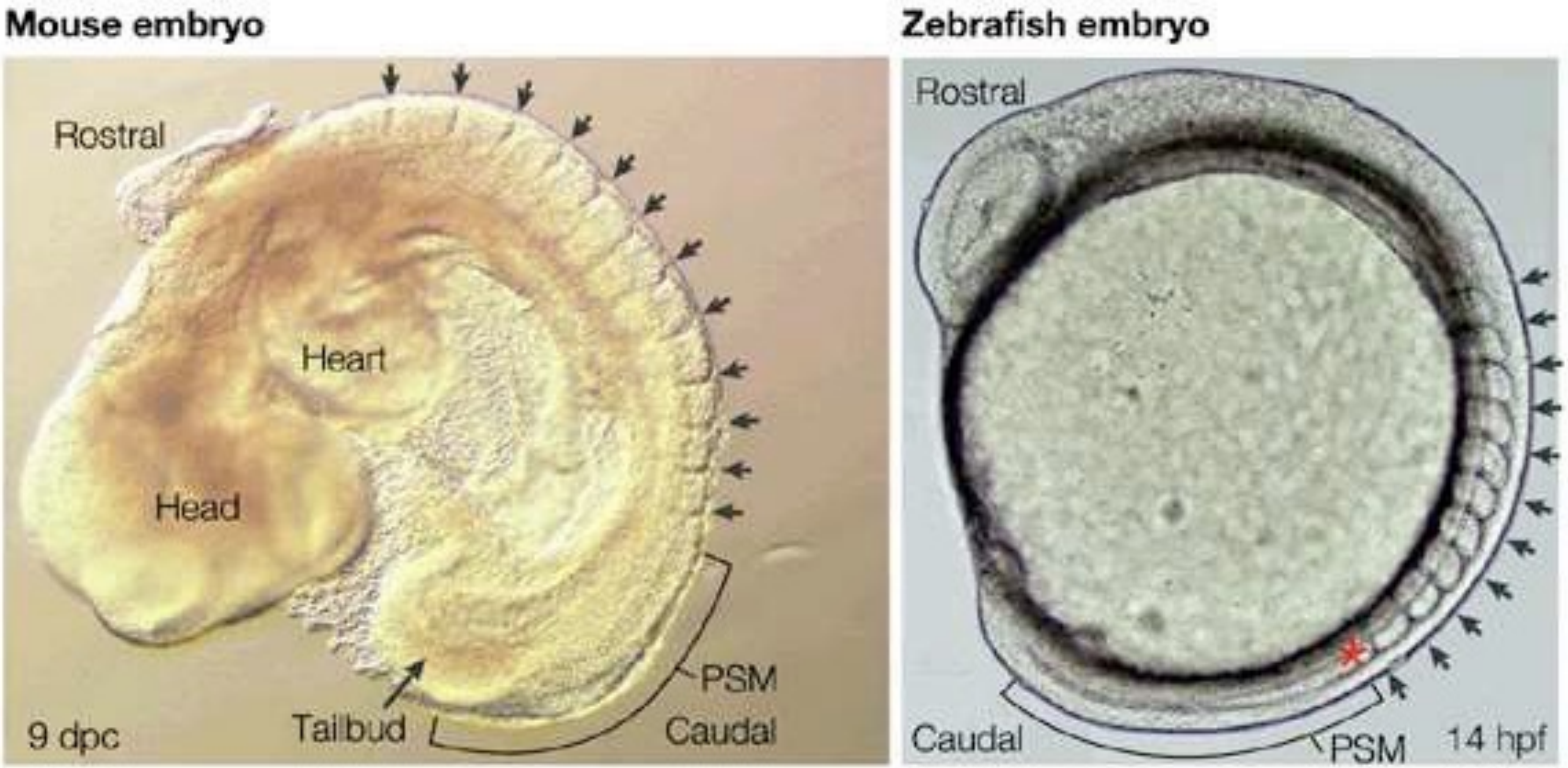


See also, Matsuda,..., Affolter, Nat. Comm (2021) for DPP.

Pattern formation in a dynamic gradient

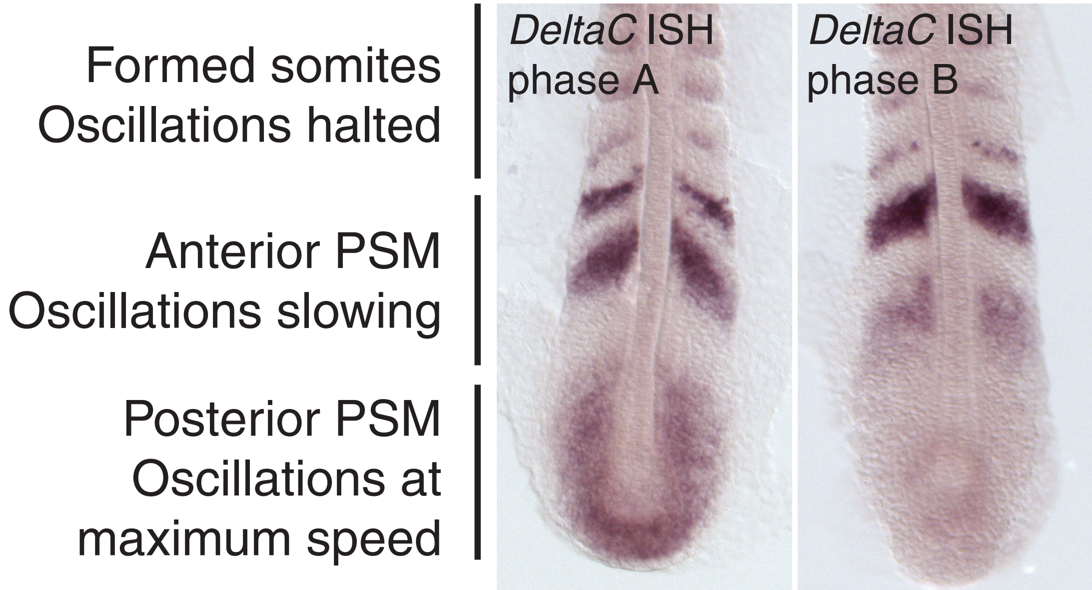
Segmentation in a dynamic gradient : somite formation in vertebrates



Y Saga, Nat Rev Gen (2001)

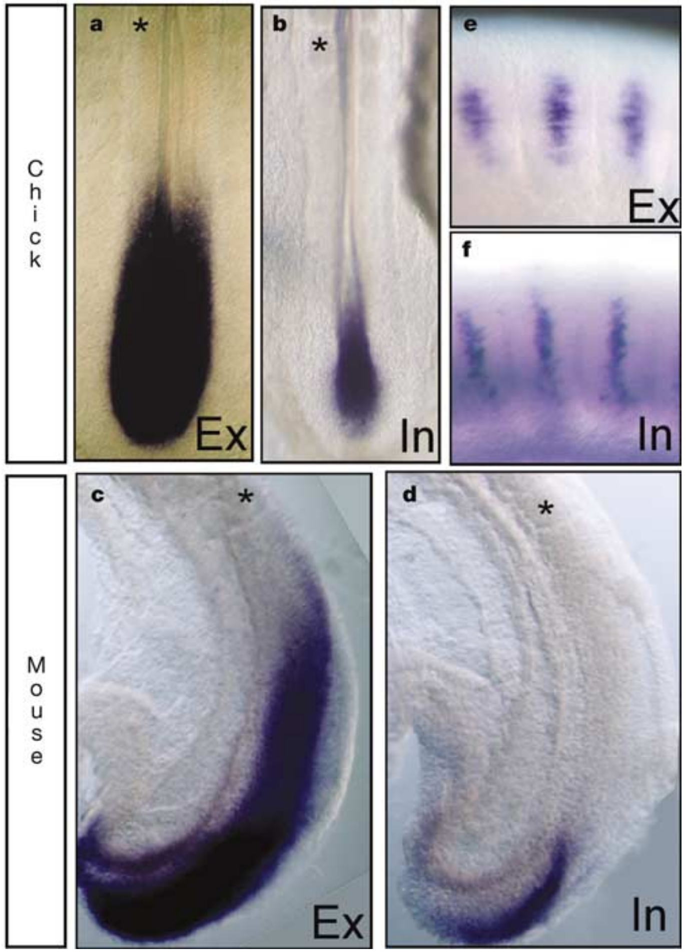
Somitogenesis and oscillations

Cooke & Zeeman (1976) -> Palmeirim et al (1997)



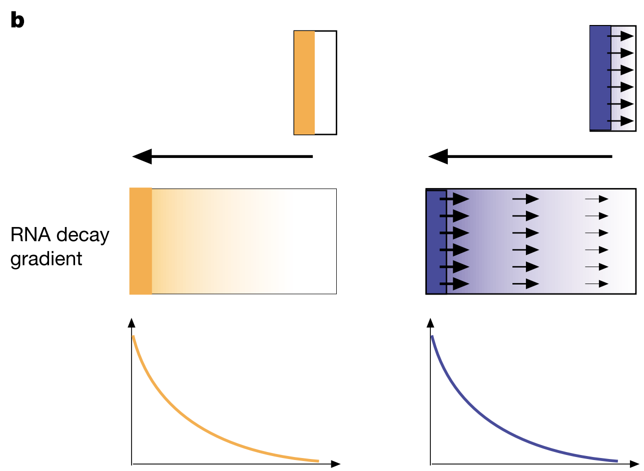
J Lewis, J Biology (2009)

FGF8 gradient without diffusion

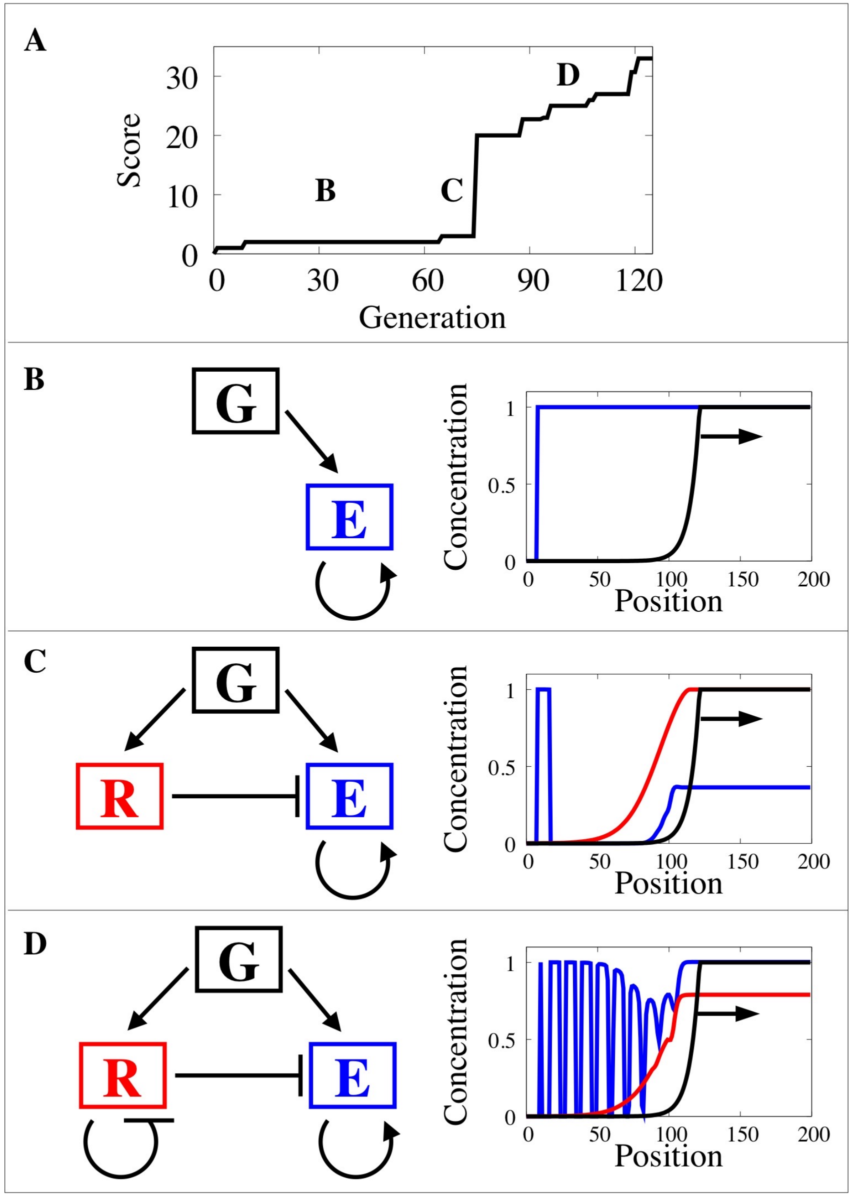


-fgf8 gene only transcribed in the tail bud (detected by intronic probe)
-fgf8 mRNA simply decay when the cells go out of the growth zone

Dubrulle & Pourquié, Nature (2004)



Somitogenesis : a transition from oscillation to bistability ?



P François et al, MSB (2007)

Segmentation is an ancient invention

Questions of evolution (evo-devo)

-How does segementation evolve?

-How does the different patternings between different insects arise?

-How does one go from an oscillatory mechanism to patterning in a « static » gradient?

See Rotschild,..., François, PLos Gen. (2016) for a model/discussion
Diaz-Cuadros, Pourquié, El-Sherif , Plos Gen (2021) for a review

The End