Physics of multicellular systems 2023

Lecture 4

Self-organization II :
Waves, localized states and cell-cell interaction

Bistability with diffusion : front

$$\partial_t u = D\partial_{xx}u + f(u)/\tau$$

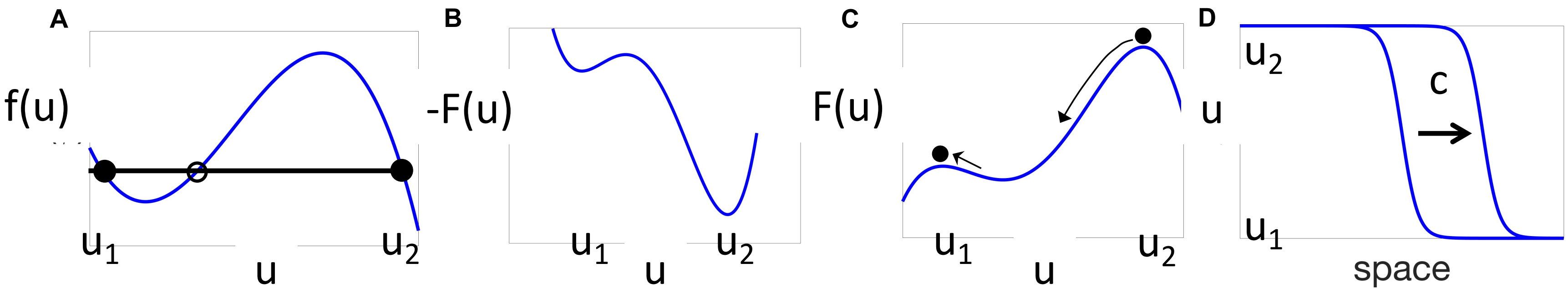
Front solution: u(x-ct)

$$-c\tau\,\partial_x u = D\tau\,\partial_{xx}u + f(u)$$

Length scale (front width) $\sim \sqrt{D\tau}$, front propagation speed $\sim \sqrt{D/\tau}$

$F'(u) = f(u)$, x<->t eq. of movement for a particle in the double-hill potential F(u)

c : **critical friction** to end on the top of the low hill starting from the top of the high one



An exactly solvable case

$$-c\tau\,\partial_x u = D\tau\,\partial_{xx} u + f(u)$$, f(u)= u(u-a)(1-u) with 0<a<1

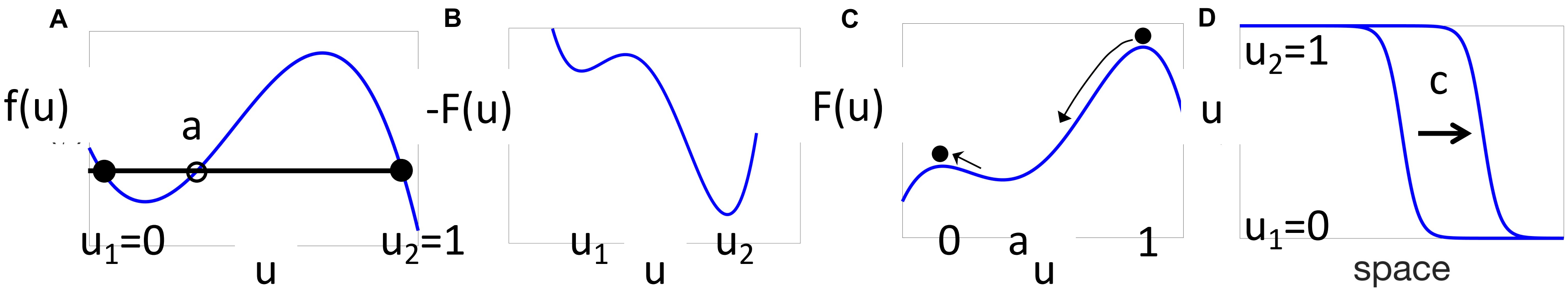
Idea : **try** the integrable form **du/dx =g(u)** and find g(u) if possible.

$$c\tau\ g(u) + D\tau g'(u)g(u) = -f(u) = u(u-a)(u-1)$$

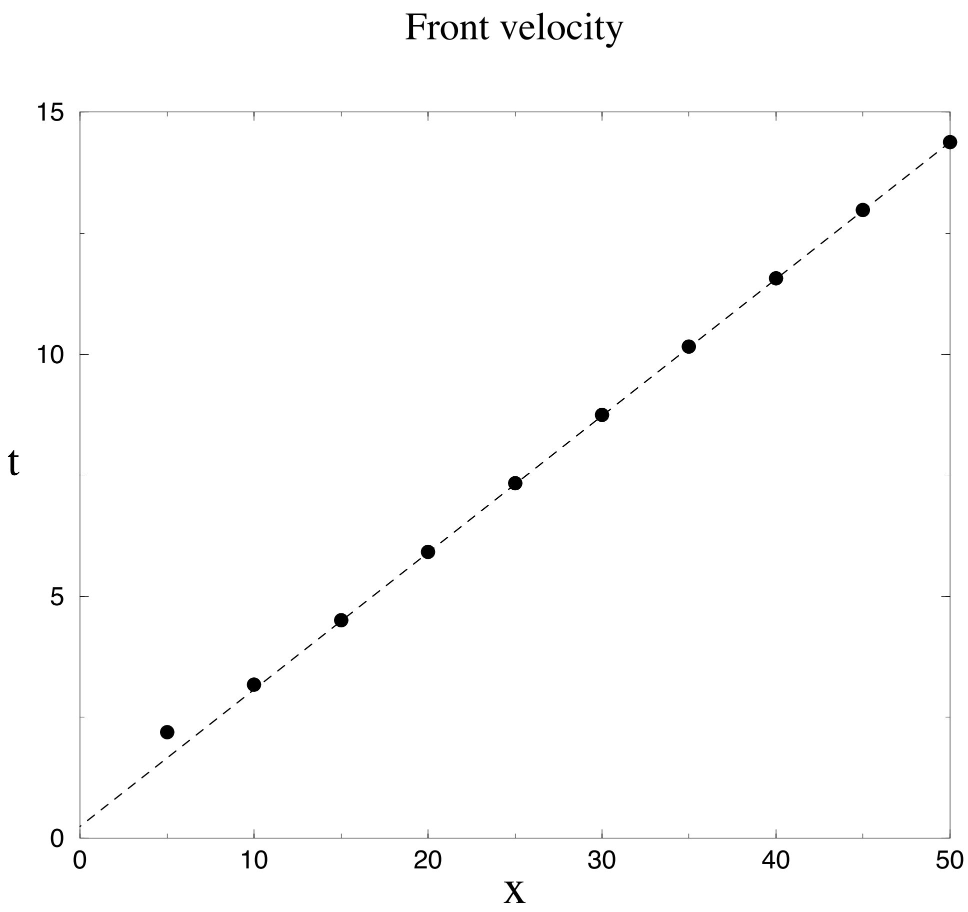
g(u) 2nd order polynomial with g(0)=g(1)=0 (boundary conditions for u)

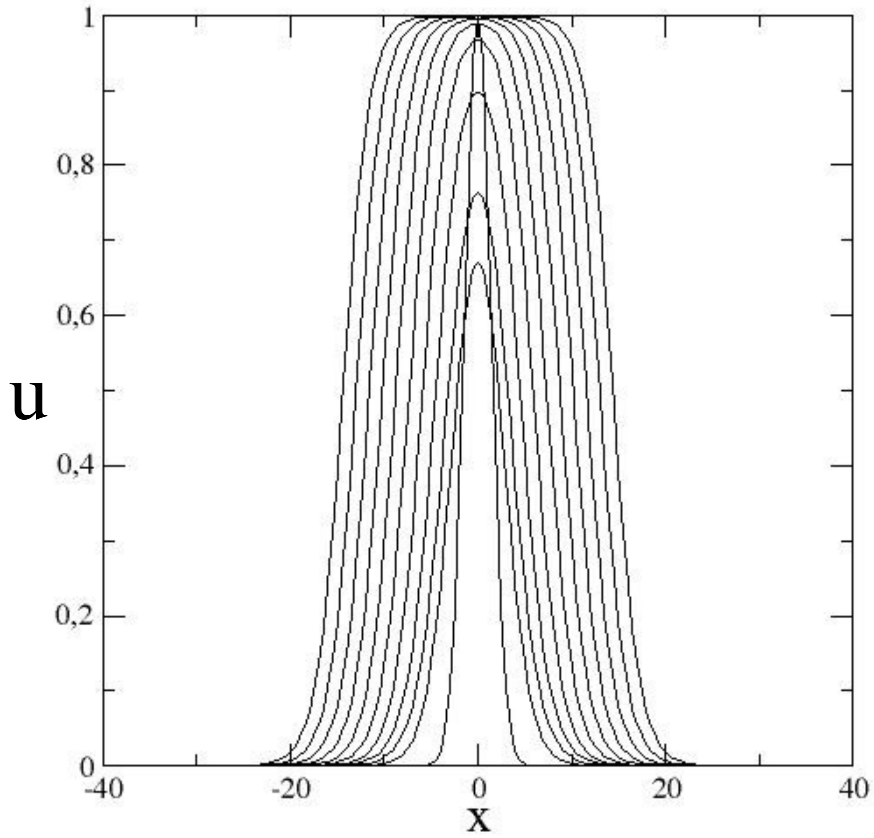
=> g(u)= K(u-1)u with $K = \frac{1}{\sqrt{2D\tau}},\ c = \sqrt{\frac{2D}{\tau}}(\frac{1}{2} - a)$

$$u(x) = \frac{\exp[(x_0 - x)/\sqrt{2D\tau}]}{1 + \exp[(x_0 - x)/\sqrt{2D\tau}]}$$



Domain growth and front velocity





Perturbative calculation of the front propagation speed

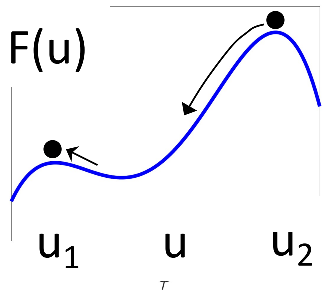
-**Equal** potential depths/**heights** $F(u_1)=F(u_2)=F_0$, no friction necessary => c=0

Front shape from particle motion integrability (conservative in a 1D potential)

$$D\tau\,\frac{d^2u_0}{dx^2}+f(u_0)=0\Rightarrow\frac{D\tau}{2}\left(\frac{du_0}{dx}\right)^2+F(u_0)=F_0$$

$$\int_{u_0(x)}^{u_0(0)}\frac{du}{\sqrt{F_0-F(u)}}=\sqrt{\frac{2}{D\tau}}x$$

-Potential with **unequal heights** $F(u)+\delta F(u)$, $u(x)=u_0(x)+u_p(x)$



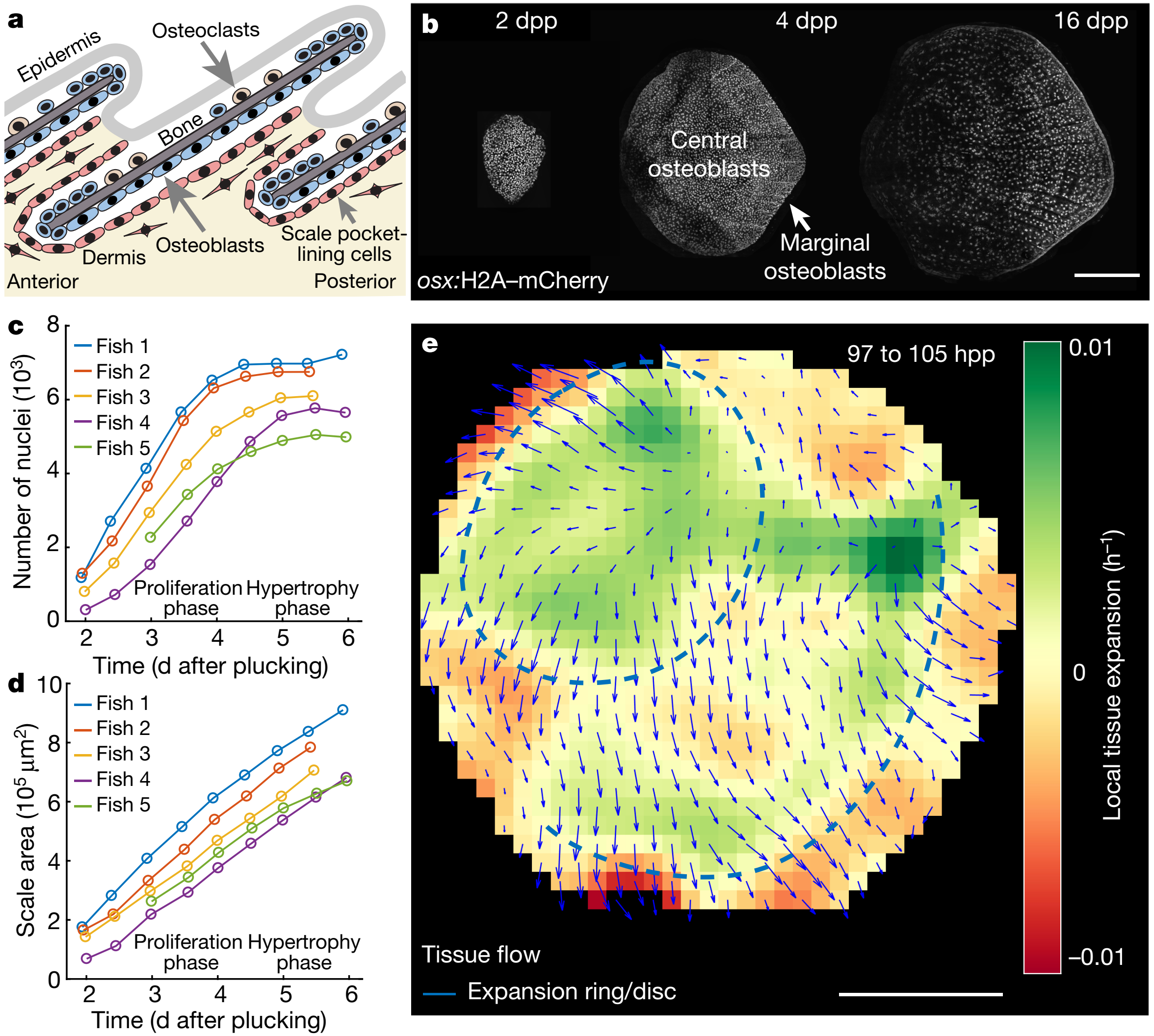
$$D\tau\,\frac{d^2u_p}{dx^2}+f'[u_0(x)]u_p=-c\tau\,\frac{du_0}{dx}-\delta f[u_0(x)]$$

du_0/dx zero-mode of the (self-adjoint) linear operator => solvability condition

$$c\tau\;=\frac{-\int_{-\infty}^{+\infty}dx\,\frac{du_0}{dx}\delta f[u_0(x)]}{\int_{-\infty}^{+\infty}dx\left(\frac{du_0}{dx}\right)^2}=\frac{\delta F(u_2)-\delta F(u_1)}{\int_{-\infty}^{+\infty}dx\left(\frac{du_0}{dx}\right)^2}$$

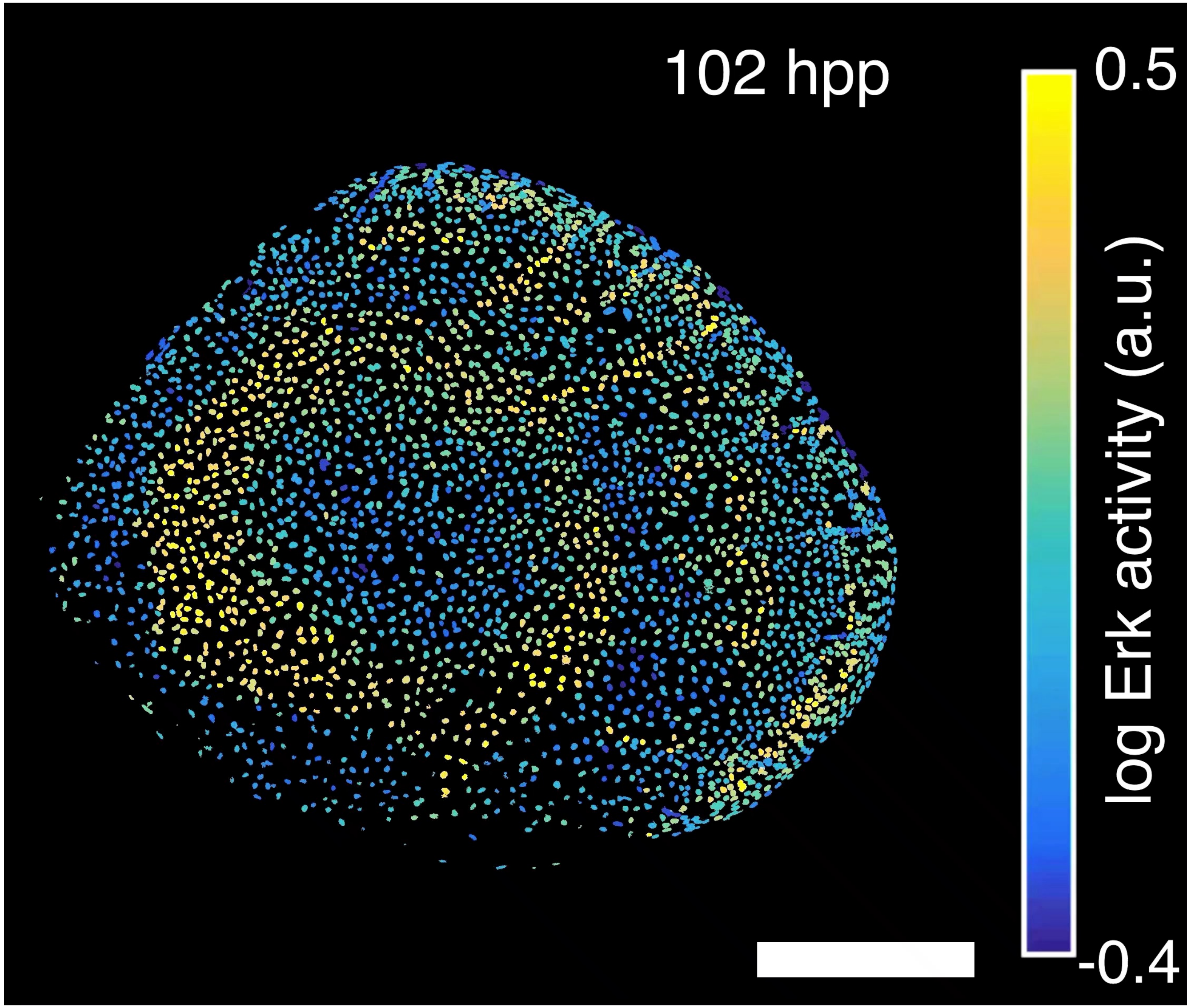
(potential energy dissipated by friction)

Regeneration of fish scales



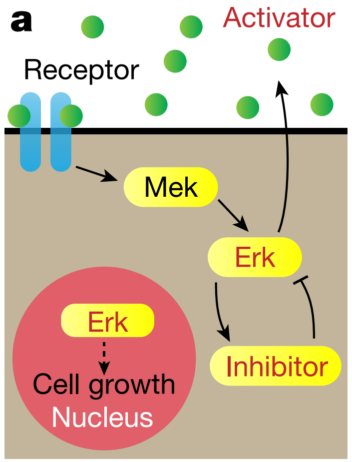
De Simone,..., Di Talia, Nature (2021)

ERK waves during regeneration



De Simone,..., Di Talia, Nature (2021)

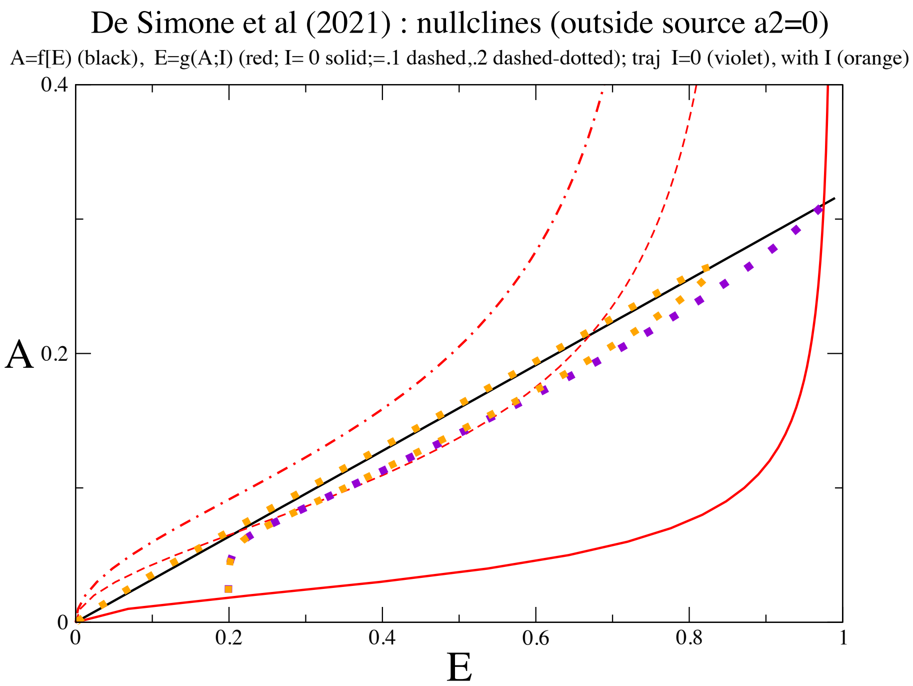
ERK auto-activation and inhibition



$$\frac{dE}{dt} = \frac{\alpha_1 A^2}{\beta_1^2 + A^2}(1 - E) - E(\gamma_1 I + \gamma_e)$$

$$\frac{\partial A}{\partial t} = \alpha_2 + \alpha_3 E - \gamma_2 A$$

$$\frac{dI}{dt} = \gamma_3(\alpha_4 E - I)$$



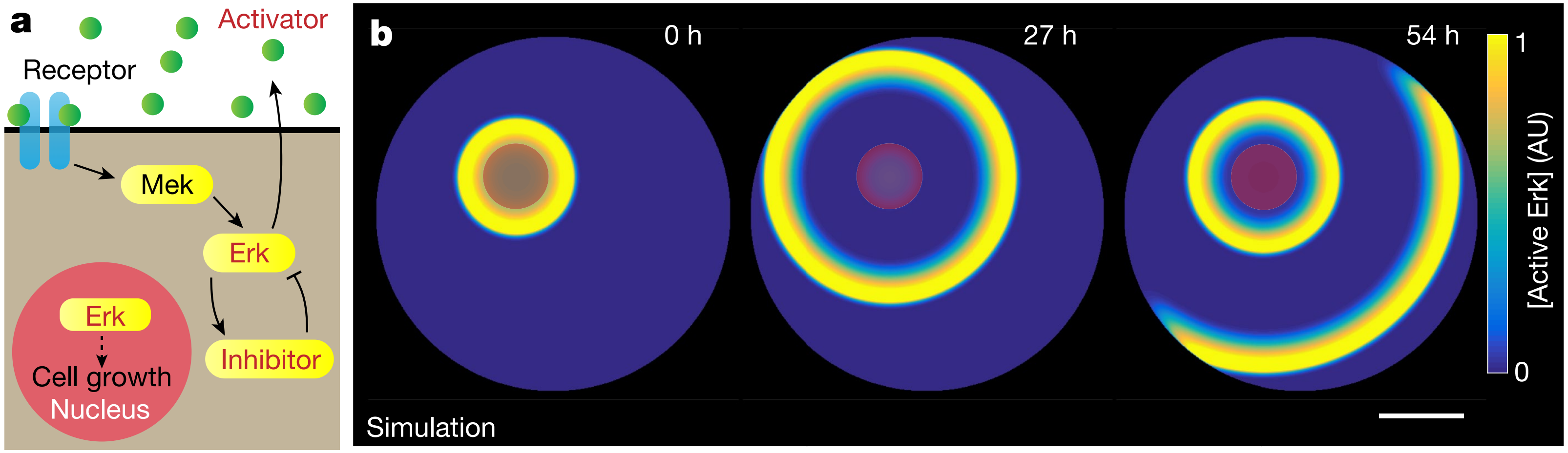
$$A = (\alpha_2 + \alpha_3 E)/\gamma_2 = f(E)$$

$$E = \frac{\alpha_1 A^2}{\beta_1 + A^2}\left[\gamma_e + \gamma_1 I + \frac{\alpha_1 A^2}{\beta_1 + A^2}\right]^{-1}$$

(α_2 =0 ; non-zero only in the source region)

De Simone,..., Di Talia, Nature (2021)

ERK waves during regeneration



$$\frac{dE}{dt} = \frac{\alpha_1 A^2}{\beta_1^2 + A^2}(1 - E) - E(\gamma_1 I + \gamma_e)$$

$$\frac{\partial A}{\partial t} = \alpha_2 + \alpha_3 E - \gamma_2 A + D\nabla^2 A$$

<- diffusion of activator

$$\frac{dI}{dt} = \gamma_3(\alpha_4 E - I)$$

Erk activation time ~ a few hrs

c_{wave}~10 μm/h -> D ~ 0.1 μm^2/s

α_2 non-zero only in the source region

De Simone,..., Di Talia, Nature (2021)

Localized states

Turing-like short-range activation, long-range inhibition

$$\partial_t u = D_u \partial_{xx} u + f(u, v)/\tau$$

$$\tau \partial_t v = \lambda^2 \partial_{xx} v + u - v$$

Ex: $f(u,v) = u(u-a-v/2)(1-u)$,
$a<1/2$: $u=1$ favored

$\lambda \gg (D\tau)^{1/2}$, almost square profile of u on the λ-scale
$u=1$ (high-state) for $-L/2<x<L/2$, $u=0$ otherwise

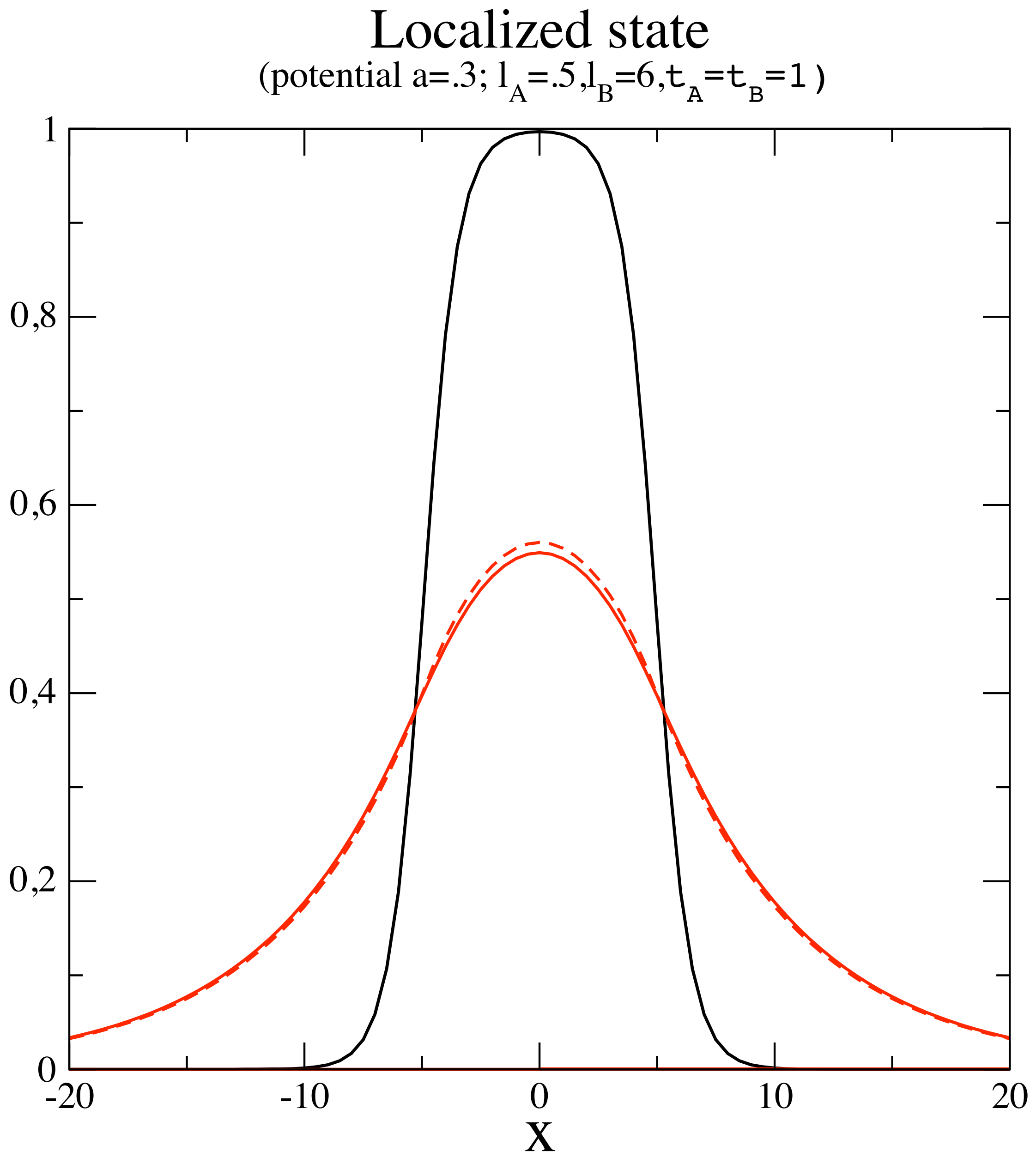
$\Rightarrow v = 1 - \alpha \cosh(x/\lambda)$, $-L/2<x<L/2$
$v = \beta \exp[-(x-L/2)/\lambda)]$, $x>L/2$

Matching at $x=L/2$ (continuous function and derivative)

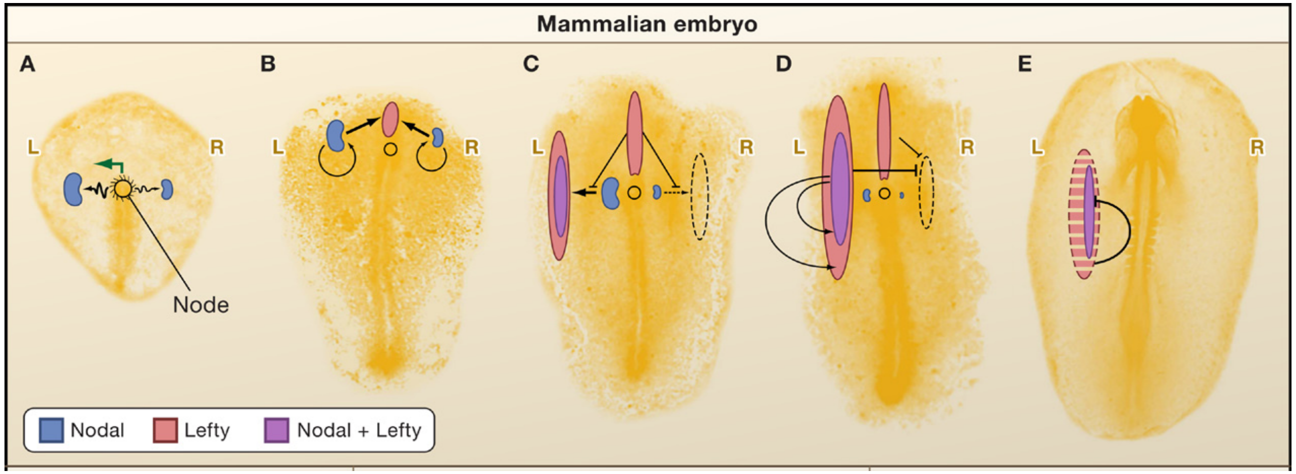
$\Rightarrow \alpha = \exp(-L/2\lambda)$
$\beta = ½[1-\exp(-L/\lambda)]$

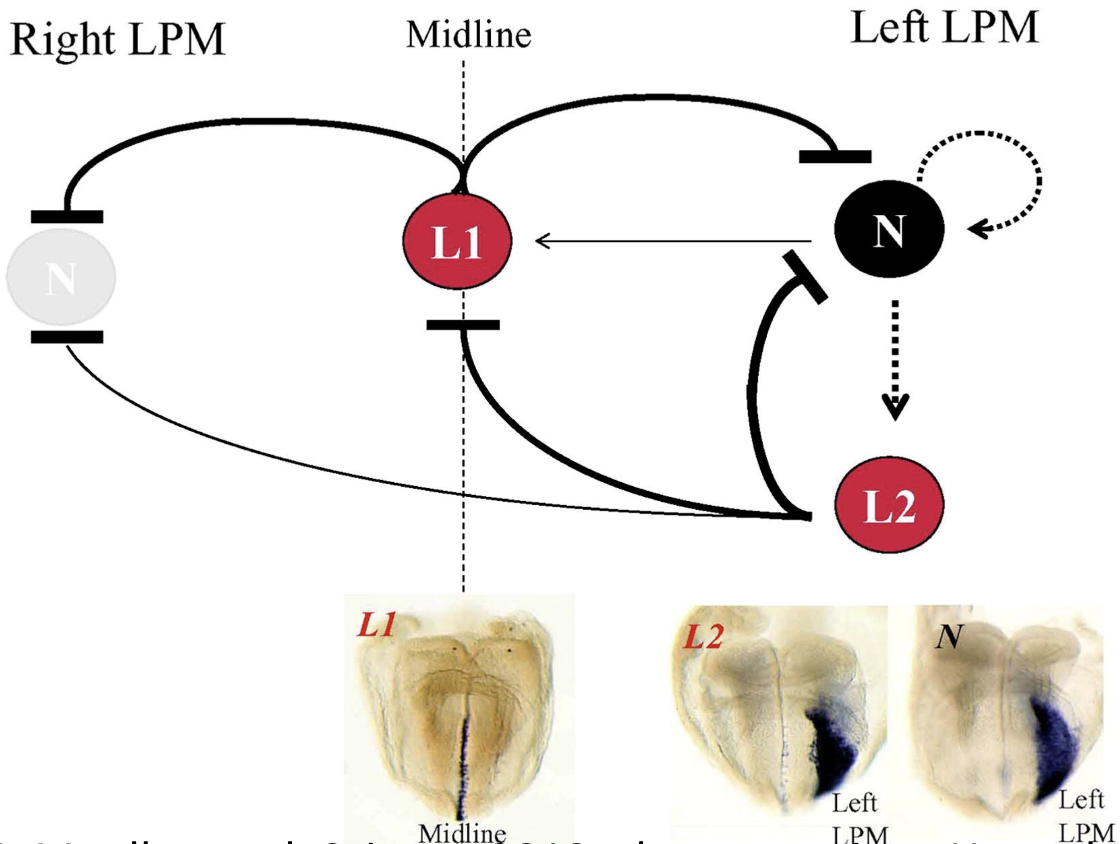
β ($=v(L/2)$) is the concentration of inhibitor at the front.
β increases with L the activated zone.
Growth of the favored activated state ($u=1$) **stops** when L large enough

Short-range activation, long-range inhibition :



Left-right asymmetry: localized expression of Nodal

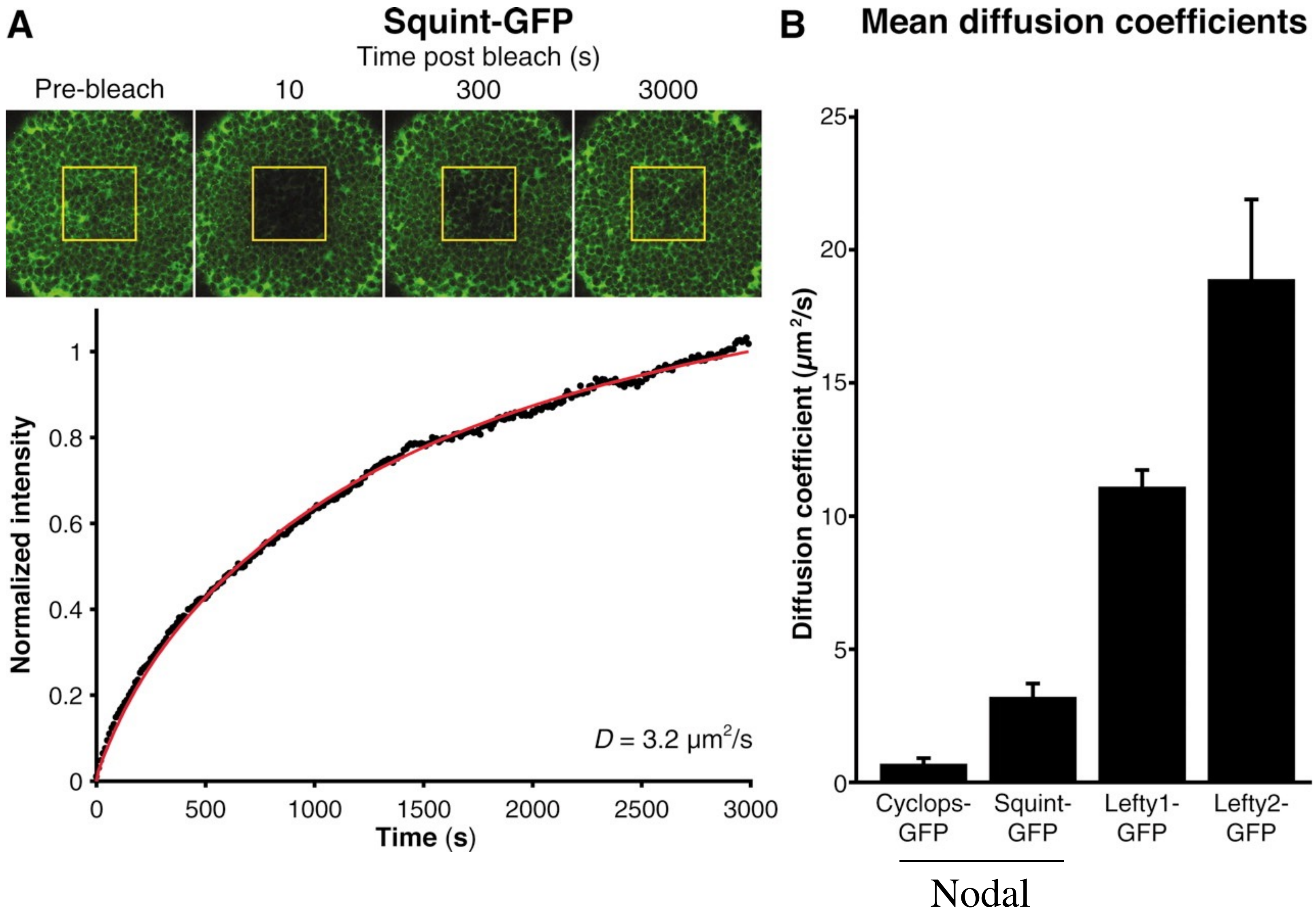




-Nodal and Lefty ligands (TGFb signalling pathway)
-Nodal activates the ` pathway (agonist)
-Lefty : antagonist

-*Nodal* and *Lefty* genes activated by Nodal

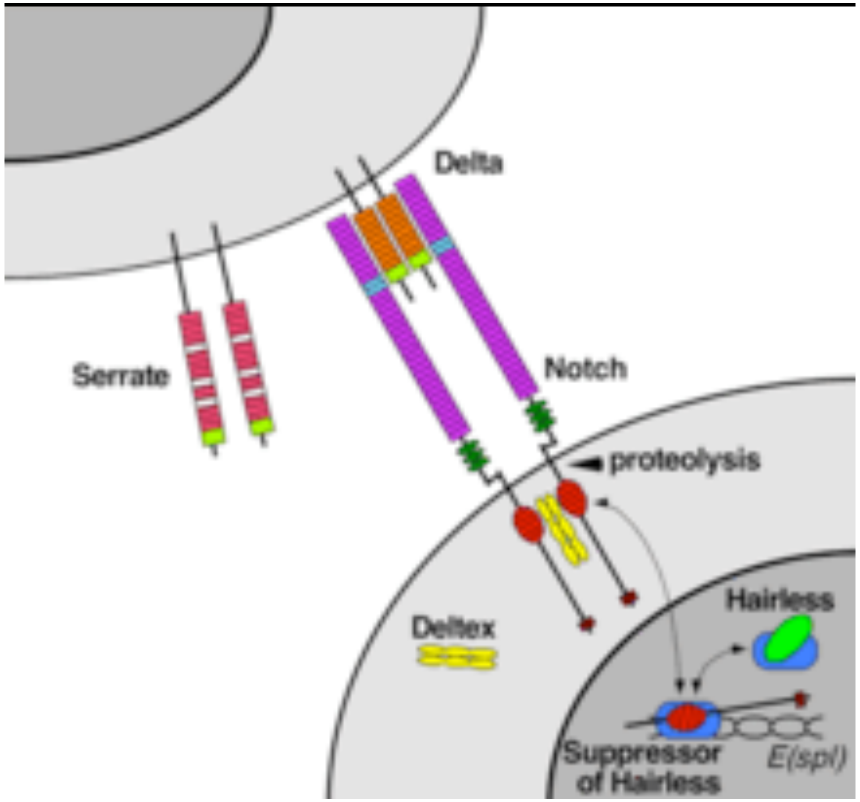
Tabin, Cell 06; Mueller et al, Science 2012 ;short overview: Hamada, Dev. Cell. (2012); also Rogers et al. eLife 2017



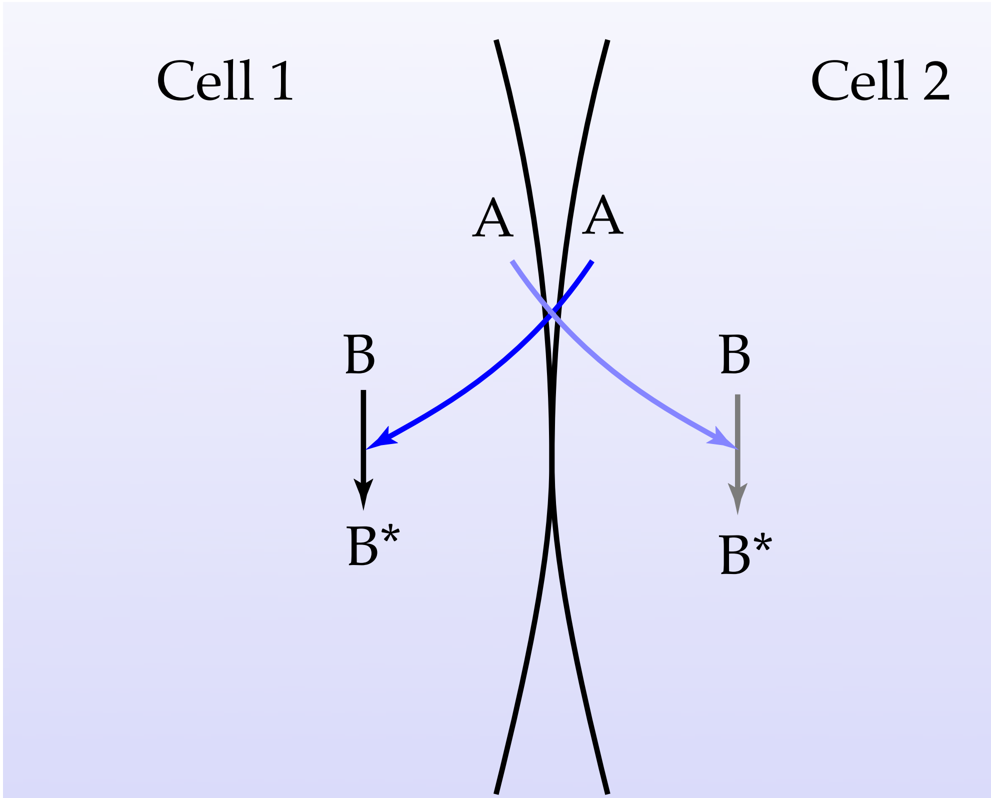
-Diffusion constant and clearance rate (pulsed photoconversion measured independently
-Caveat : ectopic expression in zebrafish embryos.

Mueller et al, Science 2012

Interactions between cells

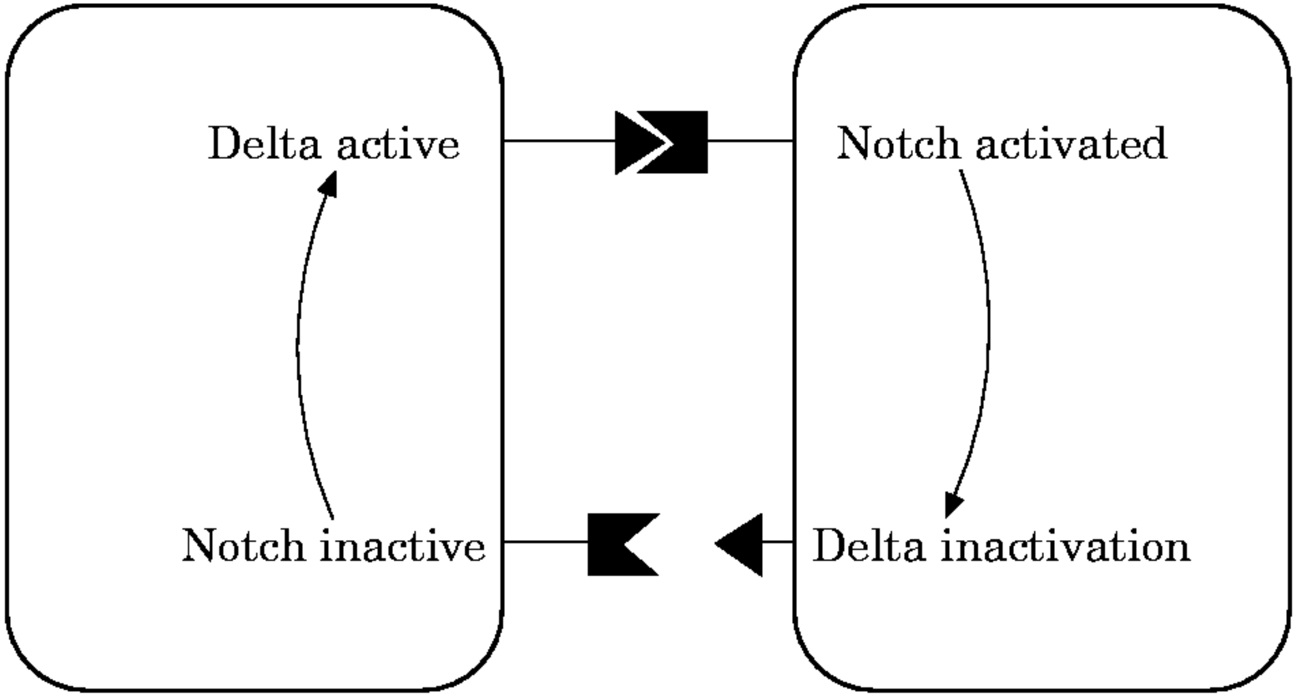


The Notch-Delta pathway
(a wikipedia view)



$$dB_2^*/dt = \gamma A_1 B_2 + \cdots$$

Lateral inhibition and symmetry-breaking



$$\frac{dN_1}{dt} = A(D_2) - \delta_N N_1$$

$$\frac{dD_1}{dt} = R(N_1) - \delta_D D_1$$

Single symmetric fixed point
D_0, N_0

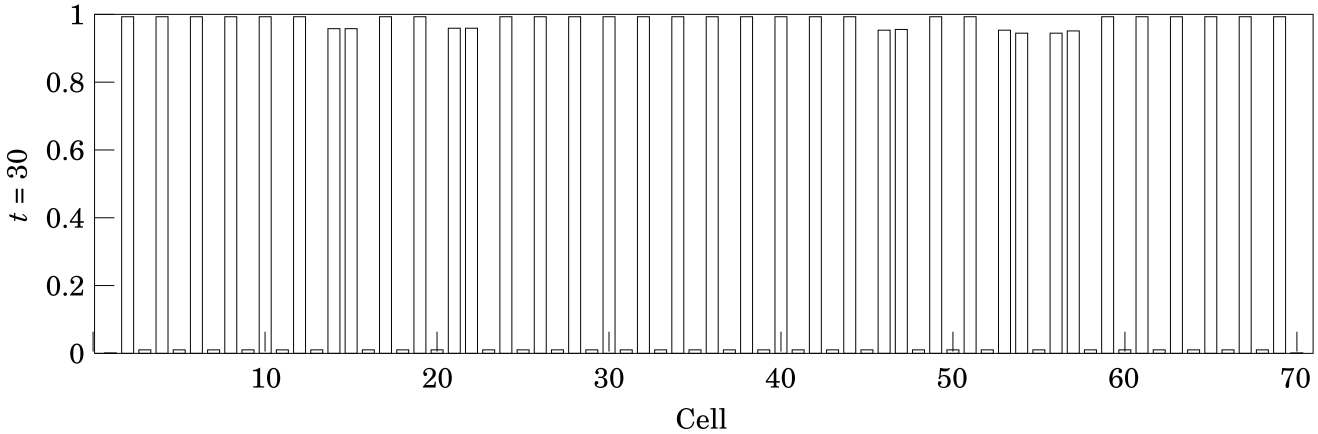
Spontaneous symetry breaking
$A'(D_0)R'(N_0)+\delta_N\delta_D < 0$

Collier, Monk et al, JTB (1996)

Lateral inhibition and symmetry-breaking

-1D patterns

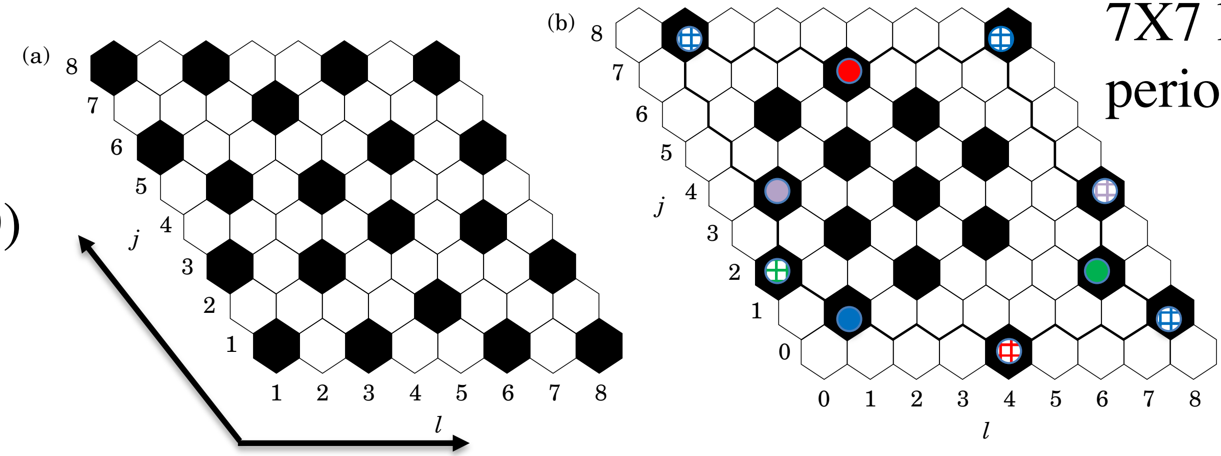
Notch level



Defects : two adjacent Notch expressing cells

-2D patterns : D expressing cells (black).

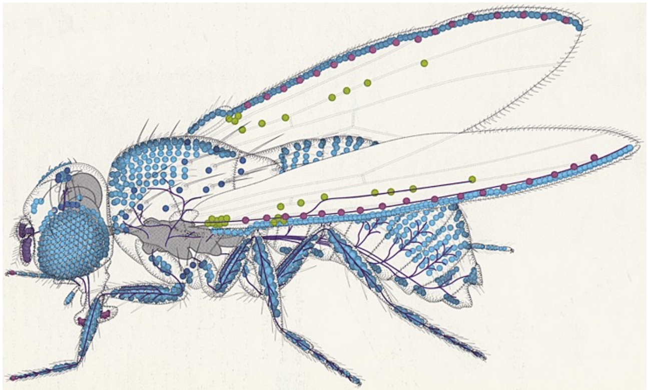
8X8 lattice
fixed boundary
condition($D_{i,j}$=0)

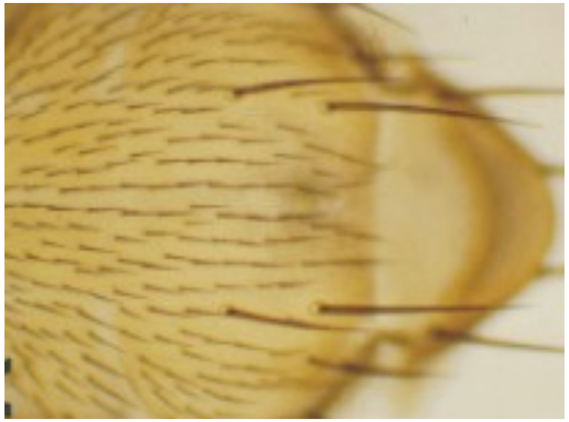


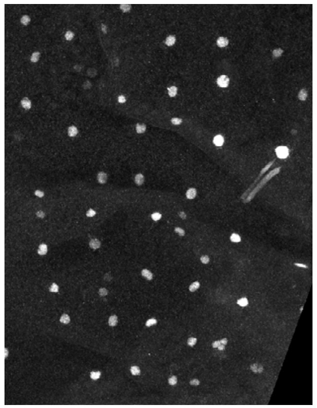
7X7 lattice
periodic boundary
condition

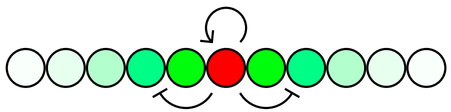
Collier, Monk et al, JTB (1996)

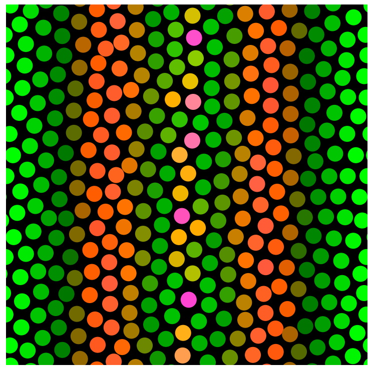
Patterns from cell-cell interactions







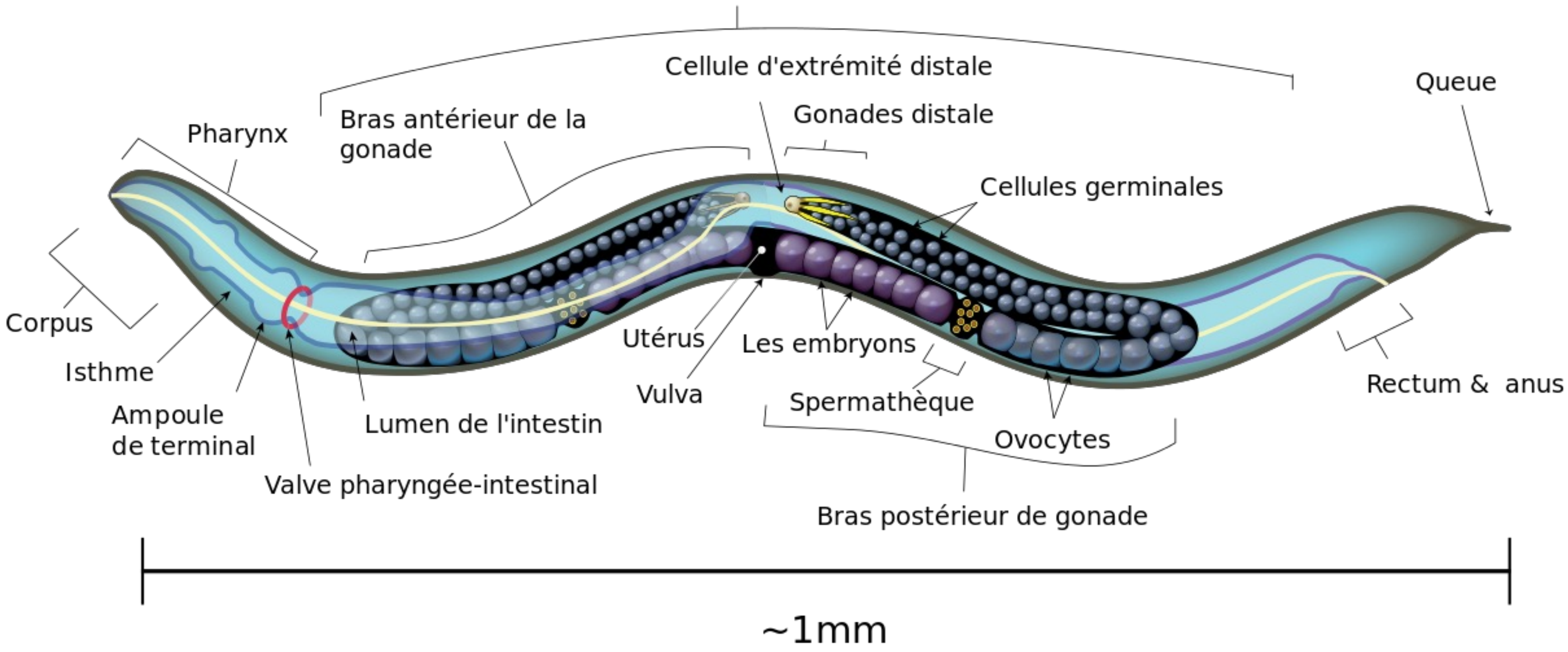




Corson,..., Schweisguth, Science (2017)

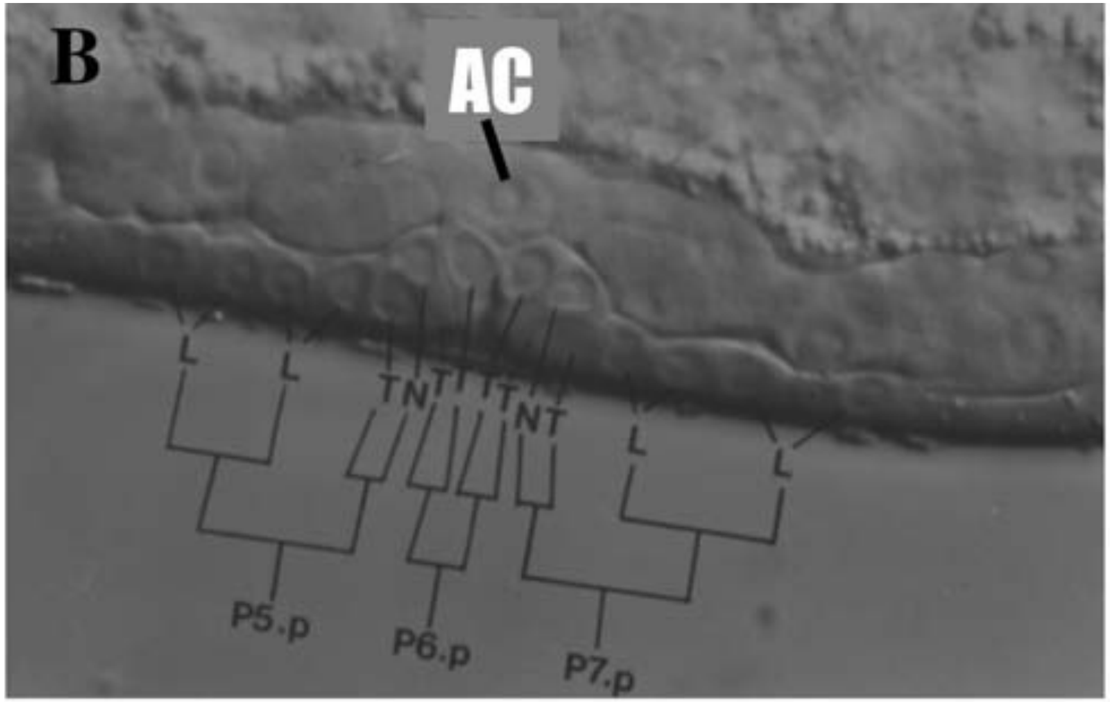
Notch-Delta signalling allows the emergence of individual Sensory-Organ-Precursor cells from the proneural stripes (also important for the stripe specification itself)

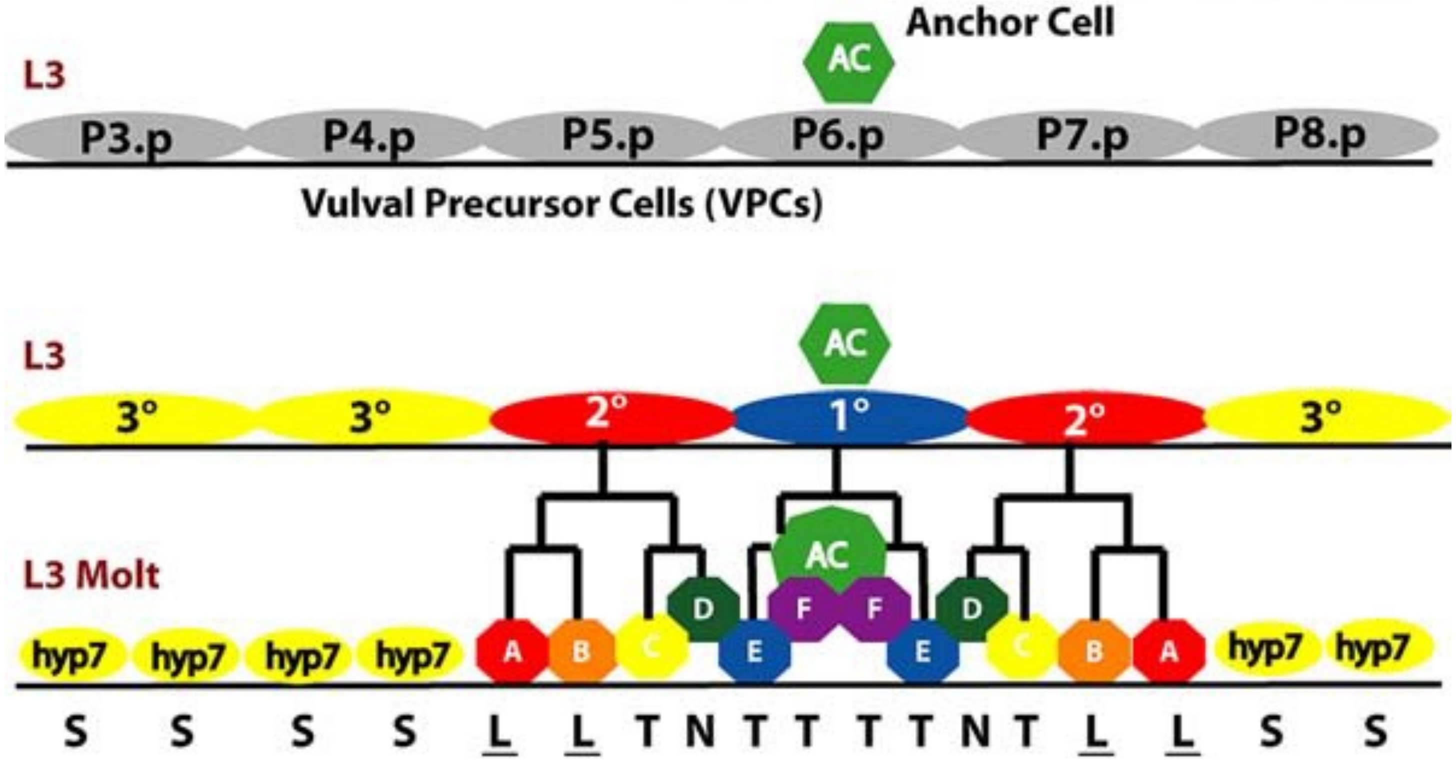
The nematode C elegans



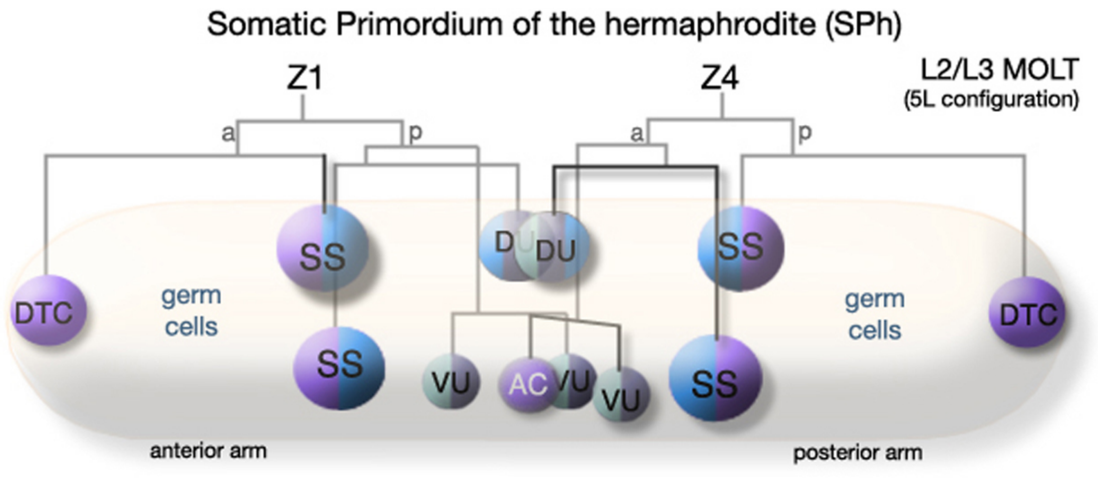
Gradient and cell-interaction : the development of the Celegans vulva.

P Sternberg, Wormbook



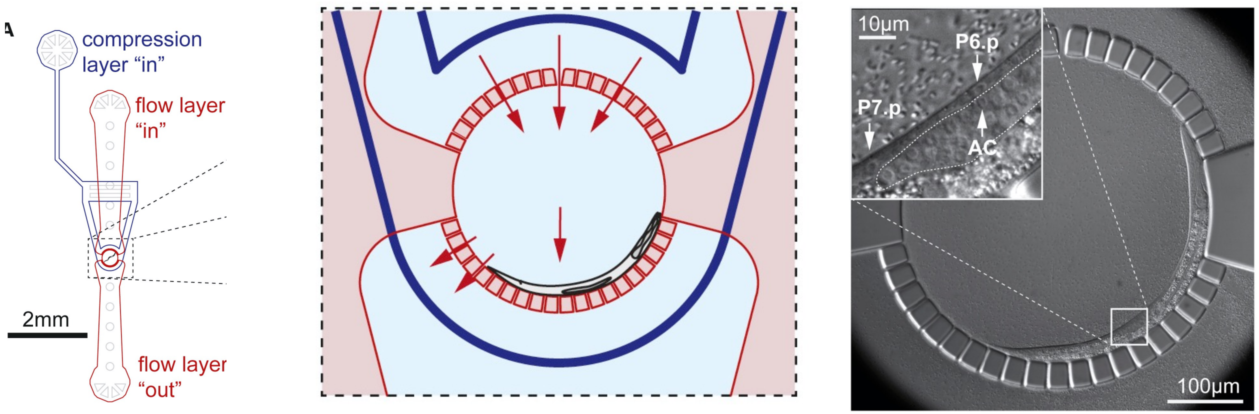


Anchor cell specification



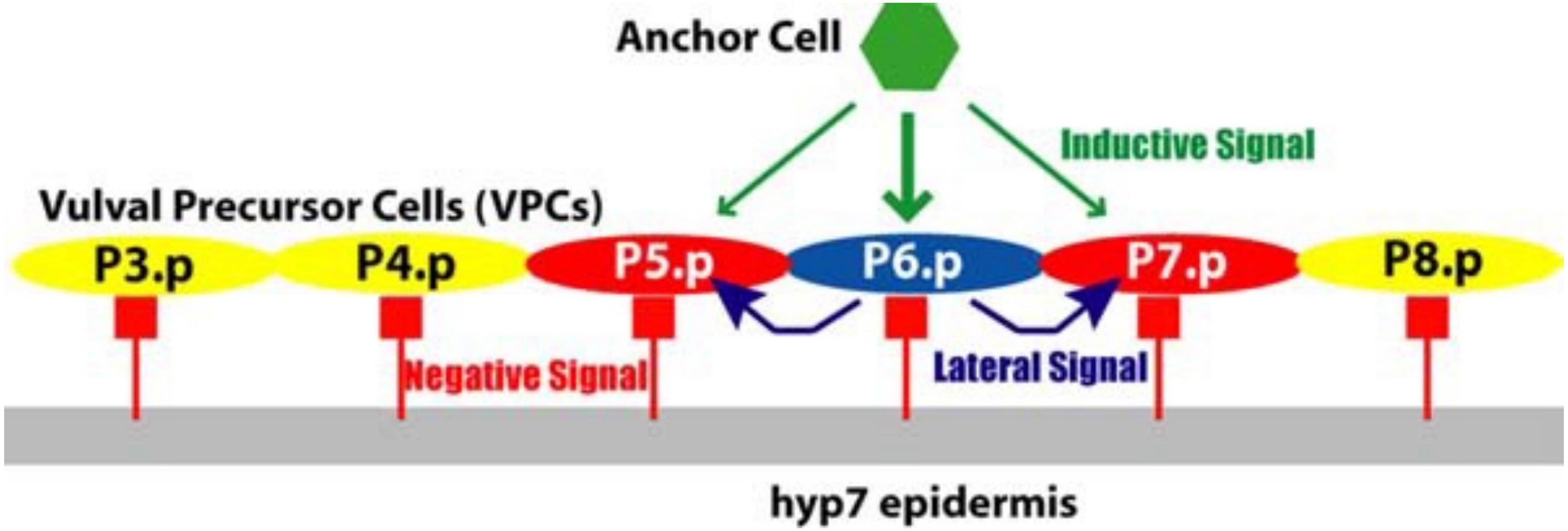
M Herman, Wormbook

Interaction between Z1ppp and Z4aaaa ->
-AC (lag2-2/Delta high) and VU (lin-12/Notch high) fates
-Stochastic but biased by birth order of cells
(Karp & Greenwald, 2003; Attner, Keil et al, 2019)



Microfluidic device for long-term imaging

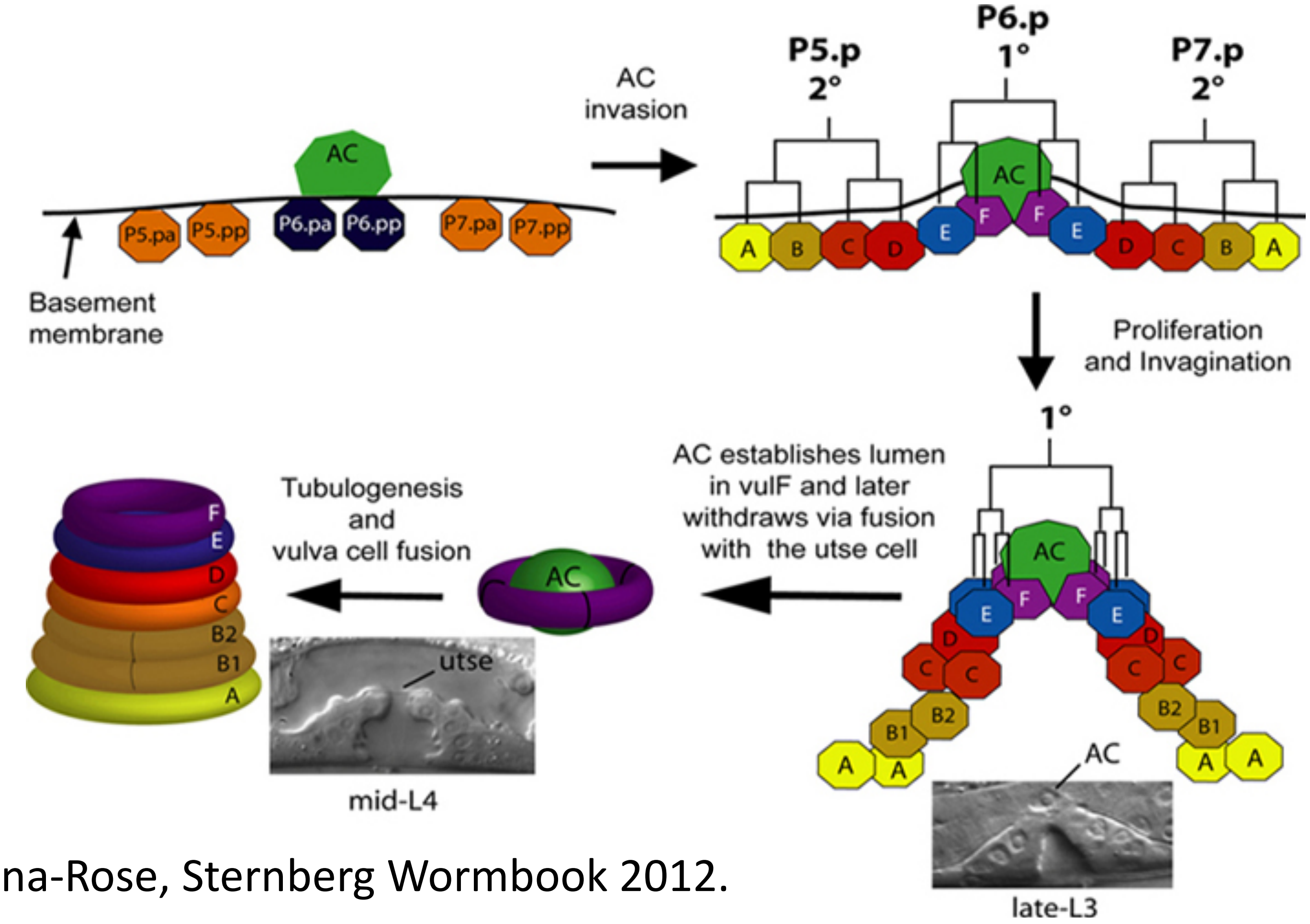
Keil et al, 2017



Both a gradient (EGF) and cell-cell interactions (Notch-Delta)

TD: geometric modeling starting from a tristable cell fate
Accounts with noise for partially penetrant mutations

Morphogenesis of the C elegans vulva



Gupta, Hanna-Rose, Sternberg Wormbook 2012.

To precisely understand and describe this kind of phenomena, one needs to incorporate **cell and tissue mechanics** and their interplay with signalling ->

Set of lectures by Hervé Turlier (and TDs)!

The End