

Physics of multicellular systems 2022

Lecture 4

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

Bistability with diffusion : front

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

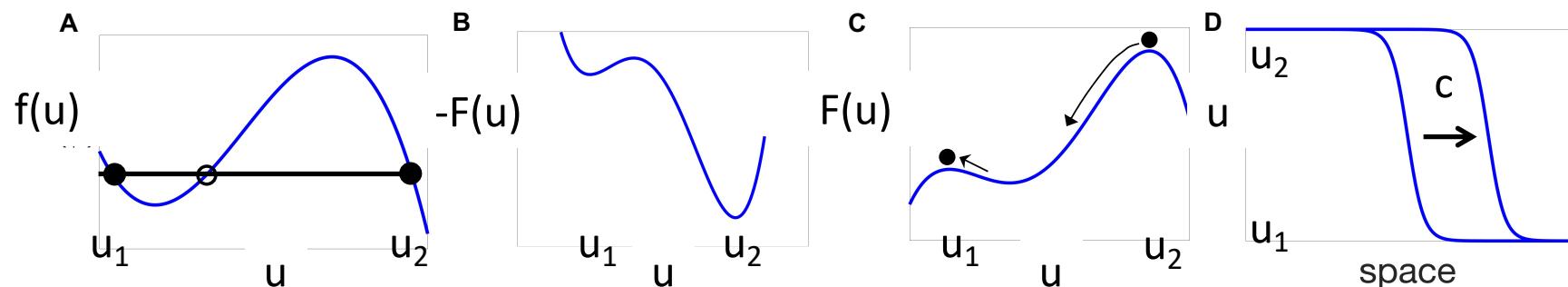
Front solution: $u(x-ct)$

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

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

$F'(u) = f(u)$, $x \leftrightarrow t$ 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

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

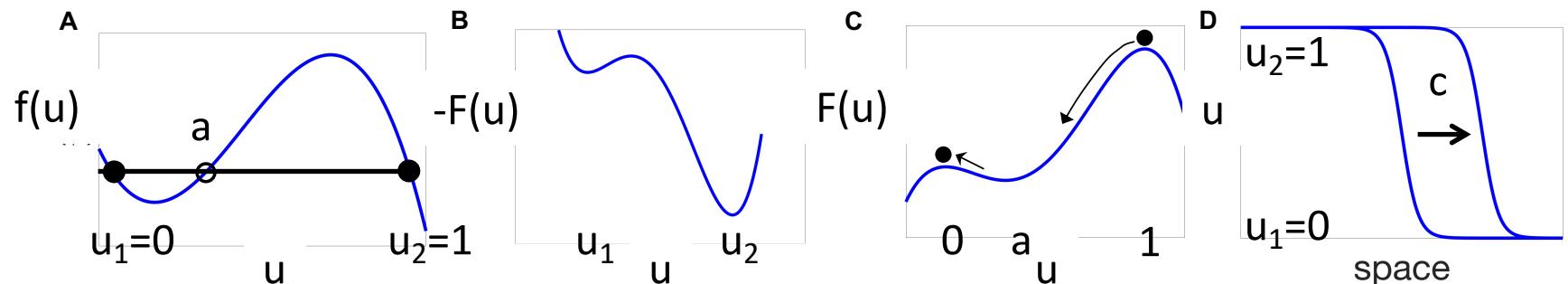
Idea : try the integrable form $\mathbf{du}/\mathbf{dx} = g(u)$ and find $g(u)$ if possible.

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

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

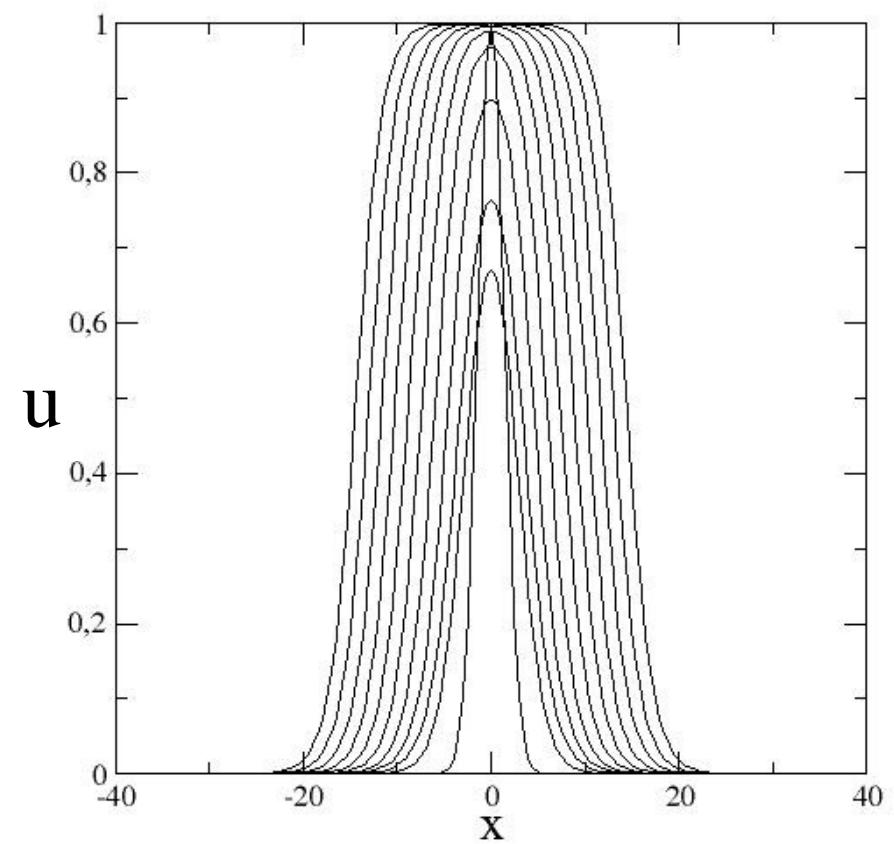
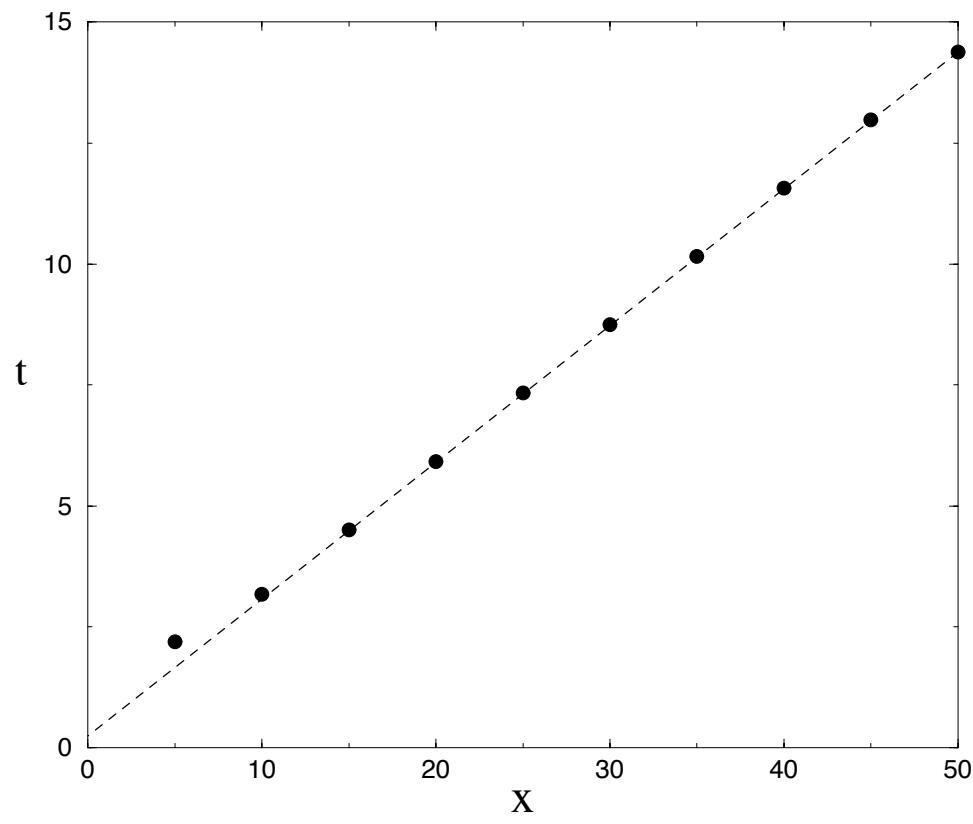
$$\Rightarrow g(u) = K(u-1)u \quad \text{with} \quad K = \frac{1}{\sqrt{2D\tau}}, \quad c = \sqrt{\frac{2D}{\tau}} \left(\frac{1}{2} - a \right)$$

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



Domain growth and front velocity

Front velocity



Perturbative calculation of the front propagation speed

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

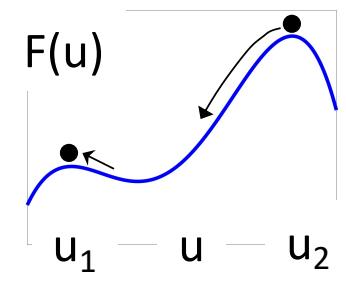
Front shape from particle motion integrability (conservative in a 1D potential)

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

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

-Potential with **unequal heights** $F(u)+\delta F(u)$, $u(x)=u_0(x)+u_1(x)$

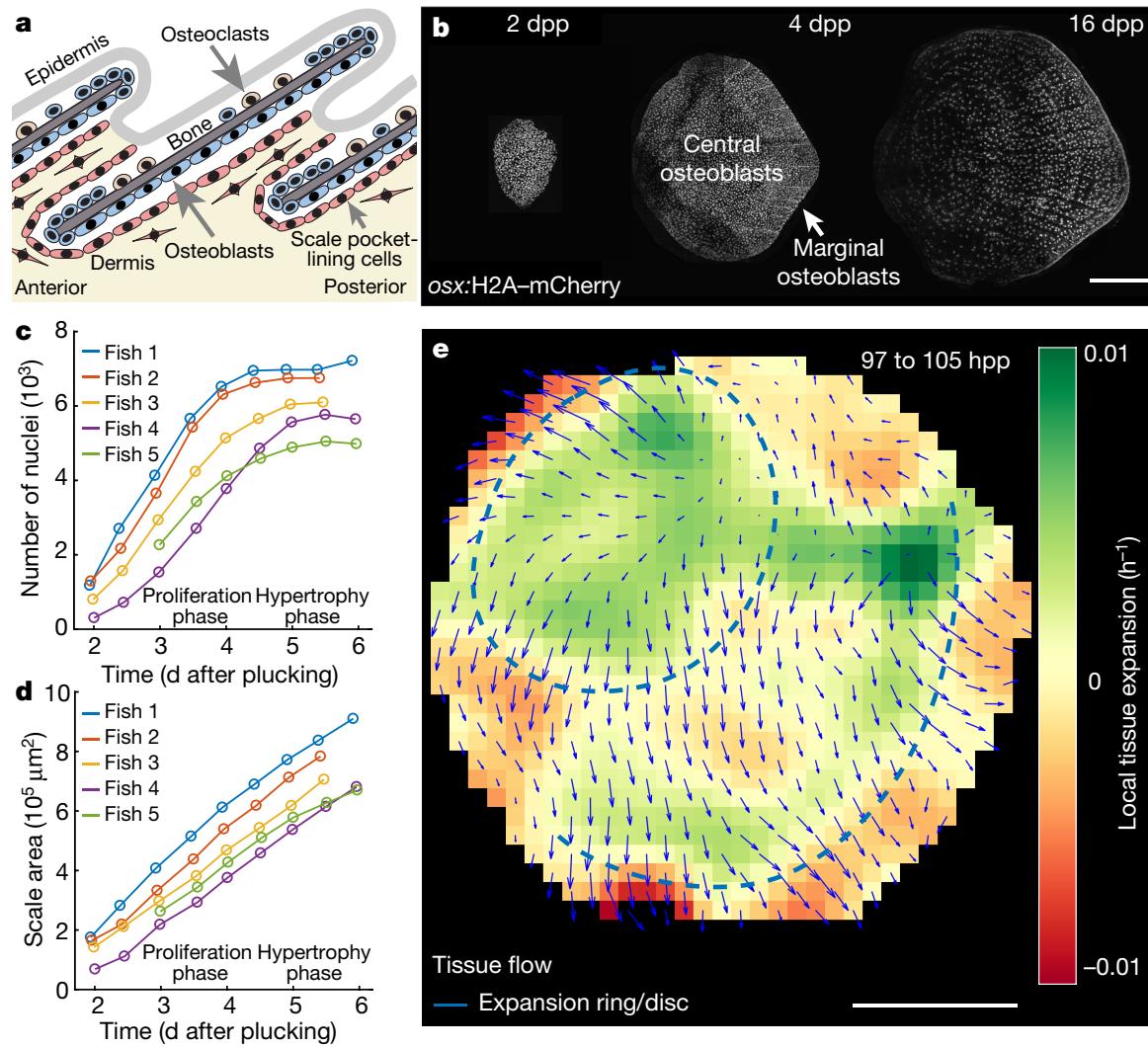
$$D\tau \frac{d^2u_1}{dx^2} + f'[u_0(x)]u_1 = -c\tau \frac{du_0}{dx} - \delta f[u_0(x)]$$



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

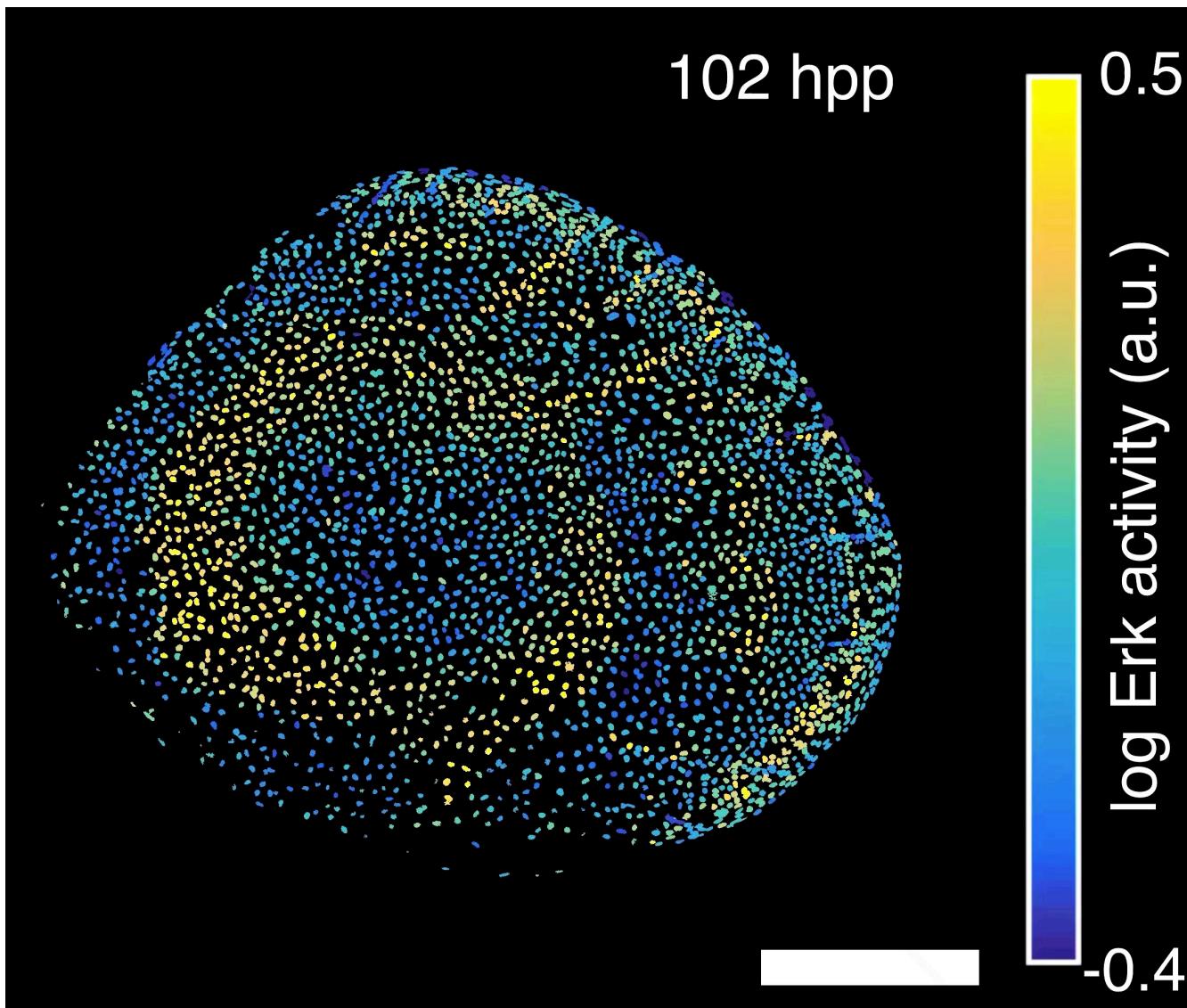
$$c\tau = \frac{-\int_{-\infty}^{+\infty} dx \frac{du_0}{dx} \delta f[u_0(x)]}{\int_{-\infty}^{+\infty} dx \left(\frac{du_0}{dx} \right)^2} = \frac{\delta F(u_2) - \delta F(u_1)}{\int_{-\infty}^{+\infty} dx \left(\frac{du_0}{dx} \right)^2} \quad (\text{potential energy dissipated by friction})$$

Regeneration of fish scales

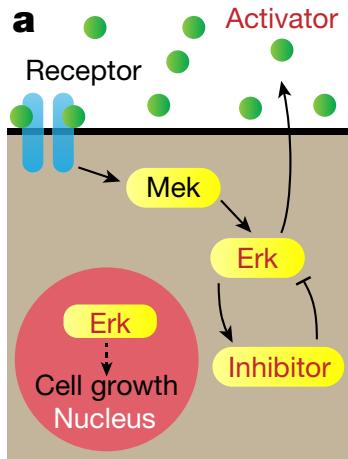


De Simone,..., Di Talia, Nature (2021)

ERK waves during regeneration



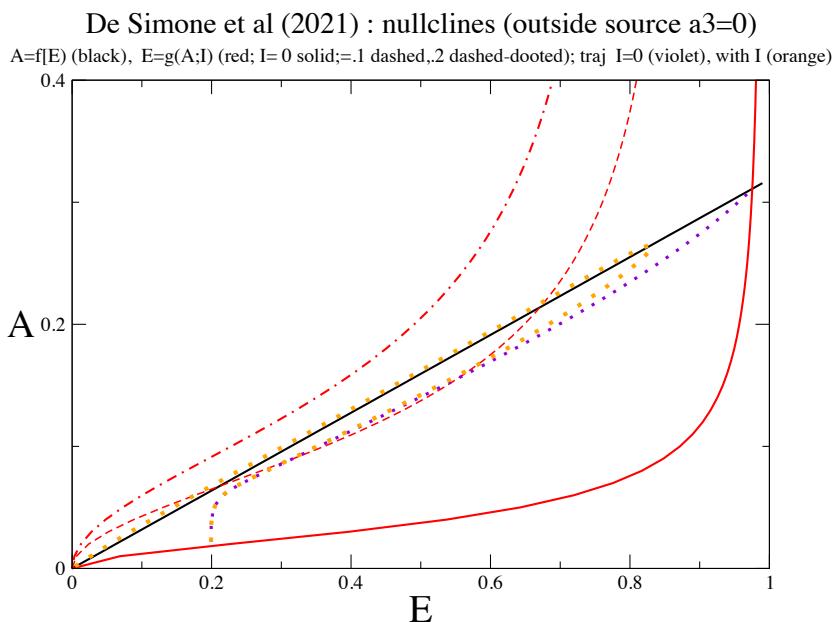
ERK auto-activation and inhibition



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

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

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



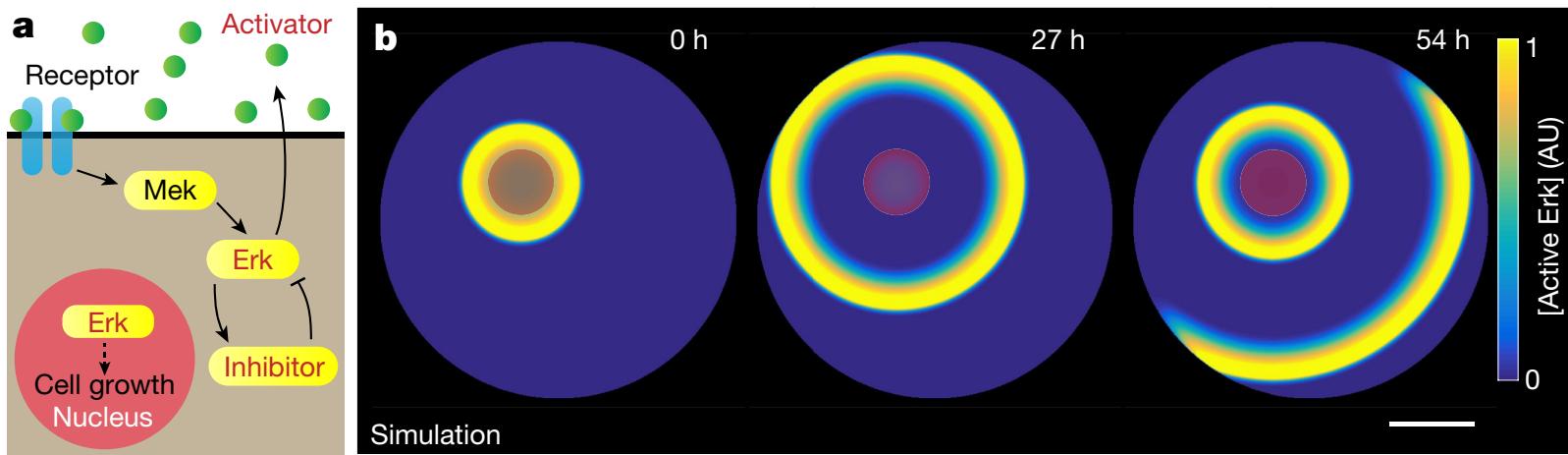
$$A = (\alpha_2 + \alpha_3 E) / \gamma_2 = f(E)$$

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

($\alpha_2 = 0$; non-zero only in the source region)

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

ERK waves during regeneration



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

$$\frac{\partial A}{\partial t} = \alpha_2 + \alpha_3 E - \gamma_2 A + D \nabla^2 A \quad \text{<- diffusion of activator}$$

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

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

$$\begin{aligned}\partial_t u &= D_u \partial_{xx} u + f(u, v)/\tau & \text{Ex: } f(u,v) = u(u-a-v/2)(1-v), \\ \tau \partial_t v &= \lambda^2 \partial_{xx} v + u - v & a < 1/2: u=1 \text{ favored}\end{aligned}$$

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

$$\begin{aligned}\Rightarrow v &= 1 - \alpha \cosh(x/\lambda), -L/2 < x < L \\ v &= \beta \exp[-(x-L/2)/\lambda], x > L/2\end{aligned}$$

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

$$\begin{aligned}\Rightarrow \alpha &= \exp(-L/2\lambda) \\ \beta &= \frac{1}{2}[1 - \exp(-L/\lambda)]\end{aligned}$$

β ($=v(L/2)$) is the concentration of inhibitor at the front.

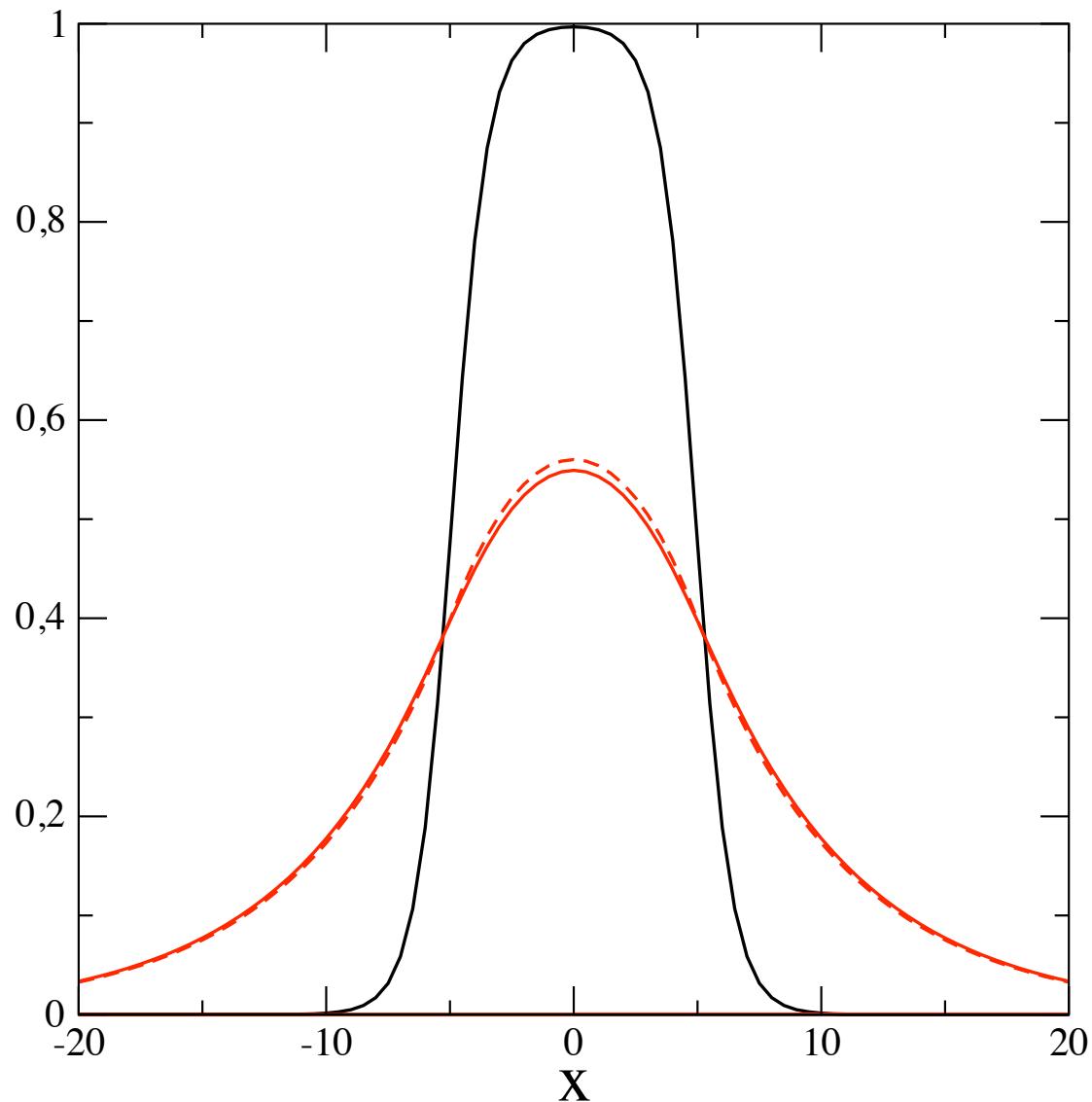
β increases with L the activated zone.

Growth of the favored activated state ($u=1$) **stops** when L large enough

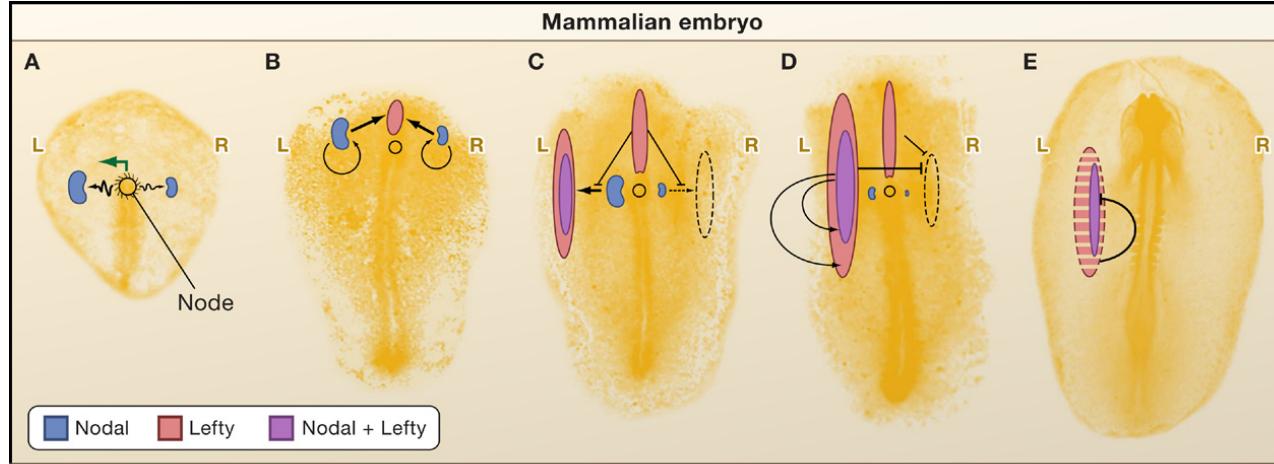
Short-range activation, long-range inhibition :

Localized state

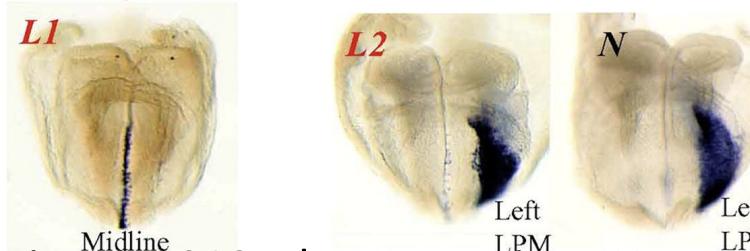
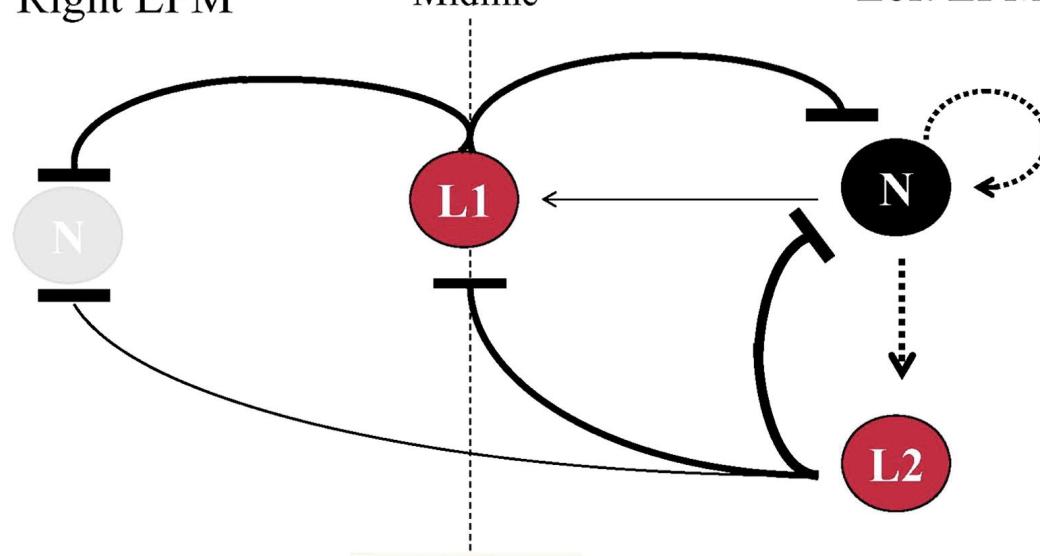
(potential $a=.3; l_A=.5, l_B=6, t_A=t_B=1$)



Left-right asymmetry: localized expression of Nodal



Right LPM Midline Left LPM

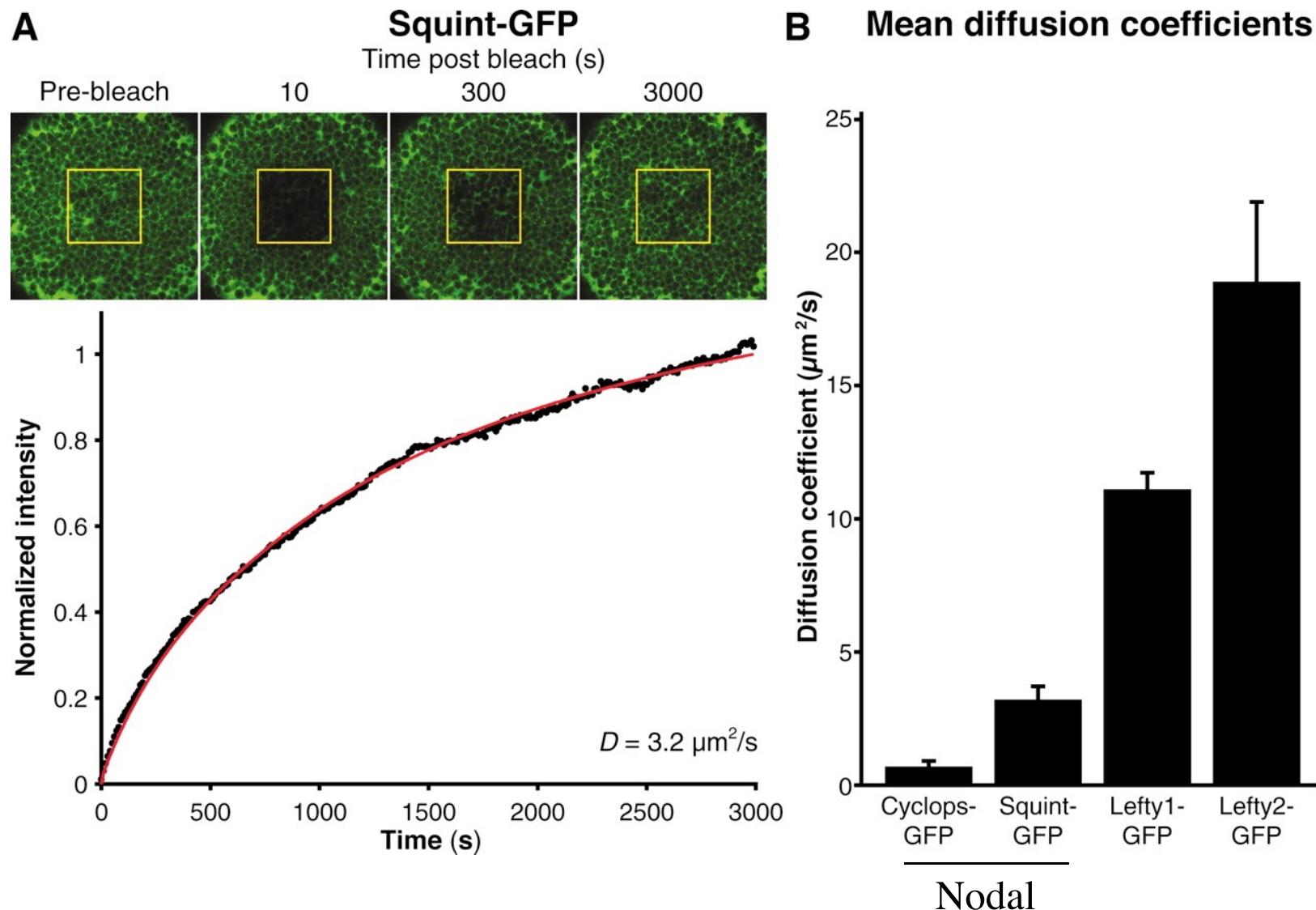


- Nodal and Lefty ligands (TGFb signalling pathway)

- Nodal activates the pathway (agonist)

- Lefty : antagonist

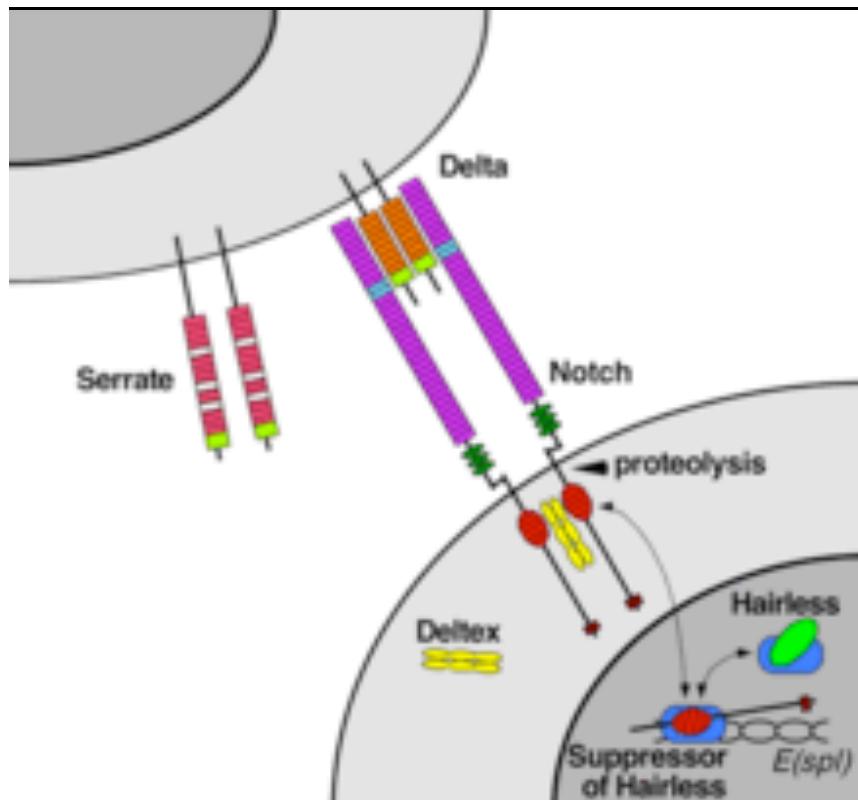
- Nodal and Lefty genes activated by Nodal*



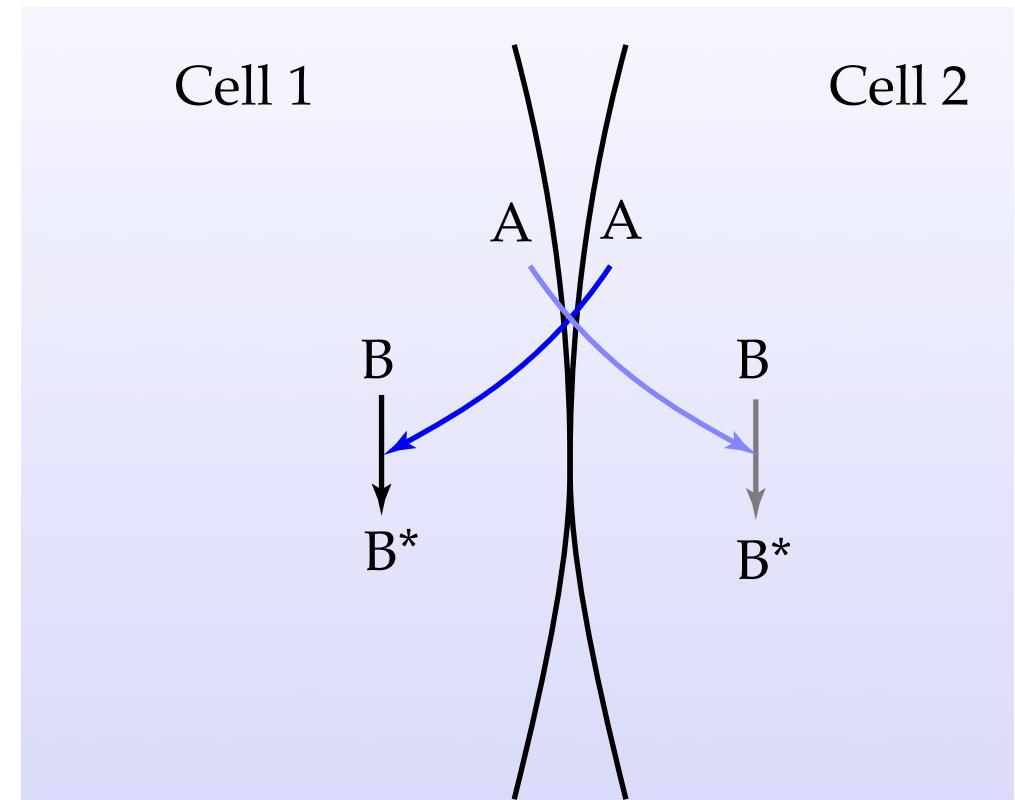
-Diffusion constant and clearance rate (pulsed photoconversion measured independently
 -Caveat : ectopic expression in zebrafish embryos.

Mueller et al, Science 2012

Interactions between cells

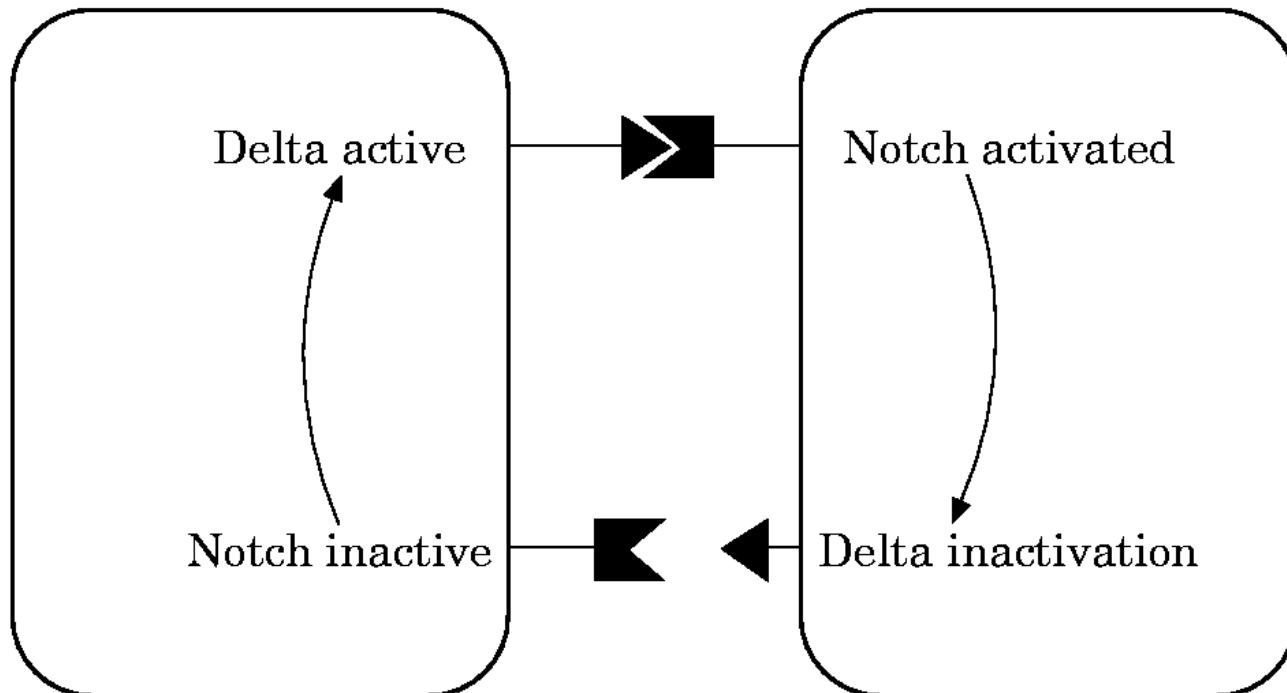


The Notch-Delta pathway
(a wikipedia view)



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

Lateral inhibition and symmetry-breaking



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

Single symmetric fixed point
 D_0, N_0

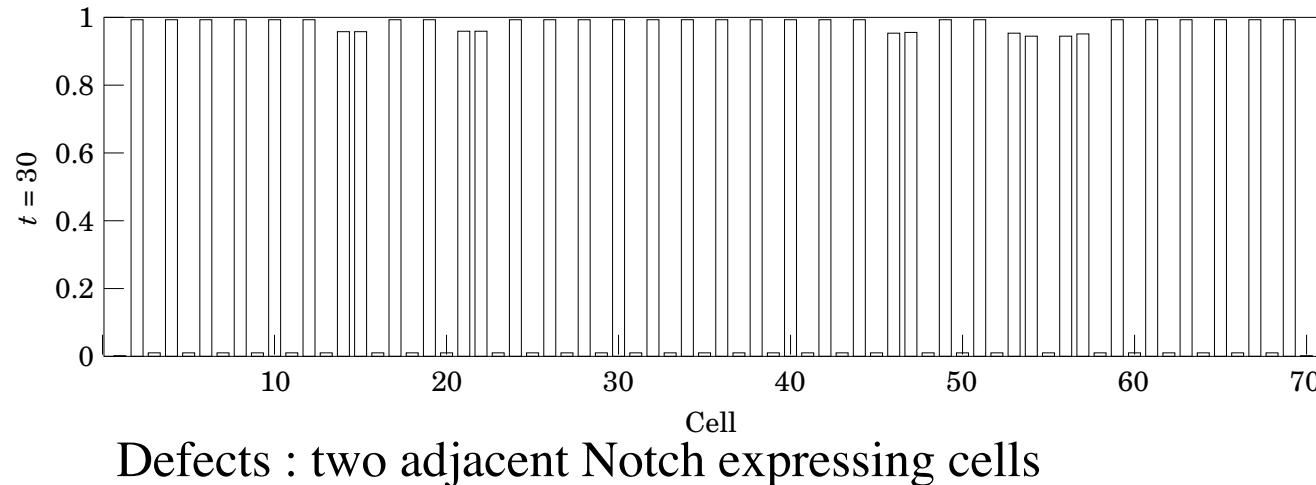
$$\frac{dD_1}{dt} = R(N_1) - \delta_D D_1$$

Spontaneous symmetry breaking
 $A'(D_0)R'(N_0) + \delta N \delta D < 0$

Lateral inhibition and symmetry-breaking

-1D patterns

Notch level

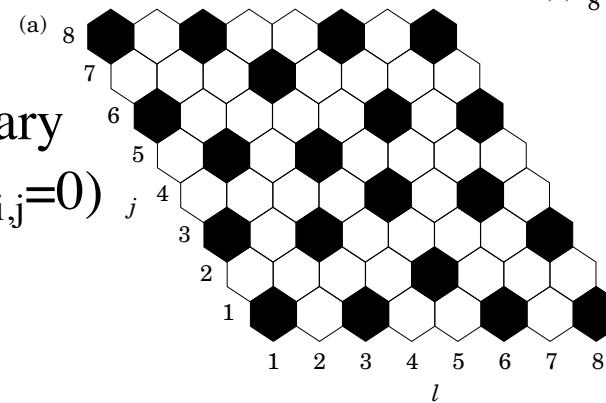


-2D patterns : D expressing cells (black).

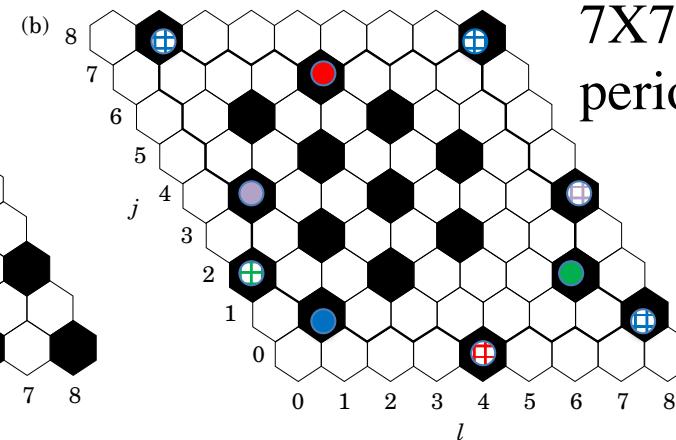
8X8 lattice

fixed boundary

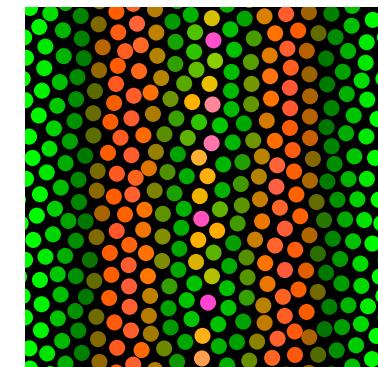
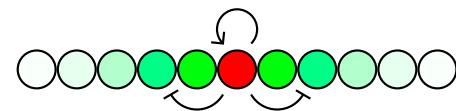
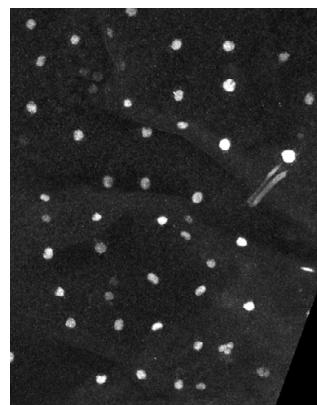
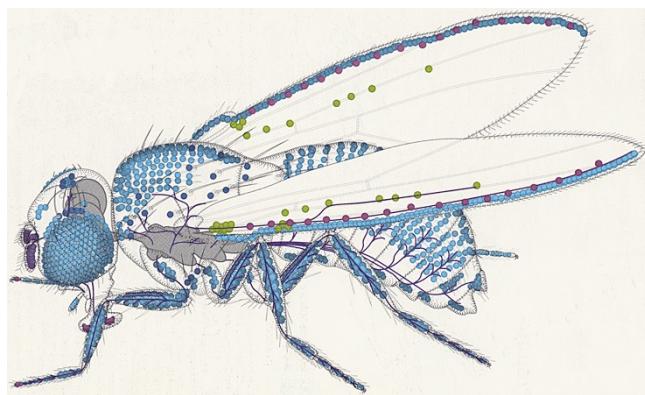
condition($D_{i,j}=0$)



7X7 lattice
periodic boundary
condition



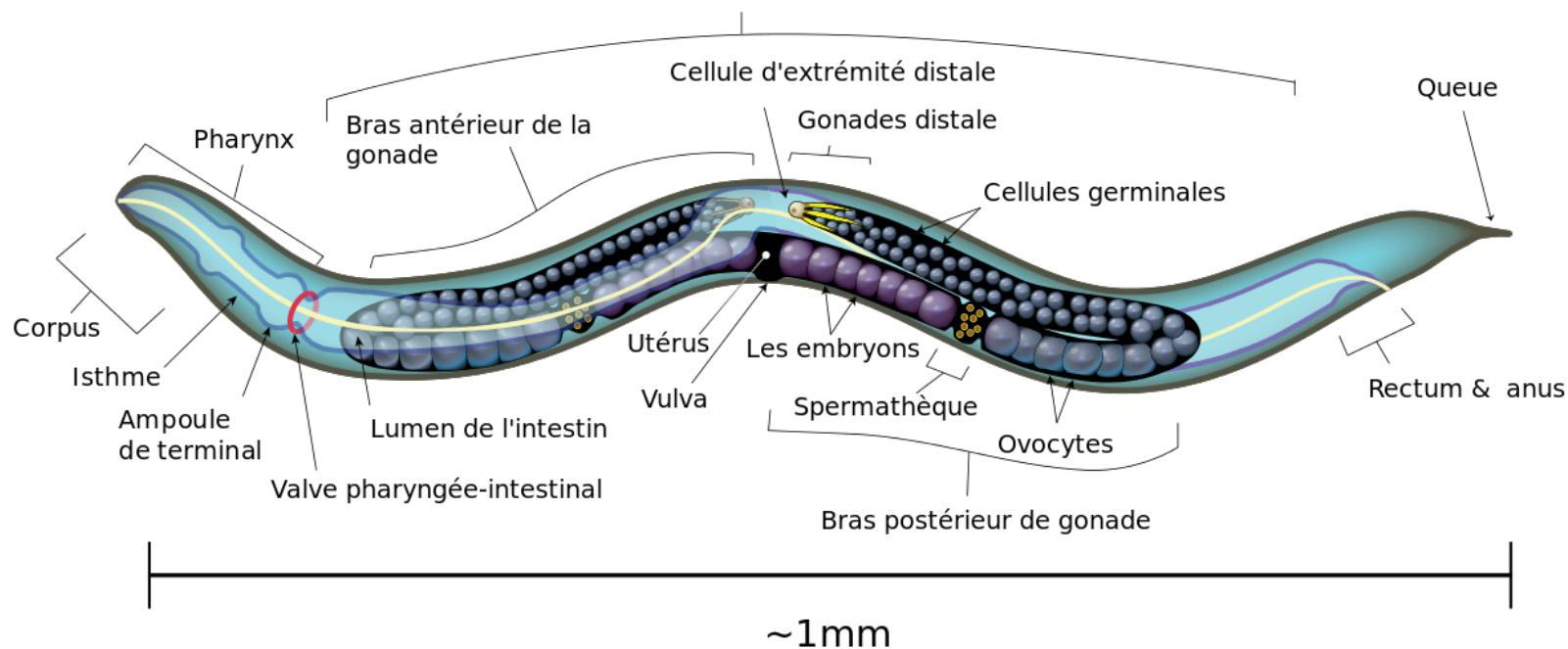
Patterns from cell-cell interactions



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

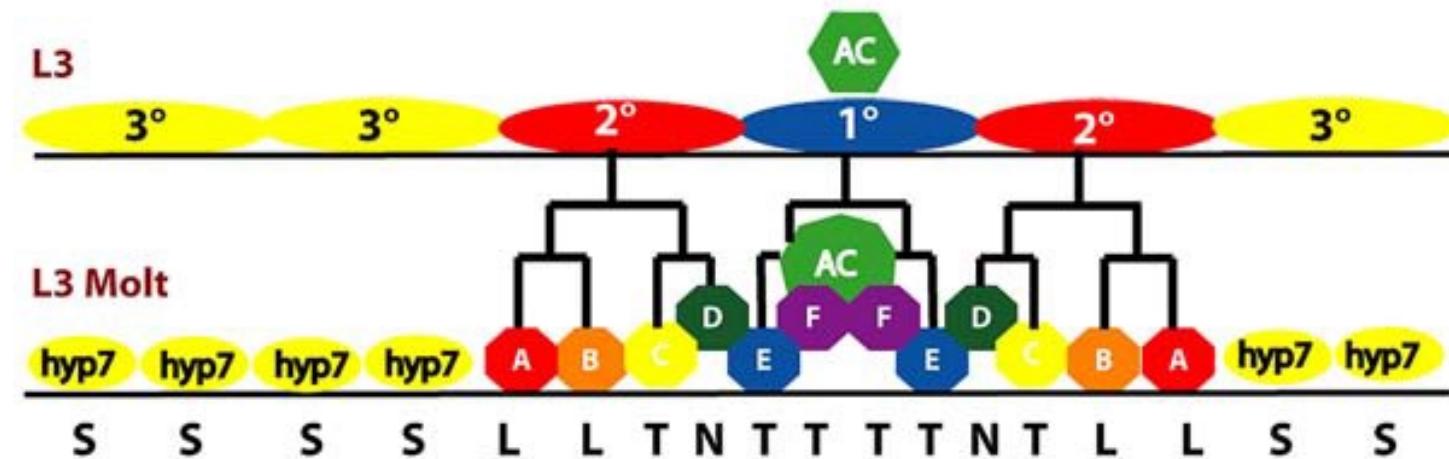
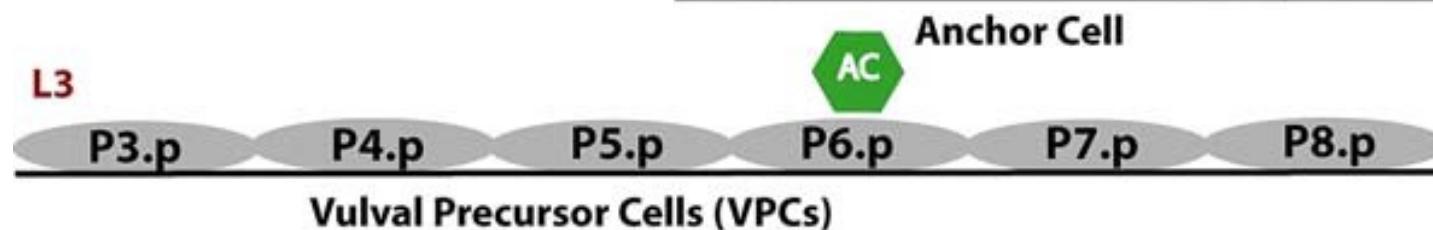
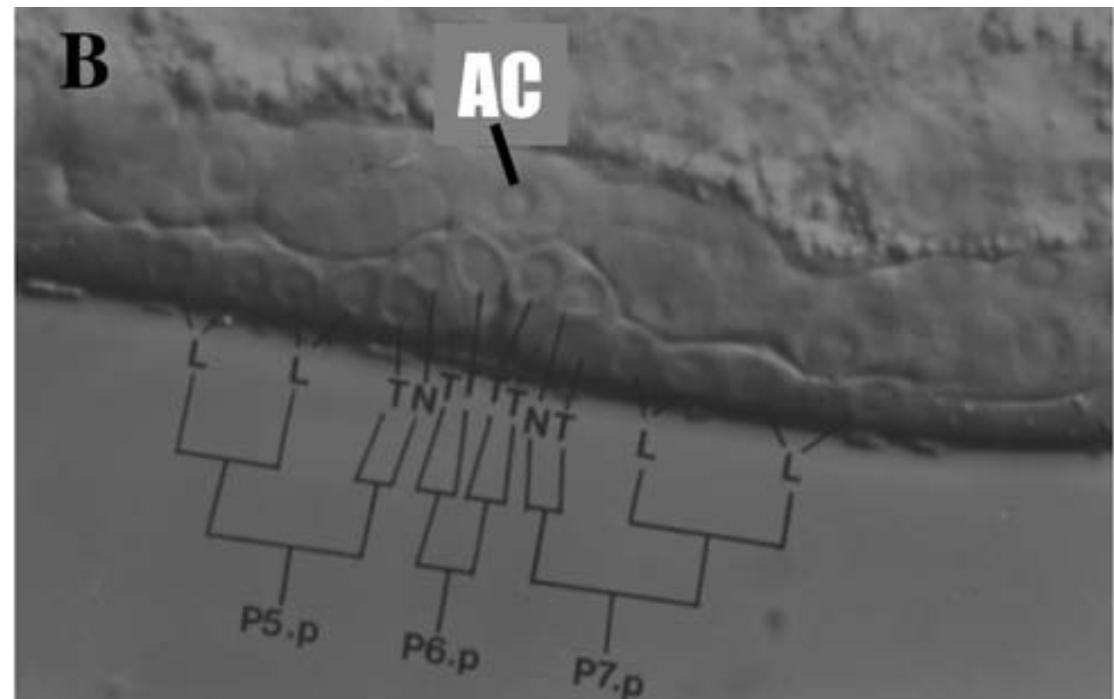
Notch-Delta signalling allows the emergence of individual Sensory-Organ-Precursor cells from the proneural stripes (also important for the stripe specification itself)

The nematode *C elegans*

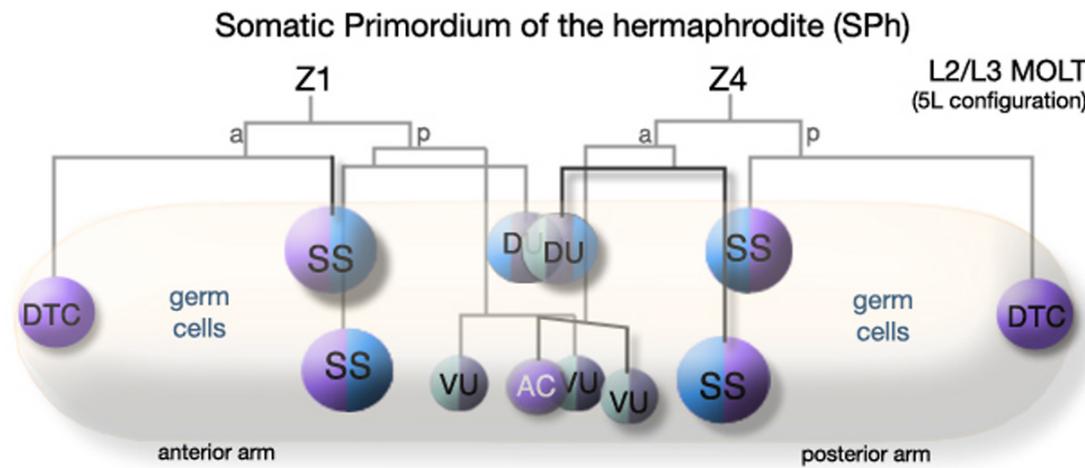


Gradient and cell-interaction : the development of the Celegans vulva.

P Sternberg, Wormbook

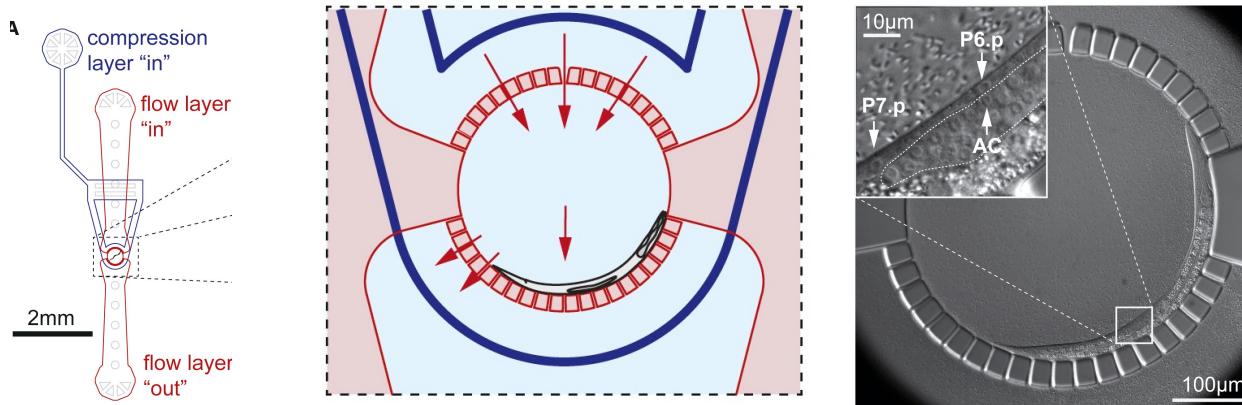


Anchor cell specification



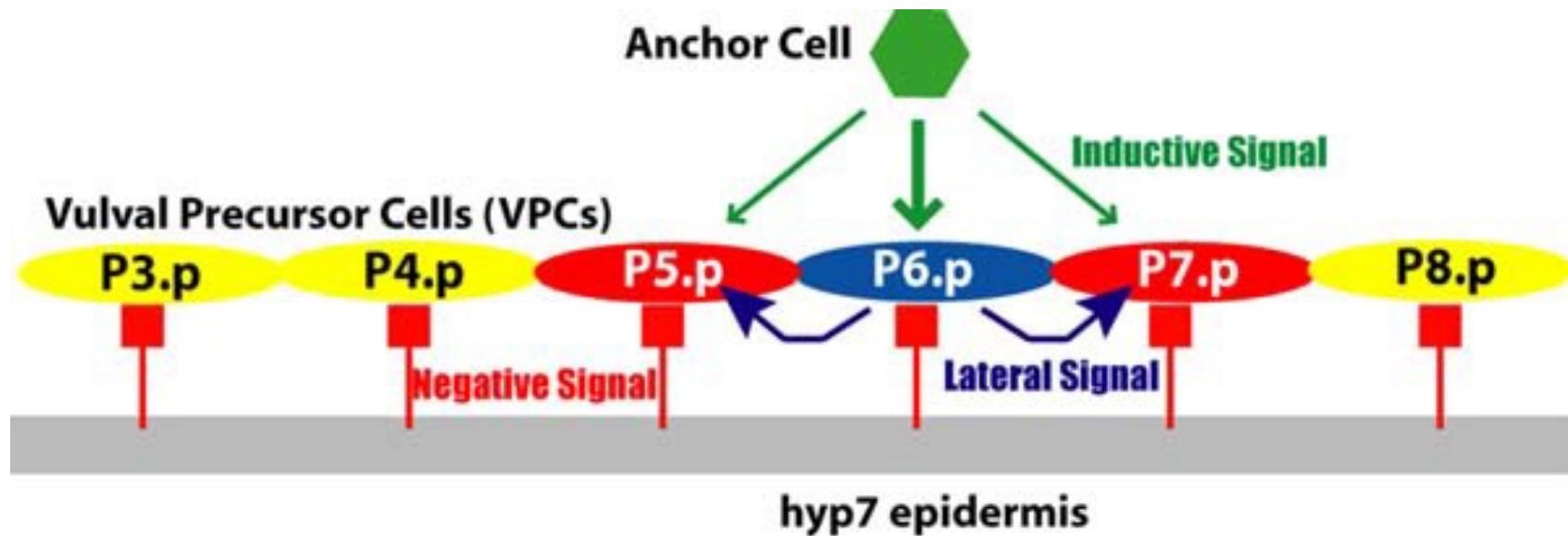
M Herman,
Wormbook

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

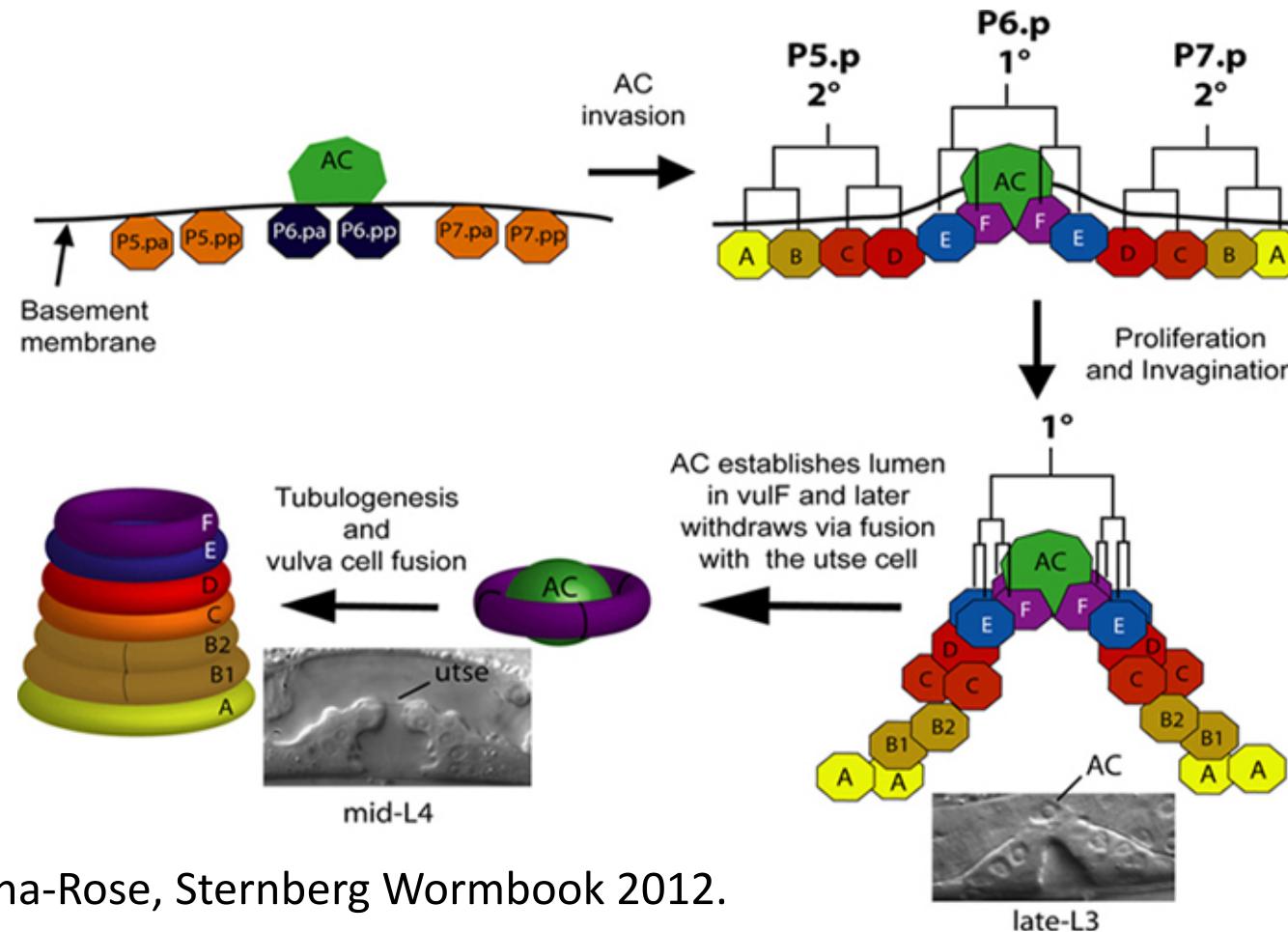
Keil et al, 2017



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 ->
Next set of lectures by Hervé Turlier (and TDs)!

The End