

# Physics of multicellular systems 2022

## Lecture 3

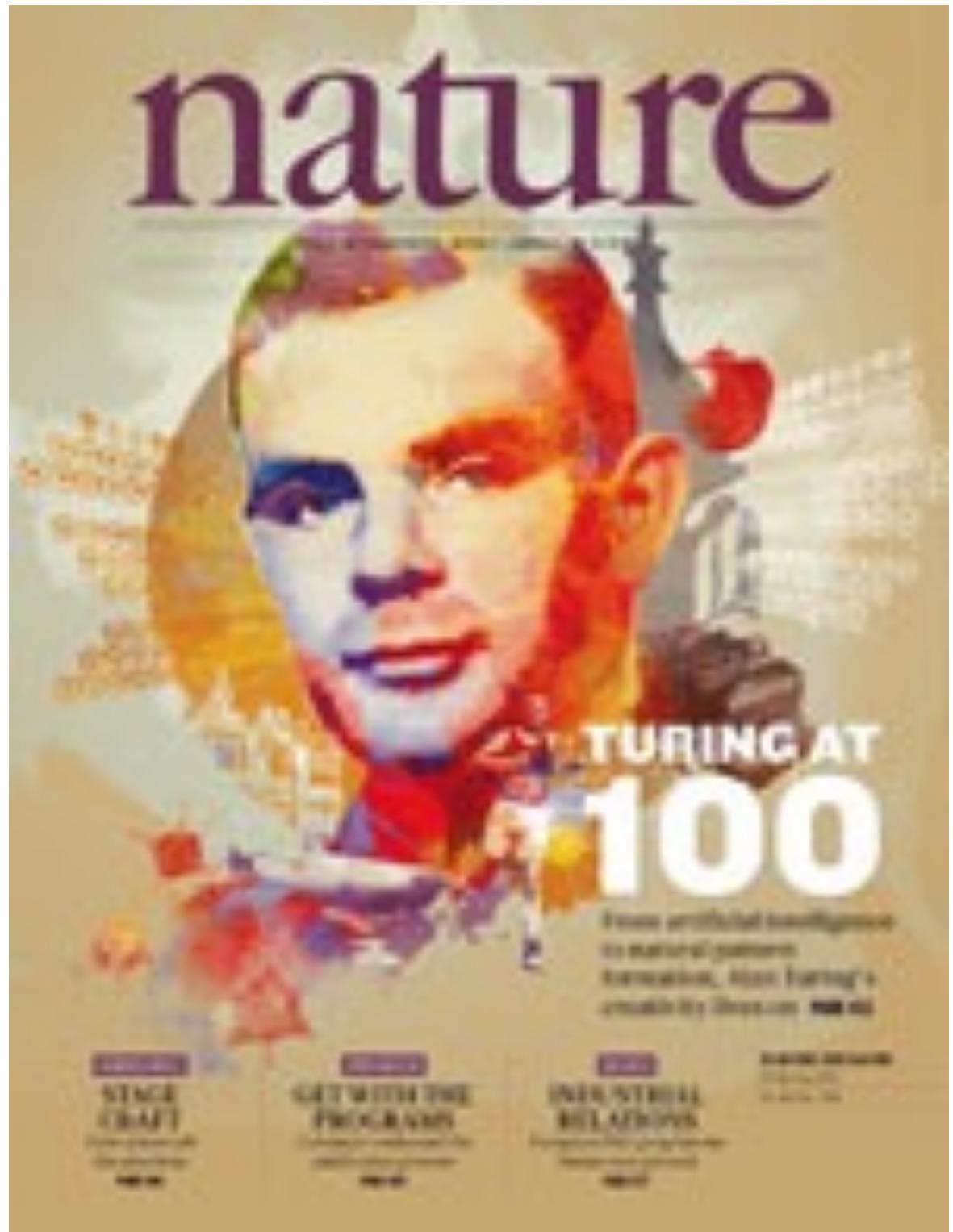
Self-organization :  
reaction-diffusion and the Turing mechanism

Turing at 100:

Legacy of a universal mind

Nature

23 february 2012



# Diffusion

$$\partial_t u = D \partial_{xx} u$$

Diffusion usually has a **stabilizing** effect.

$$u(x, t) = u_0 + u_q(t) \exp(iqx) + c.c.$$

$$\Rightarrow u_q(t) = u_q(0) \exp(-Dq^2 t)$$

Modulations decreases exponentially.

but...

**Turing : diffusion can also help to create structures.**

# Inhibition-stabilized network

$$\begin{aligned}\frac{du}{dt} &= a u + b v \\ \frac{dv}{dt} &= c u + d v\end{aligned}$$

Stability :

- 1)  $a+d<0$ , possible if  $a>0$  when  $d$  negative enough
- 2)  $ad-bc>0 \Rightarrow 0>ad>bc$ ,  $b$  and  $c$  of different signs  
activator/inhibitor system  
**=> inhibition stabilized network**

A note : paradoxical response to inhibitor stimulation

$$\frac{dv}{dt} = c u + d v + S \quad \Rightarrow v = \frac{-aS}{ad - bc} < 0$$

$S>0 \Rightarrow v$  **decreases** (when coupled to  $u$ )!

# Turing's diffusional instability

$$\frac{\partial u}{\partial t} = a u + b v + D_u \partial_{xx} u$$

$$\frac{d v}{d t} = c u + d v + D_v \partial_{xx} v$$

System invariant by translation, eigenmodes also of translation operator i.e. Fourier  
 $u(x, t) = u_1(t) \exp(iqx) + u_1^*(t) \exp(-iqx)$ ,  $v(x, t) = v_1(t) \exp(iqx) + v_1^*(t) \exp(-iqx)$

=> Back to a 2X2 matrix.

Instability when  $P = (a - D_u q^2)(d - D_v q^2) - bc = D_u D_v q^4 - (a D_v + d D_u) q^2 + ad - bc < 0$

P has a positive root requires :  $a D_v + d D_u > 0$ ,  $(a D_v + d D_u)^2 - 4 D_u D_v (ad - bc) > 0$ .

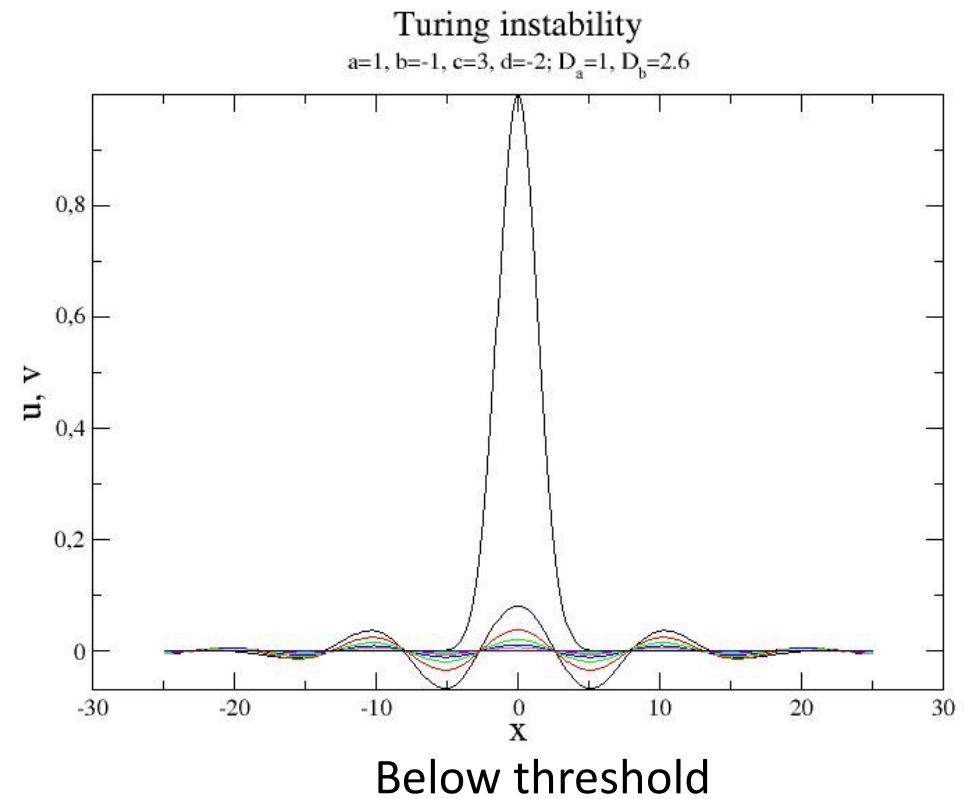
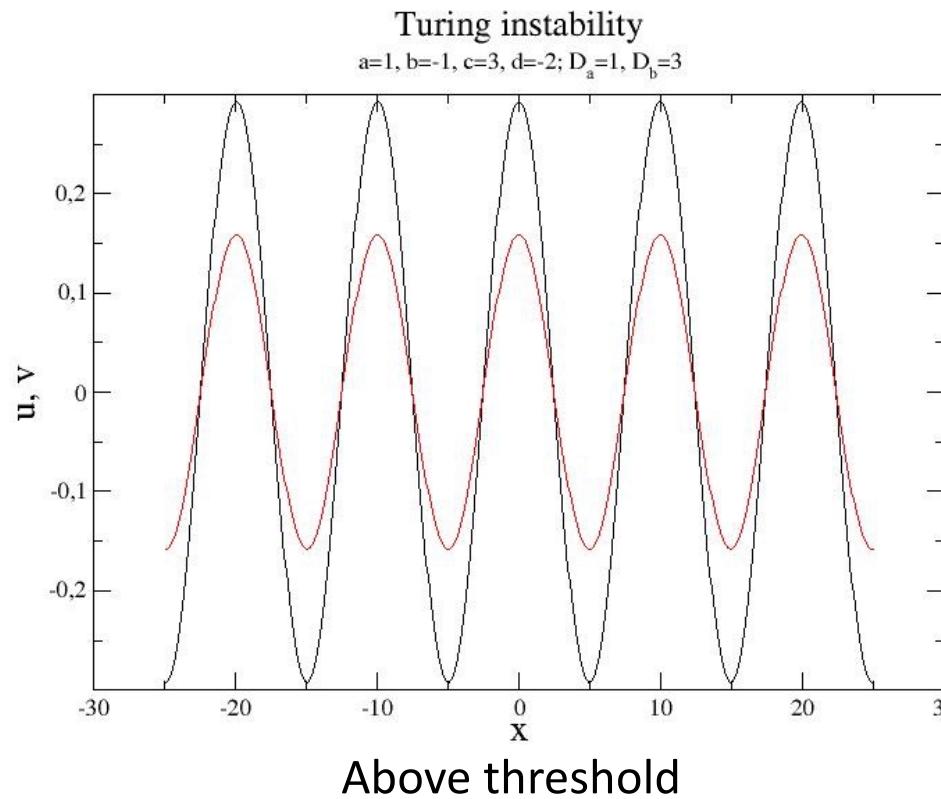
Finally:

$$\frac{D_v}{D_u} > \left[ \frac{(ad - bc)^{1/2} + (-bc)^{1/2}}{a} \right]^2$$

Wavevector at threshold:  $q_c = \left( \frac{a D_v + d D_u}{2 D_u D_v} \right)^{1/2}$

# Turing instability

$$\begin{aligned}\frac{\partial u}{\partial t} &= a u + b v + D_u \partial_{xx} u - u^3 \\ \frac{dv}{dt} &= c u + d v + D_v \partial_{xx} v\end{aligned}$$



# Turing instability : a simple non linear example

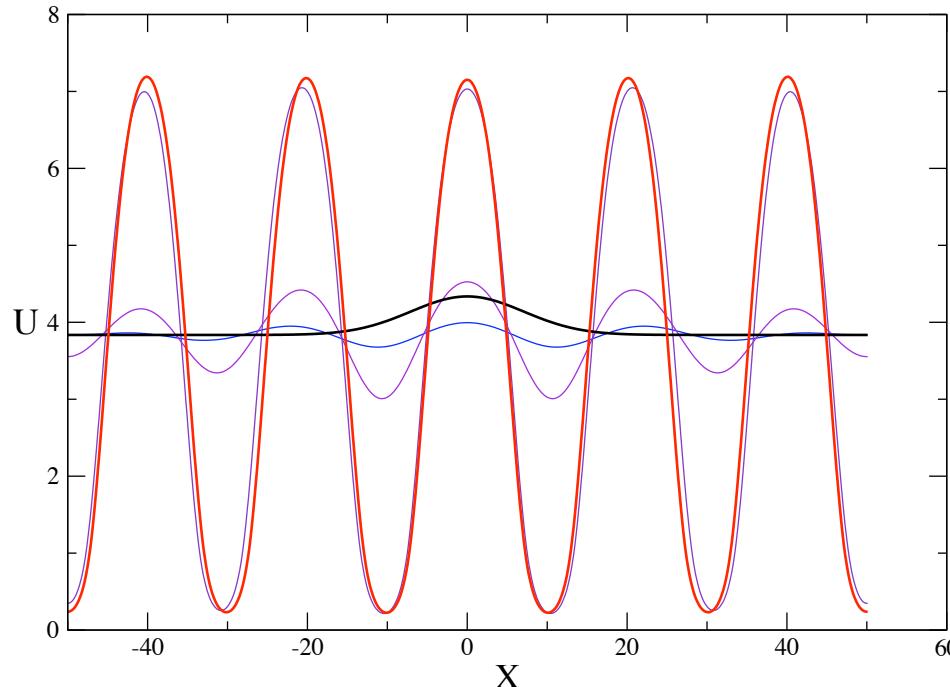
$$\frac{\partial U}{\partial t} = \rho(U) - \delta_u U - \kappa U V + D_u \partial_{xx} U$$

$$\frac{dV}{dt} = c U - \delta_v V + D_v \partial_{xx} V$$

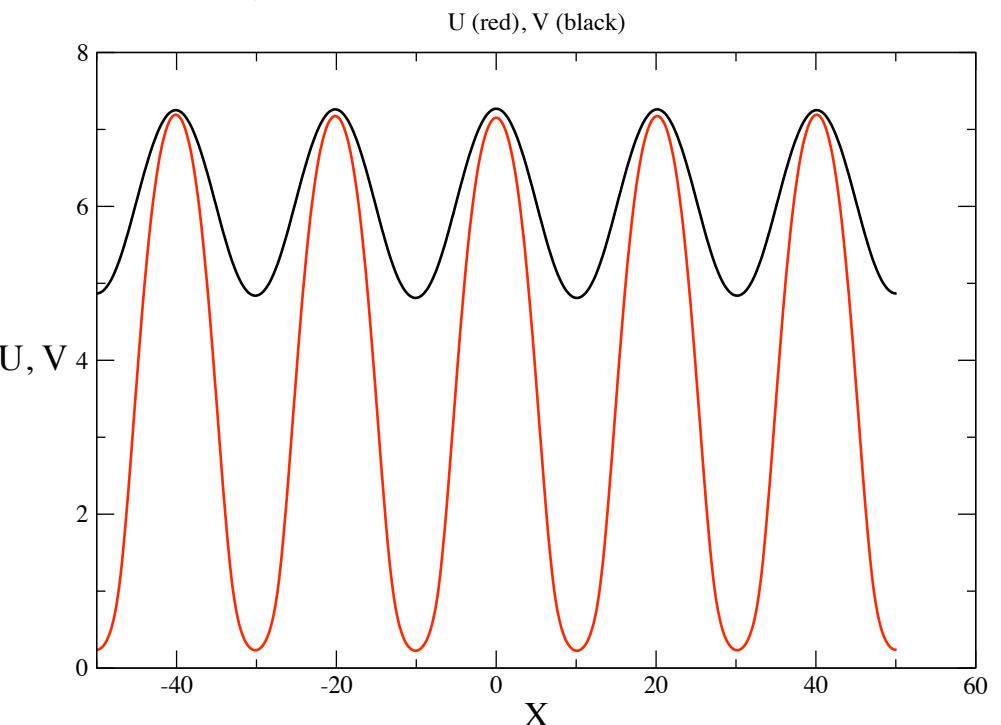
Ex:  $\rho(u)$  threshold linear,  $\rho(u)=\alpha(u-u_0)$ ,  $u>u_0$

Turing instability : a nonlinear case

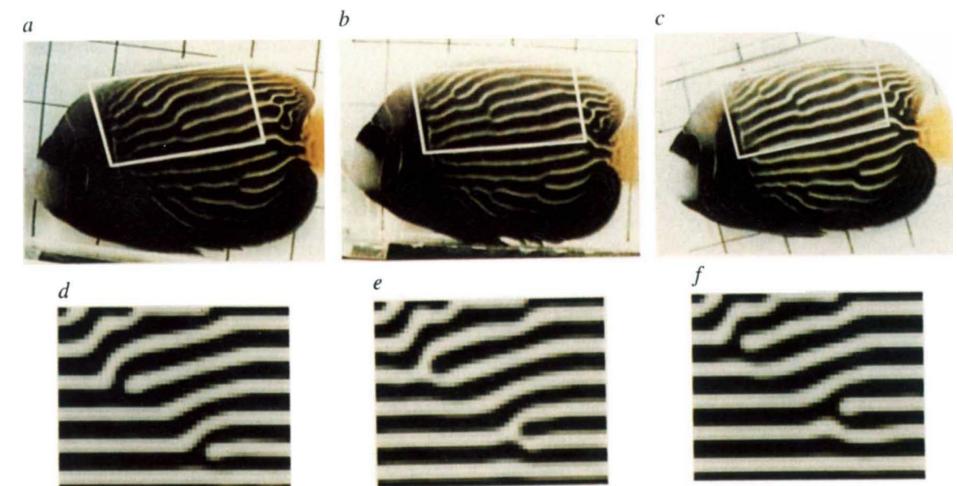
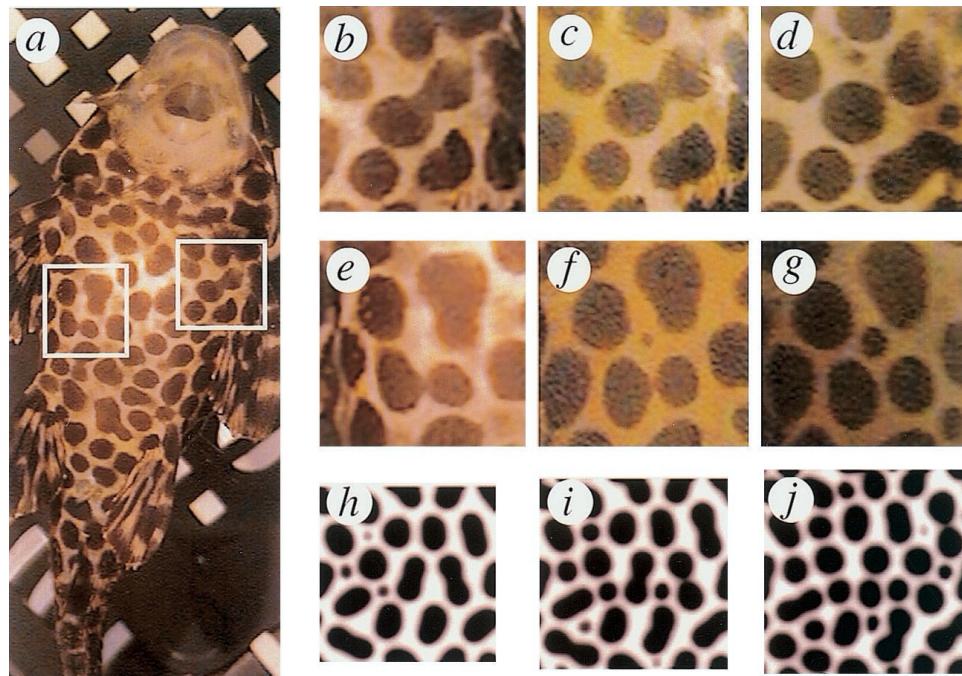
$U_0=1$ ,  $\alpha=1$ ,  $\kappa=1$ ,  $\delta_u=.1$ ,  $\delta_v=1.2$ ,  $c=2$ ,  $D_u=1$ ,  $D_v=7$



Turing instability, a nonlinear case : the final state

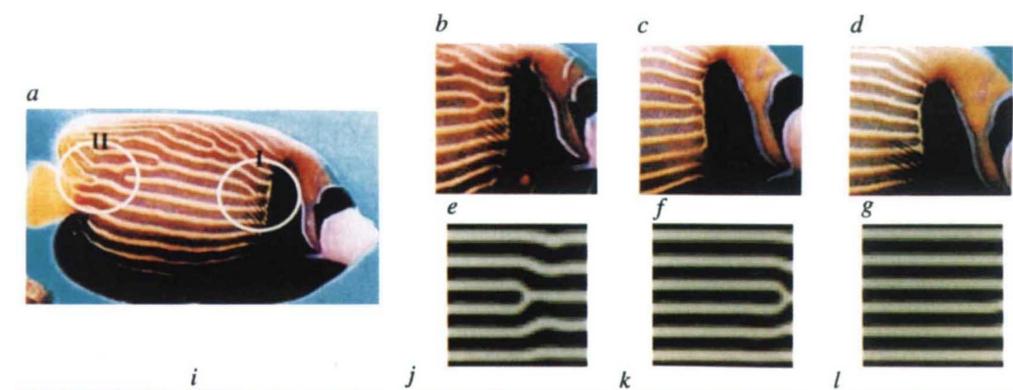


# Skin patterns



S Kondo, R Asai, Nature 376 (1995)

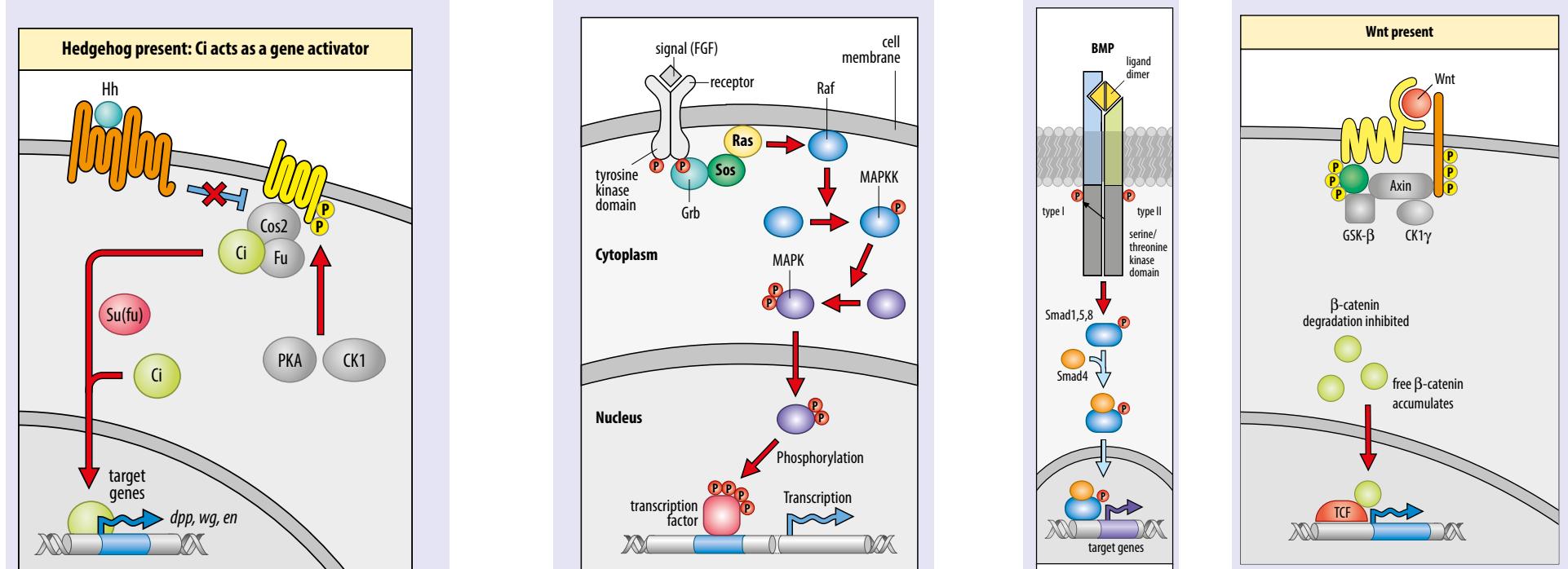
Asai, R.,..., Kondo, S. (1999).  
*Mech. Dev.* 89: 87-92.



# Signalling pathways in development

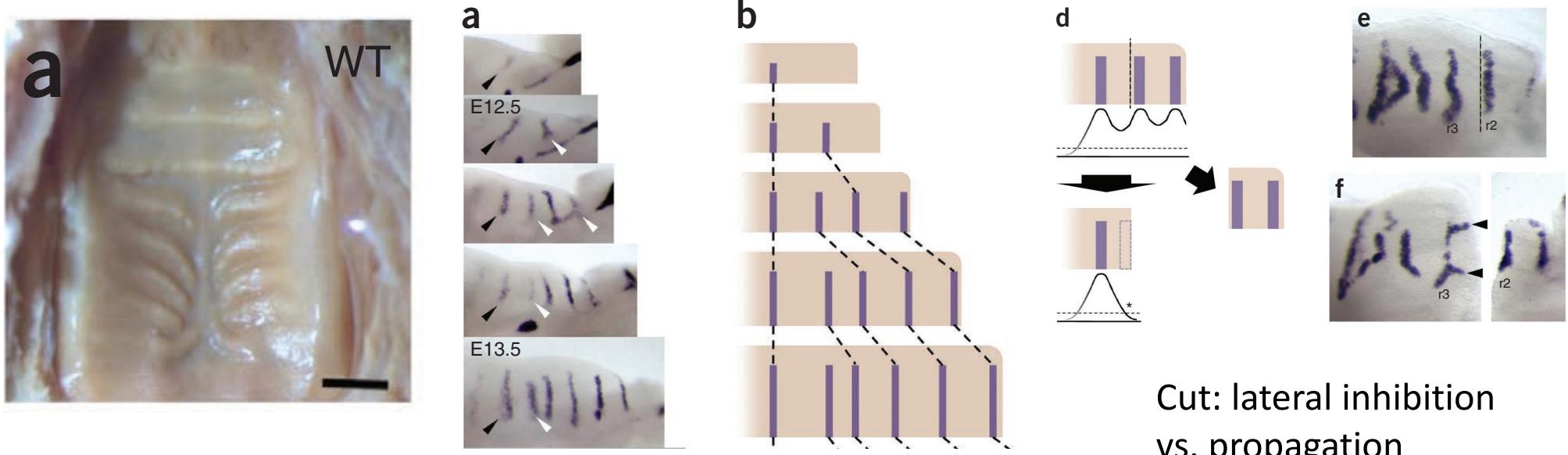
**Table 22–1 Some Signal Proteins That Are Used Over and Over Again as Inducers in Animal Development**

SIGNALING PATHWAY	LIGAND FAMILY	RECEPTOR FAMILY	EXTRACELLULAR INHIBITORS/MODULATORS
Receptor tyrosine kinase (RTK)	EGF FGF (Branchless) Ephrins	EGF receptors FGF receptors (Breathless) Eph receptors	Argos
TGF $\beta$ superfamily	TGF $\beta$ BMP (Dpp) Nodal	TGF $\beta$ receptors BMP receptors	chordin (Sog), noggin
Wnt	Wnt (Wingless)	Frizzled	Dickkopf, Cerberus
Hedgehog	Hedgehog	Patched, Smoothened	
Notch	Delta	Notch	Fringe

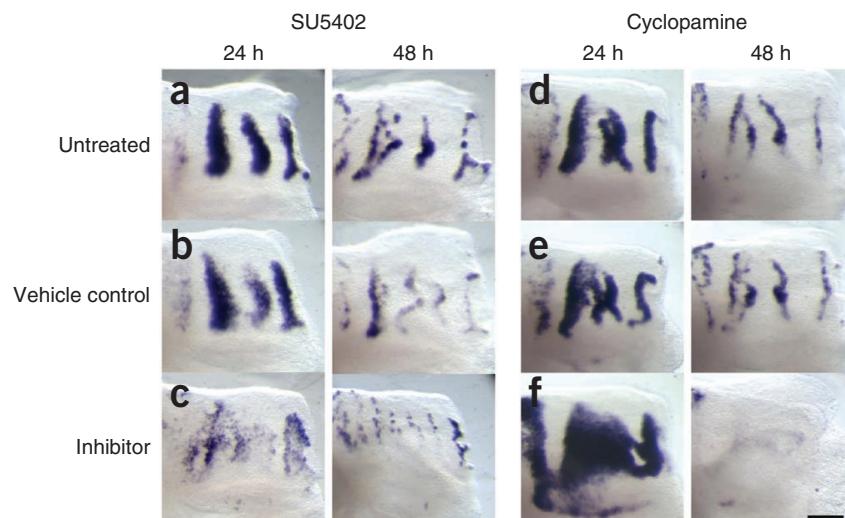


# Mammalian palate (rugae formation)

A D Economou et al, Nature Genetics 44, 348 (2012)



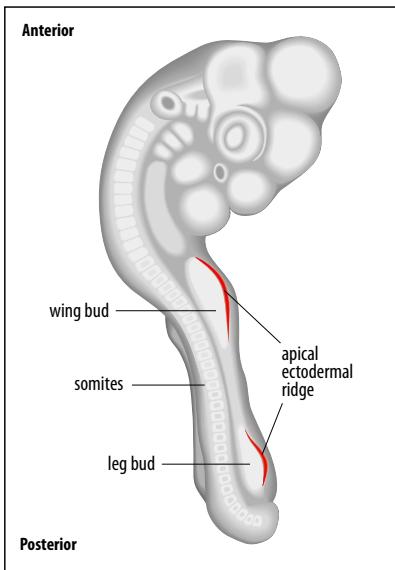
Cut: lateral inhibition  
vs. propagation



SU5402 chemical inhibitor of FGF  
-> FGF suggested Turing activator

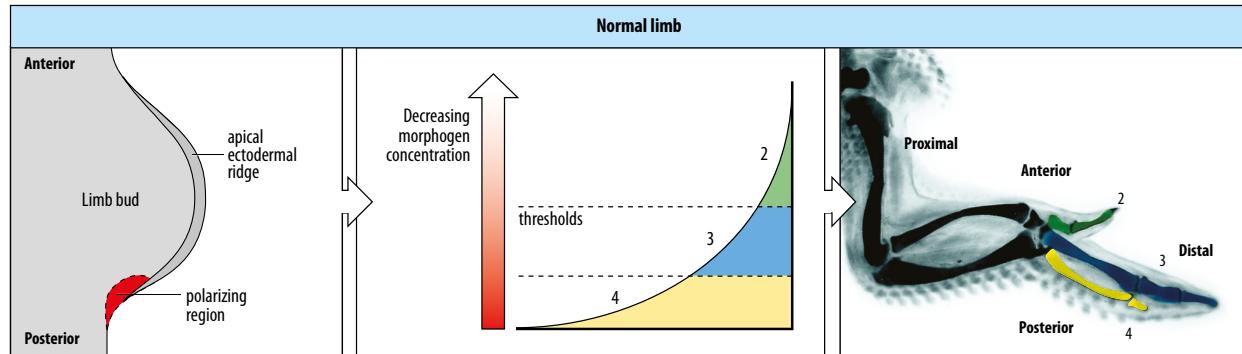
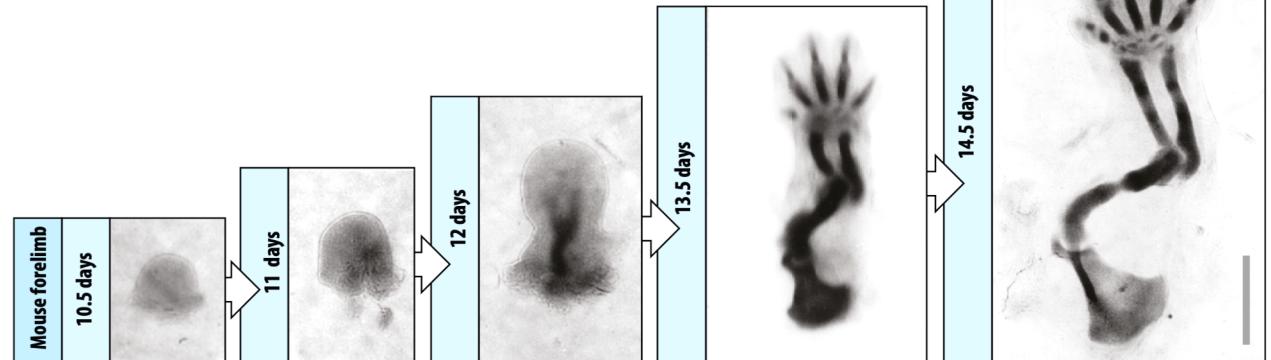
Cyclopamine Shh signalling inhibitor  
-> Shh suggested Turing inhibitor

Other pathways (Wnt, BMP) involved

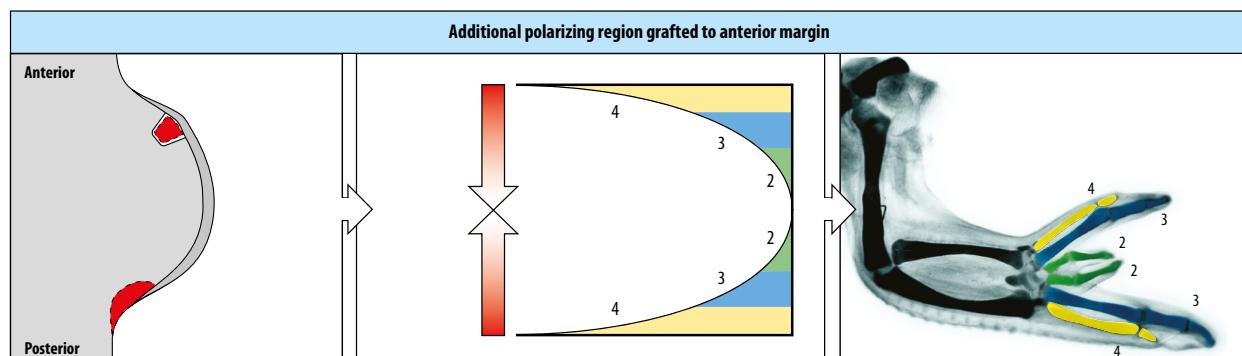


# Limb development

## Limb bud



Proximo-distal :two gradients  
 -Retinoic acid: high P>D low  
 -FGF: high D>P low  
 -some similarity to somitogenesis

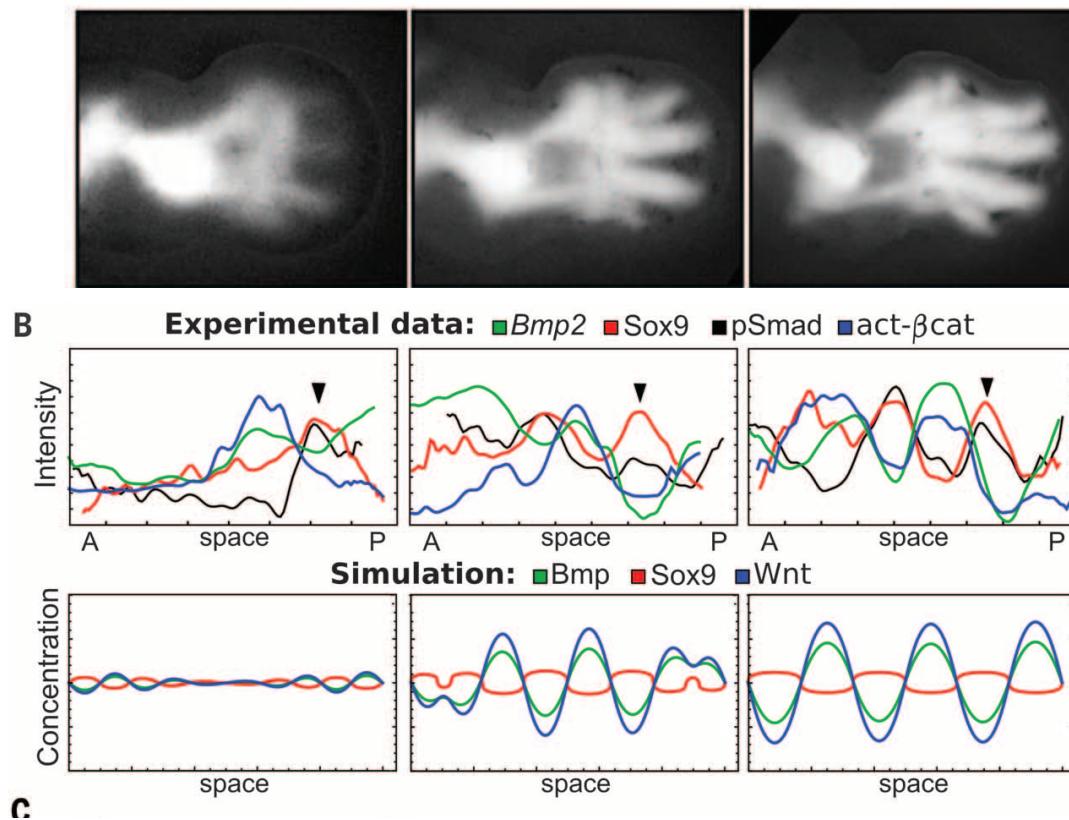


Antero-posterior  
 positional identity from  
 Zone of Polarizing Activity  
 (ZPA) ->  
 Sonic hedgehog gradient

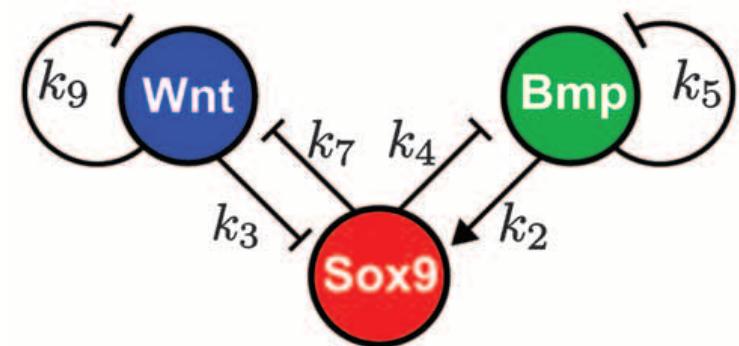
# Digit patterning

Newman and Frisch, 1979;....; Raspovic et al, 2014;...;Hiscock and Tabin, 2017

Sox9-EGFP



- Sox9 periodic pattern
- act- $\beta$ cat (Wnt activity) antiphase



- BMP more complex in experiments: Bmp2 and pSmad (active BMP pathway) out-of-phase  $\rightarrow$  more complex model, Marcon et al 2016 with Wnt -I pSmad

# Spots/hexagons or stripes/rolls?

Difficult question in general but it can be analyzed close to the instability threshold.  
 (Palm, 1960; ...; Busse, 1967; ...; Ciliberto et al, 1990; ...)

Pattern : linear superposition of the most unstable modes

$$u(\mathbf{x}, t) = \sum A_j(t) \exp(i\mathbf{k}_j \cdot \mathbf{x}) + c.c$$

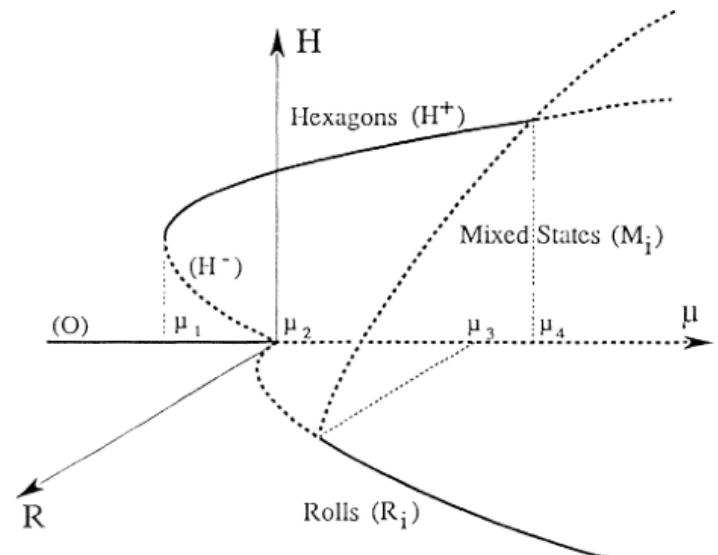
Stripes/rolls: only one mode

Hexagons : 3 modes  $\mathbf{k}_1, \mathbf{k}_2, \mathbf{k}_3$  at angles  $2\pi/3$

$$\partial_t A_1 = \mu A_1 + \alpha \bar{A}_2 \bar{A}_3 - (|A_1|^2 + \gamma |A_2|^2 + \gamma |A_3|^2) A_1 ,$$

$$\partial_t A_2 = \mu A_2 + \alpha \bar{A}_3 \bar{A}_1 - (|A_2|^2 + \gamma |A_3|^2 + \gamma |A_1|^2) A_2 ,$$

$$\partial_t A_3 = \mu A_3 + \alpha \bar{A}_1 \bar{A}_2 - (|A_3|^2 + \gamma |A_1|^2 + \gamma |A_2|^2) A_3 .$$



Ciliberto et al, PRL (1990)

If  $\alpha$  small  $\neq 0$ , spots/hexagons subcritical, stable near threshold  
 Stripes/rolls stable further away from threshold.

**The End**