Physics of multicellular systems 2022

Lecture 3

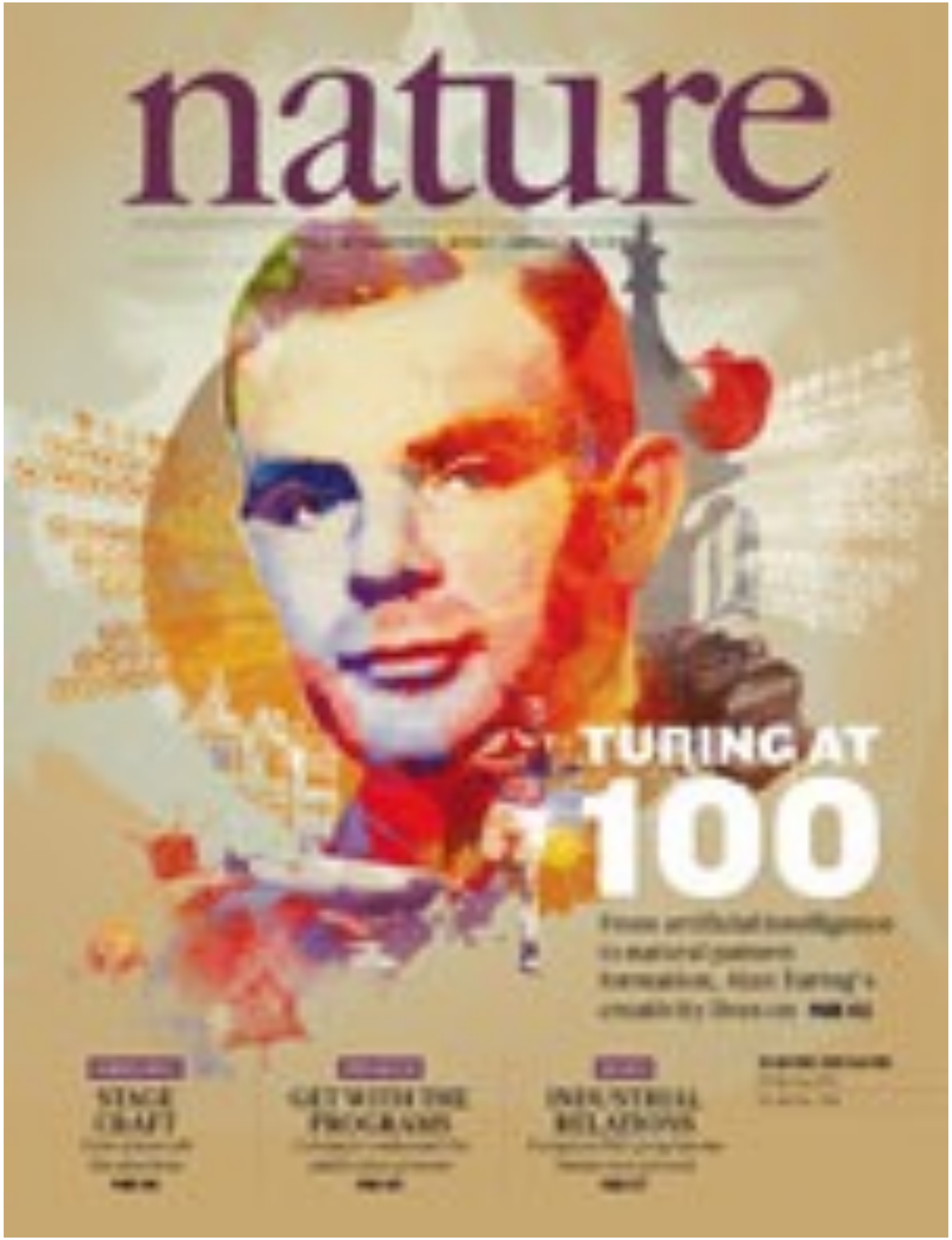
Self-organization : reaction-diffusion and the Turing mechanism

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

$$\frac{du}{dt} = a\,u + b\,v$$
$$\frac{dv}{dt} = c\,u + d\,v$$

Stability :

-1) $a+d<0$, possible if $a>0$ when d negative enough

-2) $ad-bc>0$ => $0>ad>bc$, b and c of different signs

activator/inhibitor system

=> inhibition stabilized network

A note : paradoxical response to inhibitor stimulation

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

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

Turing's diffusional instability

$$\frac{\partial u}{\partial t} = a\,u + b\,v + D_u \partial_{xx} u$$
$$\frac{dv}{dt} = c\,u + d\,v + D_v \partial_{xx} v$$

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

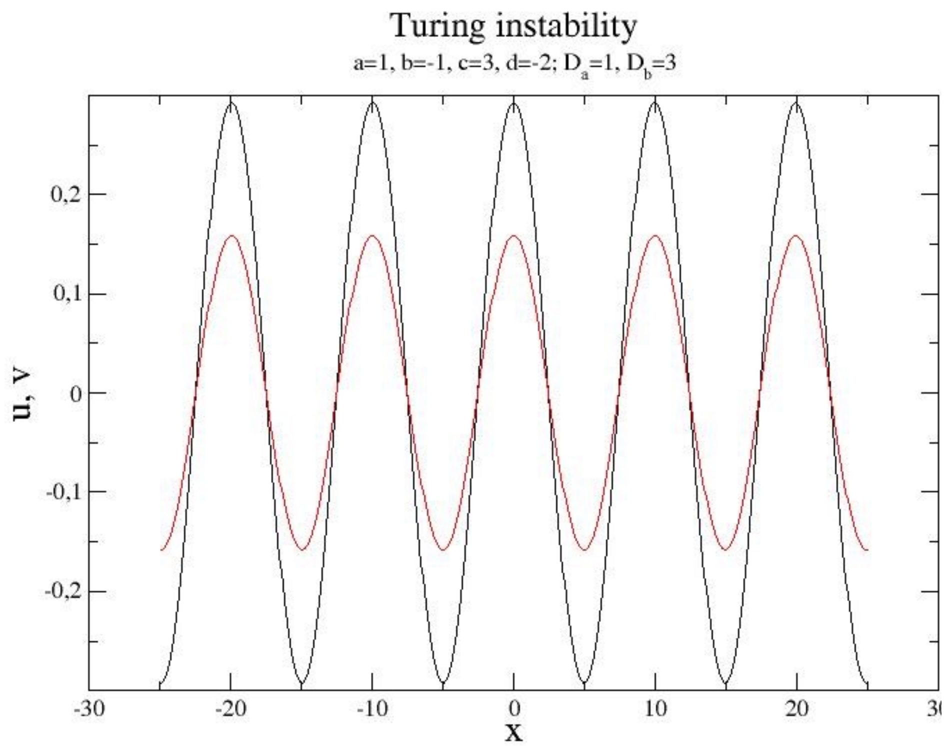
P has a positive root requires : $aD_v + dD_u > 0$, $(aD_v + dD_u)^2 - 4D_u D_v(ad - bc) > 0.$

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

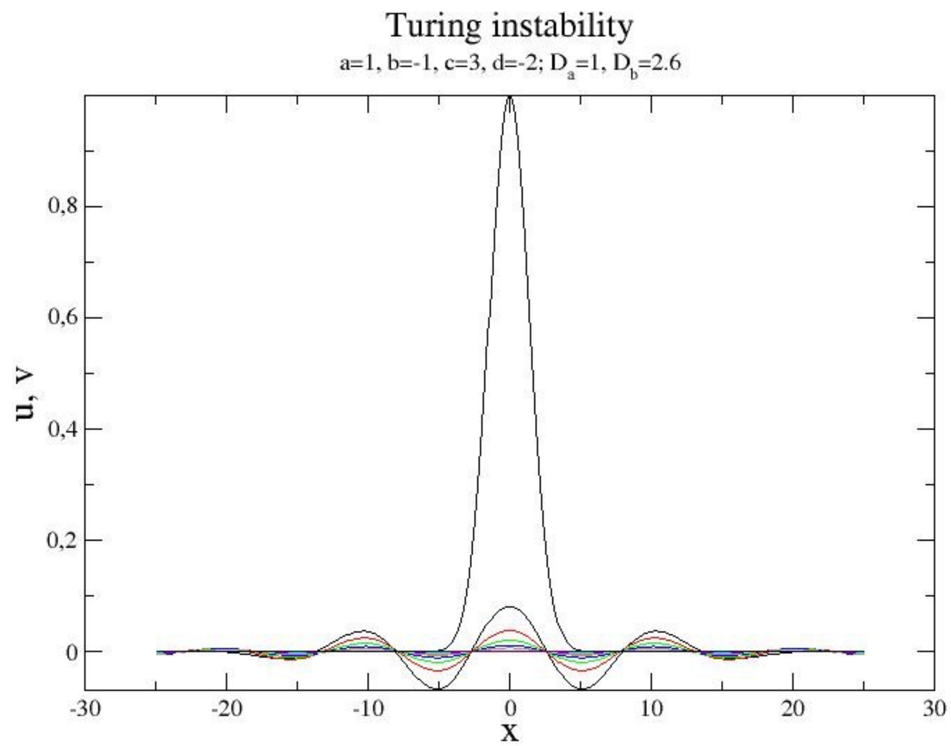
Wavevector at threshold: $$q_c = \left(\frac{aD_v + dD_u}{2D_u D_v}\right)^{1/2}$$

Turing instability

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



Above threshold



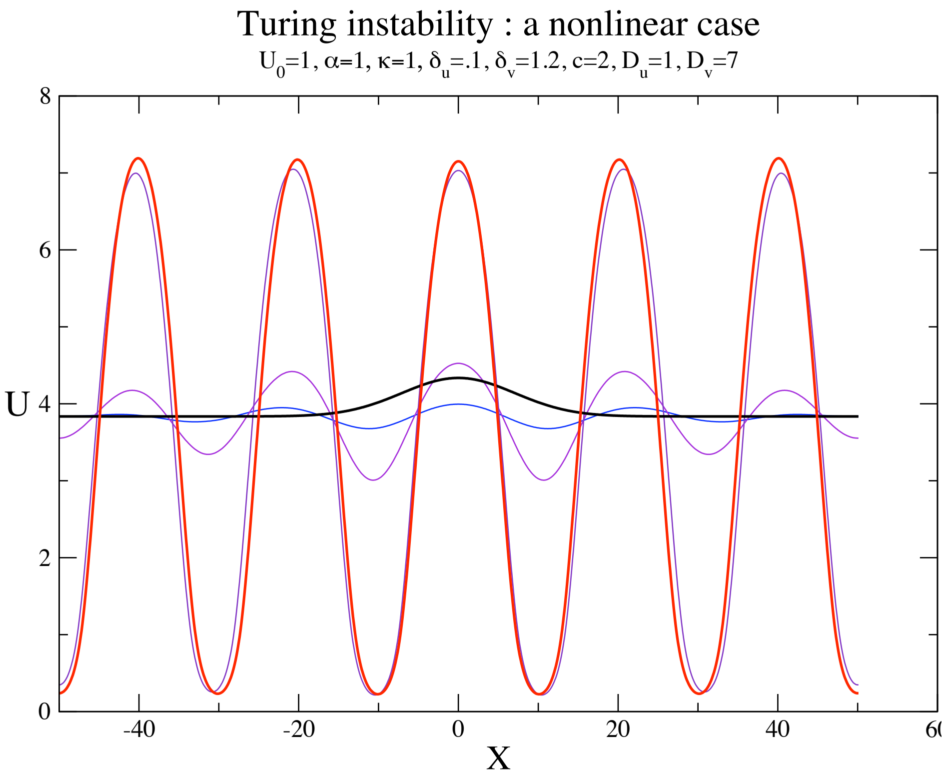
Below threshold

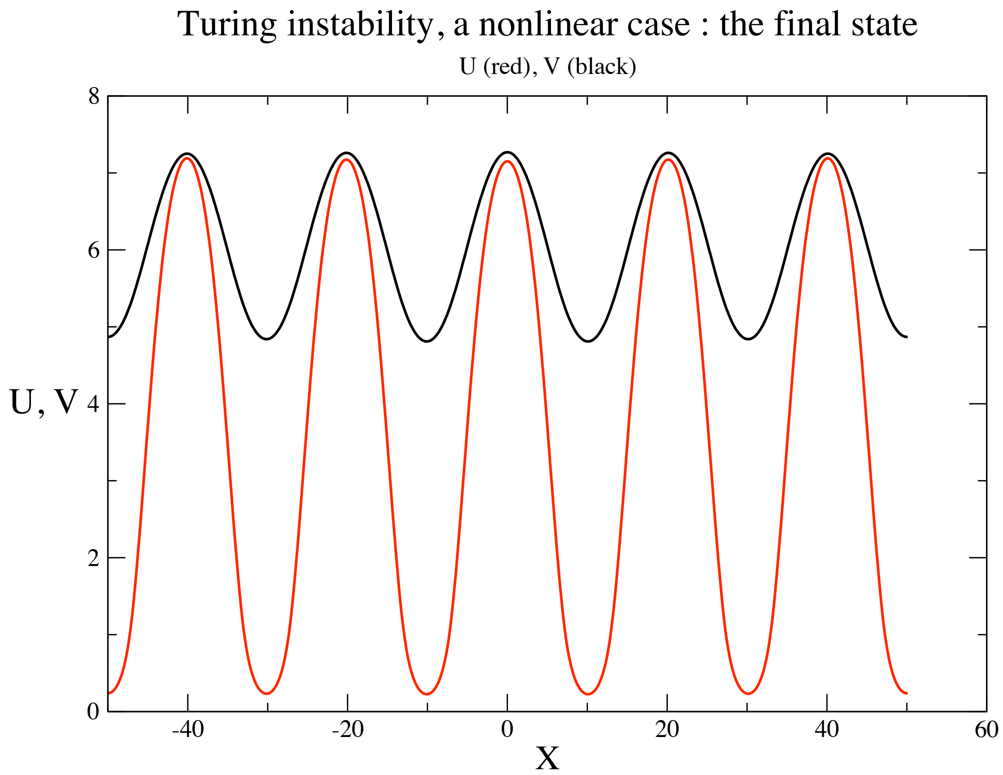
Turing instability : a simple non linear example

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

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

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





Nonlinear saturation of a linear instability

-At the linear level, instabilities grow without bound.
-Nonlinearities are required for saturation and the creation of stationary patterns.
-This can be precisely described close to the instability threshold
-> **weakly nonlinear analysis**.

A toy model, the Swift-Hohenberg equation : $\partial_t u = au - \frac{D}{q_0^2}(\partial_x^2 + q_0^2)^2 u - gu^3$

Linear stability and growth rate: $u = A\exp(\sigma t + iqx),$

$\sigma(q) = a - D(q_0^2 - q^2)^2/q_0^2$ instability for a>0, most unstable wavelength q_0.

Nonlinear dynamics and restabilisation for ε = a/g <<1 of the most unstable mode

Small A and slow growth (s<<1/g) -> perturbative analysis

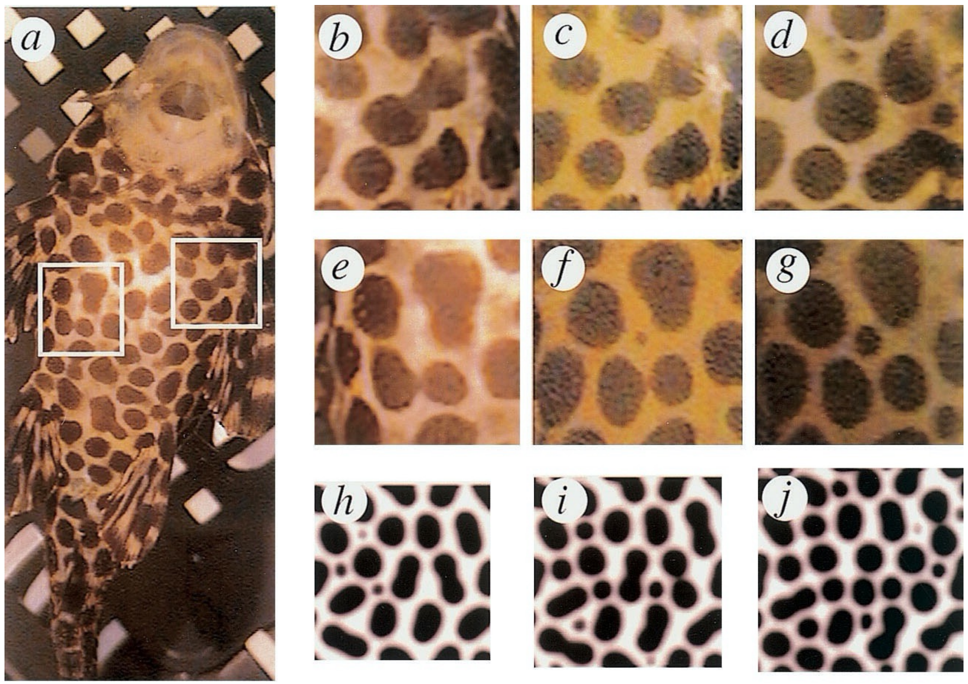
$$u(t,x) = A(t)\exp(iq_0 x) + u_1(t,x) + c.c.$$

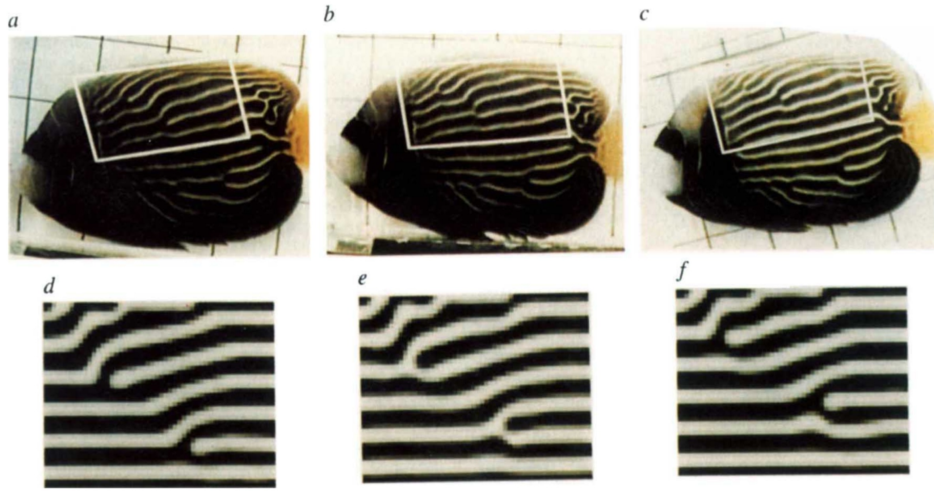
$$\mathcal{L}u_1 \equiv (\partial_x^2 + q_0^2)^2 u_1 = [aA - 3g|A|^2 A - \frac{dA}{dT}]\exp(iq_0 x) + c.c. + \text{ non secular terms}$$

Cancellation of ``secular'' terms $\frac{dA}{dT} = aA - 3g|A|^2 A$

Asymptotic restabilization at large times: $A \to \sqrt{a/(3g)}$

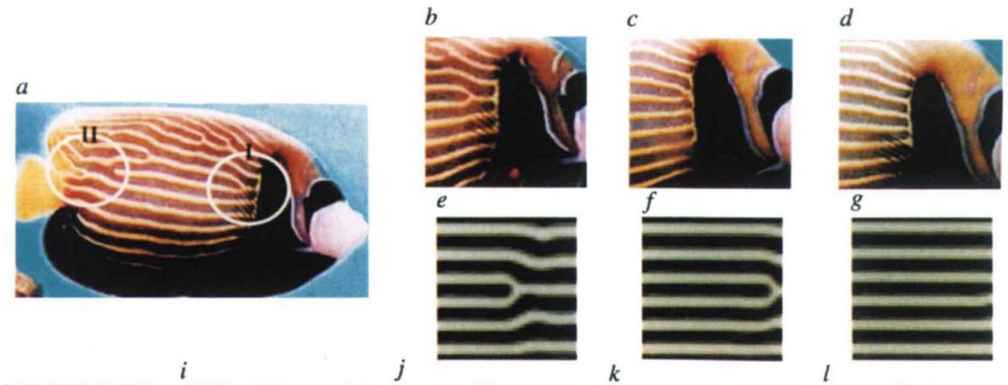
Skin patterns





S Kondo, R Asai, Nature 376 (1995)

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



Spots/hexagons or stripes/rolls?

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

Pattern : linear superposition of the most unstable modes

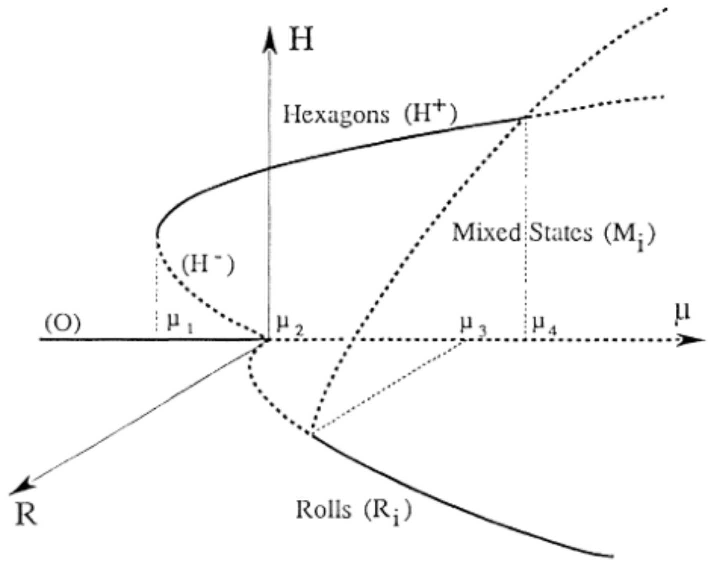
$$u(\mathbf{x}, t) = \sum_j A_j(t) \exp(i\mathbf{k}_j \cdot \mathbf{x}) + c.c$$

Stripes/rolls: only one mode
Hexagons : 3 modes $\mathbf{k}_1$, $\mathbf{k}_2$, $\mathbf{k}_3$ at angles $2\pi/3$

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

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

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



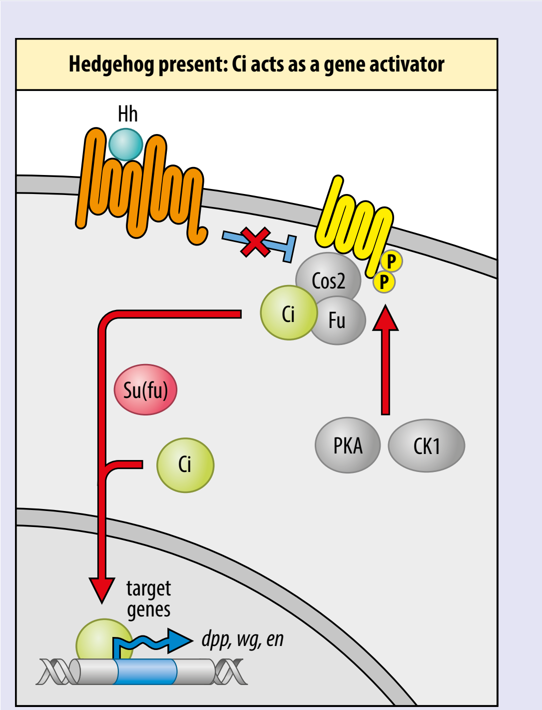
Ciliberto et al, PRL (1990)

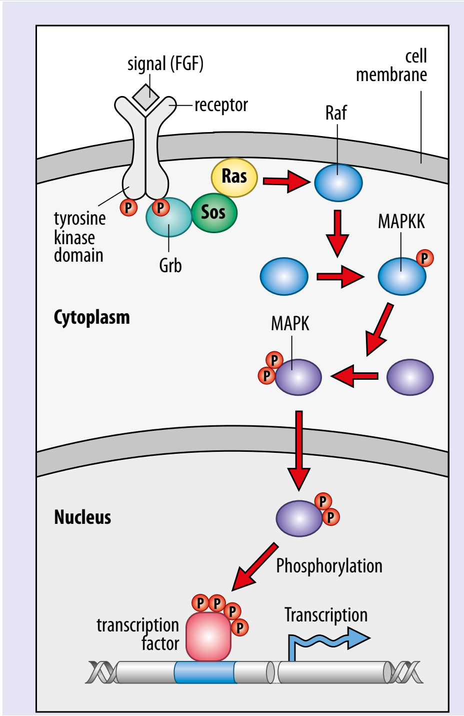
If α small ≠ 0, spots/hexagons subcritical, stable near threshold
Stripes/rolls stable further away from threshold.

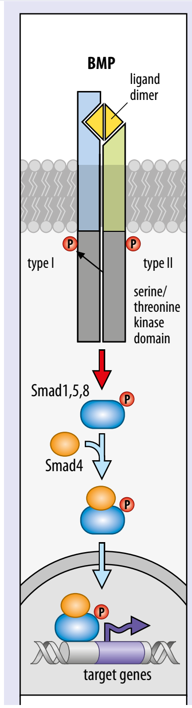
Signalling pathways in development

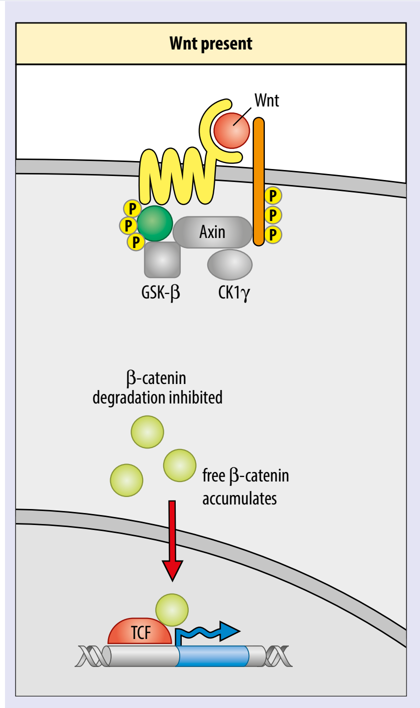
Table 22–1 Some Signal Proteins That Are Used Over and Over Again as Inducers in Animal Development

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



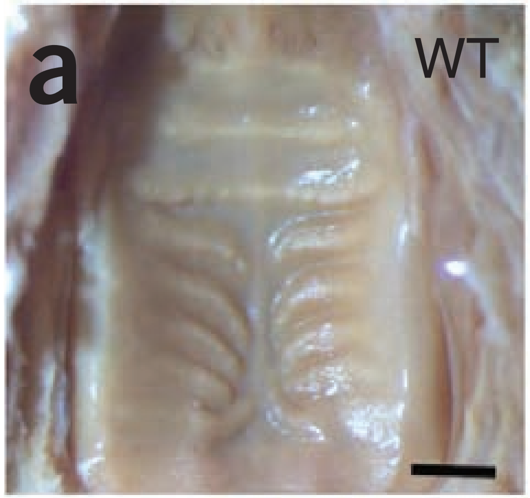


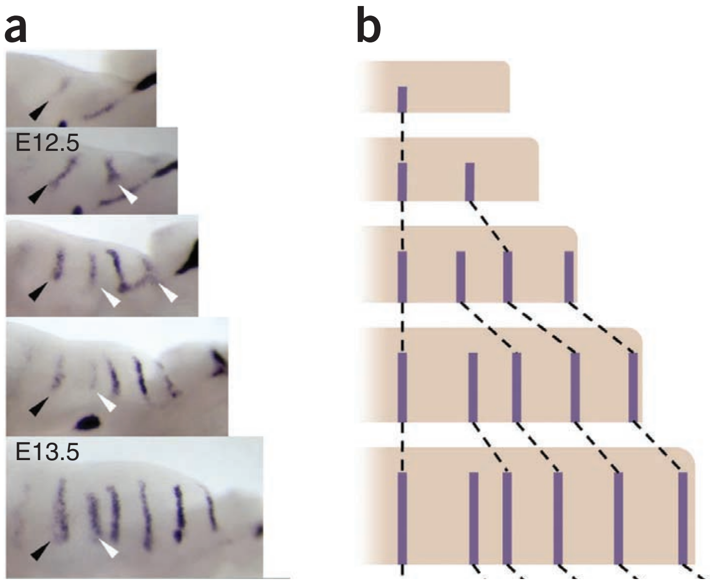


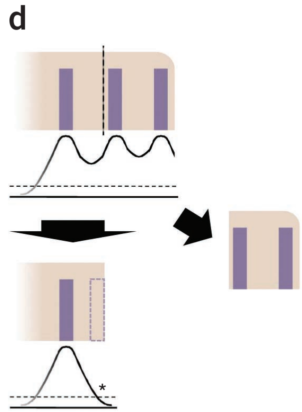


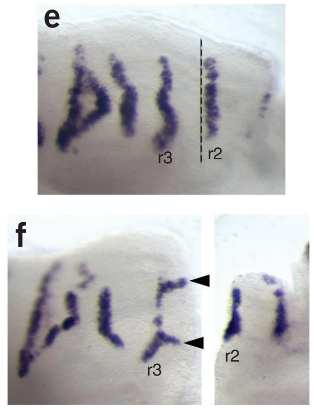
Mammalian palate (rugae formation)

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

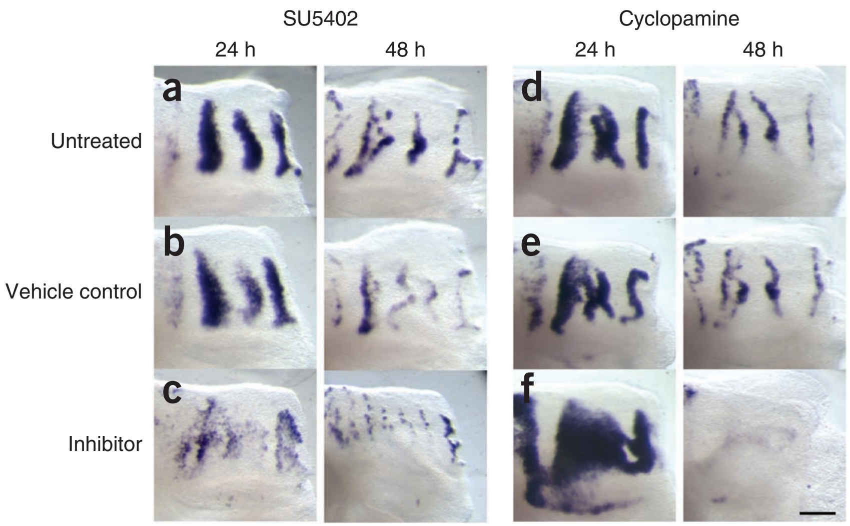








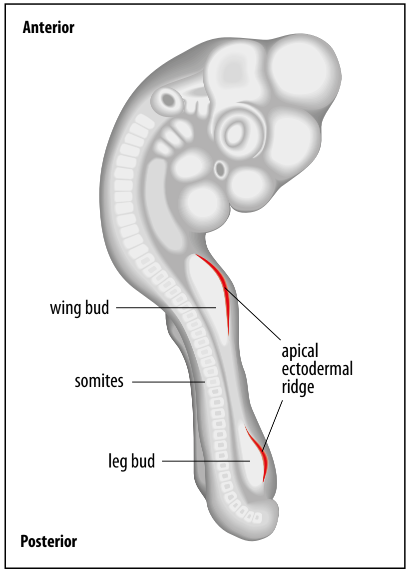
Cut: lateral inhibition
vs. propagation



SU5402 chemical inhibitor of FGF
-> FGF suggested Turing activator

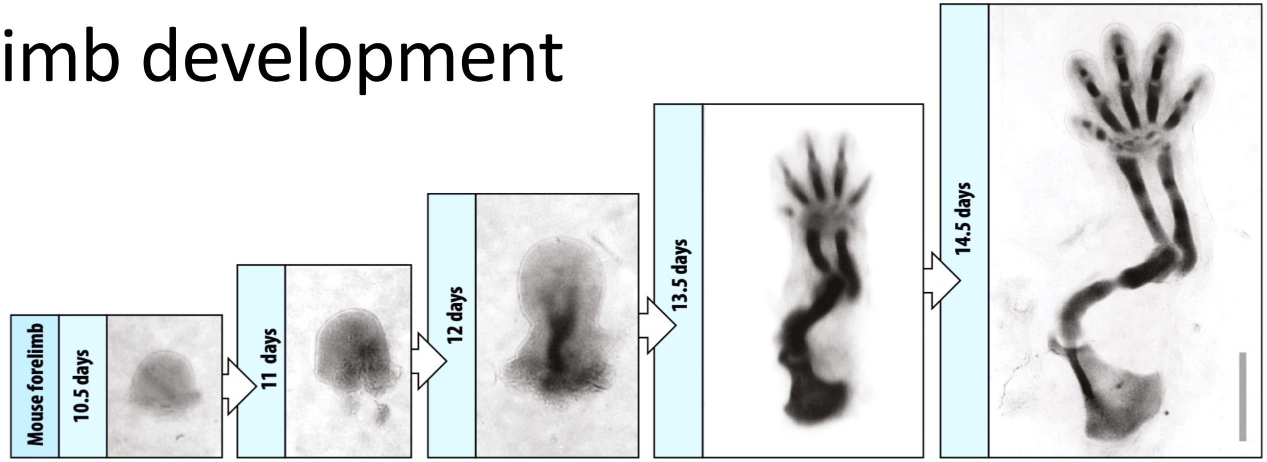
Cyclopamine Shh signalling inhibitor
-> Shh suggested Turing inhibitor

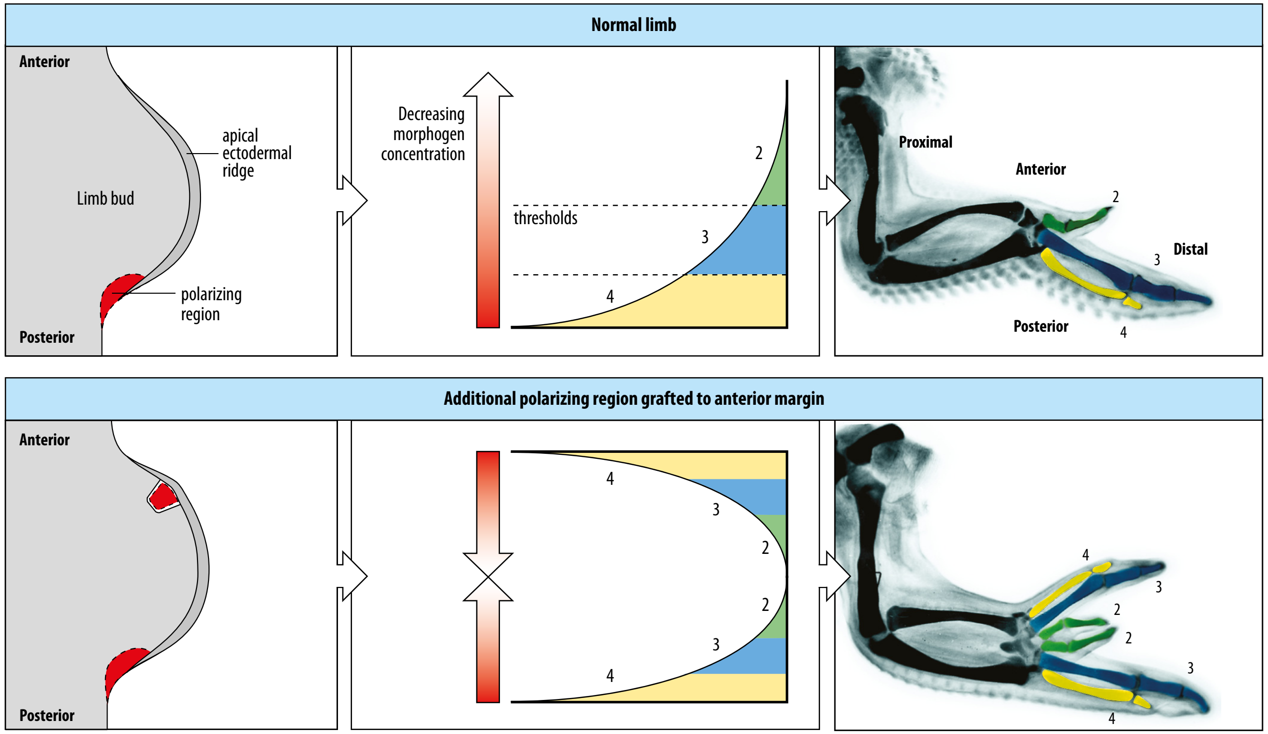
Other pathways (Wnt, BMP) involved



Limb development

Limb bud





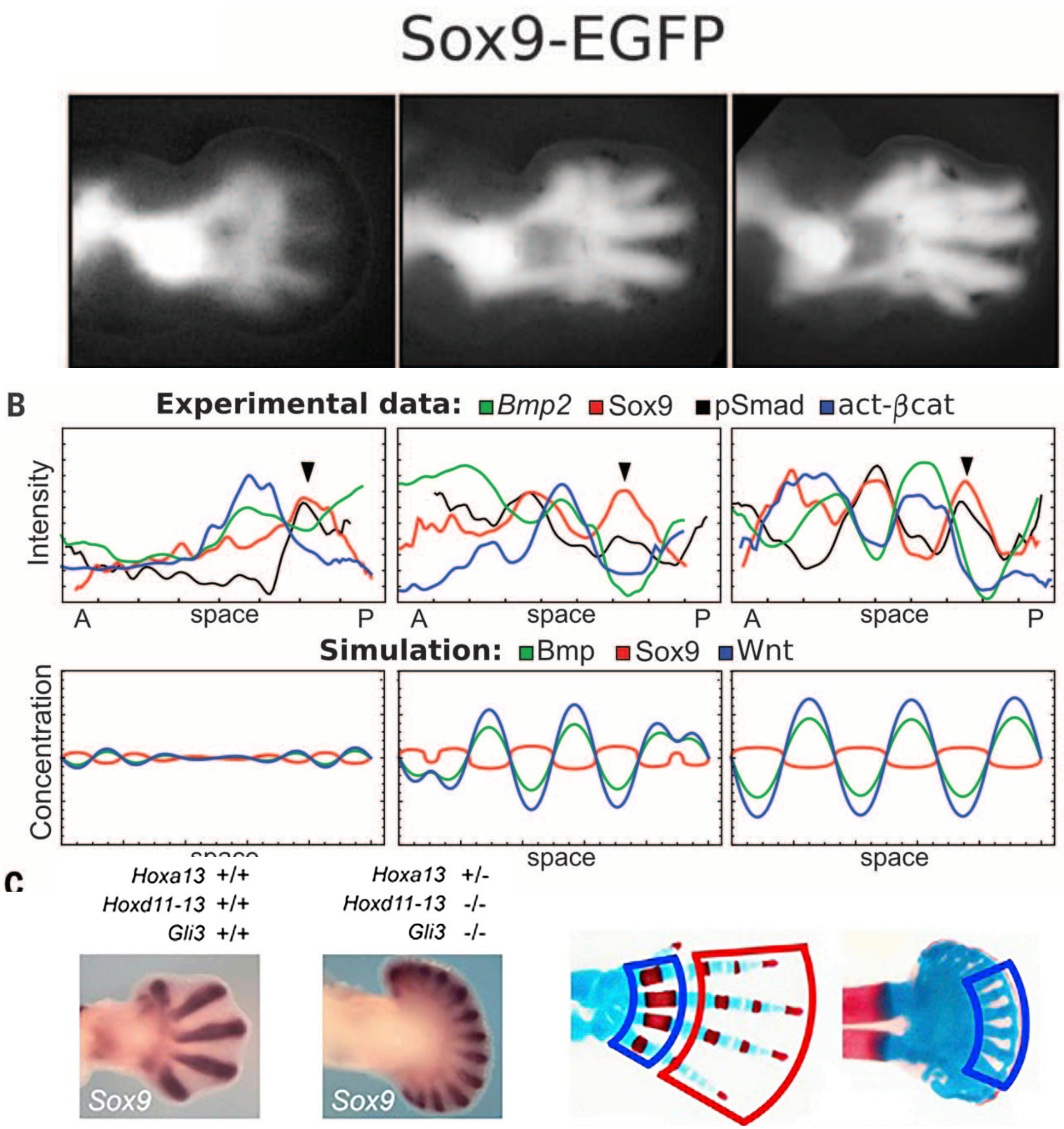
Proximo-distal :two gradients
-Retinoic acid: high P\>D low
-FGF: high D\>P low
-some similarity to
somitogenesis

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

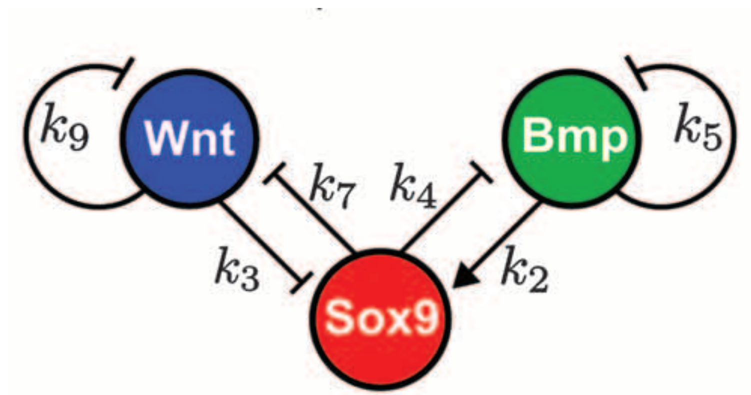
L Wolpert et al, Principles of development

Digit patterning

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



- Sox9 periodic pattern
-act-βcat (Wnt activity) antiphase



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

Mutants : polydactyly

Condensations more distal but with the same wavelength (result of cross inhibition between Hox genes?)

The End