Part V

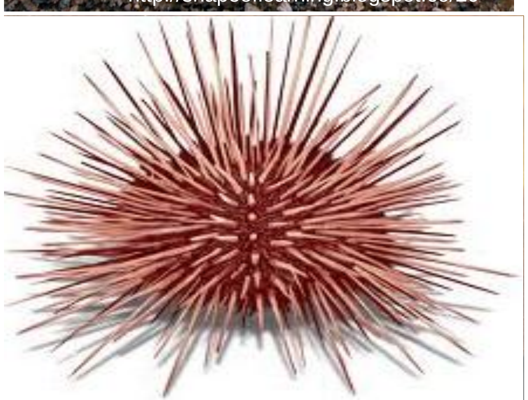
Spatial interactions and pattern models

Turing Model I: mathematics and simulation

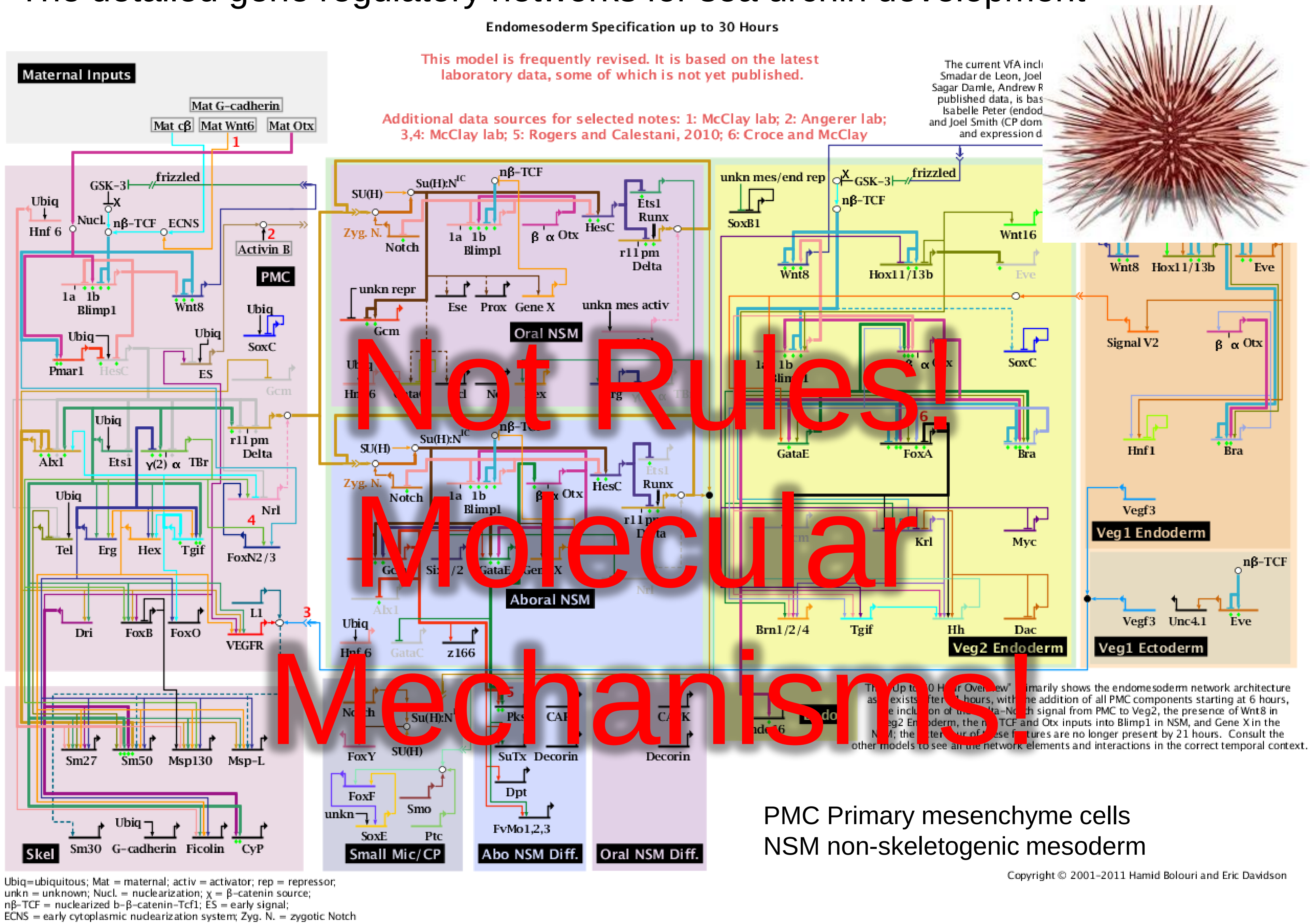
Week 12, 5/2/2017

Patterns in Nature

Rules



The detailed gene regulatory networks for sea urchin development



Not Rules! Molecular Mechanisms!

PMC Primary mesenchyme cells

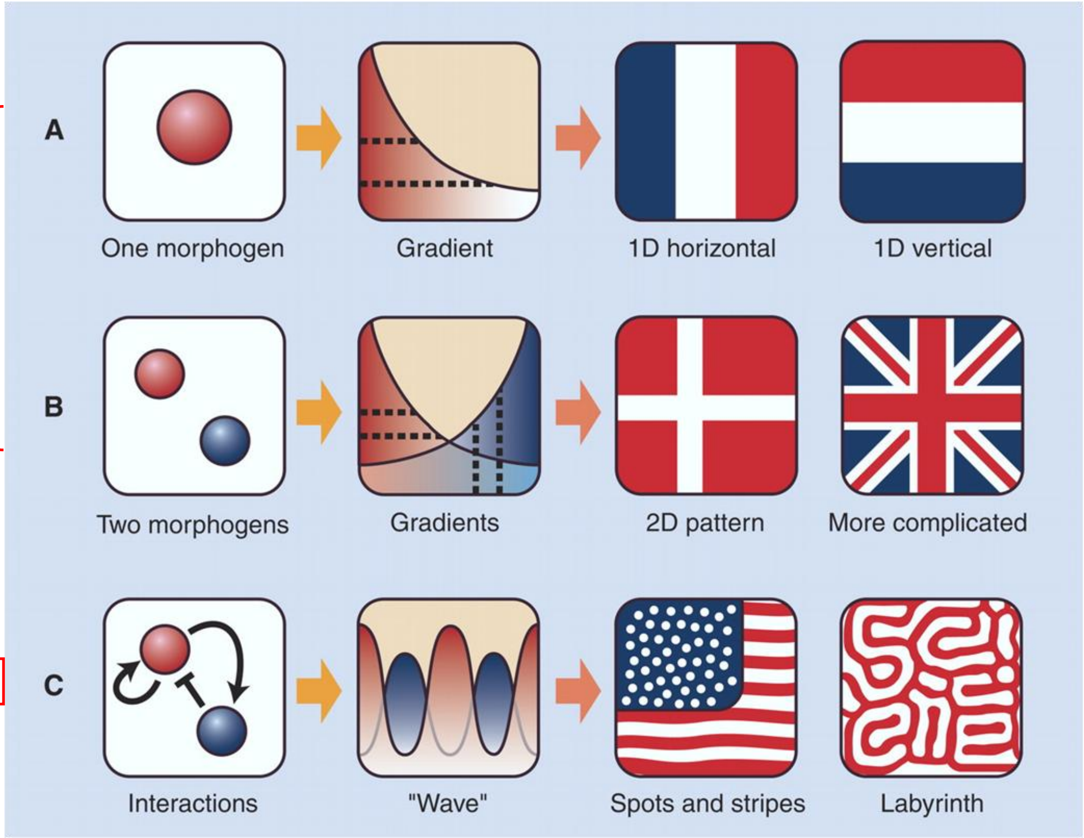
NSM non-skeletogenic mesoderm

What do we mean by pattern?

- Stable behavior in time (most commonly, cell differentiation) that is regular in space (regular =“following rules”)

Two main rules of pattern formation

- Morphogen gradient
  - Positional information laid out externally
  - Cells respond passively (gene expression and movement)
- Reaction-diffusion systems
  - Pattern formation autonomous
  - Typically involve mutual signaling and movement



Reaction-Diffusion Model as a Framework for Understanding Biological Pattern Formation, S Kondo and T Miura, *Science* 329, 1616 (2010)

Alan Turing (1912-1954)

- One of greatest scientists in 20th century
- Designer of Turing machine (a theoretical computer) in 1930's
- Breaking of U-boat Enigma, saving battle of the Atlantic
- Initiate nonlinear theory of biological growth

http://www.turing.org.uk/

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received 9 November* 1951—*Revised 15 March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

What did he discover

$$\partial_t u_1 = f_1(u_1, u_2) + D_1 \partial_x^2 u_1,$$
$$\partial_t u_2 = f_2(u_1, u_2) + D_2 \partial_x^2 u_2,$$

Generalized reaction-diffusion equations

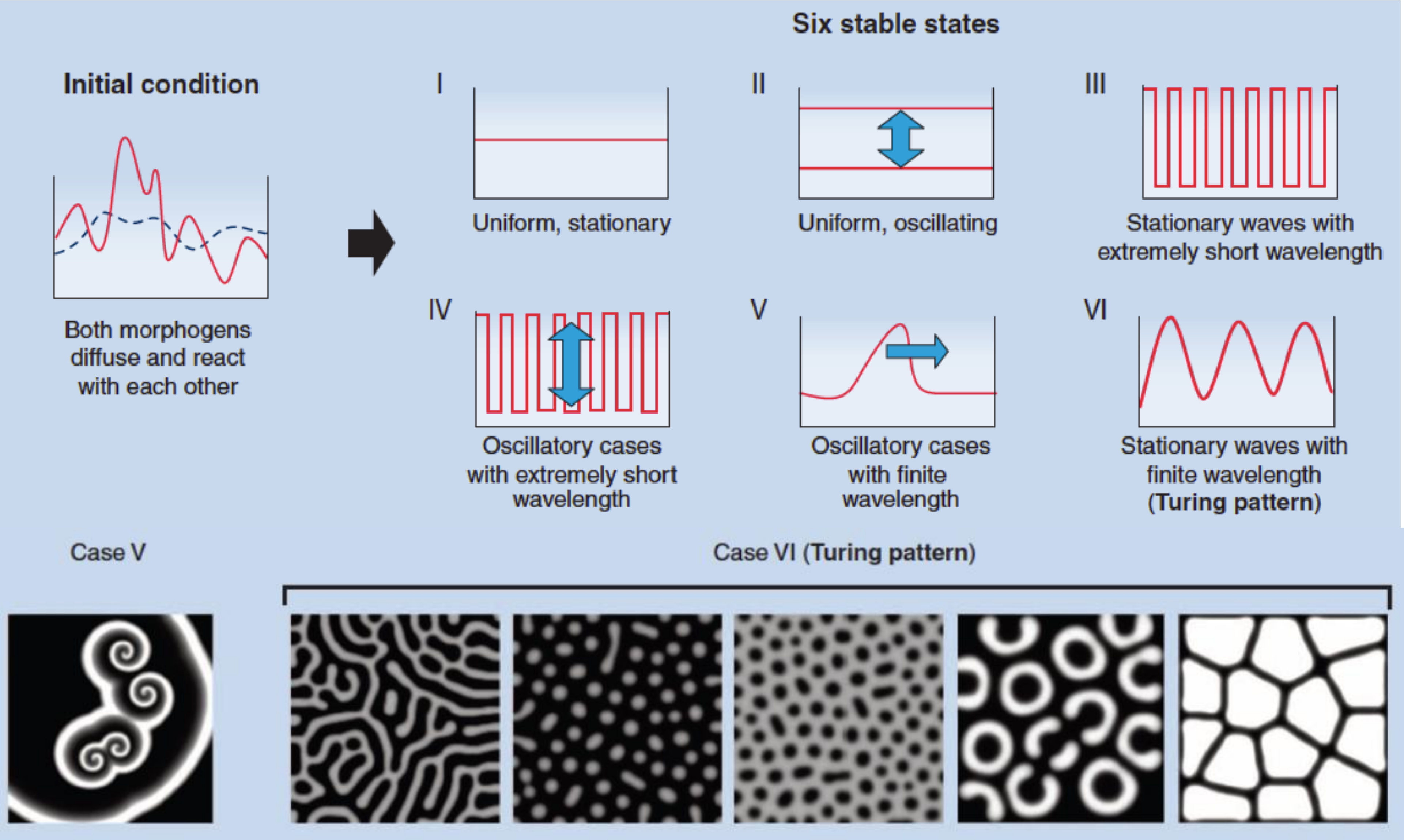
His insights:

1. ≥2 interacting chemicals are needed for pattern formation to occur.
2. Diffusion in a reacting systems can be a destabilizing influence.
3. Instability can cause growth of structure at a particular wavelength
4. Diffusion coefficients of two reagents differ substantially.

The underlying reactions relates to gene regulations and signal transduction networks

Alan Turing - one of the first systems biologists?

Six different models and patterns



Stability analysis of Turing's model

Turing's surprising and important discovery was that there are conditions: the spatially uniform state is stable in the absence of diffusion but can be unstable to nonuniform perturbation precisely because of diffusion.

$$\partial_t u_1 = f_1(u_1, u_2) + D_1 \partial_x^2 u_1,$$
$$\partial_t u_2 = f_2(u_1, u_2) + D_2 \partial_x^2 u_2,$$

Stationary uniform base solution: $\mathbf{u}_b=(u_{1b}, u_{2b})$ so that:

$$f_1(u_{1b}, u_{2b}) = 0,$$
$$f_2(u_{1b}, u_{2b}) = 0.$$

By linearizing about the base solution, perturbation $(\delta u1(t,x),\delta u2(t,x))$ follows the his equations:

$$\partial_t \delta u_1 = a_{11}\delta u_1 + a_{12}\delta u_2 + D_1 \partial_x^2 \delta u_1,$$
$$\partial_t \delta u_2 = a_{21}\delta u_1 + a_{22}\delta u_2 + D_2 \partial_x^2 \delta u_2.$$

$$a_{ij} = \left.\frac{\partial f_i}{\partial u_j}\right|_{\mathbf{u}_b} \qquad \mathbf{A} = \partial \mathbf{f}/\partial \mathbf{u}$$

It can be further expanded into:

$$\delta \mathbf{u} = \delta \mathbf{u}_q\, e^{\sigma_q t}\, e^{iqx} = \begin{pmatrix} \delta u_{1q} \\ \delta u_{2q} \end{pmatrix} e^{\sigma_q t} e^{iqx}$$

with growth rate σ_q and wave number q.

Stability analysis of Turing's model

It can be converted to an eigenvalue problem:

$$\mathbf{A}_q \, \delta \mathbf{u}_q = \sigma_q \, \delta \mathbf{u}_q$$

where

$$\mathbf{A}_q = \mathbf{A} - \mathbf{D}q^2 = \begin{pmatrix} a_{11} - D_1 q^2 & a_{12} \\ a_{21} & a_{22} - D_2 q^2 \end{pmatrix}$$

For given eigenvalue σ_{iq}, the particular solution with wave number q:

$$\left(c_{1q} \, \delta \mathbf{u}_{1q} \, e^{\sigma_{1q} t} + c_{2q} \, \delta \mathbf{u}_{2q} \, e^{\sigma_{2q} t}\right) e^{iqx}$$

The uniform solution u_b is stable if both eigenvalues σ_{iq} have negative real parts for all wave number q.

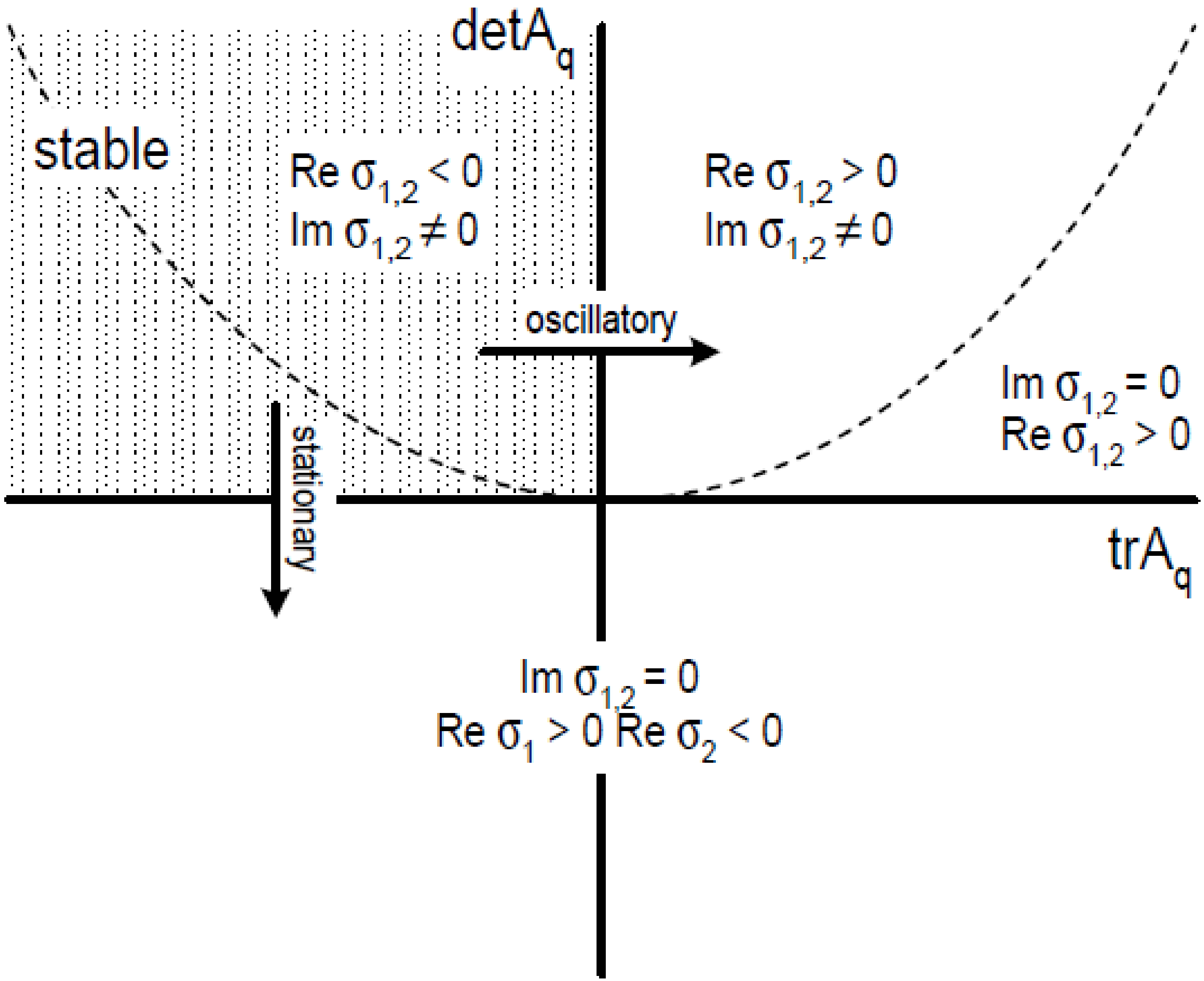
$$0 = \det\left(\mathbf{A}_q - \sigma_q \mathbf{I}\right) = \sigma_q^2 - (\mathrm{tr}\mathbf{A}_q)\sigma_q + \det \mathbf{A}_q$$

$$\sigma_q = \frac{1}{2}\mathrm{tr}\mathbf{A}_q \pm \frac{1}{2}\sqrt{(\mathrm{tr}\mathbf{A}_q)^2 - 4\det \mathbf{A}_q}$$

The criteria for stability (both)

$$\mathrm{tr}\mathbf{A}_q = a_{11} + a_{22} - (D_1 + D_2)q^2 < 0,$$
$$\det \mathbf{A}_q = (a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21} > 0.$$

Stability regions of Turing Model



Stability criteria

The criteria for stability (both)

$$\mathrm{tr}\,\mathbf{A}_q = a_{11} + a_{22} - (D_1 + D_2)q^2 < 0,$$
$$\det \mathbf{A}_q = (a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21} > 0.$$

If uniform state is stable ($D_1 = D_2 = 0$)

$$a_{11} + a_{22} < 0,$$
$$a_{11}a_{22} - a_{12}a_{21} > 0.$$

So tr$\mathbf{A}_q$ always negative, only way for diffusion to destabilize the uniform state is det$\mathbf{A}_q$ <0. Taking derivative of det$\mathbf{A}_q$ against q^2, we can find most unstable q^2_m:

$$q_m^2 = \frac{D_1 a_{22} + D_2 a_{11}}{2D_1 D_2}.$$

$$\det \mathbf{A}_{q_m} = a_{11}a_{22} - a_{12}a_{21} - \frac{(D_1 a_{22} + D_2 a_{11})^2}{4D_1 D_2}.$$

If det**A**q<0, then $$D_1 a_{22} + D_2 a_{11} > 2\sqrt{D_1 D_2 (a_{11}a_{22} - a_{12}a_{21})}$$

Therefore a11 and a22 must have opposite sign, a12 and a21 also must have.

Stability criteria

Assuming a11>0, a22<0 let's define two diffusion lengths:

$$l_1 = \sqrt{\frac{D_1}{a_{11}}} \quad \text{and} \quad l_2 = \sqrt{\frac{D_2}{-a_{22}}},$$

Then

$$q_m^2 = \frac{1}{2}\left(\frac{1}{l_1^2} - \frac{1}{l_2^2}\right) > \sqrt{\frac{a_{11}a_{22} - a_{12}a_{21}}{D_1 D_2}}.$$

Unstable condition: $l_2 > l_1$, As a11>0, "activator", a22<0, 'inhibitor".
l2>l1: local activation with long range inhibition.

This local activation with long range inhibition mechanism is not explicitly expressed by Alan Turing. 20 years later, it was rediscovered and explicitly stated by Grierer and Meinhardt:

The authors of the activator-inhibitor model: Hans Meinhardt (to the left) and Alfred Gierer.

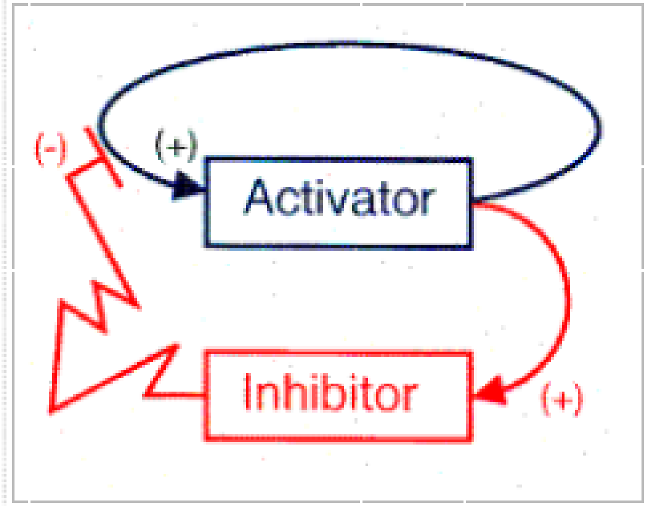


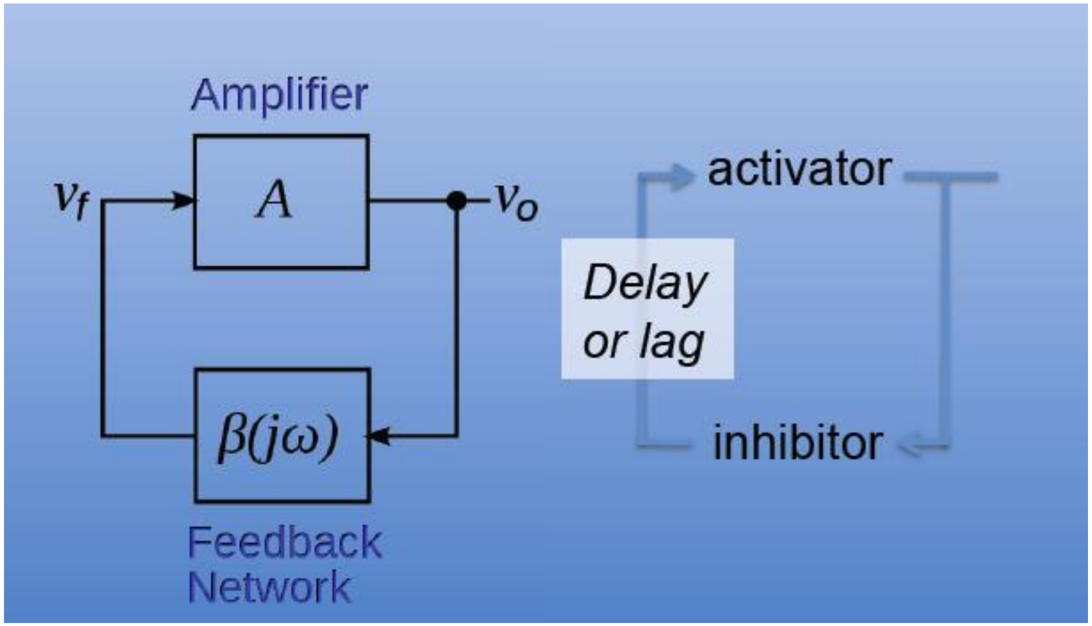
Figure 1: Short-range activator and long-range inhibitor in Gierer-Meinhardt model

$$\frac{\partial a}{\partial t} = \rho \frac{a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_a$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} + \rho_h$$

Intuitive understanding of Turing patterning

- As a spatial generalization of the delayed-feedback system oscillation in time



If feeding back an opposing signal at a different point in time can produce oscillation in time, the feeding back an opposing signal at a different point in space might be able to produce oscillation in space.

Harmonic oscillator (electronics)

Biological oscillator

The Inhibitor must act over a longer characteristic spatial scale than the activator

Intuitive understanding of Turing patterning

- As a spatial generalization of bistability

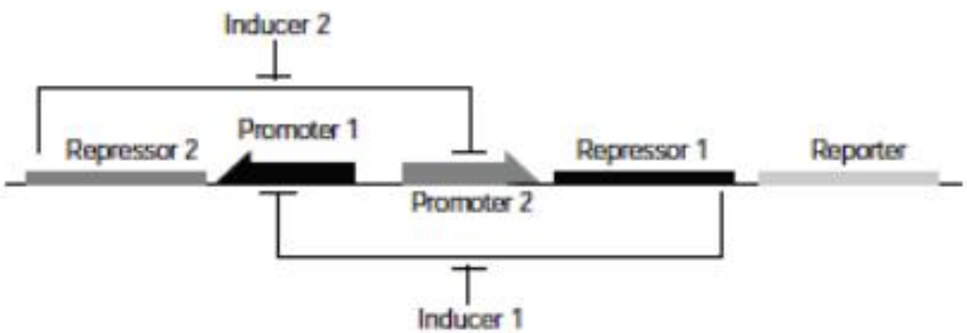


Figure 1 Toggle switch design. Repressor 1 inhibits transcription from Promoter 1 and is induced by Inducer 1. Repressor 2 inhibits transcription from Promoter 2 and is induced by Inducer 2.

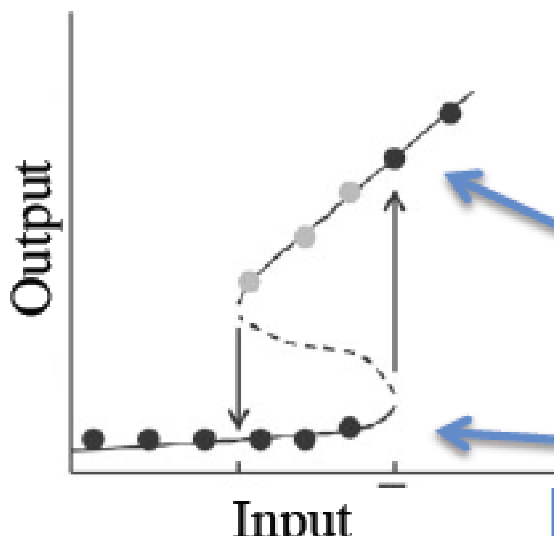
Gardner, Cantor and Collins, 2000

Dynamical systems can be bistable (or multistable) if there is nonlinear positive feedback.

Autoactivation must be more than linear sensitive.

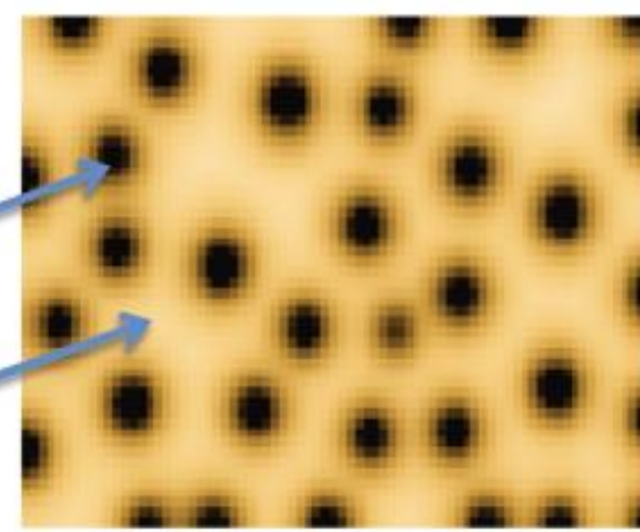
$$\frac{du}{dt} = \frac{\alpha_1}{1+v^{\beta}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^{\gamma}} - v$$



High State

Low state



Phenomena of Turing pattern

- Local rules, no long distance planning
- Exponentially amplification of small perturbation
- Select certain wavelengths for amplification

Matlab examples of 1D Grierer-Meinhardt model with uniform initial condition

- File: meinh1dflat.m
  - Parameters: nx, nt, Da, Dc, noise level
  - Results:
    - figure 1: spatial-temporal diagram of activator: x:time, y:space
    - figure 2: movie of activator and inhibitor
  - Run 4 times to show different results each time

Matlab examples of 2D Grierer-Meinhardt model with uniform initial condition

- File2: meinh2dflat.m
  - Parameters: Da, Dc
  - Results:
    - figure 1: movie of activator figure 2
- File3: meinh2dstripe.m
  - Adding saturation of activation of a to a
  - Parameters: sat (saturation of a to a)
  - Results:
    - figure 1: movie of activator figure 2
  - Run 2 times to compare no saturation vs saturation.

Occasionally the field of pattern formation is expanding, such as embryo development

- Simple implementation: time-dependent adjustment of dx, dy.

Matlab examples of 1D Grierer-Meinhardt model with growth domain

- File: meinh1dexpand.m
  - Parameters: nx, nt, Da, Dc
  - Results:
    - figure 1: spatial-temporal diagram of activator: x:time, y:space
    - figure 2: movie of activator and inhibitor in expanding space
  - Run 4 times to show different results each time

Matlab examples of 2D Grierer-Meinhardt model with growth domain

- File: meinh2dexpand.m
  - Parameters:
  - Results:
    - figure 1: movie of activator in expanding space
- File: meinh2dexpandstripe.m
  - Parameters:
  - Results:
    - figure 1: movie of activator in expanding space

This model can be used to predict the timing and location of new hair follicle formation in mouse embryo

Predicting the spatiotemporal dynamics of hair follicle patterns in the developing mouse

Chi Wa Cheng[a,1], Ben Niu[a,1], Mya Warren[b,1], Larysa Halyna Pevny[c,2], Robin Lovell-Badge[d], Terence Hwa[b,3], and Kathryn S. E. Cheah[a,3]

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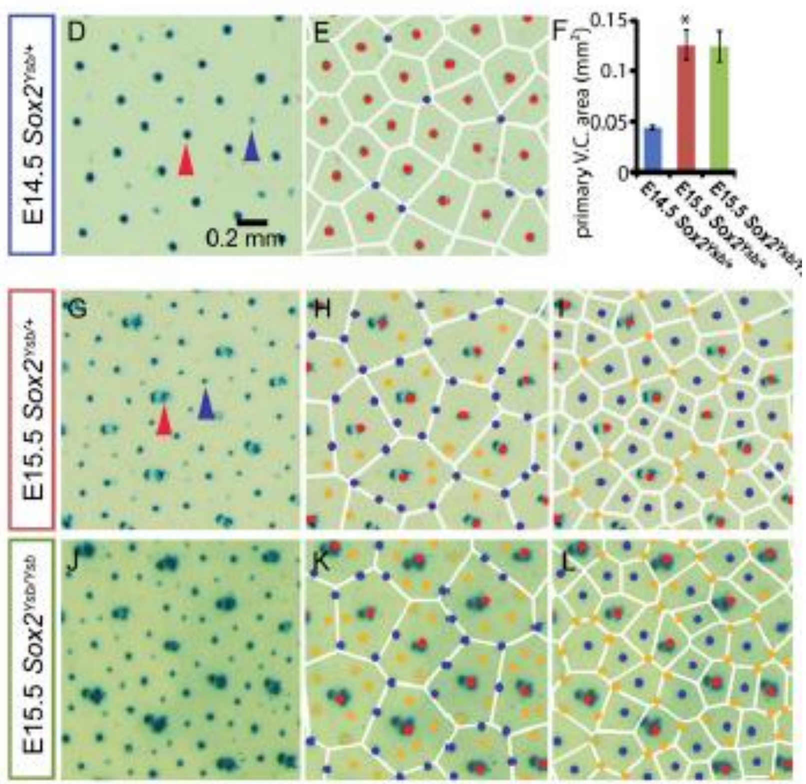
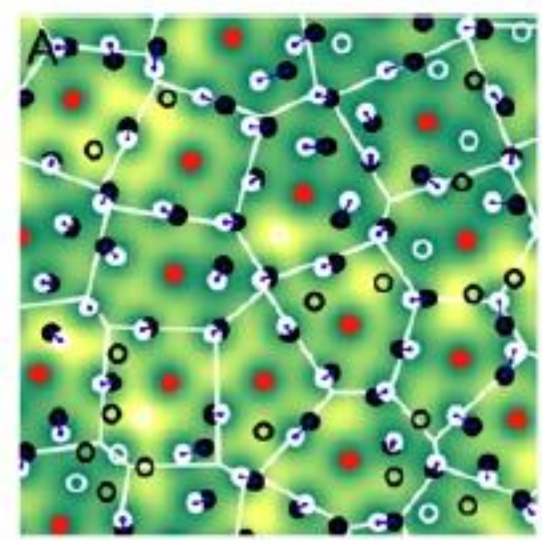
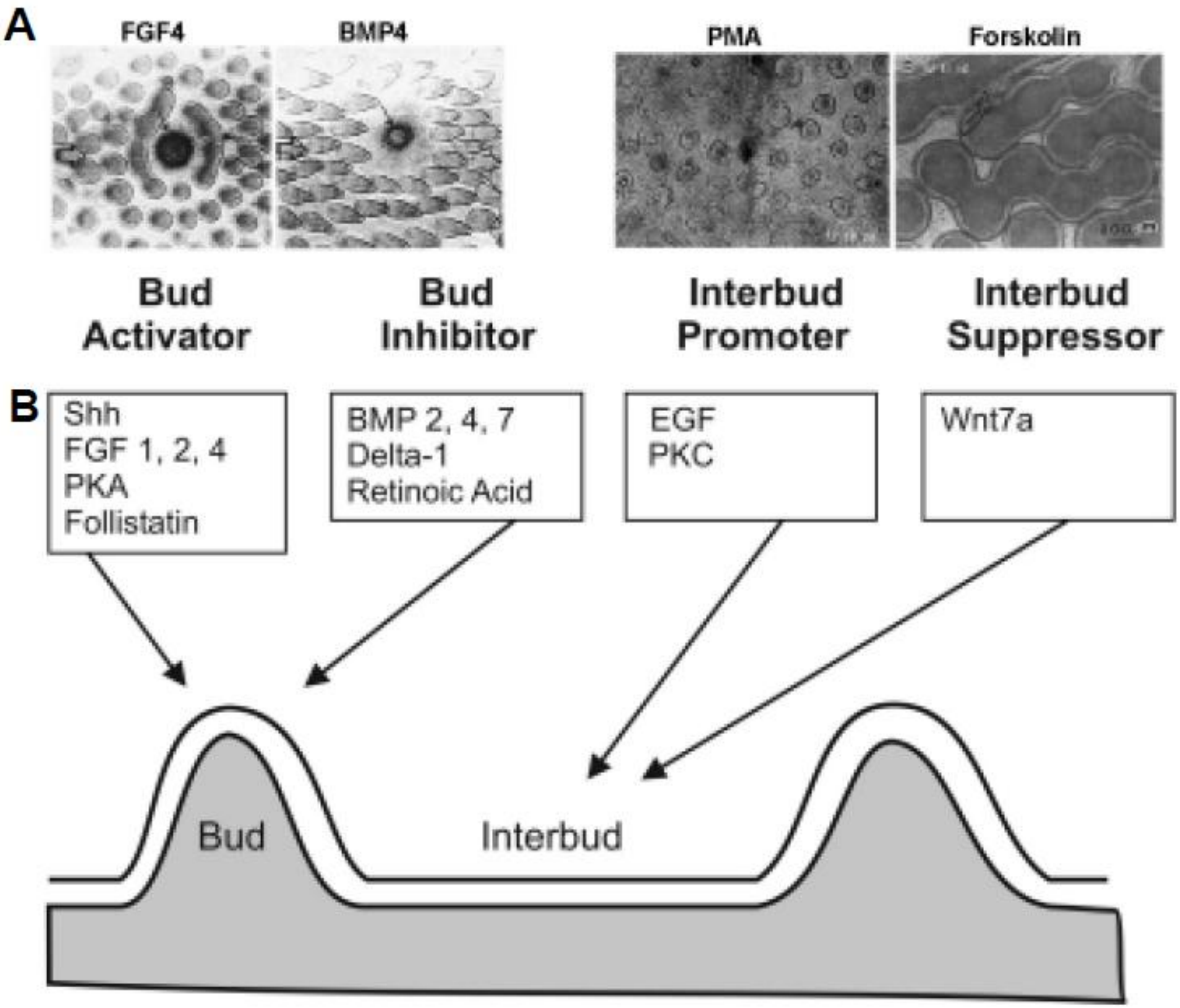




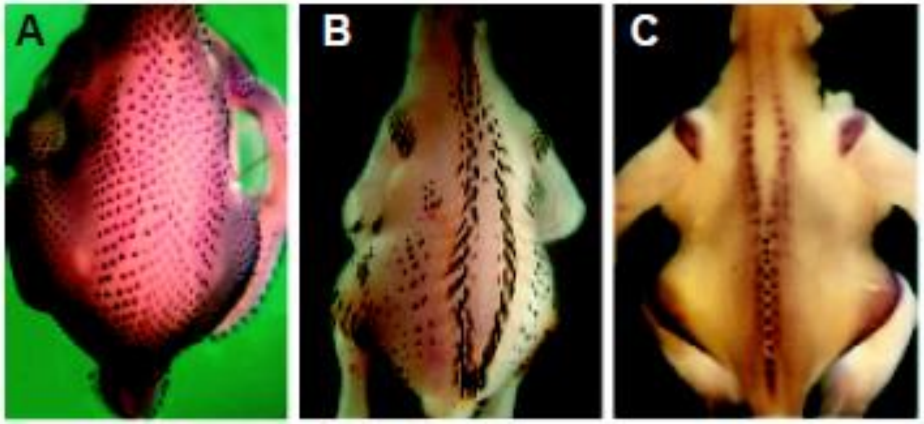
Chicken feather bud pattern and Turing modeling

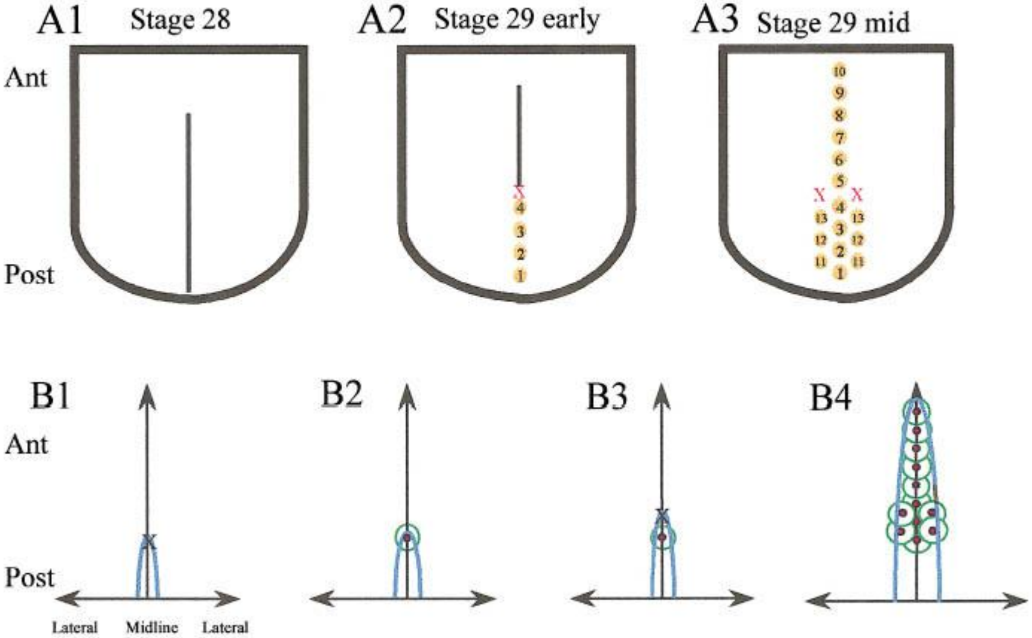
With belief in Turing model, biologists have extensively screening for activators and inhibitors.



Chicken feather bud has very different pattern

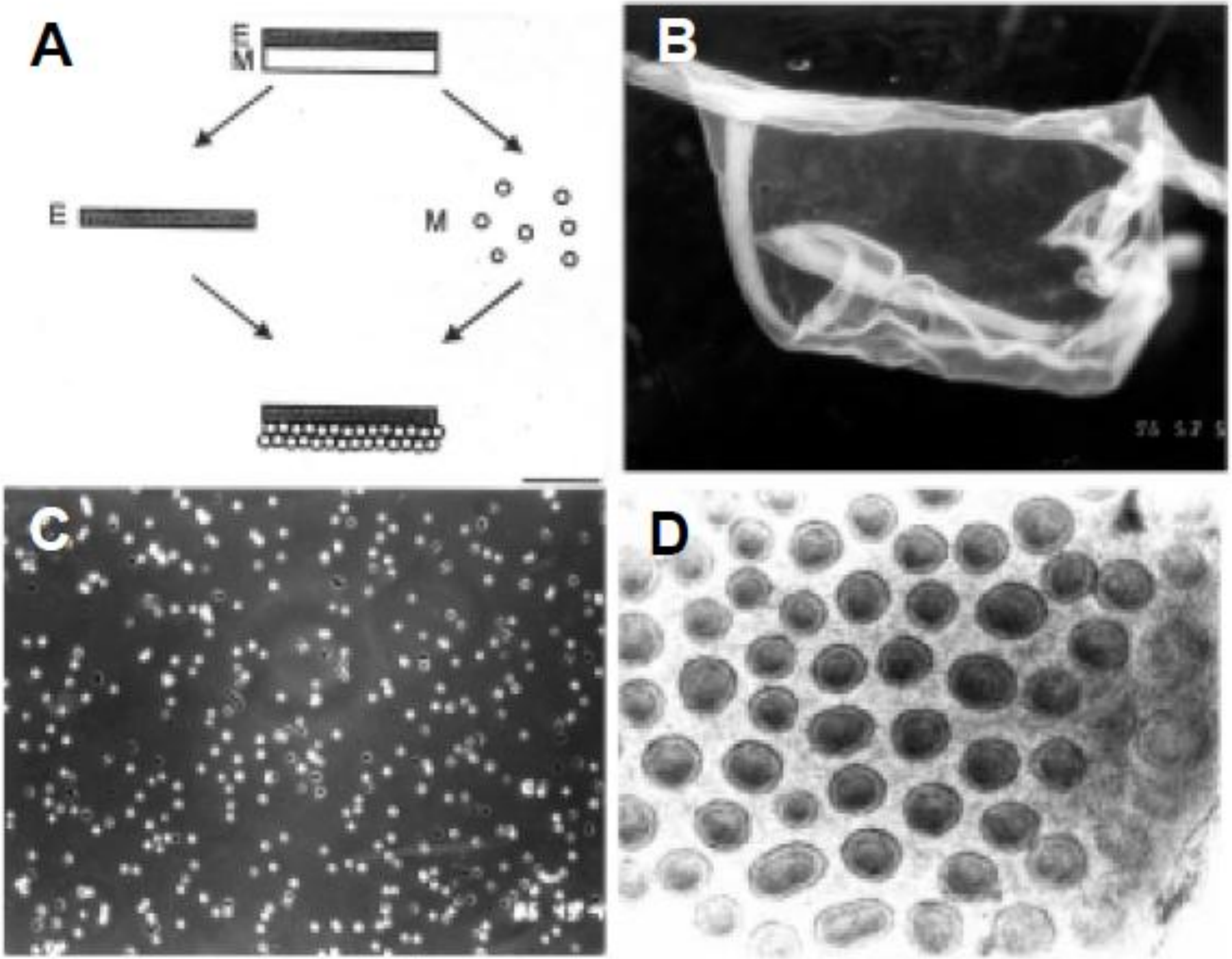
- Spatially regular (close to hexagonal)
- Temporally sequential
- Faster than expansion





Is it possible that regular chicken feather bud patterning follows Turing mechanism?

- Turing patterns are inherently spatial temporal heterogeneous.
- In vitro reconstitution experiments also demonstrated this.


A
E
M
E
M
B
C
D

Matlab examples of 1D Grierer-Meinhardt model with spatial localized initial condition

- File: meinh1dseed.m
  - Parameters: nx (250-350), noise to initial condition
  - Results:
    - figure 1: spatial-temporal diagram of activator: x:time, y:space
    - figure 2: movie of activator and inhibitor in expanding space

Without noise, to a degree, 1D model can generate sequential regular pattern

Matlab examples of 2D Grierer-Meinhardt model with spatial localized initial condition

- File: meinh2dseed.m
  - Parameters:
  - Results:
    - figure 1: spatial-temporal diagram of activator: x:time, y:space
    - figure 2: movie of activator and inhibitor in expanding space

Without noise, 2D model cannot generate sequential regular pattern

Possible mechanisms on top of Turing model for chicken feather bud

"Competent wave":

1. Move from posterior to anterior, middle line to laterial
2. Enable Turing pattern formation within area of competent
3. Mesenchymal cell competent (differentiation?)

Solid experimental proof of Turing model

- Next week, we will discuss a few critical experimental studies in the last two years.