Collective Effects

in

Equilibrium and Nonequilibrium Physics

Website: http://cncs.bnu.edu.cn/mccross/Course/

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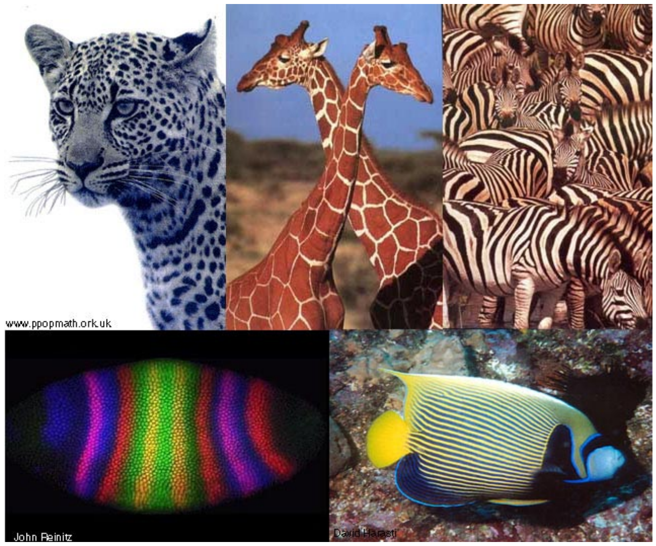
Today's Lecture: Pattern Formation in Biology

Outline

- Review of Turing patterns
- Ideas from the theory of pattern formation
- Three examples
  - ◇ Segmentation in Drosophila (fruit fly)
  - ◇ Animal and fish markings
  - ◇ Patterns on the visual cortex



Turing: The Chemical Basis of Morphogenesis

Phil. Tran. R. Soc. Lon. **B237**, 37 (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.

This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge.

Turing on Broken Symmetry

There appears superficially to be a difficulty confronting this theory of morphogenesis, or, indeed, almost any other theory of it. An embryo in its spherical blastula stage has spherical symmetry.... But a system which has spherical symmetry, and whose state is changing because of chemical reactions and diffusion, will remain spherically symmetrical for ever..... It certainly cannot result in an organism such as a horse, which is not spherically symmetrical.

There is a fallacy in this argument. It was assumed that the deviations from spherical symmetry in the blastula could be ignored because it makes no particular difference what form of asymmetry there is. It is, however, important that there are *some* deviations, for the system may reach a state of instability in which these irregularities, or certain components of them, tend to grow..…In practice, however, the presence of irregularities, including statistical fluctuations in the numbers of molecules undergoing the various reaction, will, if the system has an appropriate kind of instability, result in this homogeneity disappearing.

Modern Interpretation

- We now know that the structural information of biological organisms is encoded at the molecular level in the DNA
- Coding is in terms of base sequences that code for the production of proteins with a rate controlled by other proteins: these can be thought of as the morphogens
- How does the information at the molecular level become structure at the macroscopic level?
- This process obviously uses the laws of physics, but are the “laws” of pattern formation involved?
  - ⋄ Yes in modelling
  - ⋄ ?? in real world

Reaction-Diffusion

Two chemical species with concentrations u_1, u_2 that react and diffuse

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

- Reaction:

  $$a\,\mathrm{A} + b\,\mathrm{B} \to c\,\mathrm{C} + d\,\mathrm{D}$$

  gives the reaction rate (law of mass action)

  $$v(t) = -\frac{1}{a}\frac{d[\mathrm{A}]}{dt} = \cdots = k[A]^{m_\mathrm{A}}[B]^{m_\mathrm{B}}$$

  with $m_\mathrm{A} = a \ldots$ for elementary reactions
- Diffusion: conservation equation

  $$\partial_t u_i = -\nabla \cdot \mathbf{j}_i$$

  with

  $$\mathbf{j}_i = -D_i \nabla u_i$$

“Reaction” and “Diffusion”

The form of the equations is not actually specific to chemical systems: nonlinear local terms and second order derivatives appear in many other systems:

- nerve fibres (Hodgkin-Huxley), heart tissue etc.
  - ◇ reaction: currents across membrane through ion-channels with dynamic gate variables
  - ◇ diffusion: resistive flow of current along membrane
- neural networks
  - ◇ reaction: neuron firing as nonlinear function of inputs
  - ◇ diffusion: connectivity
- gene networks
  - ◇ reaction: gene expression controlled by other gene products
  - ◇ diffusion: transport of gene products from cell to cell

Turing Instability

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

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

- Linearize about the base state $\mathbf{u} = \mathbf{u}_b + \delta\mathbf{u}$

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

  with $a_i = \partial f_i / \partial u_j \big|_{\mathbf{u}=\mathbf{u}_b}$.

- Seek a solution $\delta\mathbf{u}(t, x)$ that is a Fourier mode with exponential time dependence:

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

Stability Analysis

- Eigenvalue equation

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

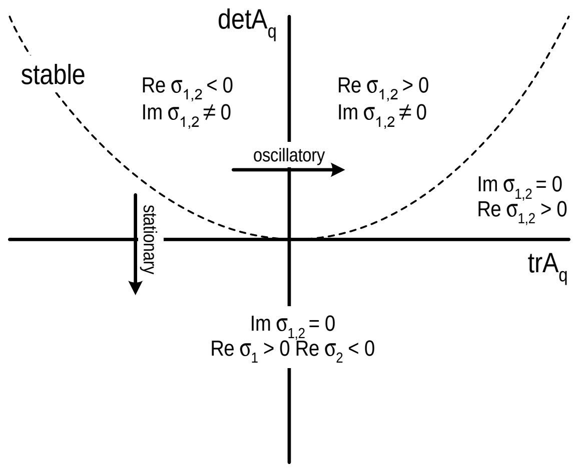
  where

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

- Eigenvalues are

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

Stability Regions



Conditions for Turing Instability

- Uniform state is stable to a spatially uniform instability

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

Take $a_{22} < 0$.

- Stationary instability at nonzero wave number ($\mathrm{Im}\,\sigma_{q_c} = 0$, $q_c \neq 0$)

$$D_1 a_{22} + D_2 a_{11} > 2\sqrt{D_1 D_2 (a_{11}a_{22} - a_{12}a_{21})}$$

and at the wave number

$$q_m^2 = \frac{1}{2}\left(\frac{a_{11}}{D_1} + \frac{a_{22}}{D_2}\right)$$

(Now we see $a_{11} > 0$ and a_{12}, a_{21} must have opposite signs)

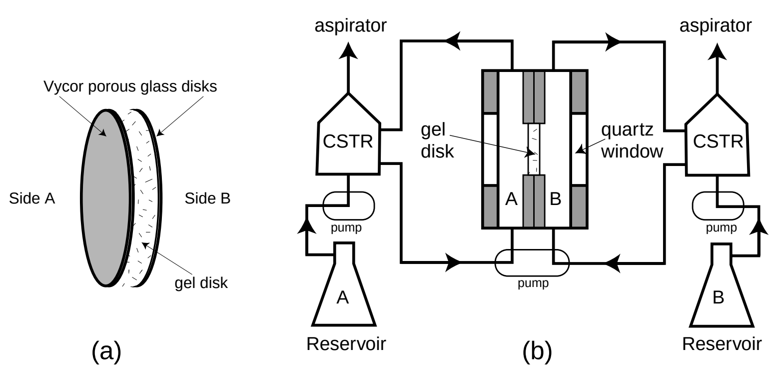
Turing Length Scale

Turing condition can be expressed as

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

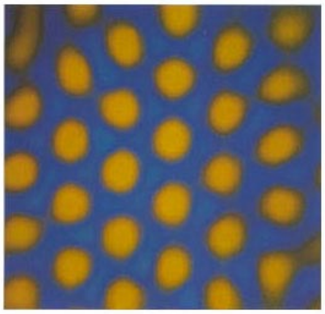
with $l_i = \sqrt{D_i/a_{ii}}$ are diffusion lengths: “local activation with long range inhibition”

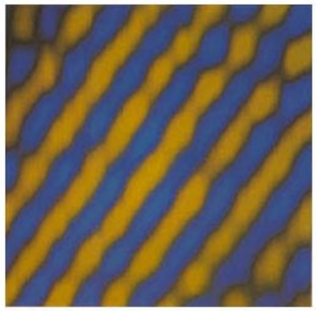
Experimental Turing Patterns: Apparatus



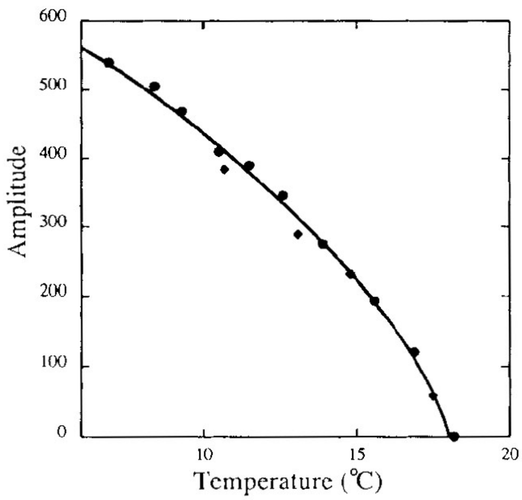
From Ouyang and Swinney (1991)

Experimental Turing Patterns





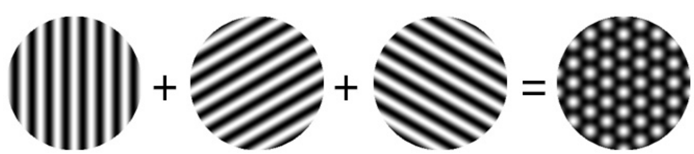
Experimental Turing Patterns: Onset



Ideas from Pattern Formation Theory and Biology

- stripes or spots (stripes v. hexagons)?
- stability balloon
- results from broken symmetry

Stripes or Spots? Amplitude Theory



Amplitudes of rolls at 3 orientations $A_i(\mathbf{r}, t),\ i = 1\ldots3$

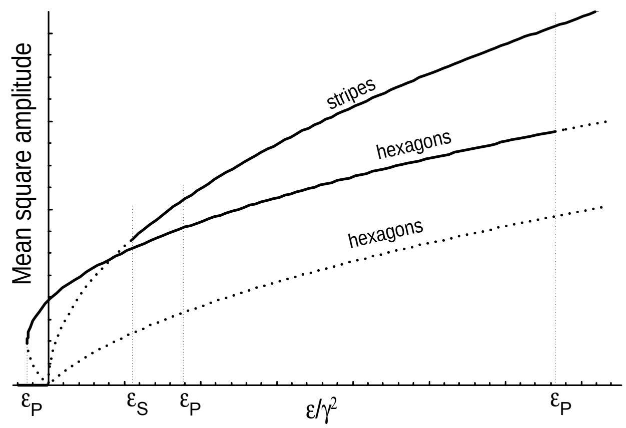
$$dA_1/dt = \varepsilon A_1 - A_1(A_1^2 + gA_2^2 + gA_3^2) + \gamma A_2 A_3$$
$$dA_2/dt = \varepsilon A_2 - A_2(A_2^2 + gA_3^2 + gA_1^2) + \gamma A_3 A_1$$
$$dA_3/dt = \varepsilon A_3 - A_3(A_3^2 + gA_1^2 + gA_2^2) + \gamma A_1 A_2$$

- $A_1 \neq 0$, $A_2 = A_3 = 0$ gives stripes
- $A_1 = A_2 = A_3 \neq 0$ gives hexagons

For $A_i \to -A_i$ symmetry, $\gamma = 0$ and stripes v. hexagons depends on g

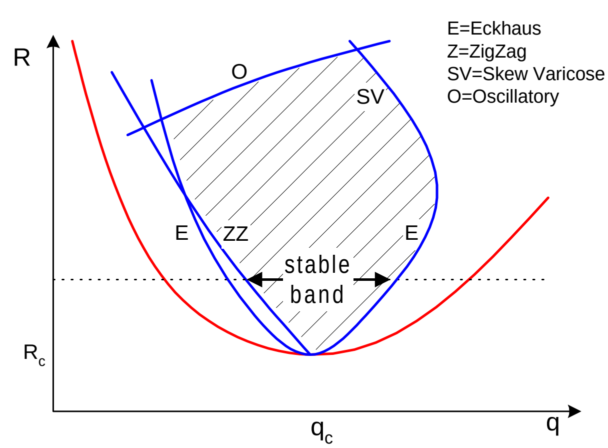
For no $A_i \to -A_i$ symmetry, $\gamma \neq 0$ and always get hexagons at onset

Stripes v. Hexagons

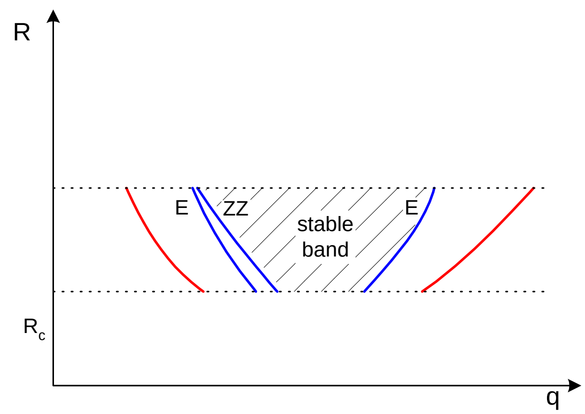


Note: this is only reliable for small γ

Stability Balloon



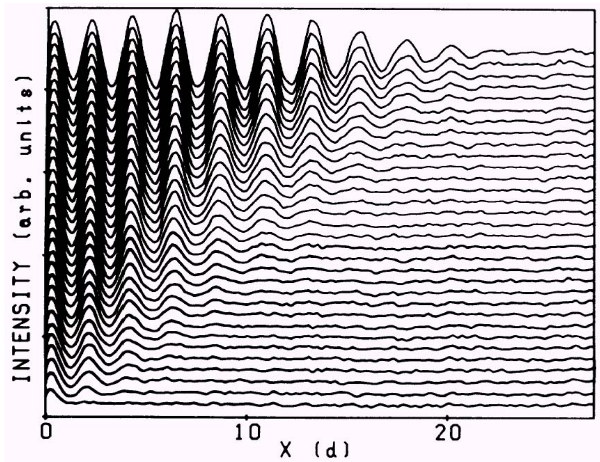
Stability Balloon



Consequences

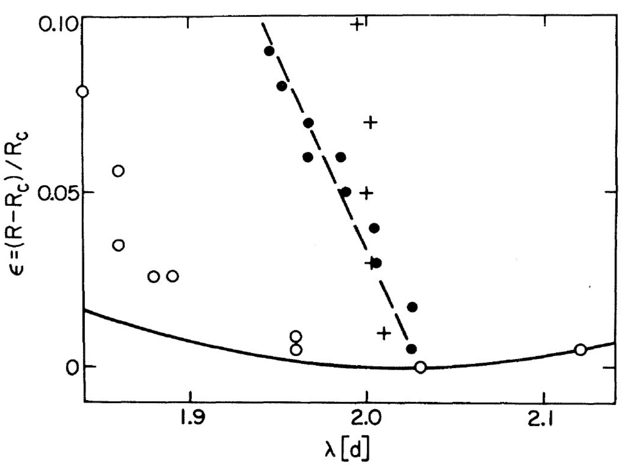
- Universality
  - ◇ Qualitative behavior is universal: reproducing (qualitative) observed behavior does not show that model is correct!
  - ◇ Need good motivation for model from other considerations
- Robustness
  - ◇ Pattern depends on parameters that may be too sensitive to external conditions (domain size, temperature…)
  - ◇ Complex feedback mechanisms?
- Uniqueness
  - ◇ Large variety of patterns possible
  - ◇ There are growth protocols that reduce the variety
    - ⋆ Propagation into domain
    - ⋆ Growth of domain

Front Propagation



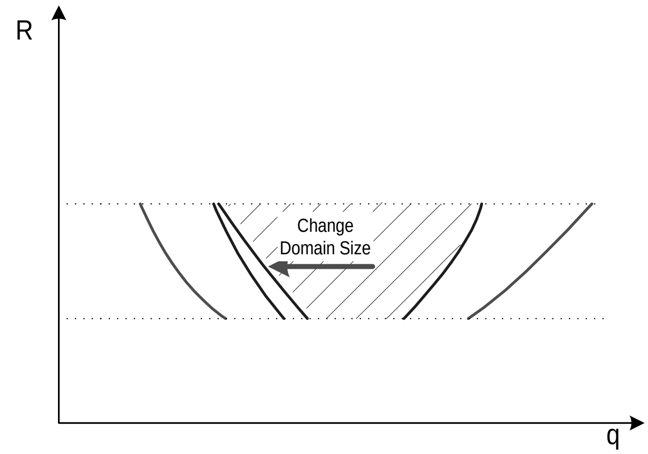
Front propagating into unstable state in Rayleigh-Bénard convection (from Fineberg and Steinberg, 1987)

Wavenumber Selection by Fronts



Taylor-Couette experiments by Ahlers and Cannell (1983)

Growth of Domain



New state forms by linear instability

Ideas from Broken Symmetry

Much of the discussion of the application of pattern formation to biology has been in terms of the linear instability to patterns

Ideas of the typical behavior of nonlinear patterns arising from symmetry breaking have not been used:

- patterns sensitive to small effects
  - ◇ boundary orientation
  - ◇ gradients
  - ◇ time dependent external conditions
- long range effects in patterns
- behavior of defects in pattern dynamics

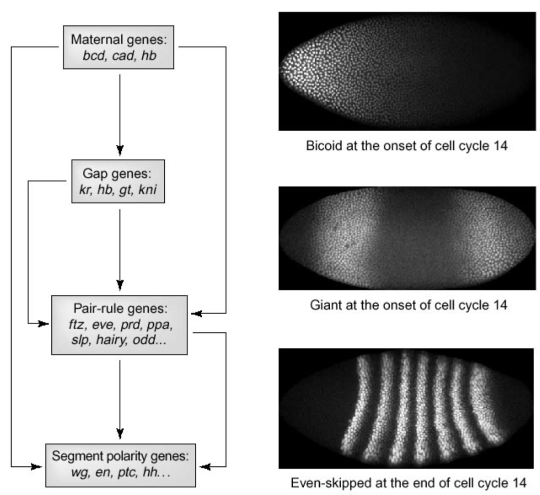
Examples of Pattern Formation in Biology

- Segmentation in Drosophila
- Animal and fish skin markings
- Patterns on the visual cortex
  - ◇ Function maps (development)
  - ◇ Hallucination patterns (activity)

Segmentation in Drosophila

Basic Facts

- body of fruit fly is composed of (nonidentical) repeating units called segments
- segments form by successive differentiation from initially identical “cells”
- immediately following the deposition of a Drosophila egg, a series of nuclear divisions takes place, without the formation of cells (up to 14th cycle)
- over division cycles 6-9 the nuclei migrate to the outside of the egg and form an approximately ellipsoidal shell of cells — the *syncytial blastoderm*
- segmentation determination takes place on the syncytial blastoderm over division cycles 10-14
- initial segment determination is under the control of about 20 genes, all believed known
- *maternal coordinate genes* — bicoid (bcd), caudal (cad), and hunchback (hb) — set up initial *gradients* (cf., Turing, Wolpert)
- segment determination occurs via successive refinement of structure in “gap” and then “pair-rule” genes



From Thieffry and Sanchez (2003)

Drosophila, the Rayleigh-Bénard Convection of Developmental Biology

The Drosophila blastoderm is a uniquely favorable system for theoretical studies of development:

- expression of segmentation genes is to a good approximation a function only of distance along the length, and so a one dimensional model is effective
- spatial effects can be treated in terms of the diffusion of protein products of genes (because there are no cell walls)
- segmentation genes do not affect nuclear divisions and morphology which are under maternal control
- enormous amounts of experimental data available e.g., the FlyEx database (http://flyex.ams.sunysb.edu/flyex/)

Drosophila Data

Example from FlyEx Database

Embryo name: **ba3**

Fly line:	Oregon R	**Genotype:**	wild type
Cleavage cycle:	14A	**Temporal class:**	8

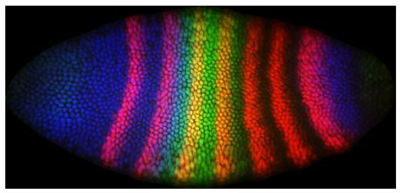
Genes:

even-skipped in channel *1* stained by *TxR* *(red)*

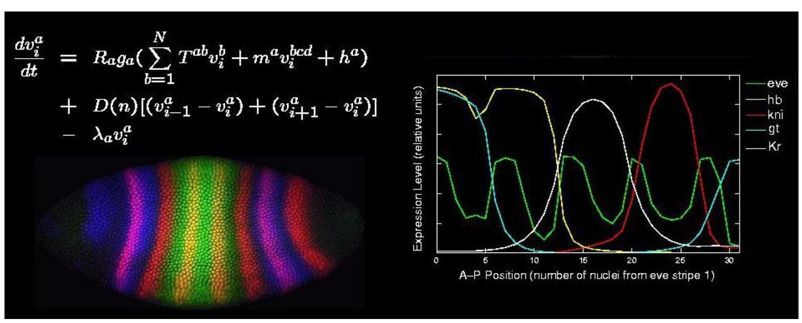
Kruppel in channel *2* stained by *Cy5* *(green)*

hunchback in channel *3* stained by *FITC* *(blue)*

Images of gene expression patterns - patterns of all genes scanned in the embryo



Drosophila Pattern Formation



From the website http://flyex.ams.sunysb.edu/ of John Reinitz

Gene Circuit Description (Reinitz et al.)

Equations for the concentrations v_i^a of gene product a at nucleus i

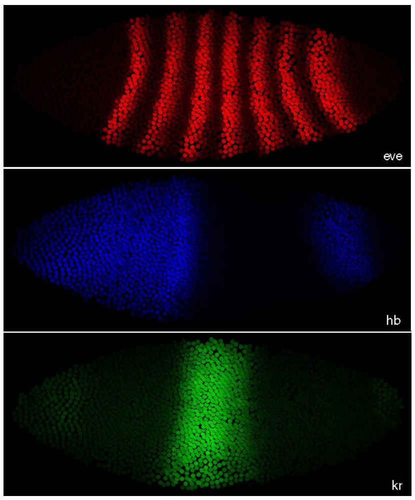
$$\dot{v}_i^a = \underbrace{R^a\, g_a\left(\textstyle\sum_b T^{ab} v_i^b + m^a v_i^{bcd} + h^a\right)}_{\text{reaction}} + \underbrace{D(n)\left[(v_{i-1}^a - v_i^a) + (v_{i+1}^a - v_i^a)\right]}_{\text{diffusion}}$$

- Reaction: nonlinear interaction term

$$g_a(u) = \frac{1}{2}\left[1 + \frac{u}{\sqrt{u^2+1}}\right], \qquad g_a(-\infty) = 0,\ g_a(\infty) = 1$$

  with T^{ab} an interaction matrix, v_i^{bcd} the (fixed) concentration of the maternal *bcd* gene product, and R^a, m^a, h^a constants.
  (Other formulations replace g_a by a binary on-off function.)
- Diffusion: discrete nuclei-nuclei transport with diffusion constant $D(n)$ depending on cleavage cycle n (geometry)
- The many parameters are fit over several cleavage cycles to large data base

Do ideas from pattern formation help?

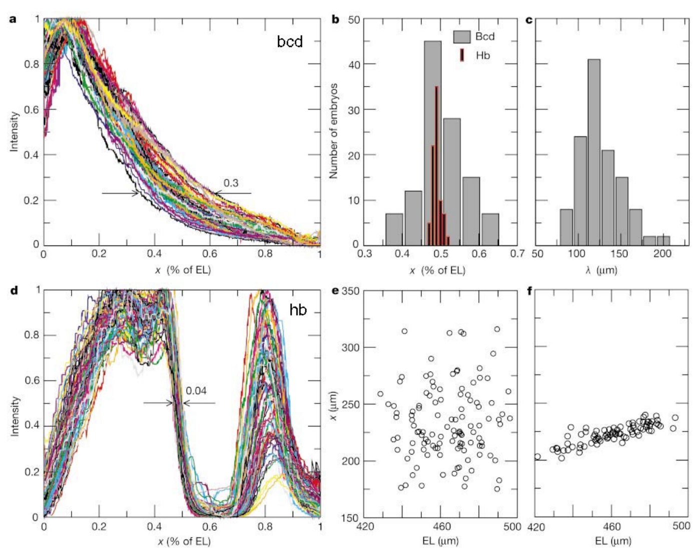


Pattern formation but:

- small systems
  - ◇ few stripes — finite size effects
  - ◇ few elements (nuclei) — noise
- preexisting gradients from maternal genes
- stripe locations “understood” in terms of individual gene interactions

Puzzles remain

- initial gradients vary amongst embryos, but stripe locations are precise



From Houchmandzadeh, Wieschaus, and Leibler (2002)

Animal and Fish Skin Markings

From the Australian Museum Fish Site

Animal and Fish Skin Markings

Favorite topic in pattern formation for many decades
(e.g., see books by Murray and by Meinhardt)

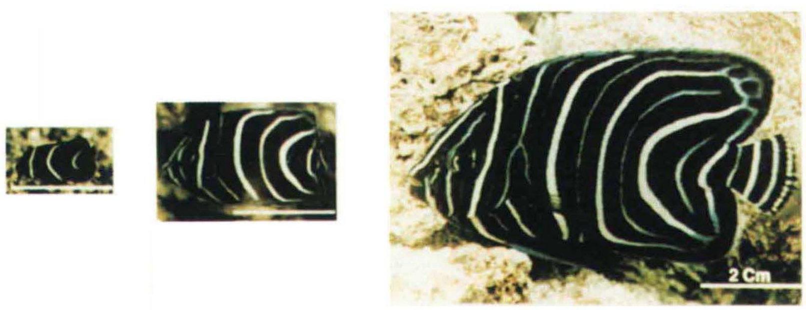
Common methodology:

- use coupled reaction diffusion equations (usually two) with reaction terms ingeniously constructed to give desired behavior
- run numerical simulations that "reproduce" observed behavior (sometimes poorly resolved)
- claim that the problem has been understood

Problems:

- behavior is not unique to model
- many parameters (or microscopic physics!) to be chosen
- no quantitative tests: reacting and diffusing species are not known
- often behavior is not understood beyond the simulations

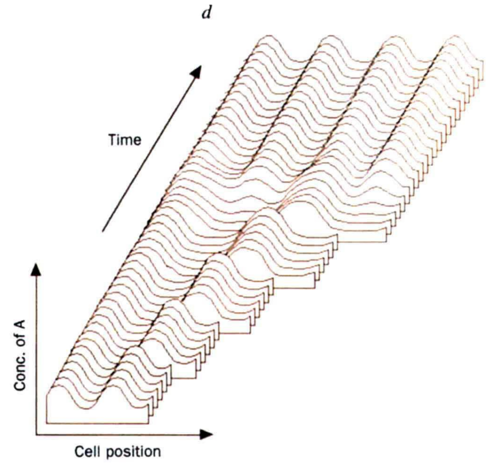
Promising Example: Angelfish Patterns



From Kondo and Asai (1995)

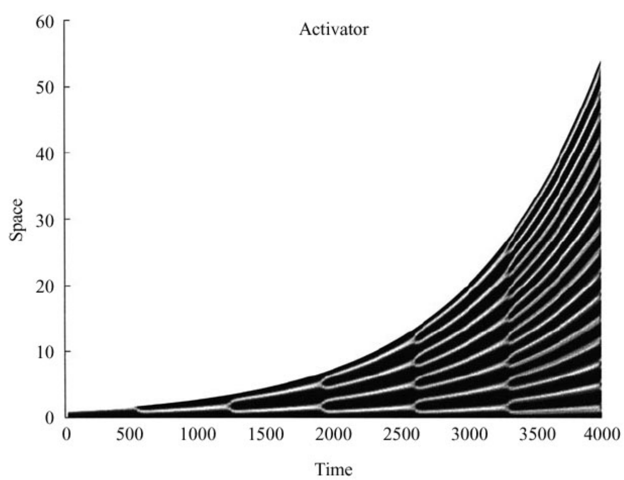
- pattern remains dynamic in growing fish
- stripe spacing remains roughly constant
- increasing size leads to introduction of new stripes
- pattern formation on a growing domain

Reaction-Diffusion Simulations



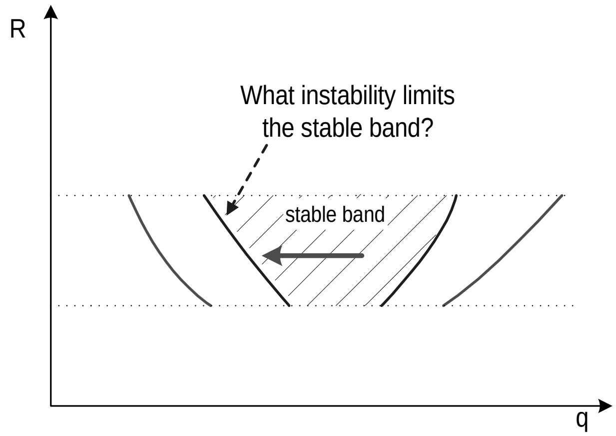
Initially Kondo and Asai suggested the "agreement" showed that a reaction-diffusion mechanism must apply, but later they stepped back from this!

Unique Patterns from a Growing Domain



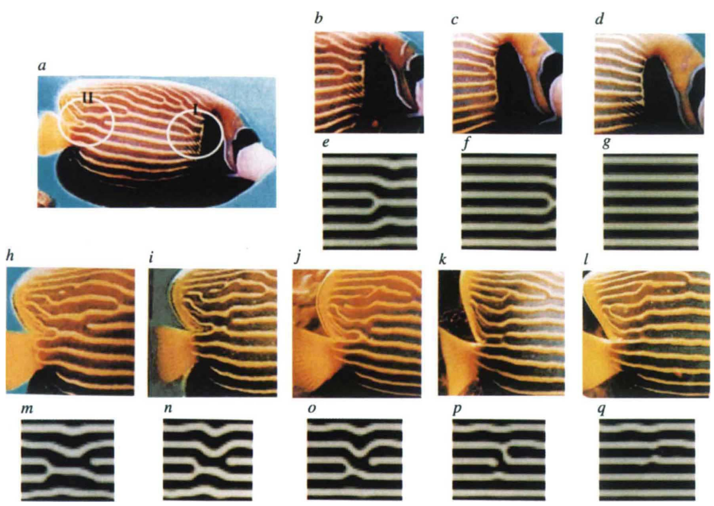
From Crampin , Gaffney and Maini (1999)

Pattern Formation Question



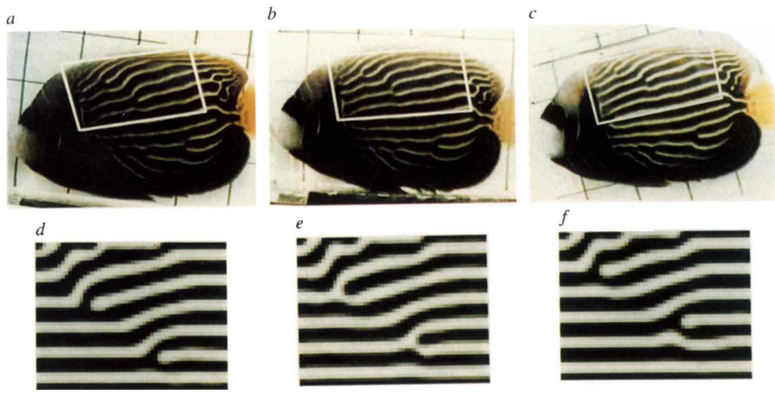
- generic behavior near onset (with rotational invariance): zigzag
- $q - 2q$ resonance: parity breaking and travelling stripes
- ??: period halving

Dislocation Climb



From Kondo and Asai (1995)

Dislocation Glide

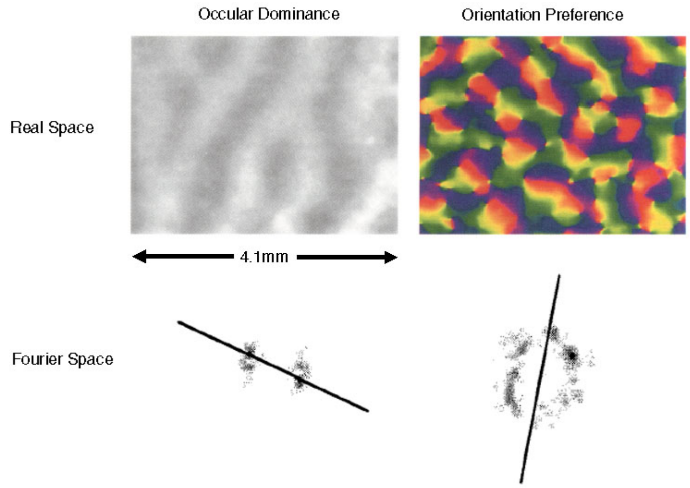


From Kondo and Asai (1995)

Patterns on the Visual Cortex

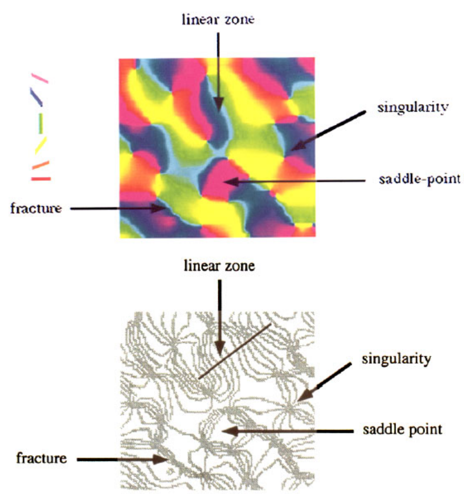
- Developmental Patterns
  - ◇ Ocular dominance: Which eye is the neuron connected to?
  - ◇ Orientation preference: Orientation of edge the neuron is most sensitive to
  - ◇ …
- Activity Patterns in Hallucinations

Patterns on the Monkey Visual Cortex



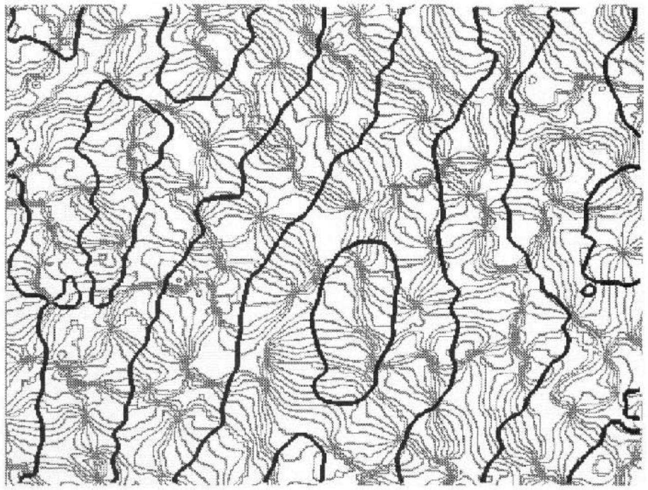
From Obermayer and Blasdel (1993)

Singularities in Orientation Preference Maps



From Obermayer and Blasdel (1993)

Ocular Dominance and Orientation Preference Patterns are Related



From Obermayer and Blasdel (1993)

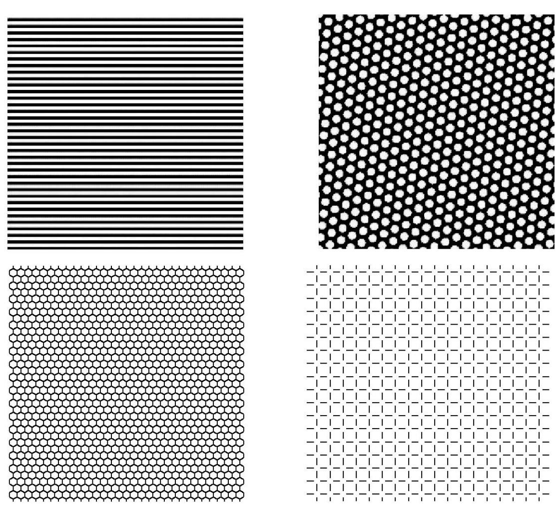
Questions

- Is there functional significance to the patterns (e.g. minimum connection length)?
- How do the patterns develop?

Patterns of Activity on the Visual Cortex

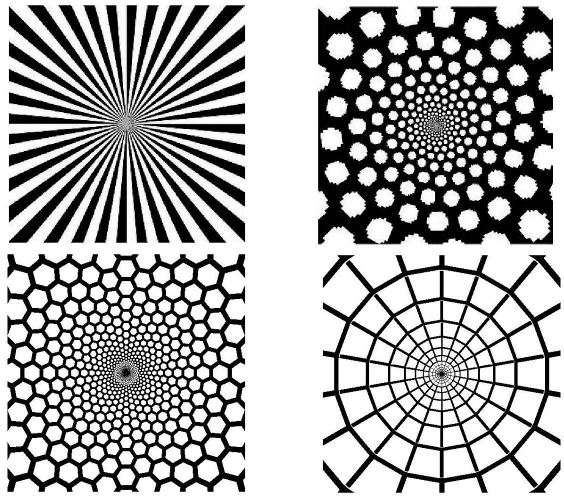
- Drugs can induce spontaneous activity on the cortex in the form of the patterns P (stripes, hexagons etc.)
- Activity on the retina due to perception is connected to activity on the visual cortex via a nonuniform map M
- Brain interprets the patterns P as activity in the retina given by $M^{-1}P$
- Regular structures on the cortex lead to forms reported in drug induced hallucinations
- Orientation preference of neurons leads to new types of patterns (Bressloff et al. (2002): anisotropy of connectivity is connected with orientation preference on neutron, cf., nematic liquid crystal)

Patterns on the Cortex



From Bressloff et al. (2002)

Patterns Mapped to the Retina



From Bressloff et al. (2002)

Conclusions

- Pattern formation in biology is a fascinating and important area that has been studied for decades
- There are very few systems where quantitative tests of any of the models have been possible
- There are few systems where more sophisticated ideas of pattern formation (beyond linear instability) have been invoked
- Perhaps the best tested system (Drosophila) raises doubts on whether ideas we have discussed on the physics of pattern formation are relevant
- I've given you three examples to illustrate the difficulties and successes: there are many more in the literature!