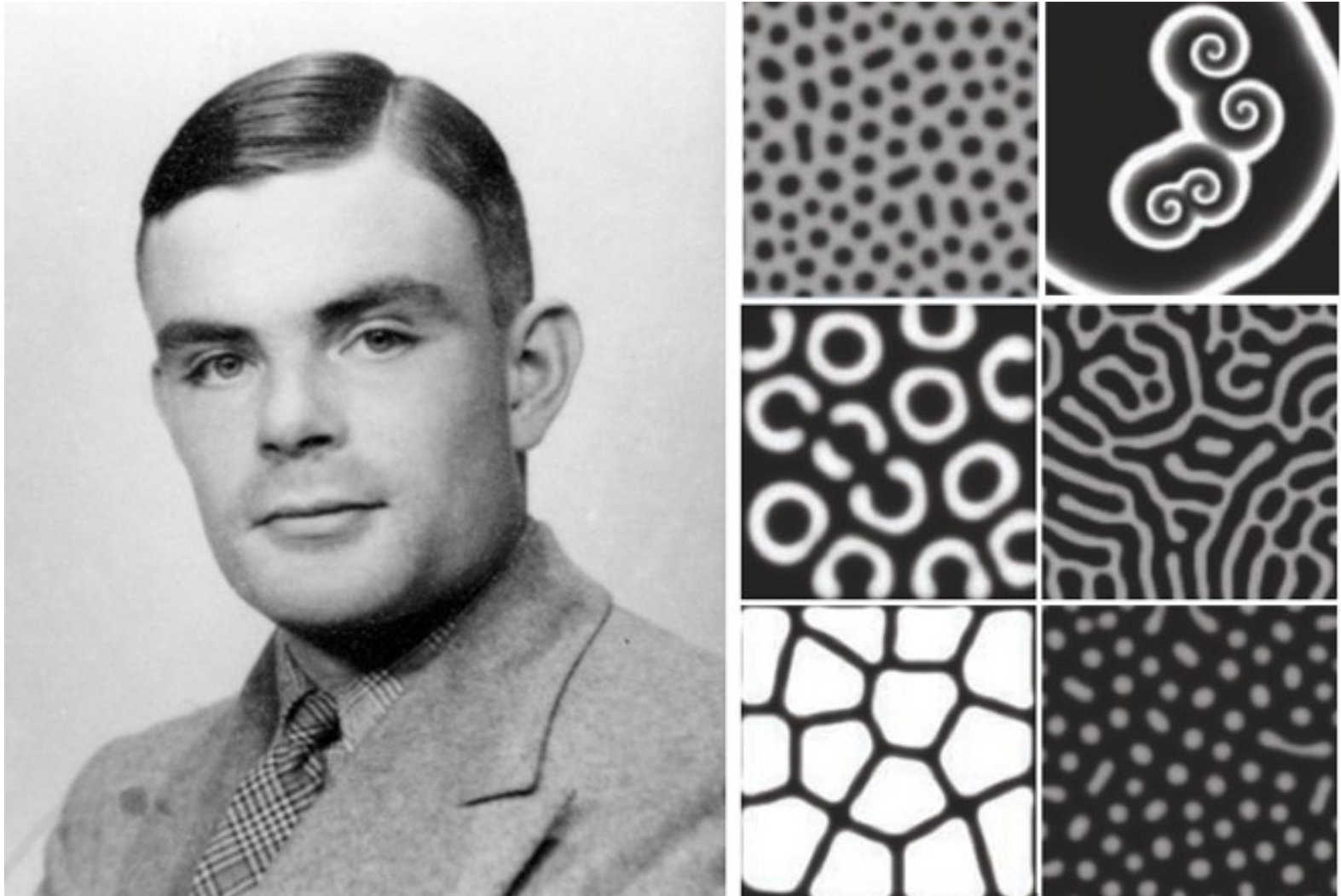# Systems Biology: A Personal View
XXIII. Spatial Patterns in Biology: Turing mechanism

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The magnificent patterns of Dr Turing

Question: How to explain the development of biological form (morphogenesis) ?

The magnificent patterns of Dr Turing

P.T. Saunders: Turing's work in biology illustrates clearly his ability to identify a fundamental problem and to approach it in a highly original way… He chose to work on the problem of form at a time when majority of biologists were primarily interested in other questions

Turing did **not** choose to work on understanding the structure of the genetic "**program**" something that may have been expected from his work on Turing machines and the contemporary interest in the problem

This would have also been consistent with the *zeitgeist*
E.g., Schrodinger's *What is Life* was speculating that "aperiodic crystals" were the physical basis for heredity being

In fact, the very next year after Turing's paper on morphogenesis, Crick and Watson discovered the structure of DNA

1953: Discovery of DNA structure

- Francis Crick
  (Cambridge University)
- James Watson
  (Harvard University)
  1962 Nobel Prize

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol con-figurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxy-ribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereo-chemical arguments.

Nature, 1953

The magnificent patterns of Dr Turing

Nor did Turing choose to work on *automata* models – in which the fate of a cell is determined by the states of its neighbors through simple sets of rules
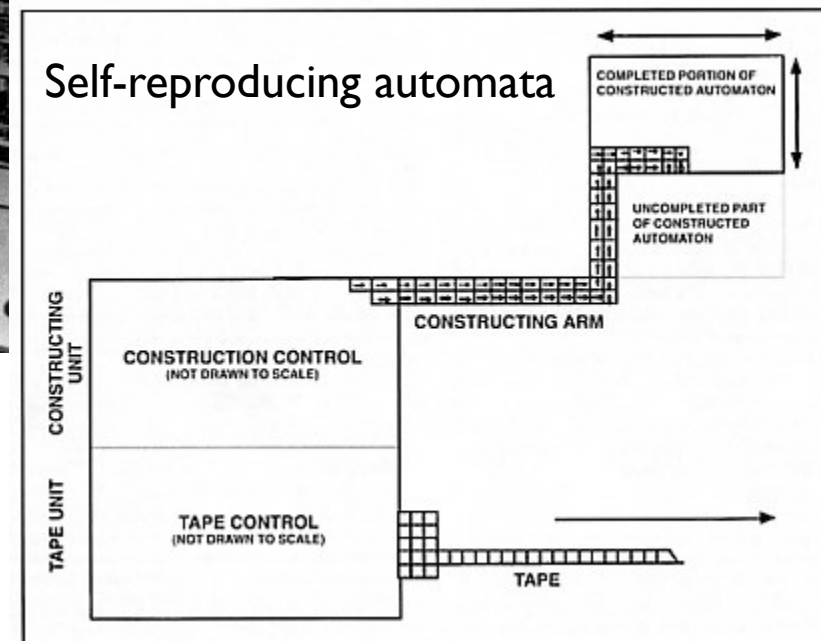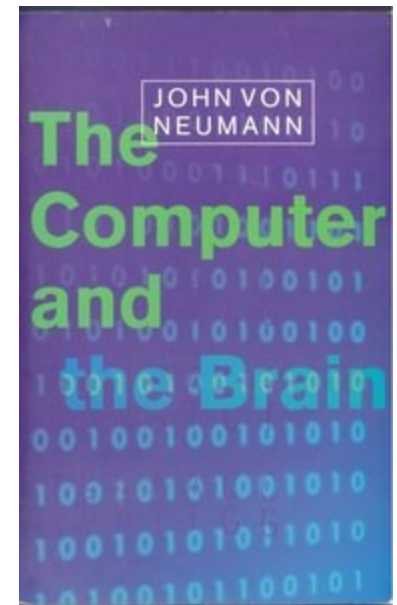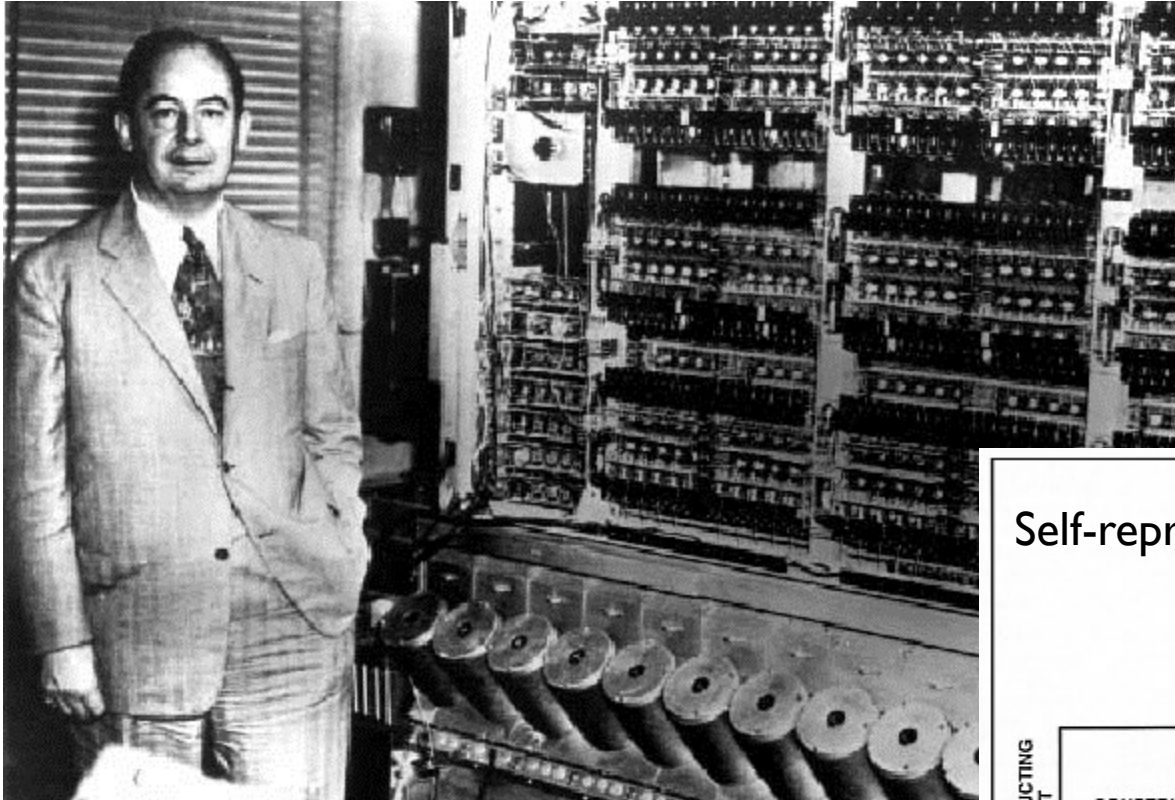
Again, this is something that would have been expected given his pioneering work on the invention of digital computers…

although some handwritten notes from the last days of his life point to an interest in random Boolean networks

Cellular automata
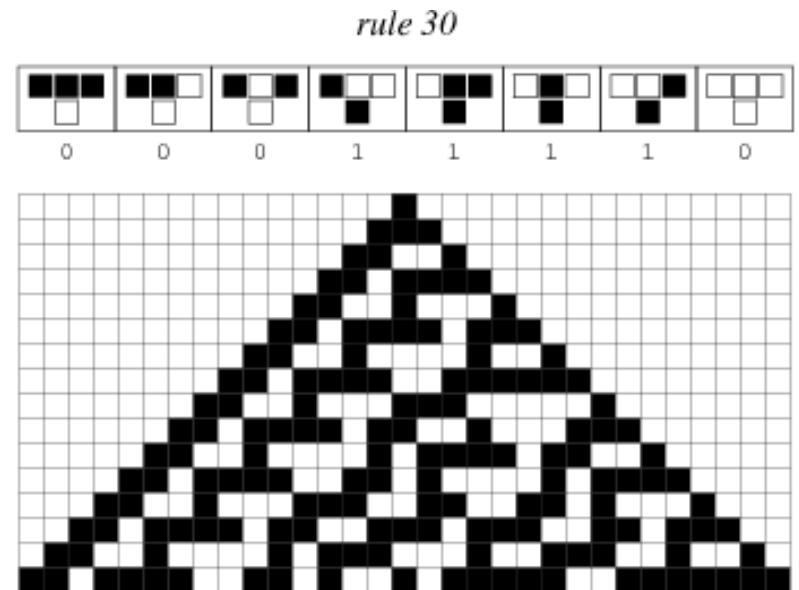
In fact is what Turing's *doppleganger* did

John von Neuman (1903-1957)

Self-reproducing automata

The magnificent patterns of Dr Turing

Instead Turing chose to "defeat the argument from design" in biology, i.e., the appeal to natural selection to any and every feature of biological systems
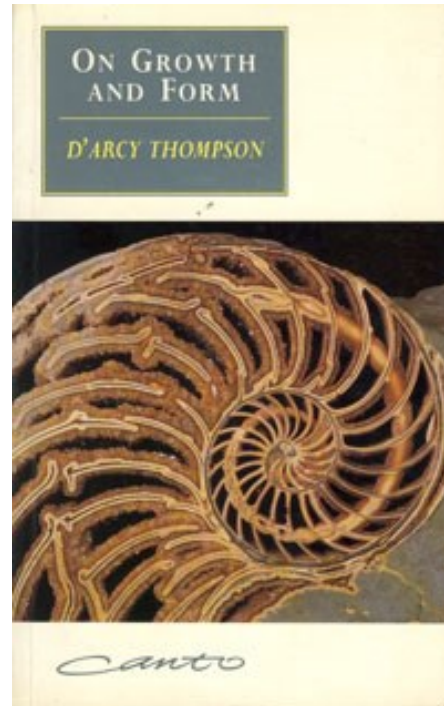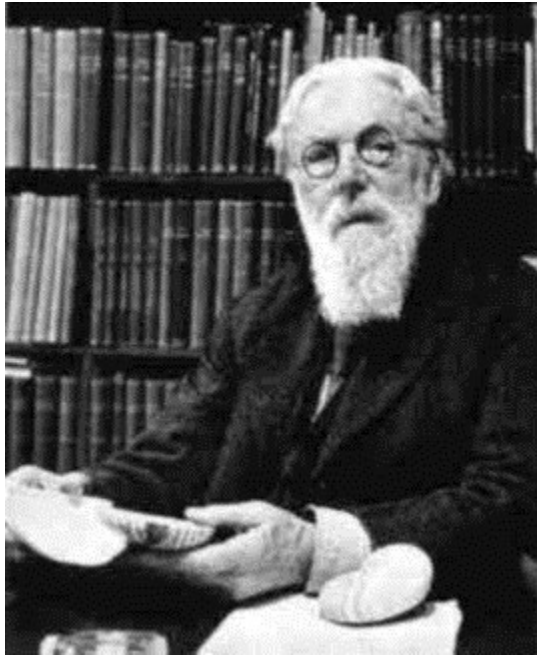
Instead of Evolution = Natural selection
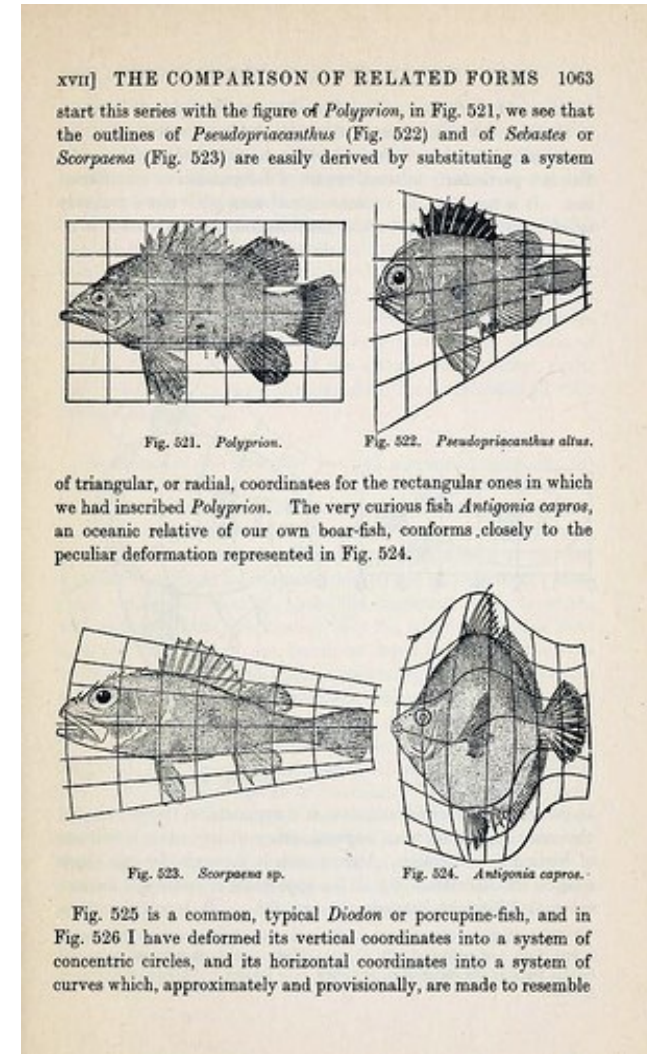Turing chose to view it as Adaptation + Self-organization

In this, he was influenced by the views of D'Arcy Thompson who insisted that biological form is to be explained chiefly in the same way as inorganic form: as the result of physical and chemical processes.
The primary task in biology is to discover the set of forms that are likely to appear – only then is it worth asking which of them will be selected.

Genesis of Biological Form: Self-organization

D'Arcy Wentworth Thompson (1860 - 1948)

ON GROWTH
AND FORM

D'ARCY THOMPSON

Canto

XVII] THE COMPARISON OF RELATED FORMS 1063

start this series with the figure of *Polyprion*, in Fig. 521, we see that
the outlines of *Pseudopriacanthus* (Fig. 522) and of *Sebastes* or
Scorpaena (Fig. 523) are easily derived by substituting a system

Fig. 521. *Polyprion*.   Fig. 522. *Pseudopriacanthus altus*.

of triangular, or radial, coordinates for the rectangular ones in which
we had inscribed *Polyprion*. The very curious fish *Antigonia capros*,
an oceanic relative of our own boar-fish, conforms closely to the
peculiar deformation represented in Fig. 524.

Fig. 523. *Scorpaena* sp.   Fig. 524. *Antigonia capros*.

Fig. 525 is a common, typical *Diodon* or porcupine-fish, and in
Fig. 526 I have deformed its vertical coordinates into a system of
concentric circles, and its horizontal coordinates into a system of
curves which, approximately and provisionally, are made to resemble
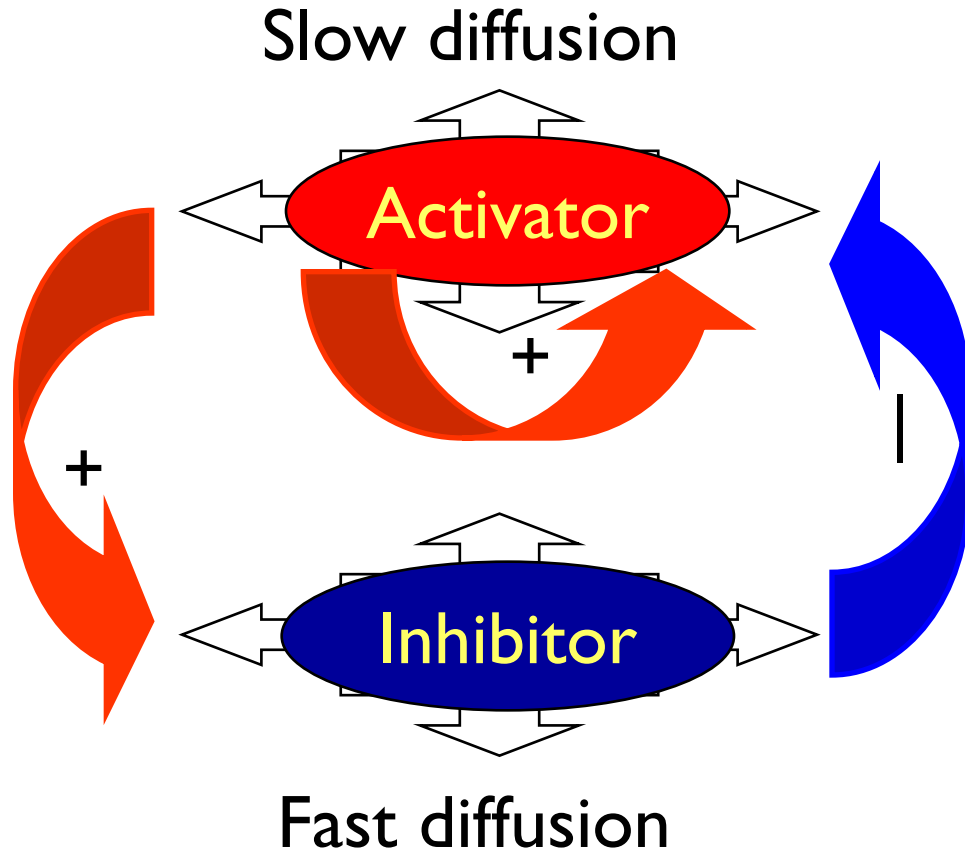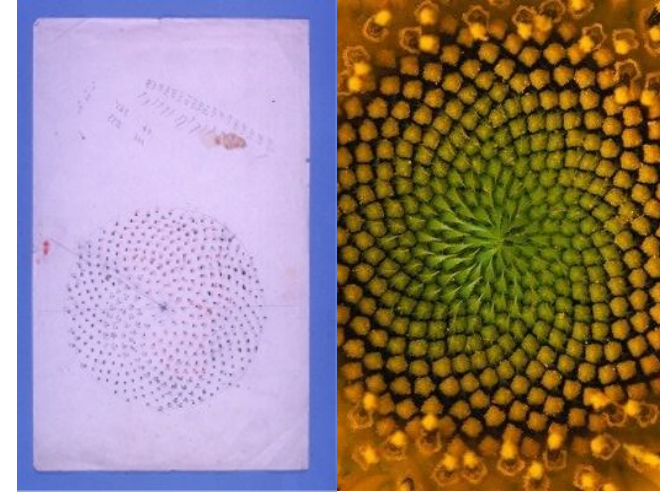
The magnificent patterns of Dr Turing

A. Turing
The Chemical Basis of Morpogenesis
Phil. Trans. Roy. Soc. Lond. B 237 (1952) 37

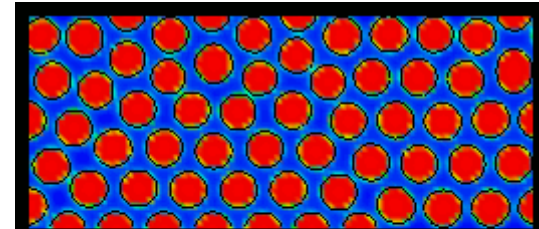*To explain phyllotaxis patterns*

sunflower florets

Slow diffusion
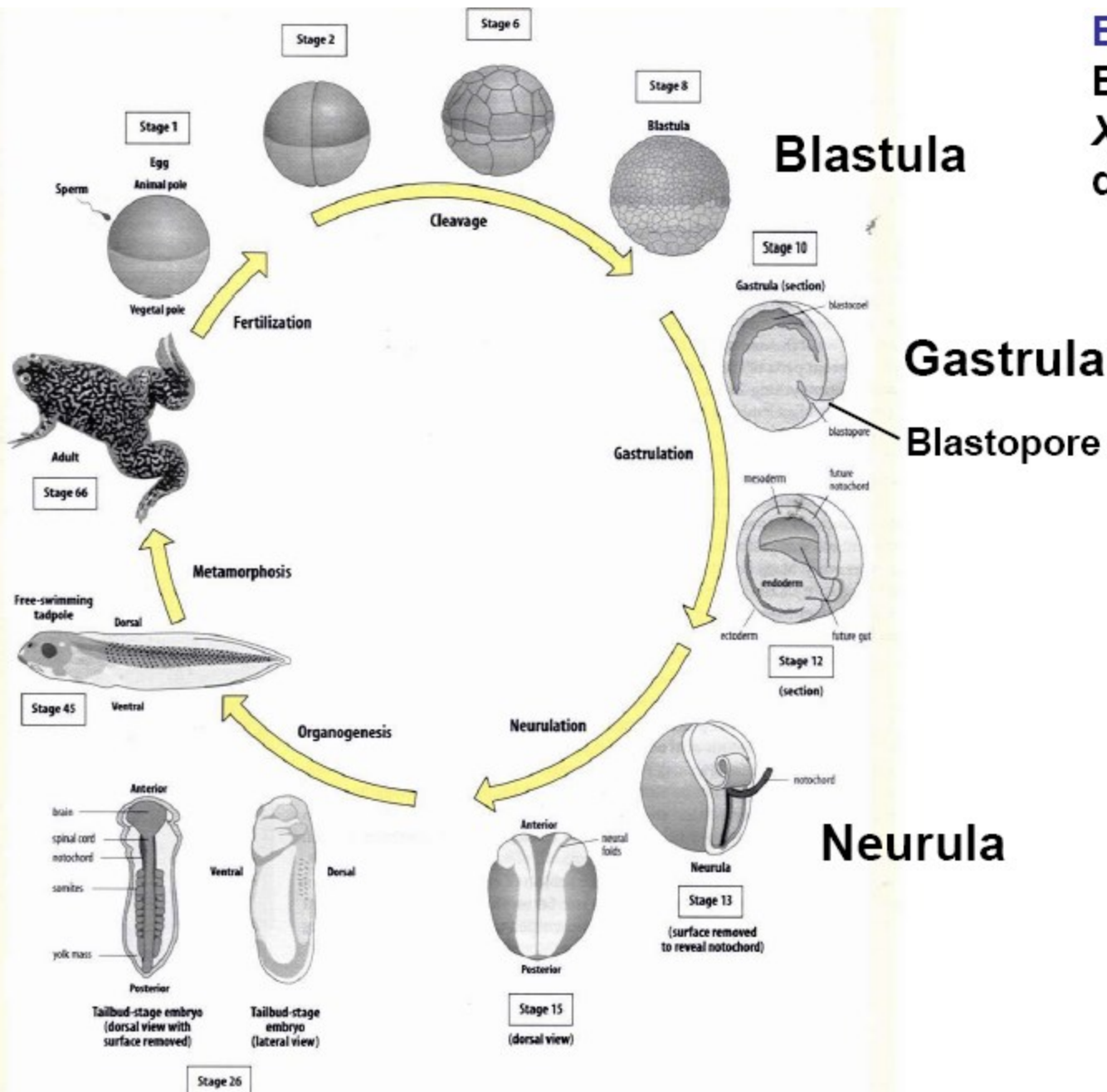
Activator

+

+

|

Inhibitor

Fast diffusion

The model produces

Spots

Stripes

BOX 1A
Basic stages of *Xenopus laevis* development

Stage 2

Stage 6

Stage 8
Blastula

Stage 1
Egg
Animal pole

Sperm

Vegetal pole

Fertilization

Cleavage

Blastula

Stage 10
Gastrula (section)
blastocoel

Gastrula

Blastopore

blastopore

mesoderm
future notochord

endoderm

ectoderm
future gut

Stage 12
(section)

Gastrulation

Adult
Stage 66

Metamorphosis

Free-swimming tadpole
Dorsal

Stage 45
Ventral

Organogenesis

Neurulation

notochord

Neurula
Stage 13
(surface removed to reveal notochord)

Neurula

Anterior
brain
spinal cord
notochord
somites

yolk mass

Posterior
Tailbud-stage embryo
(dorsal view with surface removed)

Ventral

Dorsal

Tailbud-stage embryo
(lateral view)

Anterior

neural folds

Posterior

Stage 15
(dorsal view)

Stage 26

Turing: Explaining morphogenesis

Mike Cross: In the tradition of great theoretical science, Turing set as his goal not the quantitative explanation of morphogenesis but the discovery of a clear plausible mechanism that could guide researchers in how to think about such a complex phenomenon.

The opening paragraph of his 1952 paper :

"In this section a mathematical model of the growing embryo will be described. 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."

Important (and Unexpected) Insights from Turing's work:
❑ at least two interacting chemicals are needed for pattern formation
❑ diffusion in a reacting chemical system can actually be a destabilizing influence [contrary to intuition that diffusion smooths spatial variations in concentration]
❑ can cause the growth of structure at a particular wavelength
❑ pattern formation in a chemical system will not occur unless the diffusion rates of at least two reagents differ substantially.
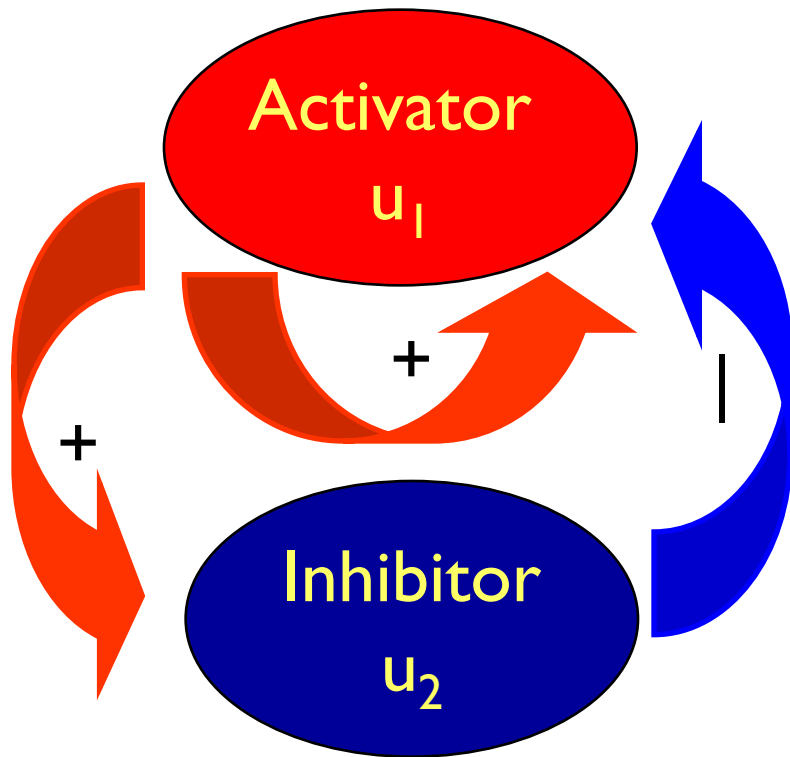
Turing: Explaining morphogenesis

Morphogenesis, i.e. development of shape or form in plants and animals explained using reaction-diffusion model systems of two substances with concentrations u_1, u_2

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

$$\equiv$$

$$\partial_t \mathbf{u} = \mathbf{f}(\mathbf{u}) + \mathbf{D} \partial_x^2 \mathbf{u}$$
$$\mathbf{D} = \begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix}$$

Activator u_1

Inhibitor u_2

+

+

+

|

- Activator u_1: substance that stimulates increase in concentration of both chemicals
- Inhibitor u_2: substance that leads to a decrease in concentrations
- Turing: such a system can produce stationary pattern through spontaneous symmetry-breaking if inhibitor diffuses much faster than activator (*local activation with lateral inhibition*).

Turing's analogy:
Missionaries vs. Cannibals

An island populated by
(i) cannibals & (ii) missionaries.
- Missionaries [*inhibitors*]
    - are all celibate
   - depend on recruiting to maintain their population as members gradually die.
- Cannibals [*activators*]
    - also die,
    - but can reproduce, increasing their population.
- When two missionaries meet a cannibal, (s)he is converted to missionary status

When both populations mixed together, <u>stable</u> balance reached between reproduction & conversion.
If disturbed by a small amount of noise, the system returns to balanced state.

Turing Archive
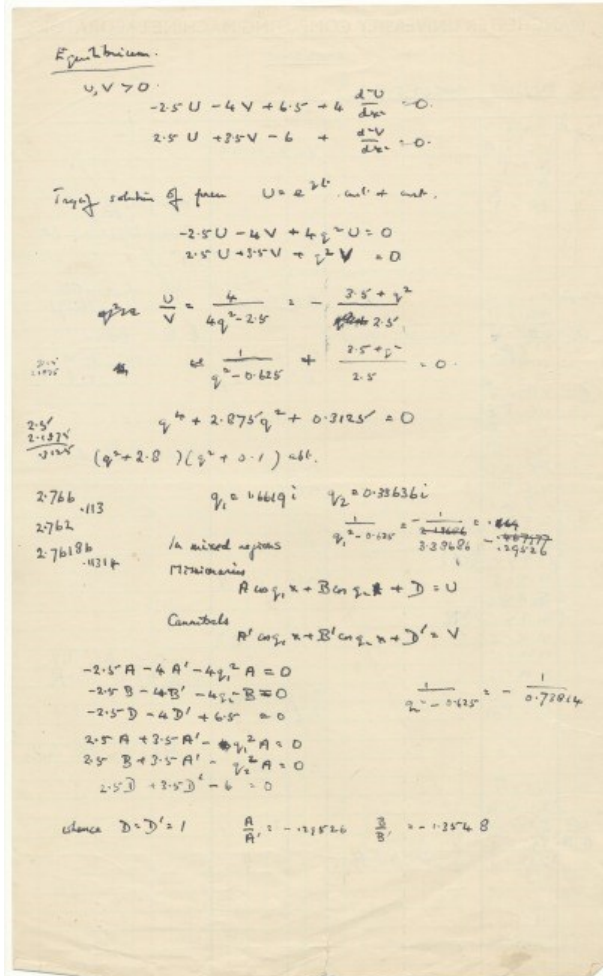
Pattern formation via diffusive instability

Missionaries (on cycles) vs. Cannibals (on foot)

http://www.swintons.net/deodands/
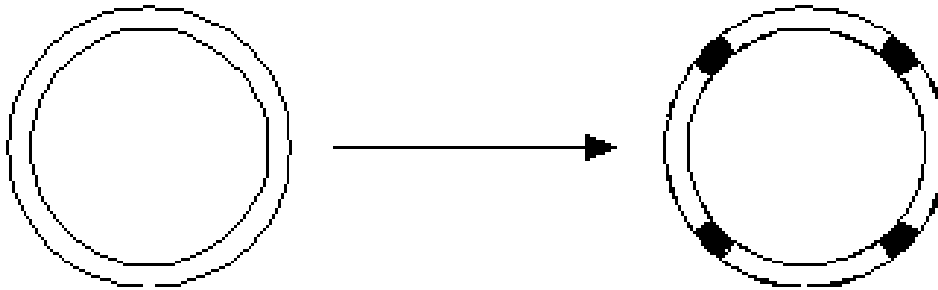
Now introduce space in the model:
• consider the populations to be spread out in a thin ring around the narrow beach of the island,
• individuals interact only with their nearest neighbors
• while diffusing at random

But the missionaries have bicycles and move faster

⇒ Instability in system:
if there is at any point a small excess of cannibals
  → excess 'production' of more cannibals
  → more missionaries
  (as more targets for conversion).

Without diffusion, extra missionaries reduce cannibal excess, system returns to balance.

But with diffusion, missionary excess transported away faster ⇒ a pattern develops with cannibal excess in center and excess missionaries at edge.

Short range activation

Long range inhibition
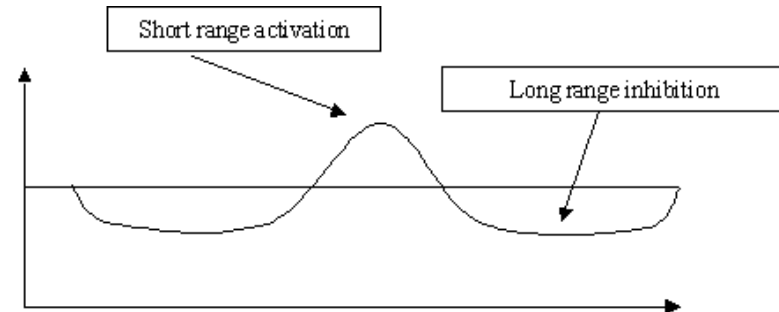
Solving Turing's Model

Begin by assuming we have found a stationary uniform solution $\mathbf{u}_b = (u_{1b}, u_{2b})$ that satisfies the Turing model with all partial derivatives set to zero:

$$f_1(u_{1b}, u_{2b}) = 0$$
$$f_2(u_{1b}, u_{2b}) = 0 \qquad \equiv \qquad \mathbf{f}(\mathbf{u}_b) = \mathbf{0}$$

Linearizing about the solution $\mathbf{u}_b = (u_{1b}, u_{2b})$ we can show that an arbitrarily small perturbation
$$\delta\mathbf{u}(t, x) = (\delta u_1(t, x), \delta u_2(t, x))$$
evolves in time as

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

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

The coefficients are from the 2x2 Jacobian matrix $\mathbf{A} = \partial\mathbf{f}/\partial\mathbf{u}$ evaluated around the uniform solution $\mathbf{u}_b = (u_{1b}, u_{2b})$

Solving Turing's Model

In other words: $\partial_t \delta\mathbf{u} = \mathbf{A}\delta\mathbf{u} + \mathbf{D}\partial_x^2 \delta\mathbf{u}$

$$\mathbf{D} = \begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix}$$

Linear eqn with constant coefficents and for very large system size (or periodic boundaries) we can use translational symmetry to obtain particular solutions of the form

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

With growth rate σ_q and wave number q

Substituting this solution we obtain the eigenvalue problem:

$$\mathbf{A}_q\,\delta\mathbf{u}_q = \sigma_q\,\delta\mathbf{u}_q \quad \text{where} \quad \mathbf{A}_q = \mathbf{A} - \mathbf{D}q^2 = \begin{pmatrix} a_{11} - D_1 q^2 & a_{12} \\ a_{21} & a_{22} - D_2 q^2 \end{pmatrix}$$

For each wavenumber q there will be one such eigenvalue problem with the solution $\left(c_{1q}\,\delta\mathbf{u}_{1q}\, e^{\sigma_{1q} t} + c_{2q}\,\delta\mathbf{u}_{2q}\, e^{\sigma_{2q} t}\right) e^{iqx}$

The coefficients c_{iq} are complex constants depending on initial perturbation (t=0) and an arbitrary perturbation $\delta\mathbf{u}(t,x)$ is a superposition of such expressions for all wavenumbers q

Solving Turing's Model

The uniform solution $\mathbf{u}_b = (u_{1b}, u_{2b})$ is stable if both eigenvalues σ_{iq} have negative real parts for all wave numbers q:
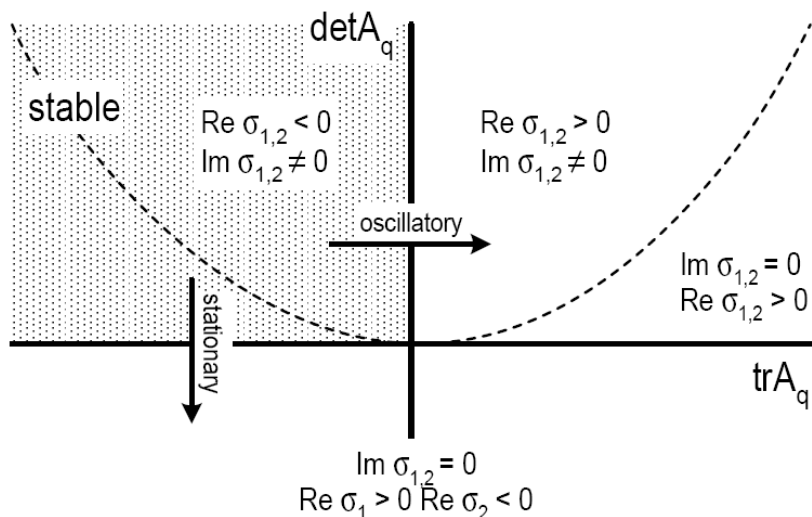
$$\max_i \max_q \operatorname{Re}(\sigma_{iq}) < 0$$

The characteristic polynomial for the eigenvalue problem is

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

and the eigenvalues are given by

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

The regions of (in)stability can be mapped with *criterion for stability*:

$$\operatorname{tr}\mathbf{A}_q = a_{11} + a_{22} - (D_1 + D_2)q^2 < 0,$$

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

Physical Implications of Turing's Solution

Turing's insight : diffusion of chemicals may cause a spontaneous symmetry breaking via a pattern-forming instability.

Starting point: switch off diffusion (setting D or q = 0)
We need to assume that the reacting chemicals form a stable stationary state in the absence of diffusion, i.e.,

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

So, when diffusion is present, as D and q^2 are non-negative

$$\text{tr}\mathbf{A}_q = a_{11} + a_{22} - (D_1 + D_2)q^2 < a_{11} + a_{22} < 0 \quad \textbf{always}$$

Thus the only way for diffusion to destabilize the uniform state is for $\det \mathbf{A}_q$ to be negative.

Physical Implications of Turing's Solution

When is $\det \mathbf{A}_q$ negative ?

We find the minimum by setting its derivative w.r.t. q^2 to zero and finding its value at this q.

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

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

As the term in the square root is +ve $\boxed{D_1 a_{22} + D_2 a_{11} > 0}$

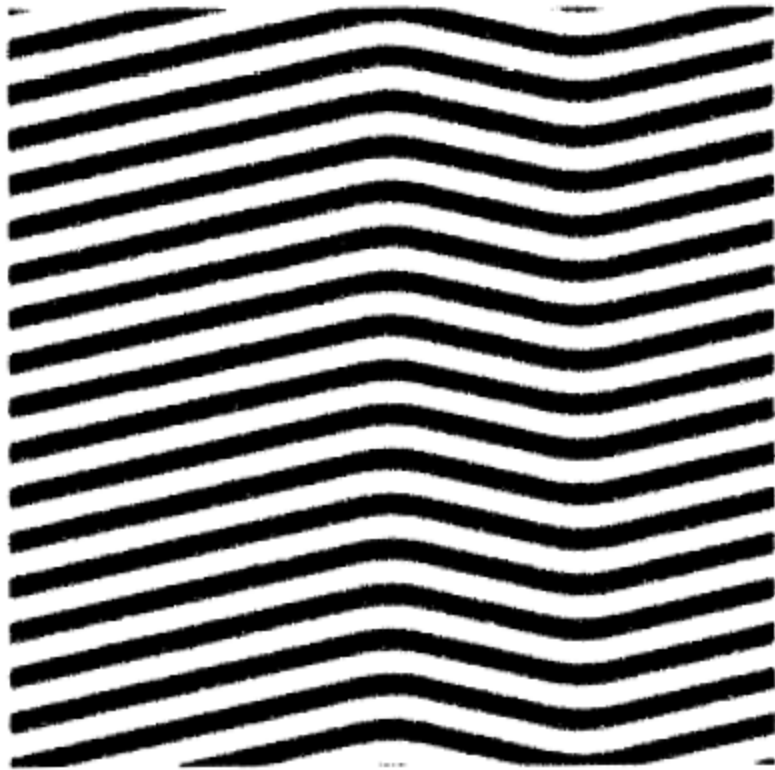Thus, $\boxed{a_{11} > 0 \text{ and } a_{22} < 0}$ (1: activator, 2: inhibitor)

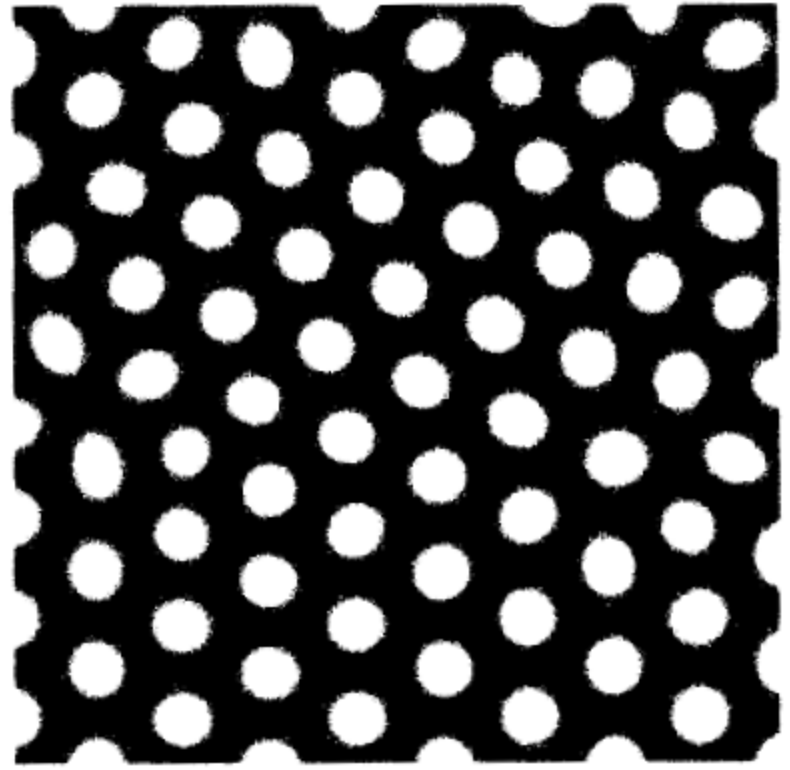In terms of the diffusion lengths $l_1 = \sqrt{\dfrac{D_1}{a_{11}}}$ and $l_2 = \sqrt{\dfrac{D_2}{-a_{22}}}$

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

Local activation with long-range inhibition

Typical patterns of 2D reaction-diffusion system

Stripes

Spots