Systems Biology: A Personal View XXIV. Turing patterns in Biological systems

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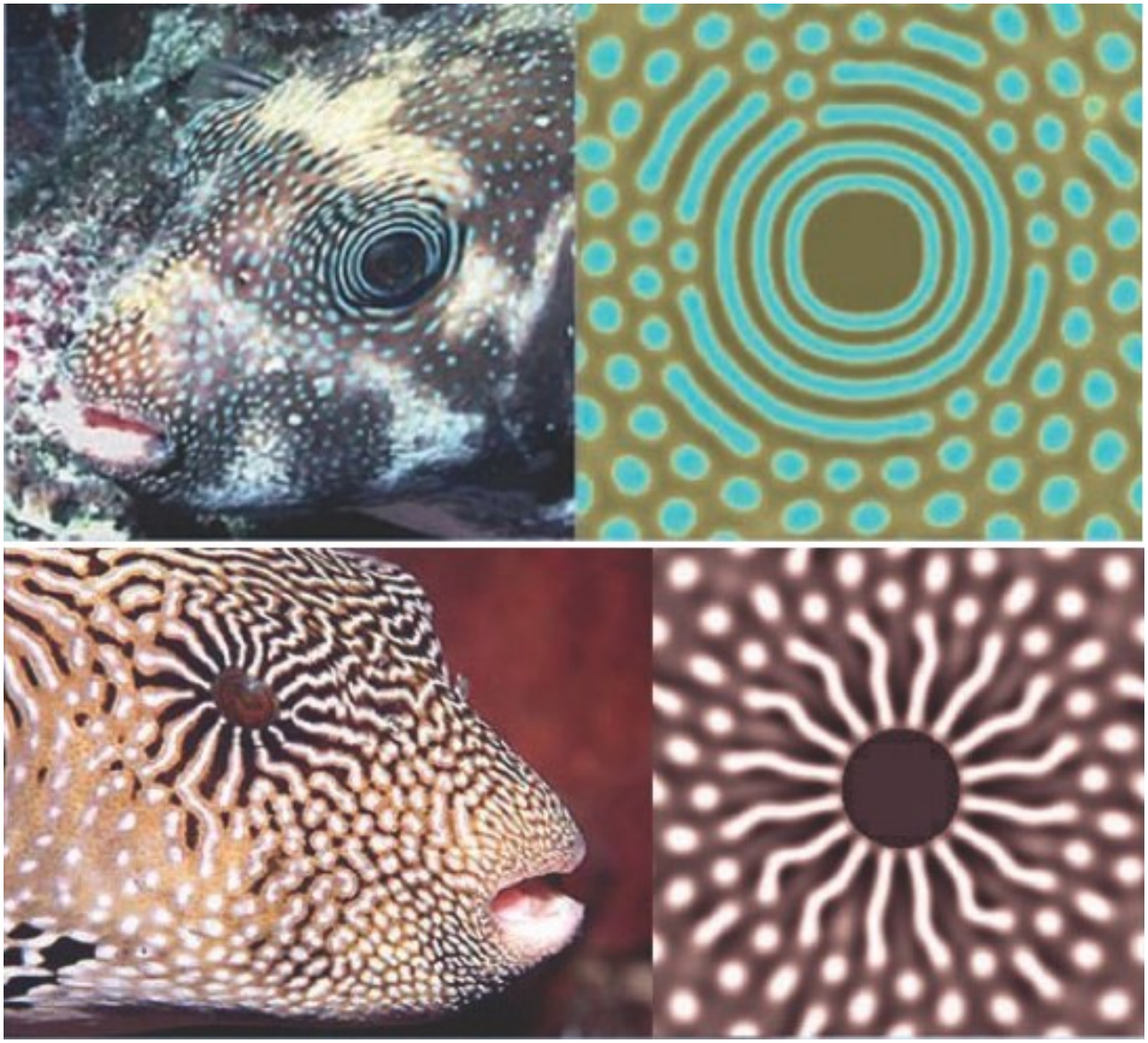
How the Jaguar got its spots ?
How did the squirrel get its stripes ?

Tambako the Jaguar/Flickr

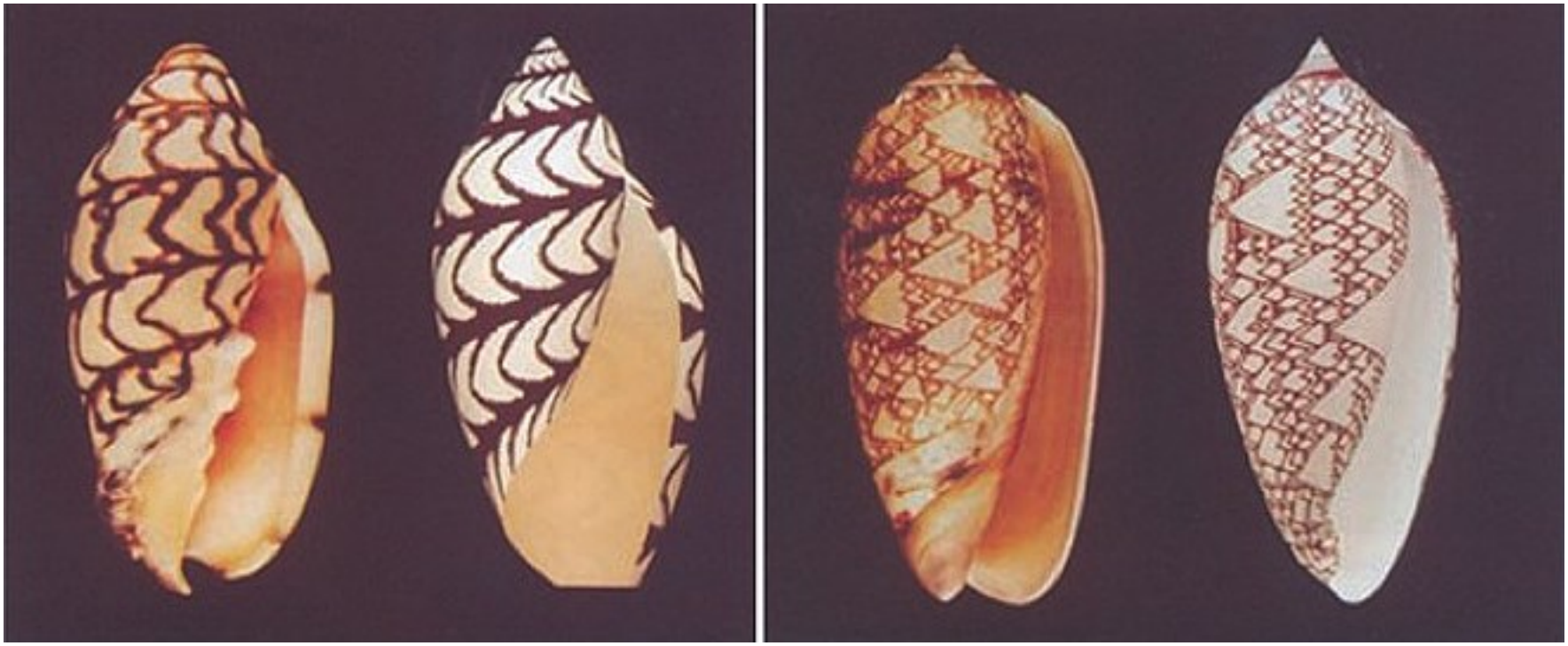
Spots on the coats of jaguars and leopards, stripes on tigers, zebras and a host of smaller animals such as squirrels, (as well as block patterns on giraffes) are thought to be Turing patterns – but unless the actual diffusing morphogen chemicals are identified, this hypothesis will remain extremely likely but not completely accepted.

Turing patterns in fish ?



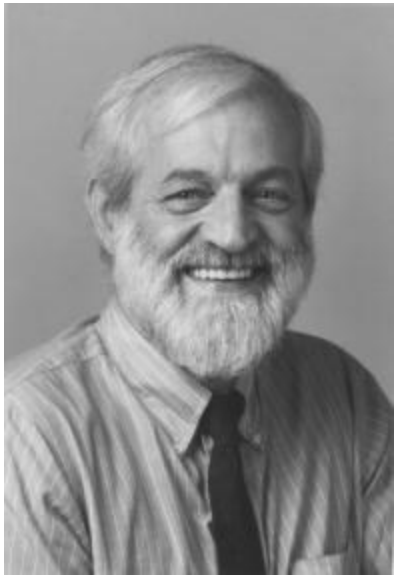
Nature Images

Turing patterns in seashells ?



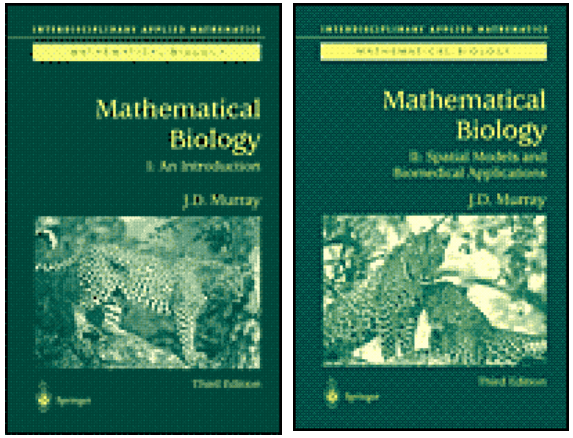
Nature Images

Explaining Animal Coat Patterns through Turing Mechanism



Jim Murray: a *single* mechanism can generate all the common animal coat patterns observed in nature

Mechanism: a reaction-diffusion system sets up patterns of *morphogen* concentrations (*Any of a number of chemicals in embryo that influences the movement & organization of cells during morphogenesis by forming a concentration gradient*)



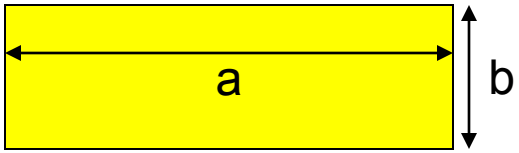
Subsequent differentiation of cells to produce *melanin (pigment affecting color of skin, hair etc)* reflects the spatial patterns of morphogen concentration

Melanoblast cells migrate on the surface of the embryo and become *melanocytes* (specialised pigment cells) – Hair color occurs through melanocytes generating melanin

Murray-Turing reaction-diffusion system for describing animal patterns

$$\begin{cases} u_t = u_{xx} + u_{yy} + \lambda f(u,v), \;\; t > 0, \;\; (x,y) \in (0,a) \times (0,b), \\ v_t = d(v_{xx} + v_{yy}) + \lambda g(u,v), \;\; t > 0, \;\; (x,y) \in (0,a) \times (0,b), \\ u_x = 0, \;\; x = 0, a, \;\; u(x,0) = u(x,b), \;\; u_x(x,0) = u_x(x,b), \\ v_x = 0, \;\; x = 0, a, \;\; v(x,0) = v(x,b), \;\; v_x(x,0) = v_x(x,b), \\ u(0,x,y) = u_0(x,y), \;\; v(0,x,y) = v_0(x,y). \end{cases}$$

Defined on a reactangle with the solutions:



$$\begin{pmatrix} u(t,x,y) \\ v(t,x,y) \end{pmatrix} = \sum_{n,m=0}^{\infty} C_{n,m} e^{\mu_{n,m} t} V_{n,m} \cos\left(\frac{n\pi x}{a}\right) \cos\left(\frac{2m\pi y}{b}\right),$$

where $\mu_{n,m}$ are the eigenvalues of matrix $\lambda J - k_{n,m}^2 D$, J is Jacobian, $D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix}$, and $k_{n,m} = \left(\frac{n^2}{a^2} + \frac{4m^2}{b^2}\right)\pi^2$.

The nature of coat patterns depends on geometry of body shape

The unstable mode is governed by $d = D_V/D_U$ and $\lambda = S/D_U$, S related to domain size

Spatial patterns occur when d is large, appearing in the order of eigenvalue sequence

$$k_{n,m} = \left(\frac{n^2}{a^2} + \frac{4m^2}{b^2}\right)\pi^2$$

When b is small, striped patterns more likely; spots become possible only for large b

$\Rightarrow$ Snakes (low b) will have stripes (rings) but not spots

Google Images

Eigenvalues depend on the geometry of the rectangle
(Geometry here means the narrowness of the rectangle.)

Example 1: $b/a = 2$

$$k_{0,0} = 0, k_{1,0} = k_{0,1} = -\pi^2, k_{1,1} = -2\pi^2, k_{2,0} = k_{0,2} = -4\pi^2,$$
$$k_{2,1} = k_{1,2} = -5\pi^2, k_{2,2} = -8\pi^2, k_{3,0} = k_{0,3} = -9\pi^2, \cdots.$$

Example 2: $b/a = 20$

$$k_{0,0} = 0, k_{1,0} = -\pi^2, k_{2,0} = -4\pi^2, k_{3,0} = -9\pi^2,$$
$$k_{4,0} = -16\pi^2, \cdots, k_{10,0} = k_{0,1} = -100\pi^2, \cdots.$$

Animals can have spotted body and striped tail – but not striped body and spotted tail

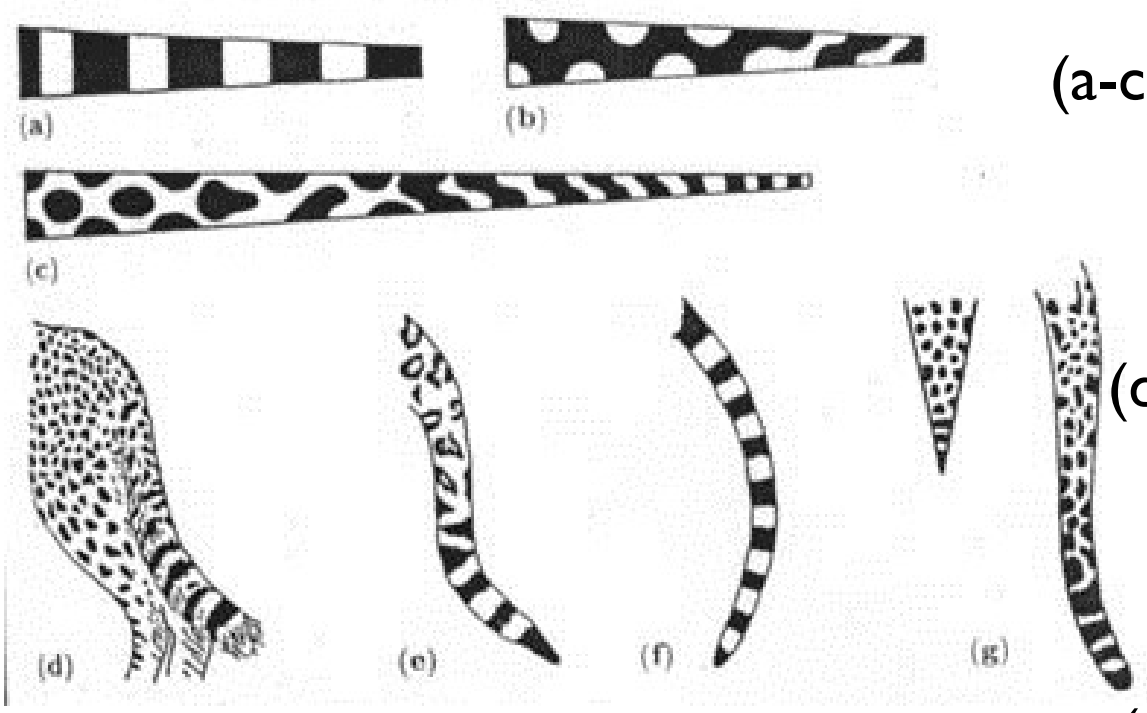
- Body always wider than tail
- same reaction-diffusion mechanism responsible for patterns on both body and tail
- If body is striped, and parameters are similar for tail and body, the tail must also be striped since stripes are favored in narrower geometry

Google Images

Tail patterns of big cats

Domain: tapering cylinder, with width becoming narrower at the end.

Predicted patterns: spots on the wider part, and stripes on the tail end; all spots; or all stripes.



(a-c) Numerical simulations of Murray-Turing model

(d) Cheetah tail markings

(e) Jaguar tail markings

(f) Genet tail markings

(g) Leopard tail markings

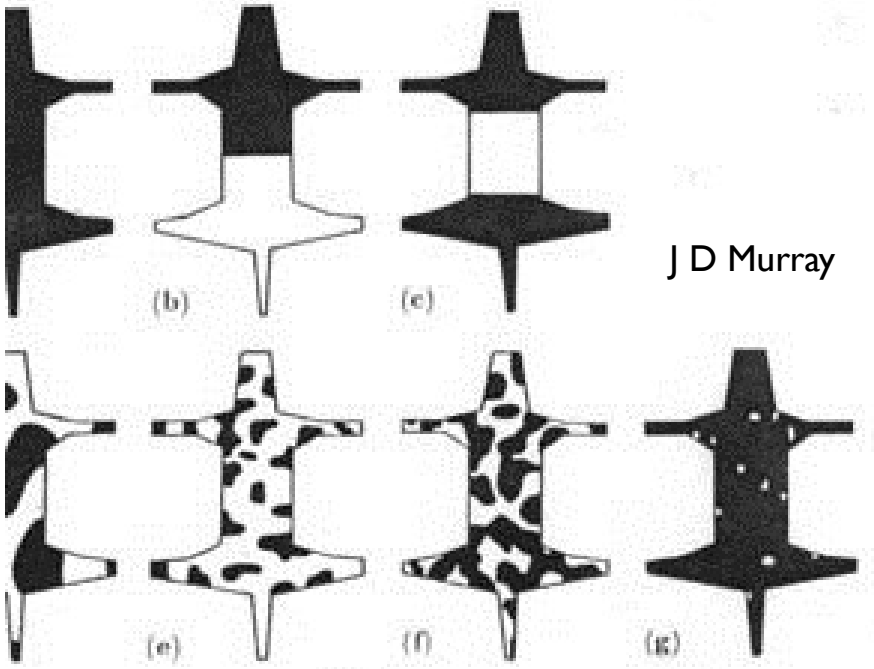
J D Murray

Effect of scale on Murray-Turing patterns

Small domain: λ is small, there is no spatial pattern, and the constant state is stable. (small animals are uniform in color: squirrel, sheep, small dogs)

Medium size domain: λ is not too large nor too small, and there are many spatial patterns. (zebra, big cats, giraffe)

Large domain: λ is large, and there are patterns but the structure is very fine. (elephant, bear)



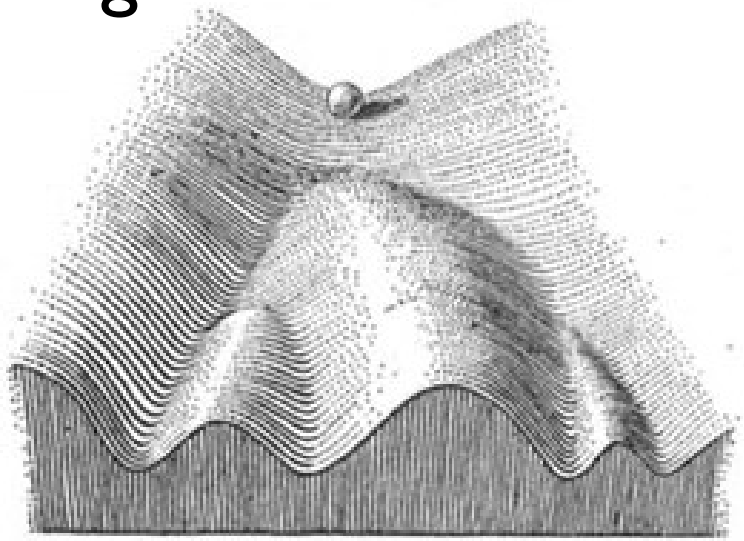
J D Murray

(a) small black cat
(b) Valais Goat
(c) Giant panda
(d) Cow
(e) giraffe
(f)
(g) Elephant

But how has Turing's work influenced subsequent developments in understanding morphogenesis ?

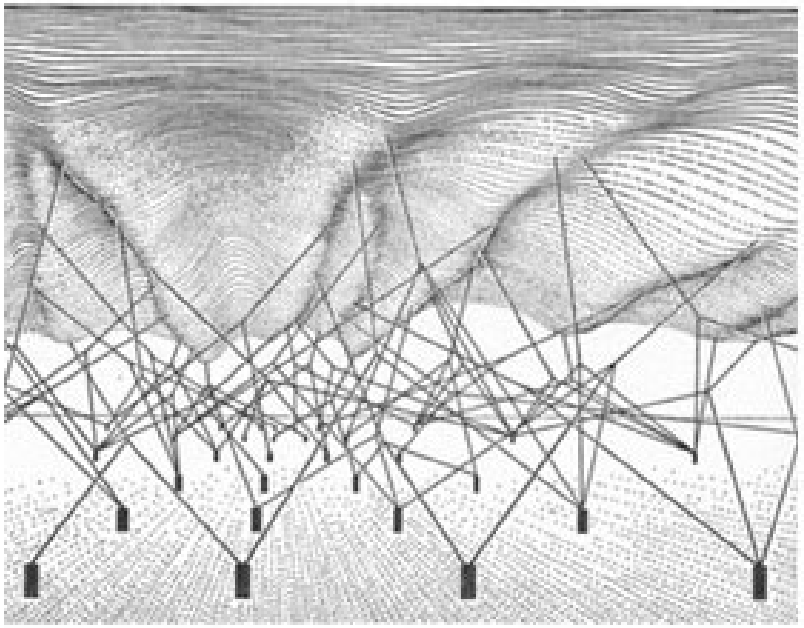
The epigenetic landscape: how gene regulation modulates development of biological form

Conrad H Waddington
(1905-1975)



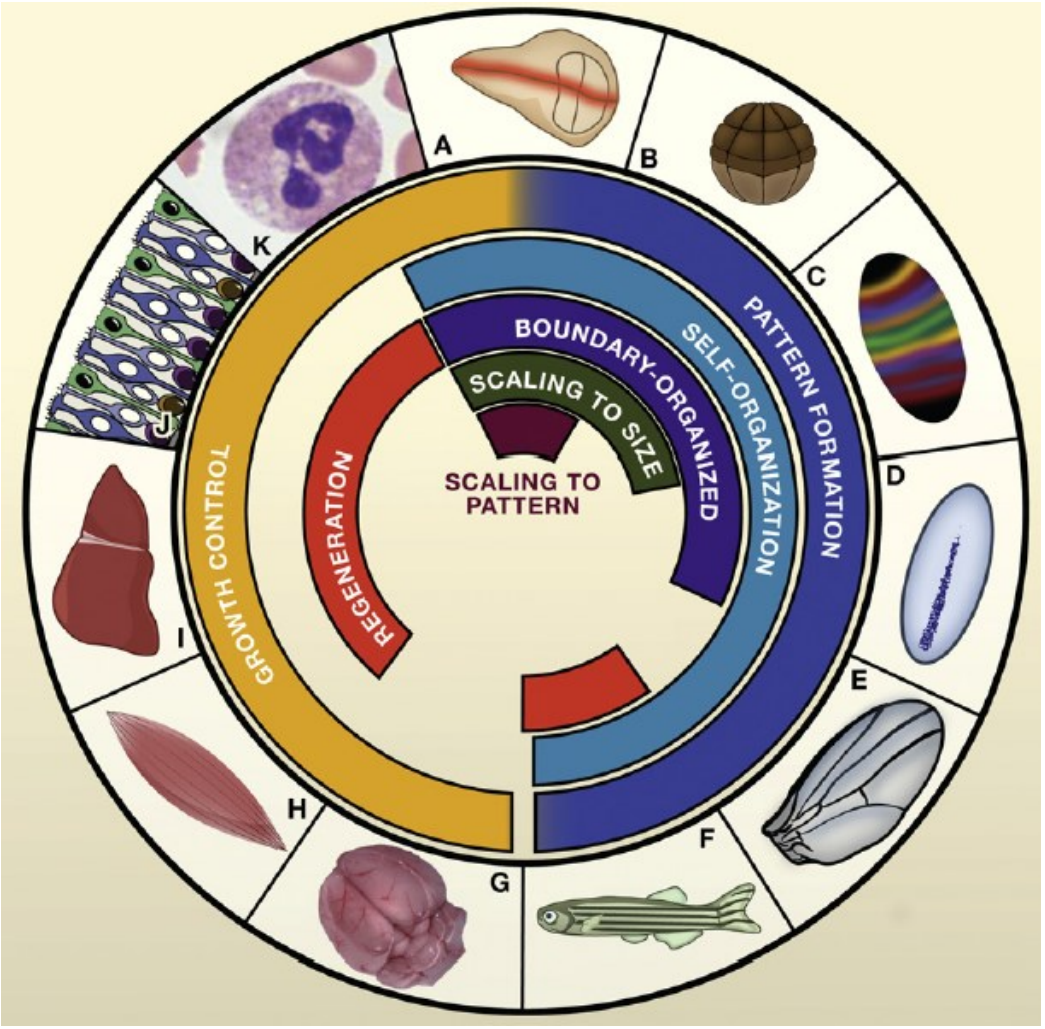
The ball represents a cell, and the bifurcating system of valleys represents the trajectories in state space.

Each valley in the landscape is formed by tension on ropes that are attached to complexes of 'genes', represented as pegs stuck in the ground.

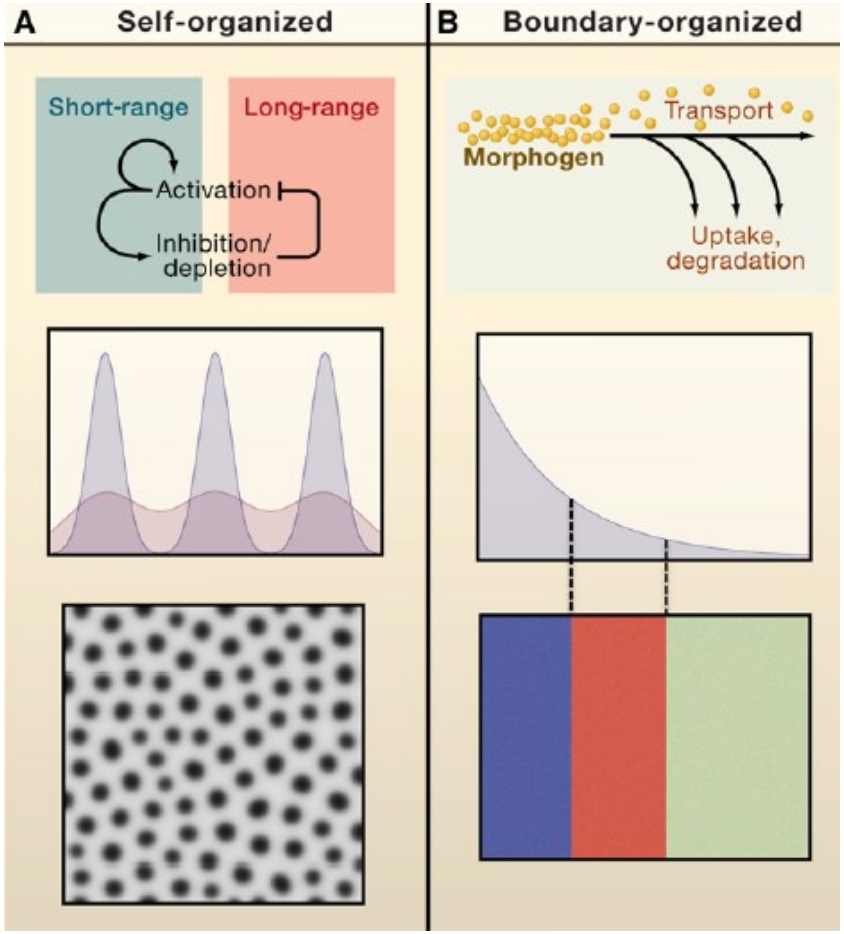


The Strategy of the Genes. 1957 London : George Allen & Unwin.

Two modes of pattern organization in biology



Lander, *Cell* (2011)



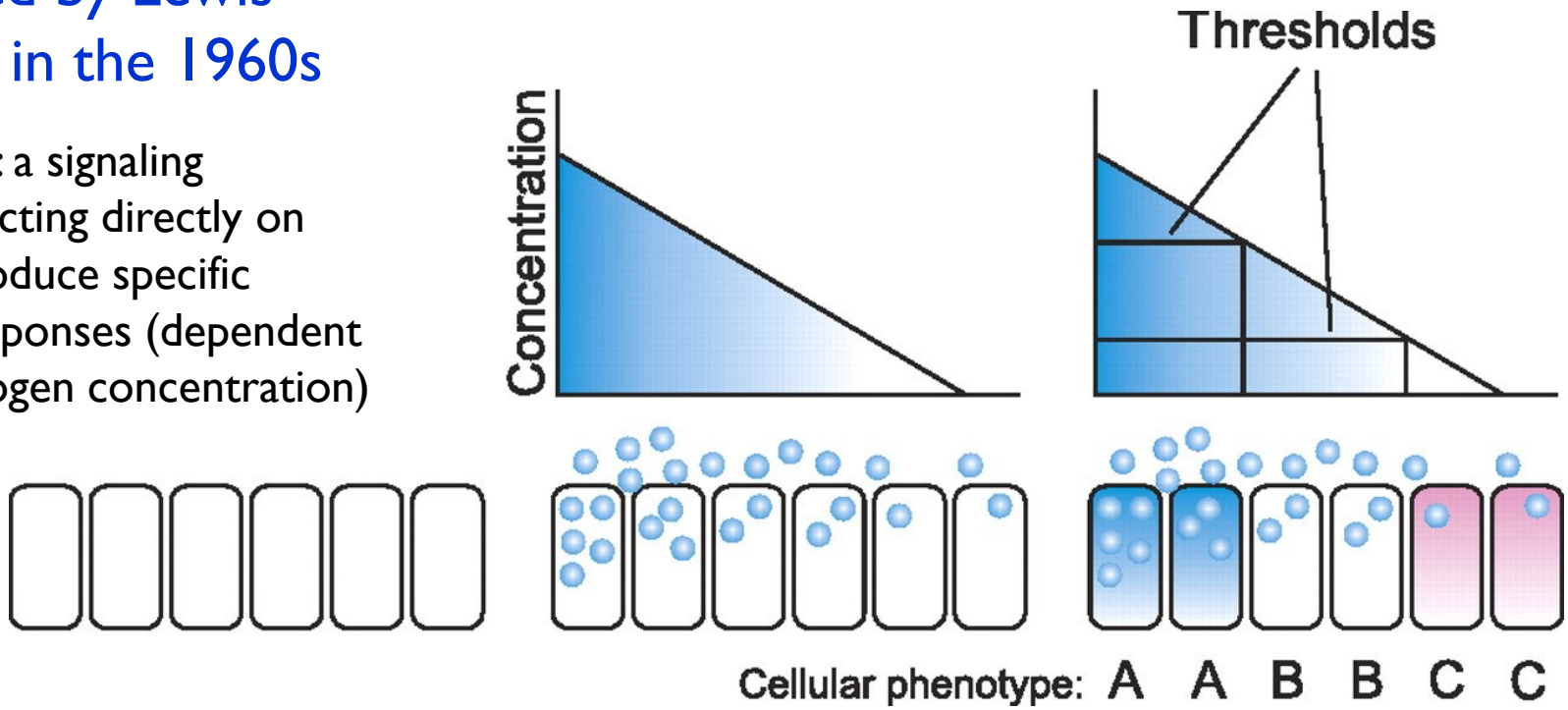
Lander, *Cell* (2011)

French flag model: Morphogen gradients generate cell types in a distinct spatial order during early development

van den Brink G R *Physiol Rev* 2007;87:1343

Described by Lewis Wolpert in the 1960s

Morphogen: a signaling molecule acting directly on cells to produce specific cellular responses (dependent on morphogen concentration)



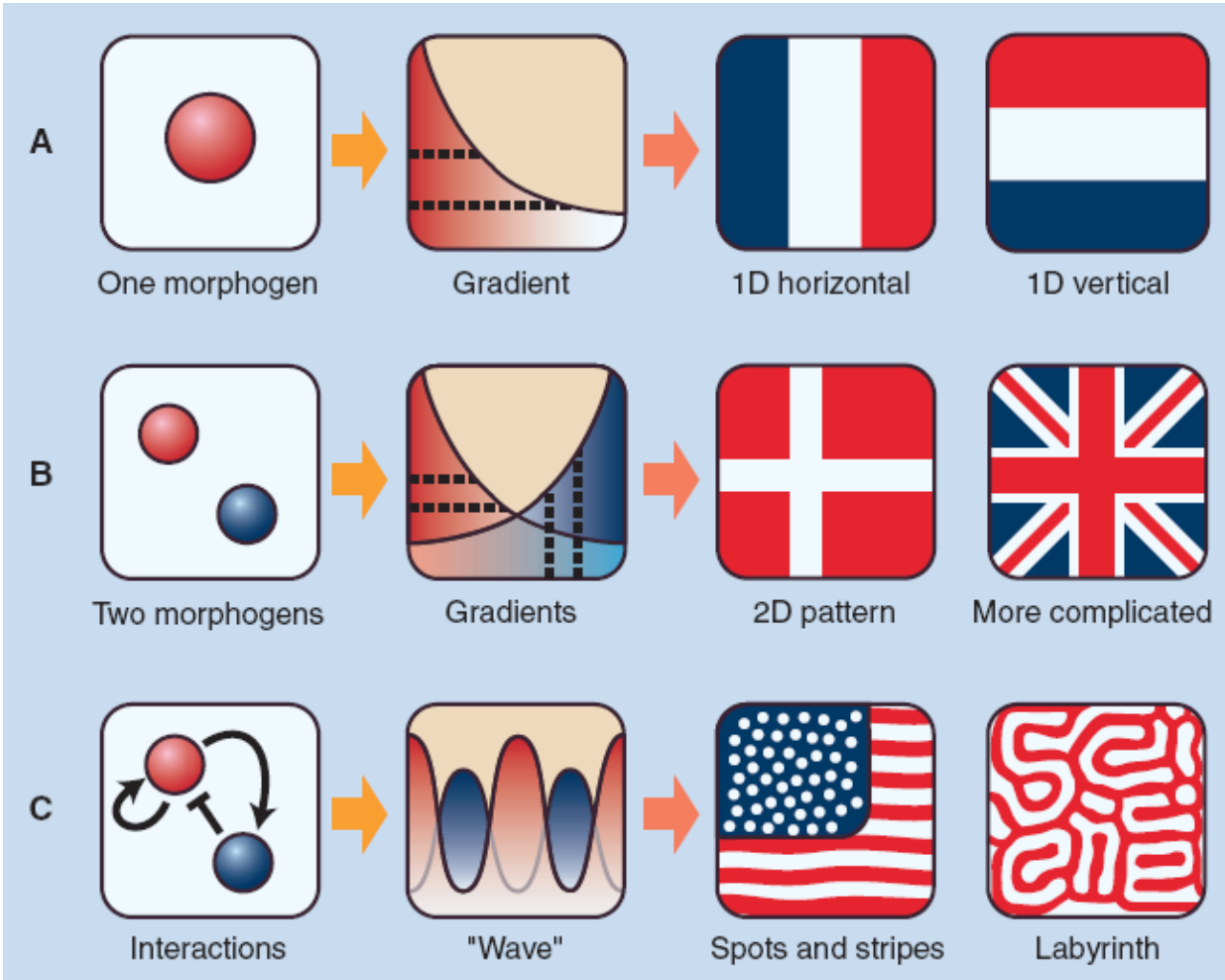
- ❑ Undifferentiated cells can choose three different cell fates (blue, white, or red) specified in a cell position-dependent manner by localized production of a morphogen
- ❑ Cells respond to different thresholds of morphogen concentration depending on their distance from the source.
- ❑ In reality many morphogens and their antagonists generate more complex patterns

Difference between morphogen gradient model and Turing mechanism

In morphogen gradient model, symmetry is not broken spontaneously as in Turing mechanism - rather the broken symmetry is inherited

S Miyazawa

- Diffusing morphogen molecules produced at one end of embryo forms a gradient dependent on pre-pattern of the morphogen source (boundary condition) – cells "know" their position from concentration of the molecule.
- Introducing a second morphogen produces a more complex pattern
- Interactions between morphogens make the system self-regulating – can form a variety of patterns independent of any initial/boundary conditions



But do Turing patterns occur in reality ?

For almost four decades Turing patterns remained only a theoretical possibility unverified by any experimental observation…

Why ?

Recall: an essential ingredient for Turing patterns →
the inhibitor must diffuse more rapidly than the activator

$$D_{inhib} / D_{activ} = r >> 1$$

However, in aqueous solution, molecules and ions have almost similar diffusion constants ⇒ obtaining the required high *r* is almost impossible in typical chemical systems.

… Until J De Kepper and co-workers first showed chemical Turing patterns in CIMA reaction taking place in an unstirred continuous flow gel reactor

First experimental observation of Turing patterns

Chlorite-Iodine-Malonic Acid (CIMA) Reaction

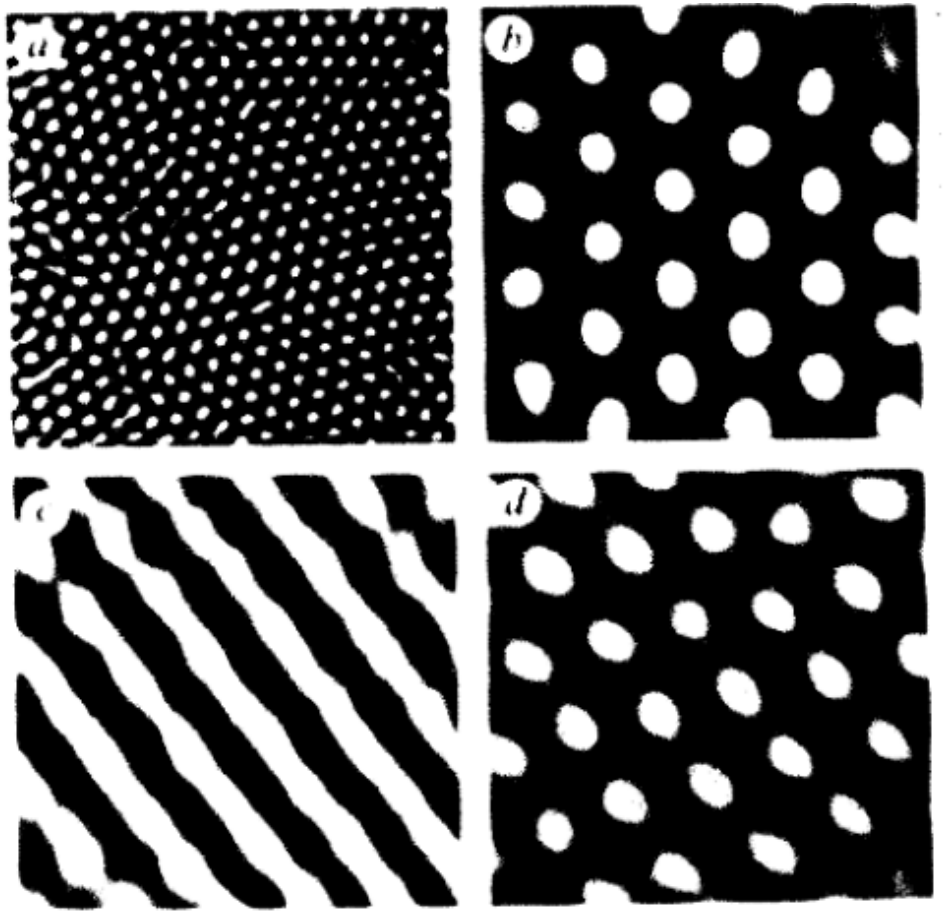


FIG. 1 Stationary chemical patterns formed in a continuously fed laboratory reactor. *a*, *b*, Hexagons; *c*, stripes; *d*, mixed state. The bar beside each picture represents 1 mm; the reactor is 25 mm in diameter. The concentrations in

Ouyang and Swinney, *Nature* 352 (1991) 610

$$MA + I_2 \rightarrow IMA + I^- + H^+$$

$$ClO_2 + I^- \rightarrow ClO_2^- + {}^1/_2 I_2$$

$$ClO_2^- + 4I^- + 4H^+ \rightarrow Cl^- + 2I_2 + 2H_2O$$

Serendipity in action:

- Starch used as an indicator to increase color contrast
- It forms an immobile and unreactive starch-triiodide complex
- Traps diffusing activator iodide ions until the complex again breaks up
- Effectively decreasing diffusion rate of iodide compared to the inhibitor chlorite

Thus, we obtain a

General recipe for demonstrating Turing patterns in chemical systems

In a system with reacting activator and inhibitor chemicals having a stable homogeneous steady state, use a **complex-forming agent** that reversibly forms an immobile, unreactive complex **with the activator**.

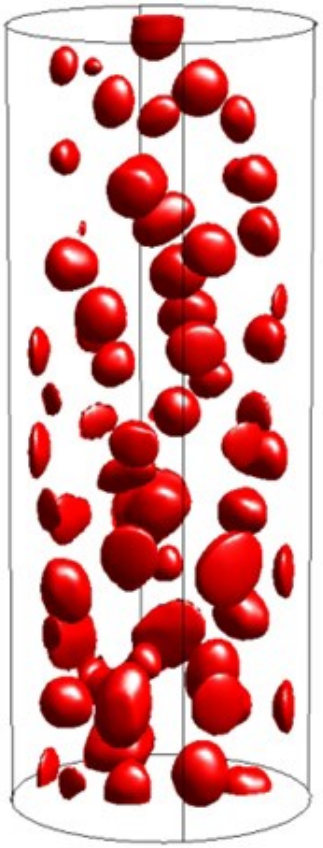
Chemical Turing patterns occur on a 2-D layer in a 3-D medium

- The different chemicals flow into two ends of a (typically) cylindrical slab of gel
- Conditions for Turing patterns are satisfied only in a relatively thin strip parallel to the gel faces, perpendicular to concentration gradients set up as a result of the input flows and diffusion of species within the gel.

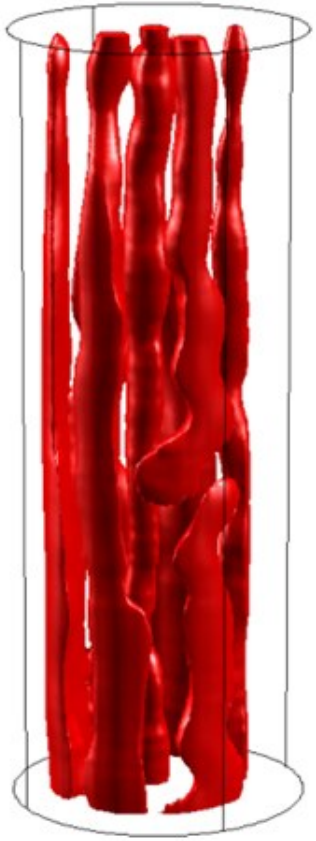
Three-dimensional Turing patterns

Could Turing mechanism be responsible for formation of 3-D biological structures such as limbs, teeth and lungs ?

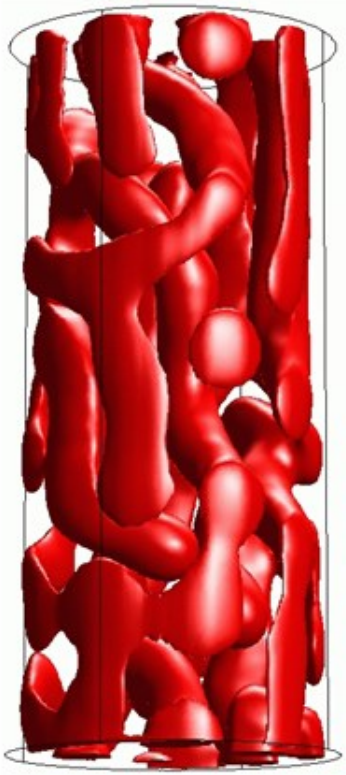
Spots



Hexagonal close-packing



Labyrinthine



3-D Turing patterns in BZ reaction incorporated into a water-in-oil aerosol (AOT) microemulsion

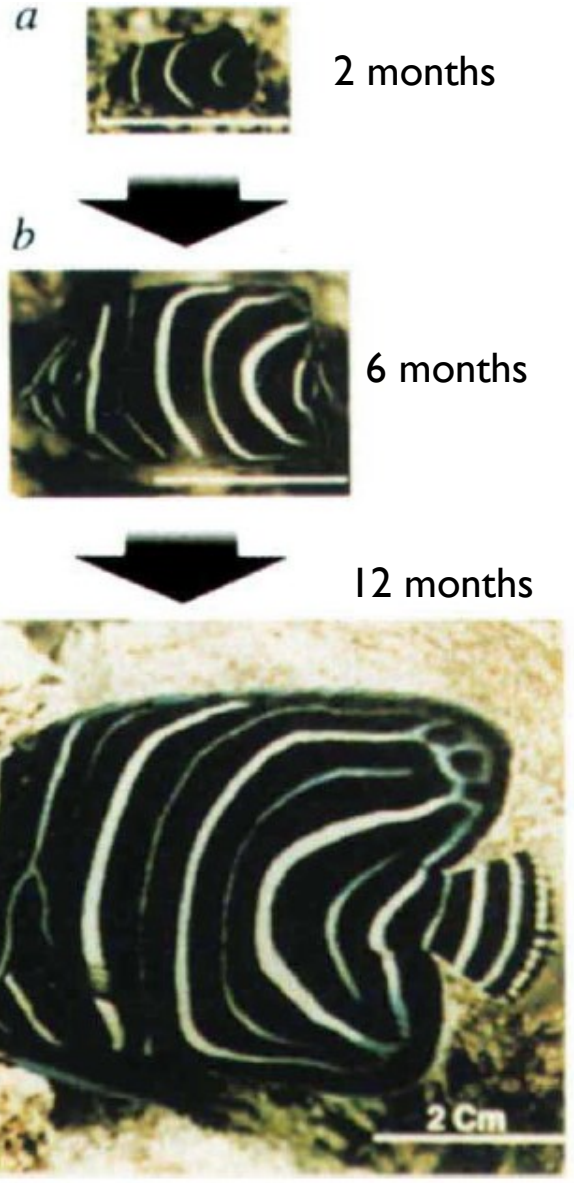
Polar BZ reagents in 10 nm water droplets surrounded by surfactant monolayer and dispersed in continuous oil phase

During reaction, inhibitor apolar intermediates (Br_2) diffuse upto 2 order faster than activator polar species ($HBrO_2$)

3-D images reconstructed from many 2D sectional views using tomography

Bansagi, Vanag and Epstein, *Science* **331** (2011) 1309

But do Turing patterns actually occur in biology ?



Kondo and Asai, *Nature* **376** (1995) 765

However striking the similarity between Turing structures and biological patterns, one can argue that it is just coincidence – unless one identifies the responsible diffusing molecules (morphogens)

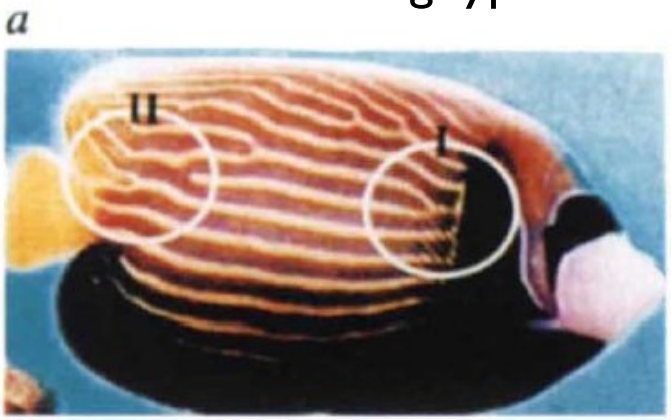
1995: Kondo and Asai explained the evolution of stripe markings on marine angelfish *Pomacanthus* as it grows using activator-inhibitor process on a growing cell array

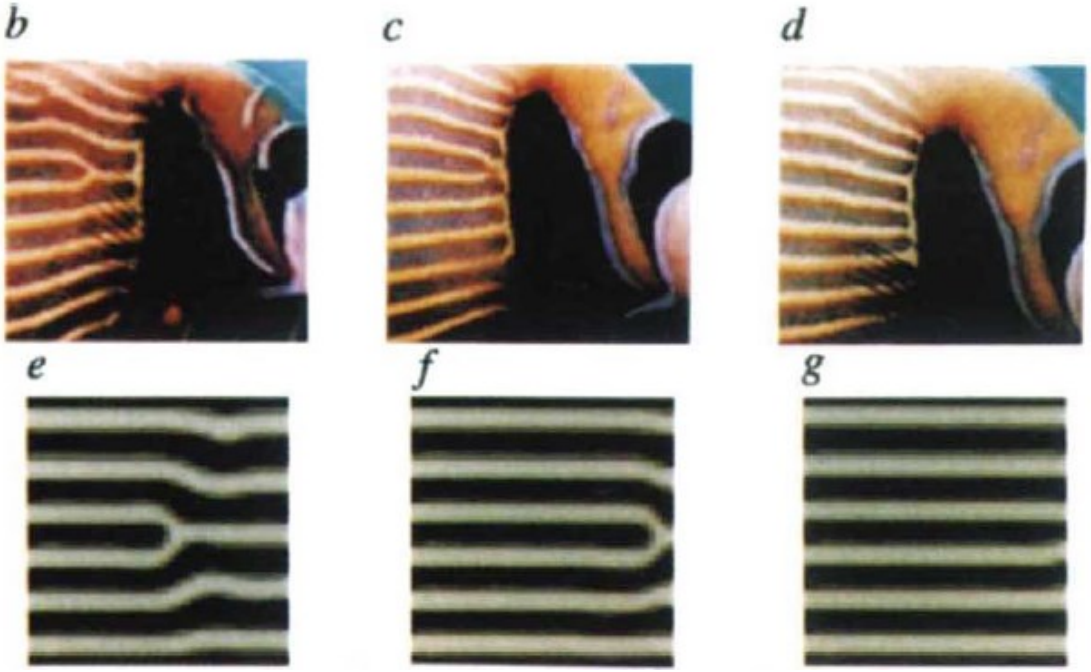
The pattern stays more or less the same as the fish gets bigger: Smaller fish have fewer stripes – As it grows stripe separation gets wider until suddenly new stripes emerge in between original ones

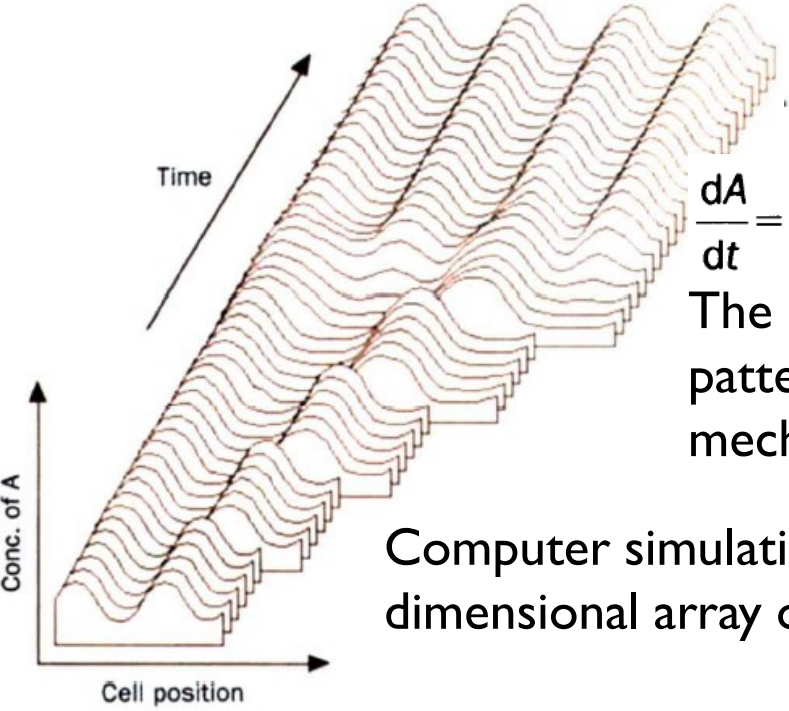
[In contrast to patterns on mammals e.g. zebra where patterns are laid down once and for all – and expand like markings on a balloon as the animal gets bigger]

Turing patterns in a growing array of cells

The "unzipping" of new stripes mimicked in a Turing type model







$$\frac{dA}{dt} = c_1 A + c_2 I + c_3 - D_A \frac{d^2 A}{dx^2} - g_A A, \qquad \frac{dI}{dt} = c_4 A + c_5 - D_I \frac{d^2 I}{dx^2} - g_I I$$

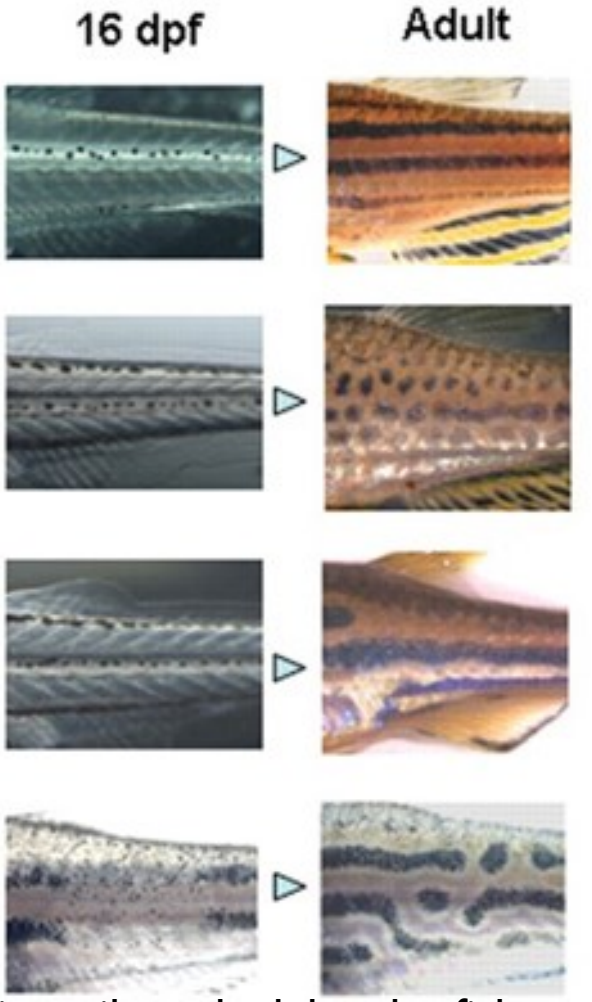
The same model is able to explain different growing patterns in distinct varieties of angelfish $\Rightarrow$ Turing mechanism is probably the correct biological process

Computer simulation of reaction-diffusion wave on a growing one-dimensional array of cells (i.e., cells duplicate periodically)

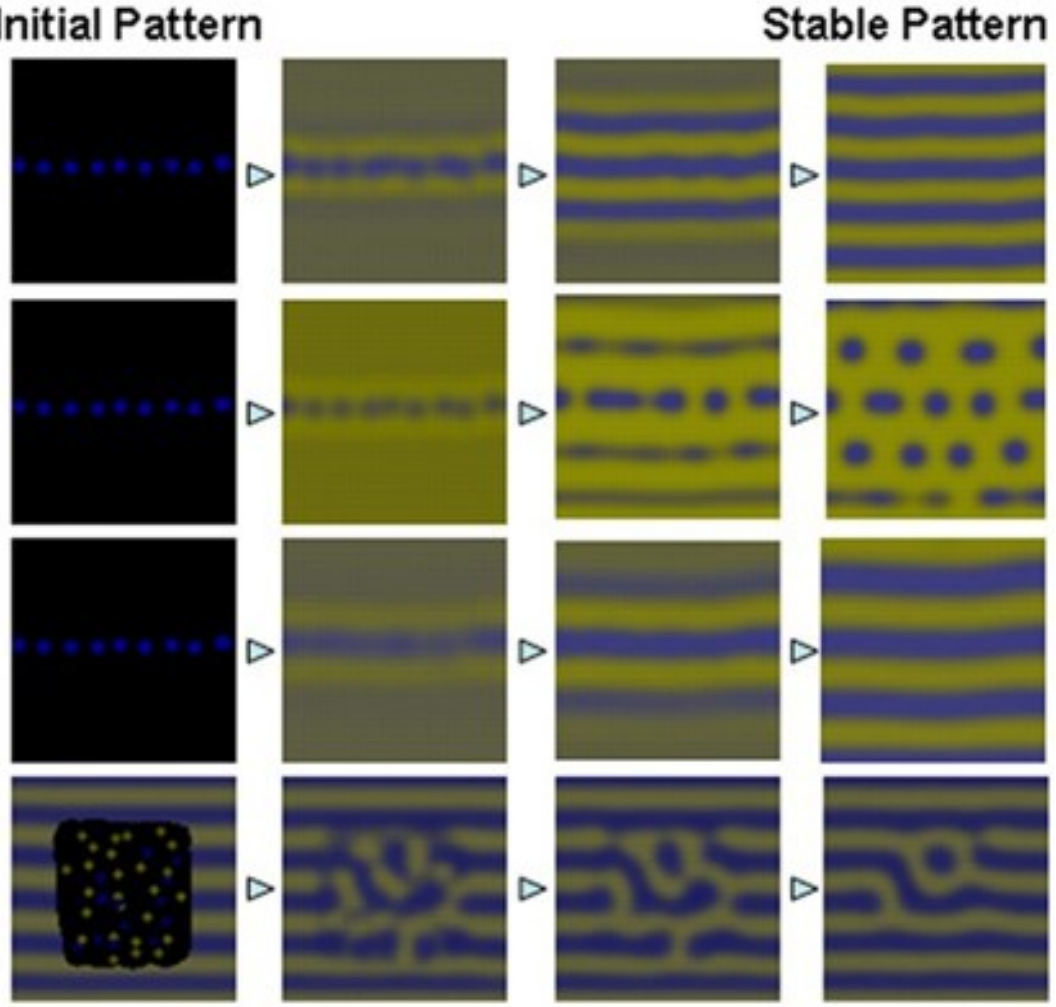
Kondo and Asai, *Nature* **376** (1995) 765

Turing patterns in the Zebrafish

Scar spots of juveniles in different ways using lasers, observe how the markings develop – patterns evolved precisely as predicted by simulations proving their Turing pattern nature.



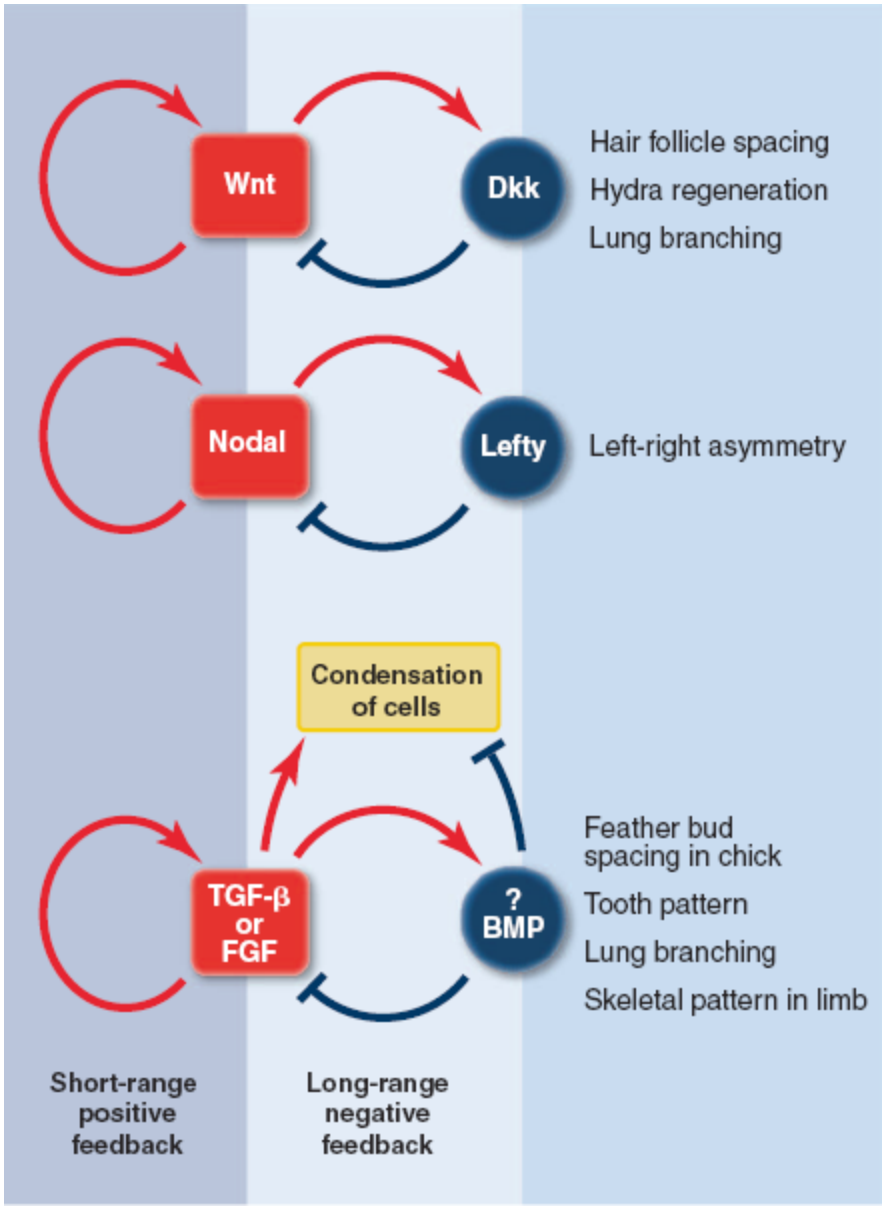
juvenile and adult zebrafish markings



Turing pattern simulations developing over time

Kondo and Nakamasu, PNAS

Genesis of Turing patterns in the embryo



Kondo and Miura, *Science* **329** (2010) 1616

Possible networks of protein ligands may give rise to Turing patterns in the embryo

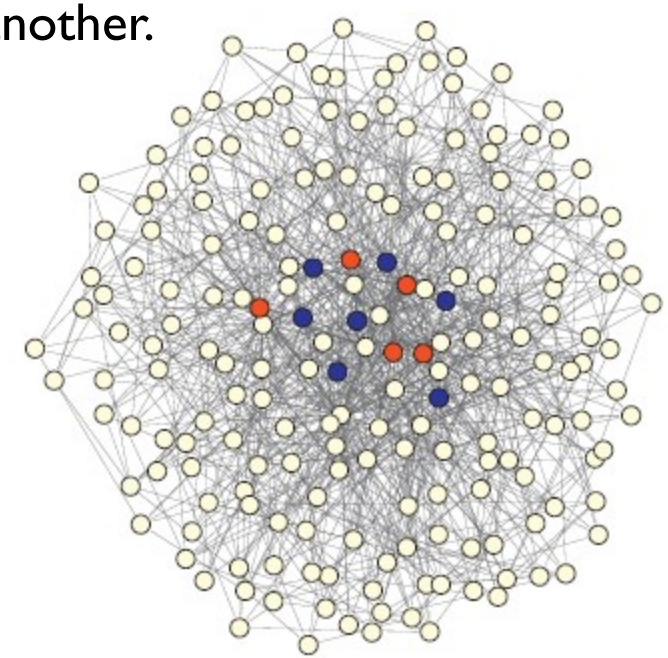
(i) Wnt-Dkk (ii) Nodal-Lefty and (iii) TGF-beta/FGF-?BM) are candidates for the reaction-diffusion mechanism proposed by molecular experiments.

Condensation of cells by migration into a local region causes sparse distribution of cells in a neighboring region – also functions as long-range inhibition.

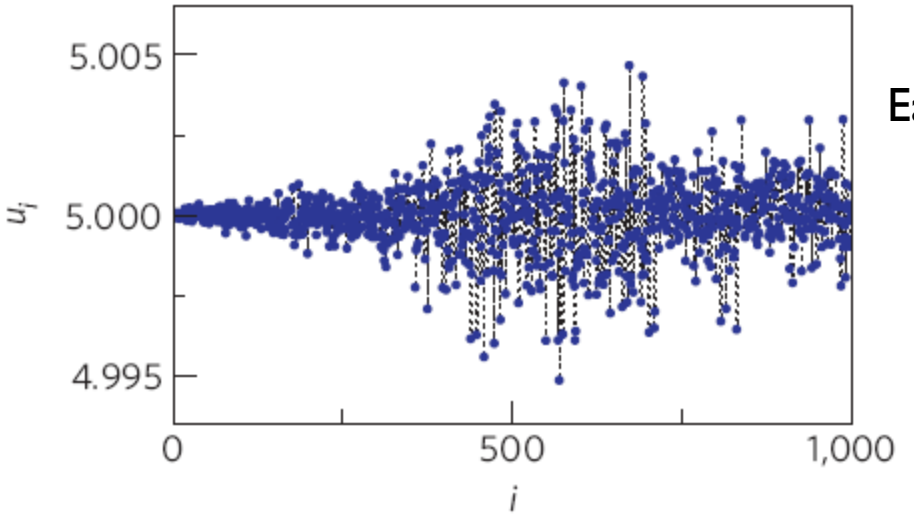
The Future: Turing patterns on Networks

Nakao and Mikhailov (*Nature Physics* 2010): Network analogue of reaction-diffusion model where activator and inhibitor species occupy discrete nodes of a network and are diffusively transported over links connecting them.

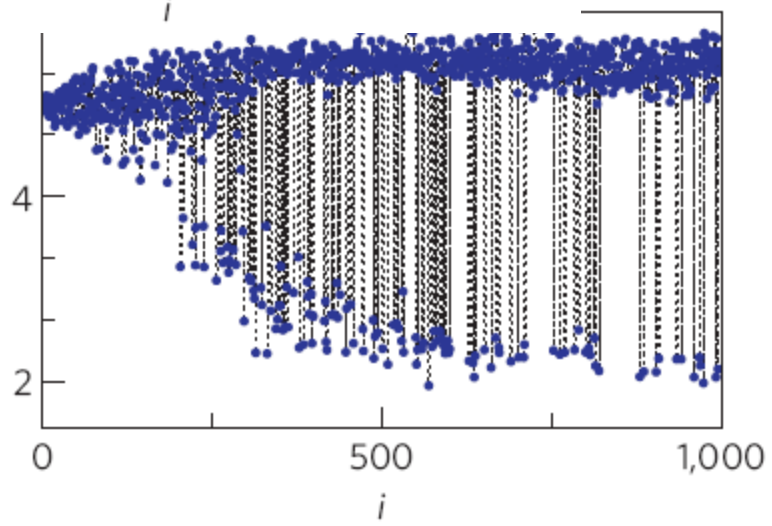
Links may represent diffusive connections between chemical reactors or dispersal of ecospecies from one habitat to another.



Nakao and Mikhailov, 2010



Early stage



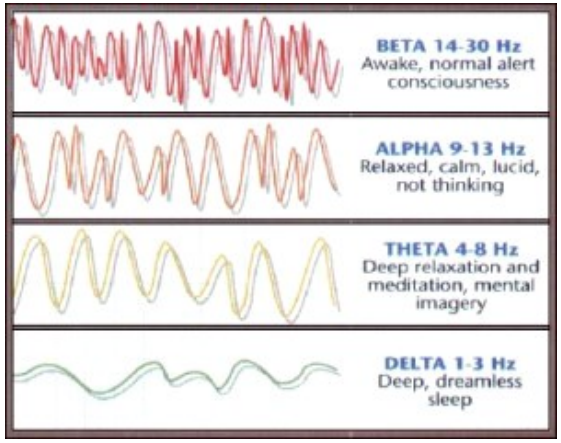
Late stage

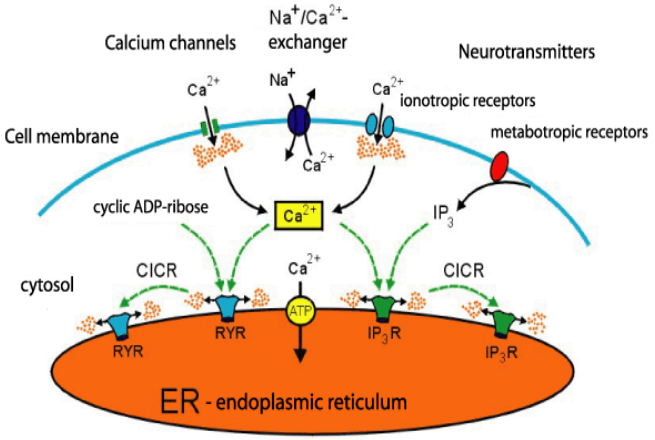
Stationary Turing pattern

Reaction-Diffusion with oscillators instead of Homogeneous Steady States

In many biological systems, the individual entities undergo periodic oscillations instead of remaining in a constant state

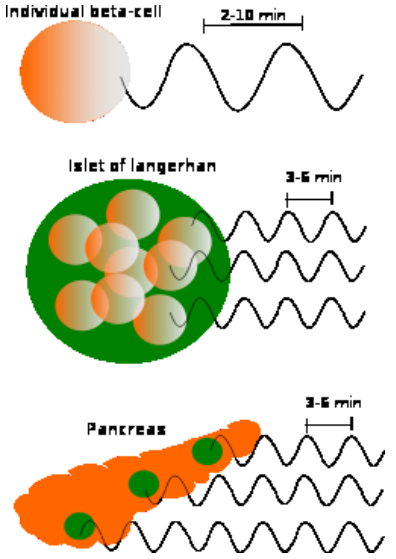
Neuronal activity oscillations





Intracellular oscillations

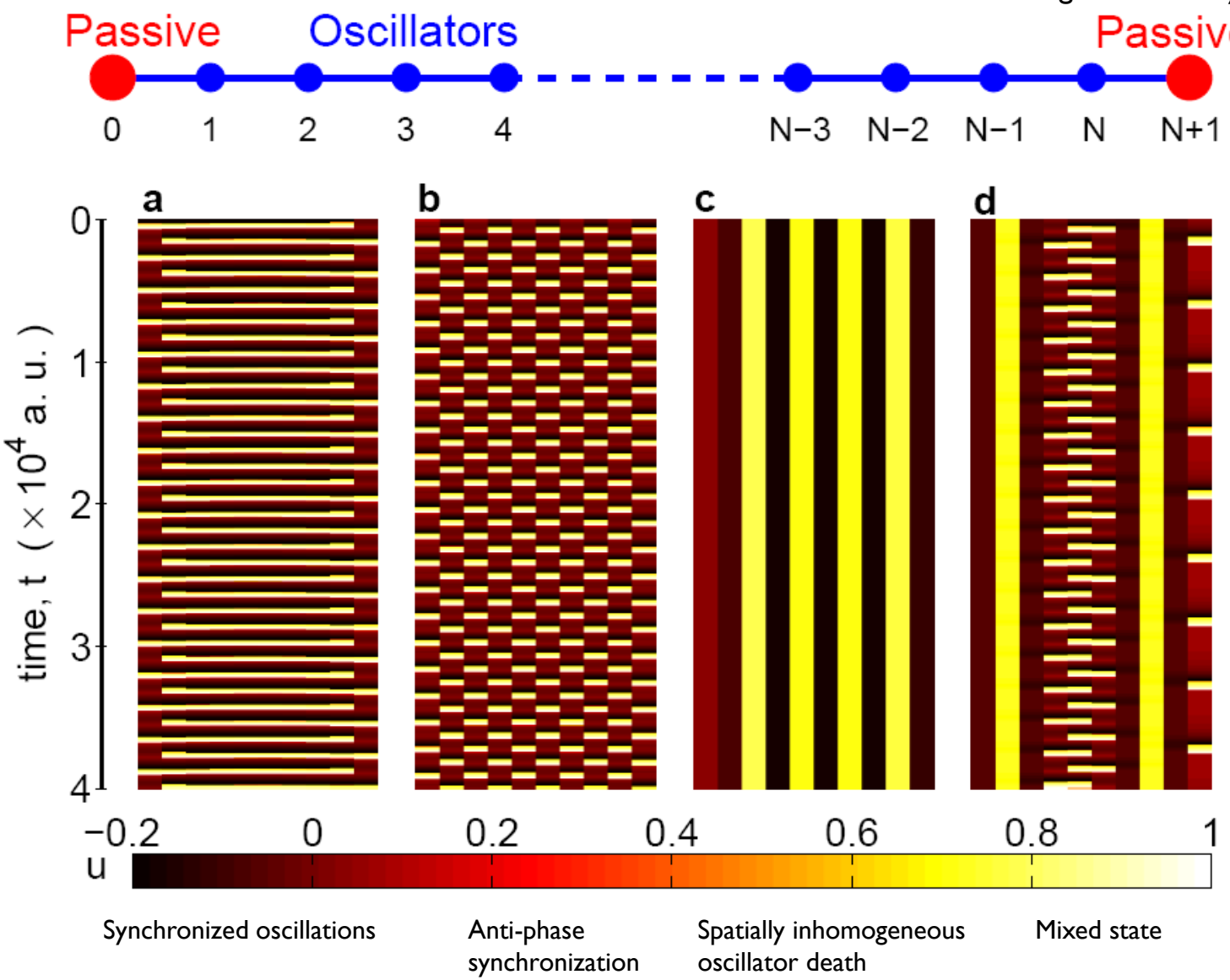
Insulin release oscillations



What will happen if we allow these oscillators to have activating-inhibiting diffusive interactions with each other ?

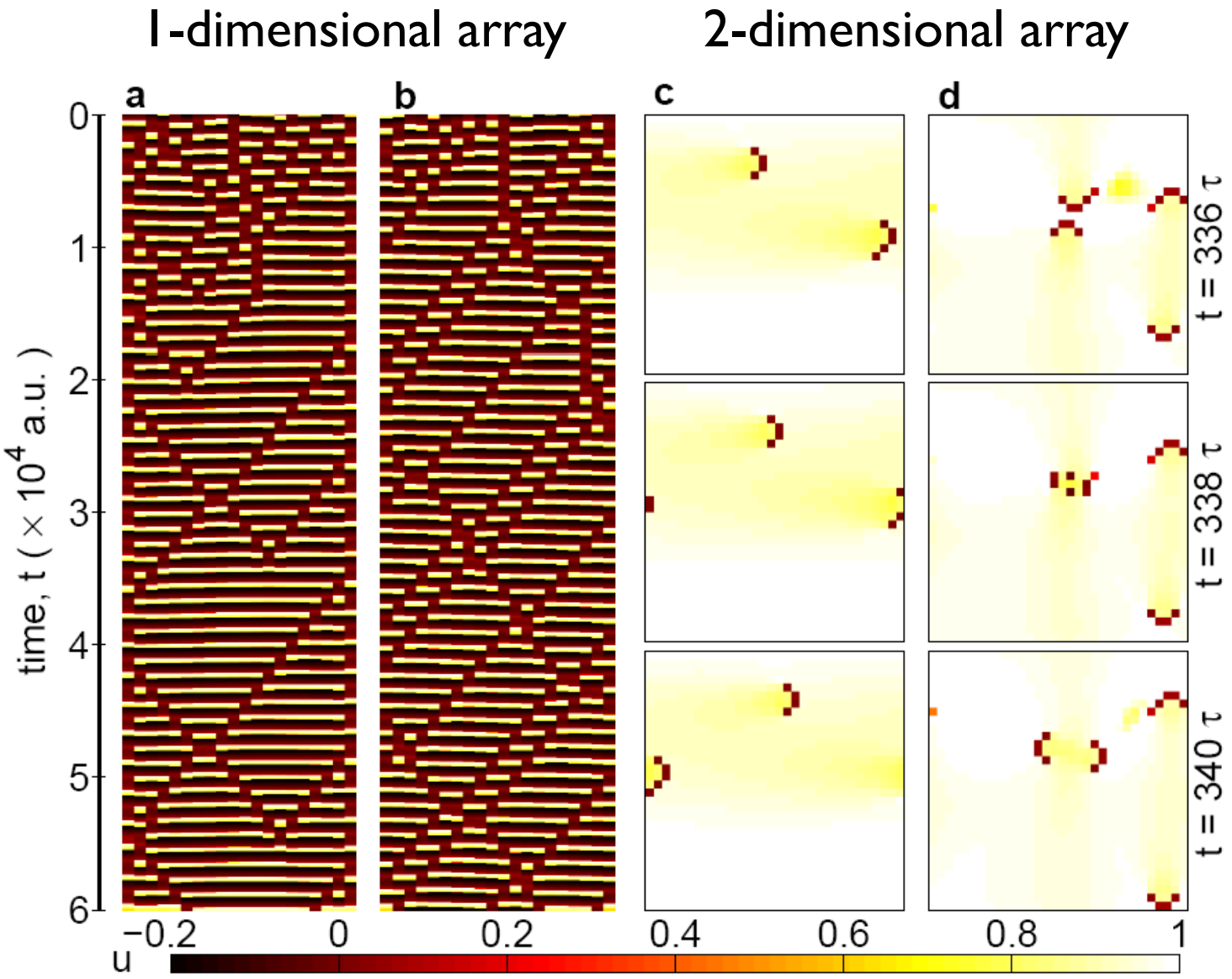
Patterns seen in diffusively coupled oscillator array

Singh & Sinha *Phys Rev E* (2012)



Traveling waves of phase defects

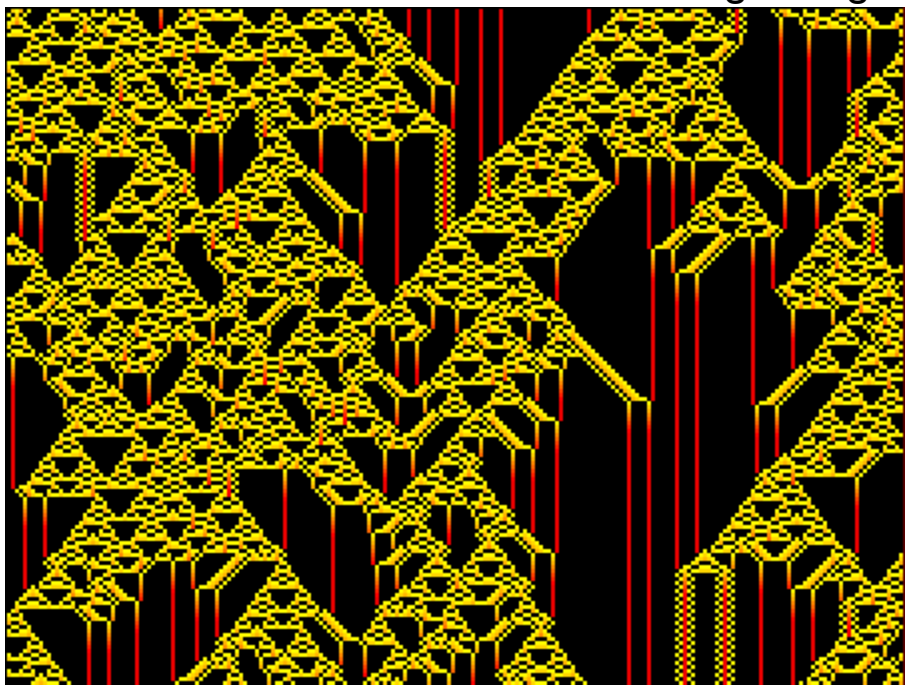
Singh & Sinha *Phys Rev E* (2012)



Towards a chemical Turing machine ?

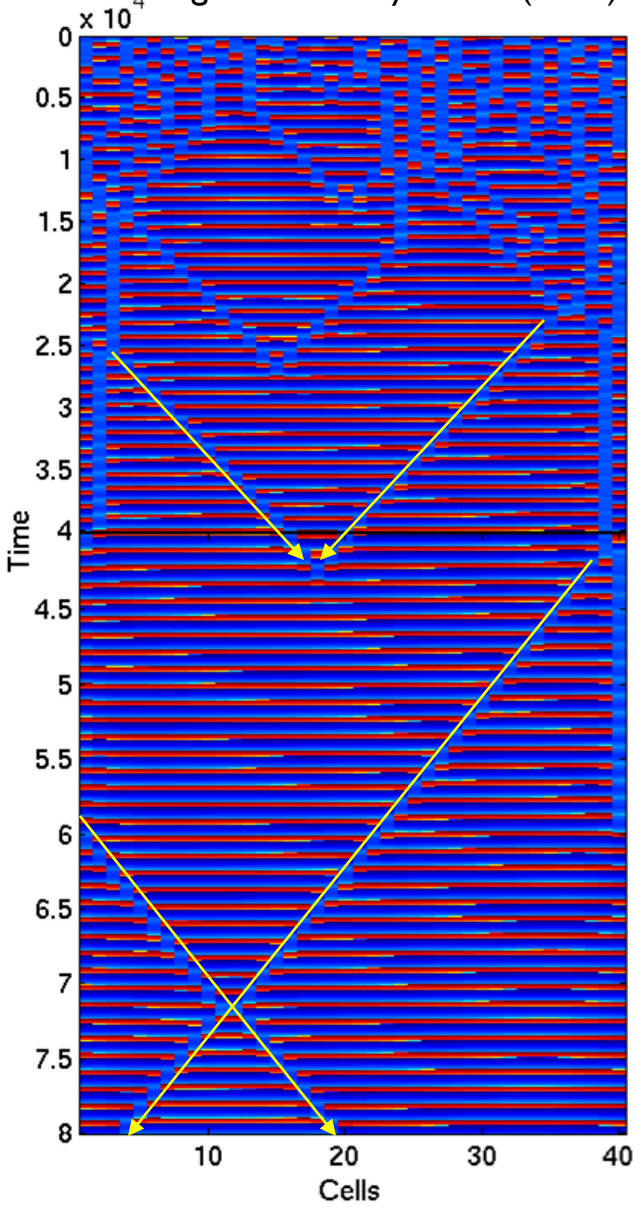
"Bubbles flowing through narrow channels can be encoded with information and made to perform logic operations like those in computer." — I Epstein, 2007.

Google Images



Traveling localized structures in one-dimensional cellular automata, class 4a

Singh & Sinha *Phys Rev E* (2012)



Interactions among traveling phase defects in a relaxation oscillator array