Dynamical Systems and Chaos
Part II: Biology Applications

Lecture 11: Reaction-Diffusion Systems.

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Reaction-Diffusion Modeling

Diffusion is the thermal motion of all (liquid or gas) particles at temperatures above absolute zero.

- Homogeneous system: probability of finding any randomly selected molecule inside volume ΔV is $\Delta V / V$.
- Homogeneous and thermal equilibrium $\rightarrow$ well-stirred (much more nonreactive than reactive collisions happen).
- Sometimes spatial effects play an important role in addition to temporal effects and we need to include diffusive effects to our modeling (spatiotemporal, inhomogeneous, heterogeneous).
- Diffusion: 1 dimensional (x) – 3 dimensional (x,y,z)

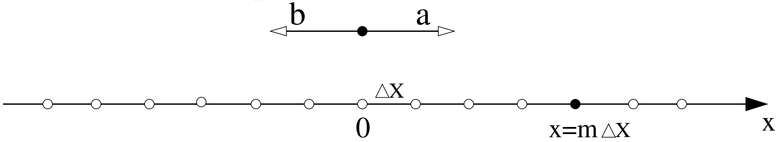
Before going further...

In an assemblage of particles (cells, bacteria, chemicals, animals etc.) each particle usually moves around in a random way. When this *microscopic* irregular movement results in some *macroscopic* or gross regular motion of the group we can think of it as a diffusion process [J. Murray *Mathematical Biology*, 3-d edition, Springer, 2003].

Let's consider simplest 1D case of random walk process.

1D random walk

Suppose a particle moves randomly backward and forward along a line in a fixed steps Δx that are taken in a fixed time Δt.



What is the probability $p(m, n)$ that a particle reaches a point m space steps to the right (that is, $x = m\Delta x$) after n time steps (that is, after time $n\Delta t$)?
Suppose that to reach $m\Delta x$ the particle has moved a steps to the right and b steps to the left. Then

$$m = a - b, \quad a + b = n \quad \Rightarrow \quad a = \frac{n+m}{2}, \quad b = n - a$$

$$p(m, n) = \frac{1}{2^n} \frac{n!}{a!(n-a)!}$$

1D random walk

$$p(m,n) = \frac{1}{2^n}\frac{n!}{a!(n-a)!}, \quad a = \frac{n+m}{2} \tag{1}$$

Stirling's formula is:

$$n! \sim (2\pi n)^{1/2} n^n e^{-n} \tag{2}$$

Given (1) and (2) we can get (!!!):

$$p(m,n) \sim \left(\frac{2}{\pi n}\right)^{1/2} e^{-m^2/(2n)}\,, \quad m \gg 1\,, \quad n \gg 1\,. \tag{3}$$

For $n = 8$ and $m = 6$ (3) is within 5% of the exact value from (1). Check it at home!

Continuous case

$$m\Delta x = x, \quad n\Delta t = t$$

where x and t are continuous.

We cannot use $p(m,n)$ as it must tend to zero since number of points on the line tends to ∞ as $\Delta x \to 0$. The relevant dependent variable is more appropriately $u = p/(2\Delta x)$: $2u\Delta x$ is the probability of finding a particle in the interval $(x, x+\Delta x)$ at time t. From (3) with $m = x/\Delta x$ and $n = t/\Delta t$

$$\frac{p(\frac{x}{\Delta x}, \frac{t}{\Delta t})}{2\Delta x} \sim \left\{ \frac{\Delta t}{2\pi t (\Delta x)^2} \right\}^{1/2} \exp\left\{ -\frac{x^2}{2t} \frac{\Delta t}{(\Delta x)^2} \right\}.$$

If we assume

$$\lim_{\substack{\Delta x \to 0 \\ \Delta t \to 0}} \frac{(\Delta x)^2}{2\Delta t} = D \neq 0; \quad D \text{ is } \textit{diffusion coefficient}$$

the last equation gives

$$u(x,t) = \lim_{\substack{\Delta x \to 0 \\ \Delta t \to 0}} \frac{p(\frac{x}{\Delta x}, \frac{t}{\Delta t})}{2\Delta x} = \left(\frac{1}{4\pi D t} \right)^{1/2} e^{-x^2/(4Dt)}.$$

Classical Fickian diffusion laws

The first Fick's law says: the flux J of material is proportional to the gradient of the concentration of the material. Thus, in 1D

$$J = -D\frac{\partial c}{\partial x}$$

where $c(x,t)$ is the concentration and D is diffusion coefficient. Conservation equation says that the rate of change of the amount of material in a region is equal to the rate of flow across the boundary plus any that is created within the boundary. If the region is $x_0 < x < x_1$ and no material is created

$$\frac{\partial}{\partial t}\int_{x_0}^{x_1} c(x,t)dx = J(x_0,t) - J(x_1,t).$$

If we take $x_1 = x_0 + \Delta x$, take the limit as $\Delta x \to 0$ and the first Fick's law we get the classical diffusion equation

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = \frac{\partial (D\frac{\partial c}{\partial x})}{\partial x}. \quad \text{If } D \text{ is constant then} \quad \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}.$$

Simple example

Consider calcium diffusing in a long dendrite. Calcium is released from a small region around $x = 0$. Let's denote the concentration of calcium along the length of the dendrite at each time t as $c(x,t)$.

The model is

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2},$$

$$-\infty < x < \infty, t > 0,$$

$$c(x,0) = c_0\delta(x),$$

where $\delta(x)$ – Dirac delta function and $\lim_{x\to\pm\infty} c(x,t) = 0$.

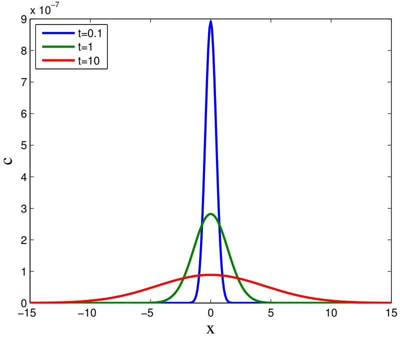


Figure: Solution is $c(x,t) = \frac{c_0}{\sqrt{4\pi Dt}}e^{-\frac{x^2}{4Dt}}$.

Gaussian function

$$G_i = \frac{1}{2\sqrt{\pi\sigma t}} \exp\left(-\frac{x^2}{4\sigma t}\right)$$

$$\frac{\partial G_i}{\partial t} = \frac{1}{2\sqrt{\pi\sigma t}} \exp\left(-\frac{x^2}{4\sigma t}\right)\left[-\frac{1}{2t} + \frac{x^2}{4\sigma t^2}\right]$$

$$\frac{\partial^2 G_i}{\partial \mathrm{x}^2} = \frac{1}{\sigma}\left\{\frac{1}{2\sqrt{\pi\sigma t}} \exp\left(-\frac{x^2}{4\sigma t}\right)\left[-\frac{1}{2t} + \frac{x^2}{4\sigma t^2}\right]\right\}$$

$$\frac{\partial G_i}{\partial t} = \sigma \frac{\partial^2 G_i}{\partial \mathrm{x}^2} \Rightarrow \boxed{D = \sigma}$$

3D case

Let S be an arbitrary surface enclosing a volume V.
The general conservation equation says that the rate of change of the amount of material in V is equal to the rate of flow of material across S into V plus the material created in V. Thus

$$\frac{\partial}{\partial t}\int_V c(\mathbf{x},t)dv = -\int_S \mathbf{J}\cdot\mathbf{ds} + \int_V f\,dv\,,$$

where $\mathbf{J}$ is the flux of material and f, which represents the source of material, may be a function of c, $\mathbf{x}$ and t.
Applying divergence theorem to the surface integral and assuming $c(\mathbf{x},t)$ is continuous, the last equation becomes

$$\int_V \left[\frac{\partial c}{\partial t} + \nabla\cdot\mathbf{J} - f(c,\mathbf{x},t)\right] dv = 0$$

$$\int_V \left[\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{J} - f(c, \mathbf{x}, t)\right] dv = 0$$

Since the volume V is arbitrary the integrand must be zero and so the conservation equation for c is

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{J} = f(c, \mathbf{x}, t).$$

If classical diffusion is the process (the first Fickian law) then

$$\mathbf{J} = -D\nabla c$$

and

$$\frac{\partial c}{\partial t} = f + \nabla \cdot (D\nabla c)$$

Generalising for a vector $u_i(\mathbf{x}, t)$, each having own diffusion D_i and interacting according to vector source term $\mathbf{f}$:

$$\frac{\partial \mathbf{u}}{\partial t} = \mathbf{f} + \nabla \cdot (D\nabla \mathbf{u}).$$

$$\boxed{\frac{\partial \mathbf{u}}{\partial t} = \mathbf{f} + \nabla \cdot (D \nabla \mathbf{u})},$$

where D is a matrix of the diffusiion coefficients which is diagonal matrix if there is no cross-diffusion.

Example of 2D model of 2 chemically non-interacting (f=0) species:

If $\mathbf{u} = (C_1 \;\; C_2)$:

$$\mathbf{D} = \begin{pmatrix} D_{11} & D_{12} \\ D_{21} & D_{22} \end{pmatrix}$$

$$\frac{\partial C_1}{\partial t} = D_{11} \frac{\partial^2 C_1}{\partial \mathrm{x}^2} + D_{12} \frac{\partial^2 C_2}{\partial \mathrm{x}^2}$$

$$\frac{\partial C_2}{\partial t} = D_{21} \frac{\partial^2 C_1}{\partial \mathrm{x}^2} + D_{22} \frac{\partial^2 C_2}{\partial \mathrm{x}^2}$$

If there is no cross-diffusion then $\mathbf{D} = \begin{pmatrix} D_{11} & 0 \\ 0 & D_{22} \end{pmatrix}$ and this is just two seperate equations, otherwise, two species interact through diffusion only, since there is no source term $\mathbf{f}$.

Systems in Space

- Partial Differential Equations (PDE).
- Reaction-diffusion systems: 2nd order parabolic type.
- General equation type:

$$\frac{\partial u}{\partial t} = F(u) + D\frac{\partial^2 u}{\partial x^2}$$

- *F(u)* – reaction term
- u – state variable (concentration), D – diffusion coefficient, x – space variable, t – time.

Types of spatial solutions

- Waves (of very different nature): triggered, phase, pulses.
- Fronts (strictly speaking, belongs to waves).
- Turing patterns.
- Otherwise, classification is complicated.

Fronts

- Two types of fronts:
  - Unstable and stable steady states (Fisher-Kolmogorov)
  - Two stable steady states (FitzHugh-Nagumo)

Fisher-Kolmogorov

- F(u) = u(1-u) : reaction term

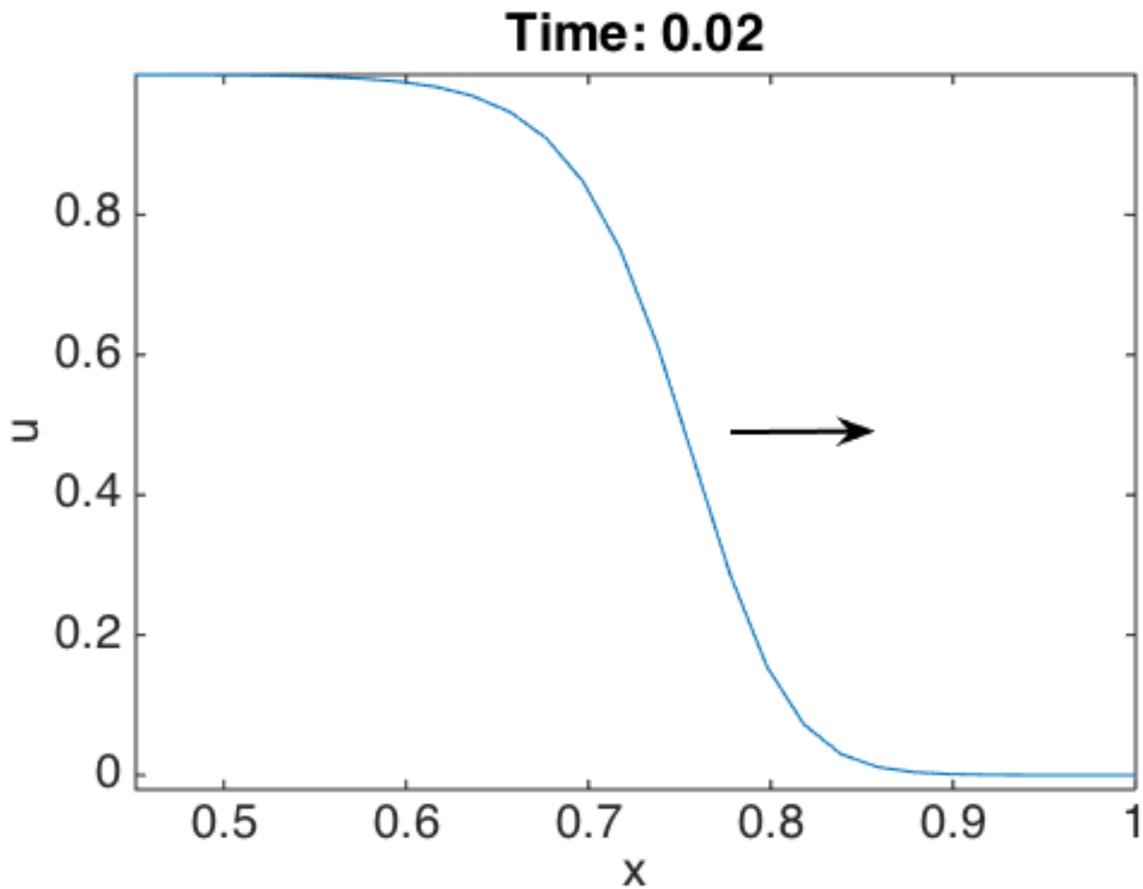
$$\frac{\partial u}{\partial t} = u(1-u) + D\frac{\partial^2 u}{\partial x^2}$$

- Two steady states:

  u = 0 (unstable) and u = 1 (stable).

- Front propagation due to movement from u=0 to u=1 steady state.

Fisher-Kolmogorov



FitzHugh-Nagumo

- F(u) = u(k-u)(u-1) : reaction term

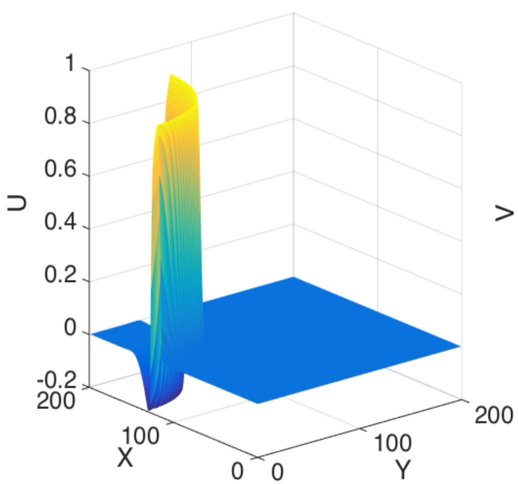
$$\frac{\partial u}{\partial t} = u(k-u)(u-1) + D\frac{\partial^2 u}{\partial x^2}$$

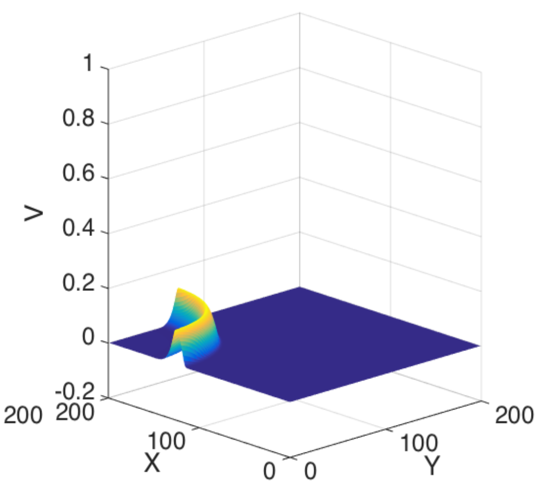
- Three steady states: u = 0 (stable), u=k(unstable) and u = 1 (stable).
- Front propagation direction depends on k:
  – k < 0.5: from left to right
  – k > 0.5: from right to left
  – k = 0.5: front is still

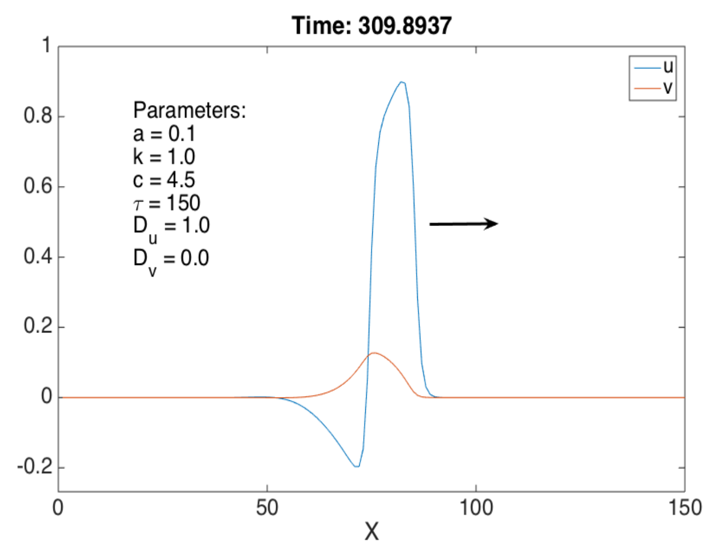
Pulses

- Pulses can appear in the excitable media (neurons).
- Full (2D) version of FitzHugh-Nagumo:

$$\begin{cases} \dfrac{\partial u}{\partial t} = u(a-u)(u-1) - kv + D_u \dfrac{\partial^2 u}{\partial x^2} \\ \dfrac{\partial v}{\partial t} = \dfrac{u - cv}{\tau} + D_v \dfrac{\partial^2 v}{\partial x^2} \end{cases}$$







Turing patterns

- Predicted by Alan Turing (Enigma code, first computer, theoretical work on *morphogenesis* in 1952).
- Only in 1990 using specialized experimental techniques in the group of De Kepper the first Turing patterns were shown experimentally (Phys. Rev. Lett, 64, 2953, 1990).

Linear stability analysis

$$\frac{\partial u}{\partial t} = F(u) + D\Delta u$$

$(\Delta = \dfrac{\partial^2}{\partial x^2})$

- Equilibrium is: $\dfrac{du}{dt} = F(u_0) = 0$
- Apply small perturbation δu and expand $F(u_0 + \delta u)$ into a Taylor series:

$$\frac{\partial(u_0 + \delta u)}{\partial t} = F(u_0) + J\delta u + D\Delta(u_0 + \delta u)$$

$$\frac{\partial(\delta u)}{\partial t} = J\delta u + D\Delta(\delta u)$$

- Solution to this equation is a function:

$$A \cdot \exp(\lambda t + ikx)$$

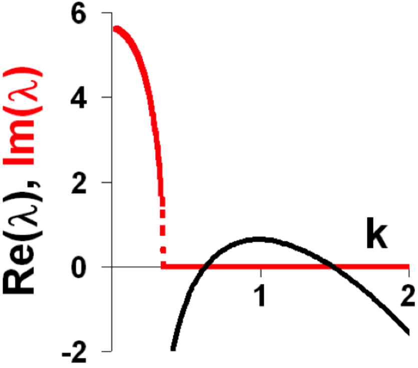
Linear stability analysis

- Characteristic equation becomes:

$$\lambda = J - k^2 D$$

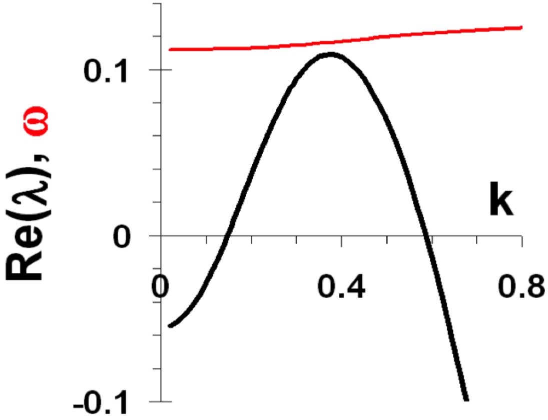
  where λ is eigenvalue, k is wave number.
- At least one positive $\mathrm{Re}(\lambda)$ indicates existence of *instabilities*.
- If $\mathrm{Im}(\lambda) = 0$, given $\mathrm{Re}(\lambda) > 0$ — inhomogeneous periodic in space structures with the wavelength of $l_c = 2\pi/k_{max}$, where k_{max} — the wavenumber at which $\mathrm{Re}(\lambda)$ is maximized. **Turing structures**, **Turing instabilities**.
- If $\mathrm{Im}(\lambda) \neq 0$, given $\mathrm{Re}(\lambda) > 0$ — "genuine waves" (not triggered in excitable media), periodic both in space (wavelength $l_c = 2\pi/k_{max}$) and time (period $T = 2\pi/\mathrm{Im}(\lambda)_{max}$, max corresponds to the wavenumber at which $\mathrm{Re}(\lambda)$ is maximized, $\mathrm{Im}(\lambda) = \omega$). **Wave instability**, **finite wavelength instability**.

Turing instability

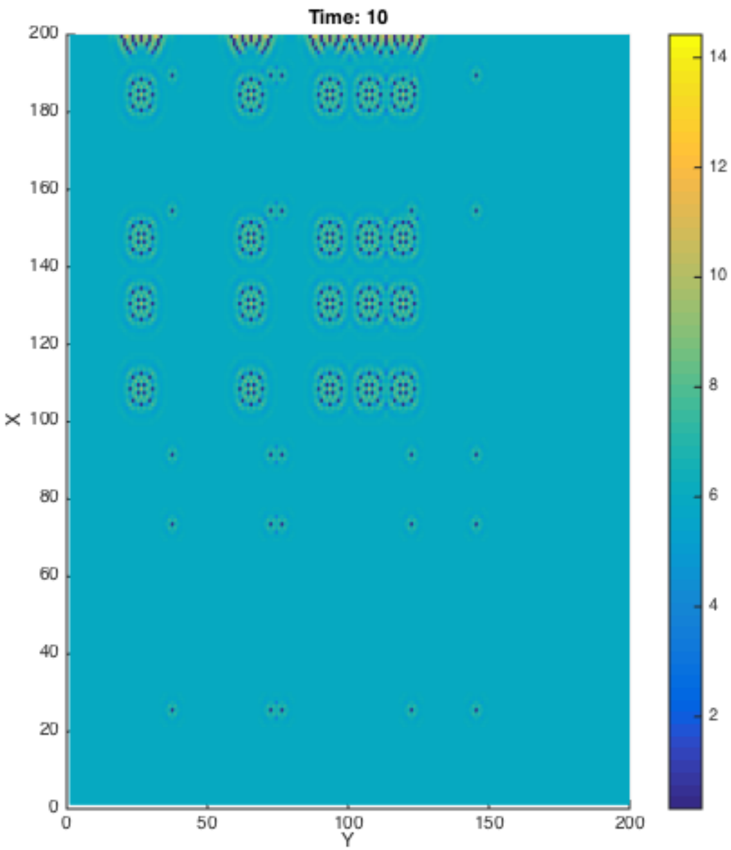


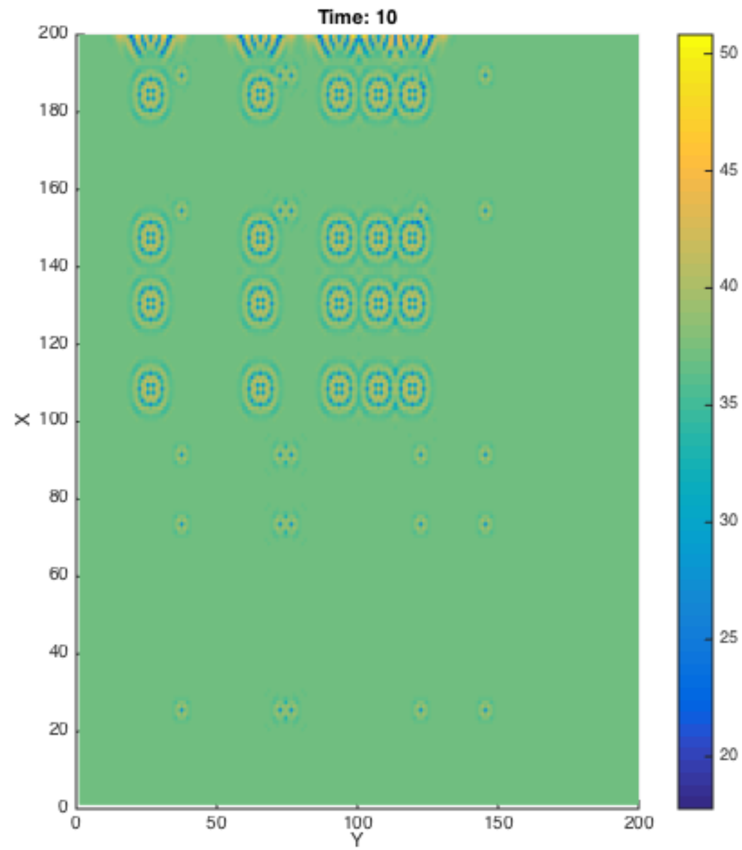
CDIMA and BZ chemical systems.

Wave instability

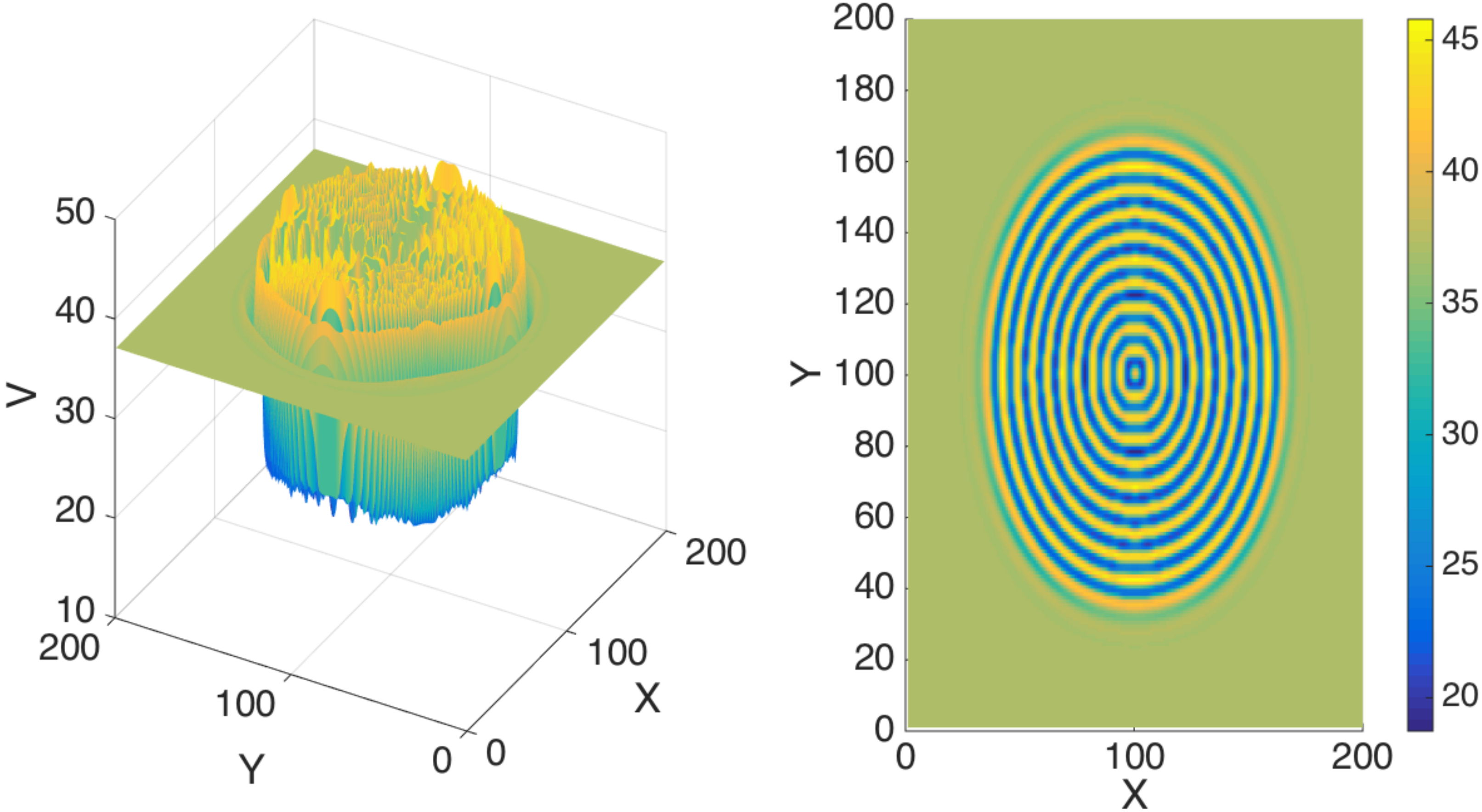


CDIMA reaction

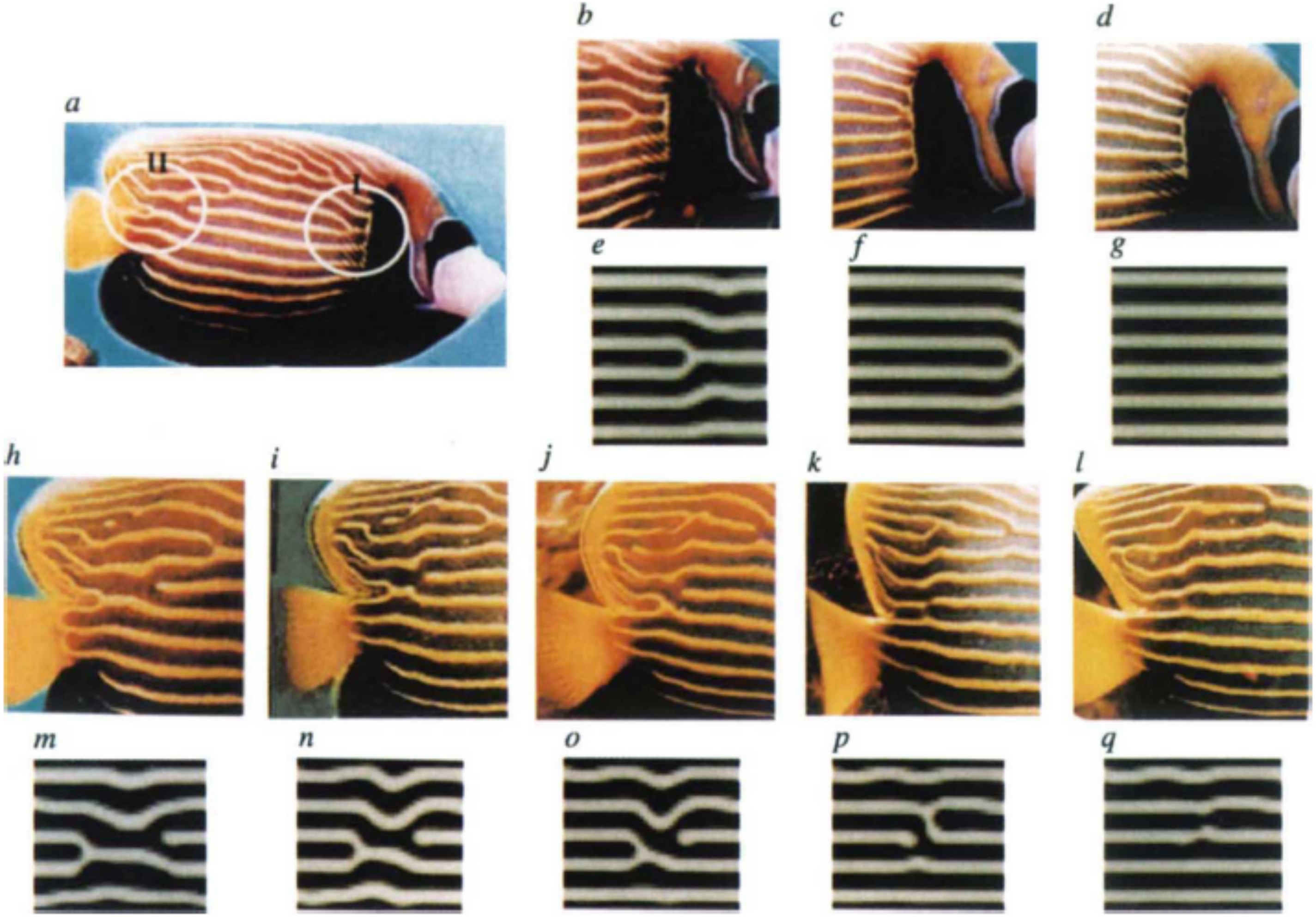




CDIMA reaction

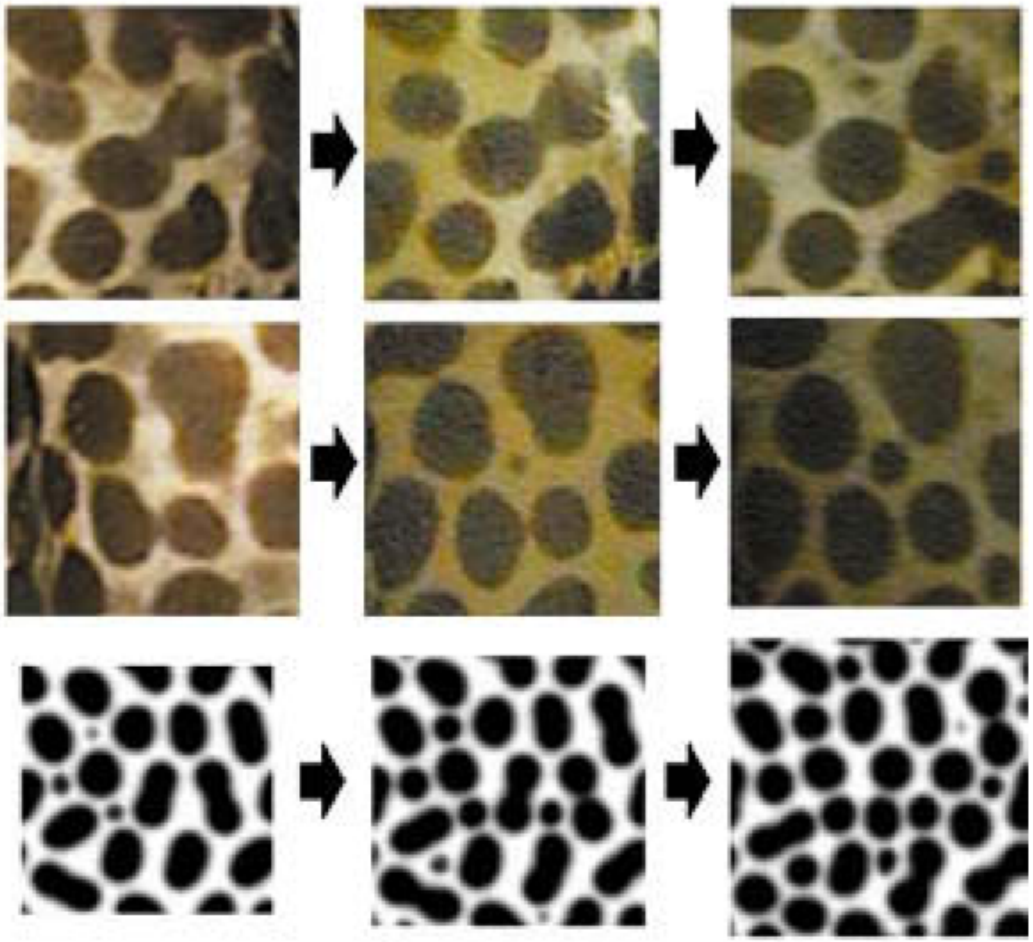


In real systems



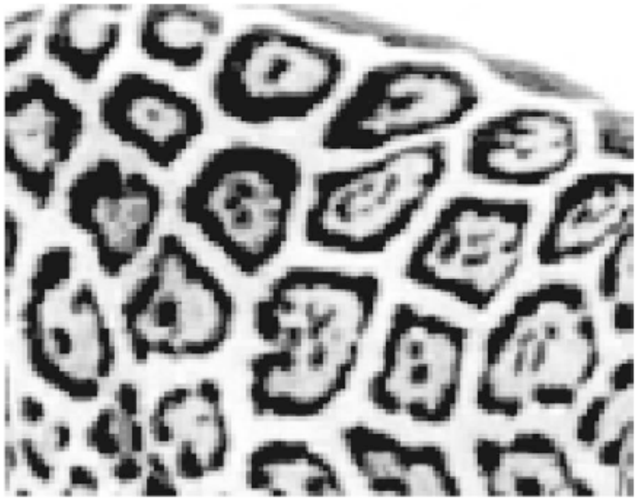
Kondo, S. and Asal, R., A reaction-diffusion wave on the skin of the marine angelfish *Pomacanthus*, Nature **376**, 765 (1995)

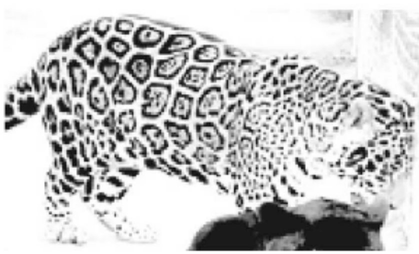
In real systems (catfish *Plecostoms*)

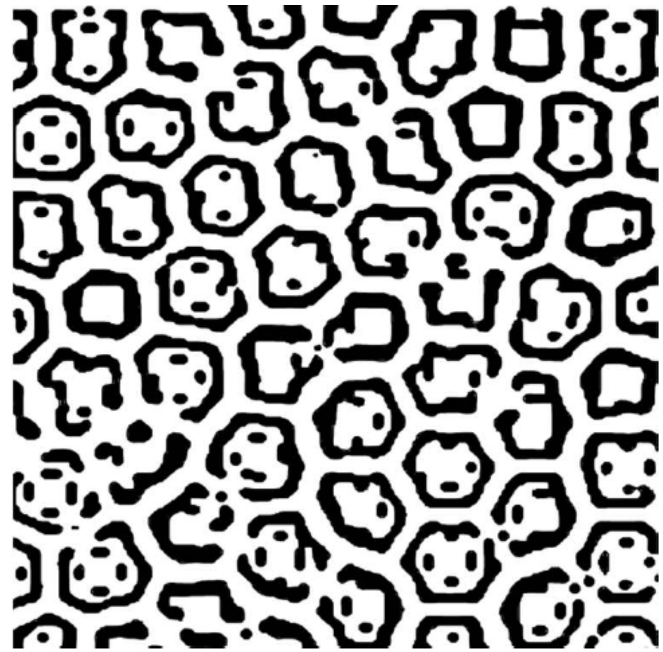


Kondo, S., The reaction-diffusion system: a mechanism for autonomous pattern formation in the animal skin**,** Genes to Cells **7**, 535 (2002).

In real systems (leopard)







Liu, R. T., Liaw, S. S., and Maini, P. K., Two-stage Turing model for generating pigment patterns on the leopard and the jaguar, Phys. Rev. E **74**, 011914 (2006).

References

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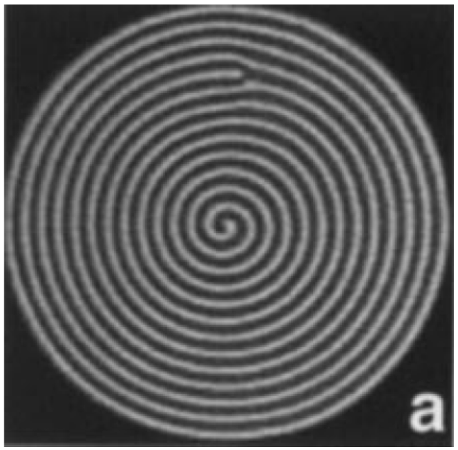
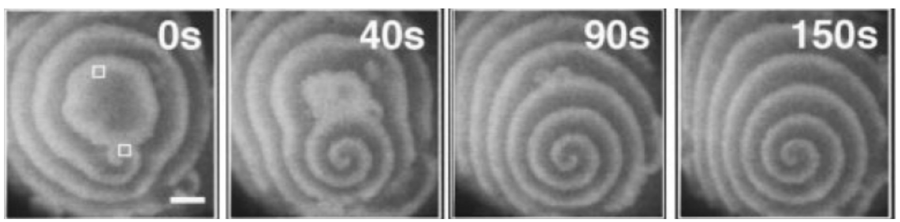
- A.M. Turing, The Chemical Basis of Morphogenesis, Phil. Trans. Royal Soc., 237, 641, pp. 37—72.

Appendix: spatial patterns

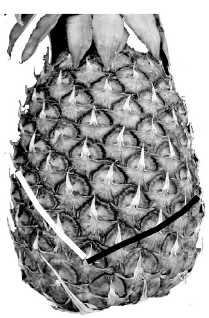
Waves in oscillatory media



<u>Spirals in hydrodynamics</u>.
E. Bodenschatz, W. Pesch, G. Ahlers. *Annu. Rev. Fluid Mech.* v. 32 (2000), 709

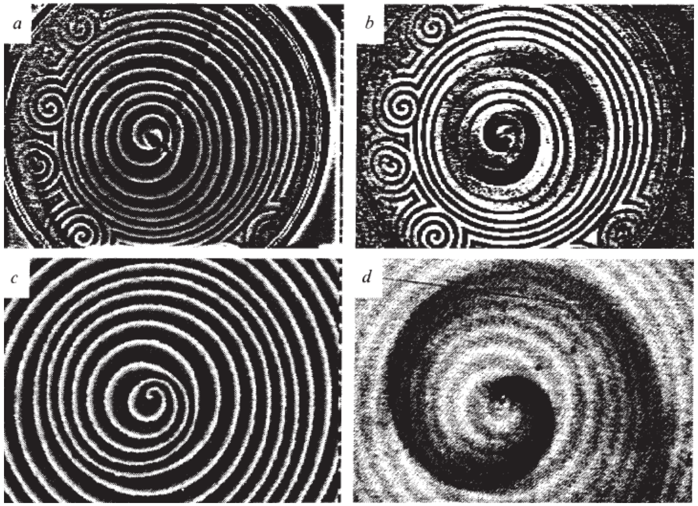


<u>Spirals in *Xenopus Laevis* oocytes</u>.
Scale bar = 100 μm.
J. D. Lechleiter, L. M. John, P. Camacho. *Biophys. Chem*. 72 (1998) 123.

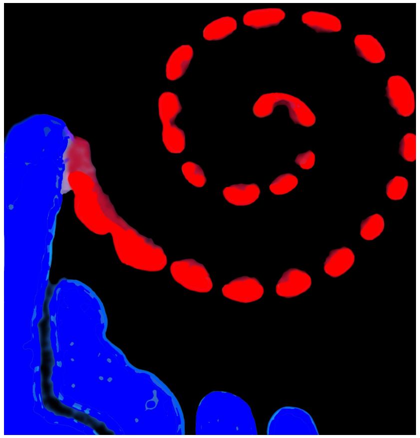


<u>Spirals in cones and pineapples</u>.
P. Atela, C. Golé, and S. Hotton, J. Nonlinear Sci. v.12 (2002) 641

Spirals

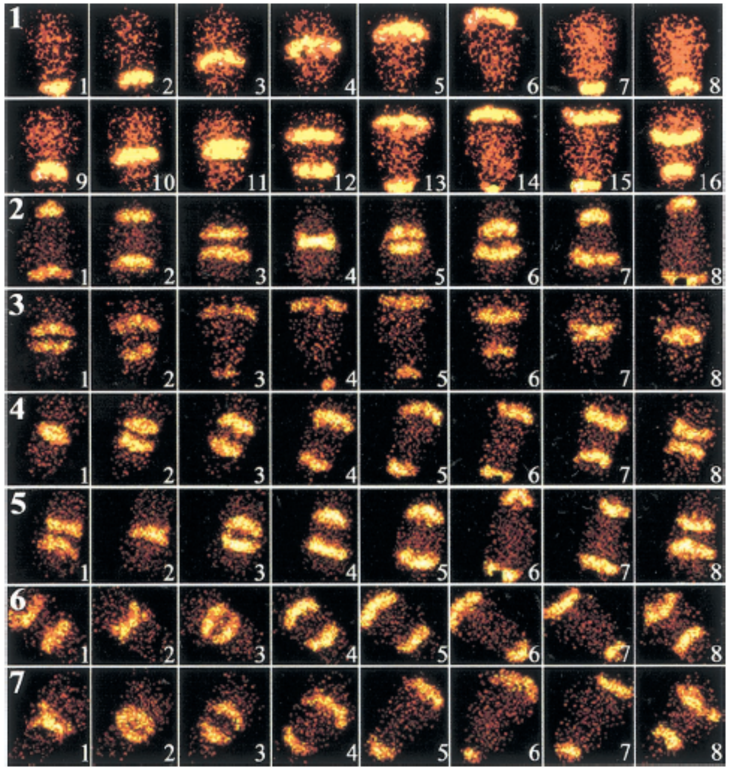


<u>Super spirals</u>.
Perez-Muñuzuri, V., Aliev, R., Vasiev, B., Perez-Villar, V. & Krinsky, V. I. *Nature* **353** (1991) 740



<u>Segmented spirals</u>.
V. K. Vanag and I. R Epstein, Proc. Natl. Acad. Sci. **100**, 14635 (2003).

“Genuine” waves



NAD(P)H waves in neutrophils. Freq. = 0.1 s. Zoom x980.
Wave speed is estimated about 15 μm/s.