
This cup is made from fully renewable resources

Week 8, Diffusion and Self Assembly

1/ Assembly instructions: Distributed pattern storage and self assembly

2/ Biology is 'small' - thermal energy matters! Behold - diffusion!

3/ Diffusion and self-assembly are paired at the hip

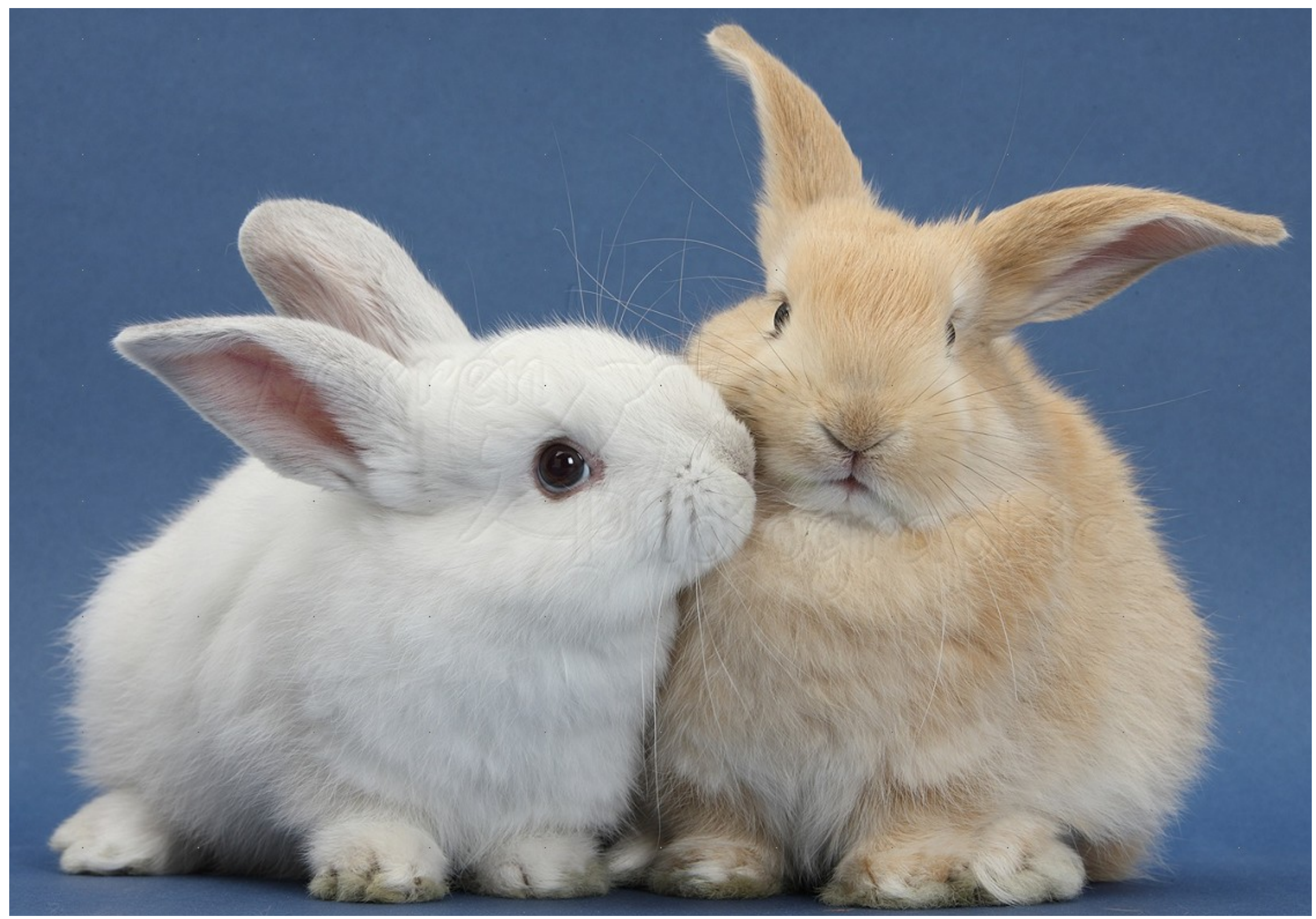
4/ Diffusion only

5/ Diffusion + Reaction

6/ Diffusion + Reaction + Logic

The fundamental mystery of living matter

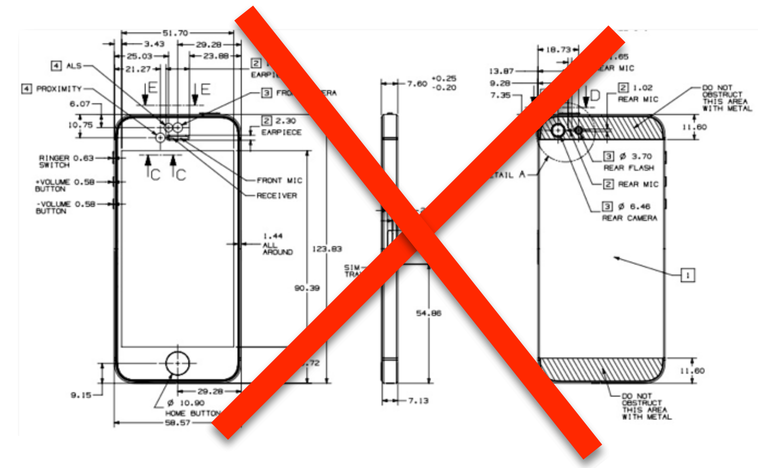
Something from soup (Patterns, Animals, Life…)



Forget macroscopic construction sites, orchestra conductors reading a score, etc.

~~Explicit and Concentrated Specification~~

```
void InitializeZebra( void )
{
   zebra_length        = 2.80; /*meters*/
   zebra_stripe_period = 0.18; /*meters*/
   zebra_stripe_color  Format(_T("Black"));
}
```



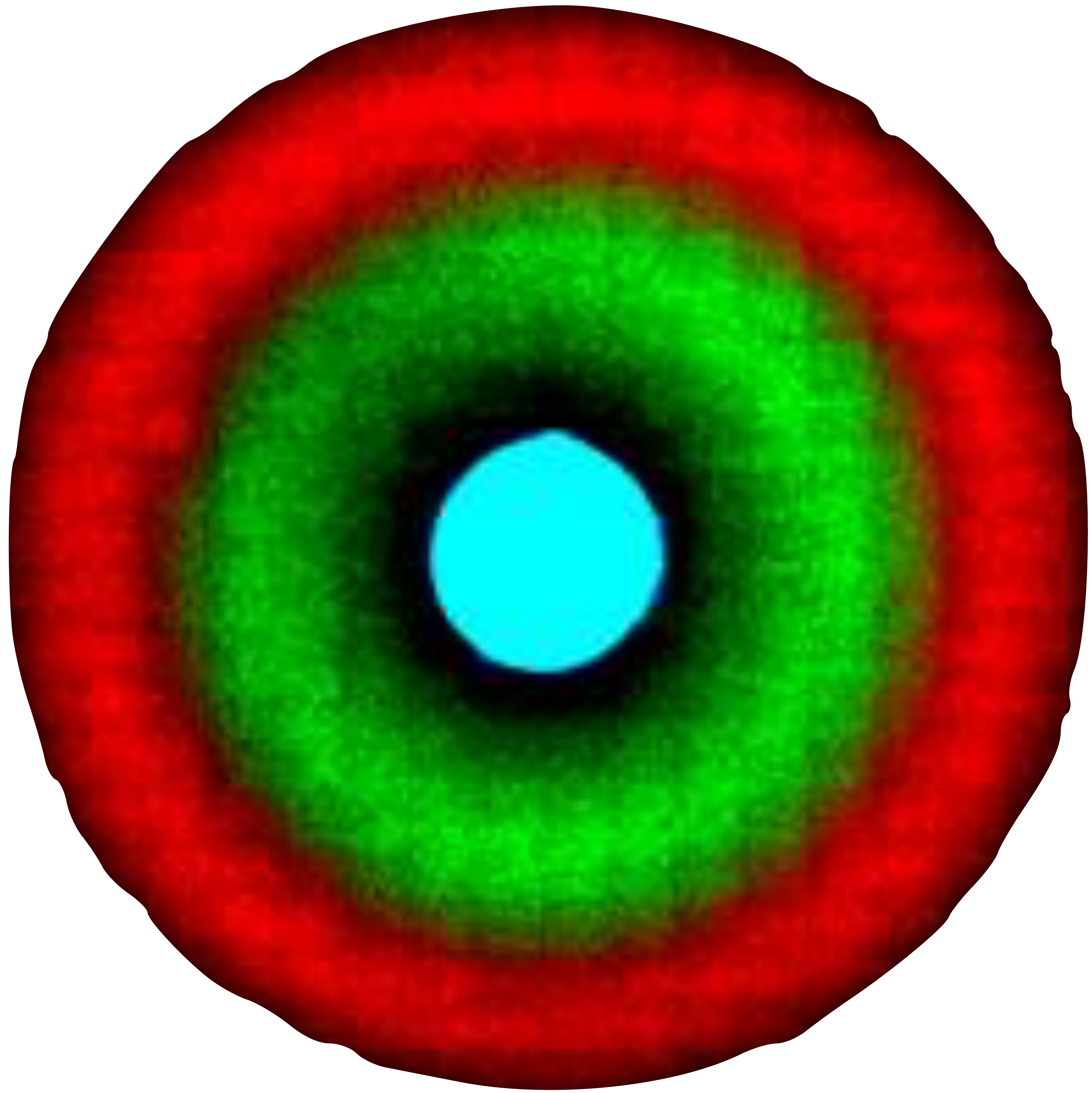
Implicit and Distributed

Hard to hack

Key question:

For a given pattern, where and how is it stored?

Your task - make me this thing with living matter



Thermal energy leads to Diffusion

Atomistic view:

All particles move due to thermal energy (1/2 k_BT per DOF)

Movement direction is random

True for everything but 1/2 k_BT is EXTREMELY SMALL so 'invisible' unless you are tiny!

Albert Einstein - worked out Stokes-Einstein equation in his Ph.D thesis for the diffusion coefficient of a "Stokes" particle undergoing Brownian Motion in a quiescent fluid at uniform temperature

Phenomenological view:

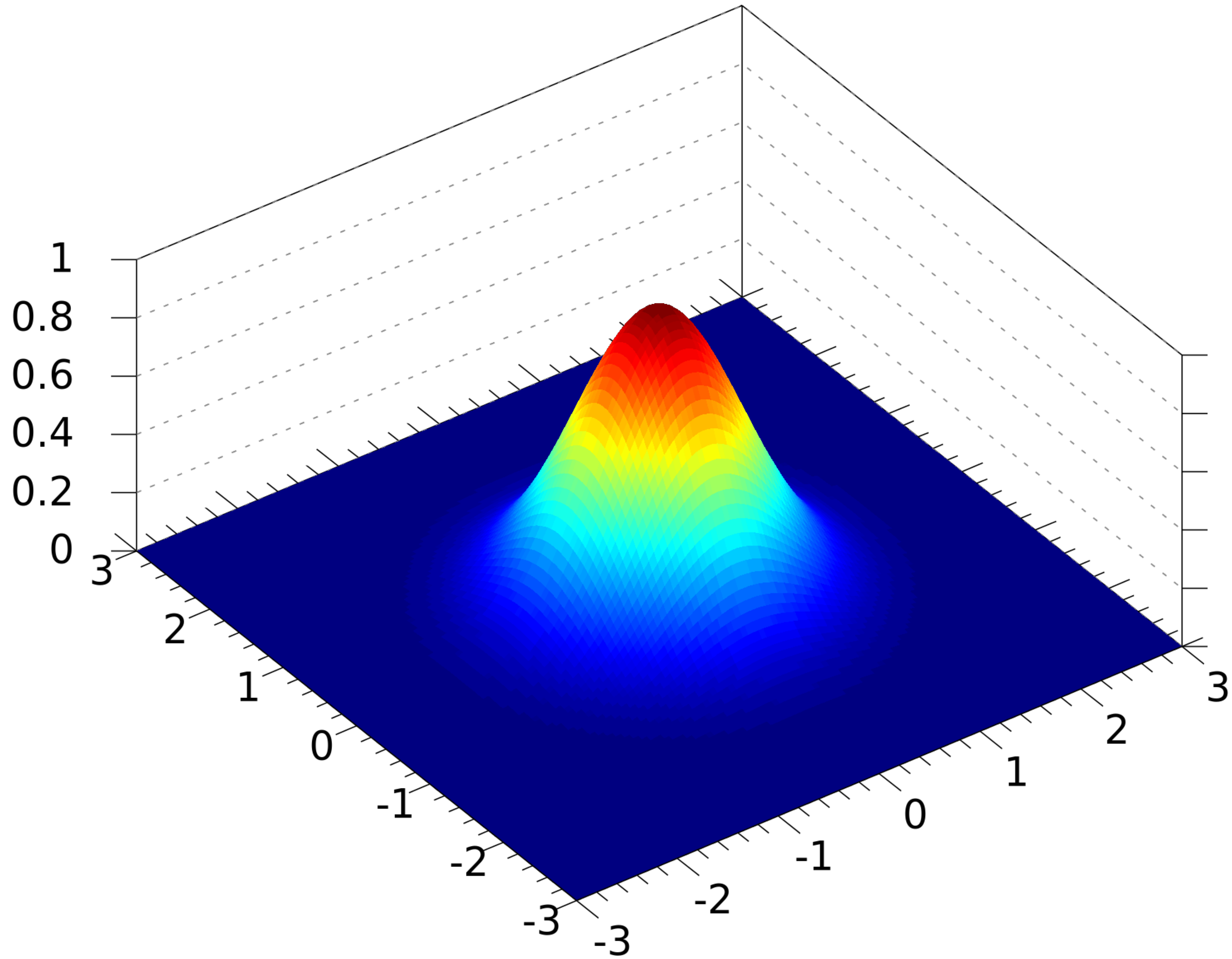
The diffusion flux is proportional to the negative gradient of concentrations

“Driving force” due to concentration difference, stuff moves until the concentration difference is zero.

Pattern at specific time T

$$P(r,t) = \frac{e^{\left(\frac{-r^2}{4D\cdot t}\right)}}{4\pi D\cdot t}$$

$$D = \frac{k_B T}{6\pi\eta \cdot R}$$



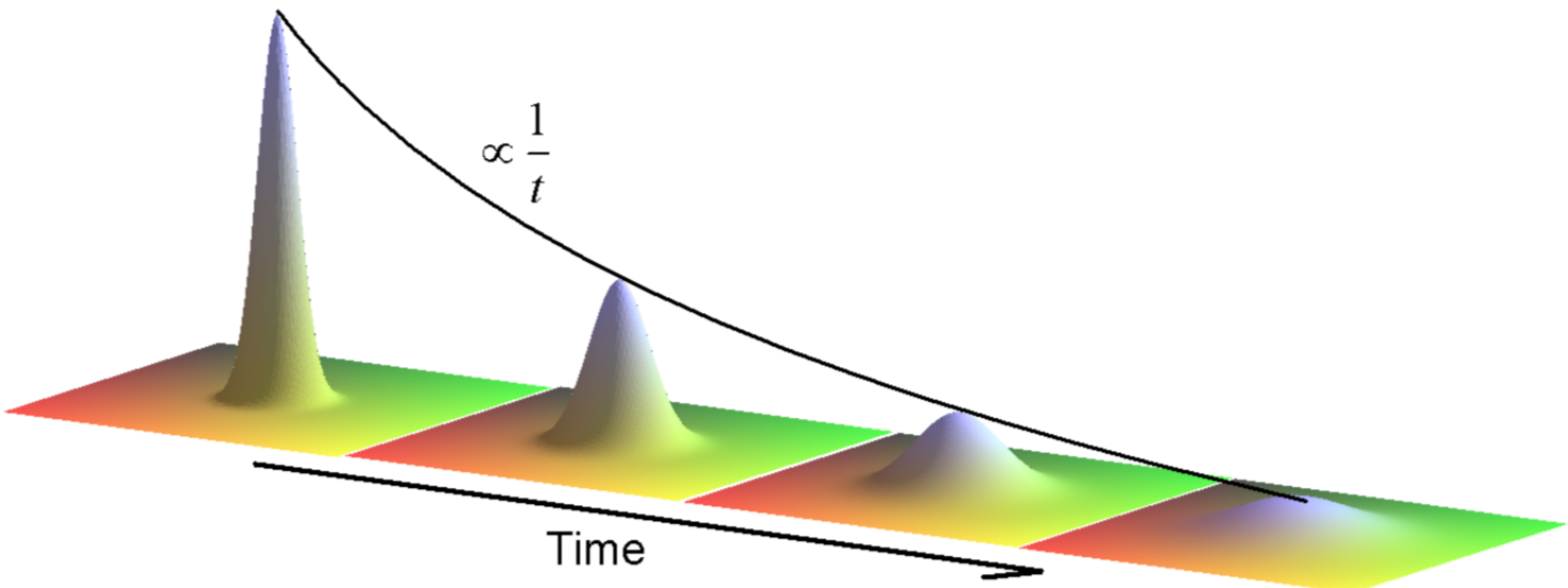
Further reading

http://www.rpgroup.caltech.edu/courses/aph162/2006/Protocols/diffusion.pdf

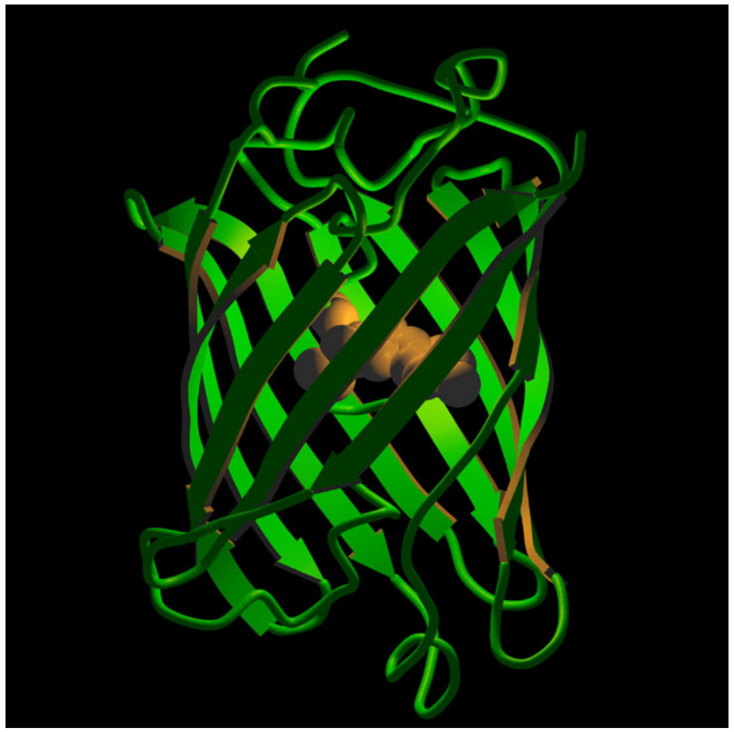
Pattern at changes over time

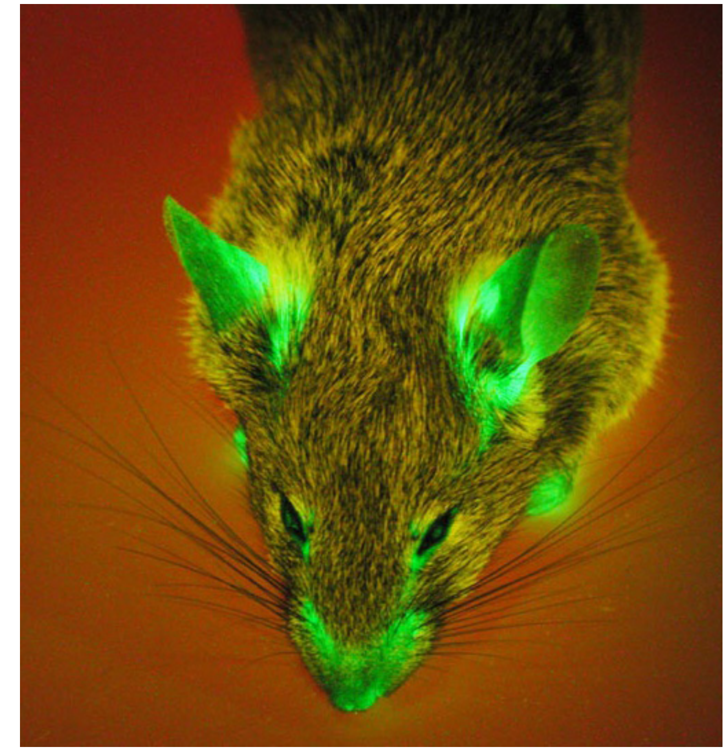
$$\boxed{P(r,t) = \frac{e^{\left(\frac{-r^2}{4D\cdot t}\right)}}{4\pi D\cdot t}}$$

$$\boxed{D = \frac{k_B T}{6\pi\eta\cdot R}}$$



Bigger proteins diffuse more slowly!





GFP

~238 aa

Sequences

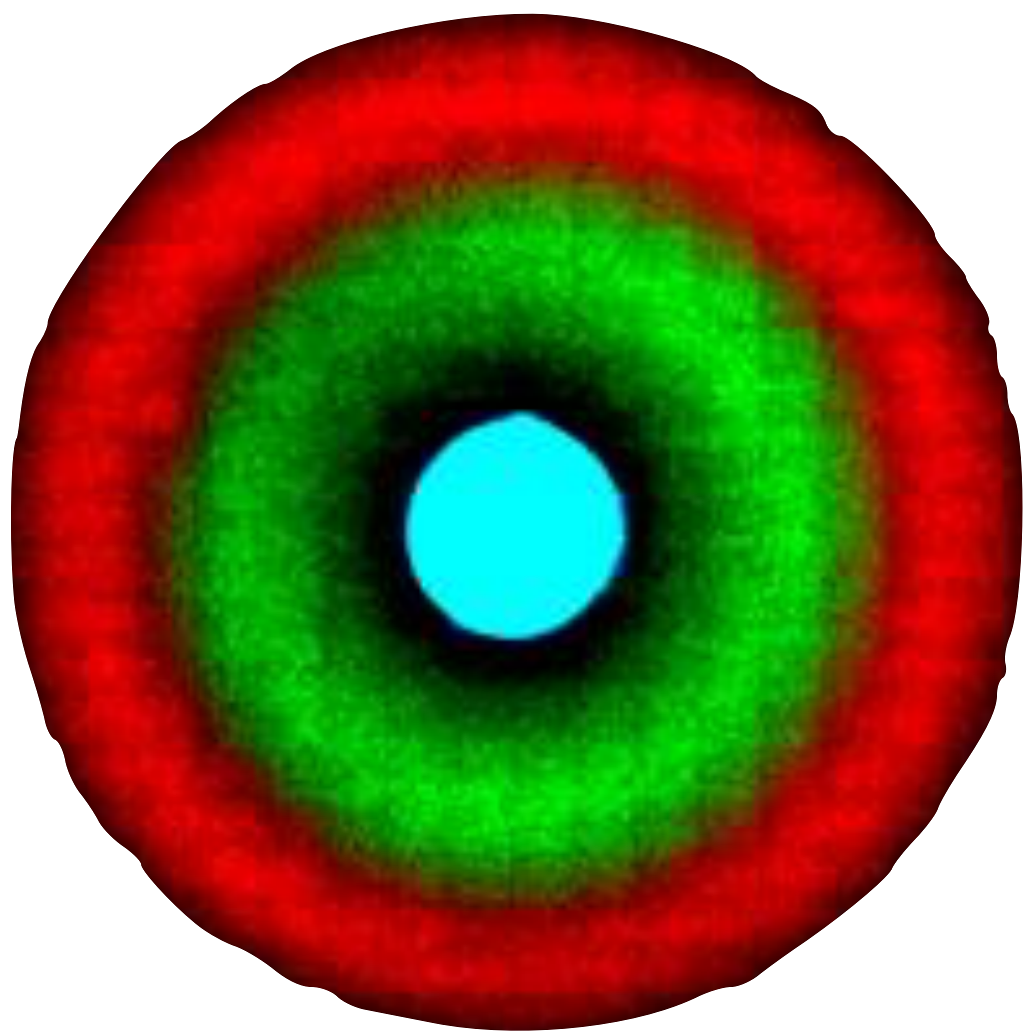
	Sequence		Length	Mass (Da)	Tools
☐	P42212 [UniParc]. Last modified November 1, 1995. Version 1. Checksum: EA5A6F21FBFB6E05	FASTA	238	26,886	Blast go

```
        10         20         30         40         50         60
MSKGEELFTG VVPILVELDG DVNGHKFSVS GEGEGDATYG KLTLKFICTT GKLPVPWPTL

        70         80         90        100        110        120
VTTFSYGVQC FSRYPDHMKQ HDFFKSAMPE GYVQERTIFF KDDGNYKTRA EVKFEGDTLV

       130        140        150        160        170        180
NRIELKGIDF KEDGNILGHK LEYNYNSHNV YIMADKQKNG IKVNFKIRHN IEDGSVQLAD

       190        200        210        220        230
HYQQNTPIGD GPVLLPDNHY LSTQSALSKD PNEKRDHMVL LEFVTAAGIT HGMDELYK
```

« Hide

Thought Experiment

Imagine you had a genome that encodes a **large green protein** and a **small red protein**, and the cell secretes these proteins. Which pattern will you get?



Implicit and Distributed

Hard to hack

Key question:

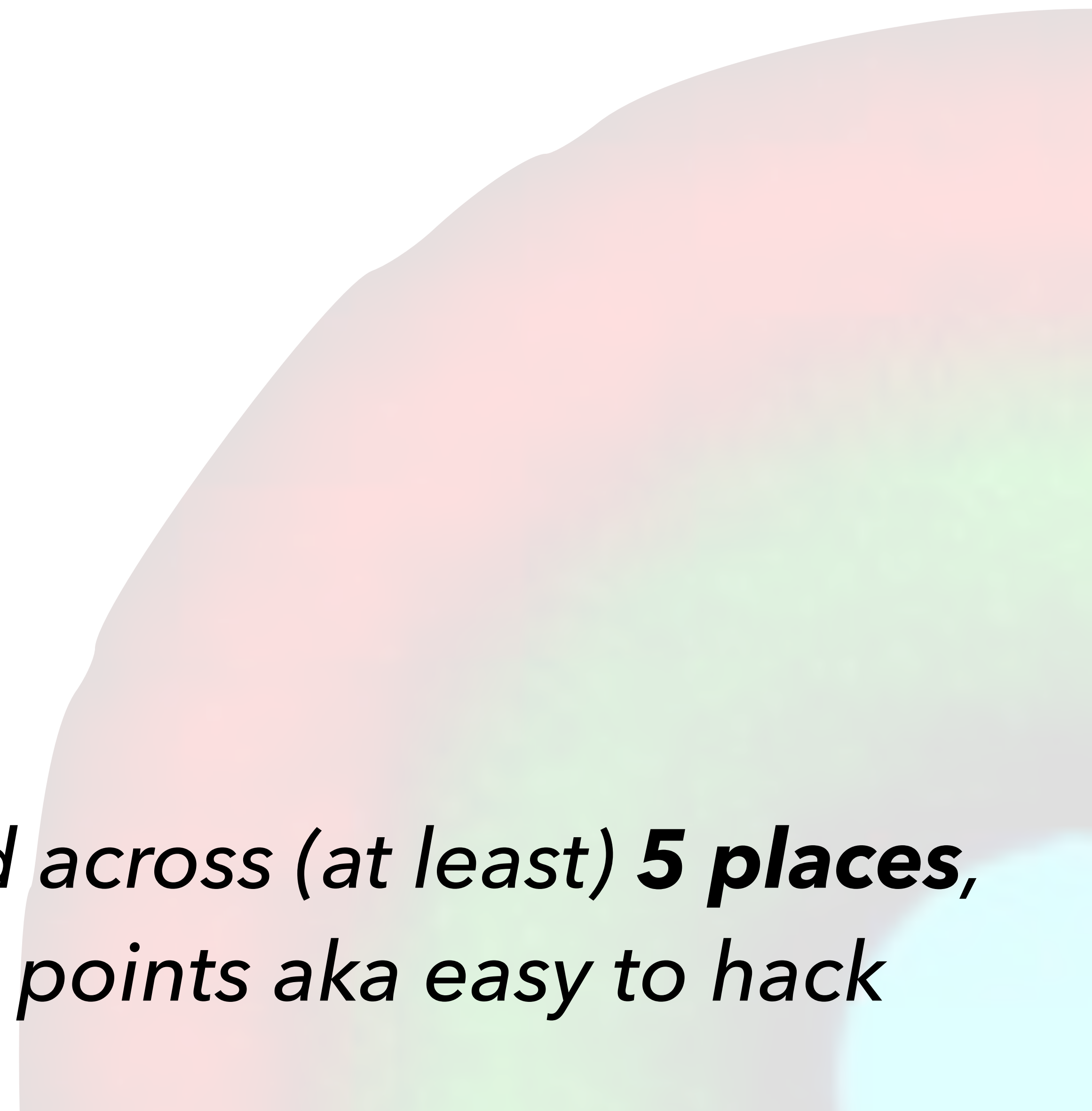
For a given pattern, where and how is it stored?

For a given pattern, where and how is it stored?

Protein size - **YES**
E.g. the green protein is 238 aa, and red protein is 450 aa
Relative protein sizes - **YES** - 238/450
Protein production rate - **YES** - for Green238 and Red450

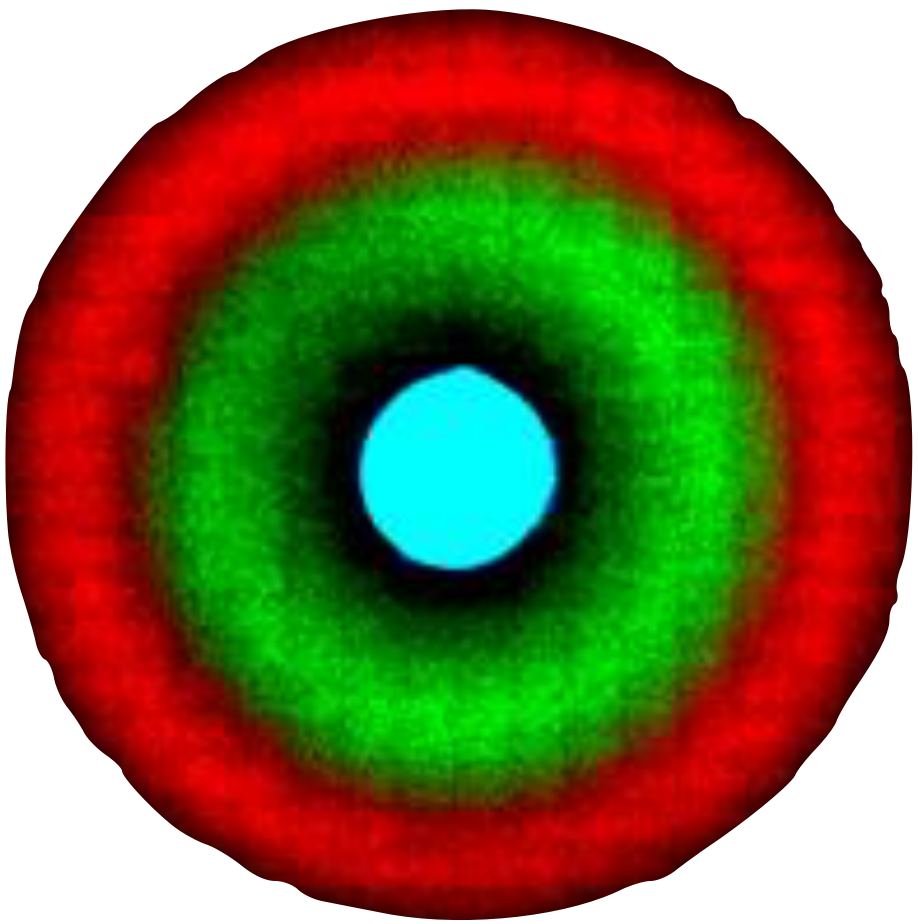
$$\boxed{D = \frac{k_B T}{6\pi\eta \cdot R}}$$

Temperature - **Yes**
Viscosity of water - **Yes**



Our simple bullseye pattern is stored across (at least) ***5 places****,*
three of which are good purchase points aka easy to hack

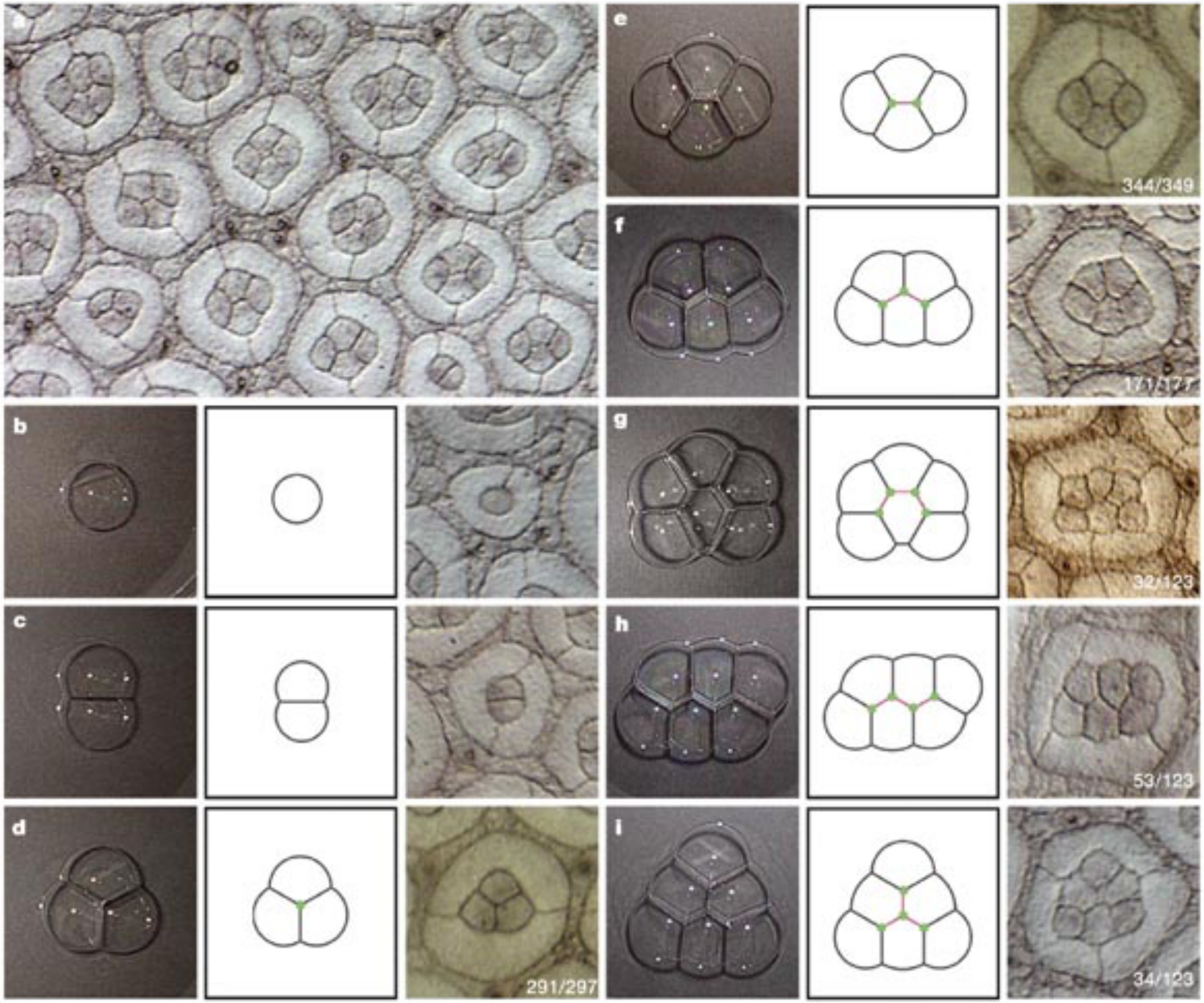
That was conceptually useful, but, there is no way you can tell me that diffusion, surface tension, + genome etc. can give more interesting patterns…



Nevermind…

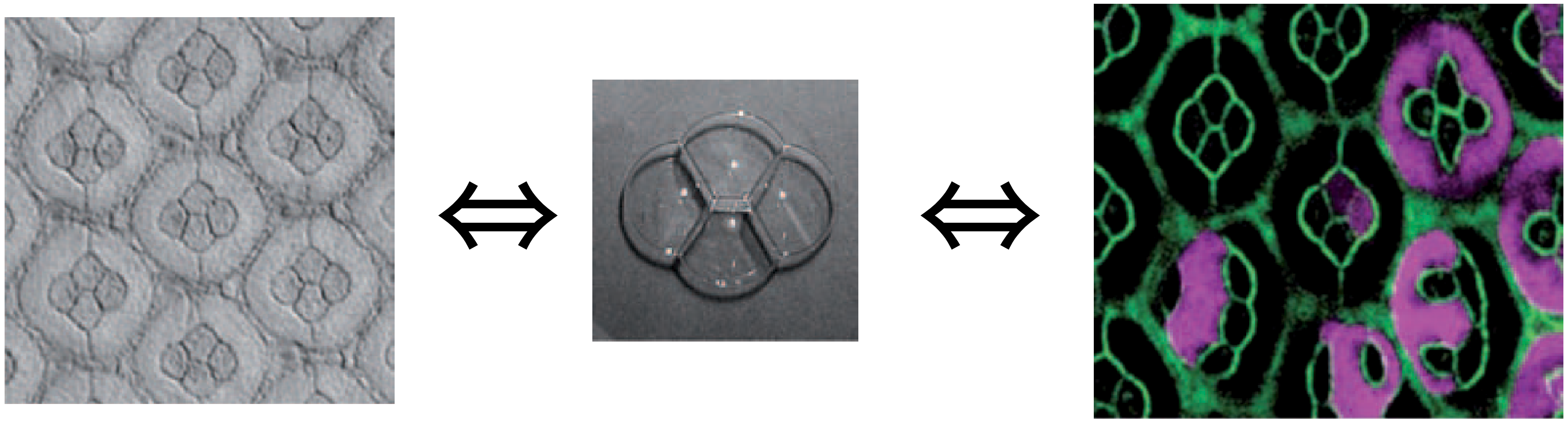
Surface mechanics mediate pattern formation in the developing retina

Takashi Hayashi & Richard W. Carthew



https://www.nature.com/nature/journal/v431/n7009/full/nature02952.html

More realistic expression
(and a taste of 21st century biology)



Physical modeling of cell geometric order in an epithelial tissue, S. Hilgenfeldt, S. Erisken, and RW. Carthew, *PNAS* (2008).

Energy functional ~ architecture

$$\boxed{\mathcal{E} = \boxed{\sum_i \frac{1}{2}\Delta_i^2 L_{0i}} - \boxed{\sum_{i,j} L_{ij}\gamma_E \delta_{i,E}\delta_{j,E} - \sum_{i,j} L_{ij}\gamma_N \delta_{i,N}\delta_{j,N}}}$$

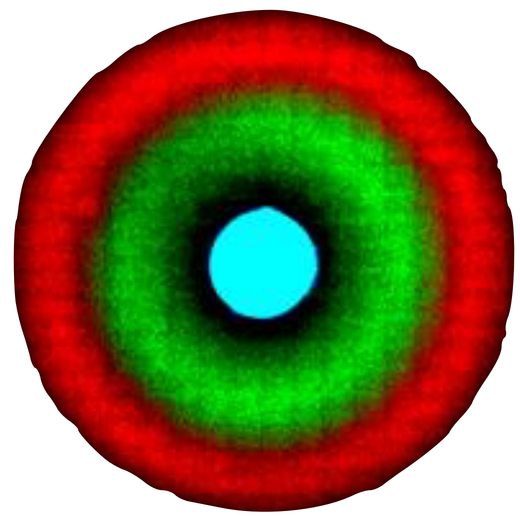
Membrane bending energy
straight out of physics/eng. textbook

E-cadherin and N-cadherin structural biology
Expression levels, noise, gene regulation
(transcription, translation, microRNAs, nuclear export)
Cancer genomics
Epigentics/Chromatin Architecture
Developmental Biology

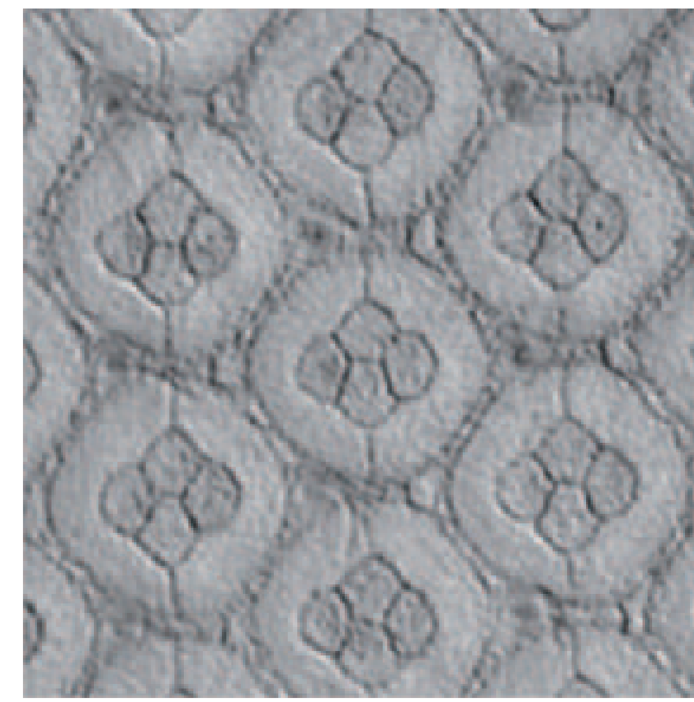
The fundamental mystery of living matter

Something from soup (Patterns, Animals, Life…)

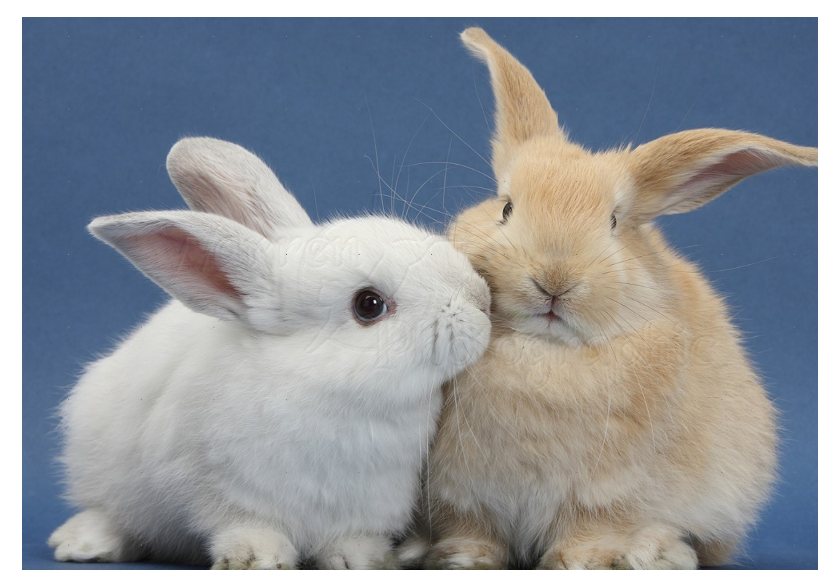
⇔



⇔



??? ⇔



The fundamental mystery of living matter

<u>Major limitations of patterns so far</u>

- ★ Not permanent/stable - change with time, and vanish at t = Inf
- ★ Cover only one length scale
- ★ Are radially symmetric - good for eyes, spheres, and donuts….

<u>What are we missing?</u>

You already answered this last time - *what if the components could react*?

Stick together, create products, degrade one another,…

Stripes, swirls, and dots

Turing patterns

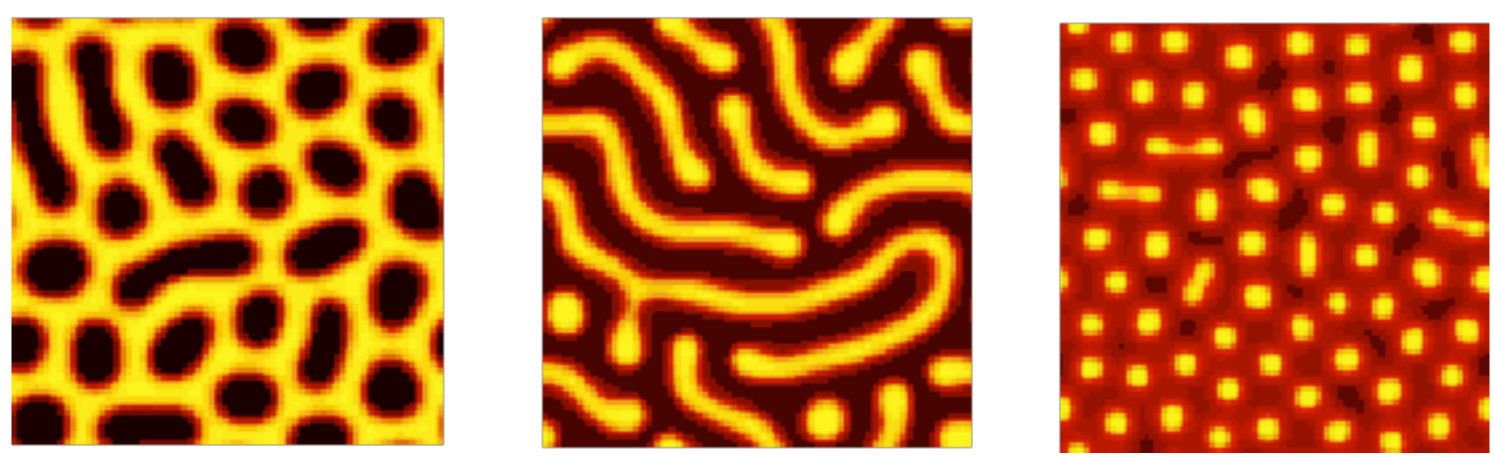
Chemical morphogenesis (Turing, 1952):

• A system of reacting and diffusing chemical species can spontaneously form stationary spatial patterns given a certain set of chemically plausible mechanisms.

• Two reacting chemical species that diffuse at very different rates.

• The system is an intrinsically non-equilibrium; both substances are continuously created (by the cells) at every point in space, and also decay or are removed at specified rates.

• In these reactions the activator makes more activator and inhibitor, and the inhibitor destroys the activator.



Erik M. Rauch and Mark M. Millonas, J. Theoretical Biology

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.

This will not be on an exam and not be in a problem set.

Reaction-diffusion equations

$$
\begin{aligned}
U_t &= D_U \Delta U + f(U,V), \\
V_t &= D_V \Delta V + g(U,V).
\end{aligned}
$$

“The Chemical Basis of Morphogenesis”, Alan Turing (1952 *Phil. Trans. Roy. Soc.*)

This will not be on an exam and not be in a problem set.

Reaction-Diffusion Equation (1)

$$U_t = D_U \Delta U + f(U,V),$$
$$V_t = D_V \Delta V + g(U,V).$$

Reaction Equation (2)

$$U_t = f(U,V),$$
$$V_t = g(U,V).$$

A constant solution u(t,x)=u0, v(t,x)=v0 can be a stable solution of (2), but an unstable solution of (1). *Thus the instability is induced by diffusion*.

Or more simply - if you combine reaction with diffusion, you can generate instabilities - you do not need an external agent to provide lighting bolt.

This will not be on an exam and not be in a problem set.

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.

Two morphogens are considered. They will be called X and Y, and the same letters will be used for their concentrations. This will not lead to any real confusion. The diffusion constant for X will be assumed to be 5×10^{-8} cm^2/s and that for Y to be 2.5×10^{-8} cm^2/s. With cells of diameter 0.01 cm this means that X flows between neighbouring cells at the rate 5×10^{-4} of the difference of X-content of the two cells per second.

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.

The reactions postulated are

$$
\begin{aligned}
Y + X &\rightarrow W, \\
W + A &\rightarrow 2Y + B \quad \text{instantly}, \\
2X &\rightarrow W, \\
A &\rightarrow X, \\
Y &\rightarrow B, \\
Y + C &\rightarrow C' \quad \text{instantly}, \\
C' &\rightarrow X + C.
\end{aligned}
$$

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.

$$\begin{array}{rl} Y+X \rightarrow W & \text{at the rate } \frac{25}{16} YX, \\ 2X \rightarrow W & \text{at the rate } \frac{7}{64} X^2, \\ A \rightarrow X & \text{at the rate } \frac{1}{16} \times 10^{-3} A, \\ C' \rightarrow X+C & \text{at the rate } \frac{55}{32} \times 10^{+3} C', \\ Y \rightarrow B & \text{at the rate } \frac{1}{16} Y. \end{array}$$

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.

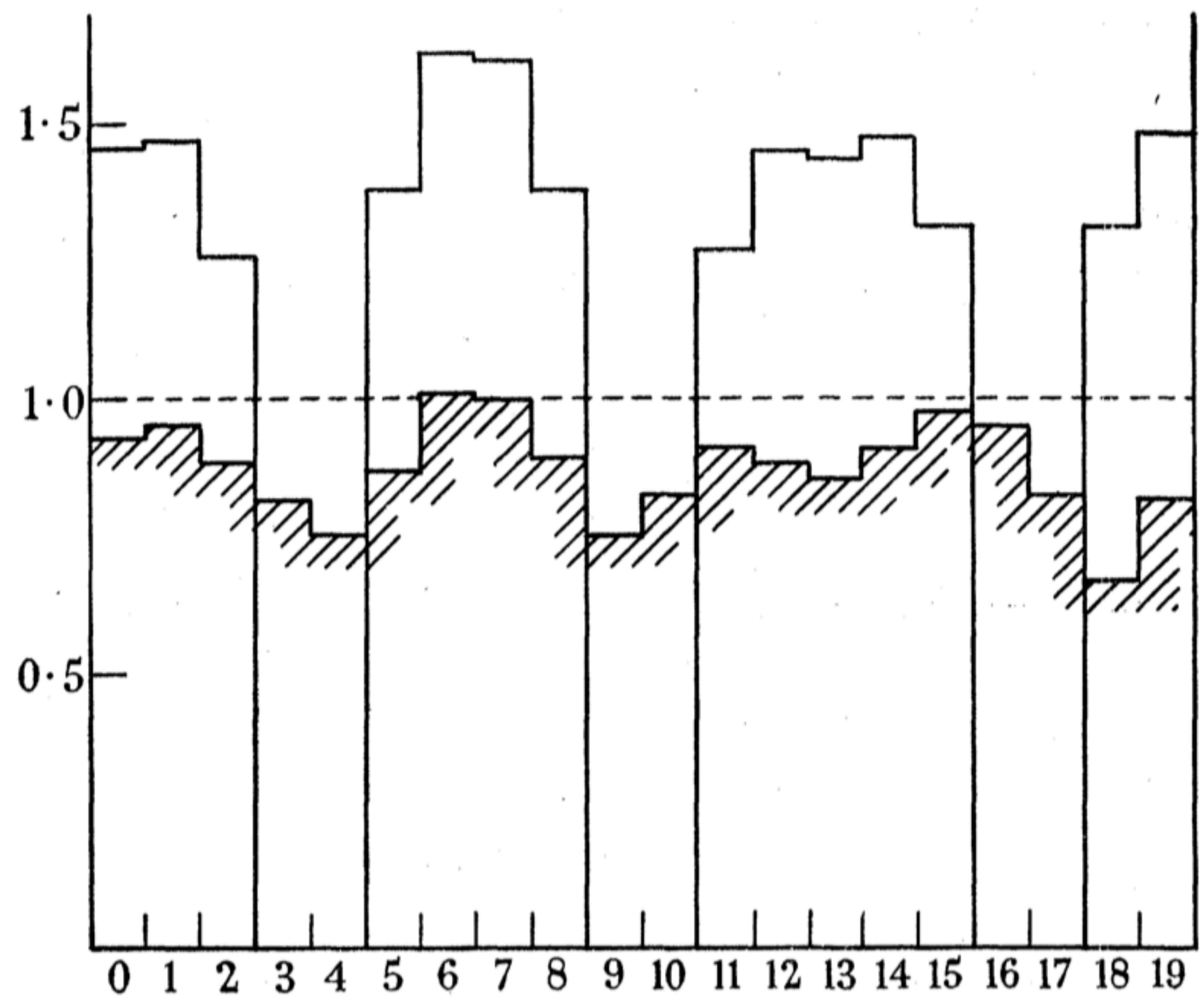


FIGURE 3. Concentrations of Y in the development of the first specimen (taken from table 1). ------- original homogeneous equilibrium; ////// incipient pattern; ——— final equilibrium.

Turing patterns

Unfortunately, the math in this paper is not so easy - you will feel more comfortable with this as senior than today. BUT - at least this way, you know *why* it's good to take math classes.

This will not be on an exam and not be in a problem set.


MAD-MONSTERS.COM

Turing patterns

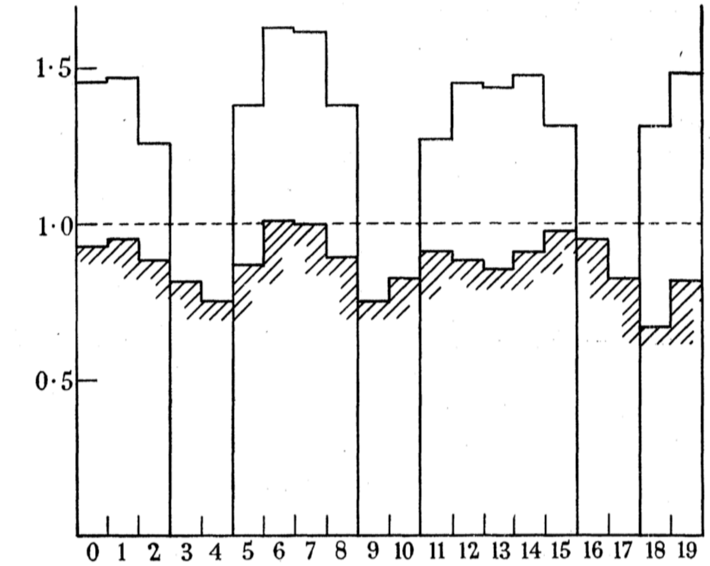


FIGURE 3. Concentrations of Y in the development of the first specimen (taken from table 1). ------- original homogeneous equilibrium; ////// incipient pattern; ——— final equilibrium.

1/ You do not need bolt of electricity to "activate" Frankenstein

2/ If a system has both reaction and diffusion, you can get instabilities, triggered by random small disturbances. Then, 2D and 3D patterns form. No lightning needed. The system "wakes up" all by itself.

3/ Can generate static 2D and 3D patterns, but also dynamic 2D and 3D movies.

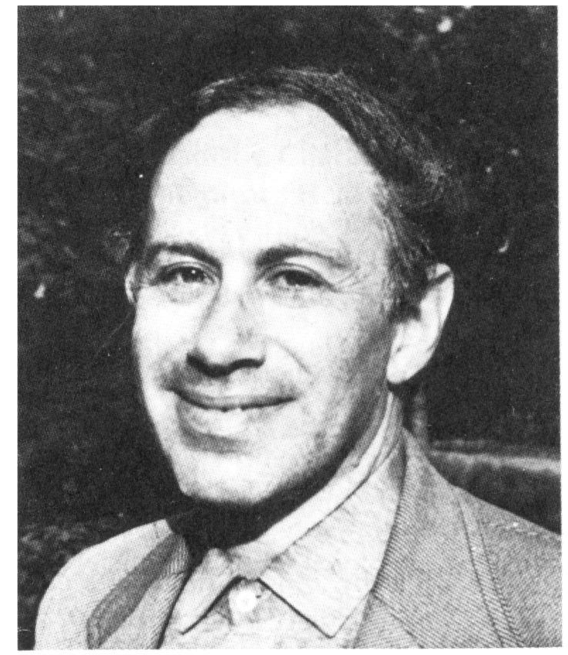
Waves in the Belousov-Zhabotinsky reaction

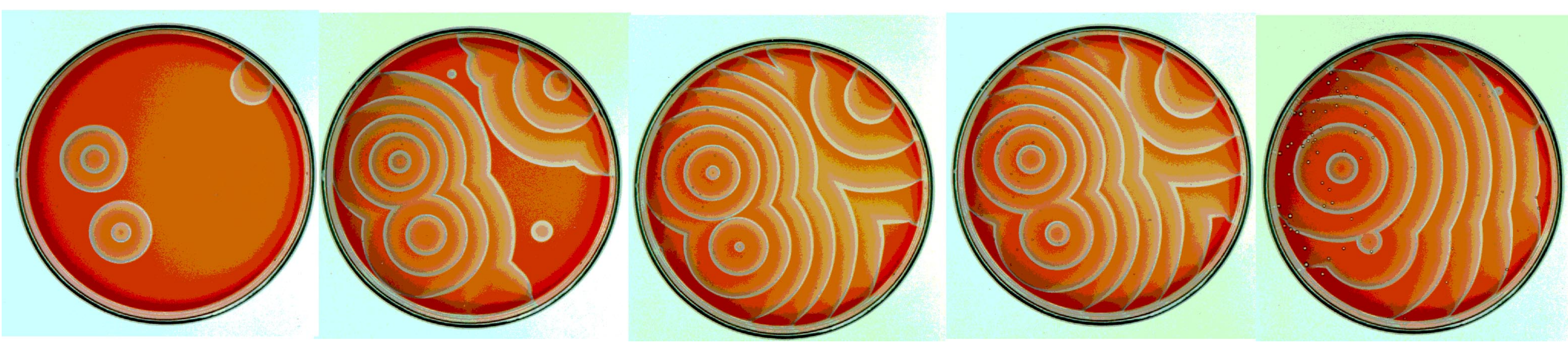
Boris P. Belousov

(Soviet Union, 1951,left)

Anatol M. Zhabotinsky

(Soviet Union, 1961,right)





Chemical reactions can be oscillatory (periodic)!

Implicit and Distributed

Hard to hack

Key question:

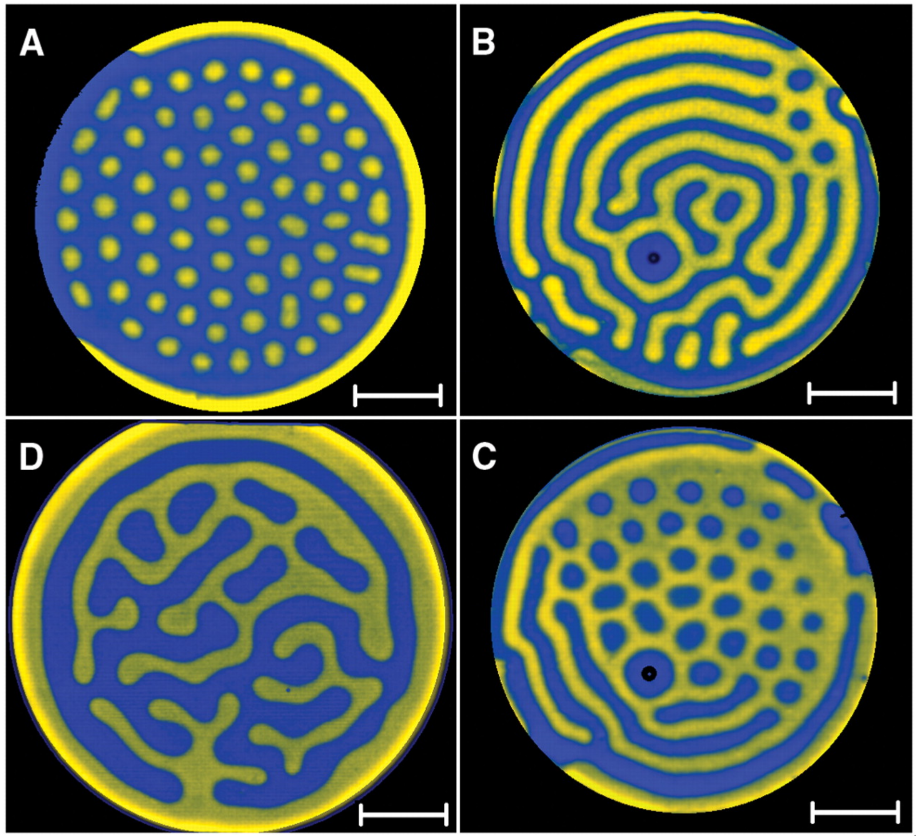
For a given pattern, where and how is it stored?

For a given pattern, where and how is it stored?

Protein size - **YES**
Number of distinct types of proteins - YES
Reaction Network - YES
Reaction Rates - YES
Initial concentrations - YES
Synthesis Rates - YES
Shape of enclosing dish - YES

$$\boxed{D = \frac{k_B T}{6\pi\eta \cdot R}}$$

Temperature - **Yes**
Viscosity of water - **Yes**



A typically biological 2D, in this framework, is stored across (at least) 9 ***places****, two of which are good purchase points aka easy to hack, 5 are ok, and two are poor*


"Biology"
"Programmable Reaction diffusion system"

Week 8, Diffusion and Self Assembly

1/ Assembly instructions: Distributed pattern storage and self assembly

2/ Biology is 'small' - thermal energy matters! Behold - diffusion!

3/ Diffusion and self-assembly are paired at the hip

<u>4/ Diffusion only</u>

<u>5/ Diffusion + Reaction</u>

<u>6/ Diffusion + Reaction + Logic</u>