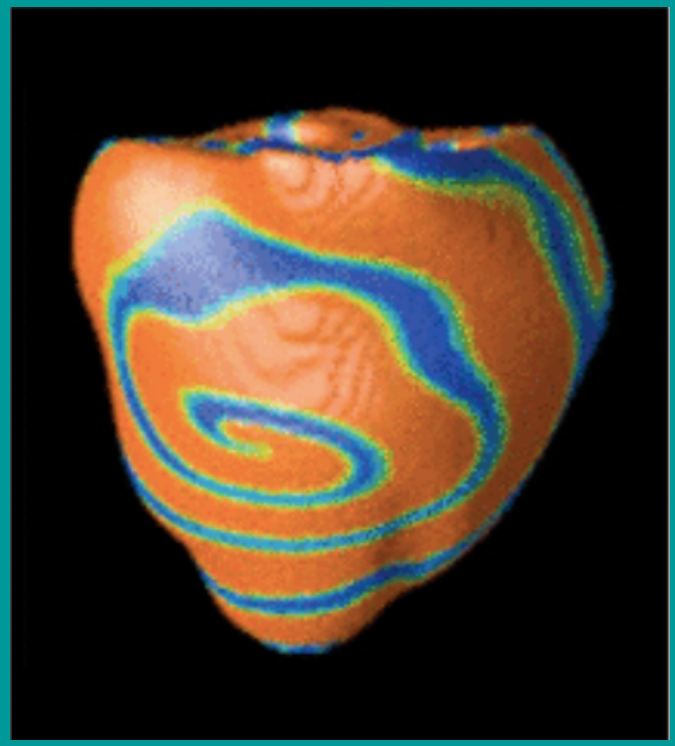
Sistemas de reacción-difusión

Dinámica espacio-temporal, patrones.

https://www.youtube.com/watch?v=0cgaUm5LPcU

https://www.youtube.com/watch?v=JOJ3ryFtMBw



Describen la variación en la concentración de especies que difunden y reaccionan con otras.

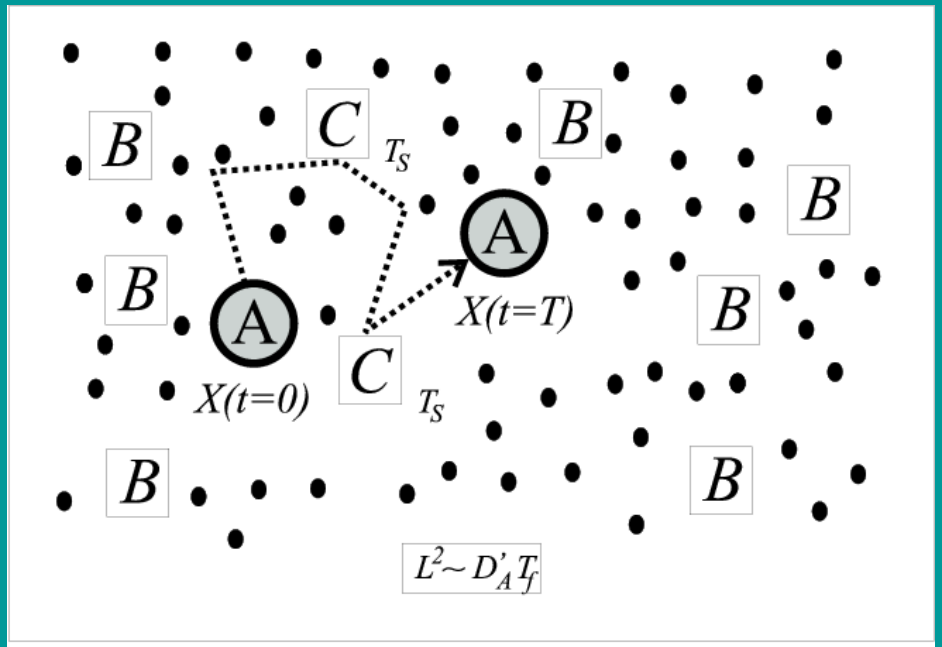


Figure 1 (b)

$$\mathrm{A} + \mathrm{B} \underset{k'}{\overset{k}{\rightleftharpoons}} \mathrm{C}$$

Dada la reacción

$$\mathrm{A} + \mathrm{B} \underset{k'}{\overset{k}{\rightleftharpoons}} \mathrm{C}$$

Las ecuaciones

$$\frac{d[A]}{dt} = -k[A][B] + k'[C]$$

$$\frac{d[B]}{dt} = -k[A][B] + k'[C]$$

$$\frac{d[C]}{dt} = k[A][B] - k'[C]$$

describen la variación de las concentraciones suponiendo que no varían en el espacio.

La ecuación de diffusion describe la variación de la concentración en el espacio y en el tiempo debido al transporte (difusivo) de las partículas cuya concentración describe la ecuación:

$$\frac{\partial [A]}{\partial t} = D_A \nabla^2 [A]$$

Las ecuaciones de reacción-difusión describen la variación local (punto a punto en el espacio) de las concentraciones debido al transporte difusivo de las partículas y las reacciones entre ellas.

$$\mathrm{A} + \mathrm{B} \underset{k'}{\overset{k}{\rightleftharpoons}} \mathrm{C}$$

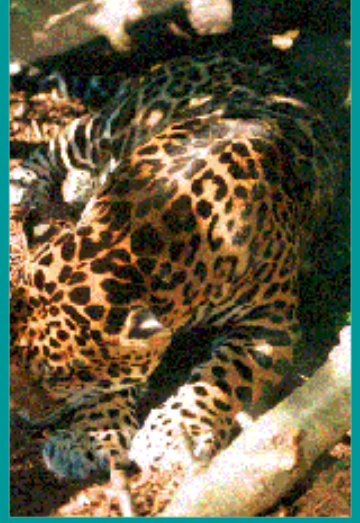
$$\frac{\partial [A]}{\partial t} = D_A \nabla^2 [A] - k[A][B] + k'[C]$$

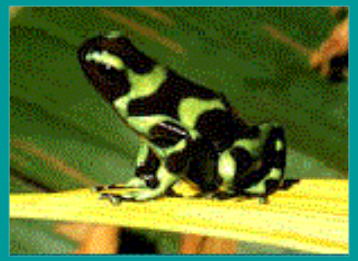
$$\frac{\partial [B]}{\partial t} = D_B \nabla^2 [B] - k[A][B] + k'[C]$$

$$\frac{\partial [C]}{\partial t} = D_C \nabla^2 [C] + k[A][B] - k'[C]$$

[A], [B] y [C] son funciones de la posición y del tiempo. [A][B] significa [A](x,y,z,t) [B](x,y,z,t) (encuentro en el mismo punto espacial descripción.

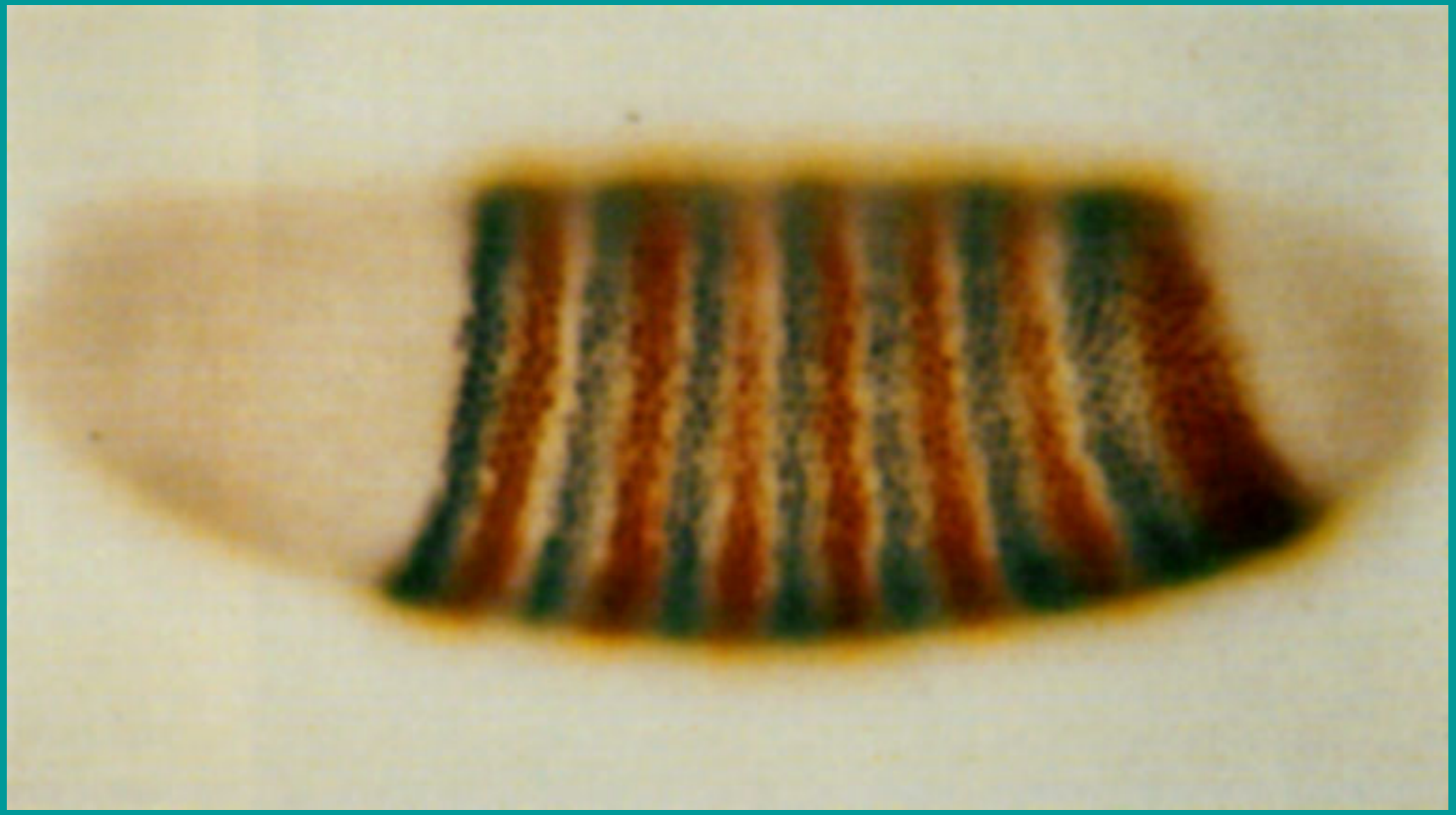
Pueden describer patrones (pattern)





Que hay en todas partes!

Estacionarios o variables en el tiempo



How does structure arise from an unpatterned background?
How do cells differentiate?

One of the first persons that tried to address this question, from a mathematical point of view, was: **Alan Turing** who came up with a simple model that could explain the apperance of structure in a spatially homogeneous system.

He proposed that a reaction-diffusion system in which species diffused at unequal rates could develop stationary patterns.

Turing, A.M. (1952).
The chemical basis of morphogenesis.
Phil. Trans. Roy. Soc. London *B* **237**: 37

Alan W. Turing

- "universal machine" (1935)
  (finite automata)
- "B-type unorganized machine" (1948)
  (neural network)
- "Chemical morphogenesis" (1952)
  (reaction-diffusion instability)

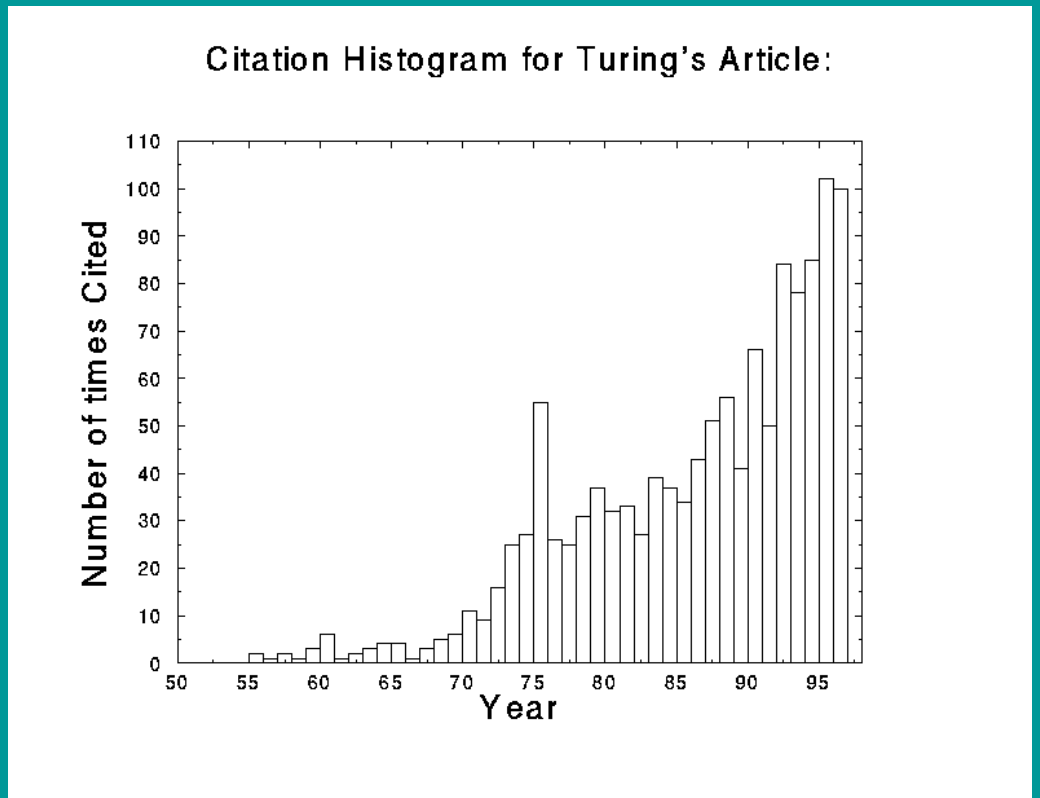
be regarded by one man as organised and by another as unorganised.

A typical example of an unorganised machine would be as follows. The machine is made up from a rather large number N of similar units. Each unit has two input terminals, and has an output terminal which can be connected to the input terminals of (0 or more) other units. We may imagine that for each integer r, $1 \leq r \leq N$ two numbers $i(r)$ and $j(r)$ are chosen at random

Breaking the Codebook of Nature

(fde una vieja página "The Alan Turing Home Page", mantenida por Andrew Hodges. Ahora: https://www.turing.org.uk/).

Alan Turing's programme for mathematical biology was so far ahead that only in the 1980s did computers really become fast enough to do justice to what he had in mind. Even now, people are investigating models not much more complicated than those he set out.



Compiled by J. E. Pearson, LANL

Reaction-diffusion model

Turing, A.M. (1952). "The chemical basis of morphogenesis".
Phil. Trans. Roy. Soc. London *B* **237**: 37

$$\frac{\partial a}{\partial t} = F(a,b) + D_a \nabla^2 a$$

$$\frac{\partial b}{\partial t} = G(a,b) + D_b \nabla^2 b$$

reaction diffusion

a,b: concentrations of chemicals that can react and diffuse in a solution

Conditions for Turing patterns

About the system:

- One of the chemicals, a, is an activator, and the other, b, an inhibitor
- The inhibitor diffuses faster than the activator, $D_a < D_b$ or equivalently, $d = D_b / D_a > 1$

About the solutions:

- There is a stationary and uniform solution of these equations: (a^*, b^*)
- (a^*, b^*) is stable for $d < d_c$ and becomes unstable for $d > d_c$ $(d_c > 1)$

This bifurcation corresponds to the appearance of a Turing pattern, when the instability is such that the fastest growing mode has finite wavelength and zero frequency. This can occur for systems that satisfy the conditions stated above.

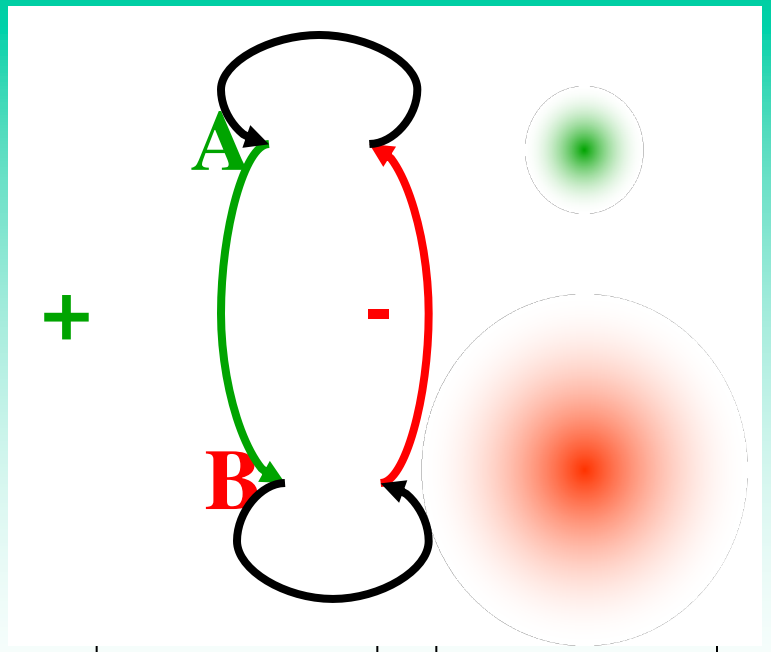
Under all these conditions, a stable pattern exists for $d_c > 1$. The wavelength of the pattern is intrinsic to the system (determined by the balance of diffusion and reactions).

The reaction-diffusion model

$$\frac{\partial a}{\partial t} = F(a,b) + D_a \nabla^2 a$$

$$\frac{\partial b}{\partial t} = G(a,b) + D_b \nabla^2 b$$

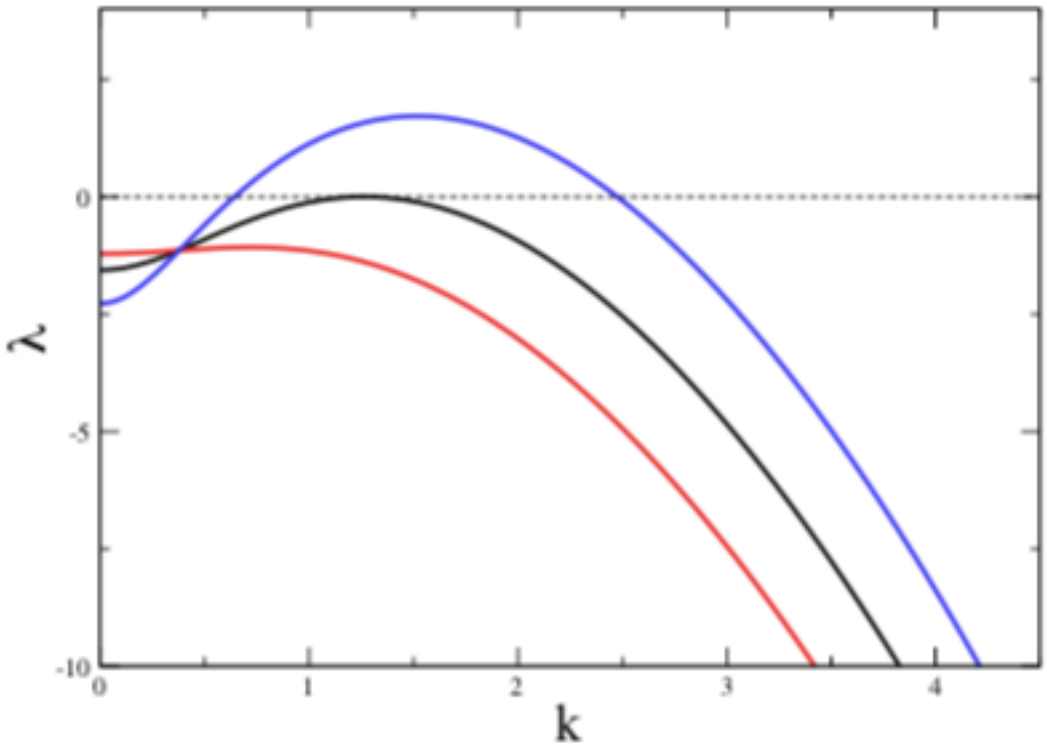
reaction diffusion



reaction diffusion

Turing, A.M. (1952). The chemical basis of morphogenesis.
Phil. Trans. Roy. Soc. London *B* **237**: 37

Autovalor como función del número de onda, k~1/longitud

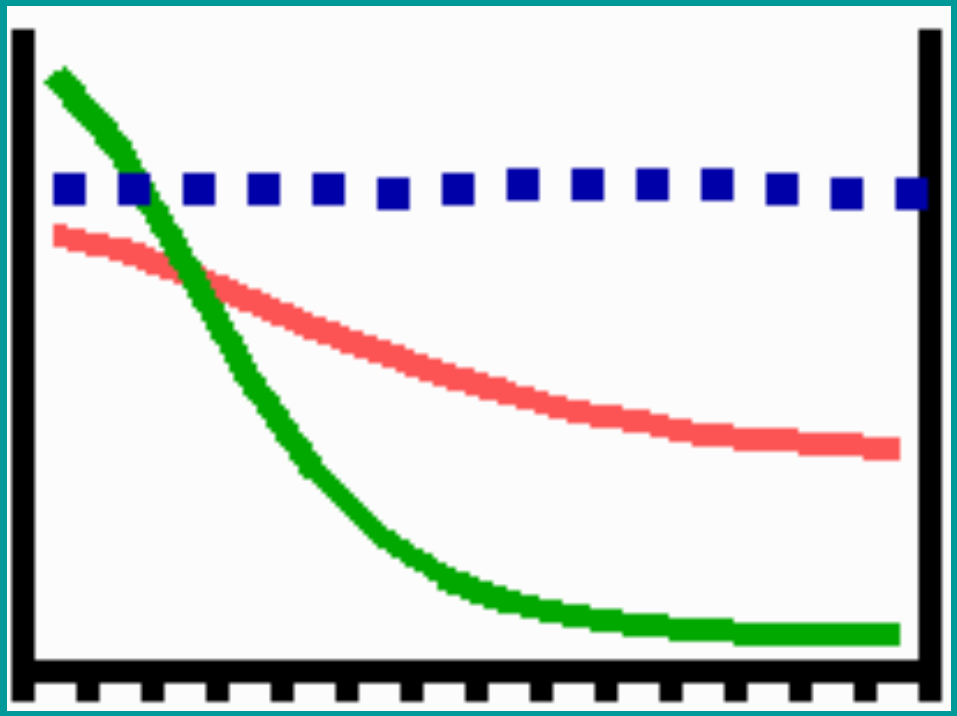


Los modos inestables tienen una longitud de onda característica, dada por los parámetros del problema, no por el tamaño del sistema

Chemical morphogenesis

- Two or more chemical species
- Different rates of diffusion
- Asymmetric chemical interactions
- Dissipative system kept out of equilibrium

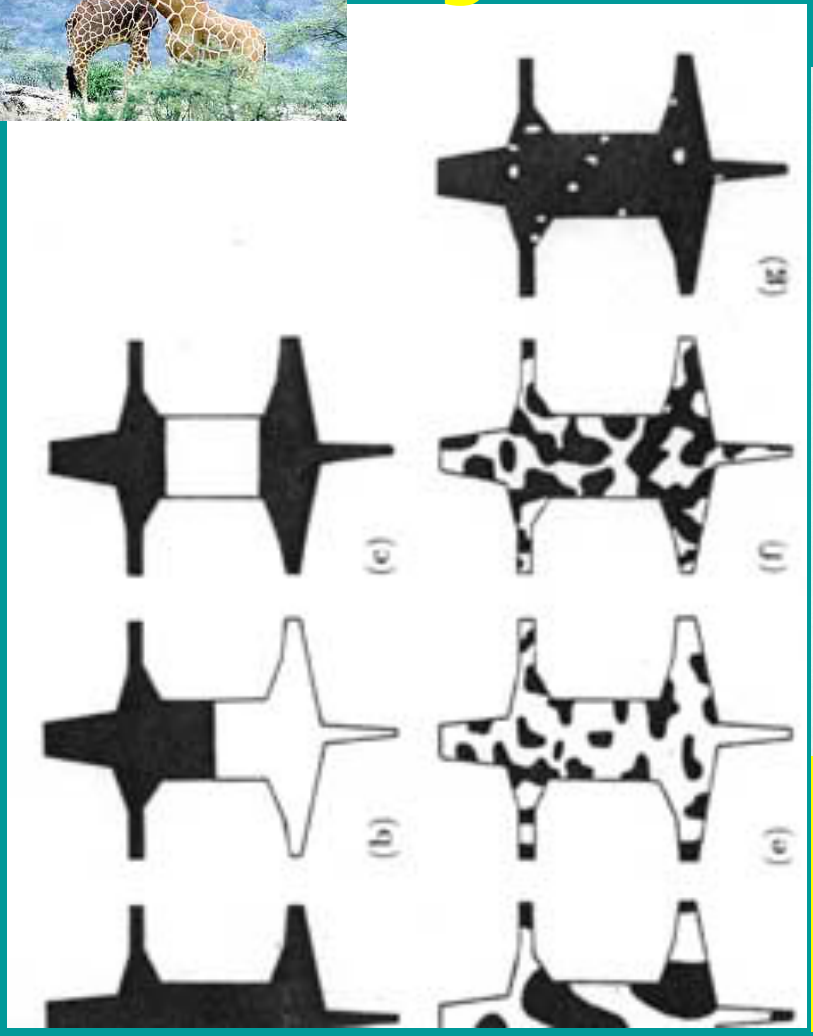
Long range inhibition
Short range activation

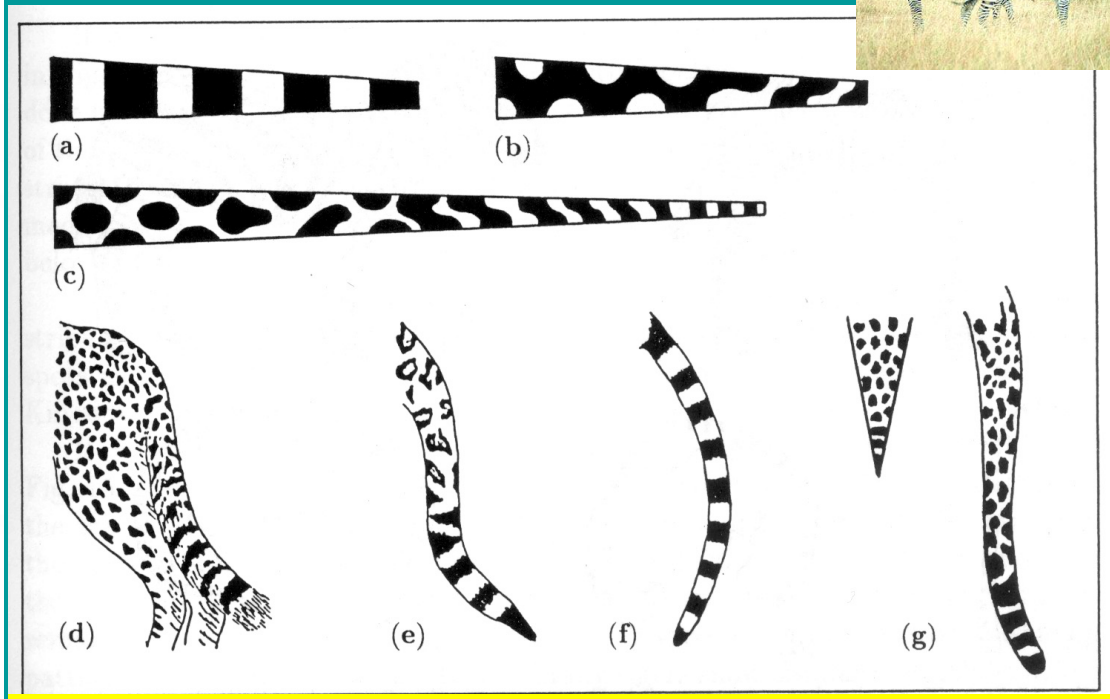


Simulation from H. Meinhardt's web page

The paper by Turing stimulated a large body of work, in particular, a variety of modeling efforts.

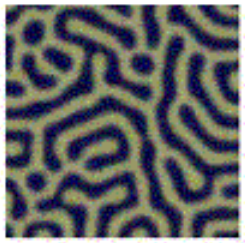
Turing Patterns in Animal Coats



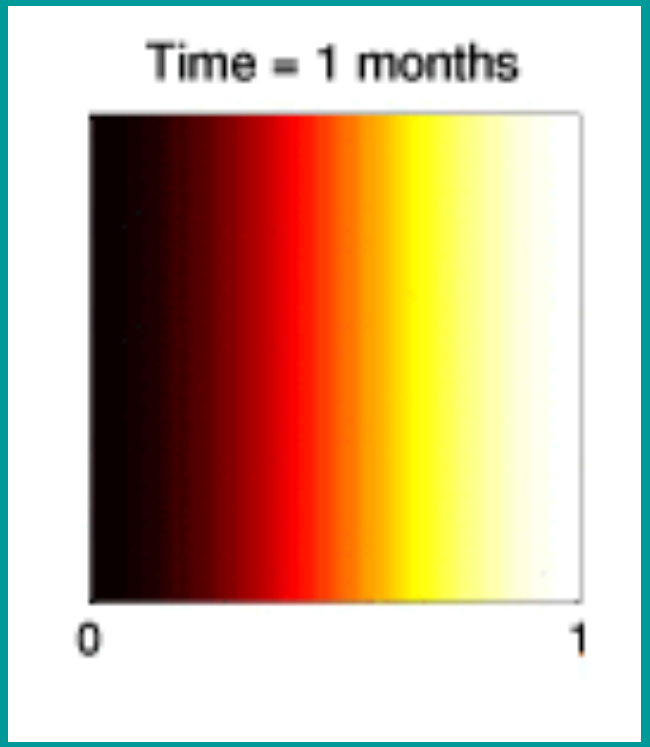


Effect of body surface scale on spatial pattern.
Left: Domain size increases from (a) to (g).
Right: (d) adult cheetah, (e) adult jaguar, (f) prenatal tail, (g) adult leopard

J. D. Murray, *Mathematical Biology*, Springer, (1989)



Stationary Wave



Kondo S. and Asai R., "A viable reaction-diffusion wave on the skin of Pomacanthus, a marine angelfish"
Nature 376, 765-768 (1995).

Modeling Pigmentation Patterns
Heriot-Watt University, Edinburgh

Other examples of Turing Patterns in biological models

Algae (Murray, Mathematical Biology, (1989))

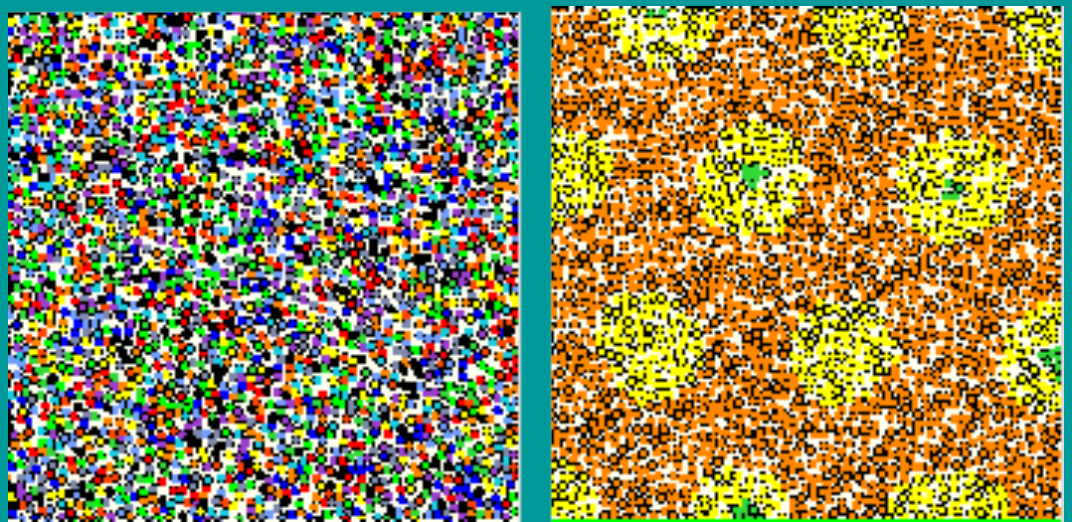
Dictyostelium (Byrne *et al*, PNAS, 84, (1987))

Glycolysis (Hasslacher *et al,* Chaos, (1993))

The paper by Hasslacher *et al*:

Are Turing patterns robust against fluctuations? Can Turing patterns arise inside a small (and highly fluctuating) region, such as, the cytosol of a cell?

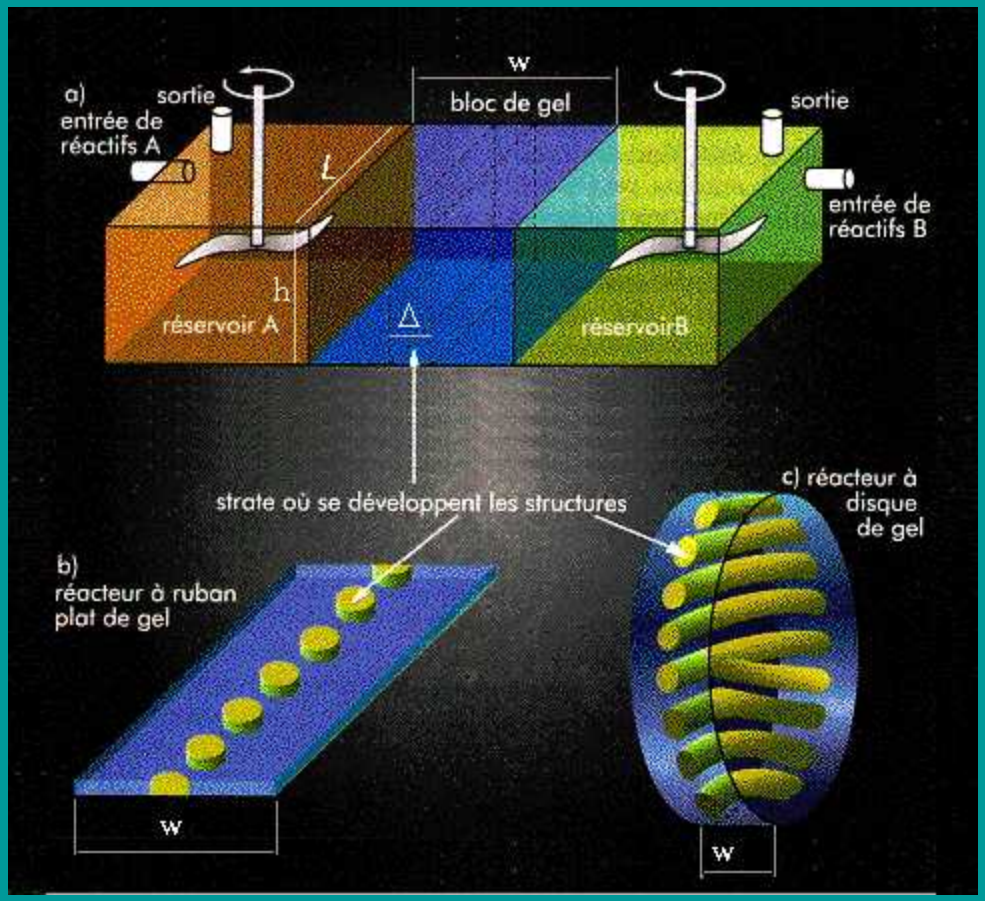
Tool of study: lattice gas. Model: 2 variable Selkov model

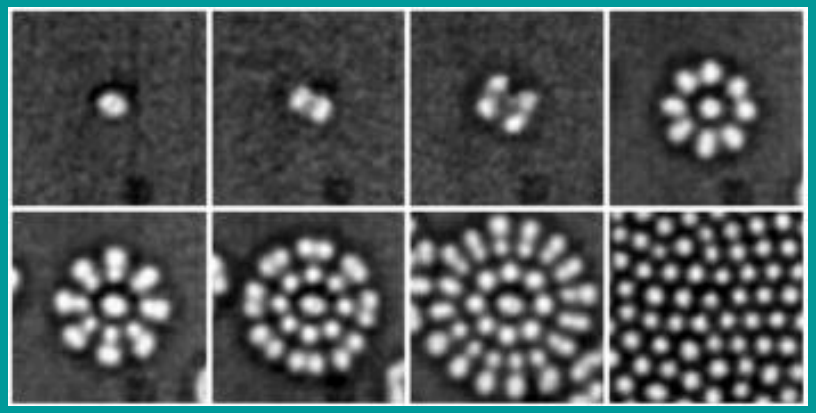


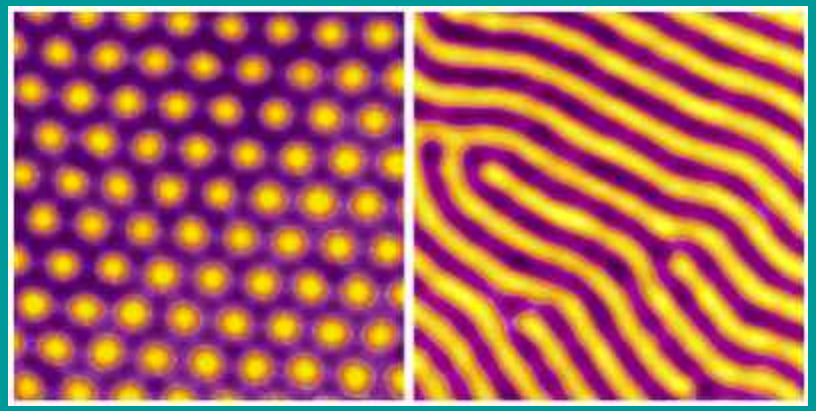
Simulation using the Gray-Scott model by *Gerald Jay Sussman*

Turing patterns in chemical systems

First observed by De Kepper's group in 1990!!, why did it take so long?







Pictures from P. De Kepper's web page

Why are the experimentally observed patterns Turing patterns?

Can the biological models described before really support Turing patterns?

System	Chemicals	D_V/D_U	d_c (according to model)
CIMA (exp)	Iodine-Chloride	~ 1	~10
Fish (model)	Unknown	--	~14
Alga (model)	cAMP-Ca++	< 1	~6
Glycolysis (model)	ATP-ADP	~ 1	~16

Explanation for the CIMA reaction
(Lengyel and Epstein, Science, **251**, (1991))

The selective interaction of the activator (iodine) with immobile species, such as the starch used for visualization purposes and the gel, reduces its diffusion coefficient. In this way, the effective diffusion coefficient of iodine becomes smaller than that of the other relevant species, allowing the formation of Turing patterns.

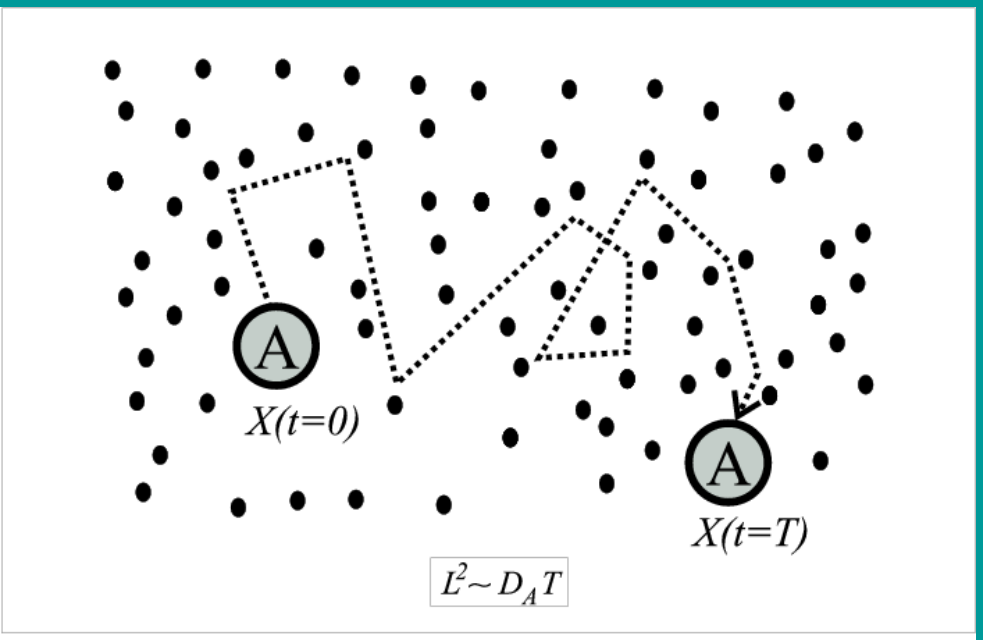


Figure 1 (a)

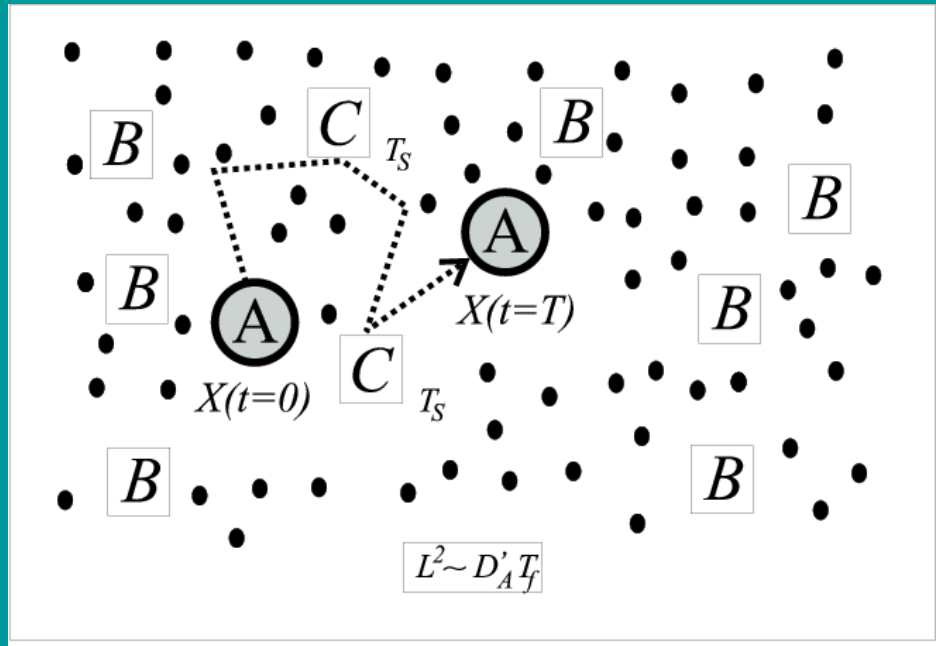


Figure 1 (b)

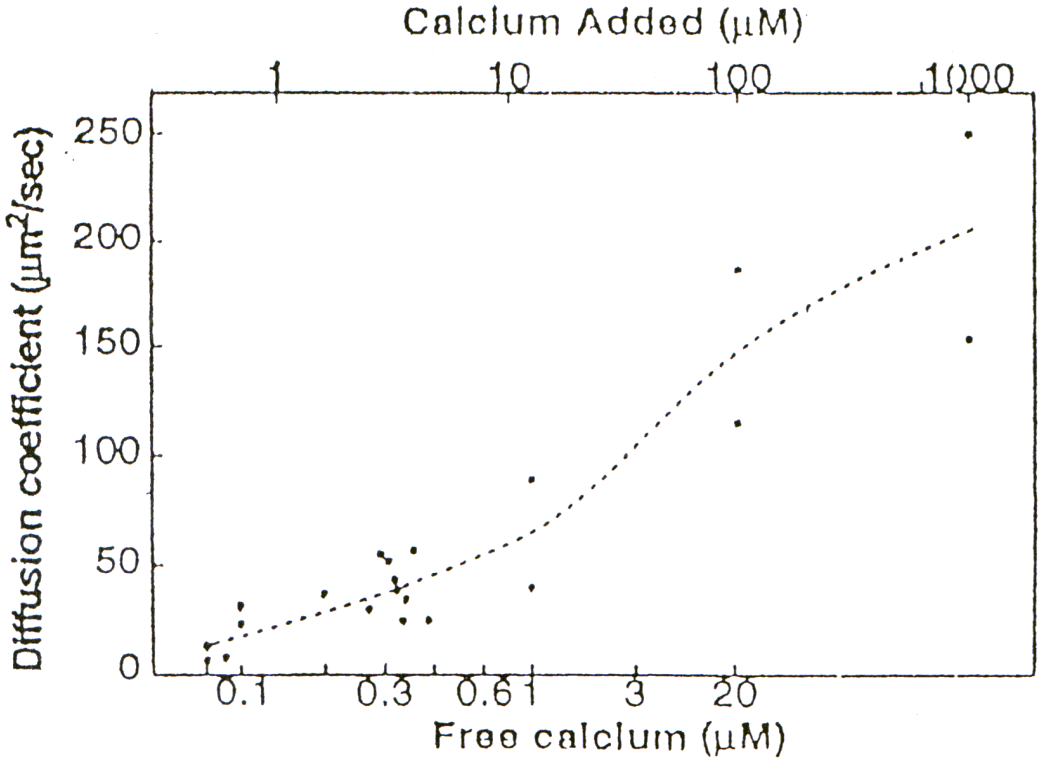


Fig. 3. Dependence of D for Ca^{2+} on the concentration of free Ca^{2+} and the amount of added Ca^{2+}. The concentration of free Ca^{2+} was determined as described in the text. The average concentration of added Ca^{2+} was determined as described (*28*). The concentration of $^{45}Ca^{2+}$ was calculated from the amount loaded and the volume over which it diffused. The dashed line was drawn empirically.

Figure from Allbritton et al, Science'92.

The idea that diffusion is rescaled by reactions with unknown species is very common in biology.

For example, calcium is highly "buffered" inside cells, and this is how the relatively small diffusion coefficient of calcium in cells is explained.

Is there an example of a biochemical pathway that can give rise to the appearance of Turing patterns?

Candidate: the glycolytic pathway.

Glycolytic oscillations have been observed in different cell types and it has been established that it is the individual cell concentrations that oscillate. This is an indication that there is a positive feedback along the pathway. Some type of "autocatalytic" behavior is necessary for Turing patterns to exist.

Previous studies of Turing patterns in glycolysis by Prigogine *et al* (1969) and Hasslacher *et al* (1993) used 2-variable models with ad hoc diffusion coefficients (to guarantee $d_c>1$).

Questions that we try to answer with our work:

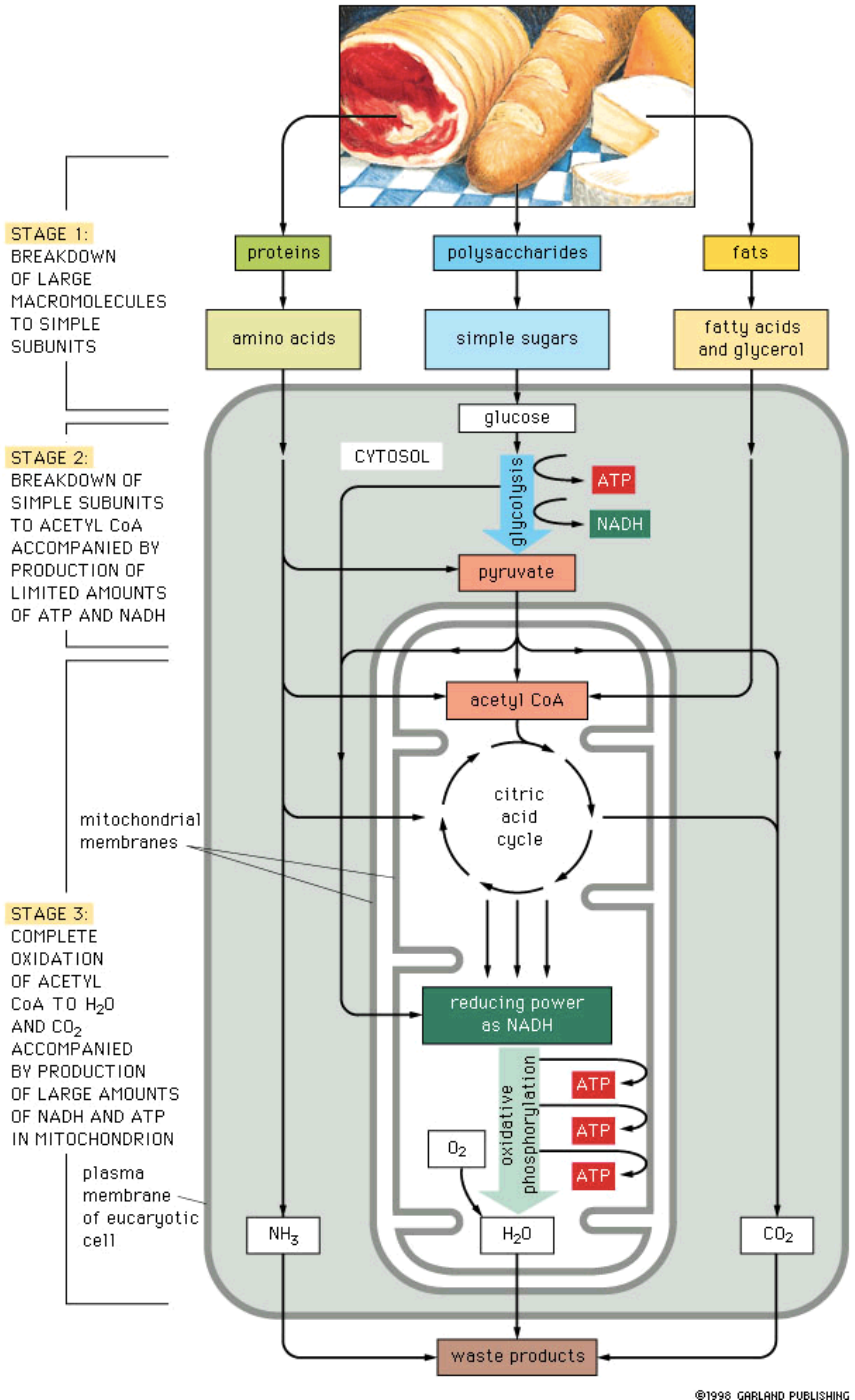
- Can the glycolytic pathway give rise to Turing patterns for realistic diffusion coefficients and reaction rates?
- Can the patterns fit inside a typical cell?

Results: we show that a 5-variable model of (part of) the glycolytic pathway can support Turing patterns for realistic diffusion coefficients due to the action of the enzymes that catalyze a step of the reaction. The patterns can fit in a cell.

Remember glycolysis & the relevant steps for glycolytic oscillations

The enzymatic breakdown of the macromolecules that come with food (catabolism) occurs in three stages.

The most important process of the second stage is GLYCOLYSIS, which can generate ATP in the absence of oxygen.



Glycolysis :

the breakdown of glucose occurs in the cytoplasm

10 steps

1) Start with 6 carbon sugar
2) Two phosphorylations (ATP->ADP)
3) Cleave into 2 3-carbon molecules
One reduction of NADH, 2 ATP formed per 3-C unit

Net per 6 carbons:
2 ATP
1 NADH

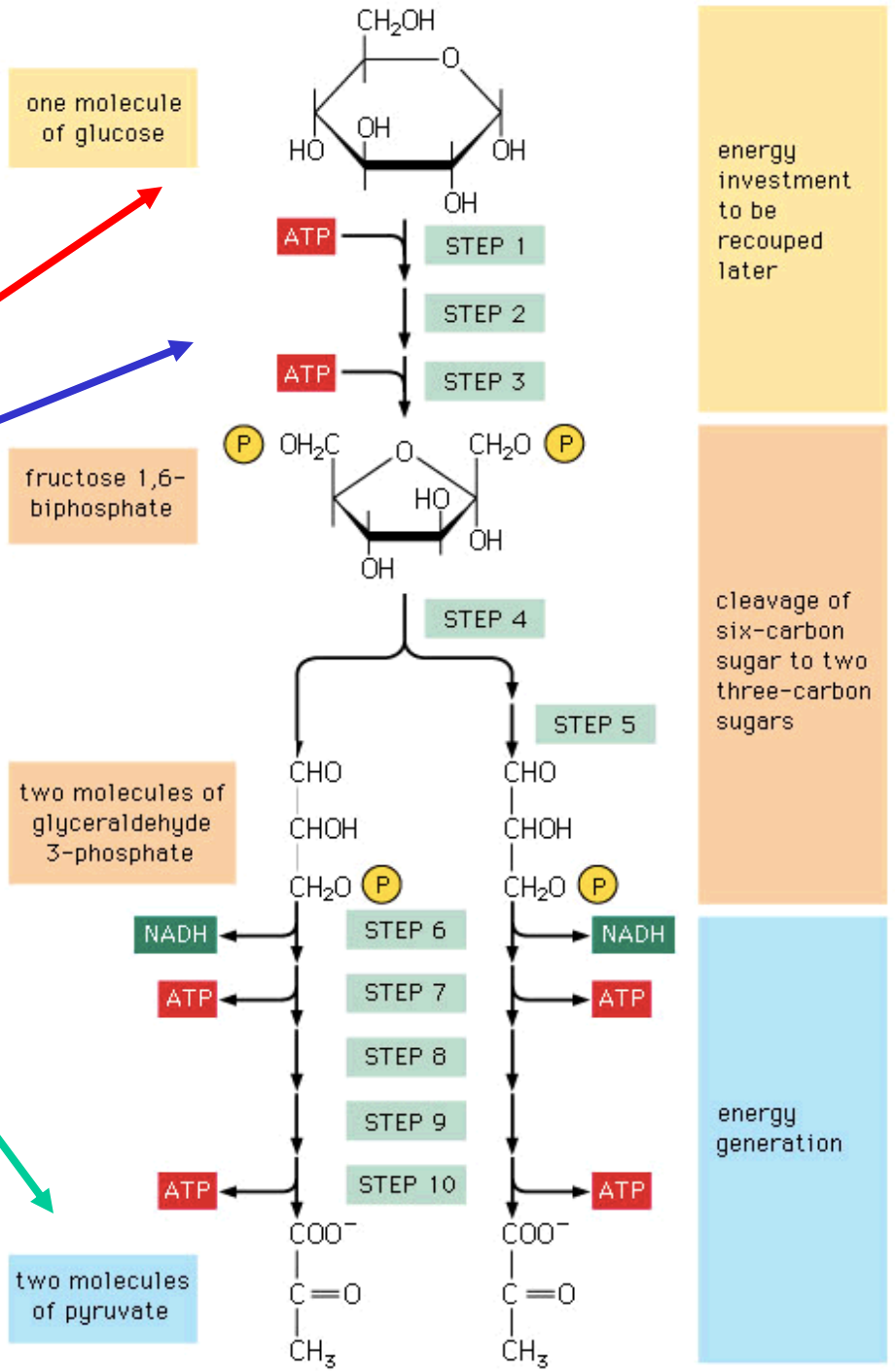
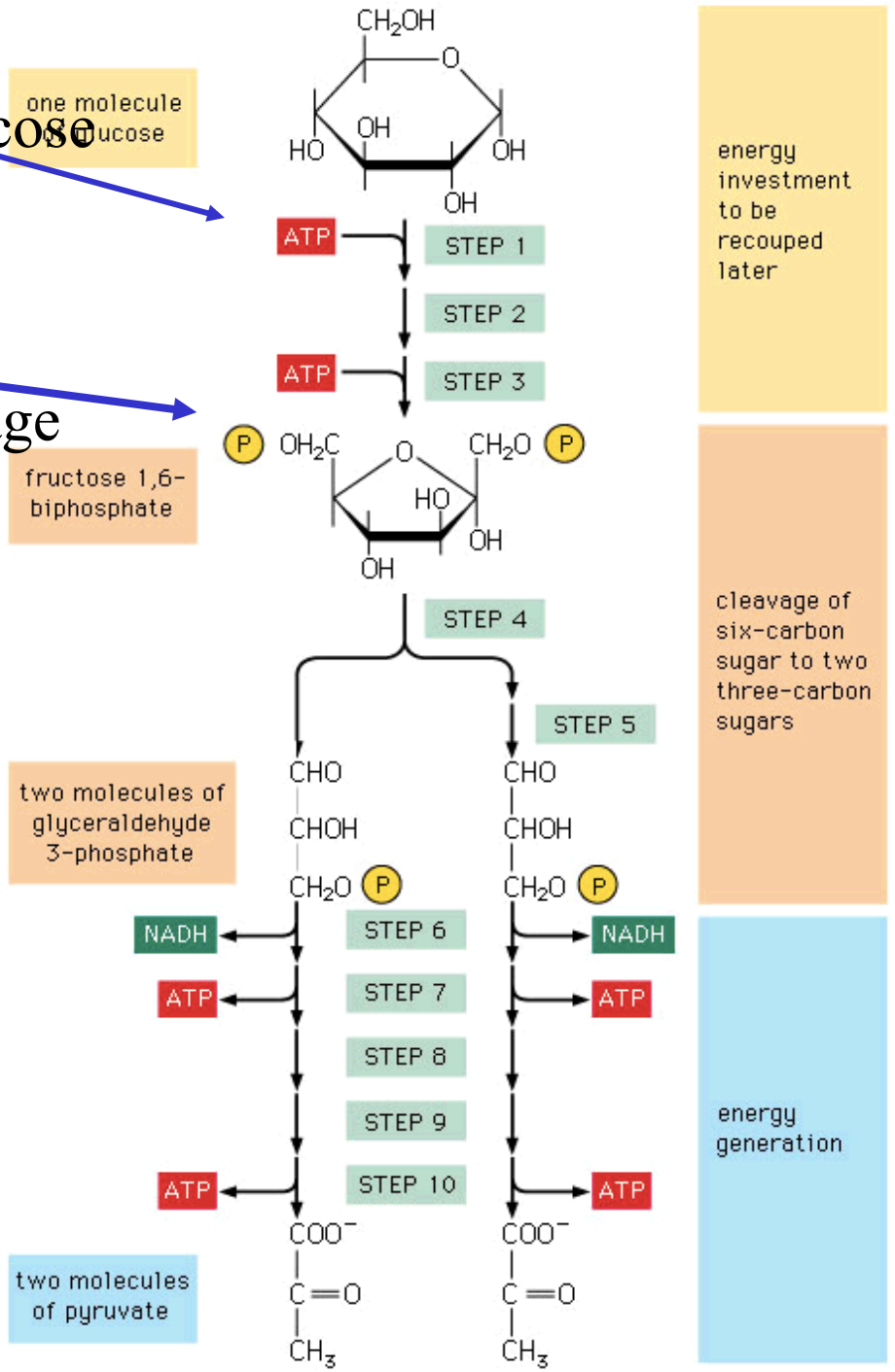


Figure 4-3

Hexokinase - phosphorylates glucose trapping it in the cell

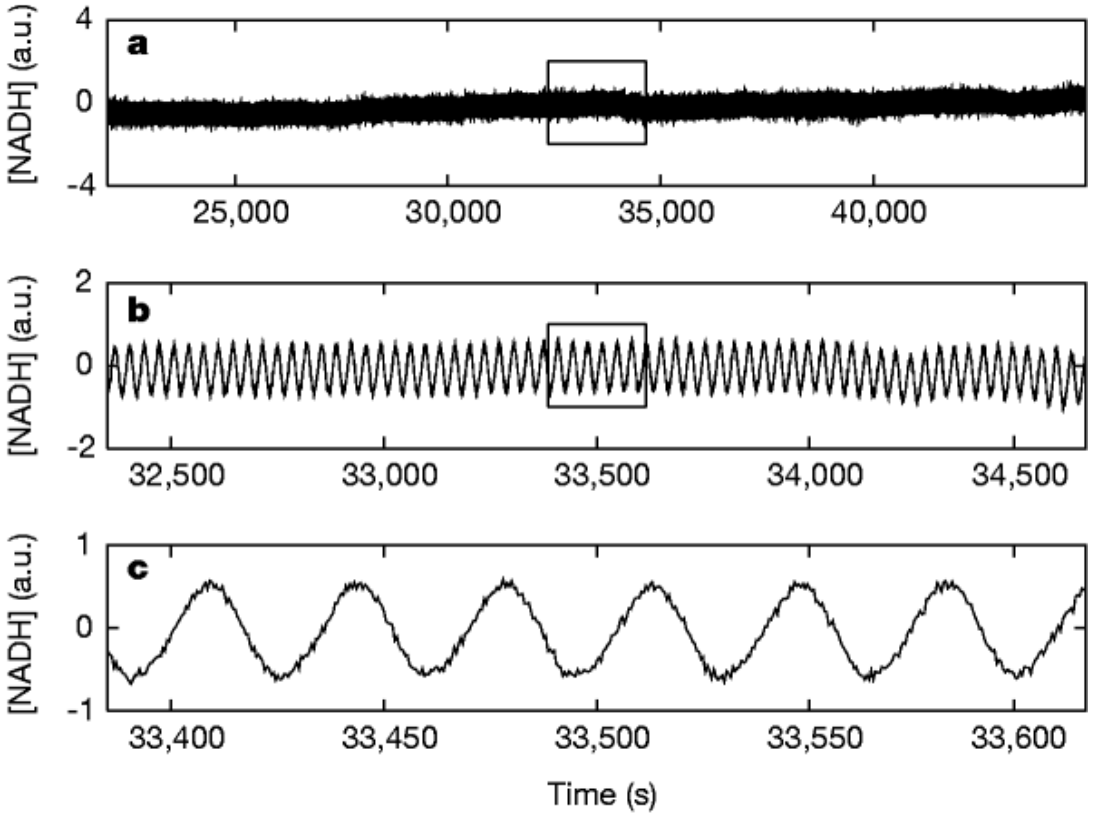
Phosphofructokinase (PFK)– sets molecule up for cleavage

Crucial step for oscillations:
The one catalyzed by PFK.



The reactions involved in the glycolytic pathway can give rise to oscillations in the concentrations of some of the reactants (observed in the 50's for the first time):

This means that there is a positive feedback at some step of the pathway.



From S.DANØ *et al*, *Nature* **402**, 320 - 322 (1999)

Oscillations appear when either glucose 6-phosphate or fructose 6-phosphate are injected, which are reactants that participate upstream the step that is catalyzed by PFK. PFK is a key factor, because oscillations disappear when it's inhibited.

E. Selkov developed a model (published in 1968) to explain these oscillations.
It describes only one step of this chain (the one catalyzed by PFK).

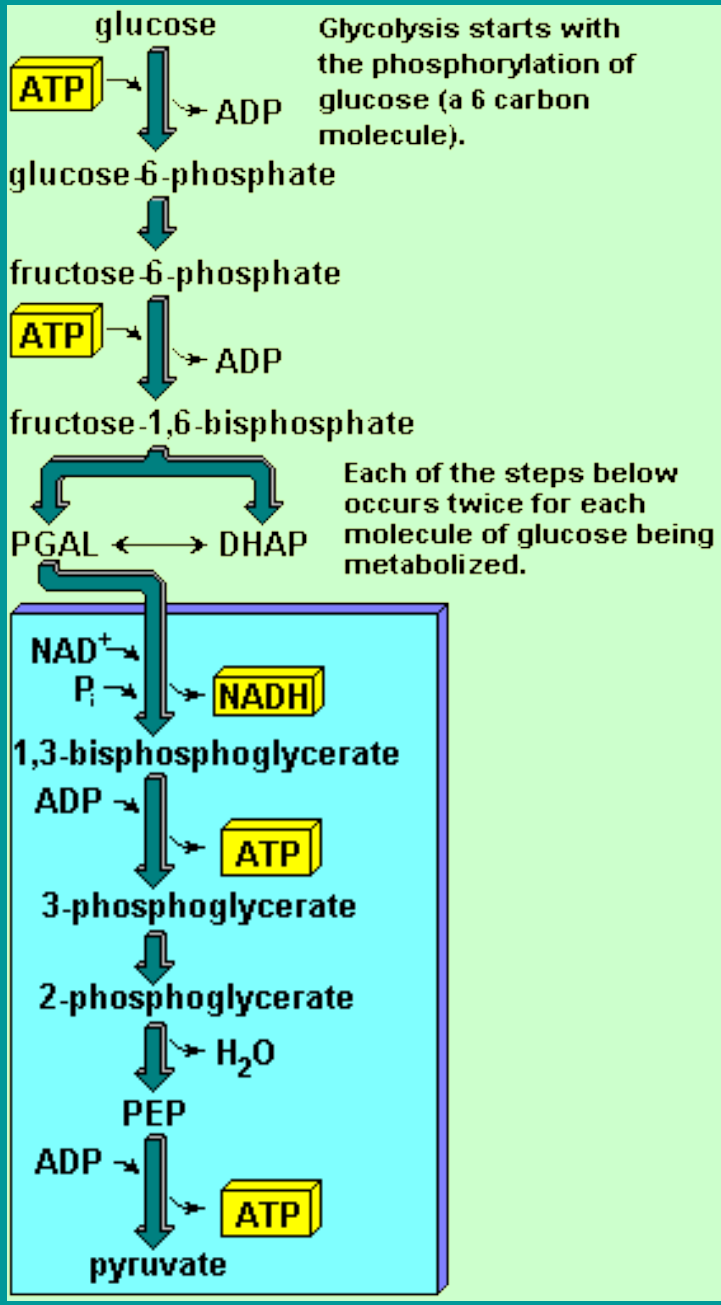
$$\xrightarrow{\nu_1} S_1 + ES_2' \underset{k_{-1}}{\overset{k_{+1}}{\leftrightarrow}} S_1ES_2',$$

$$S_1ES_2' \xrightarrow{k_{+2}} ES_2' + S_2 \xrightarrow{\nu_2},$$

$$\gamma S_2 + E \underset{k_{-3}}{\overset{k_{+3}}{\leftrightarrow}} ES_2',$$

E=PFK; S_1=ATP (injected at rate ν_1);
S_2=*ADP* (removed at rate ν_2 *[ADP]*)

The activation of PFK by ADP provides the positive feedback that can explain the oscillations.



Taking into account that the total enzyme concentration (e_0) remains constant and assuming that the enzymes are practically immobile, the evolution equations that describe the reaction-diffusion Selkov's model can be written (using dimensionless quantities) as:

$$\frac{\partial \sigma_1}{\partial \tau} = \nu - (1+K_1)\sigma_1 u_1 + K_1 u_2 + d_1 \nabla^2 \sigma_1,$$

$$\frac{\partial \sigma_2}{\partial \tau} = \alpha\left[u_2 - \gamma K_3 \sigma_2^{\gamma} u_3 + \gamma K_3 u_1\right] - \eta \sigma_2 + d_2 \nabla^2 \sigma_2,$$

$$\varepsilon \frac{\partial u_1}{\partial \tau} = u_2 - \sigma_1 u_1 + \frac{K_3}{1+K_1}\left[\sigma_2^{\gamma} u_3 - u_1\right],$$

$$\varepsilon \frac{\partial u_2}{\partial \tau} = \sigma_1 u_1 - u_2,$$

where:

$\sigma_1 \sim [ATP]$

$\sigma_2 \sim [ADP]$

$u_2 \sim [S_1 ES_2^{\gamma}]$

$u_1 \sim [ES_2^{\gamma}]$

$u_3 = 1-(u_2+u_1)$

$\varepsilon \sim e_0$

$\gamma = 2$; $\nu \sim \nu_1$;

$\eta \sim \nu_2$

In most experiments that are done to determine the activity of enzymes, ε is very small. In fact, Selkov, who only looked at the spatially uniform version of this system, used an adiabatic approximation and reduced it to two equations:

$$\frac{d\sigma_1}{d\tau} = \nu - \frac{\sigma_1 \sigma_2^{\gamma}}{\sigma_1 \sigma_2^{\gamma} + \sigma_2^{\gamma} + 1},$$

$$\frac{d\sigma_2}{d\tau} = \alpha \frac{\sigma_1 \sigma_2^{\gamma}}{\sigma_1 \sigma_2^{\gamma} + \sigma_2^{\gamma} + 1} - \eta \sigma_2.$$

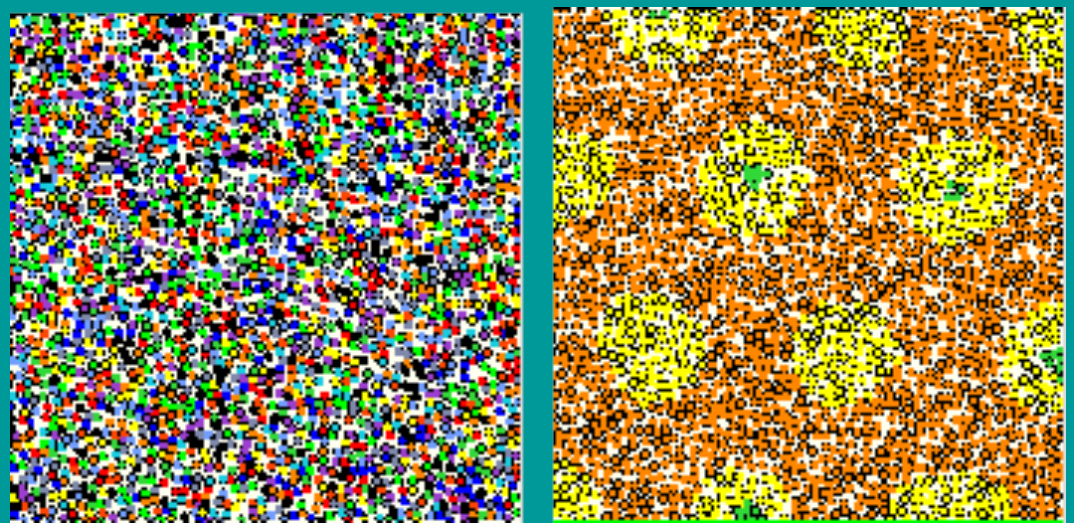
For this two variable system he showed that there was a Hopf bifurcation and that the frequency of the oscillations was similar to the experimental one.

Here we see that increasing [ADP] the growth of [ATP] decreases and viceversa: ADP:inhibitor; ATP: activator

Prigogine *et al* added diffusion terms to these two equations with diffusion coefficient values as needed to show that they could support Turing patterns ($D_{ADP}>D_{ATP}$).

The work of Hasslacher *et al* followed a similar approach but for a closely related model (developed by Richter *et al*).

The paper by Hasslacher *et al* tried to answer the following:
Are Turing patterns robust against fluctuations?
Can Turing patterns arise inside a small (and highly fluctuating) region, such as, the cytosol of a cell?
Tool of study: lattice gas. Positive answer for $d_c=D_{ADP}/D_{ATP}$ ~16.



Simulation using the Gray-Scott model by *Gerald Jay Sussman*

How could ATP and ADP diffuse at such different rates so that $d_c \sim 16$ if the two molecules are so similar?

Hasslacher et al argued that a mechanism similar to the one at work in the CIMA reaction could also exist in glycolysis. Namely, the reactions of ATP and ADP with some of the enzymes involved in the glycolytic pathway could rescale the diffusion coefficients of ATP and ADP so as to provide the "correct" ratio of diffusion coefficients.

However: how do we know that ADP is differentially slowed down by the enzymes with respect to ATP? On the other hand, establishing the existence of a fast reaction that can rescale the diffusion coefficient of a chemical is not enough to guarantee the existence of Turing patterns, since the slow reactions are rescaled too.

Our first strategy: take the 5-variable reaction-diffusion Selkov model, assume that the reactions with the immobile enzymes occur on a fast timescale and perform an adiabatic approximation to get a 2-variable reaction-diffusion model. Analyze whether this reduced system could support Turing patterns. (JChemPhys,2000)

We did find that ADP (the activator) had a smaller diffusion coefficient than ATP (the inhibitor), but couldn't find Turing patterns for a long time!

"New" strategy

We decided to work directly with the 5-variable Selkov model (with no reduction whatsoever) (PLoS,2007)

But we did not know which could be realistic parameter values in this model! (it has many more than the reduced 2-variable model analyzed by Selkov and others!)

So, first we studied the spatially homogenous system and fixed as many parameter values as we could so as to agree with the experimental evidence on glycolytic oscillations.

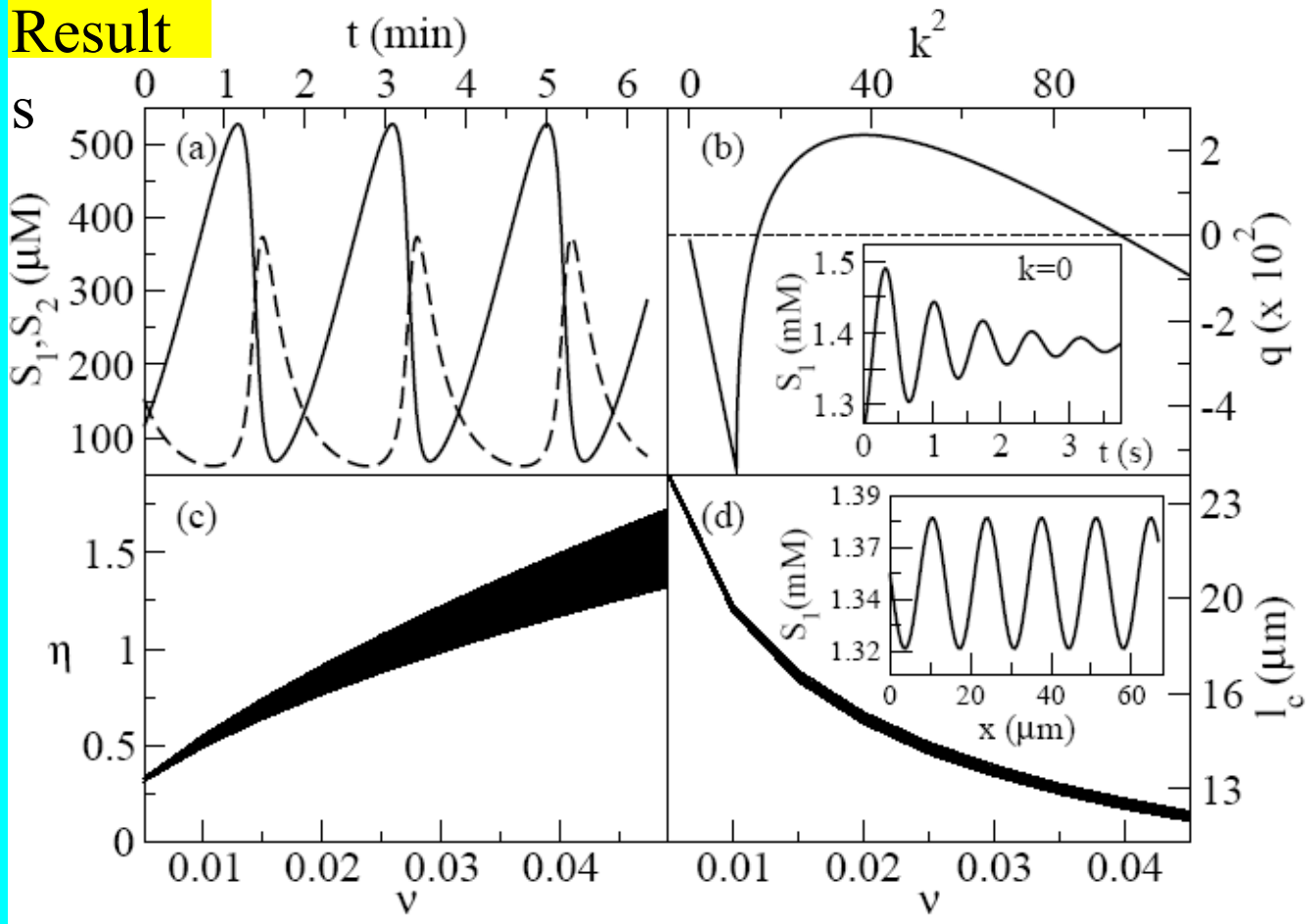
Experiments on yeast extracts: $\nu_1^* = 5.8\ uM^{-1}s^{-1}$, $\nu_2^*=0.04s^{-1}$, $3uM<e_0<10uM$, [ATP]~600uM, [ADP]~150uM, period of oscillations~ 3-5 min

Our values for the 5-variable Selkov model imply: $\nu_1^* = 5.8\ uM^{-1}s^{-1}$, $\nu_2^*=0.04s^{-1}$, e_0~7.9uM, [ATP]~150uM, [ADP]~145uM, period of oscillations~ 2.7 min

Then, we went back to the reaction-diffusion system with equal diffusion coefficients for ATP and ADP. We kept fixed the purely kinetic parameters at the previously determined values (our parameters: α, K_1 and K_3) and varied the fluxes and enzyme concentration (our parameters: ν, η, and ε) looking for a "Turing" bifurcation. We found it!

(a) Glycolytic oscillations in [ATP] and [ADP] for η=0.15, ν=0.00345, ε=10^{-6}, α=15, K_1=1500, K_3=1. (b) Linear growth rate of the unstable modes for η=1.215, ν=0.03, ε=0.0003, α=15, K_1=1500, K_3=1, and d_1=d_2=0.01. Inset: Evolution of [S_1] (c) Turing space as a function of the (dimensionless) input and output rates of *ATP* (ν) and *ADP* (η), parameters as in (b). (d) Corresponding wave-length of the most unstable mode.

Result

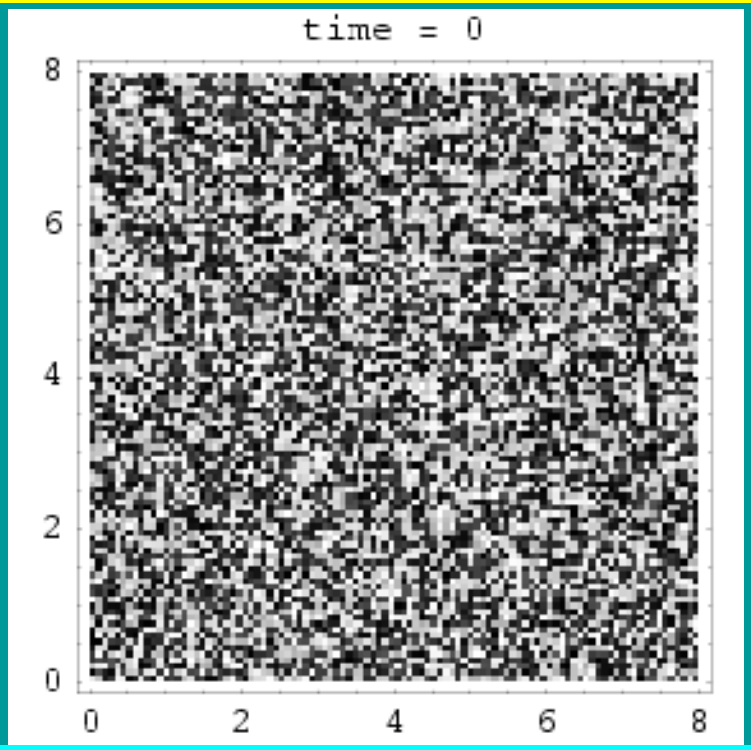


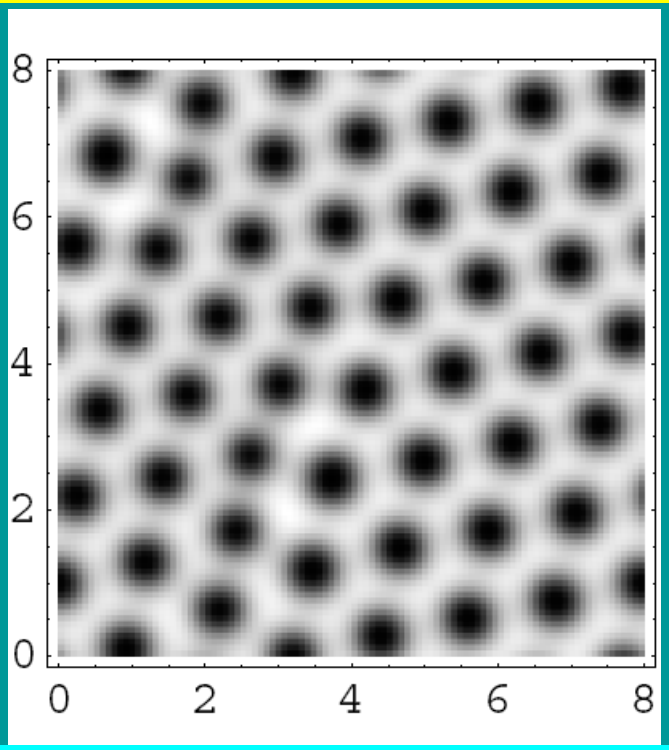
Bounded band of unstable modes for $k \neq 0$ & stable fixed point for $k = 0$. Pattens may exist for larger values of ν_1 as ν_2 also gets larger. No pattern is possible at low enzyme concentration ($e_0 \geq 800\mu M$ for the Turing instability to occur)

The patterns could fit in a cell!!! The characteristic size gets smaller as the rate of product removal, ν_2, becomes larger.

Beyond the linear stability analysis

Turing pattern that appears after 10 minutes in a 2D numerical simulation done using a square domain of size 8Lx8L con L =10.6μm. The critical wavelength is: ℓ_c= 11μm





[ATP]; black = 2.47mM ; white= 1.1mM

Pattern properties:

The pattern size decreases as the glycolytic flux is decreased (ν_1 or ν_2).

More spots fit into the domain (the "cell") as the "cell" gets larger.

Summary

The 5-variable Selkov model is able to support Turing patterns for realistic parameter values and for equal diffusion coefficients for ATP and ADP.

Although the model is highly idealized, its ability to reproduce a variety of observations allows us to think that its basic dynamical features should be common to those of the real system.

The interactions involved in the *PFK* catalyzed step of the glycolytic pathway change the "effective" diffusion coefficients of *ATP* and *ADP* in the necessary direction for Turing pattern formation.

The patterns can fit inside a typical cell size and it takes a time of the order of minutes for them to form.

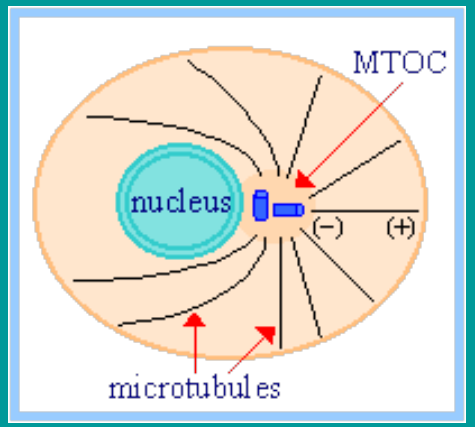
At fixed cell size, more spots fit in the cell as the glycolytic flux is decreased (ν_1 or ν_2).

More spots fit in the cell as the cell gets larger.

Is there anything that could be related to this Turing pattern in a cell? (very speculative!)

Cells contain a network of filaments that form its cytoskeleton. Among them, MICROTUBULES, which are long and stiff polymers.

In vivo, microtubules nucleate at the **centrosome** or **MTOC.**



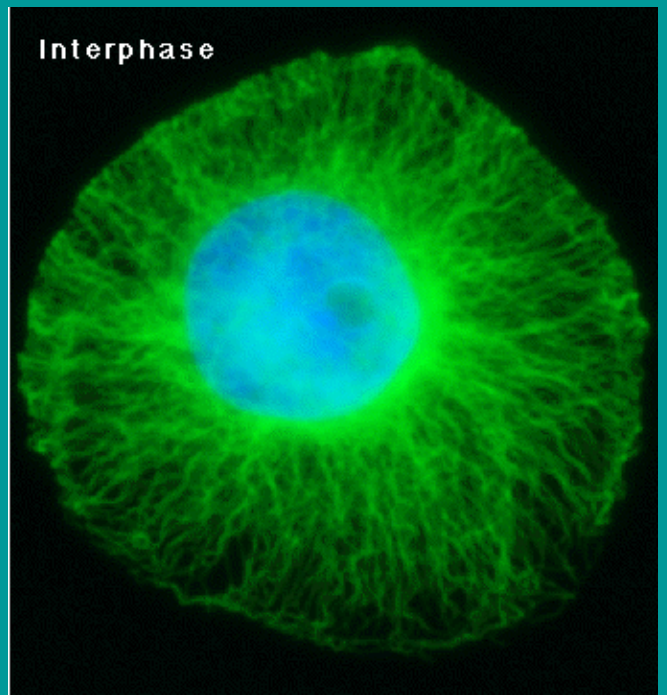
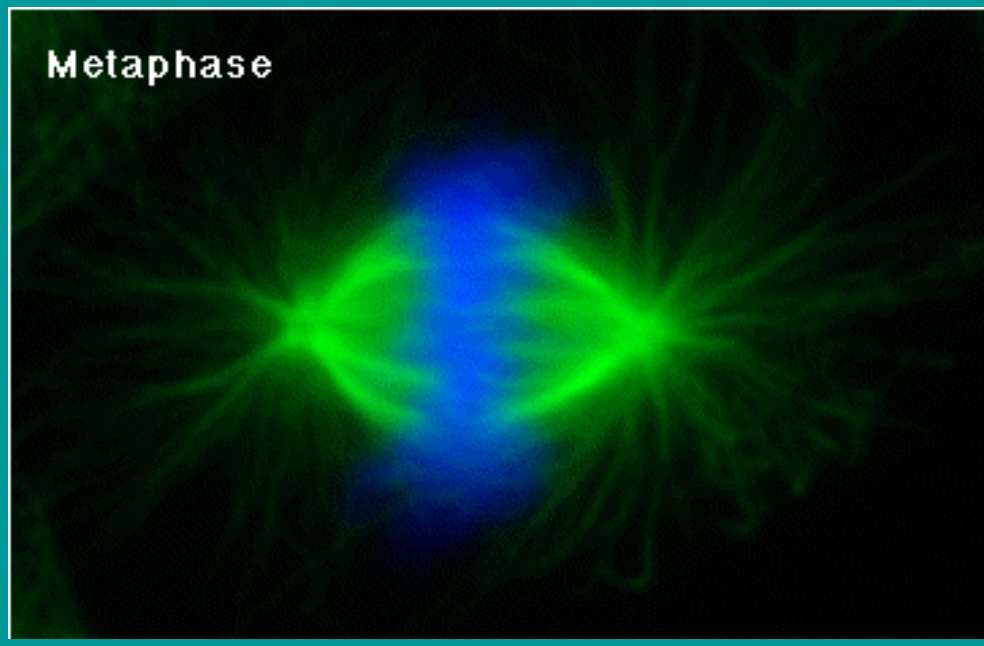
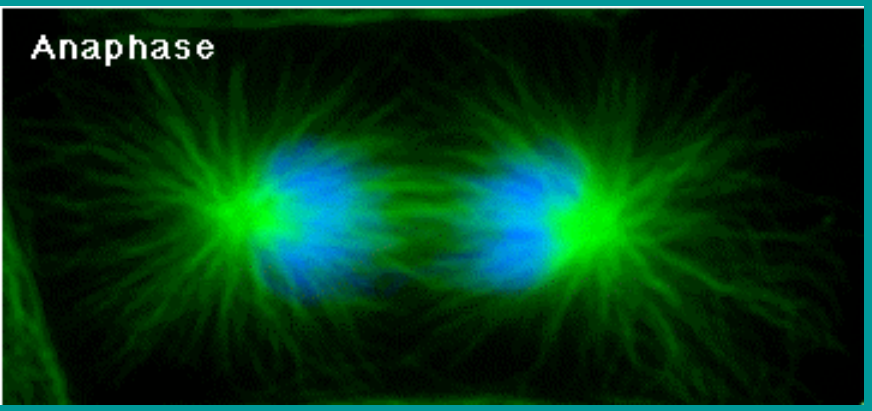
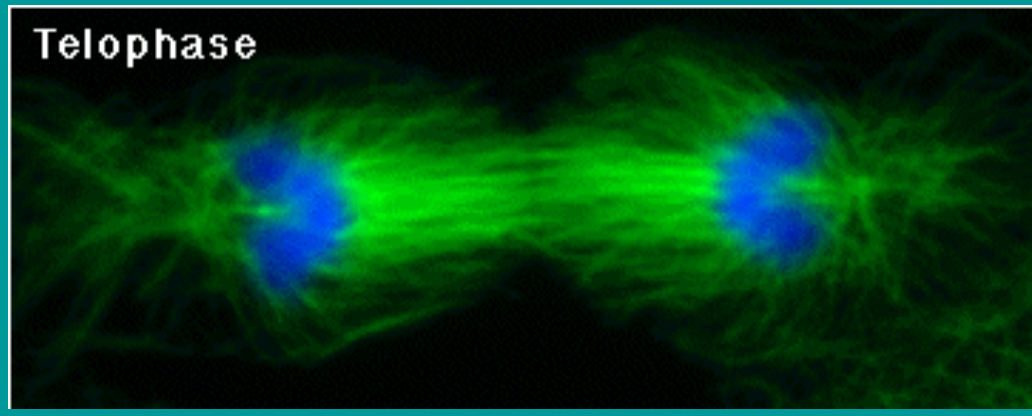


Figure from the web page of Mitchison's lab; MT in green, DNA in blue

During the cell division cycle, centrosomes replicate and microtubules grow from them. After cell division is completed, the replicated centrosomes become the “organizing centers” of the two daughter cells.







Microtubules (green) and DNA (blue) at various stages during the cell cycle.
Figures from the web page of Mitchison’s lab

The region occupied by MTOC's seems to have a fixed lengthscale:
When cells grow in size during the cell division cycle, two centrosomes are formed out of the original one.

This is similar to the way spots on animal skins divide as animals grow in size, or the way Turing patterns behave as the spatial domain grows in size (which occurs because they have an intrinsic lengthscale).

Could centrosome location be related to an underlying Turing pattern of some relevant substance (e.g., ATP)?

Even if we cannot answer this question, at least we have a mechanism that could explain the appearance of an inhomogeneous pattern in the ATP distribution inside a cell.

Los patterns de Turing son ejemplos de patterns estacionarios en sistemas de RD

Si bien intervienen procesos de transporte (en muchos casos difusivos) y reacciones químicas en la formación de gradientes de sustancias dentro de la célula (en particular, en el citosol), en general no son explicados en términos de patterns de Turing.

En muchos casos se explican en términos de propagación de frentes que estabilizan una distribución inhomogénea de alguna sustancia. Hay además otros procesos (hidrodinámicos, mecánicos o eléctricos) que, en combinación con las reacciones químicas, pueden inducir una ruptura de simetría

Sí se explican como patterns de Turing los dibujos en la piel de peces y otros animals.

La propagación de frentes es típica de los sistemas de RD con dinámica subyacente biestable (y se extiende a la excitable).

Recordemos modelo de FitzHugh-Nagumo (típico de excitabilidad)

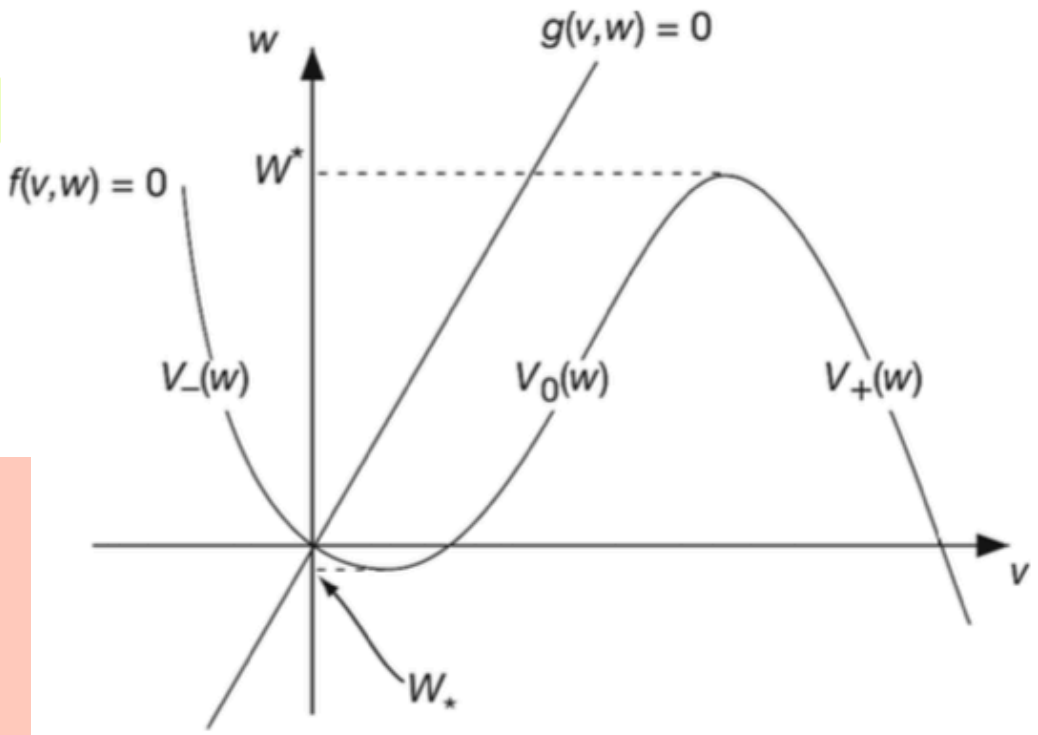
$$\epsilon \frac{dv}{dt} = f(v) - w + I_{\text{app}},$$

$$\frac{dw}{dt} = v - \gamma w,$$

con

$$f(v) = v(1-v)(v-\alpha), \qquad \text{for } 0 < \alpha < 1, \epsilon \ll 1.$$

Y nulclinas:



Que si w=const, era biestable

Pasemos al pizarrón para analizar propagación de frentes