Systems Biology Across Scales: A Personal View II. Antecedents & course outline

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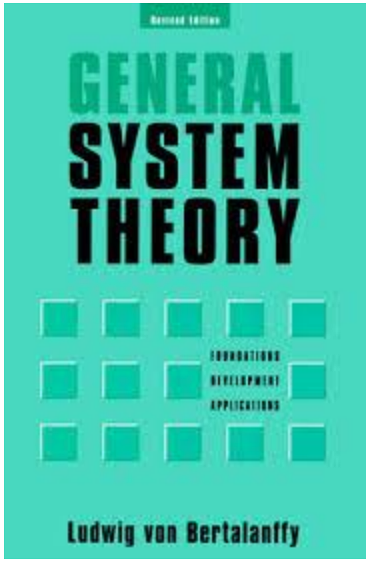
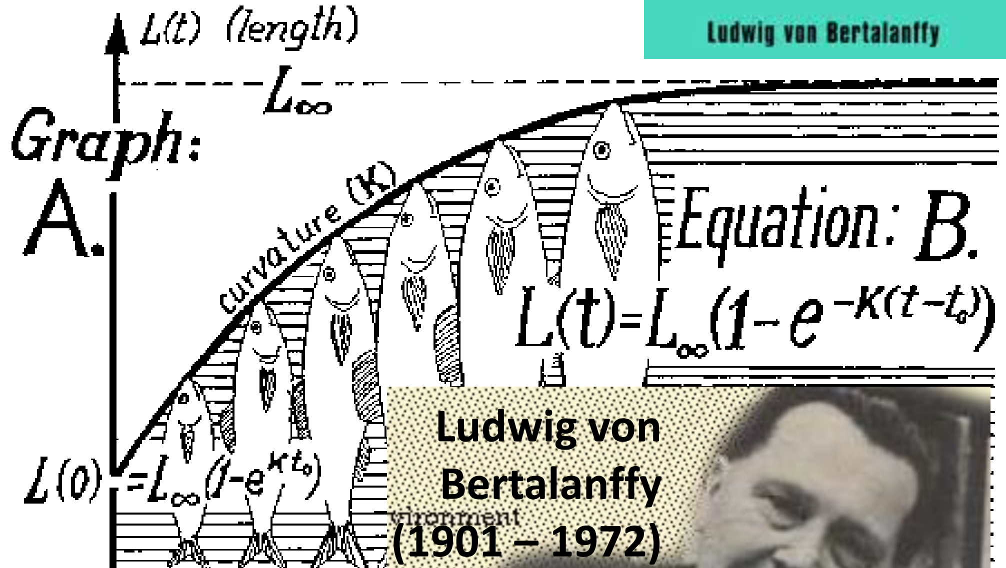
General Systems Theory and von Bertalanffy



The Quest for a General System Theory (1968)

"There exist models, principles, and laws that apply to generalized systems or their subclasses, irrespective of their particular kind, the nature of their component elements, and the relation or 'forces' between them. It seems legitimate to ask for a theory… of universal principles applying to systems in general…we postulate a new discipline called *General System Theory*. Its subject matter is the formulation and derivation of those principles which are valid for 'systems' in general."

"A consequence of the existence of general system properties is the appearance of structural similarities or isomorphisms in different fields. There are correspondences in the principles that govern the behaviour of entities that are, intrinsically, widely different. E.g., an exponential law of growth applies to certain bacterial cells, to populations of bacteria, of animals or humans, and to the progress of scientific research…"



http://www.fao.org/

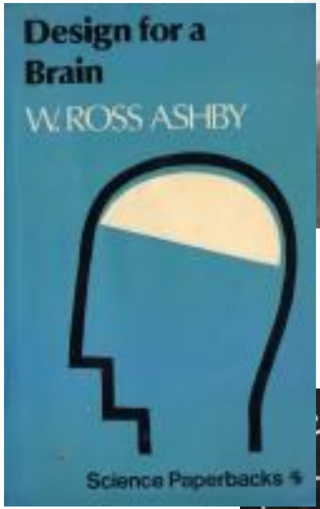
Ludwig von Bertalanffy (1901 – 1972)

Systems thinking in a slightly restricted context…

Cybernetics, Ashby and Wiener

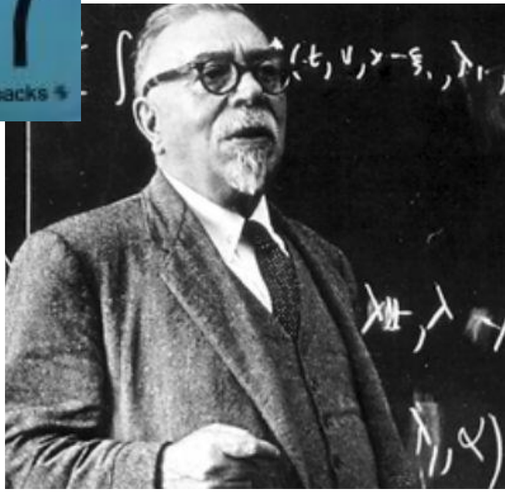
"The scientific study of control and communication in the animal and the machine" (Norbert Wiener, 1948)

Wikipedia:
"[Cybernetics] explor[es] regulatory systems, their structures, constraints, and possibilities…applicable when a system being analyzed is involved in a closed signaling loop; that is, where action by the system generates some change in its environment and that change is reflected in that system in some manner (feedback) that triggers a system change."



W. Ross Ashby
(1903-1972)

Studies how any system (physical, engineered or biological) processes information, responds to environmental & internal signals and adapts/evolves with changing circumstances – the problem being studied in a general context, abstracted from the specific situation in which an engineer or biologist may encounter it

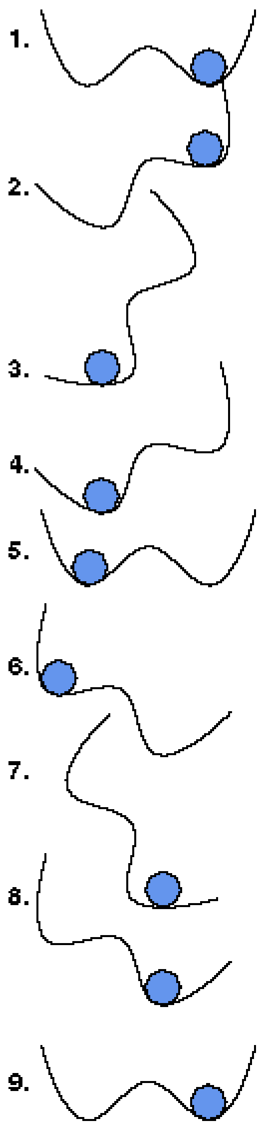


Norbert Wiener
(1894 -1964)

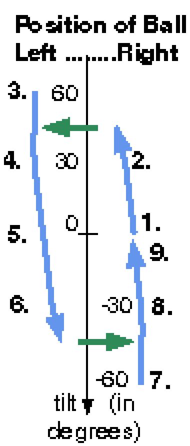
Systems thinking but in a very different "avatar"…

Catastrophe ≡ sudden change

Thom, Zeeman & Catastrophe Theory

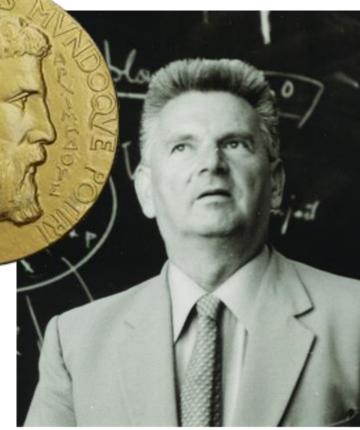


Example: A ball free to roll under gravity in a double-well container that can be tilted from side to side.



Input: tilt of the container
Output: position of ball
Continuous variation of input can cause discontinuous jump in output

1958



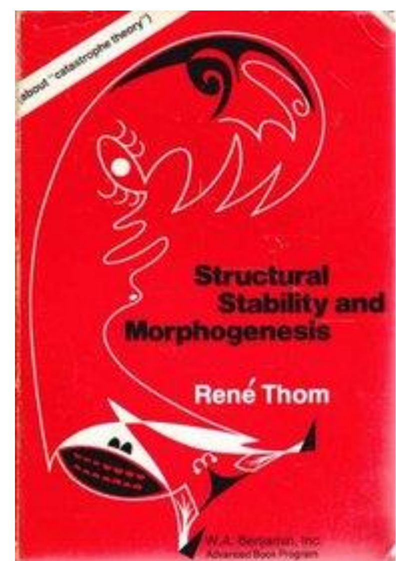
Rene Thom (1923-2002)

E. C. Zeeman (1925 -)

A mathematical catastrophe is a point in a model of an input-output system, where a vanishingly small change in the input can produce a large change in the output.

http://www.math.stonybrook.edu/~tony/

Image: Tony Phillips (SUNY)



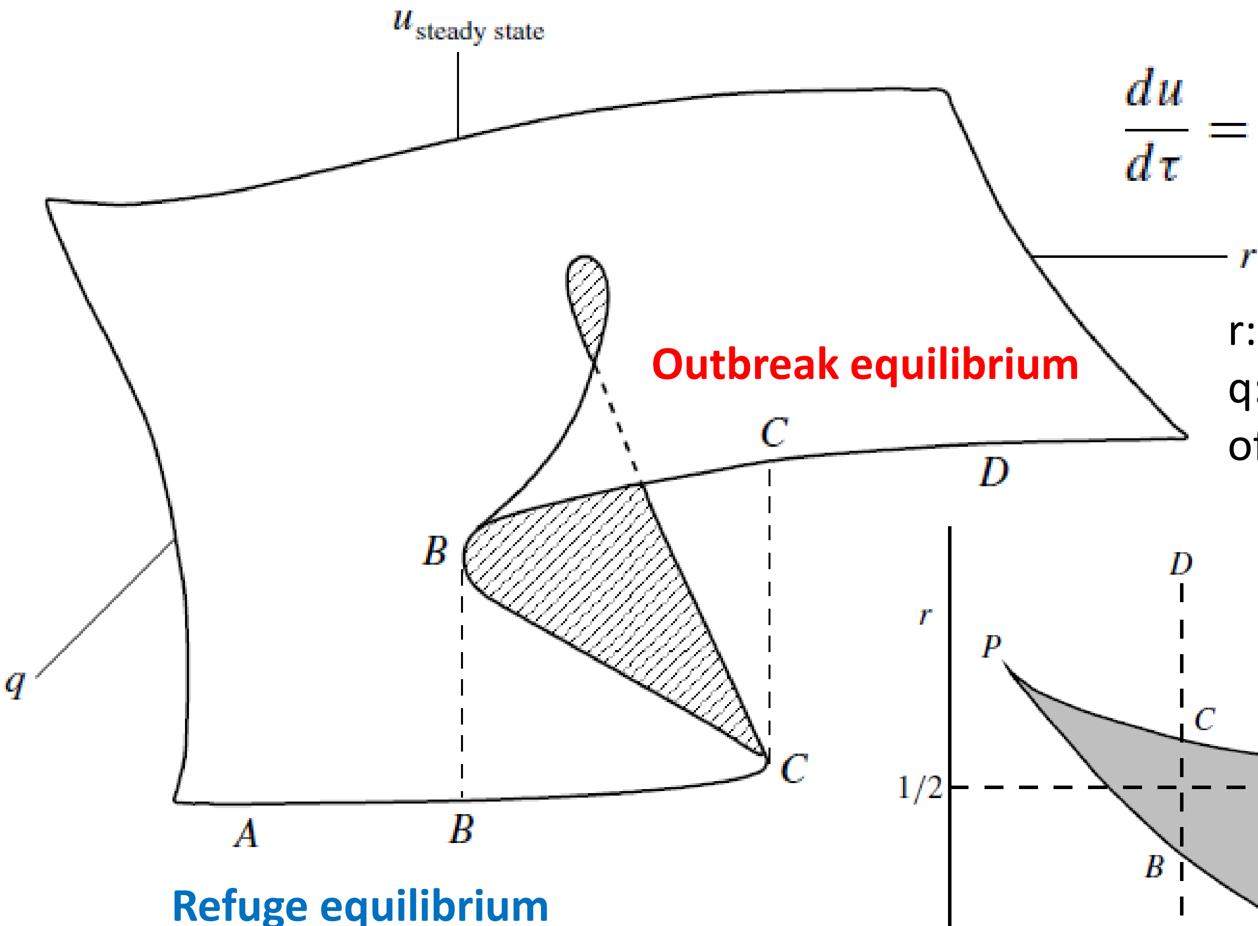
1975

Example: the Cusp Catastrophe

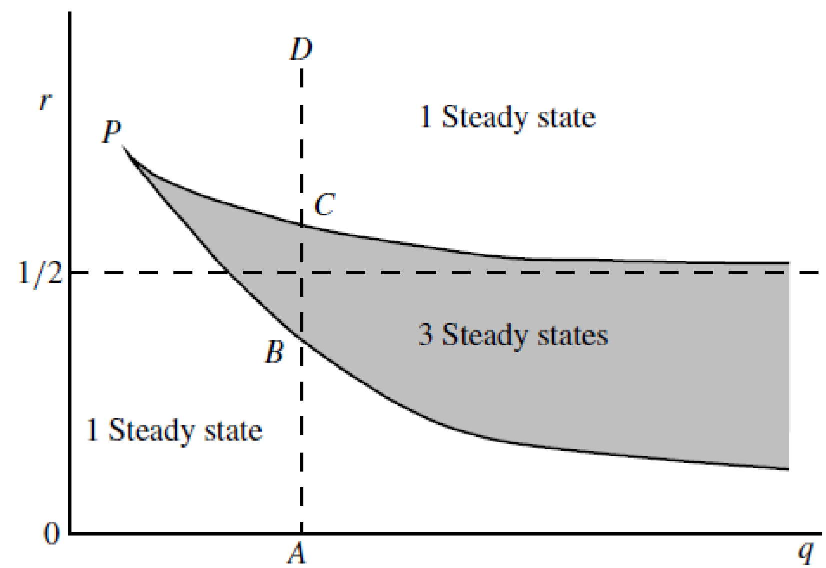
Model of an insect outbreak (the spruce budworm)

At high population densities – above a certain threshold – the insects are subject to predation (generally by birds)

$$\frac{du}{d\tau} = ru\left(1 - \frac{u}{q}\right) - \frac{u^2}{1+u^2}$$



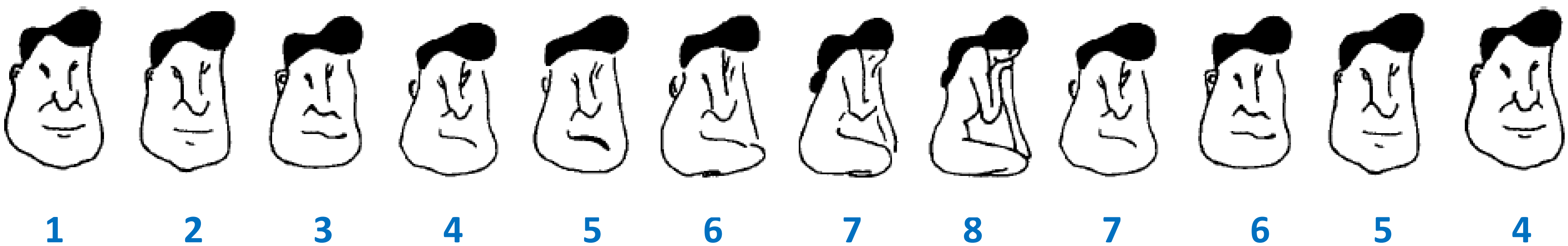
r: scaled growth rate
q: scaled carrying capacity of environment



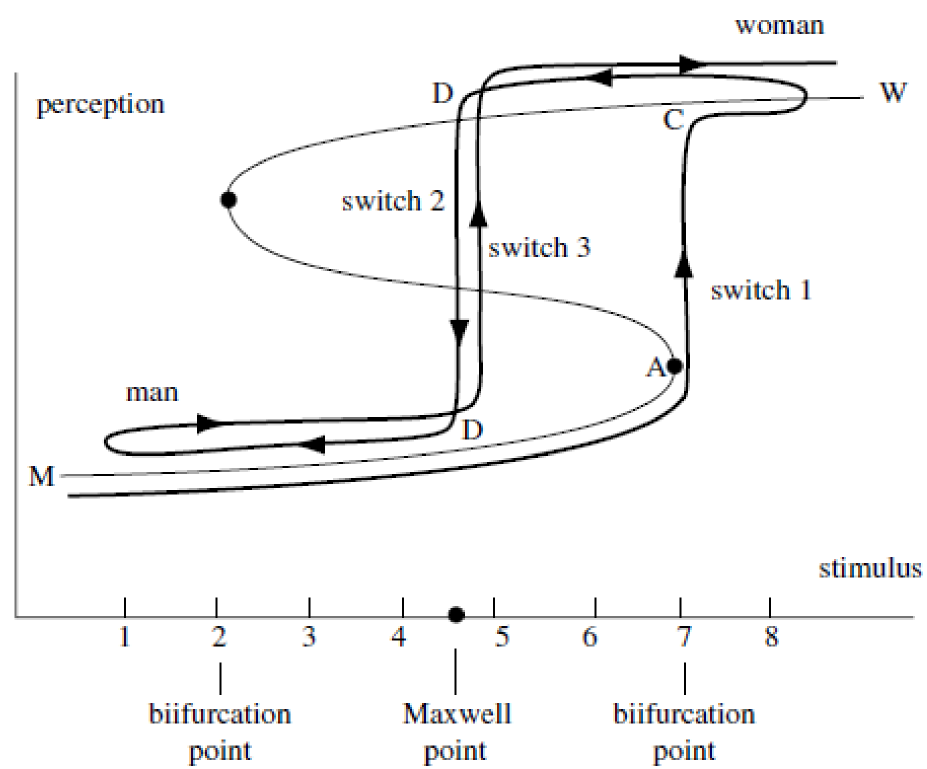
Images: J D Murray, *Mathematical Biology* vol I

Example: the Cusp Catastrophe

Model of jumps in perceptual recognition



Optical illusion: Man’s face or sitting woman ?
(Fisher 1967)



Images: J D Murray, *Mathematical Biology* vol I

Complex Adaptive Systems and the Santa Fe Way

SANTA FE INSTITUTE

Santa Fe Institute (1984 -)

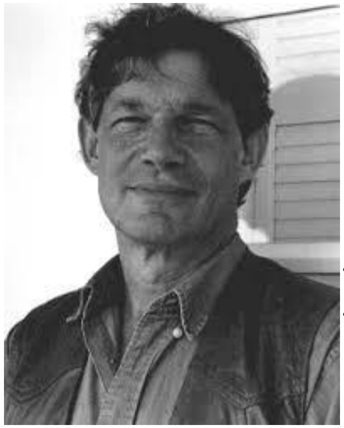
“Even though … complex systems differ in detail, the question of coherence under change is the central enigma for each. This common factor is so important that … we collect these systems under a common heading, referring to them as *complex adaptive systems* (CAS). This is more than terminology. It signals our intuition that general principles rule CAS behavior, principles that point to ways of solving the attendant problems”
(John H Holland, *Hidden Order*, 1995)

pop.katinkamatson.com

John H. Holland
(1929 -)

Evolution = Selection + Self-organization

(Stuart Kauffman, *Origins of Order*, 1992)



www.anisn.it

Stuart Kauffman
(1939 -)

“Systems Biology”

Distinctive feature of present-day systems biology: Extremely detailed models of biological phenomena bringing a high degree of realism

Precedents: Denis Noble’s program (1960s onwards) to construct more detailed models of larger portions of the heart

From 1990s the availability of large volumes of data (e.g., through high-throughput genomic assays) promoted the development of simulation platforms for modeling processes in the entire cell (e.g., E-cell of Masaru Tomita) and neurobiological systems at many scales (e.g., Genesis of Jim Bower et al – continued to be developed by Upi Bhalla).

Denis Noble (1936 -)

Hiroaki Kitano (1961 -)

Masaru Tomita (1957 -)

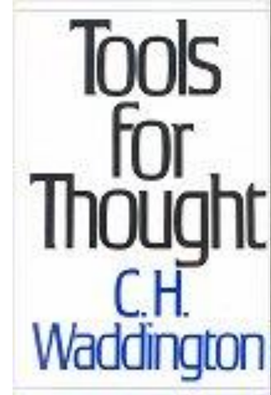
James Bower (1954 -)

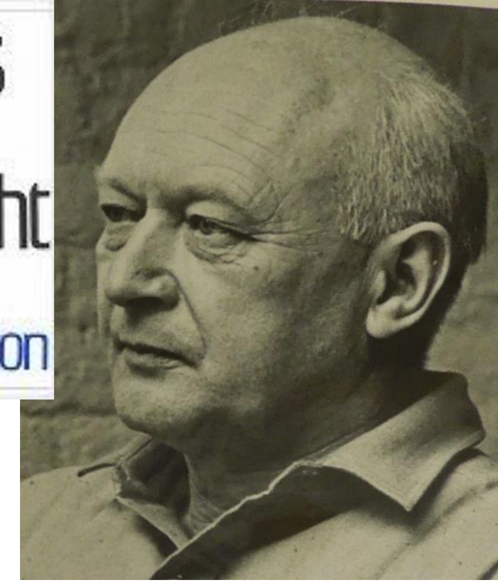
From 2000s, systems biology has gained a separate identity with dedicated institutes in various places and has been popularized by, among others, Hiroaki Kitano – and a flood of papers, conferences, textbooks and courses (including MOOCs on Coursera)

Upi Bhalla

Tools for Thought

Waddington's influential book (published posthumously) is a survey of theories and methods for dealing with complex systems, including human beings and societies
"Considerations of complex shapes, of interactions, of processes, of stabilities, traffic of information and instructions, games theories, forecasting, statistics and more classical scientific analyses…"





Conrad Hal Waddington (1905-1975)

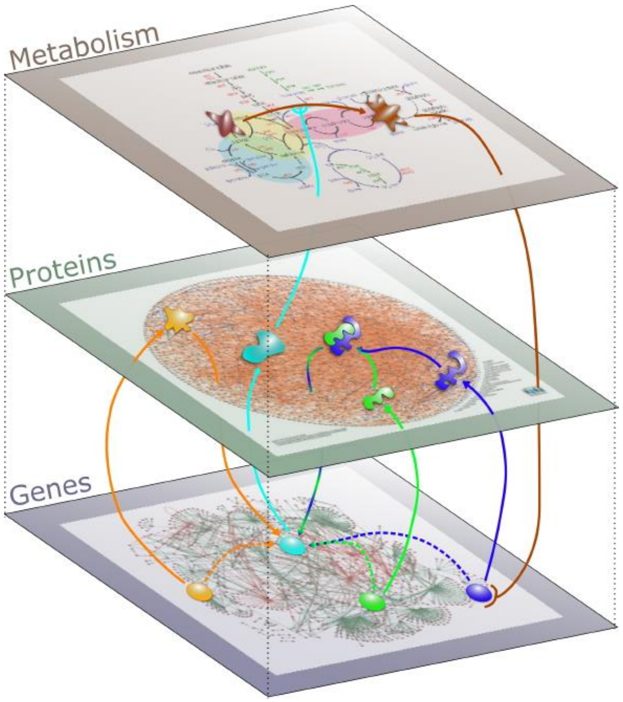
Waddington urged throughout a reassessment of how we think in order to move beyond what he calls the "Conventional Wisdom of the Dominant Group" or "COWDUNG"

In a very similar spirit

Systems biology attempts applying a set of theoretical abstractions to understand analogous phenomena across systems and across scales

The course is organized around several "tools for thinking" about biological problems :

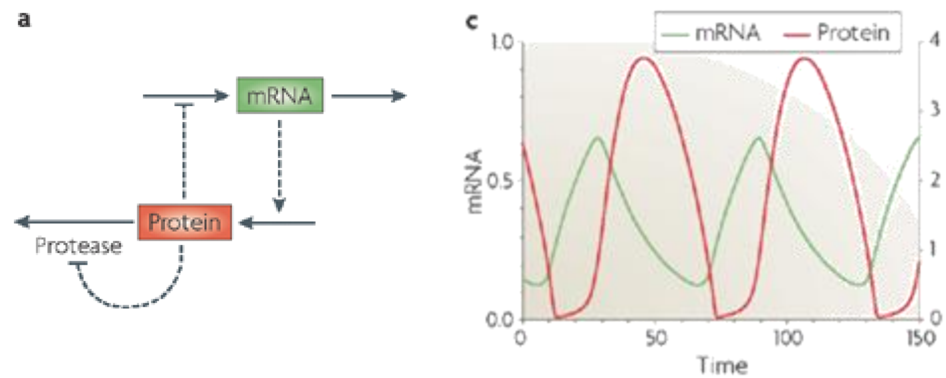
❑ Networks



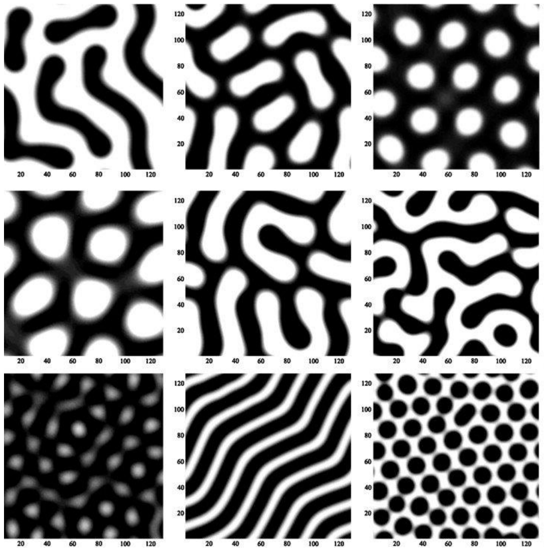
www-dsv.cea.fr

❑ Oscillations

Novak & Tyson (2008)
www.nature.com

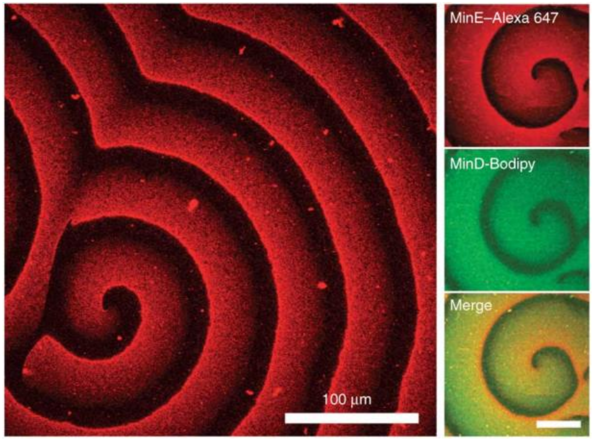


❑ Shapes



pijamasurf.com

❑ Waves



Groves & Kuriyan (2010)
www.nature.com

Networks

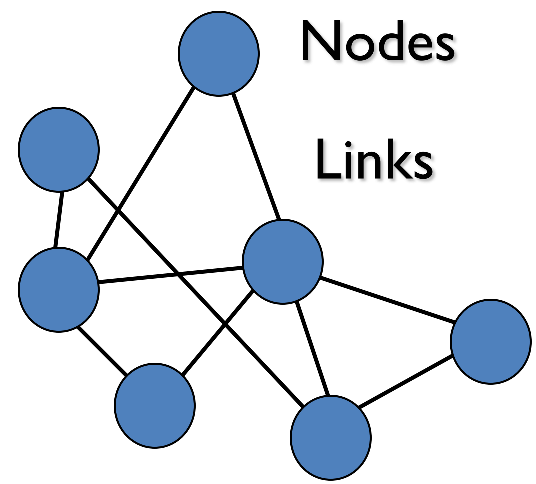
Patterns in abstract non-physical space

What is a network ?

Components = Nodes

Interactions = Links

System = Network



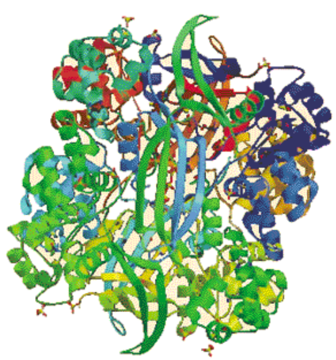
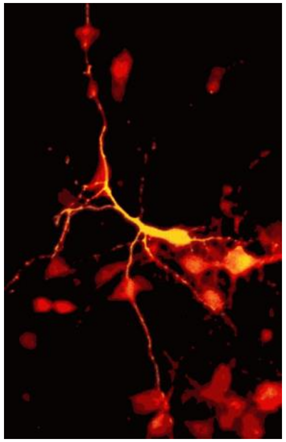
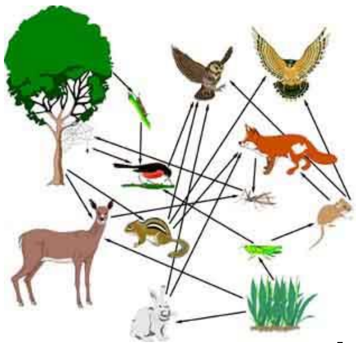
Network structure is defined by *adjacency matrix* A

A_{ij} = 1, if a link exists between i and j ($\neq$ i)

= 0, otherwise

Ubiquity of Networks

Networks appear at all scales in biology

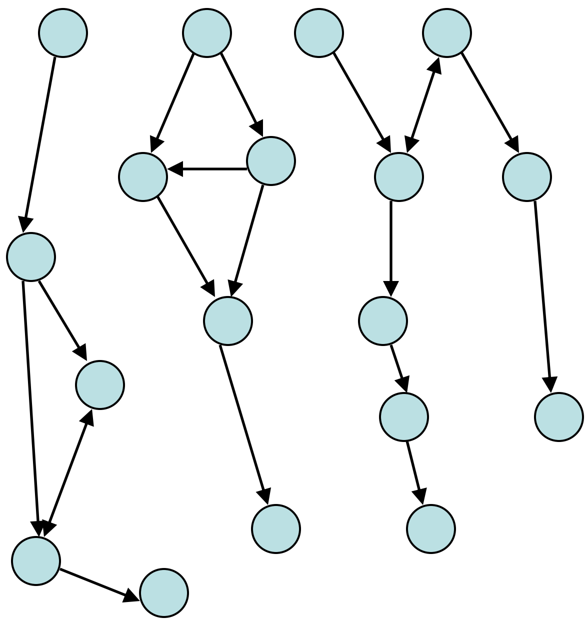
Proteins	Intra-cellular signalling	Neuronal communication	Epidemics	Food webs
				

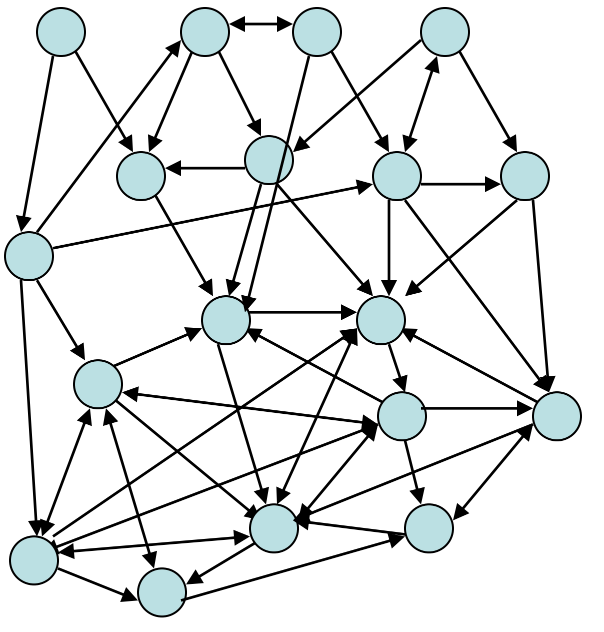
10^{-9} m — 10^{-6} m — 10^{-3} m — 1 m — 10^{3} m — 10^{6} m

Molecules	Cells	Organisms	Populations	Ecologies

Pathways vs Networks

Why did Nature opt for Networks ?

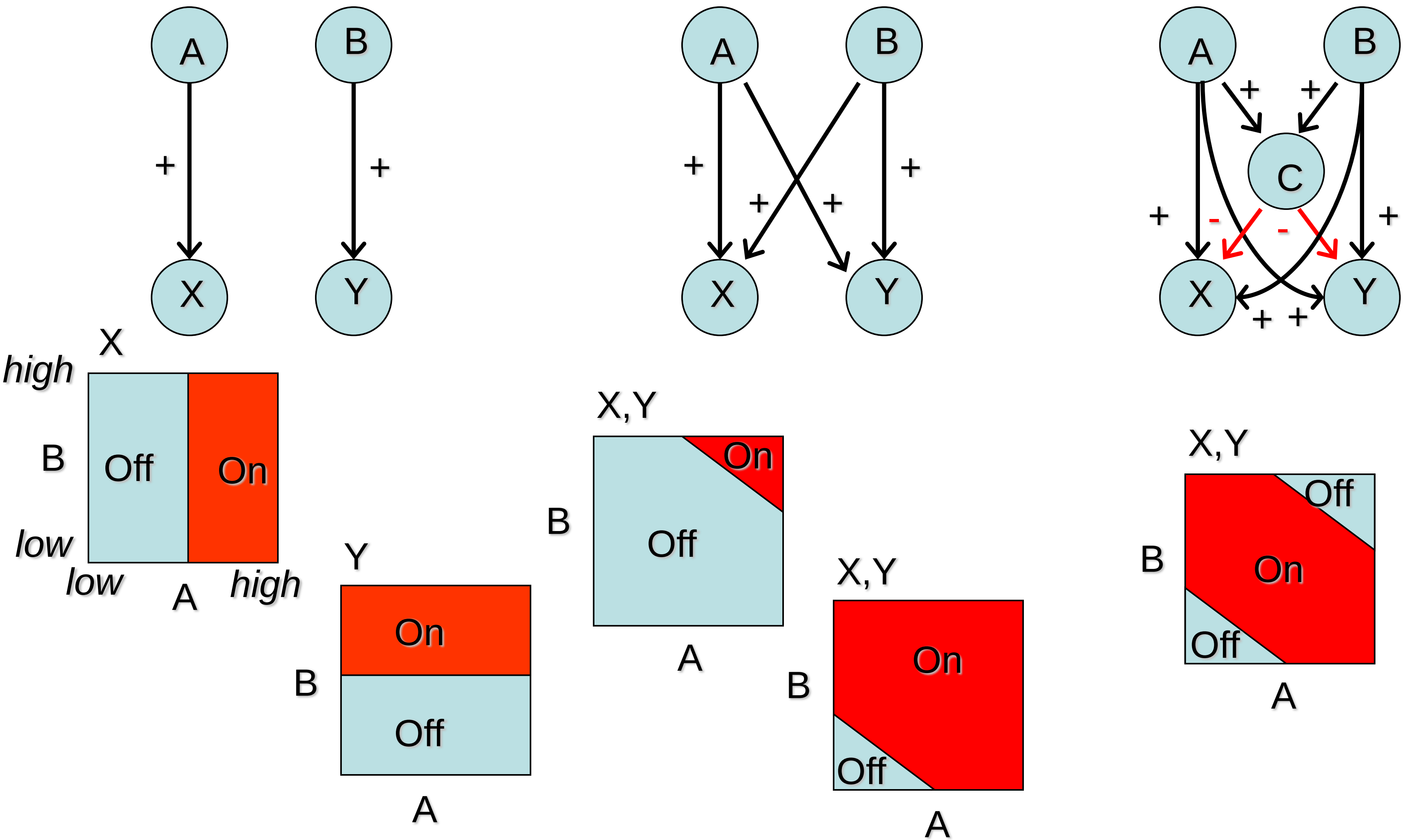




- For example, why did a central nervous system (brain) evolve at all instead of a nervous system equivalent to a collection of reflex arcs ? Also relevant for cell-signalling

Advantage of Networks: Flexibility

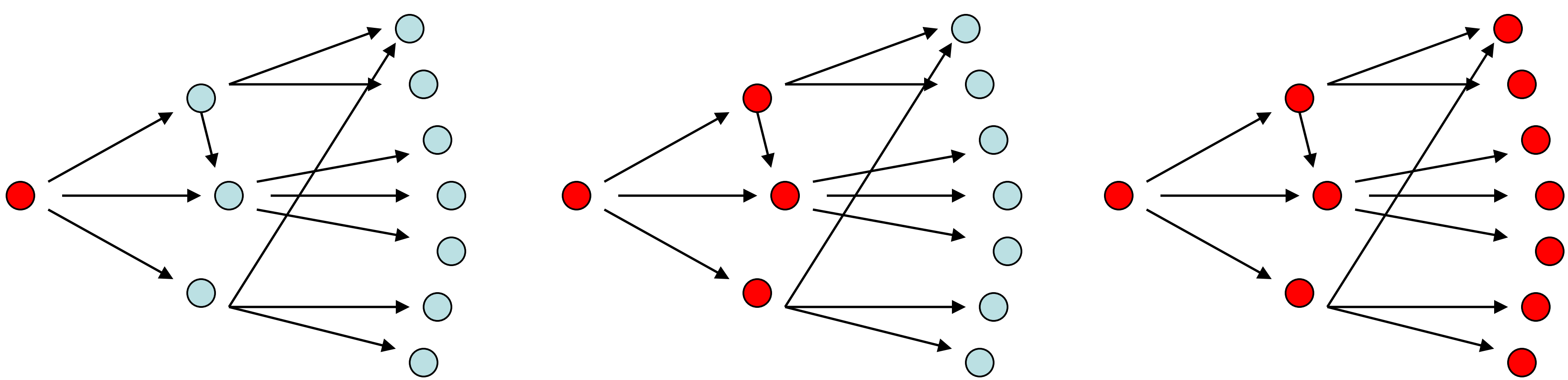
Logic Gates out of Threshold Element Networks



Disadvantage of Networks: Necessity for complex control mechanisms

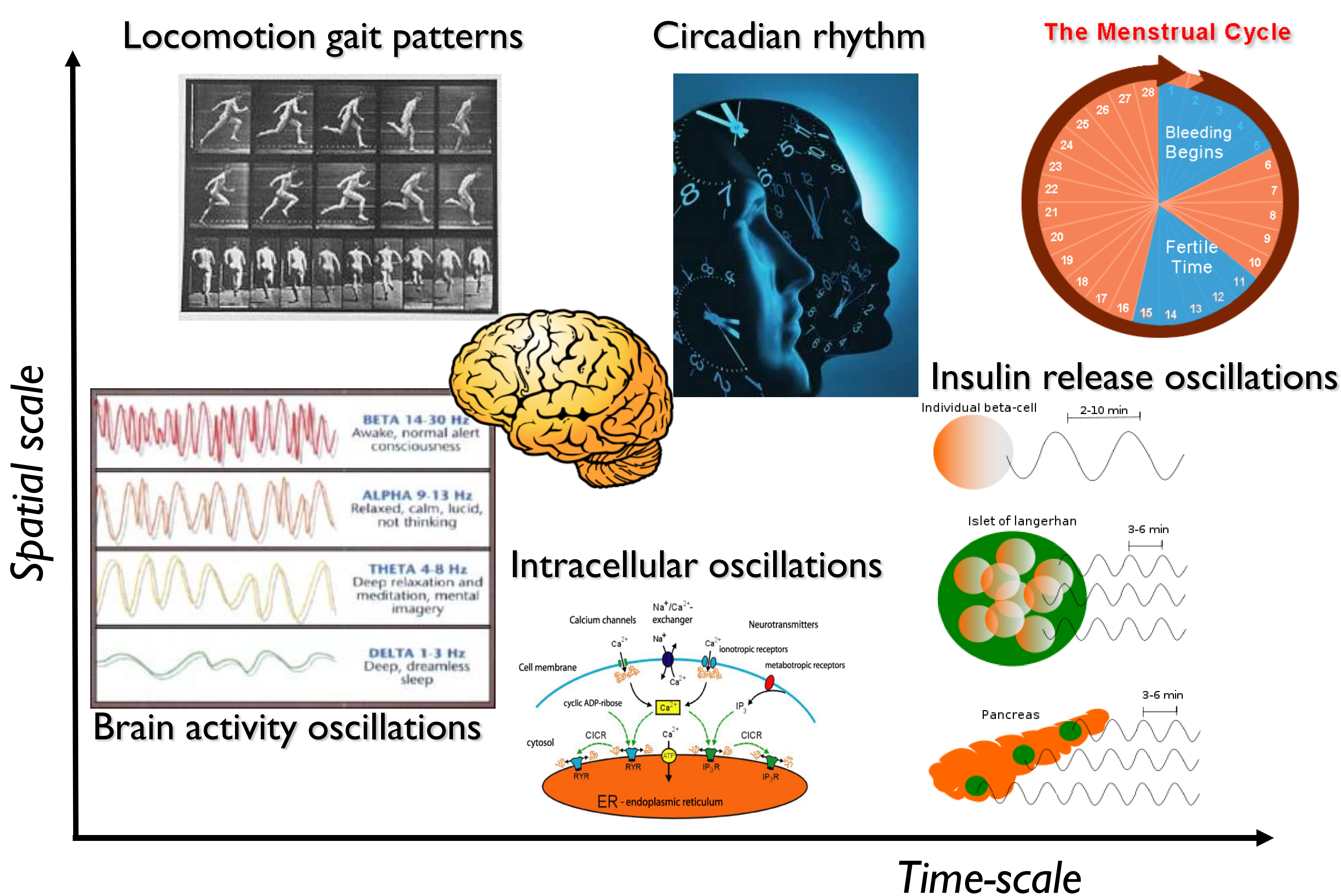
- The price to be paid for this flexibility: *Control overheads*

  Need to introduce additional control machinery to segregate different functional circuits
- E.g., stimulation of a receptor by a specific molecule should result in cell-death (apoptosis) and NOT cell-division!
- Problem: In a structurally connected network, stimulating any node will lead eventually to stimulation of all nodes through cascading activation signals



Temporal Patterns

Biological oscillators: span many space & time scales



Synchronization of spatially distributed oscillations is ubiquitous in nature…

- Pacemaker cells in the heart
- β-cells in the pancreas
- Long-range synch across brain during perception
- Contractions in the pregnant uterus
- Menstrual cycles
- Rhythmic applause
- Pedestrians on a bridge falling in step with the swinging motion of bridge

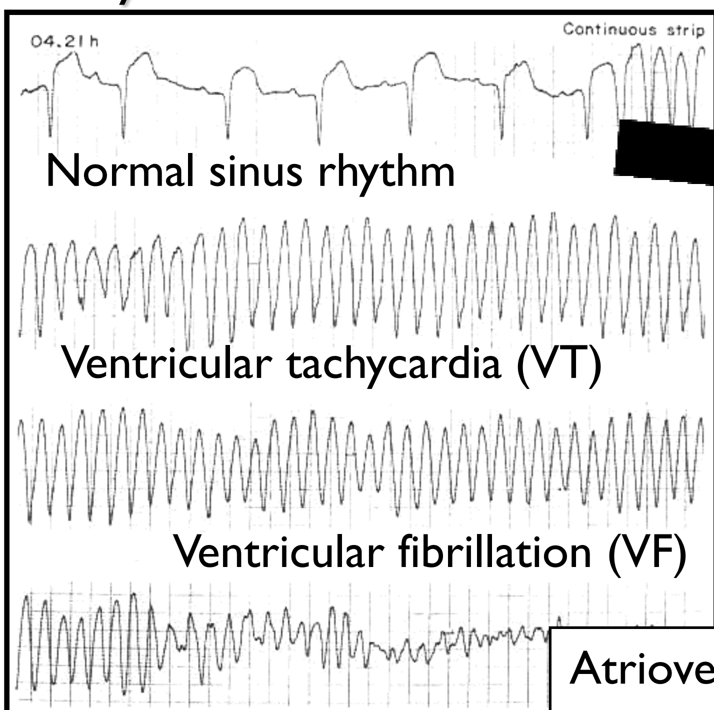
Male Fireflies flashing in unison

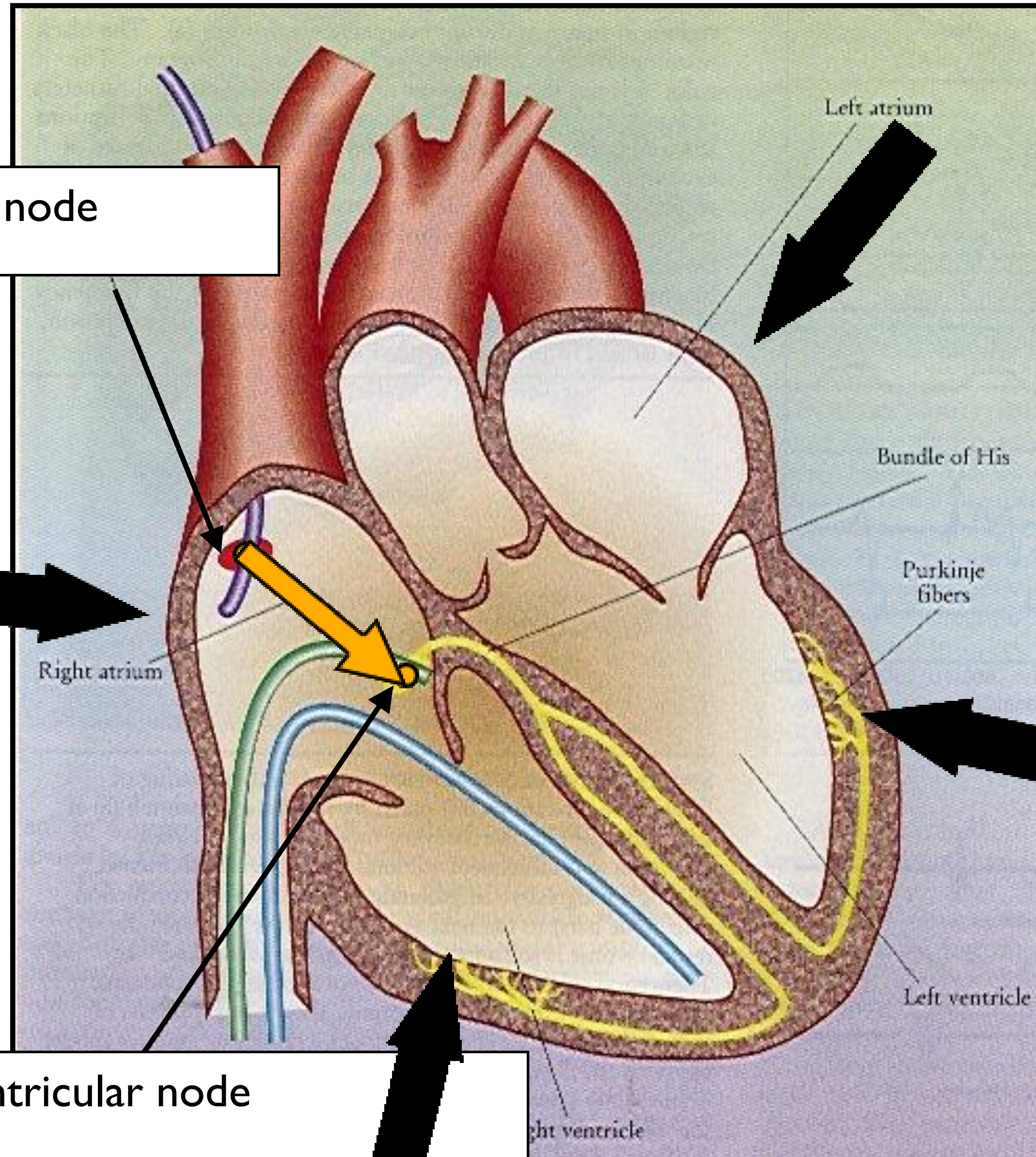
Each insect has its own rhythm – but the phase alters based on seeing its neighbors lights, bringing harmony

… and vital for the proper functioning of many biological systems

Example:

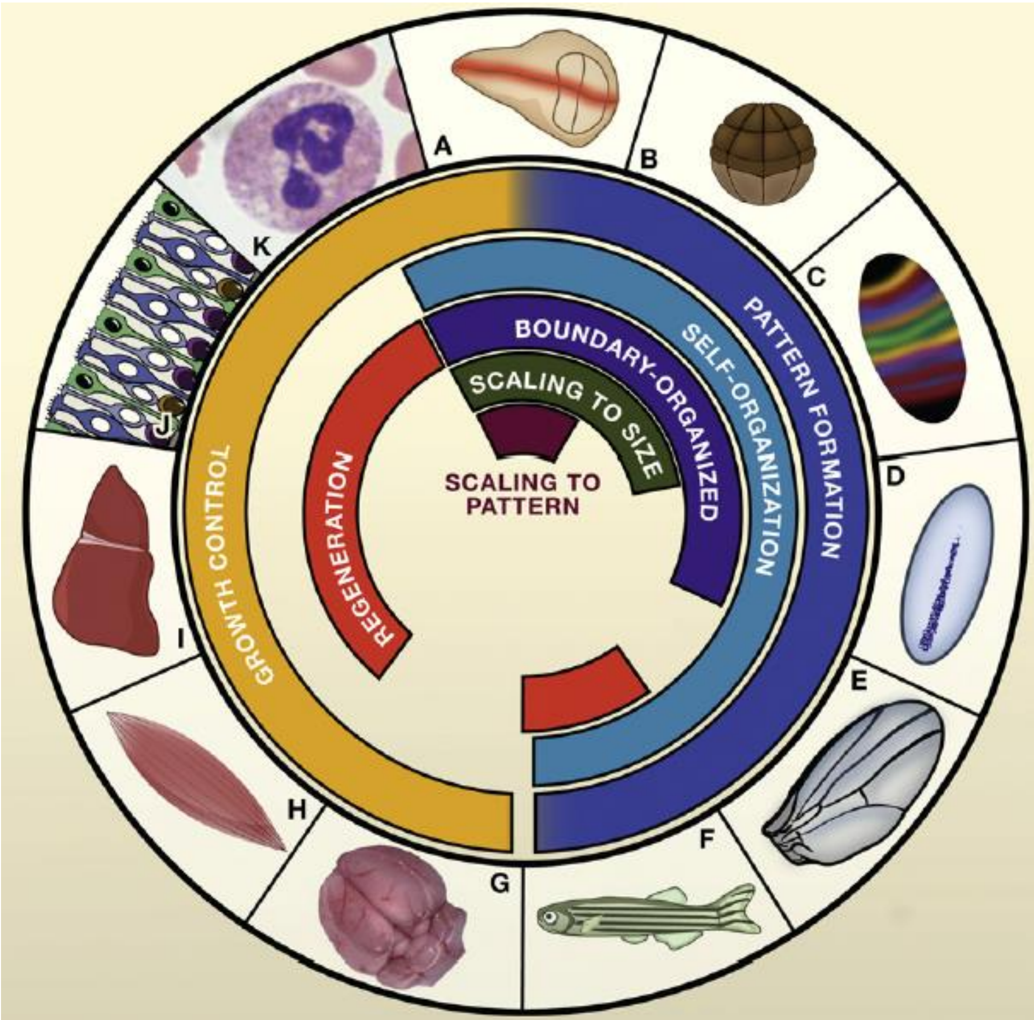
Disruption of coherent collective activity in heart can result in life-threatening arrhythmia



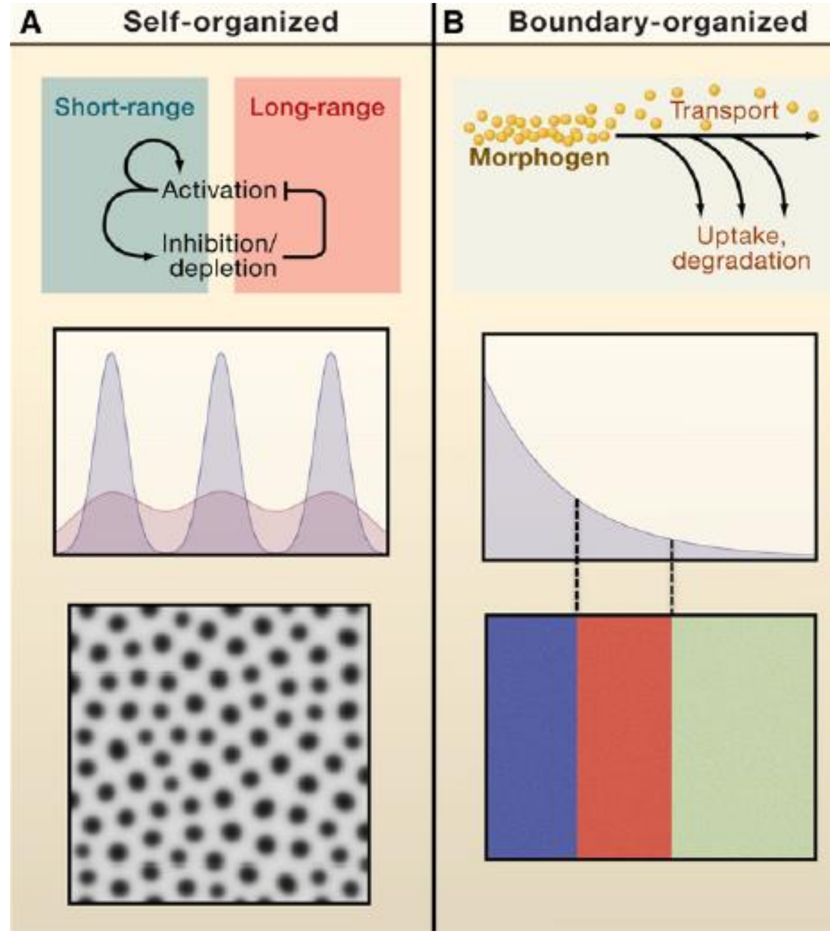


Spatial Patterns

Two modes of spatial pattern organization in biology



Lander, *Cell* (2011)



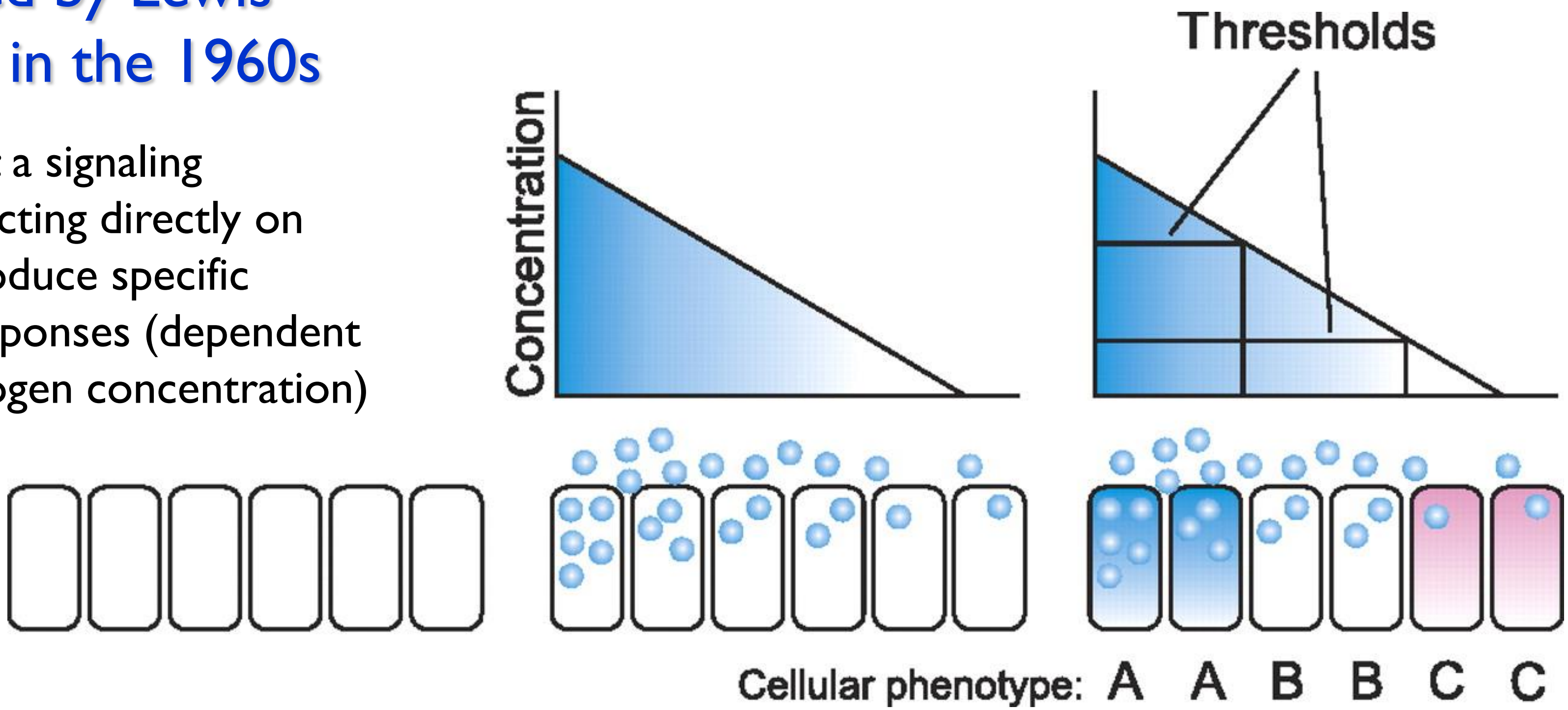
Lander, *Cell* (2011)

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

Described by Lewis Wolpert in the 1960s

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

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



- ❑ 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

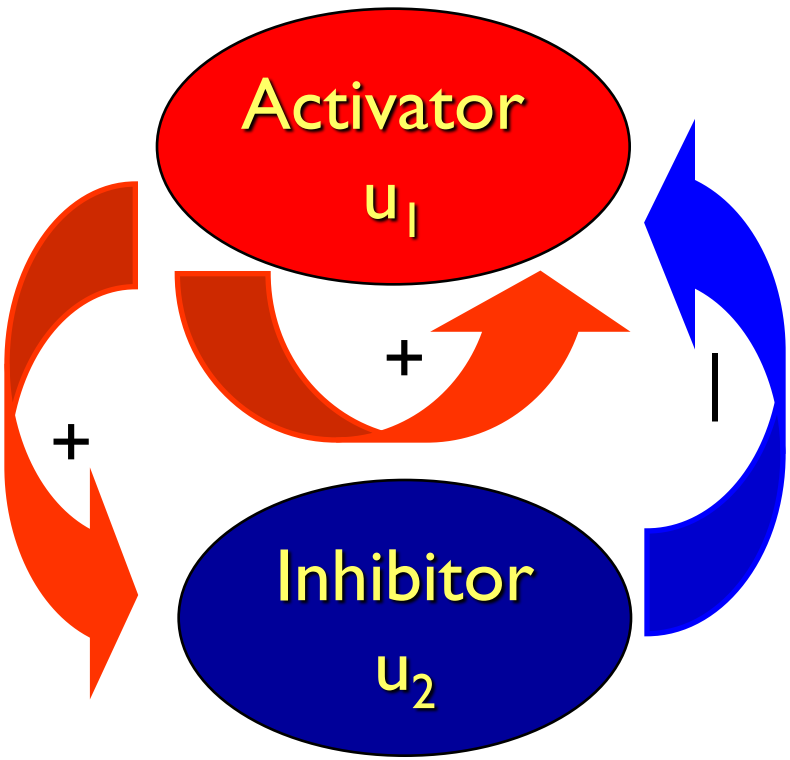
Turing: Explaining morphogenesis

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

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

$$\equiv$$

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



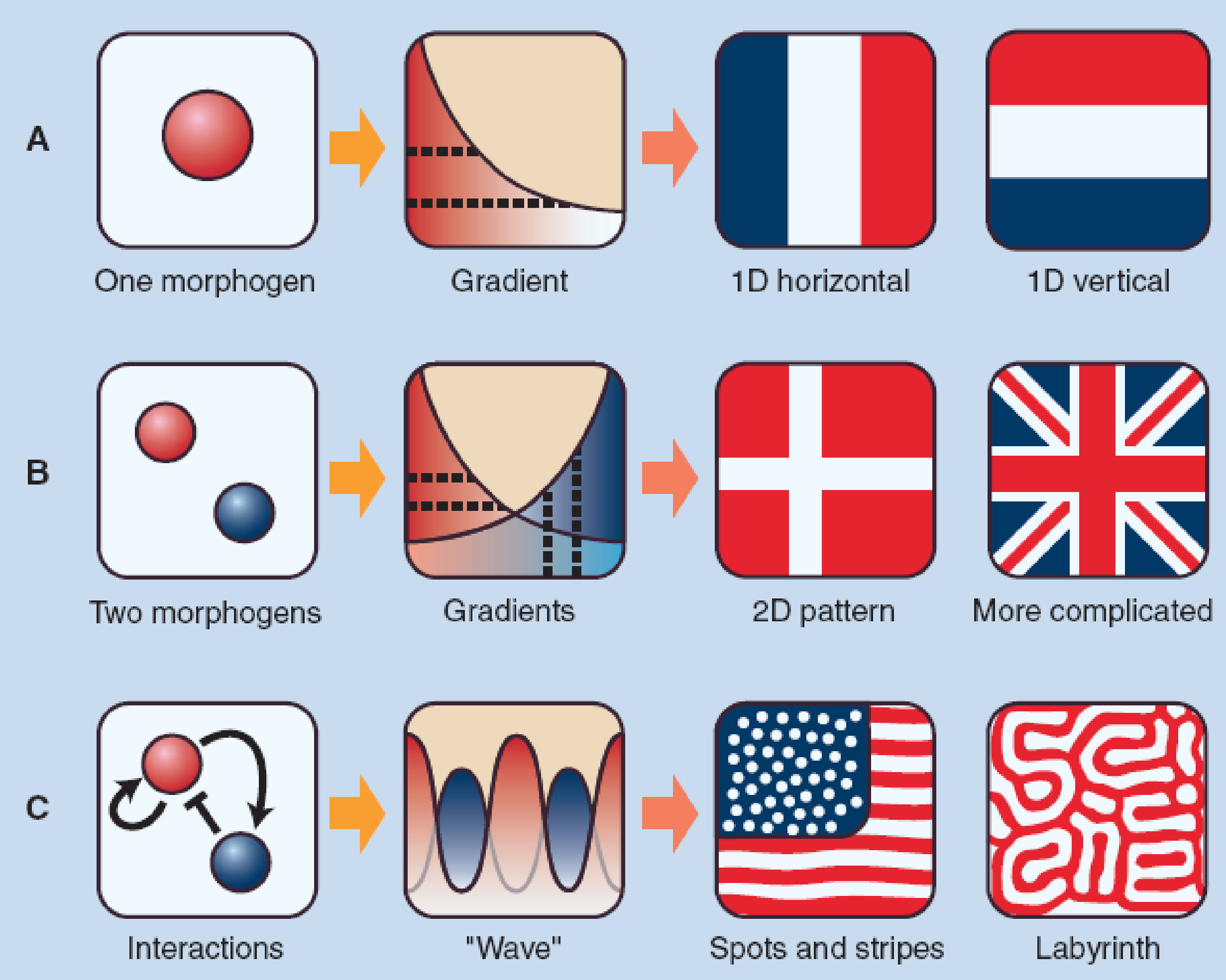
- Activator u_1: substance that stimulates increase in concentration of both chemicals
- Inhibitor u_2: substance that leads to a decrease in concentrations
- Turing: such a system can produce stationary pattern through spontaneous symmetry-breaking if inhibitor diffuses much faster than activator (*local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

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

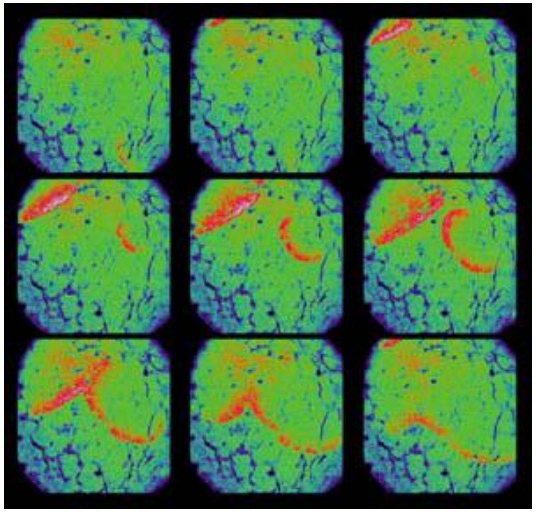


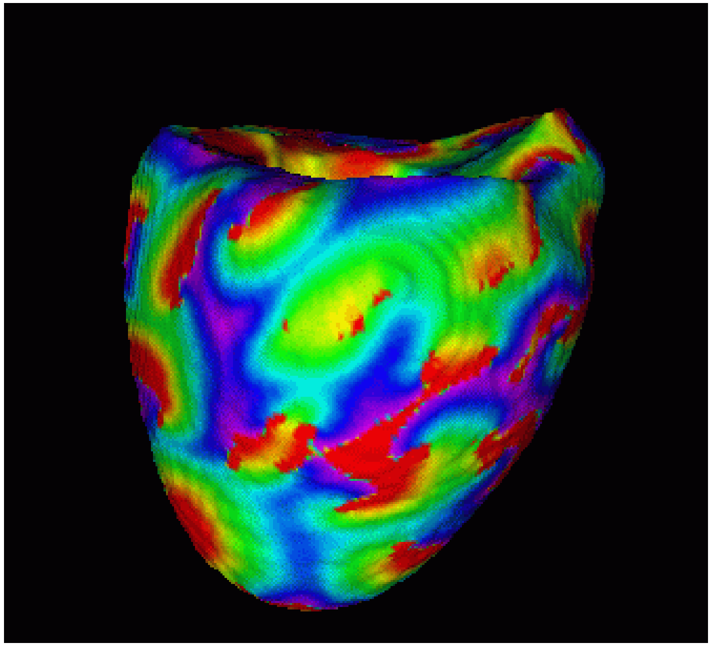
Spatio-temporal Patterns

Waves in Biological Systems

Aggregation of *Dictyostelium Discoidium* amoebae by cAMP signalling

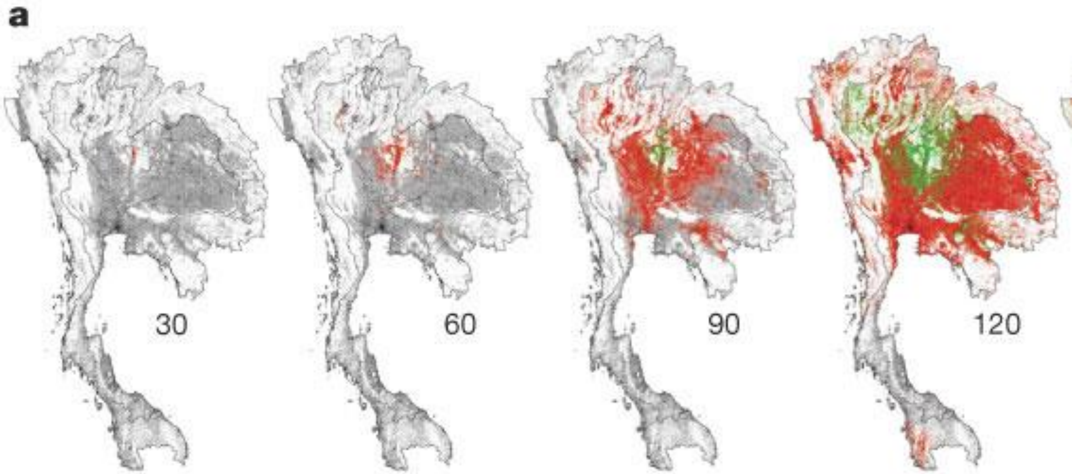
Ca^{++} waves in cytoplasm of *Xenopus* oocytes





Electrical activity in heart

Ferguson et al, Nature, 2005

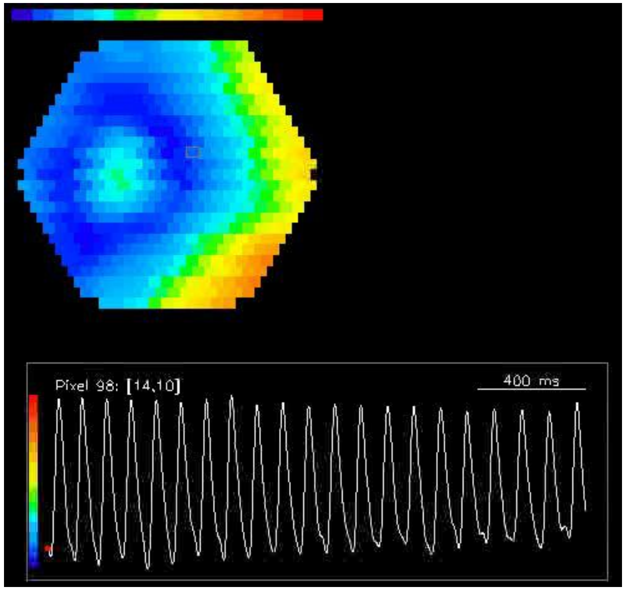


Spreading Waves in Epidemics

Propagating Waves in Rat Neocortical Slices: Spiral Waves & Bursts

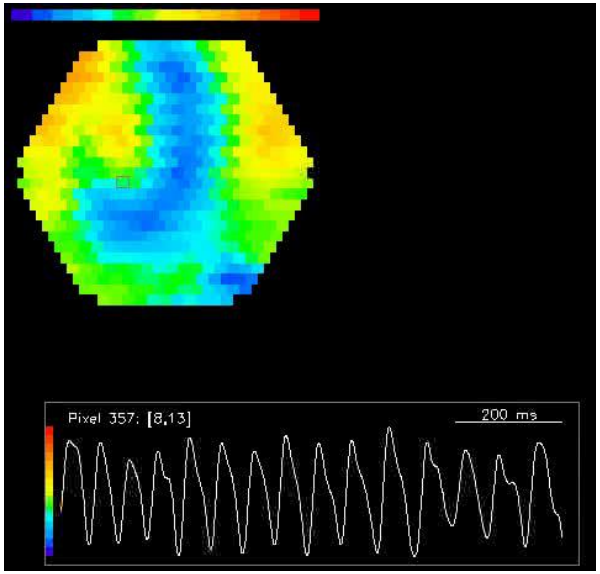
Spontaneous oscillations in slice organized spatially as propagating waves

J Wu Lab, Georgetown Univ



Ring waves

Period ~ 100ms

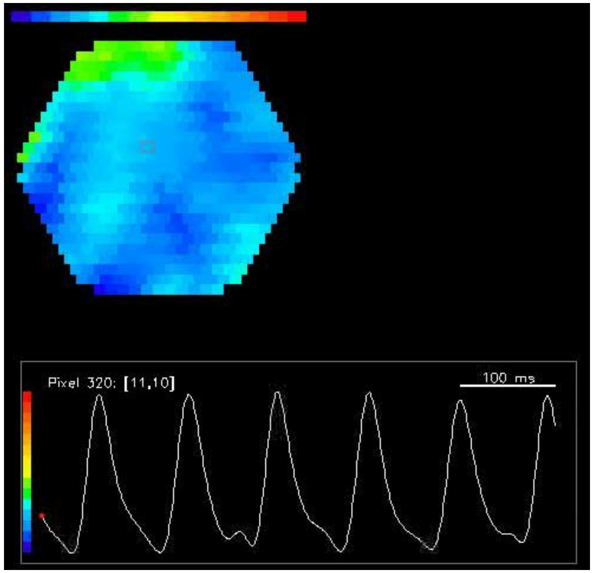


Spiral waves

Aperiodic,
dominant period ~ 70ms

Period ~ 100ms

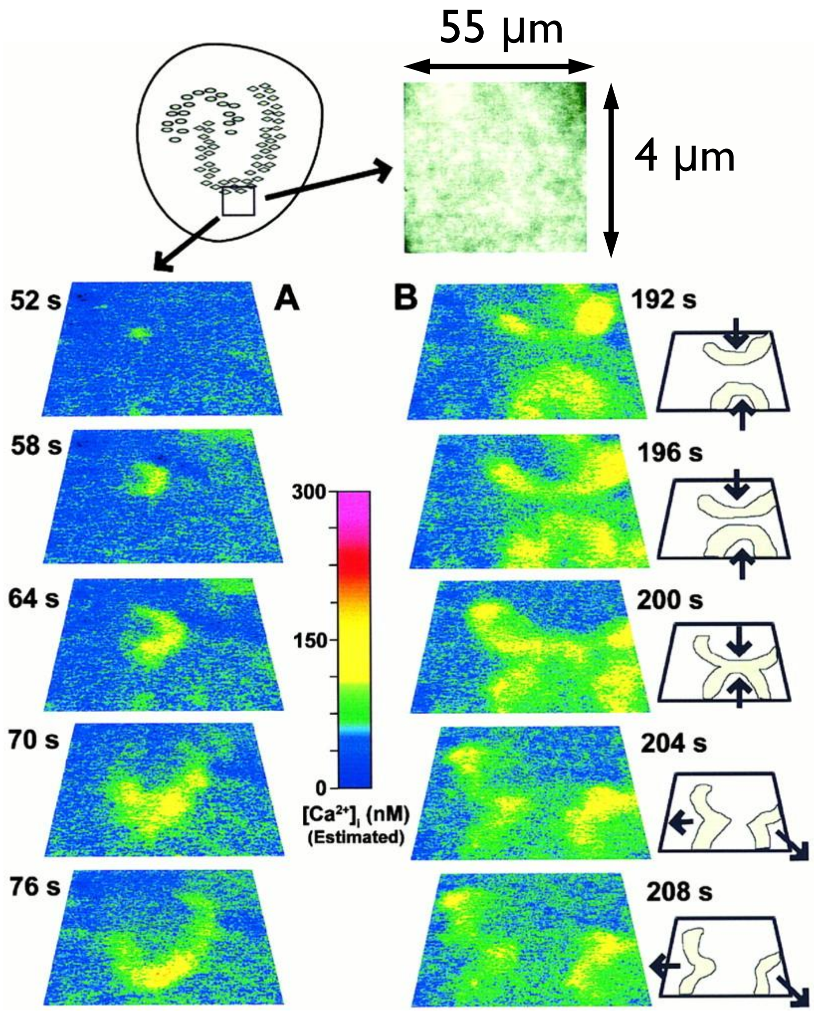
Bursts

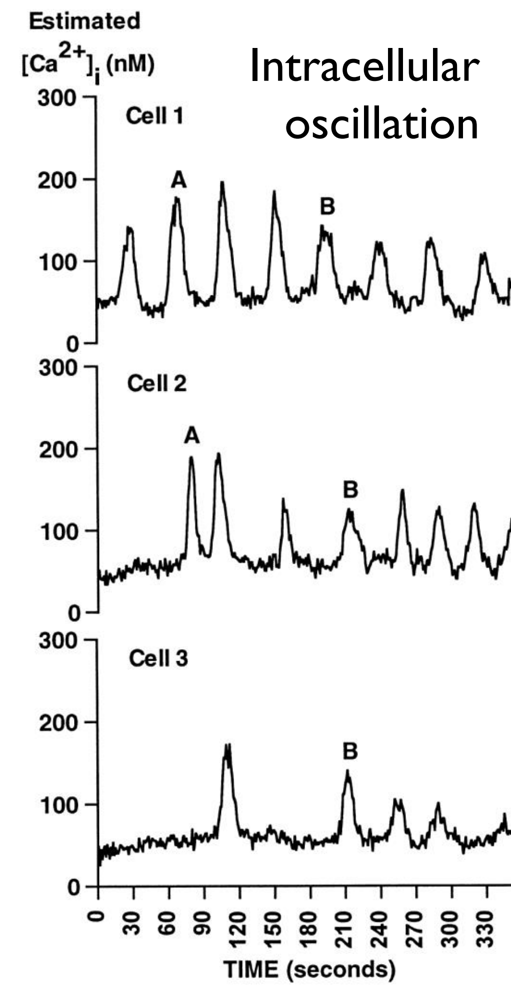


Spiral Waves in Mouse Hippocampus

Observation of intercellular Ca^{++} spiral waves in hippocampal slice cultures

- Calcium waves (traveling at 5-10 μm/s) in *glial* cell syncytium





Harris-White et al, 1998

For many biological processes

No centralized coordination

agency for activity spread across space have been identified as yet

Ordering without centralized coordination

Local interactions can lead to order without an organizing center in complex systems

Wikipedia

Wikipedia

Examples:
flocking and swarming