

Systems Biology: A Personal View

II. Antecedents & course outline

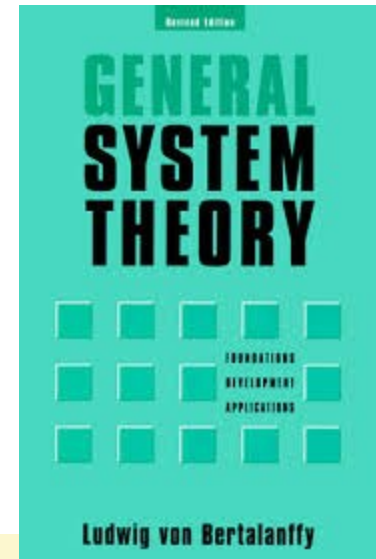
Sitabhra Sinha
IMSc Chennai

General Systems Theory and von Bertalanffy

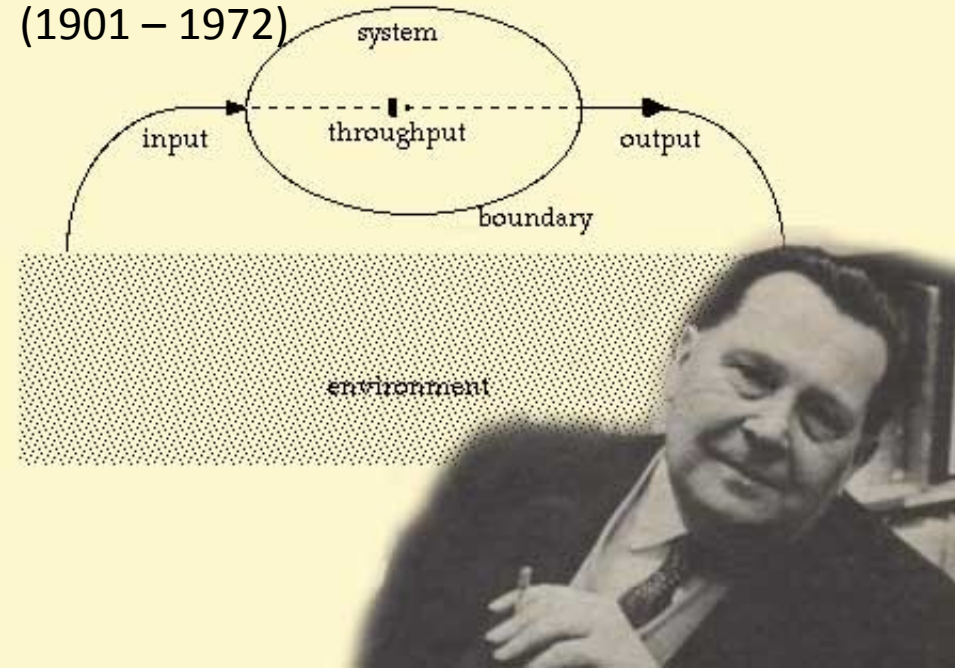
The Quest for a General System Theory (1968)

“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...”



Ludwig von Bertalanffy
(1901 – 1972)



Systems thinking in a slightly restricted context...

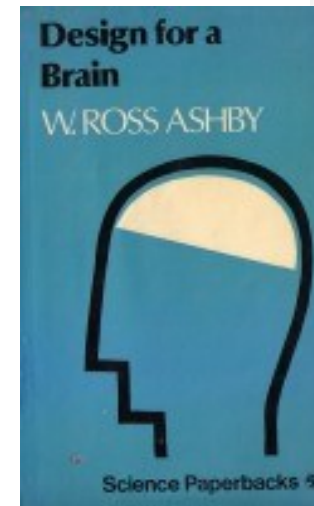
Cybernetics, Ashby and Wiener

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

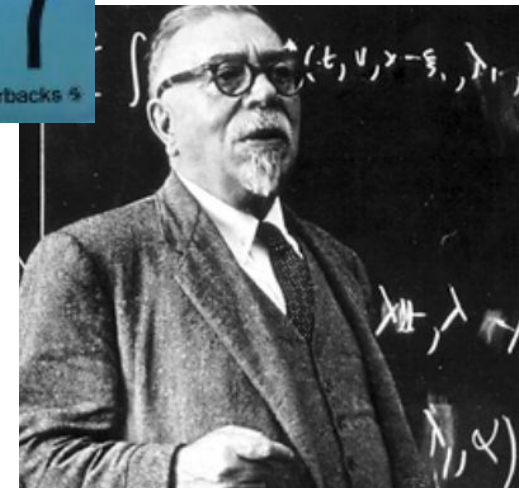
Wikipedia:

“[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.”

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



W. Ross Ashby
(1903-1972)



Norbert Wiener
(1894 -1964)

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)



John H. Holland
(1929 -)

pop.katinkamatson.com



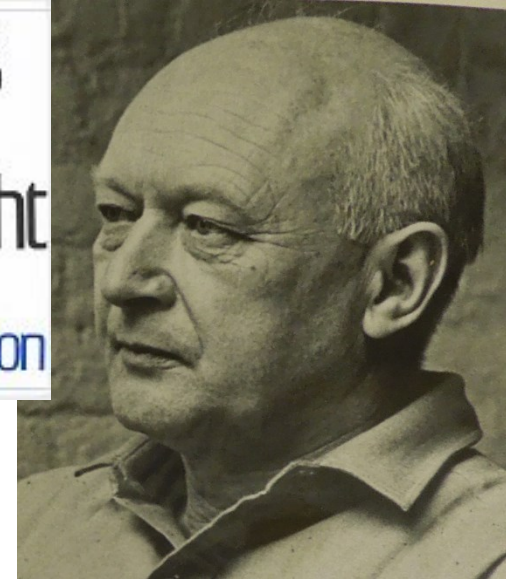
Stuart Kauffman
(1939 -)

www.anisn.it

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)

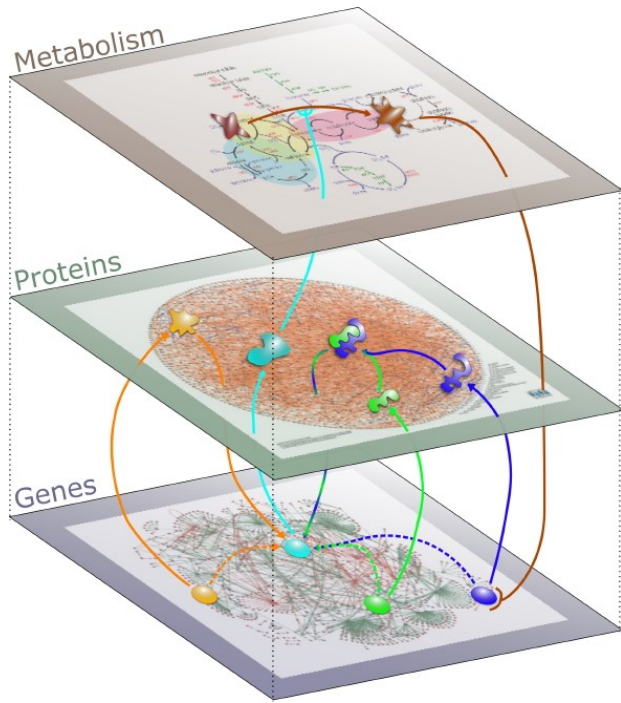
Waddington urged throughout a reassessment of how we think in order to move beyond what he calls the "Conventional Wisdom of the Dominant Group" or "COWDUNG"

In a very similar spirit

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

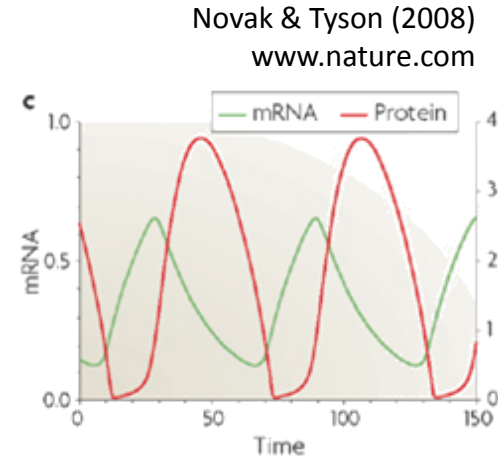
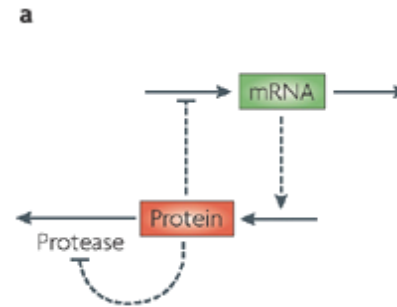
The course is organized around several “tools for thinking” about biological problems :

□ Networks

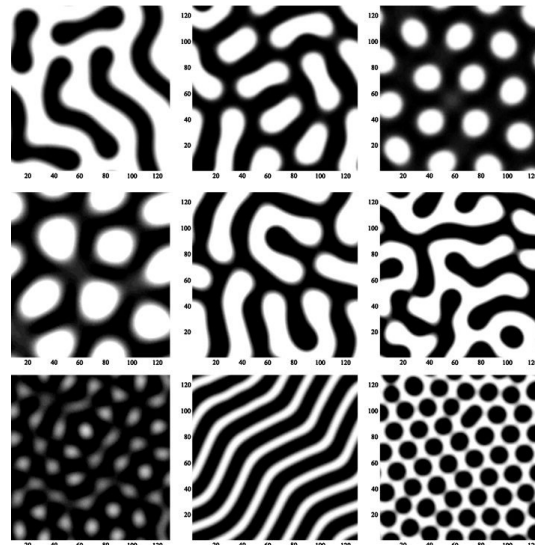


www-dsv.cea.fr

□ Oscillations

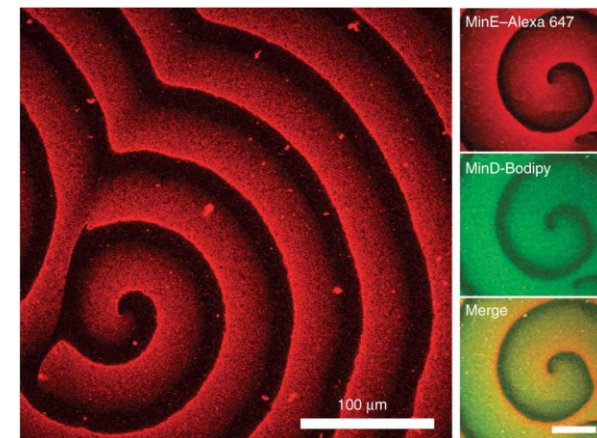


□ Shapes



pijamasurf.com

□ Waves



Groves & Kuriyan (2010)
www.nature.com

Networks

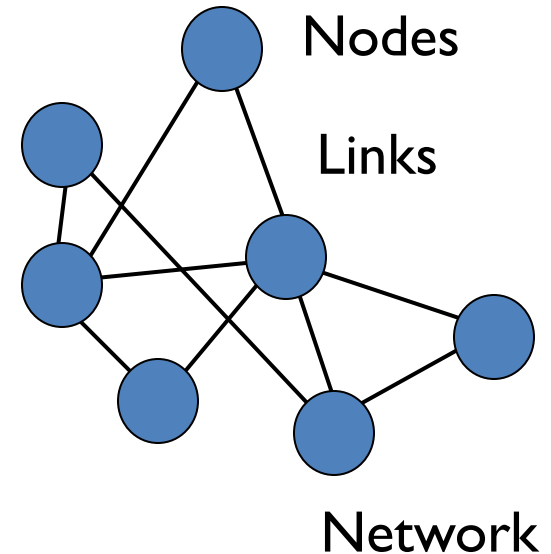
Patterns in abstract non-physical space

What is a network ?

Components = Nodes

Interactions = Links

System = Network



Network structure is defined by *adjacency matrix* A

$$A_{ij} = 1, \text{ if a link exists between } i \text{ and } j \text{ (} \neq i \text{)}$$
$$= 0, \text{ otherwise}$$

Ubiquity of Networks

Networks appear at all scales in biology

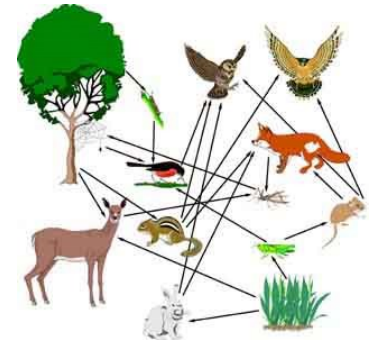
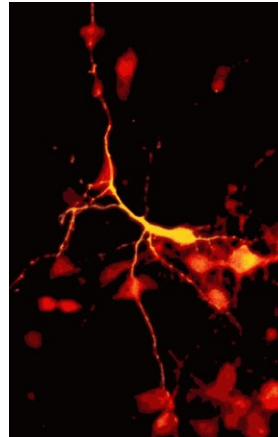
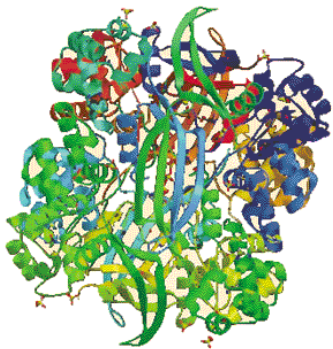
Proteins

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

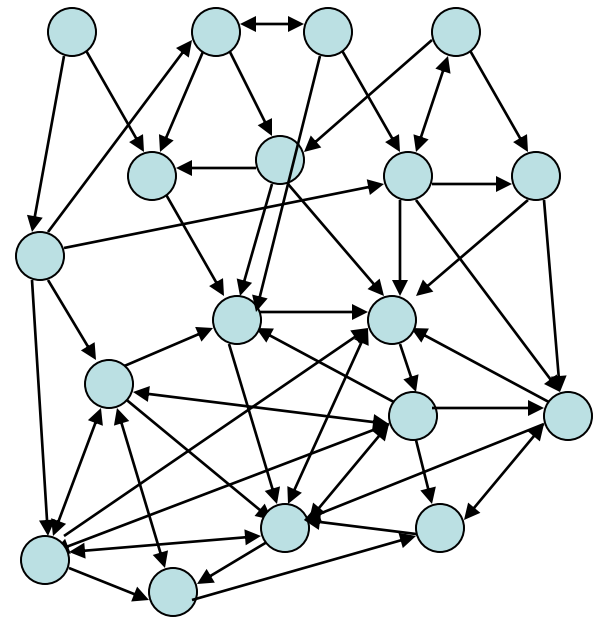
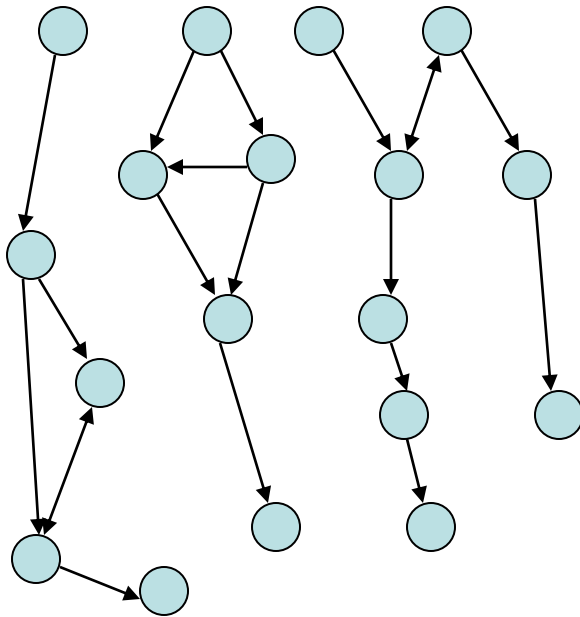
Organisms

Populations

Ecologies

Pathways vs Networks

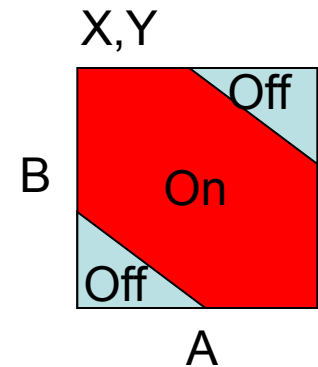
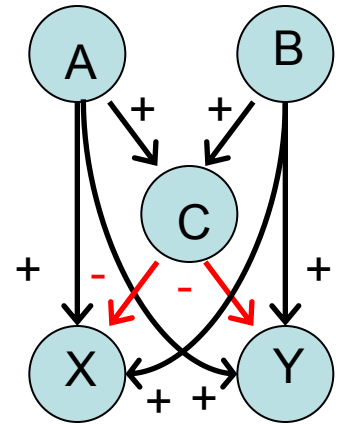
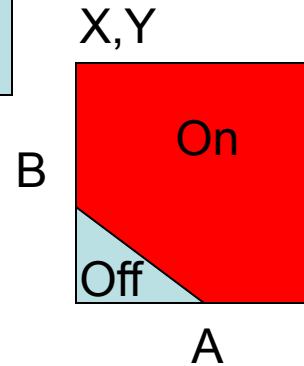
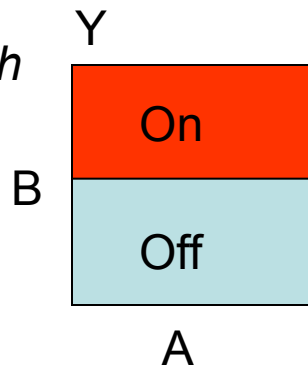
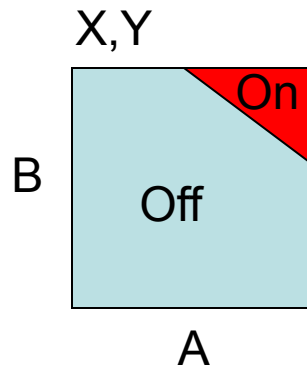
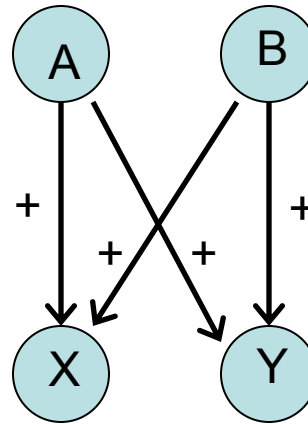
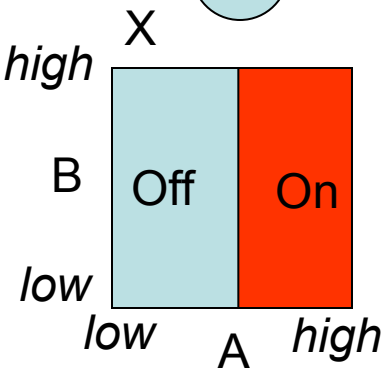
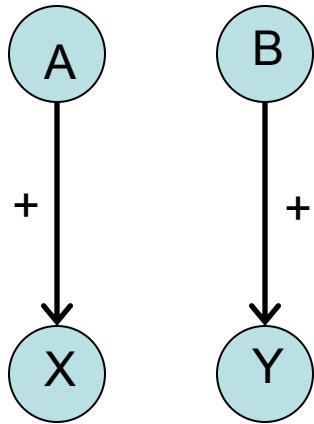
Why did Nature opt for Networks ?



- 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

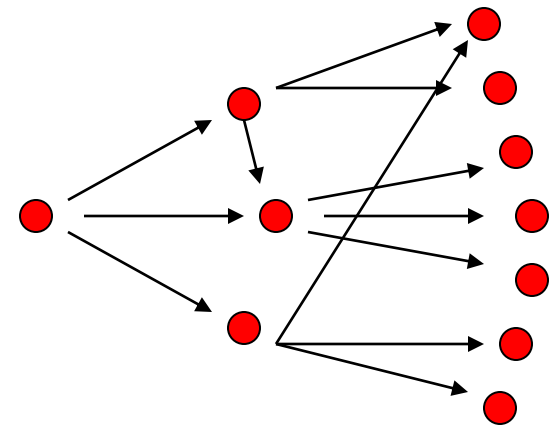
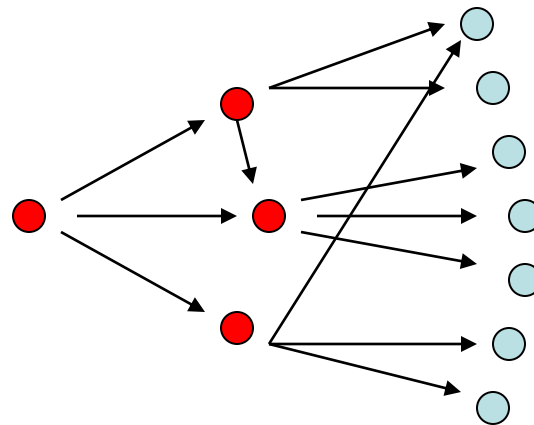
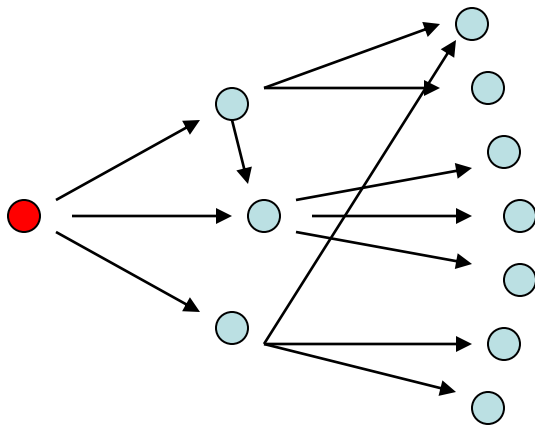
Advantage of Networks: Flexibility

Logic Gates out of Threshold Element Networks



Disadvantage of Networks: **Necessity for complex control mechanisms**

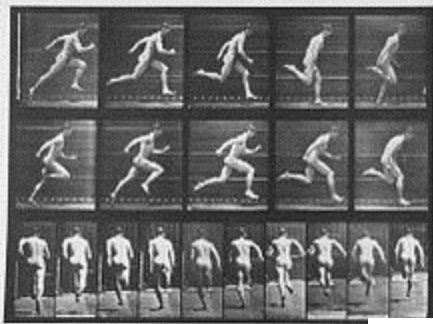
- **The price to be paid for this flexibility:** *Control overheads*
Need to introduce additional control machinery to segregate different functional circuits
- E.g., stimulation of a receptor by a specific molecule should result in cell-death (apoptosis) and NOT cell-division!
- **Problem:** In a structurally 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

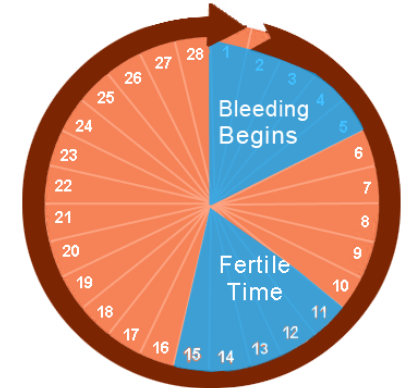
Locomotion gait patterns



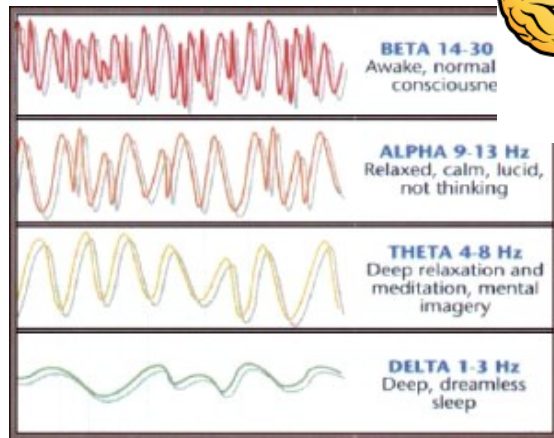
Circadian rhythm



The Menstrual Cycle



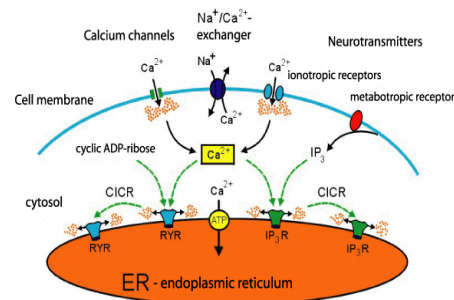
Spatial scale



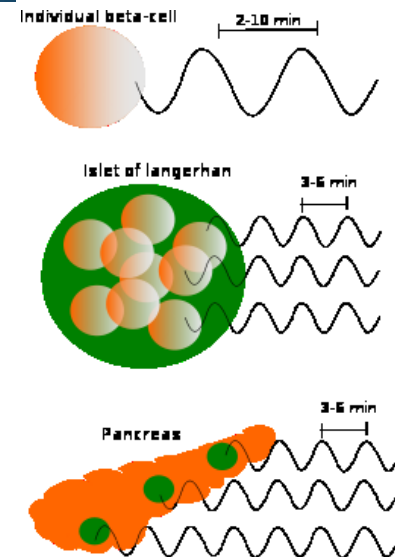
Brain activity oscillations



Intracellular oscillations



Insulin release oscillations



Time-scale

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

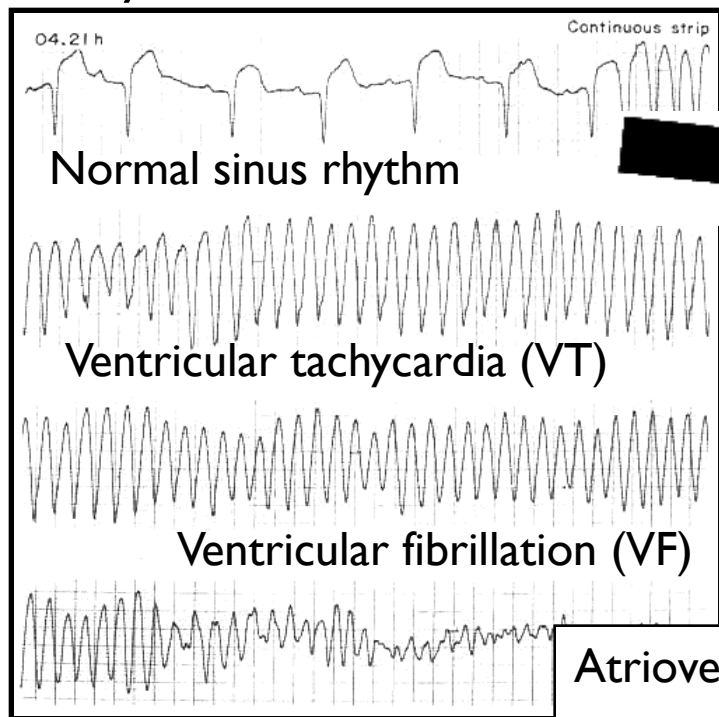
Each insect has its own rhythm – but the phase alters based on seeing its neighbors lights, bringing harmony



... and vital for the proper functioning of many biological systems

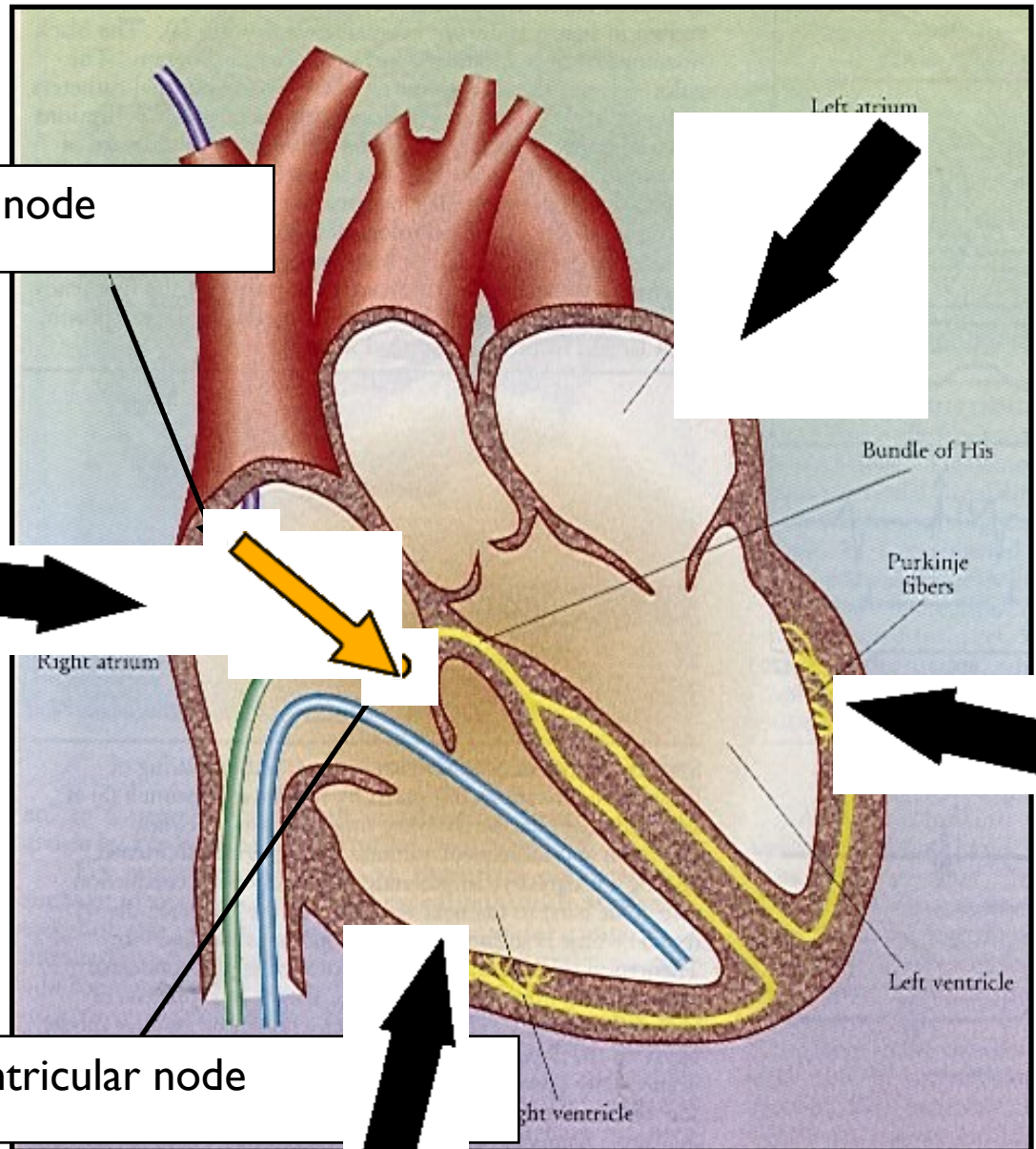
Example:

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



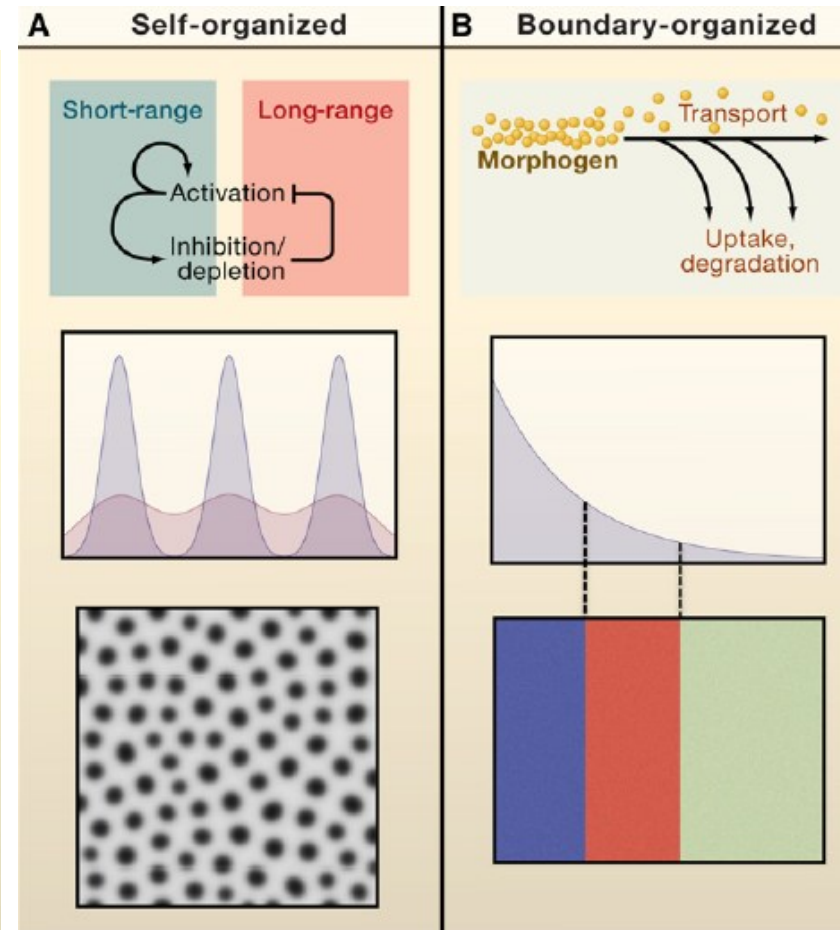
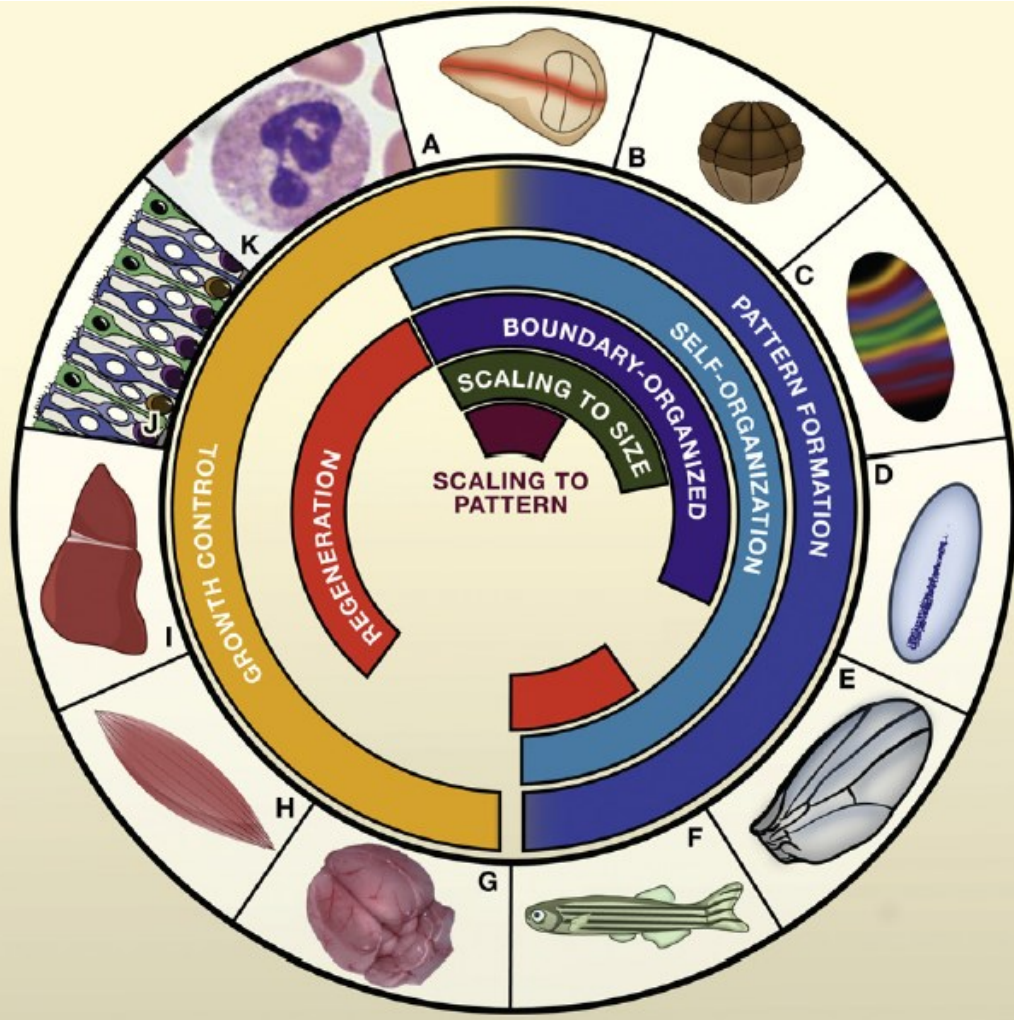
Sinus node

Atrioventricular node



Spatial Patterns

Two modes of spatial pattern organization in biology



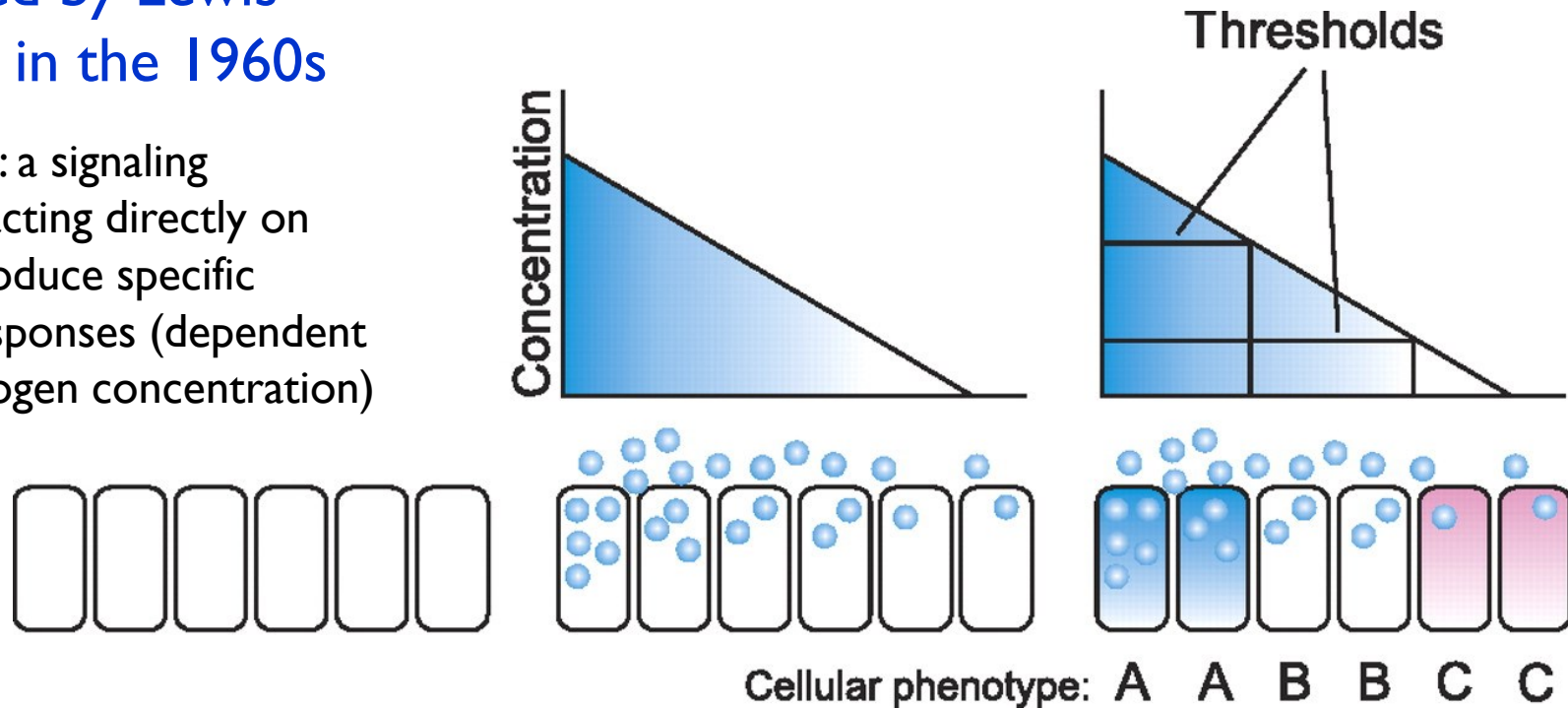
Lander, *Cell* (2011)

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

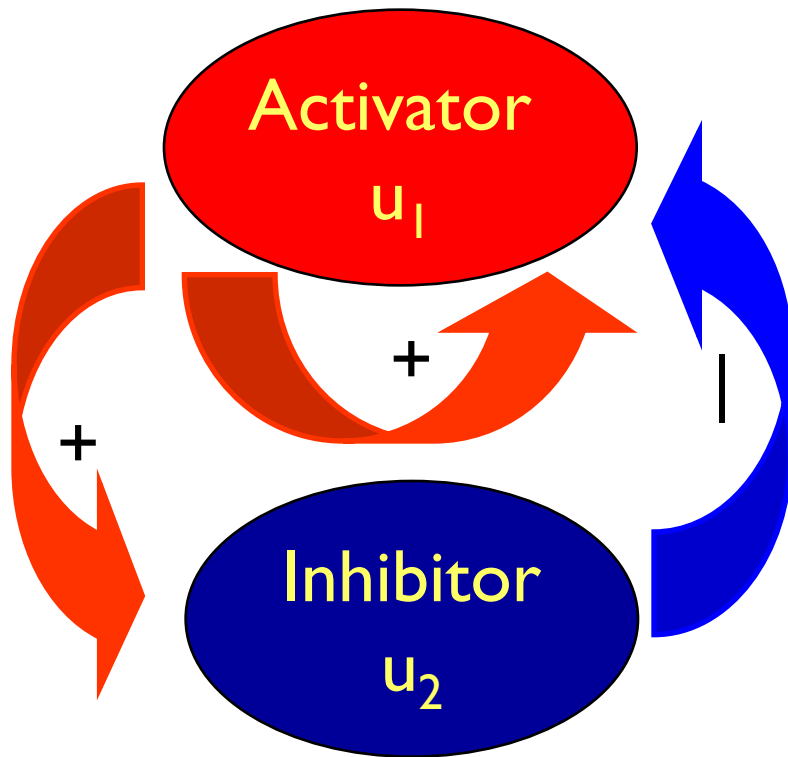
$$\partial_t u_1 = f_1(u_1, u_2) + D_1 \partial_x^2 u_1$$

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

\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

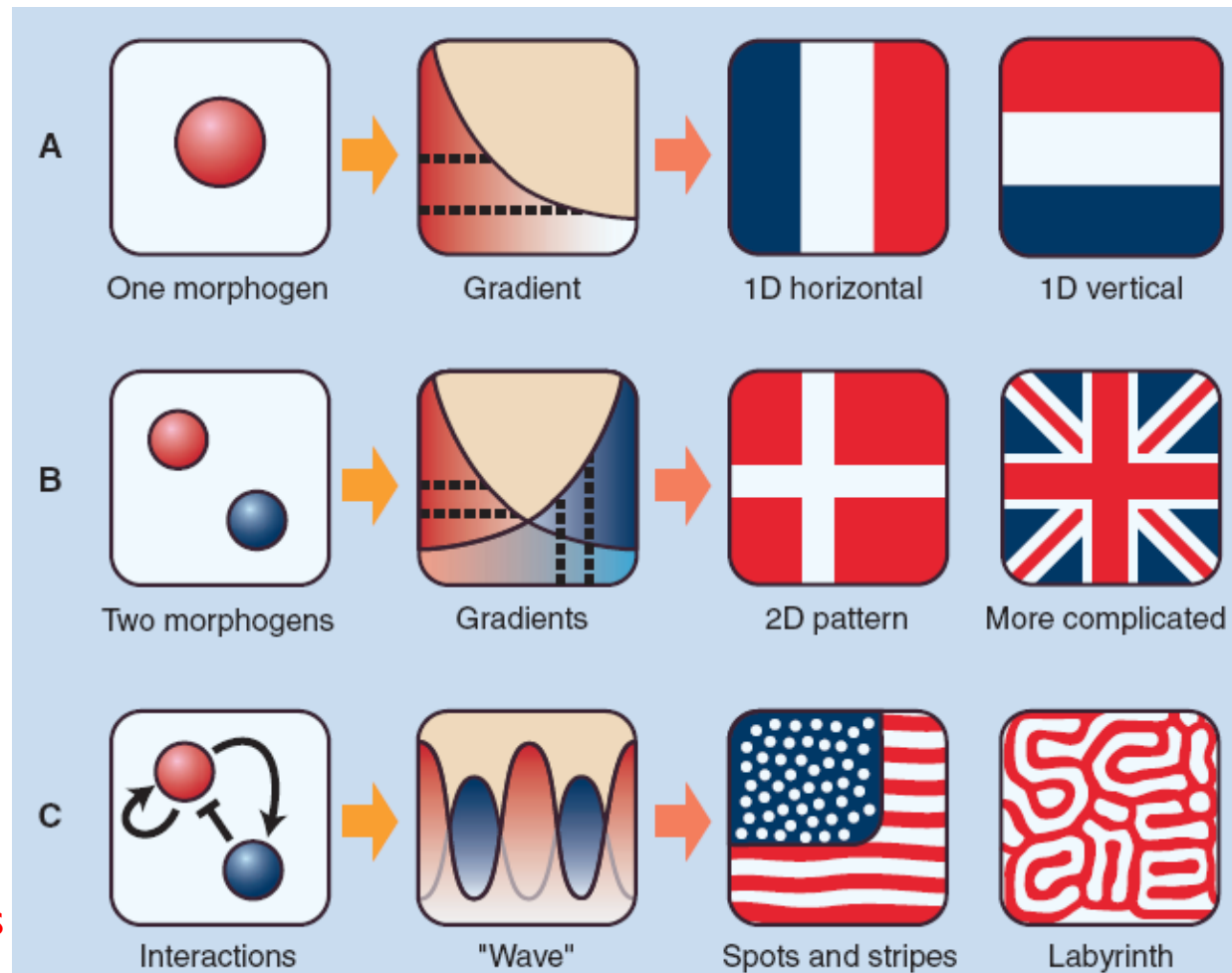
In morphogen gradient model, symmetry is not broken spontaneously as in Turing mechanism - rather the broken symmetry is inherited

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

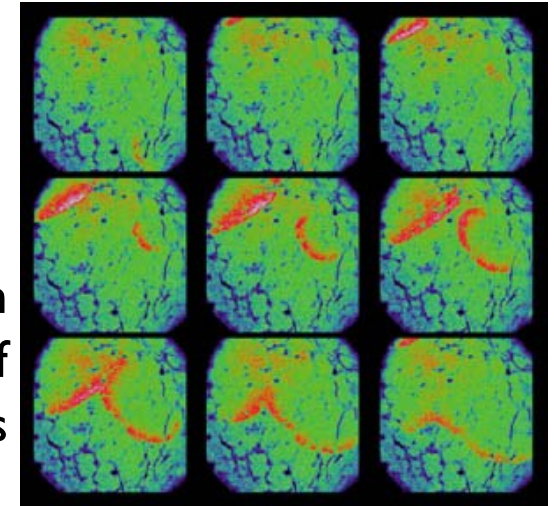


Spatio-temporal Patterns

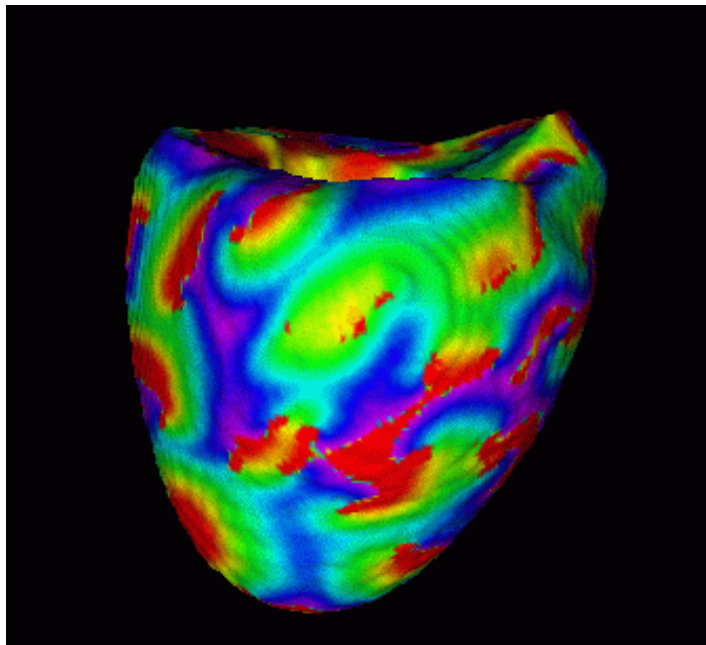
Waves in Biological Systems



Aggregation of
Dictyostelium
Discoidium amoebae
by cAMP signalling

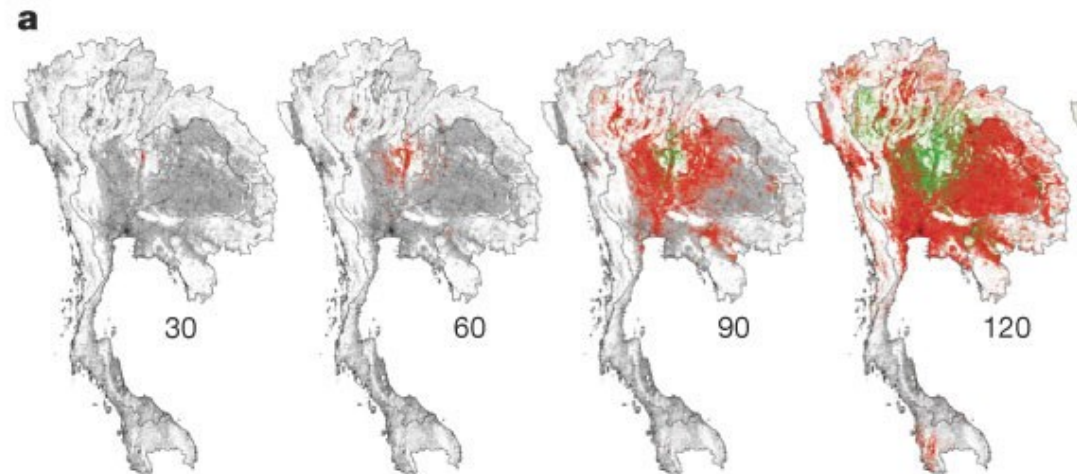


Ca⁺⁺ waves in
cytoplasm of
Xenopus oocytes



Electrical activity in heart

Ferguson et al, Nature, 2005

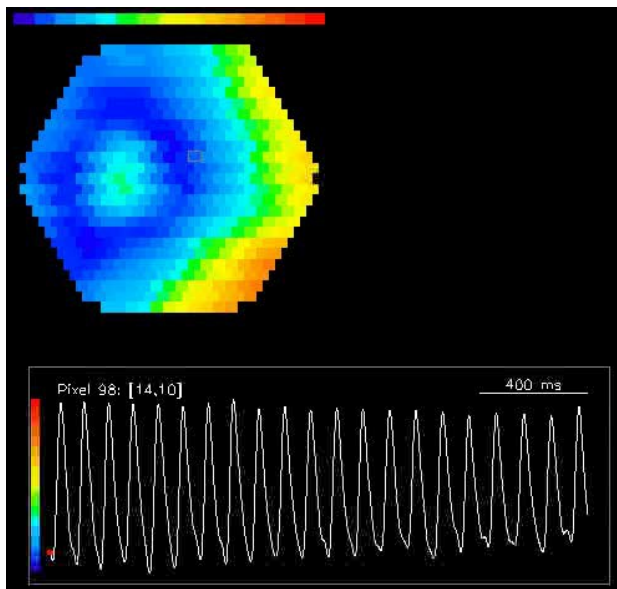


Spreading Waves in Epidemics

Propagating Waves in Rat Neocortical Slices: Spiral Waves & Bursts

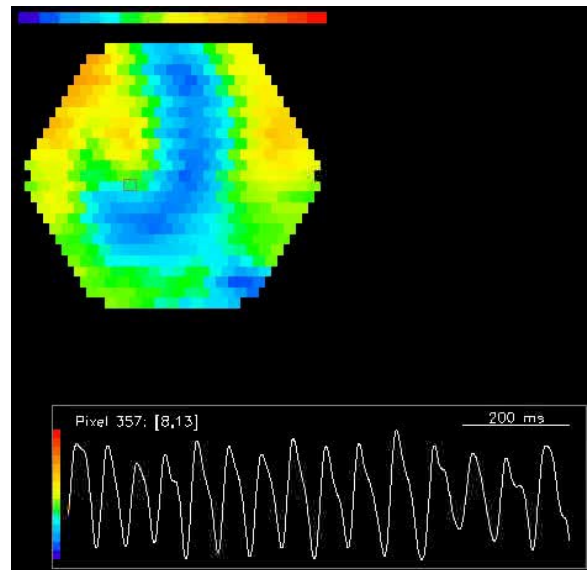
Spontaneous oscillations in slice organized spatially as propagating waves

JWu Lab, Georgetown Univ



Ring waves

Period $\sim 100\text{ms}$

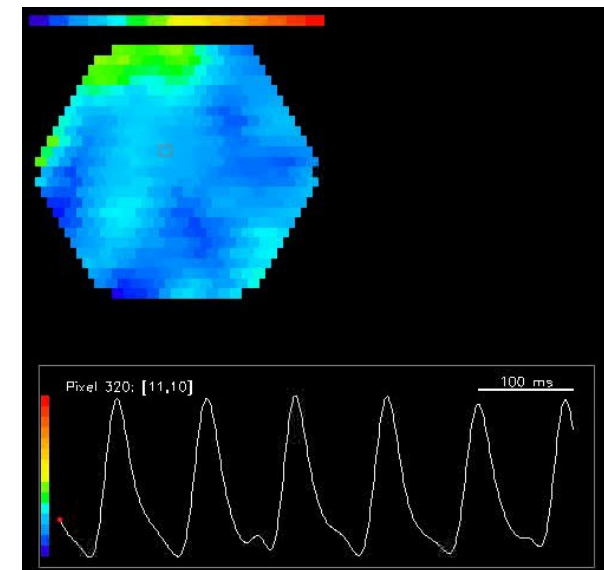


Spiral waves

Aperiodic,
dominant period $\sim 70\text{ms}$

Period $\sim 100\text{ms}$

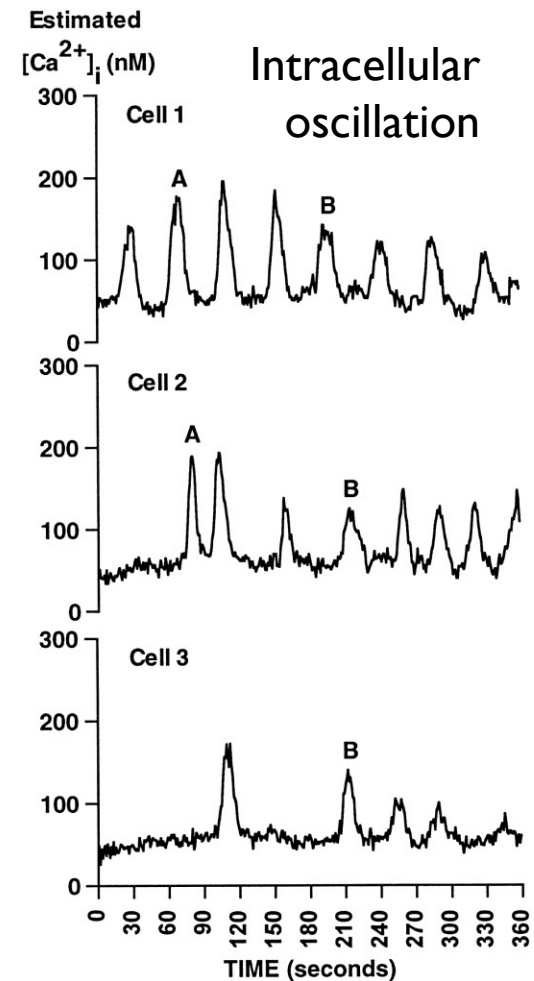
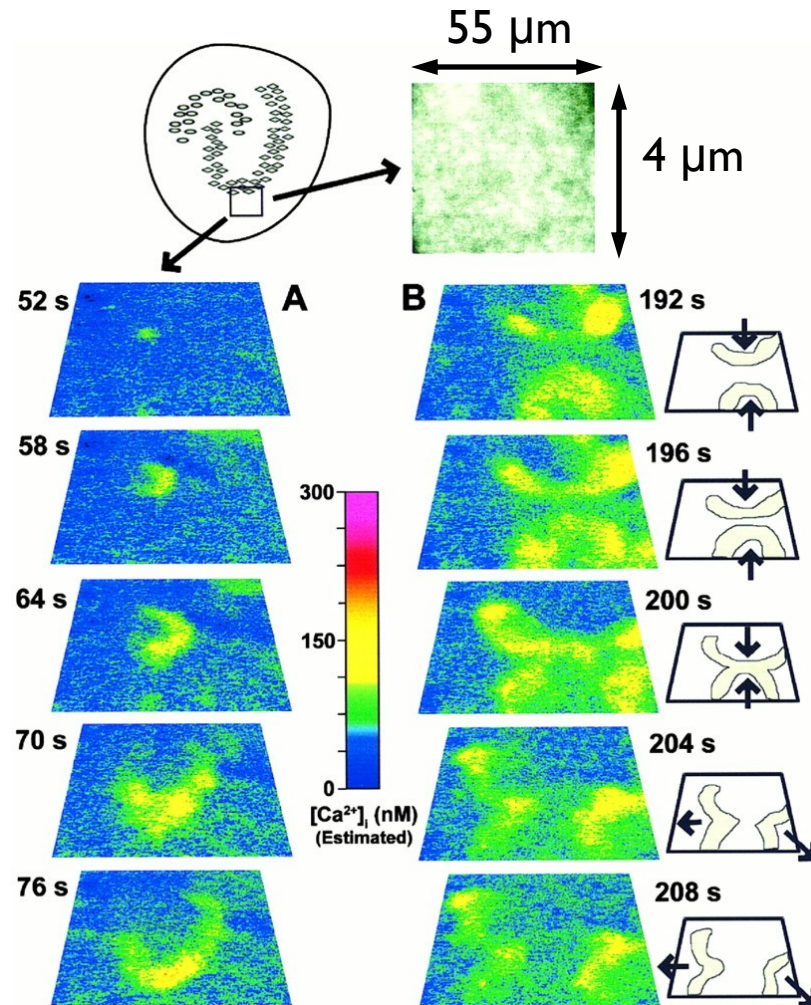
Bursts



Spiral Waves in Mouse Hippocampus

Observation of intercellular Ca^{2+} spiral waves in hippocampal slice cultures

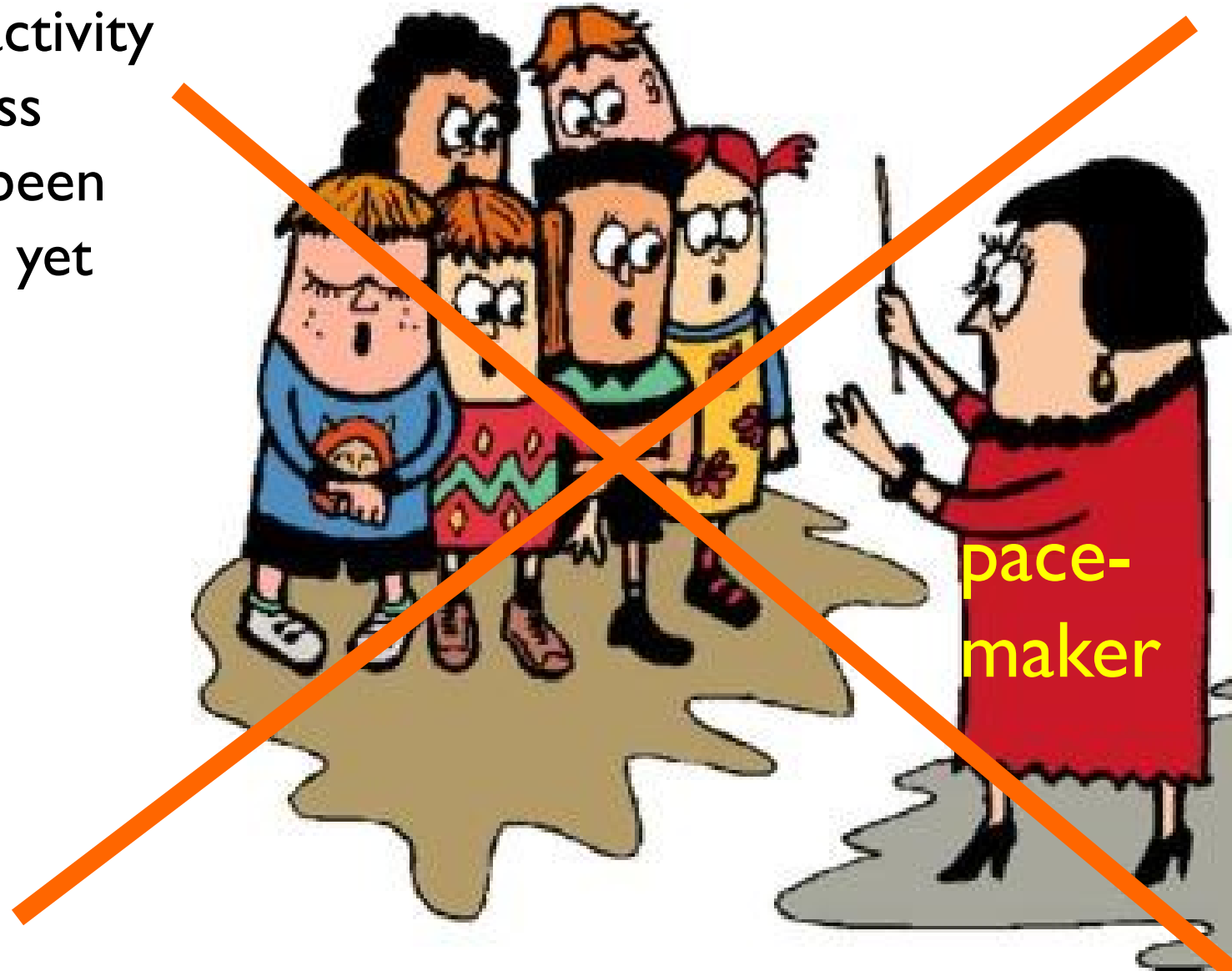
- Calcium waves (traveling at 5-10 $\mu\text{m/s}$) in *glial cell syncytium*



For many biological processes

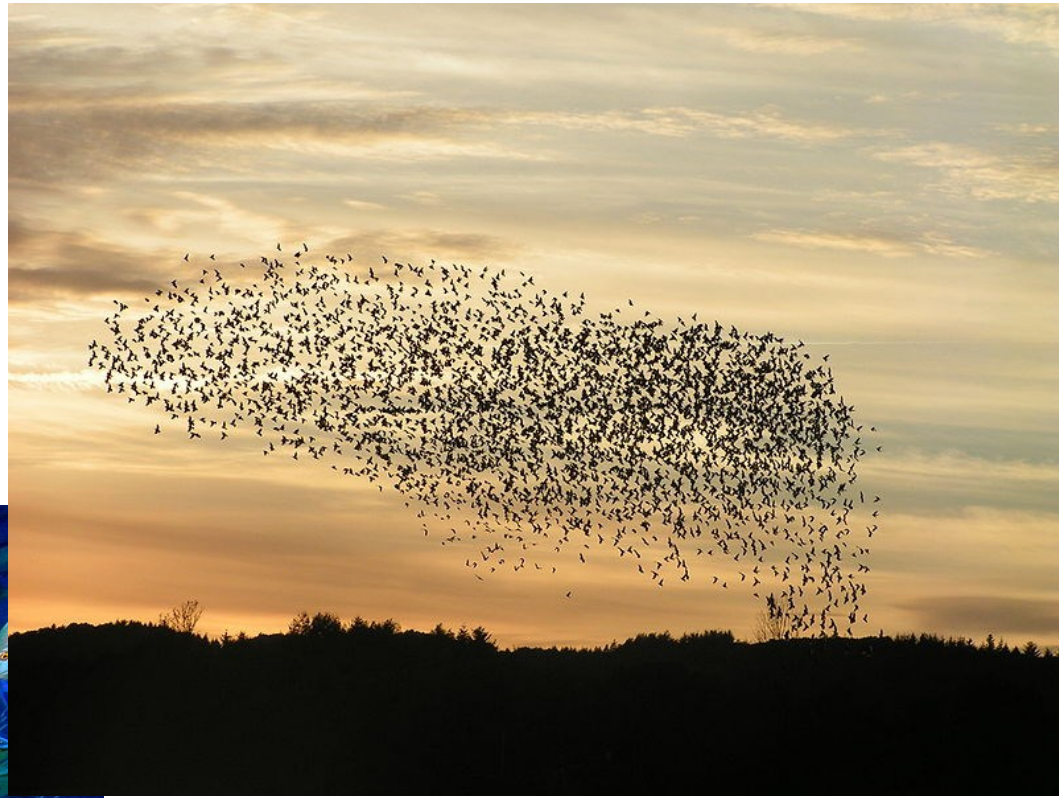
No centralized coordination

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

Examples:
flocking and swarming

Wikipedia