Systems & Biology

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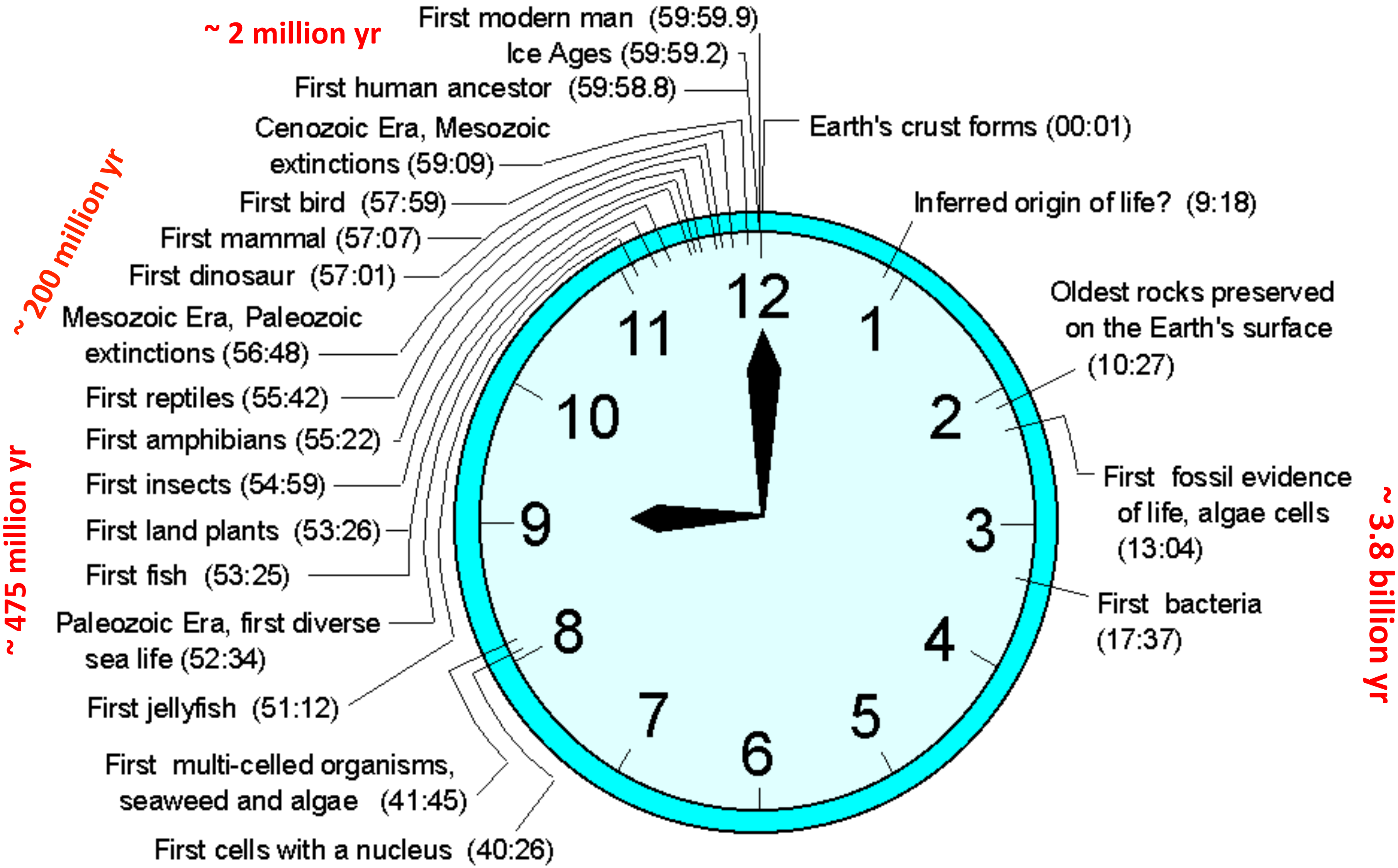
"The most beautiful experience we can have is the mysterious. It is the fundamental emotion that stands at the cradle of true art and true science. Whoever does not know it and can no longer wonder, no longer marvel, is as good as dead, and his eyes are dimmed".

Albert Einstein



4.6 billion years in one hour

Adapted from https://letstalkaboutscience.wordpress.com/tag/analogies/

In 1964, James Lovelock was requested by NASA to make a **theoretical life detection system** to look for life on Mars during the upcoming space mission.

"I'd look for an entropy reduction, since this must be a general characteristic of life."

What differentiates life from other forms of matter ?

ORGANIZATION

Living systems are open systems interacting with the environment

ORGANISATION

A structural or functional "whole" that is made up of lower level entities that interact according to certain "rules and patterns" which, in turn, can also modulate the constituent entities' behaviour.

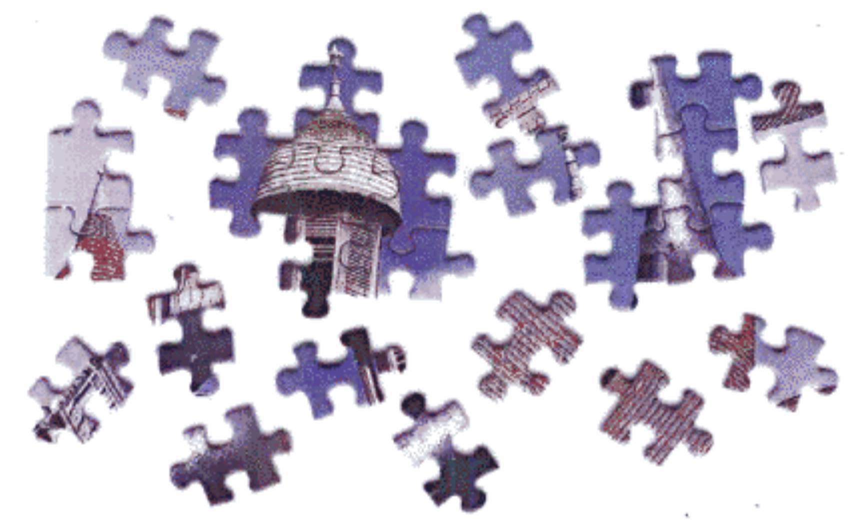
Information plus regulation.

The organization is limited by the communication between the subsystems

"I TOOK IT APART TO SEE HOW IT WORKED... AND NOW IT *DOESN'T.*"

SYSTEM

A system consists of components (*or elements*) which are *interacting, interrelated, or interdependent* in order to facilitate the flow of information, matter or energy *to form a complex whole*



Information plus regulation

The idea is to describe, analyse, and understand macroscopic properties of these systems from the properties and interactions of their components.

Systems behaviour may not be understood by investigation of the respective parts in isolation.

- *Dynamic interactions,*
- *Influence of contacts/couplings,*
- *Different structural environment,*

  etc.

A "system's approach" requires unification of structure and dynamics of individual parts to understand or predict about the whole system.

Difference between Physical and Biological pattern formation

1) Greater complexity of the subunits/parts:

   small molecules, genes, cells, ants, populations;

2) Nature of rules governing interactions among system components

   a) Physico-chemical systems:

   physical laws - surface tension, viscosity, gravity;

   b) Biological system:

   physical laws,
   physiological & behavioural interactions,
   genetically-controlled properties
   evolved through natural selection

LARGE

Ingredients for "complexity":

- Complex order parameter (exotic phases and transitions)
- Non-equilibrium (patterns, self-organisation, jamming)
- Heterogeneity (glasses, aging, optimisation)

complex

Biology: all the above and more components:

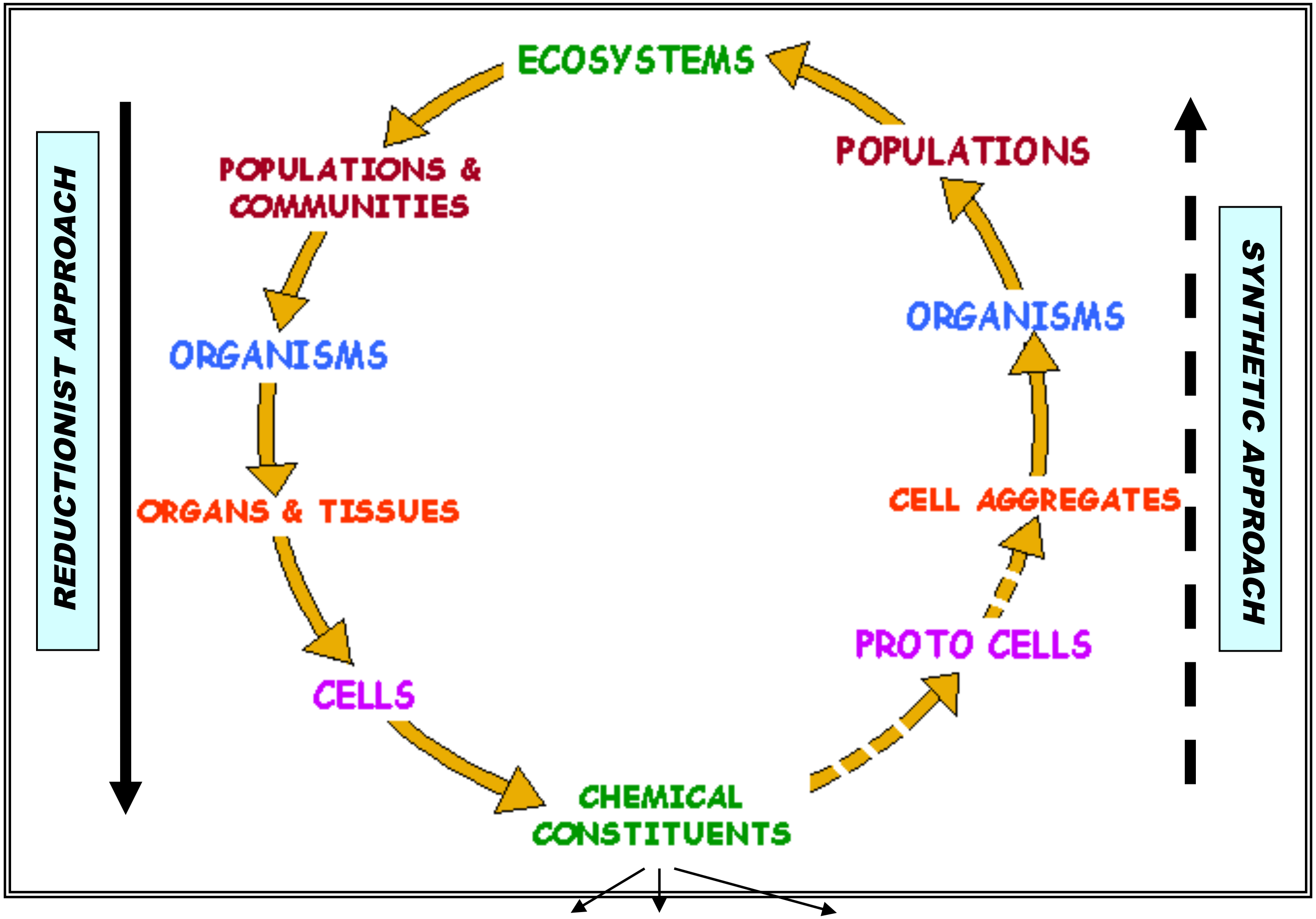
Systems & Functions:

- Adaptation and self-replication
- Communication and computation
  [Superior information processing systems provides fitness advantage in complex environments]

Driving force for biocomplexity: ***Evolution***

SMALL

LEVELS OF ORGANISATION IN BIOLOGICAL SYSTEMS

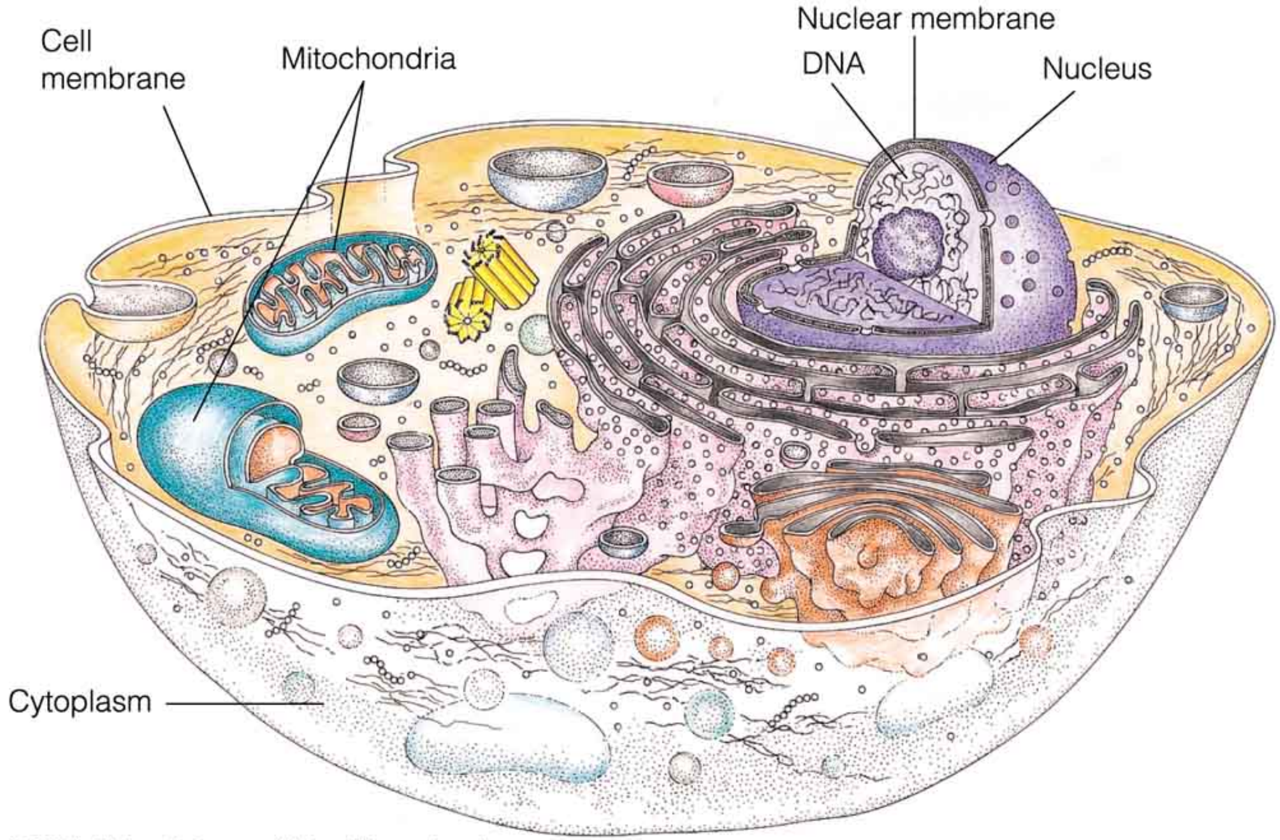


Nonlinearity
in
STRUCTURE,
FUNCTION,
REGULATION,
INTERACTION
&
PROCESSES

DNA, RNA, Proteins, Lipid bilayer, mitochondria, etc

Each level is complex, highly structured and organised network of dynamically interacting, heterogeneous, functional modules
Enormous range of time and length scales

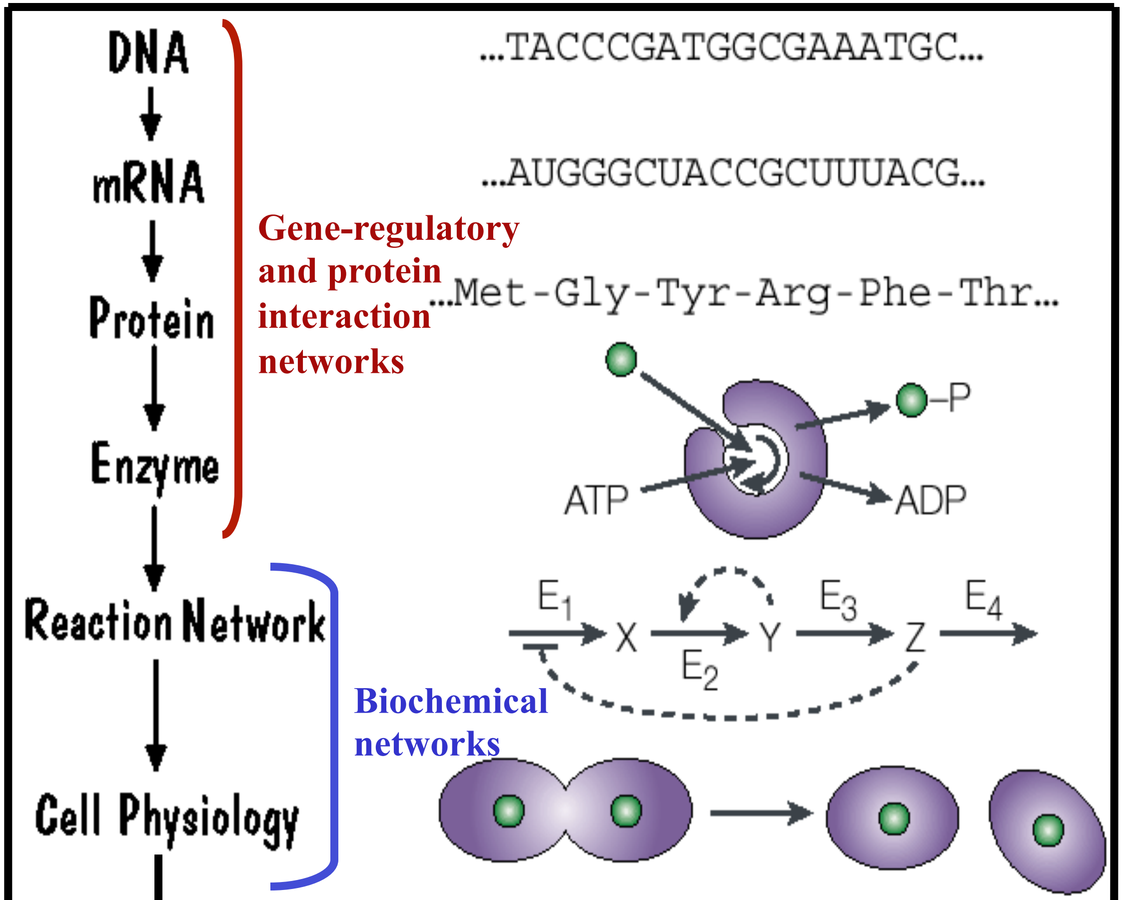
Cells have different compartments for specialized jobs



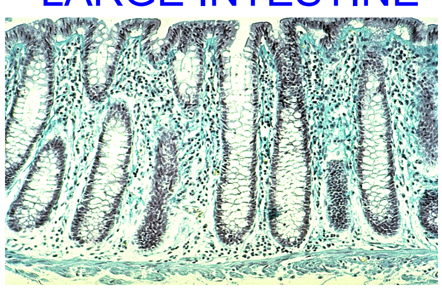
Different reactions in a biochemical pathway may take place at different cellular compartments - *transcription in nucleus, translation in cytoplasm, signal sensing in membrane, ATP in mitochondria –* **and are subjected to different environmental milieu.**

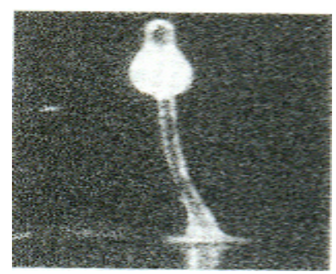
Flow of Information in Biology

FLOW of INFORMATION



LARGE INTESTINE

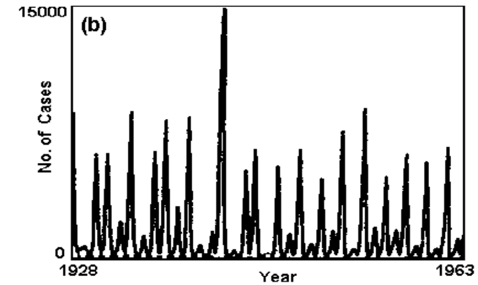




Slime mold

Ecological systems

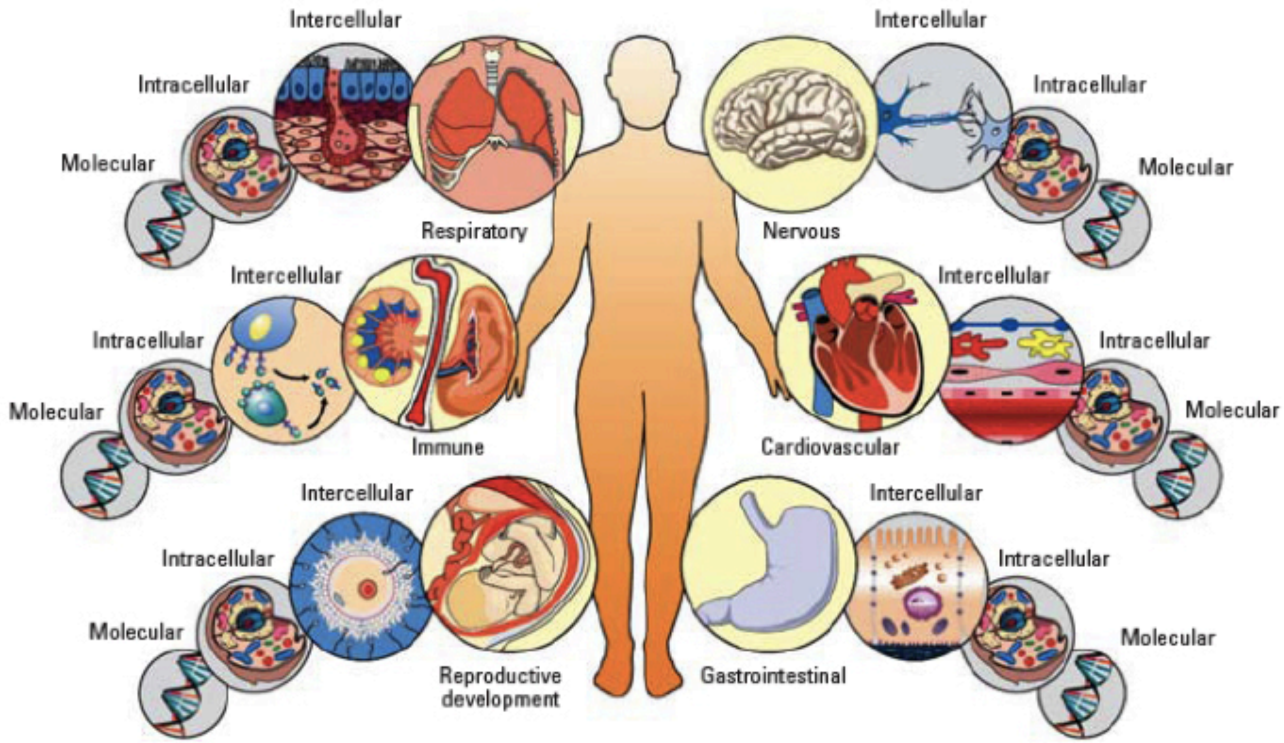
FOODWEBS, CONTACT NETWORKS IN EPIDEMIOLOGY



Social systems

Multicellular systems

A human egg divides into 2 cells in 24 hr after fertilization. The newborn human has ~10^{13} cells.



All these life processes at each level have been understood in great details by careful experimentation and observations in the laboratory.

WHAT IS NOT KNOWN IS HOW THESE DIFFERENT LEVELS (MULTIPLE SCALES) ARE INTEGRATED TO OBSERVE THE MACROSCOPIC BEHAVIOUR AT THE LARGER SCALE

SYSYEM OF SYSTEMS

Cell is the basic unit of life

large

small

Large cells - nerve cells in giraffe's neck - ~ 3 m (9.7 ft) in length.

Smallest cell (mycoplasma) ~ 10^{-7} cm diameter

The Human genome length is about 2 metre (3,000 million base pairs).

E.coli genome is ~ 1.2 mm (4 million bp).

Smallest genes are ~10,000 bases long - Ovalbumin (7.7Kbp)

Largest gene ~ 2 million bases (for a human muscle protein)

Bacterium *E. coli* divides in 20 min

Cell cycle of single-celled yeast - 90 -120 min

A rapidly dividing mammalian cell cycle ~ 24 hours

Complexity in biological systems/processes –

- Multilevel organization with cross-talk between levels
- Multi-unit structures with interacting multiple time and space scales
- Very large number of parts with nonlinear couplings, feedbacks, degeneracy, stochasticity
- Highly nonlinear processes
- History, Contingency, Robust yet Evolvable
- Exhibits different types of dynamics – homeostasis to chaotic

The aim of the whole endeavour is to find Generic Processes, Conserved Motifs, & Robust Functional Modules across evolutionary and organismic scale

Highly interdisciplinary –
needs experimental and theoretical tools and methods from

Biology

Physical sciences

(physics, chemistry)

Mathematical sciences

(mathematics, statistics)

Computer sciences

(algorithm, language (sbml.org), software, visualisation, hardware)

Engineering sciences

(biomedical, chemical, mechanical, electrical, communications)

Two ways of looking at a problem

- **Top down** or ***Bottom up***
  - **Either look at the whole organism and abstract large portions of it**
  - Or, ***try to understand each small piece and then after understanding every small piece assemble into the whole***
  - Both are used, valid and complement each other

Bottom up is the traditional approach

- You would study a process in detail not worrying about how that pathway might interact with other elements in the cell.
- You would strive to understand a gene or pathway in great detail, eventually you might extend this knowledge to other organisms and compare and contrast.

With top down you need other tools...

Definitions

- At a recent NIH SysBio retreat almost every talk started with that speakers definition of what systems biology is.
- Leroy Hood came up with the following (summary)
  - ***As global a view as possible***
  - ***Fundamentally quantitative***
  - ***Different scales integrated***

TALK 2

Complexity in biological systems/processes –

- **Multilevel organization with cross-talk between levels**
- **Multi-unit structures with interacting multiple time and space scales**
- **Very large number of parts with nonlinear couplings, feedbacks, degeneracy, stochasticity**
- **Highly nonlinear processes**
- **History, Contingency, Robust yet Evolvable**
- **Exhibits different types of dynamics – homeostasis to chaotic**

Systems biology investigates the behaviour and relationships of all of the elements in a particular biological system while it is functioning.

These data can then be integrated, graphically displayed, and ultimately modeled computationally.

SYSTEMS BIOLOGY

(1) Integration of different levels of organisation

(2) Integration of different time and space scales

(3) Interdisciplinary approach

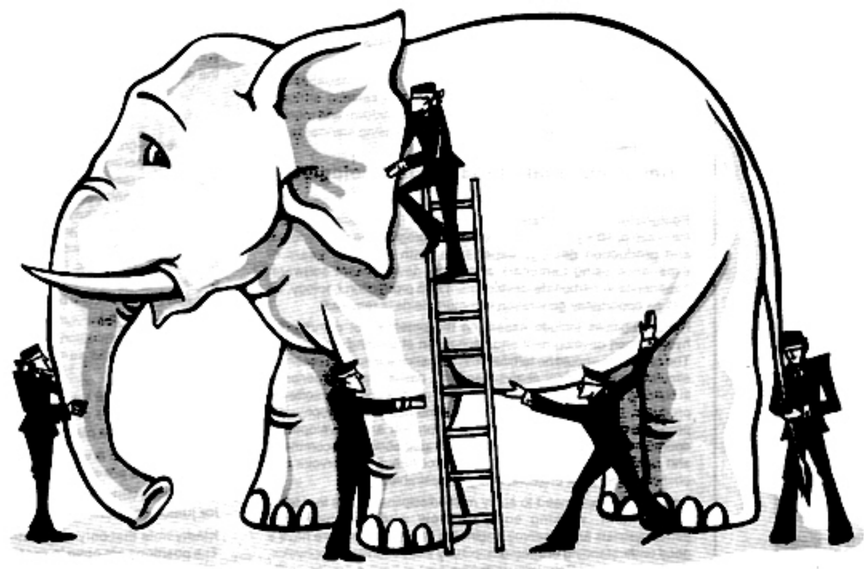
The aim of the whole endeavour is to find

Generic Processes,

Conserved Motifs, &

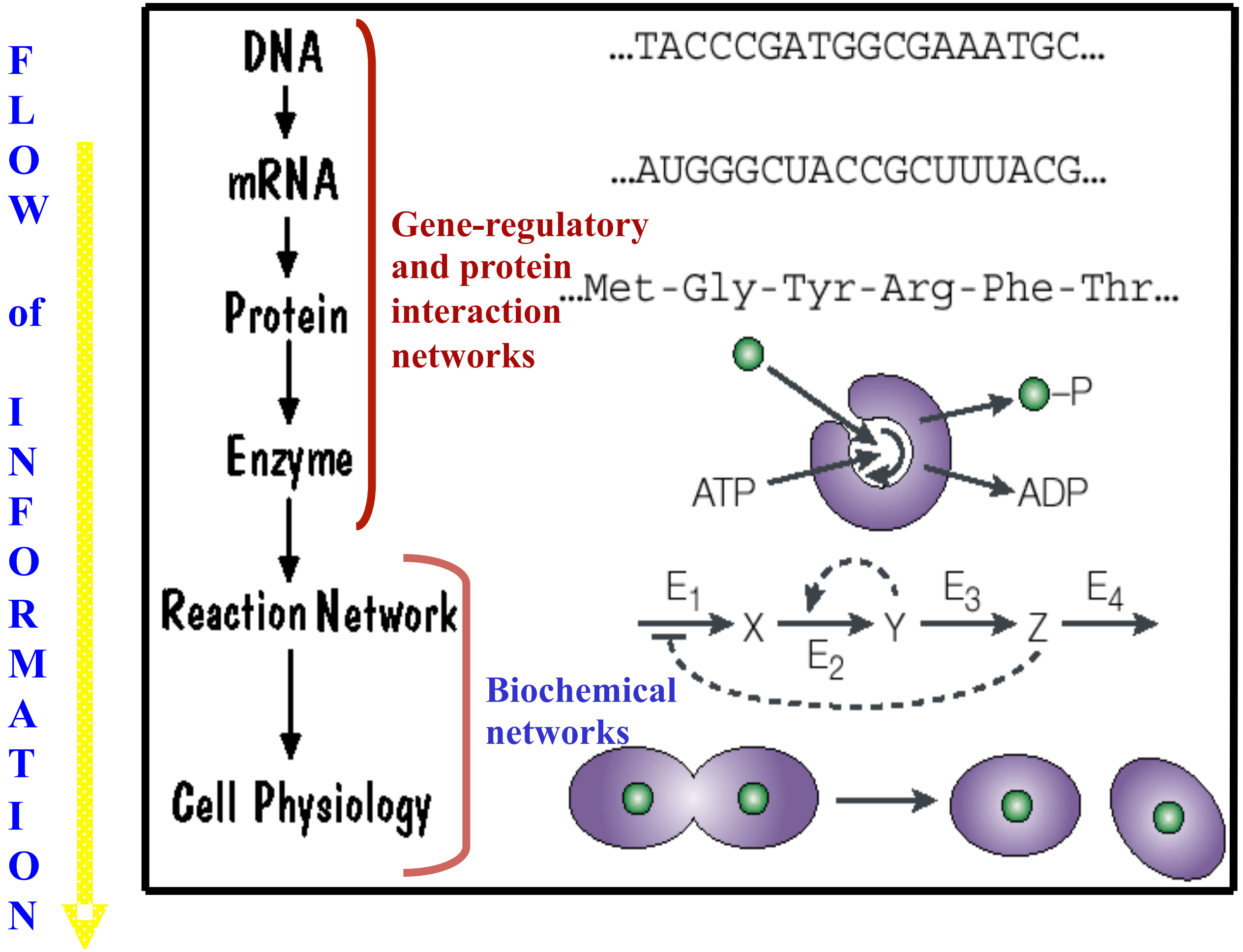
Robust Functional Modules

across evolutionary and organismic scale



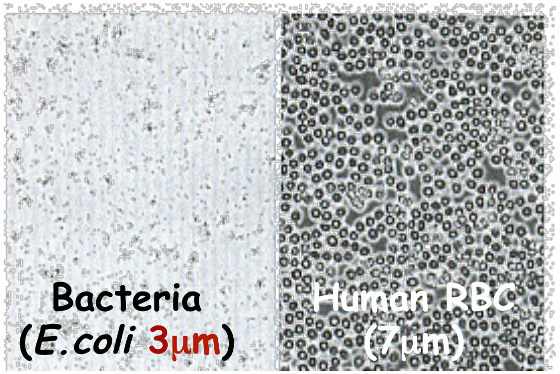
“I have often pondered over the roles of knowledge or experience, on the one hand, and imagination or intuition, on the other, in the process of discovery. I believe that there is a certain fundamental conflict between the two, and knowledge, by advocating caution, tends to inhibit the flight of imagination. Therefore, a certain naiveté, unburdened by conventional wisdom, can sometimes be a positive asset.”

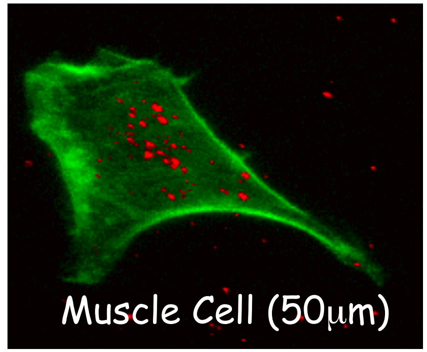
Flow of Information inside the cell

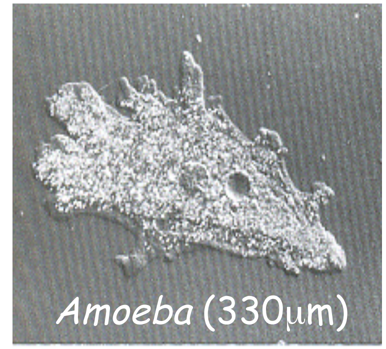


Turing Machine can be used to model transmission of information

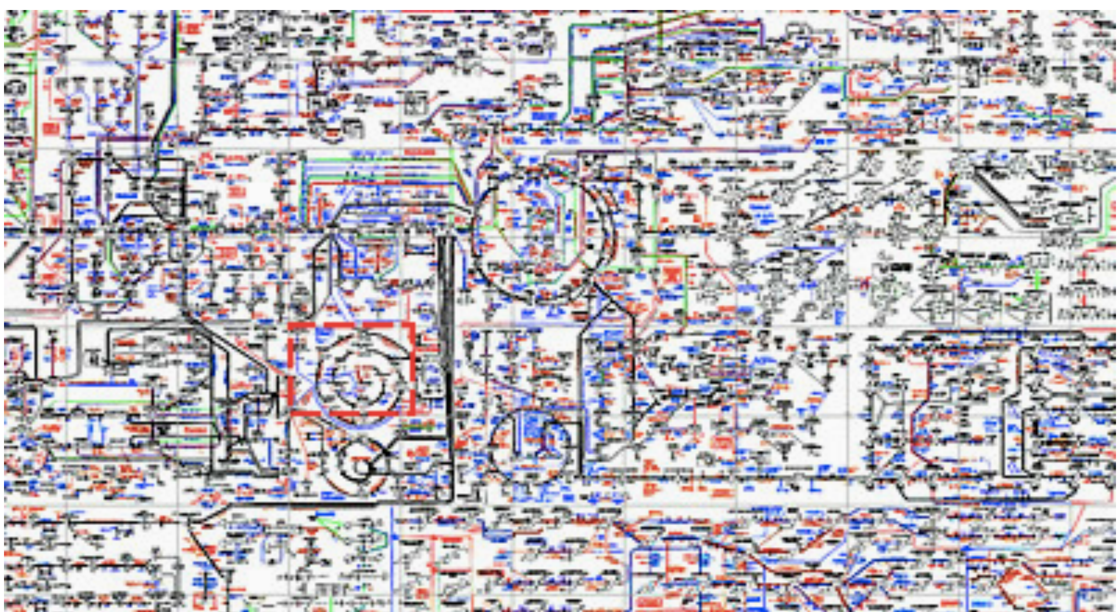
Living systems are made up of cells – *single or multi-cellular*





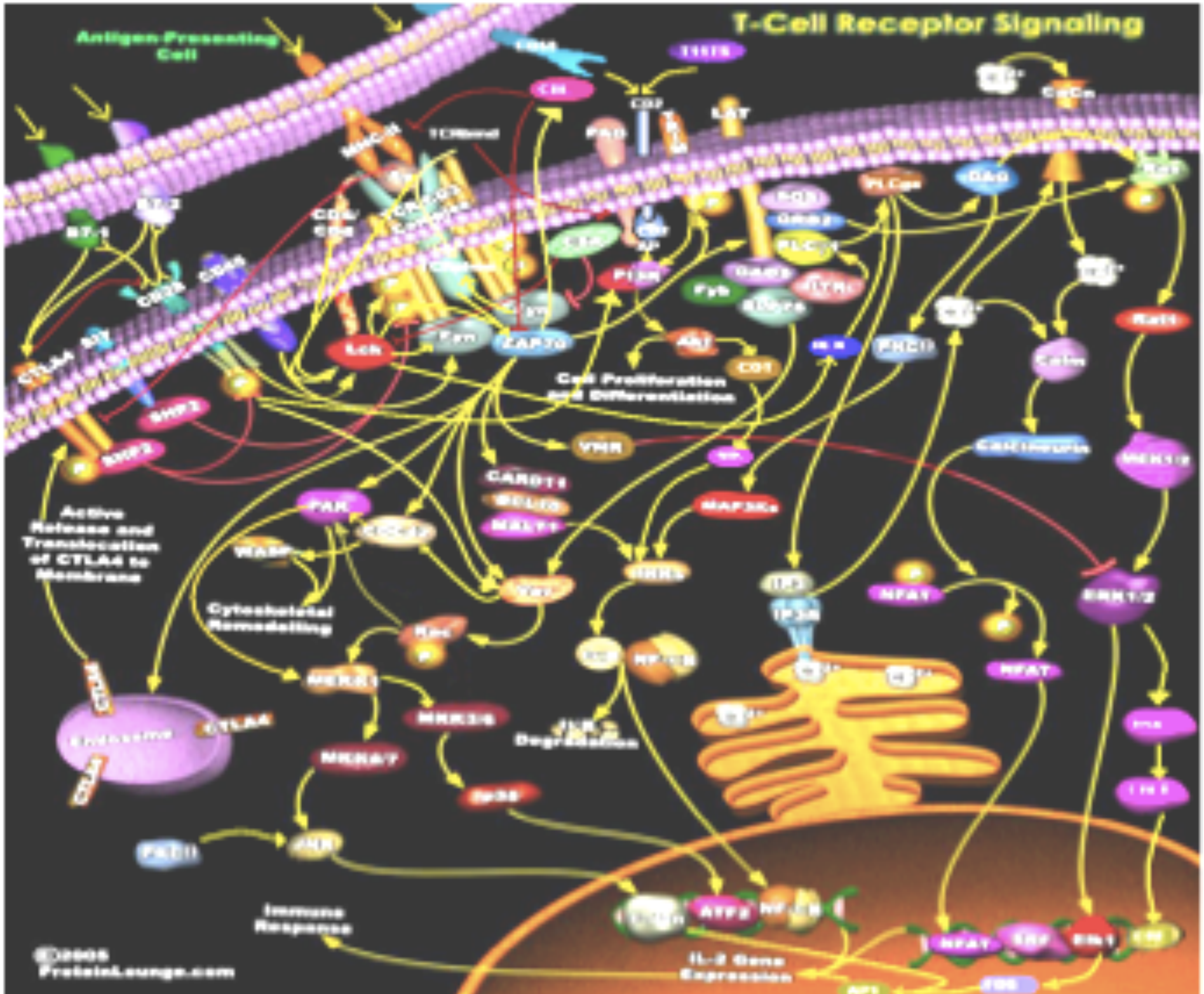


Cellular functions are controlled by networks of biochemical reactions

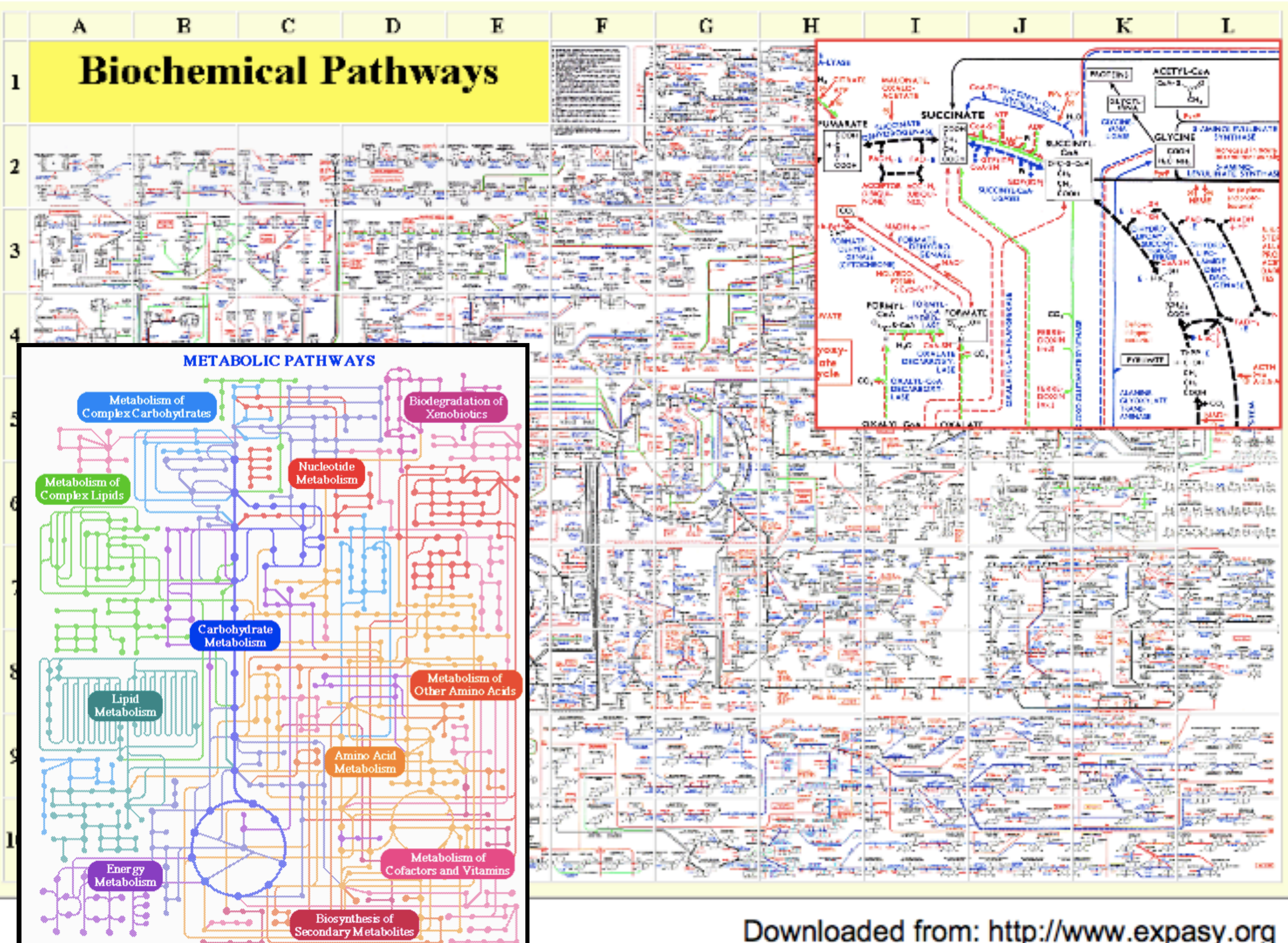


Cellular behaviour is an emergent property of networks of inter-connected chemical reactions of the molecular species in the cell.

Information processing inside the cell occurs through multiple steps and involves multi-unit systems

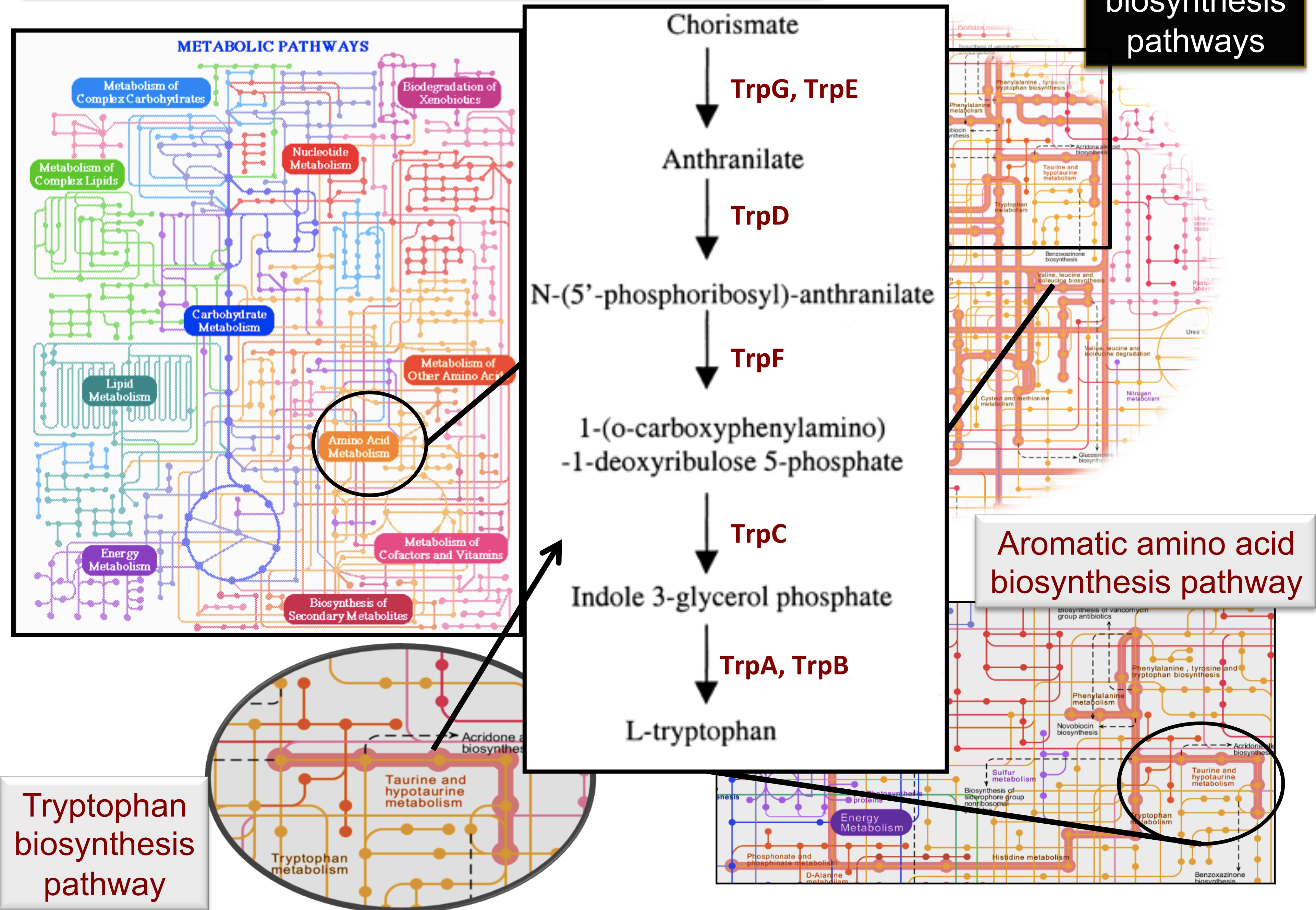


Logic Gates used to model these systems



Downloaded from: http://www.expasy.org

Metabolic pathways – scales of description

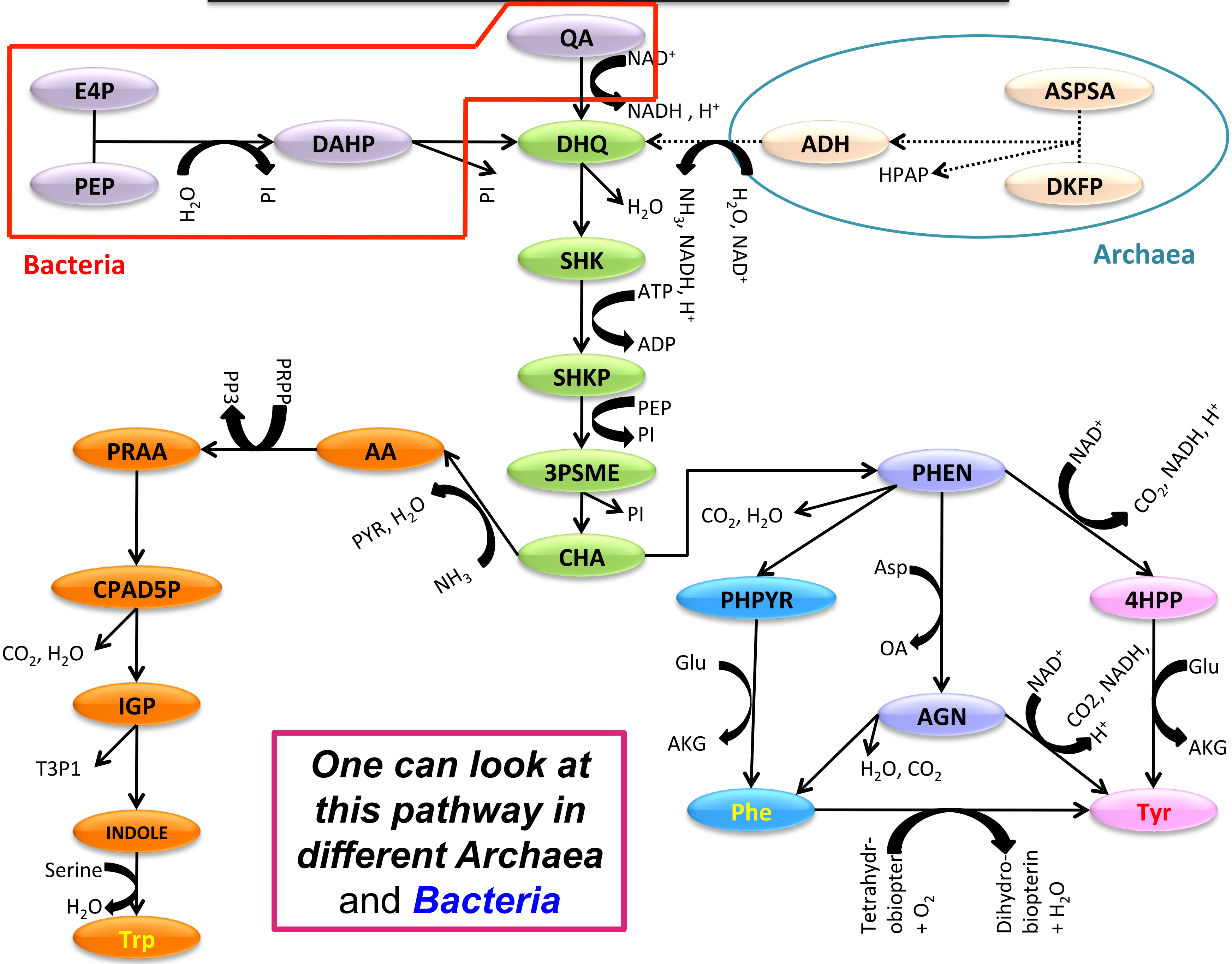


Question

Intracellular pathways are connected to each other.

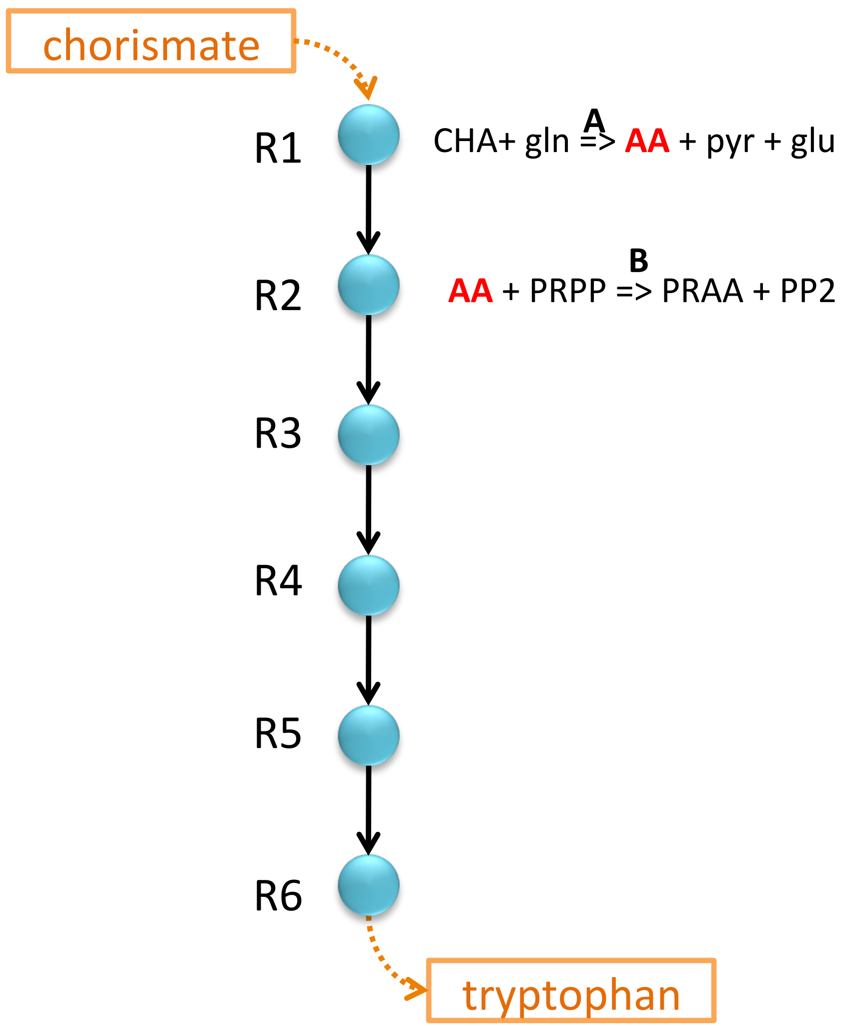
Do properties of single pathways change when it is embedded in the larger network of biochemical pathways ?

AROMATIC AMINO ACID BIOSYNTHESIS (TTP) - 4 parts



One can look at this pathway in different Archaea and ***Bacteria***

Reaction Network



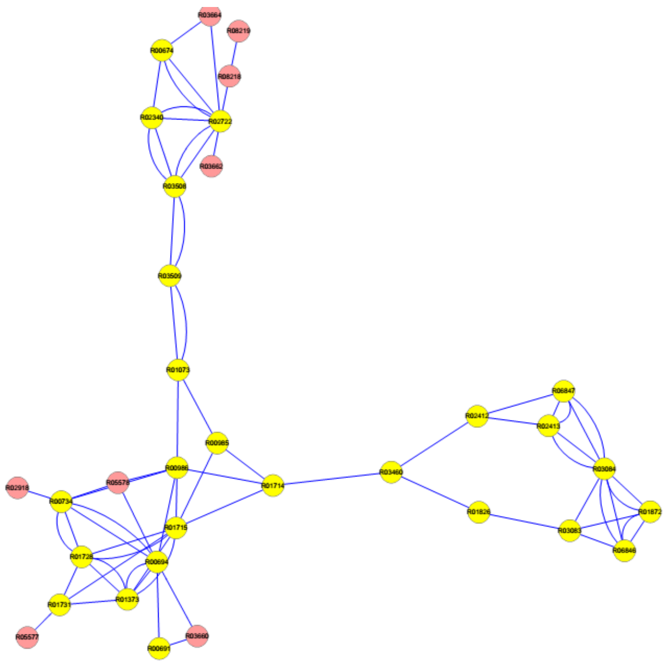
Node: **Reaction**
Edge: Metabolite

Network parameters describe topology and connectivity pattern of any network

Degree
Shortest Path
Diameter
Clustering Coefficient
Centrality measures
Assortativity
Modularity
Community structure

17 other pathways are connected to TTP pathway

Combined networks



TTP + Aminocycl-tRNA biosynthesis

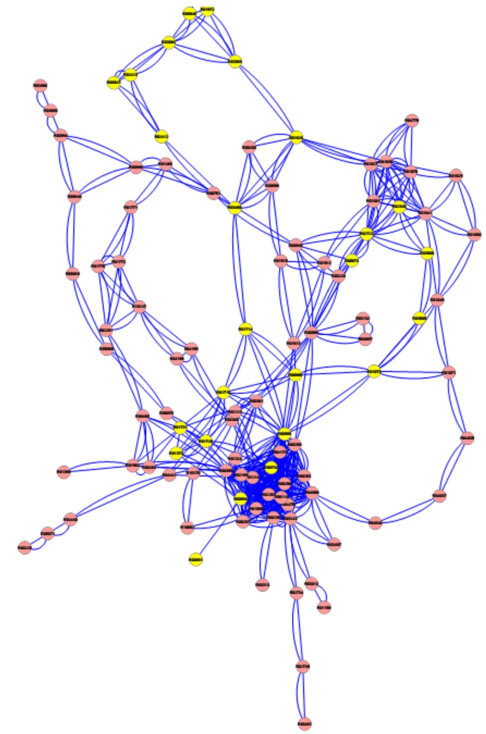
Nodes - 35

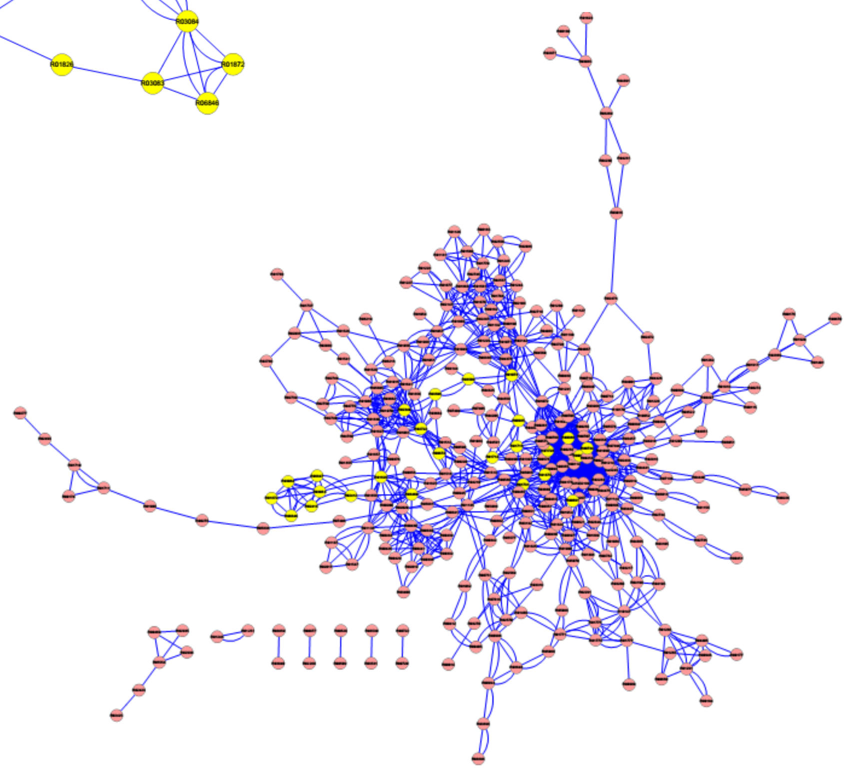
Edges - 72

TTP + Alanine, aspartate & glutamate metabolism

Nodes - 51

Edges -323





Complete Connected Network (CCN)

Nodes - 321

Edges -1479

On Addition of pathways

Increasing the number of nodes does not necessarily increase the average degree in all networks

In the combined connected network, several of the TTP nodes are betweenness or closeness hubs

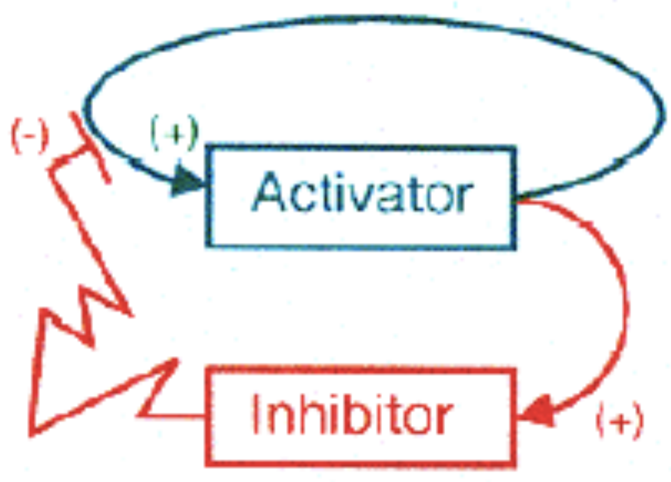
What about functional dynamics ?

For any pathway the nonlinearities involved in the multi-step chemical reactions and their kinetics, and feedback processes within the pathway, determine the kind of dynamics that the pathway will exhibit.

A tissue/organ is made up of many cells, and they all function the same way to give the tissue its property. Each cell has biochemical networks with their functional dynamics. How does it affect the tissue behaviour ?

Model biochemical pathway

Each cell incorporates a three-step biochemical pathway of regulated activator-inhibitor reactions



A simple reaction scheme:

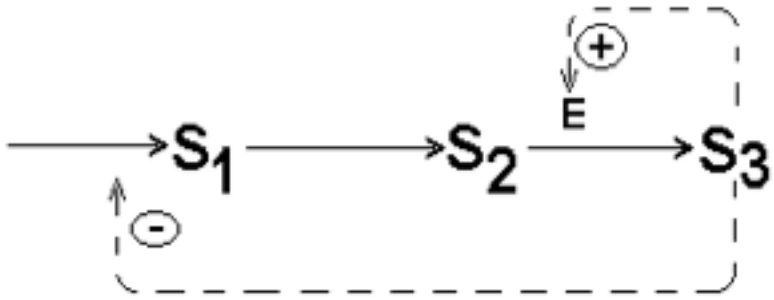
An **activator** catalyzing its own production, and a highly diffusing antagonist - **inhibitor**.

Autocatalysis and long-range inhibition

- a common mechanism underlying pattern formation in tissues.

Activator-Inhibitor Reaction Pathway

End-product inhibition & Allosteric activation



$$\frac{dx}{dt} \equiv f_1 = F(z) - kx$$

$$\frac{dy}{dt} \equiv f_2 = x - G(y,z)$$

$$\frac{dz}{dt} \equiv f_3 = G(y,z) - qz$$

x, y, z normalised concentrations of S_1, S_2, S_3 with

k, q rates of degradation of S_1 and S_3,

F(z) function for inhibition of S_1 by S_3.

Co-operative binding of n molecules of z needed for inhibition

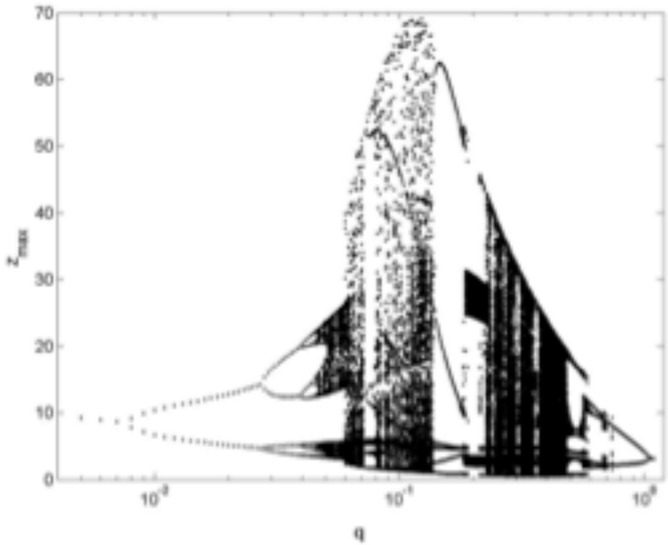
$$F(z) = \frac{1}{(1+z^n)}$$

G(y,z) Positive feedback term involving an allosteric enzyme (E)

$$G(y,z) = \frac{Ty(1+y)(1+z)^2}{L+(1+y)^2(1+z)^2}$$

Goldbeter, et al, Biophysical Chemistry, PNAS(USA); Sinha & Ramaswamy, Biosystems, J Theor Biol

Dynamic diversity of pathway behaviour in single cell



Bifurcation diagram in q-space
k=0.003

For **low and medium values of k & q**

equilibrium,

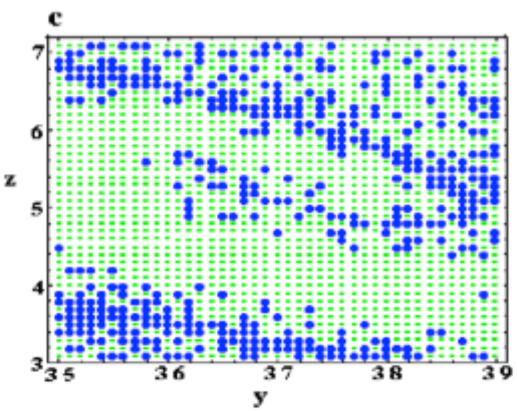
simple periodic,

limit cycles of higher periods,

Birhythmicity

(co-existence of two different limit cycles),

complex oscillation & chaos



Basins of attraction of the two attractors around the fixed point is riddled
(*Fractal Basin*)

Unpredictability in dynamics under noise

For **higher values of k & q,**

simple periodic,

***period doubling**, and*

***equilibrium** dynamics.*

Question

If the single pathway can possess such a variety of dynamics, which exhibit differential robust-ness and sensitivity to noise in parameters and variables, what ensures that robustness and regulative capacity emerge at the tissue or organism (multi-cell) level ?

Multi-cell Systems

(a) Structured group of cells: ***Tissues and Organs***

(b) Density-dependent behaviour of cell populations:

Population of similar cells emit a signal factor. Only when the number of cells reach a certain density, they respond to this factor and induce new gene expression.

Quorum Sensing, Community Effect, Biofilm

(c) Cell colonies: ***Colonial eukaryotes***

Aggregation of Cellular Slime Moulds

(A) STRUCTURED GROUP OF CELLS AND CELL ASSEMBLIES: *TISSUES & ORGANS*

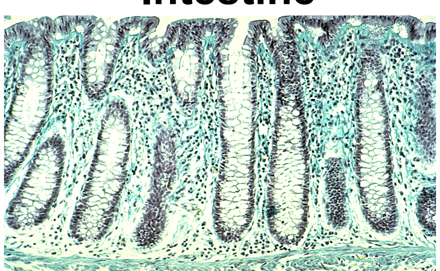
Groups of cells develop specializations in structures and biochemical properties that give them particular functional capabilities -

Muscle cells contract,

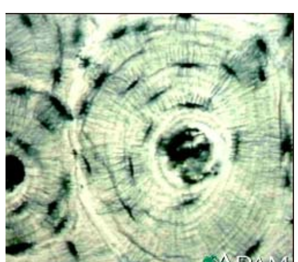
Nerve tissue conducts signals,

RBC transport oxygen

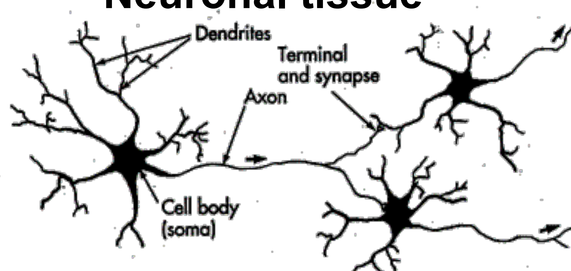
Intestine



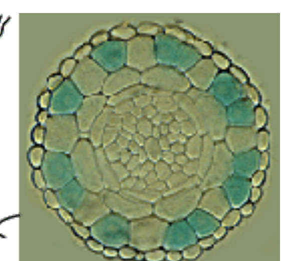
Bone



Neuronal tissue



Root



Wing

(B) DENSITY-DEPENDENT BEHAVIOUR IN CELL POPULATIONS:

Population of similar cells emit a signal factor.

Only when the number of cells reach a certain density, they respond to this factor and induce new gene expression

Quorum Sensing, Community Effect, Biofilm

Community Effect : Developmental signalling in embryos- Induction of differentiation in cells by neighbouring cells

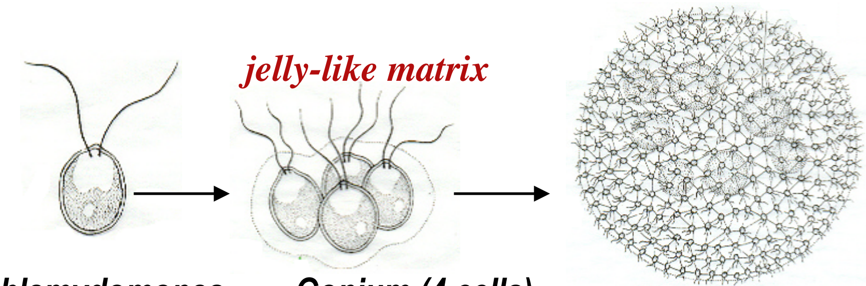
Quorum Sensing : Auto-induction of luminescence in light-emitting marine bacteria at high density

Biofilms: Groups of pathogenic organisms secrete a toxin only above certain cell density in the layer

(C) CELL COLONIES:

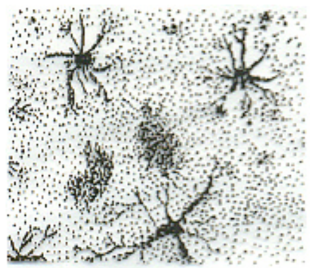
Single cell to cell collective/organism

Colonial eukaryotes

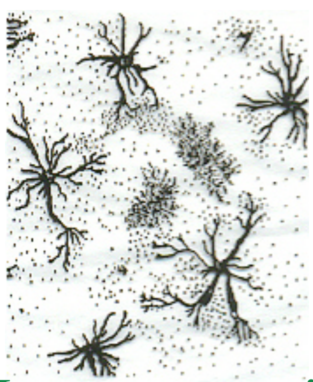


Social amoebae (*D.d*)

Free-living cells - eat and reproduce

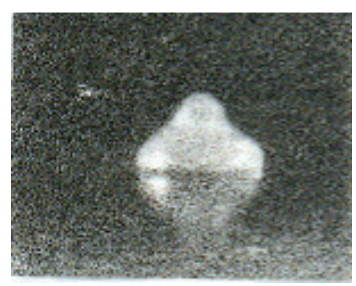


Cells aggregate (signal relay)



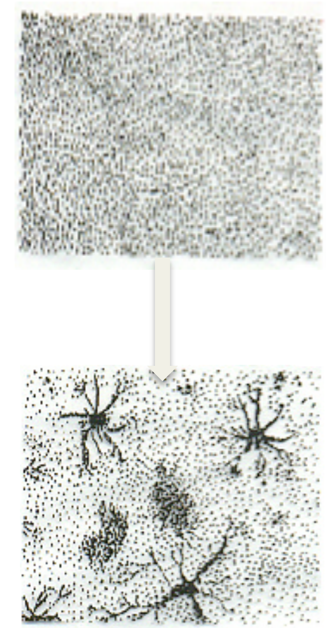
Large aggregation centres form

Differentiation of cells types



Mound of cells form slug

Fruiting body with stalk and spore cells



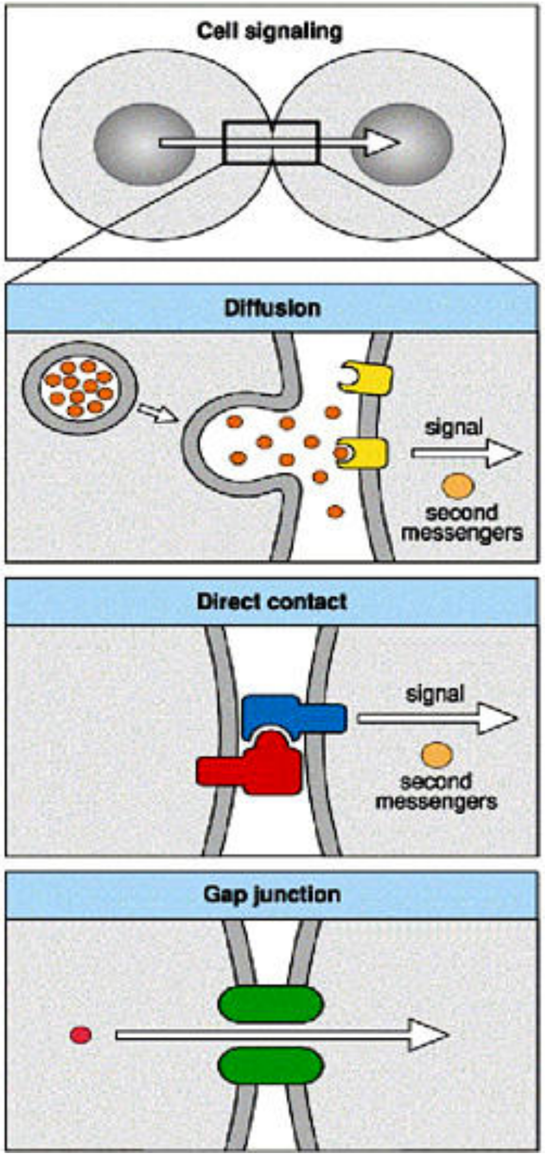
Cells aggregate
(signal relay)

Active communication and interaction among the cells in a population

Cell-to-cell communication is crucial for collective behaviour, and for the development and maintenance of multi-cellular organisms.

Diverse mechanisms of intercellular exchange of information are known and being discovered !

How do cells communicate with each other ?



Humoral - long distance

Receptor-ligand - contact signalling by membrane molecules

Junctions in membranes -
contact signalling through
Gap junction, Tight junction

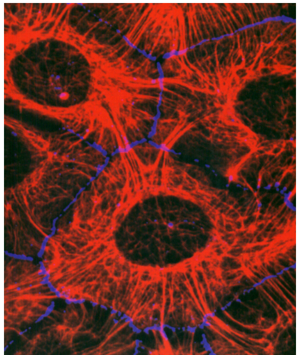
Matrix-mediated

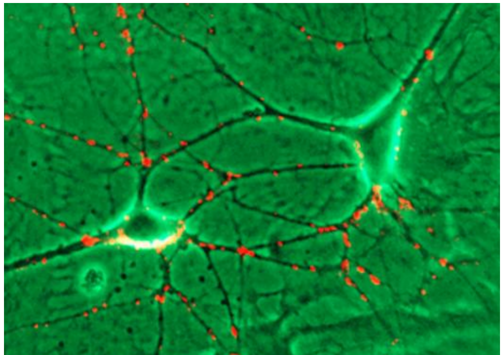
Types of Contacts in Multi-cell Systems

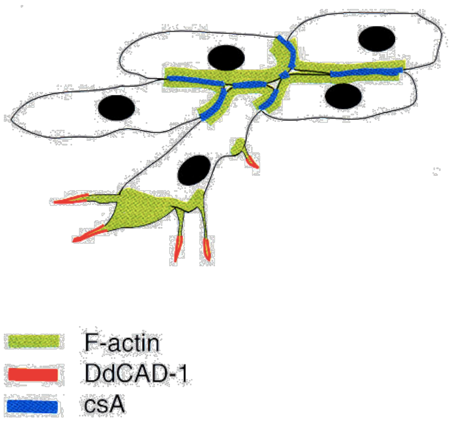
1) Nearest-neighbour,

2) Long range,

3) Transient connections

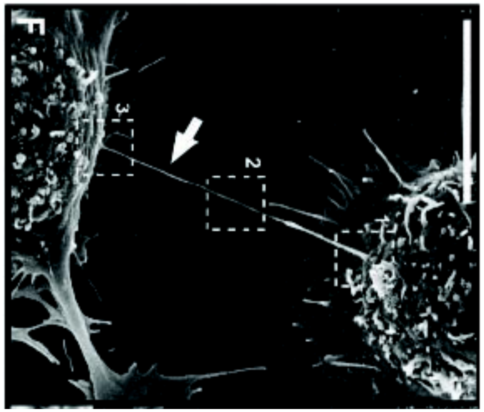






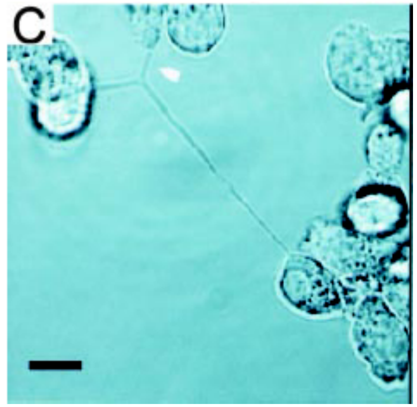
Modes of Communication - long distance

Tunneling NanoTubes (TNTs)
Ultra-fine intercellular structures



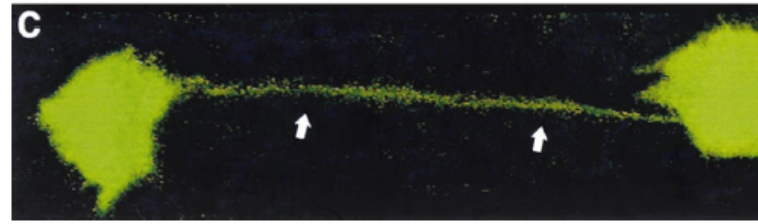
Novel biological principle of cell-to-cell interaction based on membrane continuity and intercellular transfer of organelles. *Rustom, et al, SCIENCE VOL (2004)*

TNTs in cultured rat PC12 cells. Diameter of 50 to 200 nm and a length of up to several cell diameters. These structures facilitate selective transfer of membrane vesicles and organelles but seem to impede the flow of small molecules.



Membrane nanotubes connect immune cells. *Oenfelt, et al, J. Immunology (2004)*

Three macrophage cells connected together by a nanotubular network, which can traffic cell surface proteins between immune cells over many tens of microns.



scabrous modifies epithelial cell adhesion and extends the range of lateral signalling during development of the spaced bristle pattern in *Drosophila*. *Renaud and Simpson. Dev Biol (2001)*

Cytoplasmic extensions radiating from the precursor cells that extend for several cell diameters (arrows).

Study collective dynamics in coupled cells

To investigate the roles of -

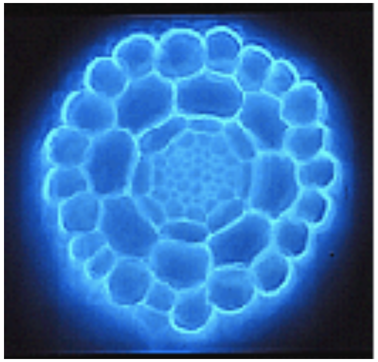
(a) local cellular dynamics,

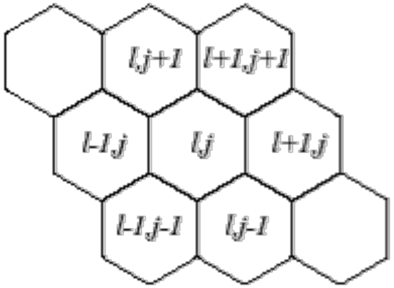
(b) cell-cell interaction strength,

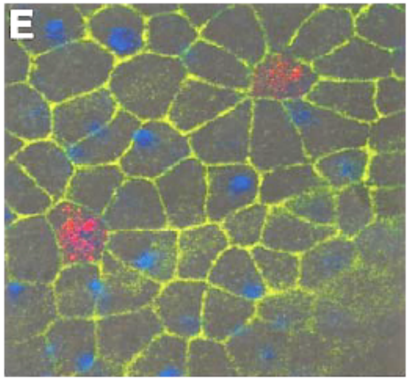
(c) inter-cellular contacts of different types,

(d) cell populations of different sizes and geometry

in the spatiotemporal dynamics of the coupled cells







MODELLING "CELL SYSTEMS"

"Cell Systems" consist of many cells interacting in space and time.

The cells may be identical or heterogeneous in properties.

The whole system behaviour is "collective behaviour"

Three major players -

a) Cells with properties that can be changed and their effect on the "collective behaviour" can be studied.

b) Different types of Interactions (*all-to-all, nearest neighbour, random, etc*).

c) Environment/structure (*constant* for all cells, *gradient* in properties, noise etc).

MODELLING THE "MULTI-CELL SYSTEMS"

Partial differential equations for microscopic modelling

Cellular Automata for individual based modelling

Cell Dynamical Systems (CDS) as explicit models for spatially extended systems with many interacting agents in space and time.

Useful to study systems at mesocopic scale

Why use this approach ?

Cells in a tissue are discrete entities having localised dynamics, interacting with each other through signals (chemicals, voltage, etc)

COUPLED MAP LATTICE SYSTEMS (CML)

Models for *spatially extended systems* using a lattice.

Each lattice site represents a dynamical system - *a "cell"*.

The "cells" interact with each other through a signal.

What can easily be done with CML

Properties of cells can be changed and their effect on the "collective behaviour" can be studied.

Different types of Interactions (*all-to-all, nearest neighbour, random, etc*) can be explicitly included.

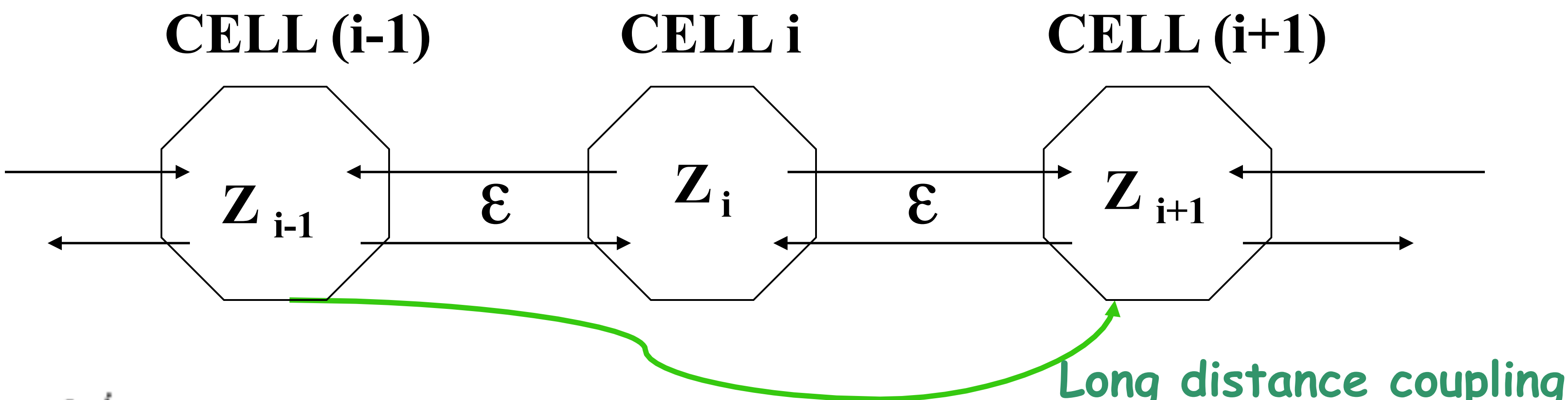
The Environment can be specified (*constant* for all cells, *gradient* in properties, etc).

Model of a one-dimensional coupled cell system

A lattice model where each lattice node is one model cell

Periodic b.c.

The cells can interact with their nearest neighbours through the diffusion of the end product of the pathway



$$\frac{dx^i}{dt} = F(z^i) - kx^i;$$

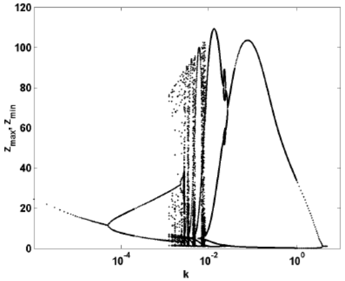
$$\frac{dy^i}{dt} = x^i - G(y^i, z^i)$$

$$\frac{dz^i}{dt} = G(y^i, z^i) - qz^i - \varepsilon(z^i) + (\varepsilon/2)^*(z^{i-1} + z^{i+1})$$

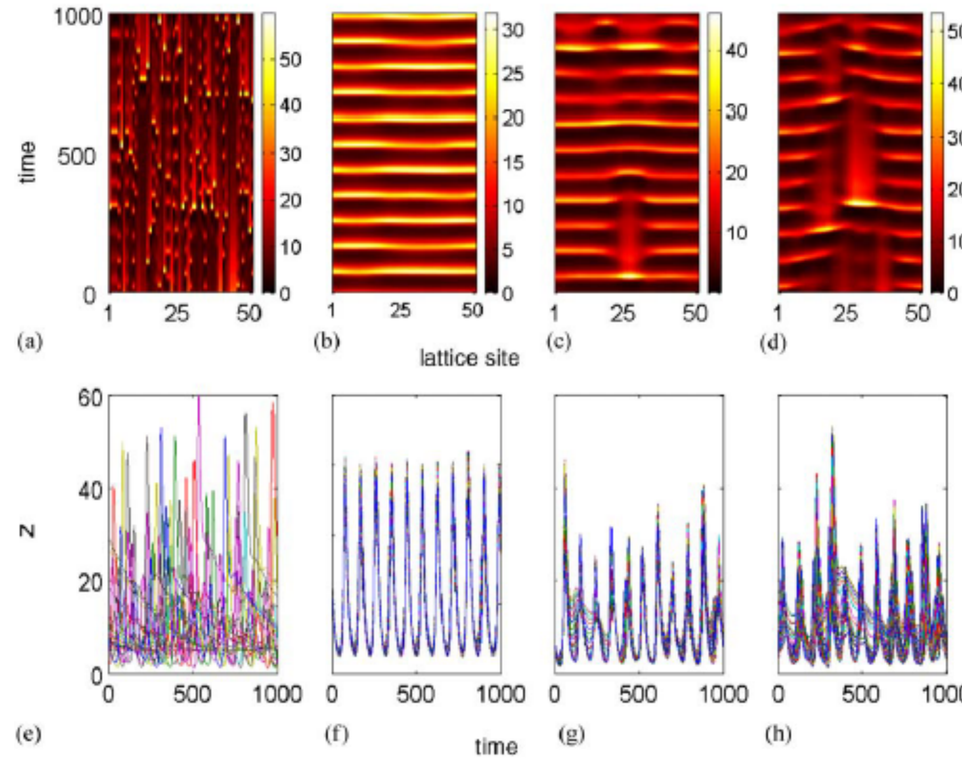
ε= coupling strength

Symmetric coupling

Homogeneous lattice

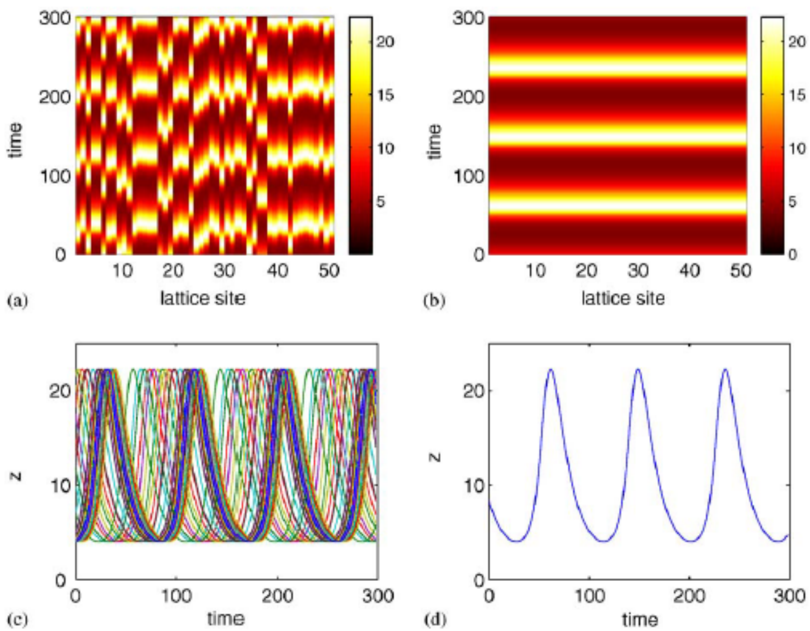


50 cells with intrinsic chaotic dynamics:



k =0.003; q=0.1; e=0.3

50 cells with intrinsic periodic dynamics:



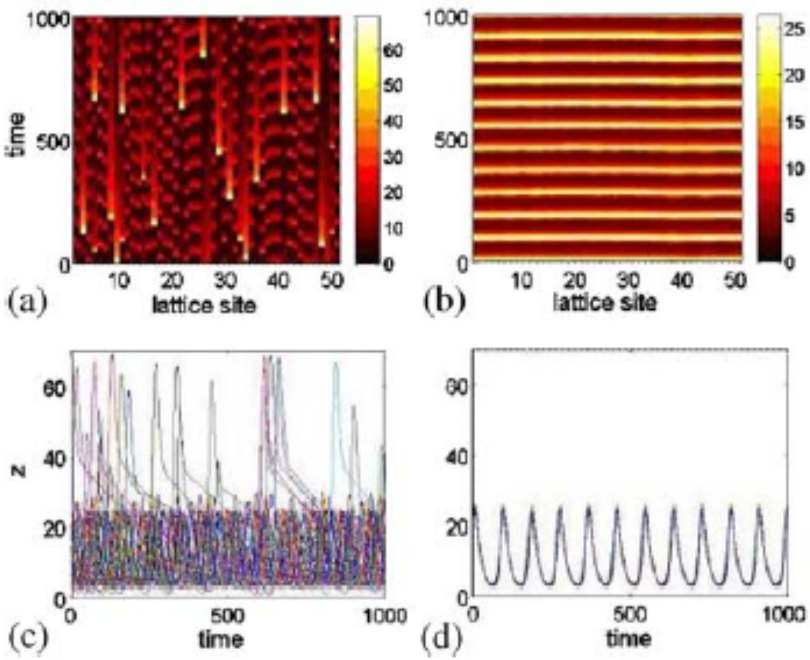
k =0.001; q=0.1; e=0.3

Heterogeneous lattice

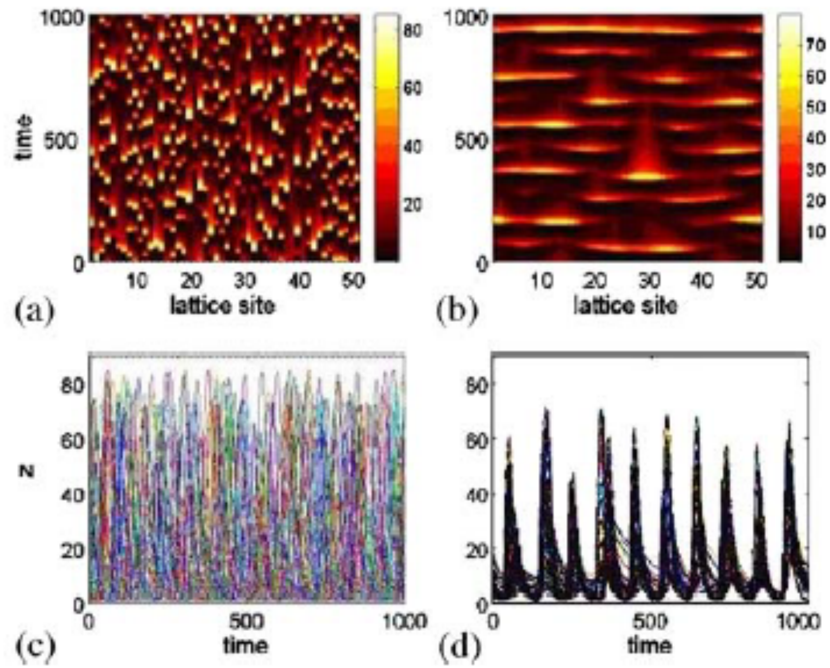
In reality, a population of cells can have different parameters due to intrinsic and extrinsic noise that permeates its environment.

Lattices (e = 0.3) with cells having k= 0:001+/- s (s=uniform random deviate)

s=(0, 0.003)



s=(0, 0.03)

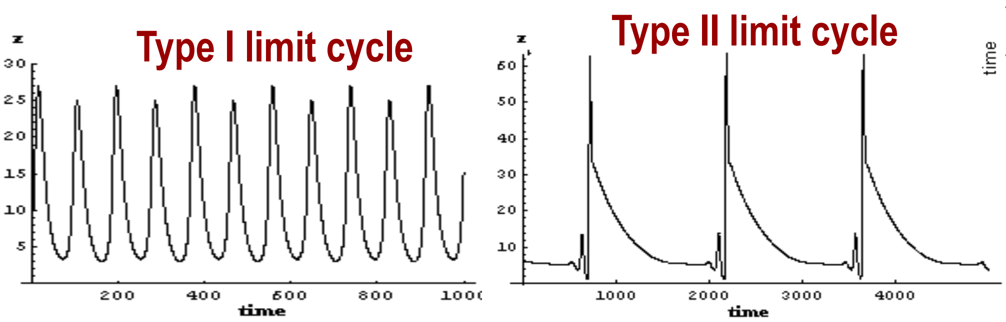


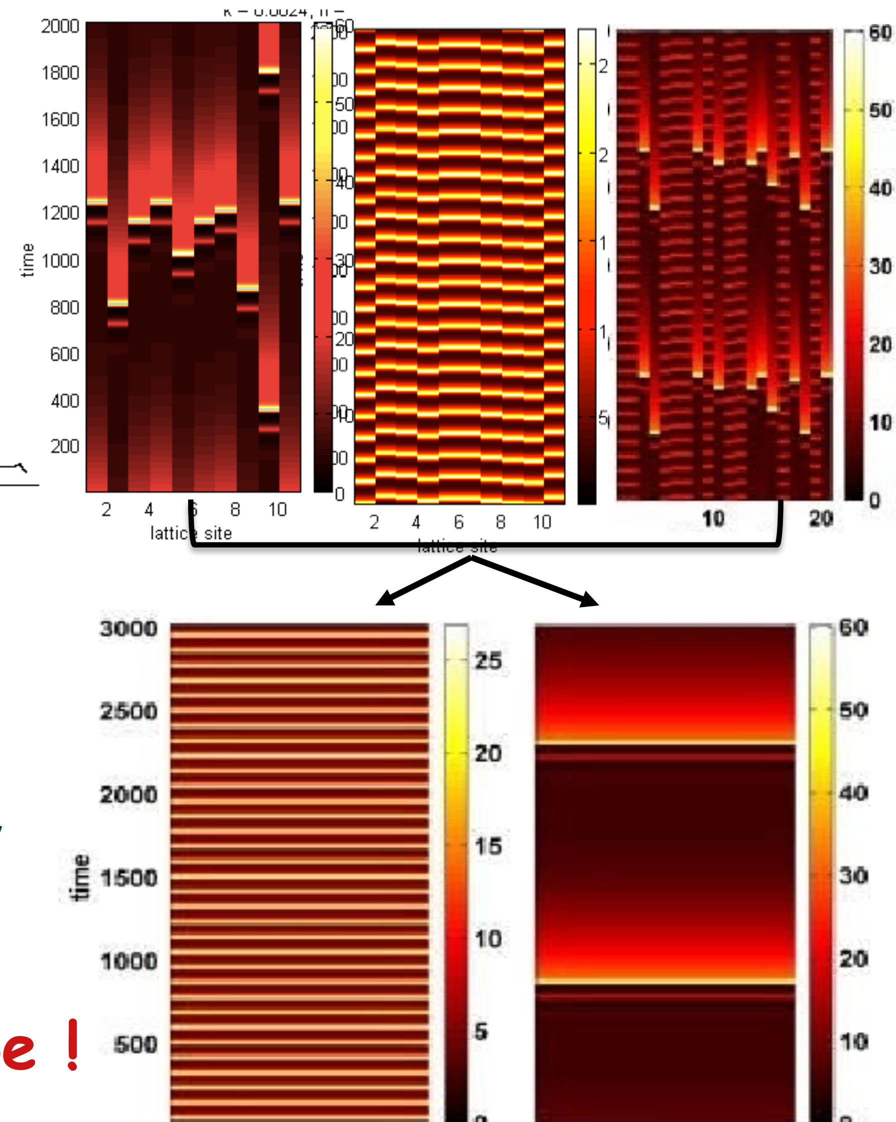
Increasing heterogeneity in cellular parameters

partial phase synchronisation

Lattice with birhythmic cells

Cells with only Type I, Type II, and mixed initial dynamics (e=0.3, 0.7)



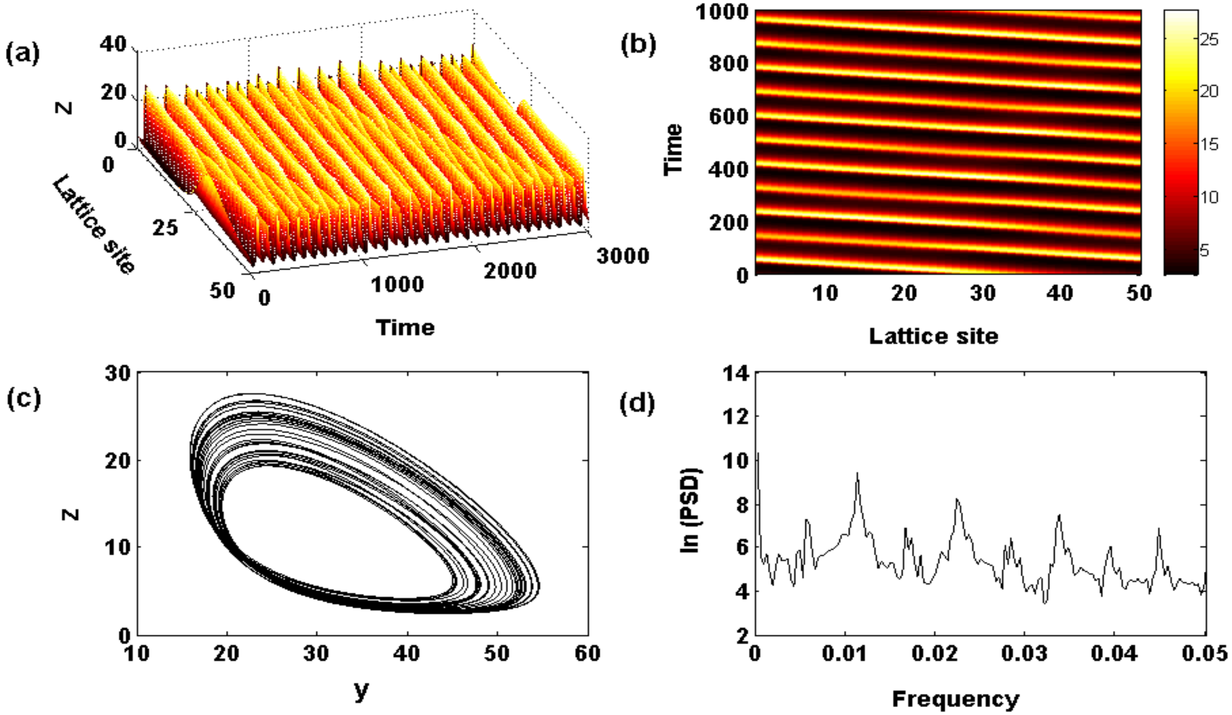


For small lattice size, irrespective of the initial dynamics of the cells, they synchronize either to Type I or Type II dynamics.

Exhibits two dynamic phenotype !

Cell populations above a **threshold size** always reliably synchronize to the higher frequency Type I oscillations. **Quorum Sensing** !!

Travelling Wave Solution



$N = 50$

$\varepsilon = 0.3$

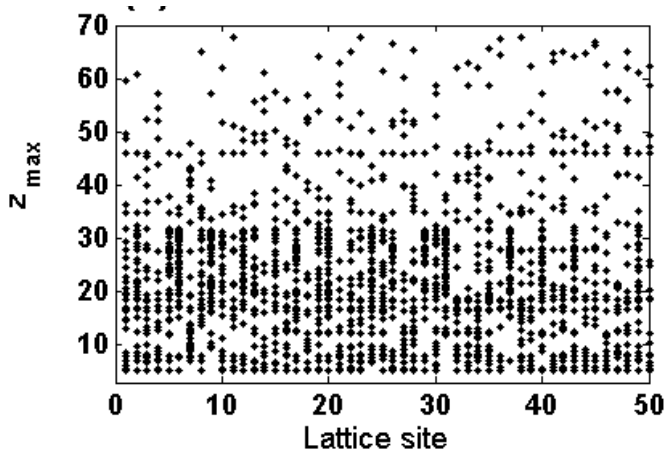
Variation of dynamics with cell number, *N*. ε=0.72

CH, chaos; CS, complete synchronization; P4, period 4 cycle; PS, phase synchronization; IPS, intermittent phase synchronization.

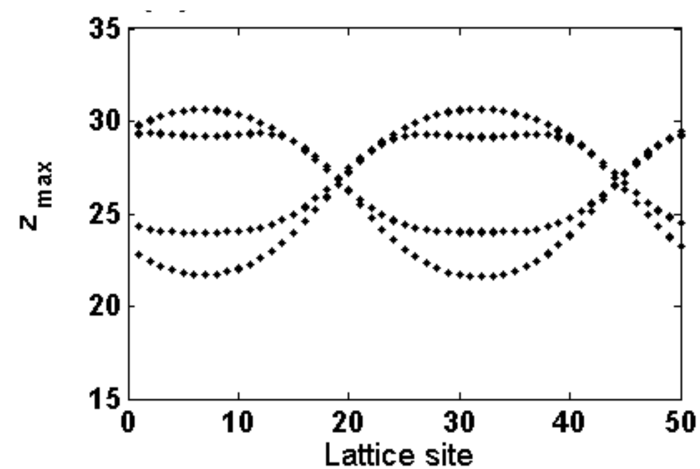
No. of cells	10	20	30	40	50	60	70	80	90	100
Global dynamics	CS	CS	IPS	IPS	PS	IPS	IPS	IPS	IPS	IPS
Local dynamics	CH	CH	CH	CH	P4	CH	CH	CH	CH	CH

Suppression of chaos and pattern formation

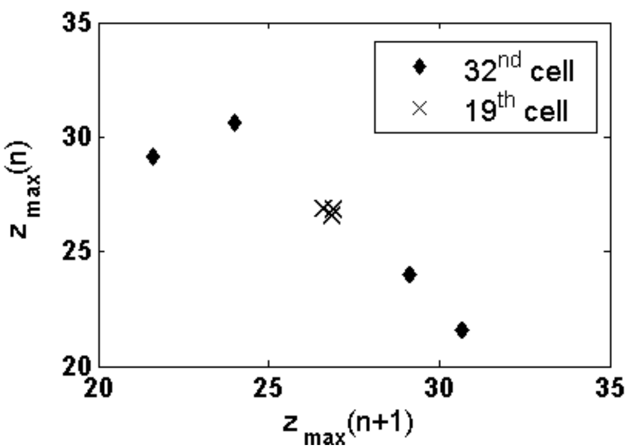
Profile of the peaks in uncoupled cells



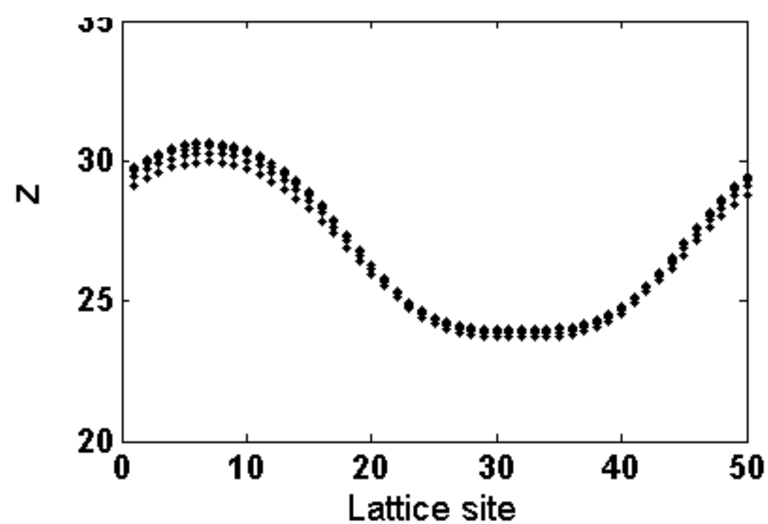
Spatial pattern in peaks of coupled cells



Return Maps



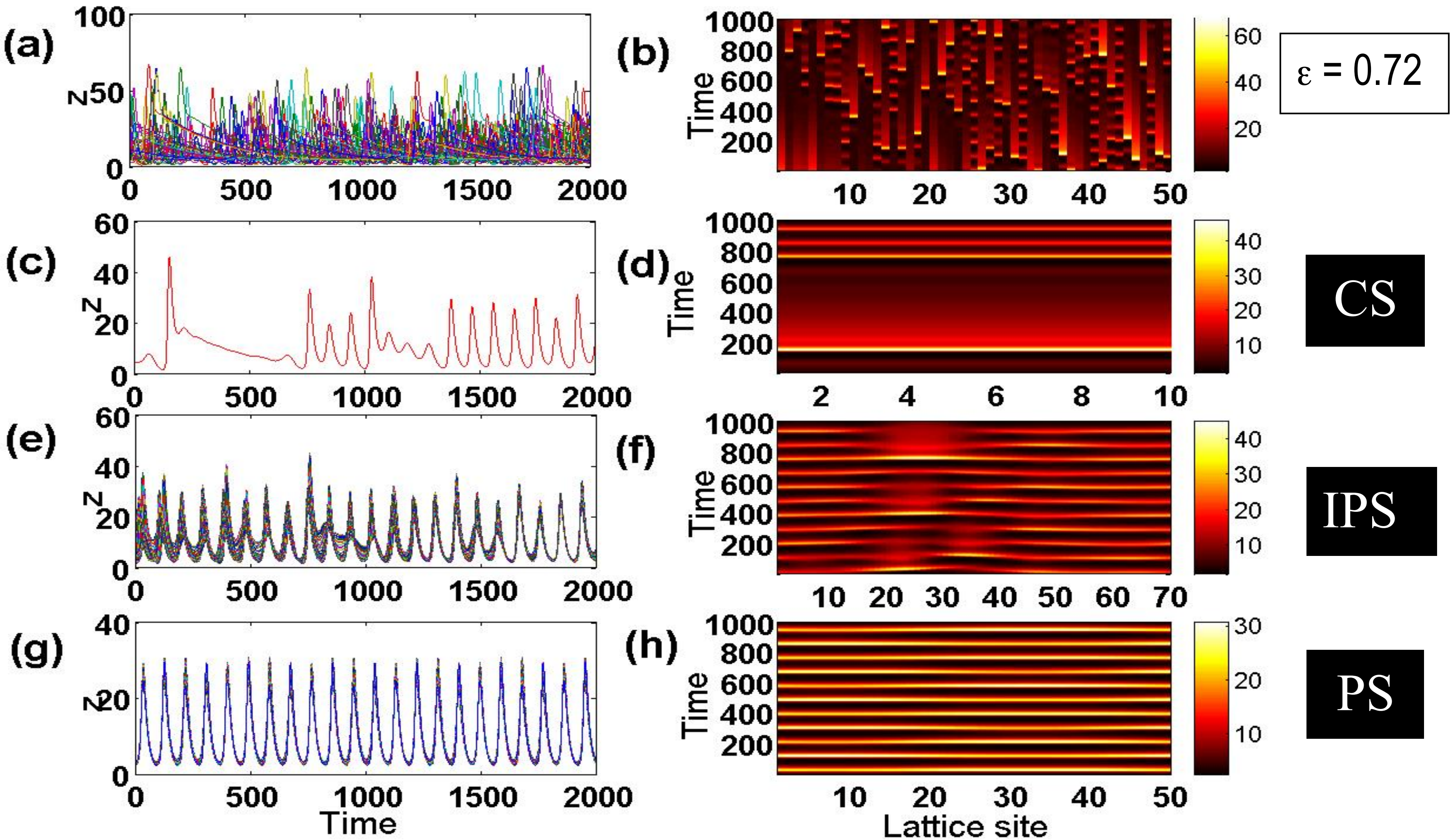
Snapshots of the cell profiles at intervals of 365 time units.



Rajesh, et al, Physical Review E,

Emergent collective behaviour of systems of different sizes (N) with intrinsic chaotic dynamics in cells

(a,b) Uncoupled cells; (c,d) chaotic synchronization, *N*=10; (e, f) intermittent phase synchronization, *N*=70; (g, h) suppression of chaos and phase synchronization, *N*=50.



(Rajesh, et al, Phys. Rev. E)

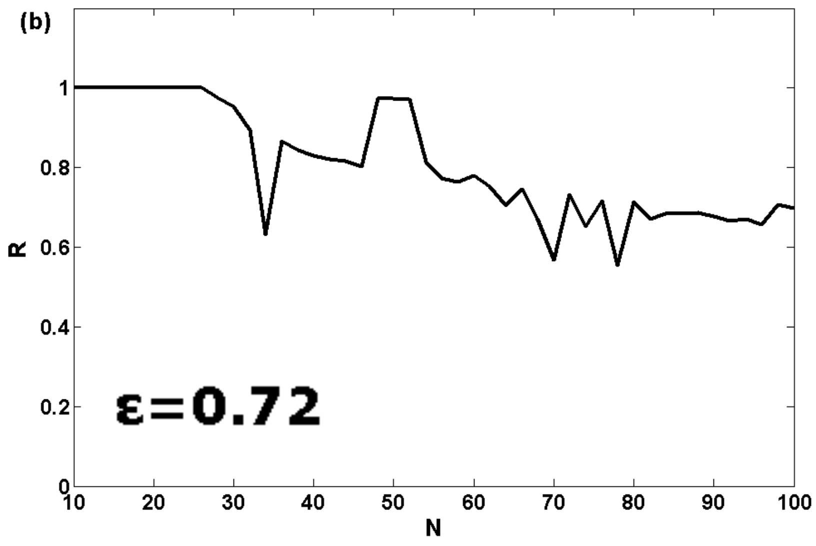
Quantitative study of synchronization

$$R = \frac{<[z_i]^2> - <[z_i]>^2}{[<z_i^2> - <z_i>^2]}$$

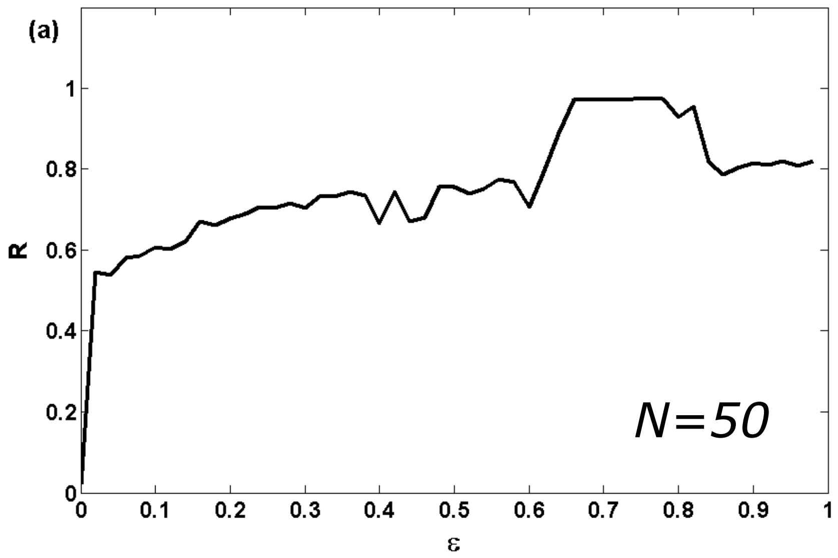
< > - Time average

[ ] - Spatial average

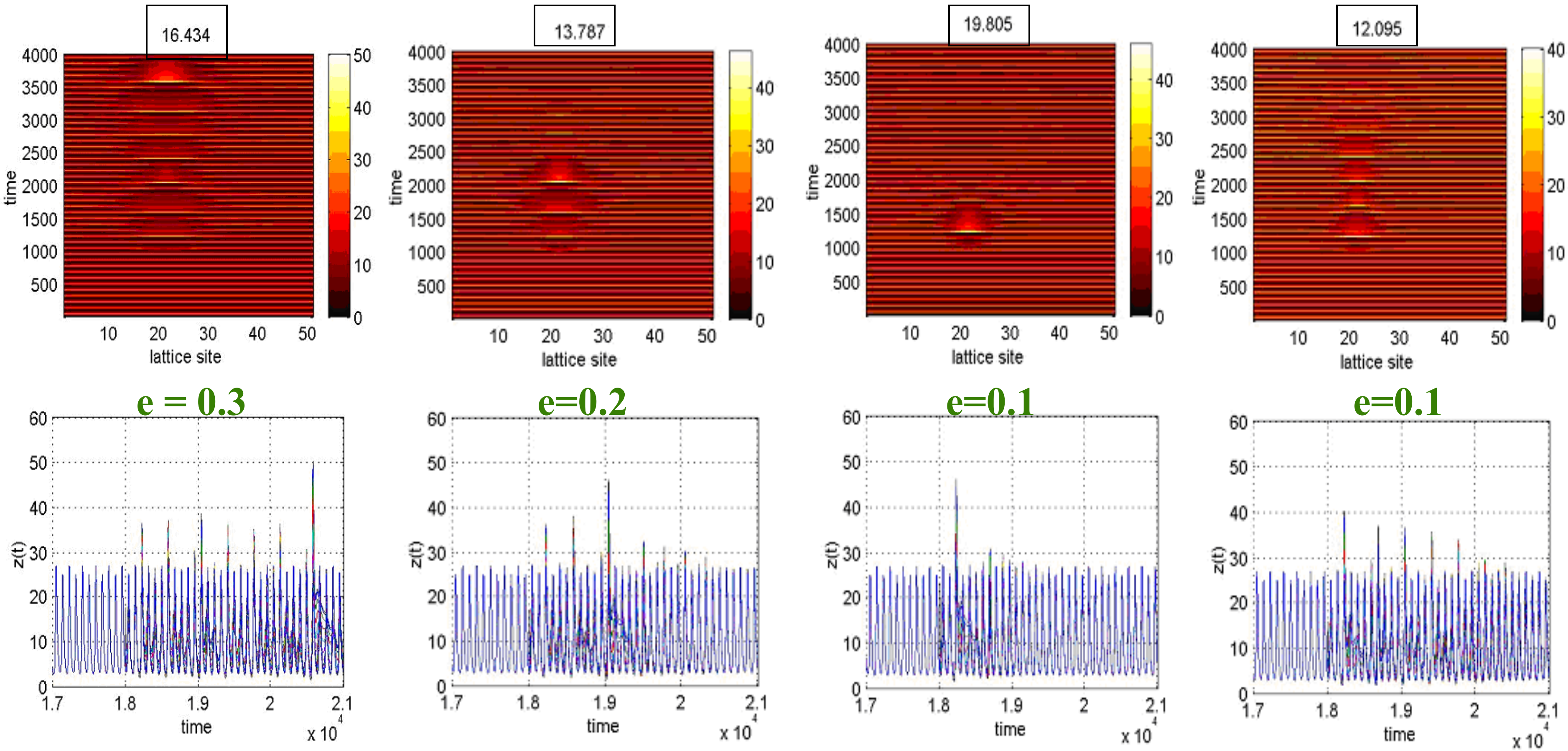
Order Parameter vs Cell Number



Order Parameter vs Coupling Strength



Effect of instantaneous perturbation in end-product of a single cell on collective dynamics



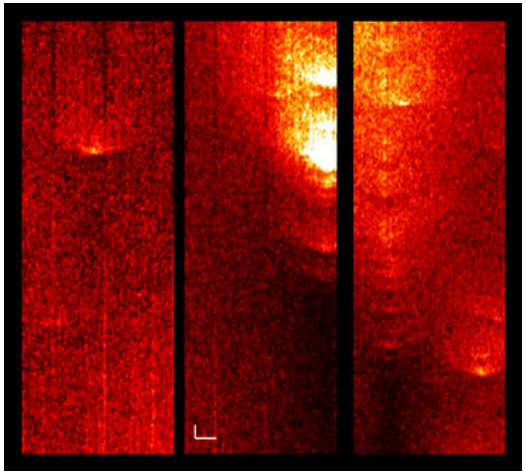
Different transient effects - depends on phase at which perturbation acts, and coupling strength (not so much on perturbation strength)

Stability of the synchronised state ?

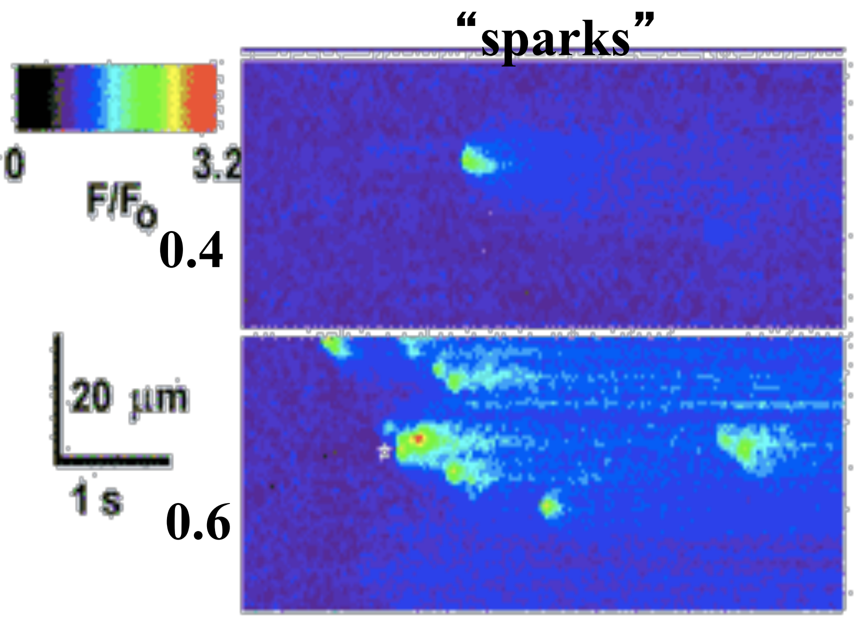
Ghosh, Rangarajan, Sinha, Eur Phys Lett A

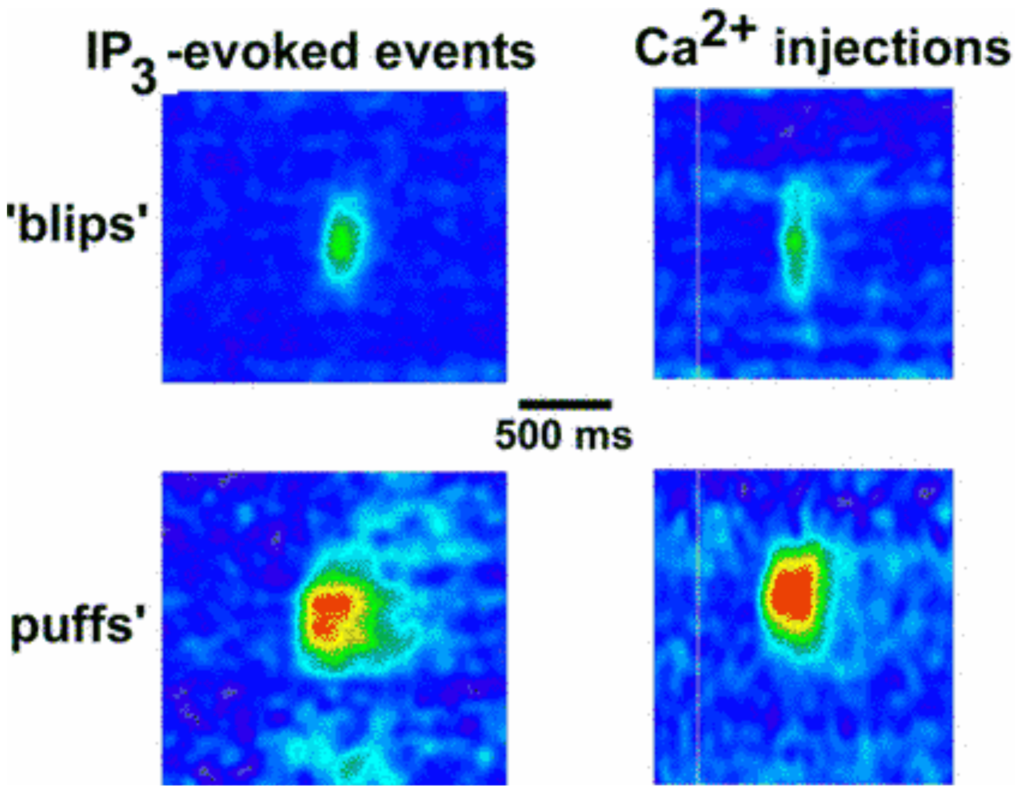
Imaging Calcium microdomains in single cells in a tissue

Calcium is injected into the *Xenopus laevis* oocyte with a micropipette



Transient processes termed based on time and space scales



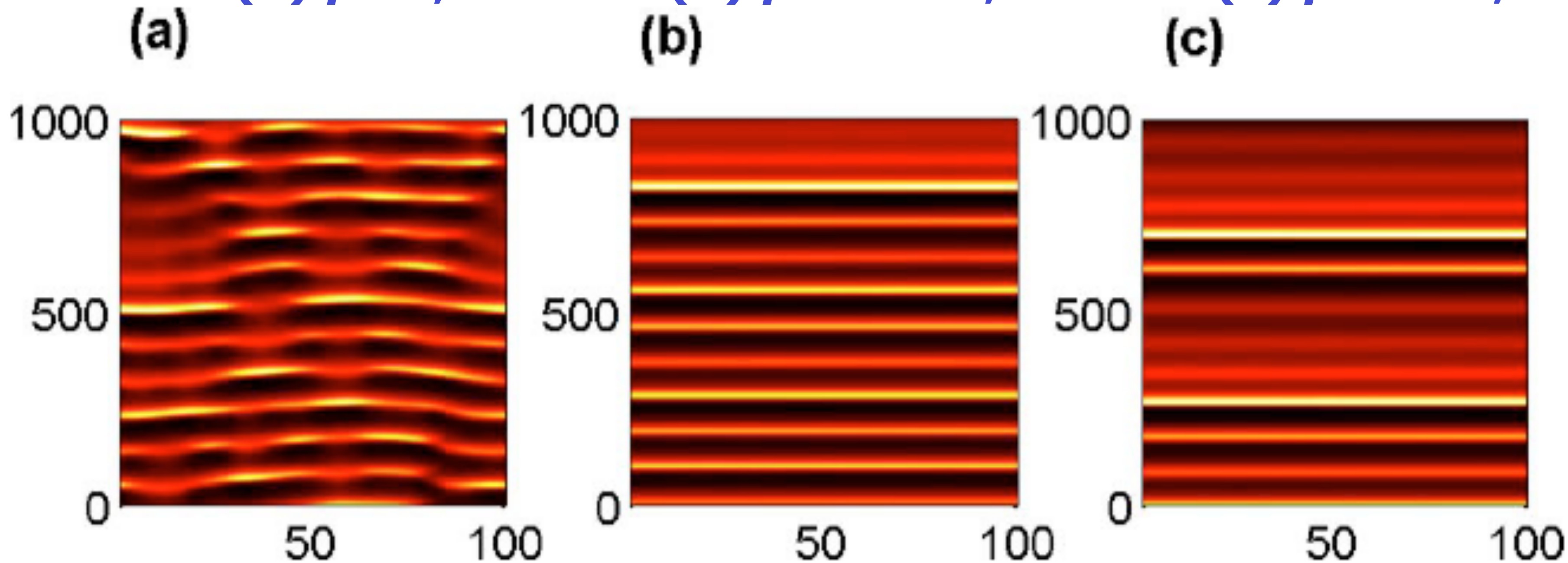


Effect of Transient Long distance Contacts

(Random-rewiring)

Space-time plots of z in coupled cells (N=100, ε=0.7) for rewiring fraction -

(a) *p*=0, (b) *p*=0.025, (c) *p*=0.05,



A small degree of randomness in the spatial coupling can lead to complete synchronization in regimes of coupling strengths which yield only intermittent synchronisation for strictly nearest neighbour coupling.

(Rajesh, et al, PRE)

Collective behaviour in multi-cell systems is primarily synchronised -

It may not always be the same as the constituent single cell dynamics.

The collective dynamics is generally robust even if the single cell behaviour is not.

***Such a property confers functional advantage to the coupled multi-cell system in natural noisy environment*.**

This theoretical study provides clues that increase the general understanding of how nature may engineer collective robustness in the face of local complexity.

Physical approaches used to study biological organisation

Cellular automata

Boolean networks

Lattices

Spin glasses

Graphs

Power Laws

Self-organised criticality

Phase transitions

Scale-free networks

Edge-of-chaos

Modelling biological organisation

Observation-based

Interpretation of system behaviour based on incomplete information.

1-dim data to n-dim reconstruction of system

Abstraction of large number of events

To simple functional forms & study their behaviour under various conditions.

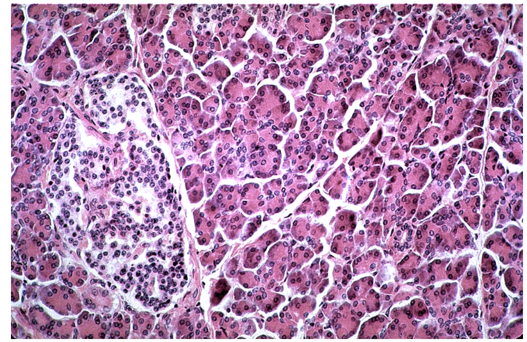
n-dim process to 1-dim data

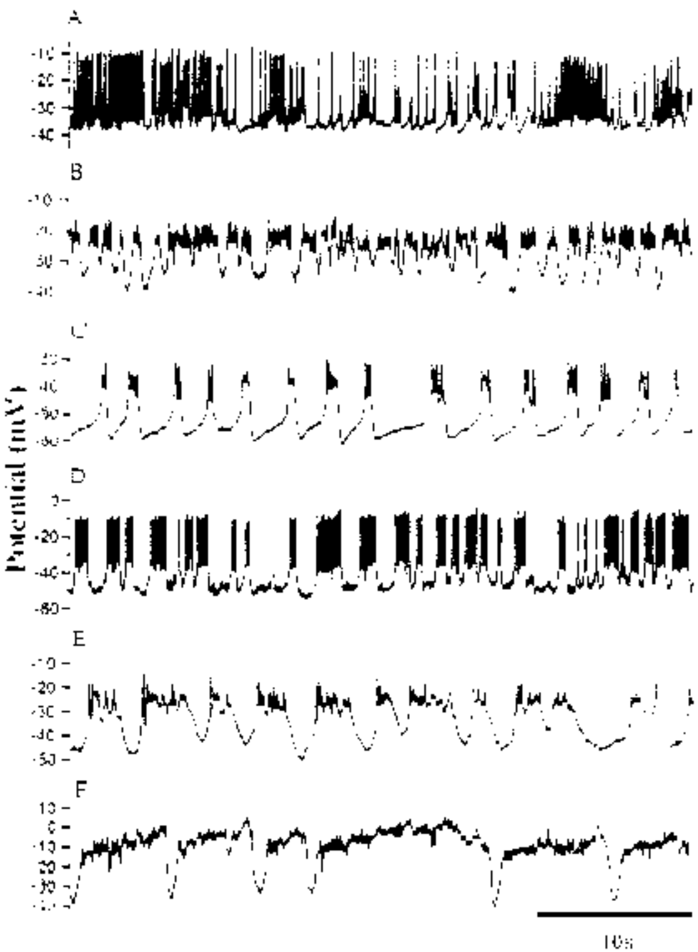
Organised Assemblies - *Electrical activity of Islets*

Beta cells in Pancreatic islets secrete insulin in response to glucose stimulation.

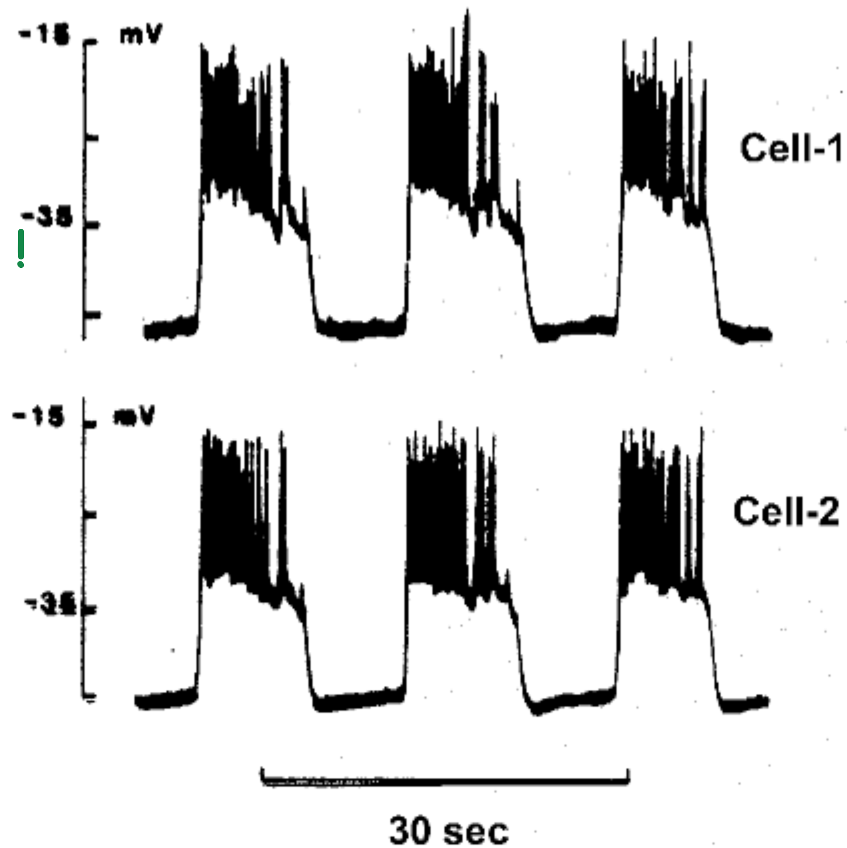
Dispersed Beta cells do not.

PANCREATIC ISLET & ACINAR CELLS





DYNAMICS !



50 years ago:

Physicists interested in biology >> biologists

"Biophysics" - Application of physical methods to problems posed by biologists

NOW:

Physicists ask new and different questions about living systems

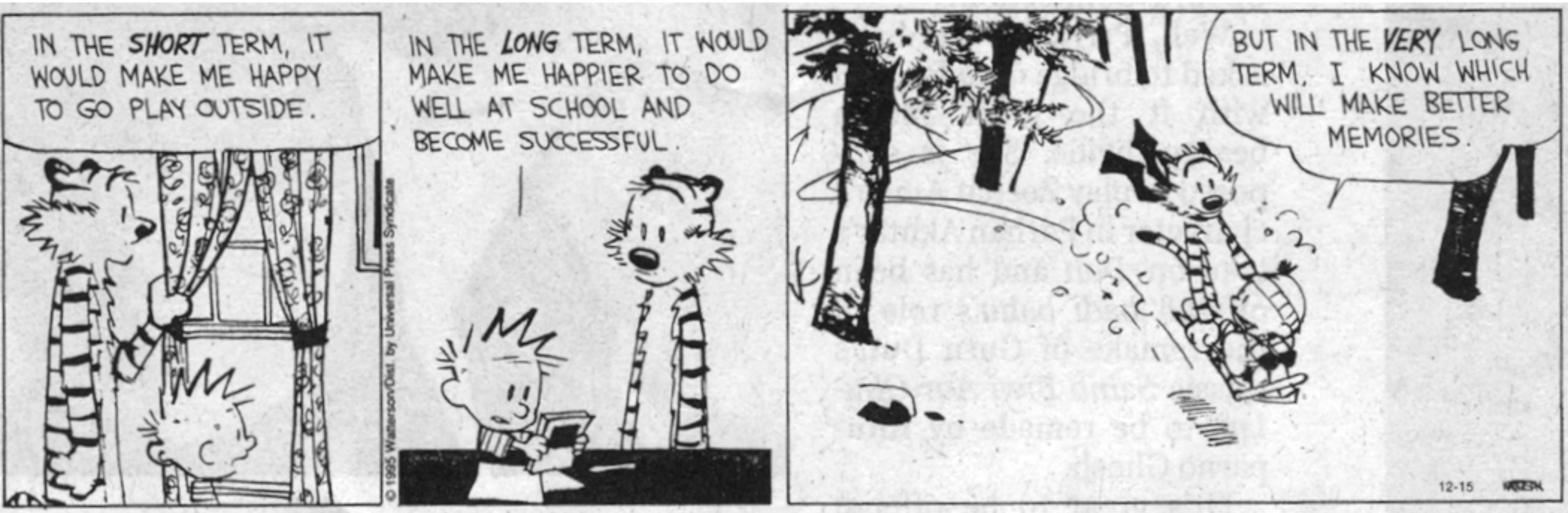
>> search for "universality" at systems level

Self-organisation

Robustness

Optimisation

Evolvability, Emergence



IN THE SHORT TERM, IT WOULD MAKE ME HAPPY TO GO PLAY OUTSIDE.
IN THE LONG TERM, IT WOULD MAKE ME HAPPIER TO DO WELL AT SCHOOL AND BECOME SUCCESSFUL.
BUT IN THE VERY LONG TERM, I KNOW WHICH WILL MAKE BETTER MEMORIES.
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12-15