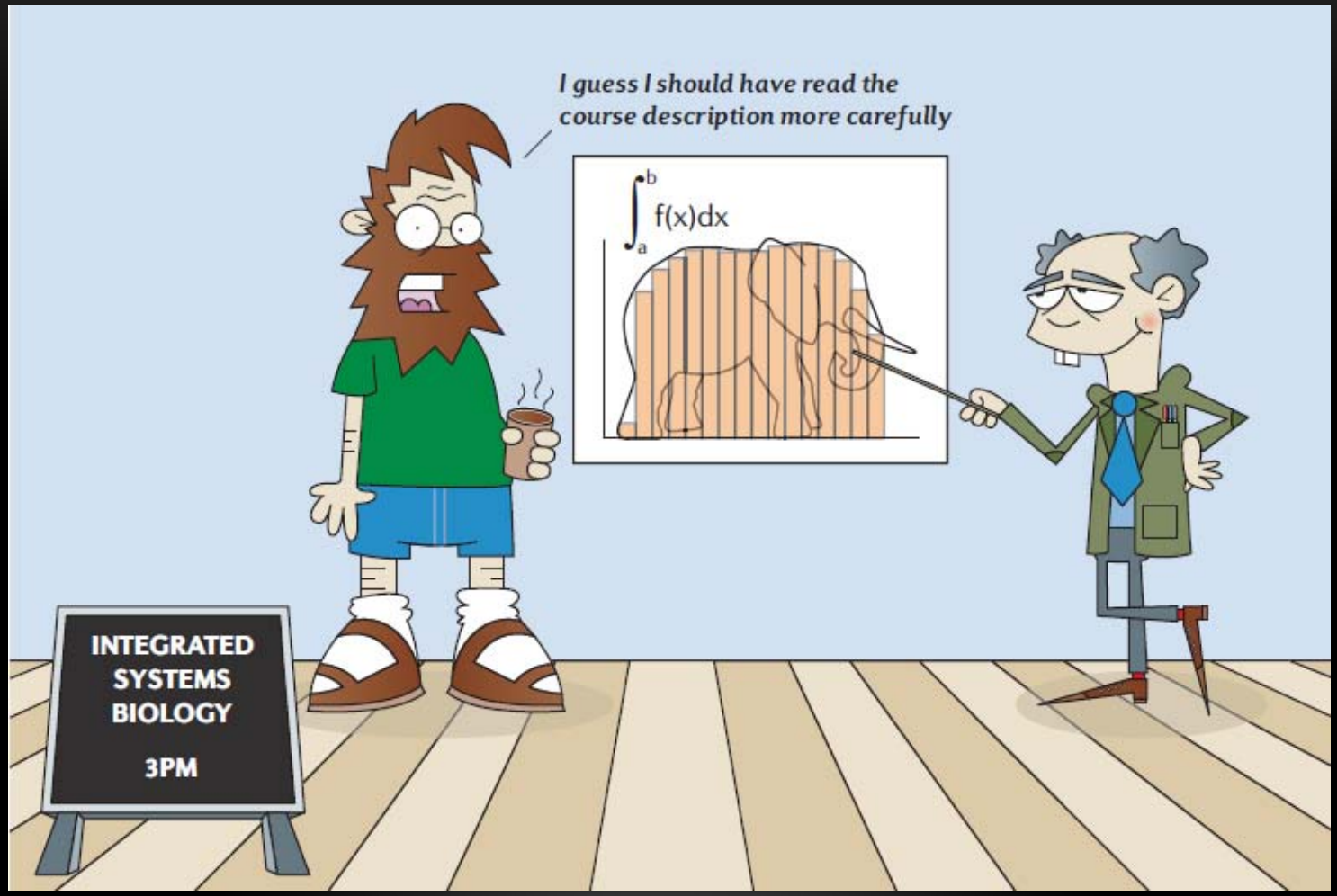
# SYSTEMS BIOLOGY: EVOLUTION OF A NEW DISCIPLINE

Advance cell and molecular biology (ICG601)

Dr. Dhiraj Kumar

Immunology Group


I guess I should have read the course description more carefully
$\int_a^b f(x)dx$
INTEGRATED SYSTEMS BIOLOGY
3PM

# SYSTEMS BIOLOGY: COURSE OUTLINE

Systems Biology: evolution of a new discipline

- What is systems biology?
- Why systems biology?
- Biological systems as complex system
- Foundation of Systems Biology

Large scale data generation and analysis

- Microarray data Analysis
- Pathway mapping and enrichment
- Clustering (clustergram, PCA, k-means cluster)
- Functional annotation of clusters
- Analysis of high-content screening data (Hit identification and validation)

# SYSTEMS BIOLOGY: COURSE OUTLINE

Complex Systems: Organization and dynamics

- Biological Networks
- Organizational Principles in Biological System
- Emergent properties of Complex systems
- Dynamics of Biological Networks

Statistical/Mathematical/Computational Models to understand Biology

- Statistical Approaches
- Mathematical Approaches
- Computational Approaches

# WHAT IS SYSTEMS BIOLOGY

- Systems biology is concerned with the study of biological functions and mechanisms, underpinning inter- and intra-cellular dynamical networks, by means of signal- and system-oriented approaches

- Systems biology is the study of the behaviour of complex biological organization and processes in terms of the molecular constituents.

- Biology invariably works in an integrative manner, different organ, tissue and cells working in sync. Biologists however have studied biology invariably in isolated fashion hoping to understand the complex behaviour of biological systems

---

# PHYSICAL WORLD VS BIOLOGICAL WORLD

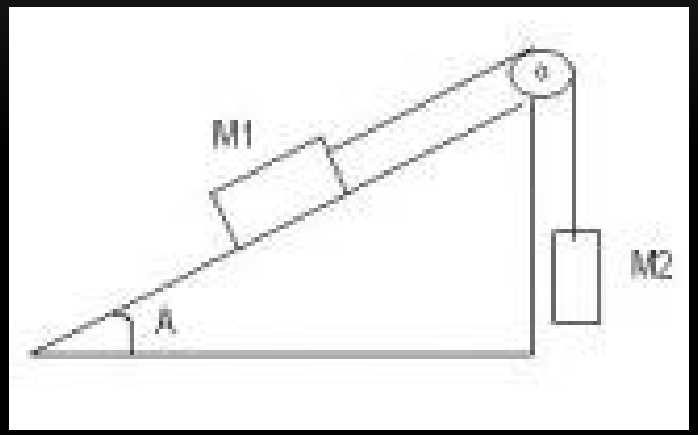
**Physical world**

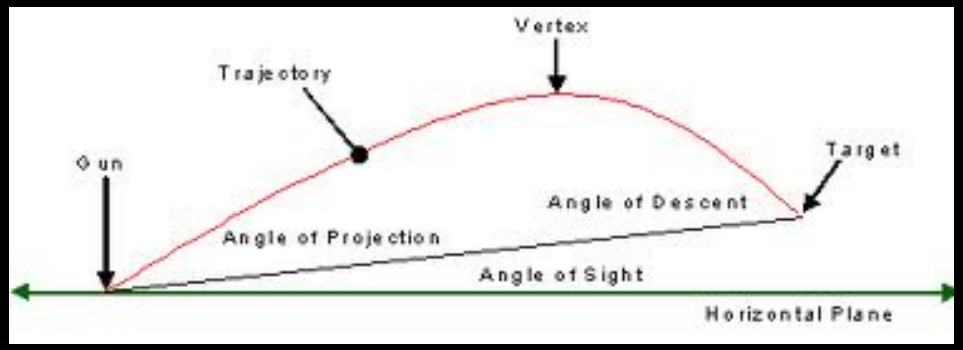
- precision
- predictive

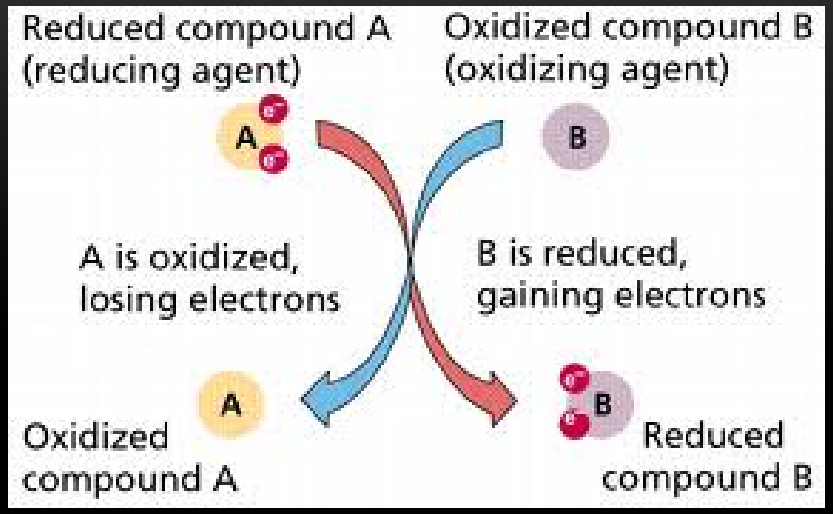
**Biological world**

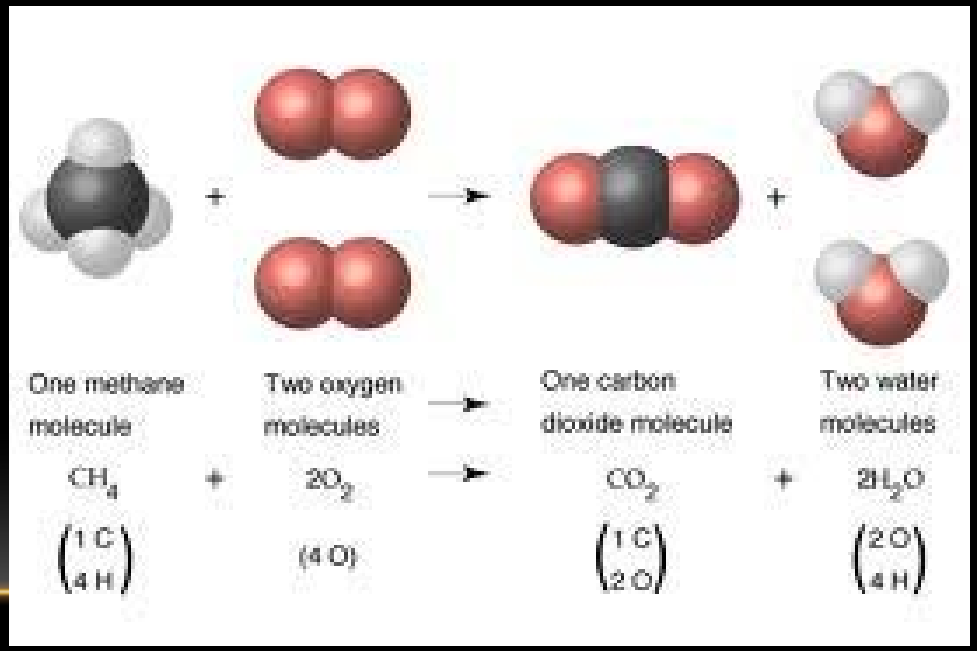
- variation
- observational

# HOW DO YOU DEFINE SCIENCE?


M1
M2
A


Vertex
Trajectory
Gun
Target
Angle of Descent
Angle of Projection
Angle of Sight
Horizontal Plane


Reduced compound A
(reducing agent)
Oxidized compound B
(oxidizing agent)
A
B
A is oxidized,
losing electrons
B is reduced,
gaining electrons
A
B
Oxidized
compound A
Reduced
compound B


One methane
molecule
Two oxygen
molecules
One carbon
dioxide molecule
Two water
molecules
$CH_4$ + $2O_2$ → $CO_2$ + $2H_2O$
(1 C, 4 H)
(4 O)
(1 C, 2 O)
(2 O, 4 H)

**Cause and effect relationship**

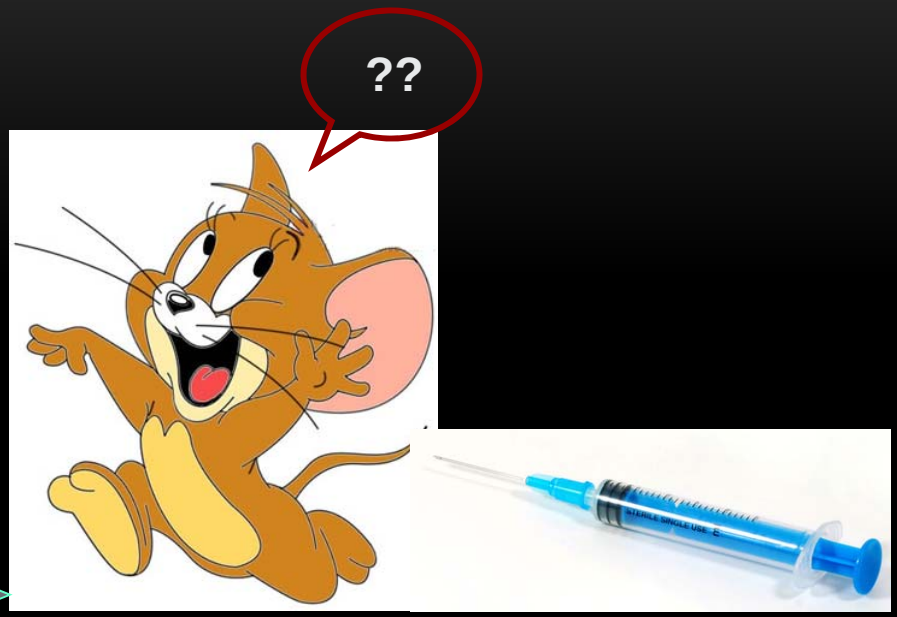
**Predictive nature**

Heat

Sound

Light

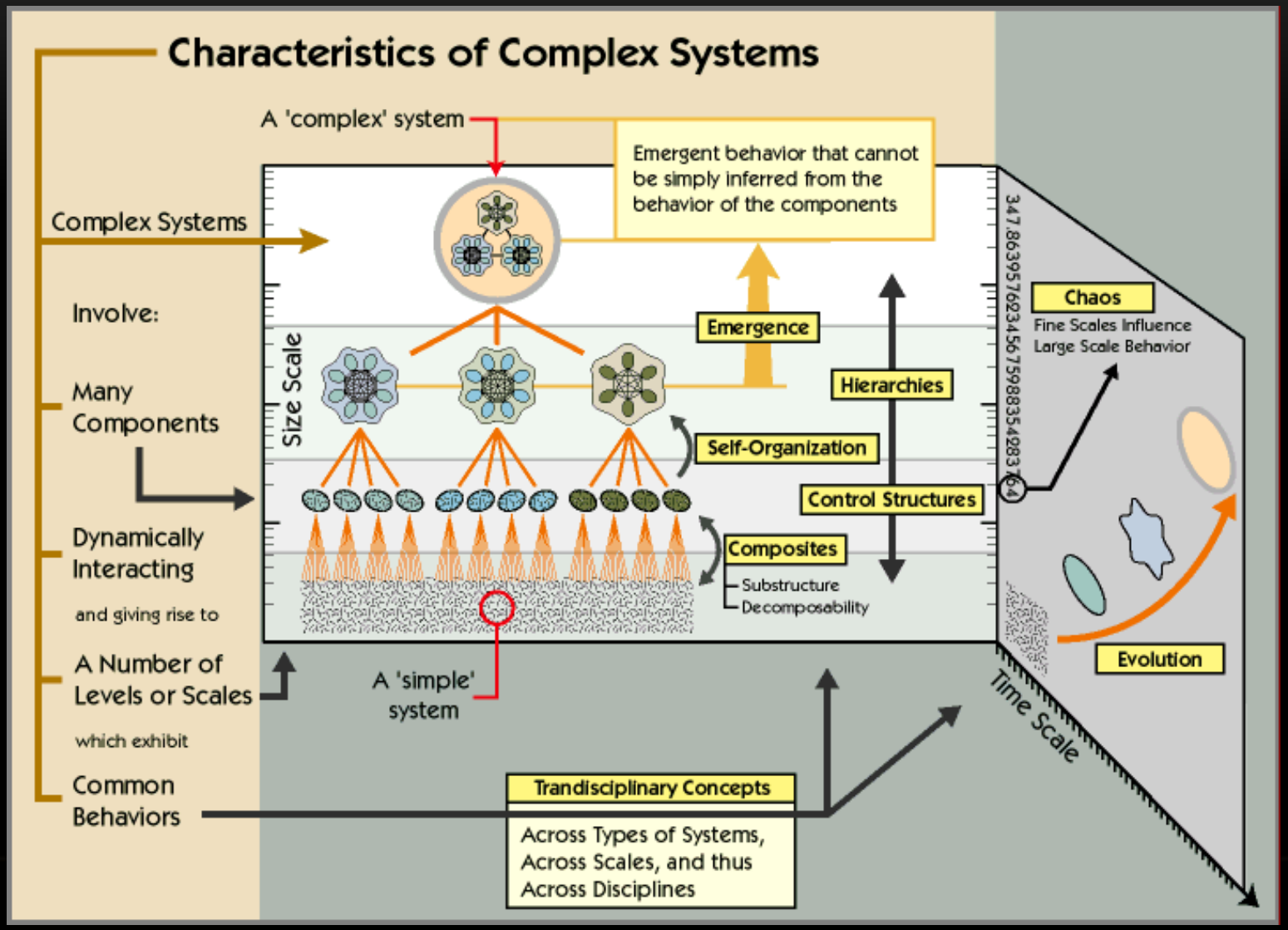
Infection



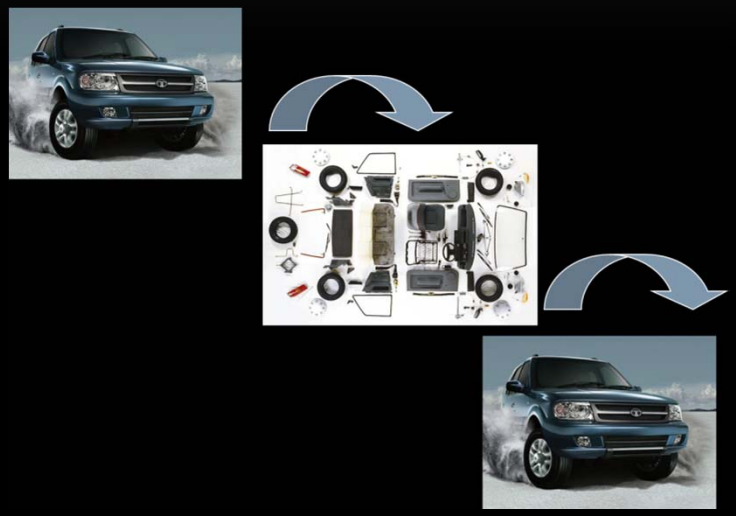

Can Response of Mice be predicted??

Biological systems are complex system and novel approaches are needed to understand them

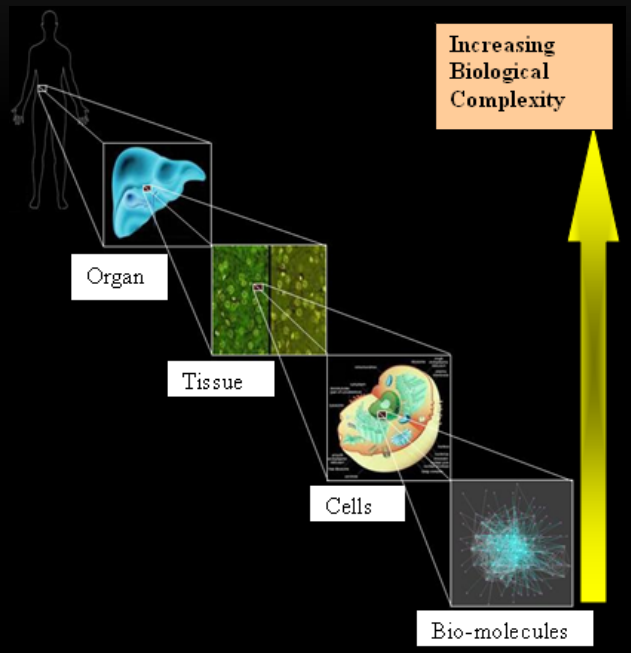
# Complexity in Biology



## Simple system can be disintegrated And re-integrated



## Can pieces be integrated in complex systems?

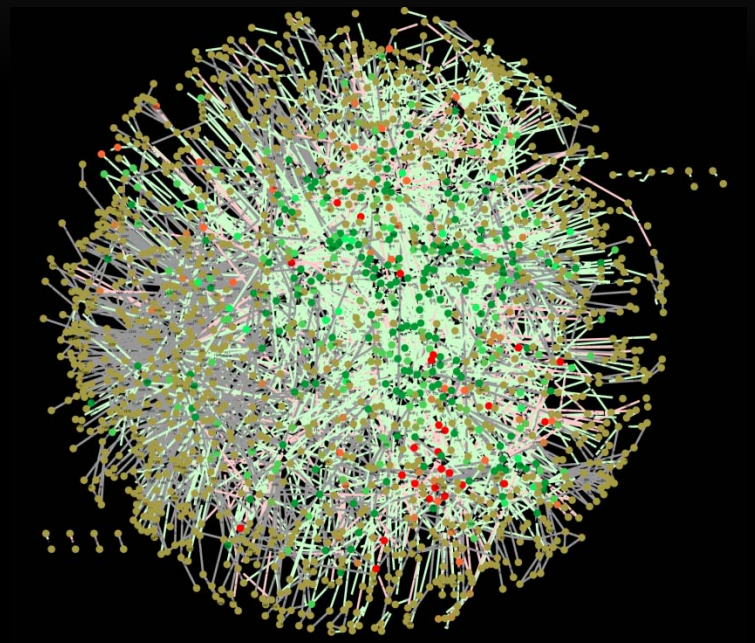


## Biological System as Complex system

Interconnected/Interacting components

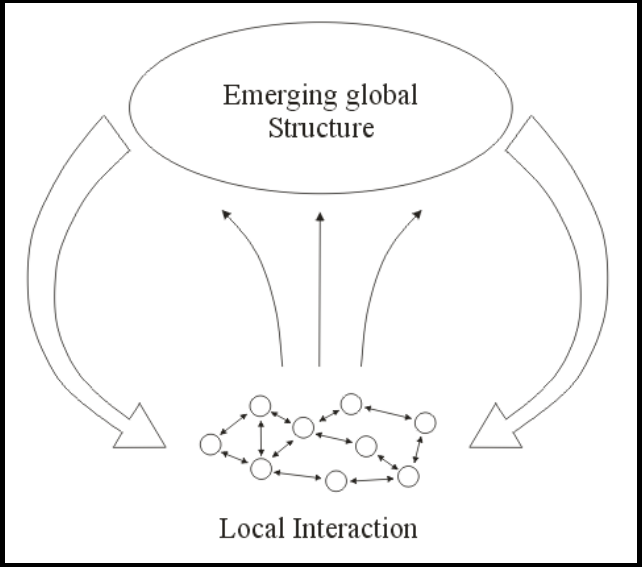
Exhibit Emergent properties (Scale-free organization)

Interactions → Emergence



## Self-Organization

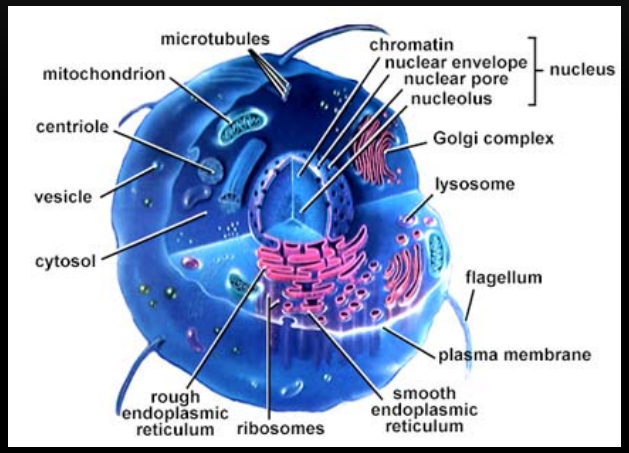
**Appearance of Specific Structure/pattern without any central regulator**

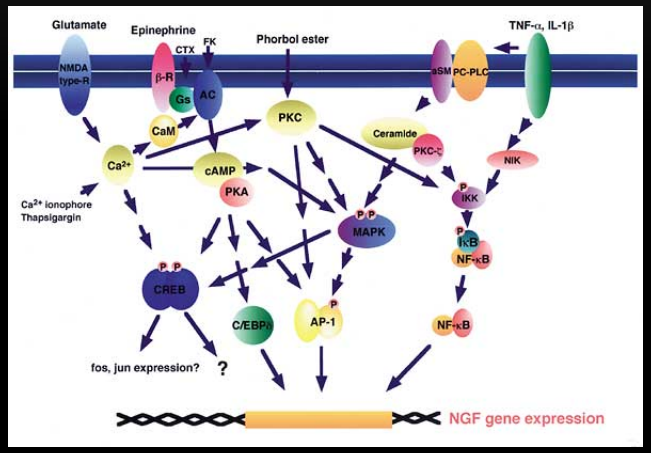



*"Life is an emergent, rather than an immanent and inherent, property of matter. Although it arises from the material world, it cannot be reduced to it"*

(E. Schrödinger)

What Biologists have achieved so far:






Molecular understanding to a great detail!!!

Response to environment: Do we know enough to predict?

# Challenges

Biological system: Have dynamic exchange with the surroundings (context)

Respond to changes in the environment→ context dependence

How changes in environmental state is sensed by the biological object?

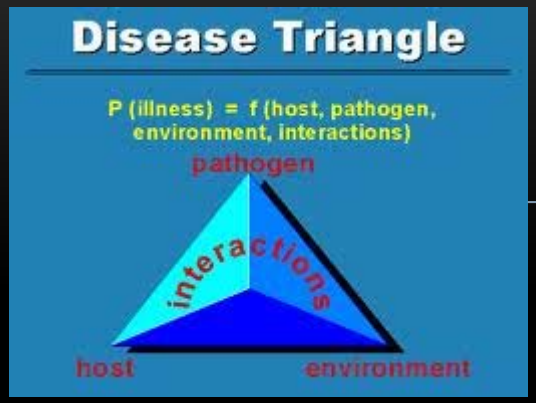
How they respond to environmental context?

How complex signaling network regulates cellular behavior?

How gene regulation is achieved at the precision level we observe?

Can molecular understanding (last 150 years) be integrated together to answer these questions?

# Success so far has been remarkable




Molecular Intervention

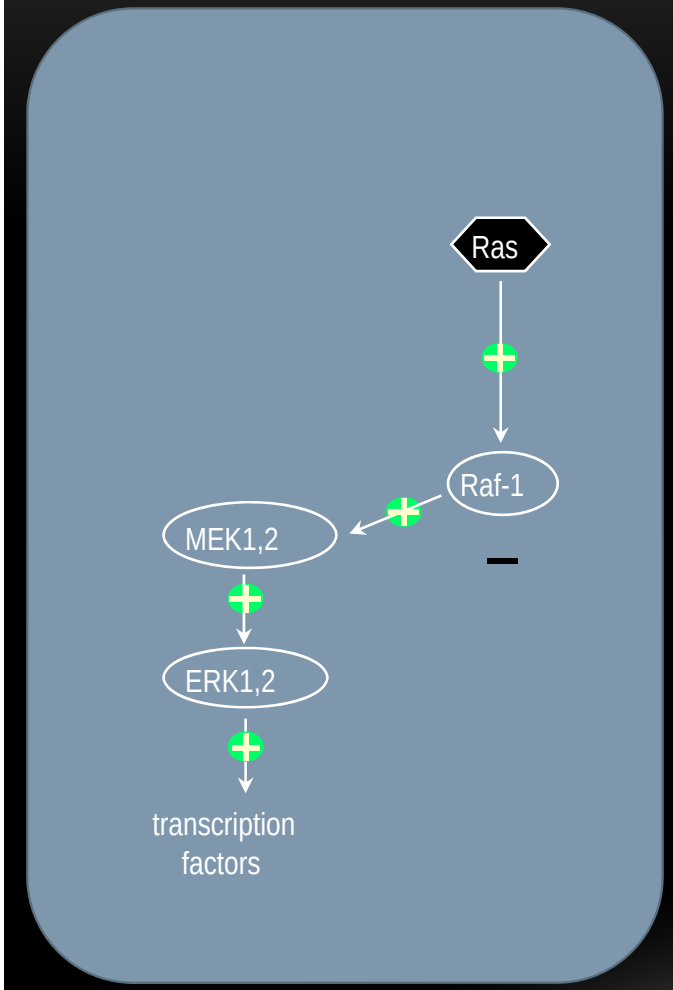
SYSTEMS BIOLOGY AND MEDICINE 381

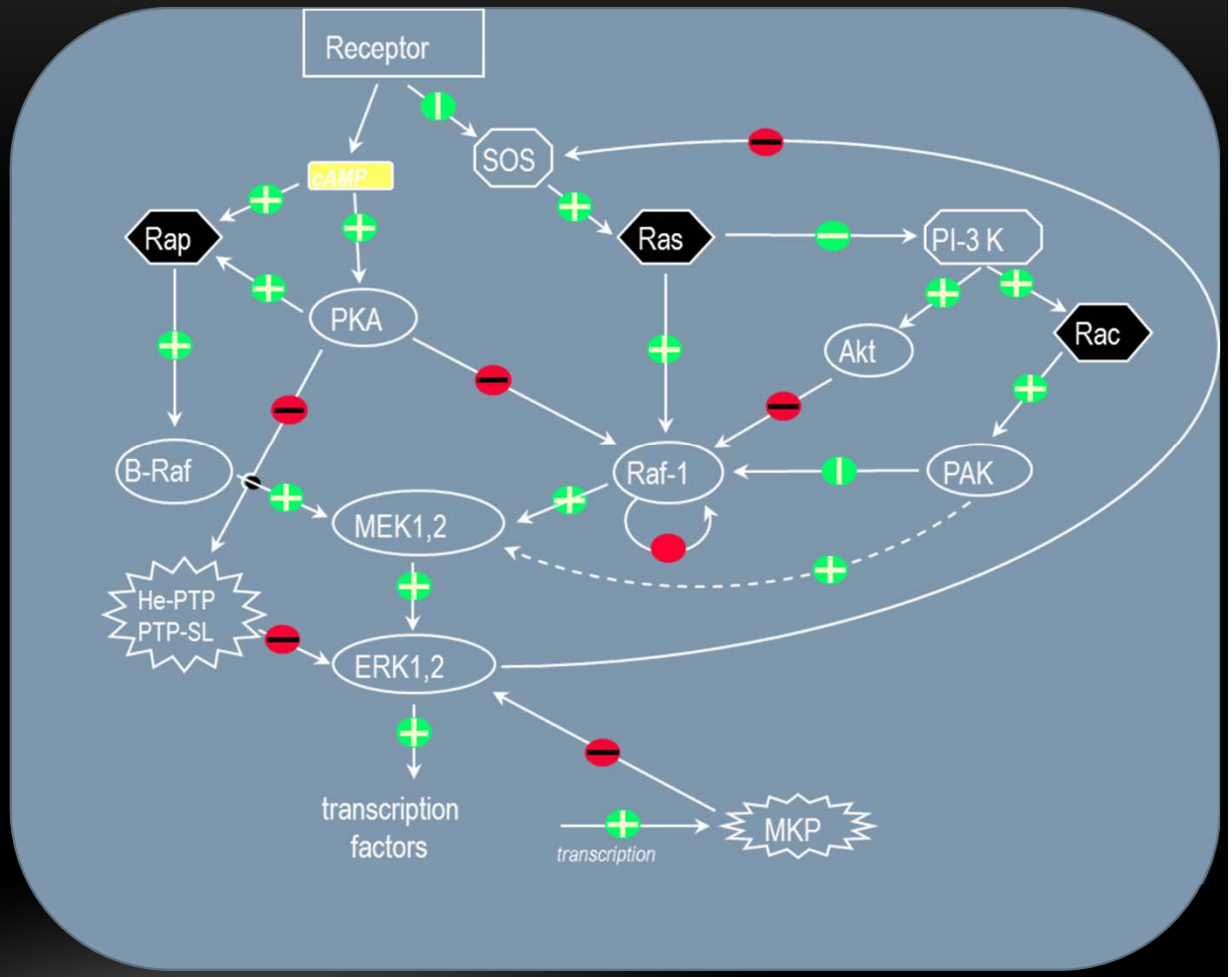
**Table 1.** List of drugs banned in India due to their side effects.

| | Generic name | Use | Reason for ban | Brand name(s) |
|---|---|---|---|---|
| 1. | Analgin | Pain-killer | Bone-marrow depression | Novalgin, Baralgan |
| 2. | Cisapride | Acidity, constipation | Irregular heart beat | Ciza, Syspride |
| 3. | Droperidol | Anti-depressant | Irregular heart beat | Droperol |
| 4. | Furazolidone | Anti-diarrhoeal | Cancer | Furoxone, Lomofen* |
| 5. | Nimesulide | Pain-killer, fever | Liver failure | Nise, Nimulid |
| 6. | Nitrofurazone | Anti-bacterial cream | Cancer | Furacin, Emfurazone |
| 7. | Phenolphthalein | Laxative | Cancer | Jetomisol-P* |
| 8. | Phenylpropanolamine | Cold & cough | Stroke | D'Cold*, Vicks Action 500* |
| 9. | Oxyphenbutazone | NSAID | Bone marrow depression | Sioril |
| 10. | Piperazine | Anti-worms | Nerve damage | Piperazine, Helmazan* |
| 11. | Quiniodochlor | Anti-diarrhoeal | Damage to sight | Enteroquinol |

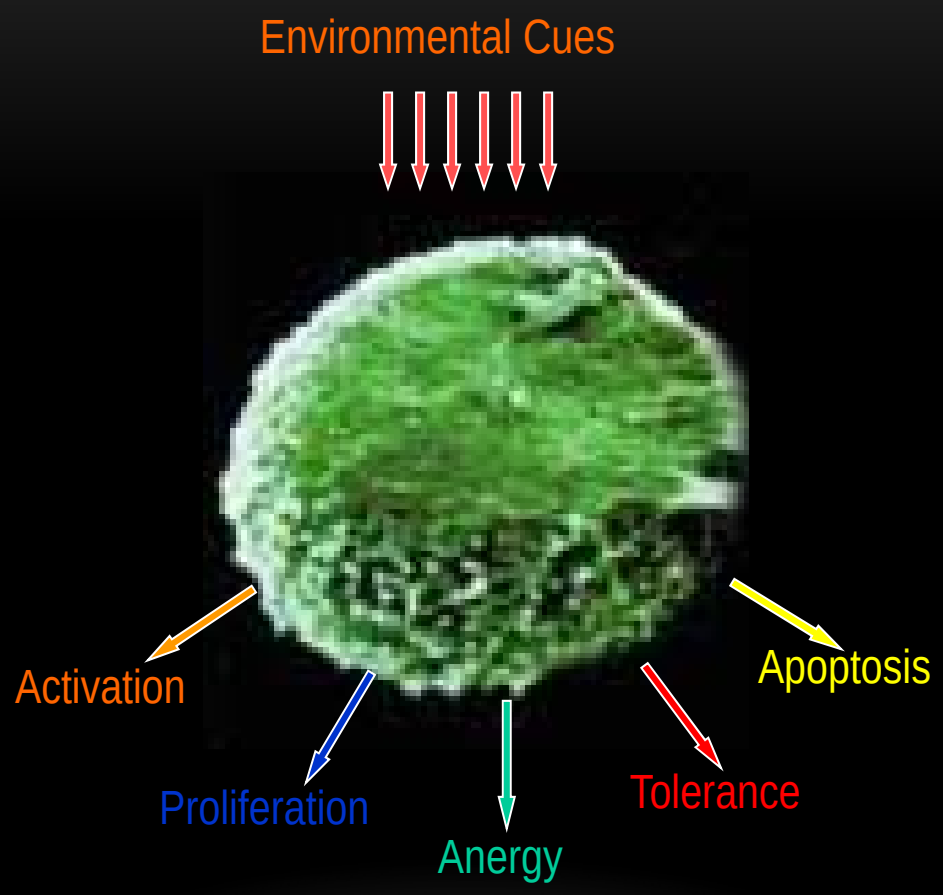
*Denotes it is a combination product.
Analgin, Furazolidone and Nitrofurazone are banned for use even in animals in the United States.
Analgin is banned in Nepal, Vietnam and Nigeria (Reference: MIMS INDIA, September, 2005).

# Reductionism: Failure to integrate the available knowledge together



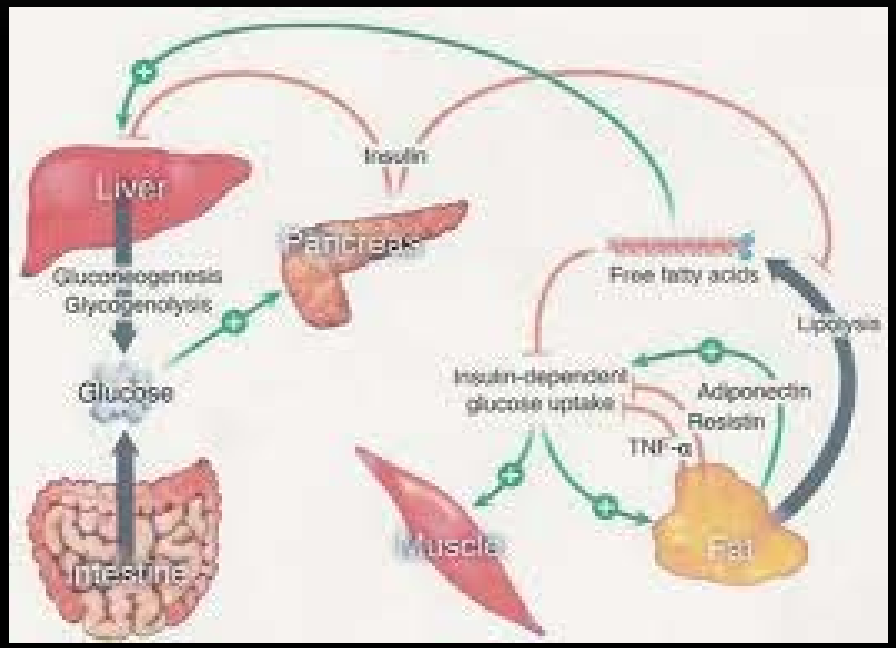



# Context

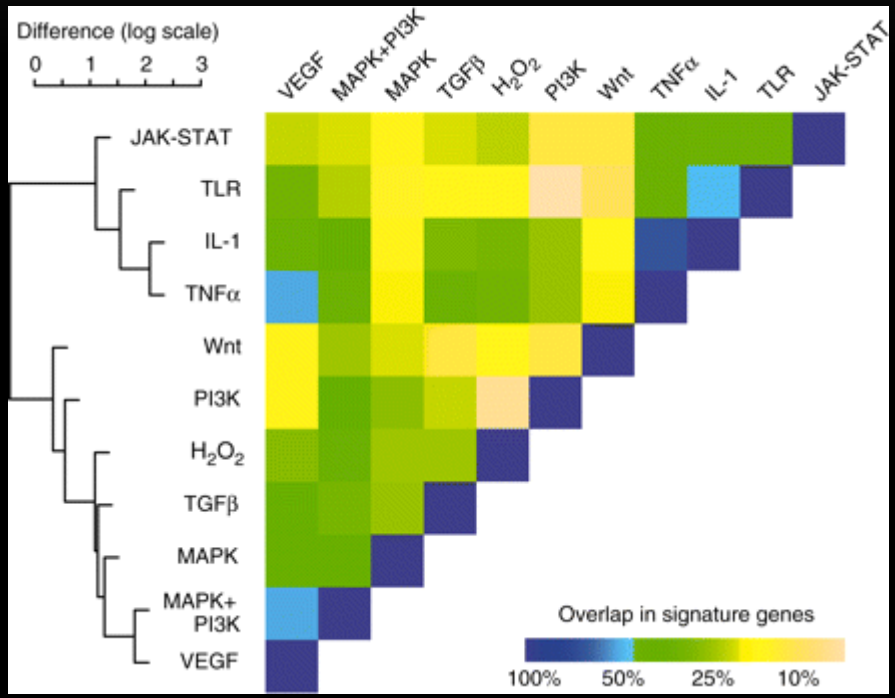

Environmental Cues
Activation
Proliferation
Anergy
Tolerance
Apoptosis

# Cross-talk

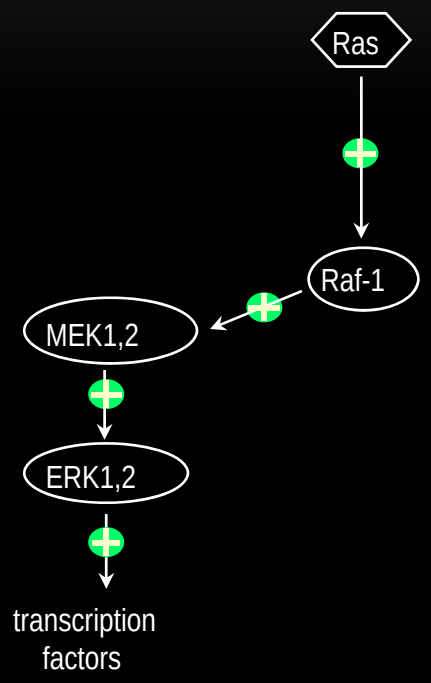
## At tissue level




## And at molecular level



# Pathway dynamics




Cell cycle

Apoptosis

Growth

Differentiation

Response to external stimuli

Movement

Stress Responses

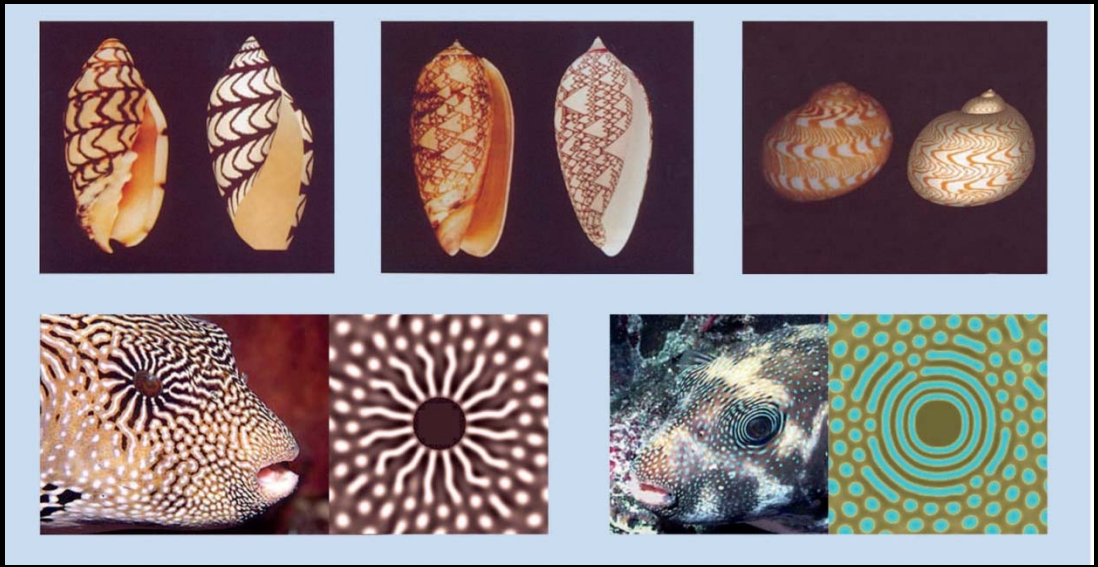
Tissue level differences in response

A radical change in our approach needed to understand biology holistically

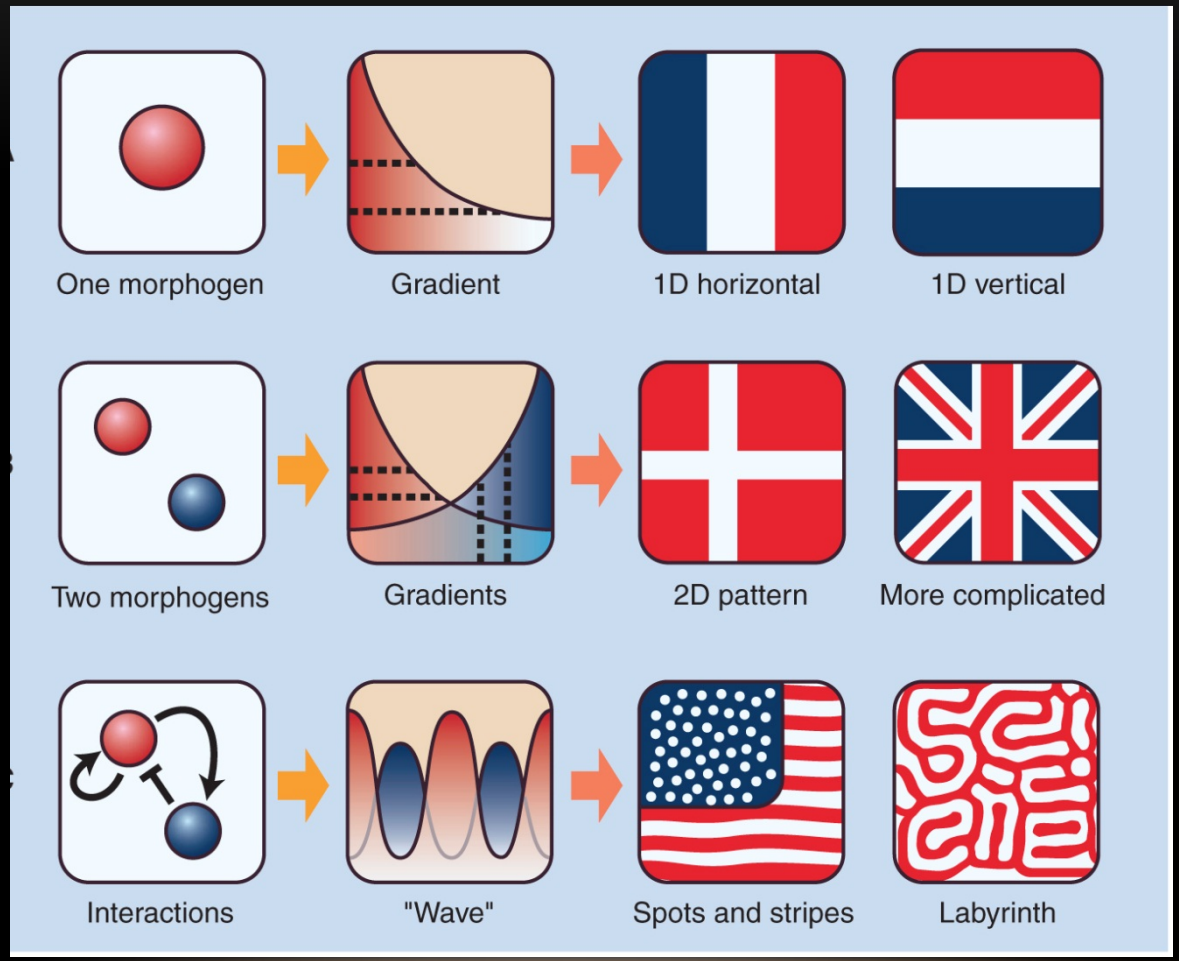
# HOW SYSTEMS BIOLOGY CAN HELP OVERCOME THE STATED OBSTACLES IN UNDERSTANDING BIOLOGY

ADVANCE CELL AND MOLECULAR BIOLOGY
(ICG601)

# Patterns in Biology

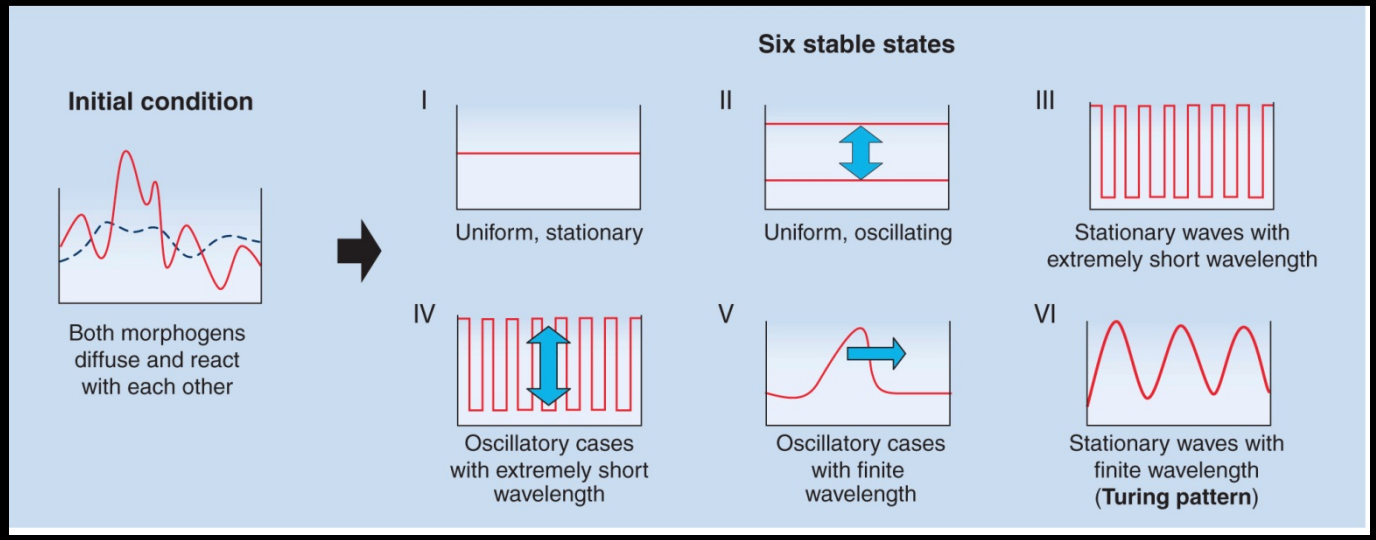


# Reaction-Diffusion (RD) model or “Turing model”

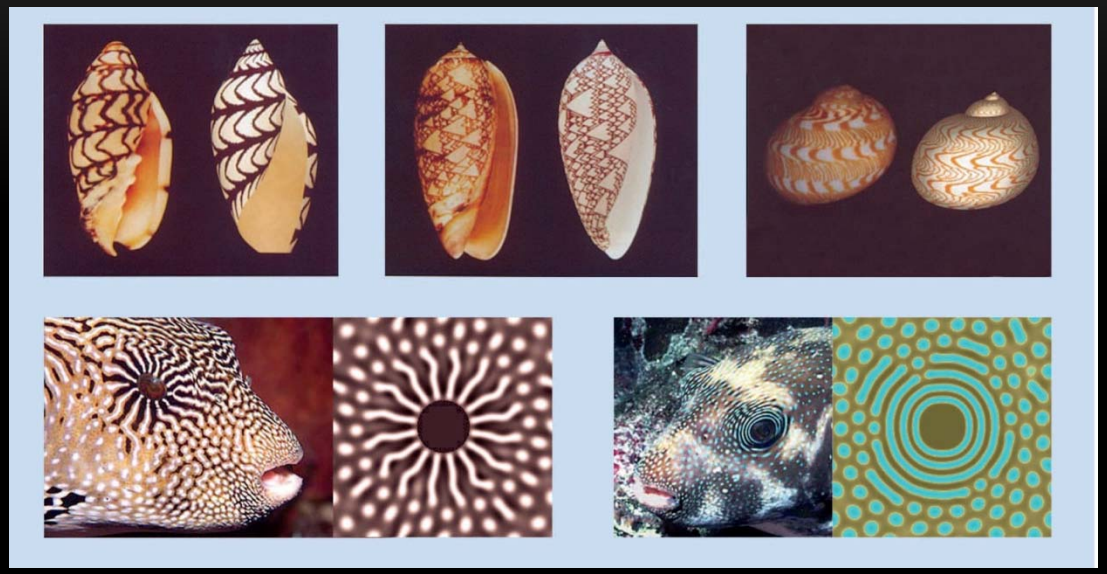



Two or more components (morphogen) with feedback interactions

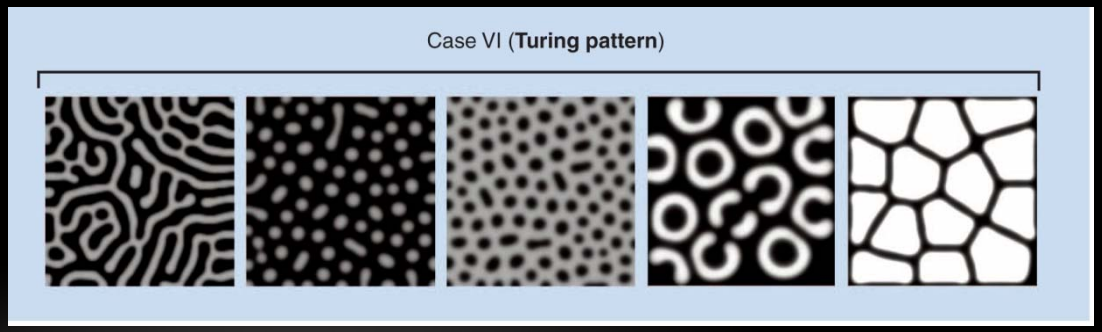
# Six possible Stable states for interactions between two morphogens



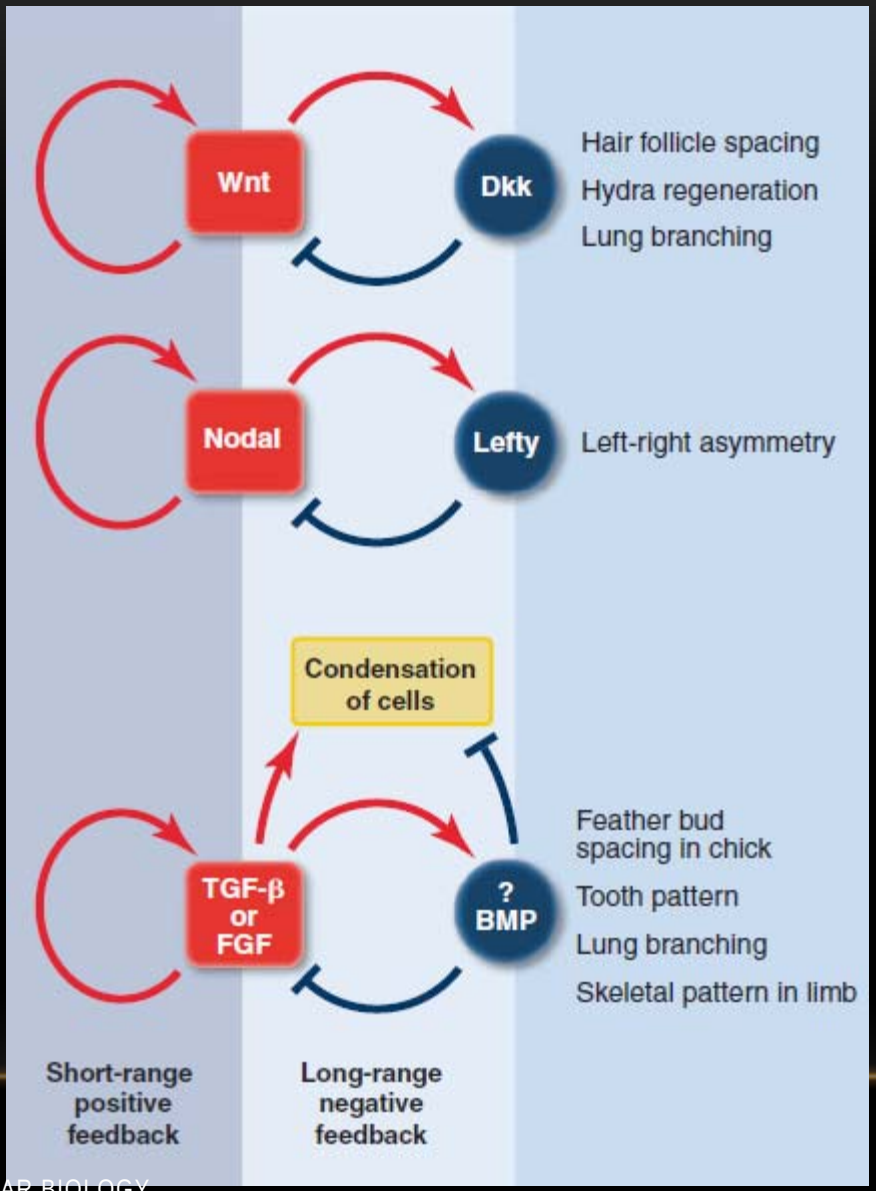
Biological Patterns



RD model simulations



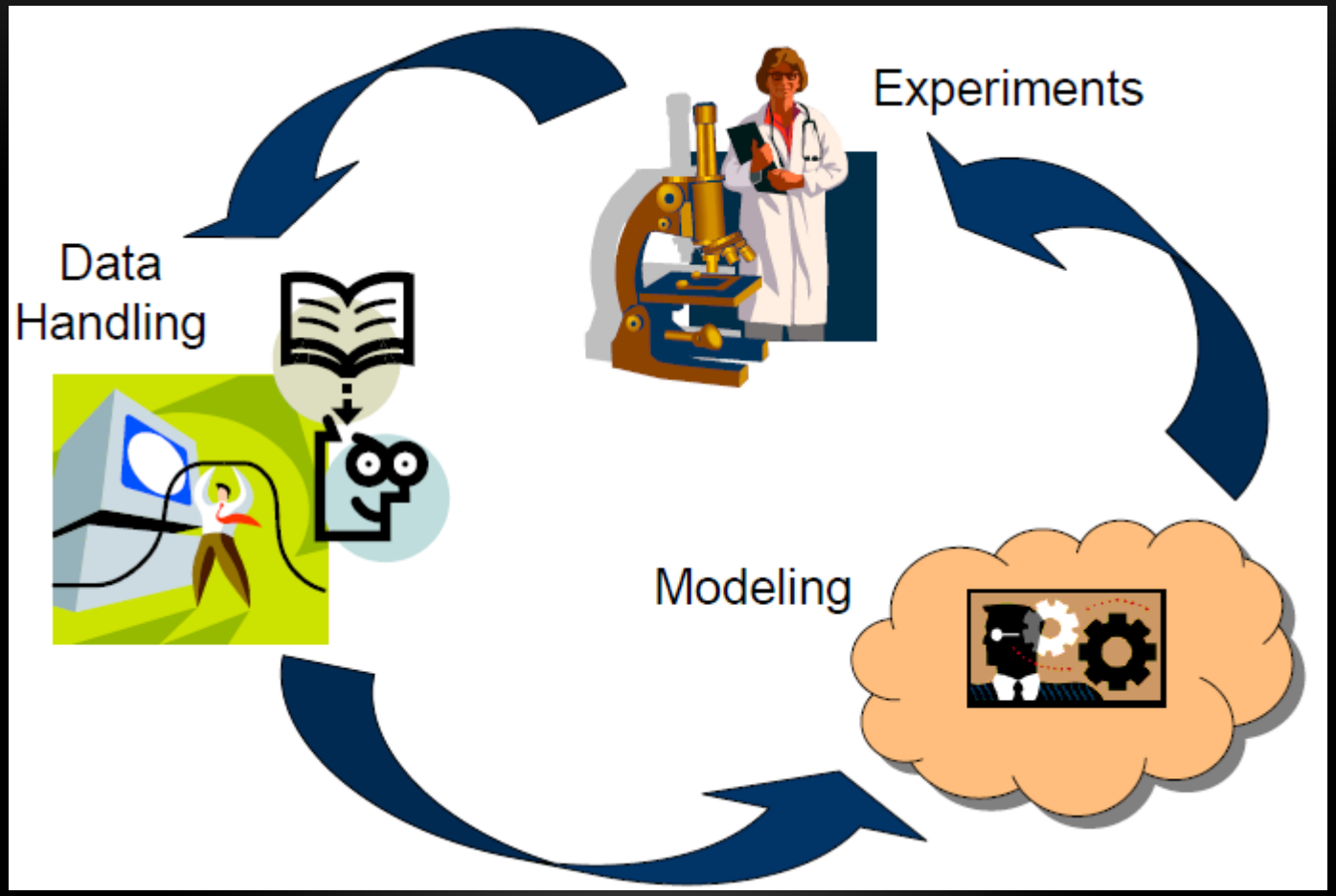
# Some Examples—experimentally verified RD model sets!!



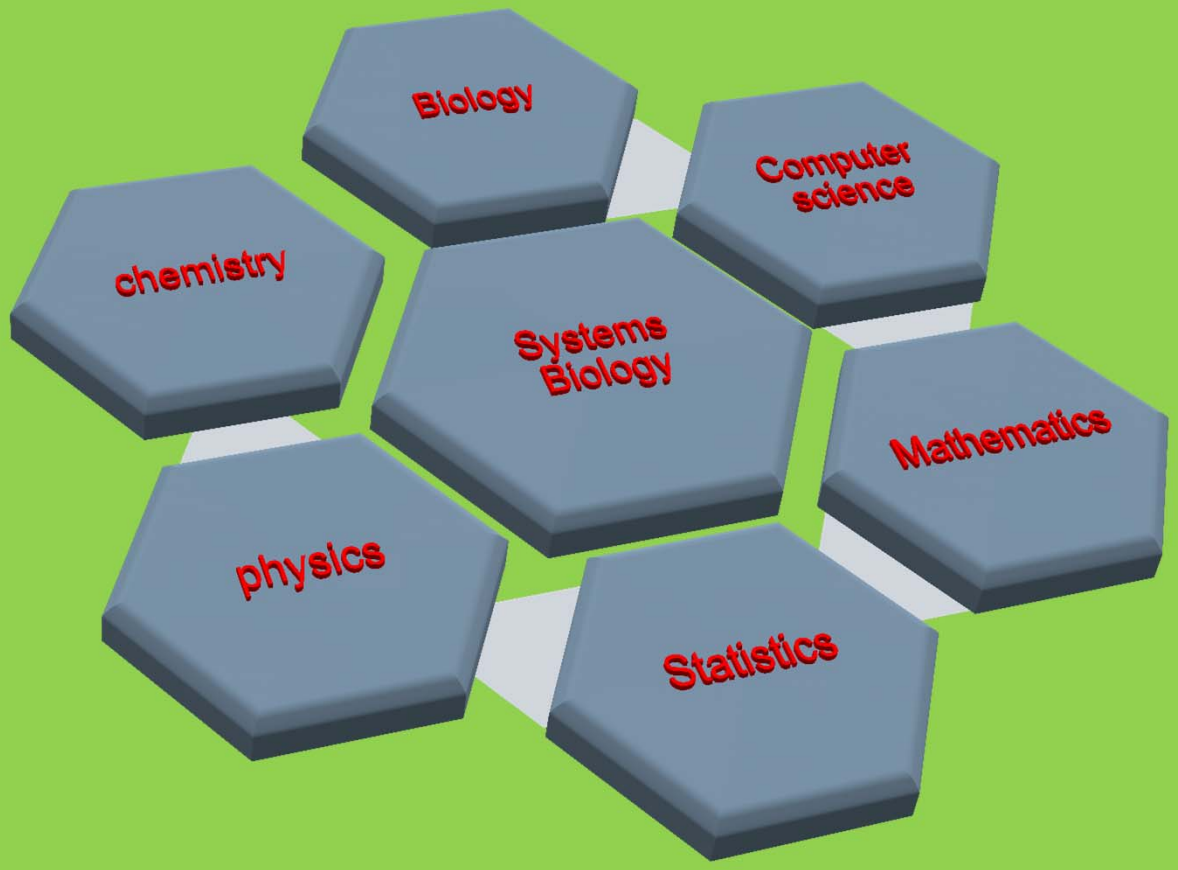
A systems biology approach means

- Investigating the components of cellular networks and their interactions
- Applying experimental high-throughput and whole-genome techniques
- Integrating computational and theoretical methods with experimental efforts

# Systems Biology discovery cycle



# Multi-disciplinary



# FOUNDATION FOR THE CURRENT DAY SYSTEMS BIOLOGY APPROACH

Improved biological knowledge with the prospect of utilization in biotechnology and health care

New experimental techniques in genomics and proteomics techniques

Classical mathematical modelling of biological processes

Computer power for simulation of complex systems

Storage and retrieval capability in large databases and data mining

Internet as the medium for the widespread availability from multiple sources of knowledge

# GOALS

Models to unveil mechanisms causing altered phenotypes and devise novel therapies and drugs

Predictive tools to design cells with desired properties cheaply and reliably

Individualized and predictive medicine

# WHAT IS A MODEL?

It depends on whom you ask?

# WHAT IS A MODEL?

Biologist: *Arabidopsis thaliana* as a model for plant biology, or mouse as a model for infectious diseases like tuberculosis

Chemist: a reaction network, described by dots (for metabolites) and arrows (for reactions)

Mathematician/Engineer: the same reaction network can be modelled by a system of nonlinear ODEs

Abstract representation of objects or processes that explains features of these objects or processes

# MATHEMATICAL MODEL

Biological processes can be described in mathematical terms

As a biological process could be studied through different experimental methods
they can also be described through different mathematical models!!

Choice of a mathematical model depends on the problem, the purpose and the intention of the investigator

Modeling has to reflect essential properties of the system, different models may highlight
Different aspects of the same instance

# DIFFERENT TYPES OF MODELS

- Mathematical model
- Computational model
- Statistical model

# REQUIREMENTS FOR MODEL DEVELOPMENT AND ANALYSIS

- Formulate the problem
- Check and collect available qualitative and quantitative knowledge
- Select model structure (level of description, deterministic or stochastic, discrete or continuous, static dynamic or spatio-temporal
- Robustness and sensitivity analysis

# FOUNDATION FOR THE CURRENT DAY SYSTEMS BIOLOGY APPROACH

Improved biological knowledge with the prospect of utilization in biotechnology and health care

New experimental techniques in genomics and proteomics techniques

Classical mathematical modelling of biological processes

Computer power for simulation of complex systems

Storage and retrieval capability in large databases and data mining

Internet as the medium for the widespread availability from multiple sources of knowledge

# NEW EXPERIMENTAL TECHNIQUES

*'Omics'*

Genomics

Transcriptomics

Proteomics

Lipidomics

Metabolomics

Experimental techniques that allow to capture the process in question in totality

# NEW EXPERIMENTAL TECHNIQUES

## Molecular Studies

- Sequencing: Genotyping, genetic associations, SNPs, evolutionary studies
- Microarray (deep sequencing): Gene expression, non-coding RNAs
- 2D gels and Mass spectrometry: Proteins, Lipids, small metabolites
- Chip-seq: DNA-protein interactions (transcriptional regulation)

## Physiological (at tissue, cell, organelle or molecular level)

- Time lapse (Live-cell) Imaging
- Tissue imaging (multi-photon)
- *In vivo* IR imaging (and other Imaging techniques like PET and PET-CT scan)
- EM-Tomography (3-D reconstruction): Very High resolution

## Perturbation studies (Phenotype)

- Genome-wide siRNA screens
- High-content screening techniques (drugs and small molecular inhibitors)

# LARGE SCALE DATA ANALYSIS AND INTEGRATION

Mammalian Genome size: $10^9$-$10^{10}$ base pairs

Sequencing

Transcriptome

Proteome

Bio-Informatics