

De las redes intracelulares a las simulaciones de sistemas multicelulares



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Apoyan:



Programa

Día 1

- Introducción a la Biología de Sistemas
- Anotación genómica y reconstrucción de redes moleculares
- Fundamentos de teoría de grafos y redes complejas

Día 2

- Redes de información
- Redes de señalización y regulación
- Modelos Booleanos

Día 3

- Redes de flujos
- Redes metabólicas
- Modelado Basado en Restricciones

Día 4

- Seminario IPMon (9h30 - 10h30)
- Modelado Basado en Agentes
- Simulaciones multi-escala I

Día 5

- Simulaciones multi-escala II
- Biología de sistemas multicelular
- Discusión de proyectos

Evaluación

- Presentación de ejercicios de clase **30%**
- Propuesta de proyecto de investigación: **70%:**
 - **Estructura de la propuesta:**
 - i. **Título y resumen**
 - ii. **Introducción** (estado del arte y planteo del problema a abordar y su relevancia)
 - iii. **Objetivos** que se pretenden alcanzar
 - iv. **Metodología** que se plantea emplear
 - v. **Resultados** esperados
 - vi. **Bibliografía**
 - **Extensión** 4-5 páginas
 - **Criterios de evaluación:**
 - i. **Completitud** (estructura completa, con revisión bibliográfica)
 - ii. **Originalidad** (novedad que aporta el proyecto en un campo o a nivel metodológico)
 - iii. **Viabilidad** (que sea un proyecto que serían capaces de realizar con pocos recursos)

Tema 1

Anotación genómica y reconstrucción de redes moleculares

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Historical context: Biochemistry

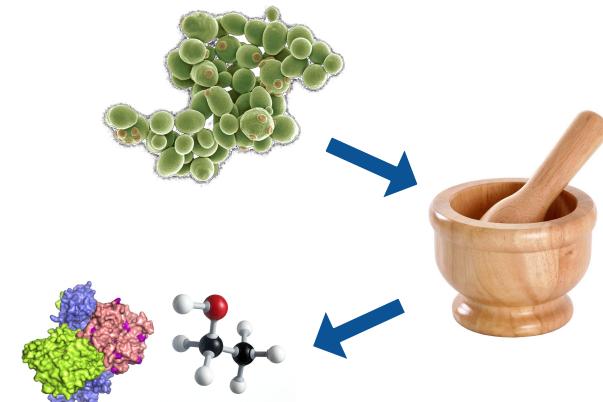


The birth of the Reductionist Approach

Discovery of cell-free fermentation by Eduard Buchner (1897)
(i.e. to transform sugars into ethanol, cells are not needed)

Reductionist method in a nutshell

1. Smash the system into its small constituents
2. Isolate single components
3. Characterize properties of single components



- Extremely useful to characterize molecular components (parts catalog of a cell)
- Current knowledge derived from reductionist approach... However...

Historical context: Molecular Biology

- Isolate **single components** (part catalog)
 - e.g. Proteins, DNA, RNA, small molecules
 - Properties of biochemical components (e.g. structure)
- Principle of **information flow** (central dogma)



- **Simple interactions**
 - Protein + Small molecule (Enzymes)
 - DNA + Protein (operon)
 - Protein-Protein (dimers or complexes)

Historical context: Molecular Biology

Elucidation of mechanisms



Diagram

$$\frac{d[\text{P}]}{dt} = V_{max} \frac{[\text{S}]}{K_M + [\text{S}]}$$

Mathematical model



“... The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry... ”

Francis Crick (1966)

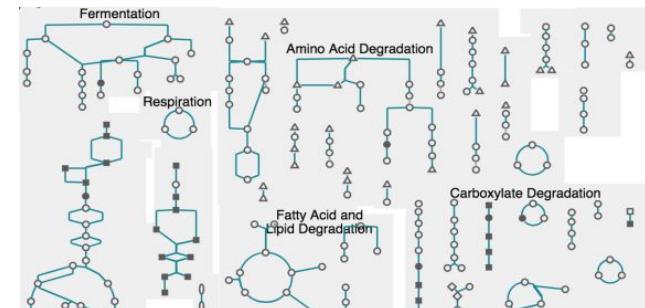
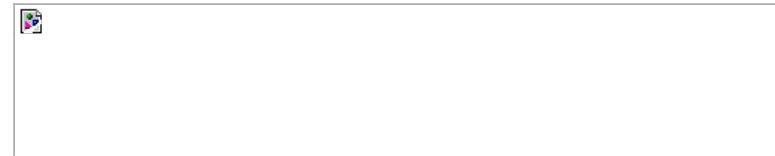
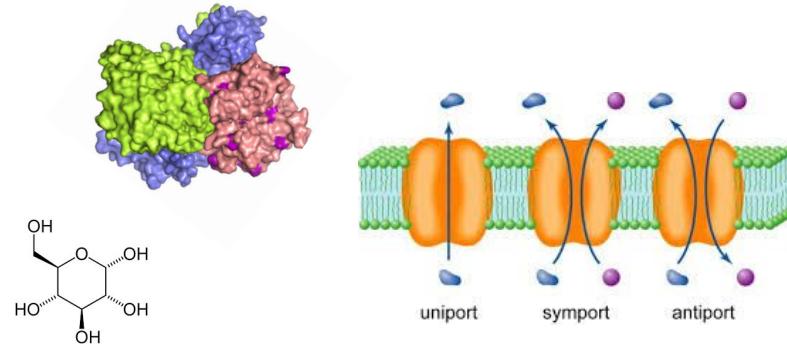


Reductionist view

Historical context: The “omics” revolution

Part catalog of cellular components

- Polypeptides → **12,826**
- Proteins → **21,702**
- Enzymes Subunits → **15,916**
- Enzymes Complexes → **13,911**
- Reactions → **19,815**
- Compounds → **18,786**
- Metabolic Pathways → **3,468**



Historical context: The “omics” revolution

(High-throughput characterization of biological components and interactions)

- . Genome sequencing → **Genome**
- . Transcript (mRNA) level characterization → **Transcriptome**
- . Characteristics of protein repertory → **Proteome**
- . Cellular localization of components → **Localizome**
- . Gene regulatory networks → **Regulome**
- . Protein interaction network → **Interactome**
- . Massive gene-phenotype studies → **Phenome**
- . Small molecules quantification → **Metabolome**
- . . .

BIOINFORMATICS

What lies beyond bioinformatics?

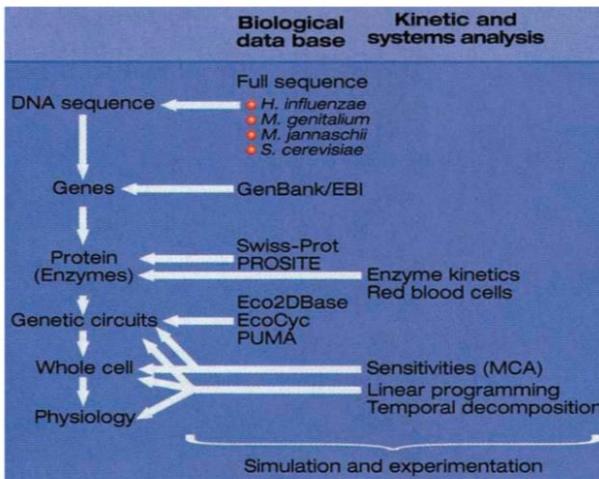
Bernhard O. Palsson

Vast amounts of basic genetic and biochemical information are rapidly becoming available. Sequencing technology is providing us with complete information about the genetic makeup of simple cells, and more complex organisms will soon follow. Commensurately, there are now well over 100 biological databases available on the World Wide Web that contain information about the genetic makeup and biochemical characteristics of a variety of cells and cellular processes^{1,2}. Links between individual databases^{3,4} are resulting in essentially complete genetic and metabolic information about such specific bacterial cells as *Escherichia coli* and *Haemophilus influenzae*. Simultaneously, genetic and regulatory similarities between such popular model organisms in developmental biology as yeast, worms, flies, and mice are being unraveled⁵. And thus enters the field of bioinformatics.

With all this information about the underlying molecular

biology will emerge. As with other applied fields of science, the dictum "nothing is more practical than a good theory" will eventually apply to cell and molecular biology. Making a statement such as this seriously was unthinkable only a few years ago.

How is this process likely to unfold? Initially, one would expect that analysis of the

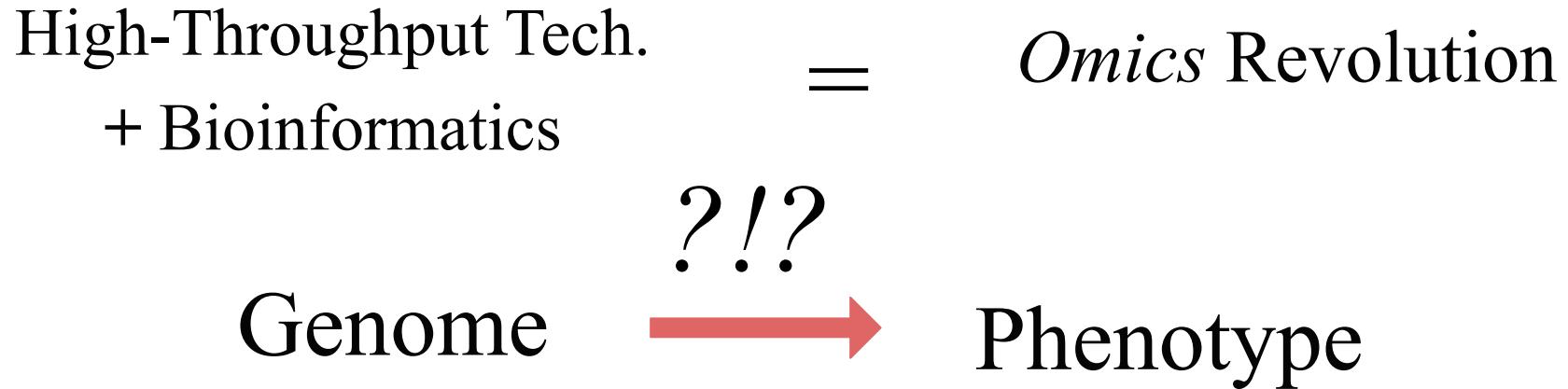


complete genome sequences grows, many more such studies will appear, deepening our understanding of basic biological processes. The base pair sequence in the human genome amounts to about one gigabyte of information, equivalent to the amount of information that many of the readers of this article store on their personal computers. We can anticipate that the use of model organisms will lead to functional assignment of most of the 70,000–100,000 human genes, and reduce their roles into much fewer multicomponent cellular functions.

How will the reduction of gene number to much fewer cellular and physiological functions take place? The relationship between genetics and physiology has many layers, as illustrated in Figure 1. Gene sequences allow the identification of open reading frames (ORFs). The base pair sequence of the ORFs in turn allows for the functional assignment of the defined gene. Although not always unambiguous, such assignments are being carried out with increasing accuracy. Sequence is

Historical context: The “omics” revolution

- **Pre-genomic era:** biological knowledge evident in the data (e.g. gel)
no post-processing/analysis required.
- **Genomic era:** massive generation of biological data
- **Post-genomic era:** data analysis and interpretation



Is the reductionist approach enough in practice?

- Failures in in-vitro and in-silico approaches
- Failures in experimental techniques of reductionist base (gene knockout,)
- *Knockout:* no effect, different effect, unspecific effect (change expression of 100's genes)

“... Some mice should, by rights, be dead. At the very least, Teyumuras Kurzchalia expected his to be critically ill. But the most prominent symptom of his genetically engineered mice was a persistent erection ...”

Pearson, H. (2002) Surviving a knockout blow. *Nature*, **415**, 8-9.

“An increasing number of scientists argue that the **reductionist approach can no longer cope with both the enormous amount of information that comes from the so-called ‘-omics’ sciences and technologies—genomics, proteomics, metabolomics and so on—and the astonishing complexity that they reveal.”**

Is the reductionist approach enough in practice?

In Biomedicine...

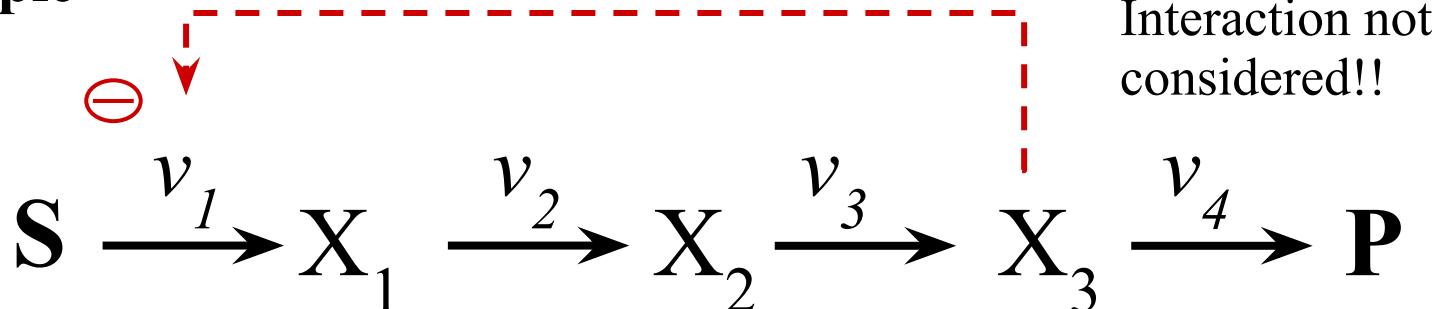
- Failure in Cancer treatment, ... in part due to the extreme reductionist approach to that complex disease. Dual drug therapies and activation of alternative resistance routes
- Reducing number of drugs in market in spite of increasing investment. (1 drug ↔ 1 target ↔ 1 disease).
- Difficulties in progression of promising therapeutic approaches of highly-reductionist base (gene therapy, single target, ...)
- No expected improvement in those approximations with the increasing number of sequenced genomes, etc.

Is the reductionist approach enough in practice?

- **Reductionism tremendously successful in Biology** → Determination of “repertories of components” and their characteristics
- Neither the number nor the characteristics of genes and proteins account for many characteristics of living beings:
 - Similar number of genes in *Drosophila* and *C. elegans*;
 - More genes in some plants than in human...
 - Virtually identical genes in human and mouse.
 - Sea urchin genome: same number of light and odor receptor than vertebrates (~1000); proteins whose orthologs in human are in the ear; ...
- Biological systems are **adaptive complex systems** → most biological phenomena could never be understood via the properties of the individual components (**“the whole is more than the sum of the parts”**)

Why reductionism is not enough?

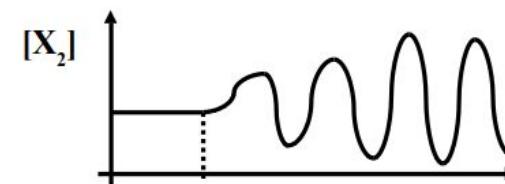
Example



We apply reductionist method...

Comp.	Param.
v_1	$E_1 \ K_M \ V_{max}$
v_2	...
v_3	
v_4	

Increase the $[E_1]$
 What happens with $[X_2]$???



Properties of complex adaptive systems

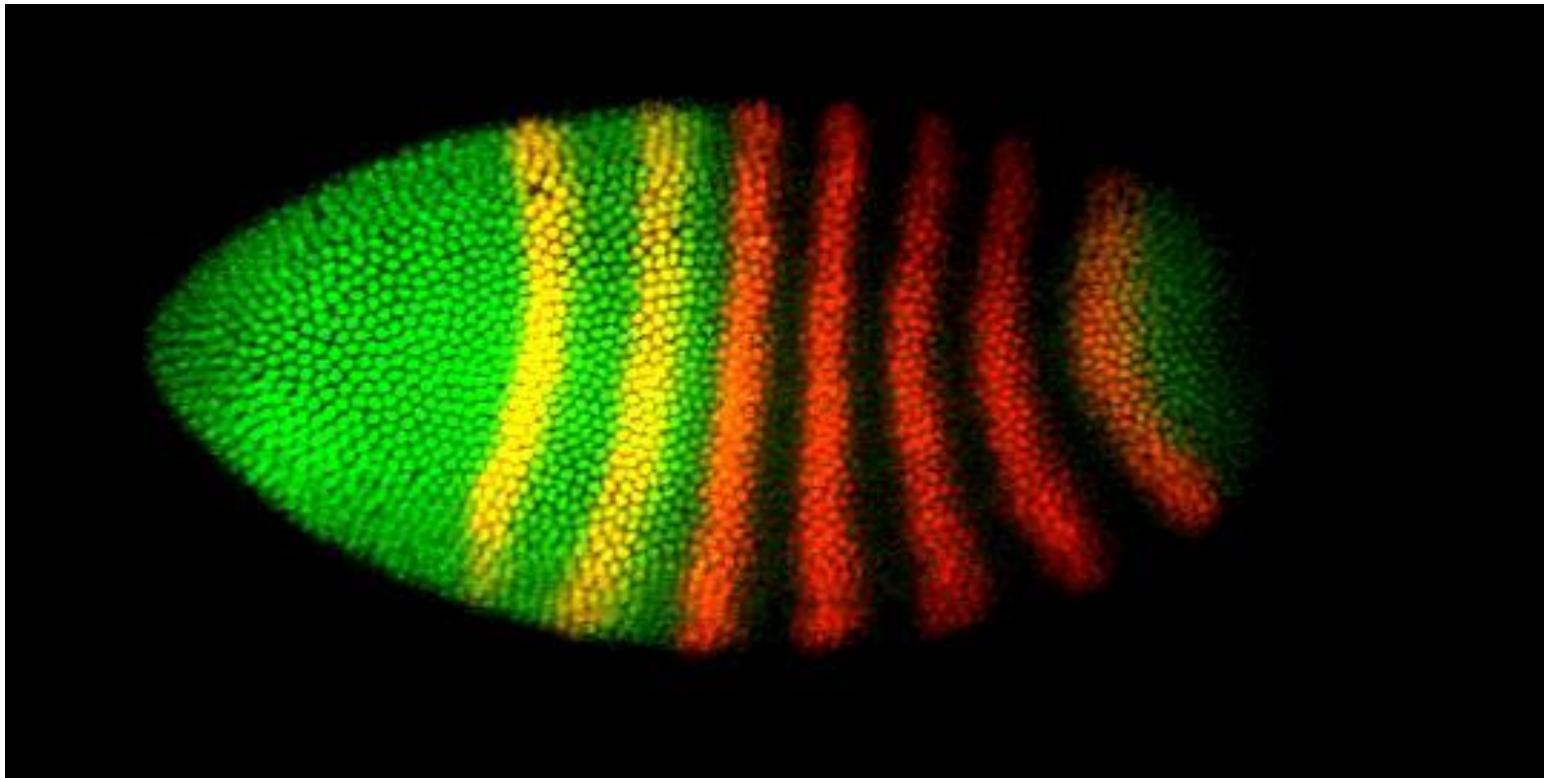
Resultant Properties

- Is either a sum or a difference of the co-operant forces.
- Are homogeneous and commensurable.
- Can be predicted from lower-level information.
- Examples: the mass, the charge, pH, individual rates, etc.

Emergent Properties

- Arise from the interactions of components.
- Not reducible to the properties of single components.
- The system is more than the sum of its parts
- Examples: Oscillations, Chaos, Self-similarity, Robustness, Evolvability

Emergence in biological systems



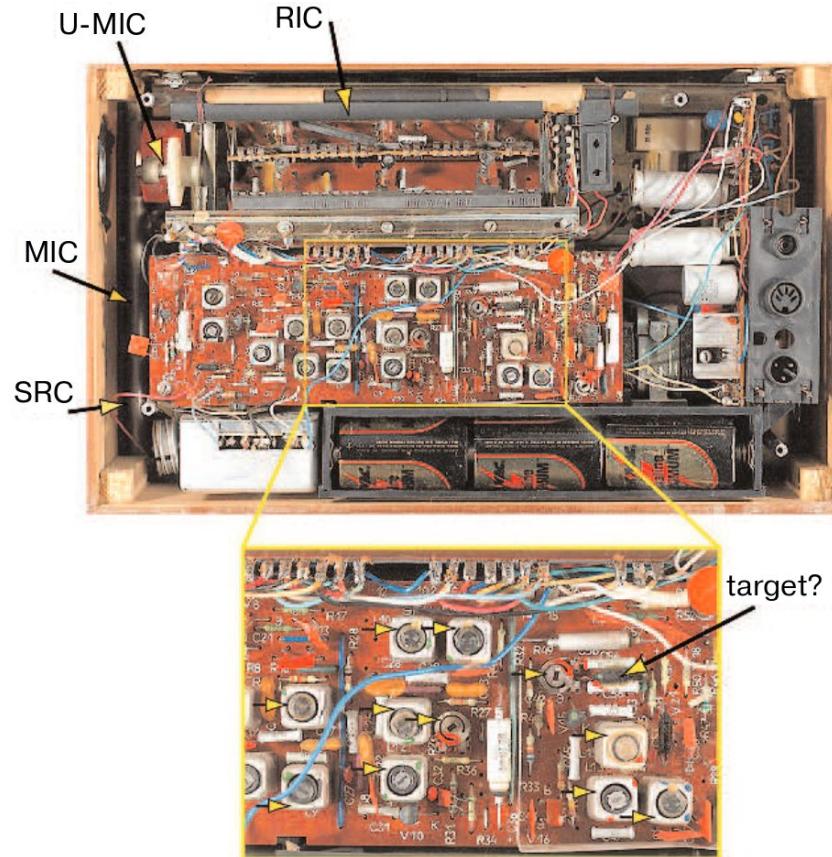
Emergence in biological systems



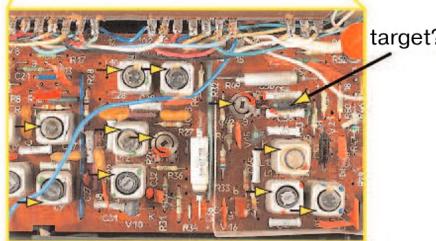
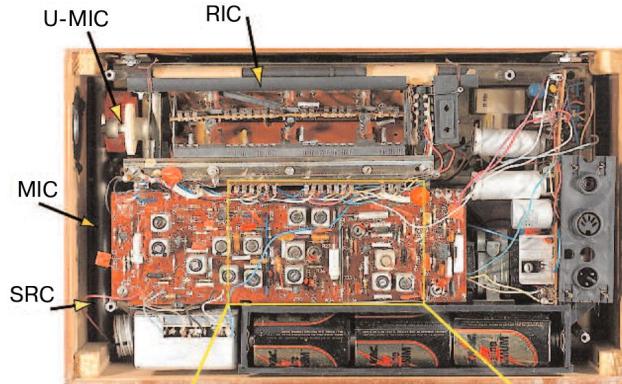
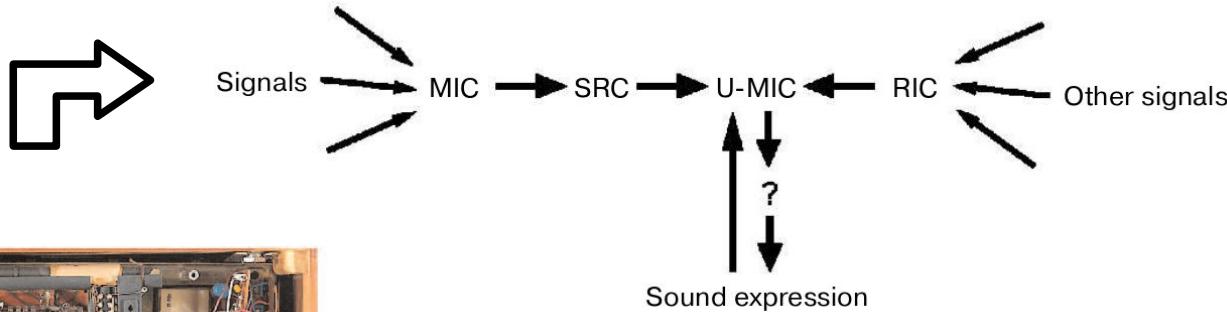
Can a biologist fix a radio?



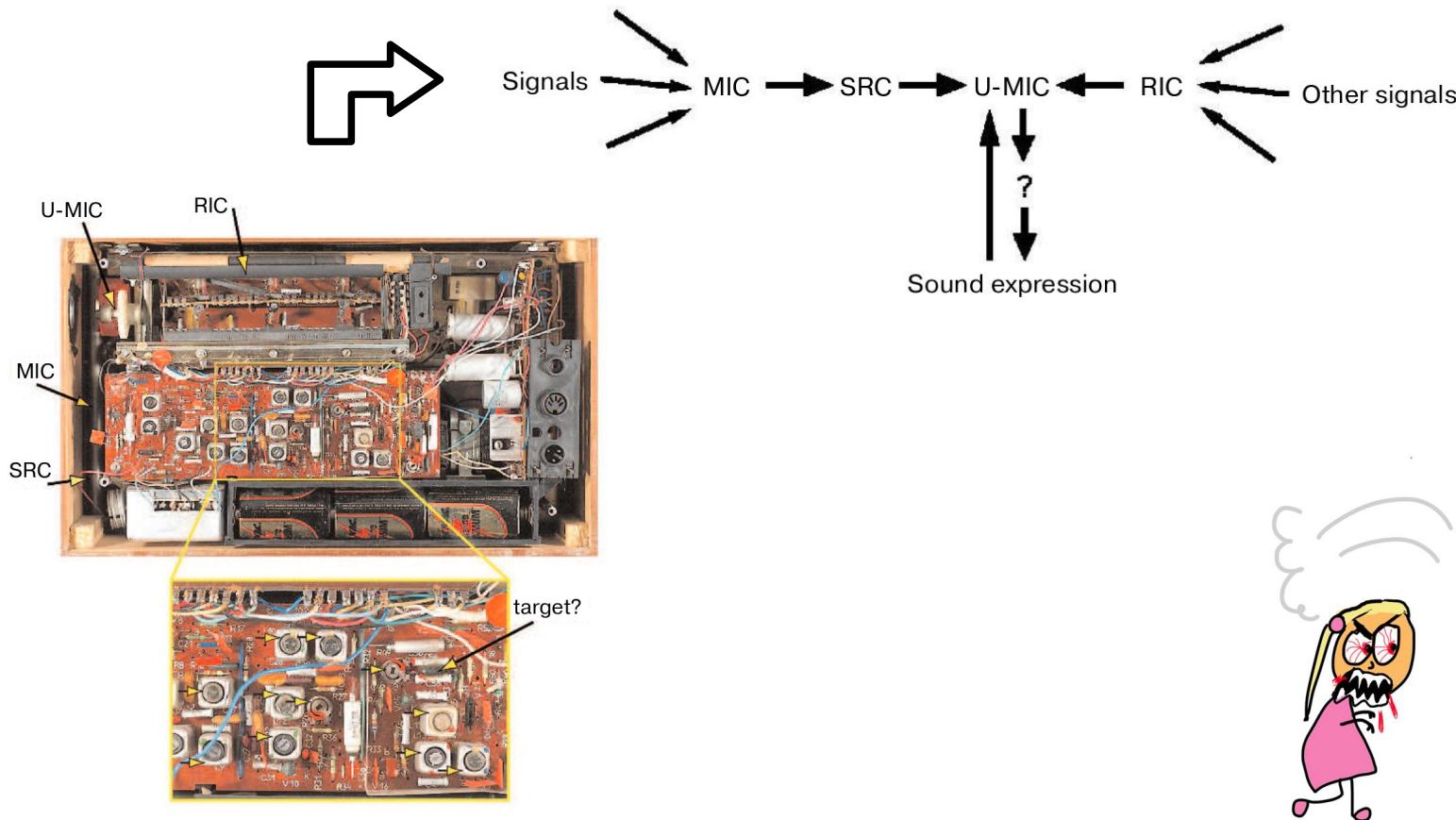
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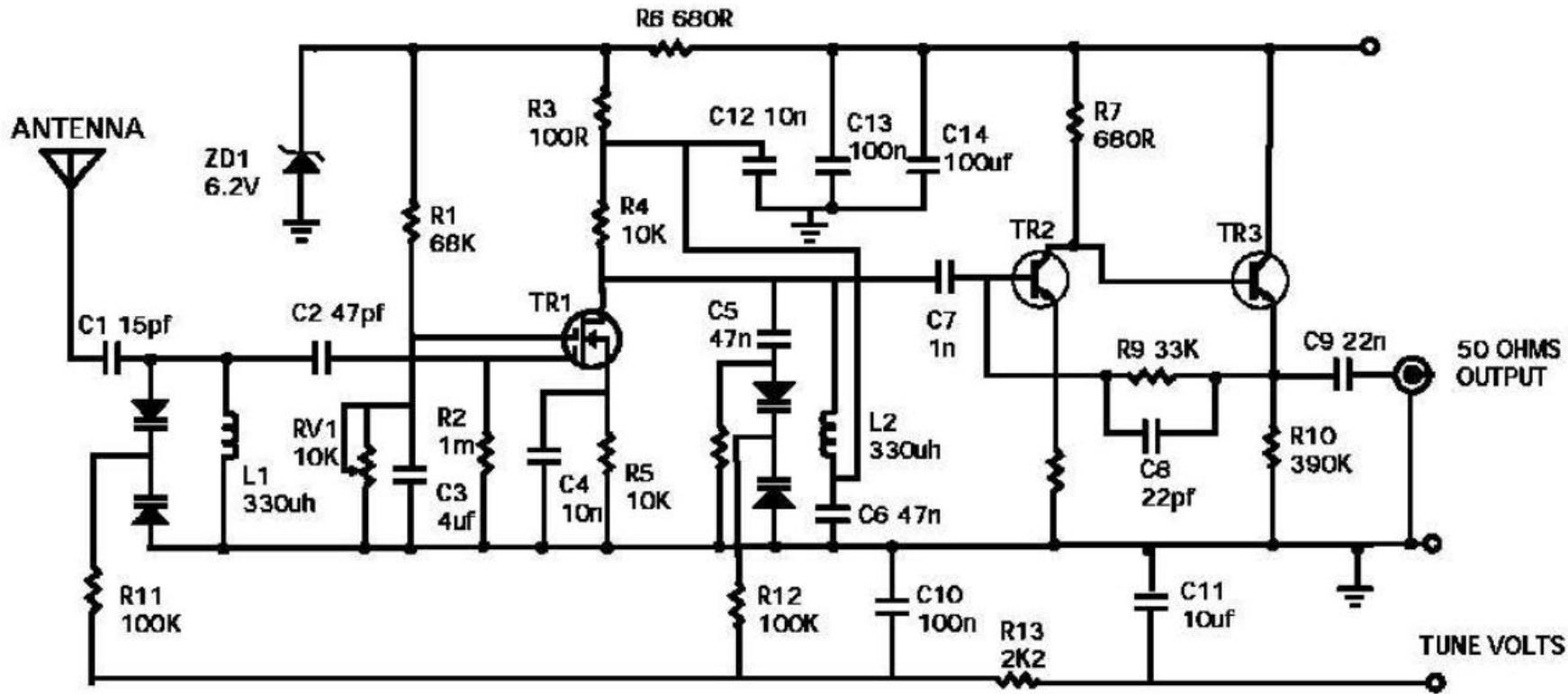
Can a biologist fix a radio?



Can a biologist fix a radio?



Can a biologist fix a radio?



Systems Biology: a brief overview

- . Mathematical models and computer simulation
- . Own vocabulary and concepts
- . Consider interactions → Network view!!!
- . Integration into a systemic view
 - Dynamical systems theory
 - Control theory
 - Complex networks theory



Systems Biology

Systems Biology: a brief overview

One (of many) definition:

Coordinated study of biological systems by:

- 1) Investigating cellular components
- 2) High-throughput techniques
- 3) Integrating data into mathematical and computational models

Paradigm shift:

Reductionism → Systemic view (holism)

From part catalogs → Diagrams and models (predictive)

Considerations

Systemic approach to biology is not new

Gain recent attention → Computers + Data (lots of)

Systems Biology: a brief overview

- **Complex adaptive systems** → complex behavior
- What do we mean by complex behavior?
 - Not intuitive
 - Can not be explained with elementary principle
 - Hard to predict!

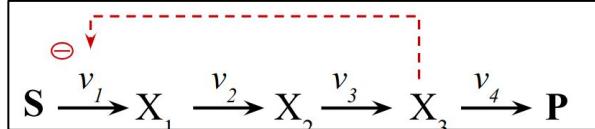
Mathematical Models & Computer Simulation

- **What is a model?**
 - It depends... (different community → different answer)
 - However...

What is a Model?

“... A model is an abstract representation of objects or processes that capture features of these objects or processes ...”

Examples:

- A String of letters **A , C , G , T** is a model of DNA
 - **ACTCTTCGAGCCGTGC**
- A chart or diagram can be model o metabolism
 - 
- In experimental biology an organism can be a model
- A set of differential equation; a computer simulation ...

What is a Model?

- **Process** → Different ways to describe (approach)
- Depends on the **Question**
 - Different experimental methods
 - Different mathematical/computational models
- Examples of different kind of **Models**:
 - Glycolytic oscillations (ODE)
 - Regulatory networks (Boolean models)
 - Gene expression (Stochastic models)

A model has to reflect or capture the essential properties of the system of interest

Properties of Models

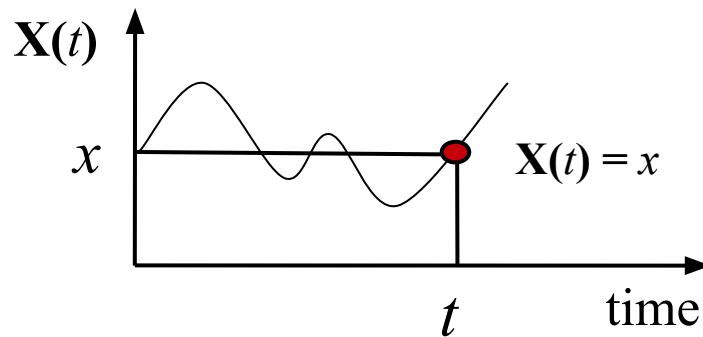
- **Constant:** is a fixed quantity (e.g. Π , e , N_A)
- **Parameter:** assigned value (K_M , V_{max}) controlled during the experiment (pH, T, etc)
- **Variables:** are quantities that can change; described systems behavior; have a domain, etc.

Some quantities can be variables or parameters depending on context

[Enzyme] { A parameter (fix the concentration)
Variable (if synth./degr. are considered)

Properties of Models: system state

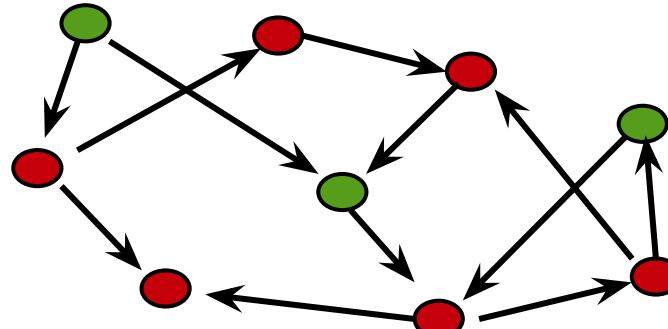
- Notion from Dynamical Systems Theory
- Defined in terms of **system variables**
- “Picture” at a given time
- Can be represent in different ways
- For example as a dynamical system:



$\left. \begin{array}{l} \textbf{X:} \text{ is some } \mathbf{\text{system variable}} \text{ such} \\ \text{as the concentration of relevant} \\ \text{component} \\ \\ \textbf{X}(t):} \text{ is the } \mathbf{\text{system state}} \text{ at a any} \\ \text{given time } t \end{array} \right\}$

Properties of Models: system state

- Notion from Dynamical Systems Theory
- Defined in terms of **system variables**
- “Picture” at a given time
- Can be represent in different ways
- For example a **Boolean Network**:

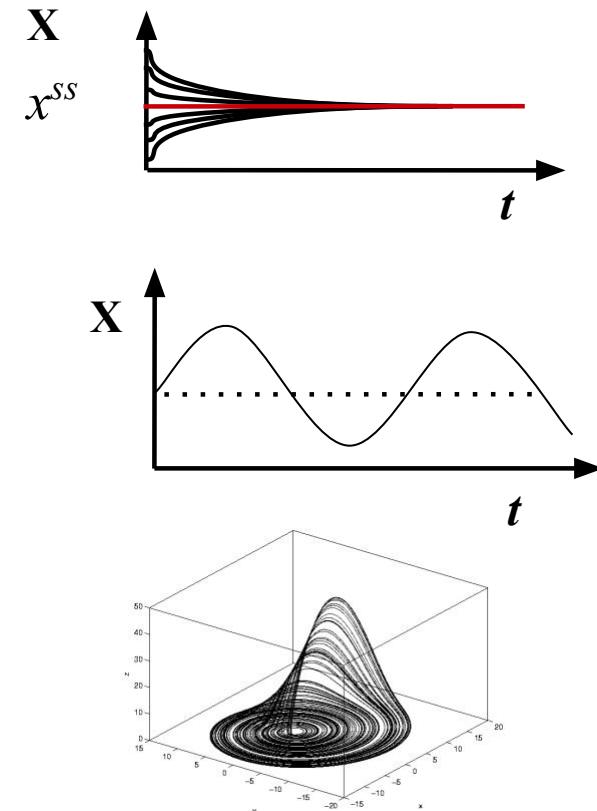


● : is an active gene (1)
● : is an inactive gene (0)

The **system state $X(t)$** is a vector $\{0,1\}^n$ which represent the state of each gene (on/off) at any given time

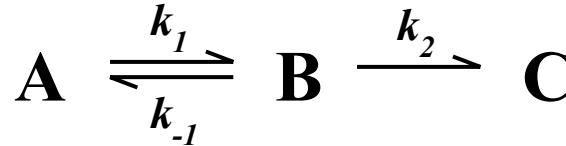
Properties of models: system dynamics

- **Steady-state** → dynamic concept
 - Fixed point (variables do not change)
 - Structural stability
- **Oscillations** → cyclic behavior
 - Period (variables oscillate)
- **Complex behavior** → Chaos
 - Complex attractors
 - Sensitivity to initial conditions
 - Unpredictability (butterfly effect)



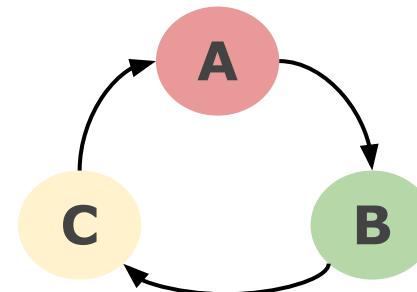
Properties of models: Process classification

- **Reversible / Irreversible** → Thermodynamics



- **Periodicity**

- Circadian clocks



Deterministic

System state at any time used to predict any future/past state

Stochastic

Probability distribution of system state at any time

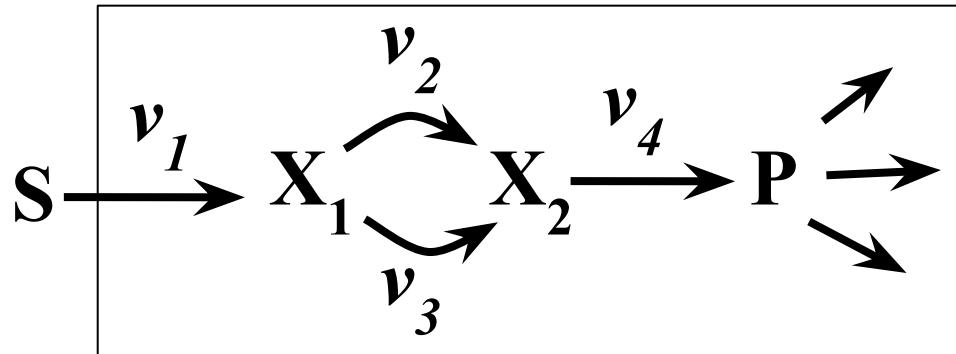
Properties of Models: behavior

Structure: relation between variables and parameters

Dynamic: time-evolution of systems variable

Causes:

- *External*: influences from the environment (input)
- *Internal*: processes within the system, noise, etc.



$$\begin{bmatrix} 1 & -1 & -1 & 0 \\ 0 & 1 & 1 & -1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix} = \begin{bmatrix} d[A] \\ \frac{d[B]}{dt} \end{bmatrix}$$

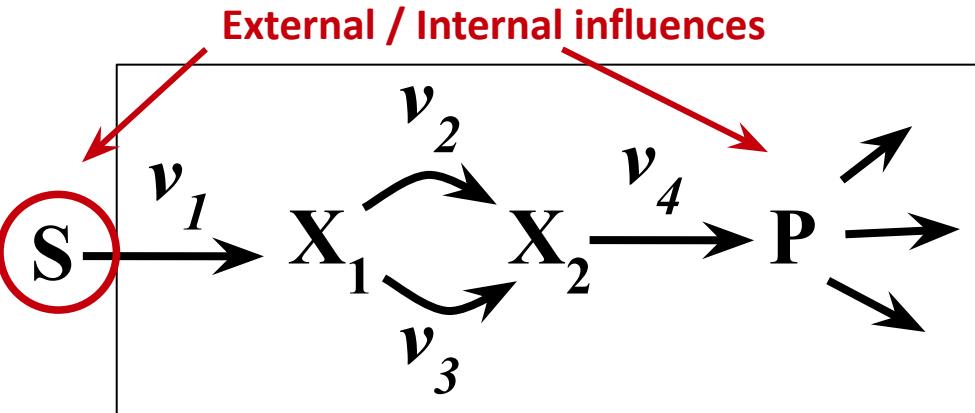
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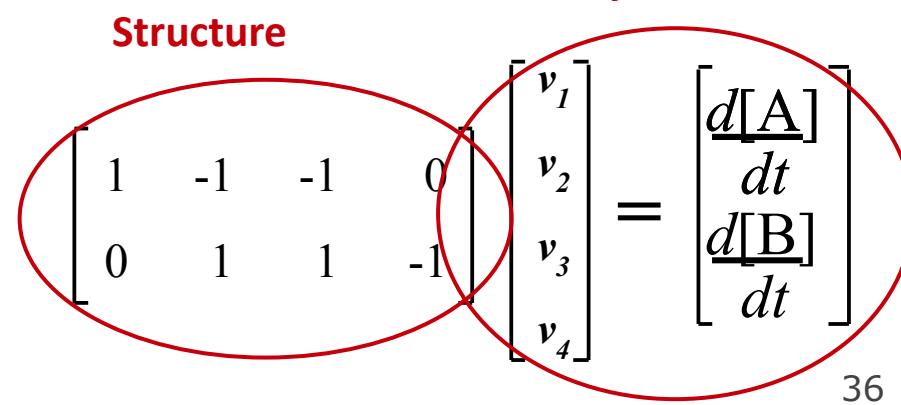
Causes:

- *External*: influences from the environment (input)
- *Internal*: processes within the system, noise, etc.



Structure

Dynamic



The structure of the system is represented by a matrix equation:

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix} = \begin{bmatrix} d[A] \\ dt \\ d[B] \\ dt \end{bmatrix}$$

The matrix A is defined as:

$$A = \begin{bmatrix} 1 & -1 & -1 & 0 \\ 0 & 1 & 1 & -1 \end{bmatrix}$$

Levels of description of a system

- **Structure**
 - Components + interactions
- **Dynamics**
 - Steady states, Bi-stability
 - Oscillations, Chaos, etc
- **Control (regulation)**
 - Homeostasis (robustness)
 - Positive or Negative Feedback loops

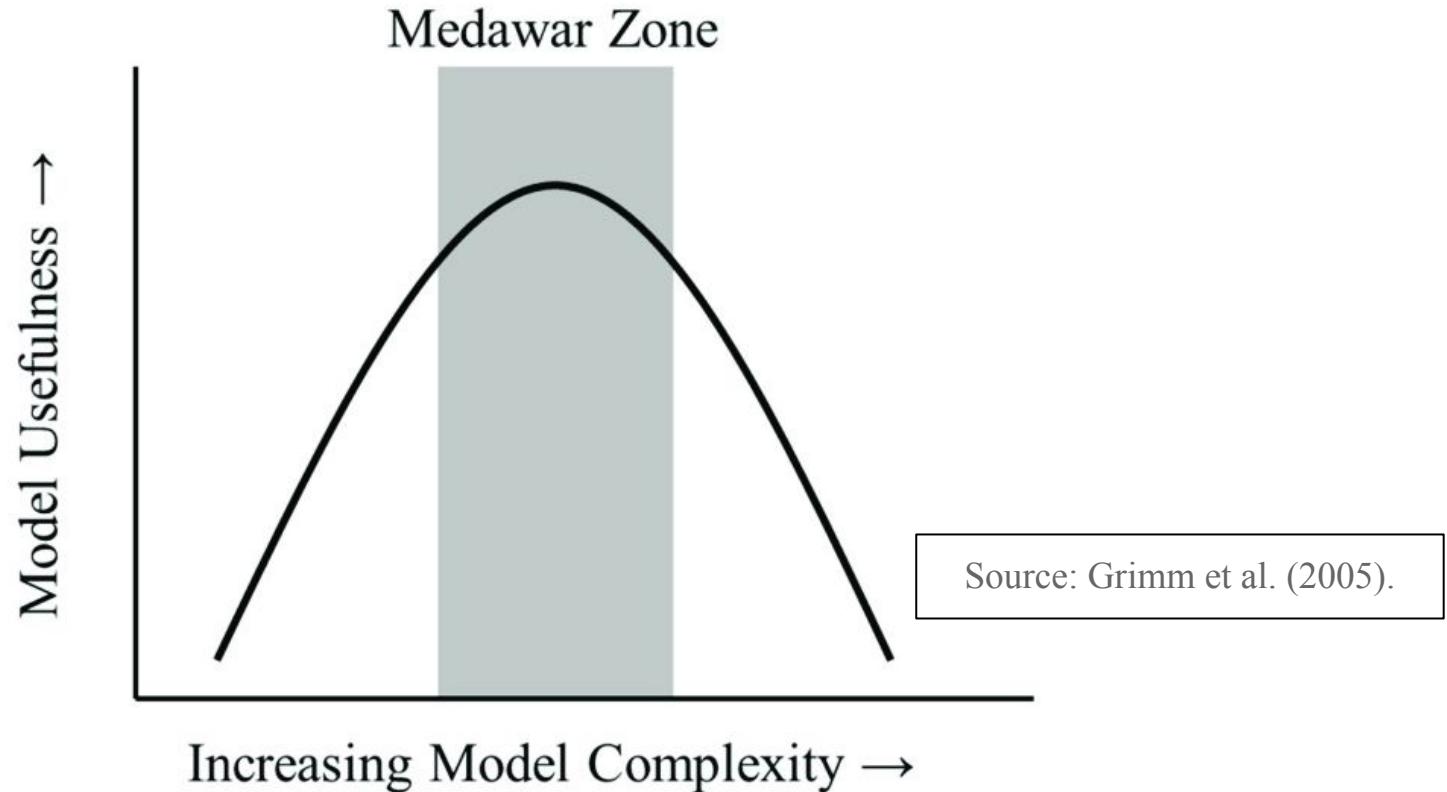


Complexity due to the large number of parameters and non-linear interactions!

“... With four parameters I can fit an elephant, and with five I can make him wiggle his trunk...”

John von Neumann (~1953)

How to choose the proper level?



As models increase in complexity, the **Medawar Zone** is the region of maximum usefulness. 38

Levels of description of a system

- **Structure**
 - Components + interactions
- **Dynamics**
 - Steady states, Bi-stability
 - Oscillations, Chaos, etc
- **Control (regulation)**
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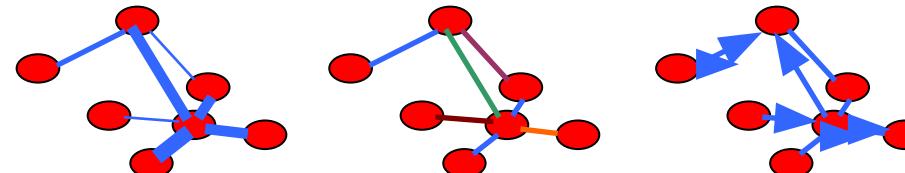
Network representation of a system

Any system or process structure can be represented as network: single components → **nodes** and relationships or interactions → **edges**

Node – Generic entity (component), physical or not (e.g. gene, protein, metabolite, cellular state, disease, etc). It can have associated features (quantitative or qualitative)



Edge – Generic relationship, in the broadest sense (physical/functional). For example, transcriptional control, binding, friendship, etc. Can have associated features (quantitative or qualitative): weight, direction, etc.



History - (1998) Networks begins to get attention

letters to nature

typically slower than $\sim 1 \text{ km s}^{-1}$) might differ significantly from what is assumed by current modelling efforts⁵. The expected equation-of-state differences among small bodies (ice versus rock, for instance) presents another dimension of study; having recently adapted our code for massively parallel architectures (K. M. Olson and E.A., manuscript in preparation), we are now ready to perform a more comprehensive analysis.

The exploratory simulations presented here suggest that when a young, non-porous asteroid (if such exist) suffers extensive impact damage, the resulting fracture pattern largely defines the asteroid's response to future impacts. The stochastic nature of collisions implies that small asteroid interiors may be as diverse as their shapes and spin states. Detailed numerical simulations of impacts, using accurate shape models and rheologies, could shed light on how asteroid collisional response depends on internal configuration and shape, and hence on how planetesimals evolve. Detailed simulations are also required before one can predict the quantitative effects of nuclear explosions on Earth-crossing comets and asteroids, either for hazard mitigation²⁸ through disruption and deflection, or for resource exploitation²⁹. Such predictions would require detailed reconnaissance concerning the composition and internal structure of the targeted object. □

Received 4 February; accepted 18 March 1998.

1. Asphaug, E. & Melosh, H.J. The Stickney impact of Phobos: A dynamical model. *Icarus* **101**, 144–164 (1993).
2. Asphaug, E. et al. Mechanical and geological effects of impact cratering on Ida. *Icarus* **120**, 158–184 (1996).
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5. Melosh, H. J. & Ryan, E. V. Asteroids: Shattered but dispersed. *Icarus* **129**, 562–564 (1997).
6. Housen, K. R., Schmidt, R. M. & Holopple, K. A. Crater ejecta scaling laws: Fundamental forms based on dimensional analysis. *J. Geophys. Res.* **88**, 2483–2499 (1983).
7. Holopple, K. A. & Schmidt, R. M. Point source solutions and coupling parameters in cratering mechanics. *J. Geophys. Res.* **92**, 6350–6376 (1987).
8. Housen, K. R. & Holopple, K. A. On the fragmentation of asteroids and planetary satellites. *Icarus* **84**, 226–233 (1990).
9. Benz, W. & Asphaug, E. Simulations of brittle solids using smooth particle hydrodynamics. *Comput. Phys. Commun.* **87**, 253–265 (1995).
10. Asphaug, E. et al. Mechanical and geological effects of impact cratering on Ida. *Icarus* **120**, 158–184 (1996).
11. Hudson, R. S. & Ostro, S. J. Shape of asteroid 4769 Castalia (1989 PB) from inversion of radar images.

(today) 28k < citations!!

Collective dynamics of 'small-world' networks

Duncan J. Watts* & Steven H. Strogatz

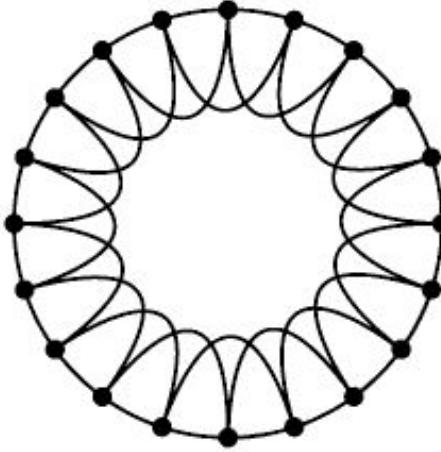
Department of Theoretical and Applied Mechanics, Kimball Hall,
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Networks of coupled dynamical systems have been used to model biological oscillators^{1–4}, Josephson junction arrays^{5,6}, excitable media⁷, neural networks^{8–10}, spatial games¹¹, genetic control networks¹² and many other self-organizing systems. Ordinarily, the connection topology is assumed to be either completely regular or completely random. But many biological, technological and social networks lie somewhere between these two extremes. Here we explore simple models of networks that can be tuned through this middle ground: regular networks 'rewired' to introduce increasing amounts of disorder. We find that these systems can be highly clustered, like regular lattices, yet have small characteristic path lengths, like random graphs. We call them 'small-world' networks, by analogy with the small-world phenomenon^{13,14} (popularly known as six degrees of separation¹⁵). The neural network of the worm *Caenorhabditis elegans*, the power grid of the western United States, and the collaboration graph of film actors are shown to be small-world networks. Models of dynamical systems with small-world coupling display enhanced signal-propagation speed, computational power, and synchronizability. In particular, infectious diseases spread more easily in small-world networks than in regular lattices.

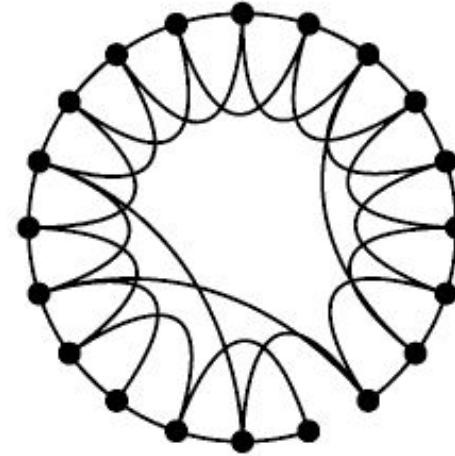
To interpolate between regular and random networks, we consider the following random rewiring procedure (Fig. 1). Starting from a ring lattice with n vertices and k edges per vertex, we rewrite each edge at random with probability p . This construction allows us to 'tune' the graph between regularity ($p = 0$) and disorder ($p = 1$), and thereby to probe the intermediate region $0 < p < 1$, about which little is known.

History - (1998) Networks begins to get attention

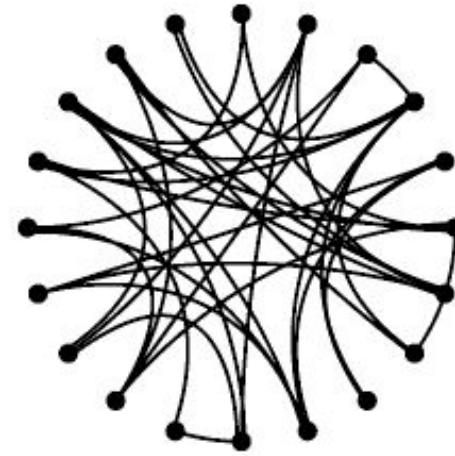
Regular



Small-world



Random



$p = 0$

→

$p = 1$

Increasing randomness

History - (1998) Networks begins to get attention

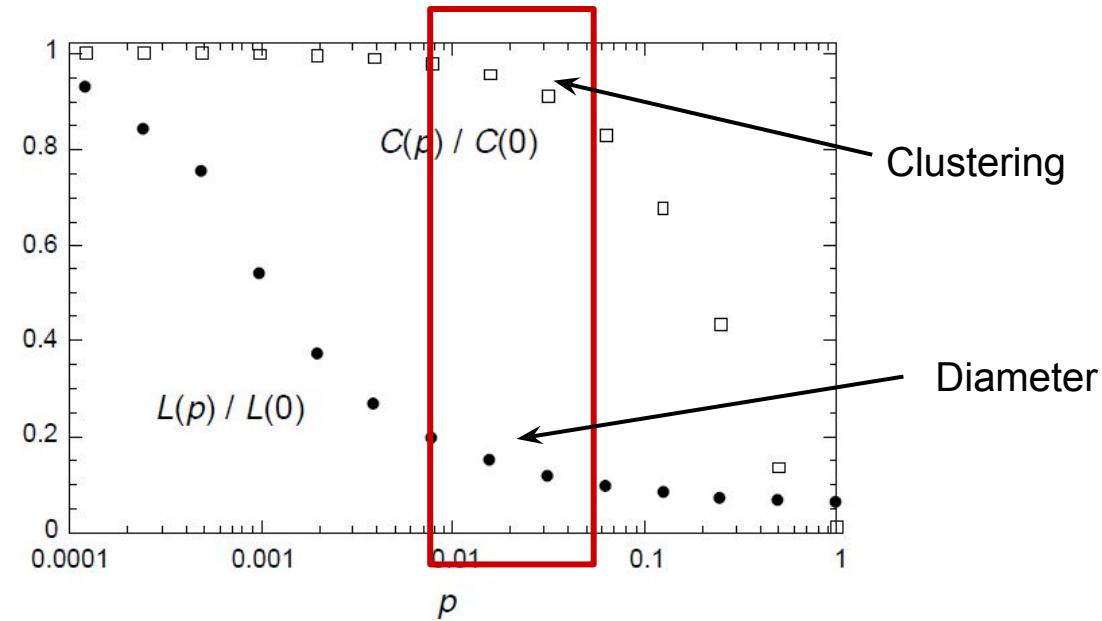


Table 1 Empirical examples of small-world networks

	L_{actual}	L_{random}	C_{actual}	C_{random}
Film actors	3.65	2.99	0.79	0.00027
Power grid	18.7	12.4	0.080	0.005
<i>C. elegans</i>	2.65	2.25	0.28	0.05

1999-2000 → Another two milestone papers

Emergence of Scaling in Random Networks

Albert-László Barabási* and Réka Albert

Systems as diverse as genetic networks or the World Wide Web are best described as networks with complex topology. A common property of many large networks is that the vertex connectivities follow a scale-free power-law distribution. This feature was found to be a consequence of two generic mechanisms: (i) networks expand continuously by the addition of new vertices, and (ii) new vertices attach preferentially to sites that are already well connected. A model based on these two ingredients reproduces the observed stationary scale-free distributions, which indicates that the development of large networks is governed by robust self-organizing phenomena that go beyond the particulars of the individual systems.

Error and attack tolerance of complex networks

Réka Albert, Hawoong Jeong & Albert-László Barabási

Department of Physics, 225 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, USA

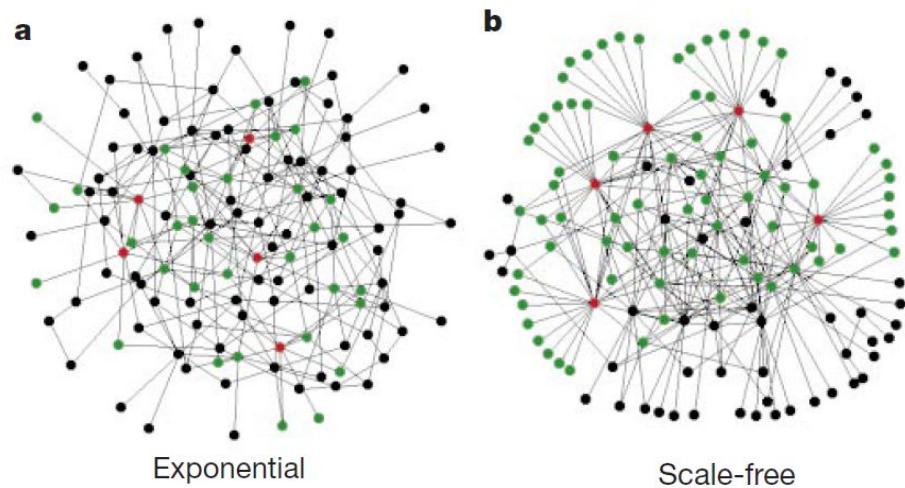
Many complex systems display a surprising degree of tolerance against errors. For example, relatively simple organisms grow, persist and reproduce despite drastic pharmaceutical or environmental interventions, an error tolerance attributed to the robustness of the underlying metabolic network¹. Complex communication networks² display a surprising degree of robustness: although key components regularly malfunction, local failures rarely lead to the loss of the global information-carrying ability of the network. The stability of these and other complex systems is often attributed to the redundant wiring of the functional web defined by the systems' components. Here we demonstrate that error tolerance is not shared by all redundant systems: it is displayed only by a class of inhomogeneously wired networks,

Barabasi & Albert (1999) Science. 24k > citations

Albert et al. (2000) Nature. 8K > citations

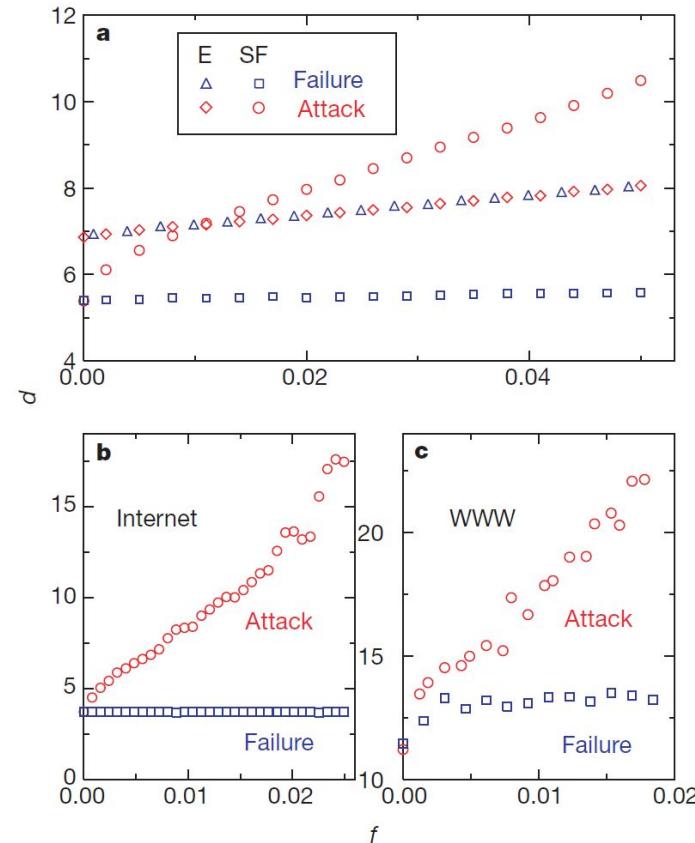
1999-2000 → Another two milestone papers

Topologies of different network classes



Network topology → Degree distribution (i.e. distribution of the number of connection of each individual node)

Robustness of different networks



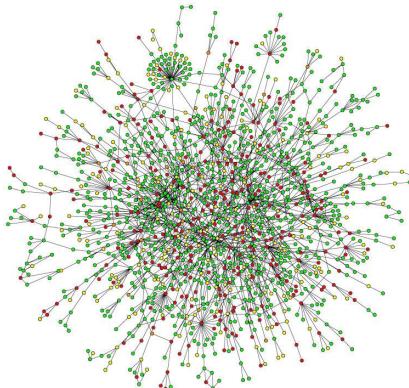


**Barcelona
Supercomputing
Center**

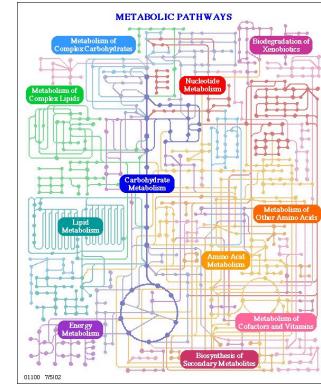
Centro Nacional de Supercomputación

Since then...

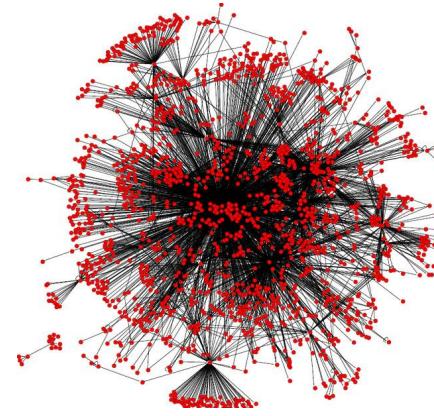
Networks are everywhere!



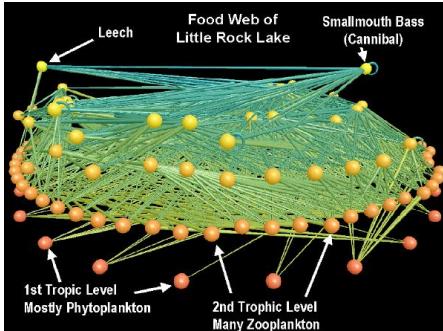
PPI networks



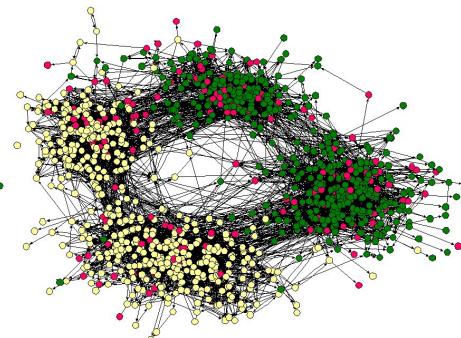
Metabolic networks



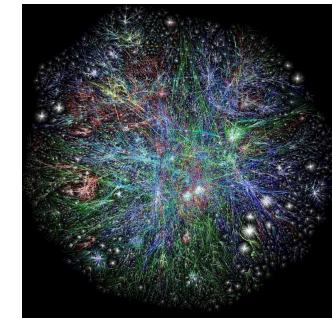
Regulatory networks



Ecological networks

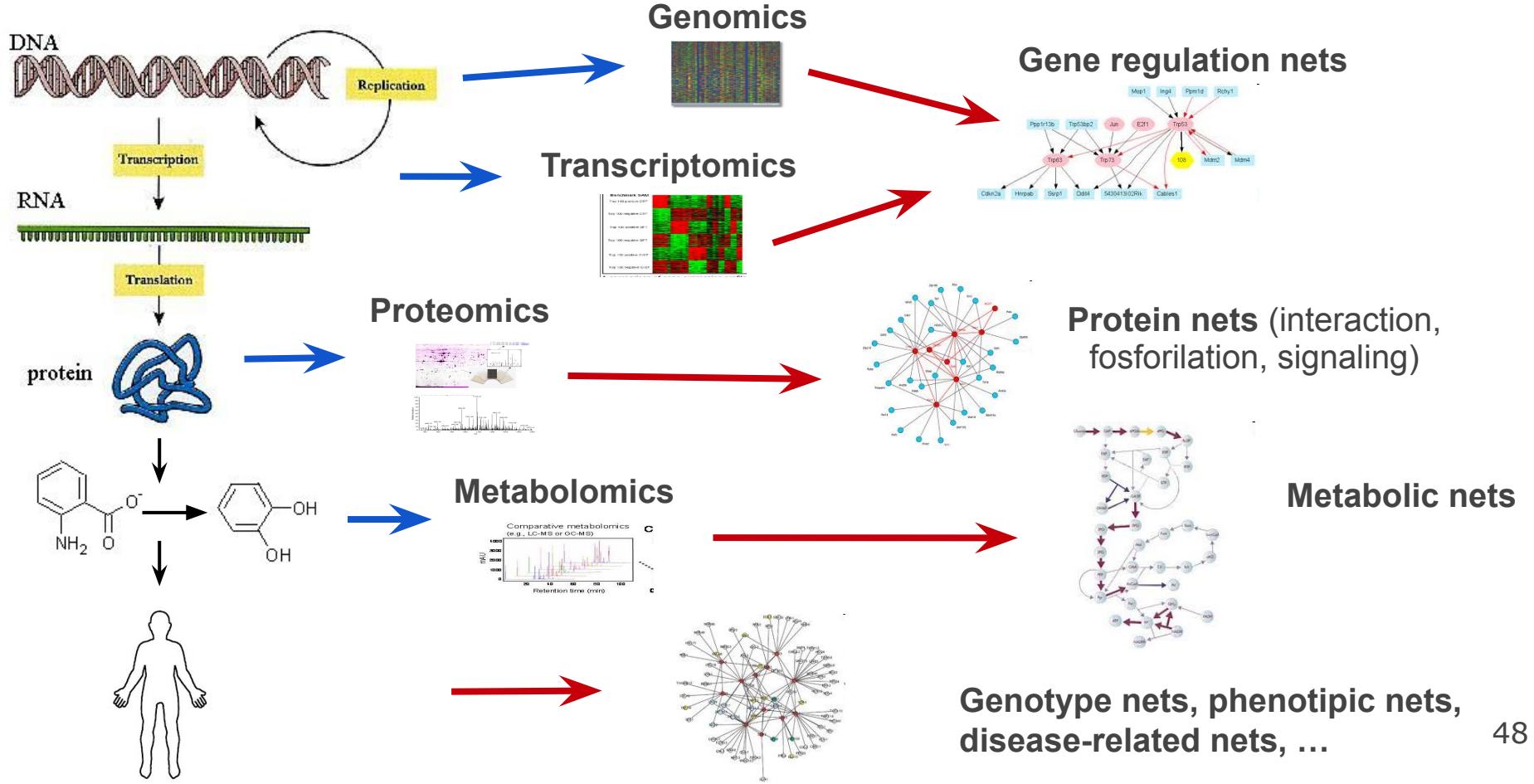


Social networks



Technological networks

From omics to network reconstruction



Concluding remarks

- Complexity of most biological phenomena cannot be reduced to the properties of single components (“**the whole is more than the sum of the parts**”)
- **Systems Biology** studies biology from a **systemic approach** opposite (and complementary) to the reductionist, traditionally used by Molecular Biology (MB).
- Systems Biology has re-emerged during the **omic revolution** to cope with the large amount of molecular data produced by high-throughput technologies. **Network theory**, together with **quantitative modeling** of large molecular systems, form the basis of modern Systems Biology.
- **Complex network** is a very broad concept. Any entity (e.g. gene, protein) or phenomena (e.g. process, disease) can be represented as a node; and any relationship/interaction between nodes as an edge. Any system structure (**components and their interactions**) can be represented as a network.
- **Structural properties** of a system (e.g. robustness to errors) can be inferred from the topological and connectivity patterns of its network representation.
- Network and systemic concepts are being applied to the study, diagnosis and treatment of diseases, study ecosystems, epidemics, markets, and any other complex system.

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Book chapter:

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