

Computational & Systems Biology

Introduction

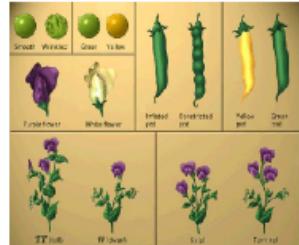
Yazdan Asgari
2020

Score Details

- Seminars (10%)
- Take Home Exams + Final Exam (Feedbacks) (20%)
- Assignments (70%)

Systems Theory, History

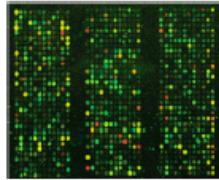
molecular bio-techniques



DNA isolation



recombinant DNA technology



sequencing technology

transgenic mouse

PCR technology

micro-array technology

Cloning of sheep Dolly

high-throughput MS technique

Next generation sequencing

discoveries

1859

"Origin of species" -Charles Darwin

1865

Mendel's model of heritance

1869

Friedrich Miescher isolates DNA

1953

DNA dubbel helix -Watson & Crick

1955

discovery # chromosomes in man

1959

1st chromosome aberration shown: Down
genetic code 'cracked'

1966

1972

introns discovered



1977

1st disease-gene mapped: Huntington's Disease

1981

total microbial sequence unraveled: H. influenza

1983

total yeast DNA sequence unraveled

1995

total human DNA sequence unraveled

1996

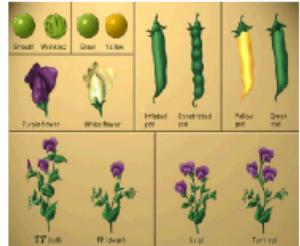
biomarker DNA chips, personalized medicine
genetic passport?

2003

2006

Systems Theory, History

molecular bio-techniques

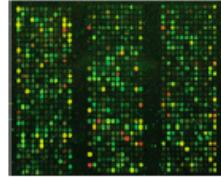


Systems Theory

DNA isolation



recombinant DNA technology



sequencing technology

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Cloning of sheep Dolly

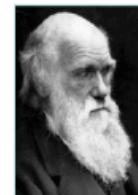
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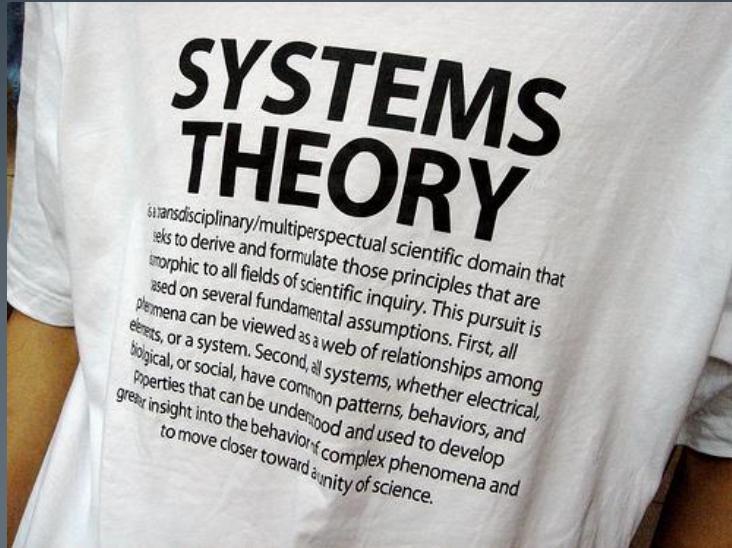
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biomarker DNA chips, personalized medicine
genetic passport?

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2006



M. D. Mesarovic, “Systems theory and biology—view of a theoretician,” in Systems Theory and Biology, pp. 59–87, Springer, NY, USA, 1968.

L. von Bertalanffy, General System Theory, NY, USA, 1969.

Ludwig von Bertalanffy

Karl Ludwig von Bertalanffy was an Austrian-born biologist known as one of the founders of general systems theory. [Wikipedia](#)

Born: September 19, 1901, Vienna

Died: June 12, 1972, New York

Education: University of Vienna



Mihajlo D. Mesarovic

Mihajlo D. Mesarovic is a Serbian scientist, who is a professor of Systems Engineering and Mathematics at Case Western Reserve University. [Wikipedia](#)

Born: 1928

Books: *Mankind at the turning point, Abstract systems theory*



1 March 2002

Science

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Systems Biology

Systems Biology - History

Genomics

Proteomics

Systems Biology

1990

1995

2000

2005

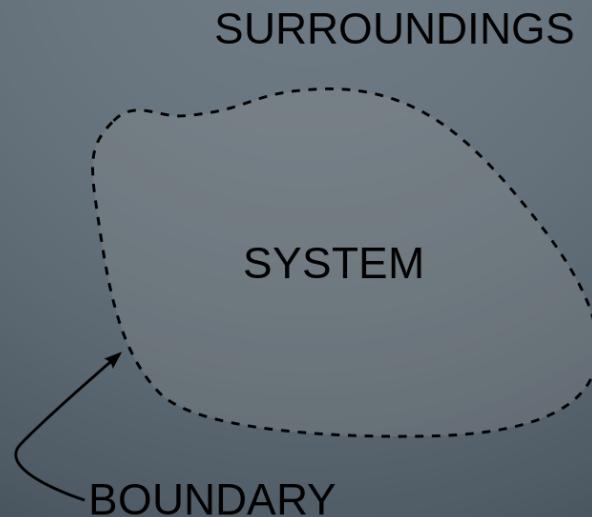
2010

2015

2020

What is a System?

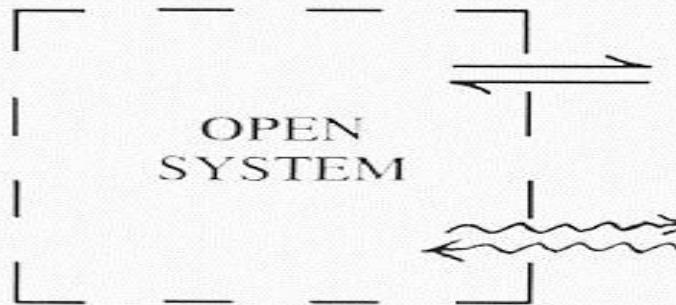
- **System** means a bunch of parts that are connected to one another and work together
- **System** is an object in which variables of different kinds interact and produce observable signals



Systems (Summary)

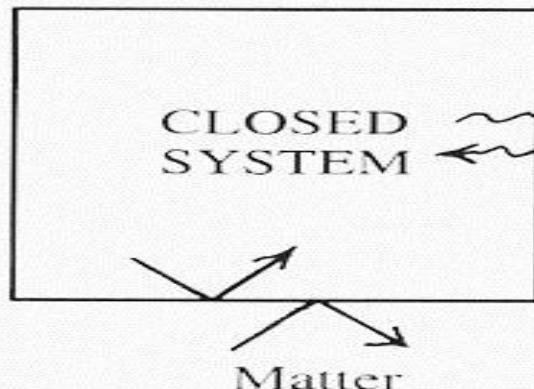
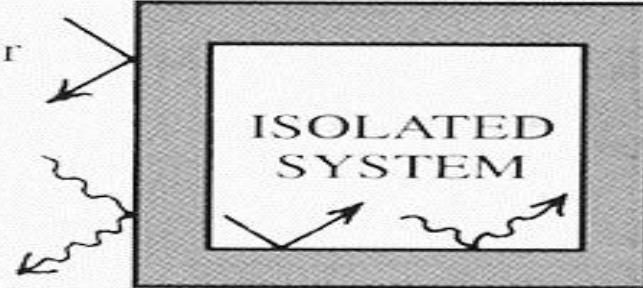
- Thermodynamics (open, closed, isolated, adiabatic)
- Mechanics (static, dynamic)
- Physics (stable, unstable)
- Statistics (discrete, continuous)
- Mathematics (linear, non-linear)
- Interdisciplinary (deterministic, probabilistic)
 - In Mathematics, Computer Science, and Physics
- Complex Theory (simple, complex)

Systems (Thermodynamic)

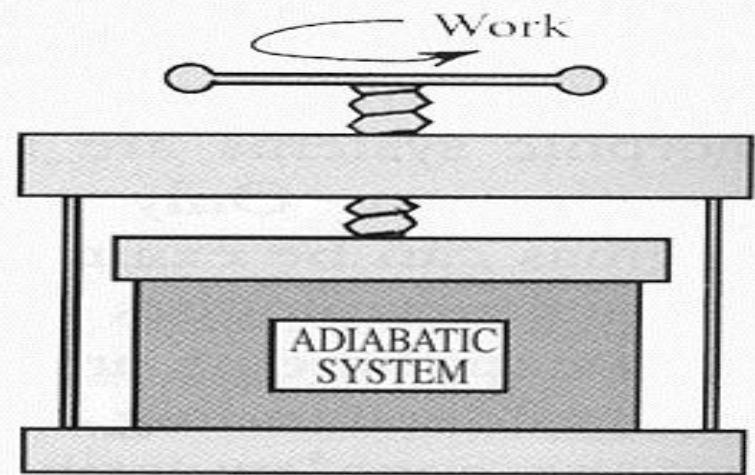


Matter

Energy
(including
work)



Energy
(including
work)

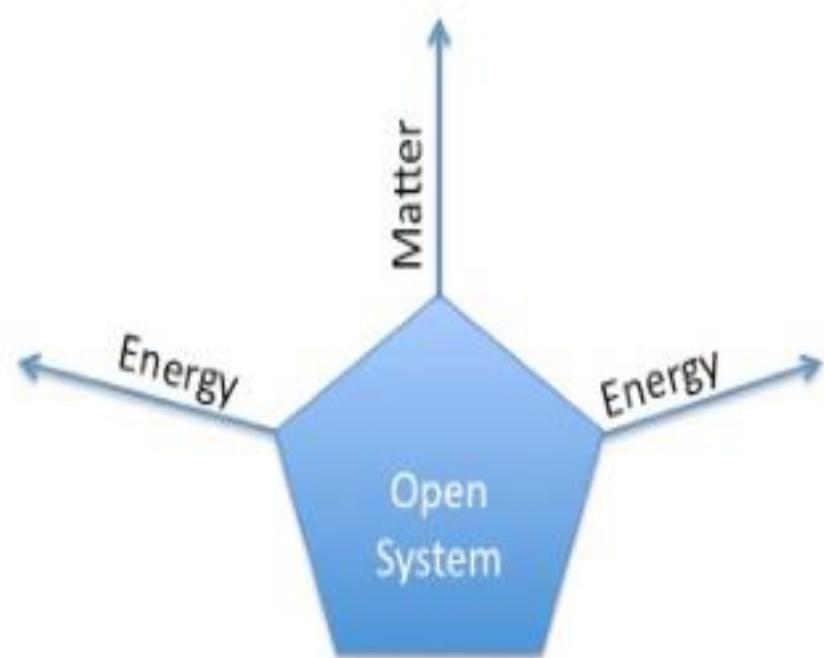


Isolated System
Adiabatic System

Open System
Closed System

Open System

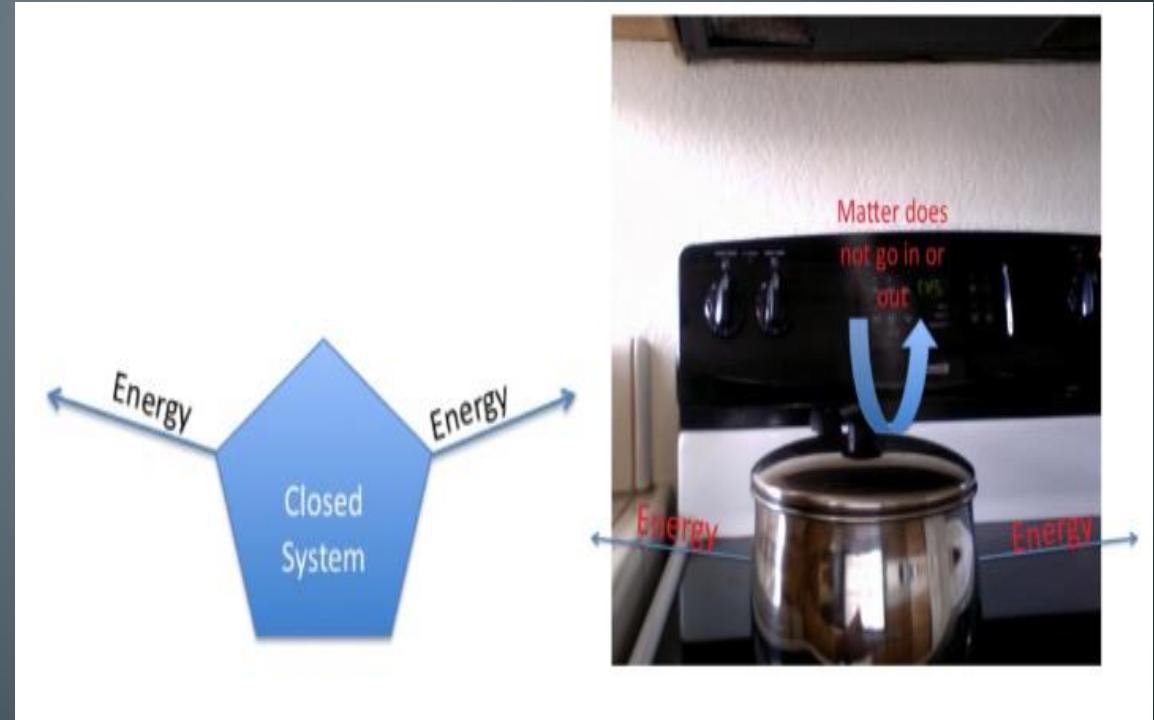
Free exchange across system boundaries



Closed System

Energy can be exchanged but matter cannot

An example of a closed system is a balloon being heated so the gas inside expands it (or a piston like in the movie) no matter is exchange, only heat



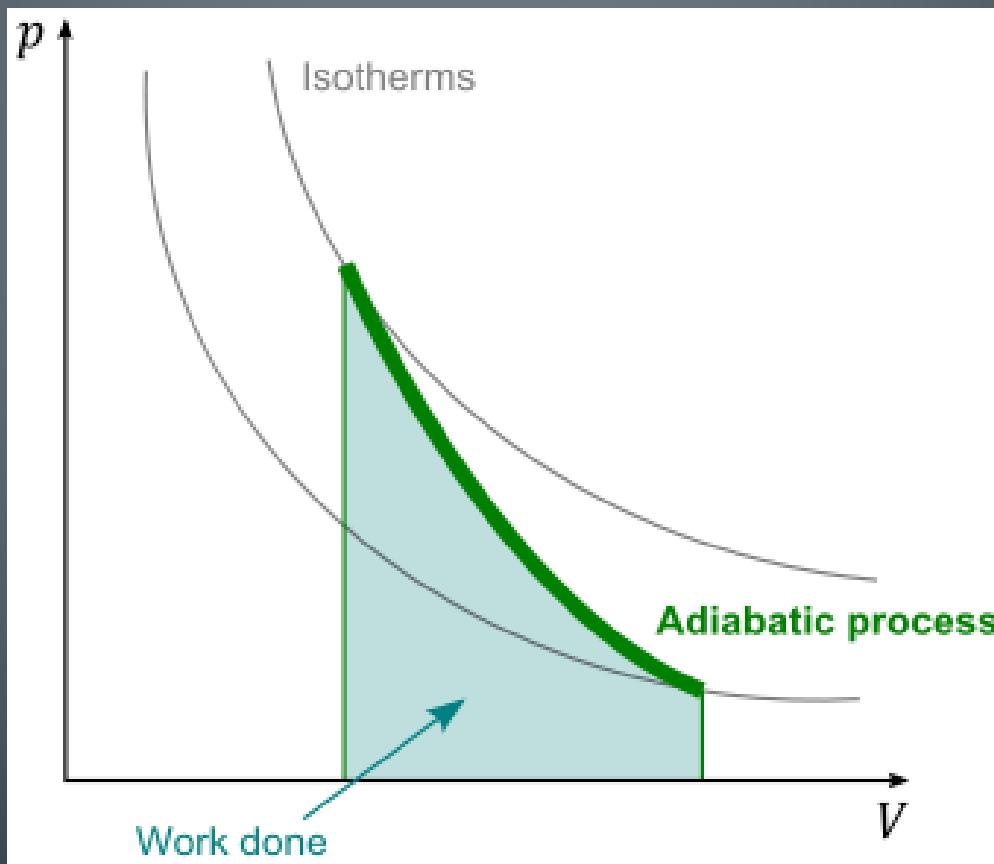
Isolated System

No matter or energy cross system boundaries.
No work can be done on the system.



Adiabatic System

Special case where no heat can be exchanged but work can be done on the system
(e.g. PV work)



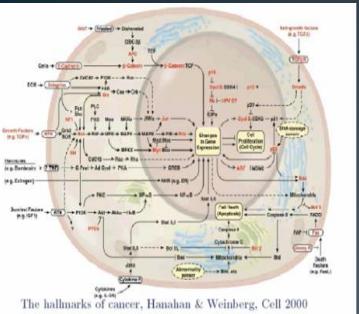
Systems (Mechanics)



Static

- ❖ States does not change or changes very slowly over time
 - Examples: Buildings, dishes, bridges, ...



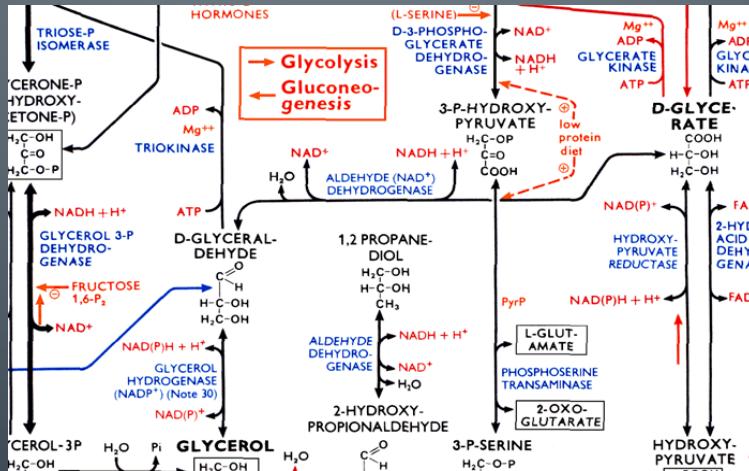


Dynamic

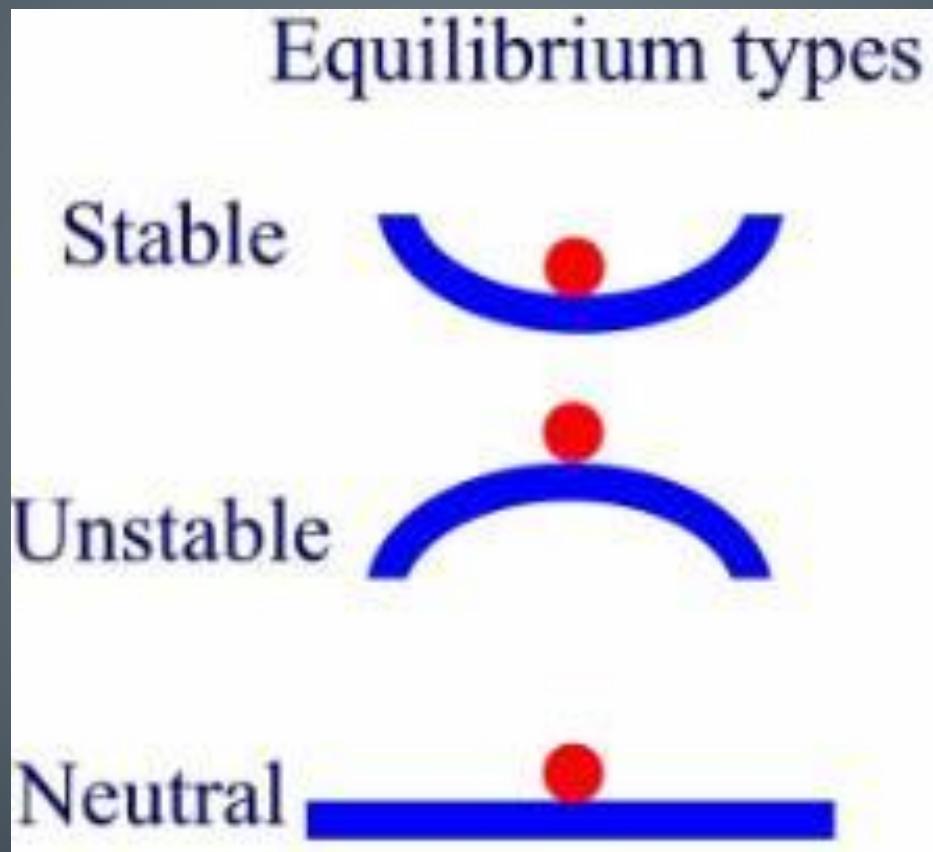
❑ **Dynamic:** State variables change over time

❑ Examples: Living Systems, vehicles, computers, ...

❑ In a **dynamical system** the current output value depends not only on the current input value but also on its earlier values

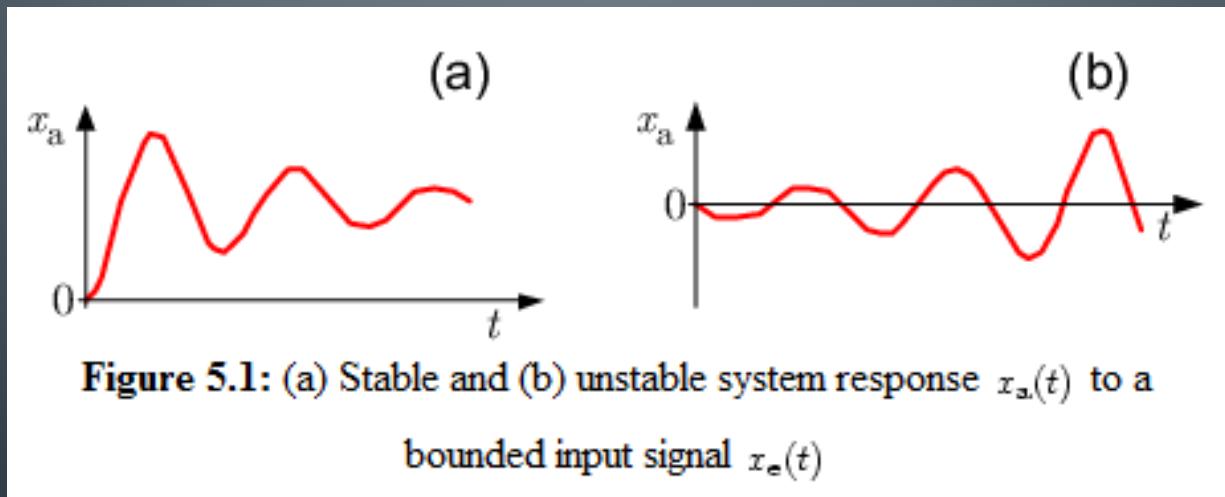


Systems (Physics)

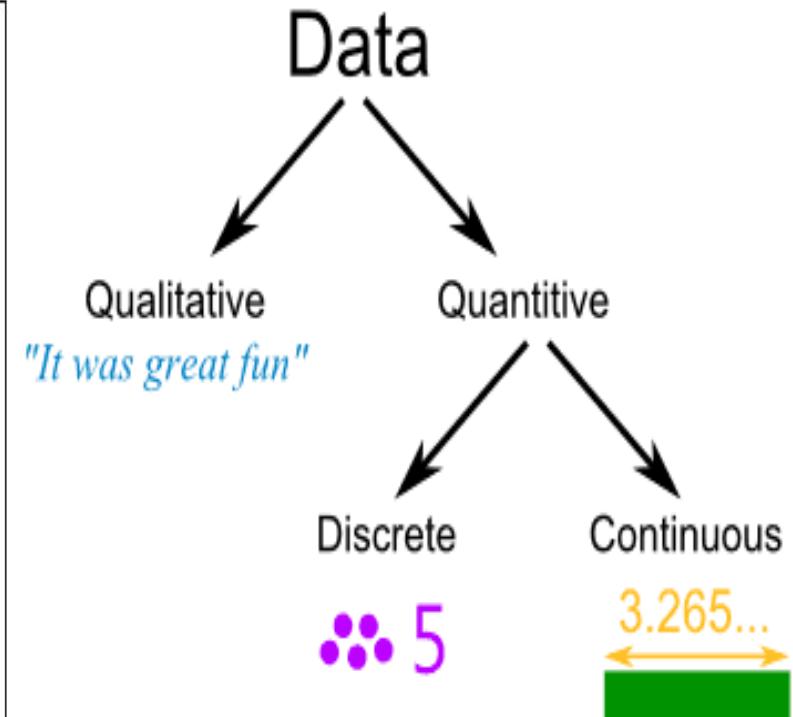
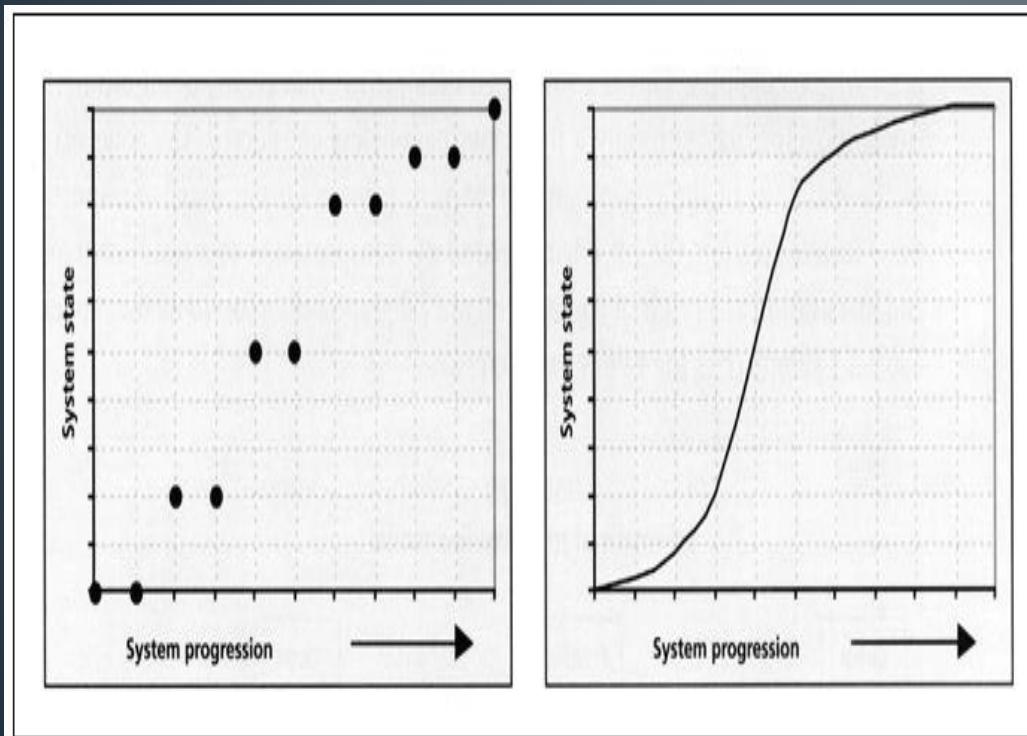


Stable vs. Unstable

- **Stable:** all nearby initial conditions converge to the equilibrium point.
- **Unstable:** some of the outputs or internal states growing without bounds
- systems can also be marginally stable or exhibit limit cycle behavior.



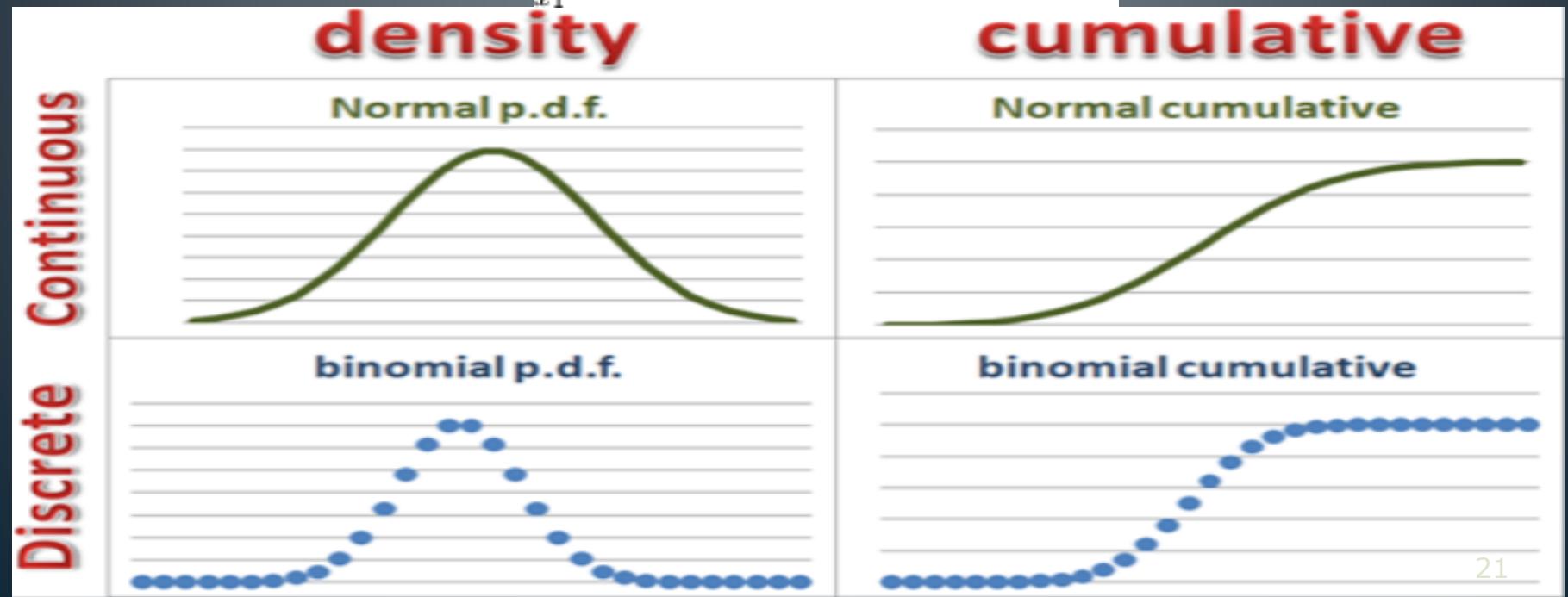
Systems (Statistics)



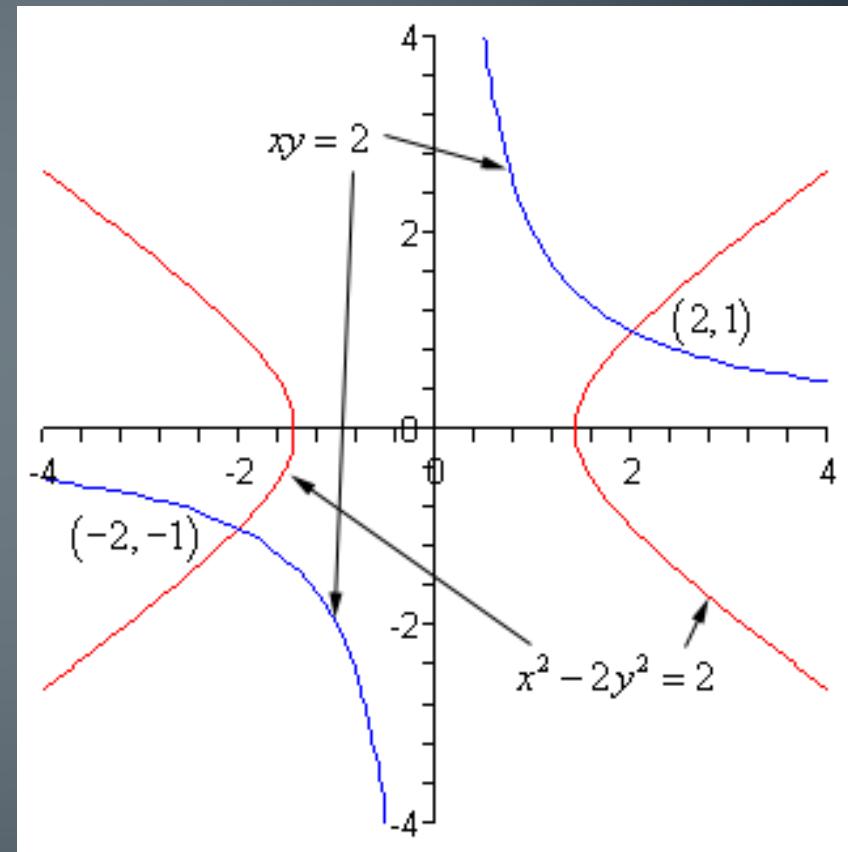
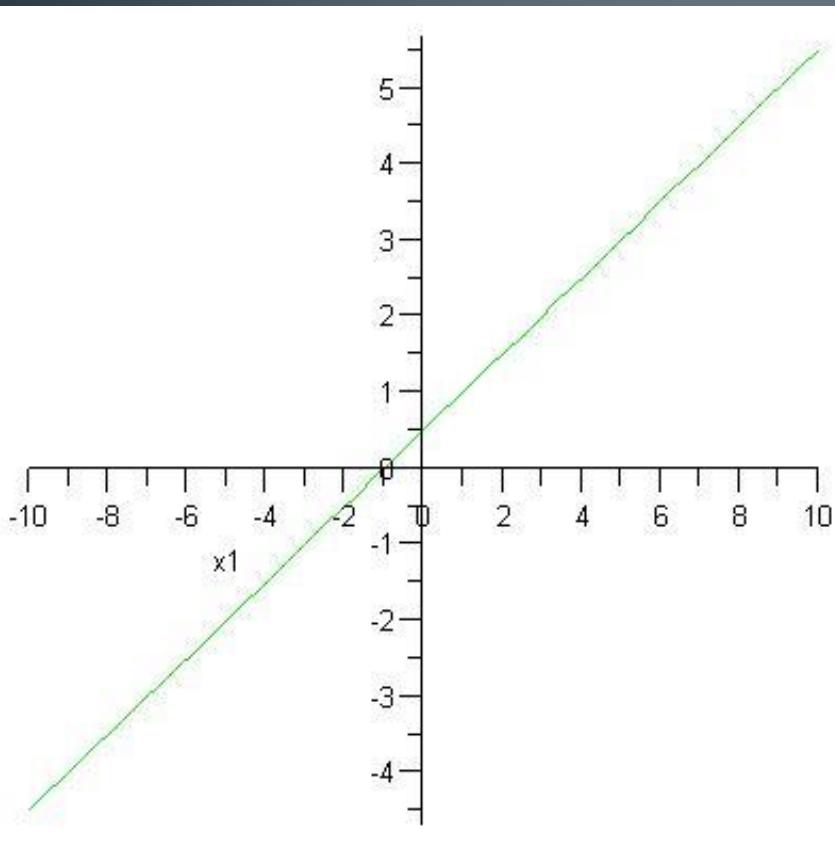
Discrete vs. Continuous models

- ❑ **Discrete** : the state variables change only at a countable number of points in time.
- ❑ **Continuous**: the state variables change in a continuous way, and not abruptly from one state to another

$$\int_{x_1}^{x_N} f(x)dx = \lim_{dx \rightarrow 0} \sum_{i=1}^N f(x_i) * dx$$



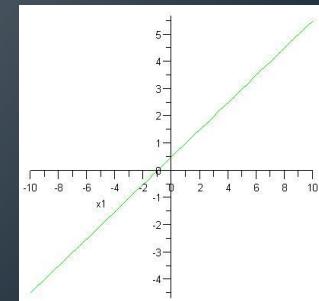
Systems (Mathematics)



Linear System - Concept

Suppose that, without much effort, you can toss a tennis ball at about 20 km per hour. Now suppose that you're riding a bicycle at 10 km per hour and toss a tennis ball straight ahead. The ball will travel forward at 30 km per hour.

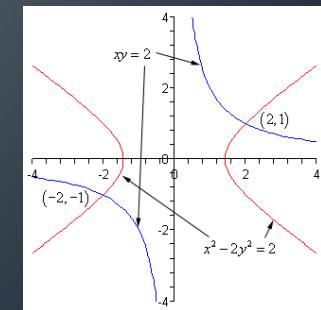
Linearity is, essentially, the idea that combining two inputs — like the velocity of your arm and the velocity of the bike — will yield the sum of their respective outputs — the velocity of the ball.



Non-Linear System - Concept

Now suppose that, instead of tossing a tennis ball, you toss a paper airplane. Depending on the airplane's design, it might sail straight ahead, or it might turn loops. Some paper planes seem to behave more erratically the harder you throw them: the bike's added velocity might make it almost impossible to get the plane to do anything predictable.

That's because airflow over a paper plane's wings can be very nonlinear.

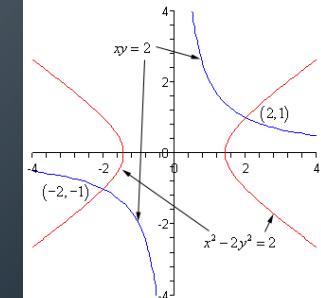
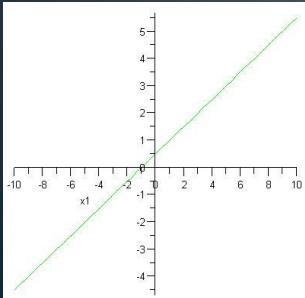


Linear vs Non-Linear - Concept

If the bicycle had built-in sensors and an onboard computer, it could calculate the velocity of the tennis ball in a fraction of a second.

But it could never hope to calculate all the airflows over the paper plane's wing in time to do anything useful.

It's a reasonable statement that we mostly understand linear phenomena.



Linear vs Non-Linear - Definition

To make the distinction between linearity and nonlinearity a bit more precise, recall that a mathematical equation can be thought of as a function — something that maps inputs to outputs.

The equation $y = x$, for instance, is equivalent to a function that takes as its input a value for x and produces as its output a value for y . The same is true of $y = x^2$.

The equation $y = x$ is linear because adding together inputs yields the sum of their respective outputs: $1 = 1$, $2 = 2$, and $3 = 1 + 2 = 1 + 2 = 3$.

But that's not true of $y = x^2$: if x is 1, y is 1; if x is 2, y is 4; but if x is 3, y is not 5.

This example illustrates the origin of the term “linear”:

The graph of $y = x$ is a straight line, while the graph of $y = x^2$ is a curve. But the basic definition of linearity holds for much more complicated equations, such as the differential equations used in engineering to describe dynamic systems.

Linear vs Non-Linear – Other Definitions

Linear system is a system with:

Variables exist with power of at most 1.

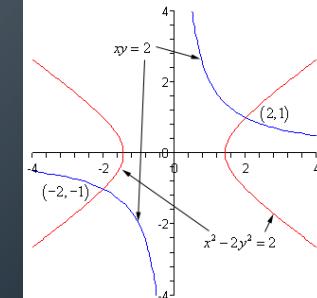
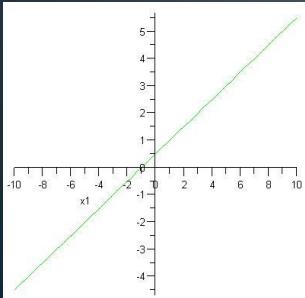
Graphical representation shows straight lines with constant slope.

Non-Linear system is a system with following features :

Variables exist with power NOT 1.

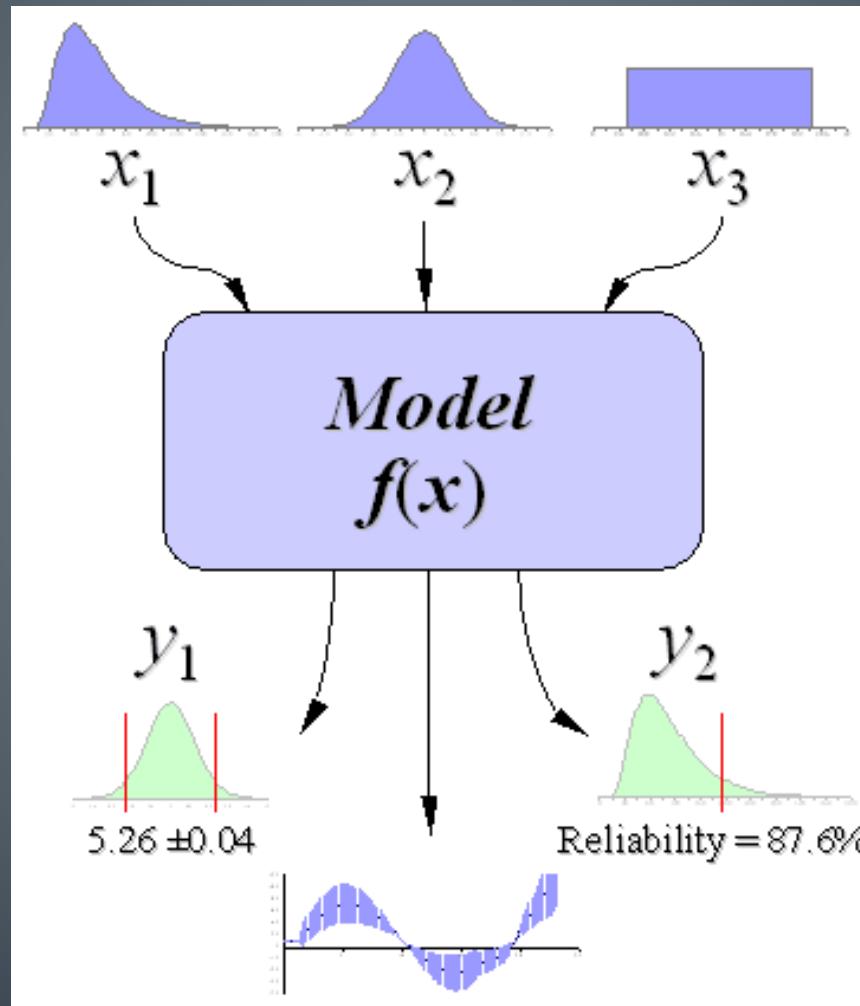
Graphical representation shows curves with variable slope.

A non-linear system is a system in which the change of the output is NOT proportional to the change of the input



Systems (interdisciplinary)

In Mathematics, Computer Science, and Physics



Deterministic vs. Probabilistic(Stochastic)

- ❑ **Deterministic** model is one whose behavior is entirely predictable. The system is perfectly understood, then it is possible to predict precisely what will happen.
- ❑ **Probabilistic** model is one whose behavior cannot be entirely predicted.



Deterministic

- A mathematically deterministic model is a representation $y=f(x)$ that allows you to make predictions of y based on x .
- The model is used like this: when $x=3$, then we predict that $y=f(3)$.
- For example, suppose $y = 2+3x-x^2$. We can predict that if $x=3$, then $y=2$

Probabilistic(Stochastic)

- ❖ A probability model is a representation $Y \sim p(y)$.
- ❖ Note that we say $Y \sim p(y)$ **not** $Y = p(y)$
- ❖ The notation " $Y \sim p(y)$ " specifically means that y is generated at random from a probability distribution whose mathematical form is $p(y)$.
- ❖ This model also allows you to make "what-if" predictions as to the value of y , but, unlike the deterministic model, it does **not allow** you to say **precisely** what the value of y will be.

Probabilistic(Stochastic)

- For example, suppose you wish to predict whether the next customer will buy either a red, gray, or a green car. The possible values of y are "red", "gray", or "green", and the distribution $p(y)$ might have the form:

y	$p(y)$
red	0.35
gray	0.40
green	0.25
Total	1.0

- The model does not tell you **precisely** what the next customer will do, because the model simply says **it is random**: y could be either "red", "gray" or "green".
- However, the model does allow aggregate what-if predictions as follows: "What if we were to sell a car to next 100 customers? Then about 35 of them would buy a red car, 40 would buy a gray car, and 25 of them would buy a green car."

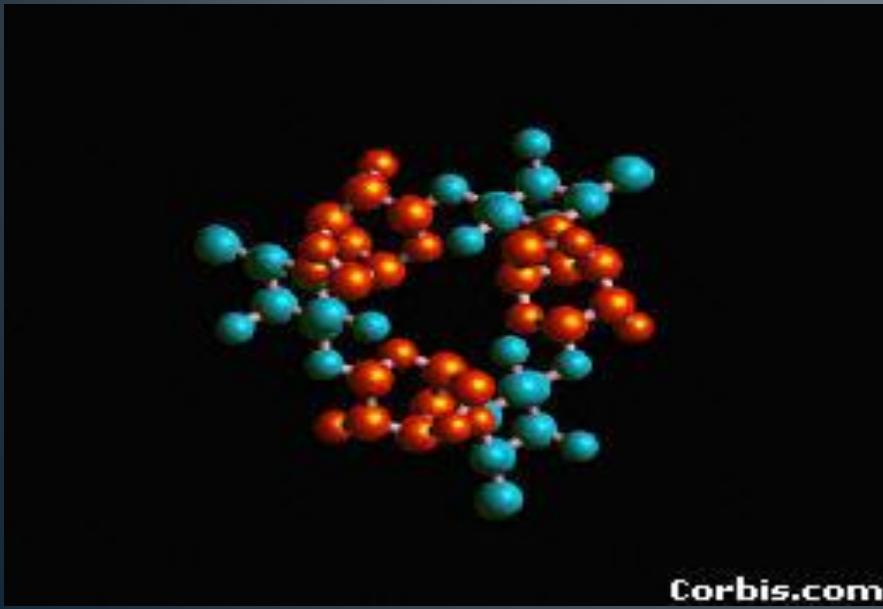
Systems (Complex systems Theory)

COMPLEXITY

simplicity

Simple

- Whole is sum of parts
- Fragmentable
- Computable
- Synthetic
- Formal System



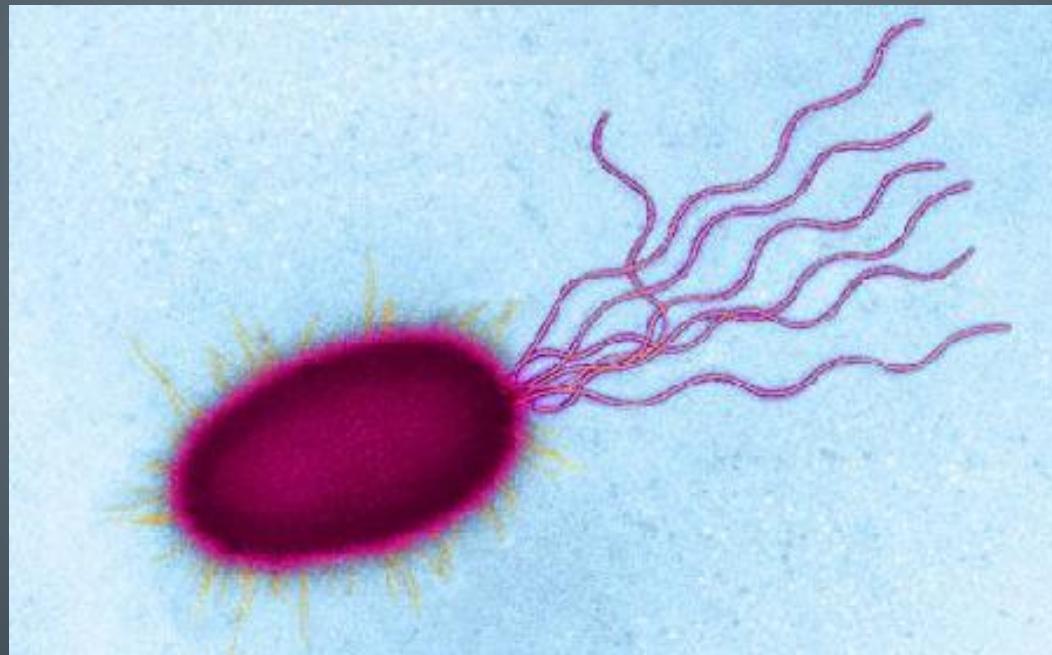
Complex

- Whole is different from sum of parts
- Non-Fragmentable
- Non-Computable
- Non-Synthetic
- Real World



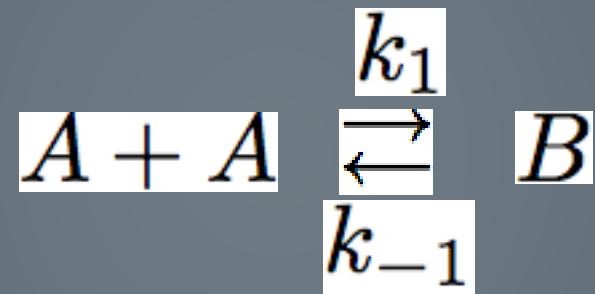
Features of complex systems

- Open systems



Features of complex systems

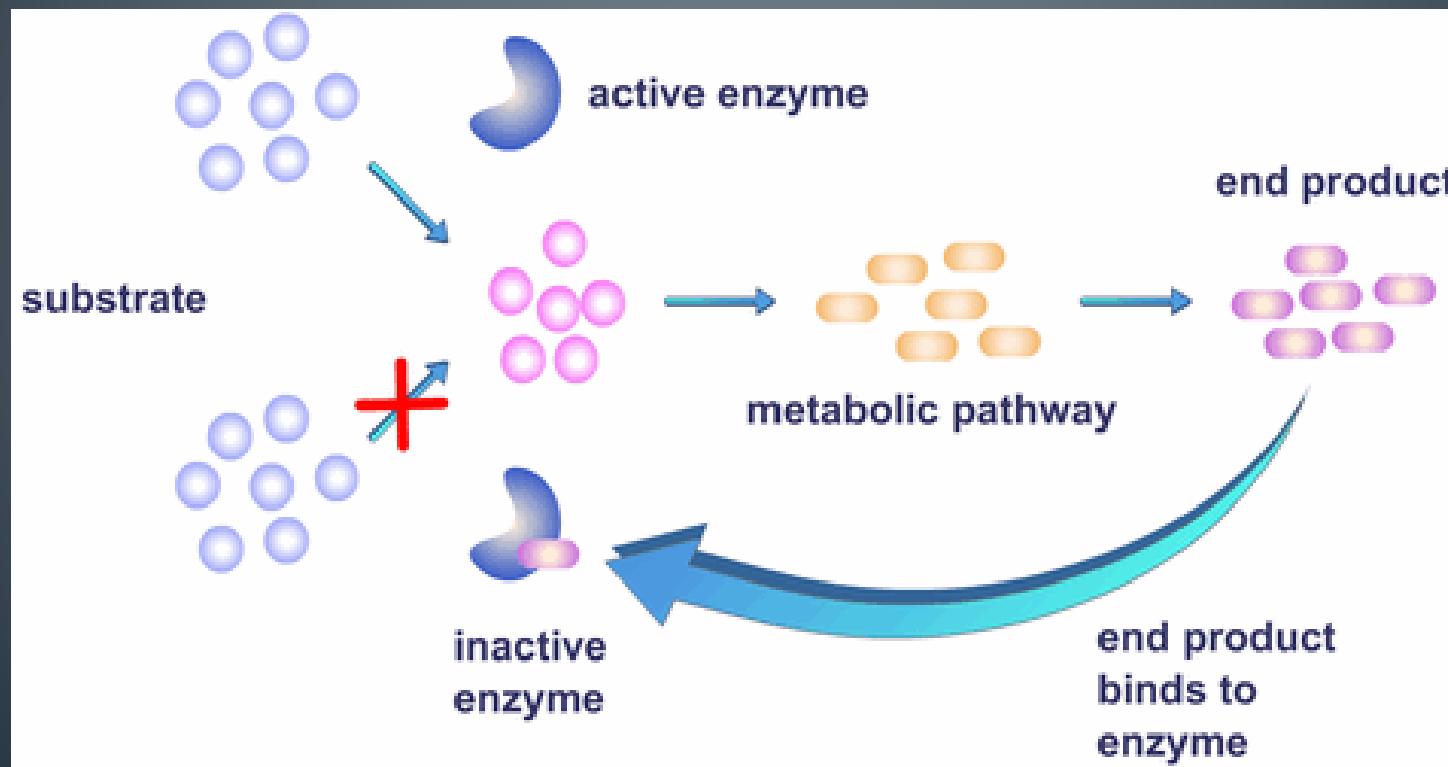
- Non-linearity



$$\frac{d[B]}{dt} = k_1[A]^2 - k_{-1}[B]$$

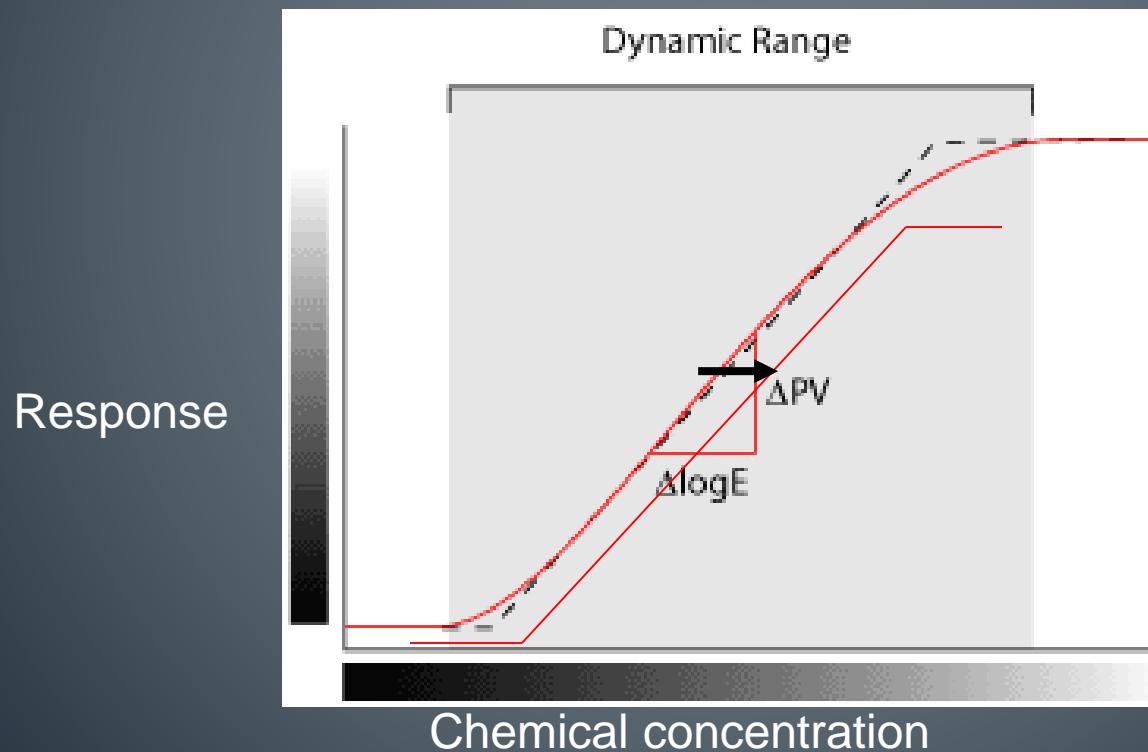
Features of complex systems

- Feedback Effects



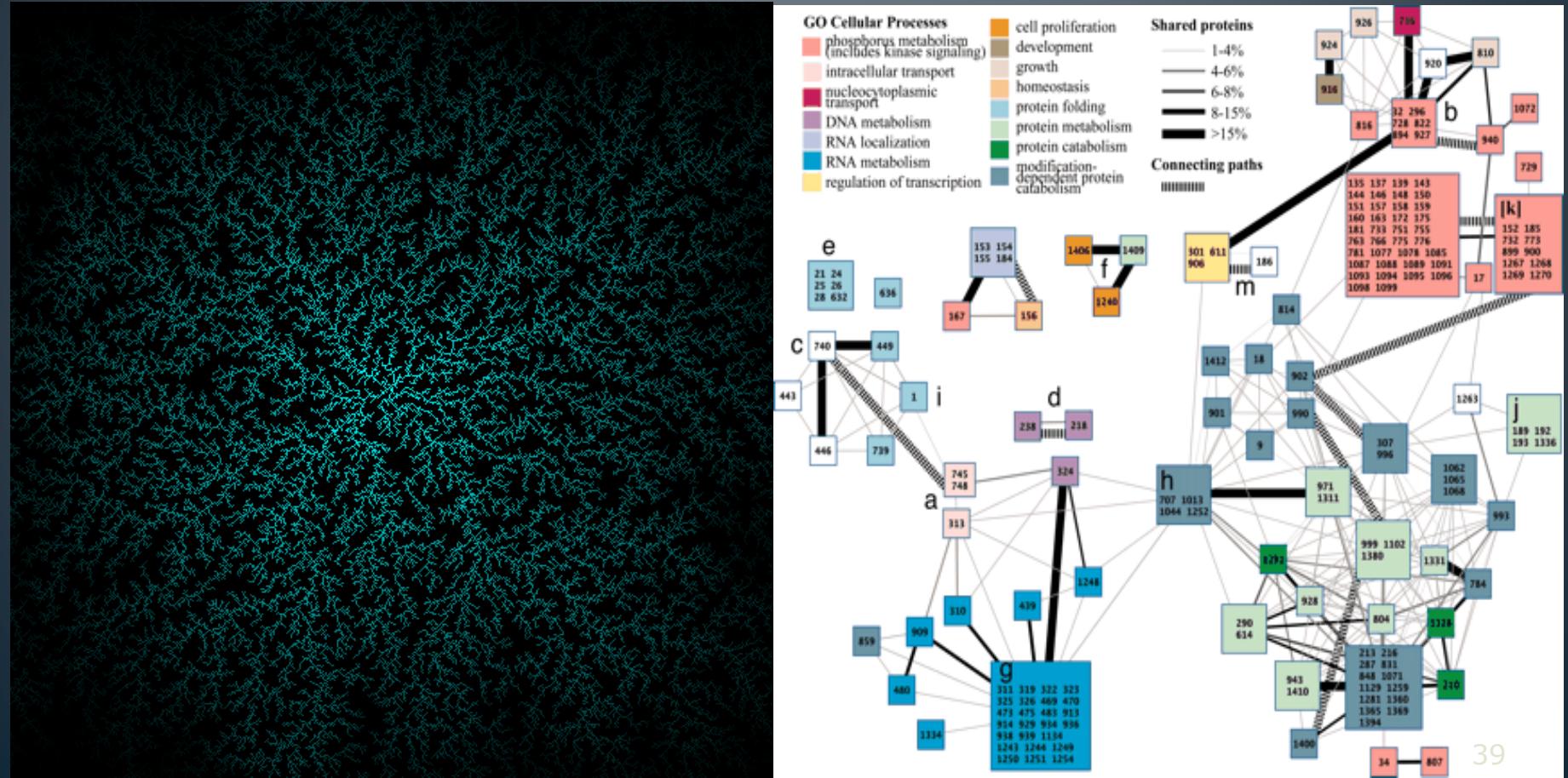
Features of complex systems

- Can have memory (response history dependent)



Features of complex systems

- Nested (modules have complexity)



Features of complex systems

- There are no precise boundaries



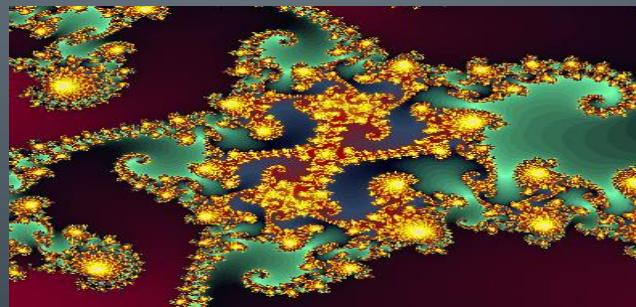
Study Complex Systems: Reductionism vs. Holism

- **Reductionism**

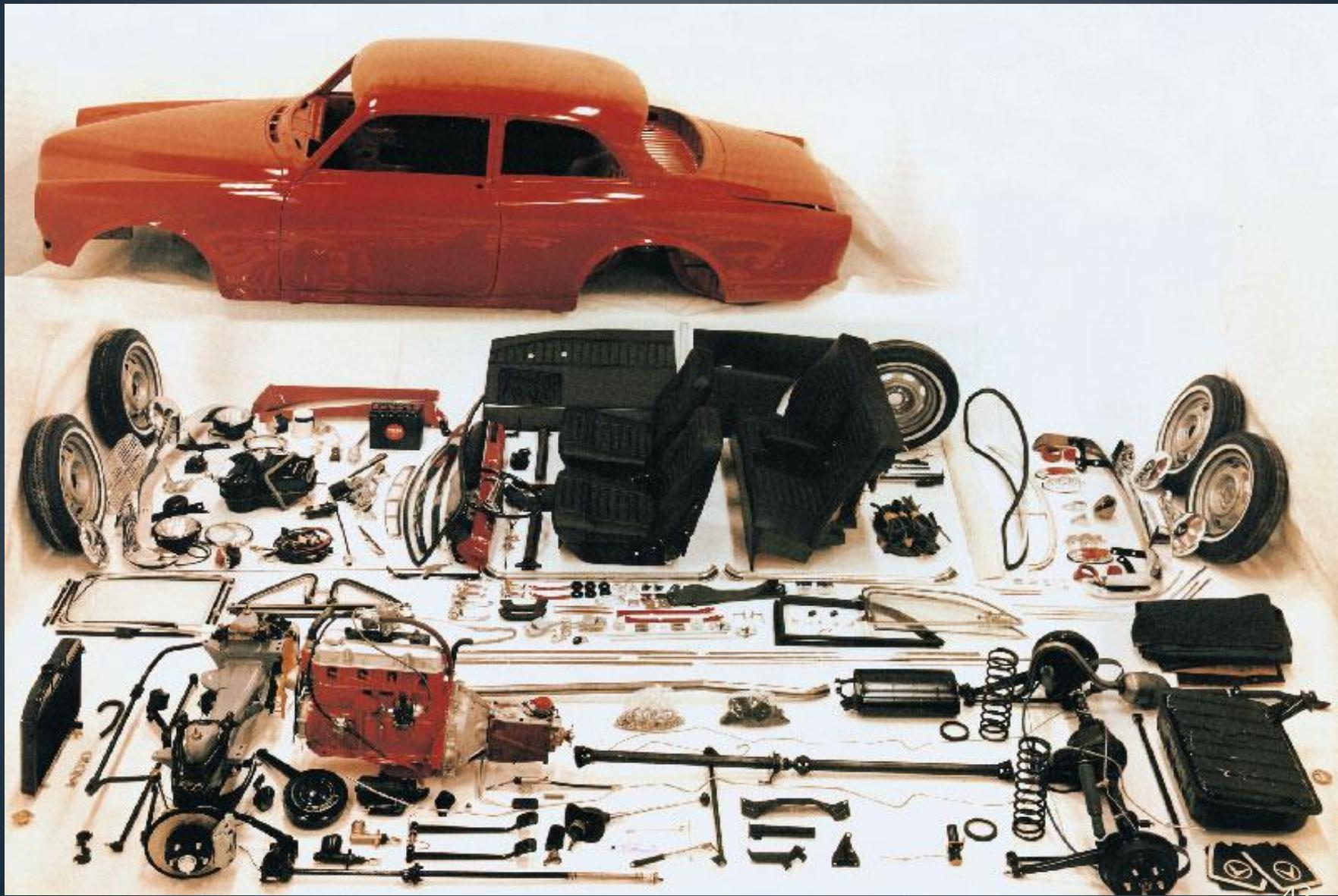
An understanding of a complex system is best sought at the **level** of the **structure** and behavior of its **component parts**.

- **Holism**

An understanding of a certain kind of complex system is best sought at the level of principles governing the behavior of the **whole system**, and **not** at the level of the structure and behavior of its component parts.



Reductionism Approach

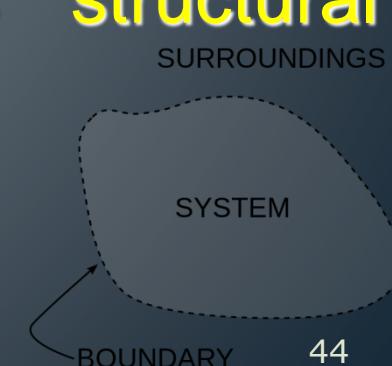


Systems (Summary)

- Thermodynamics (open, closed, isolated, adiabatic)
- Mechanics (static, dynamic)
- Physics (stable, unstable)
- Statistics (discrete, continuous)
- Mathematics (linear, non-linear)
- Interdisciplinary (deterministic, probabilistic)
 - In Mathematics, Computer Science, and Physics
- Complex Theory (simple, complex)

System Properties in Our Class

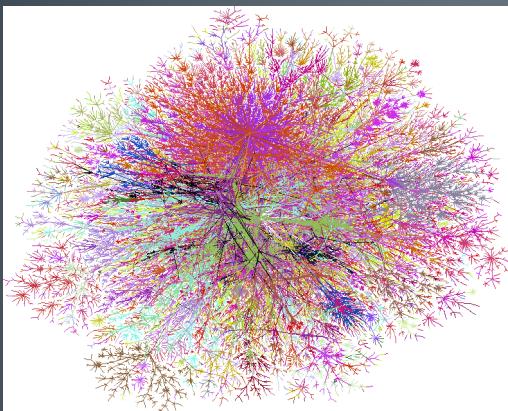
- ❖ Any part of reality that can be **separated from the environment** (boundary).
- ❖ A community in an environment.
- ❖ Consist of **interacting parts**
- ❖ Interact with the environment (**inputs, outputs**)
- ❖ Have a **structure** that is defined by parts and processes
- ❖ Parts have **functional** as well as **structural** relationships between each other.



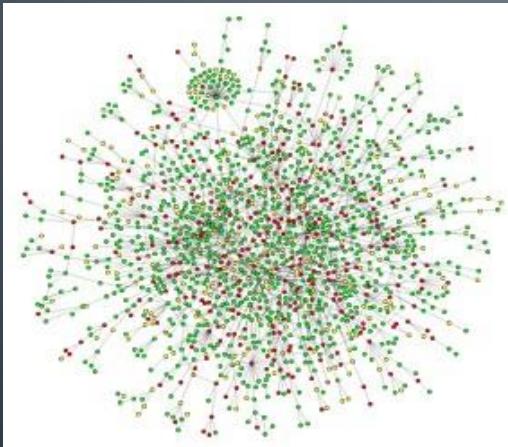
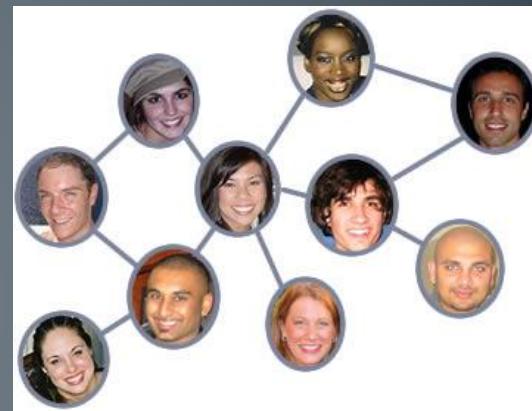
System Properties in Our Class

Size / Type

Internet



Social Network

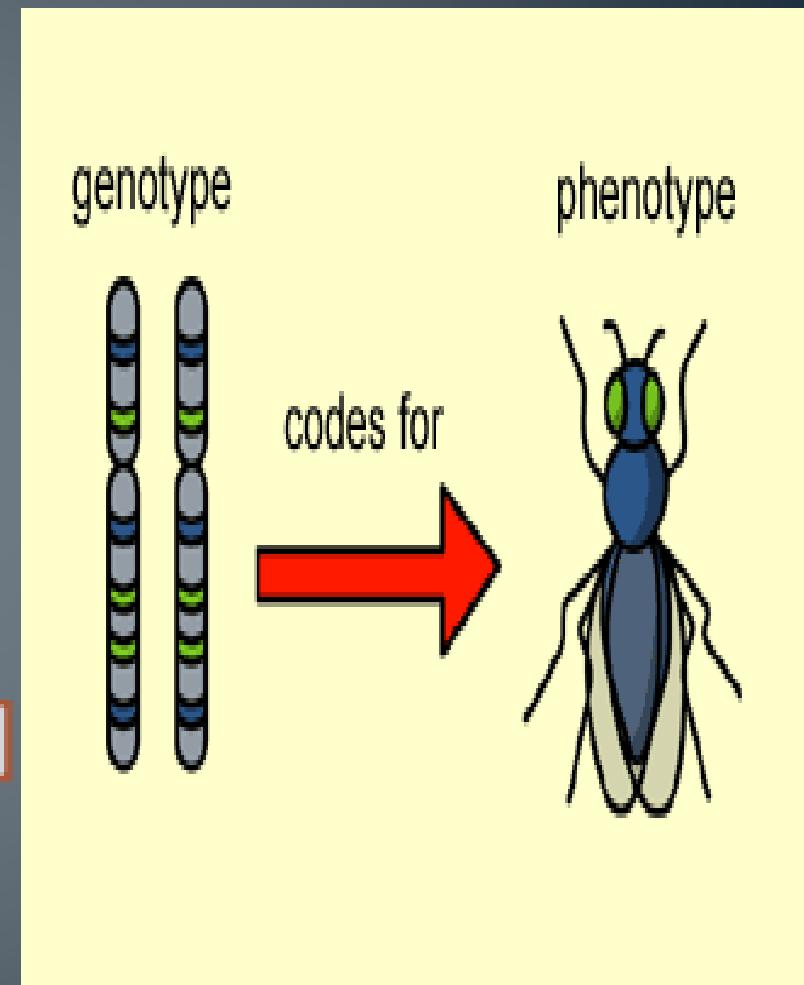
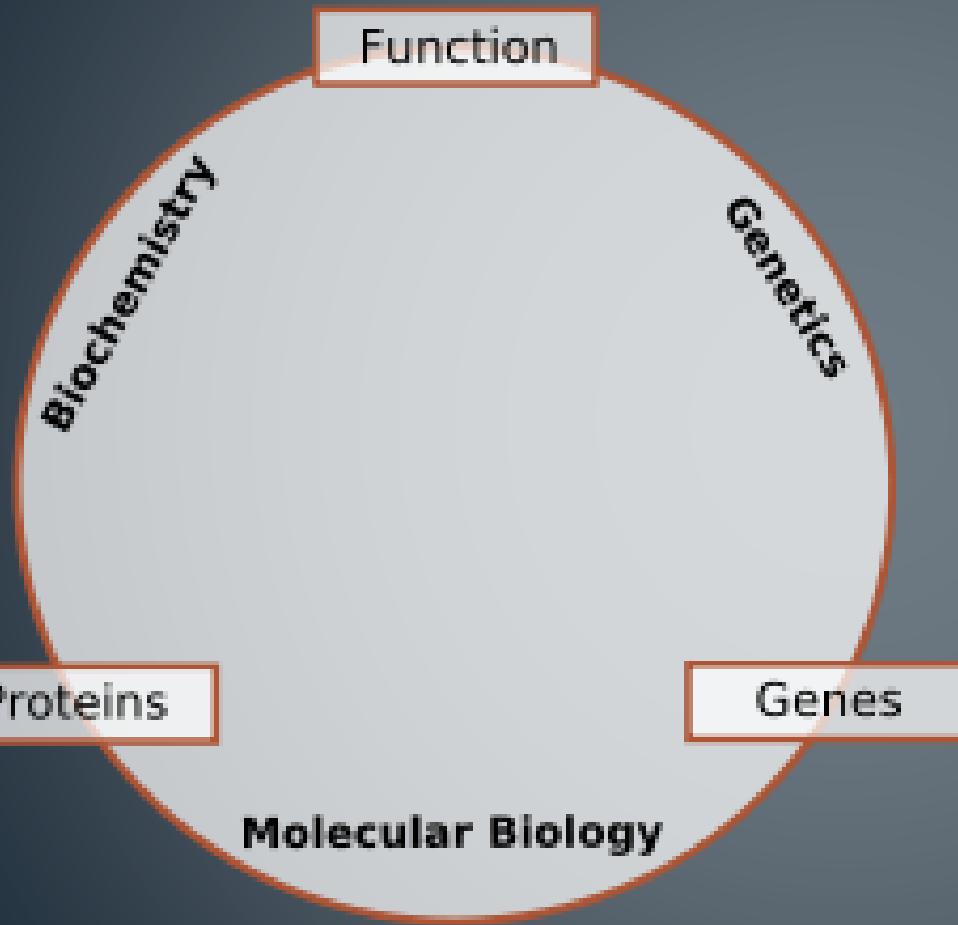


Gene Regulatory Network

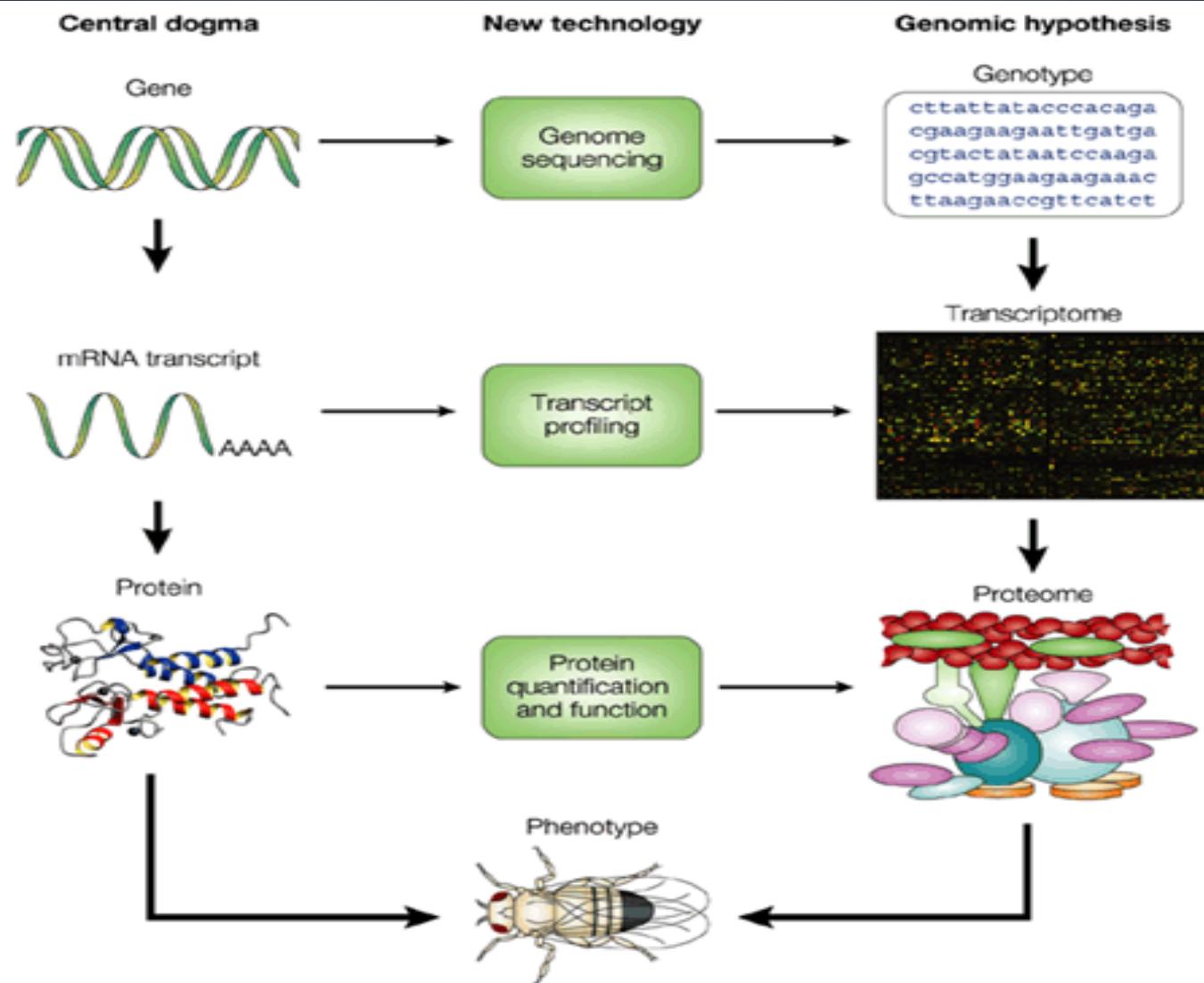


Electronic Circuit

Molecular Biology



Using new technologies and more data



Different Levels

Dynamics

Modification

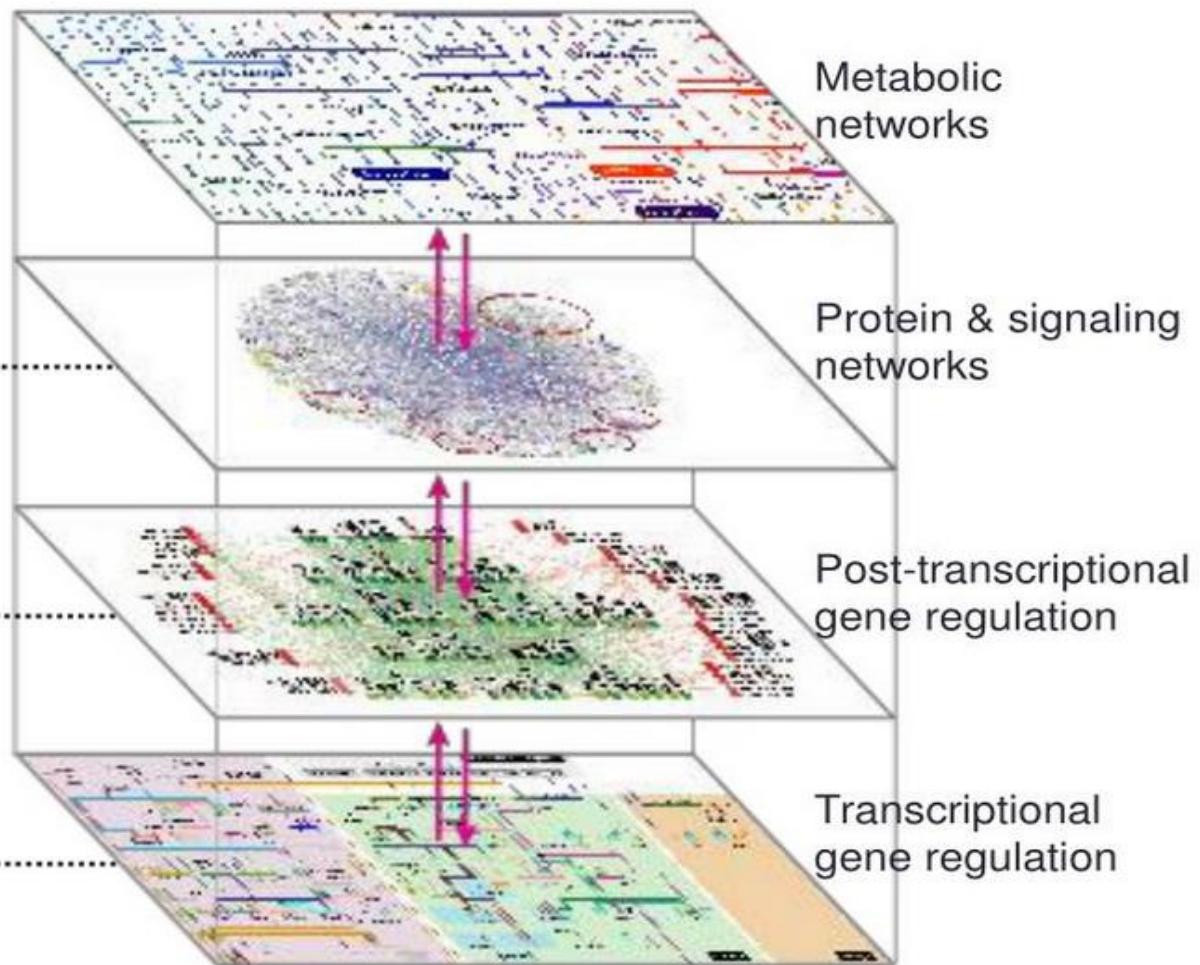
Proteins

Translation

RNA

Transcription

Genome



Systems biology: Different Definitions – Same Concept

- ❖ The study of the mechanisms underlying complex biological processes as **integrated** systems of many interacting components.
- ❖ Systems biology involves **collection** of large sets of experimental data

(Leroy Hood, 1999)

Systems biology: Different Definitions – Same Concept

- Systems biology is the study of an organism, viewed as an **integrated** and interacting network of genes, proteins and biochemical reactions which give rise to life. (*Institute of Systems Biology*)
- Instead of focusing on individual parts, the focus is on a **complete** system made up of different parts **interacting** with each other.
- Based on the philosophy that the whole is **greater** than the sum of the parts.

Systems biology: Different Definitions – Same Concept

- “Systems biology is the study of the **interactions** between the components of a biological system, and how these interactions give rise to the function and behavior of that system” ([Nir Friedman](#))
- The goal is to construct models of **complex** biological systems and diseases ([Trey Ideker](#))

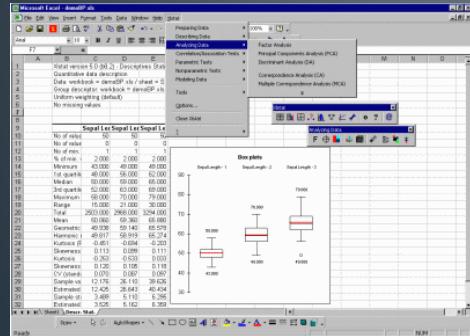
Systems Biology is About Integration

"Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different ... It means changing our philosophy, in the full sense of the term"

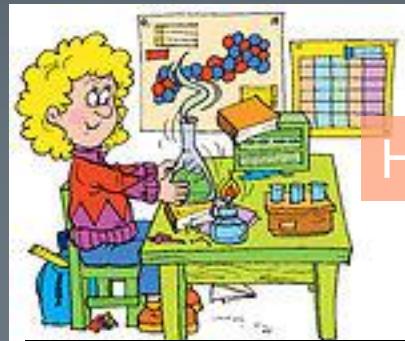
Denis Nobel, "The Music of Life," Oxford University Press, 2006.

Systems biology: How it works? An iterative approach

Data handling

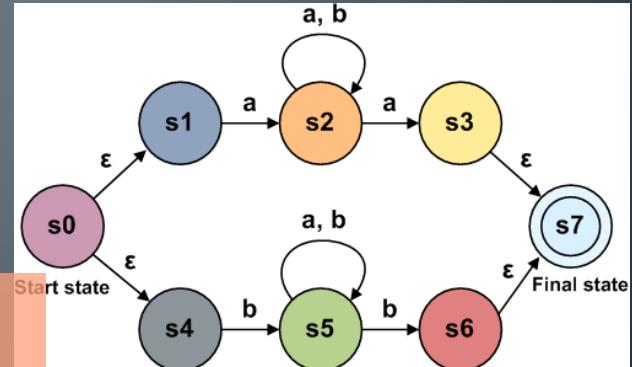


Integration of multiple forms of experiments and knowledge



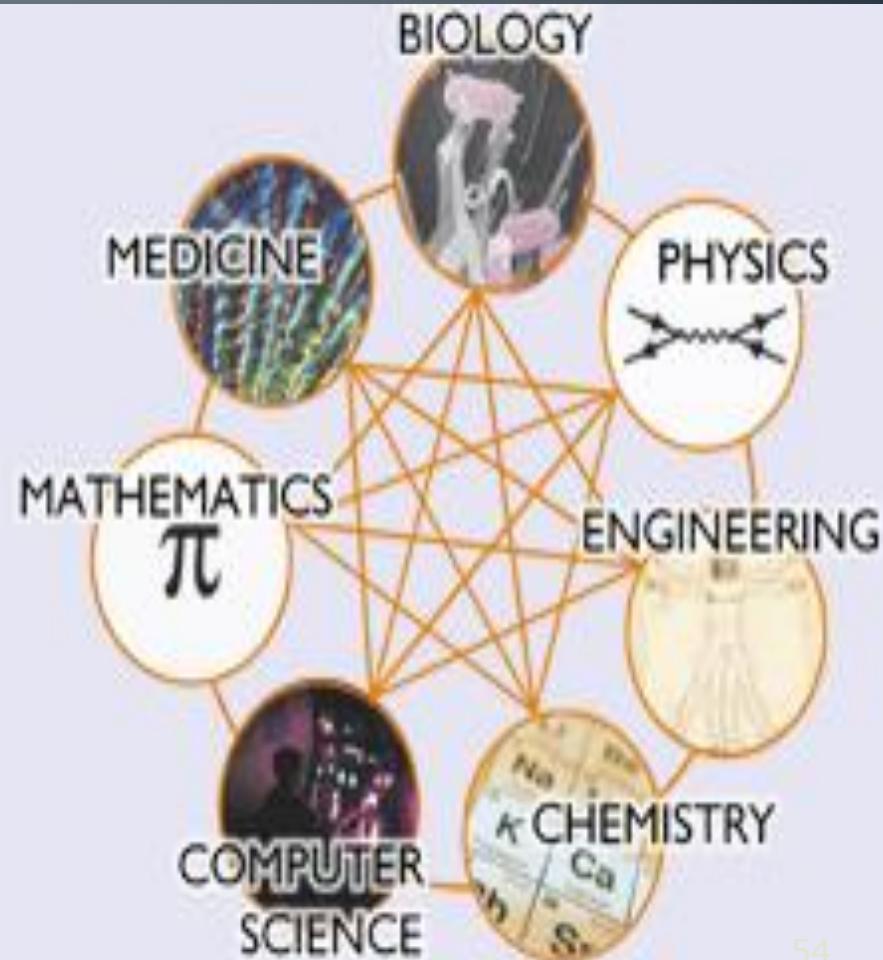
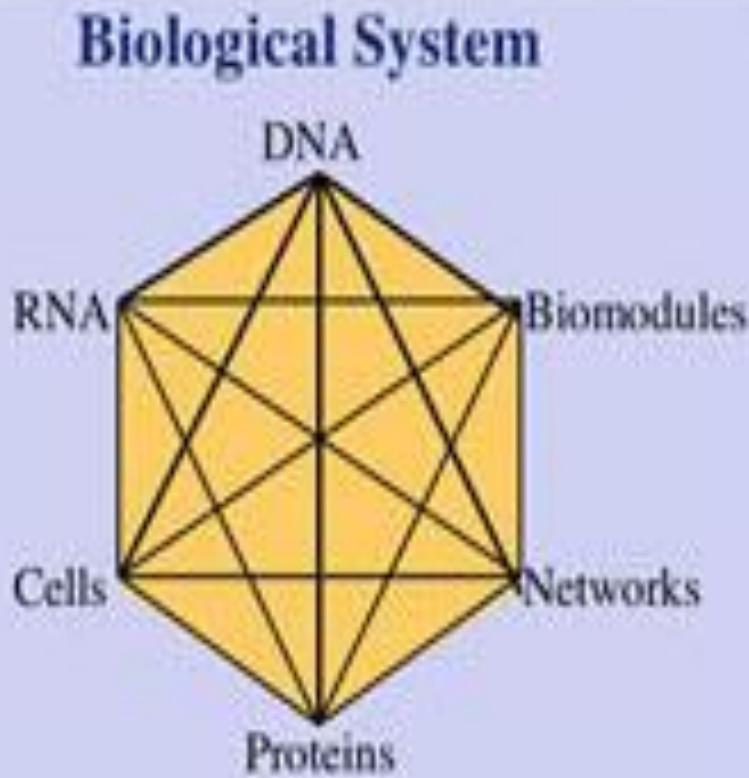
High-throughput assays

Experiments



Mathematical modeling

Systems biology: Definition is an integration of data & approaches



Systems Biology Questions

- ❖ How could we build a useful model (system)?
- ❖ What is the influence inputs have on the system?
- ❖ What do the outputs tell about the system?
- ❖ What are the consequences of differences in the model structures?

Some Goals for Systems Biology approaches

Prediction

- Individual genome sequence can be used to determine chance of developing a particular disease
- Blood fingerprints will allow early detection and stratification of disease types

New prevention strategies

- Better understanding of networks will lead to more effective therapeutic agents and drugs to prevent disease

Personalization

- Apply power of predictive and preventive medicine to individual needs

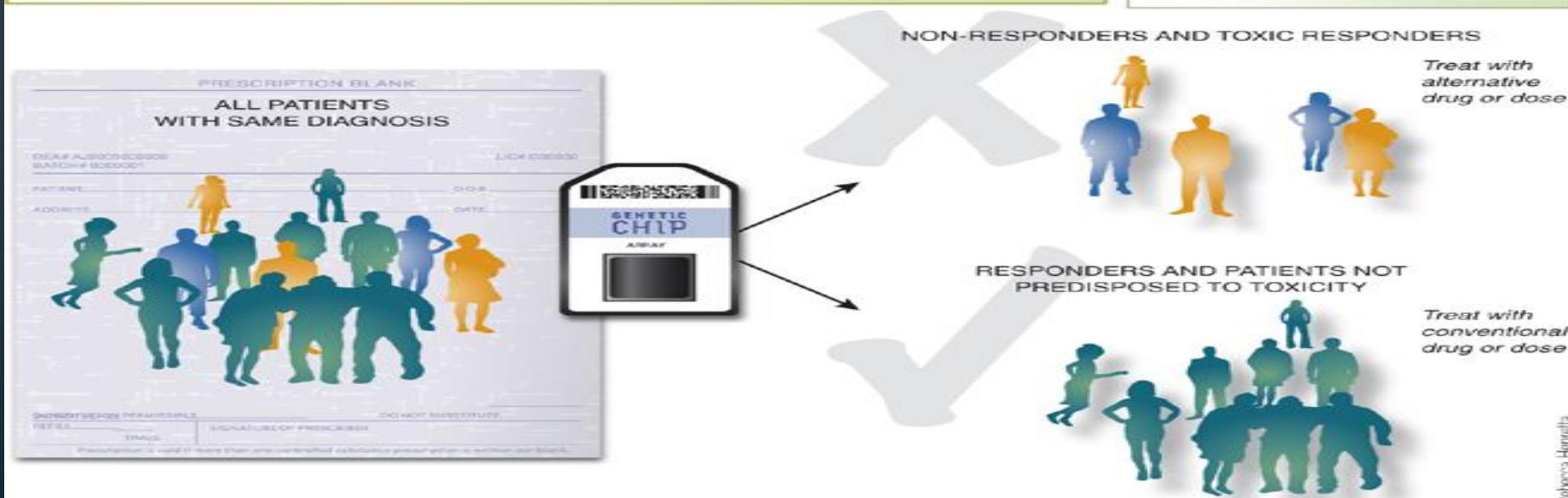
Personalized Medicine, Is it accessible?

Personalized medicine

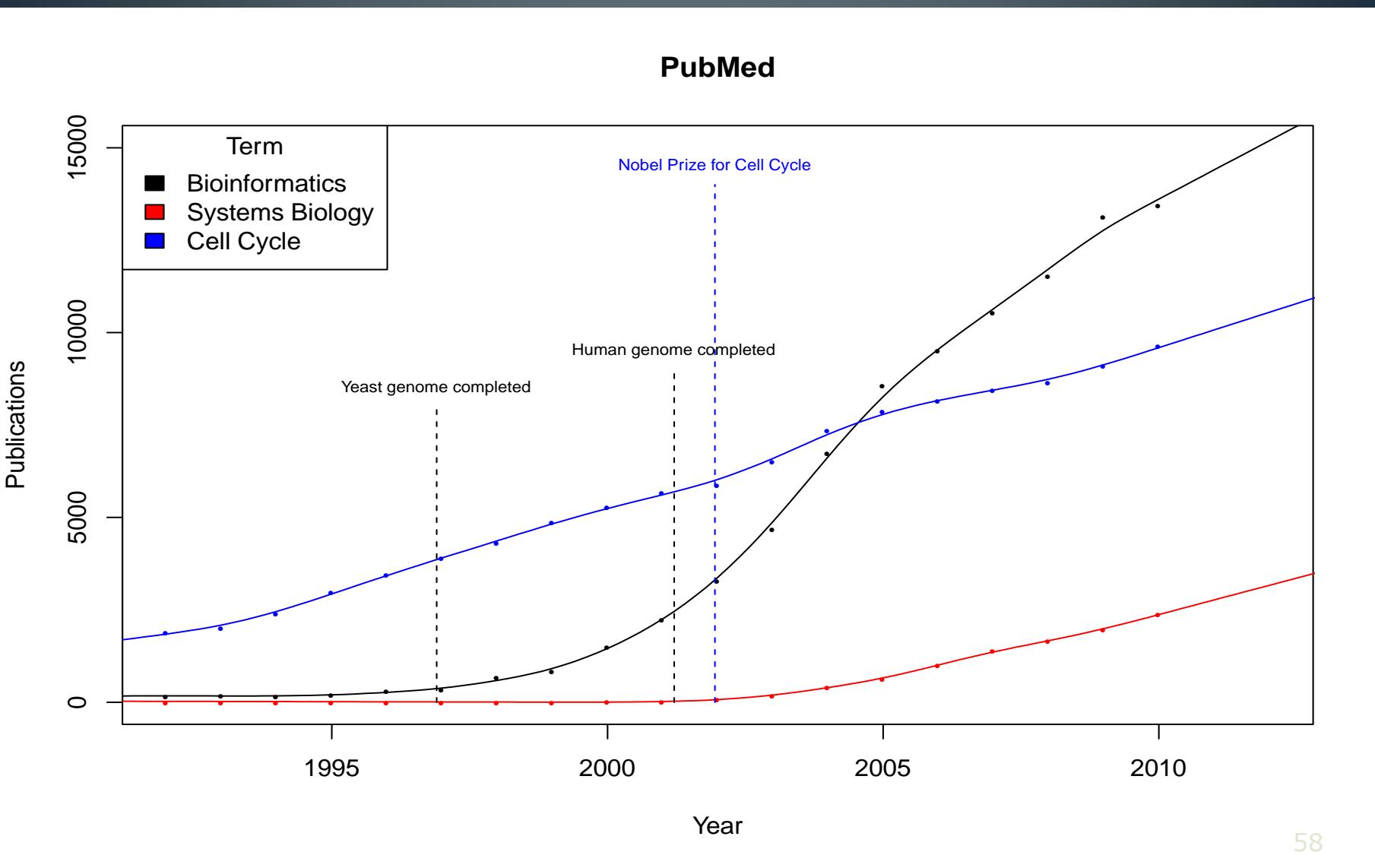


Personalized medicine is the ability to offer:

- The right drug
- To the right disease
- At the right time
- With the right dosage

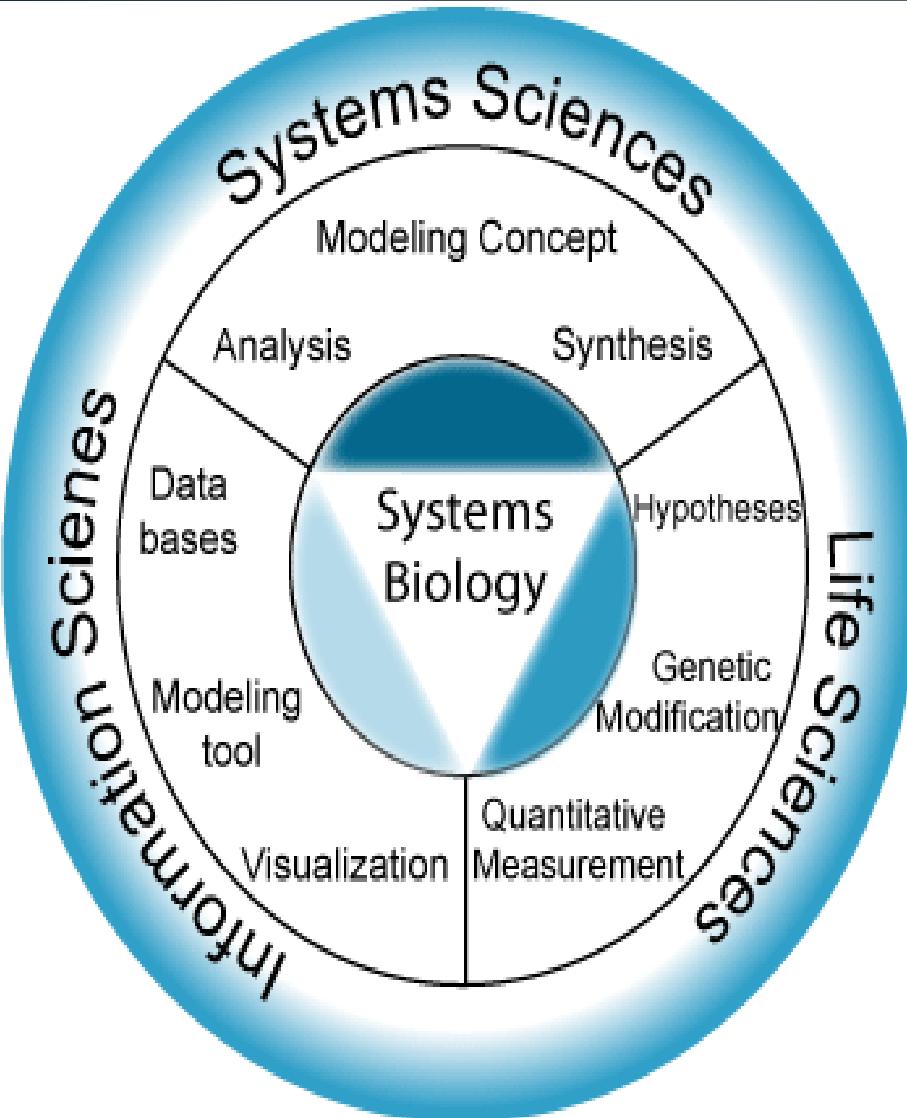


Increasing Interest in Bioinformatics & Systems Biology



Summary

- Systems
 - Thermodynamics (open, closed, isolated, adiabatic)
 - Mathematics (linear, non-linear)
 - Mechanics (static, dynamic)
 - Physics (stable, unstable)
 - Statistics (discrete, continuous)
 - Interdisciplinary (deterministic, probabilistic)
 - Complex theory (simple, complex)
- Systems Biology
 - Molecular Biology vs. Systems Biology
 - Definitions
 - Iterative Approaches, Goals, Application



*T*here are two ways to live your life.
One is as though nothing is a miracle.
The other is as though everything is a miracle.

Albert Einstein (1879–1955)