What Is Systems Biology?

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One View of Systems Biology

Molecular biology is about the structure and function of the fundamental units of cellular biology:

- DNA
- RNA
- Proteins

Systems biology is about how they work together

Goals of Systems Biology

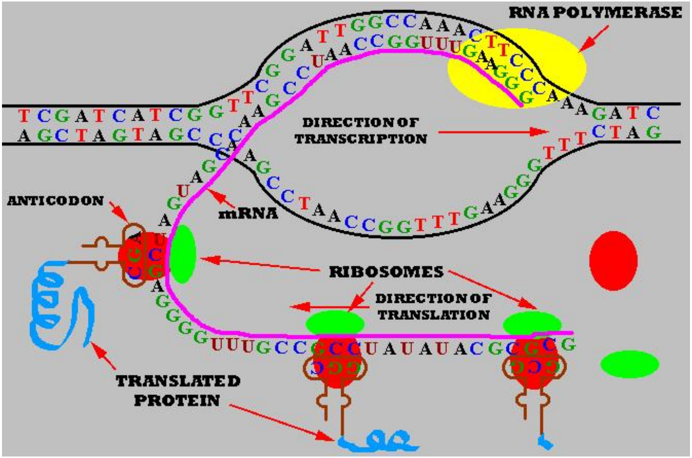
To get a better understanding of cellular mechanisms for

- Differentiation
- Immune response
- Adaptation
- Evolution

Potential benefits

- Earlier, more accurate diagnosis of diseases
- Faster, safer development of new medicines
- Development of artificial organisms

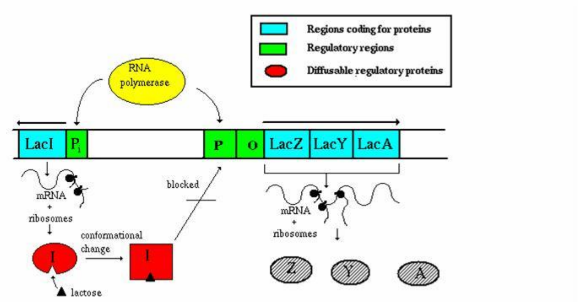
The Central Dogma of Biology



Two Important Questions

1. All cells in the same organism have the same set of genes. How do different cell types arise?
2. Cells of the same type go through a cell cycle, where different proteins are expressed at different times in the cycle. What controls the cell cycle?

The Lac Operon (Jacob & Monod)



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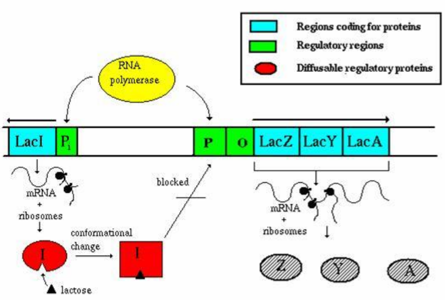
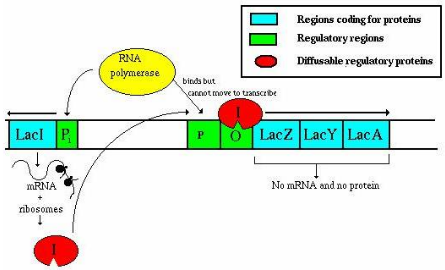




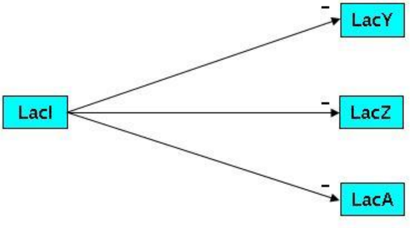
Abstracting the Lac Operon

In the presence of lactose:

Abstracting the Lac Operon

In the presence of lactose:

In the absence of lactose:



Genomic Networks

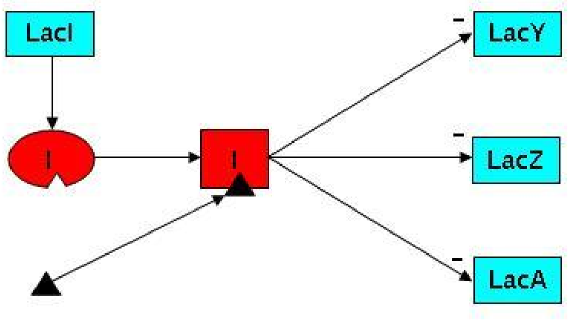
Many other instances of regulatory genes were discovered.
This led to the idea of a network of interacting genes.
A genomic net is a labeled directed graph, where

- Vertices are genes.
- Edges indicate which genes affect other genes.
- Edge labels indicate type of connection: excitatory (+) or inhibitory(-).

This is not a very satisfactory description of the genome:

- It does not show the strengths of the connections.
- In some cases, combinations of genes affect other genes.

Adding Lactose to the Network



Metabolic Networks

Metabolic networks also have vertices representing genes, but they have additional vertices representing other cellular components.
Edges can represent chemical reactions.

But the same objections still apply.

A more precise description of genomic and metabolic networks is needed.

The Classical Approach to Modeling Cellular Metabolism

Consider a system with k cellular components.
Fundamental Assumption: The system is characterized by the vector

$$(x_1, \ldots, x_k)$$

where x_i is the concentration of component i.

Dynamics: The change in $(x_1, \ldots, x_k)$ is governed by a system of ODE's

$$\frac{dx_i}{dt} = f_i(x_1, \ldots, x_k) \text{ for } i = 1, \ldots, k$$

Example

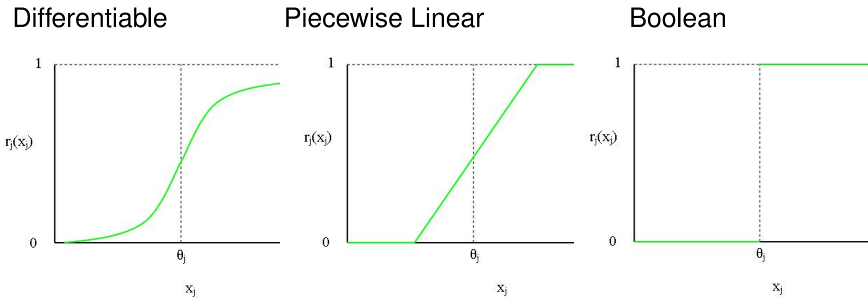
$$\frac{dx_i}{dt} = \kappa_i x_j - \gamma_i x_i$$

where κ_i and γ_i are constants. More generally,

$$\frac{dx_i}{dt} = \kappa_i r_j(x_j) - \gamma_i x_i$$

where r_j is the regulatory function associated with component j.

Three Kinds of Regulatory Functions



θ_j is the threshold of activation.

Arguments in Favor of Boolean Regulatory Functions

- A gene is either “on" (active) or “off" (inactive).
- The transition between inactive and active is rapid.
- More complex functions can overspecify the regulatory function.

Levels of Abstraction

Simplicity ↓ | Accuracy ↑

Continuous states

Discrete states

Boolean states

But the top level is not the most accurate model possible.

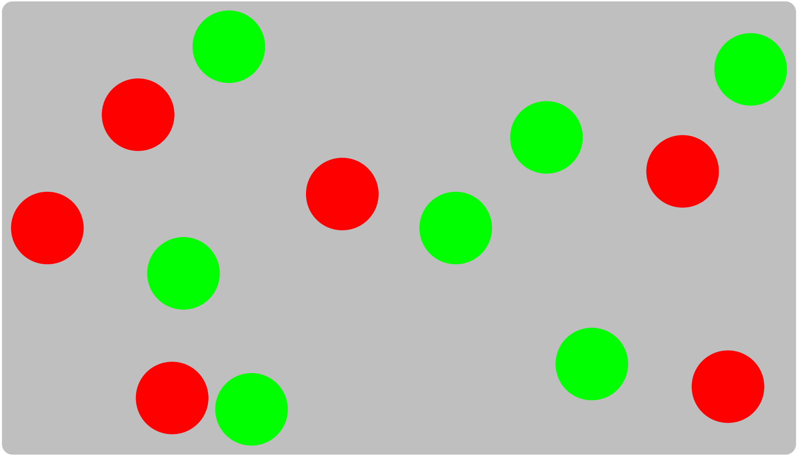
A Newer Approach to Modeling Complex Systems

An Individual-Based Model consists of populations of individuals.

It evolves via interactions among the individuals.

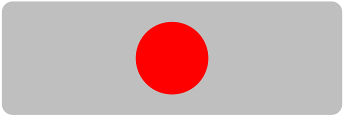
An Example

Two species: Predator and Prey.
Individuals move freely and rapidly in an enclosed space.



Interactions

Death of Predator



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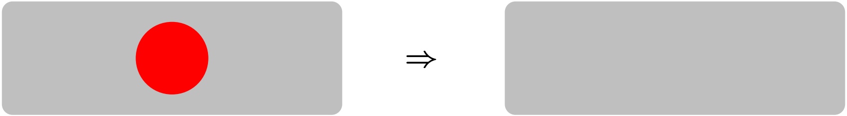

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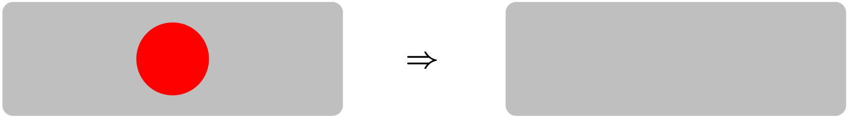
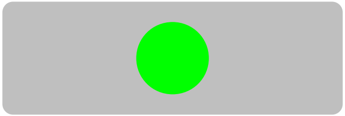


Birth of Prey



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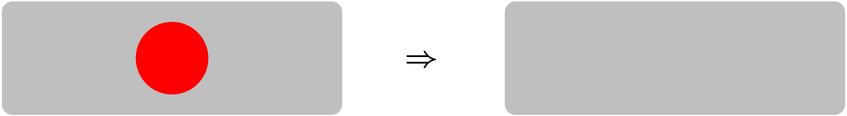

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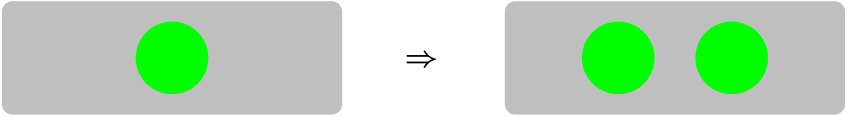

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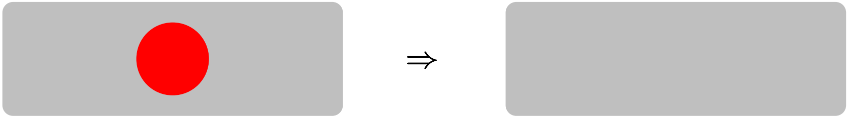

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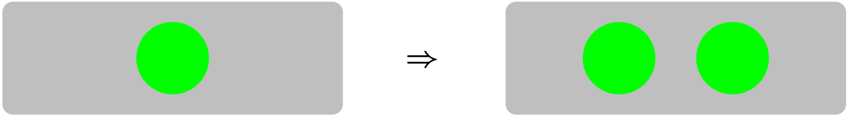
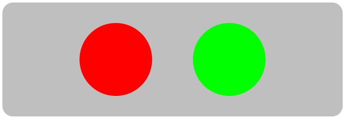
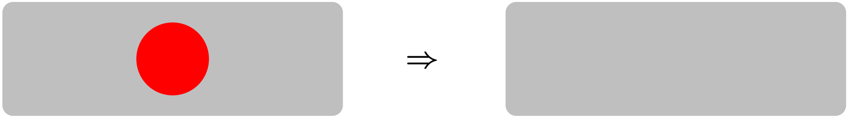


Predation



Interactions

Death of Predator



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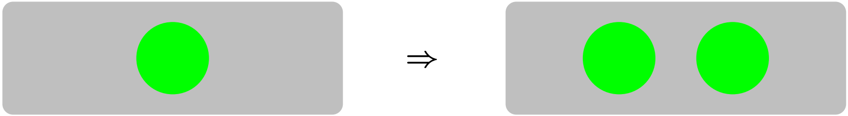

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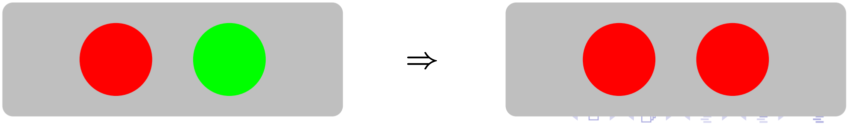
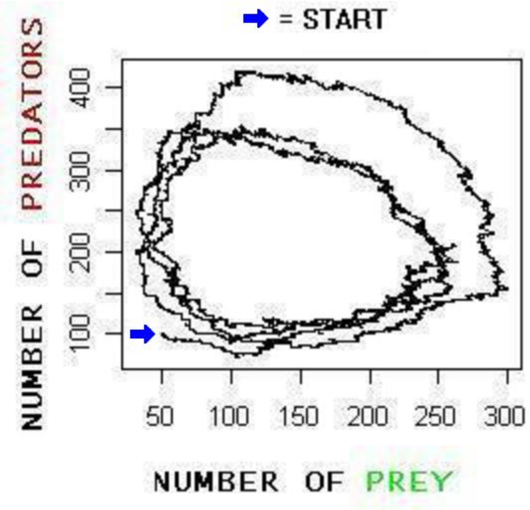
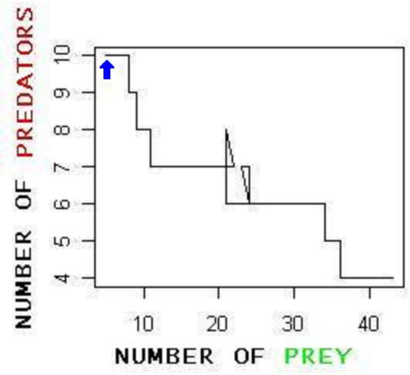


Typical Behavior

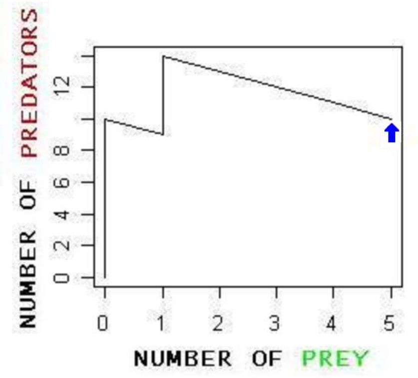


Extinction Is Inevitable

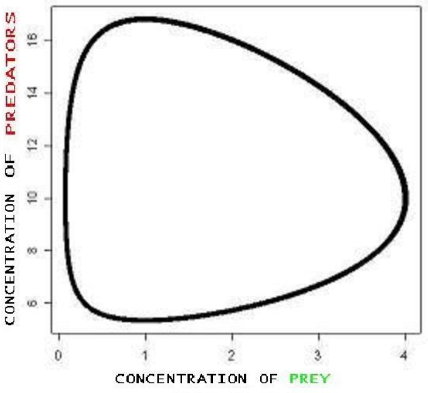
Extinction of Predator



Extinction of Both



Continuous Approximation of Large Populations (A State-Variable Model)



Lotka-Volterra Model

$$\frac{dx}{dt} = ax - bxy$$
$$\frac{dy}{dt} = -cy + bxy$$

Some Recent Results

A logical characterization of IBMs that can be approximated by SVMs.

Examples

- Models of chemical kinetics
- Lattice models of coupled chemical reactions
- Trophic webs
- Patch-occupancy models
- Graph growth models with bounded degree

Recent Results Continued

A logical characterization of IBMs that can not be approximated by SVMs.

Examples

- Chemical reaction systems controlled by membranes
- Transcription of long polymers