

Introduction to Systems Biology

COMP 572 (BIOS 572 / BIOE 564) - Fall 2011

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Systems Biology

- ❖ Systems biology is an approach by which a system of interacting entities is analyzed as a whole rather than by analyzing its individual constituent entities separately
- ❖ Systems biology is not new: in 1934, the Austrian biologist Ludwig von Bertalanffy applied general systems theory to biology as well as other fields

Systems Biology

- ❖ To fully understand the functioning of cellular processes, whole cells, organs, and even organisms, it is not enough to simply assign functions to individual genes, proteins, and other cellular components.
- ❖ We need to analyze the organization and control of the system in an integrated way by looking at the dynamic networks of genes and proteins, and their interactions with each other.
- ❖ These interacting pathways are complex dynamic systems, and often behave in a nonlinear and adaptive way.

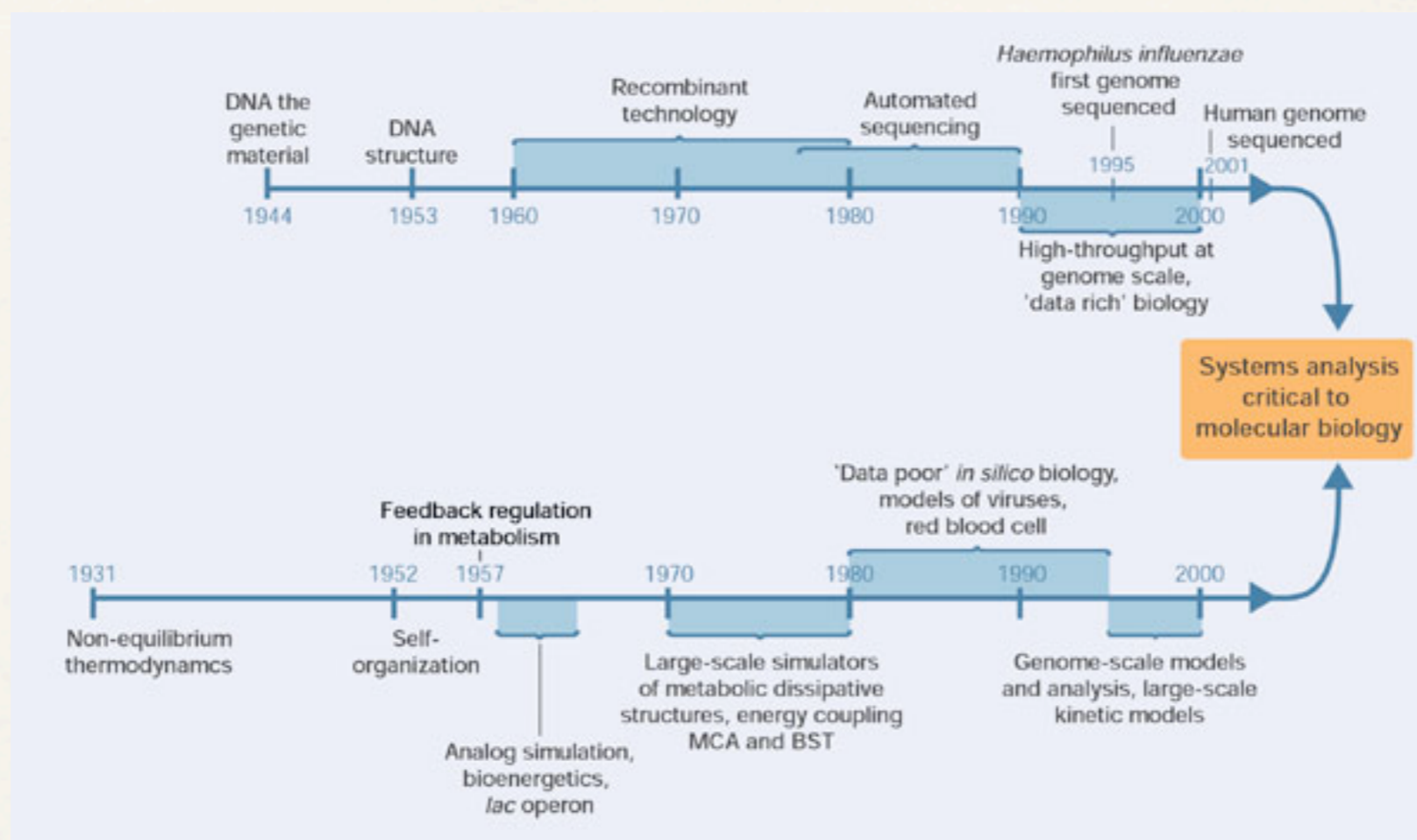
Systems Biology

- ❖ **Nonlinearity** means, for example, that doubling a stimulus (the input) does not necessarily double the response, and may even cause a qualitatively different response.
- ❖ **Adaptive systems** can modify themselves to respond in a more appropriate way in the light of previous stimuli.

Systems Biology

- ❖ The general goal of theoretical systems biology is to develop computer models that predict the properties of the large, adaptive, interconnected networks that are found in living things.

Converging Towards Systems Biology

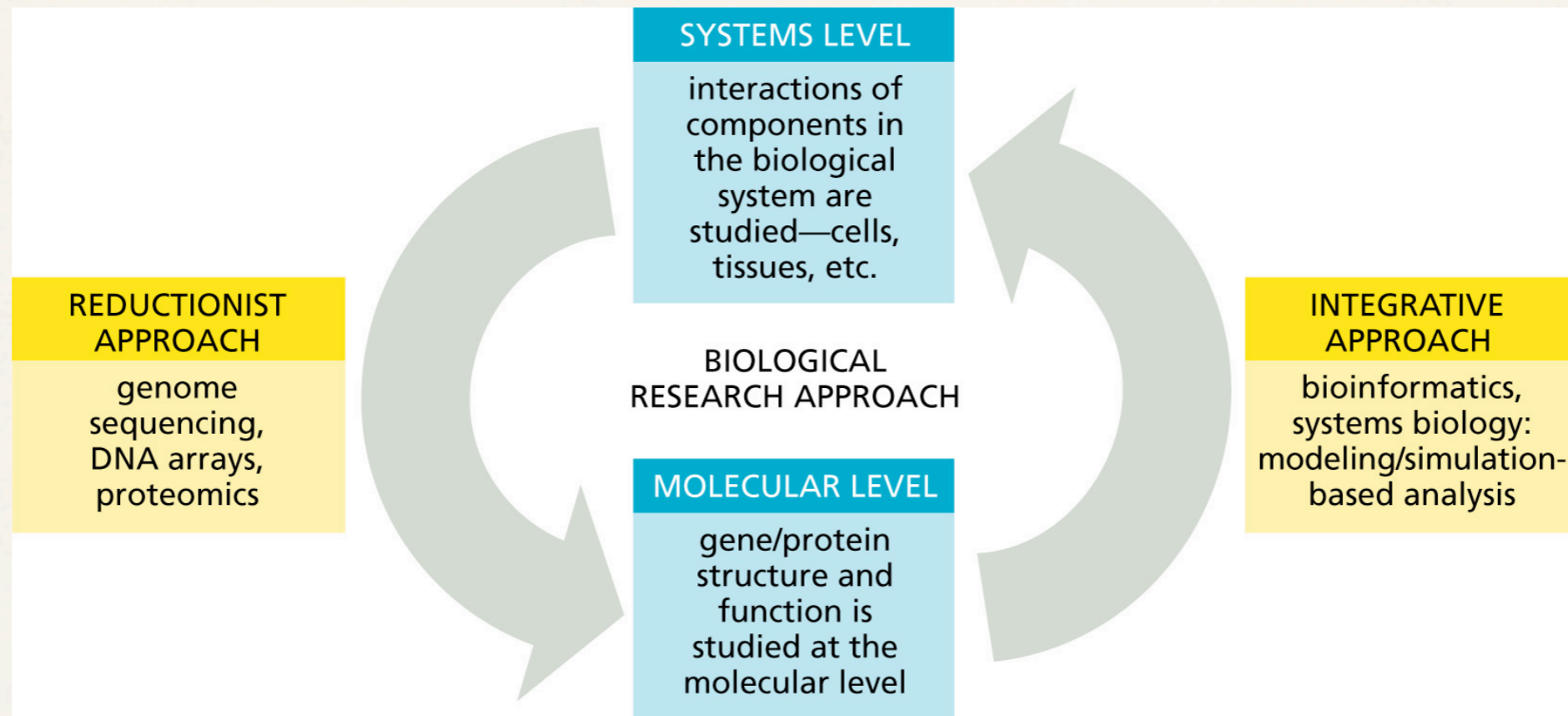


Two lines of inquiry led from the approximate onset of molecular biological thinking to present-day systems biology.

The top timeline represents the root of systems biology in mainstream molecular biology, with its emphasis on individual macromolecules. Scaled-up versions of this effort then induced systems biology as a way to look at all those molecules simultaneously, and consider their interactions. The lower timeline represents the lesser-known effort that constantly focused on the formal analysis of new functional states that arise when multiple molecules interact simultaneously.

Source: H.V. Westerhoff and B.O. Palsson, "The evolution of molecular biology into systems biology." Nature Biotechnology, 22(10): 1249-1252, 2004.

A System Is More Than the Sum of Its Parts



The description of a fully functional system must take into account the spatial organization of elements, their interactions, and their response to external stimuli, including those processes that control and stabilize the system.

A Biological System Is a Living Network

- ❖ The components (e.g., proteins) of the system are connected by interactions along which signals pass and have an effect on the function of the whole network.
- ❖ These networks too have inbuilt controls that activate or terminate particular signals.
- ❖ The biological system can also be perturbed by outside interference, ranging from the food we eat to therapeutic drugs.
- ❖ *Once we have a quantitative mathematical model that can be manipulated, and understand the normal functioning of the system, we can see what the effects of various perturbations are in silico.*



Executable cell biology

Jasmin Fisher^{1,2} & Thomas A Henzinger^{2,3}

Computational modeling of biological systems is becoming increasingly important in efforts to better understand complex biological behaviors. In this review, we distinguish between two types of biological models—mathematical and computational—which differ in their representations of biological phenomena. We call the approach of constructing computational models of biological systems ‘executable biology’, as it focuses on the design of executable computer algorithms that mimic biological phenomena. We survey the main modeling efforts in this direction, emphasize the applicability and benefits of executable models in biological research and highlight some of the challenges that executable biology poses for biology and computer science. We claim that for executable biology to reach its full potential as a mainstream biological technique, formal and algorithmic approaches must be integrated into biological research. This will drive biology toward a more precise engineering discipline.

Over the past decade, biological research has reached a point where the accumulated data exceed the human capacity to analyze it. The vast information generated by DNA microarrays, genome sequencers and other large-scale technologies requires computer power for storage, searching and integration into a coherent picture. Systems biology, which combines biology, chemistry, physics, mathematics, electrical engineering and computer science, among other disciplines, aims to integrate the data concerning individual genes and proteins and to investigate the behavior and relationships of various elements in a biological system to explain how it functions^{1–3}.

At the core of systems biology lies the construction of models describing biological systems. Over the years, biologists have used diagrammatic models to summarize a mechanistic understanding of a set of observations. Despite the many benefits of such models, as well as their simplicity, they give a rather static picture of cellular processes. The growing need to translate these models into more dynamic forms that can capture time-dependent processes, together with increases in the models’ scale and complexity, has prompted biologists to harness computers to build and analyze ever-larger models. The long-term vision is that large-scale models should revolutionize biology and medicine and enable design of new therapies.

We distinguish between two types of models: (i) those that use computer power to analyze mathematical relationships between quantities and (ii) a new variety, resembling a computer program, which is central to an emerging field that we call executable biology. Here, we explain the differences between these two approaches, explore some recent executable biology models and emphasize some challenges facing this new field.

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Published online 7 November 2007; doi:10.1038/nbt1356

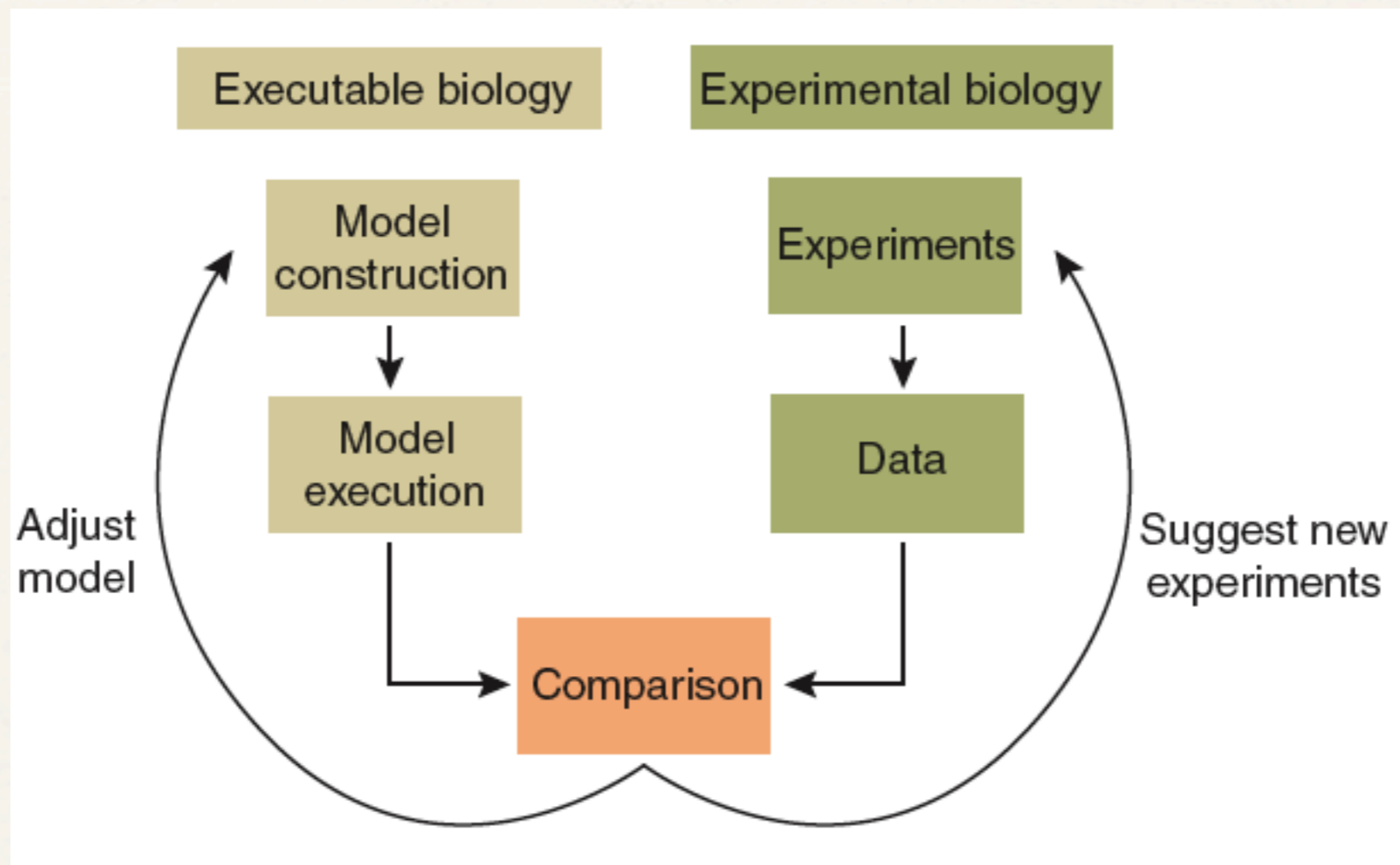
Mathematical versus computational models

Mathematical models, such as those based on differential equations, can represent many situations in the natural sciences and engineering. Although they were developed before computation became feasible on a grand scale, they are now profiting from our increasing computational ability.

In contrast, computational models present a recipe—an algorithm—for an abstract execution engine to mimic a design or natural phenomenon. Such models are ideally suited to representing complicated chains of events. They have been used recently to model biochemical processes^{4–7}, thymocyte development and cell fate determination during *Caenorhabditis elegans* development^{8–14}.

Mathematical and computational models (Box 1) differ in the languages in which they are specified. Whereas the former are specified in mathematics, typically equations, the latter are specified by computer programs, often very high-level code written in a modeling language such as Statecharts¹⁵ or Reactive Modules¹⁶. Consequently, the two types of models yield different kinds of insights. The differences are exemplified by comparing different modeling approaches to cell fate determination during *C. elegans* vulval development^{11,13,17}, which concentrate on different aspects and consequently provide different kinds of insights into the same system. In contrast with a mathematical model¹⁷ that predicts rates of intercellular reactions and suggests a time frame in which cell fate determination is established, the computational models^{11,13} predict the timing and order of signaling events as well as new modes of interaction between the epidermal growth factor receptor and LIN-12/Notch signaling pathways.

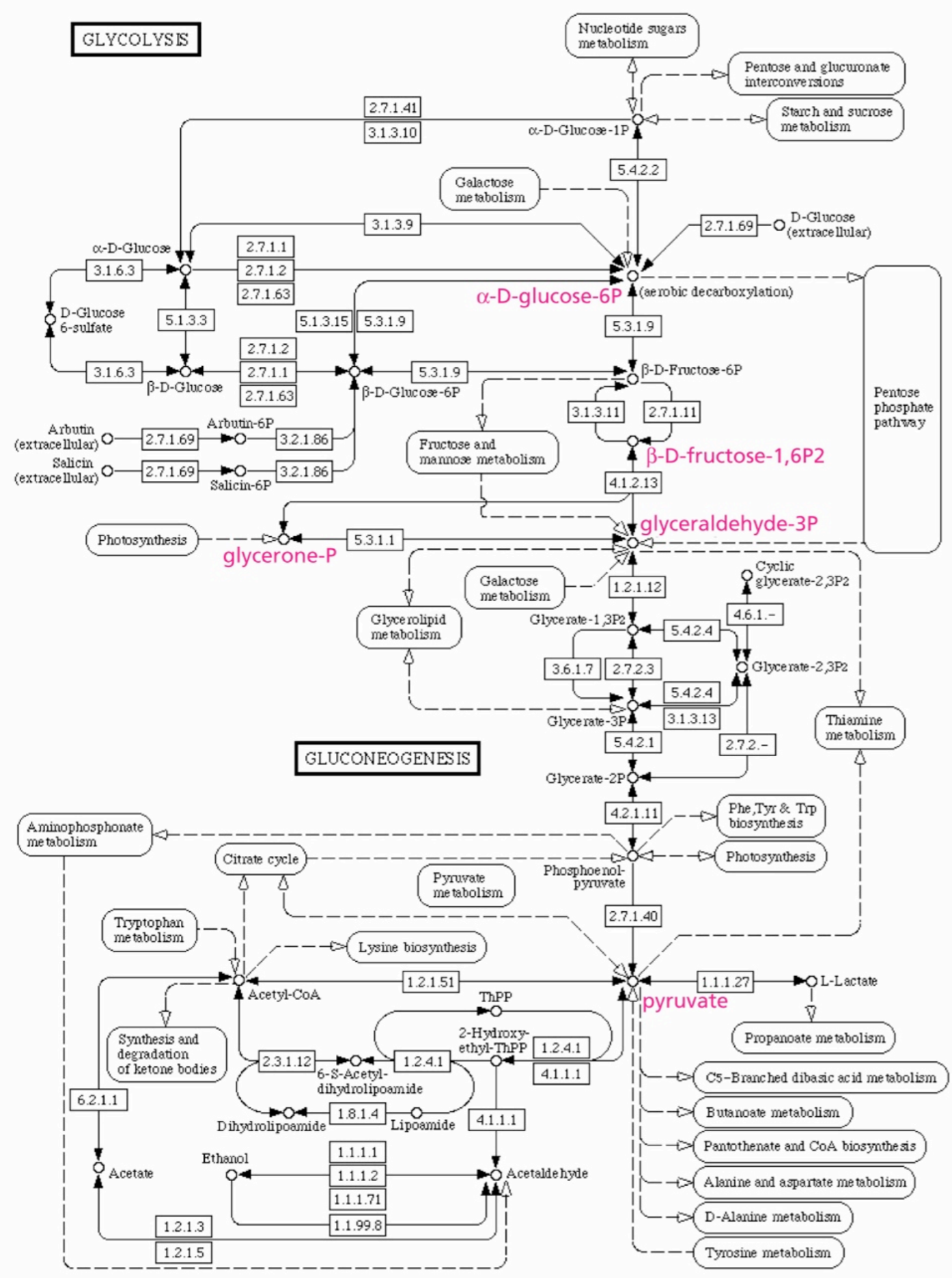
Mathematical models can be simulated and possibly solved. The basic entity of a mathematical model is the transfer function, which relates different numerical quantities to each other. A transfer function may be specified, for example, by a differential equation that relates an input to an output quantity. Complex mathematical models are constructed through the composition of transfer functions, yielding a network of interdependent quantities. If the constraints for individual transfer functions are relatively simple (e.g., linear differential equations), then mathematical models are amenable to mathematical



Source: J. Fisher and T.A. Henzinger, "Executable cell biology."
Nature Biotechnology, 25(11): 1239-1249, 2004.

The components and interactions in the **glycolysis pathway**, as obtained from the **KEGG** database

Glycolysis is the sequence of reactions that converts glucose into pyruvate, with the production of a relatively small amount of ATP, which is a source of energy for many cellular functions.



Objects	Arrows
gene product, mostly protein but including RNA	molecular interaction or relation
other molecule, mostly chemical compound	link to another map
another map	pointer used in legend
	missing interaction (eg., by mutation)

Protein-protein interactions		Gene expression relations	
+p	phosphorylation	expression	
-p	dephosphorylation	repression	
+u	ubiquitination	expression	
+g	glycosylation	indirect effect	
+m	methylation		
activation		Enzyme-enzyme relations	
inhibition		two successive reaction steps	
indirect effect			
state change			
binding / association			
dissociation			
complex			

A System Model Is More Than a Network

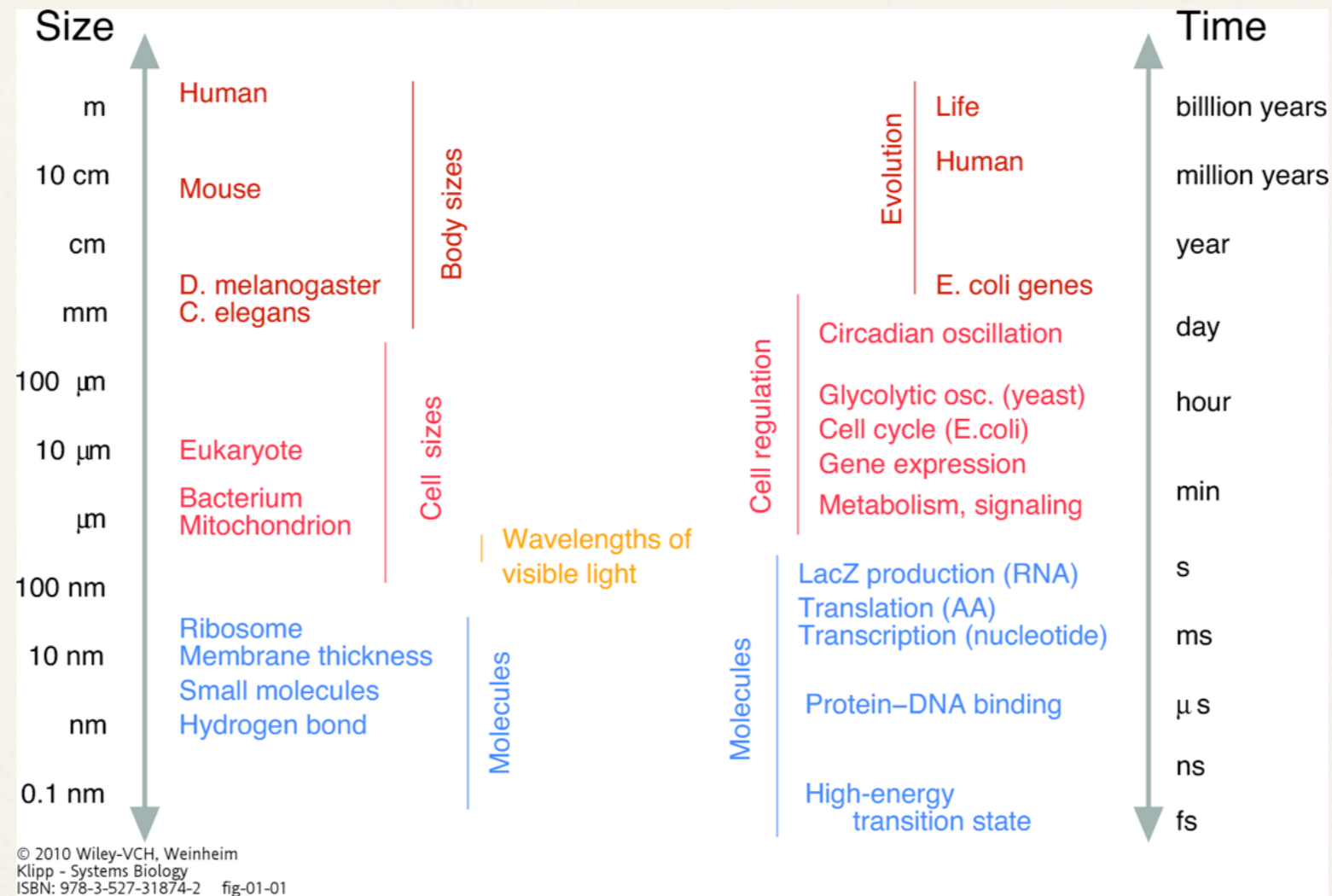
- ❖ A network structure (topology) is first defined, typically using information from databases and / or literature.
- ❖ To complete the network definition the interactions between components must be defined.
- ❖ Determine which components interact with each other, as well as the kinetics of these interactions

Three Approaches to System Modeling

- ❖ Bottom-up: Construct a network and predict its behavior starting with a collection of experimental data
- ❖ Top-down: Starts from observed behavior and then fills in the components and interactions required to generate these observations by iterative experimental results and simulations
- ❖ Middle-out: Starts at any point for which data are available, as long as it is supported by a hypothesis, and then expand either up or down in terms of both resolution and coverage

Modeling in Biology

Biology in Time and Space



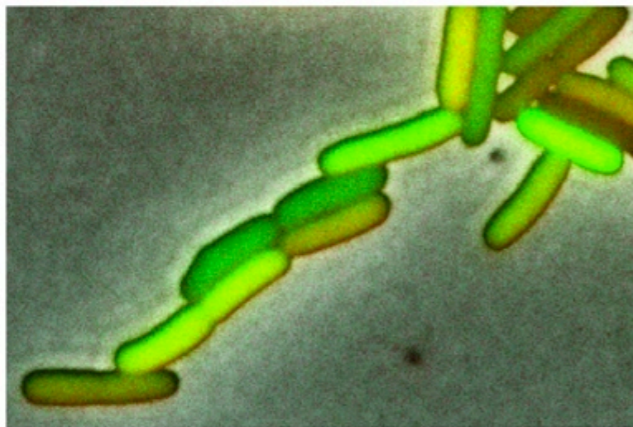
A description of biological entities and their properties encompasses different levels of organization and different time scales.

Models and Modeling

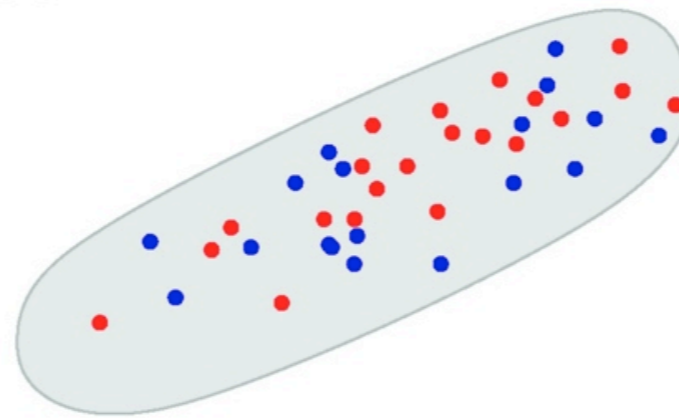
- ❖ A model is an abstract representation of objects or processes that explains features of these objects or processes.

Models and Modeling

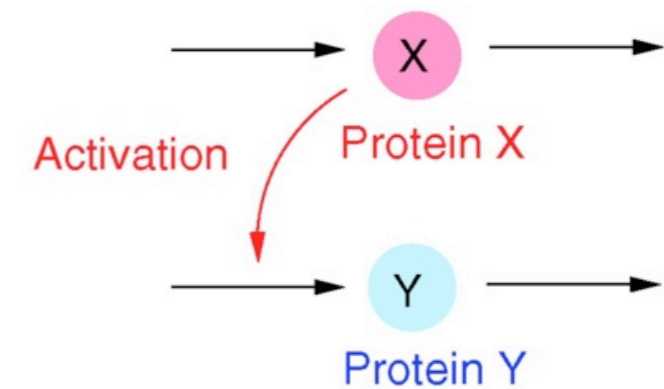
(a) Biological system



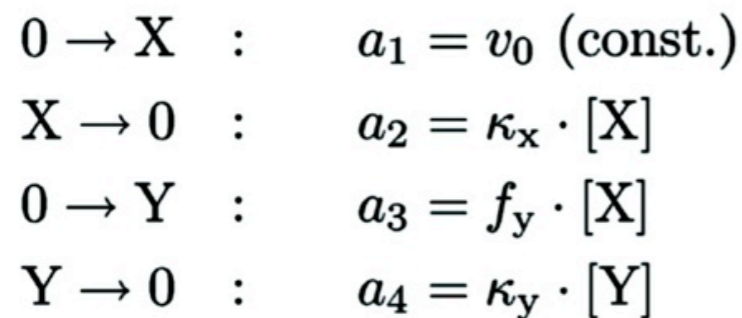
(b) Mental model



(c) Model scheme



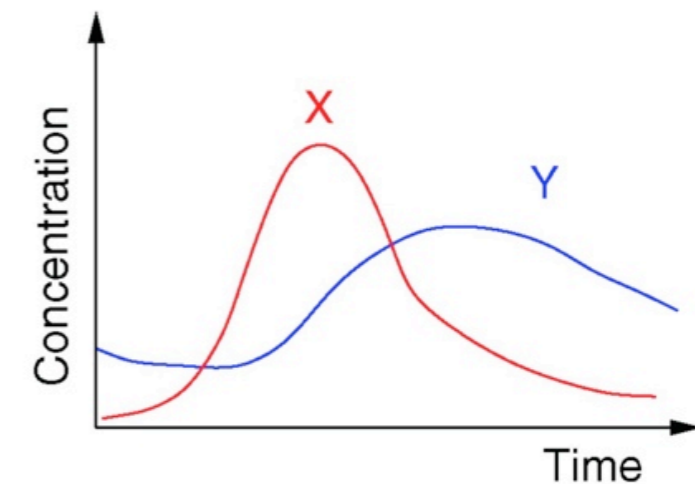
(d) Process model



(e) Dynamical model

$$\begin{aligned}
 dx/dt &= v_0 - \kappa_x x \\
 dy/dt &= f_y x - \kappa_y y \\
 x(0) &= x_0 \\
 y(0) &= y_0
 \end{aligned}$$

(f) Quantitative results



Models and Modeling

- ❖ Mathematical modeling and computer simulations can help us understand the internal nature and dynamics of processes and to arrive at predictions about their future development and the effect of interactions with the environment.

Models and Modeling

- ❖ Modeling is a subjective and selective procedure.
- ❖ A model represents only specific aspects of reality that are relevant to the question under consideration.
- ❖ How detailed a model is does not make it right or wrong; it just determines whether the model is appropriate to the problem to be solved.
- ❖ In fact...

Models and Modeling

“Essentially, all models are wrong, but some are useful.”

- George E.P. Box

Models and Modeling

- ❖ Modeling drives conceptual clarification.
- ❖ Modeling highlights gaps in knowledge or understanding.
- ❖ Modeling can assist experimentation.
- ❖ Model results can often be presented in precise mathematical terms that allow for generalization.
- ❖ Modeling allows for making well-founded and testable predictions.

Basic Notions for Computational Models

- ❖ Model scope
 - ❖ Models consist of mathematical elements (variables, parameters, constants)
 - ❖ A model describe certain aspects of the system, and simplifies / neglects all others

Basic Notions for Computational Models

- ❖ Model statements
 - ❖ Statements and equations describe facts about the model elements
 - ❖ Examples include ODEs, inequalities, probabilistic statements, etc.

Basic Notions for Computational Models

- ❖ System state

- ❖ The state of a system is a snapshot of the system at a given time.
- ❖ The state is described by the set of variables that must be kept track of in a model.

Basic Notions for Computational Models

- ❖ Variables, parameters, and constants
 - ❖ A constant is a quantity with a fixed value.
 - ❖ Parameters are quantities that have a given value.
 - ❖ Variables are quantities with a changeable value for which the model establishes relations.

Basic Notions for Computational Models

- ❖ Model behavior

- ❖ Two fundamental factors that determine the behavior of a system are
 - ❖ influences from the environment (input), and
 - ❖ processes within the system.
- ❖ Measurements of the system output often do not suffice to choose between alternative models, as different system structures may still produce similar system behavior.

Basic Notions for Computational Models

- ❖ Model classification

- ❖ A *structural* or *qualitative* model specifies the interactions among model elements. A *quantitative* model assigns values to the elements and to their interactions.
- ❖ In a *deterministic* model, the system evolution through all following states can be predicted from the knowledge of the current state. *Stochastic* descriptions give instead a probability distribution for the successive states.

Basic Notions for Computational Models

- ❖ Model classification

- ❖ The nature of values that time, state, or space may assume distinguishes a *discrete* model (where values are taken from a discrete set) from a *continuous* model (where values belong to a continuum).

Basic Notions for Computational Models

- ❖ Model classification

- ❖ *Reversible* processes can proceed in a forward and backward direction.
- ❖ *Irreversibility* means that only one direction is possible.
- ❖ *Periodicity* indicates that the system assumes a series of states in the time interval $\{t, t+\Delta t\}$ and again in the time interval $\{t+i\Delta t, t+(i+1)\Delta t\}$ for $i=1, 2, \dots$

Basic Notions for Computational Models

- ❖ Steady states

- ❖ *Steady* (or, stationary) states are determined by the fact that the values of all state variables remain constant in time.
- ❖ The asymptotic behavior of dynamic systems, that is, the behavior after a sufficiently long time, is often stationary.
- ❖ Other types of asymptotic behavior are *oscillatory* or *chaotic* regimes.