Complex Biological Systems: When are Simple Models Good Enough?

Winfried Just
Department of Mathematics
Ohio University

Madison, Wisconsin, August 4, 2012

What are we talking about?

What are we talking about?

Quote from the session description:

"Systems biology is the study of the systems-level understanding and analysis of the biology, behavior and **interactions** between the biology and behavior at all **levels of biological organization** from the small scales of molecules and cells up to the large scales of populations and communities. . . . The mathematics involved in modeling **complex systems** is wide and varied . . . "

What are we talking about?

Quote from the session description:

"Systems biology is the study of the systems-level understanding and analysis of the biology, behavior and **interactions** between the biology and behavior at all **levels of biological organization** from the small scales of molecules and cells up to the large scales of populations and communities. ... The mathematics involved in modeling **complex systems** is wide and varied ..."

Let's start from the beginning:

What are we talking about?

Quote from the session description:

"Systems biology is the study of the systems-level understanding and analysis of the biology, behavior and **interactions** between the biology and behavior at all **levels of biological organization** from the small scales of molecules and cells up to the large scales of populations and communities. ... The mathematics involved in modeling **complex systems** is wide and varied ..."

Let's start from the beginning:

What are levels of biological organization?

What are we talking about?

Quote from the session description:

"Systems biology is the study of the systems-level understanding and analysis of the biology, behavior and **interactions** between the biology and behavior at all **levels of biological organization** from the small scales of molecules and cells up to the large scales of populations and communities. ... The mathematics involved in modeling **complex systems** is wide and varied ..."

Let's start from the beginning:

What are levels of biological organization?
What is a complex (biological) system?

What are we talking about?

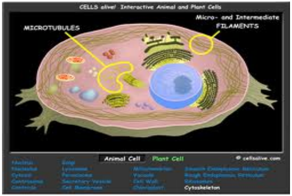
Quote from the session description:

"Systems biology is the study of the systems-level understanding and analysis of the biology, behavior and **interactions** between the biology and behavior at all **levels of biological organization** from the small scales of molecules and cells up to the large scales of populations and communities. ... The mathematics involved in modeling **complex systems** is wide and varied ..."

Let's start from the beginning:

What are levels of biological organization?
What is a complex (biological) system?
What do we want to know about complex (biological) systems?

Exhibit A: Cells



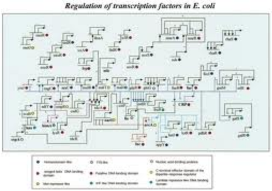
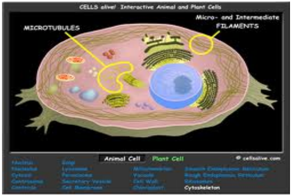
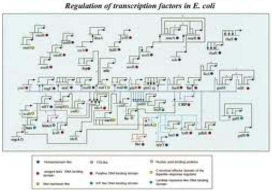
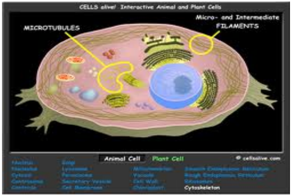


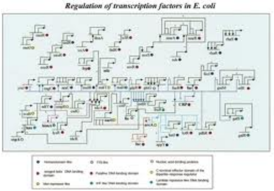
Exhibit A: Cells





At the deepest level cells are giant networks of biochemical reactions. The products of these reactions somehow *self-organize* into organelles and whole cells that interact with other cells and the external environment.





At the deepest level cells are giant networks of biochemical reactions. The products of these reactions somehow *self-organize* into organelles and whole cells that interact with other cells and the external environment.

How does this happen? Why does this work?

Exhibit B: Brains


Exhibit B: Brains


Human brains are composed of trillions of neurons that exhibit relatively simple firing patterns. Neurons are connected by dendrites and axons and communicate (receive and send signals) along these structures.

Exhibit B: Brains


Human brains are composed of trillions of neurons that exhibit relatively simple firing patterns. Neurons are connected by dendrites and axons and communicate (receive and send signals) along these structures.

How can the firing patterns of the neurons *give rise to* **perceptions, feelings, thoughts, and actions?**

Exhibit C: Ant colonies

Individual ants are capable of only a very limited set of simple behaviors. They communicate with their nestmates by using only a few distinct olfactory and tactile cues.

Exhibit C: Ant colonies

Individual ants are capable of only a very limited set of simple behaviors. They communicate with their nestmates by using only a few distinct olfactory and tactile cues.

How can an ant colony build elaborate nests and even farm fungi, which amounts to creating a habitat for another species?

What is a complex system? Working definition for this talk.

What is a complex system? Working definition for this talk.

- The microscopic level consists of many relatively simple **agents** of possibly several types.

What is a complex system? Working definition for this talk.

- The microscopic level consists of many relatively simple **agents** of possibly several types.
- Agents interact. The structure of these interactions is called the connectivity of the system.

What is a complex system? Working definition for this talk.

- The microscopic level consists of many relatively simple **agents** of possibly several types.
- Agents interact. The structure of these interactions is called the connectivity of the system.
- At the macroscopic level the system interacts with the environment **in complex ways.**

What is a complex system? Working definition for this talk.

- The microscopic level consists of many relatively simple **agents** of possibly several types.
- Agents interact. The structure of these interactions is called the connectivity of the system.
- At the macroscopic level the system interacts with the environment **in complex ways.**
- The system may even shape its environment.

When do interactions qualify as complex?

When do interactions qualify as complex?

Defining “complexity” is devilishly complex.

When do interactions qualify as complex?

Defining "complexity" is devilishly complex.

A *Scientific American* editorial entitled "From complexity to perplexity" by John Horgan mentions 31 different definitions of complexity.

When do interactions qualify as complex?

Defining “complexity” is devilishly complex.

A *Scientific American* editorial entitled “From complexity to perplexity” by John Horgan mentions 31 different definitions of complexity.
This appeared in June 1995, long before the study of complex system became as fashionable as it currently is.

When do interactions qualify as complex?

Defining “complexity” is devilishly complex.

A *Scientific American* editorial entitled “From complexity to perplexity” by John Horgan mentions 31 different definitions of complexity.
This appeared in June 1995, long before the study of complex system became as fashionable as it currently is.

Problem 1: Find the definition of “complexity” that works best for the context of your study.

What kind of questions does systems biology study?

What kind of questions does systems biology study?

In a nutshell, systems biology tries to understand how the (complex) behaviors at the macroscopic level *emerge* out of the interactions of the agents at the microscopic level.

What kind of questions does systems biology study?

In a nutshell, systems biology tries to understand how the (complex) behaviors at the macroscopic level *emerge* out of the interactions of the agents at the microscopic level.

To get an idea what it takes to do systems biology, try to think simultaneously about trees and the forest.

What kind of questions does systems biology study?

In a nutshell, systems biology tries to understand how the (complex) behaviors at the macroscopic level *emerge* out of the interactions of the agents at the microscopic level.

To get an idea what it takes to do systems biology, try to think simultaneously about trees and the forest. How does the (rather predictable) dynamics of forest growth *emerge* out of the growth of individual trees (that depends on many random events)?

What kind of questions does systems biology study?

In a nutshell, systems biology tries to understand how the (complex) behaviors at the macroscopic level *emerge* out of the interactions of the agents at the microscopic level.

To get an idea what it takes to do systems biology, try to think simultaneously about trees and the forest. How does the (rather predictable) dynamics of forest growth *emerge* out of the growth of individual trees (that depends on many random events)?

How could we build mathematical models of forest growth? Obviously, if we were to assign variables to each individual tree, we would end up with too many variables to study the resulting models. We could try to work with variables that represent averages, but this may not work due to nonlinear interactions.

Is (mathematical) systems biology even possible?

If mathematical models are to help us in studying problems as on the previous slide, they need to be simple enough to be **tractable** either mathematically or at least by computer simulations, and they need to incorporate enough details to make biologically realistic predictions or give us correct explanations of a phenomenon.

Is (mathematical) systems biology even possible?

If mathematical models are to help us in studying problems as on the previous slide, they need to be simple enough to be **tractable** either mathematically or at least by computer simulations, and they need to incorporate enough details to make biologically realistic predictions or give us correct explanations of a phenomenon.

At first glance it seems **impossible** to find such models.

Is (mathematical) systems biology even possible?

If mathematical models are to help us in studying problems as on the previous slide, they need to be simple enough to be **tractable** either mathematically or at least by computer simulations, and they need to incorporate enough details to make biologically realistic predictions or give us correct explanations of a phenomenon.

At first glance it seems **impossible** to find such models.

Fortune cookie: Doing the impossible is kind of fun.

Is (mathematical) systems biology even possible?

If mathematical models are to help us in studying problems as on the previous slide, they need to be simple enough to be **tractable** either mathematically or at least by computer simulations, and they need to incorporate enough details to make biologically realistic predictions or give us correct explanations of a phenomenon.

At first glance it seems **impossible** to find such models.

Fortune cookie: Doing the impossible is kind of fun.

Empirical fact: Such models are being found all the time.

Is (mathematical) systems biology even possible?

If mathematical models are to help us in studying problems as on the previous slide, they need to be simple enough to be **tractable** either mathematically or at least by computer simulations, and they need to incorporate enough details to make biologically realistic predictions or give us correct explanations of a phenomenon.

At first glance it seems **impossible** to find such models.

Fortune cookie: Doing the impossible is kind of fun.

Empirical fact: Such models are being found all the time.

Problem 2: Why does mathematical modeling in systems biology work as well as it does?

Dynamical systems models

Dynamical systems models

- Treat all relevant measurements that could in principle be taken as **variables** that change over **time**.

Dynamical systems models

- Treat all relevant measurements that could in principle be taken as **variables** that change over **time**.
- Study the time courses (trajectories) of the variables either by simulations or mathematical deductions (proofs).

Dynamical systems models

- Treat all relevant measurements that could in principle be taken as **variables** that change over **time**.
- Study the time courses (trajectories) of the variables either by simulations or mathematical deductions (proofs).
- **Stochastic models** allow for some randomness in the trajectories, **deterministic models** assume that the current state uniquely determines the trajectory.

Dynamical systems models

- Treat all relevant measurements that could in principle be taken as **variables** that change over **time**.
- Study the time courses (trajectories) of the variables either by simulations or mathematical deductions (proofs).
- **Stochastic models** allow for some randomness in the trajectories, **deterministic models** assume that the current state uniquely determines the trajectory.
- **Continuous** (e.g. ODE, PDE) models assume that time can take any (nonnegative) real values; **discrete time** (e.g. difference equation, Boolean) models assume that time moves in discrete steps, that is, only takes integer values.

Simplifying models

Usually, there are several different types of dynamical systems models that could be chosen for the same biological system.

Simplifying models

Usually, there are several different types of dynamical systems models that could be chosen for the same biological system.

For example, a model of a biochemical network as a stochastic process would keep track of actual numbers of molecules of each chemical species at a given time. A simpler ODE model would be based on concentrations instead of actual counts. A Boolean model would distinguish only between "high" and "low" concentrations.

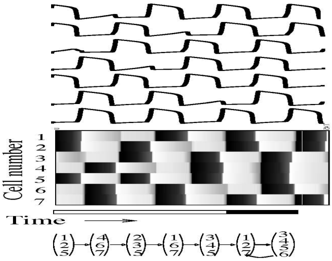
Usually, there are several different types of dynamical systems models that could be chosen for the same biological system.

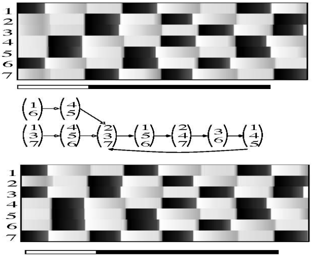
For example, a model of a biochemical network as a stochastic process would keep track of actual numbers of molecules of each chemical species at a given time. A simpler ODE model would be based on concentrations instead of actual counts. A Boolean model would distinguish only between "high" and "low" concentrations.

Problem 3: Under what conditions can we trust that the simpler models will make mathematically equivalent predictions to the more elaborate (and biologically more realistic) ones?

An example: Dynamic clustering

In several neuronal networks, it has been observed that time appears to progress in distinct episodes in which some subpopulation of cells fire synchronously; however, membership within this subpopulation may change over time. That is, two neurons may fire together during one episode but not during a subsequent episode. This phenomenon is called **dynamic clustering.**





How to explain dynamic clustering?

This is a strange phenomenon. As far as is known, there is no central pacemaker in these networks. The episodes are an *emergent property* of the internal dynamics of individual neurons and their interactions.

How to explain dynamic clustering?

This is a strange phenomenon. As far as is known, there is no central pacemaker in these networks. The episodes are an *emergent property* of the internal dynamics of individual neurons and their interactions.

The biologically most realistic models of neuronal networks are based on Hodkin-Huxley differential equations for individual neurons.

How to explain dynamic clustering?

This is a strange phenomenon. As far as is known, there is no central pacemaker in these networks. The episodes are an *emergent property* of the internal dynamics of individual neurons and their interactions.

The biologically most realistic models of neuronal networks are based on Hodkin-Huxley differential equations for individual neurons.

Problem 4: Are there classes of DE models that exhibit dynamic clustering?

A theorem

Terman D, Ahn S, Wang X, Just W, Physica D, 2008

Theorem

There exist a broad class of ODE models M for neuronal networks such that every model in this class exhibits dynamic clustering. Moreover, for every such M there exists a discrete model N with a finite state space that accurately predicts which neurons will fire in any given episode.

A theorem

Terman D, Ahn S, Wang X, Just W, Physica D, 2008

Theorem

There exist a broad class of ODE models M for neuronal networks such that every model in this class exhibits dynamic clustering. Moreover, for every such M there exists a discrete model N with a finite state space that accurately predicts which neurons will fire in any given episode.

The proof of this theorem, which relies on special intrinsic properties of individual neurons and special features of the network architecture gives a *possible explanation* of the empirically observed episodes.

A theorem

Terman D, Ahn S, Wang X, Just W, Physica D, 2008

Theorem

There exist a broad class of ODE models M for neuronal networks such that every model in this class exhibits dynamic clustering. Moreover, for every such M there exists a discrete model N with a finite state space that accurately predicts which neurons will fire in any given episode.

The proof of this theorem, which relies on special intrinsic properties of individual neurons and special features of the network architecture gives a *possible explanation* of the empirically observed episodes.

Simultaneously, the theorem assures us that the ODE models in this class can be **simplified** to the corresponding discrete models.

The discrete model in a nutshell

- Neurons fire or are at rest.
- After a neuron has fired, it has to go through a certain **refractory period** when it cannot fire.
- A neuron will fire when it has reached the end of its refractory period and when it receives firing input from at least as many other neurons as are required by its **firing threshold.**

Definition of the discrete model

Ahn S, Smith BH, Borisyuk A, Terman D, Physica D, 2010

A directed graph $D = [V_D, A_D]$ and integers n (size of the network), p_i (refractory period), th_i (firing threshold).

A state $\vec{s}(t)$ at the discrete time t is a vector:
$\vec{s}(t) = [s_1(t), \ldots, s_n(t)]$ where $s_i(t) \in \{0, 1, \ldots, p_i\}$ for each i.
The state $s_i(t) = 0$ means neuron i fires at time t.

Dynamics on the discrete network $N = < D, \vec{p}, \vec{th} >$:

- If $s_i(t) < p_i$, then $s_i(t+1) = s_i(t) + 1$.
- If $s_i(t) = p_i$, and there exists at least th_i neurons j with $s_j(k) = 0$ and $< j, i > \quad \in A_D$, then $s_i(t+1) = 0$.
- If $s_i(t) = p_i$ and there do not exist th_i neurons j with $s_j(t) = 0$ and $< j, i > \quad \in A_D$, then $s_i(t+1) = p_i$.

For a given discrete model N we may ask about the (possible, maximal, average)

- Lengths of the attractors.
- Number of different attractors.
- Sizes of their basins of attraction.
- Lengths of transients.
- ... .

Studying the discrete model

For a given discrete model N we may ask about the (possible, maximal, average)

- Lengths of the attractors.
- Number of different attractors.
- Sizes of their basins of attraction.
- Lengths of transients.
- ... .

How do these features of the network dynamics depend on the network connectivity and the firing thresholds and refractory periods of individual neurons?

Which connectivities are we interested in?

We can study these questions for special connectivities:

- Directed cycle graphs.
- Strongly connected digraphs: There is a directed path from every node to every other node.
- Complete digraphs.
- ...

Which connectivities are we interested in?

We can study these questions for special connectivities:

- Directed cycle graphs.
- Strongly connected digraphs: There is a directed path from every node to every other node.
- Complete digraphs.
- ...

Alternatively, we can study expected properties of the dynamics if the connectivity is a **random digraph.** There are several models for generating random digraphs, the most important ones being the **Erdős-Rényi model** and the **preferential attachment model.**

Commercial break

Commercial break

Many results on how the connectivity of the discrete model influences its dynamics under suitable assumptions on the refractory periods and firing thresholds are reviewed in the chapter

Neuronal Networks: A Discrete Model, Just W, Ahn S, Terman D of the forthcoming volume

Mathematical Concepts and Methods in Modern Biology, Robeva R and Hodge T eds., Elsevier 2013.

Commercial break

Many results on how the connectivity of the discrete model influences its dynamics under suitable assumptions on the refractory periods and firing thresholds are reviewed in the chapter

Neuronal Networks: A Discrete Model, Just W, Ahn S, Terman D of the forthcoming volume

Mathematical Concepts and Methods in Modern Biology, Robeva R and Hodge T eds., Elsevier 2013.

The chapter also includes eight research projects that gradually lead students from relatively easy exercises to unsolved open problems. Most of these are at a level that is accessible to undergraduates.