Complexity in Biological Signaling Systems

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2 APRIL 1999 VOL 284 SCIENCE

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Biological Signaling Systems

- Signaling in biological systems occurs at multiple levels.
- Signaling can be another way to describe communication
- In this paper, focus is on interaction within a single cell – intracellular signaling within a cell

Complexity

- Large number of components
- Connections among components
- Spatial relationship between components

Complexity in Physical Systems

- Complexity factors
  - the number of components and the intricacy of the interfaces between them,
  - the number and intricacy of conditional branches,
  - the degree of nesting, and
  - the types of data structures

Complexity in Biological Signaling

- In addition to the factors present with physical systems, biological signaling systems also incorporate
  - Dynamic assembly
  - Translocation
  - Degradation
  - Channeling of chemical reactions

Complex Behavior of Signaling Networks

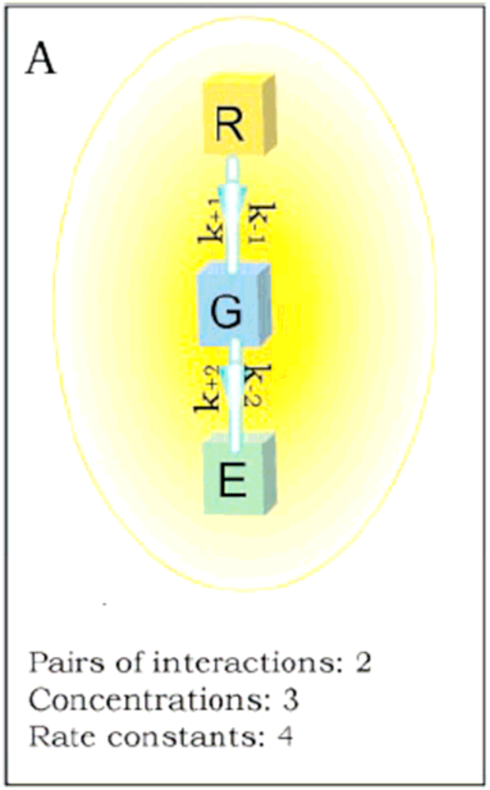
- One approach to understanding complexity is to start with a conceptually simple view of signaling and add details that introduce new levels of complexity

Simplest View

- Homogenous well-stirred cell where all molecules have equal access to each other
- Bacterial two-component signal transduction is one example of such a system: a simple three-component transmembrane signaling system

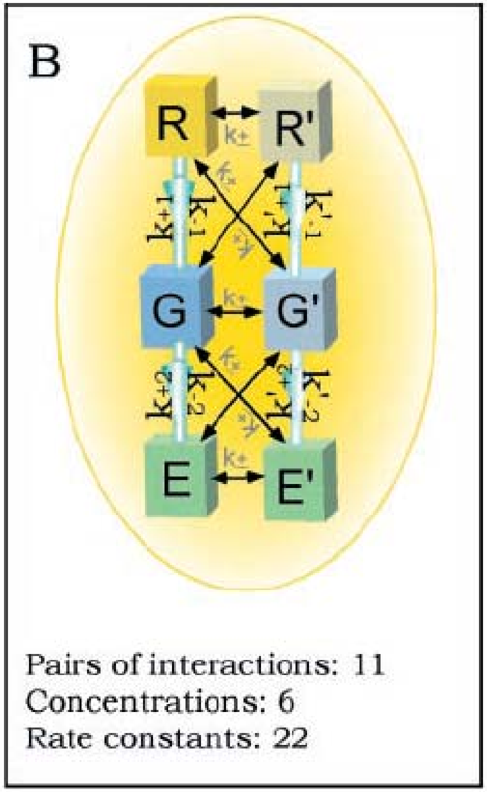
A Signaling Wire

- Properties of this system are completely determined by the concentrations of each of the components and the reaction rates
- Each pathway can be thought of as a wire carrying information



Next Layer of Complexity

- Now add interconnections that only occur between two adjacent components
- Even though the system has been simplified, such simplification often reflects the specificity in interactions between pathways
- Experimentally, a system of this size can be analyzed
- Can be analyzed using a computer model



Simple Model

- Using GENESIS, a simplified network consisting of four different interacting signaling pathways displayed the following emergent behavior
  - Integration of signals across different time scales
  - Generation of distinct outputs depending on the amplitude and duration of the input signals
  - Presence of feedback loops that behave as bistable switches to process information flow

Additional Modeling Considerations

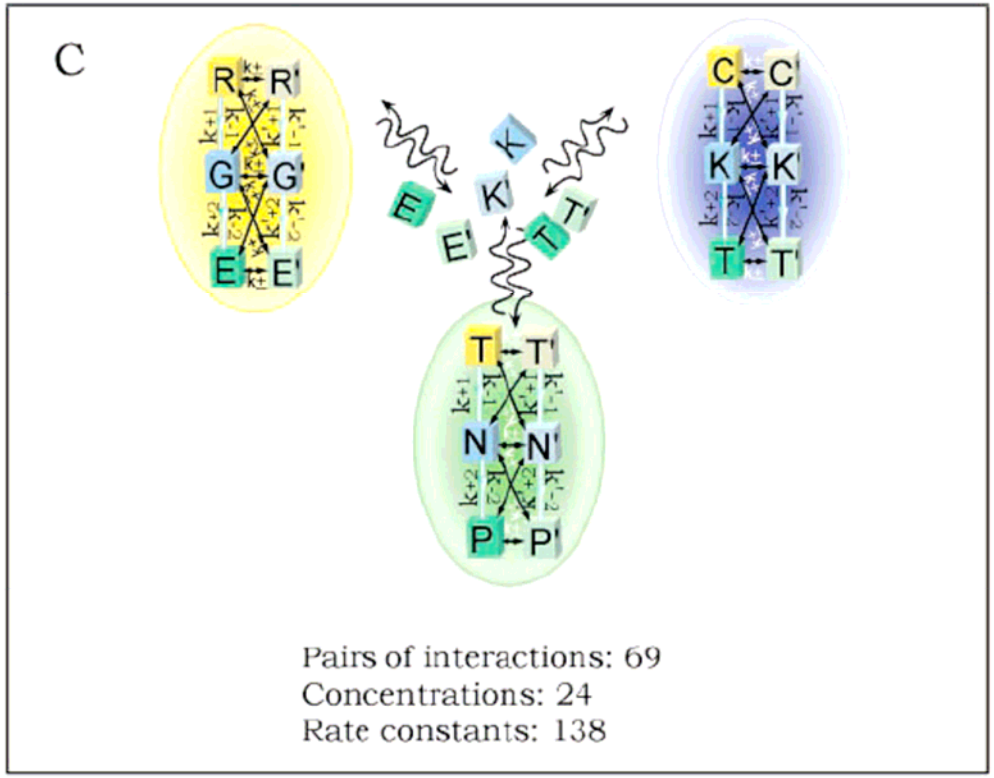
- While there exists emergent complexity in the GENESIS model, it suggested that additional considerations were necessary to develop a minimally accurate picture of a living cell:
  - Compartmentalization
  - Regional organization

Compartments

- The compartment introduces space and multiplies the number of signals that any given molecule can carry in the system
- Experimental data at the compartment level is difficult to obtain
- The number of parameters needed to accurately model the system becomes large quickly

Simple Compartment Model

- Three compartment system with six translocatable components
- Compartmentalization duplicates existing wires and separates them in space, thus multiplying the number of signals they can carry



Regional Organization

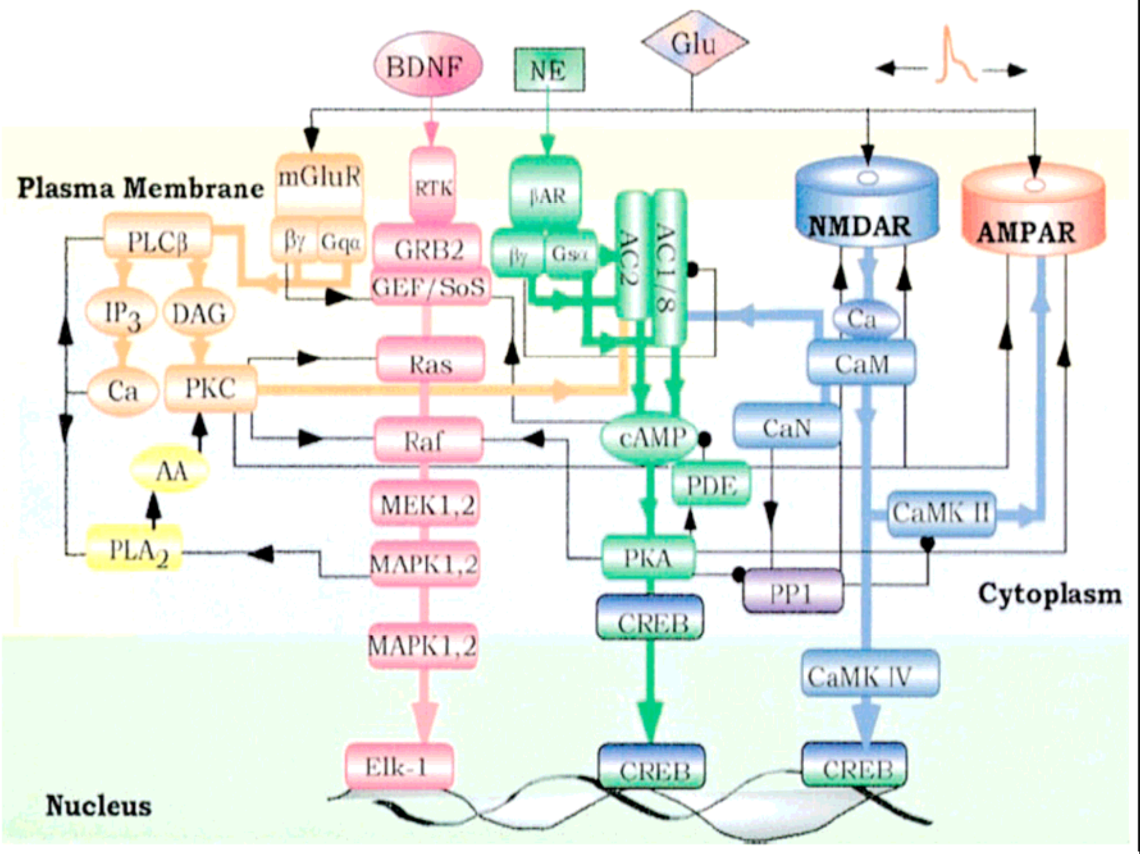
- Molecular scaffolds
- Cytoskeleton is a dynamic framework on which the cell builds this regional organization
- A prime example of its dual role is the synapse
  - Pre- and postsynaptic structures are the anchors for a wide array of synaptic signaling molecules

Scaffolds

- The term “scaffold” is also used for a new class of signaling proteins that do not have information transfer capability of their own but interact with multiple signaling proteins in a pathway.
- The scaffold provides an assembly line along which a series of enzymes process their substrates in a well-defined sequence and with an efficiency and specificity that are orders of magnitude higher than would be possible in a freely diffusing system

Regional Signaling

- Four interacting pathways in the postsynaptic region of a neuron
- Signaling components can translocate between the plasma membrane and cytoplasm and similarly between the cytoplasm and nucleus



Cytoskeleton and Compartments

- Both the cytoskeleton and compartments have a dual role in cell assembly and signaling role
- The system is self-modifying, dependent up on its situation (temporal, environmental dependencies)

Regulation in the Nucleus

- The genetic machinery
  - Enzymes
  - Compartments
  - Tightly controlled signal trafficking
  - Gigabyte-sized program written in the DNA
- The balance between intrinsic capability and the response to external signals is likely to be a central issue in understanding gene expression

Why Study Signaling?

- How does a developing organism start from a single cell and divide and differentiate into many different classes of cells?
  - Emerging data point to signaling interactions that are genetically programmed
  - Later development is dependent upon external input in addition to the “programmed” input

Analyzing a complex system

- Tightly coupled experiments and theory
- A move toward a more quantitative understanding of biology
- Access and creation of a database and tools to integrate these data would be necessary and a large project in itself

Understanding Complex Signaling Networks

- Understanding the origins of many human diseases that rely on the proper function of signaling components
- By unraveling the many combined interactions, the individual components and their contributions to the entire system can be understood
- May provide a molecular view of an individual’s interaction with its environment