

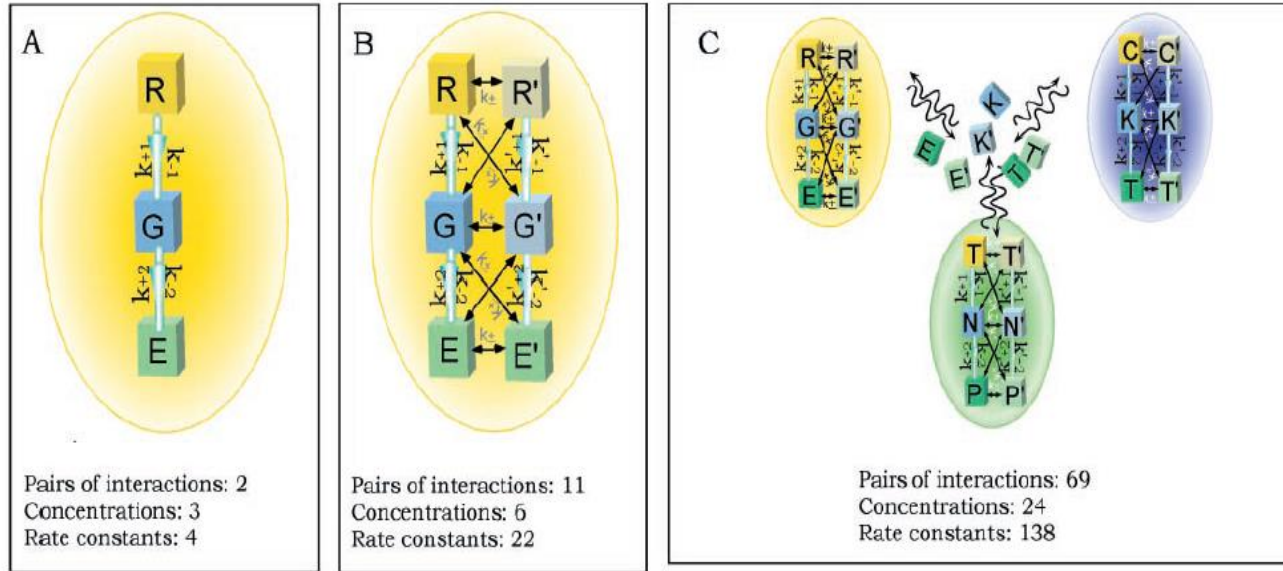
Introduction to Systems Biology

Lecture 5 - Part A -1

Iyengar

How do mathematical representations help us solve biological problems ?

Dealing with complex systems in an orderly fashion to understand and predict I/O relationships



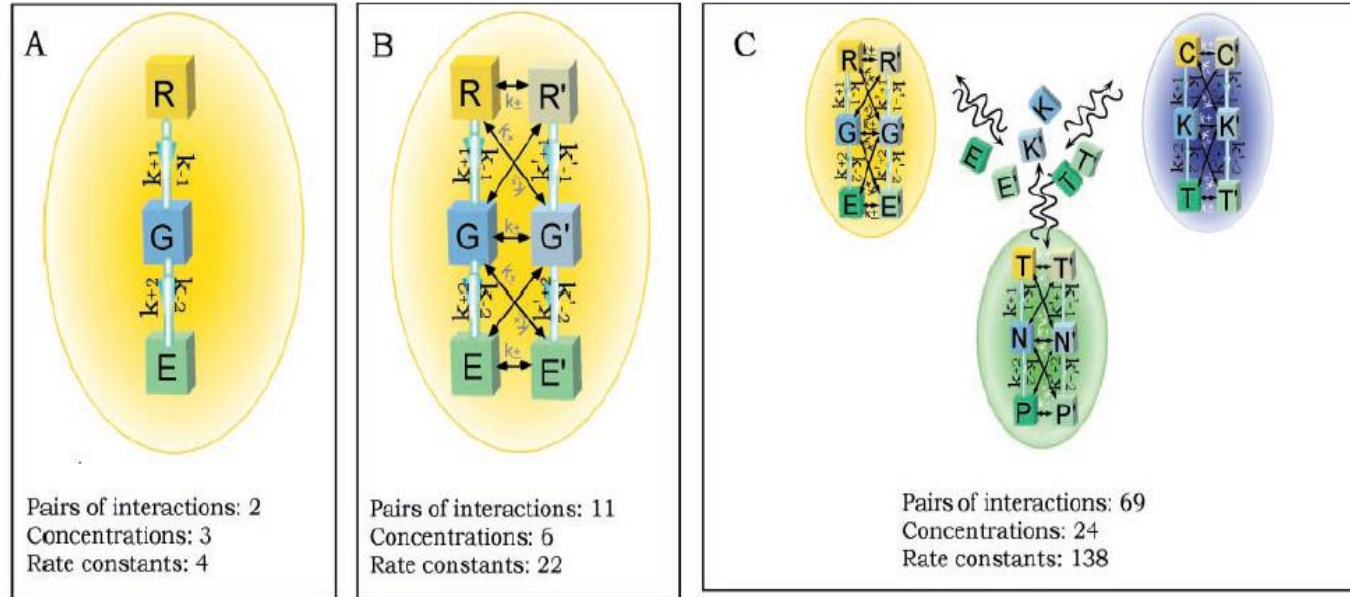
Weng, Bhalla, Iyengar. *Science* 284(5411):92-6 (1999)

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Lecture 5 Part A -2

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Even in a simple linear pathway, such that the one shown in A, we need computation to estimate the relationship between activation of R and E . In the other two cases the complexity is visually obvious.



Weng, Bhalla, Iyengar. *Science* 284(5411):92-6 (1999)

Two approaches to solving mathematical equations

Analytical Solutions: An equation or set of equations has an analytic solution if a solution can be expressed as a mathematical expression that has well-known symbolic operations that can readily be used for calculations

For example the equation $ax^2 + bx + c = 0$ has the analytical solution $x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$

Most of the time the complexity of biological systems preclude analytical solutions

Numerical Solutions (numerical analysis): Use numerical approximation (in contrast to symbolic manipulations) to solve the equations

Most commonly used for solving biological problems

Building Good Mathematical (Computational) Models to Solve Biological Problems

- Useful models are relevant to the experimentalist
- Good models need to provide answers or generate hypotheses that cannot be intuitively obtained
- Models that oversimplify or when model parameters cannot be explicitly ascribed to experimentally observable functions are generally ignored by experimental biologists

Over simplification of molecular details obscures biological mechanisms (i.e., how a biological phenomenon occurs). Getting the right balance of detail is critical in developing a good model

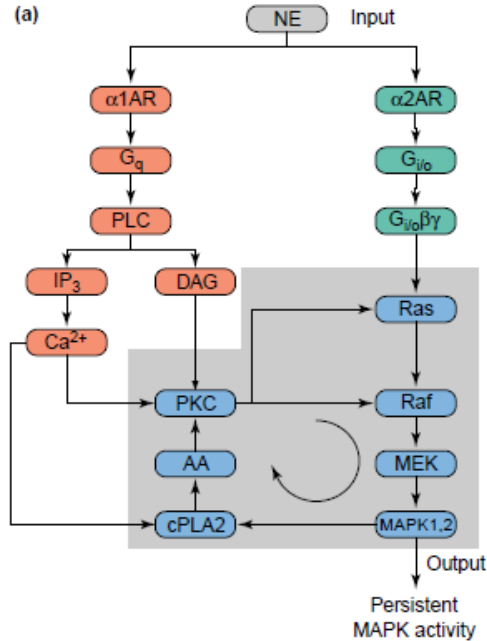
Good models make non-intuitive predictions

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Lecture 5 - Part A-5

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ODE Models



(b)

$$\frac{d[NE_α1AR]}{dt} = k_1[NE][α1AR] - k_2[NE_α1AR] - k_3[NE_α1AR][G_q] + k_4[NE_α1AR_G_q]$$

$$\frac{d[NE_α2AR]}{dt} = k_5[NE][α2AR] - k_6[NE_α2AR] - k_3[NE_α1AR][G_o] + k_4[NE_α1AR_G_o]$$

...

...

...

$$\frac{d[MAPK^*]}{dt} = \frac{k_{cat}[MEK^*][MAPK]}{k_m + [MAPK]} - k_{dephos}[MAPK^*]$$

Research Question

Why does norepinephrine (NE) cause persistent MAPK activity in some neurons?

Detail Required: Different isoforms of the NE receptors and their pathways

Numerical analysis can tell us when the positive feedback loop can function as a switch.

Advantages of Ordinary Differential Equation (ODE) Models

ODEs are reasonable representations of a large number of biochemical reactions within the cell

Kinetic parameters for ODE models can often be explicitly measured or estimated from experiments

Often there is substantial experimental data to build well constrained ODE models

There are many software suites that can be used to solve ODE models

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Lecture 5 - Part A-7

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Limitation of ODE Models

ODE models are built using the “well stirred” reactor assumption. All reactants are presumed to have equal access to all other reactants without any hindrance

The “well stirred” assumption works for processes that are solely cytoplasmic but the assumption is not valid when multiple compartments, such as cytoplasm and nucleus, are involved

Most often interactions between protein kinases and transcription factors involve multiple compartments