Introduction to Systems Biology
Lecture 11 Part B-1 Iyengar

Potential and Limitations of Different Types of Models

Current network models do not capture important cell biophysical inputs and outputs: Force & voltage

Currently cell/tissue network models typically have molecular entities as nodes. However, cellular biochemistry and biophysical functions are intertwined into cellular activities

Extracellular force signals are transduced through biochemical cell signaling pathways and in turn affect force generation by the actin cytoskeleton dynamics and myosin (molecular) motors. These interactions are not captured in current network models

Membrane voltage " communicates" cell state to many channels (i.e. voltage gated channels). Information flow through membrane voltage and capacitance has not been incorporated into cellular interaction models

How do we build mixed biochemical-biophysical network models ?

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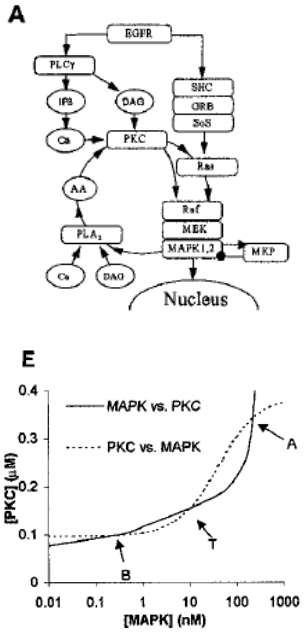
Network models have limited ability to capture temporal dynamics

Temporal dynamics is critical for understanding cell and tissue level systems behavior

Behavior of network motifs such as positive and negative feedback loops are best understood through dynamical (differential equation) based models - See schematic and plot on the right

Such dynamical behavior cannot generally be uncovered by Boolean dynamics

So network analysis needs to be coupled with dynamical modeling



Bhalla & Iyengar (1999) Science 283:381

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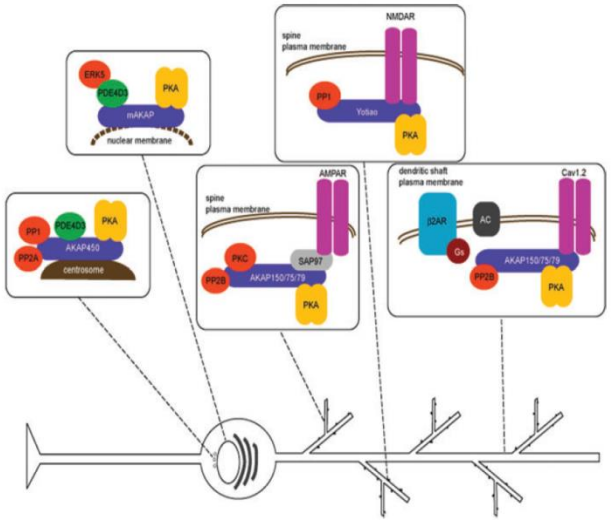
Network models are currently not well suited to capture spatial information

Cellular components that have mutual chemical specificity to interact may be localized to different parts of the cell - see schematic on right

So specifying edges based on chemical reactivity alone make a protein-protein interaction network appear more dense in connectivity than it really is.

Development and analysis of graphs where edges can be specified with multiple characteristics

As more spatial information becomes available we will need to develop and analyze spatially specified interaction network models



Lipshtat, Neves & Iyengar (2009) Ann NY Acad Sci 1158:44

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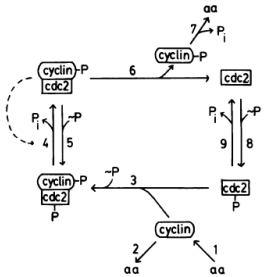
Dynamical Models provide accurate description of how a system progresses temporally and spatially

The cell cycle classic ODE model by Tyson shown on the right shows how a relatively simple model with key components can accurately represent complex cellular behavior like proliferation.

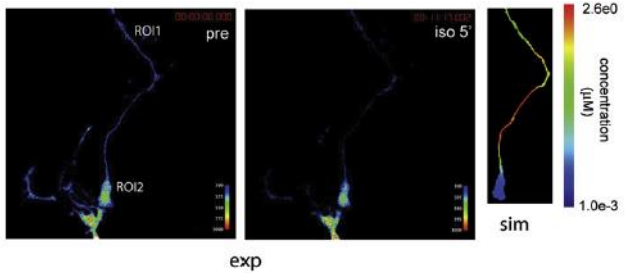


Tyson JJ (1991)
PNAS 88: 7382

Table 1. Kinetic equations governing the cyclin–cdc2 cycle in Fig. 1

$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

PDE models can accurately capture spatial dynamics of signaling as shown in this comparison between experiments (exp) and simulations (sim) in *Virtual Cell*



Neves et al (2008) Cell 133:666

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Dynamical Models can accurately describe the progression of probabilistic systems

Many important cell biological processes are inherently stochastic

Neurotransmitter release, initiation of gene expression, initiation of filapodia formation

Most cell level stochastic processes arise from stochastic biochemical reactions

The Gillespie algorithm provide an explicit feasible approach for computing the progress of stochastic reactions . This provides us with ability to simulate trajectory of individual subcellular processes

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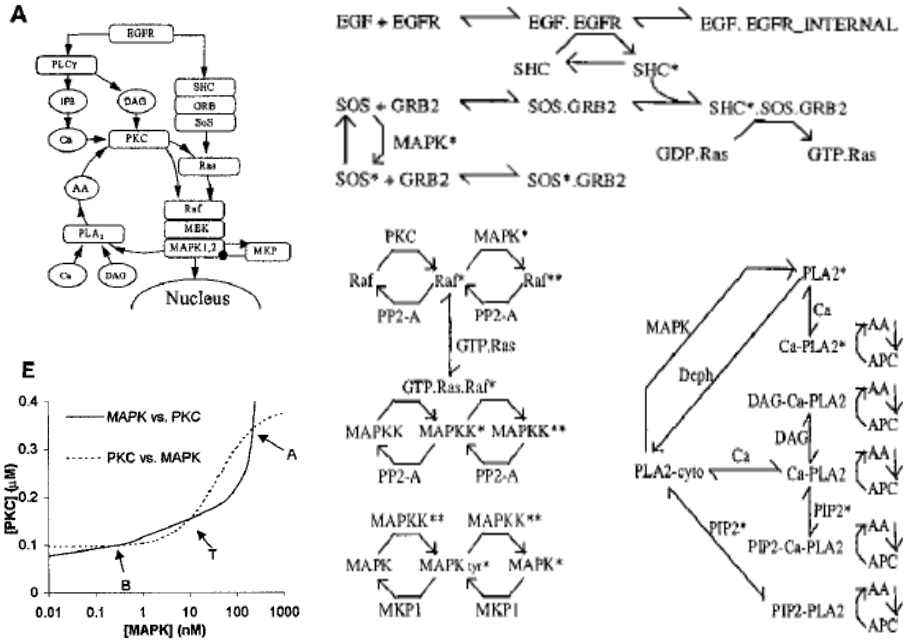
Dynamical models can estimate the ability of network motifs to process information during signal flow

ODE models can be used to get a deep understanding of network behavior

For this small network shown in A, the reactions shown on the three right panels can be used to run a dynamical model that shows how this system can function a switch

Similar models have been built for feedforward motifs and bifans



Bhalla & Iyengar (1999) Science 283:381

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Model accuracy is dependent on underlying assumptions and parameters

Parameters are often hard to find

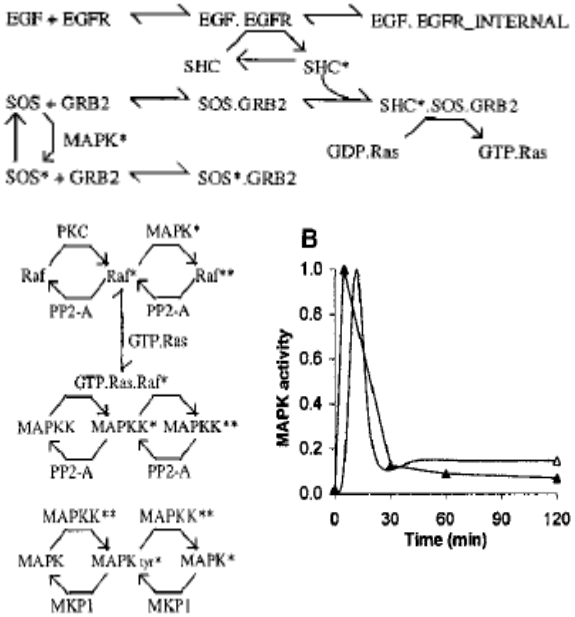
Large dynamical models need to be well constrained -- otherwise with too many parameters, any type of behavior can be simulated - On the right the plot shows the match between experiment (black triangles) and simulations using the reactions shown here for EGF stimulation of MAPK.

Note the good match of amplitude and not so good match of the time course
Kinetic parameters are from in vitro measurements
Experiment was done with intact cells.

Finding intact cell kinetic parameters is nearly impossible

Often find experimentally measured kinetic parameters in vitro and levels of cellular components is impossible.

So many parameters are estimated from time course experiments



Bhalla & Iyengar (1999) Science 283:381

This lack of data greatly limits our ability to build large dynamical models

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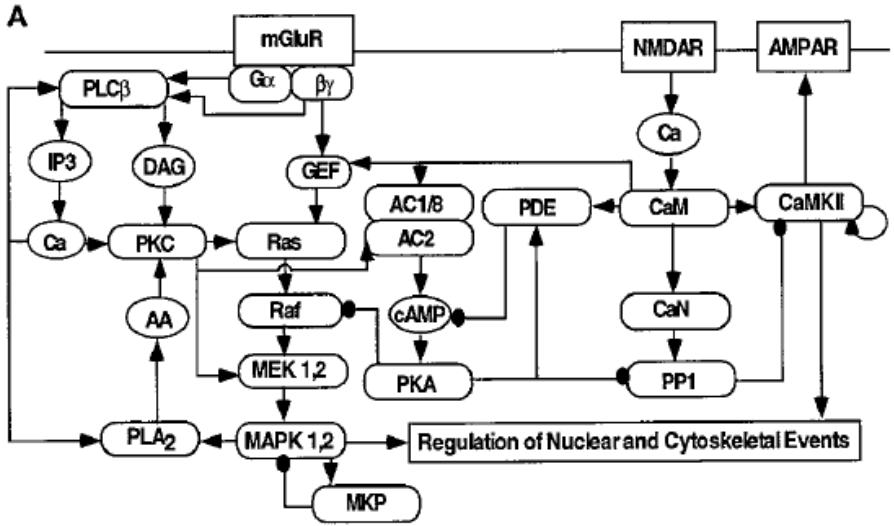
In large dynamical models it is not easy to understand how I/O relationships appear

Consider the moderately complex network on the right. The reason why activation of MAP-kinase controls the activity state CAM-KII is not clear.

However when we consider the observation that MAP-kinase is part of a positive feedback loop that through PKC can raise cAMP continuously to operate the PPI gate to keep CAMKII active the mechanism for the observed relationship becomes clear.

Need network topology to understand dynamic input/output relationships.



Bhalla & Iyengar (1999) Science 283:381

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Lecture 11 - Take Home points

- The different modeling approaches have their strengths and weaknesses in terms of the knowledge they can provide.

- Statistical models are very useful in providing in “big picture “ overview of relationships between distal entities e.g. genes and disease but do not tell anything about basis (i.e. mechanism) for the relationship.

- Network models are essential to understand how the system is organized and its capability to process information and enable regulation. Network models do not help us predict how the system will change with respect to time.

- Dynamical models enable us to understand and predict how the system changes with respect to time and space.

However in large systems it does not help us understand the basis for distal input output relationships.

To have predictive understanding of systems we need all three modeling approaches