Introduction to Systems Biology
Lecture 12 Part A-1

Iyengar

Integrated Reasoning: Merging Bottom Up and Top Down Reasoning

Identifying Emergent Properties: Bistability

What is an Emergent Property ?
An emergent property is a property the system as whole possesses but cannot be attributed to any individual component of the system. Emergent properties of cell biological systems include bistability, ultrasensitivity robustness ...probably many others waiting to be discovered.

What is Bistability ?
Bistability is the ability of a system to exist in two stable states i.e. the system can switch between states. Often the switching is stimulus driven and hence enables change in state of the cell.

Why is this Integrated Reasoning ?
The ability to use ODE based modeling to identify bistability as a property of a positive feedback loop allows us to enumerate the capability of a part of a network identified by topological analysis.

Introduction to Systems Biology
Lecture 12 Part A-2

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Dynamical Analysis of a Bistable System

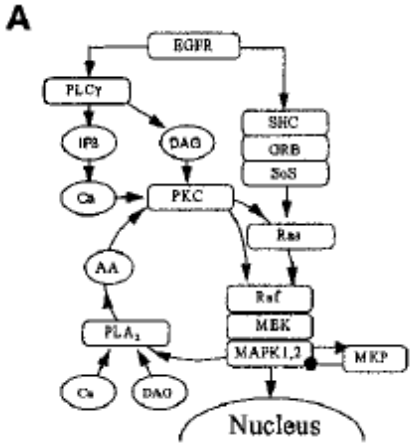
Set up an ODE Model

1. Identify the reactions involved in the model - shown below. In this case the model (network subgraph) was constructed from known binary reactions.

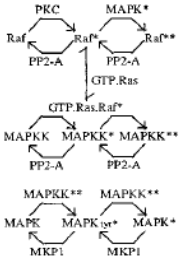
2. Parameterize the reactions
   find reaction rates, concentrations of reactions
   (most of these proteins had been purified from tissues so with some work Upi was able to find/estimate parameters)

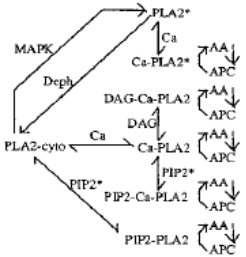
3. Constrain the model in a modular fashion data

4. Ensure that during the simulations the model obeys
   a. mass conservation
   b. microscopic reversibility



Bhalla & Iyengar (1999) Science 283:381





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Lecture 12 Part A-3

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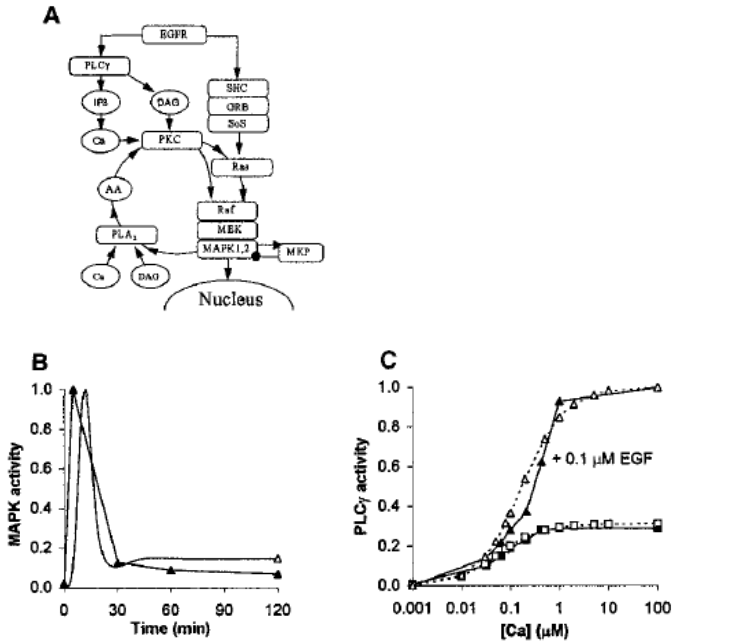
Constraining Models

Since kinetic parameters are drawn from many sources *(e.g. Different proteins were purified by different labs and may be from different cells/tissues)* it is good practice to constrain the model by running test simulations to see if the model behavior is similar to what been seen in experiments. Two examples are shown

Recommendation: *Don't tweak (change) parameters so that simulations exactly fit the experiments – Note the differences but run the model with the "most reasonably" selected parameters*

The appropriate place to change parameters is during systematic parameter variation. This is a meaningful exercise as it can tell us the "best" set of parameters for an observed experimental profile.

A hypothesis to do more accurate experiments.



Bhalla & Iyengar (1999) Science 283:381

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Lecture 12 Part A-4

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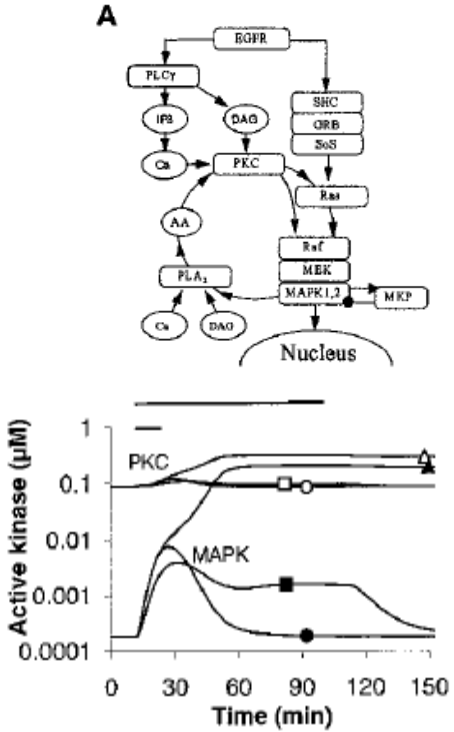
Simulations to determine the conditions for transient and sustained response

Small and short duration signals do not produce prolonged activation of the output protein kinases

A signal of sufficient amplitude (5nM EGF) and duration (100 min) moves the system into a continuously active state

How does this happen?



Introduction to Systems Biology
Lecture 12 Part A-5 Iyengar

Consider the effect of active MAPK on PKC activity---- dotted lines and active PKC on MAPK ---solid line

The two curves intersect a 3 points
A, B and T

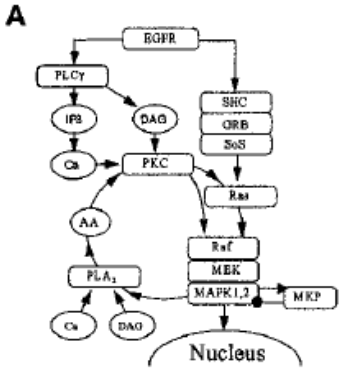
A- the Active state
B - the basal state

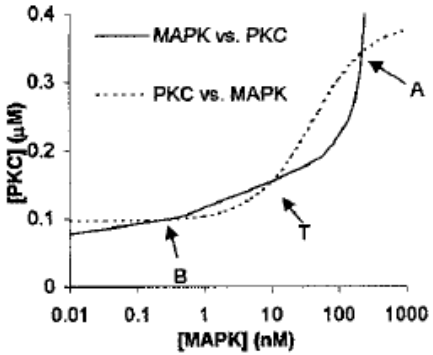
A and B are the two stable states (bistable)

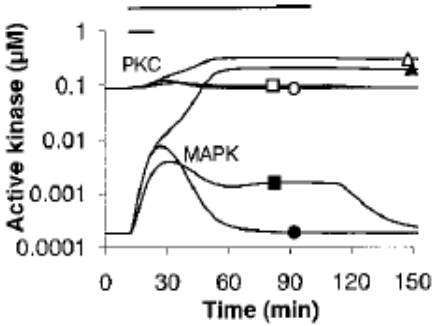
T- the metastable state - threshold

If the initial stimulation (i.e EGF signal) is of a sufficient magnitude that either MAPK or PKC is activated above the level T then the system will come to rest at A – even if signaling is withdrawn

Otherwise (initial signal below T) when signal is withdrawn the system will return to basal level - B







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Lecture 12 Part A-6

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The system is reasonably robust

Deactivation also needs to be of sufficient magnitude and duration

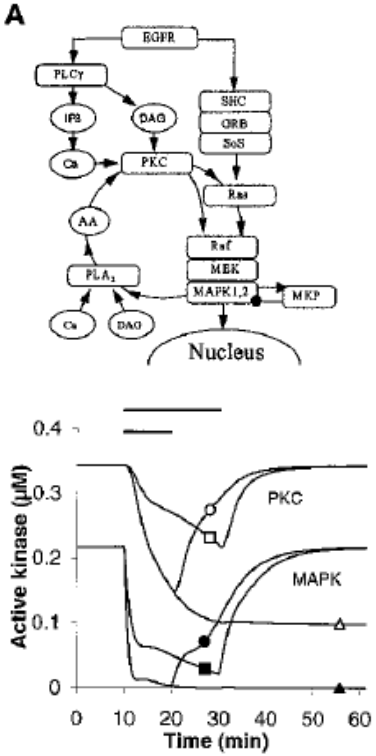
Use a phosphatase MKP that shuts down MAPK

4nM MKP for 20 mins (open circle - square)

8 nM MKP for 10 mins (closed circle – square)

8nM MKP for 20 mins (open-closed triangles)

Once activated, only deactivating signal of sufficient magnitude and duration will shut the system down



Why was such bistable behavior in signaling networks surprising ?

Coming into this in 1995-1996, it was thought that long lasting signals were produced

a. Activating mutations such as that in Src or Ras produced persistently activated signaling molecules

b. Rare biochemical reactions such as ADP-riobosylation by bacterial toxin could produce persistently activated or inhibited molecules such as cholera toxin and Gs leading to continuous activation of adenylyl cyclase and cAMP production

So simple coupling of wild-type signaling components could lead to switching behavior was unanticipated

How common are bistable systems ?

Lac Operon in E.Coli
Novick A, Weiner M (1957) Enzyme Induction as an allone none phenomenon Proc Natl Acad Sci U S A. 1957 Jul 15;43(7):553-66.

Cell Cycle in Xenopus Oocyte
Ferrell JE Jr. (2002) Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability. Curr Opin Cell Biol. 14:140-8.

Electrical Activity in Brain Regions (Rats, Guinea pigs)
Loewenstein Y, et al Bistability of cerebellar Purkinje cells modulated by sensory stimulation. Nat Neurosci. 2005 Feb;8(2):202-11