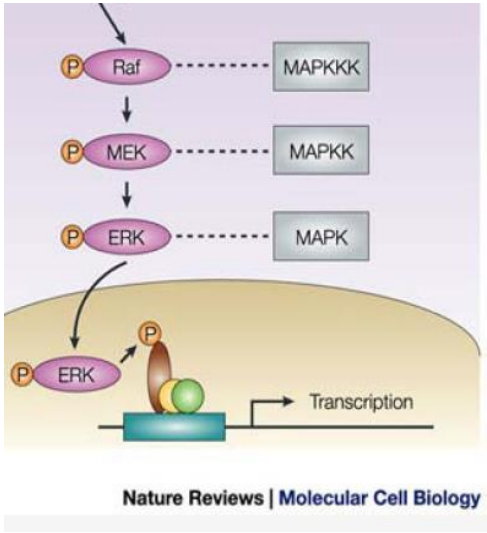
Introduction to Systems Biology
Lecture 5 - Part B1 — Iyengar

Multicompartment ODE Models



Kim & Bar Sagi. *Nat Rev Mol Cell Biol*. 5(6):441-50 (2004)

For MAPK pathway signaling to transcription factors

As shown in the simplified cartoon on the left

1) Two compartments: Cytoplasm and nucleus
2) Two reactions (and equations) in the cytoplasm (Compartment 1)
   Raf-P → MEK-P and MEK-P → ERK-P
3) A transport reaction for ERK-P from cytoplasm to nucleus
4) In nucleus (Compartment 2)
   ERK-P → TF-P

In each compartment the “well-stirred” assumption applies

Introduction to Systems Biology
Lecture 5 - Part B2

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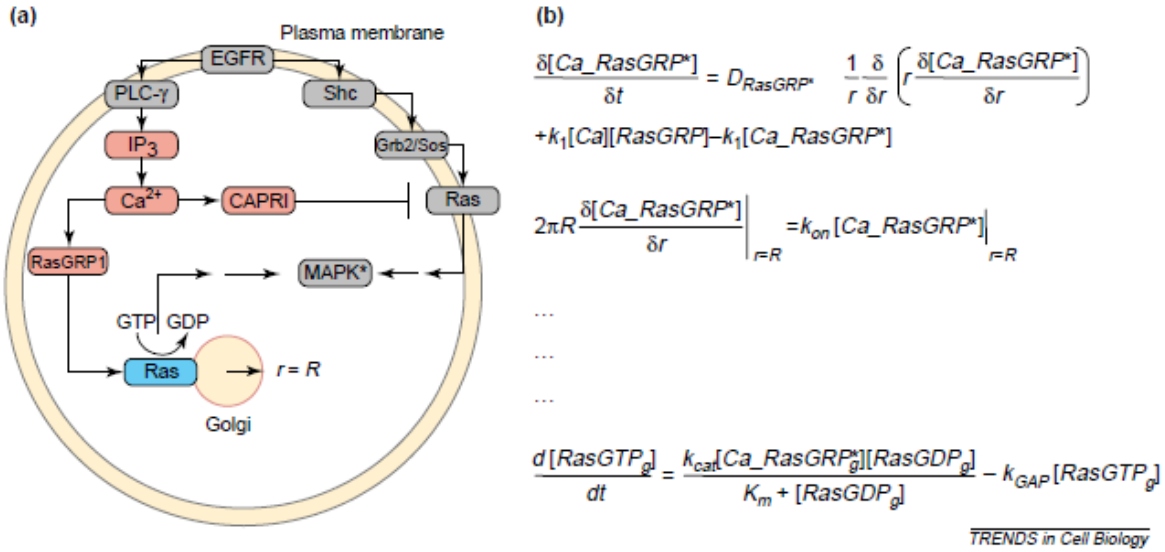
PDE Models



Eungdamrong and Iyengar *Trends Cell Biol.* 14(12):661-9 (2004)

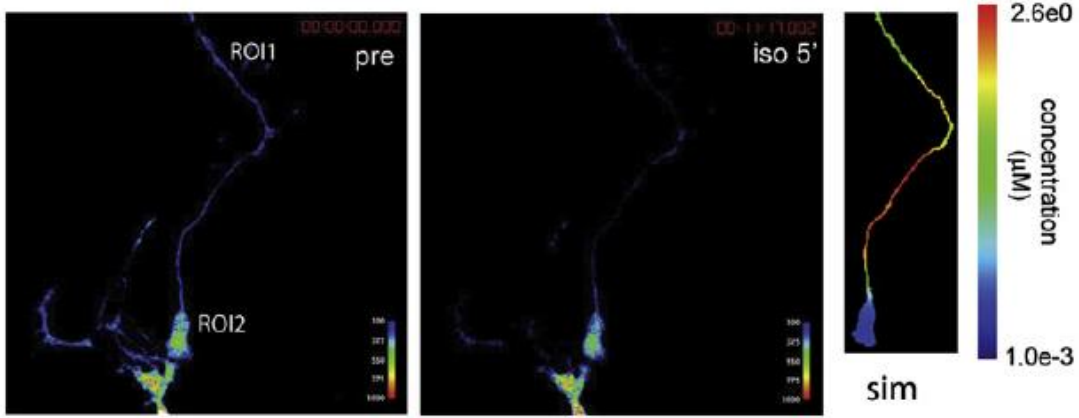
Research Question: How can EGFR activate Ras over different time scales at different locations within the cell?

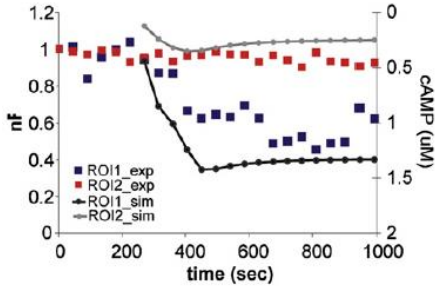
Details required: Representation of the spatial movement of EGFR generated signals to control GEFs (Ras GRP1) and GAP (CAPRI) of Ras at different locations.

Models can predict and explain time- and space-dependent activation of Ras in different locations within the cell.

Introduction to Systems Biology
Lecture 5 - Part B-3

Iyengar





Live cell imaging experiment (exp) measures increase in cAMP by decrease in fluorescence signal (compare upper panels)

Values from simulation (sim) and experiment are compared in the plot on the left

Another example of a PDE model:

Research Question: If the βAR receptors are evenly distributed on the cell surface, would the shape of a cell (neuron) lead to spatially restricted accumulation of cAMP?

Model (sim) predicts increased levels of cAMP in the dendrites.
Experiment supports the model.

Neves *et al*. *Cell* 133(4):666-80 (2008)

Deterministic vs. Stochastic Systems

Deterministic Systems: Progress (time evolution) of the system can be fully computed from specification of the initial conditions -- concentration of reactants and reaction rates.

Stochastic Systems: Progress of the system is determined both by predictable actions and by a sequence of random variables that regulate its ability to move from one state to another.

For biochemical reactions the system becomes stochastic when one reactant is present a very low concentration (e.g., transcription factor binding to gene: most genes have only 2 copies in the nucleus)

Stochastic Models

Master Equation: Generally stochastic models are computed using the *master equation* that describes the progress of the system with respect to time.
The system can be modeled as being in a defined state at a given time and moving to another state in a probabilistic manner.
This differential equation describes the variation of probability over time.

$$\frac{d\vec{P}}{dt} = \mathbf{A}\vec{P}$$

P -- column vector, A -- matrix of connections

For biochemical reactions, stochastic processes are often solved using the *Gillespie algorithm*.
The *Gillespie algorithm* enables us to discretely simulate each reaction between two reactants. The interval (time and/or space) between reactions follows a probability distribution given by the master equation

Lecture 5 – Take Home Points

- Mathematical representation of biochemical and biophysical systems help us understand system behavior and input-output relationships.

- Biological systems can be both deterministic or stochastic. Deterministic models can use either ODEs or PDEs.

- The nature of the biological process being studied determines the type of model that needs to be used.