Systems Biology Across Scales: A Personal View XIV. Intra-cellular systems IV: Signal-transduction and networks

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Intra-cellular biochemical networks

Metabolic networks

Nodes: metabolites (substrates & products of metabolism) Links: chemical reactions (directed)

Genetic regulatory networks

Nodes: Genes & Proteins

Links: regulatory interactions (directed)

Protein-Protein interaction network

Nodes: Proteins

Links: physical binding and formation of protein complex (undirected)

□ Signaling network

Nodes: Signaling molecules e.g., kinase, cyclicAMP, Ca Links: chemical reactions (directed)

Intra-cellular Signaling Network

The mechanism:

a sequence of linked biochemical reactions inside the cell, carried out by enzymes (e.g., kinases/ phosphatases that catalyzes transfer of phosphate groups from/to a substrate)



The system:

A network whose nodes are enzymes, and links are reactions

Emergence:

Interactions among reactions \rightarrow signal-transduction by which cell converts signal/stimulus to specific response

"Nervous system" for the cell Example: Chemotaxis in *E coli*

Attractant

http://2011.igem.org/

Input: chemical substances (e.g., nutrient) Output: physical movements (bacterial motion)

> Chemotaxis: Bacteria move along chemical gradient, towards food and away from noxious substances

Signaling pathway components for *E coli* chemotaxis





How does the signaling network allow the cell response to be sensitive to various different stimuli, and,

□ yet robust enough to withstand noise ?

Example: B-Cell Response signaling network



- Breakdown of communication \rightarrow disease.
- Hijacked by intracellular infectious agents for proliferating.



Reconstructing the complete set of interactions



Treatments

Correlation analysis of activity

Dheeraj Kumar, Kanury VS Rao (ICGEB)

Which nodes influence which other nodes ?

Block activation of a node, and find out how other nodes behave in its absence



Surprise: e.g., p38 affects and is affected by many other nodes !

Why?







Studying progressively more complex kinase cascades



The MAP-Kinase cascade Present in all eukaryotic cells



The Huang-Ferrell model (1996)

 $KKK + E1 \rightleftharpoons KKK \cdot E1 \longrightarrow KKK^* + E1$ k₁ [1] $KKK^* + E2 \rightleftharpoons KKK \cdot E2 \longrightarrow KKK + E2$ [2] $KK + KKK^* \rightleftharpoons KK \cdot KKK^* \longrightarrow KK \cdot P + KKK^*$ [3] KK-P + KK P'ase = KK-P·KK P'ase → KK + KK P'ase [4] + KKER & KK-PP-KK P'acies 10 Kk-PP-KK P'acies keal SPecies 22 chemiceacie + Kr K-P + K P' ase $\implies K-P \cdot K P'$ ase $\implies K + K P'$ ase [8] $K-P + KK-PP \rightleftharpoons K-P \cdot KK-PP \longrightarrow K-PP + KK-PP$ [9] K-PP + K P'ase ₩ KK-PP·K P'ase d10 → K-P + K P'ase [10]

Connects MAPK cascade structure to its dynamics





Ultrasensitivity in stimulus-response of MAPK cascade by dual phosphorylation First phosphorylation of MAPKK driven



input stimulus (E1 top in multiples of the EC50)



First phosphorylation of MAPKK driven by linearly increasing input stimulus (MAPKKK*) \Rightarrow rate & equilibrium level of phosphorylation of the substrate increase **linearly** with input. Second phosphorylation driven by a

Second phosphorylation driven by a linearly increasing input stimulus (MAPKKK*) and a linearly increasing substrate concentration (MAPKK*) \Rightarrow rate & equilibrium level increase as the square of the input stimulus.

Fit to Hill equation:

$$y = x^{nH}/(K+x^{nH})$$

nH: Hill coefficient represents degree of cooperativity in ligand binding to enzyme or receptor

AV Hill (1886-1977)

^{10⁻¹} (=1 for independent binding,

>I implies cooperative effect)

Experimental validation in Xenopus oocyte extract

[malE-Mos], µM

Agreement with model predictions

Intra-cellular signaling networks:"Neural" networks trained by evolution Multi-layer feed-forward neural

D Bray, Nature (1995)

Alberts et al, Molecular Biology of the Living Cell, 3rd ed