Overview of biological networks
Outline

• Examples of biological networks
• Problems for Systems Biology
• Molecular basis (elements of networks)
• Experimental techniques
• Network representations
Examples of biological networks

- Molecular interactions
- Functional interactions and regulation
- Metabolism and chemical networks
- Genomic data as networks
- [neuronal, mechanical, physiological]
Examples of biological networks

- Molecular interactions
- Functional interactions and regulation
- Metabolism and chemical networks
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- [neuronal, mechanical, physiological]
Examples of biological networks

- Protein-protein interactions

\[ A + B \leftrightarrow AB \]

\[ K_d = \frac{[A][B]}{[AB]} \]

- Homo
  \[ K_D = 10^{-9} - 10^{-12} \text{M} \]
- Hetero
  \[ K_D = 10^{-6} - 10^{-9} \text{M} \]
Examples of biological networks

- Protein-protein interactions
  proteins ~5000
  interactions ~7000

Databases:
- BindDB
- MIPS
- DIP

A comprehensive analysis of protein-protein interactions in S.cerevisiae.
Examples of biological networks

- Protein-DNA interactions (TF-upstream binding)

Lee TI et al. Transcriptional regulatory networks in S.cerevisiae
Examples of biological networks

• Molecular interactions
• Functional interactions and regulation
• Metabolism and chemical networks
• Genomic data as networks
• [neuronal, mechanical, physiological]
Examples of biological networks

• Regulation

Drew Endy (MIT)
Examples of biological networks

- Regulation
Examples of biological networks

- Molecular interactions
- Functional interactions and regulation
- Metabolism and chemical networks
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- [neuronal, mechanical, physiological]
Biochemical reactions

• Biochemical, metabolic reactions
  • “Chemical engine”
  • Determines cell physiology
  • Similar in all organisms.

• KEGG
• EcoCyc
• Metabolic Fluxes
Biochemical Pathways
Metabolic Pathways

KEGG database
Metabolic Pathways

KEGG database
Metabolic Pathways

KEGG database
Metabolic Pathways

KEGG database

D-erythrose 4-phosphate → 2.2.1.2 → D-sedoheptulose 7-phosphate → 2.2.1.1 → D-xylulose 5-phosphate

D-fructose 6-phosphate → 2.2.1.1 → D-glyceraldehyde 3-phosphate → 2.7.6.1 → ATP

5-phospho-alpha-D-ribose 1-diphosphate → 2.2.1.1

D-ribose 5-phosphate
Examples of biological networks

- Molecular interactions
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Functionally related genes

Your Input:
- COG0512 - Anthranilate/para-aminobenzoate synthases component II

Predicted Functional Associations: Score
- COG0147 - Anthranilate/para-aminobenzoate synthases component I 0.998
- COG0547 - Anthranilate phosphoribosyltransferase 0.958
- COG0134 - Indole-3-glycerol phosphate synthase 0.930
- COG0135 - Phosphoribosylanthranilate isomerase 0.863
- COG0159 - Tryptophan synthase alpha chain 0.843
- COG0133 - Tryptophan synthase beta chain 0.791
- COG0128 - 5-enolpyruvylshikimate-3-phosphate synthase 0.707
- COG0169 - Shikimate 5-dehydrogenase 0.707
- COG0115 - Branched-chain amino acid aminotransferase/4-amino-4-deoxychorismate 1 [...], 0.555
- COG0082 - Chorismate synthase 0.464
Problems

1. Derive networks
   - from experimental data, design of experiments.

2. Structure of the network:
   - descriptive
   - functional.

3. Dynamics:
   - steady state
   - response
   - computation
   - fluctuations

4. Evolution: cell’s point of view
Kitano’s milestones

• understanding of structure of the system, such as gene regulatory and biochemical networks, as well as physical structures,

• understanding of dynamics of the system, both quantitative and qualitative analysis as well as construction of theory/model with powerful prediction capability,

• understanding of control methods of the system,

• understanding of design methods of the system,

References:
Molecular basis
(elements of networks)

- protein-protein interactions
- regulation
- enzymatic kinetics
Molecular basis
(elements of networks)

• protein-protein interactions
  • regulation
  • enzymatic kinetics
Protein-protein interactions

A

—

B
Protein-protein interactions
Molecular basis
(elements of networks)

- protein-protein interactions
- regulation (slides from by E.Domany)
- enzymatic kinetics
Central Dogma

Gene (DNA) → Transcription → mRNA → Translation → Protein

Cells express different subset of the genes in different tissues and under different conditions.
Regulation

**TRANSCRIPTION:**
- DNA → MESSENGER RNA

**mRNA IS PROCESSED (SPILED):**

**TRANSCRIPTIONAL CONTROL**
- RNA PROCESSING CONTROL
- RNA TRANSPORT CONTROL
- RNA DEGRADATION
- TRANSLATIONAL CONTROL
- PROTEIN ACTIVITY

**PROTEIN SYNTHESIS:**
- DNA → mRNA → RIBOSOME → PROTEIN
TRANSCRIPTION – CLOSER LOOK

RNA POLYMERASE attaches to DNA, moves along it, opens double helix, synthesizes mRNA.

CONTROL of expression by assisting or blocking attachment of RNA POLYMERASE to DNA.

RNA POLYMERASE binds at a specific region, the promoter, at the start of the gene, if an activator is attached at an adjacent specific regulatory binding sequence (operator) and a repressor is not attached to its own operator.
TRANSCRIPTION – CLOSER LOOK

RNA POLYMERASE attaches to DNA, moves along it, opens double helix, synthesizes mRNA.

CONTROL of expression by assisting or blocking attachment of RNA polymerase to DNA.

RNA polymerase binds at a specific region, the promoter, at the start of the gene, if an activator is attached at an adjacent specific regulatory binding sequence (operator) and a repressor is not attached to its own operator.
TRANSCRIPTION – CLOSER LOOK

RNA POLYMERASE ATTACHES TO DNA, MOVES ALONG IT, OPENS DOUBLE HELIX, SYNTHESIZES MRNA.

CONTROL OF EXPRESSION BY ASSISTING OR BLOCKING ATTACHMENT OF RNA POLYMERASEASE TO DNA.

RNA POLYMERASE DOES NOT BIND AT THE PROMOTER, AT THE START OF THE GENE, IF A REPRESSOR IS ATTACHED TO ITS OWN OPERATOR
RECOGNITION OF BINDING MOTIFS IN DNA
RECOGNITION OF BINDING MOTIFS IN DNA 2

HOMEODOMAIN
TRYPTOPHAN REPRESSOR-SWITCH OPERON

REGULATORY “NETWORK”
lac OPERON – E-COLI (PROCARYOTIC)

OPERON – SET OF GENES PLACED ONE AFTER THE OTHER ON DNA, TAKING PART IN ONE PROCESS (BREAKDOWN OF lactose). E-COLI PREFERENCES glucose – WILL PROCESS lactose ONLY UNDER ( –glucose/+ lactose ) CONDITIONS. 4-SWITCH!

Cyclic AMP CONCENTRATION WHEN +glucose
allo lactose CONCENTRATION WHEN +lactose

ACTIVATOR: + (ACTIVE IF COMPLEX)

REPRESSOR: + (ACTIVE IF FREE)

--glucose/+lactose
EUCARYOTIC – MUCH MORE COMPLEX

- RNA POLYMERASE CANNOT INITIATE TRANSCRIPTION
- GENERAL TRANSCRIPTION FACTORS ASSEMBLE, FORM COMPLEX ON OPERATOR NEAR PROMOTER - ABUNDANT

**Human TBP / TATA Complex**
- minor groove
- bent DNA

**TBP – SUBUNIT OF TFIID**
• SPECIFIC REGULATORS OF TRANSCRIPTION (ENHANCERS) CAN ATTACH TO DNA MANY 1000 OF BP UPSTREAM, CAN EVEN BE PLACED DOWNSTREAM FROM START SITE VERY MINUTE AMOUNT PRESENT

• MAY NEED MORE THAN ONE TRANSCRIPTION FACTOR TO ACTIVATE GENE

proximity of GAL4 enhances 1000 fold the attachment of TFIIB to TFIID control of human beta-globin
REGULATORY NETWORKS

• TRANSCRIPTION FACTORS ARE PROTEINS THAT ACTIVATE OR REPRESS GENES’ TRANSCRIPTION INTO PROTEINS

• PROTEINS FORM COMPLEXES THAT INDUCE / TURN OFF / REGULATE A GENE’S TRANSCRIPTIONAL CAPACITY

COMPLEX NETWORKS OF REGULATION OF GENE EXPRESSION EMERGE
CANCER IS CAUSED BY THE BREAKDOWN OF SEVERAL IMPORTANT NETWORKS THAT GUARD AGAINST UNCONTROLLED PROLIFERATION
Experimental techniques

- Two-hybrid
- AffiChips
- Micoarrays
- ChIP
- Mass.spec/TAP
- Literature mining
- Genomics
Experimental techniques

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Protein-protein interactions

Yeast two-hybrid assay:
Does a protein A interact with B?

- BAIT: Doesn't activate transcription
- PREY: Doesn't bind DNA

Activate transcription and grow on -his media
Protein-protein interactions

**Large scale yeast two-hybrid assay:**
Find pairs of interacting proteins

A comprehensive two-hybrid analysis to explore the yeast protein interactome.
Ito T et al, *PNAS* 2001

A comprehensive analysis of protein-protein interactions in *S. cerevisiae*.
Protein-protein interactions

A ——— B

Diagram showing a network of protein-protein interactions.
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In different tissues and under different conditions
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TRANSCRIPTION:
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mRNA IS PROCESSED (SPLICED)

PROTEIN SYNTHESIS:
DNA → RIBOSOME mRNA → PROTEIN

TRANSCRIPTIONAL CONTROL
RNA PROCESSING CONTROL
RNA TRANSPORT CONTROL
RNA DEGRADATION
TRANSLATIONAL CONTROL
PROTEIN ACTIVITY
FOUR BASES AS BASE PAIRS OF DNA

Specific hydrogen bonding between G and C and between A and T (A and U in RNA) generates complementary base-pairing.
Nucleic Acid Hybridization
FREE ENERGY “LANDSCAPE”

PERFECT MATCH

IMPERFECTION

STRINGENT HYBRIDIZATION

REDUCED-STRINGENCY HYBRIDIZATION

9/12/2003 7-17

HST.592 53
cDNA microarray expt

Prepare cDNA target

"Normal" Tumor

RT / PCR
Label with Fluorescent Dyes

Combine Equal Amounts

Hybridize target to microarray

Microarray Technology

Prepare Microarray

SCAN
Experimental techniques

- Two-hybrid
- AffiChips
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- Genomics
protein-DNA interactions

Chromatin Immunoprecipitation (ChIP)
protein-DNA interactions

Chromatin Immunoprecipitation (ChIP)
Experimental techniques

- Two-hybrid
- AffiChips
- Micoarrays
- ChIP
- Mass.spec/TAP
- Literature mining
- Genomics
Network representations

- Graphs
- Bipartite graphs
- Hypergraphs