

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

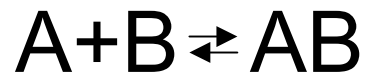
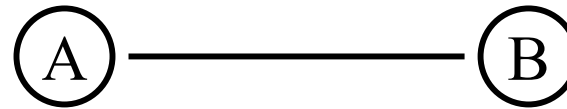
- Molecular interactions
- Functional interactions and regulation
- Metabolism and chemical networks
- Genomic data as networks
- [neuronal, mechanical, physiological]

Examples of biological networks

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Examples of biological networks

- Protein-protein interactions



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

Homo $K_D = 10^{-9} - 10^{-12} \text{M}$

Hetero $K_D = 10^{-6} - 10^{-9} \text{M}$

Examples of biological networks

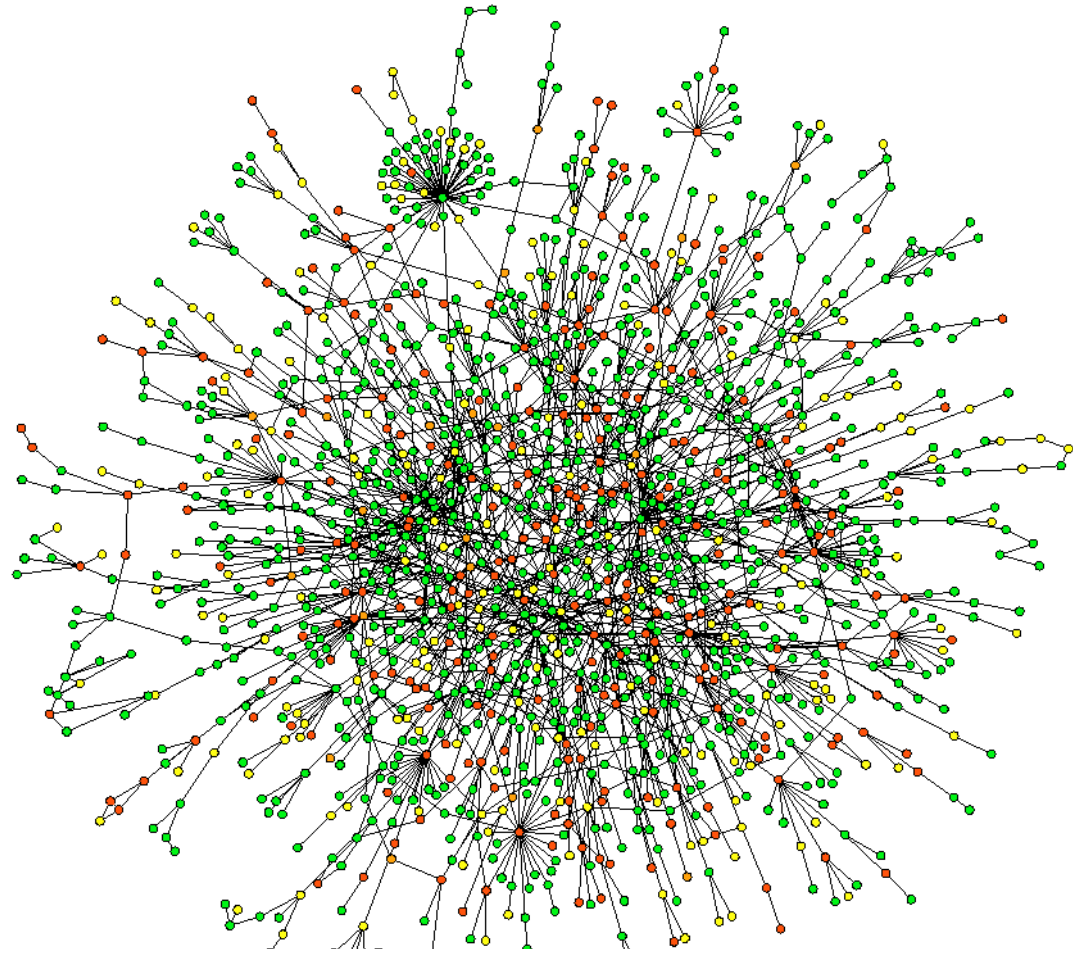
- Protein-protein interactions
proteins ~5000
interactions ~7000

Databases:

BindDB

MIPS

DIP

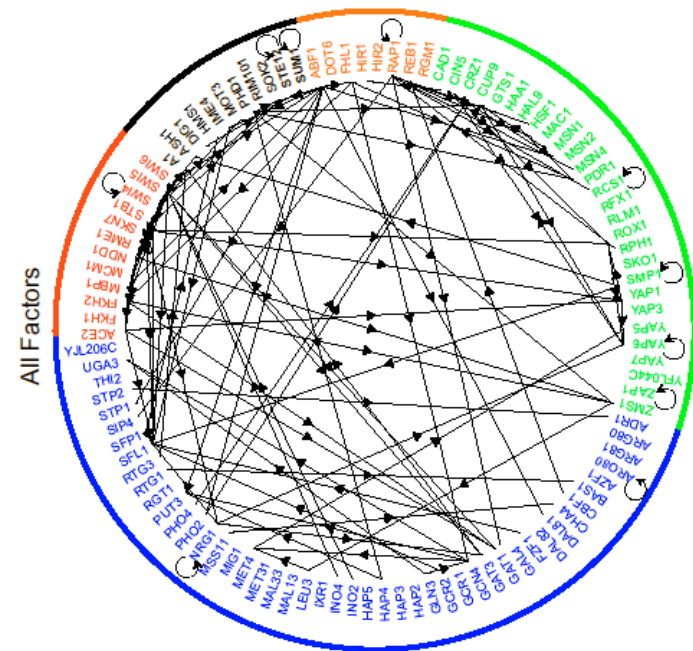


A comprehensive analysis of protein-protein interactions in *S.cerevisiae*.

Nature. 2000, 623-7. Uetz P et al

Examples of biological networks

- Protein-DNA interactions (TF-upstream binding)



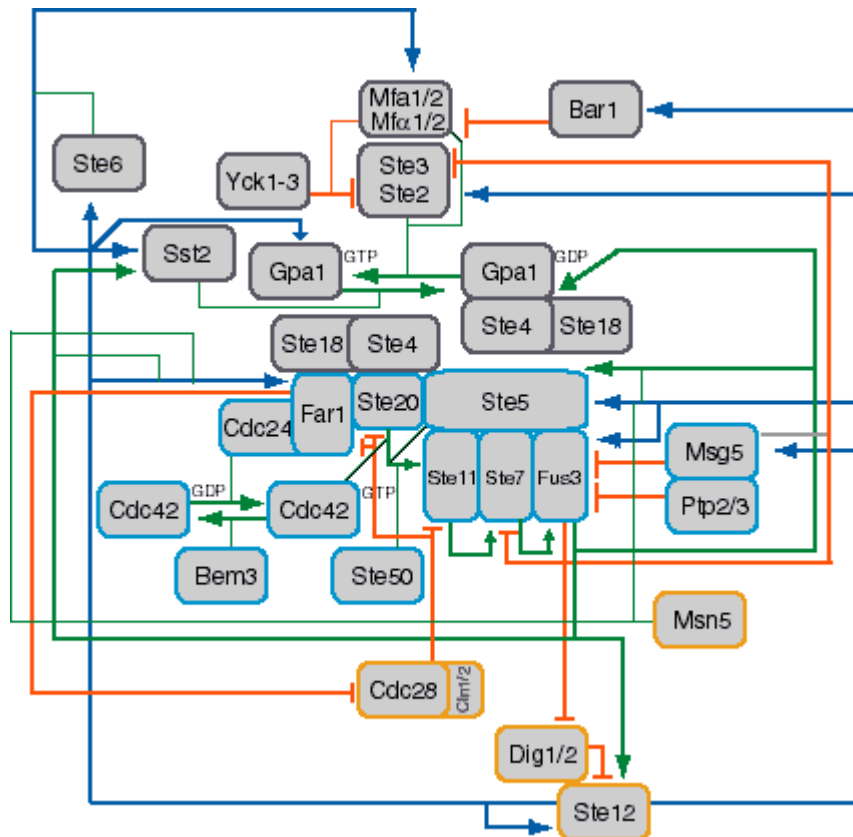
Lee TI et al. Transcriptional regulatory networks in *S. cerevisiae*
Science 2002 Oct 25; 298(5594):799-804

Examples of biological networks

- Molecular interactions
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Examples of biological networks

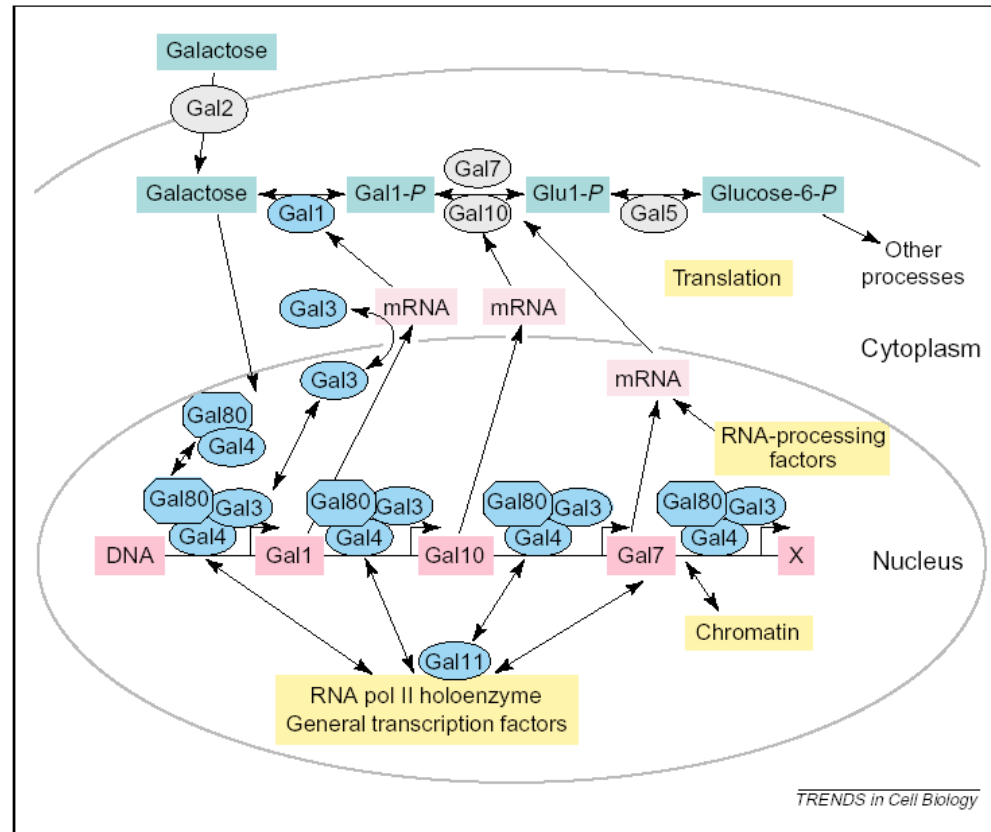
- Regulation



Drew Endy (MIT)

Examples of biological networks

- Regulation

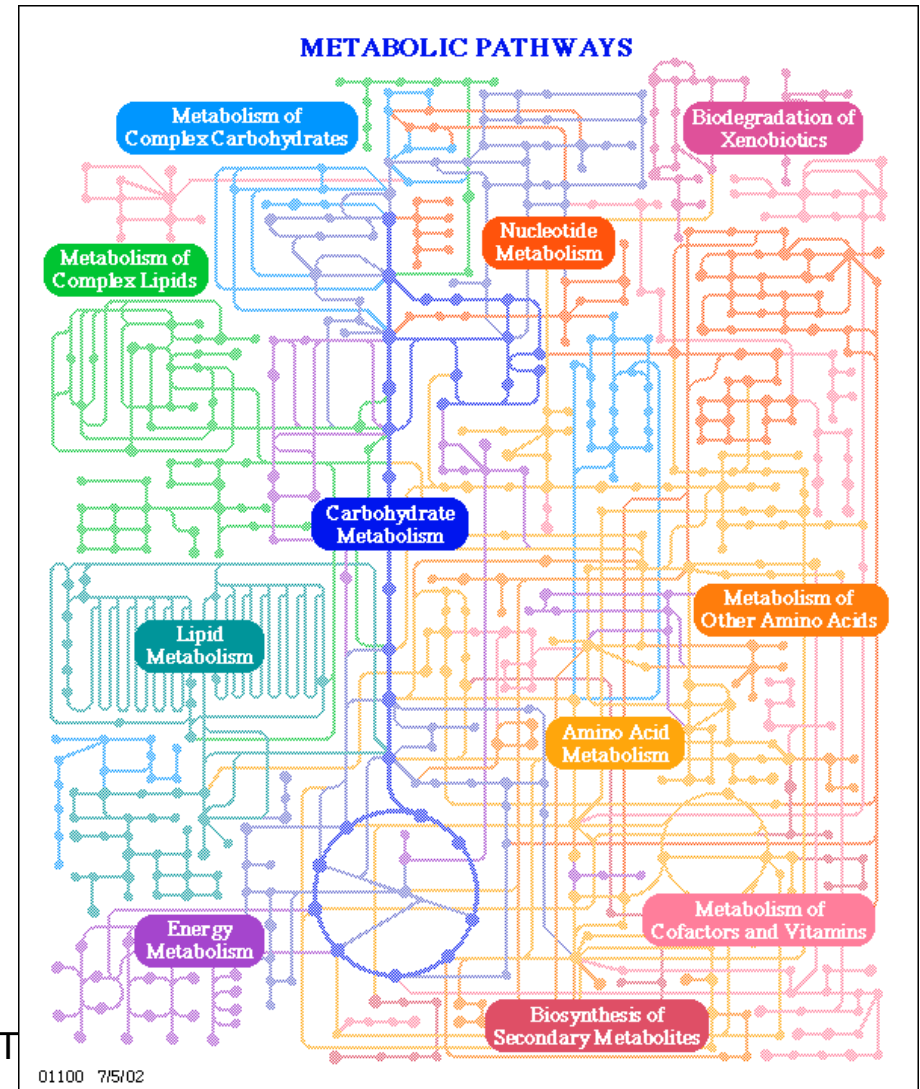


Examples of biological networks

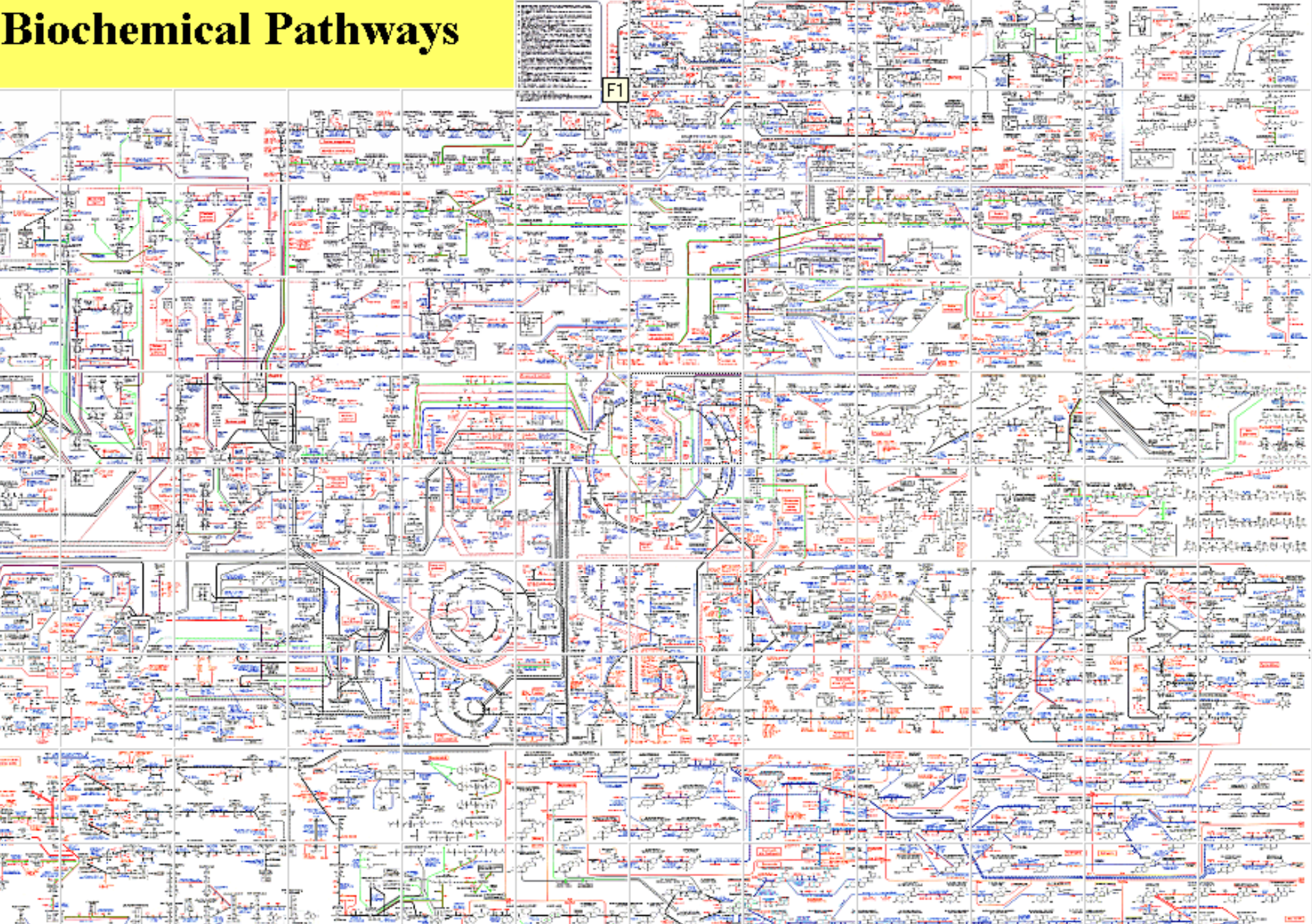
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Biochemical reactions

- Biochemical, metabolic reactions
 - “Chemical engine”
 - Determines cell physiology
 - Similar in all organisms.
- KEGG
- EcoCyc
- Metabolic Fluxes

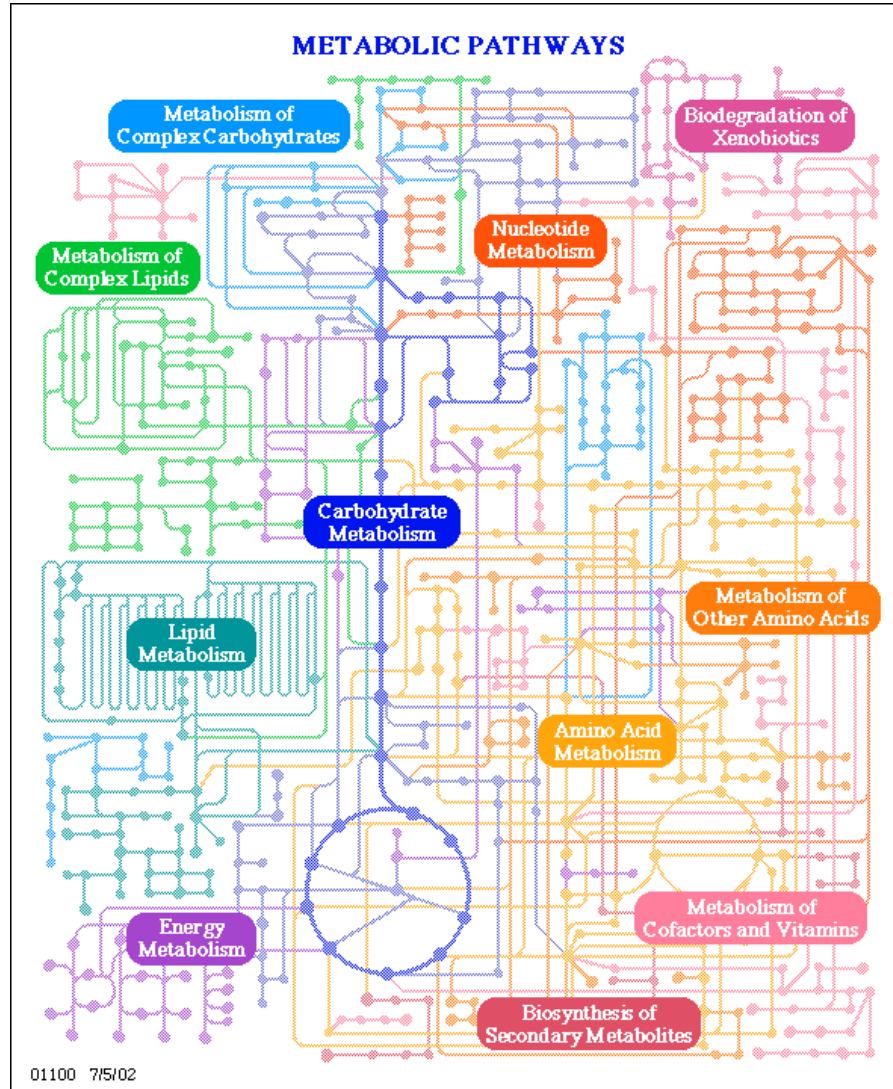


Biochemical Pathways

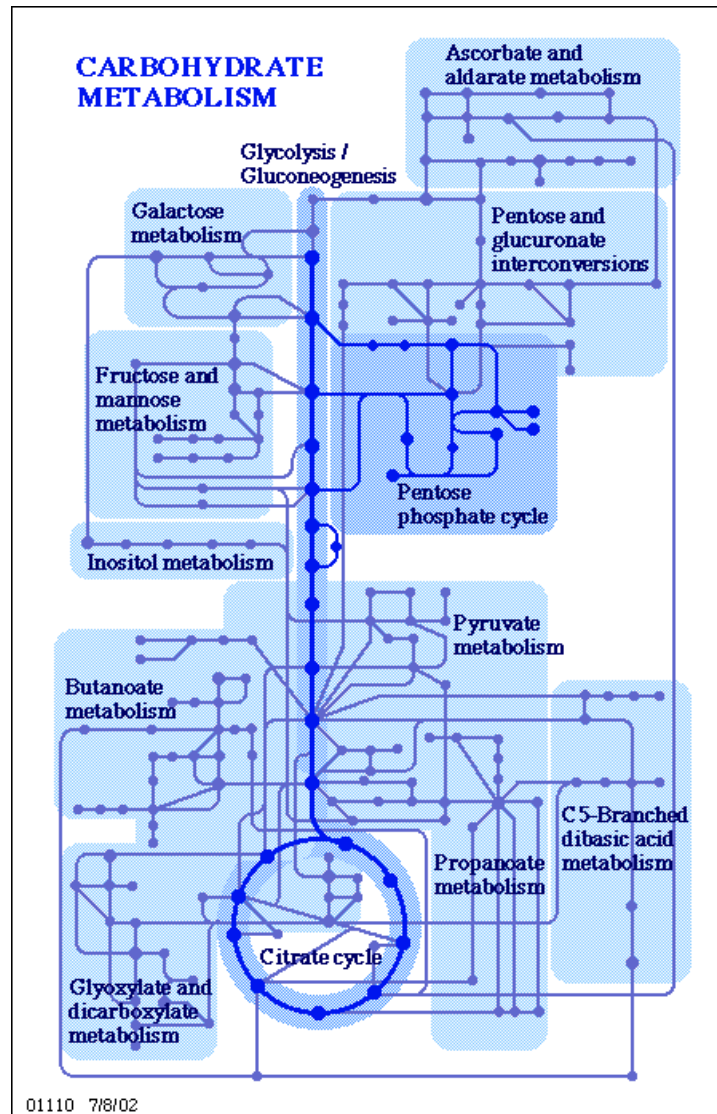


Other chart : Cellular and Molecular Processes

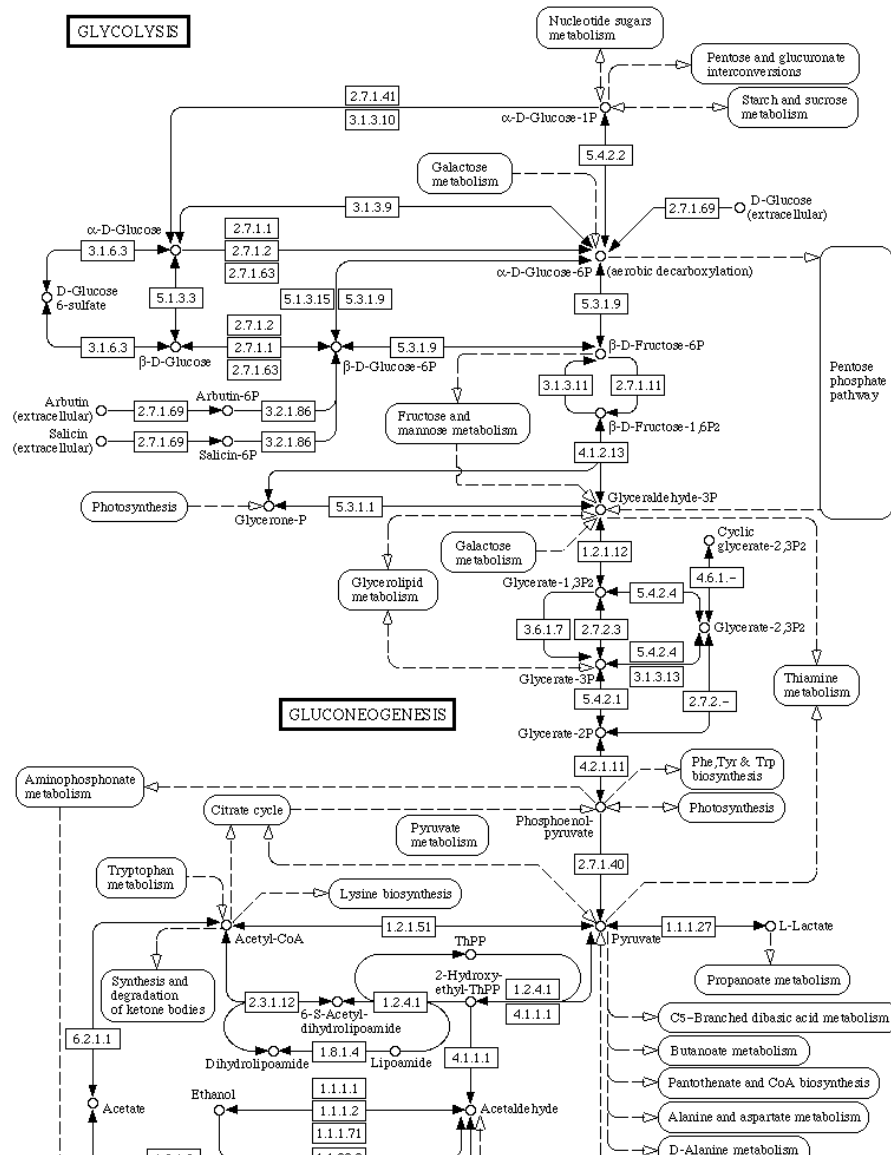
Metabolic Pathways



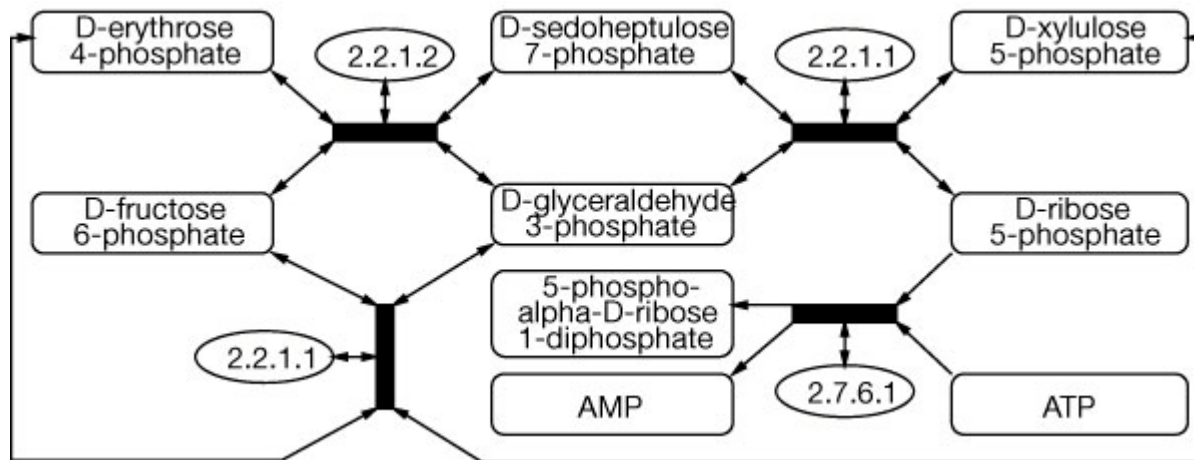
Metabolic Pathways



Metabolic Pathways



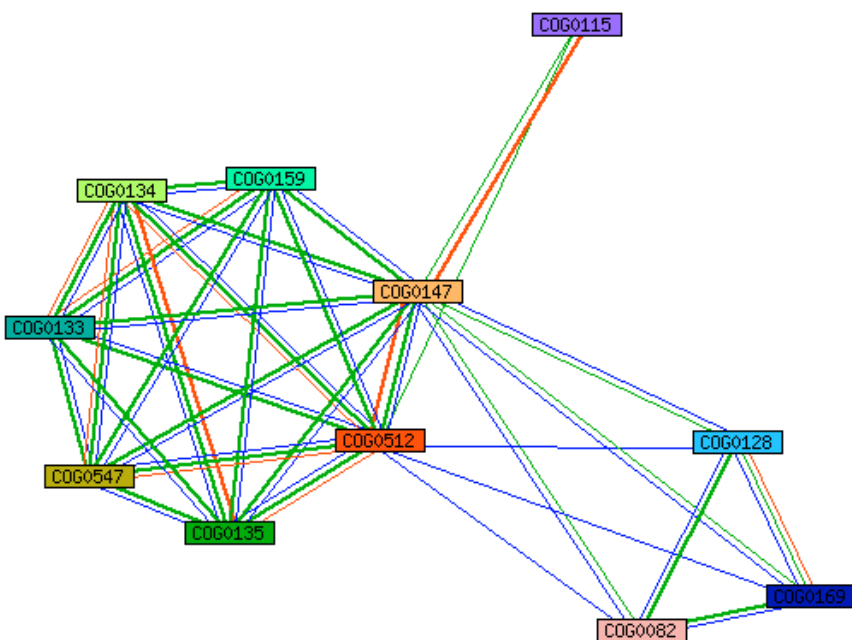
Metabolic Pathways



Examples of biological networks

- Molecular interactions
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- **Genomic data as networks**
- [neuronal, mechanical, physiological]

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	0.454

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:

- H. Kitano, Systems Biology: a brief overview, Science, 295:1662,2002
H. Kitano, Computational Systems Biology, Nature, 420:206-210, 2002

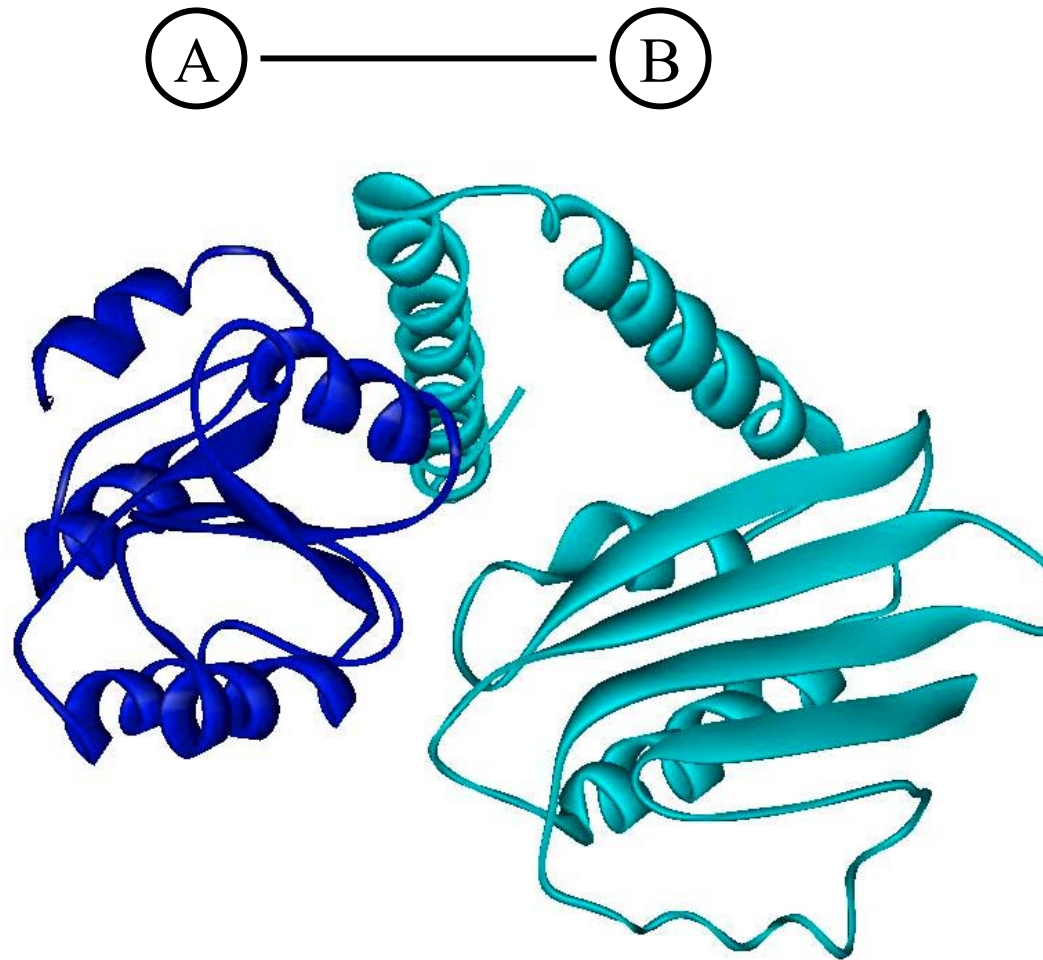
Molecular basis (elements of networks)

- protein-protein interactions
- regulation
- enzymatic kinetics

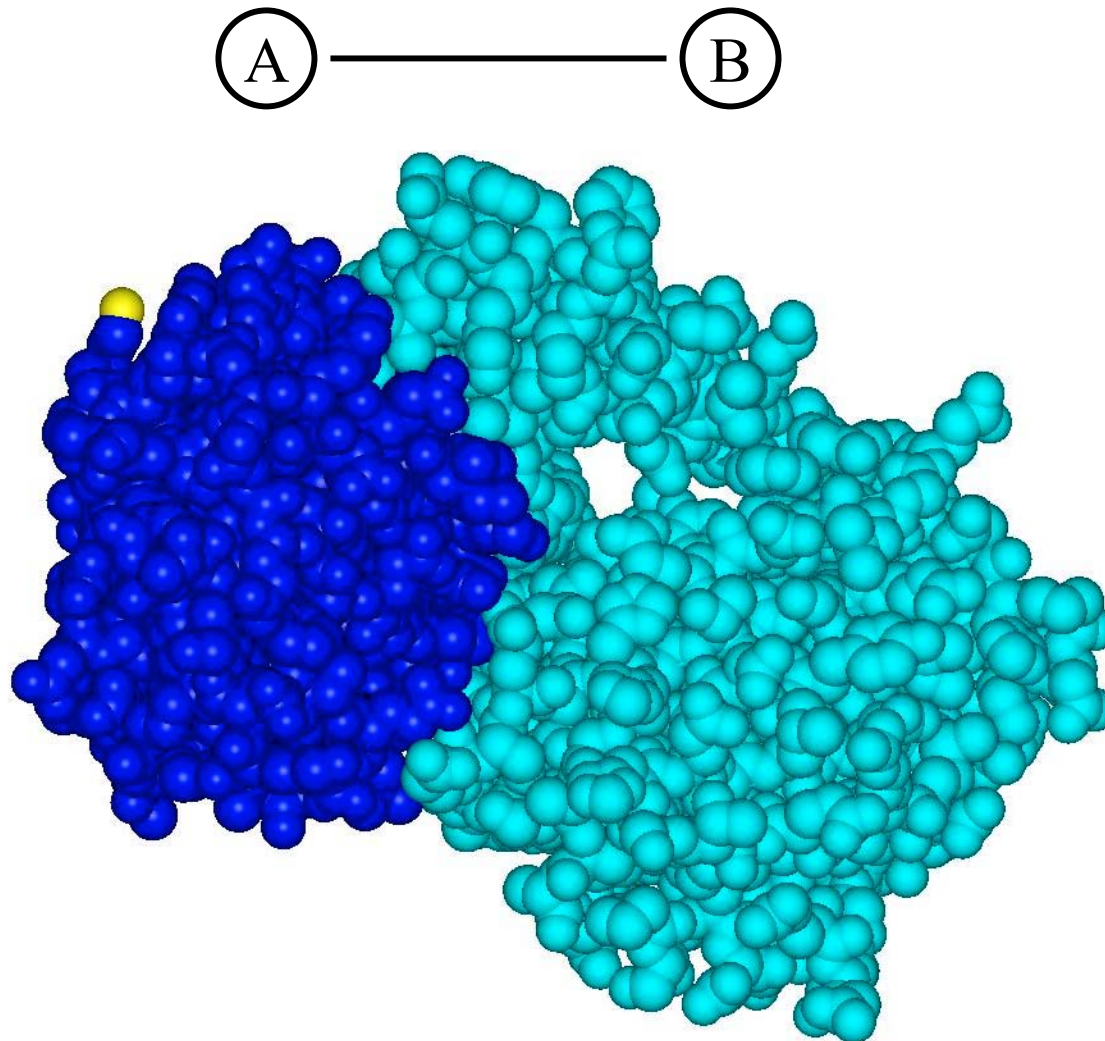
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Protein-protein interactions



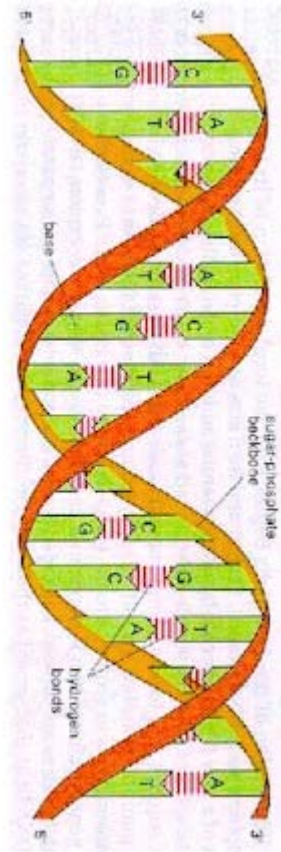
Protein-protein interactions



Molecular basis (elements of networks)

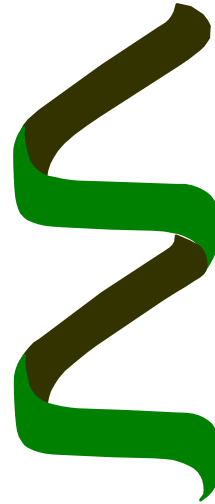
- protein-protein interactions
- regulation (slides from by E.Domany)
- enzymatic kinetics

Central Dogma



Transcription

Gene (DNA)



mRNA

Translation

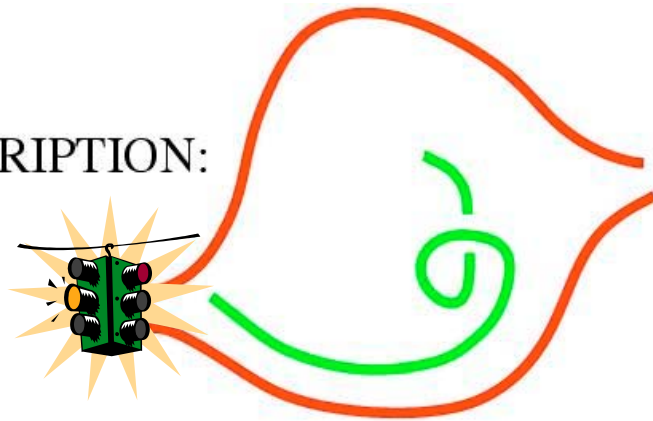


Protein

Cells express **different** subset of the genes
In different tissues and under different conditions

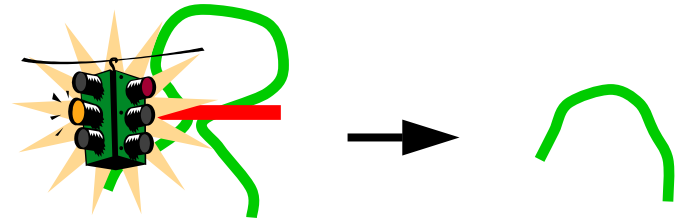
Regulation

TRANSCRIPTION:

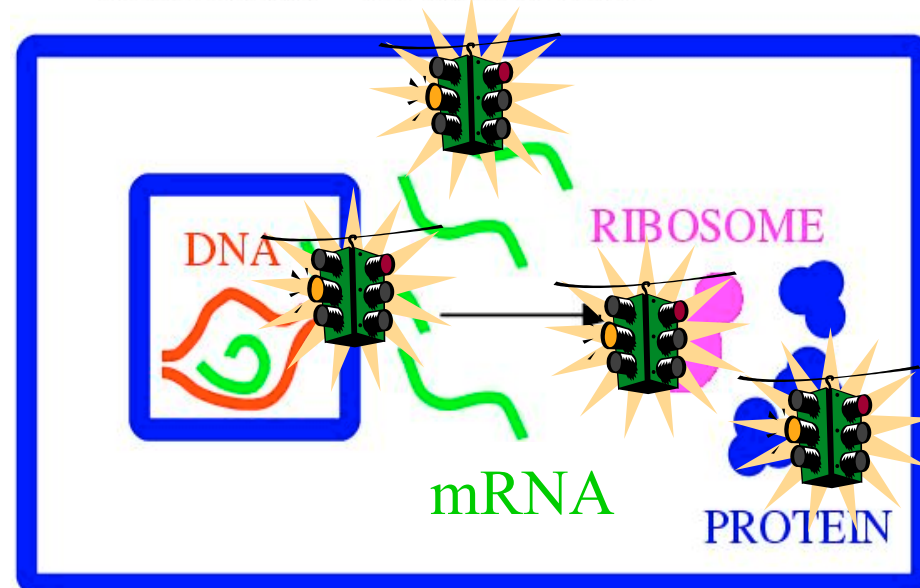


DNA → MESSENGER RNA

mRNA IS PROCESSED
(SPLICED)



PROTEIN SYNTHESIS:

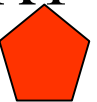
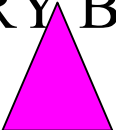


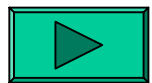
- TRANSCRIPTIONAL CONTROL
- mRNA PROCESSING CONTROL
- mRNA TRANSPORT CONTROL
- mRNA DEGRADATION
- TRANSLATIONAL CONTROL
- PROTEIN ACTIVITY

TRANSCRIPTION – CLOSER LOOK

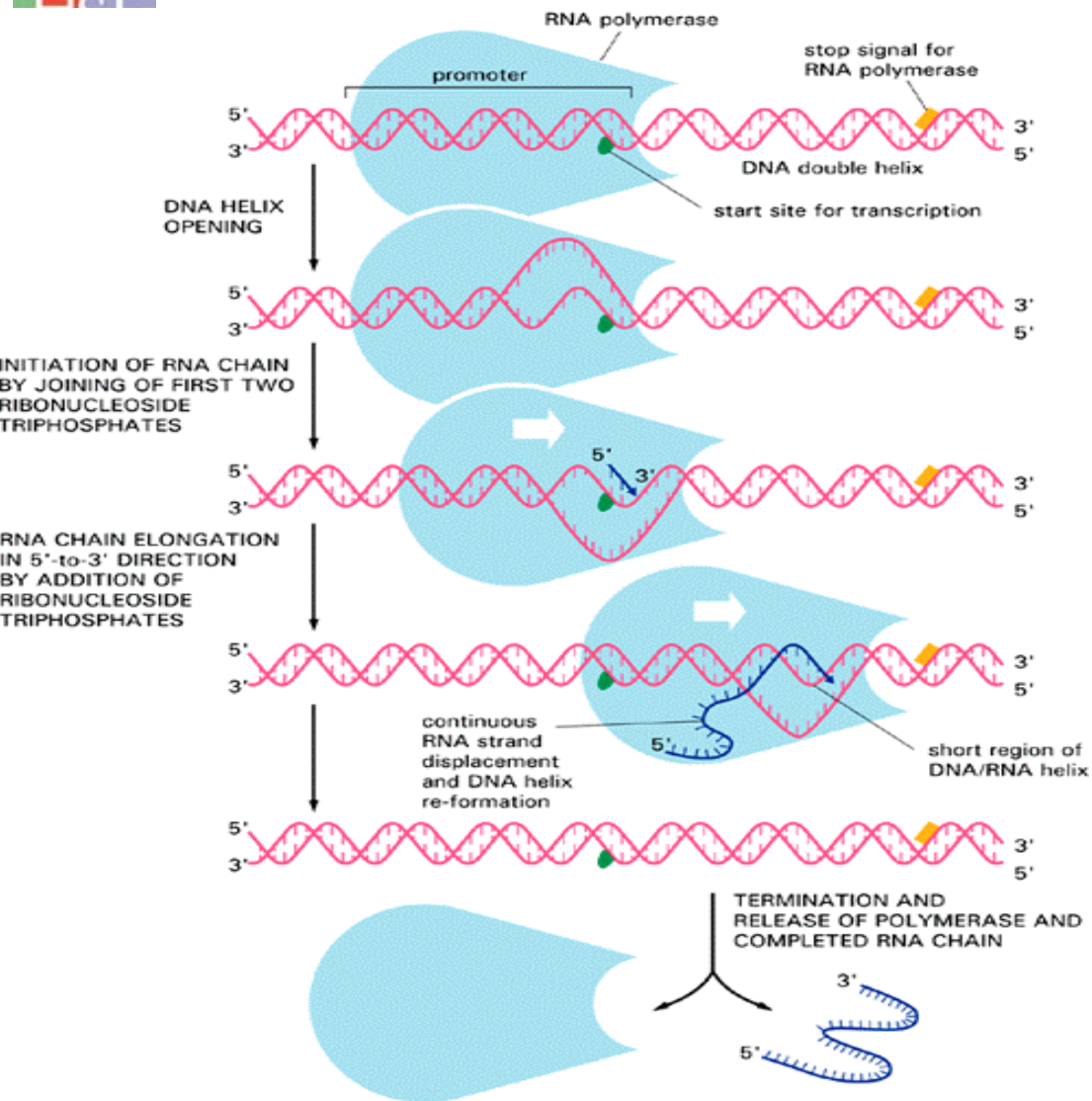
RNA POLYMERASE  ATTACHES TO DNA, MOVES ALONG IT, OPENS DOUBLE HELIX, SYNTHESIZES MRNA. 

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

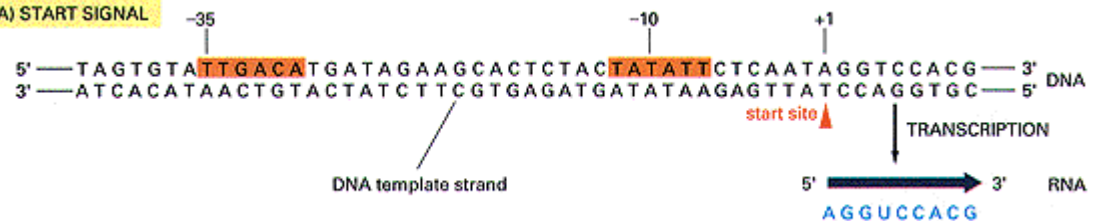
RNA POLYMERASE BINDS AT A SPECIFIC REGION, THE PROMOTER, AT THE START OF THE GENE, IF AN ACTIVATOR  IS ATTACHED AT AN ADJACENT SPECIFIC REGULATORY BINDING SEQUENCE (OPERATOR) AND A REPRESSOR  IS NOT ATTACHED TO ITS OWN OPERATOR 



TRANSCRIPTION START



(A) START SIGNAL



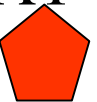
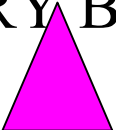
9/12/2003

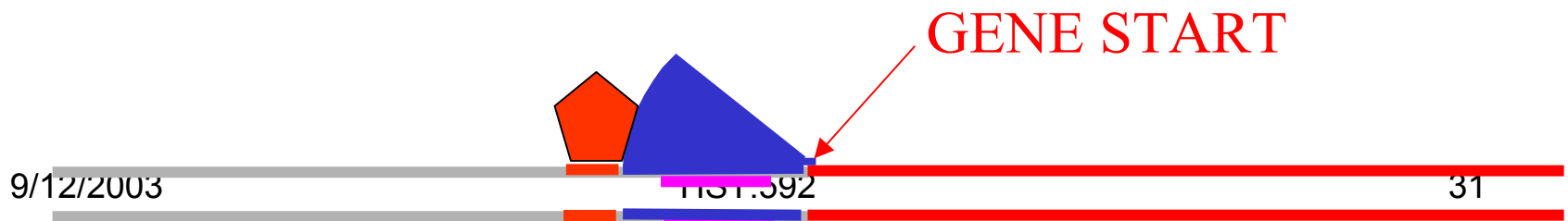


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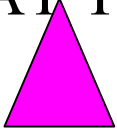
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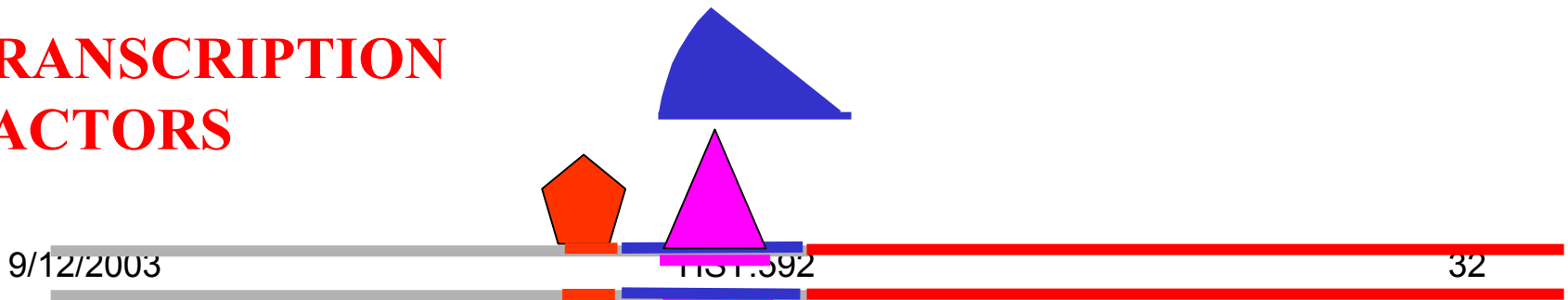
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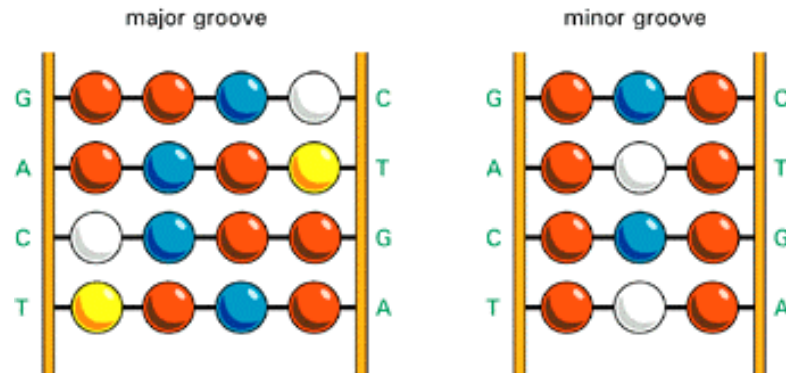
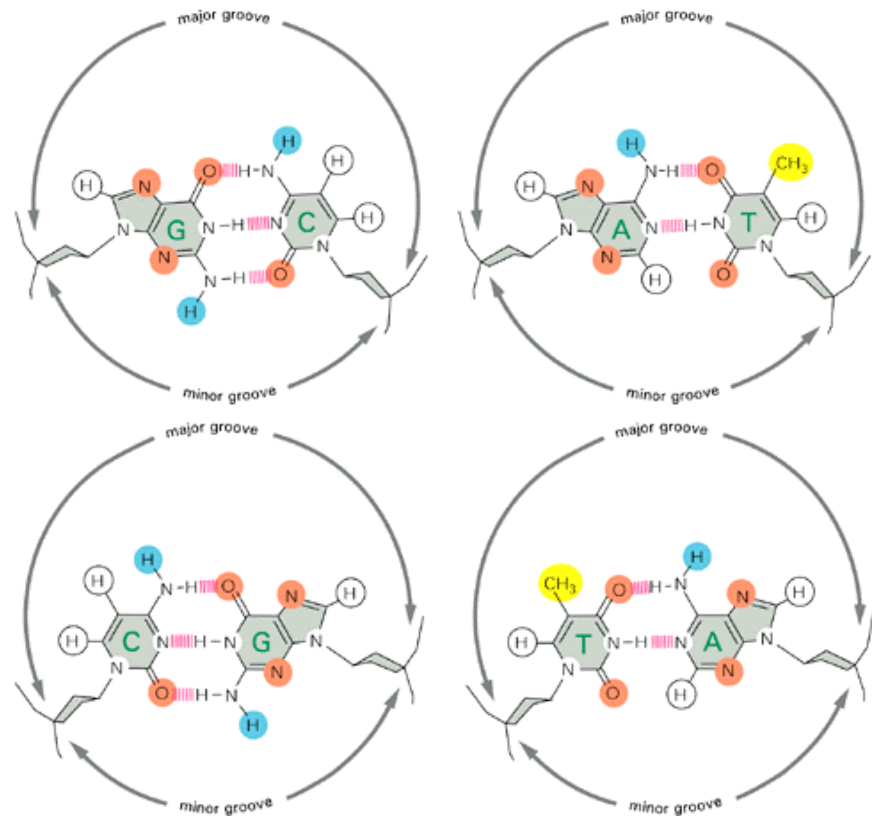
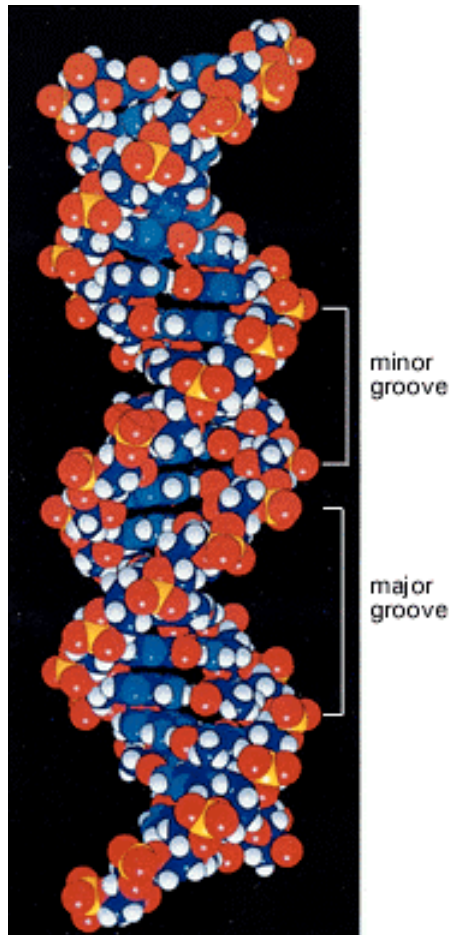
CONTROL OF EXPRESSION BY ASSISTING OR BLOCKING ATTACHMENT OF RNA POLYMERASE TO DNA.

RNA POLYMERASE DOES NOT BIND AT THE PROMOTER, AT THE START OF THE GENE, IF A REPRESSOR  IS ATTACHED TO ITS OWN OPERATOR

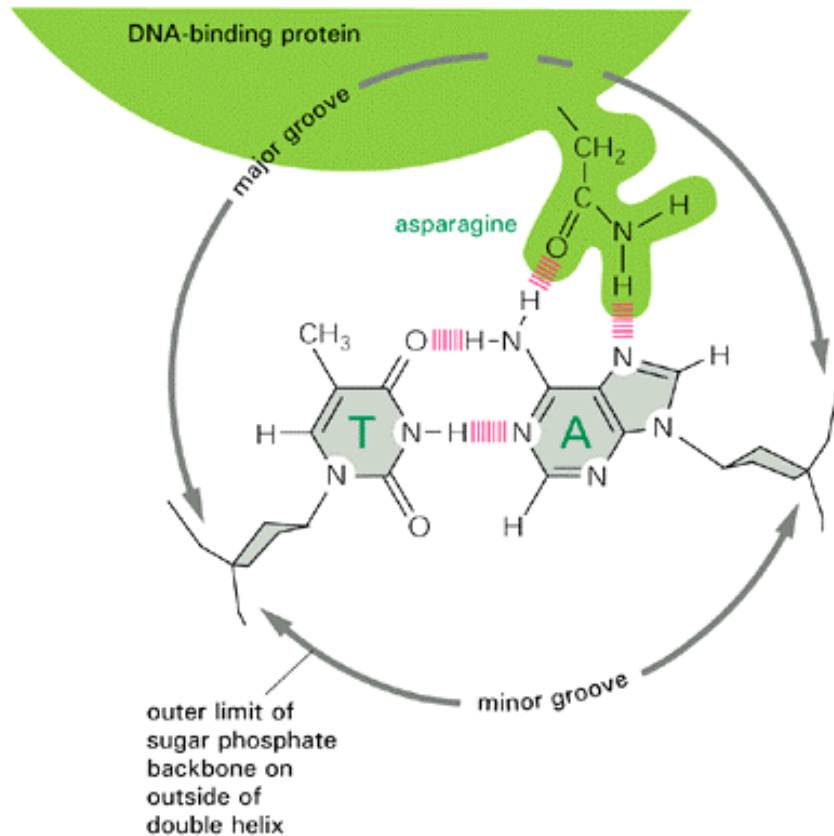
**TRANSCRIPTION
FACTORS**



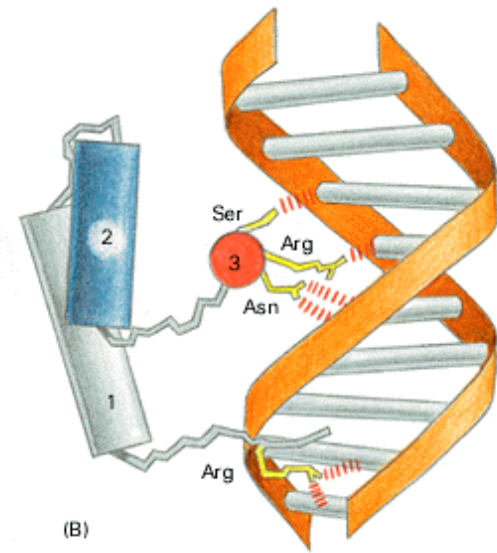
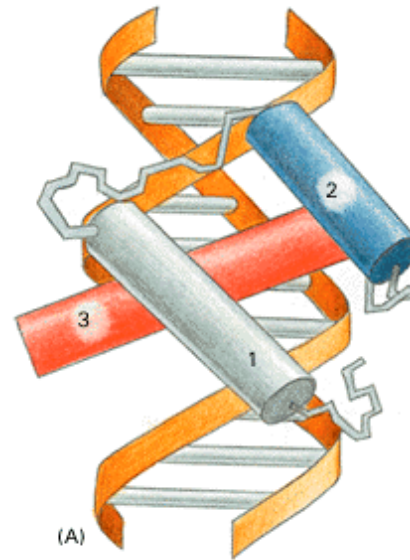
RECOGNITION OF BINDING MOTIFS IN DNA



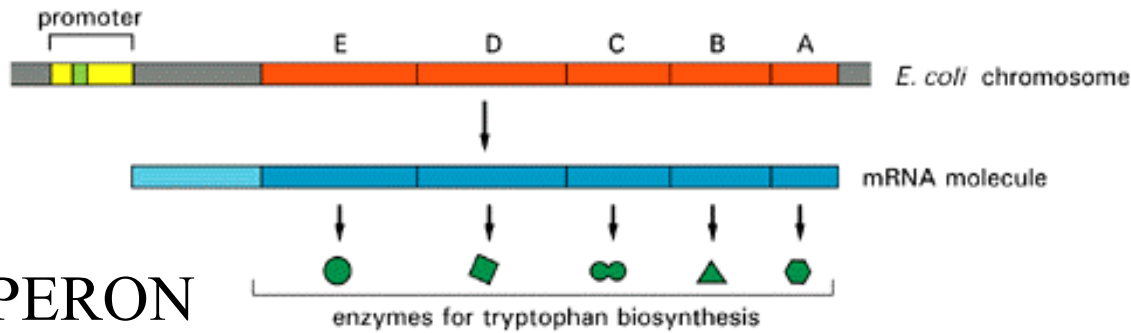
RECOGNITION OF BINDING MOTIFS IN DNA 2



HOMEODOMAIN

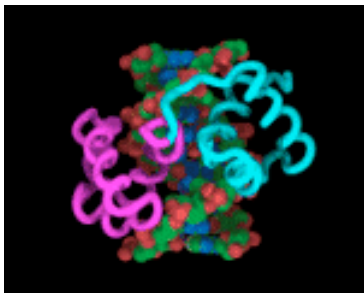
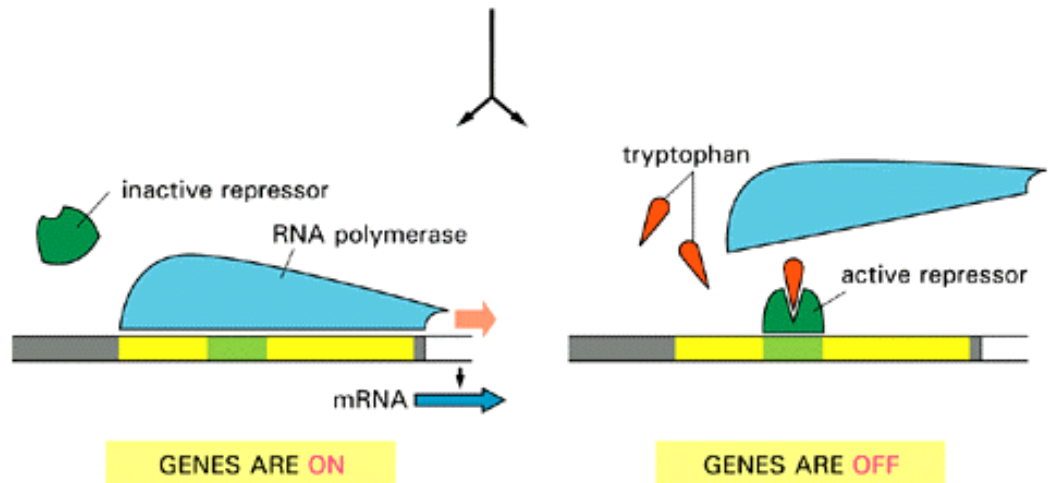
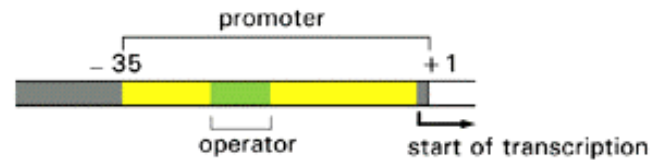


TRYPTOPHAN REPRESSOR-SWITCH



OPERON

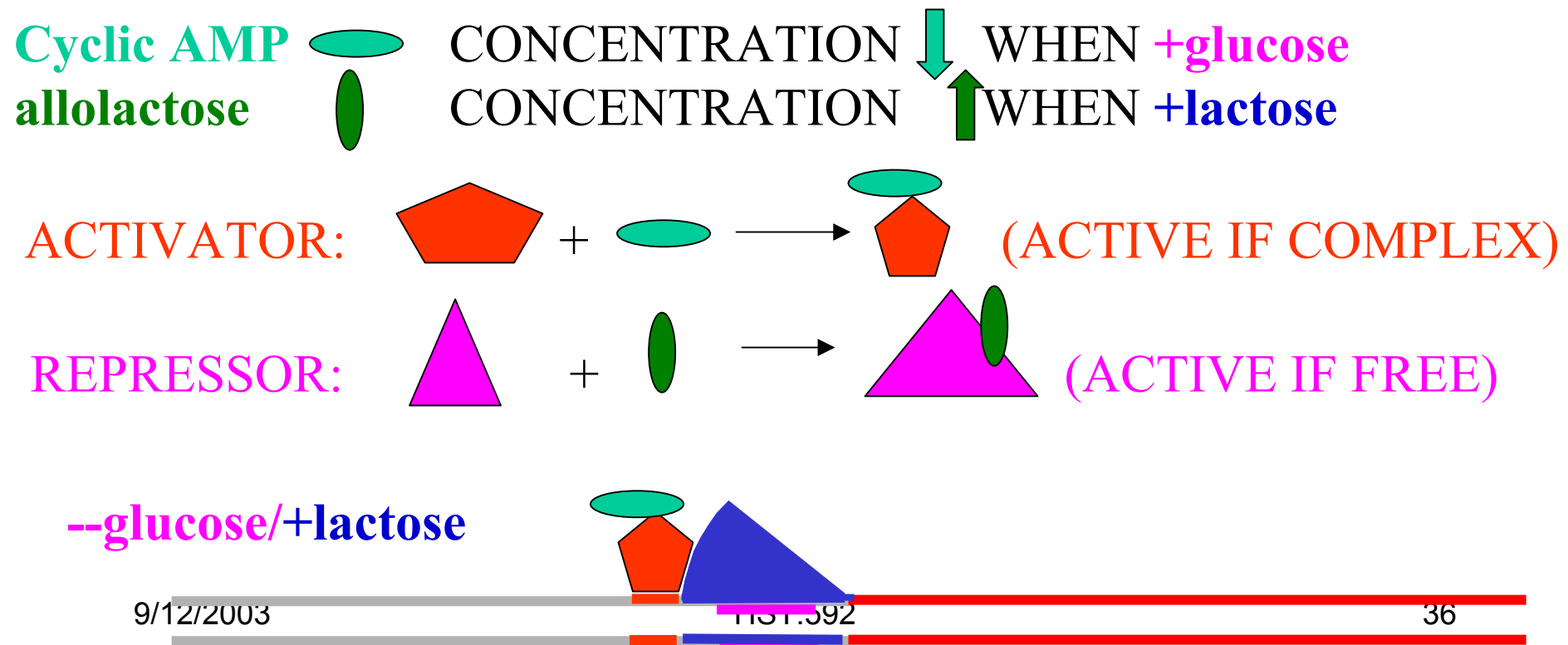
REGULATORY “NETWORK”

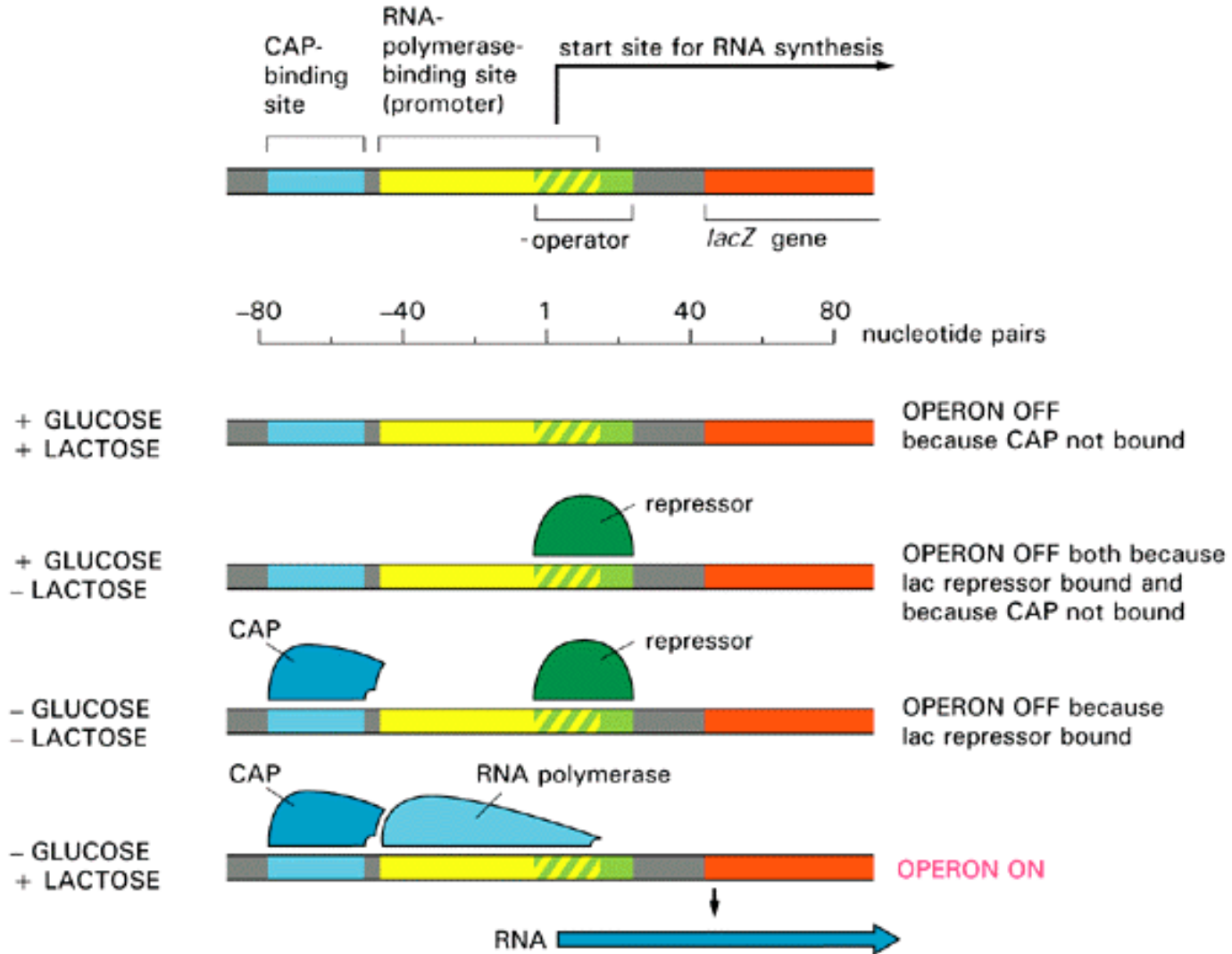


9/12/2003

lac OPERON – E-COLI (PROCARYOTIC)

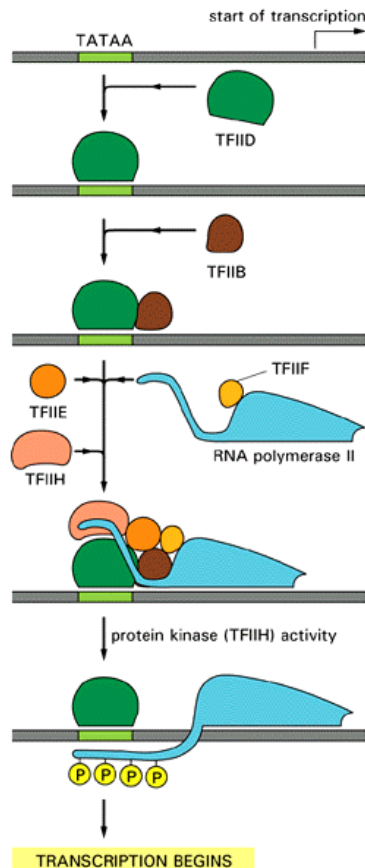
OPERON – SET OF GENES PLACED ONE AFTER THE OTHER ON DNA, TAKING PART IN ONE PROCESS (BREAKDOWN OF **lactose**). E-COLI PREFERS **glucose** – WILL PROCESS **lactose** ONLY UNDER (**–glucose/+ lactose**) CONDITIONS. **4-SWITCH!**





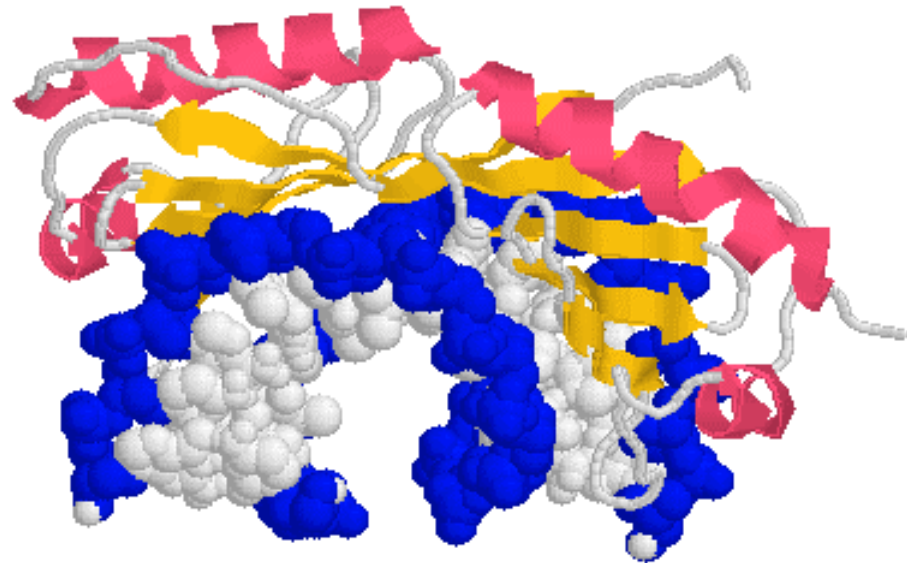
EUCARYOTIC – MUCH MORE COMPLEX

- 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^{PSL 504} SUBUNIT OF TFIID

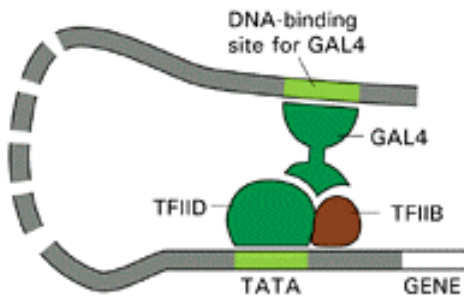
- **SPECIFIC** REGULATORS OF TRANSCRIPTION (**ENHANCERS**)

CAN ATTACH TO DNA MANY 1000 OF BP UPSTREAM,

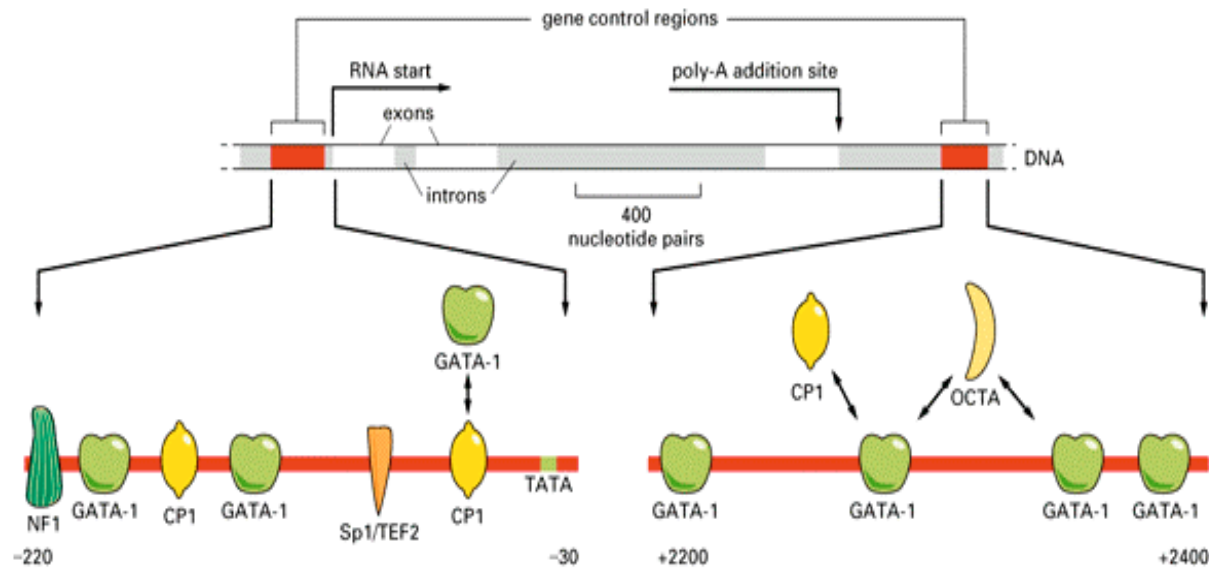
CAN EVEN BE PLACED DOWNSTREAM FROM START SITE

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



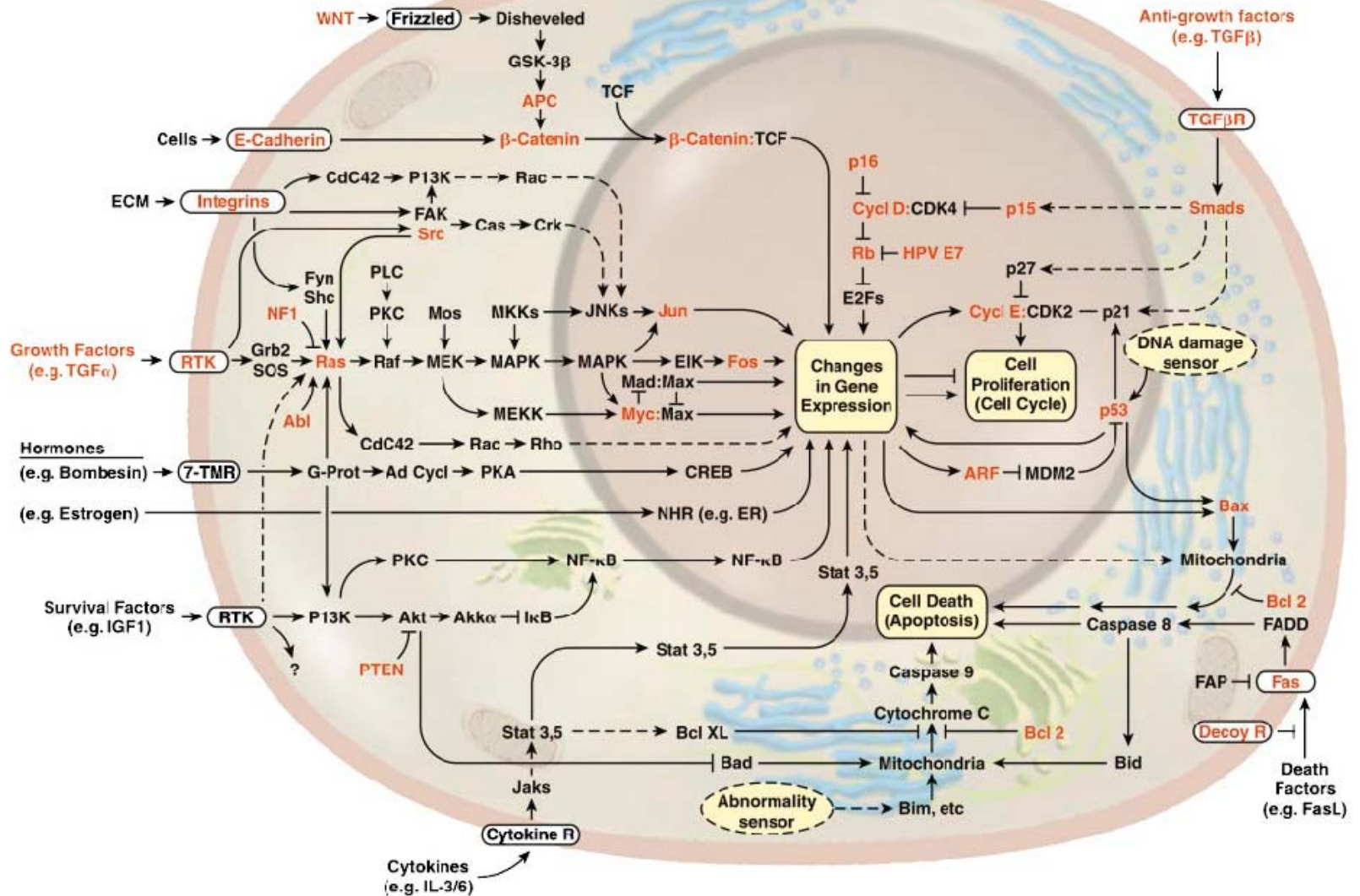
control of human beta-globin

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

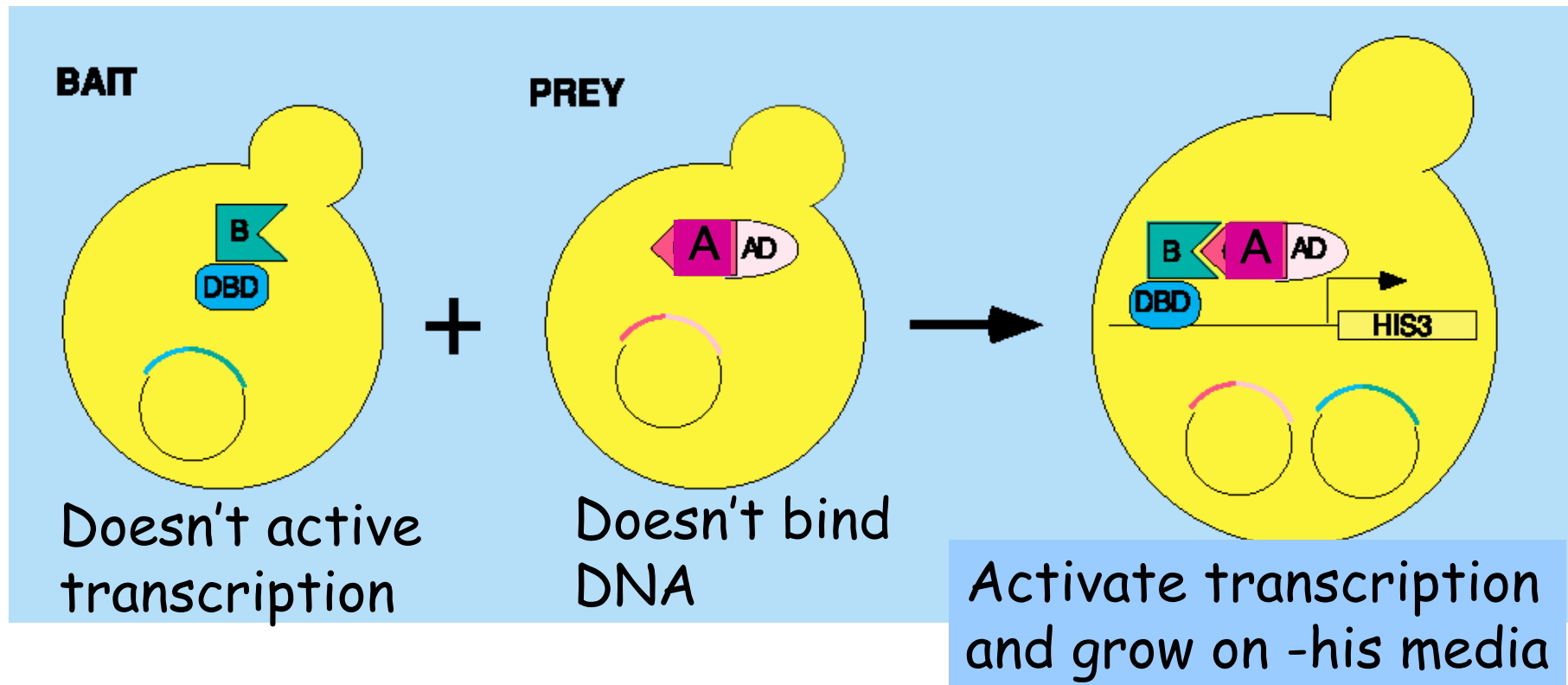
- Two-hybrid
- AffiChips
- Micoarrays
- ChIP
- Mass.spec/TAP
- Literature mining
- Genomics

Experimental techniques

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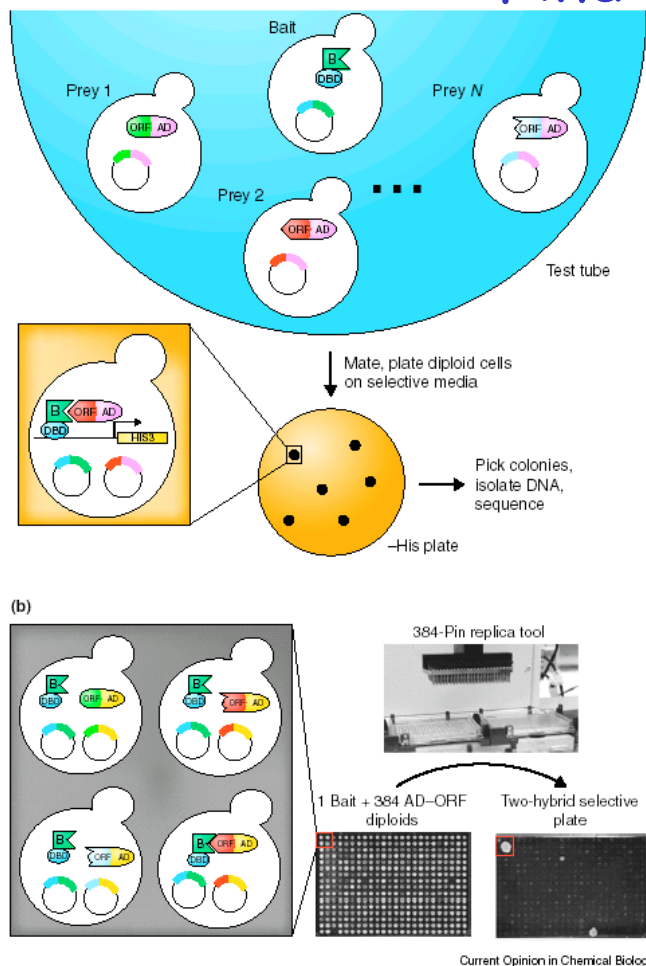
Protein-protein interactions

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



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.

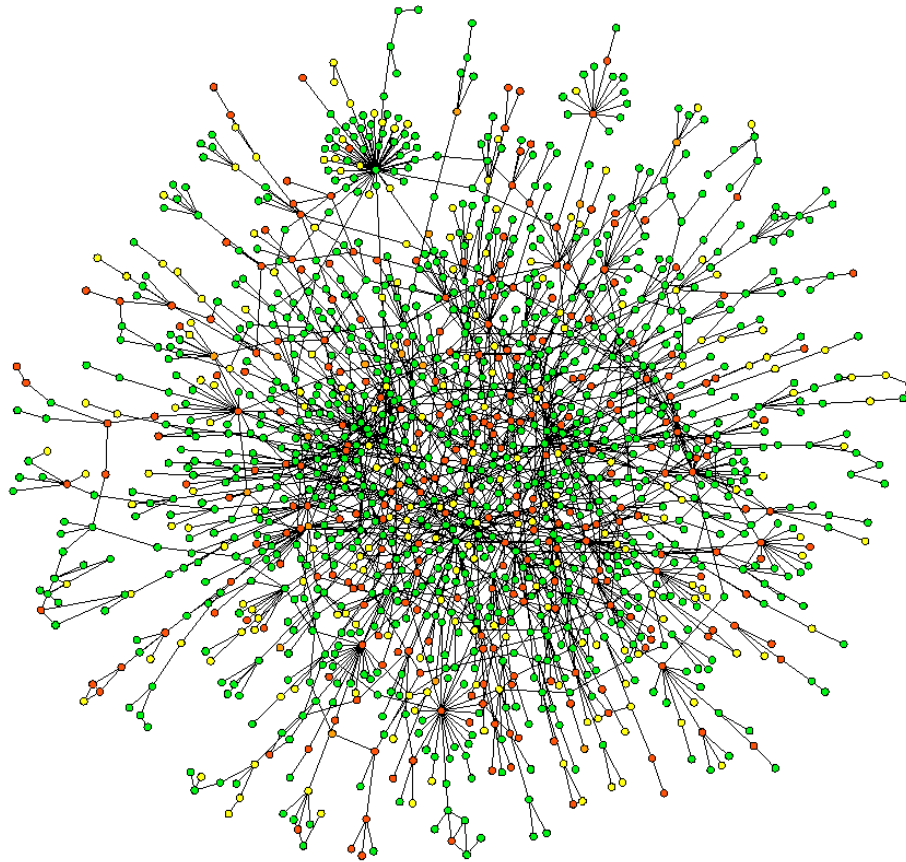
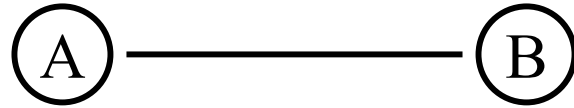
Ito T et al, *PNAS* 2001

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

P. Huetz et al, *Nature* 2000

HST 1.392

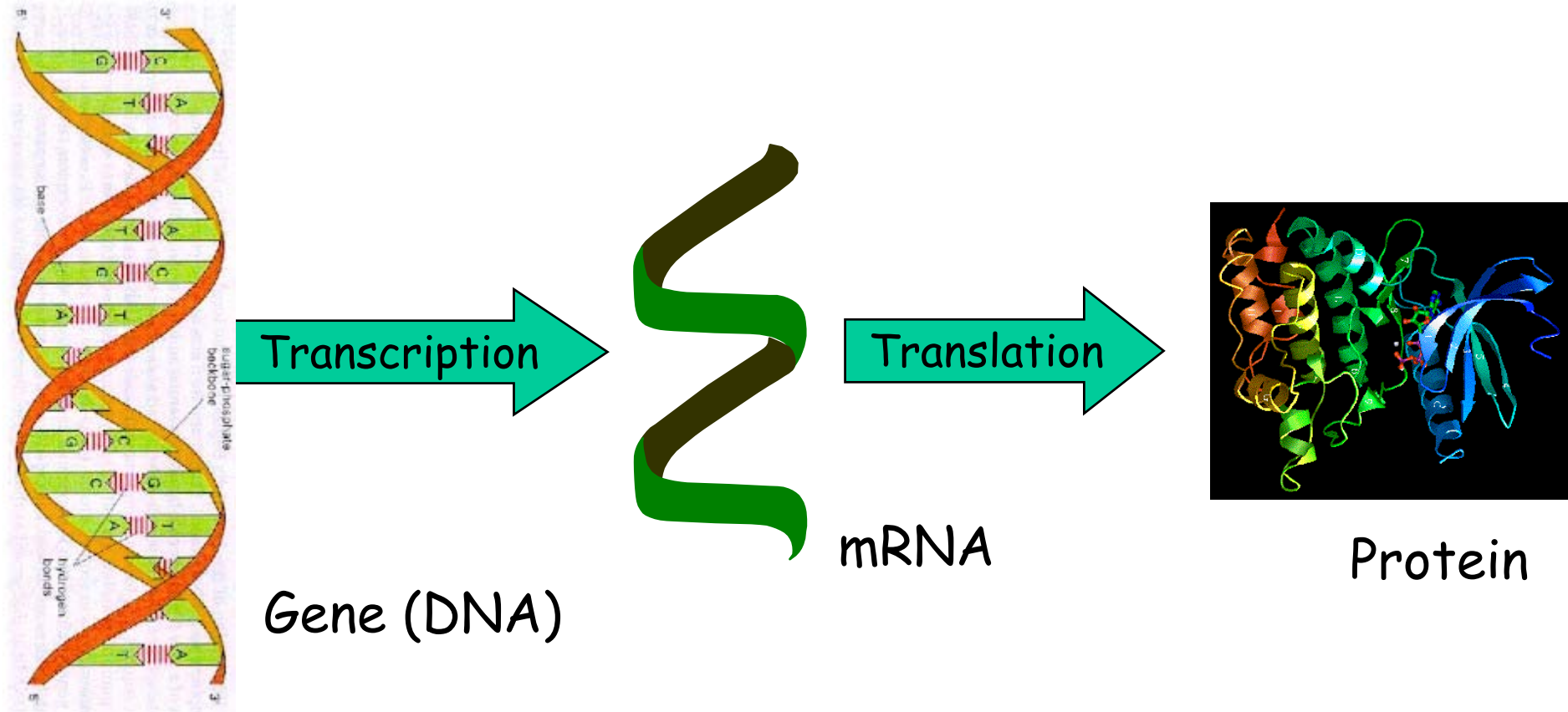
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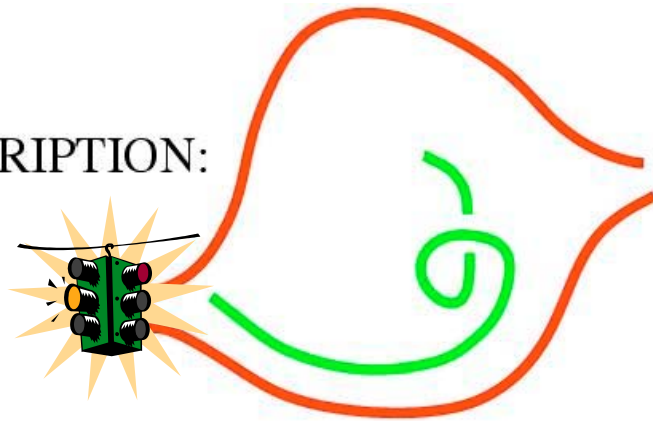
Central Dogma



Cells express **different** subset of the genes
In different tissues and under different conditions

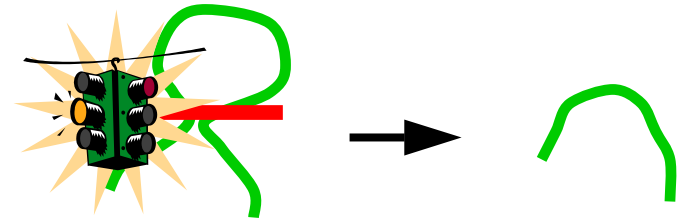
Regulation

TRANSCRIPTION:

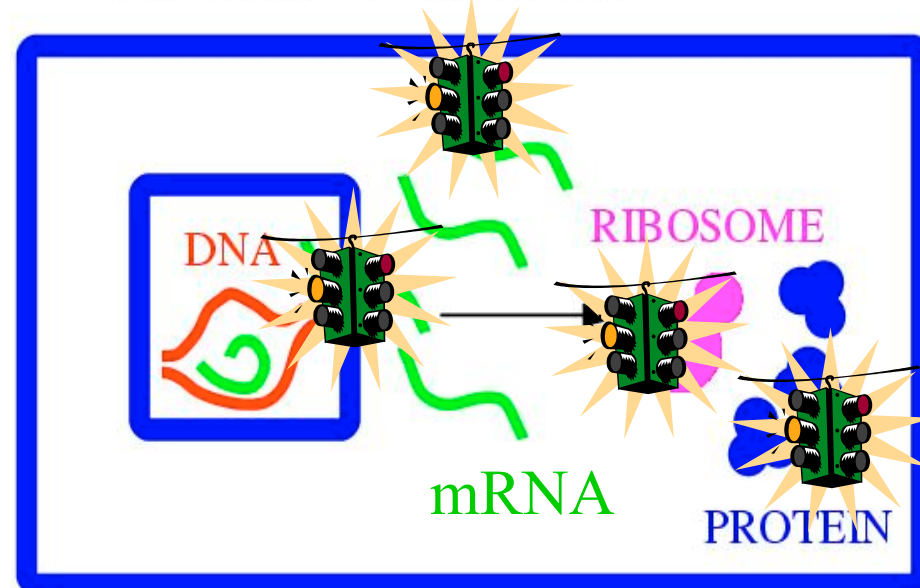


DNA → MESSENGER RNA

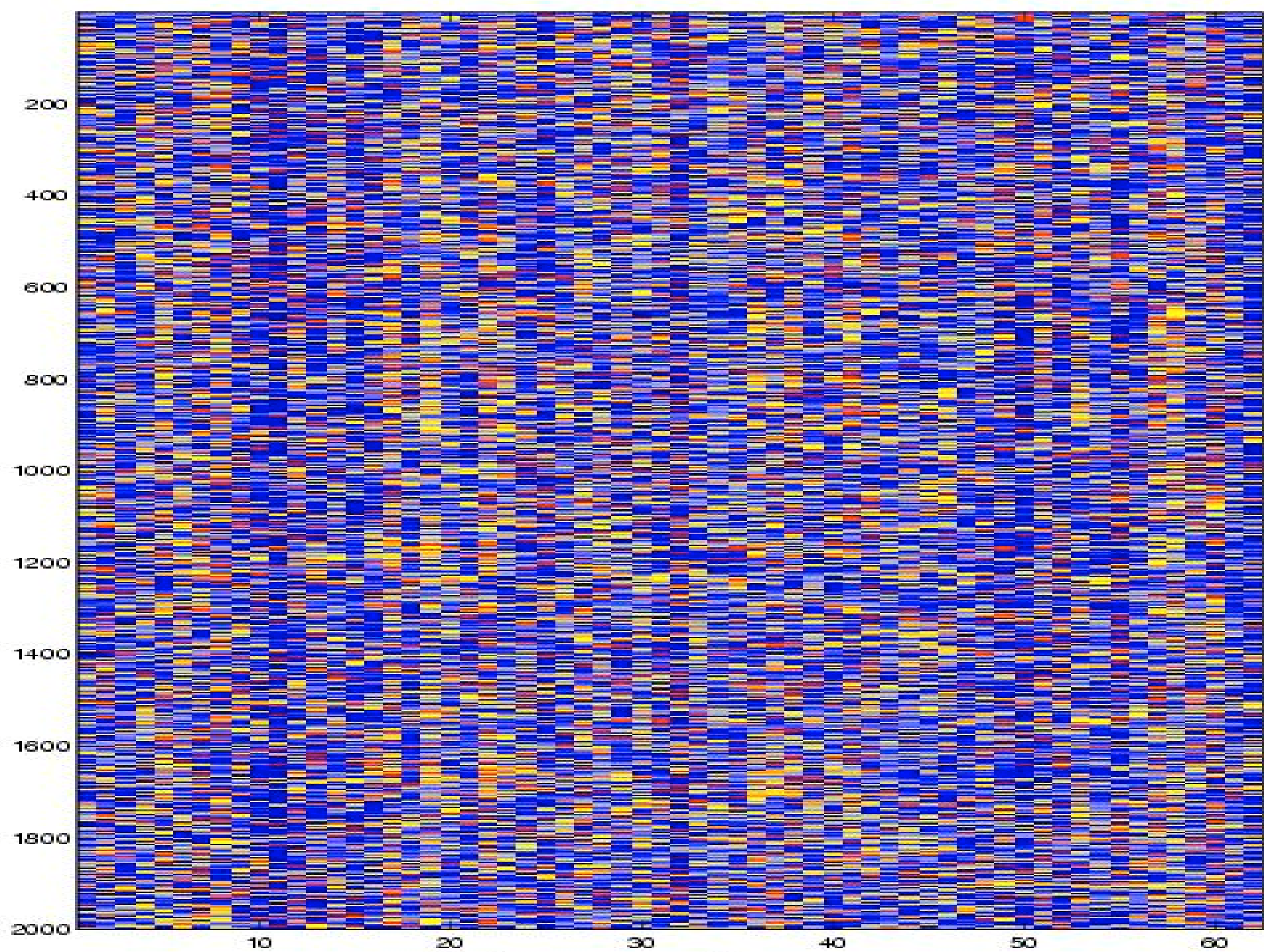
mRNA IS PROCESSED
(SPLICED)



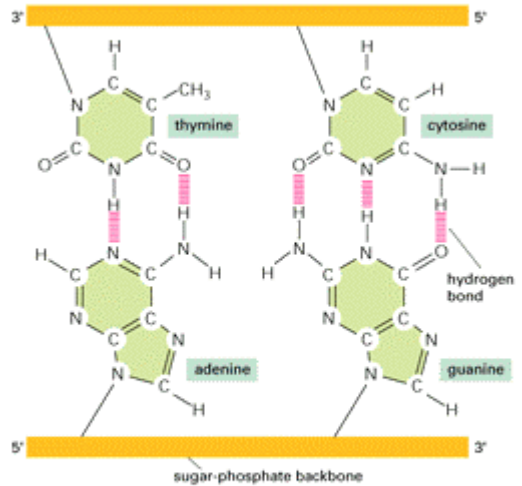
PROTEIN SYNTHESIS:



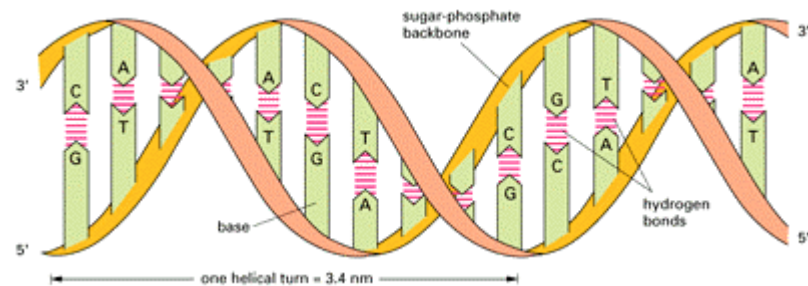
TRANSCRIPTIONAL CONTROL
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PROTEIN ACTIVITY

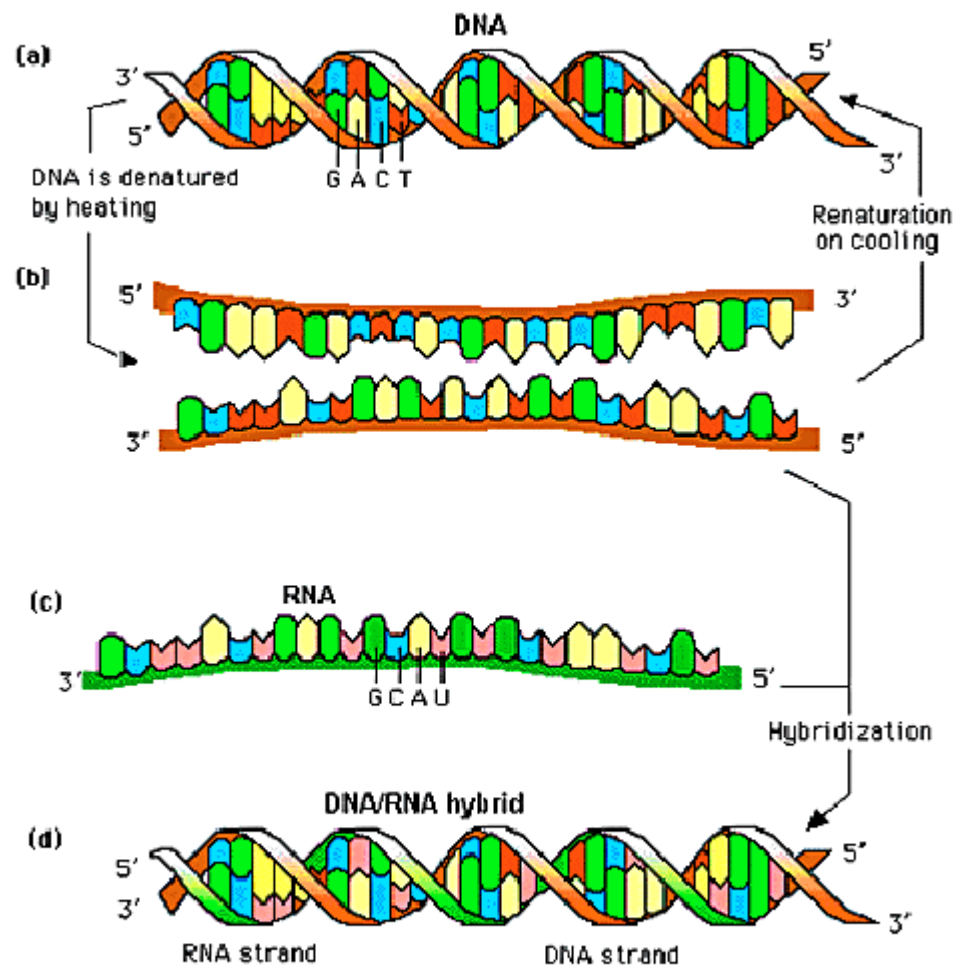


FOUR BASES AS BASE PAIRS OF DNA



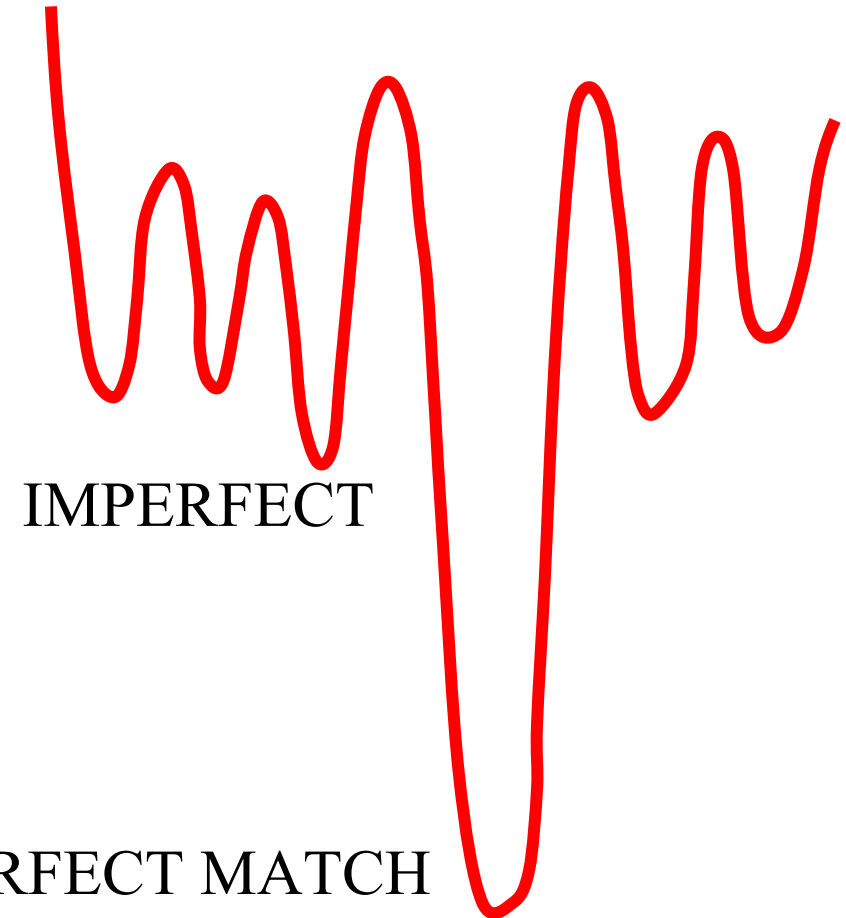
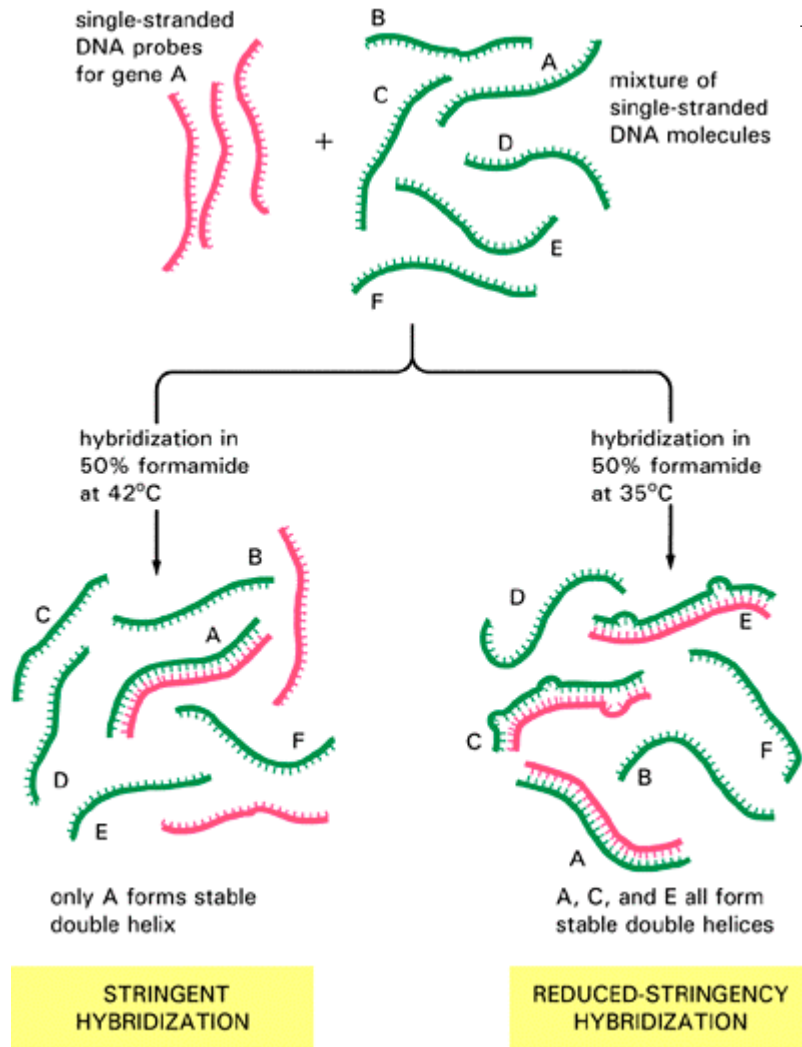
Specific hydrogen bonding between G and C and between A and T (A and U in RNA) generates complementary base-pairing.



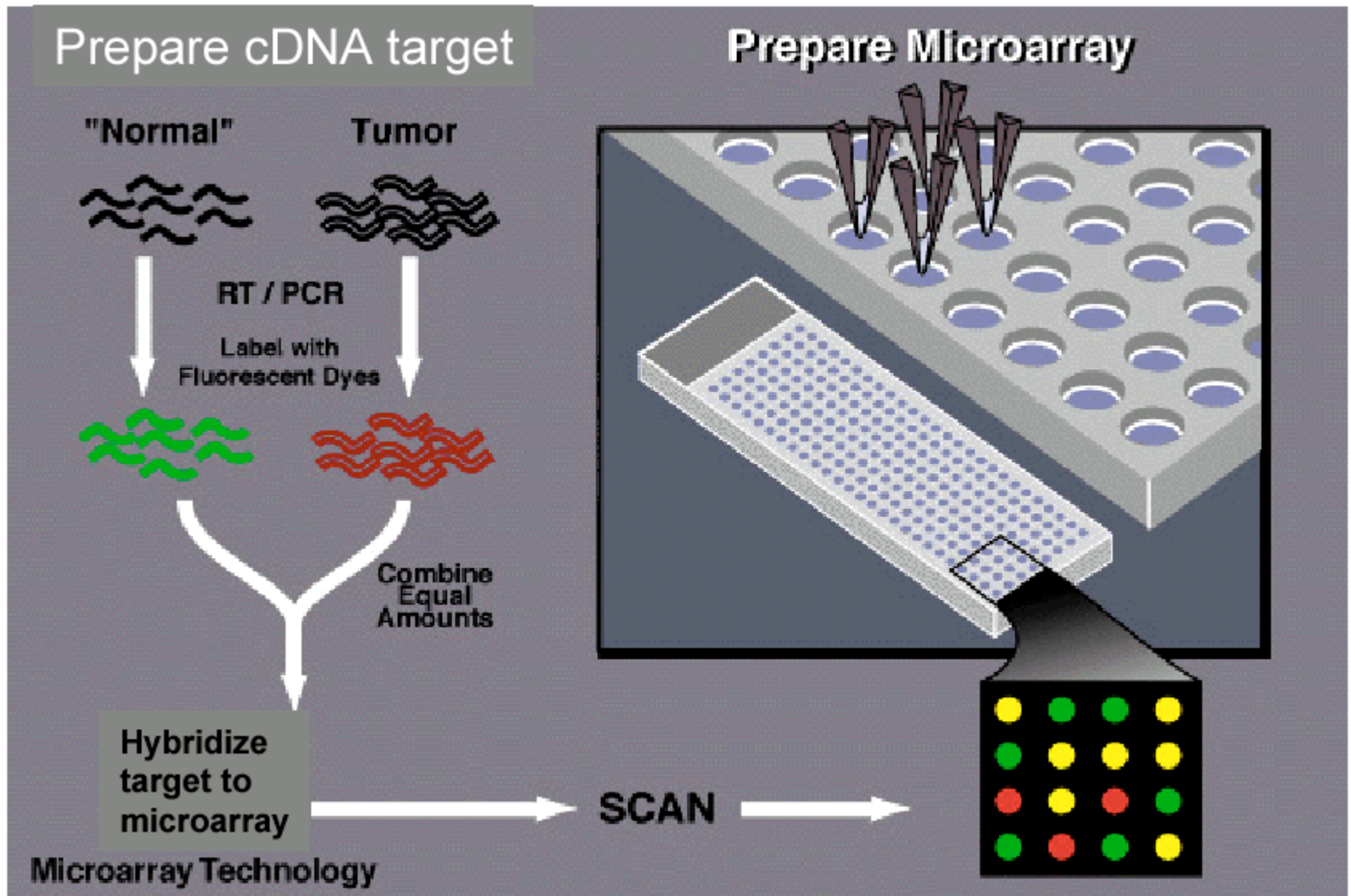


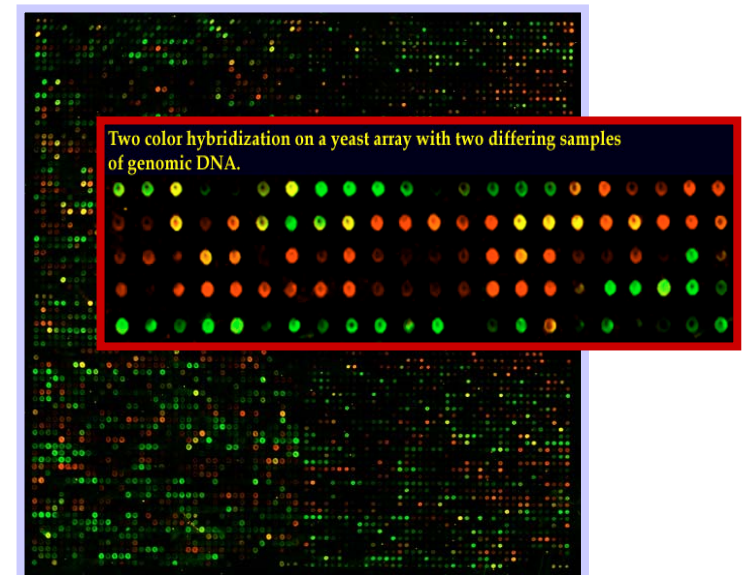
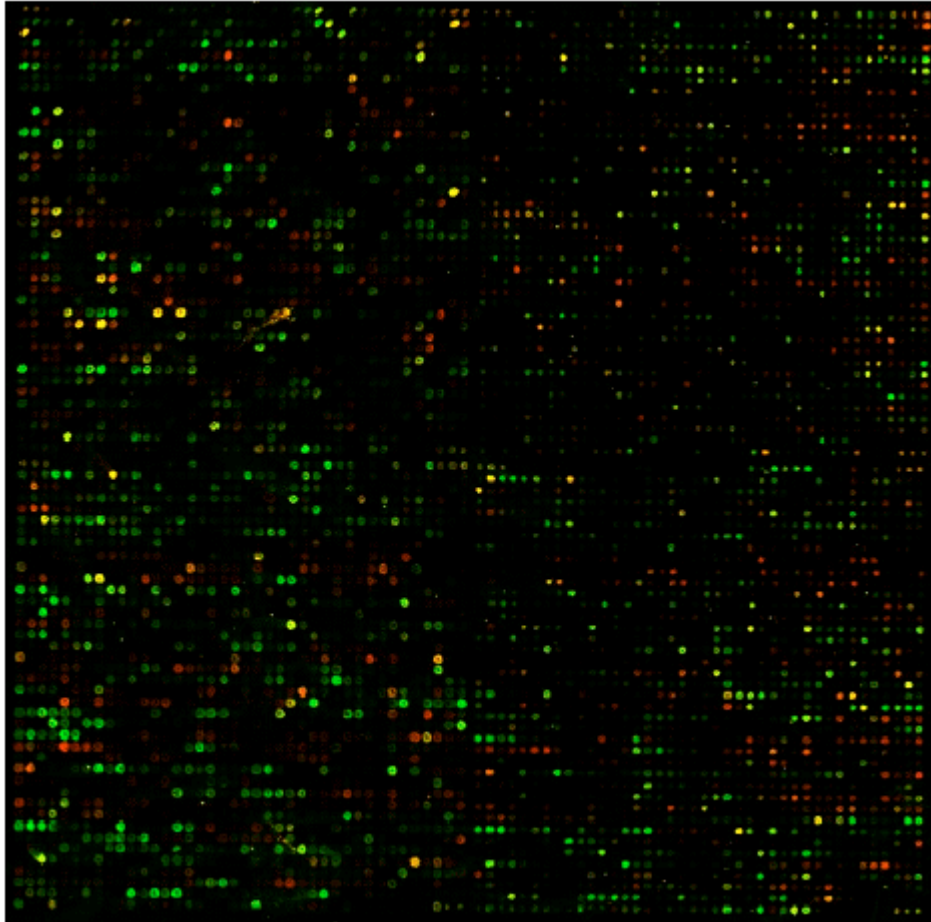
Nucleic Acid Hybridization

FREE ENERGY “LANDSCAPE”



cDNA microarray expt



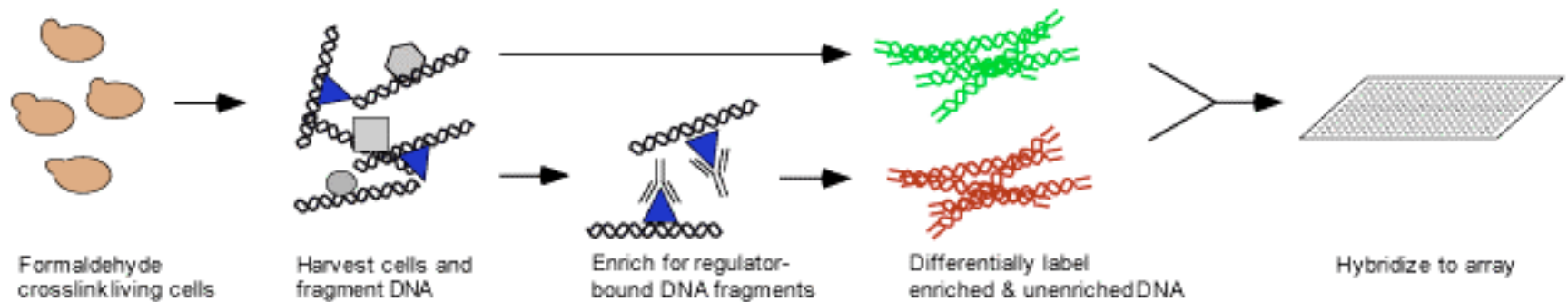


Experimental techniques

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- **ChIP**
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- Literature mining
- Genomics

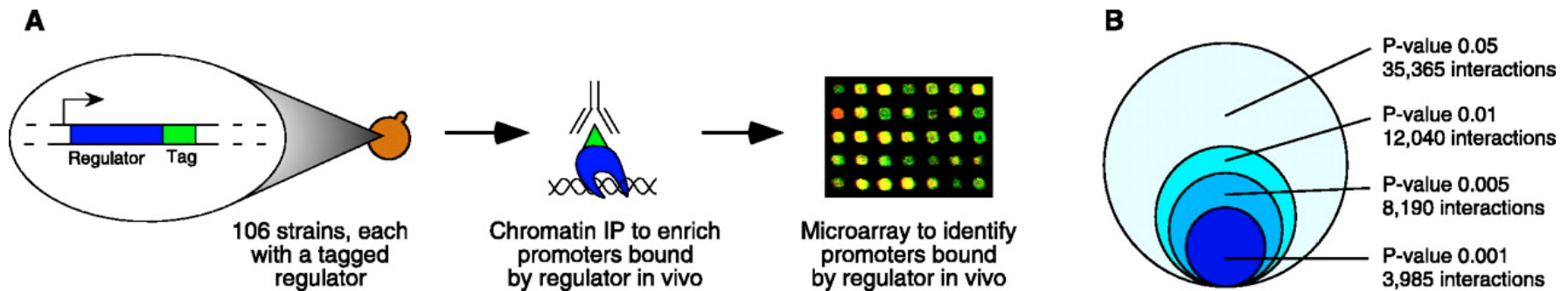
protein-DNA interactions

Chromatin Immunoprecipitation (ChIP)



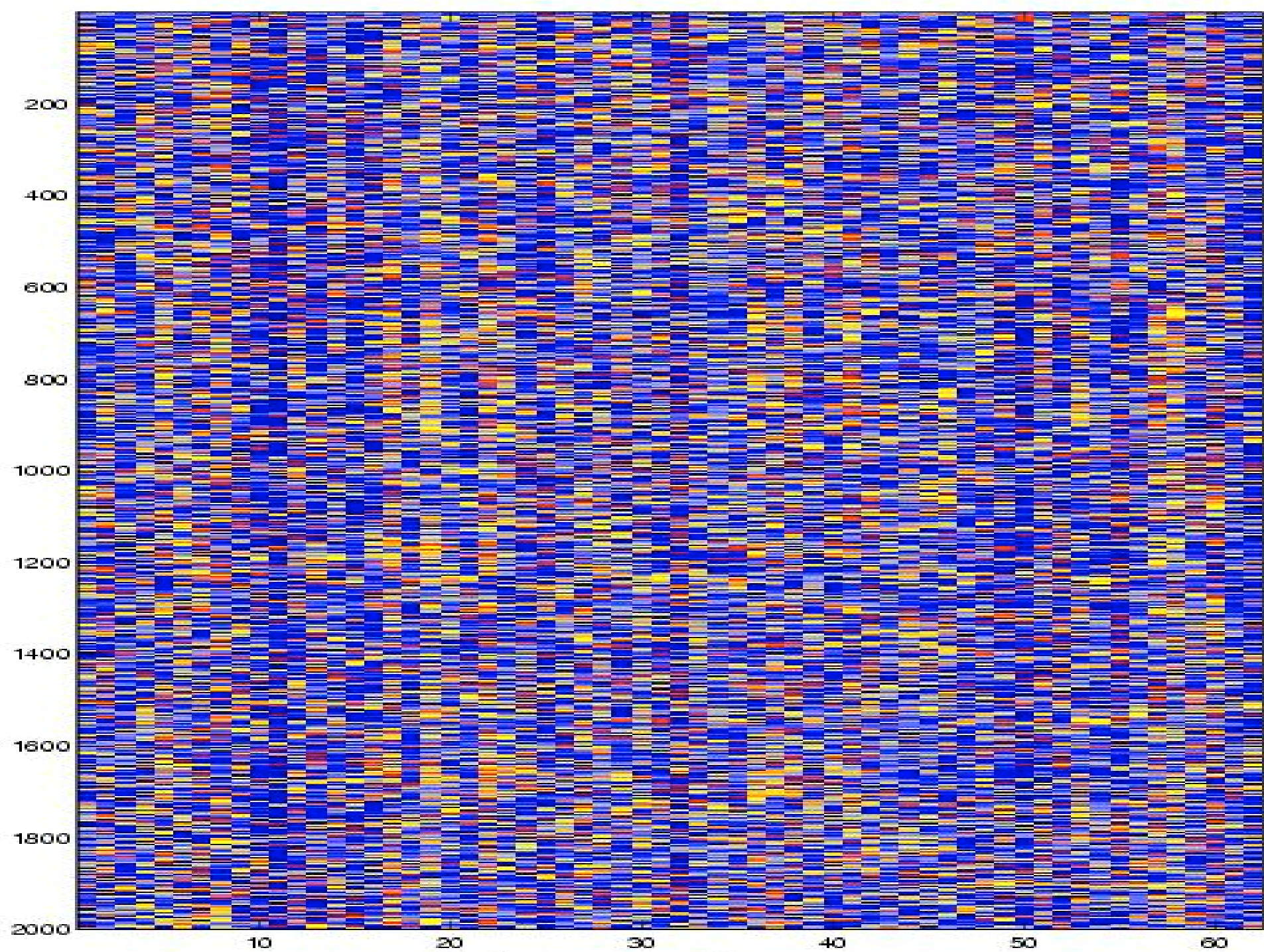
protein-DNA interactions

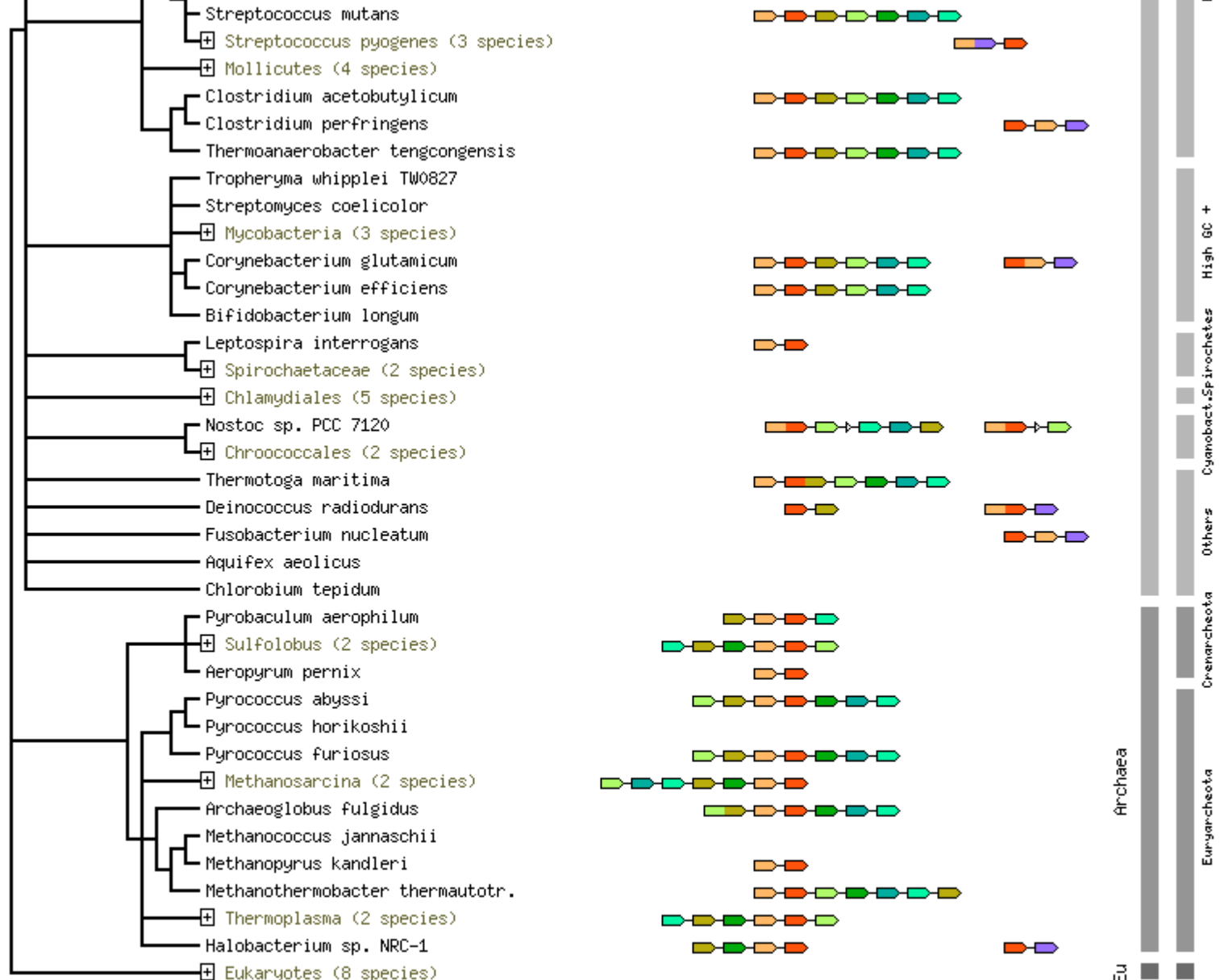
Chromatin Immunoprecipitation (ChIP)



Experimental techniques

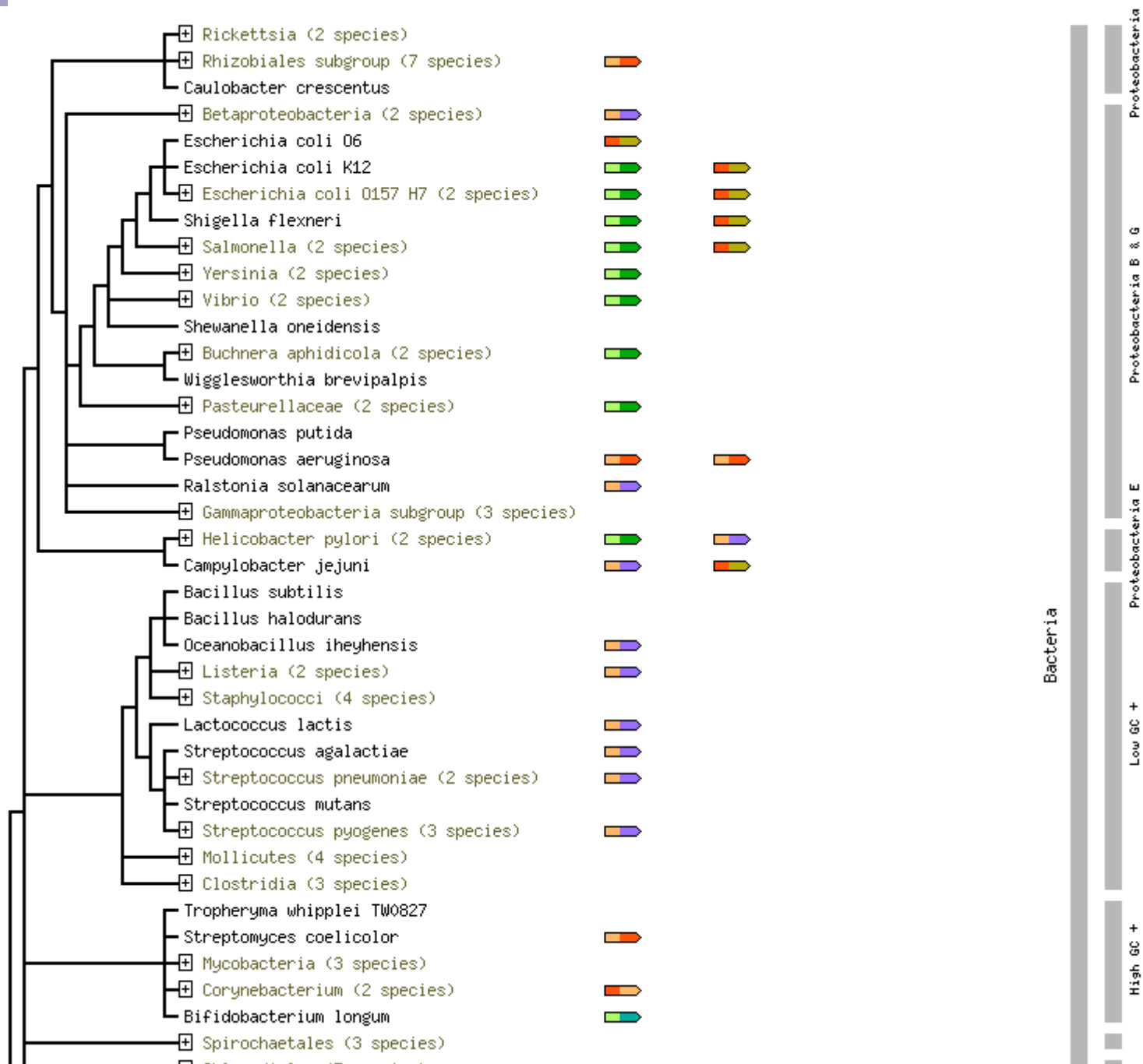
- Two-hybrid
- AffiChips
- Micoarrays
- ChIP
- Mass.spec/TAP
- Literature mining
- **Genomics**

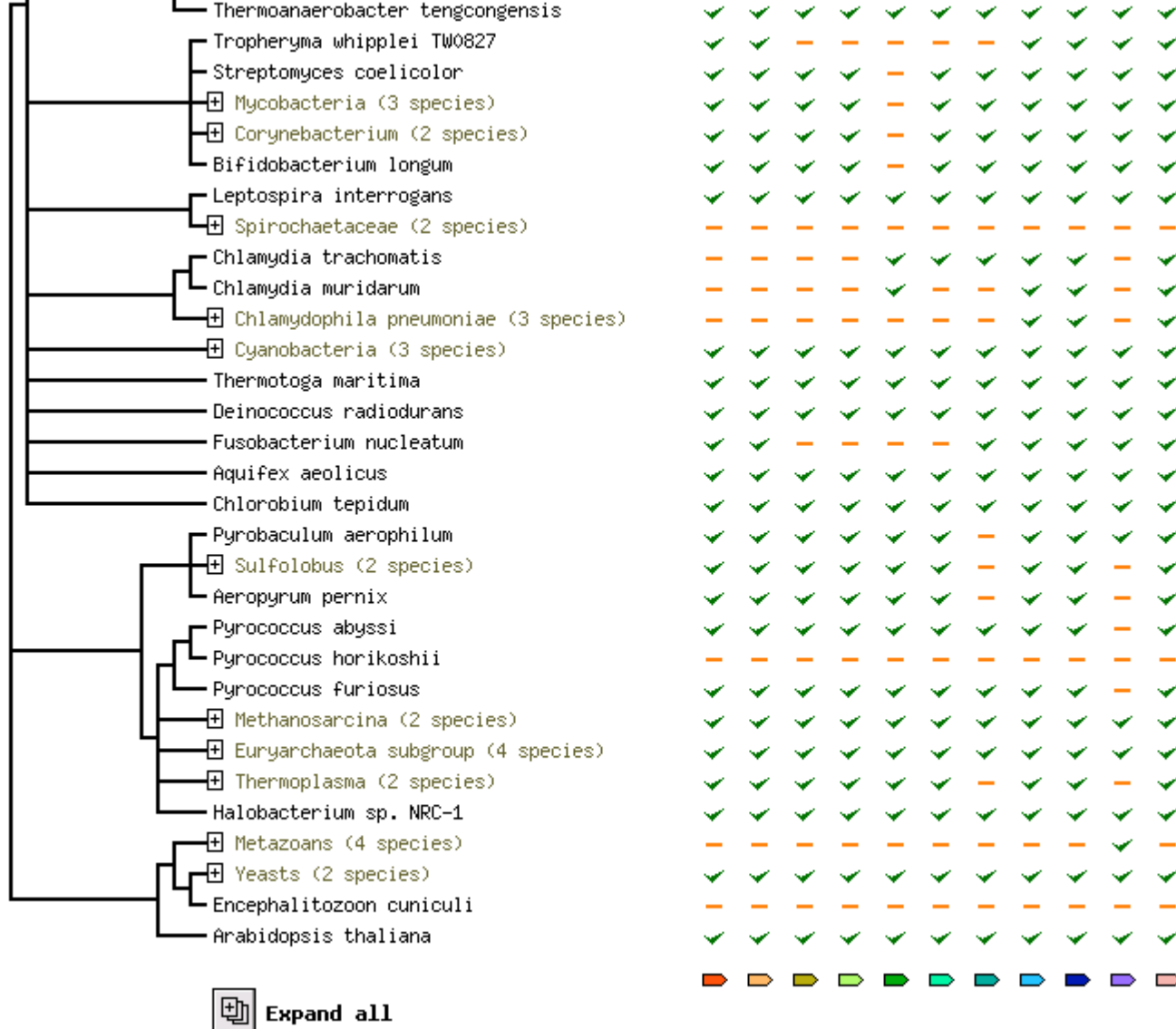




Expand all







Network representations

- Graphs
- Bipartite graphs
- Hyper-graphs