Systems Biology and Evolutionary Computation

GECCO Tutorial

July 8, 2006

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Reverse
Engineering

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Goals and Schedule

Questions

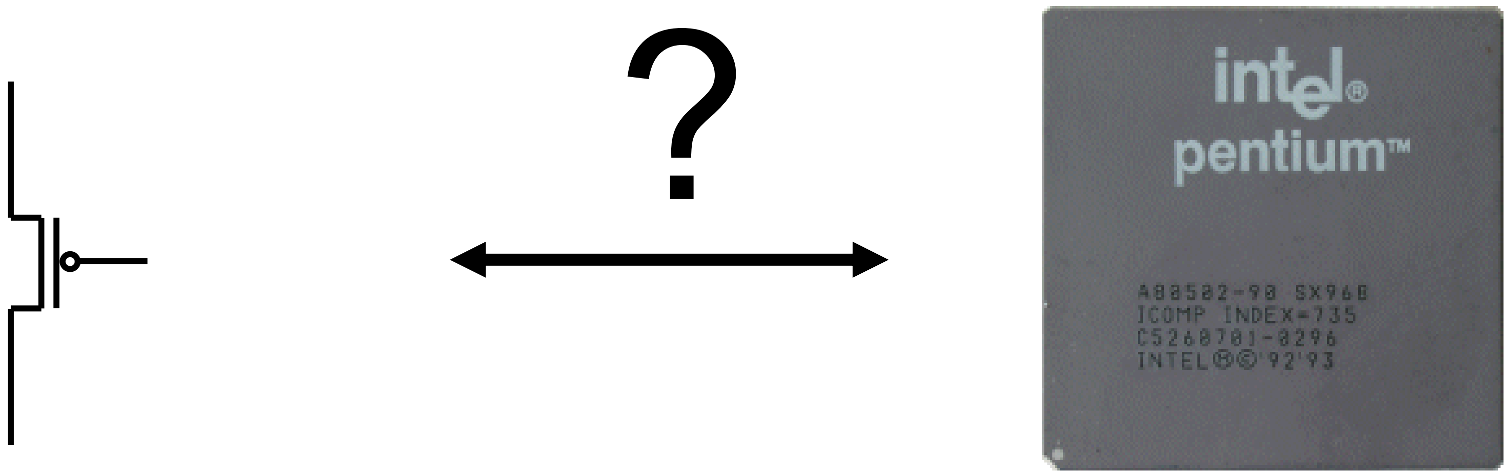
- What is Systems Biology?
- What are the basic types of biological experiments and measurements?
- What are the computational issues in Systems Biology?
- What are examples of successful application of EC in Systems Biology?

Schedule

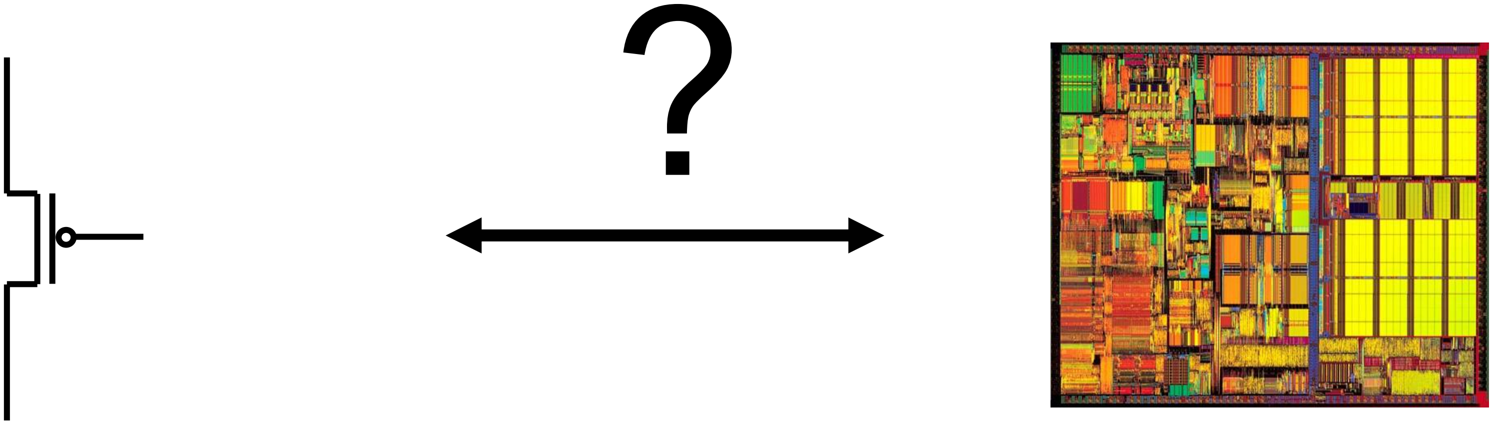
- 50 min Part 1: Introduction to Systems Biology.
- 10 min break
- 50 min Part 2: Computational Issues in Systems Biology.

1. Introduction to Systems Biology

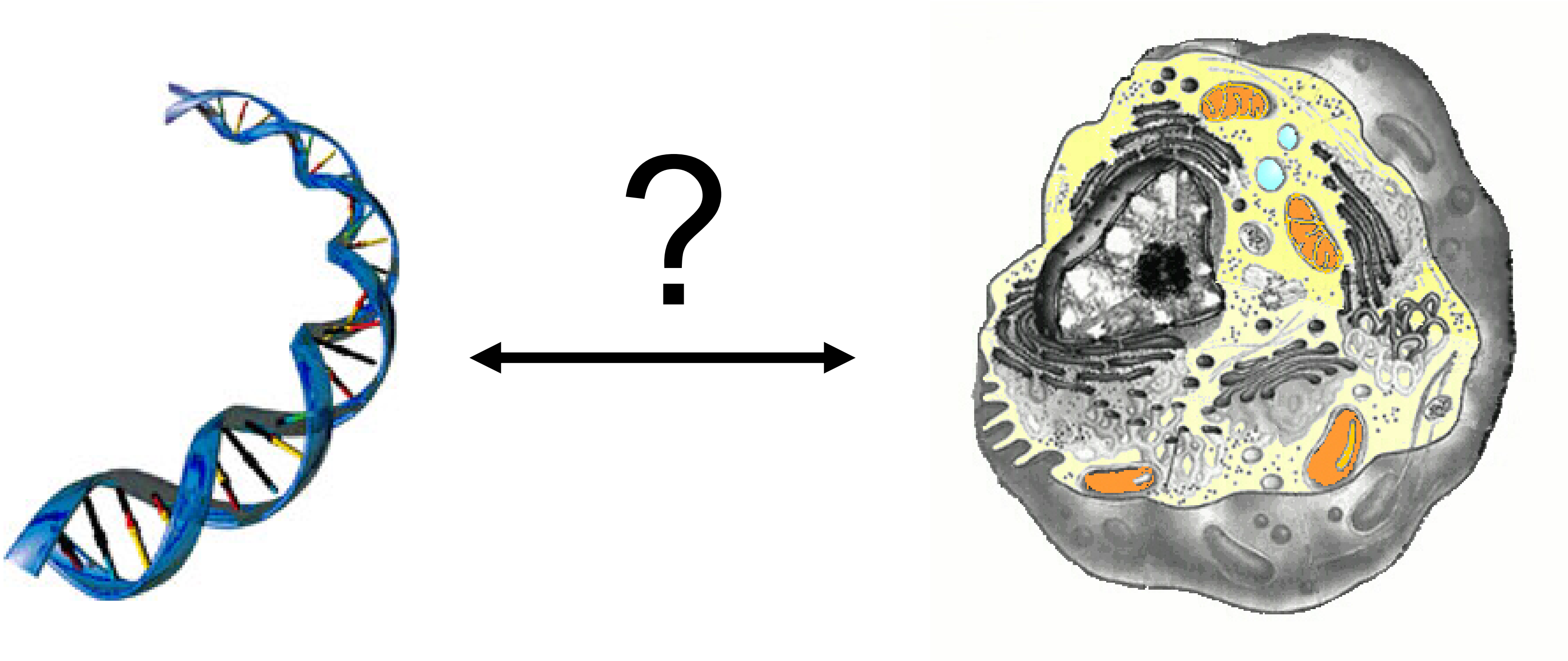
Reverse Engineering Problem



Reverse Engineering Problem



Reverse Engineering Problem II



Systems Biology

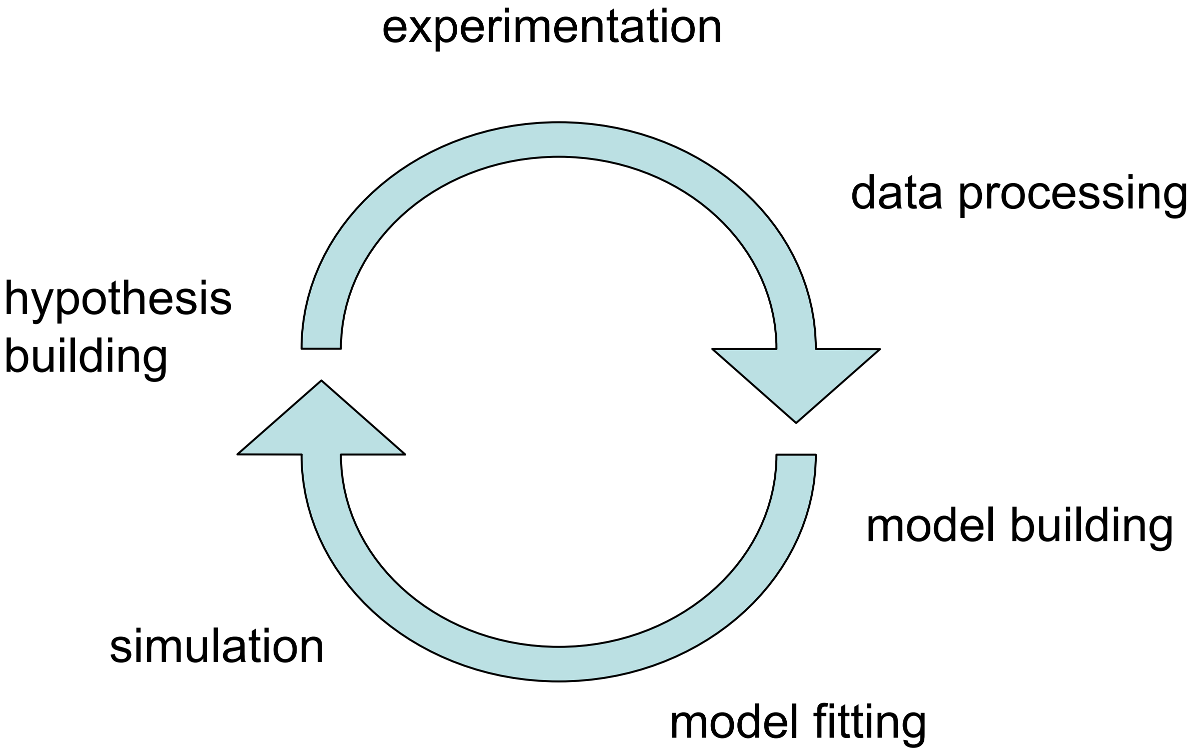
- **A Definition**: Understanding of network behavior using computational approaches tightly linked to experiments. (M. Cassman)

- **Goals:**
  - system level understanding
  - simulators for cells and organisms
  - personalized, predictive and preventive medicine

- **Methods:**
  - experiment: mostly high throughput
  - models
  - computational analysis

- **Key Idea:** capture emergent properties

Closed Loop Biology



experimentation

data processing

model building

model fitting

simulation

hypothesis building

Compared to Classical Biology

Classical Biology

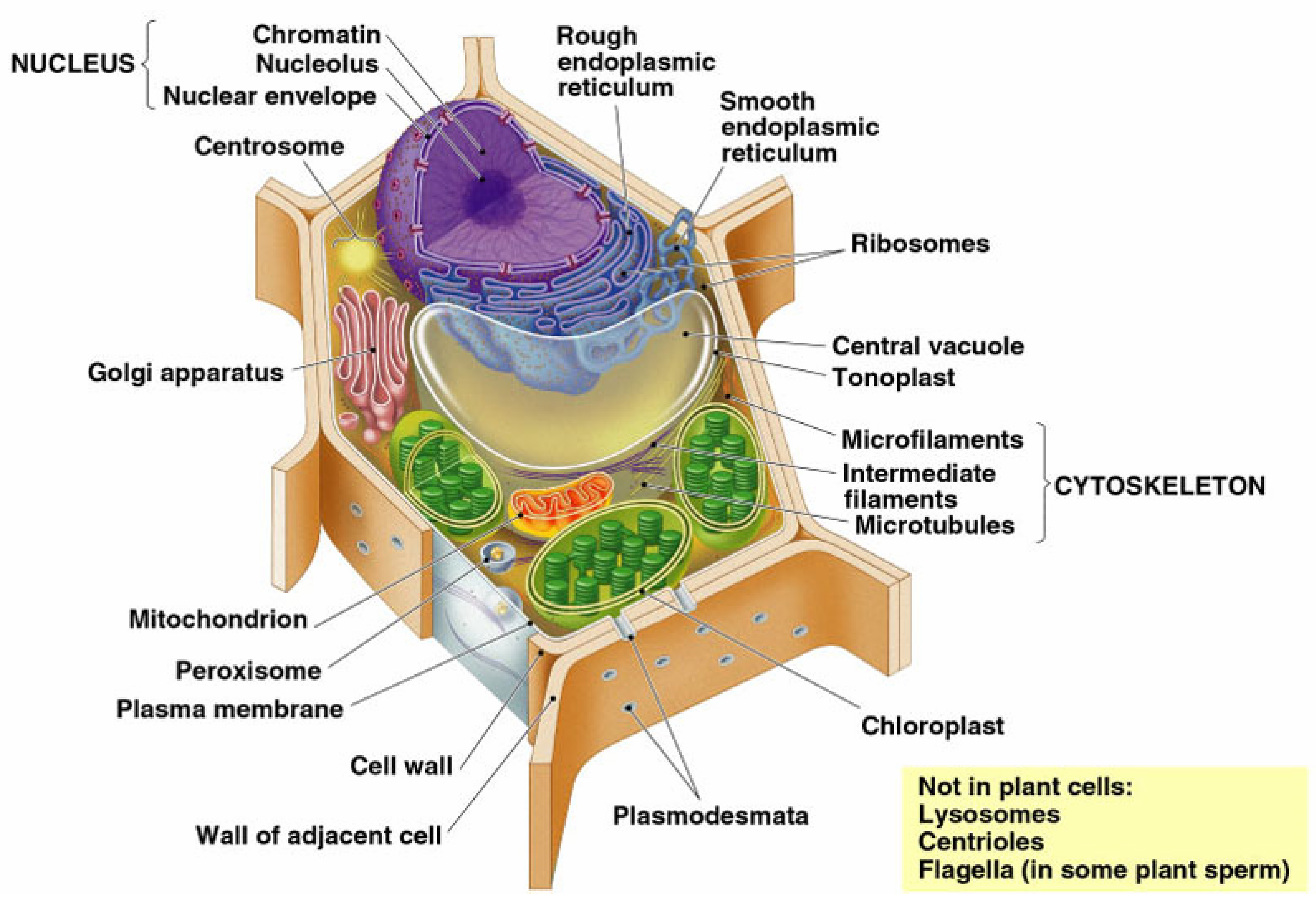
- focus on single elements (gene, protein, pathway)
- focus on building blocks
- bottom up
- interpretation
- Examples:
  - structure determination of a protein
  - study effects of knockout on one pathway

Systems Biology

- focus on all elements (genome, proteome, metabolome)
- focus on interactions
- top down
- simulation
- Examples:
  - module identification
  - robustness analysis of genetic networks

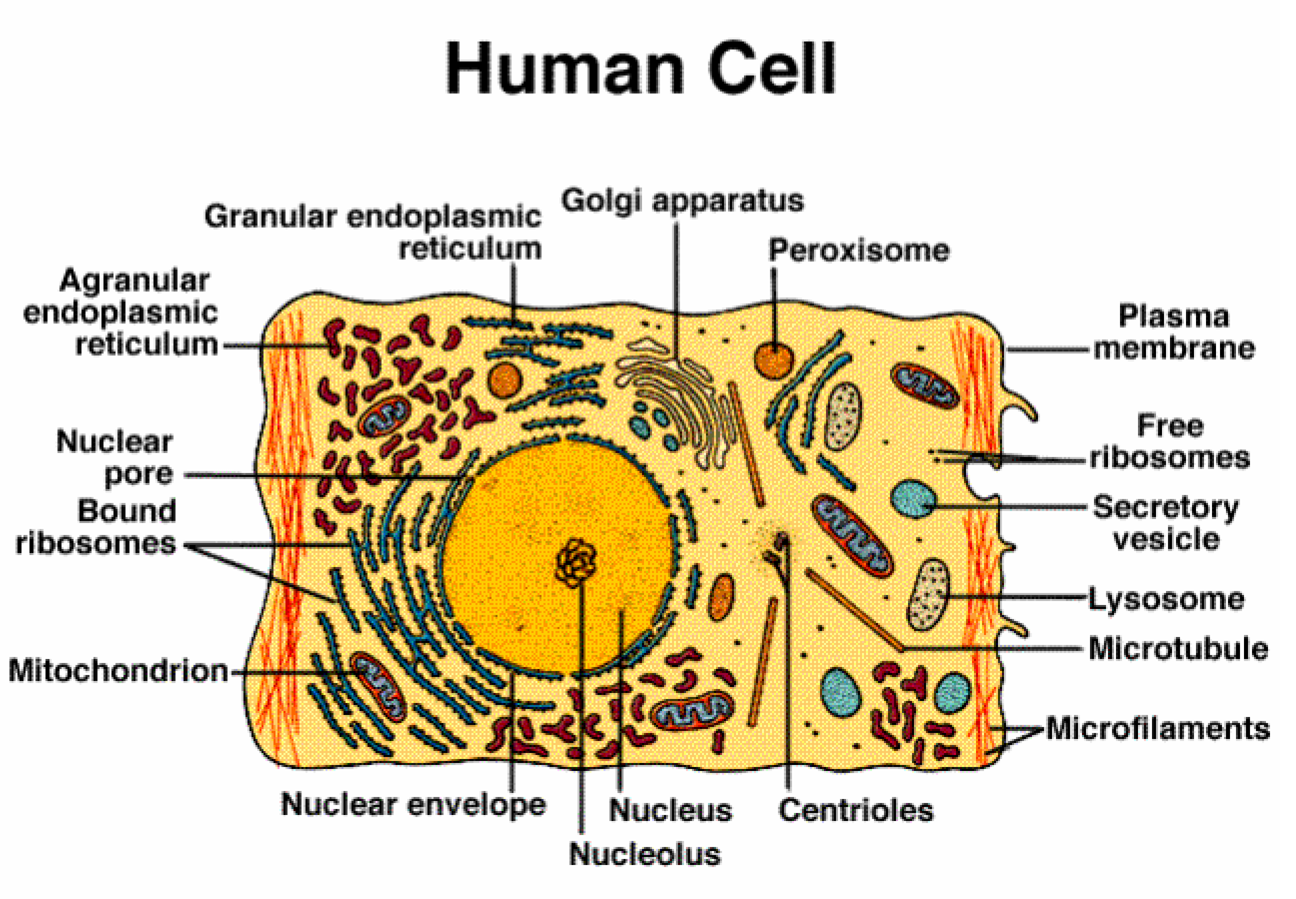
Some cell biology…

Cellular Compartments of a Plant Cell

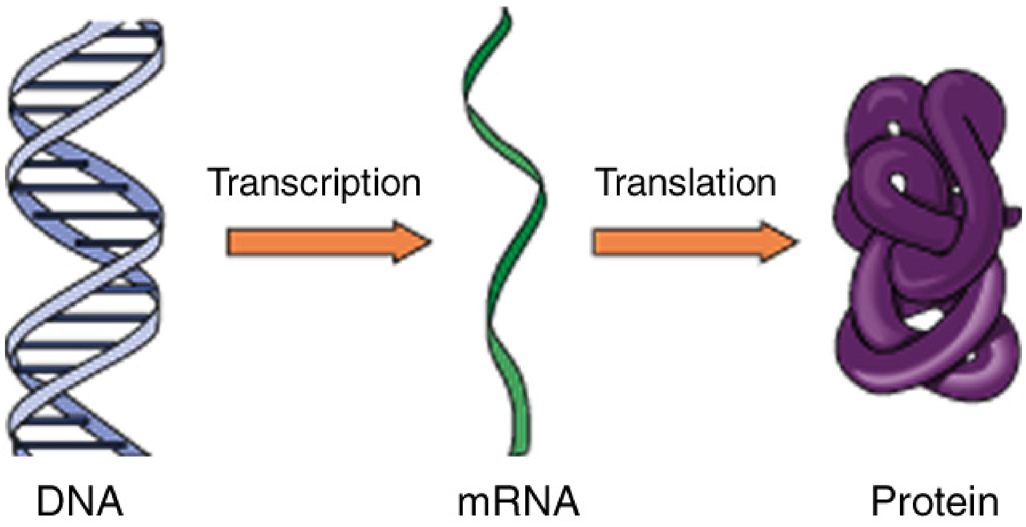


Not in plant cells:
Lysosomes
Centrioles
Flagella (in some plant sperm)

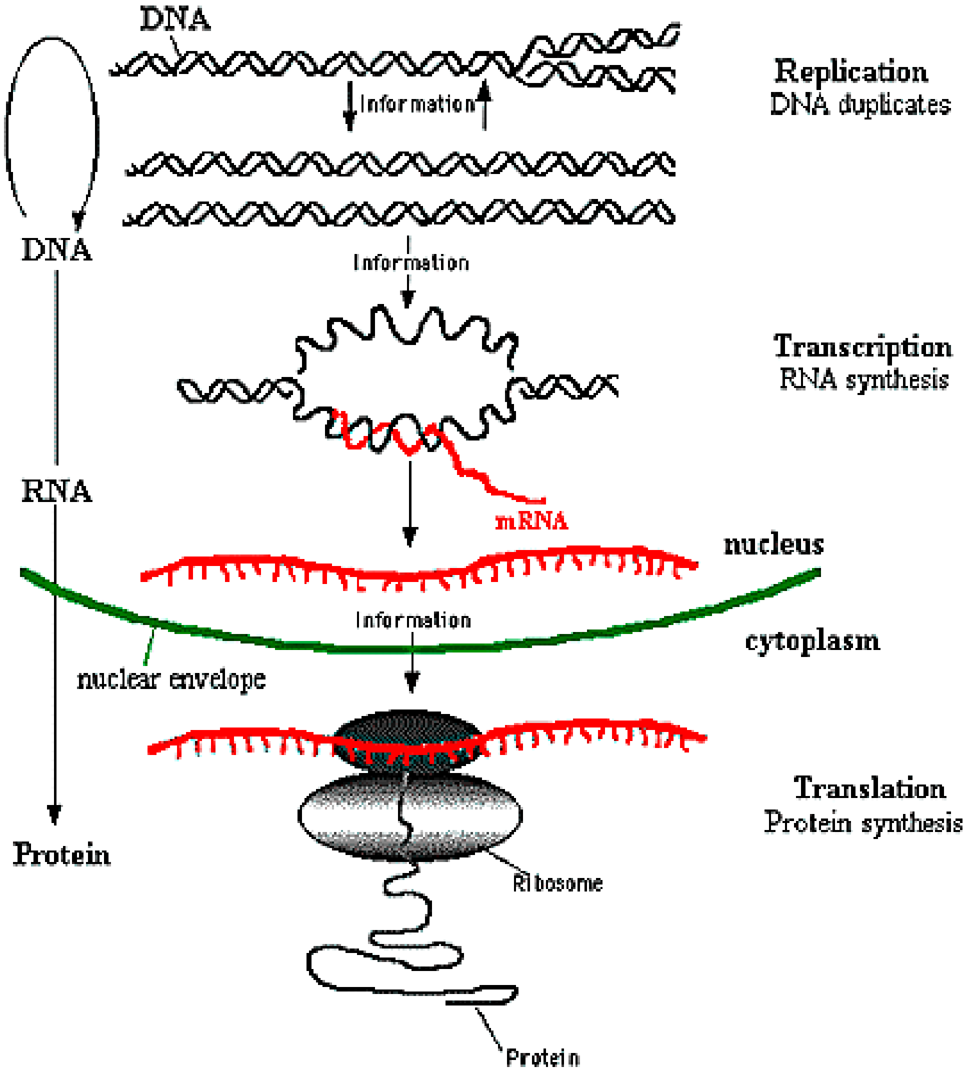
Cellular Compartments of a Human Cell



Central Dogma of Molecular Biology

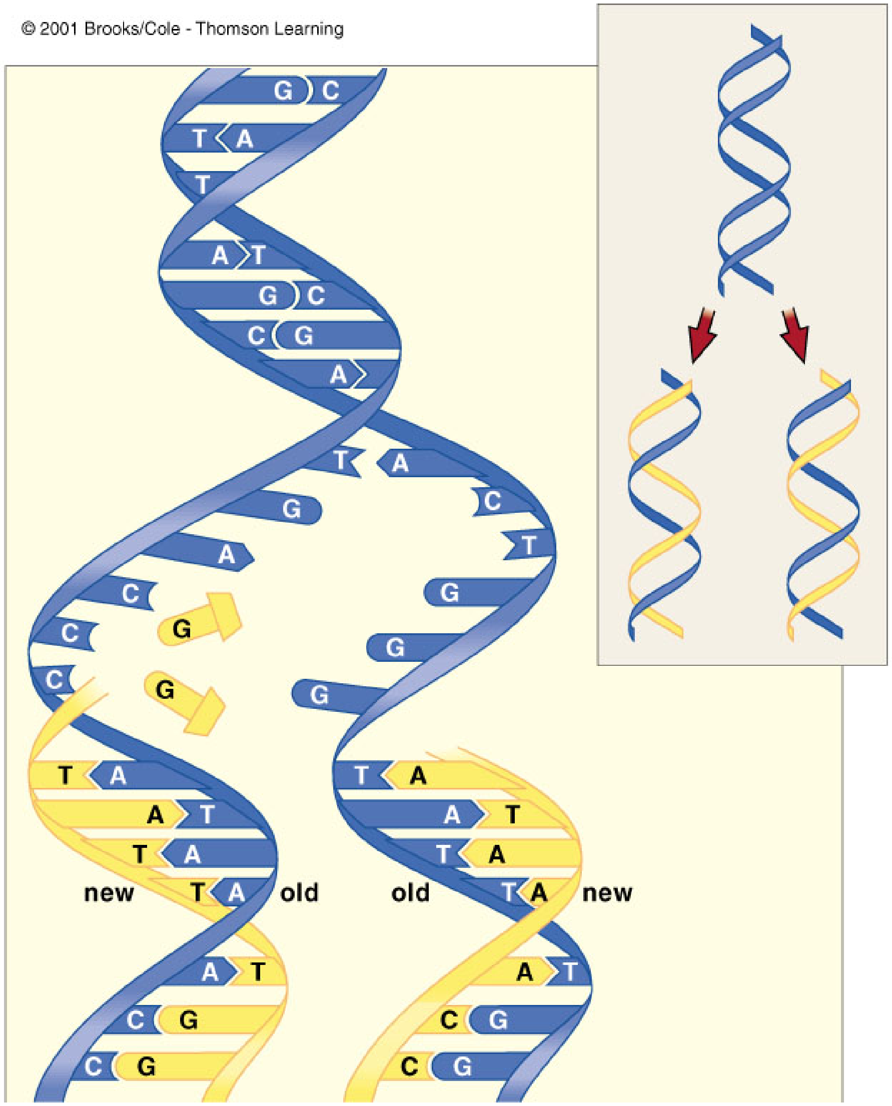


Central Dogma of Molecular Biology

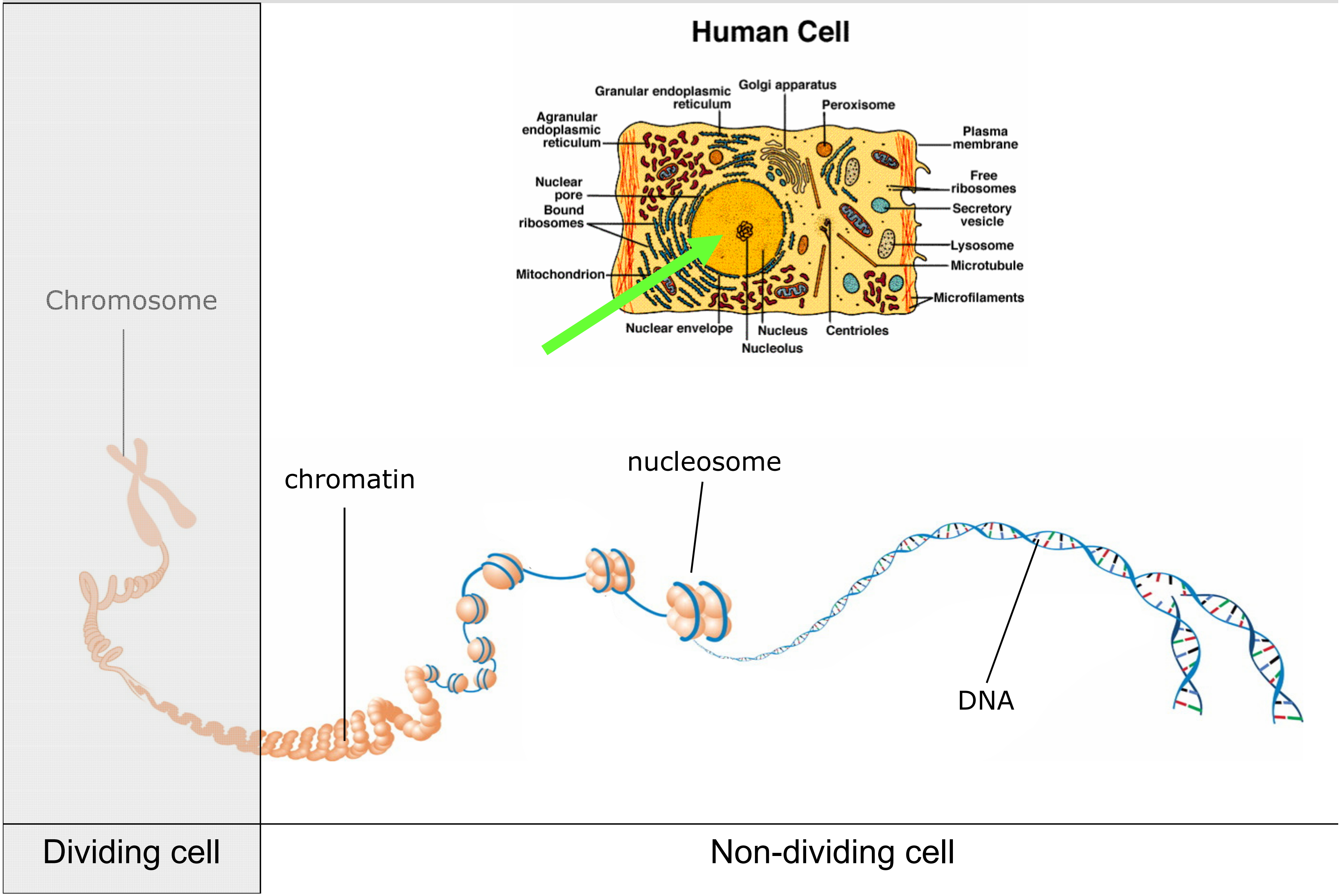


The Central Dogma of Molecular Biology

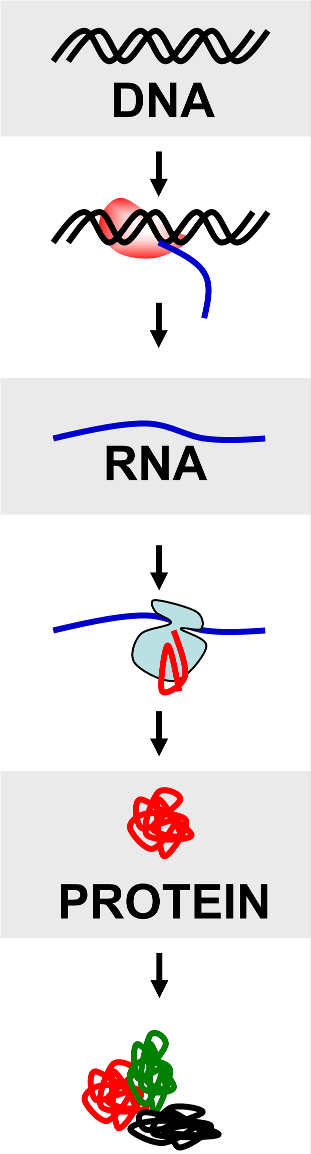
DNA Replication

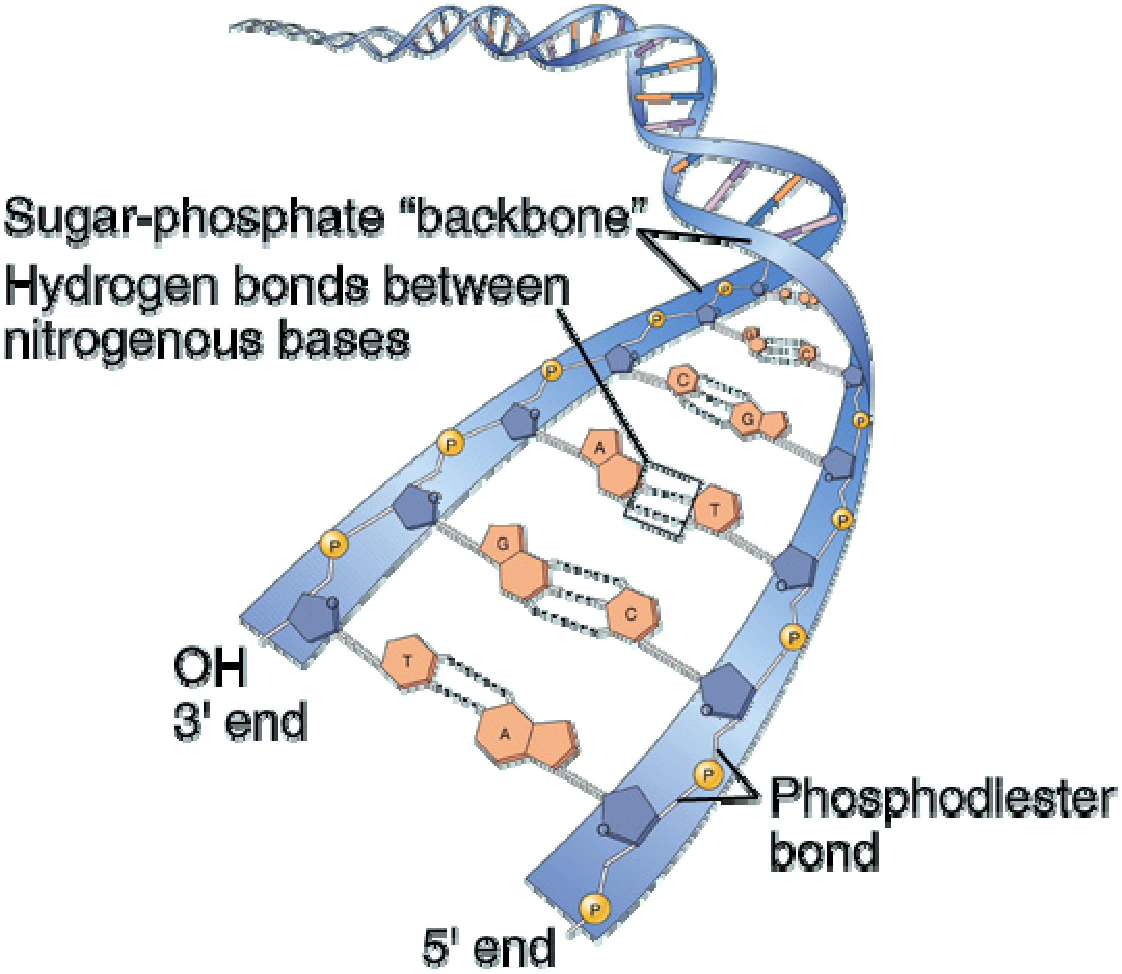


Chromosome – chromatin – nucleosome – gene

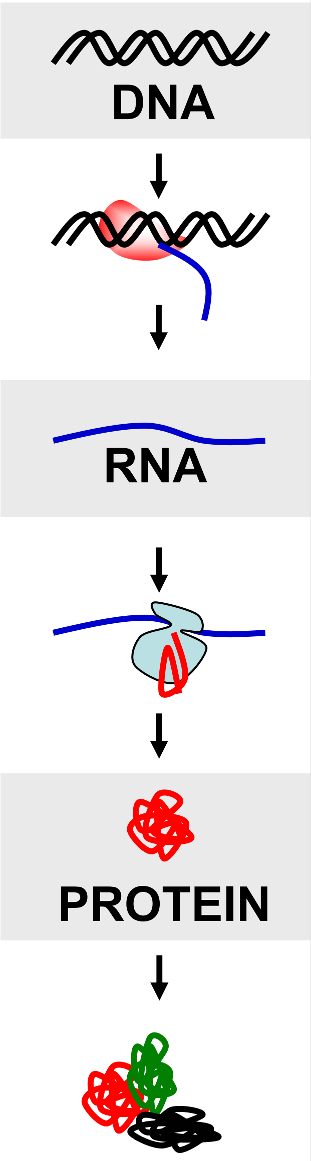


Genes

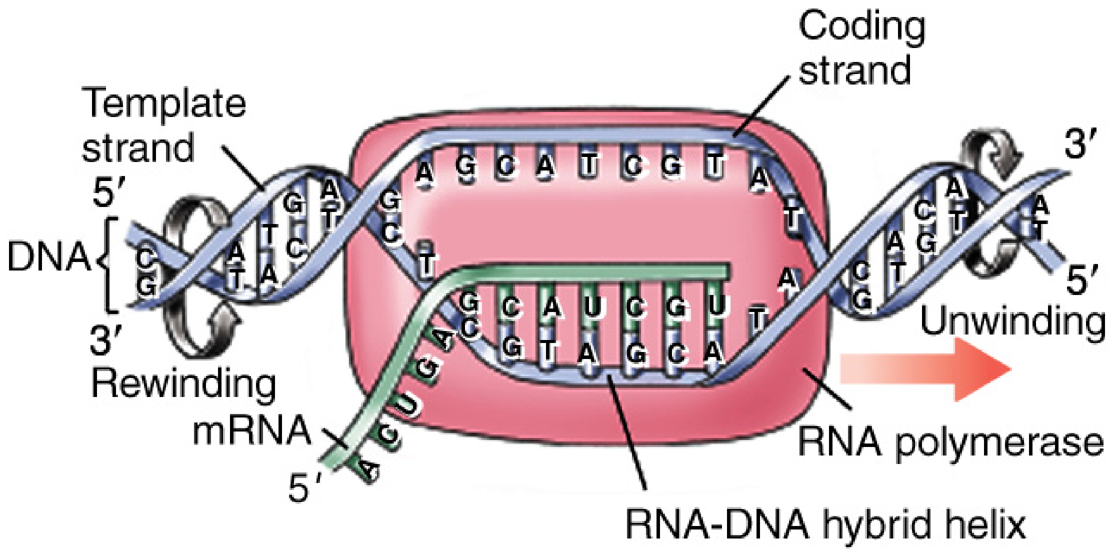

DNA
RNA
PROTEIN


Sugar-phosphate "backbone"
Hydrogen bonds between nitrogenous bases
OH
3' end
5' end
Phosphodlester bond
C
G
A
T
G
C
T
A
P

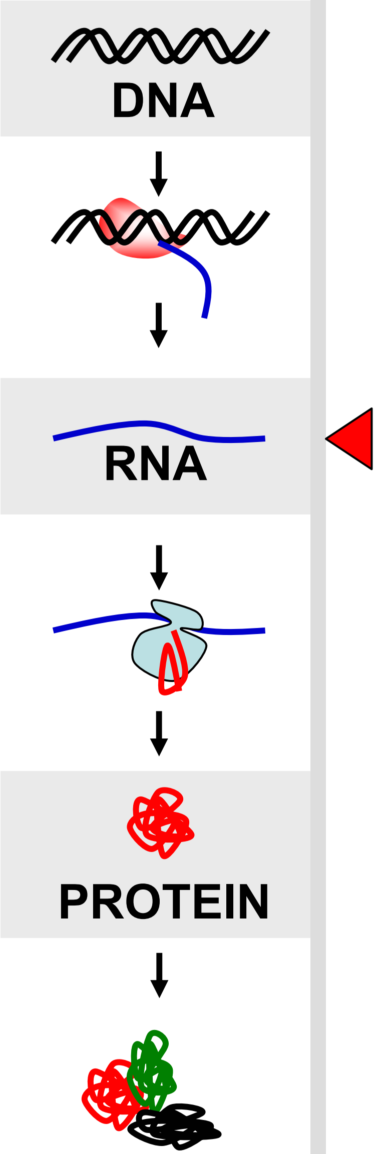
Transcription

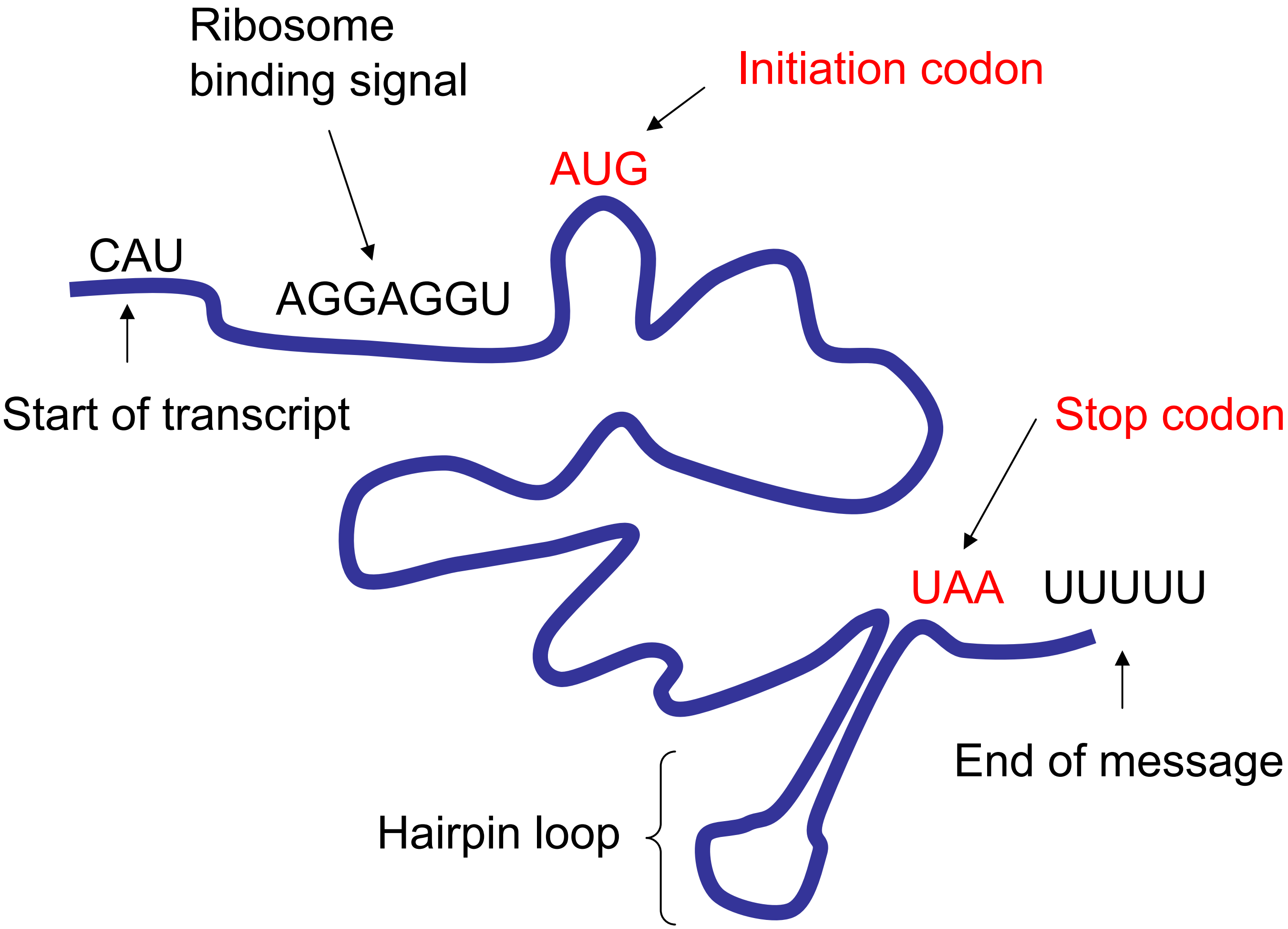


- The process by which a molecule of DNA is copied into a complementary strand of RNA.
- 1 Strand DNA → 2 Strands RNA
- RNA Polymerase



Messenger RNA





Ribosome binding signal

Initiation codon

AUG

CAU

AGGAGGU

Start of transcript

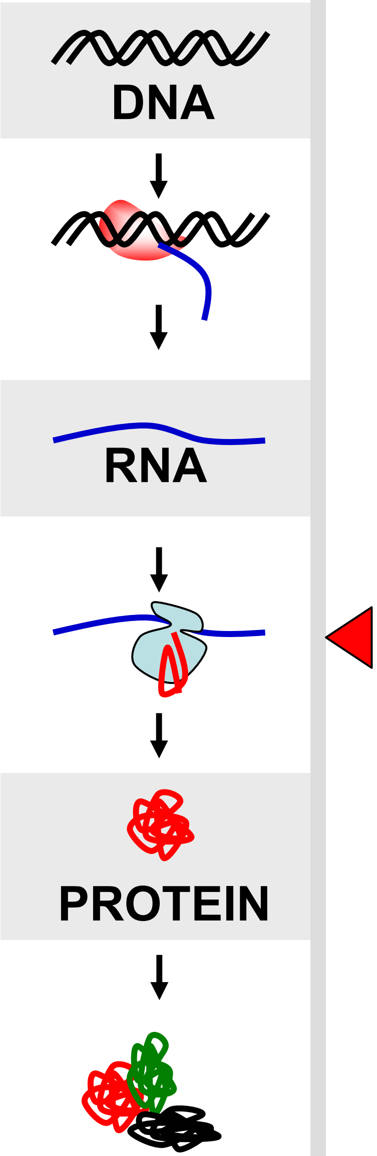
Stop codon

UAA UUUUU

End of message

Hairpin loop

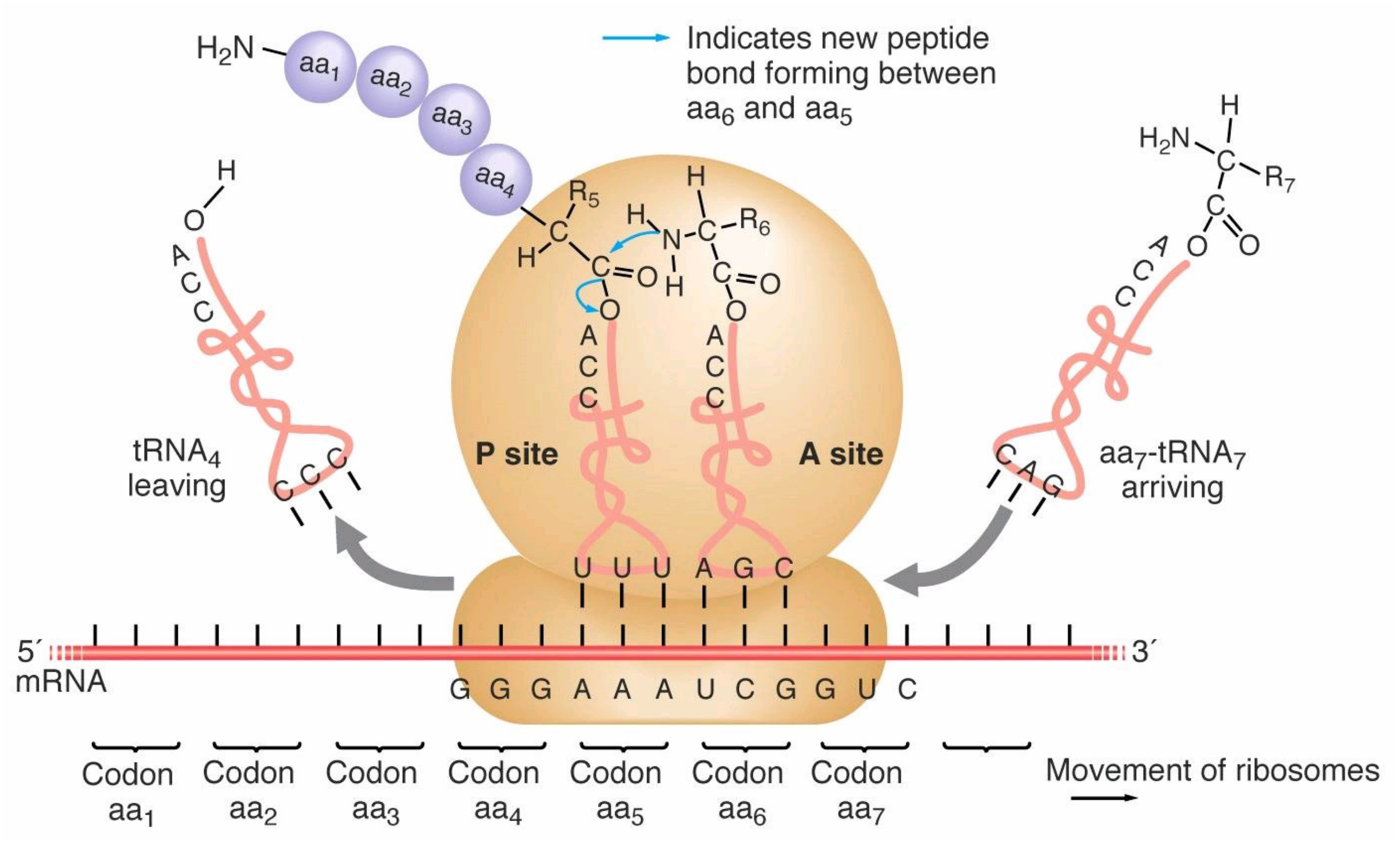
Transcription



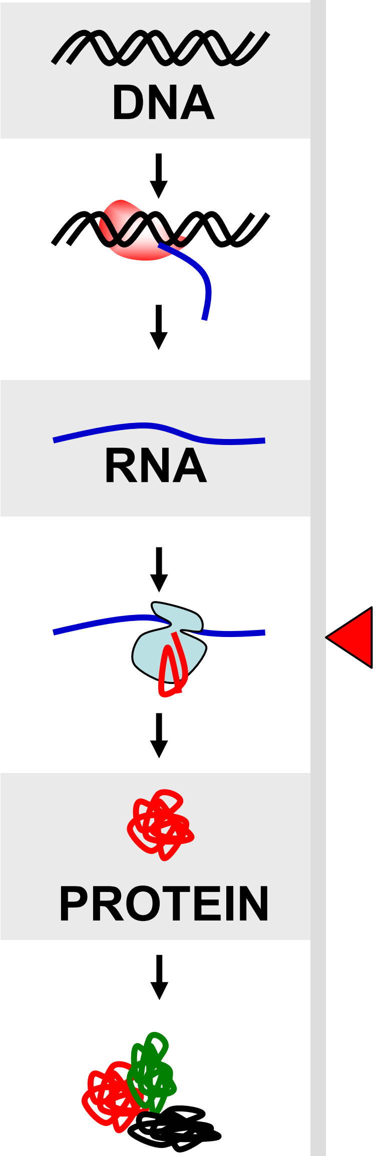
DNA

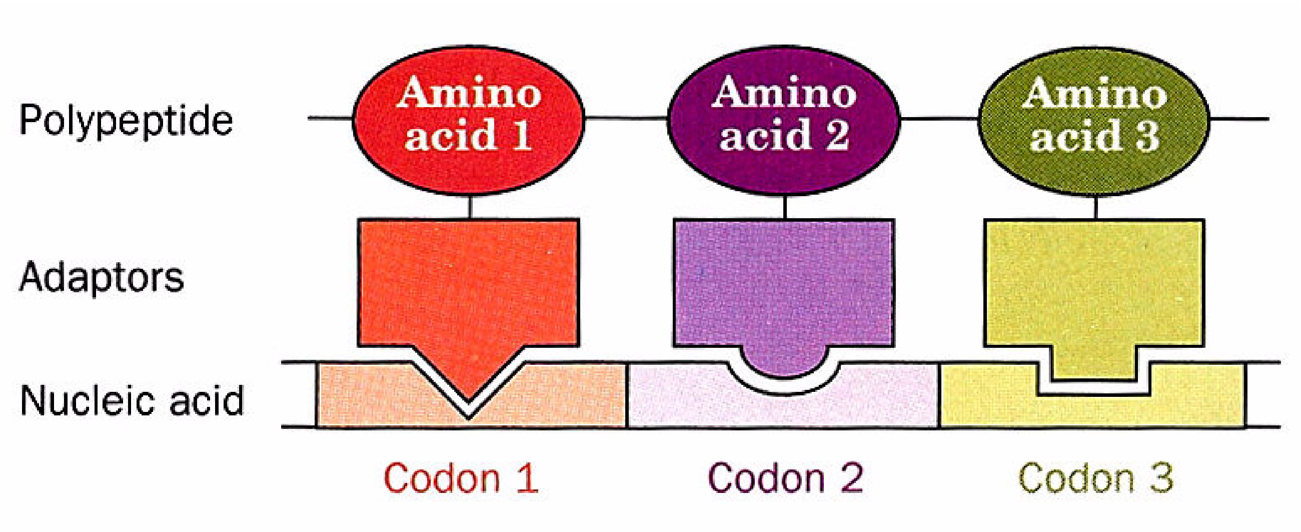
RNA

PROTEIN

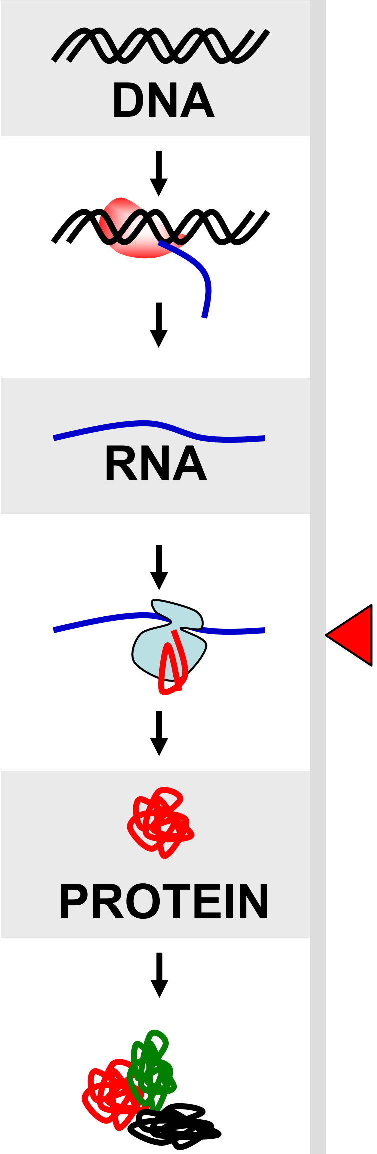


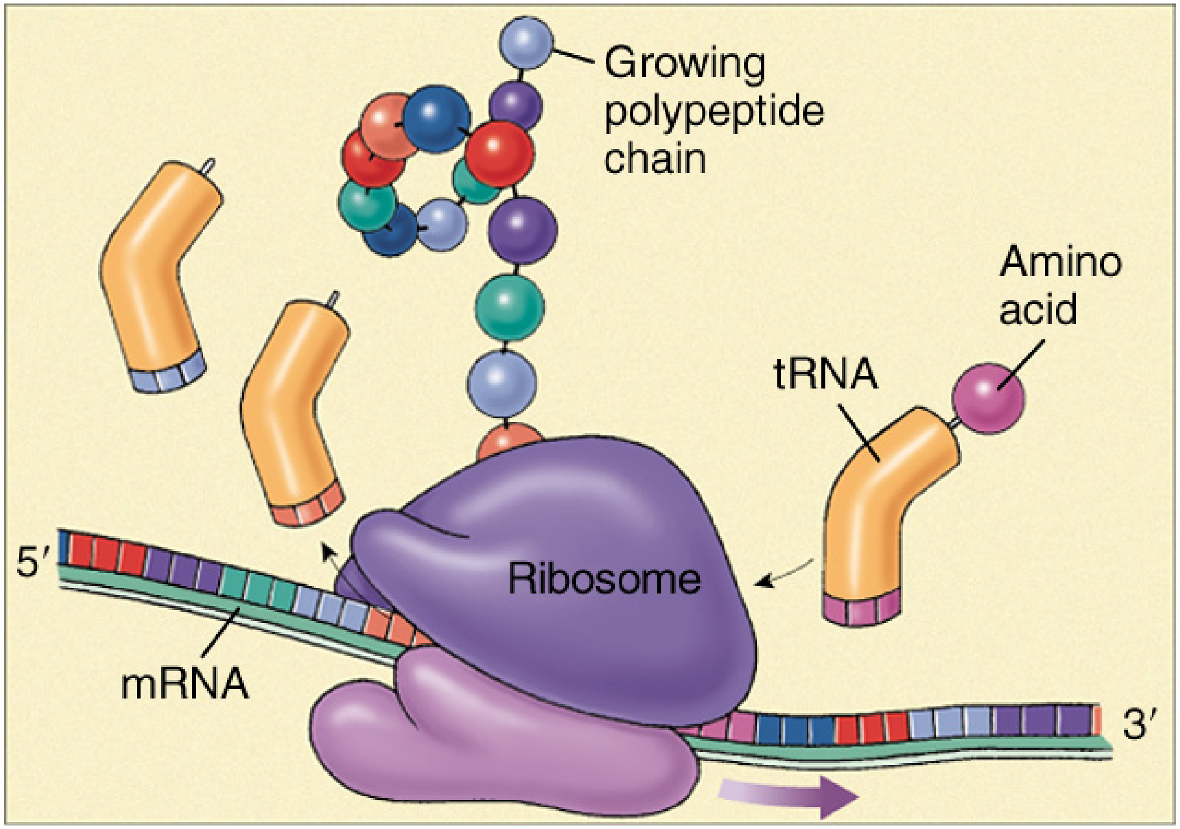
Translation



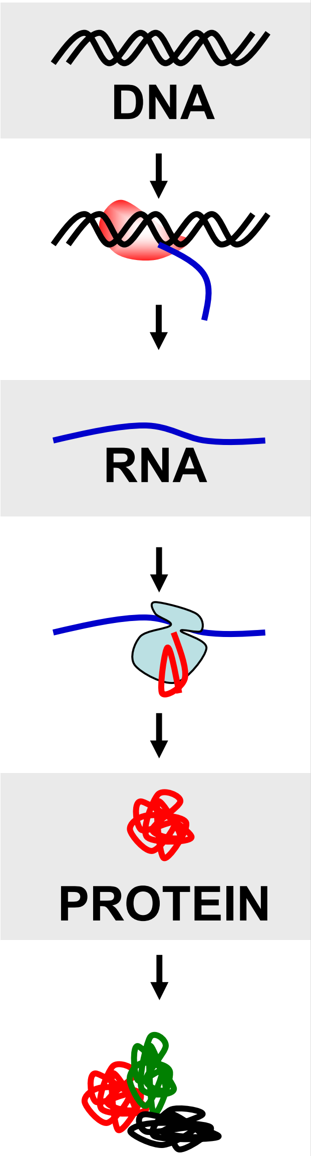


Translation





Proteins and their Functions

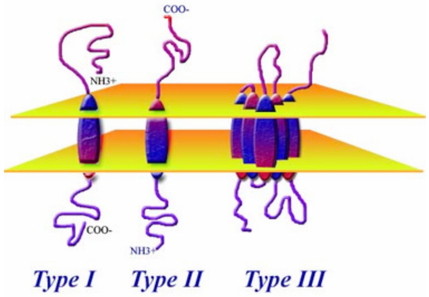

DNA

RNA

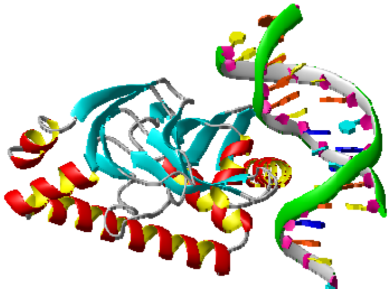
PROTEIN

In the cell, proteins can:

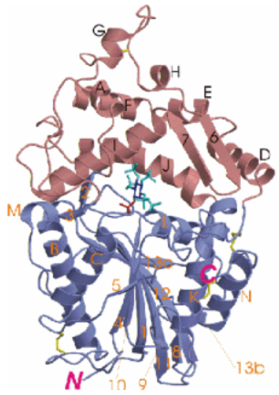
work as channels



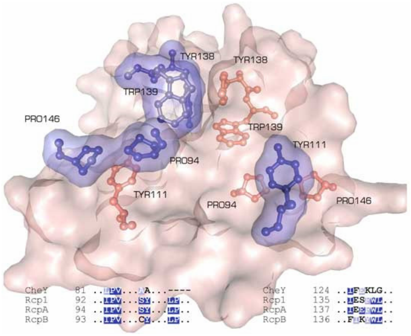
span the membrane for transport, signalling, …



bind DNA



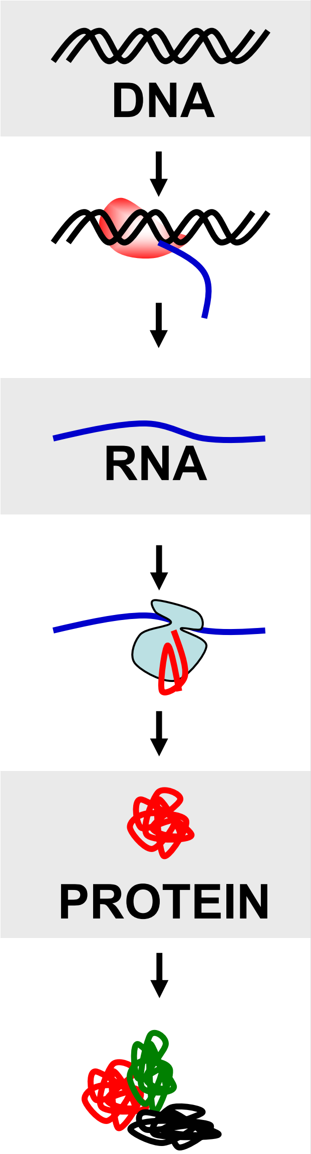
perform enzymatic reactions

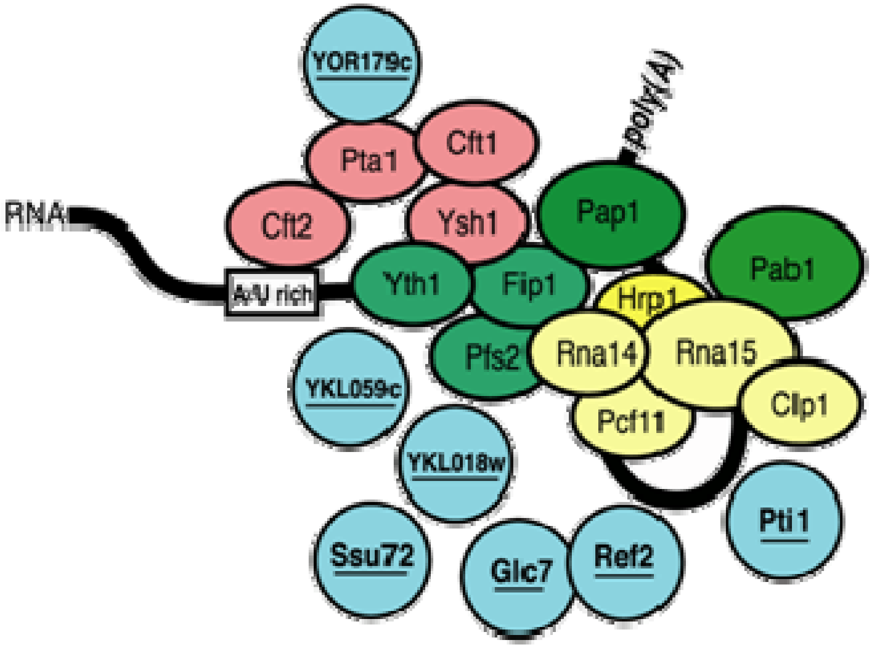


serve as ligands

… or can have many other functions

Protein Complexes





Protein complexes are like factories: efficiency is increased by proximity, interaction, and chain-like production setup.

high throughput technologies

Types of Experiments

What to target.

- different developmental stages
- different organs

How to perturb an organism.

- knock-out / knock-down
- over-expressions

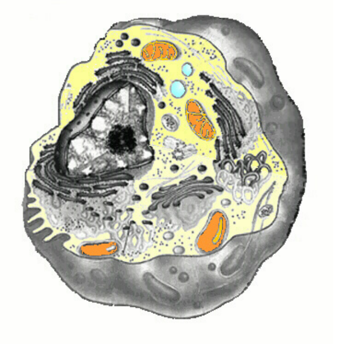
} change expression of specific genes

- stimulus
- disease

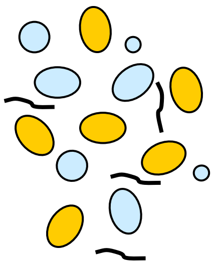
How to measure.

- steady state measurement
- time course measurements

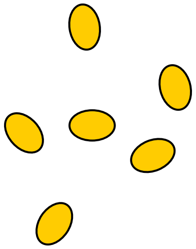
Typical Workflow of an -omics Experiment



destroy cells
from experiment sample

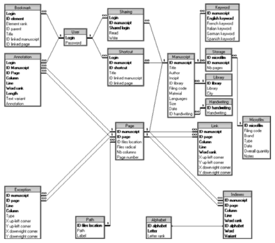


collect cell content

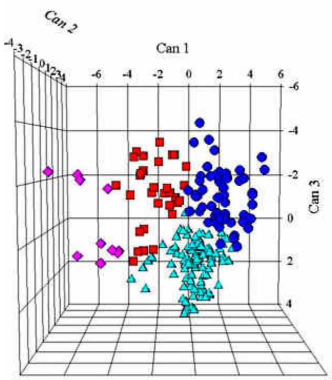


filter and/or
purify cell content

perform high-throughput
measurement



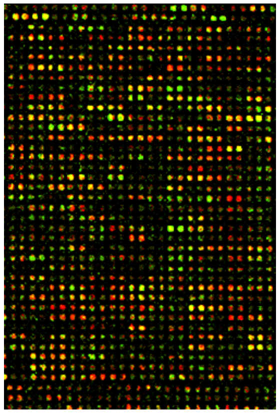
process and
store data



analyze data and
interpret results

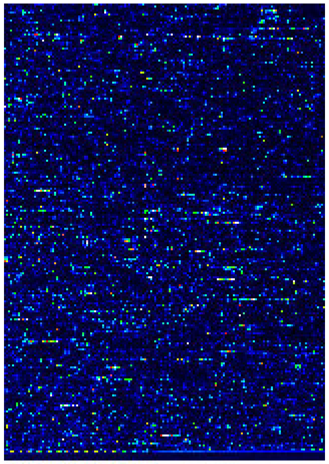
DNA Microarrays

cDNA or GST Arrays



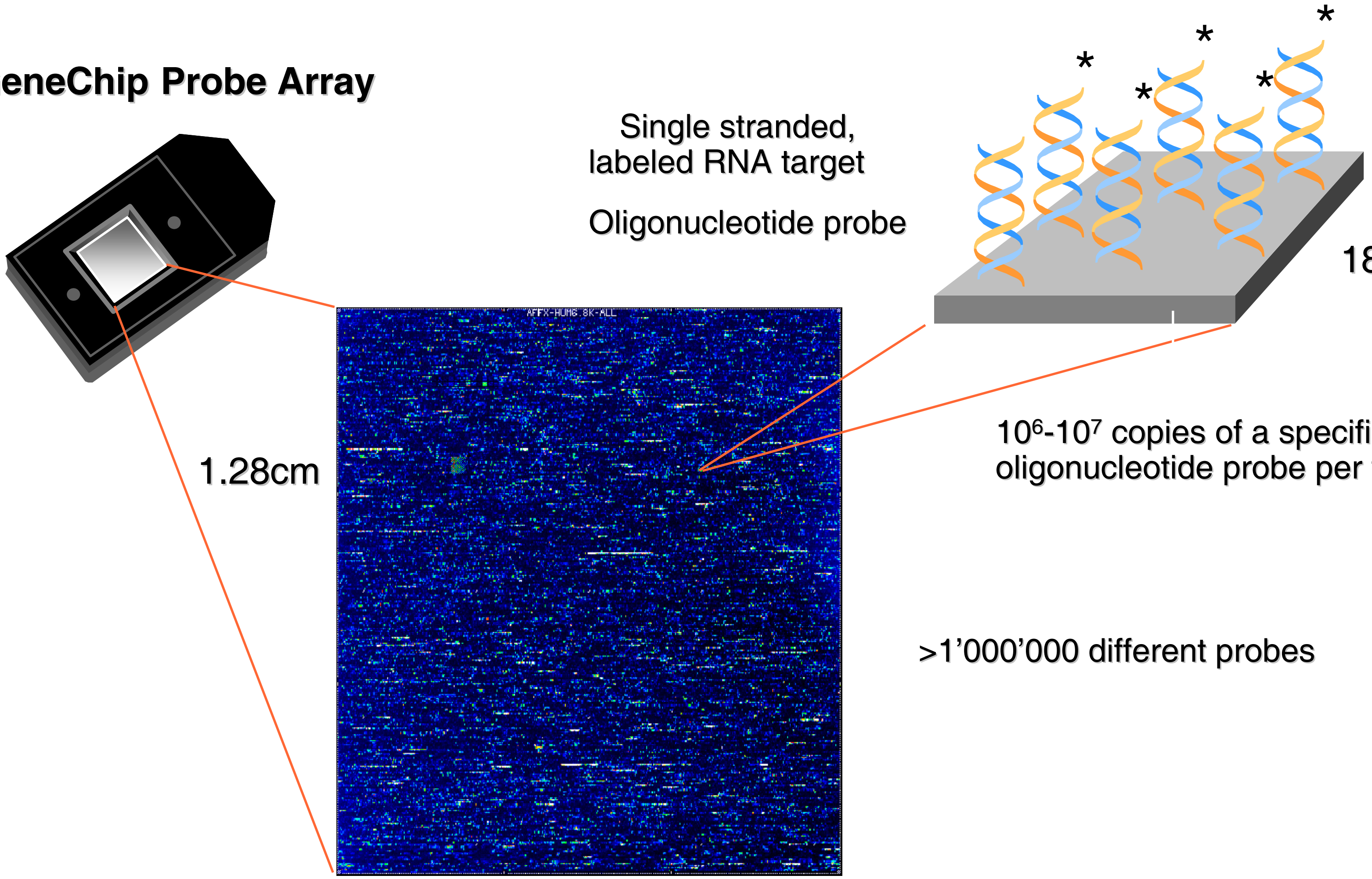
Dual dye (red/green)
(Many companies)

Oligonucleotide Arrays



Single dye (Affymetrix, Nimblegen)
Dual or single dye (Agilent)

DNA Microarrays: Oligonucleotide Arrays



GeneChip Probe Array

Single stranded,
labeled RNA target

Oligonucleotide probe

18µm

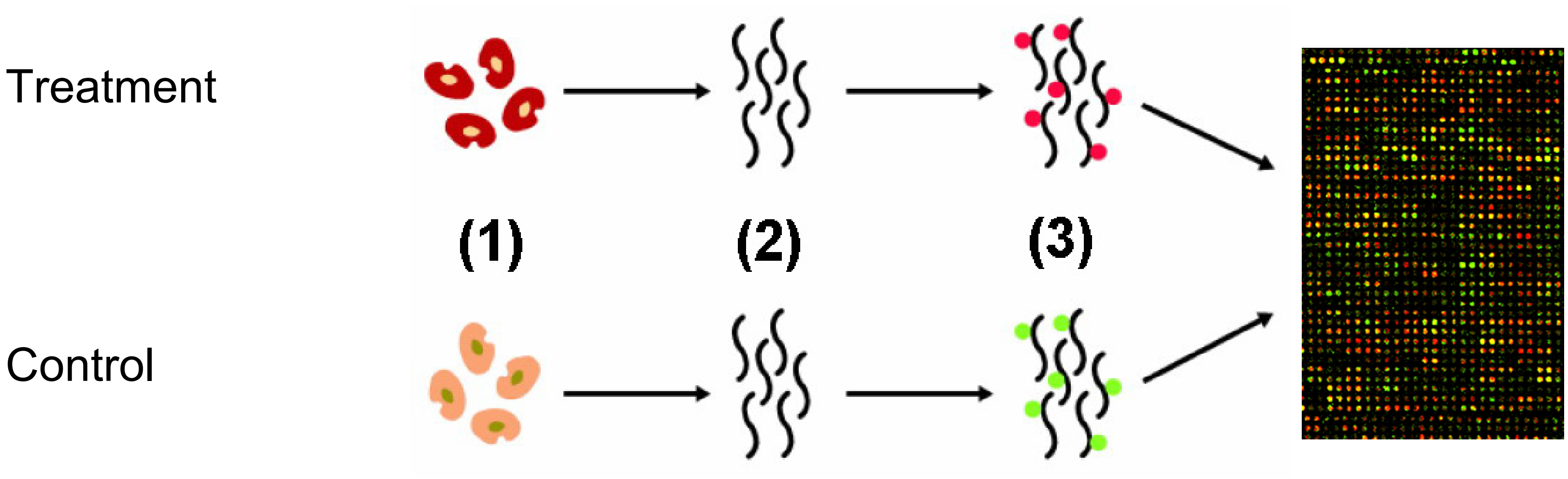
1.28cm

10^6-10^7 copies of a specific
oligonucleotide probe per feature

>1’000’000 different probes

Scanned image

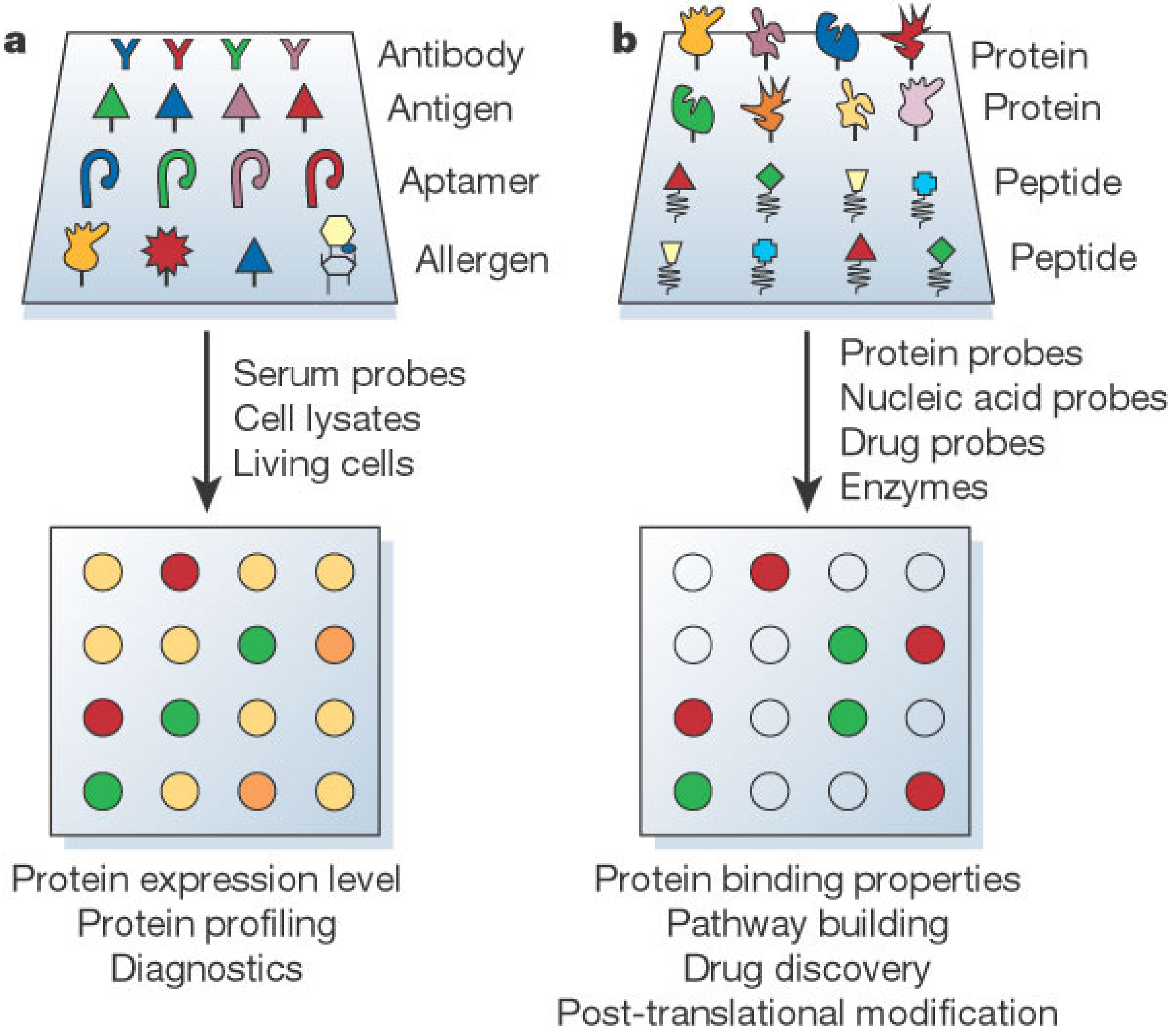
DNA microarrays: cDNA arrays



Treatment

Control

Protein Microarrays



Proteomics

Proteomics = study of the protein repertoire expressed in the cell

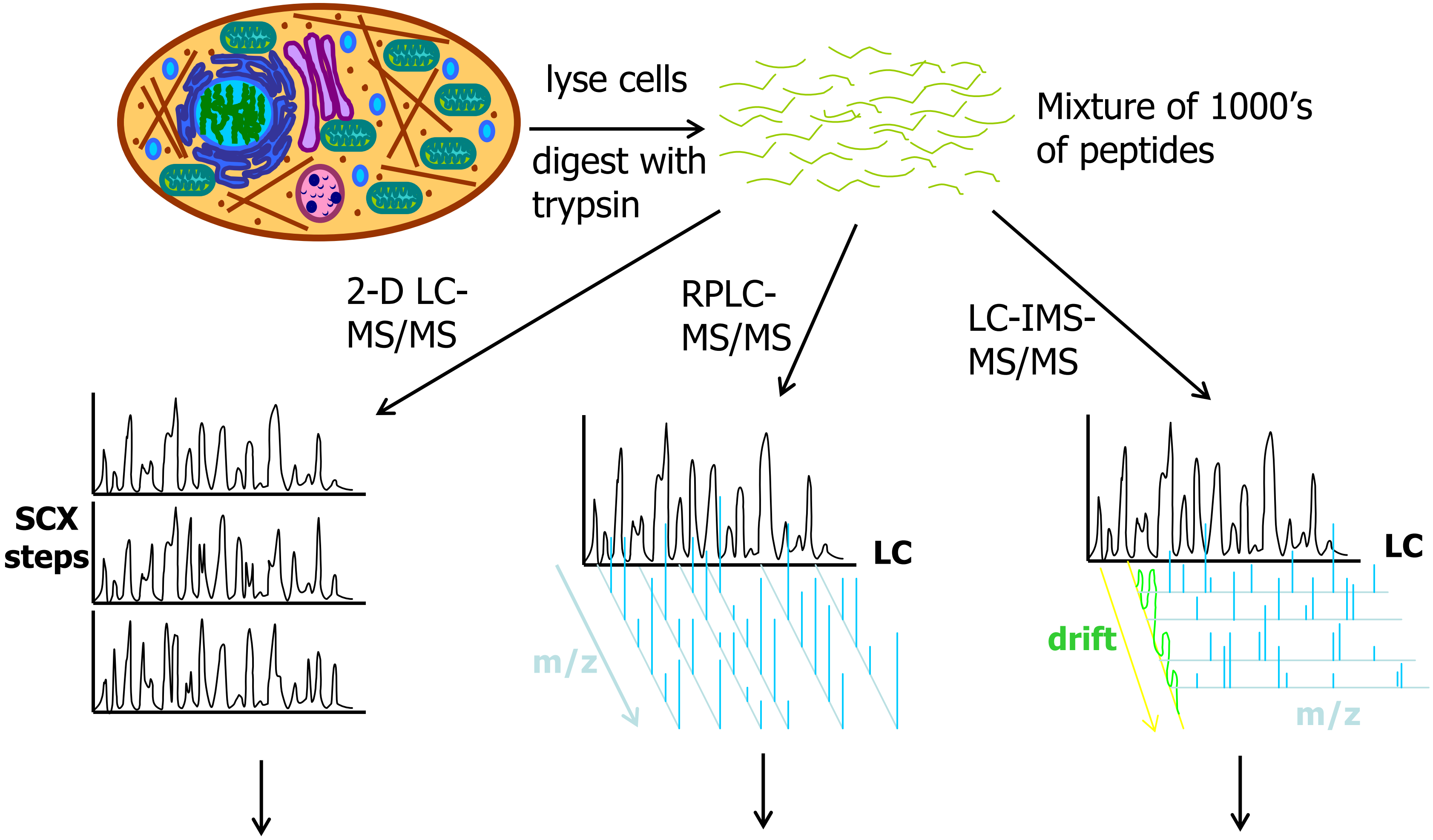
Measurements

- protein expression levels (quantitative and qualitative)
- localization
- protein interaction

Protein interactions elucidate…

- pair-wise interactions
- protein complexes

Shotgun Proteomics



lyse cells

digest with trypsin

Mixture of 1000's of peptides

2-D LC-MS/MS

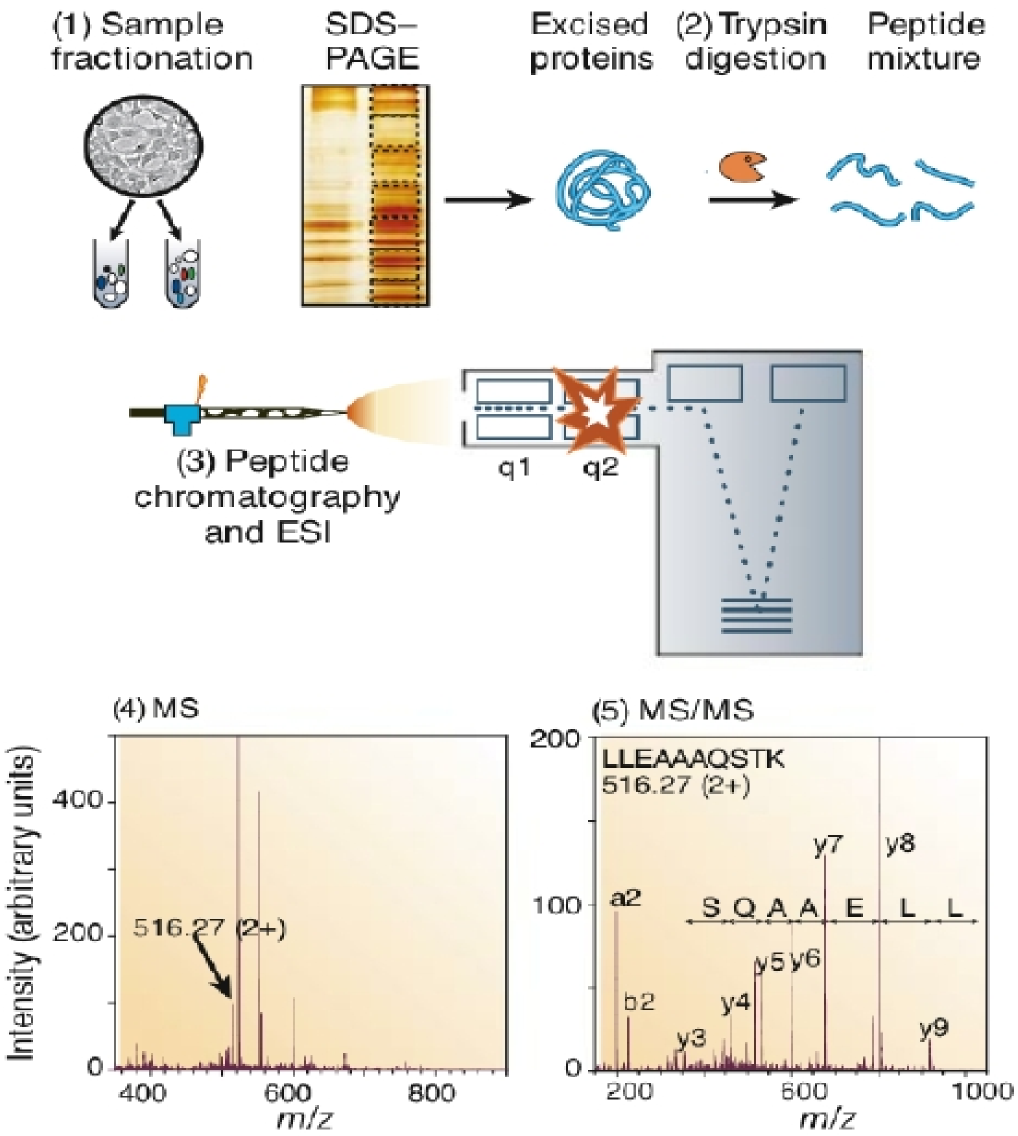
RPLC-MS/MS

LC-IMS-MS/MS

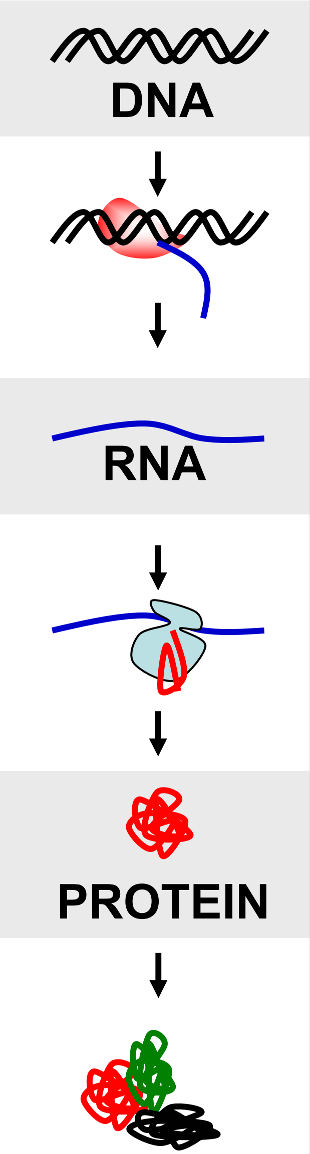
Database searching - matching MS/MS data with peptide sequence

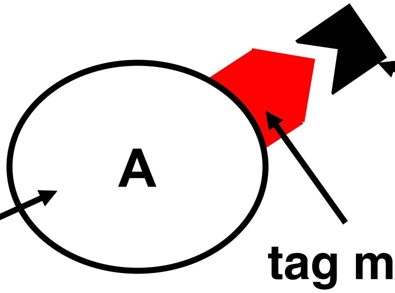
or bioinformatics de novo sequencing of proteins

Proteomics: Mass-Spectrometry Analysis



Tandem Affinity Purification



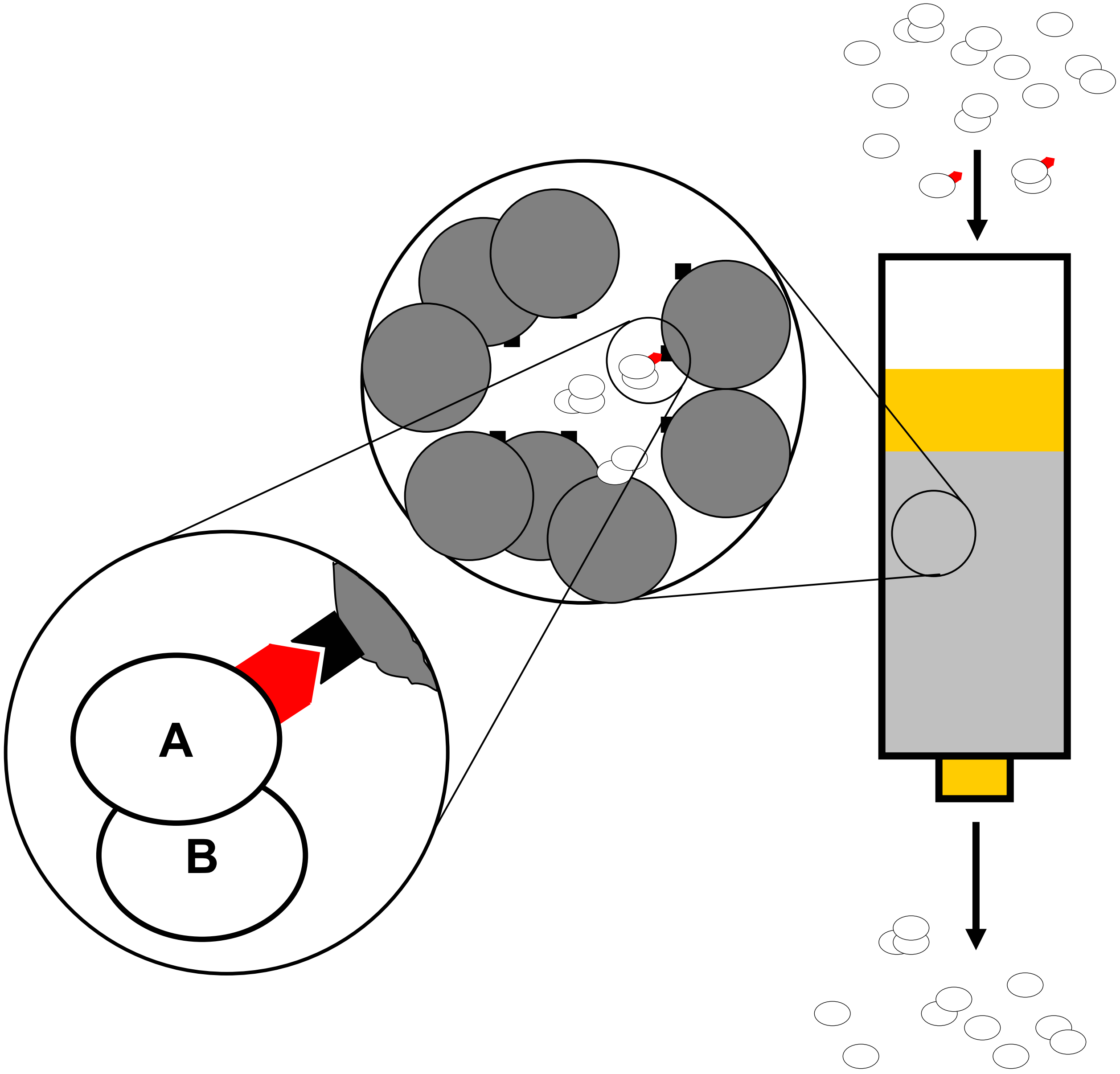


this molecule binds the ‘tag’.

tag modification (e.g. HA/GST/His)

Protein of interest

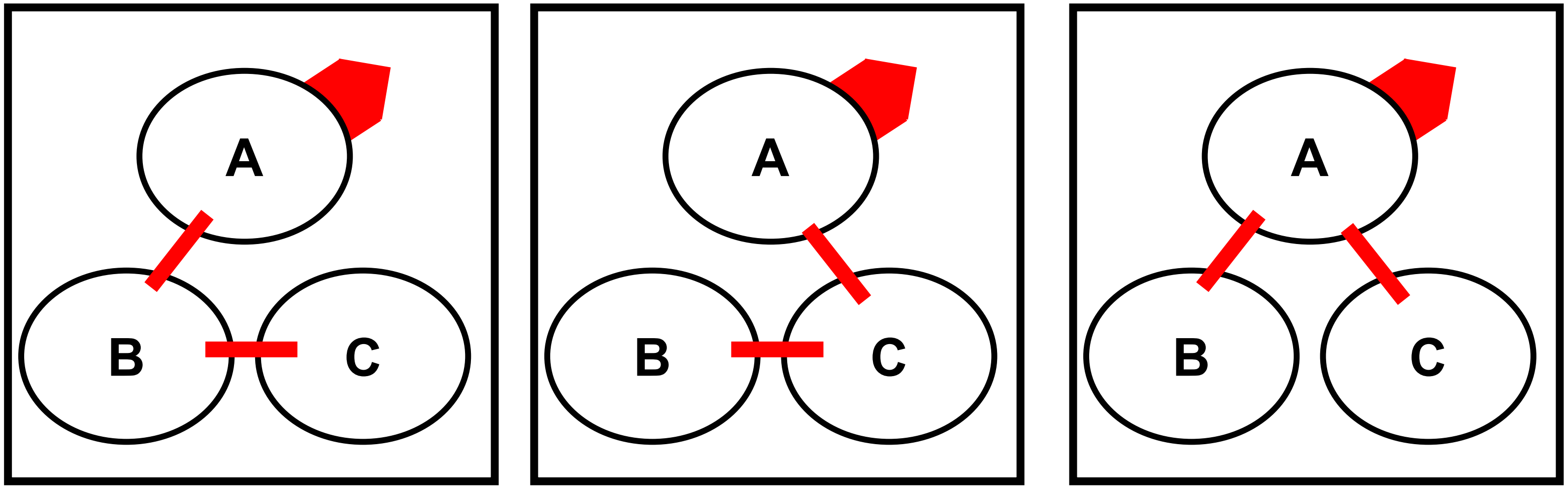
Tandem Affinity Purification (TAP)



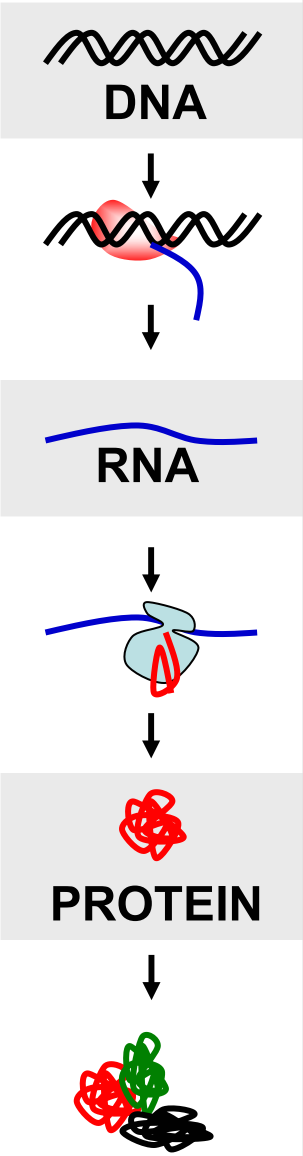
tagged proteins bind to beads

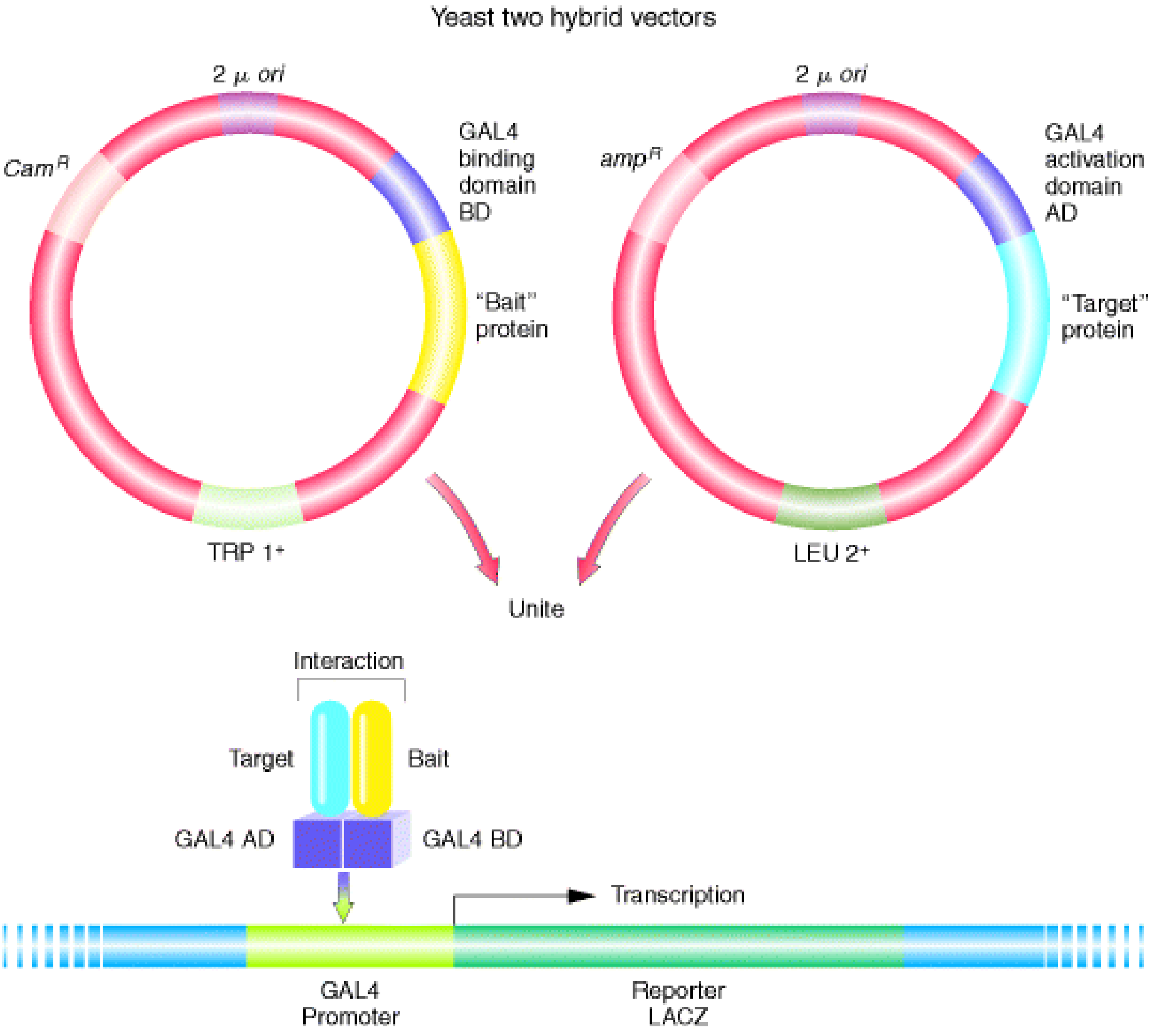
untagged proteins go through fastest (flow-through)

TAP



Yeast two-hybrid

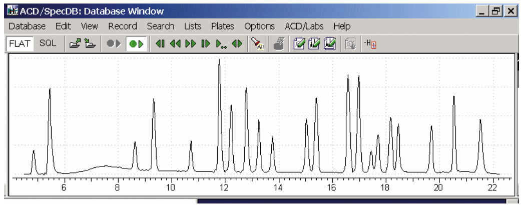




Source: Griffiths *et. al. Modern Genetic Analysis.*

Metabolomics

- Metabolomic methods:
  - Chromatography


ACD/SpecDB: Database Window
Database Edit View Record Search Lists Plates Options ACD/Labs Help
FLAT SQL
6
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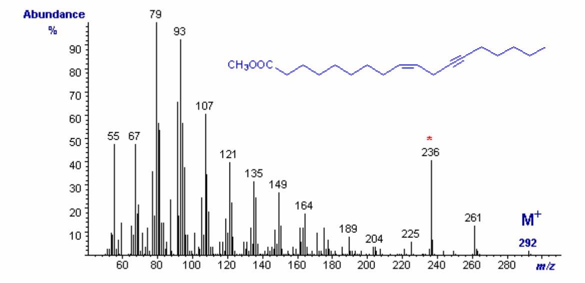
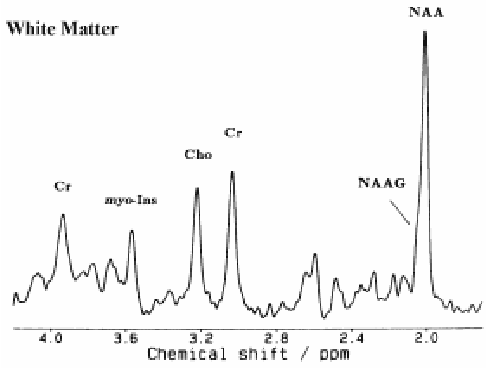
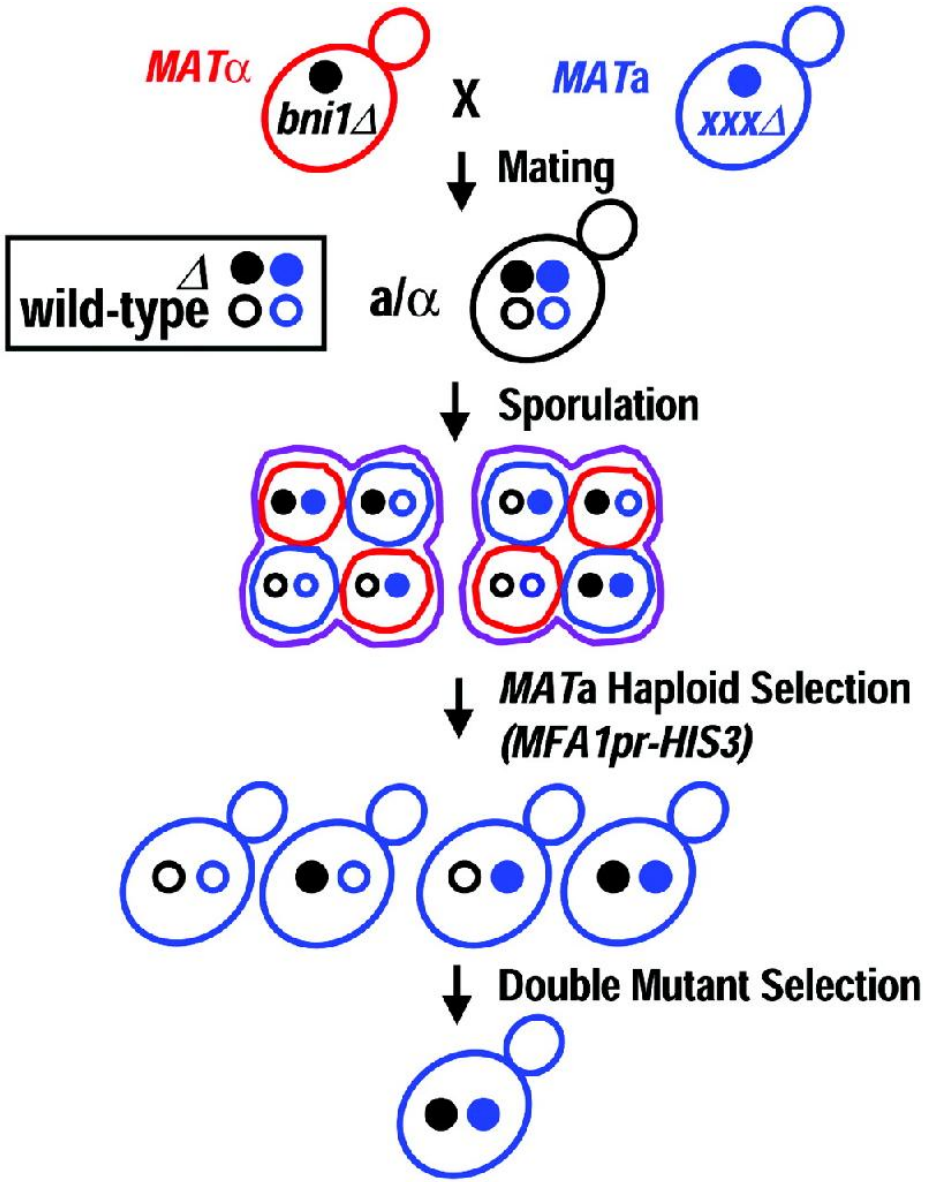
  - Mass spectrometry (MS)



  - Nuclear magnetic resonance (NMR)

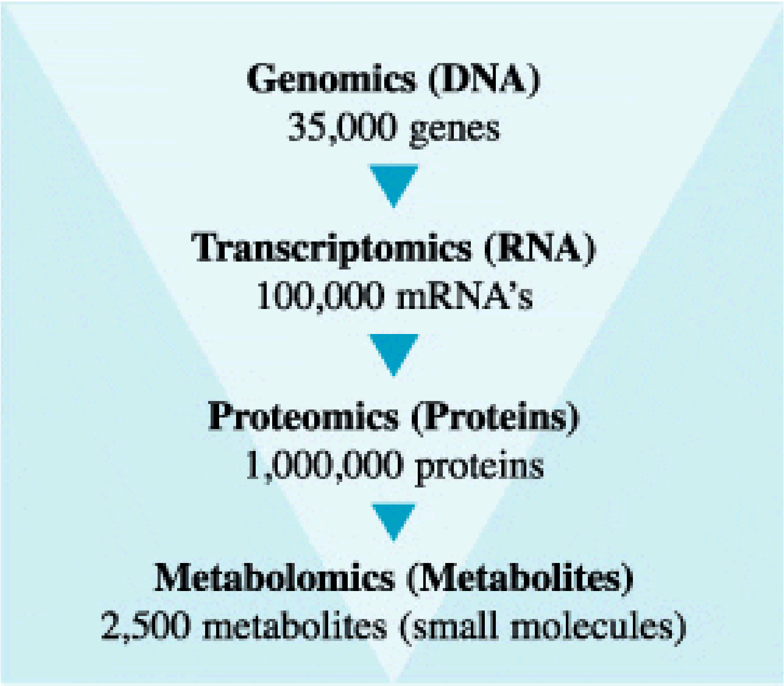


Synthetic Lethal Interactions



OMICS…

Gene - Genome - Genomics
Protein - Proteome - Proteomics
Metabolite - Metabolome - Metabolomics



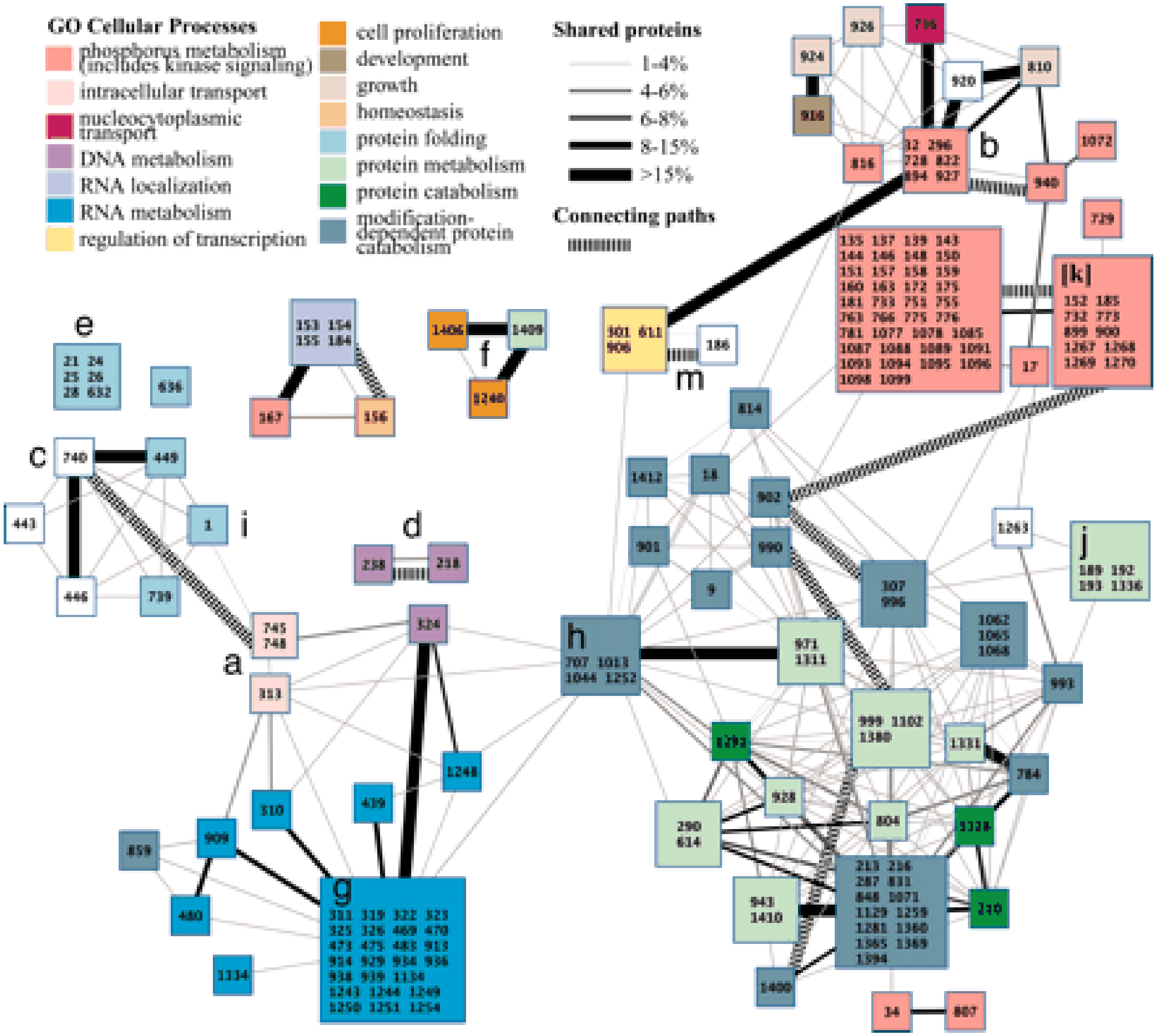
Genomics (DNA)
35,000 genes

Transcriptomics (RNA)
100,000 mRNA's

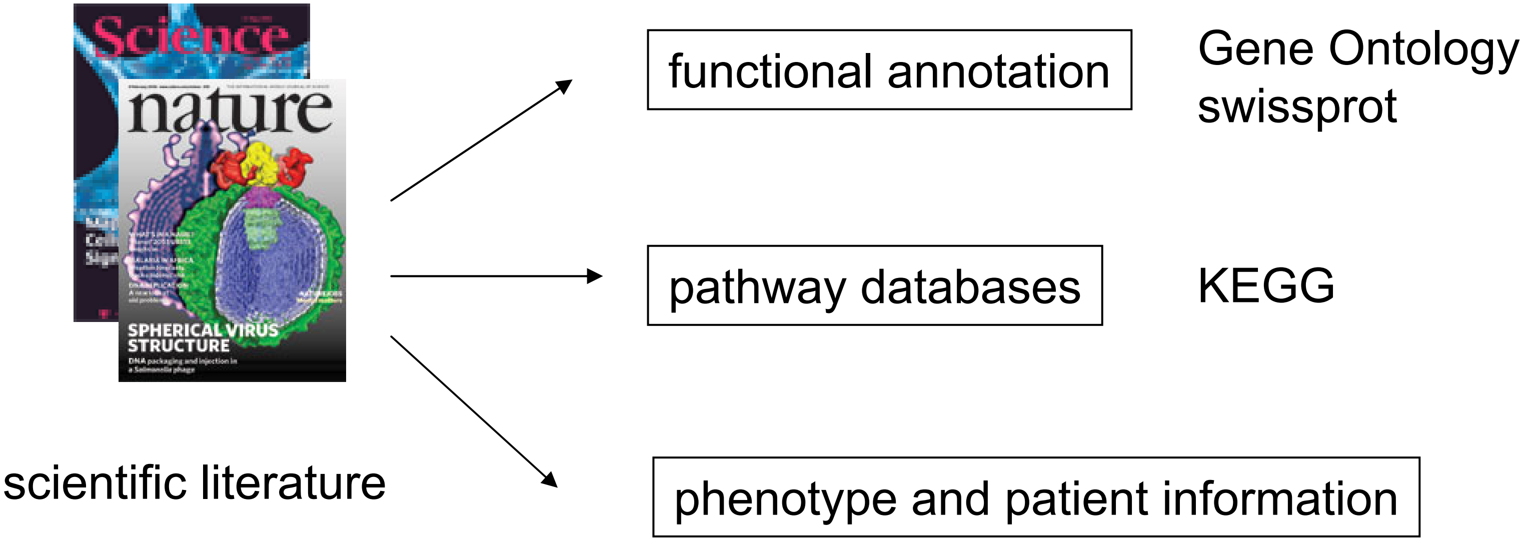
Proteomics (Proteins)
1,000,000 proteins

Metabolomics (Metabolites)
2,500 metabolites (small molecules)

Complex Systems



Formalized Biological Knowledge


Science
nature
SPHERICAL VIRUS STRUCTURE
DNA packaging and injection in a Salmonella phage

scientific literature

functional annotation

Gene Ontology
swissprot

pathway databases

KEGG

phenotype and patient information

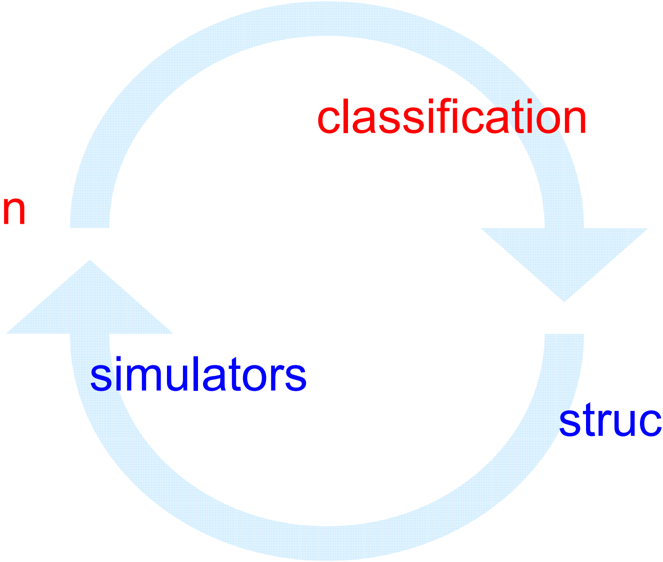
2. Computational Issues in Systems Biology

Computational Challenges

experimental design

data preprocessing

data visualization



classification

module identification

simulators

structure prediction

network inference

text mining

Classification of Tumor Samples – Problem

Goals

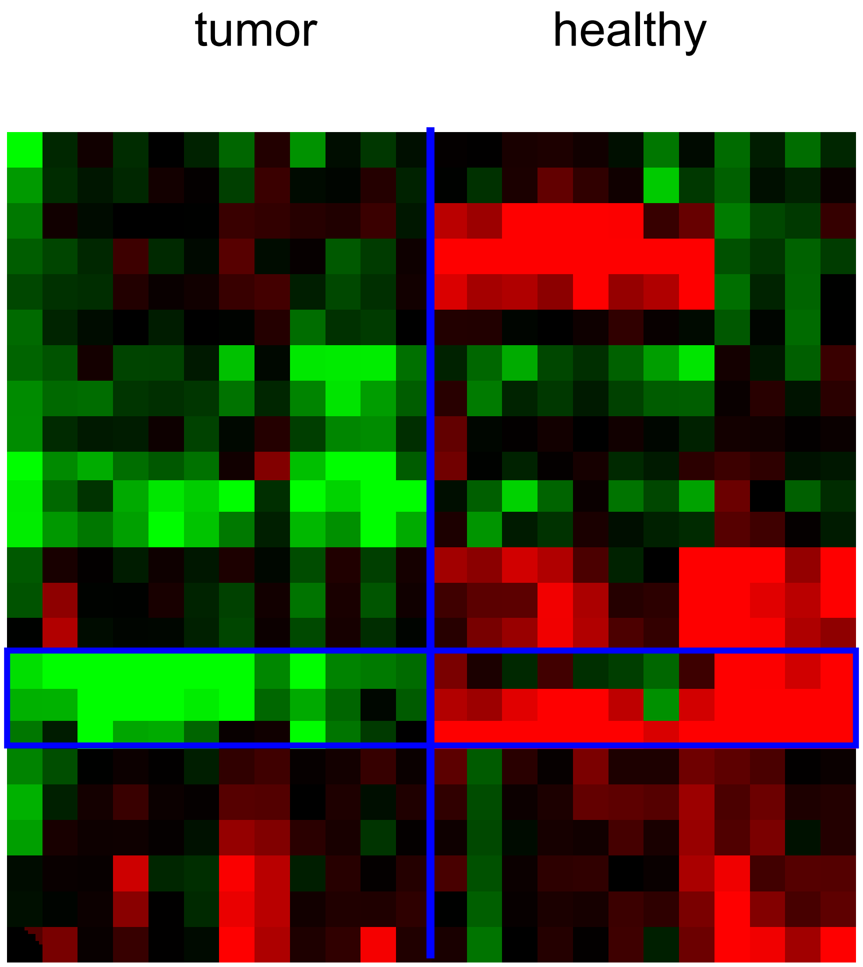
- discrimination between classes
- feature extraction

Data

- mostly gene expression
- proteomics
- known outcome

Challenges

- noisy data
- few samples, high dimensionality
- overfitting
- multiple testing



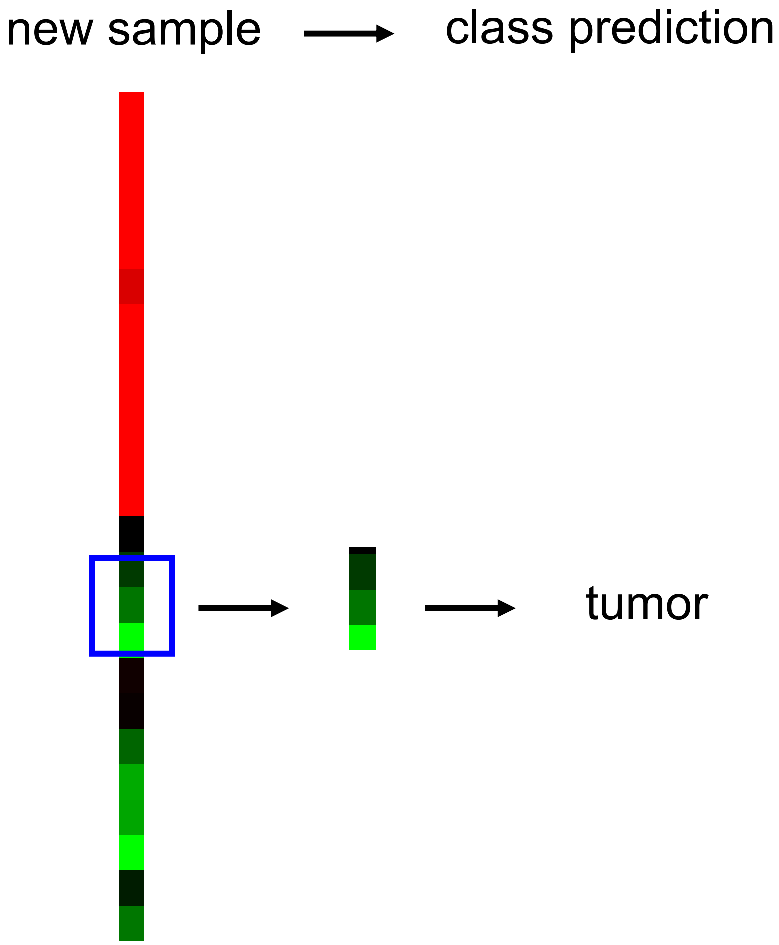
Classification of Tumor Samples – General Approach

Ingredients

- gene set selection
- classifier
- objective function
- optimizer

Fighting Overfitting

- cross validation in objective function
- keep models small



Classification of Tumor Sample – EC approaches

Optimization Approaches

- genetic programming (GP) [1, 6, 7]
- simulated annealing [4]
- multiobjective evolutionary algorithm (including size) [3, 5]

[1] J. Moore et al, **Symbolic Discriminant Analysis for Mining Gene Expression Patterns**, EMCL, 2001

[2] J. Liu et al., **Selecting Informative Genes with Parallel Genetic Algorithms in Tissue Classification**, Genome Informatics, 2001

[3] J. Liu et al., **Selecting Informative Genes Using a Multiobjective Evolutionary Algorithm**, WCCI, 2002

[4] J. M. Deutsch, **Evolutionary algorithms for finding optimal gene sets in microarray prediction**, Bioinformatics, 2003

[5] A. R. Reddy and K. Deb, **Identification of Multiple Gene Subsets Using Multi-objective Evolutionary Algorithms**, EMO, 2003

[6] J. Rowland, **Model Selection Methodology in Supervised Learning with Evolutionary Computation**, Biosystems, 2003

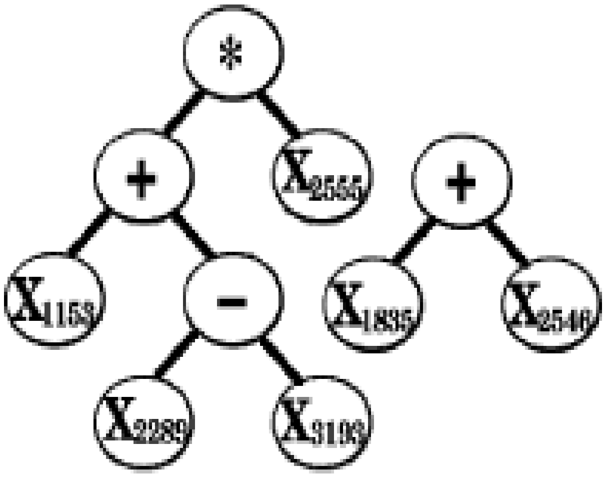
[7] W. B. Langdon and B. F. Buxton, **Genetic Programming for Mining DNA Chip data from Cancer Patients**, Genetic Programming and Evolvable Machines, 2004

[8] J. Rowland, **On Genetic Programming and Knowledge Discovery in Transcriptome Data**, CEC, 2004

Classification of Tumor Samples - Moore et al. [1]

Individual

- real valued function f of gene expression
- represented as GP tree



Classifier

- f > median of all function values

Objective Function

- classification error

Optimizer

- parallel GP

Results

- data: AML/ALL (Golub et al.) two class problem
- two nearly perfect predictors:
  - X1835 + X2546
  - X2555 * (X1153 + X2289 + X3193)

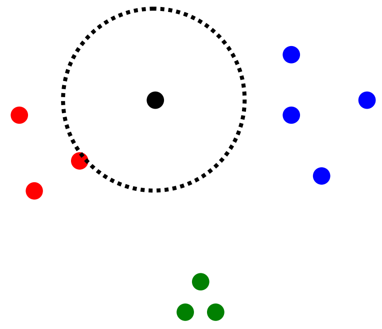
Classification of Tumor Samples - Deutsch [4]

Individual

- set of predictive genes
- represented as list

Classifier

- k-nearest neighbor (k = 1)



Objective Function

- weighted sum of LOOCV accuracy and clustering score

Optimizer

- variant of simulated annealing (replication algorithm)
- mutation: add or remove one gene

Results

- data:multiple data sets (incl. one with more than 2 classes)
- results: smaller gene sets and good classification

Classification of Tumor Samples – Liu et al. [3]

Individual

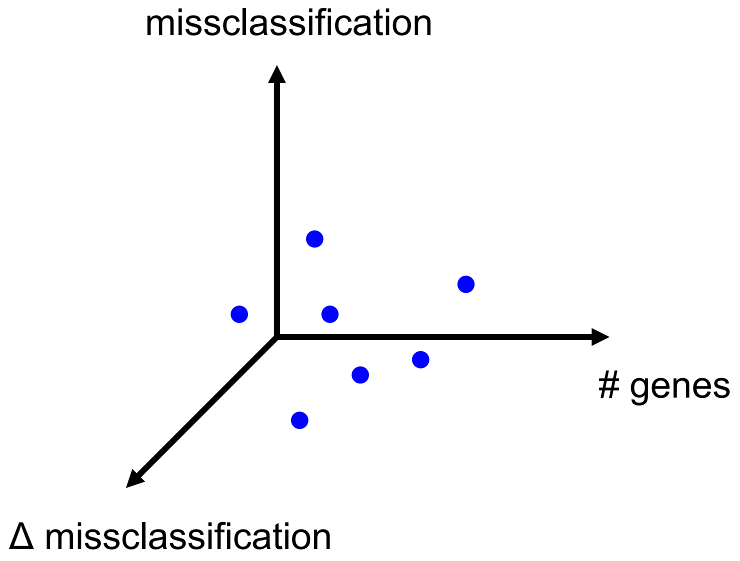
- set of predictive genes
- represented as bit string

Classifier

- normalized distance to class mean

Objective Function

1. gene set size
2. missclassification rate
3. difference of missclassification rates



Optimizer

- multiobjective EA
- called replication algorithm

Results

- data: Leukemia, Lymphoma and Colon cancer data sets
- results: many diverse and small gene sets

Classification of Tumor Samples – Langdon et al. [7]

Individual

- sum S of 5 real valued function of expression values
- represented as 5 GP trees

Classifier

- S > 0

Objective Function

- mean of LOOCV accuracies for both classes

Optimizer

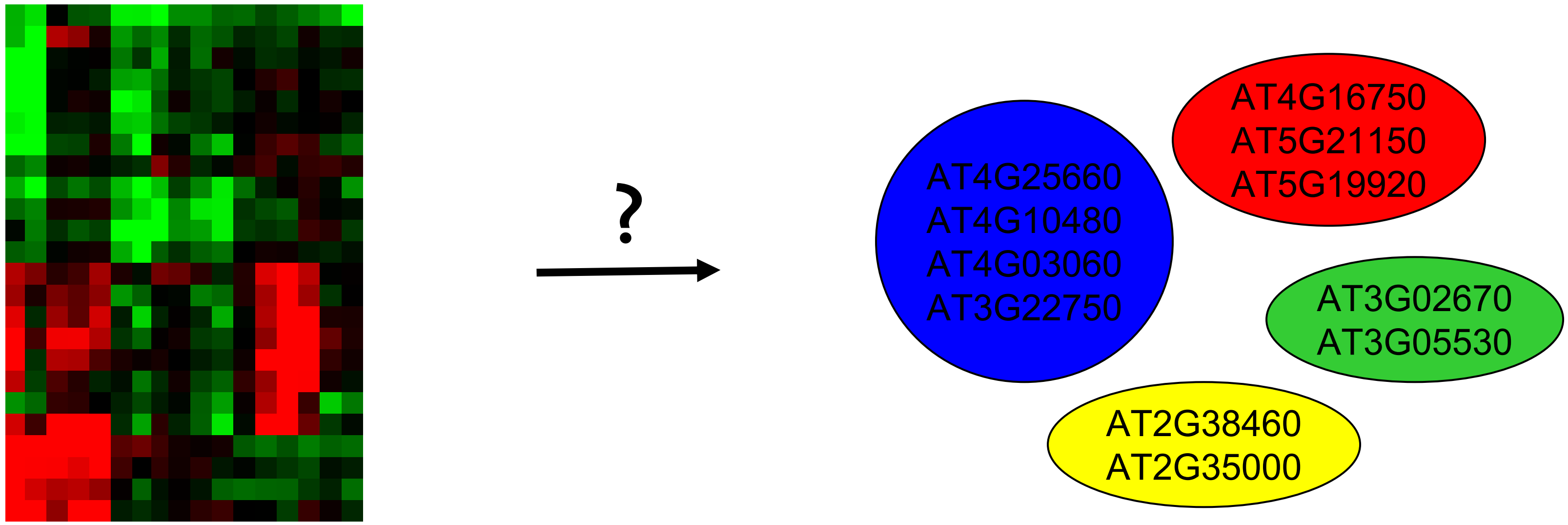
- GP

Results

- data: Central nervous system embryonal tumors [Pomeroy et al. 2002]
- results: good classification, surprisingly small gene sets

Module Identification

Goal



high throughput data

functional gene groups

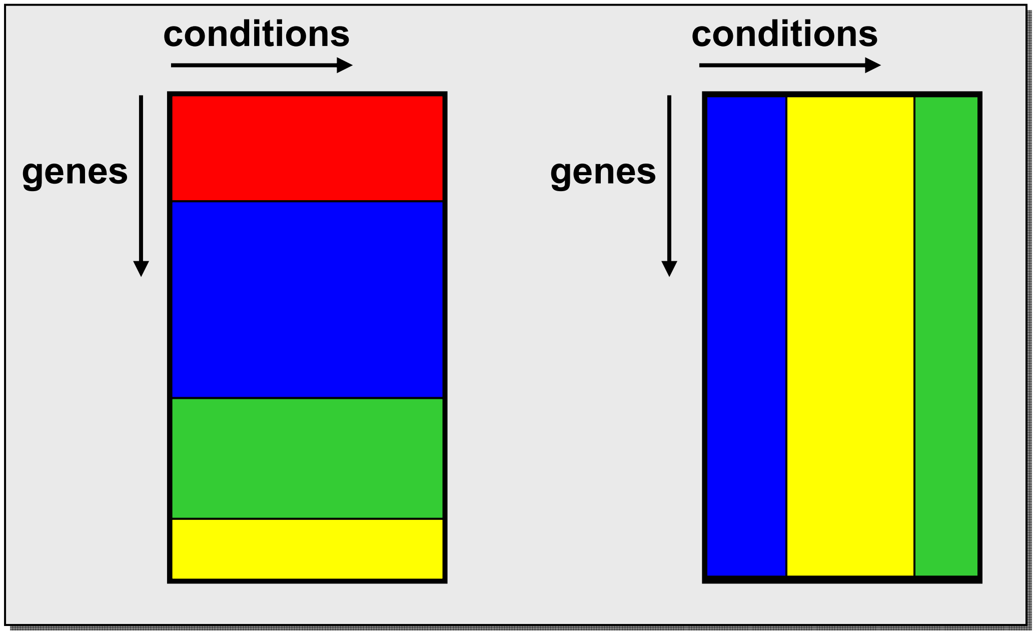
Approaches

- guilt by association
- clustering, biclustering
- integration with additional data, e.g., promoter elements

Challenges

- huge search space
- data integration

Clustering of Gene Expression Data



Inputs

- gene expression data
- number of clusters

Clustering algorithms …

… group similar things.

… partition the matrix.

… use all measurements.

Clustering with EC – Falkenauer et al. [9]

Individual

- clustering = partitioning of input matrix
- specific representation

Objective Function

- total variance within clusters

Optimizer

- Grouping Genetic Algorithm

Results

- data: 3 different gene expression data sets
- results: much better than k-means (which uses the same objective function)

[9] E. Falkenauer and A. Marchand, **Clustering Microarray Data Using Evolutionary Algorithms**, chapter in “Evolutionary Computation in Bioinformatics”, Morgan Kaufmann, 2003

Clustering with EC – Handl et al. [10]

Individual

- clustering = partitioning of input matrix
- locus based adjacency representation

Objective Function

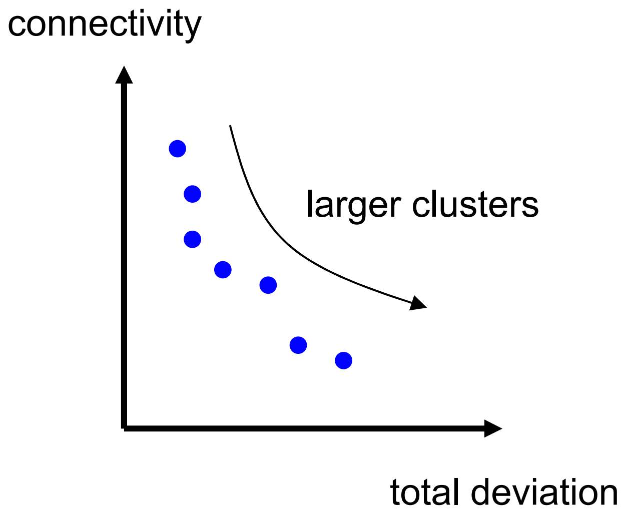
1. total deviation from cluster means
2. total connectivity (high if neighbors are not in the same cluster)

Optimizer

- multiobjective EA (PESA-II)

Results

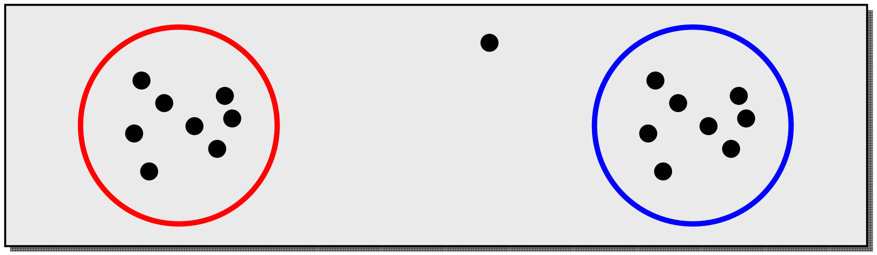
- good performance compared to k-means and average-linkage hierarchical clustering algorithms
- automatic determination of the number of clusters



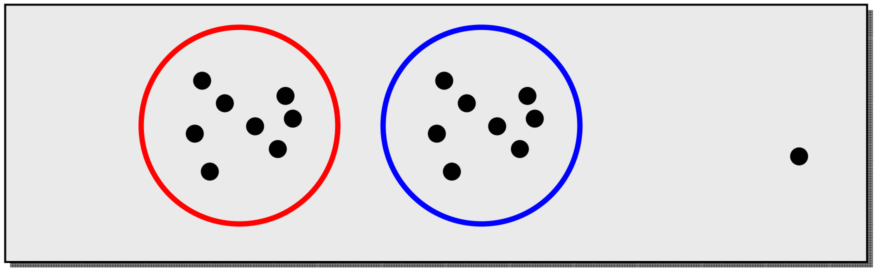
[10] J. Handl and J. Knowles, **Exploiting the Trade-off – the Benefits of Multiple Objectives in Data Clustering**, EMO, 2005

Drawbacks of Standard Clustering

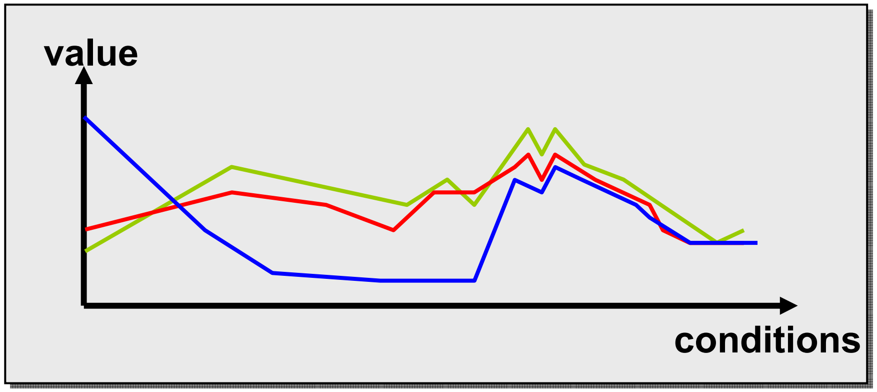
- a gene cannot be in two clusters



- each gene is assigned to a cluster



- local patterns are missed



→ **New problem formulation needed.**

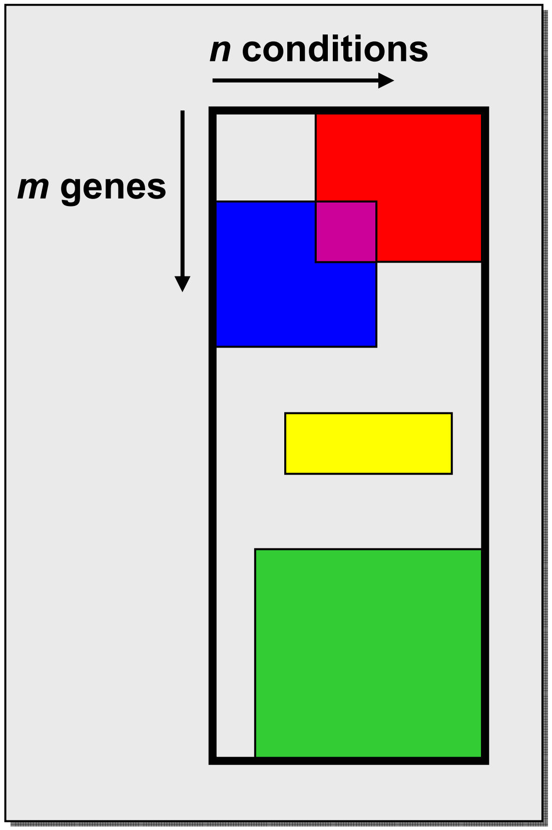
Biclustering

Goal

- find subsets of genes – subsets of conditions
- may overlap
- two objectives: size and similarity

Existing Algorithms

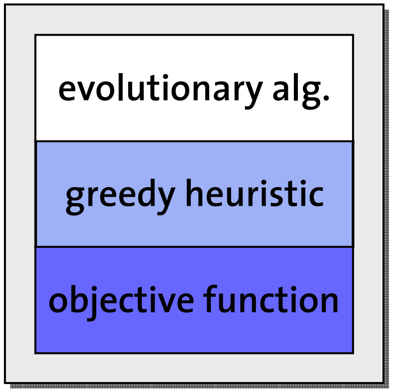
- definition of similarity
- number of biclusters
- search strategy



EC for Biclustering – Bleuler et al. [11]

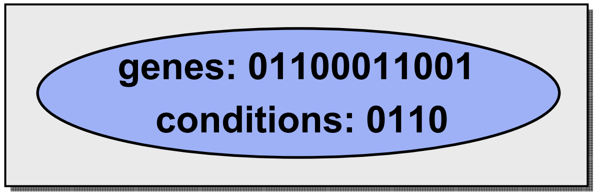
Approach

- existing algorithms as local search
- EA as global search
- systematic sampling of the search space
- applicable to many existing algorithms



Basics

- individual = submatrix
- binary encoding
- independent bit mutation
- uniform crossover
- local search
- tournament selection (t ∈{3, 20})
- 100 individuals, 50 generations



[11] S. Bleuler et al., **An EA Framework for Biclustering of Gene Expression Data**, CEC, 2004

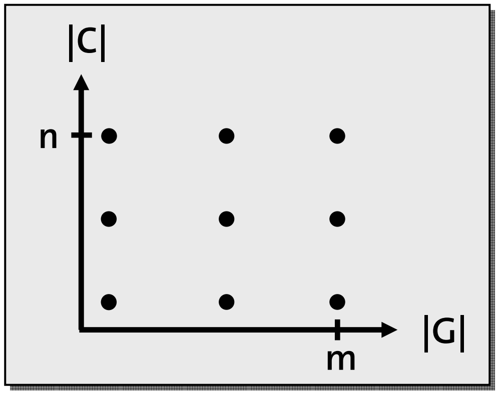
EC for Biclustering – Bleuler et al. [11]

Initialization

- set each bit to 1 with p = 0.5?

⟶ biclusters have similar size

- better: distribute bicluster sizes

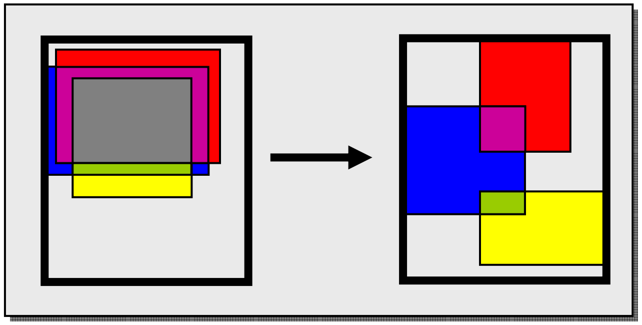


After the local search…

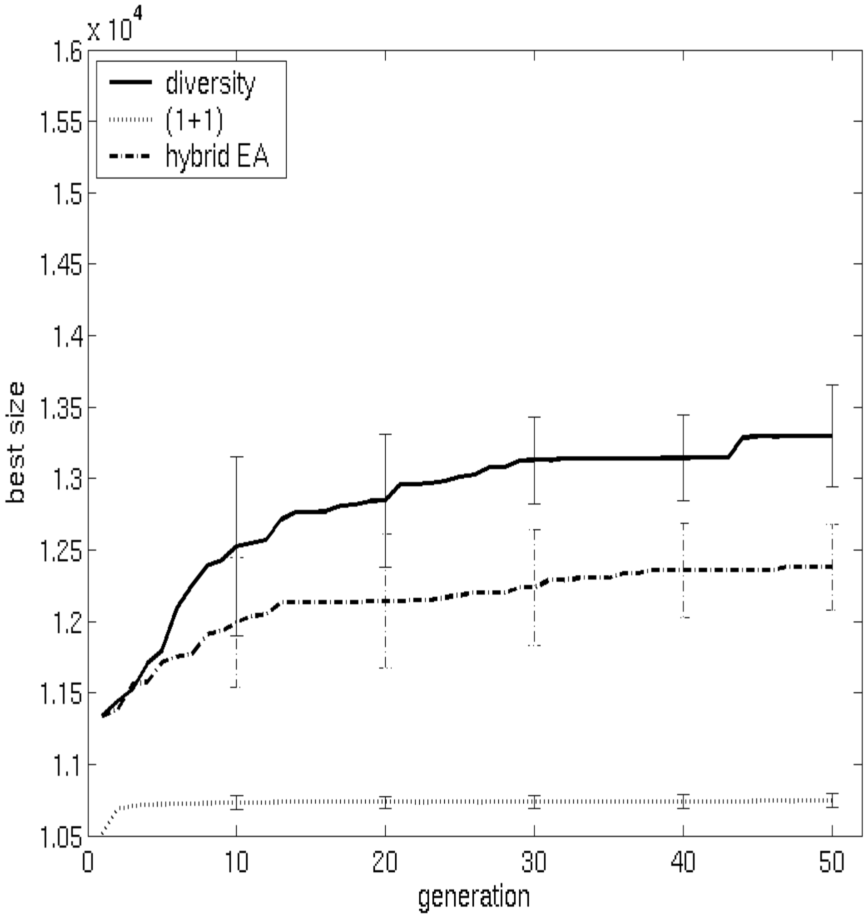
- update (Lamarckian evolution)
- don’t update (Baldwinian evolution)

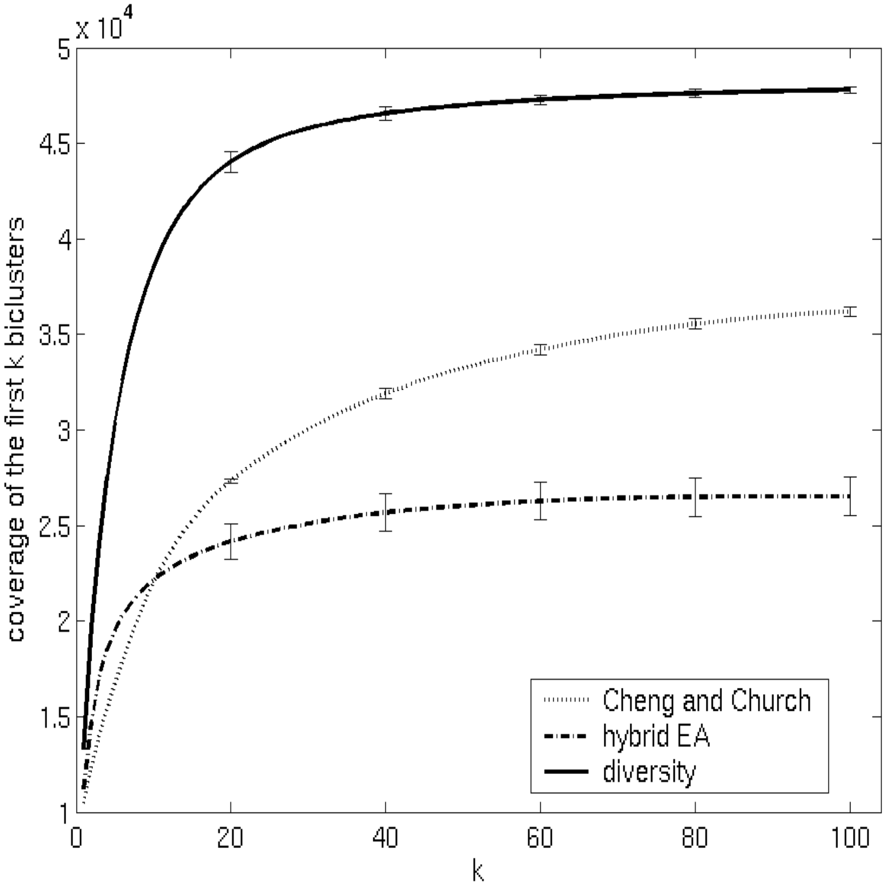
Diversity Maintenance

- N biclusters in one run
- optimize coverage
- select individual with most new area

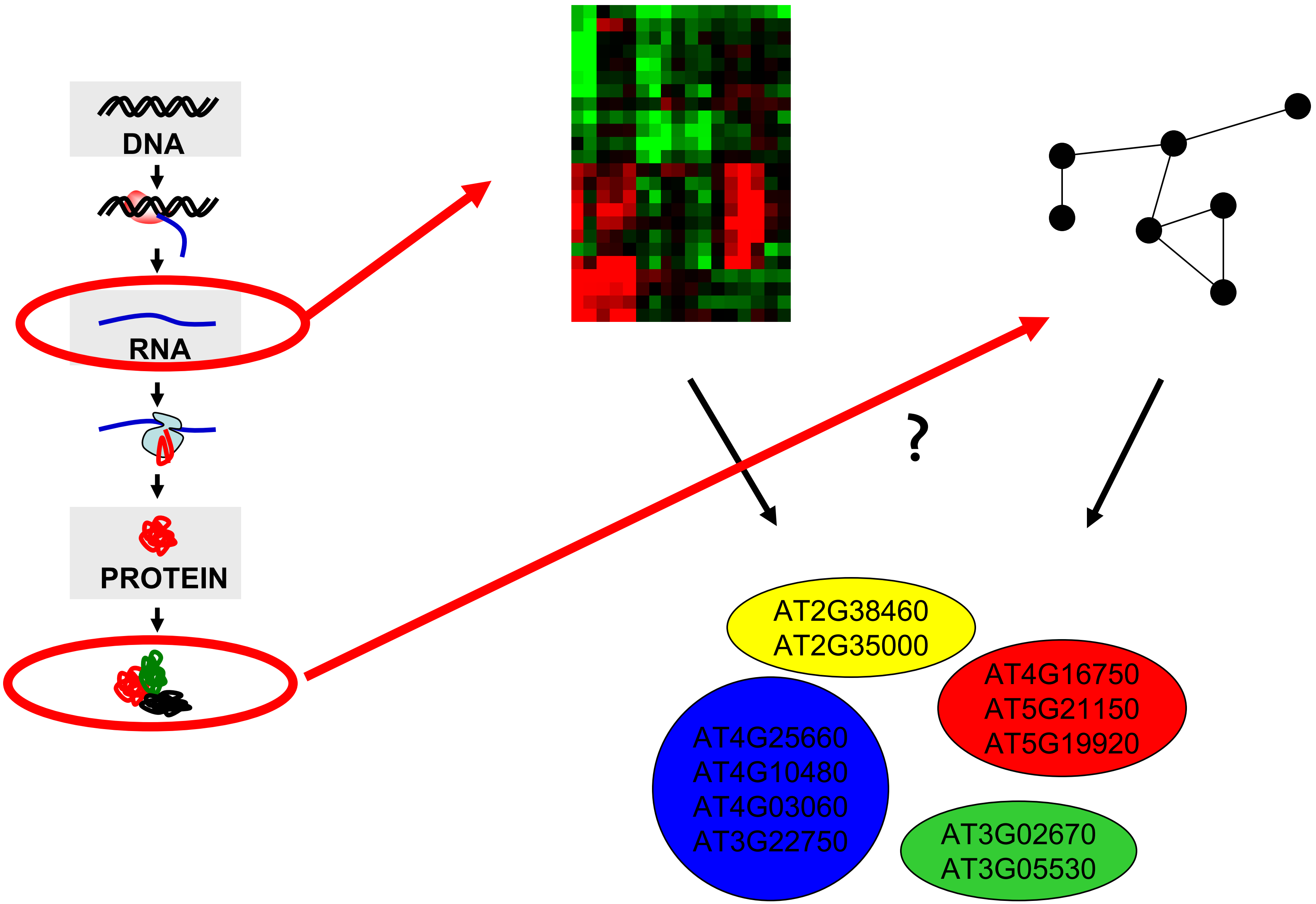


EC for Biclustering – Bleuler et al. [11]





Gene Expression is not Enough!



DNA

RNA

PROTEIN

?

AT2G38460
AT2G35000

AT4G16750
AT5G21150
AT5G19920

AT4G25660
AT4G10480
AT4G03060
AT3G22750

AT3G02670
AT3G05530

EC for Data Integration - Speer et al. [12]

Goal

- clustering of gene expression data and Gene Ontology graph

Individual

- clustering = partitioning of input matrix
- representation based on minimum spanning tree
- represented as n-1 bits determining whether to cut the MST at edge i.

Objective Function

- weighted sum of distance on gene expression and distance on Gene Ontology graph

Optimizer

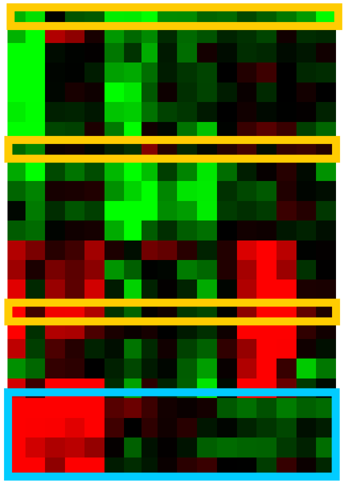
- EA with local search

Results

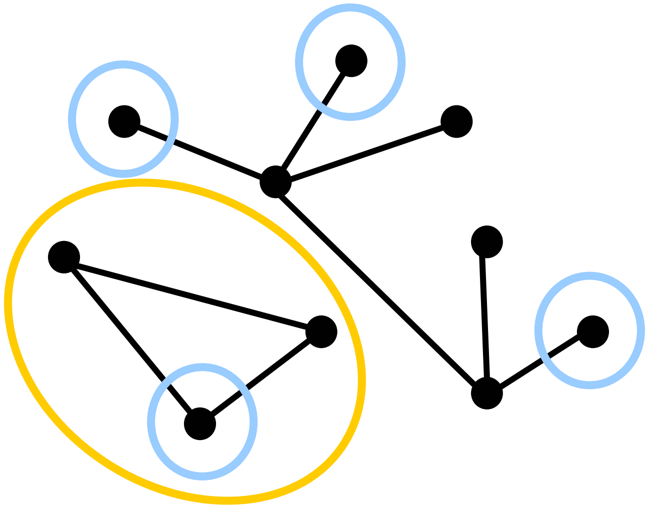
- data: gene expression data from human fibroblast and GO
- results: some clusters more gene expression oriented others more GO oriented

[12] N. Speer et al., **A Memetic Co-Clustering Algorithm for Gene Expression Profiles and Biological Annotation**, CEC, 2004

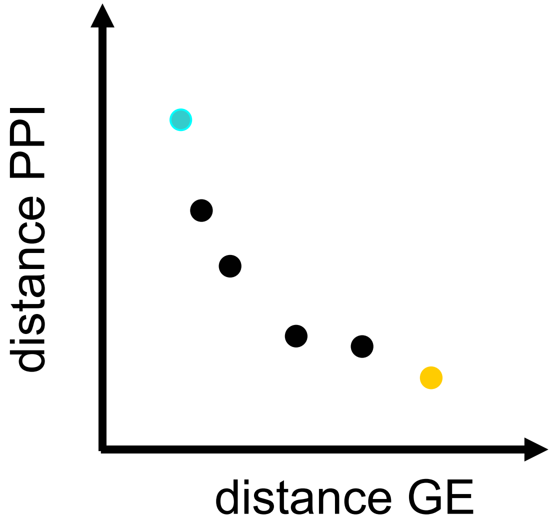
EC for Data Integration - Bleuler et al. (work in progress)



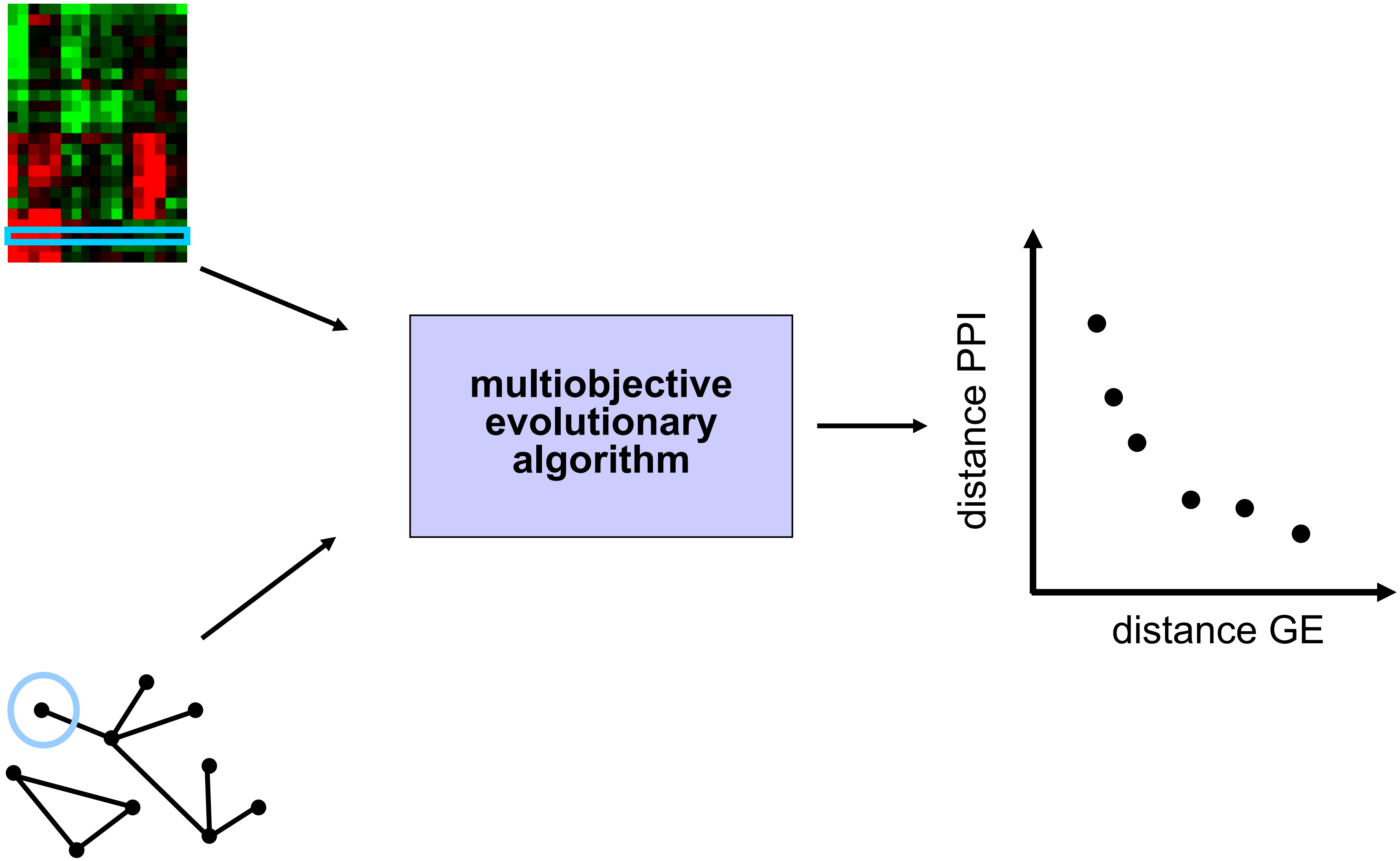
gene expression



protein-protein interactions

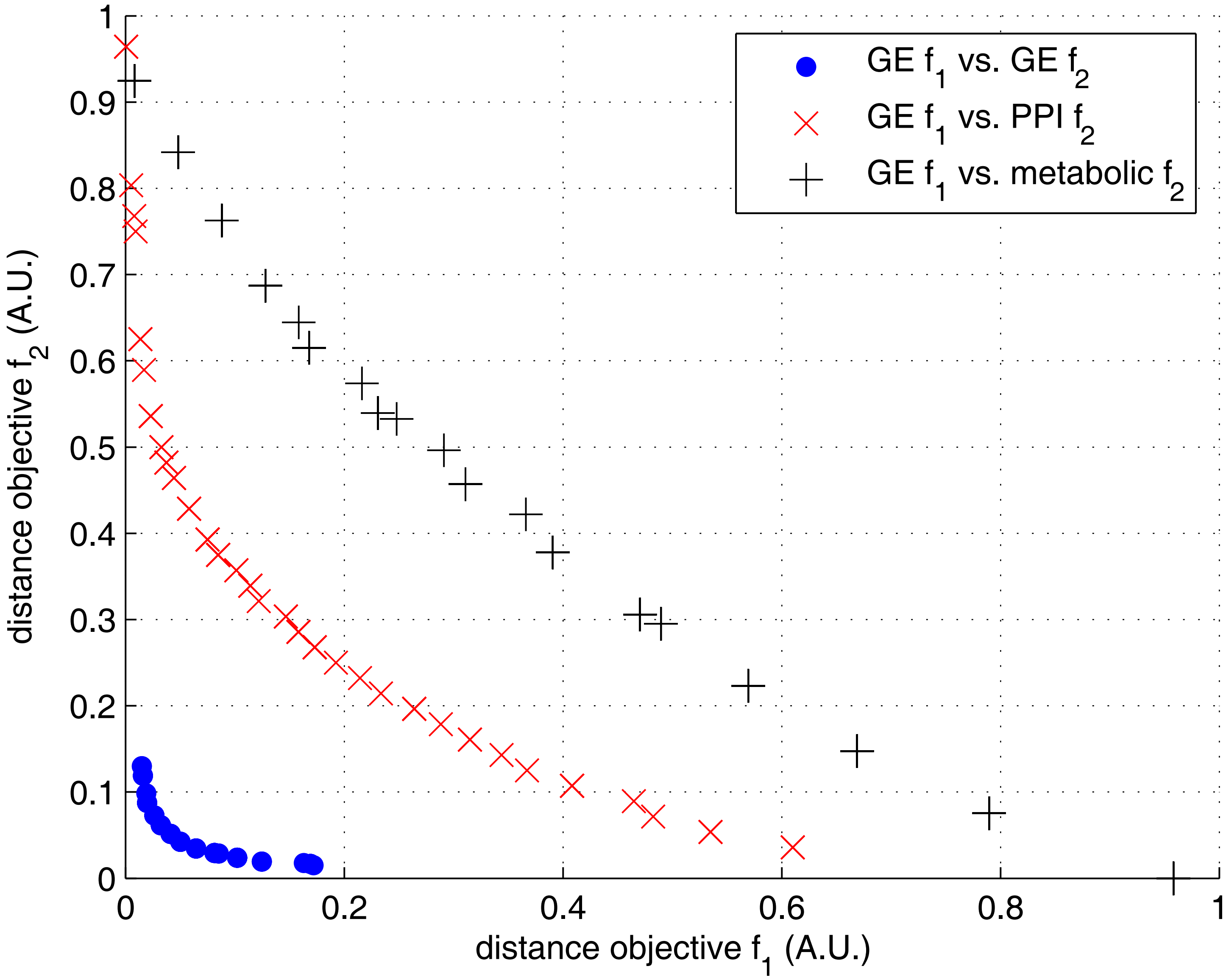


EC for Data Integration - Bleuler et al. (work in progress)



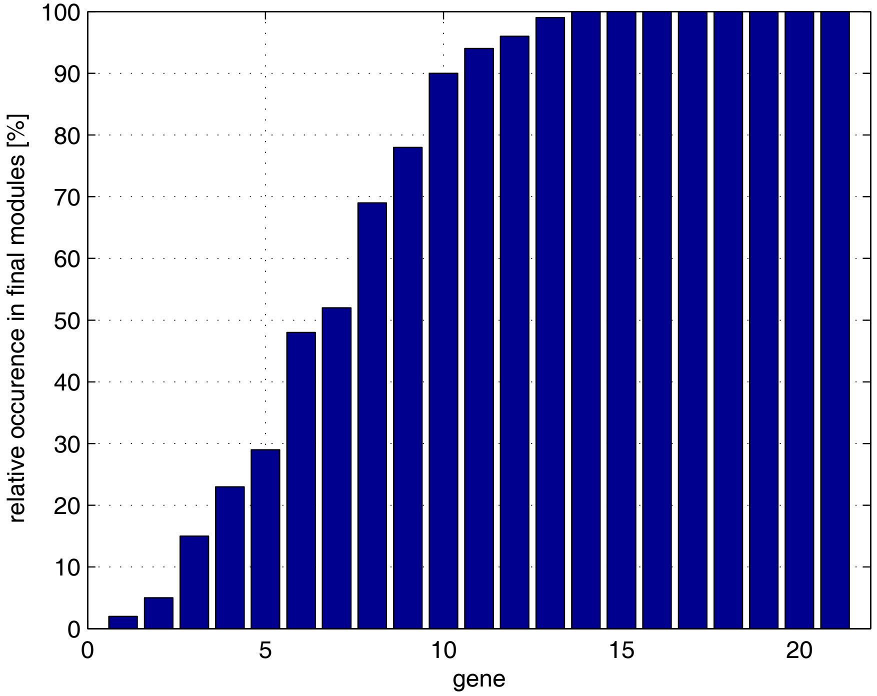
multiobjective evolutionary algorithm

EC for Data Integration - Bleuler et al. (work in progress)

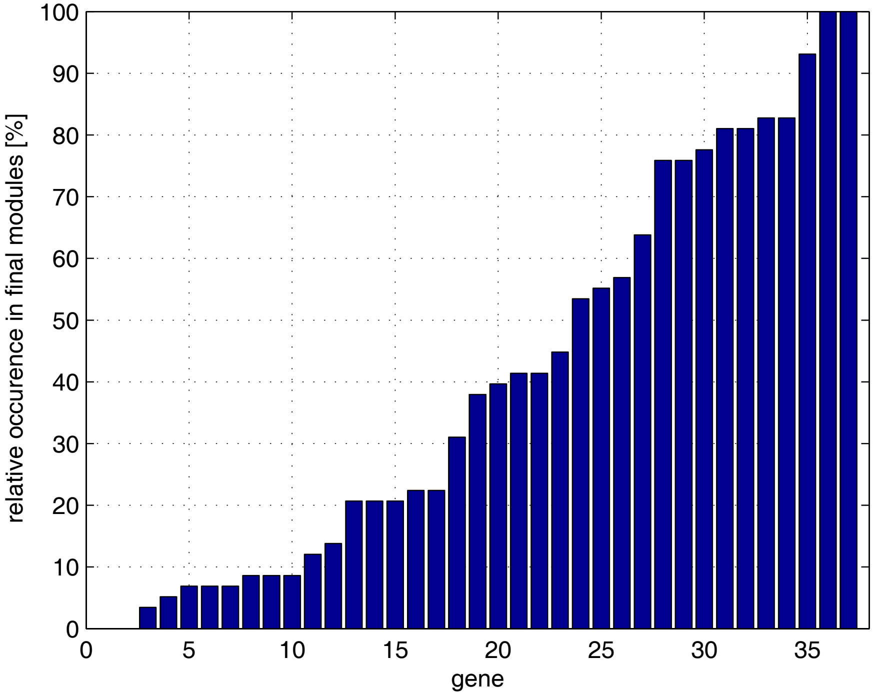


EC for Data Integration - Bleuler et al. (work in progress)

Similarity of the Clusters on the Front



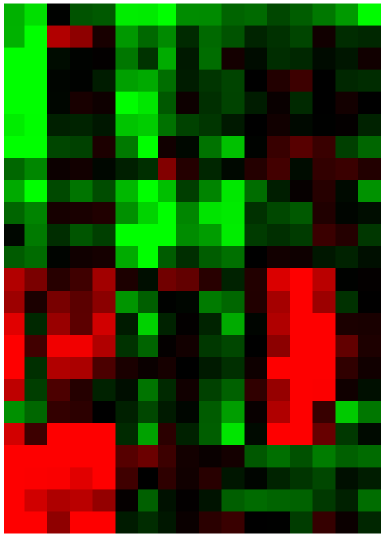
gene expression – gene expression



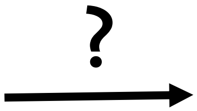
gene expression - PPI

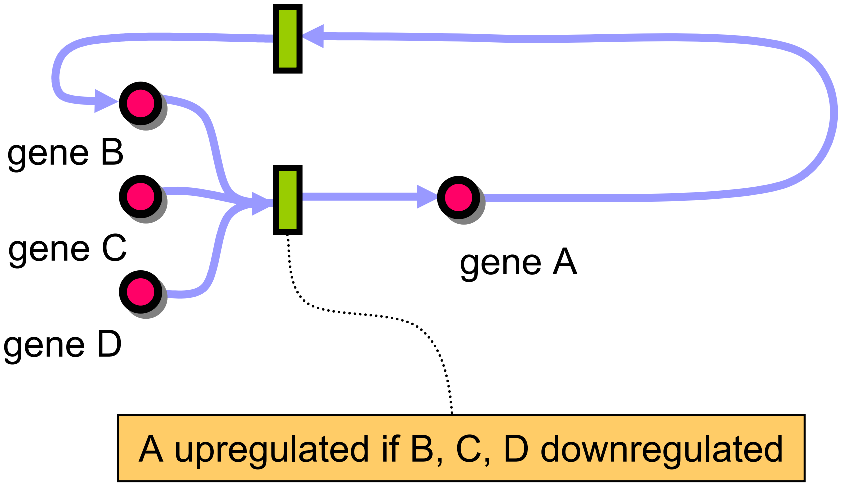
Network Inference

Goal



high throughput data





A upregulated if B, C, D downregulated

network model

Approaches

- network analysis (structure, robustness, etc.)
- inference of network topology (Bayesian networks, Gaussian Graphical Models, etc.)
- inference of network function (Boolean networks, differential equations, etc.)

Challenges

- underdetermined problem
- noisy data
- experiment design

EC for Network Inference

Network Models

- S-systems [3, 6, 7]
- Petri nets [4]
- electronic circuit [1]
- differential equations [3]
- real valued matrix [5]

[13] J. Koza et al., **Reverse Engineering of Metabolic Pathways from Observed Data Using Genetic Programming**, PSB, 2001

[14] S. Ando et al., **Modeling Genetic Network by Hybrid GP**, CEC 2002

[15] S Kikuchi et al., **Dynamic Modeling of Genetic Networks Using Genetic Algorithm and S-System**, Bioinformatics, 2003

[16] J. Kitagawa and H. Iba., **Identifying Metabolic Pathways and Gene Regulation Networks with Evolutionary Algorithms**, chapter in "Evolutionary Computation in Bioinformatics", Morgan Kaufmann, 2003

[17] D. Corne and C. Pridgeon, **Investigating Issues in Reconstructability of Genetic Regulatory Networks**, CEC 2004

[18] S. Kimura et al., **Inference of S-system models of genetic networks using a cooperative coevolutionary algorithm**, Bioinformatics, 2005

[19] D.-Y. Cho. et al., **Identification of Biochemical Networks by S-Tree Based Genetic Programming**, Bioinformatics, 2006

EC for Network Inference – Koza et al. [13]

Individual

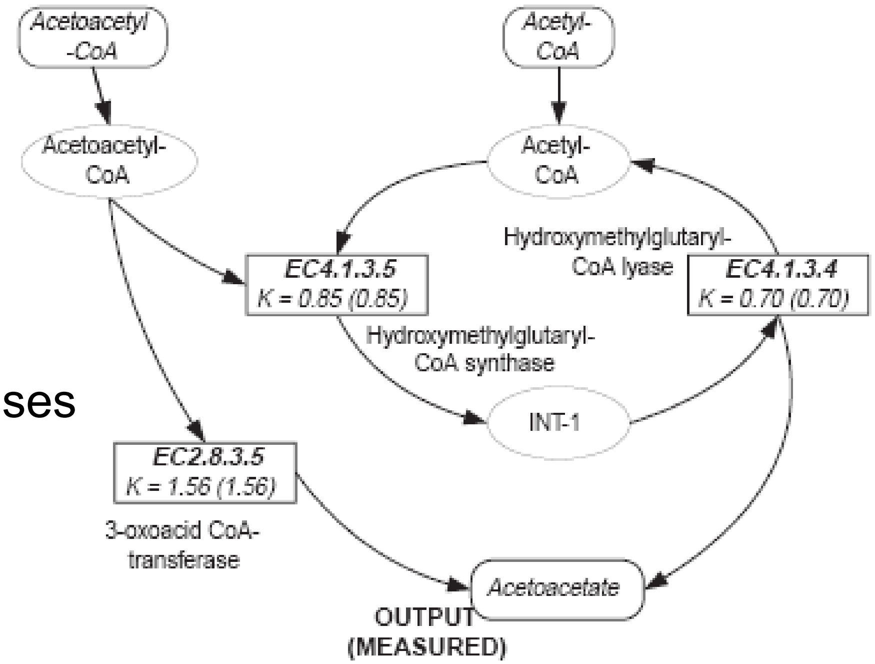
- chemical reaction network
- modeled as electronic circuit
- represented as GP tree

Objective Function

- comparing predicted and measured concentration of end product
- sum of absolute differences for test cases
- evaluated using SPICE

Optimizer

- GP
- popsize 100’000



Results

- input: E-cell simulation of phospholipid cycle (4 reactions) and synthesis of ketone bodies (3 reactions)
- good recovery of network topology and reaction rates

EC for Network Inference – Cho et al. [19]

Individual

- biochemical reaction network or gene regulatory network
- modeled as S-tree
- represented as GP tree

Objective Function

- comparing prediction to measurement on all time points and all substances
- sum of relative squared errors

Optimizer

- GP
- local hill climbing

Results

- 1. input: simulation of artificial networks modeled as S-systems
- 1. results: good recovery of network topology and parameters
- 2. input: gene expression from SOS DNA repair in *E. coli* (6 genes)
- 2. results: all but one known interaction recovered (in 35 h).

3. Status Quo and Future Trends

Status Quo

Advantages of EC Approach

- flexible
- global search method
- multiobjective

Open Problems

- benchmark problems missing
- little comparison with non-EA methods
- no common methodology

Future Trends

Biology and Measurements

- more data (more genomes, transcriptomes and proteomes)
- more data types (tiling arrays, synthetic lethal, etc.)
- more specific measurements (towards single cell analytics)
- more formalized information about experiments

Computational

Data Integration of …

- different qualities (accuracy)
- different data types (proteomics, metabolomics, etc.)
- different scales
- different precision (qualitative vs. quantitative)