STATS M254 / BIOINFO M271 / BIOMATH M271

Statistical Methods in Computational Biology

Spring 2014

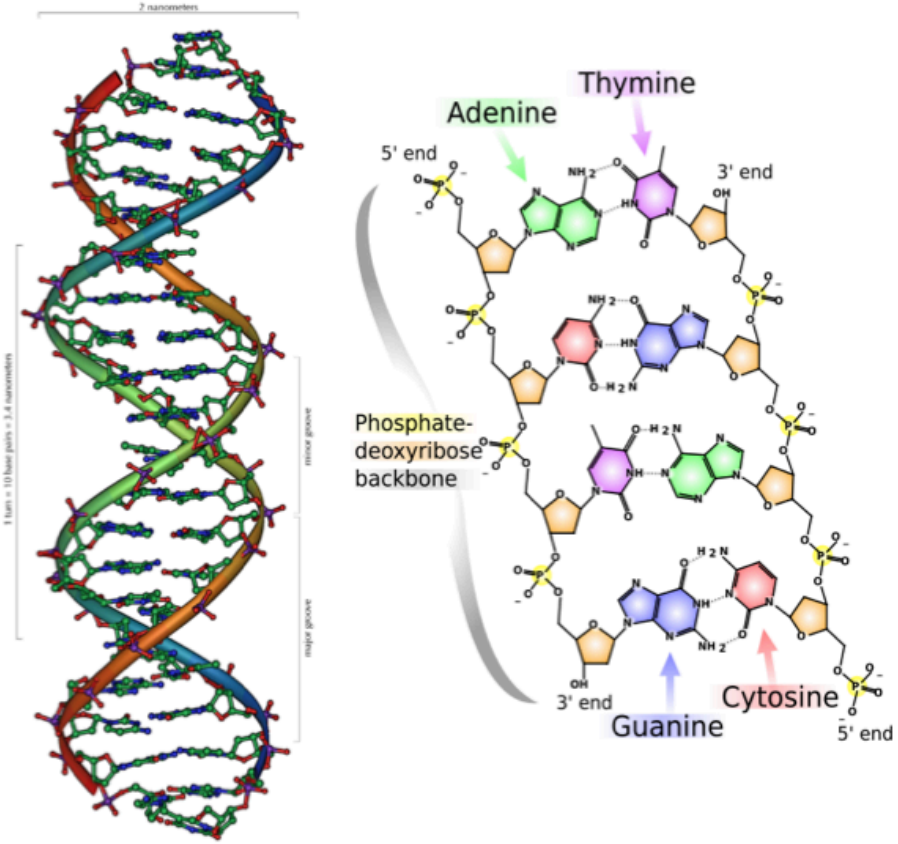
Lecture 1 Introduction and Data

Instructor: Jingyi Jessica Li

Outline

- Introduction to molecular biology
  - DNA, gene, RNA, protein, central dogma
- Typical data
  - Gene expression
  - RNA-seq
  - Regulatory sequences
  - ChIP-chip/seq

DNA



- DNA (Deoxyribonucleic acid) is a molecule to store genetic information of a living organism.
- DNA consists of two polymers made from four types of nucleotides: adenine (A), guanine (G), cytosine (C) and thymine (T).
- Purines: A, G; Pyrimidines: C, T
- Two polymers are complementary to each other and from a double-helix structure

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5′-ACCGTTCGACGGTAA-3′
   ||||||||||||||||
3′-TGGCAAGCTGCCATT-5′
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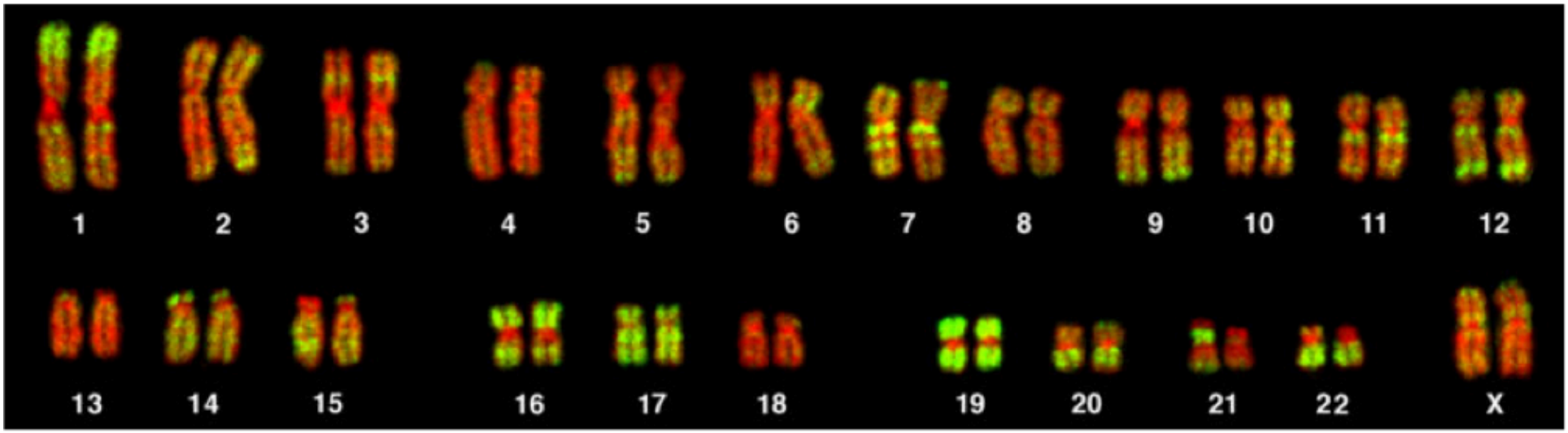
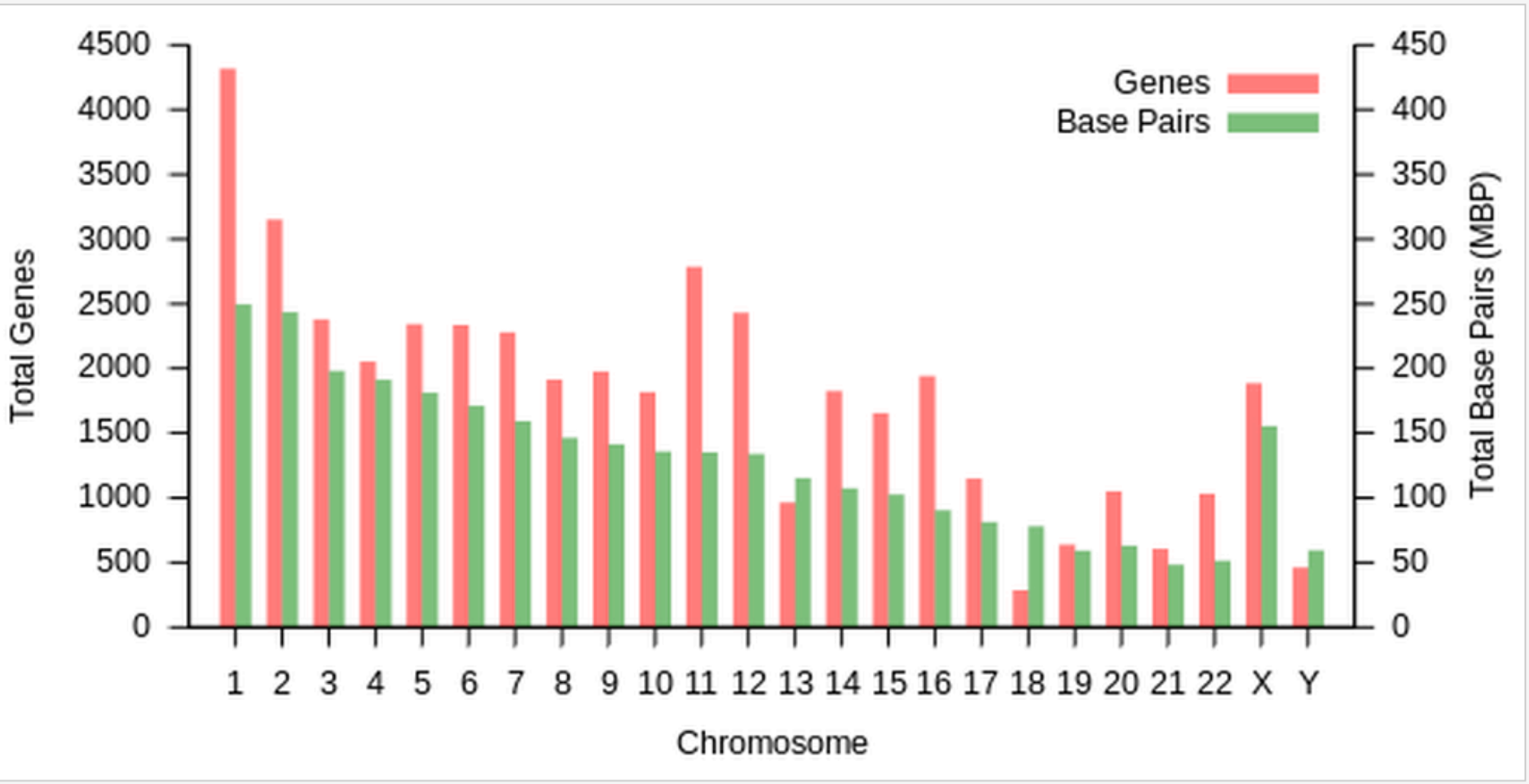
Chromosome

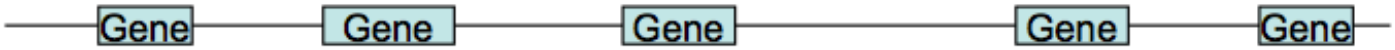


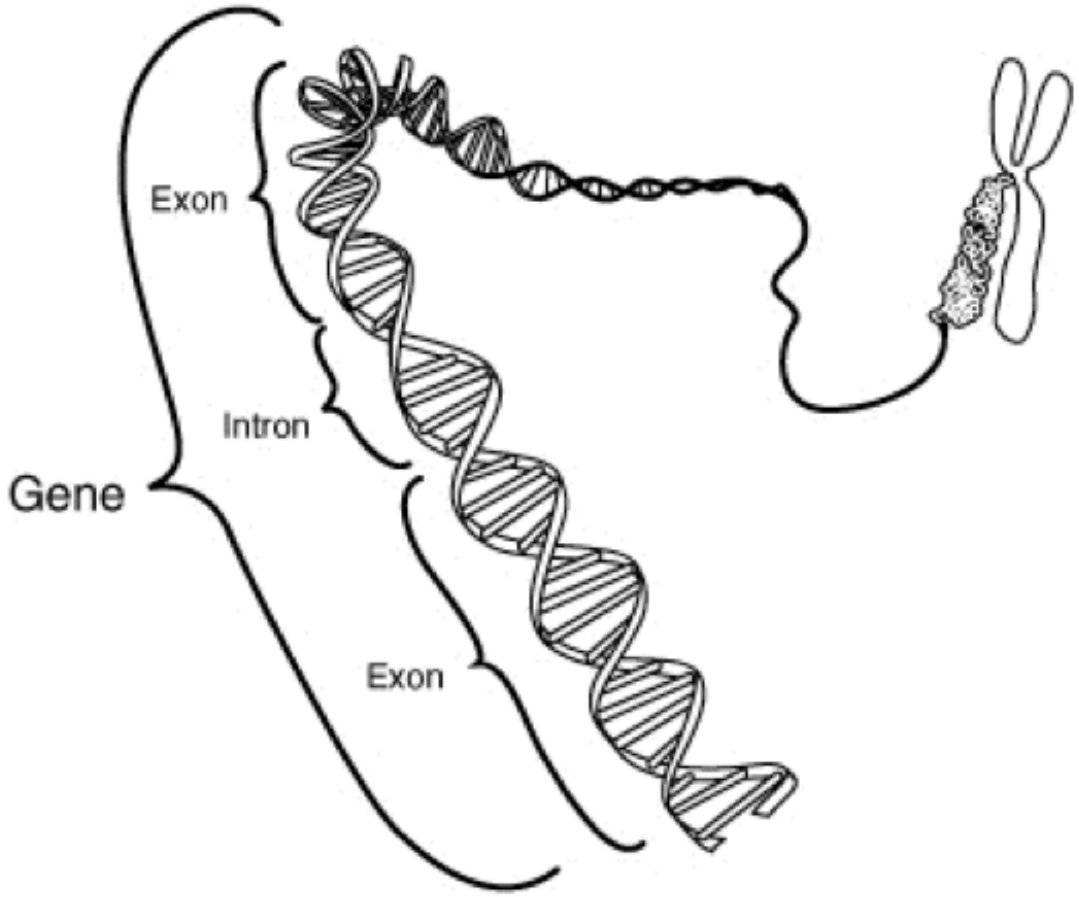
Chromosome



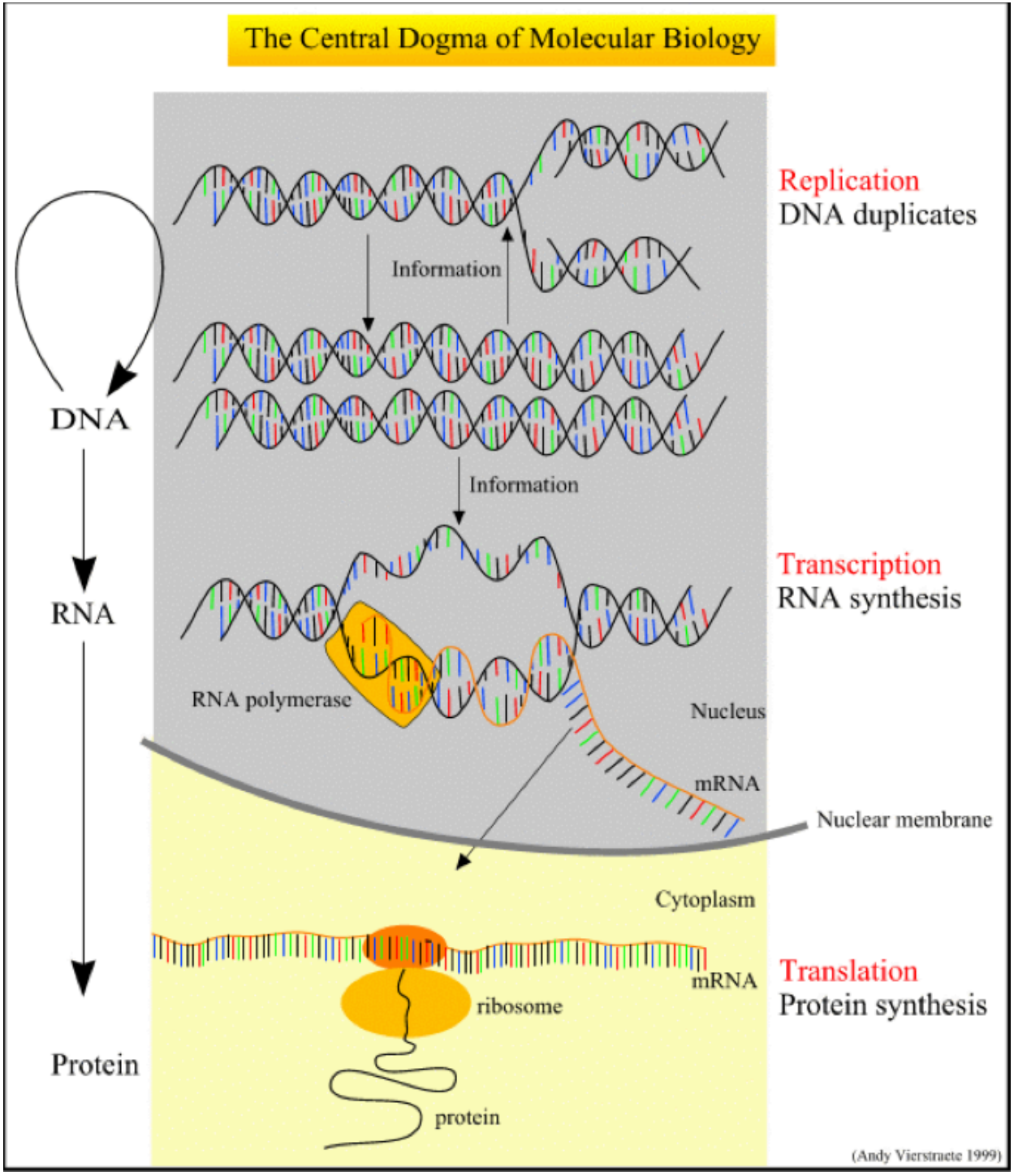
Estimated number of genes and base pairs (in mega base pairs) on each human chromosome

Gene

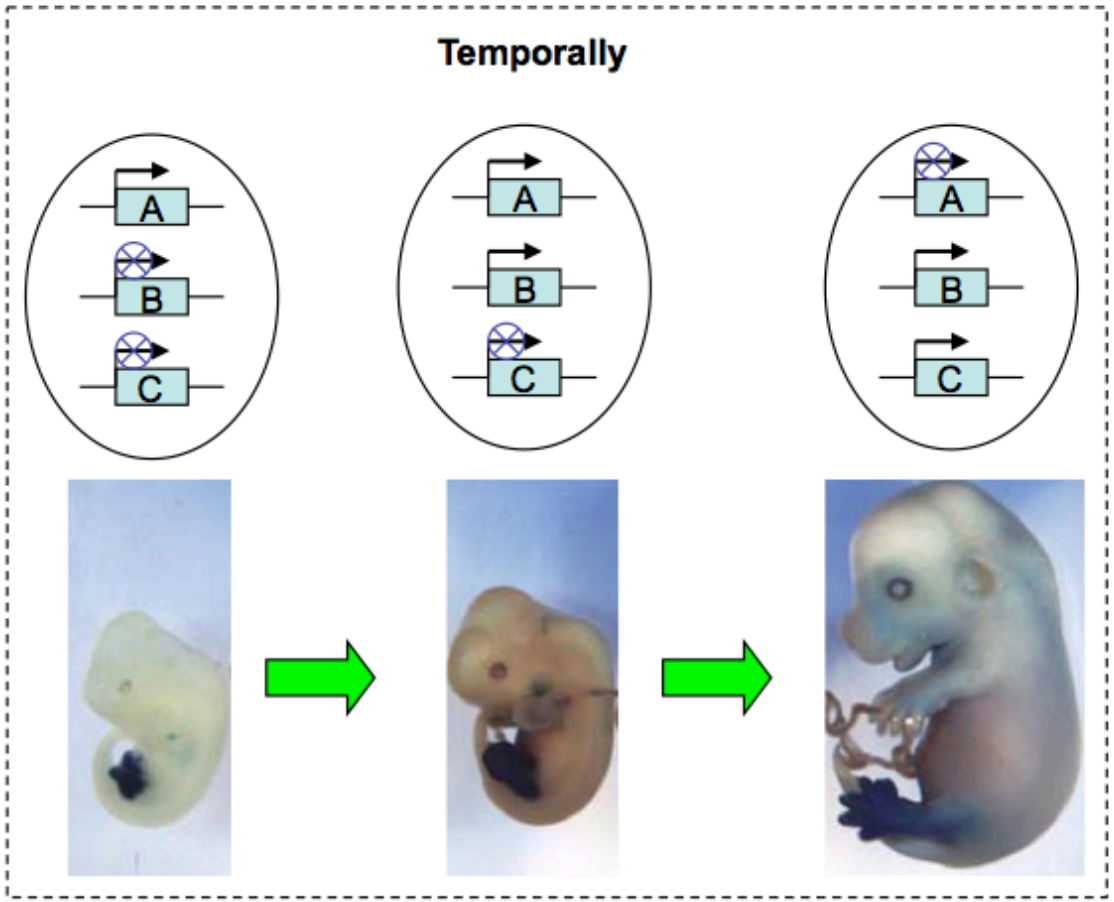


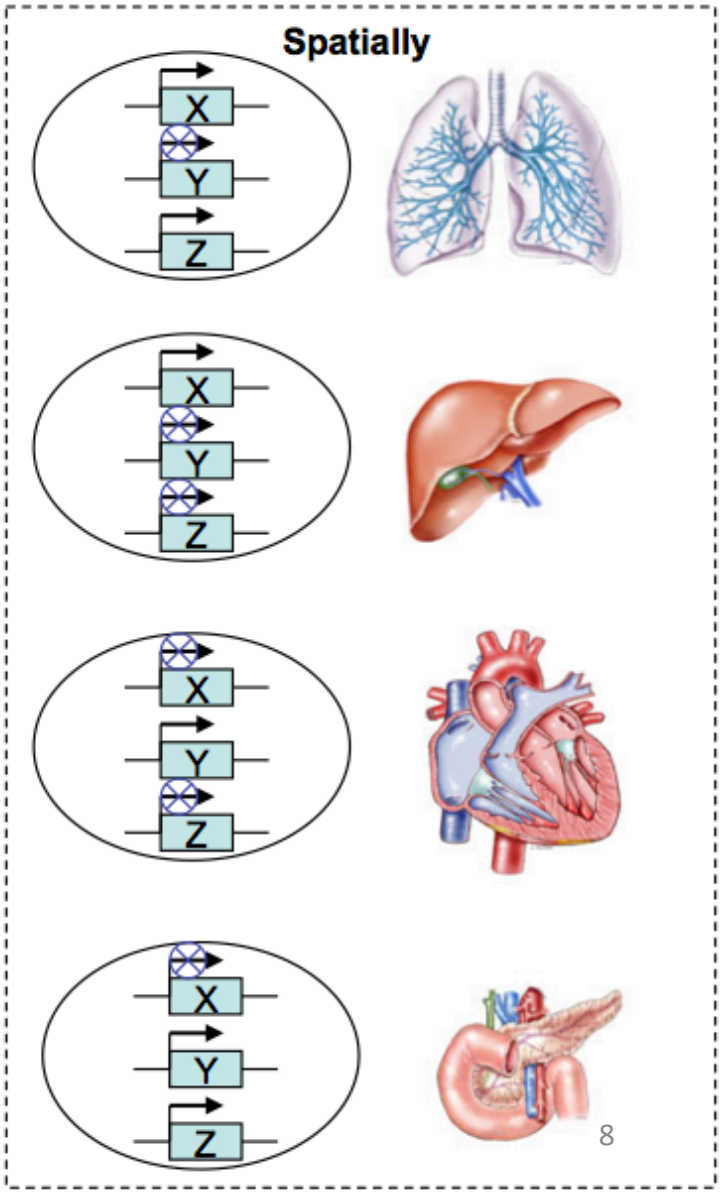


Central Dogma

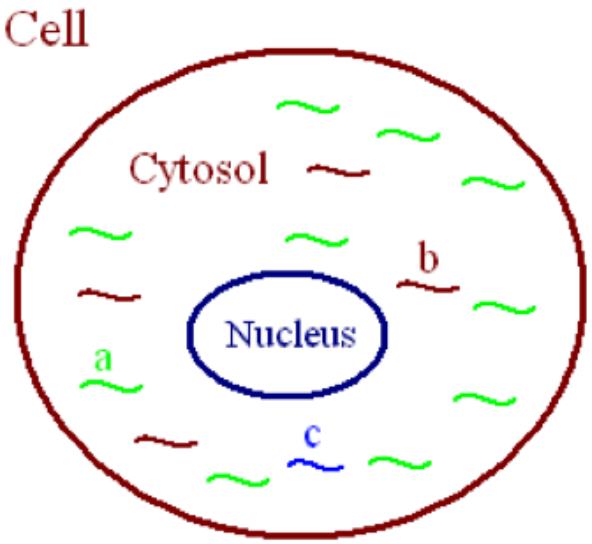


Data type 1: Gene expression data



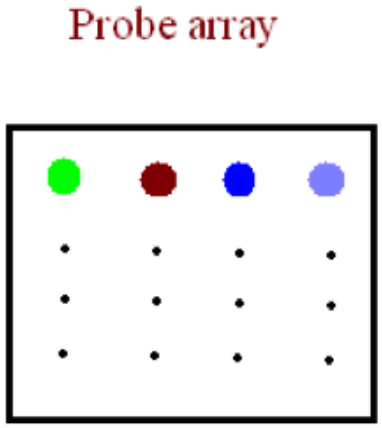


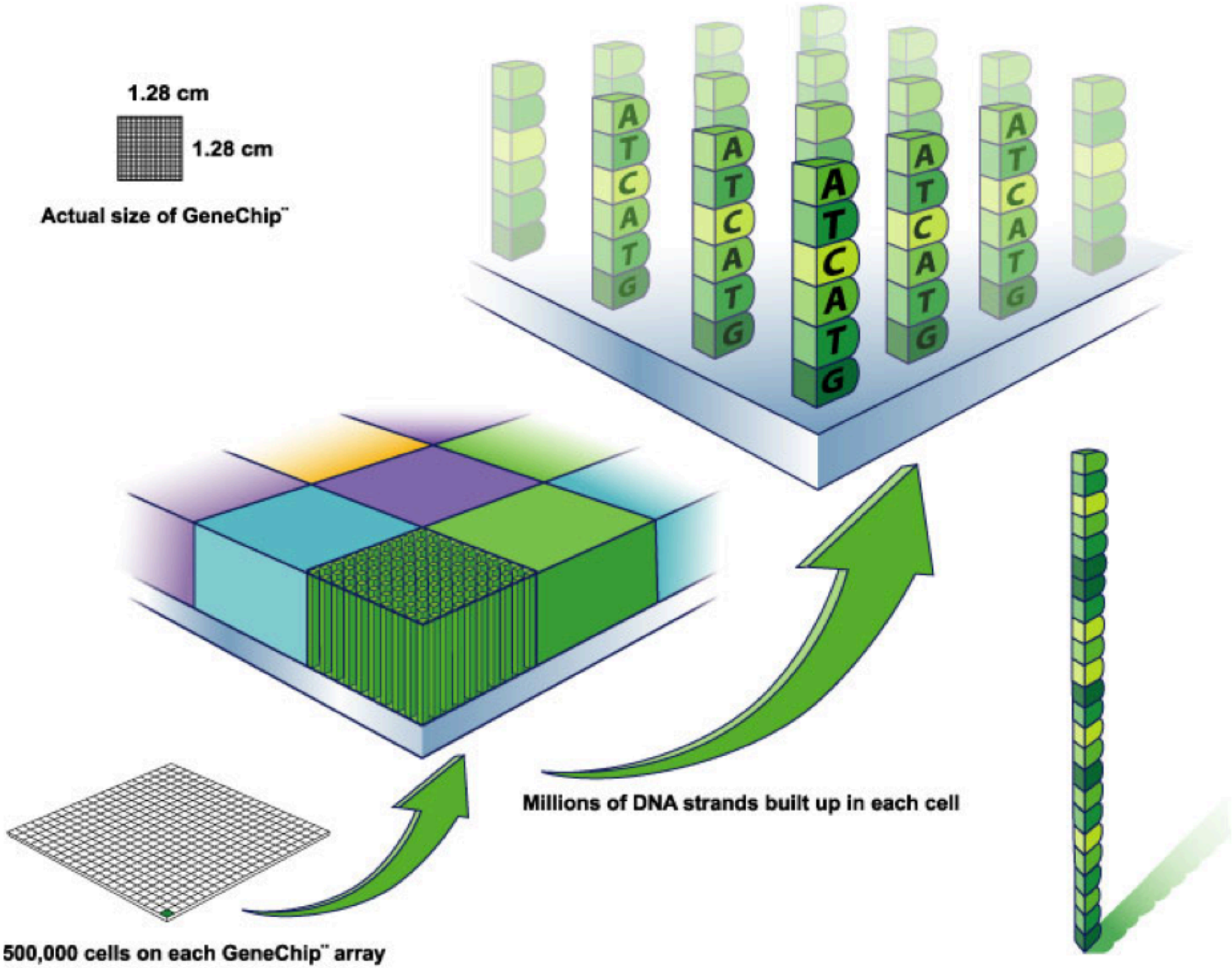
Principle of gene expression microarray



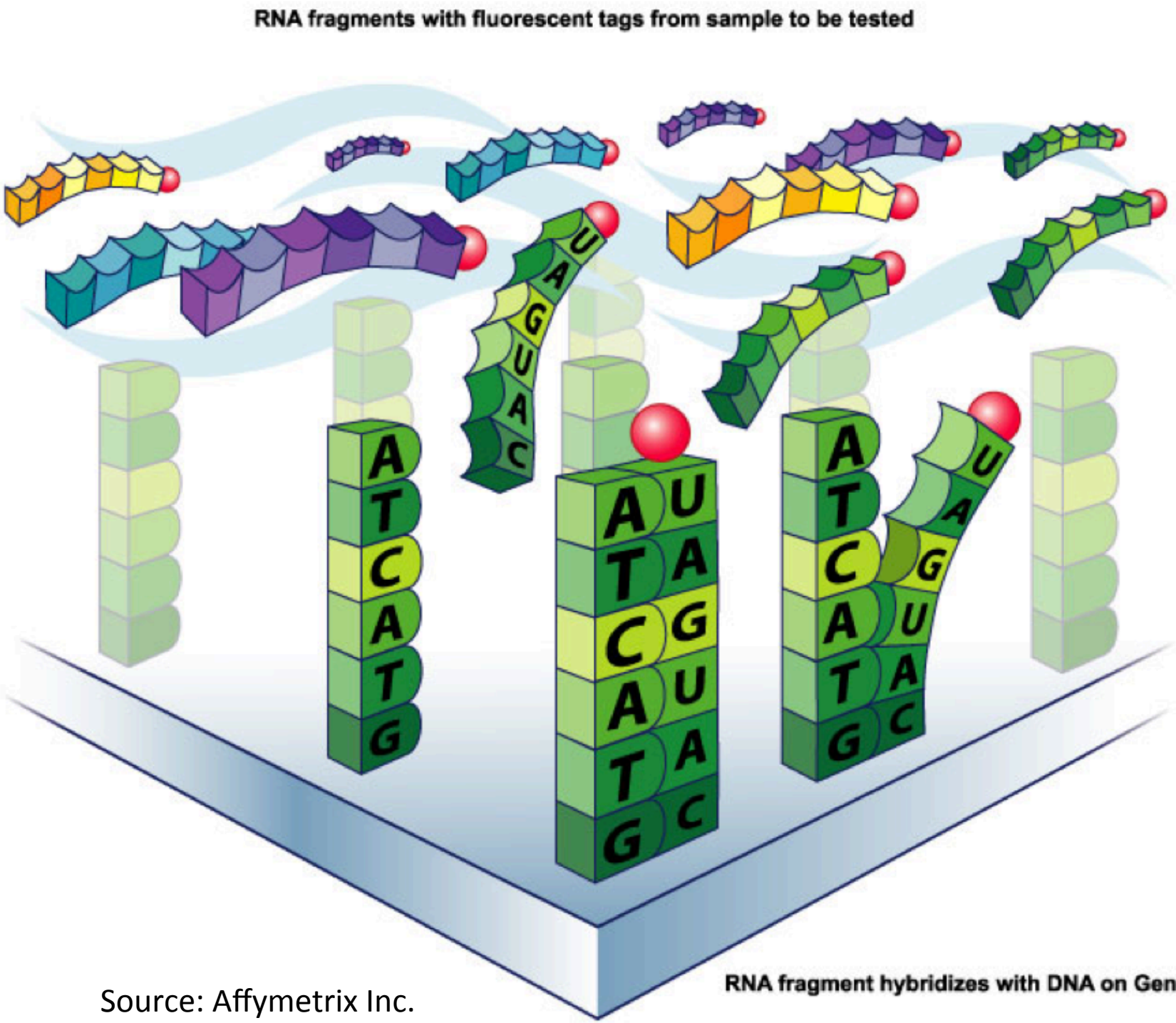
Expressoin pattern

Gene	Level
a	high
b	Medium
c	low
⋮	⋮



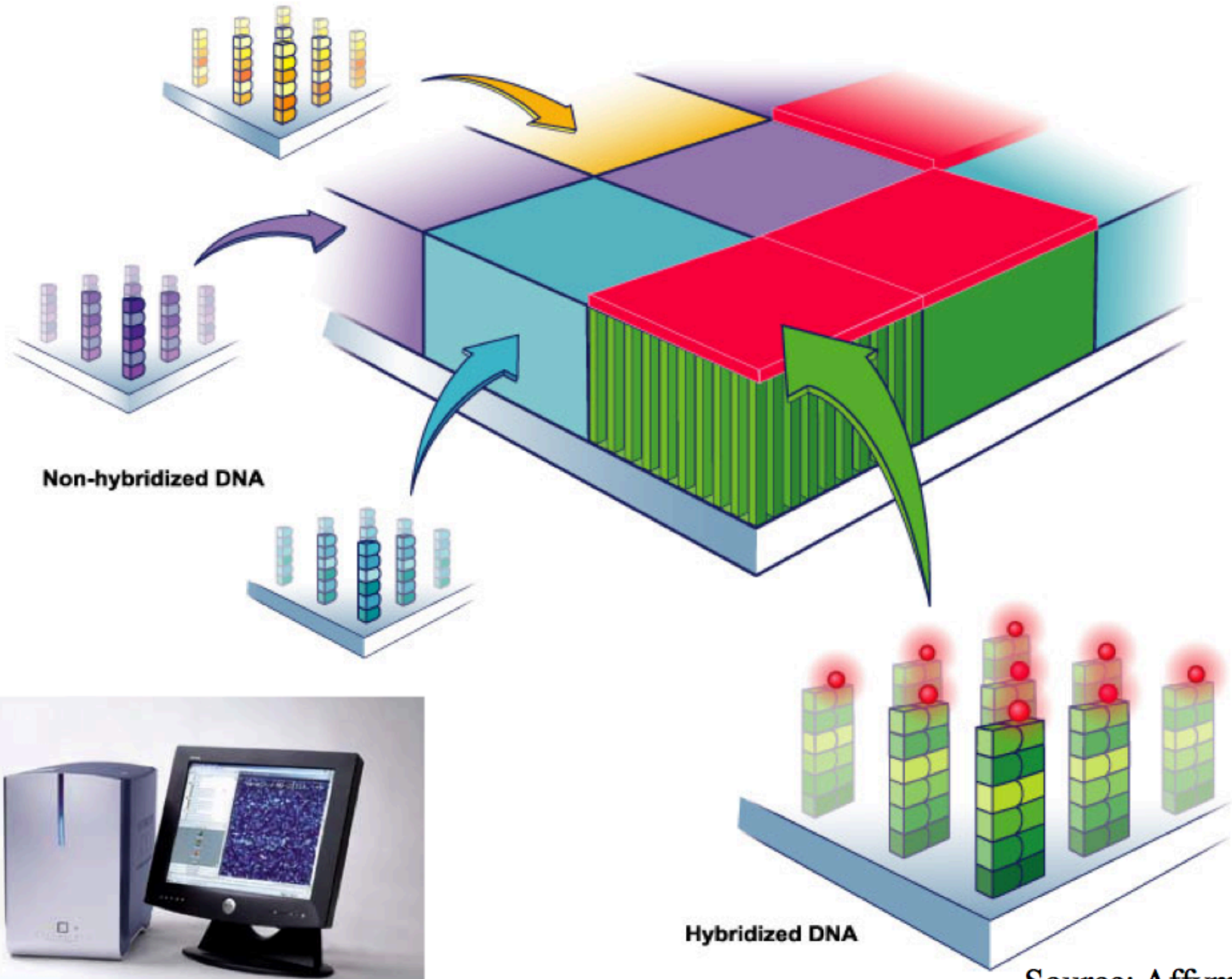


Source: Affymetrix Inc.



Source: Affymetrix Inc.

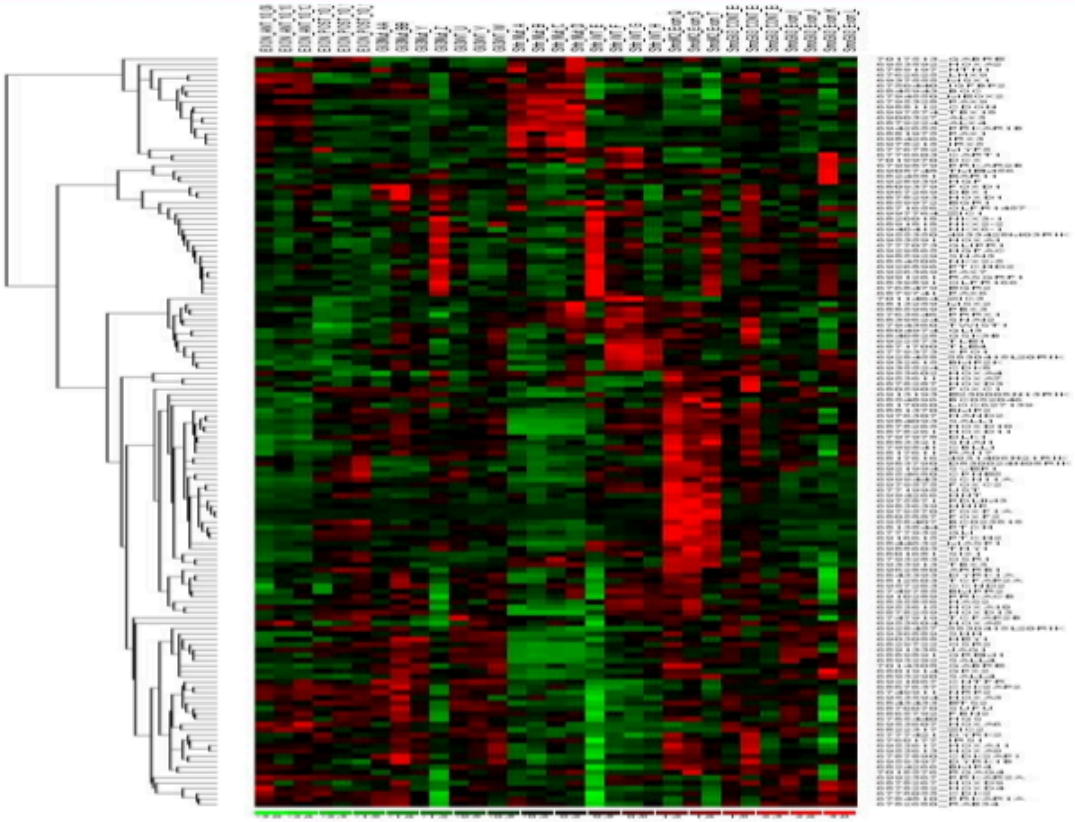
Shining a laser light at GeneChip causes tagged DNA fragments that hybridized to glow



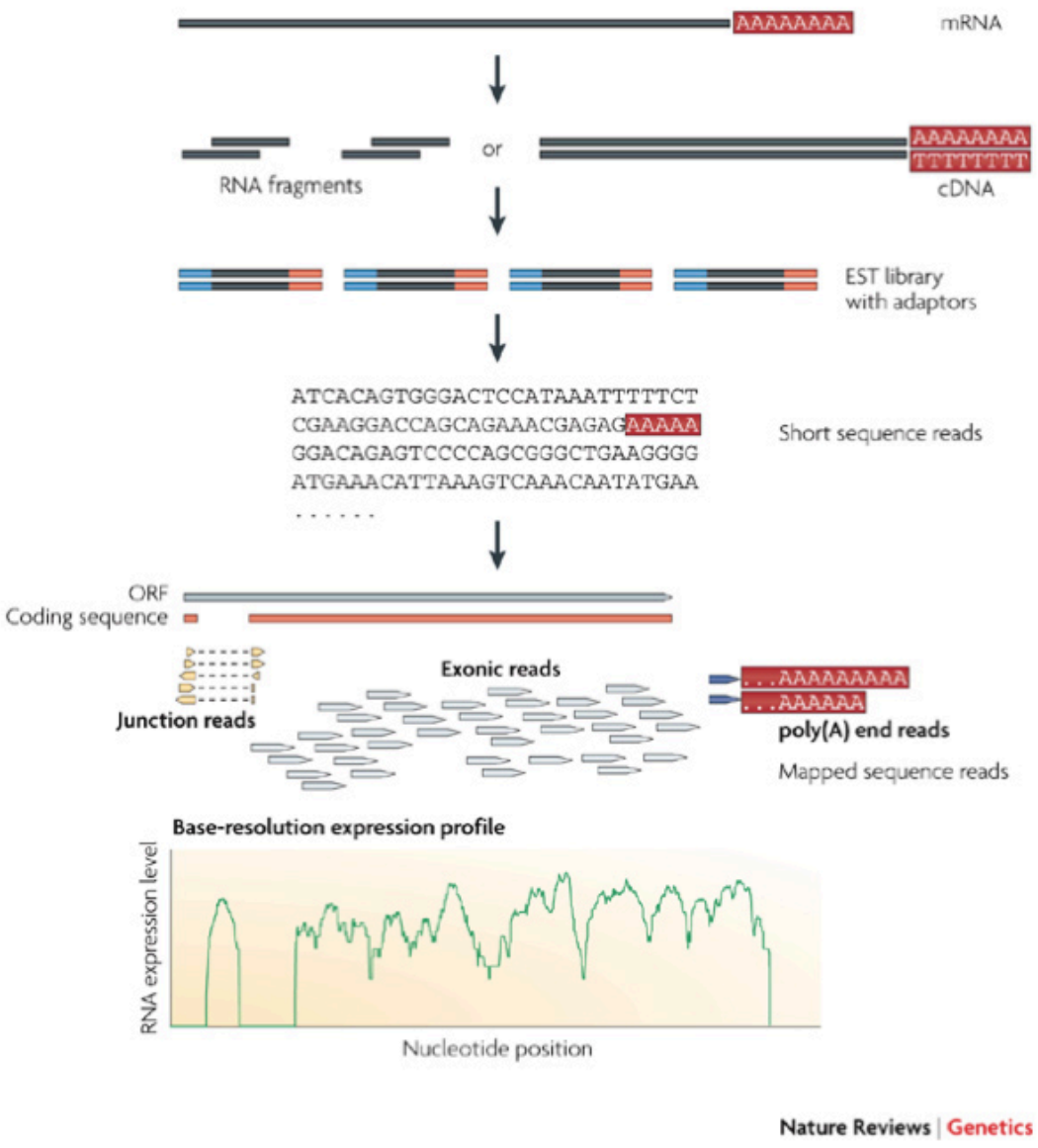
Source: Affymetrix Inc.

Gene expression data matrix

Condition	Mutant			Wild Type		
Replicate	1	2	3	1	2	3
Gene 1	132.724	112.445	128.478	154.888	122.215	138.303
Gene 2	161.825	163.304	210.121	159.003	172.366	163.199
…						
Gene I	1988.66	2063.48	1899.91	1997.77	2156.19	1977.75



RNA-Seq data

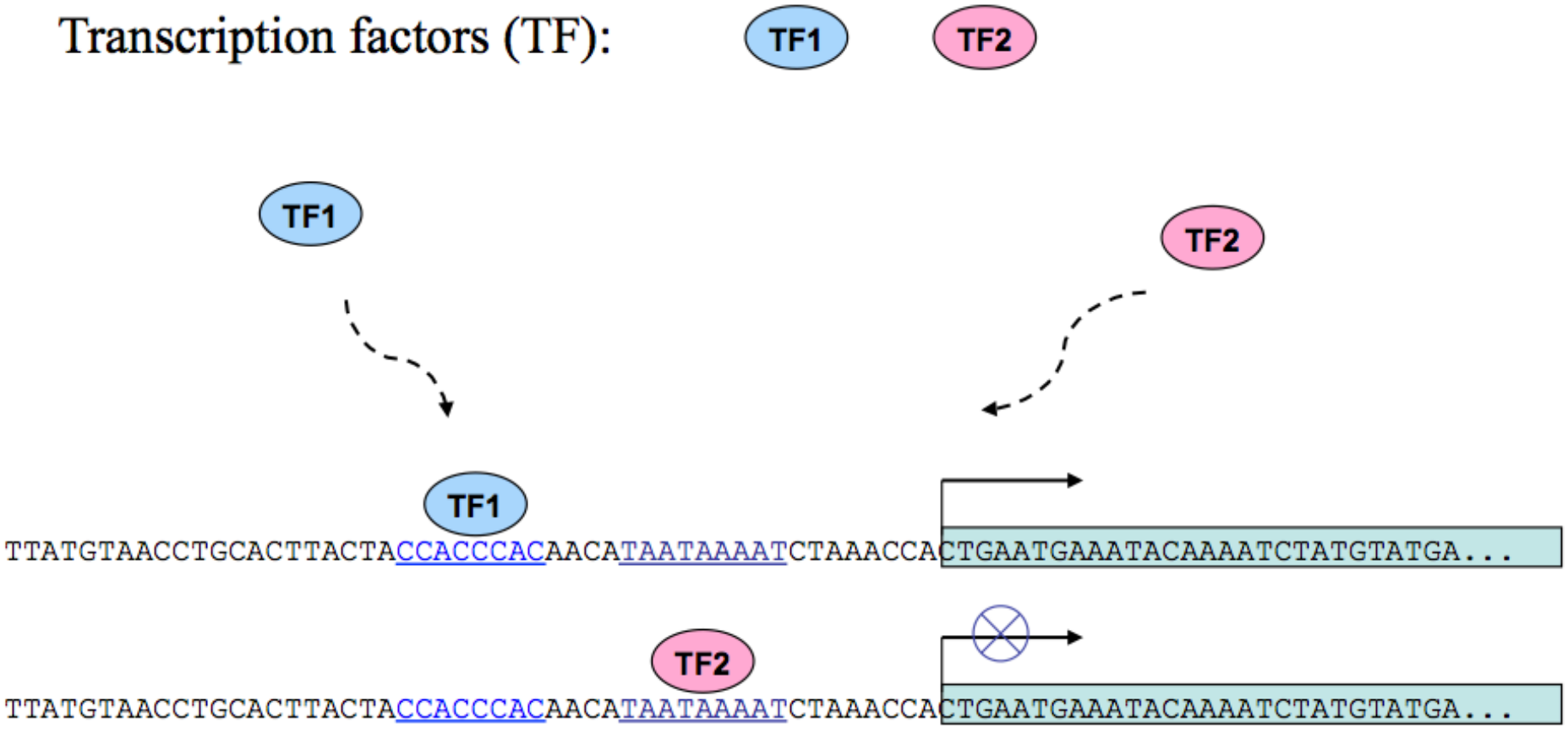


Wang, Gerstein, & Snyder (2009) *Nature Reviews Genetics* 10, 57-63.

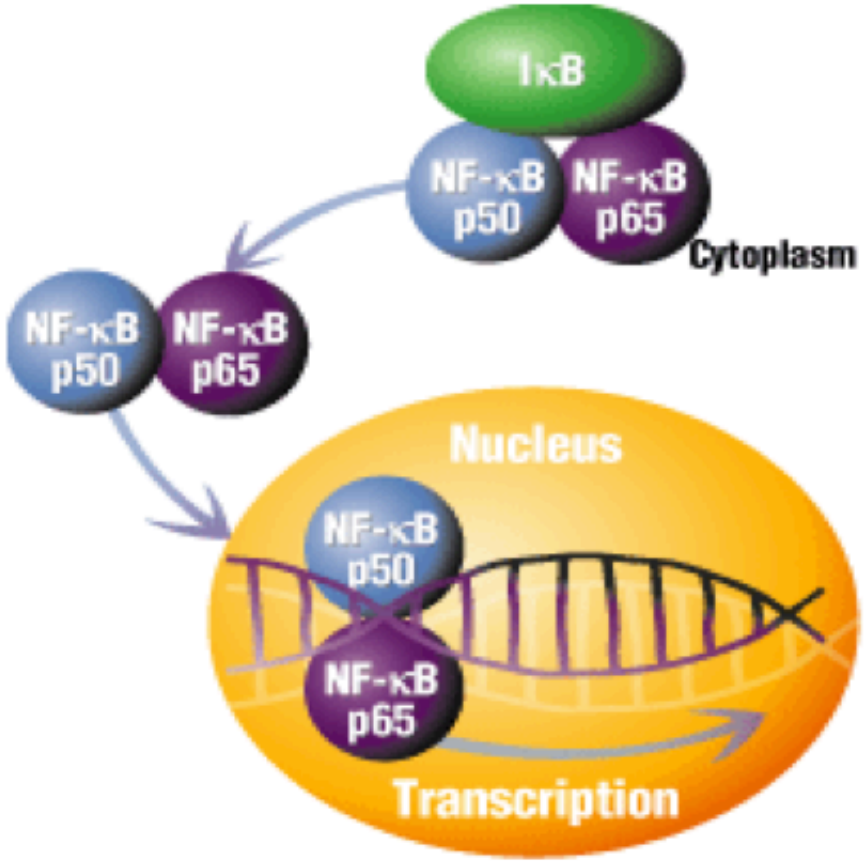
RNA-Seq data

- 1) Long RNAs are first converted into a library of cDNA fragments through either RNA fragmentation or DNA fragmentation.
- 2) Sequencing adaptors (blue) are subsequently added to each cDNA fragment and a short sequence is obtained from each cDNA using high-throughput sequencing technology.
- 3) The resulting sequence reads are aligned with the reference genome or transcriptome, and classified as three types: exonic reads, junction reads and poly(A) end-reads.
- 4) These three types are used to generate a base-resolution expression profile for each gene, as illustrated at the bottom; a yeast ORF with one intron is shown.

Data type 2: Regulatory sequences



Transcription factor binding sites & motifs

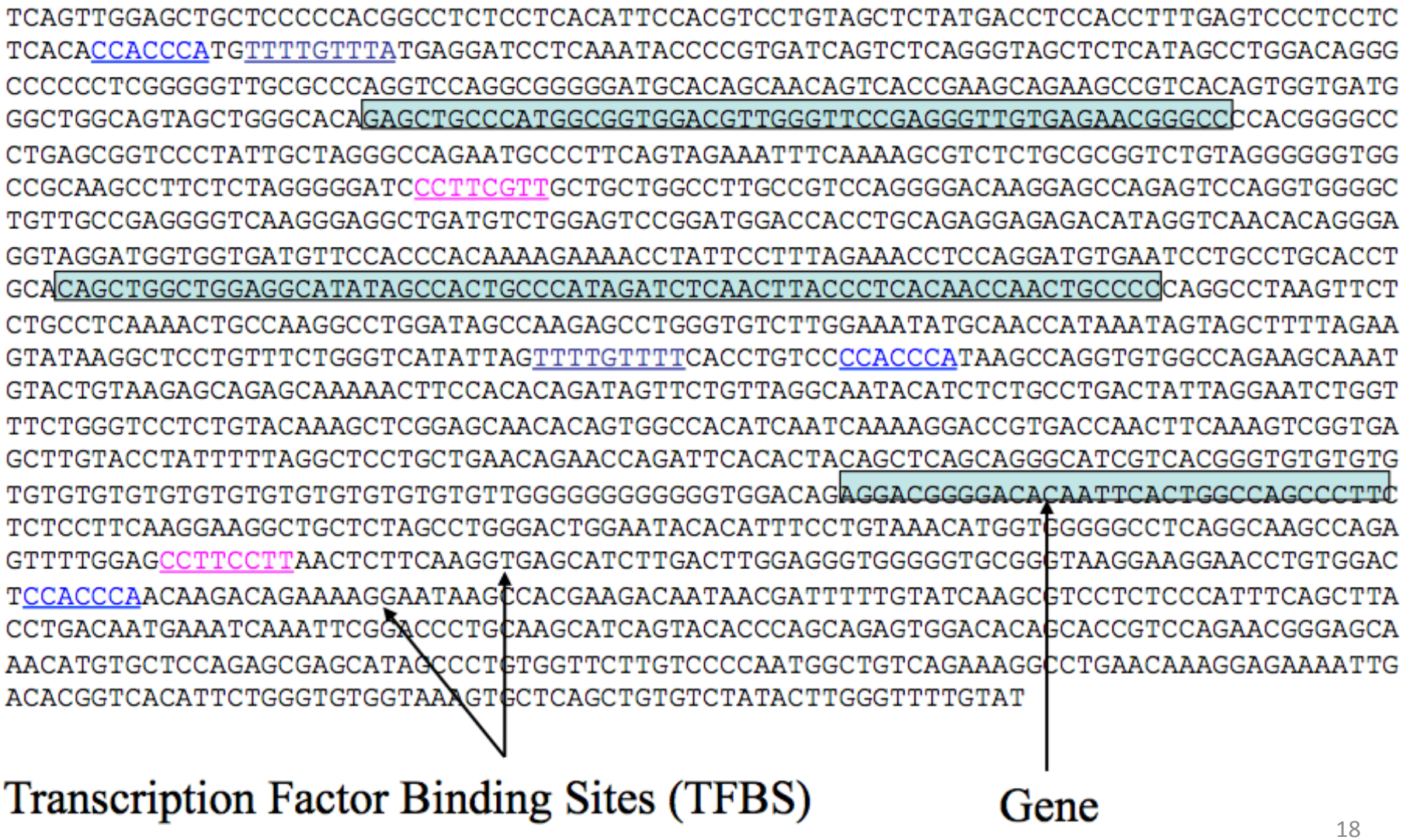


AATTTCC
CATTGCG
ATTTGCG
AATTGCA
AATTTCT

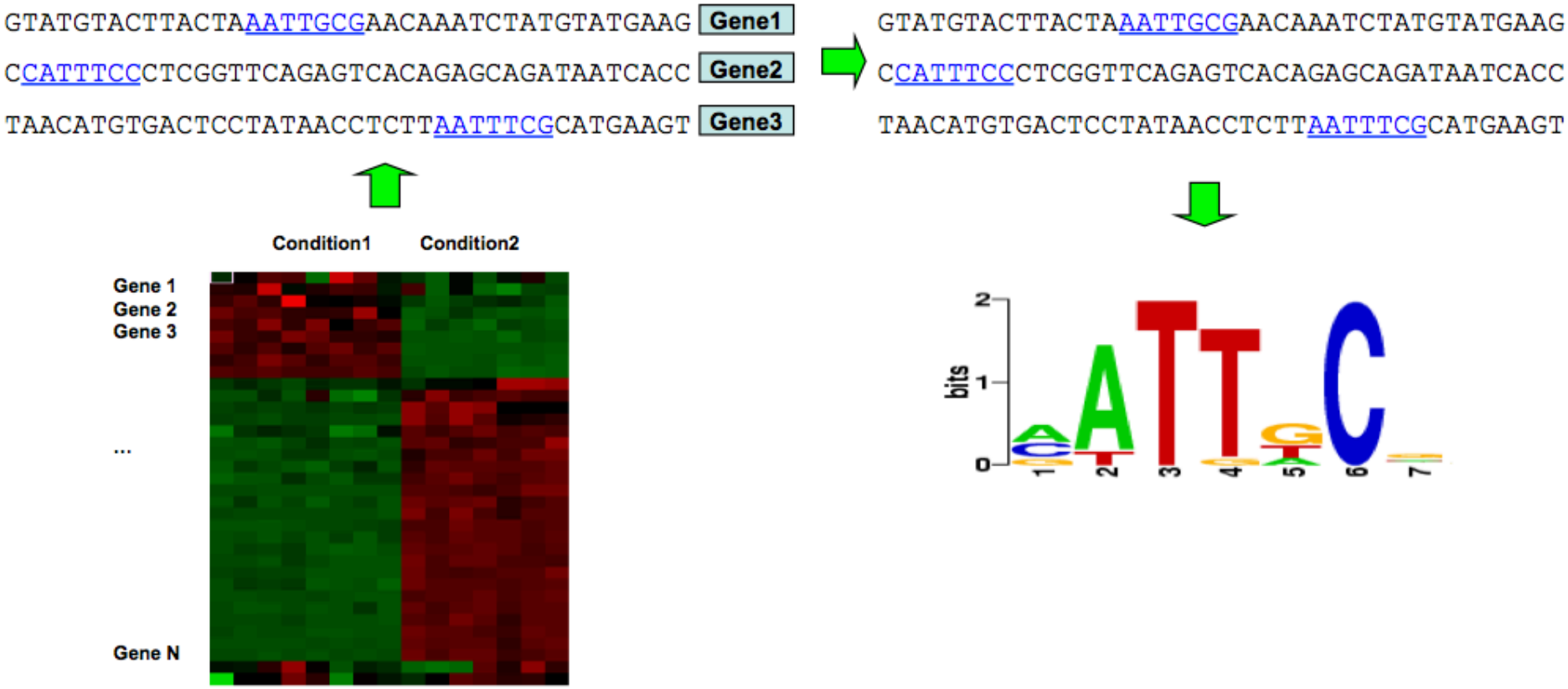
A	7	14	0	0	3	0	4
C	6	0	0	0	0	16	2
G	3	0	0	1	8	0	7
T	0	2	16	15	5	0	3

motif

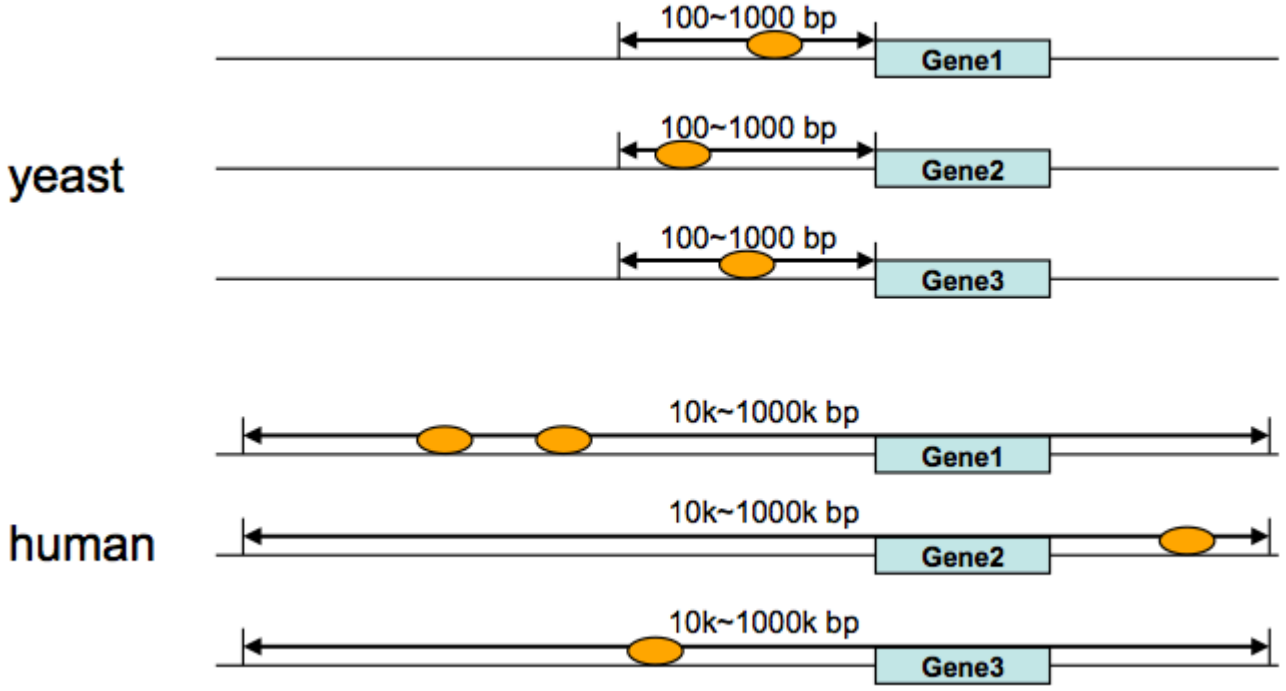
Motifs are regulatory codes



Finding motifs from co-regulated genes



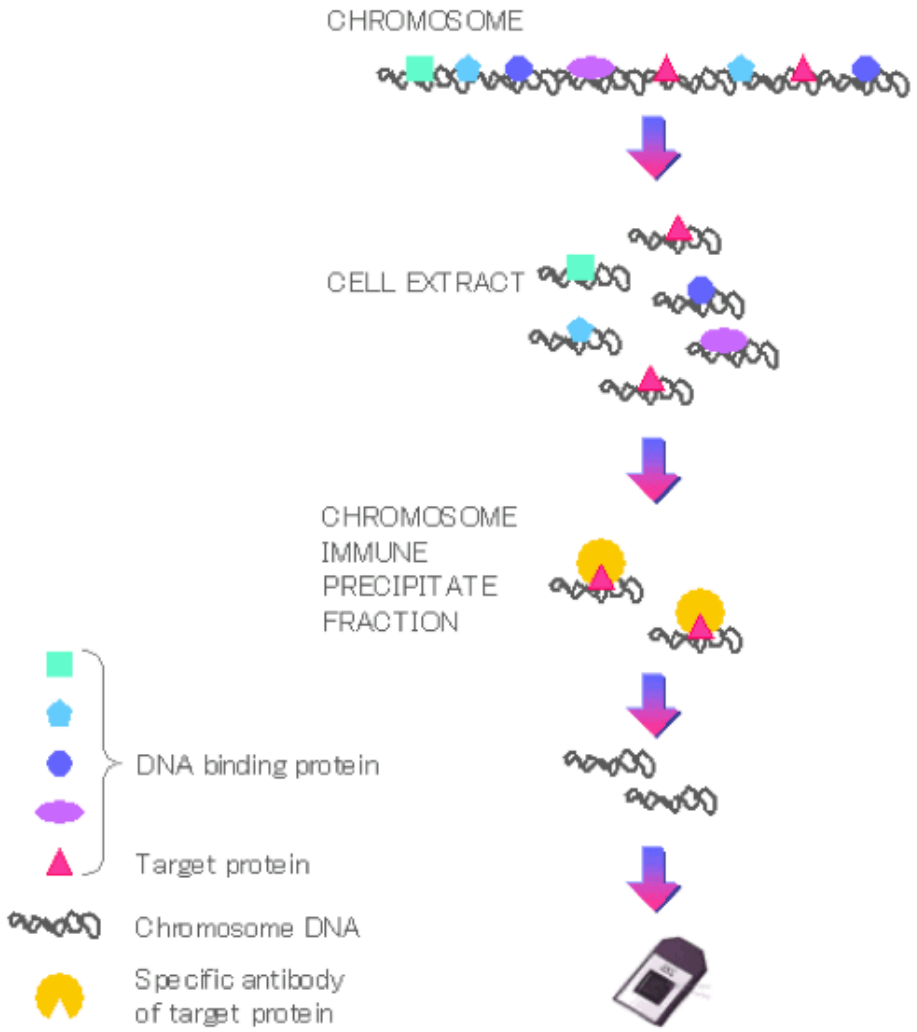
Motif discovery is difficult in mammalian genomes



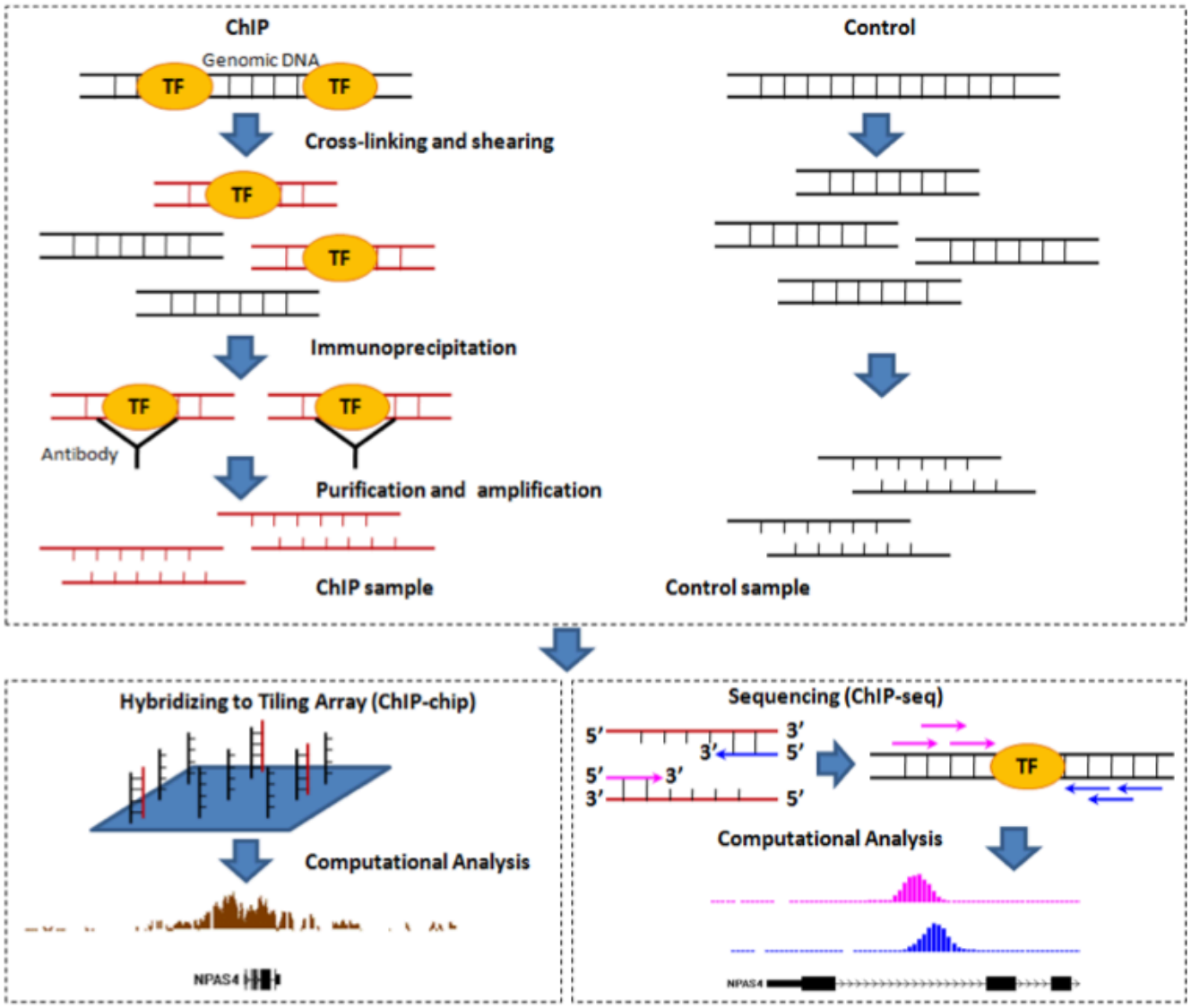
- Advanced methods in regulatory sequence analysis:
  - 1) combinatorial binding pattern
  - 2) multiple species conservation
  - 3) heterogeneity in background
  - 4) predictive modeling

Data type 3: ChIP-chip and ChIP-seq

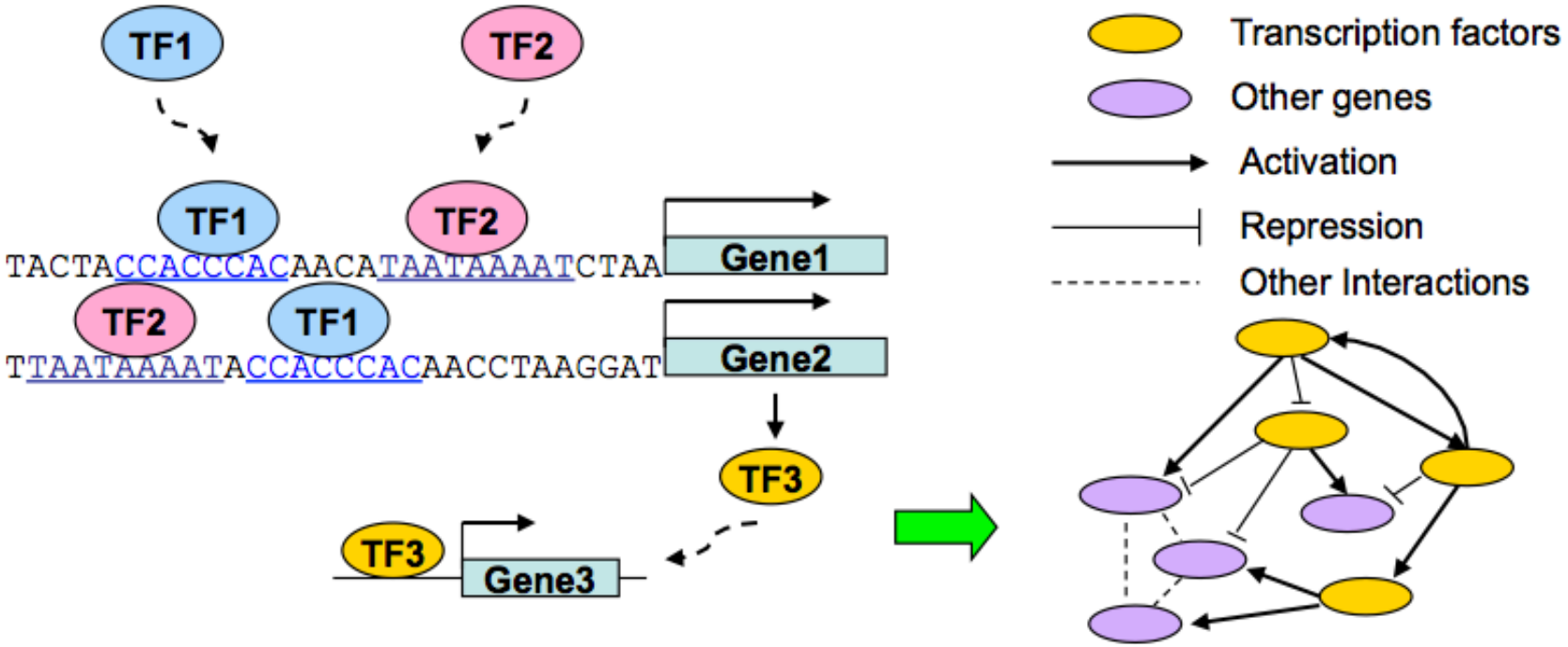
- ChIP: Chromatin ImmunoPrecipitation
- chip: DNA micorarray
- seq: massive sequencing



Array vs. Sequencing



Gene regulatory network



Combine all types of data:

Gene expression, ChIP-chip/seq, regulatory sequences.

Acknowledgments

- For sharing slides on the internet:
  - Dr. Qing Zhou, UCLA
  - Dr. Hongkai Ji, Johns Hopkins University
  - Dr. Cheng Li, Peking University