CENG 465
Introduction to Bioinformatics

Fall 2013-2014

Tolga Can (Office: B-109)
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Course web site:
http://www.ceng.metu.edu.tr/~tcan/ceng465_f1314

Goals of the course

- Working at the interface of computer science and biology
  - New motivation
  - New data and new demands
  - Real impact
- Introduction to main issues in computational biology
- Opportunity to interact with algorithms, tools, data in current practice

High level overview of the course

- A general introduction
  - what problems are people working on?
  - how people solve these problems?
  - what key computational techniques are needed?
  - how much help computing has provided to biological research?

- A way of thinking -- tackling “biological problems” computationally
  - how to look at a “biological problem” from a computational point of view?
  - how to formulate a computational problem to address a biological issue?
  - how to collect statistics from biological data?
  - how to build a “computational” model?
  - how to solve a computational modeling problem?
  - how to test and evaluate a computational algorithm?

Course outline

- Motivation and introduction to biology (1 week)
- Sequence analysis (4 weeks)
  - Sequence alignment by Dynamic Programming
  - Statistical significance of sequence alignments
  - Suffix trees
  - Profile hidden Markov models
  - Multiple sequence alignment
- Phylogenetic trees, hierarchicl clustering methods (1 week)

Course outline

- Protein structures (3 weeks)
  - Structure prediction (secondary, tertiary)
  - Structural alignment
- Microarray data analysis (2 weeks)
  - Correlations, clustering
- Gene/Protein networks, pathways (3 weeks)
  - Protein-protein, protein/DNA interactions
  - Construction and analysis of large scale networks
  - Computational systems biology

Teaching assistant

- Hilal Kilic Arslan
  - will be grading your homework assignments
- Contact info:
  - hkilic@ceng.metu.edu.tr
    Tel: +90(312)210-5522
    Office: B202

Grading

- Midterm exam - 40%
- Final exam - 40%
- Assignments - 20%

Online materials

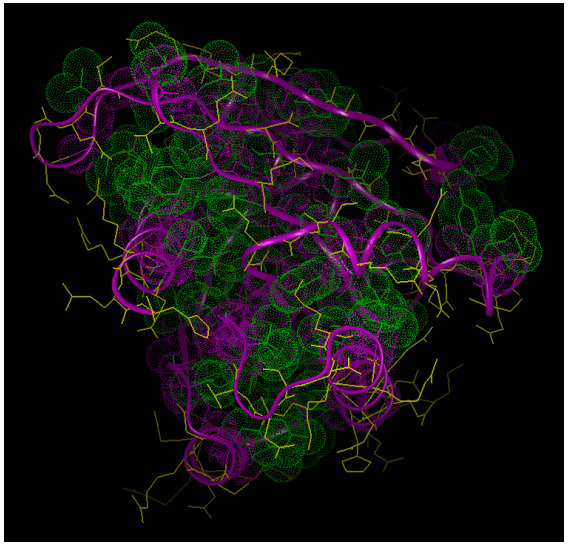
- Course web site
  - http://www.ceng.metu.edu.tr/~tcan/ceng465_f1314
  - Lecture slides and reading materials
  - Assignments
- Newsgroup
  - metu.ceng.course.465
  - Accesible via cow.ceng.metu.edu.tr/News
  - Students from other departments should get a temporary ceng account from A-210 (admins) to be able to post
- COW (Ceng On the Web)
  - Students from other departments should get a temporary ceng account from A-210 (admins) to access
  - Homeworks will be submitted via cow

What is Bioinformatics?

- *(Molecular)* **Bio - `informatics`**
- One idea for a definition?
  Bioinformatics is conceptualizing **biology in terms of molecules** (in the sense of physical-chemistry) and then applying **"informatics" techniques** (derived from disciplines such as applied math, CS, and statistics) to understand and **organize the information associated** with these molecules, **on a large-scale.**
- Bioinformatics is a practical discipline with many **applications**.

Introductory Biology

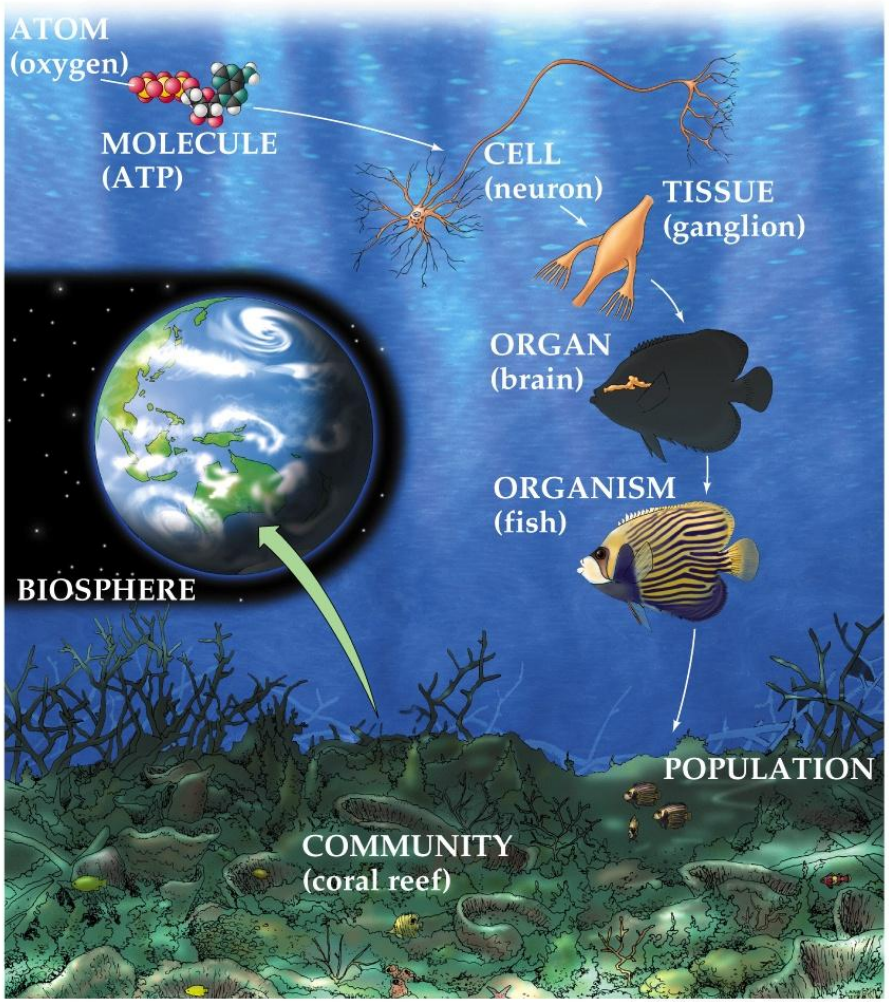
DNA
(Genotype)



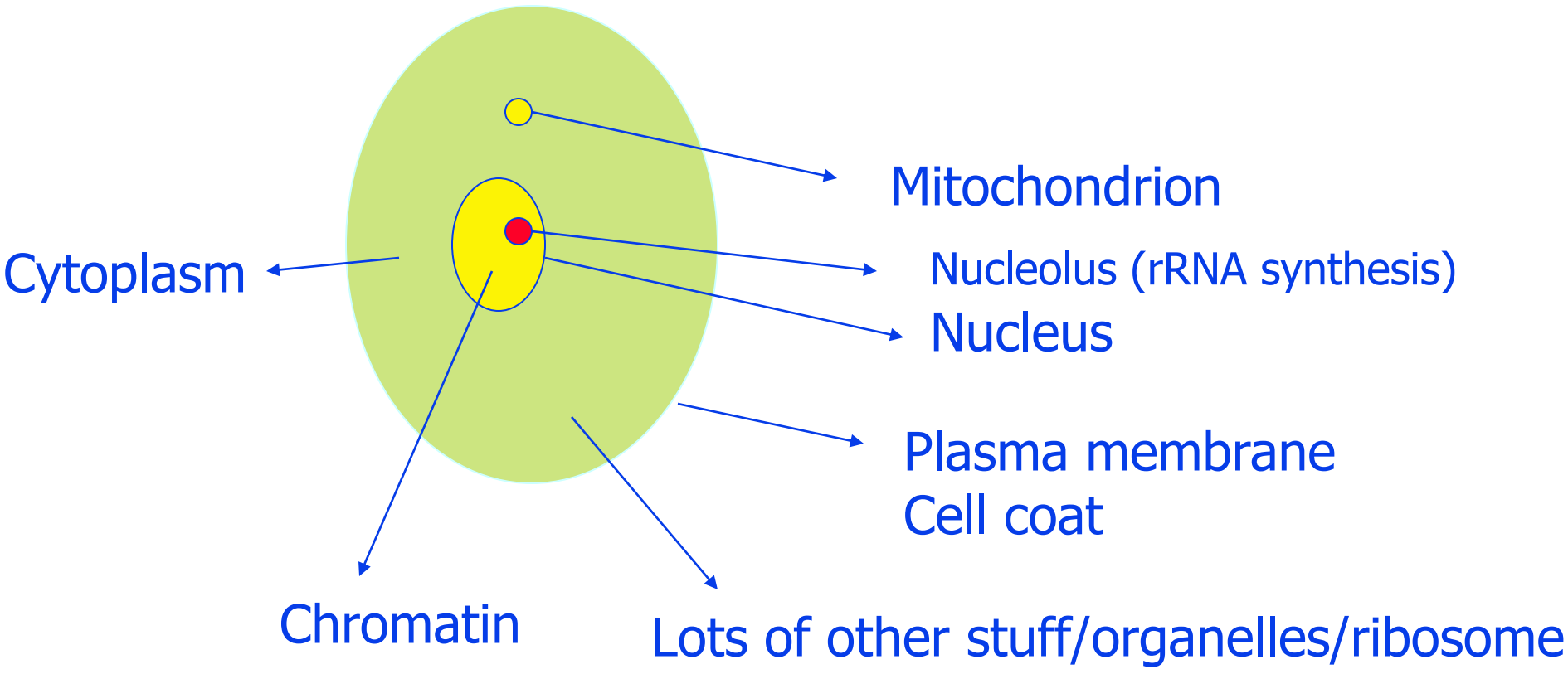
Protein

Phenotype

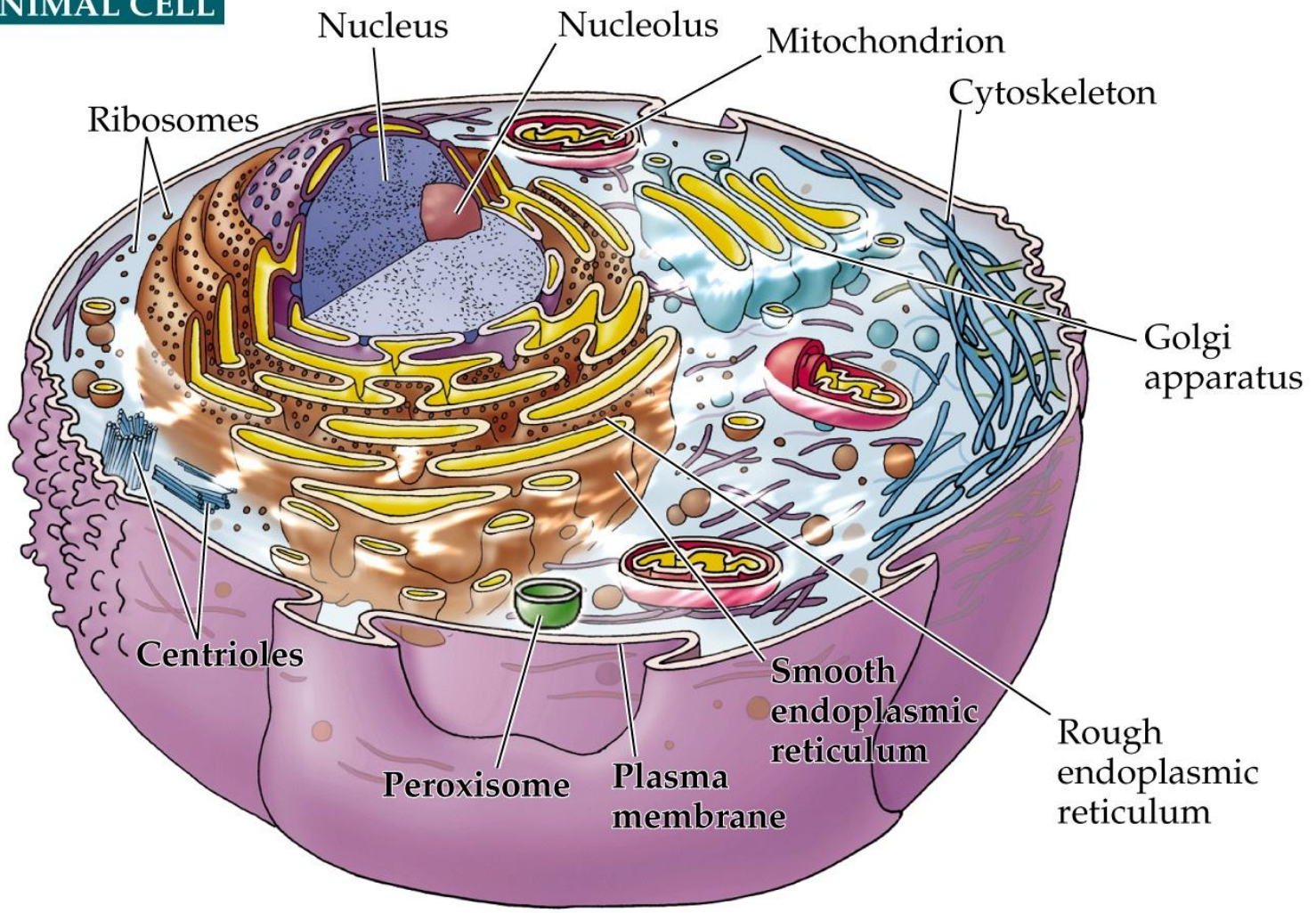
Scales of life



Animal Cell


Mitochondrion
Cytoplasm
Nucleolus (rRNA synthesis)
Nucleus
Plasma membrane
Cell coat
Chromatin
Lots of other stuff/organelles/ribosome

AN ANIMAL CELL



Two kinds of Cells

- Prokaryotes – no nucleus (bacteria)
  - Their genomes are circular
- Eukaryotes – have nucleus (animal,plants)
  - Linear genomes with multiple chromosomes in pairs. When pairing up, they look like

Middle: centromere
Top: p-arm
Bottom: q-arm

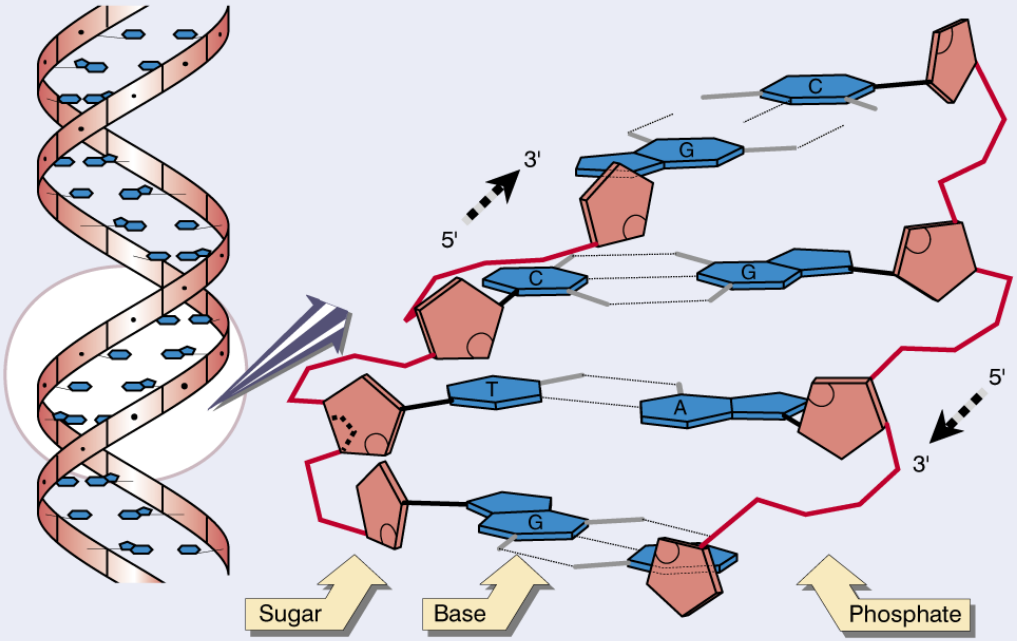
Molecular Biology Information - DNA

- Raw DNA Sequence
  - Coding or Not?
  - Parse into genes?
  - 4 bases: AGCT
  - ~1 Kb in a gene, ~2 Mb in genome
  - ~3 Gb Human

```
atggcaattaaaattggtatcaatggttttggtcgtatcggccgtatcgtattccgtgca
gcacaacaccgtgatgacattgaagttgtaggtattaacgacttaatcgacgttgaatac
atggcttatatgttgaaatatgattcaactcacggtcgtttcgacggcactgttgaagtg
aaagatggtaacttagtggttaatggtaaaactatccgtgtaactgcagaacgtgatcca
gcaaacttaaactggggtgcaatcggtgttgatatcgctgttgaagcgactggtttattc
ttaactgatgaaactgctcgtaaacatatcactgcaggcgcaaaaaaagttgtattaact
ggcccatctaaagatgcaacccctatgttcgttcgtggtgtaaacttcaacgcatacgca
ggtcaagatatcgtttctaacgcatcttgtacaacaaactgtttagctcctttagcacgt
gttgttcatgaaactttcggtatcaaagatggtttaatgaccactgttcacgcaacgact
gcaactcaaaaaactgtggatggtccatcagctaaagactggcgcggcggccgcggtgca
tcacaaaacatcattccatcttcaacaggtgcagcgaaagcagtaggtaaagtattacct
gcattaaacggtaaattaactggtatggctttccgtgttccaacgccaaacgtatctgtt
gttgatttaacagttaatcttgaaaaaccagcttcttatgatgcaatcaaacaagcaatc
aaagatgcagcggaaggtaaaacgttcaatggcgaattaaaaggcgtattaggttacact
gaagatgctgttgtttctactgacttcaacggttgtgctttaacttctgtatttgatgca
gacgctggtatcgcattaactgattctttcgttaaattggtatc . . .

. . .   caaaaatagggttaatatgaatctcgatctccattttgttcatcgtattcaa
caacaagccaaaactcgtacaaatatgaccgcacttcgctataaagaacacggcttgtgg
cgagatatctcttggaaaaactttcaagagcaactcaatcaactttctcgagcattgctt
gctcacaatattgacgtacaagataaaatcgccatttttgcccataatatggaacgttgg
gttgttcatgaaactttcggtatcaaagatggtttaatgaccactgttcacgcaacgact
acaatcgttgacattgcgaccttacaaattcgagcaatcacagtgcctatttacgcaacc
aatacagcccagcaagcagaatttatcctaaatcacgccgatgtaaaaattctcttcgtc
ggcgatcaagagcaatacgatcaaacattggaaattgctcatcattgtccaaaattacaa
aaaattgtagcaatgaaatccaccattcaattacaacaagatcctctttcttgcacttgg
```

DNA structure

Figure 1.7 Flat base pairs lie perpendicular to the sugar-phosphate backbone.



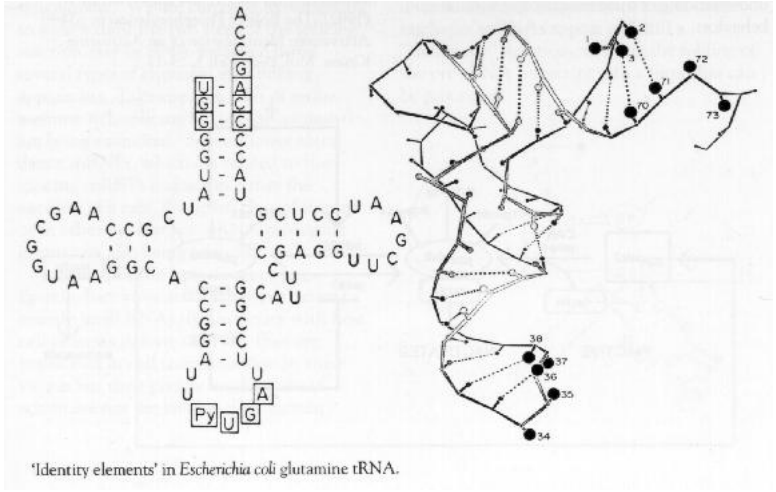
Molecular Biology Information: Protein Sequence

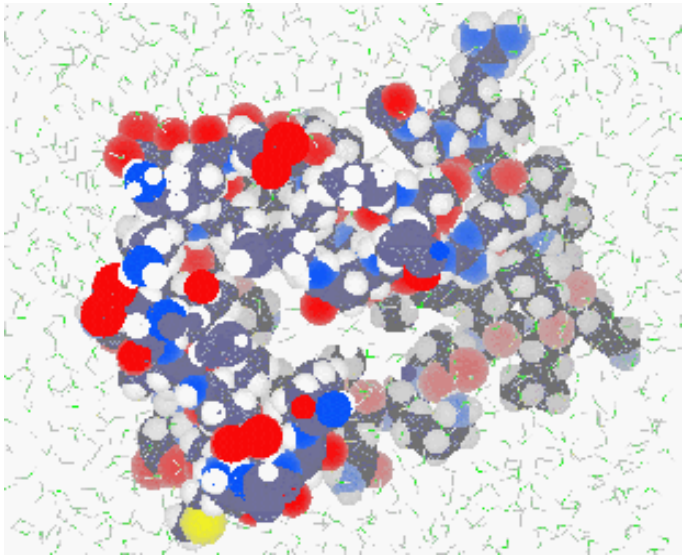
- 20 letter alphabet
  - ACDEFGHIKLMNPQRSTVWY but not BJOUXZ
- Strings of ~300 aa in an average protein (in bacteria),
  ~200 aa in a domain
- ~1M known protein sequences

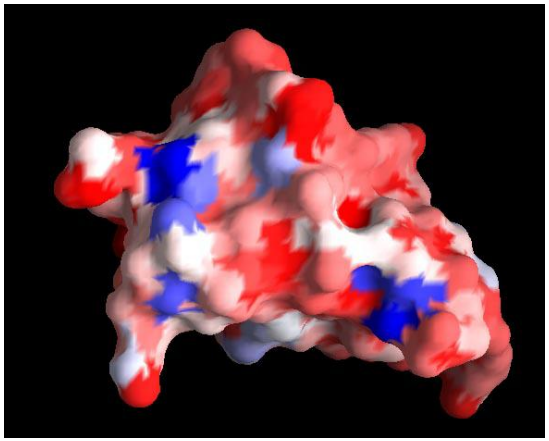
```
d1dhfa_ LNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMTTTSSVEGKQ-NLVIMGKKTWFSI
d8dfr__ LNSIVAVCQNMGIGKDGNLPWPPLRNEYKYFQRMTSTSHVEGKQ-NAVIMGKKTWFSI
d4dfra_ ISLIAALAVDRVIGMENAMPWN-LPADLAWFKRNTL--------NKPVIMGRHTWESI
d3dfr__ TAFLWAQDRDGLIGKDGHLPWH-LPDDLHYFRAQTV--------GKIMVVGRRTYESF

d1dhfa_ LNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMTTTSSVEGKQ-NLVIMGKKTWFSI
d8dfr__ LNSIVAVCQNMGIGKDGNLPWPPLRNEYKYFQRMTSTSHVEGKQ-NAVIMGKKTWFSI
d4dfra_ ISLIAALAVDRVIGMENAMPW-NLPADLAWFKRNTLD--------KPVIMGRHTWESI
d3dfr__ TAFLWAQDRNGLIGKDGHLPW-HLPDDLHYFRAQTVG--------KIMVVGRRTYESF
```

Molecular Biology Information: Macromolecular Structure

- DNA/RNA/Protein
  - Almost all protein

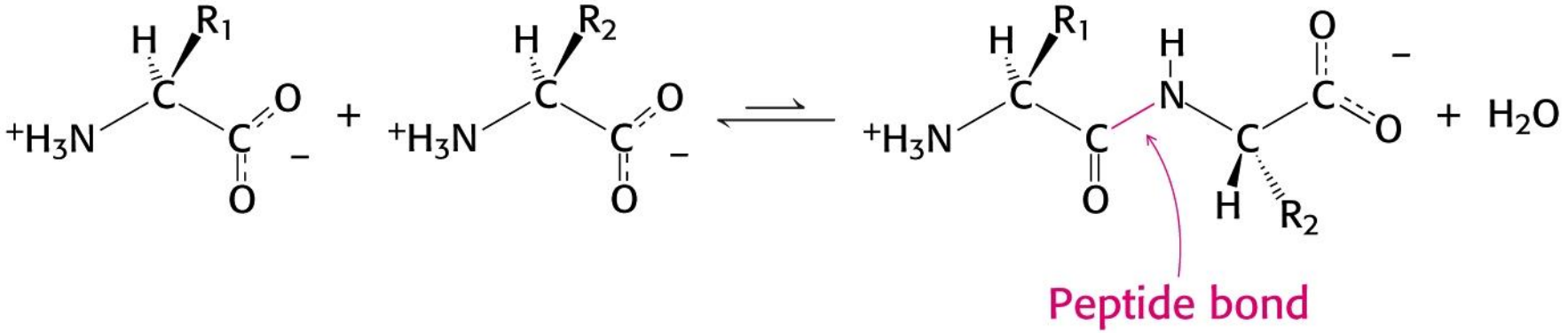






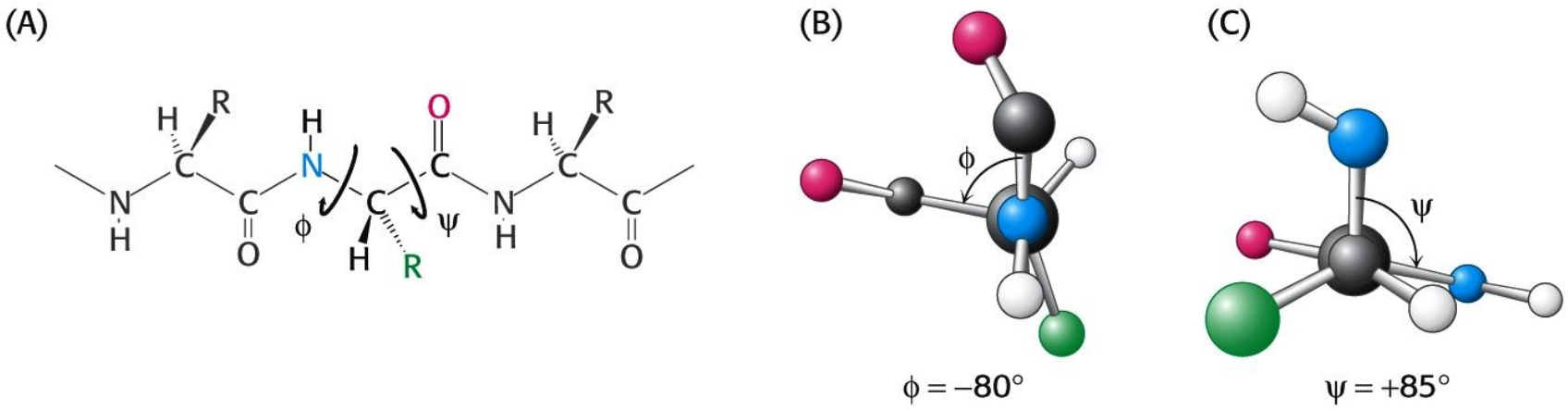
More on Macromolecular Structure

- Primary structure of proteins
  - Linear polymers linked by peptide bonds
  - Sense of direction

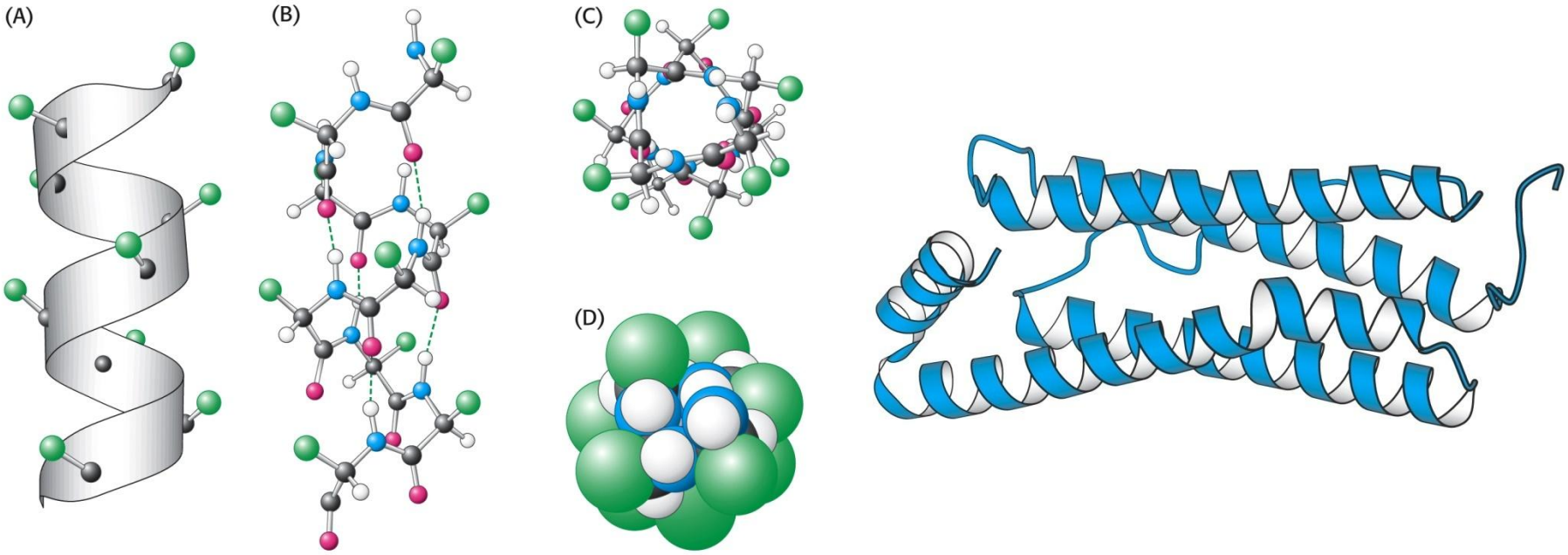


Secondary Structure

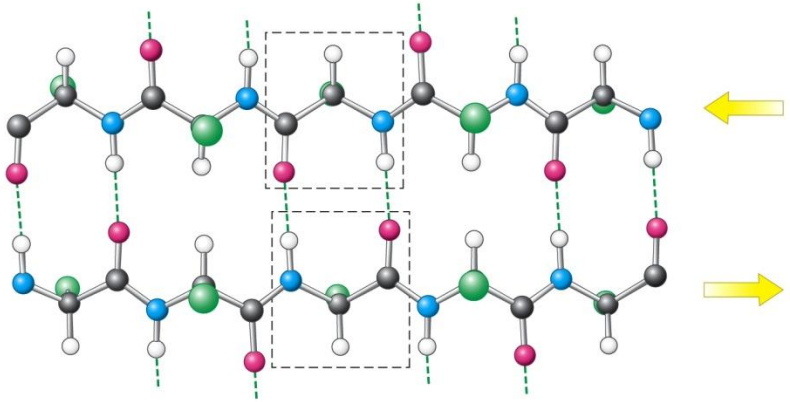
- Polypeptide chains fold into regular local structures
  - alpha helix, beta sheet, turn, loop
  - based on energy considerations
  - Ramachandran plots



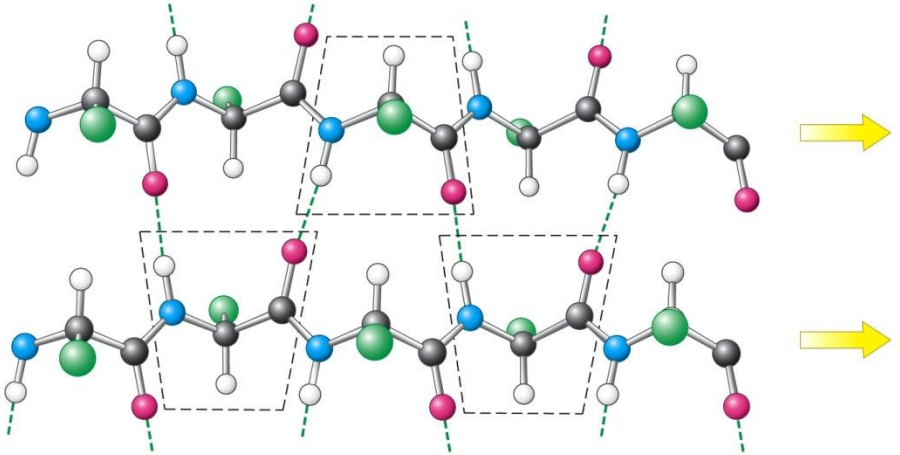
Alpha helix



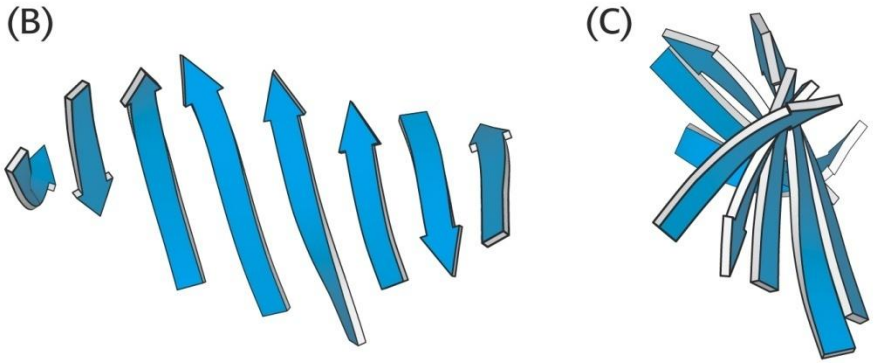
Beta sheet



anti-parallel



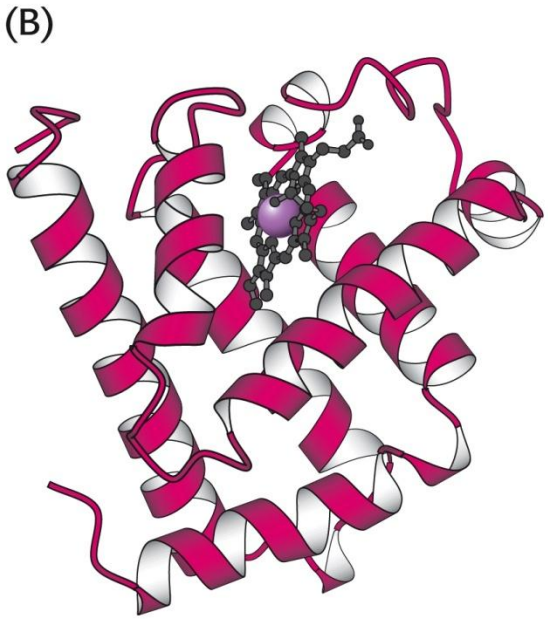
parallel



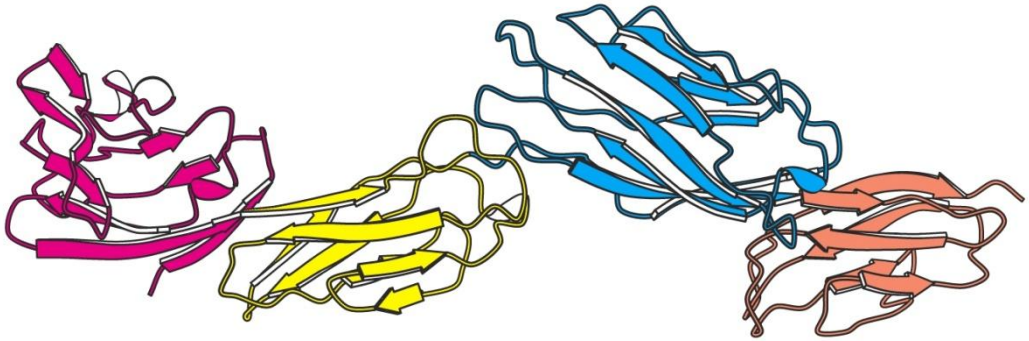
schematic

Tertiary Structure

- 3-d structure of a polypeptide sequence
  - interactions between non-local and foreign atoms
  - often separated into domains



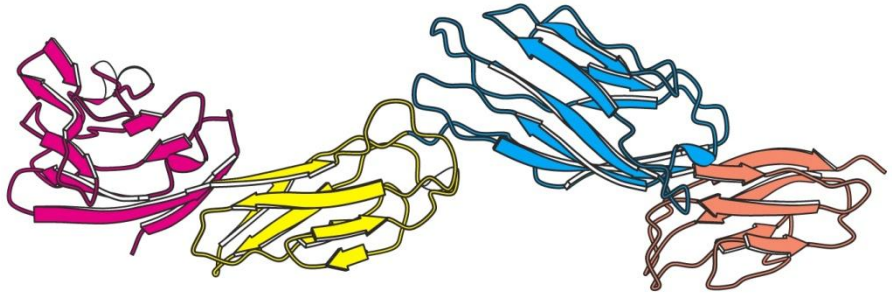
tertiary structure of myoglobin



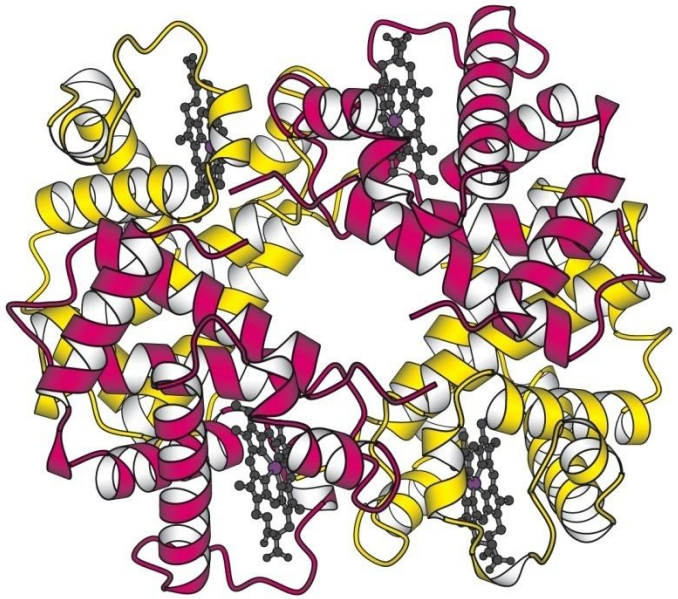
domains of CD4

Quaternary Structure

- Arrangement of protein subunits
  - dimers, tetramers



quaternary structure
of Cro



human hemoglobin
tetramer

Structure summary

- 3-d structure determined by protein sequence
- Cooperative and progressive stabilization
- Prediction remains a challenge
  - ab-initio (energy minimization)
  - knowledge-based
    - Chou-Fasman and GOR methods for SSE prediction
    - Comparative modeling and protein threading for tertiary structure prediction
- Diseases caused by misfolded proteins
  - Mad cow disease
- Classification of protein structures

Genes and Proteins

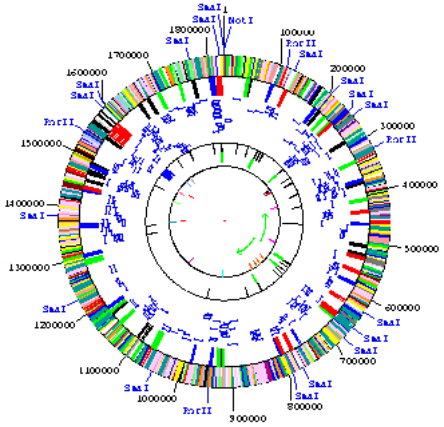
- One gene encodes one* protein.
- Like a program, it starts with start codon (e.g. ATG), then each three code one amino acid. Then a stop codon (e.g. TGA) signifies end of the gene.
- Sometimes, in the middle of a (eukaryotic) gene, there are introns that are spliced out (as junk) during transcription. Good parts are called exons. This is the task of gene finding.

A.A. Coding Table

Glycine (GLY)	GG*
Alanine(ALA)	GC*
Valine (VAL)	GT*
Leucine (LEU)	CT*
Isoleucine (ILE)	AT(*-G)
Serine (SER)	AGT, AGC
Threonine (THR)	AC*
Aspartic Acid (ASP)	GAT,GAC
Glutamic Acid(GLU)	GAA,GAG
Lysine (LYS)	AAA, AAG
Start: ATG, CTG, GTG	

Arginine (ARG)	CG*
Asparagine (ASN)	AAT, AAC
Glutamine (GLN)	CAA, CAG
Cysteine (CYS)	TGT, TGC
Methionine (MET)	ATG
Phenylalanine (PHE)	TTT,TTC
Tyrosine (TYR)	TAT, TAC
Tryptophan (TRP)	TGG
Histidine (HIS)	CAT, CAC
Proline (PRO)	CC*
Stop	TGA, TAA, TAG

Molecular Biology Information: Whole Genomes



Genome sequences now accumulate so quickly that, in less than a week, a single laboratory can produce more bits of data than Shakespeare managed in a lifetime, although the latter make better reading.

-- G A Pekso, *Nature* **401**: 115-116 (1999)

1995

Bacteria,
1.6 Mb,
~1600 genes
[*Science* **269**: 496]

1997

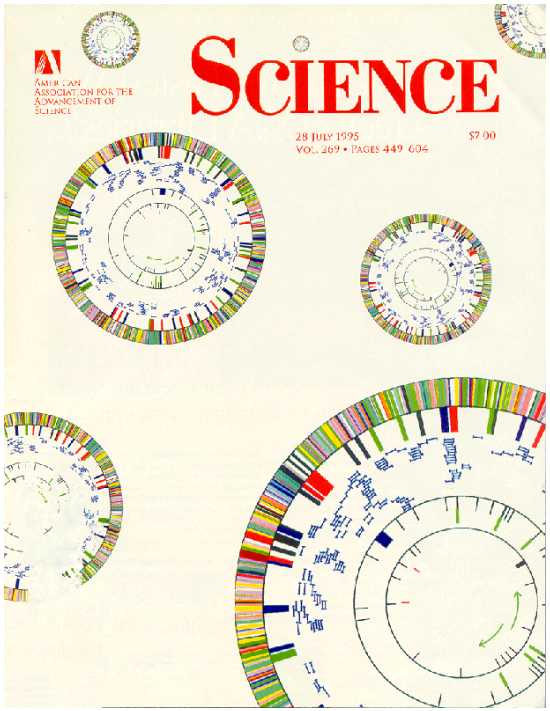
Eukaryote,
13 Mb,
~6K genes
[Nature **387**: 1]

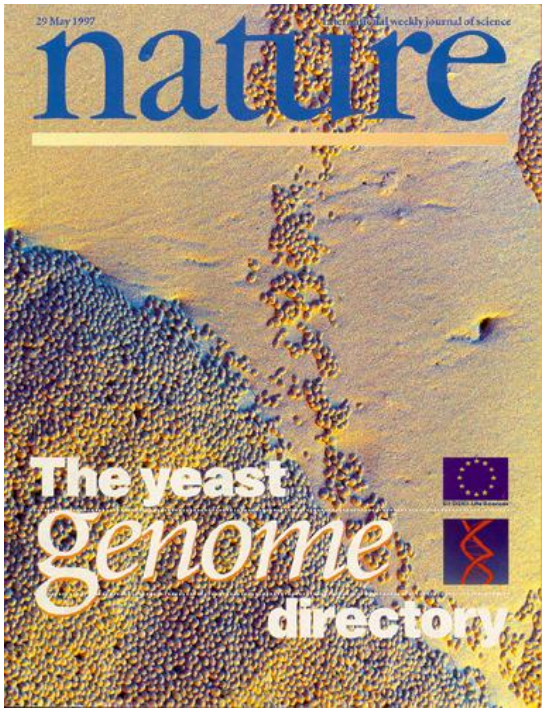
1998

Animal,
~100 Mb,
~20K genes
[*Science* **282**:
1945]

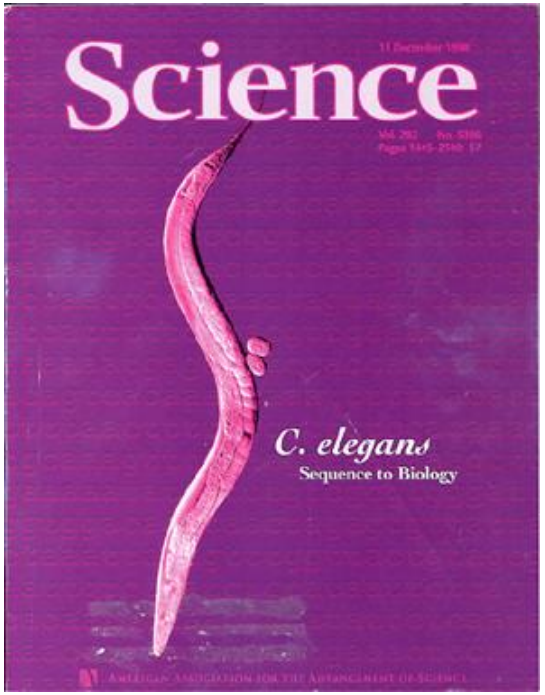
2000?

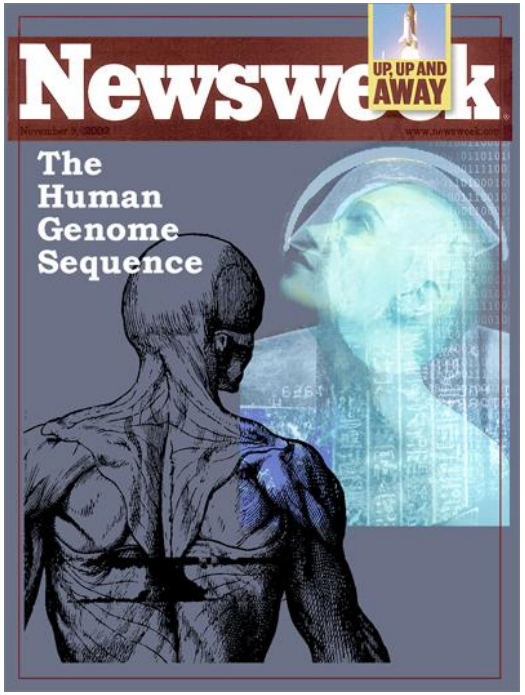
Human,
~3 Gb,
~100K
genes [???]



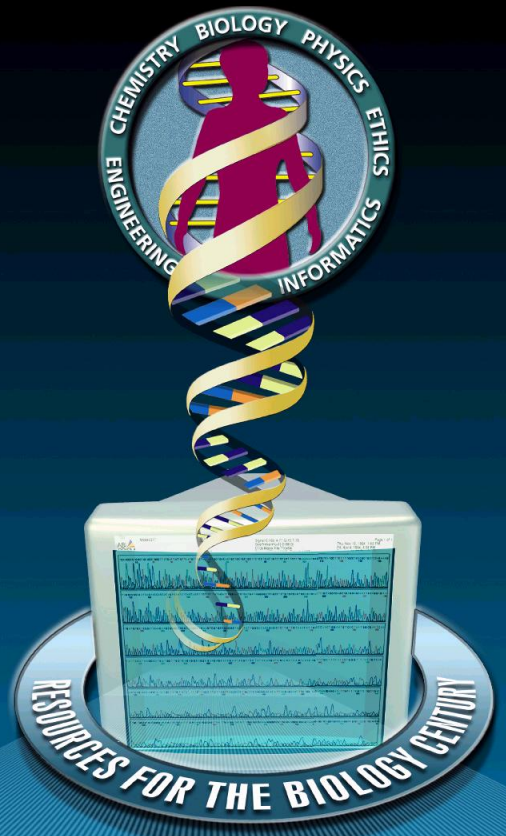


Genomes highlight the Finiteness **of the "Parts" in Biology**





Human Genome Project



Impacting many disciplines

Courtesy
U.S. Department of Energy
Human Genome Program

Global Carbon Cycles
Industrial Resources • Bioremediation
Evolutionary Biology • Biofuels • Agriculture • Forensics
Molecular and Nuclear Medicine • Health Risks

YGA 99-1133R

Gene Expression Datasets: the Transcriptome

Cell, Vol. 95, 717–728, November 25, 1998, Copyright ©1998 by Cell Press

Dissecting the Regulatory Circuitry of a Eukaryotic Genome

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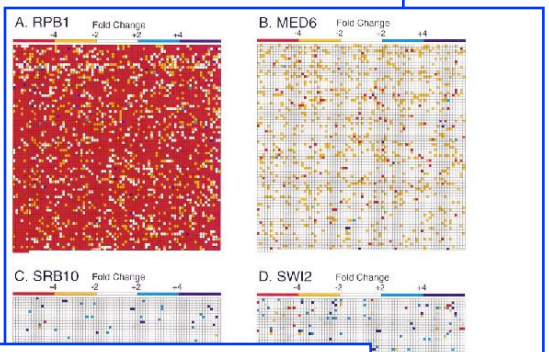
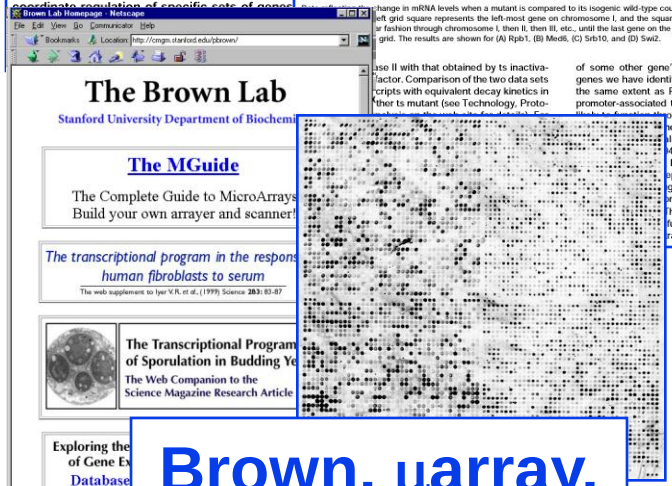


Figure 2. Genome-Wide Expression Data for Selected Components of the RNA Polymerase II Holoenzyme

Young/Lander, Chips, Abs. Exp.



Brown, μarray, Rel. Exp. over Timecourse

Also: SAGE; Samson and Church, Chips; Aebersold, Protein Expression

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 190–195, January 1997
Genetics

A multipurpose transposon system for analyzing protein production, localization, and function in *Saccharomyces cerevisiae*

PETRA ROSS-MACDONALD, AMY SHEEHAN, G. SHIRLEEN ROEDER, AND MICHAEL SNYDER*

Department of Biology, Yale University, P.O. Box 208103, New Haven, CT 06520-8103

Communicated by Gerald R. Fink, Whitehead Institute, Cambridge, MA, October 30, 1996 (received for review July 15, 1996)

ABSTRACT **Analysis of the function of a particular gene** product typically involves determining the expression profile of the gene, the subcellular location of the protein, and th phenotype of a null strain lacking the protein. Conditiona alleles of the gene are often created as an additional tool. W have developed a multifunctional, transposon-based syste that simultaneously generates constructs for all the abov analyses and is suitable for mutagenesis of any given *Saccha romyces cerevisiae* gene. Depending on the transposon used, th yeast gene is fused to a coding region for β-galactosidase green fluorescent protein. Gene expression can therefore b monitored by chemical or fluorescence assays. The trans posons create insertion mutations in the target gene, allowin phenotypic analysis. The transposon can be reduced by *cre–lo* site-specific recombination to a smaller element that leaves a epitope tag inserted in the encoded protein. In addition to it utility for a variety of immunodetection purposes, the epitop tag element also has the potential to create conditional allele of the target gene. We demonstrate these features of th transposons by mutagenesis of the *SPA2*, *ARP100*, *SER1*, an *BDF1* genes.

The yeast *Saccharomyces cerevisiae* has proved of great impo tance in characterizing basic biological processes. This utili can only become more marked now that the sequence of th entire yeast genome has been obtained, and additional homolo of yeast genes are identified in other organisms (1). Determini

antibody into a protein of interest, the time and expense of generating specific antibodies and associated reagents is avoided

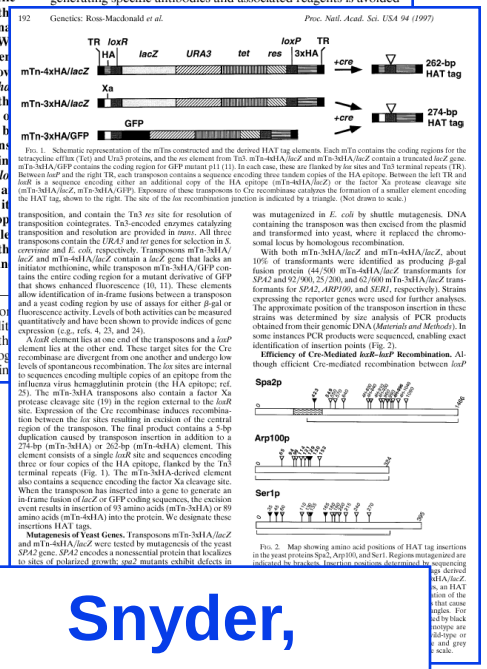


FIG. 1. Schematic representation of the mTns constructed and the derived HAT tag elements. Each mTn contains the coding regions for the tetracycline efflux (Tet) and Ura3 proteins, and the *res* element from Tn3. mTn-4xHA/*lacZ* and mTn-3xHA/*lacZ* contain a truncated *lacZ* gene. mTn-3xHA/GFP contains the coding region for GFP mutant p11 (11). In each case, these are flanked by *lox* sites and Tn3 terminal repeats (TR). Between *loxP* and the right TR, each transposon contains a sequence encoding three tandem copies of the HA epitope. Between the left TR and *loxR* is a sequence encoding either an additional copy of the HA epitope (mTn-4xHA/*lacZ*) or the factor Xa protease cleavage site (mTn-3xHA/*lacZ*, mTn-3xHA/GFP). Exposure of these transposons to Cre recombinase catalyzes the formation of a smaller element encoding the HAT tag, shown to the right. The site of the *lox* recombination junction is indicated by a triangle. (Not drawn to scale.)

Snyder, Transposons, Protein Exp.

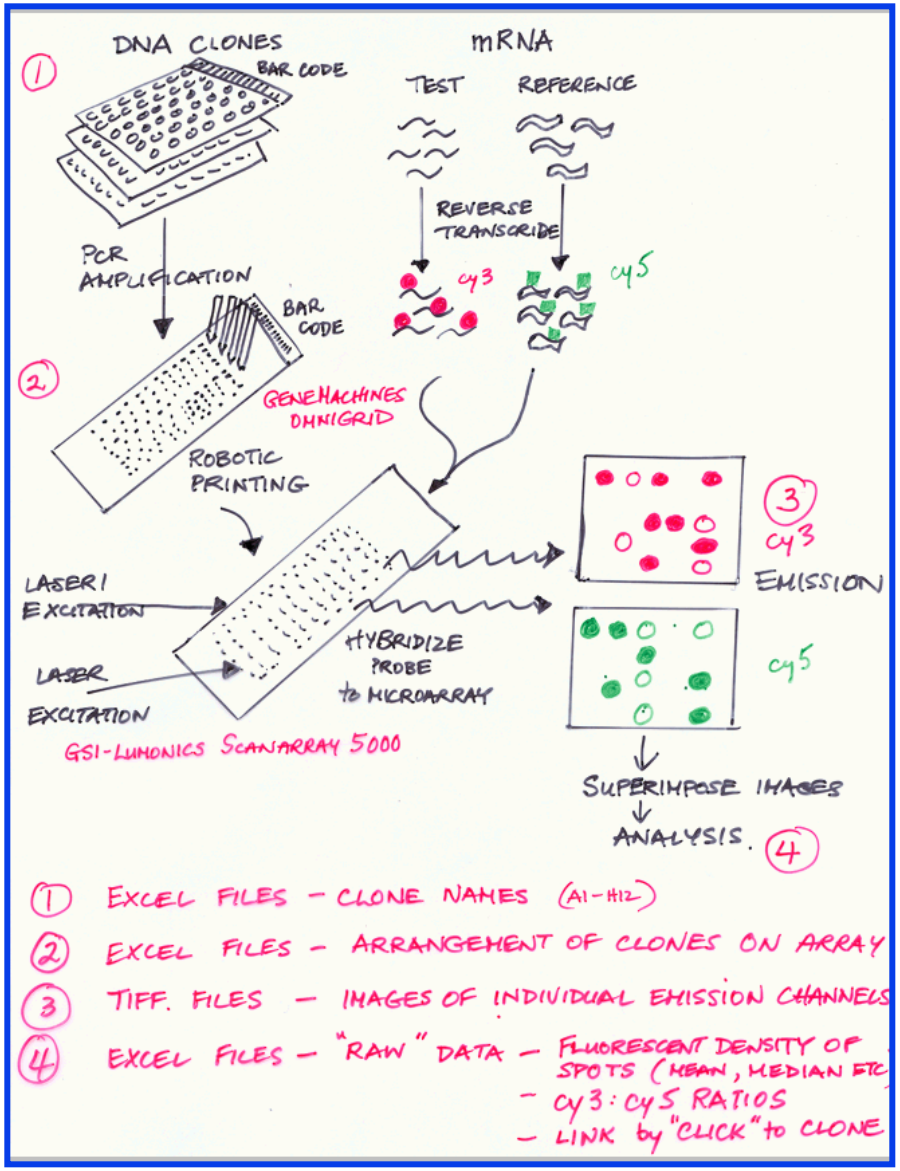
Array Data

Yeast Expression Data in Academia:
levels for all 6000 genes!

Can only sequence genome once but can do an infinite variety of these array experiments

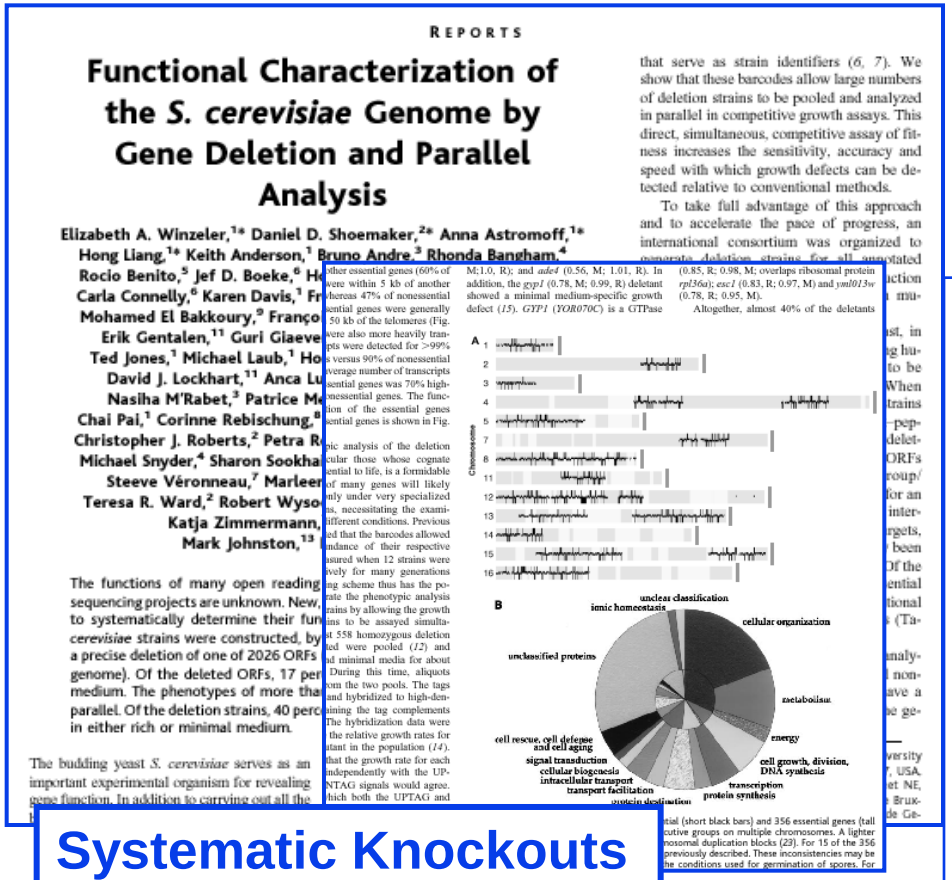
at 10 time points,
6000 x 10 = 60K floats

telling signal from background



(courtesy of J Hager)

Other Whole-Genome Experiments



REPORTS

Functional Characterization of the *S. cerevisiae* Genome by Gene Deletion and Parallel Analysis

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The functions of many open reading … sequencing projects are unknown. New, … to systematically determine their fun… *cerevisiae* strains were constructed, by … a precise deletion of one of 2026 ORFs … genome). Of the deleted ORFs, 17 per… medium. The phenotypes of more tha… parallel. Of the deletion strains, 40 perc… in either rich or minimal medium.

The budding yeast *S. cerevisiae* serves as an important experimental organism for revealing gene function. In addition to carrying out all the

that serve as strain identifiers (*6*, *7*). We show that these barcodes allow large numbers of deletion strains to be pooled and analyzed in parallel in competitive growth assays. This direct, simultaneous, competitive assay of fitness increases the sensitivity, accuracy and speed with which growth defects can be detected relative to conventional methods.

To take full advantage of this approach and to accelerate the pace of progress, an international consortium was organized to generate deletion strains for all annotated …

…ther essential genes (60% of …were within 5 kb of another …whereas 47% of nonessential …ential genes were generally …50 kb of the telomeres (Fig. …were also more heavily tran…pts were detected for >99% …s versus 90% of nonessential …average number of transcripts …ential genes was 70% high…nessential genes. The func…tion of the essential genes …ential genes is shown in Fig.

…gic analysis of the deletion …cular those whose cognate …ential to life, is a formidable …of many genes will likely …nly under very specialized …s, necessitating the exami…different conditions. Previous …ed that the barcodes allowed …ndance of their respective …sured when 12 strains were …vely for many generations …ng scheme thus has the po…tate the phenotypic analysis …rains by allowing the growth …ms to be assayed simulta…st 558 homozygous deletion …ted were pooled (*12*) and …d minimal media for about … During this time, aliquots …om the two pools. The tags …and hybridized to high-den…aining the tag complements …The hybridization data were …the relative growth rates for …tant in the population (*14*). …hat the growth rate for each …independently with the UP…NTAG signals would agree. …hich both the UPTAG and

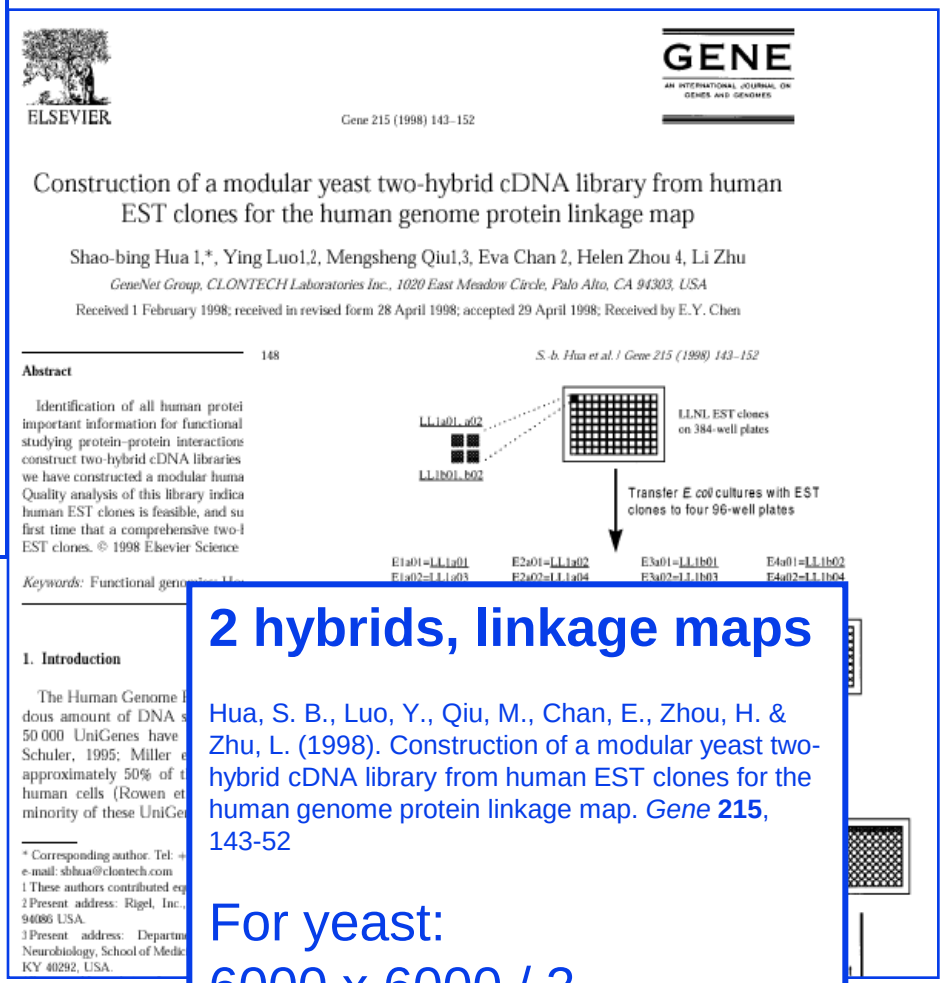
M;1.0, R); and *ade4* (0.56, M; 1.01, R). In addition, the *gyp1* (0.78, M; 0.99, R) deletant showed a minimal medium-specific growth defect (*15*). *GYP1* (*YOR070C*) is a GTPase …(0.85, R; 0.98, M; overlaps ribosomal protein *rpl36a*); *esc1* (0.83, R; 0.97, M) and *yml013w* (0.78, R; 0.95, M).

Altogether, almost 40% of the deletants …

…tial (short black bars) and 356 essential genes (tall …cutive groups on multiple chromosomes. A lighter …nosomal duplication blocks (*23*). For 15 of the 356 …previously described. These inconsistencies may be …he conditions used for germination of spores. For

Systematic Knockouts

Winzeler, E. A., Shoemaker, D. D., Astromoff, A., Liang, H., Anderson, K., Andre, B., Bangham, R., Benito, R., Boeke, J. D., Bussey, H., Chu, A. M., Connelly, C., Davis, K., Dietrich, F., Dow, S. W., El Bakkoury, M., Foury, F., Friend, S. H., Gentalen, E., Giaever, G., Hegemann, J. H., Jones, T., Laub, M., Liao, H., Davis, R. W. & et al. (1999). Functional characterization of the S. cerevisiae genome by gene deletion and parallel analysis. *Science* **285**, 901-6



ELSEVIER

GENE
AN INTERNATIONAL JOURNAL ON GENES AND GENOMES

Gene 215 (1998) 143–152

Construction of a modular yeast two-hybrid cDNA library from human EST clones for the human genome protein linkage map

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148 S.-b. Hua et al. / Gene 215 (1998) 143–152

Abstract

Identification of all human protei… important information for functional … studying protein–protein interactions … construct two-hybrid cDNA libraries … we have constructed a modular huma… Quality analysis of this library indica… human EST clones is feasible, and su… first time that a comprehensive two-h… EST clones. © 1998 Elsevier Science

Keywords: Functional geno…

1. Introduction

The Human Genome … dous amount of DNA … 50 000 UniGenes have … Schuler, 1995; Miller … approximately 50% of … human cells (Rowen et … minority of these UniGe…

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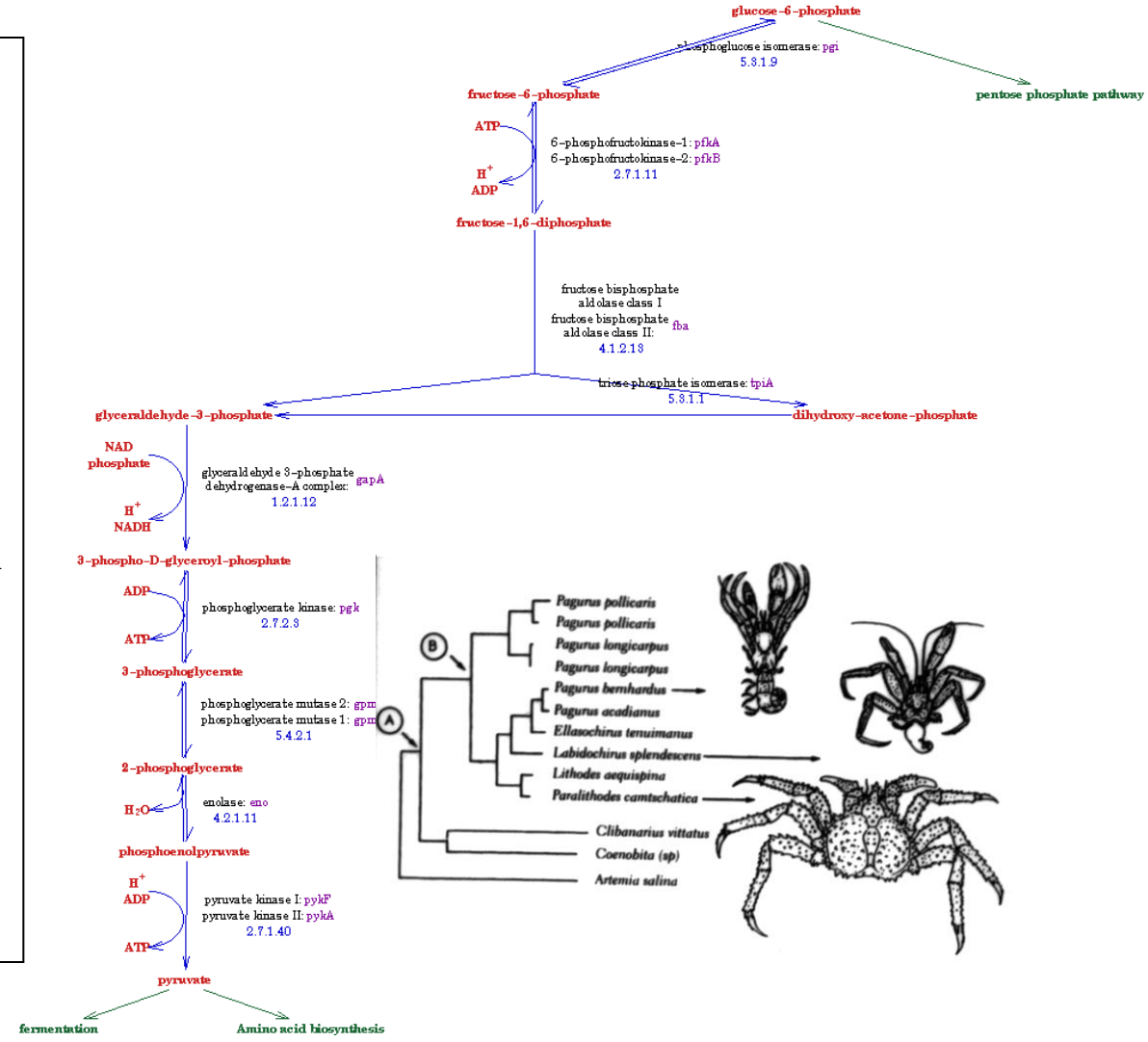
2 hybrids, linkage maps

Hua, S. B., Luo, Y., Qiu, M., Chan, E., Zhou, H. & Zhu, L. (1998). Construction of a modular yeast two-hybrid cDNA library from human EST clones for the human genome protein linkage map. *Gene* **215**, 143-52

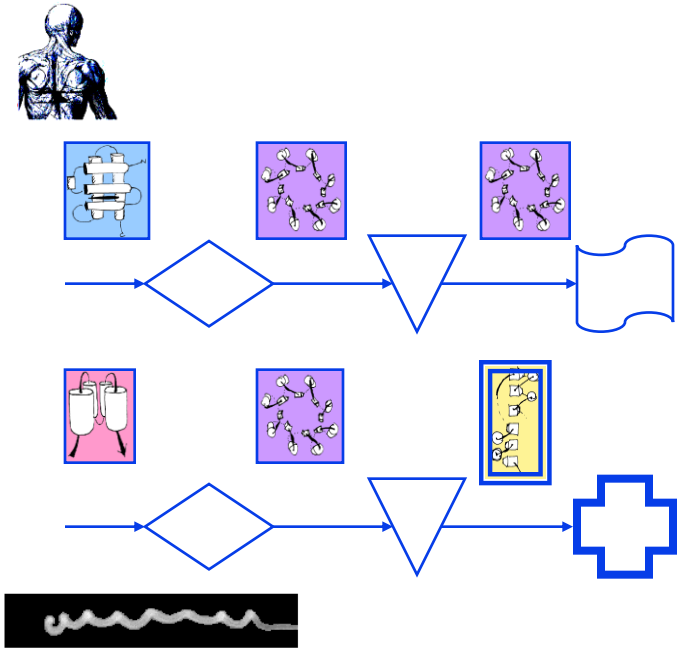
For yeast:
6000 x 6000 / 2
~ 18M interactions

Molecular Biology Information: Other Integrative Data

- Information to understand genomes
  - Metabolic Pathways (glycolysis), traditional biochemistry
  - Regulatory Networks
  - Whole Organisms Phylogeny, traditional zoology
  - Environments, Habitats, ecology
  - The Literature (MEDLINE)
- The Future....



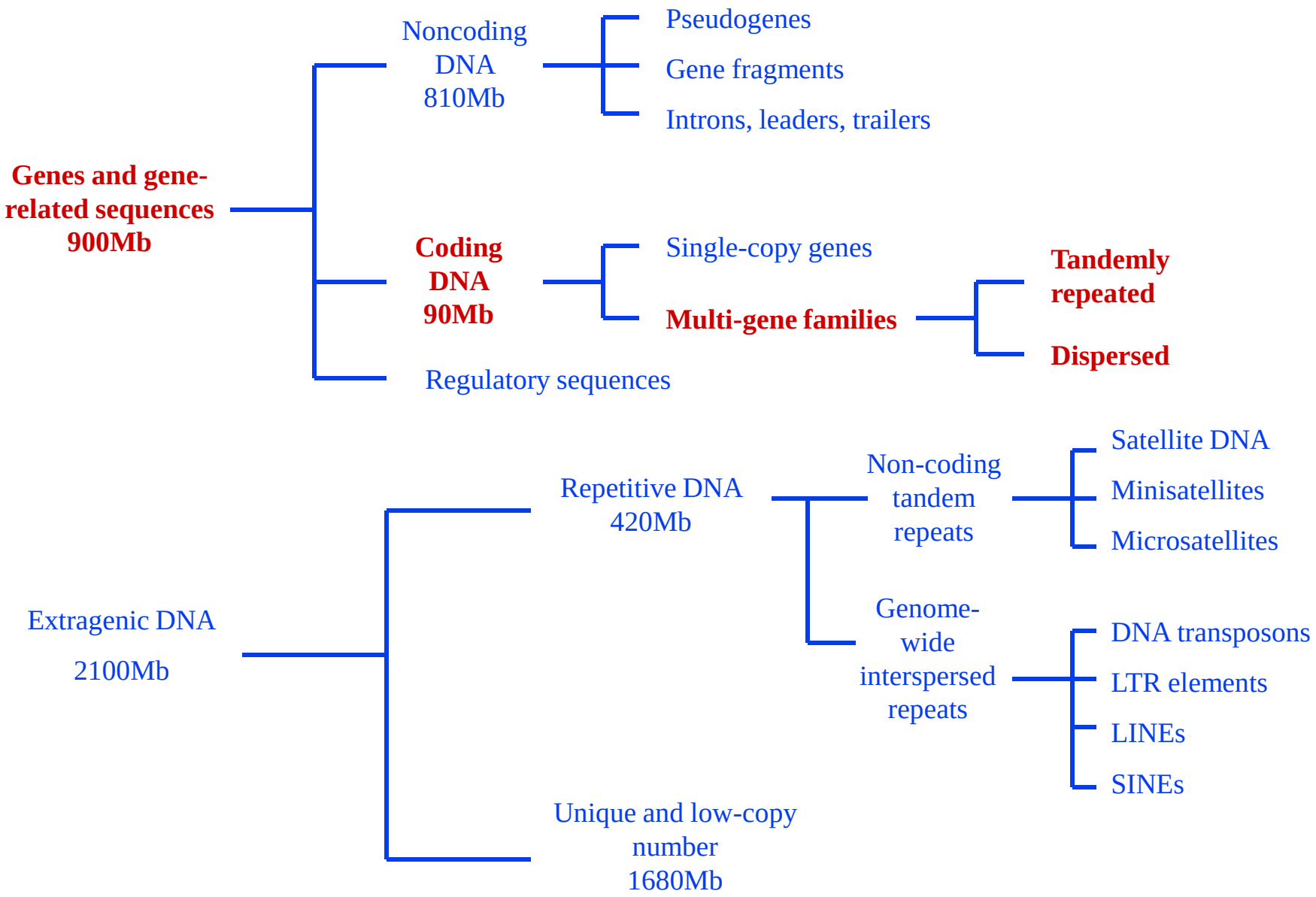
Organizing
Molecular Biology Information:
Redundancy and Multiplicity



- Different Sequences Have the Same Structure
- Organism has many similar genes
- Single Gene May Have Multiple Functions
- Genes are grouped into Pathways
- Genomic Sequence Redundancy due to the Genetic Code
- **How do we find the similarities?.....**

Integrative Genomics - genes ↔ structures ↔ **functions** ↔ **pathways** ↔ expression levels ↔ regulatory systems ↔ ….

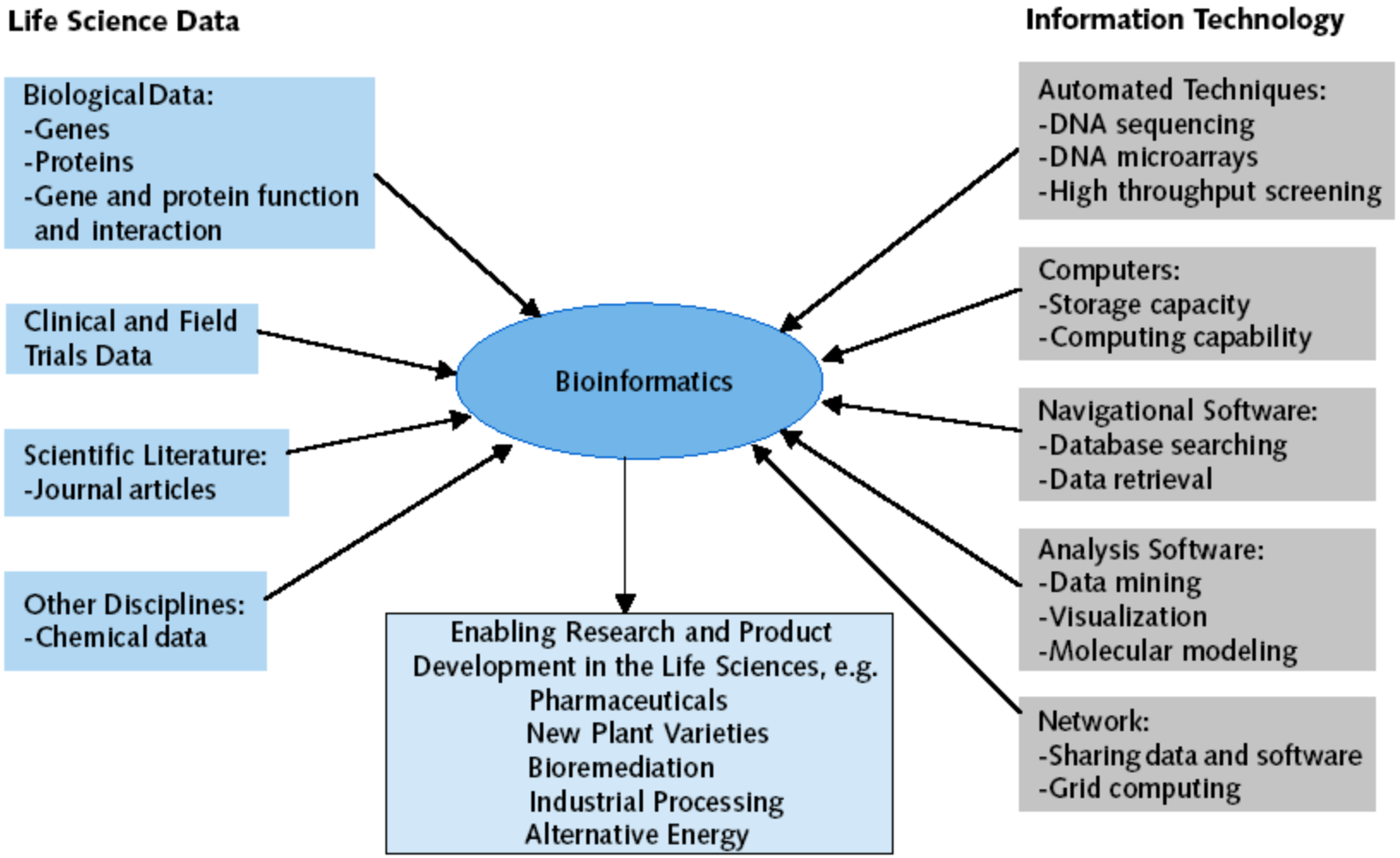
Human genome



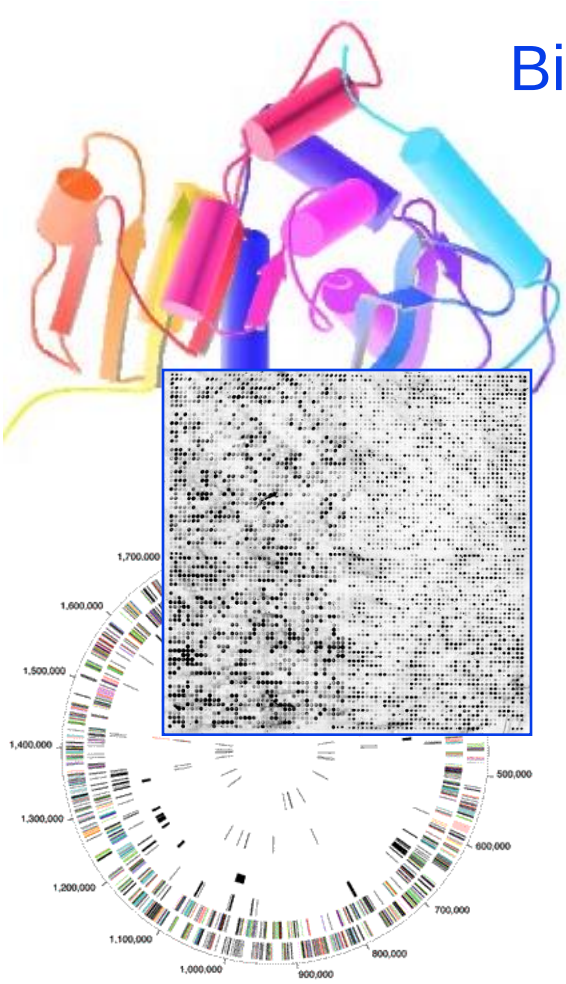
Where to get data?

- GenBank
  - http://www.ncbi.nlm.nih.gov
- Protein Databases
  - SWISS-PROT: http://www.expasy.ch/sprot
  - PDB: http://www.pdb.bnl.gov/
- And many others

Figure 6.1. Bioinformatics Uses Information Technology to Manage and Analyze Information Generated by the Life Sciences



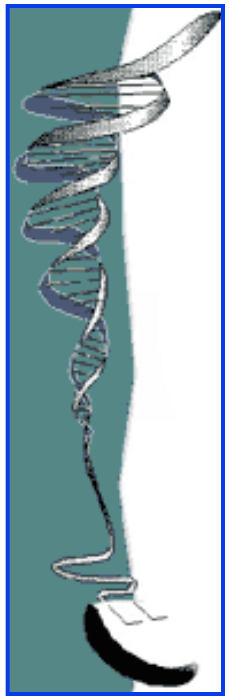
Bioinformatics: A simple view



Biological Data

+

Computer Calculations



Application domains

Table 6.2. Number of Survey Respondents Indicating Bioinformatics Research Activities by Application, 2002

Application	Number of firms in application	Conduct bioinformatics research
Human Health	780	247
Animal Health	144	37
Agricultural & Aquacultural/Marine	128	41
Marine & Terrestrial Microbial	41	19
Industrial and Agricultural-Derived Processing	132	45
Environmental Remediation and Natural Resource Recovery	41	12
Other	160	30

Bio-defense

Note: The total number of firms that responded to the biotechnology survey was 1,031, and 304 of these firms indicated that they had some activity in bioinformatics. The number of firms by biotechnology application does not add up to the total number of firms that responded to the survey because firms were classified in an application if they indicated it as either a "primary" or "secondary" focus.

Source: Survey data from *Critical Technology Assessment of Biotechnology in U.S. Industry*, U.S. Department of Commerce, Technology Administration and Bureau of Industry and Security, August 2002.

Kinds of activities

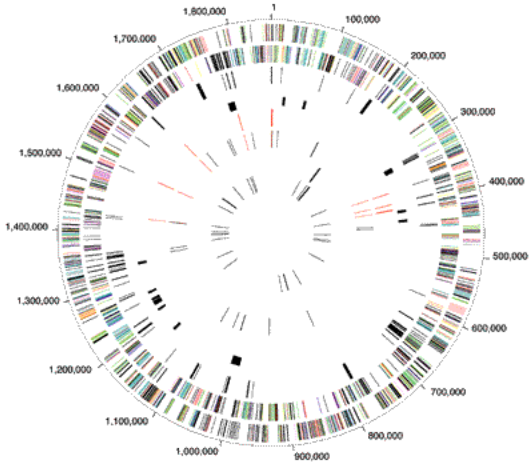
	Conduct research on/in	Approved, marketed, or in production		Total
		Product(s)	Process(es)	
DNA-based				
Bioinformatics	29	2	1	30
Genomics, pharmacogenetics	29	3	2	30
DNA sequencing/synthesis/ amplification, genetic engineering	39	5	3	43
Biochemistry/Immunology				
Drug design & delivery	33	4	2	38
Synthesis/sequencing of proteins and peptides	27	3	1	30
Combinatorial chemistry, 3-D molecular modeling	18	1	0	19

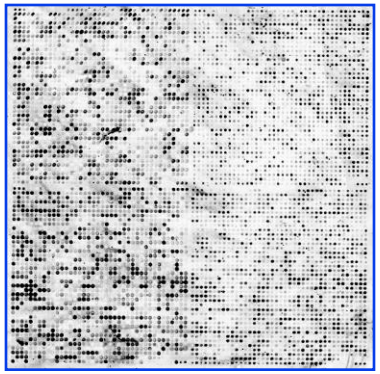
Note: The total number of responses to the biotechnology activity question was 1021. Percents do not add up to 100 percent because firms can have more than one activity.

Source: Survey data from *Critical Technology Assessment of Biotechnology in U.S. Industry*, U.S. Department of Commerce, Technology Administration and Bureau of Industry and Security, August 2002.

Motivation

- Diversity and size of information
  - Sequences, 3-D structures, microarrays, protein interaction networks, *in silico* models, bio-images



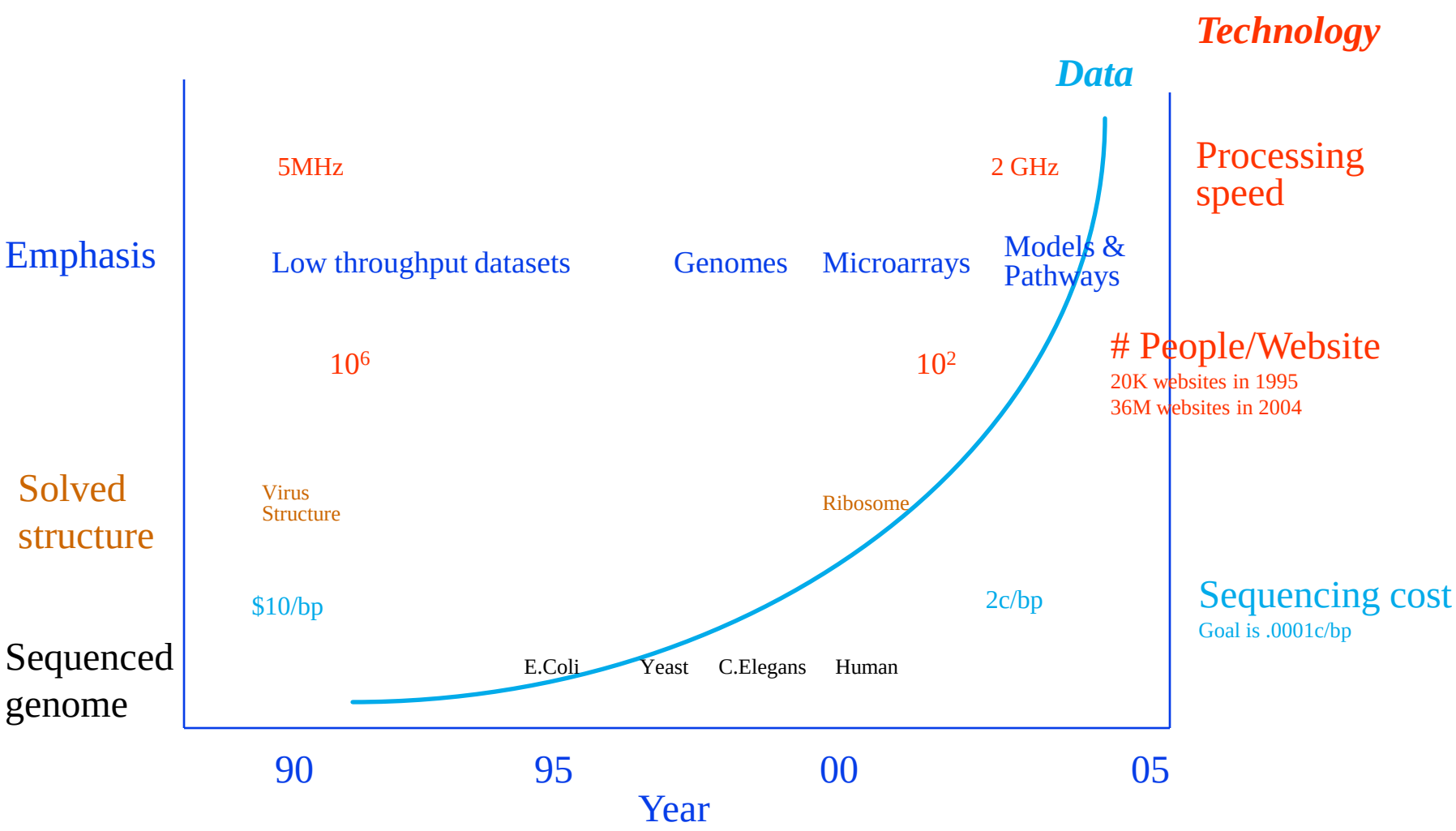


- Understand the relationship
  - Similar to complex software design

Bioinformatics - A Revolution

Biological Experiment → Data → *Information* → *Knowledge* → *Discovery*

Collect — *Characterize* — *Compare* — *Model* — *Infer*



Computing *versus* Biology

- *what computer science is to molecular biology is like what mathematics has been to physics .....*

  -- Larry Hunter, ISMB'94

- *molecular biology is (becoming) an information science .....*

  -- Leroy Hood, RECOMB'00

- *bioinformatics ... is the research domain focused on linking the behavior of biomolecules, biological pathways, cells, organisms, and populations to the information encoded in the genomes* --Temple Smith, Current Topics in Computational Molecular Biology

Computing *versus* Biology

looking into the future

- *Like physics, where general rules and laws are taught at the start, biology will surely be presented to future generations of students as a set of basic systems ..... duplicated and adapted to a very wide range of cellular and organismic functions, following basic evolutionary principles constrained by Earth's geological history.* --Temple Smith, Current Topics in Computational Molecular Biology

Scalability challenges

- Recent issue of NAR devoted to data collections contains 719 databases
  - Sequence
    - Genomes (more than 150), ESTs, Promoters, transcription factor binding sites, repeats, ..
  - Structure
    - Domains, motifs, classifications, ..
  - Others
    - Microarrays, subcellular localization, ontologies, pathways, SNPs, ..

Challenges of working in bioinformatics

- Need to feel comfortable in interdisciplinary area
- Depend on others for primary data
- Need to address important biological *and* computer science problems

Skill set

- Artificial intelligence
- Machine learning
- Statistics & probability
- Algorithms
- Databases
- Programming

Current problems

- Next generation sequencing
- Gene regulation
- Epigenetics and genetics of diseases, aging
  - SNPs, DNA methylation, histone modification
- Comparison of whole genomes
- Computational systems biology
  - Complexity, dynamics
- Structural bioinformatics, molecular dynamics simulations
- Text mining --- the BioCreative challenge
- …. and many more