CENG 465
Introduction to Bioinformatics

Spring 2010-2011

Tolga Can (Office: B-109)
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Course Web Page:
http://www.ceng.metu.edu.tr/~tcan/ceng465_s1011/

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 problems in bioinformatics
- Opportunity to interact with algorithms, tools, data in current practice

High level overview of the course

- 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)
  - Analyze DNA and protein sequences for clues regarding function
  - Identification of homologues
    - Pairwise sequence alignment
  - Statistical significance of sequence alignments
  - Profile HMMS
  - Multiple sequence alignment
  - Efficient pattern search: suffix trees
- Phylogenetic trees (1 week)

Course outline

- Protein structures (4 weeks)
  - Structure prediction (secondary, tertiary)
  - Analyze protein structures for clues regarding function
    - Structure alignment
- Microarray data analysis (2 weeks)
  - Correlations, clustering
- Gene/Protein networks, pathways (2 weeks)
  - Protein-protein, protein/DNA interactions
  - Construction and analysis of large scale networks

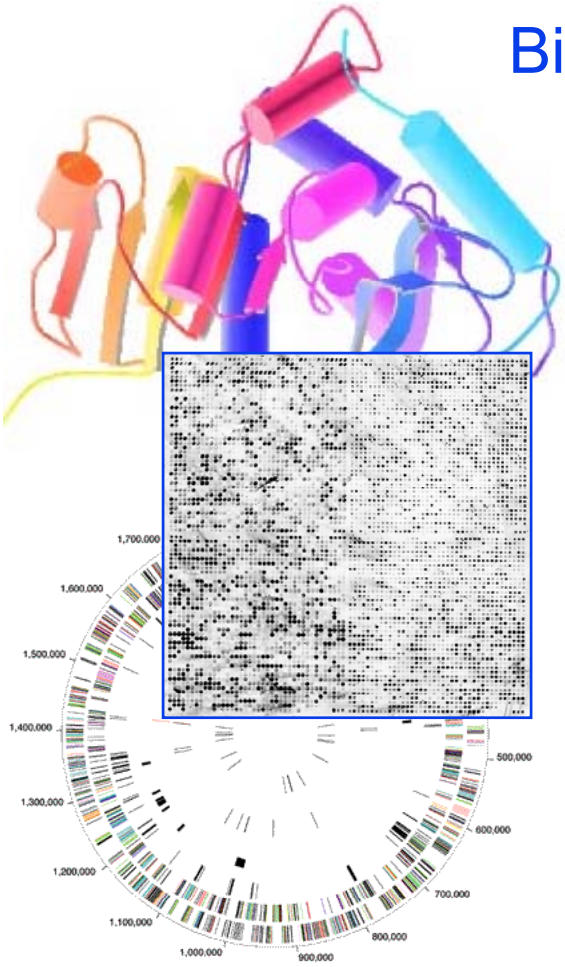
Grading

- Midterm exam - 30%
- Final exam - 40%
- Assignments (written/programming) - 30%

Miscellaneous

- Course webpage
  - http://www.ceng.metu.edu.tr/~tcan/ceng465_s1011/
  - Lecture slides and reading materials
  - Assignments
  - Teaching assistant: Sefa Kilic (sefa@ceng, B-204)
- Newsgroup
  - metu.ceng.course.465
  - You should follow the newsgroup for course related announcements
  - Students from other departments should get a CENG account for this semester (Room: A-210) in order to access the newsgroup

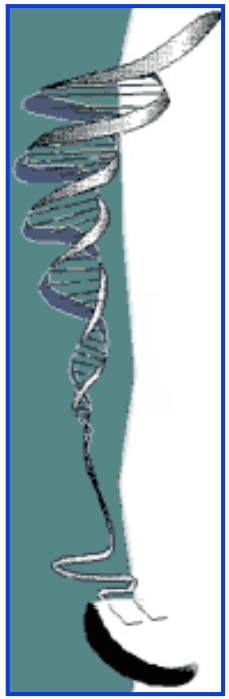
Bioinformatics: A simple view



Biological Data

+

Computer Calculations



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**.

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

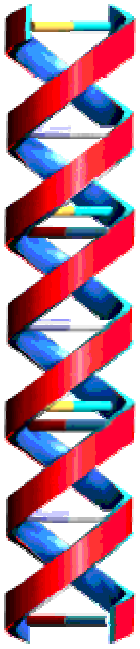
- *bioinformatics ... is the research domain focused on linking the behavior of biomolecules, biological pathways, cells, organisms, and populations to the information encoded in the genomes* --Temple Smith, Current Topics in Computational Molecular Biology

Computing *versus* Biology

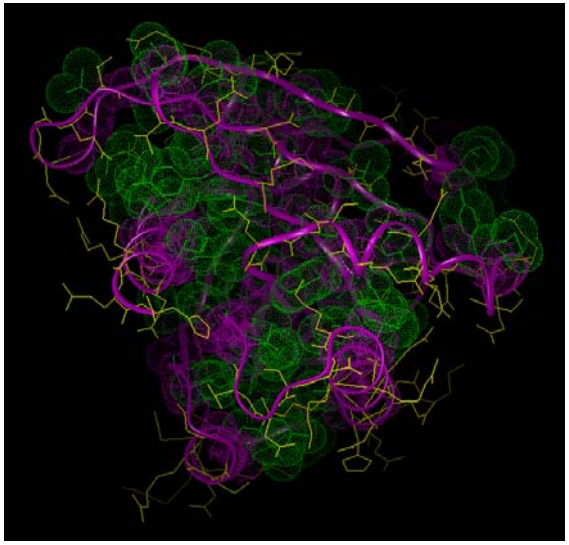
looking into the future

- *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

Introductory Biology



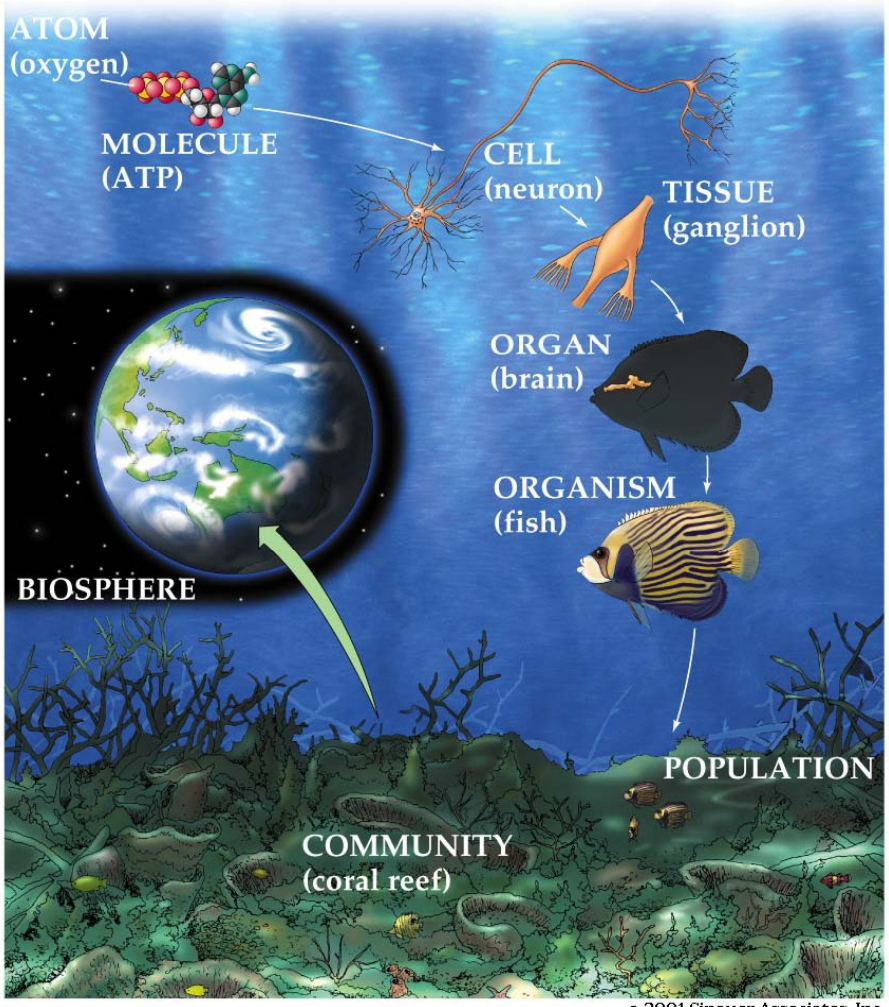
DNA
(Genotype)



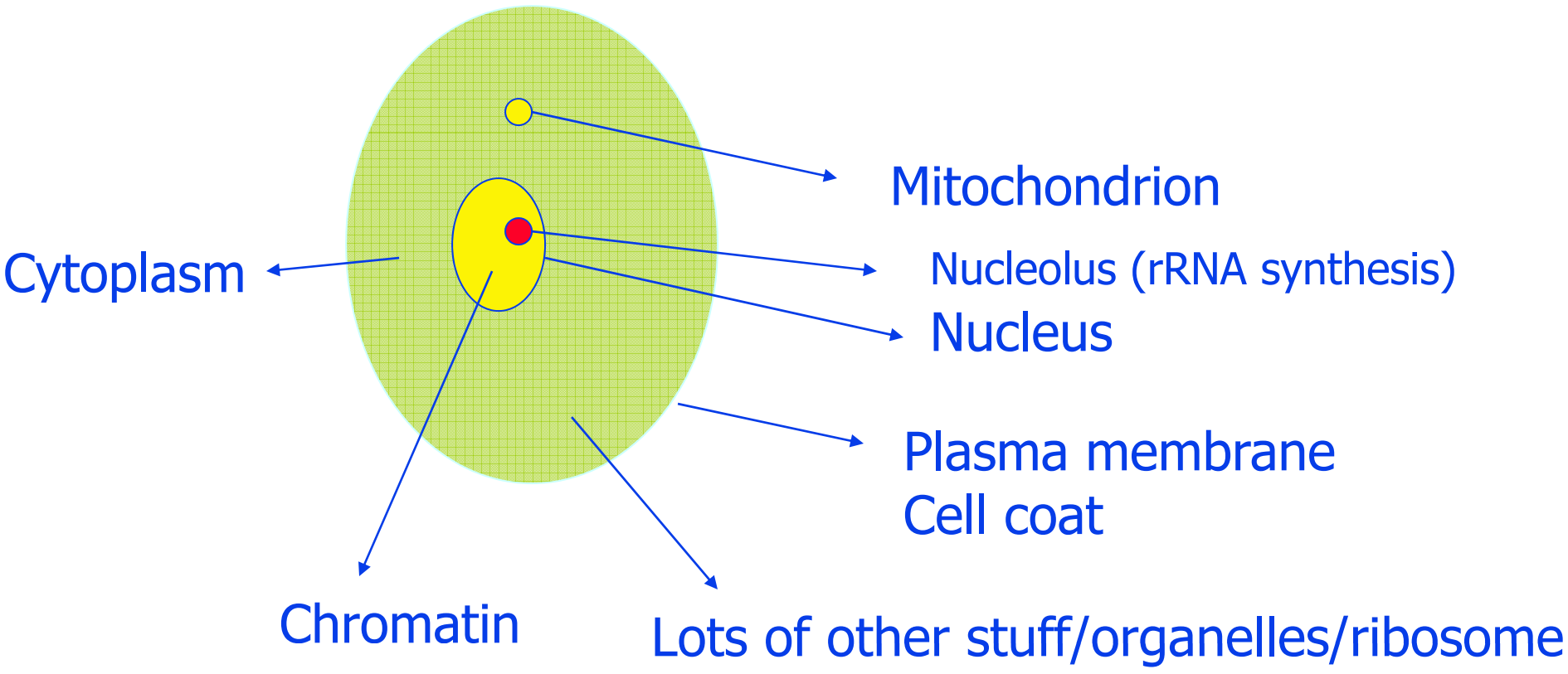
Protein

Phenotype

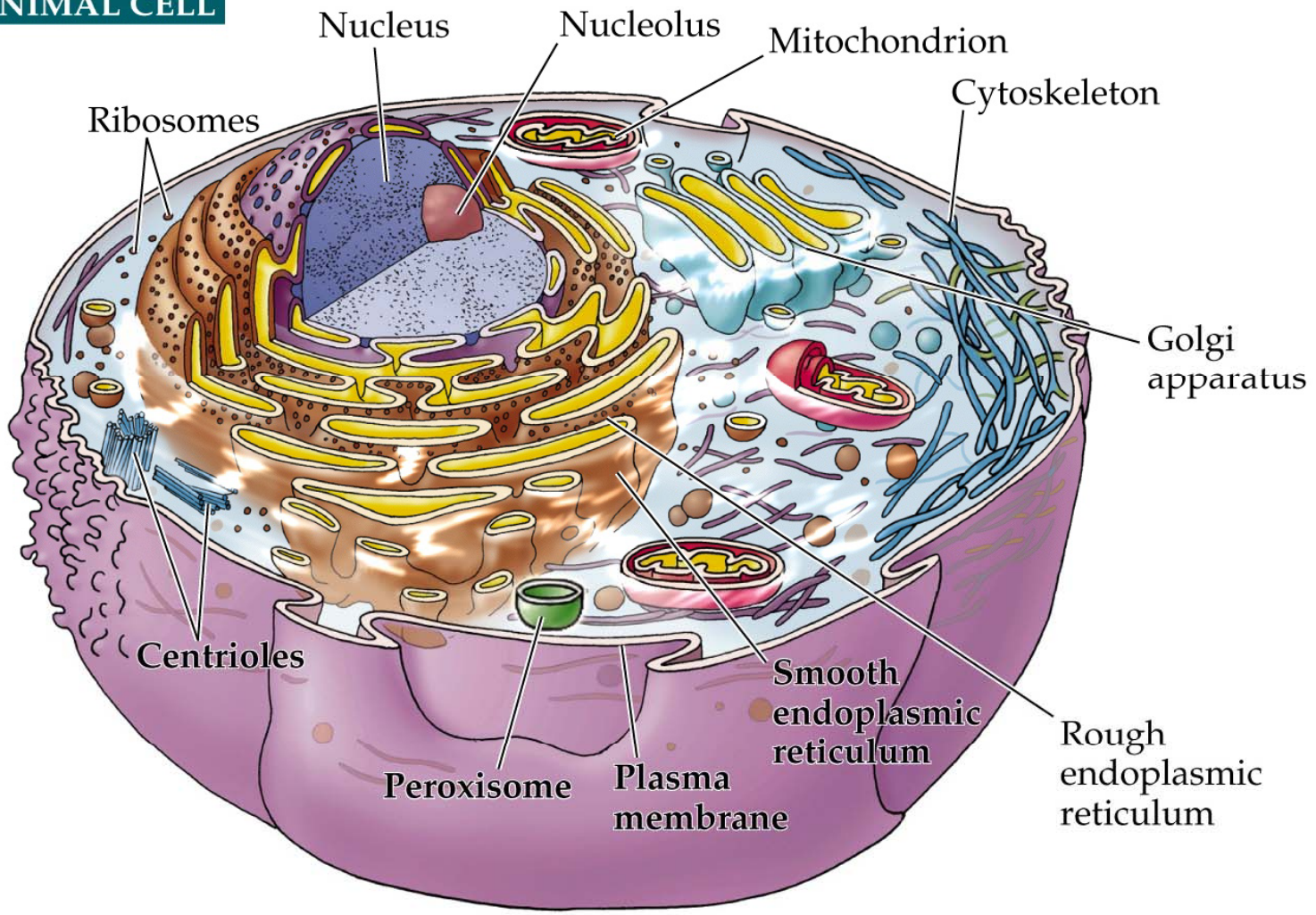
Scales of life



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
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aaagatgcagcggaaggtaaaacgttcaatggcgaattaaaaggcgtattaggttacact
gaagatgctgttgtttctactgacttcaacggttgtgctttaacttctgtatttgatgca
gacgctggtatcgcattaactgattctttcgttaaattggtatc . . .

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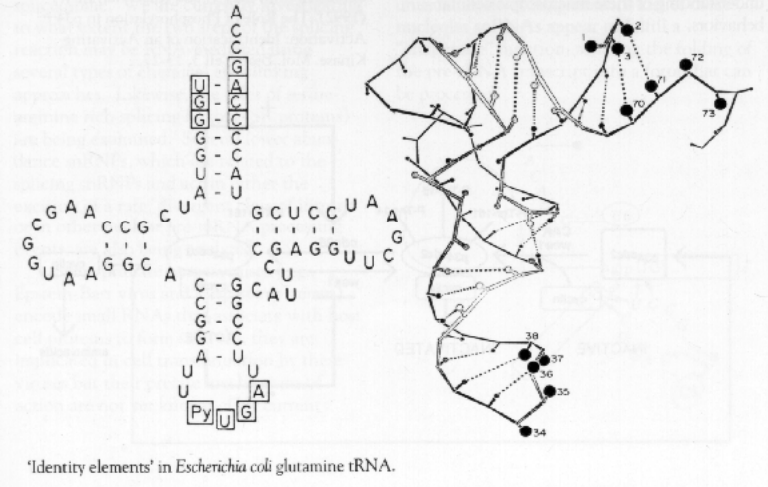

Molecular Biology Information: Protein Sequence

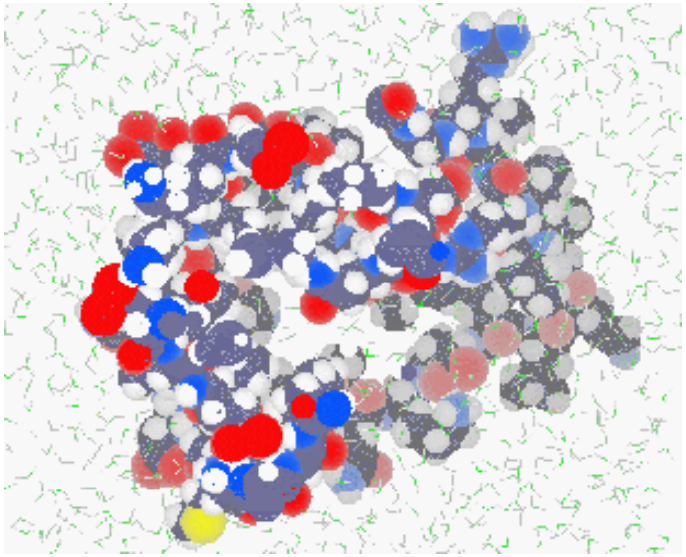
- 20 letter alphabet
  - ACDEFGHIKLMNPQRSTVWY but not BJOUXZ
- Strings of ~300 aa in an average protein (in bacteria),
  ~200 aa in a domain
- ~1M known protein sequences

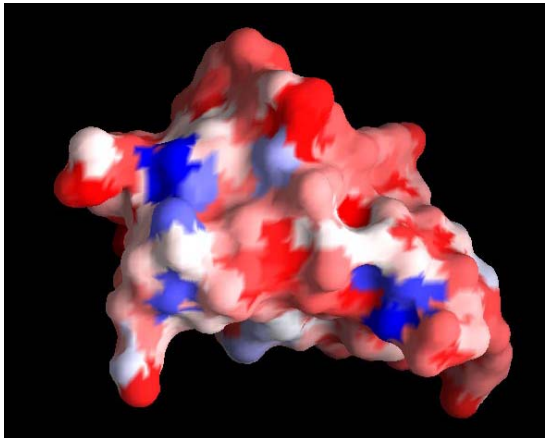
```
d1dhfa_ LNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMTTTSSVEGKQ-NLVIMGKKTWFSI
d8dfr__ LNSIVAVCQNMGIGKDGNLPWPPLRNEYKYFQRMTSTSHVEGKQ-NAVIMGKKTWFSI
d4dfra_ ISLIAALAVDRVIGMENAMPWN-LPADLAWFKRNTL--------NKPVIMGRHTWESI
d3dfr__ TAFLWAQDRDGLIGKDGHLPWH-LPDDLHYFRAQTV--------GKIMVVGRRTYESF

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







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

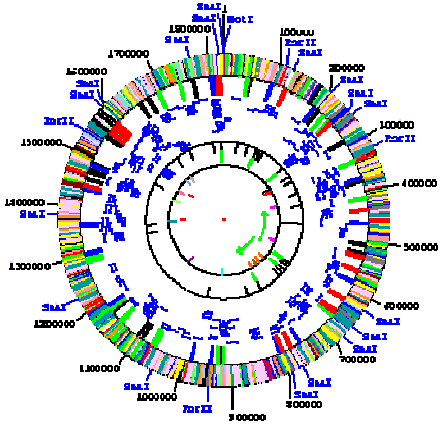
- One gene encodes one* protein.
- Like a program, it starts with start codon (e.g. ATG), then each three code one amino acid. Then a stop codon (e.g. TGA) signifies end of the gene.
- Sometimes, in the middle of a (eukaryotic) gene, there are introns that are spliced out (as junk) during transcription.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

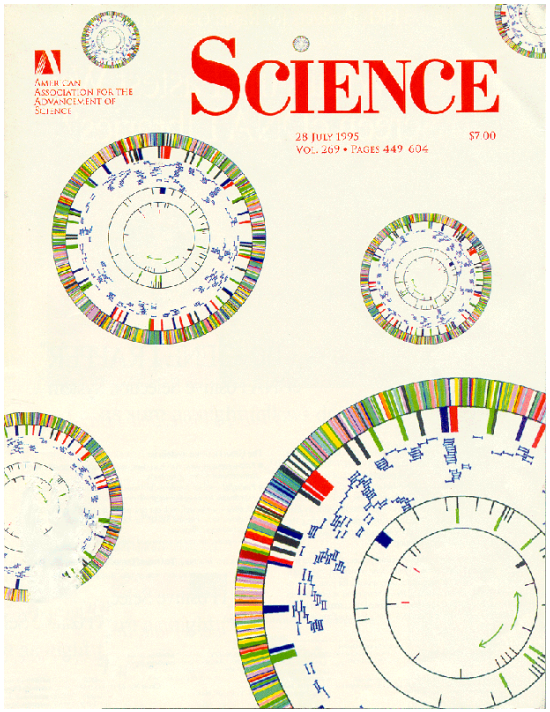


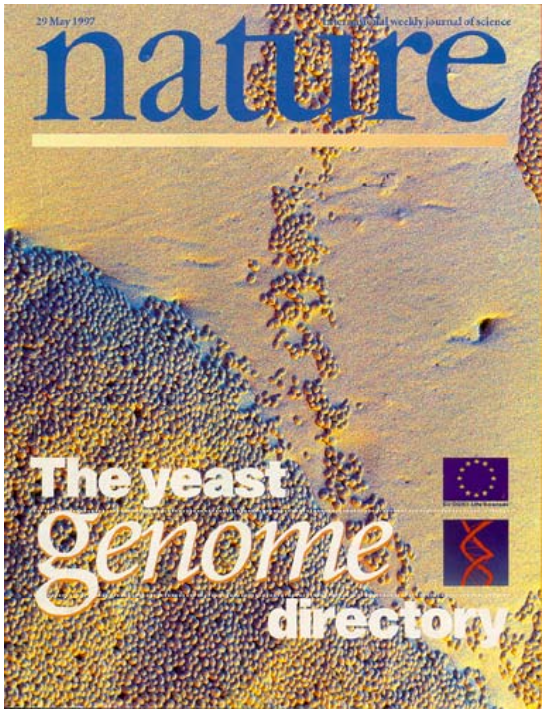
Genome sequences now accumulate so quickly that, in less than a week, a single laboratory can produce more bits of data than Shakespeare managed in a lifetime, although the latter make better reading.

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

1995

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





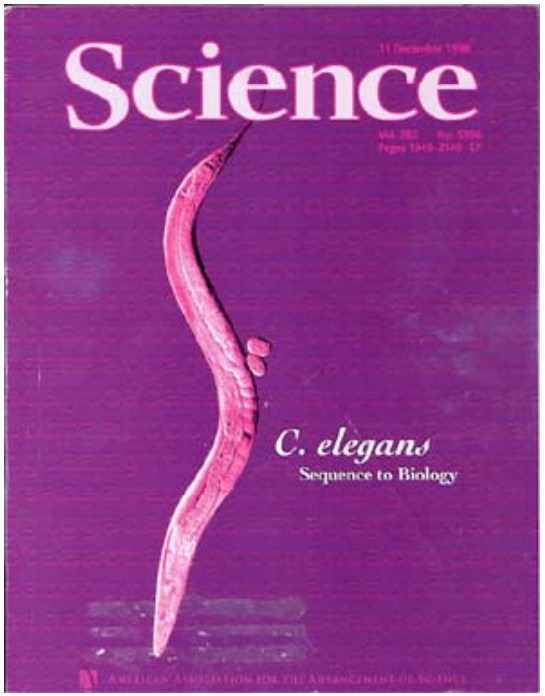
Genomes highlight the Finiteness of the "Parts" in Biology

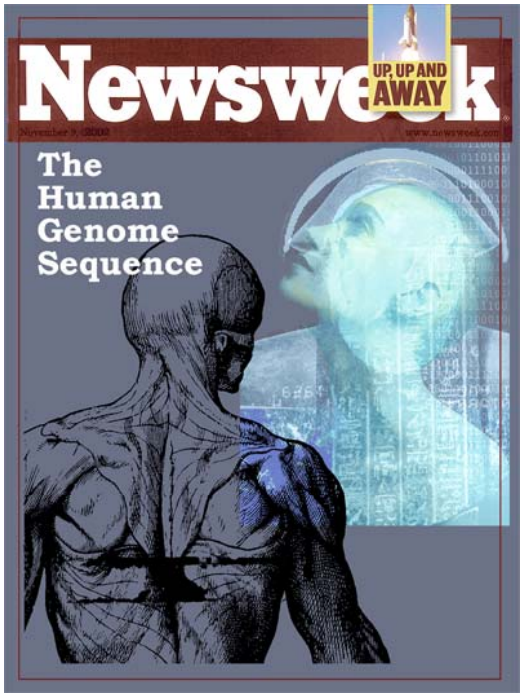
1997

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

1998

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





2000?

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


Human Genome Project
CHEMISTRY
BIOLOGY
PHYSICS
ETHICS
INFORMATICS
ENGINEERING
RESOURCES FOR THE BIOLOGY CENTURY
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

Frank C. P. Holstege,* Ezra G. Jennings,*†
John J. Wyrick,*† Tong Ihn Lee,*†
Christoph J. Hengartner,*† Michael R. Green,‡
Todd R. Golub,*§ Eric S. Lander,*†
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University of Massachusetts Medical Center
Worcester, Massachusetts 01605
§Dana-Farber Cancer Institute and
Harvard Medical School
Boston, Massachusetts 02115

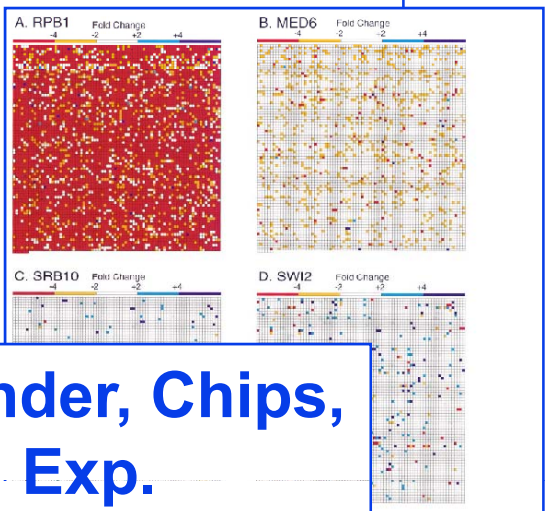


Figure 2. Genome-Wide Expression Data for Selected Components of the RNA Polymerase II Holoenzyme

Young/Lander, Chips, Abs. Exp.

Brown, μarray, Rel. Exp. over Timecourse

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

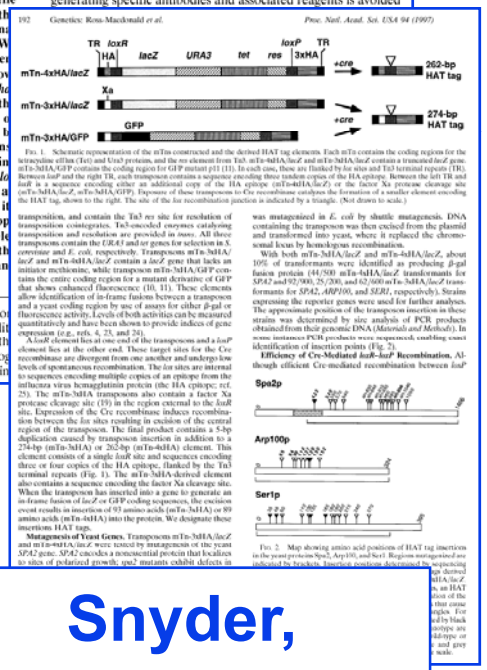
A multipurpose transposon system for analyzing protein production, localization, and function in *Saccharomyces cerevisiae*

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** antibody into a protein of interest, the time and expense of generating specific antibodies and associated reagents is avoided **product typically involves determining the expression profile of the gene, the subcellular location of the protein, and the phenotype of a null strain lacking the protein. Conditional alleles of the gene are often created as an additional tool. We have developed a multifunctional, transposon-based system that simultaneously generates constructs for all the above analyses and is suitable for mutagenesis of any given *Saccharomyces cerevisiae* gene. Depending on the transposon used, the yeast gene is fused to a coding region for β-galactosidase or green fluorescent protein. Gene expression can therefore be monitored by chemical or fluorescence assays. The transposons create insertion mutations in the target gene, allowing phenotypic analysis. The transposon can be reduced by *cre–lox* site-specific recombination to a smaller element that leaves a single epitope tag inserted in the encoded protein. In addition to its utility for a variety of immunodetection purposes, the epitope tag element also has the potential to create conditional alleles of the target gene. We demonstrate these features of the transposons by mutagenesis of the *SPA2*, *ARP100*, *SER1*, and *BDF1* genes.**

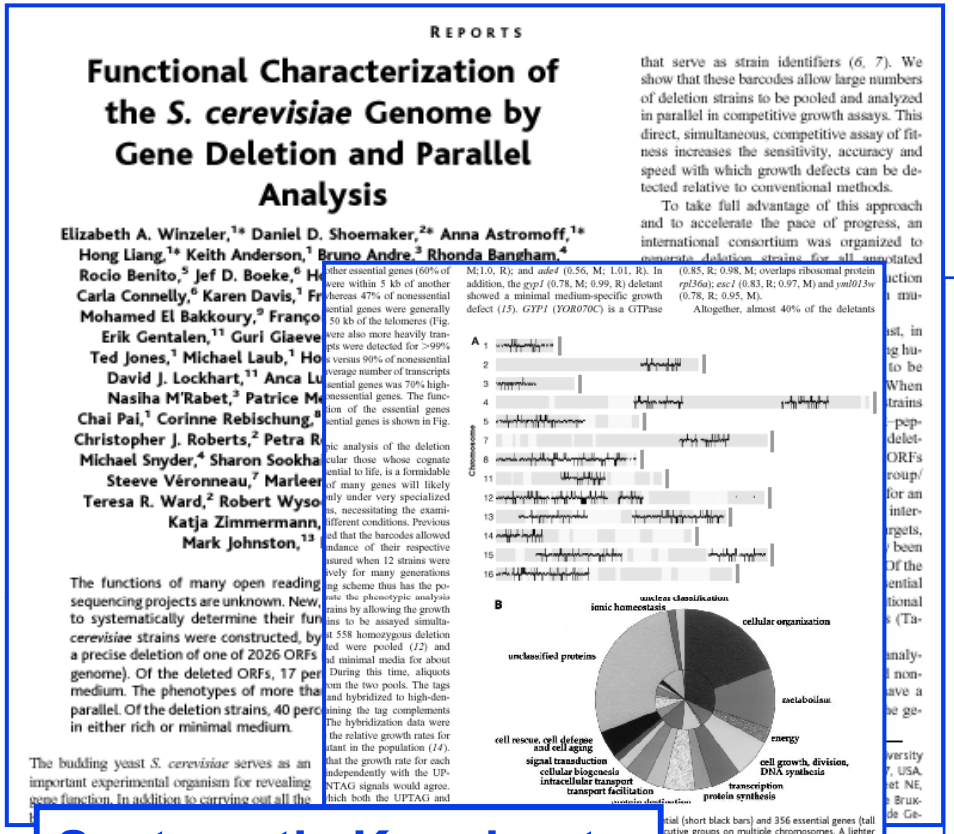
The yeast *Saccharomyces cerevisiae* has proved of great importance in characterizing basic biological processes. This utility can only become more marked now that the sequence of the entire yeast genome has been obtained, and additional homologs of yeast genes are identified in other organisms (1).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



Snyder, Transposons, Protein Exp.

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

Other Whole-Genome Experiments



REPORTS

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

Elizabeth A. Winzeler,[1]* Daniel D. Shoemaker,[2]* Anna Astromoff,[1]* Hong Liang,[1]* Keith Anderson,[1] Bruno Andre,[5] Rhonda Bangham,[4] Rocio Benito,[5] Jef D. Boeke,[6] H… Carla Connelly,[6] Karen Davis,[1] Fr… Mohamed El Bakkoury,[9] Franço… Erik Gentalen,[11] Guri Giaeve… Ted Jones,[1] Michael Laub,[1] Ho… David J. Lockhart,[11] Anca Lu… Nasiha M'Rabet,[3] Patrice M… Chai Pai,[1] Corinne Rebischung,[8] Christopher J. Roberts,[2] Petra R… Michael Snyder,[4] Sharon Sookha… Steeve Véronneau,[7] Marleen… Teresa R. Ward,[2] Robert Wyso… Katja Zimmermann,[1] Mark Johnston,[13]

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

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

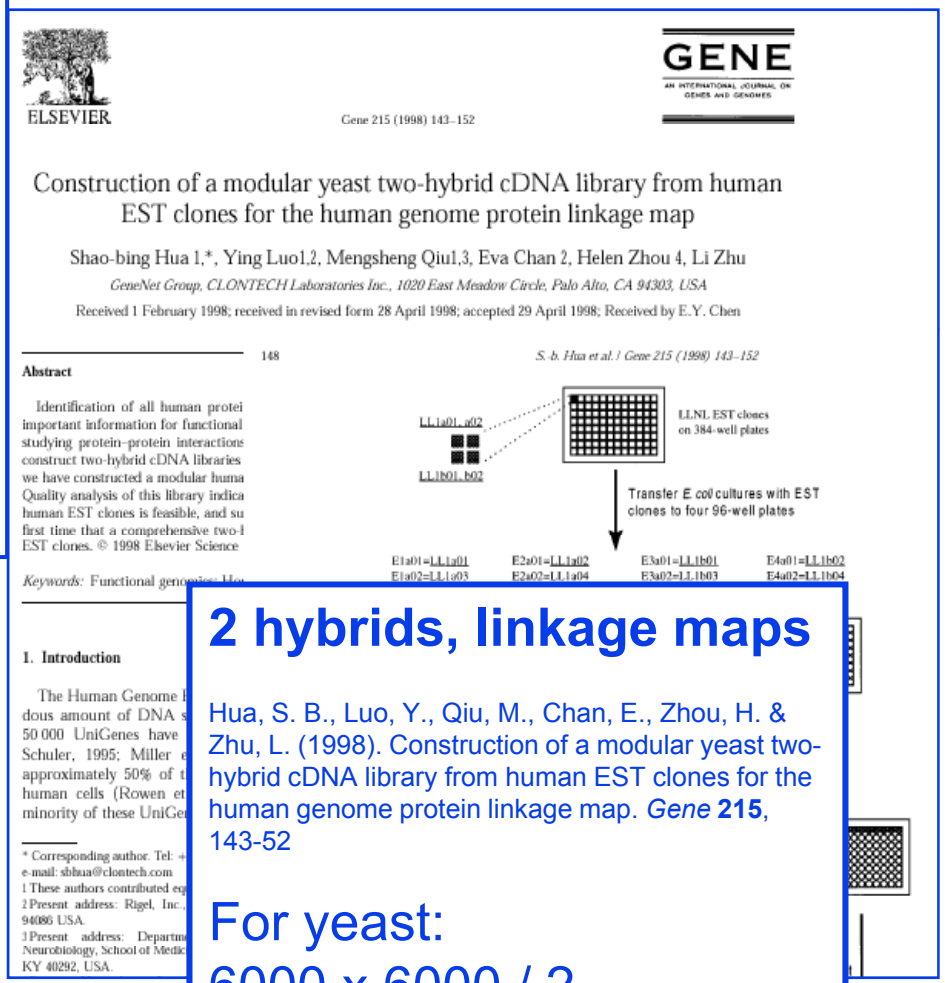
other essential genes (60% of were within 5 kb of another whereas 47% of nonessential sential genes were generally 50 kb of the telomeres (Fig. were also more heavily tran- pts were detected for >99% s versus 90% of nonessential average number of transcripts sential genes was 70% high- nessential genes.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

gic analysis of the deletion cular those whose cognate sential to life, is a formidable of many genes will likely nly under very specialized es, necessitating the exami- different conditions. Previous ed that the barcodes allowed ndance of their respective asured when 12 strains were vely for many generations ng scheme thus has the po- ntate 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*). that the growth rate for each independently with the UP- NTAG signals would agree. hich both the UPTAG and

tial (short black bars) and 356 essential genes (tall utive groups on multiple chromosomes. A lighter osomal 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

Shao-bing Hua 1,*, Ying Luo1,2, Mengsheng Qiu1,3, Eva Chan 2, Helen Zhou 4, Li Zhu

GeneNet Group, CLONTECH Laboratories Inc., 1020 East Meadow Circle, Palo Alto, CA 94303, USA

Received 1 February 1998; received in revised form 28 April 1998; accepted 29 April 1998; Received by E.Y. Chen

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…

* Corresponding author. Tel: … e-mail: shhua@clontech.com
1 These authors contributed eq…
2 Present address: Rigel, Inc., … 94086 USA.
3 Present address: Departm… Neurobiology, School of Medic… KY 40292, USA.

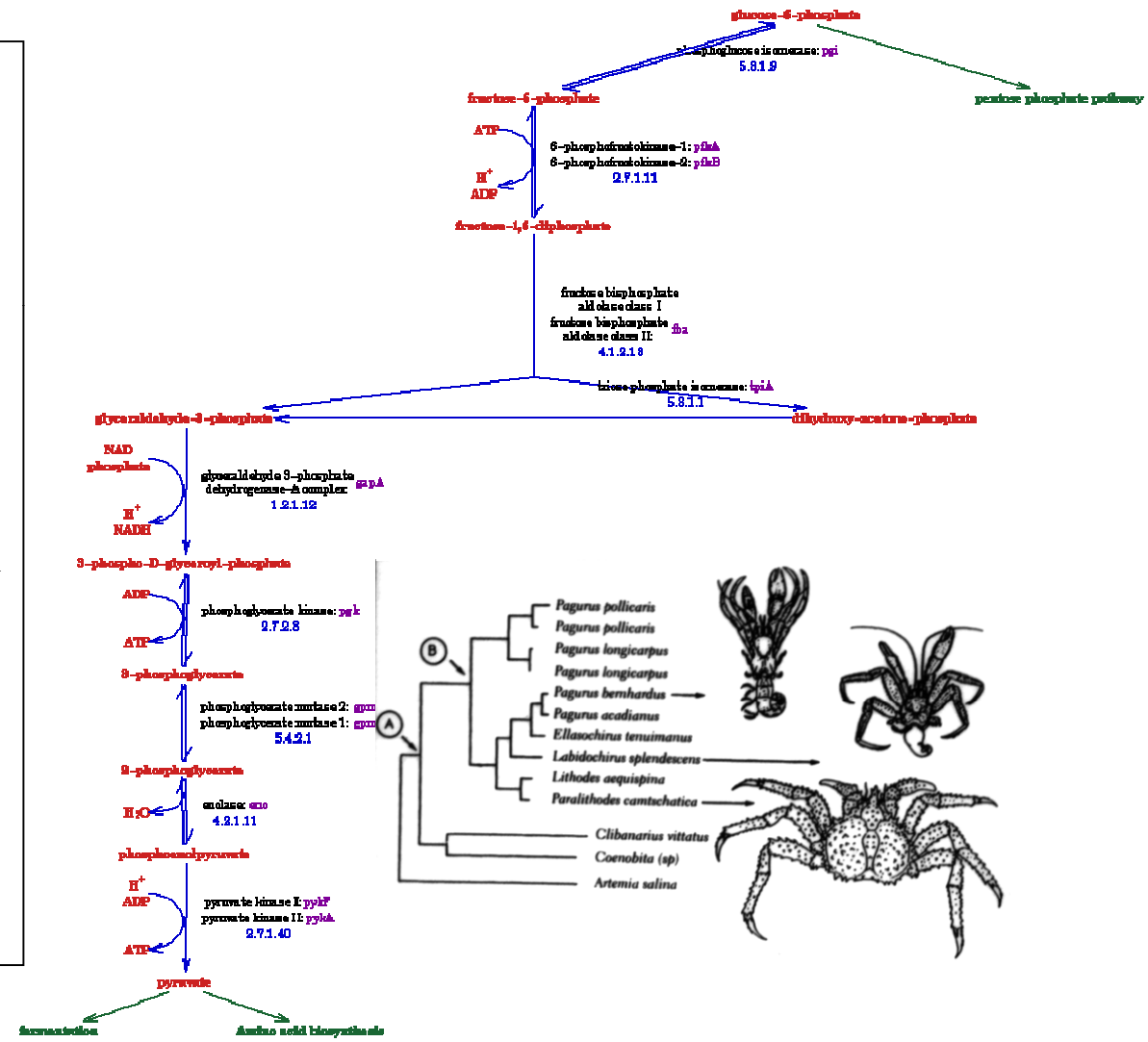
2 hybrids, linkage maps

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

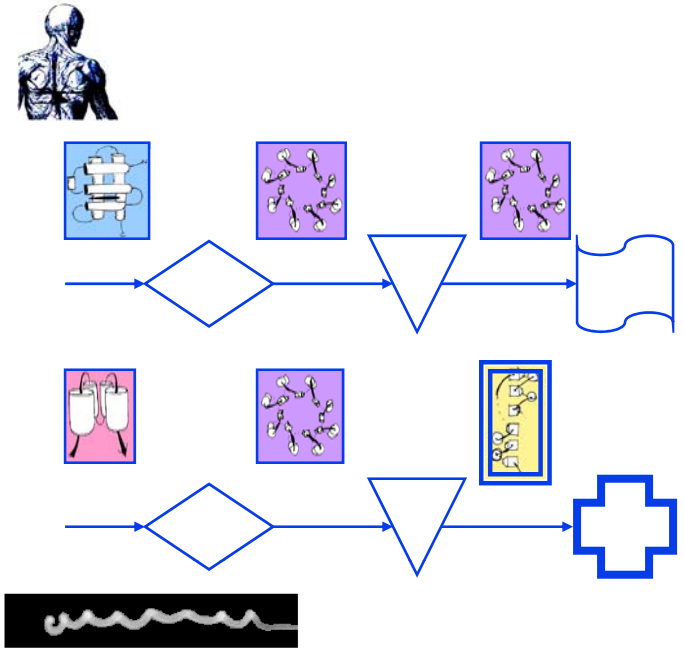
For yeast:
6000 x 6000 / 2
~ 18M interactions

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....



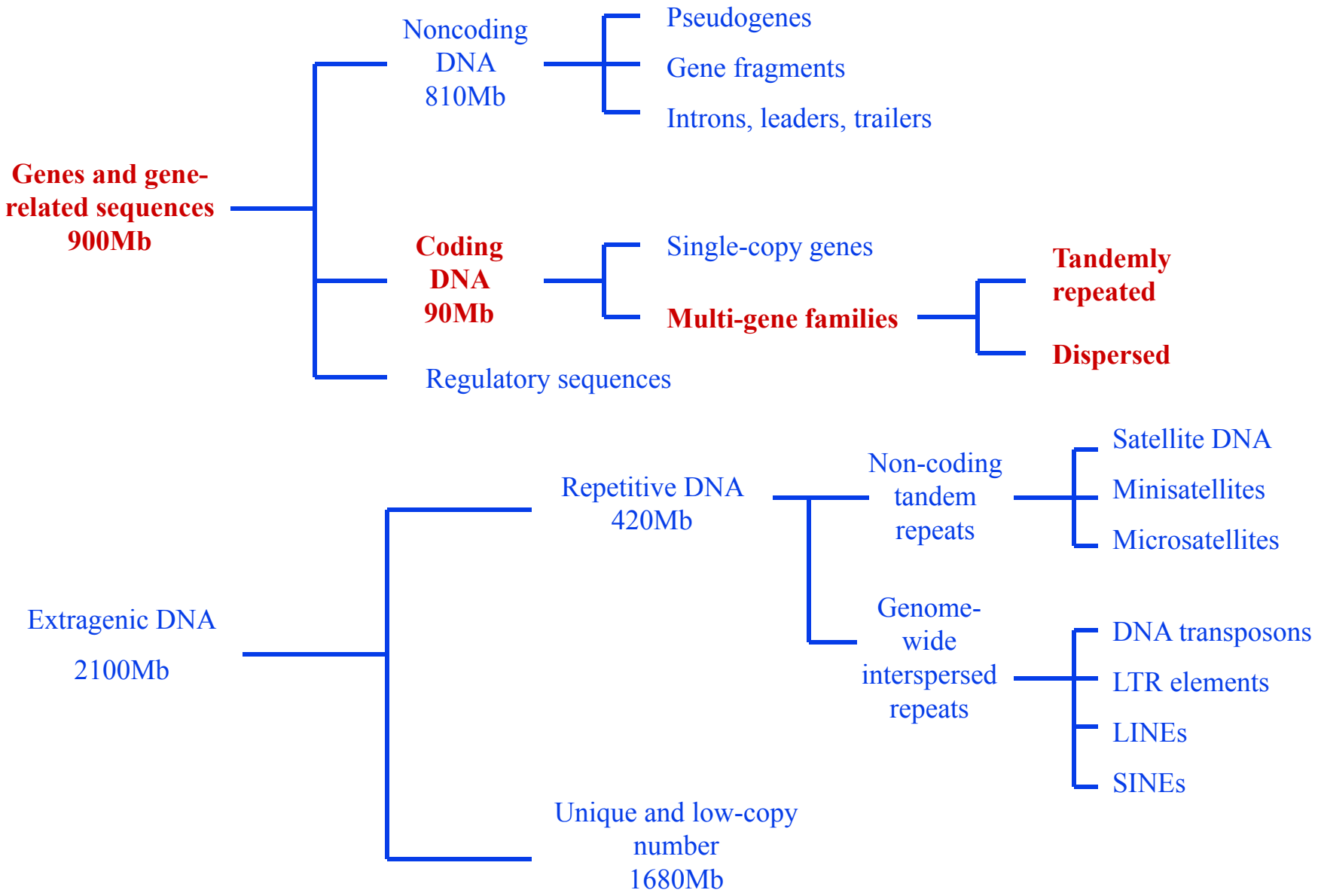
Organizing
Molecular Biology Information:
Redundancy and Multiplicity



- 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

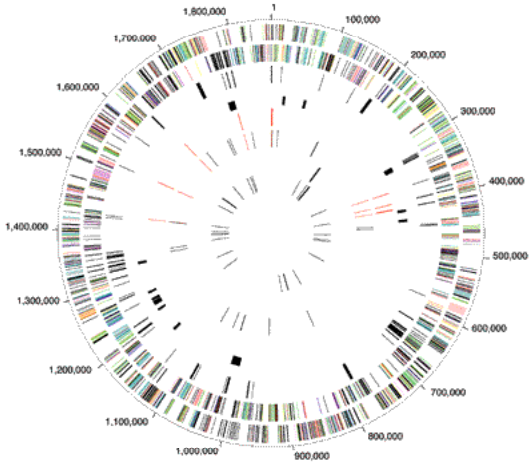


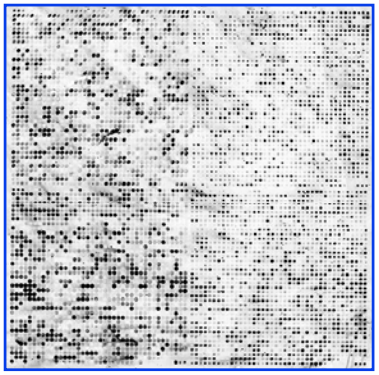
Where to get data?

- 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

Data

- 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

Scalability challenges

- As of December 2009, NAR online Database Collection, available at http://www.oxfordjournals.org/nar/database/a/, lists 1230 carefully selected databases covering various aspects of molecular and cell biology
  - 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

- Programming
- Algorithms
- Machine learning/Pattern recognition/AI
- Statistics & probability
- Mathematics