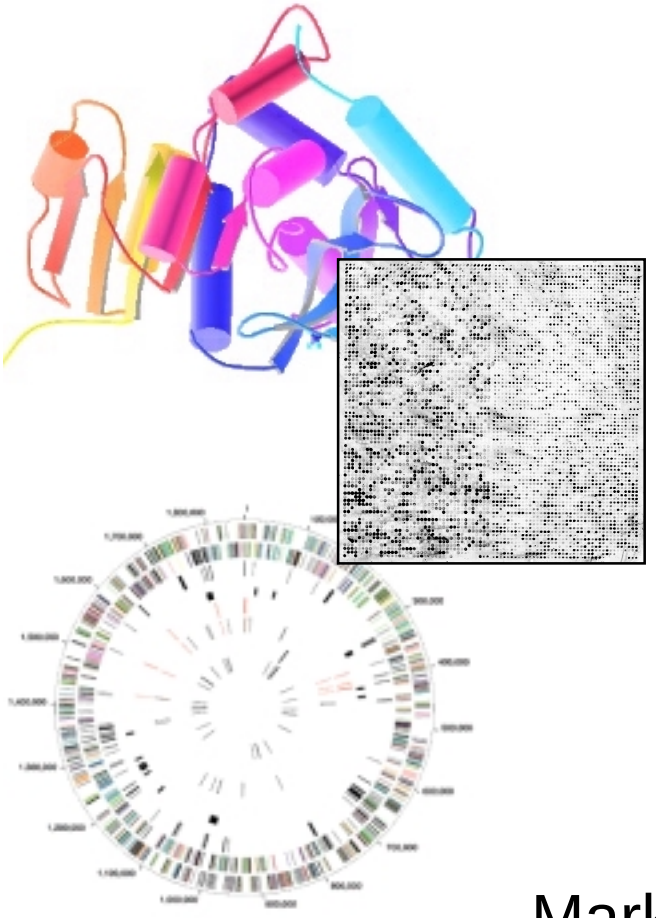
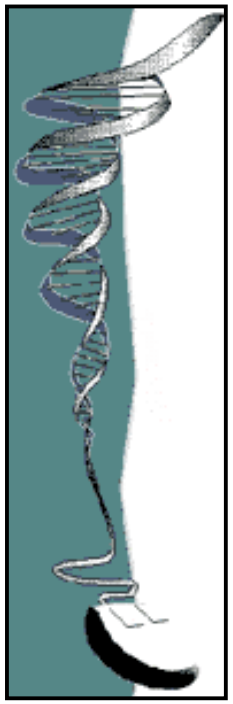
BIOINFORMATICS
Introduction

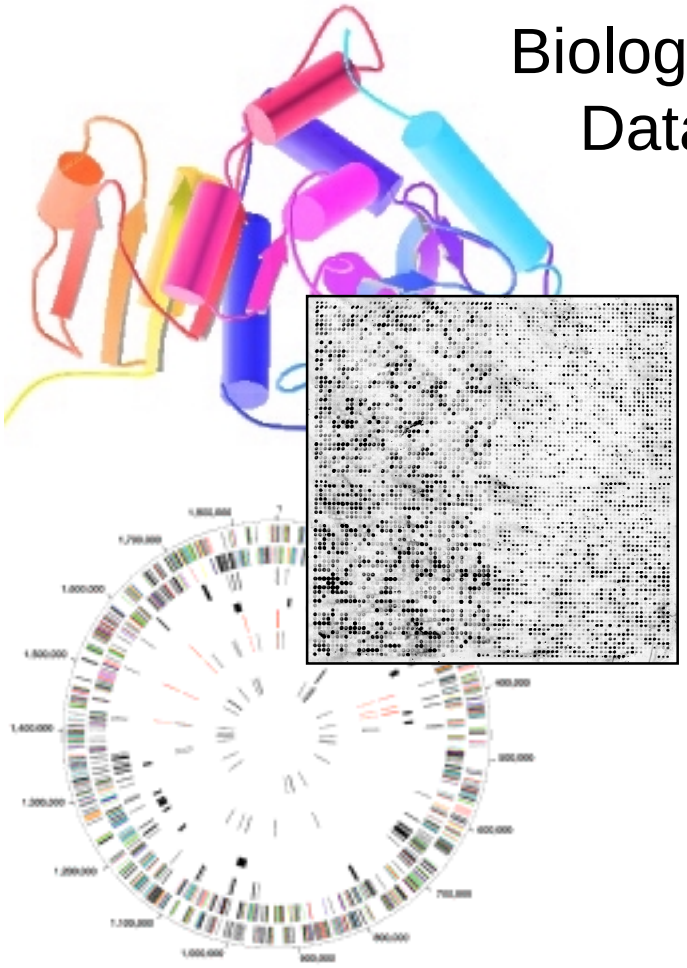




Mark Gerstein, Yale University

bioinfo.mbb.yale.edu/mbb452a

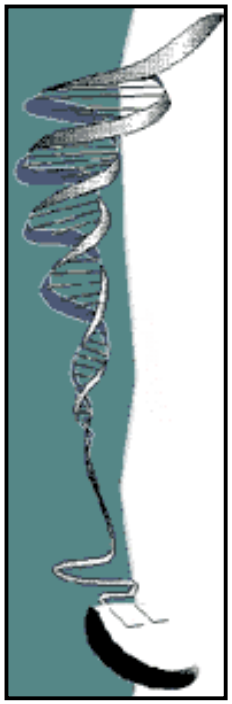
Bioinformatics



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 "MIS" for Molecular Biology Information

Molecular Biology: an Information Science

- Central Dogma of Molecular Biology

```
DNA
 -> RNA
  -> Protein

   -> Phenotype
    -> DNA
```

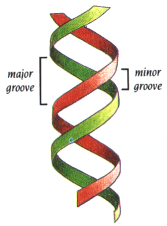
- Molecules
  - ◊ Sequence, Structure, Function
- Processes
  - ◊ Mechanism, Specificity, Regulation

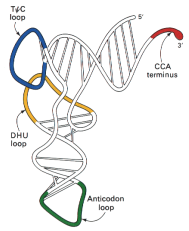
- Central Paradigm for Bioinformatics

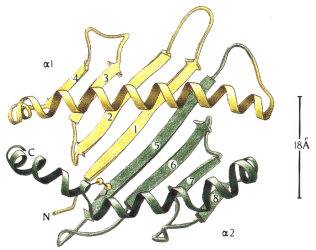
```
Genomic Sequence Information
 -> mRNA (level)
  -> Protein Sequence
   -> Protein Structure
    -> Protein Function
     -> Phenotype
```

- Large Amounts of Information
  - ◊ Standardized
  - ◊ Statistical

(idea from D Brutlag, Stanford, graphics from S Strobel)







•Most cellular functions are performed or facilitated by proteins.

•Primary biocatalyst

•Cofactor transport/storage

•Mechanical motion/support

•Immune protection

•Control of growth/differentiation

•Genetic material

•Information transfer (mRNA)
•Protein synthesis (tRNA/mRNA)
•Some catalytic activity

Molecular Biology Information - DNA

- Raw DNA Sequence
  - ◊ Coding or Not?
  - ◊ Parse into genes?
  - ◊ 4 bases: AGCT
  - ◊ ~1 K in a gene, ~2 M in genome

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


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

Molecular Biology Information: Protein Sequence

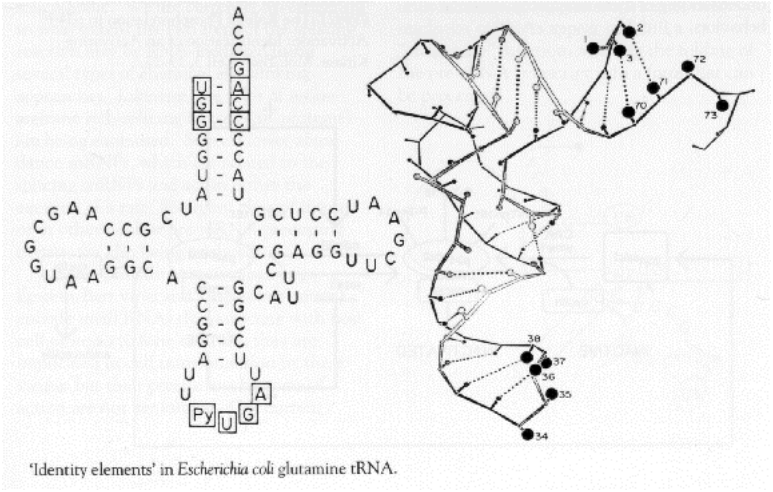
- 20 letter alphabet
  - ◊ ACDEFGHIKLMNPQRSTVWY but not BJOUXZ
- Strings of ~300 aa in an average protein (in bacteria), ~200 aa in a domain
- ~200 K known protein sequences

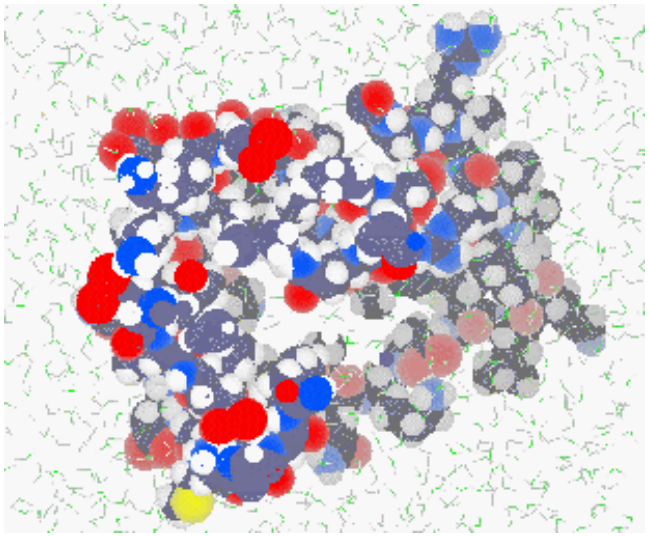
```
d1dhfa_ LNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMTTTSSVEGKQ-NLVIMGKKTWFSI
d8dfr__ LNSIVAVCQNMGIGKDGNLPWPPLRNEYKYFQRMTSTSHVEGKQ-NAVIMGKKTWFSI
d4dfra_ ISLIAALAVDRVIGMENAMPWN-LPADLAWFKRNTL--------NKPVIMGRHTWESI
d3dfr__ TAFLWAQDRDGLIGKDGHLPWH-LPDDLHYFRAQTV--------GKIMVVGRRTYESF

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

d1dhfa_ VPEKNRPLKGRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIVGGSSVYKEAMNHP
d8dfr__ VPEKNRPLKDRINIVLSRELKEAPKGAHYLSKSLDDALALLDSPELKSKVDMVWIVGGTAVYKAAMEKP
d4dfra_ ---G-RPLPGRKNIILS-SQPGTDDRV-TWVKSVDEAIAACGDVP------EIMVIGGGRVYEQFLPKA
d3dfr__ ---PKRPLPERTNVVLTHQEDYQAQGA-VVVHDVAAVFAYAKQHLDQ----ELVIAGGAQIFTAFKDDV

d1dhfa_ -PEKNRPLKGRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIVGGSSVYKEAMNHP
d8dfr__ -PEKNRPLKDRINIVLSRELKEAPKGAHYLSKSLDDALALLDSPELKSKVDMVWIVGGTAVYKAAMEKP
d4dfra_ -G---RPLPGRKNIILSSSQPGTDDRV-TWVKSVDEAIAACGDVPE-----  IMVIGGGRVYEQFLPKA
d3dfr__ -P--KRPLPERTNVVLTHQEDYQAQGA-VVVHDVAAVFAYAKQHLD----QELVIAGGAQIFTAFKDDV
```

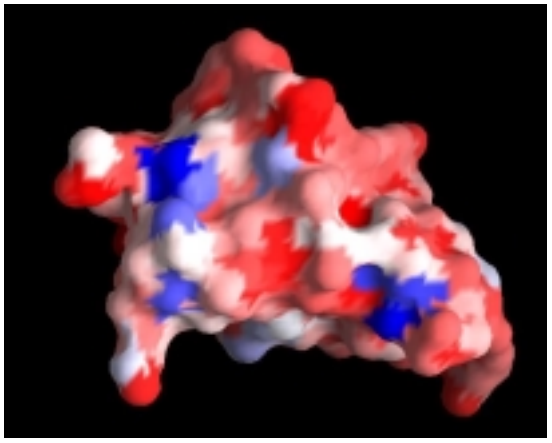
Molecular Biology Information: Macromolecular Structure

- DNA/RNA/Protein
  - ◊ Almost all protein

(RNA Adapted From D Soll Web Page,
Right Hand Top Protein from M Levitt web page)



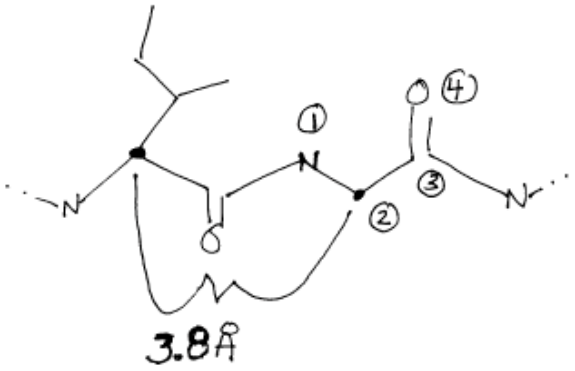




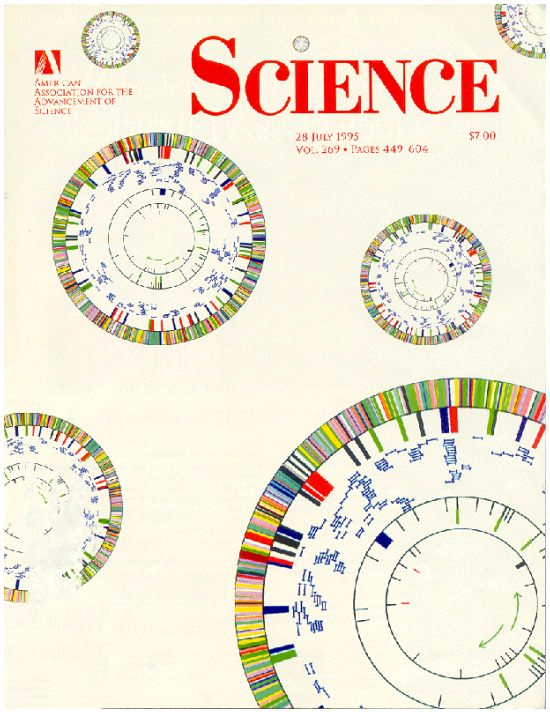
Molecular Biology Information: Protein Structure Details

- Statistics on Number of XYZ triplets
  - ◊ 200 residues/domain -> 200 CA atoms, separated by 3.8 A
  - ◊ Avg. Residue is Leu: 4 backbone atoms + 4 sidechain atoms, 150 cubic A
    - => ~1500 xyz triplets (=8x200) per protein domain
  - ◊ 10 K known domain, ~300 folds

```
ATOM      1  C   ACE     0       9.401  30.166  60.595  1.00 49.88      1GKY  67
ATOM      2  O   ACE     0      10.432  30.832  60.722  1.00 50.35      1GKY  68
ATOM      3  CH3 ACE     0       8.876  29.767  59.226  1.00 50.04      1GKY  69
ATOM      4  N   SER     1       8.753  29.755  61.685  1.00 49.13      1GKY  70
ATOM      5  CA  SER     1       9.242  30.200  62.974  1.00 46.62      1GKY  71
ATOM      6  C   SER     1      10.453  29.500  63.579  1.00 41.99      1GKY  72
ATOM      7  O   SER     1      10.593  29.607  64.814  1.00 43.24      1GKY  73
ATOM      8  CB  SER     1       8.052  30.189  63.974  1.00 53.00      1GKY  74
ATOM      9  OG  SER     1       7.294  31.409  63.930  1.00 57.79      1GKY  75
ATOM     10  N   ARG     2      11.360  28.819  62.827  1.00 36.48      1GKY  76
ATOM     11  CA  ARG     2      12.548  28.316  63.532  1.00 30.20      1GKY  77
ATOM     12  C   ARG     2      13.502  29.501  63.500  1.00 25.54      1GKY  78
...
ATOM   1444  CB  LYS   186      13.836  22.263  57.567  1.00 55.06      1GKY1510
ATOM   1445  CG  LYS   186      12.422  22.452  58.180  1.00 53.45      1GKY1511
ATOM   1446  CD  LYS   186      11.531  21.198  58.185  1.00 49.88      1GKY1512
ATOM   1447  CE  LYS   186      11.452  20.402  56.860  1.00 48.15      1GKY1513
ATOM   1448  NZ  LYS   186      10.735  21.104  55.811  1.00 48.41      1GKY1514
ATOM   1449  OXT LYS   186      16.887  23.841  56.647  1.00 62.94      1GKY1515
TER    1450      LYS   186                                              1GKY1516
```

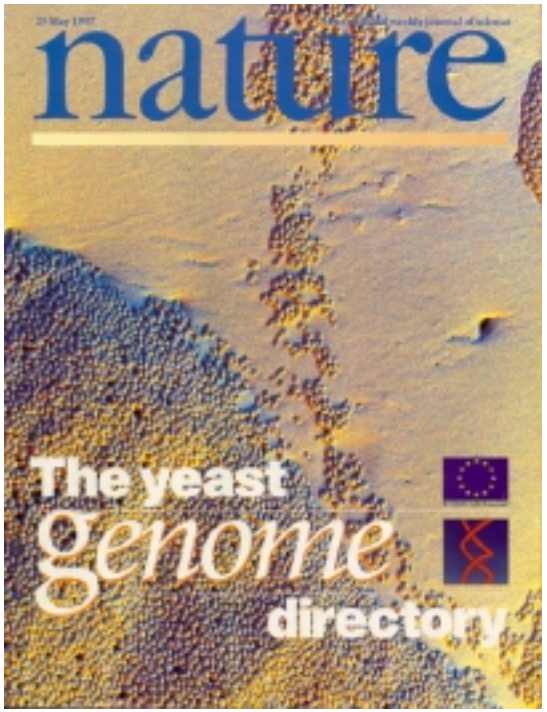


Genomes highlight the **Finiteness** of the World of Sequences



1995

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



1997

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

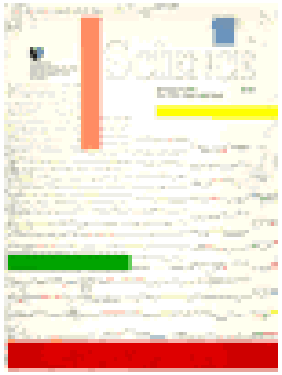
1998

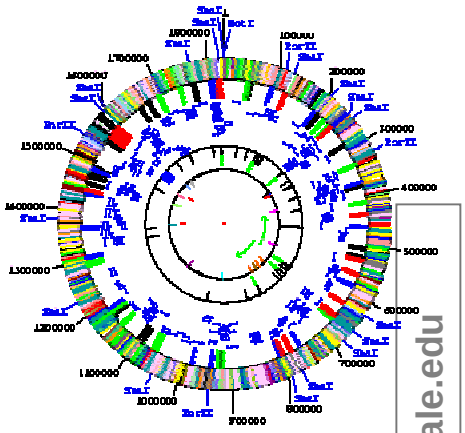
Animal, ~100 Mb, ~20K genes [*Science* **282**: 1945]

2000?

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

Molecular Biology Information: Whole Genomes





- The Revolution Driving Everything

  Fleischmann, R. D., Adams, M. D., White, O., Clayton, R. A., Kirkness, E. F., Kerlavage, A. R., Bult, C. J., Tomb, J. F., Dougherty, B. A., Merrick, J. M., McKenney, K., Sutton, G., Fitzhugh, W., Fields, C., Gocayne, J. D., Scott, J., Shirley, R., Liu, L. I., Glodek, A., Kelley, J. M., Weidman, J. F., Phillips, C. A., Spriggs, T., Hedblom, E., Cotton, M. D., Utterback, T. R., Hanna, M. C., Nguyen, D. T., Saudek, D. M., Brandon, R. C., Fine, L. D., Fritchman, J. L., Fuhrmann, J. L., Geoghagen, N. S. M., Gnehm, C. L., McDonald, L. A., Small, K. V., Fraser, C. M., Smith, H. O. & Venter, J. C. (1995). "Whole-genome random sequencing and assembly of Haemophilus influenzae rd." *Science* 269: 496-512.

  (Picture adapted from TIGR website, http://www.tigr.org)

- Integrative Data

  1995, HI (bacteria): 1.6 Mb & 1600 genes done

  1997, yeast: 13 Mb & ~6000 genes for yeast

  1998, worm: ~100Mb with 19 K genes

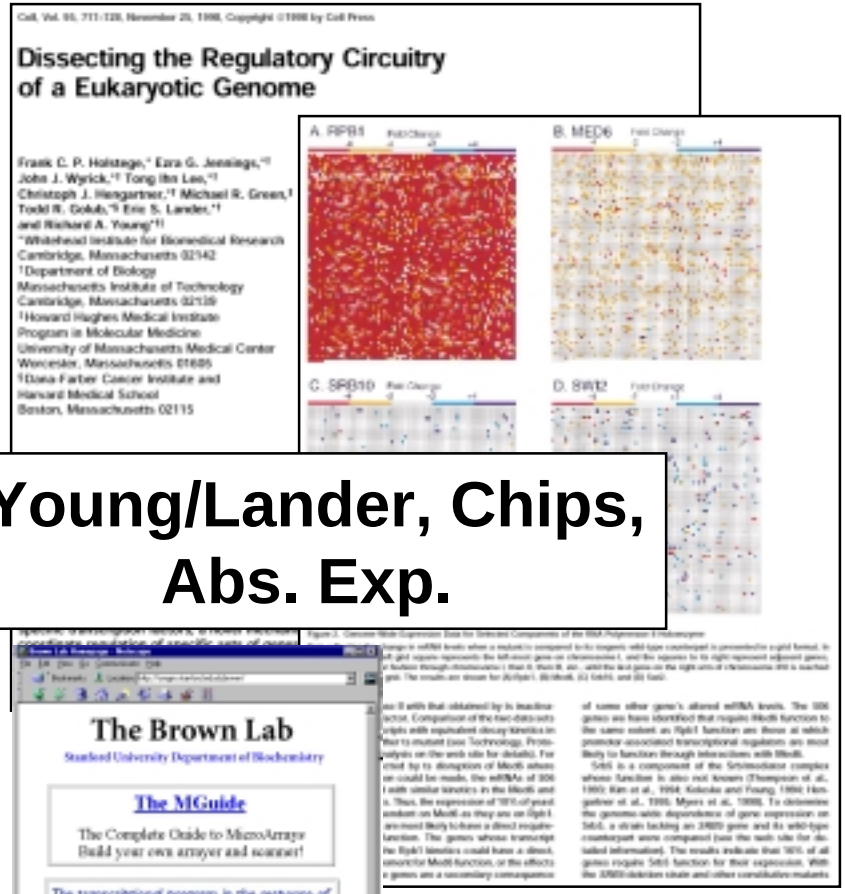
  1999: >30 completed genomes!

  2003, human: 3 Gb & 100 K genes...

Genome sequence 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)

Gene Expression Datasets: the Transcriptosome


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,*† and Richard A. Young*†

*Whitehead Institute for Biomedical Research, Cambridge, Massachusetts 02142
†Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139
‡Howard Hughes Medical Institute, Program in Molecular Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts 01605
§Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts 02115

Young/Lander, Chips, Abs. Exp.

The Brown Lab

Stanford University Department of Biochemistry

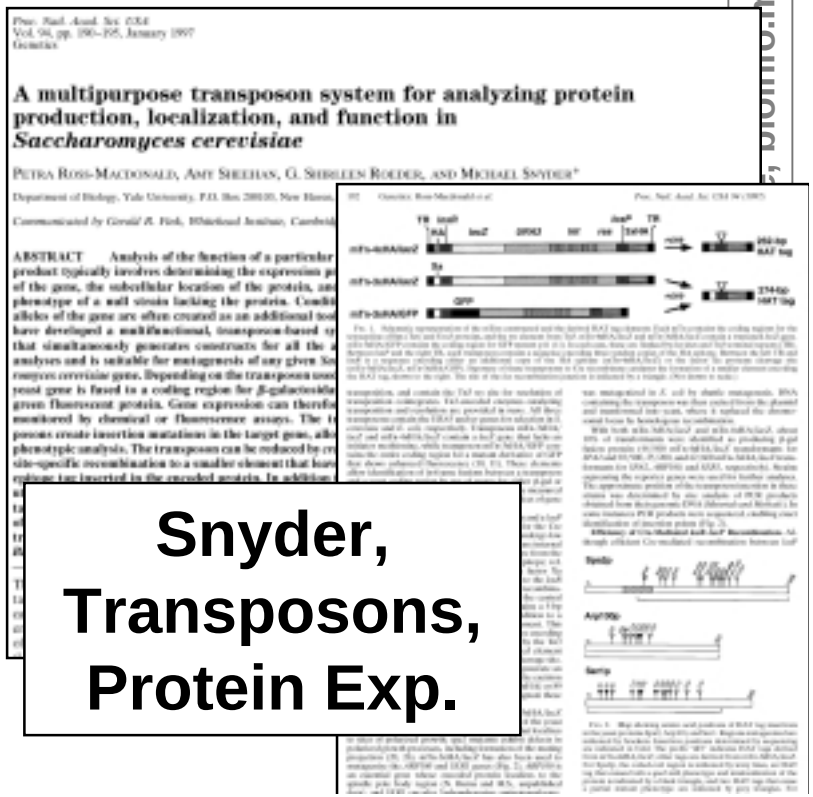
The MGuide

The Complete Guide to MicroArrays
Build your own arrayer and scanner!

The transcriptional program in the response of human fibroblasts to serum

Brown, μarray, Rel. Exp. over Timecourse

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


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*

Snyder, Transposons, Protein Exp.

http://bioinfo.mbb.yale.edu

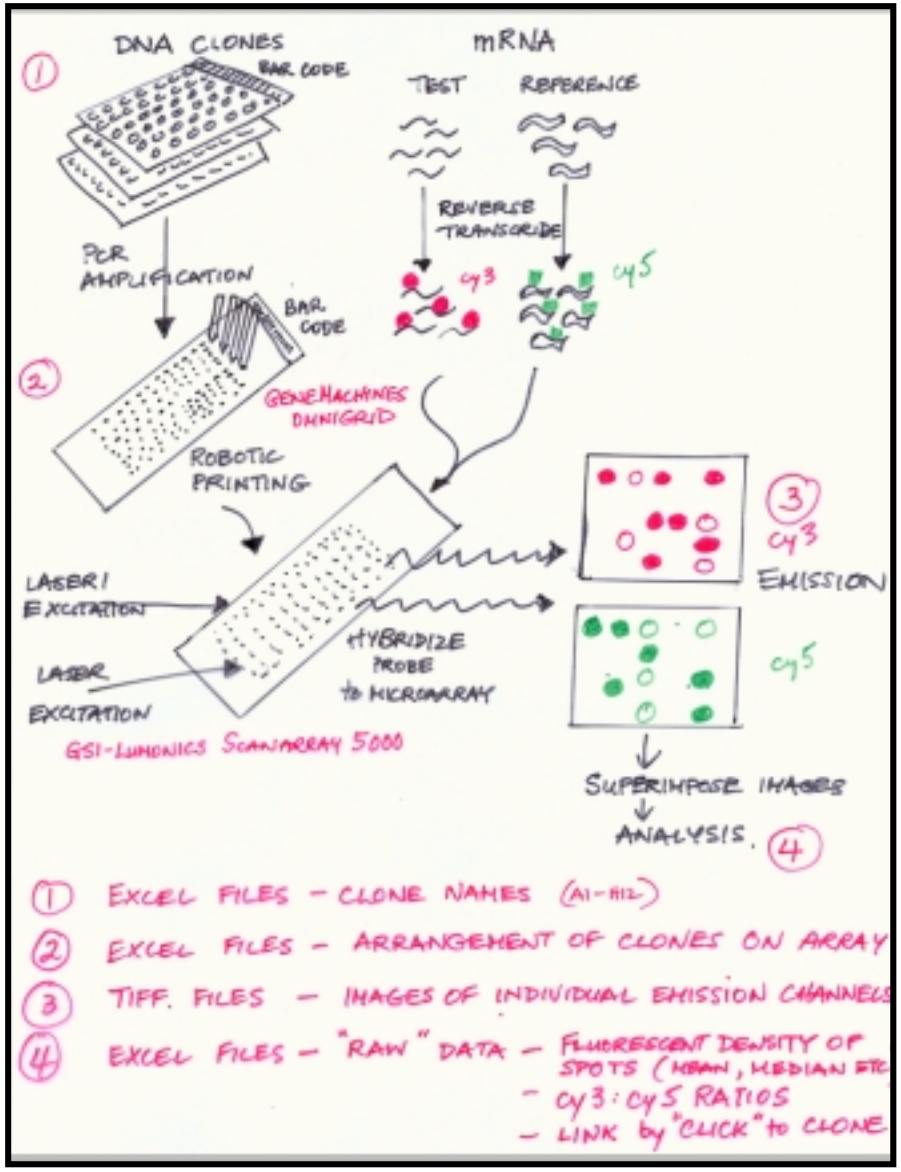
Array Data

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

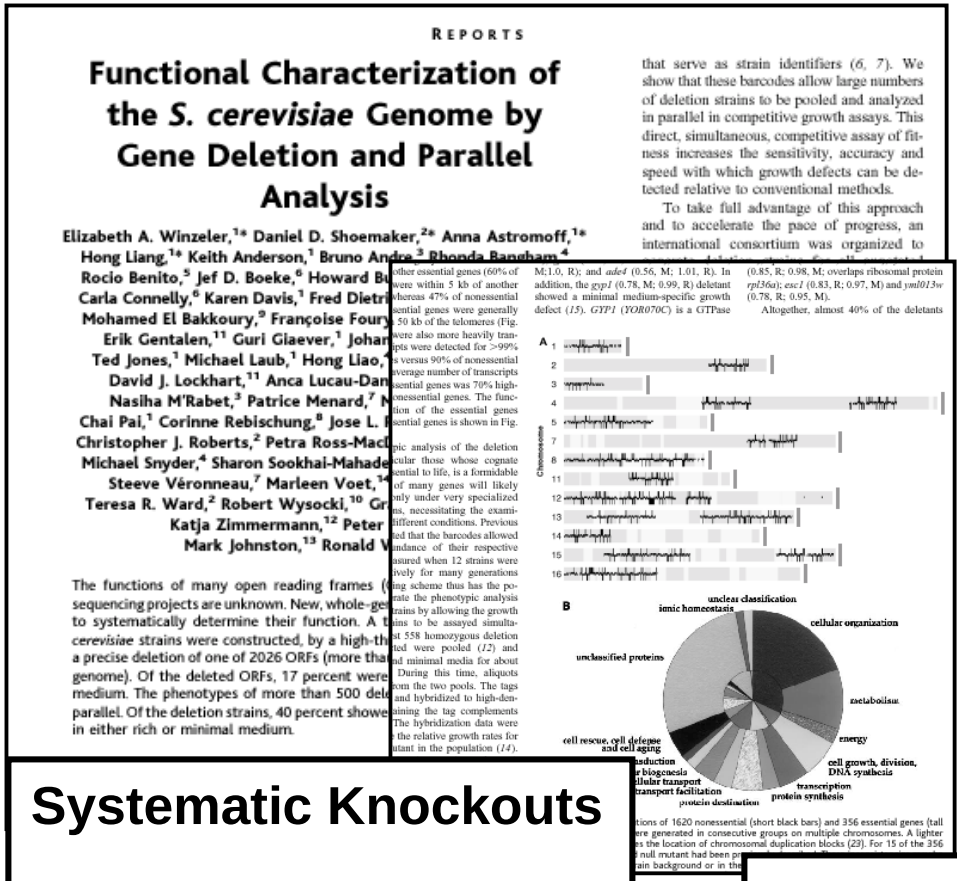
at 10 time points,
6000 x 10 = 60K floats

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

Elizabeth A. Winzeler,[1]* Daniel D. Shoemaker,[2]* Anna Astromoff,[1]* Hong Liang,[1]* Keith Anderson,[1] Bruno Andre,[3] Rhonda Bangham,[4] Rocio Benito,[5] Jef D. Boeke,[6] Howard Bu[1] Carla Connelly,[6] Karen Davis,[1] Fred Dietri[1] Mohamed El Bakkoury,[9] Françoise Foury,[9] Erik Gentalen,[11] Guri Giaever,[1] Johar[1] Ted Jones,[1] Michael Laub,[1] Hong Liao,[1] David J. Lockhart,[11] Anca Lucau-Dan[1] Nasiha M'Rabet,[3] Patrice Menard,[7] N[1] Chai Pai,[1] Corinne Rebischung,[8] Jose L. R[1] Christopher J. Roberts,[2] Petra Ross-Mack[1] Michael Snyder,[4] Sharon Sookhai-Mahade[1] Steeve Véronneau,[7] Marleen Voet,[14] Teresa R. Ward,[2] Robert Wysocki,[10] Gr[1] Katja Zimmermann,[12] Peter [1] Mark Johnston,[13] Ronald W[1]

The functions of many open reading frames (... sequencing projects are unknown. New, whole-ge... to systematically determine their function. A t... *cerevisiae* strains were constructed, by a high-th... a precise deletion of one of 2026 ORFs (more tha... genome). Of the deleted ORFs, 17 percent were ... medium. The phenotypes of more than 500 dele... parallel. Of the deletion strains, 40 percent showe... in either rich or minimal medium.

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

other essential genes (60% of ... were within 5 kb of another ... whereas 47% of nonessential ... essential genes were generally ... 50 kb of the telomeres (Fig. ... were also more heavily tran... ...pts were detected for >99% ... versus 90% of nonessential ... average number of transcripts ... essential genes was 70% high... ...nonessential genes. The func... ...tion of the essential genes ... essential 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 ... only under very specialized ... ...ns, necessitating the exami... different conditions. Previous ... ...ed that the barcodes allowed ... ...undance of their respective ... ...sured when 12 strains were ... ...ively for many generations ... ...ing scheme thus has the po... ...rate the phenotypic analysis ... ...strains by allowing the growth ... ...ains 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 ... ...utant in the population (*14*).

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*). *GTP1* (*YOR070C*) is a GTPase

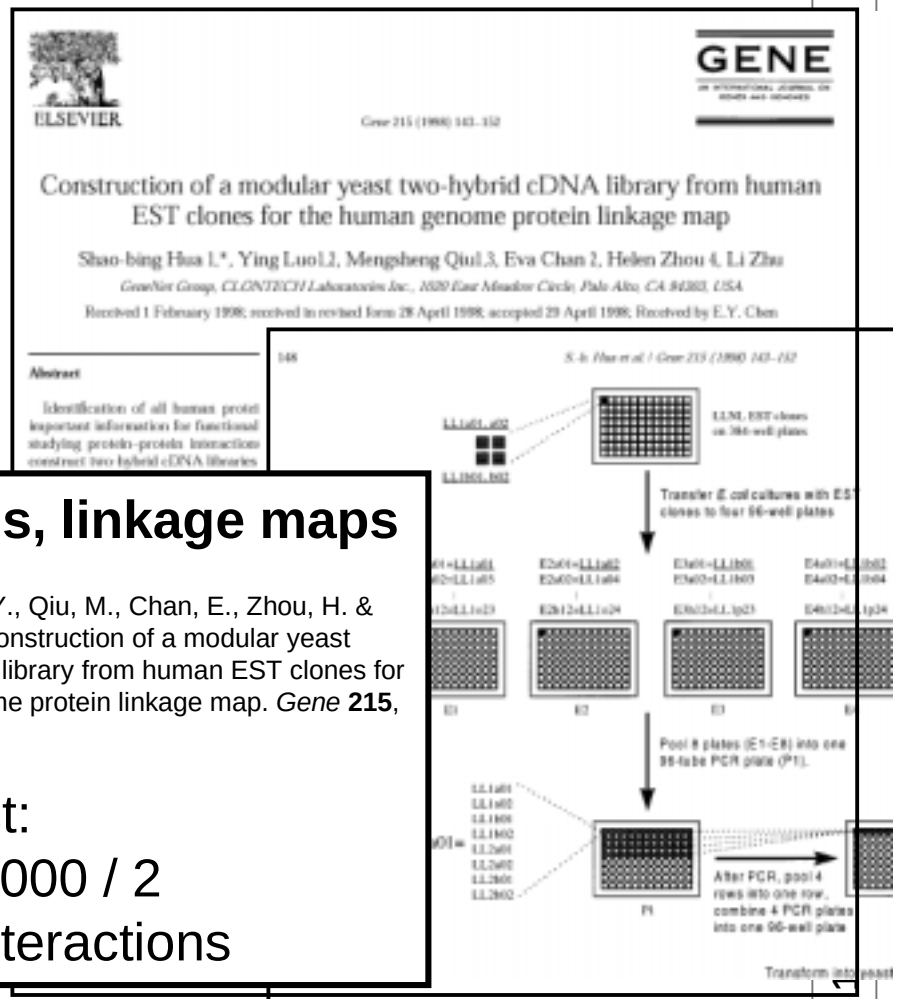
(0.85, R; 0.98, M; overlaps ribosomal protein *rpl36a*); *esc1* (0.83, R; 0.97, M) and *yml013w* (0.78, R; 0.95, M).

Altogether, almost 40% of the deletants

...tions of 1620 nonessential (short black bars) and 356 essential genes (tall ...re generated in consecutive groups on multiple chromosomes. A lighter ...s the location of chromosomal duplication blocks (*23*). For 15 of the 356 ...l null mutant had been p... ...ain background or in the

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

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 l.*, Ying Luo l,2, Mengsheng Qiu l,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

Abstract

Identification of all human protei... important information for functional ... studying protein-protein interaction... construct two hybrid cDNA libraries

2 hybrids, linkage maps

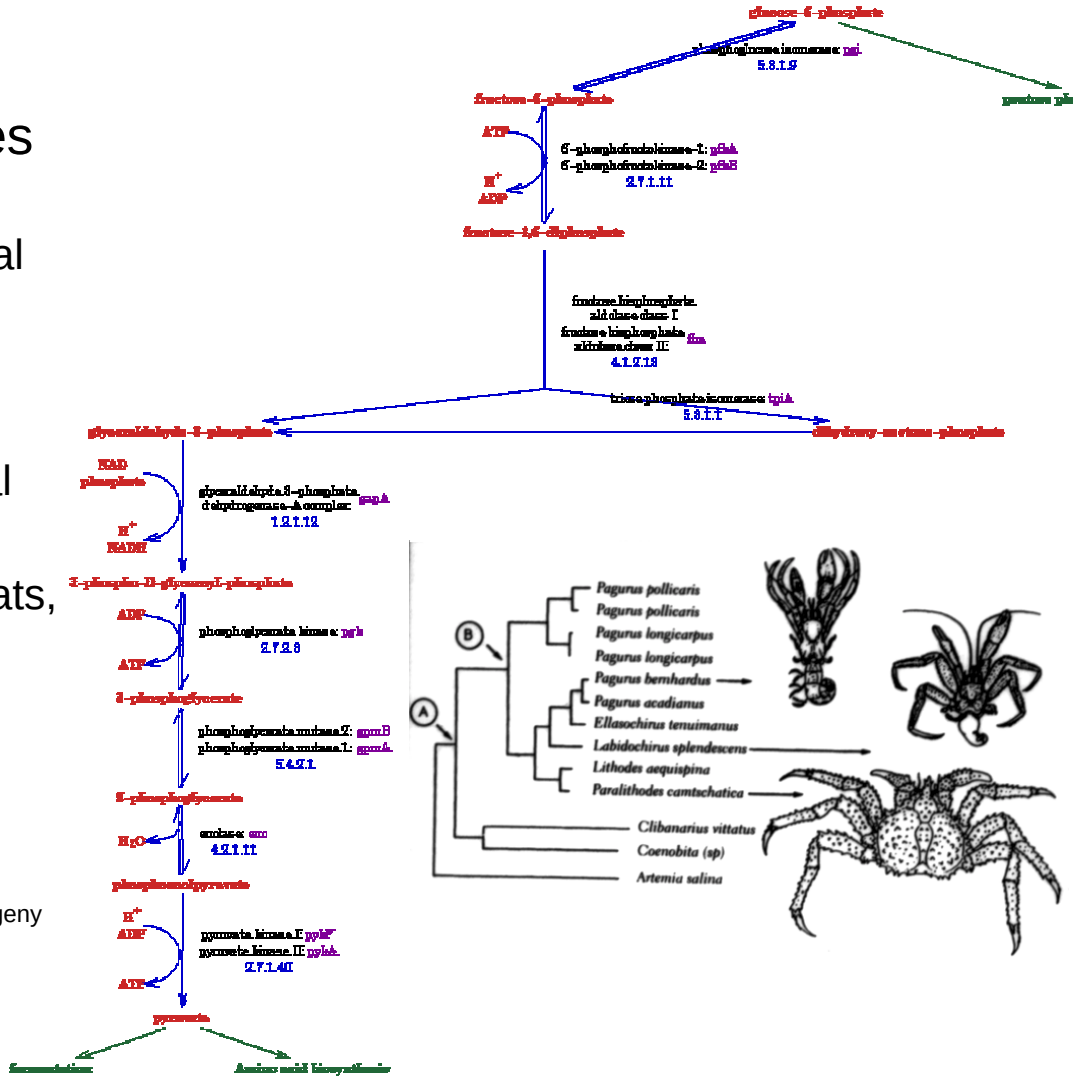
Hua, S. B., Luo, Y., Qiu, M., Chan, E., Zhou, H. & Zhu, L. (1998). Construction of a modular yeast two-hybrid cDNA library from human EST clones for the human genome protein linkage map. *Gene* **215**, 143-52

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....

(Pathway drawing from P Karp's EcoCyc, Phylogeny from S J Gould, Dinosaur in a Haystack)

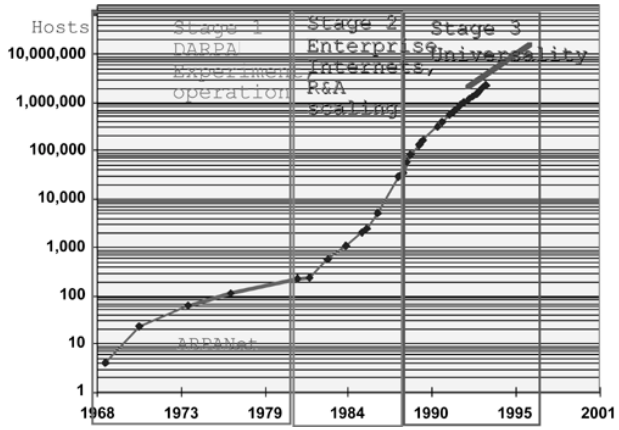


Explonential Growth of Data Matched by Development of Computer Technology

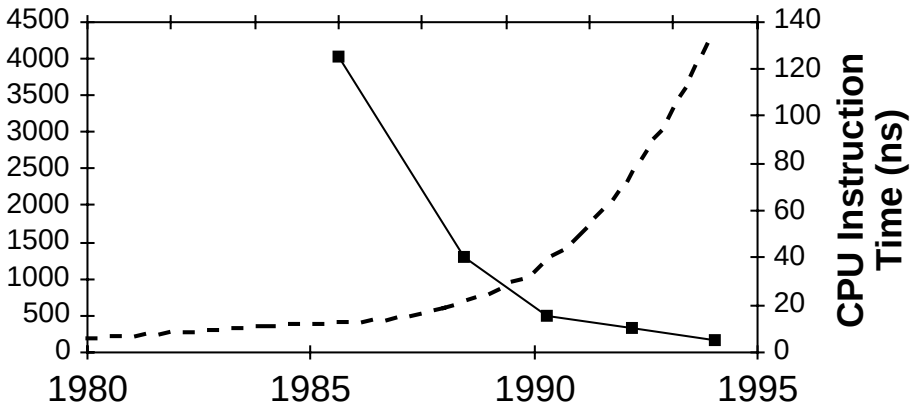
- CPU vs Disk & Net
  - ◊ As important as the increase in computer speed has been, the ability to store large amounts of information on computers is even more crucial
- Driving Force in Bioinformatics

(Internet picture adapted from D Brutlag, Stanford)

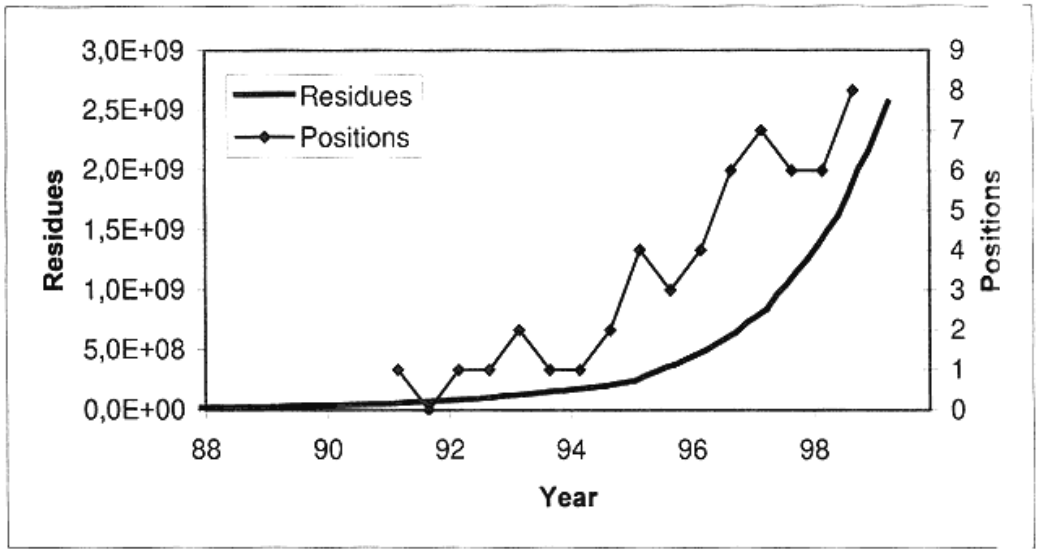
Internet Hosts



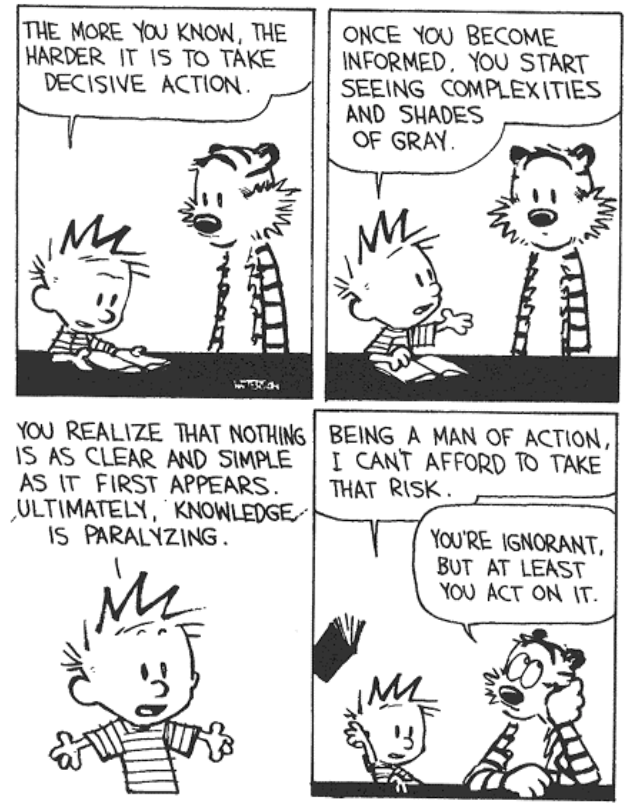
Num. Protein Domain Structures



Bioinformatics is born!



Growth in number of residues in Genbank, a central database for sequence data, compared to the request for people with competence in bioinformatics. The request for scientists is estimated from the number of relevant positions advertised in the first number of Nature in March and September of each year.



B. Watterson, "*There's treasure everywhere*", Andrews and McMeel, 1996.

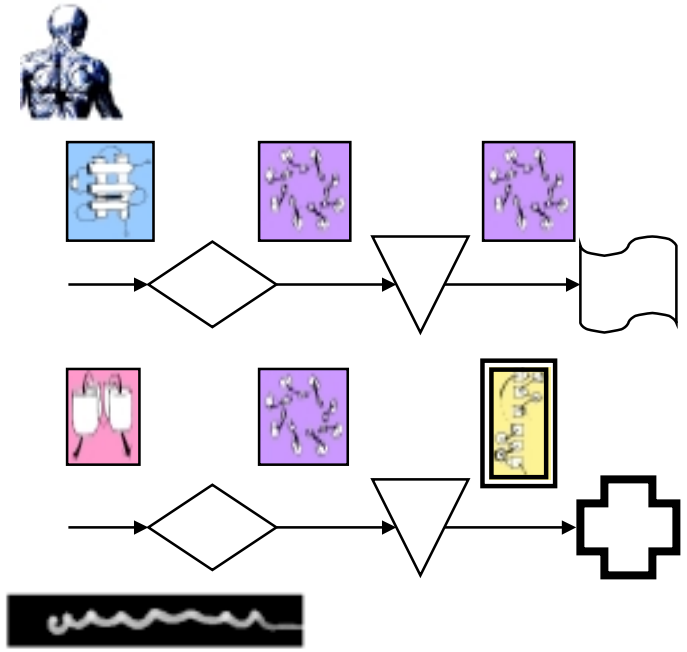
(courtesy of Finn Drablos)

Weber Cartoon

"Don't just sit there! If you've processed all the data there is, go out and find more data!"

Reproduced in R.L. Weber, "*A random walk in science*", IOP Publishing, 1973

The Character of 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 ↔ ….

New Paradigm for Scientific Computing

- Because of increase in data and improvement in computers, new calculations become possible
- But Bioinformatics has a new style of calculation...
  - ◊ Two Paradigms
- Physics
  - ◊ Prediction based on physical principles
  - ◊ Exact Determination of Rocket Trajectory
  - ◊ Supercomputer, CPU
- Biology
  - ◊ Classifying information and discovering unexpected relationships
  - ◊ globin ~ colicin~ plastocyanin~ repressor
  - ◊ networks, “federated” database

General Types of "Informatics" in Bioinformatics

- Databases
  - ◊ Building, Querying
  - ◊ Object DB
- Text String Comparison
  - ◊ Text Search
  - ◊ 1D Alignment
  - ◊ Significance Statistics
  - ◊ Alta Vista, grep
- Finding Patterns
  - ◊ AI / Machine Learning
  - ◊ Clustering
  - ◊ Datamining
- Geometry
  - ◊ Robotics
  - ◊ Graphics (Surfaces, Volumes)
  - ◊ Comparison and 3D Matching (Visision, recognition)
- Physical Simulation
  - ◊ Newtonian Mechanics
  - ◊ Electrostatics
  - ◊ Numerical Algorithms
  - ◊ Simulation

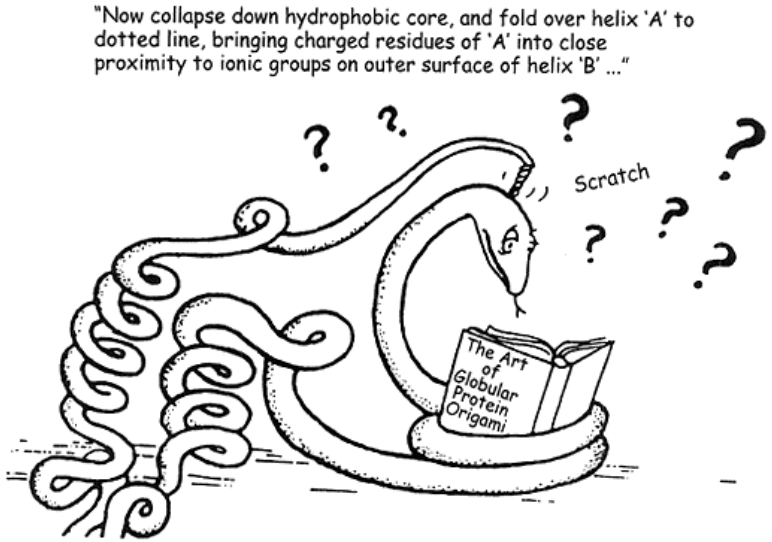
Bioinformatics Topics -- Genome Sequence

- Finding Genes in Genomic DNA
  - ◊ introns
  - ◊ exons
  - ◊ promotors
- Characterizing Repeats in Genomic DNA
  - ◊ Statistics
  - ◊ Patterns
- Duplications in the Genome

Bioinformatics Topics -- Protein Sequence

- Sequence Alignment
  - ◊ non-exact string matching, gaps
  - ◊ How to align two strings optimally via Dynamic Programming
  - ◊ Local vs Global Alignment
  - ◊ Suboptimal Alignment
  - ◊ Hashing to increase speed (BLAST, FASTA)
  - ◊ Amino acid substitution scoring matrices
- Multiple Alignment and Consensus Patterns
  - ◊ How to align more than one sequence and then fuse the result in a consensus representation
  - ◊ Transitive Comparisons
  - ◊ HMMs, Profiles
  - ◊ Motifs
- Scoring schemes and Matching statistics
  - ◊ How to tell if a given alignment or match is statistically significant
  - ◊ A P-value (or an e-value)?
  - ◊ Score Distributions (extreme val. dist.)
  - ◊ Low Complexity Sequences

Bioinformatics Topics -- Sequence / Structure



Reproduced in U. Tollemar, "*Protein Engineering i USA*", Sveriges Tekniska Attachéer, 1988

- Secondary Structure "Prediction"
  - ◊ via Propensities
  - ◊ Neural Networks, Genetic Alg.
  - ◊ Simple Statistics
  - ◊ TM-helix finding
  - ◊ Assessing Secondary Structure Prediction
- Tertiary Structure Prediction
  - ◊ Fold Recognition
  - ◊ Threading
  - ◊ Ab initio
- Function Prediction
  - ◊ Active site identification
- Relation of Sequence Similarity to Structural Similarity

Topics -- Structures

- Basic Protein Geometry and Least-Squares Fitting
  - ◊ Distances, Angles, Axes, Rotations
    - Calculating a helix axis in 3D via fitting a line
  - ◊ LSQ fit of 2 structures
  - ◊ Molecular Graphics
- Calculation of Volume and Surface
  - ◊ How to represent a plane
  - ◊ How to represent a solid
  - ◊ How to calculate an area
  - ◊ Docking and Drug Design as Surface Matching
  - ◊ Packing Measurement
- Structural Alignment
  - ◊ Aligning sequences on the basis of 3D structure.
  - ◊ DP does not converge, unlike sequences, what to do?
  - ◊ Other Approaches: Distance Matrices, Hashing
  - ◊ Fold Library

Topics -- Databases

- Relational Database Concepts
  - ◊ Keys, Foreign Keys
  - ◊ SQL, OODBMS, views, forms, transactions, reports, indexes
  - ◊ Joining Tables, Normalization
    - Natural Join as "where" selection on cross product
    - Array Referencing (perl/dbm)
  - ◊ Forms and Reports
  - ◊ Cross-tabulation
- Protein Units?
  - ◊ What are the units of biological information?
    - sequence, structure
    - motifs, modules, domains
  - ◊ How classified: folds, motions, pathways, functions?
- Clustering and Trees
  - ◊ Basic clustering
    - UPGMA
    - single-linkage
    - multiple linkage
  - ◊ Other Methods
    - Parsimony, Maximum likelihood
  - ◊ Evolutionary implications
- The Bias Problem
  - ◊ sequence weighting
  - ◊ sampling

Topics -- Genomics

- Expression Analysis
  - ◊ Time Courses clustering
  - ◊ Measuring differences
  - ◊ Identifying Regulatory Regions
- Large scale cross referencing of information
- Function Classification and Orthologs
- The Genomic vs. Single-molecule Perspective

- Genome Comparisons
  - ◊ Ortholog Families, pathways
  - ◊ Large-scale censuses
  - ◊ Frequent Words Analysis
  - ◊ Genome Annotation
  - ◊ Trees from Genomes
  - ◊ Identification of interacting proteins
- Structural Genomics
  - ◊ Folds in Genomes, shared & common folds
  - ◊ Bulk Structure Prediction
- Genome Trees
-

Topics -- Simulation

- Molecular Simulation
  - ◊ Geometry -> Energy -> Forces
  - ◊ Basic interactions, potential energy functions
  - ◊ Electrostatics
  - ◊ VDW Forces
  - ◊ Bonds as Springs
  - ◊ How structure changes over time?
    - How to measure the change in a vector (gradient)
  - ◊ Molecular Dynamics & MC
  - ◊ Energy Minimization
- Parameter Sets
- Number Density
- Poisson-Boltzman Equation
- Lattice Models and Simplification

Bioinformatics Schematic

Depth: Rational Drug Design, physics ↓	Breadth: Homologues, Large-scale Surveys, informatics →			
		pairwise comparison, sequence & structure alignment	multiple alignment, patterns, templates, trees	databases, scoring schemes, censuses
	Genome Sequence	g1 ↔ g2	↔ g3, g4… g50	↔ g50… g10000…
gene finding	↓			
	Protein Sequence	p1 ↔ p2	↔ p3, p4… p50	↔ p50… p10000…
structure prediction	↓			
	Protein Structure	s1 ↔ s2	↔ s3, s4… s50	↔ s50… s10000…
geometry calculation	↓			
	Protein Surface			
molecular simulation	↓			
	Force Field			
structure docking	↓			
	Ligand Complex			

Background

	Math	Biology
Need to Know Today	Calculation of Standard Deviation, a Bell-shaped Distribution (of test scores), a 3D vector	DNA, RNA, alpha-helix, the cell nucleus, ATP
What You'll Learn	Force is the Derivative (grad) of Energy, Rotation Matrices (3D), a P-value of .01 and an Extreme Value Distribution	Proteins are tightly packed, sequence homology twilight zone, protein families
Not really necessary….	Poisson-Boltzman Equation, Design a Hashing Function, Write a Recursive Descent Parser	What GroEL does, a worm is a metazoa, E. coli is gram negative, what chemokines are

Are They or Aren't They Bioinformatics? (#1)

- Digital Libraries
  - ◊ Automated Bibliographic Search and Textual Comparison
  - ◊ Knowledge bases for biological literature
- Motif Discovery Using Gibb's Sampling
- Methods for Structure Determination
  - ◊ Computational Crystallography
    - Refinement
  - ◊ NMR Structure Determination
    - Distance Geometry
- Metabolic Pathway Simulation
- The DNA Computer

Are They or Aren't They Bioinformatics? (#1, Answers)

- **(YES?)** Digital Libraries
  - ◊ Automated Bibliographic Search and Textual Comparison
  - ◊ Knowledge bases for biological literature
- **(YES)** Motif Discovery Using Gibb's Sampling
- **(NO?)** Methods for Structure Determination
  - ◊ Computational Crystallography
    - Refinement
  - ◊ NMR Structure Determination
    - **(YES)** Distance Geometry
- **(YES)** Metabolic Pathway Simulation
- **(NO)** The DNA Computer

Are They or Aren't They Bioinformatics? (#2)

- Gene identification by sequence inspection
  - ◊ Prediction of splice sites
- DNA methods in forensics
- Modeling of Populations of Organisms
  - ◊ Ecological Modeling
- Genomic Sequencing Methods
  - ◊ Assembling Contigs
  - ◊ Physical and genetic mapping
- Linkage Analysis
  - ◊ Linking specific genes to various traits

Are They or Aren't They Bioinformatics? (#2, Answers)

- **(YES)** Gene identification by sequence inspection
  - ◊ Prediction of splice sites
- **(YES)** DNA methods in forensics
- **(NO)** Modeling of Populations of Organisms
  - ◊ Ecological Modeling
- **(NO?)** Genomic Sequencing Methods
  - ◊ Assembling Contigs
  - ◊ Physical and genetic mapping
- **(YES)** Linkage Analysis
  - ◊ Linking specific genes to various traits

Are They or Aren't They Bioinformatics? (#3)

- RNA structure prediction
  Identification in sequences
- Radiological Image Processing
  - ◊ Computational Representations for Human Anatomy (visible human)
- Artificial Life Simulations
  - ◊ Artificial Immunology / Computer Security
  - ◊ Genetic Algorithms in molecular biology
- Homology modeling
- Determination of Phylogenies Based on Non-molecular Organism Characteristics
- Computerized Diagnosis based on Genetic Analysis (Pedigrees)

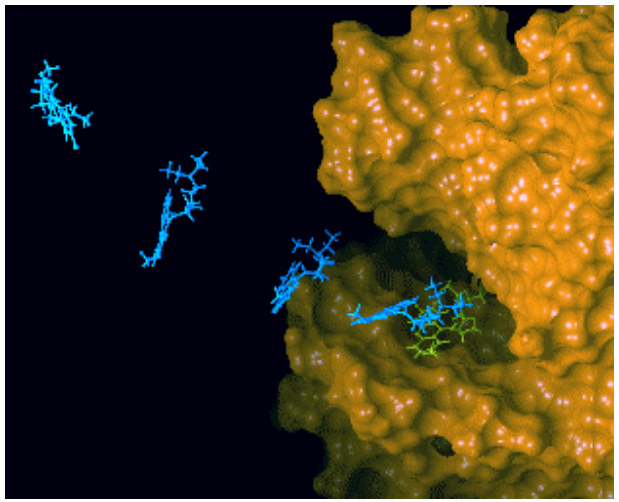
Are They or Aren't They Bioinformatics? (#3, Answers)

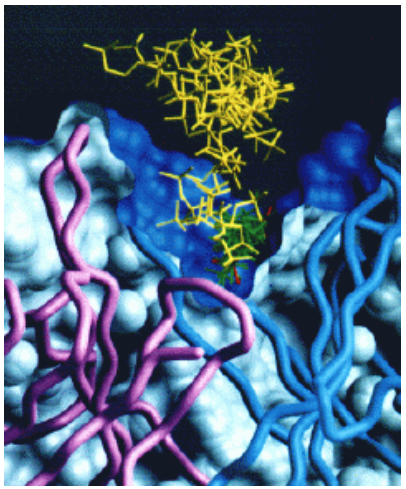
- **(YES)** RNA structure prediction
  Identification in sequences
- **(NO)** Radiological Image Processing
  - ◊ Computational Representations for Human Anatomy (visible human)
- **(NO)** Artificial Life Simulations
  - ◊ Artificial Immunology / Computer Security
  - ◊ **(NO?)** Genetic Algorithms in molecular biology
- **(YES)** Homology modeling
- **(NO)** Determination of Phylogenies Based on Non-molecular Organism Characteristics
- **(NO)** Computerized Diagnosis based on Genetic Analysis (Pedigrees)

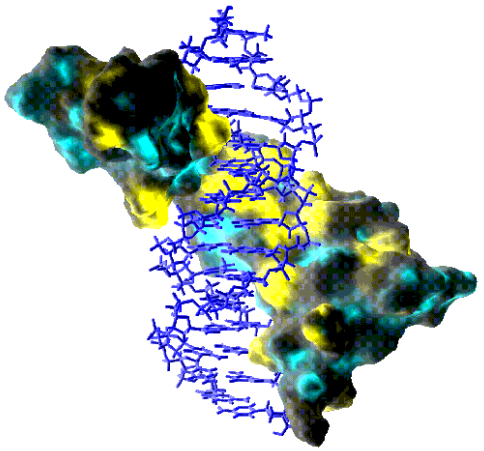
Major Application I: Designing Drugs

- Understanding How Structures Bind Other Molecules (Function)
- Designing Inhibitors
- Docking, Structure Modeling

(From left to right, figures adapted from Olsen Group Docking Page at Scripps, Dyson NMR Group Web page at Scripps, and from Computational Chemistry Page at Cornell Theory Center).







Major Application II: Finding Homologues

- Find Similar Ones in Different Organisms
- Human vs. Mouse vs. Yeast
  - ◊ Easier to do Expts. on latter!

(Section from NCBI Disease Genes Database Reproduced Below.)

Best Sequence Similarity Matches to Date Between Positionally Cloned Human Genes and S. cerevisiae Proteins

Human Disease	MIM #	Human Gene	GenBank Acc# for Human cDNA	BLASTX P-value	Yeast Gene	GenBank Acc# for Yeast cDNA	Yeast Gene Description
Hereditary Non-polyposis Colon Cancer	120436	MSH2	U03911	9.2e-261	MSH2	M84170	DNA repair protein
Hereditary Non-polyposis Colon Cancer	120436	MLH1	U07418	6.3e-196	MLH1	U07187	DNA repair protein
Cystic Fibrosis	219700	CFTR	M28668	1.3e-167	YCF1	L35237	Metal resistance protein
Wilson Disease	277900	WND	U11700	5.9e-161	CCC2	L36317	Probable copper transporter
Glycerol Kinase Deficiency	307030	GK	L13943	1.8e-129	GUT1	X69049	Glycerol kinase
Bloom Syndrome	210900	BLM	U39817	2.6e-119	SGS1	U22341	Helicase
Adrenoleukodystrophy, X-linked	300100	ALD	Z21876	3.4e-107	PXA1	U17065	Peroxisomal ABC transporter
Ataxia Telangiectasia	208900	ATM	U26455	2.8e-90	TEL1	U31331	PI3 kinase
Amyotrophic Lateral Sclerosis	105400	SOD1	K00065	2.0e-58	SOD1	J03279	Superoxide dismutase
Myotonic Dystrophy	160900	DM	L19268	5.4e-53	YPK1	M21307	Serine/threonine protein kinase
Lowe Syndrome	309000	OCRL	M88162	1.2e-47	YIL002C	Z47047	Putative IPP-5-phosphatase
Neurofibromatosis, Type 1	162200	NF1	M89914	2.0e-46	IRA2	M33779	Inhibitory regulator protein
Choroideremia	303100	CHM	X78121	2.1e-42	GDI1	S69371	GDP dissociation inhibitor
Diastrophic Dysplasia	222600	DTD	U14528	7.2e-38	SUL1	X82013	Sulfate permease
Lissencephaly	247200	LIS1	L13385	1.7e-34	MET30	L26505	Methionine metabolism
Thomsen Disease	160800	CLC1	Z25884	7.9e-31	GEF1	Z23117	Voltage-gated chloride channel
Wilms Tumor	194070	WT1	X51630	1.1e-20	FZF1	X67787	Sulphite resistance protein
Achondroplasia	100800	FGFR3	M58051	2.0e-18	IPL1	U07163	Serine/threoinine protein kinase
Menkes Syndrome	309400	MNK	X69208	2.1e-17	CCC2	L36317	Probable copper transporter

Major Application II: Finding Homologues (cont.)

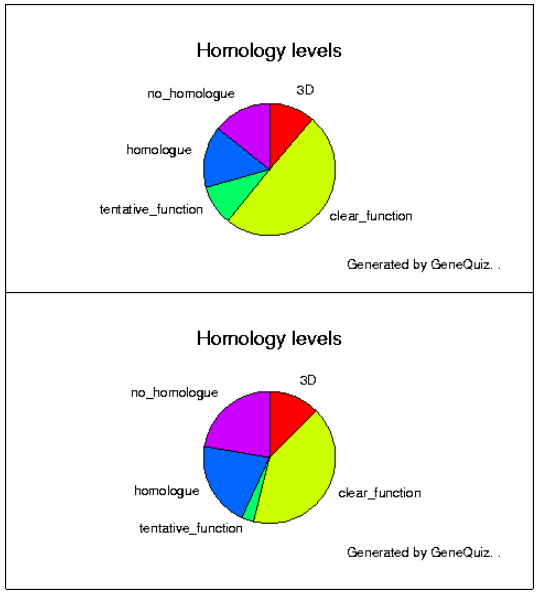
- Cross-Referencing, one thing to another thing
- Sequence Comparison and Scoring
- Analogous Problems for Structure Comparison
- Comparison has two parts:
  (1) Optimally **Aligning** 2 entities to get a Comparison **Score**
  (2) Assessing **Significance** of this score in a given **Context**

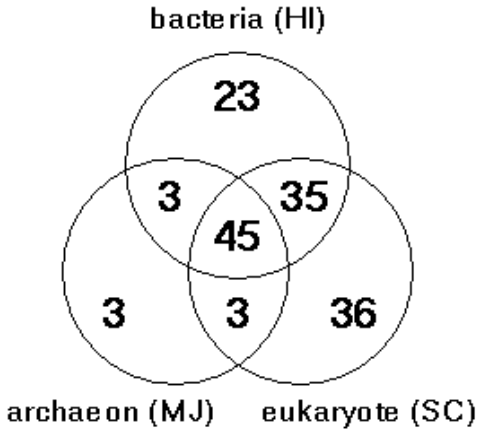
- **Integrated Presentation**
  ◊ Align Sequences
  ◊ Align Structures
  ◊ Score in a Uniform Framework

Major Application III: Overall Genome Characterization

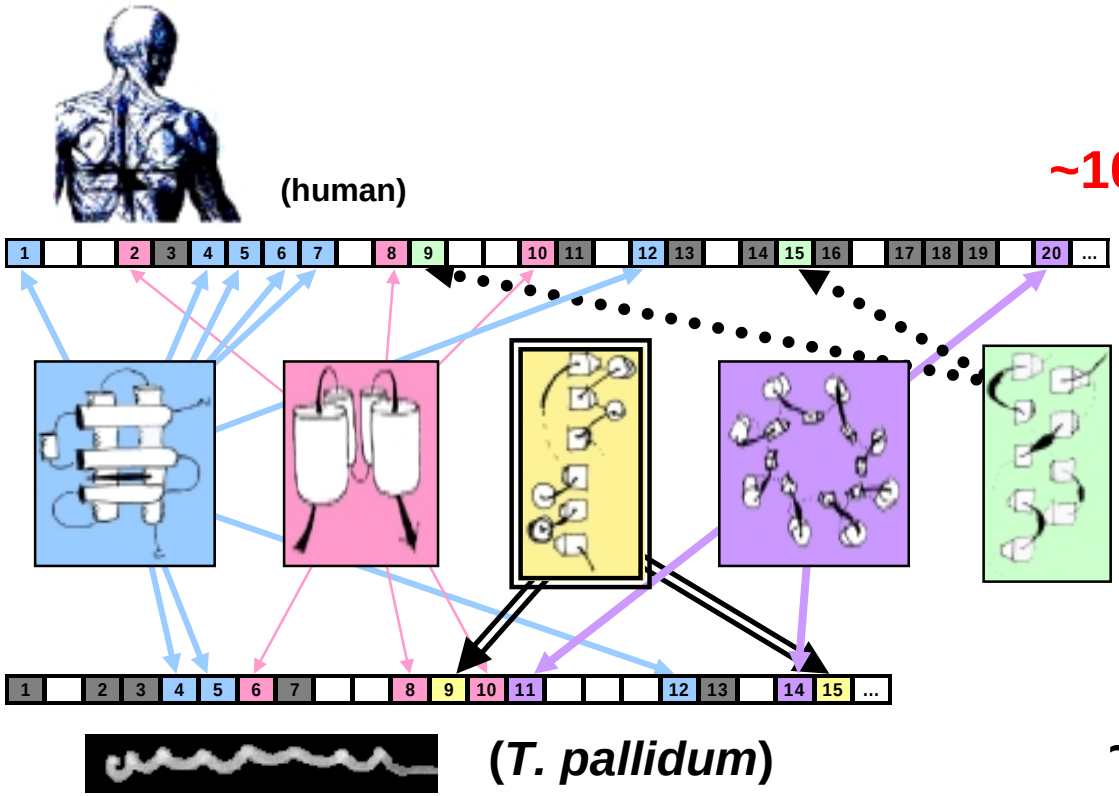
- Overall Occurrence of a Certain Feature in the Genome
  - ◊ e.g. how many kinases in Yeast
- Compare Organisms and Tissues
  - ◊ Expression levels in Cancerous vs Normal Tissues
- Databases, Statistics

(Clock figures, yeast v. Synechocystis,
adapted from GeneQuiz Web Page, Sander Group, EBI)

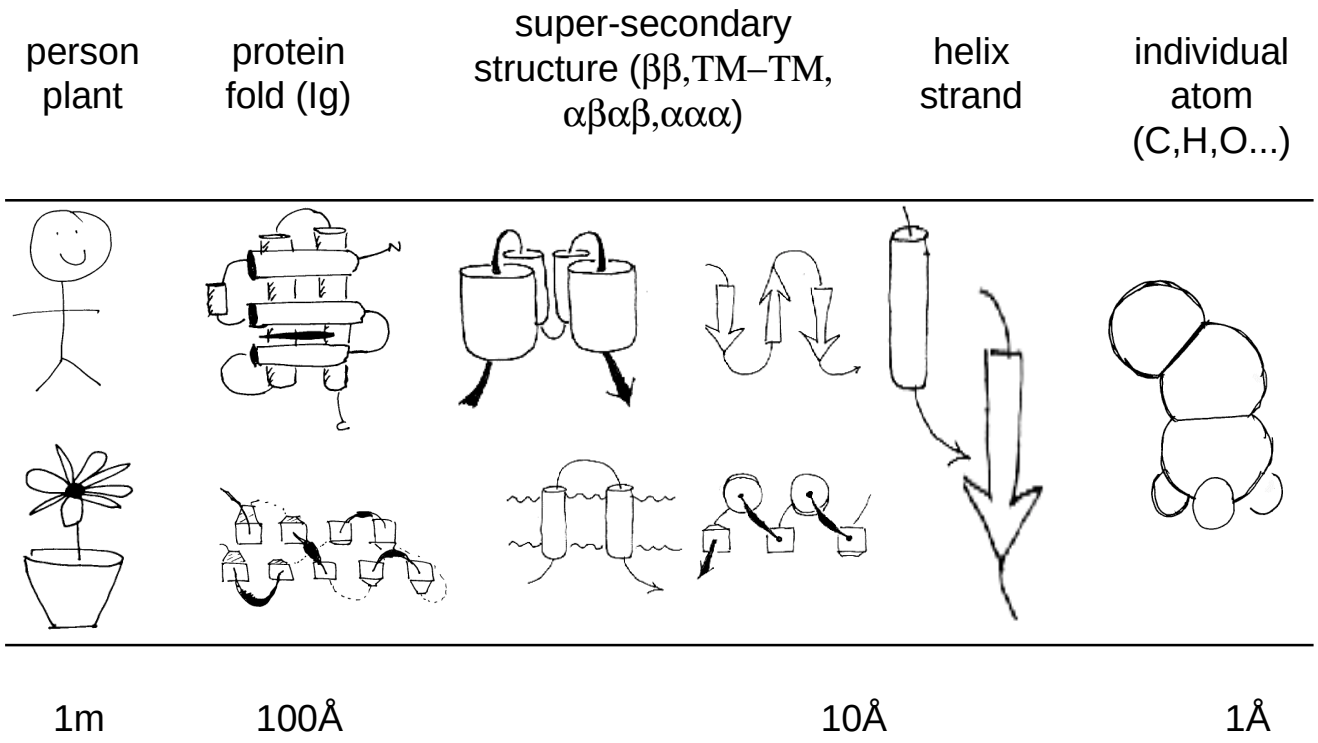


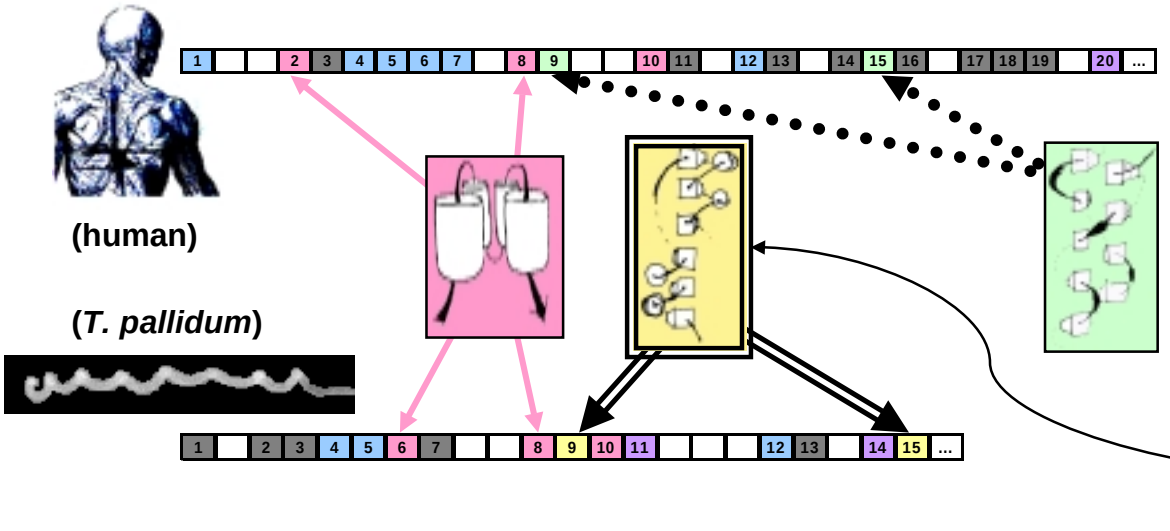


Simplfying Genomes with Folds, Pathways, &c



At What Structural Resolution Are Organisms Different?





Practical Relevance

(Pathogen only folds as possible targets)