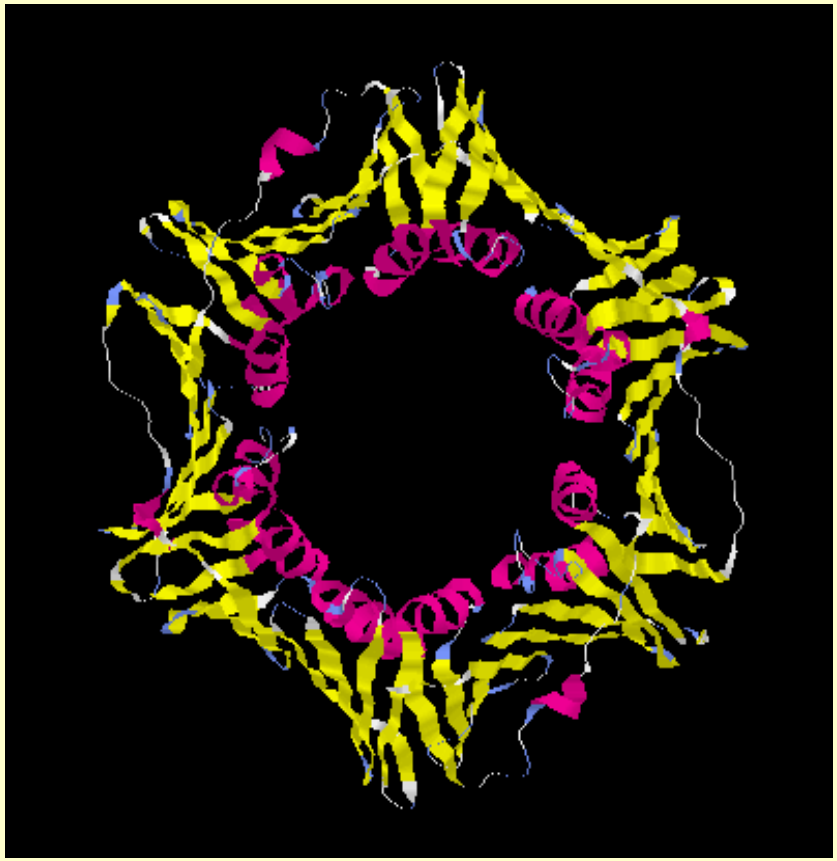
Computational Molecular Biology

Biochem 218 – BioMedical Informatics 231

http://biochem218.stanford.edu/

Genomics and Bioinformatics



Doug Brutlag
Professor Emeritus
Biochemistry & Medicine (by courtesy)

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Faculty, TAs and Staff

Doug Brutlag

Lee Kozar

Maeve O'Huallachain

Dan Davison

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Course and Video Availability

- Alway M114
  - Tuesdays & Thursdays 2:15-3:30 PM
- Course Web Site
  - http://biochem218.stanford.edu/
- Stanford Center for Professional Development
  - http://scpd.stanford.edu/
- Videos available 24 hours/day, 7 days/week
- Course offered Autumn, Winter and Spring quarters

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Course Requirements

- Lectures
  - Theoretical background of current methods
  - Strengths and weaknesses of current approaches
  - Future directions for improvements
- Demonstrations
  - Applications (Mac, PC, Unix, Web)
  - Web applications
  - Illustrate homework
- All homework and questions must be submitted by email to homework218@cmgm.stanford.edu
- Several homework assignments (35%)
  - Due one week after assigned
- Final project (Due March 12th)
  - A critical or comparative review of computational approaches to any problem in computational molecular biology
  - Propose new approach
  - Implement a new approach
  - Examples of previous projects for the class can be found at http://biochem218.stanford.edu/Projects.html

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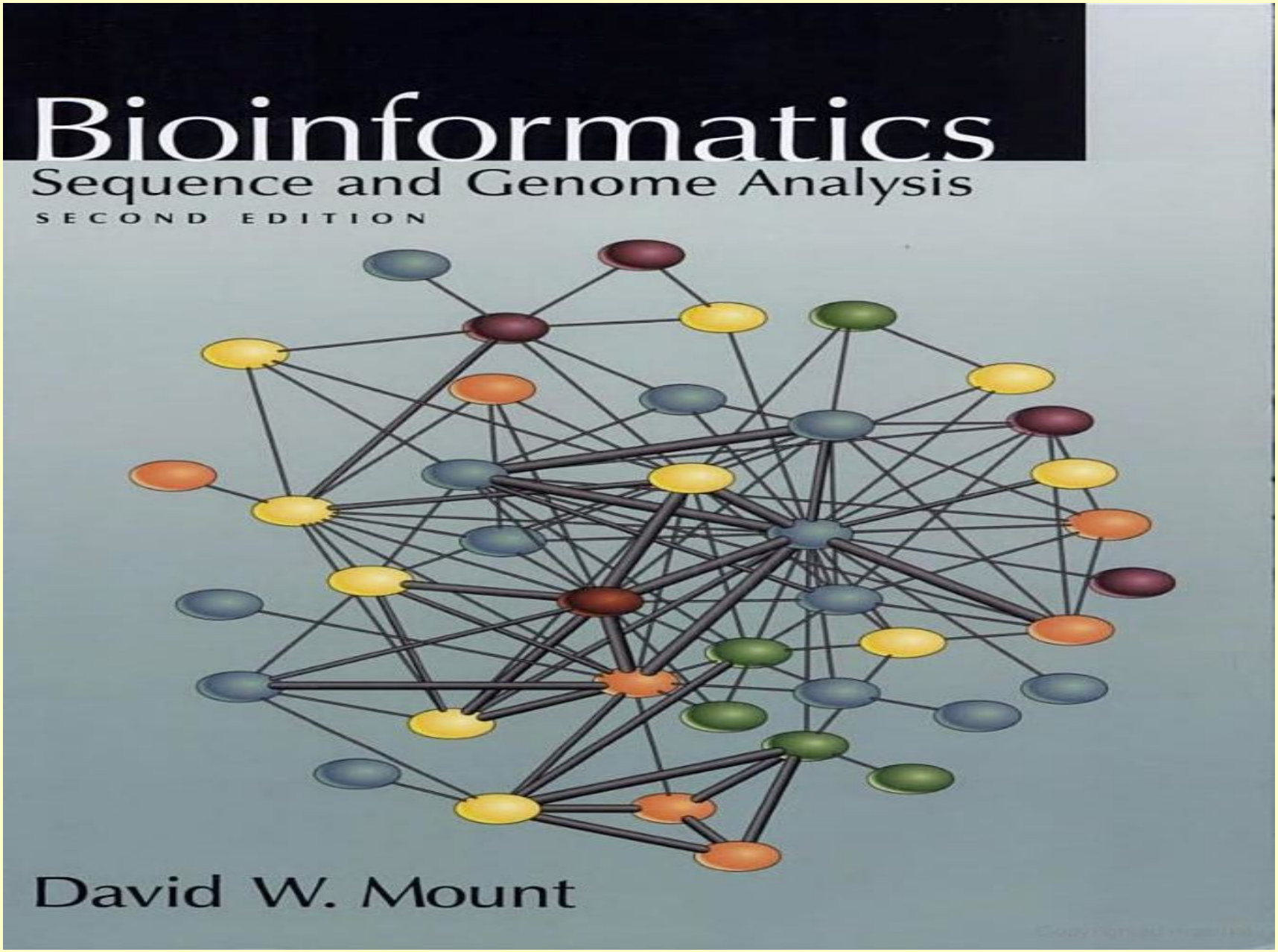
David Mount

Bioinformatics: Sequence and Genome Analysis 2nd Edition



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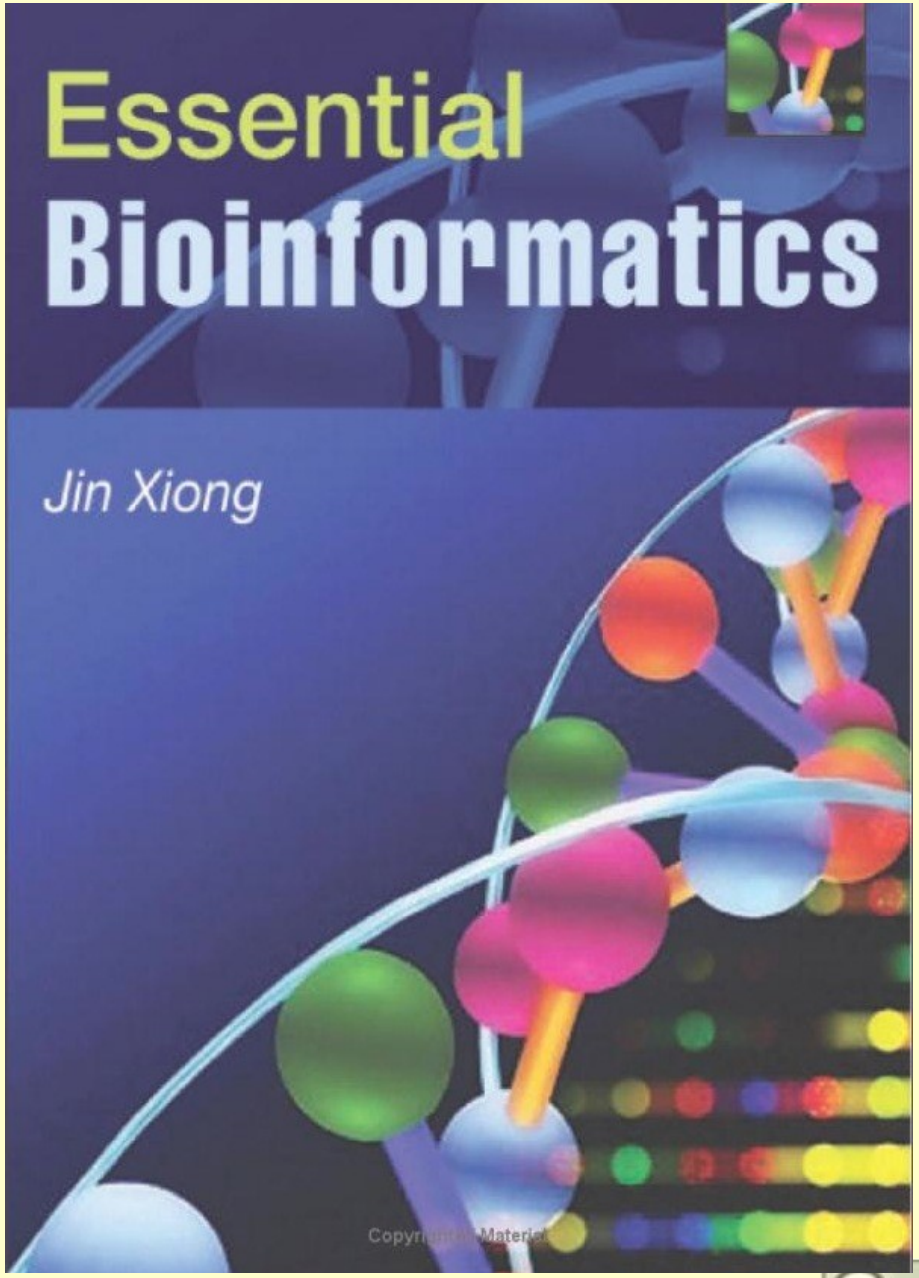
Jin Xiong
Essential Bioinformatics



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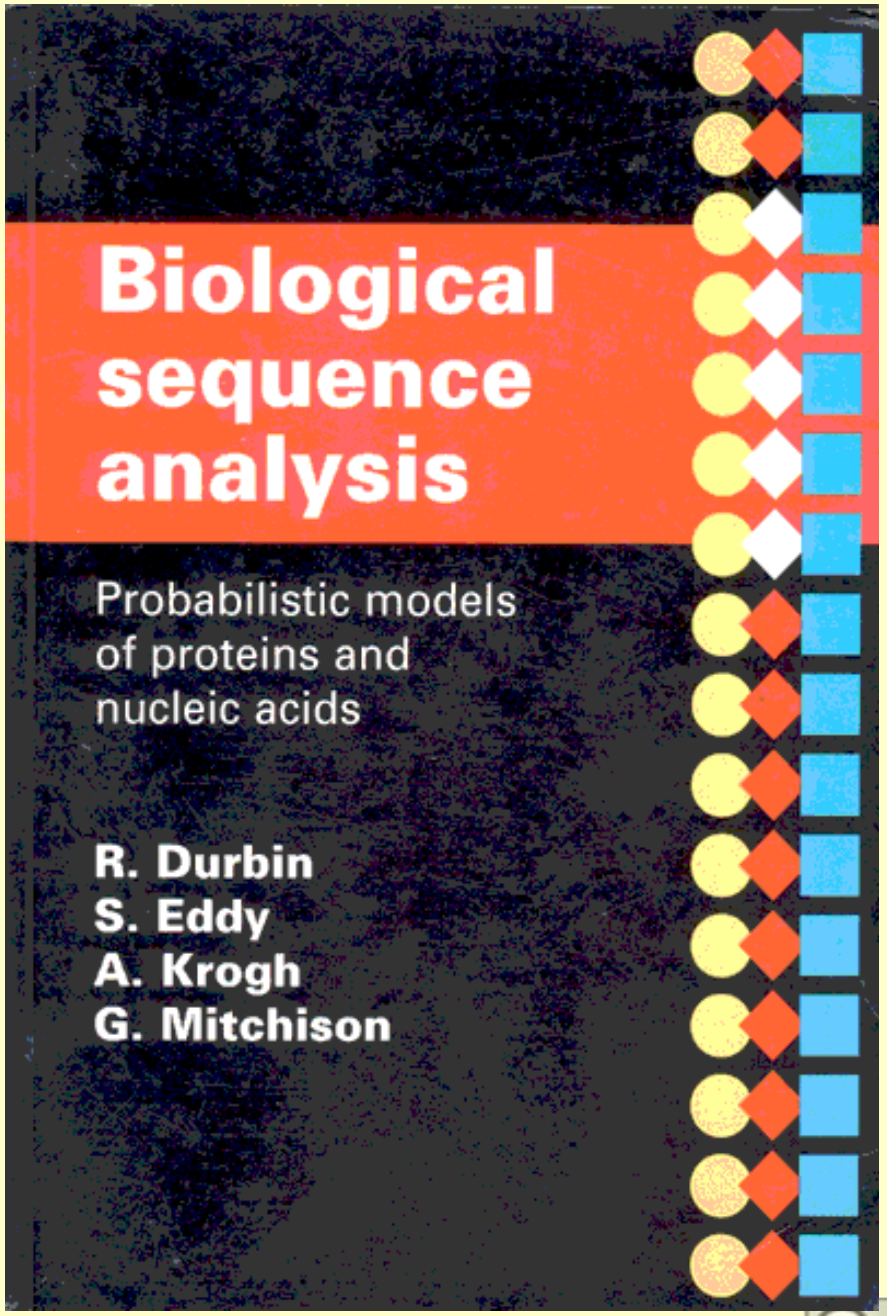
Richard Durbin *et al.*
Biological Sequence Analysis



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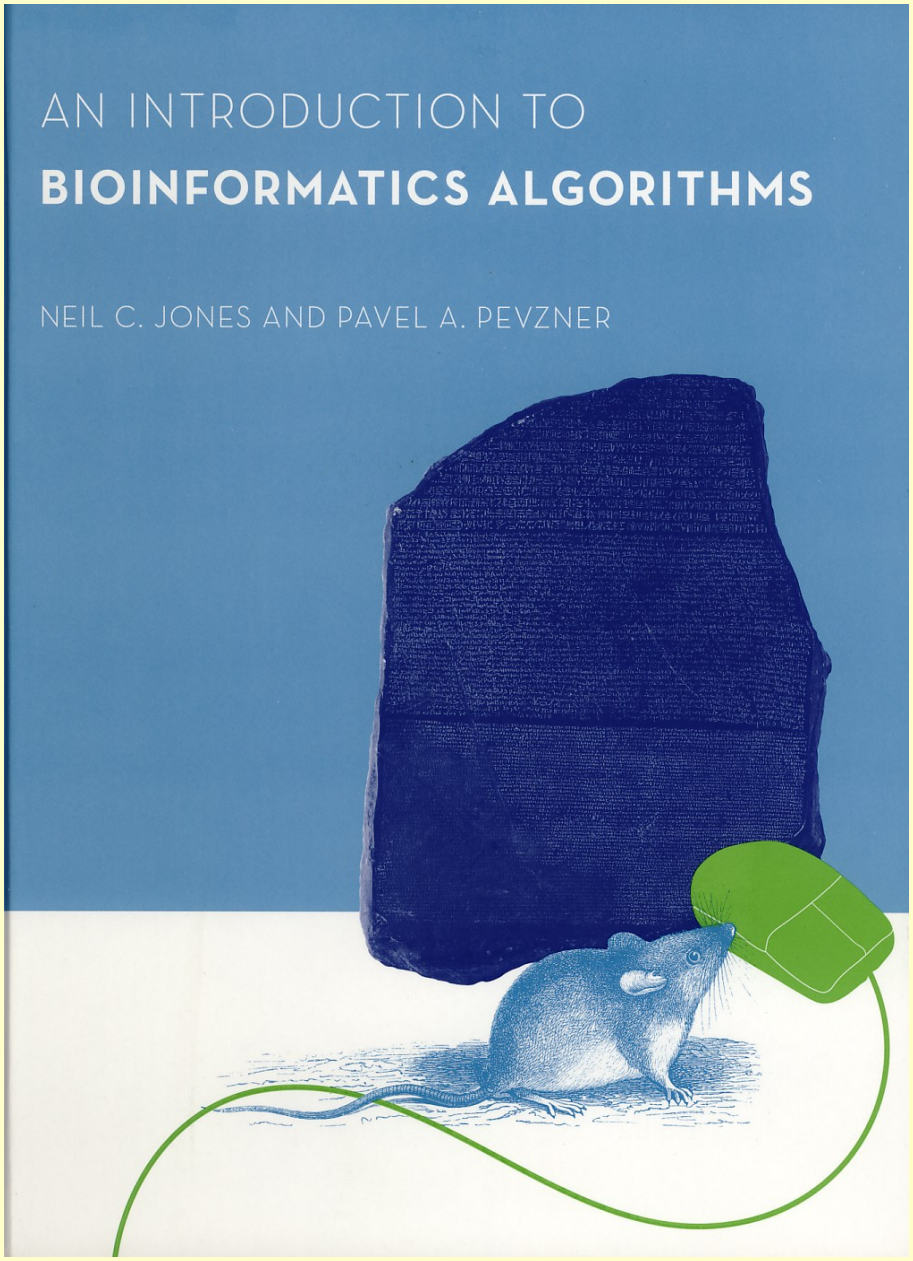
Jones & Pevzner
Bioinformatics Algorithms



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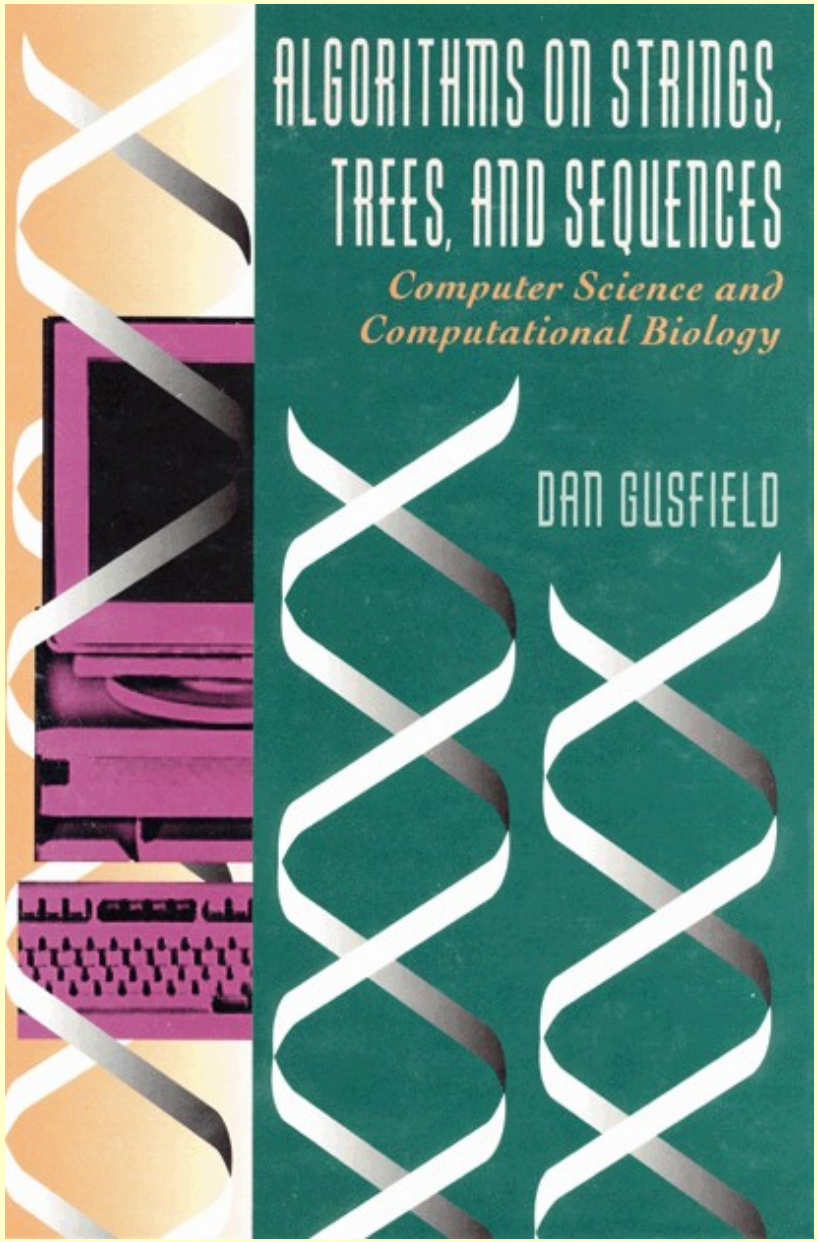
Dan Gusfield

Algorithms on Strings, Trees & Sequences



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Baldi & Brunak

Bioinformatics: The Machine Learning Approach

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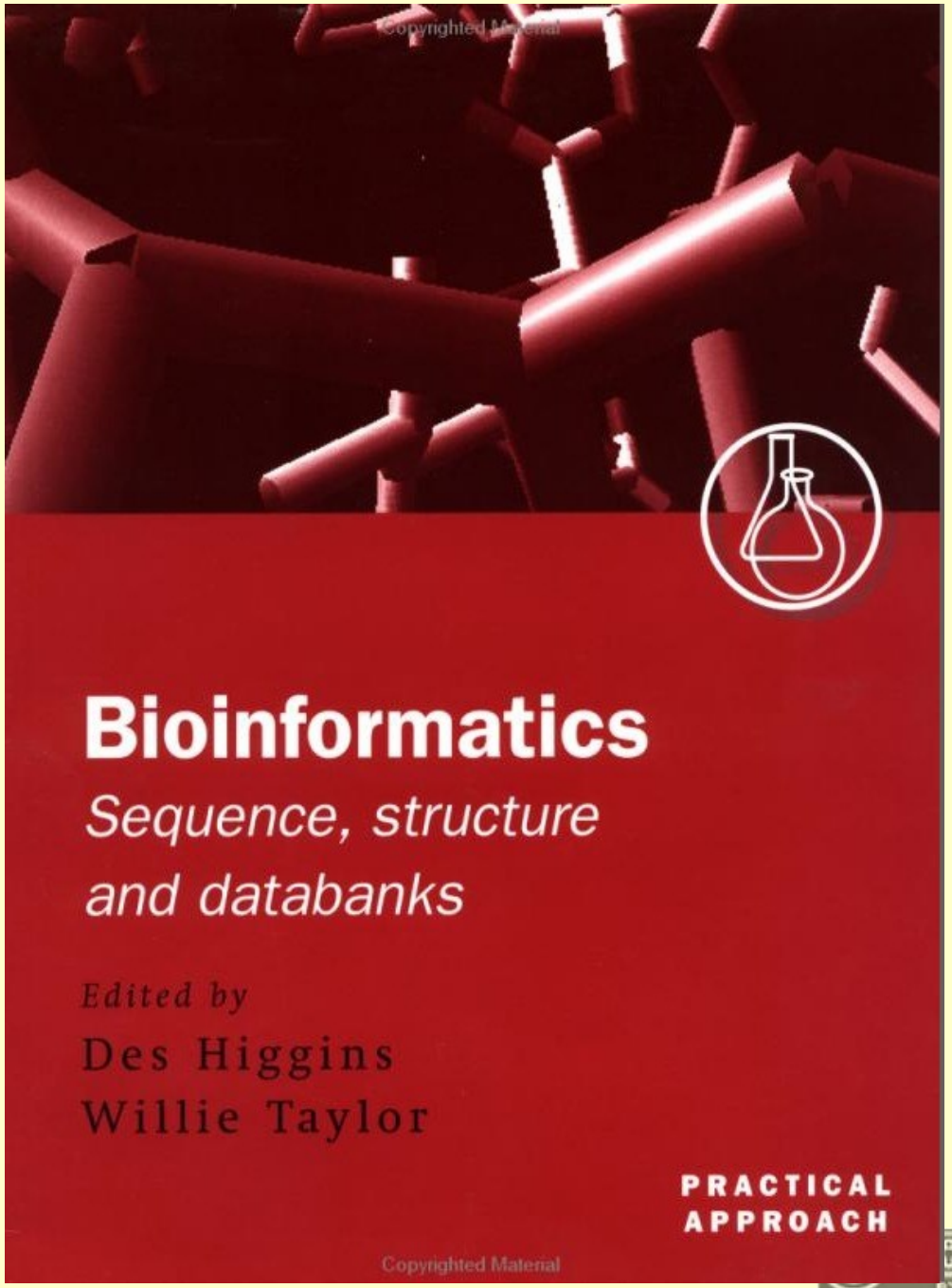
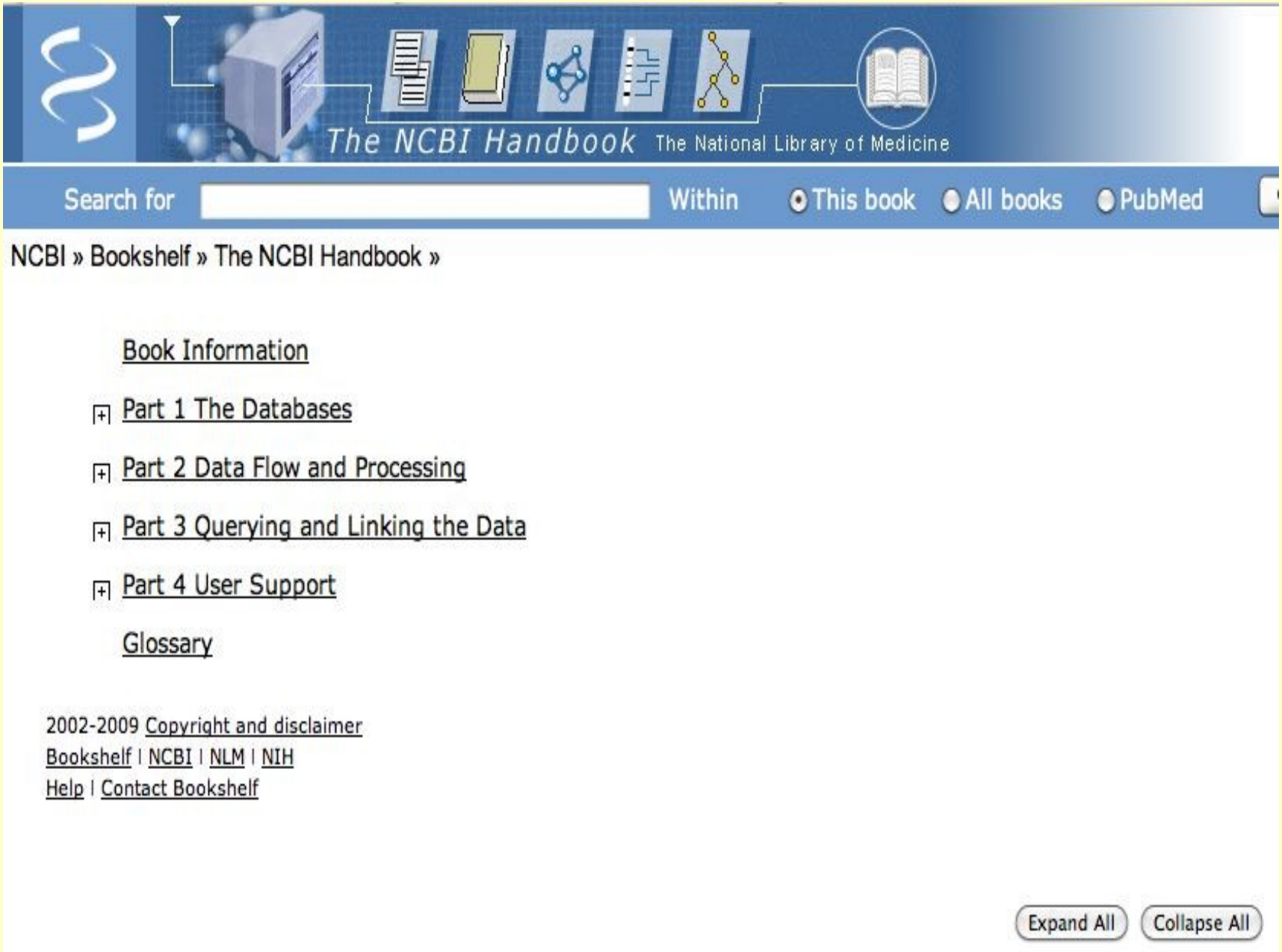
Higgins & Taylor

Bioinformatics: Sequence, Structure & Databanks



NCBI Handbook

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=handbook



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NCBI Handbook

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=handbook

NCBI » Bookshelf » The NCBI Handbook » The Databases

The Databases

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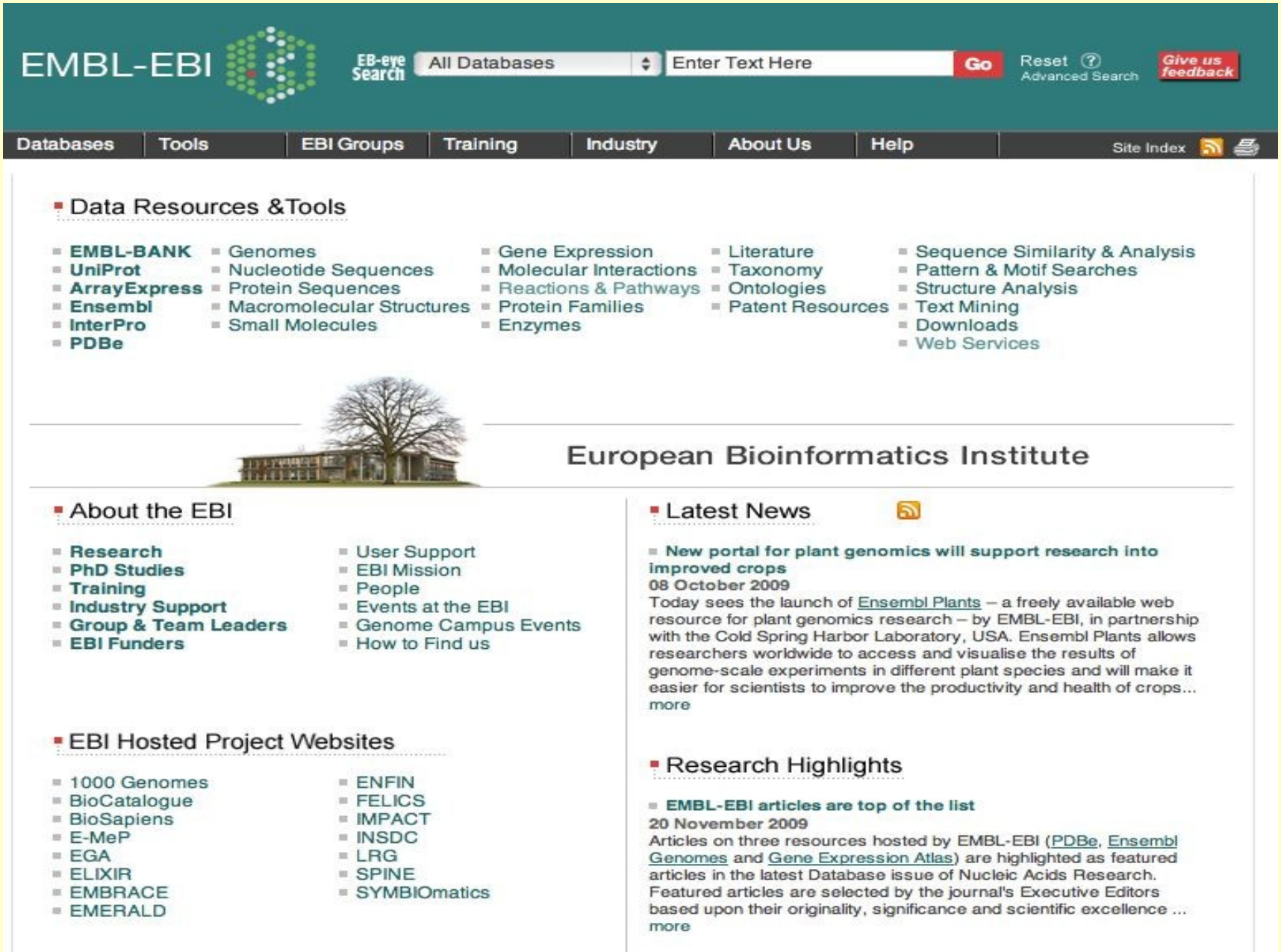
EMBL-EBI Home Page
http://www.ebi.ac.uk/



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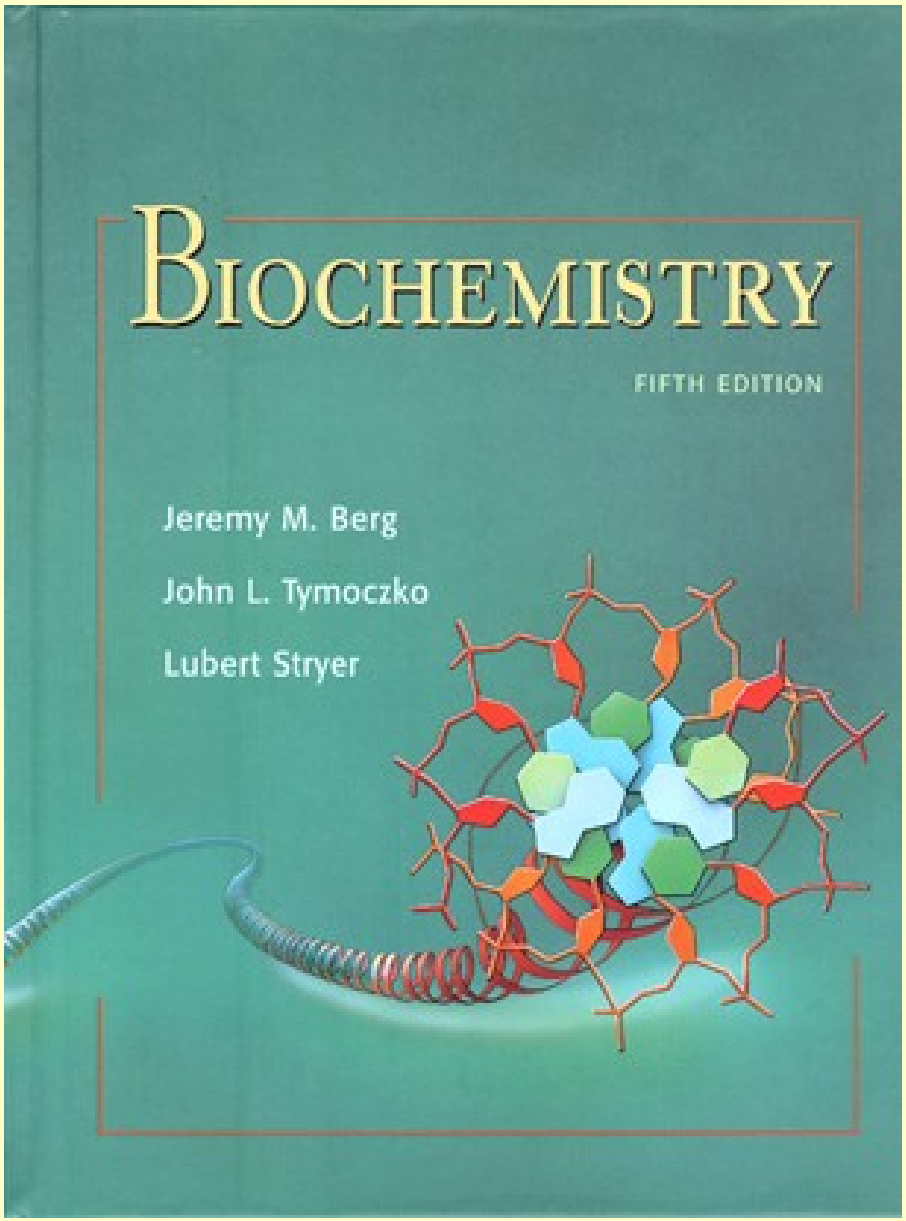
Berg, Tymoczko & Stryer

Biochemistry, Fifth Edition



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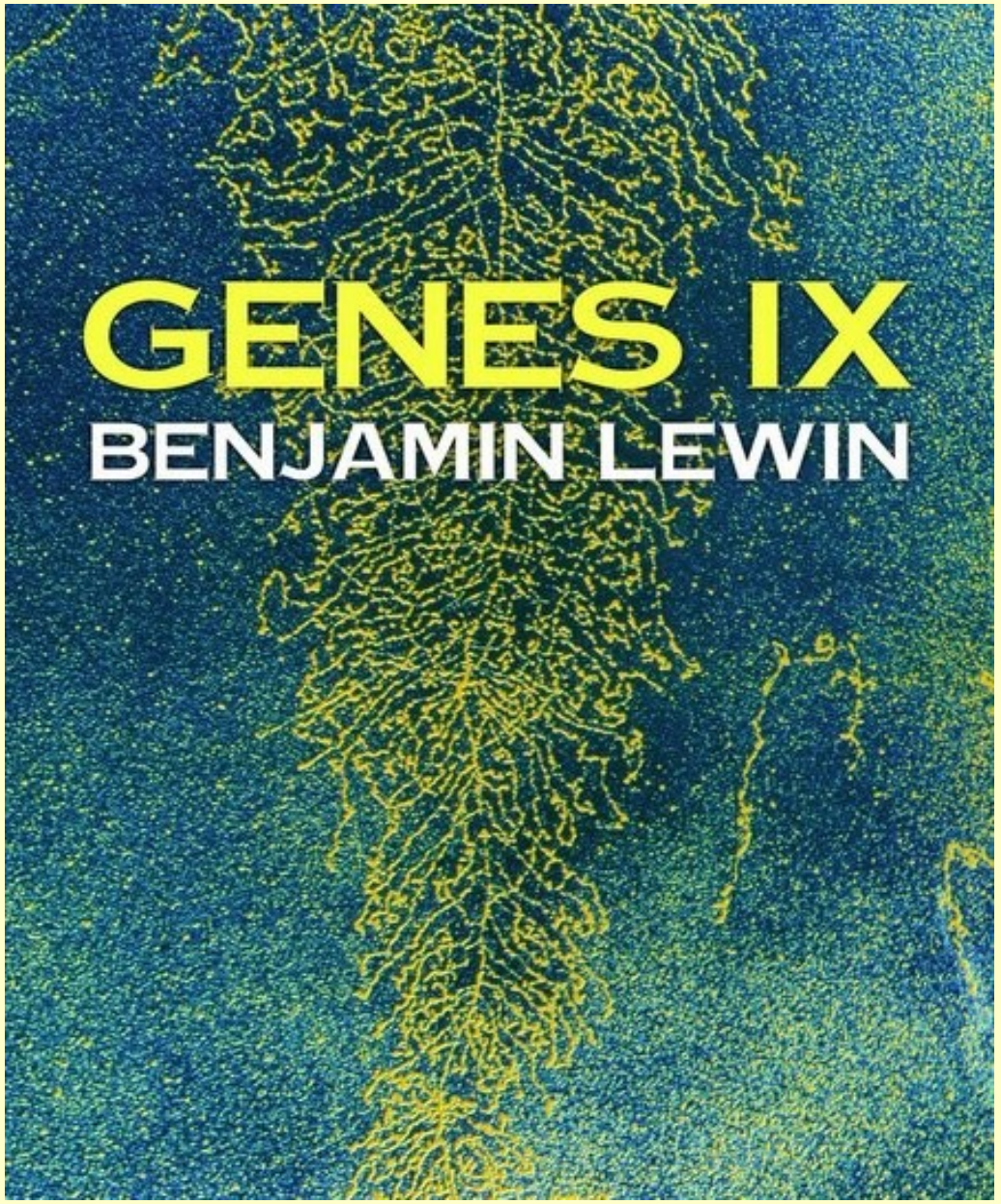
Benjamin Lewin

Genes IX



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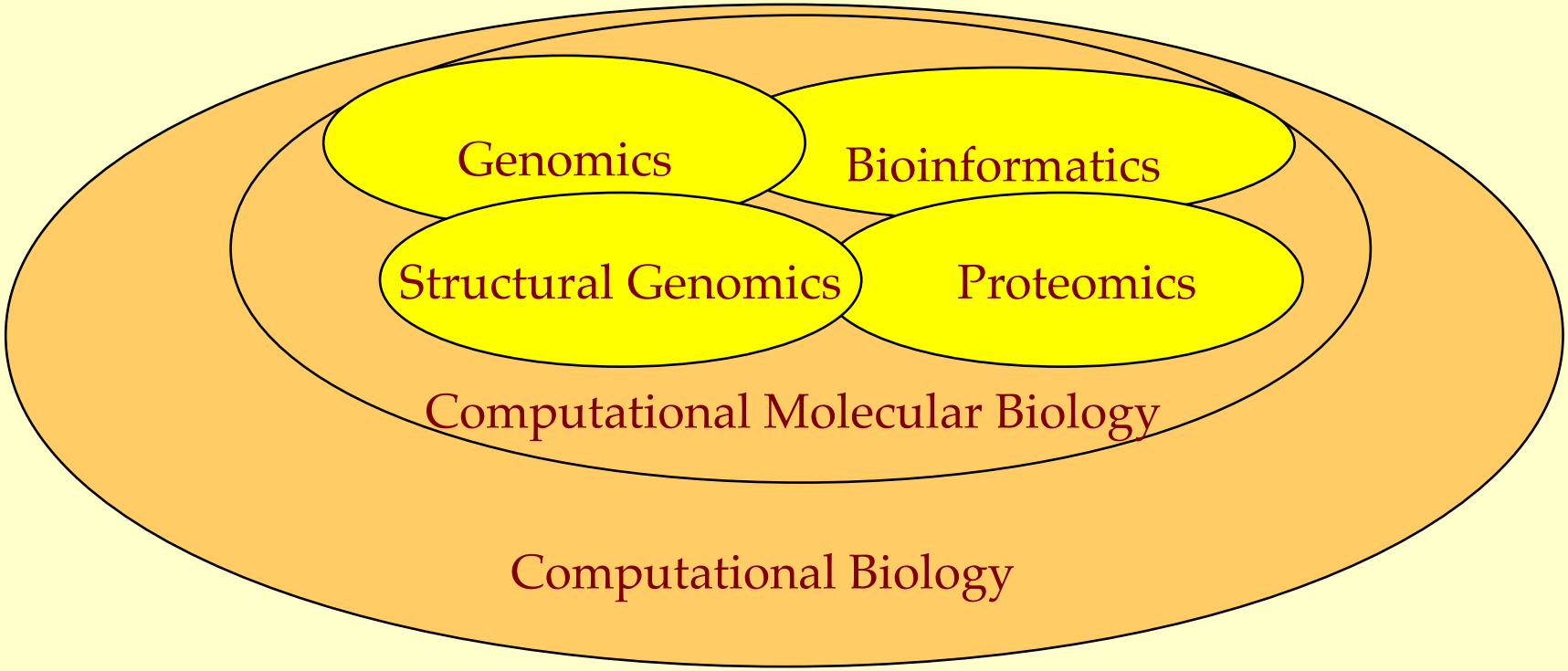
Genomics, Bioinformatics & Computational Biology



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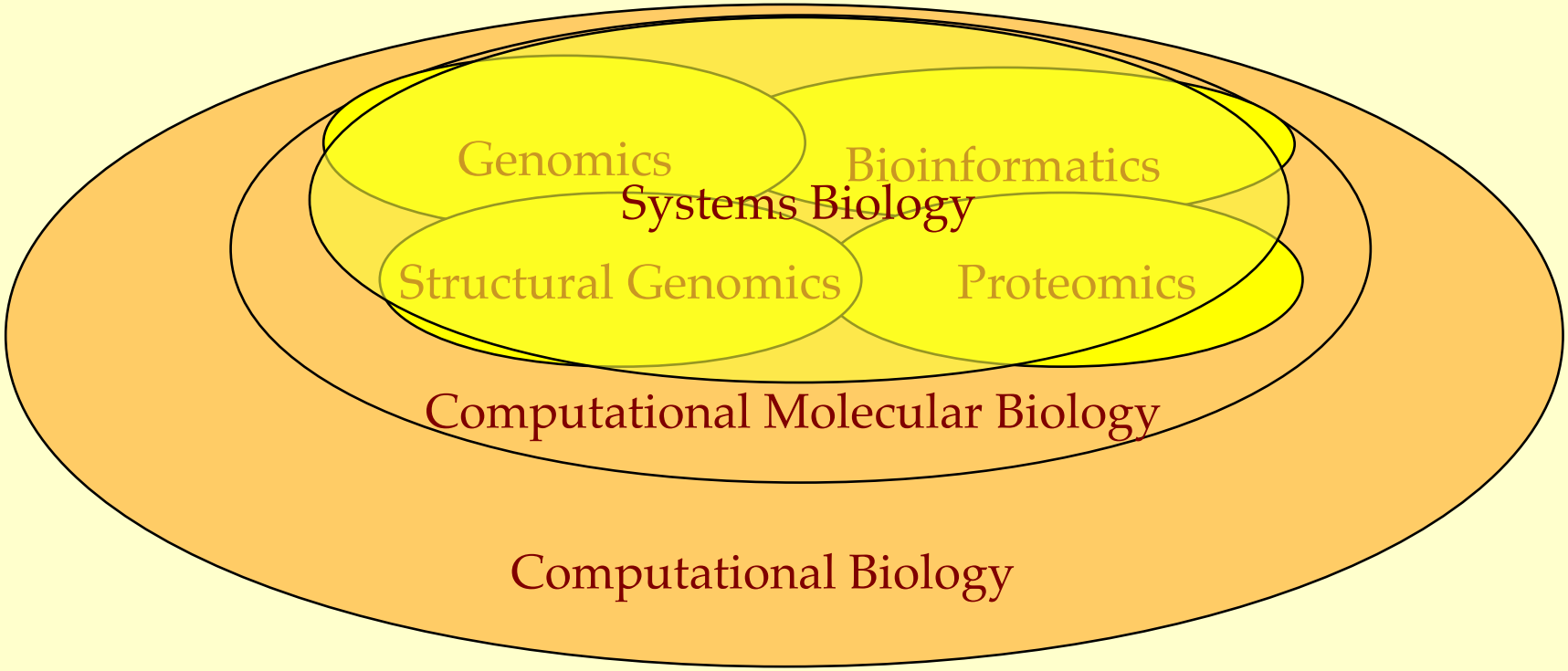
Genomics, Bioinformatics & Computational Biology



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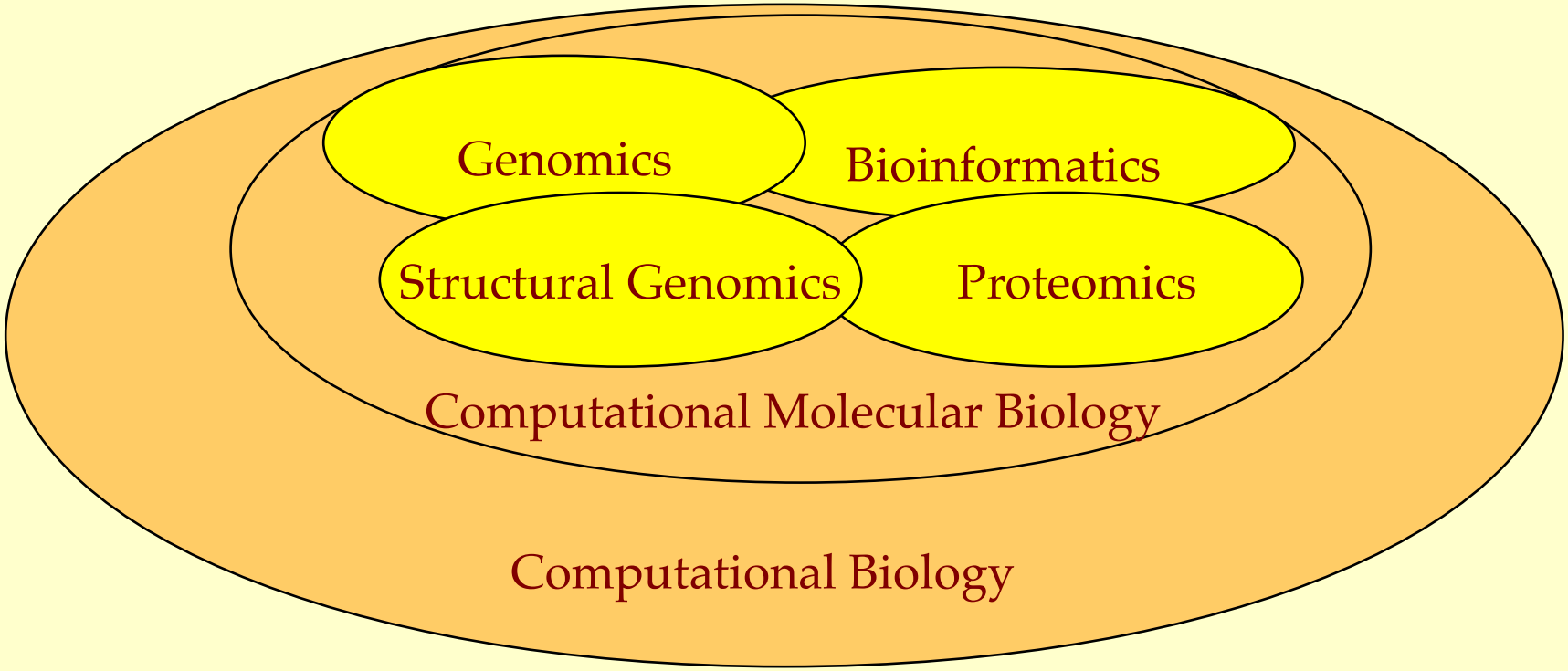
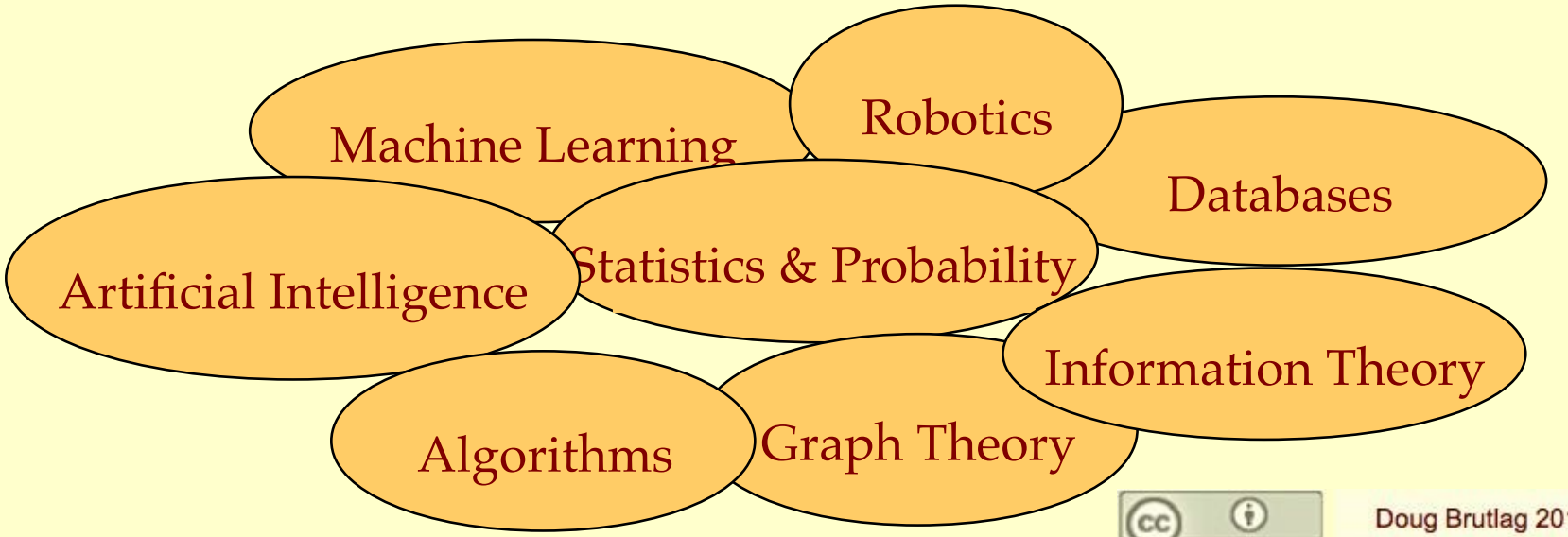
Genomics, Bioinformatics & Computational Biology





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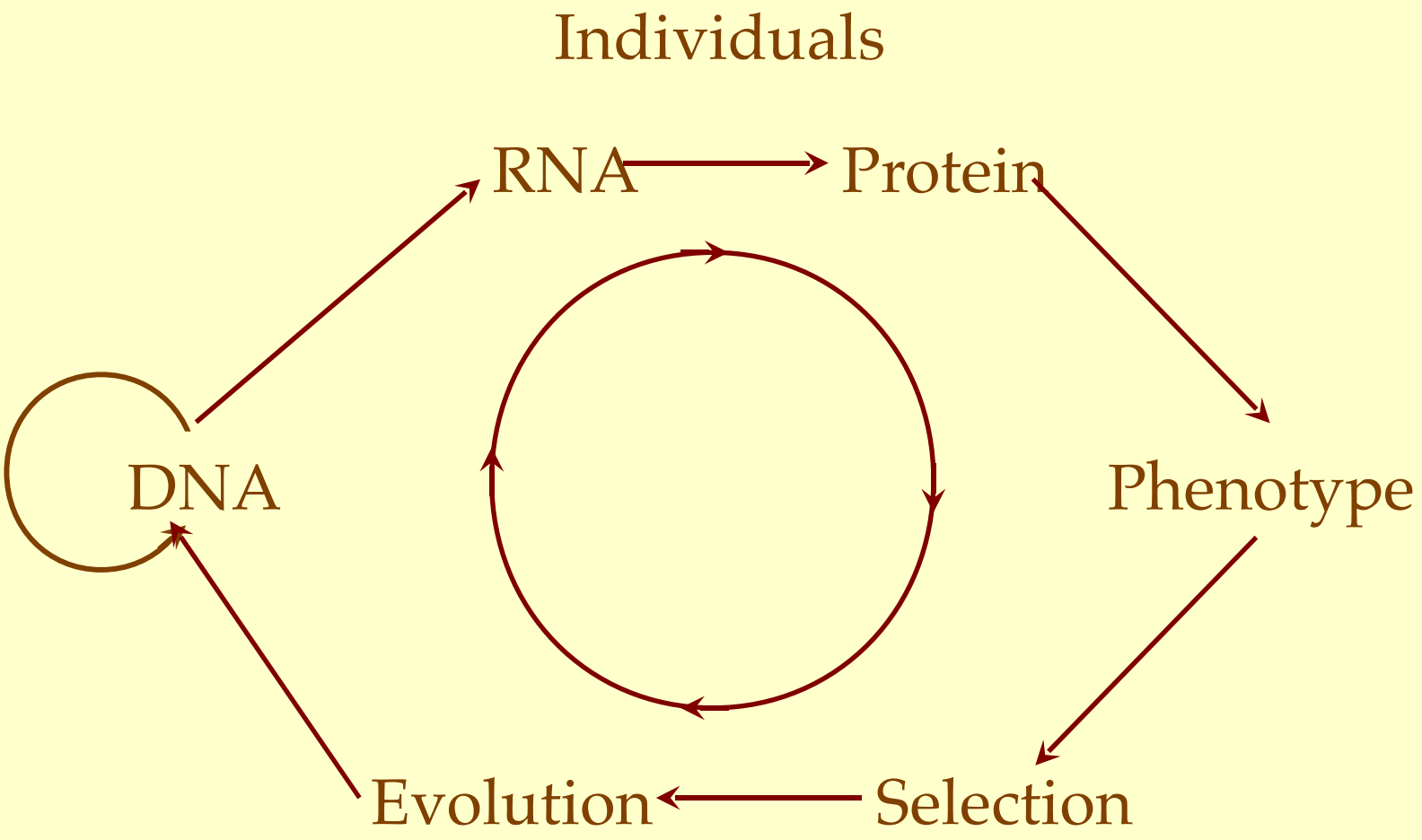
What is Bioinformatics?



Biological Information

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Computational Goals of Bioinformatics

- Learn & Generalize: Discover conserved patterns (models) of sequences, structures, interactions, metabolism & chemistries from well-studied examples.
- Prediction: Infer function or structure of newly sequenced genes, genomes, proteins or proteomes from these generalizations.
- Organize & Integrate: Develop a systematic and genomic approach to molecular interactions, metabolism, cell signaling, gene expression…
- Simulate: Model gene expression, gene regulation, protein folding, protein-protein interaction, protein-ligand binding, catalytic function, metabolism…
- Engineer: Construct novel organisms or novel functions or novel regulation of genes and proteins.
- Gene Therapy: Target specific genes, or mutations, RNAi to change a disease phenotype.

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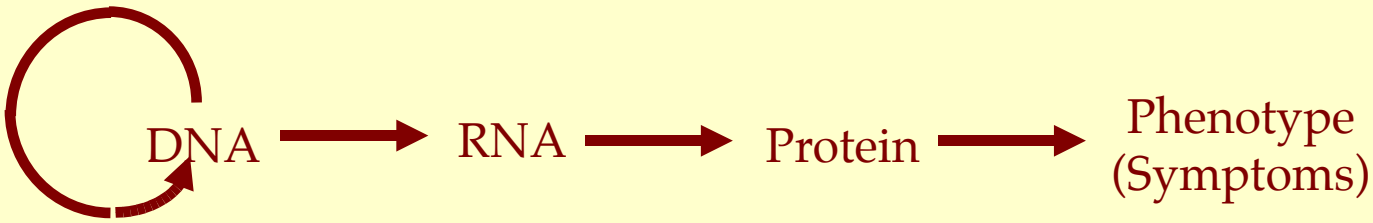
Central Paradigm of Molecular Biology



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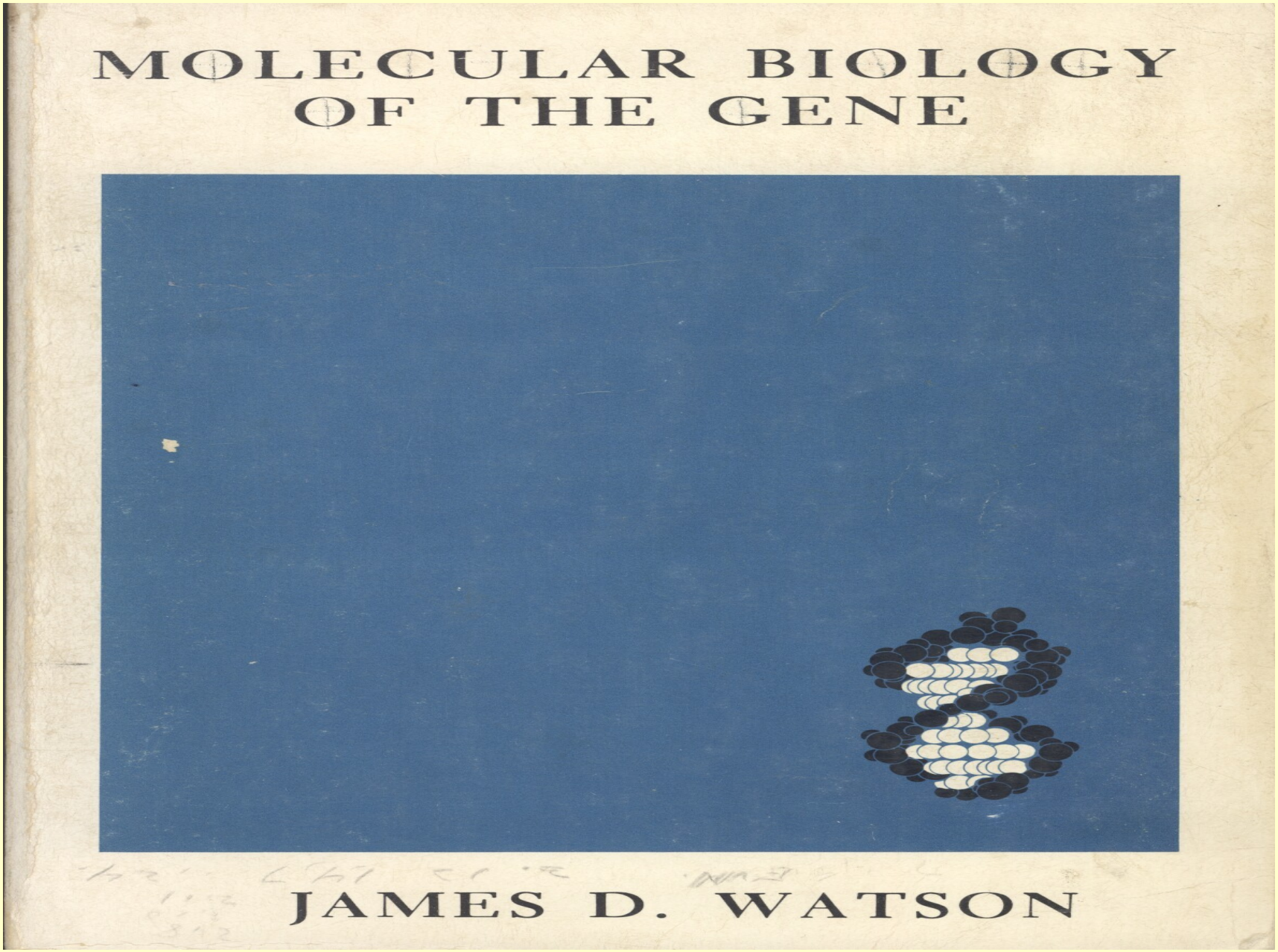
Molecular Biology of the Gene 1965



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Central Paradigm of Bioinformatics

Genetic Information → Molecular Structure → Biochemical Function → Phenotype (Symptoms)

MVHLTPEEKT
AVNALWGKVN
VDAVGGEALG
RLLVVYPWTQ
RFFESFGDLS
SPDAVMGNPK
VKAHGKKVLG
AFSDGLAHLD
NLKGTFSQLS
ELHCDKLHVD
PENFRLLGNV
LVCVLARNFG
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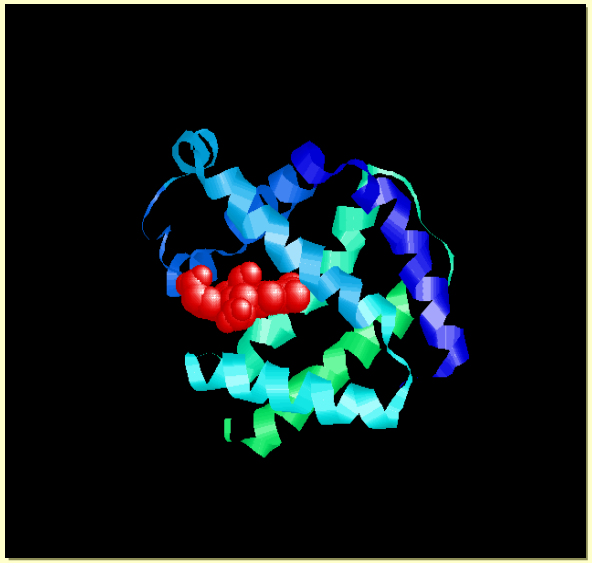
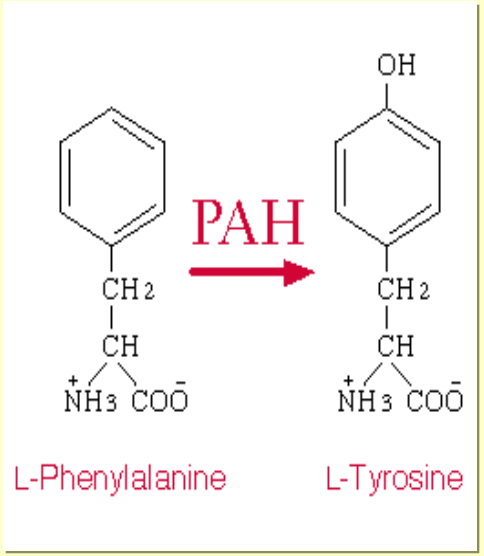
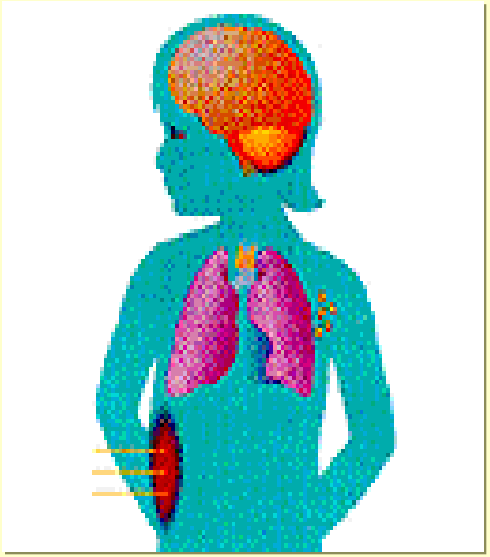
ALAHKYH







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Central Paradigm of Bioinformatics

Genetic Information → Molecular Structure → Biochemical Function → Phenotype (Symptoms)

MVHLTPEEKT
AVNALWGKVN
VDAVGGEALG
RLLVVYPWTQ
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SPDAVMGNPK
VKAHGKKVLG
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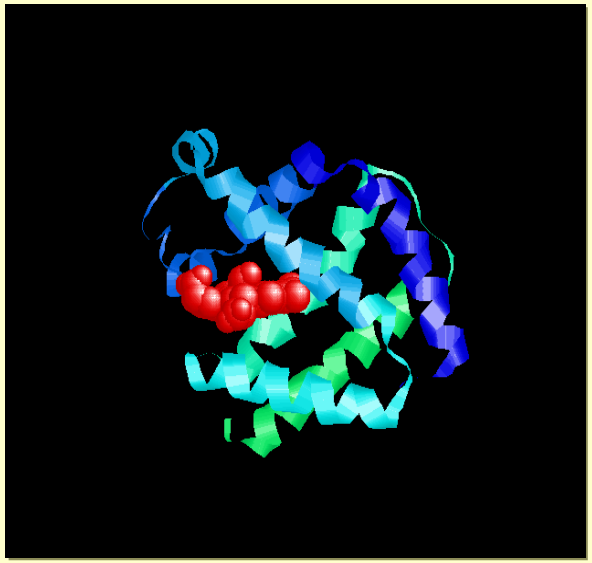

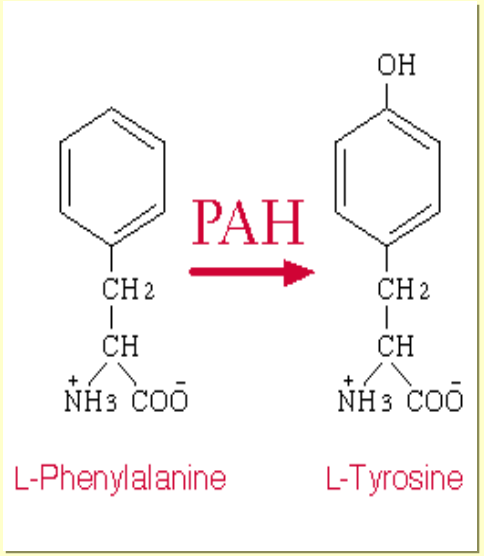

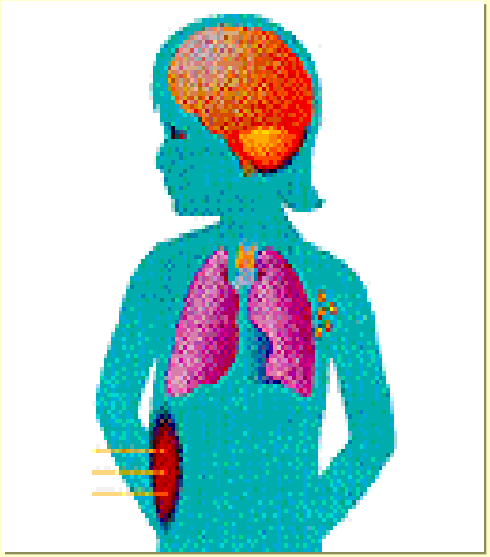

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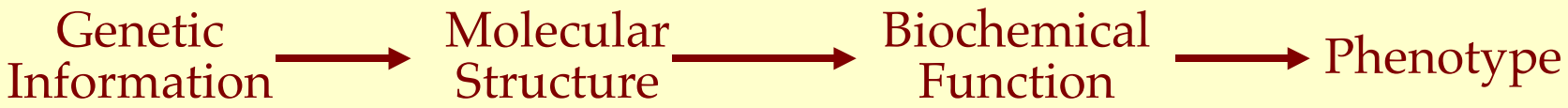
Challenges Understanding Genetic Information



- Genetic information is redundant
- Structural information is redundant
- Genes and proteins are meta-stable
- Single genes have multiple functions
- Genes are one dimensional but function depends on three-dimensional structure

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Redundancy in Genomic & Protein Sequences

- DNA is double-stranded
- Genetic code
- Acceptable amino-acid replacements
- Intron-exon variation
- Alternative splicing
- Strain variations (SNPs)
- Sequencing errors

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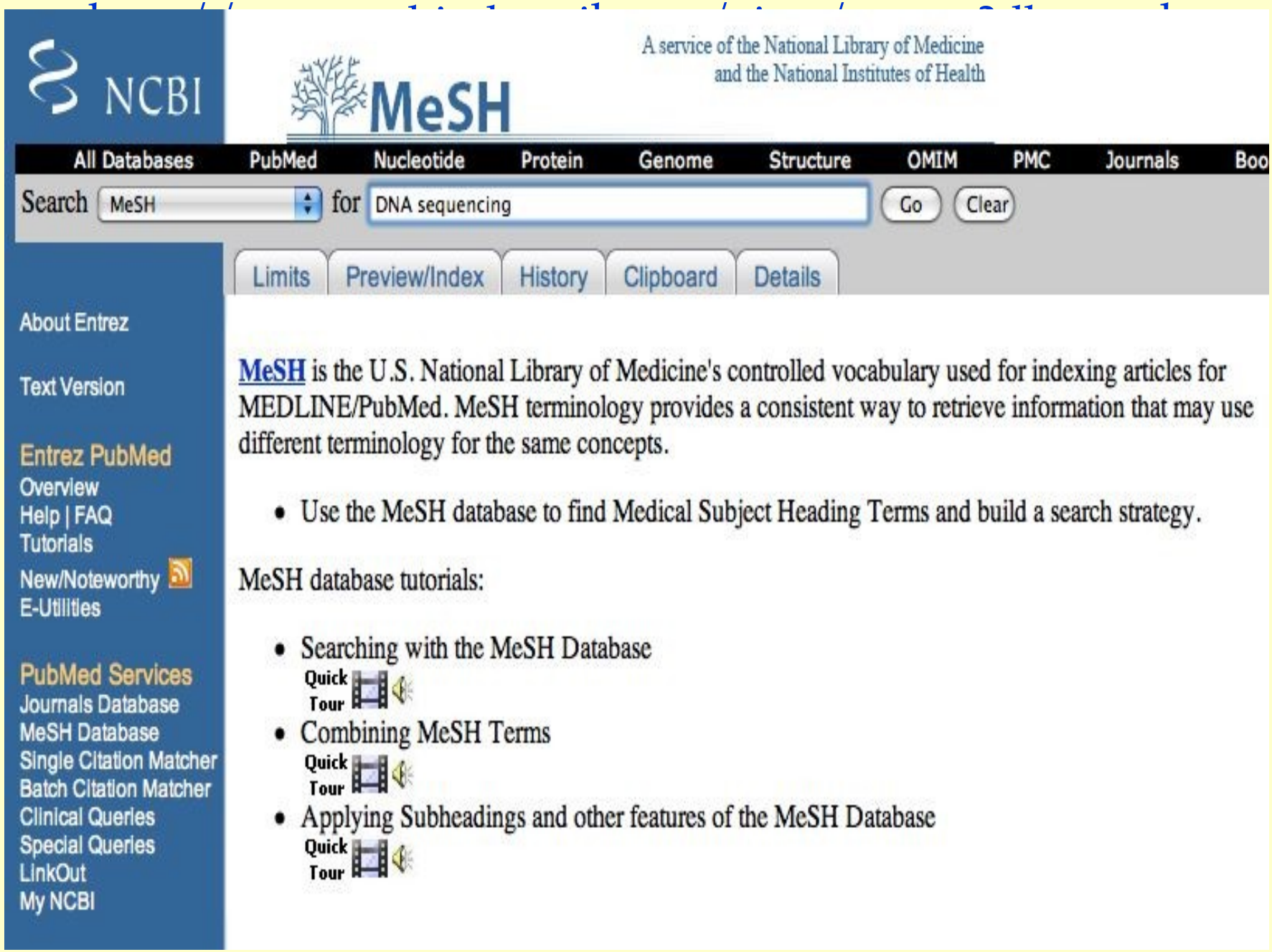
Using A Controlled Vocabulary for Literature Search



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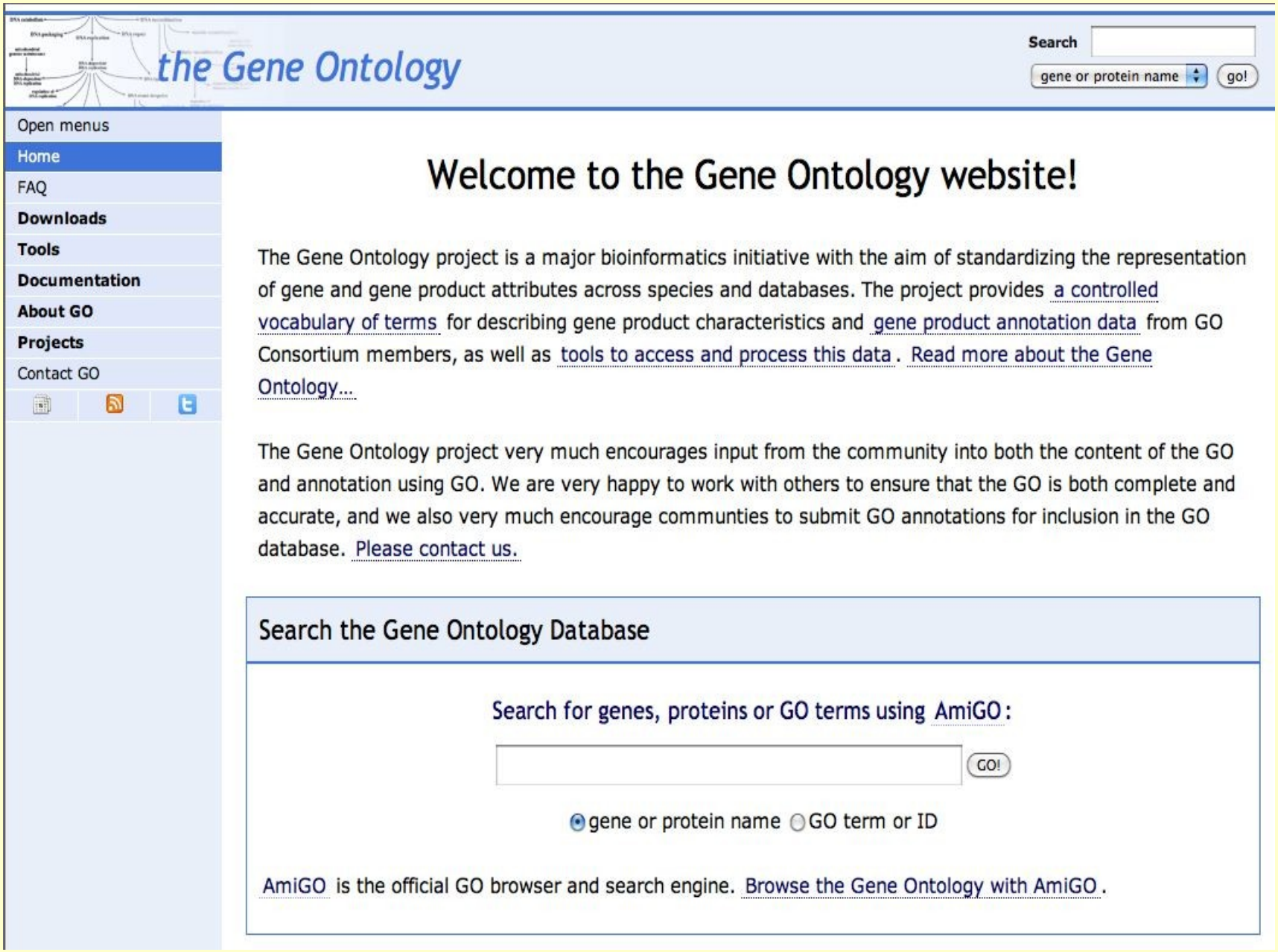
Gene Ontology Database

http://www.geneontology.org/



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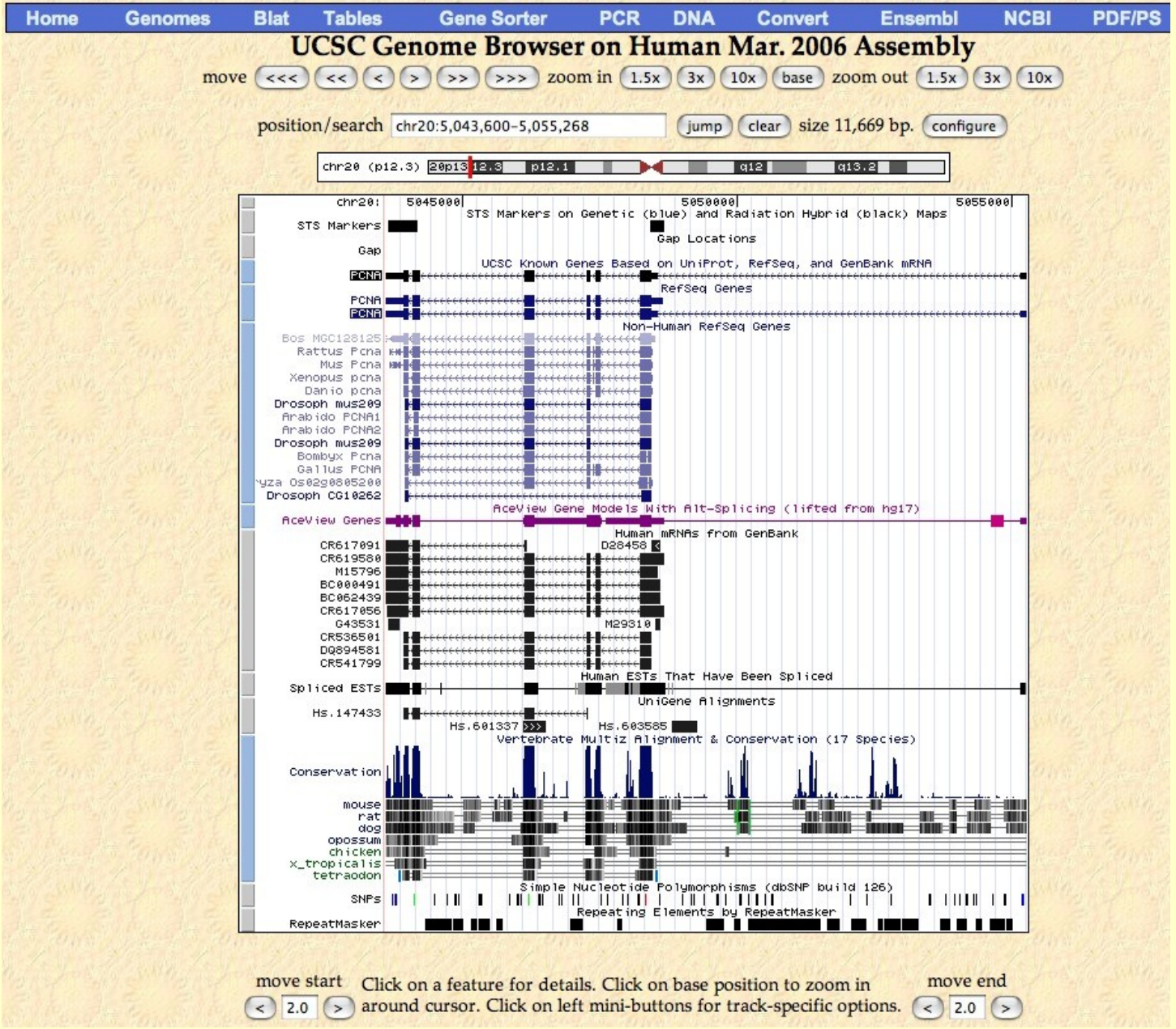
UCSC Genome Browser

http://genome.ucsc.edu/



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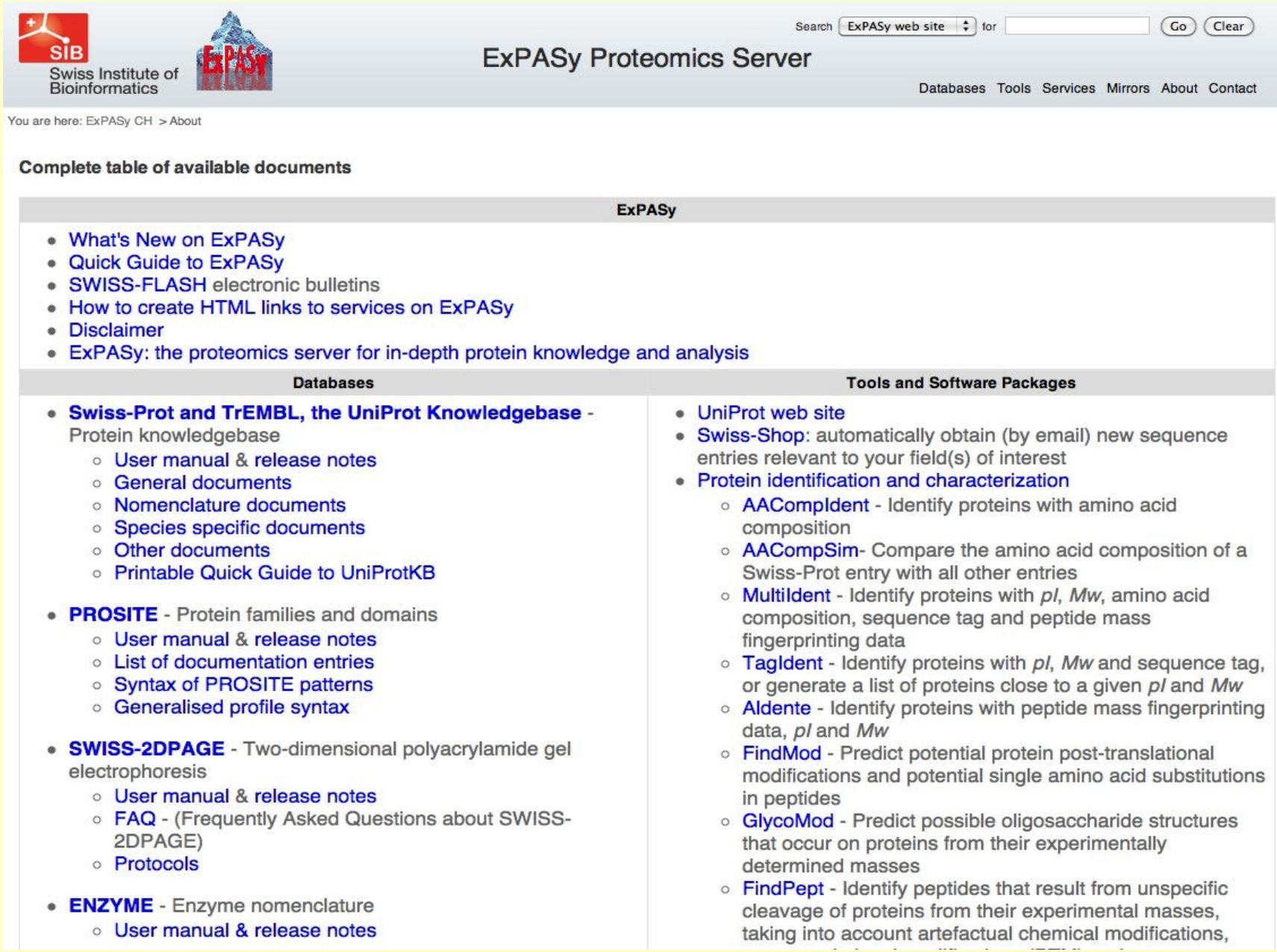
ExPASy Proteomics Server

http://www.expasy.ch/doc.html



Search ExPASy web site for Go Clear

Swiss Institute of Bioinformatics

ExPASy Proteomics Server

Databases Tools Services Mirrors About Contact

You are here: ExPASy CH > About

Complete table of available documents

ExPASy

- What's New on ExPASy
- Quick Guide to ExPASy
- SWISS-FLASH electronic bulletins
- How to create HTML links to services on ExPASy
- Disclaimer
- ExPASy: the proteomics server for in-depth protein knowledge and analysis

Databases

- **Swiss-Prot and TrEMBL, the UniProt Knowledgebase** - Protein knowledgebase
  - User manual & release notes
  - General documents
  - Nomenclature documents
  - Species specific documents
  - Other documents
  - Printable Quick Guide to UniProtKB
- **PROSITE** - Protein families and domains
  - User manual & release notes
  - List of documentation entries
  - Syntax of PROSITE patterns
  - Generalised profile syntax
- **SWISS-2DPAGE** - Two-dimensional polyacrylamide gel electrophoresis
  - User manual & release notes
  - FAQ - (Frequently Asked Questions about SWISS-2DPAGE)
  - Protocols
- **ENZYME** - Enzyme nomenclature
  - User manual & release notes

Tools and Software Packages

- UniProt web site
- Swiss-Shop: automatically obtain (by email) new sequence entries relevant to your field(s) of interest
- Protein identification and characterization
  - AACompIdent - Identify proteins with amino acid composition
  - AACompSim- Compare the amino acid composition of a Swiss-Prot entry with all other entries
  - MultiIdent - Identify proteins with *pI*, *Mw*, amino acid composition, sequence tag and peptide mass fingerprinting data
  - TagIdent - Identify proteins with *pI*, *Mw* and sequence tag, or generate a list of proteins close to a given *pI* and *Mw*
  - Aldente - Identify proteins with peptide mass fingerprinting data, *pI* and *Mw*
  - FindMod - Predict potential protein post-translational modifications and potential single amino acid substitutions in peptides
  - GlycoMod - Predict possible oligosaccharide structures that occur on proteins from their experimentally determined masses
  - FindPept - Identify peptides that result from unspecific cleavage of proteins from their experimental masses, taking into account artefactual chemical modifications,

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Inferring Biological Function from Protein Sequence

Consensus Sequences or Sequence Motifs

Zinc Finger (C2H2 type)
C x {2,4} C x {12} H x {3,5} H

Sequences of Common Structure or Function

Sequence Similarity

```
                10        20        30        40                  50
Query VLSPADKTNVKAAWGKVGAHAGEVGAEALERMFLSFPTTKTYFPHF------DLSHGS
      |:| :|: | |:|||||     | |:||| |: : :|:|  :|  |       |:  |
Match HLTPEEKSAVTALWGKV--NVDEYGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGN
                10        20        30        40        50
```

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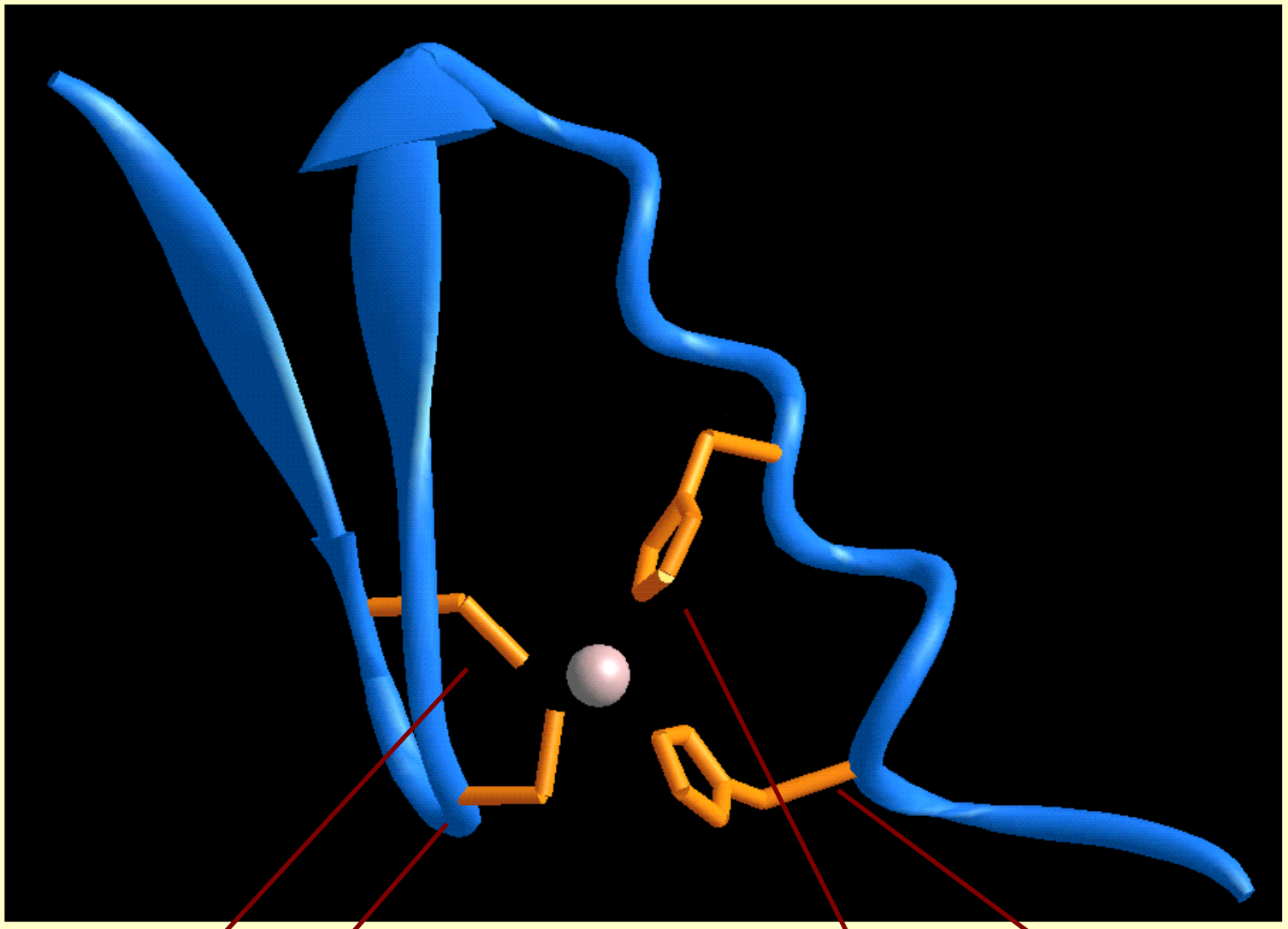
A Typical Motif:
Zinc Finger DNA Binding Motif



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Inferring Biological Function from Protein Sequence

Weight Matrices or Position-Specific Scoring Matrices

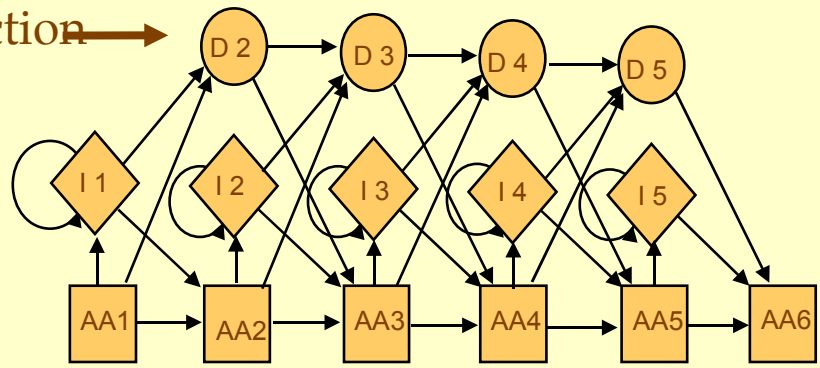
A	2	1	3	13	10	12	67	4	13	9	1	2
R	7	5	8	9	4	0	1	16	7	0	1	0
N	0	8	0	1	0	0	0	2	1	1	10	0
D	0	1	0	1	13	0	0	12	1	0	4	0
C	0	0	1	0	0	0	0	0	0	2	2	1
Q	1	1	21	8	10	0	0	7	6	0	0	2
E	2	0	0	9	21	0	0	15	7	3	3	0
G	9	7	1	4	0	0	8	0	0	0	46	0
H	4	3	1	1	2	0	0	2	2	0	5	0
I	10	0	11	1	2	10	0	4	9	3	0	16
L	16	1	17	0	1	31	0	3	11	24	0	14
K	3	4	5	10	11	1	1	13	10	0	5	2
M	7	1	1	0	0	0	0	0	5	7	1	8
F	4	0	3	0	0	4	0	0	0	10	0	0
P	0	6	0	1	0	0	0	0	0	0	0	0
S	1	17	0	8	3	1	3	0	2	2	2	0
T	5	22	3	11	1	5	0	2	2	2	0	5
W	2	0	0	0	0	0	0	0	0	1	0	1
Y	1	0	4	2	0	1	0	0	2	4	0	1
V	6	3	1	1	2	15	0	0	2	12	0	28

Consensus Sequences or Sequence Motifs

Zinc Finger (C2H2 type)
C x {2,4} C x {12} H x {3,5} H

Sequences of Common Structure or Function

Profiles, PSI-BLAST Hidden Markov Models



Sequence Similarity

```
                10        20        30        40                  50
Query VLSPADKTNVKAAWGKVGAHAGEVGAEALERMFLSFPTTKTYFPHF------DLSHGS
      |:| :|: | |:|||||     | |:||| |: : :|:|  :|  |       |:  |
Match HLTPEEKSAVTALWGKV--NVDEYGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGN
                10        20        30        40        50
```

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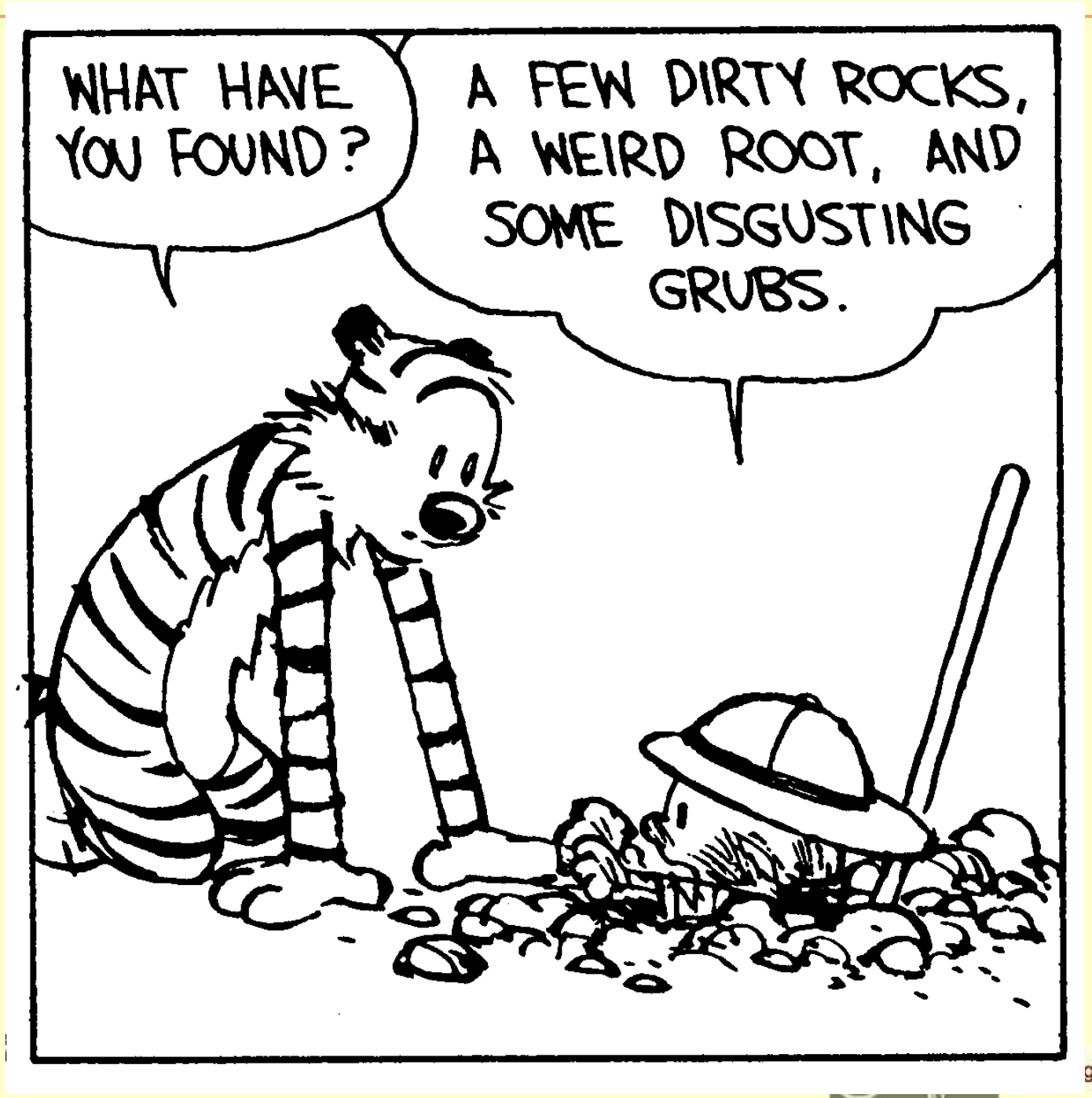
Buried Treasure

Buried Treasure



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Buried Treasure

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Clustal Globin Alignment

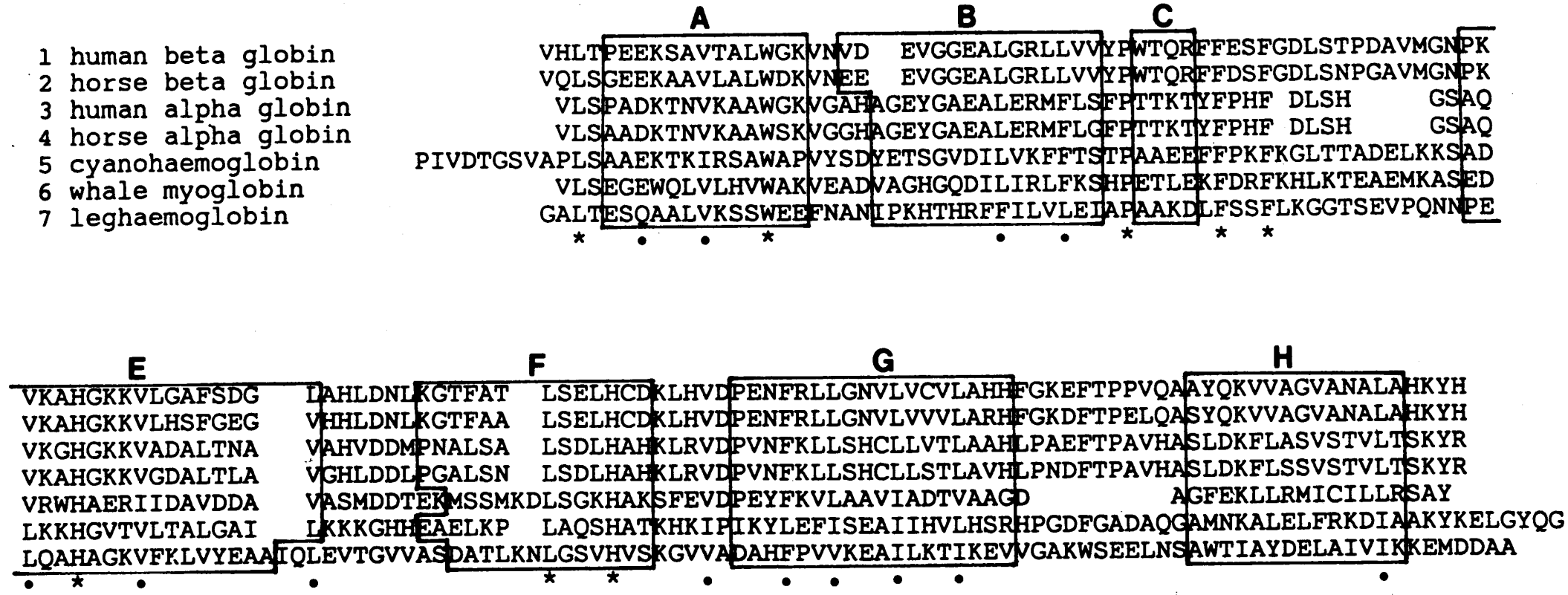

Fig. 3. CLUSTAL-produced multiple alignment of seven globin sequences taken from Lesk and Chothia (1980) (see RESULTS, section

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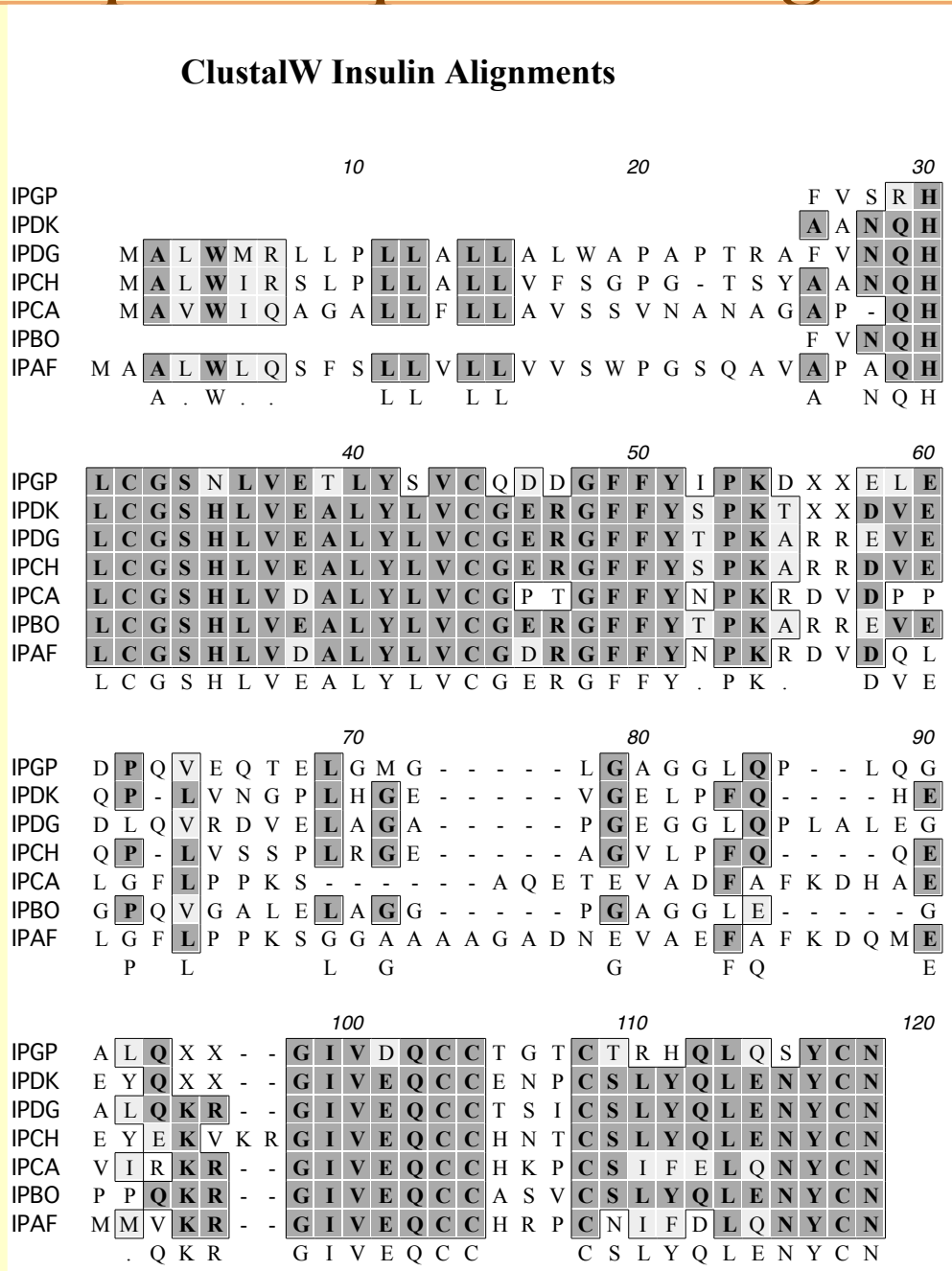
Consensus Sequence From a Multiple Sequence Alignment



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HMM Model of Hemoglobins

http://decypher.stanford.edu/

ClustalW Search on DeCypher|... | Results for Job CGI_Temp7772...

Home Page

HMM Model created from: ClustalW Search on DeCypher Protein Sequences

Download (For Internet Explorer Browsers, Right Click on Hyperlink and Select "Save Target As...")

Search with this Model

```
HMMER2.0
NAME  d:\decypher\output\CGI_Temp77466aad91_H
DESC
LENG  161
ALPH  Amino
RF    no
CS    no
MAP   yes
COM   D:\decypher\bin\hmmbuild.exe d:\decypher\output/CGI_Temp7772fbe351.out.tmp d:\decypher\output\CGI_Temp77466aad91_H.seq
NSEQ  7
DATE  Thu Feb 15 10:29:18 2007
CKSUM 1944
XT      -8455     -4  -1000  -1000  -8455     -4  -8455     -4
NULT      -4  -8455
NULE     595  -1558     85    338   -294    453  -1158    197    249    902  -1085   -142    -21   -313     45    531    201
HMM        A       C       D       E       F       G       H       I       K       L       M       N       P       Q       R       S       T
         m->m    m->i    m->d    i->m    i->i    d->m    d->d    b->m    m->e
         -606       *   -1543
     1   -820   -1123   -1229   -1315   -2065   -1220   -1331   -2014   -1345   -2133   -1685   -1232    3693   -1331   -1440   -1011   -1095
     -   -149    -500     233      43    -381     399     106    -626     210    -466    -720     275     394      45      96     359     117
     -    -34   -5976   -7018    -894   -1115    -701   -1378    -606       *
     2   -958    -760   -2548   -2272    -535   -2401   -1765    2979   -1942     375     395   -2092   -2523   -1850   -1979   -1799    -993
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     -    -34   -5976   -7018    -894   -1115    -701   -1378       *       *
     3   -641    -619   -2245   -2036    -813   -1897   -1637    1127   -1762     -54      76   -1764   -2218   -1697   -1826   -1292    -764
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     5      1    -504   -1094   -1024   -1493    -825    -961    -774    -860   -1268    -782    -771   -1401    -850   -1002    -231    2989
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     -    -34   -5976   -7018    -894   -1115    -701   -1378       *       *
     6   -654   -1010   -1195   -1358   -2342    3274   -1442   -2362   -1583   -2515   -1948   -1206   -1681   -1458   -1665    -851    -984
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     -    -34   -5976   -7018    -894   -1115    -701   -1378       *       *
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     8   -641    -619   -2245   -2036    -813   -1897   -1637    1127   -1762     -54      76   -1764   -2218   -1697   -1826   -1292    -764
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     -    -34   -5976   -7018    -894   -1115    -701   -1378       *       *
     9   1686    -842   -2427   -2196   -2039    1808   -1802   -1205   -2040   -1858   -1181   -1585   -1986   -1795   -2118    -663    -682
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     -    -15   -7120   -8162    -894   -1115    -701   -1378       *       *
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```

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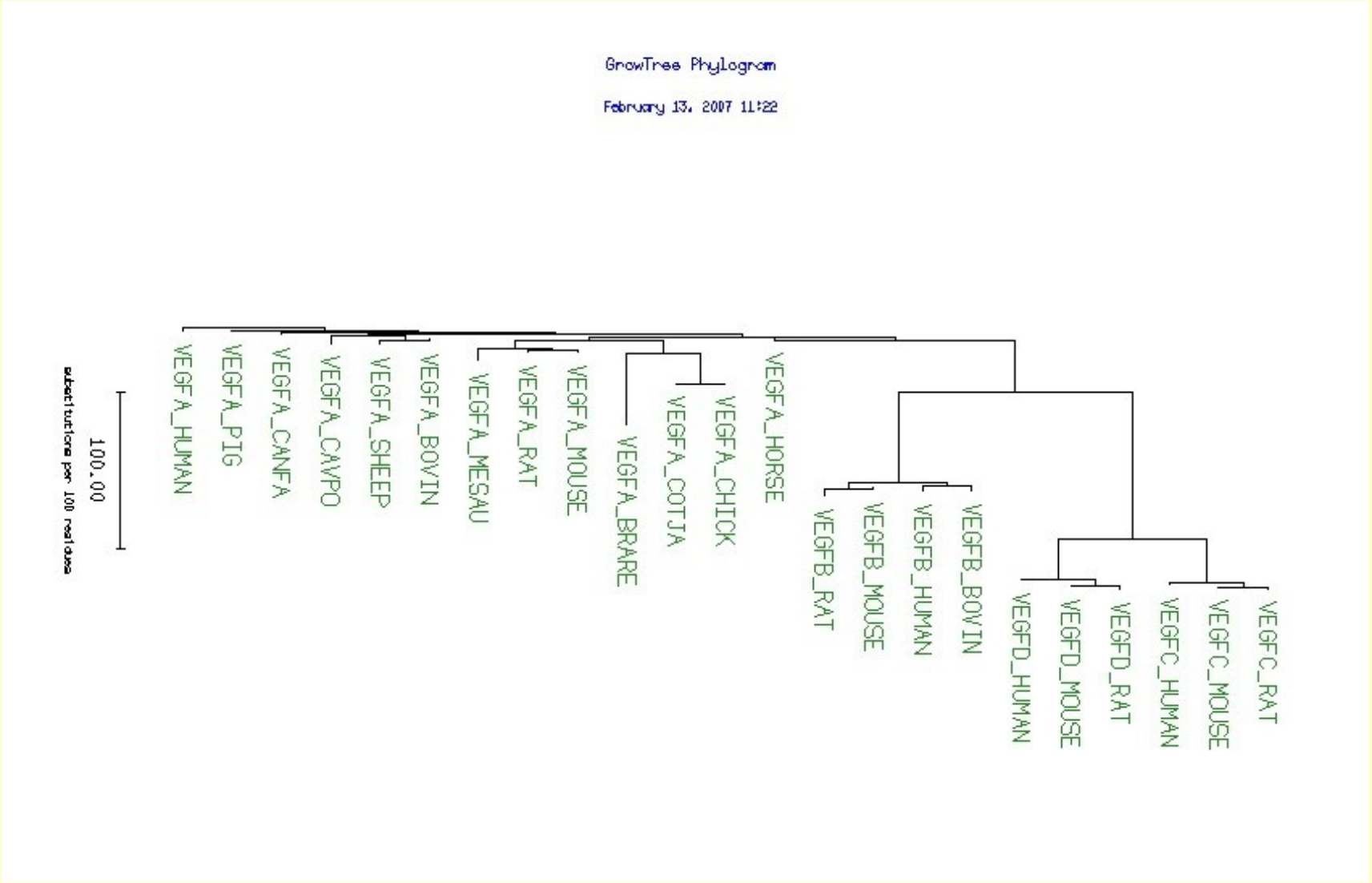
GrowTree VegF Neighbor Joining Tree



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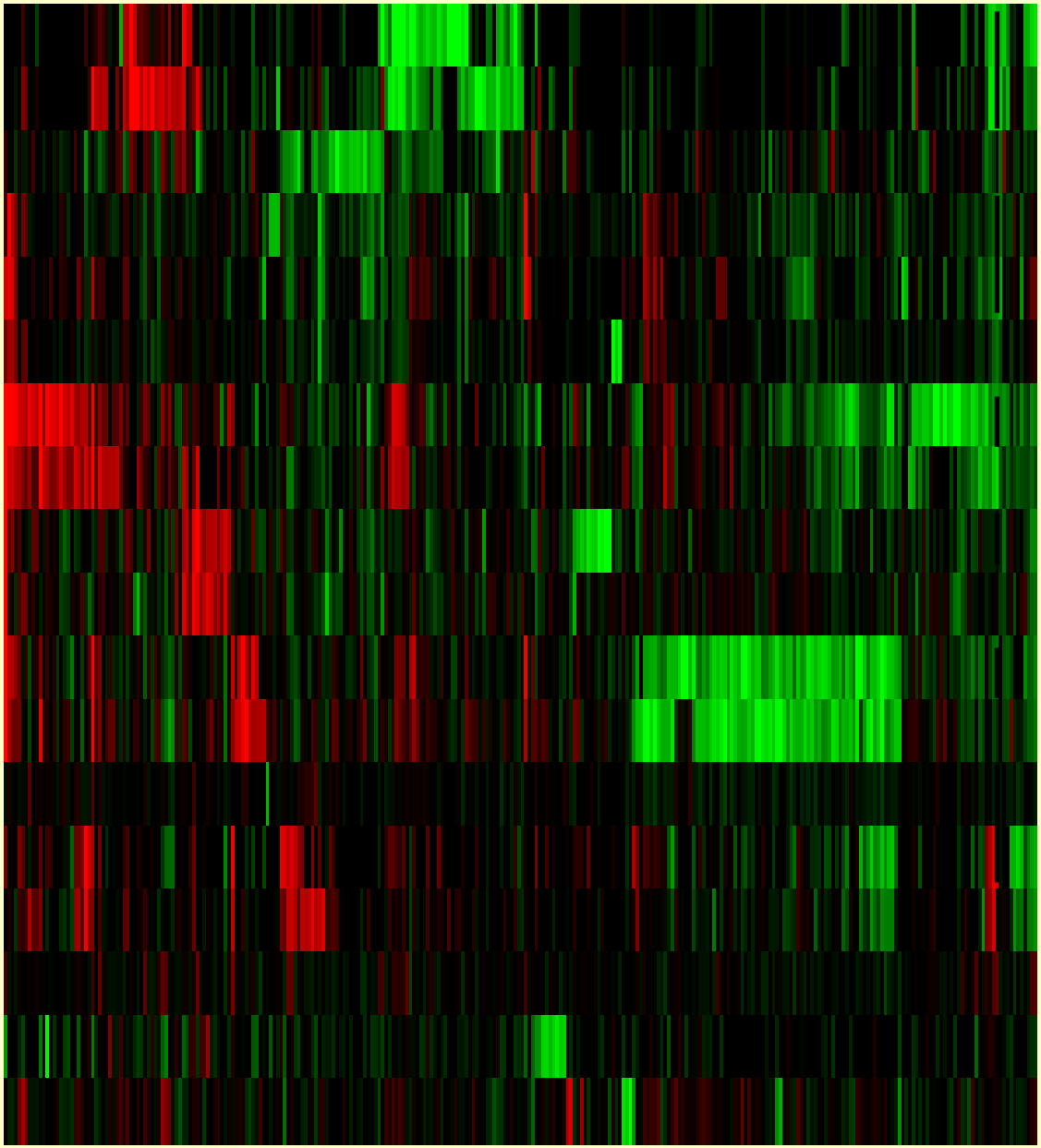
Human Gene Expression Signatures



T Cells Signaling

DNA Damage

Fibroblast Stimulation

B Cells Signaling

CMV Infection

Anoxia

Polio Infection

Monocytes Signaling IL4

Hormone

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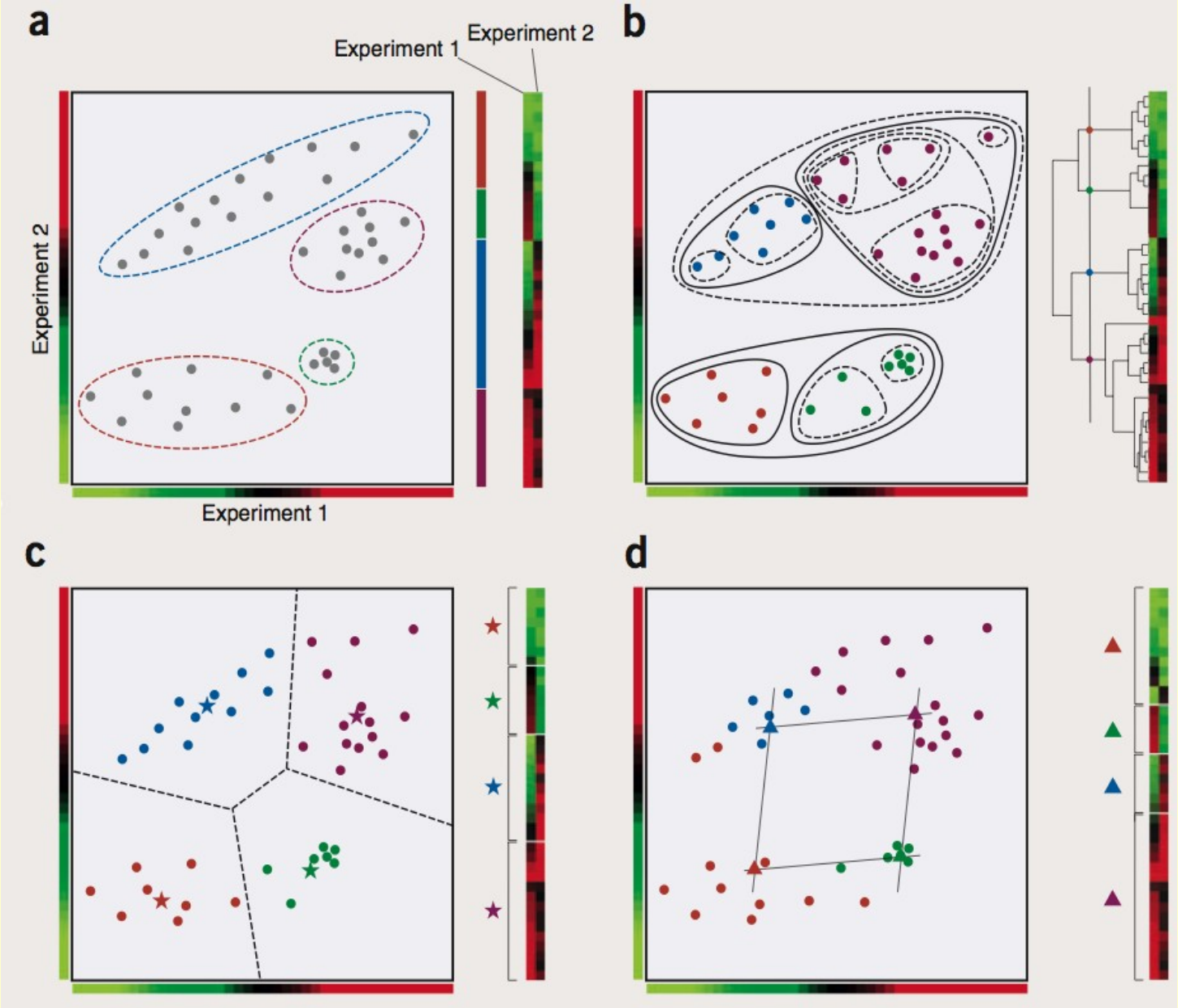
Clustering Gene Expression Profiles: Comparison of Methods



D'haeseleer P (2005). *Nat Biotechnol.* 23,1499-501.

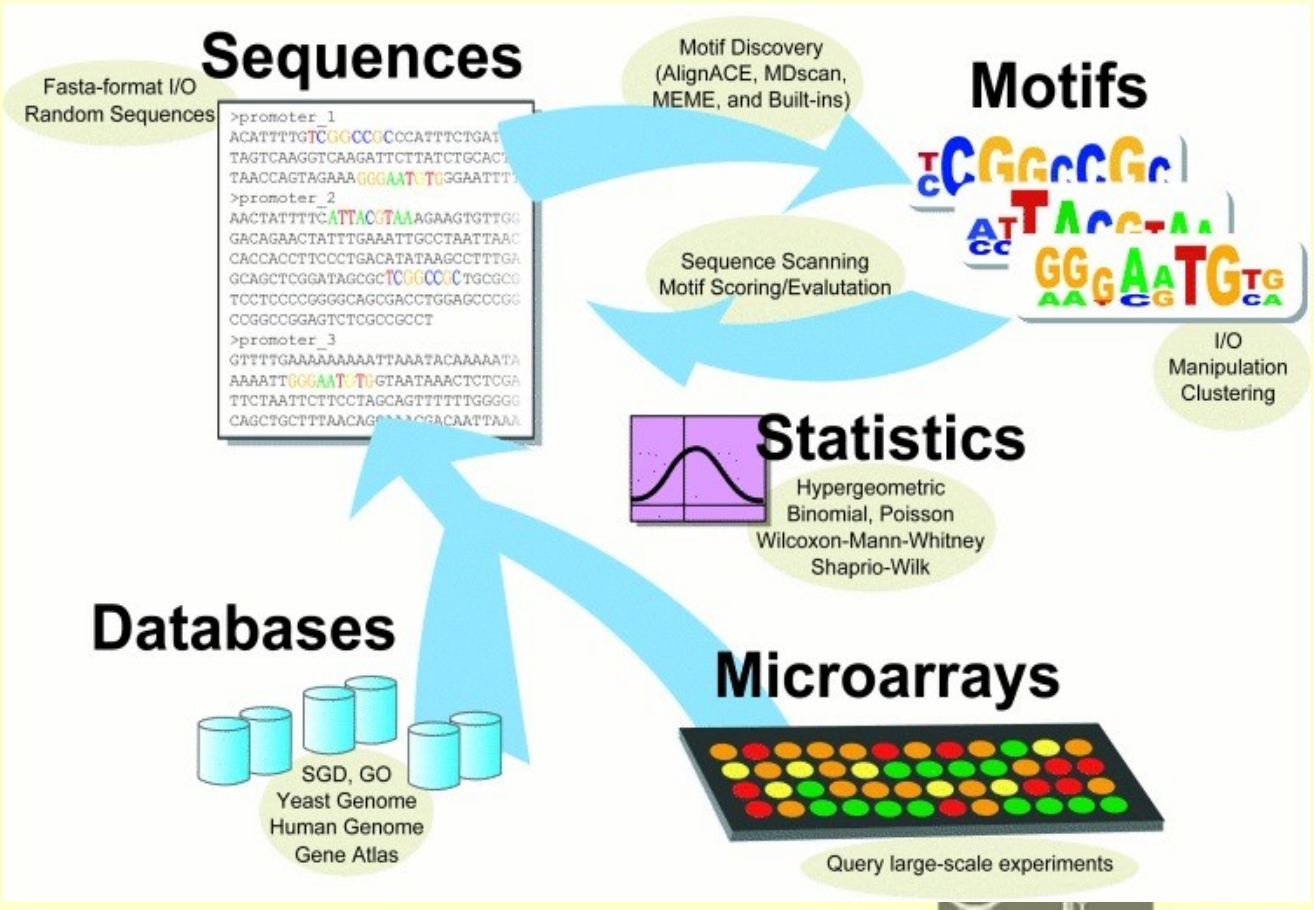
The Fraenkel Lab
TAMO -- Tools for the Analysis of MOtifs
Download and Support for the TAMO package

The TAMO package can be downloaded from this page. Support information, and possibly new modules will be distributed from this location.

- Click here for the package overview.
- Click here for short descriptions of each file.
- Click here for an introductory tutorial.
- Download the package.
- Browse the automatically generated documentation (via pydoc).
  - For each command-line program that can be executed from the unix shell, (e.g. Sitemap.py, AlignAce.py, MotifMetrics.py, UPGMA.py, etc...) documentation is obtained by executing the program without any arguments.
  - If you're looking for a place to start, the core data structure is the Motif object. This file also includes tools for constructing motifs from different data sources.
- Installation instructions are here.

License:

- The TAMO package is free for academic use. Please contact Ernest Fraenkel for commerical licensing.



Finding Transcription Factor Binding Sites

Upstream Regions

Co-expressed

GATGGCTGCACCACGTGTATGC...ACG

CACATCGCATCACGTGACCAGT...GAC

GCCTCGCACGTGGTGGTACAGT...AAC

TCTCGTTAGGACCATCACGTGA...ACA

CGCTAGCCCACGTGGATCTTGA...AGAATGACTGGC

Pho 5

Pho 8

Pho 81

Pho 84

Pho …

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Finding Transcription Factor Binding Sites

Upstream Regions — Co-expressed Genes

GATGGCTGCACCACGTGTATGC...ACGATGTCTCGC

CACATCGCATCACGTGACCAGT...GACATGGACGGC

GCCTCGCACGTGGTGGTACAGT...AACATGACTAAA

TCTCGTTAGGACCATCACGTGA...ACAATGAGAGCG

CGCTAGCCCACGTGGATCTTGT...AGAATGGCCTAT

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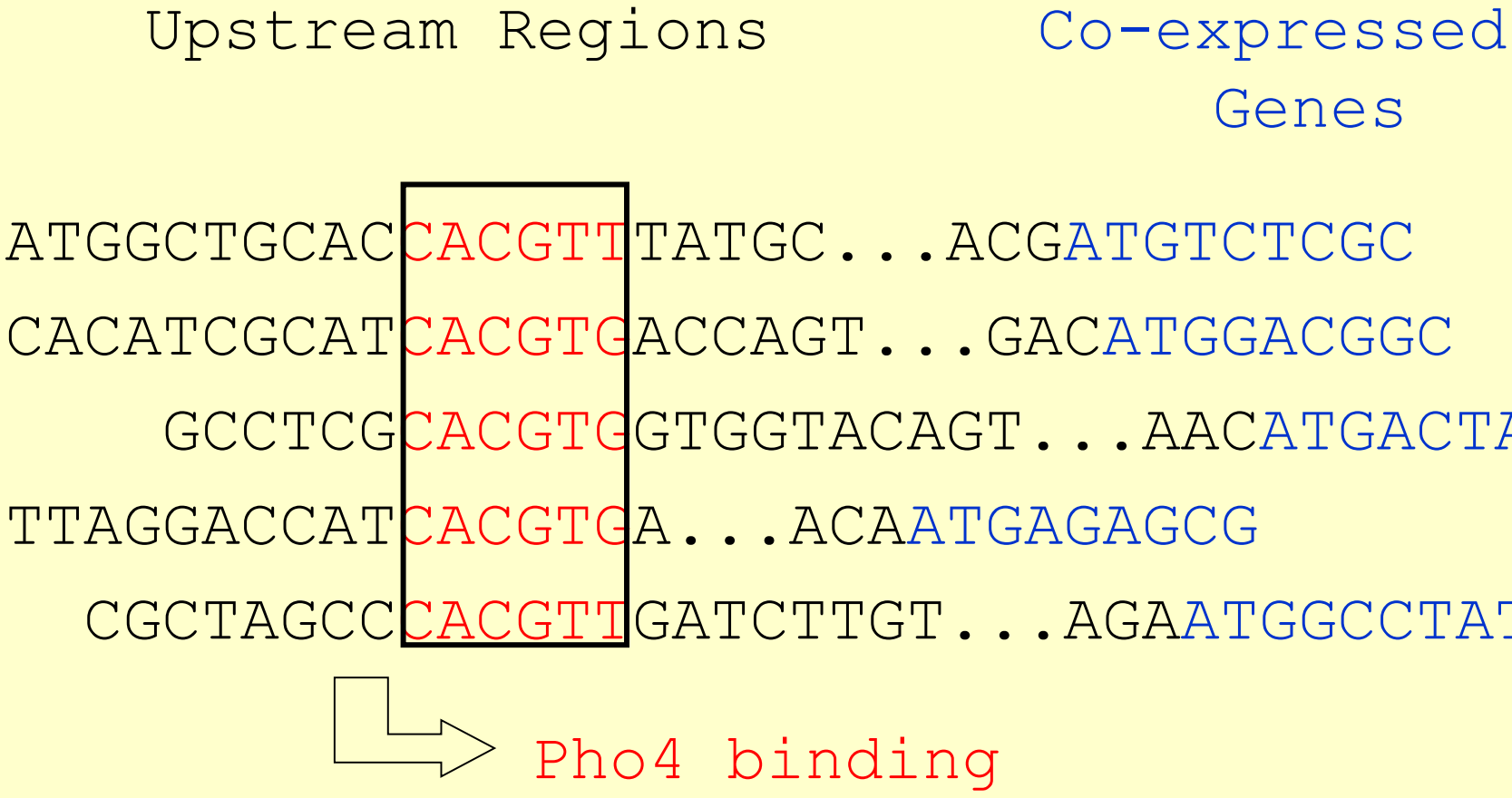
Finding Transcription Factor Binding Sites



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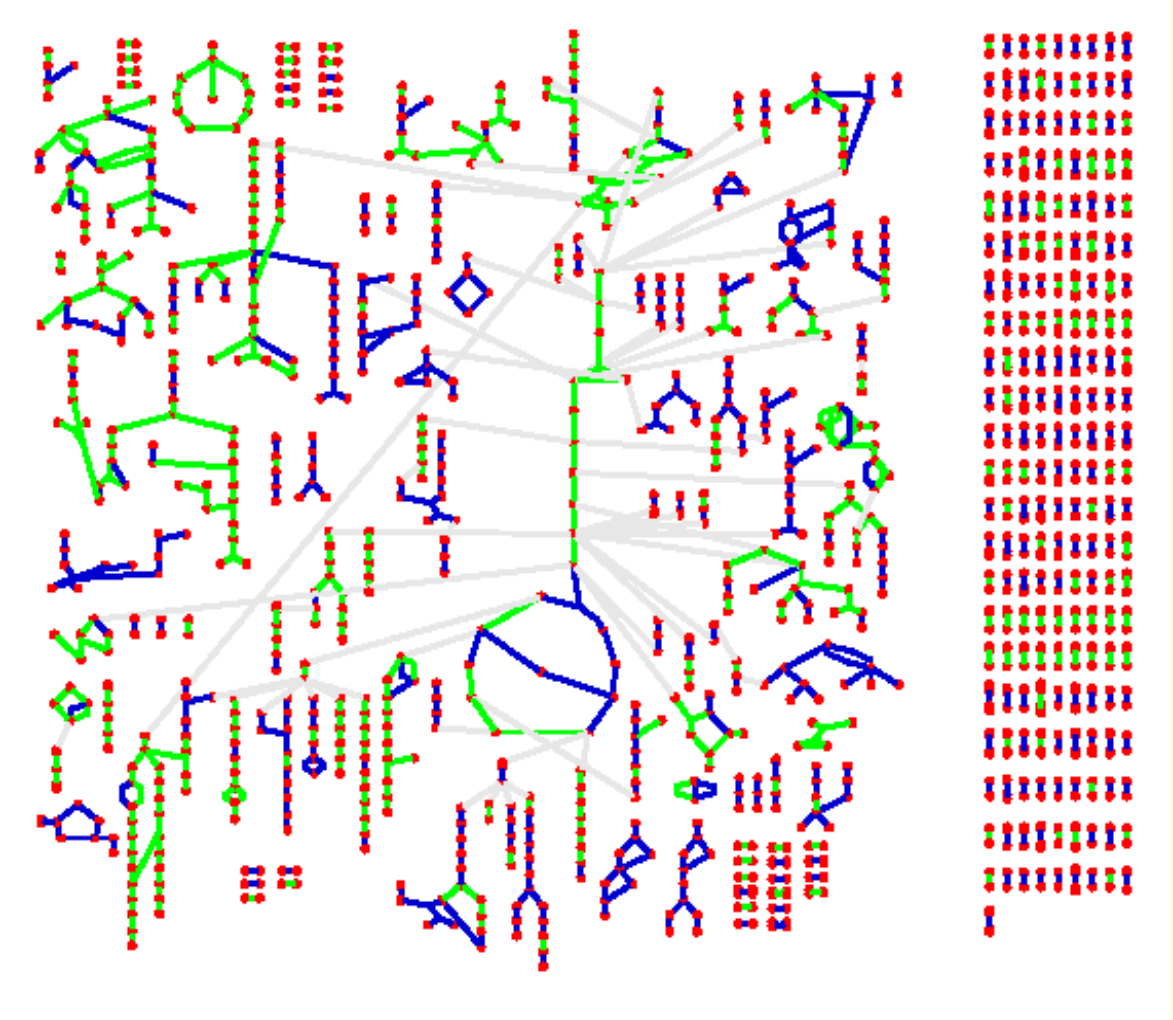
Metabolic Networks: BioCyc

http://biocyc.org/



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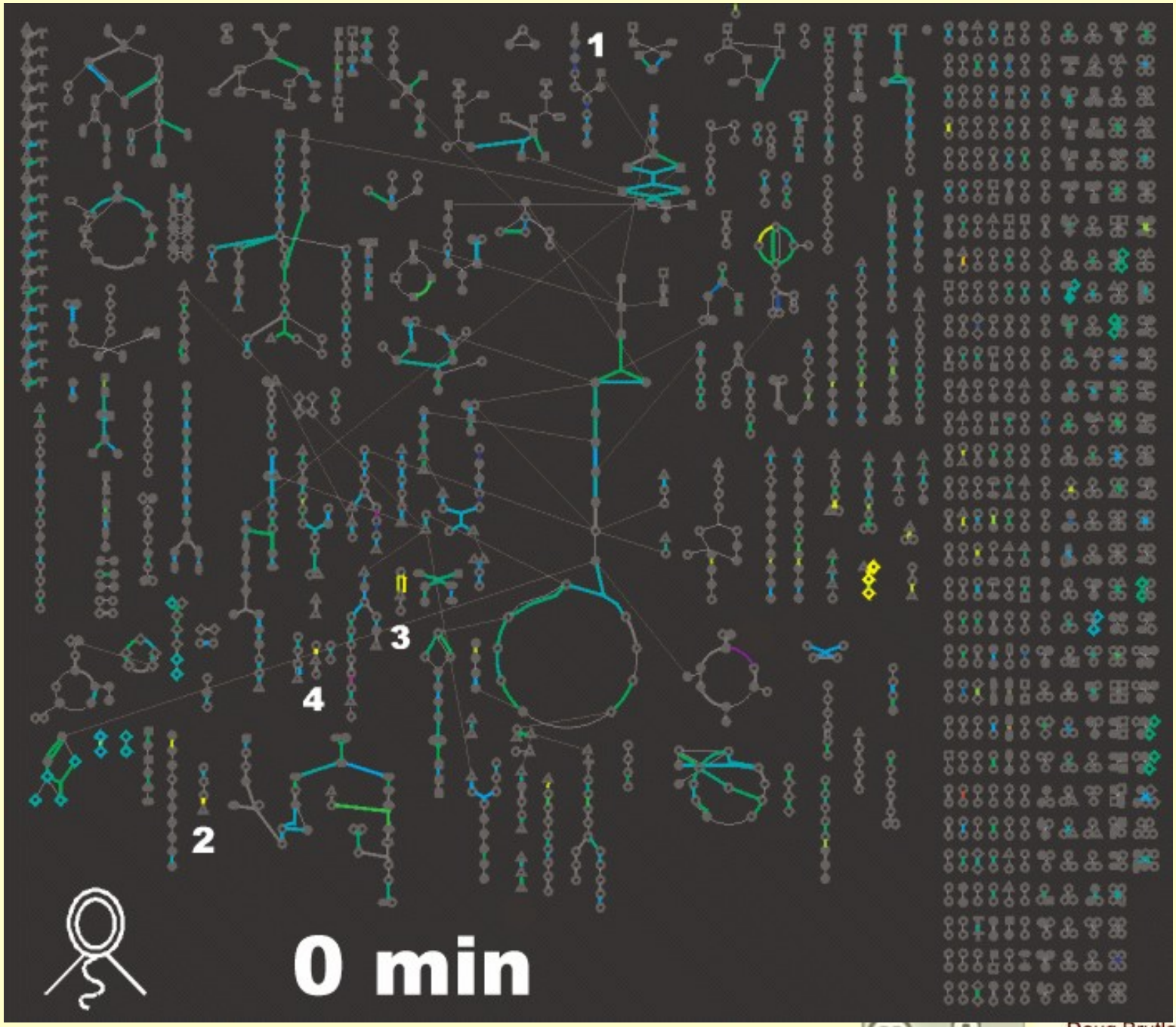
C. crescentus Cell Cycle Gene Expression



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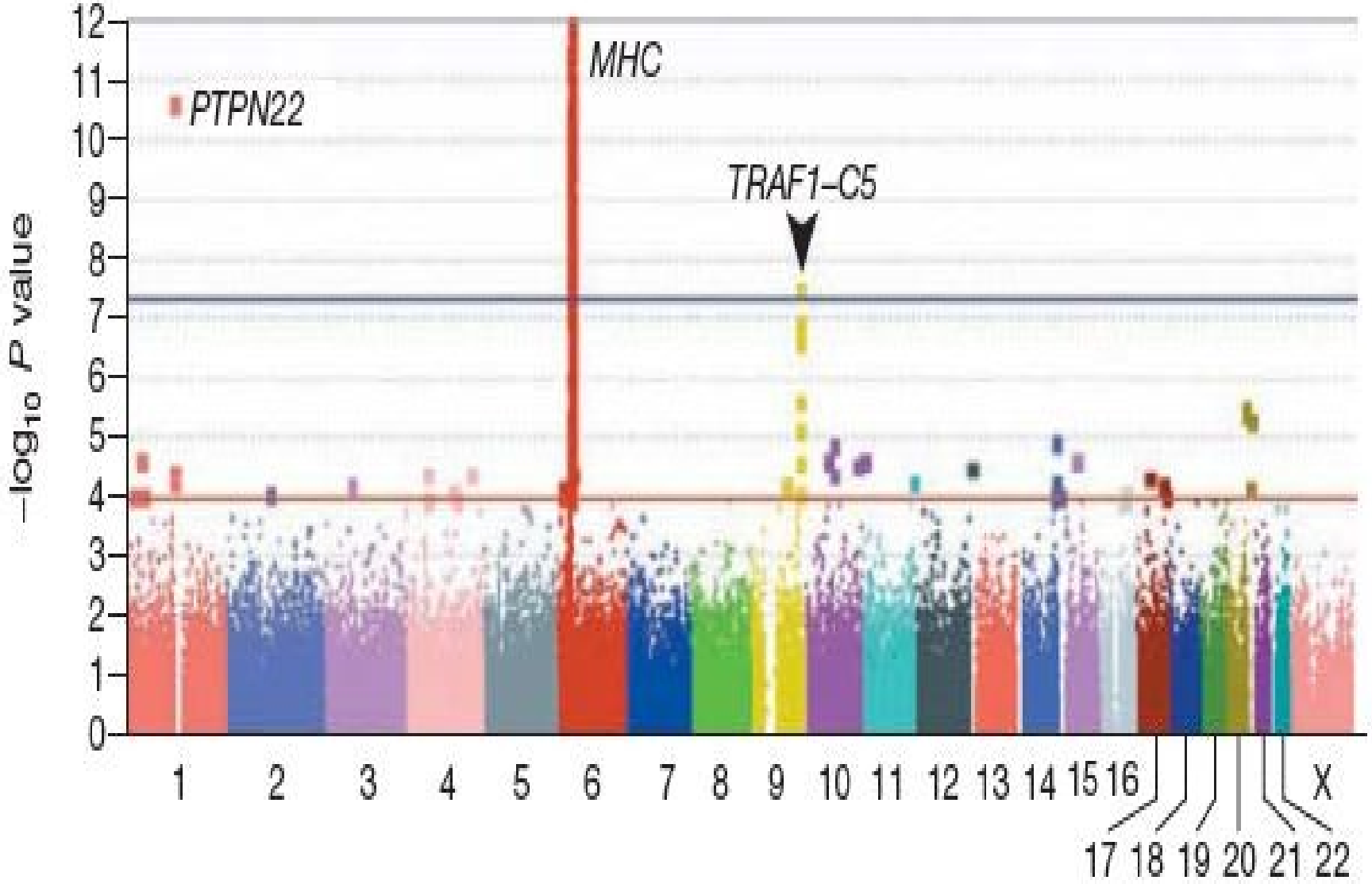
Genome Wide Associations in

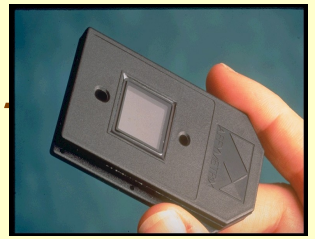
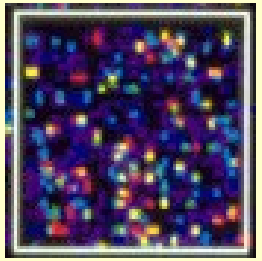
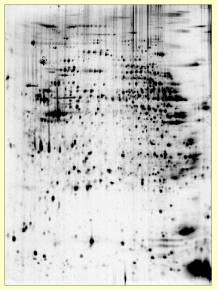
Figure 3. Genome-wide Association Findings in Rheumatoid Arthritis



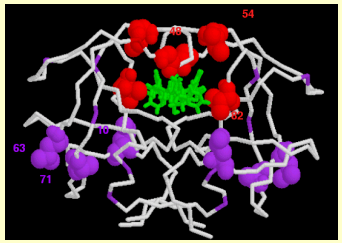
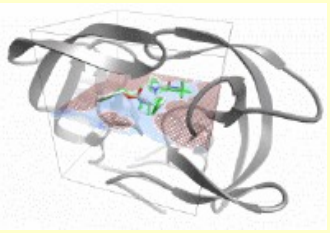
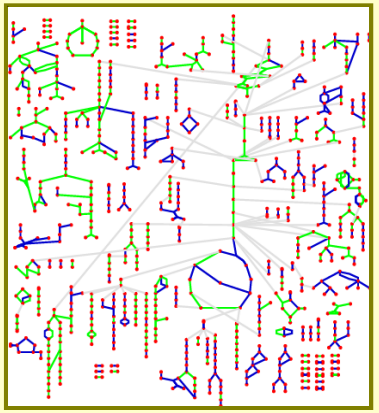
Pearson, T. A. et al. JAMA 2008;299:1335-1344

Leveraging Genomic Information in Medicine

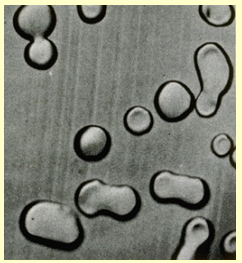
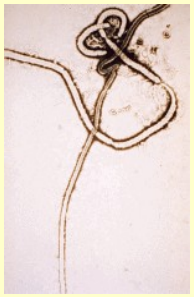
- Novel Diagnostics
  - Microchips & Microarrays
  - Gene Expression - RNA
  - Proteomics - Protein

- Novel Therapeutics
  - Drug Target Discovery
  - Rational Drug Design
  - Molecular Docking
  - Gene Therapy
  - Stem Cell Therapy

- Understanding Metabolism
- Understanding Disease
  - Inherited Diseases - OMIM
  - Infectious Diseases
    - Pathogenic Bacteria
    - Viruses

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