CENG 734
Advanced Topics in Bioinformatics

Fall 2011-2012

Instructor Info

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  - Office: B-109
  - e-mail me to schedule an appointment or to ask any course related question
  - Past courses:
    - http://www.ceng.metu.edu.tr/~tcan/

Class Web Page & newsgroup

http://www.ceng.metu.edu.tr/~tcan/ceng734_f1112/

- Lecture slides
- Syllabus
- Reading material (next week's reading material are already posted)

I will use the newsgroup metu.ceng.course.ceng734 for announcements

- Request an account from admins (A-210) if you don't have one

Prerequisites

- No formal prerequisites. However, some familiarity with Bioinformatics will help the students get the most benefit out of the course.
- Programming: required for the project
- Algorithms and Complexity Analysis
- Basic probability and statistics
- Some molecular and cellular biology terminology is required
- If you are new to Bioinformatics, I encourage you to take CENG 465 offered in Spring

Prerequisites

- Motivation is the most important prerequisite.
- This is a research oriented course. Take it if your thesis is going to be on Bioinformatics.

Course Objectives

- The primary objectives of this course are to expose students to recent developments in the field of bioinformatics and to enable students initiate research in this area. Upon completion of this course the students will:
  - be aware of the current challenges in Bioinformatics,
  - have learnt the state-of-the-art methods to tackle important biological problems,
  - and be able to initiate and conduct research in the area of Bioinformatics.

Reading Material

- Reading material will be provided online on the course web site
- Mostly papers from recent conferences or journals

Grading

- Reading : 40%
  - 8-10 quizzes about reading material
- Term project: 40%
- Final exam: 20%

Project

- May be related to your current research or what you may want to do for research
- Groups of 1-4 students
- You are free to choose project topics but will discuss details/goals/work plan with the instructor before starting to work on the project
- Project topic examples:
  - Small improvements on techniques/algorithms discussed in class
  - Application of a technique on a different data set.

Outline of the course

- This week: Introduction and characteristics of biological data. Who is working on what?
- Challenges in sequence analysis: next generation sequencing
  - Genome assembly, RNA-Seq
- Whole genome analysis, genome annotation
- Evolution and phylogeny
- Protein structure, functional classification

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- Gene regulation and transcriptomics
- Text mining in bioinformatics
- Protein interactions and molecular networks
- Challenges in heterogeneous data integration
- Bioimage informatics

Biological Data

- Comes in many different forms
  - Sequence Databases:
    - Nucleotide (GenBank), SWISS-PROT, Whole genome databases
  - Structure databases
    - Protein Data Bank
  - Expression data
    - NCBI GEO dataset
  - Interaction data, Pathways
  - Taxonomy data
  - Publication data (PubMed)
  - Domain, annotation information

NCBI Entrez

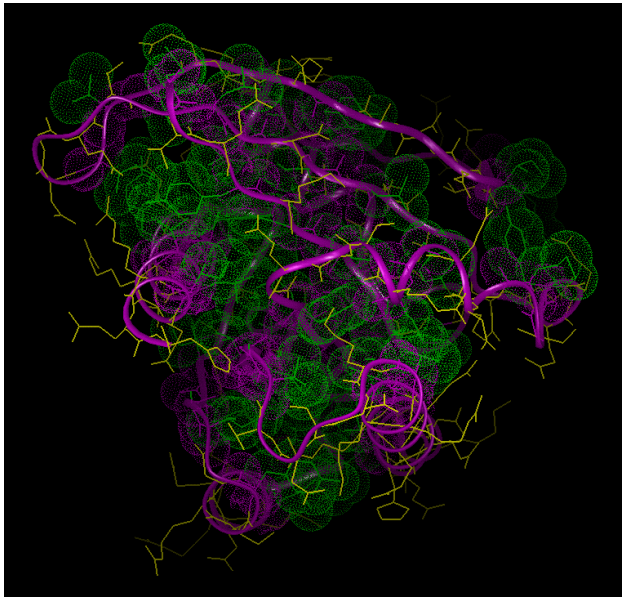
Welcome to the Entrez cross-database search page

- **PubMed:** biomedical literature citations and abstracts
- **PubMed Central:** free, full text journal articles
- **Site Search:** NCBI web and FTP sites
- **Books:** online books
- **OMIM:** online Mendelian Inheritance in Man
- **OMIA:** online Mendelian Inheritance in Animals

- **Nucleotide:** sequence database (includes GenBank)
- **Protein:** sequence database
- **Genome:** whole genome sequences
- **Structure**: three-dimensional macromolecular structures
- **Taxonomy:** organisms in GenBank
- **SNP:** single nucleotide polymorphism
- **Gene:** gene-centered information
- **HomoloGene:** eukaryotic homology groups
- **PubChem Compound:** unique small molecule chemical structures
- **PubChem Substance:** deposited chemical substance records
- **Genome Project:** genome project information
- **UniGene:** gene-oriented clusters of transcript sequences
- **CDD:** conserved protein domain database
- **3D Domains:** domains from Entrez Structure
- **UniSTS:** markers and mapping data
- **PopSet:** population study data sets
- **GEO Profiles:** expression and molecular abundance profiles
- **GEO DataSets:** experimental sets of GEO data
- **Cancer Chromosomes:** cytogenetic databases
- **PubChem BioAssay:** bioactivity screens of chemical substances
- **GENSAT:** gene expression atlas of mouse central nervous system
- **Probe:** sequence-specific reagents

- **Journals:** detailed information *about* the journals indexed in PubMed and other Entrez databases
- **NLM Catalog:** catalog of books, journals, and audiovisuals in the NLM collections
- **MeSH:** detailed information about NLM's controlled vocabulary

Introductory Biology

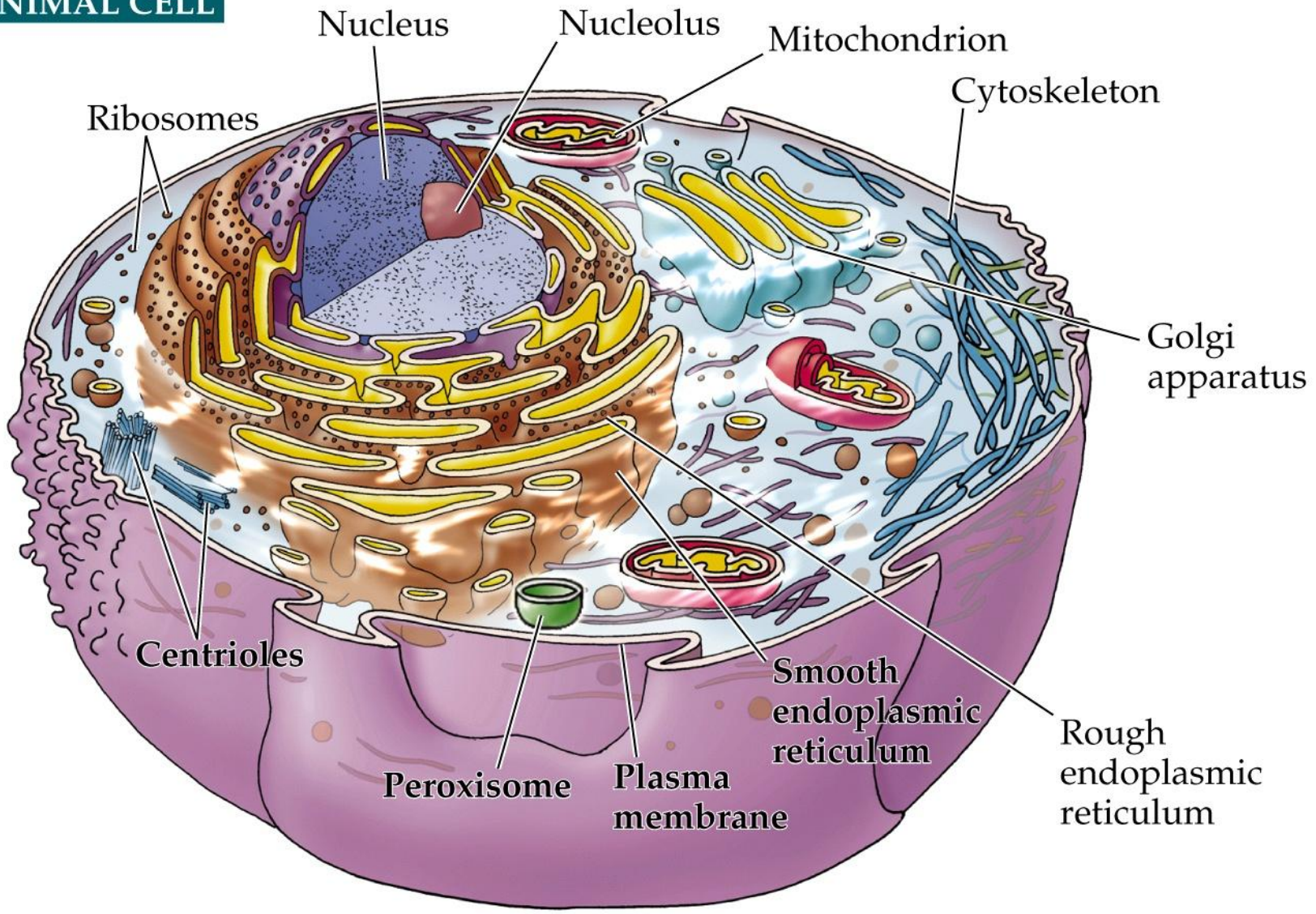


DNA
(Genotype)

Protein

Phenotype

AN ANIMAL CELL



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
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ggtcaagatatcgtttctaacgcatcttgtacaacaaactgtttagctcctttagcacgt
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gcaactcaaaaaactgtggatggtccatcagctaaagactggcgcggcggccgcggtgca
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gcattaaacggtaaattaactggtatggctttccgtgttccaacgccaaacgtatctgtt
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gaagatgctgttgtttctactgacttcaacggttgtgctttaacttctgtatttgatgca
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caacaagccaaaactcgtacaaatatgaccgcacttcgctataaagaacacggcttgtgg
cgagatatctcttggaaaaactttcaagagcaactcaatcaactttctcgagcattgctt
gctcacaatattgacgtacaagataaaatcgccatttttgcccataatatggaacgttgg
gttgttcatgaaactttcggtatcaaagatggtttaatgaccactgttcacgcaacgact
acaatcgttgacattgcgaccttacaaattcgagcaatcacagtgcctatttacgcaacc
aatacagcccagcaagcagaatttatcctaaatcacgccgatgtaaaaattctcttcgtc
ggcgatcaagagcaatacgatcaaacattggaaattgctcatcattgtccaaaattacaa
aaaattgtagcaatgaaatccaccattcaattacaacaagatcctctttcttgcacttgg
```
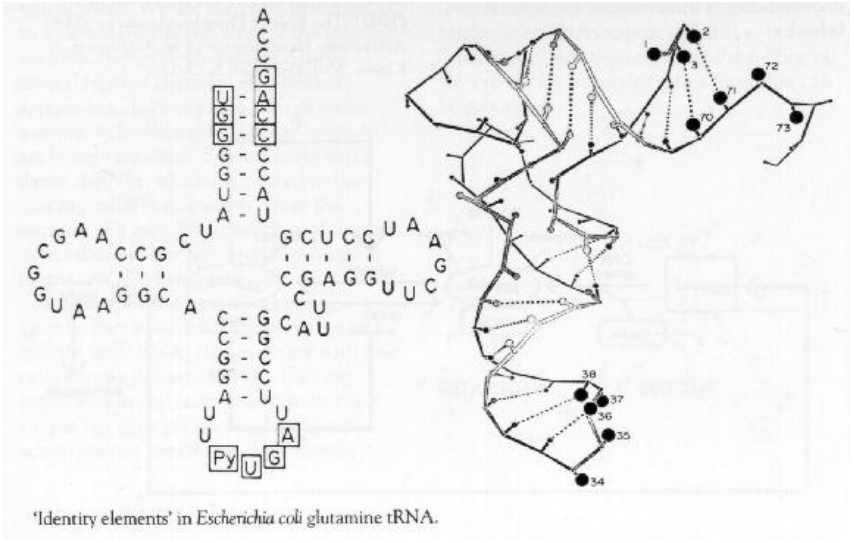
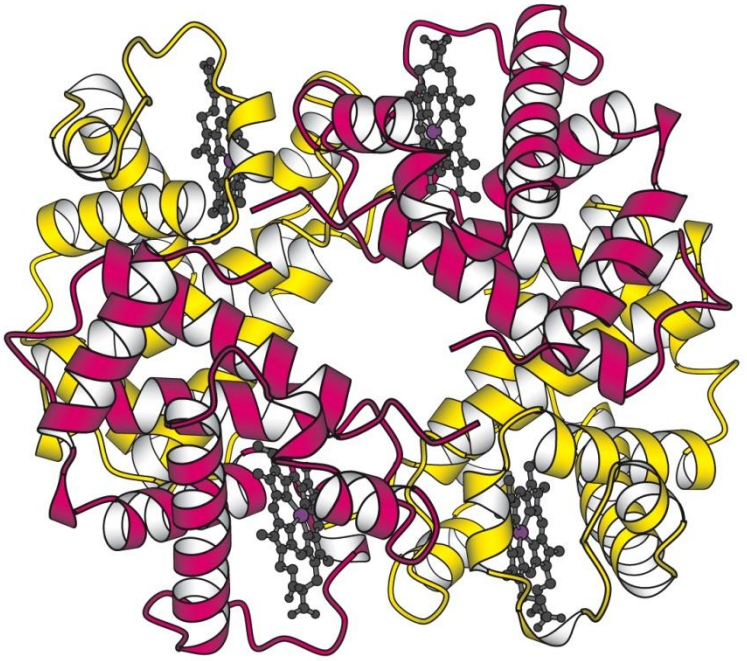

Protein Sequence

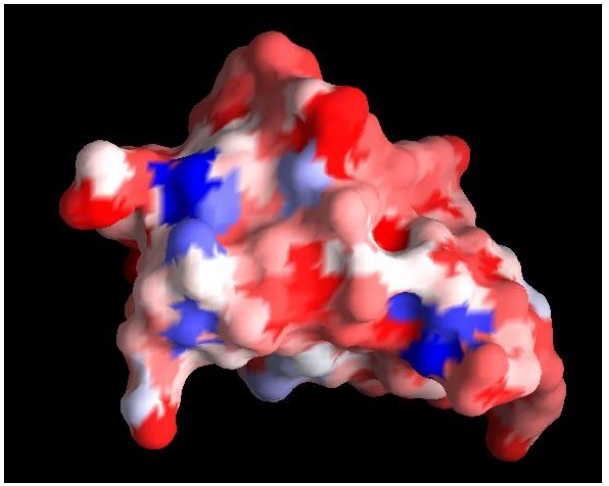
- 20 letter alphabet
  - ACDEFGHIKLMNPQRSTVWY but not BJOUXZ
- Strings of ~300 aa in an average protein (in bacteria),
  ~200 aa in a domain
- >3M known protein sequences
- Uniprot
  - **UniProtKB/Swiss-Prot**: proteins with high level of annotation (such as the description of the function of a protein, its domains structure, post-translational modifications, variants, etc.) 519348 entries in August 10 release.
  - **UniProtKB/TrEMBL**: a computer-annotated supplement of Swiss-Prot that contains all the translations of EMBL nucleotide sequence entries not yet integrated in Swiss-Prot. 11636205 entries in August 10 release.

Structures

- DNA/RNA/Protein
  - Mostly protein structures at PDB







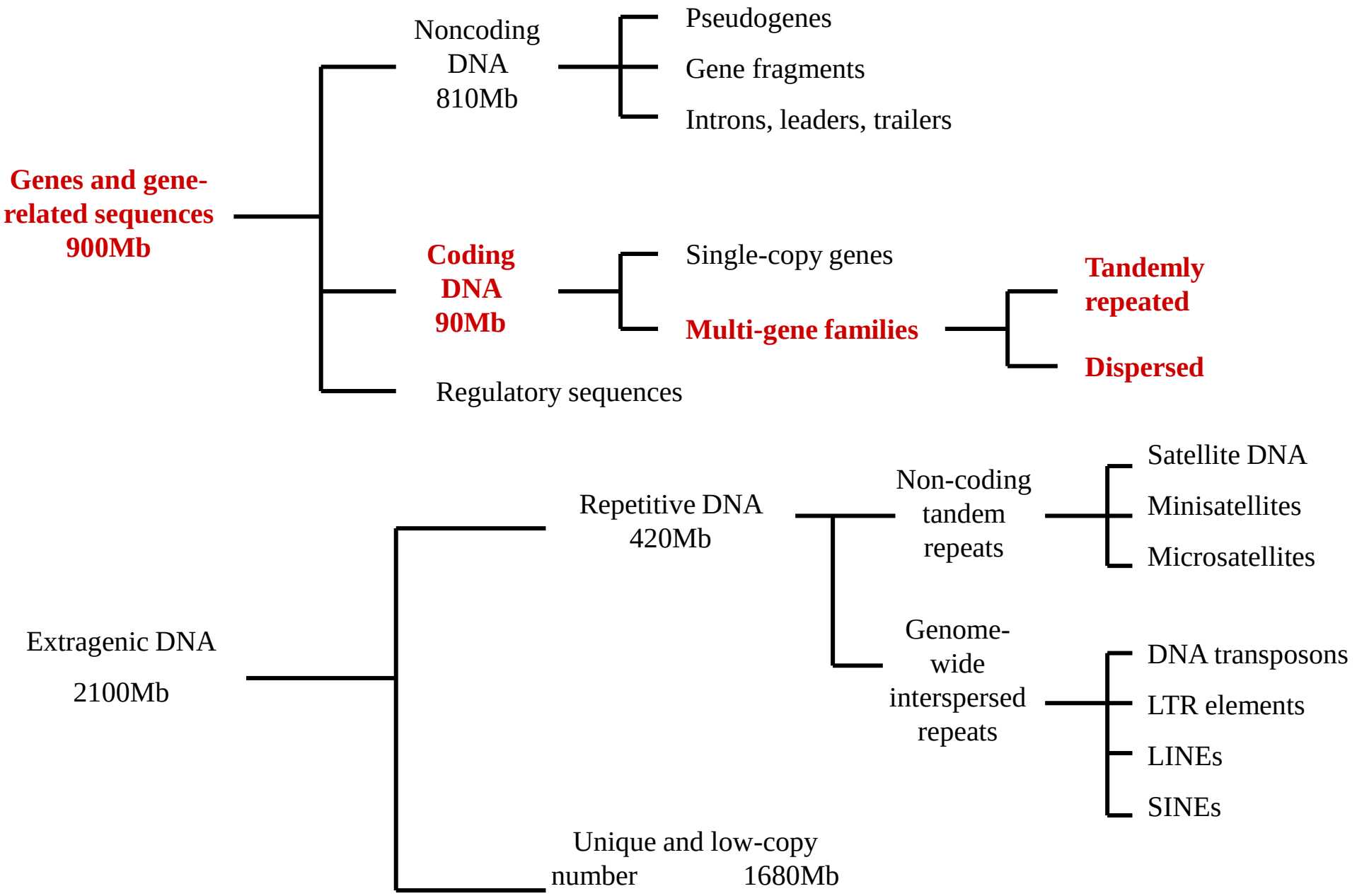
Genes and Proteins

- 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. Used parts are called exons. This is the task of gene finding.

Complete Genomes

- NCBI Entrez Genome Database
  - http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome
- Sequences from 6597 species
  - Achaea: 102
  - Bacteria: 1534
  - Eukaryote: 2455
  - Viruses: 2426
  - Viroids: 41
  - Plasmids: 39

Human genome



Gene expression data

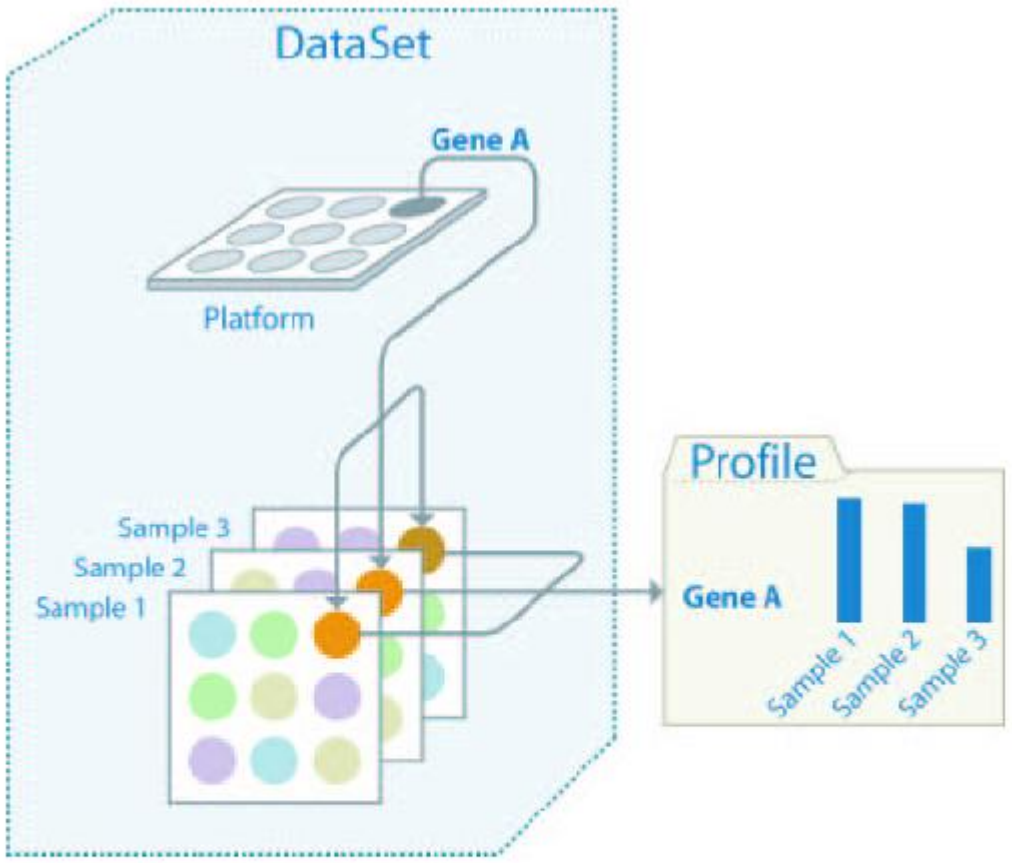


Figure 1. Schematic diagram of the relationships between GEO Platform, Sample, DataSet and Profiles. For each gene on a Platform (e.g. Gene A), multiple Sample measurement values are generated (Sample1–Sample3). Related Samples make up a DataSet, from which multiple, individual gene profile entities are generated.

from NCBI GEO NAR 2005 paper

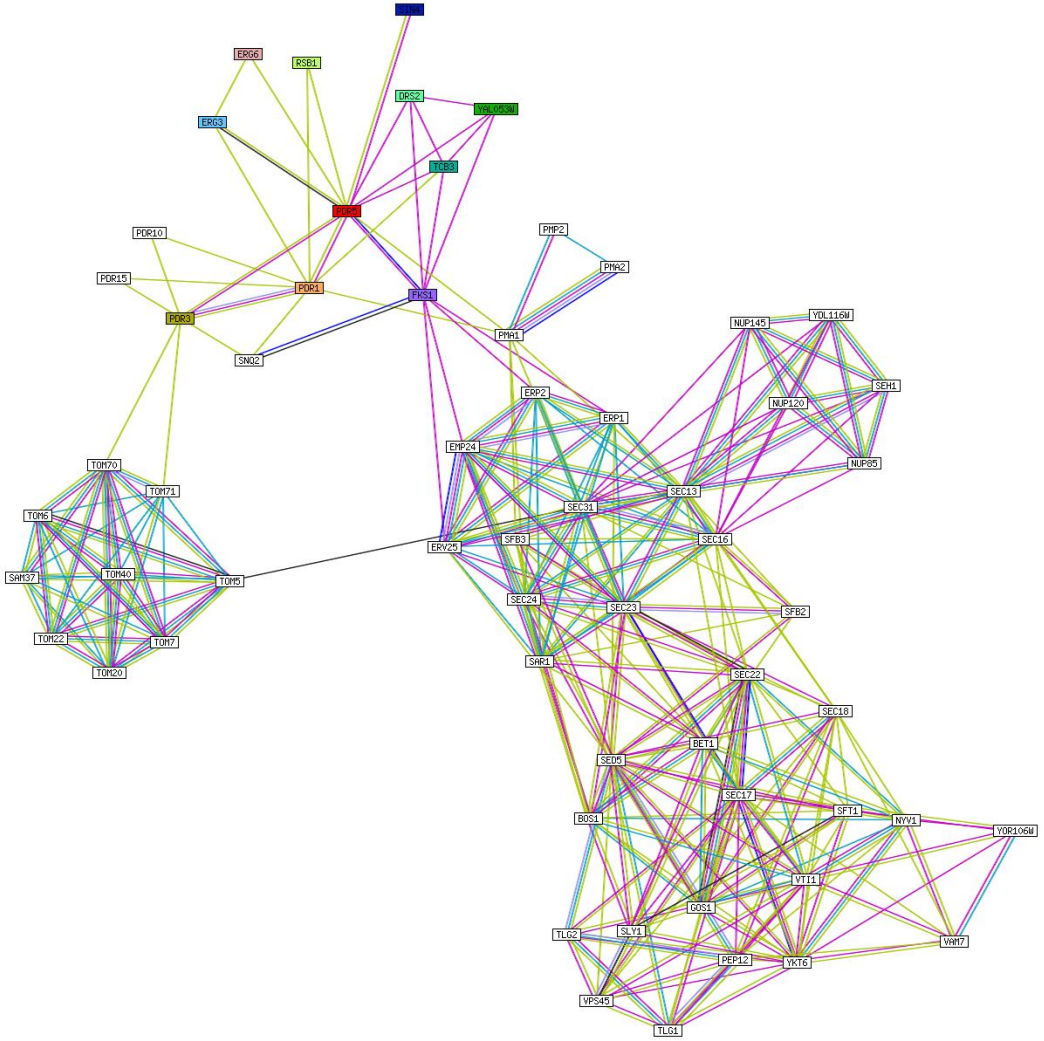
Site contents

Public data

Platforms	7,867
Samples	479,831
Series	18,896

as of September 26

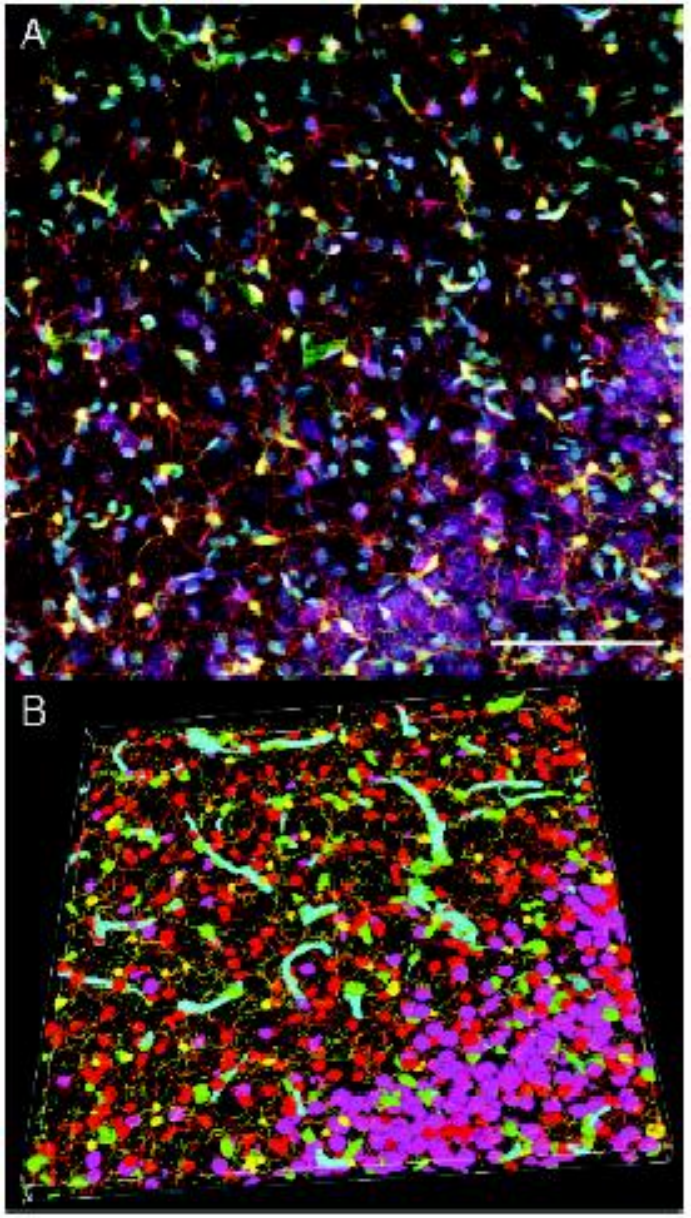
Protein Network Data

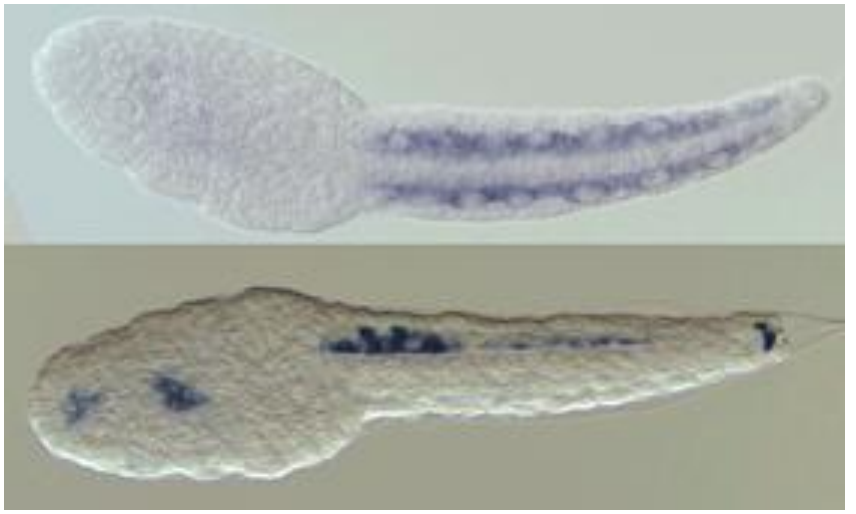


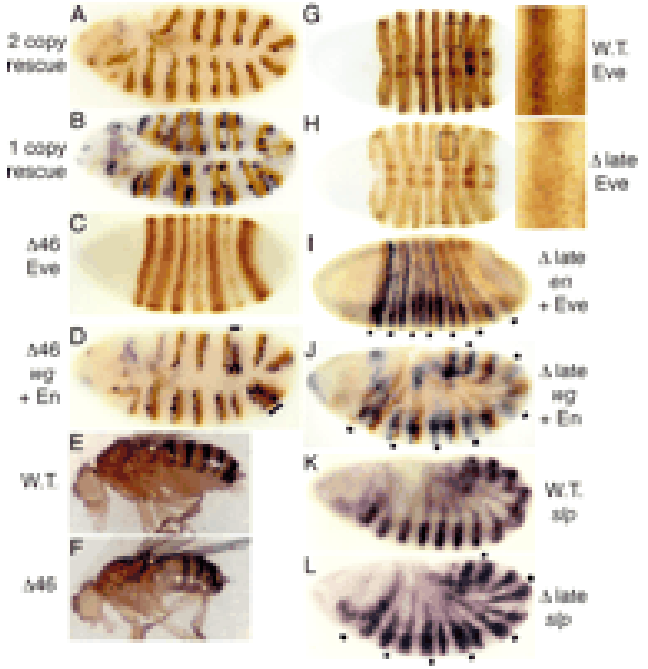
from STRING database

The database covers 2,590,259 proteins from 630 organisms as of September 26.

Bioimages

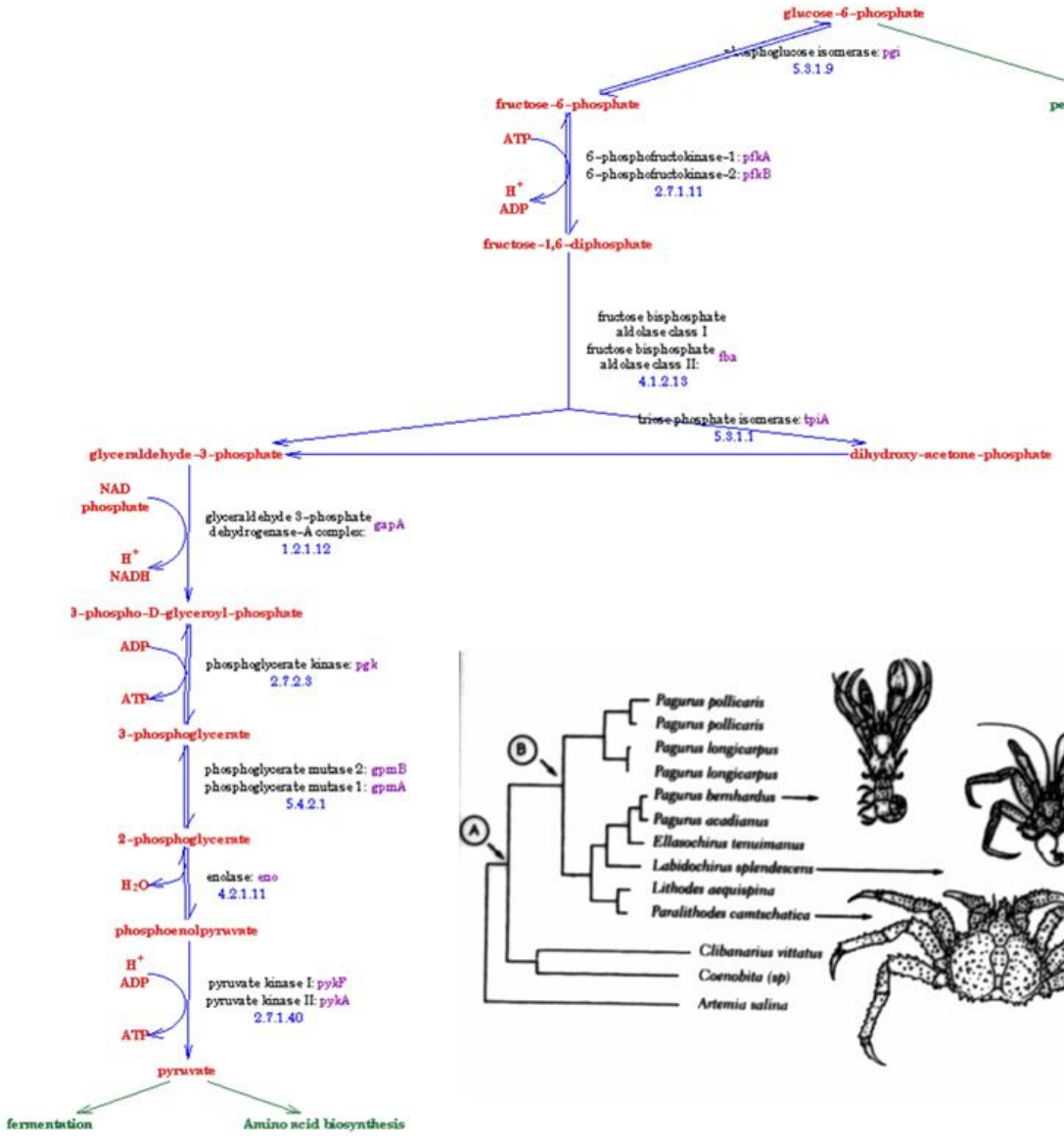

A
B




A
2 copy rescue
B
1 copy rescue
C
Δ46 Eve
D
Δ46 wg + En
E
W.T.
F
Δ46
G
W.T. Eve
H
Δ late Eve
I
Δ late en + Eve
J
Δ late wg + En
K
W.T. slp
L
Δ late slp

Other Types of Data

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



Data sources

- NAR (Nucleic Acids Research) journal maintains a list of data collections
- http://www.oxfordjournals.org/nar/database/c/
  - Sequence
    - Genomes, 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 an interdisciplinary area
- Depend on others for primary data
- Need to address important biological *and* computer science problems

Skill set

- Artificial intelligence
- Machine learning
- Statistics & probability
- Algorithms
- Databases
- Programming
- Molecular and Cellular Biology
- More?

Challenging sequence related problems

- More sensitive pairwise alignment
  - Dynamic programming is O(mn)
    - m is the length of the query
    - n is the length of the database
- Scalable multiple alignment
  - Dynamic programming is exponential in number of sequences
  - Currently feasible for around 10 protein sequences of length around 1000
- Shotgun alignment
  - Current techniques will take over 200 days on a single machine to align the mouse genome

Challenging structure related problems

- Alignment against a database
  - Single comparison usually takes seconds.
  - Comparison against a database takes hours.
  - All-against-all comparison takes weeks.
- Multiple structure alignment and motifs
- Combined sequence and structure comparison
- Secondary and tertiary structure prediction

- And many more other challenging problems in other areas of bioinformatics....

Top journals

- Science
- Nature (Nature Genetics, Nature Biotechnology)
- PNAS (Proceedings of the National Academy of Sciences)
- NAR (Nucleic Acids Research)
- Bioinformatics
- JCB (Journal of Computational Biology)
- BMC Bioinformatics
- Genome Research
- Proteins: Structure and Function, and Bioinformatics
- PLoS Computational Biology
- PLoS One
- IEEE/ACM Transactions on Computational Biology and Bioinf.

Top conferences

- RECOMB: Research in COmputational Molecular Biology
- ISMB: Intelligent Systems for Molecular Biology
- ECCB: European Conference on Computational Biology
- PSB: Pacific Symposium on Biocomputing
- CSB: Computational Systems Bioinformatics
- CIBCB: IEEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology
- BIBE: IEEE International Conference on Bioinformatics and Bioengineering

Current research?

- Bioinformatics jounal
- BMC Bioinformatics journal
- PLoS Computational Biology journal
- RECOMB 2011 accepted papers
- ISMB/ECCB 2011 accepted papers
- CSB and PSB conferences
- IEEE TCBB journal

Next week

- Next generation sequencing: Transcriptome assembly
- Reading:
  - RNA-Seq Intro: Nature Reviews article
  - IsoLasso: A LASSO Regression Approach to RNA-Seq Based Transcriptome Assembly RECOMB 2011 paper