CSE 527

Computational Biology

http://www.cs.washington.edu/527

Lecture 1: Overview & Bio Review

Autumn 2005

Larry Ruzzo

CSE 527: Computational Biology, Autumn 2005

An introduction to the use of computational methods for the understanding of biological systems at the molecular level. Intended for graduate students in biological sciences interested in learning about algorithms and computational methods, and for graduate students in computer science, mathematics or statistics interested in applications of those fields to molecular biology.

Time: MW 12:00-1:20

Place: MEB 237

Instructor: Larry Ruzzo (CSE 554, ruzzo@cs.washington.edu)

Course web pages: `http://www.cs.washington.edu/527`

Course mailing list: `cse527@cs.washington.edu`

Catalog Description (somewhat out of date): CSE 527 Computational Biology (3) Introduces computational methods for understanding biological systems at the molecular level. Problem areas such as mapping and sequencing, sequence analysis, structure prediction, phylogenic inference, regulatory analysis. Techniques such as dynamic programming, Markov models, expectation-maximization, local search. Prerequisite: graduate standing in biological, computer, mathematical or statistical science, or permission of instructor.

Workload: Notes, problem sets, project. We encourage projects in which a biologist and a mathematical scientist collaborate to model/solve a biological problem.

Desired Prerequisites: Ideally, students will have a considerable knowledge of one of computer science, biology, or probability/statistics, plus introductory knowledge of the other two. We'll try to supplement as needed (via lecture, outside reading, project teams, etc.) so that everyone has enough background in the immediately relevant areas to fruitfully proceed.

Rough Course Outline

I am unlikely to have time to cover all of this. If you have particular interests, let me know and I'll try to prioritize the in-demand topics.

Essential Background from Molecular Biology

Sequence Analysis Statistical modeling of families of DNA or protein sequences: profiles, motif discovery, hidden Markov Models, Expectation - Maximization algorithm Gibbs sampling. Gene finding.

Molecular Structure Prediction RNA secondary structure prediction, SCFGs and covariance models; the protein folding problem; protein threading.

Microarray Analysis Clustering, classification, feature selection for analysis of large scale gene expression data sets generated by microarrays and similar technologies.

He who asks is a fool for five minutes, but he who does not ask remains a fool forever.

-- Chinese Proverb

Related Courses

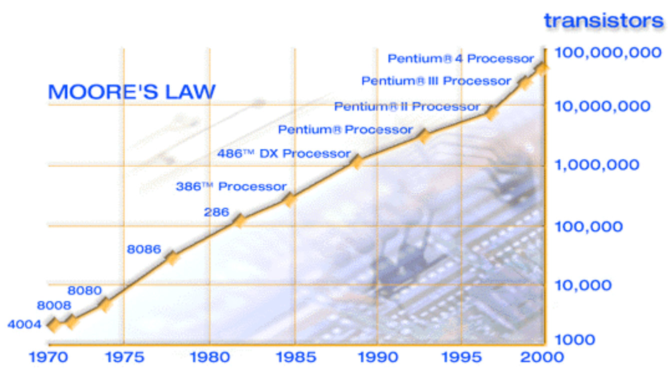
- Genome 540/541 (Winter/Spring)
  - Intro. To Comp. Mol. Bio.
- Stat/Biostat 578 (A 2005, TuTh 9:00-10:20)
  - Statistical Analysis of Microarrays , J. Storey
- MEDED 534, Autumn 2005
  - Biology and Informatics
- CSE590C (AWS)
  - Reading & Research in Comp. Bio.
  - Monday's, 3:30 (MGH 284 this quarter)
  - http://www.cs.washington.edu/590c
- Combi Seminar (Genome 521; AWS)
  - Wednesday's 1:30 K069 (sometimes 3:30 Hitch 132)

Today's Combi

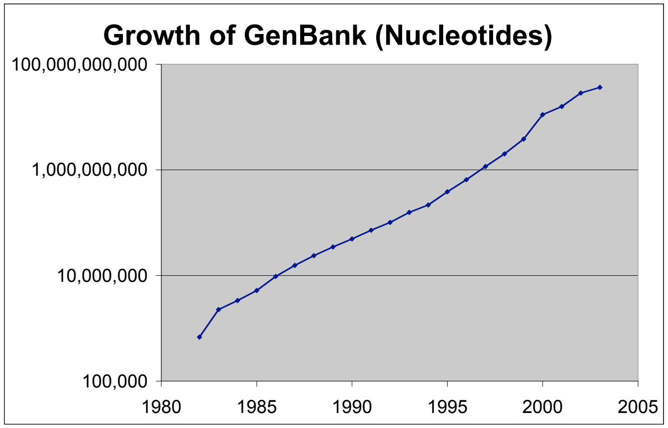
- Dr. Hamid Bolouri
- Pointillist: an open source tool for high throughput data integration
- Wednesday, September 28
- 1:30-2:30
- HSB K-069

Homework #1

- Find & read a good primer on "bio for cs" (or vice versa, as appropriate)
  e.g., see ones listed on 590c page
- Post a few sentences saying
  - What you read (give me a link or citation)
  - Critique it for your meeting your needs
  - Who would it have been good for, if not you
- See class web for more details



Source: http://www.intel.com/research/silicon/mooreslaw.htm



Source: http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html

What’s all the fuss?

- The human genome is “finished”…
- Even if it were, that’s only the beginning
- Explosive growth in biological data is revolutionizing biology & medicine

“All pre-genomic lab techniques are obsolete”

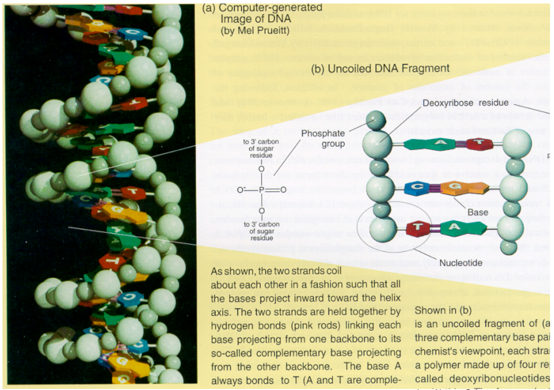
(and computation and mathematics are crucial to post-genomic analysis)

A *VERY* Quick Intro To Molecular Biology

The Genome

- The hereditary info present in every cell
- DNA molecule -- a long sequence of *nucleotides* (A, C, T, G)
- Human genome -- about 3 x 10^9 nucleotides
- The genome project -- extract & interpret genomic information, apply to genetics of disease, better understand evolution, …

The Double Helix



Los Alamos Science

DNA

- Discovered 1869
- Role as carrier of genetic information - much later
- The Double Helix - Watson & Crick 1953
- Complementarity
  - A ←→ T   C ←→ G

Genetics - the study of heredity

- A *gene* -- classically, an abstract heritable attribute existing in variant forms (*alleles*)
- *Genotype* vs *phenotype*
- Mendel
  - Each individual two copies of each gene
  - Each parent contributes one (randomly)
  - Independent assortment

Cells

- Chemicals inside a sac - a fatty layer called the *plasma membrane*
- *Prokaryotes* (e.g., bacteria) - little recognizable substructure
- *Eukaryotes* (all multicellular organisms, and many single celled ones, like yeast) - genetic material in nucleus, other organelles for other specialized functions

Chromosomes

- 1 pair of DNA molecules (+ protein wrapper)
- Most prokaryotes have just 1 chromosome
- Eukaryotes - all cells have same number of chromosomes, e.g. fruit flies 8, humans & bats 46, rhinoceros 84, …

Mitosis/Meiosis

- Most “higher” eukaryotes are *diploid* - have homologous pairs of chromosomes, one maternal, other paternal (exception: sex chromosomes)
- *Mitosis* - cell division, duplicate each chromosome, 1 copy to each daughter cell
- *Meiosis* - 2 divisions form 4 *haploid* gametes (egg/sperm)
  - *Recombination/crossover* -- exchange maternal/paternal segments

Proteins

- Chain of amino acids, of 20 kinds
- Proteins are the major functional elements in cells
  - Structural
  - Enzymes (catalyze chemical reactions)
  - Receptors (for hormones, other signaling molecules, odorants,…)
  - Transcription factors
  - …
- 3-D Structure is crucial: the protein folding problem

The “Central Dogma”

- Genes encode proteins
- DNA transcribed into messenger RNA
- RNA translated into proteins
- Triplet code (codons)

The Genetic Code

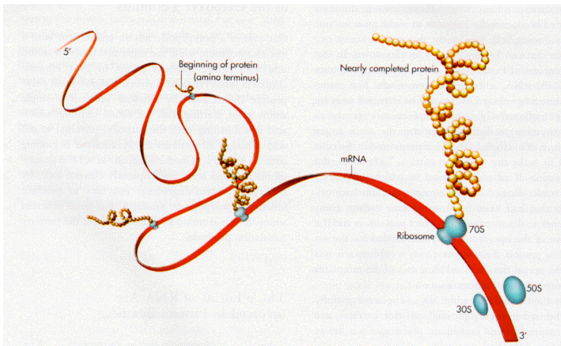
(a) RNA Codons for the Twenty Amino Acids

First base	Second base: U	C	A	G	Third base
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met (start)	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Amino-acid abbreviations

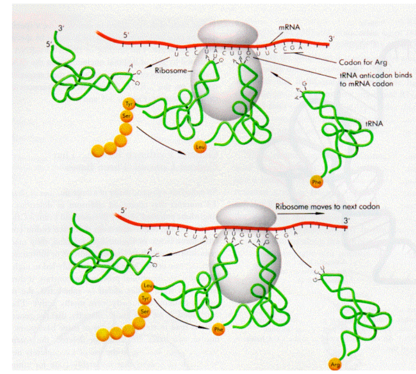
Ala = Alanine
Arg = Arginine
Asp = Aspartic acid
Asn = Asparagine
Cys = Cysteine
Glu = Glutamic acid
Gln = Glutamine
Gly = Glycine
His = Histidine
Ile = Isoleucine
Leu = Leucine
Lys = Lysine
Met = Methionine
Phe = Phenylalanine
Pro = Proline
Ser = Serine
Thr = Threonine
Trp = Tryptophan
Tyr = Tyrosine
Val = Valine

Translation: mRNA → Protein



Watson, Gilman, Witkowski, & Zoller, 1992

Ribosomes



Watson, Gilman, Witkowski, & Zoller, 1992

Gene Structure

- Transcribed 5' to 3'
- Promoter region and transcription factor binding sites precede 5'
- Transcribed region includes 5' and 3' untranslated regions
- In eukaryotes, most genes also include introns, spliced out before export from nucleus, hence before translation

Genome Sizes

	Base Pairs	Genes
Mycoplasma genitalium	580,073	483
MimiVirus	1,200,000	1,260
E. coli	4,639,221	4,290
Saccharomyces cerevisiae	12,495,682	5,726
Caenorhabditis elegans	95.5×10^6	19,820
Arabidopsis thaliana	115,409,949	25,498
Drosophila melanogaster	122,653,977	13,472
Humans	3.3×10^9	~25,000

Genome Surprises

- Humans have < 1/3 as many genes as expected
- But perhaps more proteins than expected, due to *alternative splicing*
- There are unexpectedly many *non-coding RNAs*
- Many other non-coding regions are highly conserved, e.g., across all mammals

… and much more …

- Read one of the many intro surveys or books for much more info.