CSEP590A
Computational Biology

http://www.cs.washington.edu/csep590a

Larry Ruzzo
Summer 2006

UW CSE Computational Biology Group

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

-- Chinese Proverb

Tonight

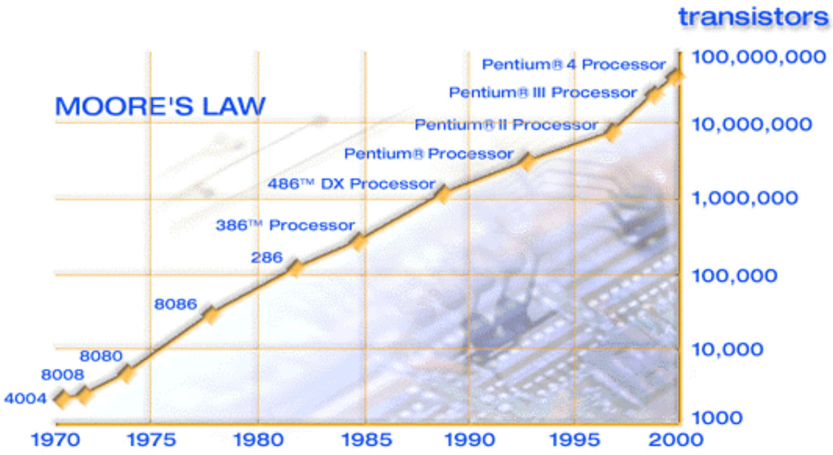
- Admin
- Why Comp Bio?
- The world’s shortest Intro. to Mol. Bio.

Admin Stuff

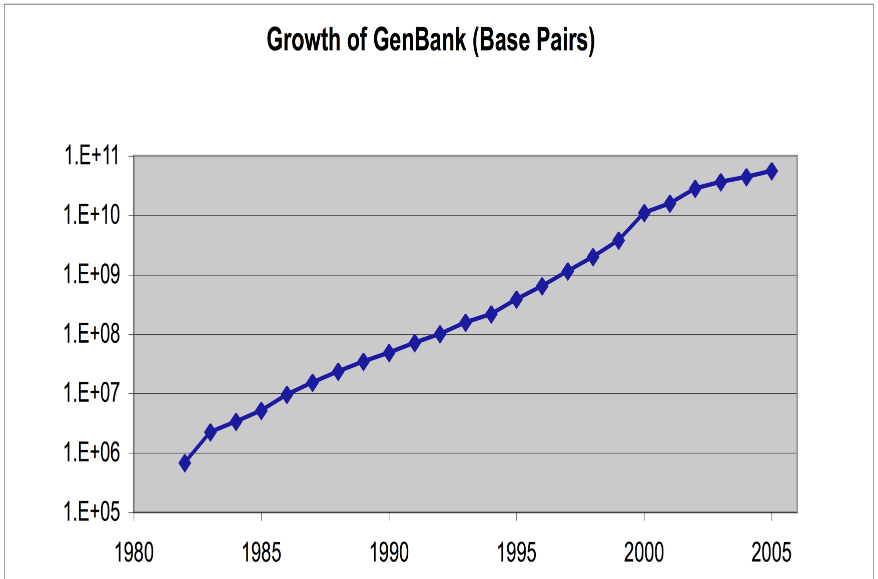
Course Mechanics & Grading

- Reading
- In class discussion
- Homeworks
  - reading blogs
  - paper exercises
  - programming
- No exams, but possible oversized last homework in lieu of final

Background & Motivation



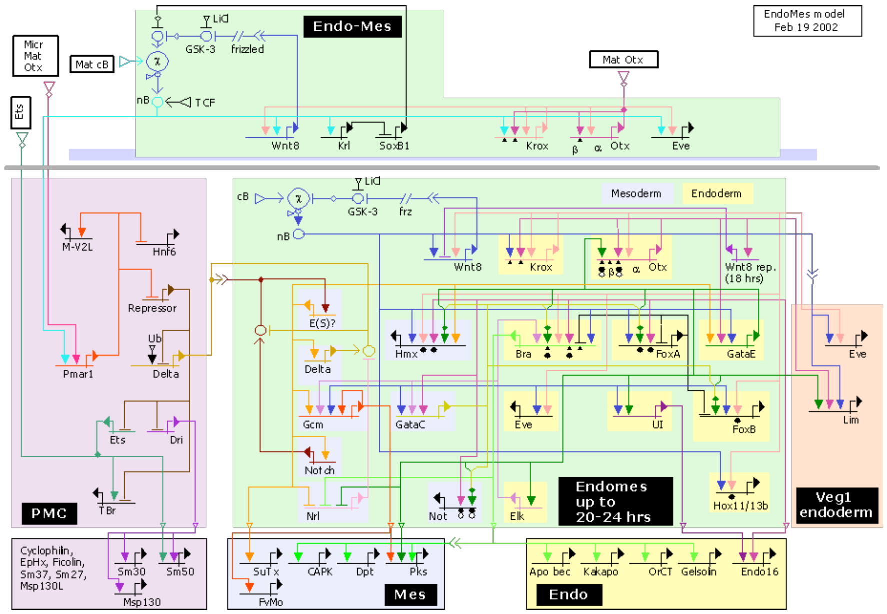
Source: http://www.intel.com/research/silicon/mooreslaw.htm



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

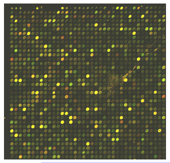
The Human Genome Project

```
   1 gagcccggcc cgggggacgg gcggcgggat agcgggaccc cggcgcggcg gtgcgcttca
  61 gggcgcagcg gcggccgcag accgagcccc gggcgcggca agaggcggcg ggagccggtg
 121 gcggctcggc atcatgcgtc gagggcgtct gctggagatc gccctgggat ttaccgtgct
 181 tttagcgtcc tacacgagcc atggggcgga cgccaatttg gaggctggga acgtgaagga
 241 aaccagagcc agtcggccca agagaagagg cggtggagga cacgacgcgc ttaaaggacc
 301 caatgtctgt ggatcacgtt ataatgctta ctgttgccct ggatggaaaa ccttacctgg
 361 cggaaatcag tgtattgtcc ccatttgccg gcattcctgt ggggatggat tttgttcgag
 421 gccaaatatg tgcacttgcc catctggtca gatagctcct tcctgtggct ccagatccat
 481 acaacactgc aatattcgct gtatgaatgg aggtagctgc agtgacgatc actgtctatg
 541 ccagaaagga tacataggga ctcactgtgg acaacctgtt tgtgaaagtg gctgtctcaa
 601 tggaggaagg tgtgtggccc caaatcgatg tgcatgcact tacggattta ctggacccca
 661 gtgtgaaaga gattacagga caggcccatg ttttactgtg atcagcaacc agatgtgcca
 721 gggacaactc agcgggattg tctgcacaaa acagctctgc tgtgccacag tcggccgagc
 781 ctggggccac ccctgtgaga tgtgtcctgc ccagcctcac ccctgccgcc gtggcttcat
 841 tccaaatatc cgcacgggag cttgtcaaga tgtggatgaa tgccaggcca tccccgggct
 901 ctgtcaggga ggaaattgca ttaatactgt tgggtctttt gagtgcaaat gccctgctgg
 961 acacaaactt aatgaagtgt cacaaaaatg tgaagatatt gatgaatgca gcaccattcc
1021 ...
```

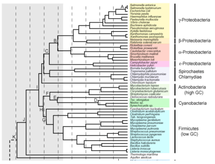


Goals

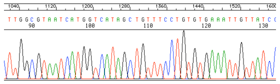
- Basic biology
- Disease diagnosis/prognosis/treatment
- Drug discovery, validation & development
- Individualized medicine
- …

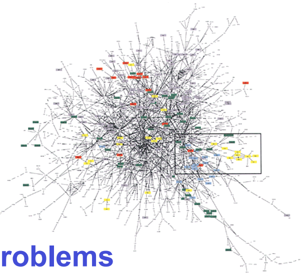


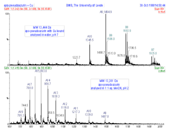
"High-Throughput BioTech"



- Sensors
  - DNA sequencing
  - Microarrays/Gene expression
  - Mass Spectrometry/Proteomics
  - Protein/protein & DNA/protein interaction
- Controls
  - Cloning
  - Gene knock out/knock in
  - RNAi







Floods of data

"Grand Challenge" problems

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”

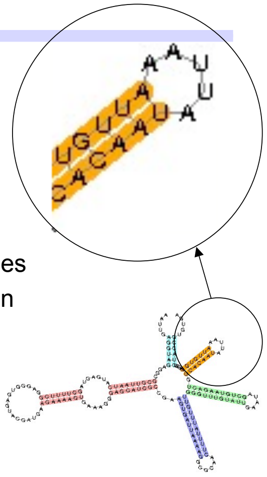
(and computation and mathematics are crucial to post-genomic analysis)

CS Points of Contact & Opportunities

- Scientific visualization
  - Gene expression patterns
- Databases
  - Integration of disparate, overlapping data sources
  - Distributed genome annotation in face of shifting underlying genomic coordinates
- AI/NLP/Text Mining
  - Information extraction from journal texts with inconsistent nomenclature, indirect interactions, incomplete/inaccurate models,…
- Machine learning
  - System level synthesis of cell behavior from low-level heterogeneous data (DNA sequence, gene expression, protein interaction, mass spec,…)
- …
- Algorithms

An Algorithm Example: ncRNAs

- The “Central Dogma”:
  DNA -> messenger RNA -> Protein
- Last ~5 years: many examples of functionally important ncRNAs
  - 175 -> 350 families just in last 6 mo.
- Much harder to find than protein-coding genes
- Main method - Covariance Models (based on stochastic context free grammars)
- Main problem - Sloooow … O(nm^4)



“Rigorous Filtering” - Z. Weinberg

- Convert CM to HMM
  (AKA: stochastic CFG to stochastic regular grammar)
- Do it so HMM score *always* ≥ CM score
- Optimize for most aggressive filtering subject to constraint that score bound maintained
  - A large convex optimization problem
- Filter genome sequence with (fast) HMM, run (slow) CM only on sequences above desired CM threshold; guaranteed not to miss anything
- Newer, more elaborate techniques pulling in key secondary structure features for better searching
  (uses automata theory, dynamic programming, Dijkstra, more optimization stuff,…)

Details
CENSORED
(but stay tuned…)
Plenty of CS here

Results

- Typically 200-fold speedup or more
- Finding dozens to hundreds of new ncRNA genes in many families
- Has enabled discovery of many new families

- Newer, more elaborate techniques pulling in key secondary structure features for better searching
  (uses automata theory, dynamic programming, Dijkstra, more optimization stuff,…)

The Mission

"Solving Today's challenging Computer Science problems for Tomorrow's biologists"

More Admin

Course Focus & Goals

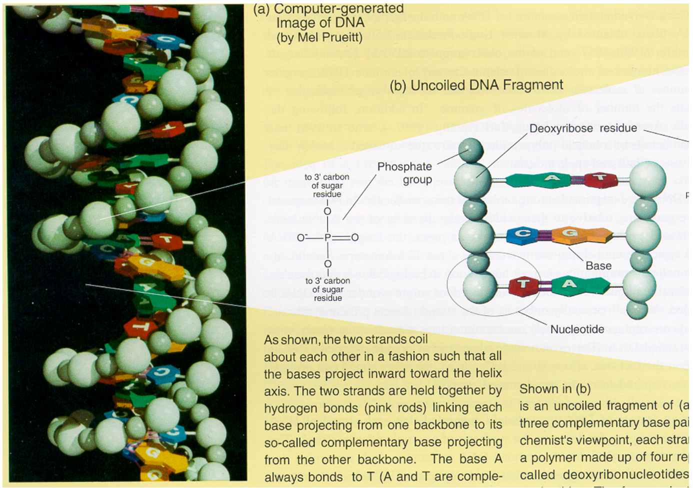
- Mainly sequence analysis
- Algorithms for alignment, search, & discovery
- specific sequences, general types ("genes", etc.)
- Single sequence and comparative analysis
- Techniques: HMMs, EM, MLE, Gibbs, Viterbi…

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


(a) Computer-generated Image of DNA (by Mel Prueitt)
(b) Uncoiled DNA Fragment
Deoxyribose residue
Phosphate group
to 3' carbon of sugar residue
O
O⁻—P═O
O
to 3' carbon of sugar residue
A
T
C
G
Base
T
A
Nucleotide

As shown, the two strands coil about each other in a fashion such that all the bases project inward toward the helix axis. The two strands are held together by hydrogen bonds (pink rods) linking each base projecting from one backbone to its so-called complementary base projecting from the other backbone. The base A always bonds to T (A and T are comple-

Shown in (b) is an uncoiled fragment of (a three complementary base pai chemist's viewpoint, each stra a polymer made up of four re called deoxyribonucleotides

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 (complementary) 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

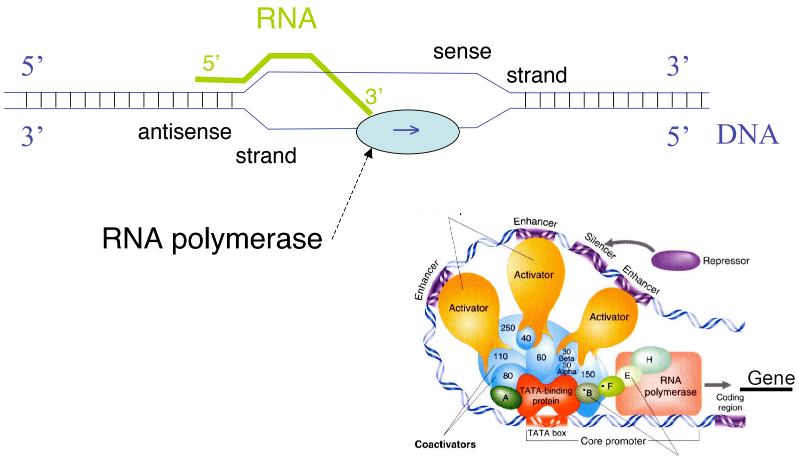
Proteins

- 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
- mRNA translated into proteins
- Triplet code (codons)

Transcription: DNA → RNA



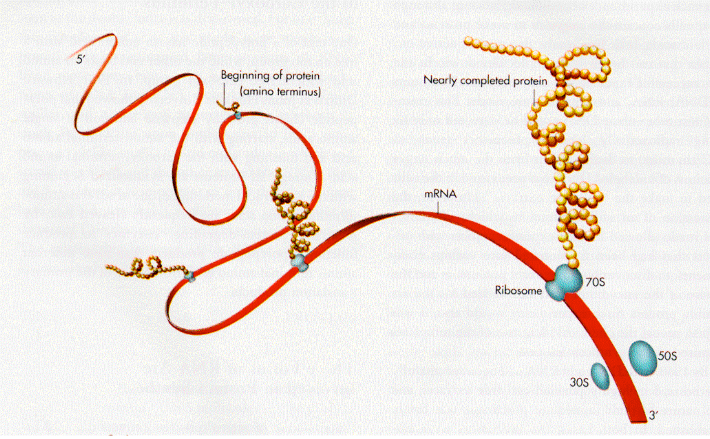
Codons & The Genetic Code

		Second Base				
		U	C	A	G	
First 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

Third Base

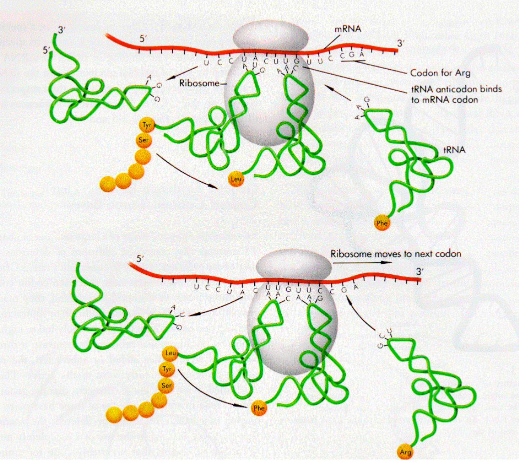
Ala	: Alanine
Arg	: Arginine
Asn	: Asparagine
Asp	: Aspartic acid
Cys	: Cysteine
Gln	: Glutamine
Glu	: Glutamic acid
Gly	: Glycine
His	: Histidine
Ile	: Isoleucine
Leu	: Leucine
Lys	: Lysine
Met	: Methionine
Phe	: Phenylalanine
Pro	: Proline
Ser	: Serine
Thr	: Threonine
Trp	: Tryptophane
Tyr	: Tyrosine
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 (usually) 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	95,500,000	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* -- more than protein-coding genes, by some estimates
- Many other non-coding regions are highly conserved, e.g., across all vertebrates

… and much more …

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

Homework #1 (partial)

- Read Hunter's "bio for cs" primer;
- Find & read another
- 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, sometime tomorrow