# CSEP590B
# Computational Biology

http://www.cs.washington.edu/csep590b

Larry Ruzzo

Spring 2011

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

-- Chinese Proverb

University of Washington

Computer Science & Engineering

http://www.cs.washington.edu/csep590b

...utational Biology

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**Assignments**

**Lecture Slides**

**Resources**
- Pubmed
- BLAST
- PDB
- NCBI Science Primer
- NHGRI Talking Glossary
- ORNL Genome Glossary
- A Molecular Biology Glossary

**Lecture:**

**Instructor:** Larry Ruzzo, ruzzo at cs TBA

**Course Email:** cse527a_au09@u.washington.edu. Use this list to ask and/or a... ...is subscribed to this list. All messages are automatically archived. Questions not of general interest may be di... ...your subscription options.

**Catalog Description:** Introduces computational methods for understanding biological systems at the molecular level. Pro... sequencing, sequence analysis, structure prediction, phylogenic inference, regulatory analysis. Techniques such as dynamic progra... expectation-maximization, local search.

**Prerequisite:** Prerequisite: graduate standing in biological, computer, mathematical or statistical science, or permission of instructor.

**Credits:** 3

**Learning Objectives:** The availability of the complete genome sequences of humans and other organisms is one of the landmark achievements of science. Understanding this enormous volume of data is a problem that will challenge scientists for decades to come, and the nature and scope of the problem means that computer scientists will play a vital role. The primary objective of the course is for students to understand the variety of computational problems and solutions that arise in this interdisciplinary field. Students will learn enough of the basic concepts of molecular biology to understand the context for the computational problems presented in the rest of the course. They will learn how some of the computational methods they have encountered in other courses can be applied to solve problems in modern molecular biology. An important component is to learn the nature and capabilities of some of the key public databases available for the solution of these problems, as well as publicly available computational analysis tools and the algorithmic principles underlying them.

**Textbook:** Richard Durbin, Sean R. Eddy, Anders Krogh and Graeme Mitchison, *Biological Sequence Analysis: Probabilistic models of proteins and nucleic acids*, Cambridge, 1998. (Available from Amazon, etc.) Errata.

**References:** See Schedule & Reading

# Tonight

Admin

Why Comp Bio?

The world's shortest Intro. to Mol. Bio.

# Admin Stuff

# Course Mechanics & Grading

Web http://www.cs.washington.edu/csep590b

Reading

In class discussion

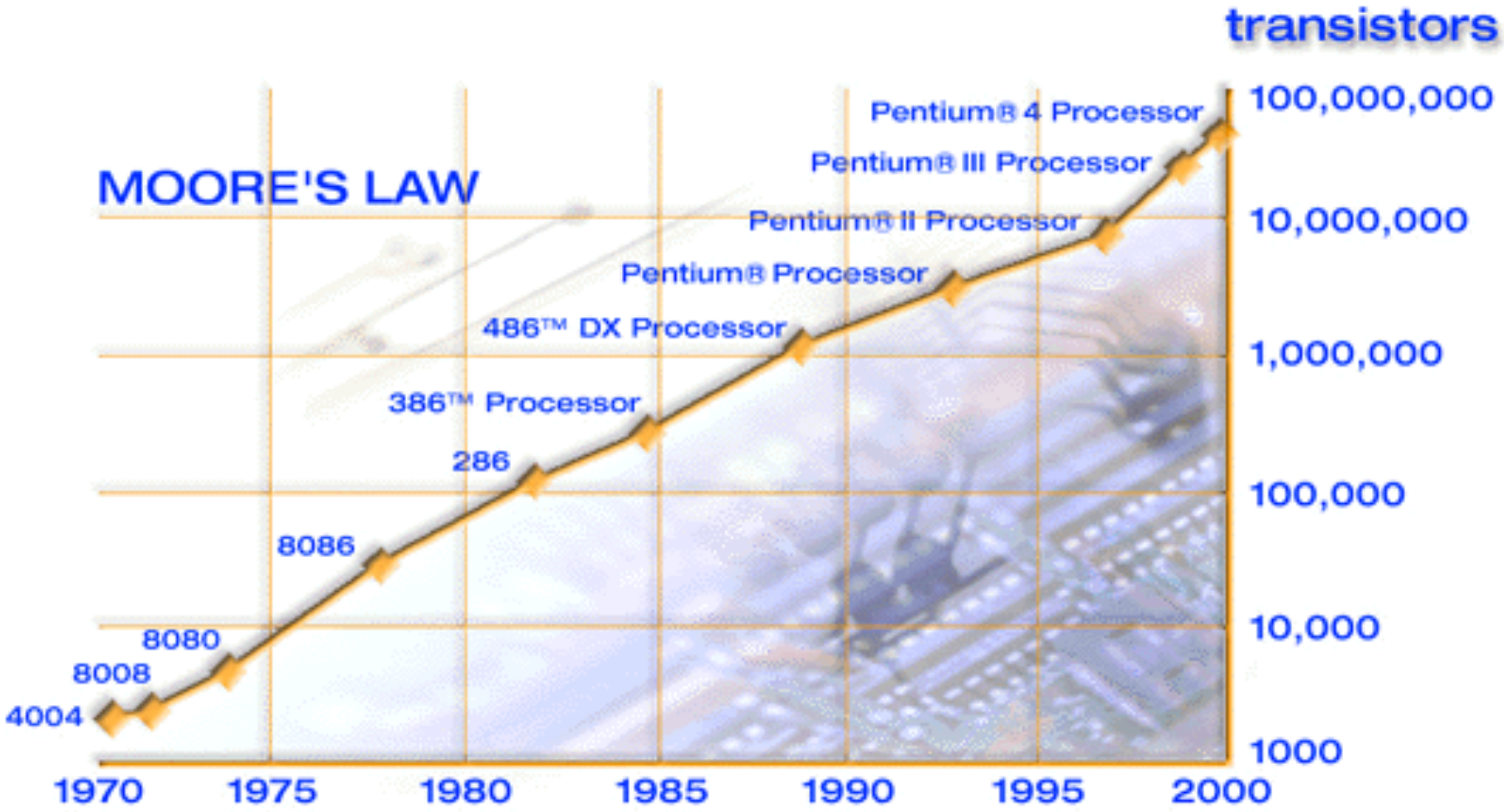
Homeworks

- reading blogs
- paper exercises
- programming

← Check web for 1st, soon

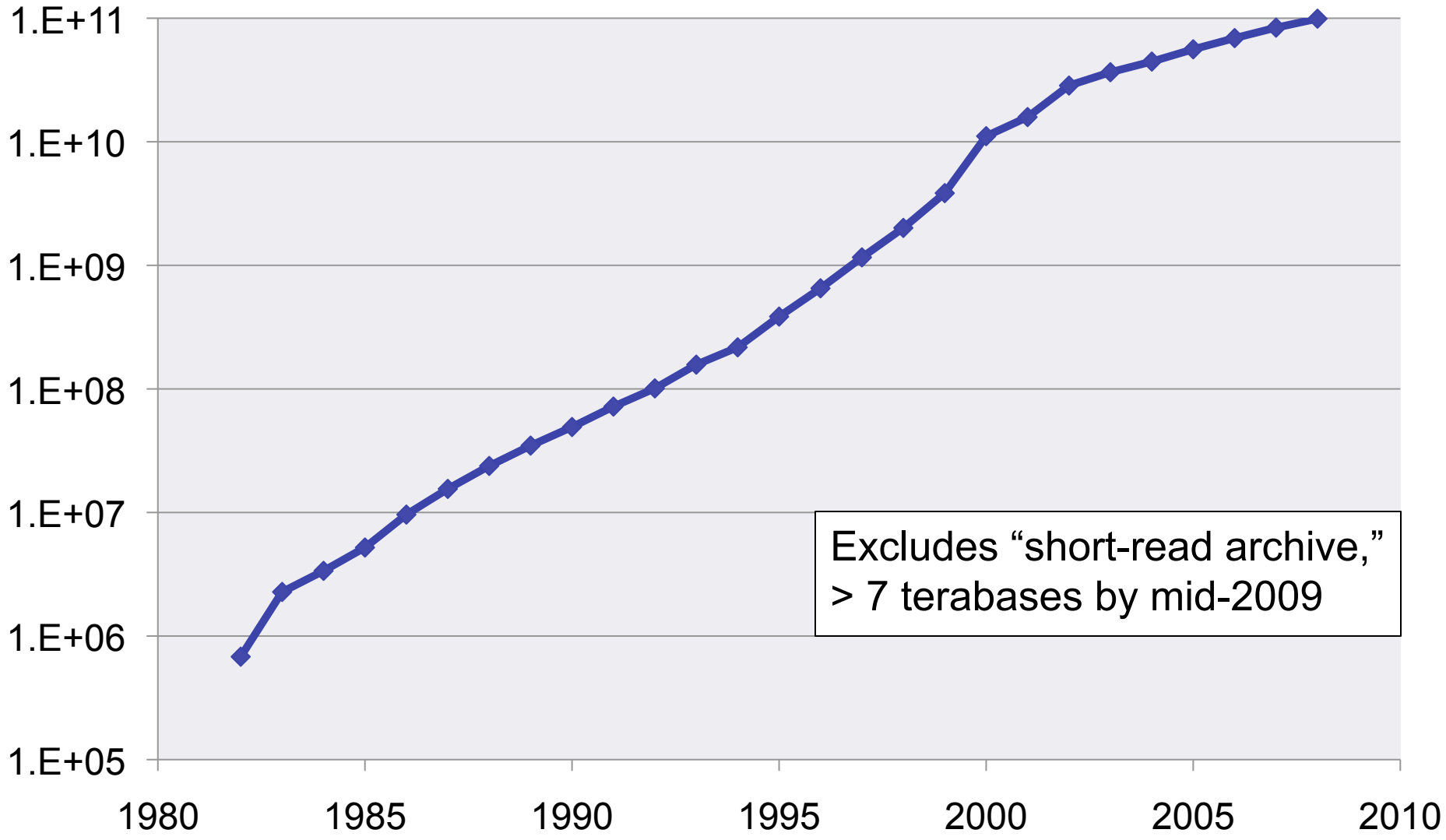
No exams, but possible oversized last homework in lieu of final

# Background & Motivation




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

## Growth of GenBank (Base Pairs)

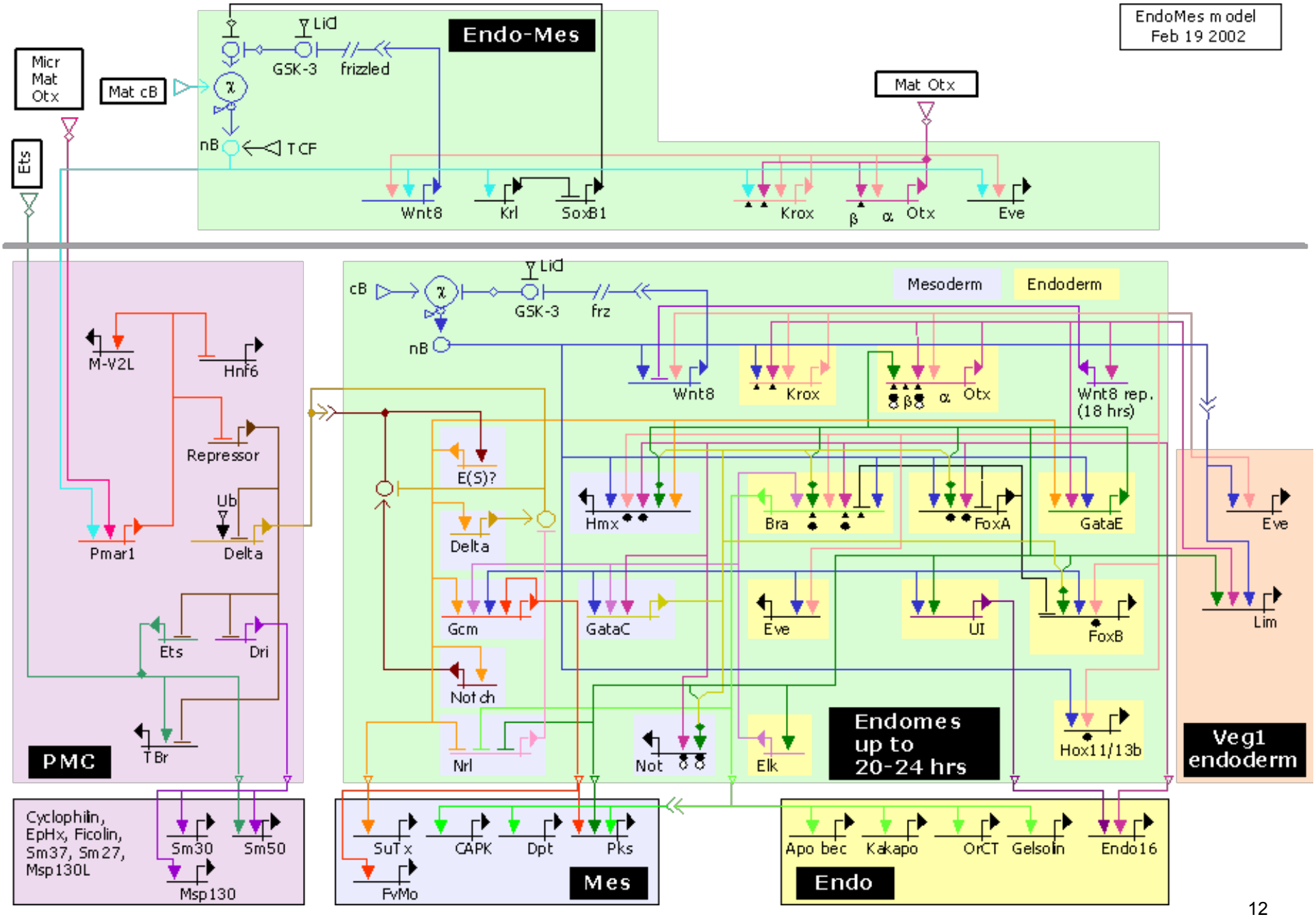



Source: http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html

# 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 agtcgggcca 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 ...
```

The sea urchin *Strongylocentrotus purpuratus*


EndoMes model
Feb 19 2002
Endo-Mes
Micr
Mat
Otx
Mat cB
Ets
LiCl
GSK-3
frizzled
nB
TCF
Wnt8
Krl
SoxB1
Mat Otx
Krox
β
α
Otx
Eve
cB
LiCl
GSK-3
frz
nB
Mesoderm
Endoderm
Wnt8
Krox
β
α
Otx
Wnt8 rep.
(18 hrs)
M-V2L
Hnf6
Repressor
Ub
Pmar1
Delta
E(S)?
Delta
Hmx
Bra
FoxA
GataE
Eve
Gcm
GataC
Eve
UI
FoxB
Lim
Ets
Dri
Notch
TBr
Nrl
Not
Elk
Endomes
up to
20-24 hrs
Hox11/13b
PMC
Veg1
endoderm
Cyclophilin,
EpHx, Ficolin,
Sm37, Sm27,
Msp130L
Sm30
Sm50
Msp130
SuTx
CAPK
Dpt
Pks
FyMo
Mes
Apo bec
Kakapo
OrCT
Gelsolin
Endo16
Endo

# Goals

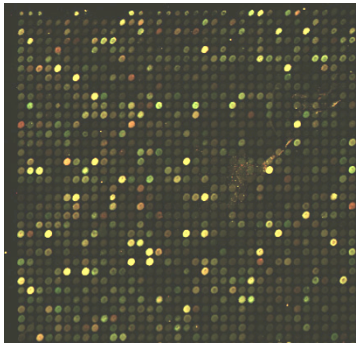
Basic biology

Disease diagnosis/prognosis/treatment

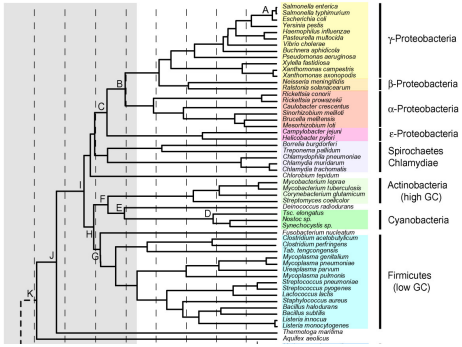
Drug discovery, validation & development

Individualized medicine

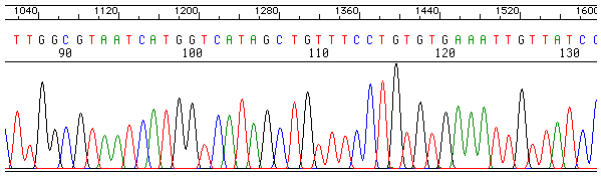
…

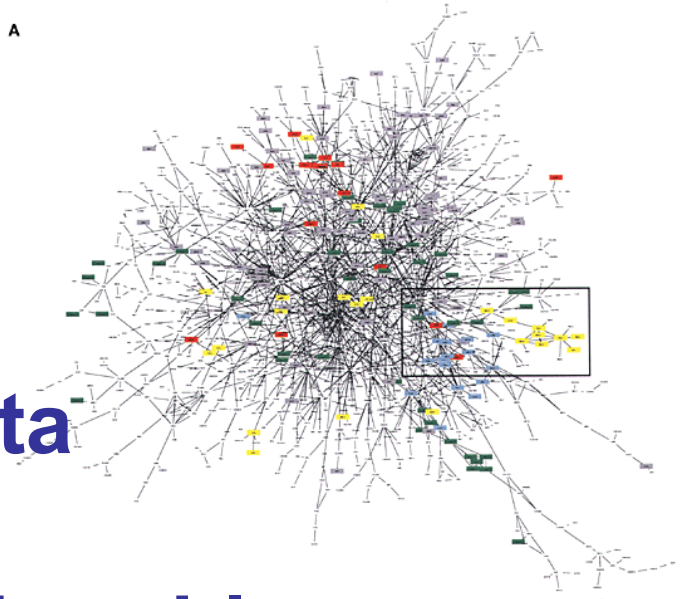


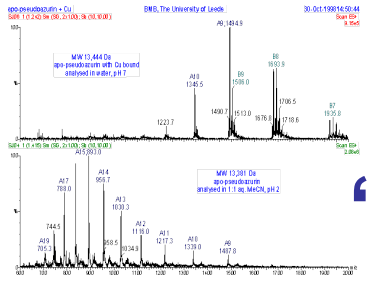
# "High-Throughput BioTech"




- 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, individual variation, …

AI/NLP/Text Mining

- Information extraction from text with inconsistent nomenclature, indirect interactions, incomplete/inaccurate models, …

Machine learning

- System level synthesis of cell behavior from low-level heterogeneous data (DNA seq, gene expression, protein interaction, mass spec,…)

...

Algorithms

# Computers in biology: Then & now

**Trends in Biochemical Sciences**
Volume 12 , 1987, Pages 279-280

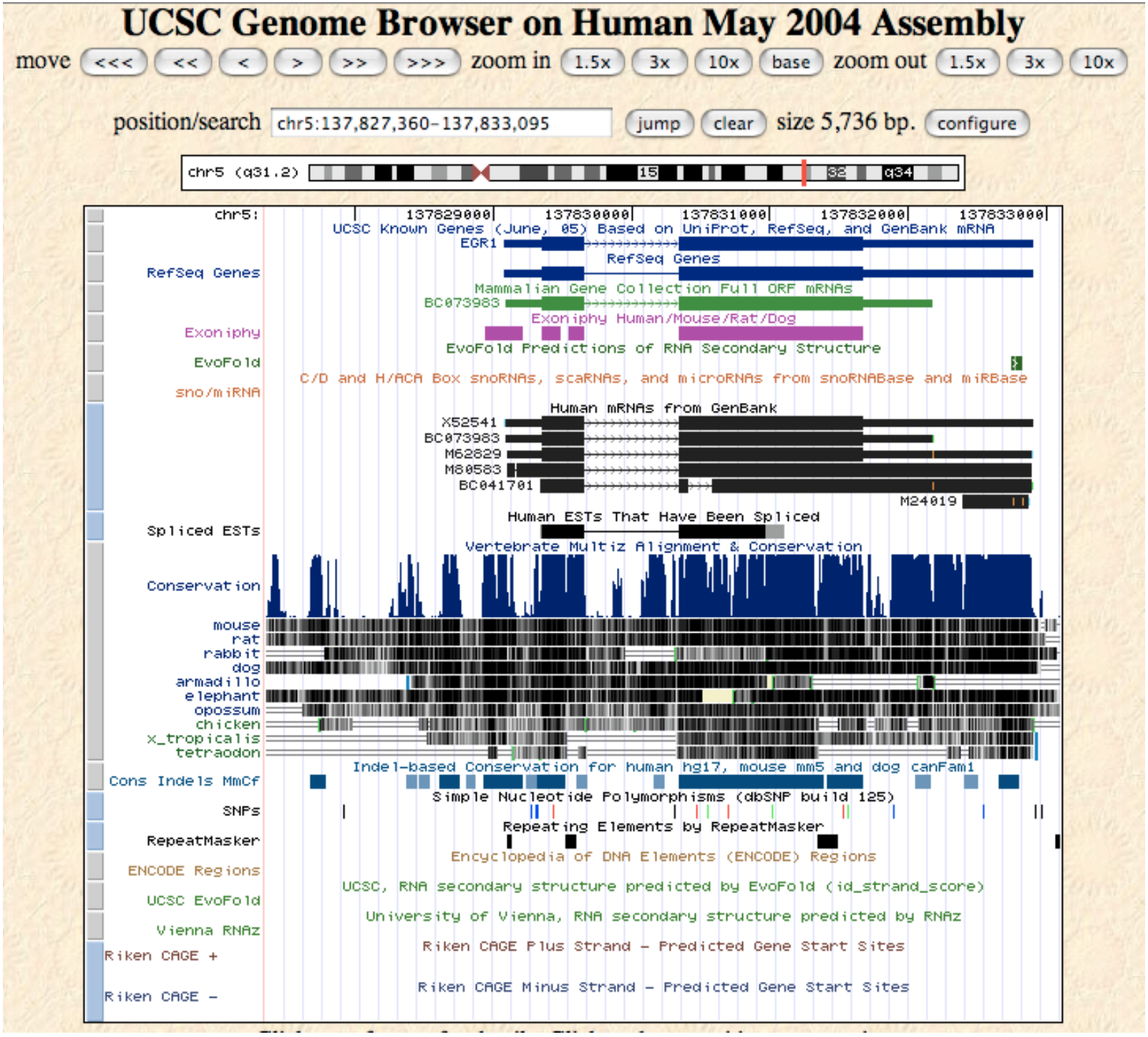


**Microfile**

## Sequence alignment by word processor

**D. Ross Boswell**

Department of Haematological Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's H
Road, Cambridge CB2 2QL, UK


UCSC Genome Browser on Human May 2004 Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x
position/search chr5:137,827,360-137,833,095 jump clear size 5,736 bp. configure
chr5 (q31.2)
chr5:
137829000 137830000 137831000 137832000 137833000
UCSC Known Genes (June, 05) Based on UniProt, RefSeq, and GenBank mRNA
EGR1
RefSeq Genes
RefSeq Genes
Mammalian Gene Collection Full ORF mRNAs
BC073983
Exoniphy Human/Mouse/Rat/Dog
Exoniphy
EvoFold Predictions of RNA Secondary Structure
EvoFold
C/D and H/ACA Box snoRNAs, scaRNAs, and microRNAs from snoRNABase and miRBase
sno/miRNA
Human mRNAs from GenBank
X52541
BC073983
M62829
M80583
BC041701
M24019
Human ESTs That Have Been Spliced
Spliced ESTs
Vertebrate Multiz Alignment & Conservation
Conservation
mouse
rat
rabbit
dog
armadillo
elephant
opossum
chicken
x_tropicalis
tetraodon
Indel-based Conservation for human hg17, mouse mm5 and dog canFam1
Cons Indels MmCf
Simple Nucleotide Polymorphisms (dbSNP build 125)
SNPs
Repeating Elements by RepeatMasker
RepeatMasker
Encyclopedia of DNA Elements (ENCODE) Regions
ENCODE Regions
UCSC, RNA secondary structure predicted by EvoFold (id_strand_score)
UCSC EvoFold
University of Vienna, RNA secondary structure predicted by RNAz
Vienna RNAz
Riken CAGE Plus Strand - Predicted Gene Start Sites
Riken CAGE +
Riken CAGE Minus Strand - Predicted Gene Start Sites
Riken CAGE -

# An Algorithm Example: ncRNAs

The “Central Dogma”:

- DNA -> messenger RNA -> Protein

Last ~5 years:

- 100s – 1000s of examples of functionally important ncRNAs

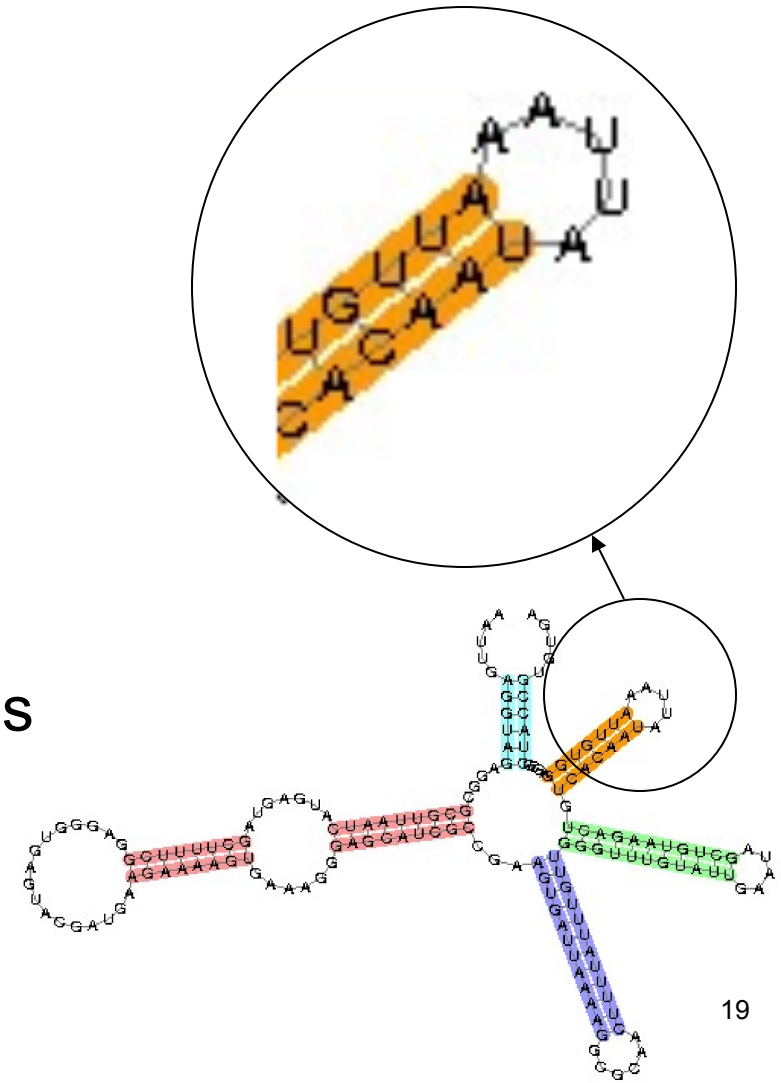
Much harder to find than protein-coding genes

Main method - Covariance Models

- ≈ 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,…)

CENSORED
Details
(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

The *computational* advance has enabled new *biological* discoveries

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

# 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…

Enough bio to motivate these problems

- including very light intro to modern biotech supporting them

Math/stats/cs underpinnings thereof

Applied to real data

# A *VERY* Quick Intro To Molecular Biology

# The Genome

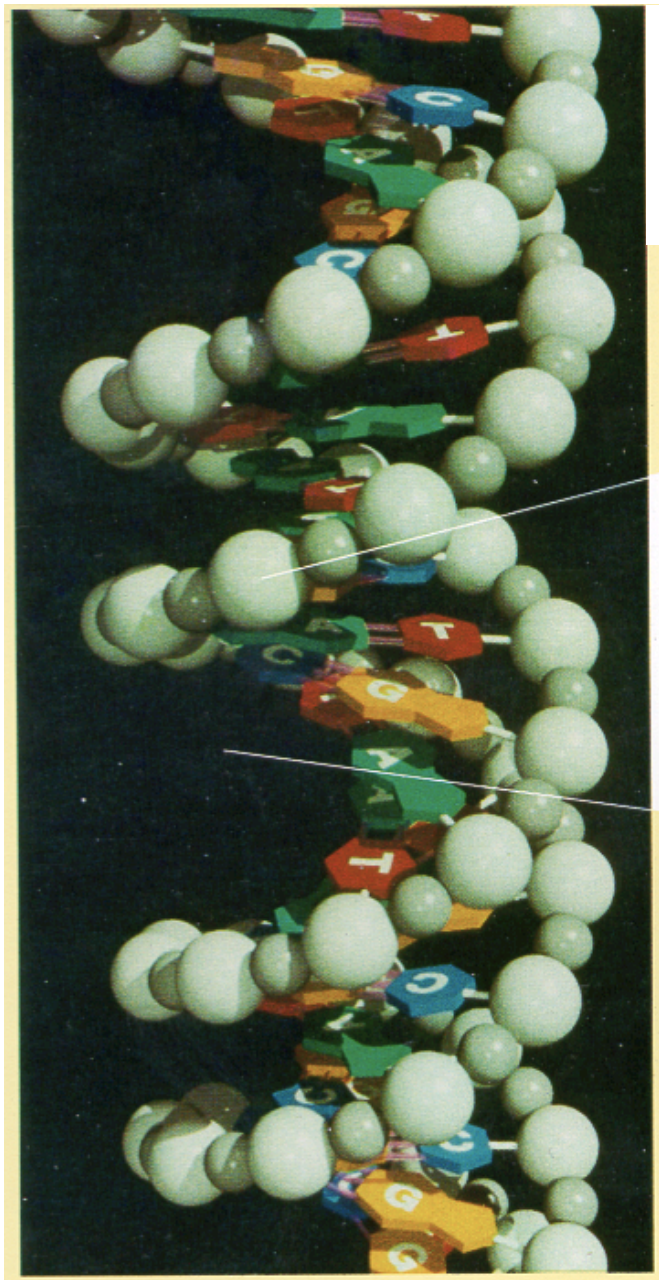
The hereditary info present in every cell

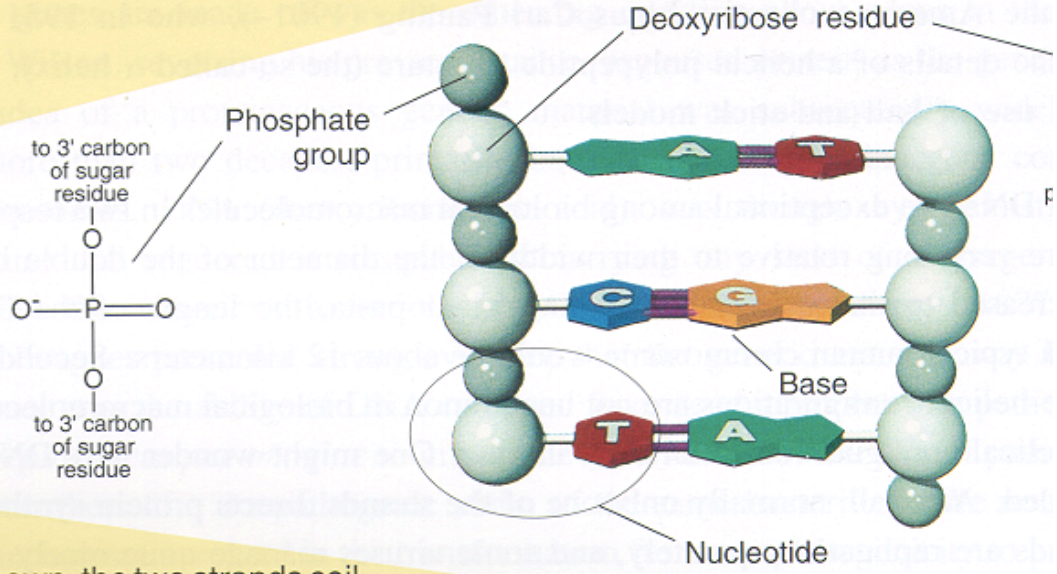
DNA molecule -- a long sequence of *nucleotides* (A, C, T, G)

Human genome -- about $3 \times 10^9$ nucleotides

The genome project -- extract & interpret genomic information, apply to genetics of disease, better understand evolution, …

# The Double Helix






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

# DNA

Discovered 1869

Role as carrier of genetic information - much later

4 “bases”:

adenine (A), cytosine (C), guanine (G), thymine (T)

The Double Helix - Watson & Crick 1953

Complementarity

A ⟷ T  C ⟷ G

Visualization:

http://www.rcsb.org/pdb/explore.do?structureId=123D

# Genetics - the study of heredity

A *gene* -- classically, an abstract heritable attribute existing in variant forms (*alleles*)

- ABO blood type–1 gene, 3 alleles

Mendel

- Each individual two copies of each gene
- Each parent contributes one (randomly)
- Independent assortment (approx, but useful)

*Genotype* vs *phenotype*

- I.e., genes vs their outward manifestation
- AA or AO genotype →“type A” phenotype

# Cells

Chemicals inside a sac - a fatty layer called the *plasma membrane*

*Prokaryotes* (bacteria, archaea) - 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: just 1 chromosome

most

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: the major functional elements in cells

- Structural/mechanical
- 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”

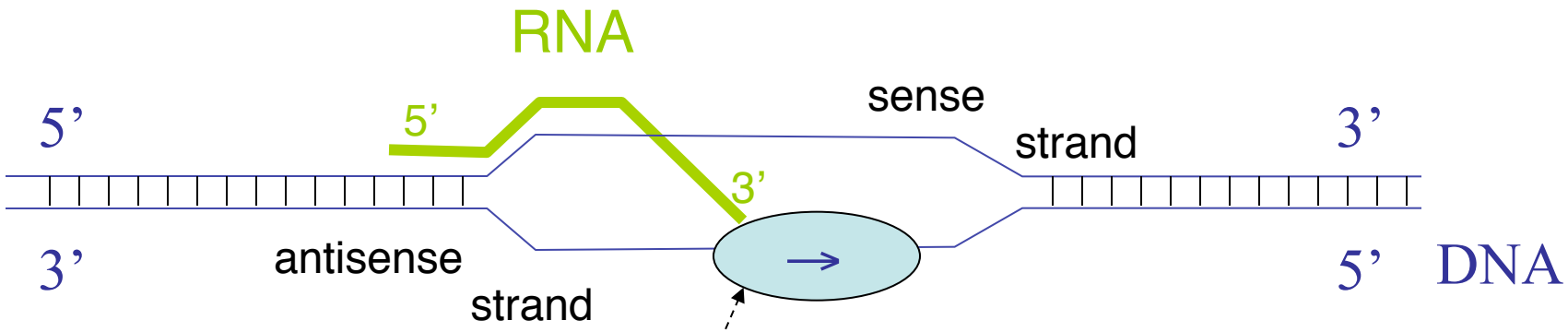
Genes encode proteins

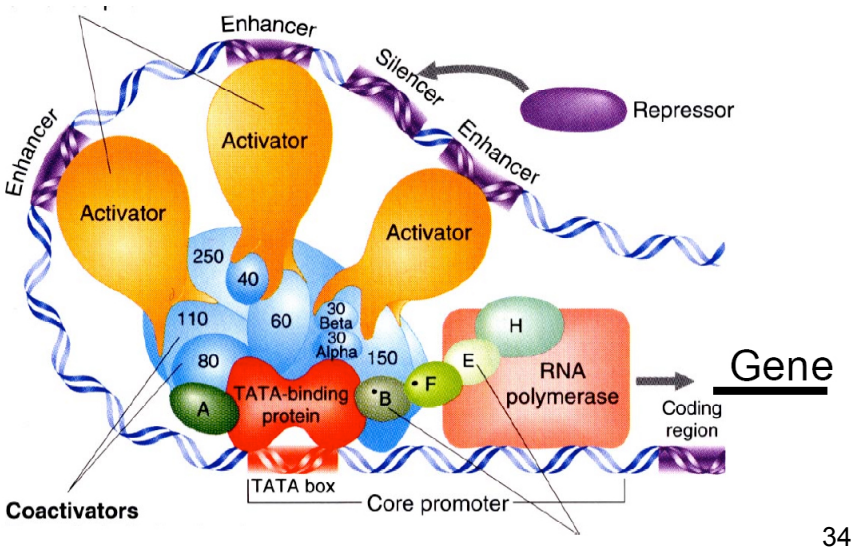
DNA transcribed into messenger RNA

mRNA translated into proteins

Triplet code (codons)

# Transcription: DNA → RNA



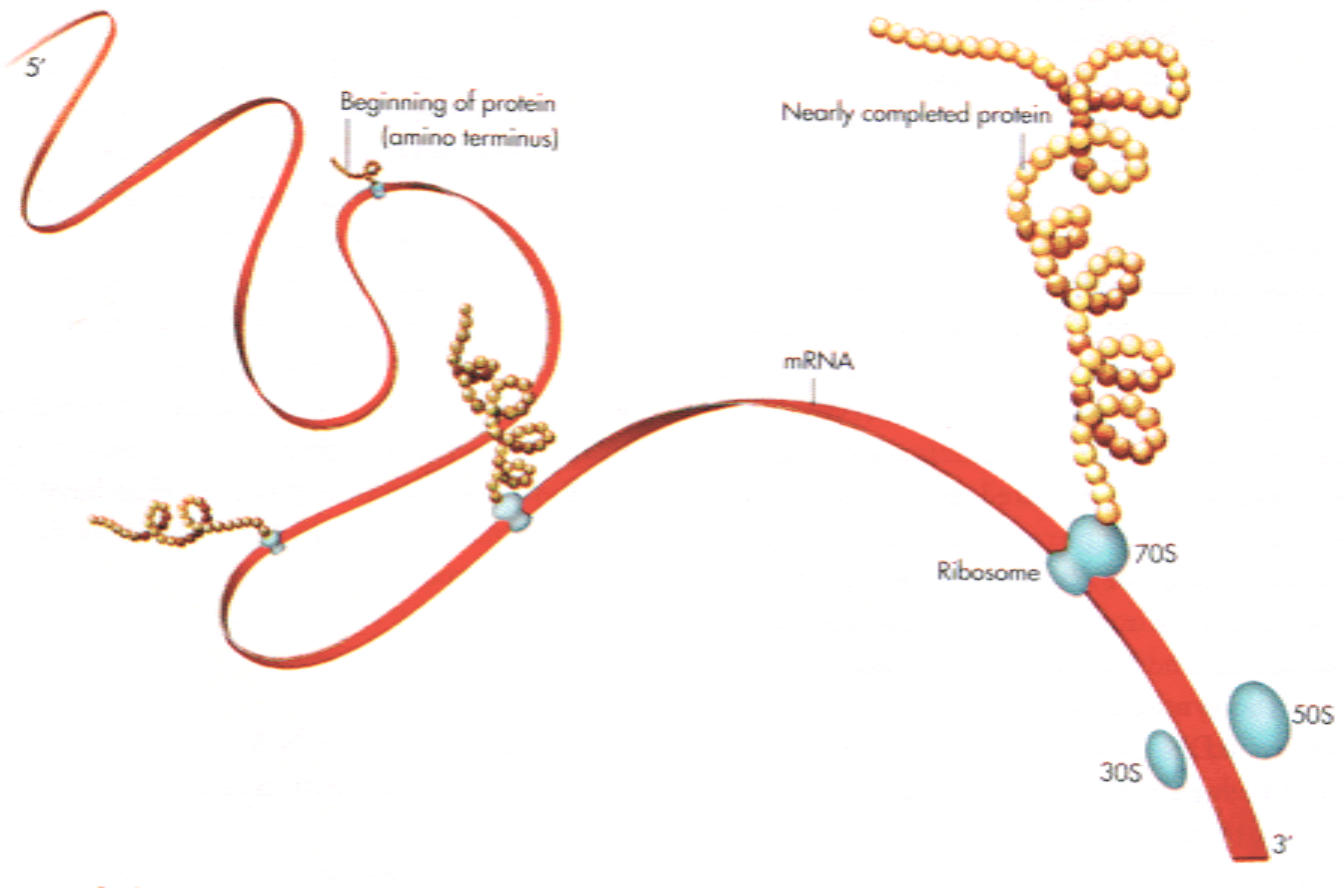



# Codons & The Genetic Code

| First Base | Second Base U | Second Base C | Second Base A | Second Base 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 |

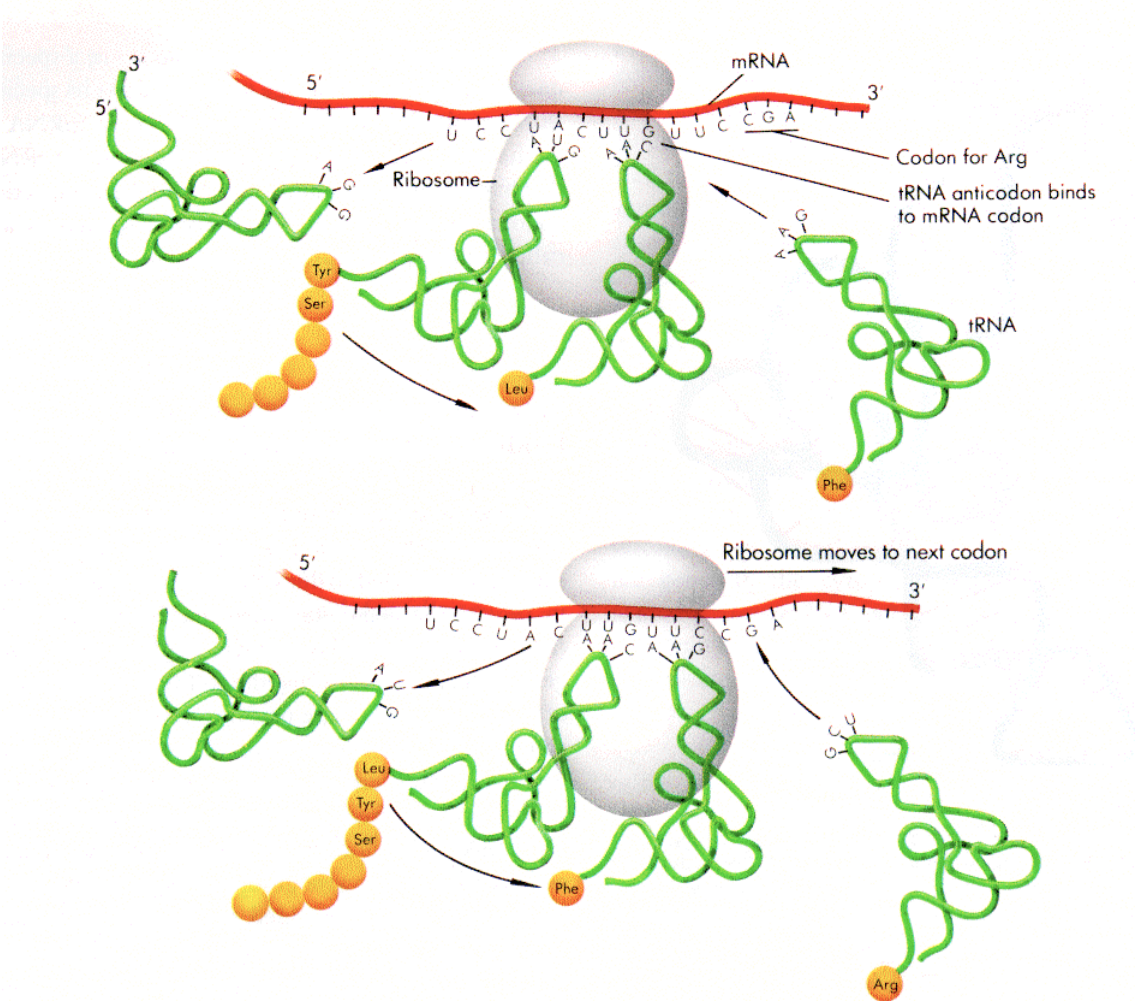
Ala : Alanine
Arg : Arginine
Asn : Asparagine
Asp : Aspartic acid
Cys : Cysteine
Gln : Glutamine
Glu : Glutamic acid
Gly : Glycine
His : Histidine
Ile : Isoleucine
Leu : Leucine
Lys : Lysine
Met : Methionine
Phe : Phenylalanine
Pro : Proline
Ser : Serine
Thr : Threonine
Trp : Tryptophane
Tyr : Tyrosine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

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 | $3.3 \times 10^9$ | ~25,000 |

# Genome Surprises

Humans have < 1/3 as many genes as expected

But perhaps more proteins than expected, due to *alternative splicing, alt start, alt end*

Protein-wise, all mammals are just about the same

But more individual variation than expected

And many more *non-coding RNAs* -- more than protein-coding genes, by some estimates

Many other non-coding regions are highly conserved, e.g., across all vertebrates

Subset of DNA being transcribed is >> 2% coding

Complex, subtle “epigenetic” information

# … and much more …

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