CSE527
Computational Biology

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

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Autumn 2007

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

-- Chinese Proverb

Today

Admin

Why Comp Bio?

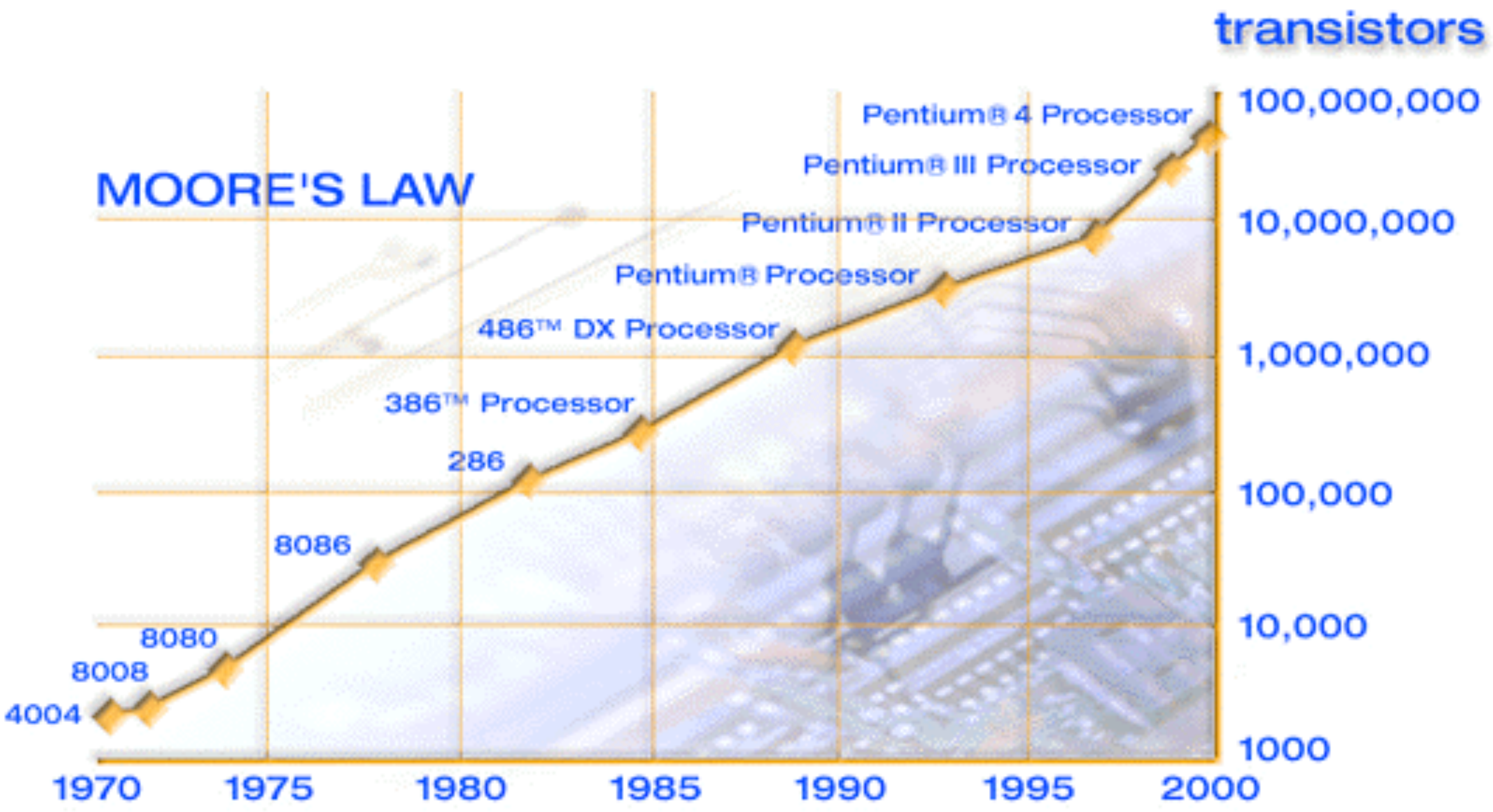
The world’s shortest Intro. to Mol. Bio.

Admin Stuff

Course Mechanics & Grading

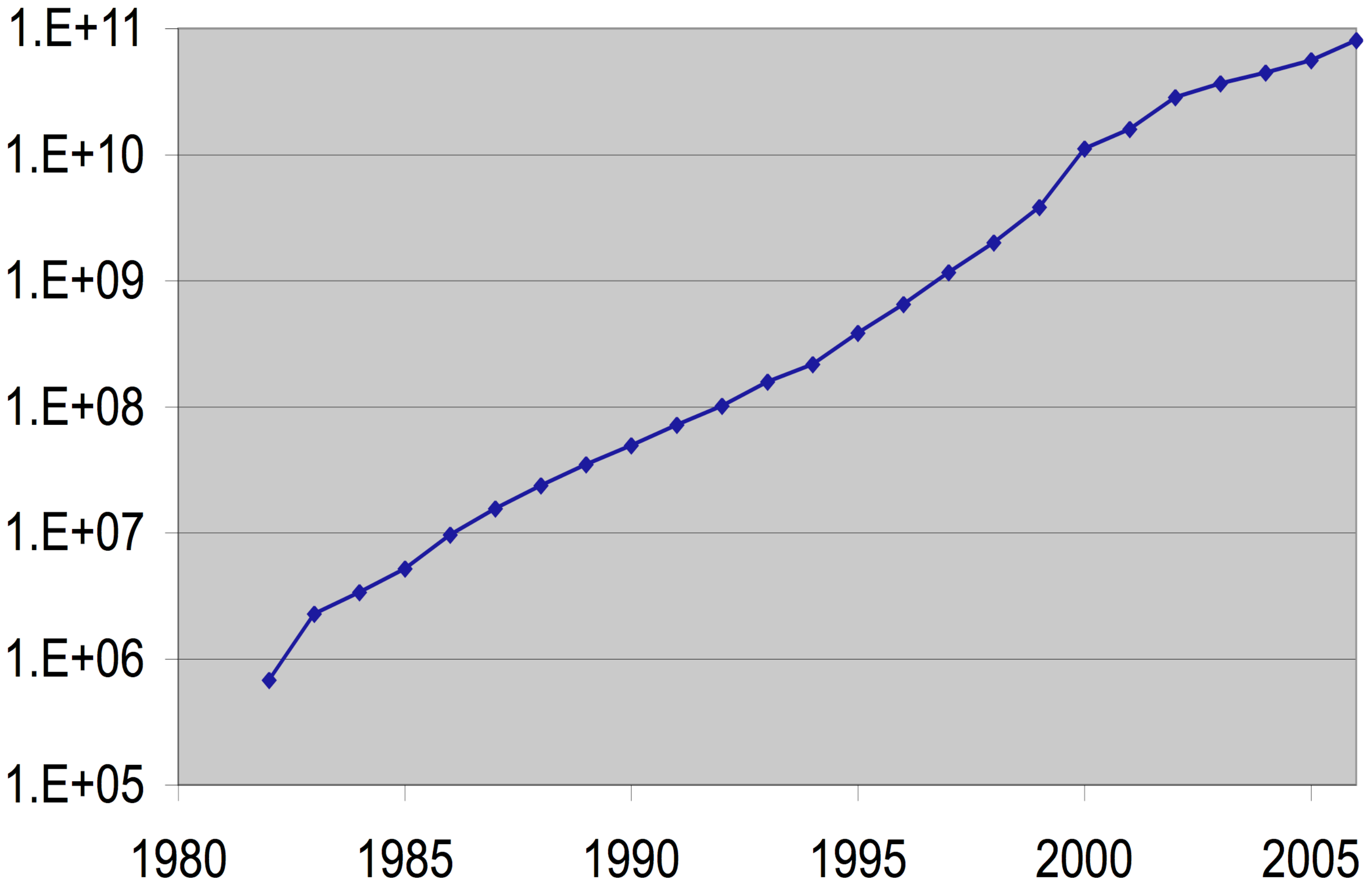
- Reading
- In class discussion
- Lecture scribes
- Homeworks
  - reading
  - paper exercises
  - programming
- Project
- No exams

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
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 241 aaccagagcc agtcgggcca agagaagagg cggtggagga cacgacgcgc ttaaaggacc
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 481 acaacactgc aatattcgct gtatgaatgg aggtagctgc agtgacgatc actgtctatg
 541 ccagaaagga tacataggga ctcactgtgg acaacctgtt tgtgaaagtg gctgtctcaa
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 901 ctgtcaggga ggaaattgca ttaatactgt tgggtctttt gagtgcaaat gccctgctgg
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1021 ...
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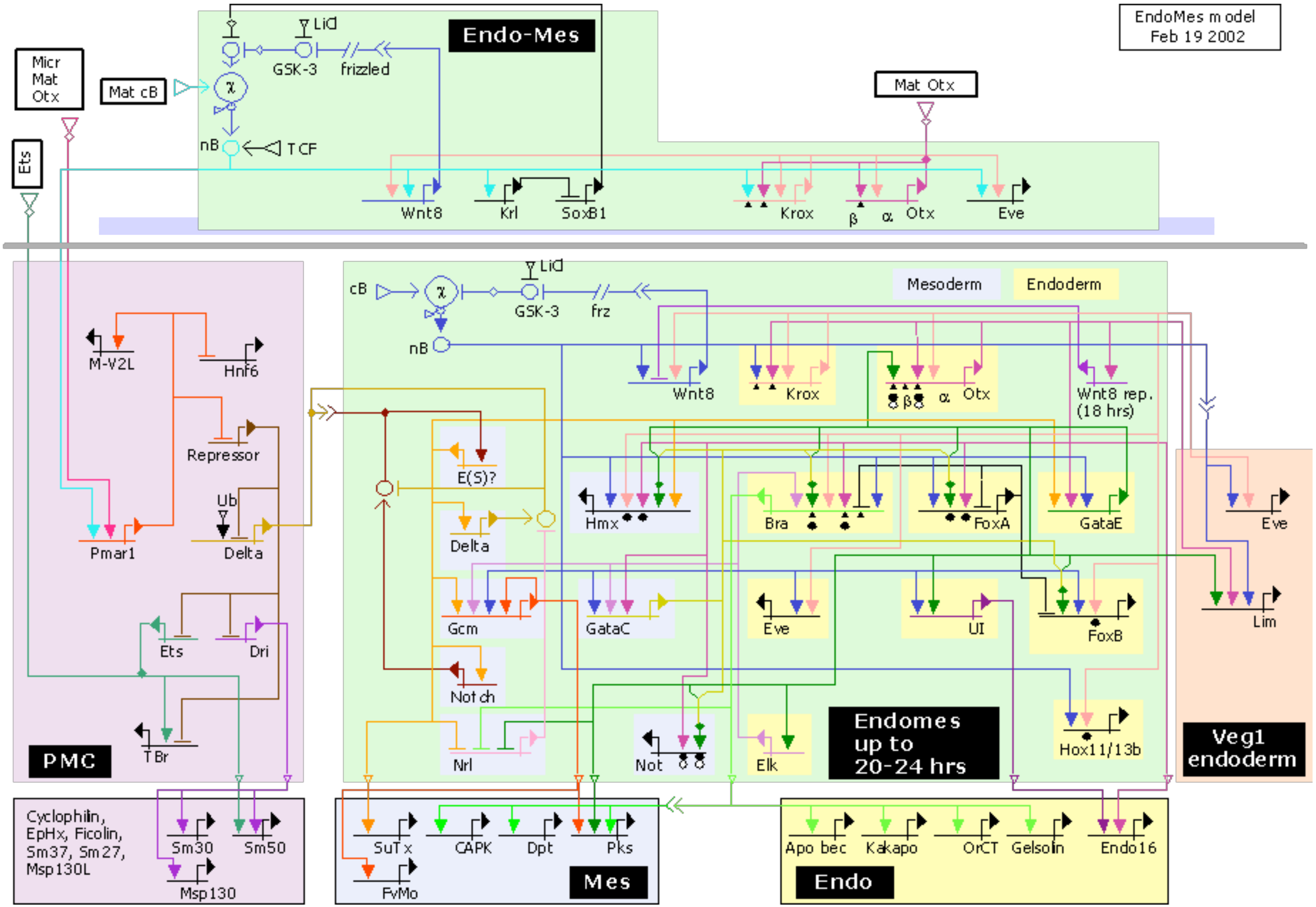
EndoMes model
Feb 19 2002
Micr
Mat
Otx
Mat cB
Ets
LiCl
GSK-3
frizzled
Endo-Mes
nB
TCF
Mat Otx
Wnt8
Krl
SoxB1
Krox
β
α
Otx
Eve
M-V2L
Hnf6
Repressor
Ub
Pmar1
Delta
Ets
Dri
TBr
PMC
cB
LiCl
GSK-3
frz
nB
Mesoderm
Endoderm
Wnt8
Krox
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Otx
Wnt8 rep.
(18 hrs)
E(S)?
Hmx
Bra
FoxA
GataE
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Delta
Gcm
GataC
Eve
Ul
FoxB
Lim
Notch
Nrl
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Elk
Endomes
up to
20-24 hrs
Hox11/13b
Veg1
endoderm
Cyclophilin,
EpHx, Ficolin,
Sm37, Sm27,
Msp130L
Sm30
Sm50
Msp130
SuTx
CAPK
Dpt
Pks
FvMo
Mes
Apo bec
Kakapo
OrCT
Gelsolin
Endo16
Endo

Goals

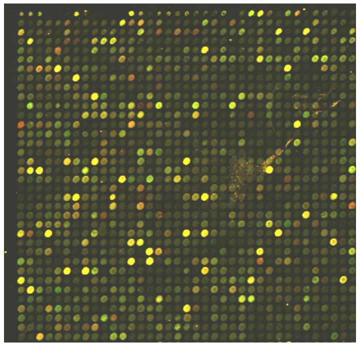
Basic biology

Disease diagnosis/prognosis/treatment

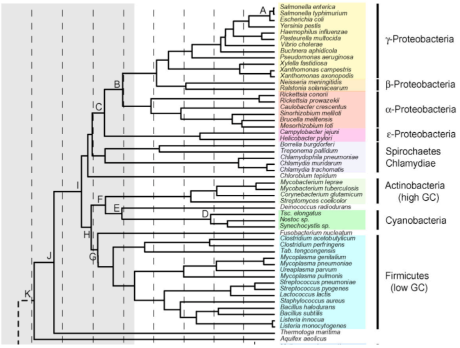
Drug discovery, validation & development

Individualized medicine

…



“High-Throughput BioTech”

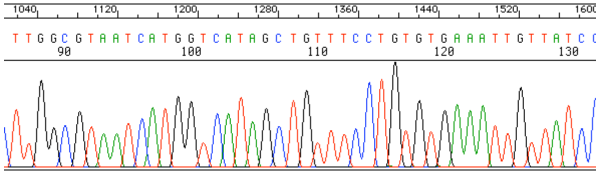


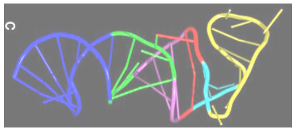
Sensors

- DNA sequencing
- Microarrays/Gene expression
- Mass Spectrometry/Proteomics
- Protein/protein & DNA/protein interaction

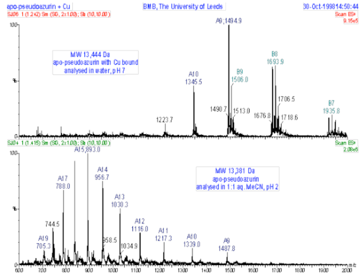
Controls

- 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
- 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

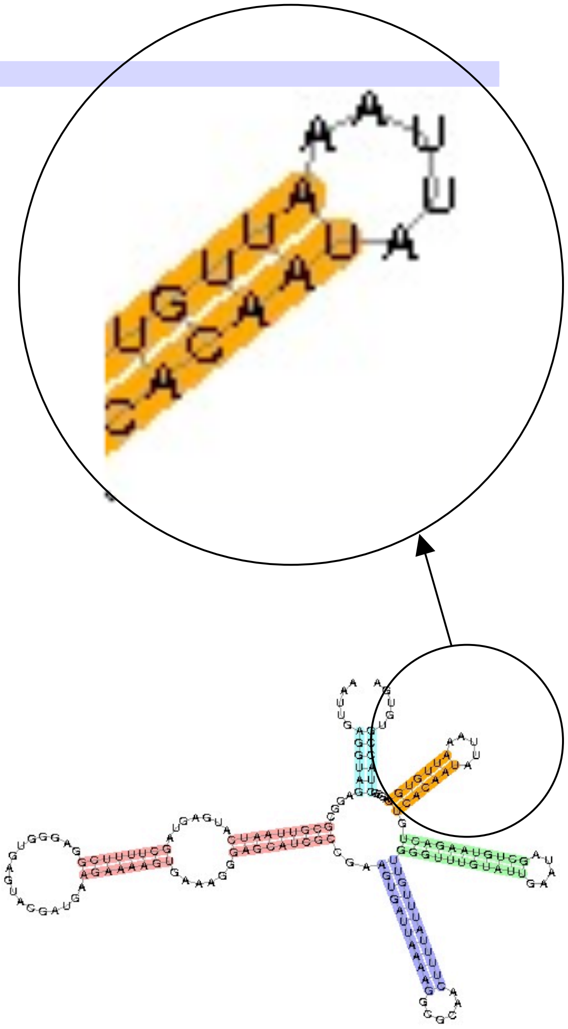
Last ~5 years: many examples of functionally important ncRNAs

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,…)

More Admin

Course Focus & Goals

Sequence analysis, maybe some microarrays

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

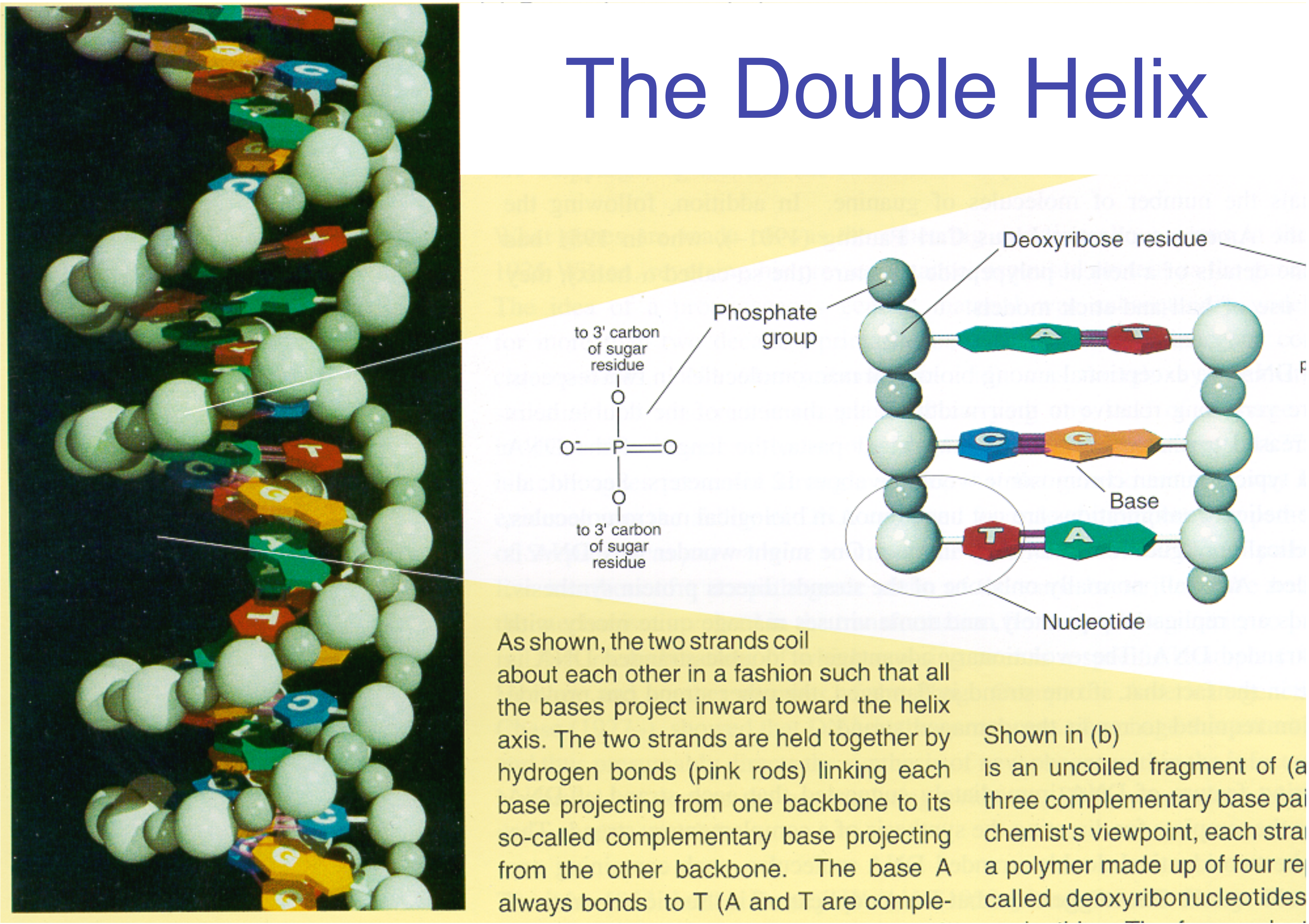
The hereditary info present in every cell

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

Human genome -- about 3 x 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

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

Visualizations:

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*)

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 (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 have just 1 chromosome

Eukaryotes - ~~all~~ most 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”

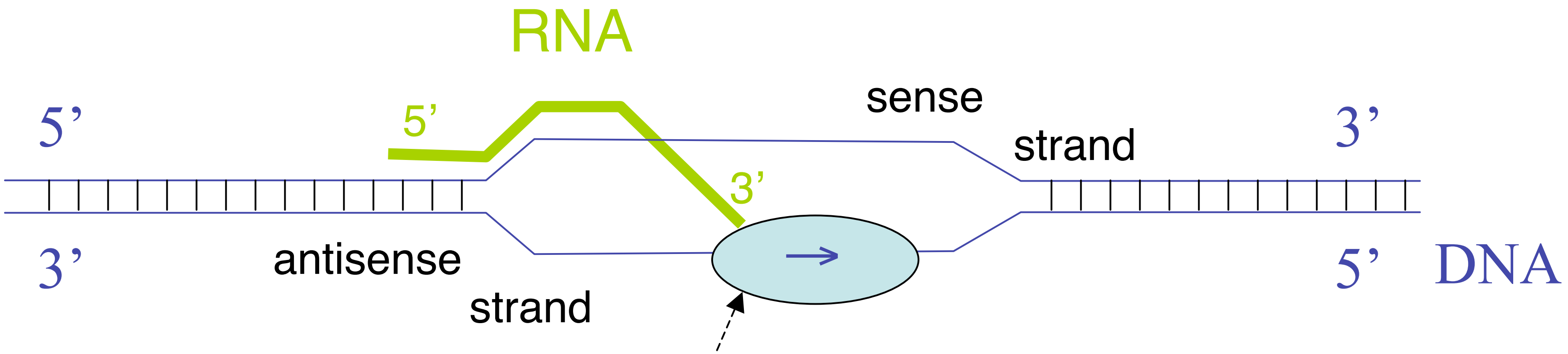
Genes encode proteins

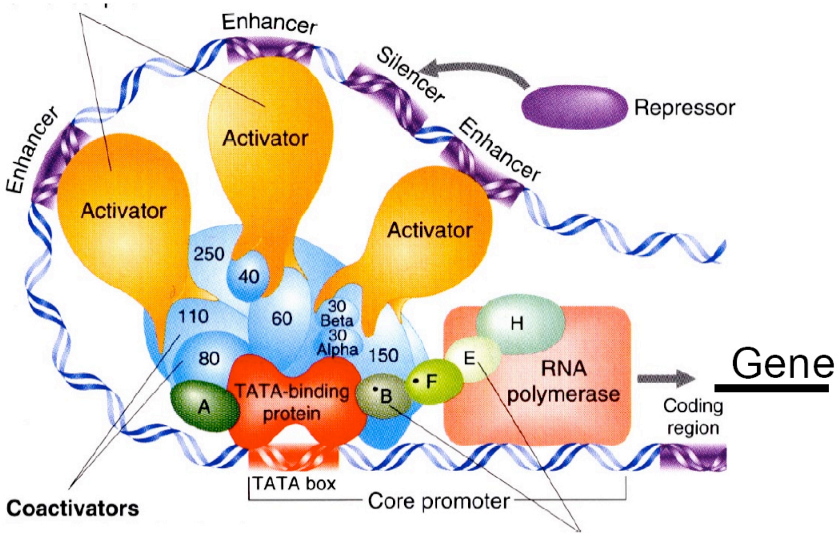
DNA transcribed into messenger RNA

mRNA translated into proteins

Triplet code (codons)

Transcription: DNA → RNA



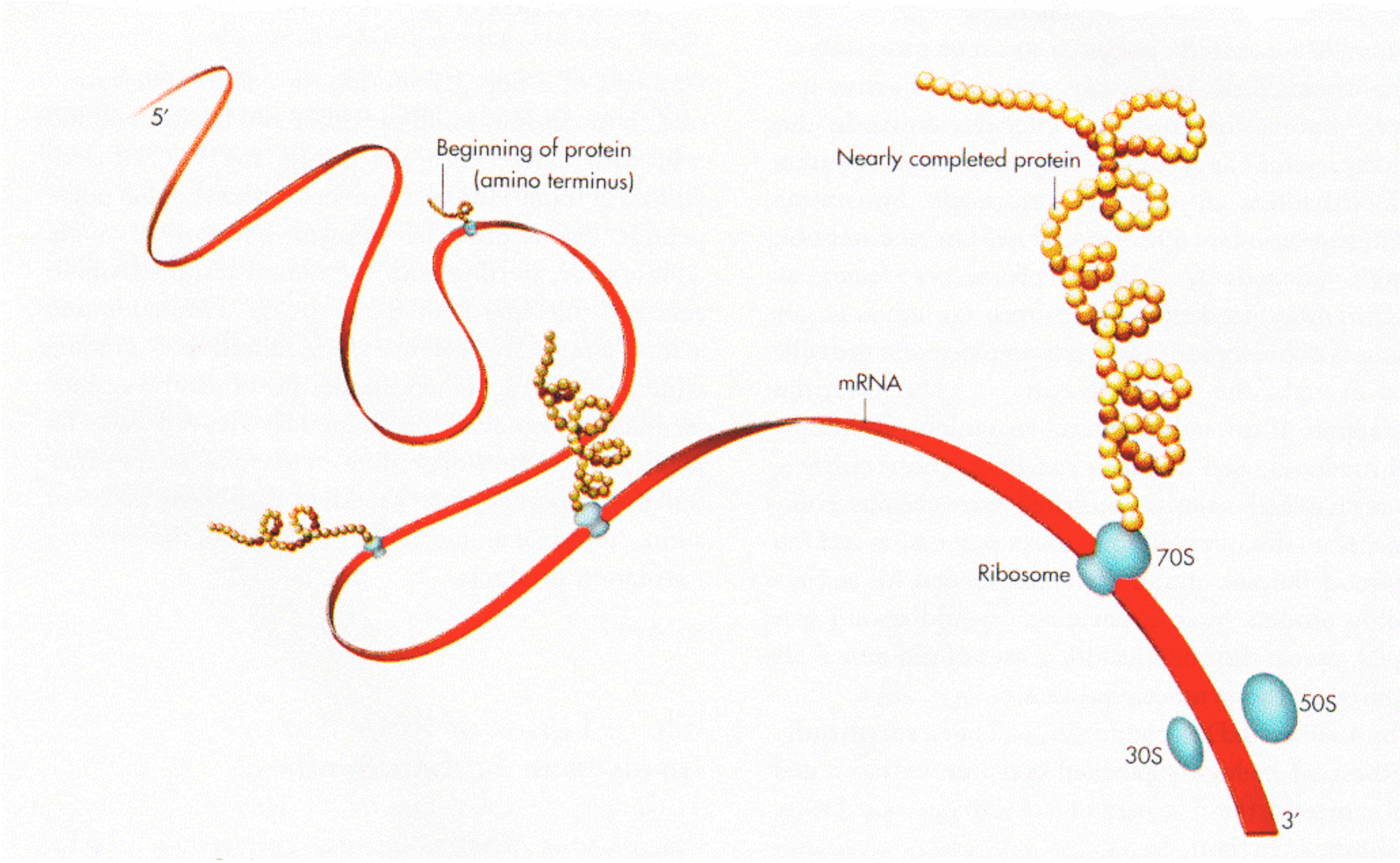


Codons & The Genetic Code

		Second Base					
		U	**C**	**A**	**G**		
First Base	**U**	Phe	Ser	Tyr	Cys	**U**	**Third Base**
		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**	

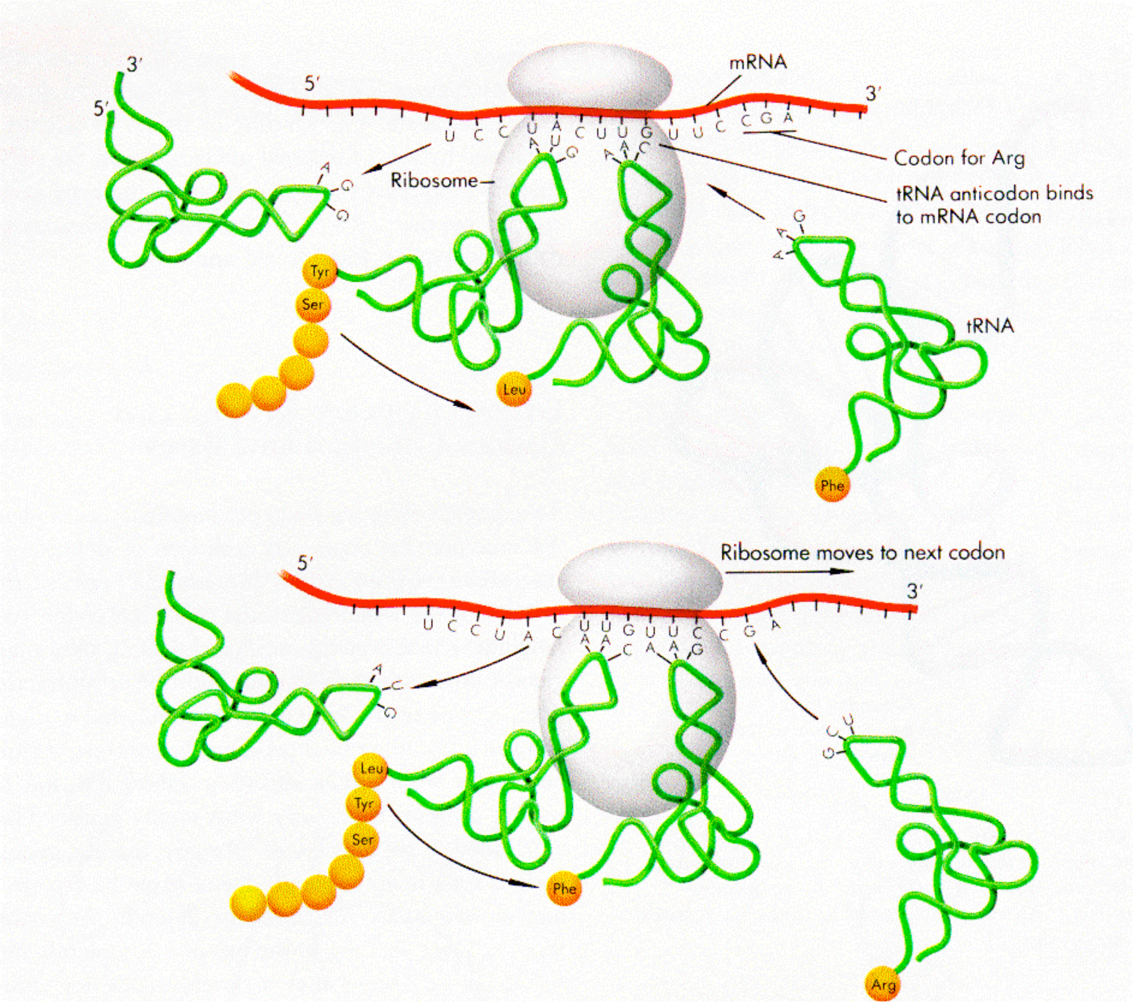
Ala	: Alanine
Arg	: Arginine
Asn	: Asparagine
Asp	: Aspartic acid
Cys	: Cysteine
Gln	: Glutamine
Glu	: Glutamic acid
Gly	: Glycine
His	: Histidine
Ile	: Isoleucine
Leu	: Leucine
Lys	: Lysine
Met	: Methionine
Phe	: Phenylalanine
Pro	: Proline
Ser	: Serine
Thr	: Threonine
Trp	: Tryptophane
Tyr	: Tyrosine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

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

90% of DNA is transcribed (< 2% coding)

Complex, subtle “epigenetic” information

… 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