CSE P 527
Computational Biology

http://courses.cs.washington.edu/courses/csep527/20au

Larry Ruzzo

Autumn 2020

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?

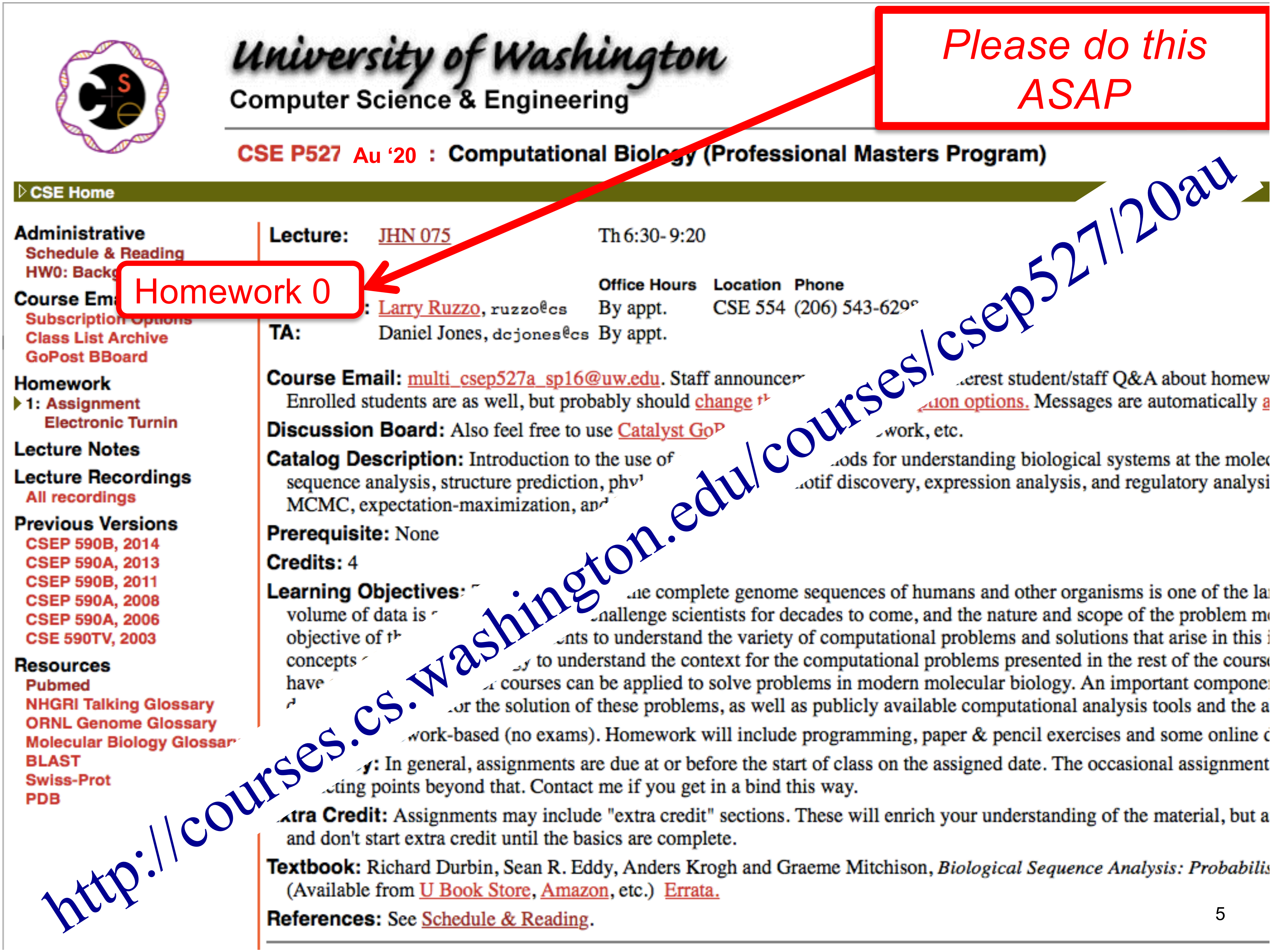
The world’s shortest Intro. to Mol. Bio.

Admin Stuff

Please do this ASAP

Homework 0

http://courses.cs.washington.edu/courses/csep527/20au



University of Washington
Computer Science & Engineering

CSE P527 Au ‘20 : Computational Biology (Professional Masters Program)

Administrative
Schedule & Reading
HW0: Backg

Course Ema
Subscription Options
Class List Archive
GoPost BBoard

Homework
▶ 1: Assignment
Electronic Turnin

Lecture Notes

Lecture Recordings
All recordings

Previous Versions
CSEP 590B, 2014
CSEP 590A, 2013
CSEP 590B, 2011
CSEP 590A, 2008
CSEP 590A, 2006
CSE 590TV, 2003

Resources
Pubmed
NHGRI Talking Glossary
ORNL Genome Glossary
Molecular Biology Glossar
BLAST
Swiss-Prot
PDB

Lecture: JHN 075 Th 6:30-9:20

		Office Hours	Location	Phone
:	Larry Ruzzo, ruzzo@cs	By appt.	CSE 554	(206) 543-629
TA:	Daniel Jones, dcjones@cs	By appt.		

Course Email: multi_csep527a_sp16@uw.edu. Staff announcem ...erest student/staff Q&A about homew Enrolled students are as well, but probably should change th ...ion options. Messages are automatically a

Discussion Board: Also feel free to use Catalyst GoP ...work, etc.

Catalog Description: Introduction to the use of ...ods for understanding biological systems at the molec sequence analysis, structure prediction, phy ...otif discovery, expression analysis, and regulatory analysi MCMC, expectation-maximization, and

Prerequisite: None

Credits: 4

Learning Objectives: ...he complete genome sequences of humans and other organisms is one of the la volume of data is ...challenge scientists for decades to come, and the nature and scope of the problem m objective of th ...nts to understand the variety of computational problems and solutions that arise in this i concepts ...y to understand the context for the computational problems presented in the rest of the cours have ...r courses can be applied to solve problems in modern molecular biology. An important compone d ...or the solution of these problems, as well as publicly available computational analysis tools and the a

...work-based (no exams). Homework will include programming, paper & pencil exercises and some online c

...y: In general, assignments are due at or before the start of class on the assigned date. The occasional assignment ...ting points beyond that. Contact me if you get in a bind this way.

...xtra Credit: Assignments may include "extra credit" sections. These will enrich your understanding of the material, but a and don't start extra credit until the basics are complete.

Textbook: Richard Durbin, Sean R. Eddy, Anders Krogh and Graeme Mitchison, *Biological Sequence Analysis: Probabilis* (Available from U Book Store, Amazon, etc.) Errata.

References: See Schedule & Reading.

Course Mechanics & Grading

Web

http://courses.cs.washington.edu/courses/csep527/20au

Reading

In class discussion

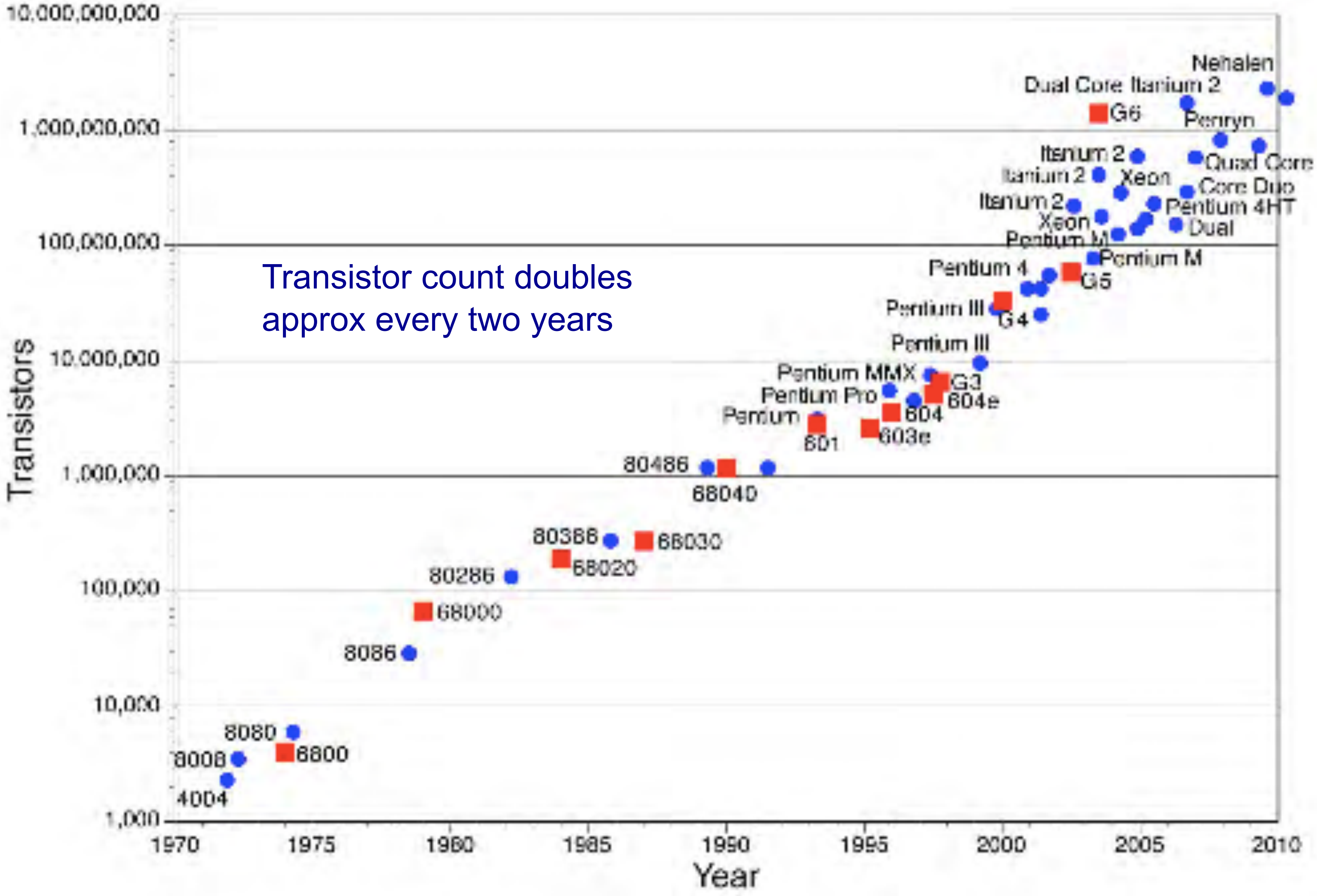
Homeworks ← Check web for 1st, ~~soon~~ now

- reading blogs
- paper exercises
- programming

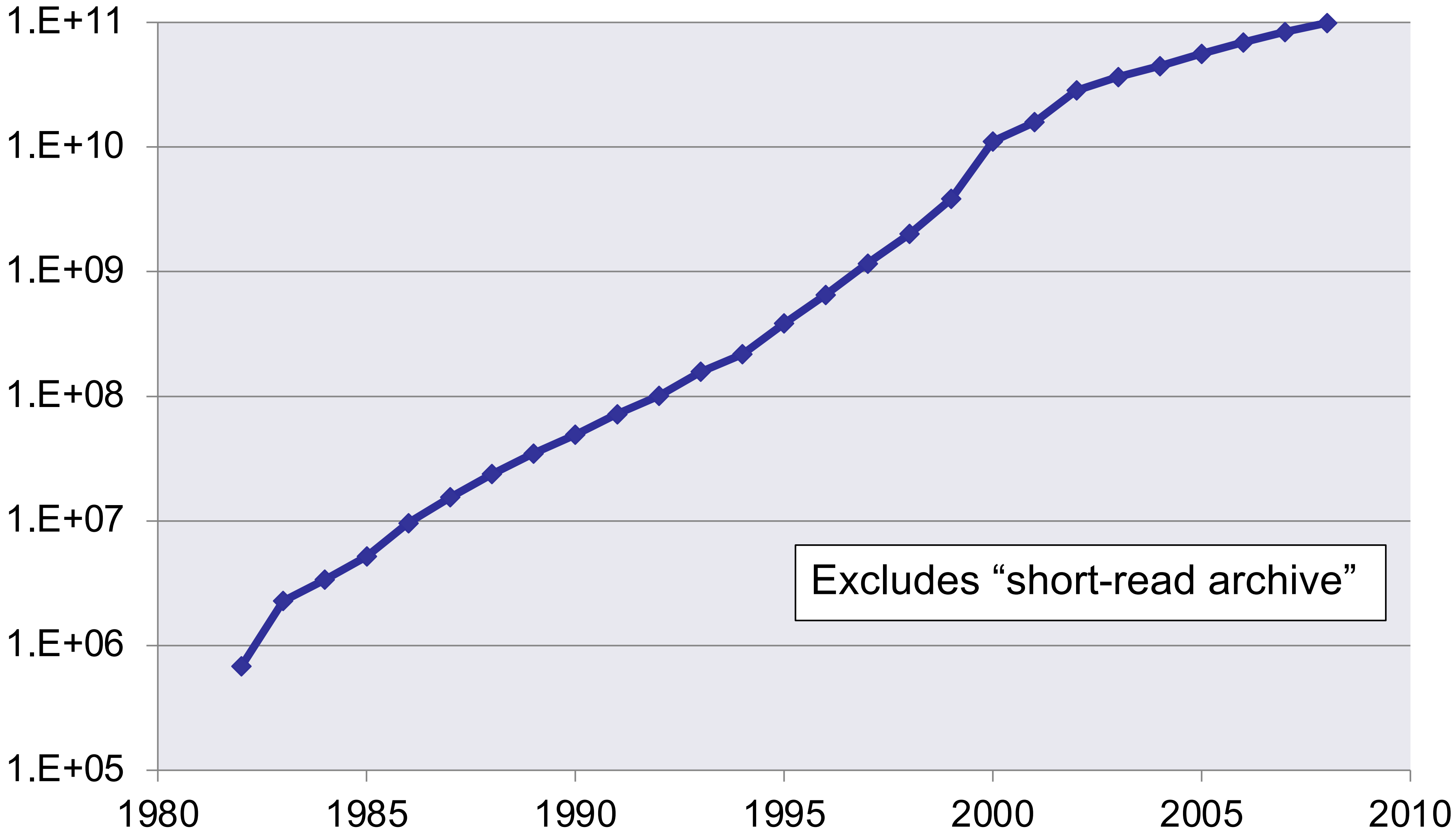
No exams, but possible oversized last homework in lieu of final

Background & Motivation

Moore’s Law


Transistor count doubles approx every two years

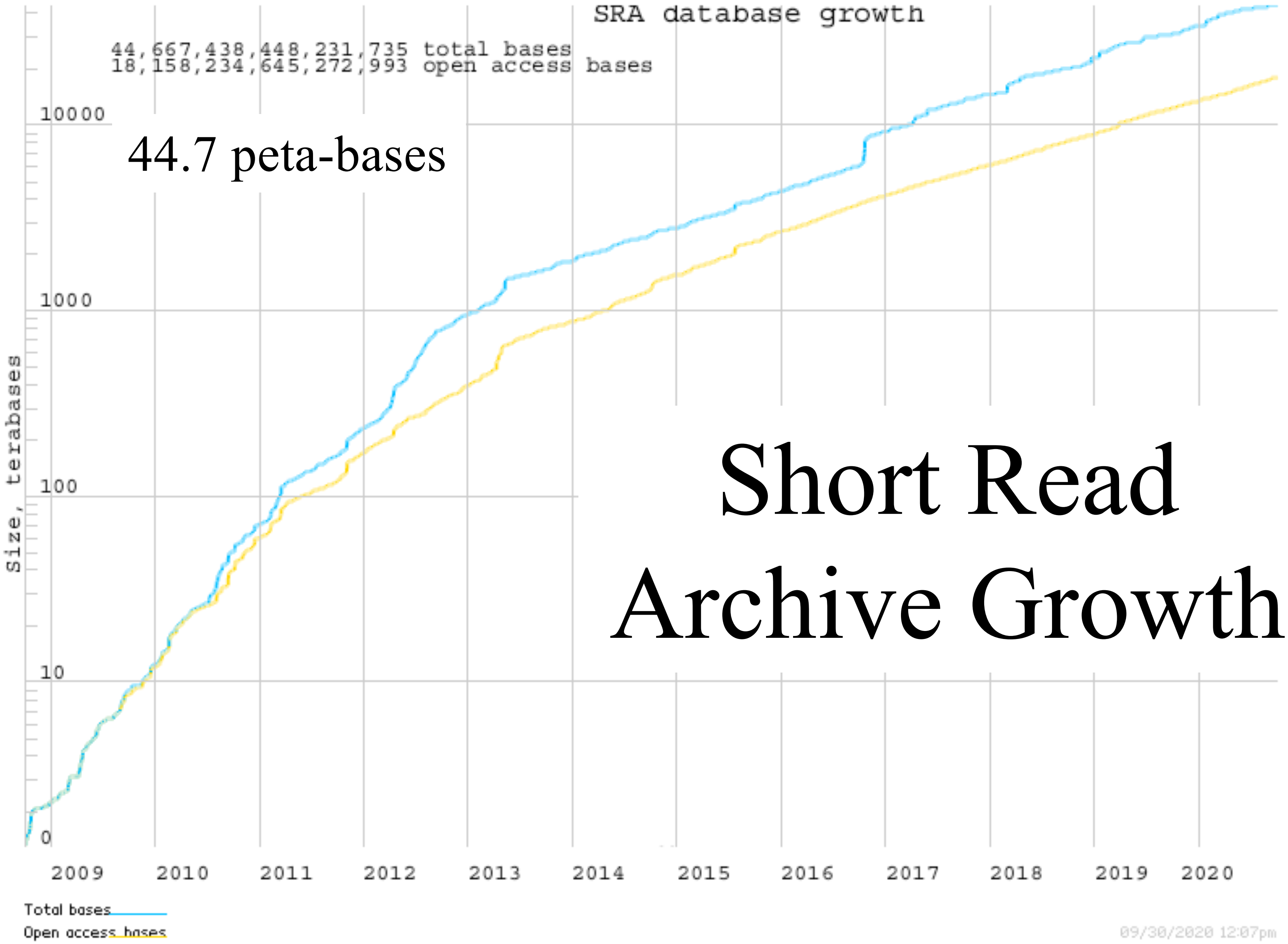
Growth of GenBank (Base Pairs)



Excludes “short-read archive”

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

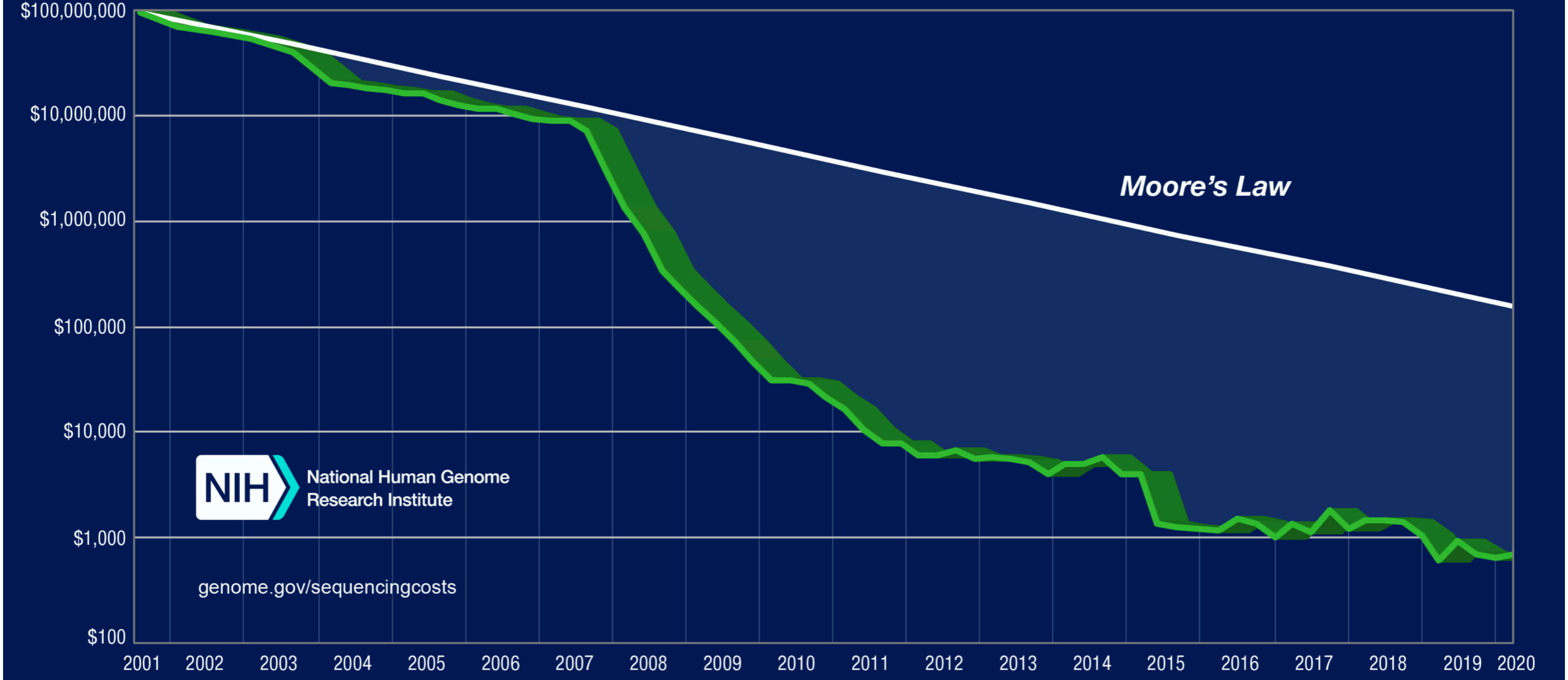
Short Read Archive Growth



44.7 peta-bases

http://www.ncbi.nlm.nih.gov/Traces/sra/

Cost per Human Genome



Modern DNA Sequencing

A box the size of a double oven

(but costs a bit more … ;-)

can generate

~3 x 10^{12} BP of DNA seq/day; i.e.,

1st 30 yrs of genbank

1000 x your genome

Big Data: Astronomical or Genomical?

Stephens, et al. (2015). PLoS Biol 13(7): e1002195. doi:10.1371/journal.pbio.1002195

Table 1. Four domains of Big Data in 2025.

In each of the four domains, the projected annual storage and computing needs are presented across the data lifecycle.

Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year
Analysis	In situ data reduction	Topic and sentiment mining	Limited requirements	Heterogeneous data and analysis
	Real-time processing	Metadata analysis		Variant calling, ~2 trillion CPU hours
	Massive volumes			All-pairs genome alignments, ~10,000 trillion CPU hours
Distribution	Dedicated lines from antennae to server (600 TB/s)	Small units of distribution	Major component of modern user's bandwidth (10 MB/s)	Many small (10 MB/s) and fewer massive (10 TB/s) data movements

PLOS | BIOLOGY

The Human Genome Project

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   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 ...
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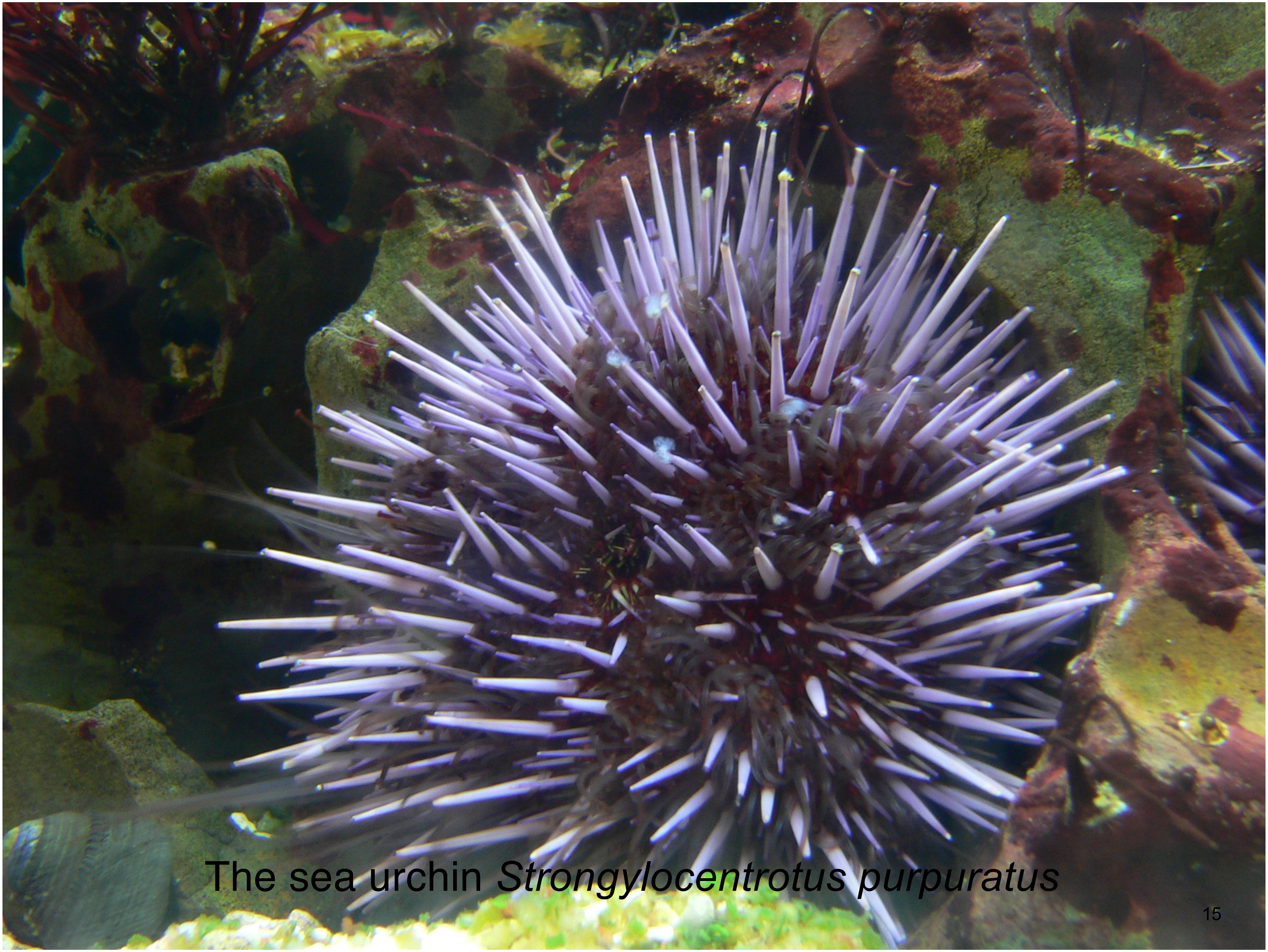
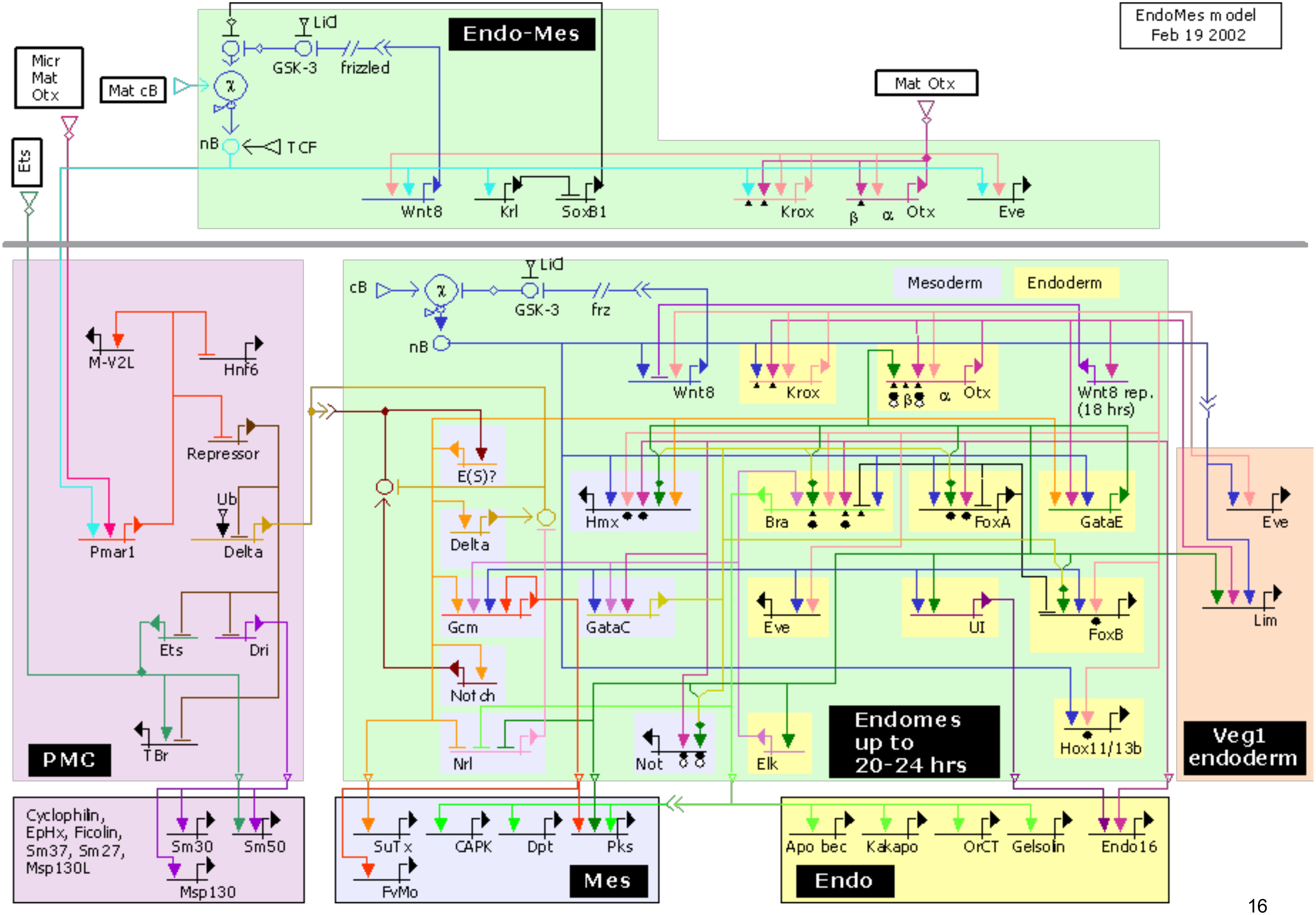


The sea urchin *Strongylocentrotus purpuratus*

EndoMes model
Feb 19 2002



Goals

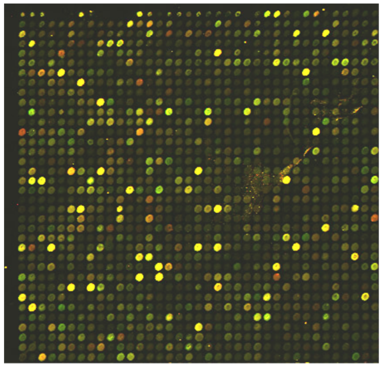
Basic biology

Drug discovery, validation & development

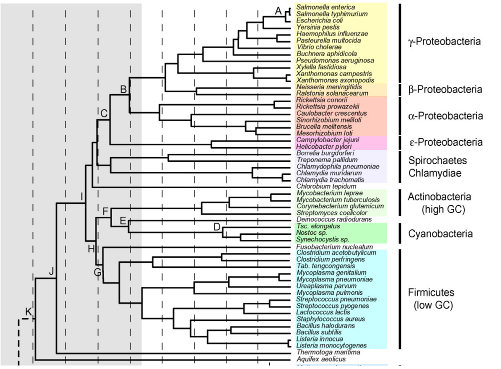
Disease diagnosis/prognosis/treatment

Individualized/precision medicine

…

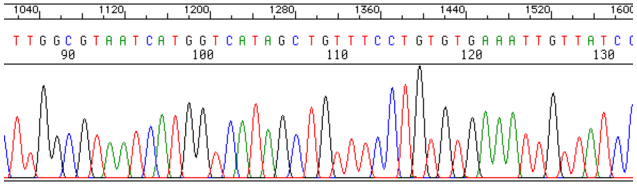


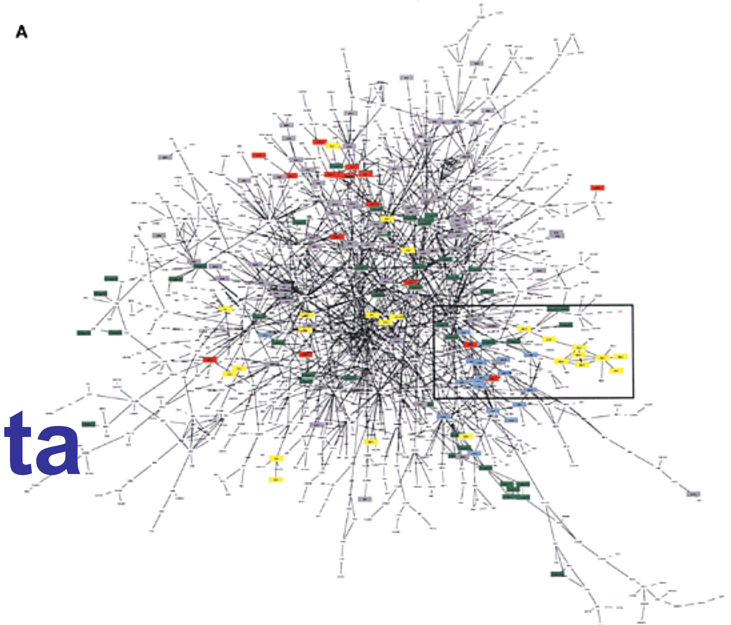
“High-Throughput BioTech”



Sensors

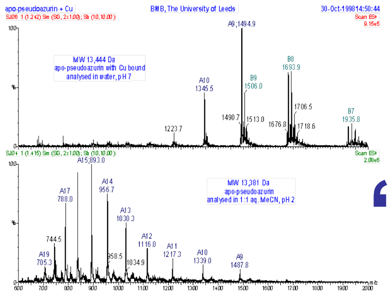
- DNA / RNA sequencing
- Gene expression
- Mass Spectrometry/Proteomics
- Protein/protein & DNA/protein interaction





Controls

- Cloning
- Gene knock out/knock in
- CRISPR



***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, development, immune response, …

Databases

- Integration of complex, 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, …

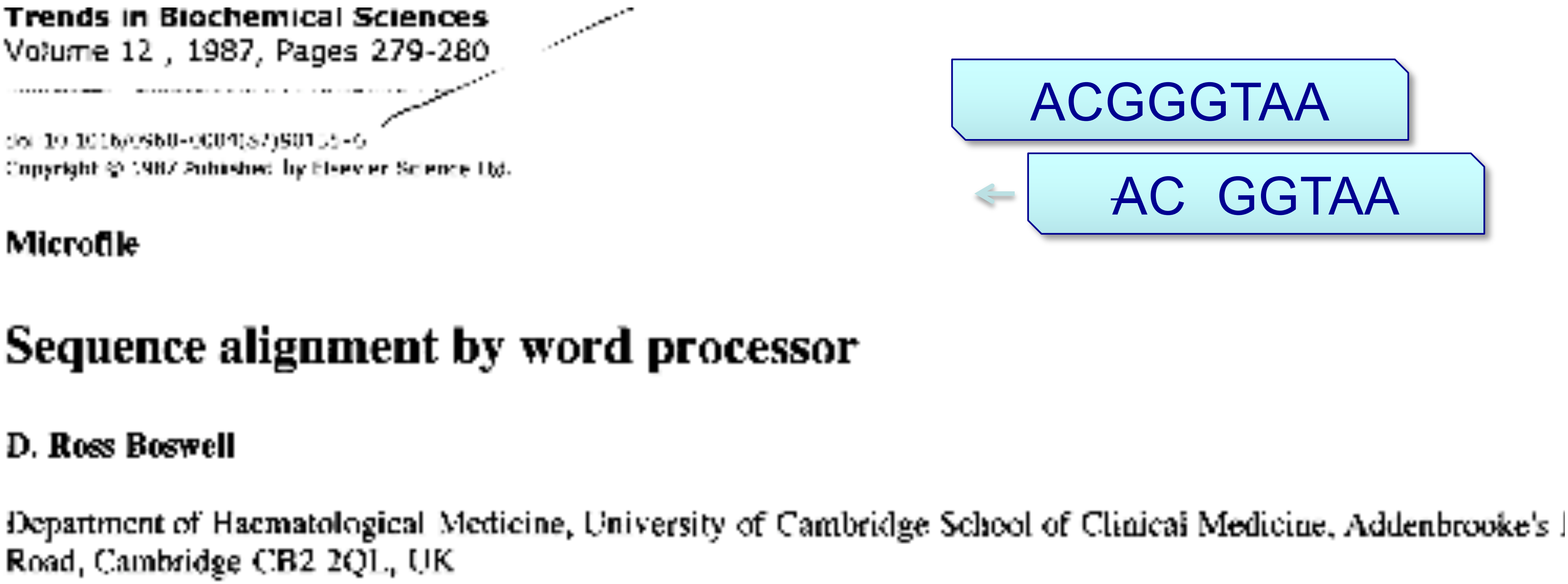
Machine learning

- 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

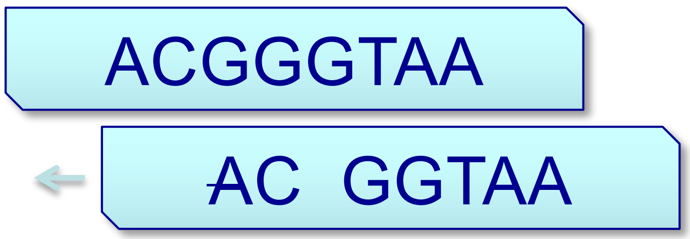
doi:10.1016/0968-0004(87)901[illegible]-6

Microfile

Sequence alignment by word processor

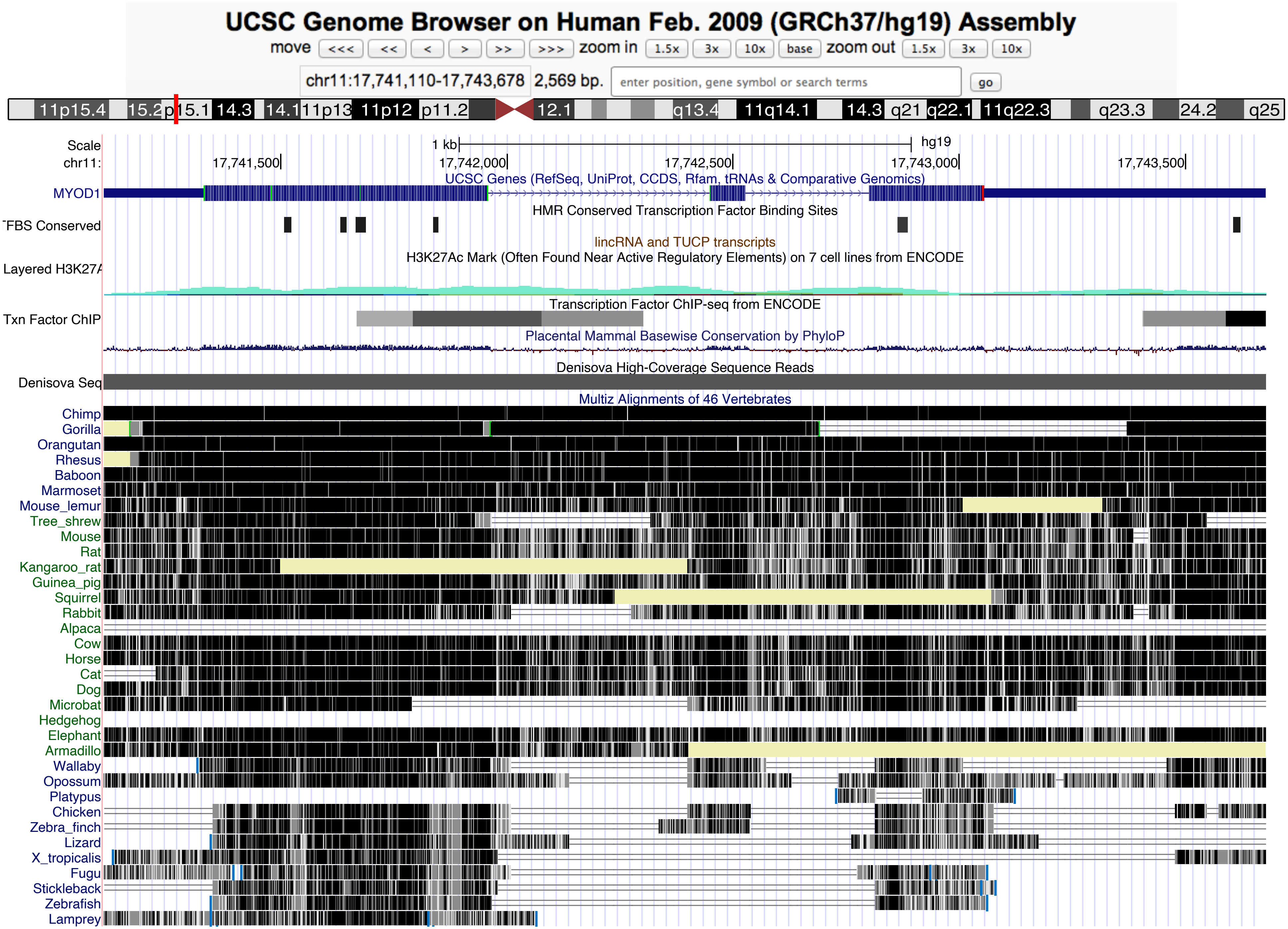
D. Ross Boswell

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



ACGGGTAA

AC GGTAA



UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly

chr11:17,741,110-17,743,678 2,569 bp.

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

Why Take This Course?

IT and Genomics are, and probably will remain, the 2 most explosively transformative technologies of your lifetimes

Even if you don’t choose to work at that interface, having some knowledge of it will be valuable

Hopefully, you will learn useful alg, ML, stats techniques and ideas for how to apply them in novel domains

A *VERY* Quick Intro To Molecular Biology

The Genome

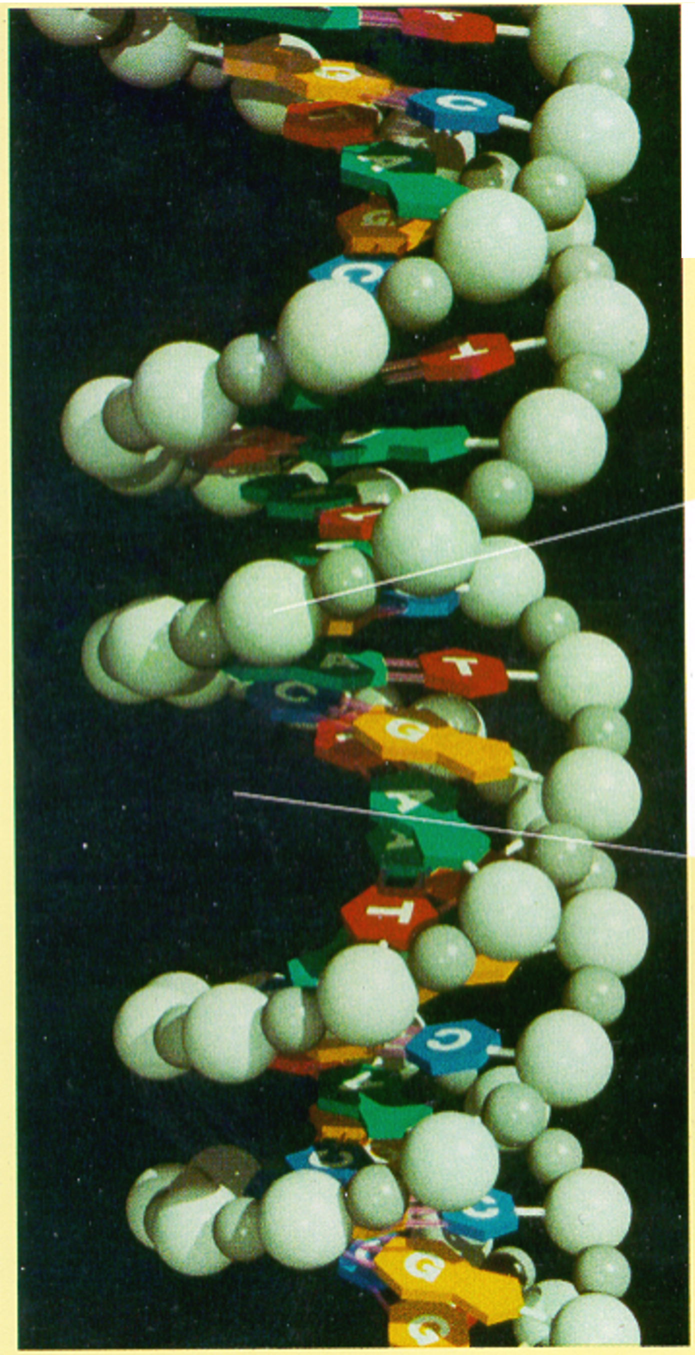
The hereditary info present in every cell

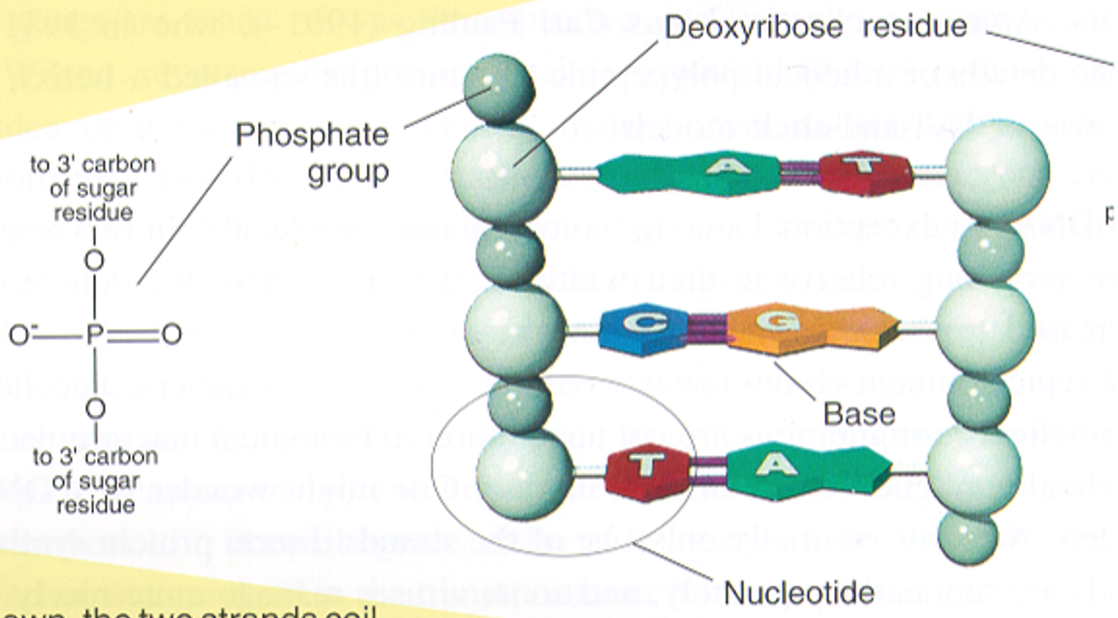
DNA molecule -- a long sequence of *nucleotides* (A, C, T, G)

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

DNA

Discovered 1869

Role as carrier of genetic information – 1940’s

4 “bases”:

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

The Double Helix - Watson & Crick (& Franklin) 1953

Complementarity

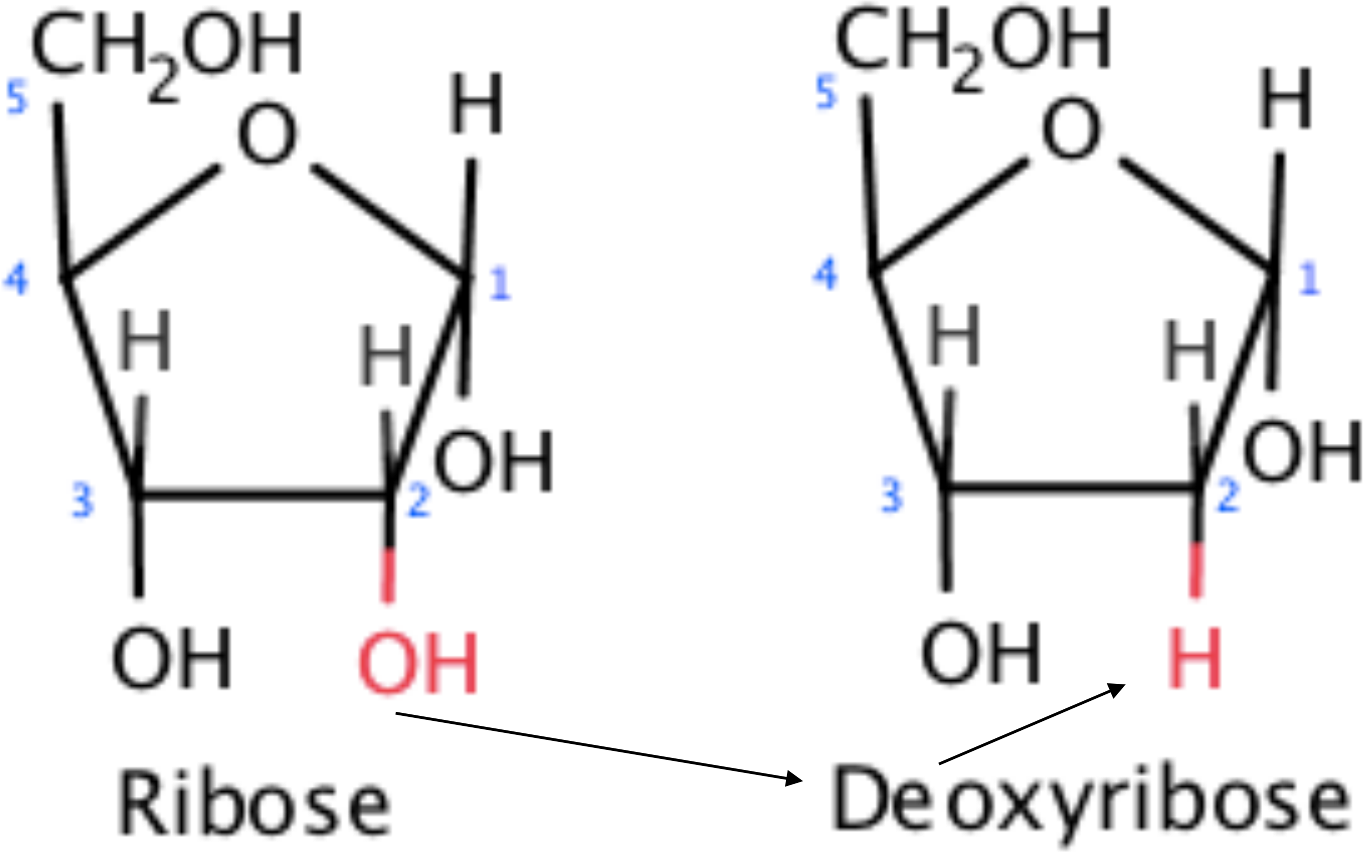
A ←→ T   C ←→ G

Visualization:

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

More on DNA/RNA

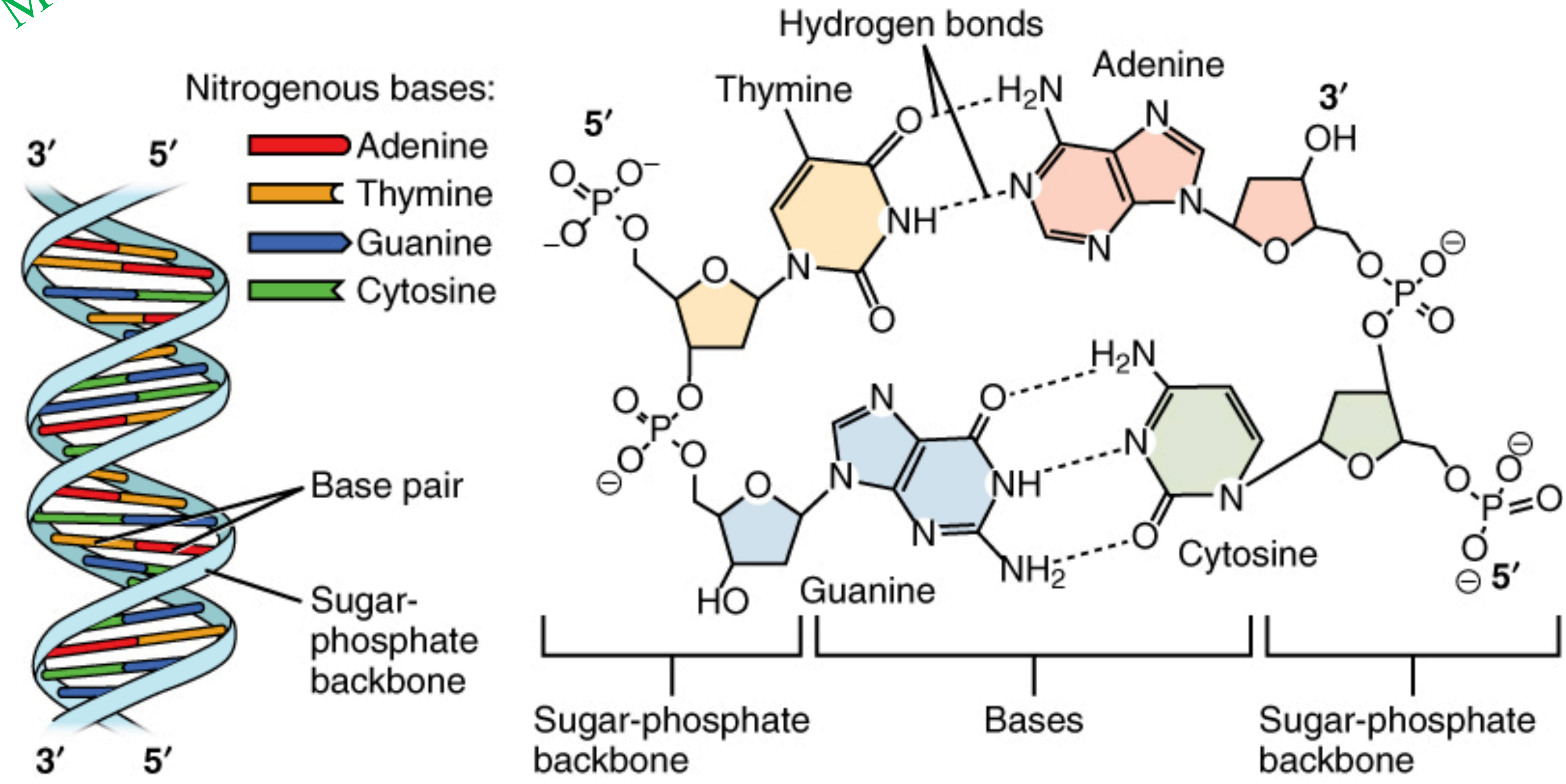
DNA, RNA, 3’, 5’, …



https://en.wikipedia.org/wiki/Ribose

More on DNA/RNA

Nucleotides



https://en.wikipedia.org/wiki/Nucleotide

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 has 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

Eukaryotes - ~~all~~ most cells have same number of chromosomes, e.g. fruit flies 8, humans & bats 46, rhinoceros 84, …

Mitosis/Meiosis

Most 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 specialized 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”

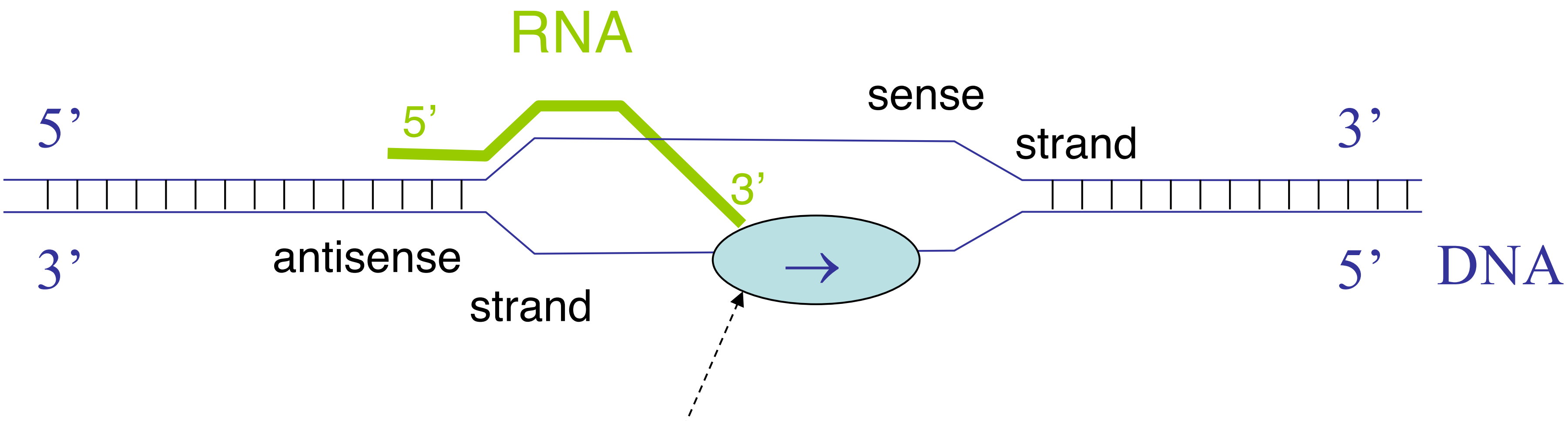
Genes encode proteins

DNA transcribed into messenger RNA

mRNA translated into proteins

Triplet code (codons)

Transcription: DNA → RNA



RNA

5’

3’

sense

strand

5’

3’

3’

antisense

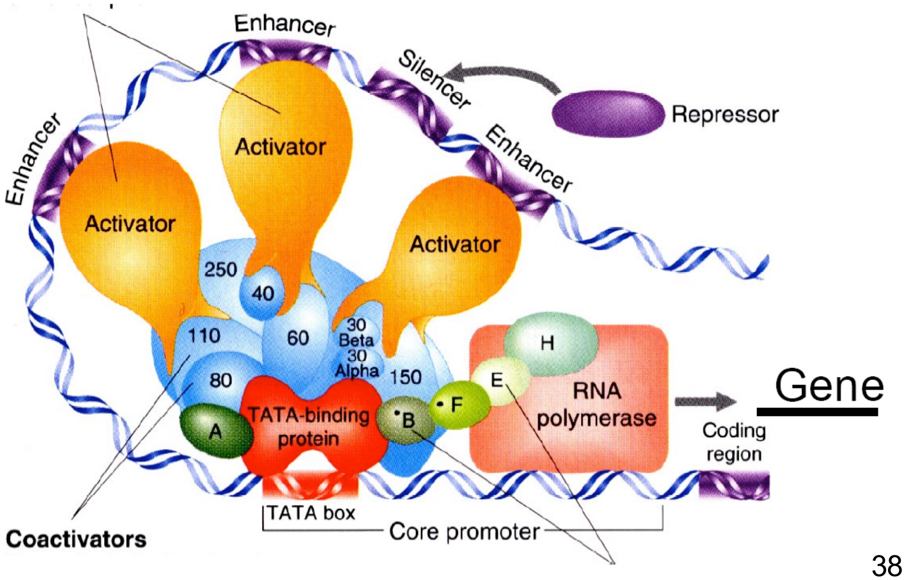
strand

→

3’

5’ DNA

RNA polymerase

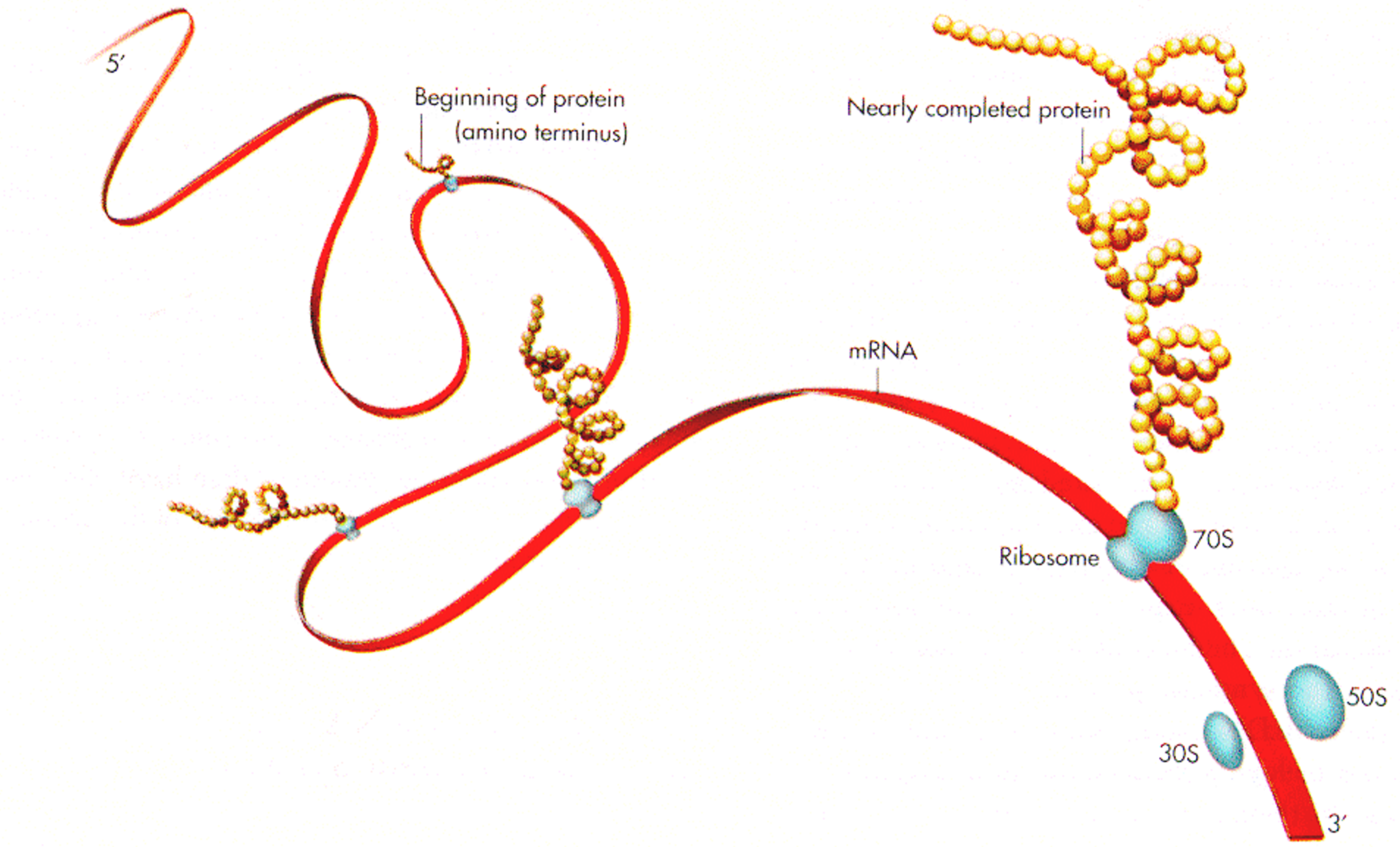


Codons & The Genetic Code

		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**	

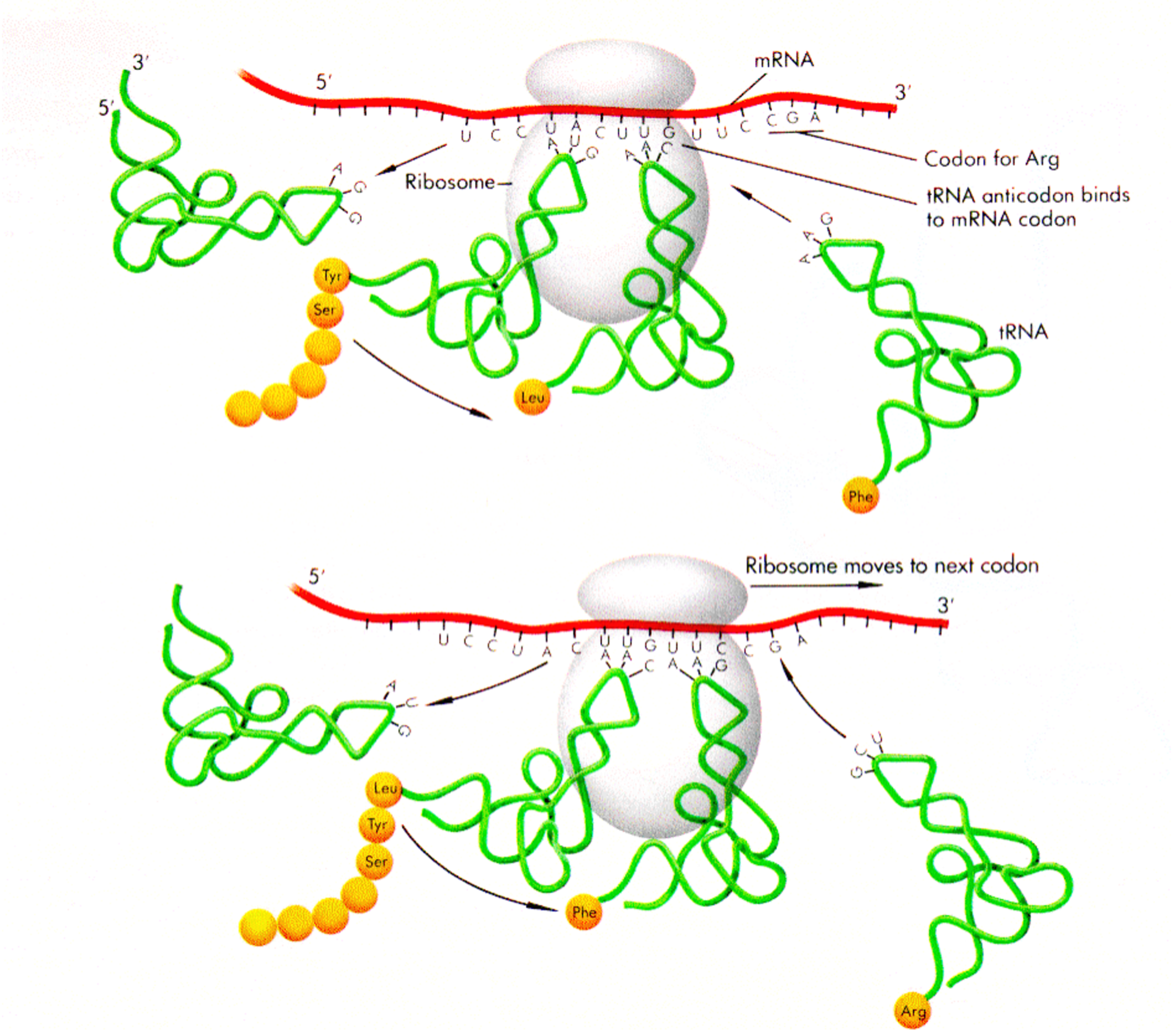
Ala	: Alanine
Arg	: Arginine
Asn	: Asparagine
Asp	: Aspartic acid
Cys	: Cysteine
Gln	: Glutamine
Glu	: Glutamic acid
Gly	: Glycine
His	: Histidine
Ile	: Isoleucine
Leu	: Leucine
Lys	: Lysine
Met	: Methionine
Phe	: Phenylalanine
Pro	: Proline
Ser	: Serine
Thr	: Threonine
Trp	: Tryptophane
Tyr	: Tyrosine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

Translation: mRNA → Protein



Watson, Gilman, Witkowski, & Zoller, 1992

Ribosomes



Watson, Gilman, Witkowski, & Zoller, 1992

Gene Structure

mRNA built 5’ to 3’

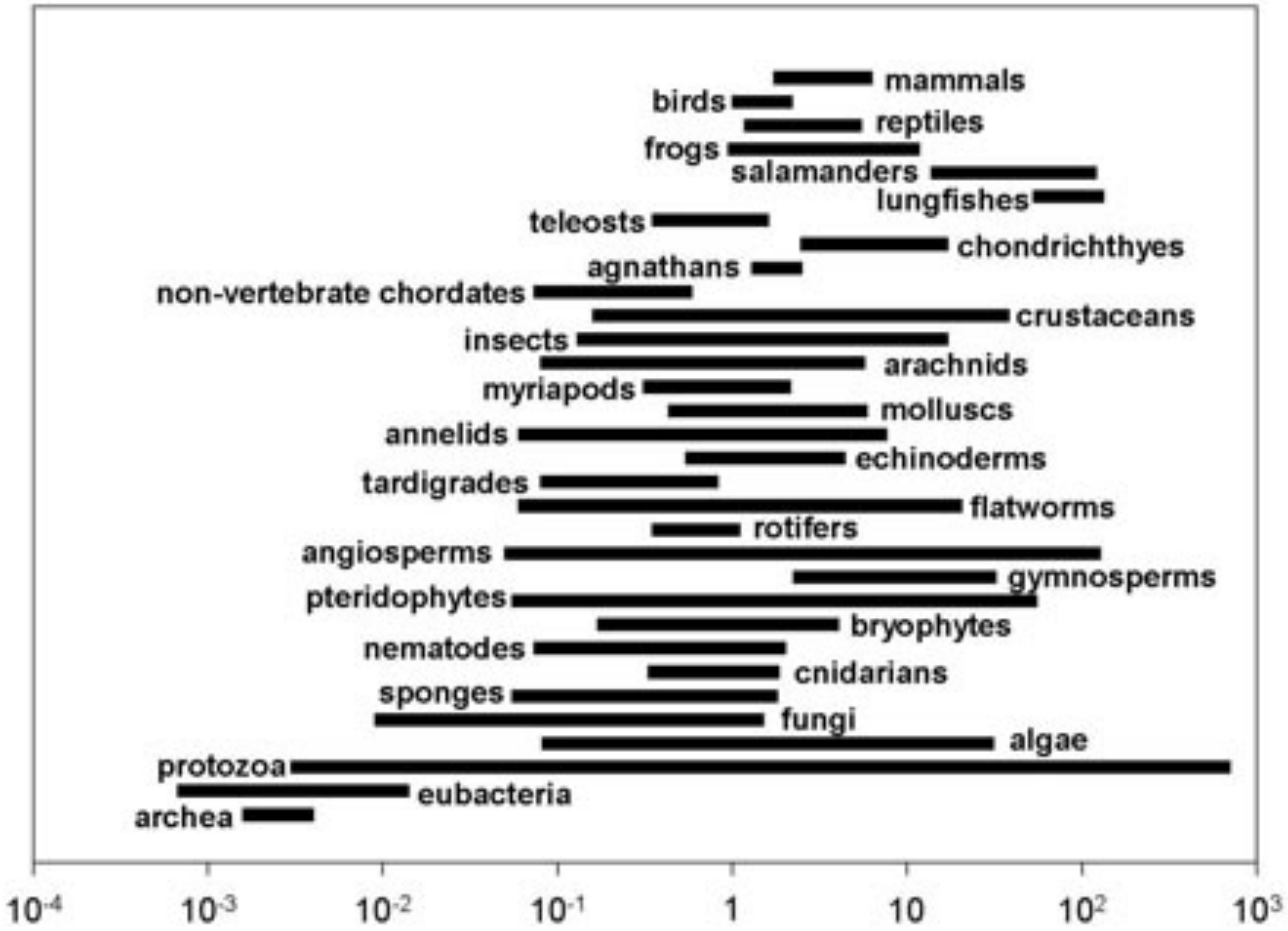
Promoter region and transcription factor binding sites (usually) precede 5’ end

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

	Bases	Genes
SARS-CoV-2	29,903	12
Mycoplasma genitalium	580,073	483
Pandora Virus	2,900,000	2,500
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	~21,000
Amoeba dubia	~ 200 x human	



DNA content (picograms)

http://www.genomesize.com/statistics.php

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

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

Subset of DNA being transcribed is >> 2% coding, giving many *non-coding RNAs* -- more than protein-coding genes, by some estimates

Complex, subtle “epigenetic” information

… and much more …

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

Homework #0, part 2

Meet your professor!

I’d like to schedule a 5-10 minute zoom with each of you over the next few days.

Just chat, no nefarious agenda, ungraded.

Sign up via Google Doc linked from class web page.

Homework #1 (summary)

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 (~~coming soon~~) for full details

Bio Concept Summary

cells

DNA

base pairing

genome

replication, transcription, translation