CSEP 527
Computational Biology

http://courses.cs.washington.edu/courses/csep527/16sp

Larry Ruzzo

Spring 2016

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

University of Washington

Computer Science & Engineering

Please do this ASAP

Homework 0

CSE P527, Sp '16: Computational Biology (Professional Masters Program)

CSE Home

Administrative
- Schedule & Reading
- HW0: Back

Course Em
- 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 announcer ...erest student/staff Q&A about homew
Enrolled students are as well, but probably should change t ...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, an

Prerequisite: None

Credits: 4

Learning Objectives: ...e complete genome sequences of humans and other organisms is one of the la
volume of data is ...allenge scientists for decades to come, and the nature and scope of the problem m
objective of t ...nts to understand the variety of computational problems and solutions that arise in this
concepts ... to understand the context for the computational problems presented in the rest of the cours
have ... courses can be applied to solve problems in modern molecular biology. An important compone
... 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.

...tra 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.

http://courses.cs.washington.edu/courses/csep527/16sp

Course Mechanics & Grading

Web

http://courses.cs.washington.edu/courses/csep527/16au

Reading

In class discussion

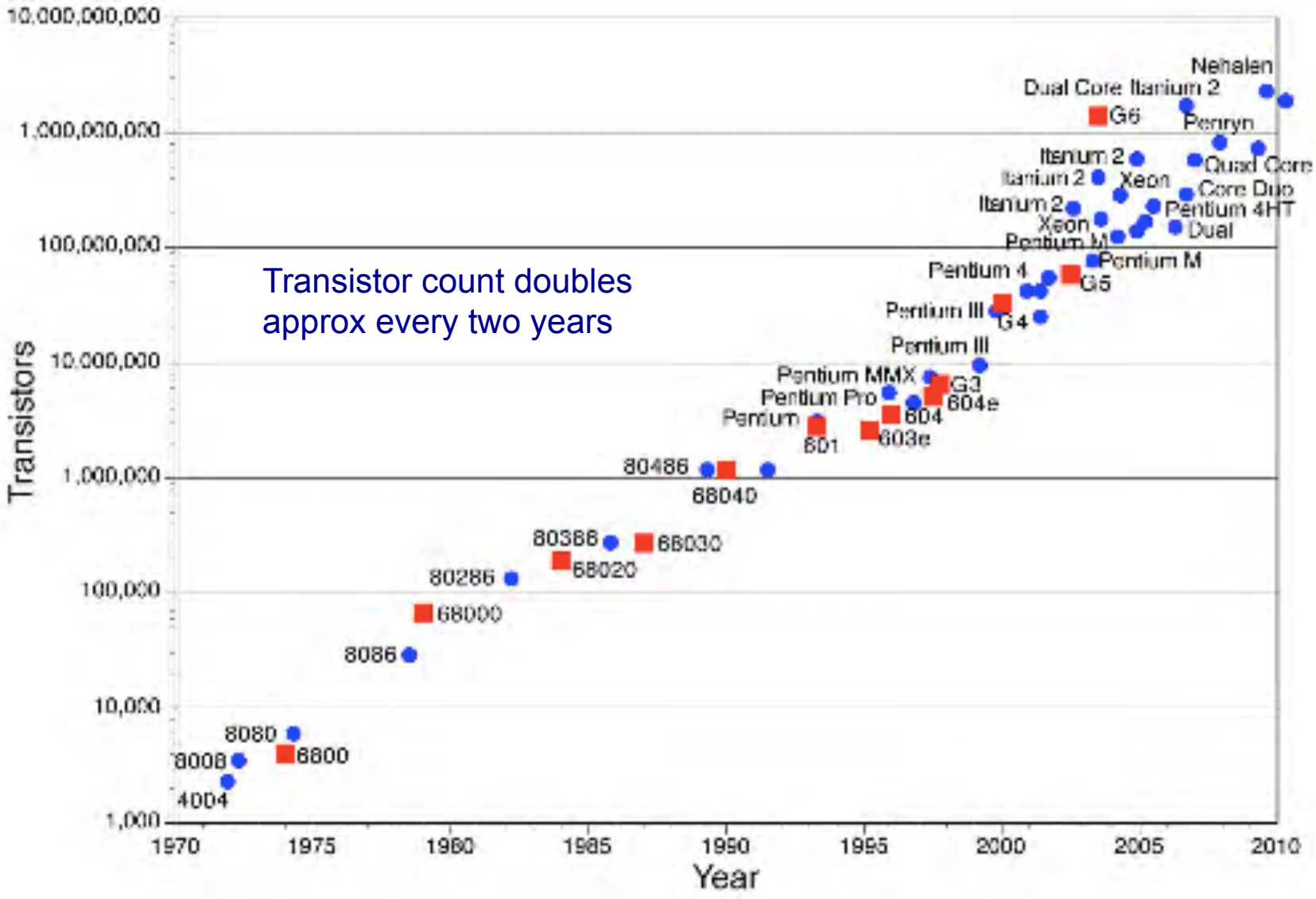
Homeworks

- 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
Transistors
Year
10,000,000,000
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100,000,000
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Nehalem
Dual Core Itanium 2
G6
Penryn
Itanium 2
Quad Core
Itanium 2
Xeon
Core Duo
Itanium 2
Pentium 4HT
Xeon
Dual
Pentium M
Pentium M
Pentium 4
G5
Pentium III
G4
Pentium III
Pentium MMX
G3
Pentium Pro
604e
Pentium
604
601
603e
80486
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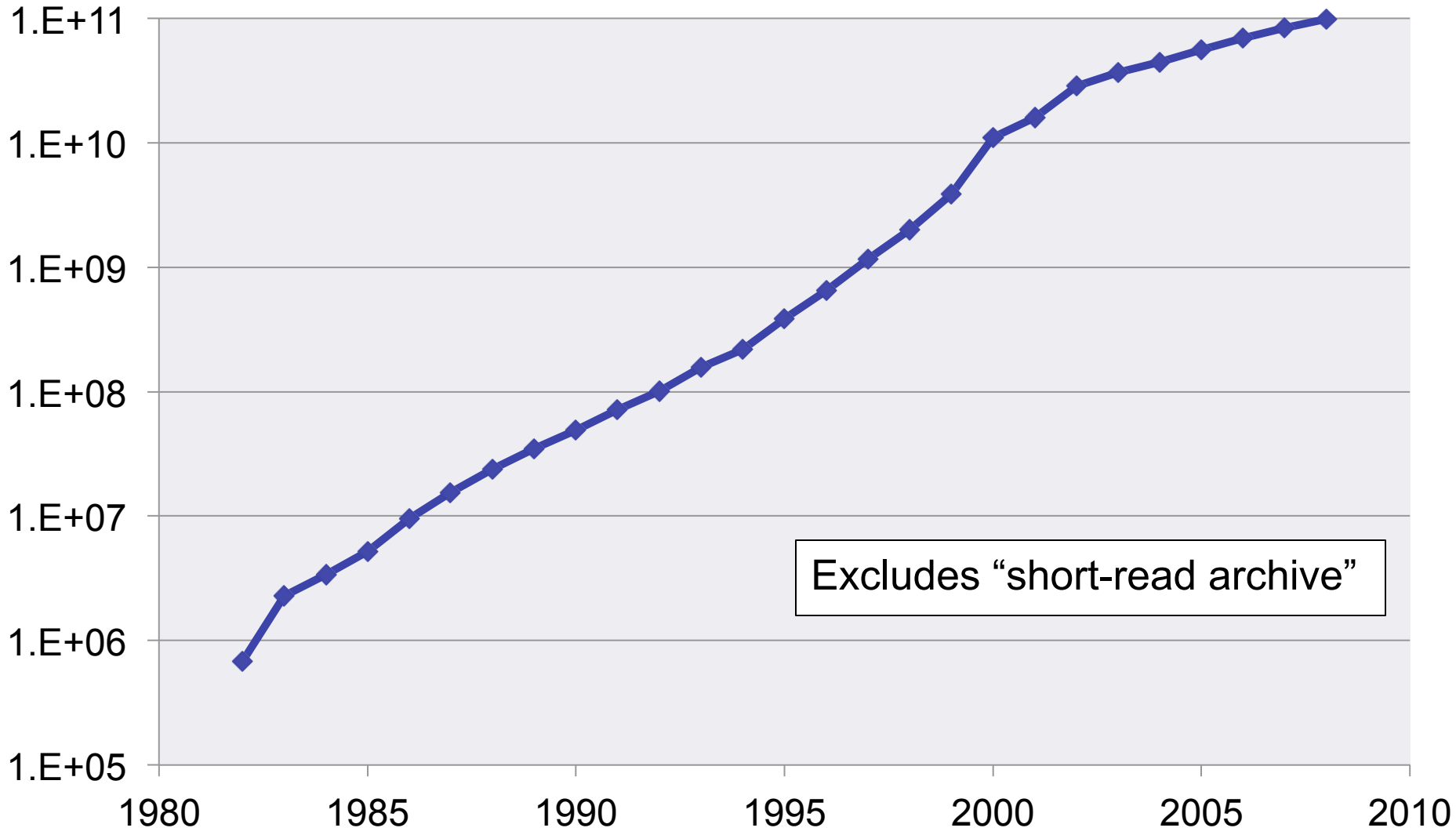
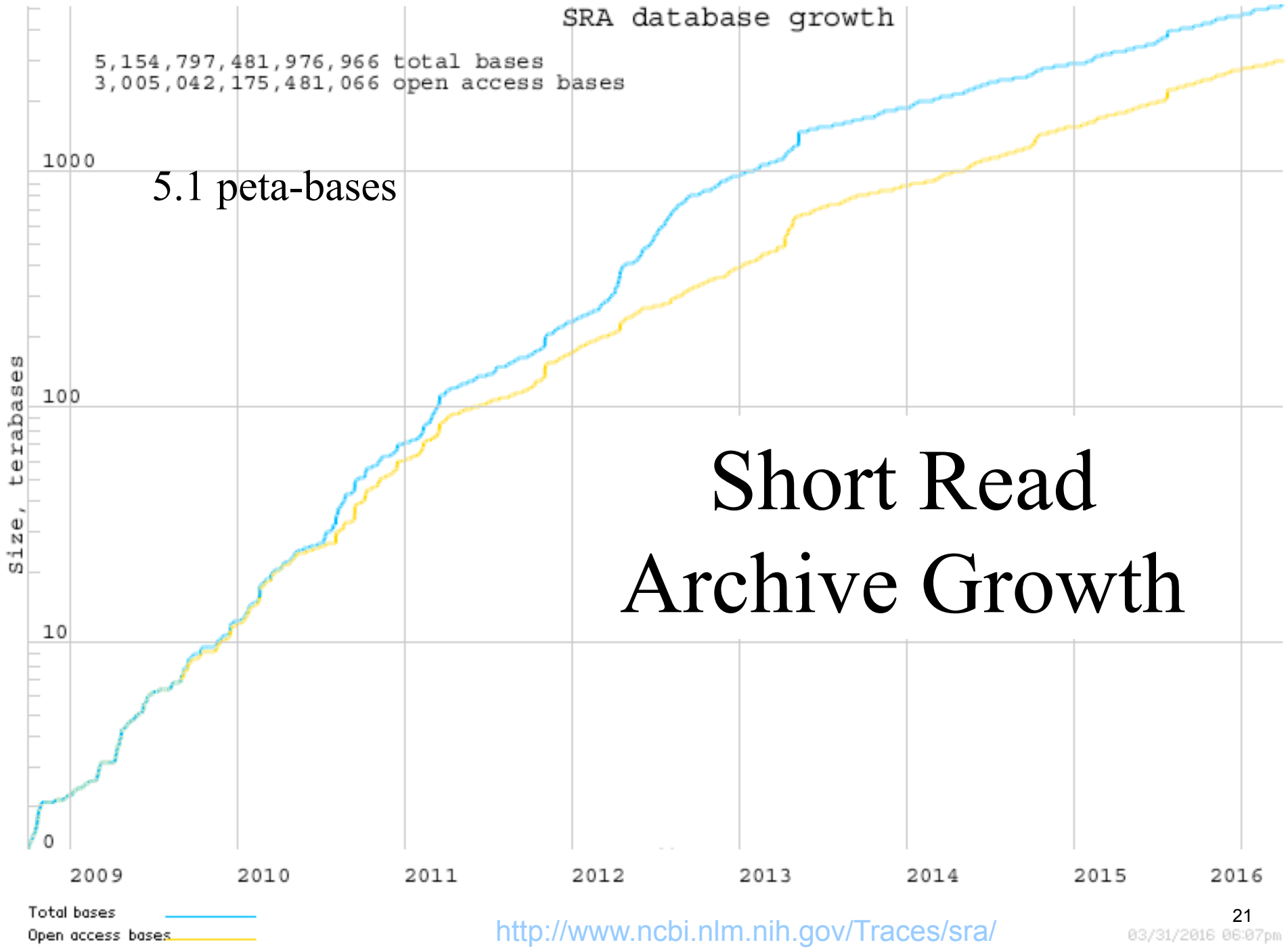
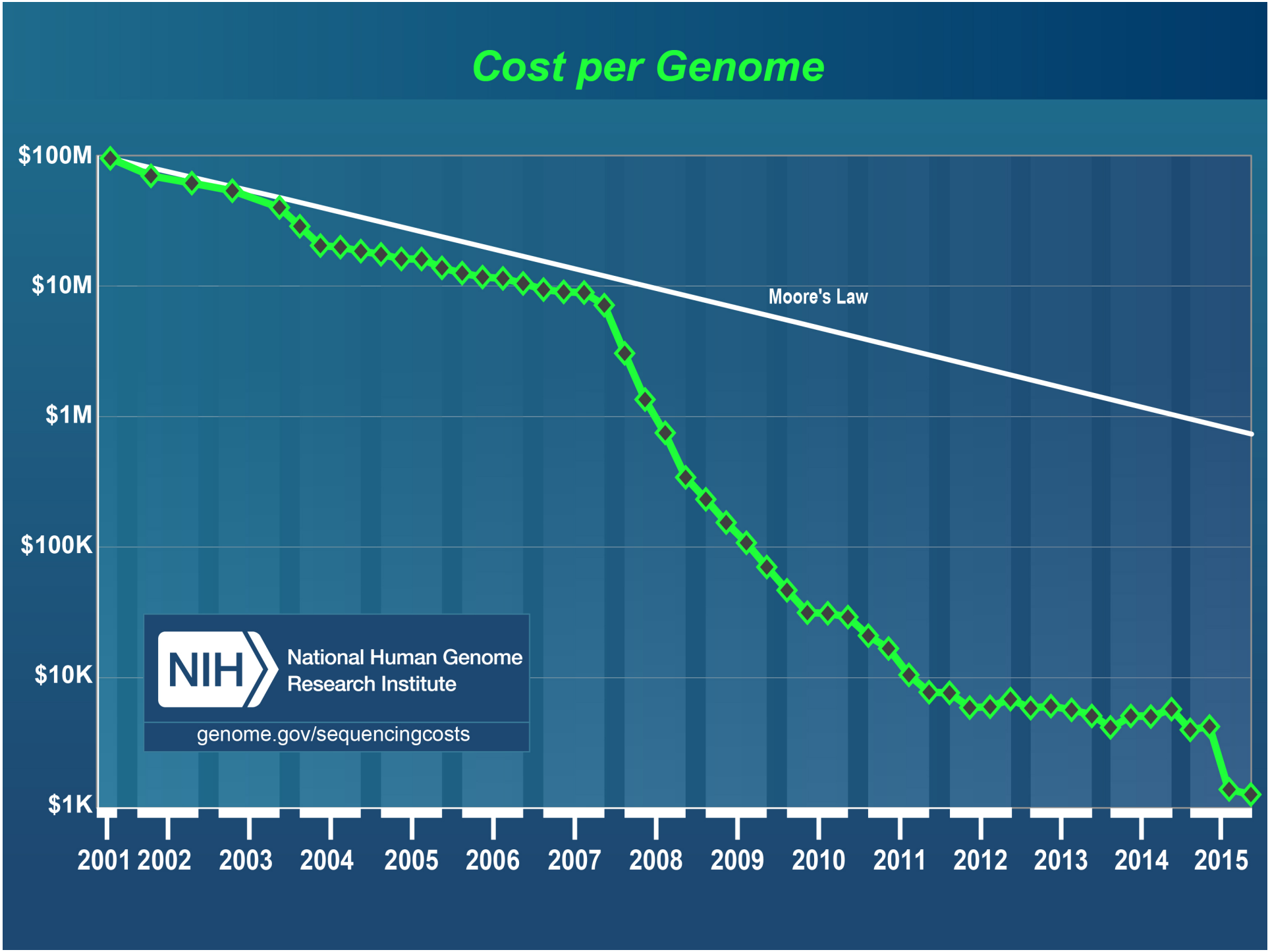
68030
68020
80286
68000
8086
8080
8008
6800
4004

Growth of GenBank (Base Pairs)



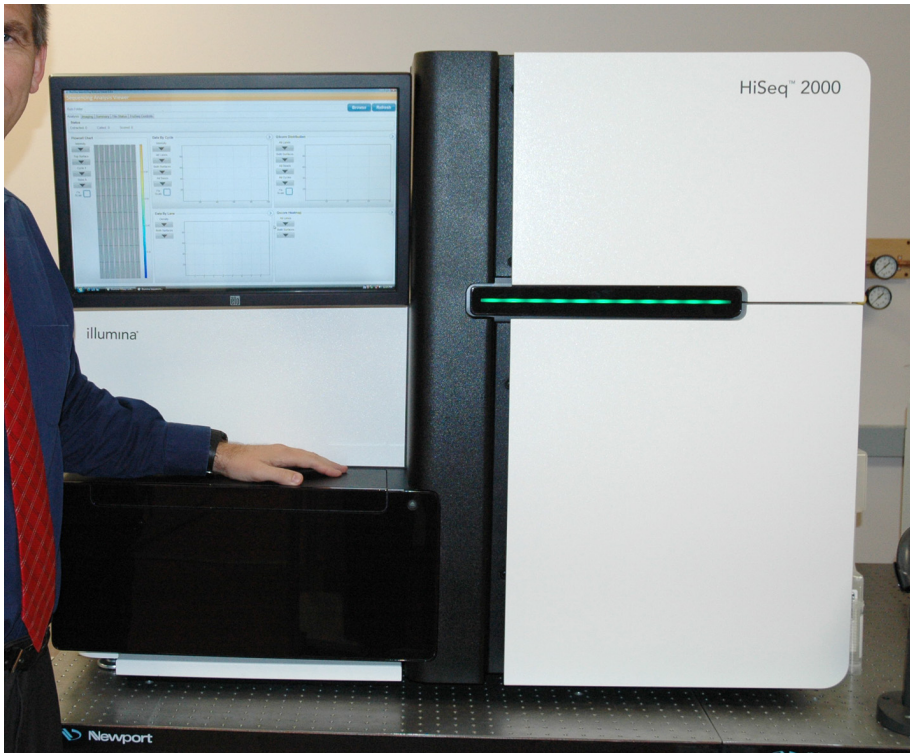
Source: http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html


SRA database growth
5,154,797,481,976,966 total bases
3,005,042,175,481,066 open access bases
5.1 peta-bases
Size, terabases
1000
100
10
0
2009
2010
2011
2012
2013
2014
2015
2016
Total bases
Open access bases
Short Read
Archive Growth
http://www.ncbi.nlm.nih.gov/Traces/sra/
03/31/2016 06:07pm


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

Modern DNA Sequencing

A table-top box the size of your oven
(but costs a bit more … ;-)
can generate
~100 billion BP of DNA seq/day; i.e.
= 2008 genbank,
= 30x your genome



PLOS | BIOLOGY

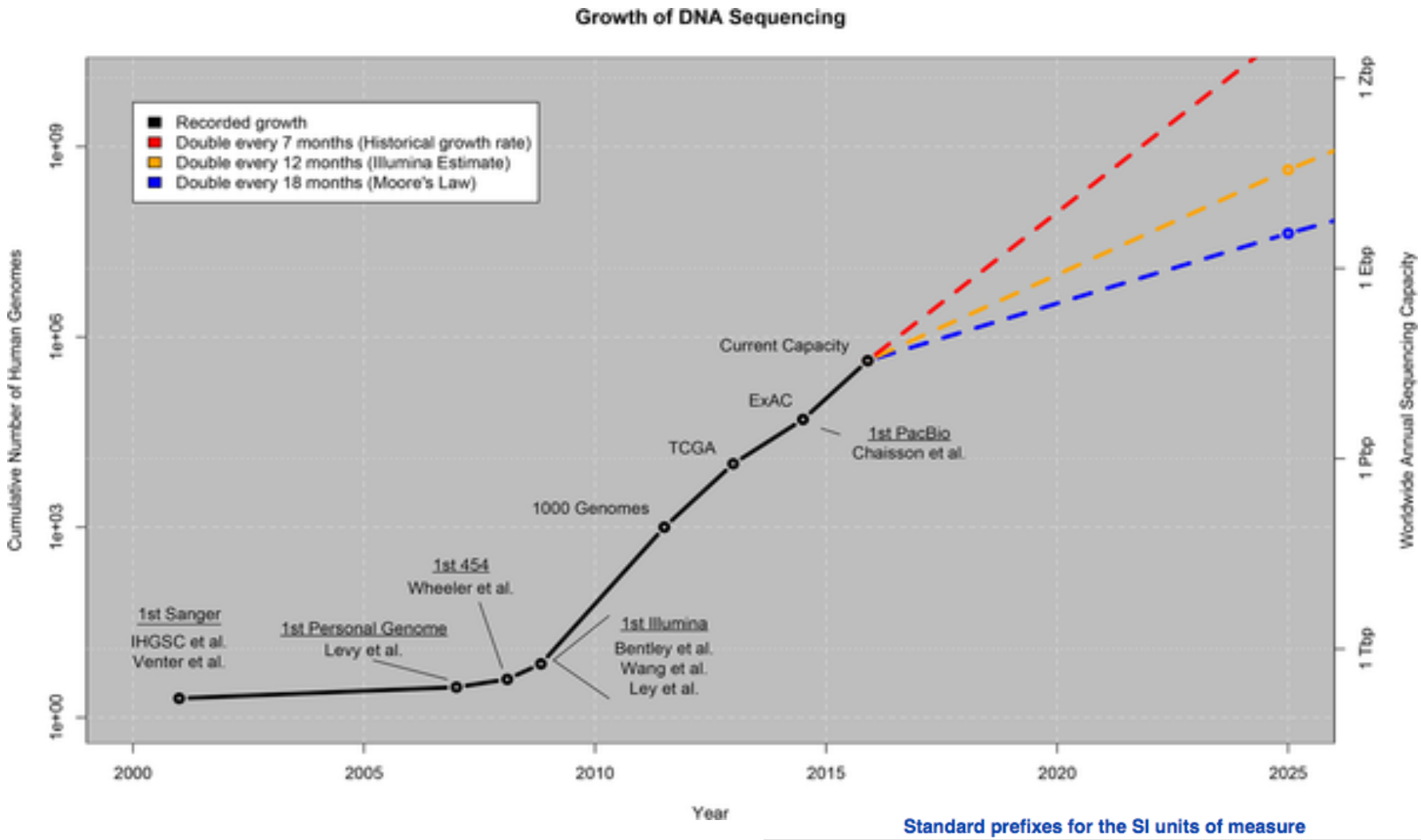
PERSPECTIVE

Big Data: Astronomical or Genomical?

Zachary D. Stephens[1], Skylar Y. Lee[1], Faraz Faghri[2], Roy H. Campbell[2], Chengxiang Zhai[3], Miles J. Efron[4], Ravishankar Iyer[1], Michael C. Schatz[5]*, Saurabh Sinha[3]*, Gene E. Robinson[6]*

PLoS Biol 13(7): e1002195. doi:10.1371/journal.pbio.1002195
http://127.0.0.1:8081/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002195

Fig 1. Growth of DNA sequencing.



Standard prefixes for the SI units of measure

Prefix name		deca	hecto	kilo	mega	giga	tera	peta	exa	zetta
Prefix symbol		da	h	k	M	G	T	P	E	Z
Factor	10^0	10^1	10^2	10^3	10^6	10^9	10^{12}	10^{15}	10^{18}	10^{21}

Stephens ZD, Lee SY, Faghri F, Campbell RH, Zhai C, et al. (2015) Big Data: Astronomical or Genomical?. PLoS Biol 13(7): e1002195. doi:10.1371/journal.pbio.1002195
http://127.0.0.1:8081/plosbiology/article?id=info: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.

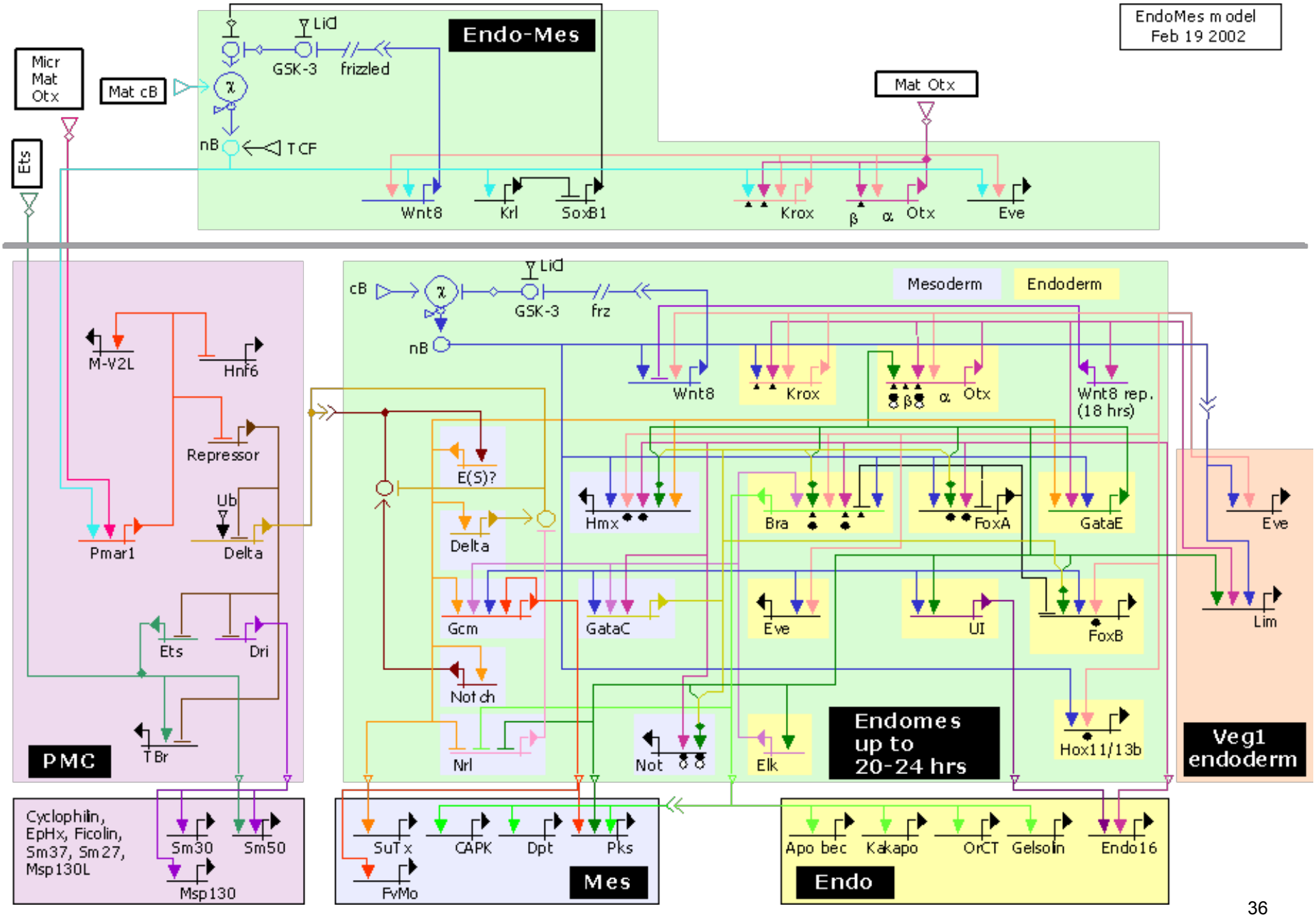
Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year
Analysis	In situ data reduction	Topic and sentiment mining	Limited requirements	Heterogeneous 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

Stephens ZD, Lee SY, Faghri F, Campbell RH, Zhai C, et al. (2015) Big Data: Astronomical or Genomical?. PLoS Biol 13(7): e1002195. doi: 10.1371/journal.pbio.1002195
http://127.0.0.1:8081/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002195

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
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Wnt8 rep.
(18 hrs)
M-V2L
Hnf6
Repressor
Ub
Pmar1
Delta
E(S)?
Delta
Hmx
Bra
FoxA
GataE
Eve
Lim
Gcm
GataC
Eve
UI
FoxB
Ets
Dri
Notch
TBr
Nrl
Not
Elk
Hox11/13b
PMC
Endomes
up to
20-24 hrs
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

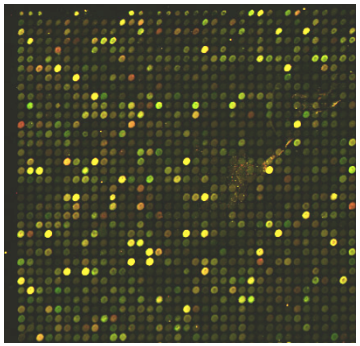
Basic biology

Disease diagnosis/prognosis/treatment

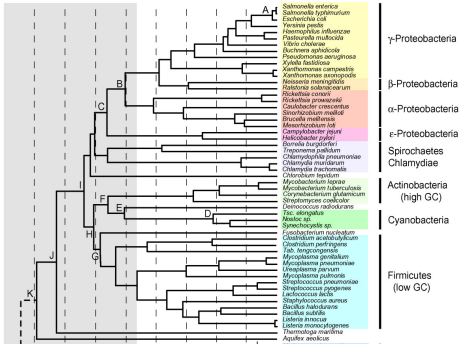
Drug discovery, validation & development

Individualized medicine

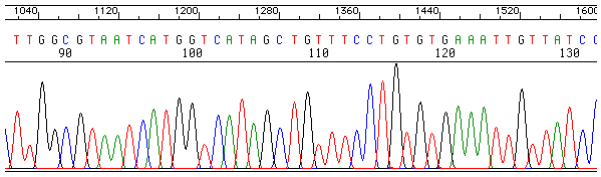
…

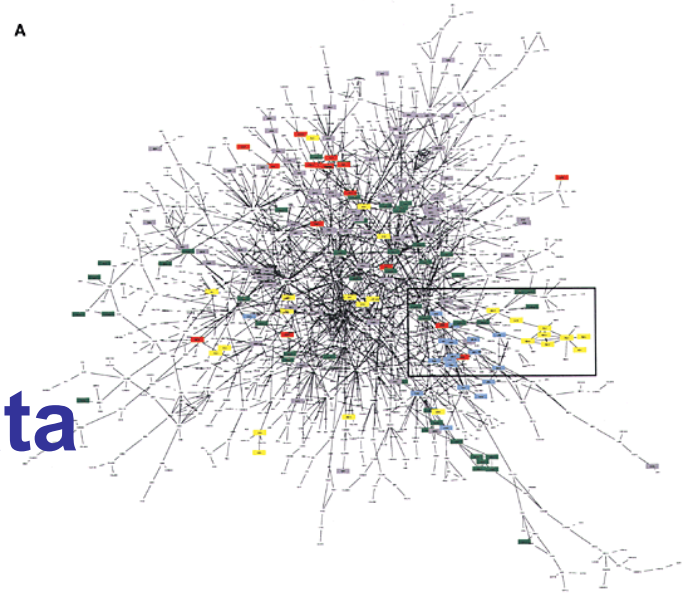


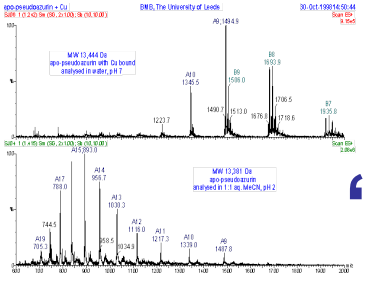
“High-Throughput BioTech”



- 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 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

ACGGGTAA

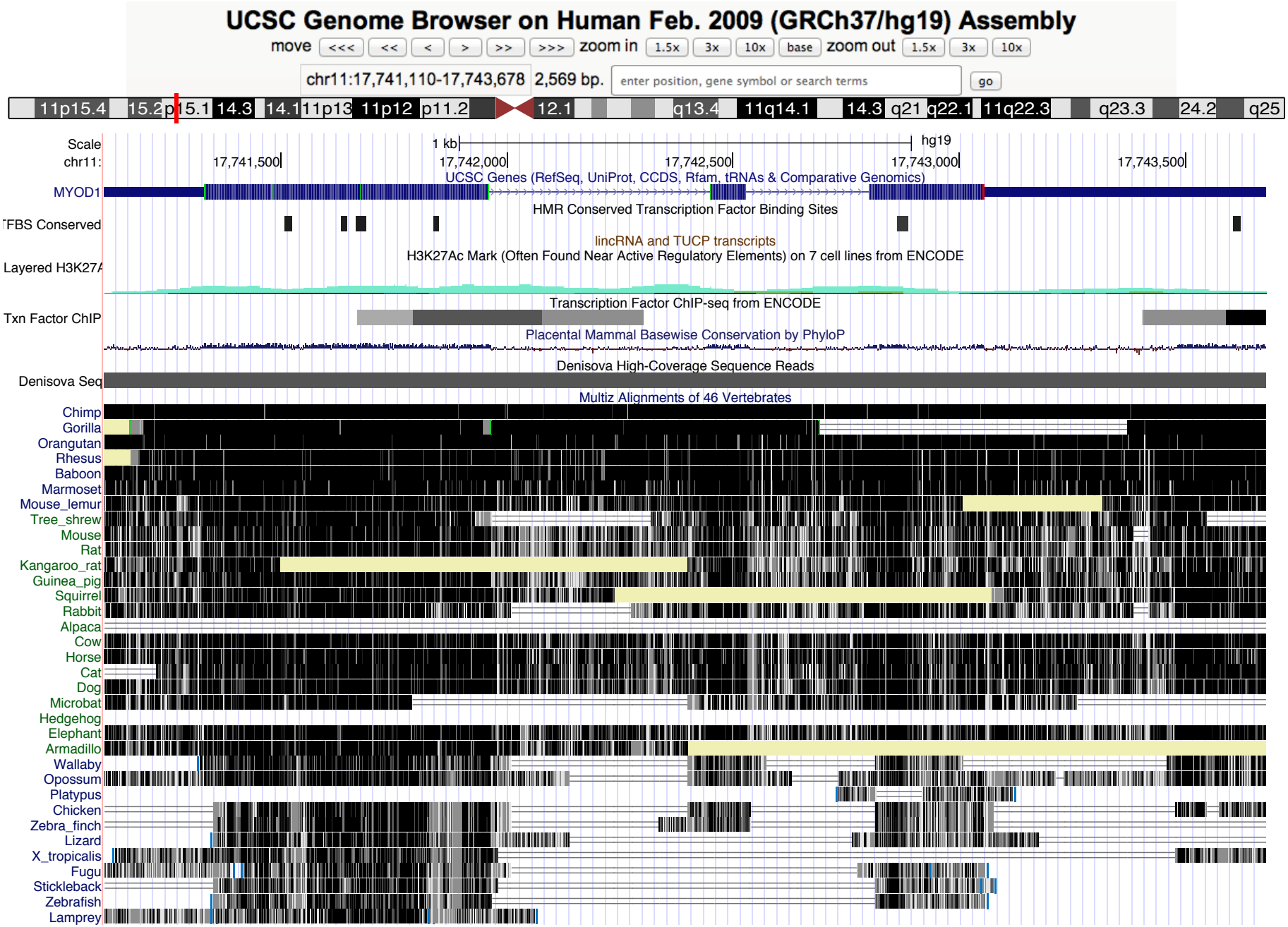
AC GGTAA

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


UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x
chr11:17,741,110-17,743,678 2,569 bp.
enter position, gene symbol or search terms
go
11p15.4 15.2 p15.1 14.3 14.1 11p13 11p12 p11.2 12.1 q13.4 11q14.1 14.3 q21 q22.1 11q22.3 q23.3 24.2 q25
Scale
chr11:
1 kb
hg19
17,741,500
17,742,000
17,742,500
17,743,000
17,743,500
UCSC Genes (RefSeq, UniProt, CCDS, Rfam, tRNAs & Comparative Genomics)
MYOD1
TFBS Conserved
HMR Conserved Transcription Factor Binding Sites
lincRNA and TUCP transcripts
Layered H3K27A
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
Txn Factor ChIP
Transcription Factor ChIP-seq from ENCODE
Placental Mammal Basewise Conservation by PhyloP
Denisova Seq
Denisova High-Coverage Sequence Reads
Multiz Alignments of 46 Vertebrates
Chimp
Gorilla
Orangutan
Rhesus
Baboon
Marmoset
Mouse_lemur
Tree_shrew
Mouse
Rat
Kangaroo_rat
Guinea_pig
Squirrel
Rabbit
Alpaca
Cow
Horse
Cat
Dog
Microbat
Hedgehog
Elephant
Armadillo
Wallaby
Opossum
Platypus
Chicken
Zebra_finch
Lizard
X_tropicalis
Fugu
Stickleback
Zebrafish
Lamprey

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

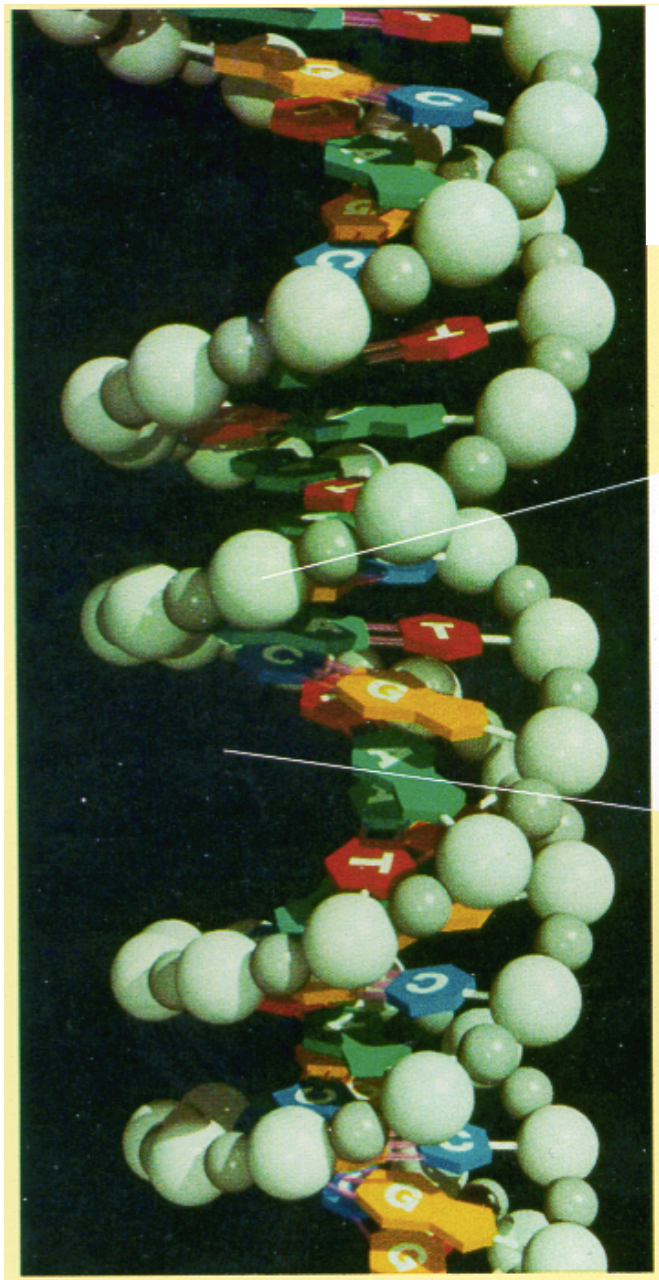
The hereditary info present in every cell

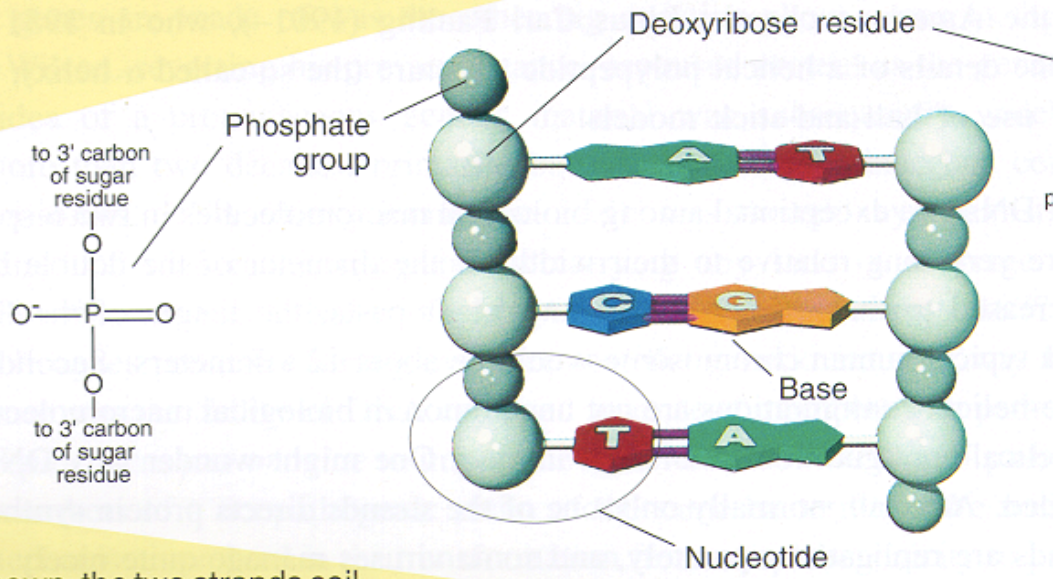
DNA molecule -- a long sequence of *nucleotides* (A, C, T, G)

Human genome -- about 3×10^9 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

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

Eukaryotes - 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”

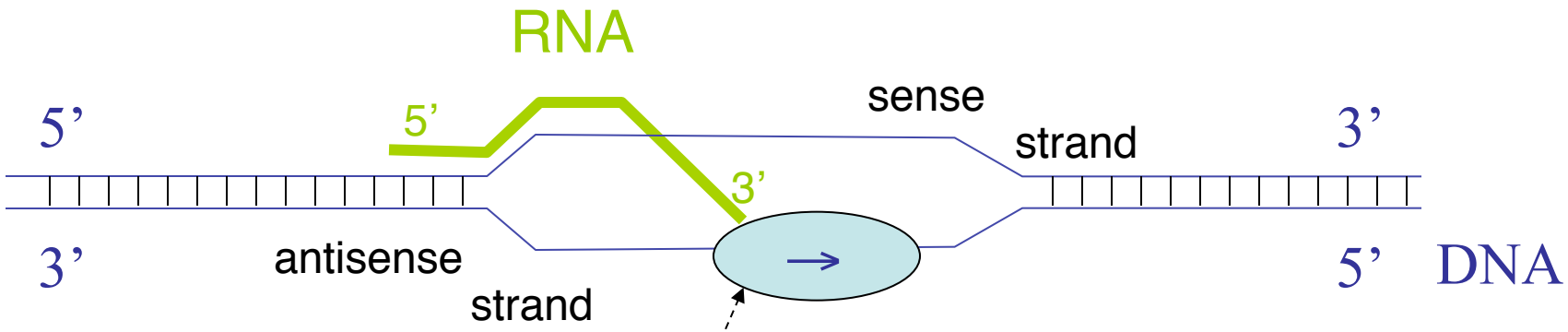
Genes encode proteins

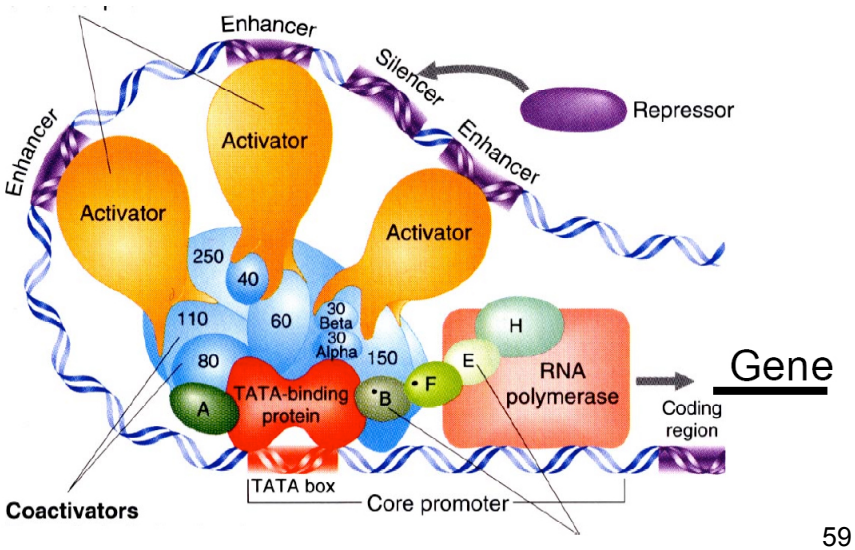
DNA transcribed into messenger RNA

mRNA translated into proteins

Triplet code (codons)

Transcription: DNA → RNA



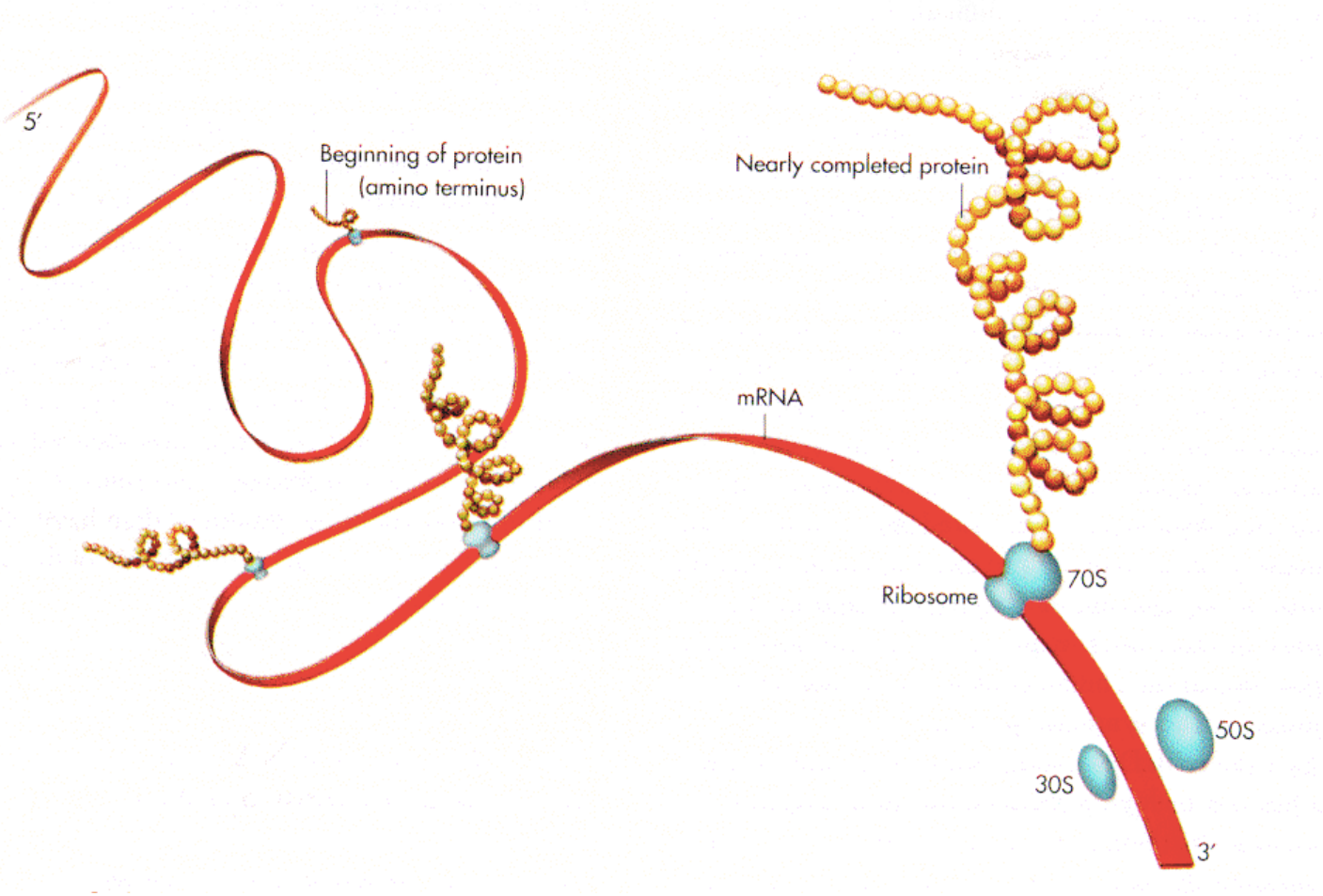


Codons & The Genetic Code

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

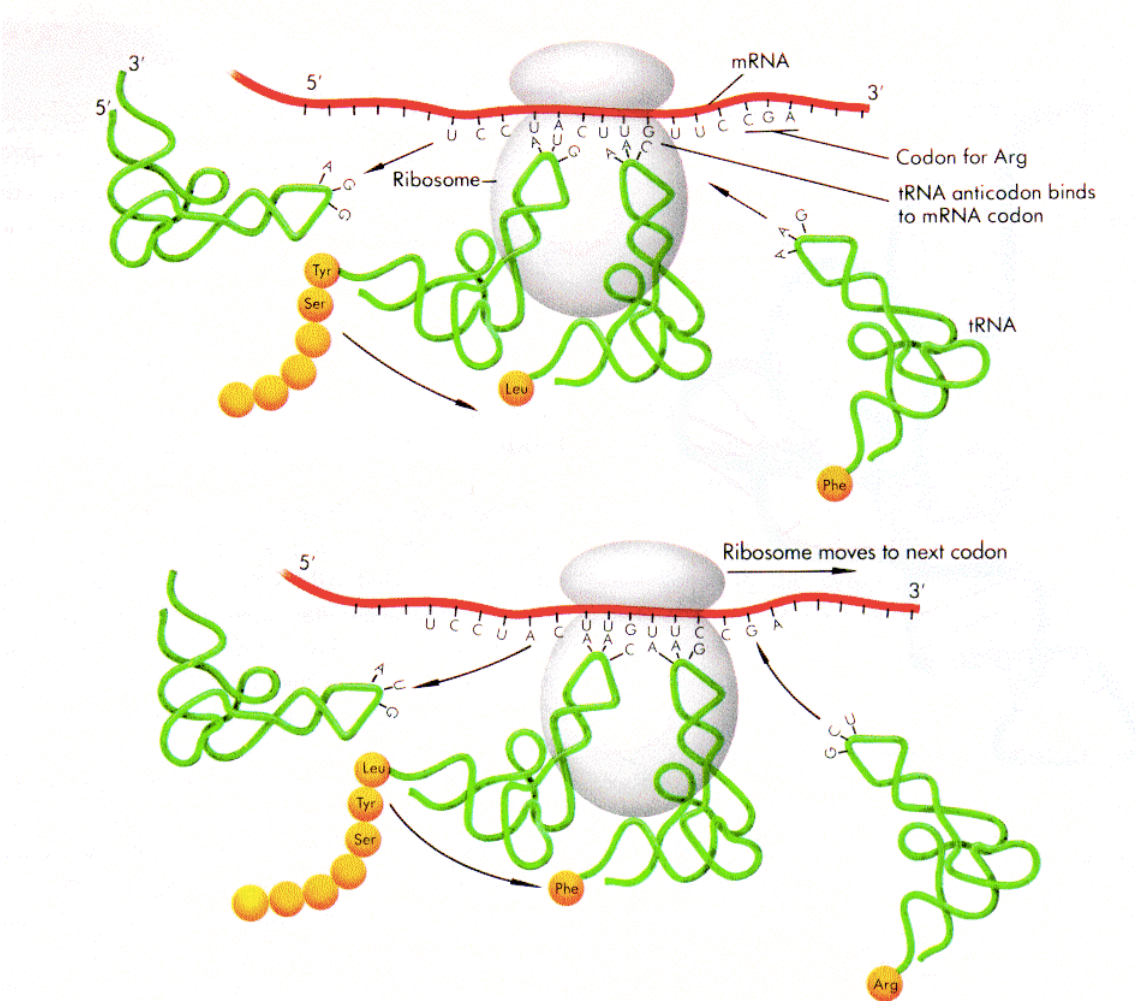
Ala : Alanine
Arg : Arginine
Asn : Asparagine
Asp : Aspartic acid
Cys : Cysteine
Gln : Glutamine
Glu : Glutamic acid
Gly : Glycine
His : Histidine
Ile : Isoleucine
Leu : Leucine
Lys : Lysine
Met : Methionine
Phe : Phenylalanine
Pro : Proline
Ser : Serine
Thr : Threonine
Trp : Tryptophane
Tyr : Tyrosine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

Translation: mRNA → Protein



Watson, Gilman, Witkowski, & Zoller, 1992

Ribosomes



Watson, Gilman, Witkowski, & Zoller, 1992

Gene Structure

mRNA built 5’ to 3’

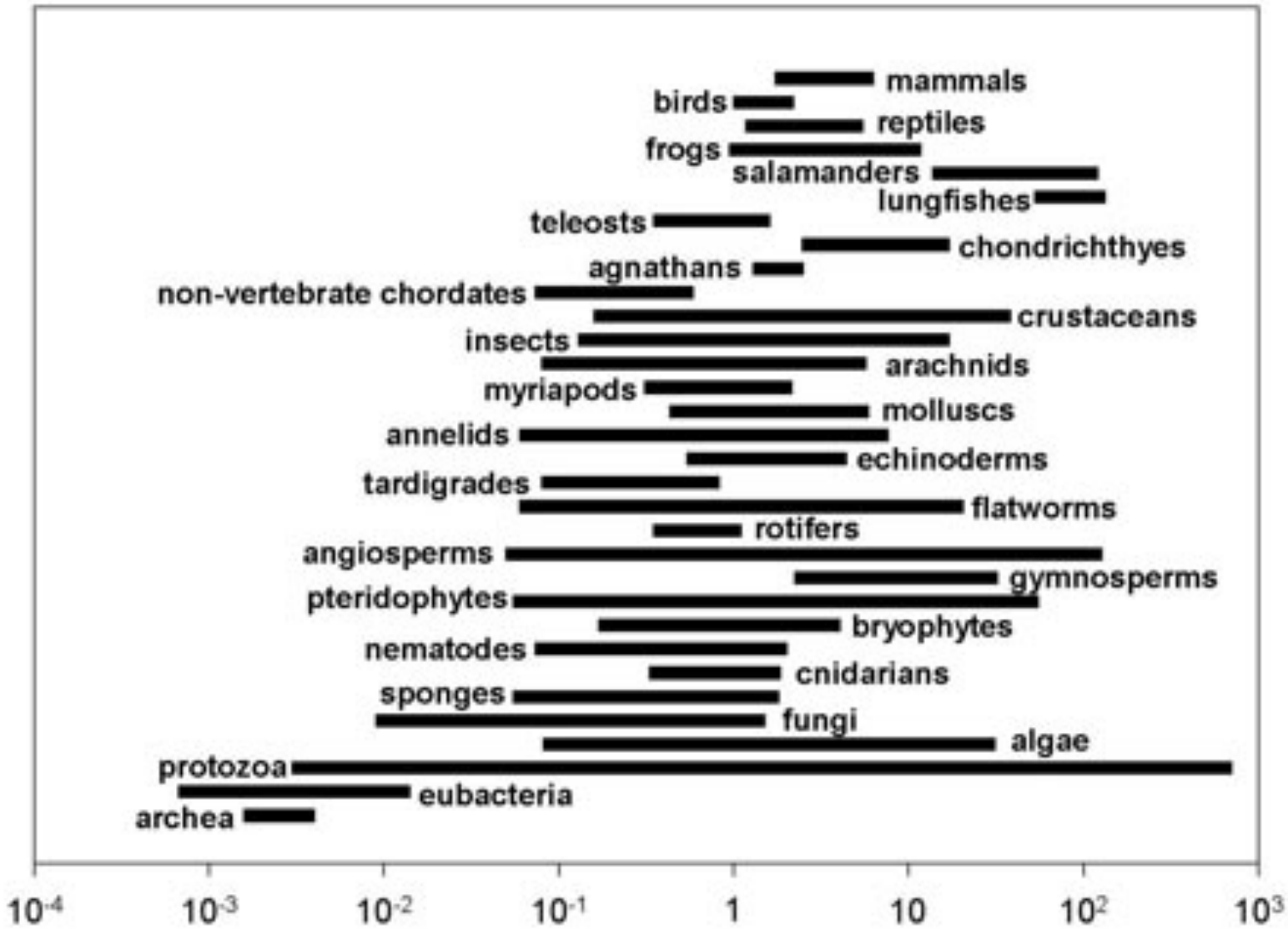
Promoter region and transcription factor binding sites (usually) precede 5’ end

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

	Base Pairs	Genes
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

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.

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 ~~(coming soon)~~ for more details

Bio Concept Summary

cells

DNA

base pairing

genome

replication, transcription, translation