

CMSC 858D: Algorithms Data Structures & Inference for High-Throughput Genomics

Fall 2019

Course Info

Instructor: Rob Patro (rob@cs.umd.edu)

Office: 3220 IRB

Office Hours: By appointment (though I'm often in my office)

Website: <https://rob-p.github.io/CMSC858D/>

ADS: <https://www.counseling.umd.edu/ads/>

Academic Integrity: <https://academiccatalog.umd.edu/graduate/policies/academic-record/#text>

Piazza Page: <https://piazza.com/umd/fall2019/cmssc858d>

If you have a class-related e-mail: Please prefix the subject with [CMSC858D], so that My filter will pick it up and it won't be accidentally routed to SPAM.

Coursework & Grading

Coursework and grading: The coursework will consist of 2-3 homework projects, a final project, and a final exam (on the University-scheduled date of Dec 17.). Students will have an opportunity to select their final project in mid Oct.; there will be a few projects to choose from, and students will also be allowed to propose their own projects. The projects are to be done either alone, or in teams of 2. For the final project, the deliverables will consist of runnable code (including a link to a version-controlled repository containing the source), and a short (4-5 page) research-style paper describing the work you've done. The breakdown of weights for these different assignments will be as follows:

- Homeworks — 20%
- Final Project — 50%
- Final Exam — 30%

Academic Integrity

maintain it!

Academic integrity: [From the University's Graduate Catalog Statement on Academic Integrity](#) :

On every examination, paper or other academic exercise not specifically exempted by the instructor, the student will write by hand and sign the following pledge: I pledge on my honor that I have not given or received any unauthorized assistance on this examination.

Failure to sign the pledge is not an honors offense, but neither is it a defense in case of violation of this Code. Students who do not sign the pledge will be given the opportunity to do so. Refusal to sign must be explained to the instructor. Signing or non-signing of the pledge will not be considered in grading or judicial procedures. Material submitted electronically should contain the pledge; submission implies signing the pledge.

On examinations, no assistance is authorized unless given by or expressly allowed by the instructor. On other assignments, the pledge means that the assignment has been done without academic dishonesty, as defined in the Code of Academic Integrity, available online.

The pledge is a reminder that at the University of Maryland students carry primary responsibility for academic integrity because the meaningfulness of their degrees depends on it. Faculty are urged to emphasize the importance of academic honesty and of the pledge as its symbol.

Academic integrity is a very serious issue. Any assignment, project or exam you complete in this course is expected to be your own work. If you are allowed to discuss the details of or work together on an assignment, this will be made explicit. Otherwise, you are expected to complete the work yourself. *Plagiarism is not just the outright copying of content.* If you paraphrase someone else's thoughts, words, or ideas and you don't cite your source, this constitutes plagiarism. It is always much better to turn in an incorrect or incomplete assignment representing your own efforts than to attempt to pass off the work of another as your own. **If you are academically dishonest in this course, you will receive a grade of XF, and you will be reported to the university's Office of Student Conduct.**

Textbooks

None-required ... but :

Genomics algorithms, data structures, and statistical models:

- [Genome Scale Algorithm Design](#) (Mäkinen, Belazzougui, Cunial, Tomescu 2015)
- [Bioinformatics Algorithms: An Active Learning Approach](#) (Pevzner and Compeau, 2018)
- [Biological Sequence Analysis](#) (Durbin, Eddy, Krogh, Mitchinson 1998)

Basics of algorithms and data structures:

This course will assume familiarity with basic algorithms and data structures, though I will attempt to refresh everyone's memory on relevant concepts when we cover them. If you need a refresher on algorithmic basics, I recommend the following resources:

- [Algorithms](#) (Dasgupta, Papadimitriou, and Vazirani 2006)
- [Algorithm Design](#) (Kleinberg and Tardos 2006)
- [Introduction to Algorithms, 3rd edition](#) (Cormen, Leiserson, Rivest and Stein, 2009)

Molecular biology:

We will cover the basic required molecular Biology in the course. However if you're not familiar with basic molecular Biology, there are some useful resources worth reading:

- [Molecular Biology of the Cell](#) (Alberts, Johnson, Lewis, Raff, Roberts and Walter, 2002)
- [Molecular Biology: Principles of Genome Function 2nd Edition](#) (Craig, Green, Greider, Storz, Wolberger, Cohen-Fix, 2014)
- [Molecular Biology](#) (Clark and Pazdernik 2012)

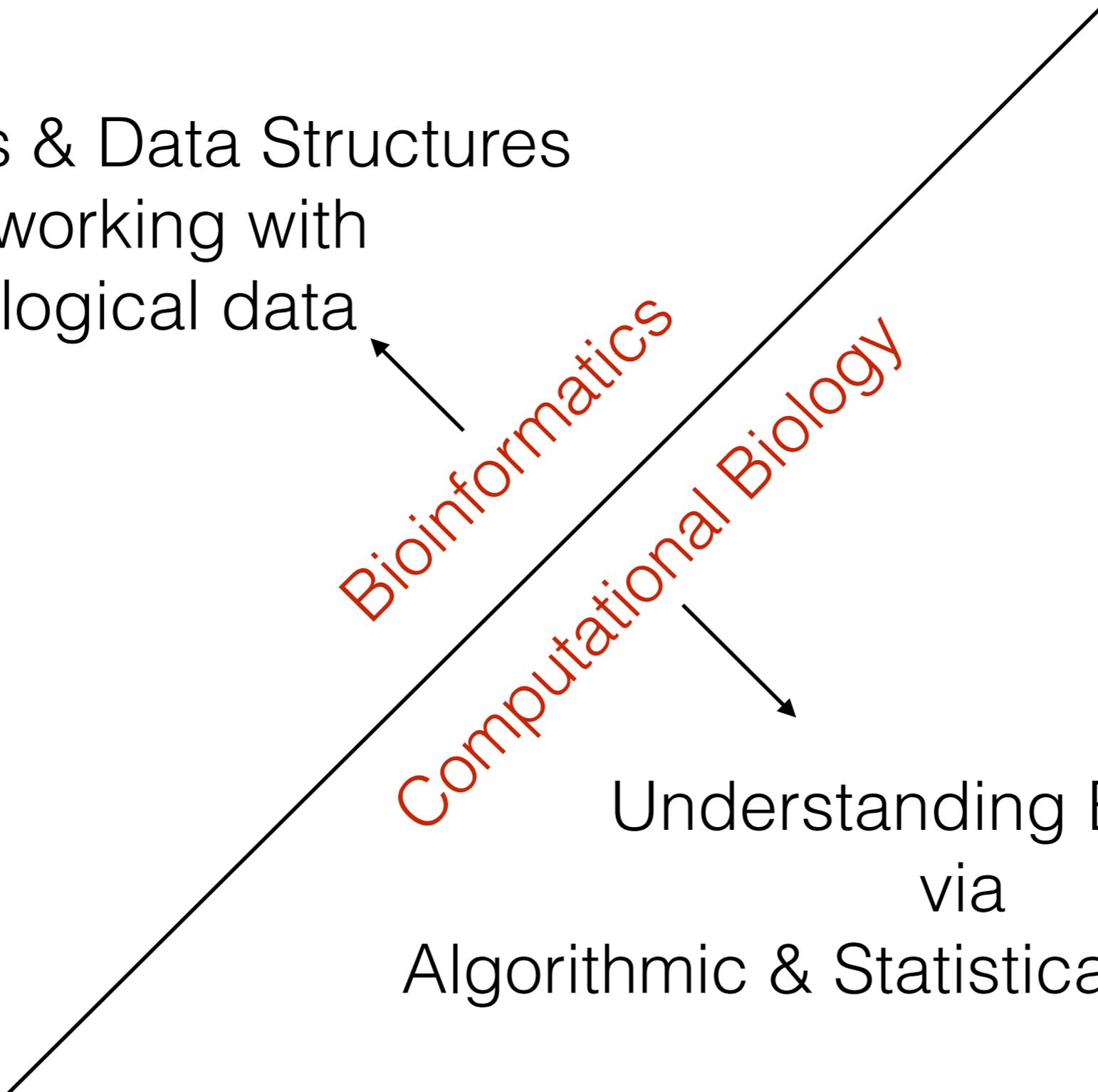
Bioinformatics & Computational Biology

Algorithms & Data Structures
for working with
Biological data

Bioinformatics

Computational Biology

Understanding Biology
via
Algorithmic & Statistical Approaches



Bioinformatics & Computational Biology

We'll treat this as two sides of the same coin
&
try to ignore this distinction

Why Computational Biology?

Our capabilities for *high-throughput* measurement of Biological data has been transformative

1990 - 2000

Sequencing the first human genome took ~10 years and cost ~\$2.7 **billion**

Today

Sequencing a genome costs ~\$100 - 1,000*
(depending on how you count)

~18 Tb per “run” at maximum capacity

Progression of sequencing capacity

\$3,000,000,000	2003 Human Genome Project	
\$20,000,000	2006 1 st individual genome	
\$2,000,000	2007 1 st NGS Genome	
\$200,000	2008 1 st 30x genome	
\$10,000	2010 1 st sub-10K genome	
\$1,000	2014 1 st \$1,000 genome	
\$100	2017 1 st \$100 genome	

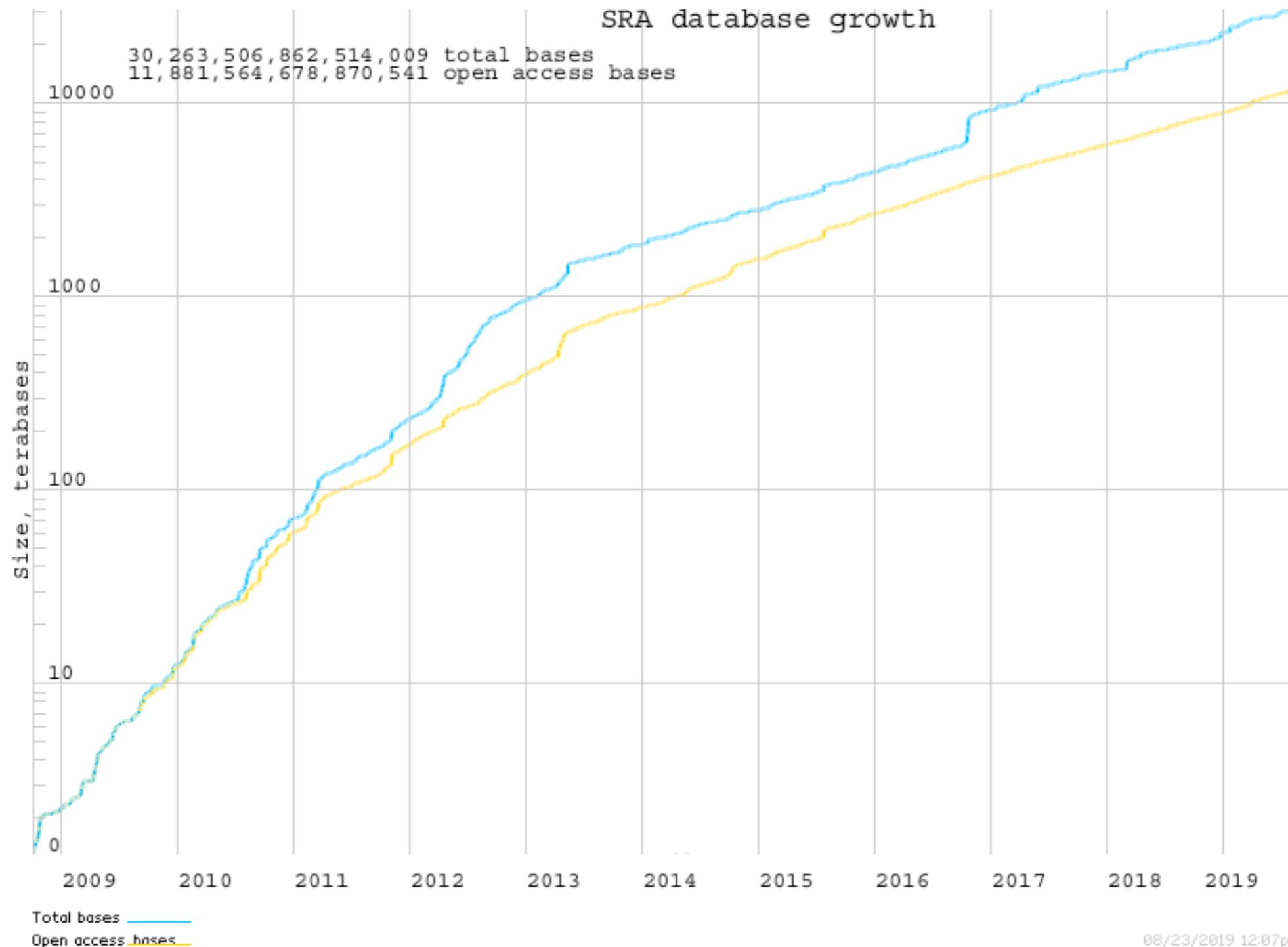
Tons of Data, but we need Knowledge

We'll discuss a bit about how sequencing works soon.
But the hallmark *limitations* are:

- Short “reads” (75 — 250) characters when the texts we’re interested in are 1,000s to 1,000,000,000s of characters long.
- Imperfect “reads” — results in infrequent but considerable “errors”; modifying, inserting or deleting one or more characters in the “read”
- Biased “reads” — as a result of the underlying chemistry & physics, sampling is not perfectly uniform and random. Biases are not always known.
- Emerging “long read” technologies exist, but have their own set of limitations.

despite these limitations, scientists have taken a very subtle and nuanced approach . . .

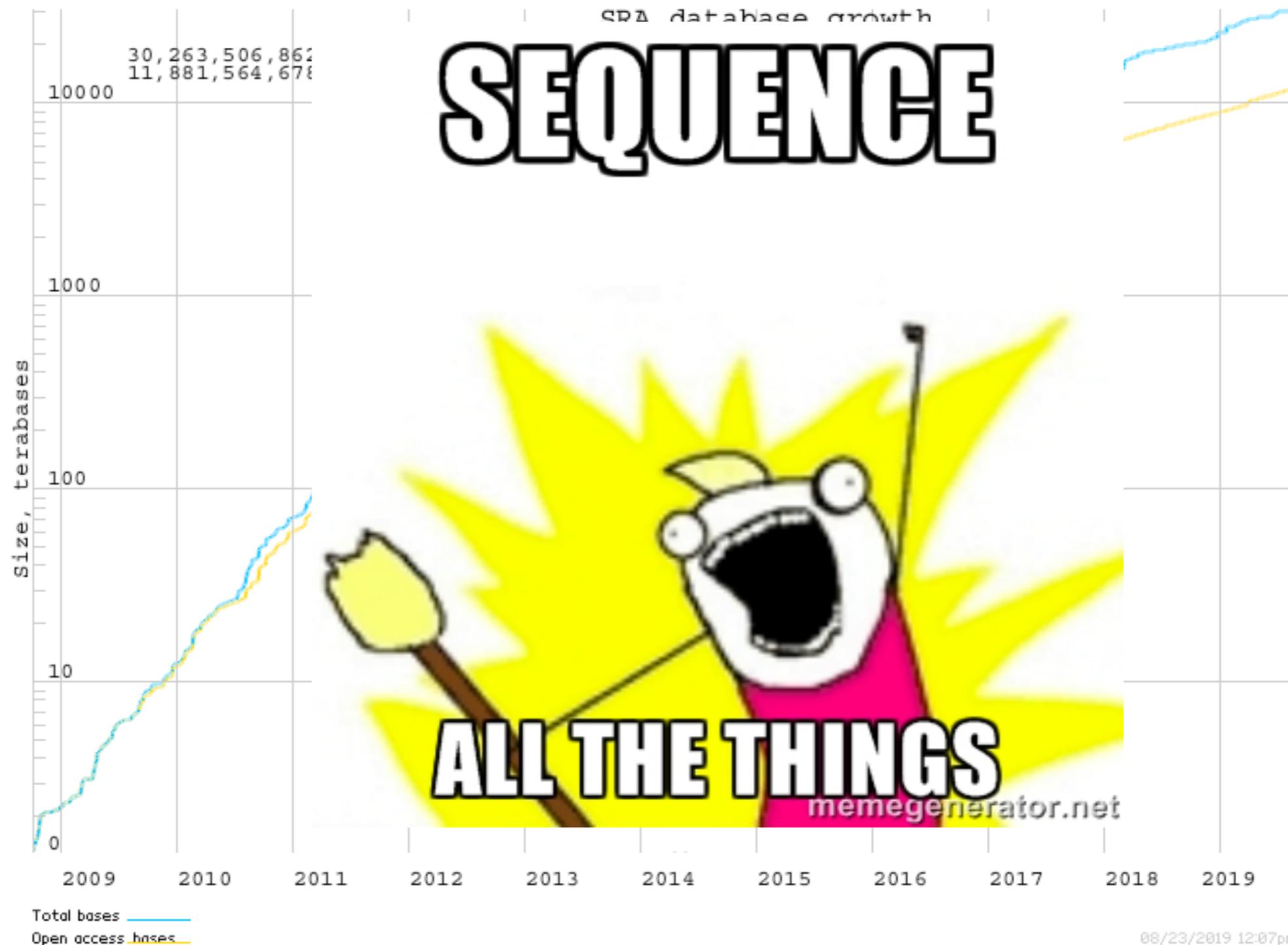
Growth of the Sequence Read Archive (SRA)



data from: <http://www.ncbi.nlm.nih.gov/Traces/sra/>

As a result, scientists have taken a very subtle and nuanced approach . . .

Growth of the Sequence Read Archive (SRA)



data from: <http://www.ncbi.nlm.nih.gov/Traces/sra/>

Answer questions “in the large”

What is the genome of the terrapin? (**genomics**)

Which genes are expressed in healthy vs. diseased tissue?
(**transcriptomics**)

How do environment changes affect the microbial ecosystem of the Chesapeake bay? (**metagenomics**)

How do genome changes lead to changes & diversity in a population? (**population genetics/genomics**)

How related are two species if we look at their whole genomes? (**phylogenetics / phylogenomics**)

Some Computational Challenges

Answering questions on such a scale becomes a *fundamentally* computational endeavor:

Assembly — Find a likely “super string” that parsimoniously explains 200M short sub-strings (string processing, graph theory)

Alignment — Find an *approximate* match for 50M short string in a 5GB corpus of text (string processing, data structure & algorithm design)

Expression / Abundance Estimation — Find the most probable mixture of genes / microbes that explain the results of a sequencing experiment (statistics & ML)

Phylogenomics — Given a set of related gene sequences, and an assumed model of sequence evolution, determine how these sequences are related to each other (statistics & ML)

Today & Thurs.

Some differences between CS & Biology as academic fields.

Biology for Computer Scientists

Some *very basic* fundamentals about molecular Biology (parts relevant to what we will study)

Basics of sequencing; how it works & its characteristics / limitations.

“Scientific” differences

Biology deals with *very* complex natural systems that arise through evolution

Biological systems can be indirect, redundant and counterintuitive

Nothing is “always” true/false — Biological laws are not like Physical or Mathematical laws; more stochastic truths or rules of thumb.

Biological laws *are* a result of Physical laws, but treating them that way is computationally infeasible

Try to understand mechanisms by probing and measuring complex systems and obtaining (often noisy) measurements

Experiments often *very* expensive

“Scientific” differences

Computer Science deals with *less* complex (won't say simple) systems that arise through design

CS is more about invention than discovery (philosophy aside)

Things are always formally true or false in CS & detailed theoretical analysis allows precise description

Computational outcomes *are* a result of mathematical laws & effective algorithms often have an intuitive explanation

Some subfields of CS (e.g. network measurement) do bear a resemblance to the natural sciences — many are much closer to math.

Experiments often dirt cheap and easy to re-run

“Cultural” differences

Biology

Only journals matter

Larger labs:

PI → postdoc → grad students

Student may study a specific gene for their entire PhD

Focus on being “right” and discovering something interesting about the natural world. (focus on knowledge)

CS

Selective conferences often preferred to journals

Smaller labs:

PI → a few grad students

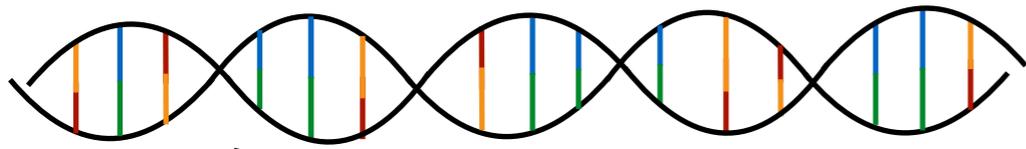
Students typically work on a wide variety of projects in PhD

More weight given to being “different”. Need not be 1st often just be “best”, fastest or simplest. (focus on methods)

Many of these differences start to vanish at the interface of data-intensive Biology, where computational savvy is a necessity.

“Flow” of information in the cell

DNA



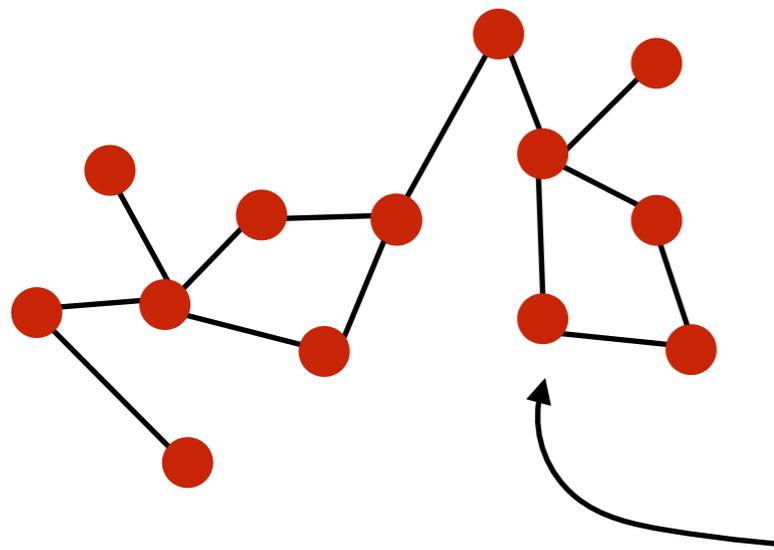
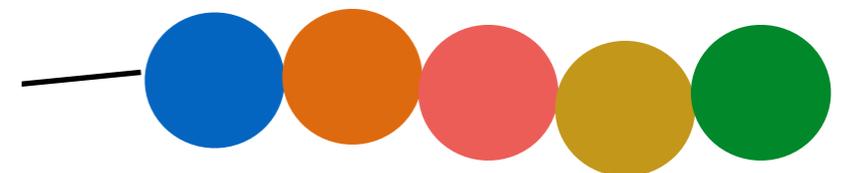
RNA Polymerase
(transcription)

RNA



Ribosomes
(translation)

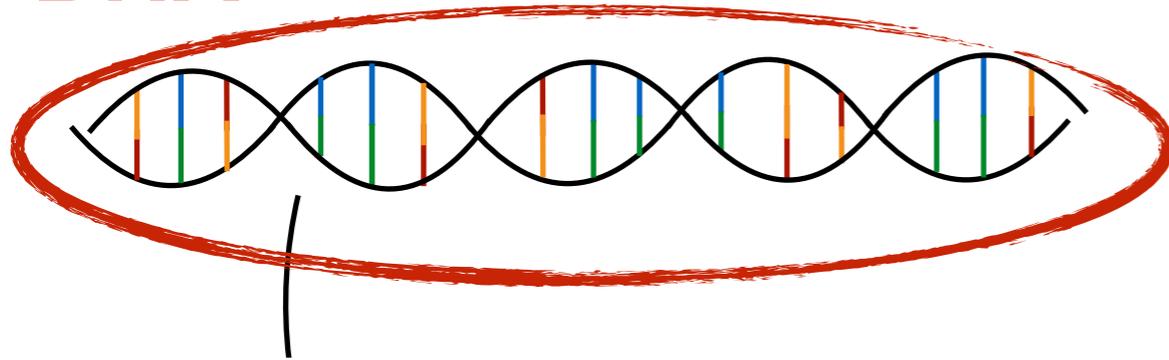
Protein



Form networks & pathways; perform a vast set of cellular functions

“Flow” of information in the cell

DNA



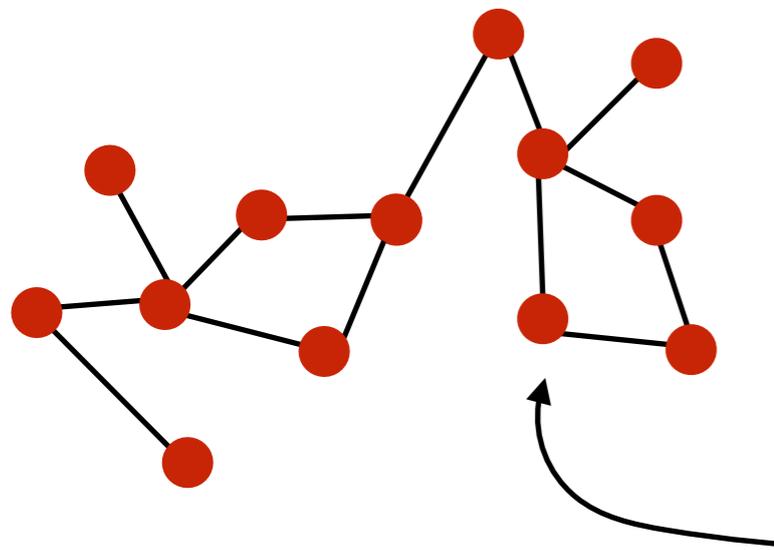
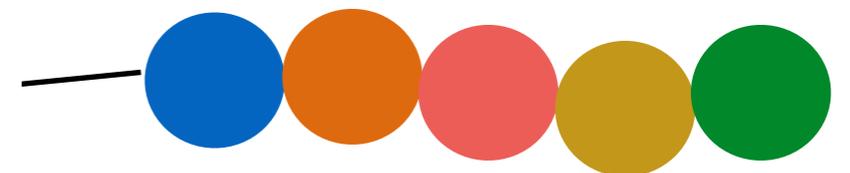
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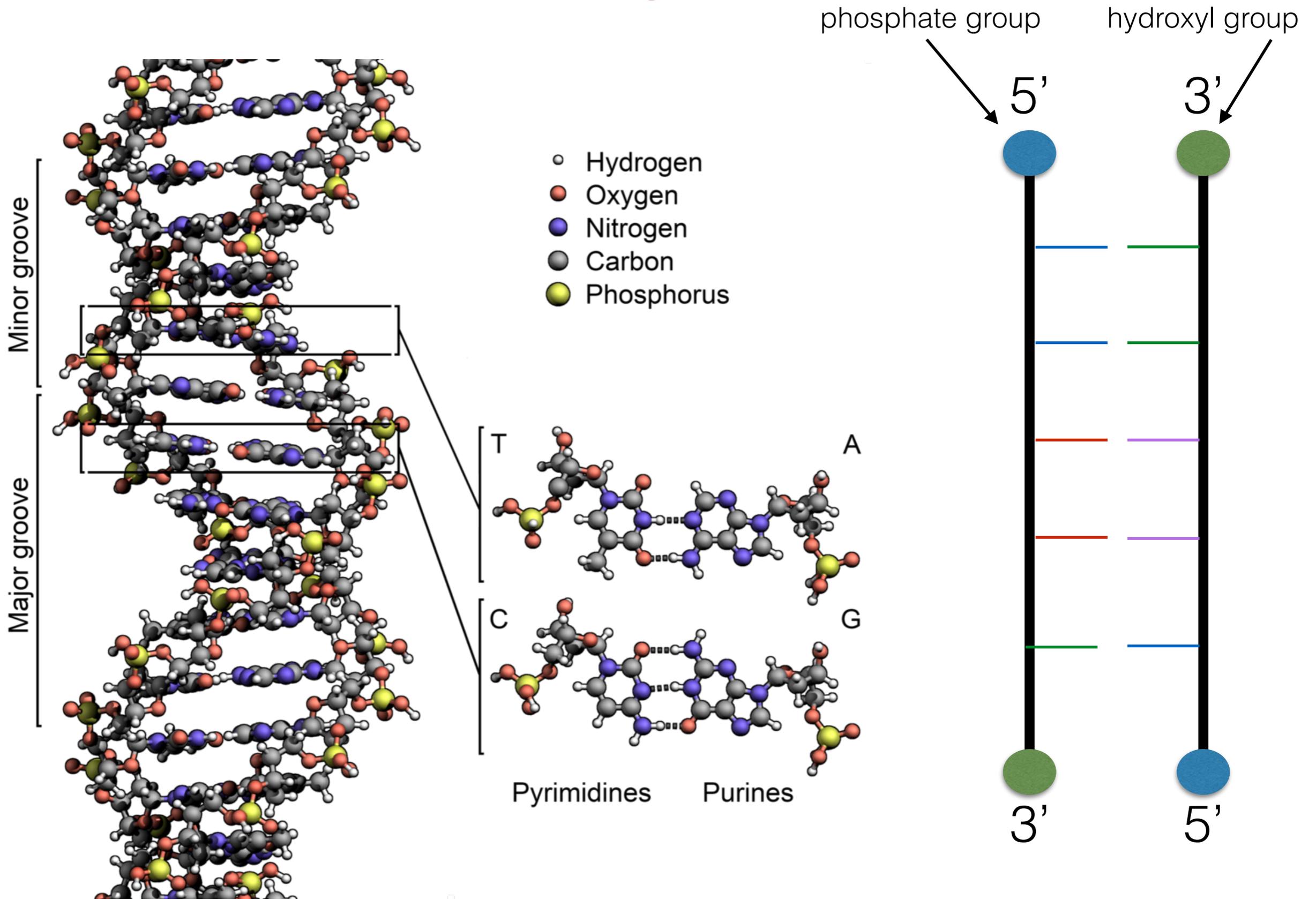
Ribosomes
(translation)

Protein

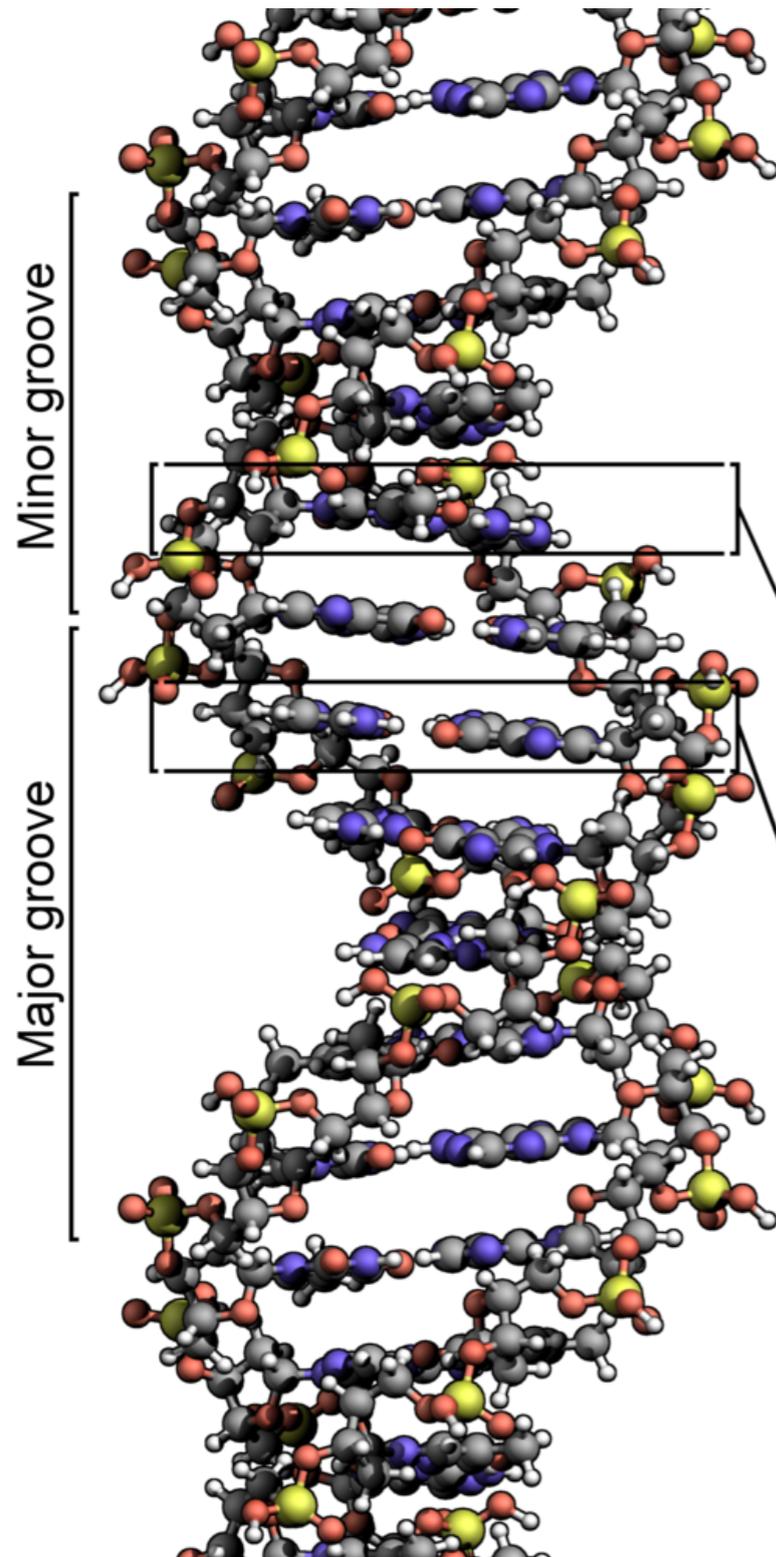


Form networks & pathways; perform a vast set of cellular functions

DNA (the genome)



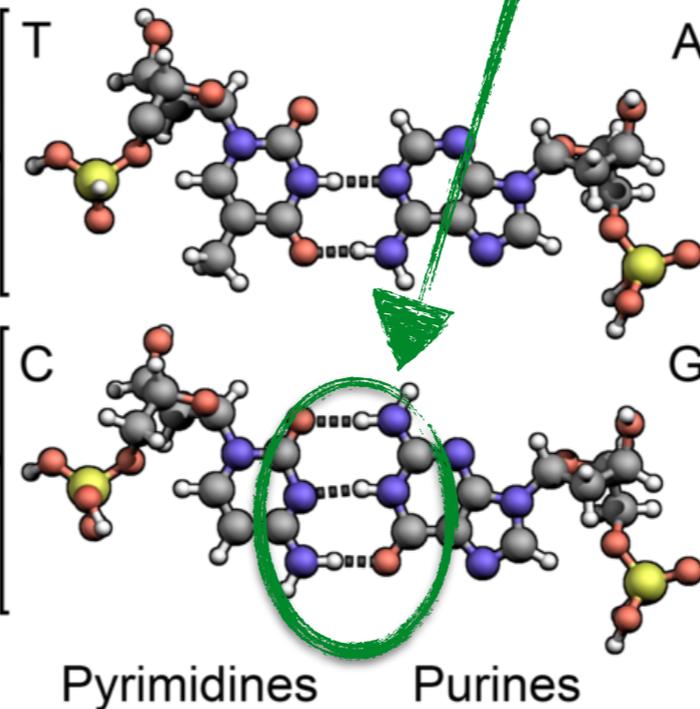
DNA (the genome)



- Hydrogen
- Oxygen
- Nitrogen
- Carbon
- Phosphorus

G-C pairing generally stronger than A-T pairing

Ratio of G+C bases — the “GC content” — is an important sequence feature



DNA (the genome)

gene — will go on to become a protein



“non-coding DNA” — may or may not produce transcripts (e.g. functional non-coding RNA)

In humans, most DNA is “non-coding” ~98%

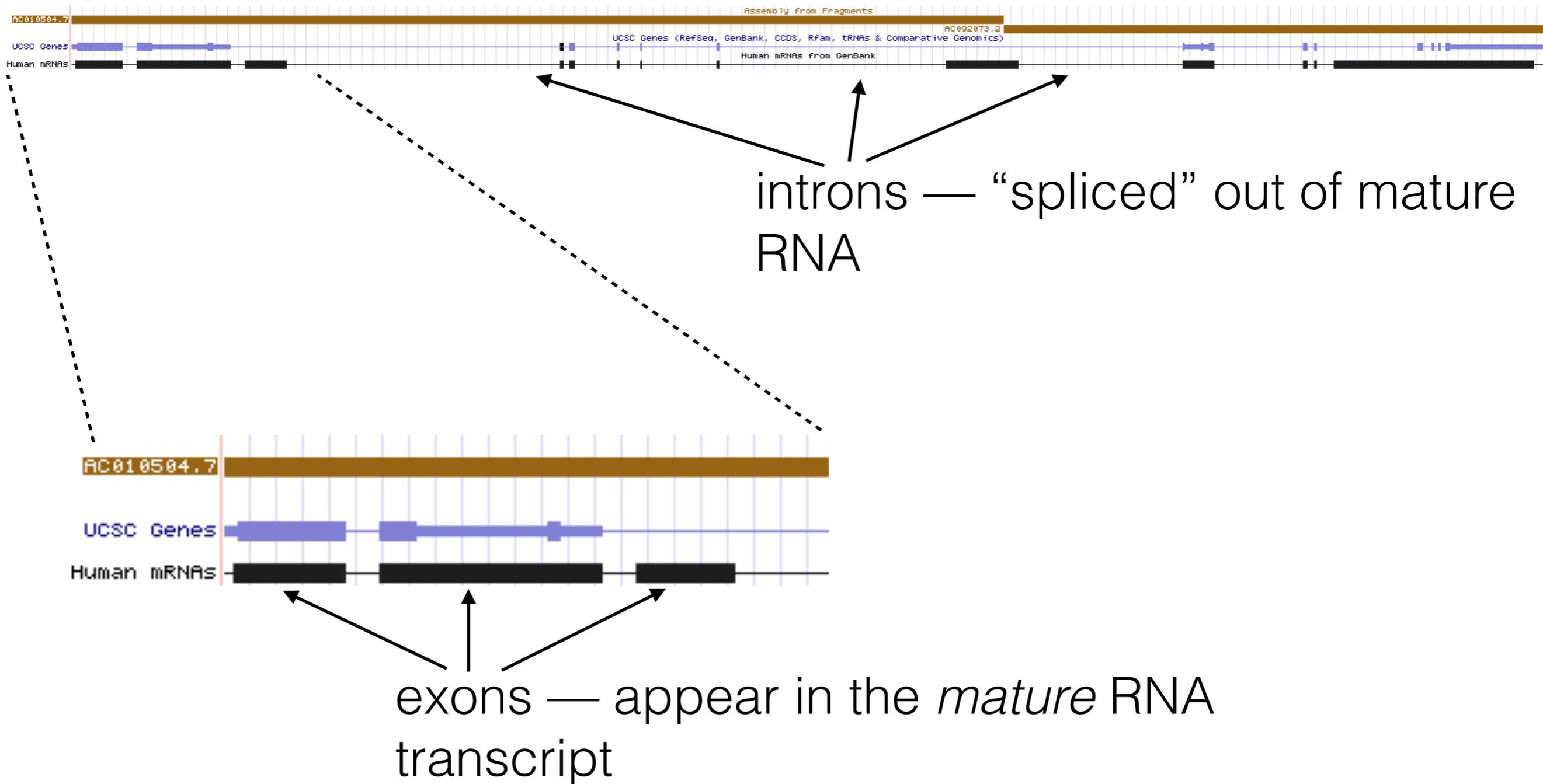
In typical bacterial genome, only small fraction — ~2% — of DNA is “non-coding”

Sometimes referred to as “junk” DNA — much is not, in any way, “junk”

DNA (the genome)

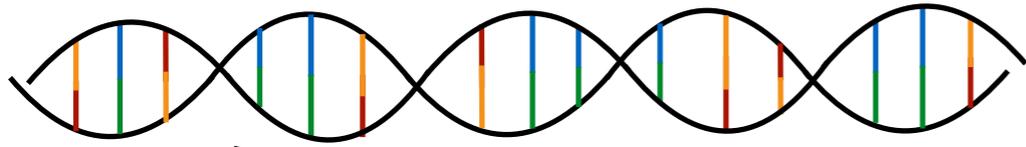
In **prokaryotes**, genes are typically contiguous DNA segment

In **eukaryotes**, genes can have complex structure



“Flow” of information in the cell

DNA



RNA Polymerase
(transcription)

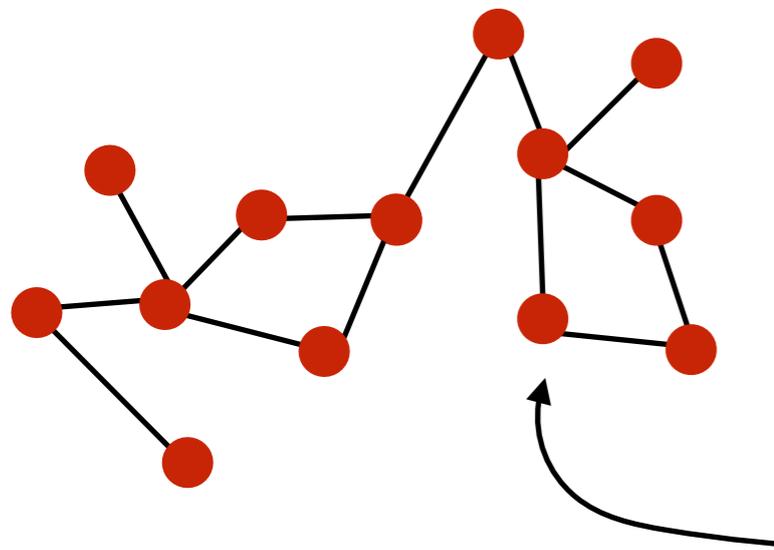
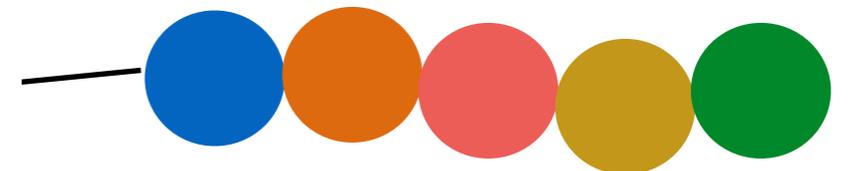
See video on course website

RNA



Ribosomes
(translation)

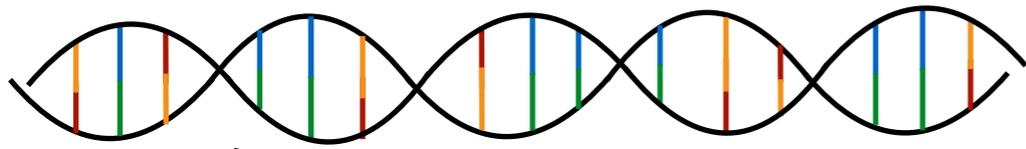
Protein



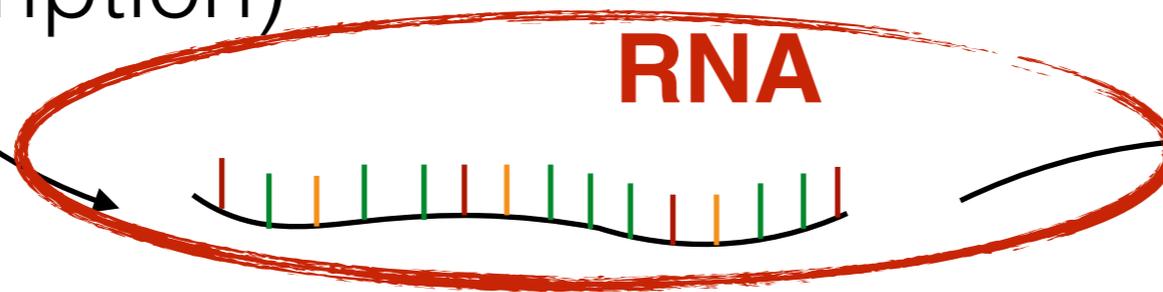
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“Flow” of information in the cell

DNA

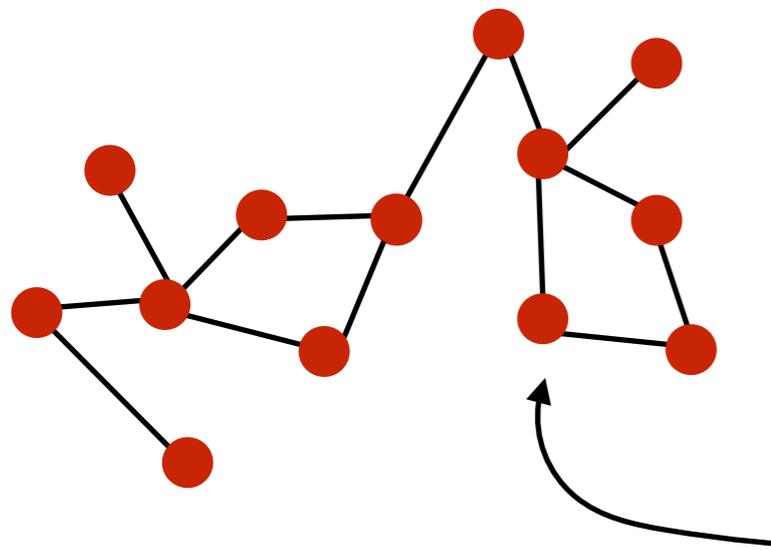
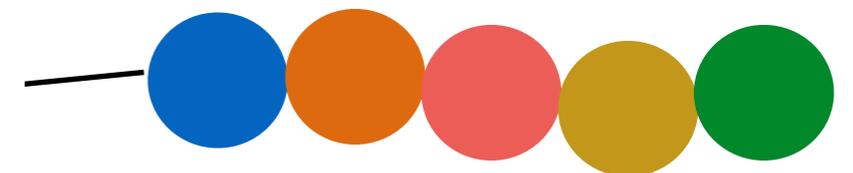


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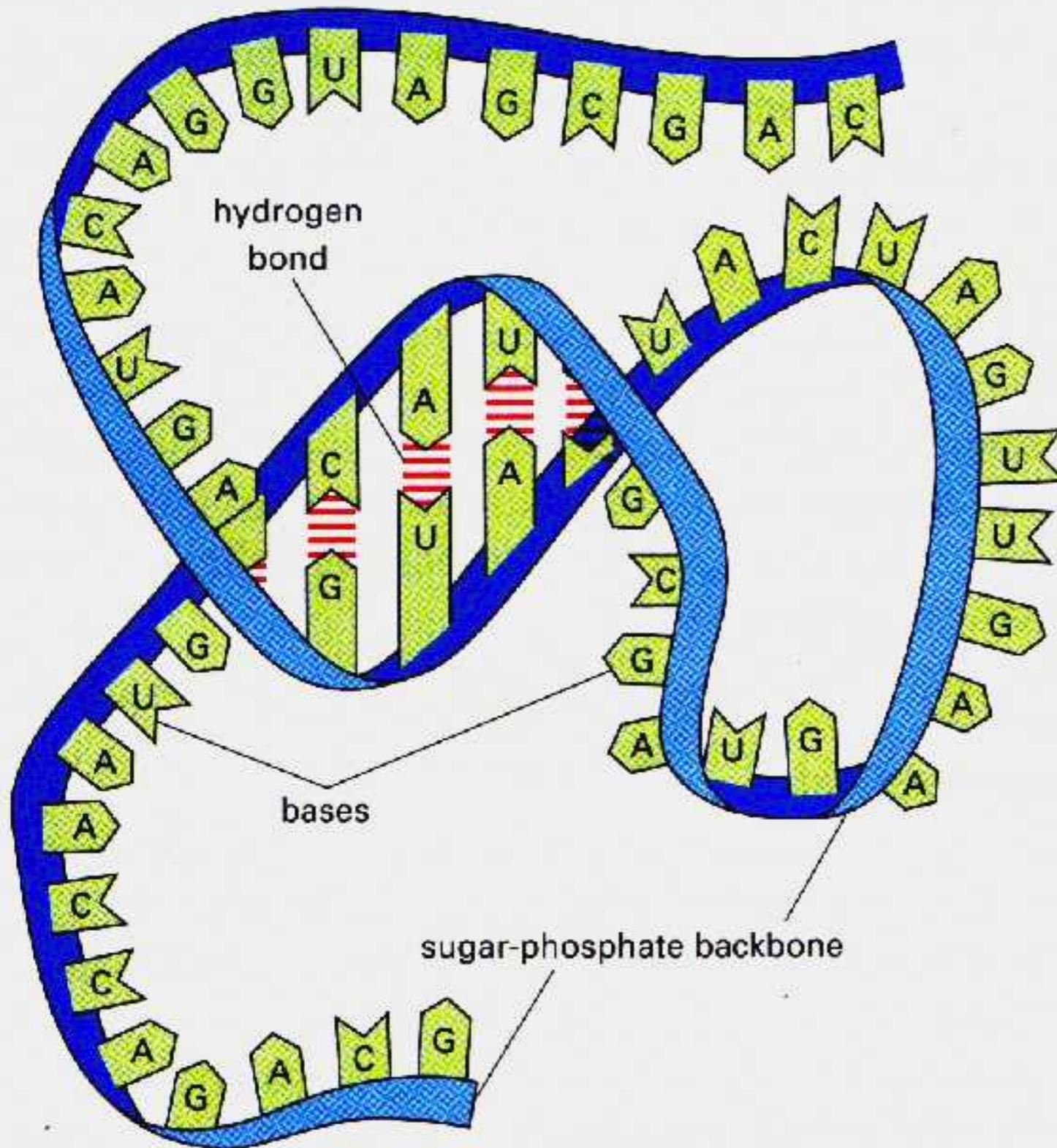
Ribosomes
(translation)

Protein



Form networks & pathways; perform a vast set of cellular functions

RNA



Less regular structure than DNA

Generally a single-stranded molecule

Secondary & tertiary structure can affect function

Act as transcripts for protein, but also perform important functions themselves

Same “alphabet” as DNA, except thymine replaced by uracil

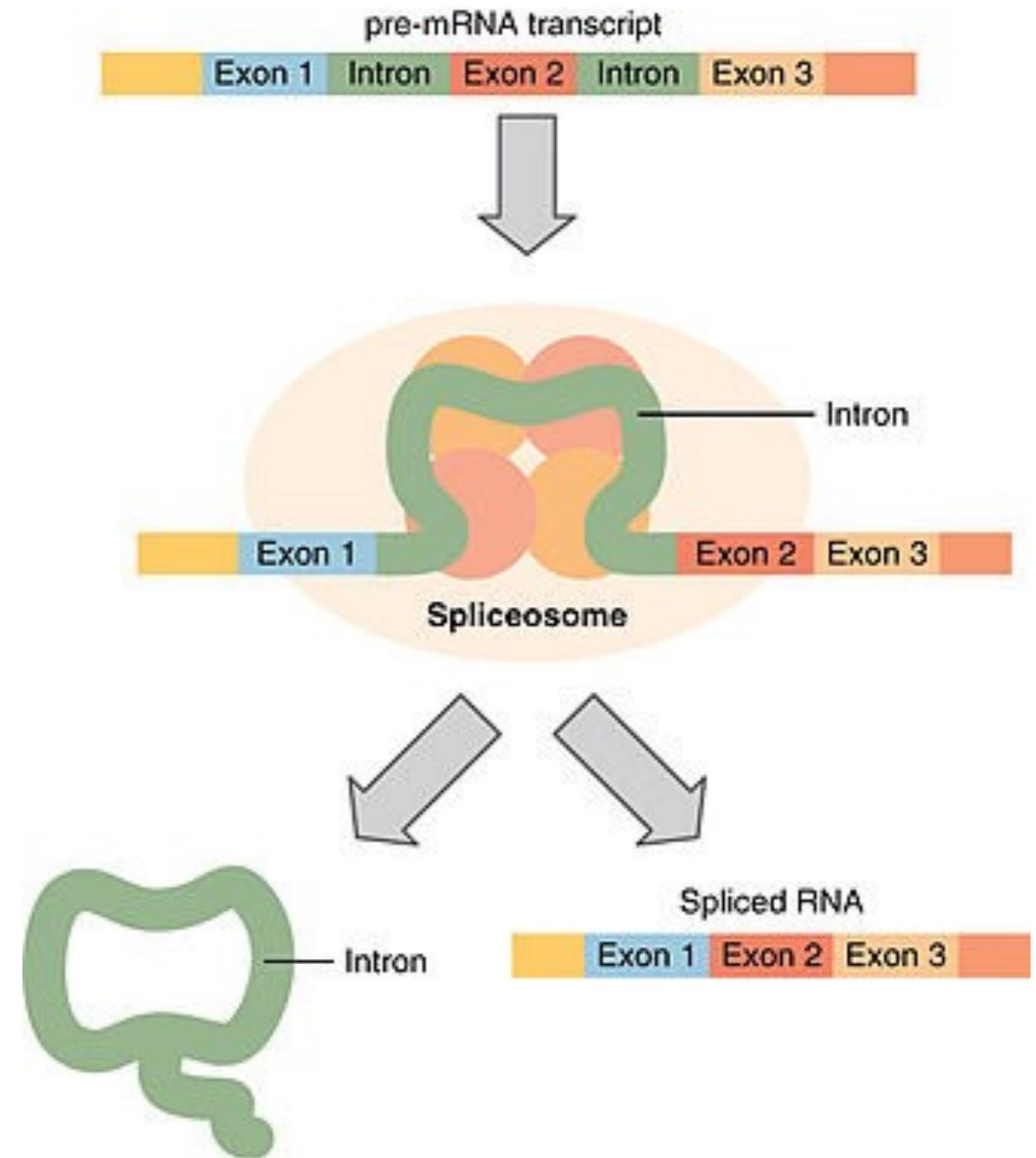
RNA Splicing

DNA transcribed into pre-mRNA

Some “processing occurs”
capping & polyadenylation

Introns removed from pre-mRNA

Introns removed resulting in
mature mRNA

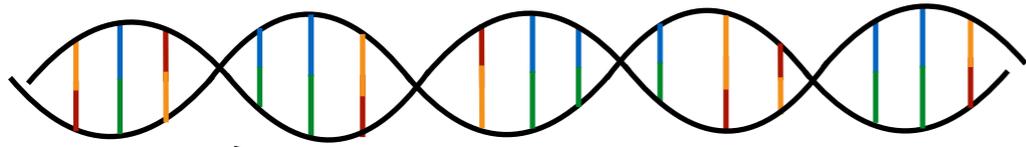


Alternative Splicing & Isoform Expression

- Expression of genes can be measured via RNA-seq (sequencing transcripts)
- Sequencing gives you short (35-300bp length reads)

“Flow” of information in the cell

DNA



RNA Polymerase
(transcription)

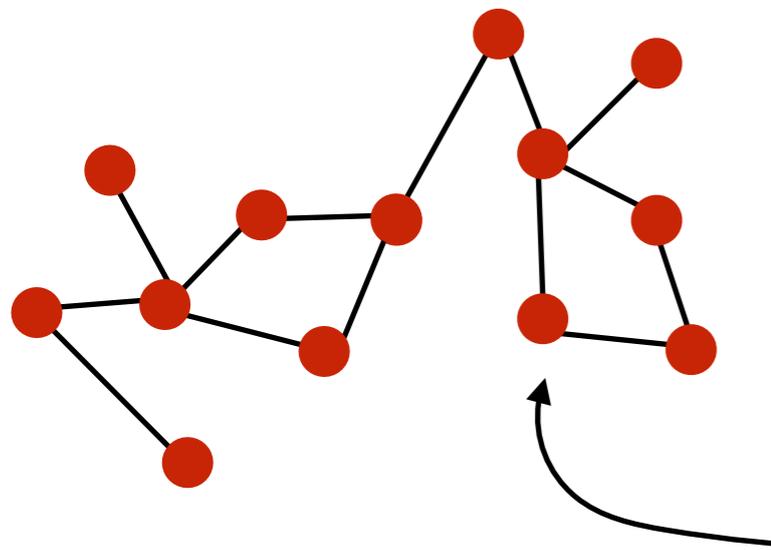
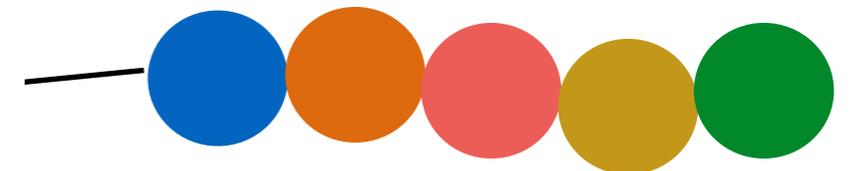
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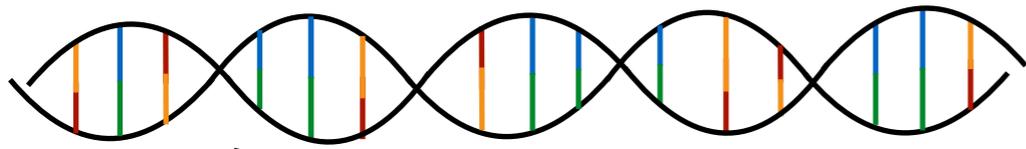
Protein



Form networks & pathways; perform a vast set of cellular functions

“Flow” of information in the cell

DNA

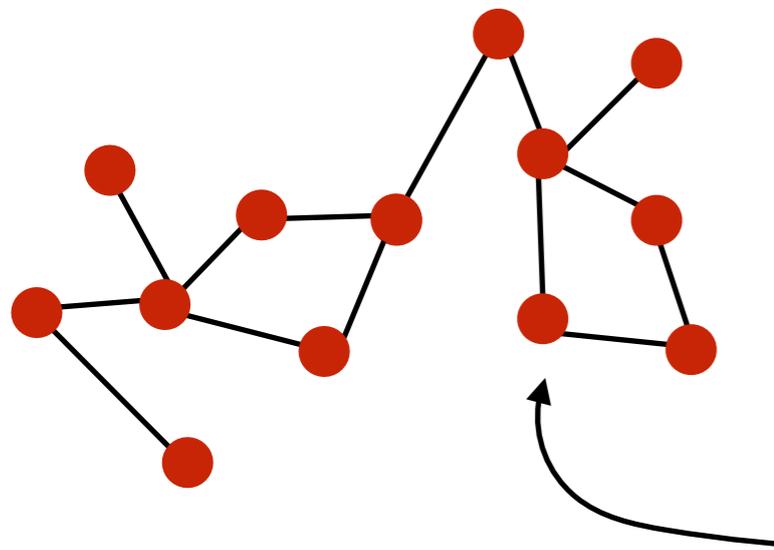


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Ribosomes
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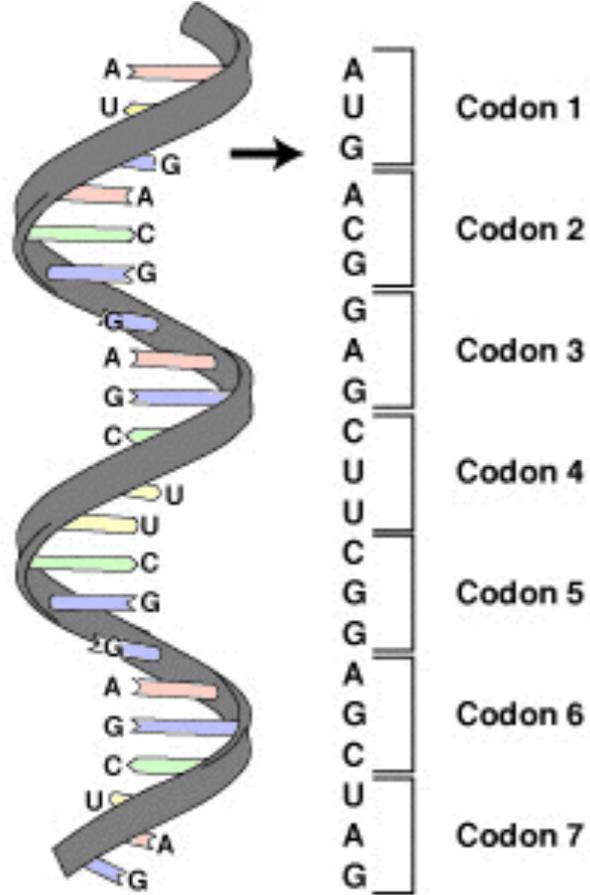


Form networks & pathways; perform a vast set of cellular functions

Protein



Protein



Triplets of mRNA bases (codons) correspond to specific amino acids

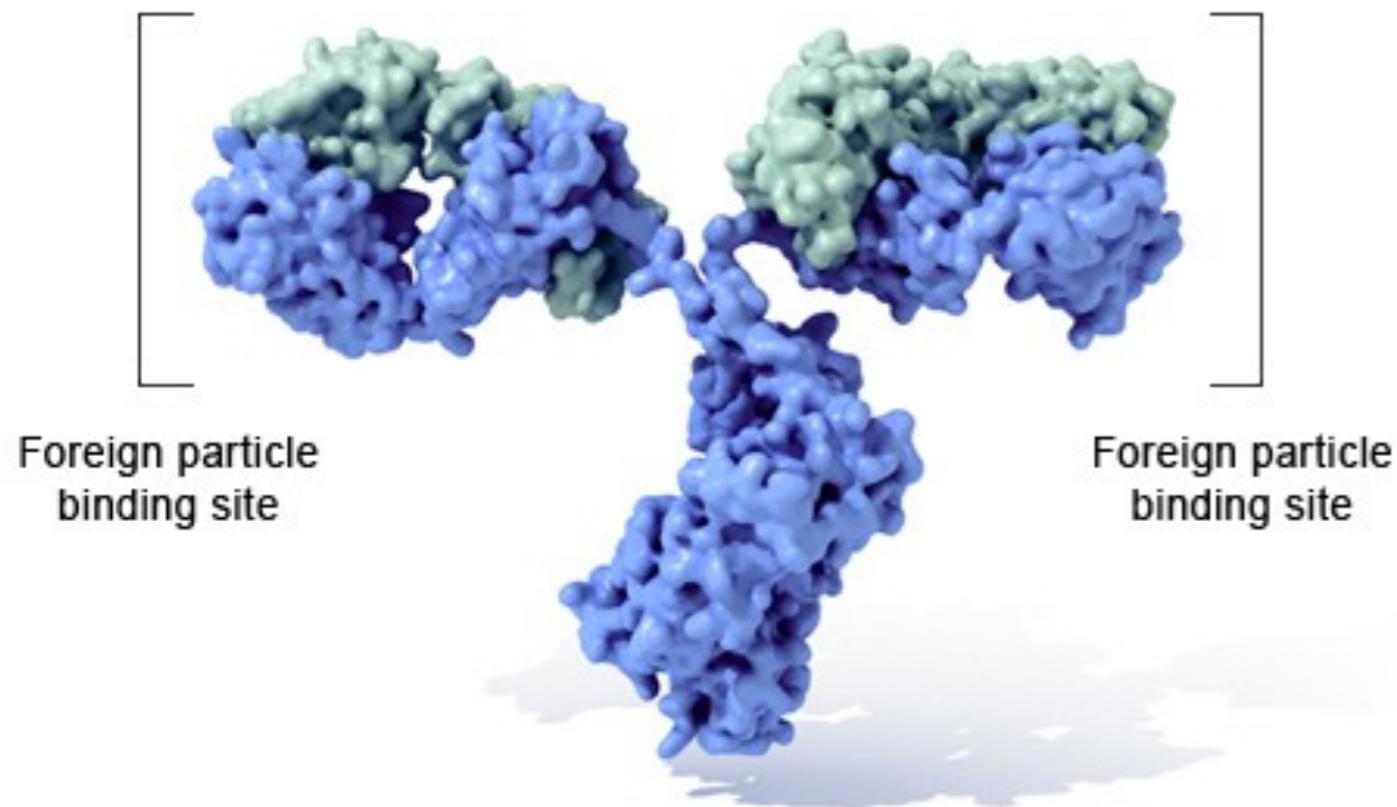
This mapping is known as the “genetic code” — an *almost* law of molecular Biology

Inverse table (compressed using **IUPAC notation**)

Amino acid	Codons	Compressed	Amino acid	Codons	Compressed
Ala/A	GCU, GCC, GCA, GCG	GCN	Leu/L	UUA, UUG, CUU, CUC, CUA, CUG	YUR, CUN
Arg/R	CGU, CGC, CGA, CGG, AGA, AGG	CGN, MGR	Lys/K	AAA, AAG	AAR
Asn/N	AAU, AAC	AAY	Met/M	AUG	
Asp/D	GAU, GAC	GAY	Phe/F	UUU, UUC	UUY
Cys/C	UGU, UGC	UGY	Pro/P	CCU, CCC, CCA, CCG	CCN
Gln/Q	CAA, CAG	CAR	Ser/S	UCU, UCC, UCA, UCG, AGU, AGC	UCN, AGY
Glu/E	GAA, GAG	GAR	Thr/T	ACU, ACC, ACA, ACG	ACN
Gly/G	GGU, GGC, GGA, GGG	GGN	Trp/W	UGG	
His/H	CAU, CAC	CAY	Tyr/Y	UAU, UAC	UAY
Ile/I	AUU, AUC, AUA	AUH	Val/V	GUU, GUC, GUA, GUG	GUN
START	AUG		STOP	UAA, UGA, UAG	UAR, URA

Protein

Immunoglobulin G (IgG)



U.S. National Library of Medicine

Perform vast majority of intra & extra cellular functions

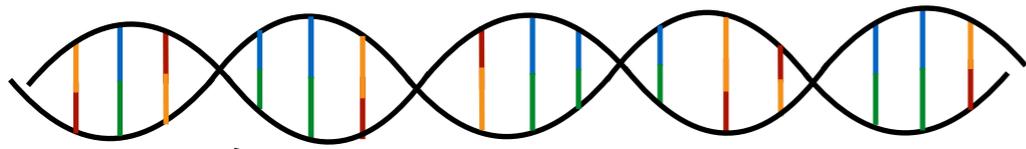
Can range from a few amino acids to *very* large and complex molecules

Can bind with other proteins to form protein complexes

The shape or *conformation* of a protein is intimately tied to its function. Protein shape, therefore, is strongly conserved through evolution — even more so than sequence. A protein can undergo sequence mutations, but fold into the same or a similar shape and still perform the same function.

“Flow” of information in the cell

DNA



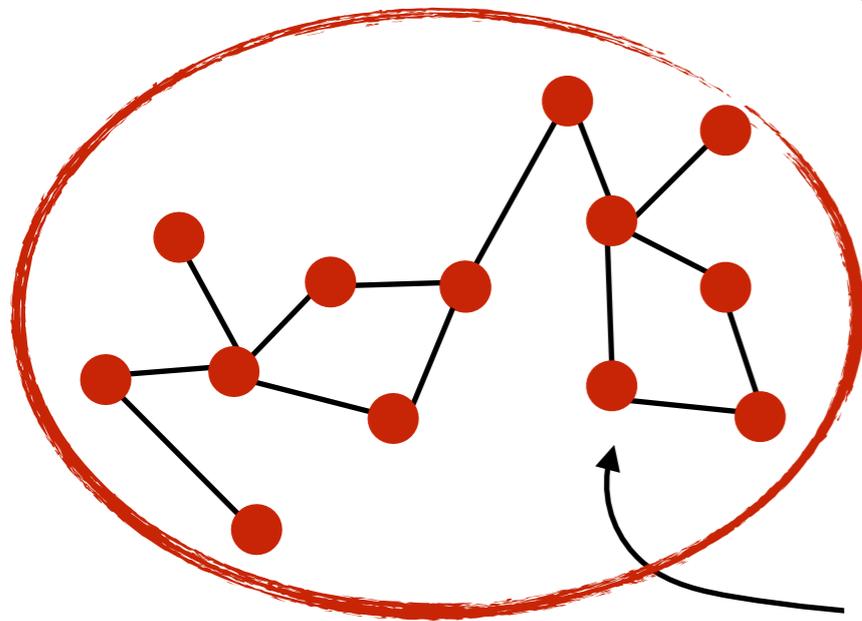
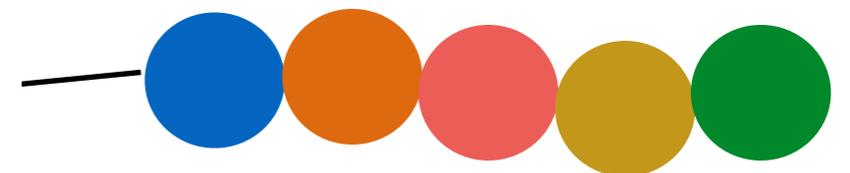
RNA Polymerase
(transcription)

RNA



Ribosomes
(translation)

Protein



Form networks &
pathways; perform a
vast set of cellular
functions

One way in which this “central dogma” is violated ... retroviruses

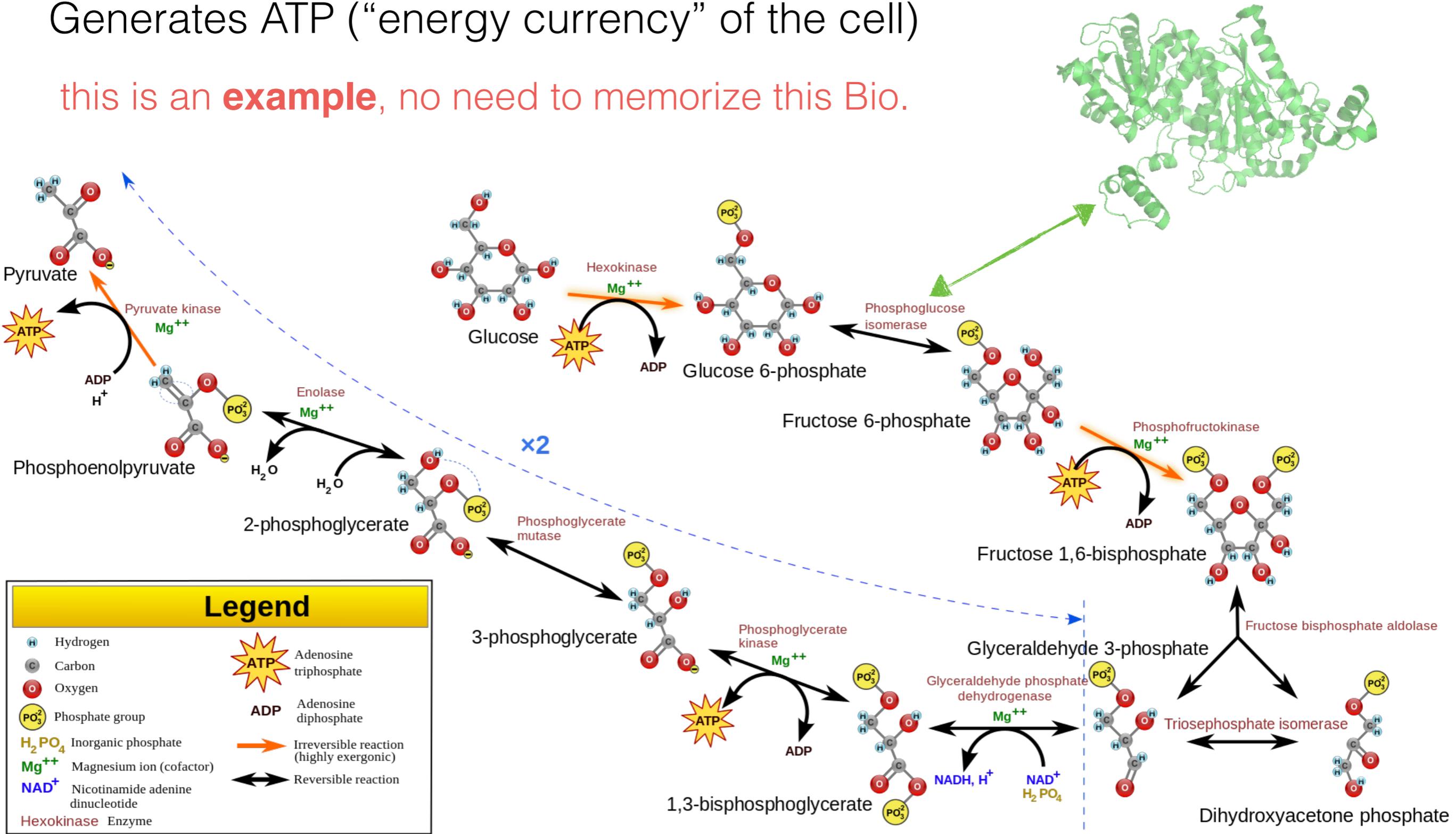
Glycolysis Pathway

Converts glucose → pyruvate

Generates ATP (“energy currency” of the cell)

this is an **example**, no need to memorize this Bio.

phosphoglucose isomerase



Some Interesting Facts

Organism	Genome size	# of genes
ϕ X174 (<i>E. coli</i> virus)	~5kb	11
<i>E. coli</i> K-12	~4.6Mb	~4,300
Fruit Fly	~122Mb	~17,000
Human	~3.3Gb	~21,000
Mouse	~2.8Gb	~23,000
<i>P. abies</i> (a spruce tree)	~19.6Gb	~28,000

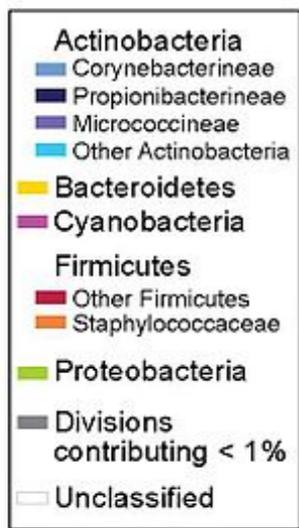
No strong link between genome size & phenotypic complexity

Plants can have **huge** genomes (adapt to environment while stationary!)

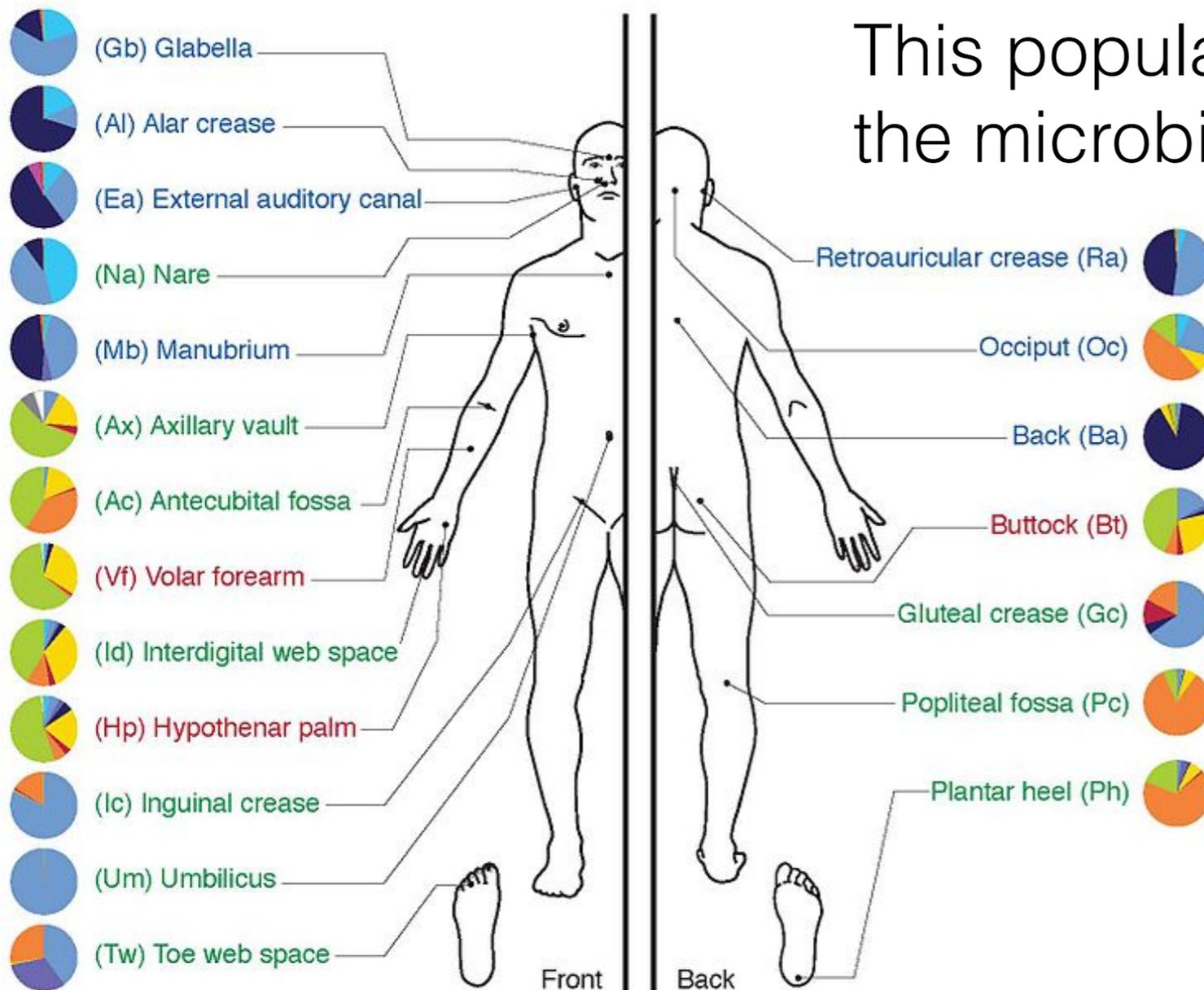
Some Interesting Facts

You are mostly bacteria, fungi & arches

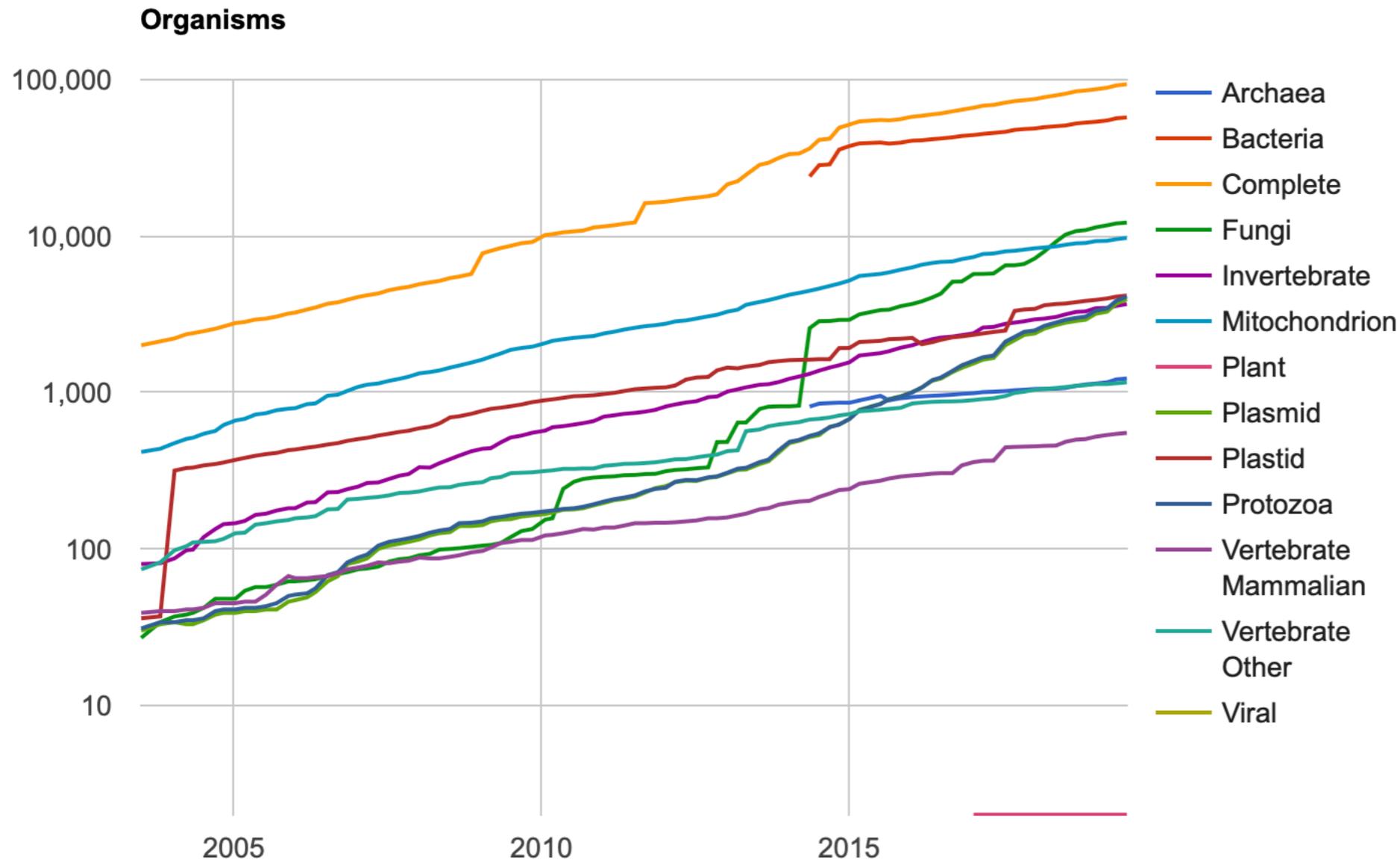
Non-human cells outnumber human cells in the human body



This population of organisms is called the microbiome



Some Interesting Facts



<https://www.ncbi.nlm.nih.gov/refseq/statistics/>

. . . Out of 8.7 ± 1.3 Mil*

Vast majority of species unsequenced & *can not be cultivated in a lab* (one of the many motivations for metagenomics)

*Mora, Camilo, et al. "How many species are there on Earth and in the ocean?." PLoS biology 9.8 (2011): e1001127.