INTRODUCTION & OVERVIEW

BIOI 607: Data Structures and Algorithms for Bioinformatics

Course Information

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Website: https://umd-bioi607.github.io/s2024

Course Information

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

Academic Integrity: https://academiccatalog.umd.edu/undergraduate/registration-academic-requirements-regulations/academic-integrity-student-conduct-codes/

Piazza Page: https://piazza.com/umd/spring2024/bioi607

Gradescope: https://www.gradescope.com/courses/720443

If you have a class-related e-mail: Please **prefix the subject with [BIOI607_S24]**, so that my filter will pick it up and it won't be accidentally routed to SPAM.

Academic Integrity (maintain it)!

TLDR : Don't cheat. Don't copy code from friends, classmates, or the internet for the short programming assignments or the projects. Don't provide code to classmates for any of the assignments or projects. Don't cheat on the exams. Be cool, and everything will be cool.

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. *Plagarism 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 constitues plagraism. 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 recieve a grade of XF, and you will be reported to the university's Office of Student Conduct**.

Textbooks

There *is no required text,* recommended texts for different background subjects are listed on the course website.

Additional material will be made available on the course website as needed.

However, and you should *absolutely* seek out other sources explaining these topics from different angles, using different notations and examples, etc.

If you seek out other sources and still are having difficulty with an idea, *please* reach out to me. Also, consider reaching out to your peers *via* Piazza.

Other Textbooks

Basics of algorithms and data structures:

Though we will cover the basic algorithms and data structures we need in this course, you may find that you need to spend more time learning about these concepts. Additionally, you may want to dive deeper into these *interesting* topics. 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)

Genomics algorithms, data structures, and statisitcal models:

I recommend the following supplementary material with respect to genomics algorithms in particular:

- Genome Scale Algorithm Design (Mäkinen, Belazzougui, Cunial, Tomescu 2015)
- Biological Sequence Analysis (Durbin, Eddy, Krogh, Mitchinson 1998)

Other Textbooks

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)

Programming, software development, and using the command line

In general in this course, we are going to be doing some programming. There are many ways to develop software, but the vast majority of bioinformatics software runs from, and is developed with, command line tools. Therefore, we will learn the basics of using these tools (e.g. how to properly create a tarball, how to invoke the compiler from the command line / a script, etc.).

I realize it may have been a while since you have used these skills, or you may not have learned them at all. If you feel you need a refresher on these topics, or as an alternative resource to what I will cover, I would strongly suggest checking out "The missing semester" (an MIT course dedicated to these various miscellaneous topics).

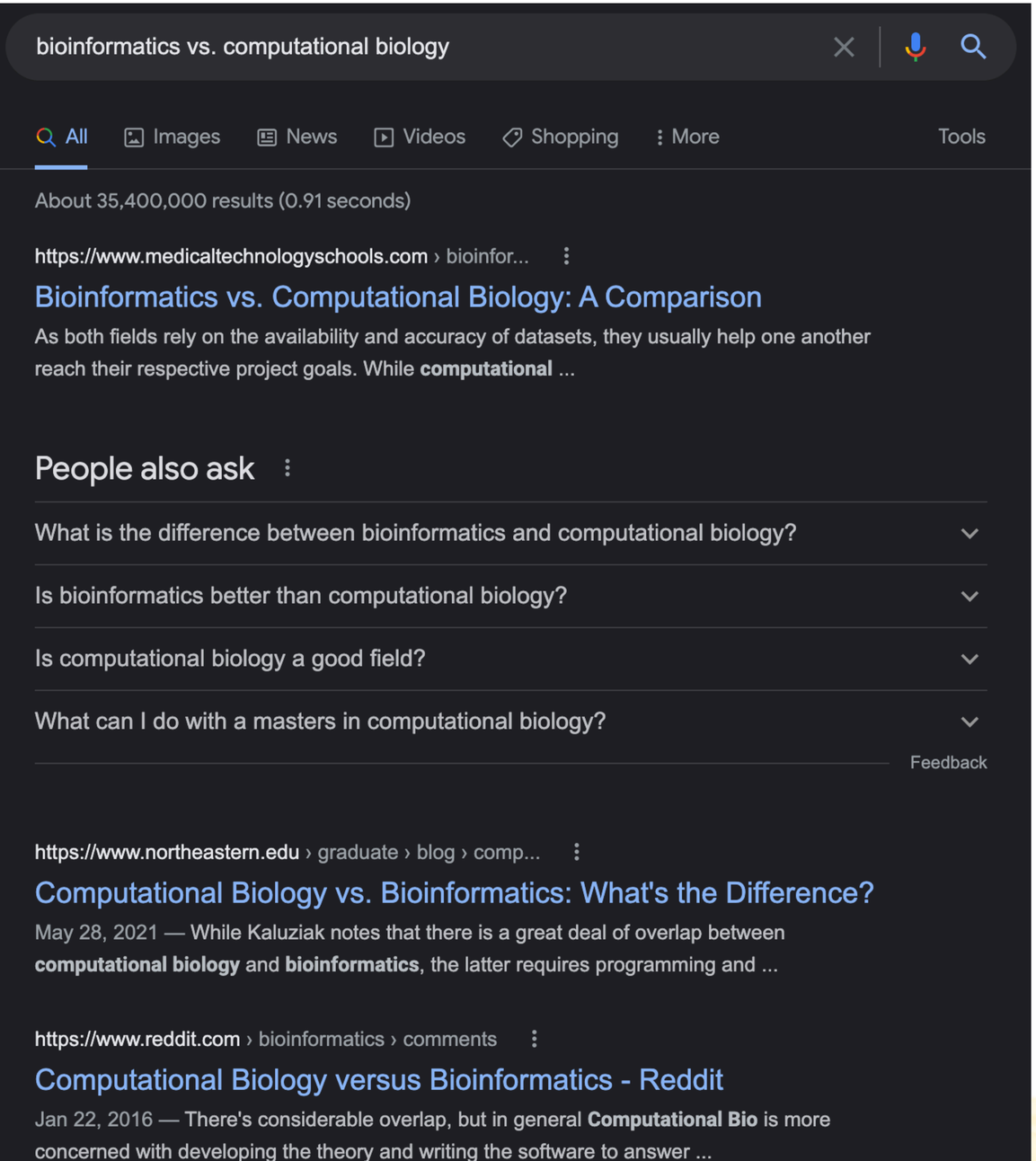
Expectations: Since this is a course on data structures and algorithms for bioinformatics, you will be expected to become familiar with the relevant biology — it is an important and inextricable part of the material, and the underlying biology provides motivation for the computational problems we will tackle. However, our focus will be on the computational aspects of bioinformatics and genomics.

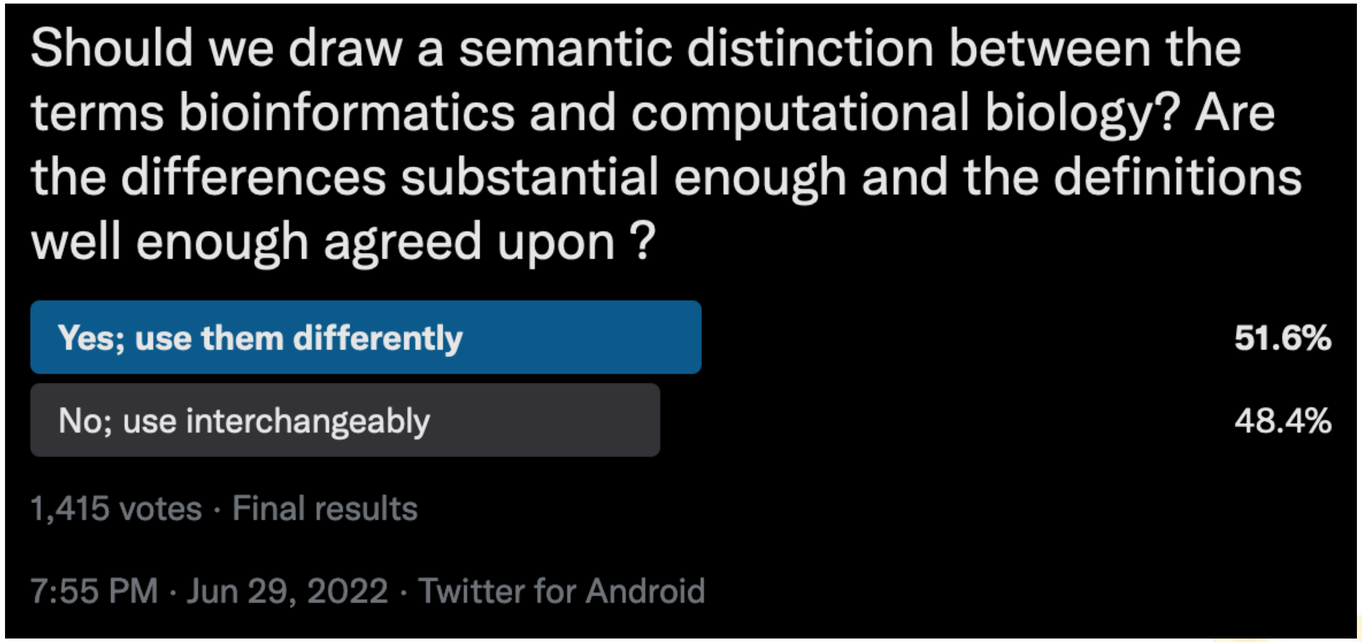
More syllabus stuff

Course Objectives

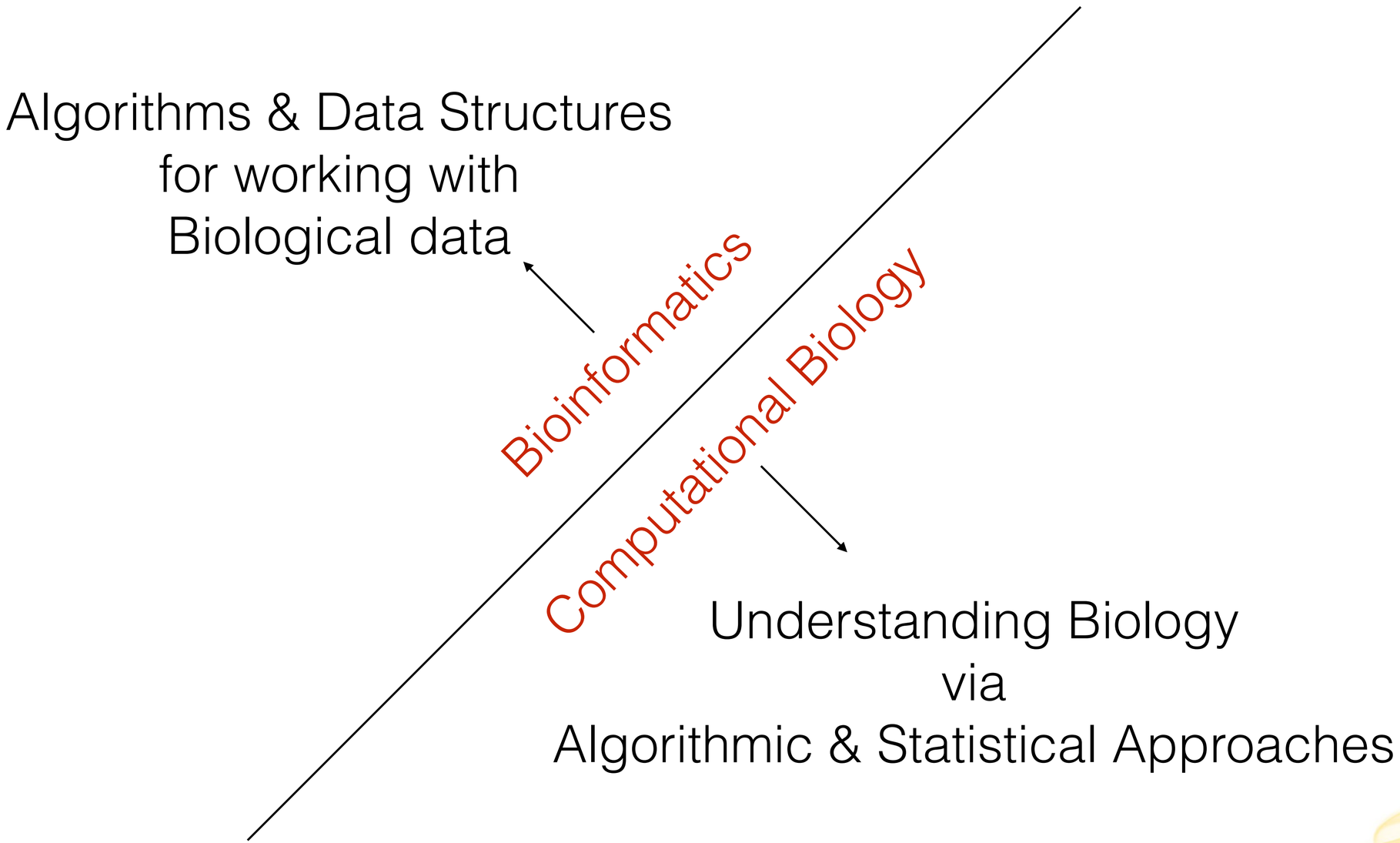
The main objective of this course will be to provide an understanding of some of the algorithms, data structures, and methods that underlie *modern* computational genomics. This course is intended as a broad introduction to common data structure and algorithms in genomics, and the problems that some of these algorithms are intended to solve. However, this is a huge field, so we will certainly not cover everything, and what we do cover will not all be at the same depth. Our perspective will be a computational and algorithmic one, though we will take the time to understand the necessary biology and motivation for the problems we discuss. At the end of this course, you should have a good understanding of how new challenges in genomics drive algorithmic innovations and how algorithmic innovations enable new and improved biological analyses.

A rose by any other name





Bioinformatics & Computational Biology



Bioinformatics & Computational Biology

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

Why Bioinformatics (genomics)?

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 1st individual genome	
$2,000,000	2007 1st NGS Genome	
$200,000	2008 1st 30x genome	
$10,000	2010 1st sub-10K genome	
$1,000	2014 1st $1,000 genome	
$100	2017 1st $100 genome	

Tons of Data, but we want Knowledge

We'll discuss a bit about how sequencing works later. 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.

A cartoon view of sequencing

Orig. genome: GACGATGAAGCCAGCTCGGCTGAACACGATTCCAACGTCTAACGCTCGGTAGGTCTGGCAGGTAGCCGGGCGGAA

Many copies:
GACGATGAAGCCAGCTCGGCTGAACACGATTCCAACGTCTAACGCTCGGTAGGTCTGGCAGGTAGCCGGGCGGAA
GACGATGAAGCCAGCTCGGCTGAACACGATTCCAACGTCTAACGCTCGGTAGGTCTGGCAGGTAGCCGGGCGGAA
GACGATGAAGCCAGCTCGGCTGAACACGATTCCAACGTCTAACGCTCGGTAGGTCTGGCAGGTAGCCGGGCGGAA
…
GACGATGAAGCCAGCTCGGCTGAACACGATTCCAACGTCTAACGCTCGGTAGGTCTGGCAGGTAGCCGGGCGGAA

"random" fragmentation into short sequences:

ATGAAGCCAGC
TCTAACGCTCG
GATTCCAACGT
TAACGCTCGGTAGCTCTGGC

TTCCAACGTCTAA
AACGCTCGGTAGGTC
CGATGAACCCAGCT

CCAACGTCTAAC
CGTCTAACGC
ATTCCAACGTCTAAC

GTCTAACGCTCGGTAGGTC
TGAAGCCAGCTCG
TAAGTCTGGCAGG
TCTGGCAGGGAG

ACGATGAAGCCAGCTCG
CGTCTCACGC
GACCATGAAGCCAGCTCGG
TCTGGCAGGT

CTGATCACGATTCCAACGT
CTGAACACGATTCCA
TTCCAACGTCTAGCGCTTGG
GCTCGGCTGAACACG

sequencing "read"

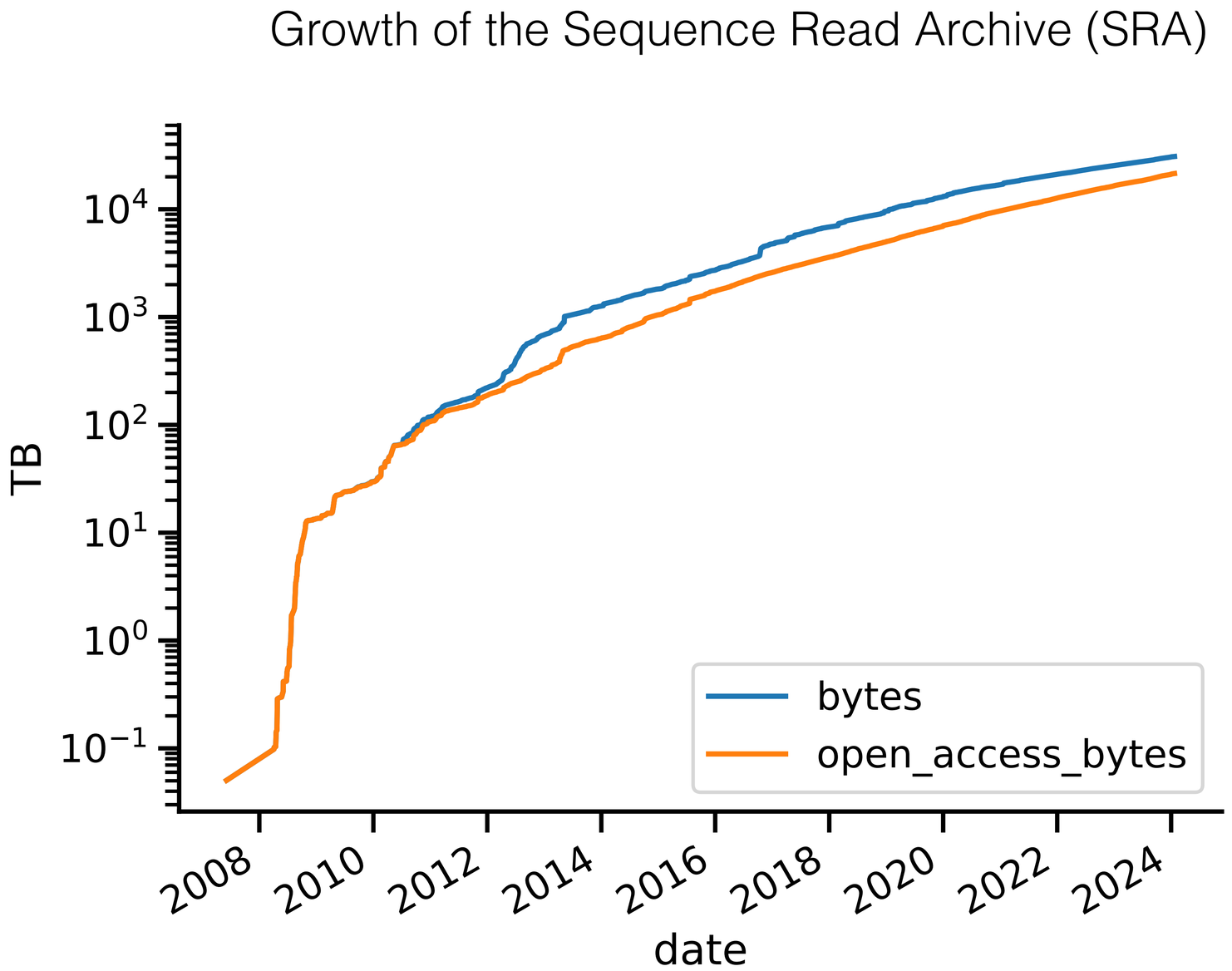
AAGCCAGCTCGGCTGAACA
GCTCGGCTGAACACTATT
TAGGTCTGGCA

TAACGCTCGGTAGGTCTGGC
TGTACACGATTCCGA
CGGCTGAACACGATTC
ACGATTCCAACGTCTAACG
CTCGGAAGGTCTGGCAGG

How we get our data (FASTA & FASTQ formats)

How we get our data (FASTA & FASTQ formats)

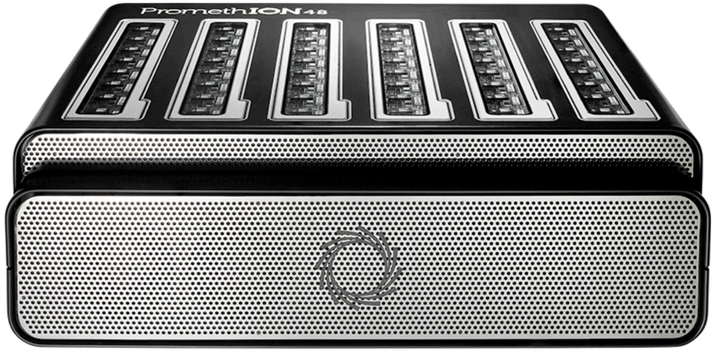
despite these limitations, scientists have used sequencing at a breakneck pace



data from:

Short Reads -> Long Reads

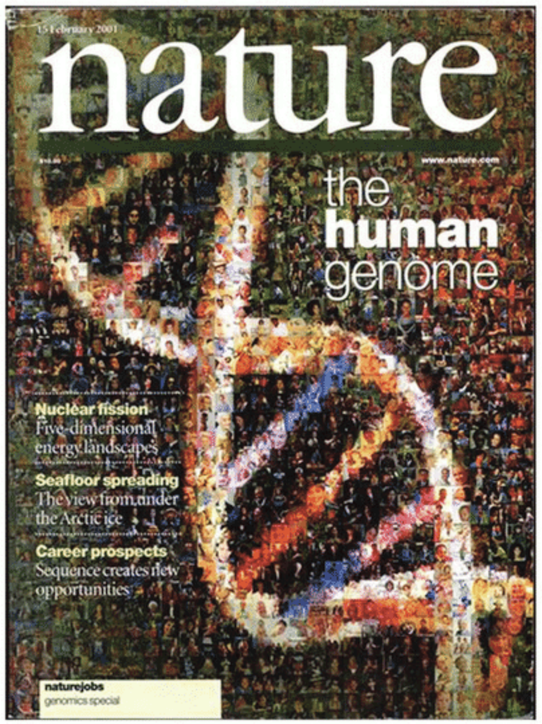
A lot of our focus will be on short-read technologies, but recent improvements in long-read technologies have been transformative:

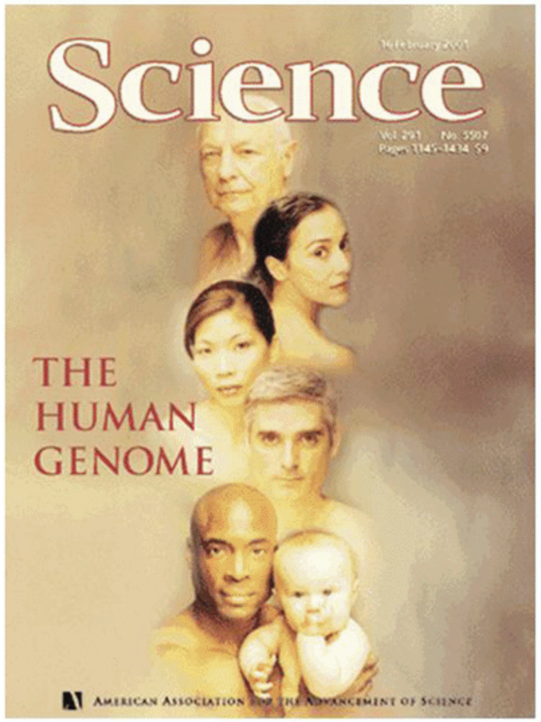


- Much longer reads (10-25kb for PacBio HiFi, up to ~1MB for ONT)
- Many fewer independent samples (long reads, but fewer of them)
- ONT error rate higher than “short reads” 1-5%, PacBio can match Illumina error rates but is *very* expensive

Actually Completing the Human Genome

2001

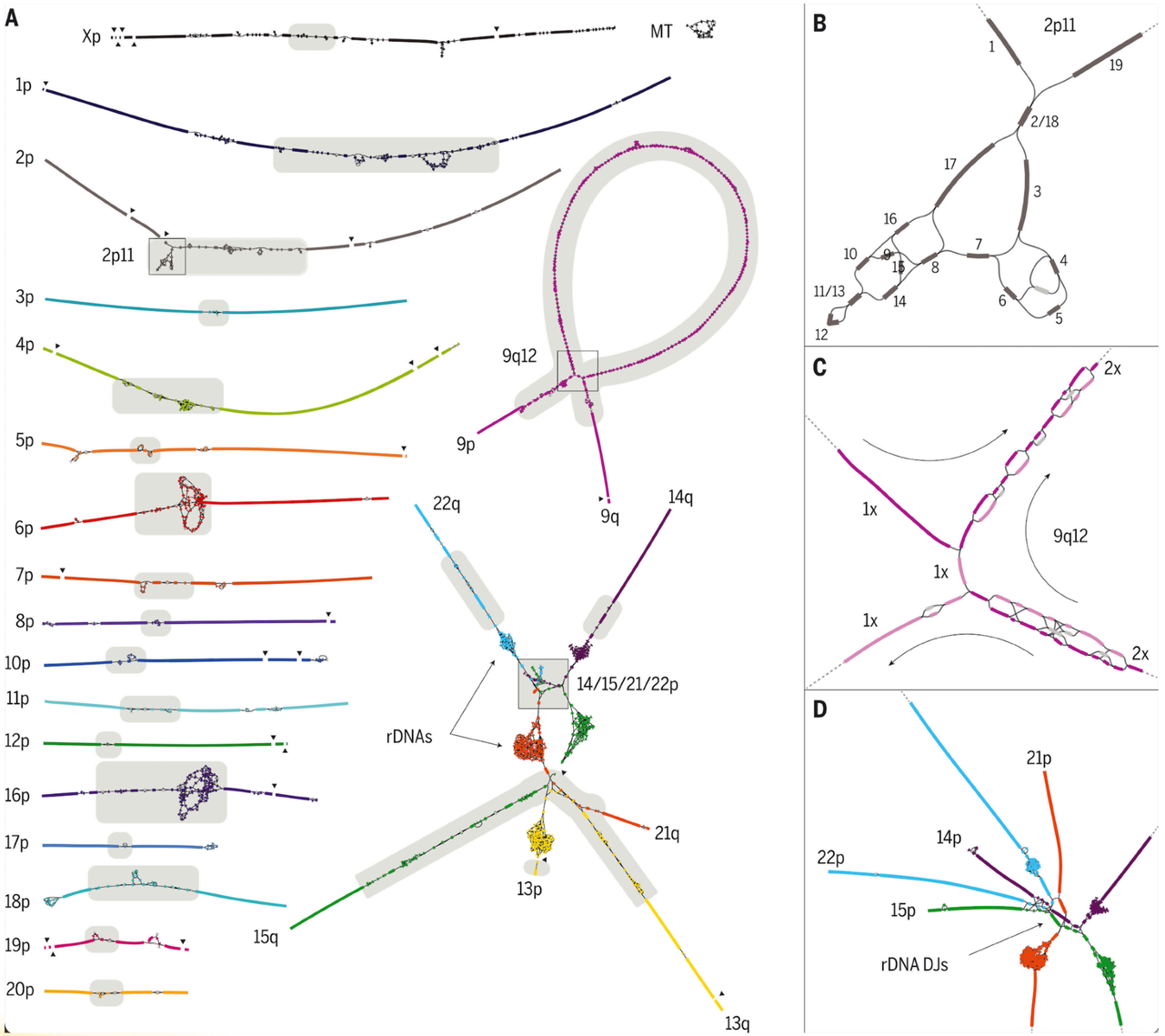




algorithmic
&
biotech
progress

2022

Assembly of the human genome



Nurk, Sergey, et al. "The complete sequence of a human genome." *Science* 376.6588 (2022): 44-53.

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)

Establishing a Basic Lexicon

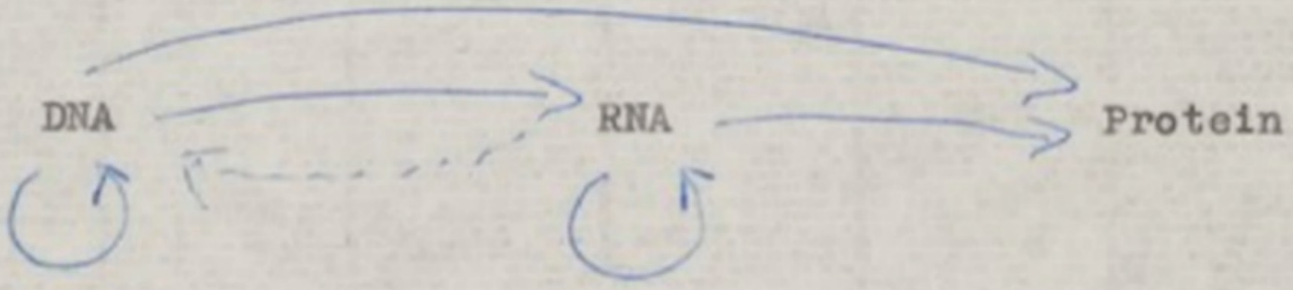
This course will focus on algorithms and data structures (with a little bit of probability & statistics), but the ***problems*** we will explore derive directly from biological questions.

In order to motivate our Computer Science, we will need a basic understanding of the Molecular Biology in which the problems are phrased.

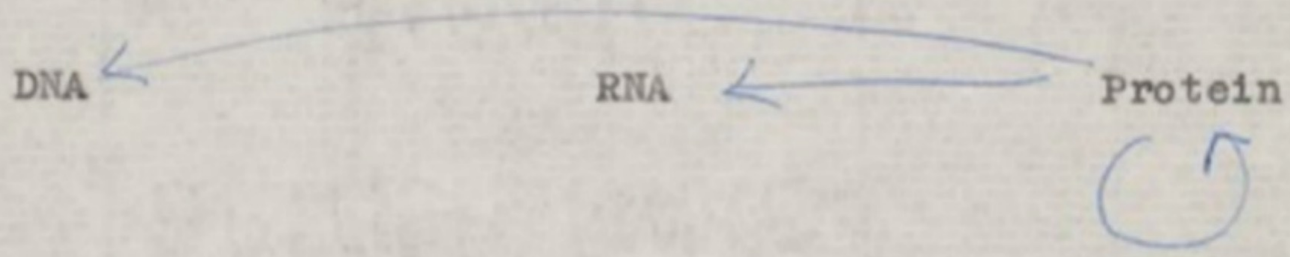
“Flow” of information in the cell

The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have

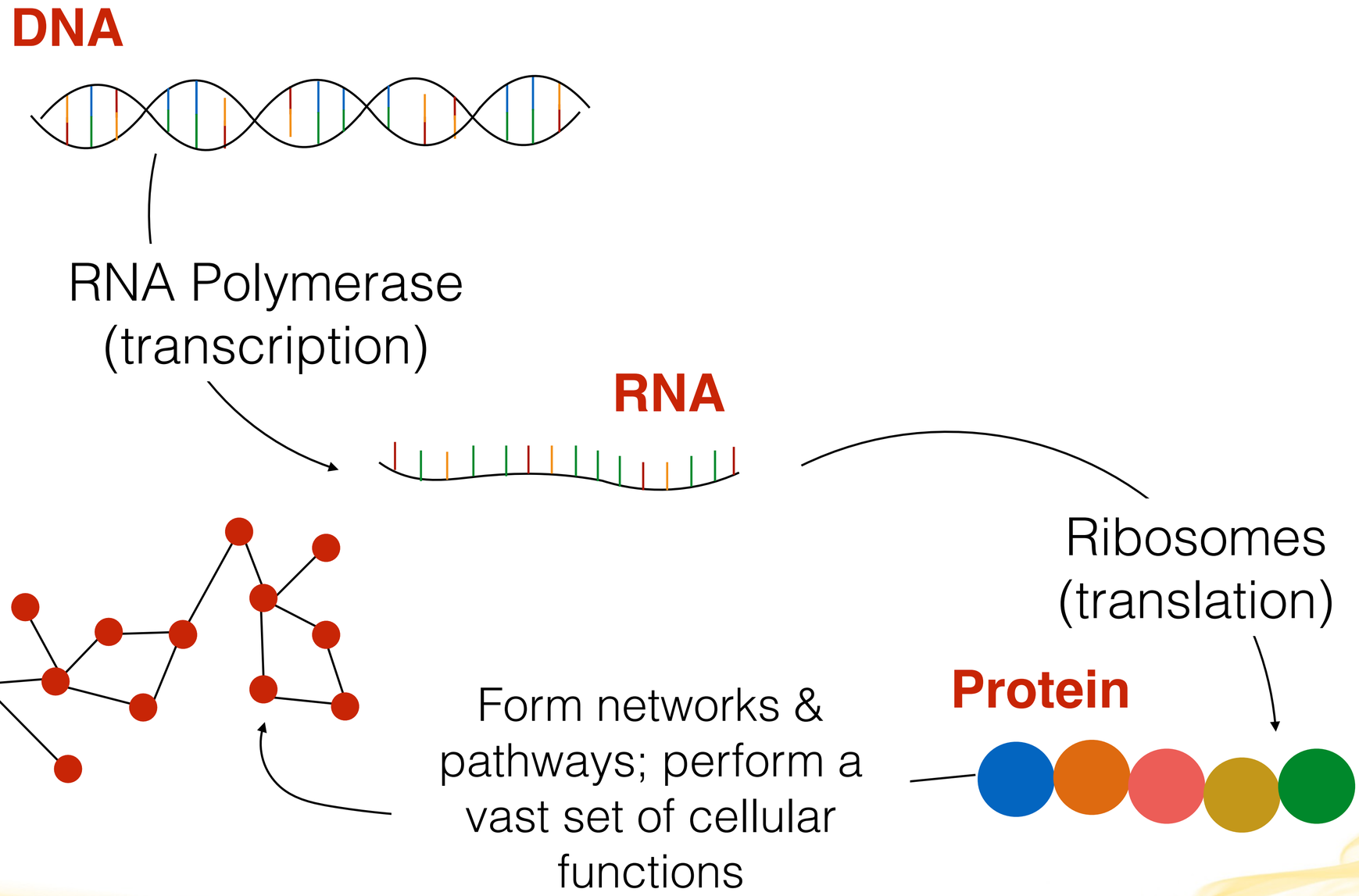


but never



where the arrows show the transfer of information.

“Flow” of information in the cell



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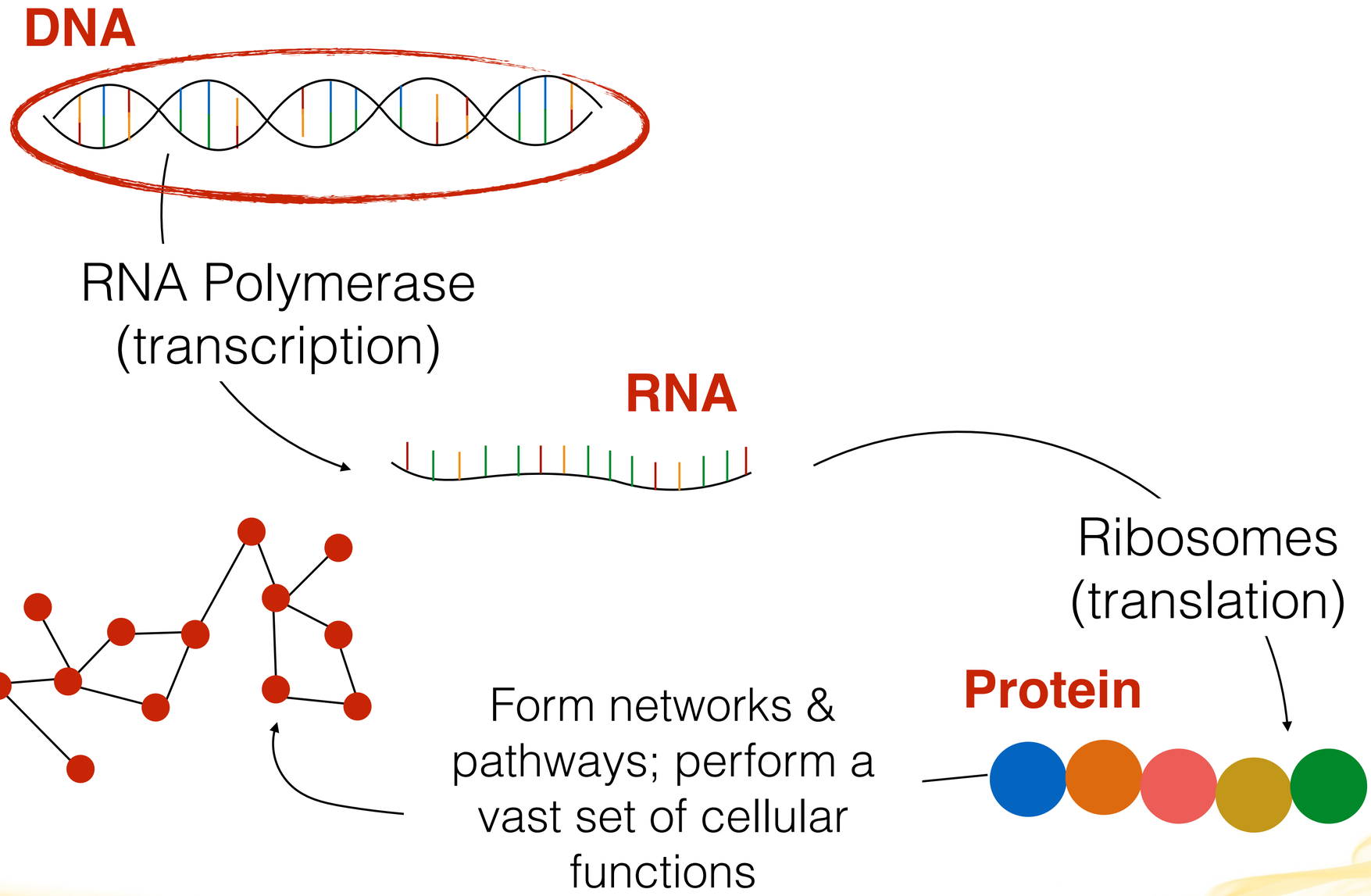
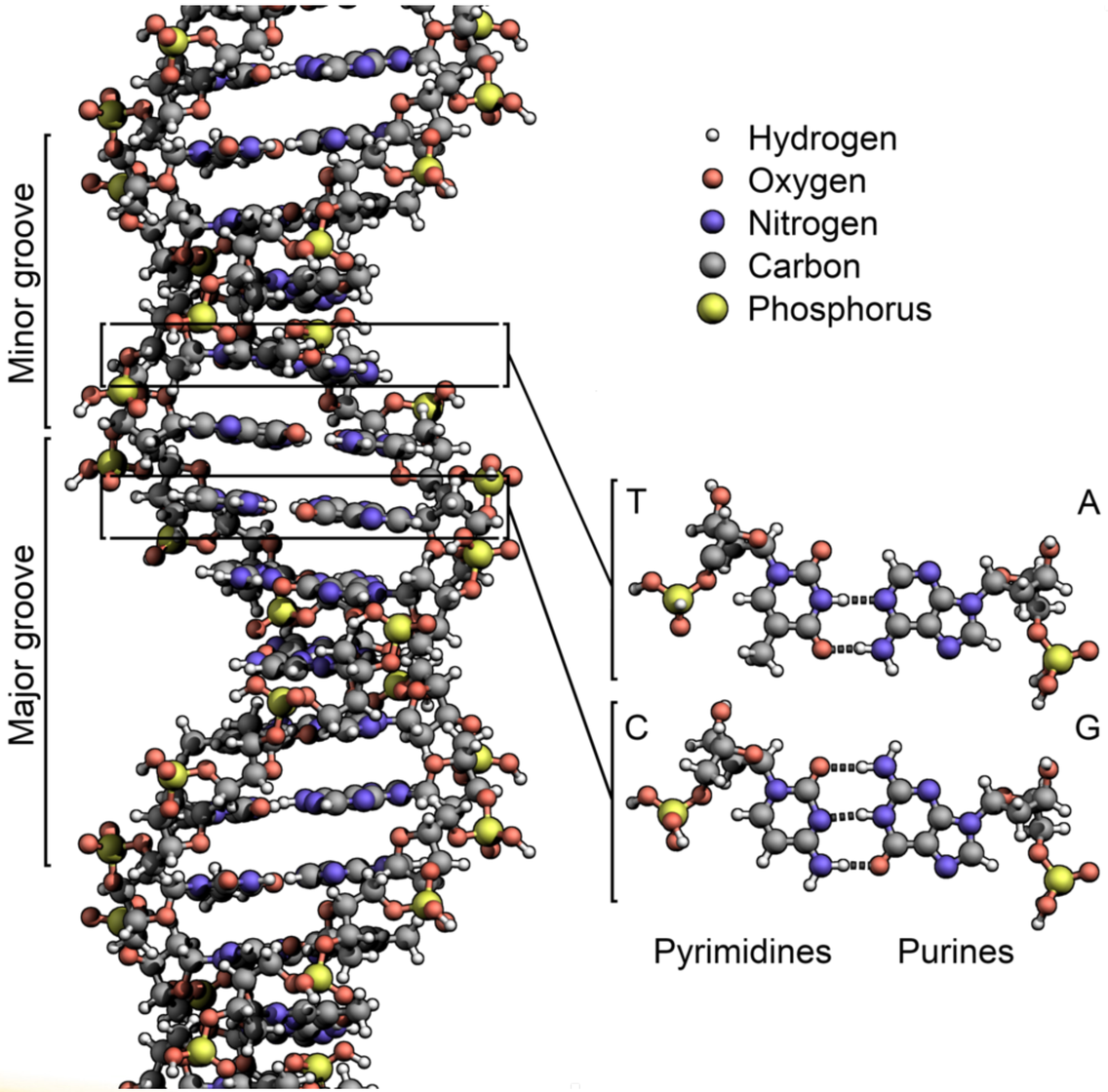
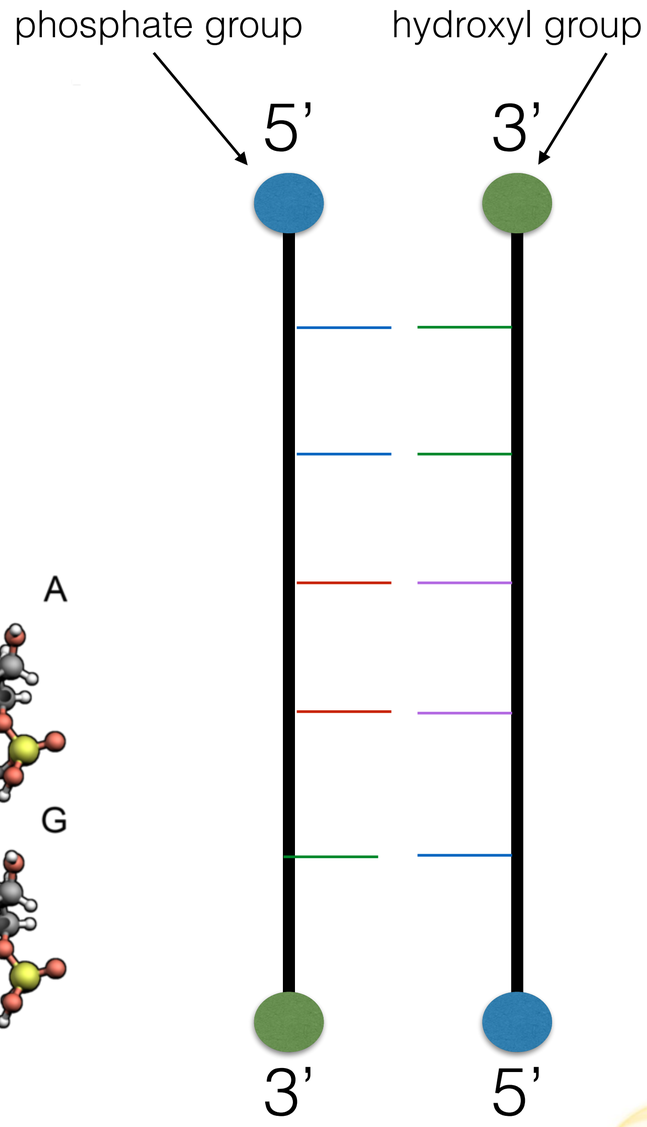


DNA (the genome)





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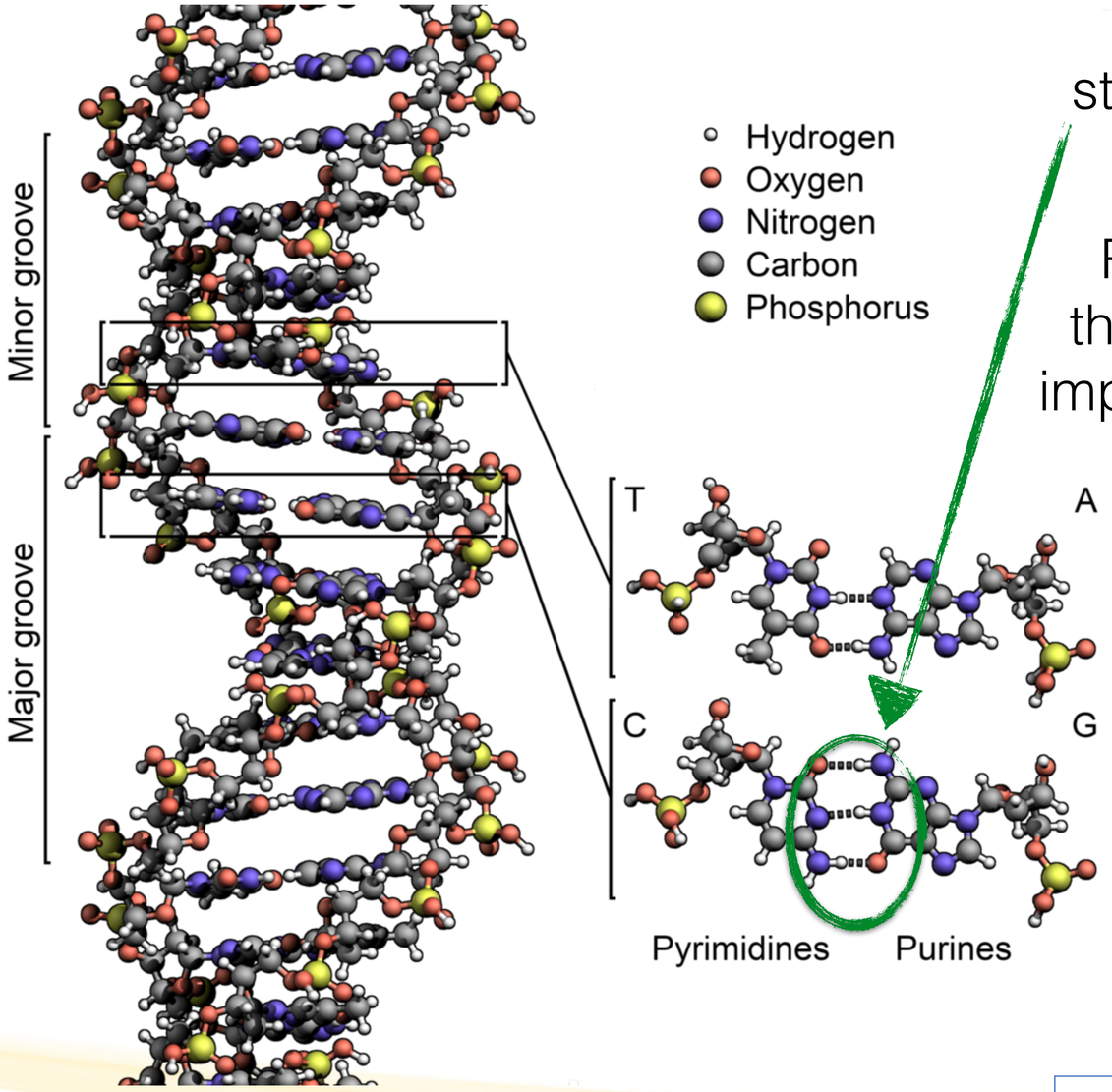
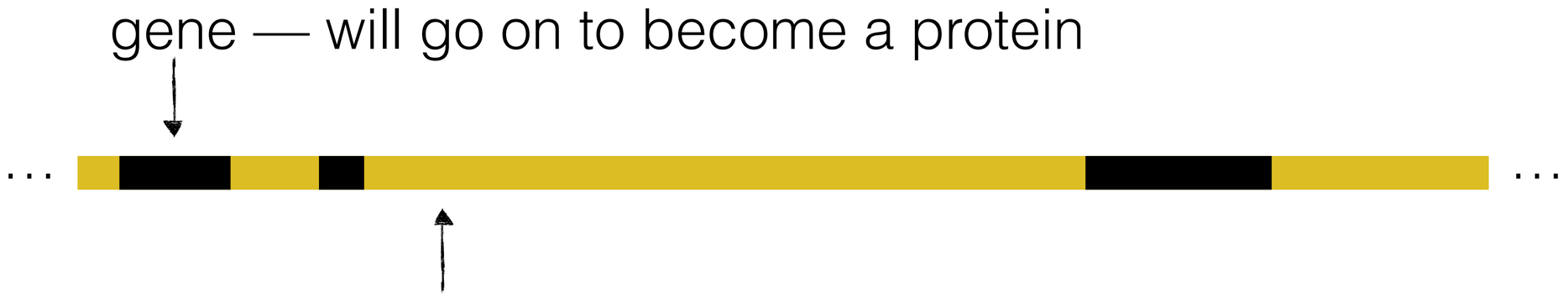


G-C pairing generally stronger than A-T pairing

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

DNA (the genome)



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

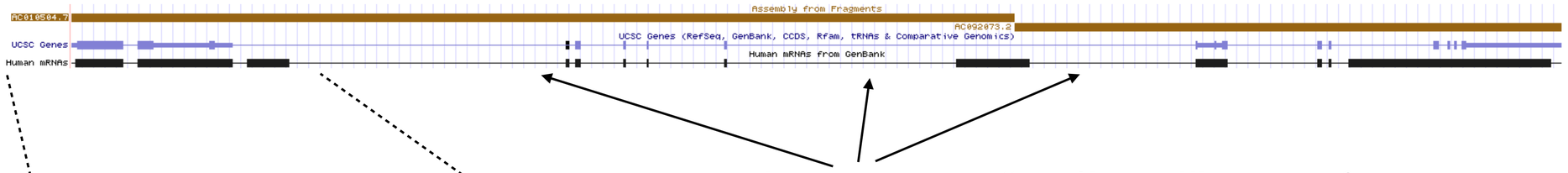
In typical bacterial genome, only small fraction — ~2% — of DNA is “non-coding”

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

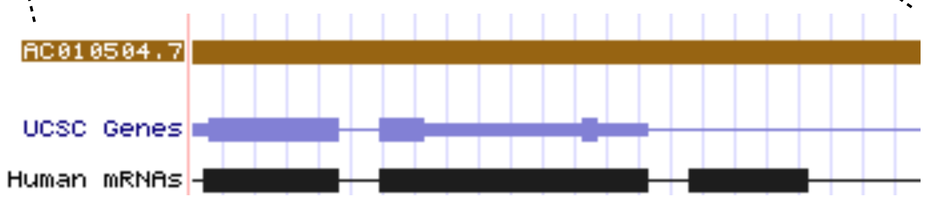
DNA (the genome)

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

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

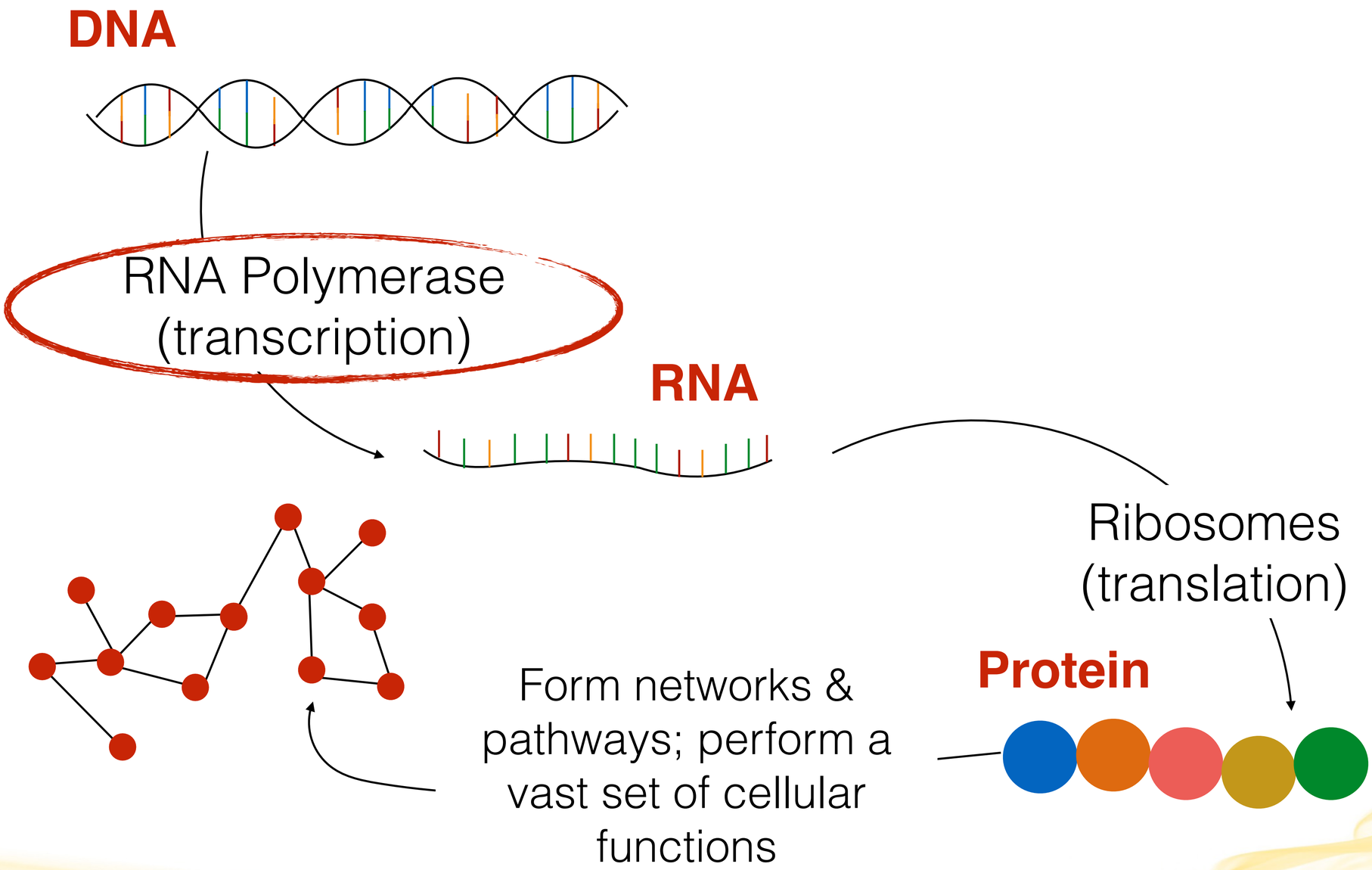


introns — “spliced” out of mature RNA



exons — appear in the *mature* RNA transcript

“Flow” of information in the cell



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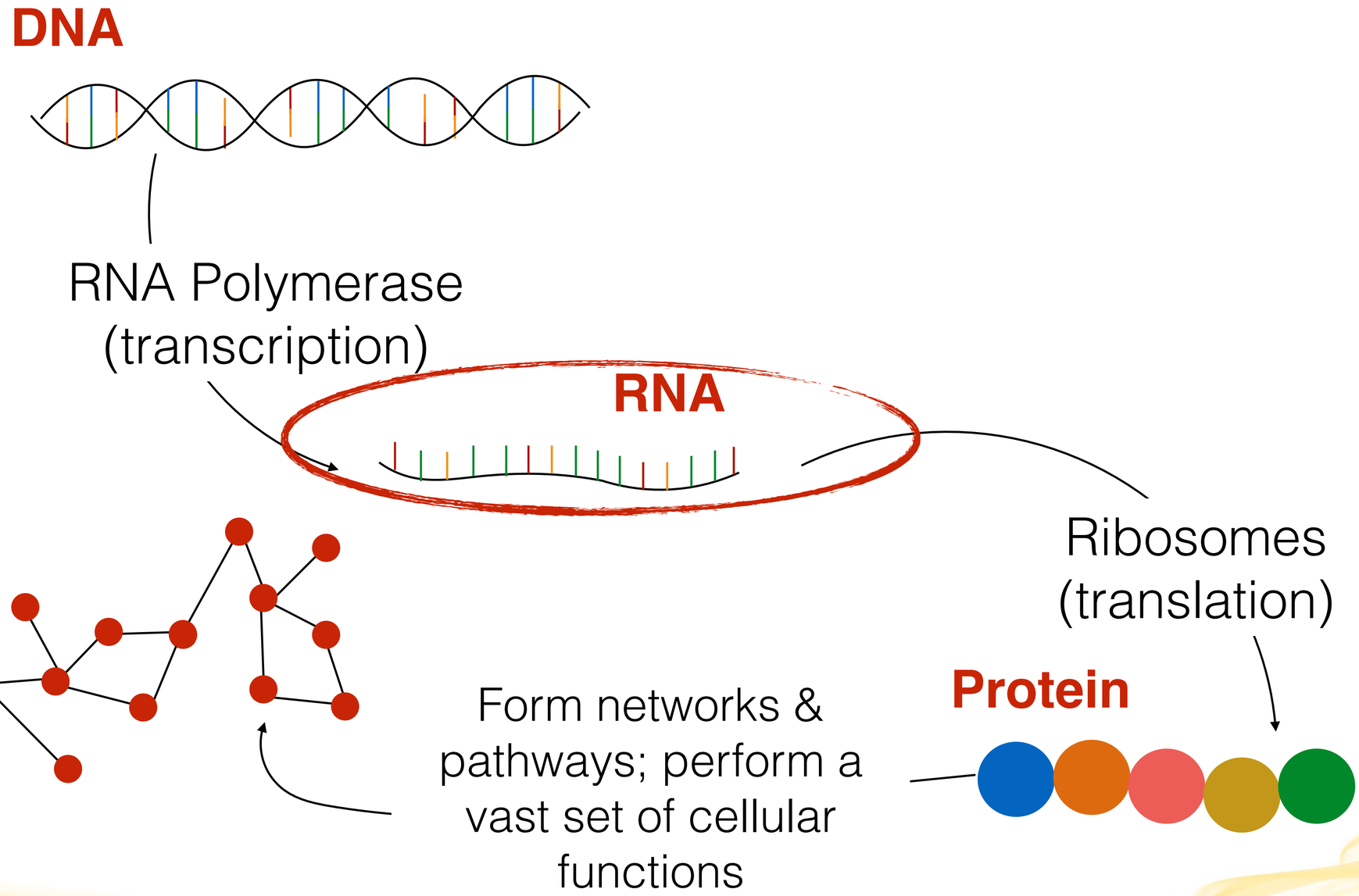
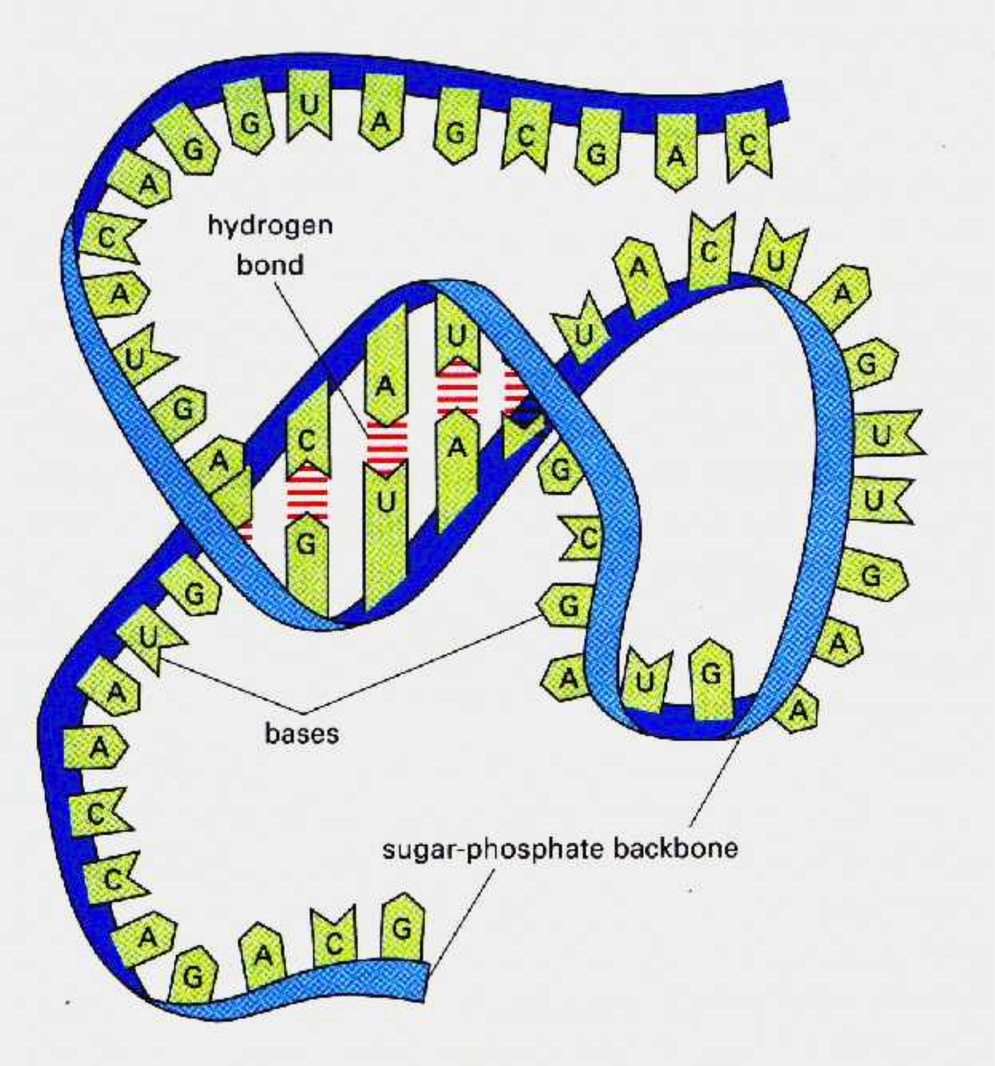


RNA



http://tigger.uic.edu/classes/phys/phys461/phys450/ANJUM04/RNA_sstrand.jpg

Less regular structure than DNA

Generally a single-stranded molecule

Secondary & tertiary structure can affect function

Act as transcripts for protein, but <u>also perform important functions themselves</u>

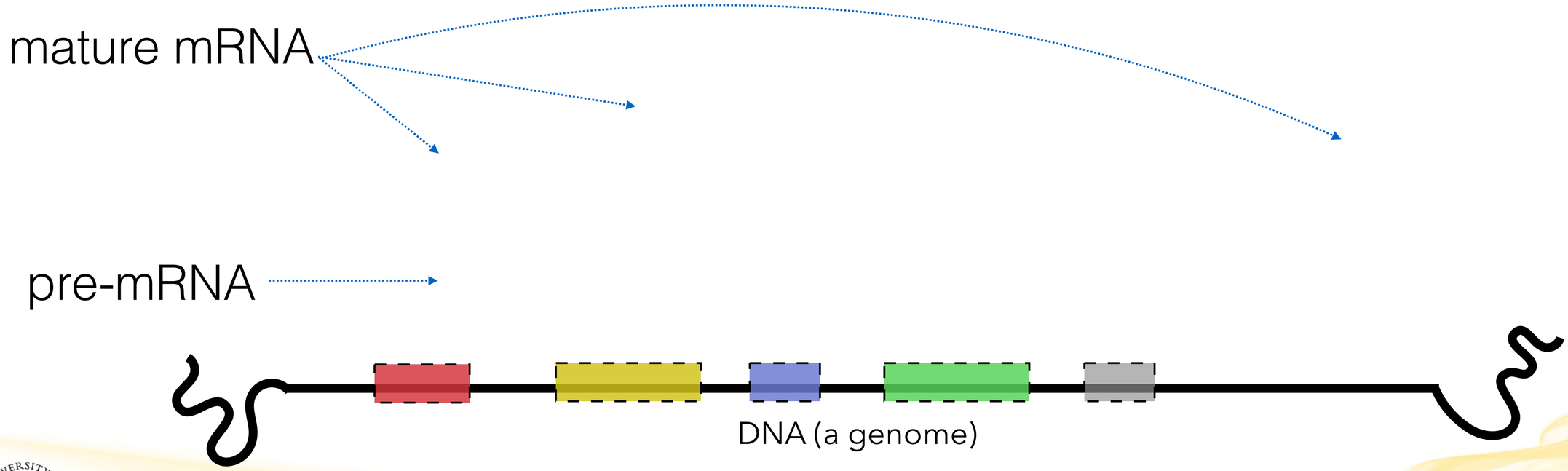
Same “alphabet” as DNA, except thymine replaced by uracil

RNA splicing

DNA transcribed into pre-mRNA

Some “processing” occurs **capping** & **polyadenylation**

Introns removed from pre-mRNA resulting in mature mRNA



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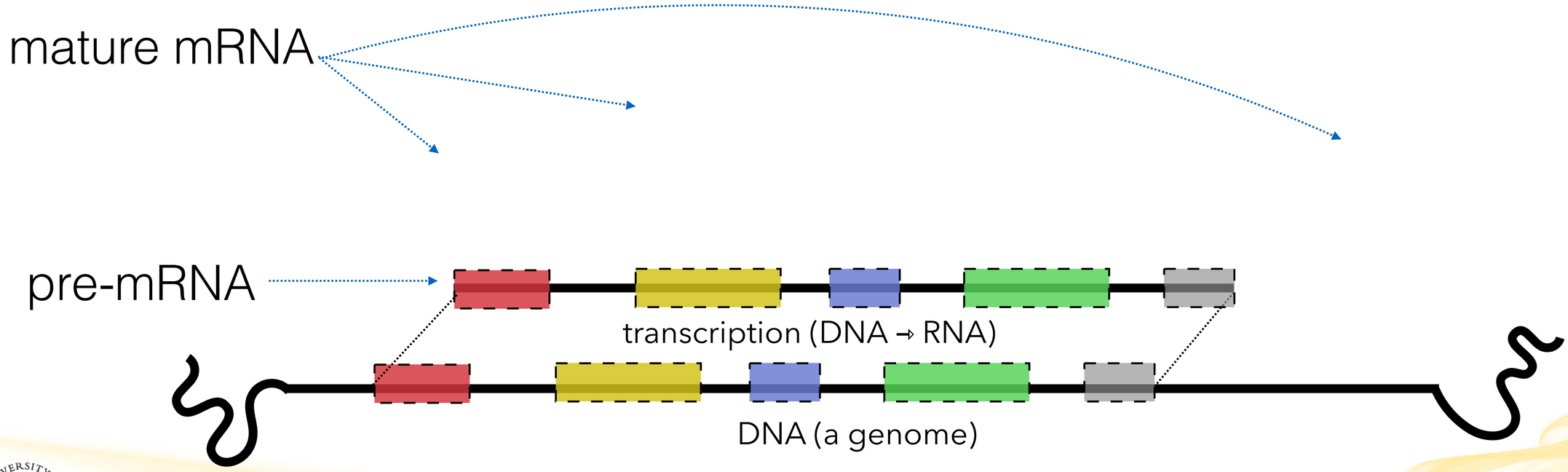

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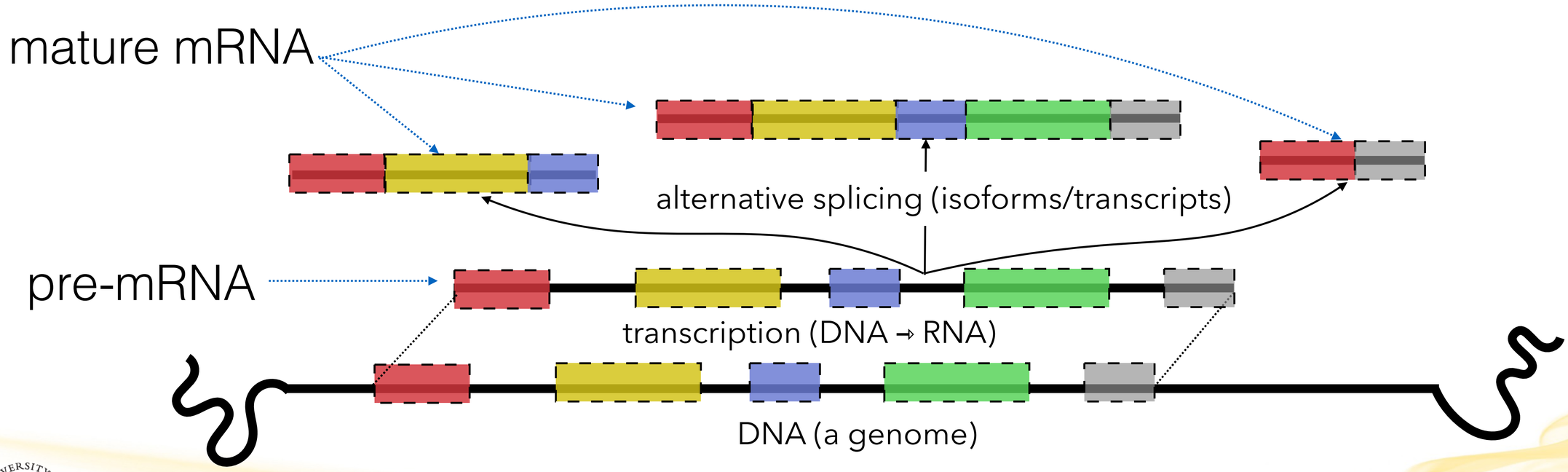
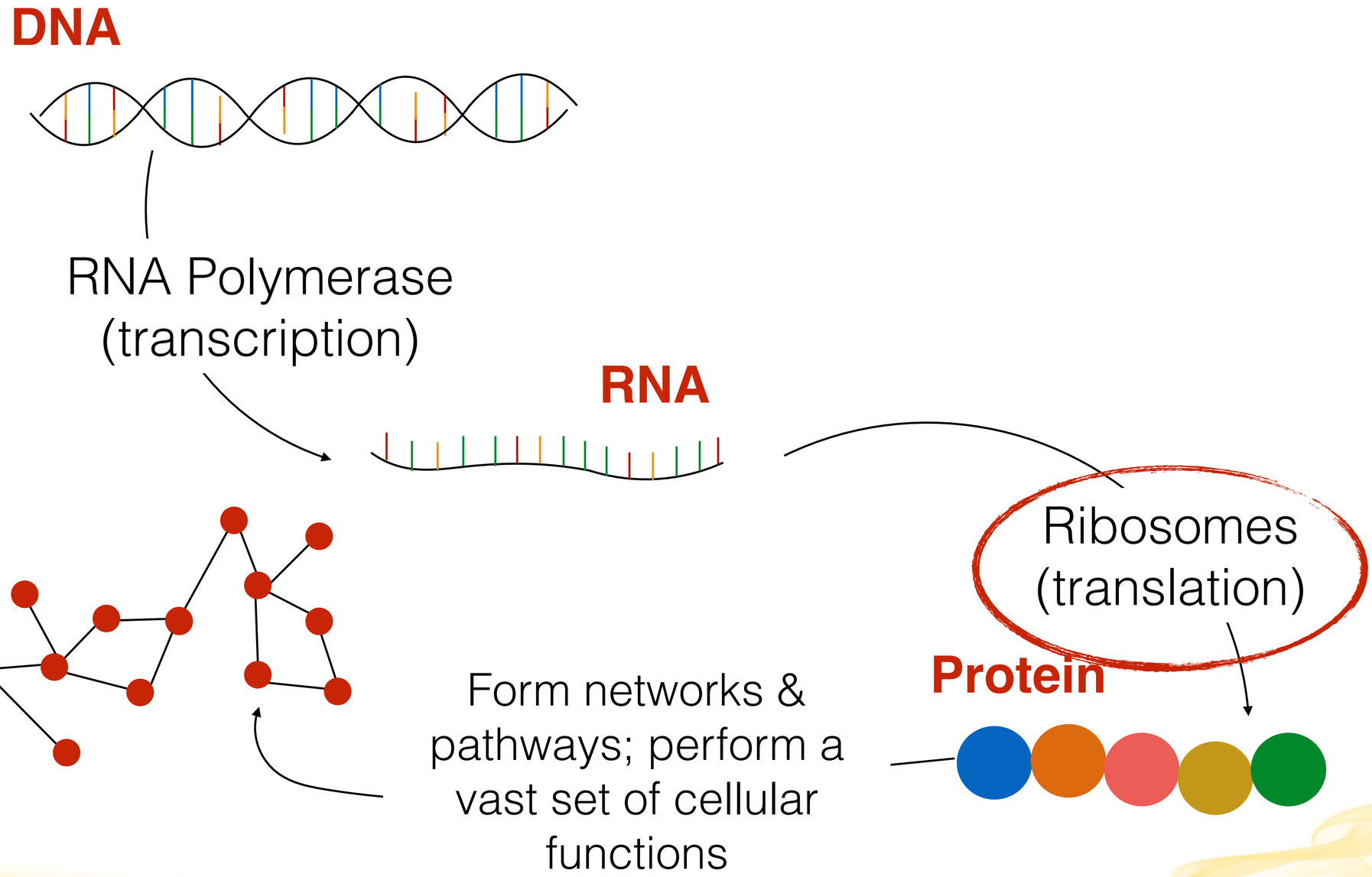


“Flow” of information in the cell



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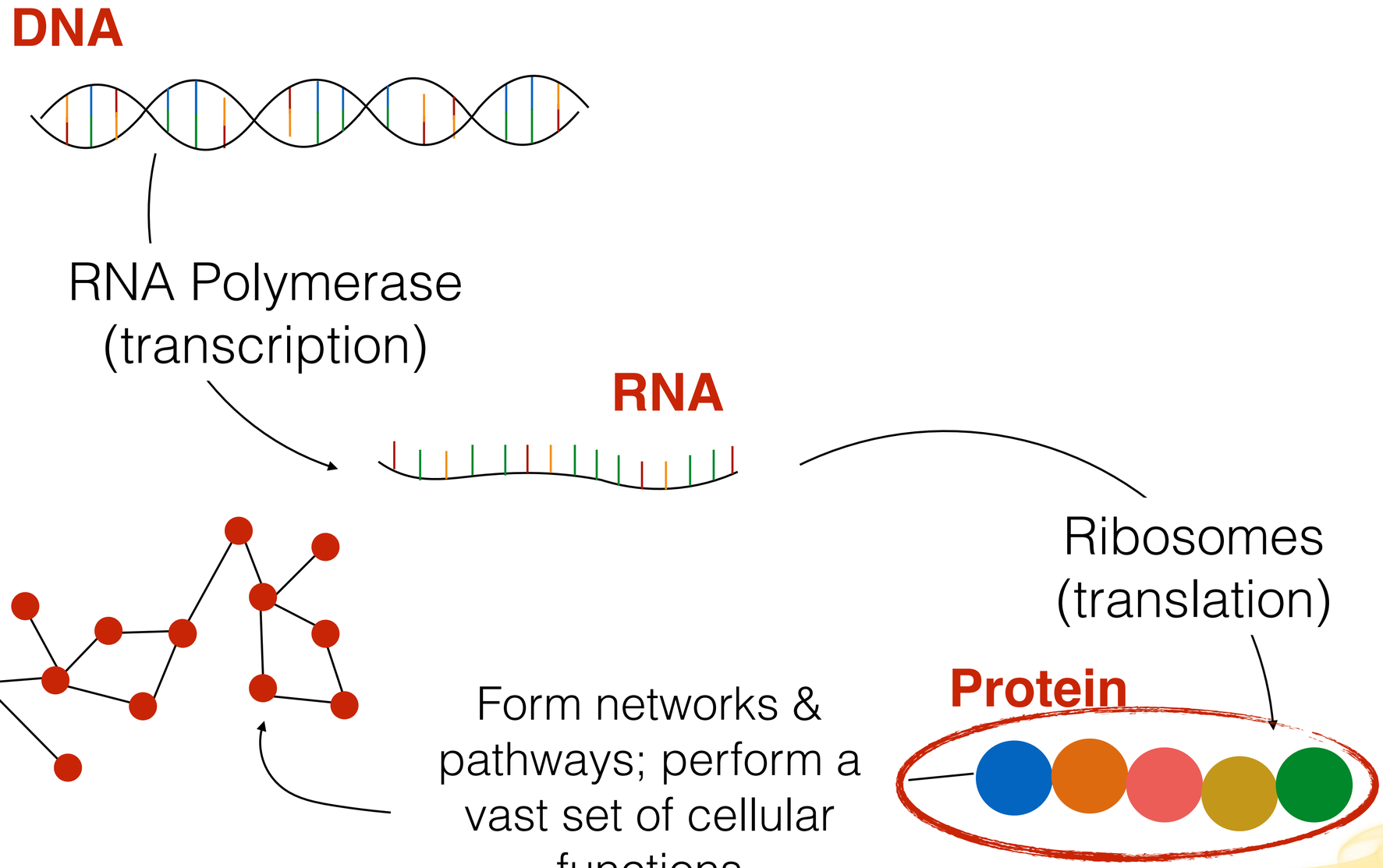
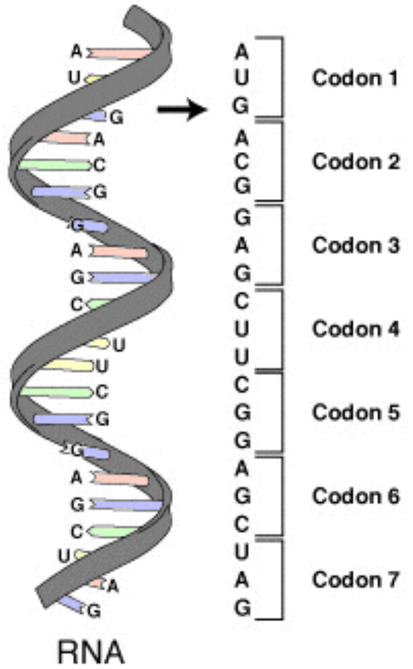


Protein



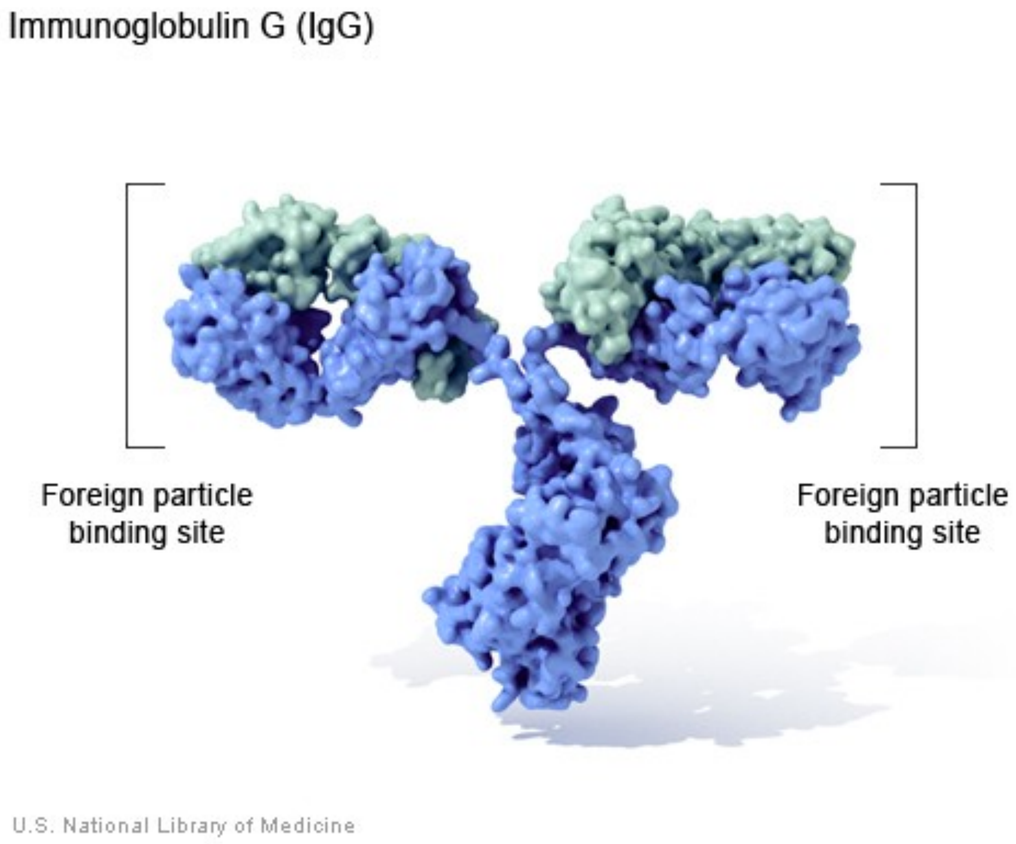
Triplets of mRNA bases (codons) correspond to specific amino acids

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



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

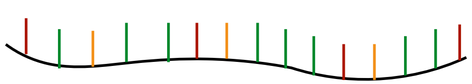
The shape or *conformation* of a protein is intimately tied to its function. Protein shape, therefore, is strongly conserved through evolution — even more so than sequence. A protein can undergo sequence mutations, but fold into the same or a similar shape and still perform the same function.

“Flow” of information in the cell

DNA

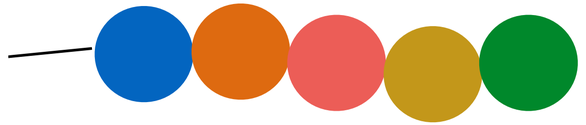
RNA Polymerase
(transcription)

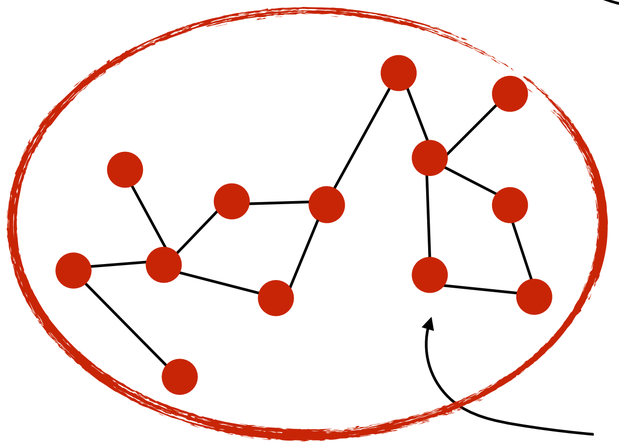
RNA



Ribosomes
(translation)

Protein





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

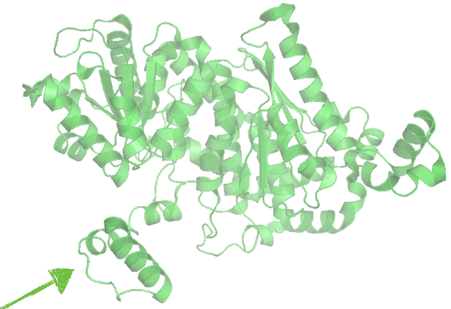
One way in which this “central dogma” is violated … retroviruses

Glycolysis Pathway

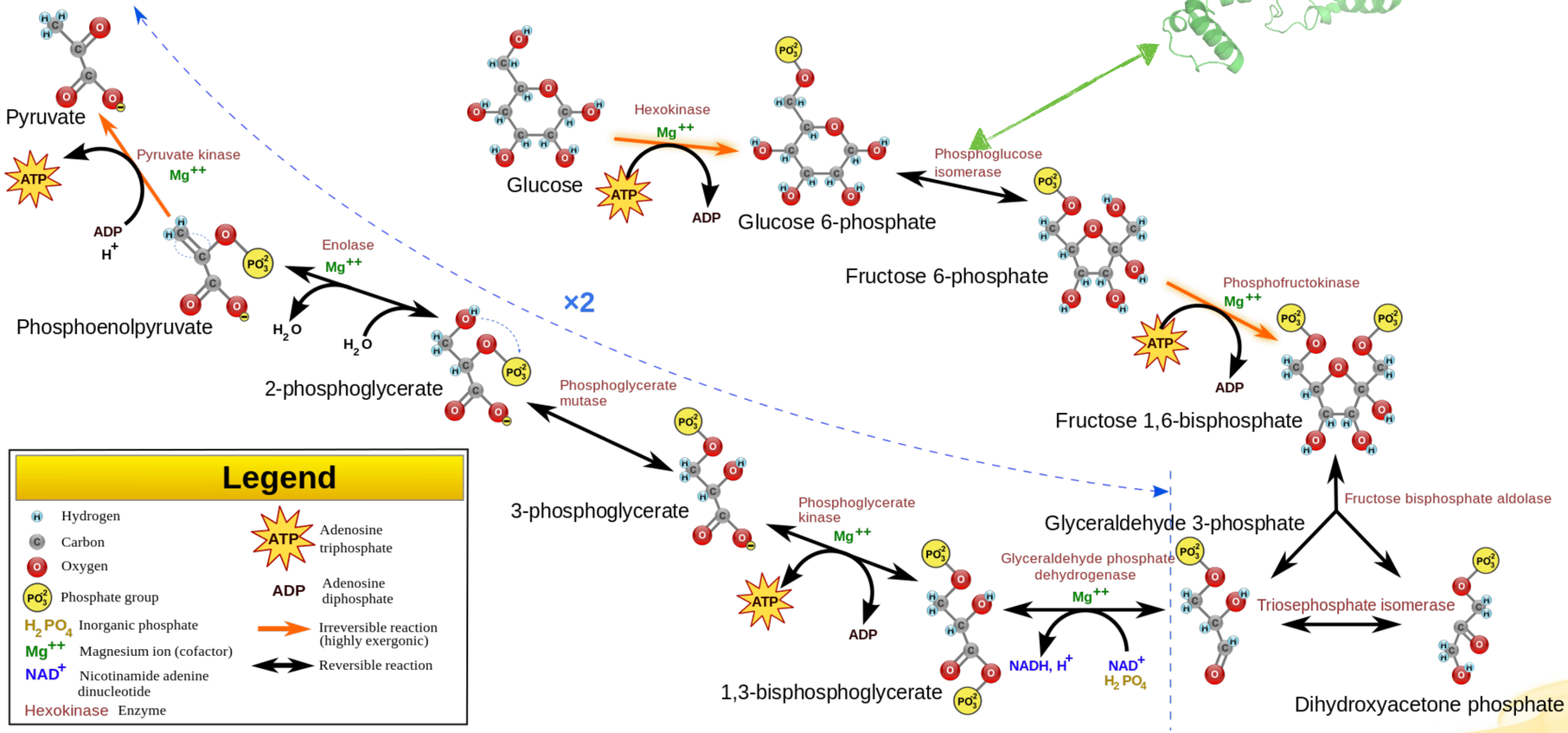
Converts glucose → pyruvate

Generates ATP ("energy currency" of the cell)

phosphoglucose isomerase



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



Some Interesting Facts

Organism	Genome size	# of genes (protein coding)
ϕX174 (*E. coli* virus)	~5kb	11
E. coli K-12	~4.6Mb	~4,300
Fruit Fly	~122Mb	~17,000
Human	~3.05Gb	~21,000
Mouse	~2.8Gb	~23,000
P. abies (a spruce tree)	~19.6Gb	~28,000

No strong link between genome size & phenotypic complexity

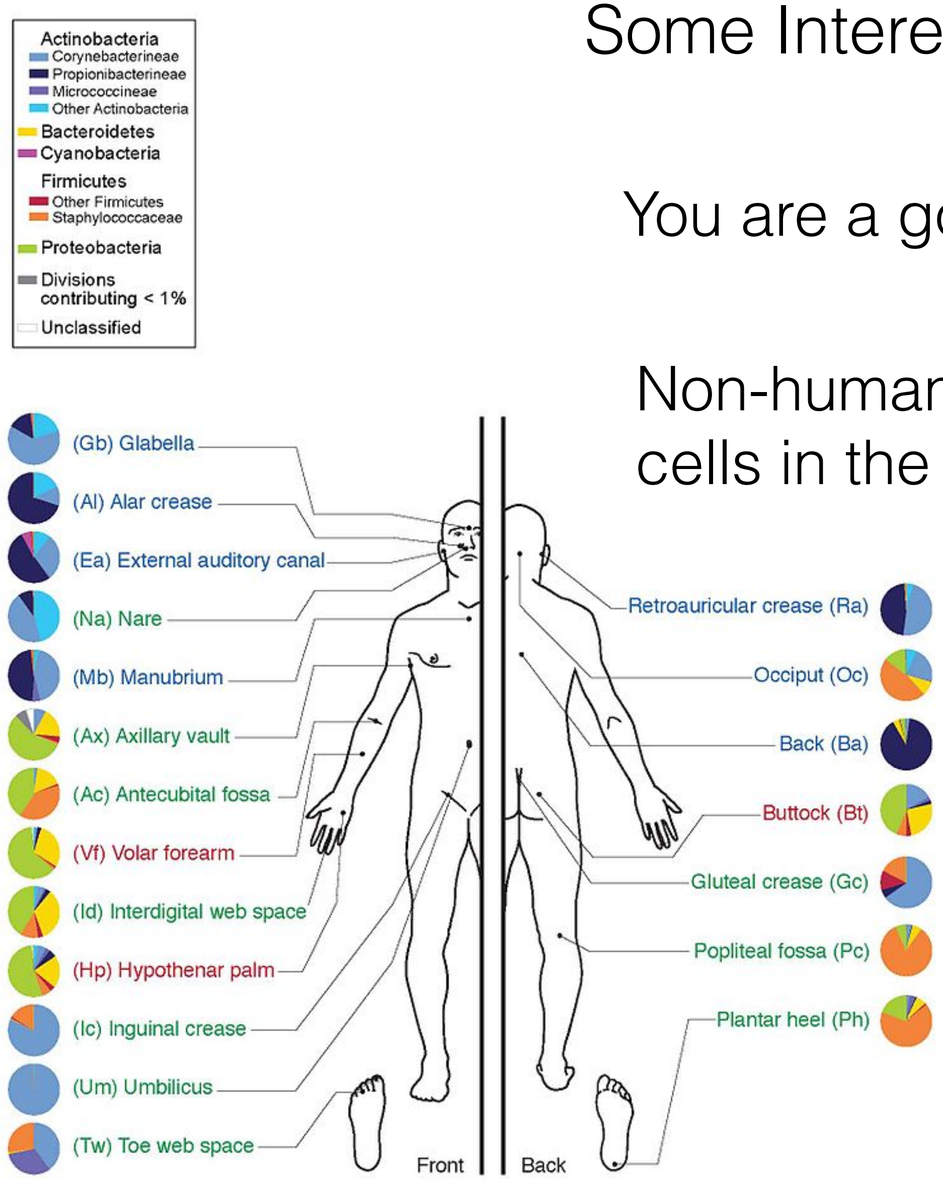
Plants can have **huge** genomes (adapt to environment while stationary!)

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/G/GenomeSizes.html

Some Interesting Facts

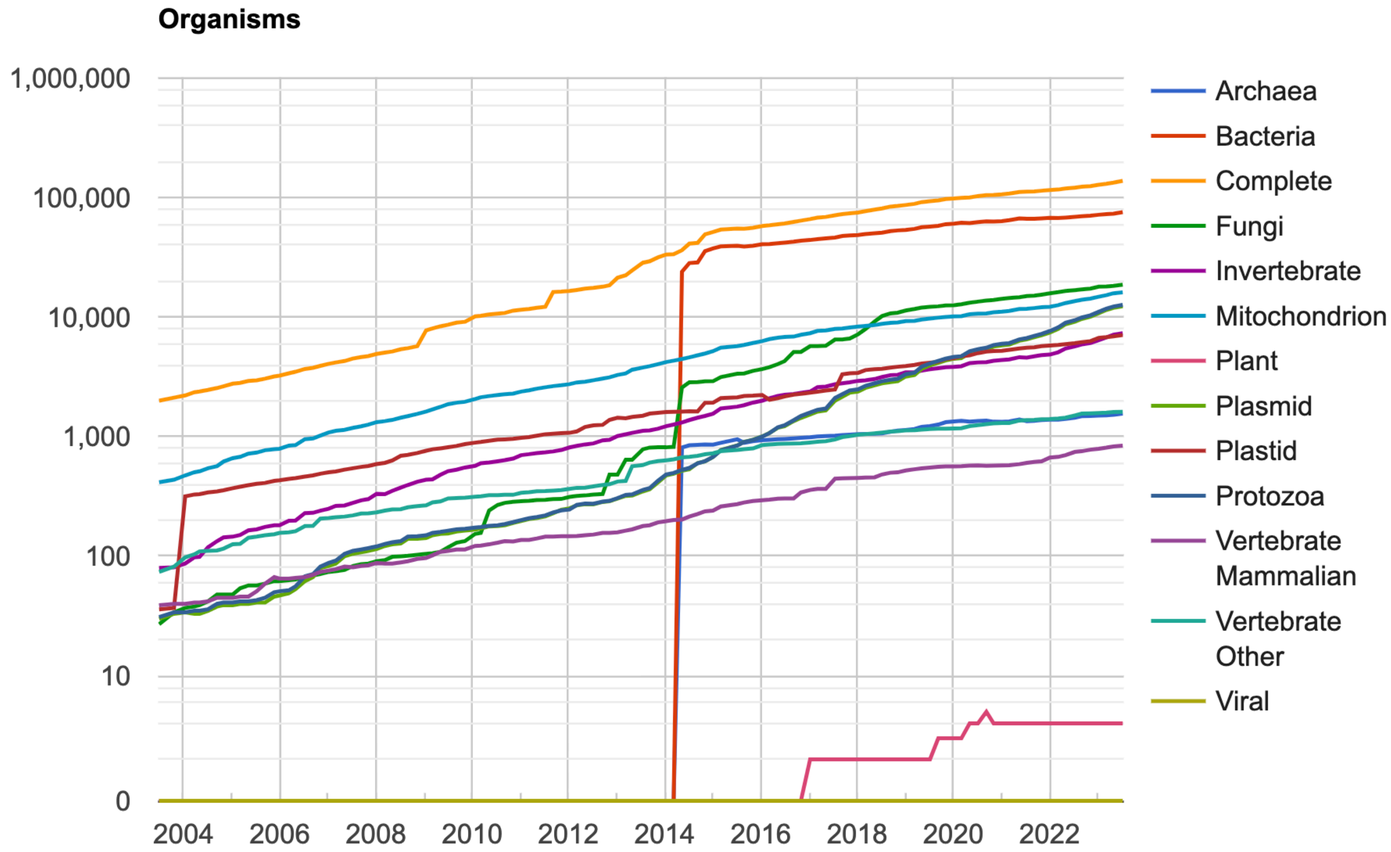
You are a good part non-human cells (e.g. bacteria)

Non-human cells equal or outnumber human cells in the human body



en.wikipedia.org : public domain

This population of organisms is called the microbiome



. . . 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.