
# Bioinformatics
# BS (CS – 460)
# Lecture 01

Dr. Hafeez Ur Rehman

# Course Outline

- Introduction to Bioinformatics
- Molecular Biology
- Biological Databases
- **Sequence Storage**, Retrieval and Analysis
- Sequence Similarity and Homology
- Creating alignments, Local and Global Alignment
- Pair wise and Multiple Sequence Alignments

# Course Outline (contd…)

- Phylogenetic Analysis
- Dot Matrix Plots
- Dynamic Programming Algorithms
- Word (k-tuple) methods
- Substitution Matrices PAM and BLOSUM
- Significance of scoring and the effect of gap penalties etc.
- Implementation of Research Papers plus Research Work

# Consultation and Recommended Book

- Dr. Hafeez Ur Rehman, hafeez.urrehman@nu.edu.pk (please send an email to make an appointment - Room 31)
- Recommended Books:

1. **Bioinformatics Computing** by Bryan Bergeron, Harvard Medical School and MIT Massachusetts, USA.
2. **Molecular Biology of the Cell, 5th Edition:** Bruce Albert, Alexander Johnson and others..published by Garland Science.
3. **Introduction to Bioinformatics** by T K Attwood, D J Parry-Smith, Samiron Phukan, Pearson Education (Latest edition)

# What is Bioinformatics?

- Bioinformatics is an interdisciplinary scientific field that develops **methods** and **software tools** for **storing, retrieving, organizing** and **analyzing biological data**.
- "The mathematical, statistical and computing methods that aim to solve biological problems using DNA and amino acid sequences and related information."

# DNA Sequencing

- **Bioinformatics** is **based on the fact** that **DNA sequencing** is cheap, and becoming easier and cheaper very quickly.
  - The Human Genome Project cost roughly $3 billion and took 12 years (1991-2003).
  - Sequencing James Watson's genome in 2007 cost $2 million and took 2 months
  - Today, you could get your genome sequenced for about $1,000 and it would take few days.

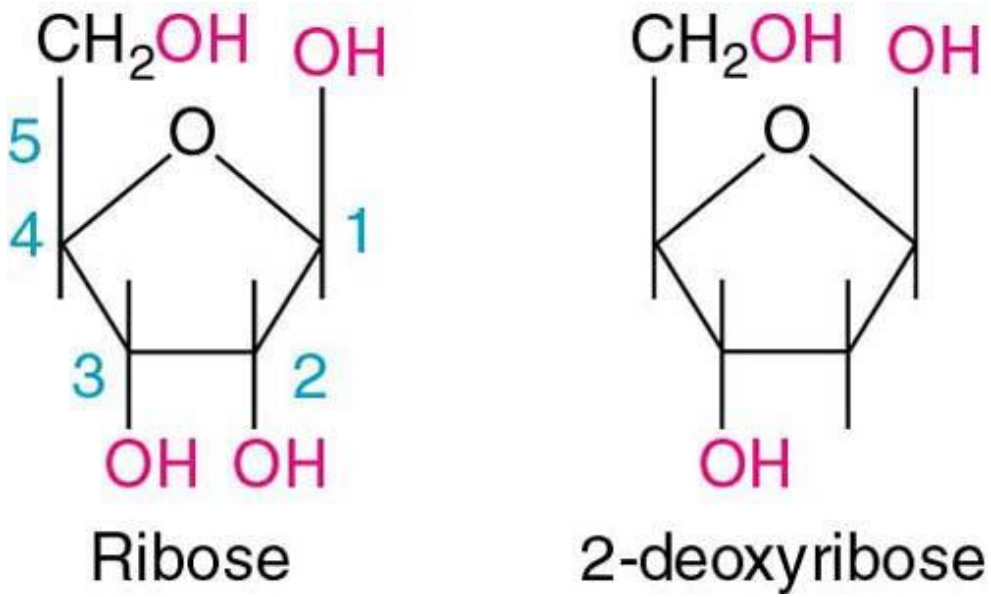
# DNA Structure

- **D**eoxyribo**N**ucleic **A**cid (DNA)
- **Blueprint** that carries **genetic information** from one generation to the next
- **Resides** in cell nucleus
- Double helix
- DNA consists of four nucleotides: Adenine, Cytosine, Guanine, Thymine (A, C, G, T)
- Base Pairs: A-T, C-G

**G A A T T C**
**C T T A A G**

# Background: What is DNA?

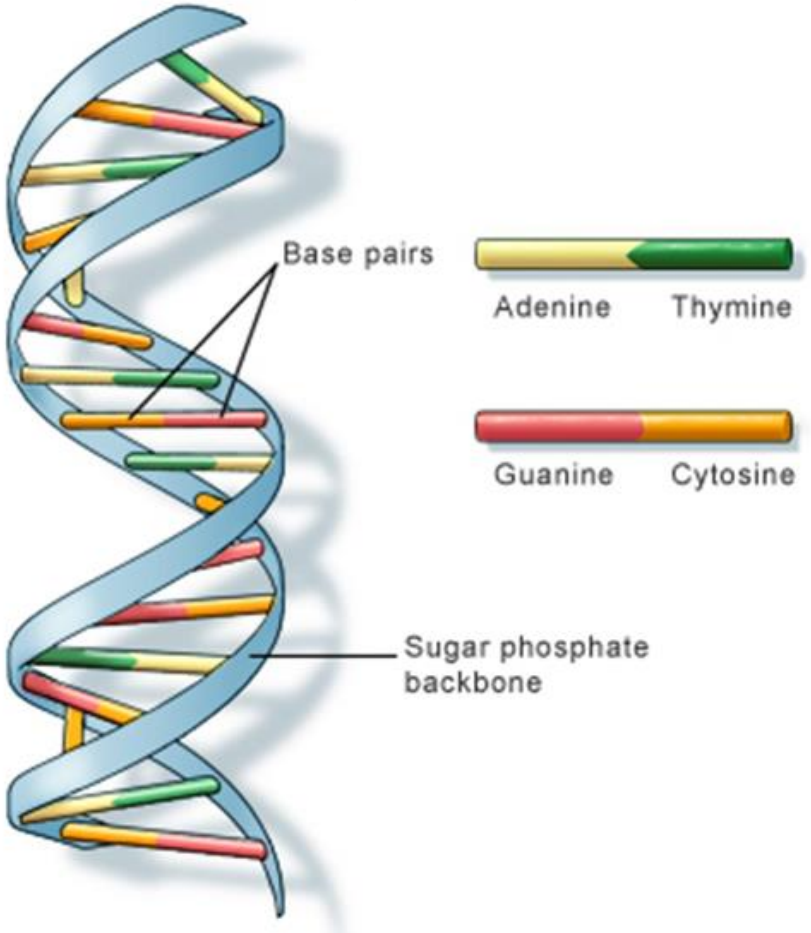
- 5 prime (beginning), 3 prime (end)



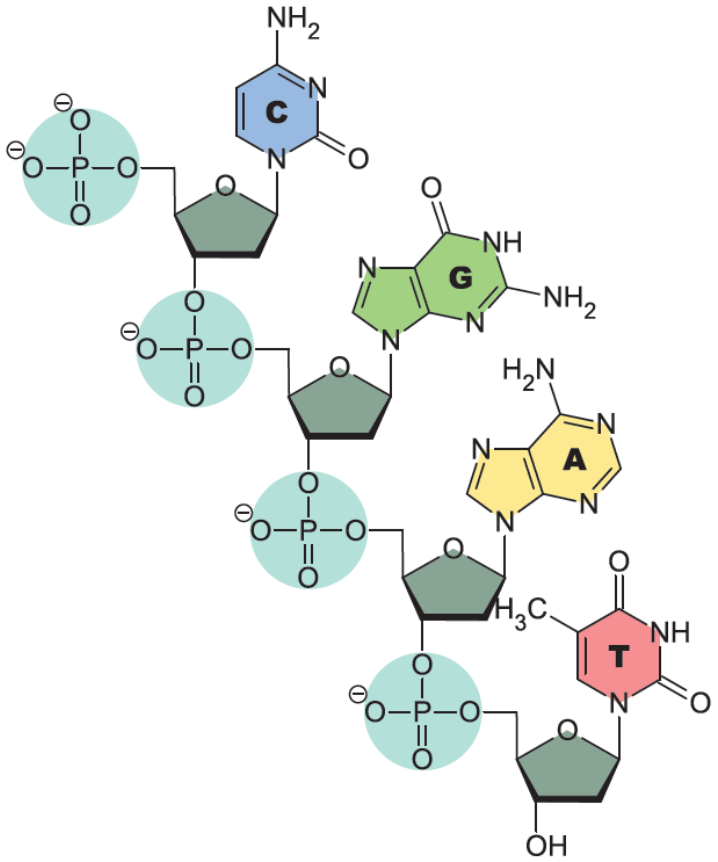

- Ordering of these pairs is a *sequence.*

# DNA Structure

## Physical



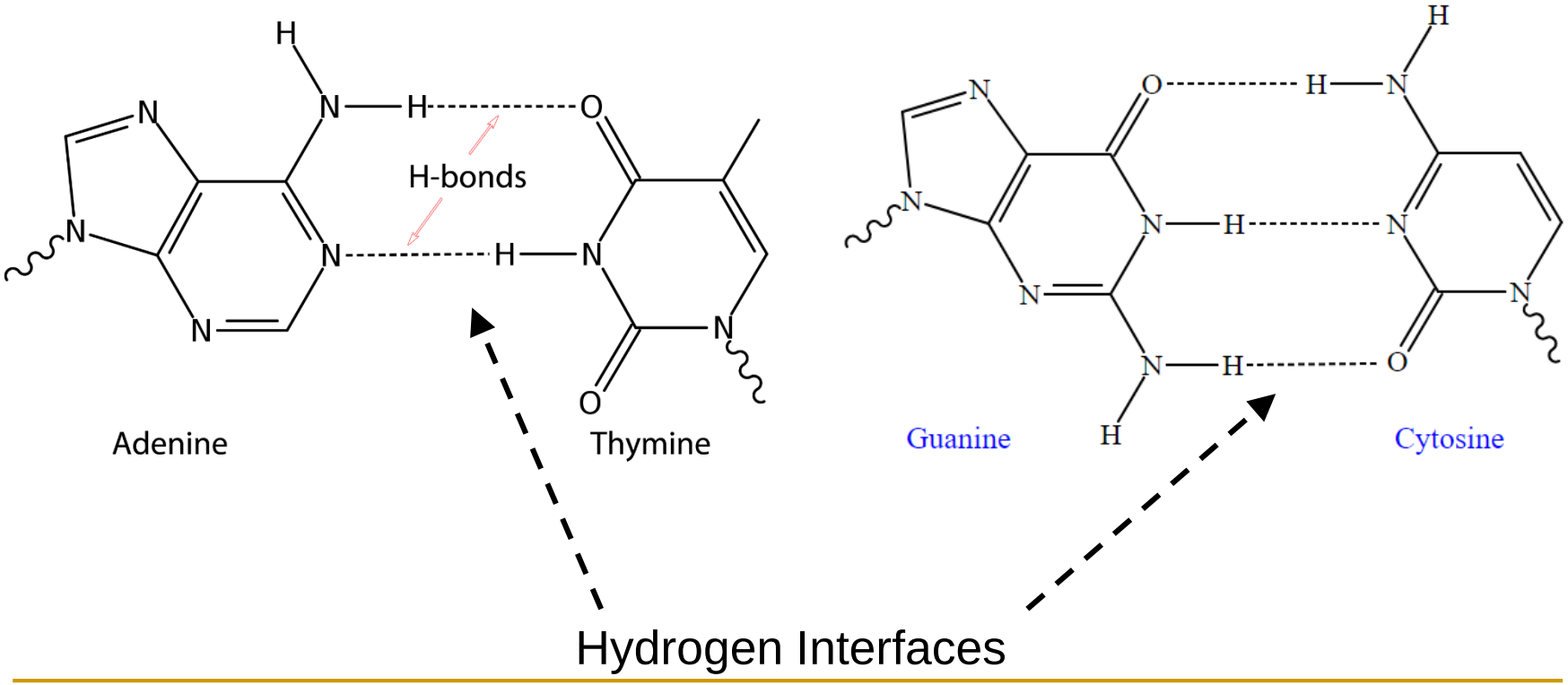

## Chemical



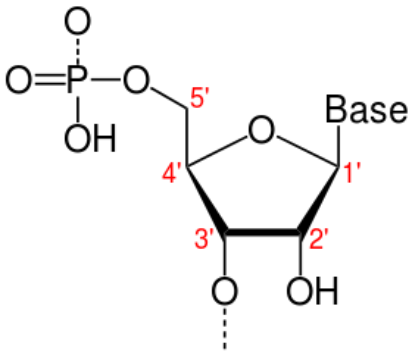
# Why specific base pairs bond?

## A to T bonding

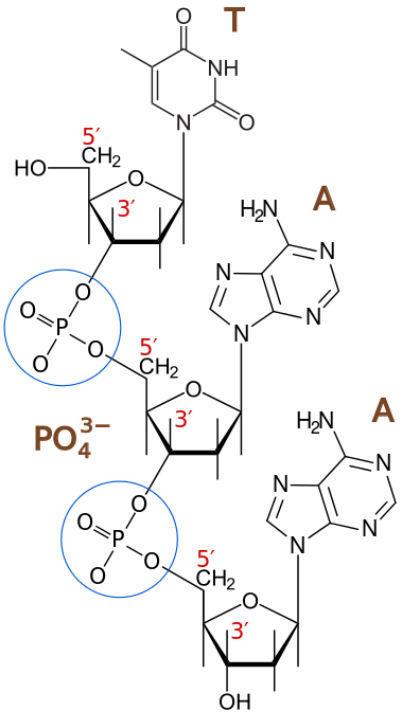
## C to G bonding

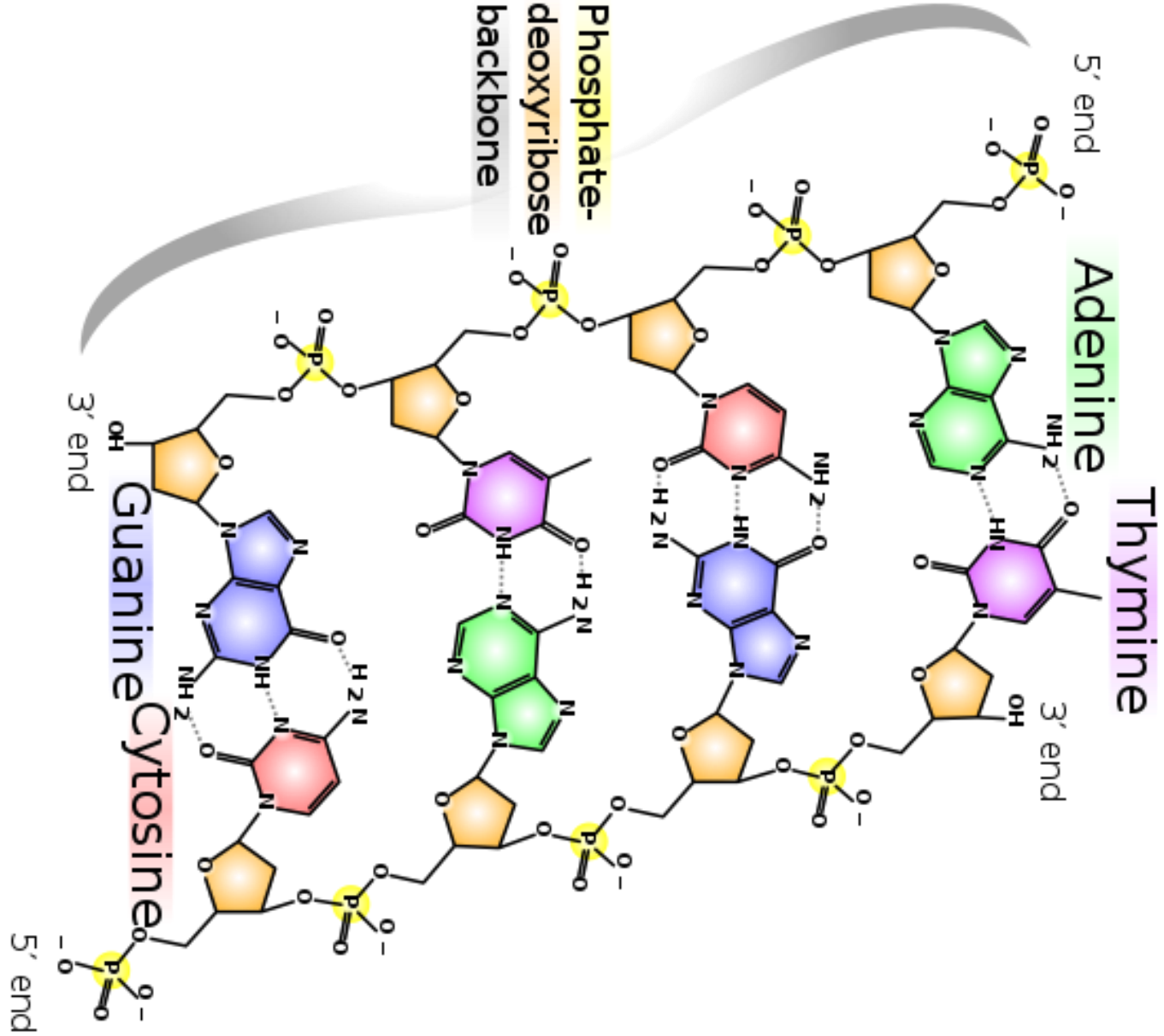


# DNA Structure (Directionality)




- **Directionality**, in molecular biology and biochemistry, is the end-to-end chemical orientation of a single strand of nucleic acid.
- The 5′-end (pronounced "five prime end") designates the end of the DNA or RNA strand that has the fifth carbon in the sugar-ring of the deoxyribose or ribose at its terminus.
- The 3′-end of a strand is so named due to it terminating at the hydroxyl group of the third carbon in the sugar-ring, and is known as the *tail end*.




Phosphate-
deoxyribose
backbone
Adenine
Thymine
Guanine
Cytosine
5′ end
3′ end
3′ end
5′ end

# DNA replication

- In molecular biology, **DNA replication** is the biological process of producing two identical replicas of DNA from one original DNA molecule.
- This process occurs in all living organisms and is the basis for biological inheritance.
- The cell possesses the distinctive property of division, which makes replication of DNA essential.
- Why is DNA double stranded?
  - More stable
    - Replication consists of half-new, half old
  - Allows for error-correction
    - If a base is damaged, can correct
    - Like a RAID

# Why so many base pairs?

- “Junk” DNA (or non-coding DNA)
- Portions of DNA sequence for which no function identified
- 98.5% of human genome
- May serve functions that are not yet understood

# Why is DNA useful?

- Every living thing on earth uses DNA to store and transmit information
- Catalogs all the different functions performed in an organism
- Identify similarities among organisms
- Identify inherited traits
- Solving crimes

# Why is DNA useful? (contd…)

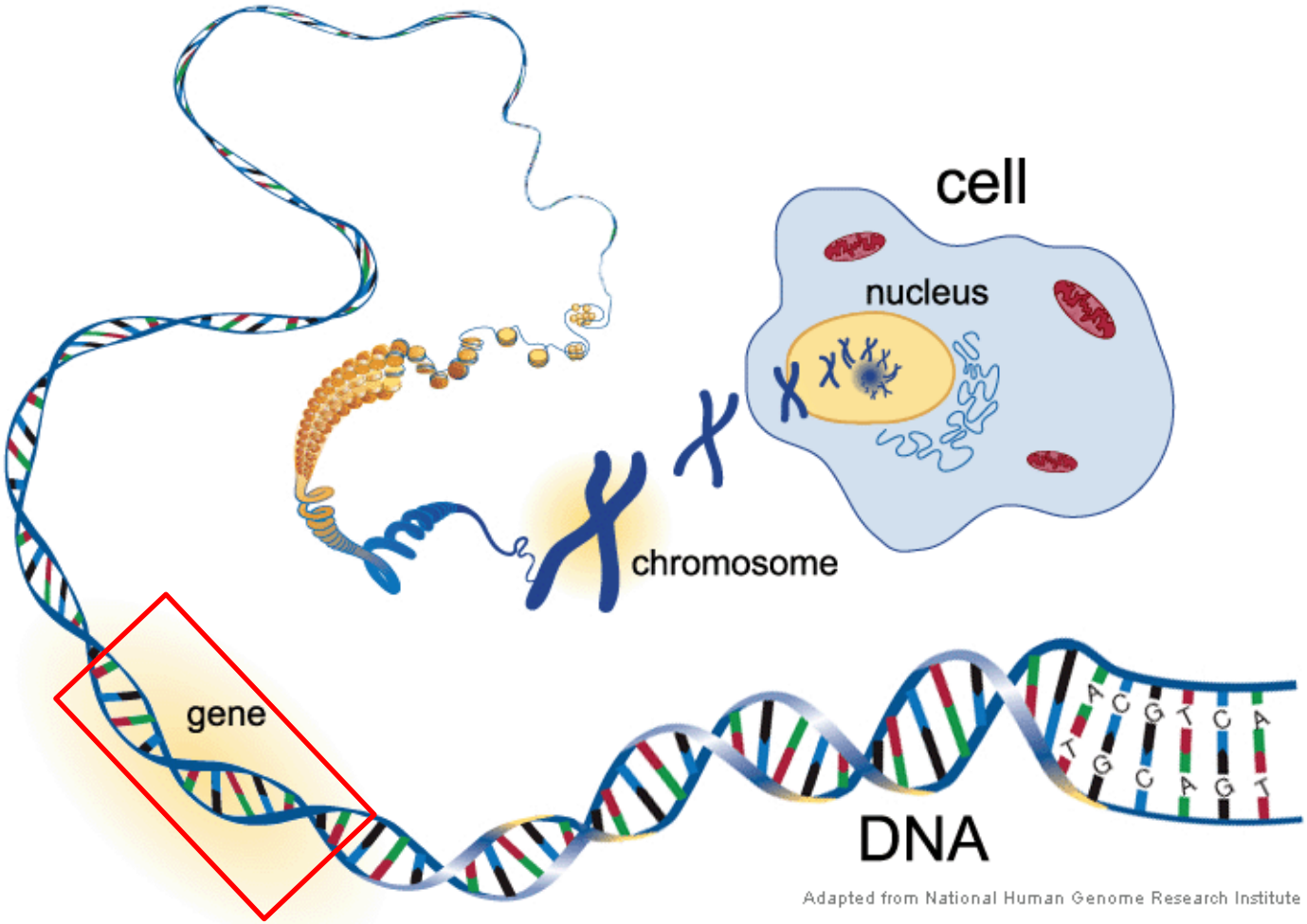
- All of the information needed to build an organism is contained in its DNA. If we could understand it, we would know how life works.
  - Preventing and curing diseases like cancer (which is caused by mutations in DNA) and inherited diseases.
  - Curing infectious diseases (everything from AIDS and malaria to the common cold). If we understand how a **microorganism** works, we can figure out how to block it.
  - Understanding genetic and evolutionary relationships between species.
  - Understanding gene expression for personalized medicine.

# More about DNA…

- DNA contains ***genes***
- Each gene is responsible for the production of a particular ***protein***
- A strand of DNA is called a ***chromosome.***
- Set of chromosomes carried by an organism is a ***Genome***

# Chromosome

- Each chromosome is a long piece of DNA
  - Human chromosomes are 100-200 million bases long. We have 46 chromosomes (2 sets of 23, one set from each parent).



# Genes

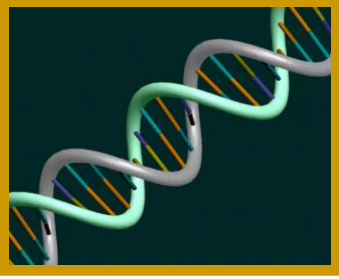
- Genes are just regions on that DNA.  It is not obvious where genes are if you look at a DNA sequence.
  - there is a lot of DNA that is not part of genes: in humans only 2% at most of the DNA is part of any gene.
  - Bacteria use more of their DNA: upto 80-90% of the chromosomes comprise of genes.
- Humans have about 25,000 genes.
  - We are far more complicated than bacteria: regulation of the genes is very complicated in humans
  - We use the same gene in different ways in different tissues

# Example Genome Sizes

| Species | Number of base pairs | Number of genes |
|---|---|---|
| E. coli | 4,600,000 | 3200 |
| Fruit fly | 180,000,000 | 13,600 |
| Chicken | 1,000,000,000 | 23,000 |
| Mouse | 2,500,000,000 | 30,000 |
| Corn | 2,500,000,000 | 59,000 |
| Human | 3,000,000,000 | 25,000-30,000 |
| Grasshopper | 180,000,000,000 | ? |
| Amoeba | 670,000,000,000 | ? |

# How does DNA work?

# The "Central Dogma"

| | |
|---|---|
| DNA ⇩ |  |
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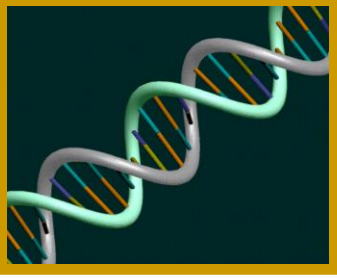
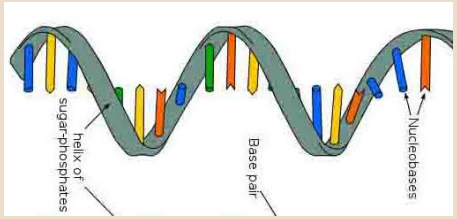
# The "Central Dogma"

**DNA**

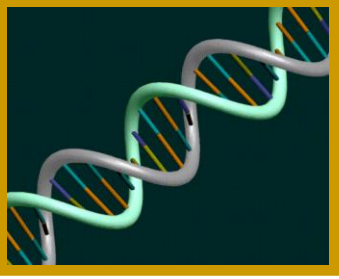


RNA

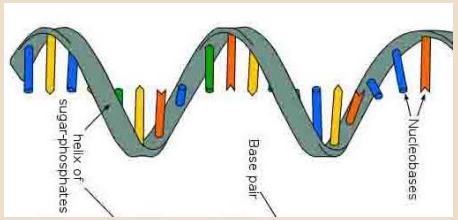


# The "Central Dogma"

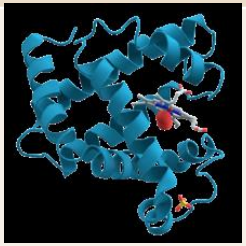
**DNA**



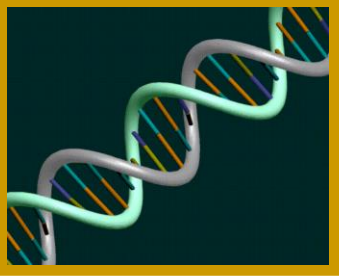
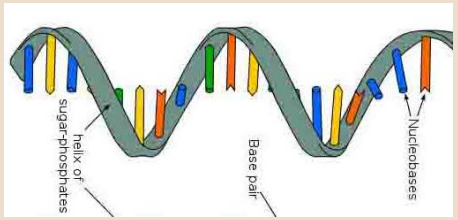
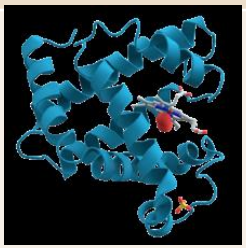
RNA



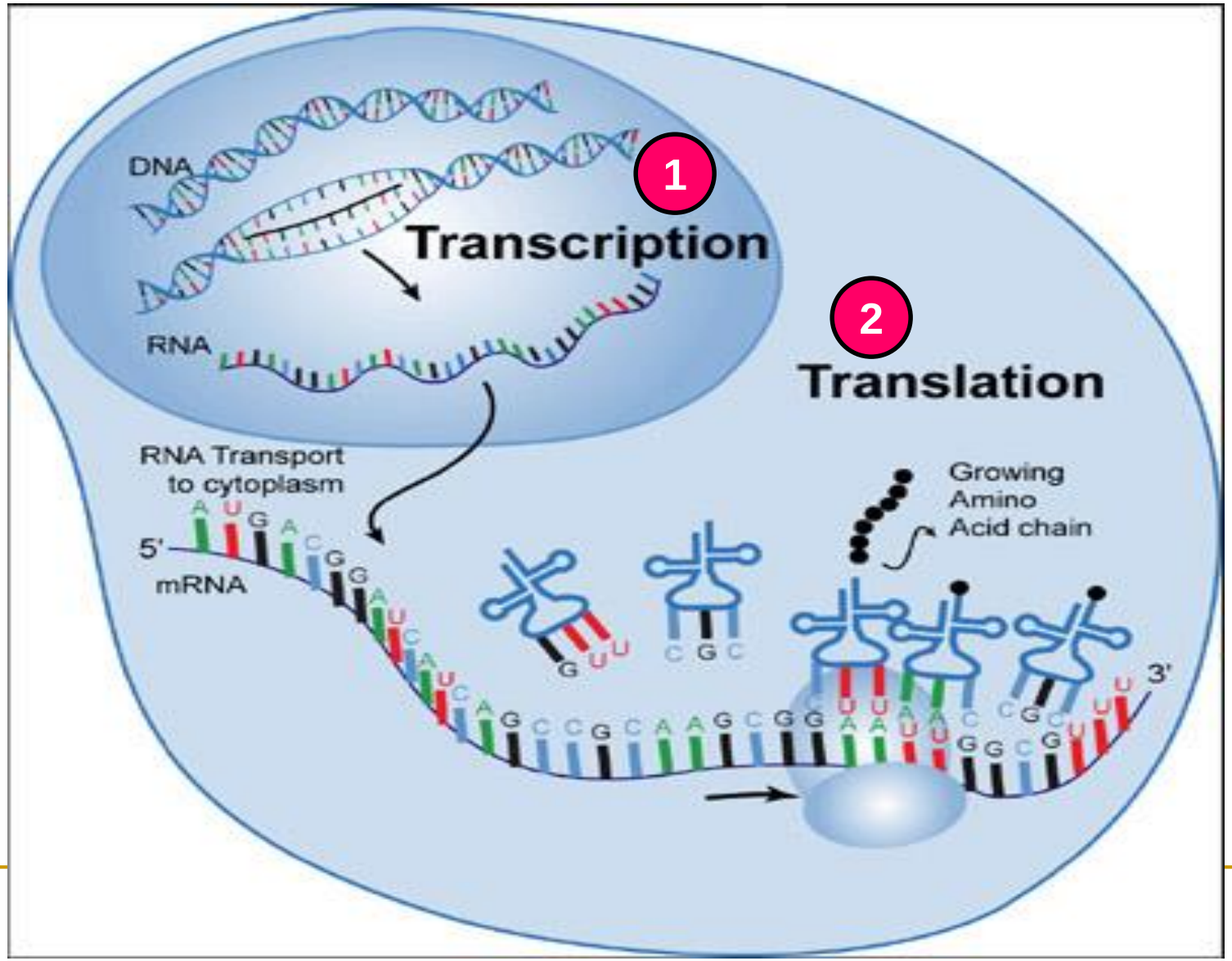

proteins



# The "Central Dogma"

| | |
|---|---|
| **DNA** ⇩ |  |
| RNA ⇩ |  |
| proteins ⇩ |  |
| you |  |

# Big picture of protein synthesis



# RNA vs DNA

Five differences between RNA and DNA

1. Sugar in RNA is ribose instead of deoxyribose
2. RNA is single stranded
3. RNA contains **Uracil base** instead of Thymine
4. RNA is disposable
5. RNA can be outside the nucleus, DNA can't

If you are going from DNA to RNA – what nitrogenous base would pair with following?

DNA: C A G T T A

RNA: _ _ _ _ _ _

# ANSWER:

DNA: C A G T T A

RNA: G U C A A U

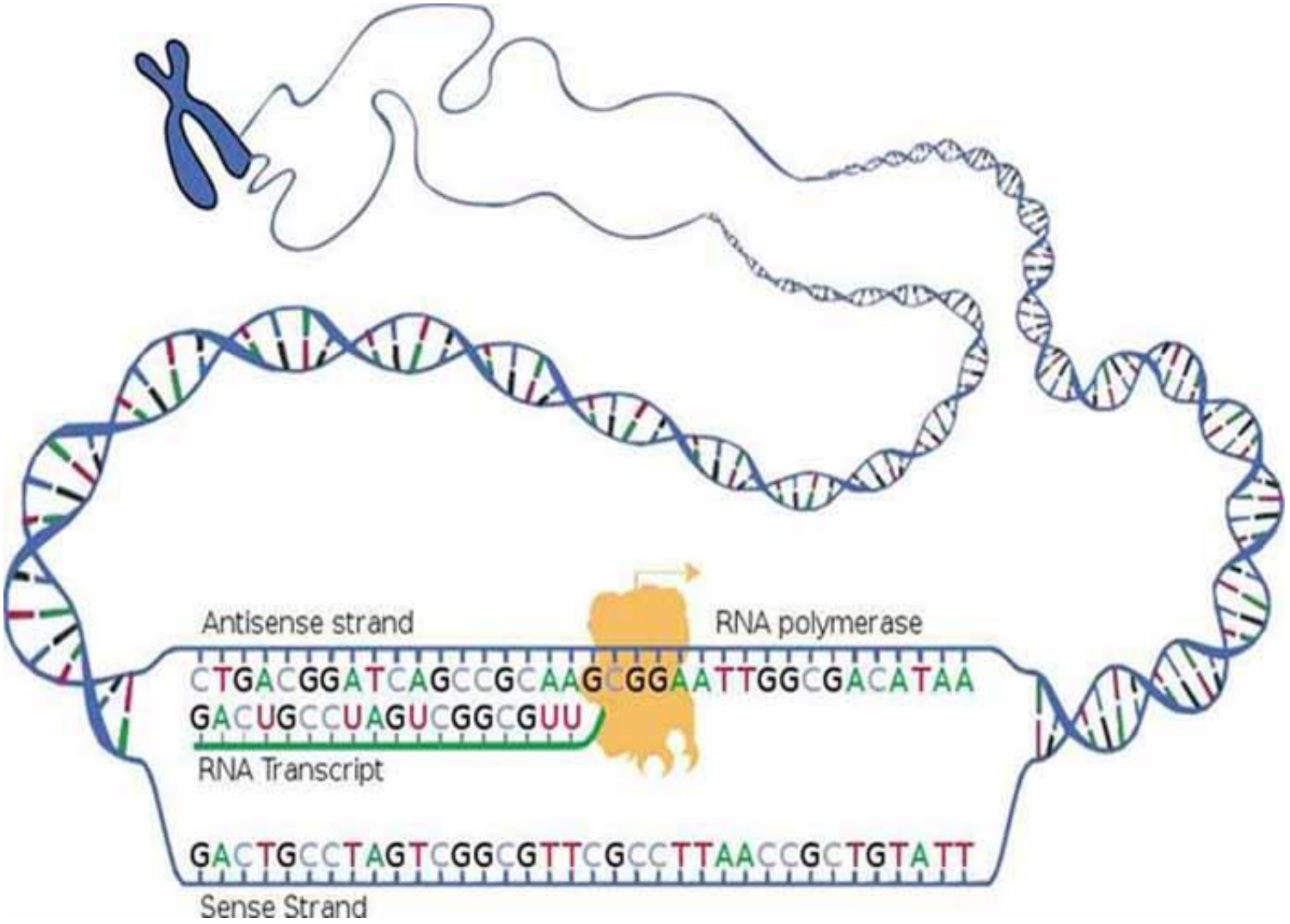
# RNA

- DNA is blueprint, doesn't do much on its own
- Transcription – copy DNA into RNA
  - Only genes get transcribed
  - **Promoter** – DNA sequence that enables gene to be transcribed
  - **Exon** – protein coding sequence of gene
  - **Intron** – sections of DNA that are spliced out after transcription
- Messenger RNA (mRNA) moves out of cell nucleus to provide building plans for *proteins*
- RNA alphabet: Uracil (U) instead of Thymin (T)

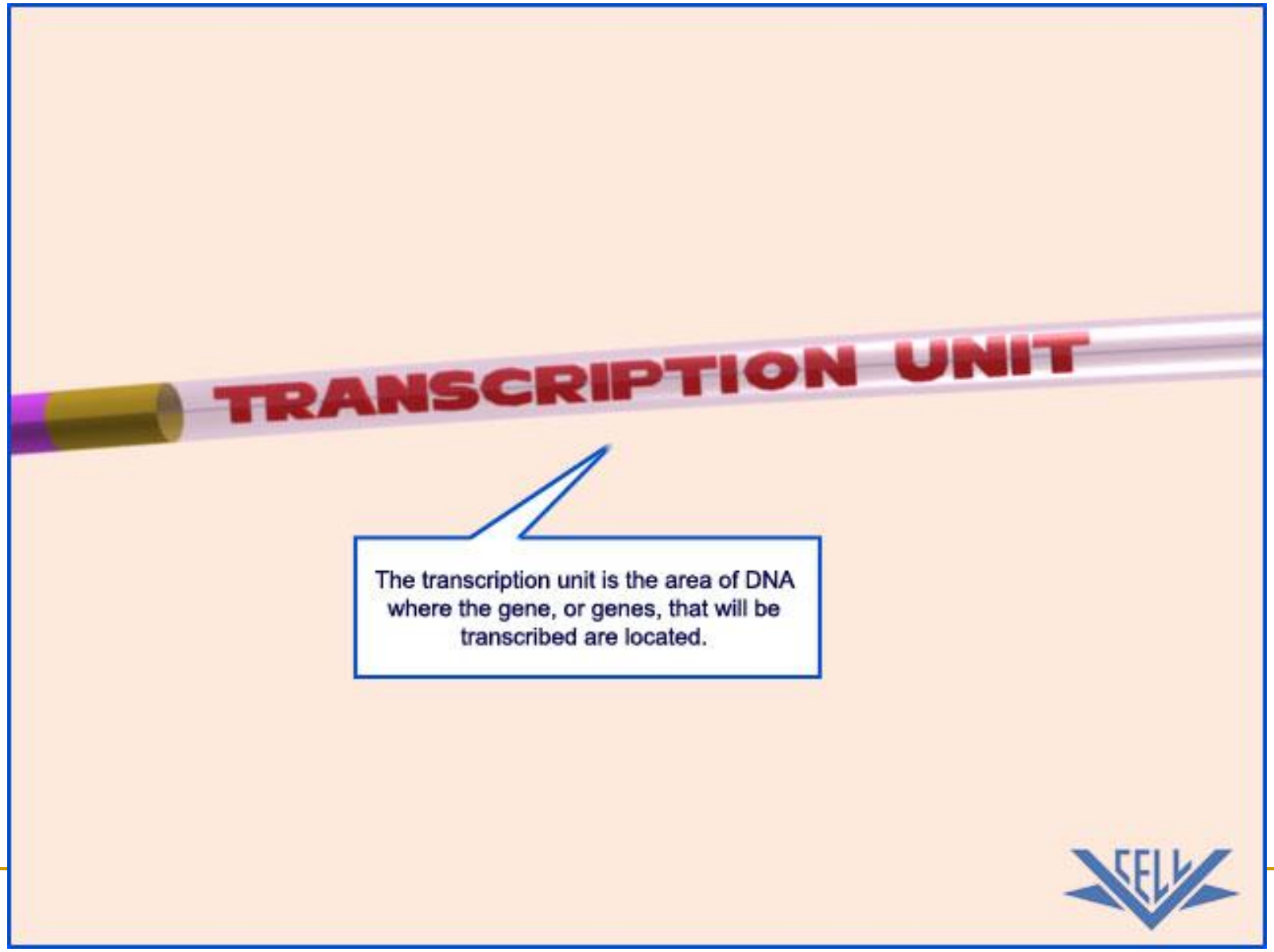
# The Key Players: Types of RNA

- Key players in Protein Synthesis -
  - Messenger RNA (mRNA): carry instruction copies
  - Ribosomal RNA (rRNA): makes up ribosome along with other proteins
  - Transfer RNA (tRNA): brings amino acids to the ribosome

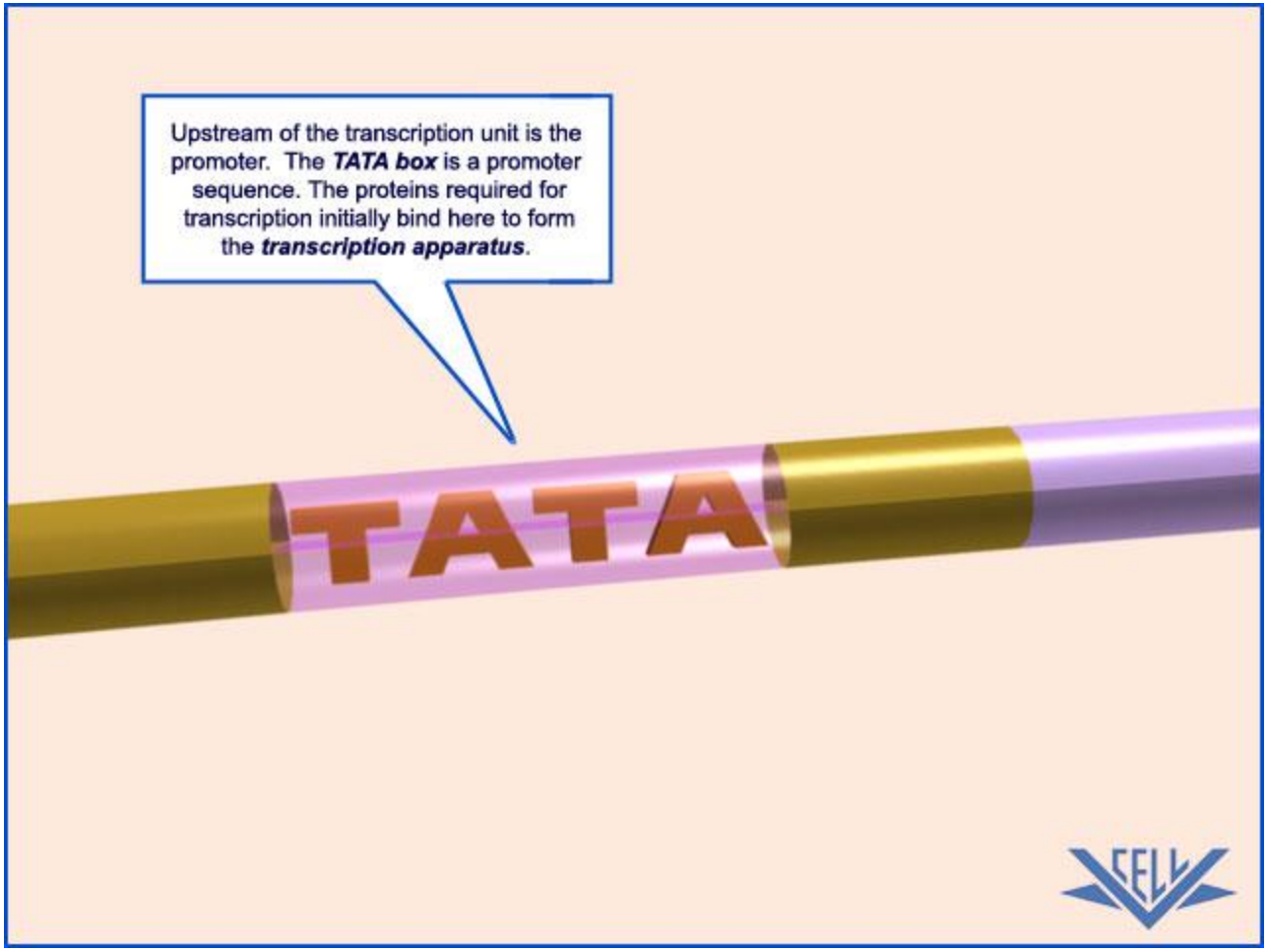
# Transcription



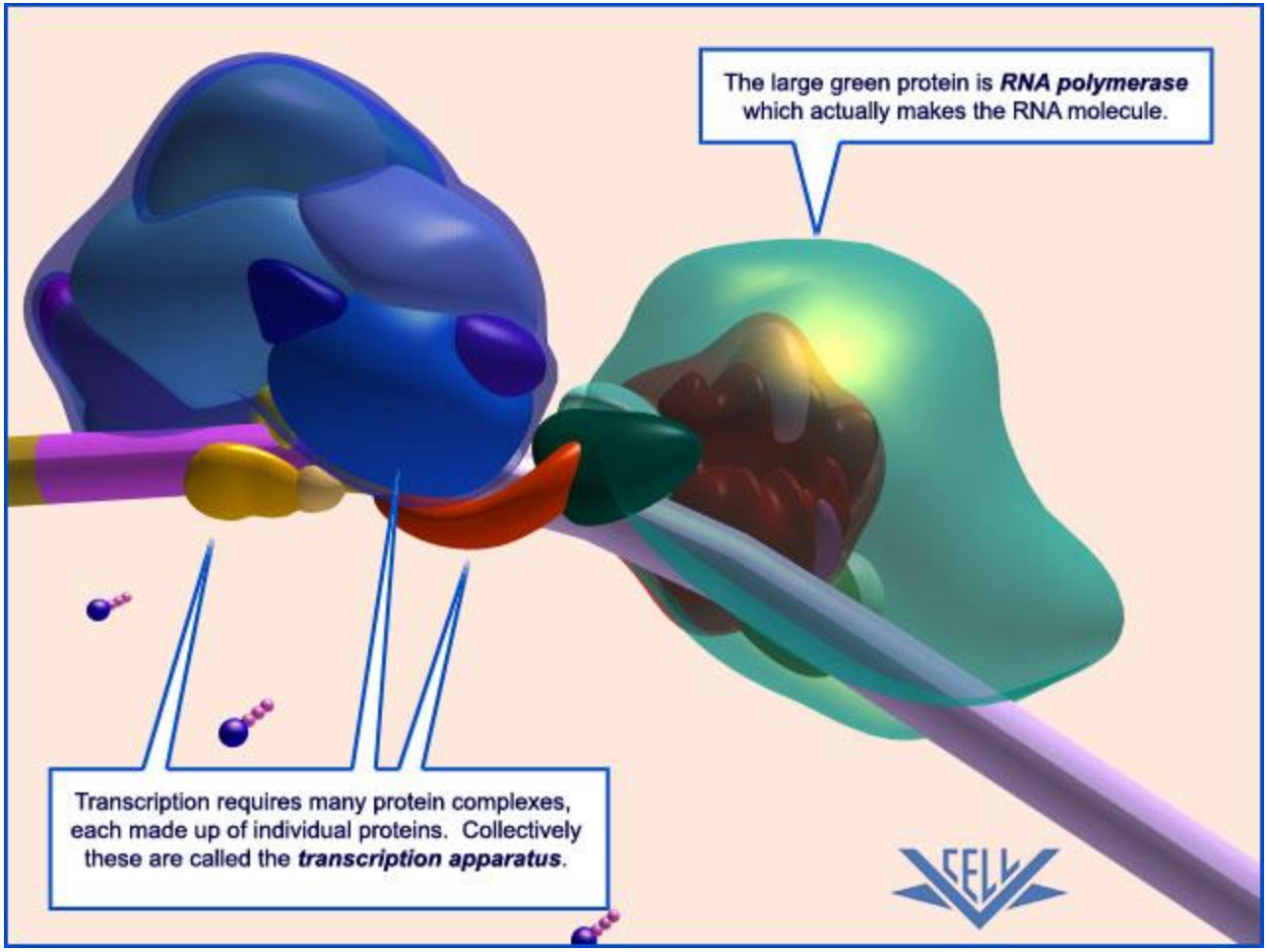
# *Transcription unit.*



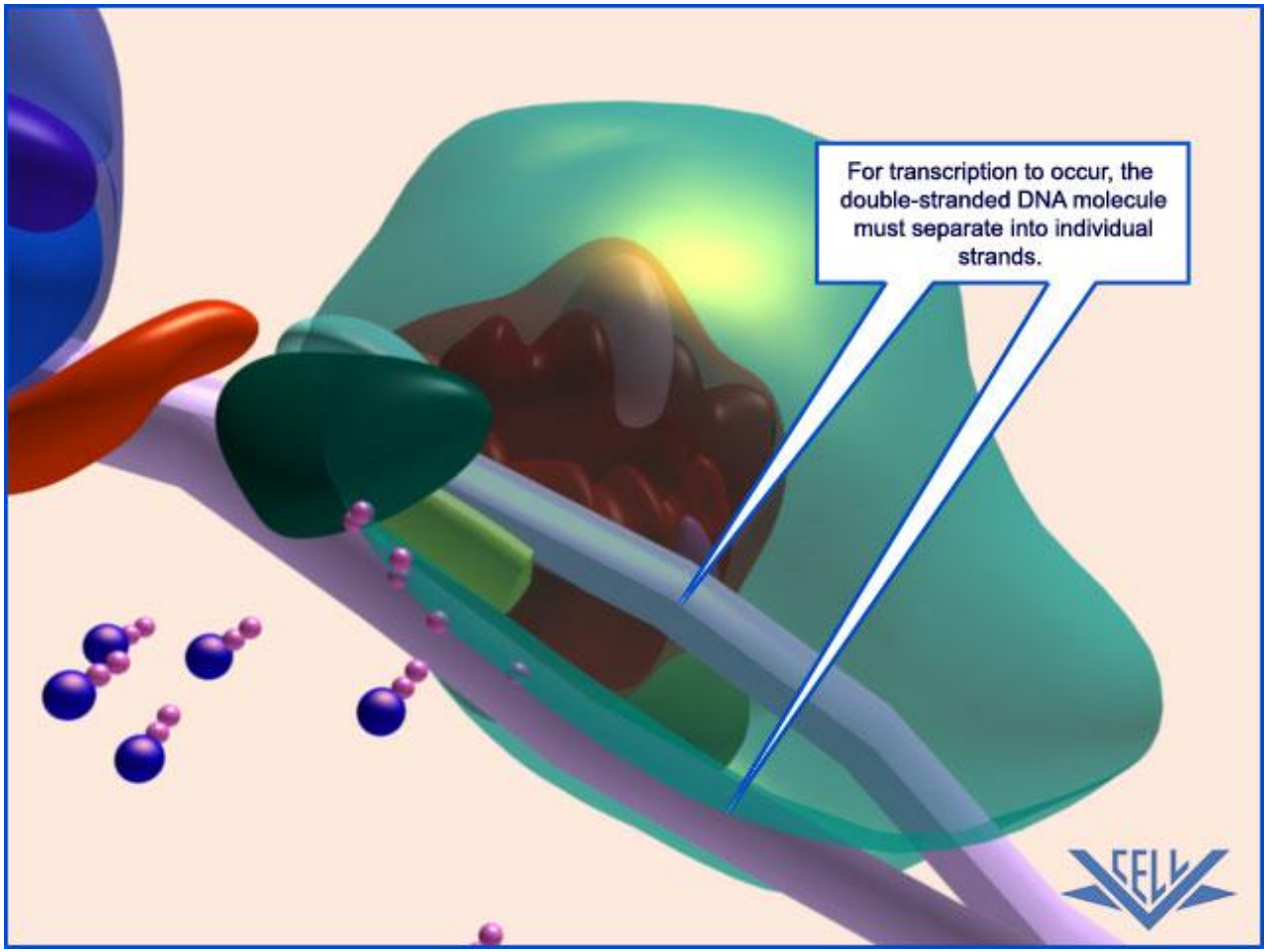
# *Promoter* and the *TATA box.*



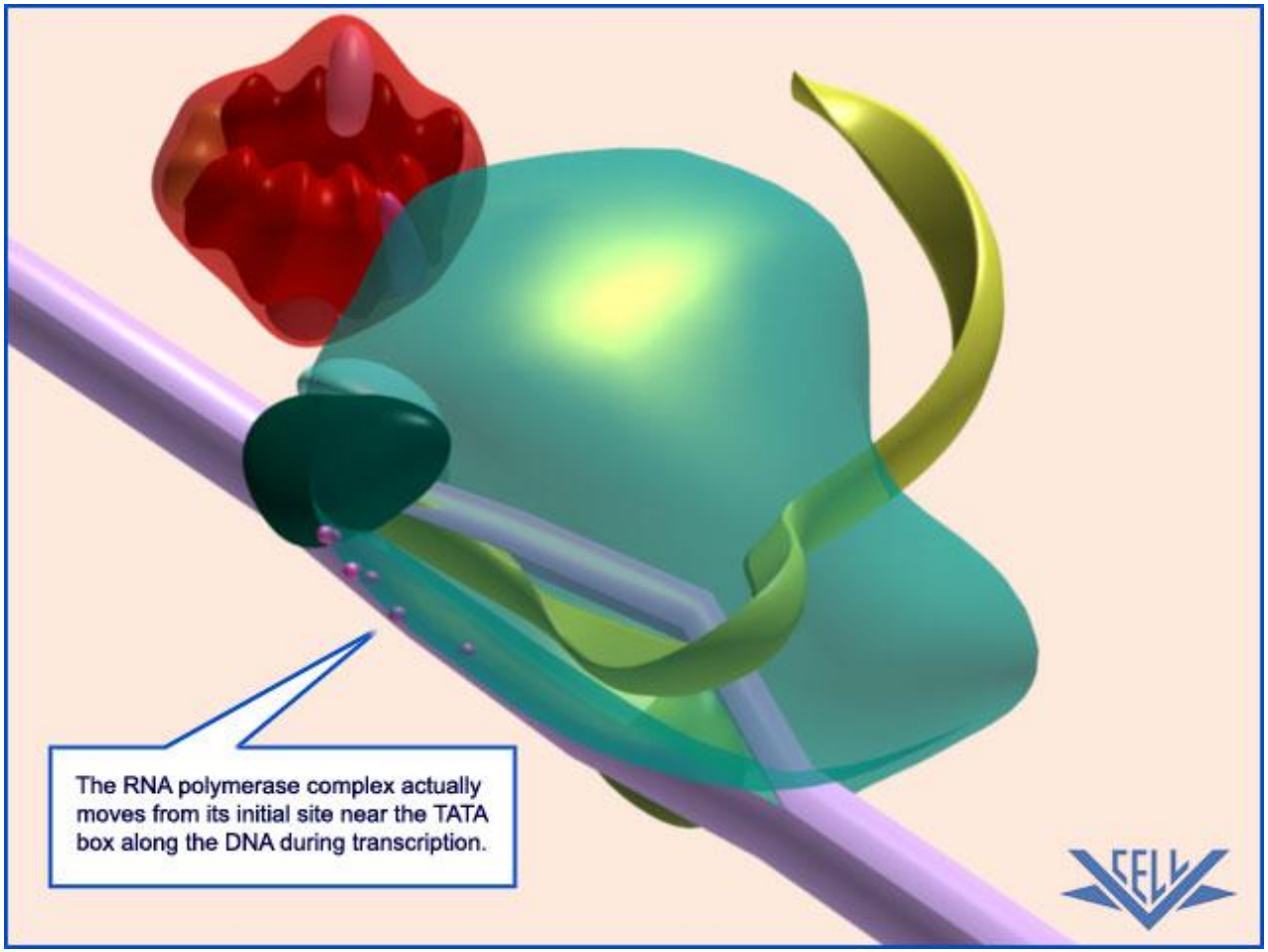
# *Transcription apparatus.*



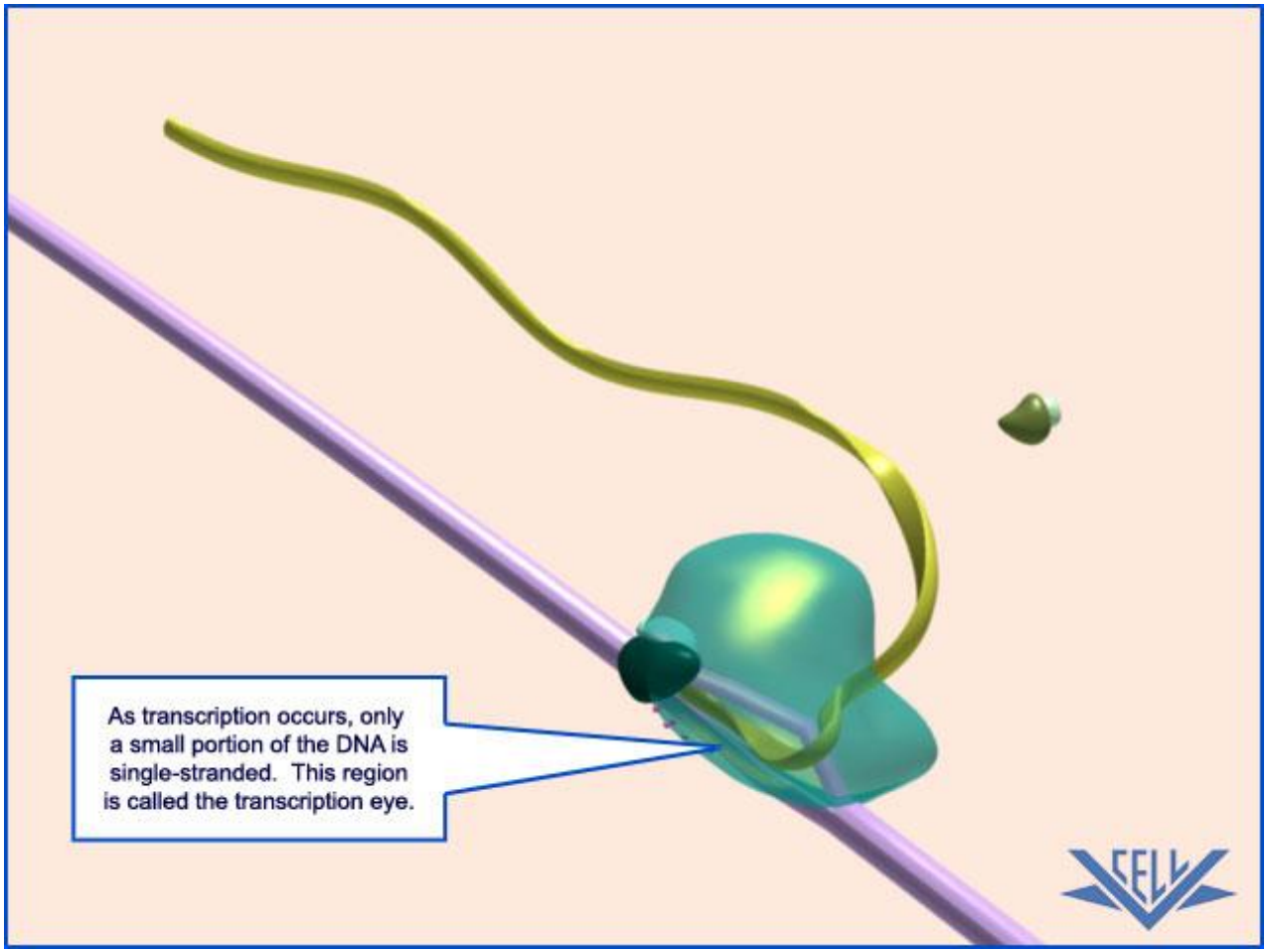
# ***Strand separation*** is necessary for ***RNA Polymerase*** to transcribe RNA.



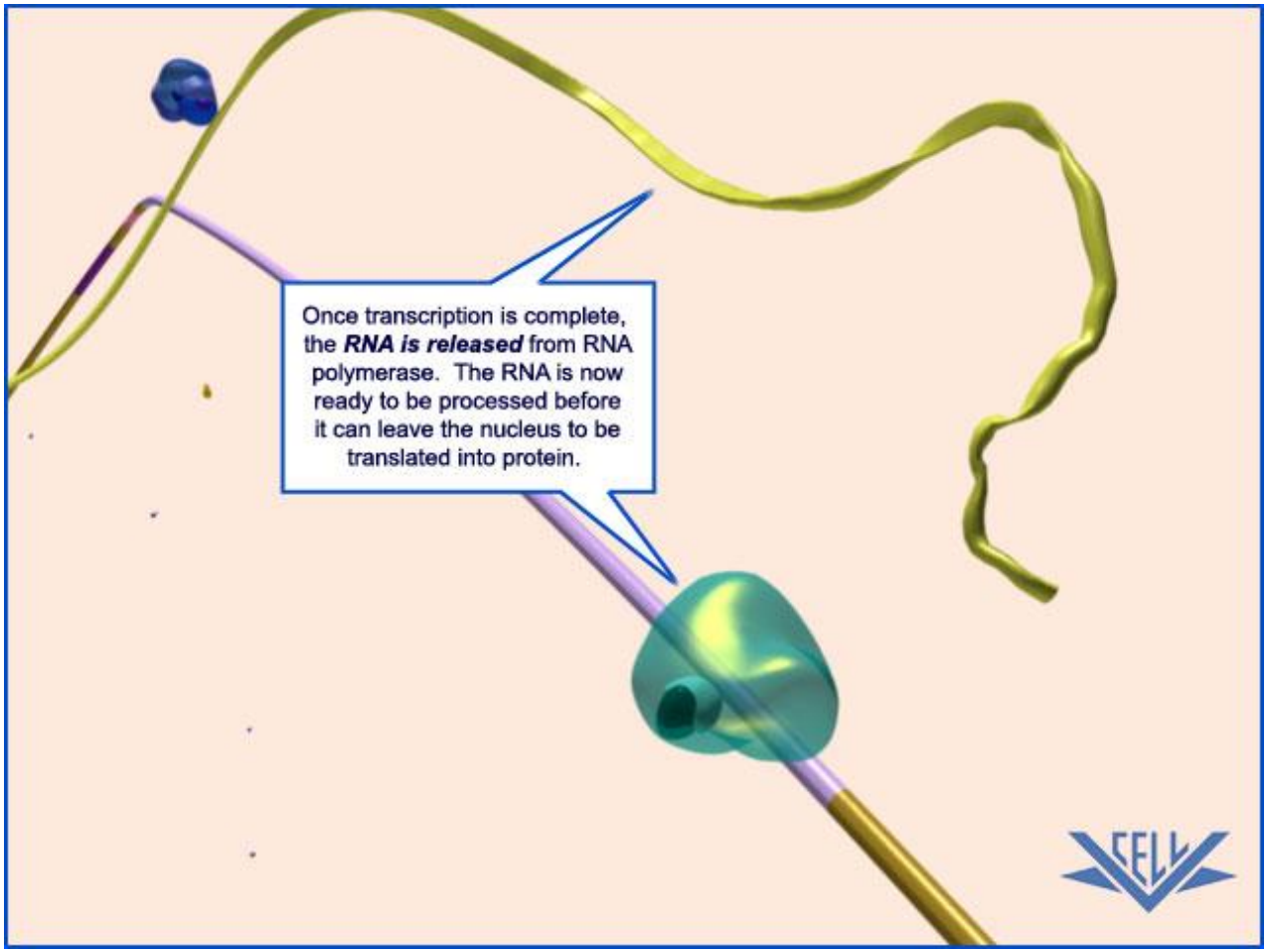
# ***RNA polymerase moves*** along the DNA.



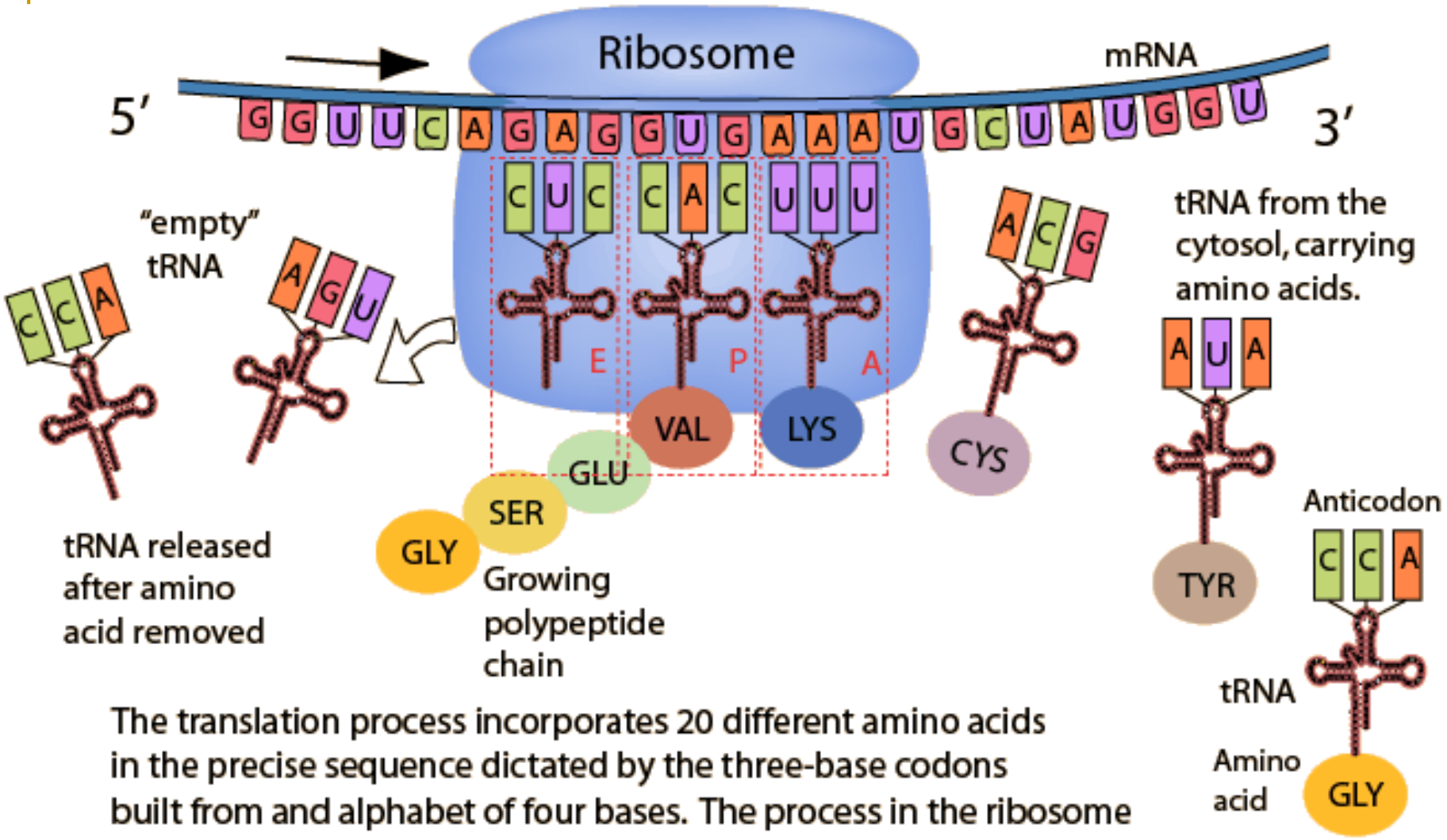
# *Transcription eye.*



# *Transcription is complete.*



# 2. Translation




The translation process incorporates 20 different amino acids in the precise sequence dictated by the three-base codons built from and alphabet of four bases. The process in the ribosome builds the polypeptide chains tha will become proteins.

# Just Like Construction…

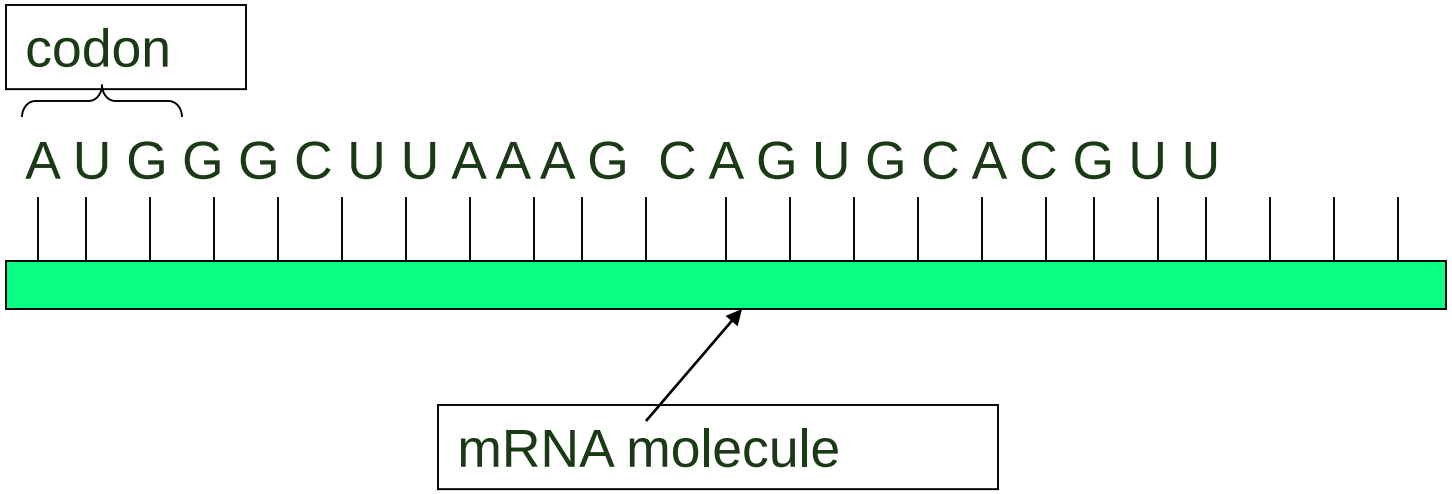
- DNA is the master plan
- mRNA is the everyday blueprint
- rRNA is the builder
- tRNA is the provider
- Amino Acids are the wood
- Proteins are the building

# Translation of the Genetic Code -

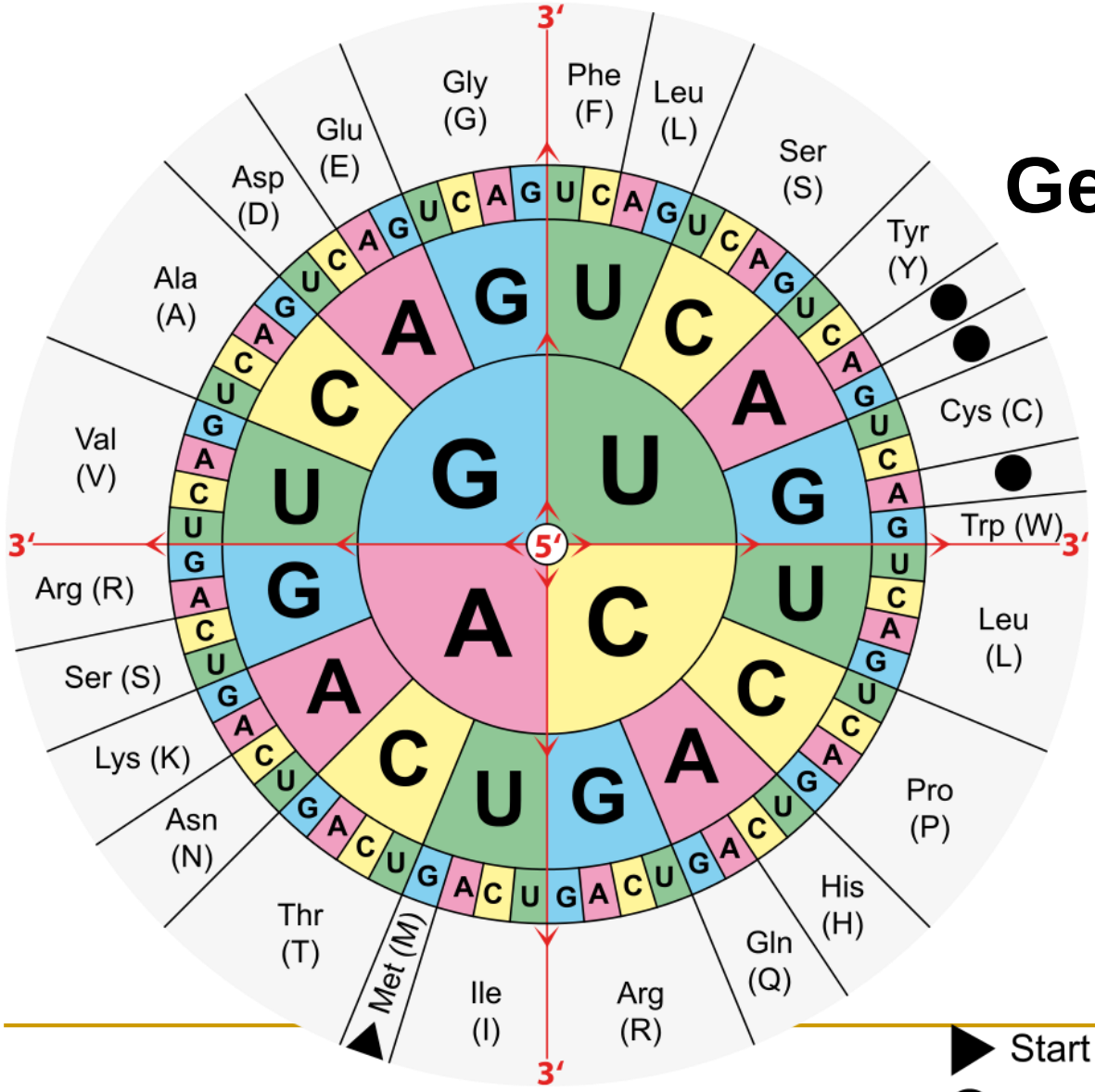
# Protein Synthesis

This is a molecule of messenger RNA.

mRNA is <u>transcribed</u> in the nucleus.



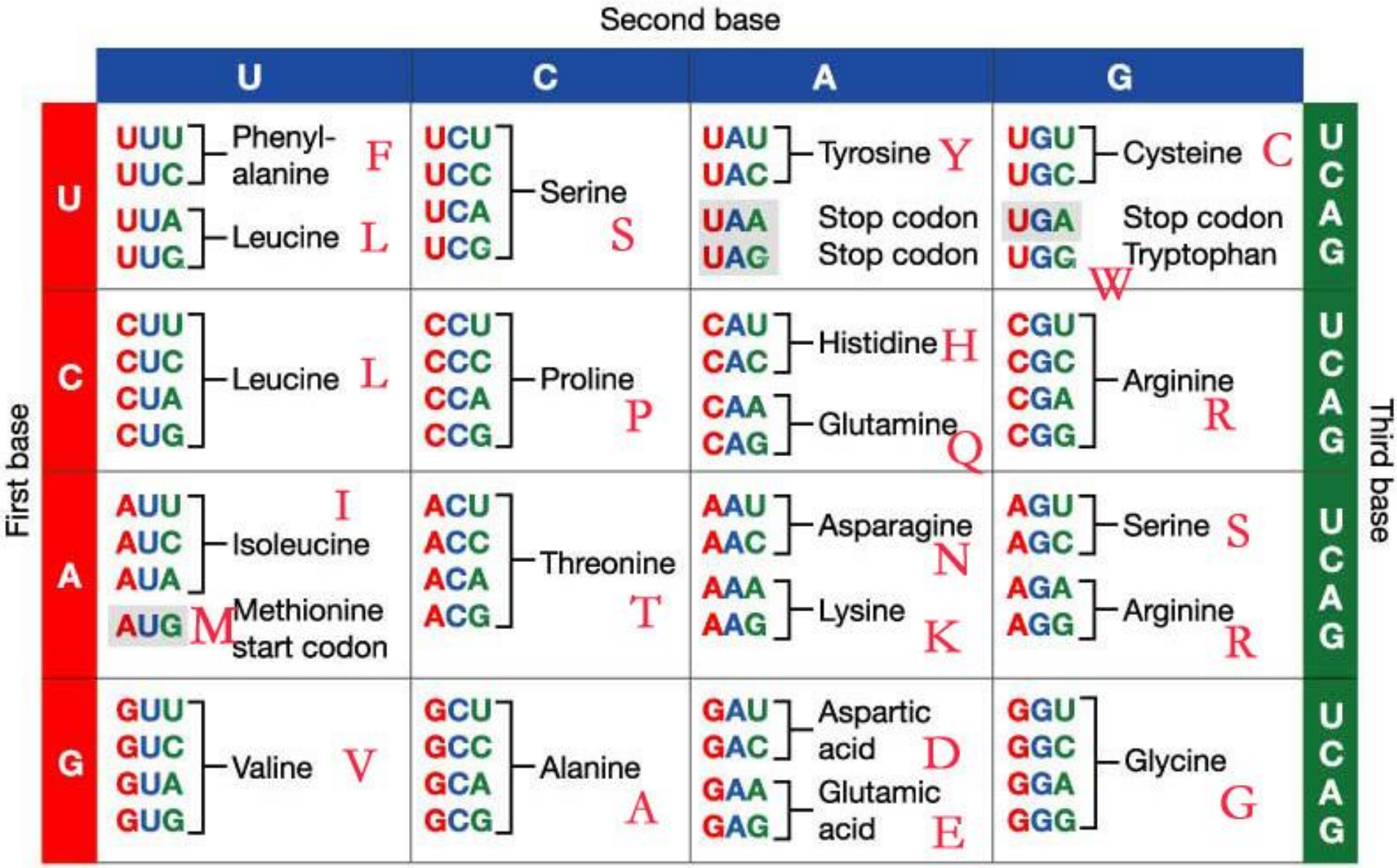
# The CODON TABLE



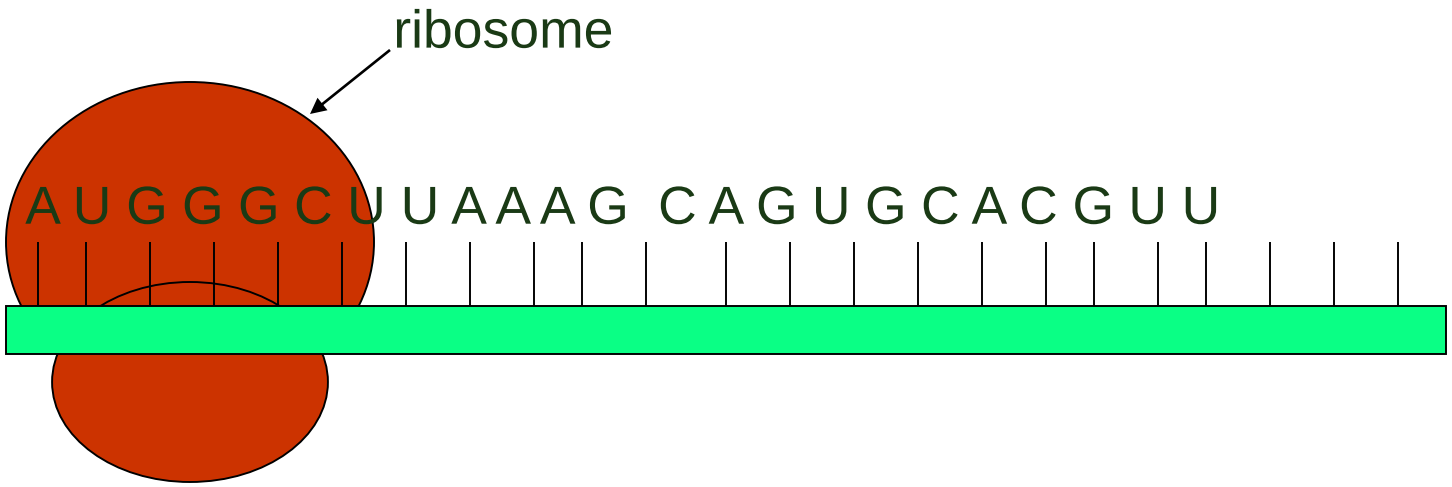

**Reading Genetic Material**

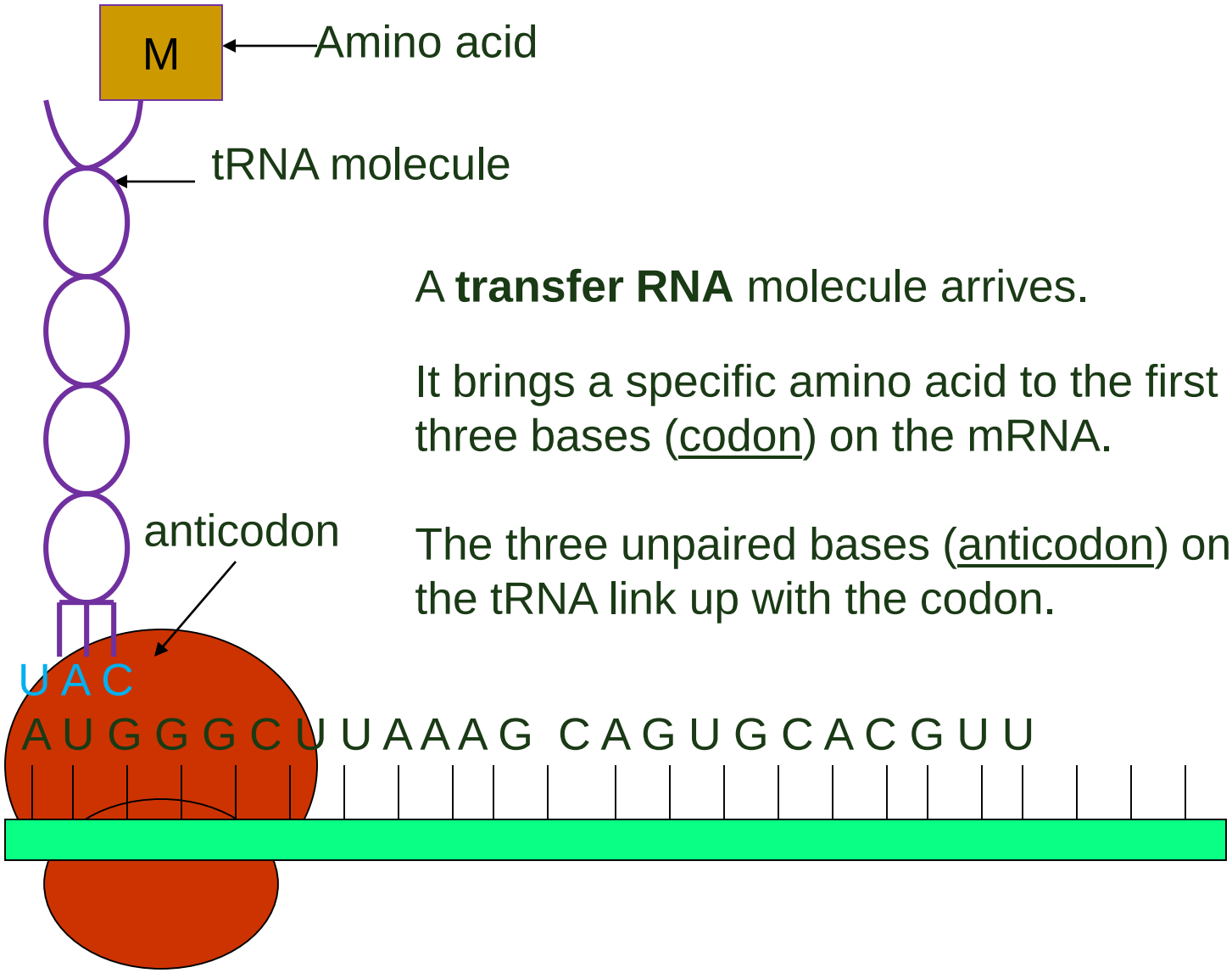
# The CODON TABLE

**Reading Genetic Material**



**A large molecule called ribosome, attaches to the mRNA molecule.**

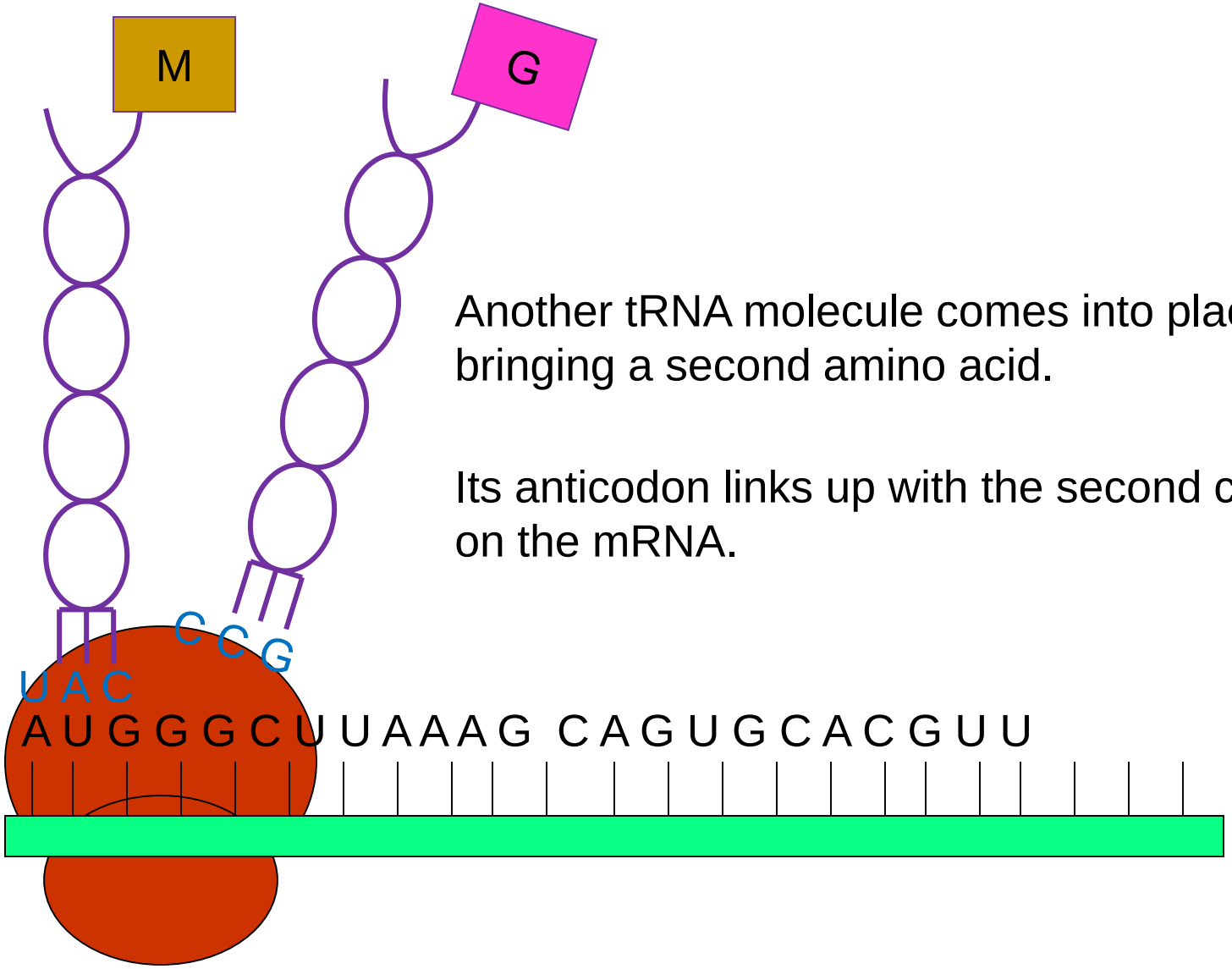





A **transfer RNA** molecule arrives.

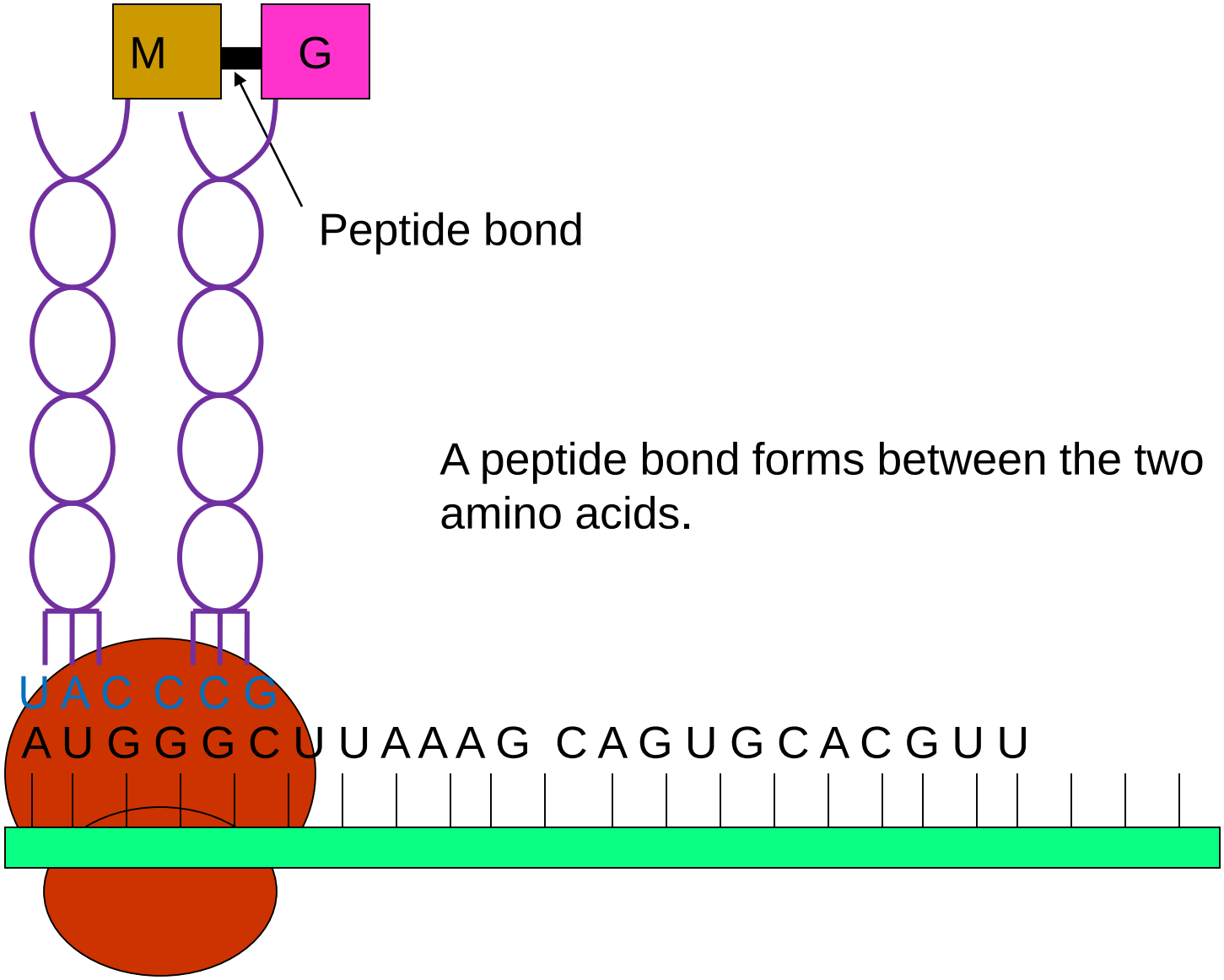
It brings a specific amino acid to the first three bases (codon) on the mRNA.

The three unpaired bases (anticodon) on the tRNA link up with the codon.

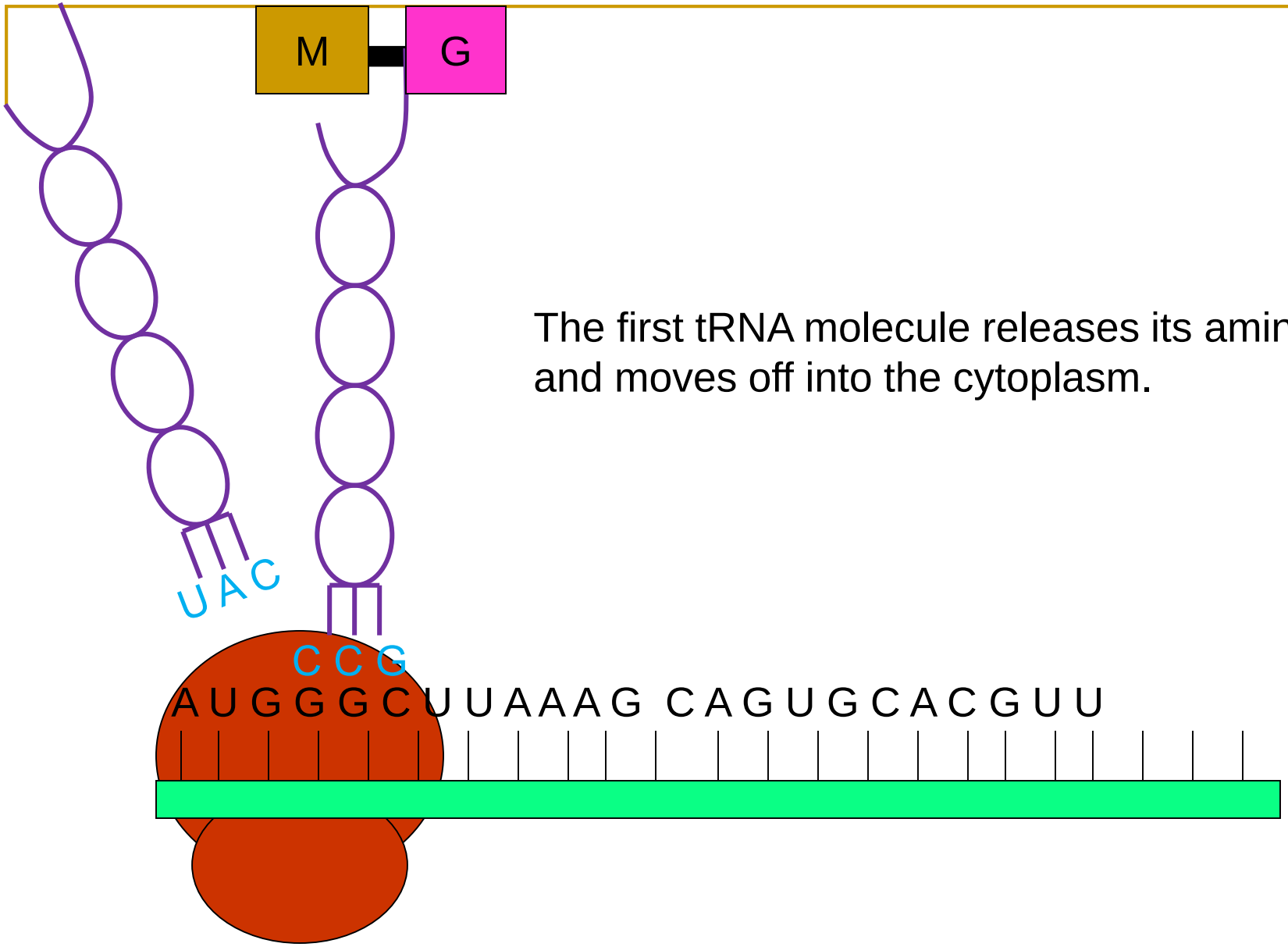



Another tRNA molecule comes into place, bringing a second amino acid.

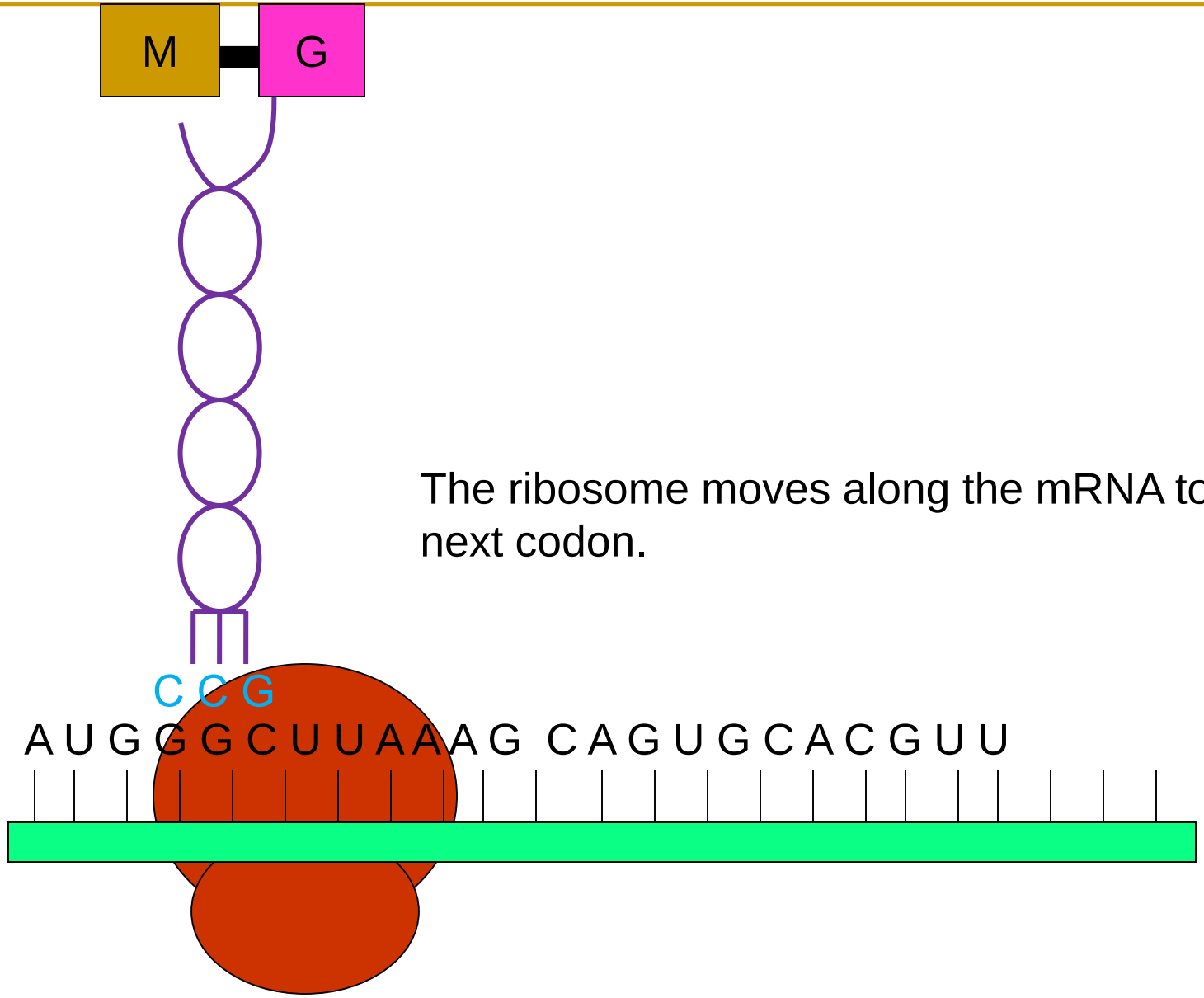
Its anticodon links up with the second codon on the mRNA.



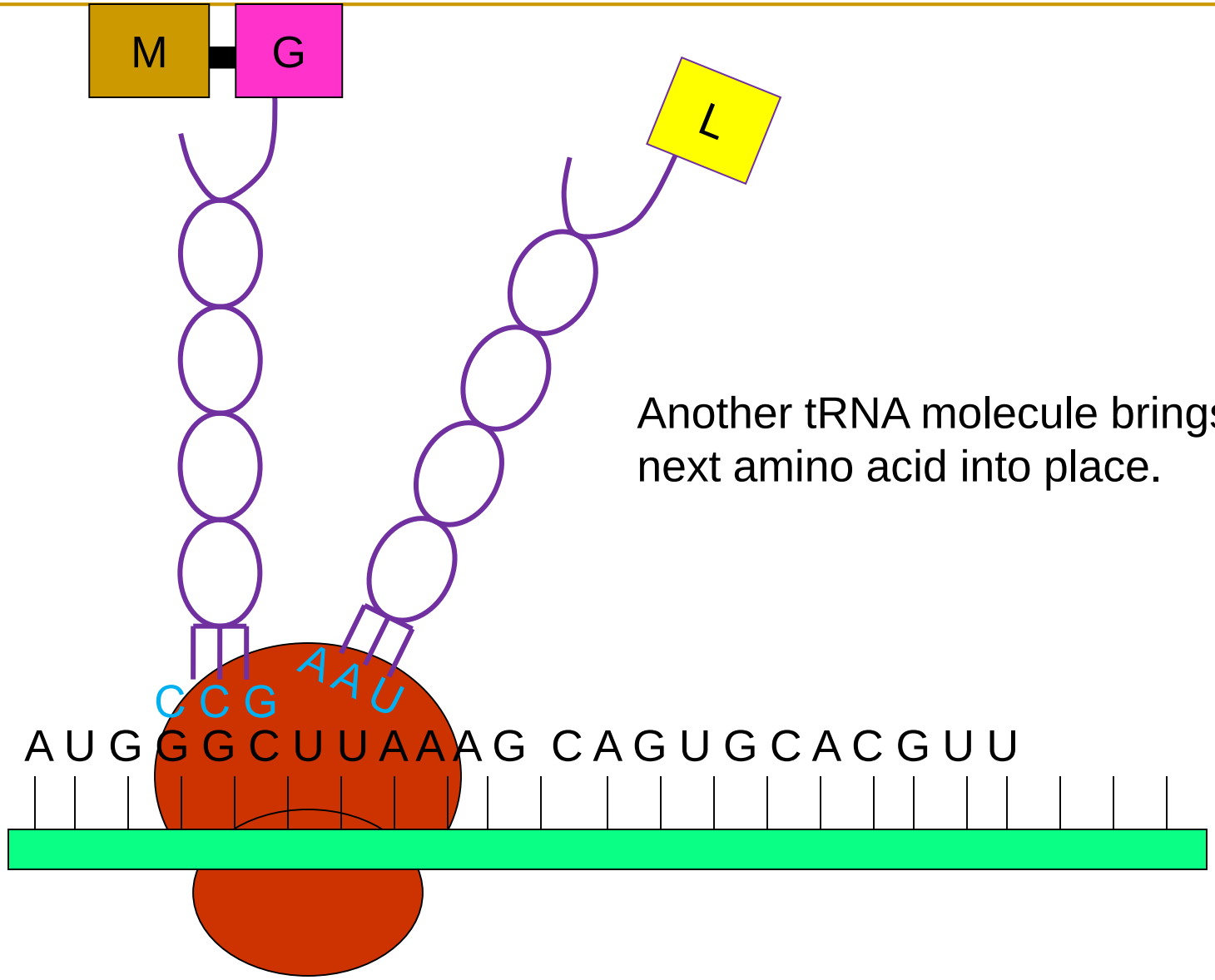

A peptide bond forms between the two amino acids.



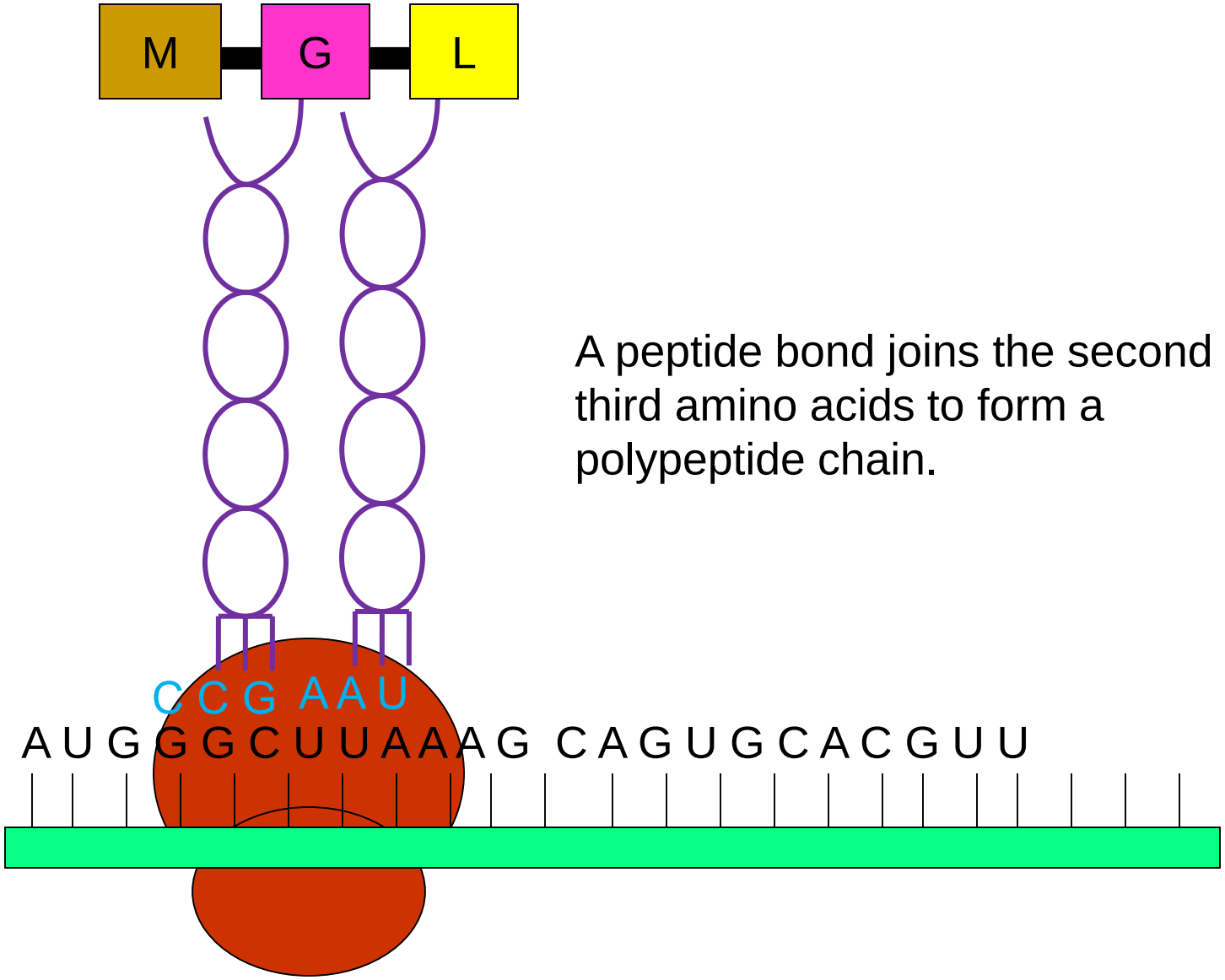

The first tRNA molecule releases its amino acid and moves off into the cytoplasm.




The ribosome moves along the mRNA to the next codon.




Another tRNA molecule brings the next amino acid into place.



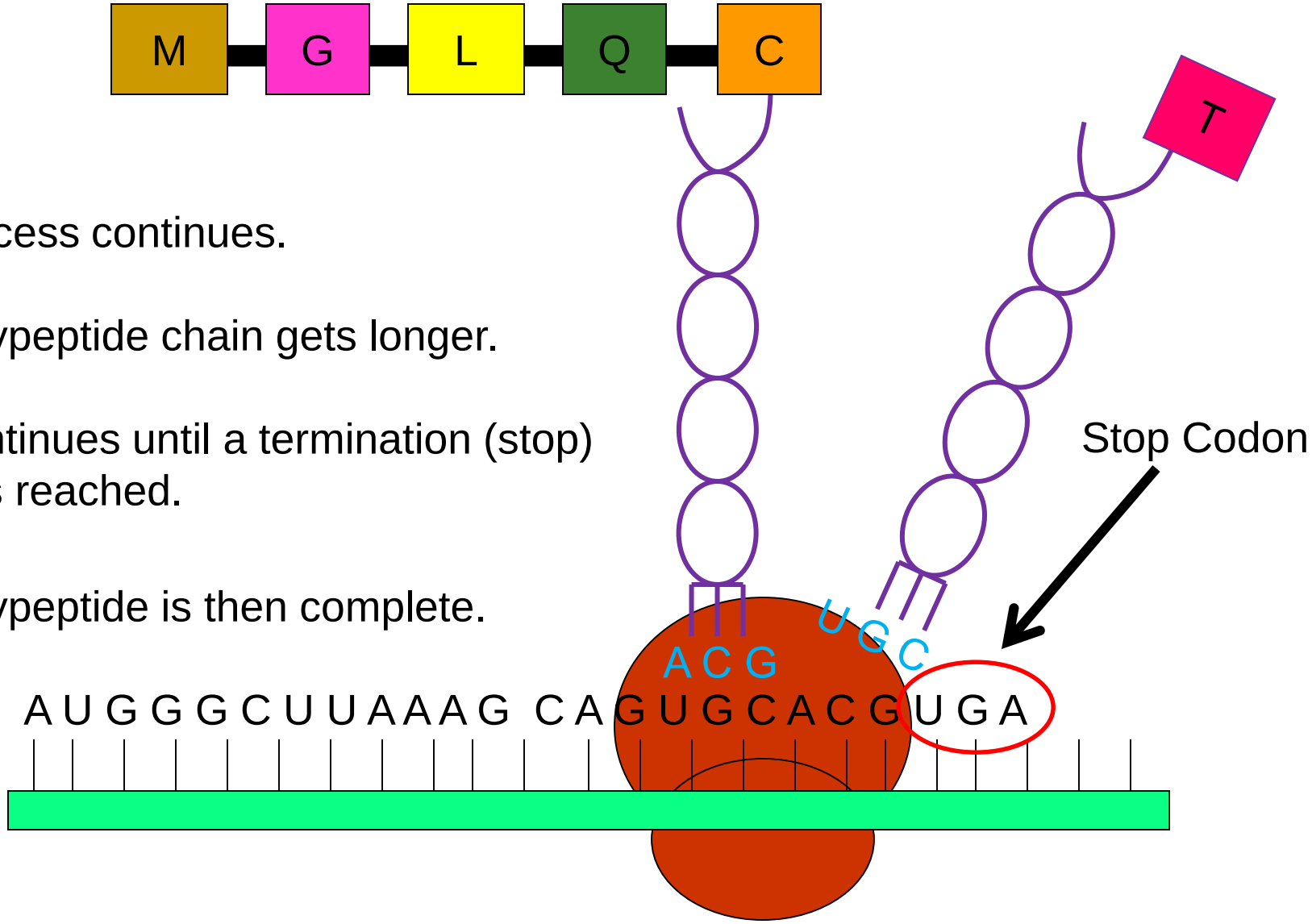

A peptide bond joins the second and third amino acids to form a polypeptide chain.

The process continues.

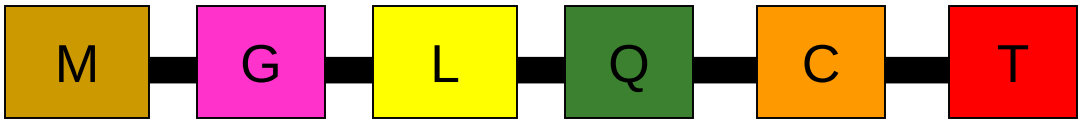
The polypeptide chain gets longer.

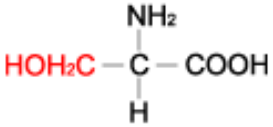
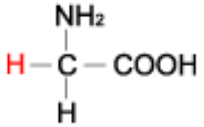
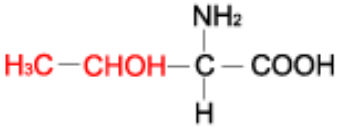
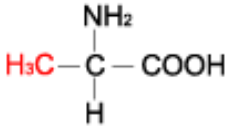
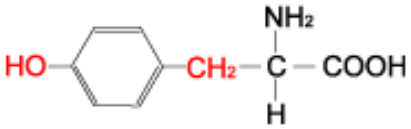
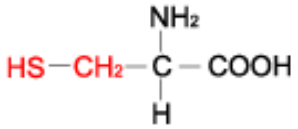
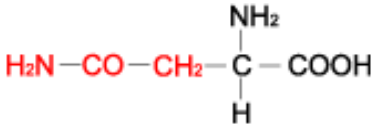
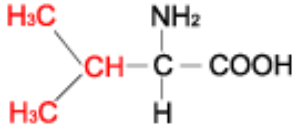
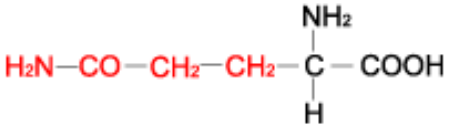
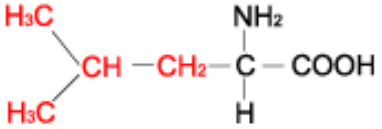
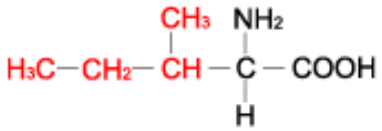
This continues until a termination (stop) codon is reached.

The polypeptide is then complete.

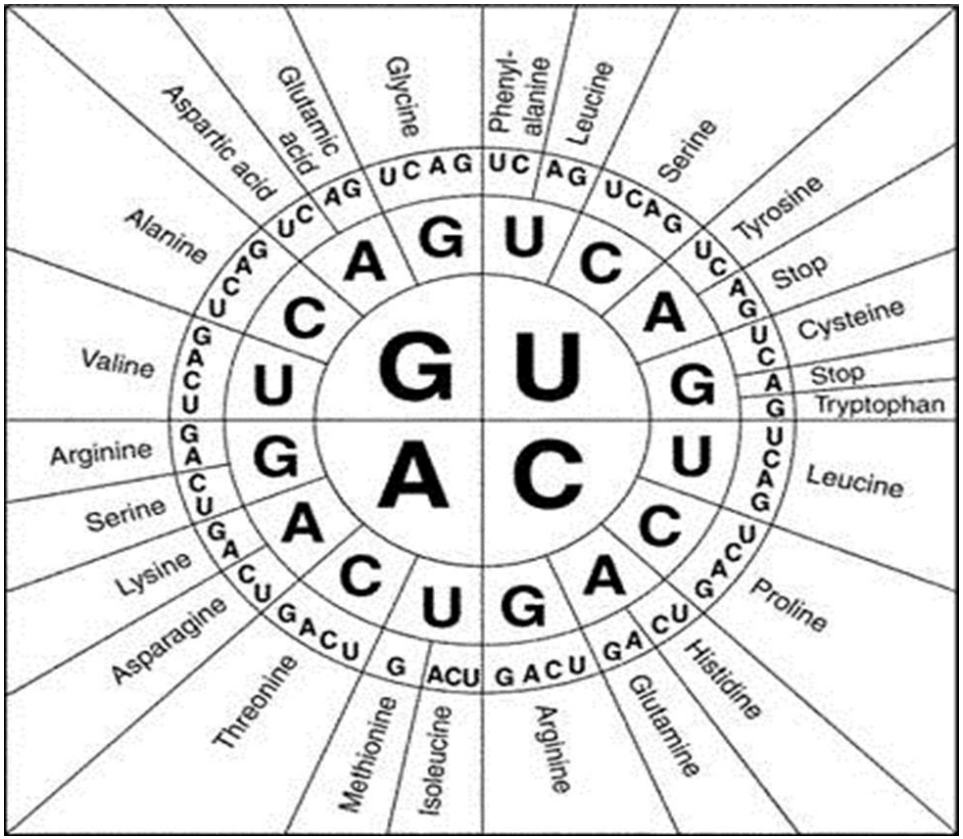


# Newly formed protein



| POLAR SIDE CHAINS | | NON POLAR SIDE CHAINS | |
|---|---|---|---|
| SERINE |  | GLYCINE |  |
| THREONINE |  | ALANINE |  |
| TYROSINE |  | CYSTEINE [1] |  |
| ASPARAGINE |  | VALINE |  |
| GLUTAMINE |  | LEUCINE |  |
| | | ISOLEUCINE |  |

# Example:



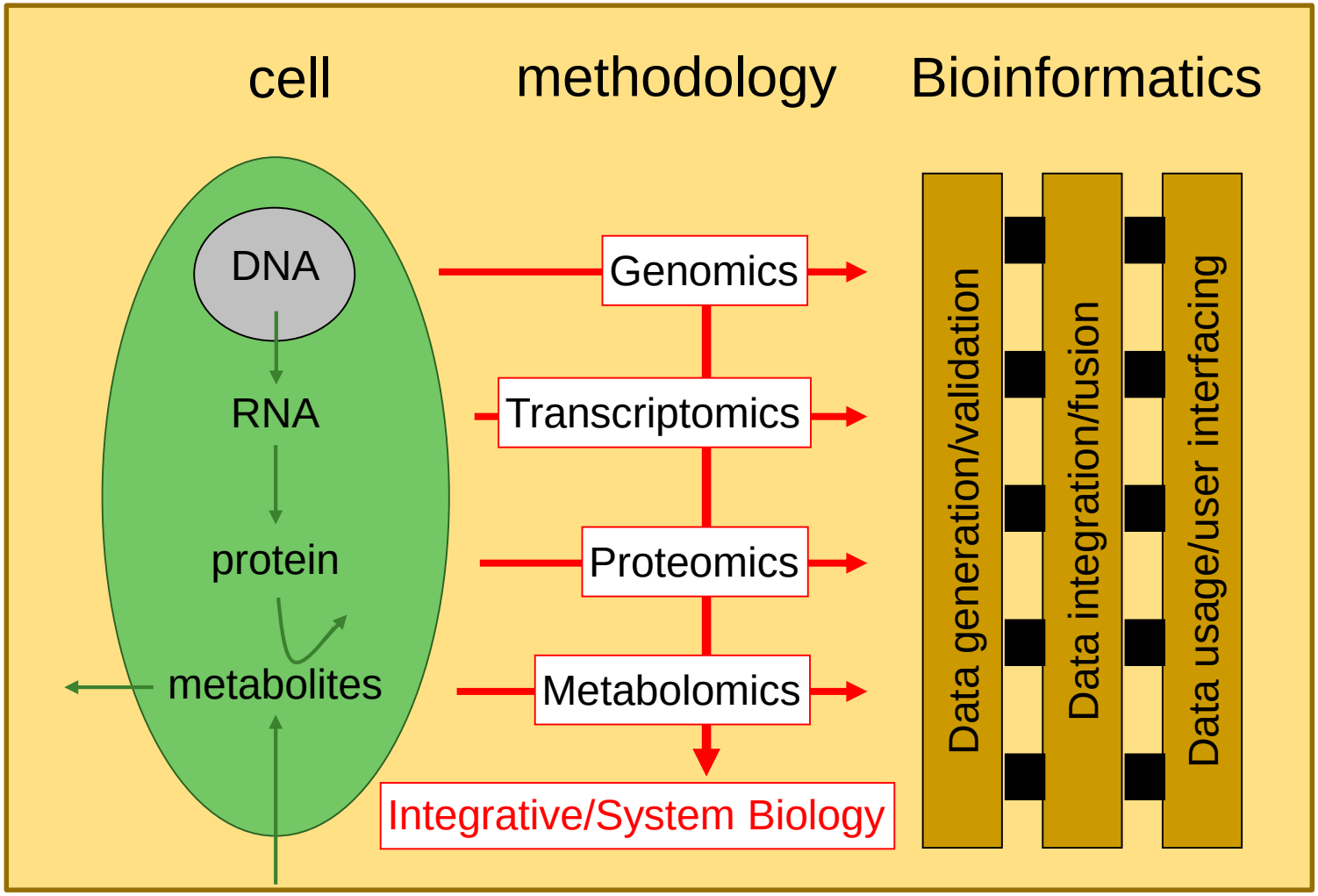

1. What amino acids would be coded by the following DNA sequence?

TACCGGACCGC TATC

2. What would be the DNA sequence for a polypeptide chain (protein) that had the following amino acids?

Lysine-Cysteine-Proline

# Role of Bioinformatics



# Applications/Impact

# Personalized Medicine

- An individual's genetic inheritance affects the body's response to drugs:
  - ***At present***, some drugs fail to make it to the market because a small percentage of the clinical patient population show adverse affects to a drug due to sequence variants in their DNA. As a result, potentially life saving drugs never makes it to the marketplace.
  - ***Today***, doctors have to use **trial and error** to find the best drug to treat a particular patient as those with the same clinical symptoms can show a wide range of responses to the same treatment.
  - ***In future***, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy and dosage from the beginning.

# Preventative Medicine

- With the specific details of the genetic mechanisms of diseases being unraveled, the development of diagnostic tests to measure a persons susceptibility to different diseases may become a distinct reality.
- Preventative actions such as change of lifestyle or having treatment at the earliest possible stages when they are more likely to be successful, could result in huge advances in our struggle to conquer disease.

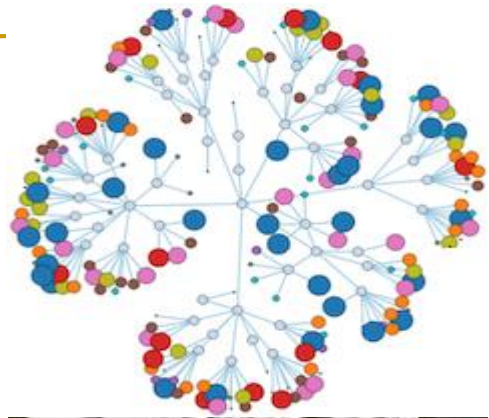
# Biological complexity & Networks An Example of Gene Regulatory Networks

# Complex Systems

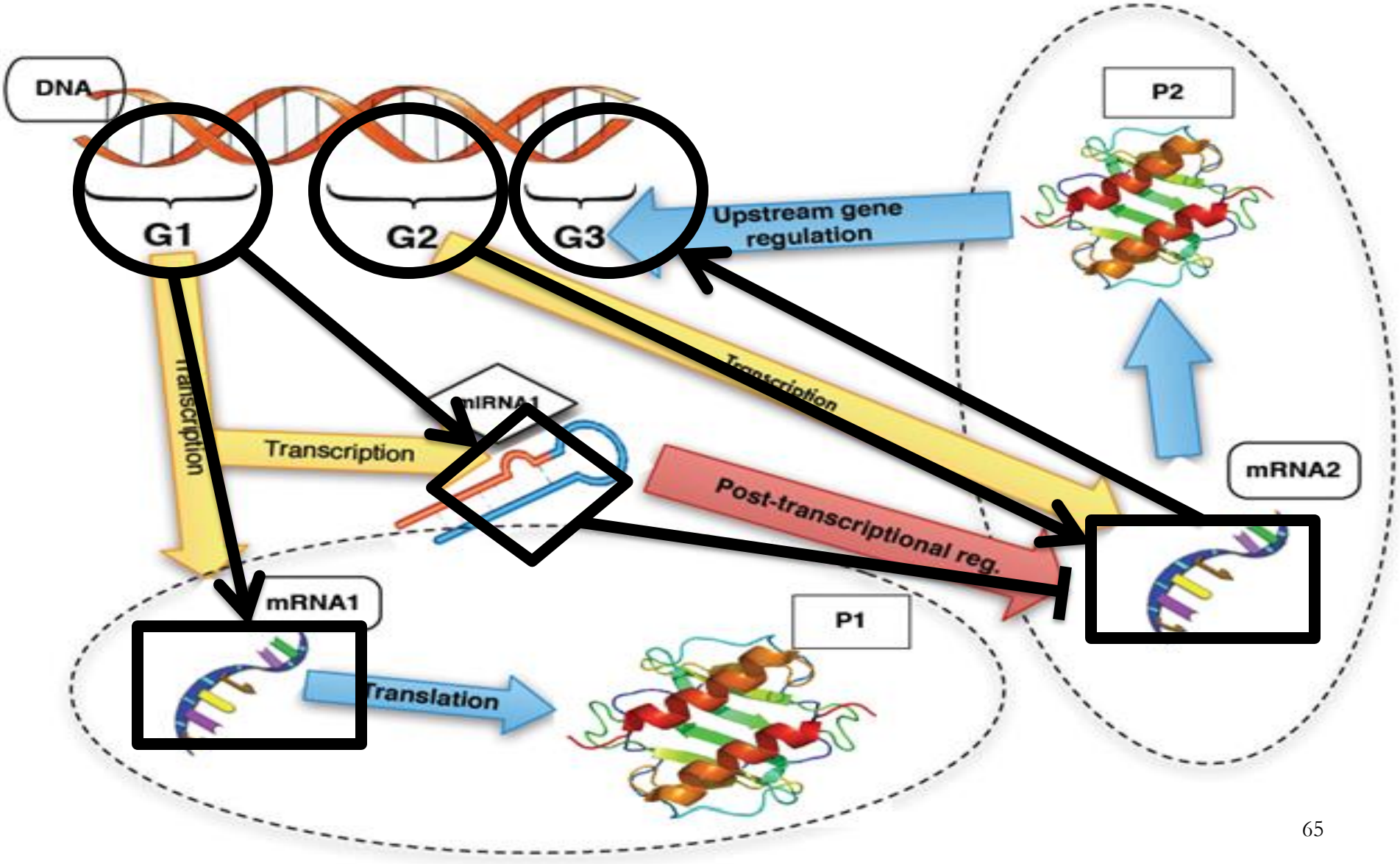
- A **system** is a set of interacting or interdependent components forming a complex/intricate whole.
- A **complex system** is a system that exhibits some (and possibly all) of the following characteristics:
  - feedback loops;
  - some degree of spontaneous order/organization;
  - the order is robust;
  - Numer`osity;
  - hierarchical organization.
- Examples of complex systems are, the **human brain**, **social organization (e.g. cities, towns etc)**, **an ecosystem**, **a living cell**, and ultimately the entire universe.

# Why Networks?

- Networks are a useful model to study COMPLEX SYSTEMS, as most biological systems are.
- Complex systems cannot be described by a single rule and they exhibit properties that emerge from the interaction of their parts and which **cannot be predicted only from the properties of their parts**.
- Networks allow to easily model the interconnections between different components of a complex system and study its emerging properties.

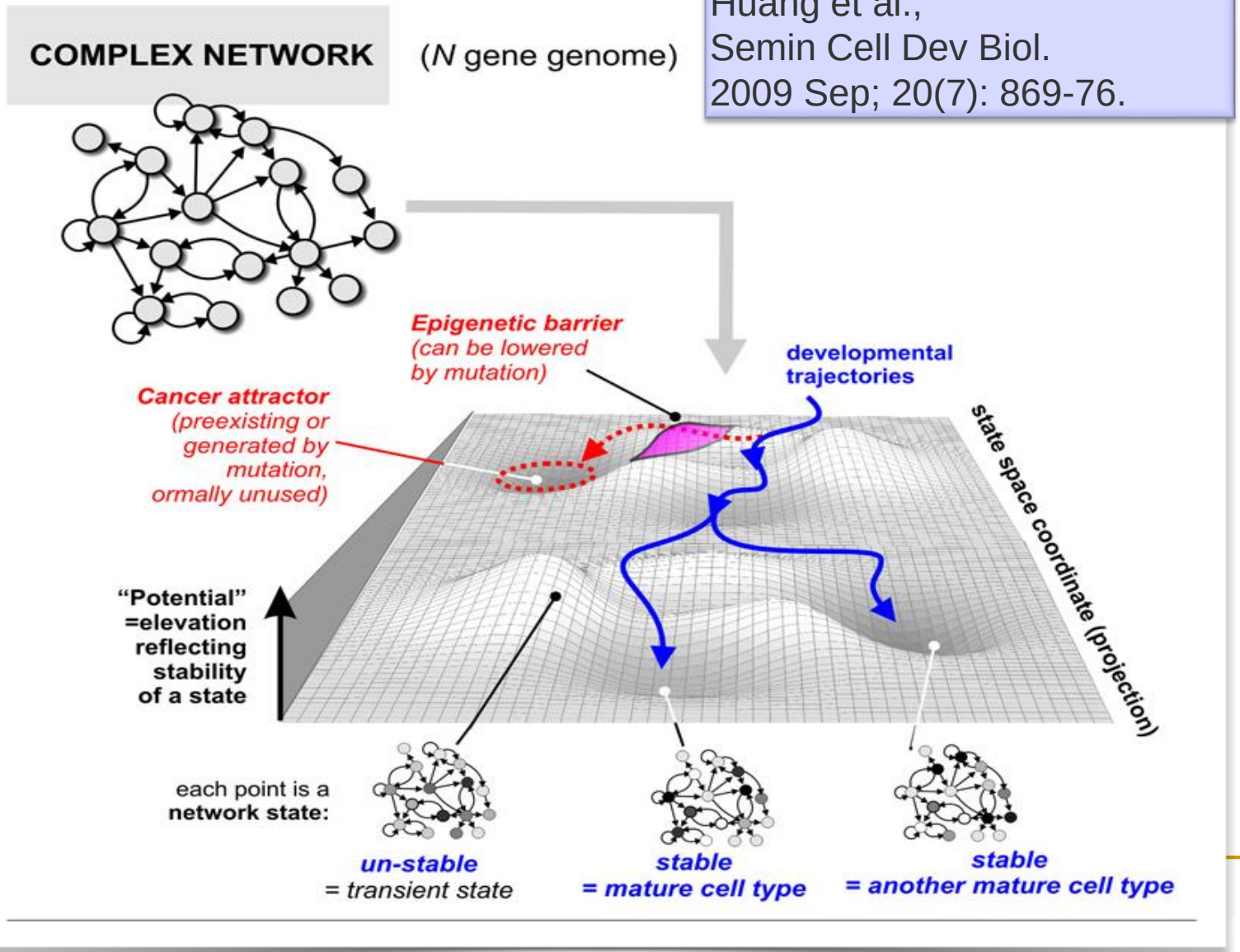


# Gene Regulatory Networks (GRN)

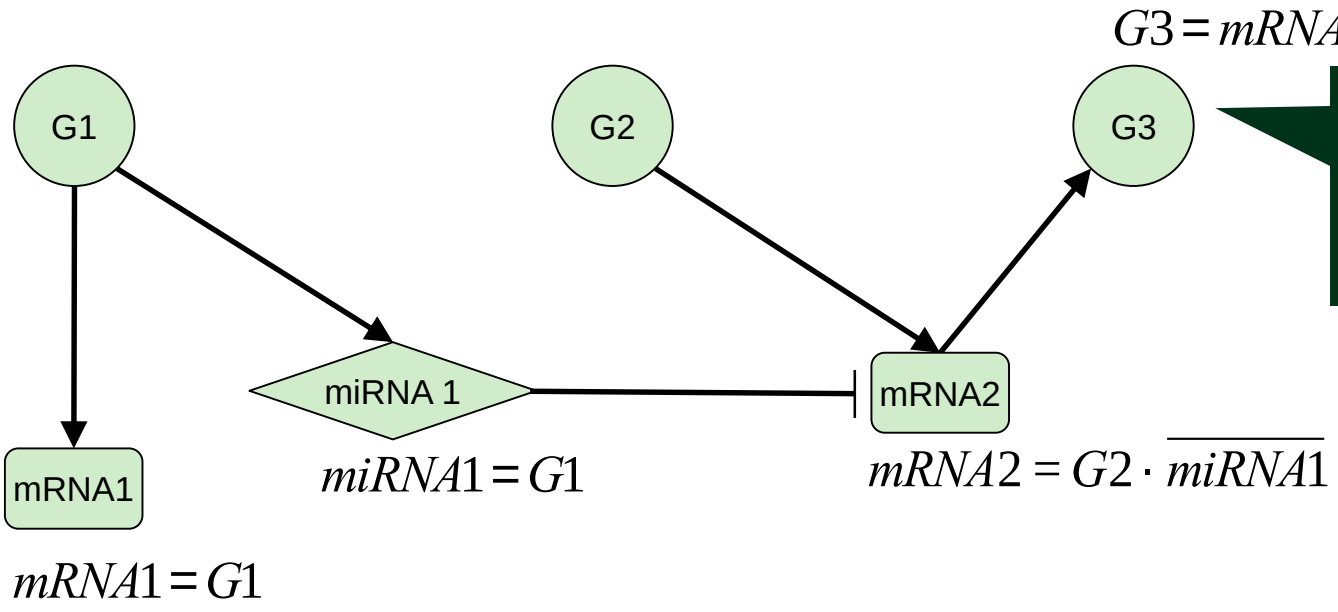


# Impact: Epigenetic Landscape

Huang et al.,
Semin Cell Dev Biol.
2009 Sep; 20(7): 869-76.



# Boolean Network Model




The state of a node at time (t+1) is determined by the Boolean function of its k-inputs at time (t).

Biological constraints

$C1 = mRNA1 \cdot \overline{G1}$

$C2 = miRNA1 \cdot \overline{G1}$

$C3 = mRNA2 \cdot \overline{G2}$

**Must be false**

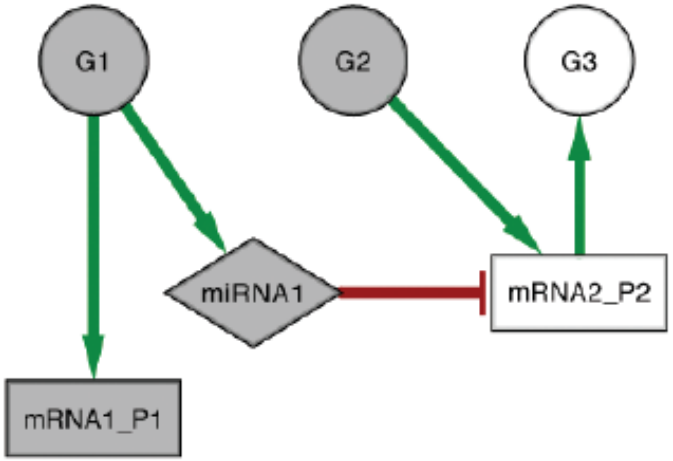
The network is simulated to identify

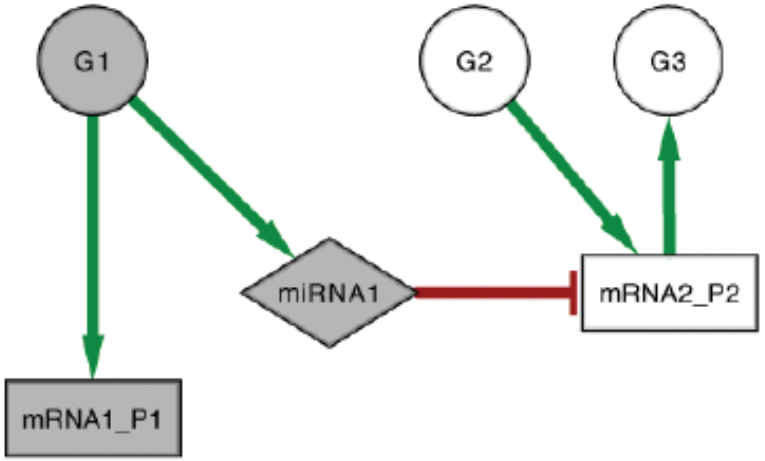
- stable states (**attractors**)
- trajectories
- state spaces
- state potentials

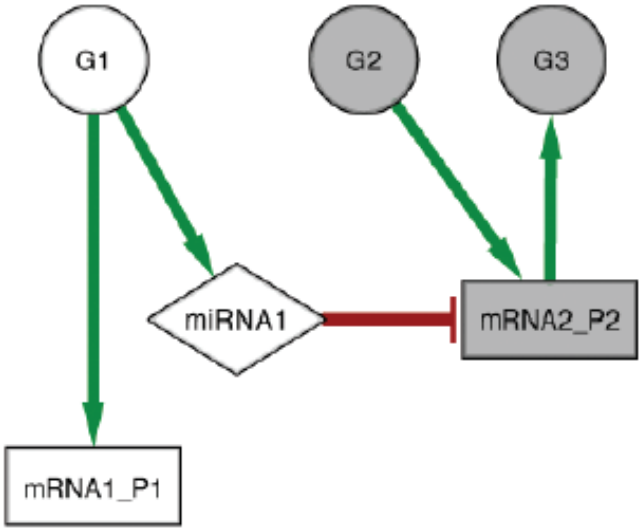
# Gene Regulatory Networks (GRNs)

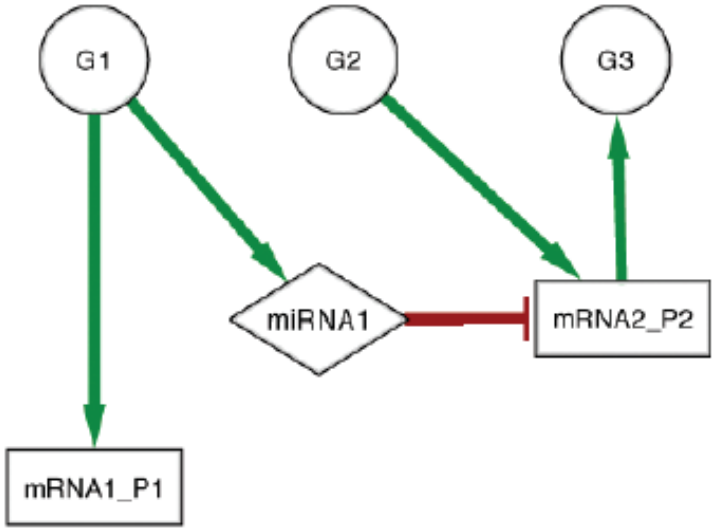
- Modeling GRNs with Boolean Networks (BNs):
  - Directed graphs
  - Nodes are Genes/Proteins/mRNAs/miRNAs
  - State of Every Node is 0/1.
- Simulator identifies:
  - Stable States (attractors)
  - Trajectories
  - State Space
- Avoids:
  - Biologically impossible states

# Identified Attractor States

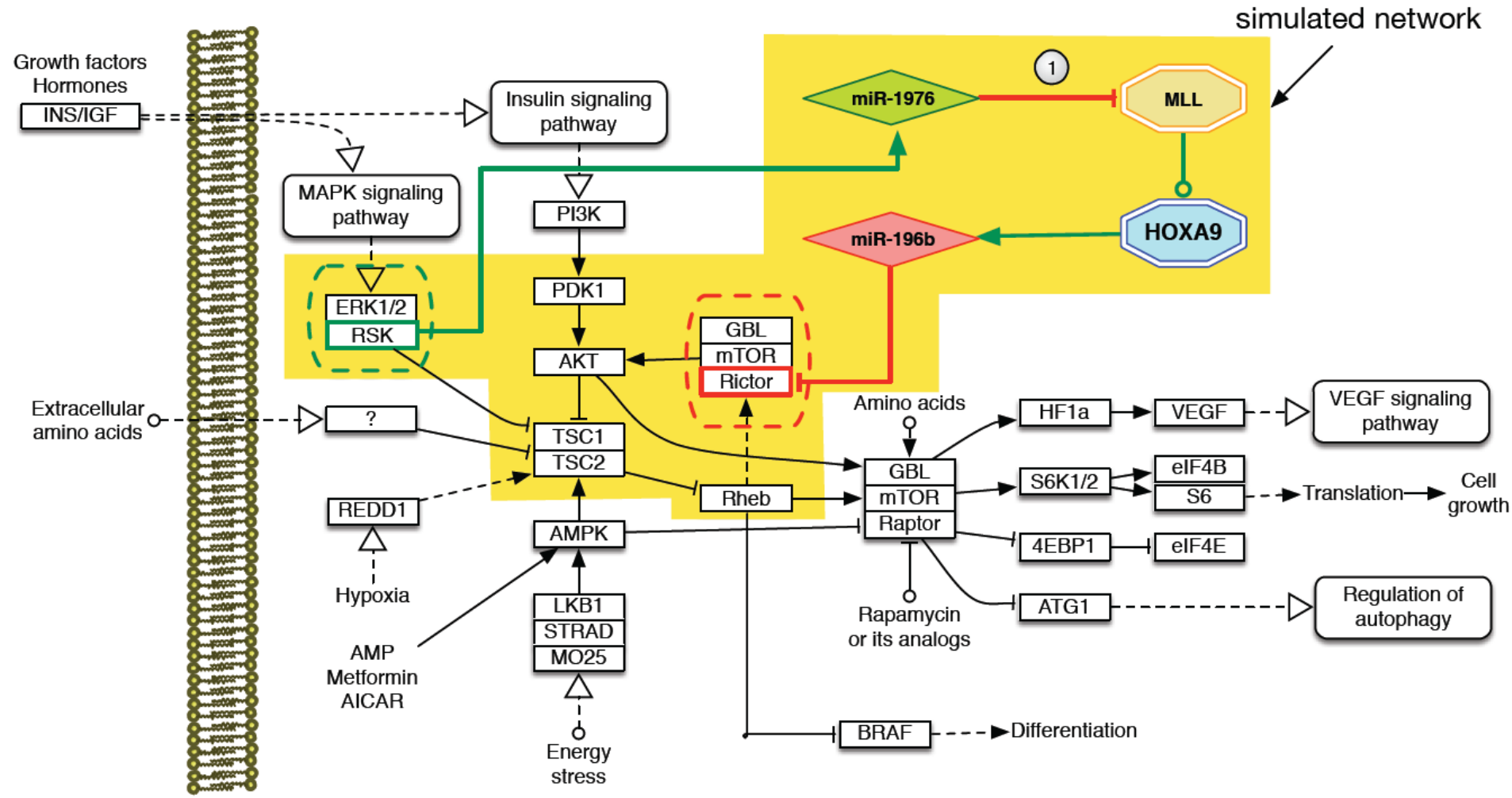


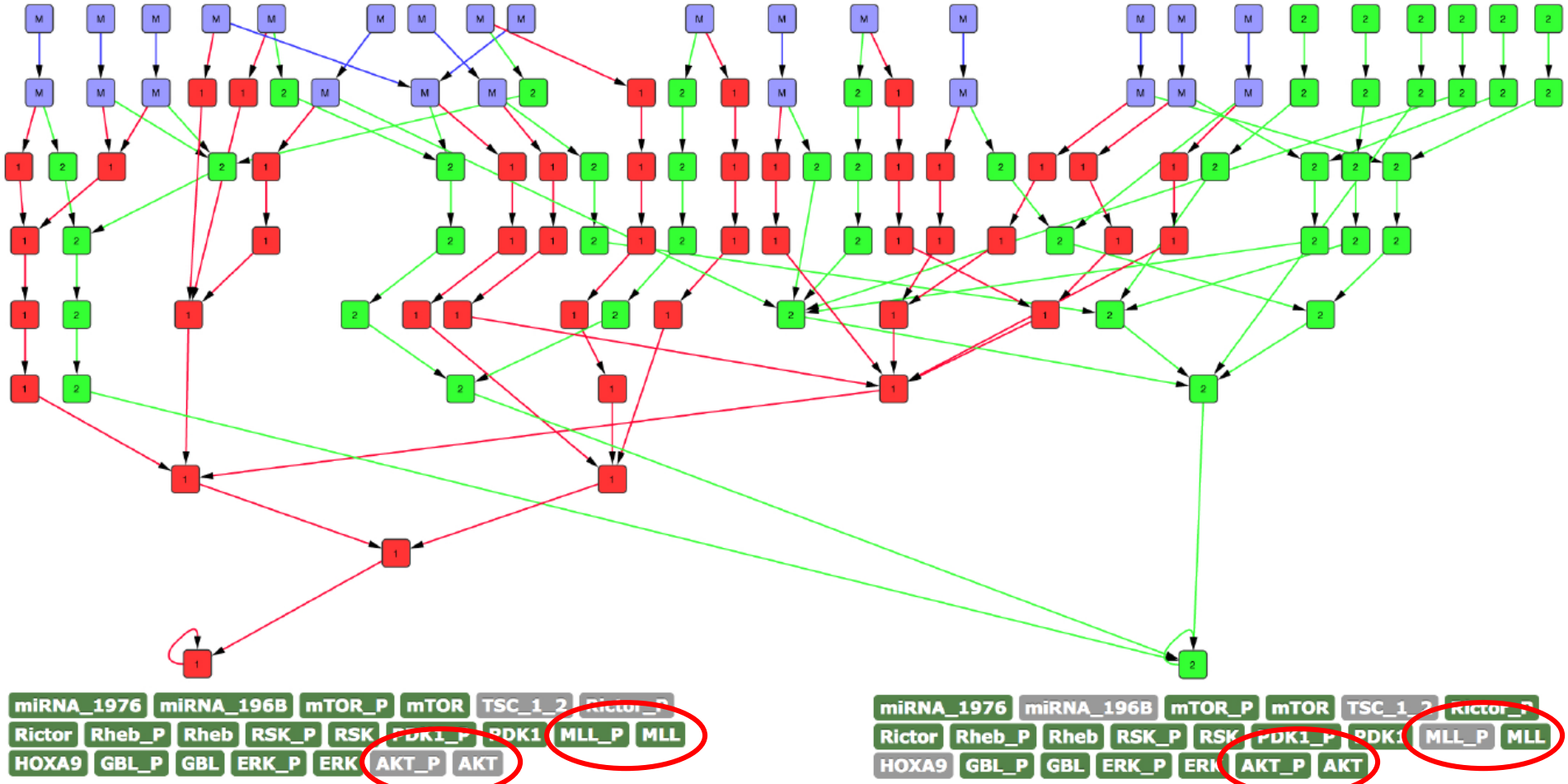



# Tool to Study Dynamics (Example: mTOR Pathway)



# Simulation Result



# End of Lecture Set 01