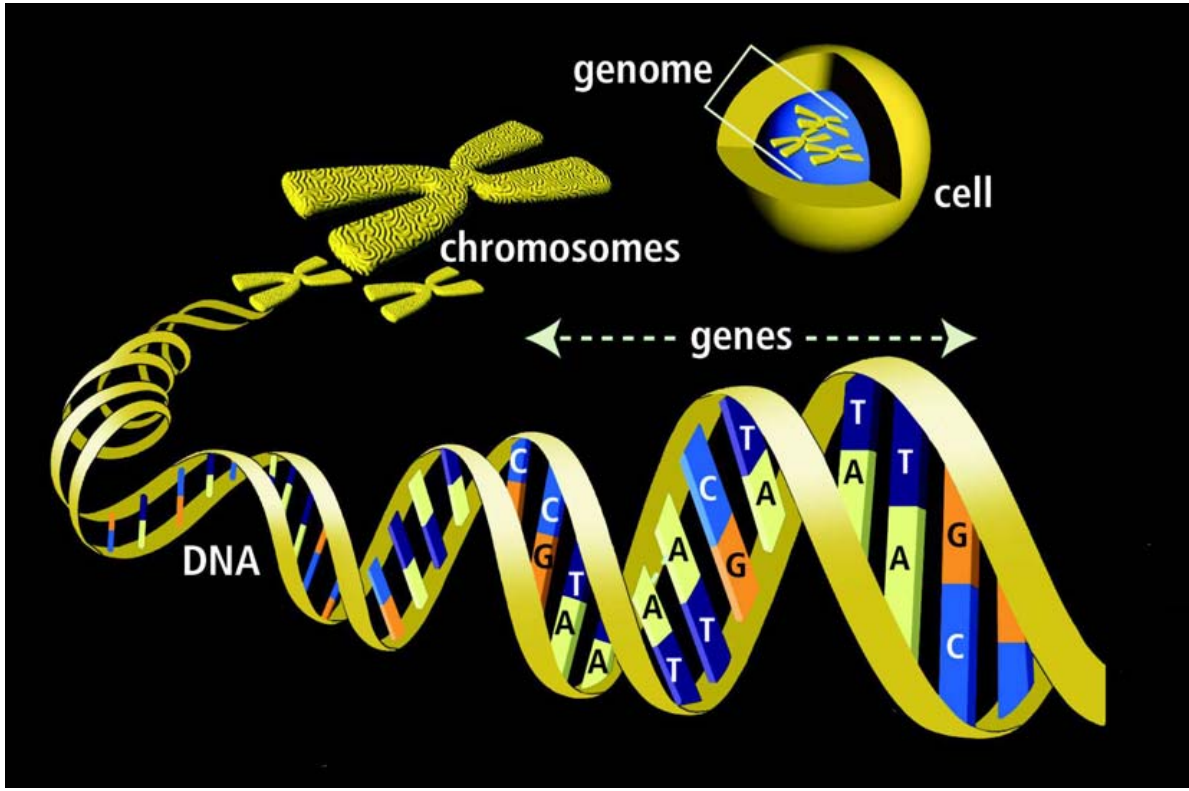
BME 5742 Biosystems Modeling and Control

Lecture 27
Gene Regulatory Networks
Part 1
Unregulated Gene Expression Model

DNA and Genes

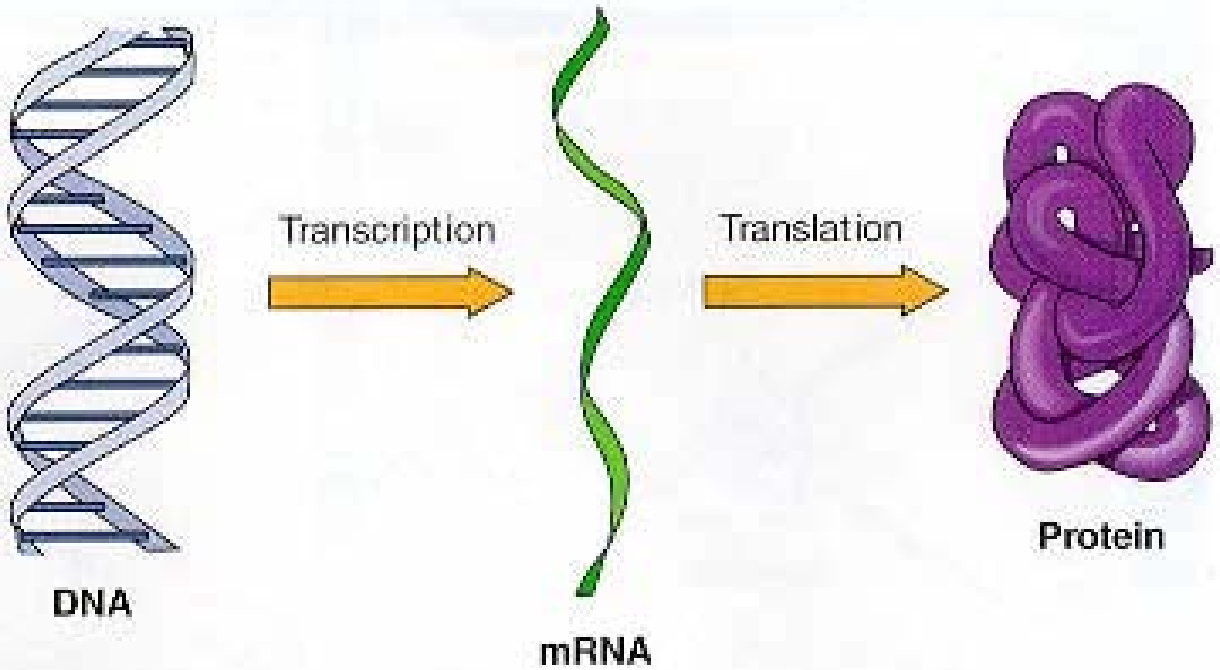
- The genetic material inside a cell, encoded in its DNA, governs the response of a cell to various conditions.
- DNA is organized into collections of genes, with each gene encoding a corresponding protein that performs a set of functions in the cell.



Introductory Comments about Gene Expression

- All cellular functions are driven by proteins
- Protein production occurs through Gene Expression
- Gene expression is a two-step process that involves at the start the reading of information encoded in the DNA and at the end a synthesis of a protein molecule
- The production rate of each protein is controlled by proteins called Transcription Factors

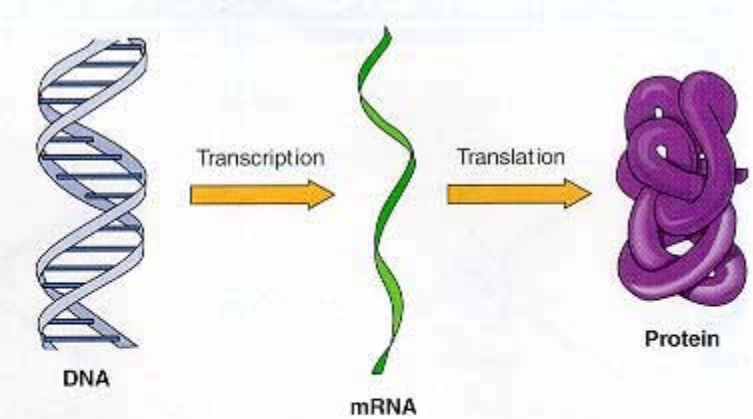
The Central Dogma of Biology



Central Dogma of Gene Expression.

Through the production of mRNA (transcription) and the synthesis of proteins (translation), the information contained in DNA is expressed.

Transcription Definition

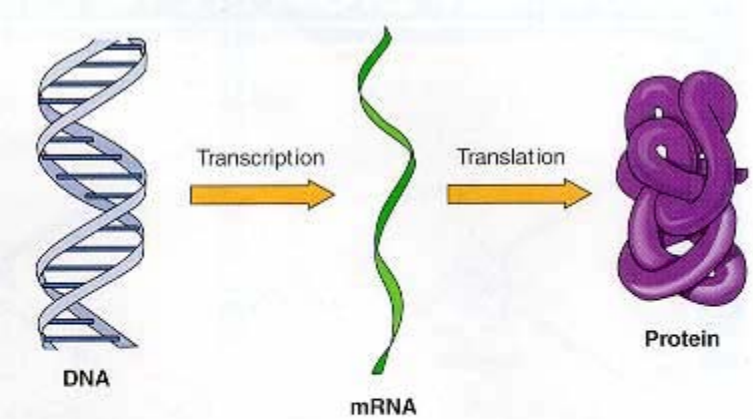


Central Dogma of Gene Expression.

Through the production of mRNA (transcription) and the synthesis of proteins (translation), the information contained in DNA is expressed.

- The process by which the coding region of a gene is “rewritten” in the form of a complementary RNA strand called messenger RNA (mRNA)

Translation Definition

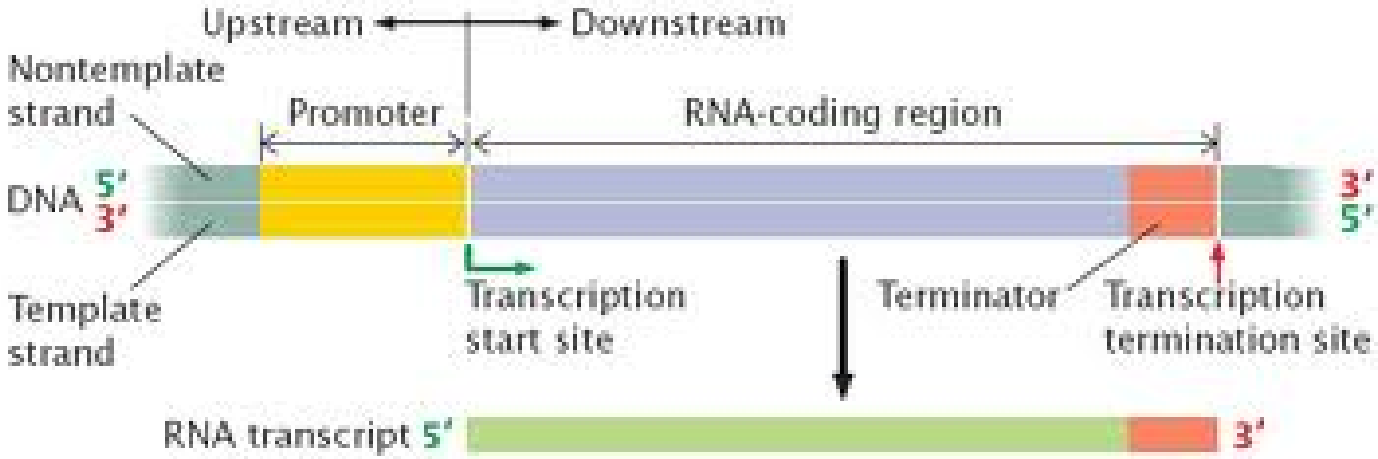


Central Dogma of Gene Expression.

Through the production of mRNA (transcription) and the synthesis of proteins (translation), the information contained in DNA is expressed.

- The process by which the mRNA binds to a ribosome which reads the nucleotide sequence and produces a corresponding polypeptide chain
- That chain, when done, spontaneously folds to create the protein

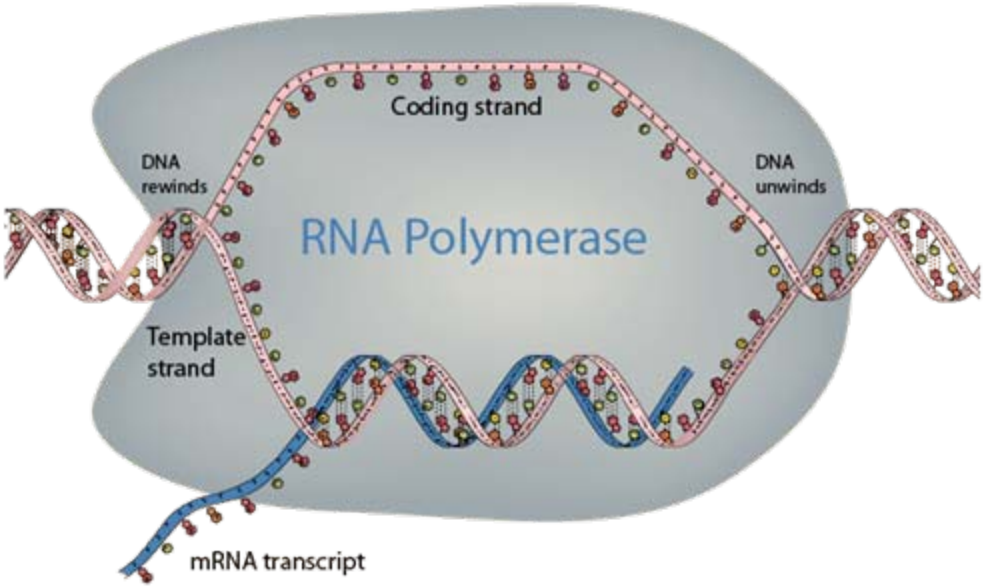
Gene Regions



- Any DNA segment that encodes some protein production must include specific regions:
- Promoter, Regulation, Coding and Termination

The Transcription Process

- RNA Polymerase enzyme first binds to the promoter part of the gene.
- Once bound it splits open the DNA strands.
- Then the enzyme moves along the coding part of the gene to create an mRNA sequence

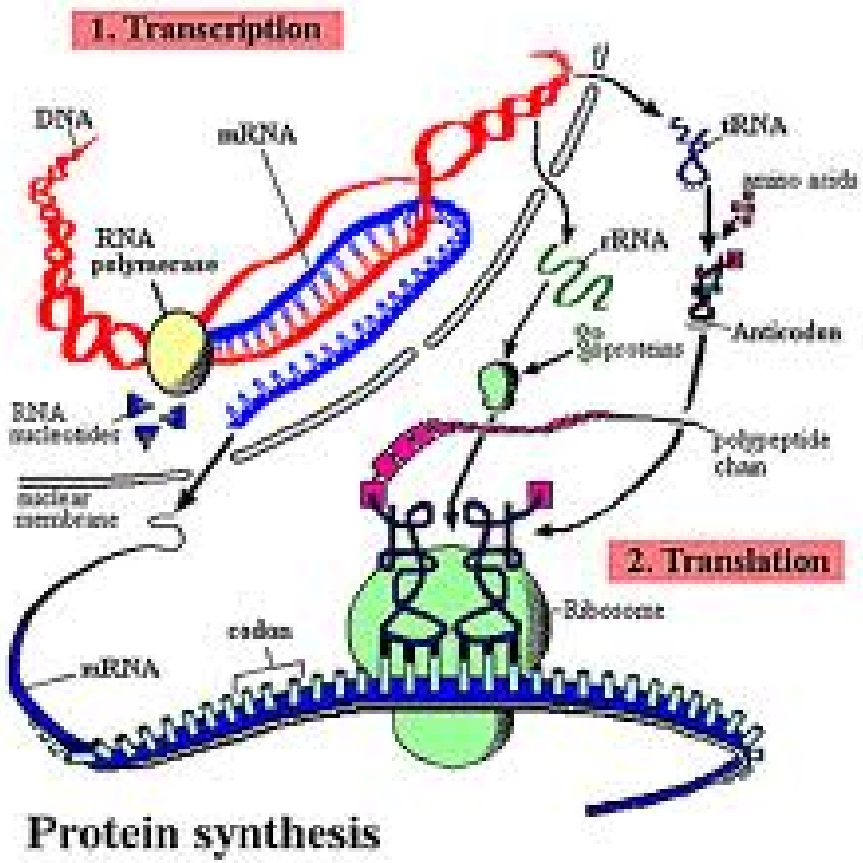


Once the enzyme finds the termination sequence it detaches from the DNA and the transcription ends

Cell and mRNA – Typical Timing Figures

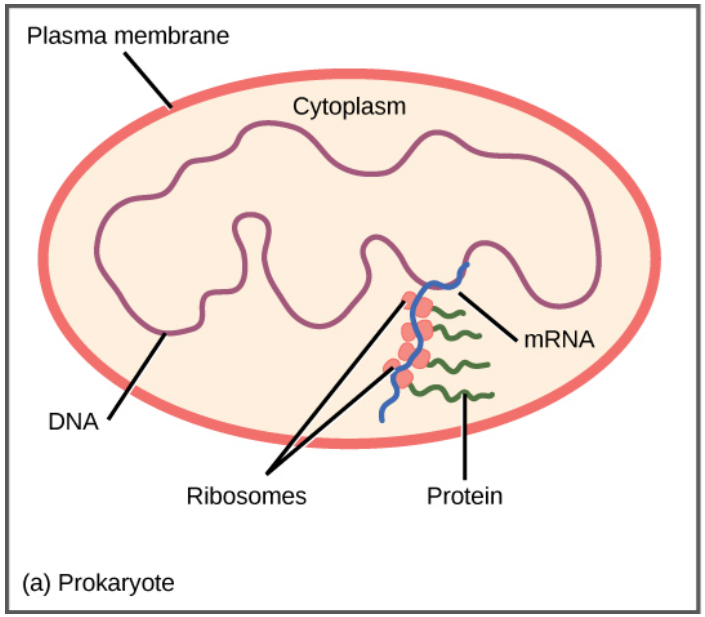
- Production rate of mRNA = 10-30 base pairs per second
- Half life of mRNA is around 100 seconds
- Cell division time is around 3000 seconds

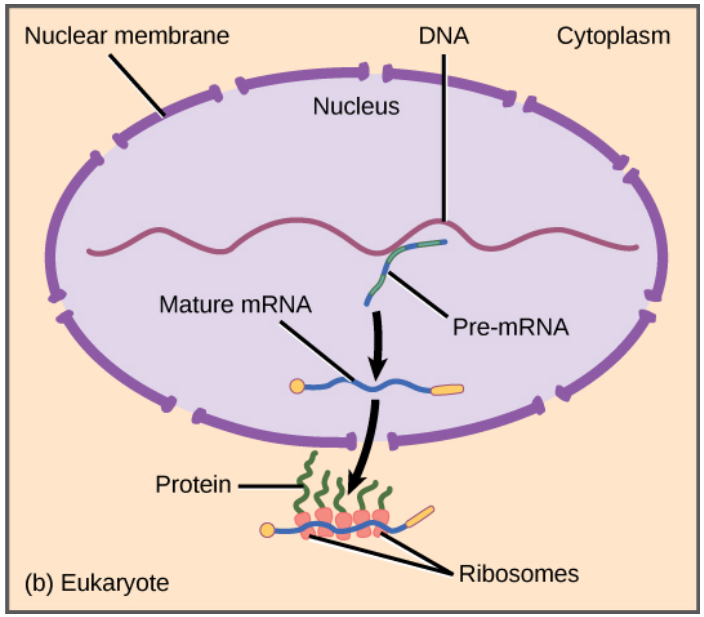
From Transcription to Translation



- DNA strands re-attach, become ready for more copies of the same mRNA or other ones.
- RNA goes through some pre-processing steps, and is eventually transported out of the nucleus and into the cytoplasm
- RNA then encounters the ribosomes

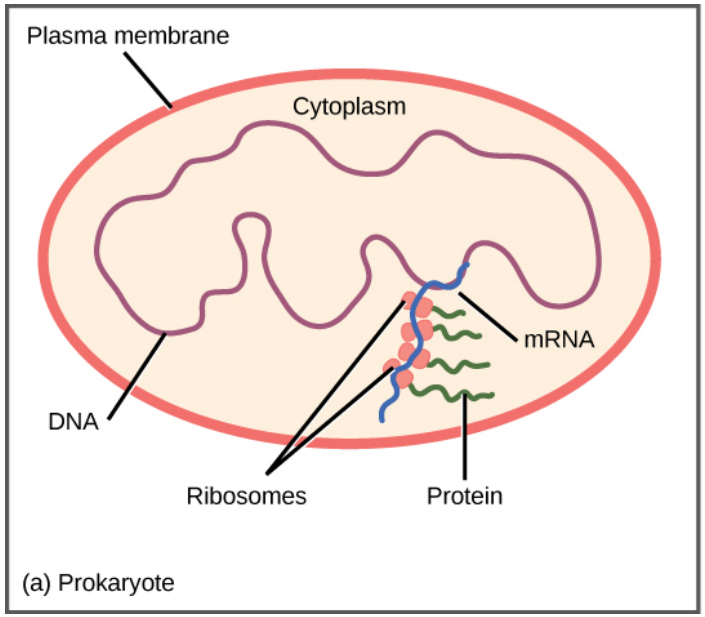
From Transcription to Translation in Prokaryotic and Eukaryotic Cells

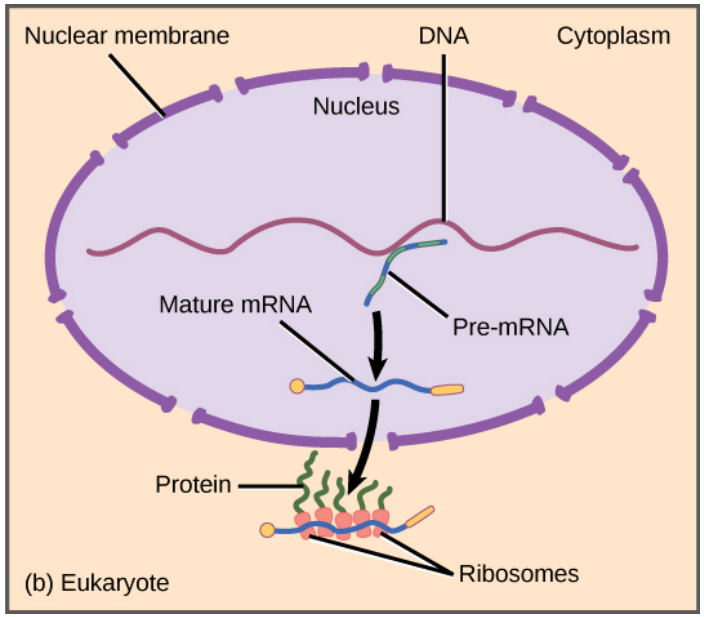




- No nucleus in prokaryotic cells → mRNA as it is produced encounters the ribosomes → Translation starts

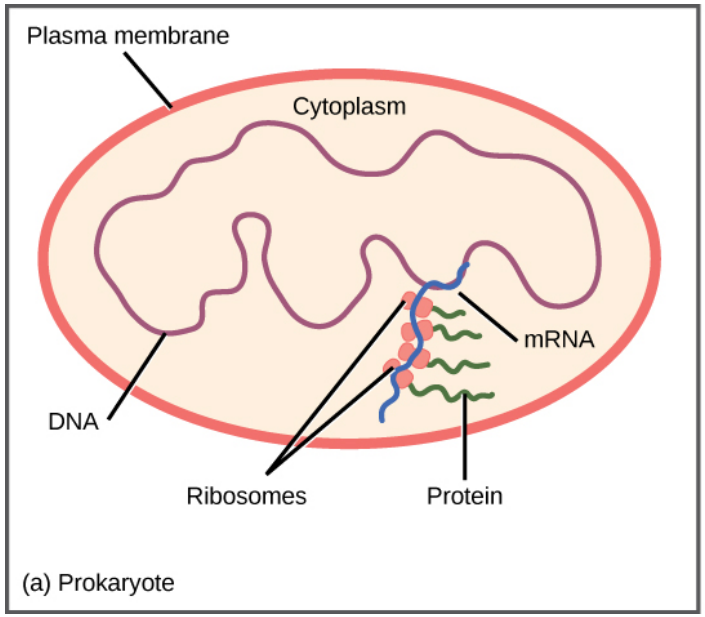
From Transcription to Translation in Prokaryotic and Eukaryotic Cells

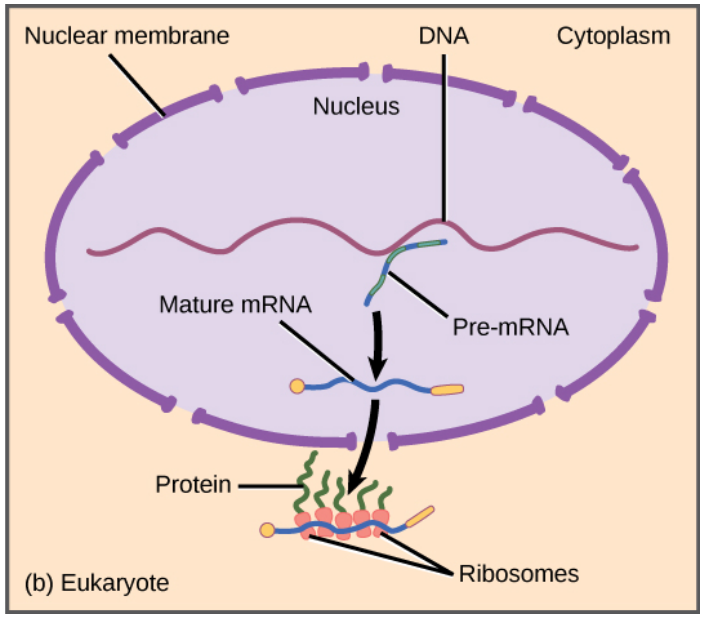




- In eukaryotic cells → mRNA needs to be transported from the nucleus to the cytoplasm ←→ Some "pre-processing" of the mRNA is needed

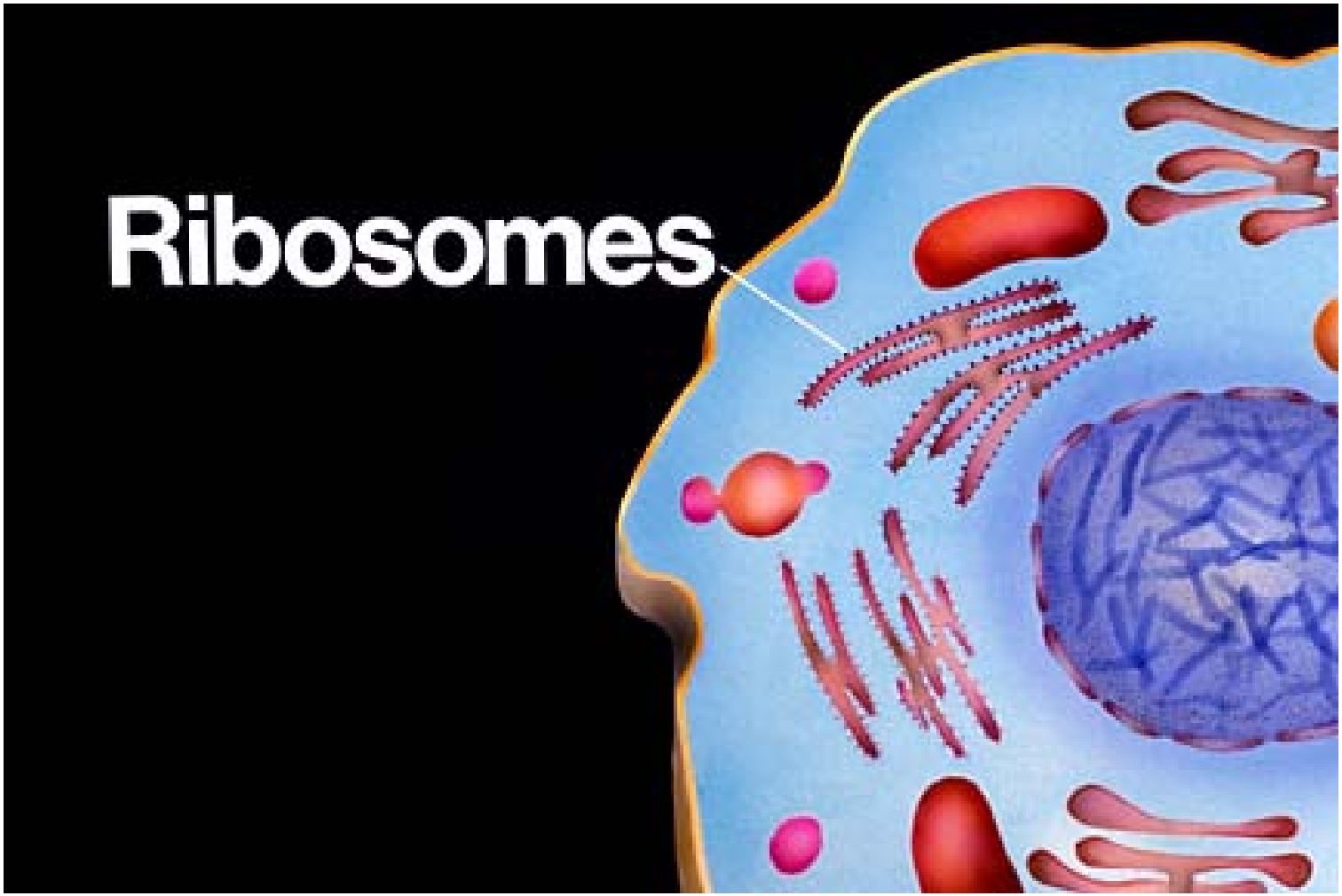
From Transcription to Translation in Prokaryotic and Eukaryotic Cells



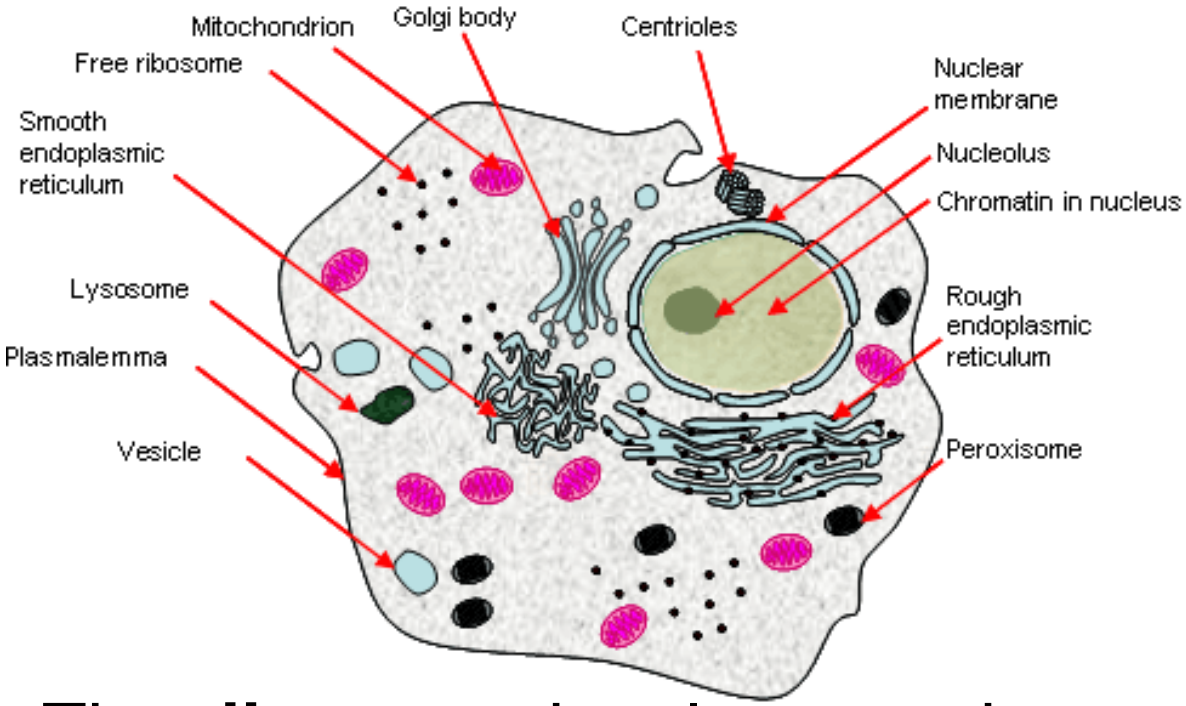


- In eukaryotic cells → In pre-mRNA needs to excise of introns, splice of exons, attach an ending segment (polyadenylation) → Mature mRNA → Transport out of the nucleus

Ribosomes



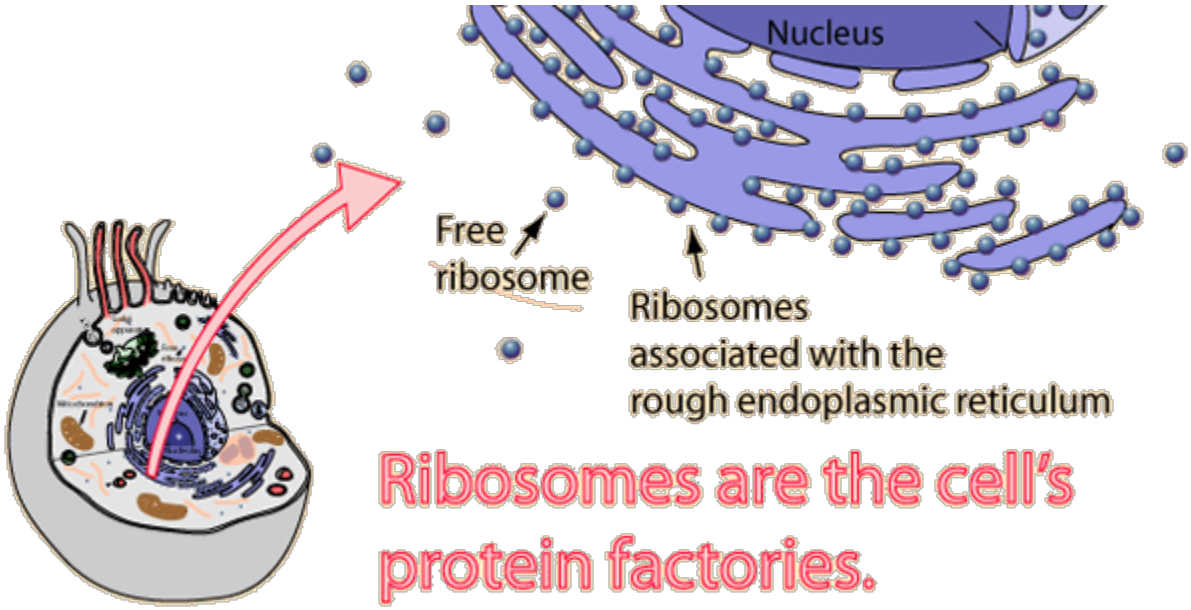
What are Ribosomes?



The **ribosome** is a large and complex molecular machine, found within all living cells, that serves as the primary site of biological protein synthesis (translation).

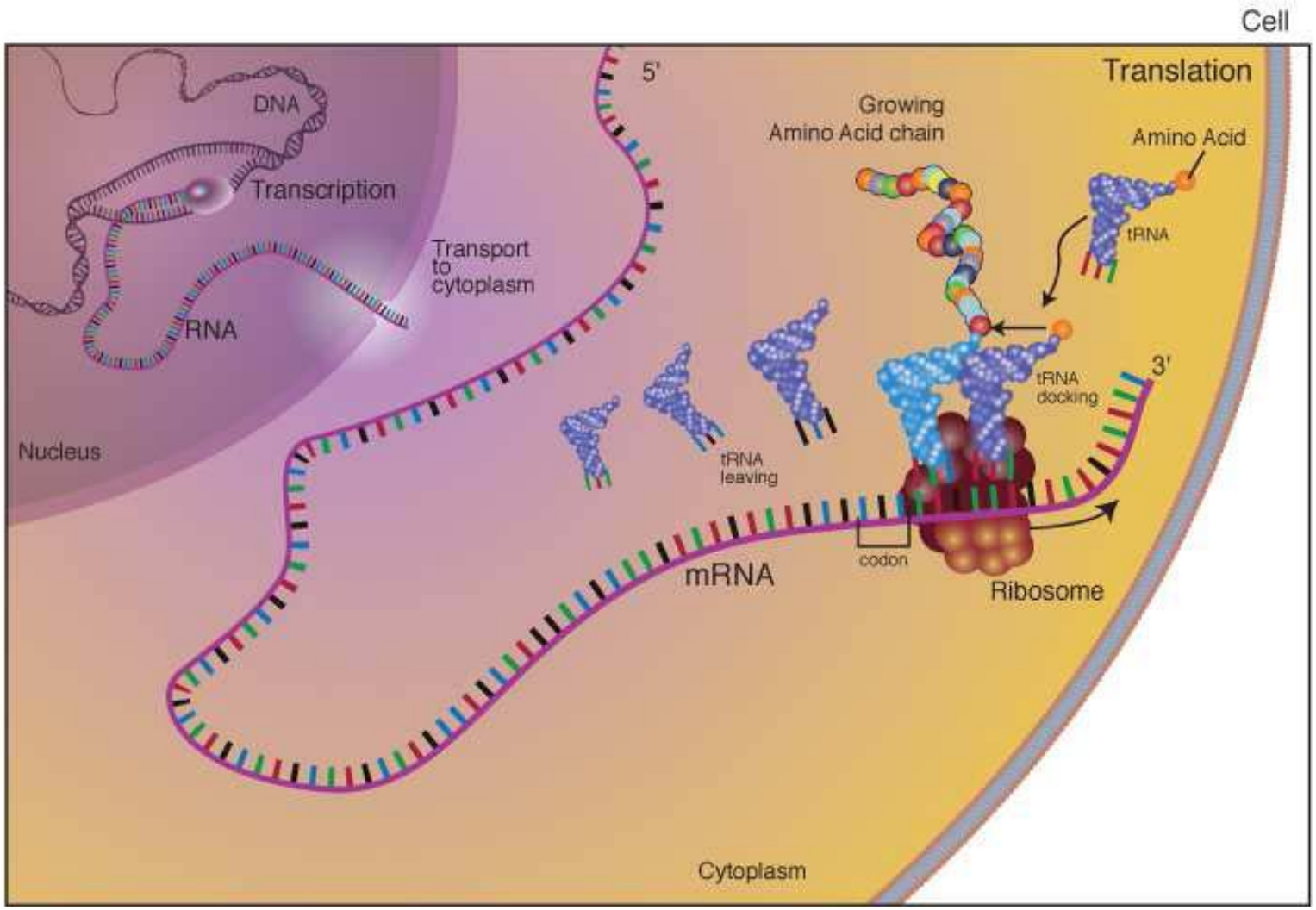
Ribosomes link amino acids together in the order specified by messenger RNA (mRNA) molecules.

Ribosomes Major Subunits

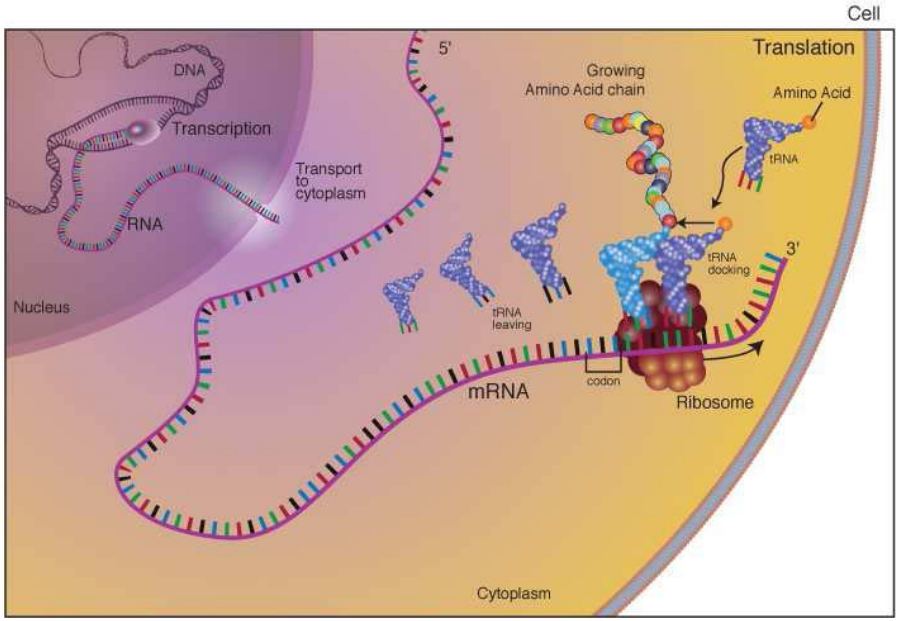


Ribosomes consist of two major subunits—the small ribosomal subunit reads the mRNA, while the large subunit joins amino acids to form a polypeptide chain. Each subunit is composed of one or more ribosomal RNA (rRNA) molecules and a variety of proteins.

The Translation Process

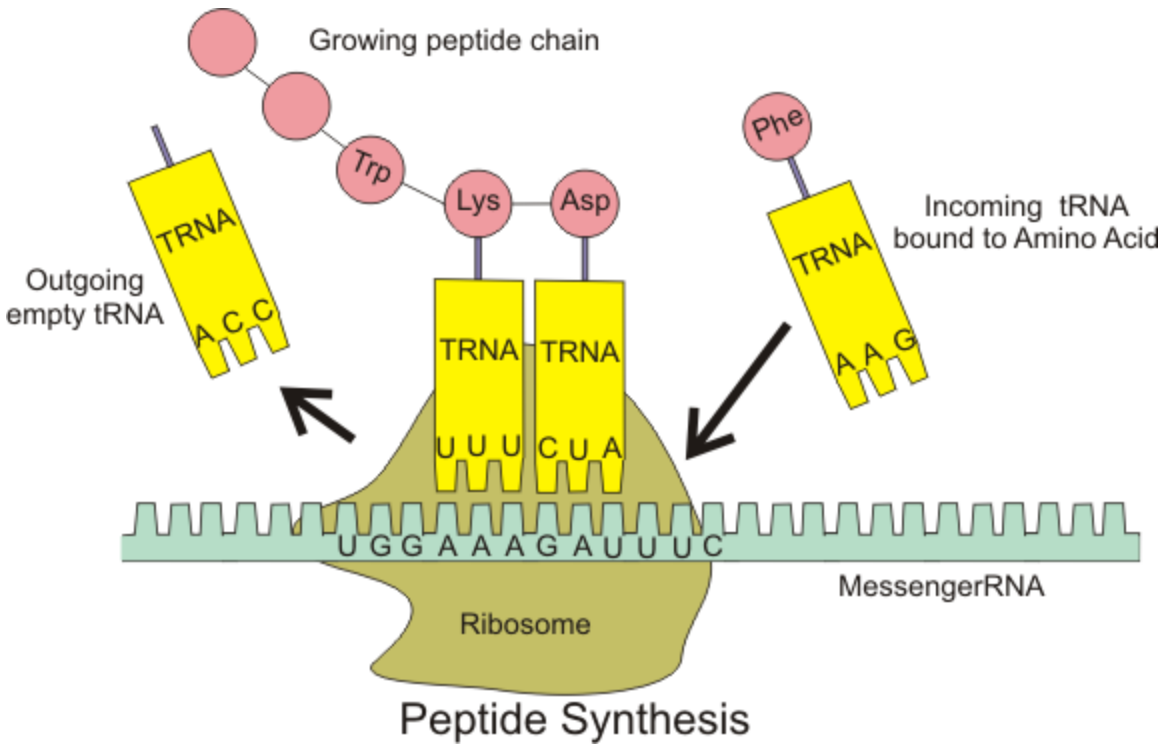


Translation: the role of tRNA



- The mRNA goes through the ribosome.
- Each mRNA codon is translated by tRNA as to what would be the next protein link to be assembled (selecting one of 20 possible amino acids)

Ribosomes, mRNA, tRNA and Translation



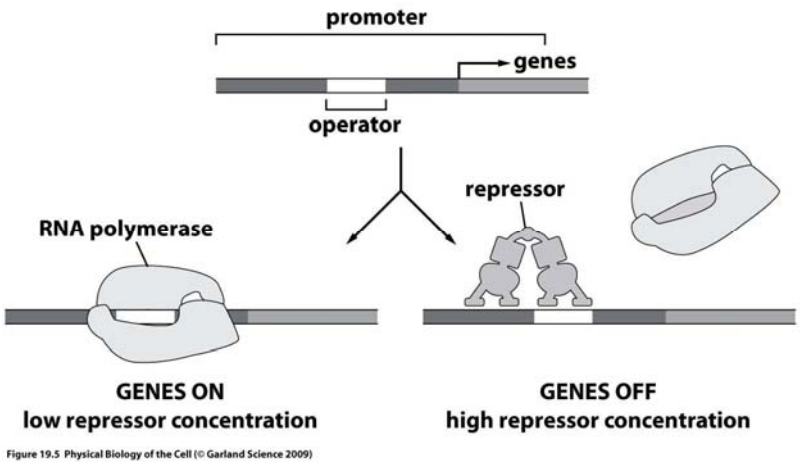
The cell must have sufficient number of types of tRNA molecules (between 31 and 61)

The assembled protein folds on itself to create its functional 3D shape.

Protein – typical timing figures

- Protein production time is around 10-30 amino acids per second
- Protein half life is around 50,000 seconds (much larger than the cell's division time).

Transcriptional Regulation



- DNA transcription may be regulated by Repressors and Activators
- Transcription factors (such as proteins that bind the DNA near its promoter region – operator region) may turn the gene off.
- Activators enhance the binding of RNA Polymerase to the promoter.

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t)$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t)$$

- A highly approximated prokaryotic gene expression
- Concentration of mRNA molecules = m(t)
- Concentration of gene's protein product = p(t)

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t)$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t)$$

- Average transcription rate = k_0
- The rate k_0 depends on the number of gene copies, the abundance of RNA polymerase, the affinity of gene's promoter to the transcription factor and the availability of nucleotide building blocks

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t)$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t)$$

- Per-mRNA translation rate = k_1
- The rate k_1 depends on availability of ribosomes, affinity of the mRNA to the ribosome binding site, availability of tRNA and free amino acids.

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t)$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t)$$

- Transcription and translation are balanced by the decay of the mRNA and protein pools, characterized by the δ rates.
- There are enzymes that their role is to decimate the mRNA and specific protein molecues.

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t)$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t)$$

- The δ rates also include the dilution effect due to the increase of cell volume to accommodate the constructed new protein molecules.

Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t) \qquad \frac{dm(t)}{dt} = 0 \rightarrow \boxed{m_e = \frac{k_0}{\delta_m}}$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t) \qquad \frac{dp(t)}{dt} = 0 \rightarrow \boxed{p_e} = \frac{k_1}{\delta_p} m_e = \boxed{\frac{k_1}{\delta_p}\frac{k_0}{\delta_m}}$$

- So, this simplified unregulated gene expression model is linear
- Equilibrium point is shown above.
- Typically, m(t) reaches equilibrium much faster than p(t)

More Simplified Mathematical Model of Unregulated Gene Expression

$$\frac{dm(t)}{dt} = k_0 - \delta_m m(t) \qquad \frac{dm(t)}{dt} = 0 \rightarrow \boxed{m_e = \frac{k_0}{\delta_m}}$$

$$\frac{dp(t)}{dt} = k_1 m(t) - \delta_p p(t) \qquad \frac{dp(t)}{dt} = 0 \rightarrow \boxed{p_e} = \frac{k_1}{\delta_p} m_e = \boxed{\frac{k_1}{\delta_p}\frac{k_0}{\delta_m}}$$

- Typically, m(t) reaches equilibrium in minutes which is much faster than p(t) that reaches equilibrium in hours.

$$\boxed{\frac{dp(t)}{dt} \approx \frac{k_1 k_0}{\delta_m} - \delta_p p(t)}$$

Simplified model for protein synthesis, where k_1k_0/δ_m is the expression rate