# REGULATION OF GENE EXPRESSION:

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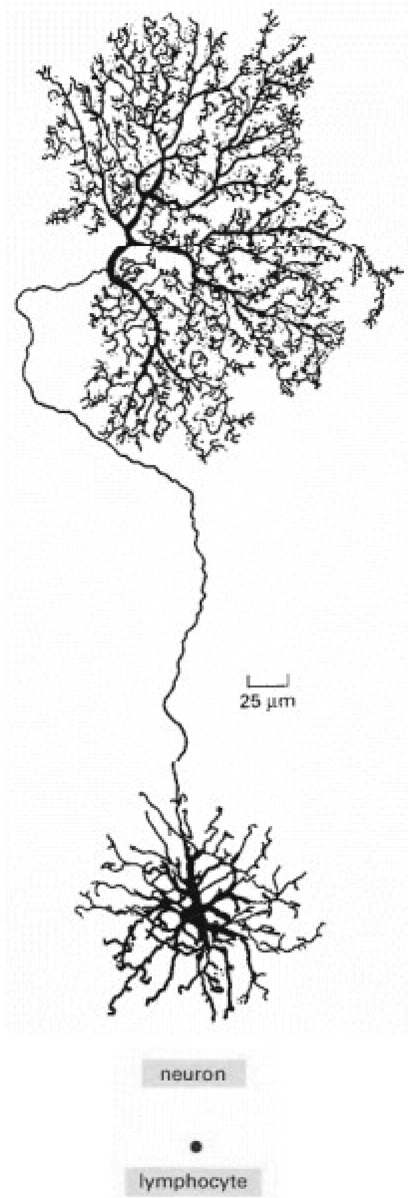
# What is Gene Expression?

- It is the process by which information from a gene is used in the synthesis of a functional gene product.
- These products are often proteins, but in non-protein coding genes such as rRNA genes or tRNA genes, the product is a functional RNA .




**Gene expression regulation:**

Both of these cells contain the same genome, but they express different RNAs and proteins.

# *Classification of gene with respect to their Expression:*

- **Constitutive ( house keeping) genes:**
- 1- Are expressed at a fixed rate, irrespective to the cell condition.
- 2- Their structure is simpler
- ***Controllable genes:***
- 1- Are expressed only as needed. Their amount may increase or decrease with respect to their basal level in different condition.
- 2- Their structure is relatively complicated with some response elements

- Several steps in the gene expression process may be modulated, including the
- 1.transcription,
- 2. RNA splicing
- 3.translation, and
- 4.post-translational modification of a protein.

- Process of alteration of gene expressis been studied has been studied in in detail&involves modulation of gene trascription.

  transcription control can result in tissue specific gene expression&influenced by hormones,heavy metals.

  In simple terms,regulation of gene expression is of two types
  1.positive regulation.
  2.negative regulation.

# *1.positive regulation:*

When the expression of genetic is quantitatively increased by the presence of specific regulatory element is known as positive regulation.

Element modulating positive regulation is known as activator or positive regulator.

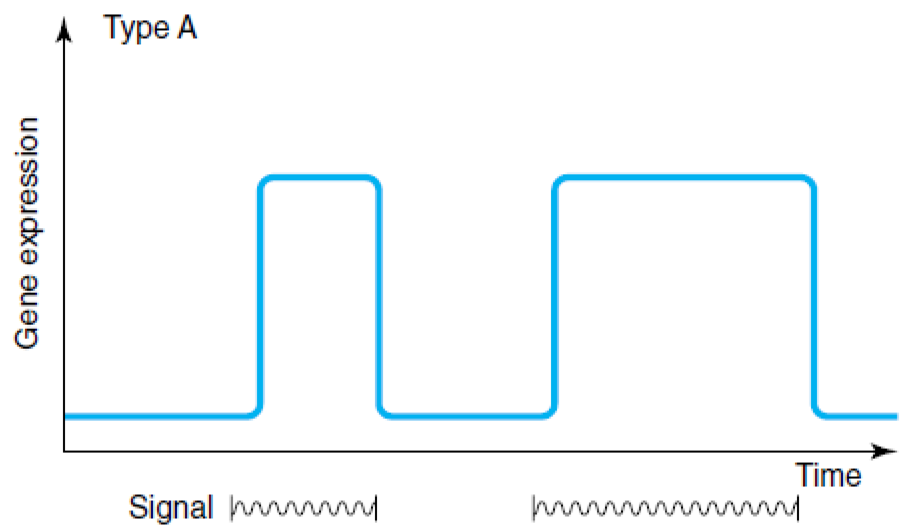
# 2.Negative regulation.

- when the expression of genetic information diminished by the presence of specific regulatory element.
- The element or molecule mediating the negative regulation is said to be repressor.

# *Biological systems exhibits 3 types of temporal responses:*

- Type A response: incresed extent of gene expression is continued in presence of inducing signal.
- This is commonly observed in prokaryotes in responce to intracellular conc. Of nutrient.
- TYPE B response:incrsed amount of g.ex. Is transient even in presence of regulatory signal.
- This is seen in commonly during development of organism.

| | Rate of Gene Expression | |
|---|---|---|
| | Negative Regulation | Positive Regulation |
| Regulator present | Decreased | Increased |
| Regulator absent | Increased | Decreased |



Type c response:increased gene expression that persists even after termination of signal.

It is seen in development of tissur or organ.

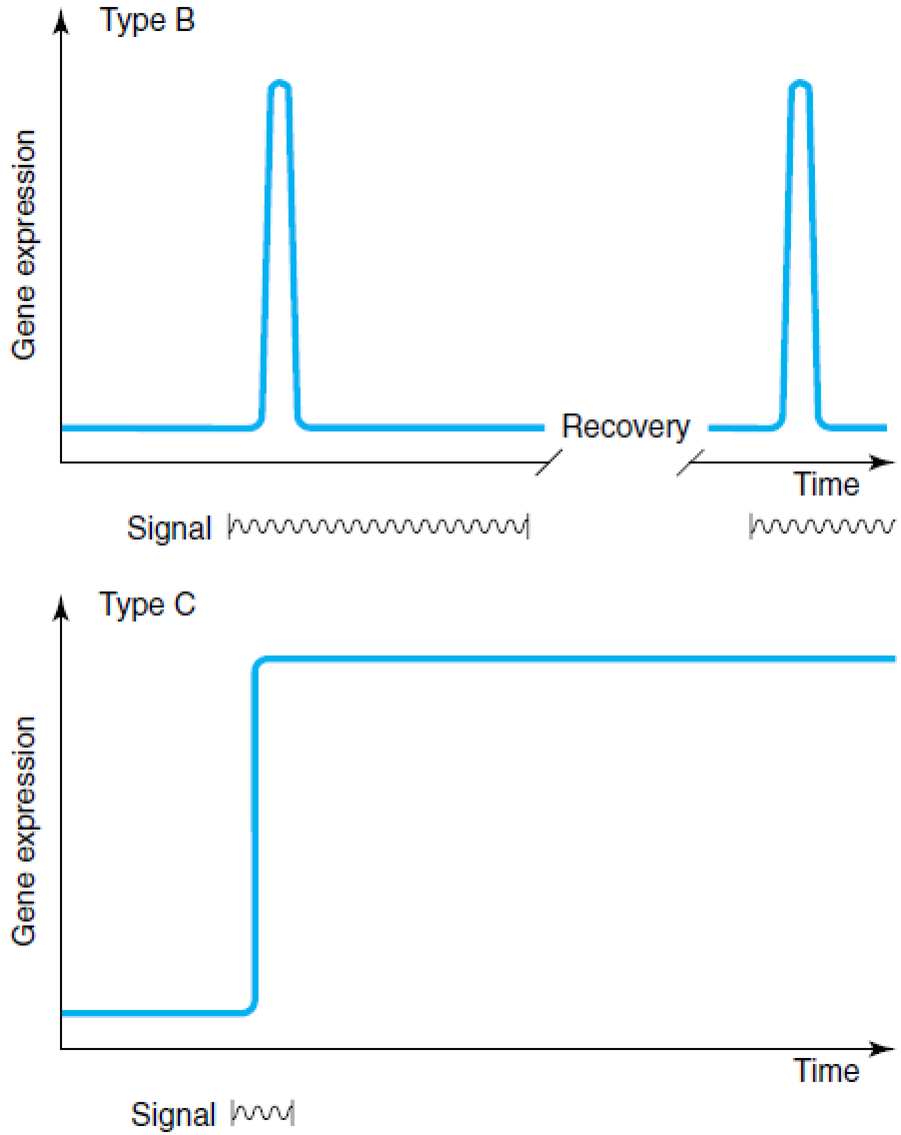
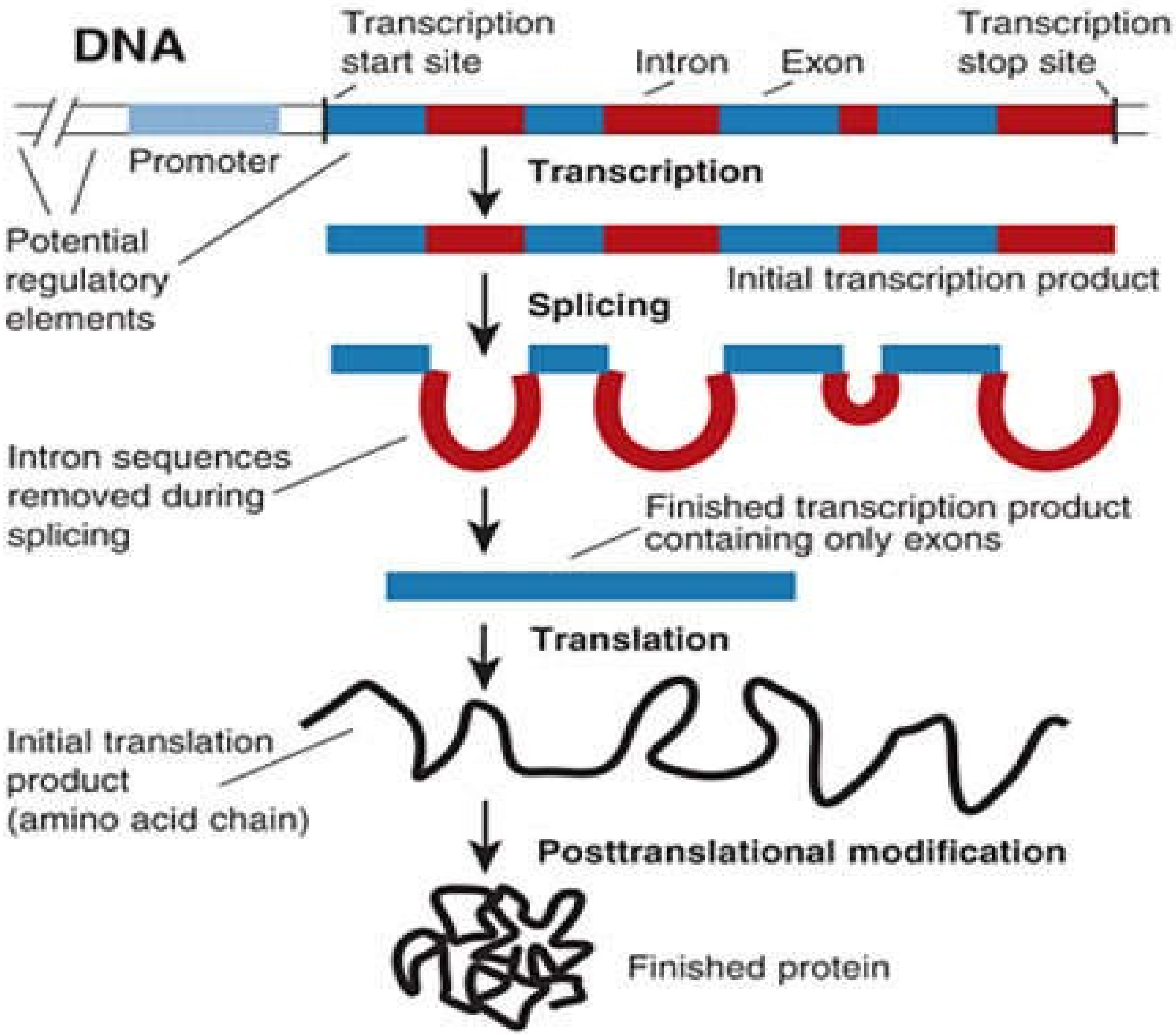



***Figure 39–1.*** Diagrammatic representations of the responses of the extent of expression of a gene to specific regulatory signals such as a hormone.

## ***To know and explain:***

- Regulation of Bacterial Gene Expression
- Constitutive ( house keeping) vs. Controllable genes
- OPERON structure and its role in gene regulation
- Regulation of Eukaryotic Gene Expression at different levels:
  - DNA methylation
  - Increasing the number of gene copies (gene amplification)
  - Changing the rate of initiation of transcription
  - Alternate splicing
  - mRNA stability
  - Changing the rate of initiation of translation
  - Using of Untranslating Region (UTR)
  - protein stability
  - Hormonal regulation
- Cross talk between different regulatory pathways

- ***Regulation of gene expression*** *(or* ***gene regulation****):*
- _includes the processes that cells and viruses use to turn the information in genes into gene products.
- Although a functional gene product may be an RNA or a protein, the majority of known mechanisms regulate protein coding genes
- Any step of the gene's expression may be modulated, from DNA-RNA transcription to the post-translational modification of a protein.


DNA
Transcription start site
Intron
Exon
Transcription stop site
Promoter
Transcription
Potential regulatory elements
Initial transcription product
Splicing
Intron sequences removed during splicing
Finished transcription product containing only exons
Translation
Initial translation product (amino acid chain)
Posttranslational modification
Finished protein

Gene regulation is essential for viruses, prokaryotes and eukaryotes as it increases the versatility and adaptability of an organism by allowing the cell to express protein when needed.

The first discovered example of a gene regulation system was the lac operon, discovered by Jacques Monod, in which protein involved in lactose metabolism are expressed by *E.coli* only in the presence of lactose and absence of glucose.

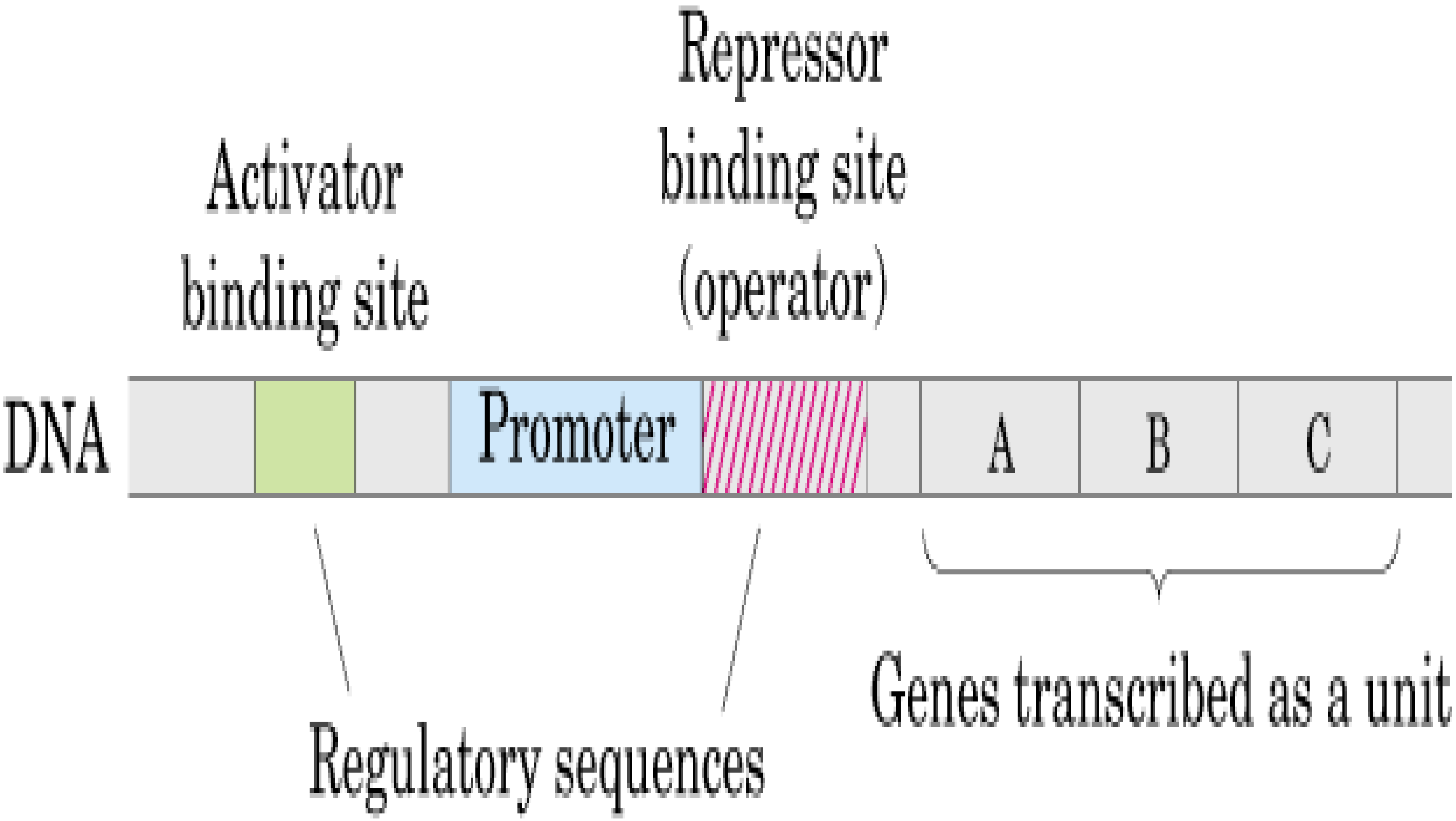
- Furthermore, gene regulation drives the processes of cellular differentiation and morphogenesis, leading to the creation of different cell types in multicellular organisms where the different types of cells may possess different gene expression profile.

## *Regulation of Gene Expression:*

- Principles of gene regulation
- Regulation of gene expression in prokaryotes
- Regulation of gene expression in eukaryotes

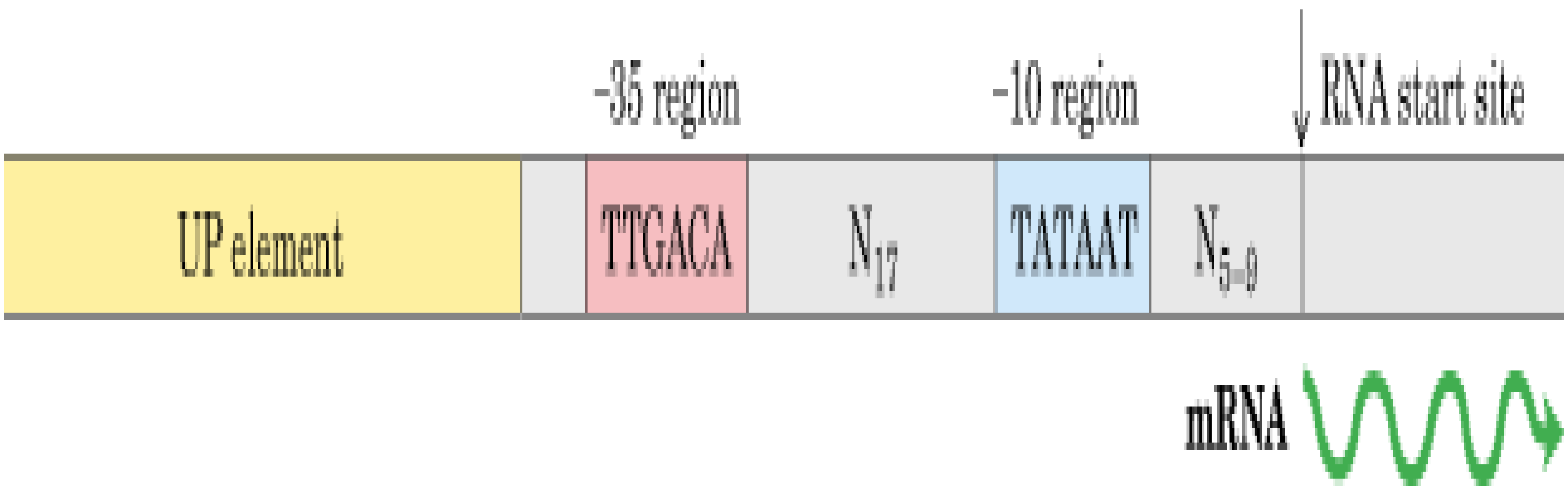
*__Principles of Gene Regulation:__*
Most prokaryotic genes are regulated in units
called operons.
Francois Jacob & Jacques Monod, 1961.
This is largely based on regulation of lactose metabolism. By intestina

# *Operon:*


Activator binding site
Repressor binding site (operator)
DNA
Promoter
A
B
C
Regulatory sequences
Genes transcribed as a unit

## ***Principles of Gene Regulation:***

1) RNA polymerase binds to DNA at promoters



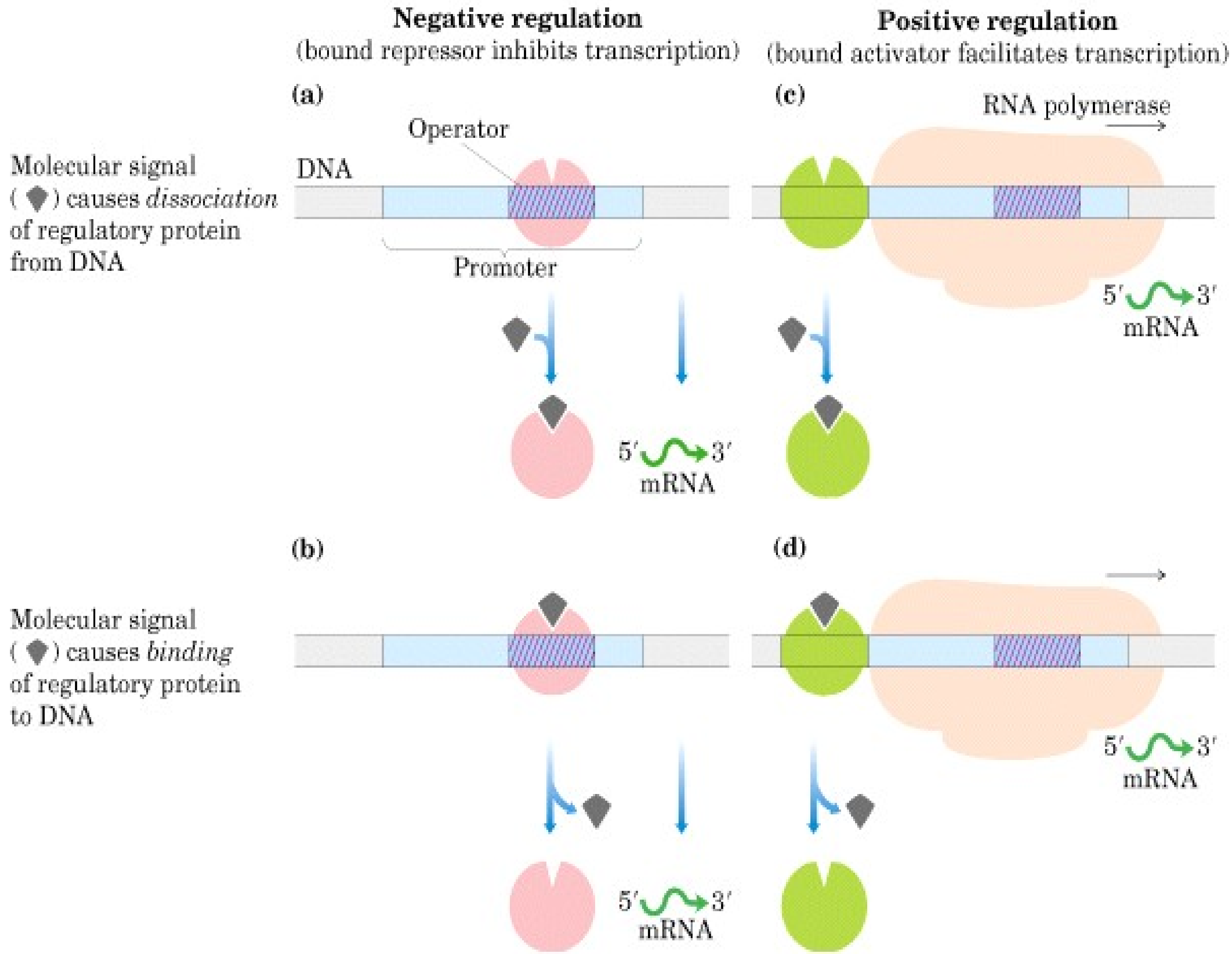
2) Transcription initiation is regulated by proteins that bind to or near promoters.

Repression of a repressible gene:(*i.e., negative regulation)* repressors (vs. activators) bind to operators of DNA.

Repressor is regulated by an effector, usually a small molecule or a protein, that binds and causes a conformational change.

Activator binds to DNA sites called enhancer to enhance the RNA polymerase activity. (*i.e., positive regulation)*

Induction of an inducible gene, *e.g., heat-shock genes.*


Negative regulation
(bound repressor inhibits transcription)
Positive regulation
(bound activator facilitates transcription)
(a)
Operator
DNA
Promoter
5′ 3′
mRNA
(c)
RNA polymerase
5′ 3′
mRNA
Molecular signal ( ) causes dissociation of regulatory protein from DNA
(b)
5′ 3′
mRNA
(d)
5′ 3′
mRNA
Molecular signal ( ) causes binding of regulatory protein to DNA

# Gene Regulation in Prokaryotes

# *Different ways for regulation of gene expression in bacteria:*

- **1- Promoter recognition.**
- **2-Transcription elongation( Attenuation).**

Regulation of gene expression can be done by some operon pathways such as

1.lac operon.

2.tryptophan operon.

# *OPERON in gene regulation of prokaryotes:*

**Definition:** **a few genes that are controlled collectively by one promoter**

**Its structure:** **Each Operon is consisted of few structural genes( cistrons) and**

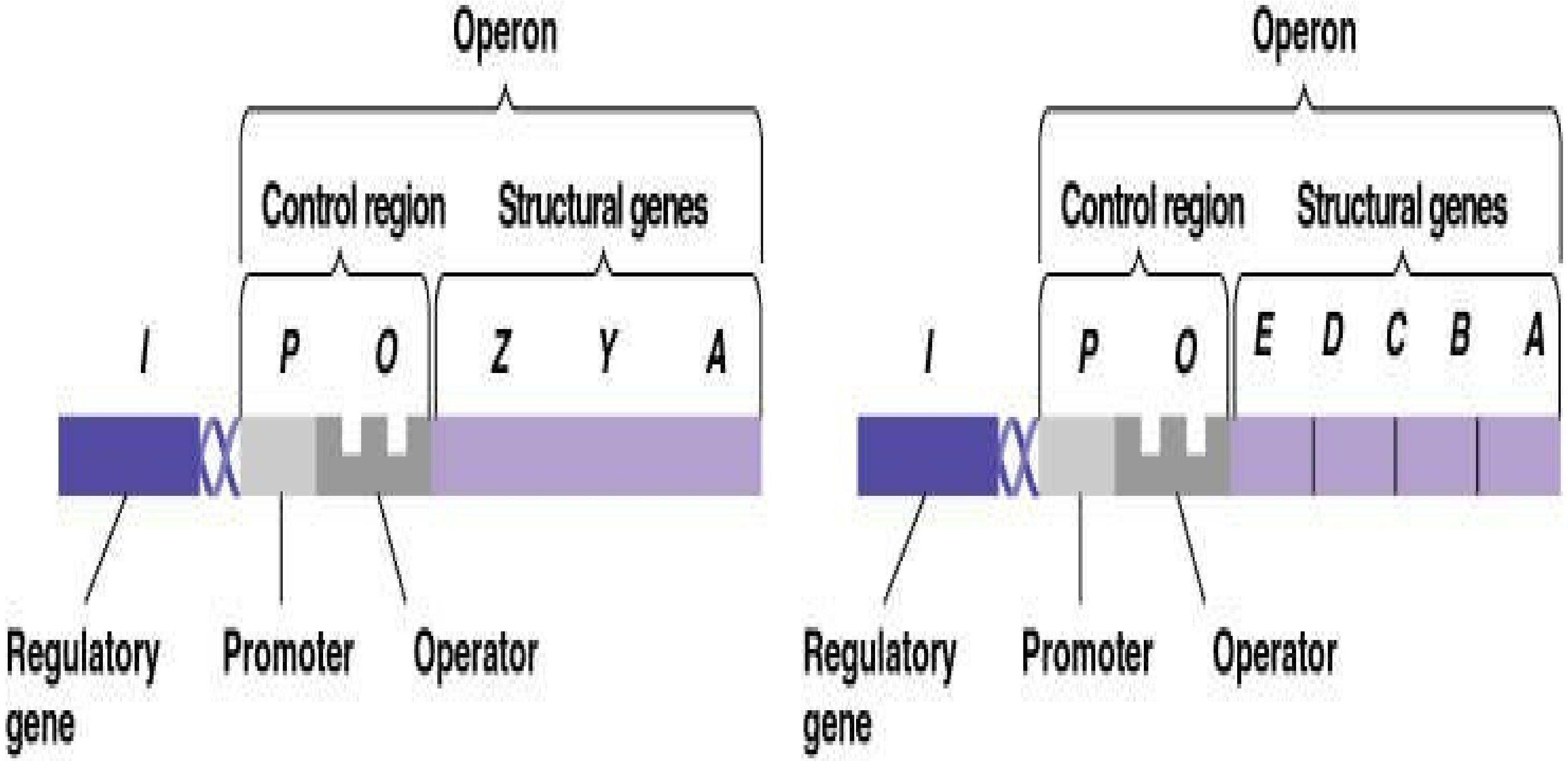
**some cis-acting element such as promoter (P) and operator (O).**

**Its regulation:** **There are one or more regulatory gene outside of the Operon that produce trans-acting factors such as repressor or activators.**

**Classification:**

**1- Catabolic (inducible) such as Lac OPERON**
**2- Anabolic (repressible) such as ara OPERON**
**3- Other types**

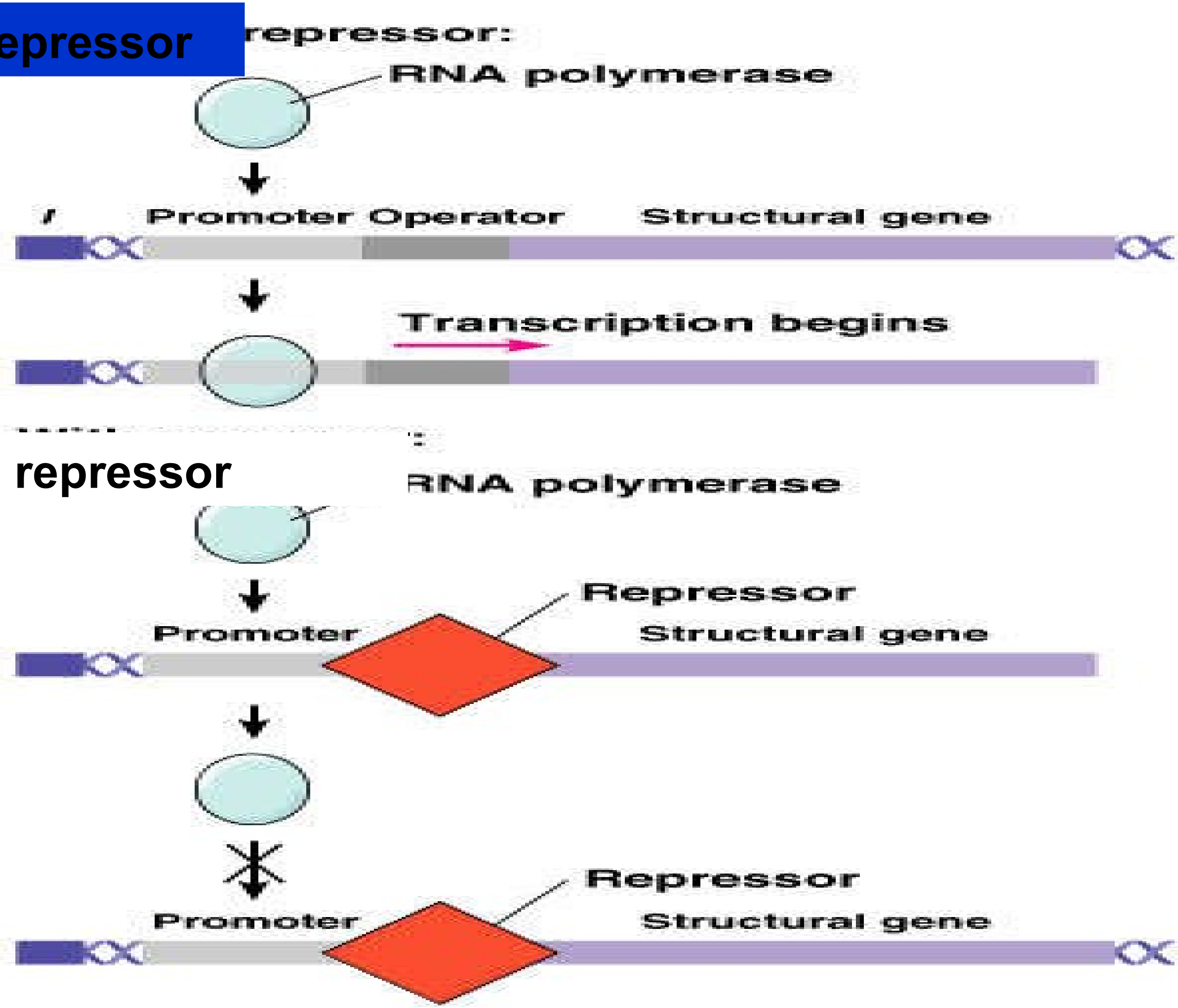
# General structure of an OPERON




1 **Structure of the operon.** The operon consists of the promoter (*P*), and operator (*O*) sites, and structural genes which code for the protein. The operon is regulated by the product of the regulatory gene (*I*).

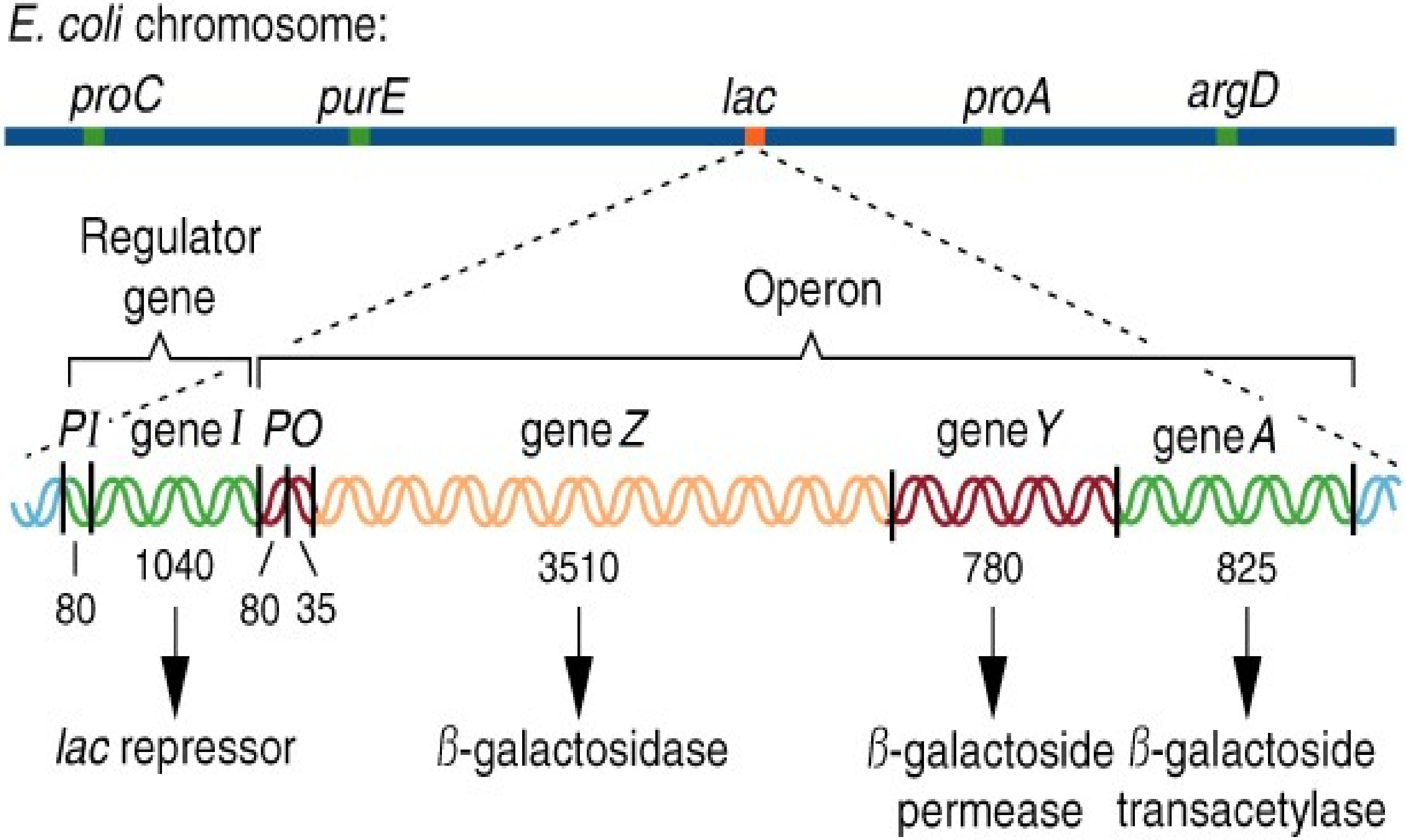
# The activity of an Operon in the presence or the absence of repressor:

No repressor

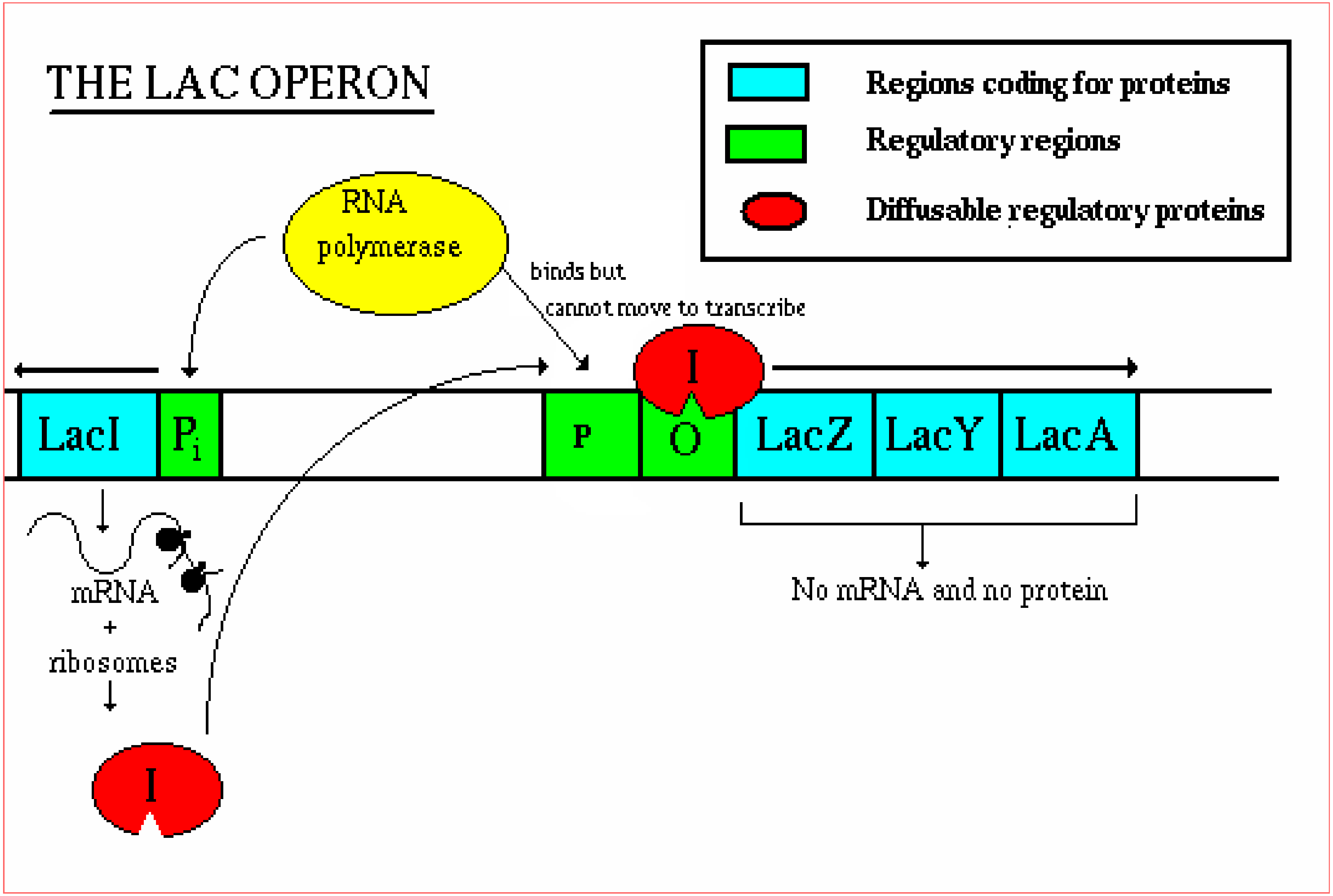



With repressor

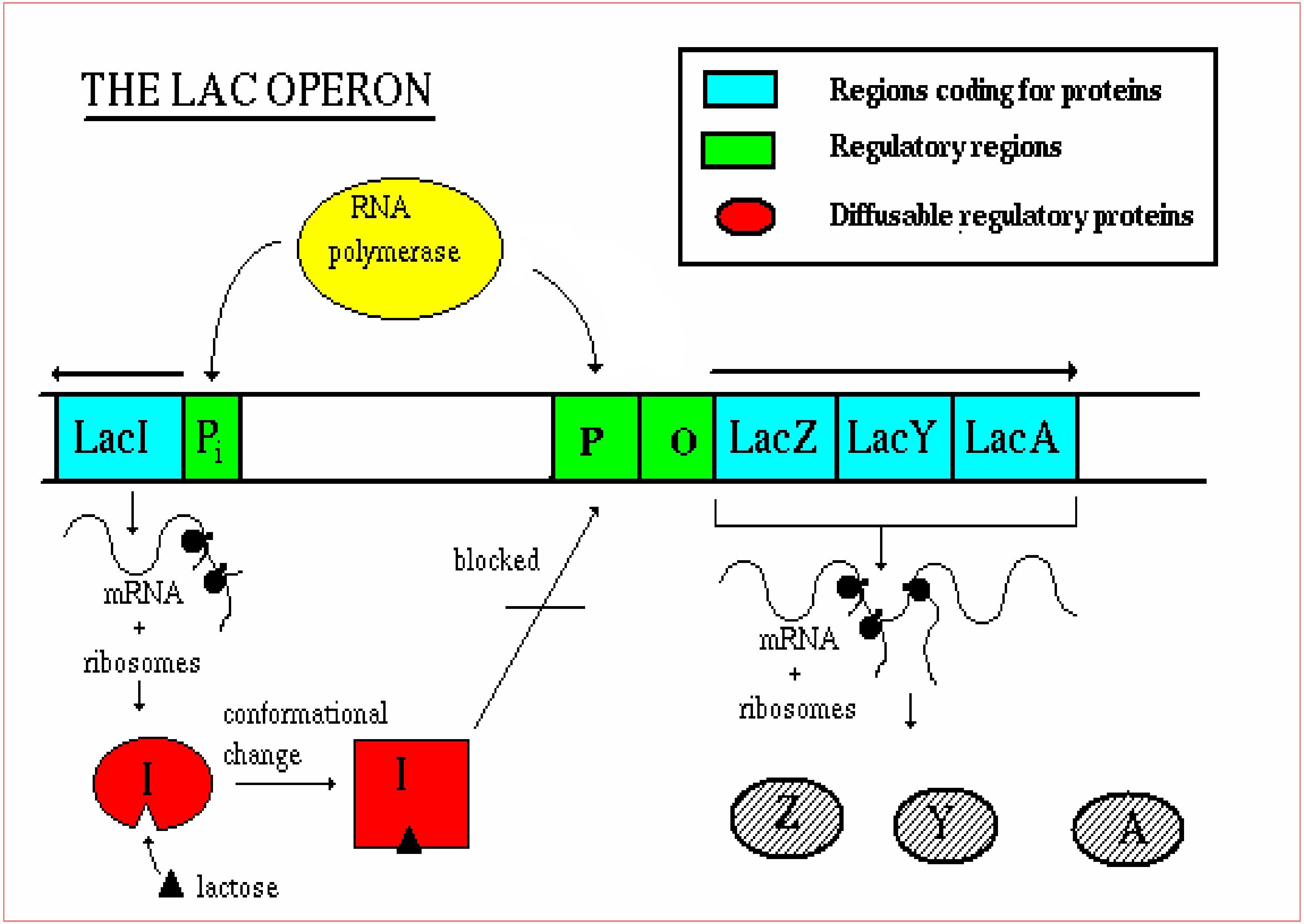
# ***<u>The lac operon of E. Coli:.</u>***



# Absence of lac operon:



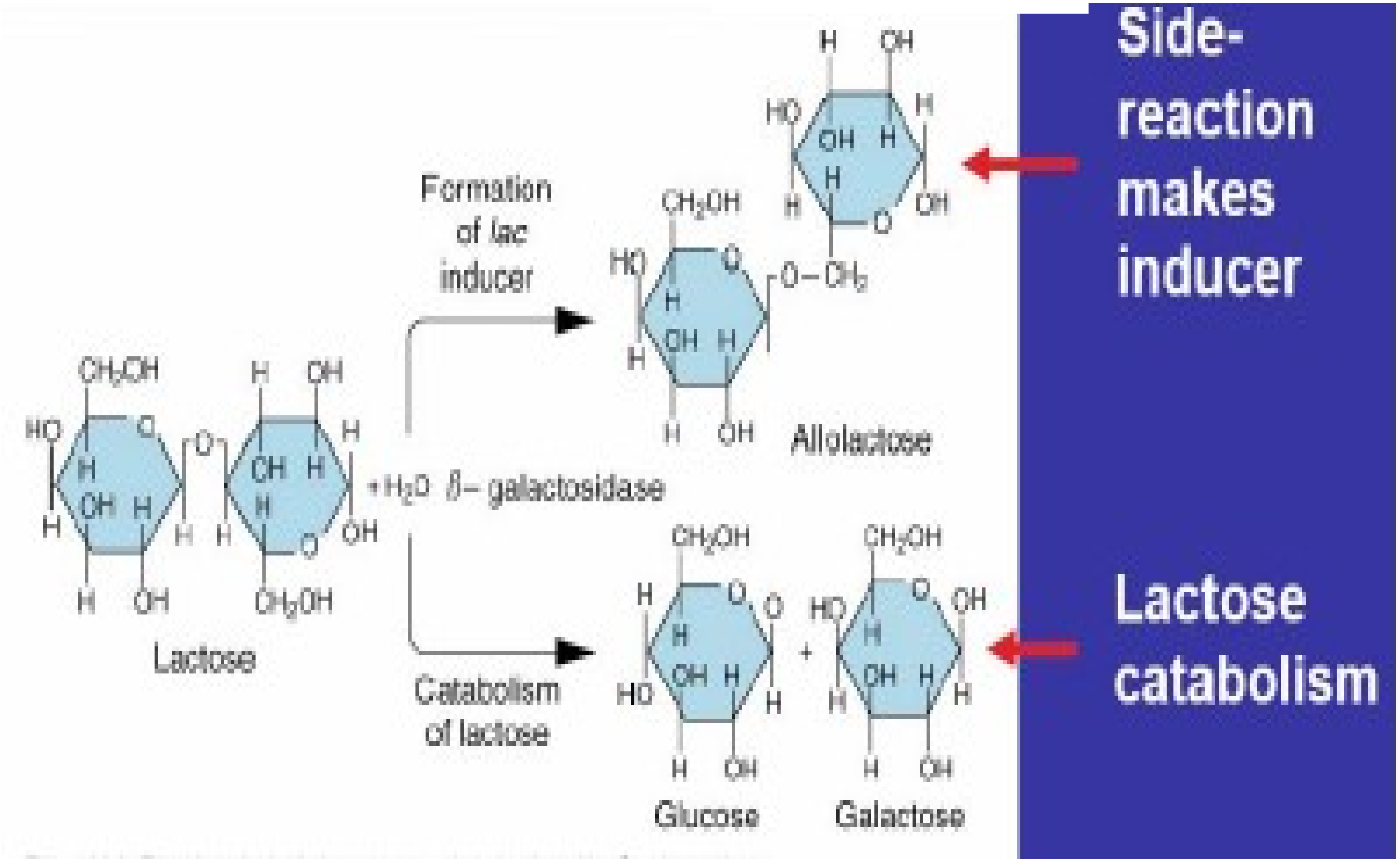
# Presence of lac preron:



# Lac OPERON an inducible Operon

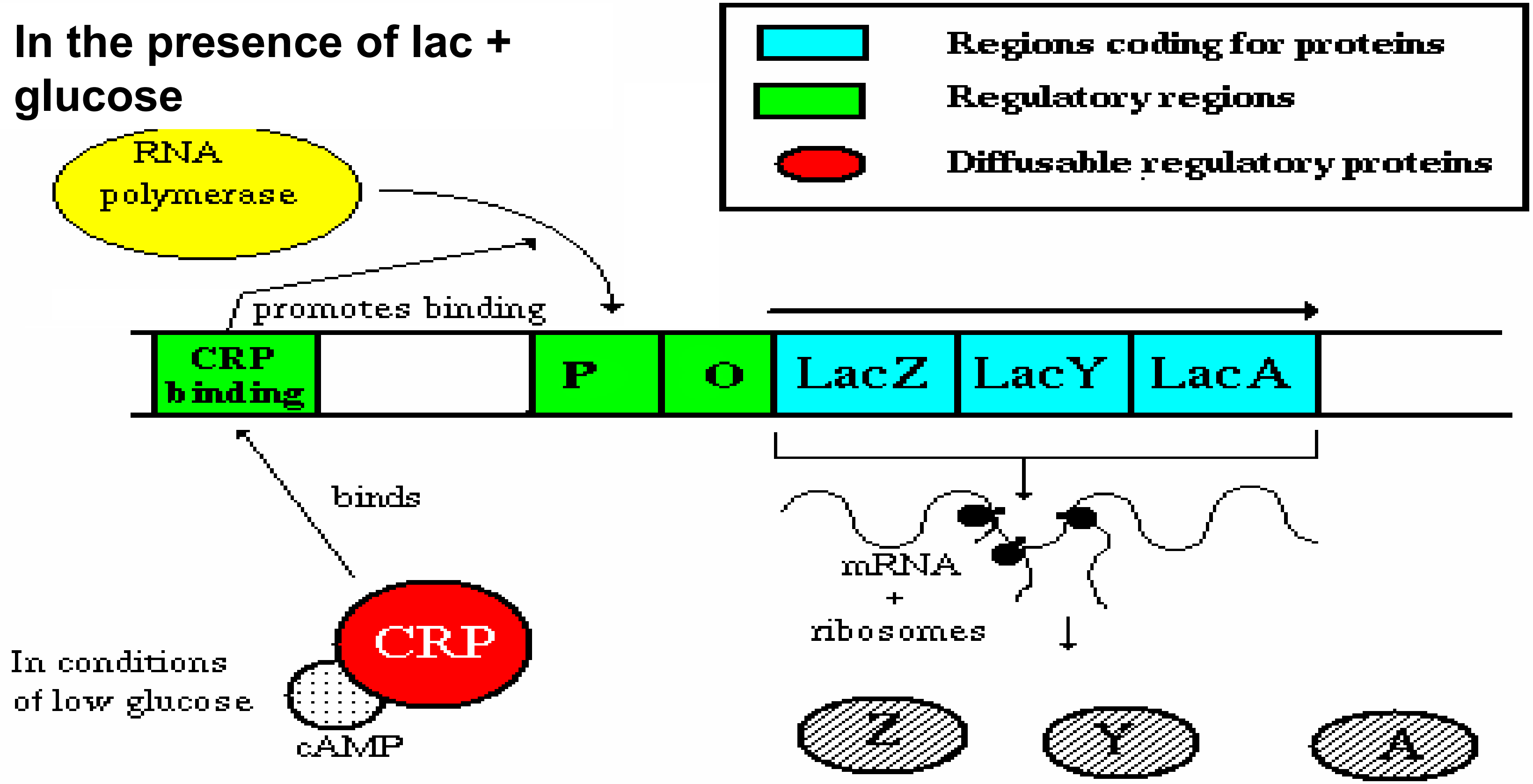
**In the absence of lac**

**In the presence of lac**



# CRP or CAP is positive regulator of Lac and some other catabolic Operons:

In the presence of lac + glucose



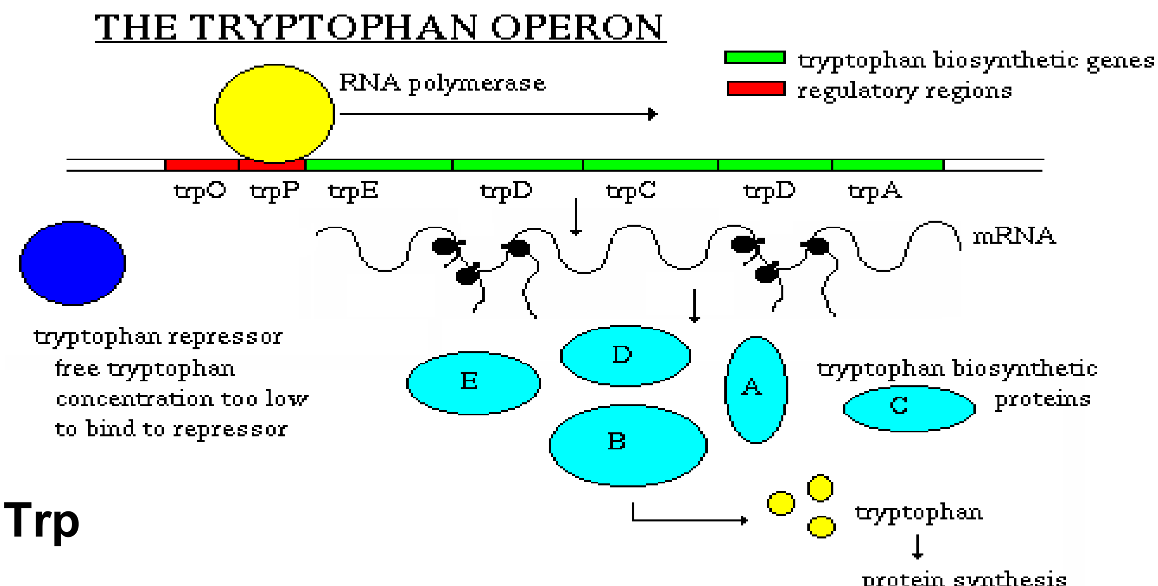

CRP= Catabolic gene regulatory Protein

CRP= cAMP receptor Protein

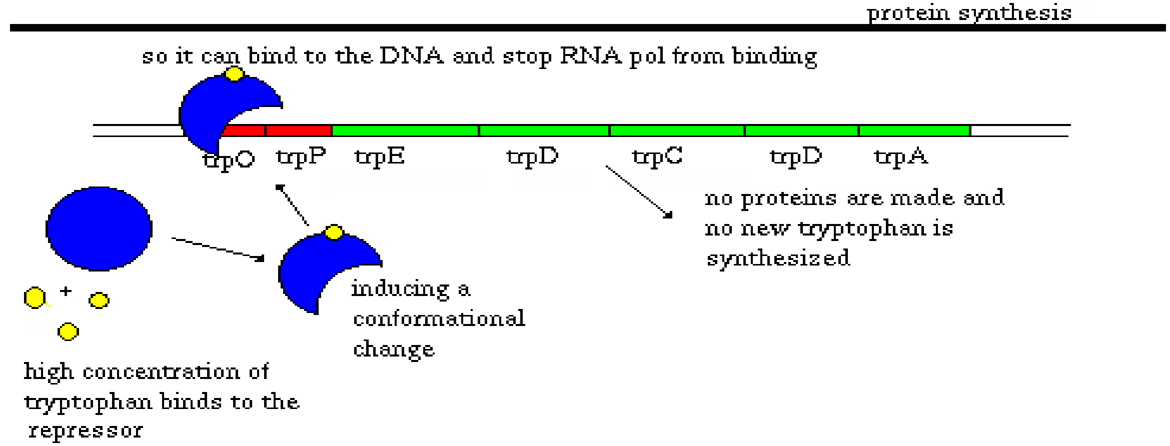
CAP= Catabolic gene Activating Protein

# Trp OPERON a repressible example:

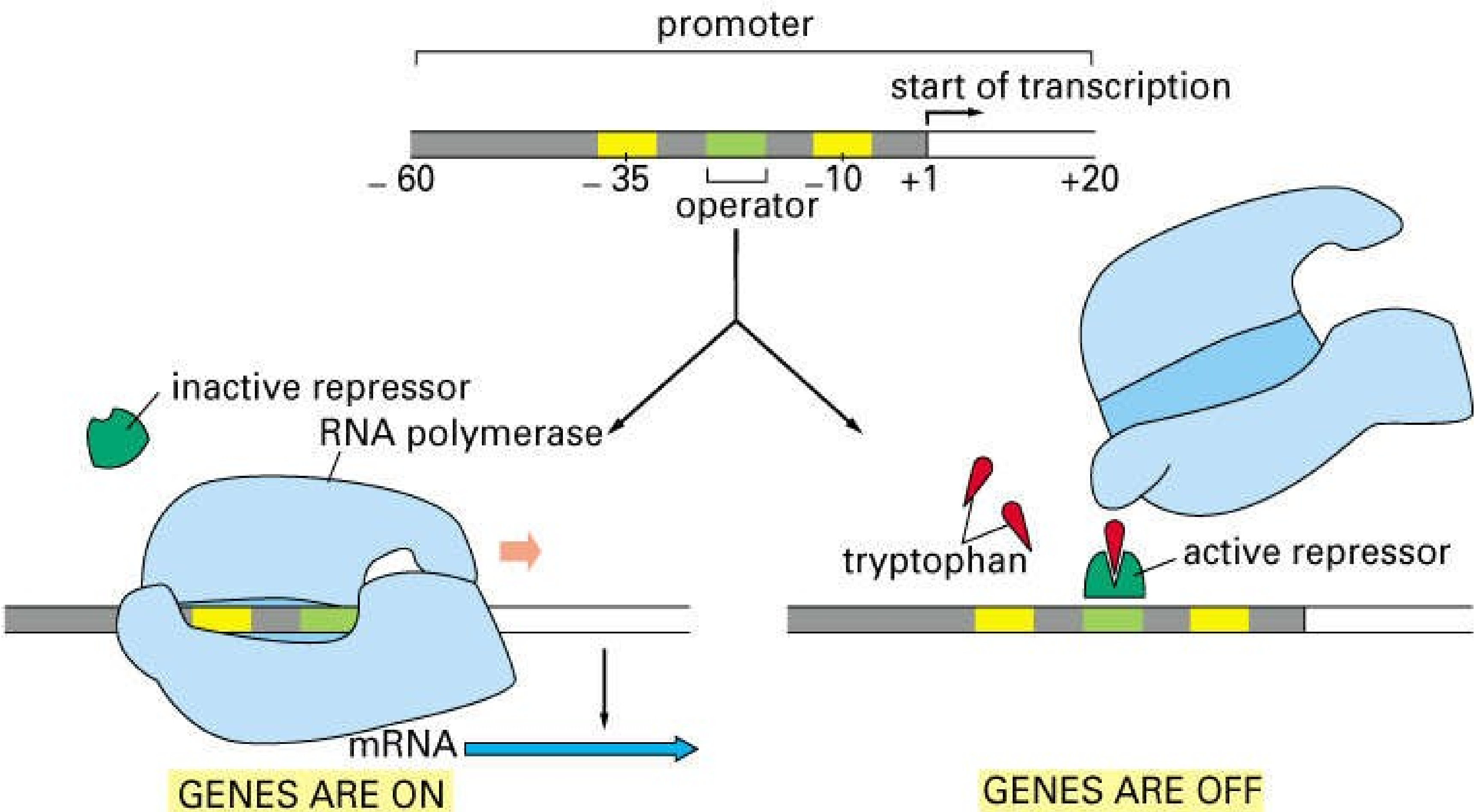
## In the absence of Trp




## In the presence of Trp



# Tryptophan Gene Regulation (Negative control):



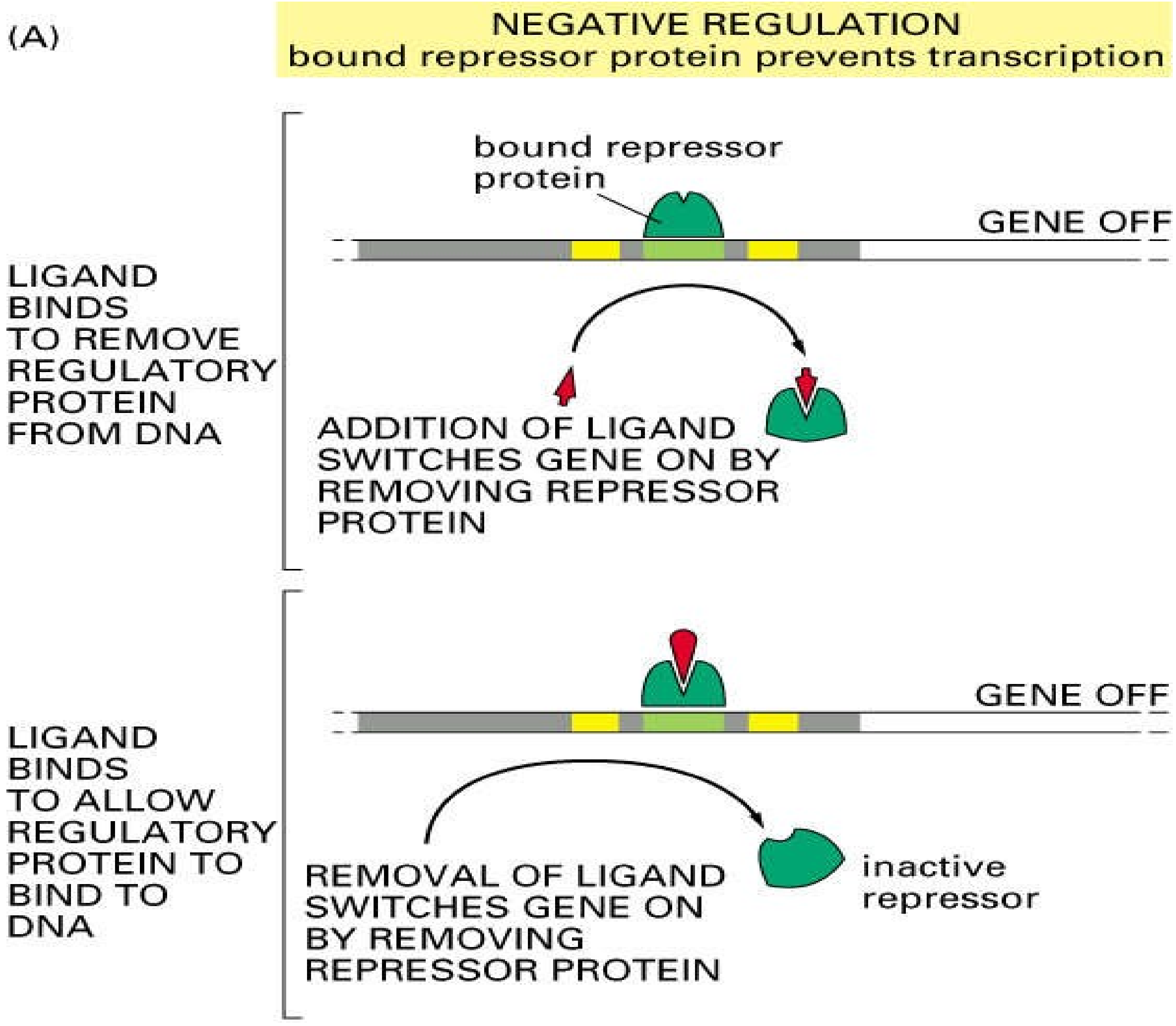



Figure 7–36 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

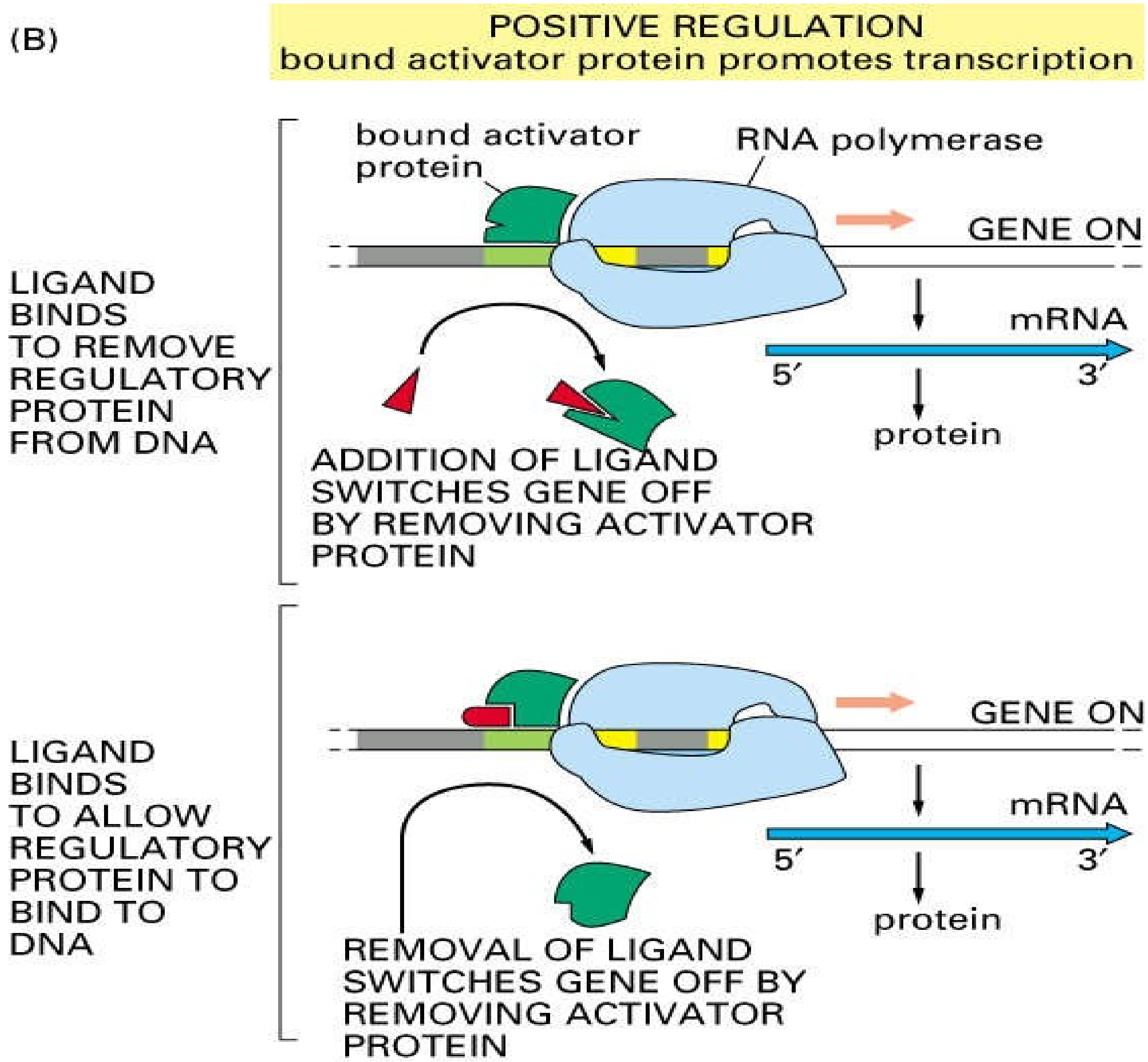



Figure 7–36 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

The binding site of Lambda Repressor determines its function

Act as both activator and repressor

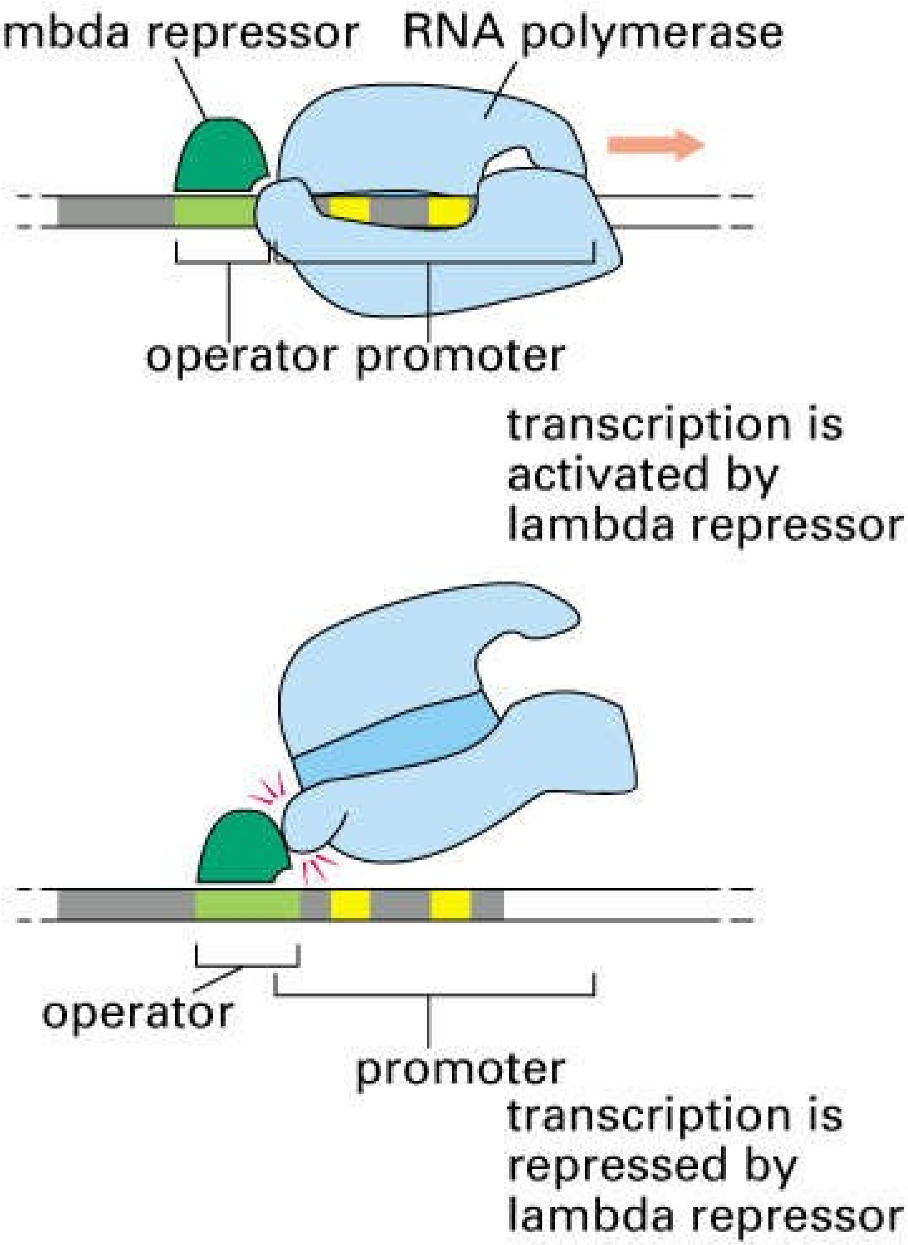
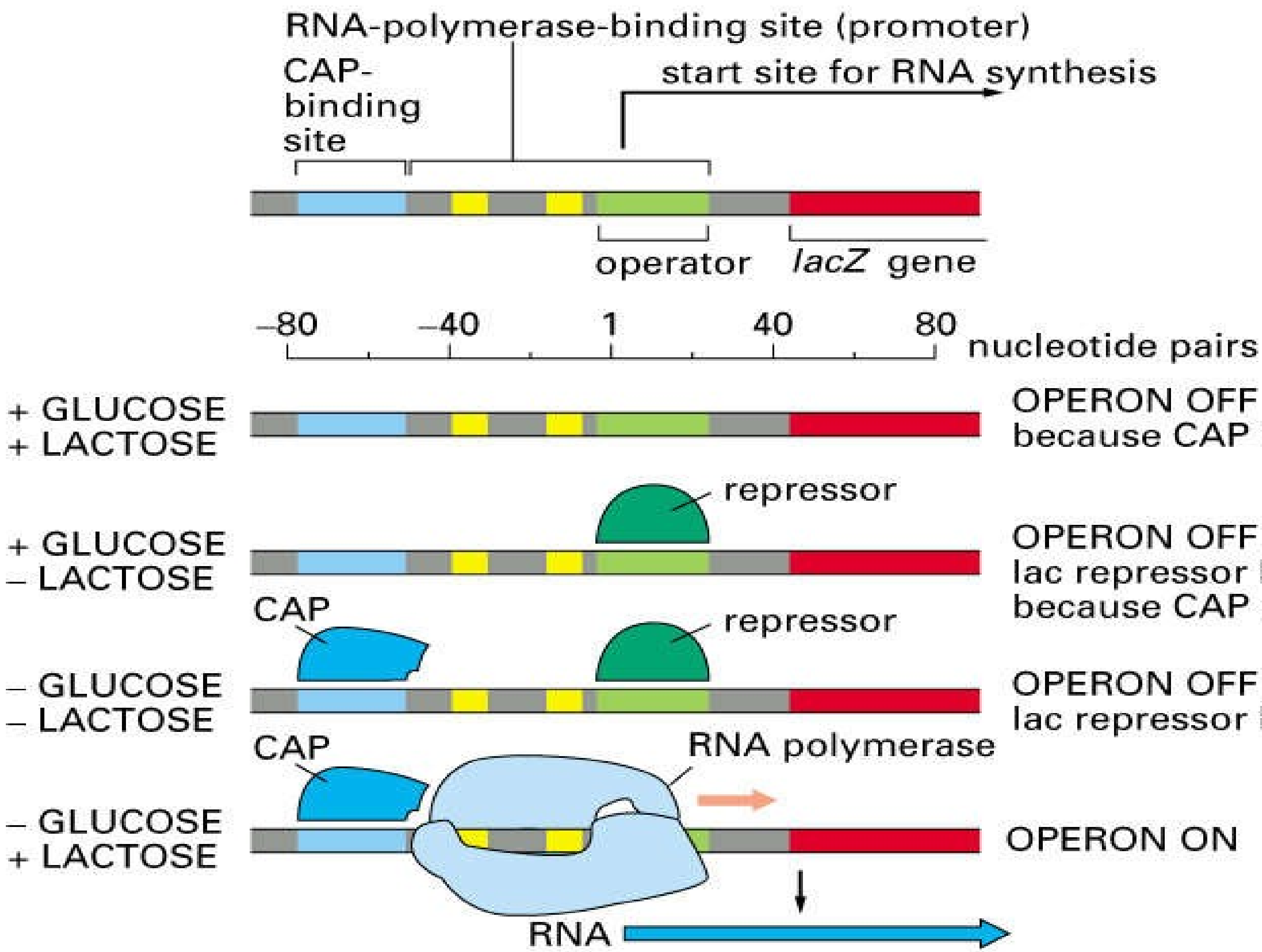



Figure 7–37. Molecular Biology of the Cell, 4th Edition.

Combinatory Regulation of Lac Operon:

CAP: catabolite activator protein; breakdown of lactose when glucose is low and lactose is present



# Gene Regulation in Eukaryotes

[redacted]

1.Transcriptional control.

2.RNAprocessing control.

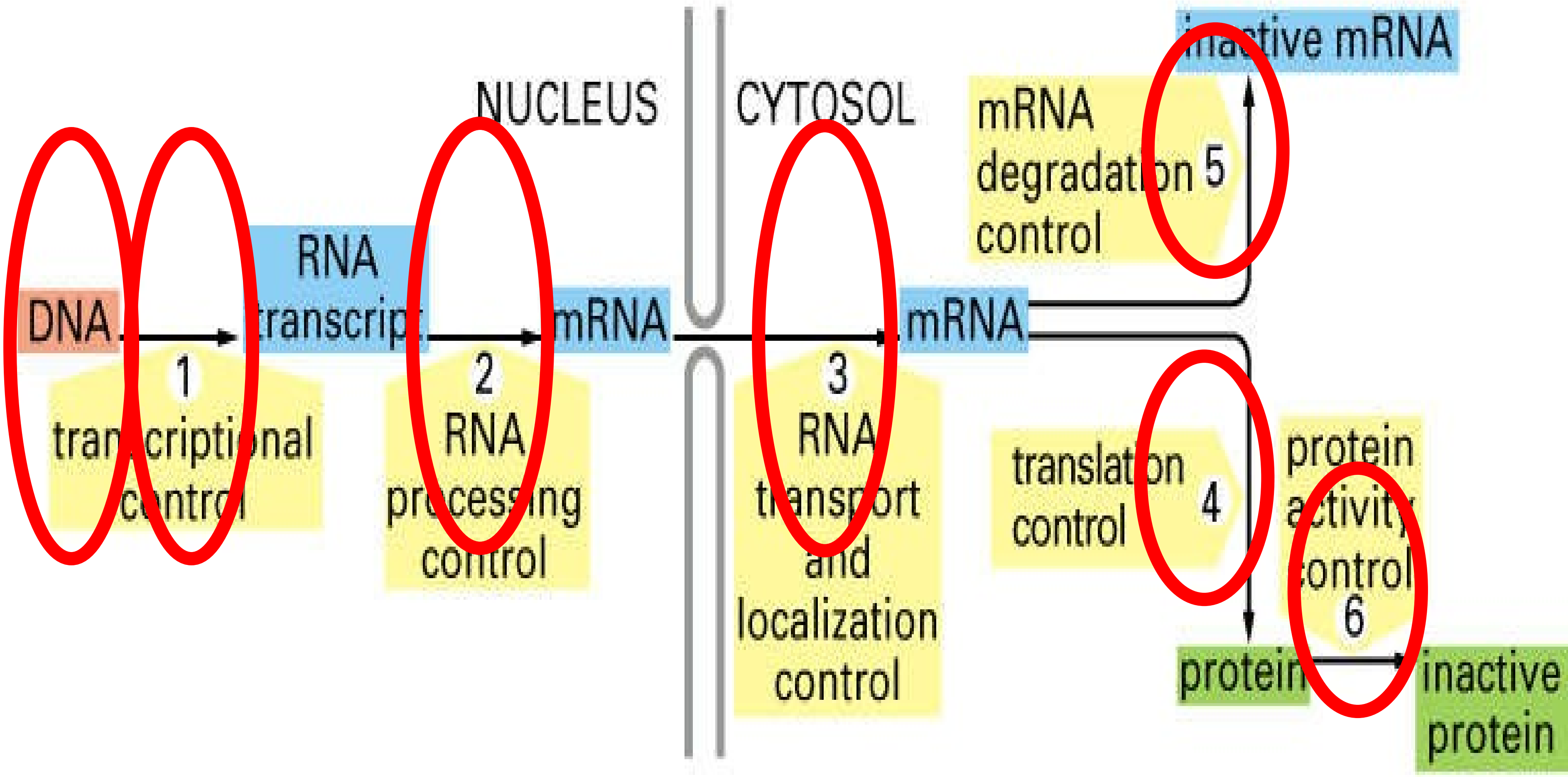
3.RNA transport&localisation control.

4.Translation control.

5.mRNAdegradation control.

6.Protein activator control.

# *Eukaryotic gene regulation occurs at several levels:*



**Transcriptional control:**

… controlling when and how often a given gene is Transcribed

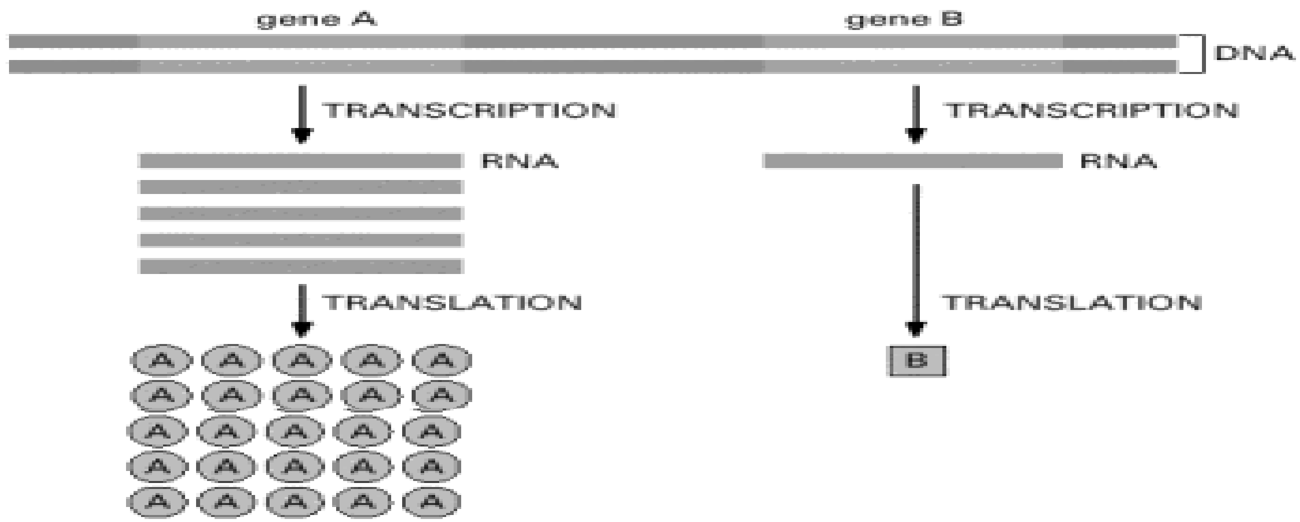
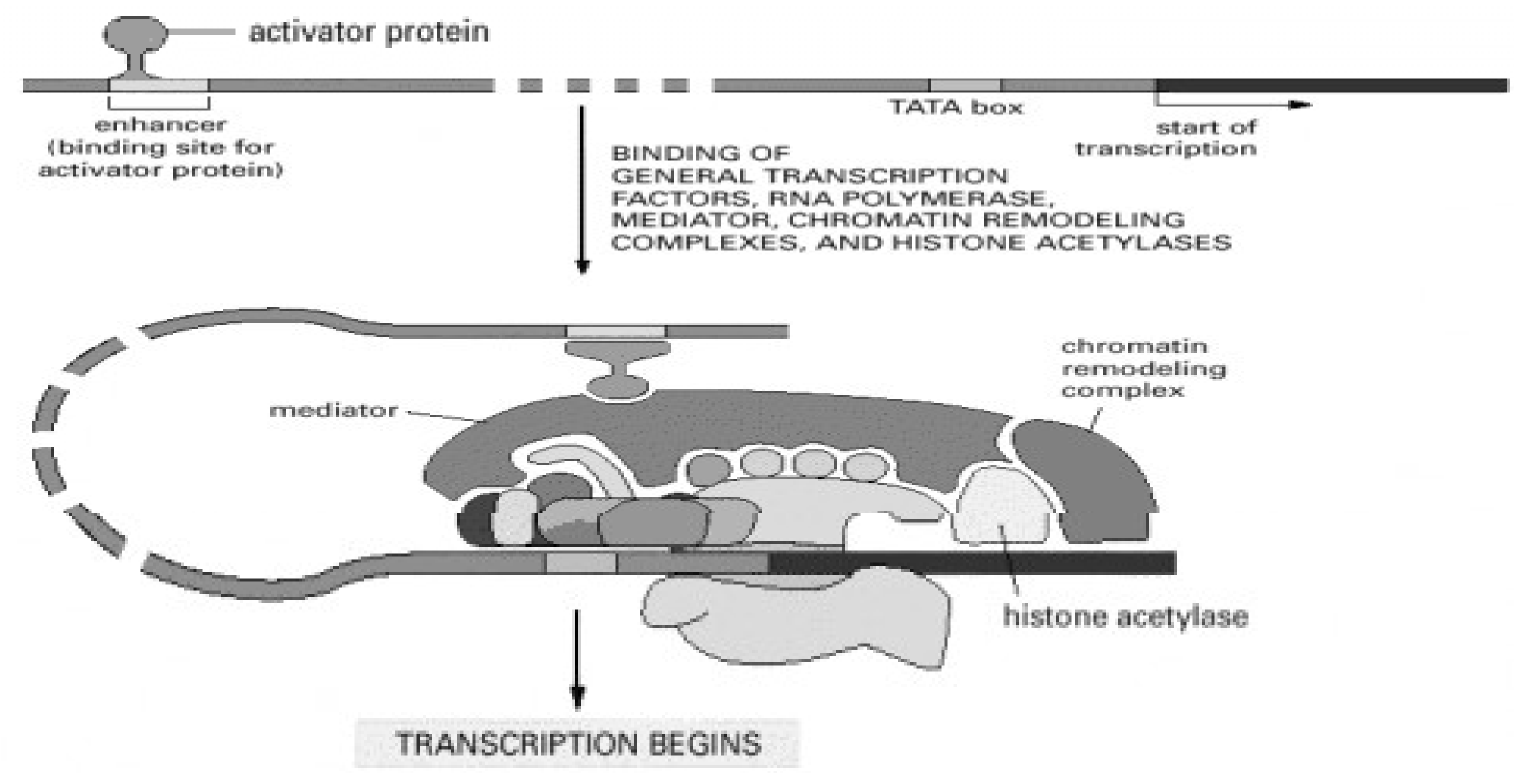



**Figure 6. Genes can be expressed with different efficiencies. Gene A is transcribed and**

translated much more efficiently than gene B. This allows the amount of protein A in the cell to bemuch greater than that of protein B.

# ***Transcriptional control – regulation by RNA polymerase:***



**Transcriptional control –**
**Epigenetic Modifications:**

*“Epi“ – above, over, outside or beside*

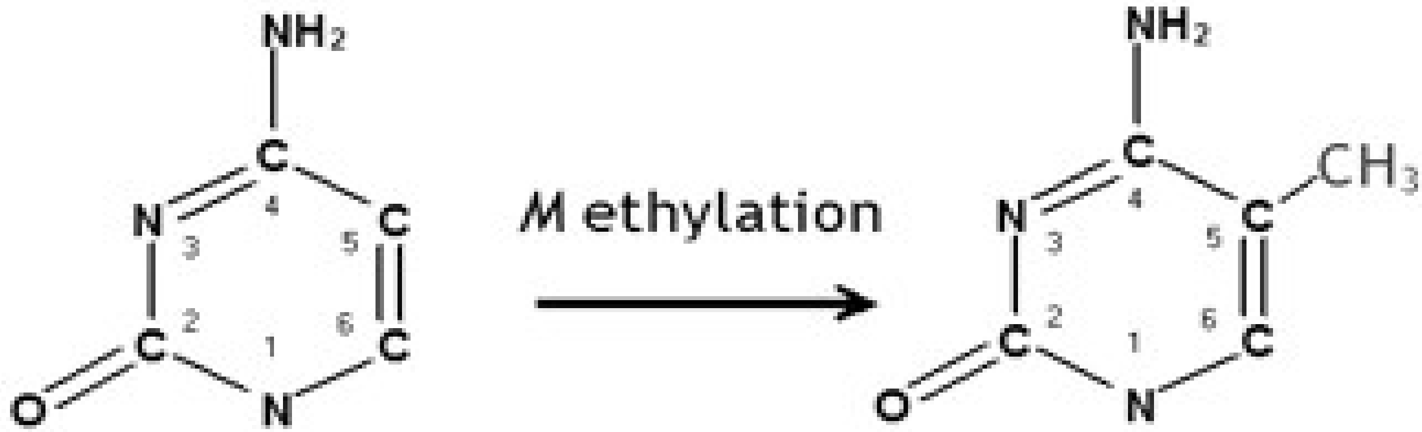
a) Methylation

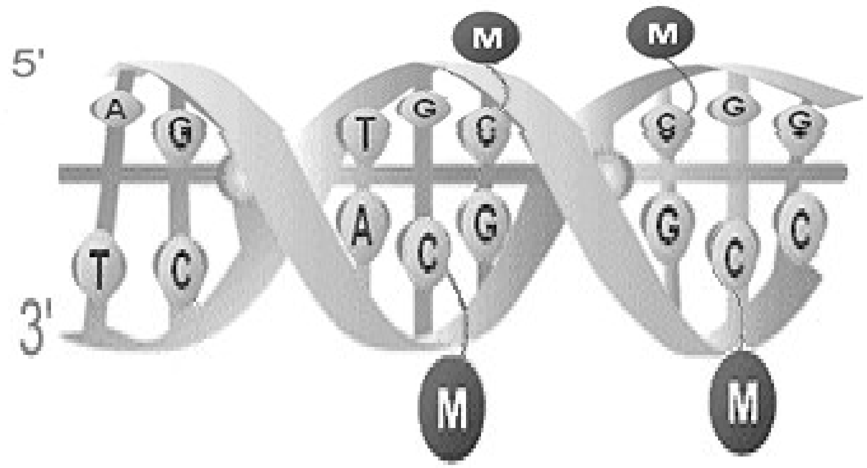
b) Histone modifications (Biotinylation, Poly(ADPribosylation)

c) X-chromosome inactivation

d) Genomic Imprinting

**DNA methylation:**is the addition or removal of a methyl group predominantely where cytosine bases occur consecutively.



# 1- Control at DNA level by DNA methylation:

- Heterochromatin is the most tightly packaged form of DNA. transcriptionally silent, different from cell to cell

- Methylation is related to the Heterochromatin formation

- Small percentages of newly synthesized DNAs (~3% in mammals) are chemically modified by methylation.

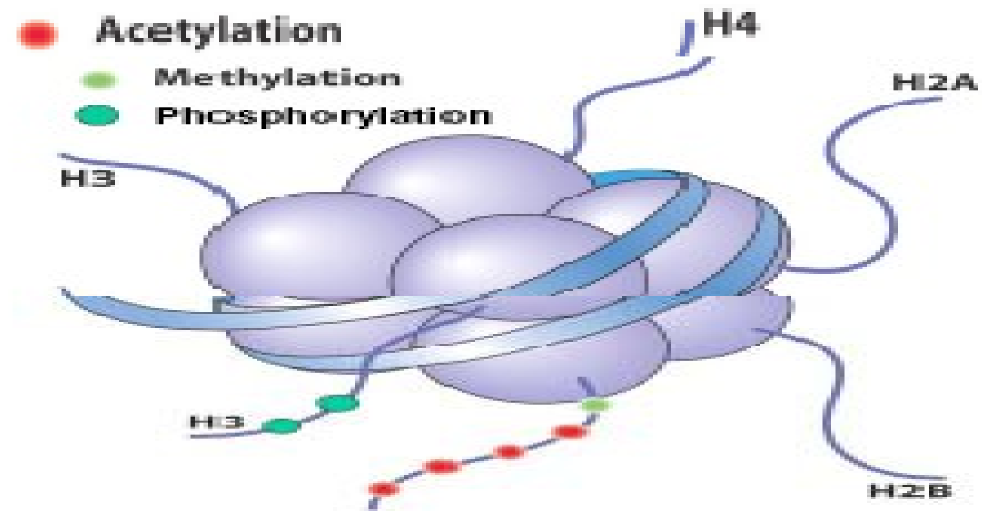
- Methylation occurs most often in symmetrical CG sequences.

- Transcriptionally active genes possess significantly lower levels of methylated DNA than inactive genes.

- Methylation results in a human disease called fragile X syndrome; FMR-1 gene is silenced by methylation.

## ***Histone modifications:***

… modifications at the amino acids that constitute the N-terminal tails of histones.




Histones are small proteins that mediate the folding of DNA into chromatin

→ DNA is wrapped around octamers of core histones

## X-chromosome inactivation:

Sex is determined by the X and Y – chromosome. To balance the unequal X-chromosome dosage between the XX female and XY male, mammals have adopted a unique form of dosage compensation:

**The X-chromosome inactivation (one of the two X** chromosomes is transcriptionally silenced through epigenetic mechanisms)
The silencing involves only those genes that are on the same X chromosome. The inactive state of those X chromosomes is maintained during cell divisions.

***<u>Genomic imprinting</u>*****:**

Two copies of every autosomal gene are inherited.
Both copies are functional for the majority of these genes.
**Imprinted genes are those genes in which one copy**
is turned off in a parent-of-origin dependent manner.

Examples:

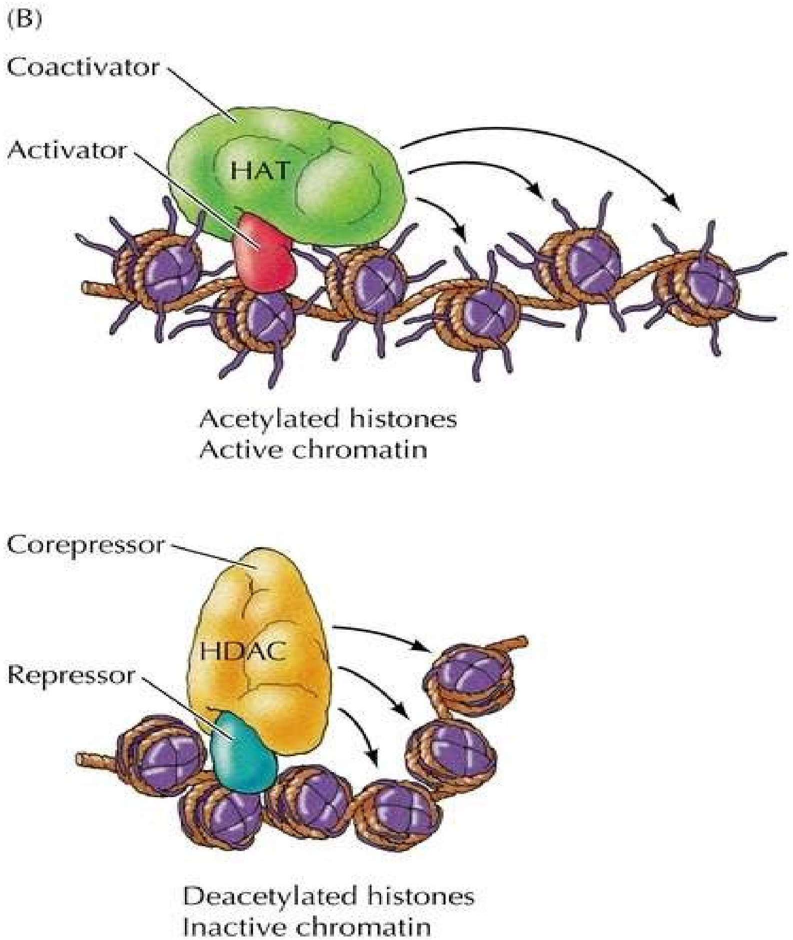
– Paternally expressed imprinted genes tend to promote growth while it is suppressed by those genes which are maternally expressed.

– Paternally expressed imprinted genes enhance the extraction of nutrients from the mother during pregnancy.

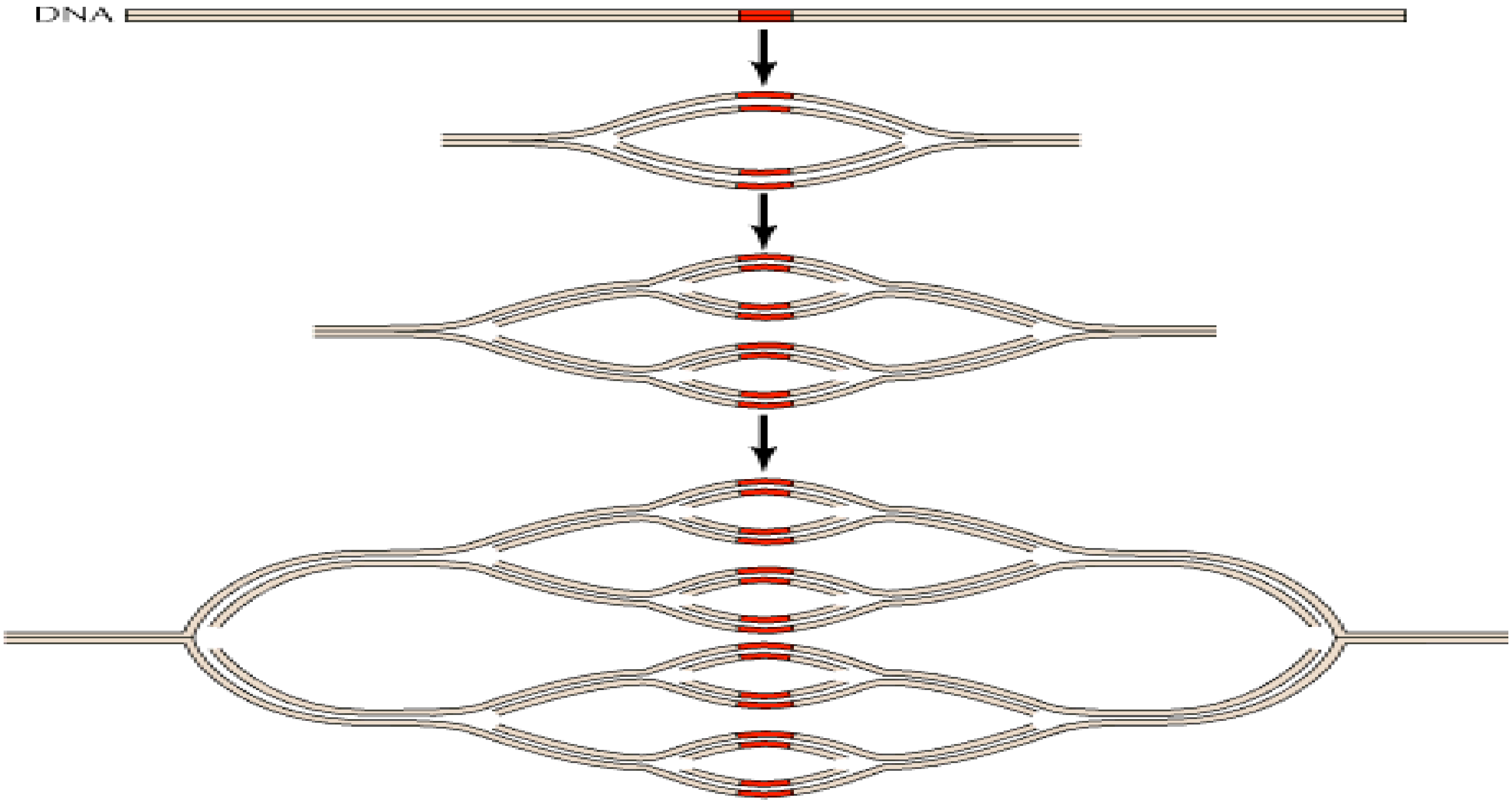
# 2- Control at DNA level by Histon modifications(Chromatin Remodeling):

- ***Acetylation*** ***by HATs and coactivators leads to euchromatin formation***

- ***Methylation*** ***by HDACs and corepressors leads to heterochromatin formation***



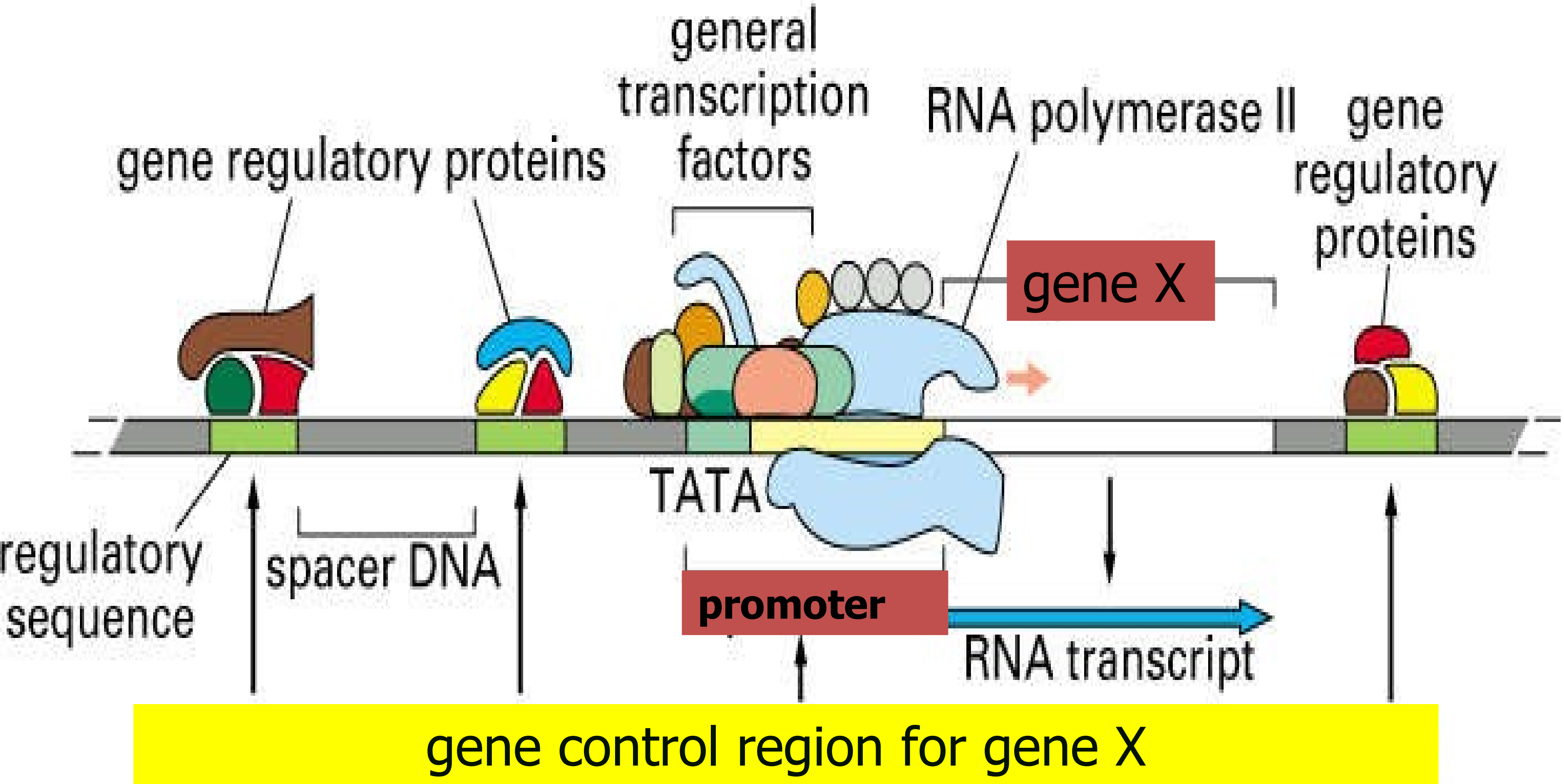
# 3-Control at DNA level by gene amplification:




**Repeated rounds of DNA replication yield multiple copies of a particular chromosomal region.**

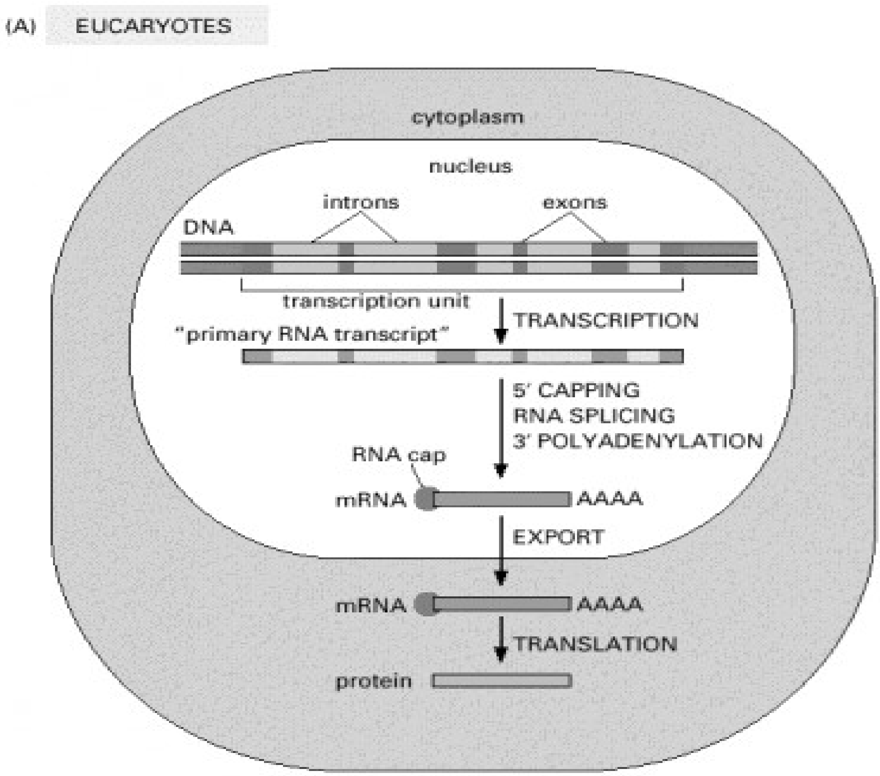
# 4- Control at transcription initiation:

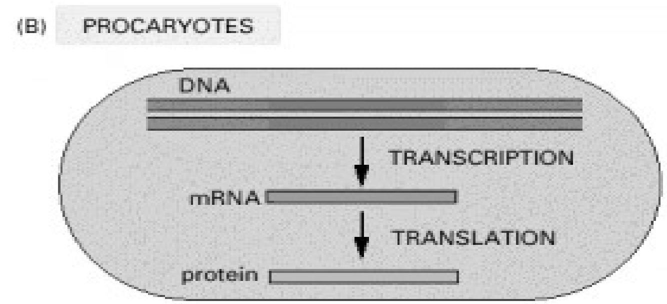
**By using different sequences (promoter, enhancer or silencer sequences) and factors, the rate of transcription of a gene is controlled**



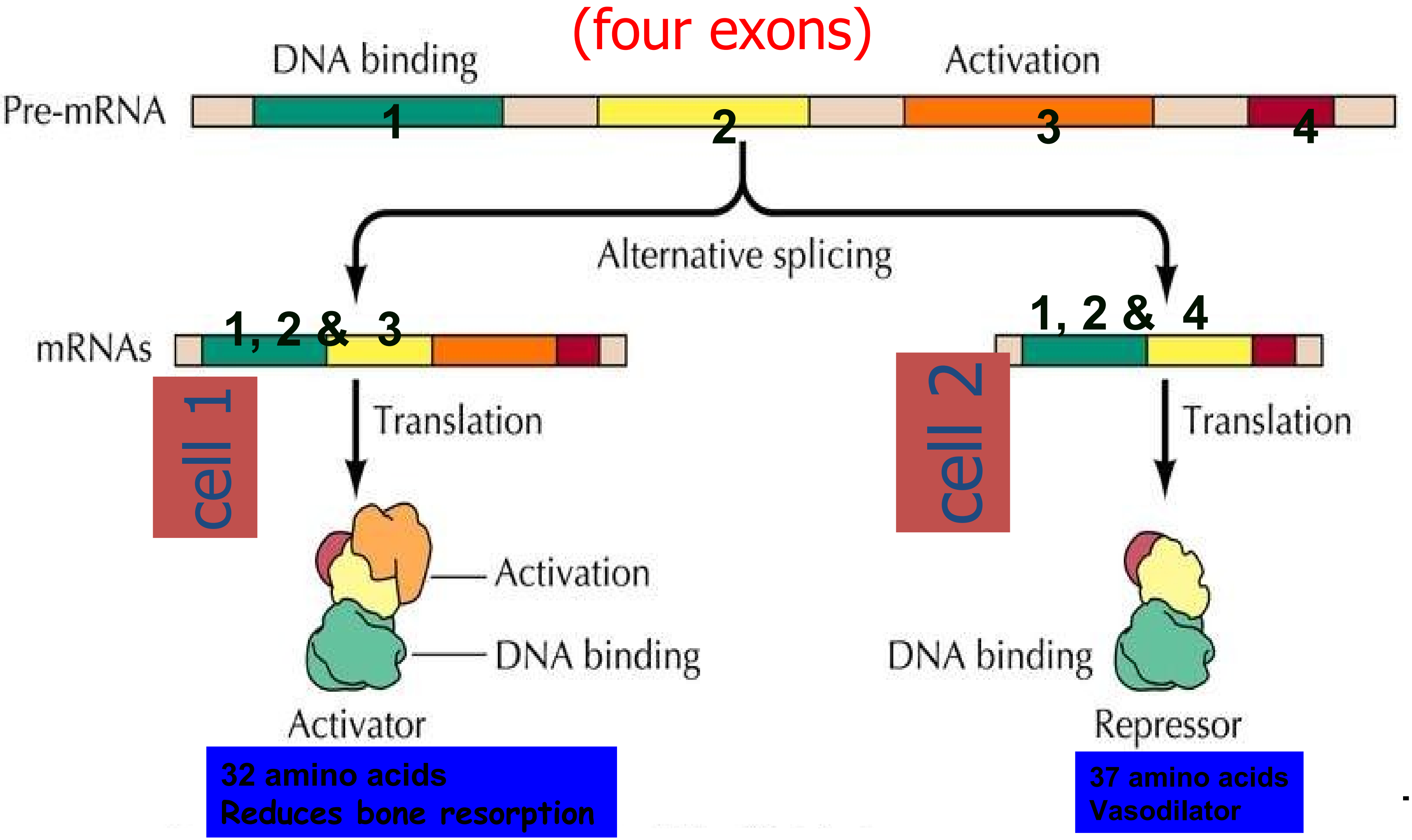
**RNA-processing control:**

Capping, Splicing, Polyadenylation



# 5- Control at mRNA splicing (alternate splicing) :



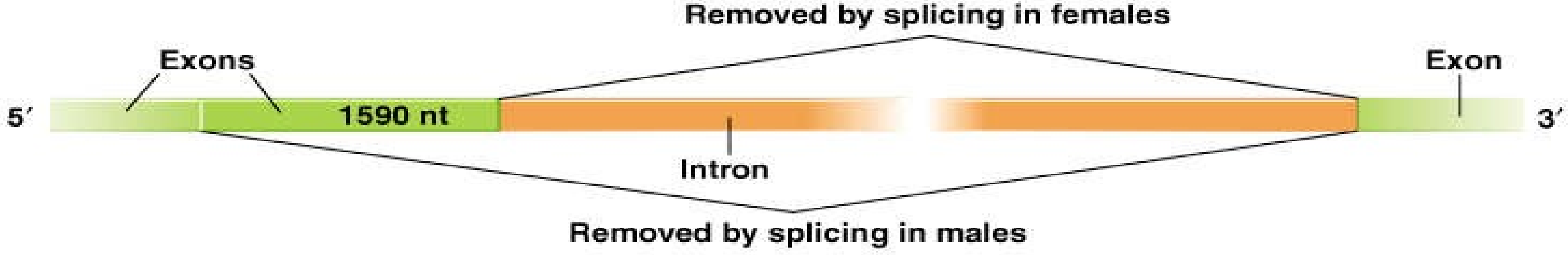
# 5- Alternative splicing: A Role in Sexual Behavior in Drosophila

a. In Drosophila courtship, the male behaviors include: Following, Singing & …

b. Regulatory genes (fruitless= fru) in the sex determination pathways control these behaviors.

c. Physiologically, the CNS (central nervous system) is responsible for key steps in male courtship behavior.

The sex-specific fru mRNAs are synthesized in only a few neurons in the CNS (500/100,000). The proteins encoded by these mRNAs regulate transcription of a set of specific genes, showing that fru is a regulatory gene. Its expression seems to be confined to neurons involved in male courtship



**Translational control**

… selecting which mRNAs in the cytoplasm are translated by ribosomes

Mechanisms of translation control:

• transport control (only the mRNA which is transported to the cytoplasm can be translated)

• number of ribosomes

• translation factors (if the concentration of these factors is too low in the cell, the translation start or the elongation process can be decelerated or inhibited

• mRNA localisation (a specific place in the cytoplasm leads to the production of the protein at a specific position in the cell)

• Regulation by untranslated regions (UTRs)

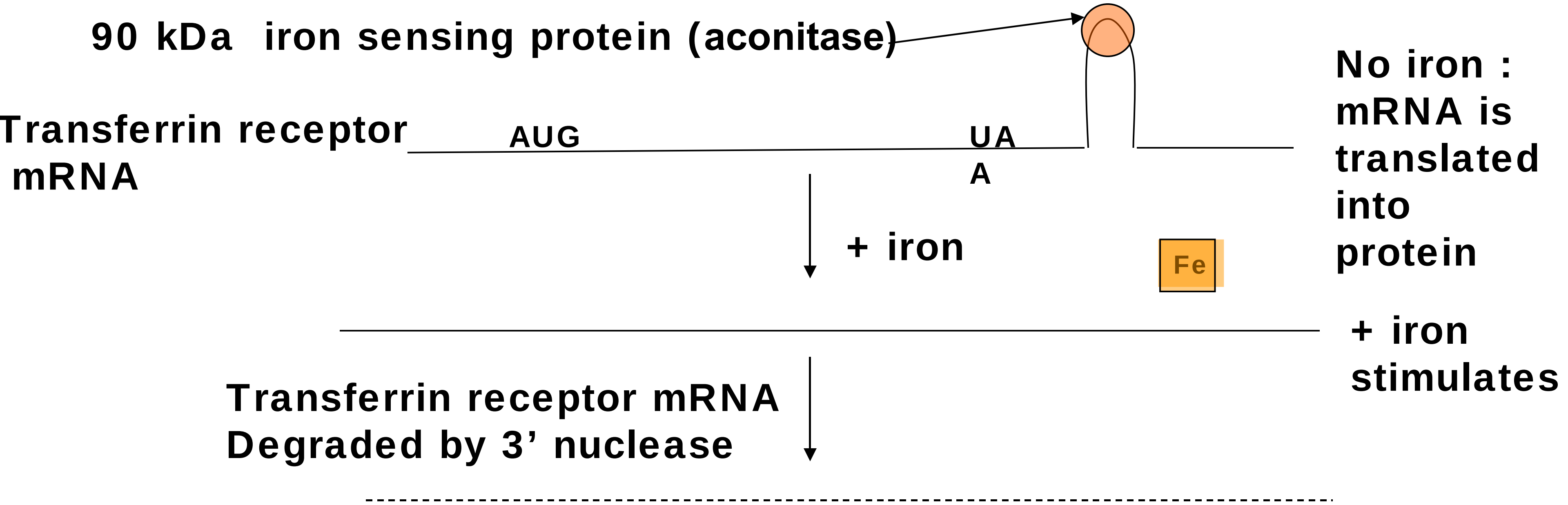
**mRNA degradation control:**

…selectively destabilizing certain mRNA molecules in the cytoplasm

- the stability of different mRNAs in the cytoplasm varies widely.
- many eukaryotic mRNAs are quite stable, some have unusually short half-lives.
- the stability is determined by the cap-structure and the length of the poly-A tail of the mRNA.
- mRNA degradation is carried out by ribonucleases (deadenylation, degradation of the poly-A tail).
- mRNA stability is also dependent on base pair structure of the

# 6- Control at mRNA stability

- The stem loop at 3'end is an' iron response element'.
- The stem loop is stabilised by a 90 kDa protein in the absence of iron and protects the mRNA from degradation.

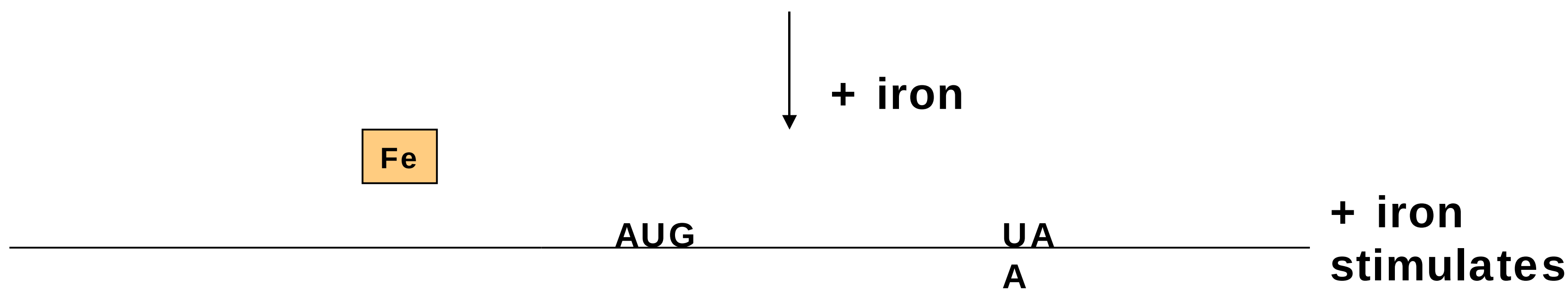



- In the presence of iron, transferrin receptor protein synthesis is reduced.

# 6- Control at mRNA stability

- A stem loop is stabilised by the 90 kDa protein in the absence of iron.
- This time, the stem loop is at the 5' end of the mRNA.


- The presence of the stem loop prevents translation of this mRNA by blocking the progress of the ribosomes along the mRNA.




- In the presence of iron, the hairpin is lost, the ribosomes can translate the mRNA and ferritin protein synthesis is increased.

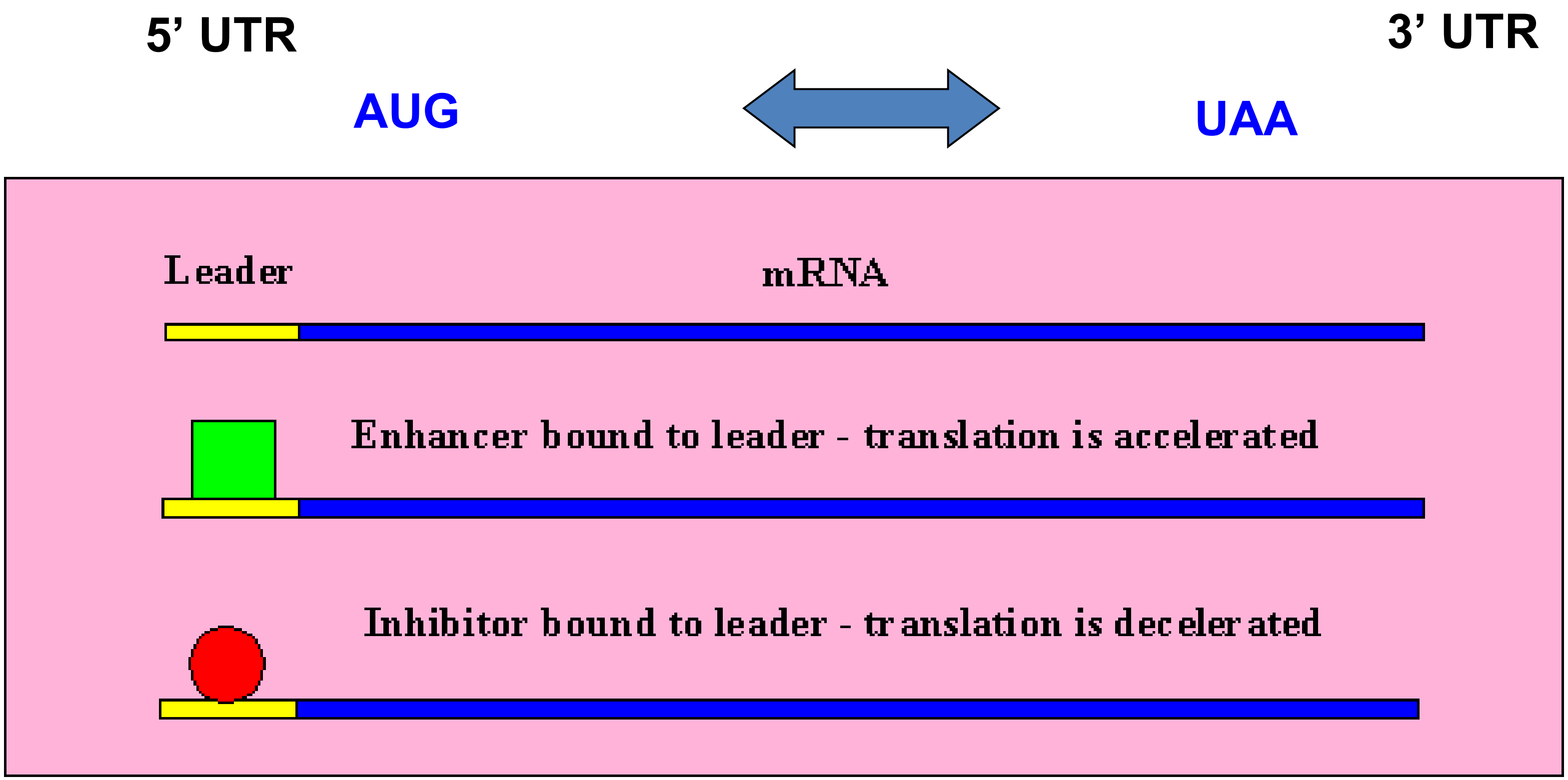
# 6- Control at mRNA stability

- Some hormones which enhance the production of proteins also increase the half life of the protein's mRNA.

  Estrogen : ovalbumin $t_{1/2}$ from 2- 5hr to >24hr

  Prolactin : casein $t_{1/2}$ from 5 hr to 92hr

# 7- Control at initiation of translation:




**Specific sequences make specific secondary structures**

**Specific protein factors bind to these secondary structures**

**<u>Protein activity control:</u>**

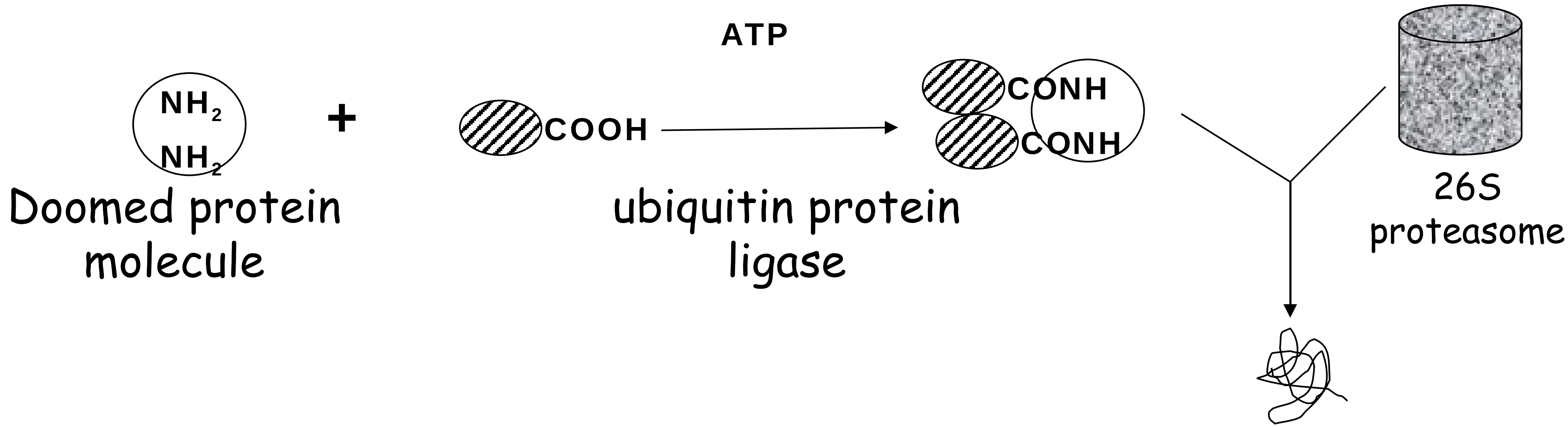
… selectively activating, inactivating, or compartmentalizing
specific protein molecules after they have been made.

Proteins builded after translation can be

- functional or
- have to undergo a maturation process (exo/-endopeptidasen)
- or functional groups (phosphorylation, acetylation,
methylation … ) have to be added.

# 8-Regulation by protein stability:

- Ubiquitin-dependent proteolysis. Cyclins control of cell cycle.
- Protein molecule is tagged for degradation by attachment of a 20 kDa protein, ubiquitin




- The stability of a protein depends upon its *N*-terminal amino acid (the *N*-end rule).

N-terminal : For example arginine , lysine : protein t1/2 = 3 min

N-terminal : For example methionine, alanine, : t1/2 >20 hrs.

## *Gene Expression Regulation*

## *Transcription:*

# *Protein Assembled to form complex to Regulate Gene Expression:*

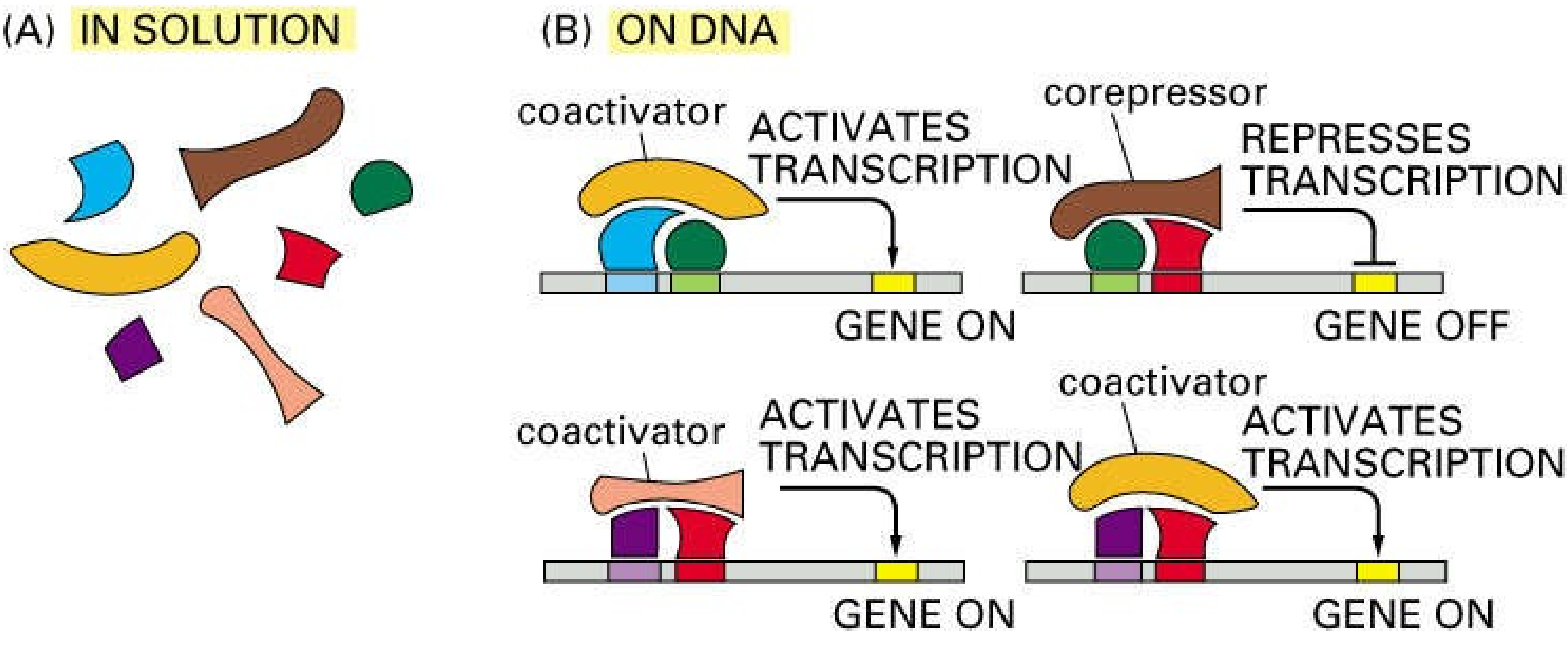



Figure 7–50. Molecular Biology of the Cell, 4th Edition.

# Integration for Gene Regulation:

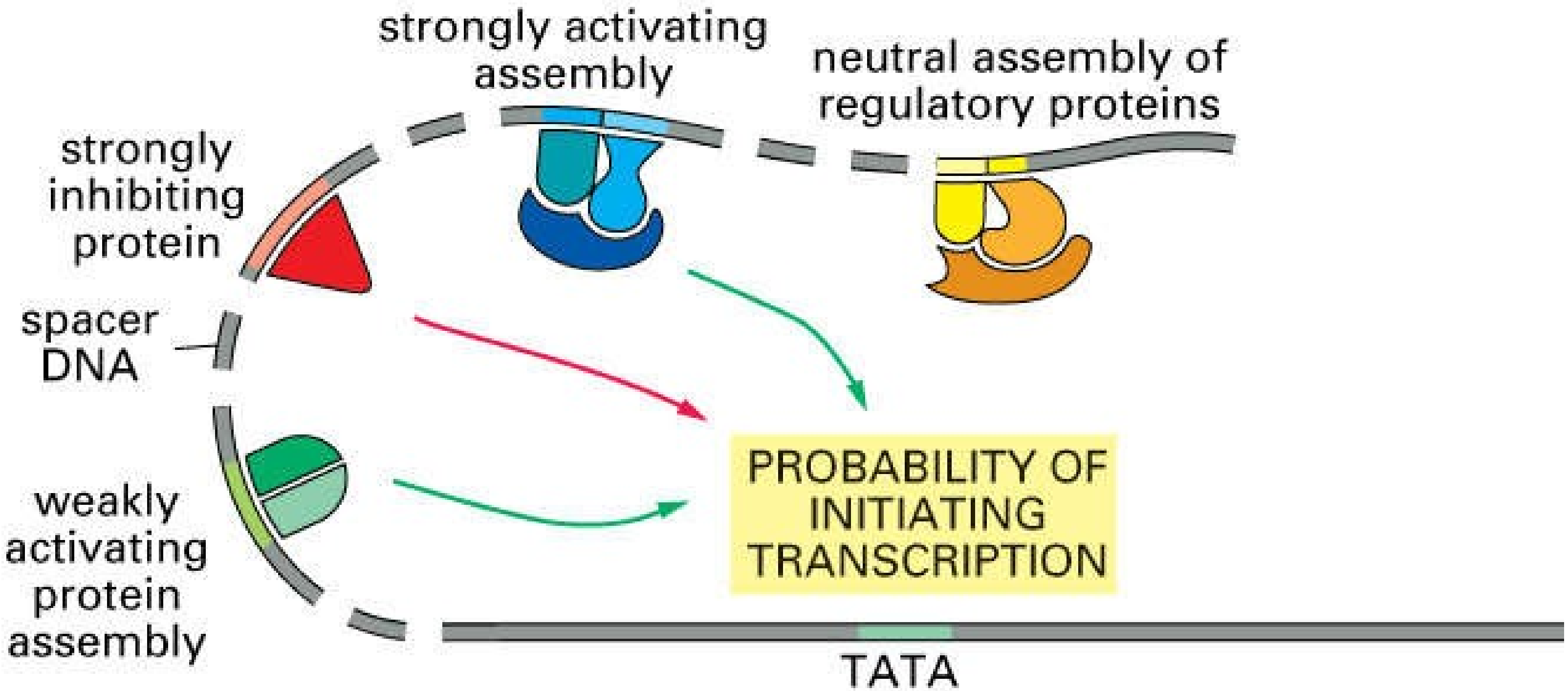
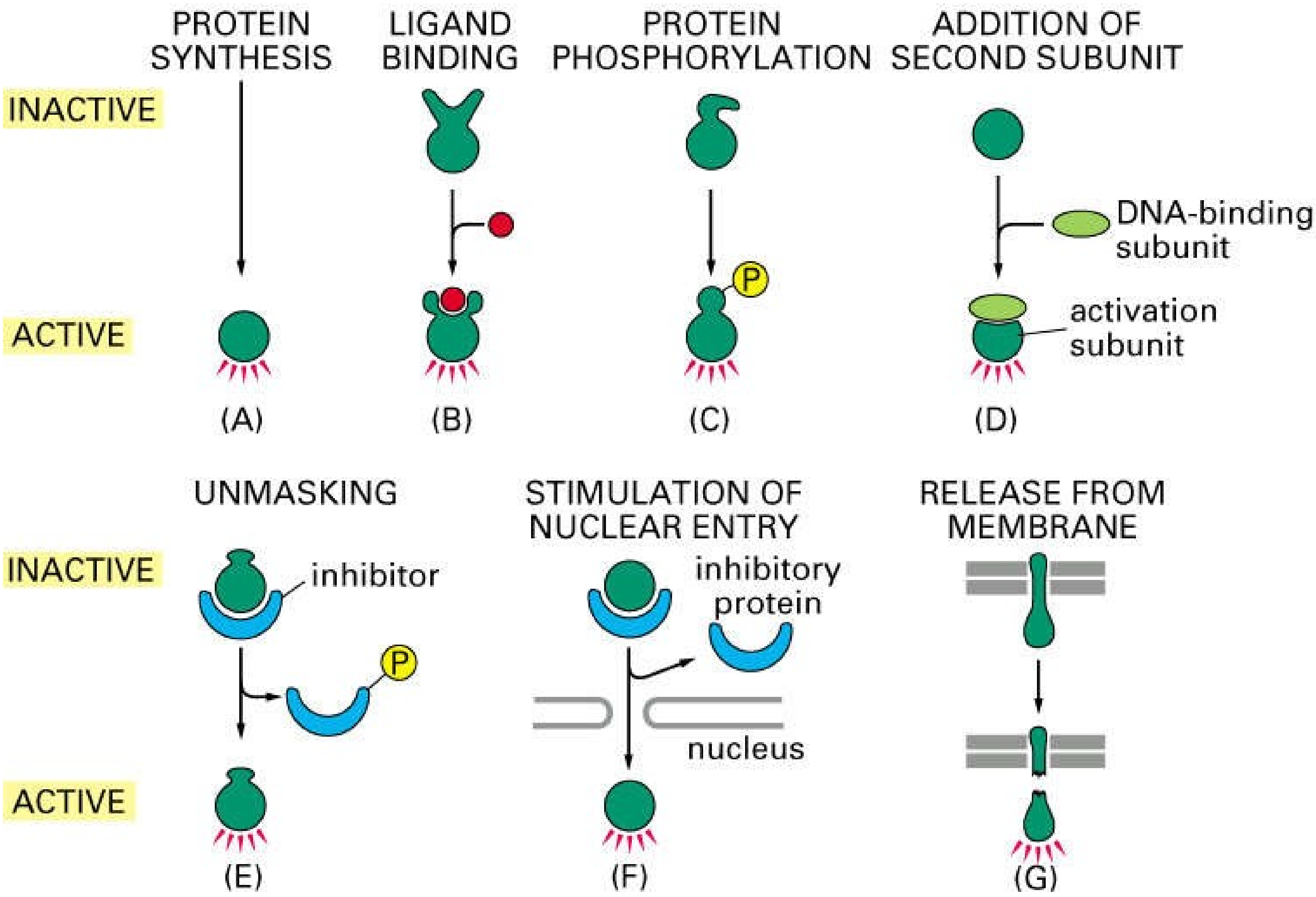



Figure 7–57. Molecular Biology of the Cell, 4th Edition.

# Regulation of Gene Activation Proteins:



# Insulator Elements (boundary elements) help to coordinate the regulation:

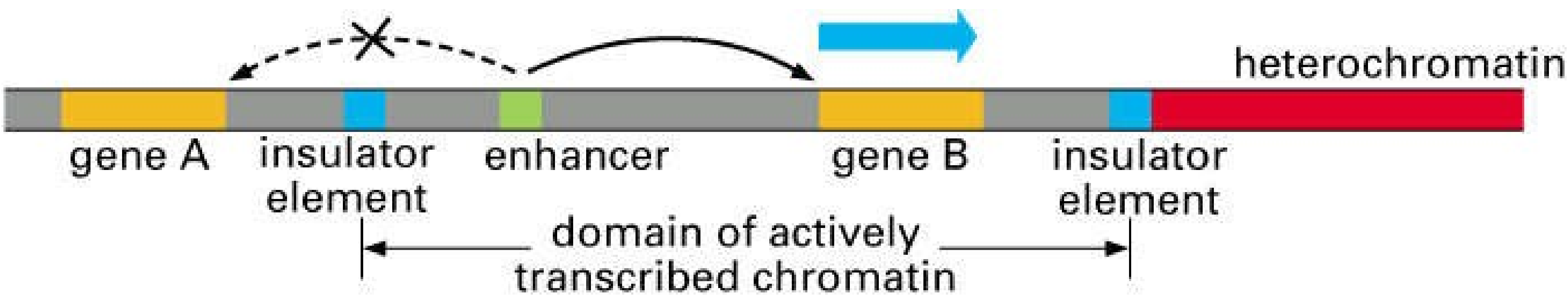



Figure 7–61. Molecular Biology of the Cell, 4th Edition.

Gene regulatory proteins can affect transcription process at different steps

The order of process may be different for different genes

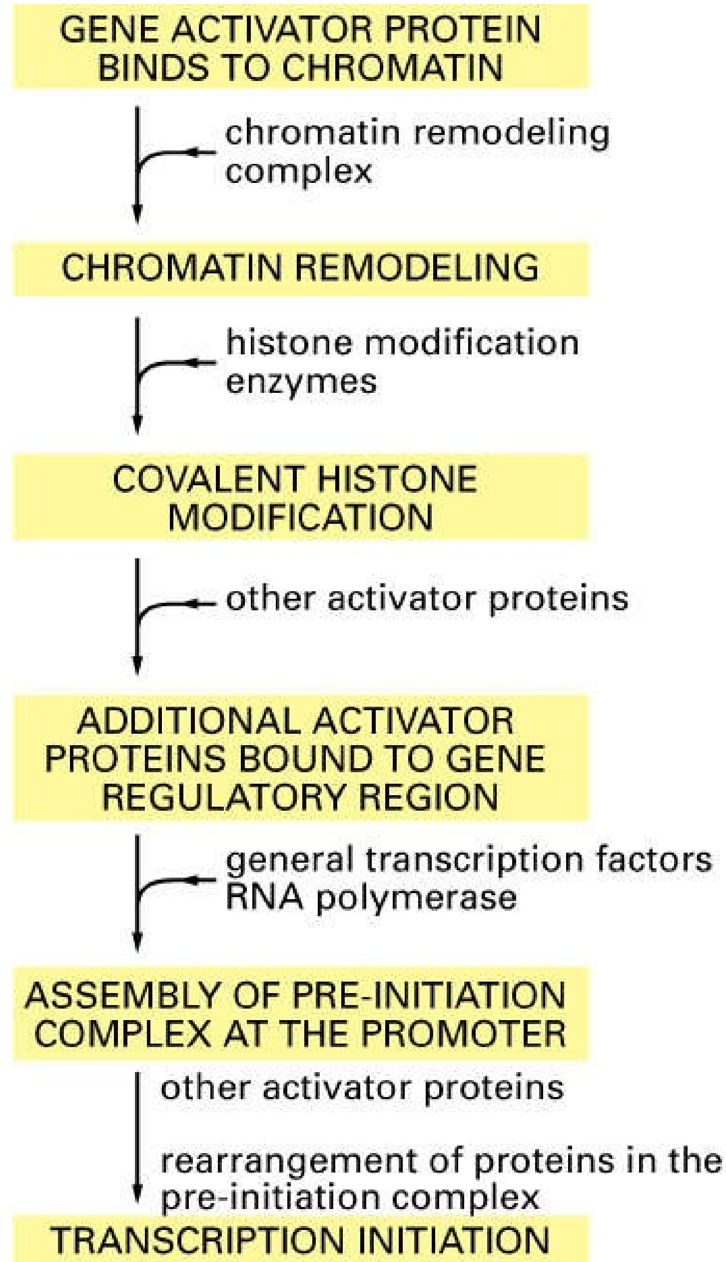



Figure 7–48. Molecular Biology of the Cell, 4th Edition.

References:

1Harper's illustrated biochemistry
2.Genes IX.
3.MOLECULAR BIOLOGY OF CELL 4th edition.
4.concepts of genetics.
**5.**http://www.hschickor.de/genregu1.html

# THANK YOU.