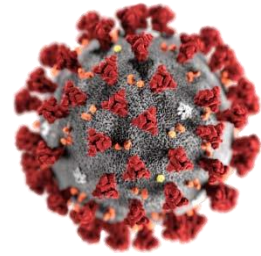




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Universidade de São Paulo



# **Programa de Pós-Graduação em Bioquímica e Biologia Molecular**

## **BBM5002 - Bioquímica e Biologia Molecular**

### **Docente:**

Prof. Dr. Felipe S. Chambergo – [fscha@usp.br](mailto:fscha@usp.br)

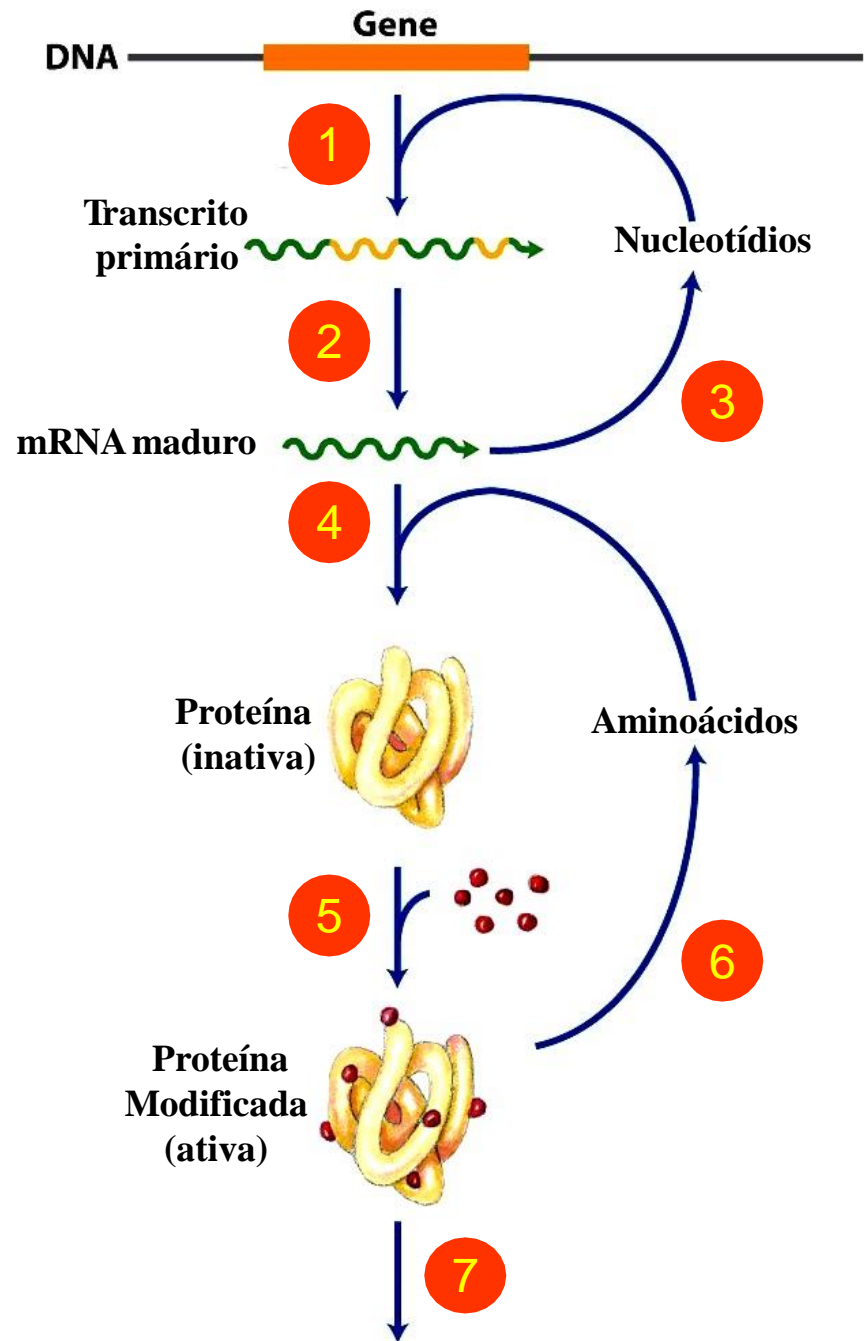
<https://sites.usp.br/lbbp/>

**Data:** Segunda-feira 14 – 16 h / Sexta-feira 8 - 12 h.

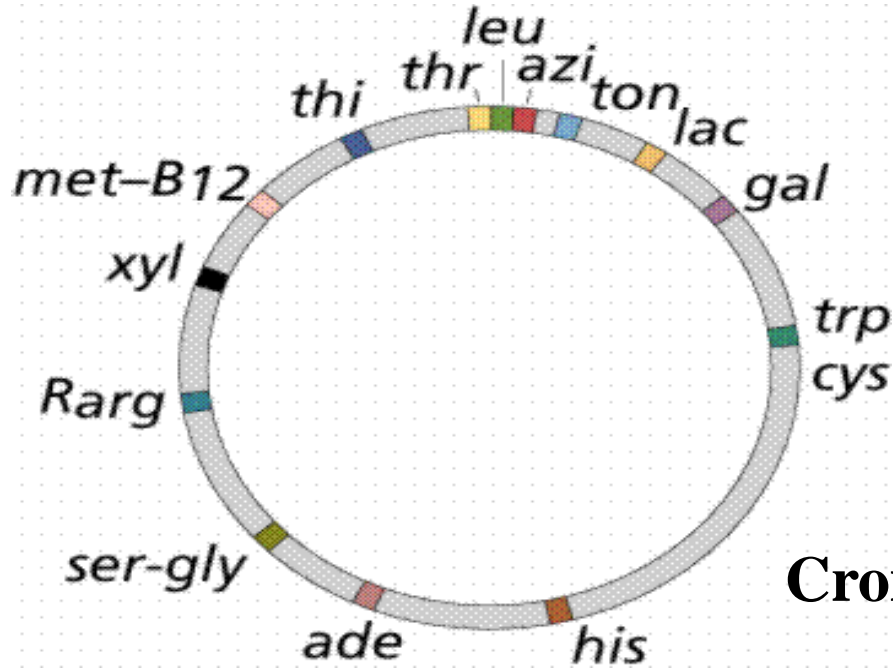
**USP – 2021-1S**

# Controle da Expressão Gênica em Eucariotes

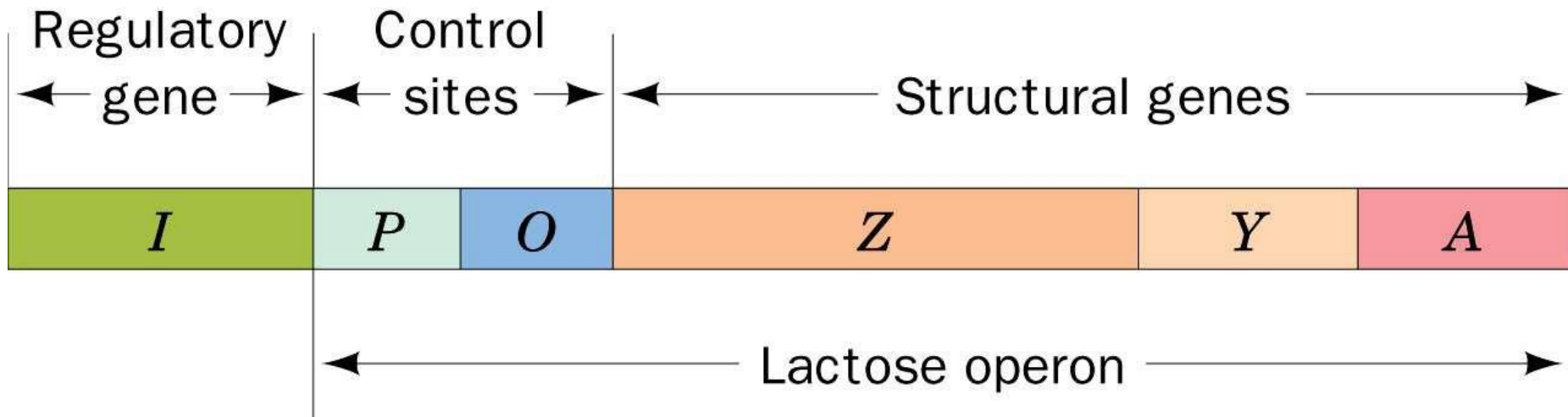
- 1 Transcrição:** Expressão/Ativação do gene
- 2 Processamento Pós-transcrição:** Remoção de introns/poliadenilação, Capping, Transporte
- 3 Degradação mRNA:** Estabilidade e tempo de vida
- 4 Tradução:** Leitura correta
- 5 Processamento Pós-tradução:** Formação de enlaces, adição de outras moléculas.
- 6 Degradação de proteínas:** Proteínas inativa ou desenoveladas
- 7 Endereçamento e Transporte:** Destino da proteína



# Organização e estrutura dos genes em procariotos

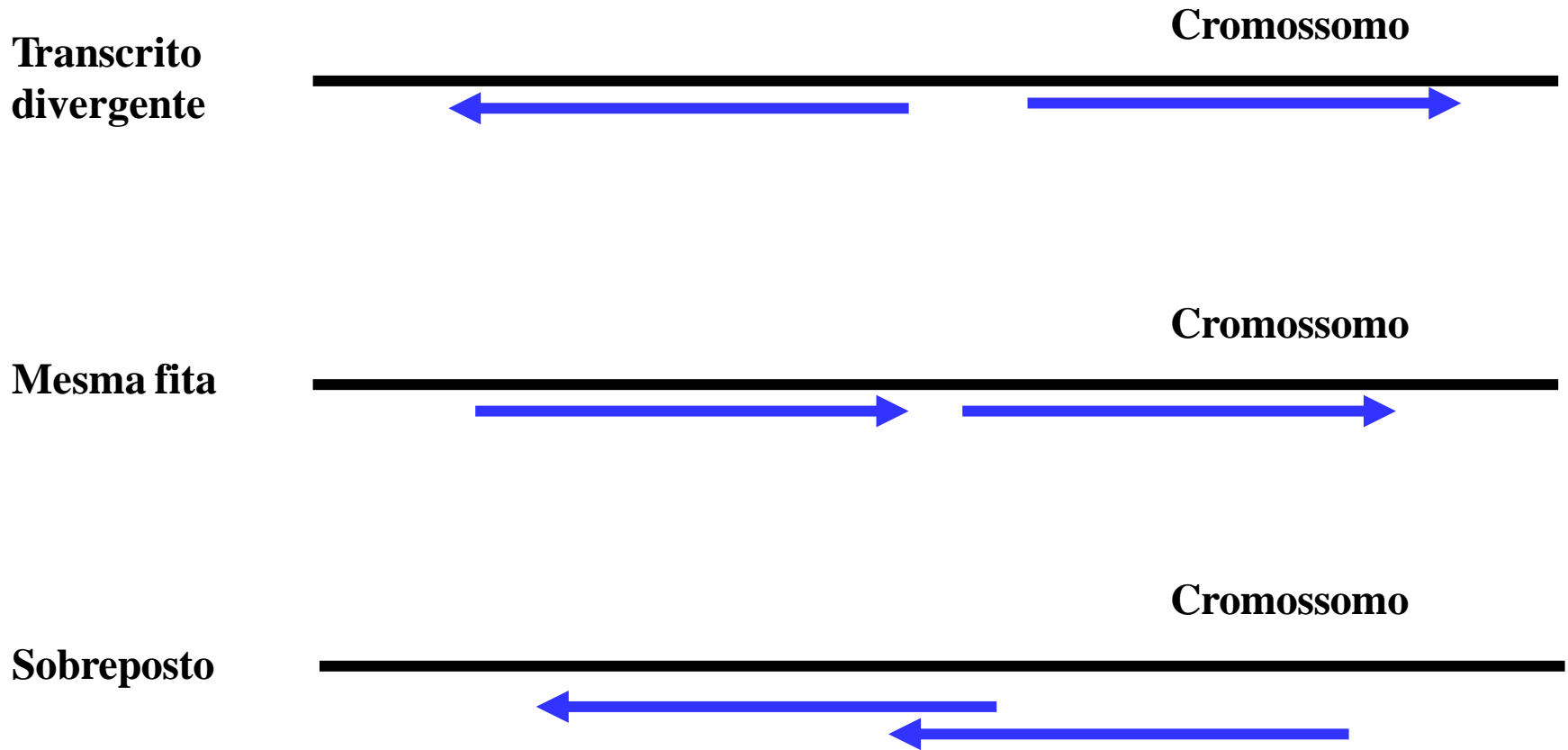


**Cromossomo de *E. coli***



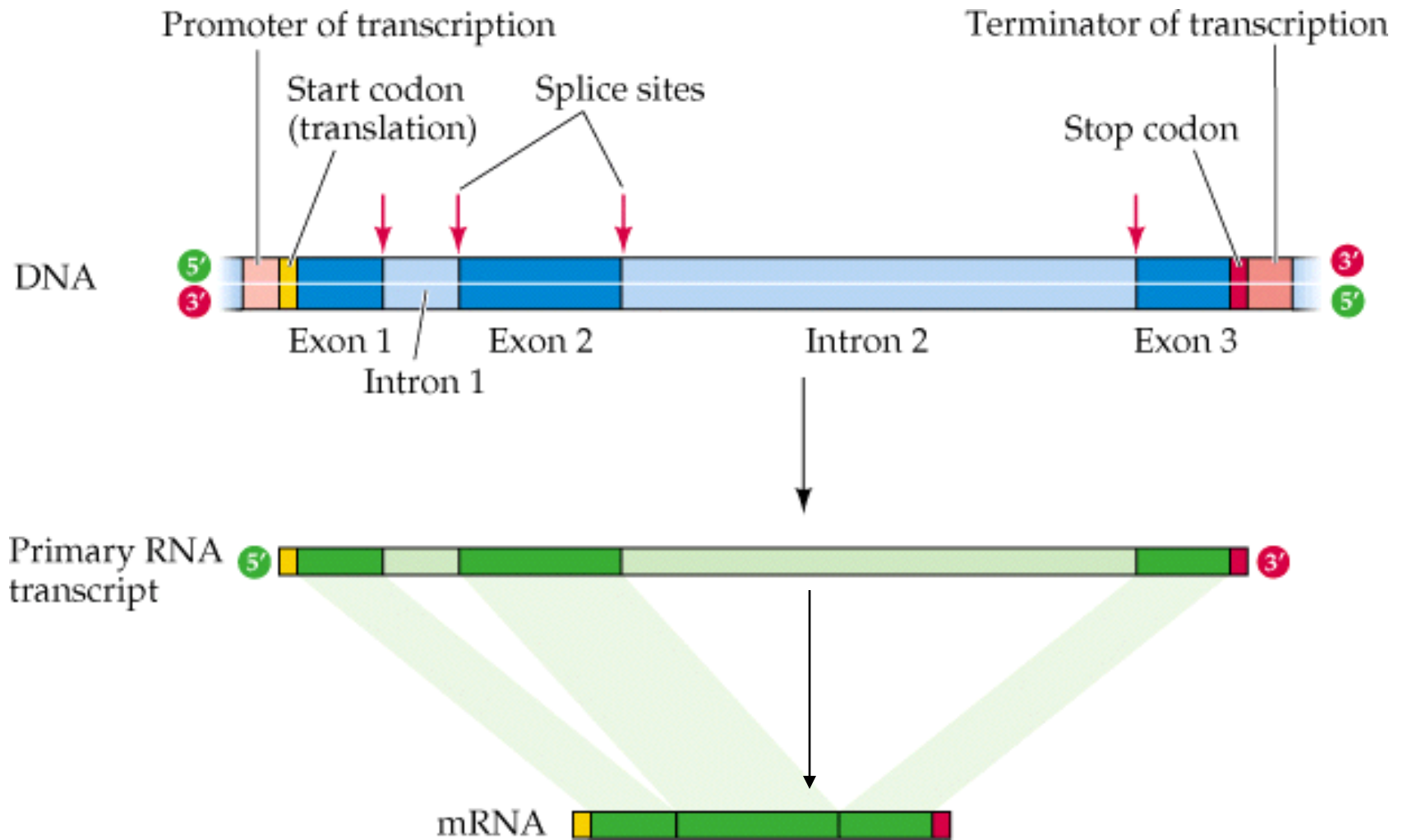
**Genetic map of the *E. coli lac* operon.**

# Disposição dos genes no genoma eucariótico

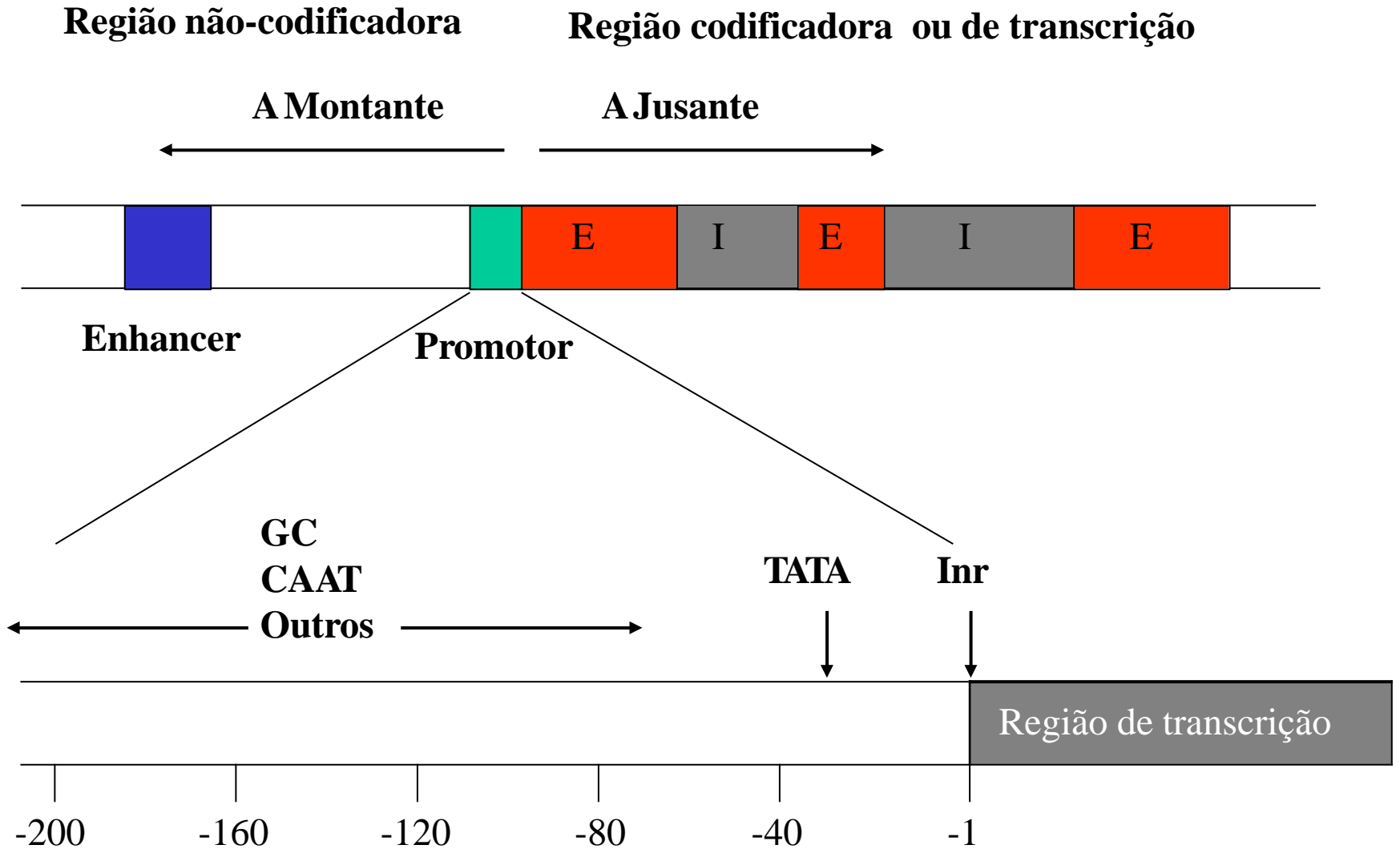


(Takai *et al.*, 2004)

# Estrutura do gene eucariótico

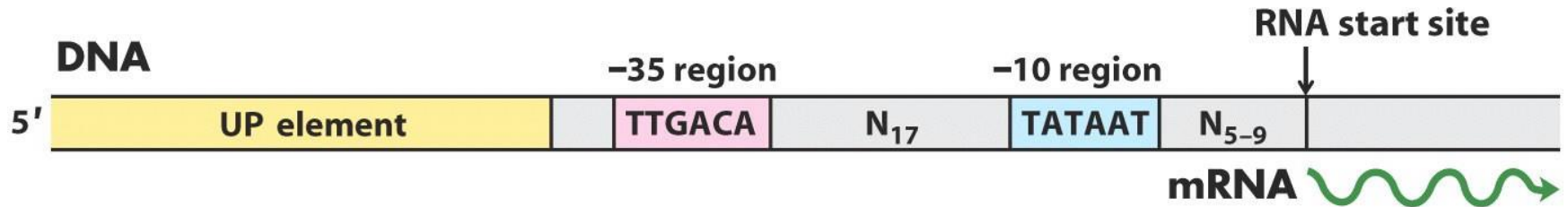


# Organização e estrutura de um gene eucariótico

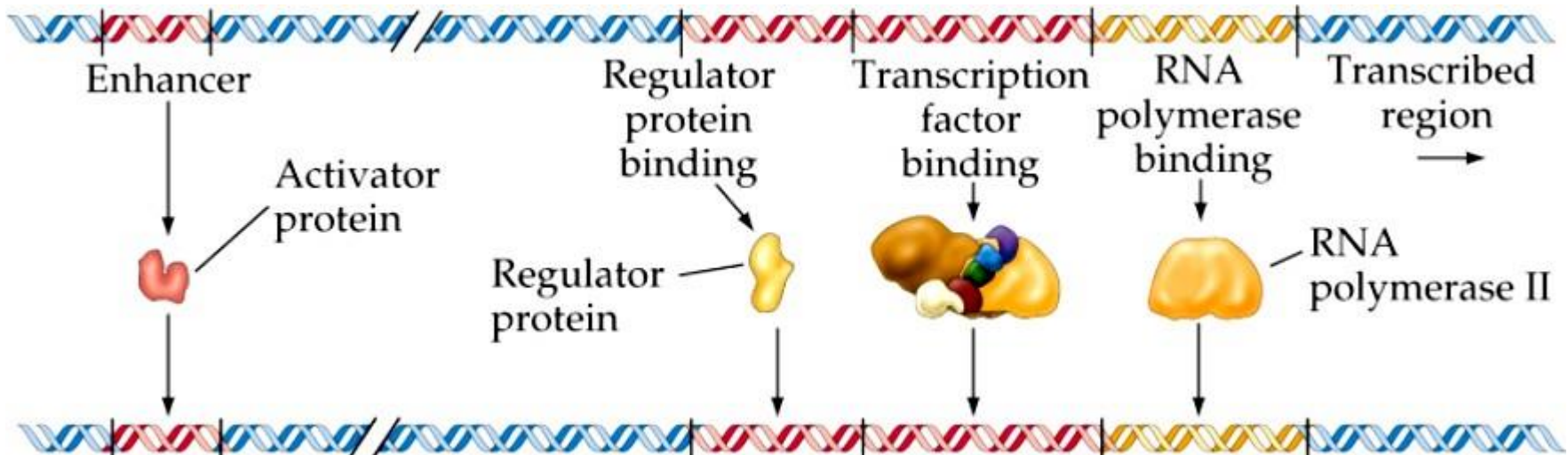


# Transcrição: Expressão/Ativação do gene

1. Expressão gênica constitutiva: Vias metabólicas centrais
2. Expressão gênica regulada: Indução/Repressão, em resposta ao estado metabólico ou sinais.

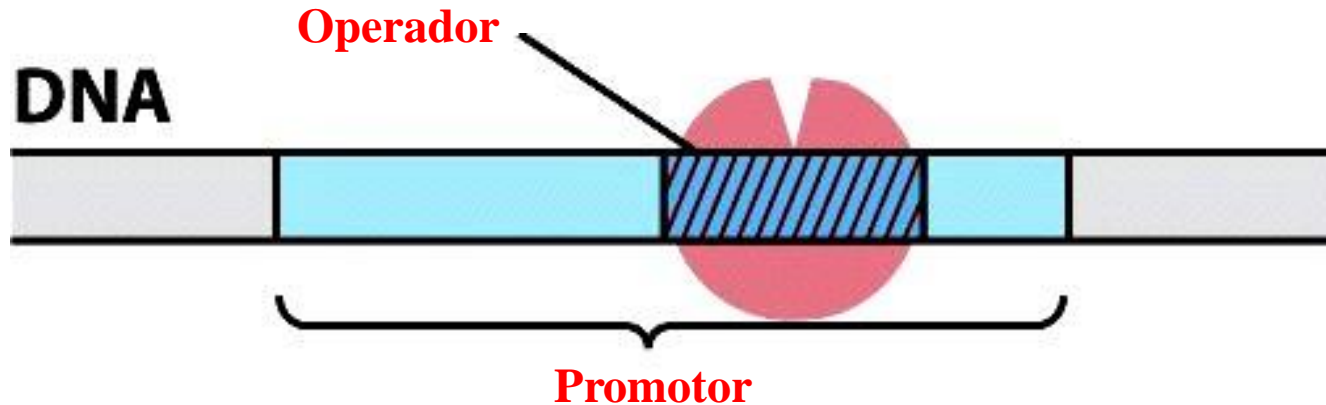


## Interação Proteínas : DNA

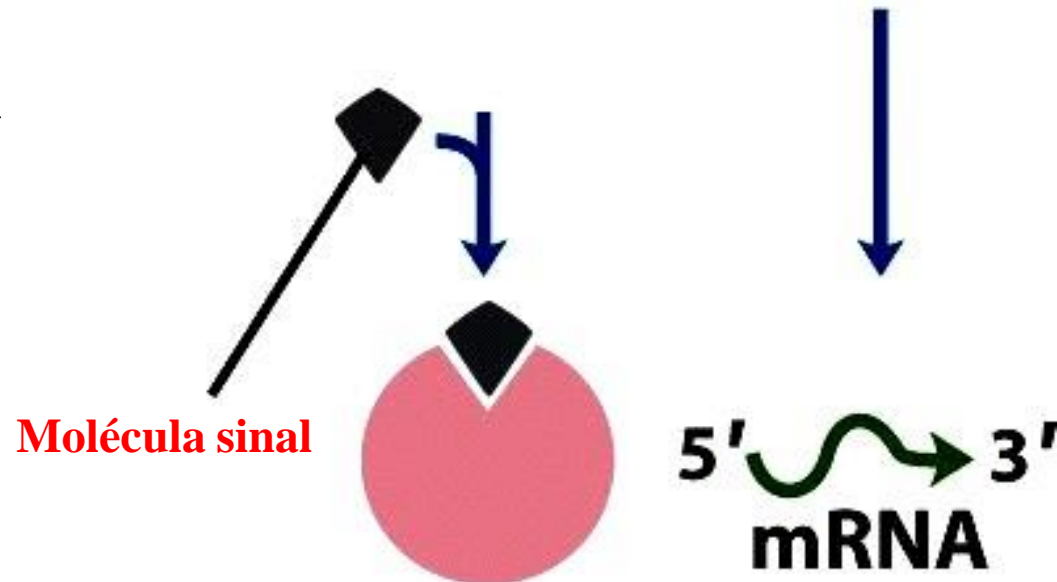


# Mecanismos de regulação da iniciação da transcrição

Regulação negativa (Repressor ligado inibe a transcrição)

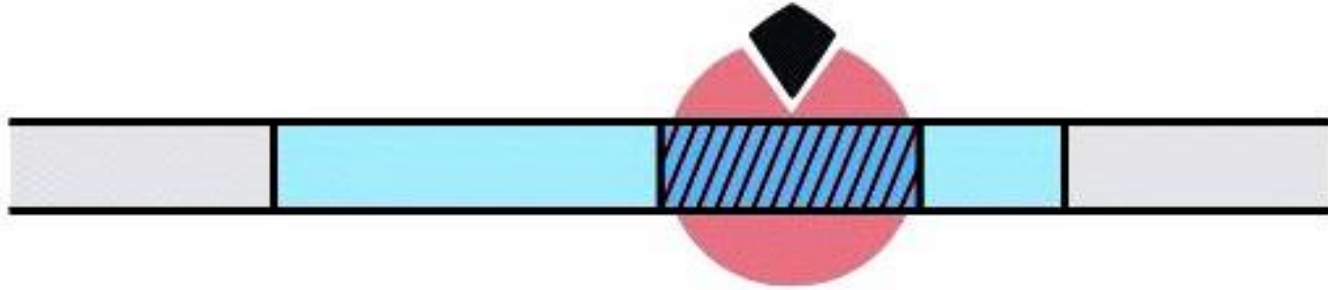


1- Molécula sinal  
causa a dissociação da  
proteína reguladora  
do DNA

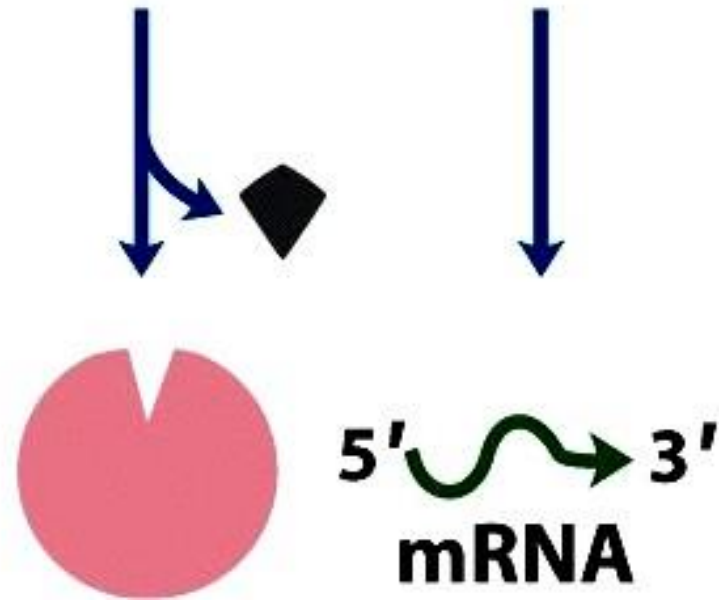




## Regulação negativa (Repressor ligado inibe a transcrição)



**2- Molécula sinal  
induz a ligação da  
proteína reguladora  
do DNA**

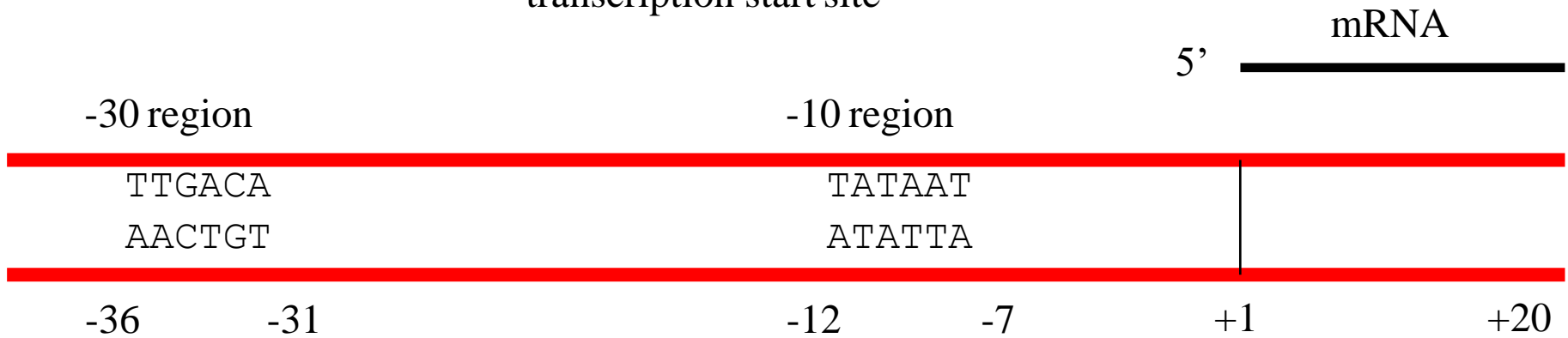
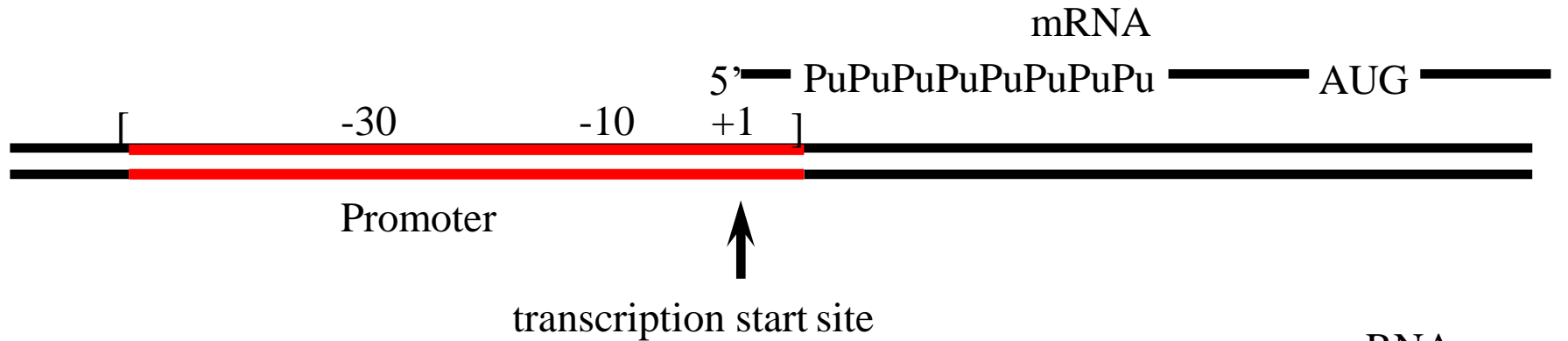


# The sense (nontemplate) strand sequences of selected *E. coli* promoters.

Operon	-35 region	-10 region (Pribnow box)	Initiation site (+1)
<i>lac</i>	ACCCAGGCTTTTACACTTTATGCTTCCGGCTCGT	TATGTTGTGTGGA	ATTGTGAGCGG
<i>lacI</i>	CCATCGAATGGCGCAAAACCTTTCGCGGTATGG	CATGATAGCGCCCGGAAGAGAGTC	
<i>galP2</i>	ATTTATTCCATGTCACACTTTTCGCATCTTTGTT	TATGCTATGGTTA	TTTCATACCAT
<i>araBAD</i>	GGATCCTACCTGACGCTTTTTATCGCAACTCTCT	ACTGTTTCTCCATA	CCCGTTTTT
<i>araC</i>	GCCGTGATTATAGACACTTTTGTACGCGTTTTT	TGTCATGGCTTTGGT	CCCGCTTTG
<i>trp</i>	AAATGAGCTGTTGACAATTAATCATCGAACTAG	TAACTAGTACGCAAGTTCACGTA	
<i>bioA</i>	TTCCAAAACGTGTTTTTTTGTGTTAATTCGGTGT	TAGACTTGTA	AACCTAAATCTTTT
<i>bioB</i>	CATAATCGACTTGTAACCAAATTGAAAAGATTT	TAGGTTTACAAGTCT	TACACCGAAT
<i>tRNA<sup>Tyr</sup></i>	CAACGTAACACTTTACAGCGGCGCGTCATTTGAT	TATGATGCGCCCCGCTT	CCCGATA
<i>rrnD1</i>	CAAAAAAATACTTGTGCAAAAAATTGGGATCCCT	TATAATGCGCCTCCGTTGAGACGA	
<i>rrnE1</i>	CAATTTTTCTATTGCGGCCTGCGGAGAACTCCCT	TATAATGCGCCTCCATCGACACGG	
<i>rrnA1</i>	AAAATAAATGCTTGACTCTGTAGCGGGAAGGCGT	ATTATGCACACCCCGCGCGCTG	

Consensus sequence:	-35 region	...	-10 region	...	Initiation site
	T T G A C A	... 16-19 bp ...	T A T A A T	... 5-8 bp ...	A
	69 79 61 56 54 54		77 76 60 61 56 82		51
					C 48
					55 G
					42

# Promoter structure in prokaryotes

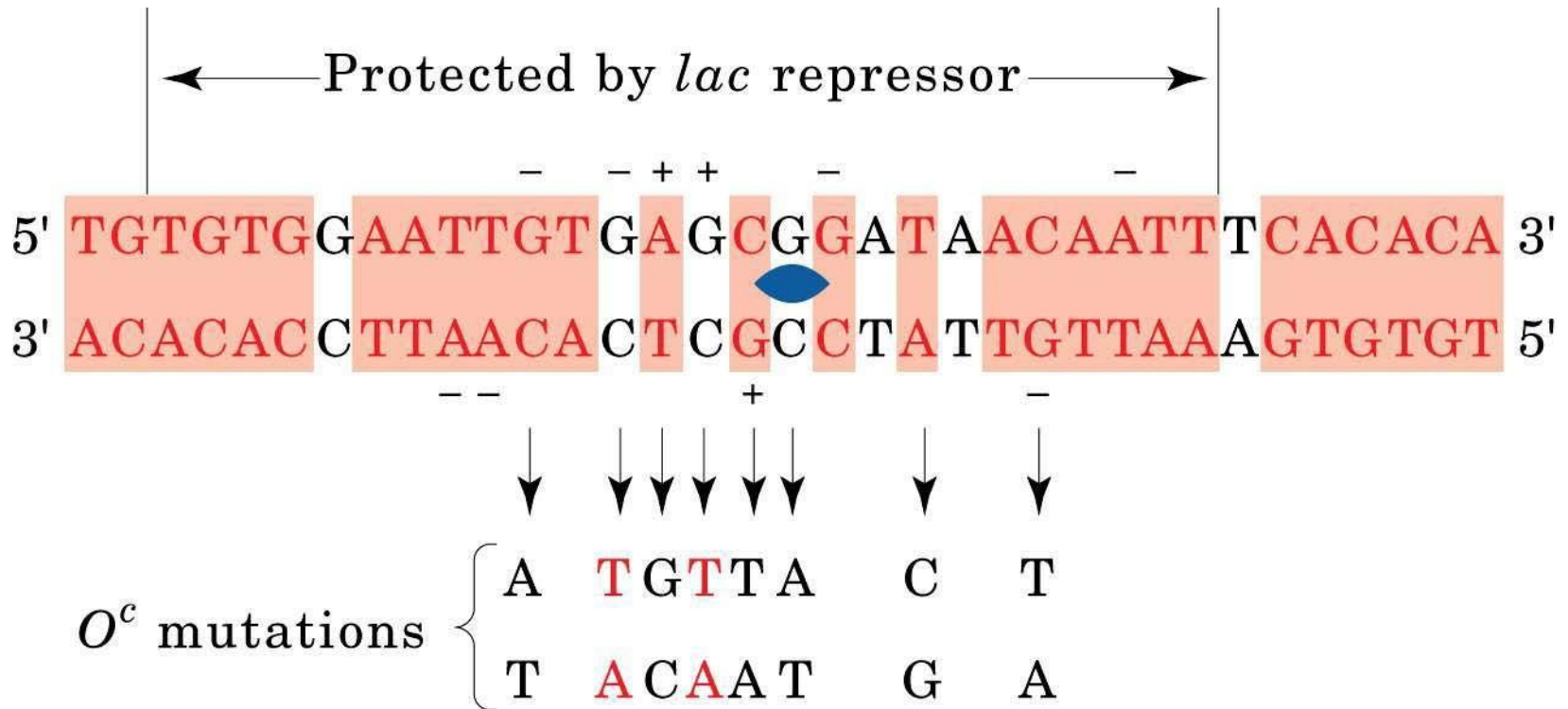


T T G A C A  
 82 84 79 64 53 45%

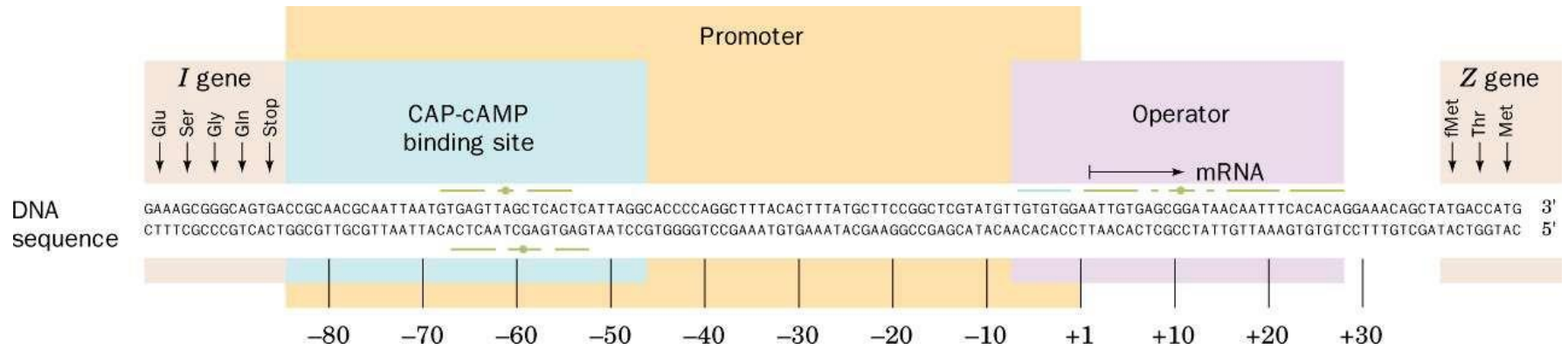
T A T A A T  
 79 95 44 59 51 96%

consensus sequences

# The base sequence of the *lac* operator.



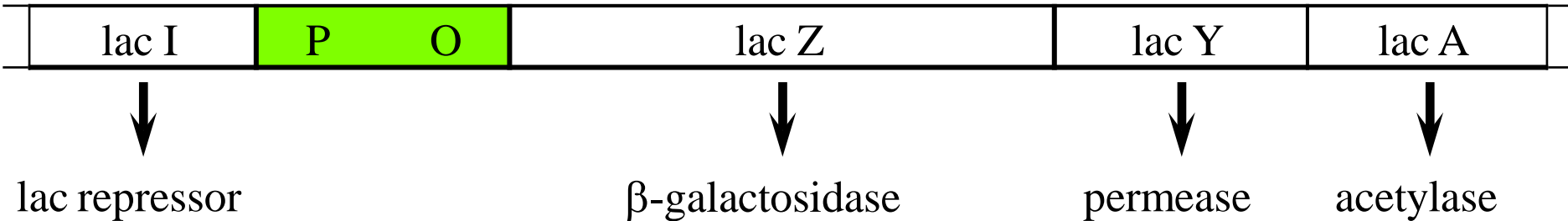
# The nucleotide sequence of the *E. coli lac* promoter–operator region.



# The lactose operon in *E. coli*

- promoter binds CAP and RNA polymerase
- operator binds the lac repressor

promoter - operator

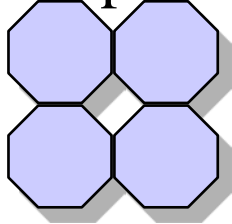


- the function of the lactose (lac) operon is to produce the enzymes required to metabolize lactose for energy when it is required by the cell

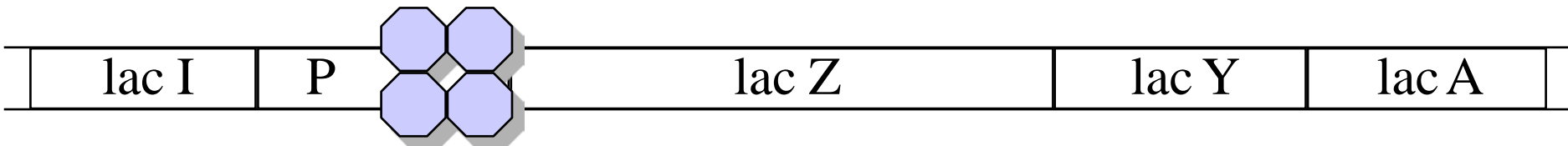
# Regulation of the lactose operon - negative control



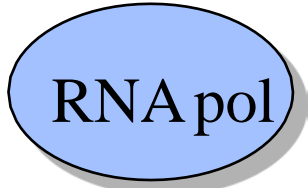
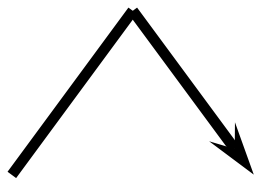
lac repressor



- the **repressor tetramer** binds to the operator and prevents RNA polymerase from binding to the promoter



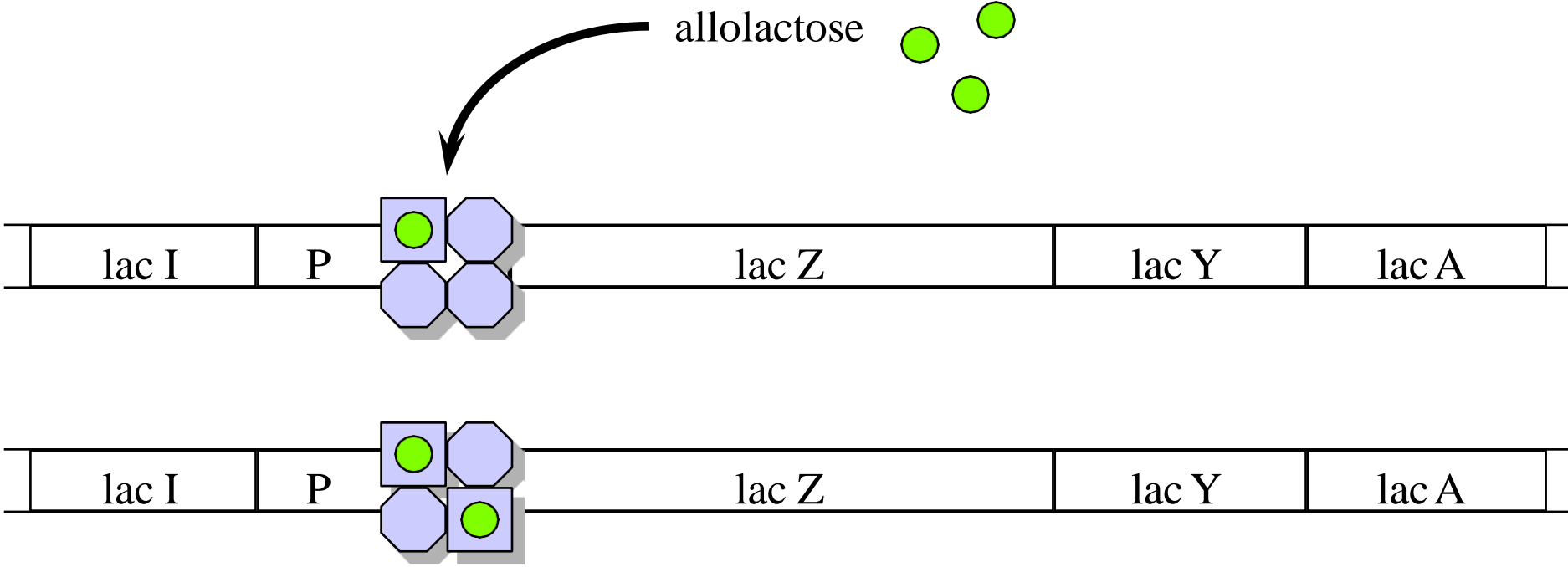
**NO TRANSCRIPTION**



- RNA polymerase is blocked from the promoter

# Alleviation of negative control - action of the inducer of the lac operon

- when lactose becomes available, it is taken up by the cell
- allolactose (an intermediate in the hydrolysis of lactose) is produced
- one molecule of allolactose binds to each of the repressor subunits
- binding of allolactose results in a conformational change in the repressor
- the conformational change results in decreased affinity of the repressor for the operator and dissociation of the repressor from the DNA

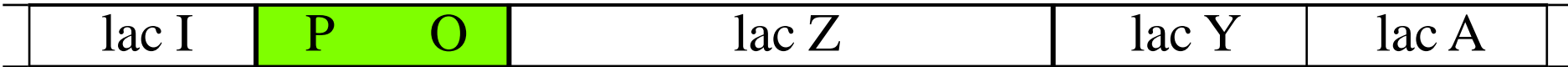
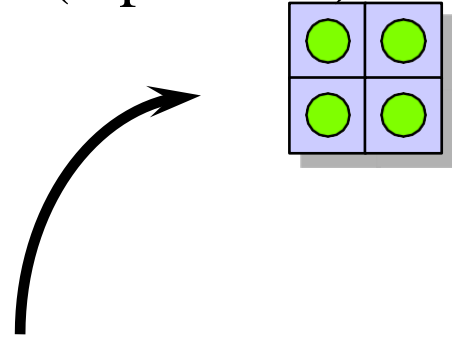


**NO TRANSCRIPTION**

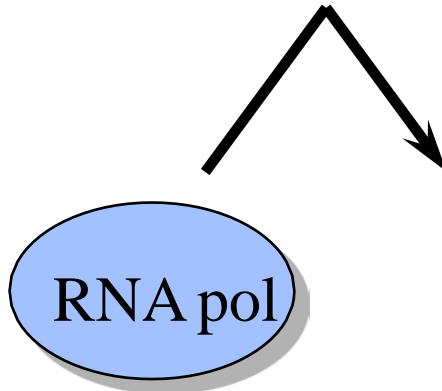
- IPTG (isopropyl thiogalactoside) is also used as a (non-physiological) inducer



- repressor (with bound allolactose) dissociates from the operator
- negative control (repression) is alleviated, however...



**NO TRANSCRIPTION**

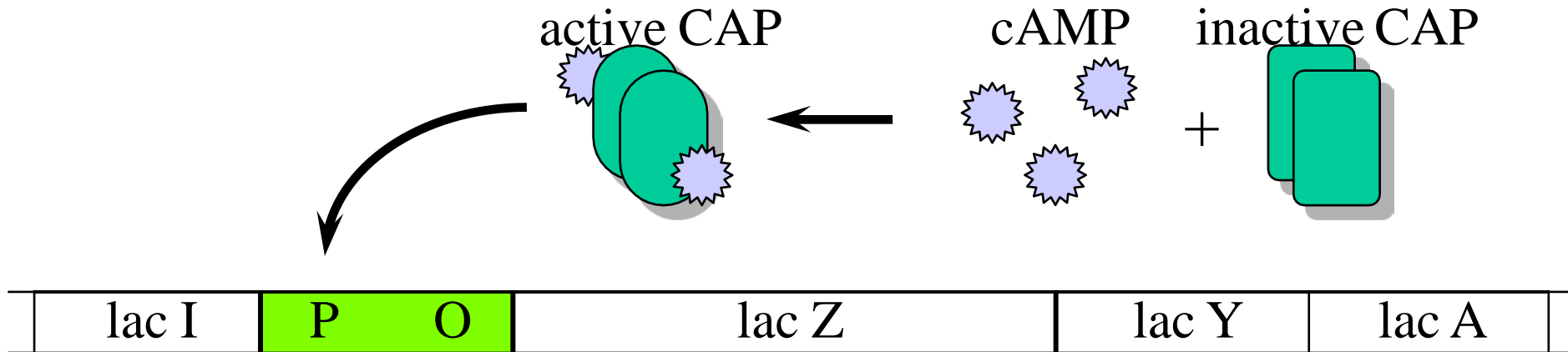


- RNA polymerase cannot form a stable complex with the promoter

# Regulation of the lactose operon - positive control

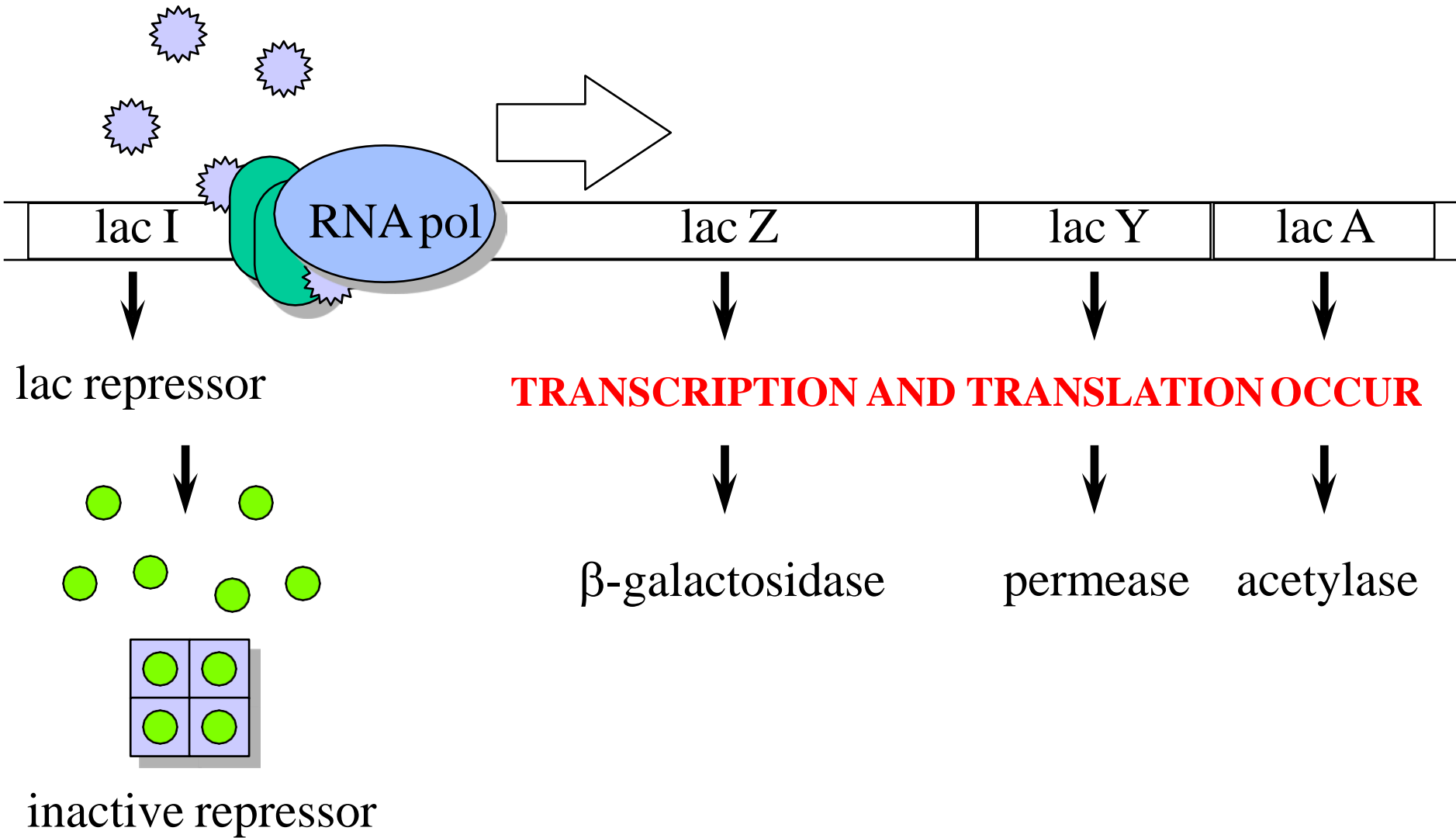
- in the presence of both lactose and glucose it is not necessary for the cell to metabolize lactose for energy
- in the absence of glucose and in the presence of lactose it becomes advantageous to make use of the available lactose for energy
- in the absence of glucose cells synthesize cyclic AMP (cAMP)
- cAMP<sup>1</sup> serves as a positive regulator of catabolite operons (lac operon)
- cAMP binds the dimeric cAMP binding protein (CAP)<sup>2</sup>
- binding of cAMP increases the affinity of CAP for the promoter
- binding of CAP to the promoter facilitates the binding of RNA polymerase

<sup>1</sup> cAMP = 3', 5' cyclic adenosine monophosphate



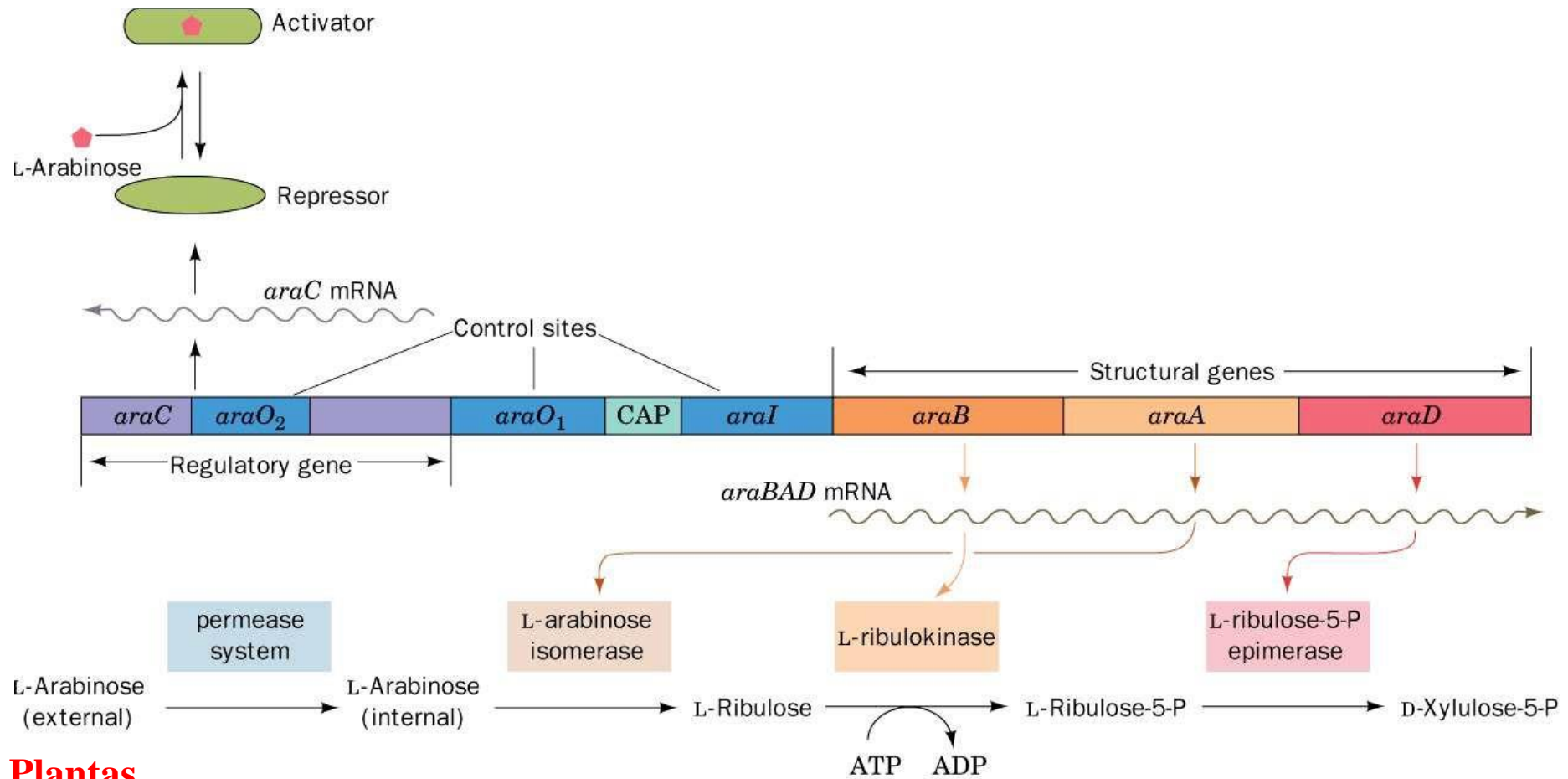
<sup>2</sup> also termed catabolite activator protein

# Activation of lac operon transcription

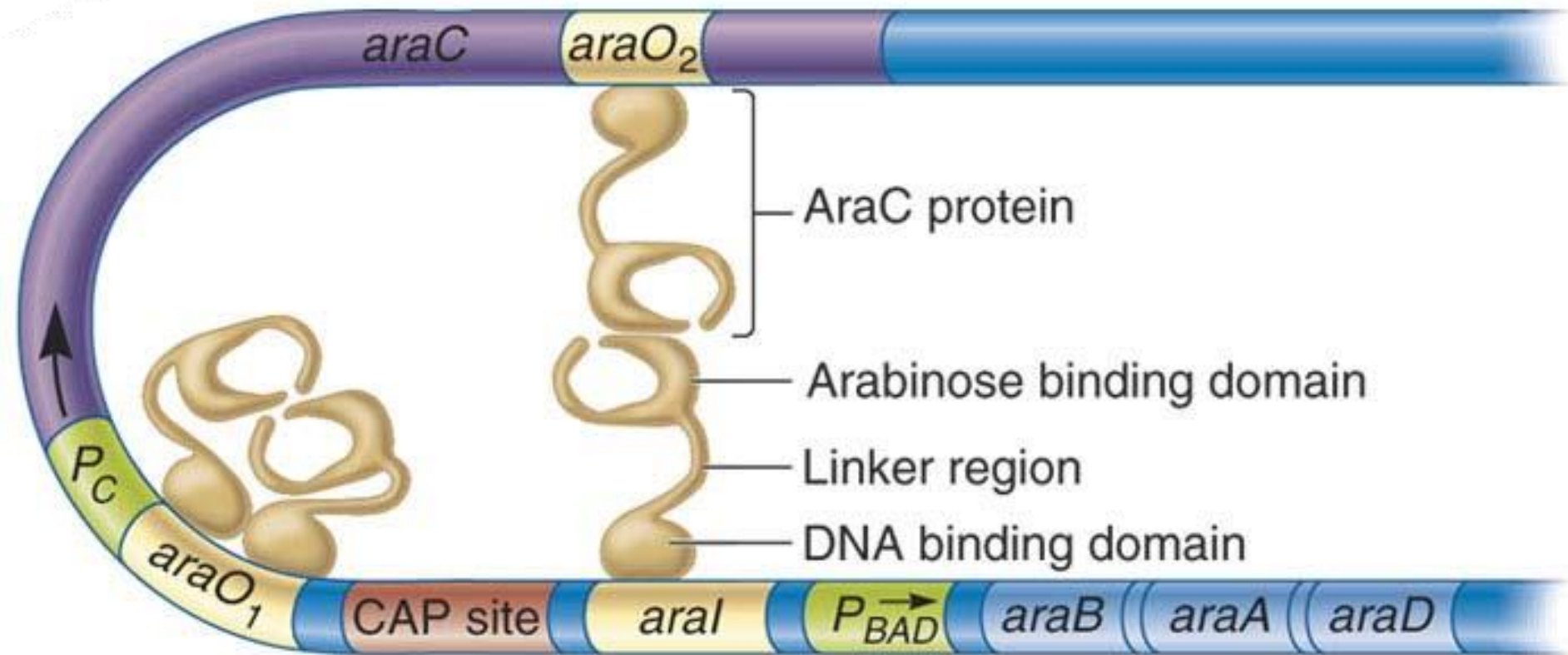


- the function of the lactose (lac) operon is to produce the enzymes required to metabolize lactose for energy when it is required by the cell

# A genetic map of the *E. coli* *araC* and *araBAD* operons.

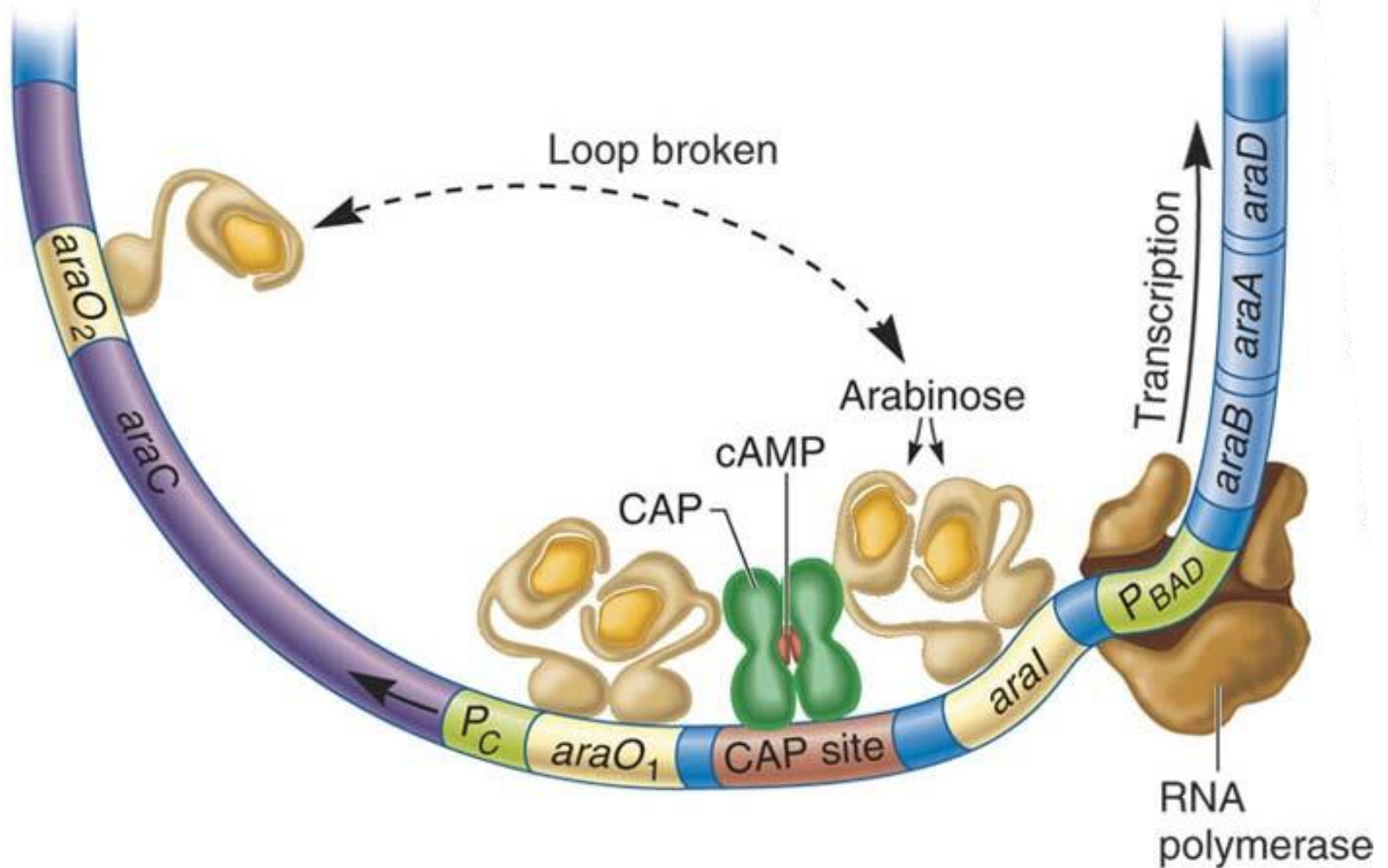


In the absence of arabinose, the *araC* protein inhibits the expression of the *ara* operon.



(a) Operon inhibited in the absence of arabinose

With arabinose, the araC protein activates transcription.

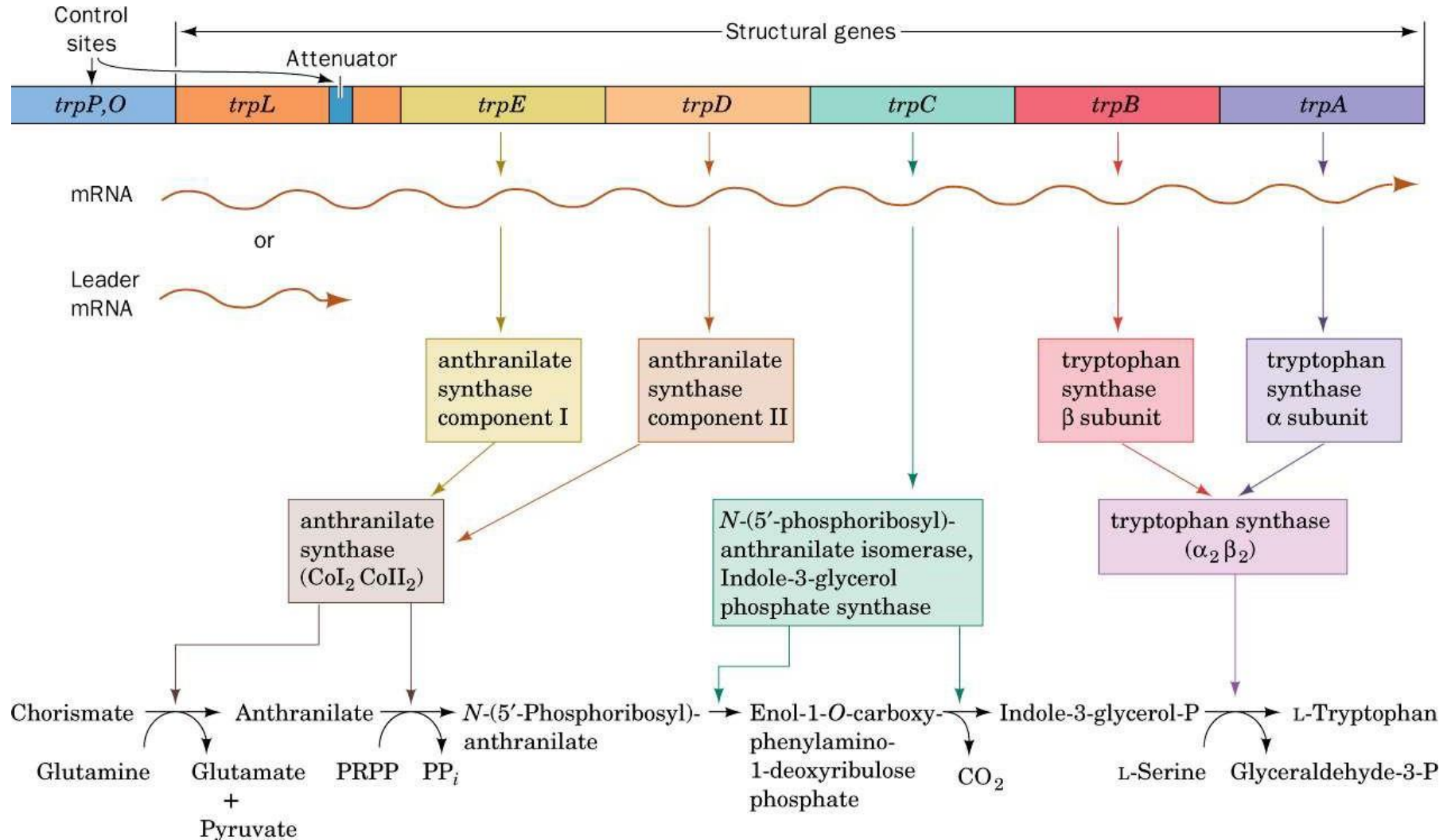


(b) Operon activated in the presence of arabinose



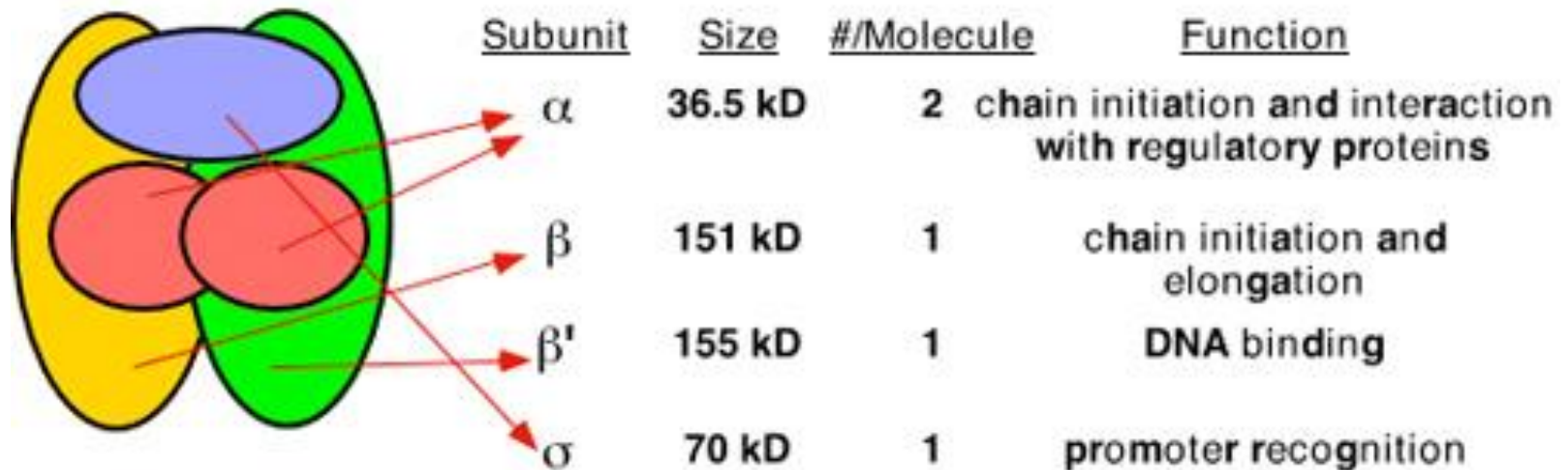


# A genetic map of the *E. coli trp* operon indicating the enzymes it specifies and the reactions they catalyze.



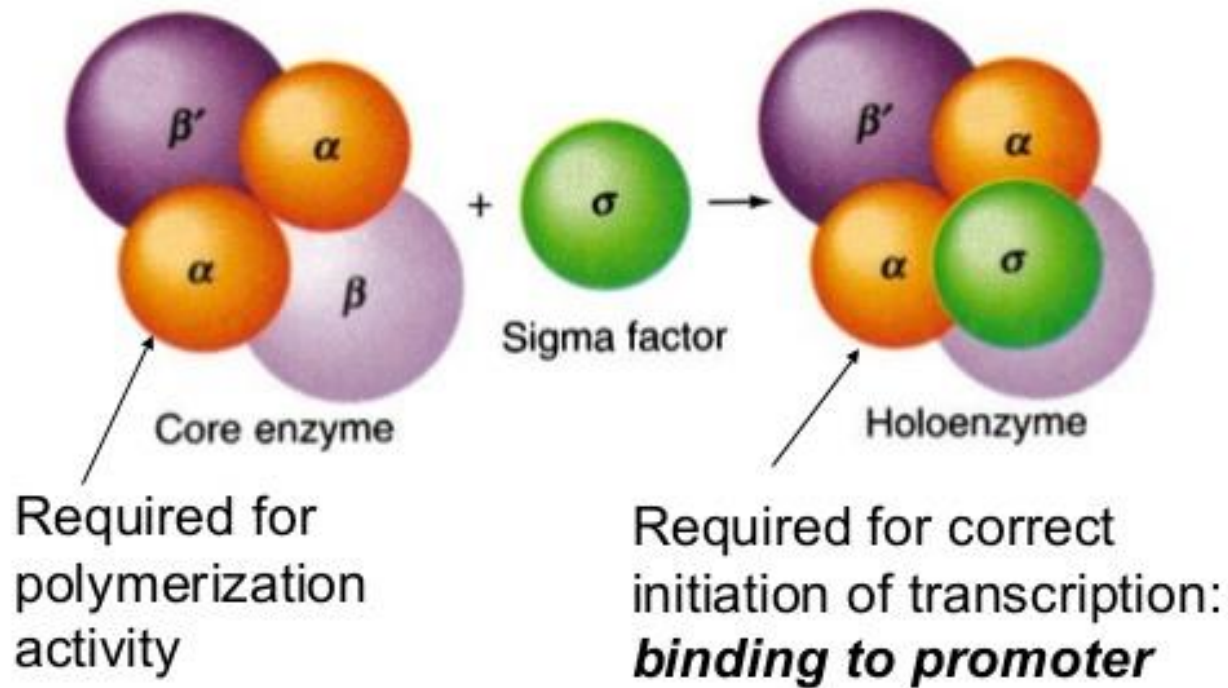


## Prokaryotic RNA Polymerase: Holoenzyme Enzyme



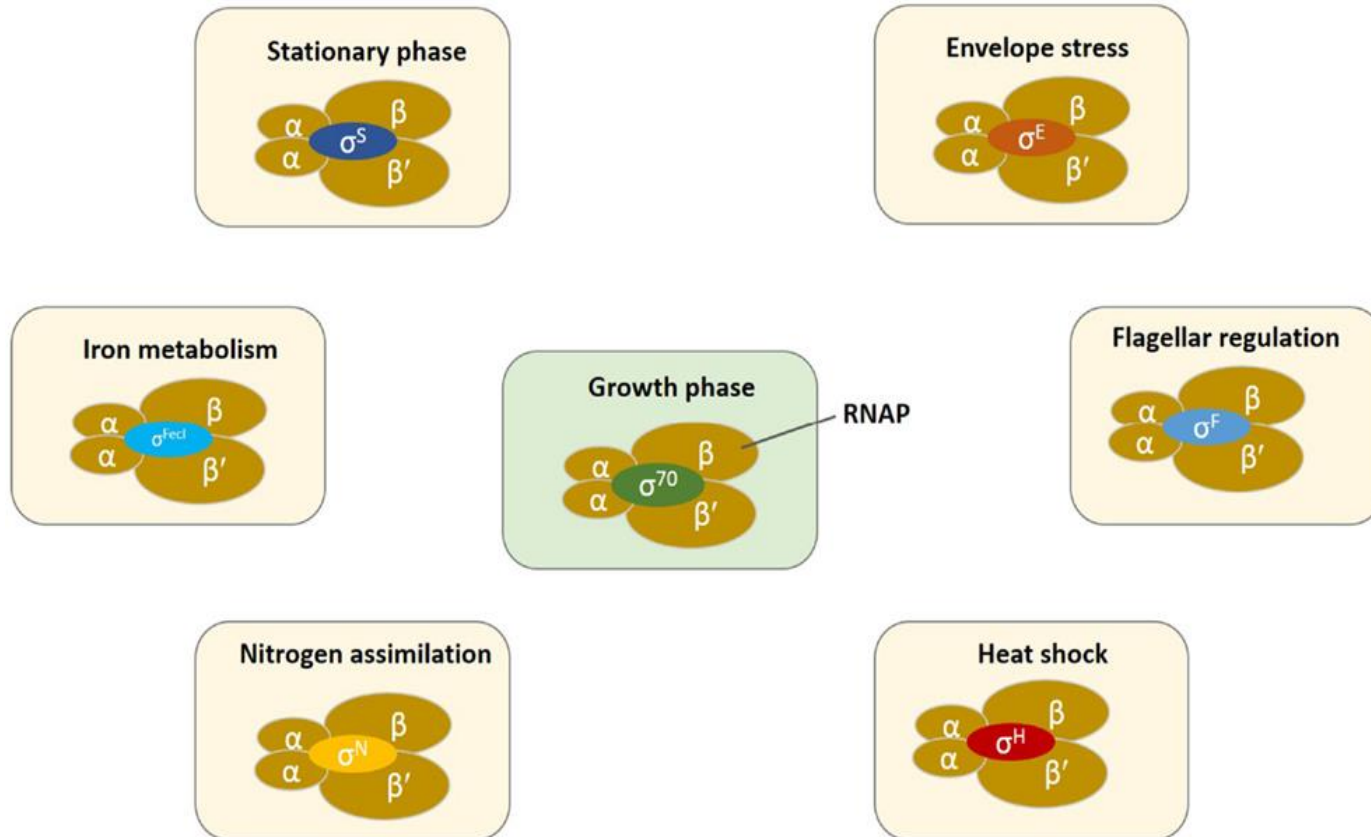
# *E. coli* RNA polymerase

2 $\alpha$ , 1 $\beta$ , 1 $\beta'$ , 1 $\omega$  and  $\sigma$  factor



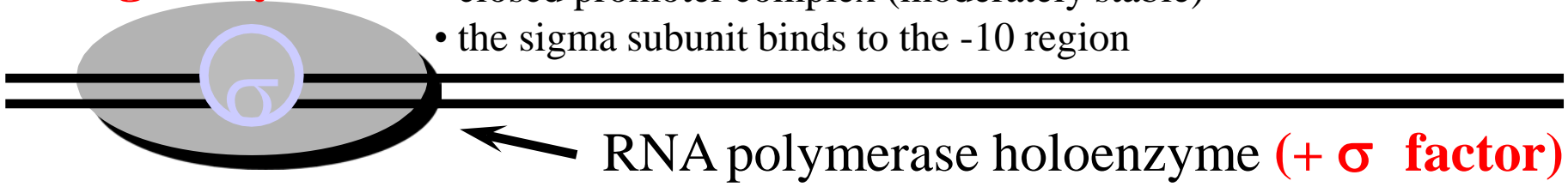
# The function of sigma factor

- the sigma subunit of RNA polymerase is an “initiation factor”
- there are several different sigma factors in *E. coli* that are specific for different sets of genes
- sigma factor functions to ensure that RNA polymerase binds stably to DNA only at promoters
- sigma destabilizes nonspecific binding to non-promoter DNA, sigma stabilizes specific binding to promoter DNA, this accelerates the search for promoter DNA

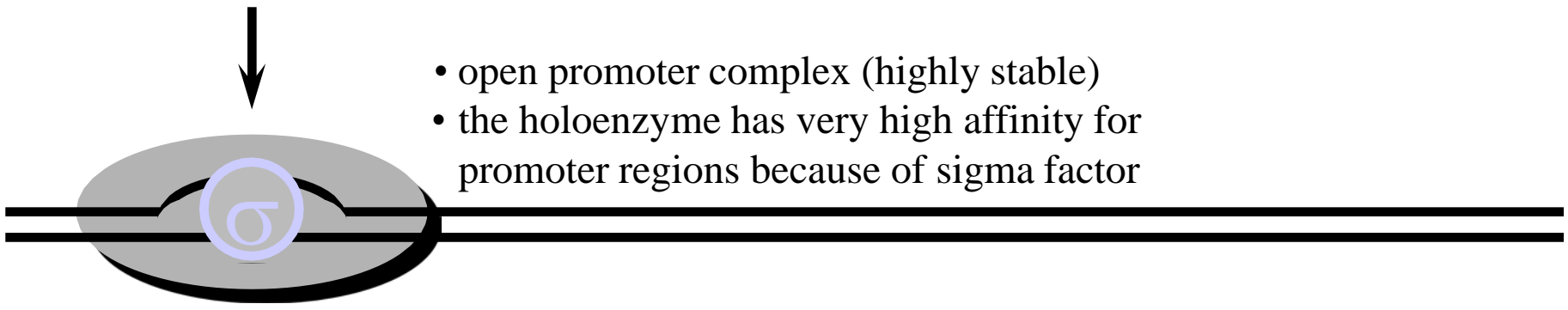


# The sigma cycle

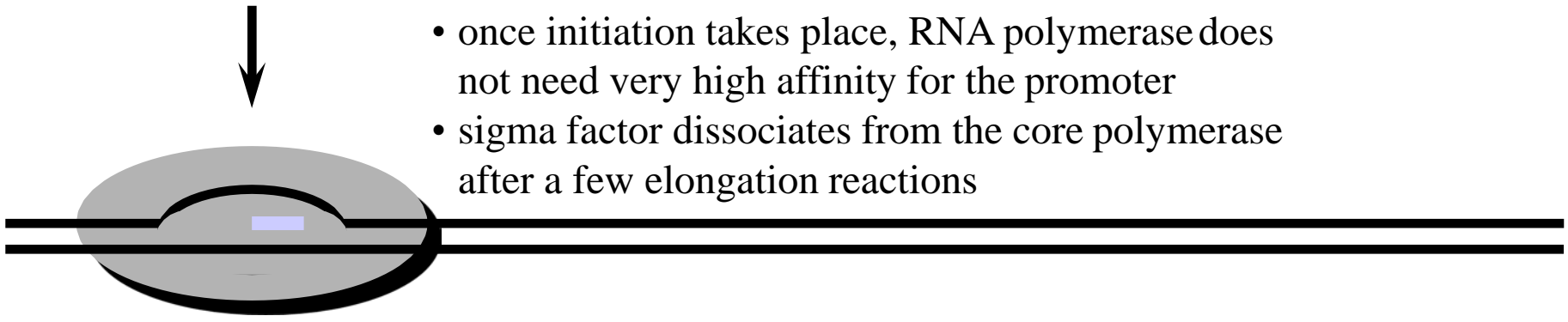
- closed promoter complex (moderately stable)
- the sigma subunit binds to the -10 region



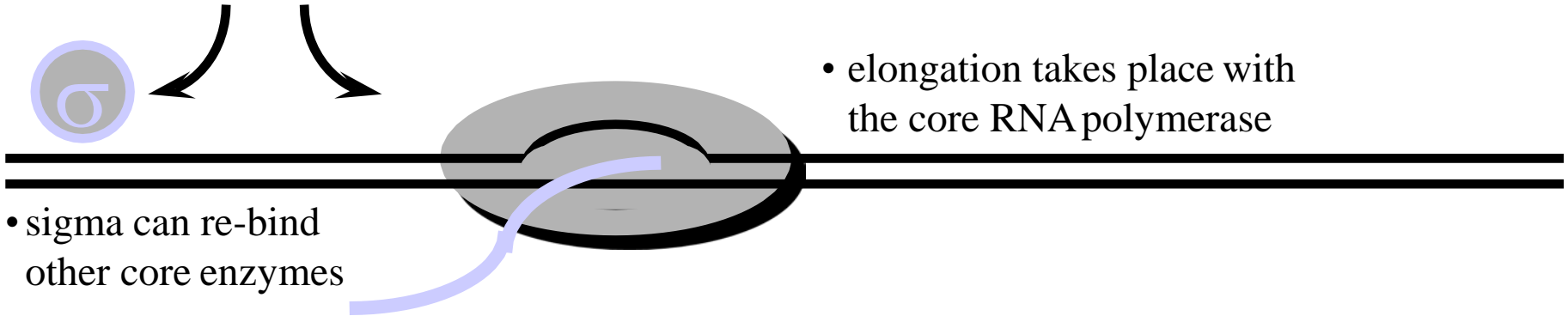
- open promoter complex (highly stable)
- the holoenzyme has very high affinity for promoter regions because of sigma factor



- once initiation takes place, RNA polymerase does not need very high affinity for the promoter
- sigma factor dissociates from the core polymerase after a few elongation reactions

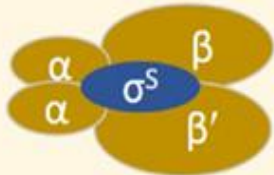


- elongation takes place with the core RNA polymerase

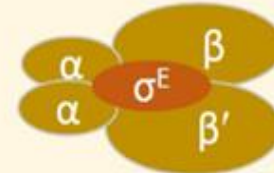


- sigma can re-bind other core enzymes

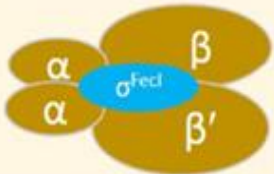
**Stationary phase**



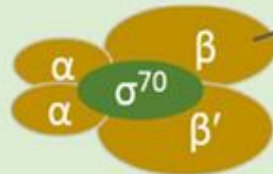
**Envelope stress**



**Iron metabolism**

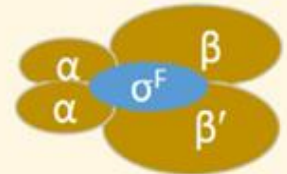


**Growth phase**

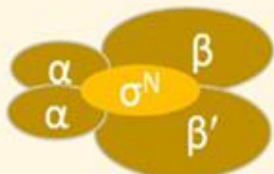


RNAP

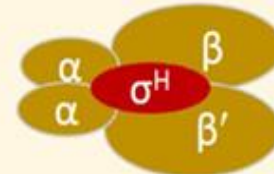
**Flagellar regulation**



**Nitrogen assimilation**

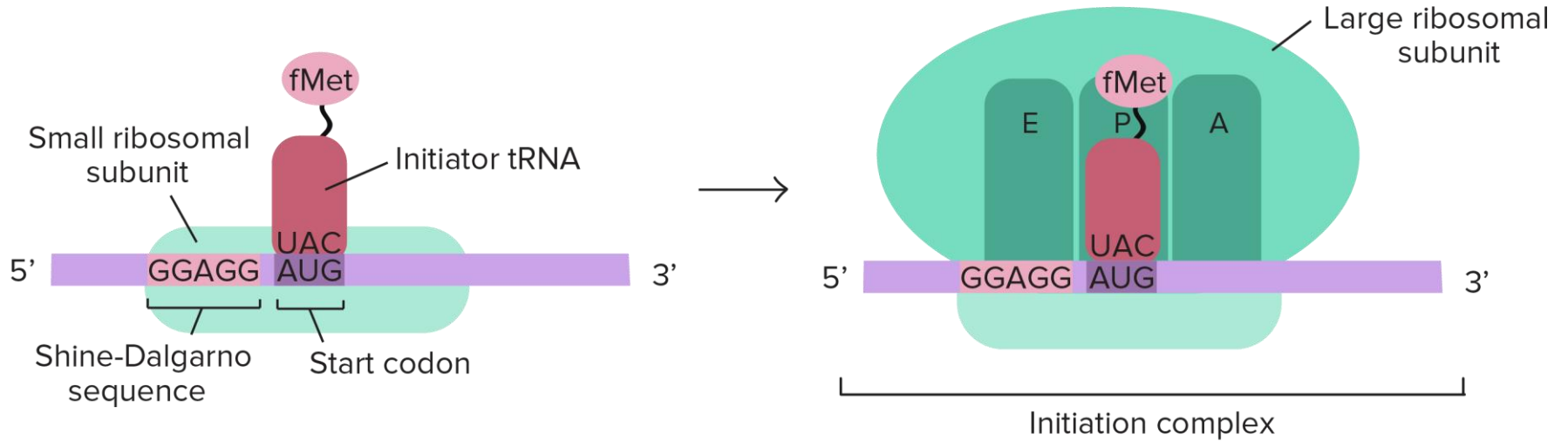


**Heat shock**



# Sítio de ligação ao Ribossomo

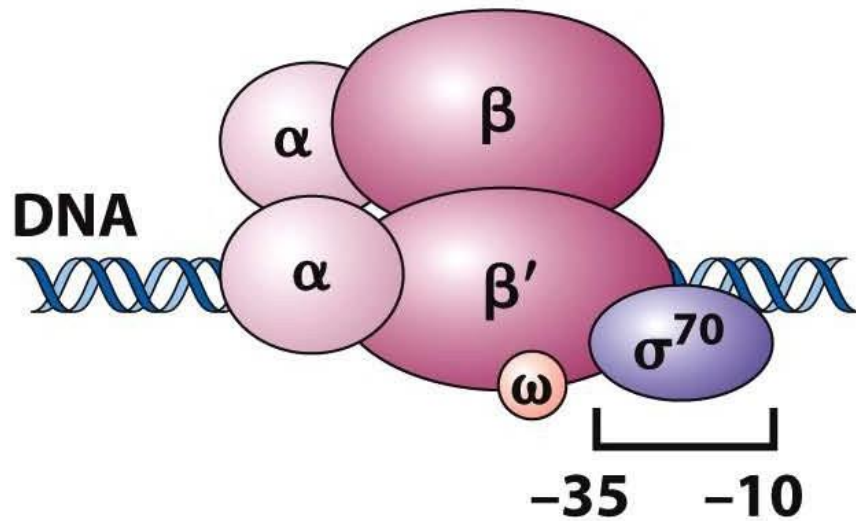
## Bacterial translation initiation



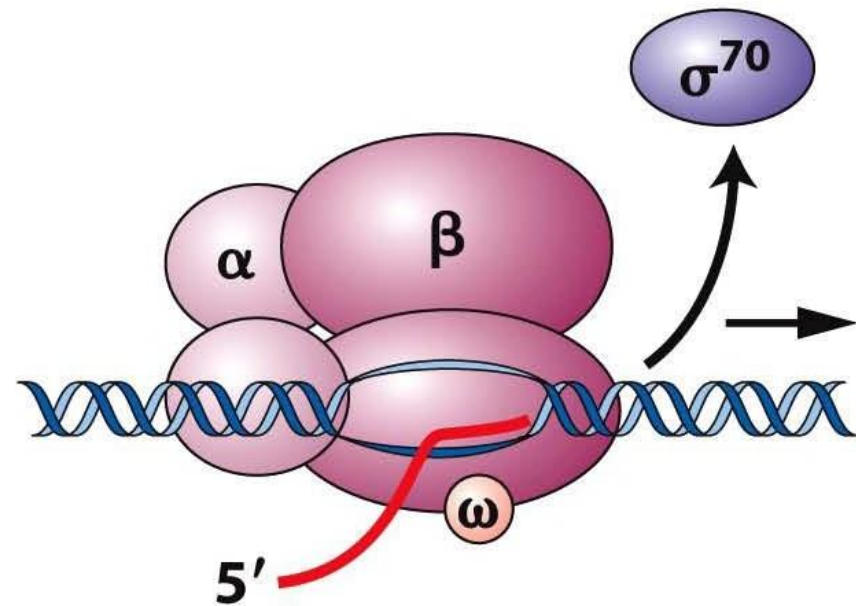
## Transcription initiation in prokaryotes:

sigma factor binds to the -35 and -10 regions and then the RNA polymerase subunits bind and begin transcription

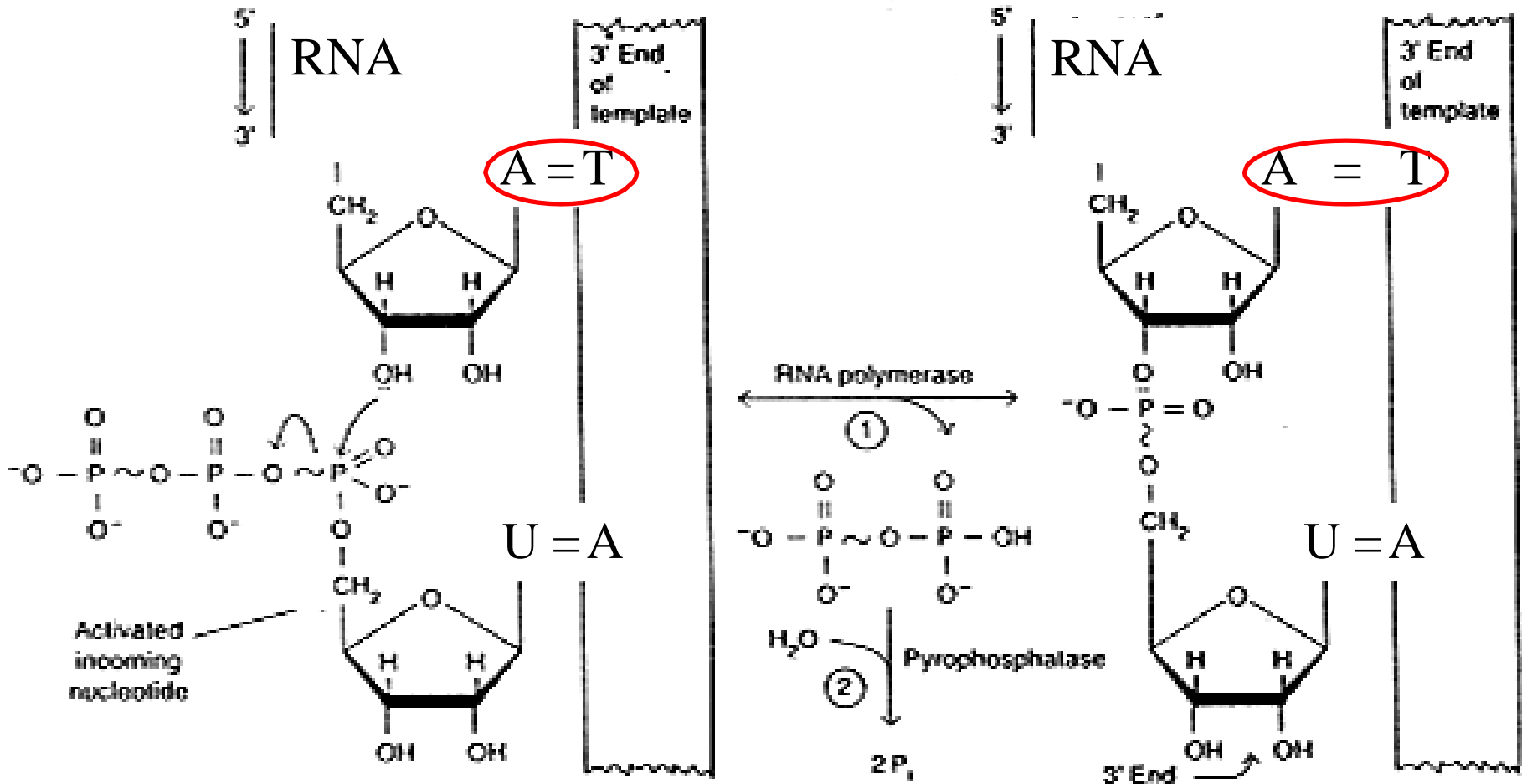
**(a) RNA polymerase binding to promoter**



**(b) Initiation**

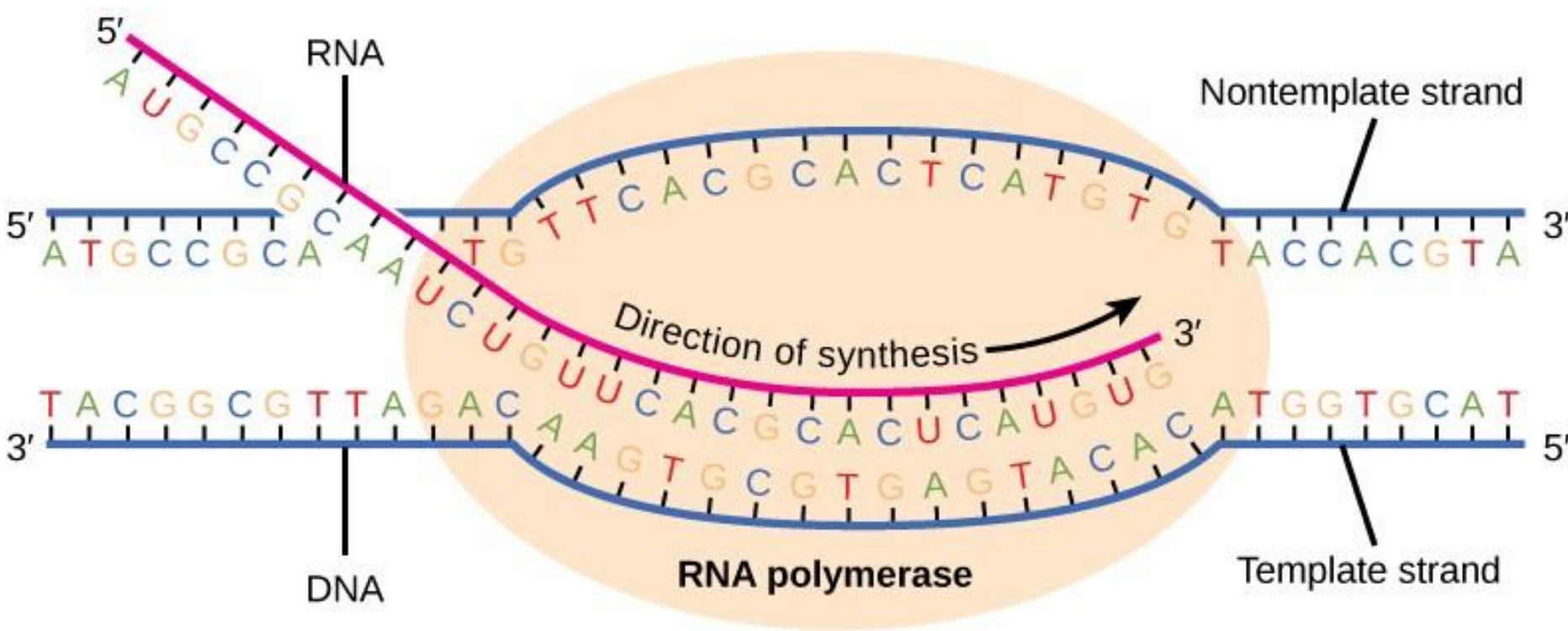


# Mechanism of RNA synthesis

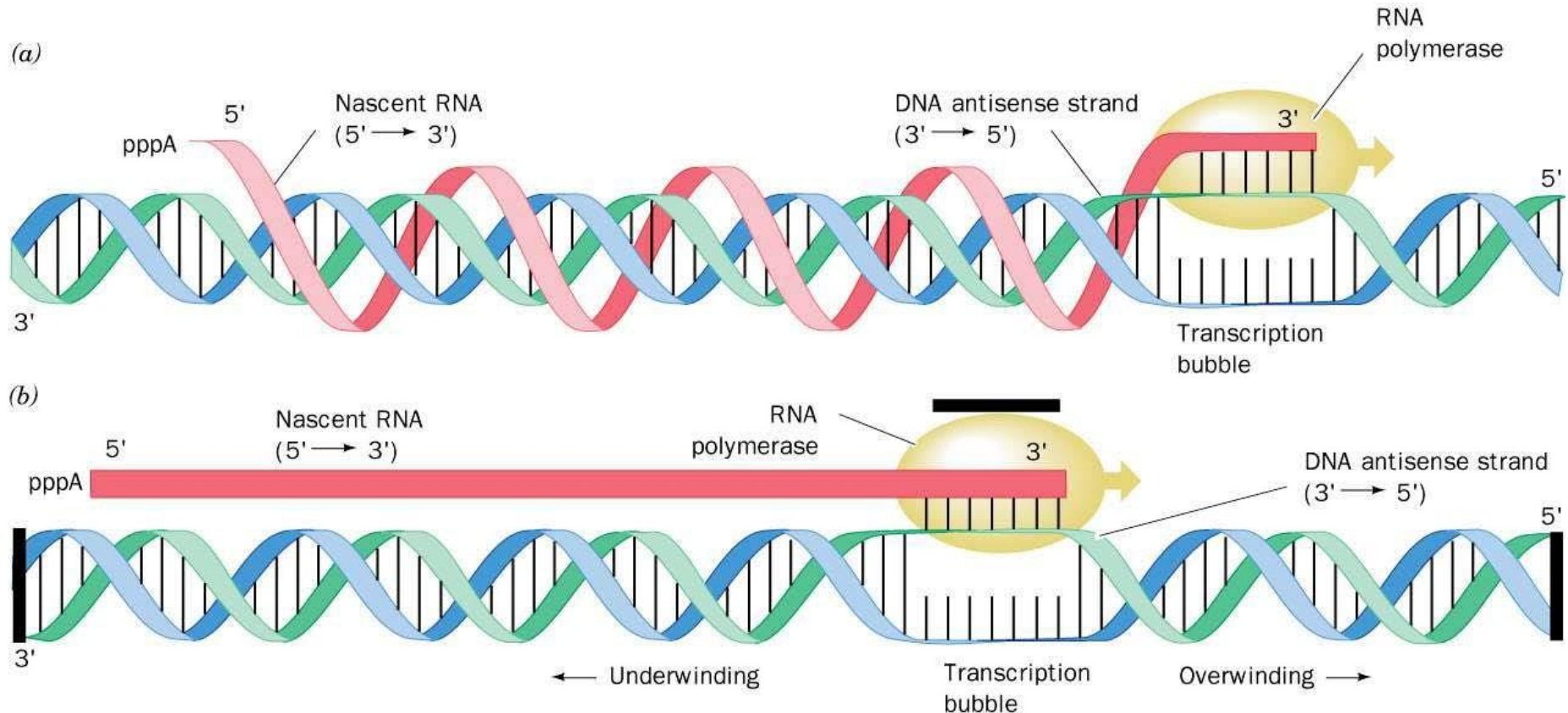


- RNA synthesis usually initiated with ATP or GTP (the first nucleotide)
- RNA chains are synthesized in a 5' to 3' direction
- Termination of some transcripts makes use of the Rho protein, which is a termination factor that catalyzes the dissociation of the RNA and polymerase

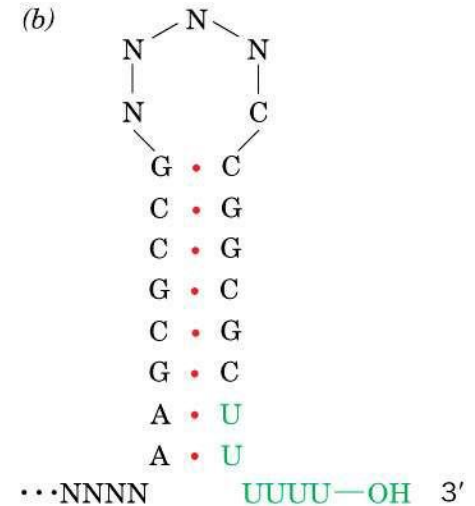
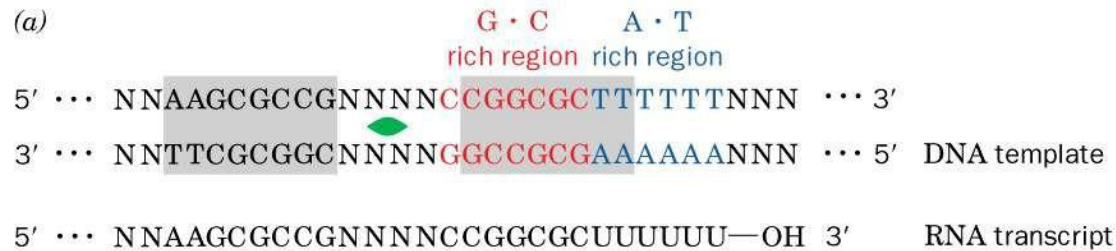


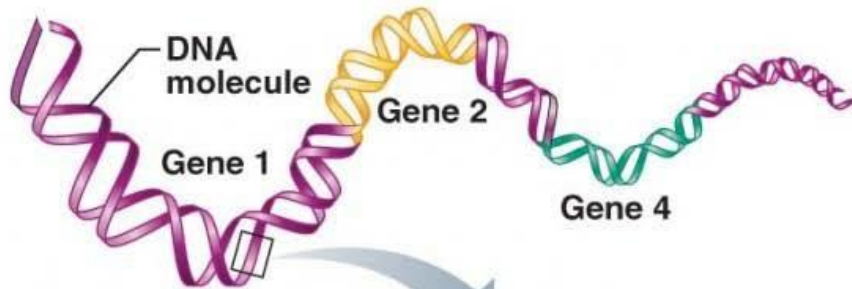


# RNA chain elongation by RNA polymerase.

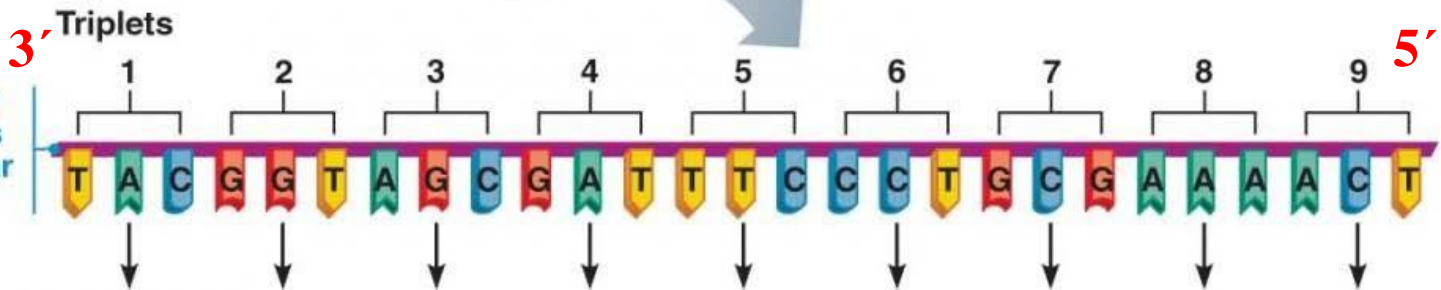


# A hypothetical strong (efficient) *E. coli* terminator.

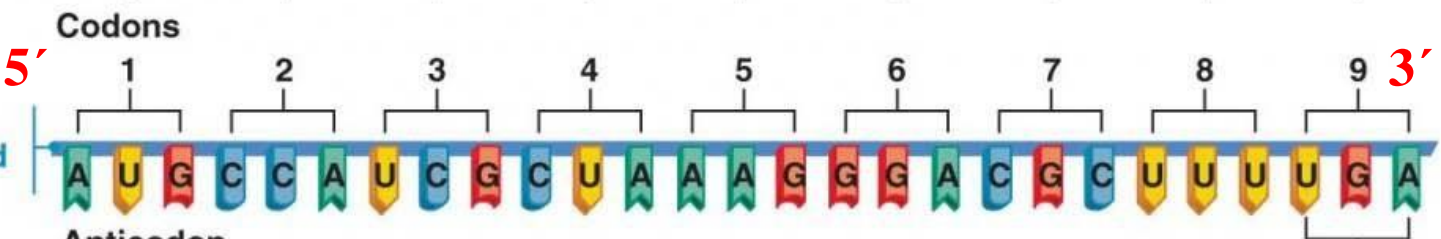




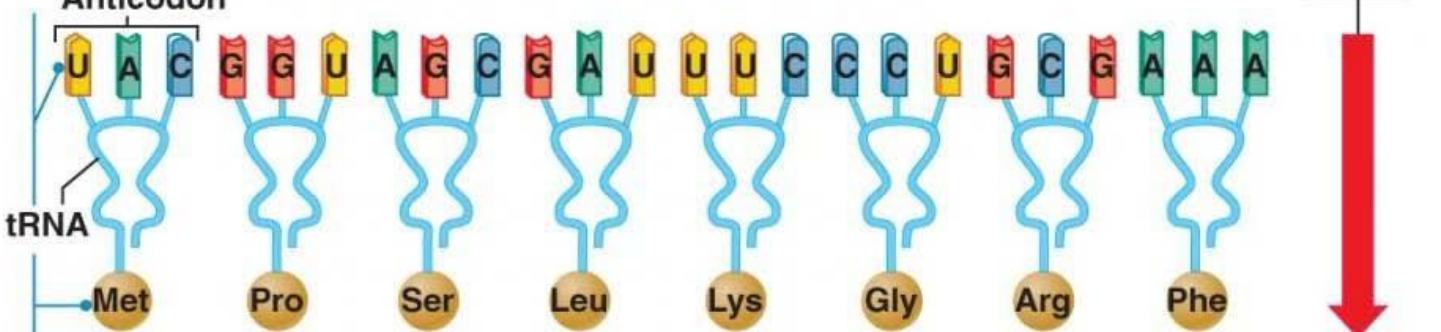
**DNA:** DNA base sequence (triplets) of the gene codes for synthesis of a particular polypeptide chain



**mRNA:** Base sequence (codons) of the transcribed mRNA



**tRNA:** Consecutive base sequences of tRNA anticodons recognize the mRNA codons calling for the amino acids they transport



**Polypeptide:** Amino acid sequence of the polypeptide chain



# Classes of eukaryotic cellular RNAs

- ribosomal RNA (rRNA)
  - 18S (small subunit)
  - 28S (large subunit)
  - 5.8S (large subunit)
  - 5S (large subunit)
- transfer RNA (tRNA)
- **messenger RNA (mRNA)**
- heterogeneous nuclear RNA (hnRNA) (precursors of mRNA)
- small nuclear RNA (snRNA)
  - U1, U2, U3, U4, U5, U6, U7, U8, U9, U10...
- small cytoplasmic RNA (scRNA)
  - 7SL RNA

What are the enzymes responsible for the synthesis of these RNAs?

# DNA dependent RNA polymerase

- Cells contain 3 DNA dependent RNA polymerases:
- **RNA pol I**: transcribes pre-rRNA; no known viral templates
- **RNA pol II**: transcribes pre-mRNA & snRNA; polymerase for most viral DNAs.
- **RNA pol III**: transcribes pre-tRNAs, 5S rRNA, U6 snRNA; polymerase for some viral DNAs.



- The transcriptional machinery must:
  - Be directed to **initiate** transcription at the correct location on a DNA template (the *transcriptional start site*).
  - **elongate** through the entire gene
  - Be directed to **terminate** transcription at the correct location.
- All of these functions require the assistance of
  - **Cis-acting sequences** along the DNA
  - **Trans-acting factors** (accessory proteins)

# The human RNA polymerases

<u>Polymerase</u>	<u>Location</u>	<u>Product</u>
RNA polymerase I	nucleolus	18S, 28S, 5.8S rRNA
<b>RNA polymerase II</b>	<b>nucleoplasm</b>	<b>hnRNA/mRNA, U1, U2, U4, U5 snRNA</b>
RNA polymerase III	nucleoplasm	tRNA, 5S RNA, U6 snRNA, 7SL RNA
mitochondrial RNA polymerase	mitochondrion	all mitochondrial RNA

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## Sensitivity of the nuclear RNA polymerases to $\alpha$ -amanitin<sup>1</sup>

RNA pol I	resistant
RNA pol II	high sensitivity (binds with $K = 10^{-8}$ M)
RNA pol III	low sensitivity (binds with $K = 10^{-6}$ M)

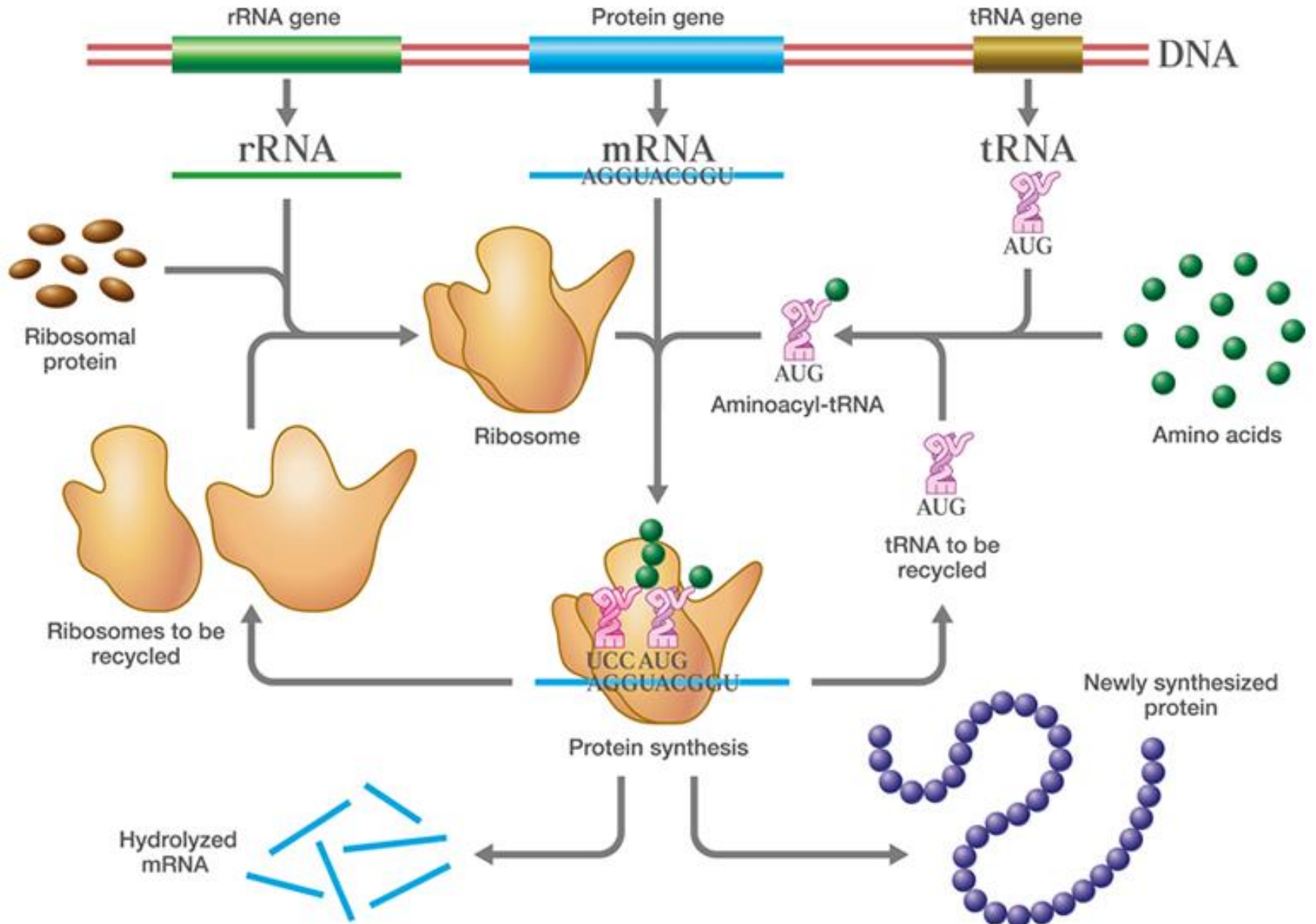
<sup>1</sup> cyclic octapeptide from the poisonous mushroom *Amanita phalloides*



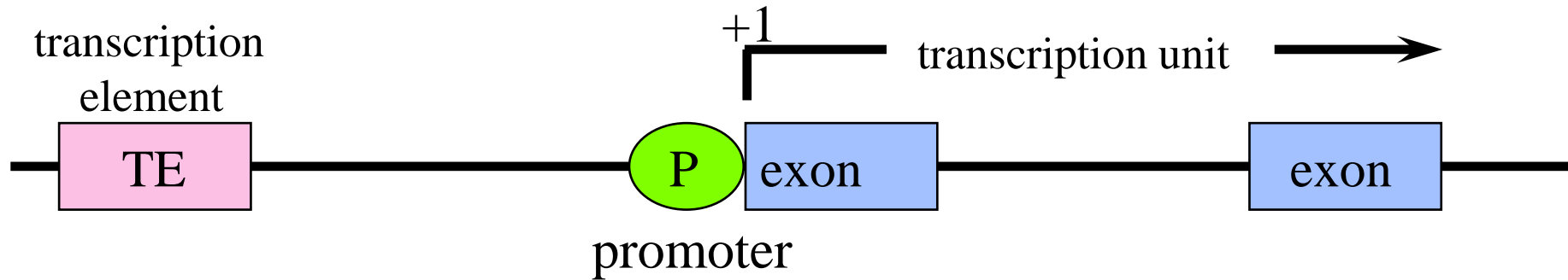
# RNA pol I

# RNA pol II

# RNA pol III



# Transcription and promoter elements for RNA polymerase II



Promoter (DNA sequence upstream of a gene)

- determines start site (+1) for transcription initiation
- located immediately upstream of the start site
- allows basal (low level) transcription

Transcription element (DNA sequence that regulates the gene)

- determines frequency or efficiency of transcription
- located upstream, downstream, or within genes
- can be very close to or thousands of base pairs from a gene
- includes
  - enhancers (increase transcription rate)
  - silencers (decrease transcription rate)
  - response elements (target sequences for signaling molecules)
- genes can have numerous transcription elements

# Transcription by RNA Pol. II.

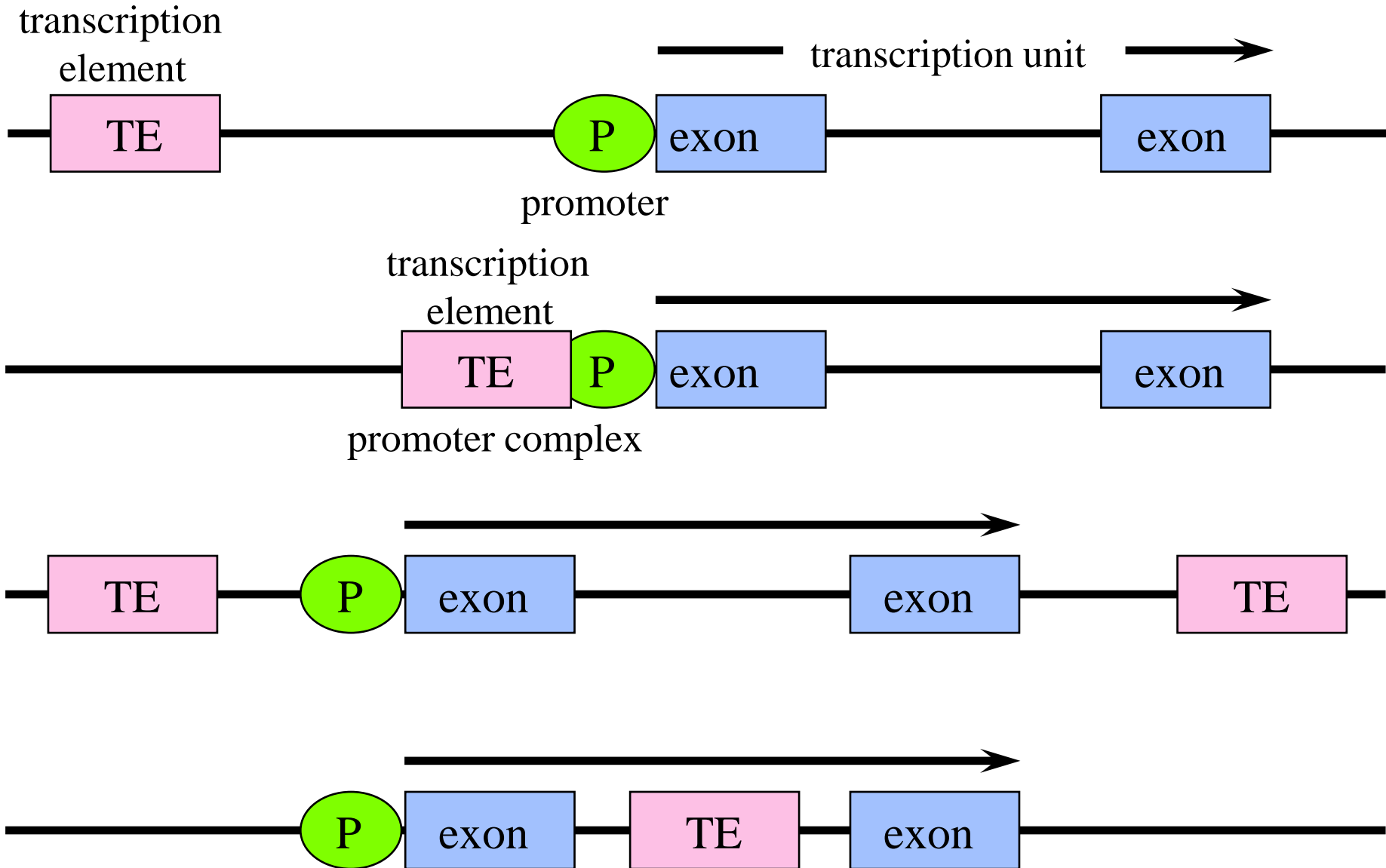
- At least 40 proteins required: Pol. II itself + accessory proteins.
- Accurate transcription initiated at the *promoter*.
- Promoter + additional DNA sequence that controls transcription = *Transcriptional control region (TCR)*.
  - The adenovirus type 2 major late promoter was the first TCR ever recapitulated *in vitro*.
- Initiation is a multistep process:
  - Promoter *recognition* by RNA Pol. II
  - Formation of open initiation complex (*unwinding*)
  - Promoter *clearance*
  - 3' *movement* of complex away from promoter

# Regulation of Pol. II transcription

Transcription must be regulated: genes must be turned on and off in temporal patterns

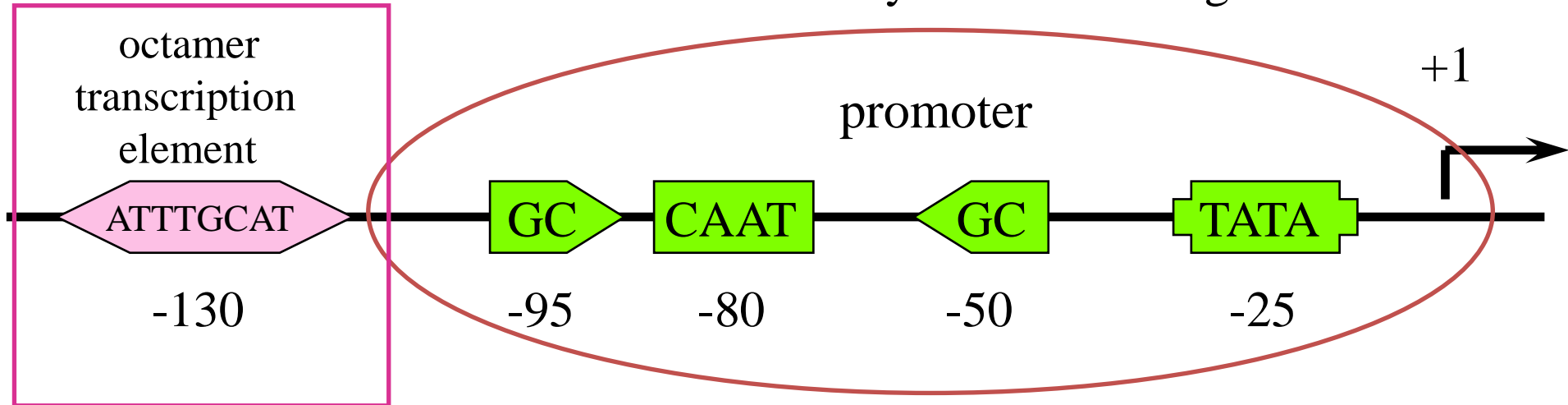
- Viral gene expression: early and late genes
- Transcriptional regulation is controlled by:
  - *Cis*-acting sequences in DNA - both local and distal
  - *Trans*-acting factors - both protein and RNA
- *Trans*-acting factors specifically bind to *cis*-acting sequences to either
  - *activators* stimulate transcription
  - *repressors* prevent transcription

# Transcription and promoter elements for RNA polymerase II



# Sequence elements within a typical eukaryotic gene<sup>1</sup>

<sup>1</sup> based on the thymidine kinase gene



## TATA box (TATAAAA)

- located approximately 25-30 bp upstream of the +1 start site
- determines the exact start site (not in all promoters)
- binds the TATA binding protein (TBP) which is a subunit of TFIID

## GC box (CCGCCC)

- binds Sp1 (Specificity factor 1)

## CAAT box (GGCCAATCT)

- binds CTF (CAAT box transcription factor)

## Octamer (ATTGTCAT)

- binds OTF (Octamer transcription factor)

# Proteins regulating eukaryotic mRNA synthesis

## General transcription factors

- TFIID (a multisubunit protein) binds to the TATA box to begin the assembly of the transcription apparatus
  - the TATA binding protein (TBP) directly binds the TATA box
  - TBP associated factors (TAFs) bind to TBP
- TFIIA, TFIIB, TFIIE, TFIIIF, TFIIH<sup>1</sup>, TFIIF assemble with TFIID

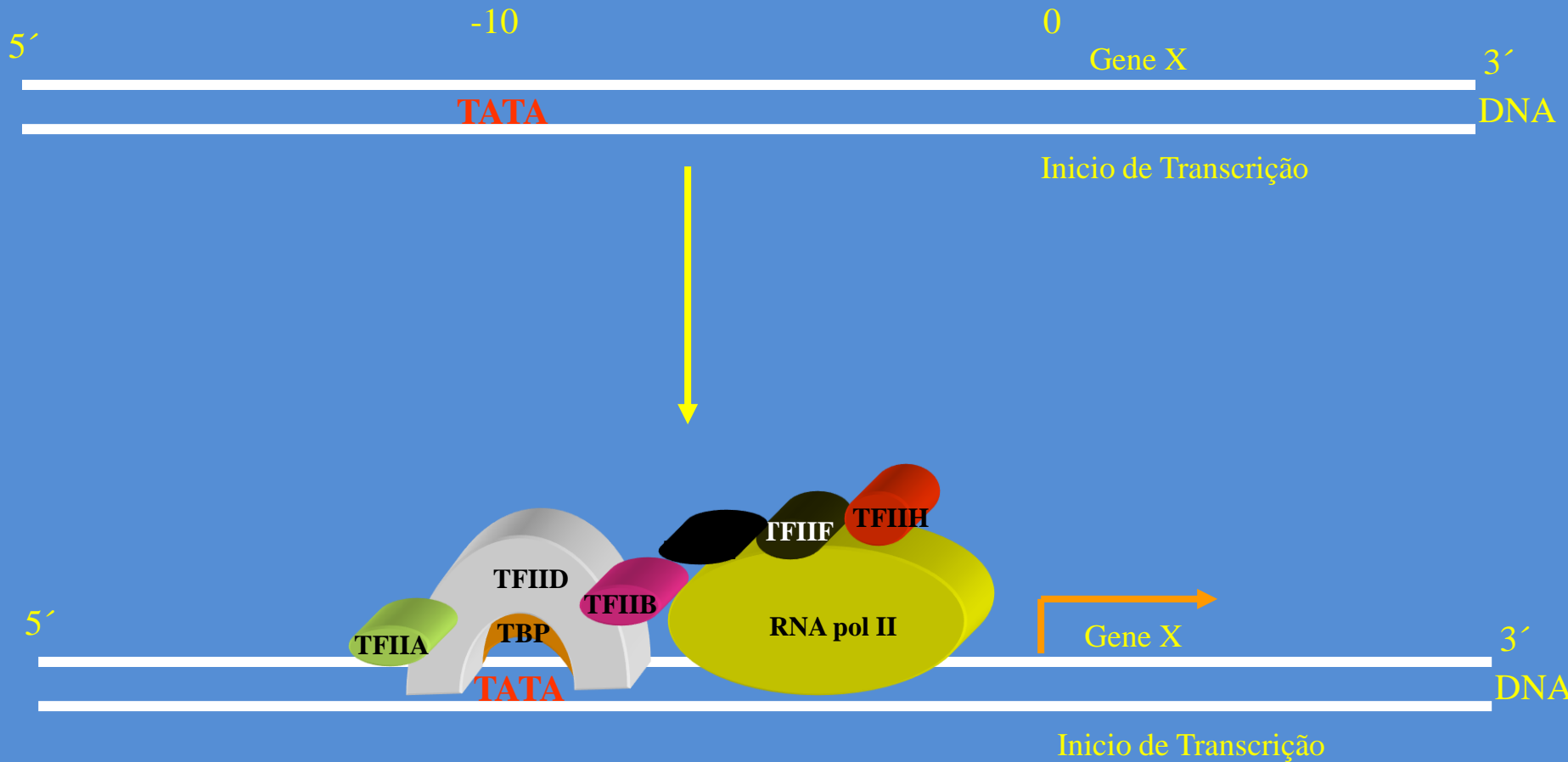
RNA polymerase II binds the promoter region via the TFII's

Transcription factors binding to other **promoter elements** and **transcription elements** interact with proteins at the promoter and further stabilize (or inhibit) formation of a functional preinitiation complex

<sup>1</sup>TFIIH is also involved in phosphorylation of RNA polymerase II.

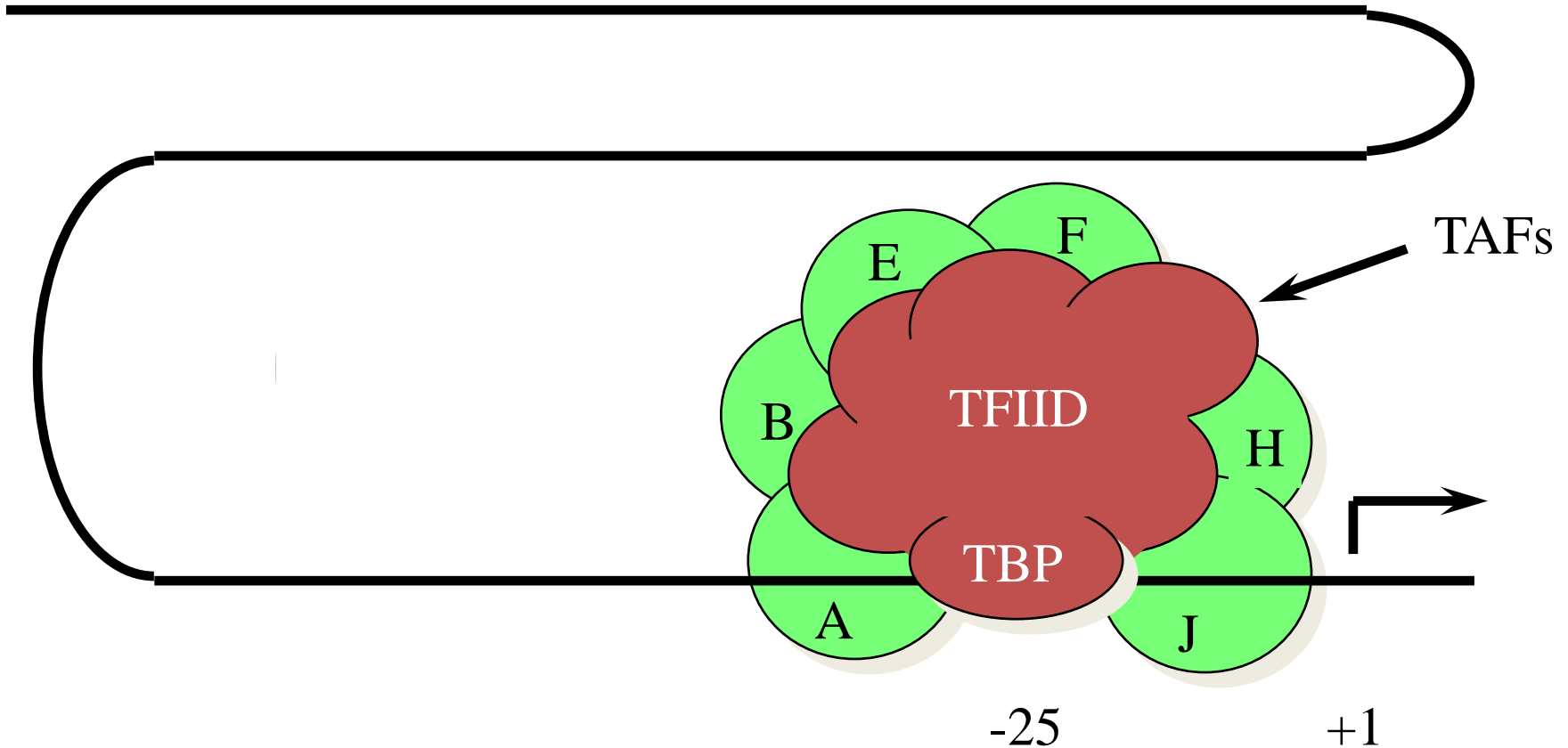
# TRANSCRIÇÃO

## Formação do complexo funcional de preiniciação



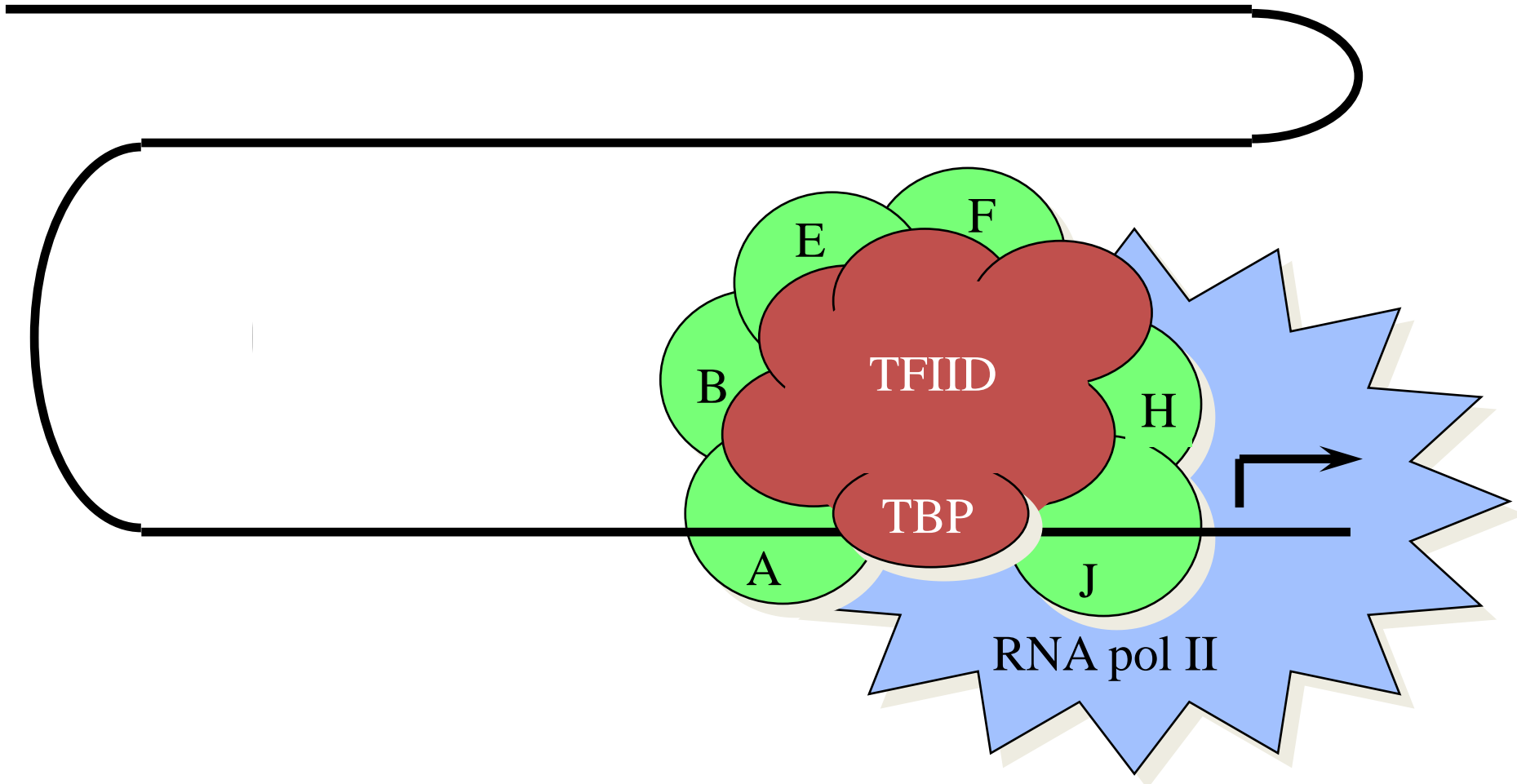


## Binding of the general transcription factors



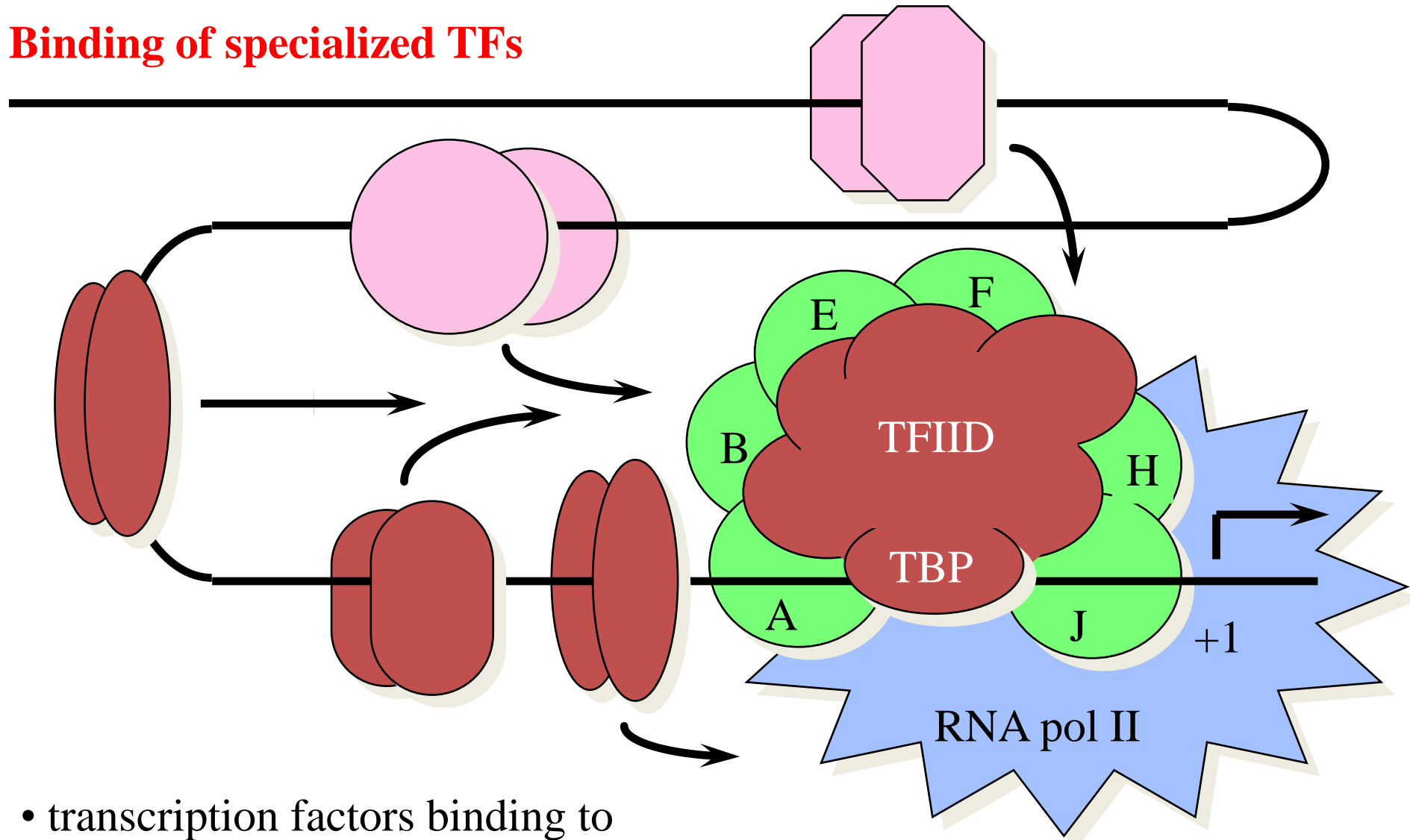
- TFIID (a multisubunit protein) binds to the TATA box to begin the assembly of the transcription apparatus
  - the TATA binding protein (TBP) directly binds the TATA box
  - TBP associated factors (TAFs) bind to TBP
- TFIIA, TFIIB, TFIIIE, TFIIF, TFIIH, TFIIJ assemble with TFIID

## Binding of RNA polymerase II



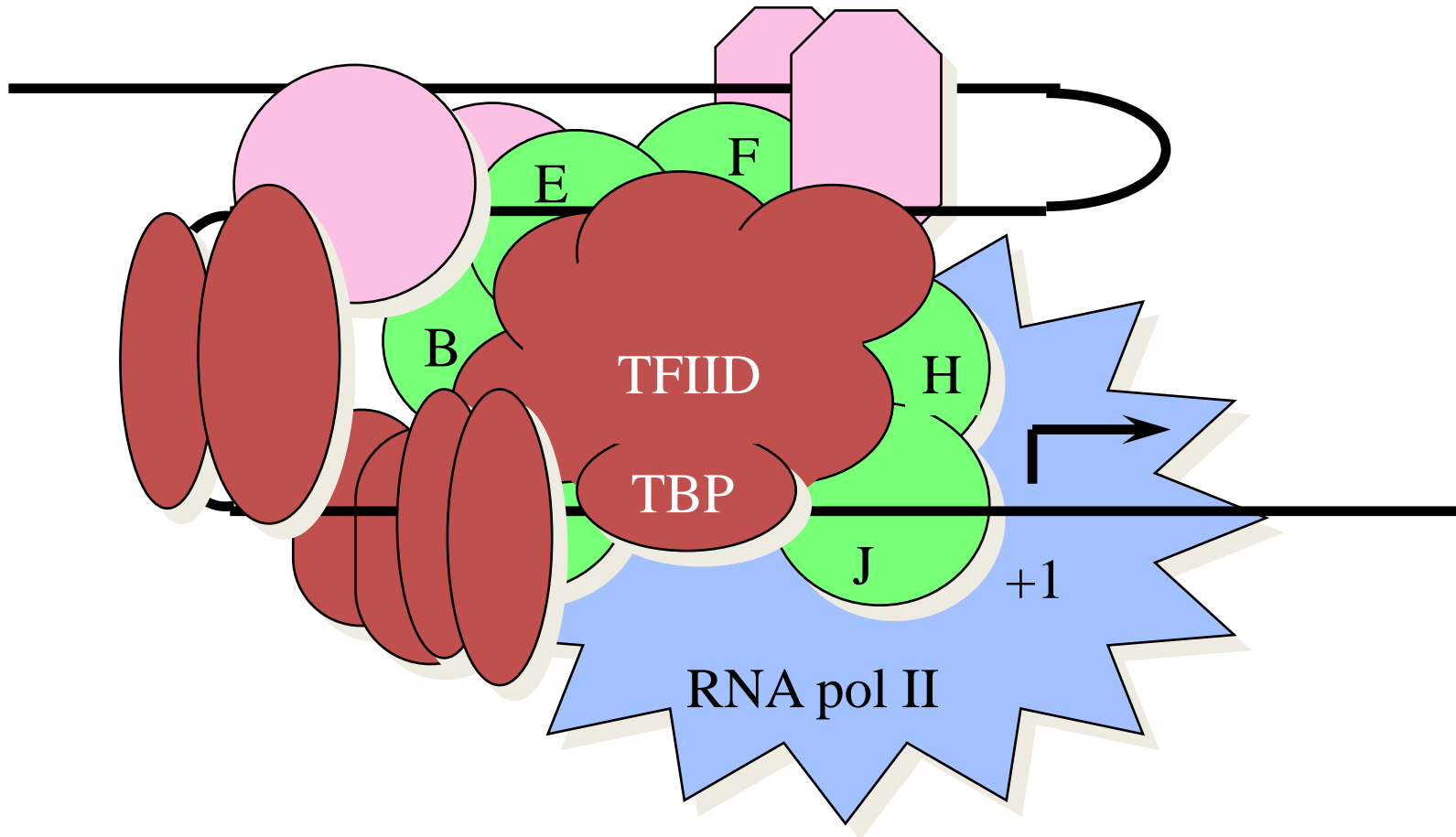
- RNA polymerase II (a multisubunit protein) binds to the promoter region by interacting with the TFII's
- TFs recruit histone acetylase to the promoter

## Binding of specialized TFs



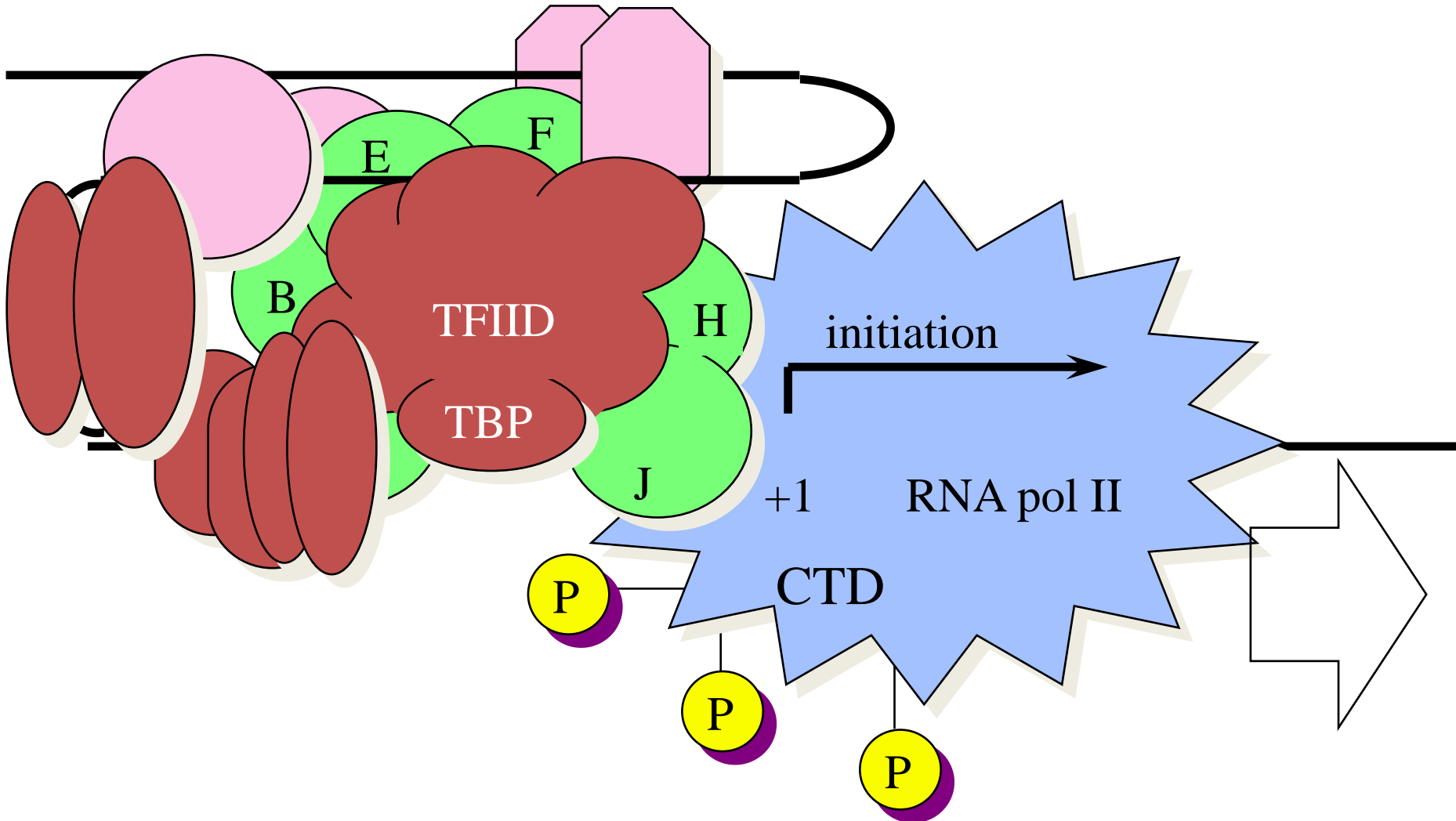
- transcription factors binding to other **promoter elements** and **transcription elements** interact with proteins at the promoter and further stabilize (or inhibit) formation of a functional preinitiation complex
- this process is called **“transactivation”**

## Formation of a stable preinitiation complex



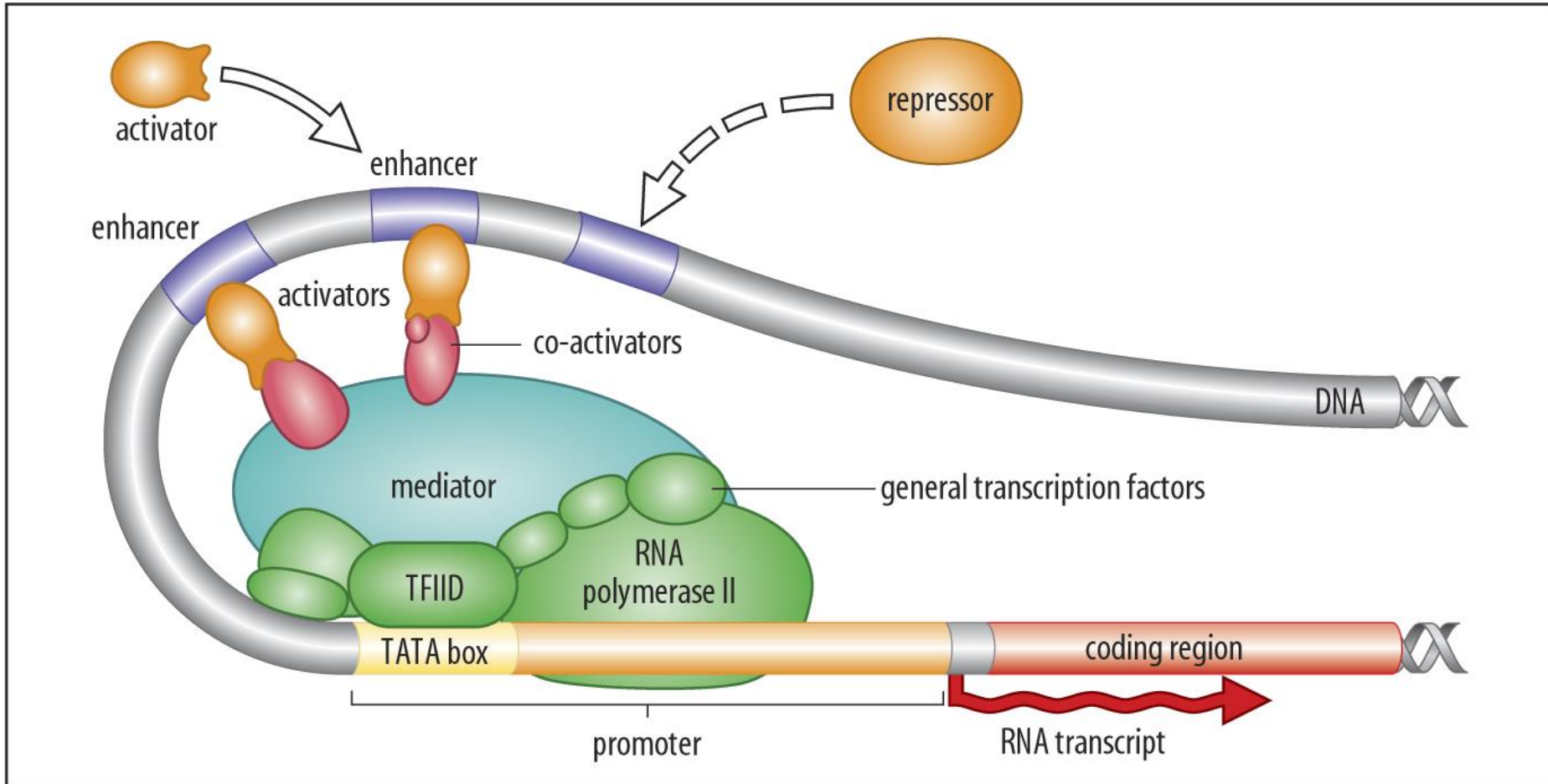
- the stability and frequency with which complexes are formed determines the rate of initiation of transcription
- the rate of initiation of transcription is of major importance in determining the abundance of an mRNA species

## Initiation of transcription and promoter clearance



- RNA pol II is **phosphorylated** by TFIIH on the carboxy terminal domain (CTD), releasing it from the preinitiation complex and allowing it to initiate RNA synthesis and move down the gene

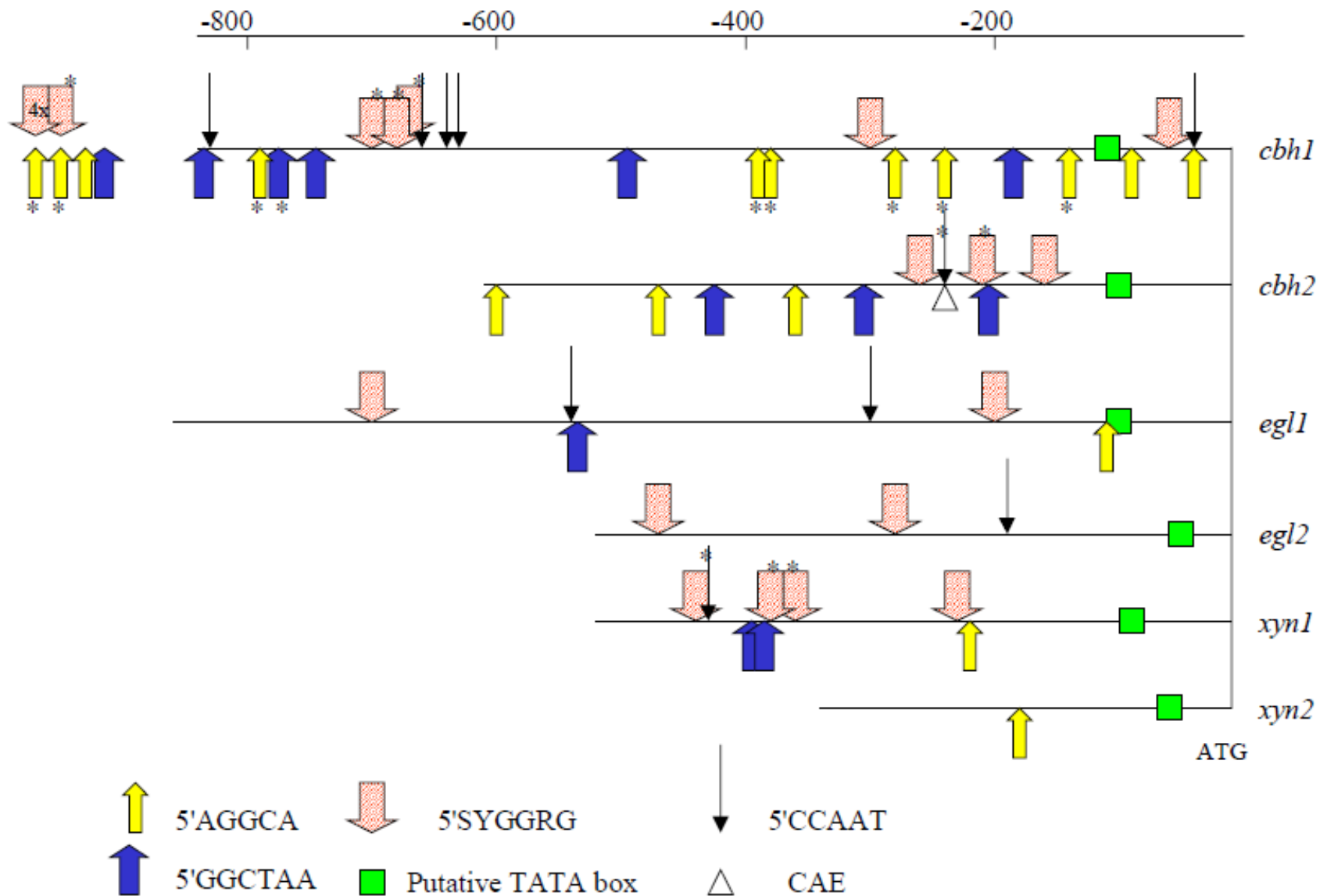
# RNA polymerase and associated proteins to start transcription.



## Transcription factors (partial list)

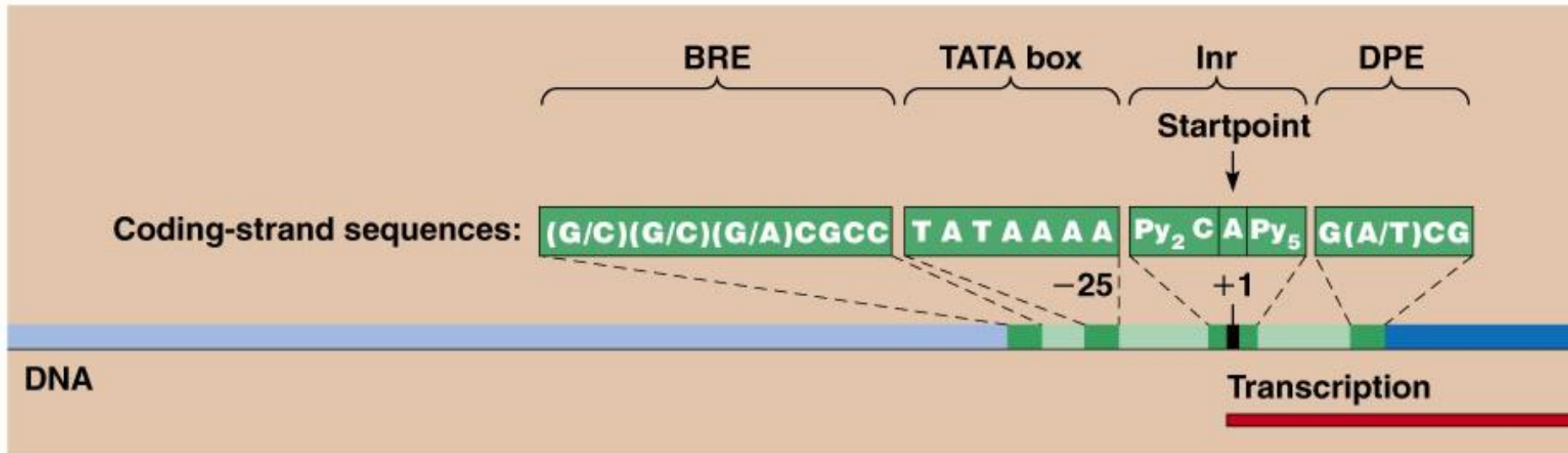
Factor	Full name or function
CREB	Cyclic AMP response element binding protein
CTF	CAAT box transcription factor (=NF1) (binds <u>GGCCAATCT</u> )
NF1	Nuclear factor-1 (=CTF)
<b>AP1</b>	<b>Activator protein-1 (dimer of the Fos-Jun proteins)</b>
Sp1	Specificity factor-1 (binds <u>CCGCC</u> )
OTF	Octamer transcription factor (binds <u>ATTTGCAT</u> )
NF- $\kappa$ B	Nuclear factor $\kappa$ B
HSTF	Heat shock transcription factor
MTF	Metal transcription factor
USF	Upstream factor
ATF	Activating transcription factor
HNF4	Hepatocyte nuclear factor-4 (nuclear receptor superfamily)
GR	Glucocorticoid receptor (nuclear receptor superfamily)
AR	Androgen receptor (nuclear receptor superfamily)
<b>ER</b>	<b>Estrogen receptor (nuclear receptor superfamily)</b>
TR	Thyroid hormone receptor (nuclear receptor superfamily)
C/EBP	CAAT/enhancer binding protein
E2F	E2 factor (named for the adenovirus E2 gene)
p53	p53 (tumor suppressor protein)
Myc	Product of the c-myc protooncogene (dimerizes with Max)

# Putativos Sítios de ligação de fatores de Transcrição e TATA Box em promotores de genes de celulasas e xilanases de *Trichoderma reesei*



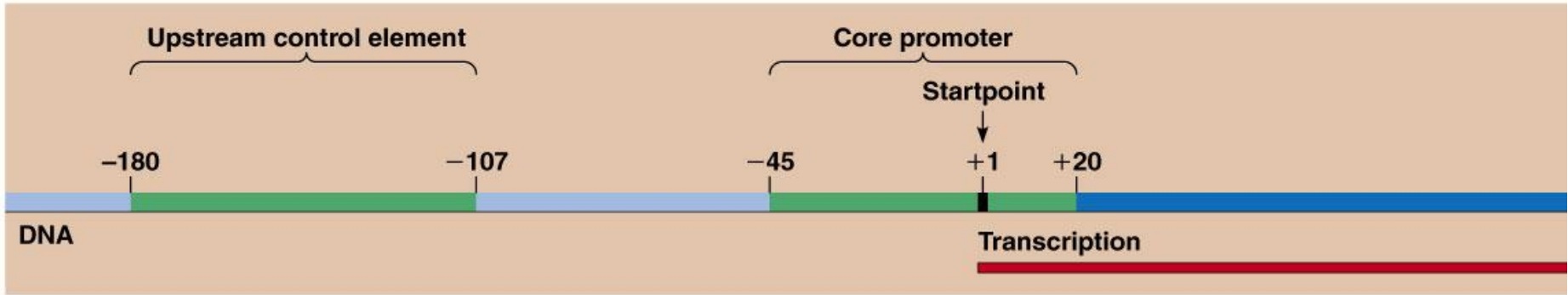


# Promotor para RNA pol II



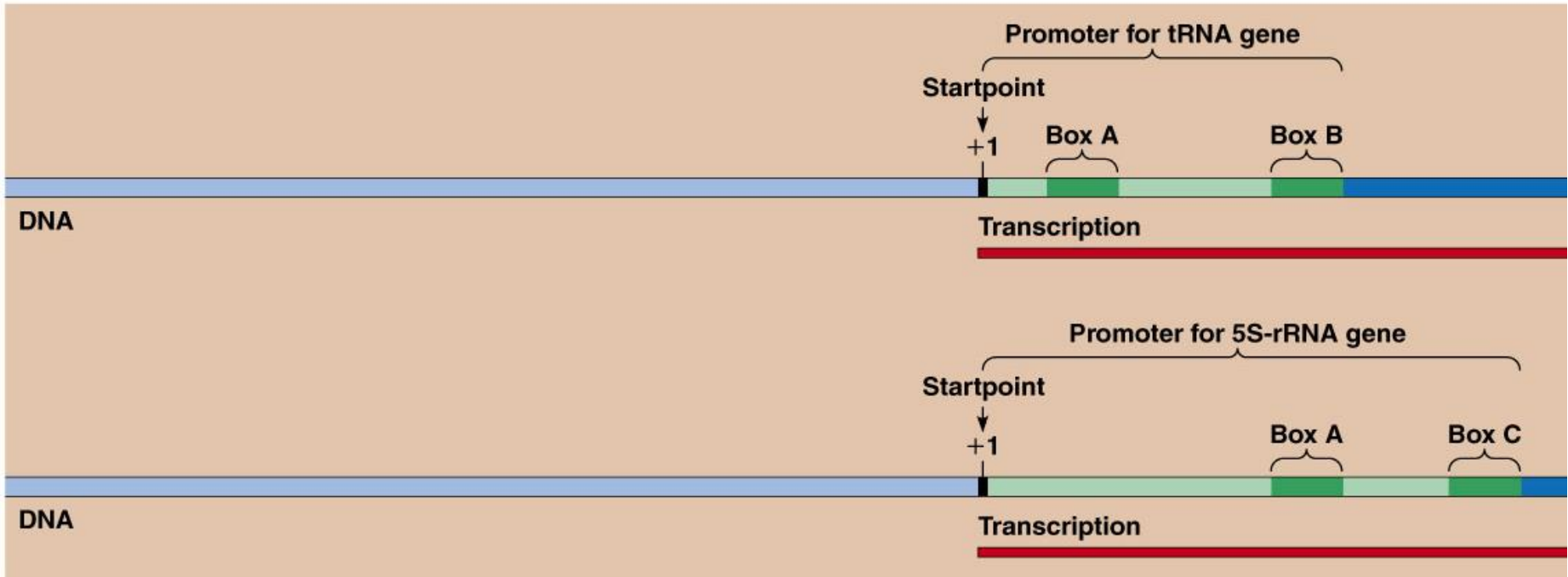
**(b)** Core promoter elements for RNA polymerase II

# Promotor para RNA pol I



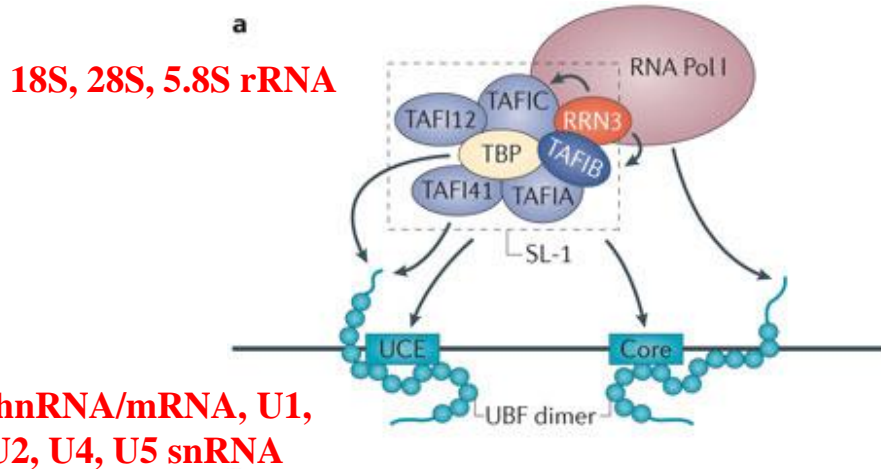
(a) Promoter for RNA polymerase I

# Promotor para RNA pol III

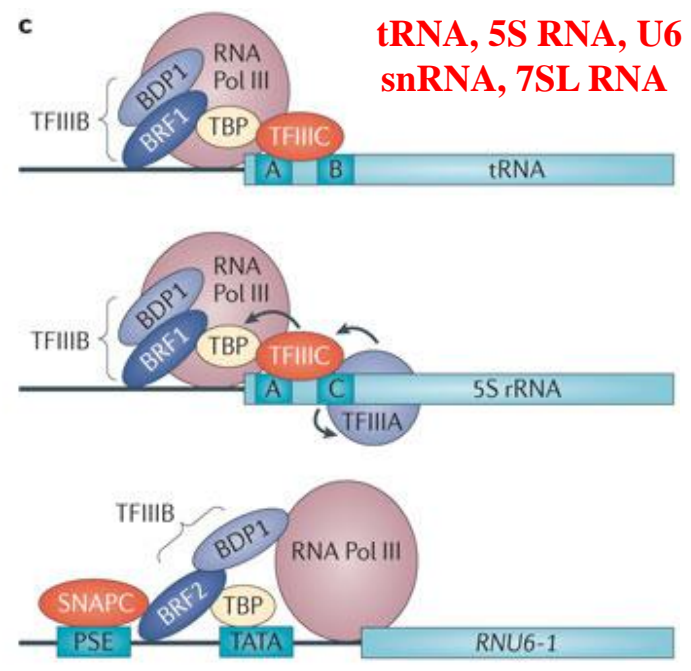
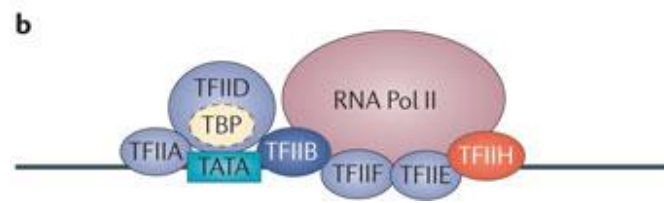


(c) Two types of promoters for RNA polymerase III

# Assembly of the pre-initiation complex (PIC)

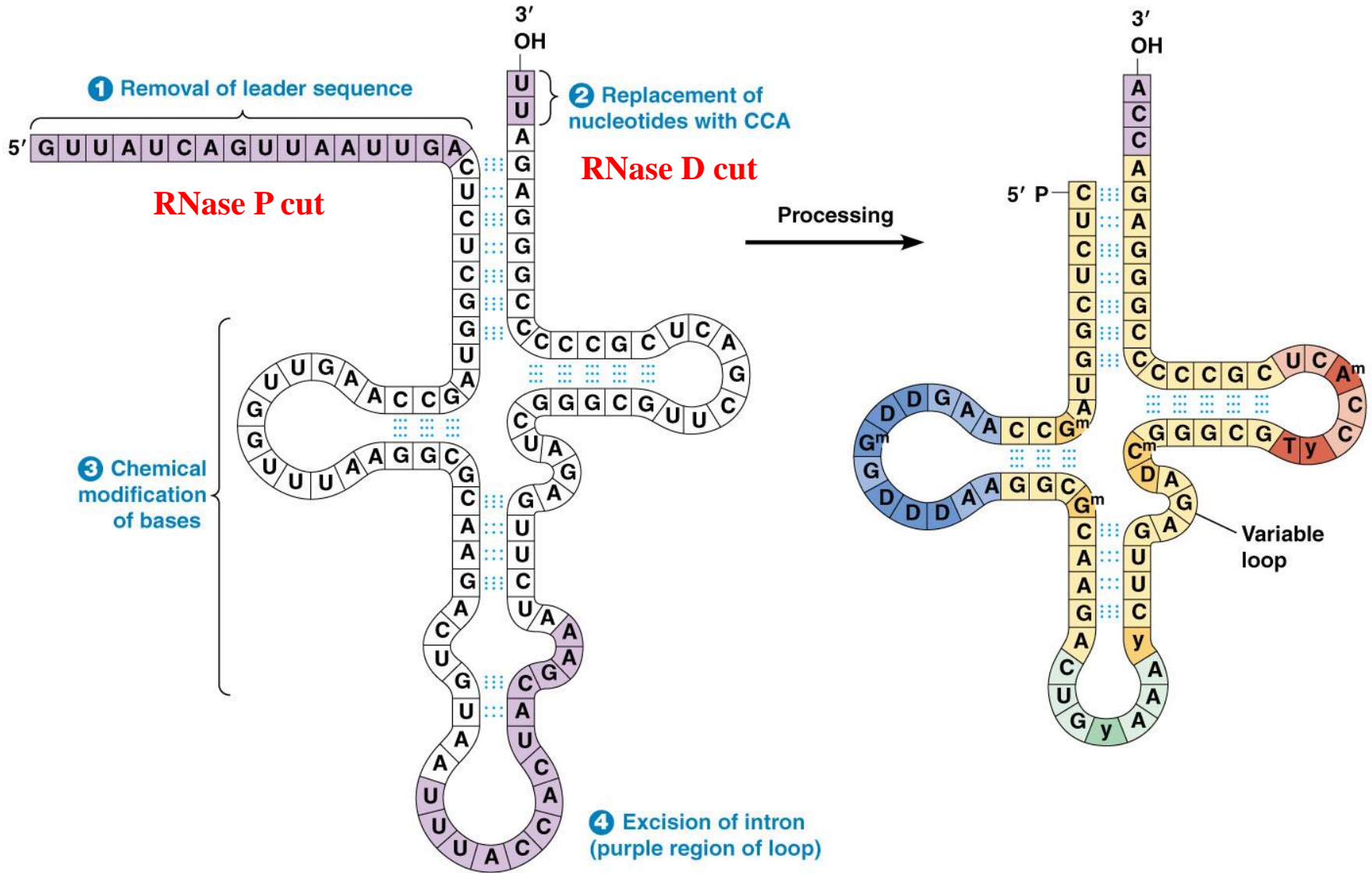


**hnRNA/mRNA, U1, U2, U4, U5 snRNA**



- binding of upstream binding factor (UBF) to the upstream control elements (UCEs) and core element of the rDNA promoter, leading to the recruitment of the SL-1 initiation factor, which contains TATA-box-binding protein (TBP) and at least five TATA-box-associated factors (TAFs). The resultant stable UBF–SL-1 complex recruits an initiation-competent form of RNA Pol I, which contains RRN3 that mediates interactions between RNA Pol I and SL-1
- RNA Pol III-transcribed genes (for example, those that encode tRNAs) have internal promoters that comprise two sequence blocks (A and B) that are located in the transcribed region. The A and B blocks are recognized by TFIIC that recruits TFIIB, which is composed of the subunits B-related factor 1 (BRF1), BDP1 and TBP. Finally, TFIIB recruits RNA Pol III.
- For 5S rDNA promoters the B block is replaced by a sequence, termed block C, to which TFIIA binds and recruits and orientates TFIIB, following which transcription initiation proceeds as for tRNA genes.
- For a small number of RNA Pol III-transcribed genes (for example, U6 snRNA (RNU6-1)) the promoters are located upstream of the gene and contain TATA boxes bound by TBP, and proximal sequence elements (PSEs) bound by a complex called small nuclear RNA-activating protein complex (SNAPC). These upstream promoters are bound by a different form of TFIIB from tRNA genes, which is composed of BRF2, BDP1 and TBP9

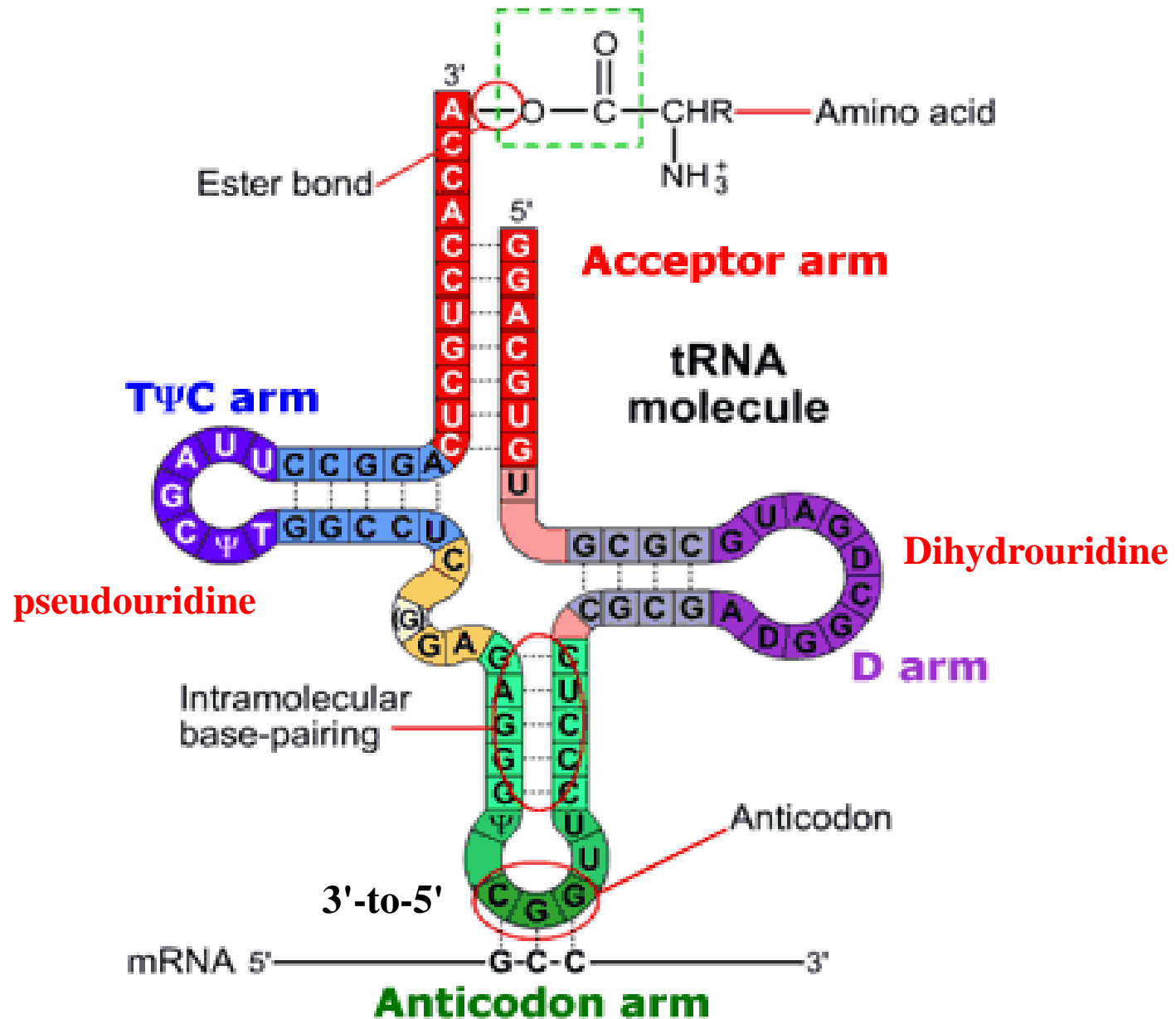
# tRNA- This RNA type is a small chain of about 80 nucleotides.



(a) Primary transcript (precursor) for yeast tyrosine tRNA

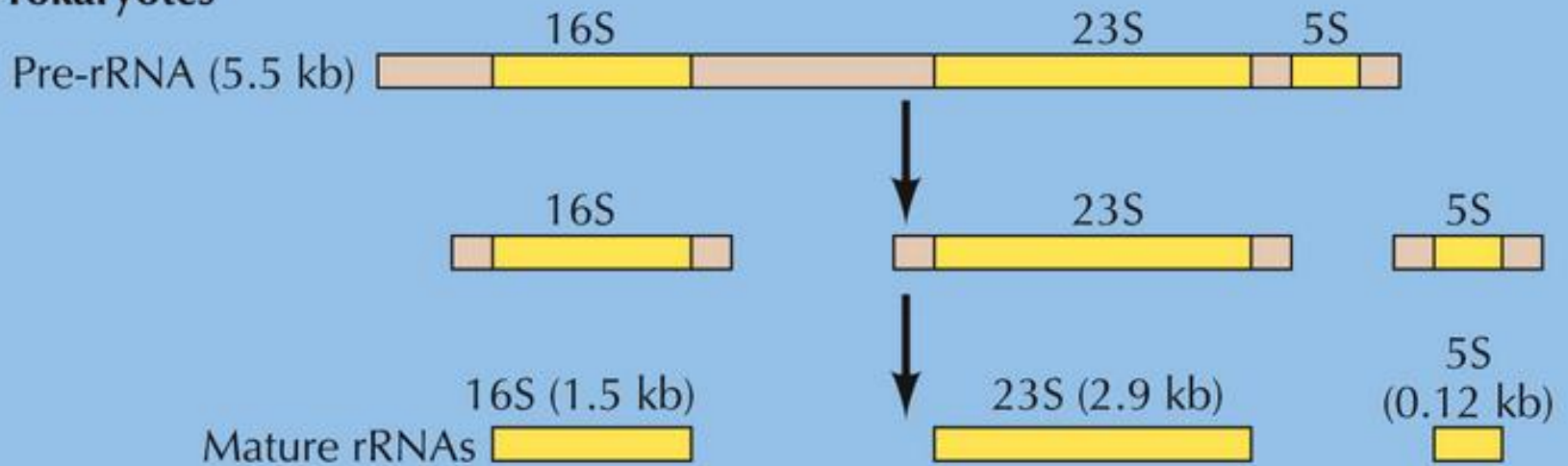
(b) Mature tRNA, secondary structure

The tRNA has a clover leaf model with arms each with a specific function. The tRNA also has an anticodon region that can base pair with the codon region on the mRNA.

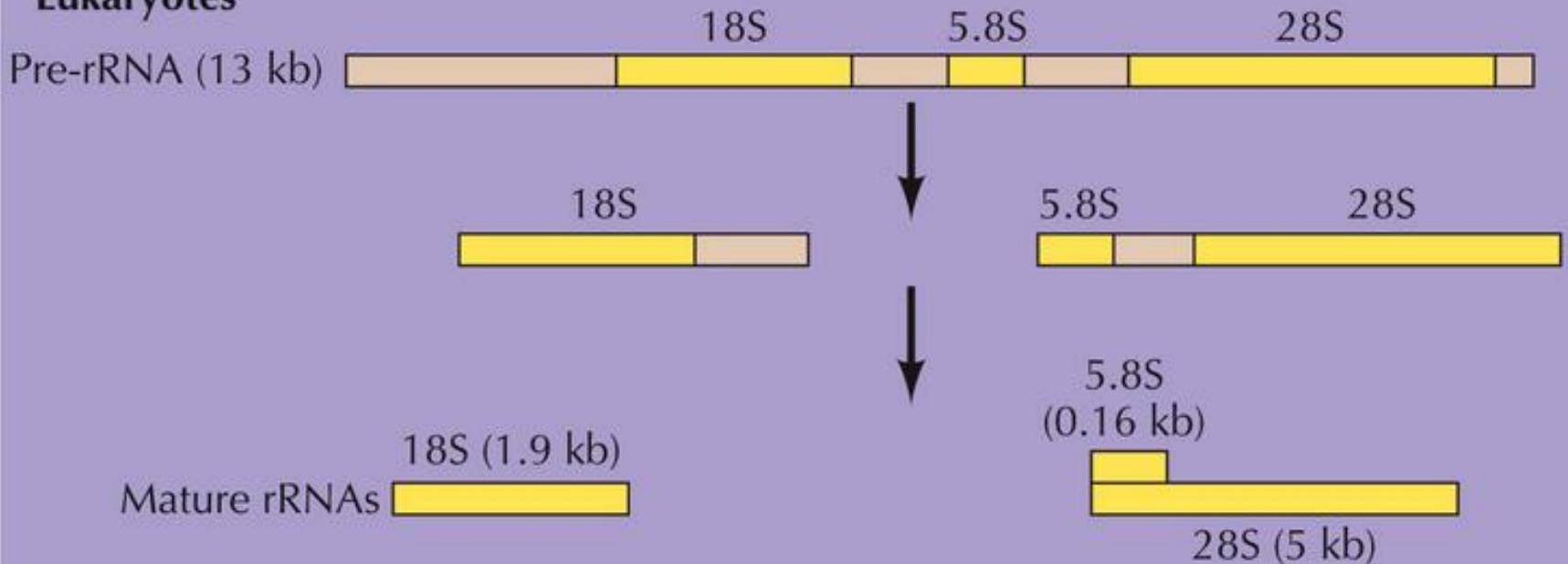


# Pre-Processamento de rRNA

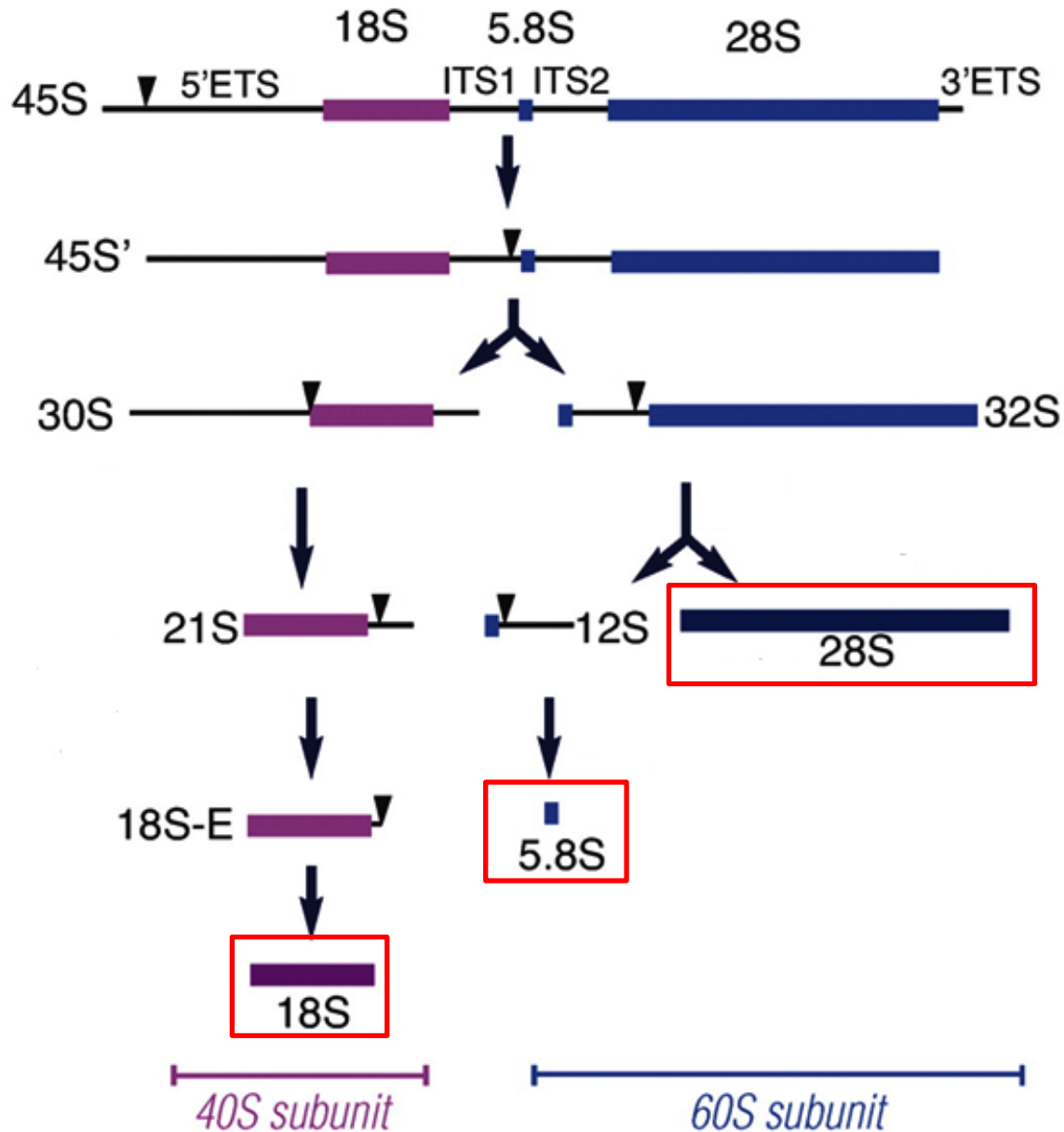
## Prokaryotes



## Eukaryotes

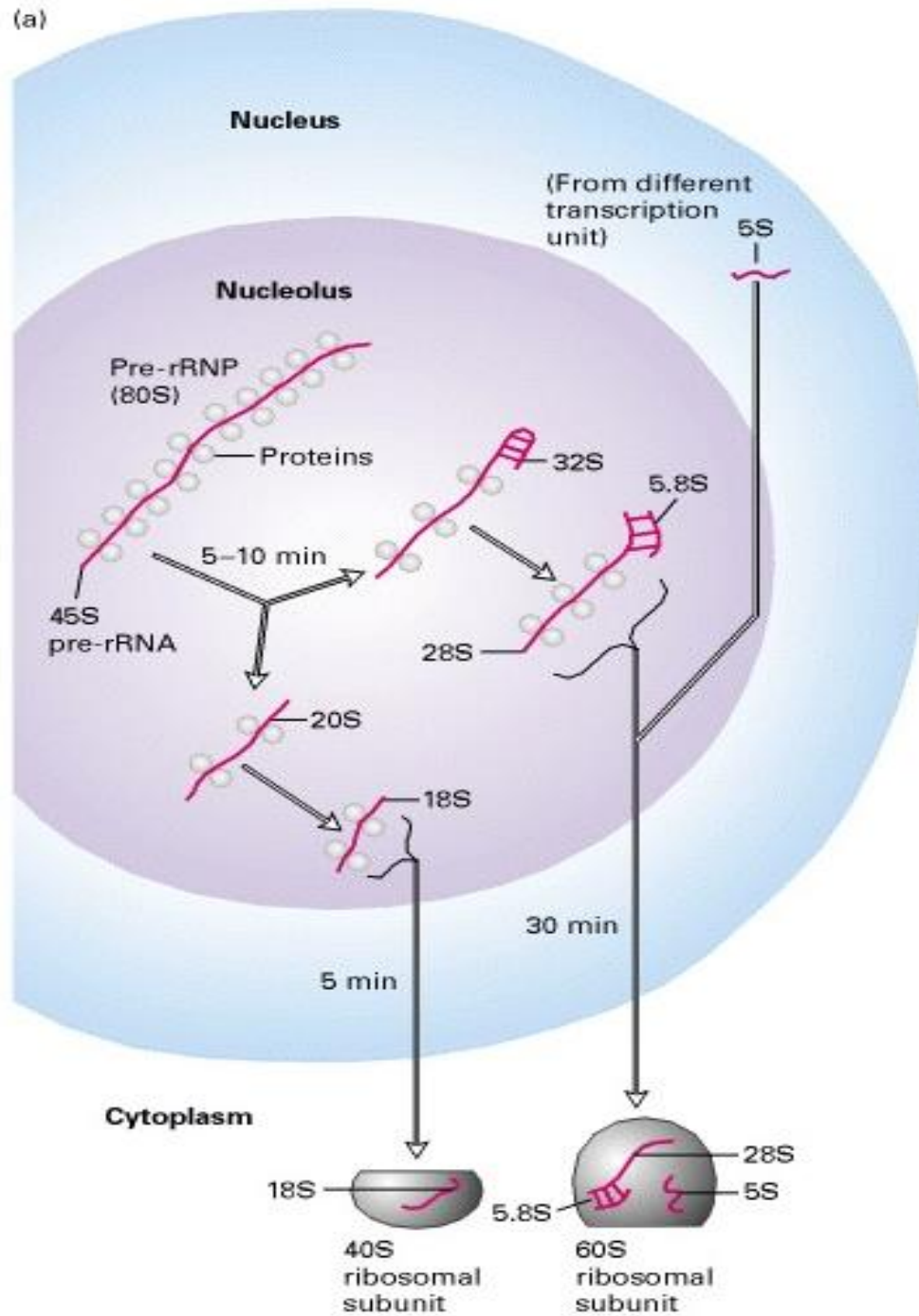


# Pre-Processamento de rRNA em células humanas



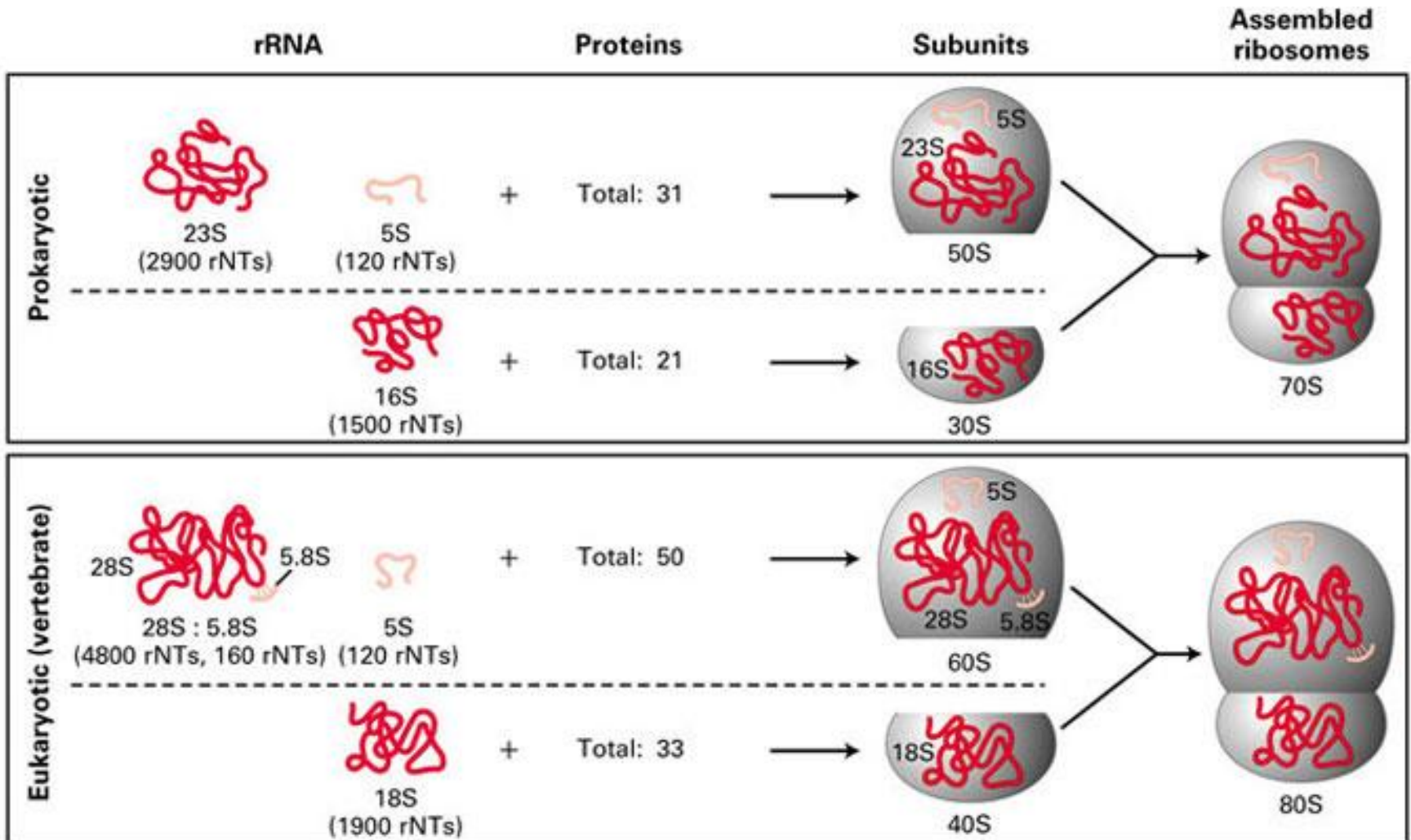


(a)





**rRNA-** The rRNA is synthesized in the nucleolus. In the cytoplasm, ribosomal RNA and protein combine together to form a nucleoprotein called a ribosomes. The ribosomal RNAs form two subunits namely; the large subunit and small subunit. The Eukaryotic cells have 4 different types of rRNA namely; 28S rRNA, 18S rRNA, 5.8S rRNA and 5S rRNA.



Svedberg value = sedimentation coefficient, a measure of time ( $10^{-13}$  sec)

# mRNA Structure

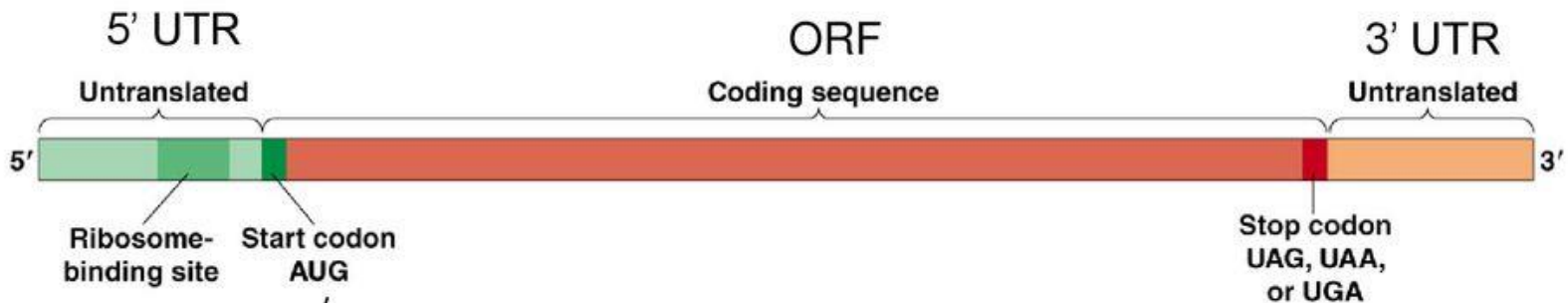
## Bacterial mRNA only

- Ribosome-binding sites; **also called Shine-Dalgarno sequence**

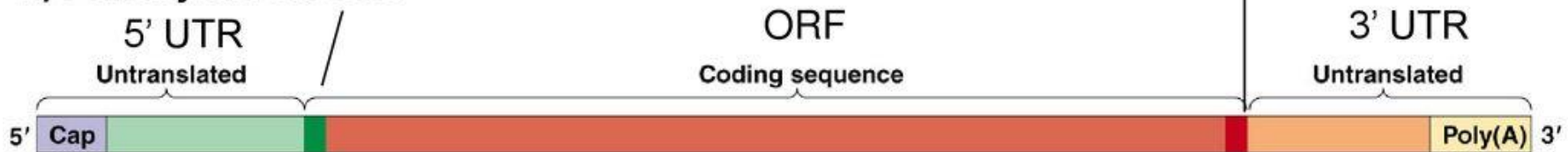
## Eukaryotic mRNA only

- 5' Cap (methylated guanine)
- Poly A tail
- Kozak Sequence (sometimes present); enhances ribosome binding

### a) Bacterial mRNA

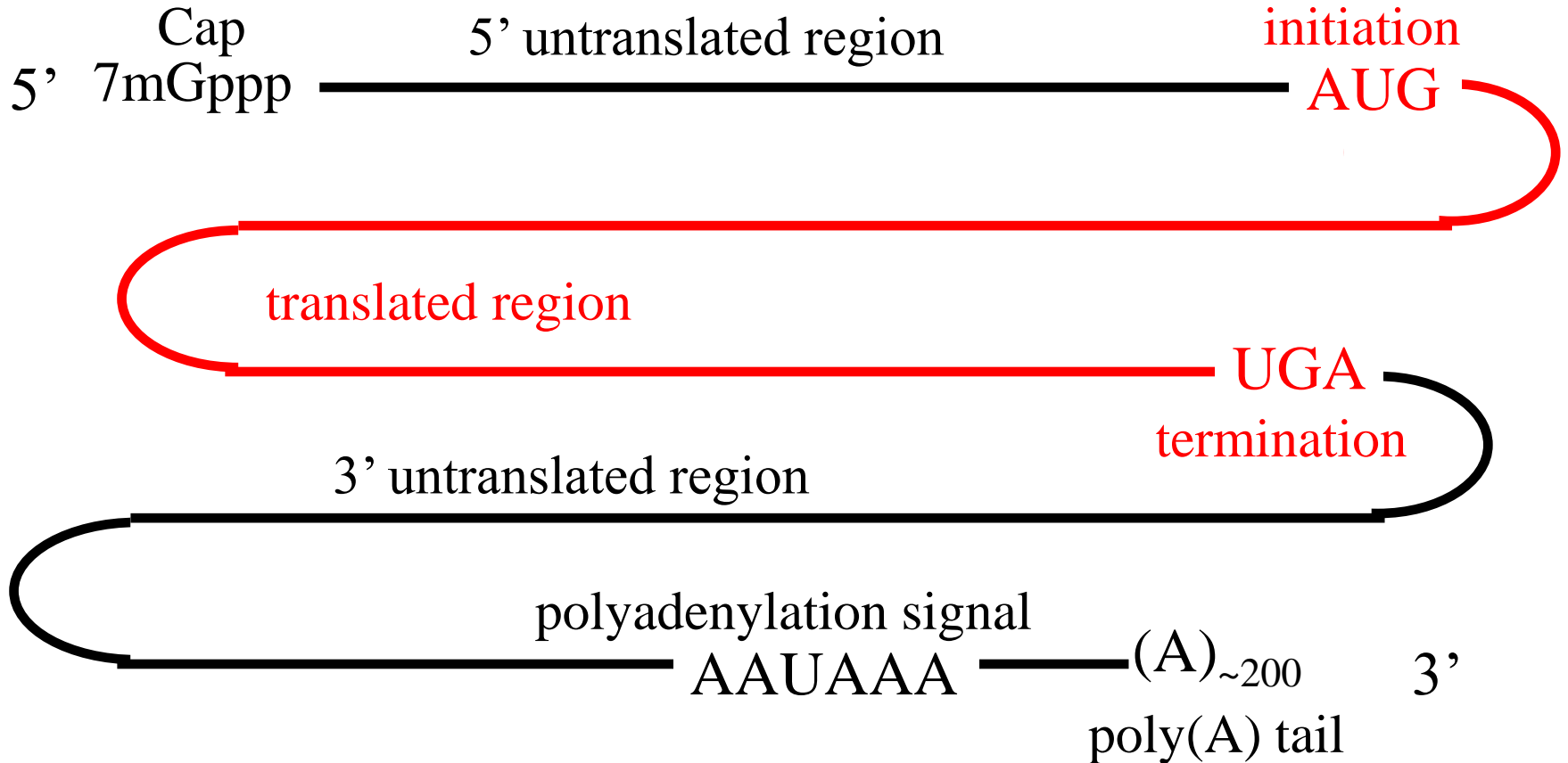


### b) Eukaryotic mRNA

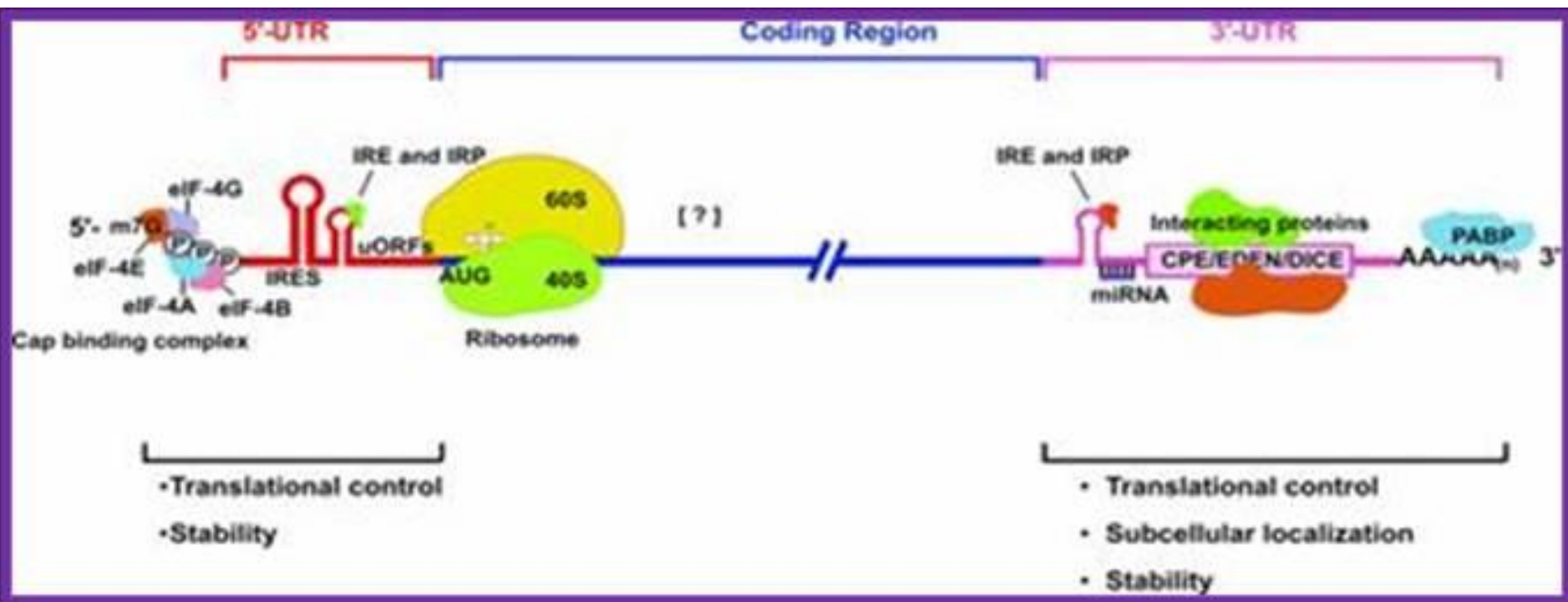


### (b) Eukaryotic mRNA

# RNA polII - Structure of eukaryotic mRNA



- all mRNAs have a 5' cap and all mRNAs (with the exception of the histone mRNAs) contain a poly(A) tail
- the 5' cap and 3' poly(A) tail prevent mRNA degradation
- loss of the cap and poly(A) tail results in mRNA degradation



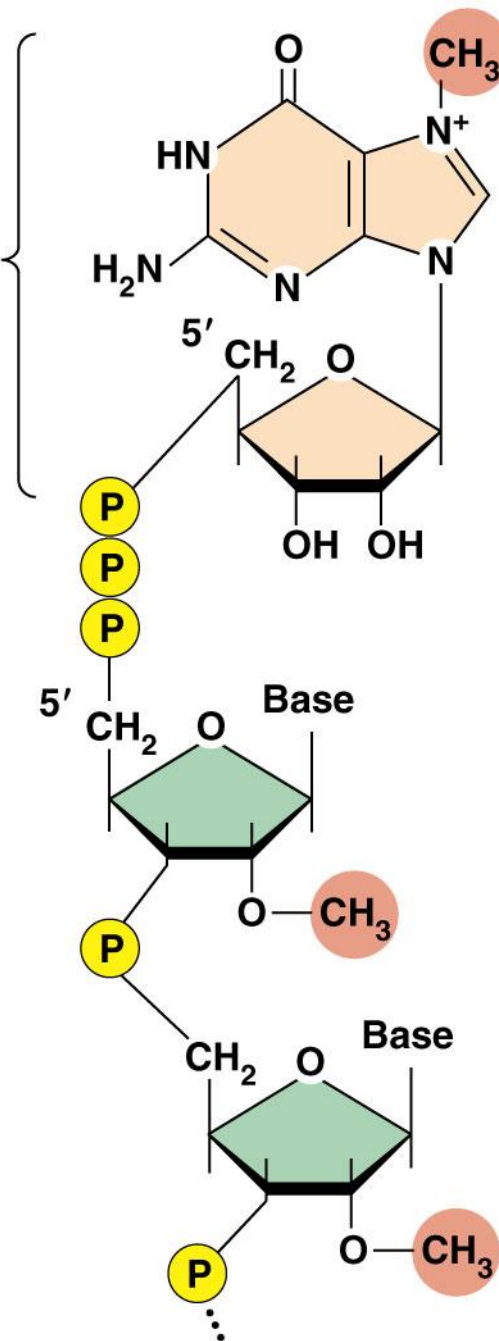
# Structure of the 5' cap

7mG = 7-methyl guanosine

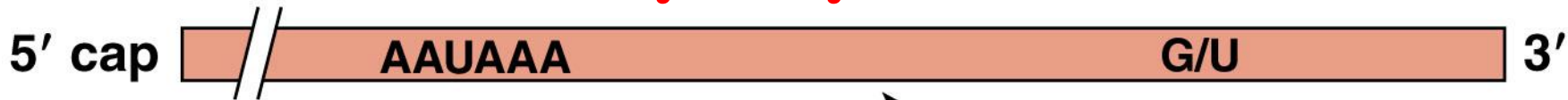
capping enzyme complex  
+ S-adenosyl-L-methionine (SAM)

7-methylguanosine

5' end of  
RNA chain



# Polyadenylation



Cleavage 10-35 nucleotides downstream from AAUAAA sequence

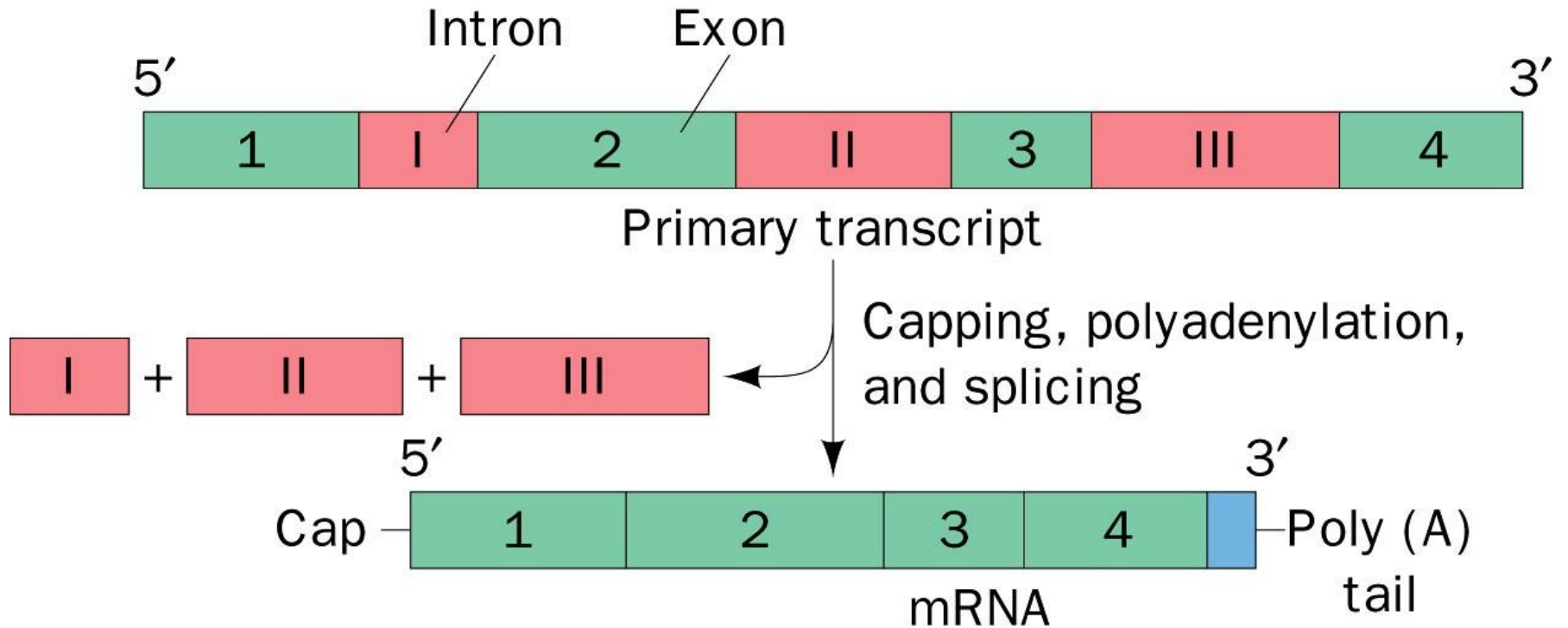


Poly(A) polymerase



Poly(A) tail

# Post-transcriptional processing of eukaryotic mRNAs.





# Types of Introns.

Intron Type	Where Found
GU–AG introns	Eukaryotic nuclear pre-mRNA
AU–AC introns	Eukaryotic nuclear pre-mRNA
Group I	Eukaryotic nuclear pre-mRNA, organelle RNAs, a few bacterial RNAs
Group II	Organelle RNAs, a few prokaryotic RNAs
Group III	Organelle RNAs
Twintrons (composites of two and/or more group II or III introns)	Organelle RNAs
Pre-tRNA introns	Eukaryotic nuclear pre-tRNAs
Archaeal introns	Various RNAs



**The consensus sequence at the exon–intron junctions of vertebrate pre-mRNAs.**

Splicing Consensus Sequences

5' Exon  
↓

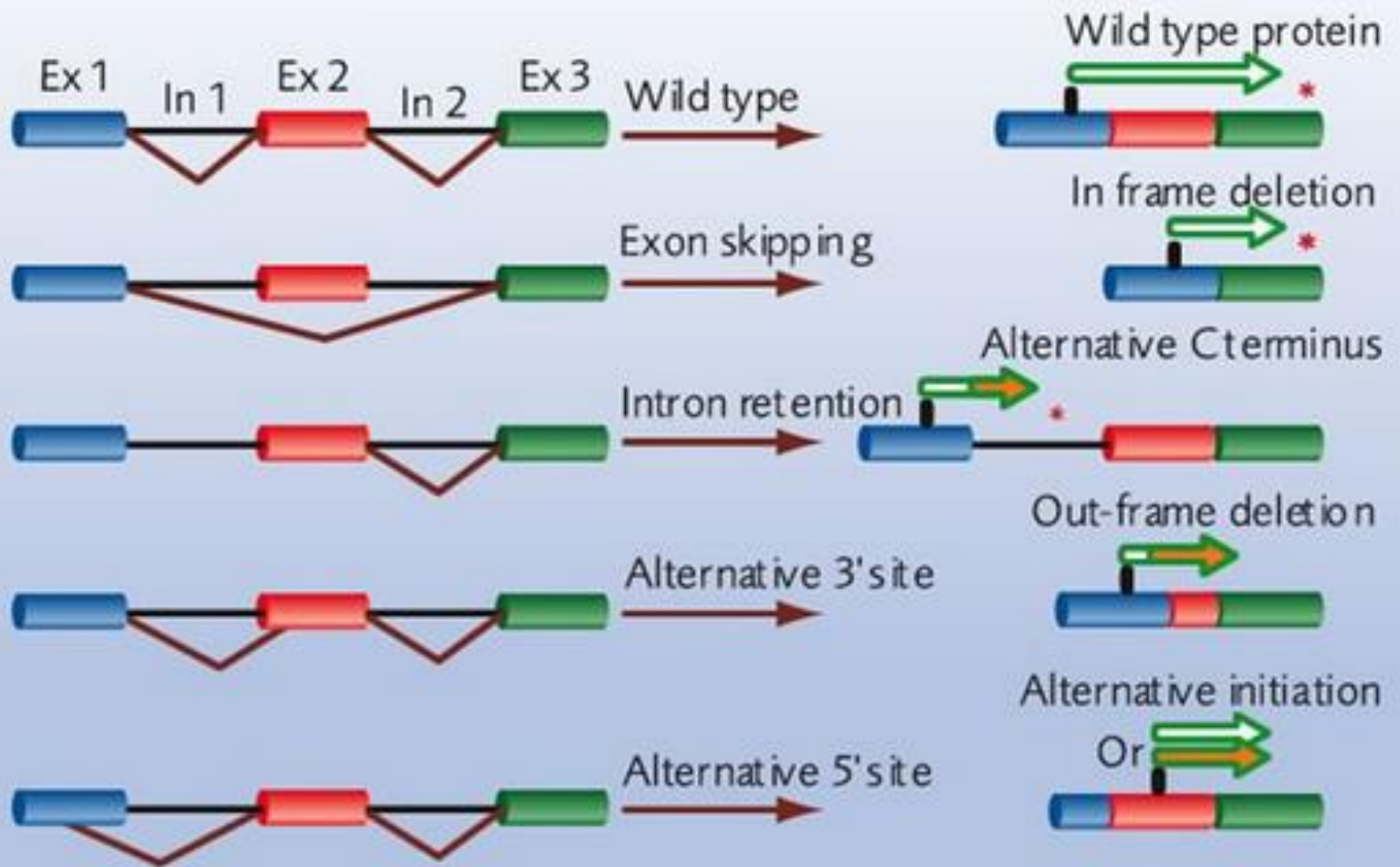
Intron  
↓

3' Exon  
↓



Numbers = Frequency (%)

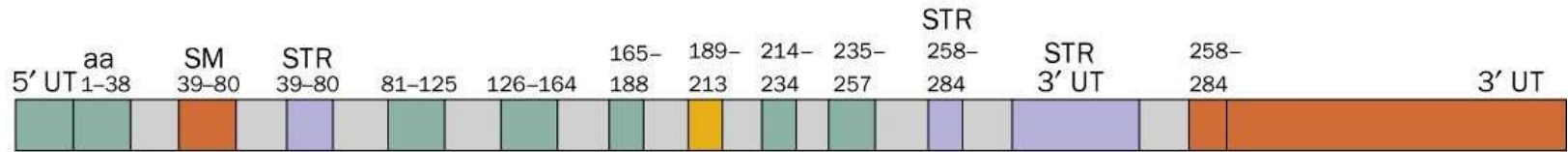
# Splicing Alternative



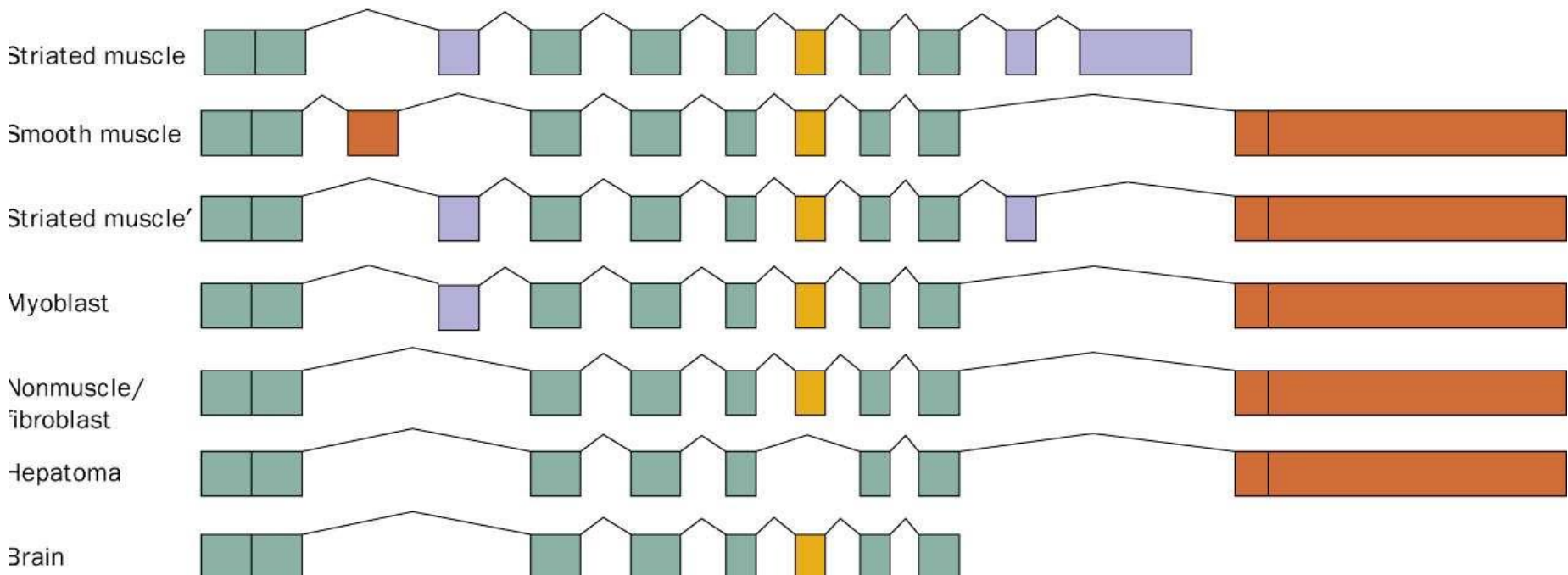
© 2003 ExonHit Therapeutics

■ initiation codon    \* Stop codon    → wild type amino-acid sequence    → alternative amino-acid sequence

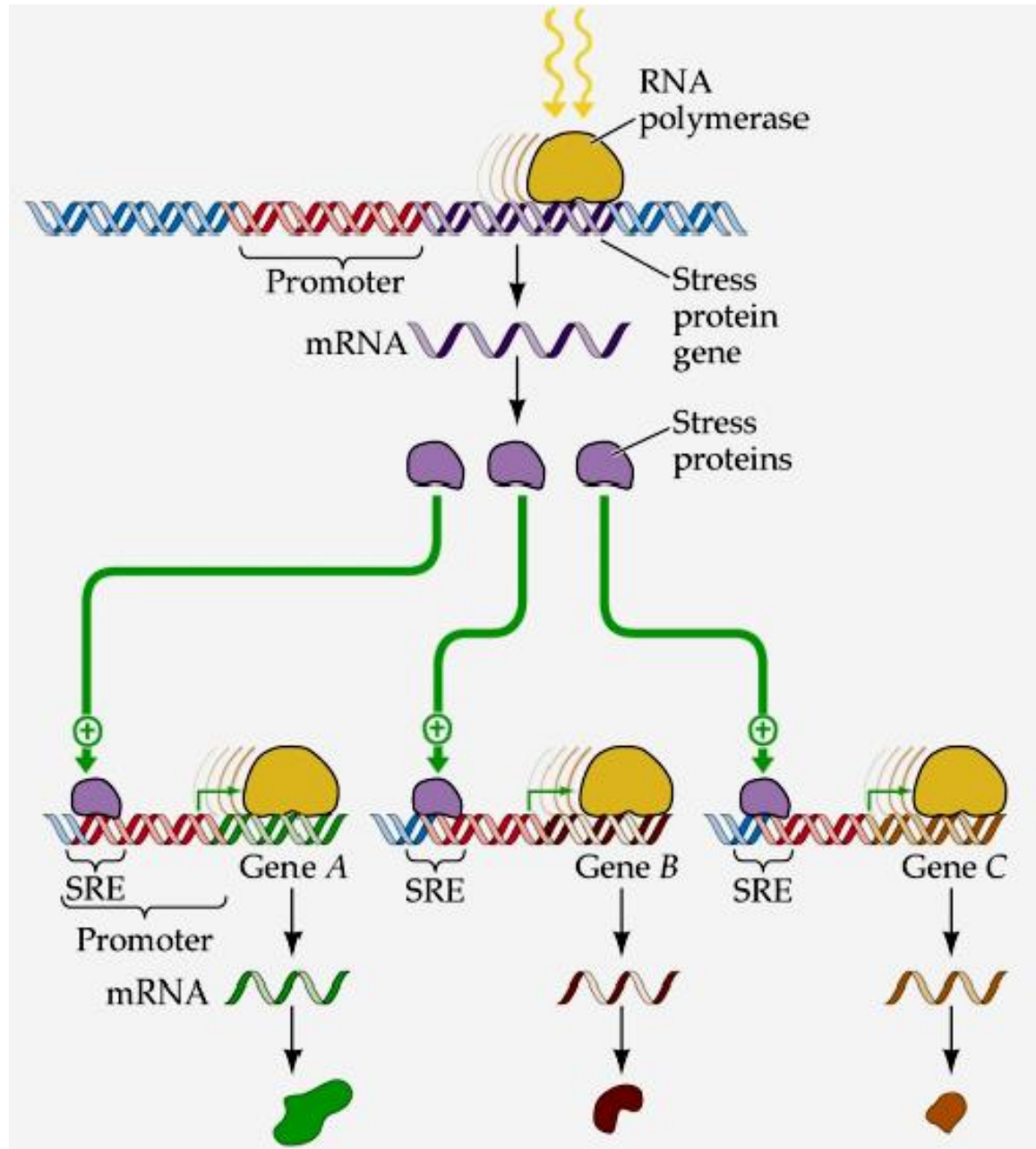
# The organization of the rat $\alpha$ -tropomyosin gene and the seven alternative splicing pathways that give rise to cell-specific $\alpha$ -tropomyosin variants.



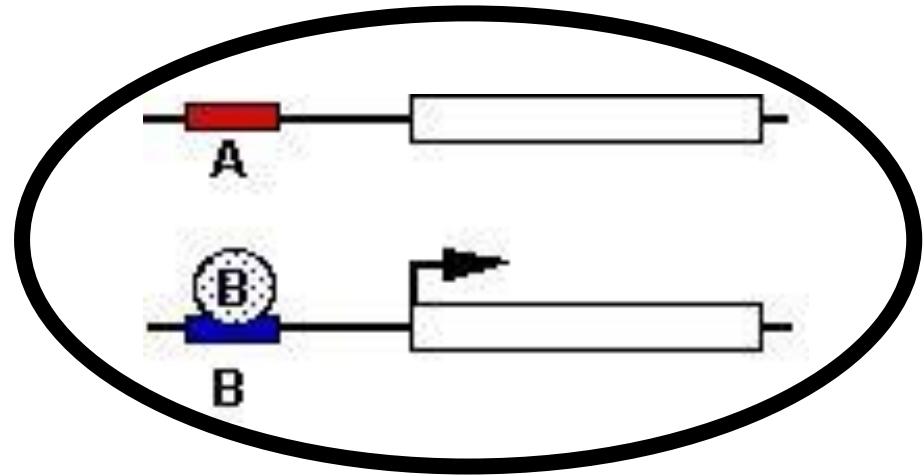
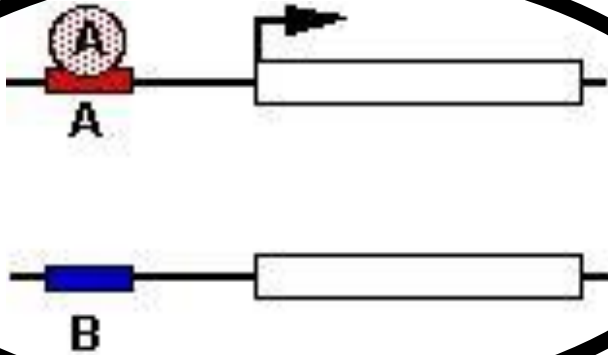
## mRNA transcripts

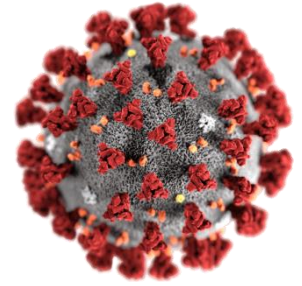


# Expressão coordenada de genes



# Expressão gênica tecido específica





# Obrigado

fscha@usp.br

**USP – 1º Semestre 2021**