

**QBQ1151 - 2019**

**Nucleotídeos  
Ácidos Nucleicos**

# Nucleotídeos

- Compostos por
  - ❑ base nitrogenada
  - ❑ pentose
  - ❑ fosfato
  
- ❑ Base + pentose = nucleosídeo

# Nucleotídeos

- Presentes em:

- ❑ coenzimas

- ATP, NAD<sup>+</sup>/NADH, FAD/FADH<sub>2</sub>, coenzima A

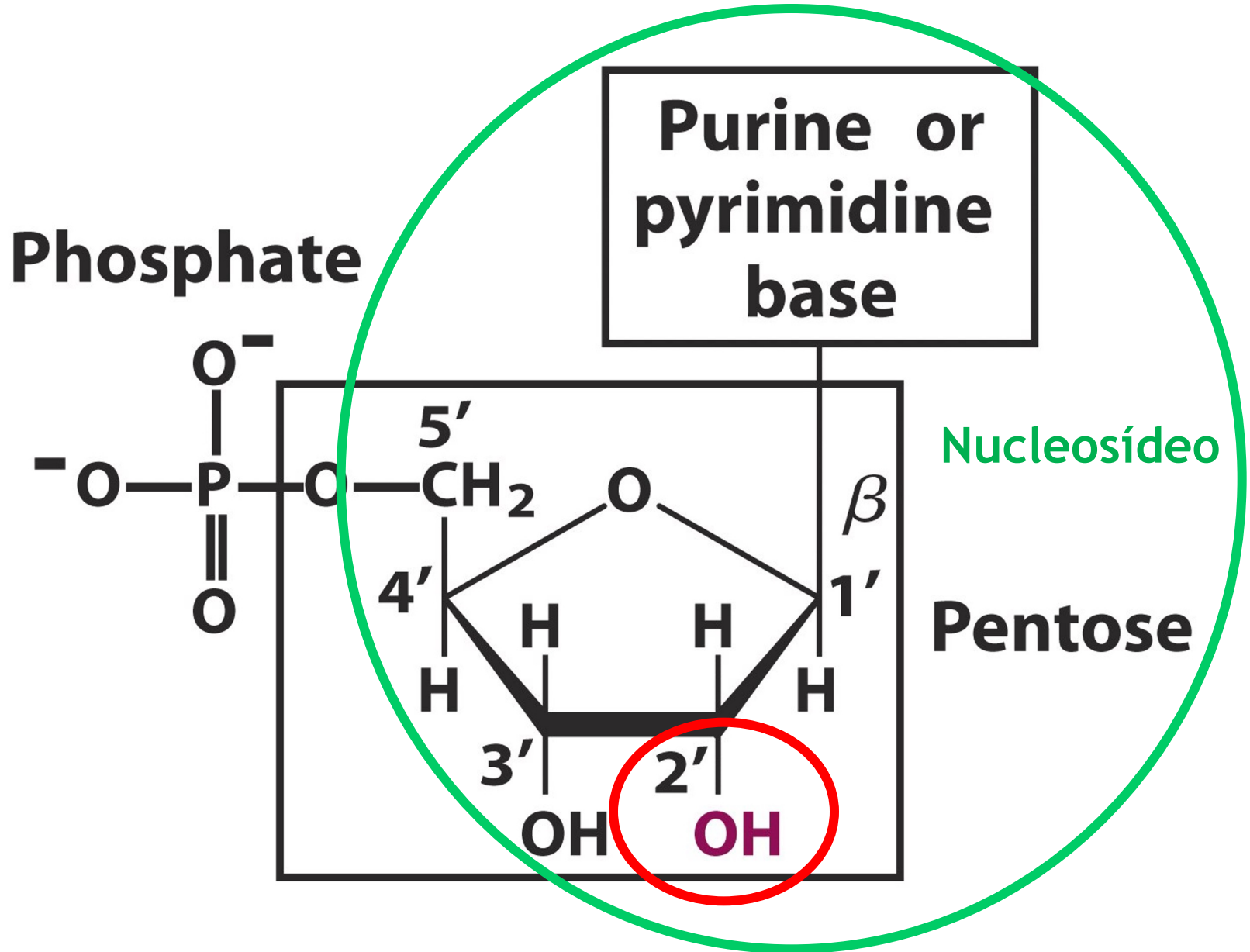
- ❑ ácidos nucleicos

- DNA e RNA

- ❑ vias de sinalização e regulação

- cAMP, cGMP, (p)ppGpp, c-di-GMP

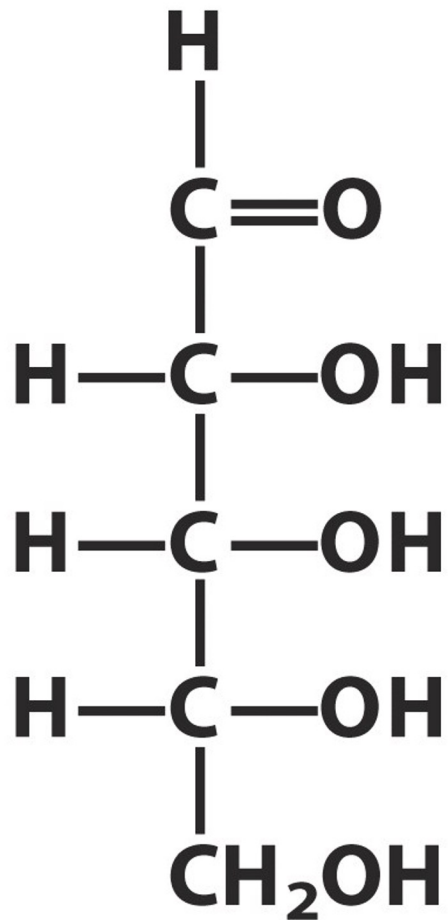
# Componentes dos Nucleotídeos



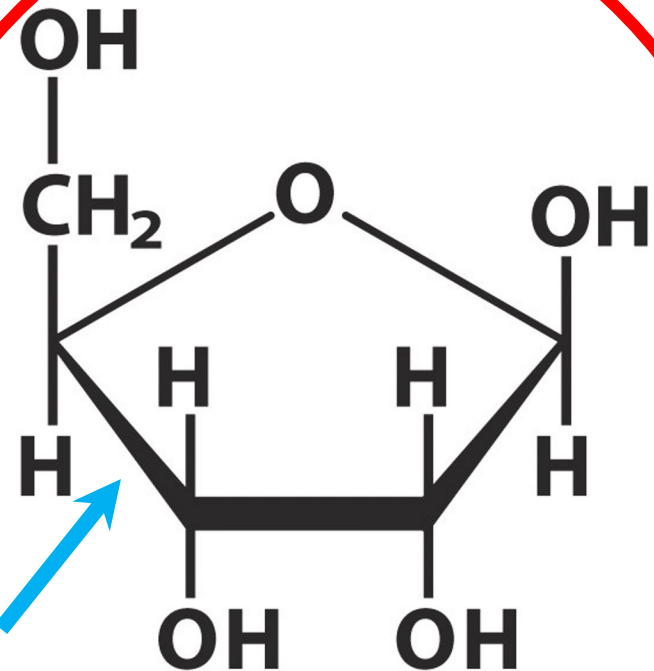


# **Estrutura de Nucleotídeos e Ácidos Nucleicos**

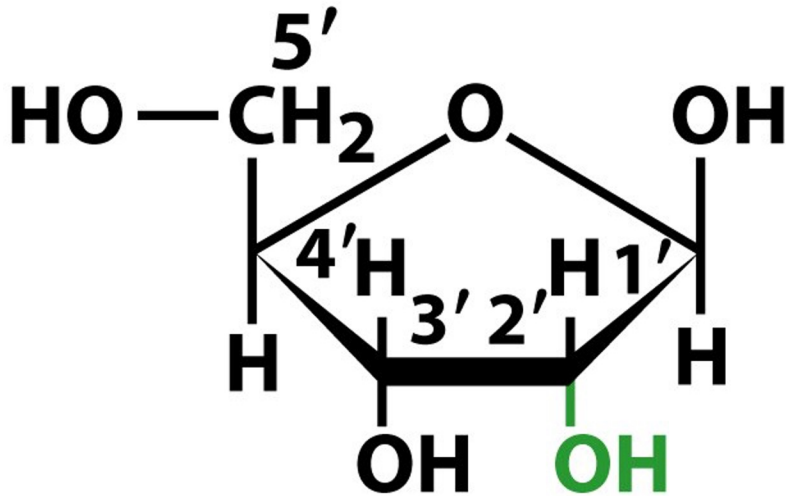
# Conformações da Pentose



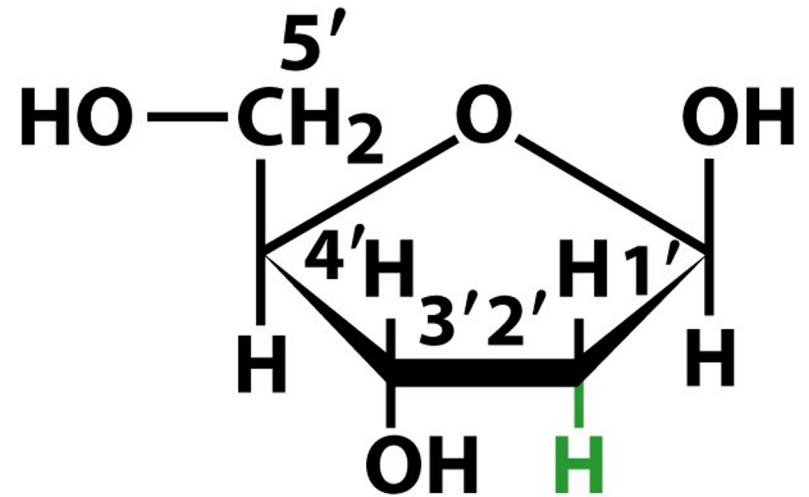
**Aldehyde**



# Pentoses



**Ribose**

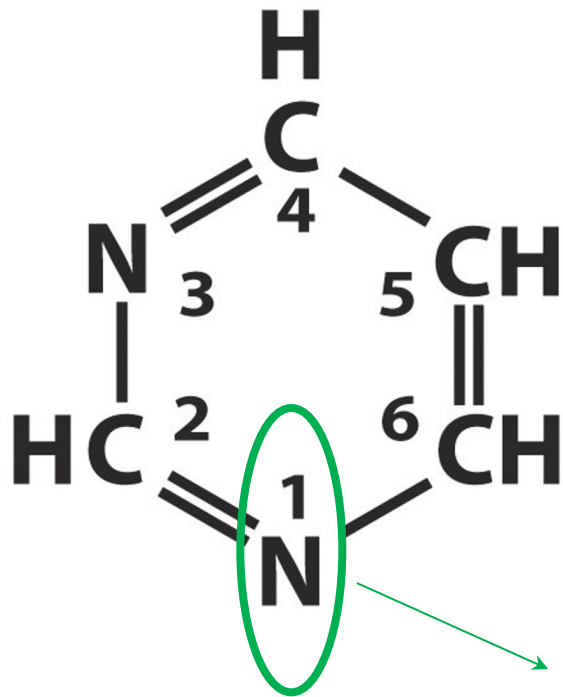


**Deoxyribose**

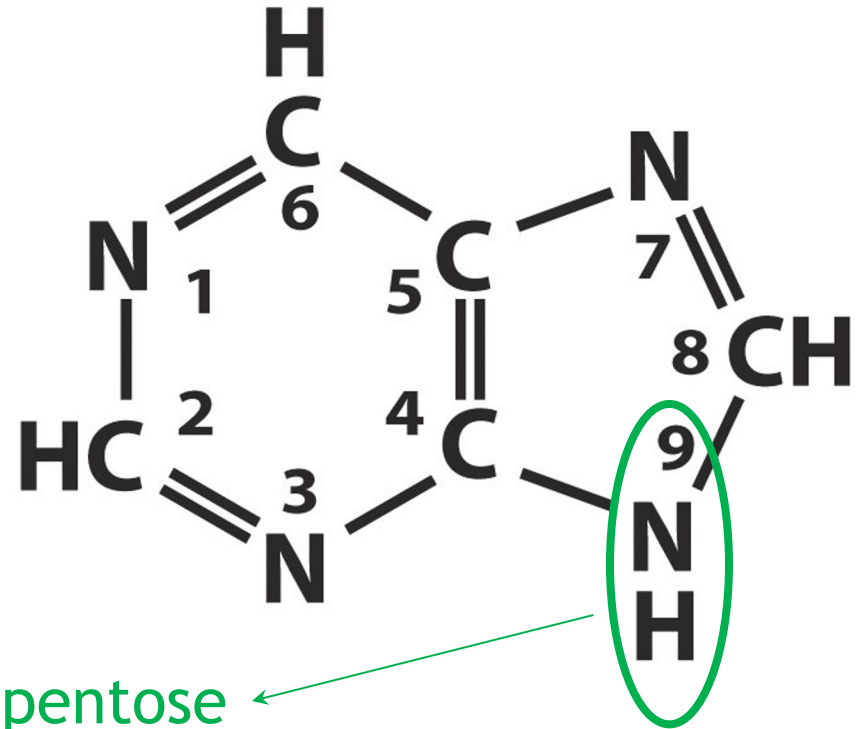
Unnumbered figure pg 42 Fundamentals of Biochemistry, 2/e  
© 2006 John Wiley & Sons

Atenção para a numeração dos carbonos:  
1' a 5'

# Bases nitrogenadas

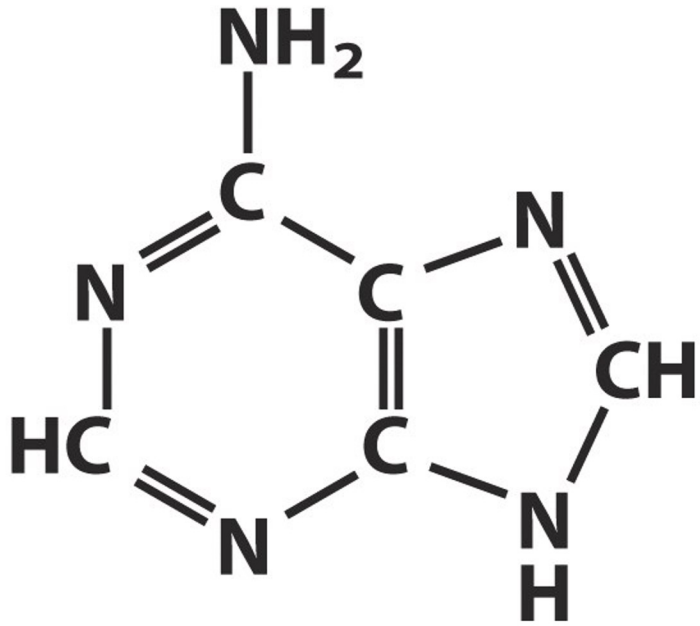


**Pyrimidine**

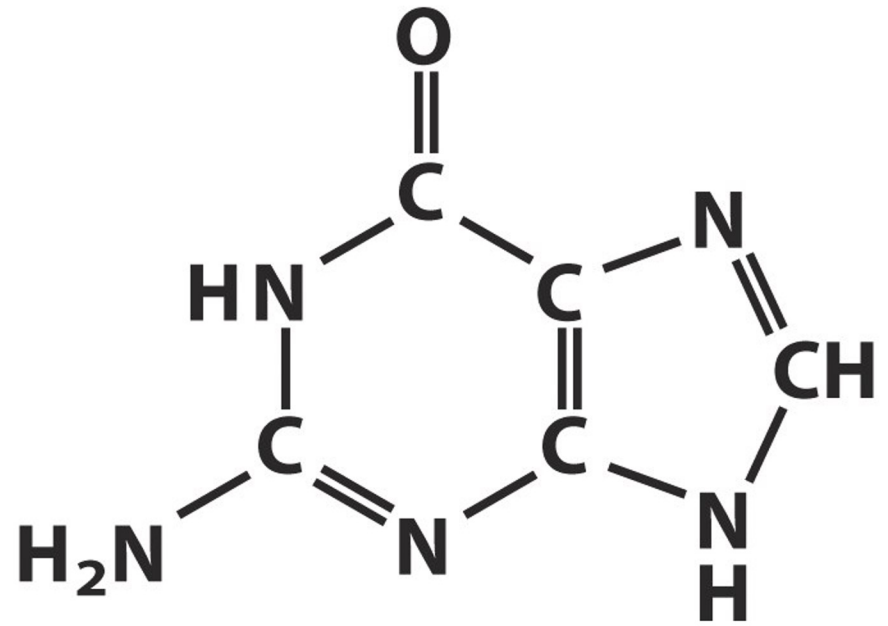


**Purine**

Ligação à pentose

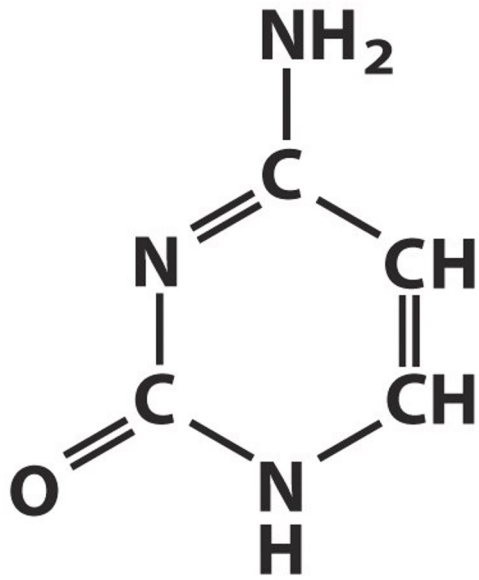


**Adenine**

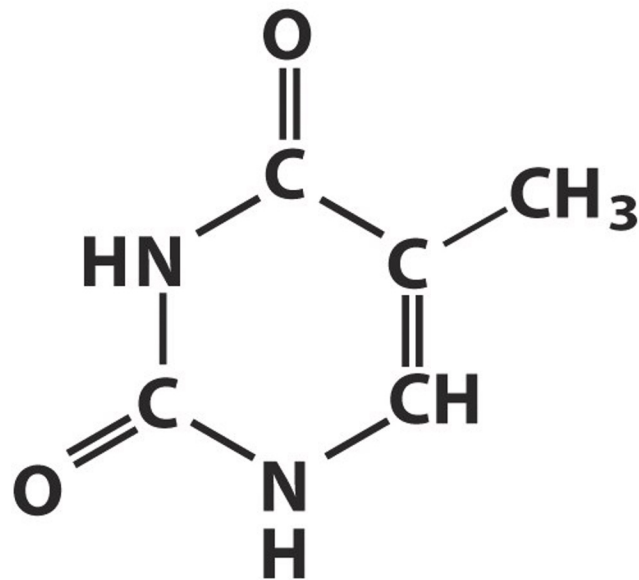


**Guanine**

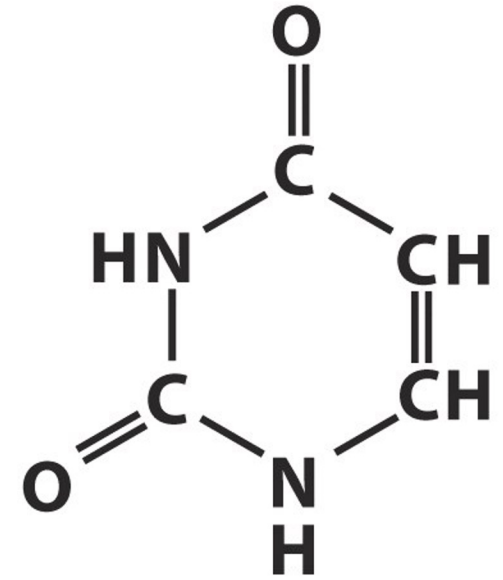
**Purines**



**Cytosine**



**Thymine  
(DNA)**

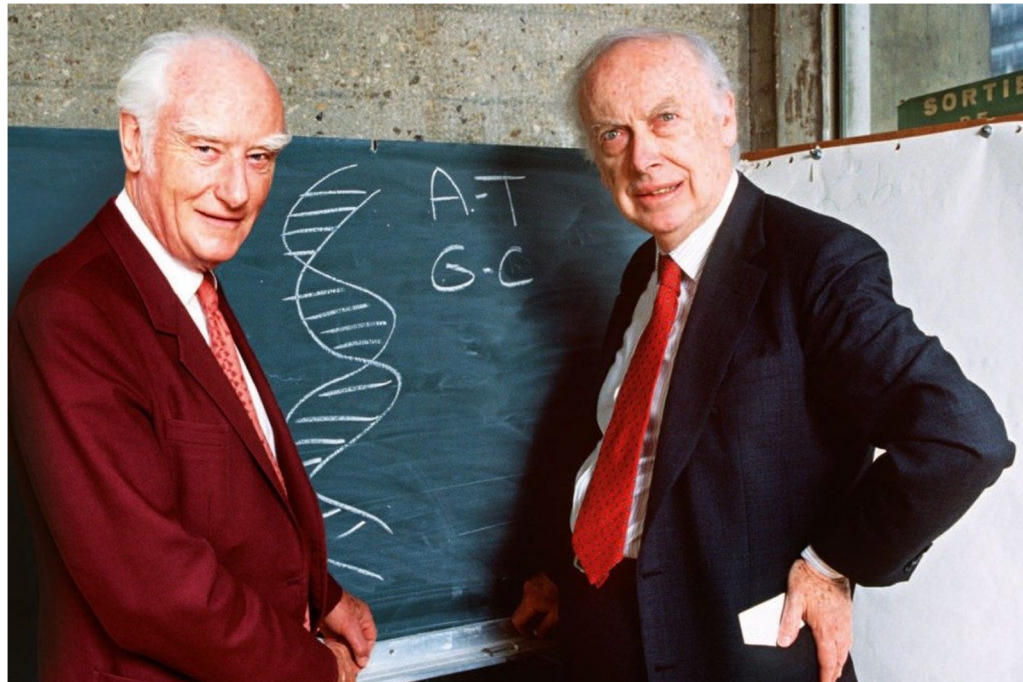


**Uracil  
(RNA)**

**Pyrimidines**

# Estrutura do DNA

## Watson e Crick, 1953



# Descoberta da estrutura do DNA

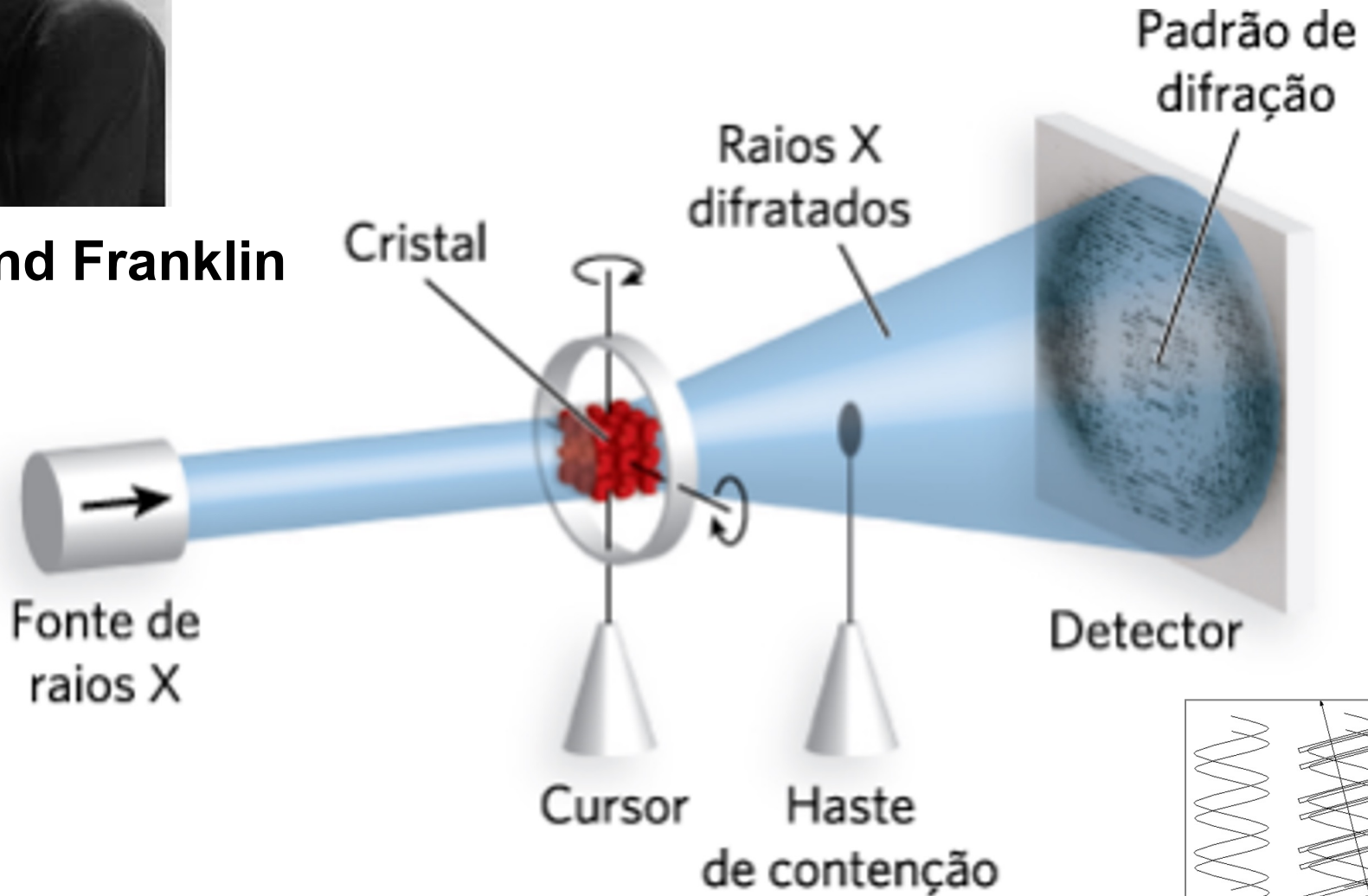
- Dados biofísicos
- Padrões de difração de raio X



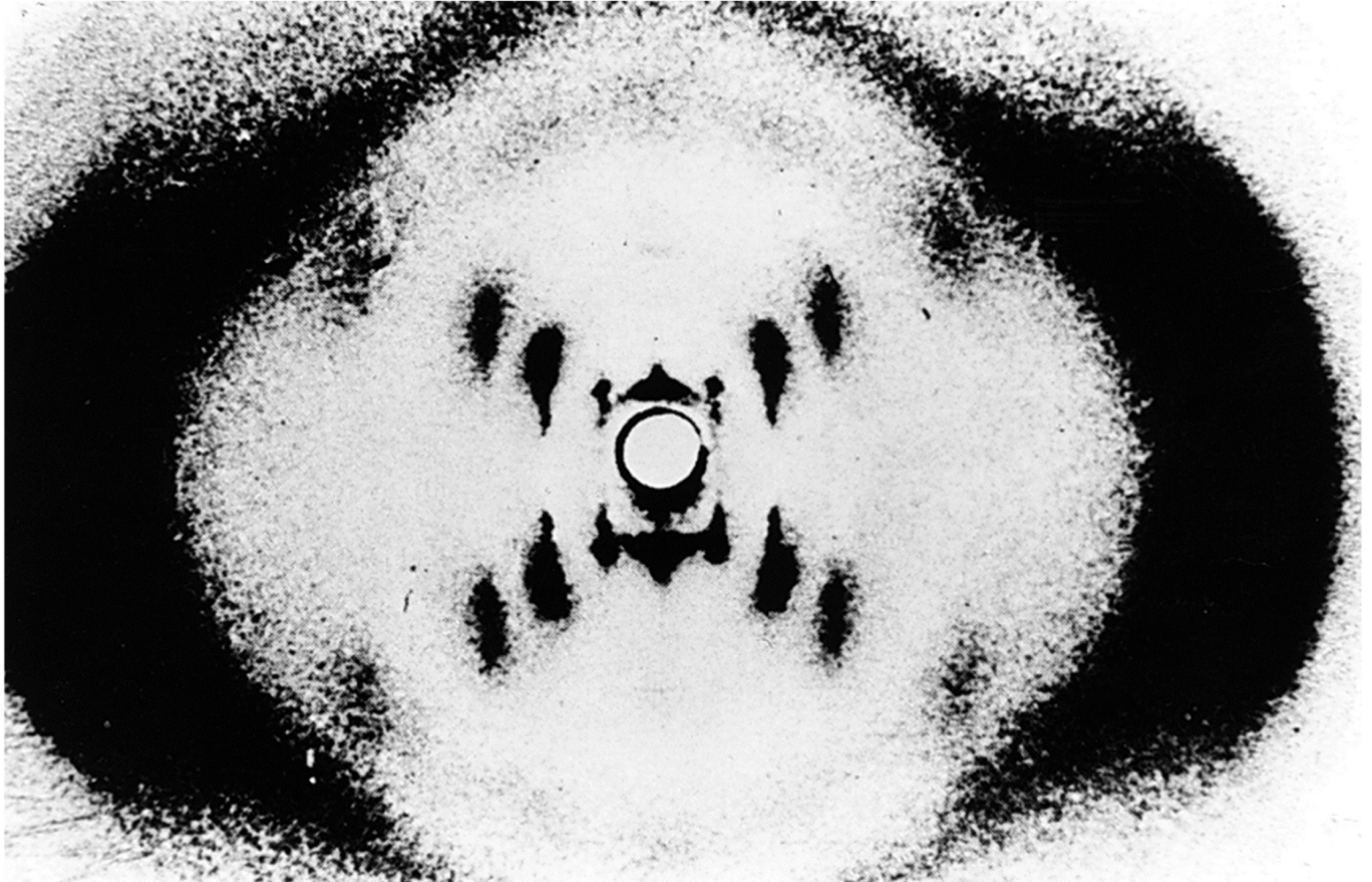


# Difração de Raio X do DNA

Rosalind Franklin



# Difração de raio X



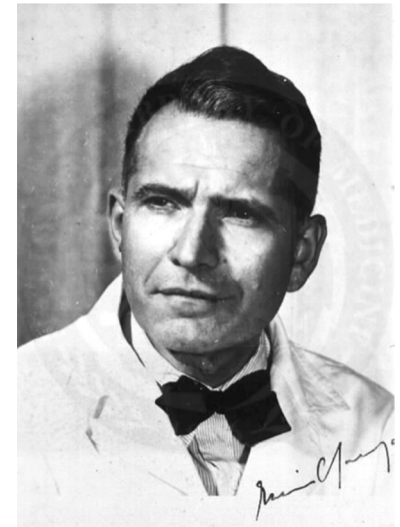
Rosalind Franklin and Maurice Wilkins, ~1950

# Descoberta da estrutura do DNA

- Dados biofísicos
- Padrões de difração de raio X
- Razão entre as bases - regras de Chargaff

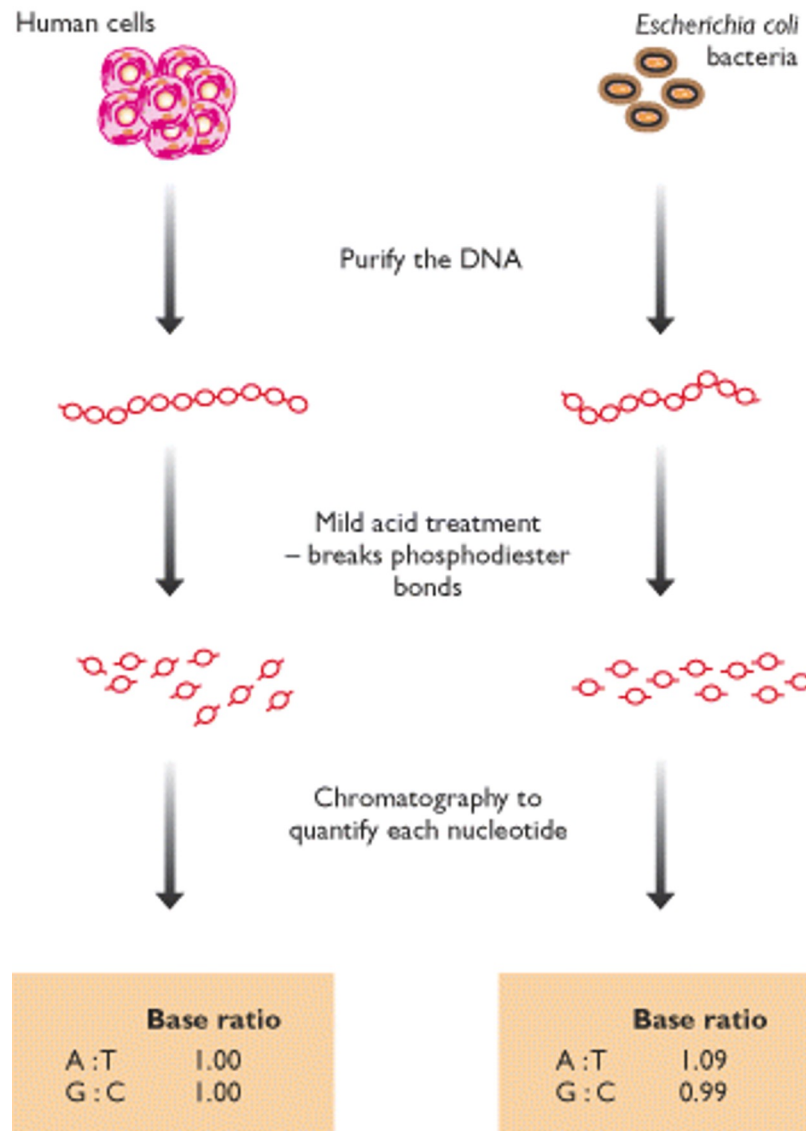
# Regras de Chargaff

- Composição de bases do DNA (%)
  - ❑ varia de uma espécie a outra
  - ❑ invariável entre indivíduos da mesma espécie
  - ❑ não muda com idade, nutrição ou ambiente
- Em todos os DNAs:
  - ❑  $A = T$
  - ❑  $G = C$
  - ❑  $A + G = T + C$



Erwin Chargaff, 1940's

# Regras de Chargaff



Erwin Chargaff, 1940's

# Descoberta da estrutura do DNA

- Dados biofísicos
- Padrões de difração de raio X
- Razão entre as bases - regras de Chargaff
- Modelos estruturais



# Modelo Estrutural

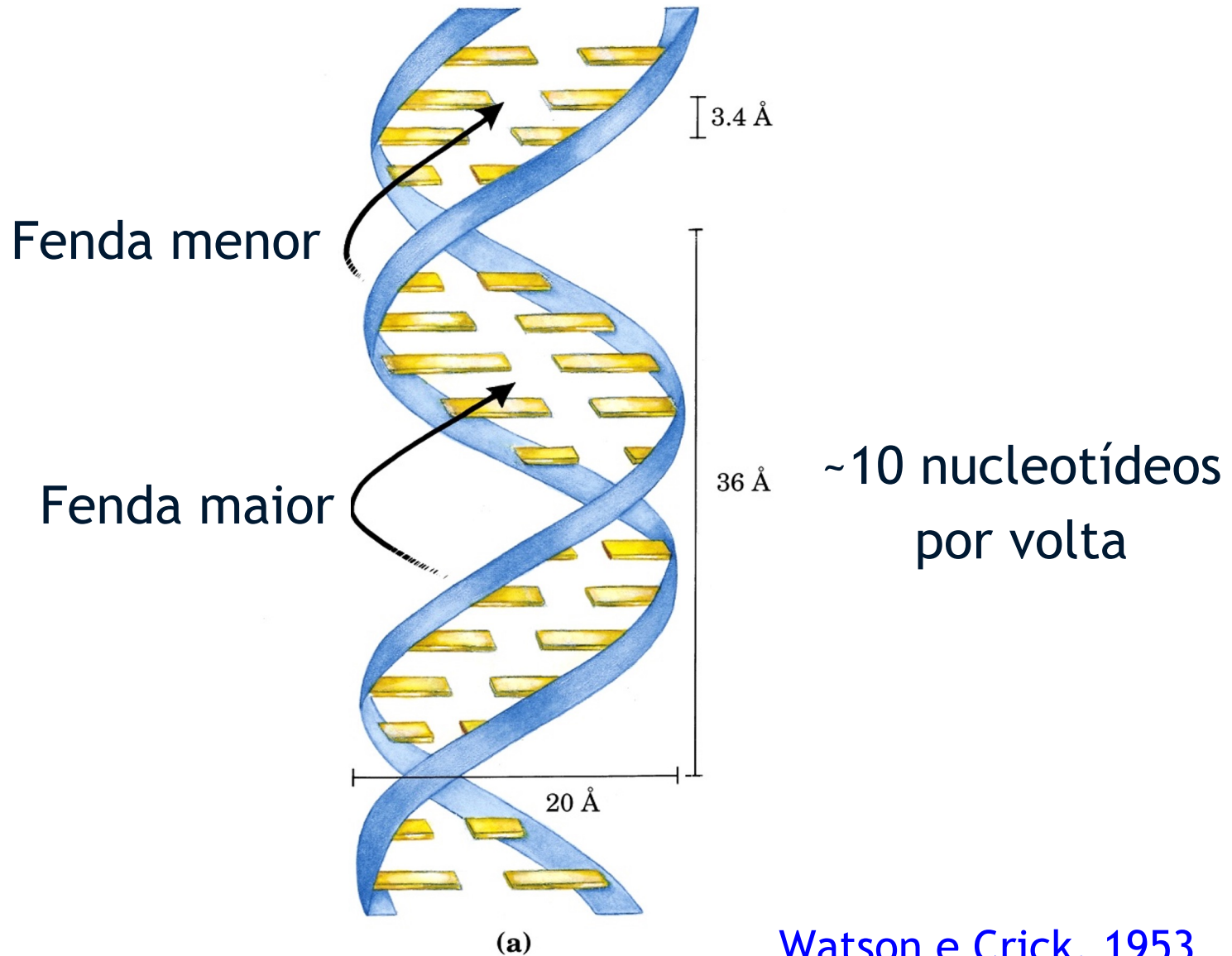


James Watson

Francis Crick

1953

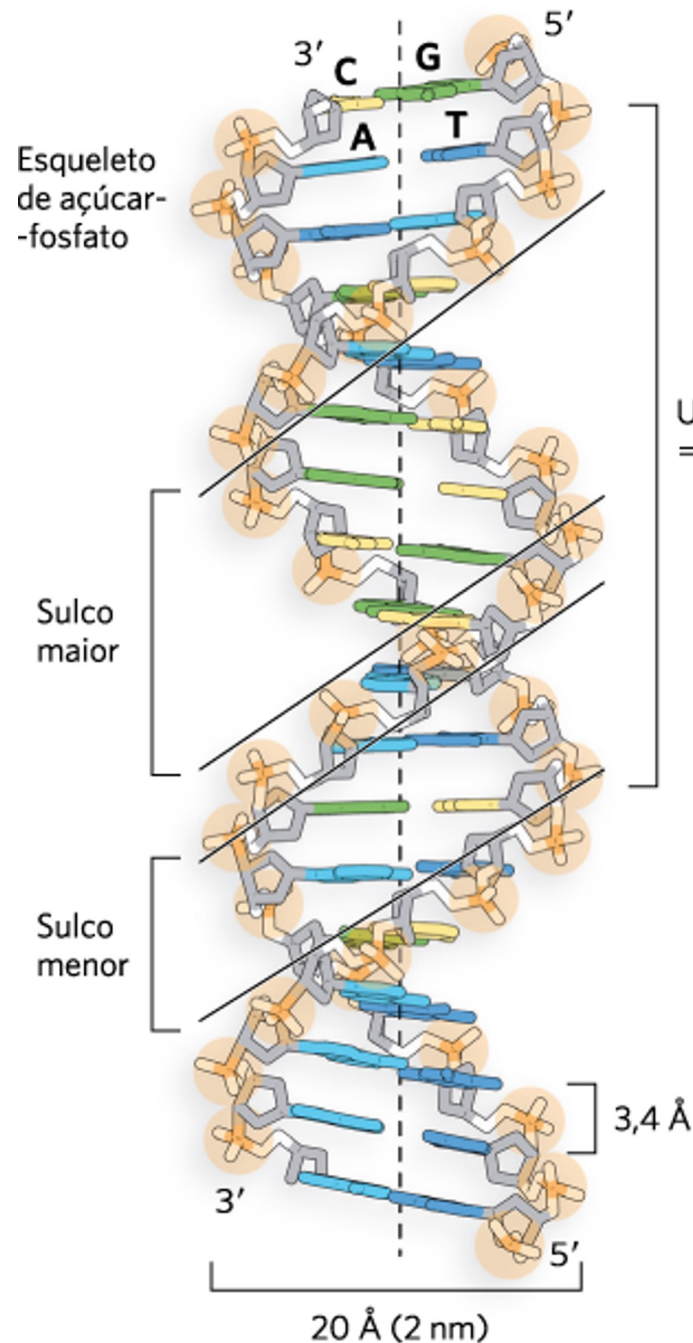
# Modelo de Dupla Hélice



Watson e Crick, 1953



# Dupla hélice de DNA: Watson-Crick, 1953



- duas cadeias antiparalelas enroladas em torno de um eixo
- esqueleto de fosfato para fora/ pares de bases para dentro da hélice dupla
- bases perpendiculares ao eixo da hélice, separadas por 3,4 angstroms
- diâmetro da hélice = 20 angstroms



## The Nobel Prize in Physiology or Medicine 1962

Francis Crick, James Watson, Maurice Wilkins

The Nobel Prize in Physiology or Medicine 1962	▼
Nobel Prize Award Ceremony	▼
Francis Crick	▼
James Watson	☑
Maurice Wilkins	▼



Francis Harry  
Compton Crick



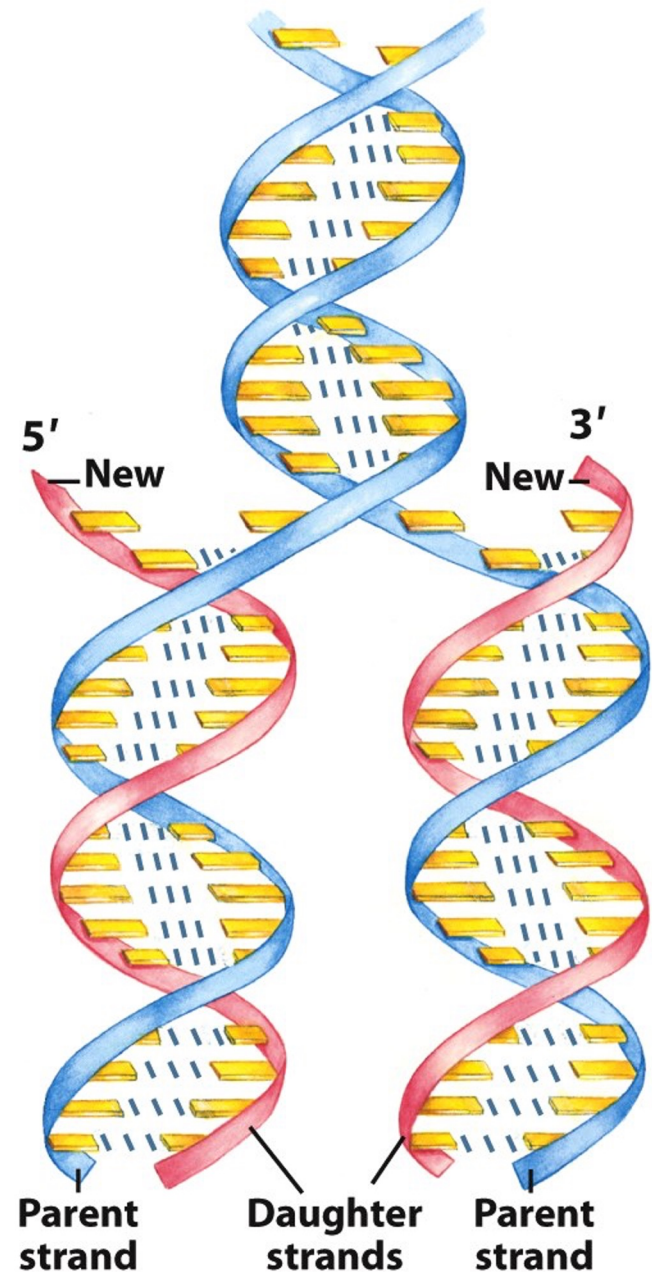
James Dewey  
Watson



Maurice Hugh  
Frederick Wilkins

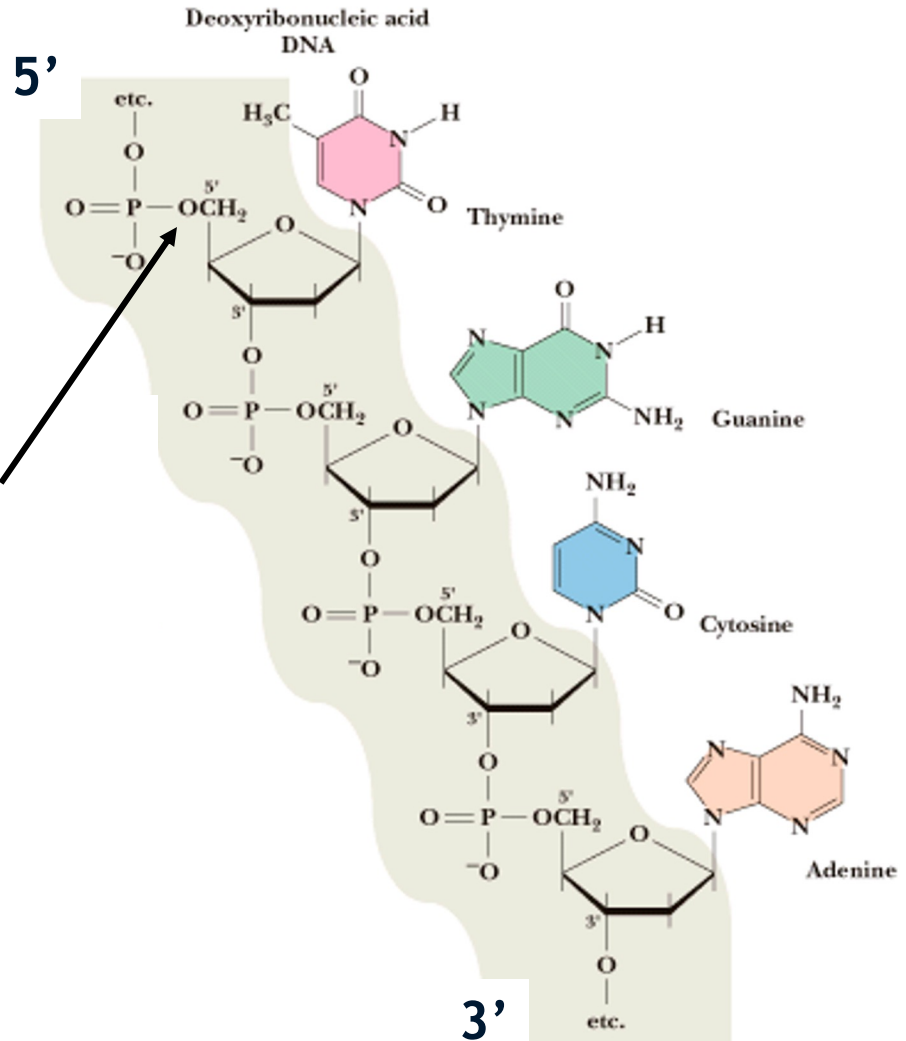
The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to Francis Harry Compton Crick, James Dewey Watson and Maurice Hugh Frederick Wilkins *"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"*.

# Função do DNA: Estoque e transferência da informação genética



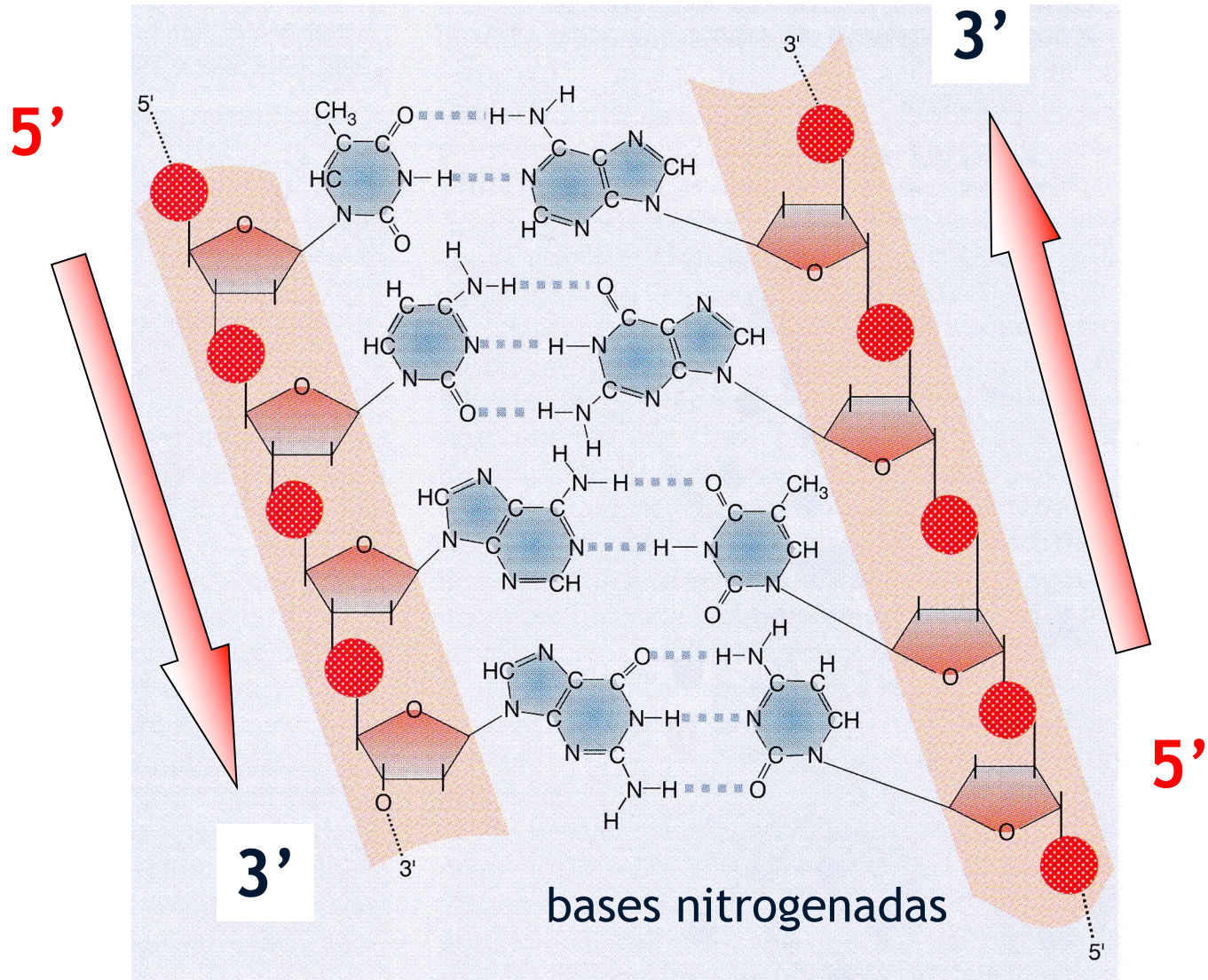
# Esqueleto da molécula de DNA

Ligações fosfodiéster  
(covalentes)





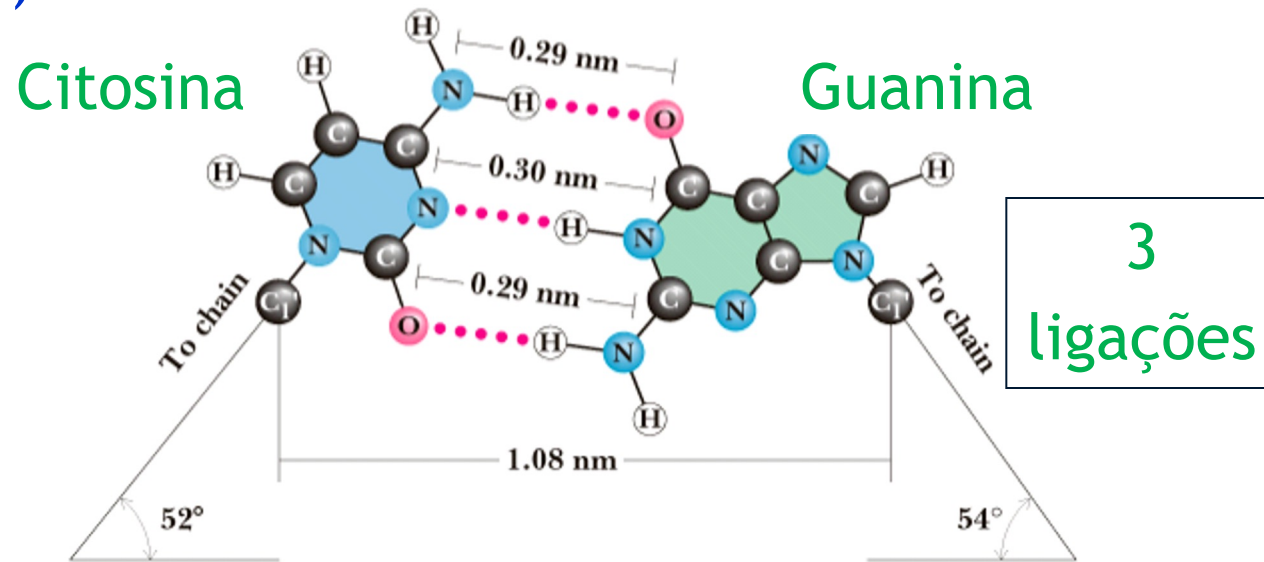
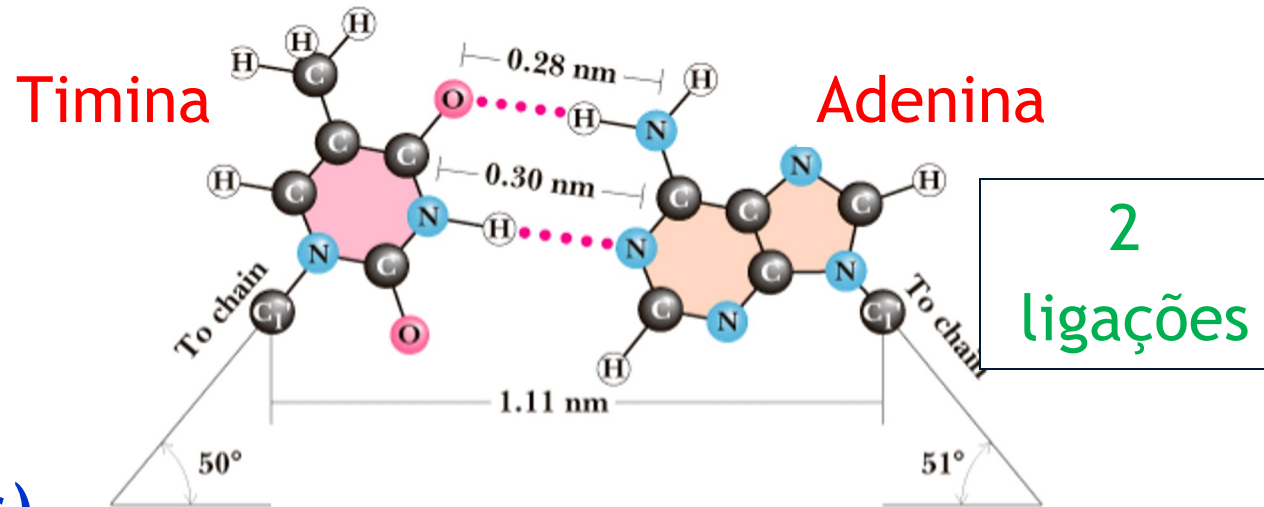
# Fitas são antiparalelas



# Pareamento entre as bases

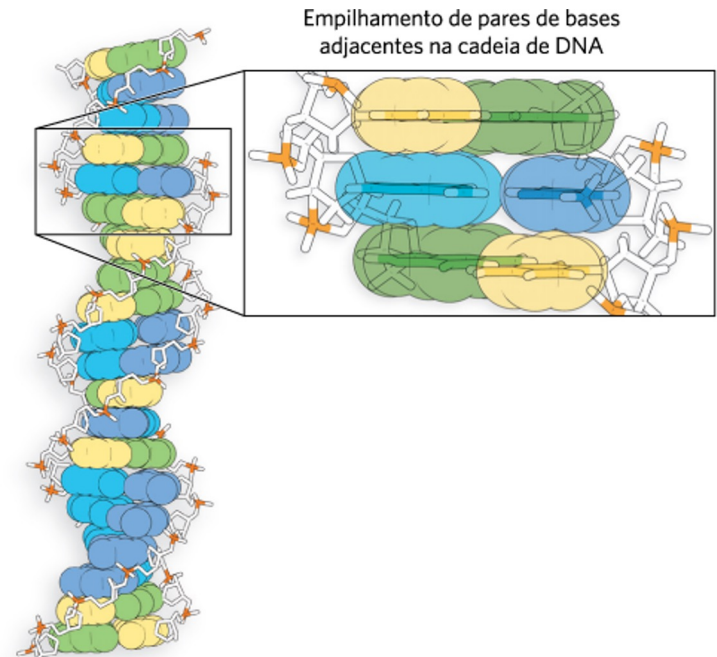
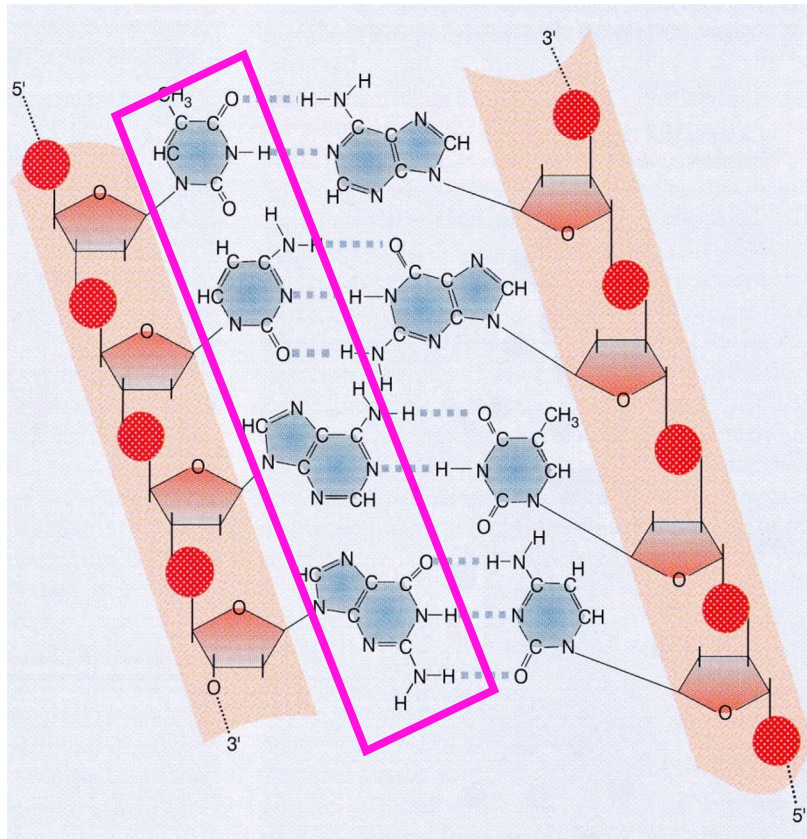
Ligações de Hidrogênio (não-covalentes)

Especificidade dos pares entre as fitas





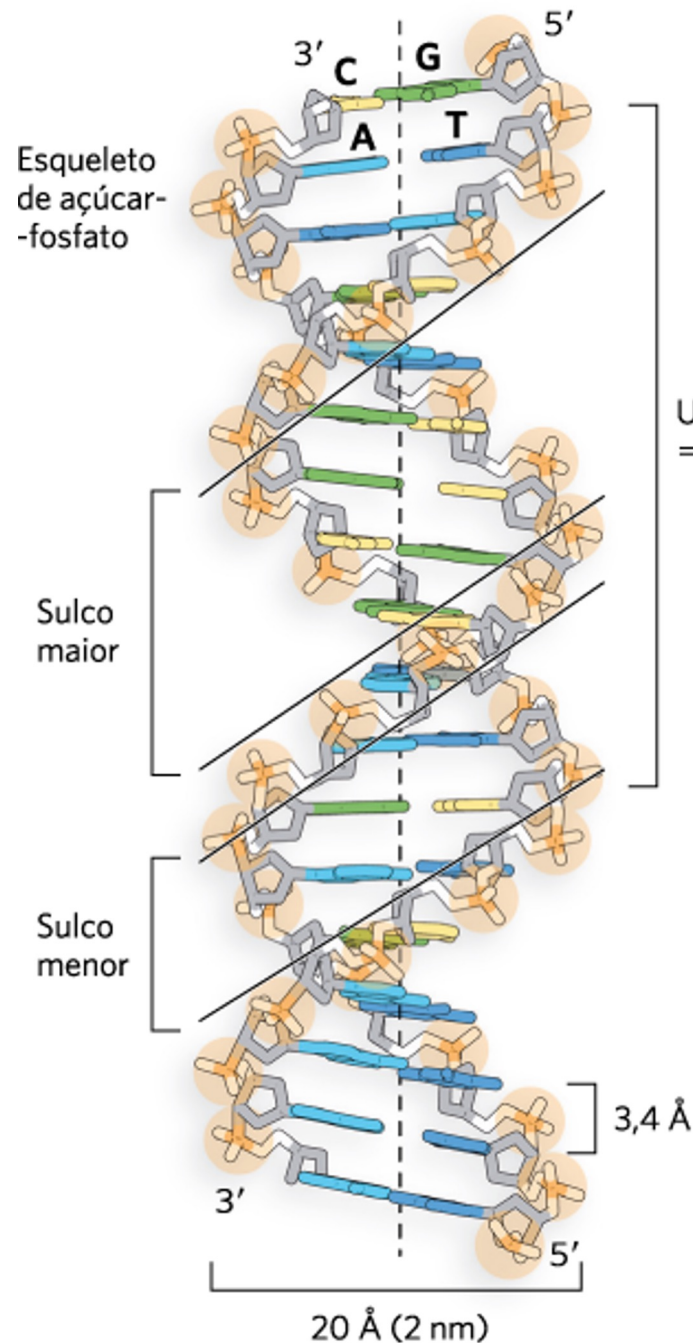
# Interações hidrofóbicas entre bases adjacentes



**FIGURA 3-18** Interações hidrofóbicas na molécula de DNA. O empilhamento dos anéis de bases adjacentes na cadeia de DNA envolve interações hidrofóbicas favoráveis. A sobreposição de orbitais moleculares entre as bases estabiliza a hélice dupla. A cadeia principal do DNA é mostrada em branco, com

Estabilidade da dupla fita

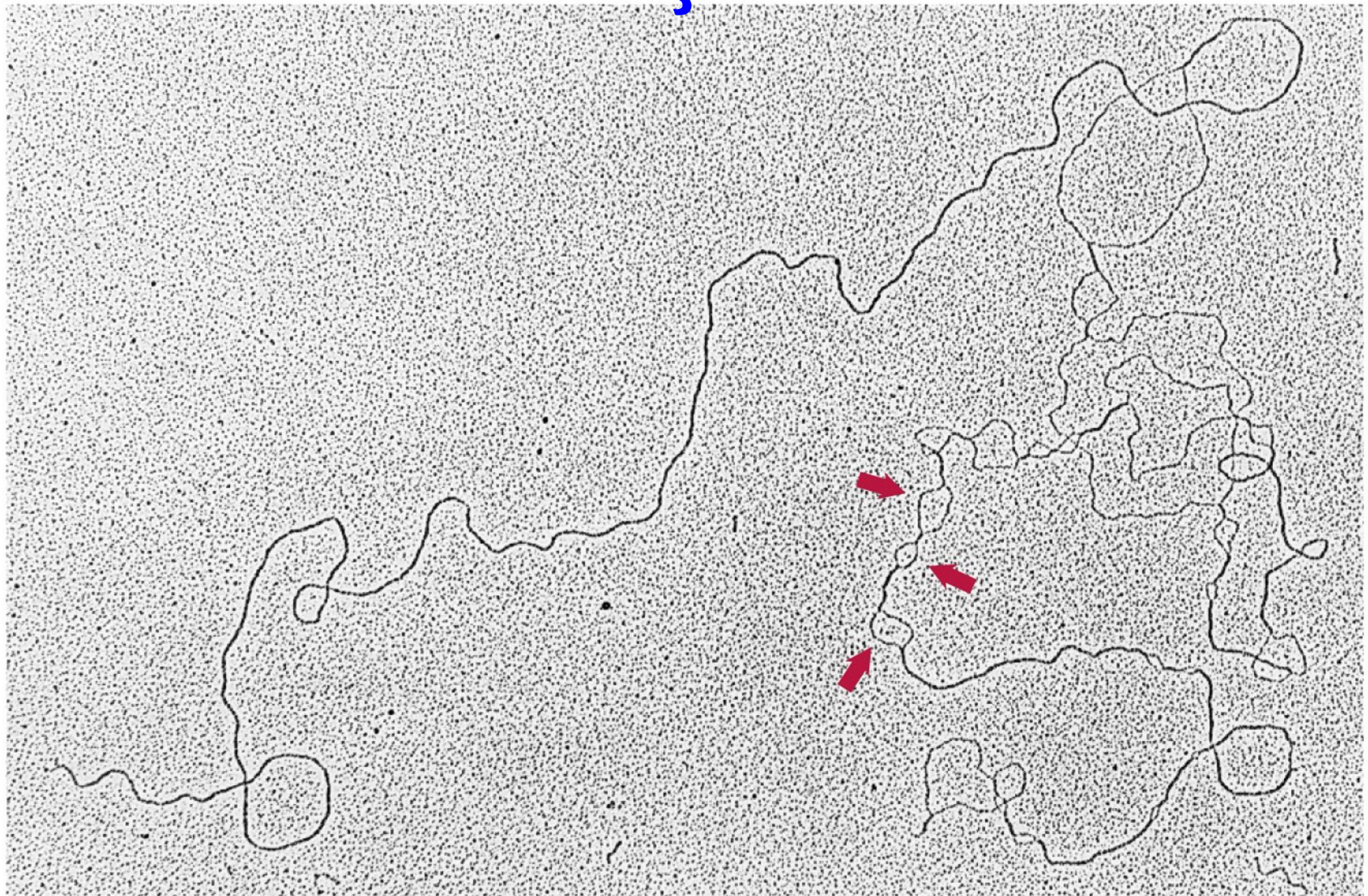
# Dupla hélice de DNA: Watson-Crick, 1953



- duas cadeias antiparalelas enroladas em torno de um eixo
- esqueleto de fosfato para fora/ pares de bases para dentro da hélice dupla
- bases perpendiculares ao eixo da hélice, separadas por 3,4 angstroms
- diâmetro da hélice = 20 angstroms

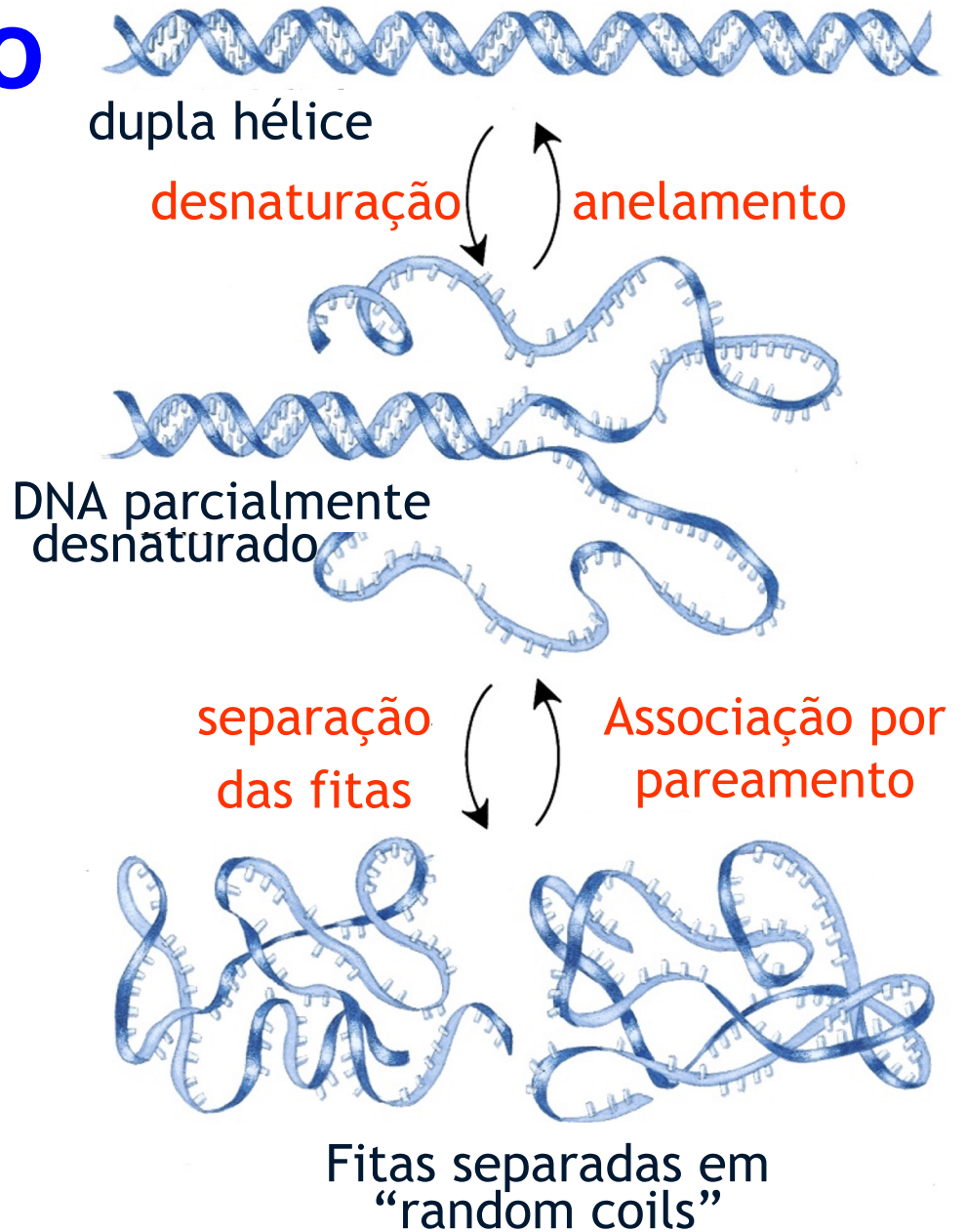


# Desnaturação do DNA



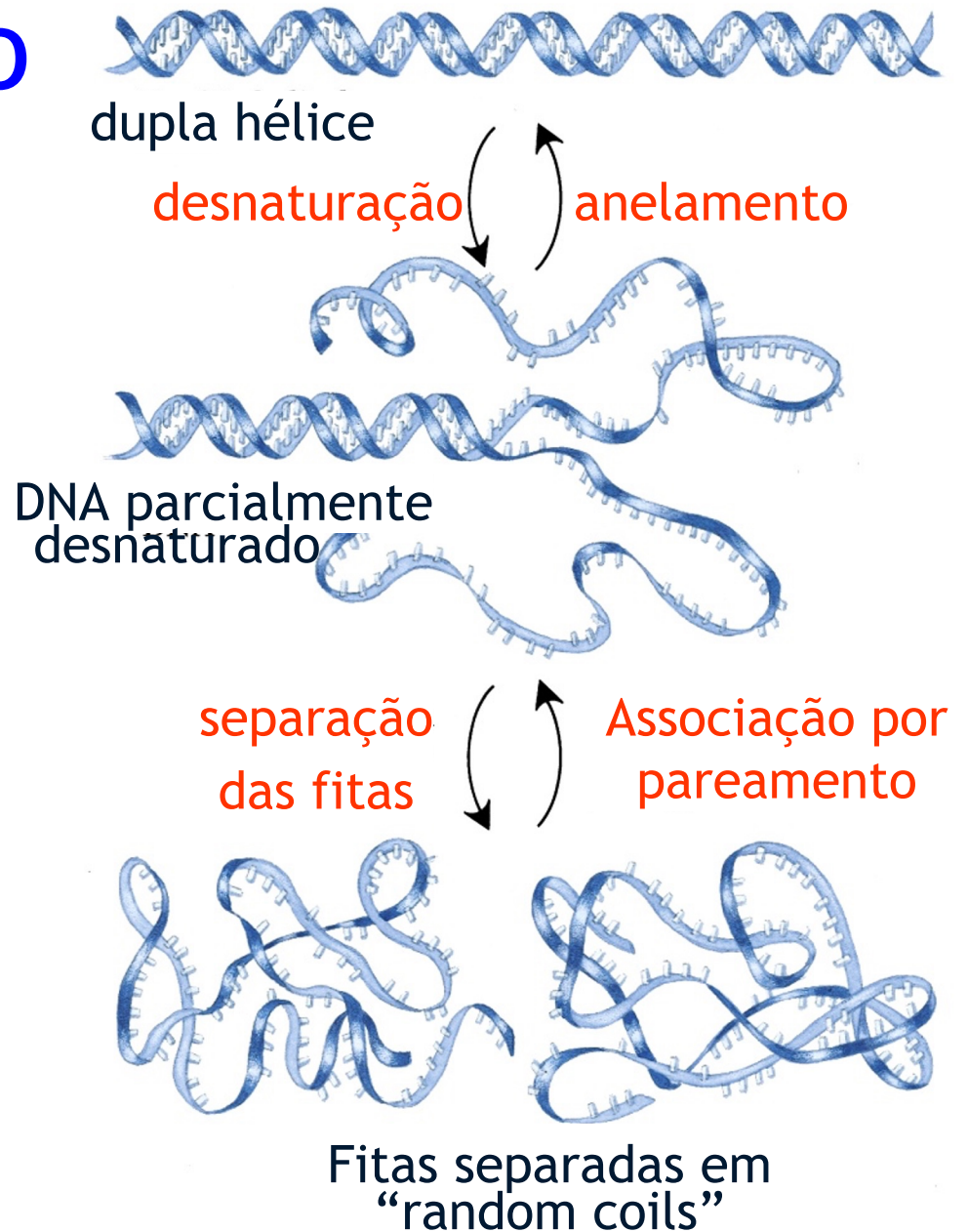
3  $\mu\text{m}$

# Desnaturação do DNA



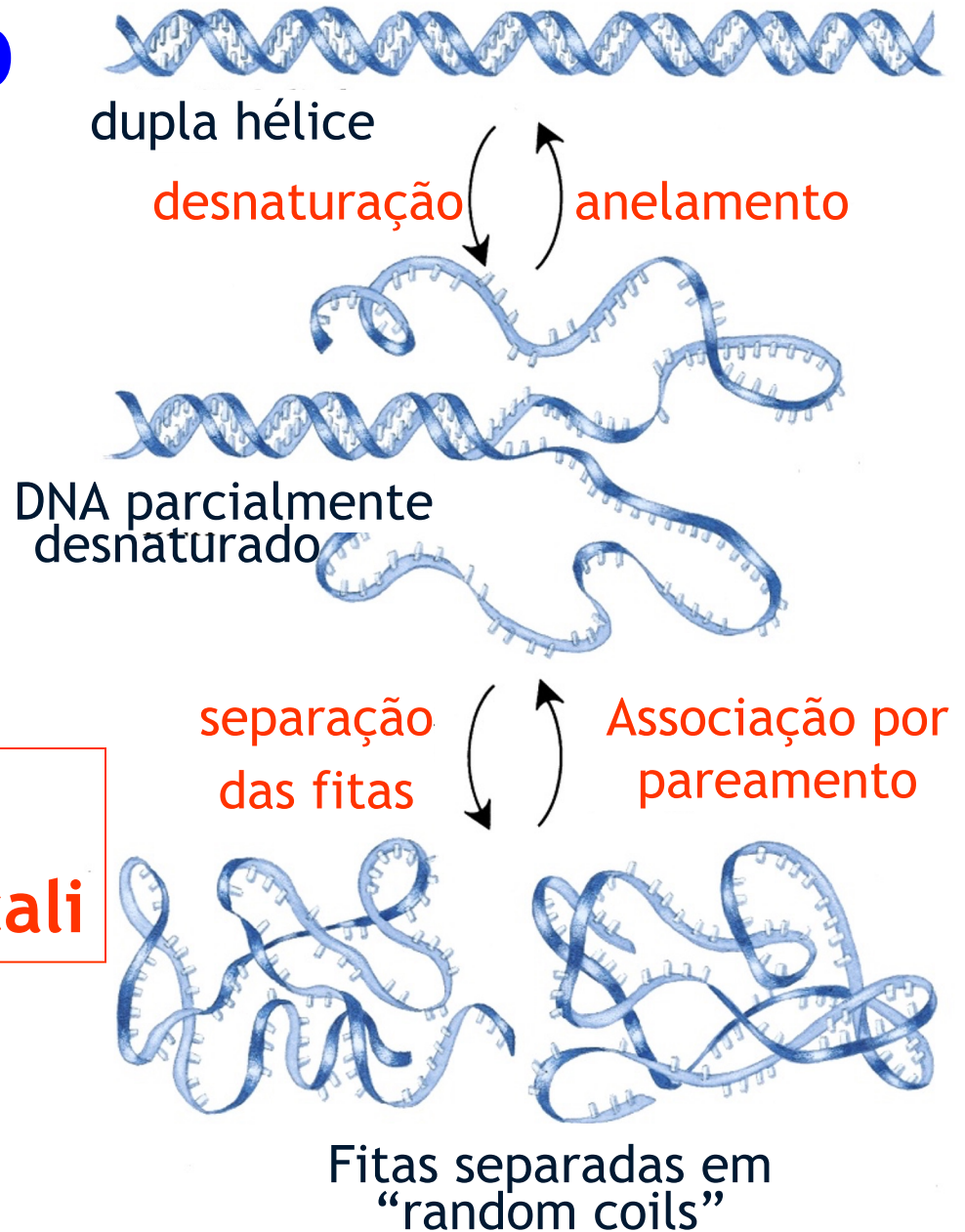


# Desnaturação do DNA = Abertura das fitas

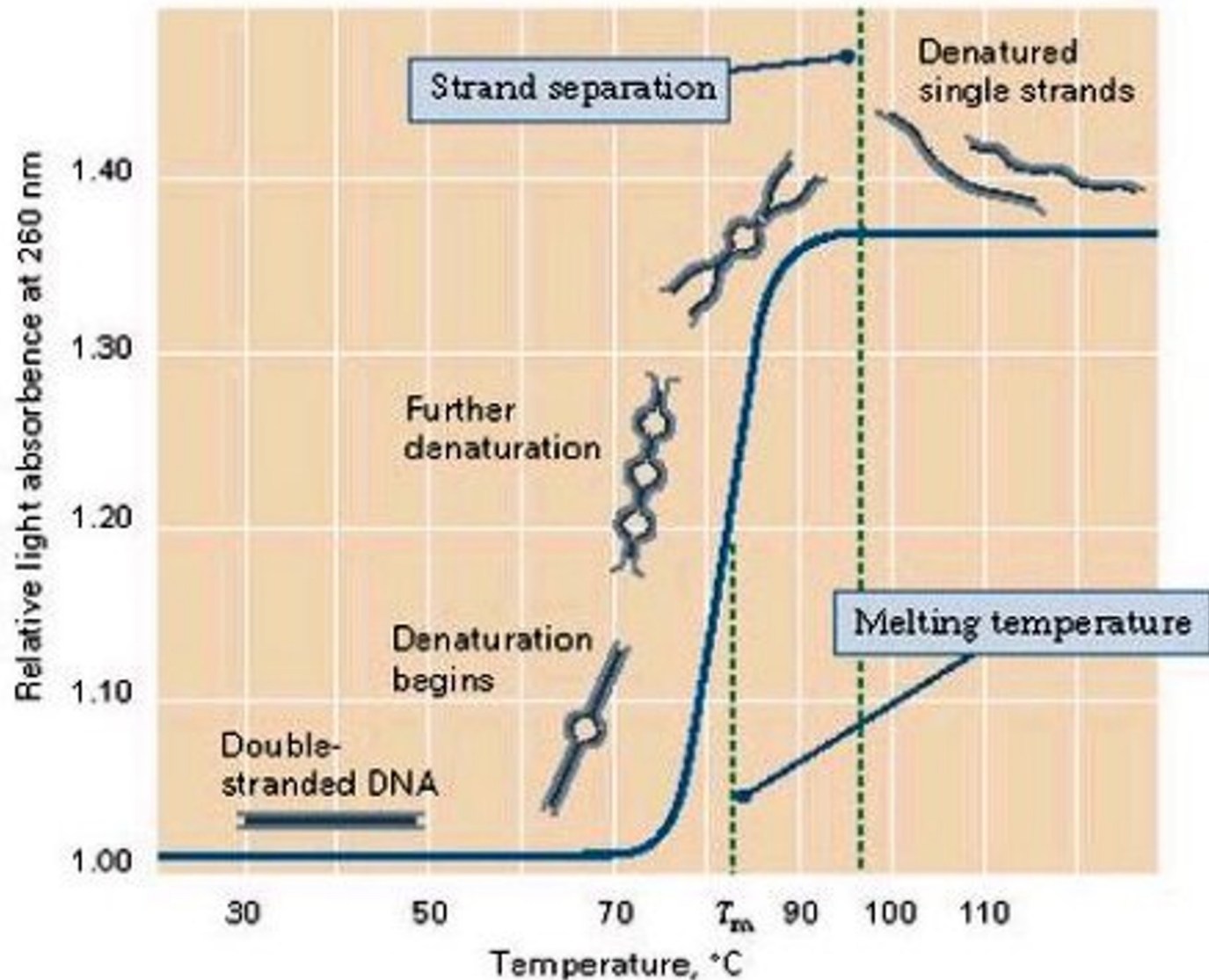


# Desnaturação do DNA = Abertura das fitas

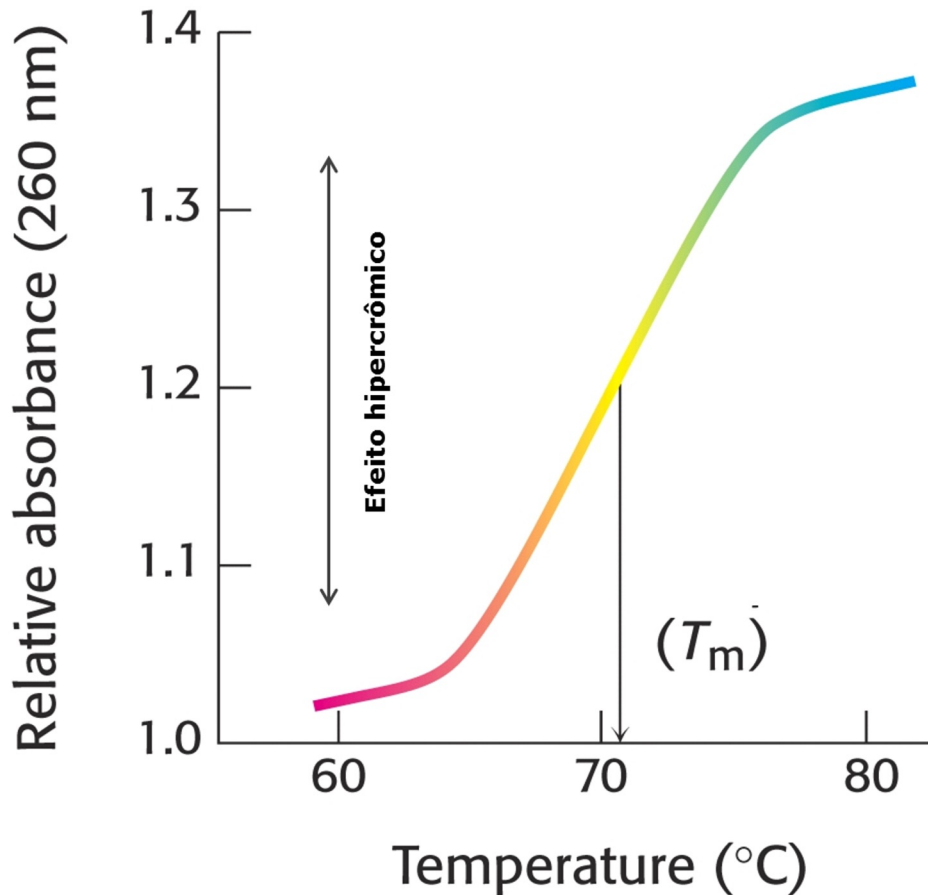
**Calor**  
**Tratamento com álcali**



# Desnaturação: rompimento das ligações de H entre os pares de base



# Desnaturação do DNA

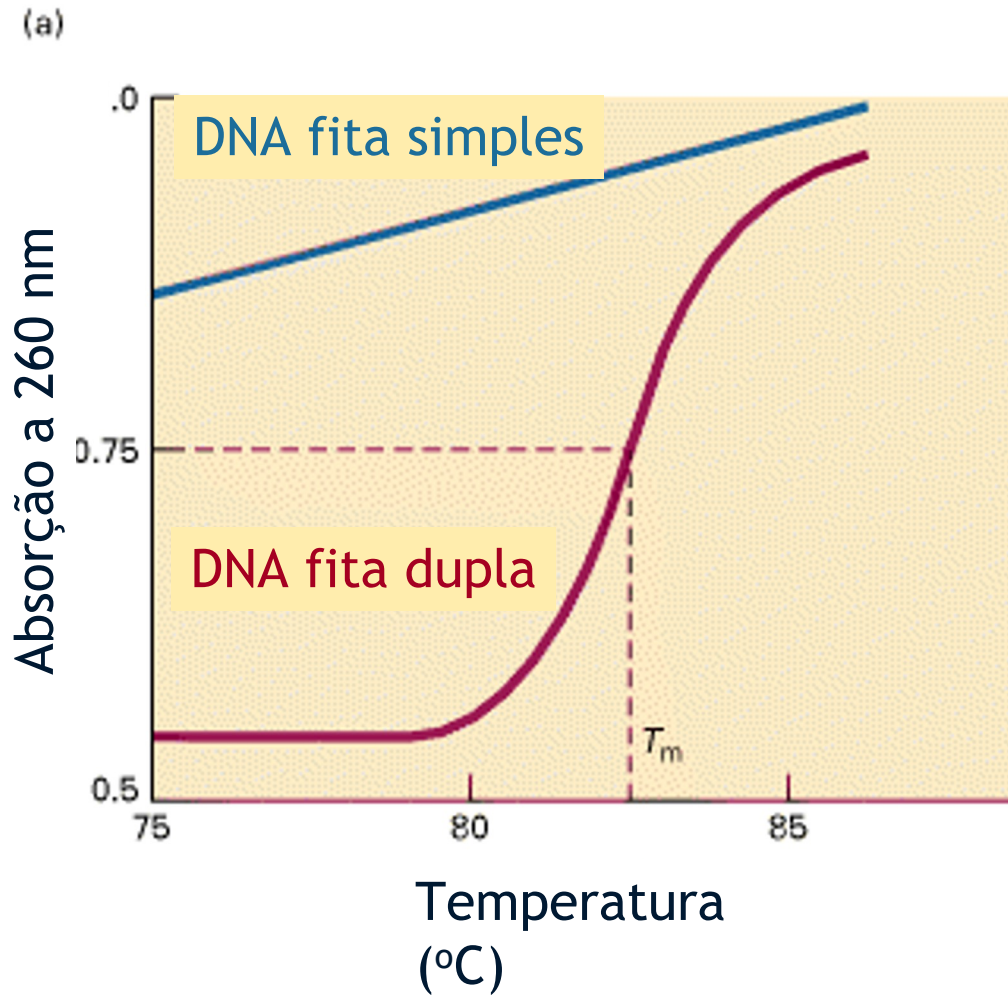


Rompimento das ligações de H entre as bases

$T_m$  = Temperatura de fusão (50% do DNA está desnaturado)

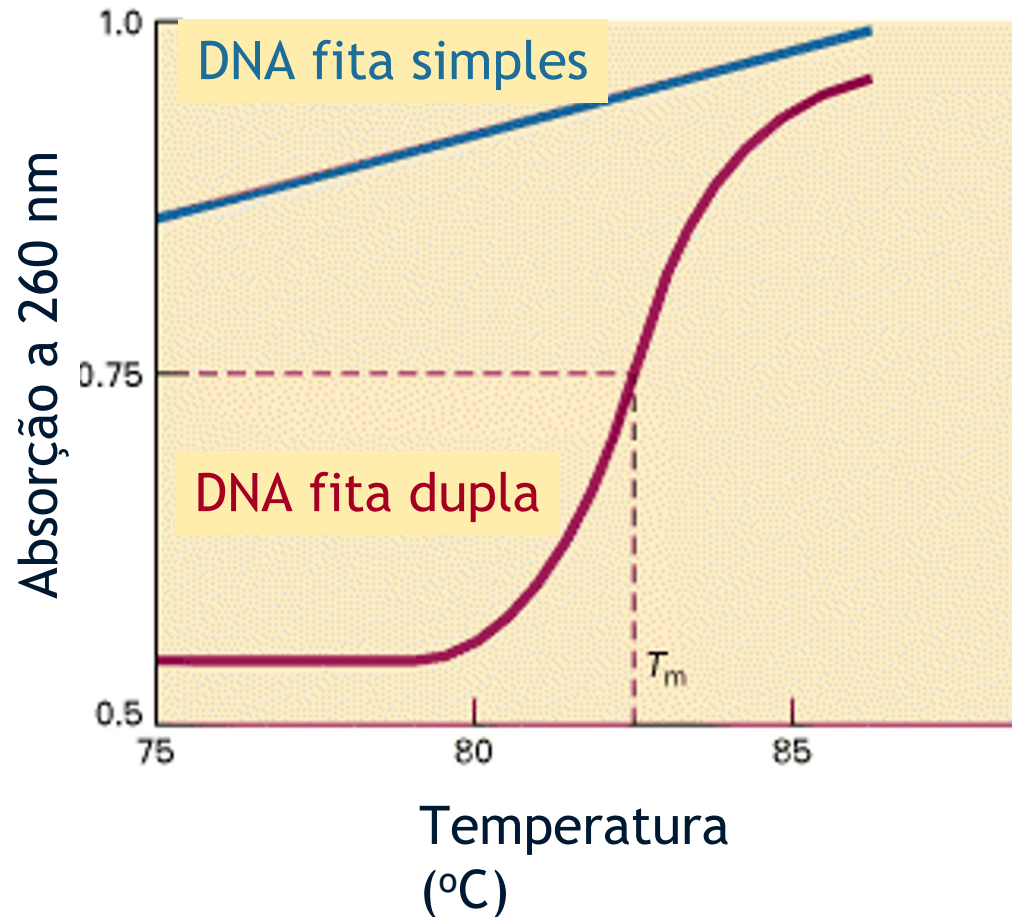
Efeito hiper-crômico (aumento da absorvância pela maior exposição dos anéis das bases)

# Desnaturação do DNA





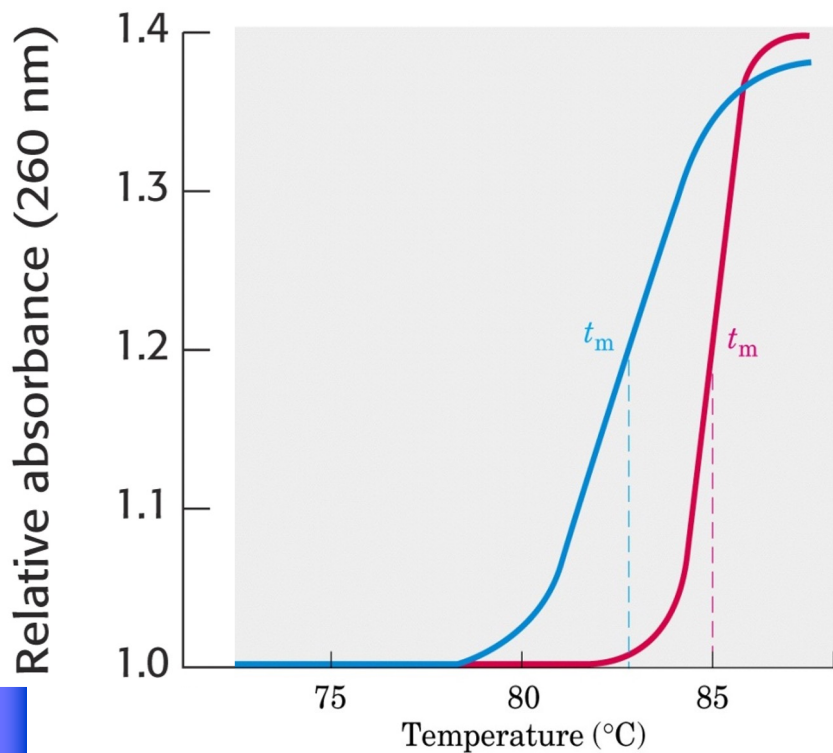
# Desnaturação do DNA



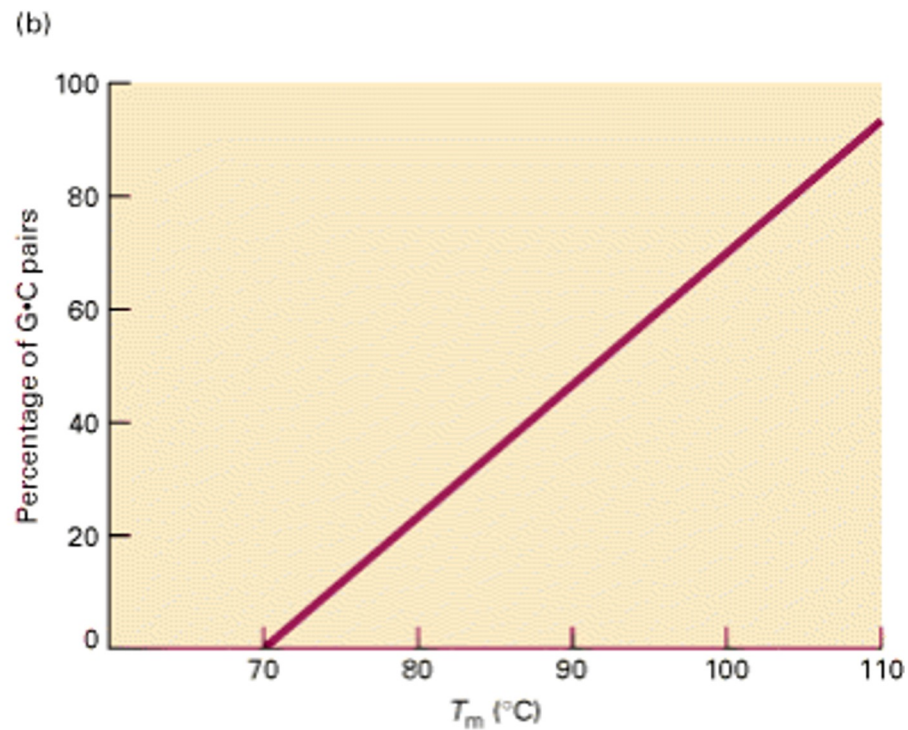
$T_m$ : temperatura em que 50% das fitas estão dissociadas



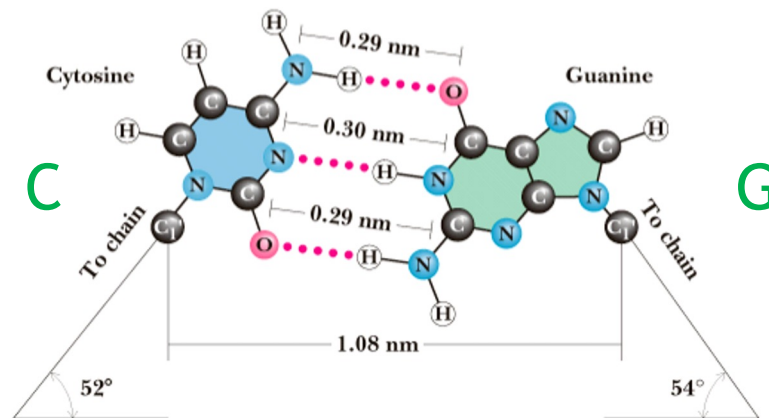
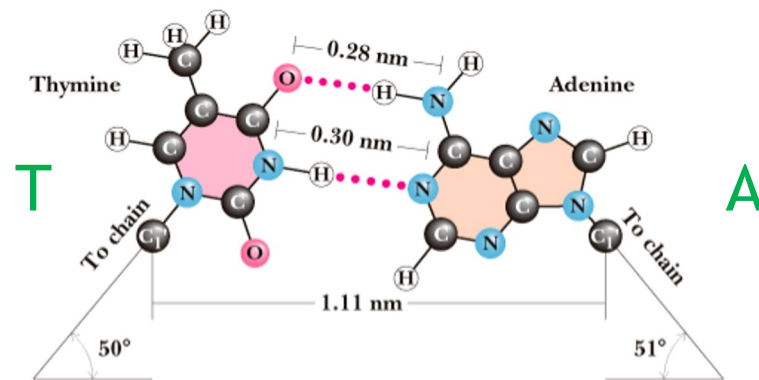
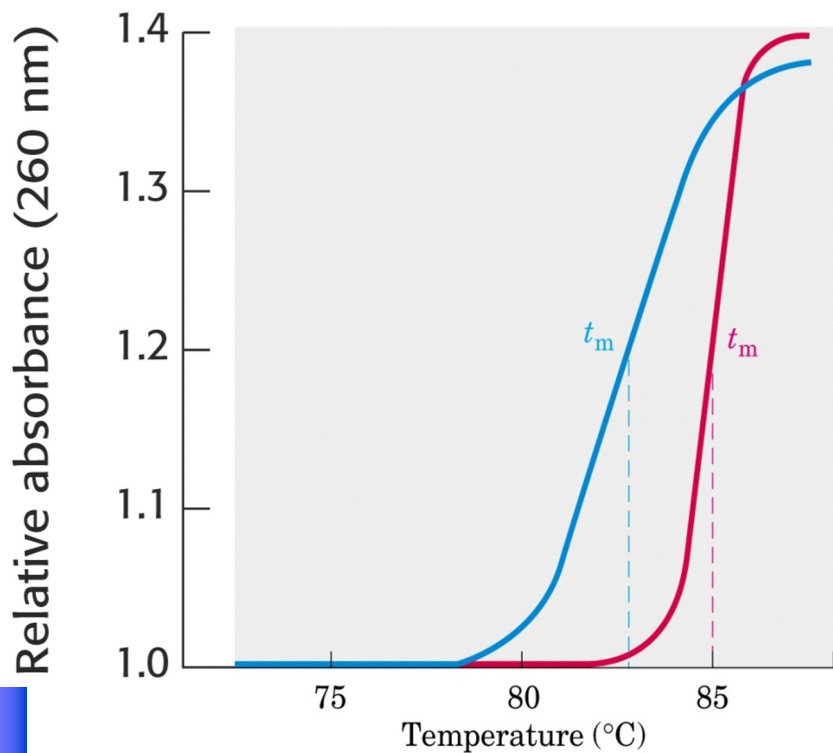
# $T_m$ varia com %G+C



Por quê?

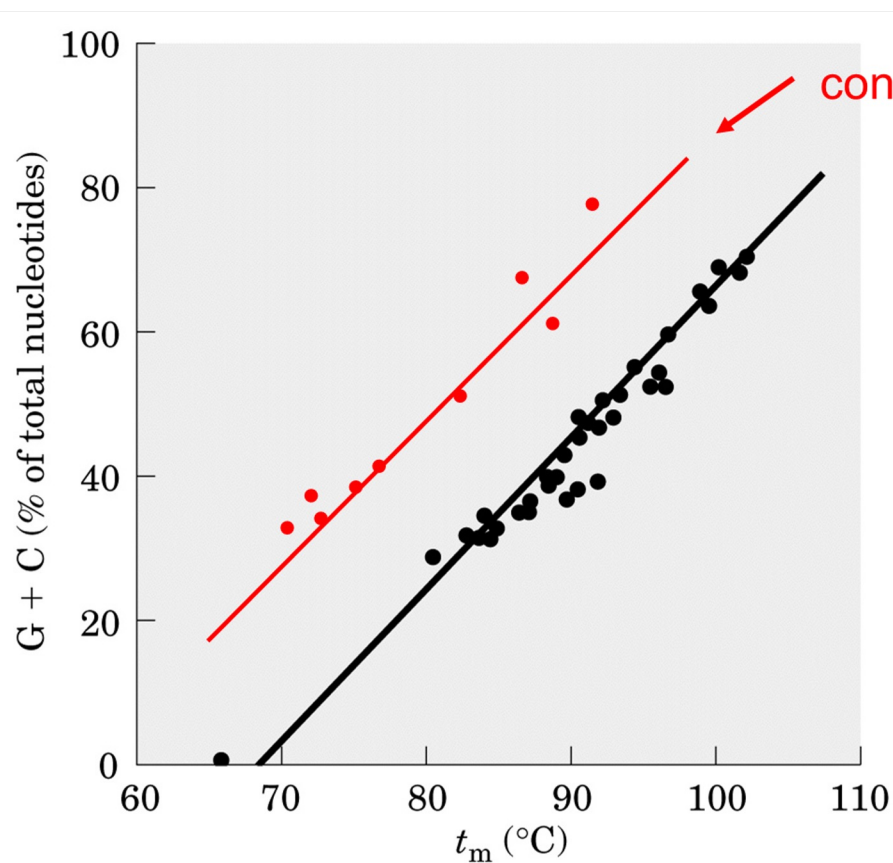


# T<sub>m</sub> varia com %G+C



Por quê?

# T<sub>m</sub> varia com a concentração de sal

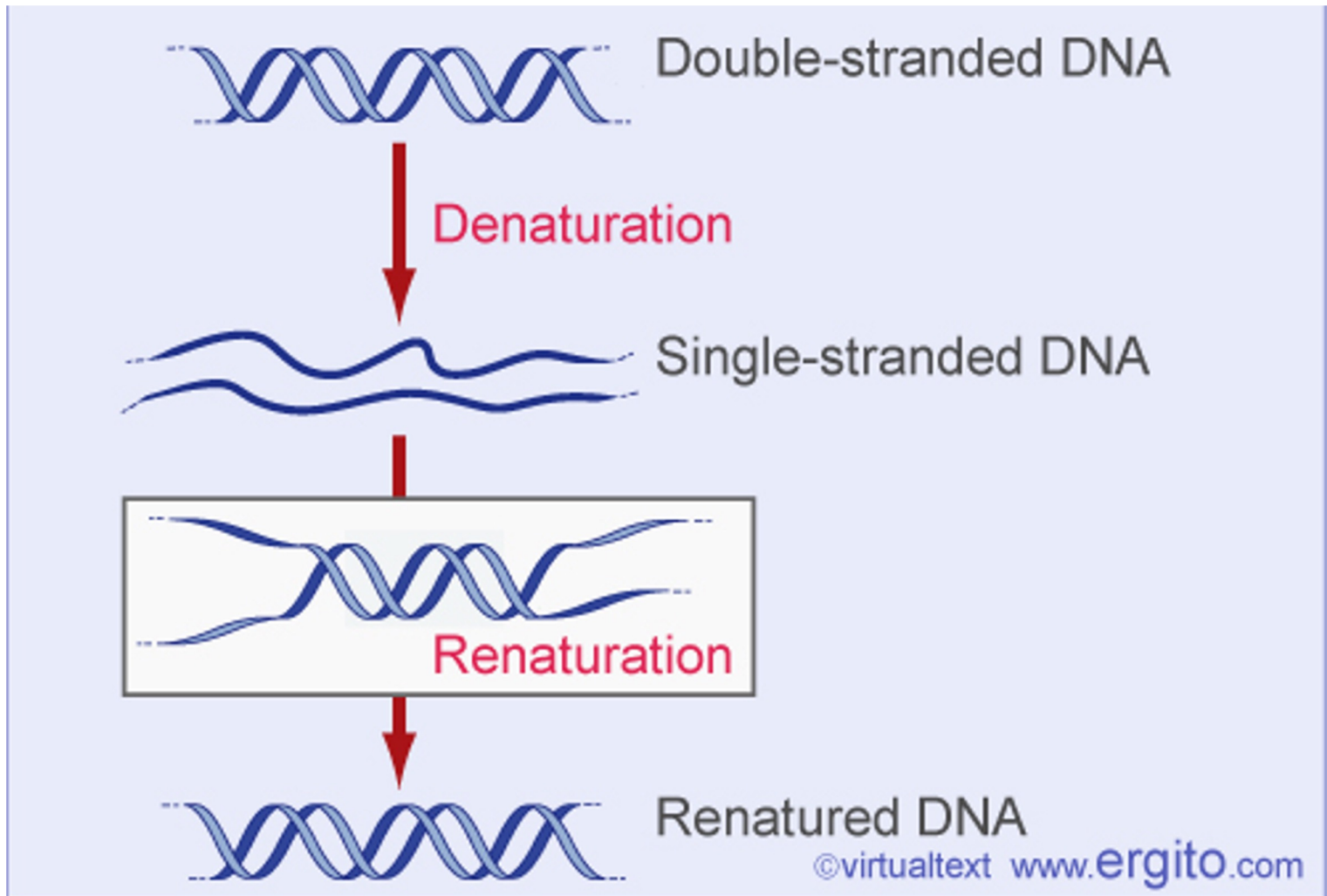


Baixa  
concentração  
de sal

↓sal □ repulsão eletrostática  
das fitas do DNA carregado  
negativamente favorece a  
separação (diminui a T<sub>m</sub>)

↑sal □ A dupla fita é mais  
estável (aumenta a T<sub>m</sub>)

# Desnaturação é reversível





# Estrutura do RNA

# RNAs são muito mais diversos e heterogêneos que DNA!

- **Funções variadas**

- ❑ estoque de informação genética (alguns vírus)
- ❑ “transporte” da informação entre DNA e proteínas
- ❑ síntese proteica
- ❑ regulação da expressão gênica em diferentes níveis

- **Alguns tem atividade catalítica**

- ❑ Splicing, ligações peptídicas no ribossomo, RNases

- **Evoluíram antes do DNA?**

- ❑ **MUNDO DE RNA**

DNA

RNA

Ligação  
fosfodiester

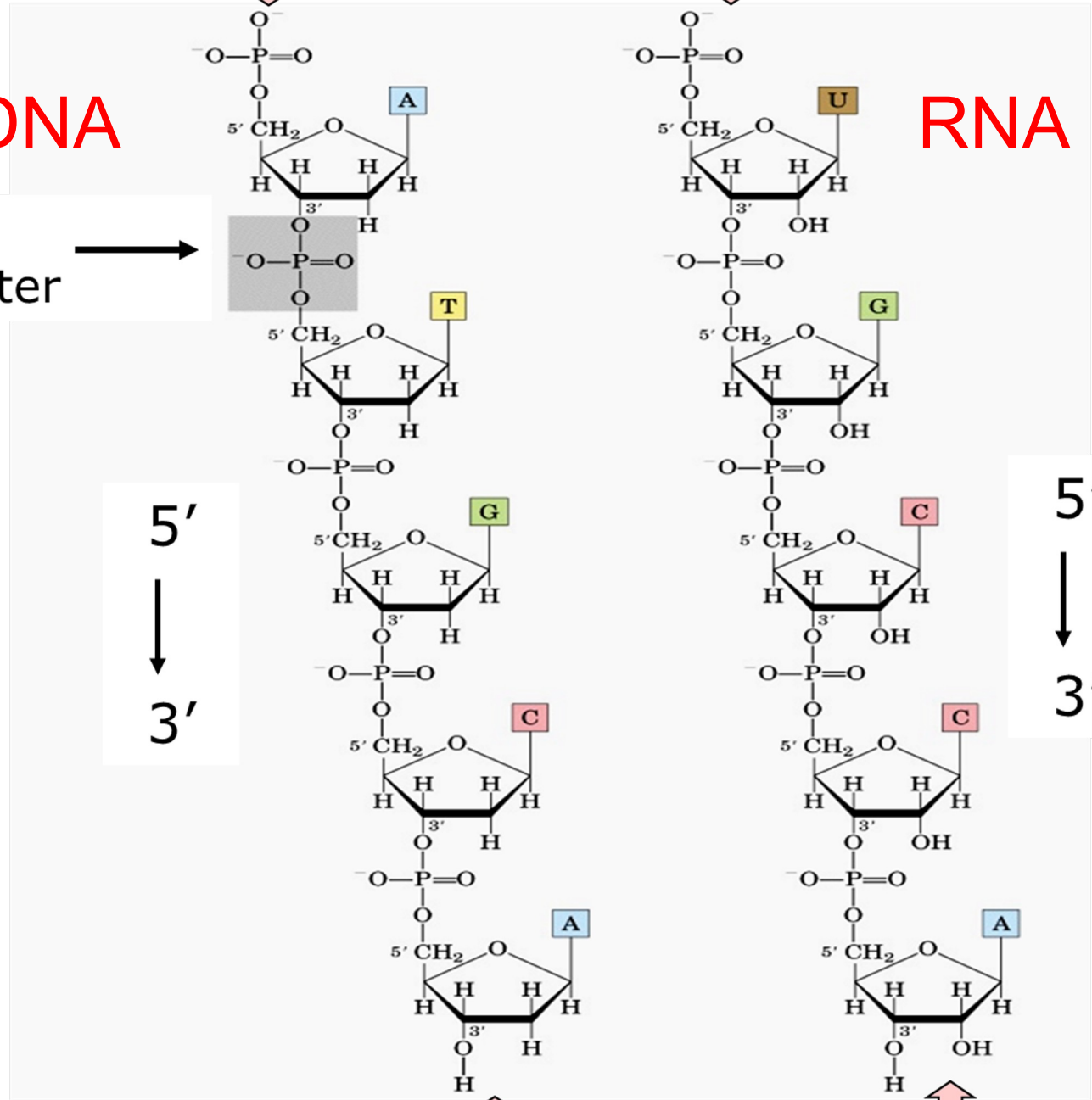


Extremidade 5'

Extremidade 3'

5'  
↓  
3'

5'  
↓  
3'

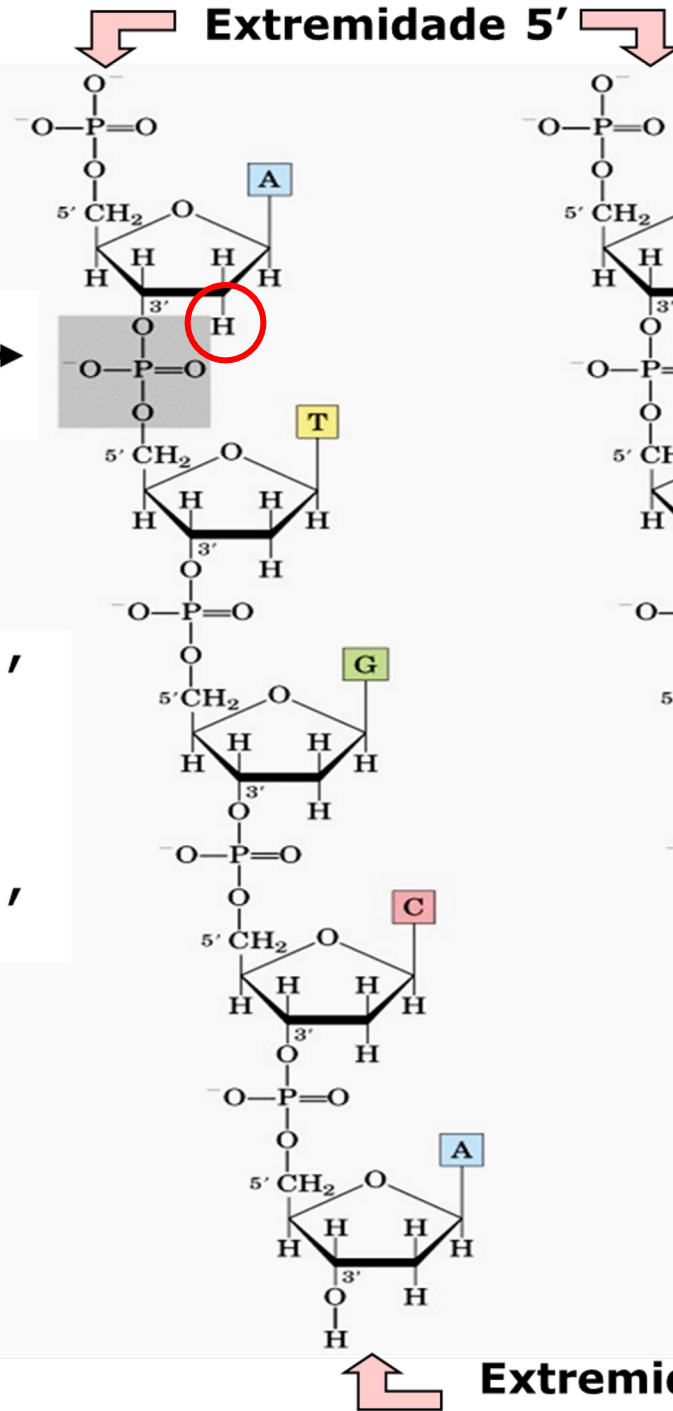




DNA

RNA

Ligação  
fosfodiester

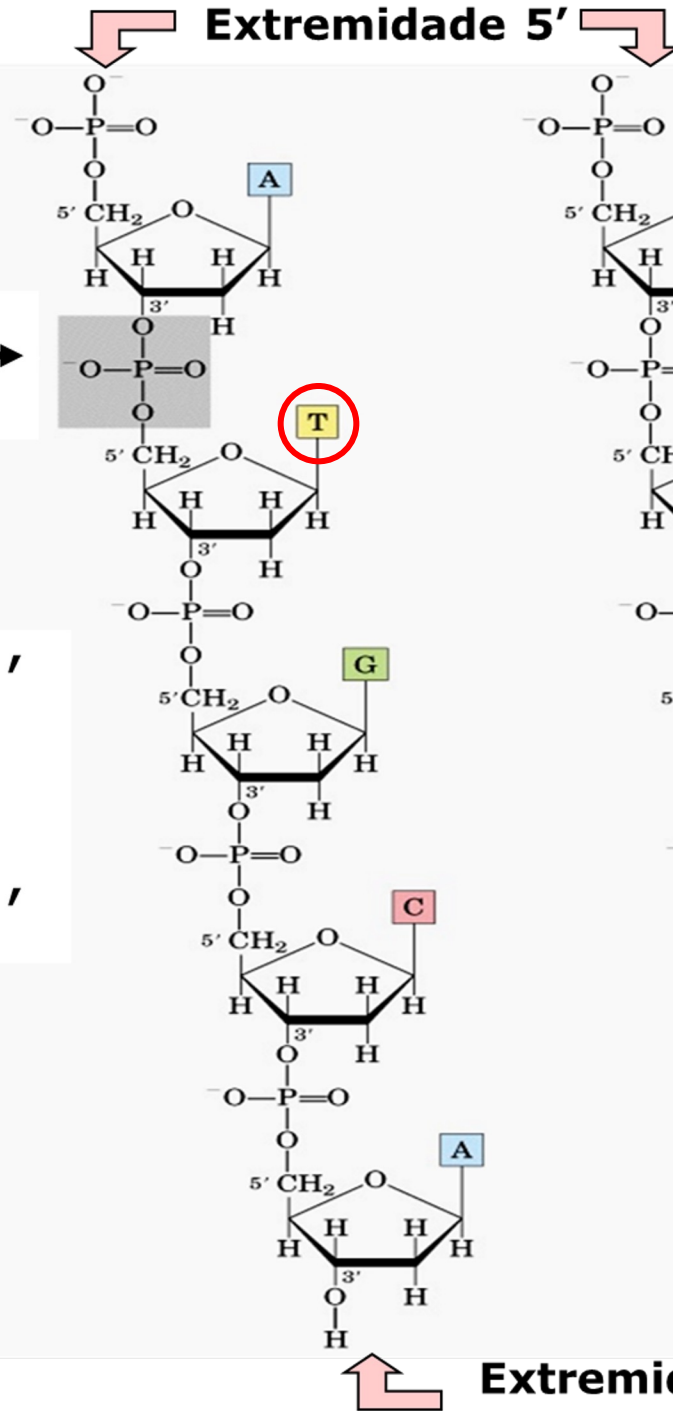




DNA

RNA

Ligação  
fosfodiester

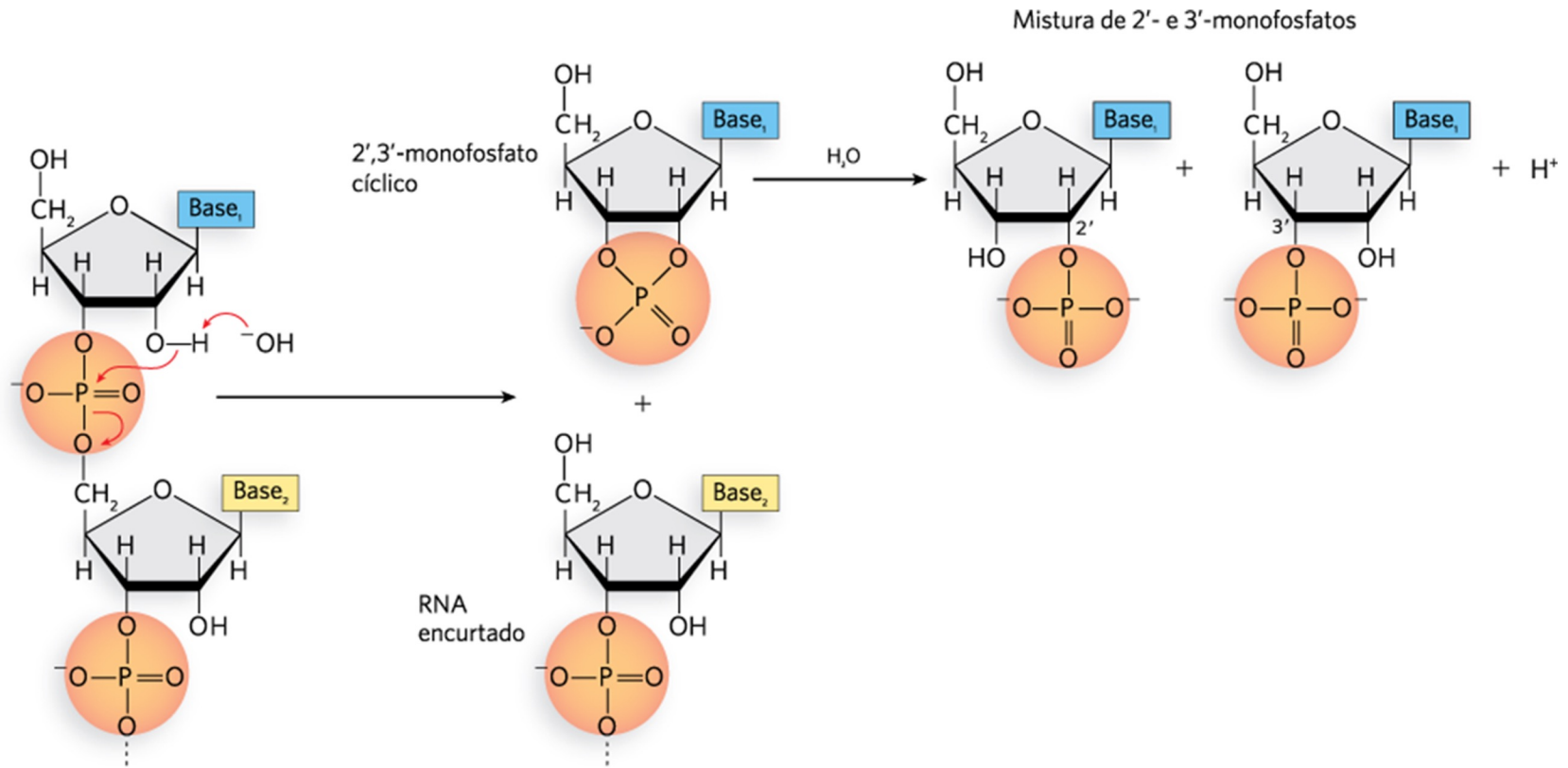


5'  
↓  
3'

5'  
↓  
3'

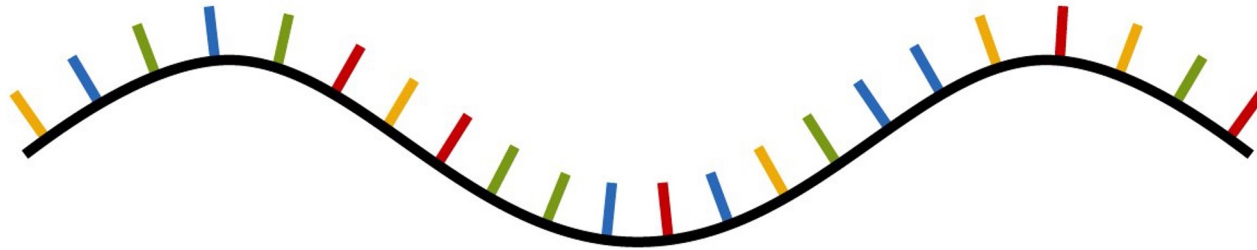
Extremidade 3'

# RNA pode ser hidrolisado em condições alcalinas

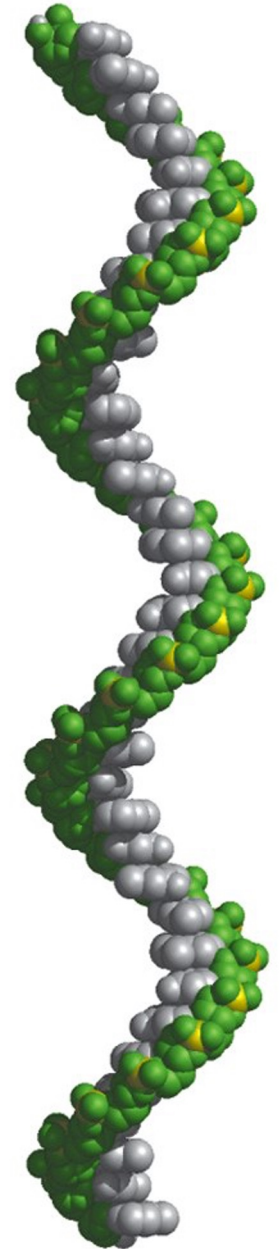
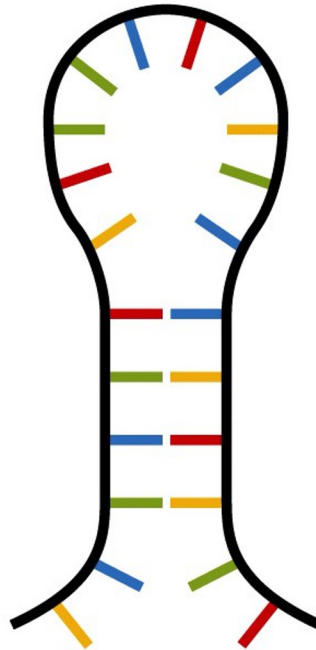


**FIGURA 6-7 A hidrólise do RNA.** O grupamento 2'-hidroxila pode ser ativado como um nucleófilo em condições alcalinas ( $\text{pH} > 7$ ) ou por ribonucleases. O produto 2',3'-monofosfato cíclico é adicionalmente hidrolisado formando uma mistura de 2'- e 3'-monofosfatos.

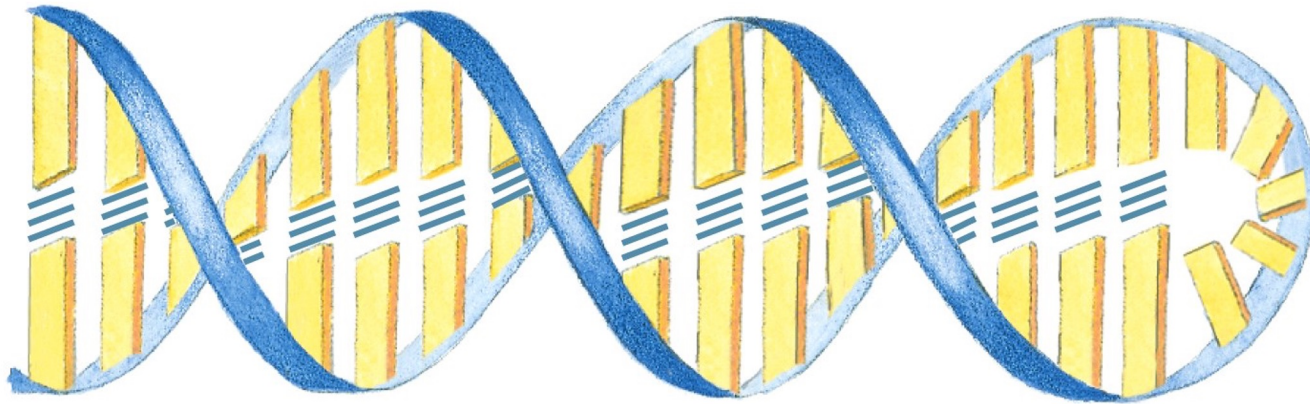
# Estrutura de RNA



Fita simples pode se dobrar e parear entre si

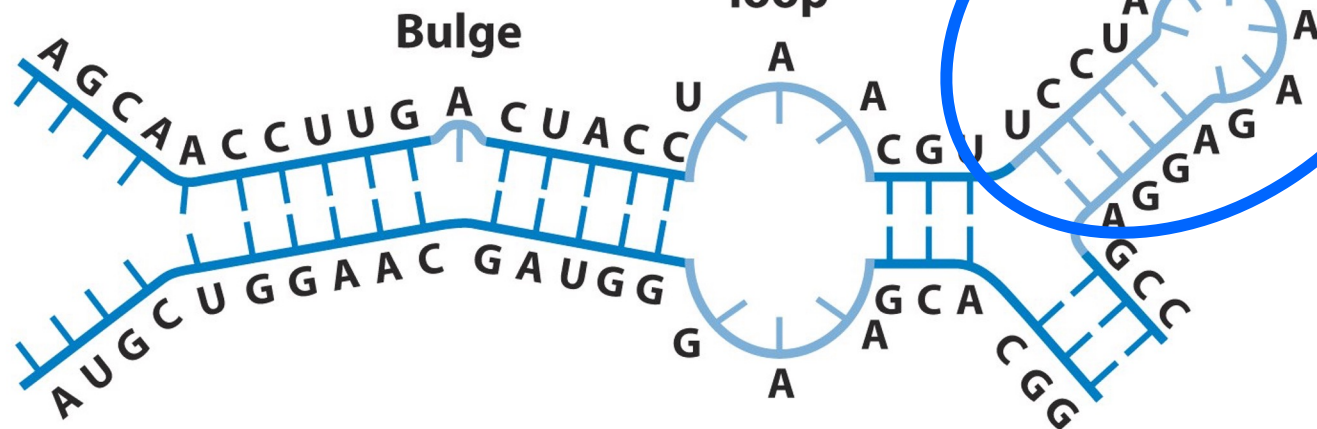


# Estrutura secundária de RNA

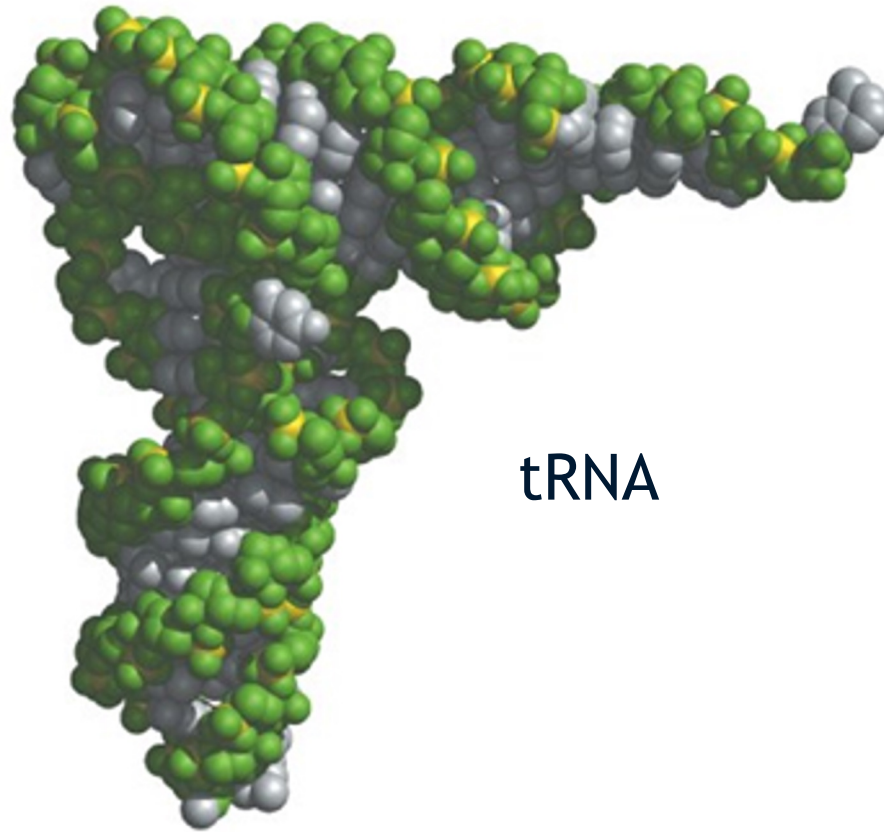


## Hairpin double helix

Single strands



# Estrutura terciária de RNA





# Classes de RNAs

RNAs codificadores de proteínas:

mRNA (RNA mensageiro)

RNAs não codificadores ou funcionais:

tRNA (RNA transportador)

rRNA (RNA ribossomal)

outros ncRNAs

**QUADRO 5.2** Moléculas de RNA em *E. coli*

Tipo	Quantidade Relativa (%)	Coefficiente de Sedimentação (S)	Massa (kd)	Número de Nucleotídeos
RNA ribossômico (rRNA)	80	23	$1,2 \times 10^3$	3.700
		16	$0,55 \times 10^3$	1.700
		5	$3,6 \times 10^1$	120
RNA transportador (tRNA)	15	4	$2,5 \times 10^1$	75
RNA mensageiro (mRNA)	5		Heterogêneo	

# Classes de RNA funcionais

RNA é o produto final

- tRNA: transporta os aminoácidos ativados até os ribossomos
  - rRNA: principal componente dos ribossomos
  - snoRNA\* (RNA nucleolar pequeno): maturação de ribossomos e tRNAs
  - snRNA\* (RNA nuclear pequeno): processamento do mRNA
  - sRNA (*small* RNA): modula tradução e estabilidade de mRNAs
  - miRNA\* (micro RNA)
  - siRNA\* (RNA de interferência)
  - outros....
- } silenciamento gênico

\* apenas em eucariotos

# Classes de ncRNAs

- tRNA: transporta os aminoácidos até os ribossomos
- rRNA: principal componente dos ribossomos
- snoRNA\* (RNA nucleolar pequeno): modificação de ribossomos e tRNAs
- snRNA\* (RNA nuclear pequeno): processamento do mRNA
- sRNA (*small RNA*): regulação e estabilidade de mRNAs
- miRNA\* (micro RNA) } silenciamento
- siRNA\* (RNA de interferência) } gênico
- outros...

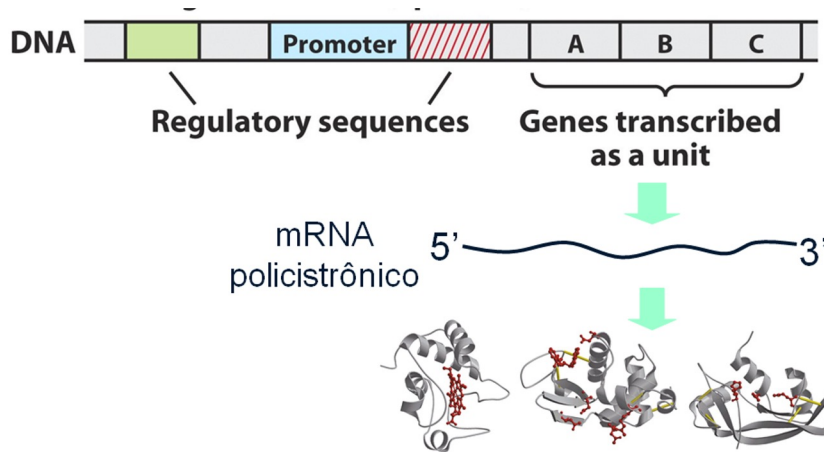
Biologia Molecular

\* apenas em eucariotos

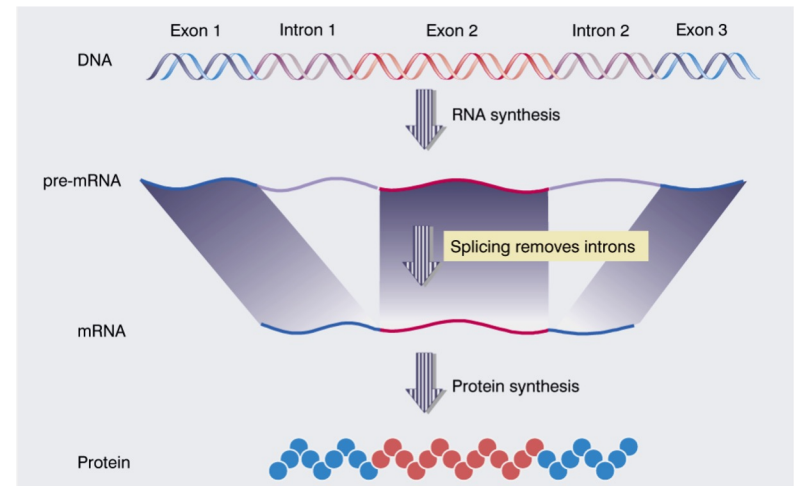


# RNA mensageiro (mRNA)

- Informação para a síntese de proteínas
- Um ou mais genes em bactérias

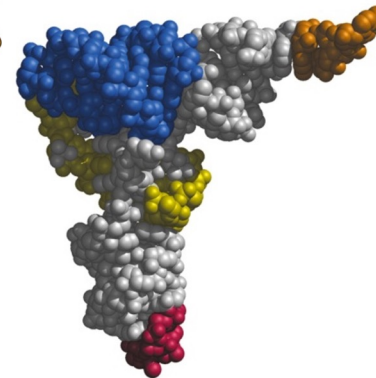
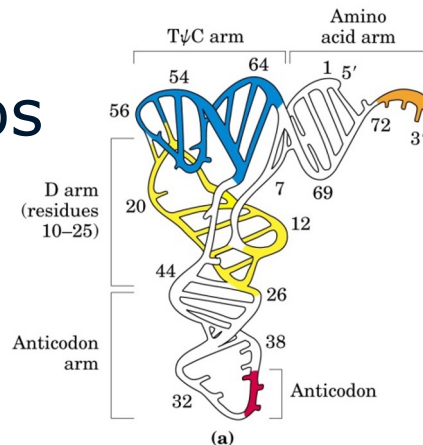
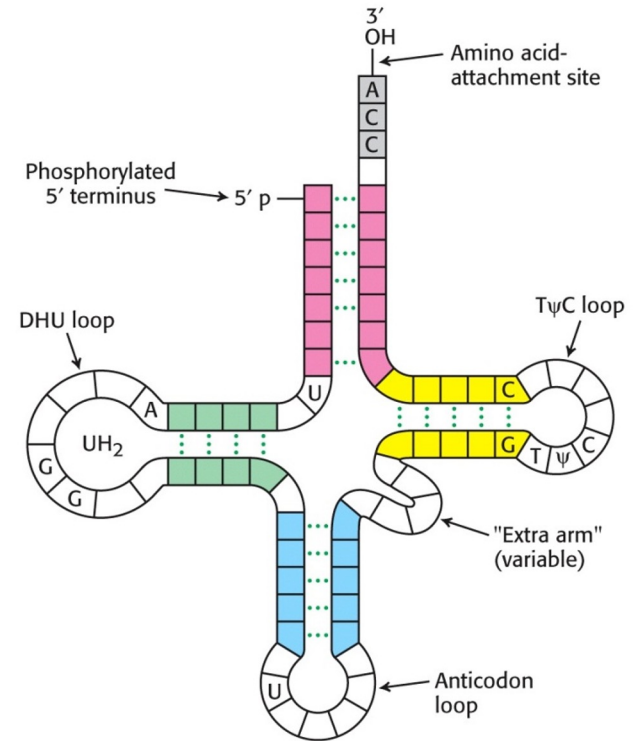


- Processamento no núcleo (eucariotos)

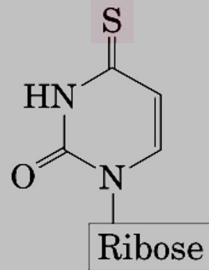


# RNA transportador (tRNA)

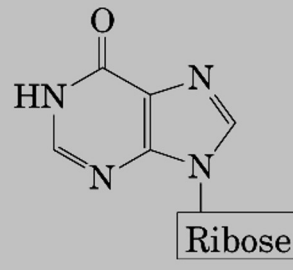
- Estrutura secundária com grampos e alças formando um trevo
- Bases modificadas depois da transcrição
- ~ 70-100 nucleotídeos



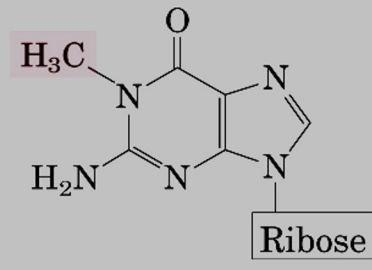
# Bases modificadas no tRNA



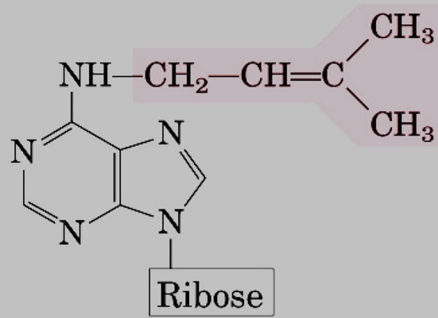
4-Thiouridine (S<sup>4</sup>U)



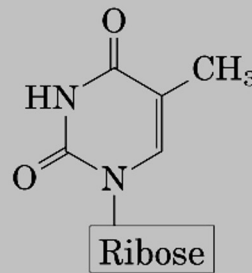
Inosine (I)



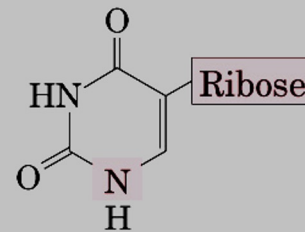
1-Methylguanosine (m<sup>1</sup>G)



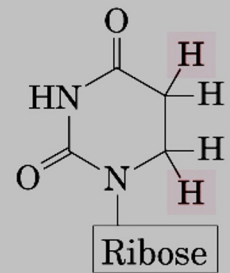
N<sup>6</sup>-Isopentenyladenosine (i<sup>6</sup>A)



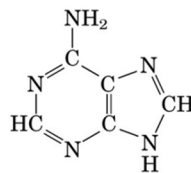
Ribothymidine (T)



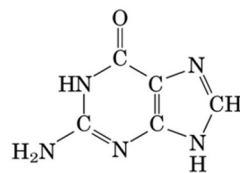
Pseudouridine (ψ)



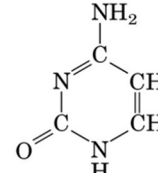
Dihydrouridine (D)



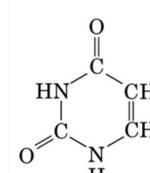
Adenine



Guanine



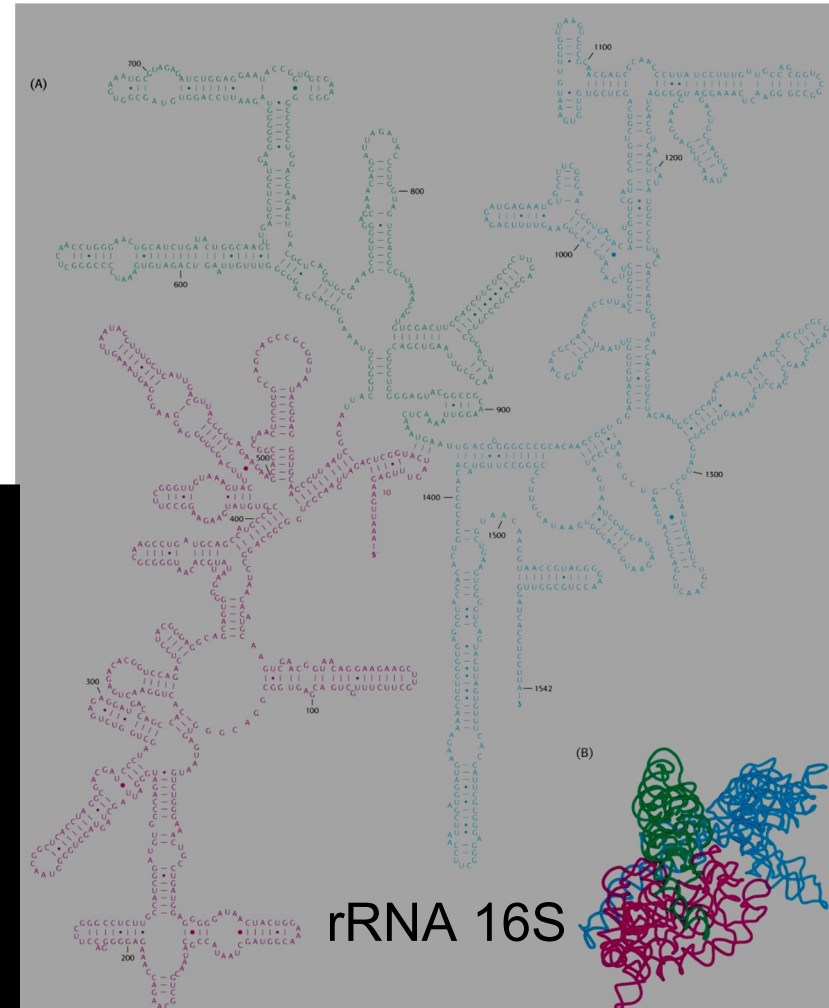
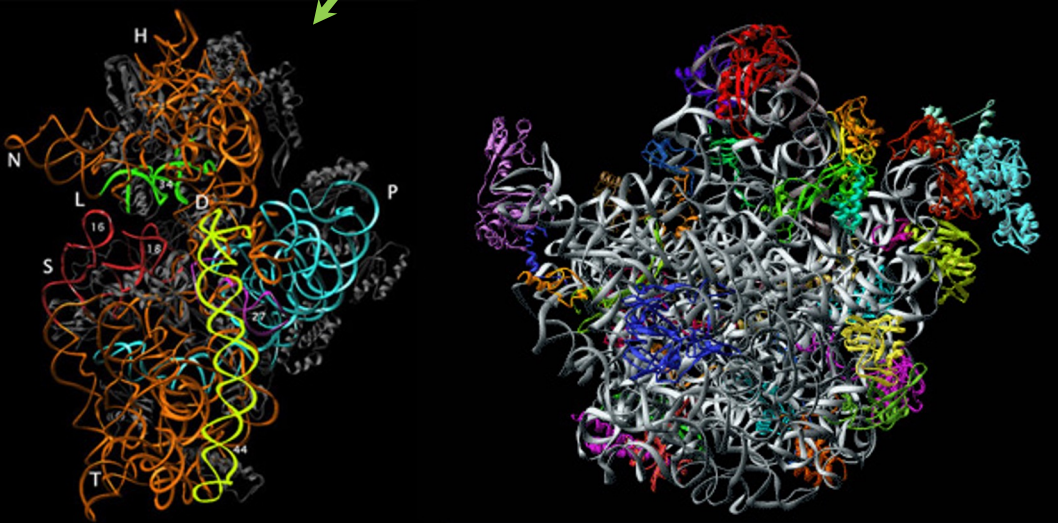
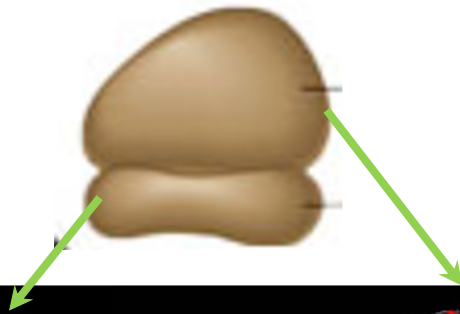
Cytosine



Uracil

# RNA ribossomal (rRNA)

- 90% do RNA total da célula
- Associado a proteínas ribossomais



# RNA

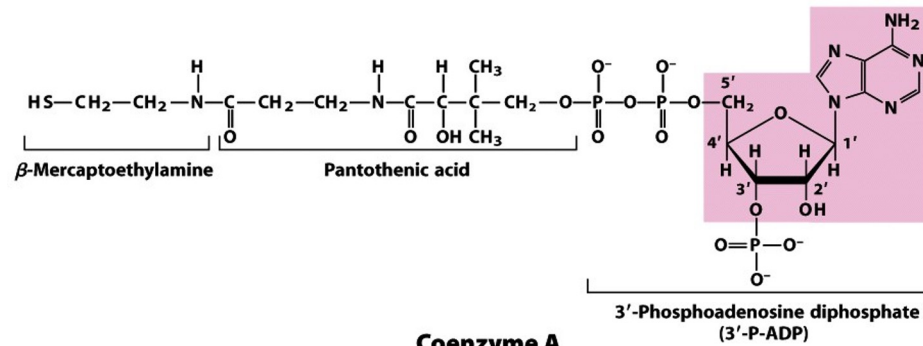
- Pode formar estruturas muito mais complexas do que a dupla hélice do DNA
- Estruturas dependem da sequência e do pareamento entre bases na mesma fita
- Funções diferentes para estruturas diferentes!



# Nucleotídeos não estão apenas em ácidos nucleicos!

- ATP e GTP
- NAD(H) e NADP(H)
- FAD/FADH<sub>2</sub>
- Coenzima A
- Nucleotídeos cíclicos
  - ❑ cAMP
  - ❑ cGMP
  - ❑ c-diGMP (bactérias)
- Outros
  - ❑ (p)ppGpp (bactérias)

# Cofatores de enzimas



## Coenzyma A

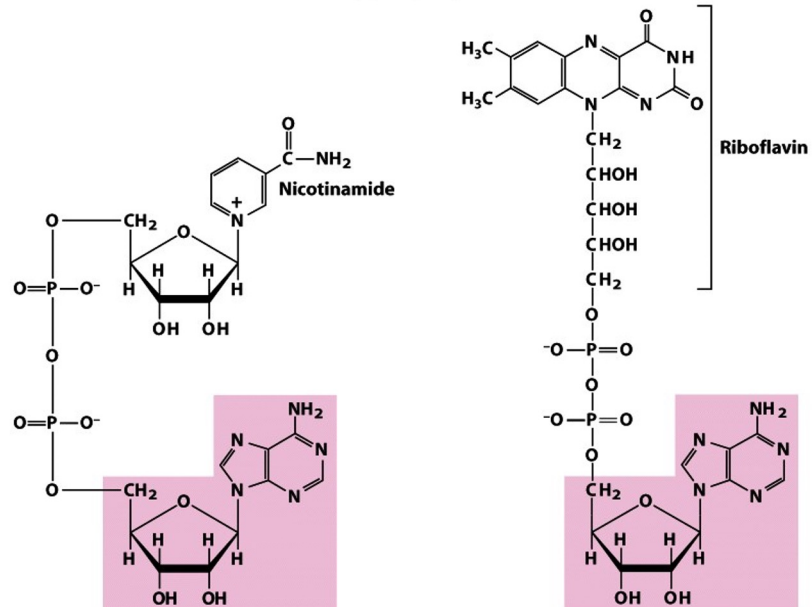


Figure 8-38

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# Função regulatória

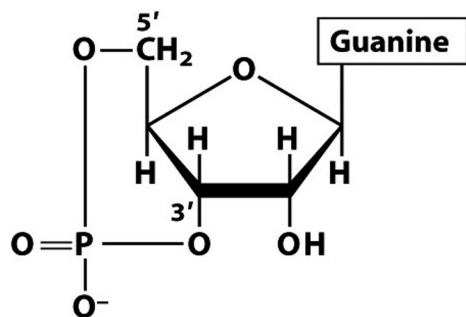
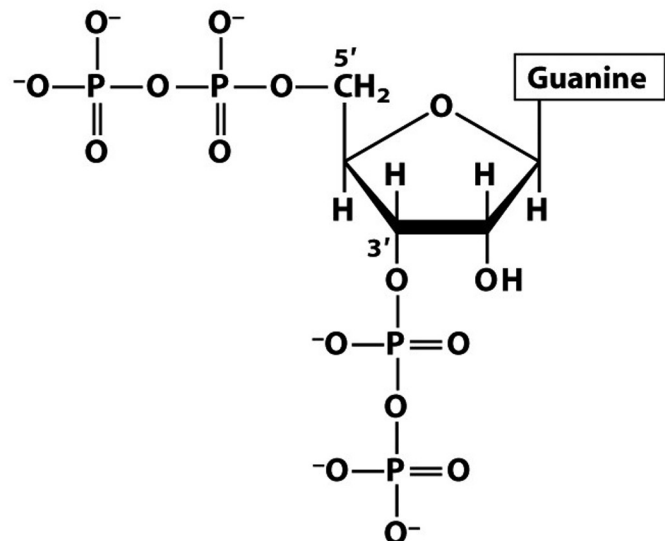
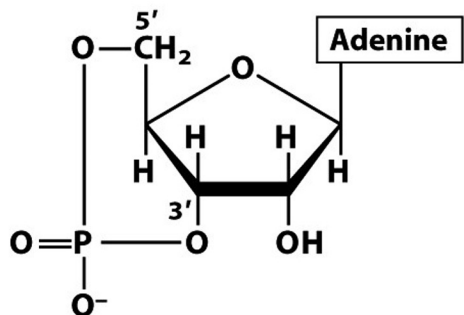


Figure 8-39

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# The lost language of the RNA World

Nelson and Breaker, *Sci. Signal.* **10**, eam8812 (2017) 13 June 2017

The possibility of an RNA World is based on the notion that life on Earth passed through a primitive phase without proteins, a time when all genomes and enzymes were composed of ribonucleic acids. Numerous apparent vestiges of this ancient RNA World remain today, including many nucleotide-derived coenzymes, self-processing ribozymes, metabolite-binding riboswitches, and even ribosomes. Many of the most common signaling molecules and second messengers used by modern organisms are also formed from RNA nucleotides or their precursors. For example, nucleotide derivatives such as cAMP, ppGpp, and ZTP, as well as the cyclic dinucleotides c-di-GMP and c-di-AMP, are intimately involved in signaling diverse physiological or metabolic changes in bacteria and other organisms. We describe the potential diversity of this "lost language" of the RNA World and speculate on whether additional components of this ancient communication machinery might remain hidden though still very much relevant to modern cells.

A

## RNA-derived compounds

### Coenzymes

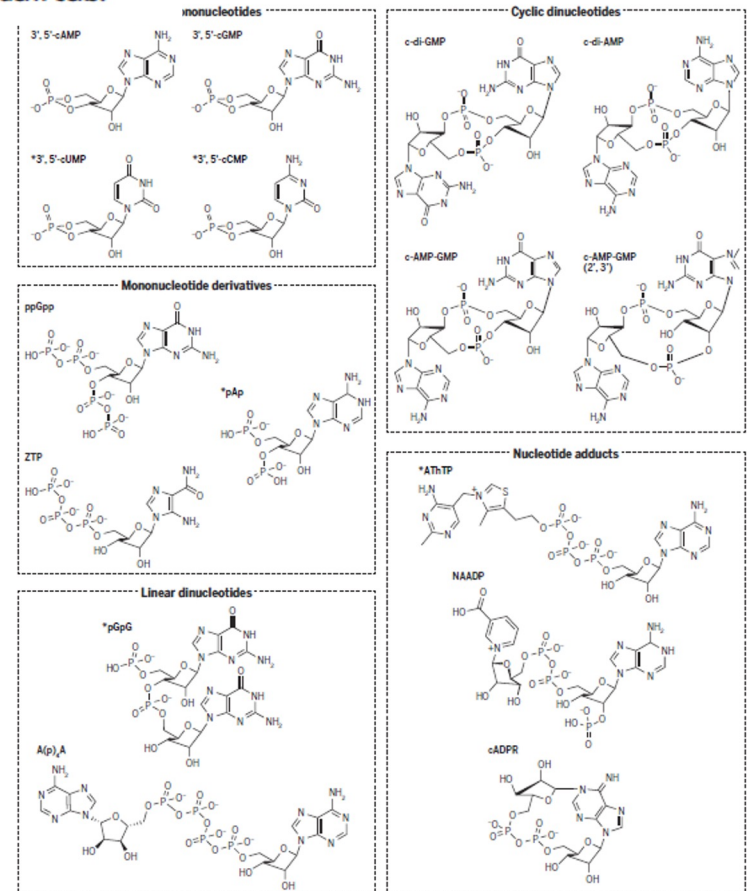
Adenosylcobalamin  
Aquacobalamin  
Thiamin pyrophosphate  
Flavin mononucleotide  
S-Adenosylmethionine  
Molybdenum cofactor  
Tungsten cofactor  
Tetrahydrofolate  
S-Adenosylhomocysteine

### Nucleotide derivatives

Guanine  
Adenine  
Prequeuosine<sub>1</sub>  
2'-Deoxyguanosine

### Signaling molecules

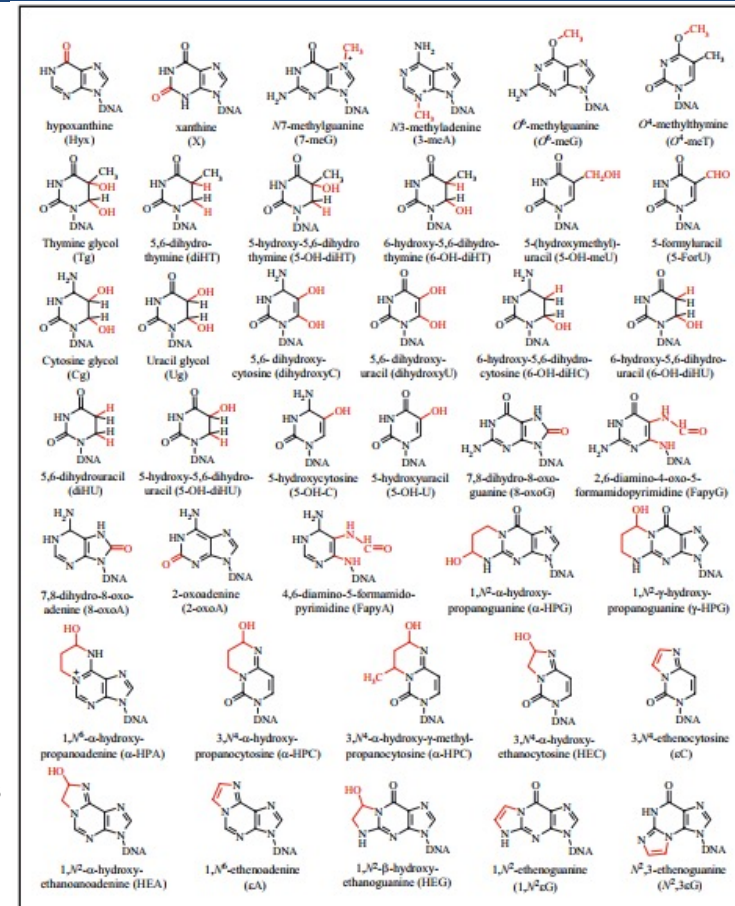
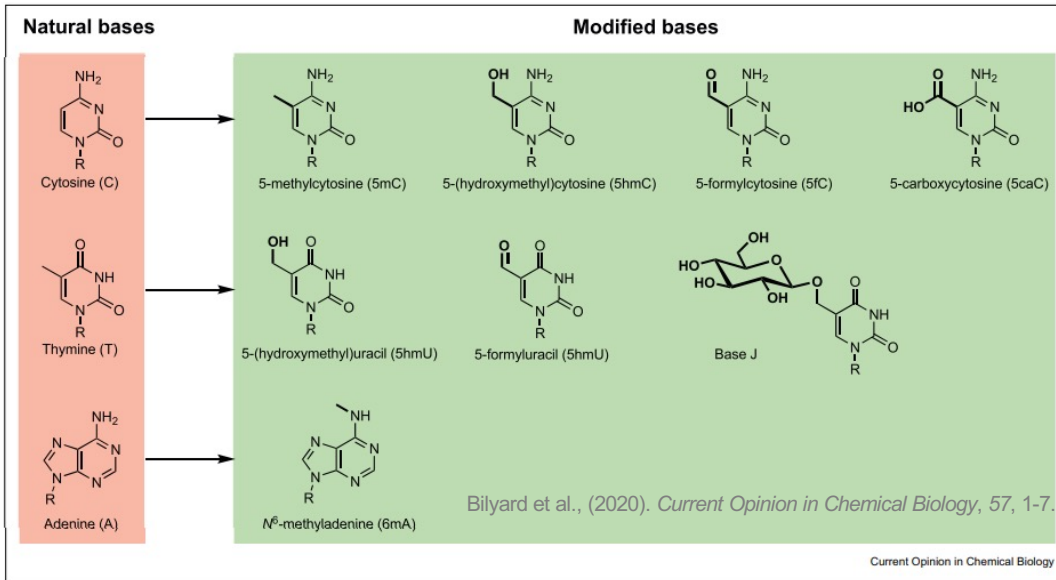
Cyclic di-GMP  
Cyclic di-AMP  
Cyclic AMP-GMP  
ZTP



**Fig. 2. Known natural signaling compounds derived from RNA nucleotides or their precursors.** The compound ppGpp, which carries a pyrophosphate both at the 5' and 3' positions, is derived from a pentaphosphate precursor (pppGpp) that carries a triphosphate on the 5' position and is not shown. ZTP is AICA ribonucleoside 5'-triphosphate; ATHTP is adenosine thiamine triphosphate. Asterisks denote putative signaling compounds for which biological roles and phylogenetic distributions have not been well established.

# Curiosidade: bases nitrogenadas dos nucleotídeos podem sofrer modificações

Ex de modificações naturais que ocorrem nas bases nitrogenadas do DNA de eucariotos.



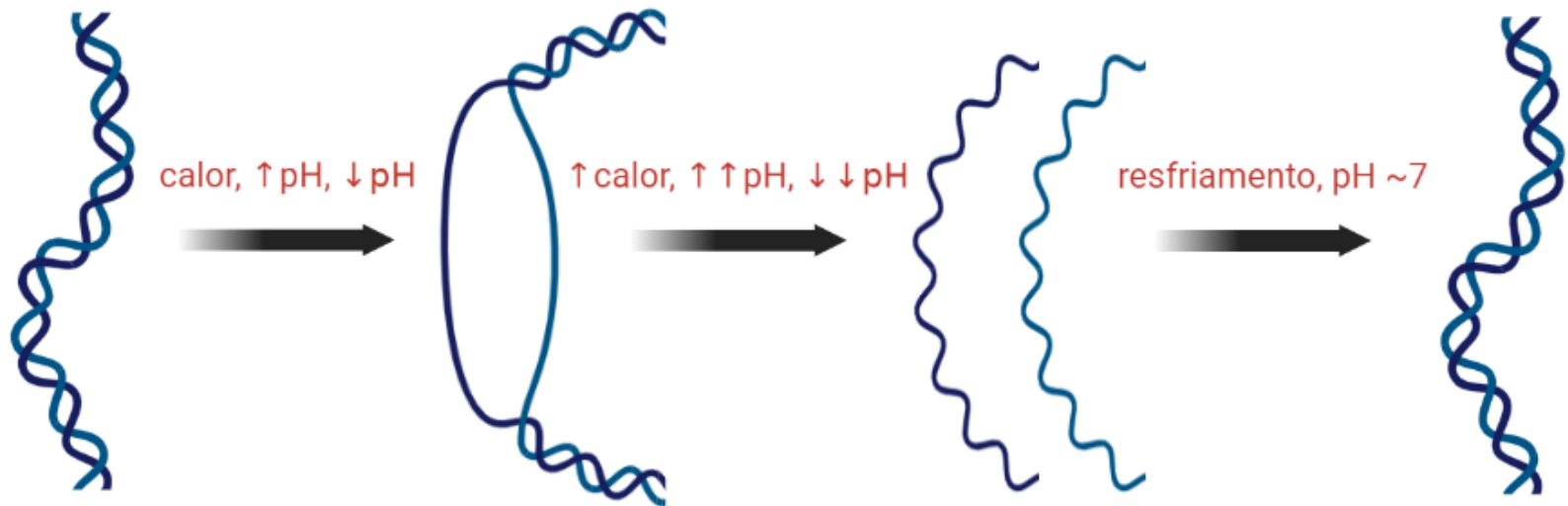
As principais modificações endógenas que ocorrem nas bases nitrogenadas do DNA dos organismos vivos (procariotos e eucariotos) estão destacadas em vermelho.

Krwawicz et al., (2007). *Acta Biochimica Polonica*, 54(3), 413-434.

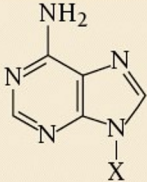
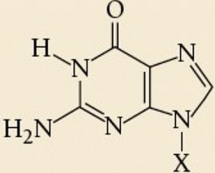
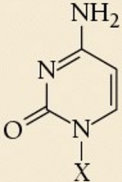
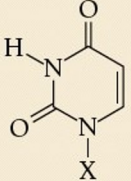
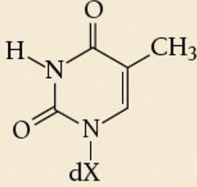




# Variações de temperatura e pH influenciam o processo de desnaturação e renaturação do DNA



**Table 3-1** Names and Abbreviations of Nucleic Acid Bases, Nucleosides, and Nucleotides

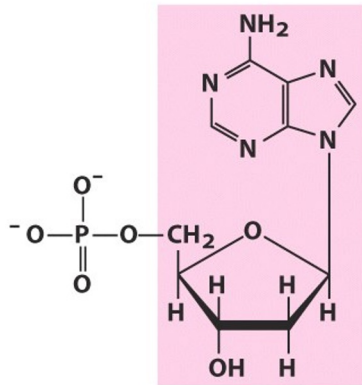
Base Formula	Base (X = H)	Nucleoside (X = ribose <sup>a</sup> )	Nucleotide <sup>b</sup> (X = ribose phosphate <sup>a</sup> )
	Adenine Ade A	Adenosine Ado A	Adenylic acid Adenosine monophosphate AMP
	Guanine Gua G	Guanosine Guo G	Guanylic acid Guanosine monophosphate GMP
	Cytosine Cyt C	Cytidine Cyd C	Cytidylic acid Cytidine monophosphate CMP
	Uracil Ura U	Uridine Urd U	Uridylic acid Uridine monophosphate UMP
	Thymine Thy T	Deoxythymidine dThd dT	Deoxythymidylic acid Deoxythymidine monophosphate dTMP

<sup>a</sup>The presence of a 2'-deoxyribose unit in place of ribose, as occurs in DNA, is implied by the prefixes "deoxy" or "d." For example, the deoxy-nucleoside of adenine is deoxyadenosine or dA. However, for thymine-containing residues, which rarely occur in RNA, the prefix is redundant and may be dropped. The presence of a ribose unit may be explicitly implied by the prefix "ribo."

<sup>b</sup>The position of the phosphate group in a nucleotide may be explicitly specified as in, for example, 3'-AMP and 5'-GMP.

**Table 3-1 Fundamentals of Biochemistry, 2/e**

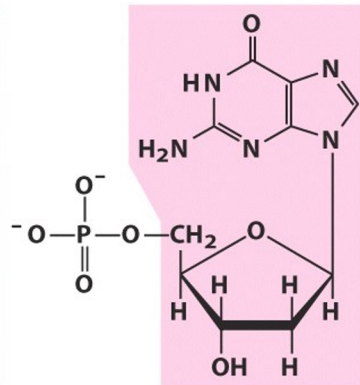
© 2006 John Wiley & Sons



**Nucleotide:** Deoxyadenylate  
(deoxyadenosine  
5'-monophosphate)

**Symbols:** A, dA, dAMP

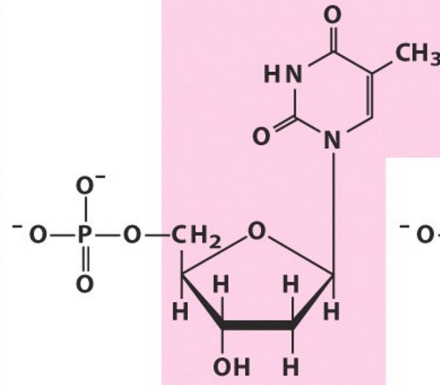
**Nucleoside:** Deoxyadenosine



**Nucleotide:** Deoxyguanylate  
(deoxyguanosine  
5'-monophosphate)

**Symbols:** G, dG, dGMP

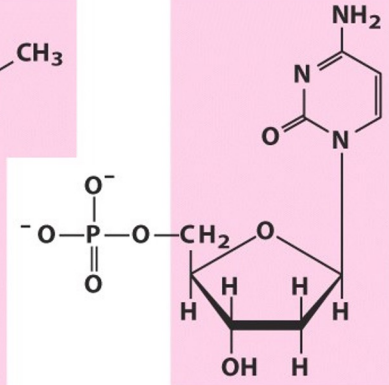
**Nucleoside:** Deoxyguanosine



**Nucleotide:** Deoxythymidylate  
(deoxythymidine  
5'-monophosphate)

**Symbols:** T, dT, dTMP

**Nucleoside:** Deoxythymidine

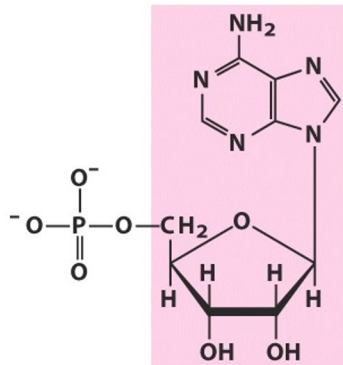


**Nucleotide:** Deoxycytidylate  
(deoxycytidine  
5'-monophosphate)

**Symbols:** C, dC, dCMP

**Nucleoside:** Deoxycytidine

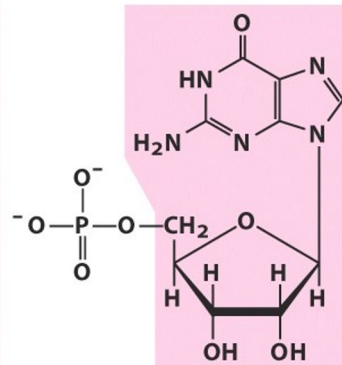
### (a) Deoxyribonucleotides



**Nucleotide:** Adenylate (adenosine  
5'-monophosphate)

**Symbols:** A, AMP

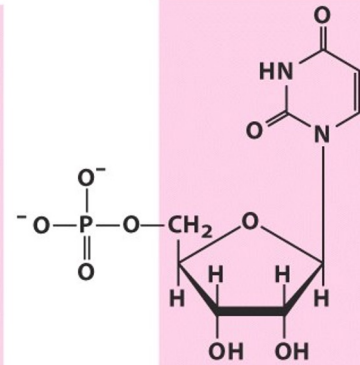
**Nucleoside:** Adenosine



**Nucleotide:** Guanylate (guanosine  
5'-monophosphate)

**Symbols:** G, GMP

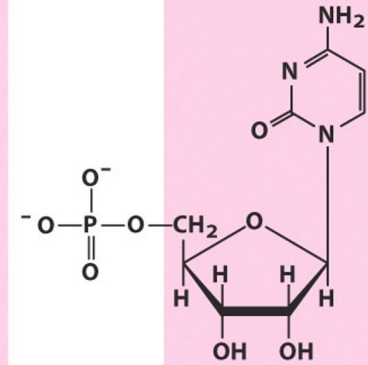
**Nucleoside:** Guanosine



**Nucleotide:** Uridylate (uridine  
5'-monophosphate)

**Symbols:** U, UMP

**Nucleoside:** Uridine



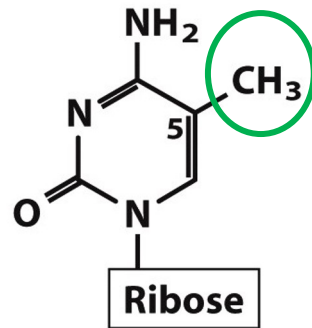
**Nucleotide:** Cytidylate (cytidine  
5'-monophosphate)

**Symbols:** C, CMP

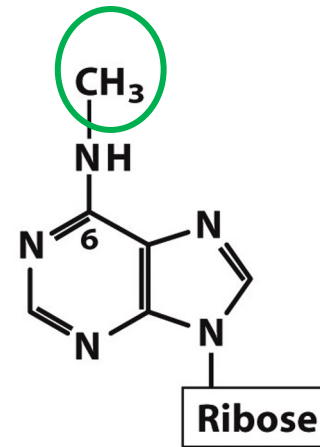
**Nucleoside:** Cytidine

### (b) Ribonucleotides

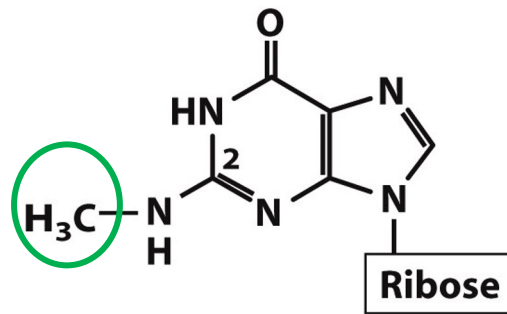
# Bases no DNA podem sofrer modificações químicas fisiológicas



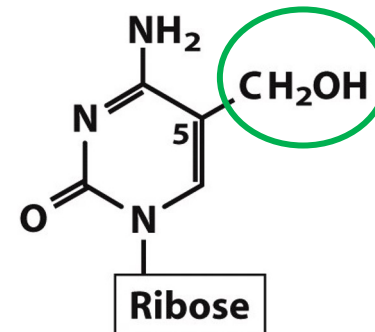
5-Methylcytidine



N<sup>6</sup>-Methyladenosine



N<sup>2</sup>-Methylguanosine



5-Hydroxymethylcytidine

Figure 8-5a  
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Epigenética



# Curiosidade: Tamanho do genoma humano

O genoma humano tem cerca de 6 mil milhões de pares de base de comprimento. Cada par de base tem  $3,4 \times 10^{-10}$  m de comprimento (3,4 Angstrom). Portanto, cada célula terá cerca de 2 m de DNA.

Assim, se multiplicarmos esse valor pelo número de células do corpo humano ( $1 \times 10^{13}$ ), obtemos o valor de  $2 \times 10^{10}$  km. Dividindo pelo dobro da distância ao Sol (ida e volta), concluímos que temos DNA suficiente para ir e vir ao Sol ~66,8 vezes!



# Pareamento tRNA-mRNA

