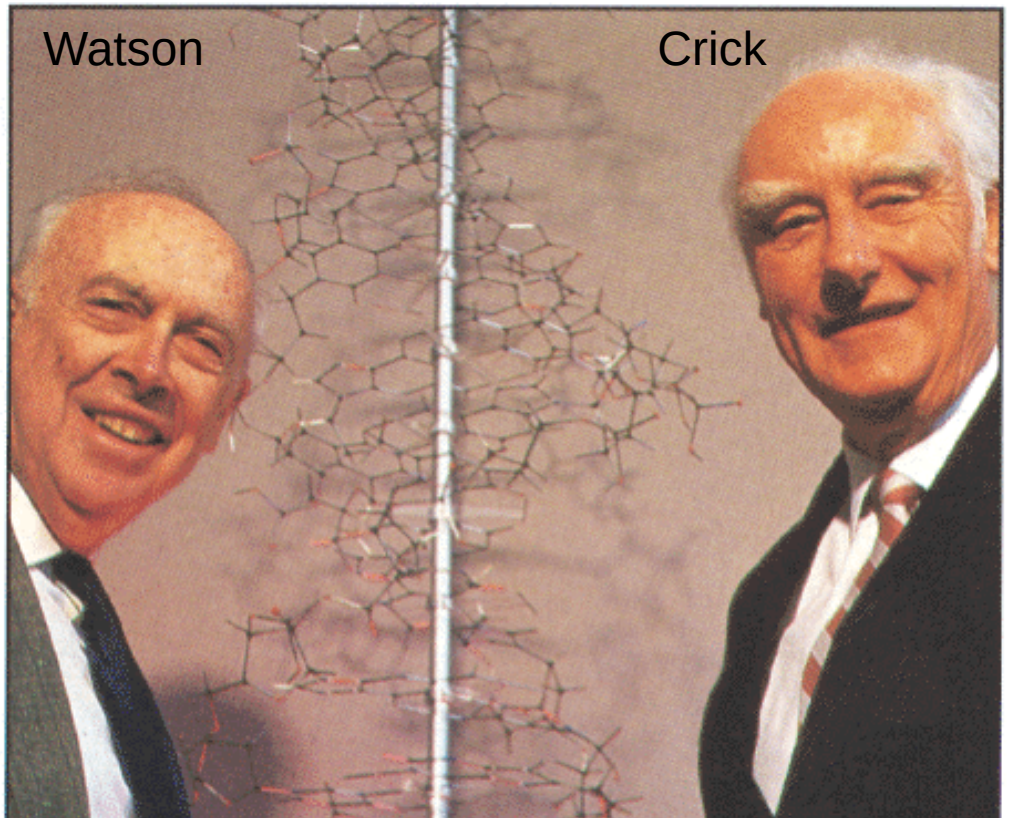
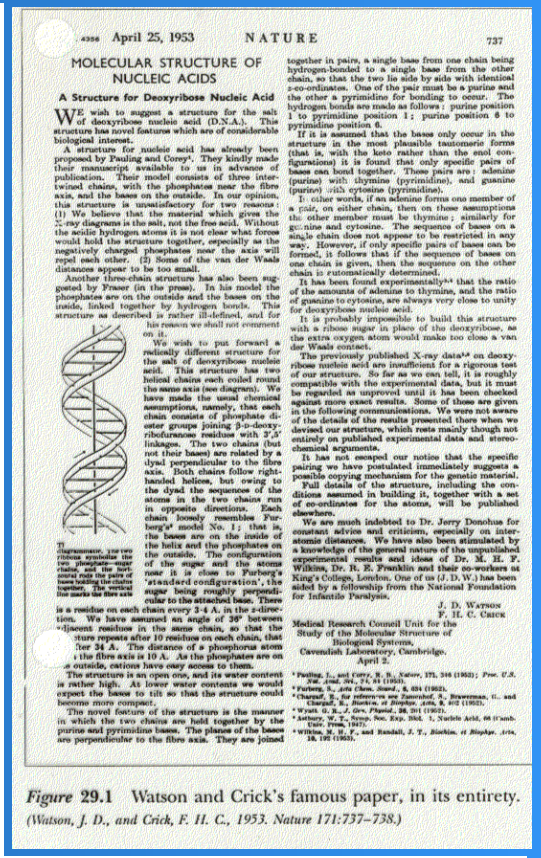




4356 April 25, 1953 NATURE 737

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for his reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.

[1] Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
[3] Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
[5] Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Cambridge Univ. Press, 1947).
[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).

Figure **29.1** Watson and Crick's famous paper, in its entirety.
(Watson, J. D., and Crick, F. H. C., 1953. Nature 171:737–738.)

Published: 25 April 1953

Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid

J. D. WATSON & F. H. C. CRICK

+ Rosalind Franklin + Erwin Chargaff

Nature **171**, 737–738 (1953) | Cite this article

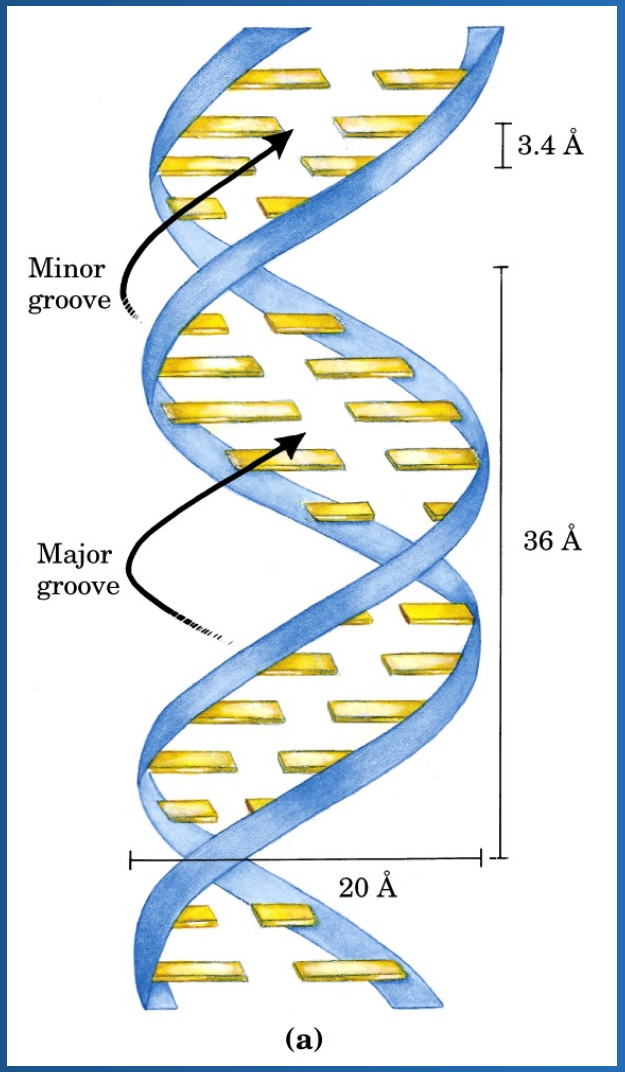
We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Fur-berg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration

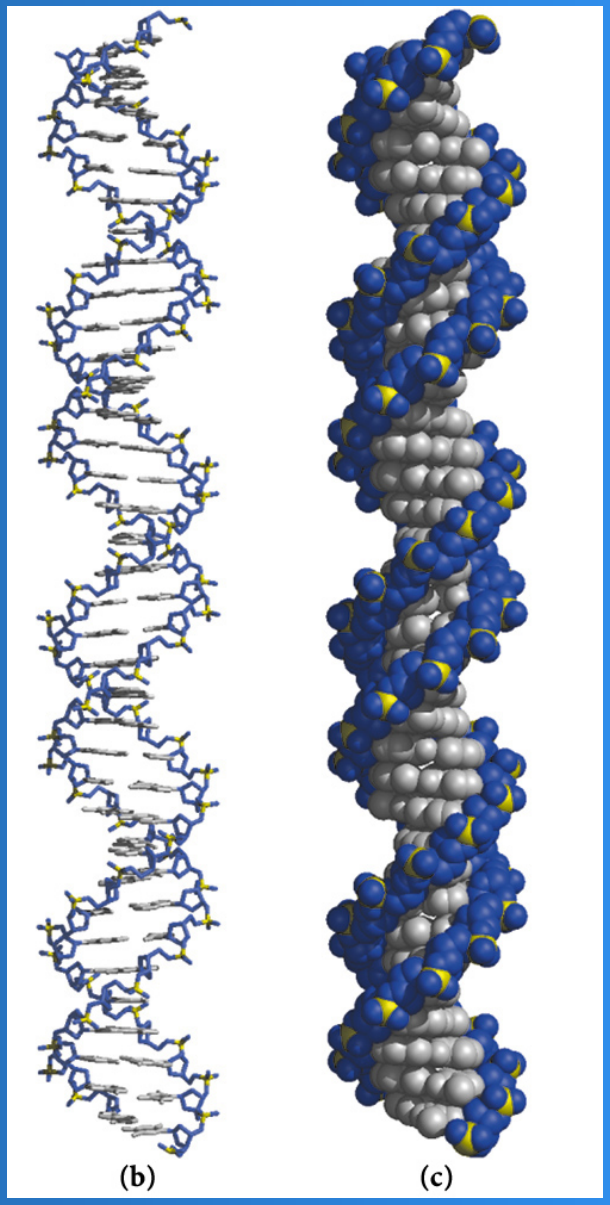
Two chains coiled round the same axis

b-D-deoxyribofuranose
=
Deossiribosio
=
desossiribosio

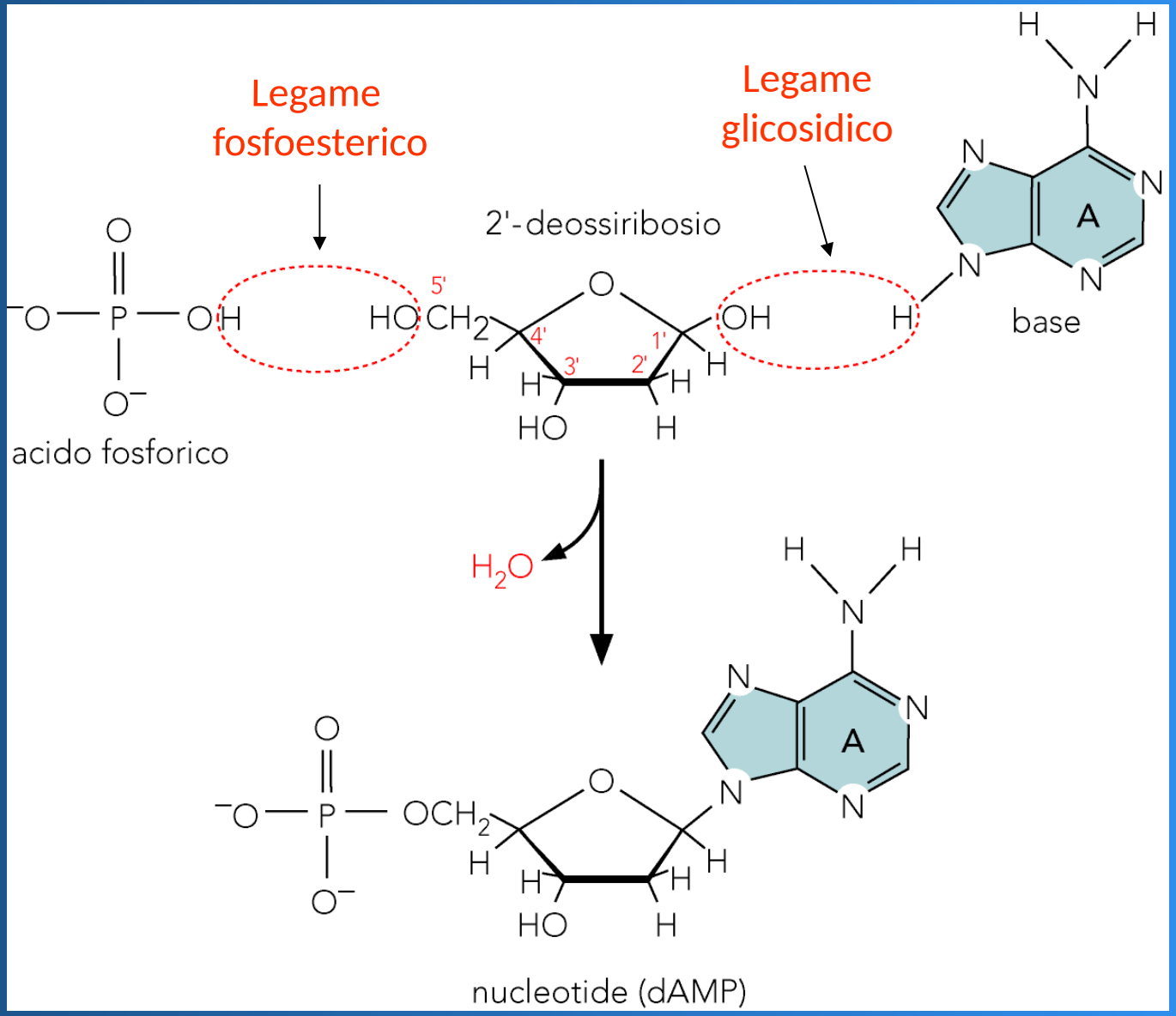
Both chains follow right handed helices […] the two chains run in opposite directions

YouTube

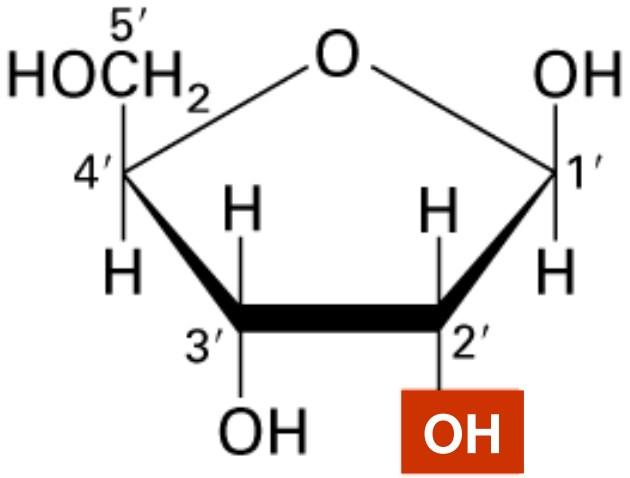




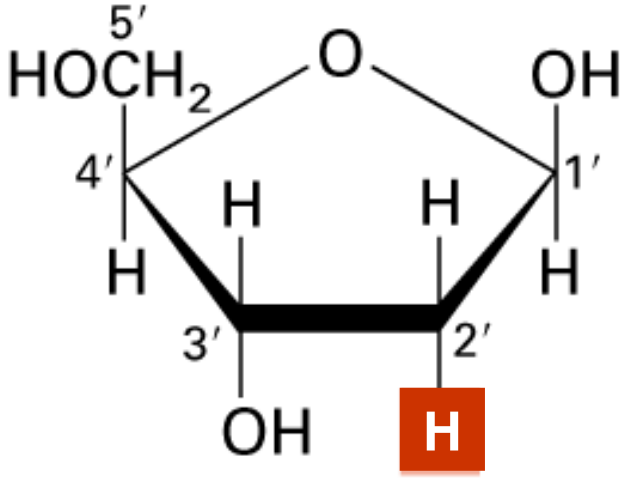
Chimica del DNA



Zuccheri pentosi (C5) negli acidi nucleici



ribosio

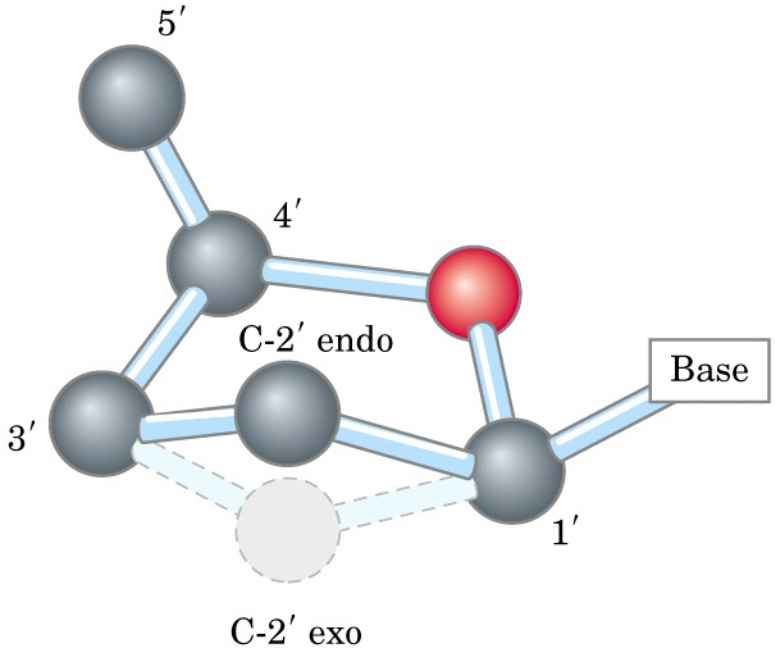


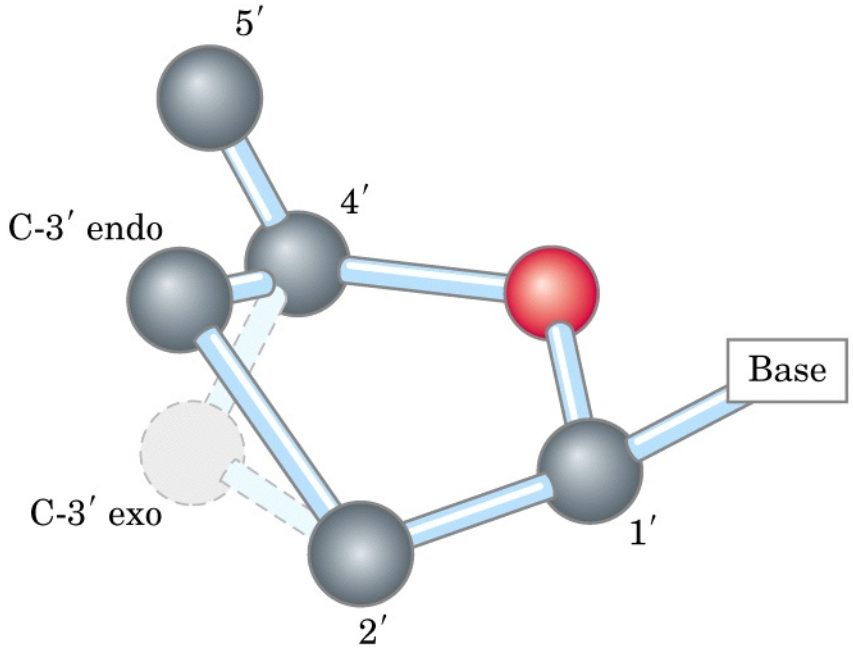
2-deossiribosio

RNA

DNA

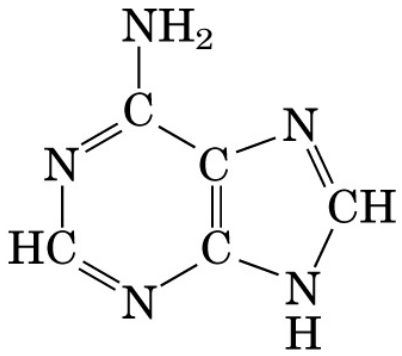
Struttura non planare



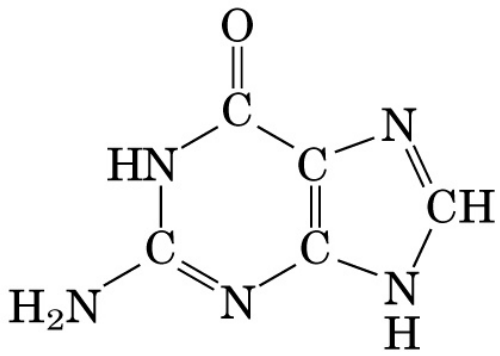


maggiormente stabili le configurazioni C-2' e C-3' endo (verso il 5')

Le basi azotate

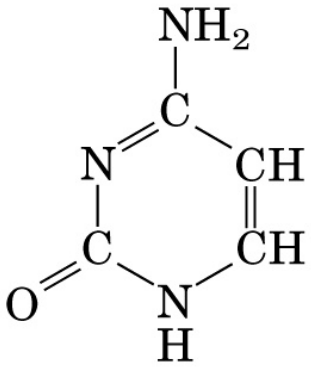


Adenine

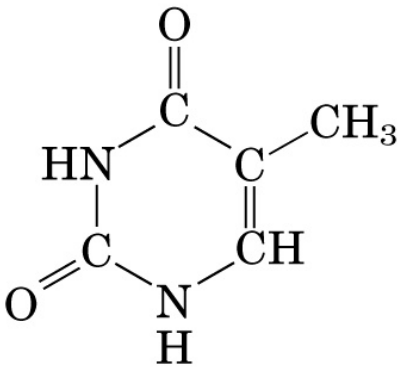


Guanine

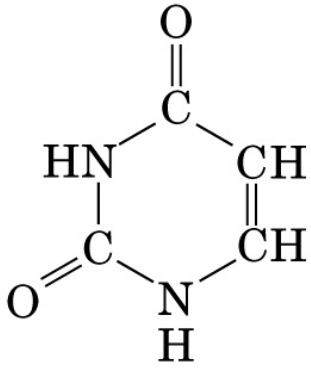
Purines



Cytosine



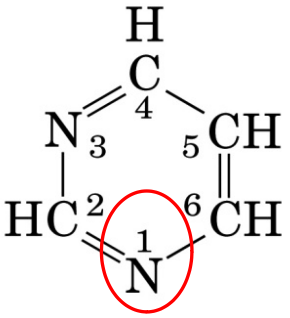
Thymine
(DNA)



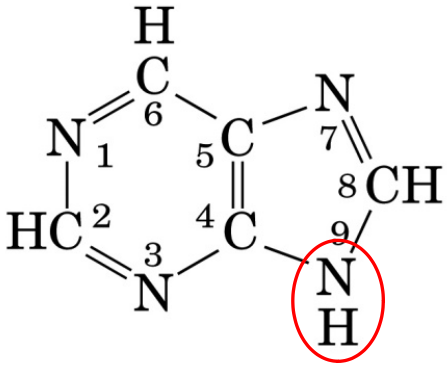
Uracil
(RNA)

Pyrimidines

Diverso legame con lo zucchero



Pyrimidine **1**



Purine **9**

Nomenclatura degli acidi nucleici

table 10–1

Nucleotide and Nucleic Acid Nomenclature

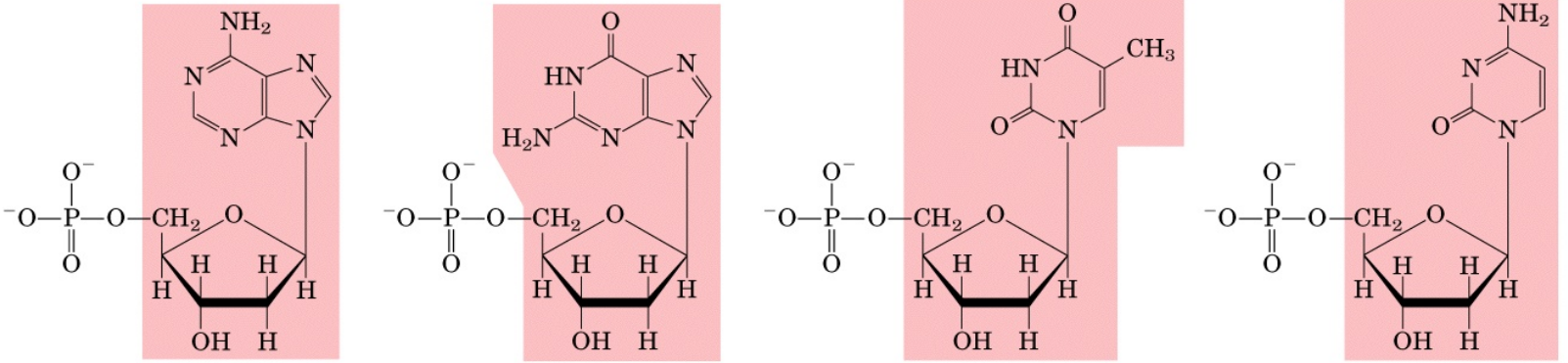
Base	Nucleoside*	Nucleotide*	Nucleic acid
Purines			
Adenine	Adenosine	Adenylate	RNA
	Deoxyadenosine	Deoxyadenylate	DNA
Guanine	Guanosine	Guanylate	RNA
	Deoxyguanosine	Deoxyguanylate	DNA
Pyrimidines			
Cytosine	Cytidine	Cytidylate	RNA
	Deoxycytidine	Deoxycytidylate	DNA
Thymine	Thymidine or deoxythymidine	Thymidylate or deoxythymidylate	DNA
Uracil	Uridine	Uridylate	RNA

Ribonucleotide mono fosfato (NMP) ≈ 340 Da

Desossiribonucleotide mono fosfato (dNMP) ≈ 330 Da

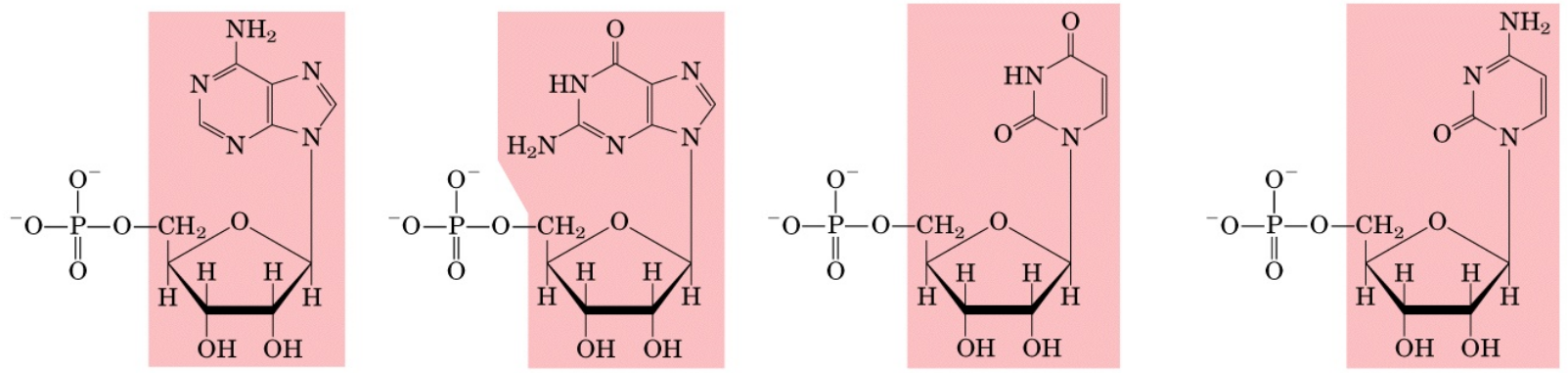
Bp = base pair ≈ 660 Da ⟶ 1000 bp ≈ 660 kDa

I nucleotidi



	Deoxyadenylate (deoxyadenosine 5′-monophosphate)	Deoxyguanylate (deoxyguanosine 5′-monophosphate)	Deoxythymidylate (deoxythymidine 5′-monophosphate)	Deoxycytidylate (deoxycytidine 5′-monophosphate)
Symbols:	A, dA, dAMP	G, dG, dGMP	T, dT, dTMP	C, dC, dCMP
Nucleoside:	Deoxyadenosine	Deoxyguanosine	Deoxythymidine	Deoxycytidine

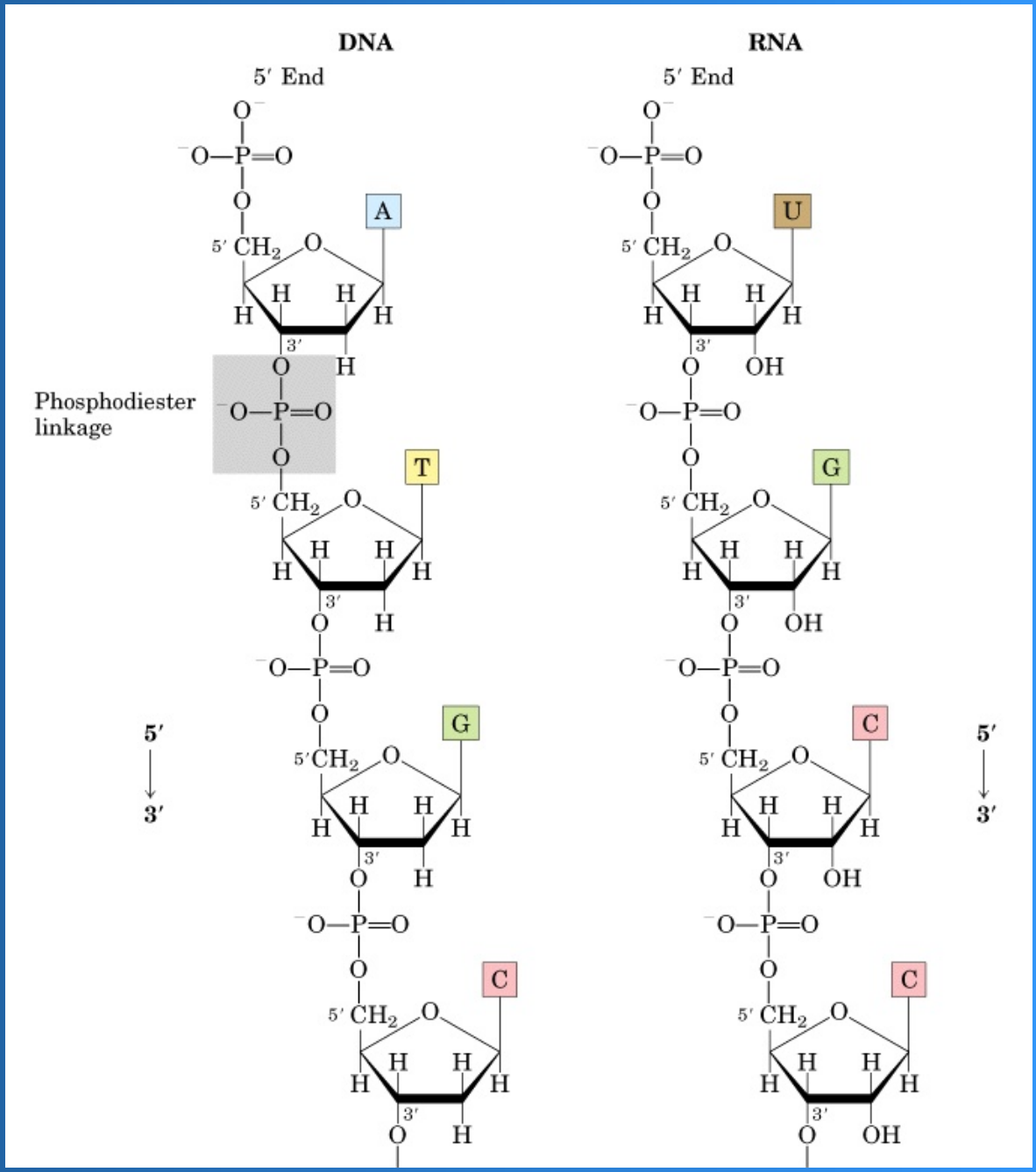
(a) Deoxyribonucleotides



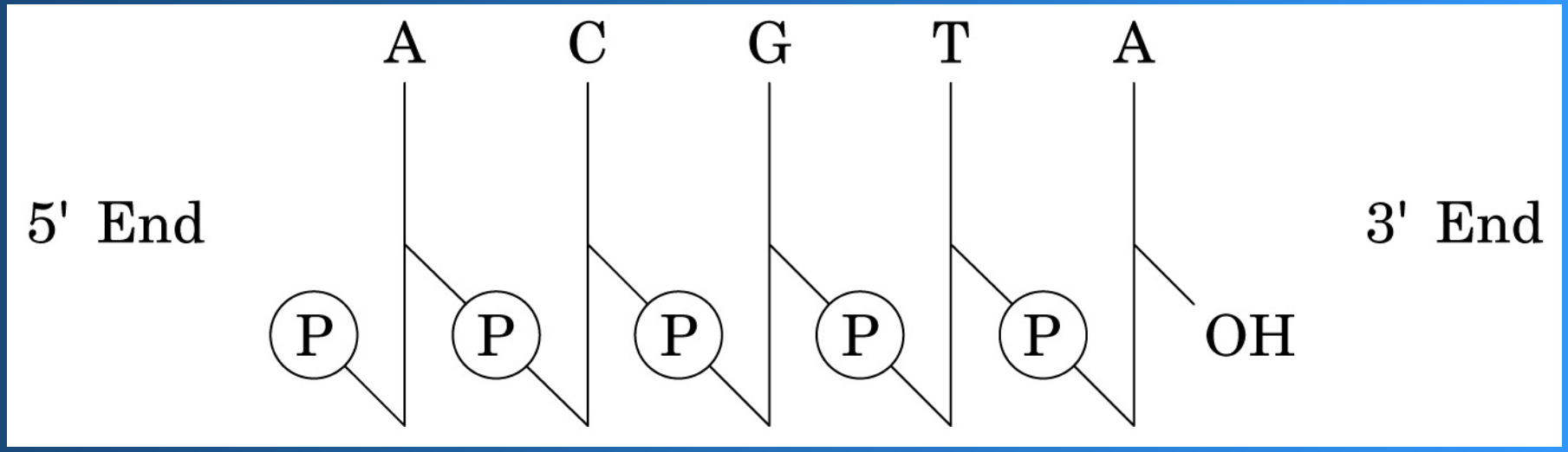
	Adenylate (adenosine 5′-monophosphate)	Guanylate (guanosine 5′-monophosphate)	Uridylate (uridine 5′-monophosphate)	Cytidylate (cytidine 5′-monophosphate)
Symbols:	A, AMP	G, GMP	U, UMP	C, CMP
Nucleoside:	Adenosine	Guanosine	Uridine	Cytidine

(b) Ribonucleotides

Il legame fosfodiestere unisce le basi lungo i singoli filamenti



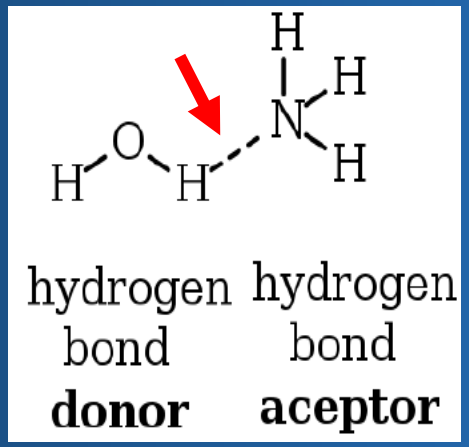
Schema del legame fosfodiesterico negli acidi nucleici

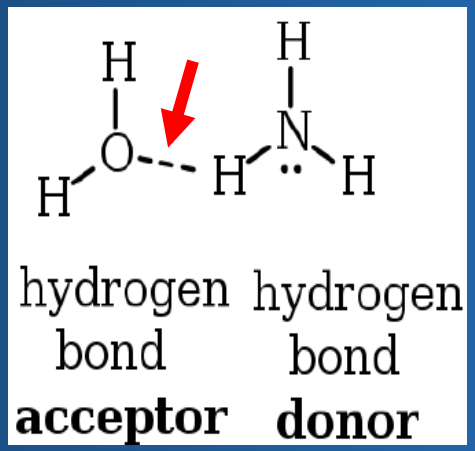


Gli acidi nuceici vanno sempre letti in direzione 5'-3'

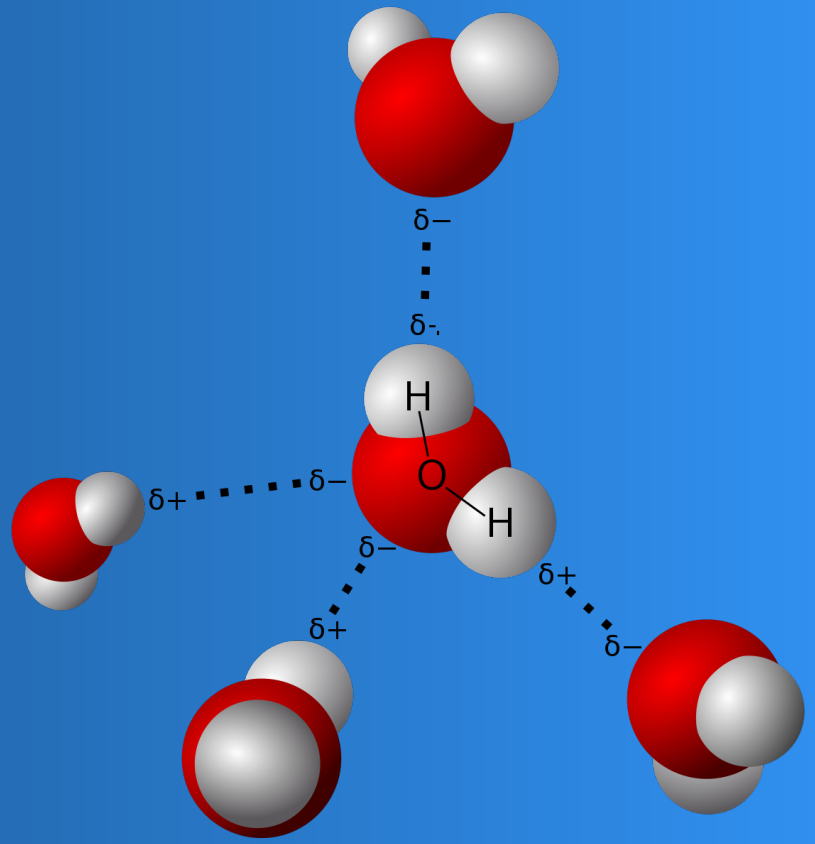
5' ⟶ 3'

Le basi azotate dei due filamenti antiparalleli si appaiano mediante legami a idrogeno



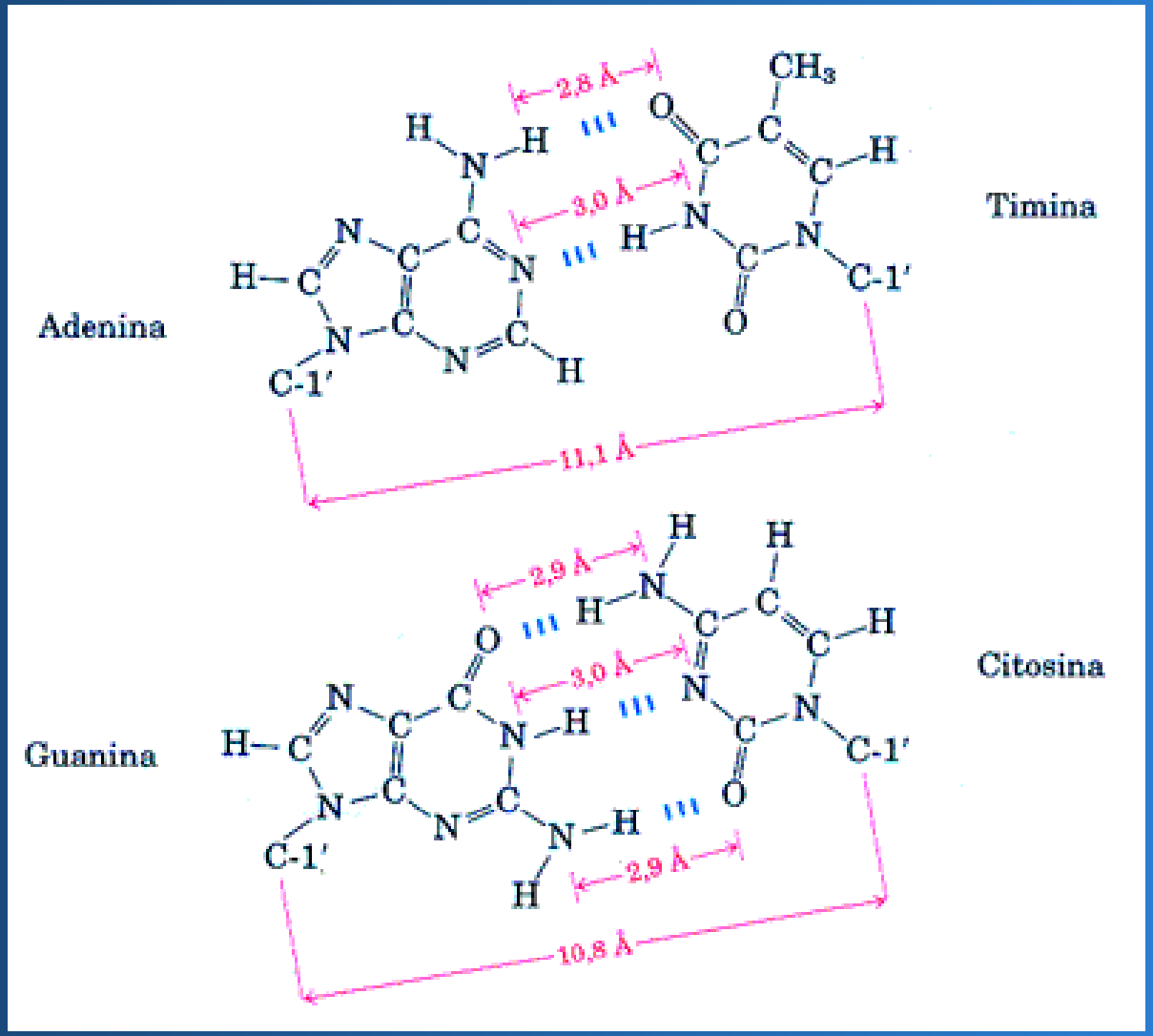


Interazione acqua / ammoniaca



Acqua H_2O

Chimica dell' appaiamento tra basi azotate

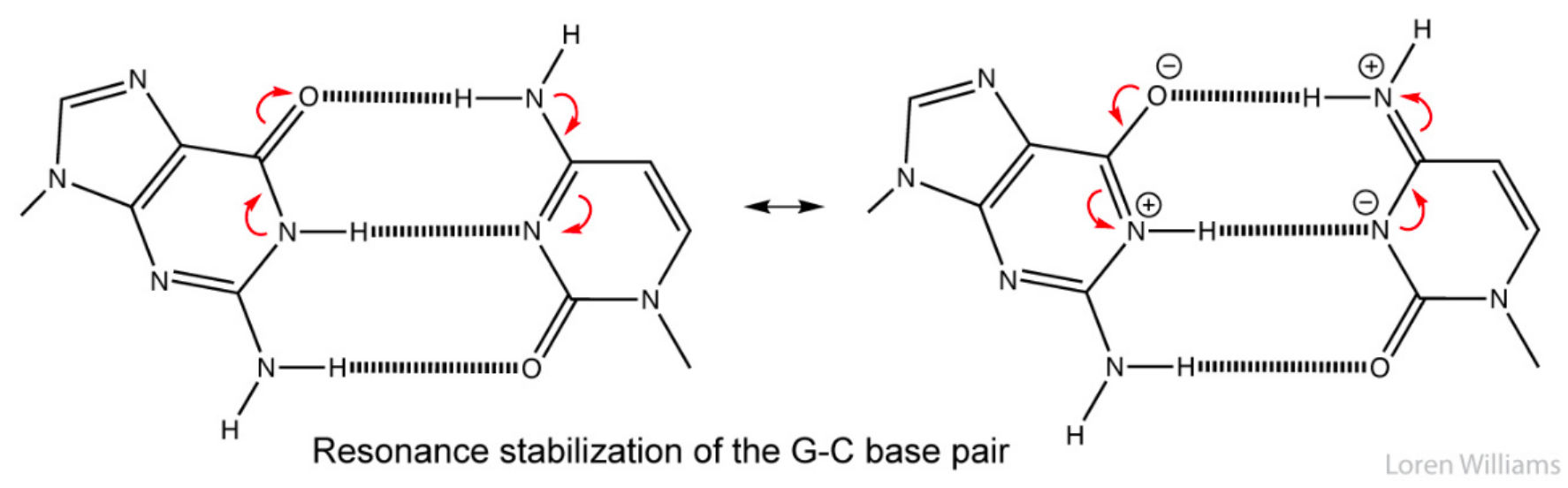


A:T
due
legami
a idrogeno

G:C
tre
legami
a idrogeno

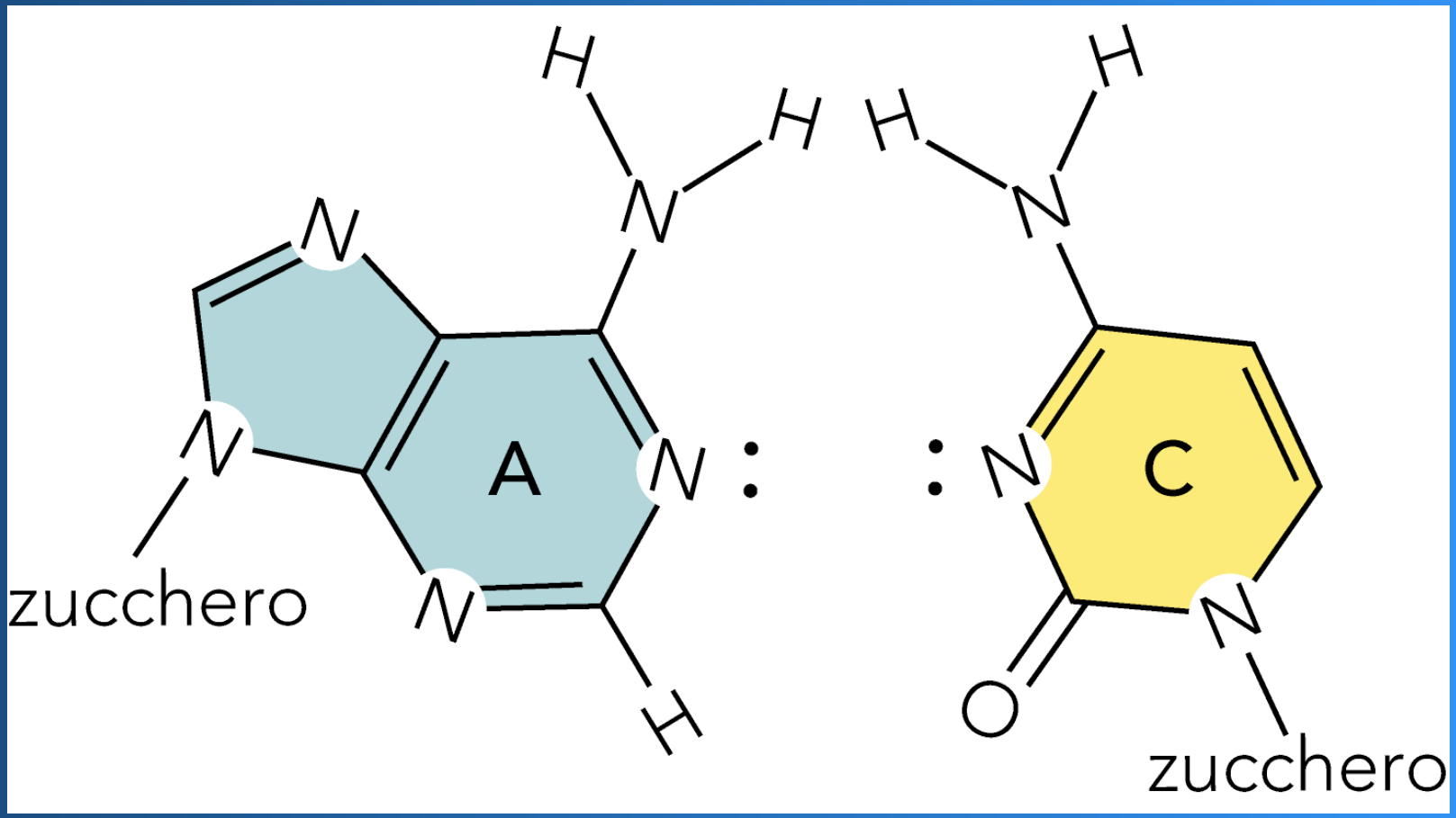
Risonanza dei ponti idrogeno

La presenza di ponti idrogeno adiacenti stimola una ulteriore stabilizzazione legata alla condivisione degli elettroni tra le due molecole.



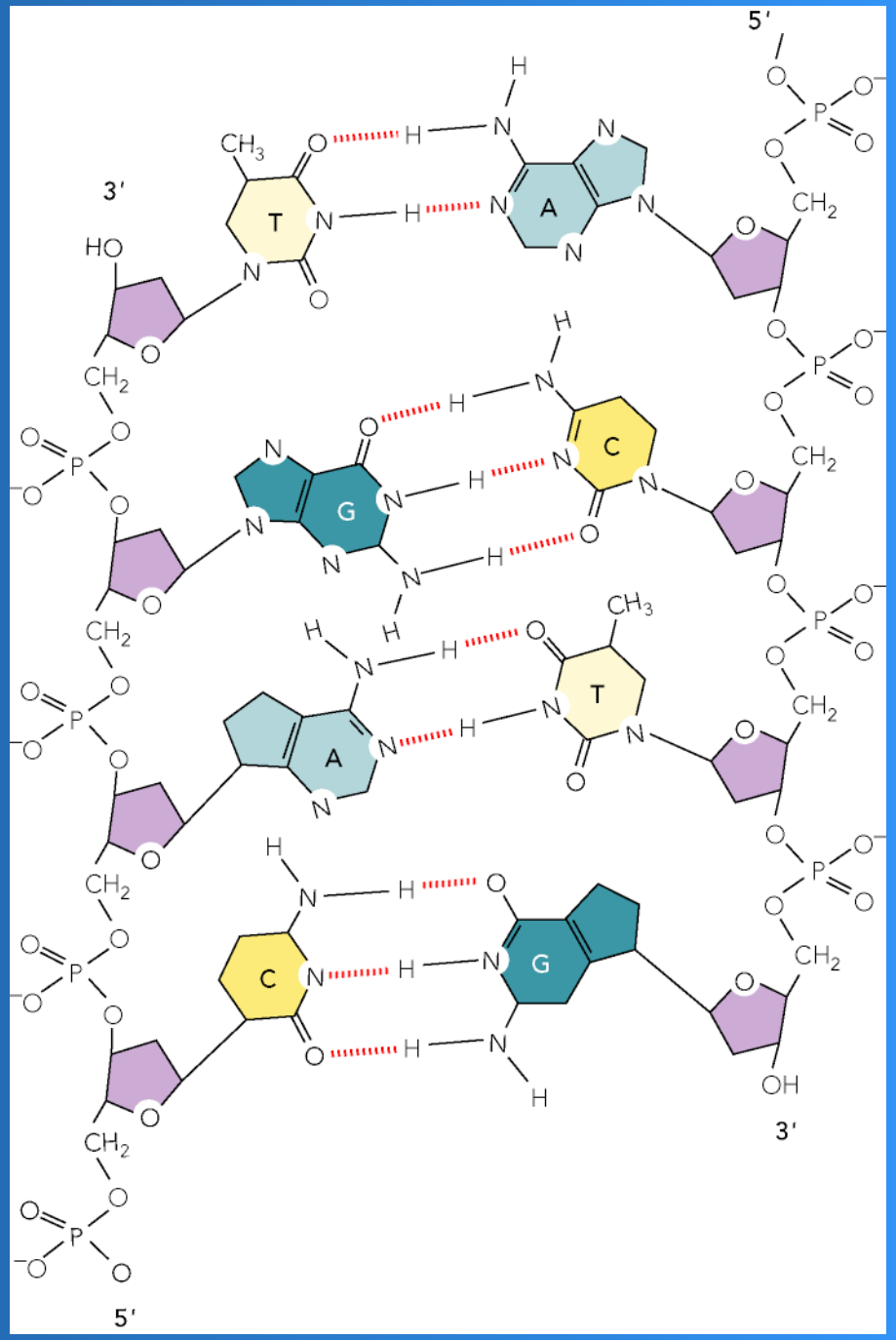
In presenza di legami idrogeno multipli si instaura una **risonanza** tra di essi e
ogni legame è rinfozato dai legami adiacenti.

Incompatibilità di appaiamento

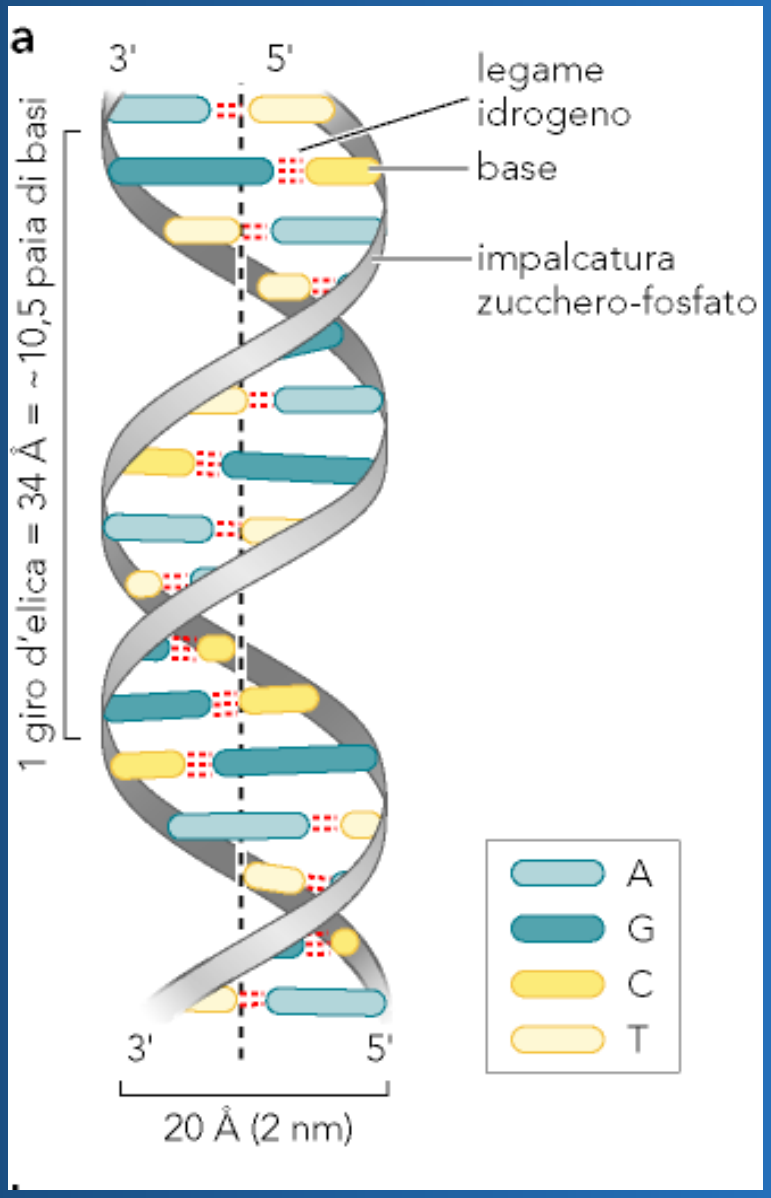


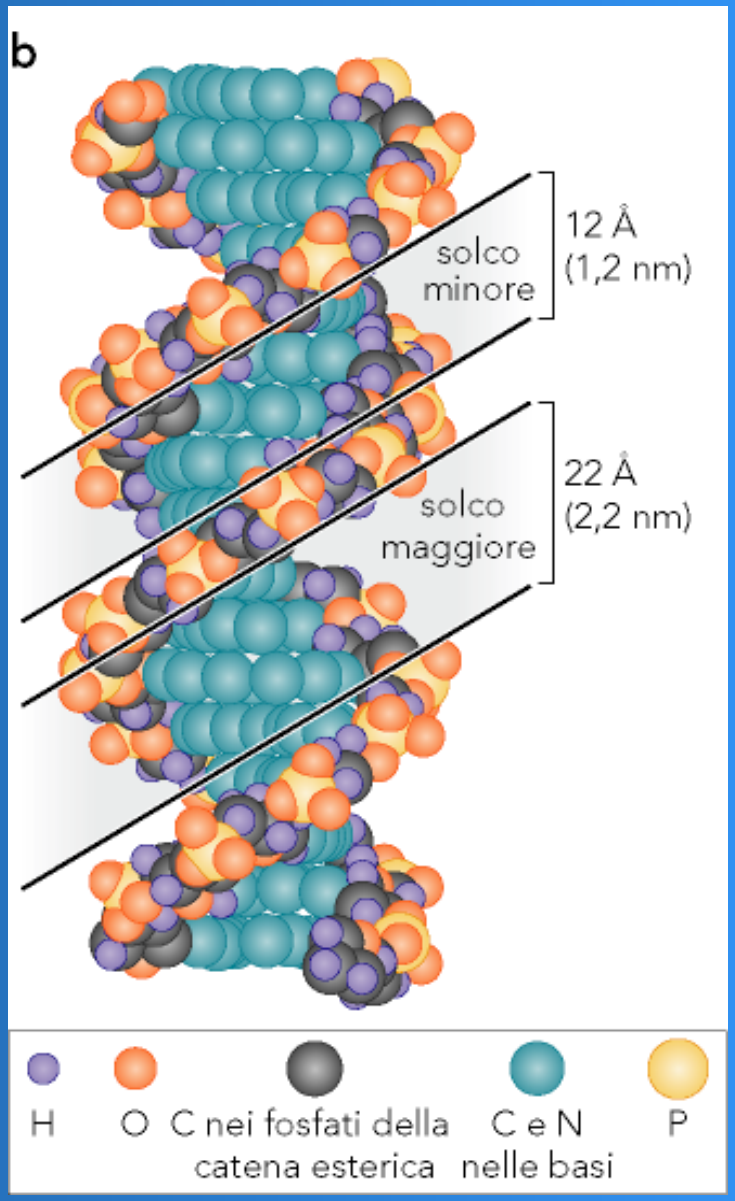
Direzioni inverse nei due filamenti (antiparalleli)

5' zucchero – fosfato – zucchero 3'
|
base
: : :
: : :
: : :
base
|
5' zucchero – fosfato – zucchero 3'



L'esterno del DNA presenta due solchi



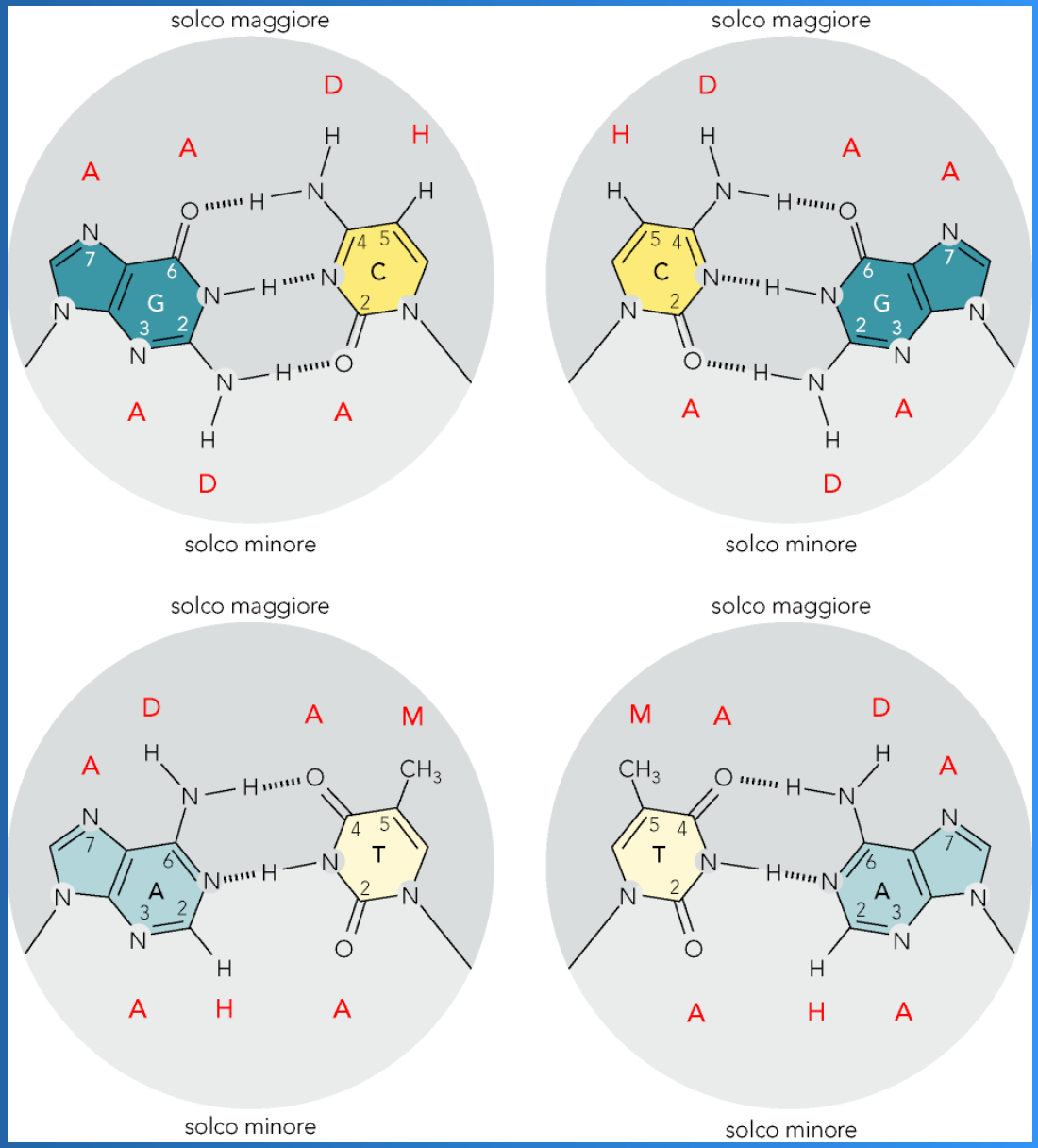


L'esterno del DNA presenta due solchi

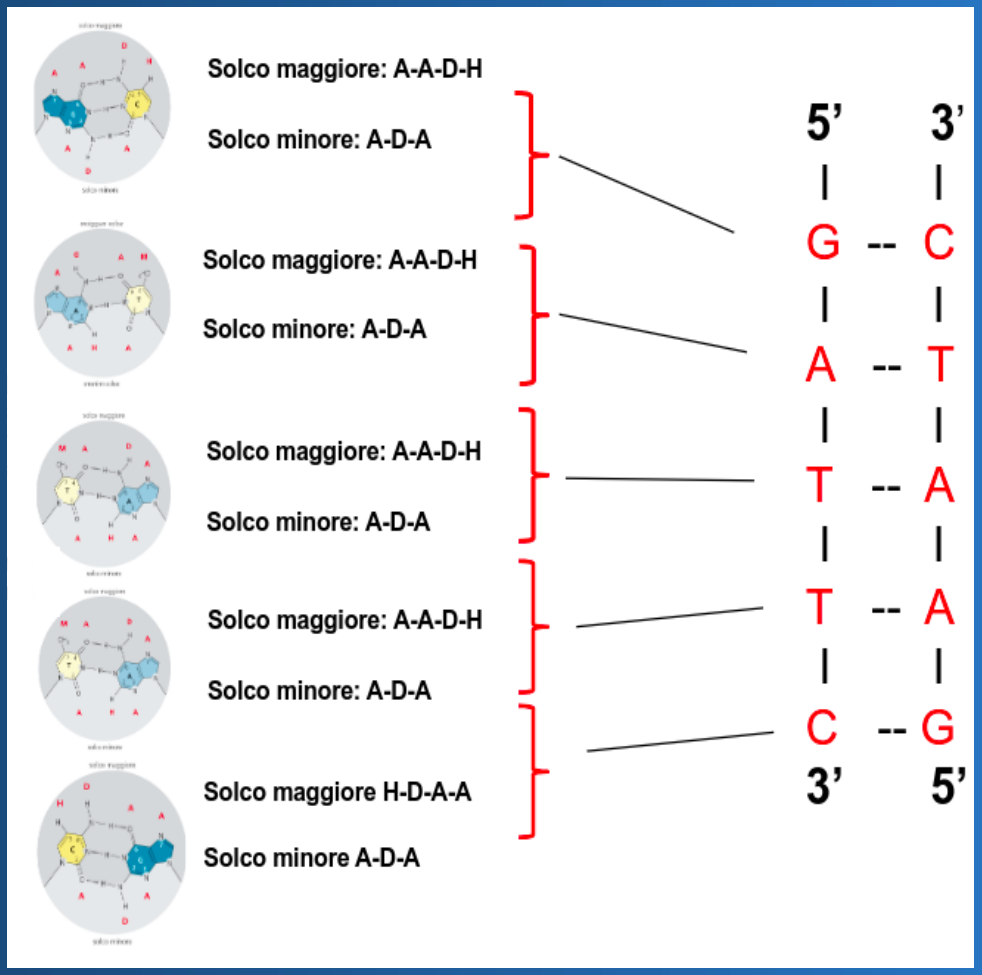
A accettore legami H
D donatore legami H
M gruppi metilici
H idrogeno non polare

proteine che scorrono sui solchi vedono pattern chimici diversi

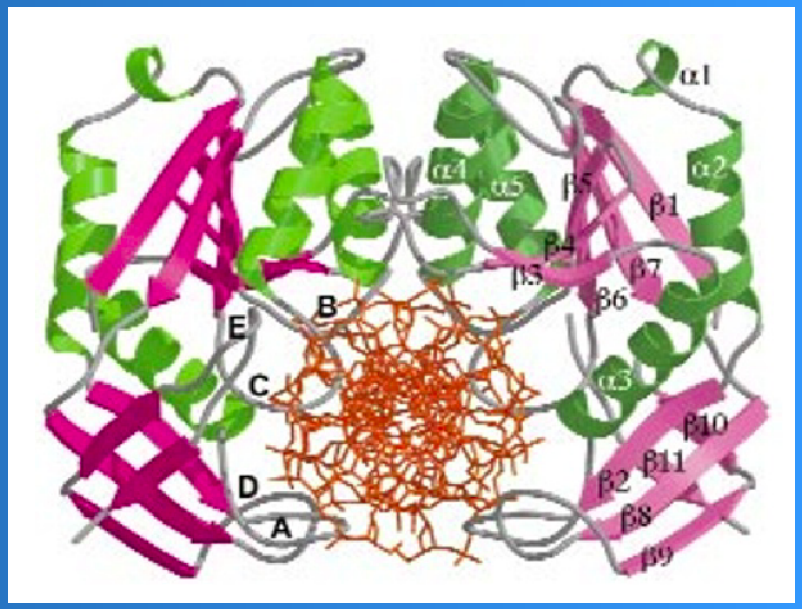
è possibile leggere il DNA senza aprire la doppia elica



Riconoscimento della sequenza

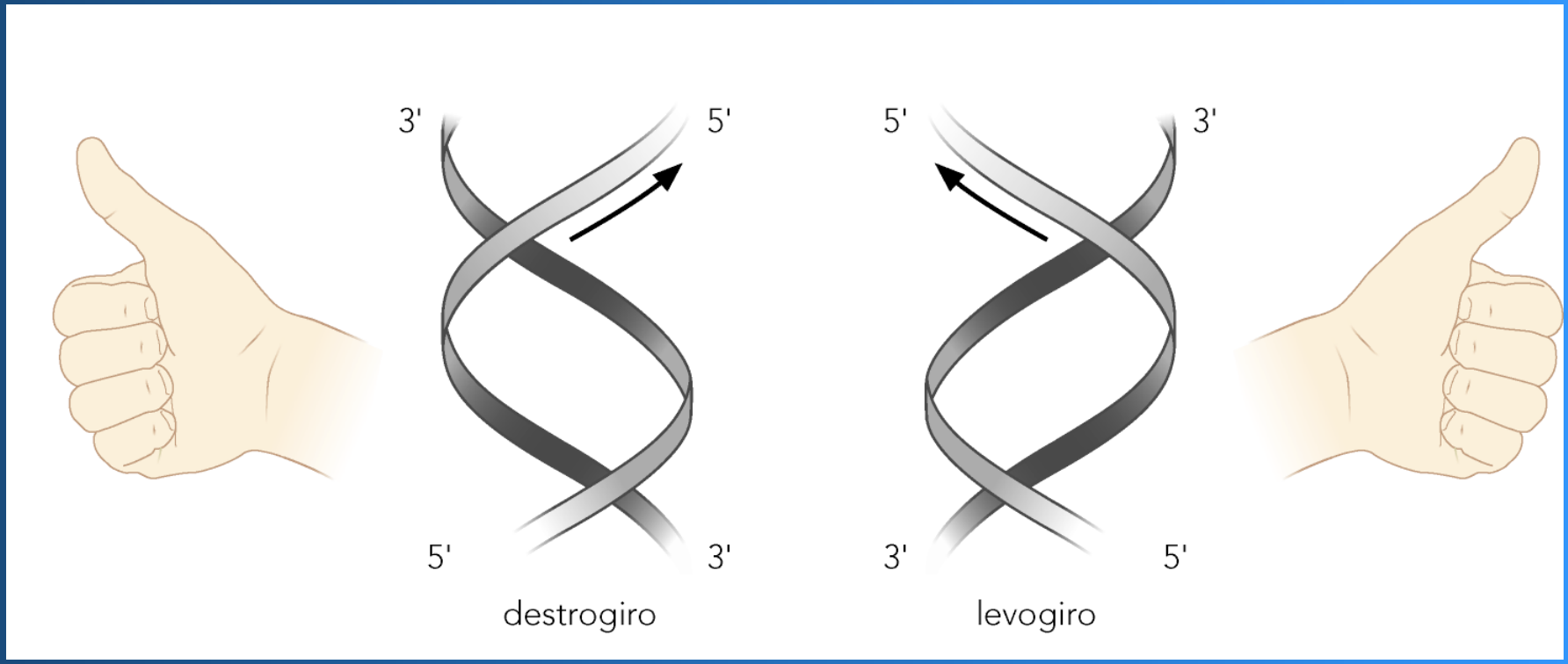


Proteina



DNA

Il DNA si avvolge prevalentemente in modo destrorso (destrogiro)



L'andamento sinistrorso (levogiro) è possibille anche se molto meno frequente

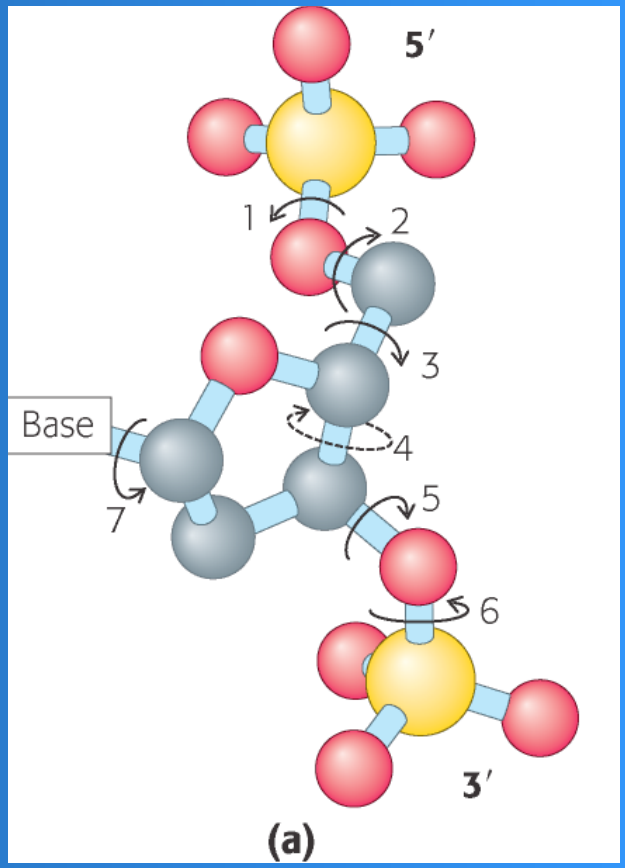
Rotazione dei legami nel DNA

La geometria dell'elica del DNA dipende dalle configurazioni dei legami:

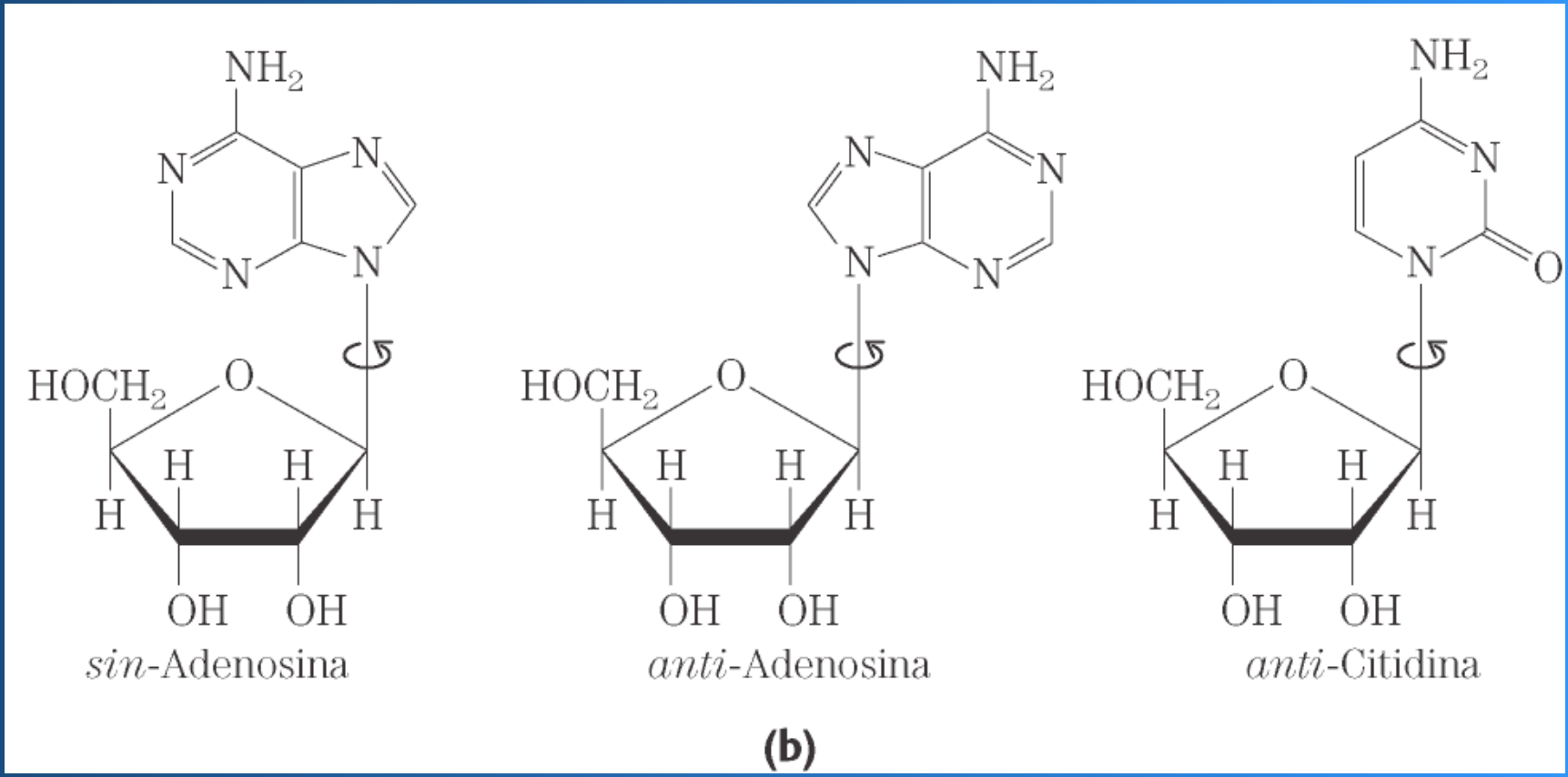
- **all'interno dello zucchero**
  - **eso/endo** : non planarità

- **tra zucchero e base**
  - **sin** : entrambi nello stesso versante del legame glicosidico
  - **anti** : su versanti opposti rispetto al legame glicosidico (più frequente)

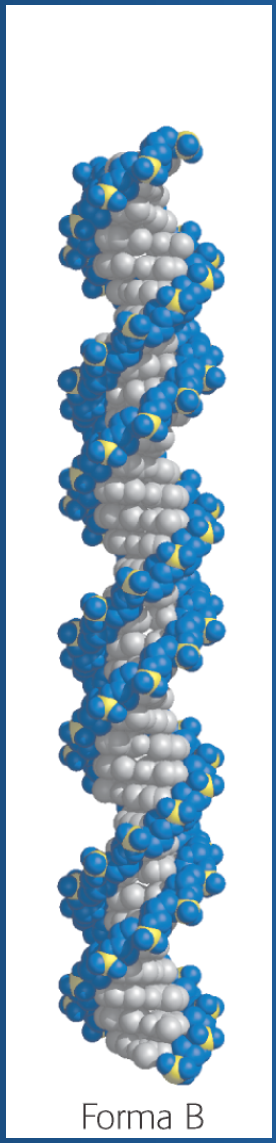
- **tra zucchero e gruppo fosfato**



Rotazione dei legami nel DNA



Forme principali della doppia elica

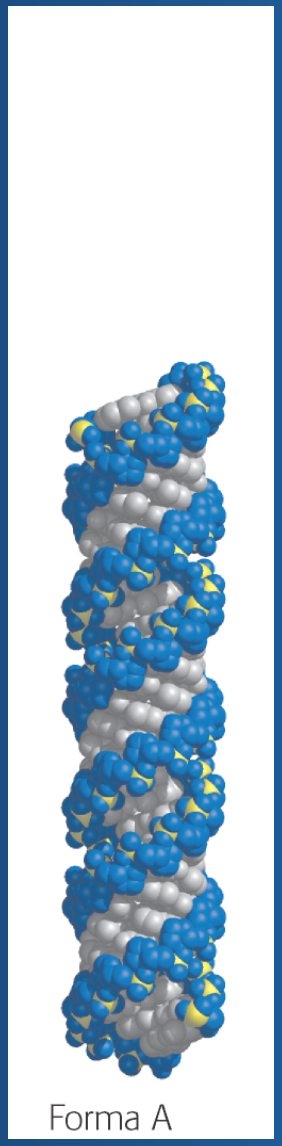

Forma B

FORMA B

La più comune e stabile:

- simile a quella prevista da Watson e Crick
- contiene 10.5 coppie di basi per giro d'elica
- le basi sporgono perpendicolari alla fibra
- espone un solco maggiore e un solco minore

Forme principali della doppia elica

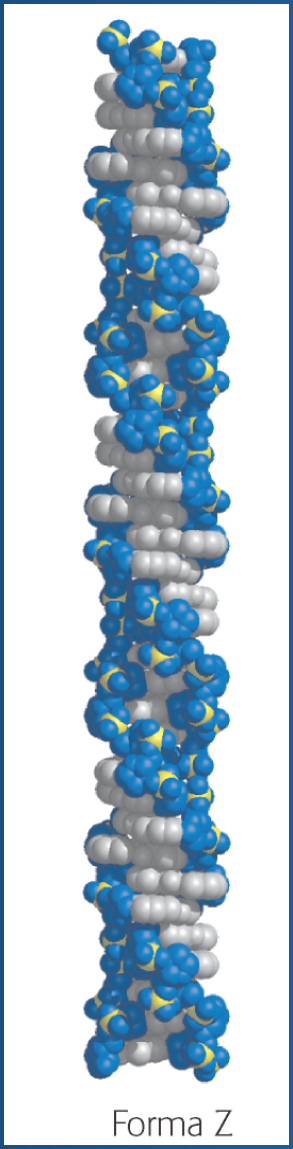

Forma A

FORMA A

Meno comune della B:

- più compatta
- favorita in disidratazione
- basi inclinate di 20° circa rispetto all'asse
- 11 basi per giro d'elica
- solchi di uguali dimensioni (circa)
- si trova nelle doppie eliche di RNA

Forme principali della doppia elica


Forma Z

FORMA Z

La meno rappresentata:

- è sinistrorsa

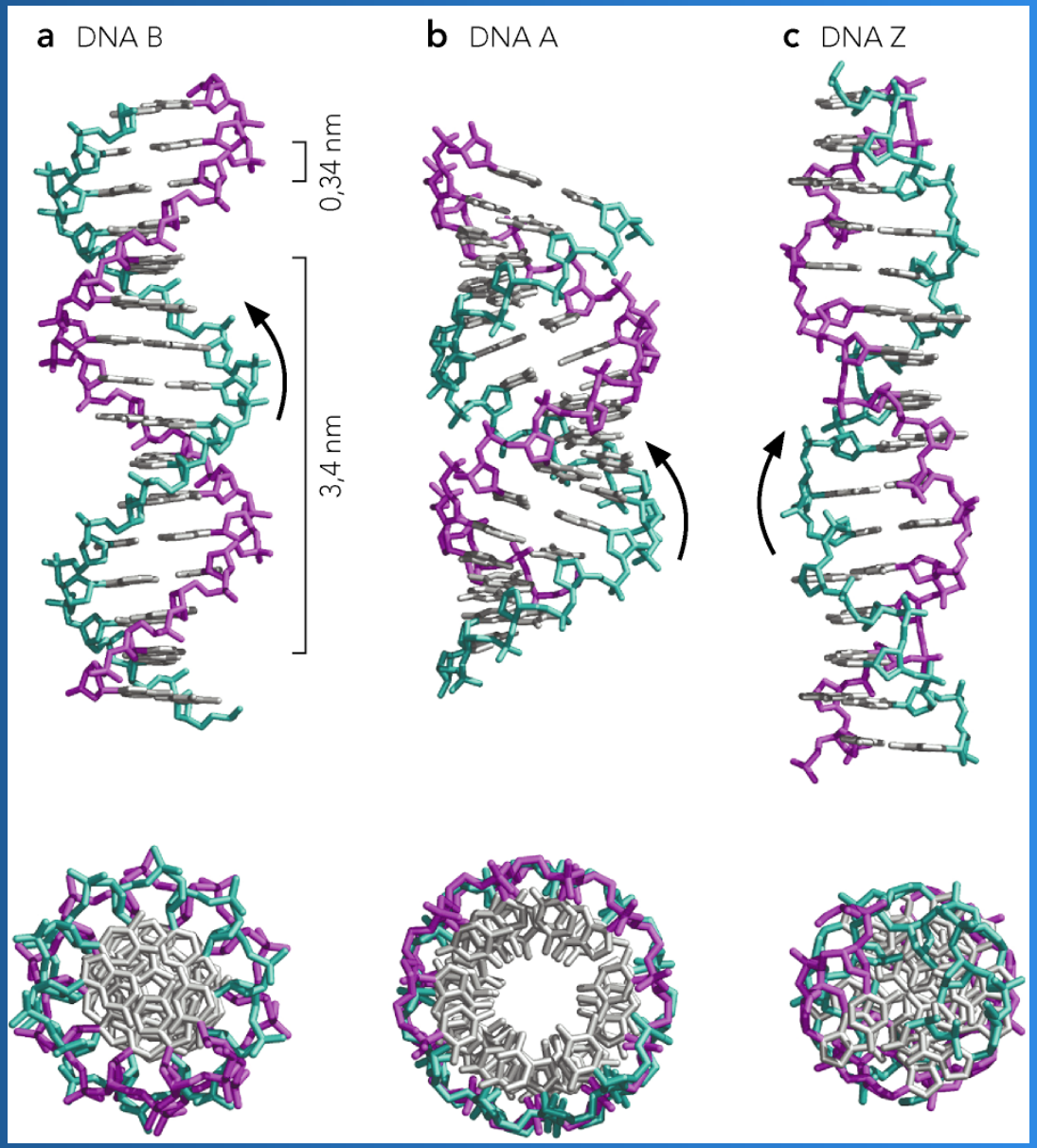
- ha una forma a zig-zag

- 12 coppie di basi per giro d'elica

- dovuta a pur e pyr che si alternano regolarmente

- è la meno caratterizzata

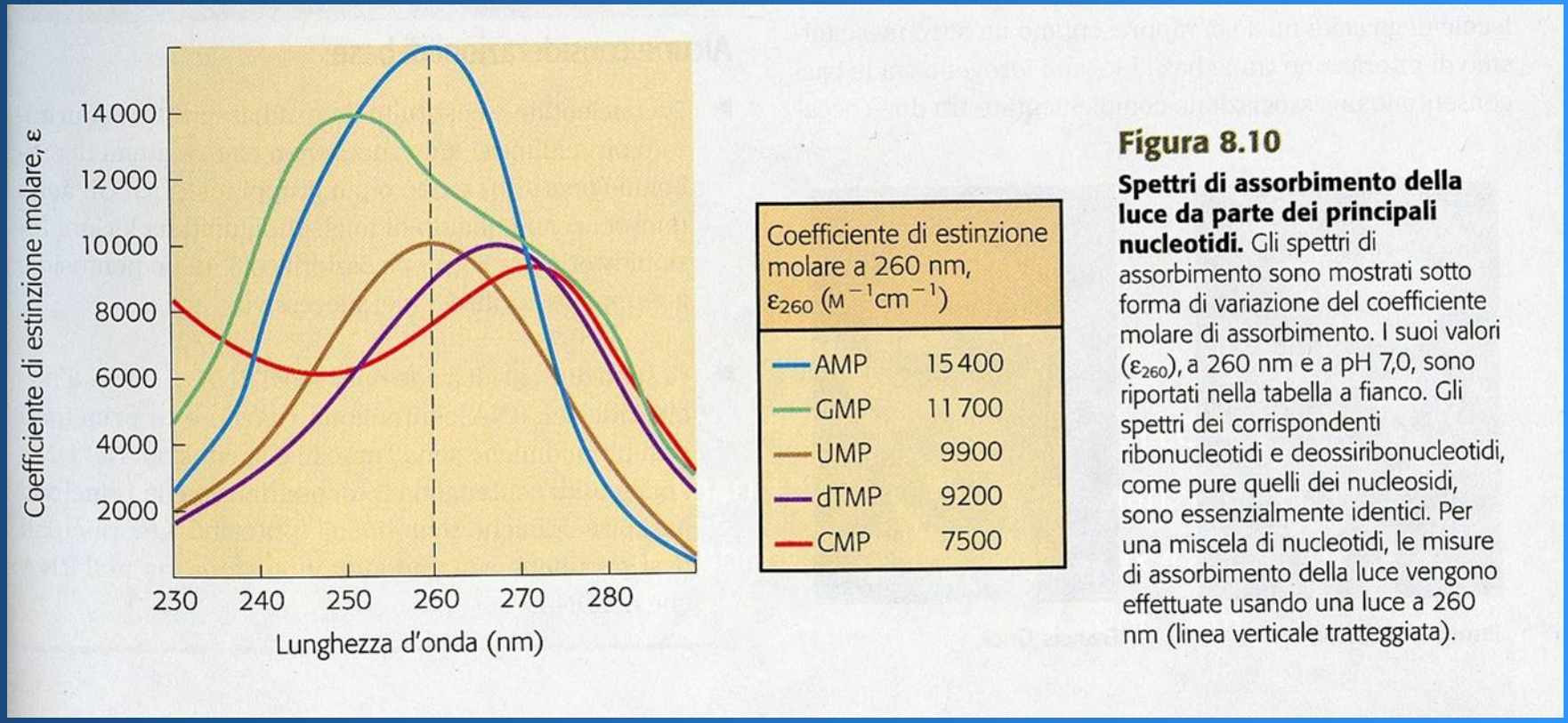
Forme principali della doppia elica



Confronto tra le tre forme

	Forma A	Forma B	Forma Z
Senso dell'elica	Destrorsa	Destrorsa	Sinistrorsa
Diametro	26 Å	20 Å	18 Å
Coppie basi/giro	11	10.5	12
Distanza fra le basi	2.6 Å	3.4 Å	3.7 Å
Piegamento basi rispetto alla normale all'asse	20°	6°	7°
Conformazione zucchero	C3'-endo	C2'-endo	C2'-endo (Py) C3'-endo (Pu)
Conformazione legame N-glicosidico	Anti	Anti	Anti (Py) Syn (Pu)

Spettro di assorbimento dei nucleotidi



Coefficiente di estinzione molare a 260 nm, ε_{260} ($M^{-1}cm^{-1}$)	
AMP	15400
GMP	11700
UMP	9900
dTMP	9200
CMP	7500

Figura 8.10

Spettri di assorbimento della luce da parte dei principali nucleotidi. Gli spettri di assorbimento sono mostrati sotto forma di variazione del coefficiente molare di assorbimento. I suoi valori (ε_{260}), a 260 nm e a pH 7,0, sono riportati nella tabella a fianco. Gli spettri dei corrispondenti ribonucleotidi e deossiribonucleotidi, come pure quelli dei nucleosidi, sono essenzialmente identici. Per una miscela di nucleotidi, le misure di assorbimento della luce vengono effettuate usando una luce a 260 nm (linea verticale tratteggiata).

Coefficiente di estinzione molare ε

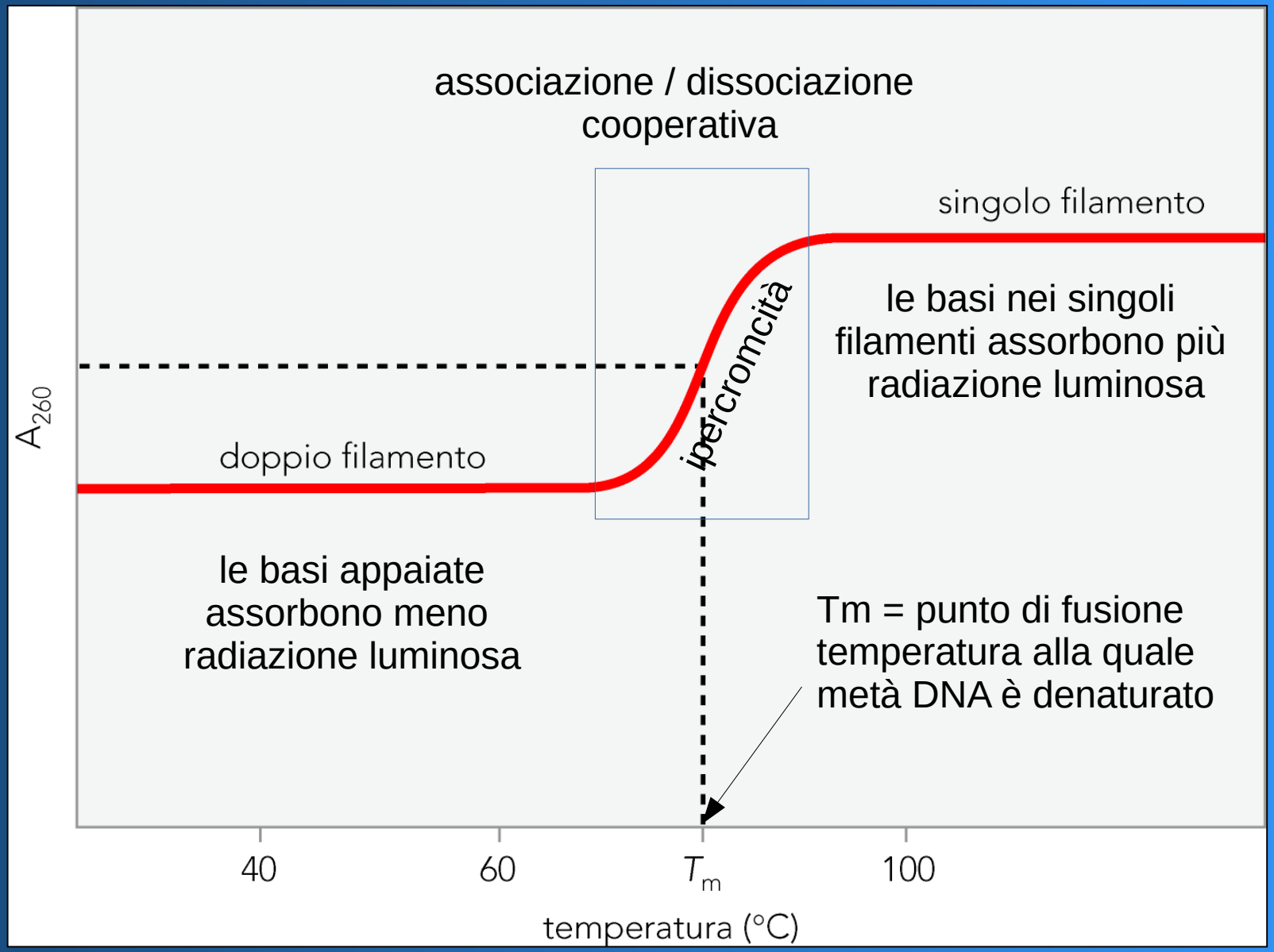
Assorbanza (densità ottica) di una soluzione a concentrazione 1M attraverso una cuvetta a cammino ottico di 1 cm, ad una certa lunghezza d'onda.

Spettro di assorbimento del nucleotidi

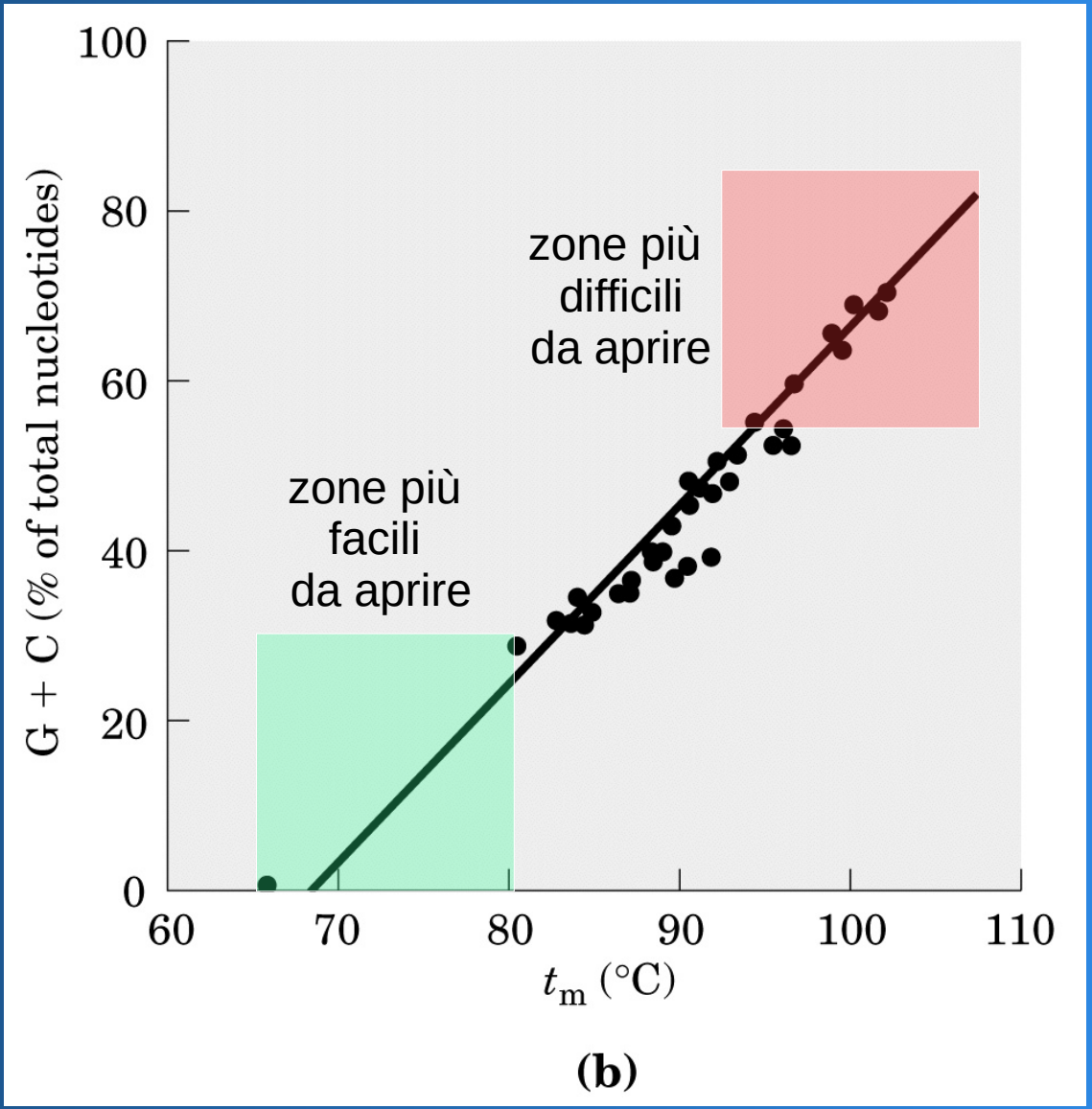
Tabella 13-2. Costanti spettrofotometriche per i nucleosidi purinici e pirimidinici

Nucleosidi	*Coefficiente di estinzione molare* $\times 10^{-3}$	λ_{max} *pH 7*
Adenosina	15.4	259
Guanosina	13.7	253
Citidina	8.9	271
Uridina	10.0	262
Timidina	10.0	262

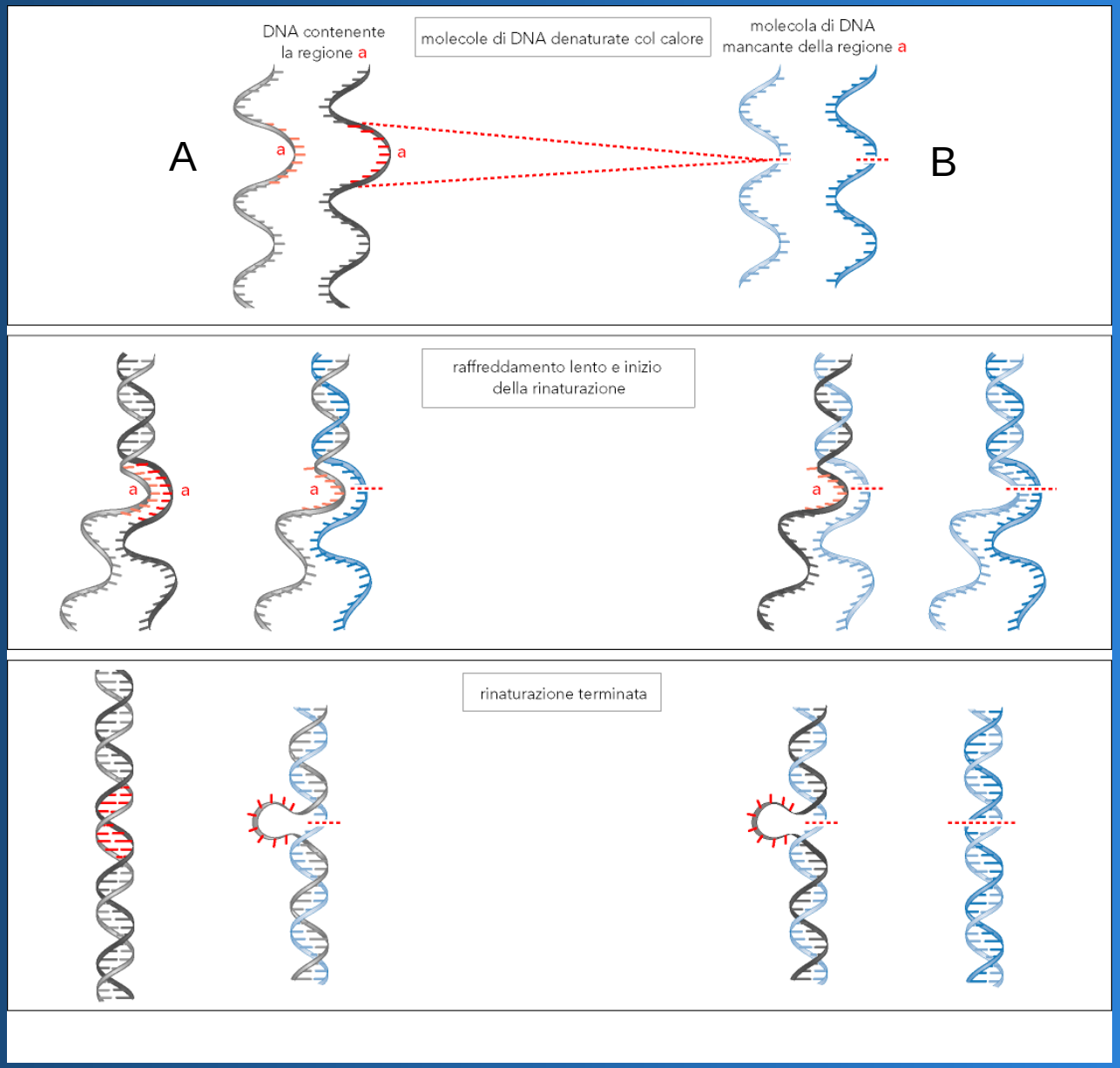
Curva di melting del DNA



Relazione tra GC% e resistenza alla denaturazione



Ibridazione del DNA



zona rossa presente in A ma non in B

↓

denaturazoine termica

↓

raffreddamento della miscela

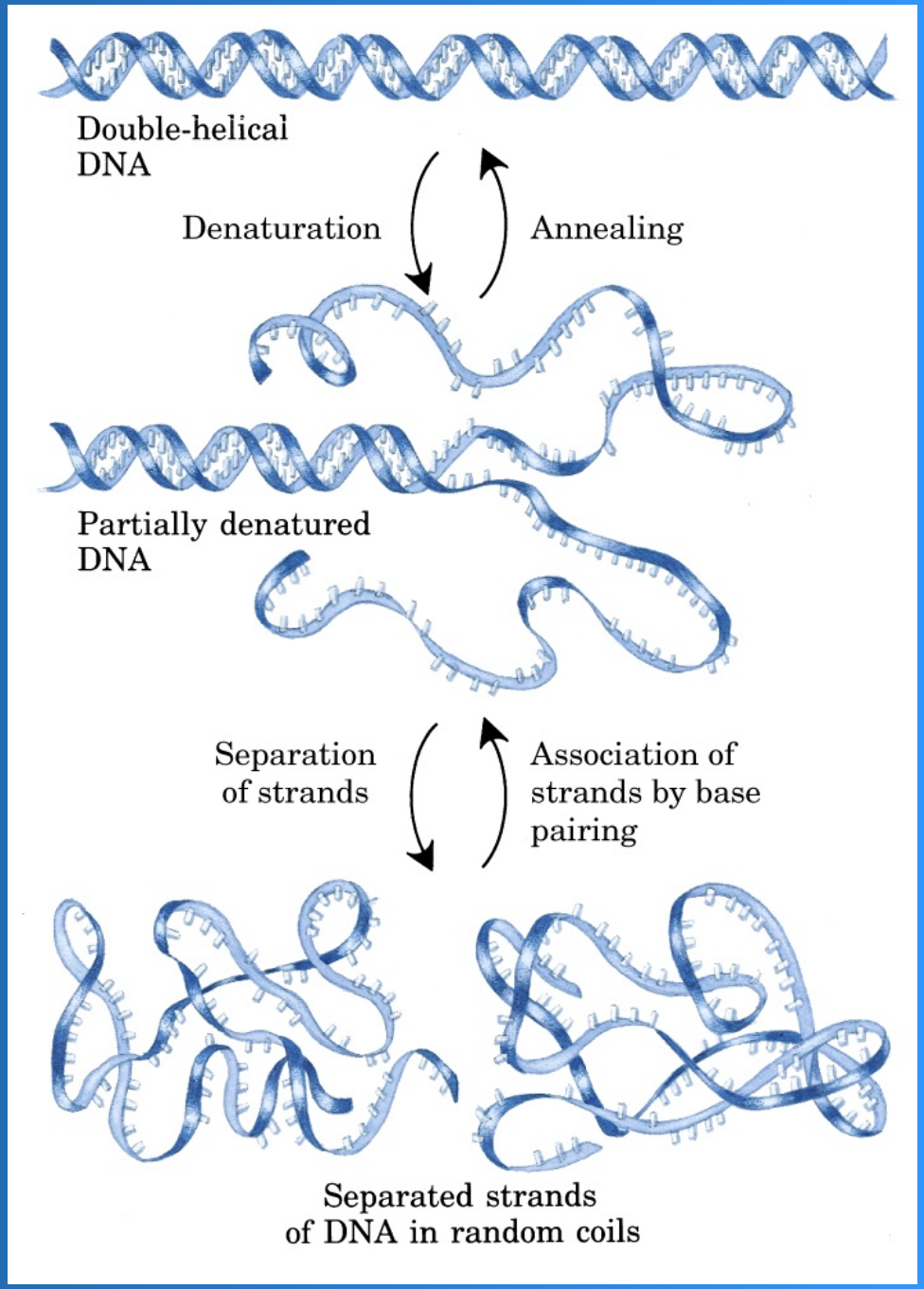
↓

inizio rinaturazione

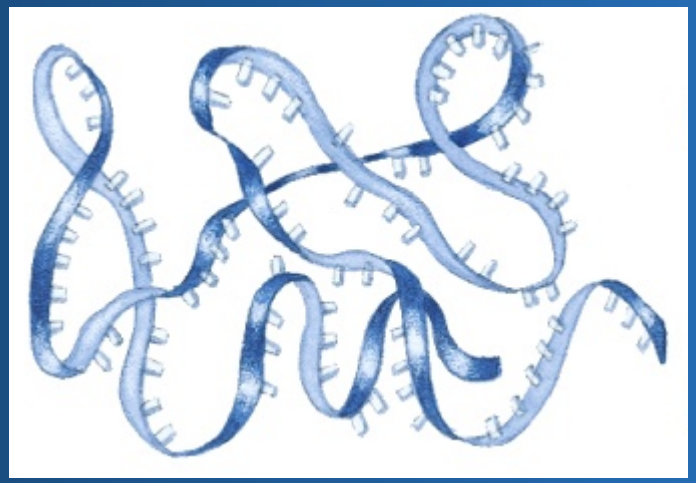
↓

formazione anse se forte complemementareità ai lati

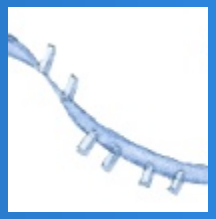
Denaturazione reversibile e riassociazione del DNA



Rinaturazione e competizione



Bersaglio



Frammento complementare

Filamento complementare

In una gara di ibridazione

Chi vince?

Chi si associa più velocemente?