DNA structure

Structural Biology

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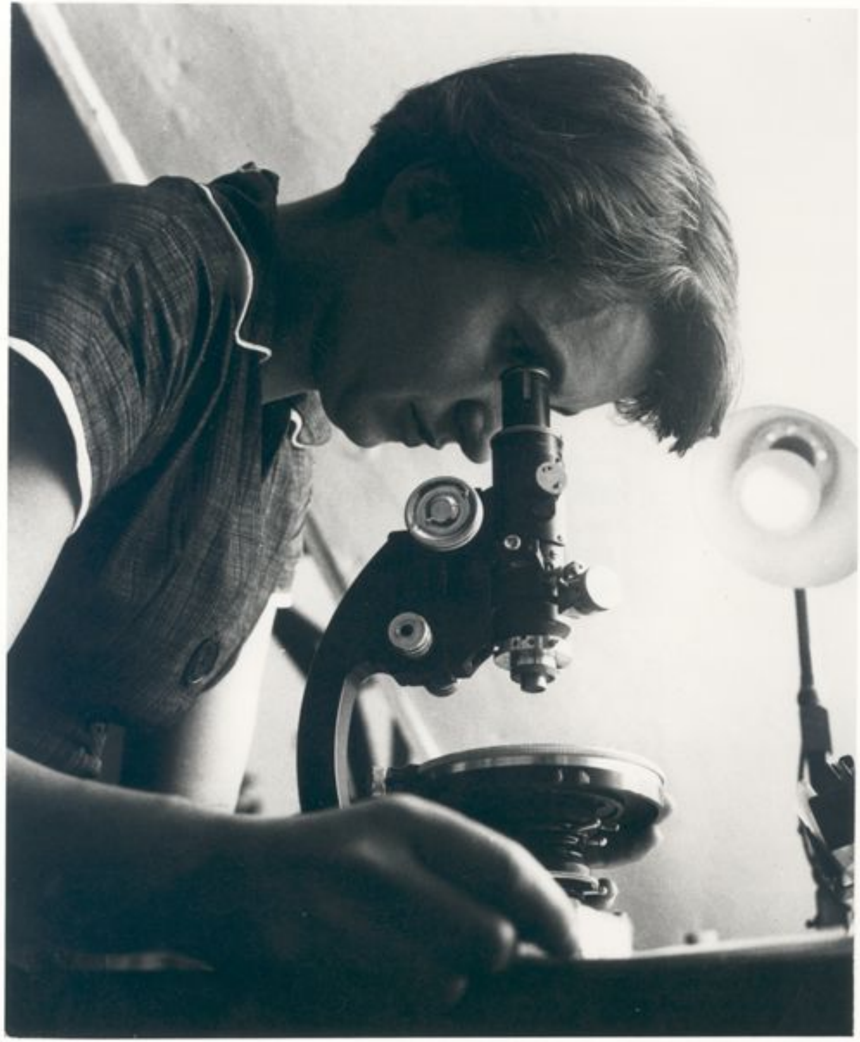
Andrés Martín
Adrià Mas
Ferran Pegenaute

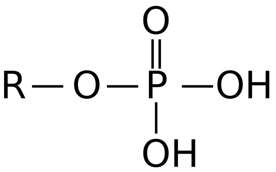


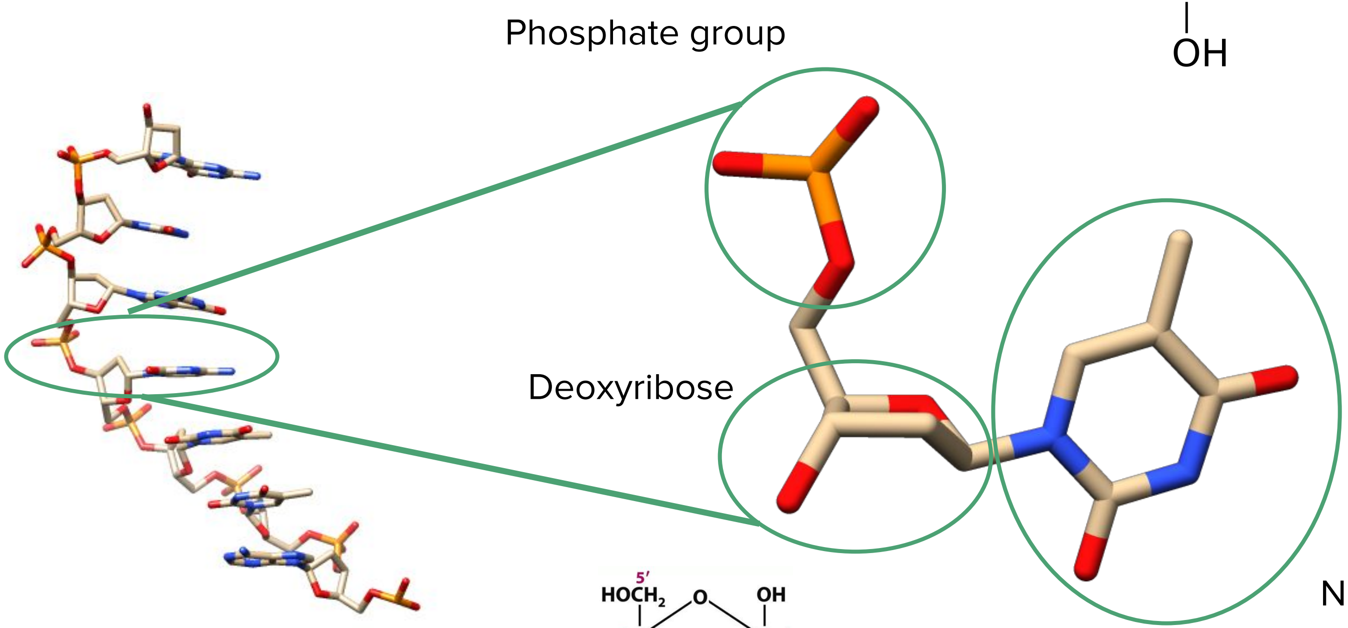
History

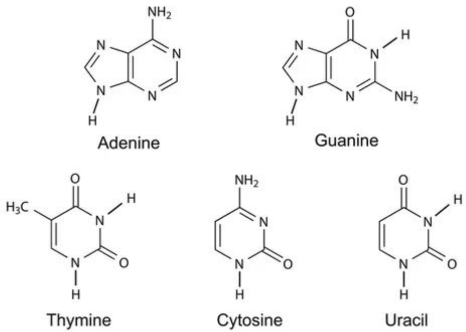
- 1866: Gregor Mendel - Mendelian inheritance
- 1869: Friedrich Miescher - isolation of nucleic acid
- 1910: Thomas Morgan - role of chromosome
- 1923: Frederick Griffith - bacterial transformation
- 1944: Oswald Avery - “DNA makes genes and chromosomes”
- 1950: Erwin Chargaff - Chargaff’s rules
- 1952: Rosalind Franklin, et al - B-DNA image
- 1965: Marshall Nirenberg - genetic code
- 1974: Recombinant DNA
- 1977: Frederick Sanger
- 1990-2003: Human Genome Project
- 1996: Dolly
- 2000: DNA nanotechnology
- 2008: 23andMe
- 2013: CRISPR-Cas9
- 2018: first human baby modified by CRISPR-Cas9

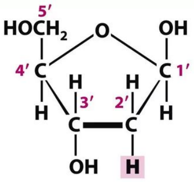
Primary structure

Primary structure: nucleotide



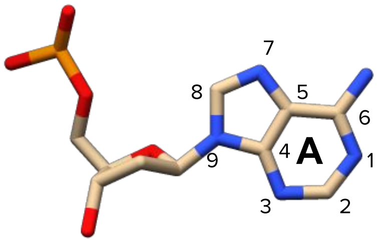


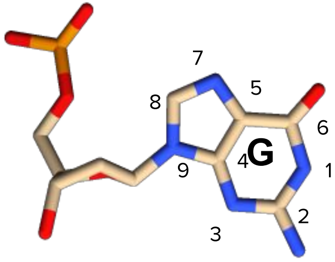




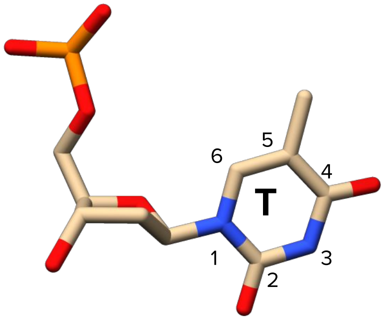
Primary structure: nitrogenous bases

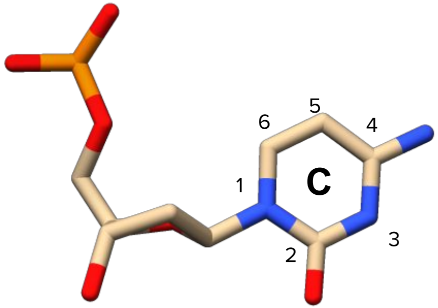
Purines

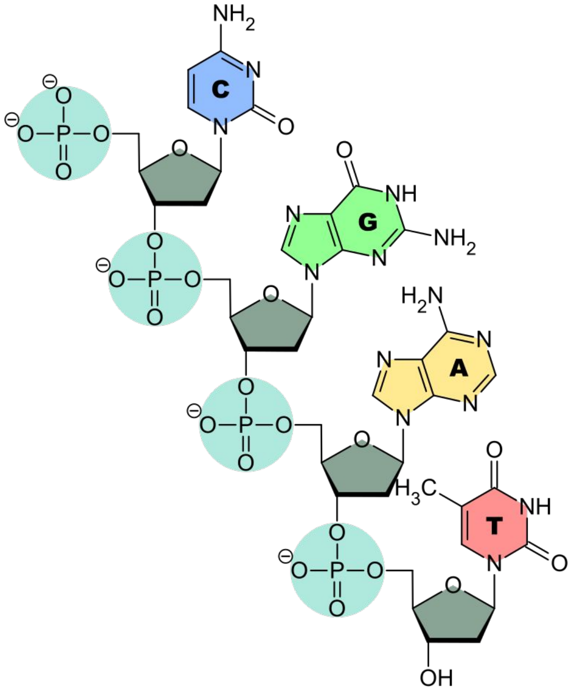




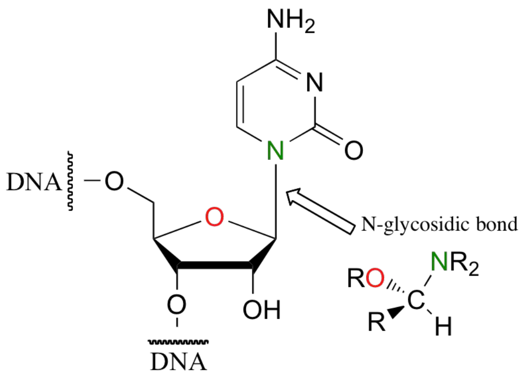
Pyrimidines

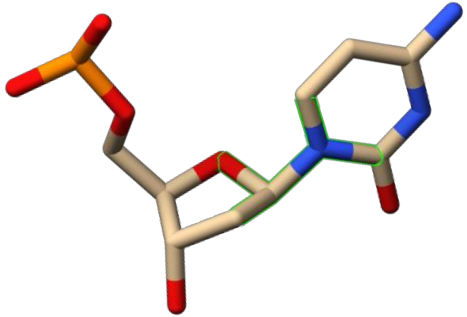


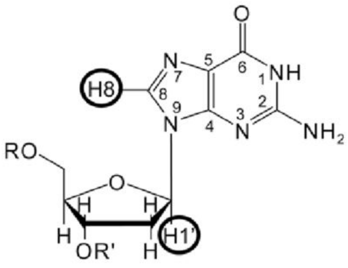




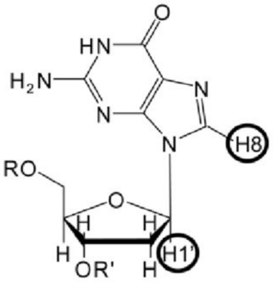
Primary structure: N-glycosidic bond





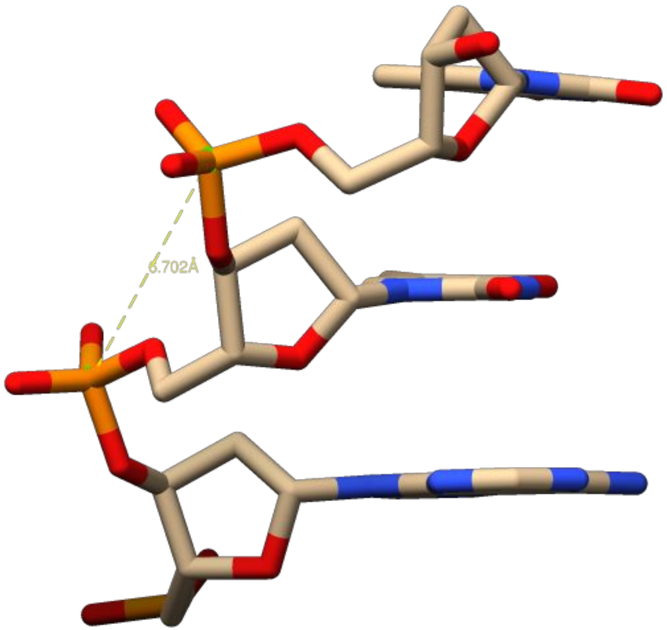


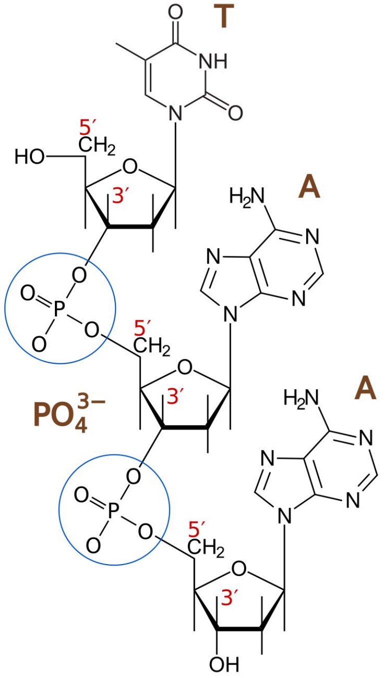
anti



syn

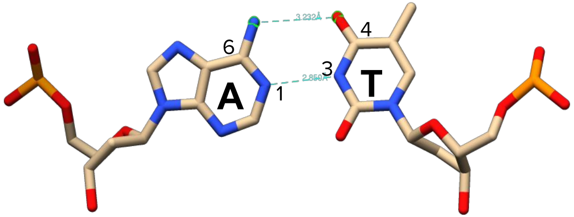
Primary structure: phosphodiester bond

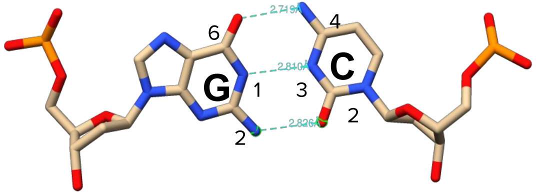




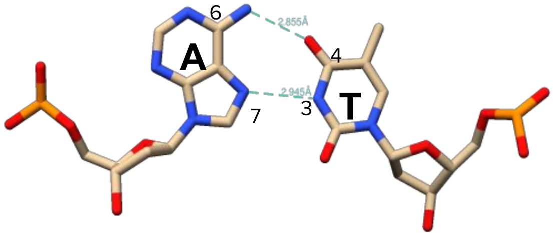
Primary structure: hydrogen bonds

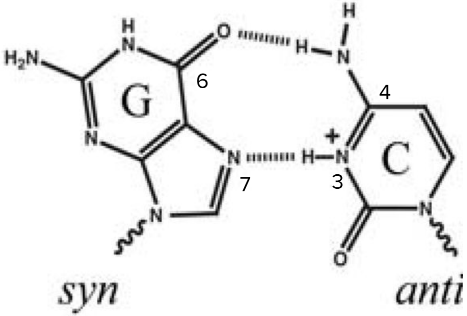
Watson & Crick

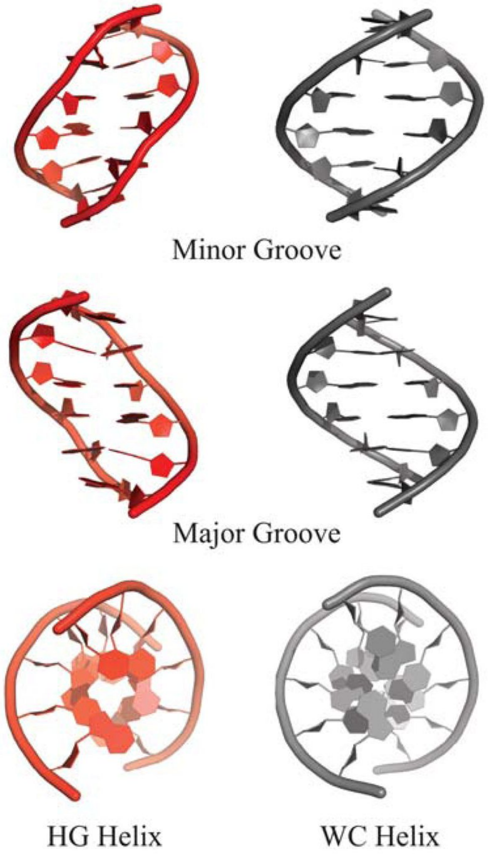




Hoogsteen



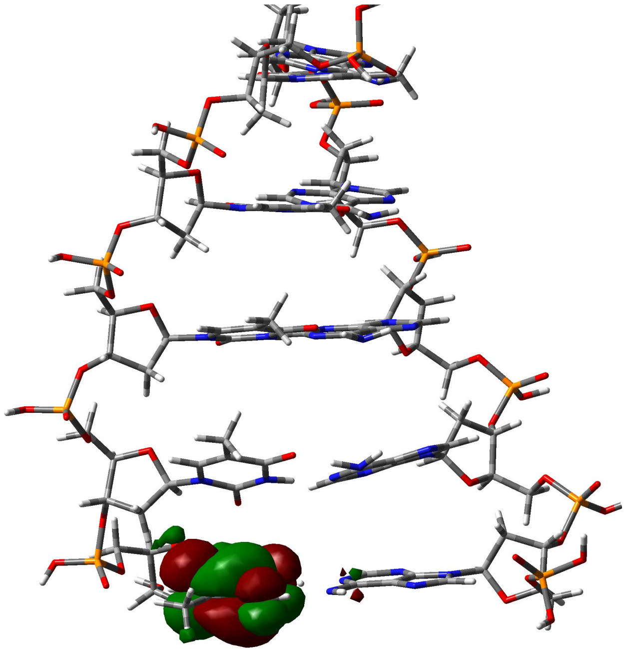




Nikolova E, Zhou H, Gottardo F, Alvey H, Kimsey I, Al-Hashimi H. A historical account of hoogsteen base-pairs in duplex DNA. *Biopolymers*. 2013;99(12):doi:955-968

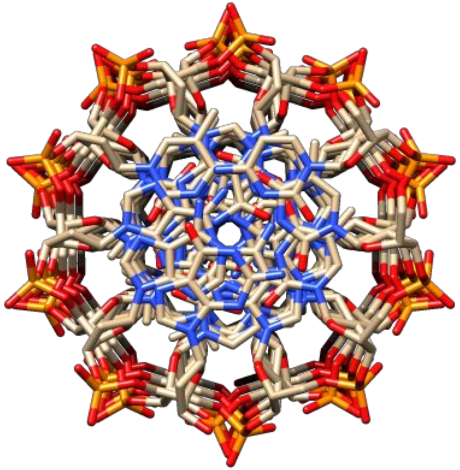
Primary structure: Π stacking

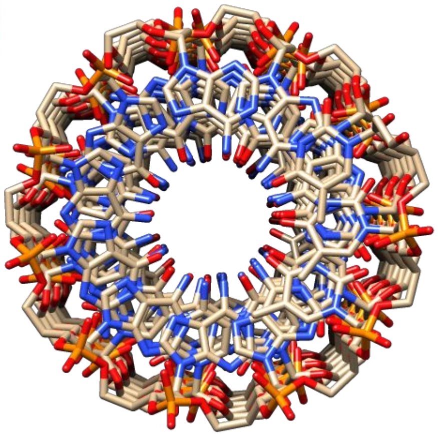
- Non-covalent interactions
- Attraction
- Aromatic molecules (nucleosides)

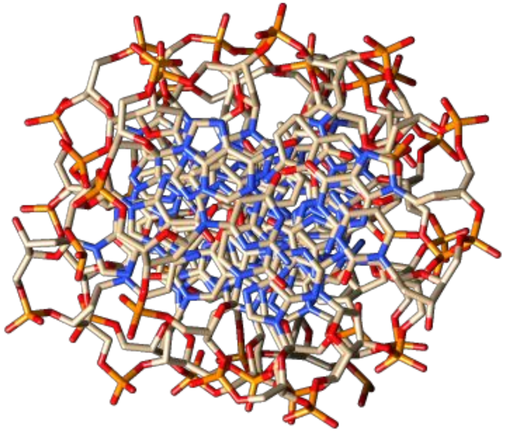


DNA types:Canonical DNA

Parameter	A-DNA	B-DNA	Z-DNA
Helix sense	right-handed	right-handed	left-handed
Residues per turn	11	10.5	12
Axial rise [Å]	2.55	3.4	3.7
Helix pitch(°)	28	34	45
Base pair tilt(°)	20	−6	7
Rotation per residue (°)	33	36	-30
Diameter of helix [Å]	23	20	18
Glycosidic bond configuration dA,dT,dC dG	 anti anti	 anti anti	 anti syn
Sugar pucker dA,dT,dC dG	 C3'-endo C3'-endo	 C2'-endo C2'-endo	 C2'-endo C3'-endo

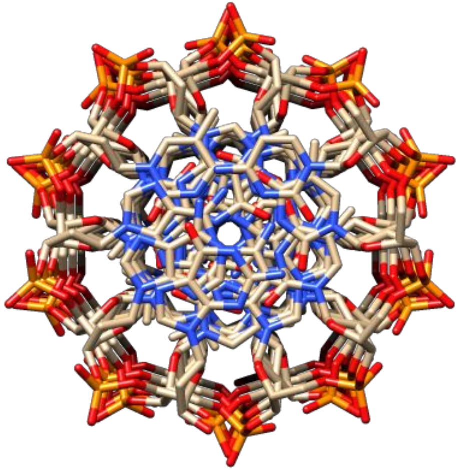


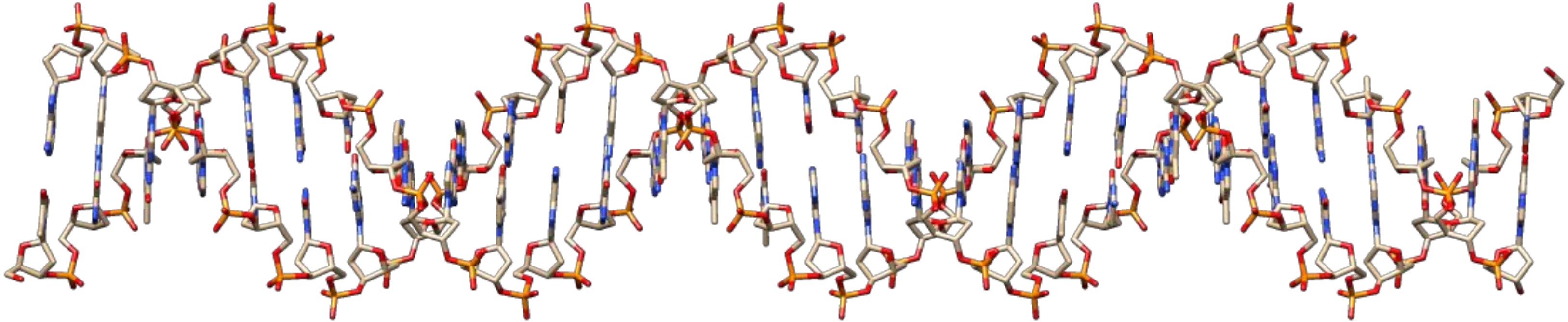




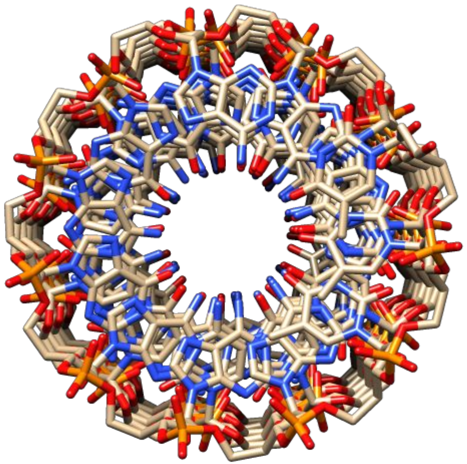
Overview: B-DNA

- Most common DNA conformation *in vivo*
- 10,5 bases per turn of helix
- Bases almost perpendicular to axis
- Glycosidic bond: Anti
- Wide major groove: transcription factor access.
- Narrow minor groove

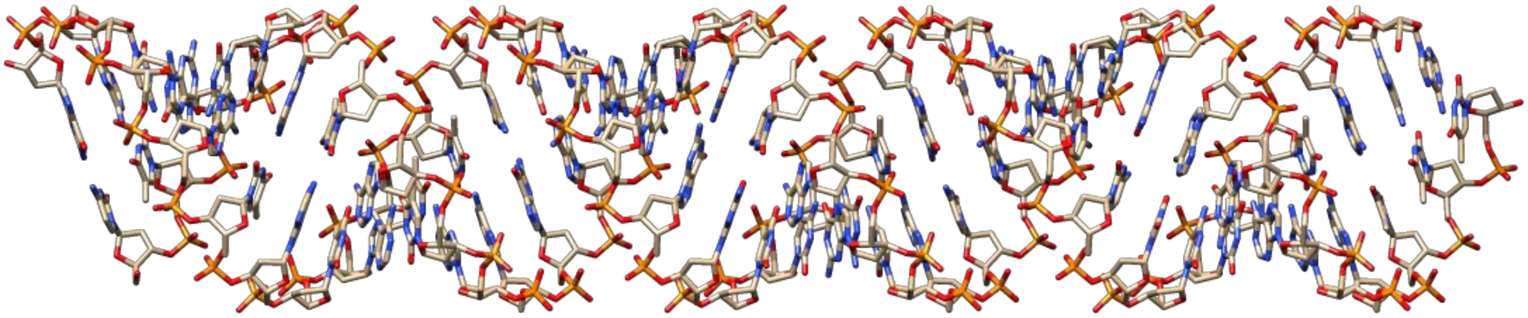




Overview: A-DNA

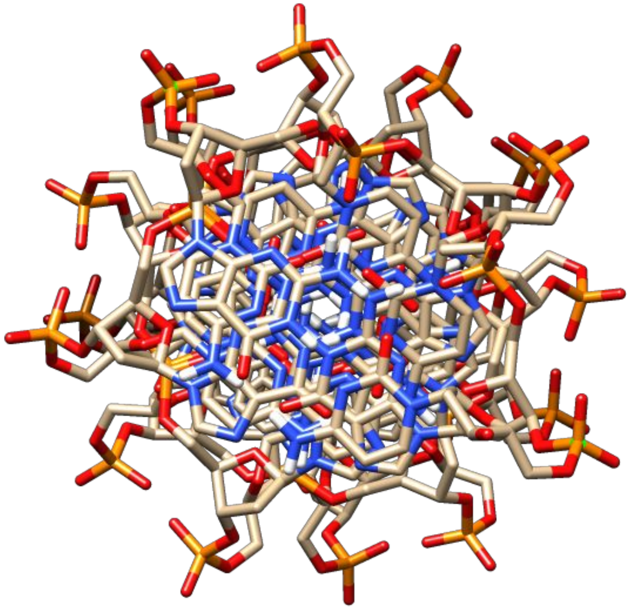


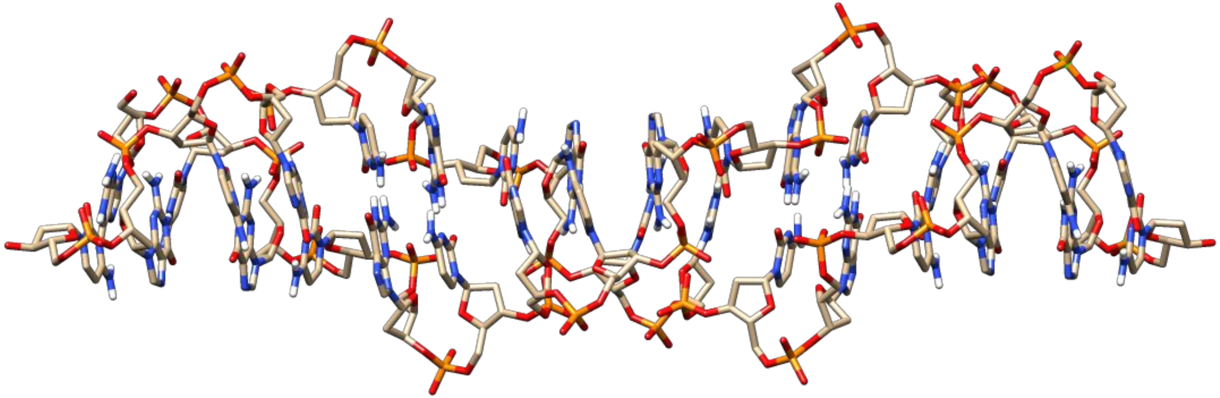
- Occurs at low hydration
- 11 bases per helix turn
- Bases tilted 20° from axis
- Glycosidic bond: Anti
- Major groove: Narrow & deep
- Minor groove: Wide & shallow



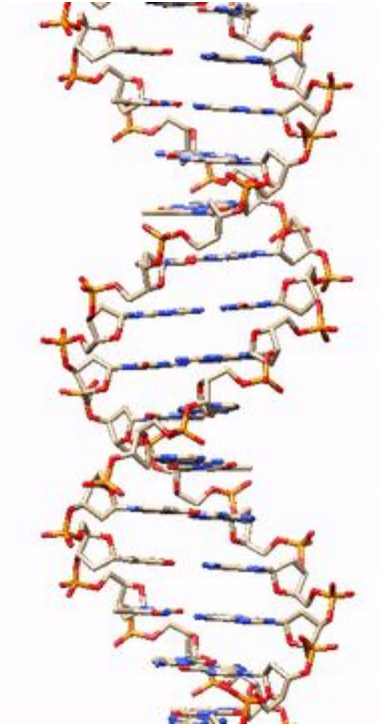
Overview: Z-DNA

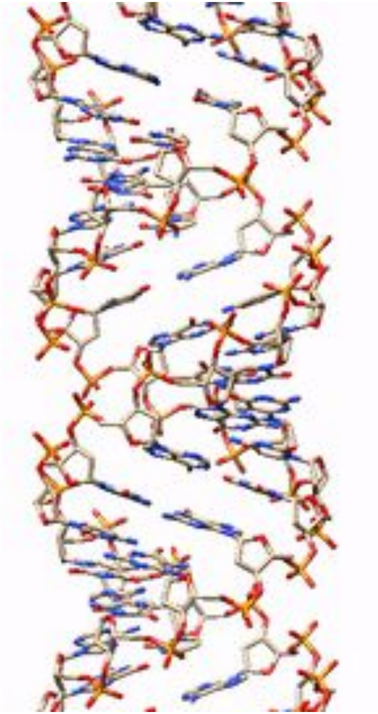
- Left-handed helix
- Needs specific sequence & conditions
- Narrow, long backbone in zigzag pattern
- 12 bases per helix turn
- Glycosidic bond: Syn/anti
- Only one groove

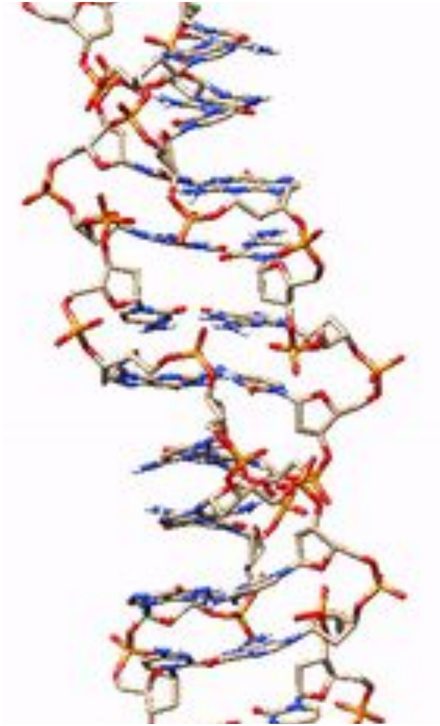




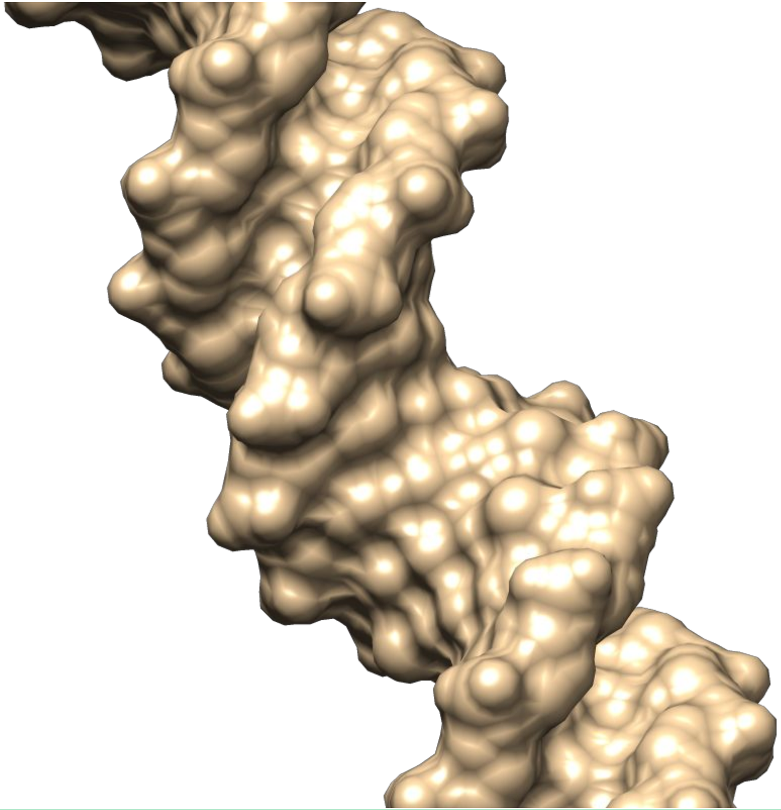
Canonical DNA comparison: Helix direction

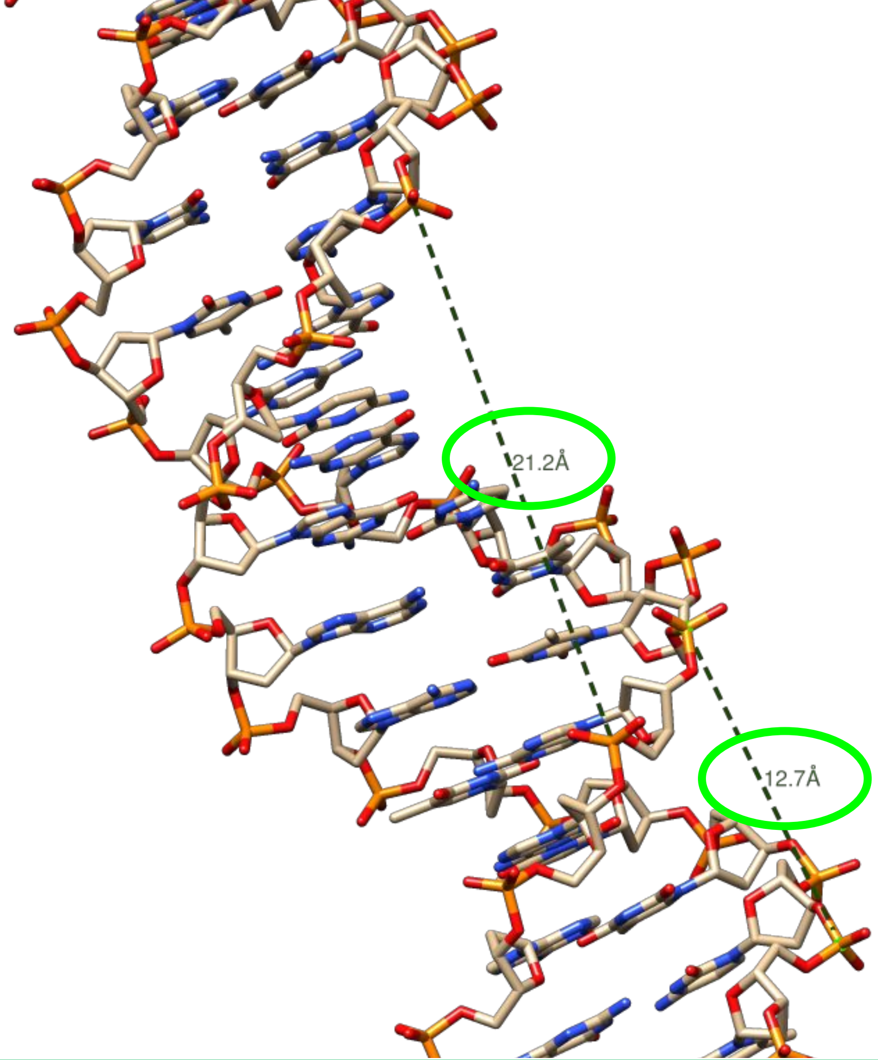




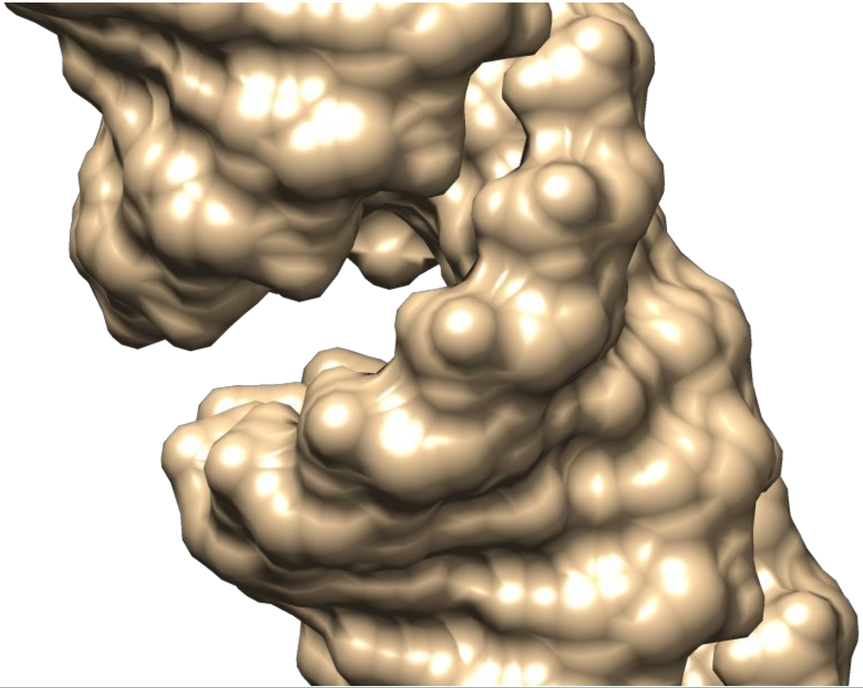


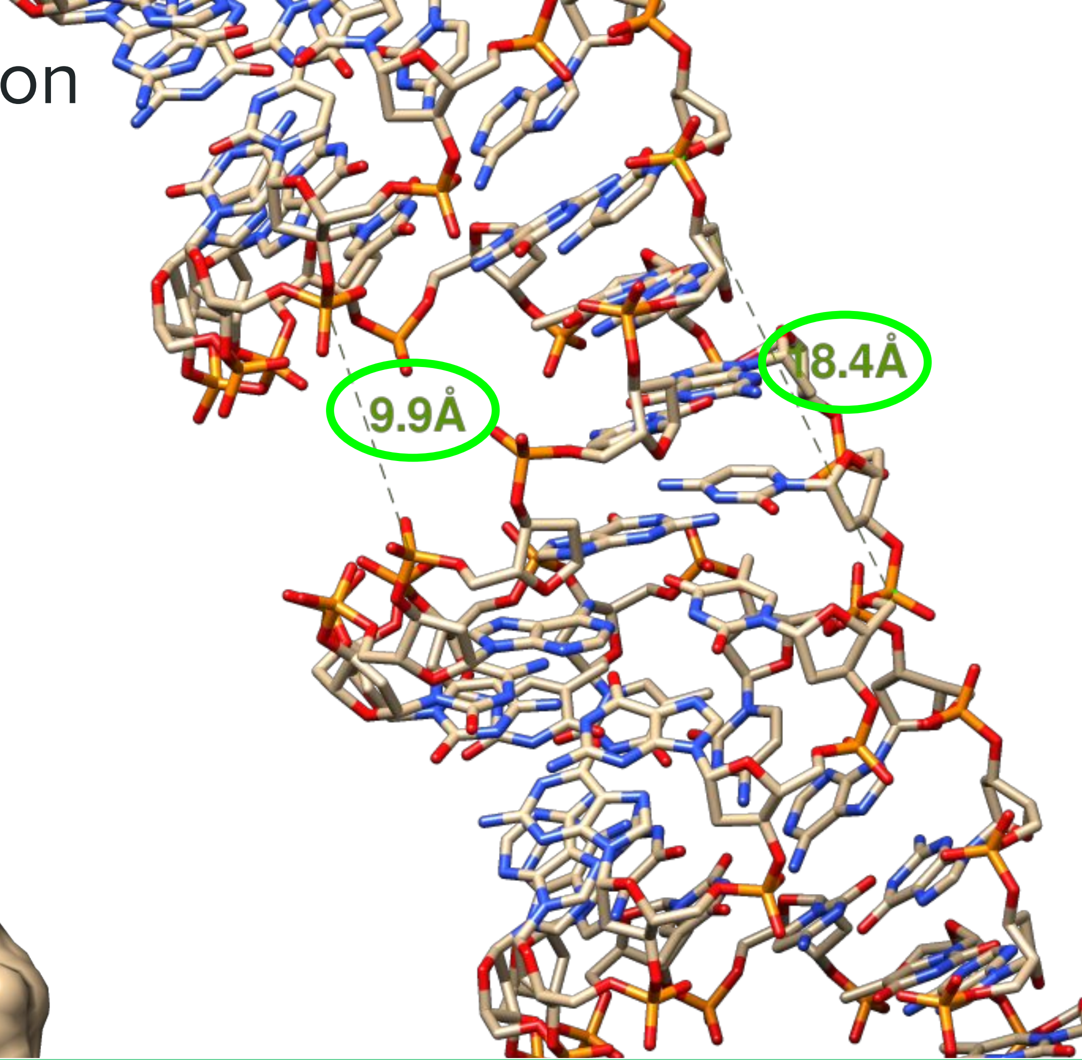
Canonical DNA comparison
Grooves: B-DNA



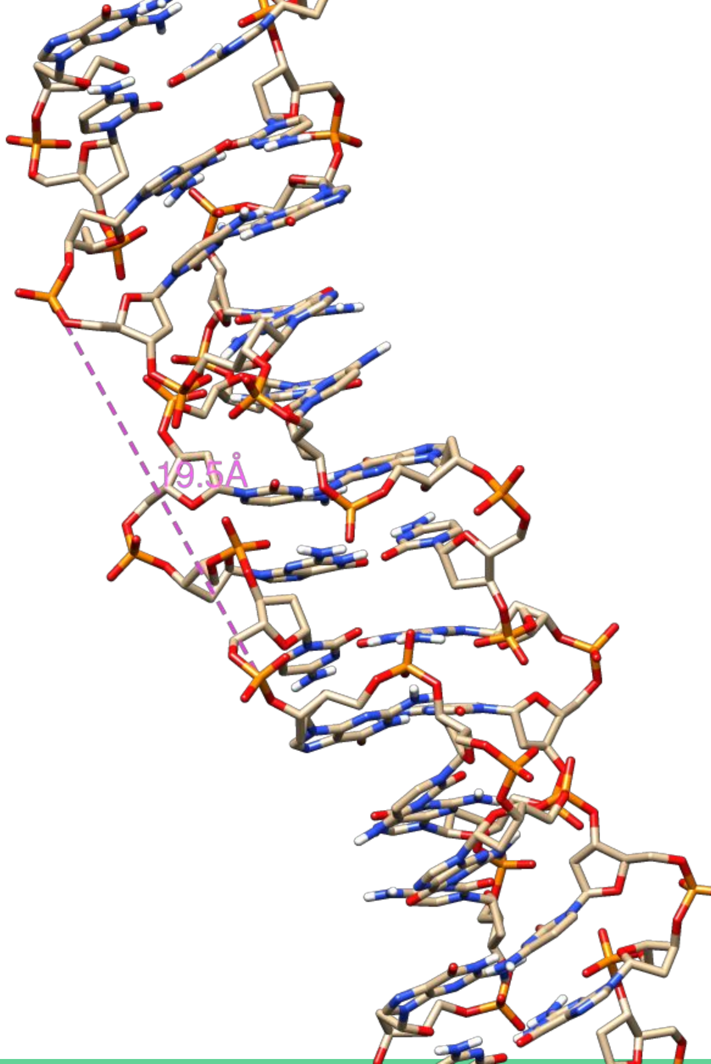


Canonical DNA comparison
Grooves: A-DNA

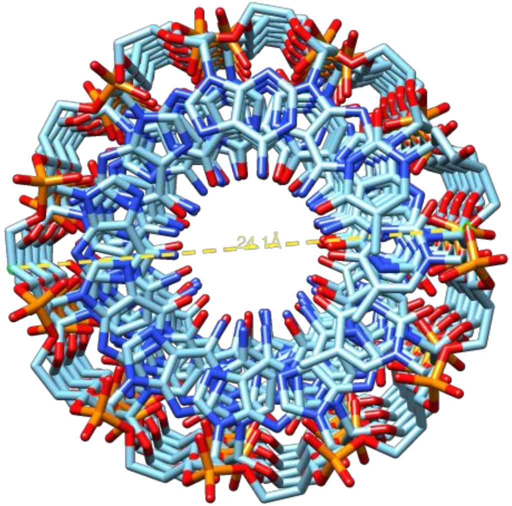




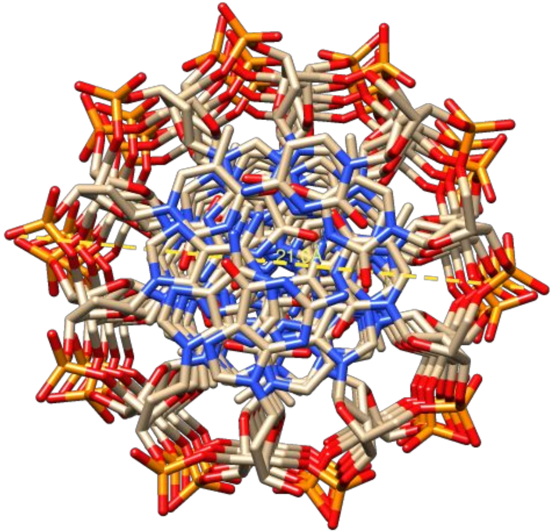
Canonical DNA comparison
Grooves: Z-DNA



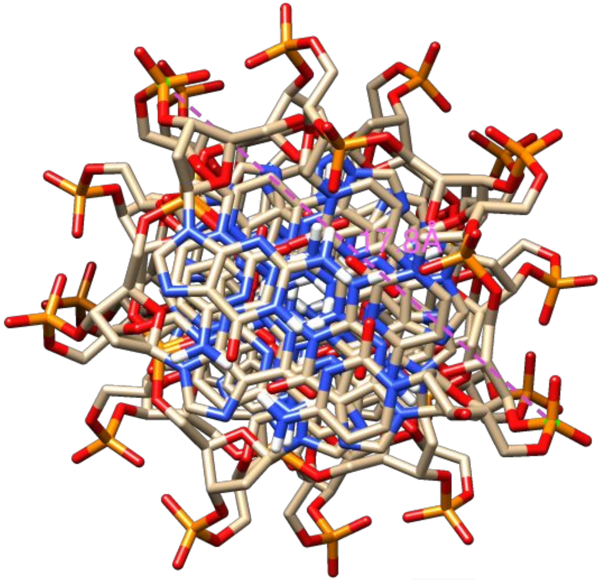
Canonical DNA comparison: Helical diameter



A (23 Å)

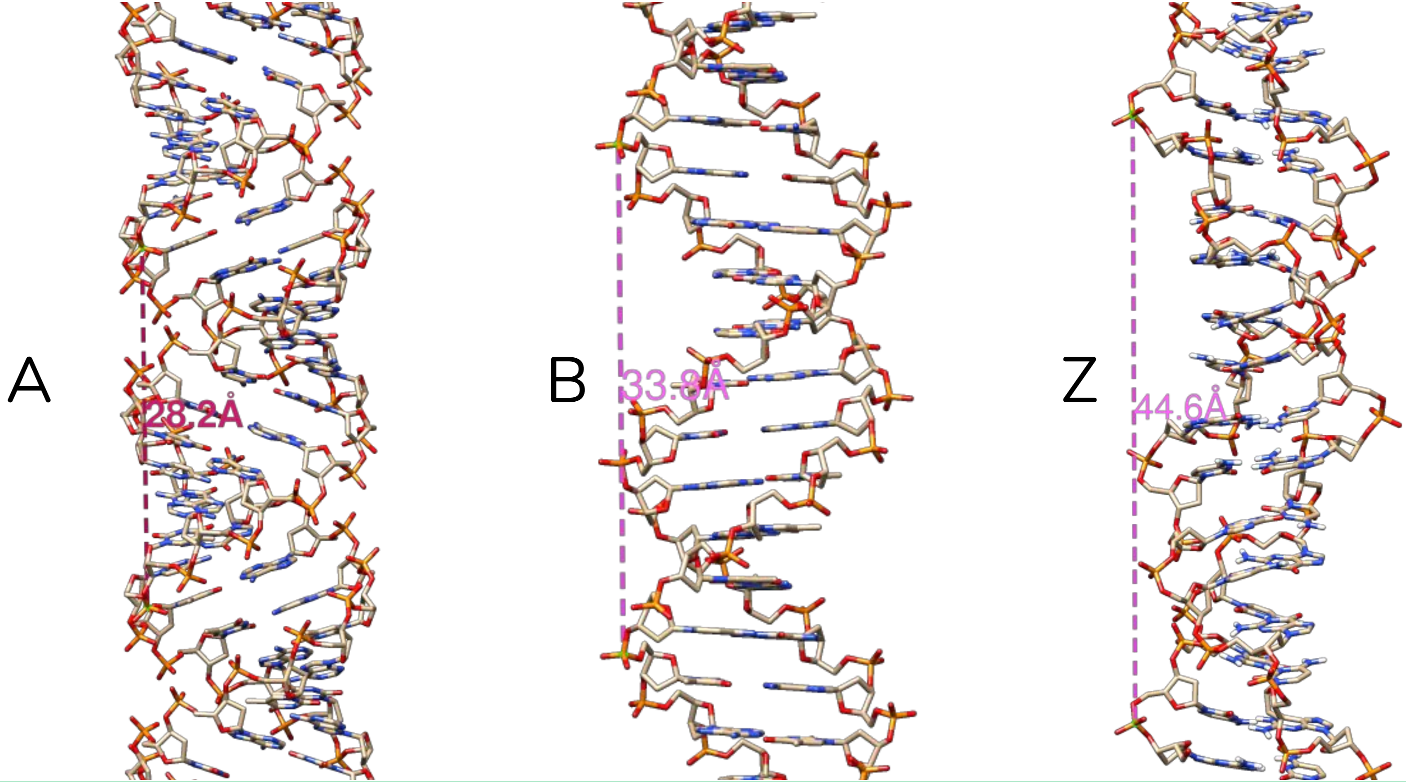


B (20Å)

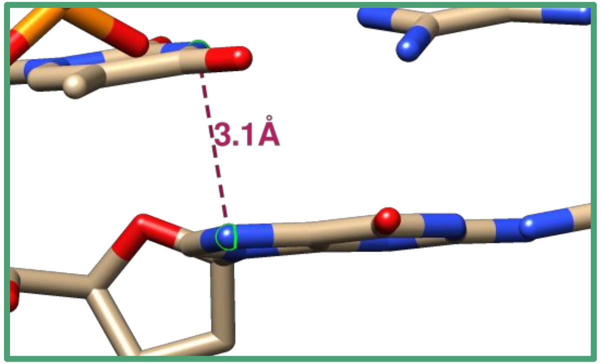


Z (18Å)

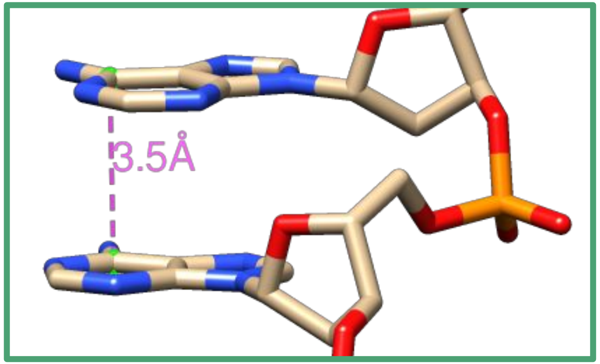
Canonical DNA comparison: Helical pitch



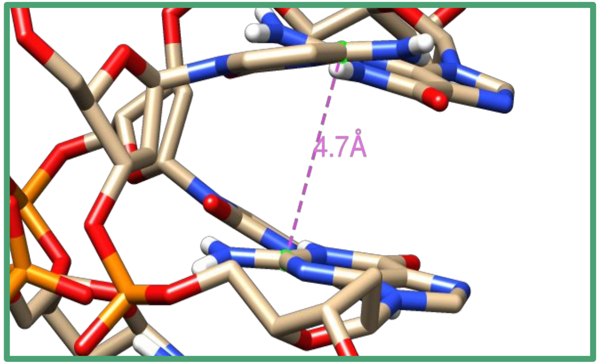
Canonical DNA comparison: Axial rise



A

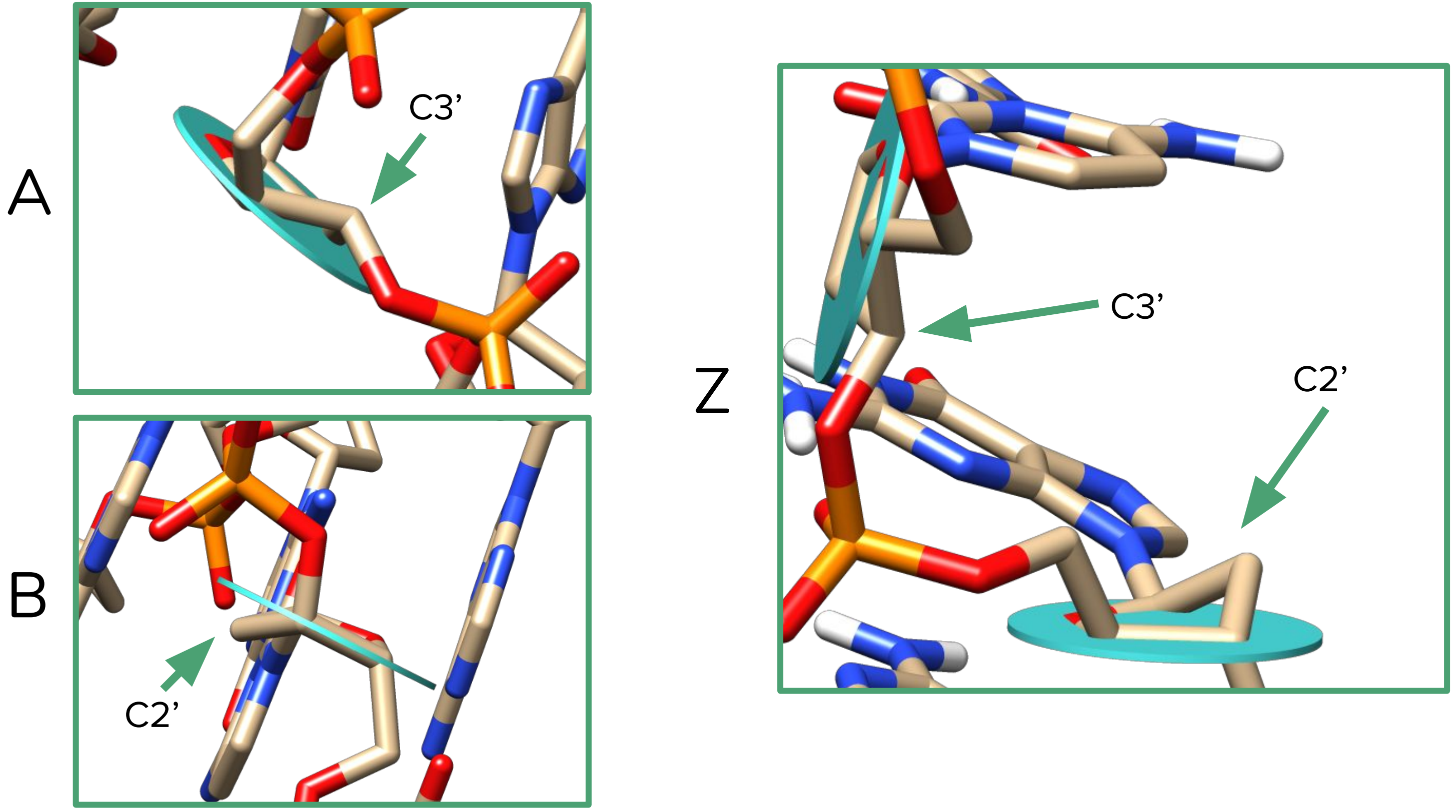


B



Z

Canonical DNA comparison: Sugar pucker



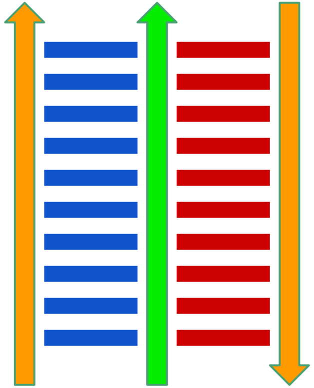
Non-canonical DNA

Triplex DNA

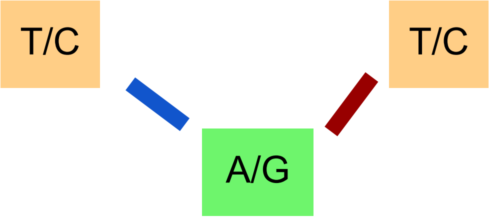
PDB: 1BWG (From: Asensio J, Brown T, Lane A. Solution conformation of a parallel DNA triple helix with 5′ and 3′ triplex–duplex junctions. Structure. 1999;7(1):1-11.)

Triplex DNA: Motifs

Parallel/Py.Pu.Py



Pyrimidine Motif



Interactions

Watson & Crick

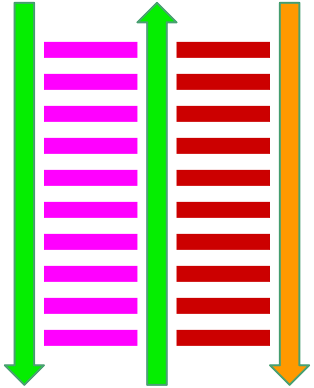
Hoogsteen

Rev. Hoogsteen

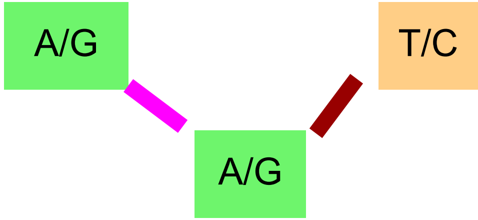
Purines

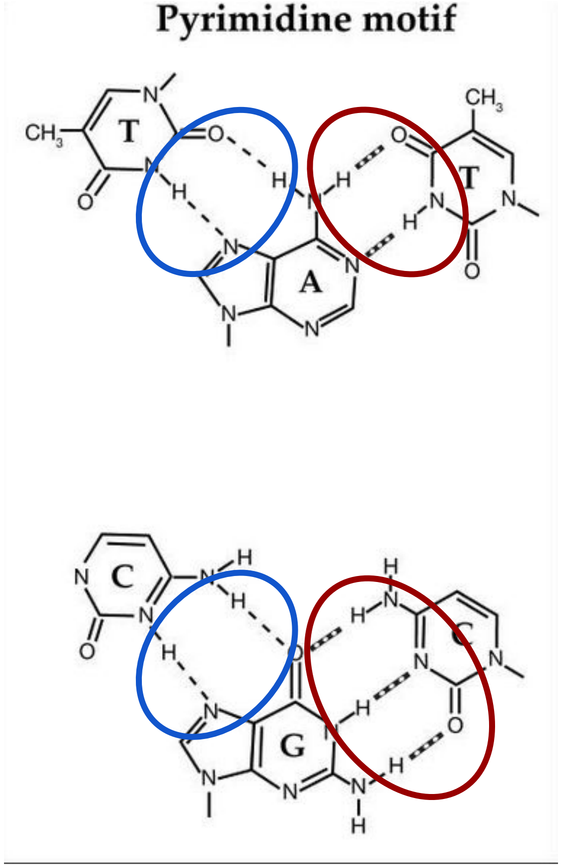
Pyrimidines

Antiparallel/Pu.Pu.Py



Purine Motif





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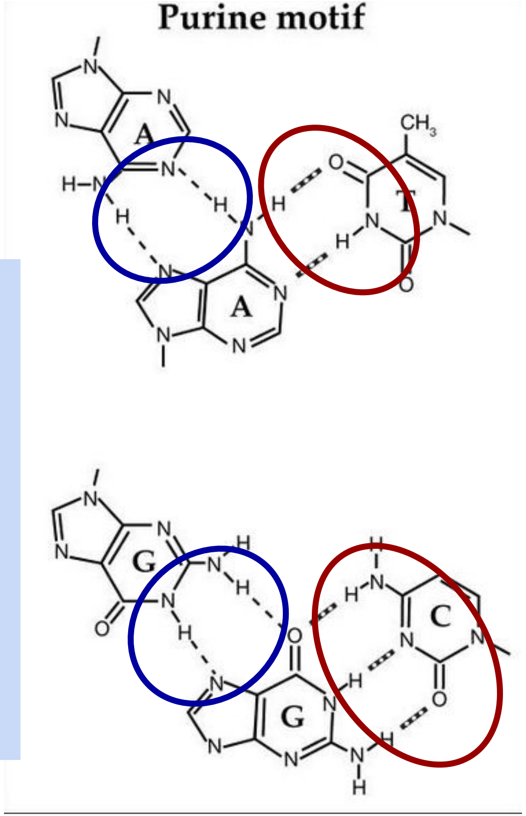
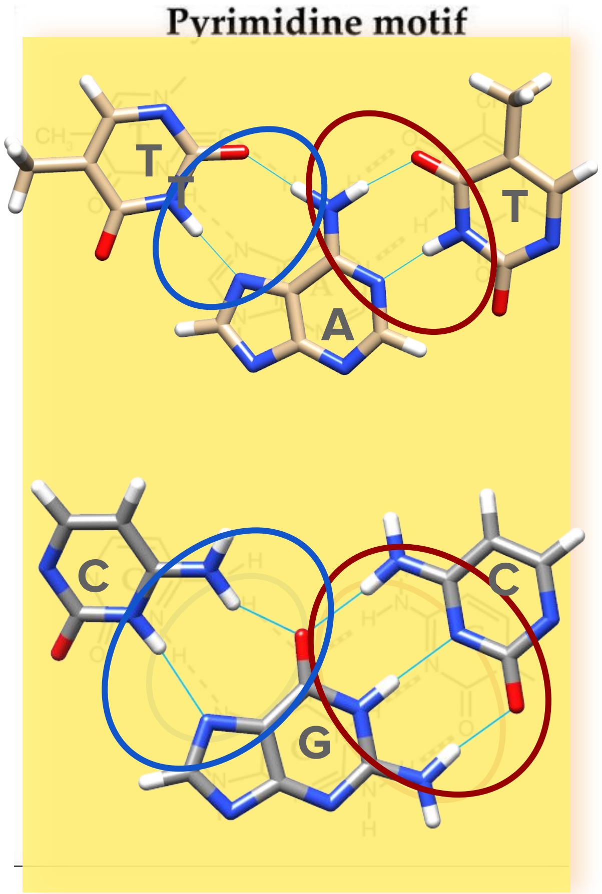
Rev. Hoogsteen



Parallel/ Py.Pu.Py

Antiparallel/Pu.Pu.Py



Interactions

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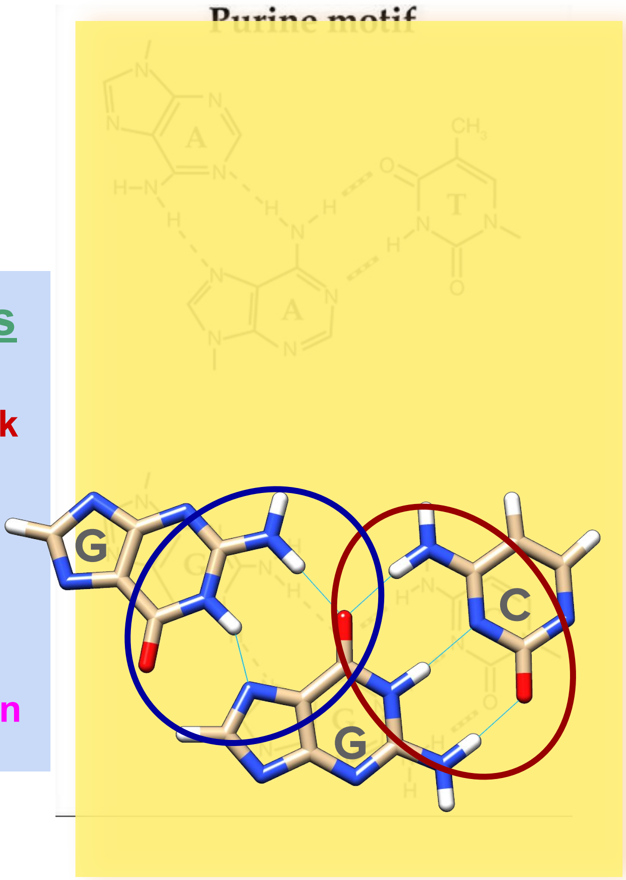
Rev. Hoogsteen

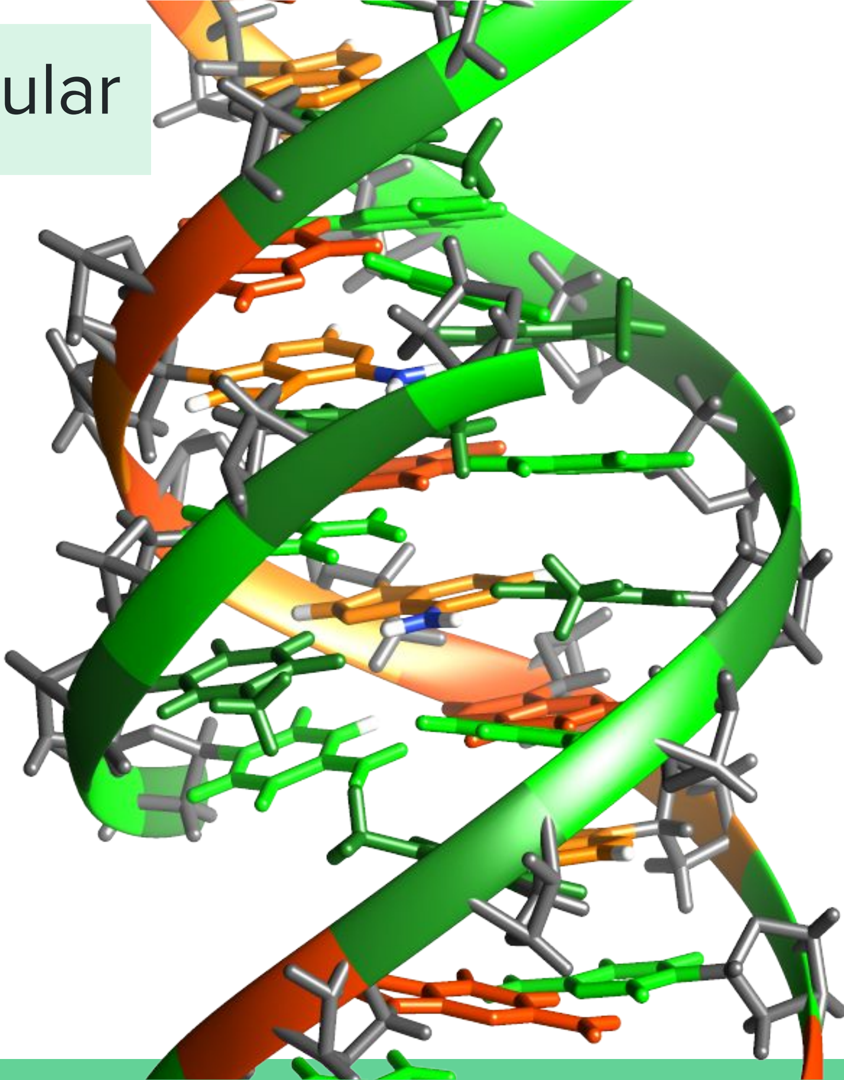


Parallel/ Py.Pu.Py

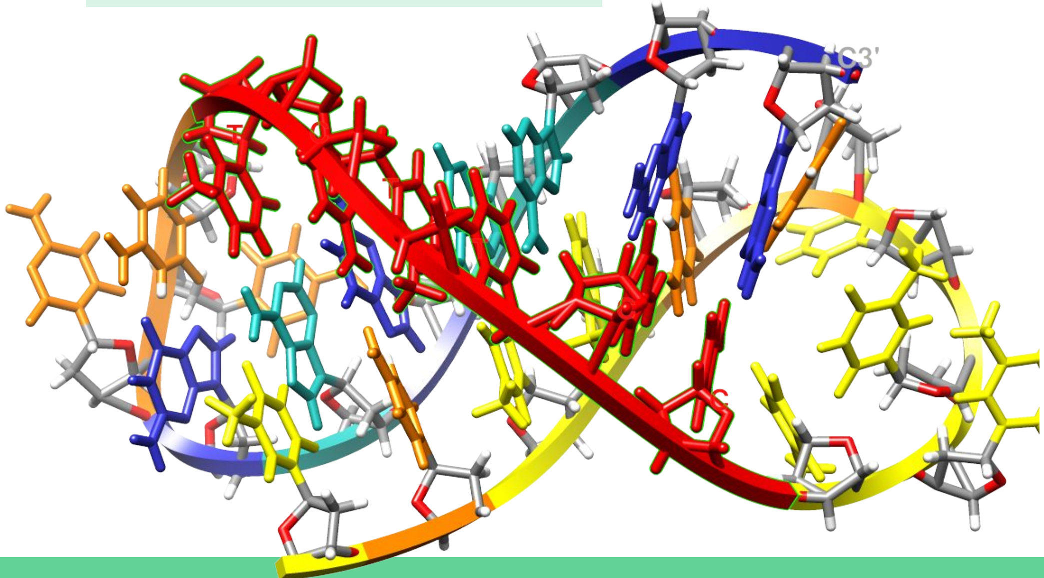
Antiparallel/Pu.Pu.Py

Triplex DNA

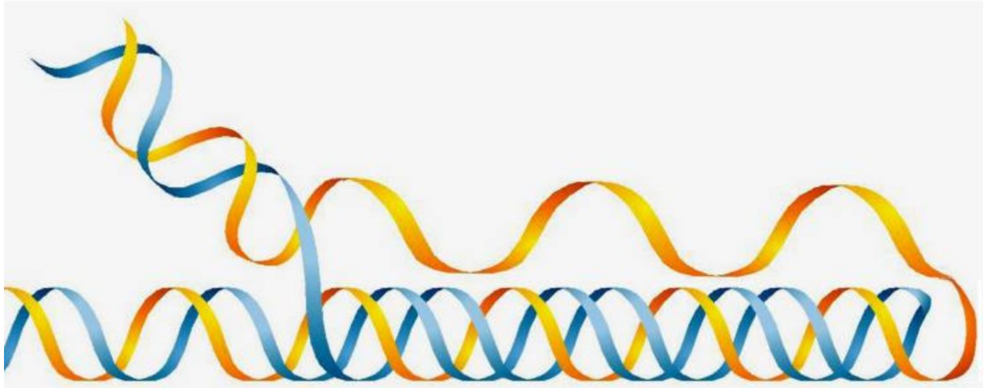
Intermolecular



Intramolecular



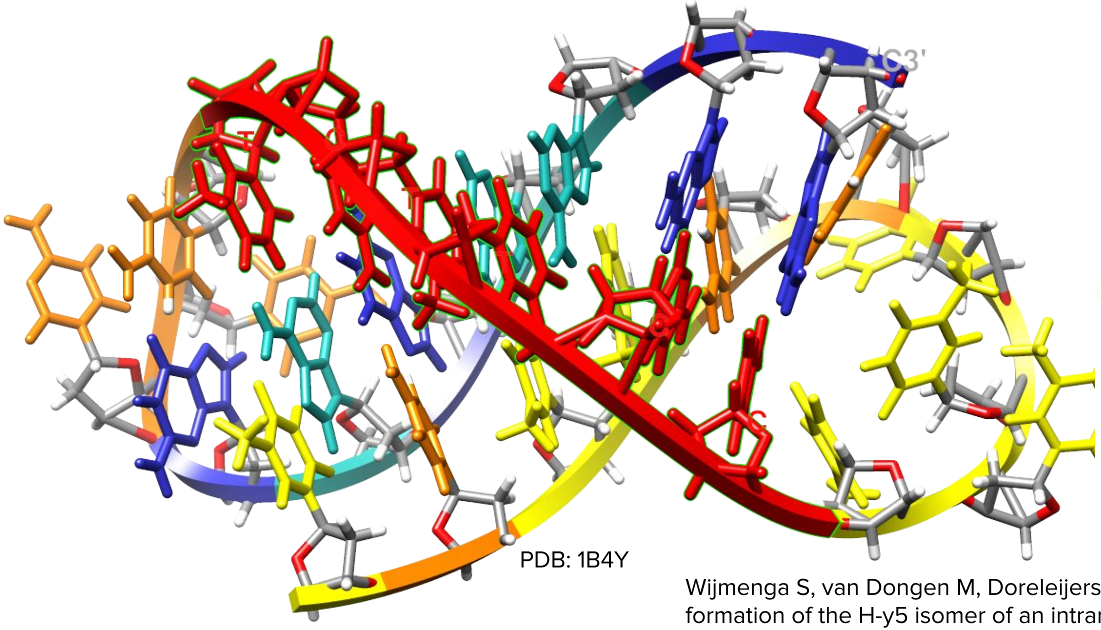
Intramolecular Triplex DNA



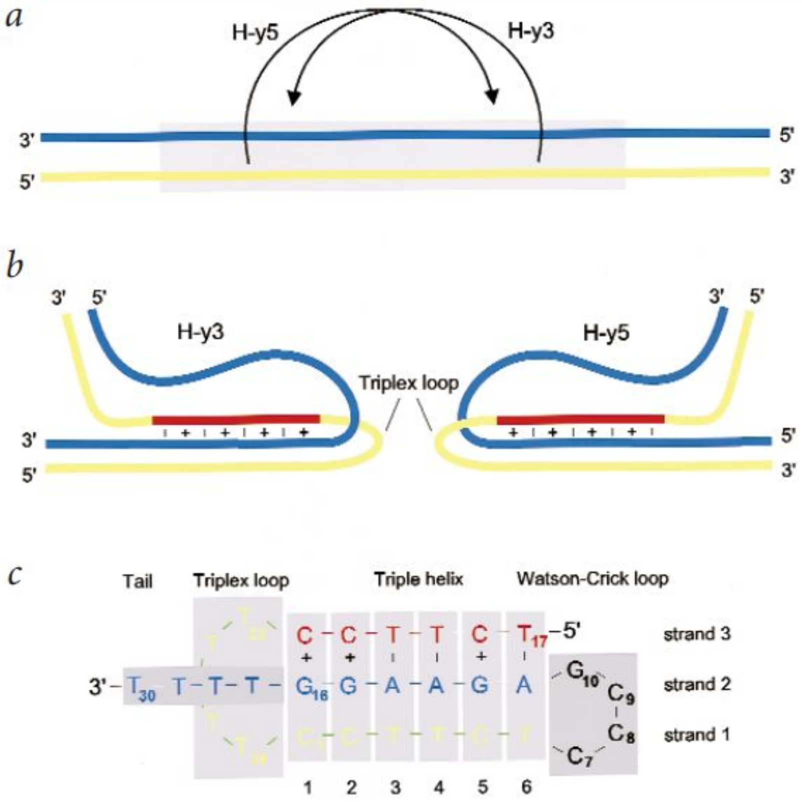
Jain A, Wang G, Vasquez K. DNA triple helices: Biological consequences and therapeutic potential. Biochimie. 2008;90(8):1117-1130.

Intramolecular Triplex DNA

H motifs H-y5

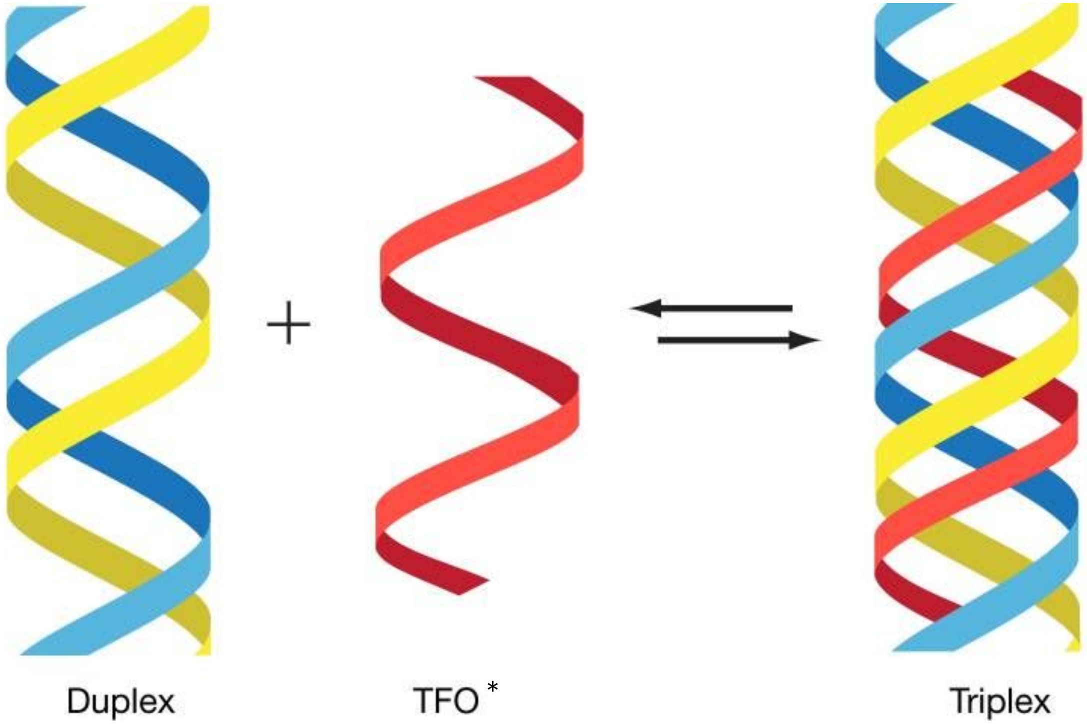


PDB: 1B4Y



Wijmenga S, van Dongen M, Doreleijers J, van der Marel G, van Boom J, Hilbers C.Structure and mechanism of formation of the H-y5 isomer of an intramolecular DNA triple helix. Nature Structural Biology. 1999;6(9):854-859.

Intermolecular Triplex DNA

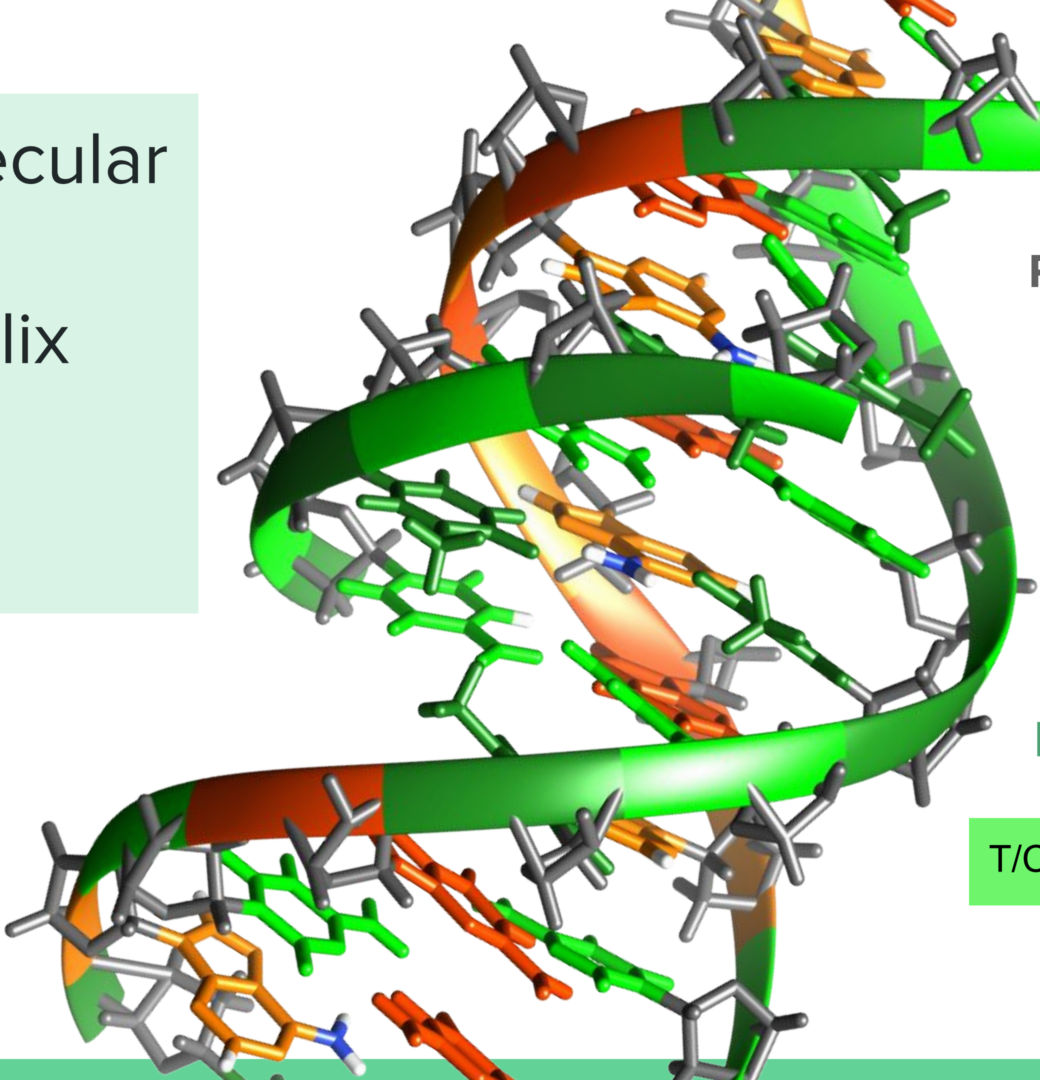


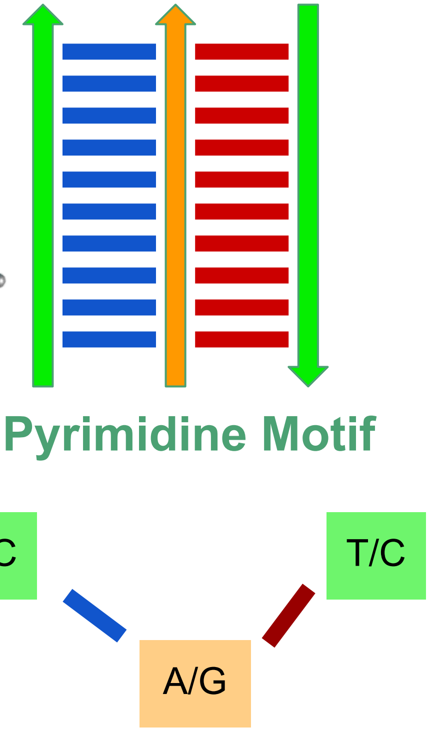
Jain A, Wang G, Vasquez K. DNA triple helices: Biological consequences and therapeutic potential. Biochimie. 2008;90(8):1117-1130.

***TFO:**

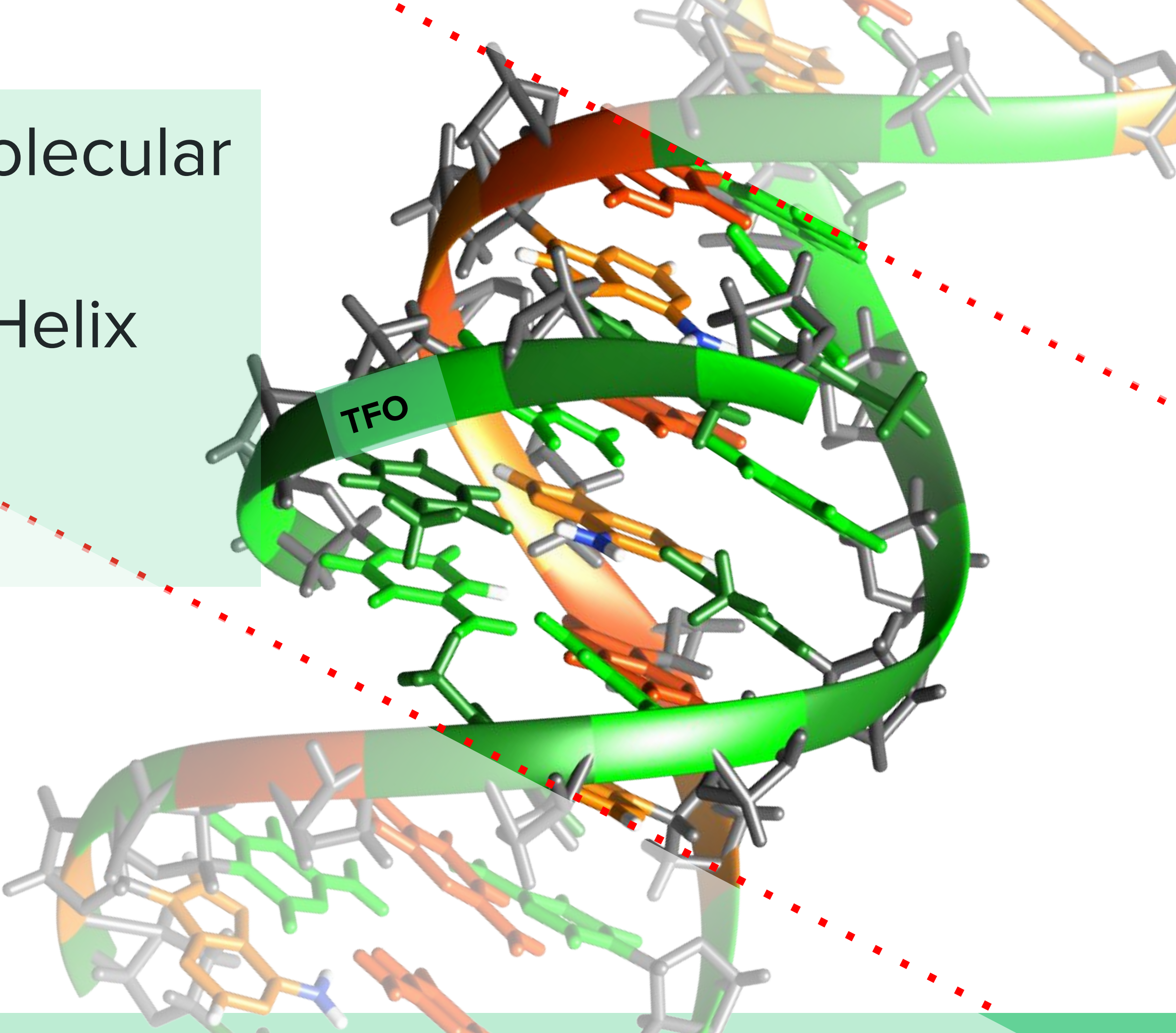
Triplex-forming oligonucleotide

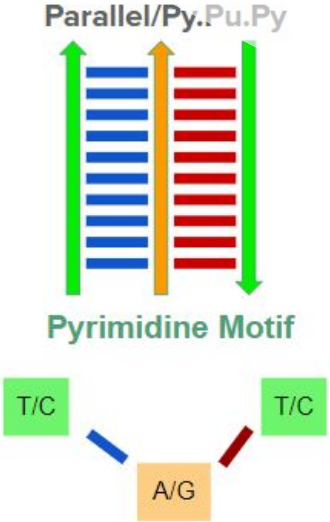
Intermolecular DNA Triple Helix



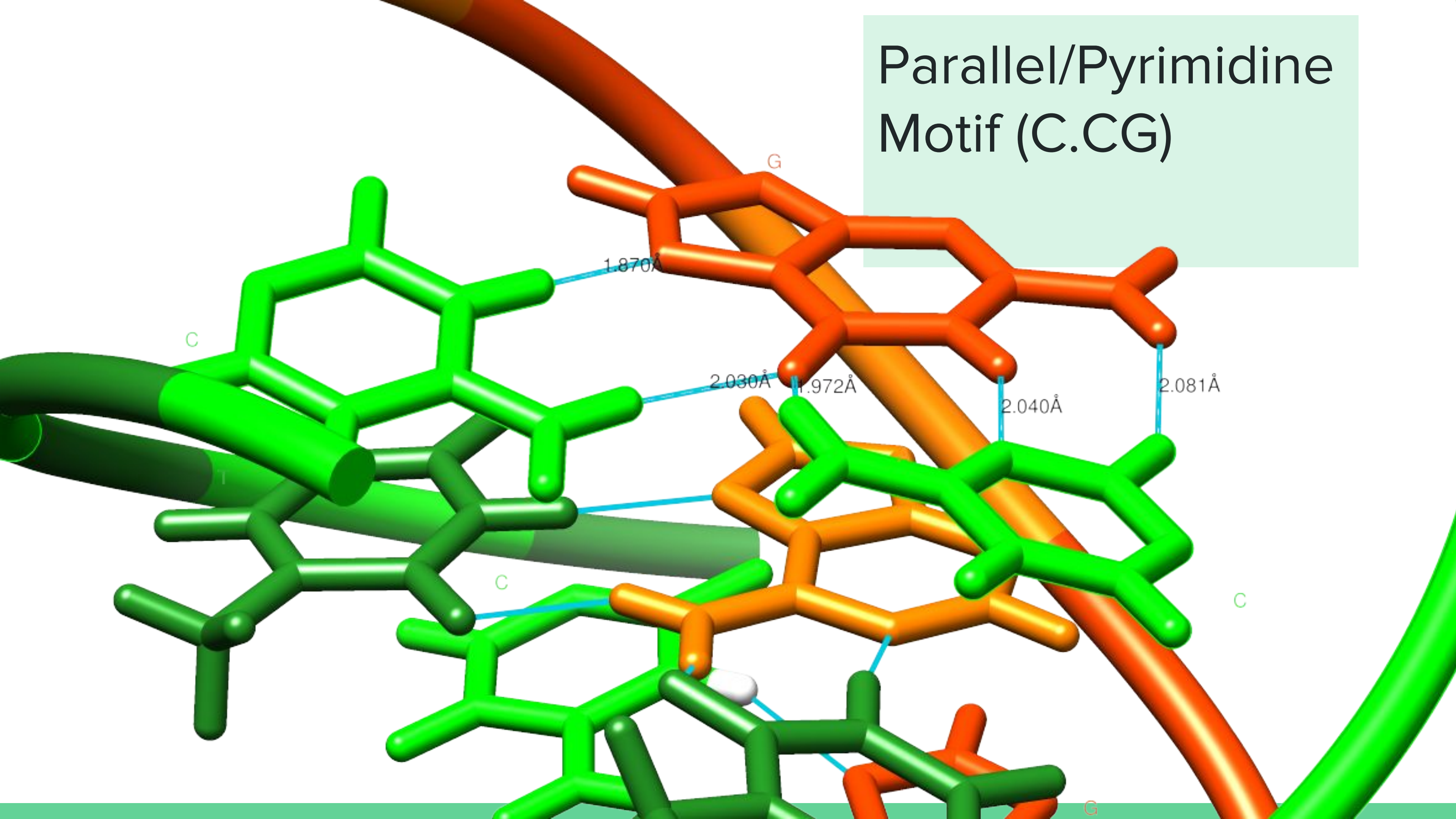


Intermolecular DNA Triple Helix

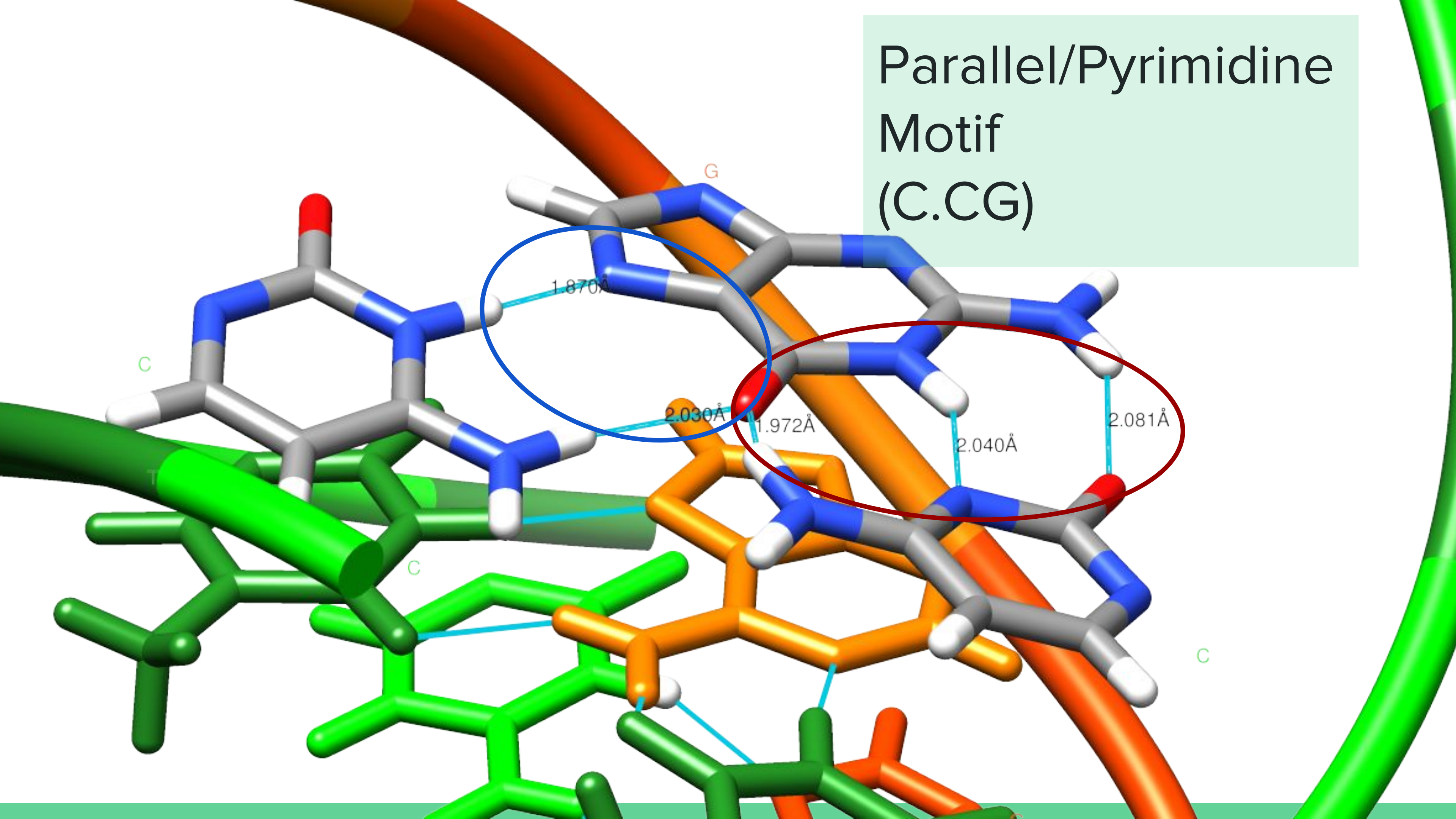




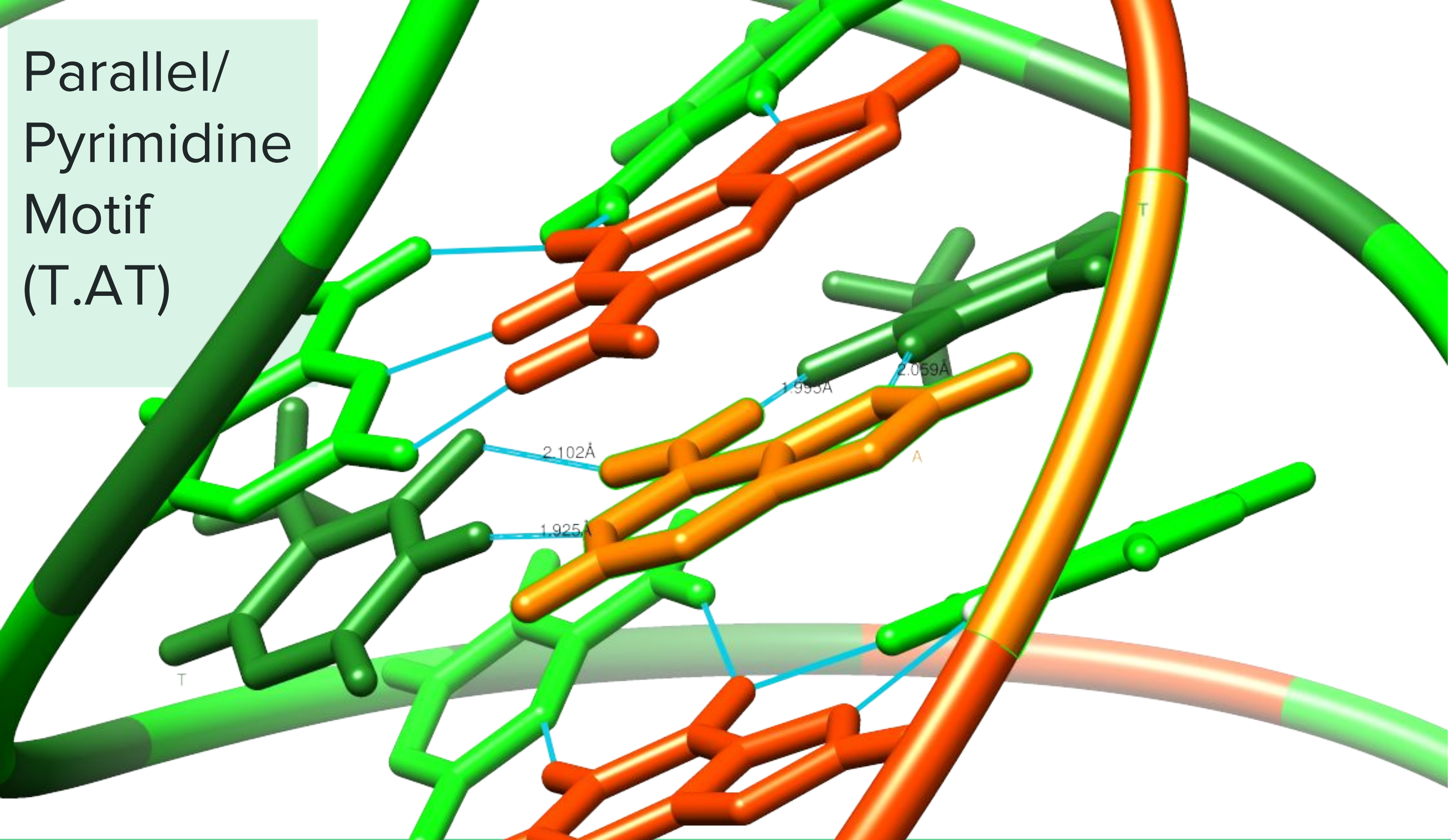
Parallel/Pyrimidine Motif (C.CG)



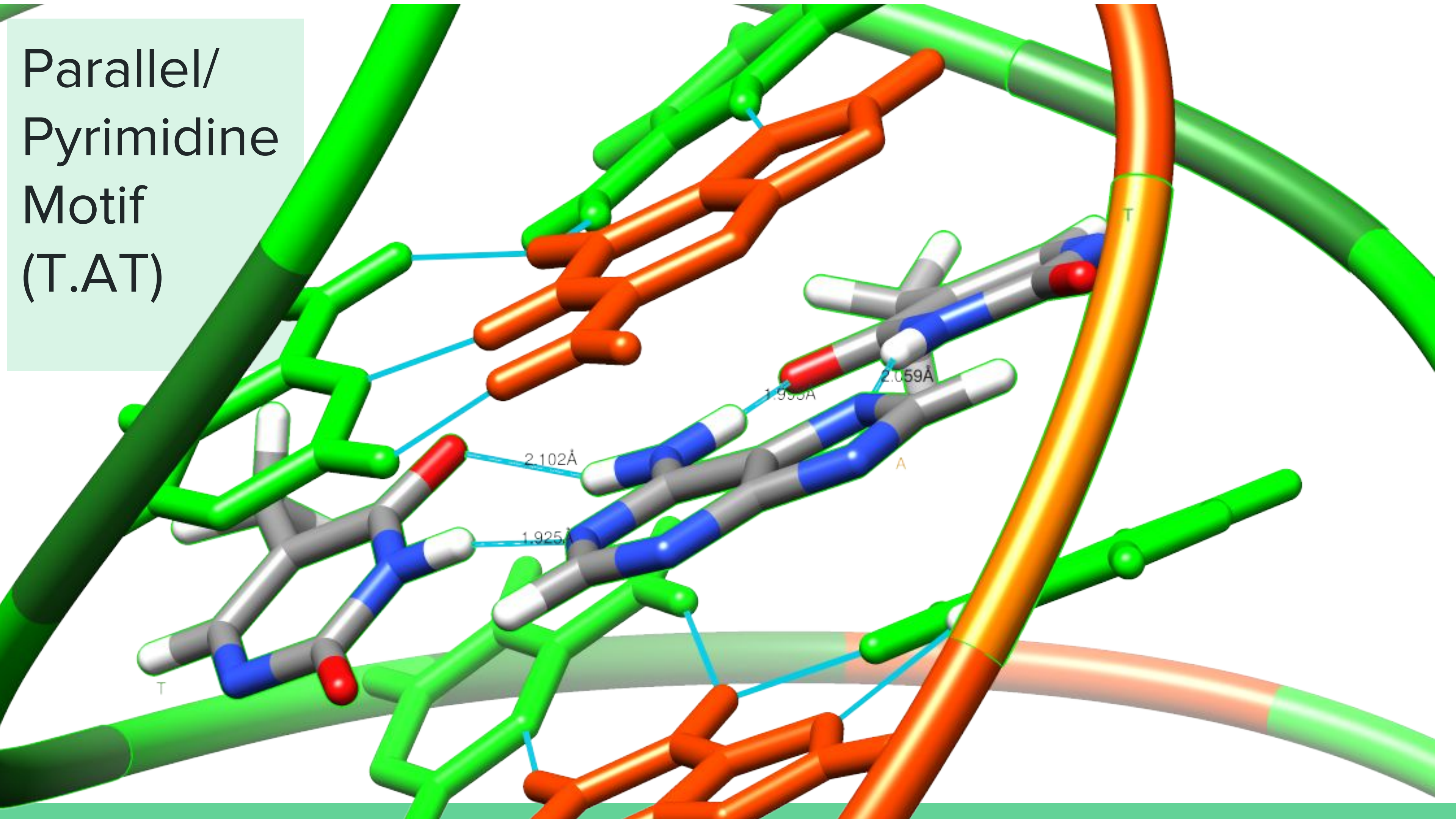
Parallel/Pyrimidine Motif (C.CG)



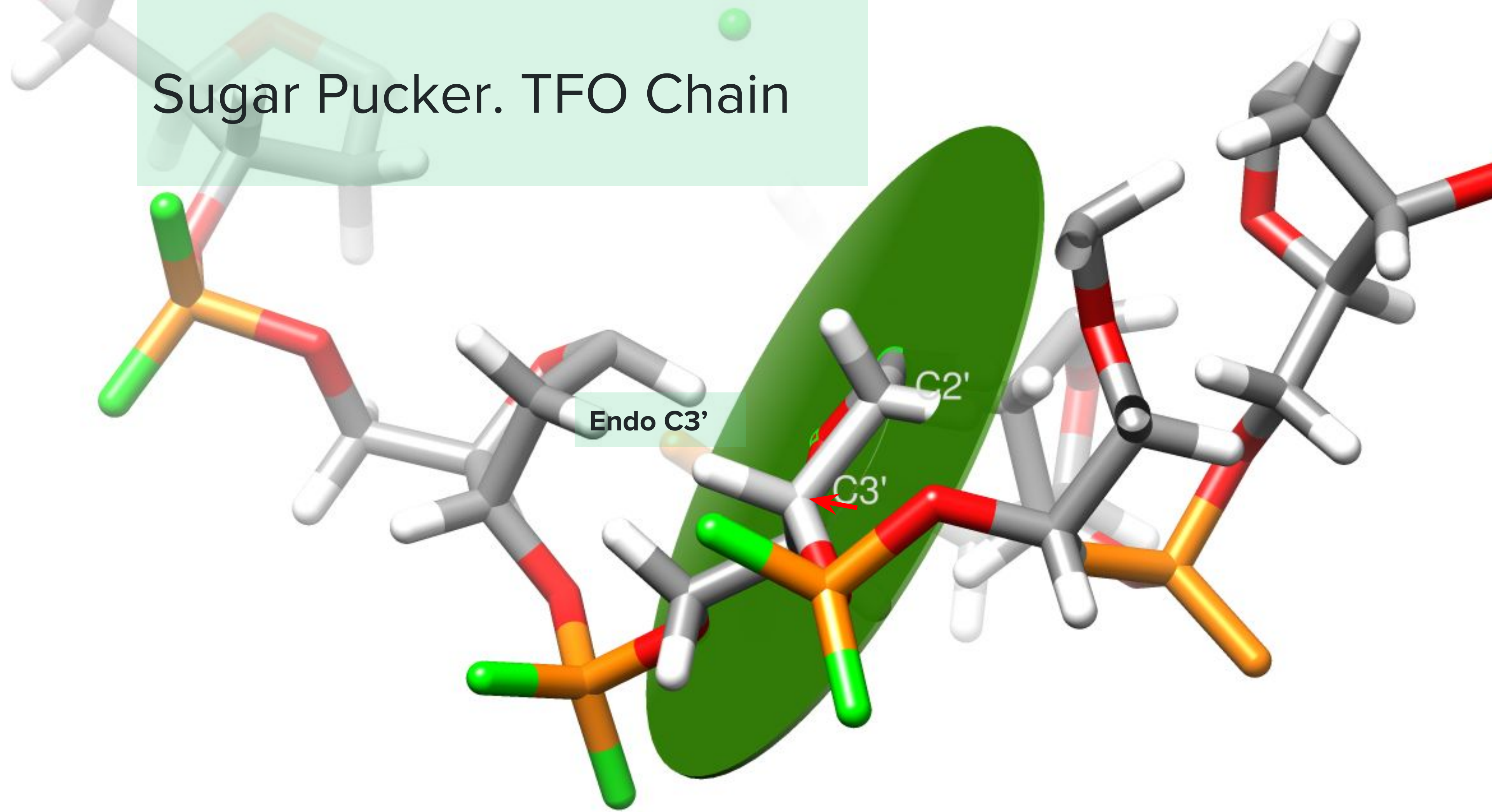
Parallel/ Pyrimidine Motif (T.AT)

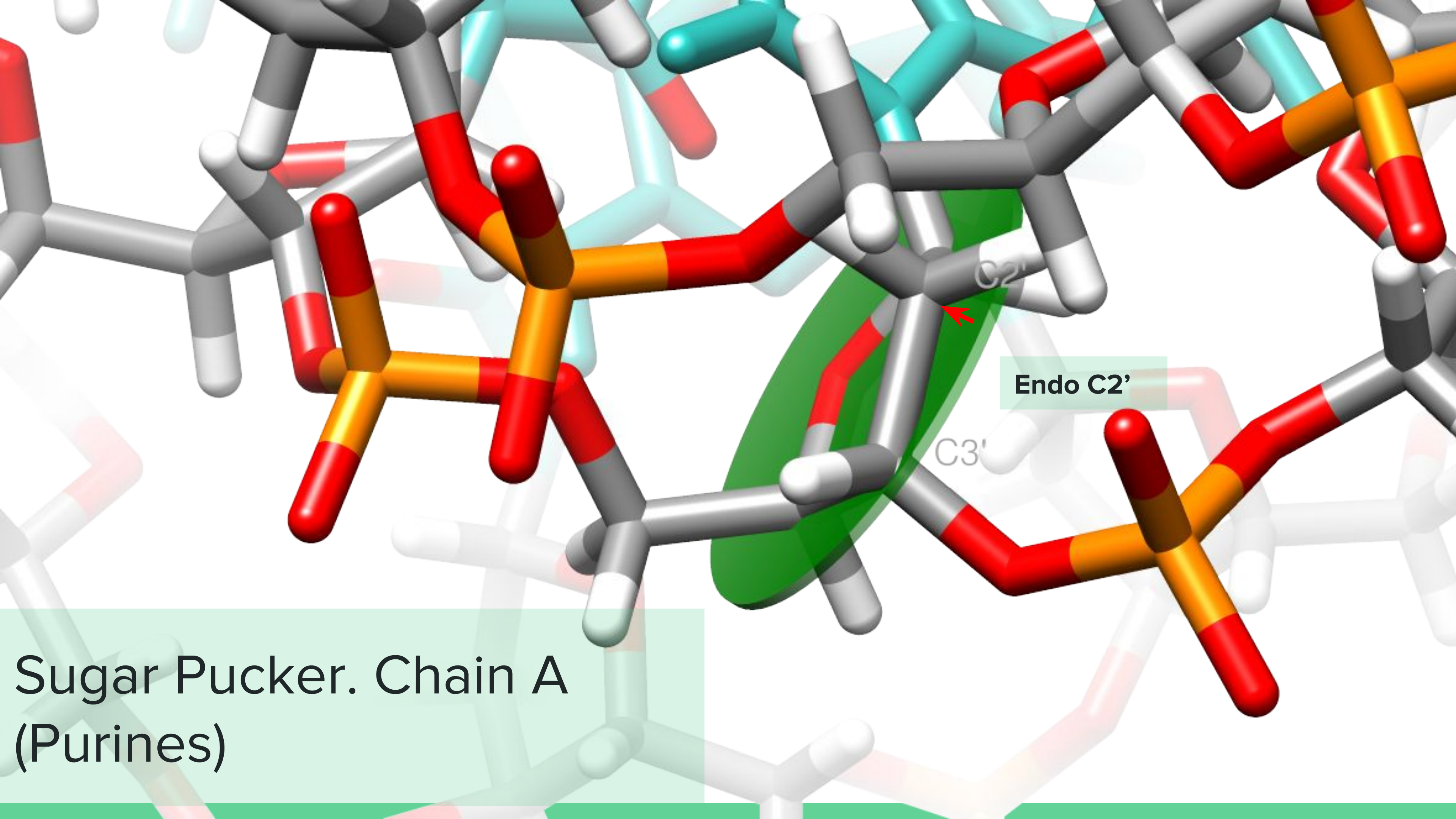


Parallel/ Pyrimidine Motif (T.AT)

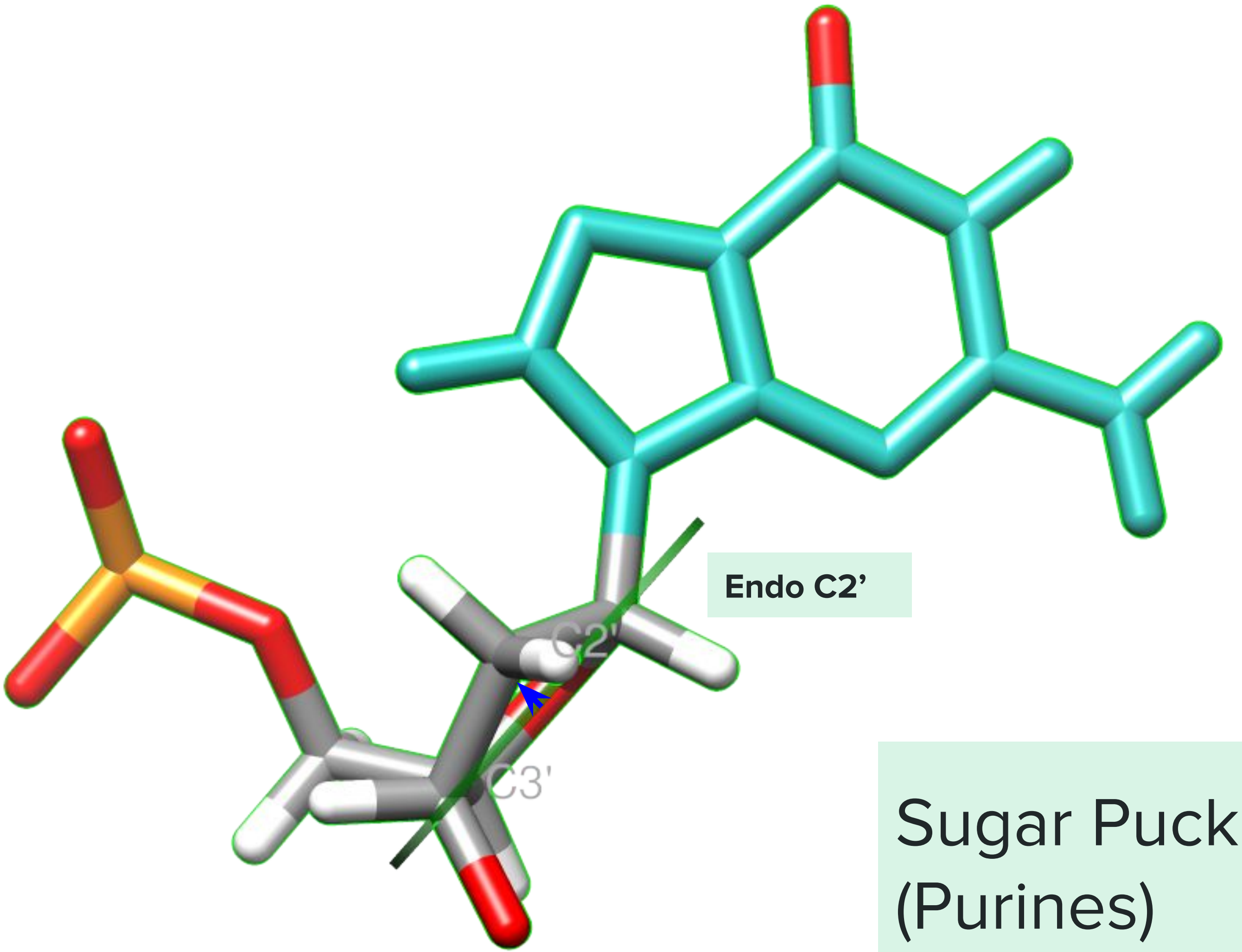


Sugar Pucker. TFO Chain



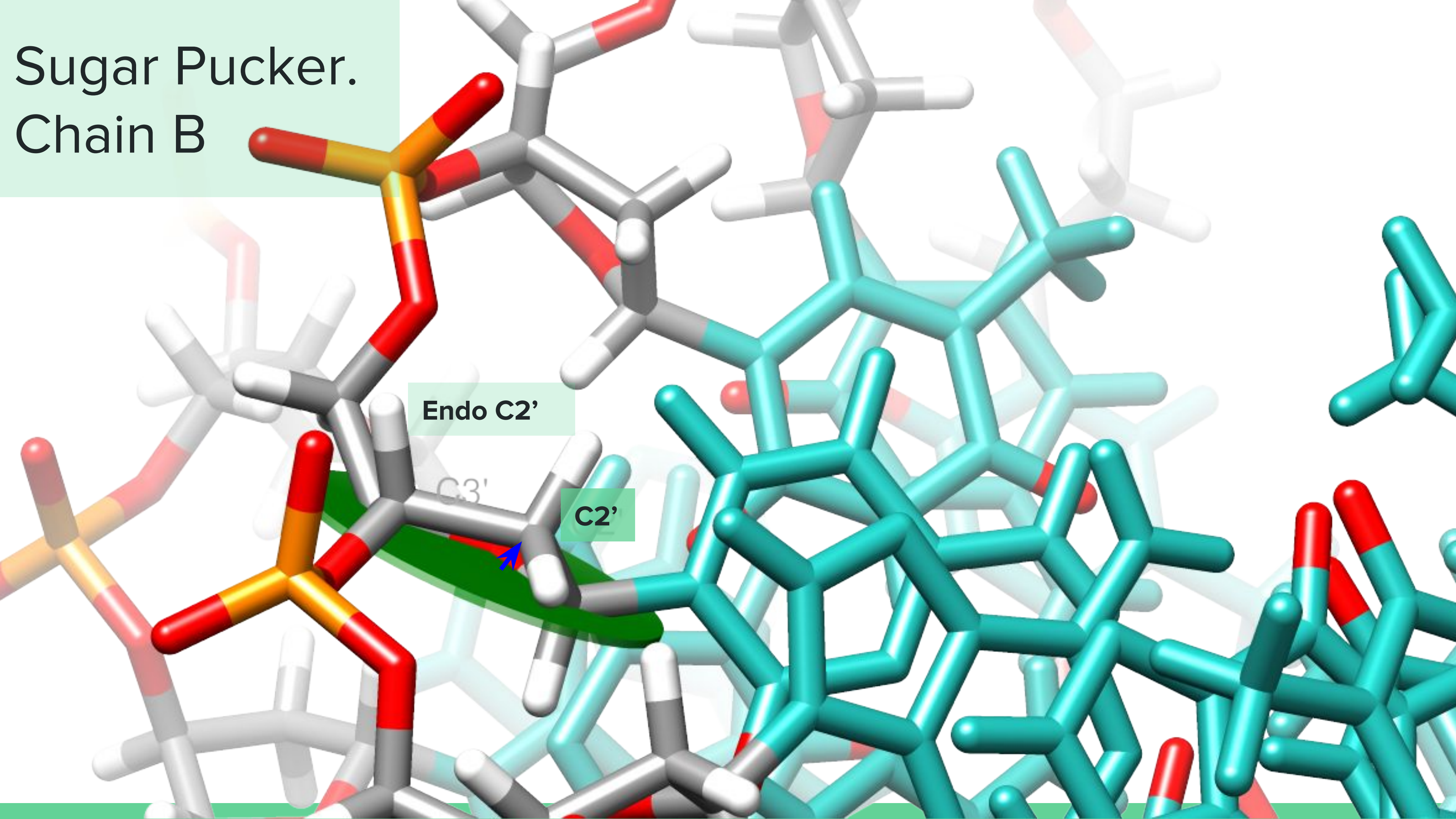


Sugar Pucker. Chain A (Purines)

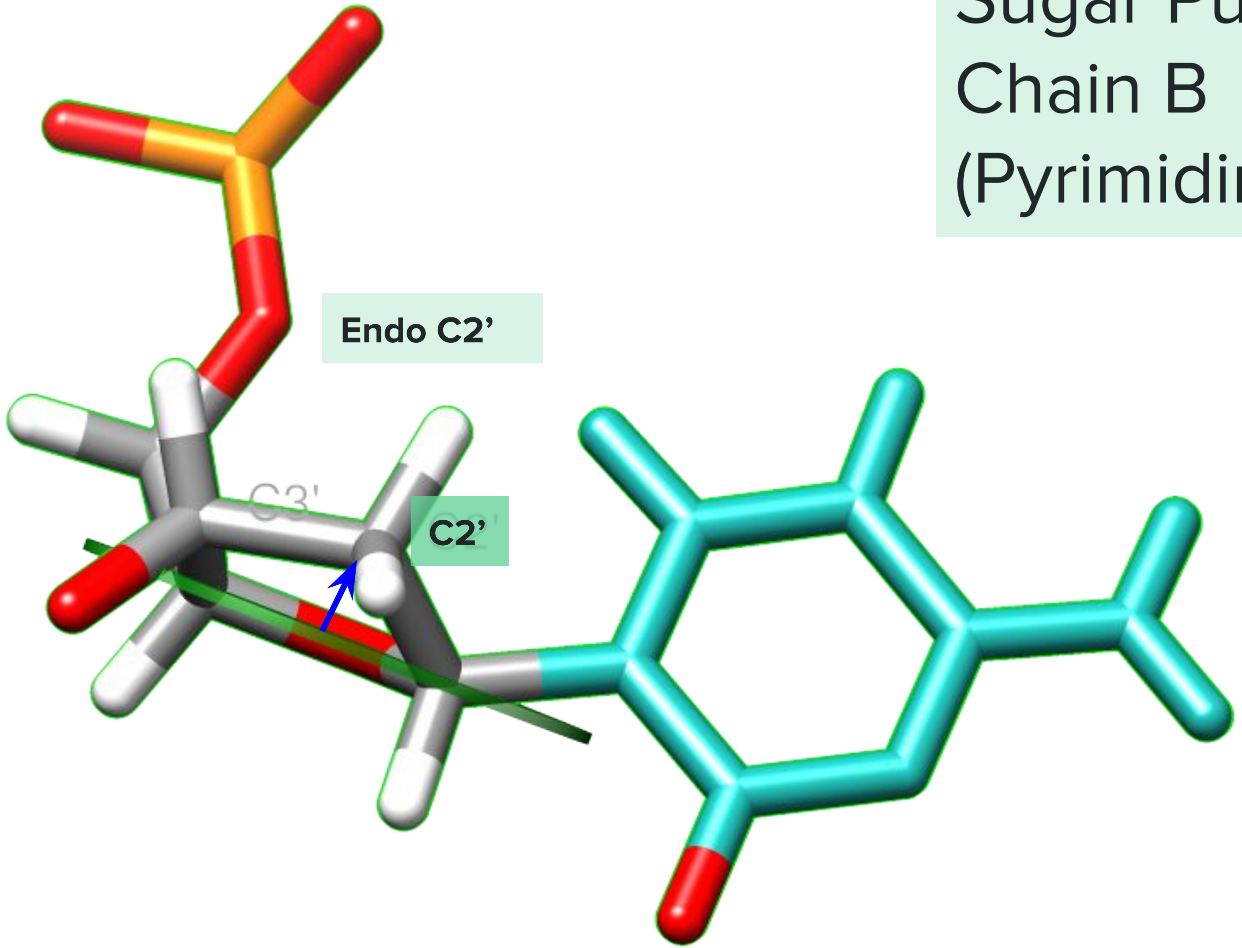


Sugar Pucker. Chain A (Purines)

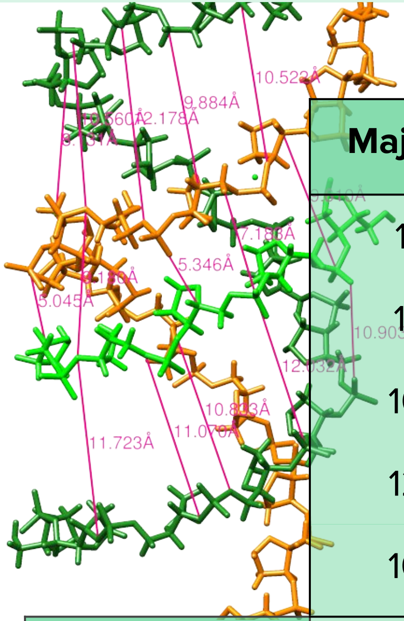
Sugar Pucker.
Chain B



Sugar Pucker. Chain B (Pyrimidines)



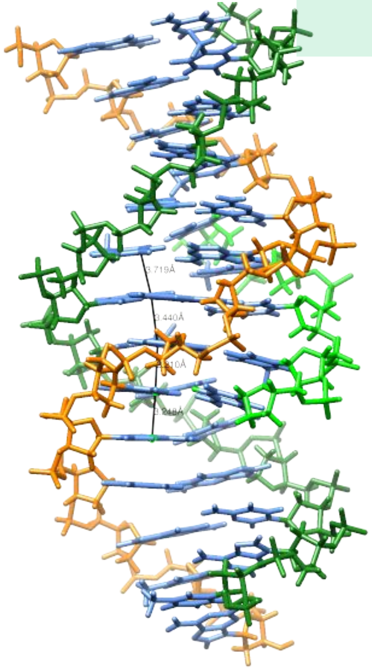
Grooves



	Maj (B-TFO)	Min	Maj(A-B)
	11,723	5,045	8,131
	11,070	3,180	10,560
	10,803	5,346	12,178
	12,032	7,183	9,884
	10,904	9,610	10,523
Total	56,532	30,364	51,276
Mean	11,306	6,073	10,255

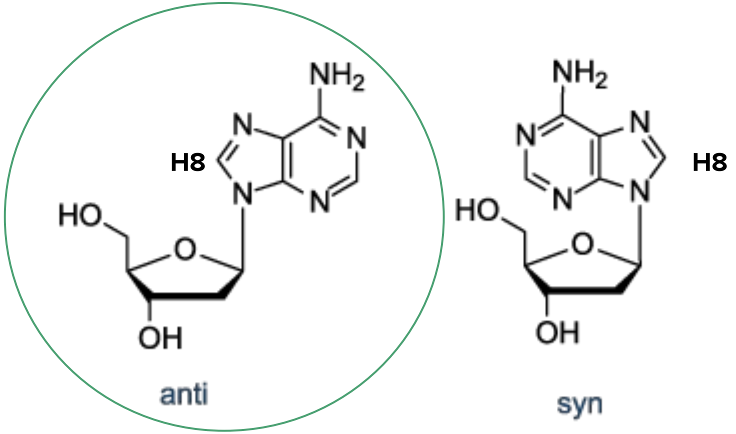
All the measures are expressed in angstroms (Å)

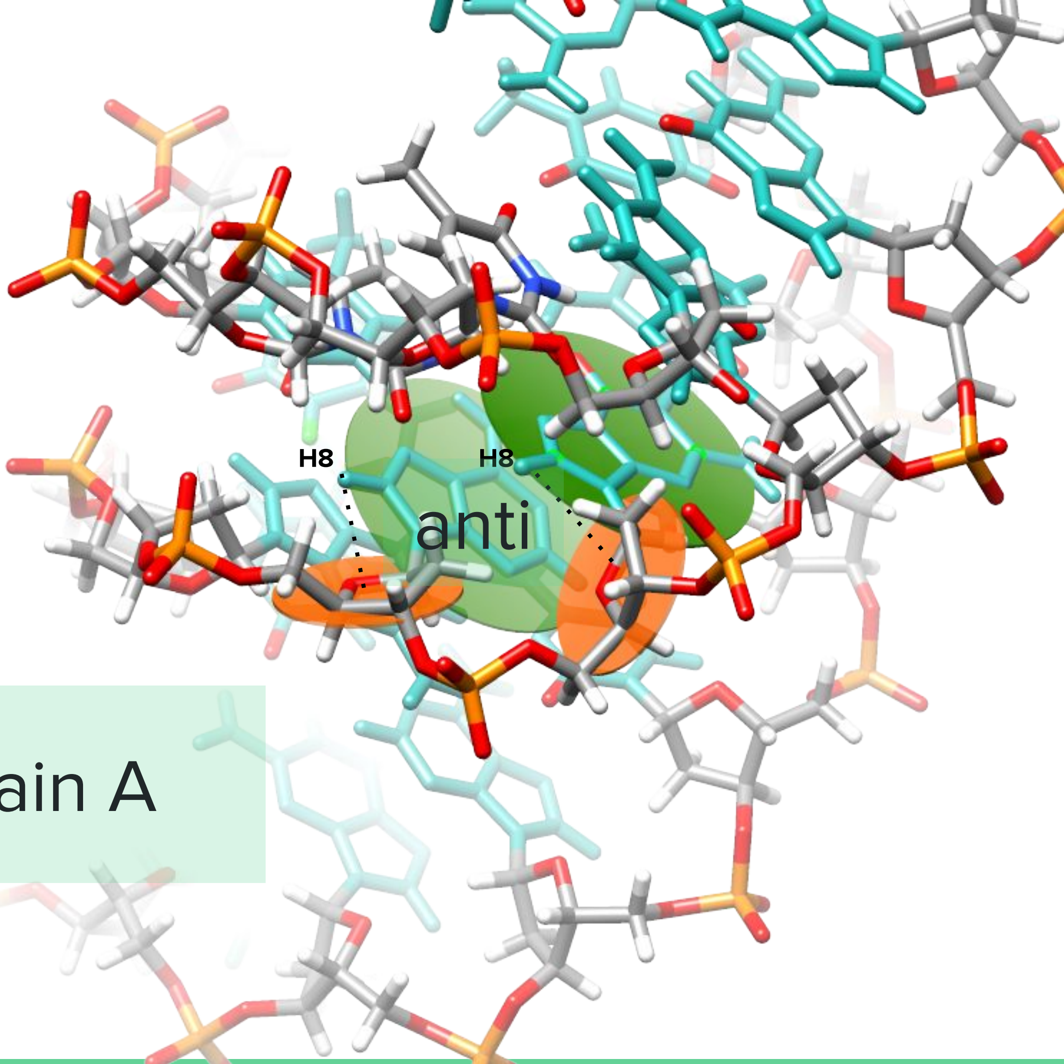
Axial Rise



	Measures
	3,719
	3,440
	3,210
	3,240
Total	13,609
Mean	3,402

Glycosidic Bond

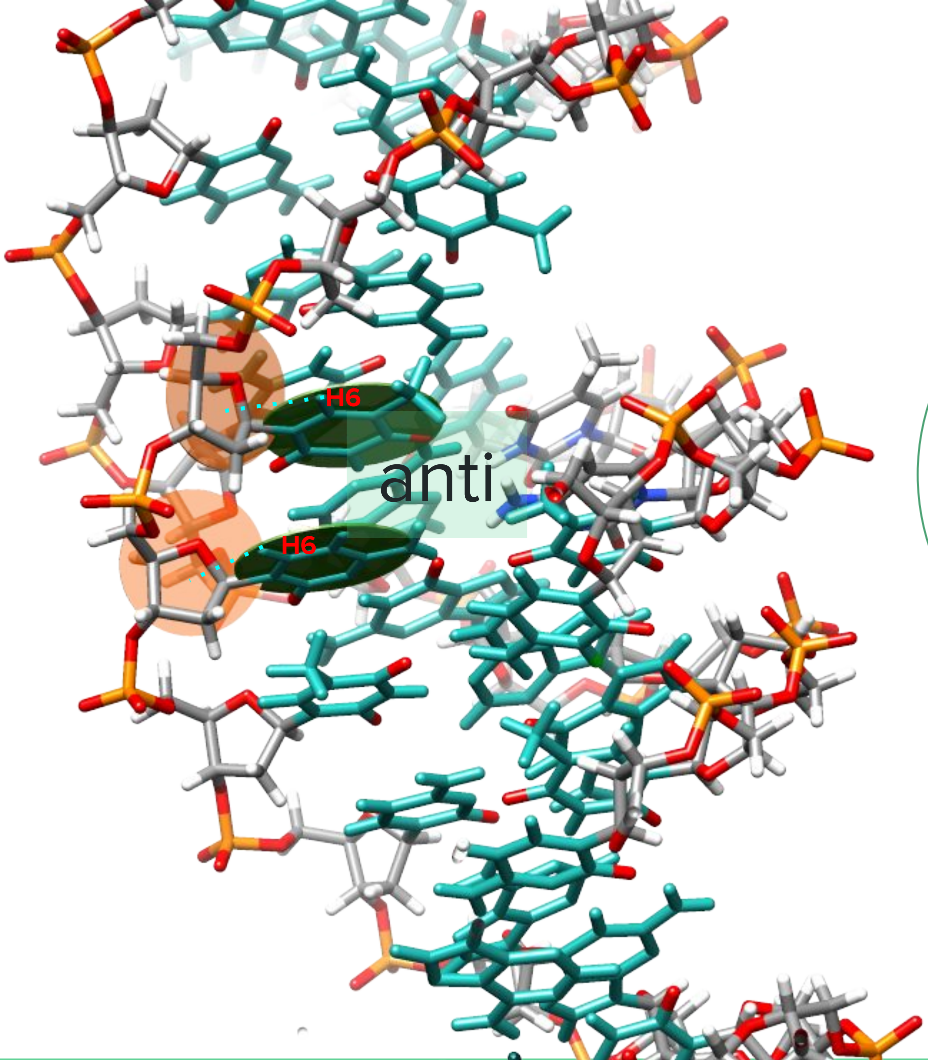


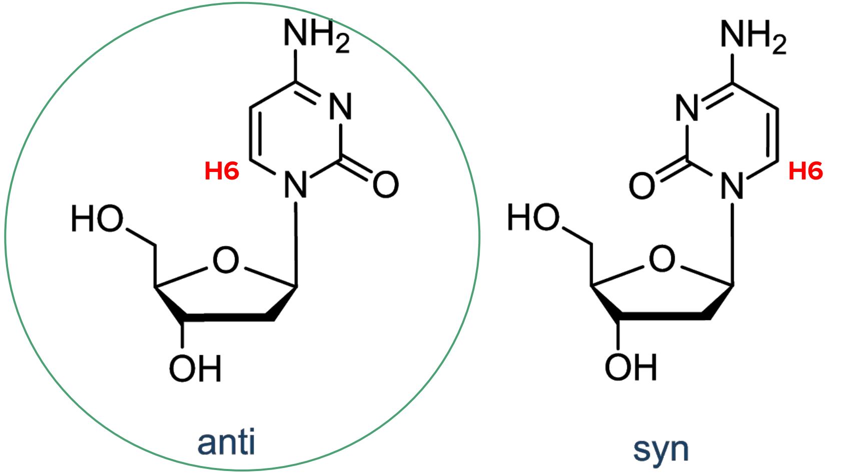


Chain A

Nucleic acid structure [Internet]. Atdbio.com. 2019 [cited 4 March 2019]. Available from: https://www.atdbio.com/content/5/Nucleic-acid-structure

Glycosidic Bond

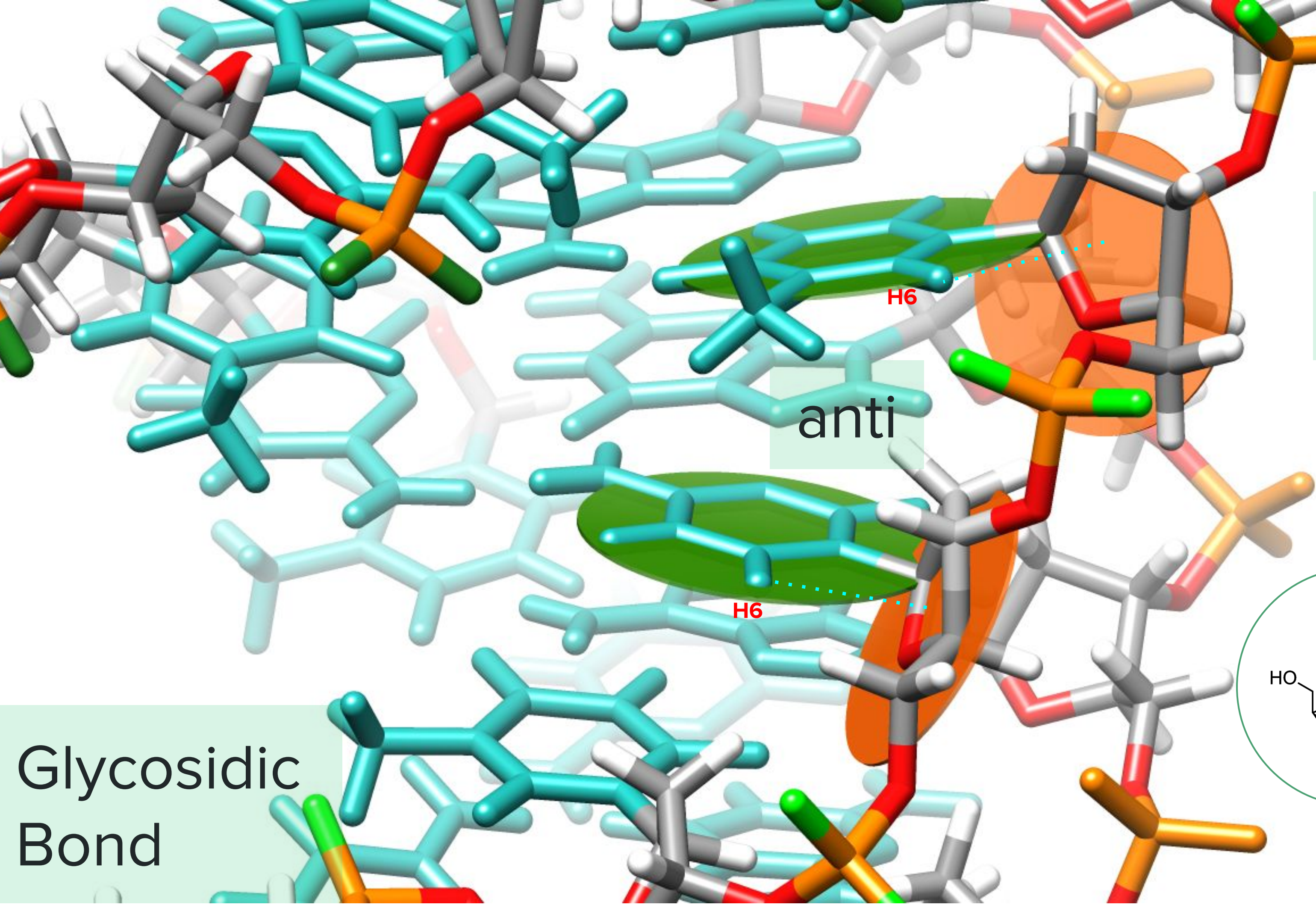


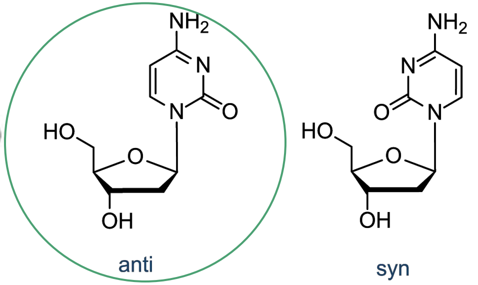


Nucleic acid structure [Internet]. Atdbio.com. 2019 [cited 4 March 2019]. Available from: https://www.atdbio.com/content/5/Nucleic-acid-structure

Chain B

Glycosidic Bond



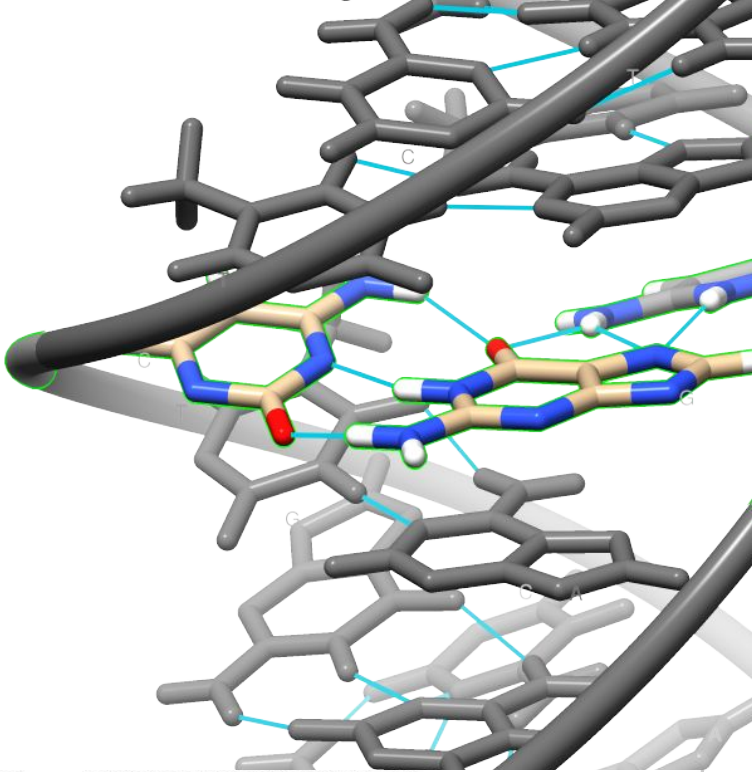


Nuclei
[Internet]. At
[cited

https://www.a
ent/5/Nuclei

Therapeutic Applications of triplex DNA

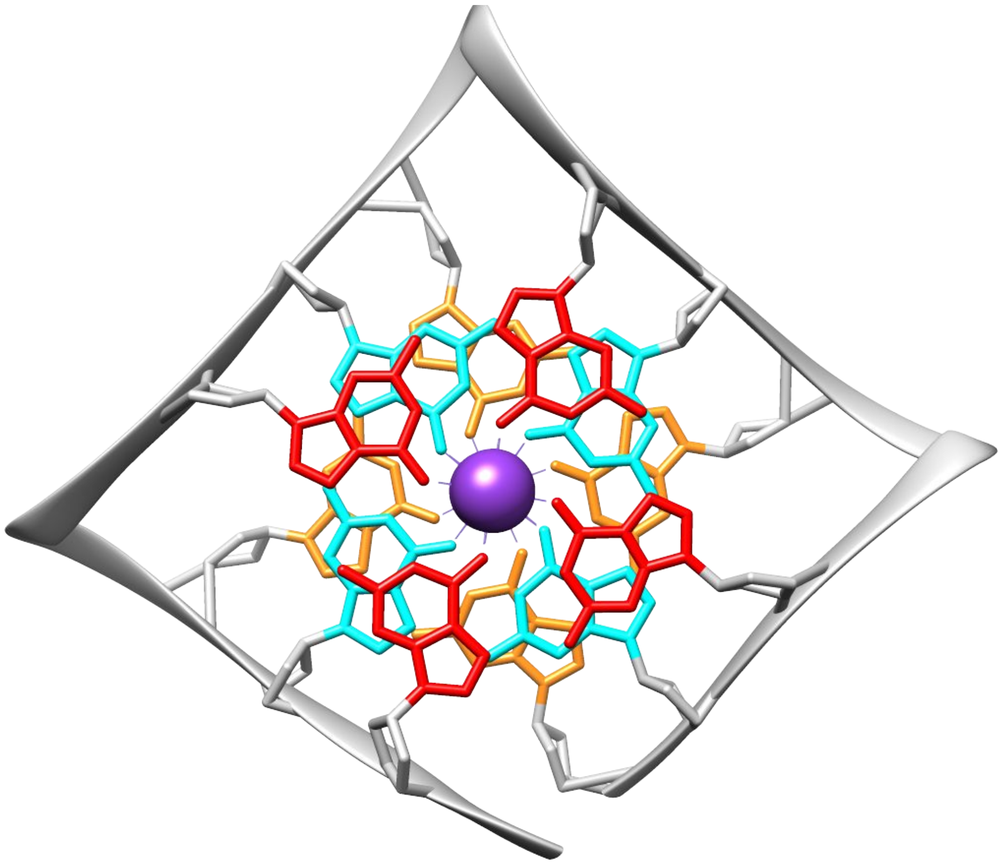
- Gene inhibition
- Stimulation of DNA repair
- Homologous recombination
- Site specific mutations



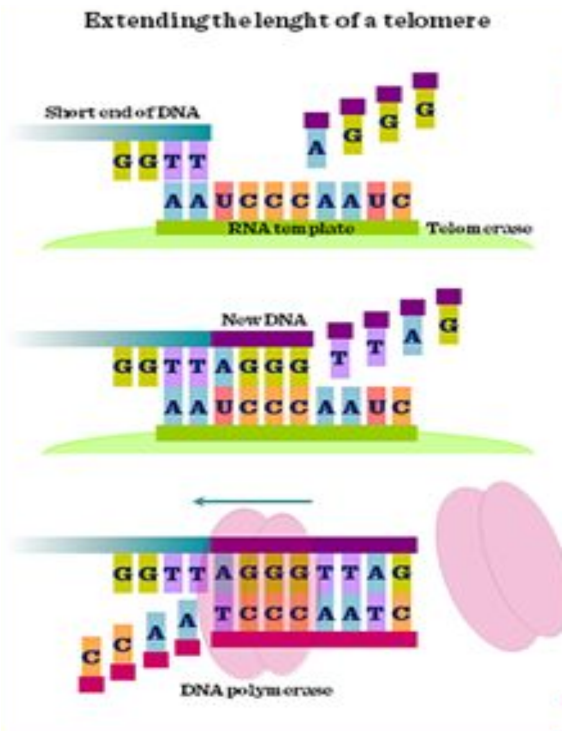
Triplex formation with a polypurine TFO sequence specific for the human *c-MYC* P2 promoter. *Jain A, Wang G, Vasquez K. DNA triple helices: Biological consequences and therapeutic potential. Biochimie. 2008;90(8):1117-1130.*

Quadruplex DNA

Folding of the telomeric structure
G-Quadruplex



Telomeres



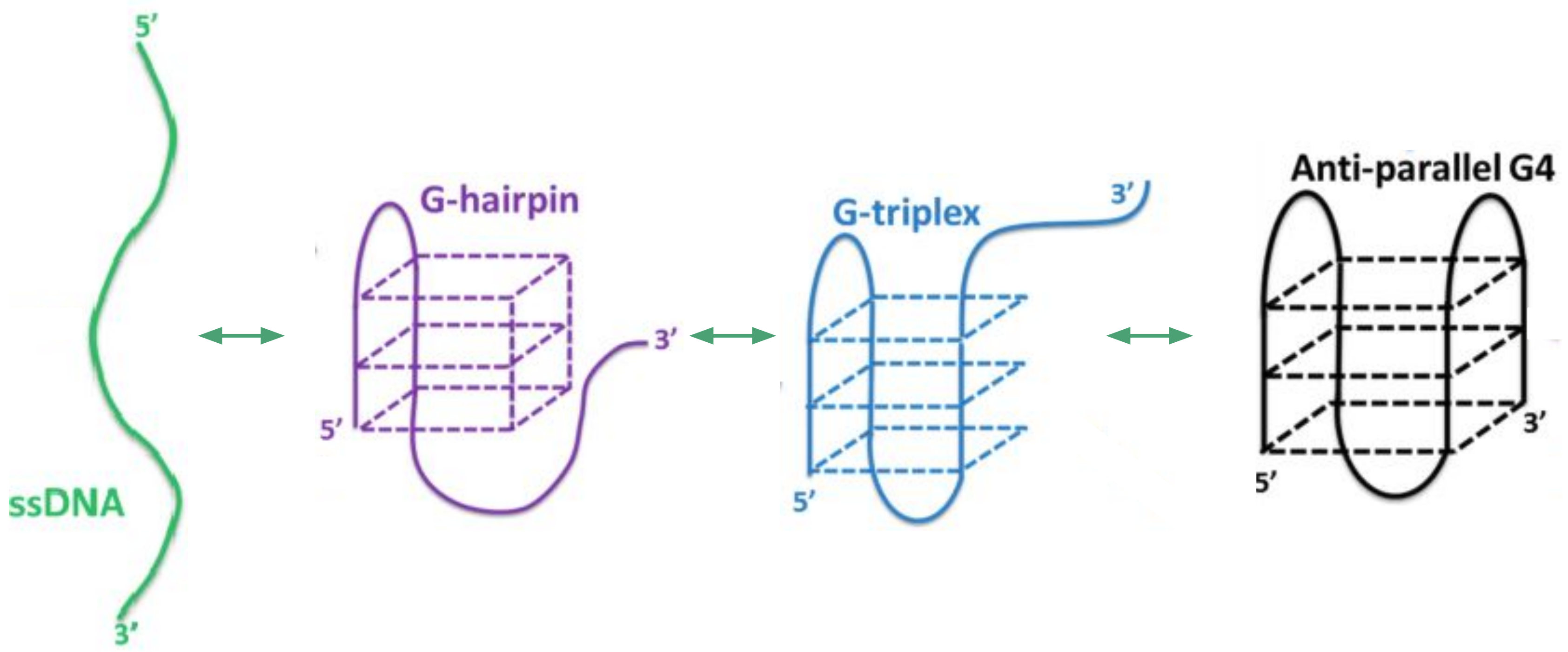
3’ - … (A A T C C C)i - 5’

5’ - … (T T A G G G)i (T T A G G G)n - 3’

ssDNA 3’ overhang

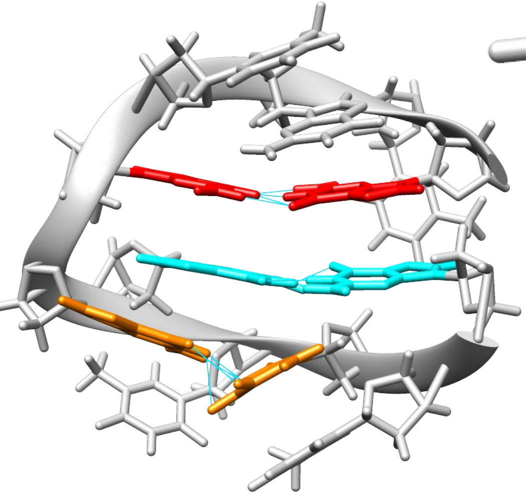
Molecular and Clinical Basics of Gerontology|Digitális Tankönyvtár [Internet]. Tankonyvtar.hu. 2019 [cited 5 March 2019]. Available from: https://www.tankonyvtar.hu/hu/tartalom/tamop425/0011_1A_Gerontologia_en_book/ch02s04.html

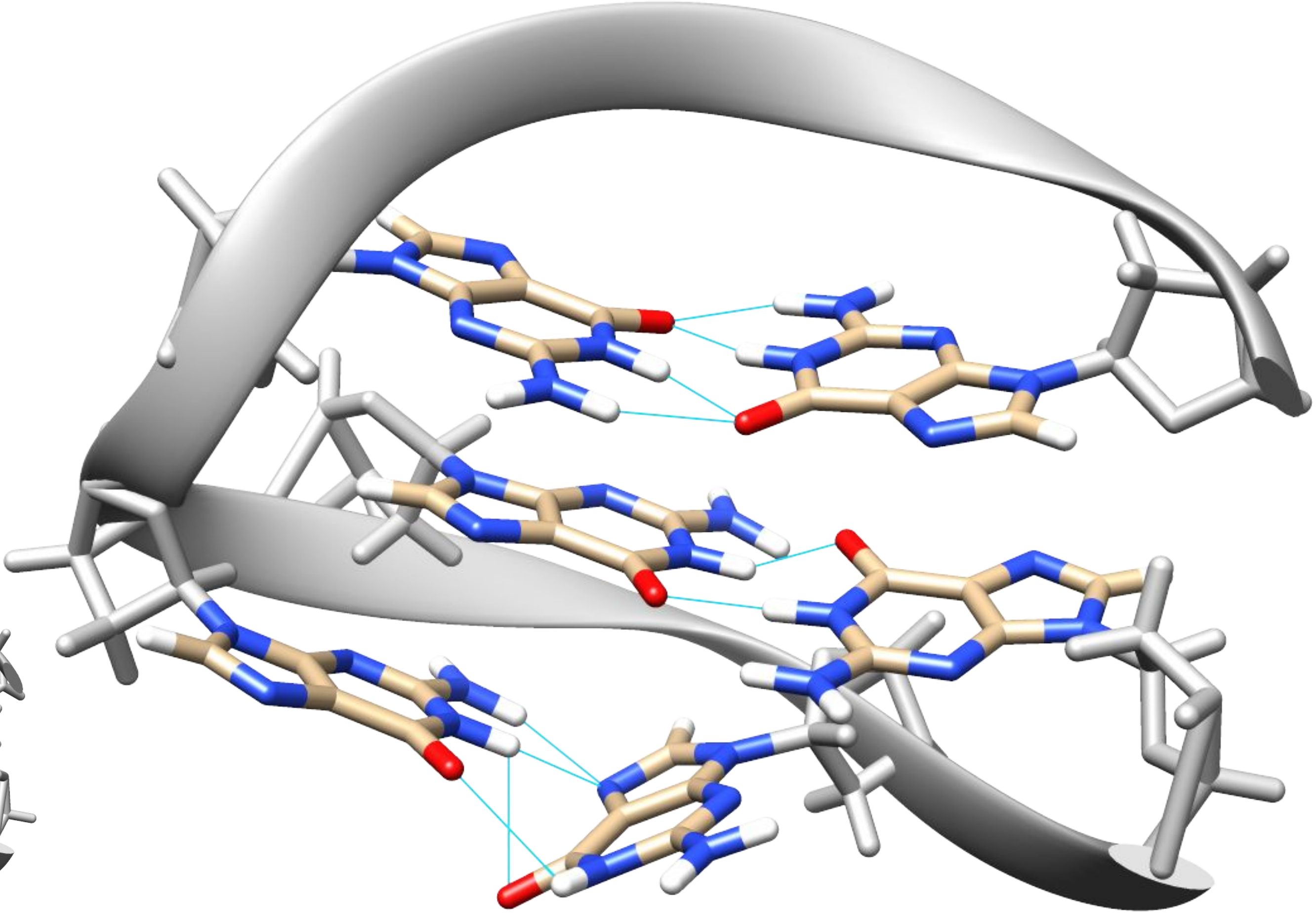
Telomerase folds



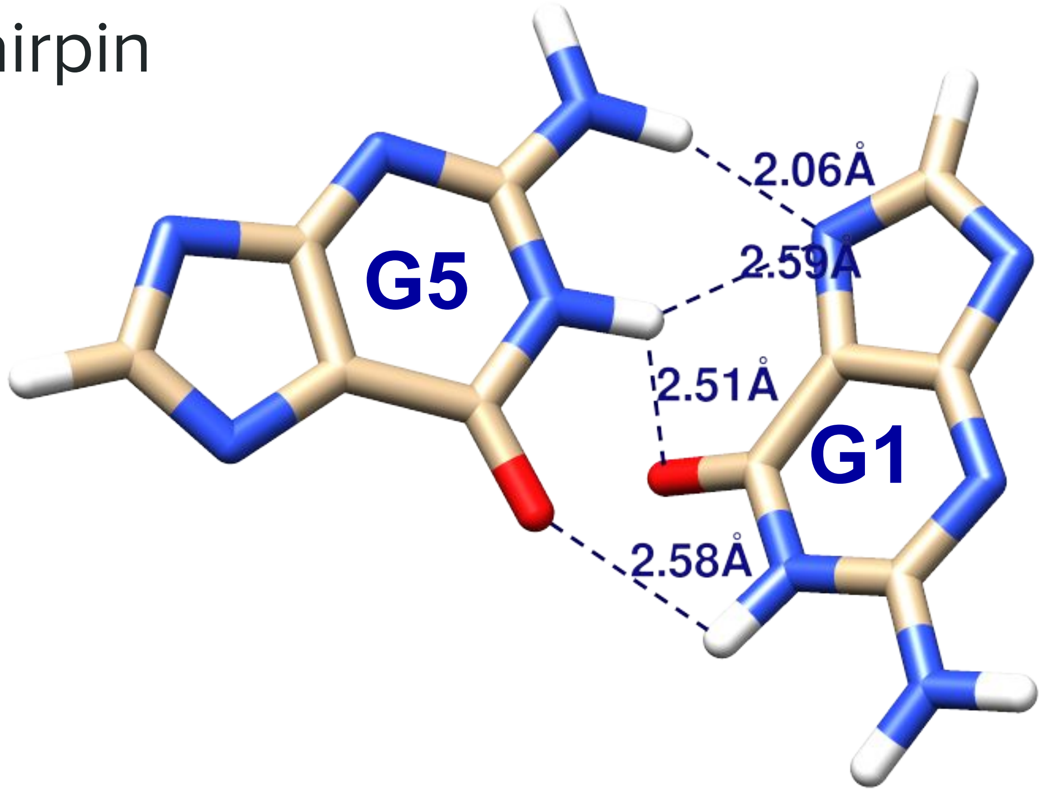
Adapted from : Hou X-M et al. Involvement of G-triplex and G-hairpin in the multi-pathway folding of human telomeric G-quadruplex. *Nucleic Acids Res*. 2017;45(19):11401–12.

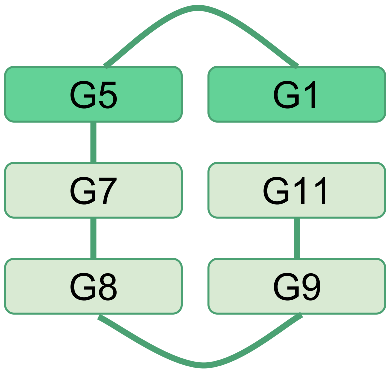
G-Hairpin



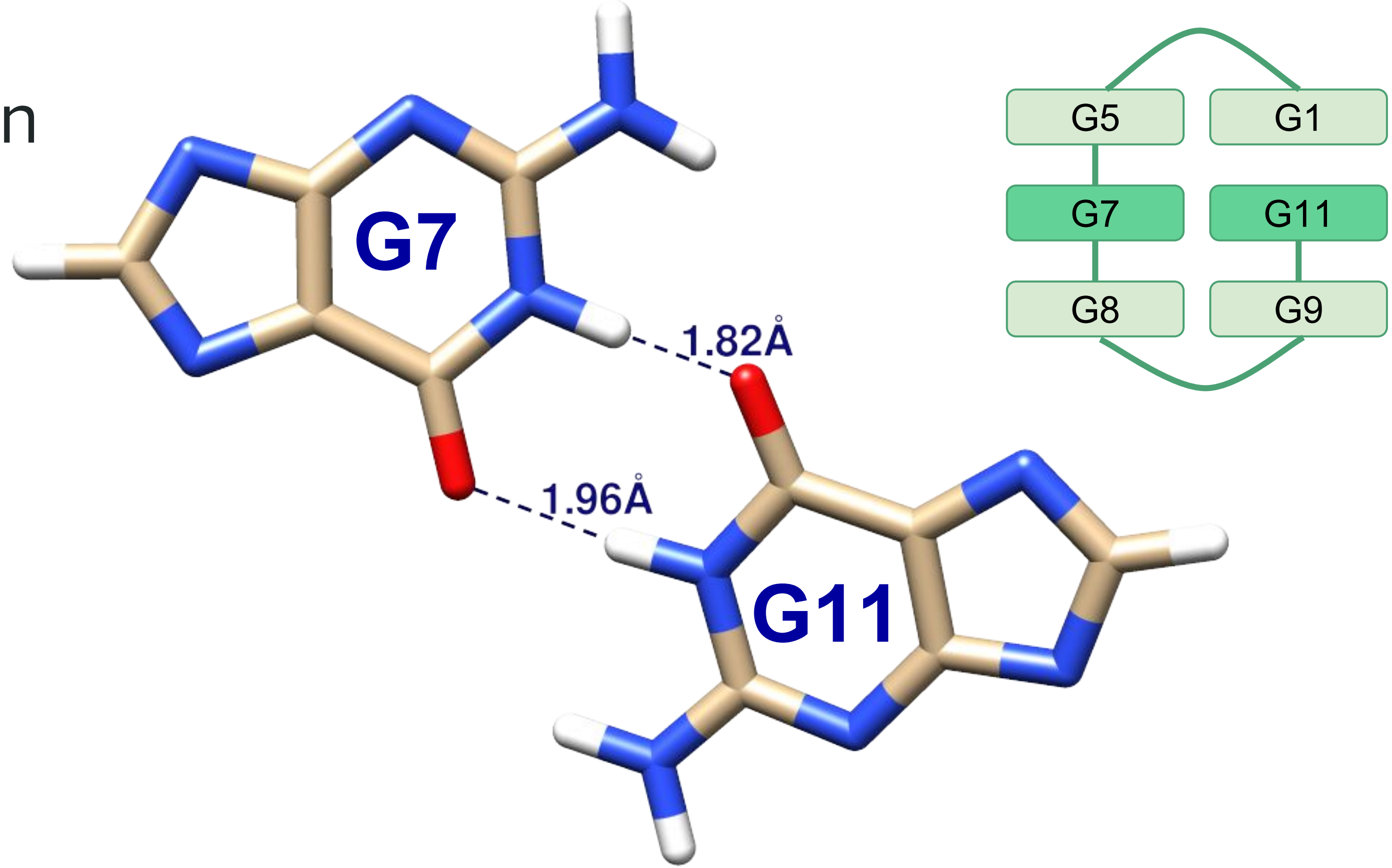


G-Hairpin

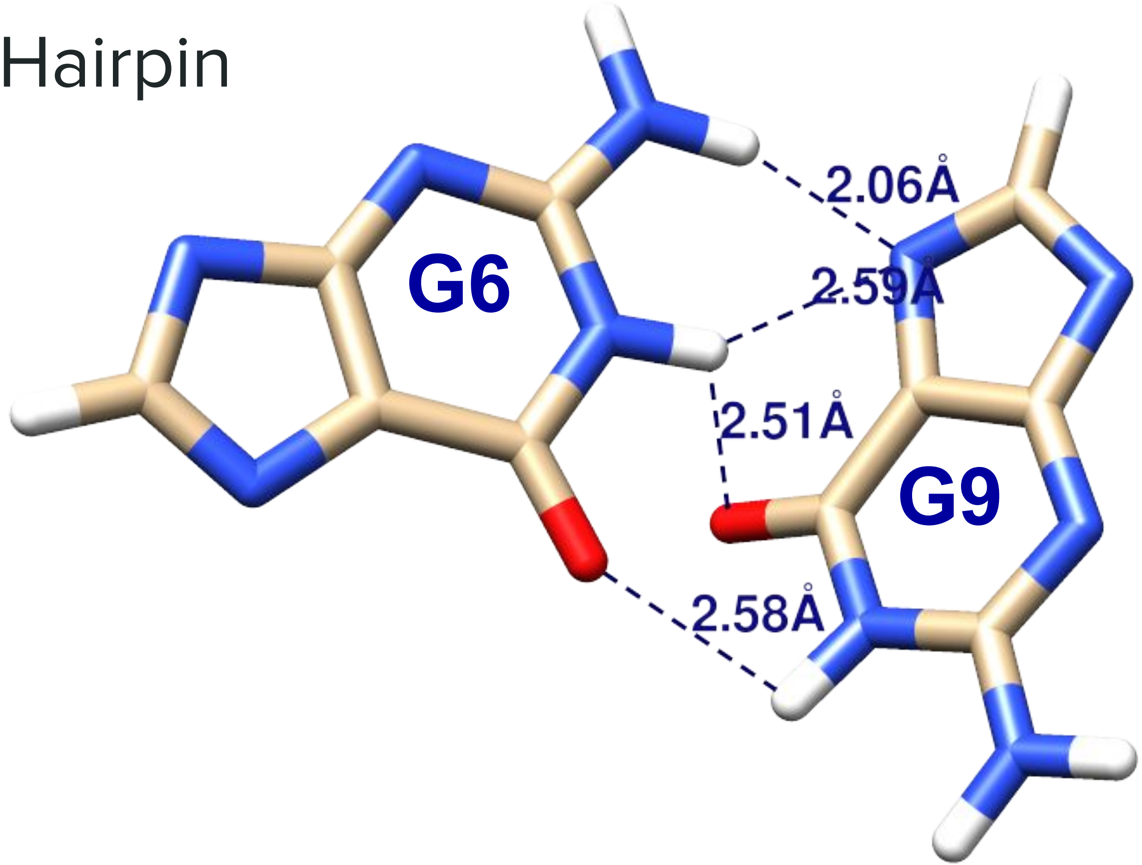


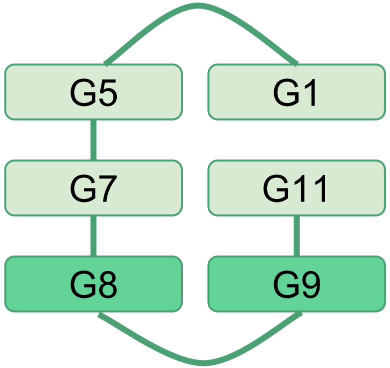


G-Hairpin

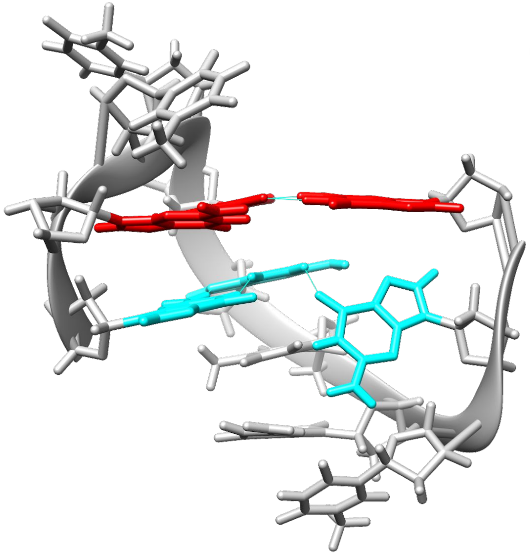


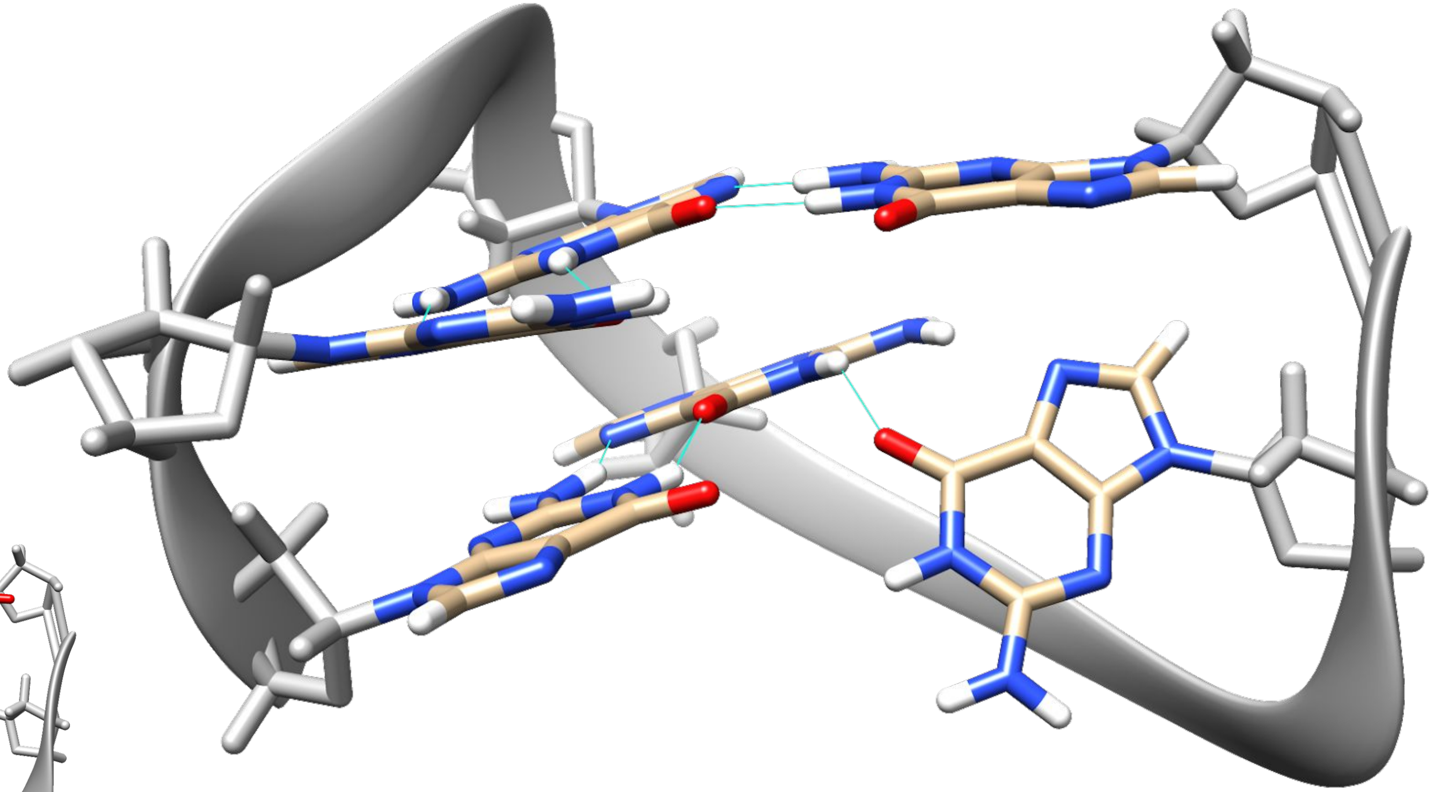
G-Hairpin



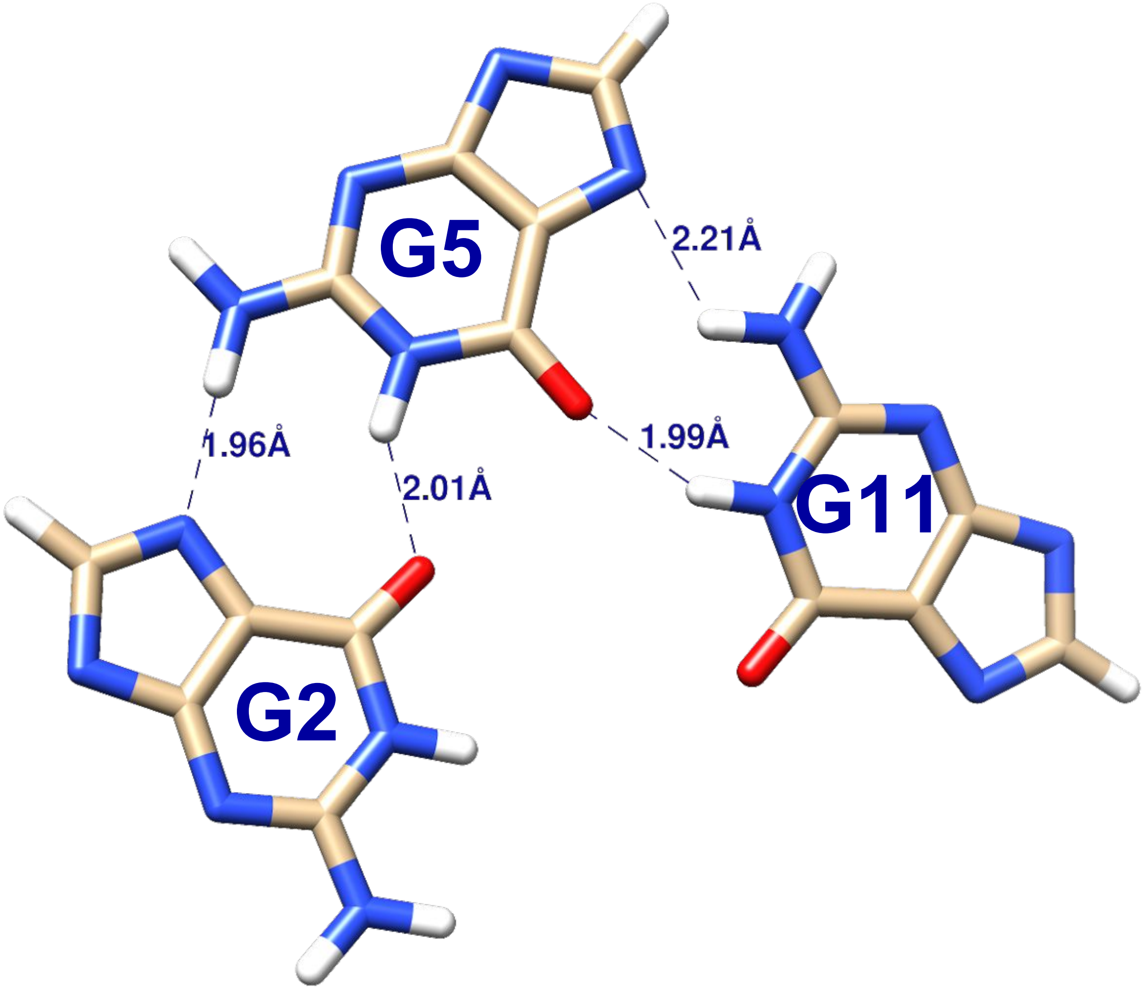


G-triplex

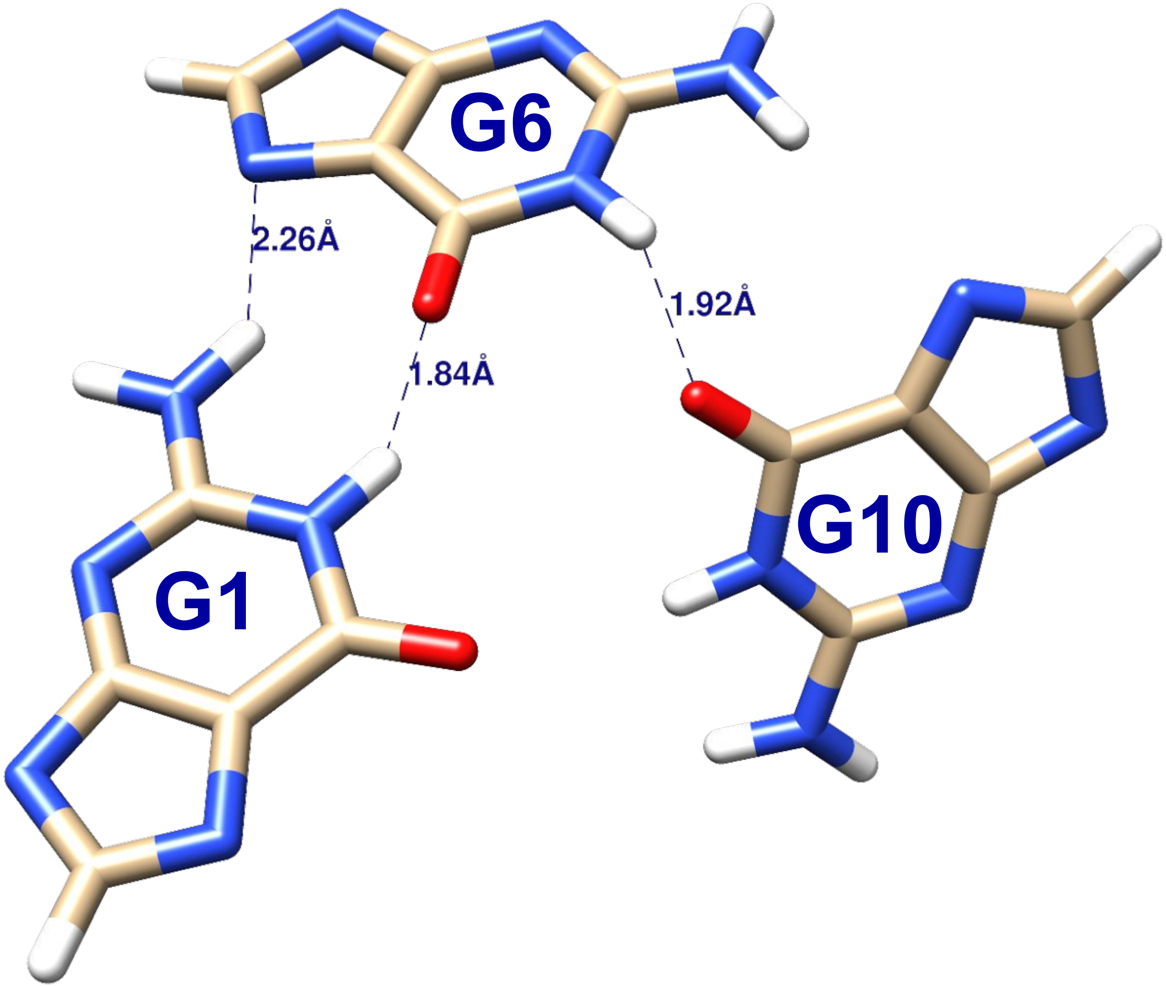




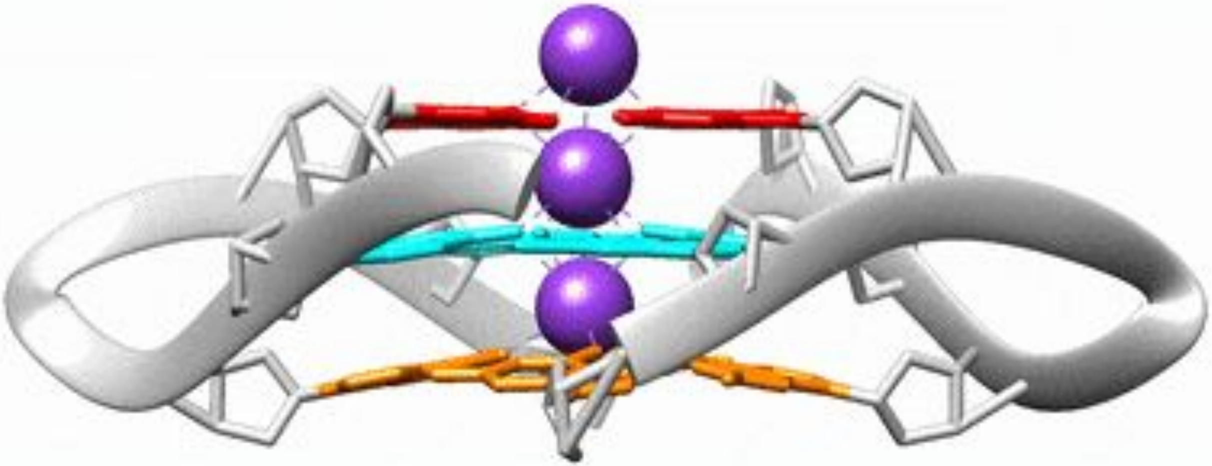
G-triplex

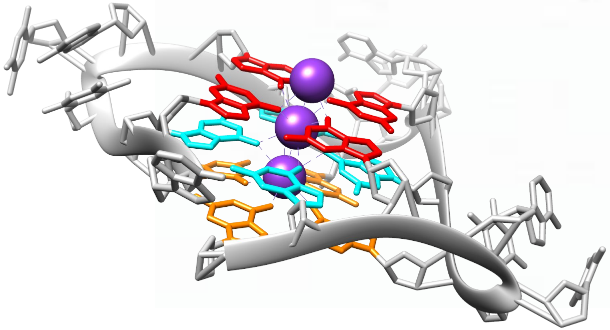


G-triplex

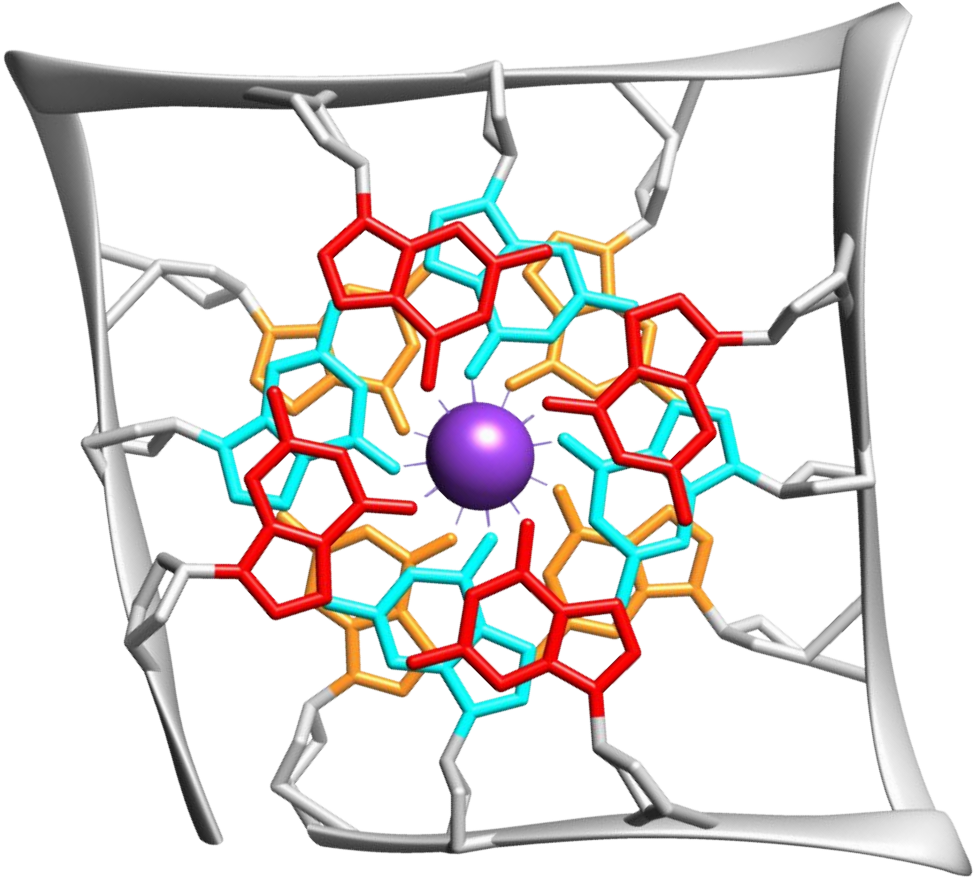


G-quadruplex

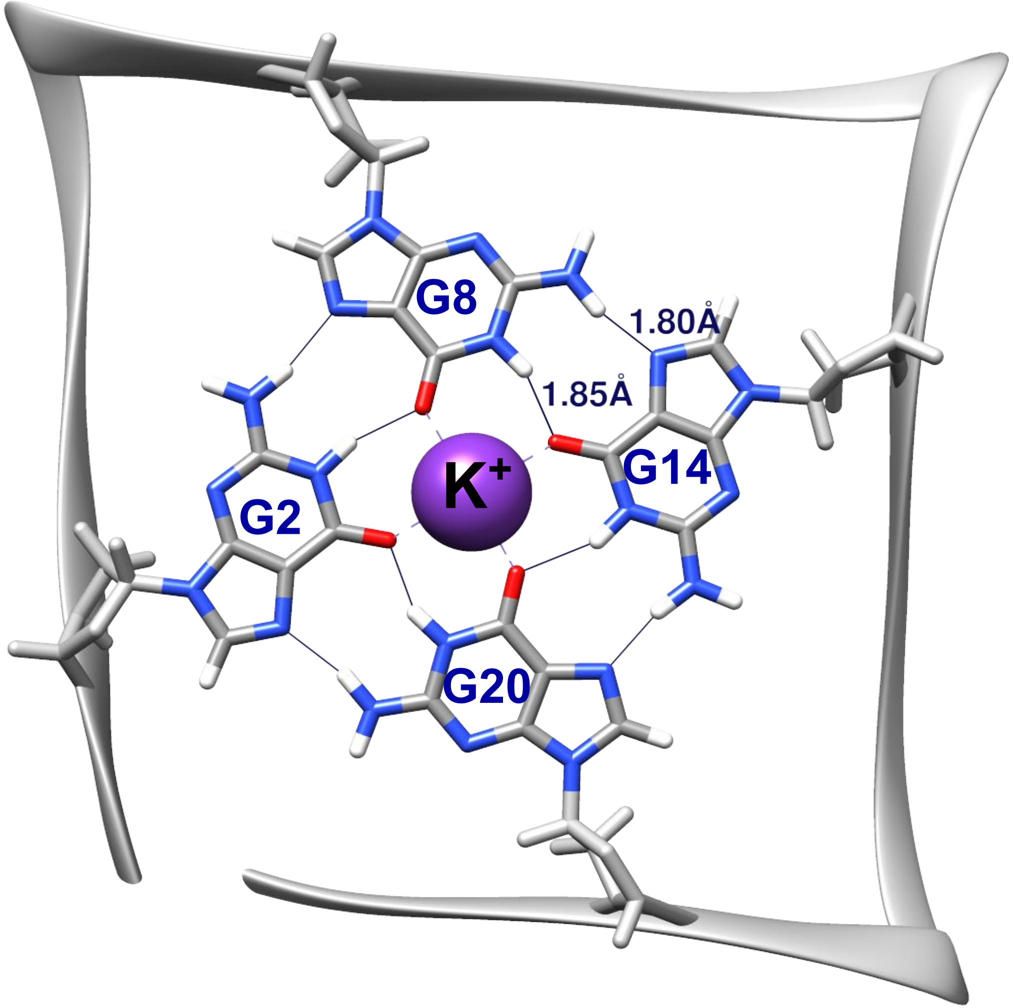




G-quadruplex

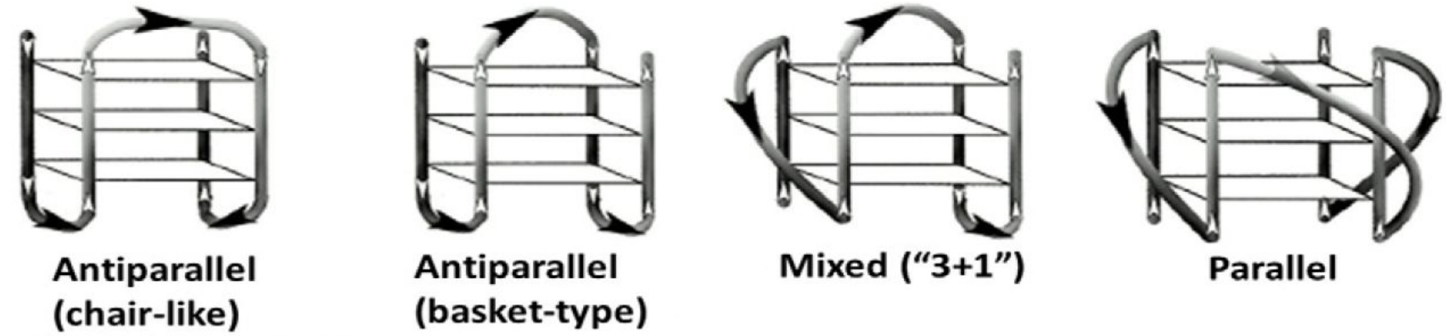


G-quadruplex

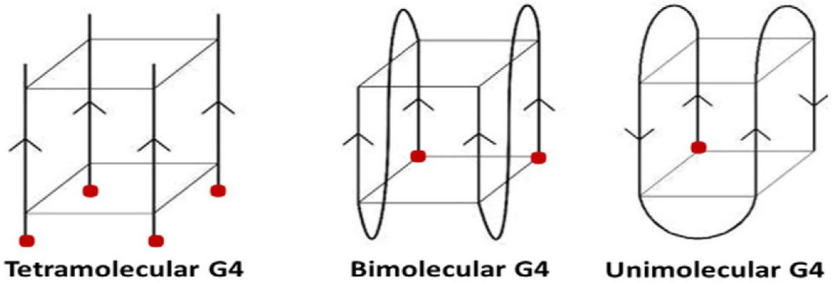


G-quadruplex variety

Types of unimolecular g-quadruplex



Types of g-quadruplex

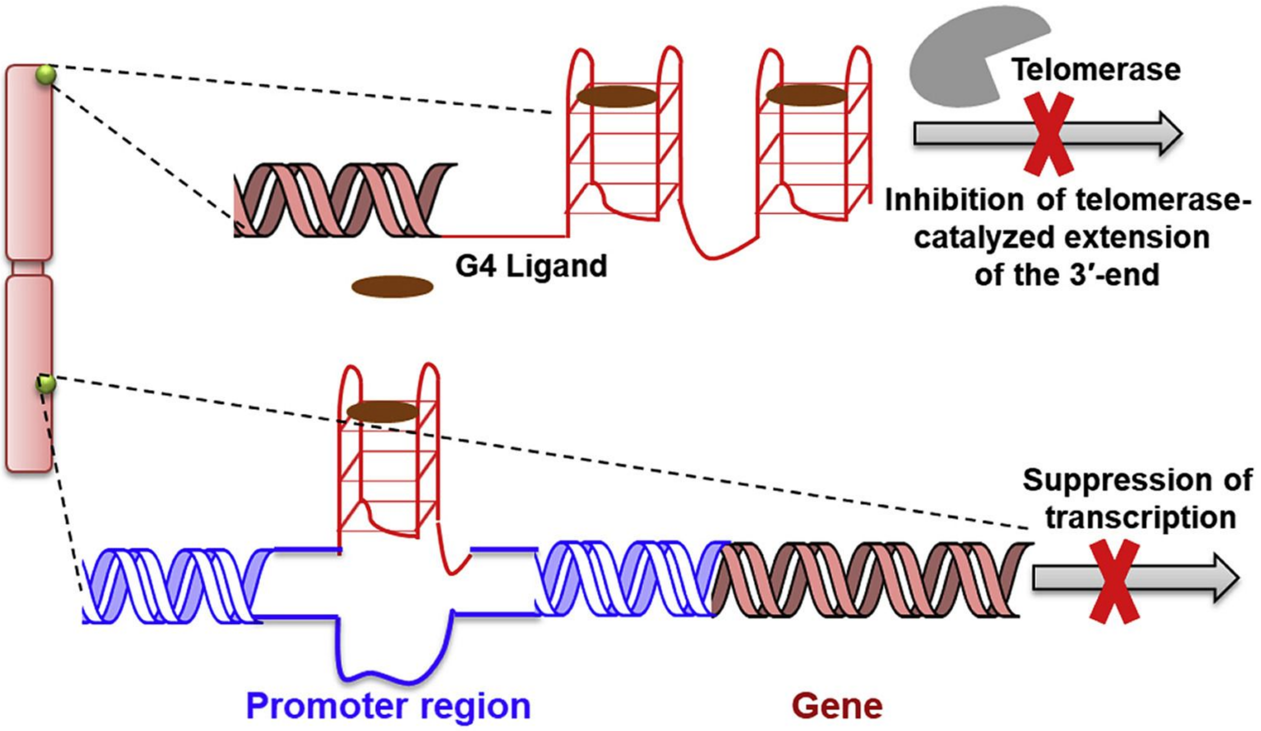


Adapted: Platella et al. G-quadruplex-based aptamers against protein targets in therapy and diagnostics. *Biochim. Biophys. Acta.* 2017;1861(5):1429-1447.

G-quadruplex in cancer therapies

Inhibition of telomerase

Oncogene suppression



Kaulage M et al. Targeting G-quadruplex DNA structures in the telomere and oncogene promoter regions by benzimidazole–carbazole ligands. *Eur. J. Med. Chem.* 2018;148:178-194.

Take home messages

DNA structure and properties are a compound of diversal types of interactions between its fundamental constituents

DNA can adopt different conformations depending on its medium and sequence

Non canonical DNA secondary structures have relevant roles in biology (such as telomere conservation, transcription, etc.)

Triple DNA helix structures have therapeutic potential

Telomeres play a crucial role in DNA conservation and their G-quadruplex structures are potential therapeutic targets

Questions

TFO stands for

a) Thermal Force Onset
b) Triplex Forming Oligonucleotide
c) All of the above
d) None of the above

The therapeutic potential of DNA triple helices includes:

a) Gene inhibition
b) Homologous recombination
c) Site specific mutations
d) All of the above

A-DNA:

a) Does not occur in living beings
b) Has a left-handed helix
c) Has the shorter distance between nucleotides
d) All of the above

Which of the following is false:

a) DNA turns to the Z configuration under low humidity conditions
b) Sugar puckering affects the conformation of DNA backbone
c) A-DNA has the wider and shorter helix of the canonical DNa forms
d) All of the above

Which of the following ions are coordinated providing stability to the G-quadruplex fold of telomeres?

a) K^+
b) Na^+
c) a) and b) are correct
d) Cl^-
e) All of the above

Which of the following statements are true regarding the relation between cancer and telomeres:

1. Telomere shortening is a promoter of cancer
2. G-quadruplex bound to pharmacological compounds may prevent telomerase activity in cancer cells
3. G-quadruplex bound to pharmacological compounds may suppress oncogene expression
4. G-quadruplex formation promotes carcinogenesi

a) 1, 2, 3
b) 1 and 3
c) 2 and 4
d) 4
e) 1,2,3,4

Questions

DNA phosphodiester bond is formed by

a) Phosphate group
b) Deoxyribose
c) a) nd b) are correct
d) Ribose
e) All of the above

Which of the following statements is true:

a) Hydrogen bond (HB) forces are determined only by the quantity of them
b) HB forces are determined only by the quality of them
c) HB forces are determined by the quantity, the quality and the angle
d) None of them

Which of the following statements are true

1. In Hoogsteen (HG) base pairs, the minor groove is less electronegative than in Watson-Crick (WC) base pairs
2. The backbone is formed exclusively by phosphate groups
3. Pi stacking occurs between two nucleosides
4. Pyrimidines are composed by an imidazole and a pyrimidine group

a. 1, 2, 3
b. 1 and 3
c. 2 and 4
d. 4
e. 1,2,3,4

References

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Thank you for your attention