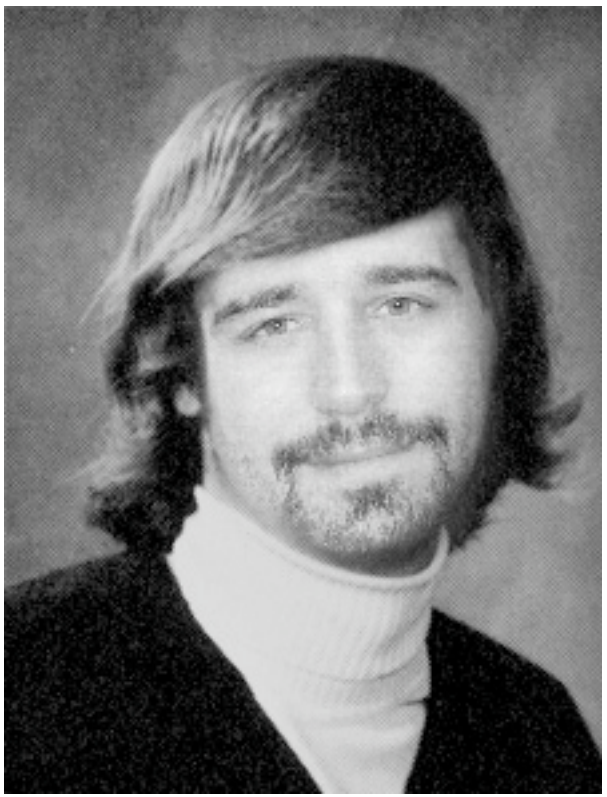
Structural Bioinformatics

Francisco Martínez

David Dufour

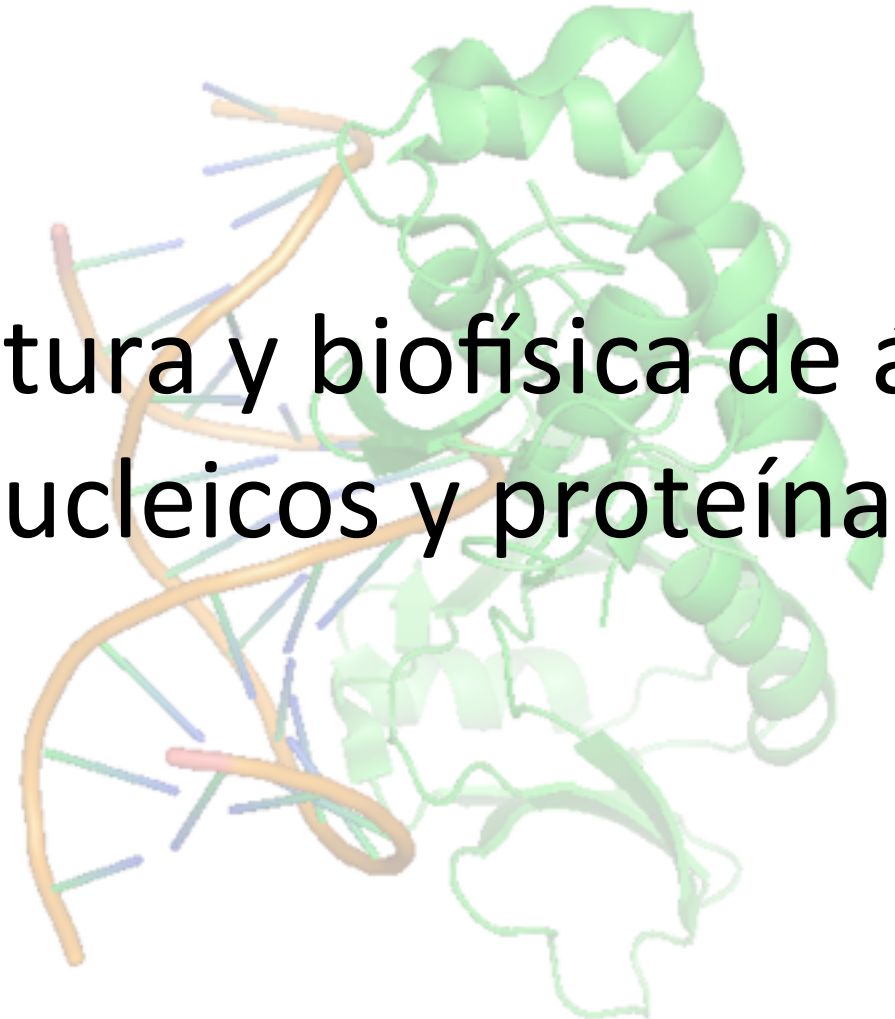
• Estructura y biofísica de ácidos nucleicos y proteínas	25 febrero (DD)
• Bases de datos de estructura de proteínas, ácidos nucleicos y pequeñas moléculas	11 marzo (DD)
• Alineamiento y clasificación de estructura	25 marzo (DD)
• Predicción de estructura tridimensional de ácidos nucleicos y proteínas	15 abril (DD)
• Docking de pequeñas moléculas en la superficie de estructura de proteínas	29 abril (FM)
• Aplicaciones para el desarrollo de nuevos fármacos	13 mayo (FM)

Structural Bioinformatics



- Intro Genómica Estructural
- Laboratorios 15 abril y 13 mayo

Estructura y biofísica de ácidos nucleicos y proteínas



Summary

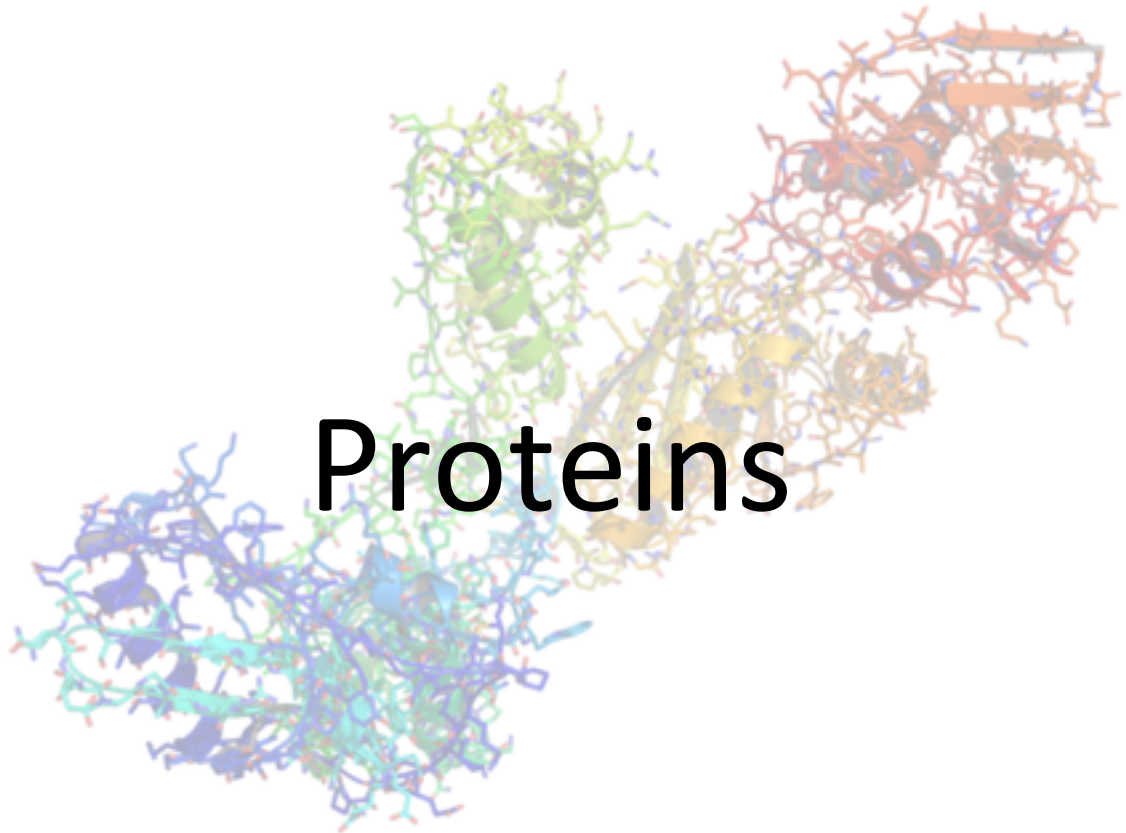
Proteins

- Primary to quaternary structure
- Peptide Bond
- Amino acids
- Torsion angles
- Ramachandran plot
- Secondary structures: α-helix, β-sheets
- Fold space
- SCOP, CATH, PDB

Summary

Nucleic Acids (DNA, RNA)

- Bases, sugar, phosphate
- Phosphodiester bond
- Numbering system
- Sugar Puckering
- Orientation around glycosidic angle
- C4'-C5' torsion angle
- RNA rotamers
- Base pairs
- Triples
- Helical parameters
- Helical grooves
- Secondary structures in RNA
- Forces that drive RNA folding
- NDB



Proteins

Nomenclature

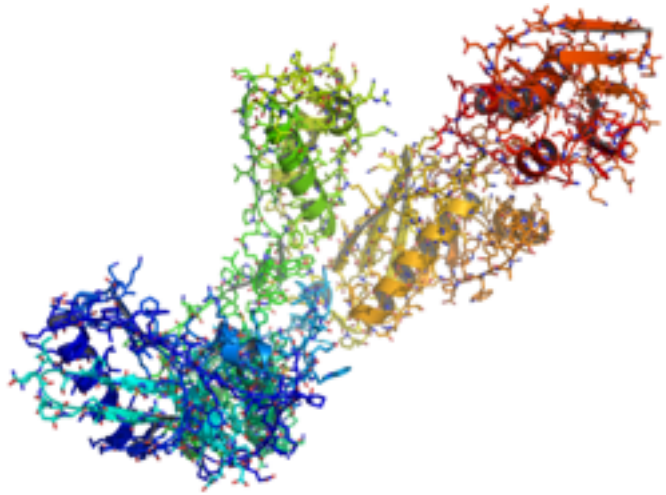
Fold: Three dimensional conformation of a protein sequence (usually at domain level).

Domain: Structurally globular part of a protein, which may independently fold.

Secondary Structure: Regular sub-domain structures composed by alpha-helices, beta-sheets and coils (or loops).

Backbone: Protein structure skeleton composed by the carbon, nitrogen and oxygen atoms.

Side-Chain: Specific atoms identifying each of the 20 residues types.

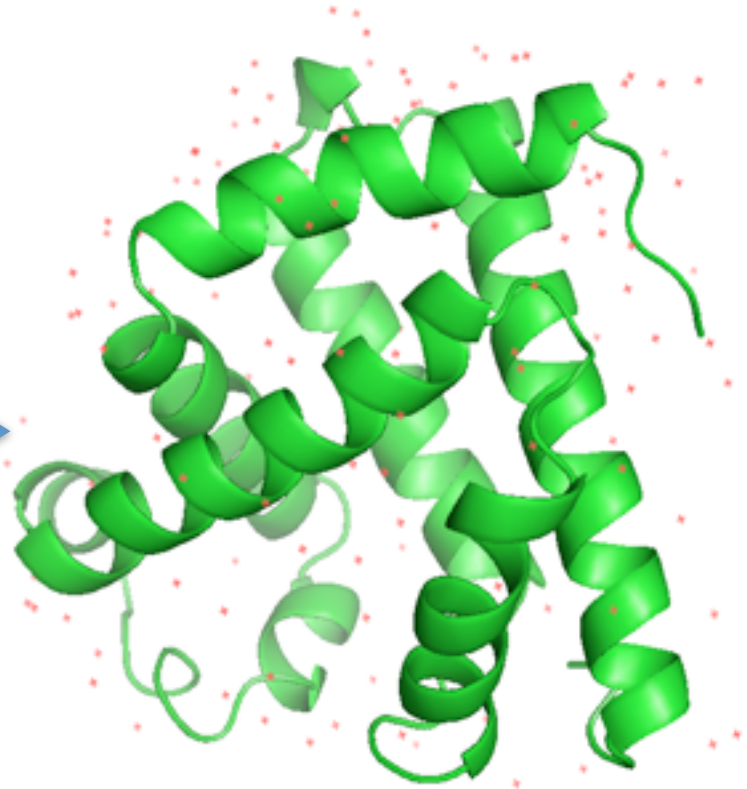


Primary structure

Secondary structure

Tertiary structure

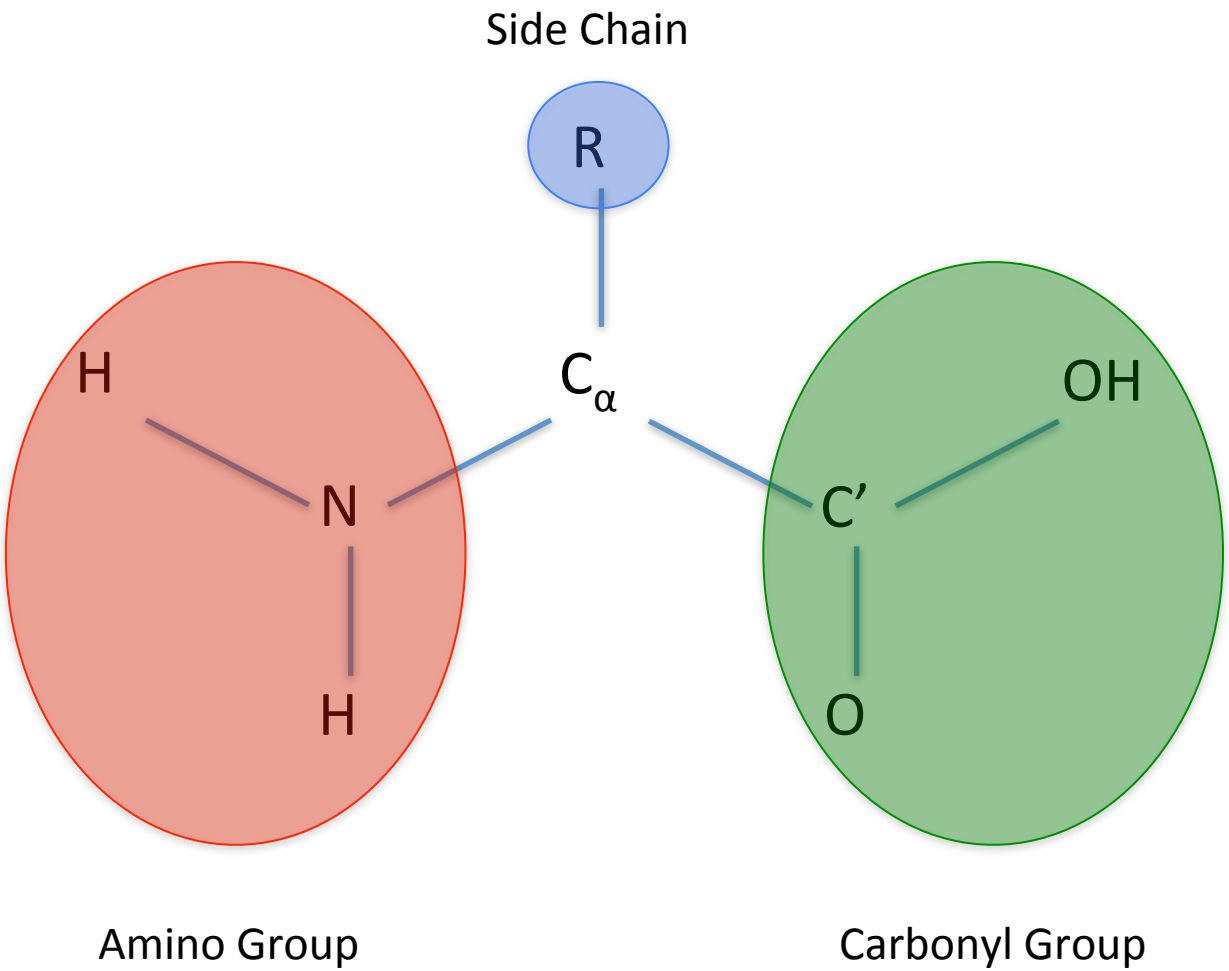
MVLSEGEWQLVLHVWAKVEAD
VAGHGQDILIRLFKSHPETLEKFD
RFKHLKTEAEMKASEDLKKHGVT
VLTALGAILKKKGHHEAELKPLAQ
SHATKHKIPIKYLEFISEAIIHVLHS
RHPGNFGADAQGAMNKALELFR
KDIAAKYKELGYQG



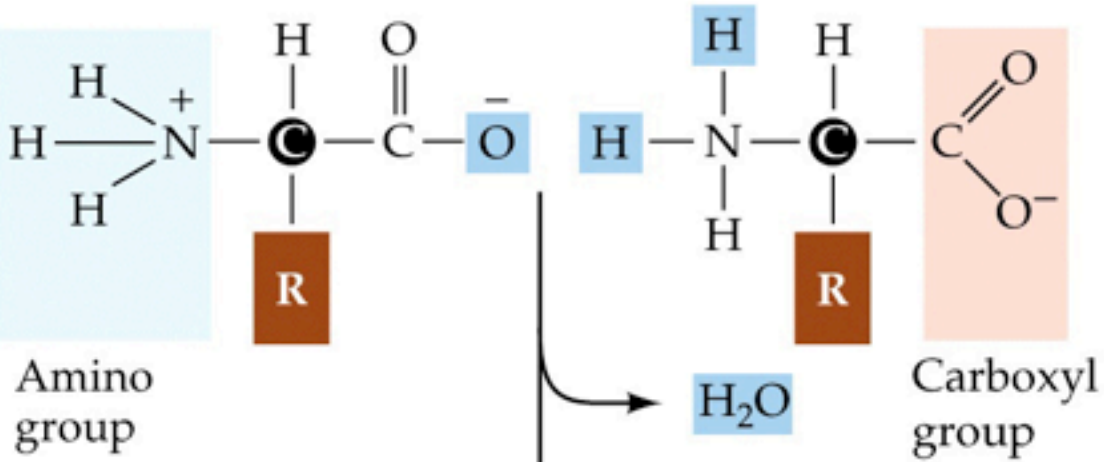
(Myoglobin)

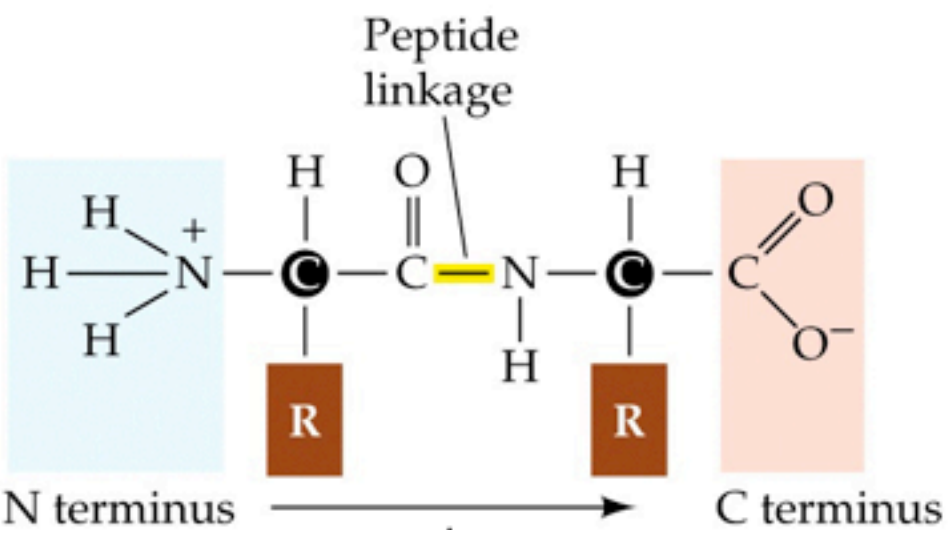
Quaternary structure

Proteins are polypeptide chains

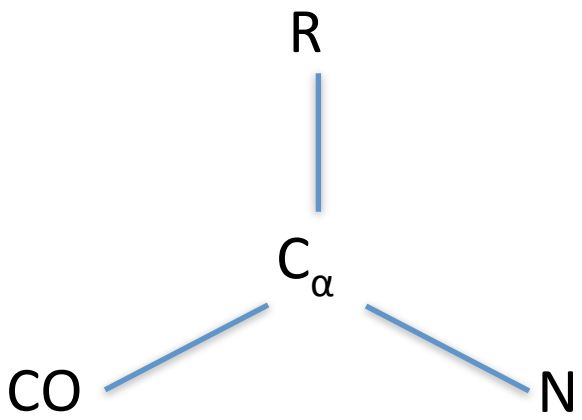


Peptide Bond

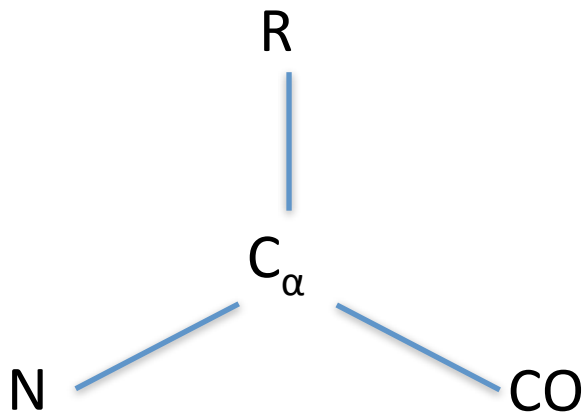




L- and D- forms

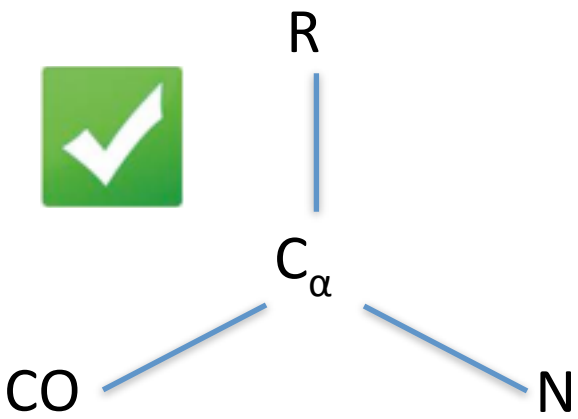


L-form

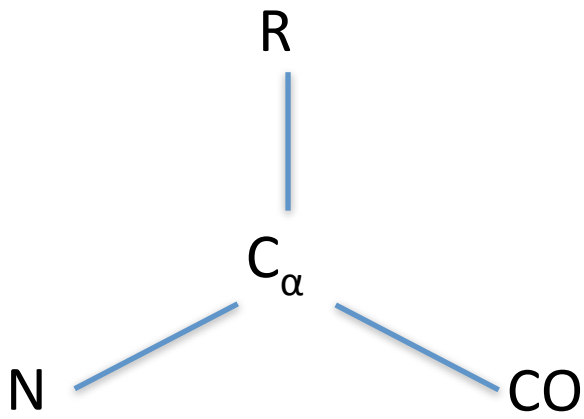


D-form

L- and D- forms

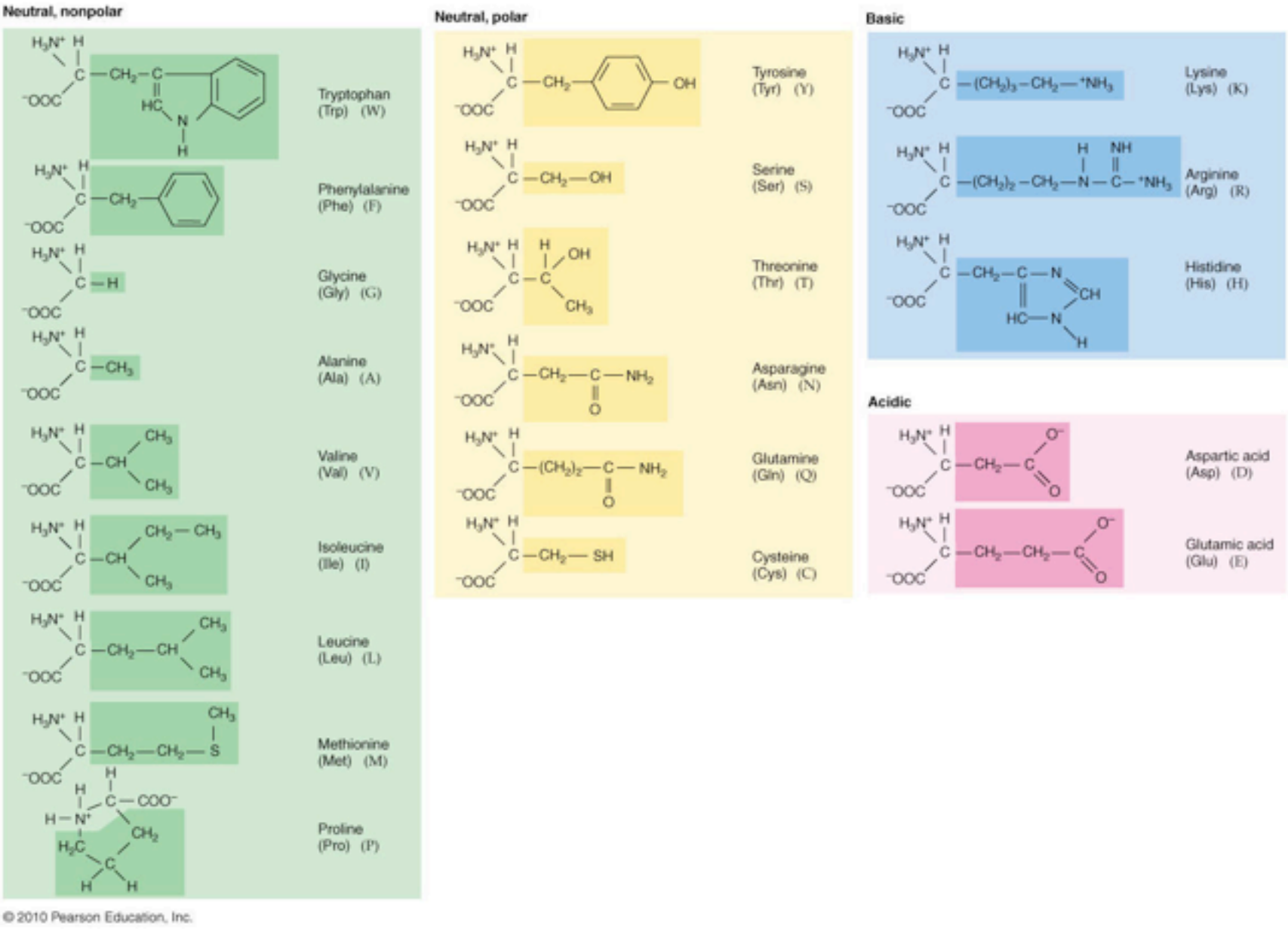


L-form



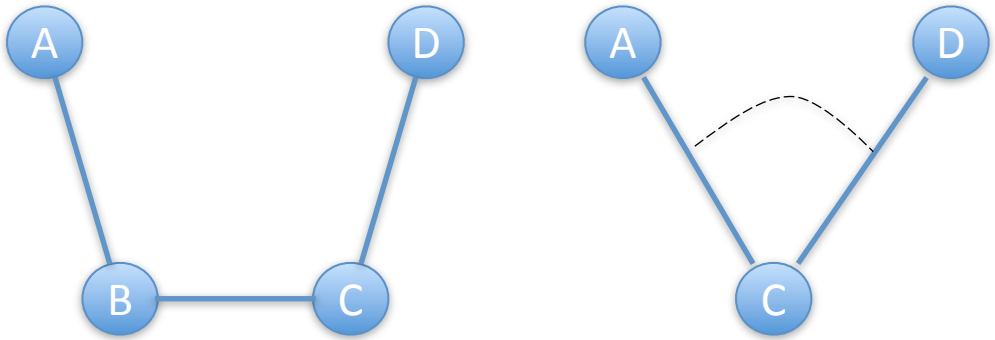
D-form

The 20 amino acids

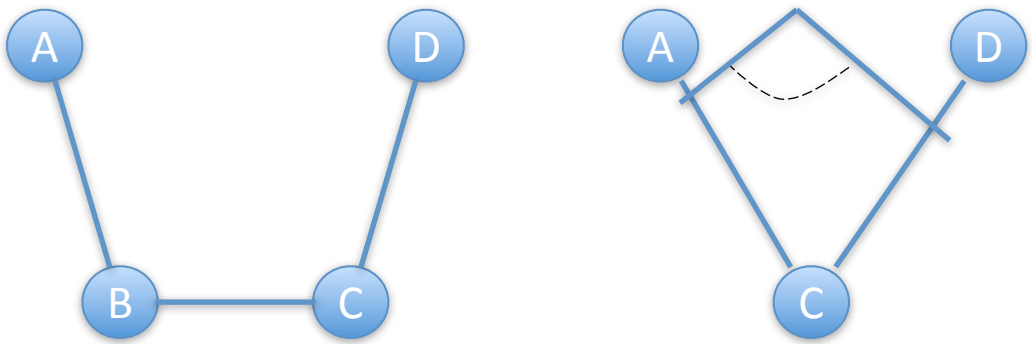


Torsion and dihedral angles

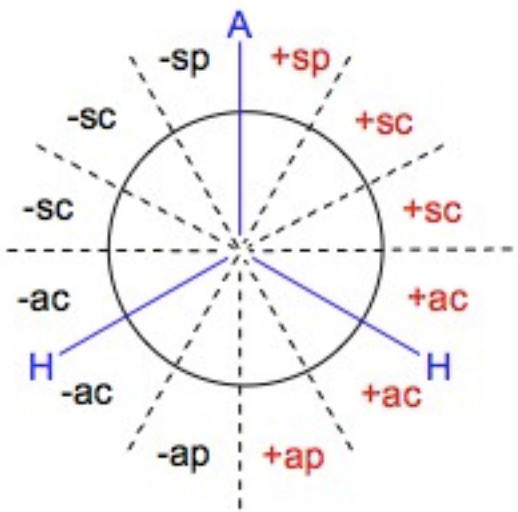
Torsion angle



Dihedral angle

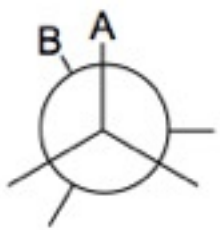


Torsion angle classification

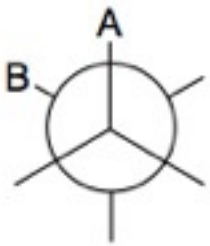


Klyne-Prelog system

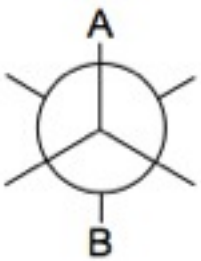
s: syn
p: periplanar
a: anti
c: clinal



Cis



Gauche

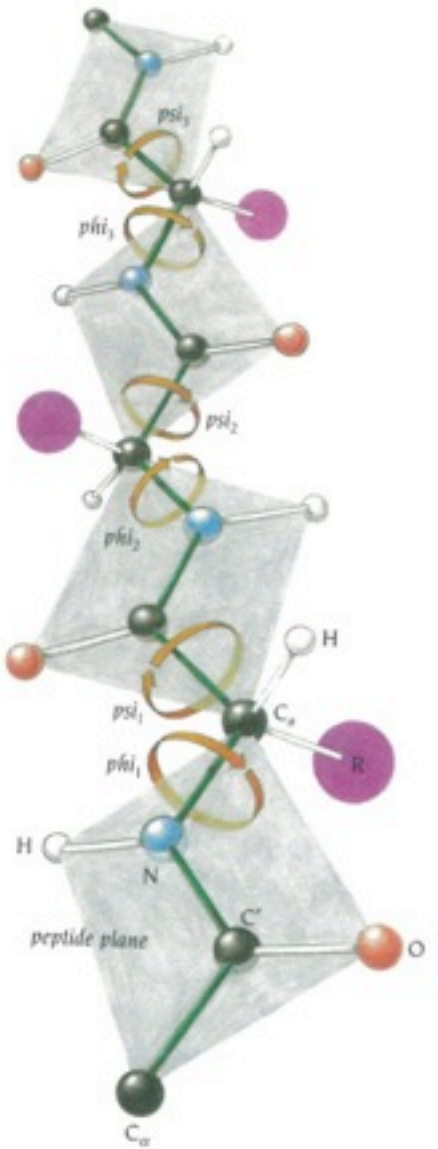


Trans

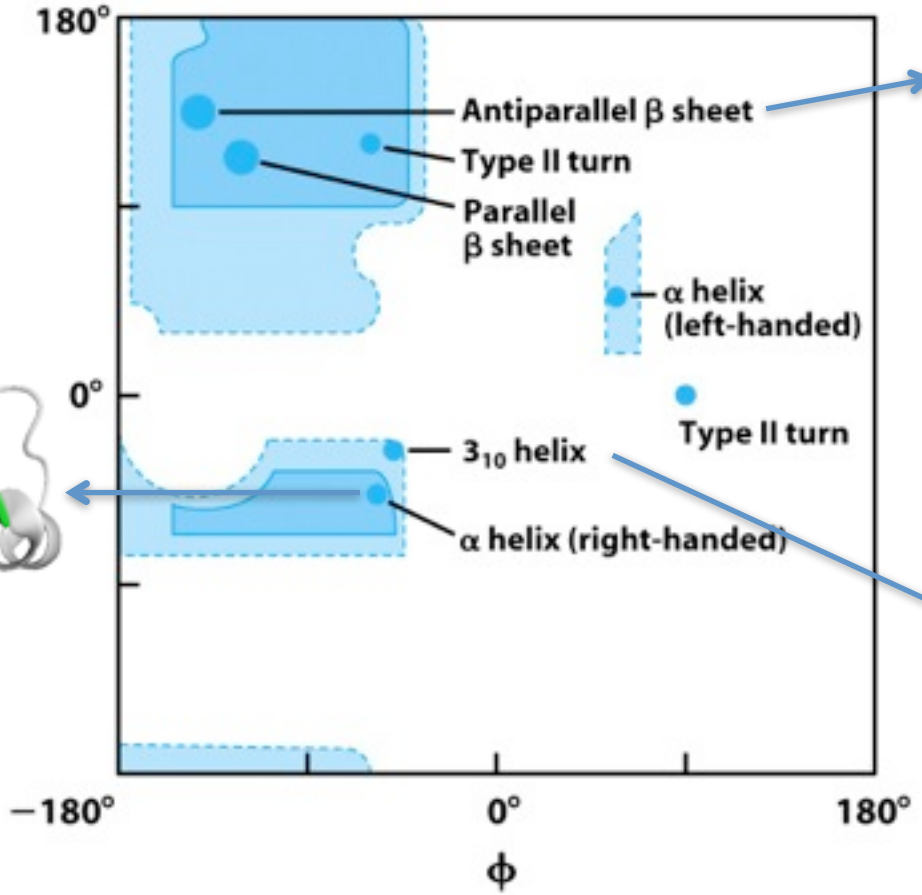
Peptide units = suits

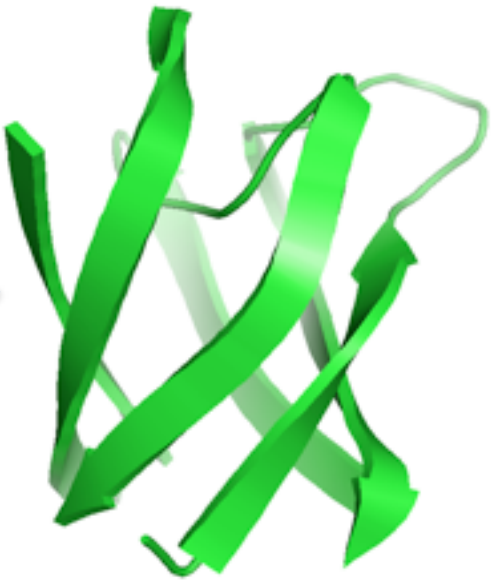
Phi (φ) = C'-C_α-N-C'^{+1},
rotation around C_α-N

Psi (Ψ) = N-C'-C_α-N^{+1},
rotation around C'-C_α



Ramachandran plot





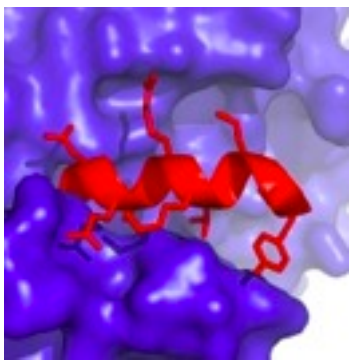
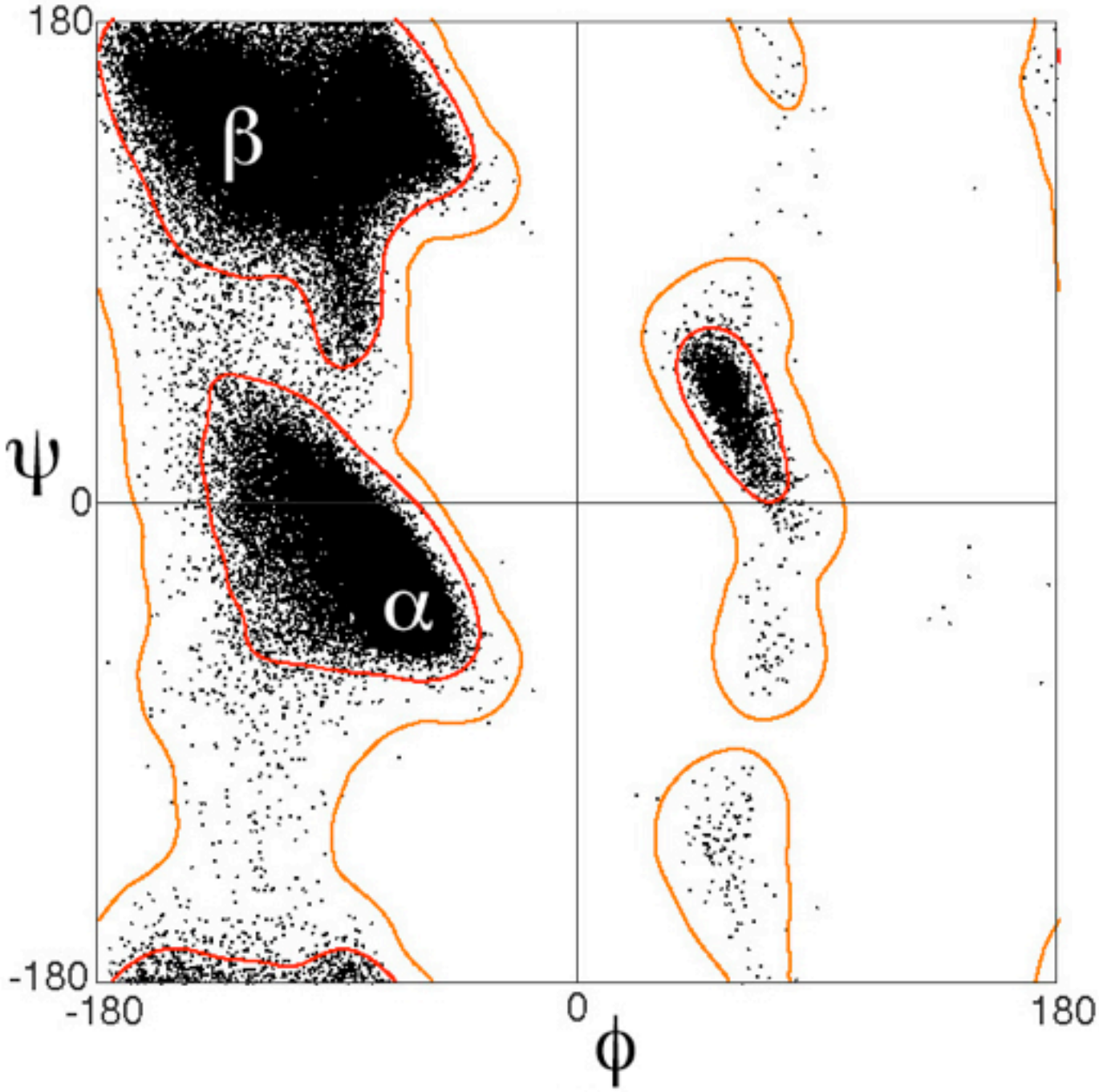
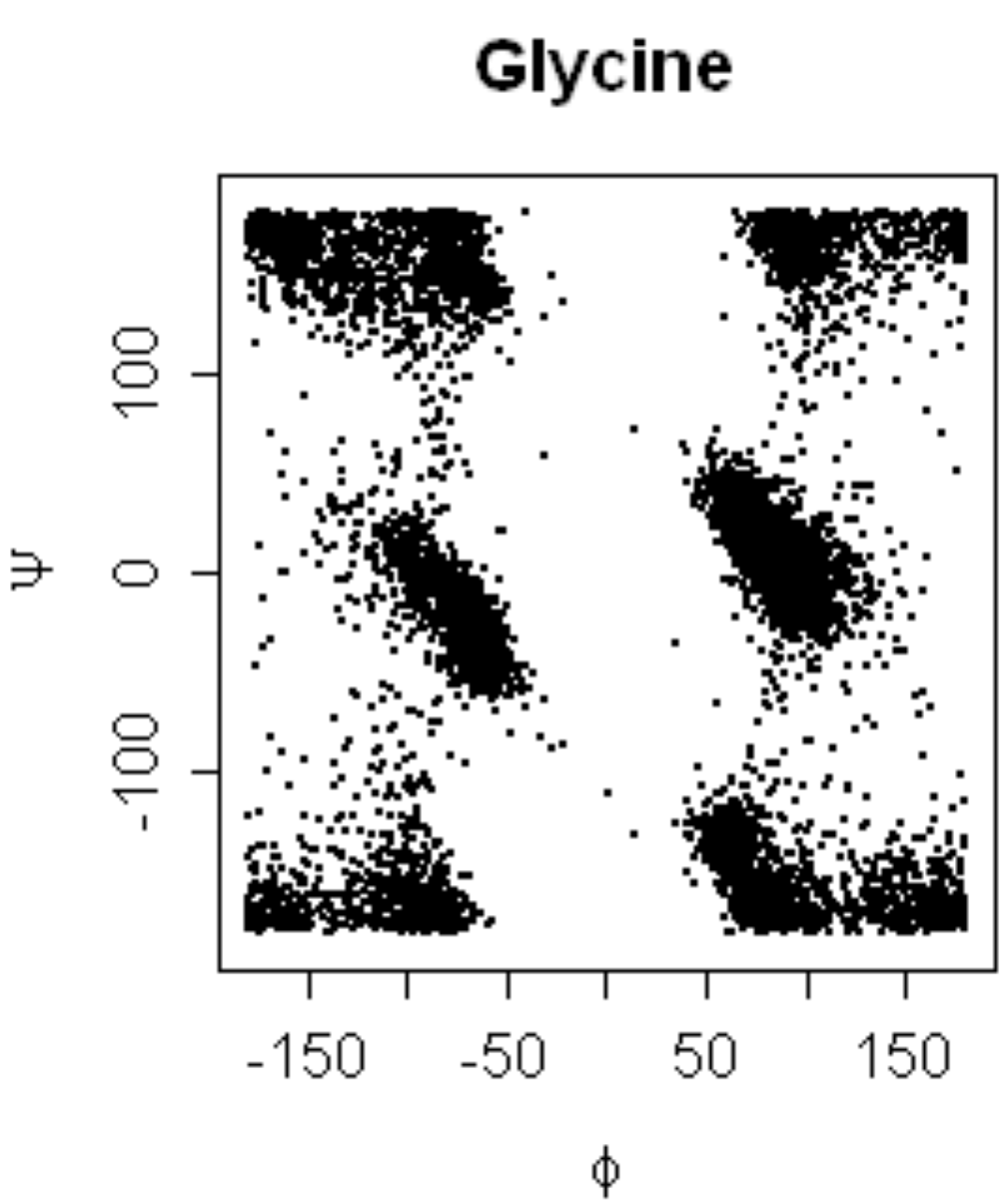
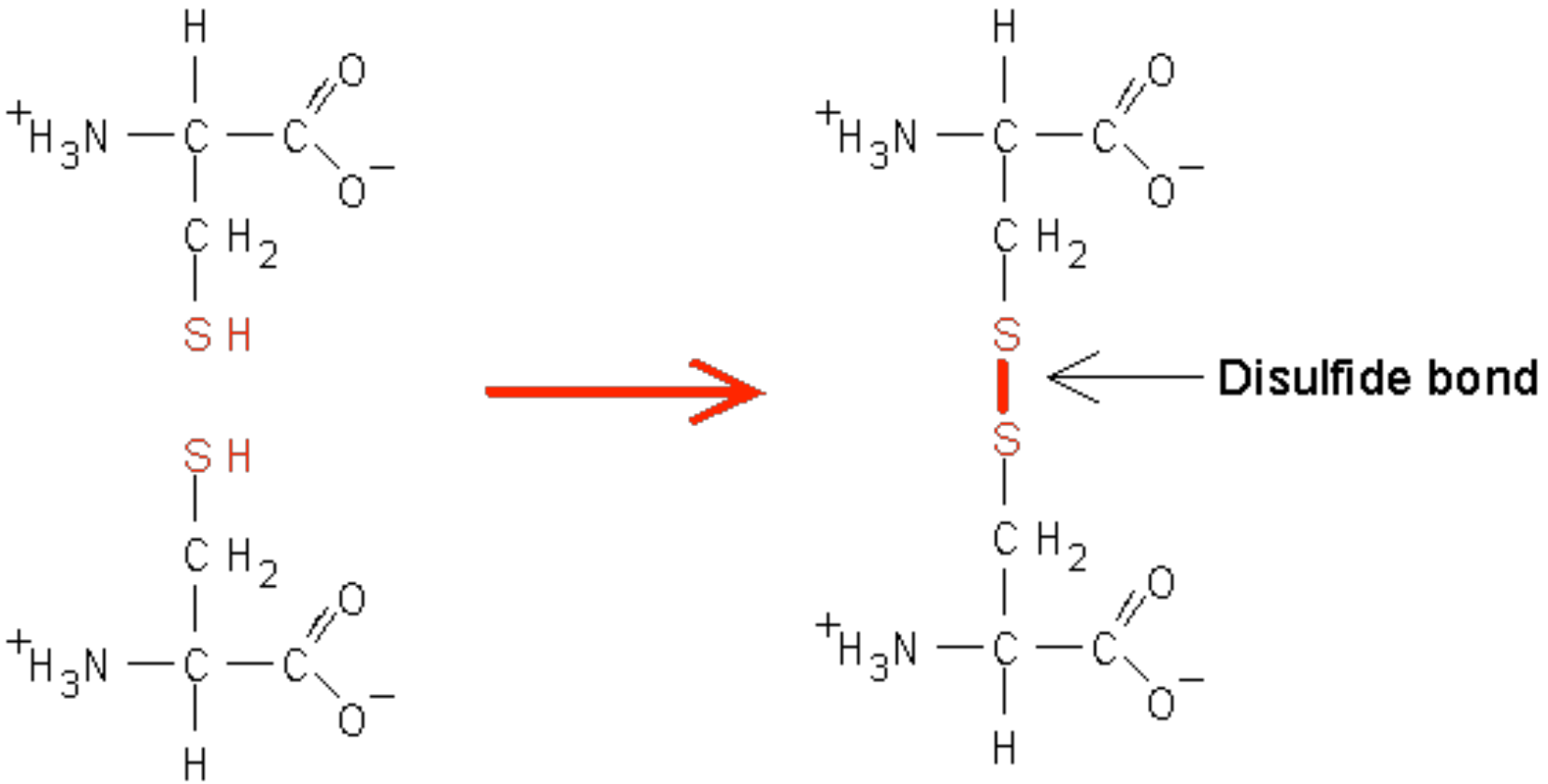


Figure 4-9a Principles of Biochemistry, 4/e
© 2006 Pearson Prentice Hall, Inc.

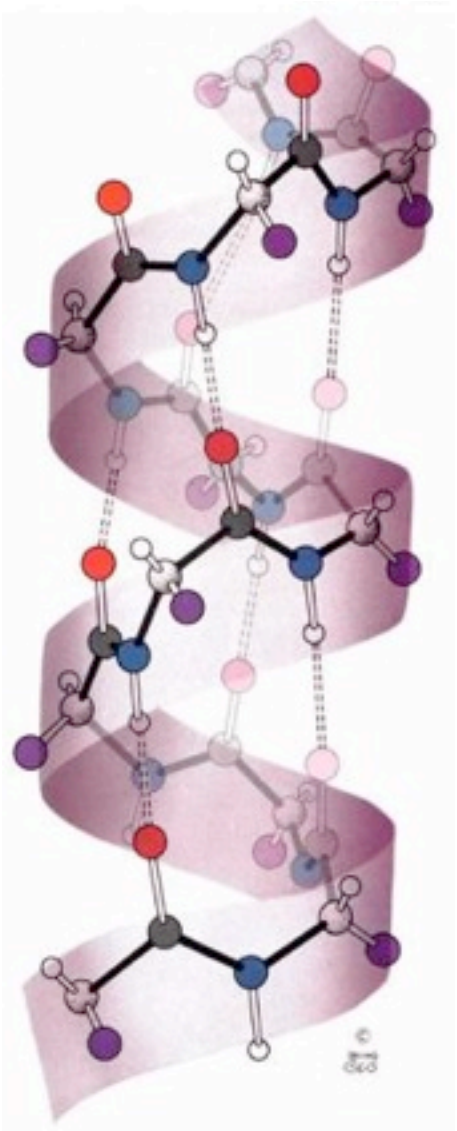

180
β
ψ
0
α
-180
-180
0
180
ϕ


Glycine
ψ
100
0
-100
-150
-50
50
150
ϕ

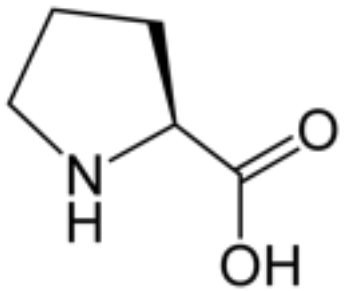
Cysteine disulfide bond



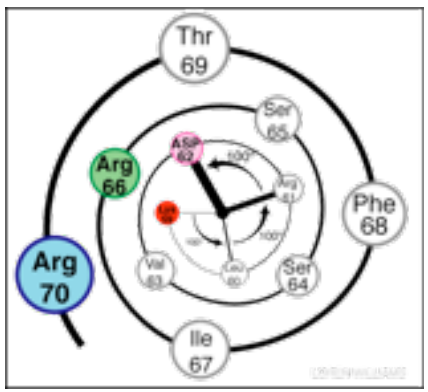
α-helix



- Backbone angles:
  - ψ = -50º
  - ϕ = -60º
- Dipole moment
- Proline bending

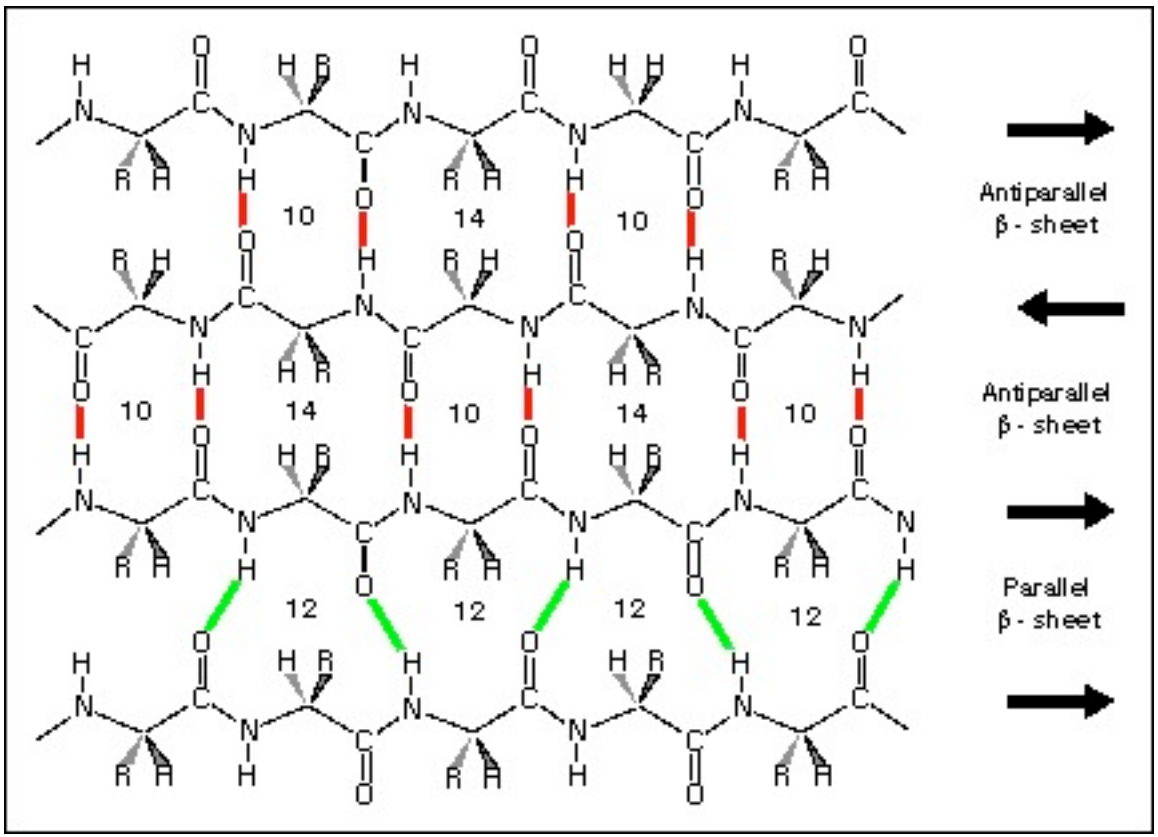


Proline

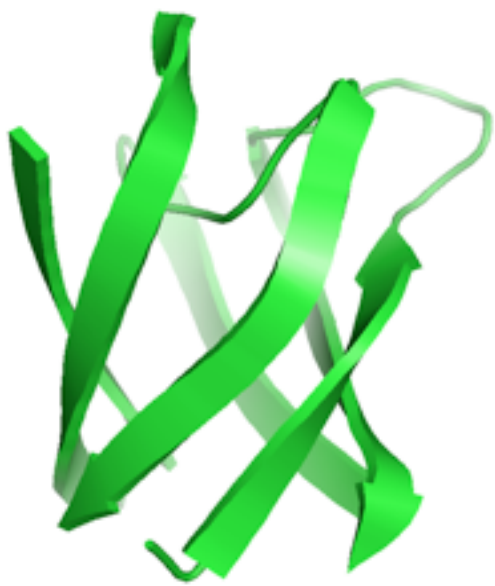


Helical wheel projection

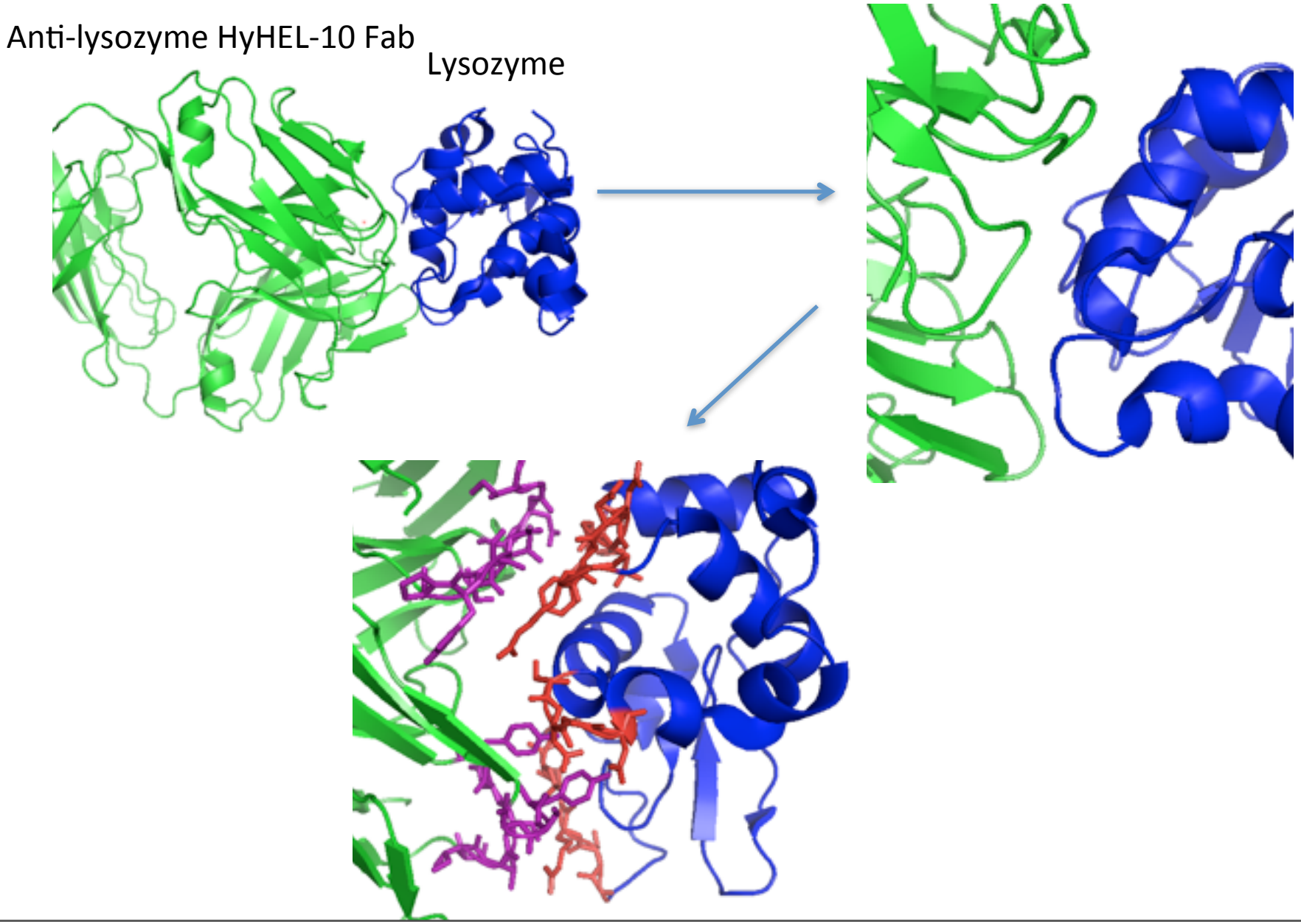
β-sheet



- First quadrant in Ramachandran's plot
- Parallel or antiparallel

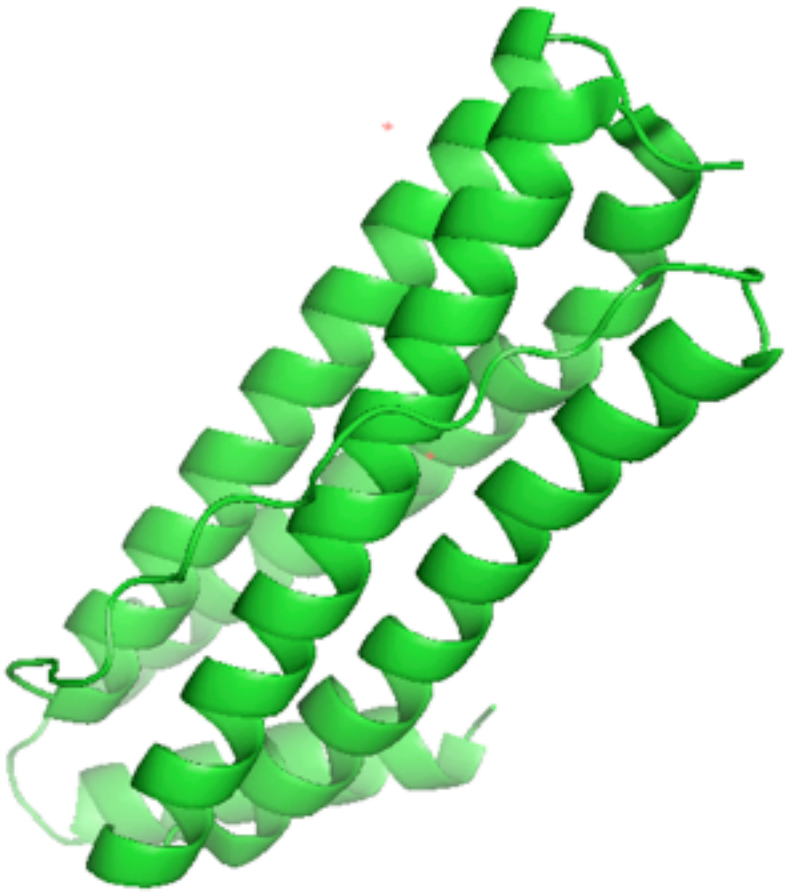


Loops and function



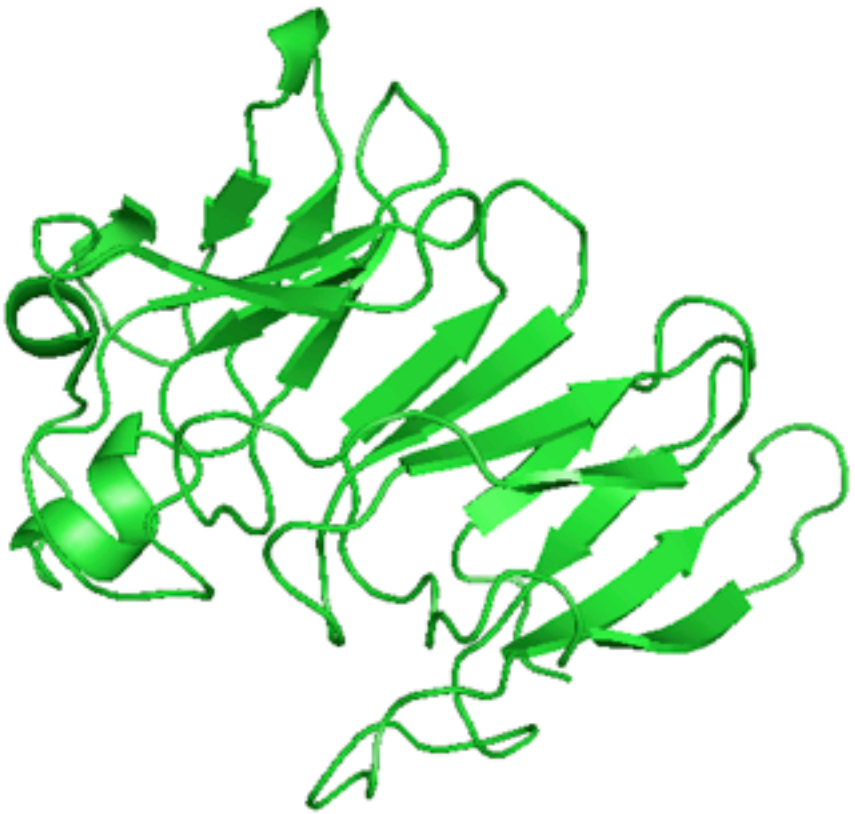
Tertiary structures - Fold space

Mainly alpha:



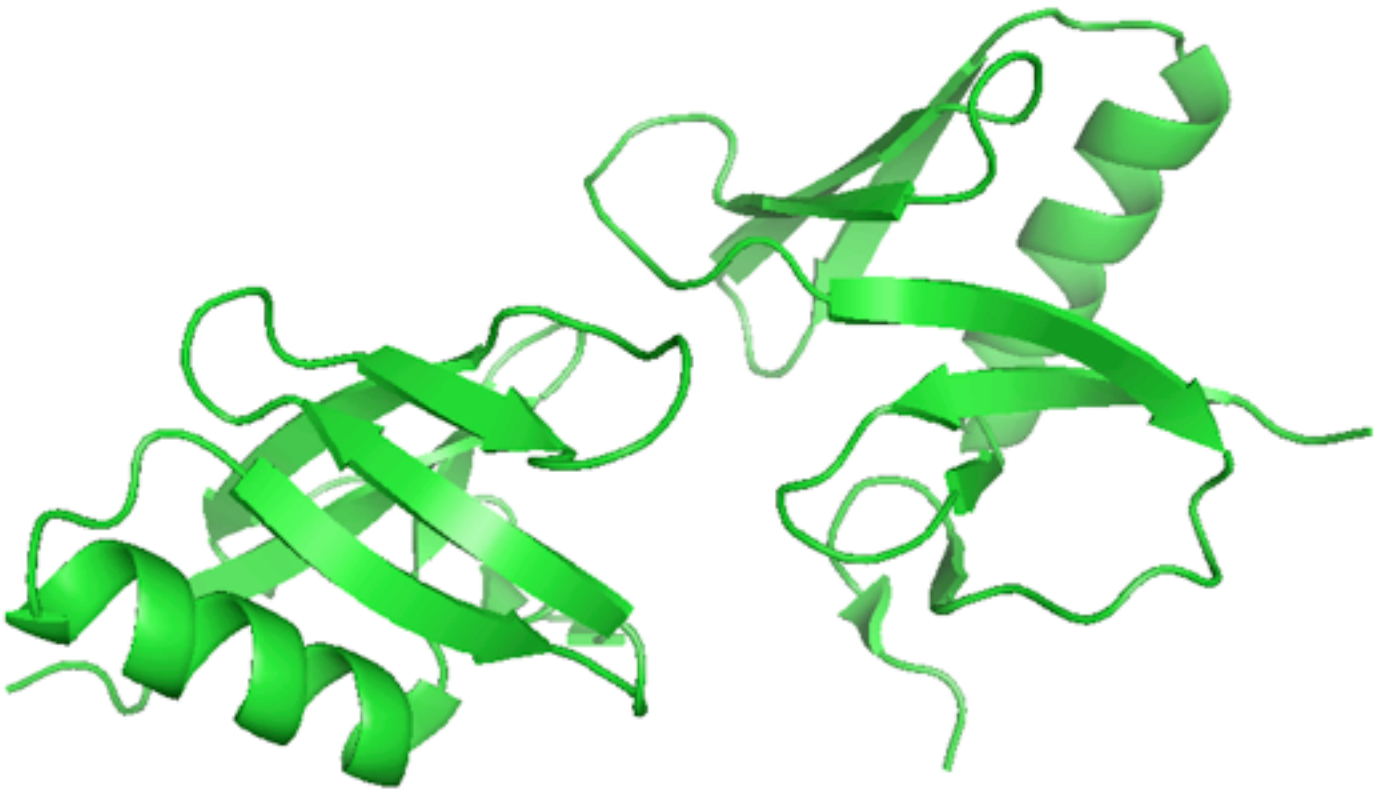
Tertiary structures - Fold space

Mainly beta:



Tertiary structures - Fold space

Alpha beta:



SCOP$_{1.75}$ database

http://scop.mrc-lmb.cam.ac.uk/scop/

Murzin A. G.,el at. (1995). J. Mol. Biol. ***247****, 536-540.*

- ✓ **Largely recognized as "standard of gold"**
- ✓ **Manually classification**
- ✓ **Clear classification of structures in:**

CLASS
FOLD
SUPER-FAMILY
FAMILY

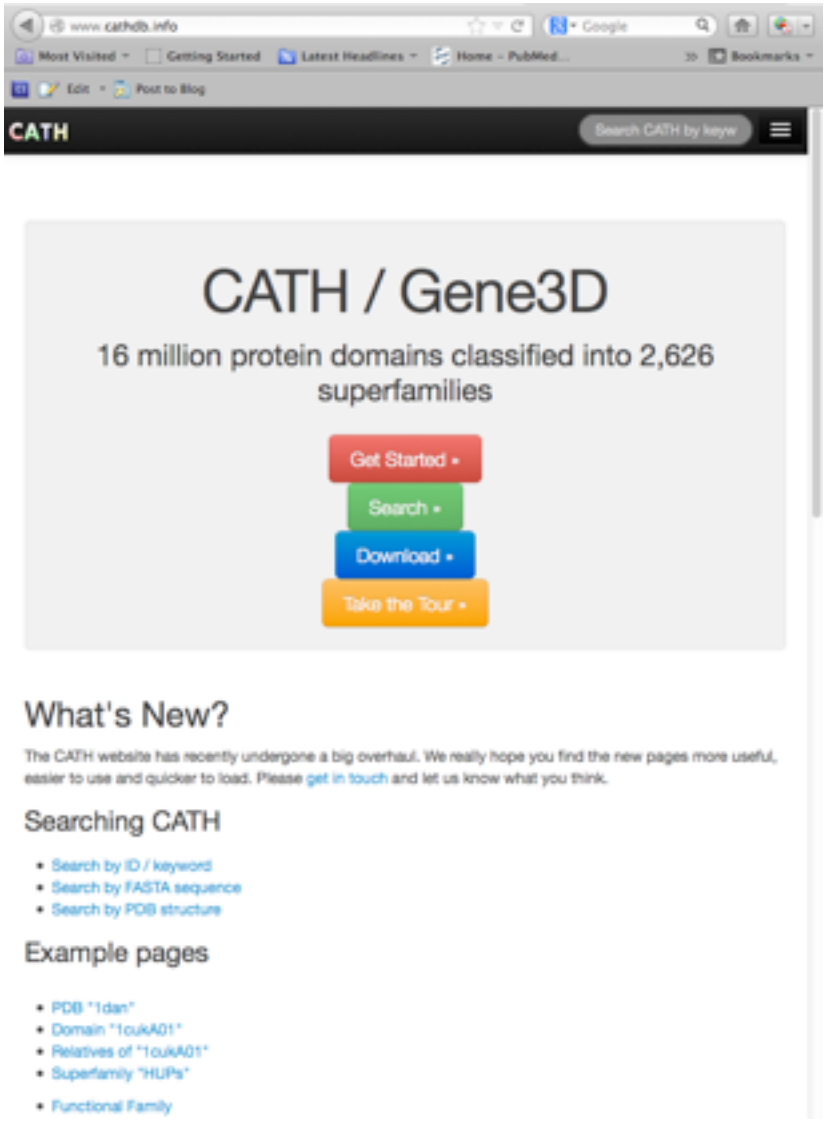
- ✓ **Some large number of tools already available**

Manually classification
Not 100% up-to-date
Domain boundaries definition

Class	Number of folds	Number of superfamilies	Number of families
All alpha proteins	284	507	871
All beta proteins	174	354	742
Alpha and beta proteins (a/b)	147	244	803
Alpha and beta proteins (a+b)	376	552	1055
Multi-domain proteins	66	66	89
Membrane and cell surface proteins	58	110	123
Small proteins	90	129	219
Total	1195	1962	3902

CATH$_{3.5}$ database

http://www.cathdb.info



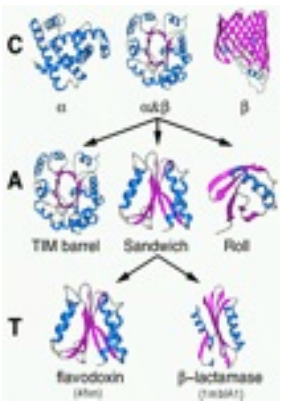
Uses FSSP for superimposition

- ✓ Recognized as “standard of gold”
- ✓ Semi-automatic classification
- ✓ Clear classification of structures in:

CLASS
ARCHITECTURE
TOPOLOGY
HOMOLOGOUS SUPERFAMILIES

- ✓ Some large number of tools already available
- ✓ Easy to navigate

Semi-automatic classification
Domain boundaries definition



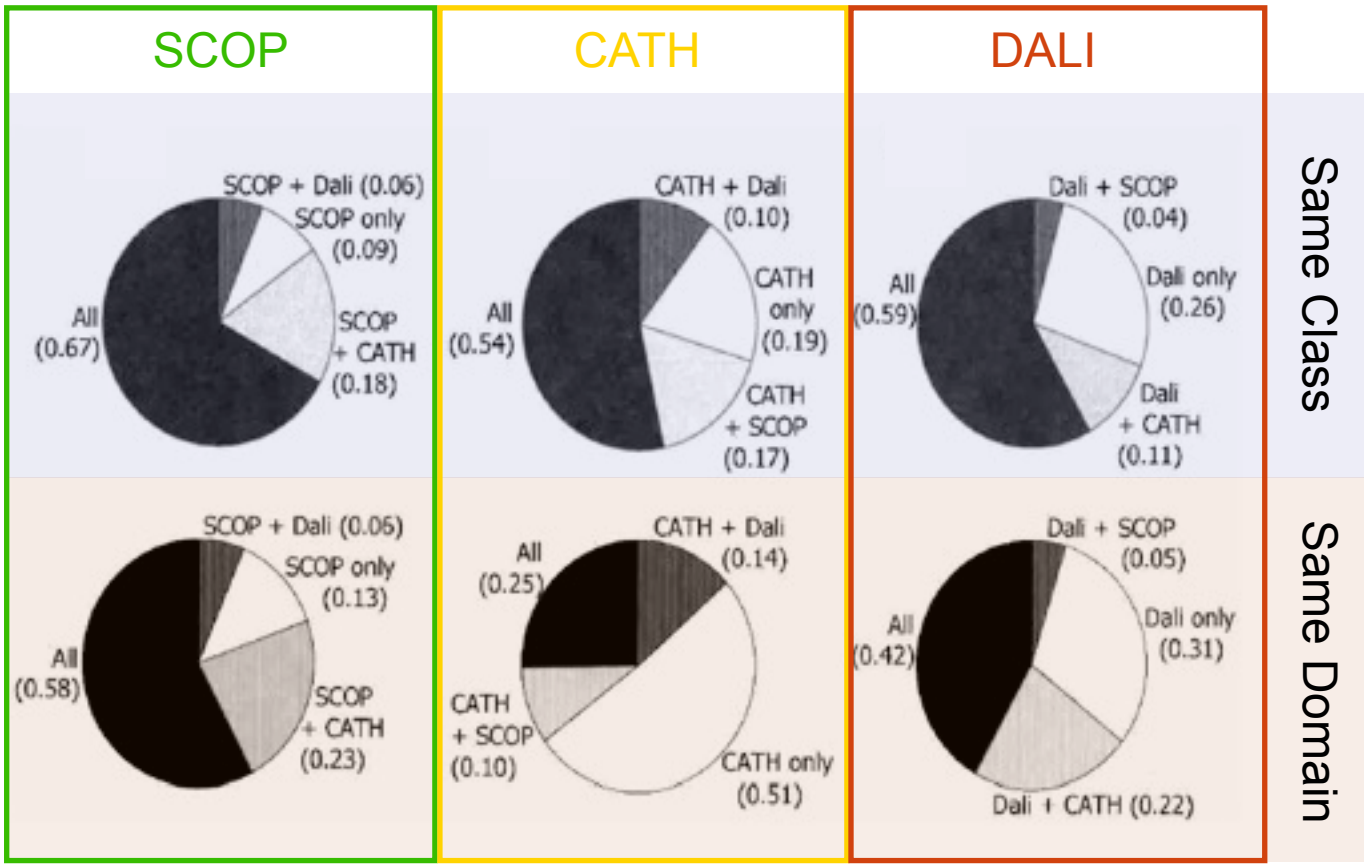
173,536 CATH Domains
2,626 CATH Superfamilies
51,334 PDBs

*Orengo, C.A., et al. (1997) Structure. **5**. 1093-1108.*

Classification of the structural space

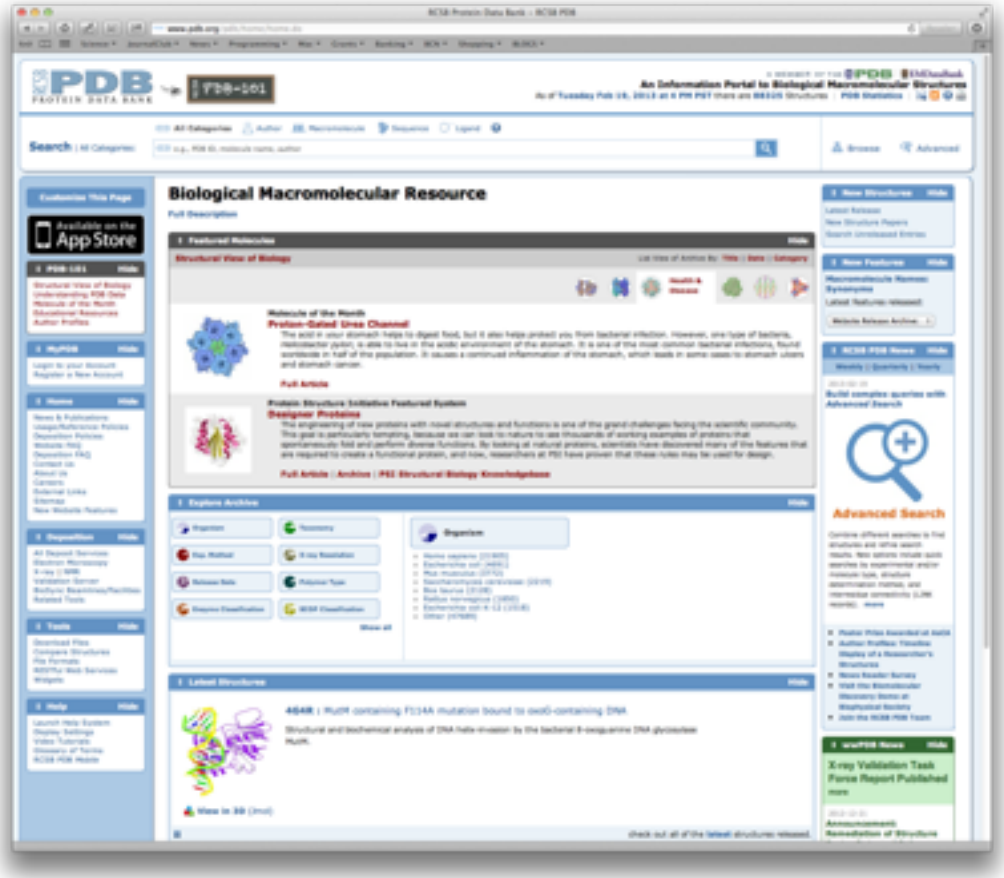
Not an easy task!

Domain definition AND domain classification



*Day, et al. (2003) Protein Sciences, **12** pp2150*

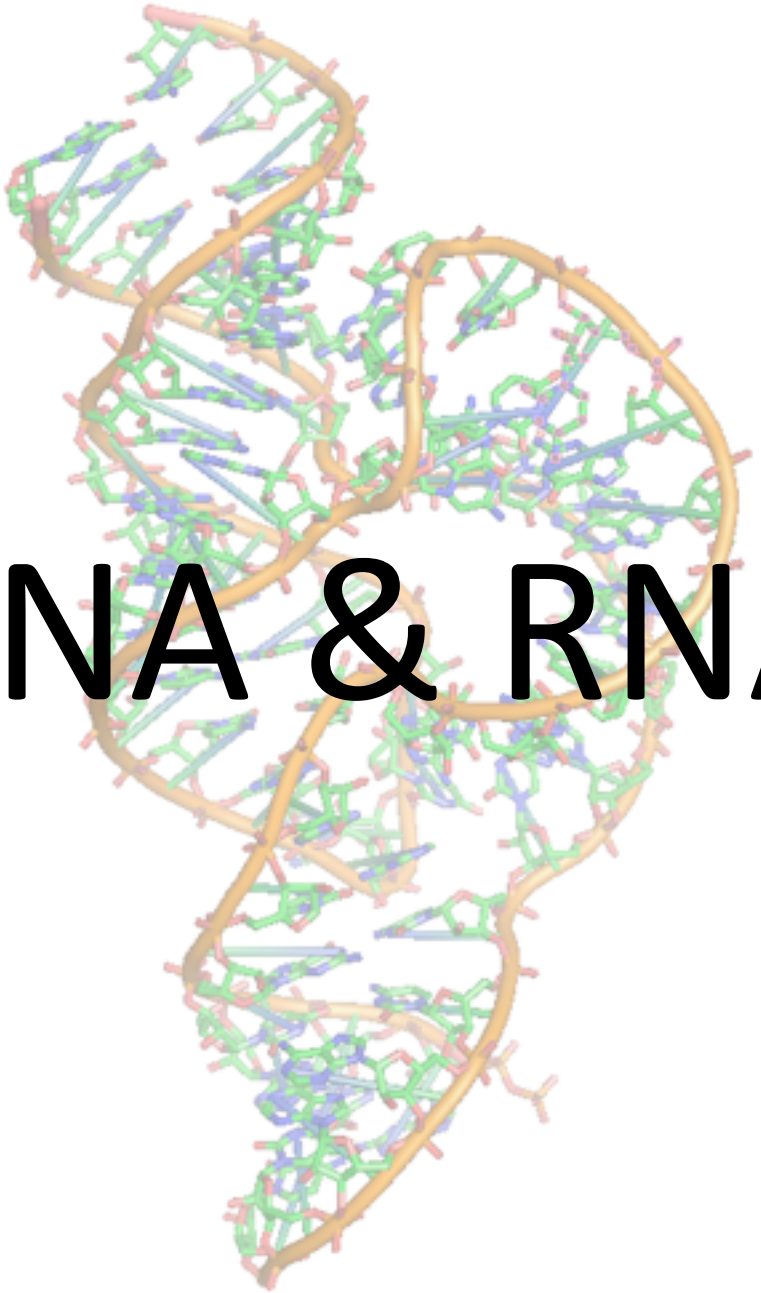
PDB



Yearly and total PDB structures per year

Yearly

Total



DNA & RNA

RNA function

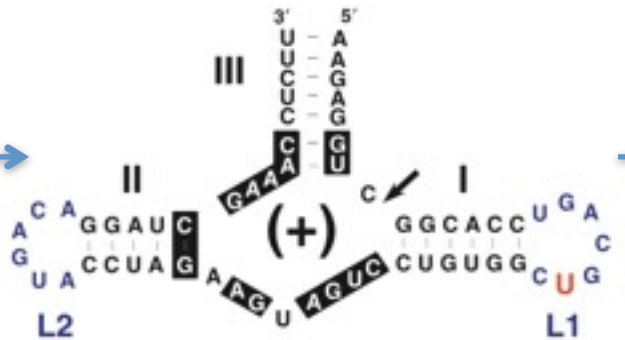
- 1) Informative
- 2) Structural
- 3) Catalytic
- 4) Regulatory

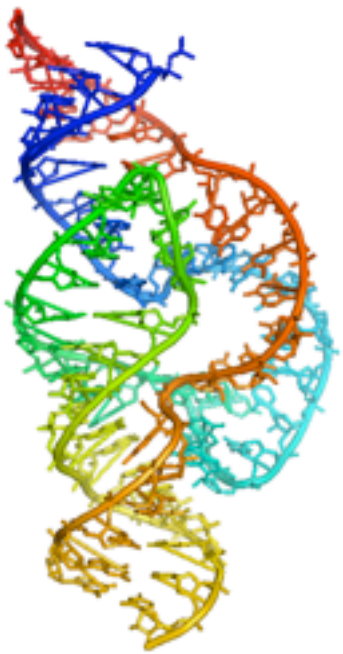
Primary structure

Secondary structure

Tertiary structure (3D)

CAGACCGAAGUGAUGAAGCG
AUUGGUUAAUCUGGGCAAA
GCGUCUGAAGGUUGUGGUU
UCGAC



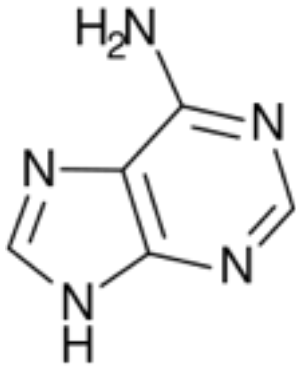


Bases

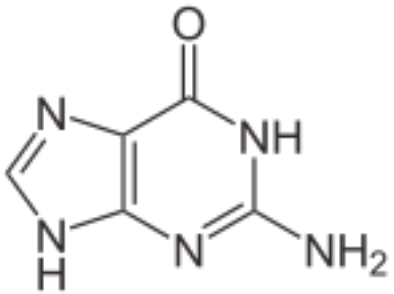
(aka nucleotidic bases, aromatic bases)

Purines

Adenine
(A)

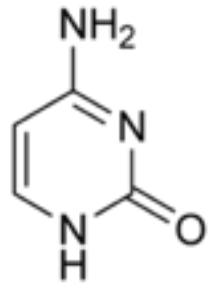


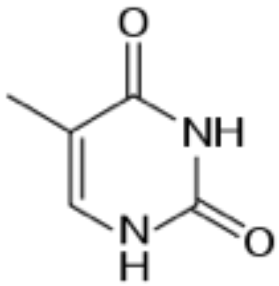
Guanine
(G)



Pyrimidines

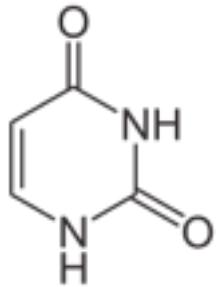
Cytosine
(C)





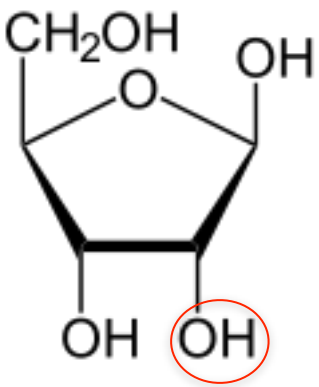
Thymidine
(T)

Uracil
(U)

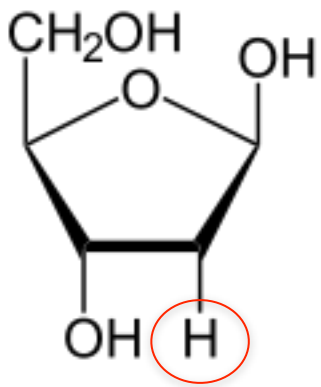


Sugars

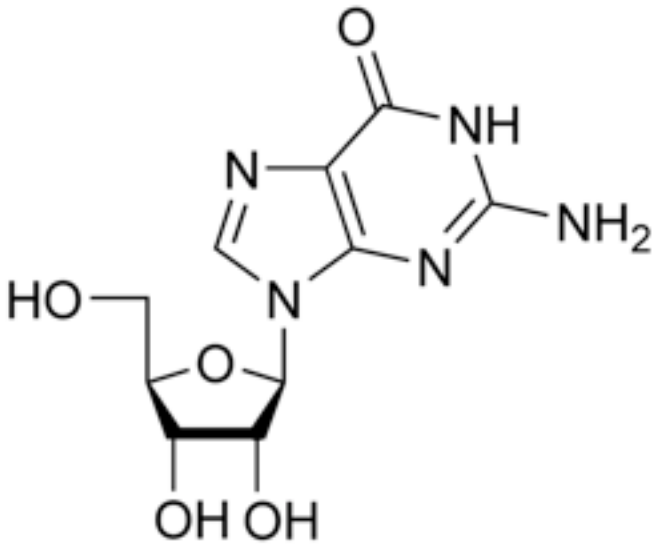
β-D-ribose



β-D-2-Deoxyribose

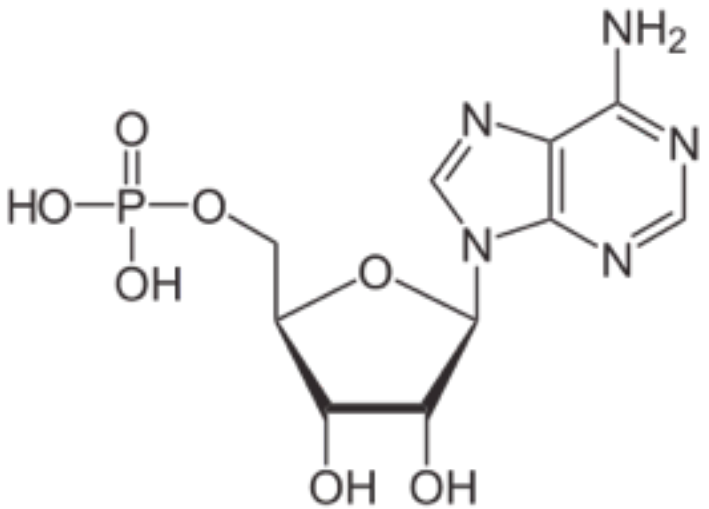


Nucleoside



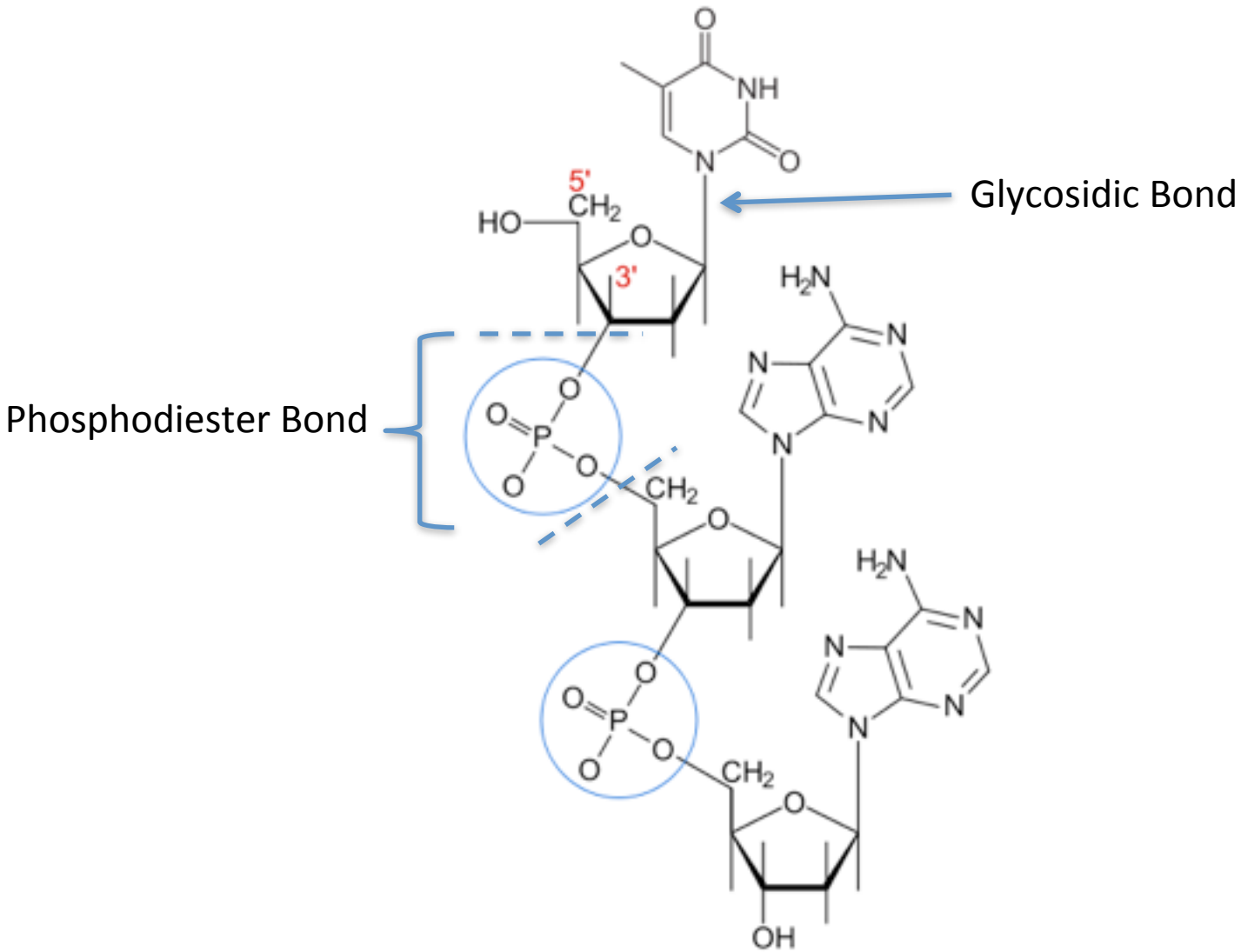
Sugar + base

Nucleotide monophosphate



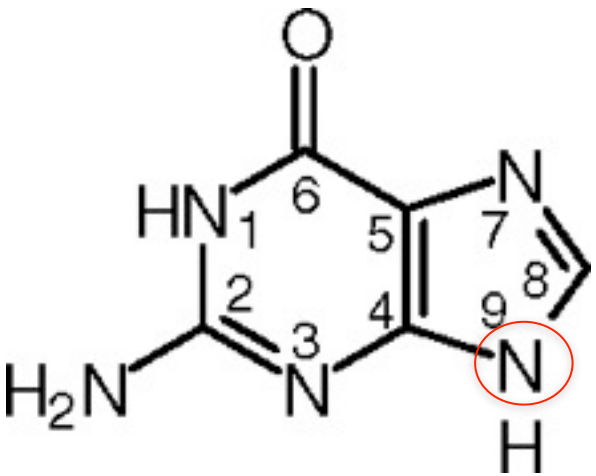
Phosphate + sugar + base

Phosphodiester Bond

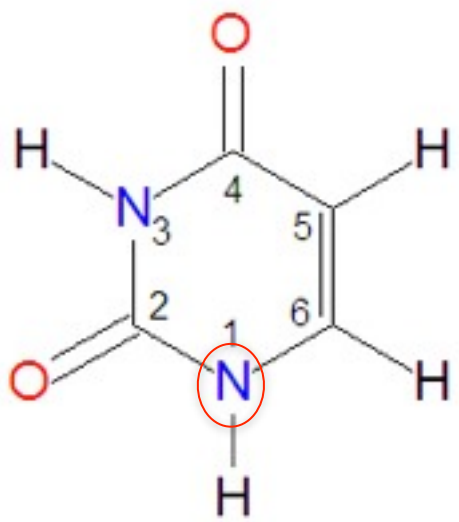


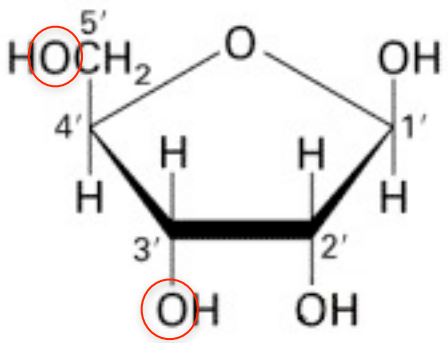
Numbering system

Guanine



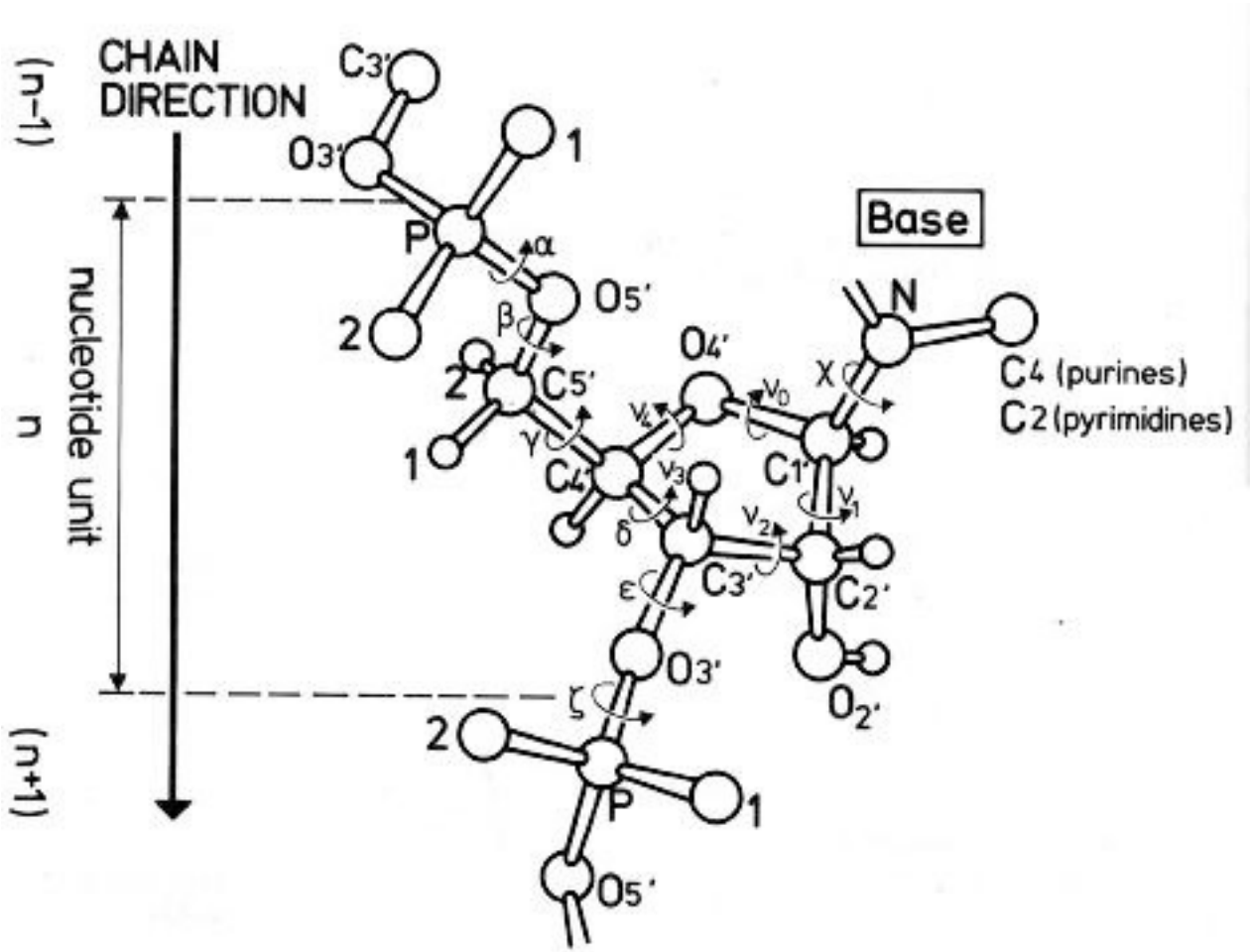
Uracil



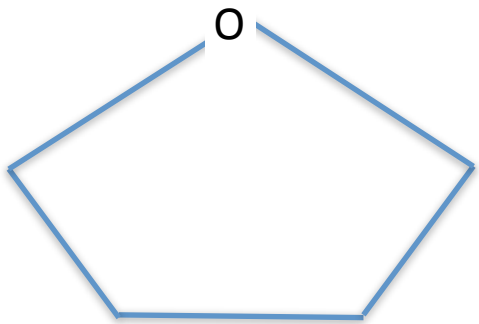


Ribose

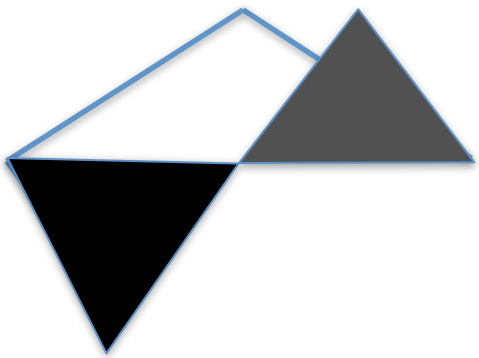
Nucleic acid torsion angles

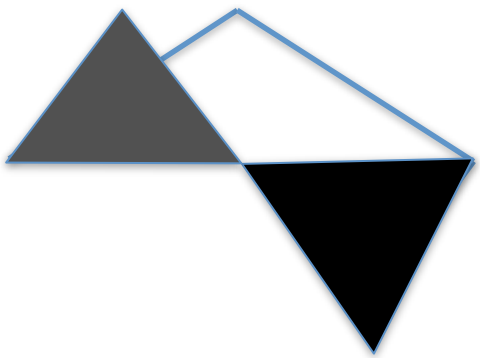


Furanose ring

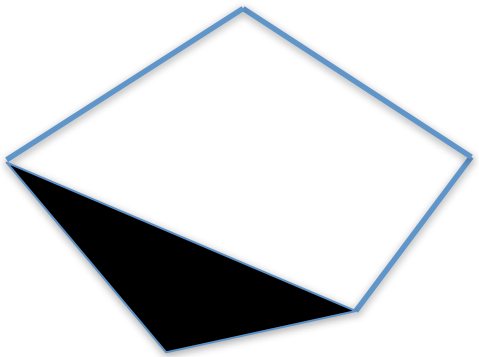


Twisted
(T)

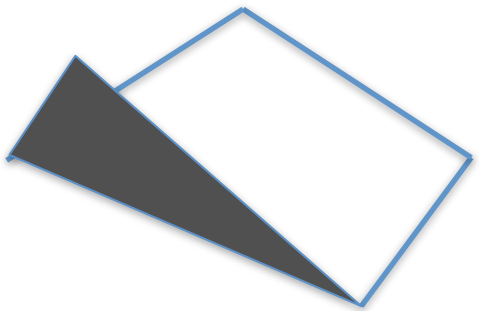




Envelope
(E)

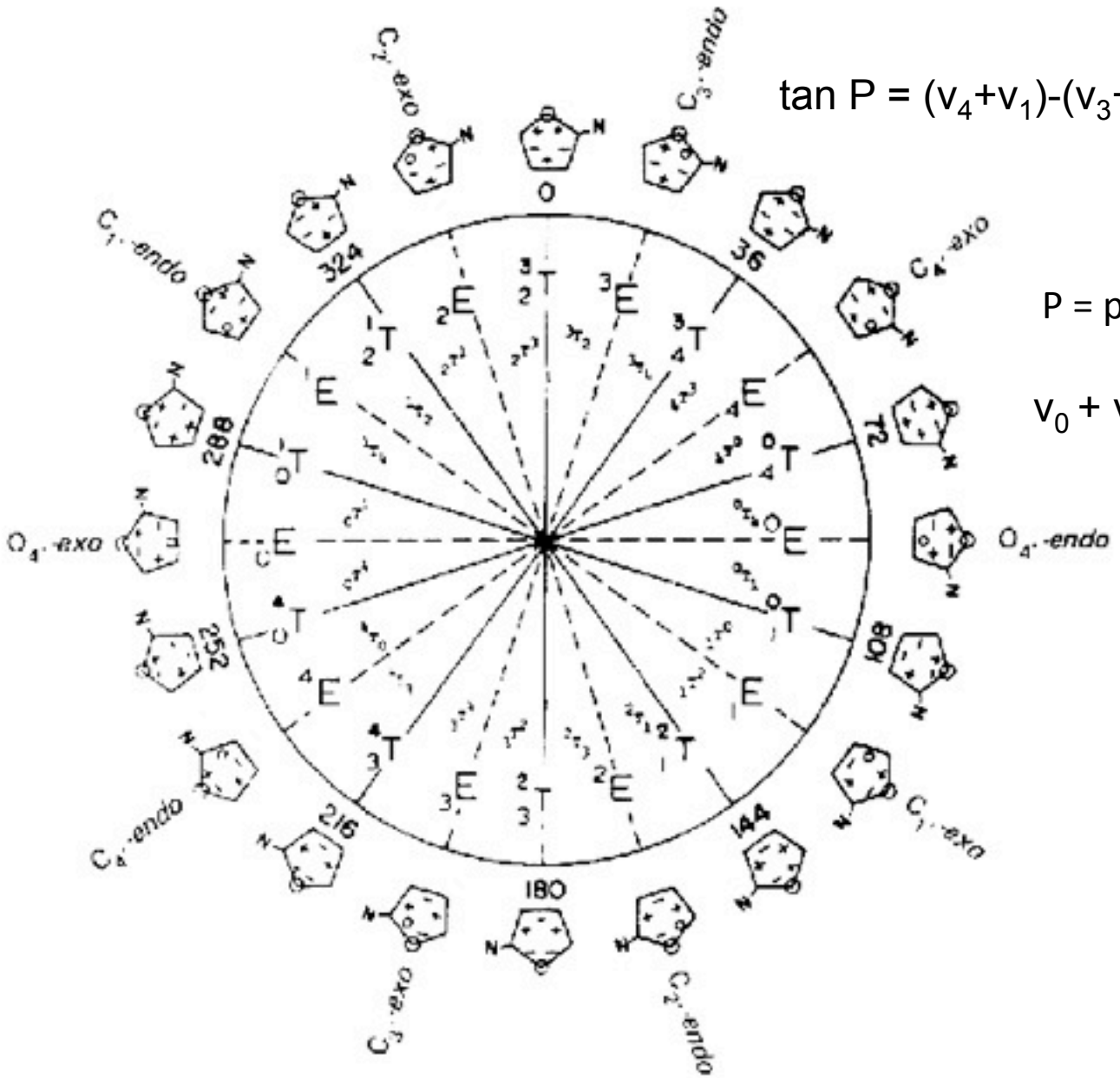


C3’ exo



C3’ endo

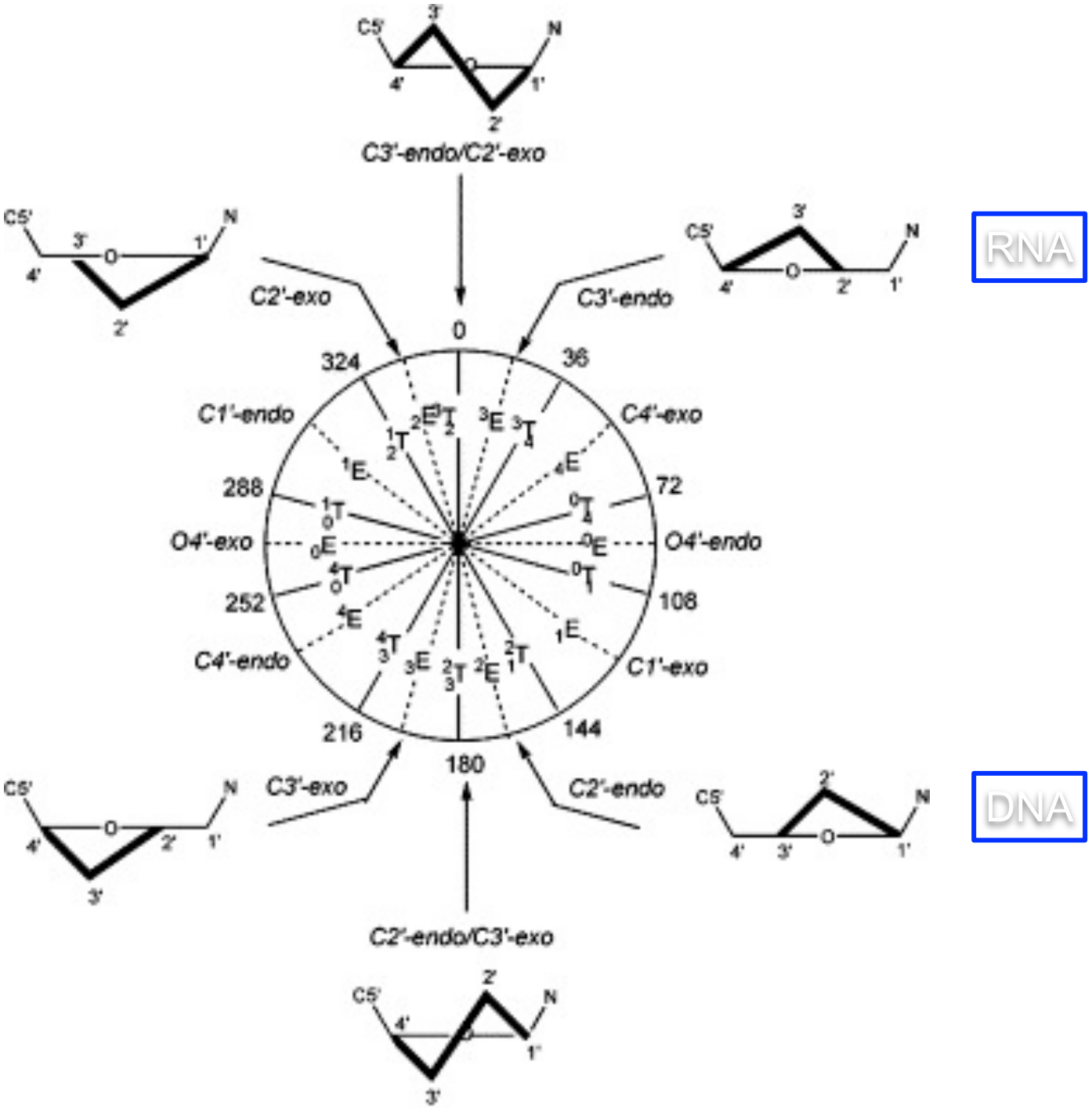
Sugar Puckering



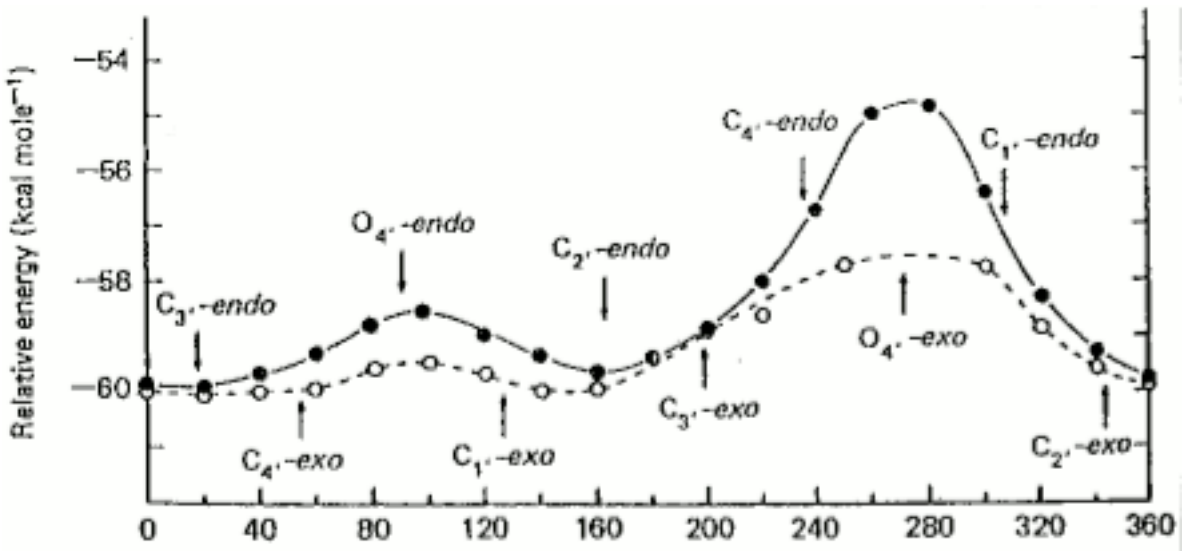
$$\tan P = (v_4+v_1)-(v_3+v_0)/[2v_2(\text{sen}36^\circ + \text{sen}72^\circ)]$$

P = pseudorotation angle

$$v_0 + v_1 + v_2 + v_3 + v_4 = 0$$

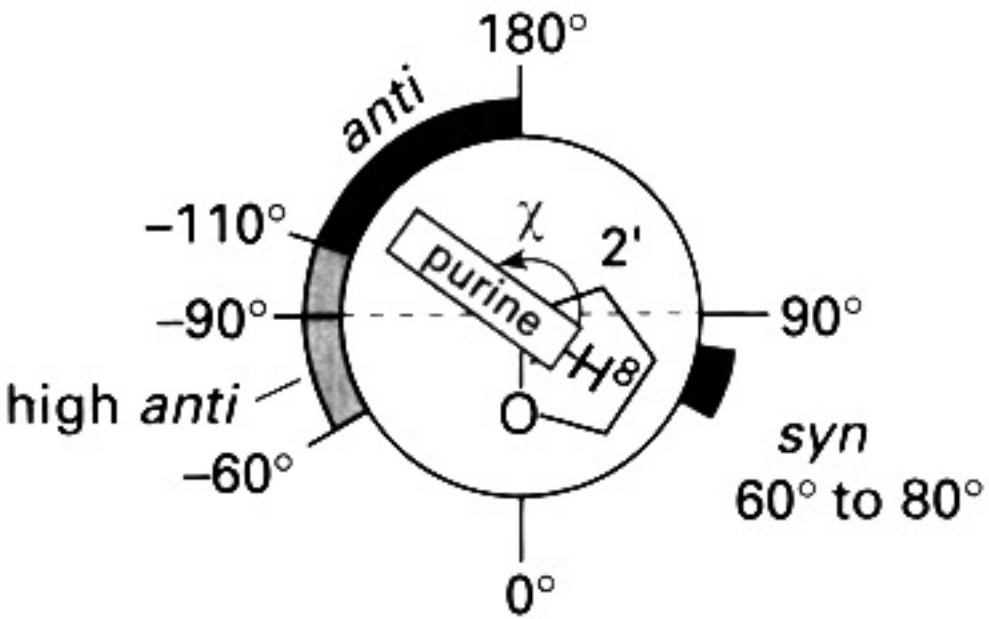

C3'-endo/C2'-exo
C2'-exo
C3'-endo
C1'-endo
C4'-exo
O4'-exo
O4'-endo
C4'-endo
C1'-exo
C3'-exo
C2'-endo
C2'-endo/C3'-exo
0
36
72
108
144
180
216
252
288
324
RNA
DNA

Energy variation related to *P*

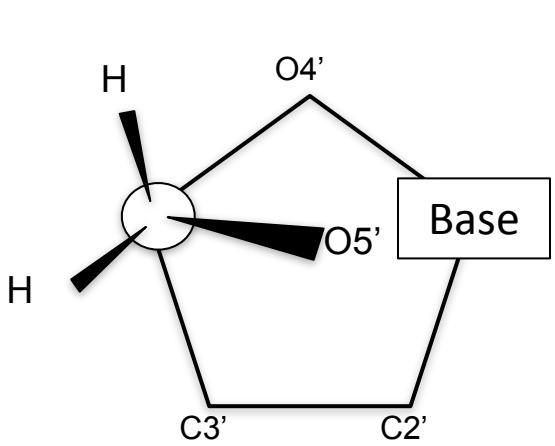


Pseudorotation phase angle *P* (degrees)

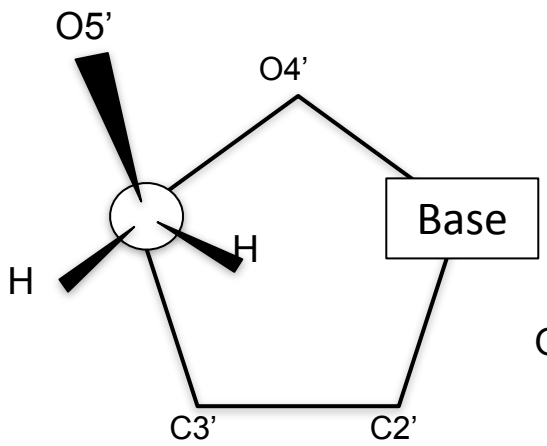
Orientation around glycosidic angle



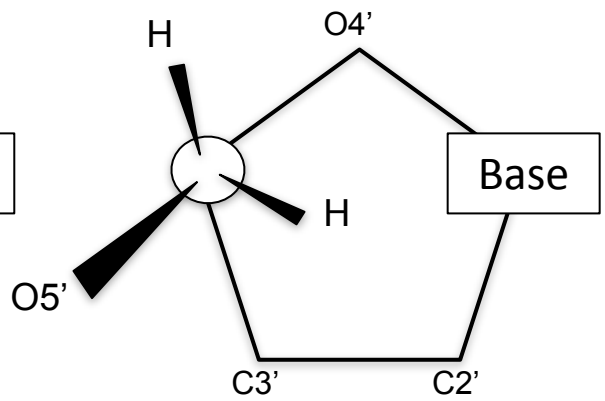
C4’-C5’ torsion angle



+sc
(gauche, gauche)



ap
(gauche, trans)



-sc
(trans, gauche)

Ramachandran plot

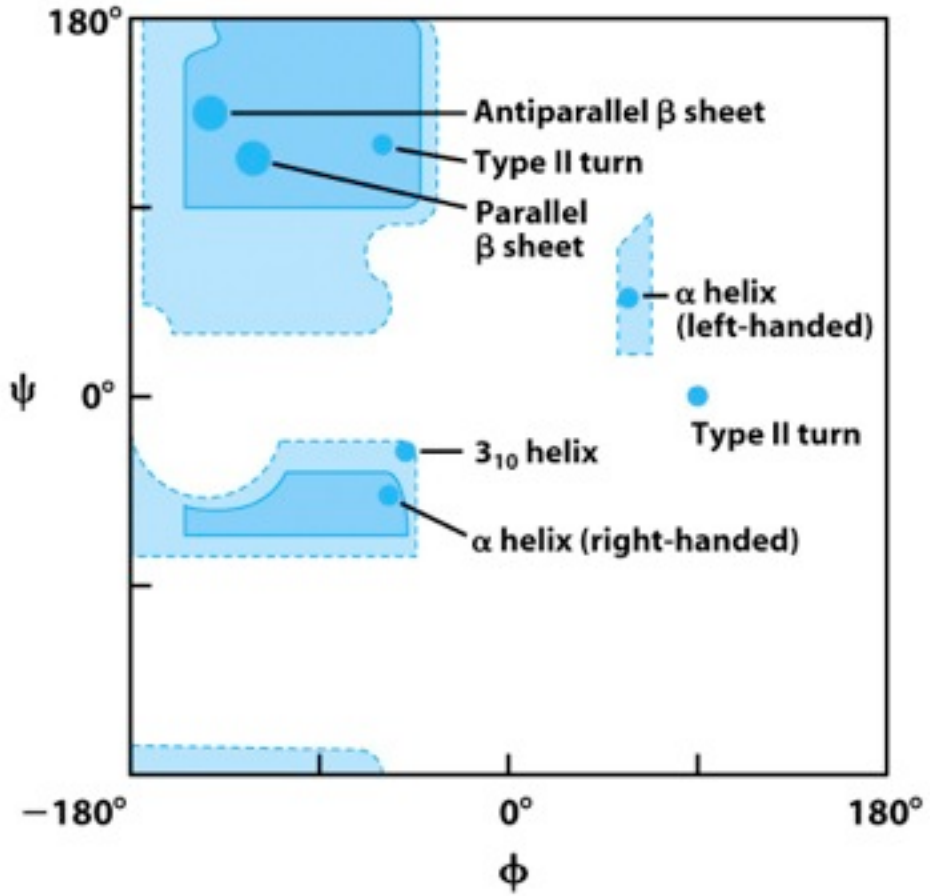
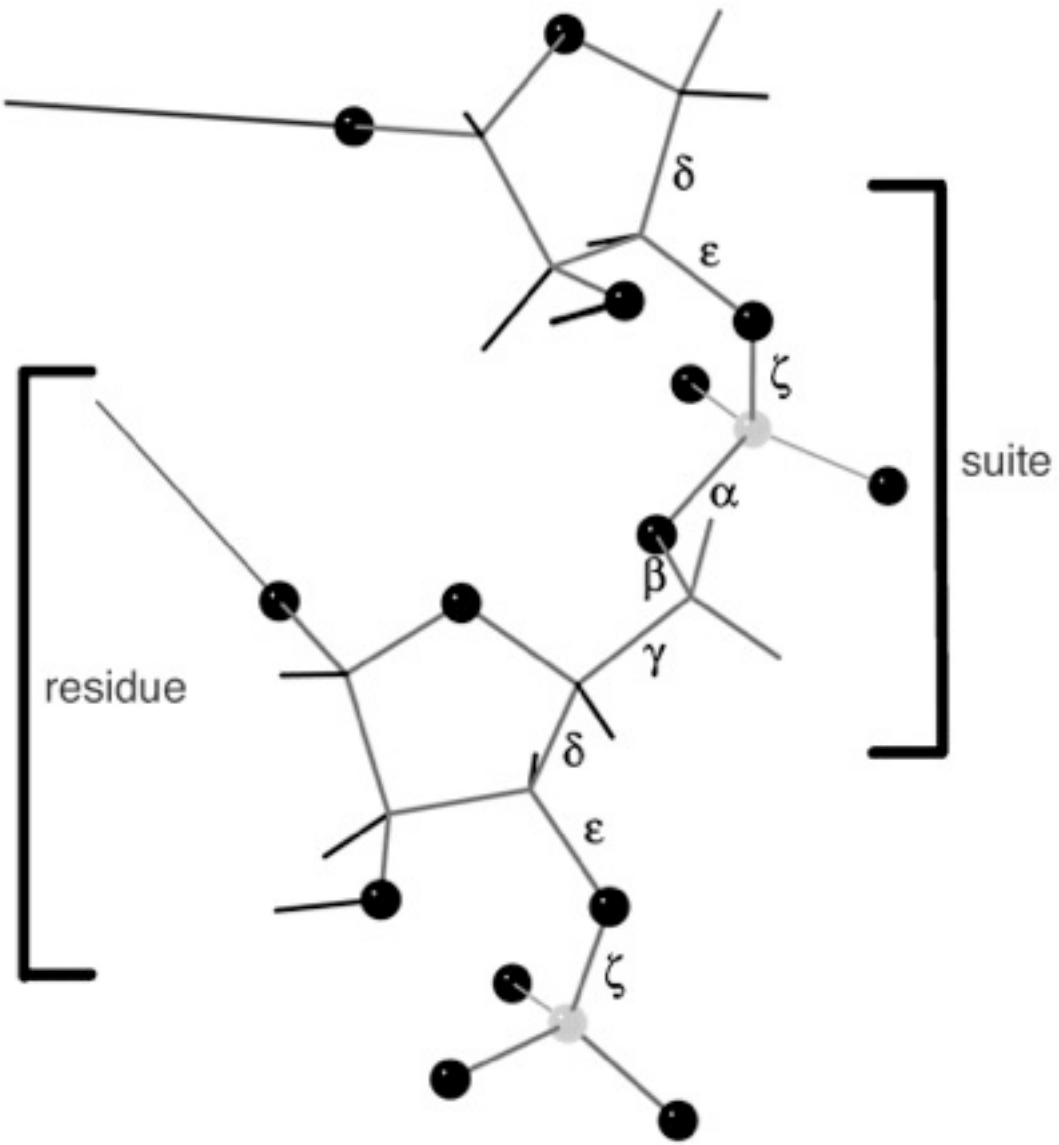
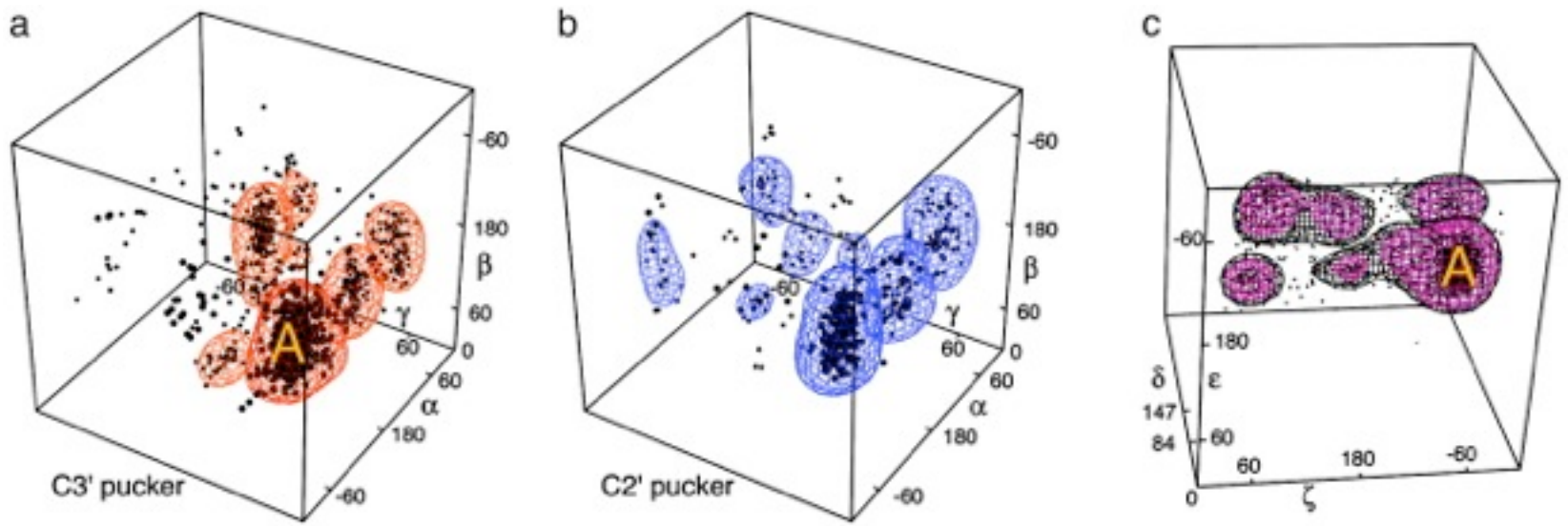


Figure 4-9a Principles of Biochemistry, 4/e

RNA backbone is rotameric



Plots of the heminucleotide angle triplets for data filtered by clashes and B > 60, with smoothed contours enclosing the top 7–10 peak clusters: (a) α–β–γ plot for adjacent sugar pucker C3′ endo.



Murray L J W et al. PNAS 2003;100:13904-13909

RNA backbone rotamers

	α δ / β ε / γ ζ	C3' ε p	C3' ε t	C3' ε -140	C3' ε m	C2' ε p	C2' ε t	C2' ε m
C3' (2nd)	p t p	*		*	*	**	*	*
	p 110 t	*						
	p t t					*[a]		
	t t p				***[b]	*	**	*
	t 135 t				*			
	t t t				***[c]			
	m t p		**	**	**A**[d]		**[e]	***
	m -135 p				*			
	-110 80 t				**[f]			
	m t t							*
C2' (2nd)	p t p	*	*	*		**	*	
	p 110 t	*						
	p t m			*				
	t t p	**[g]			*[h]			
	t t t				*			
	m t p		*	*	***	*	*	*[i]
	m -135 p				***[j]			*
	m t m				*			*

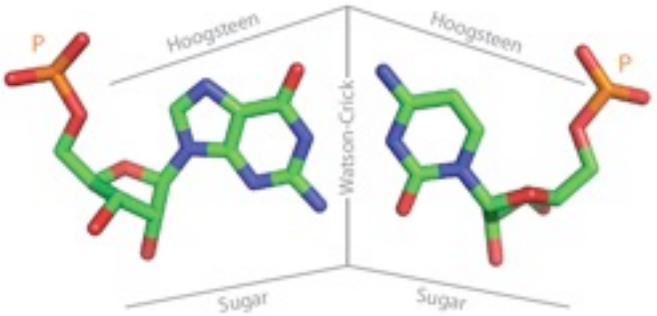
Conformer frequencies:

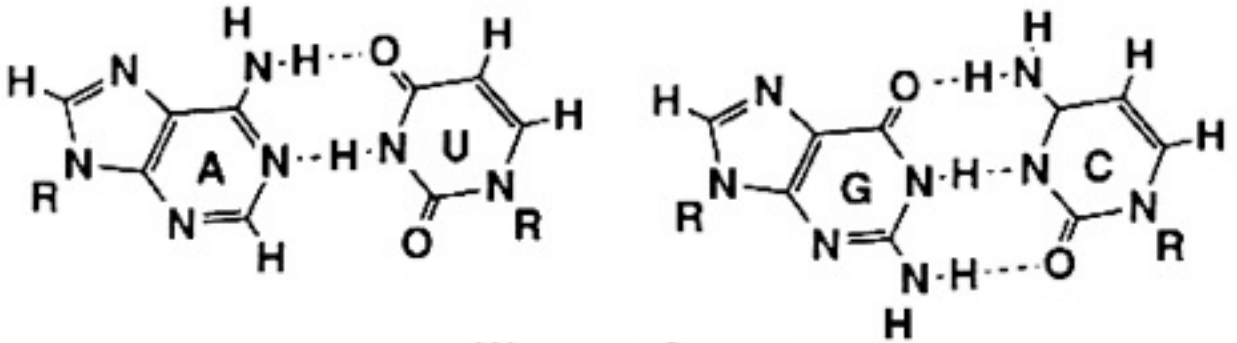
*	~1% of non-A
**	2-3% of non-A
***	4-20% of non-A

Angle codes:

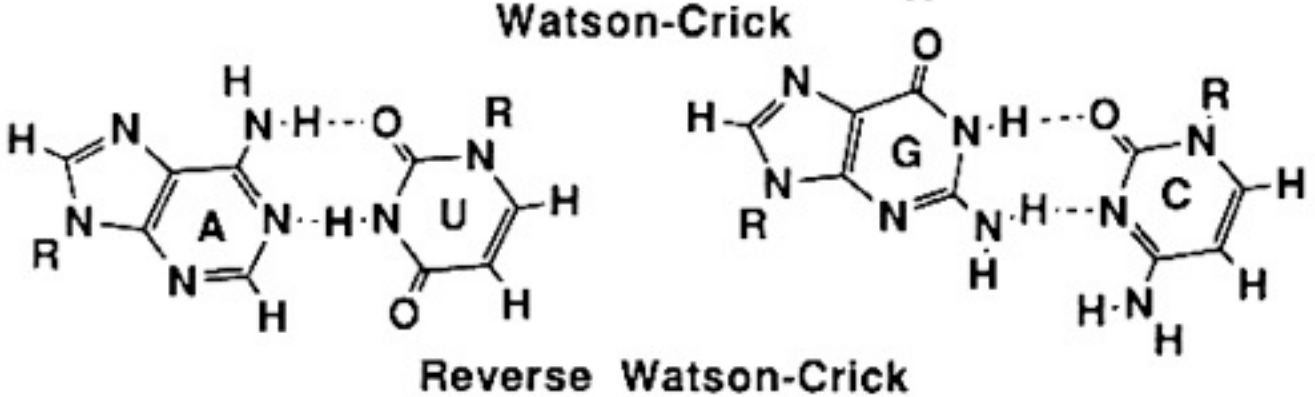
t	trans
m	gauche minus
p	gauche plus
e	eclipsed

Base pairs



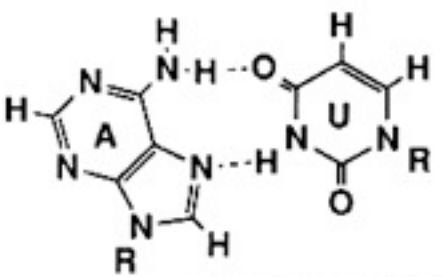


Watson-Crick

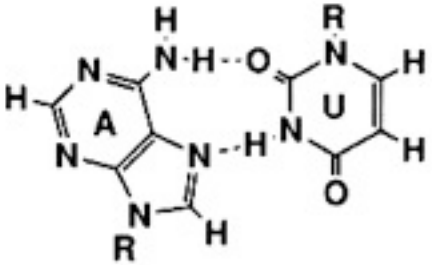


Reverse Watson-Crick

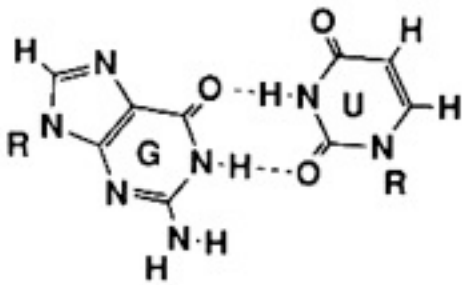
Hoogsteen, Wobble



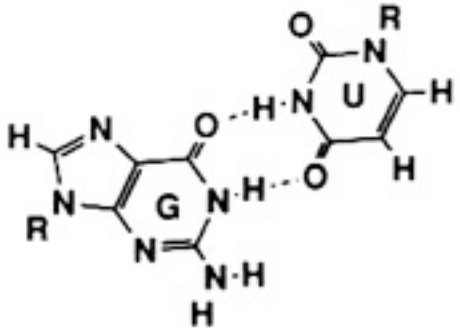
A•U Hoogsteen



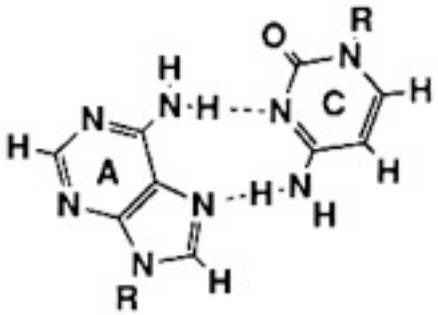
A•U Reverse Hoogsteen



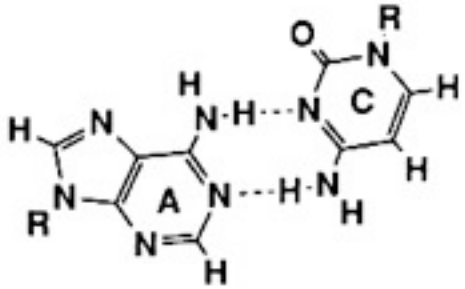
G•U Wobble



G•U Reverse Wobble

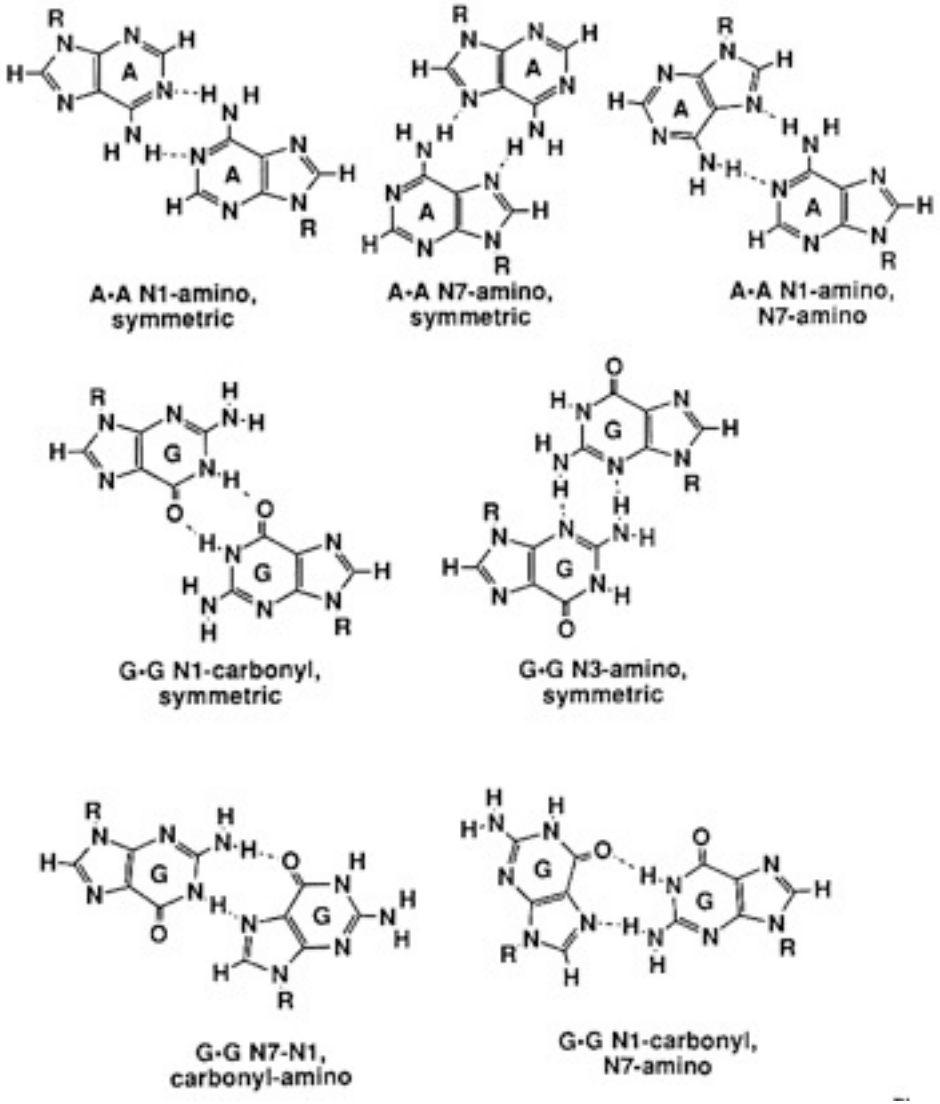


A•C Reverse Hoogsteen

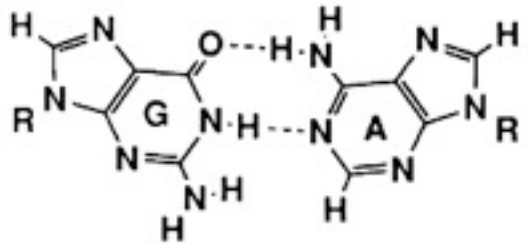


A•C Reverse Wobble

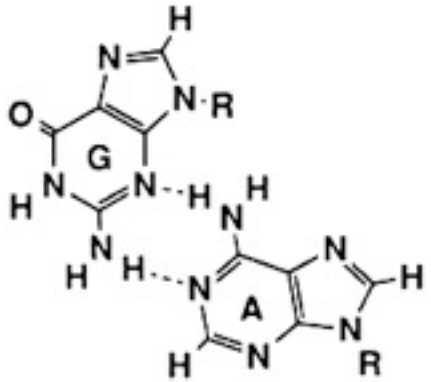
Homopurines



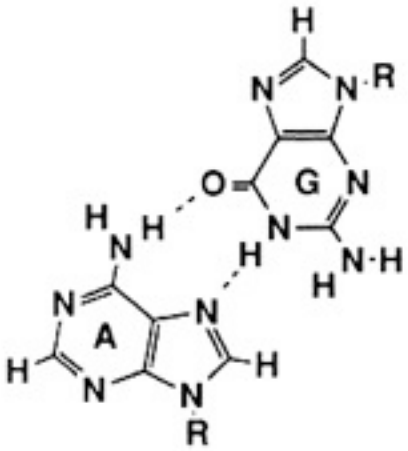
Heteropurines



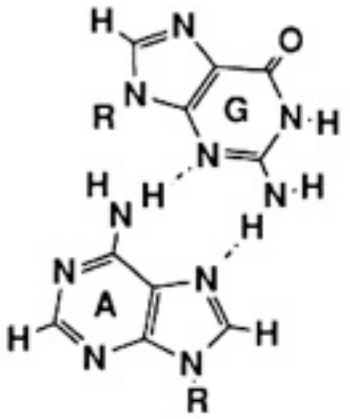
G·A N1-N1,
carbonyl-amino



G·A N3-amino,
amino-N1

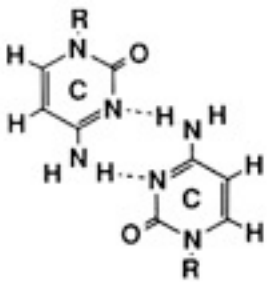


A·G N7-N1,
amino-carbonyl

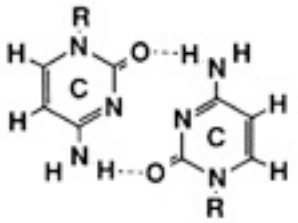


A·G N7-amino,
amino-N3

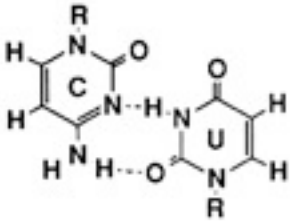
Pyrimidines



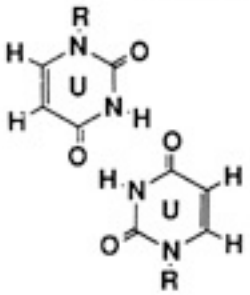
C·C N3-amino, symmetric



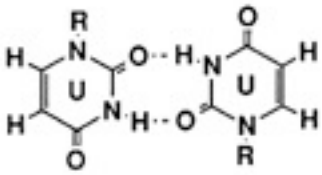
C·C carbonyl-amino, symmetric



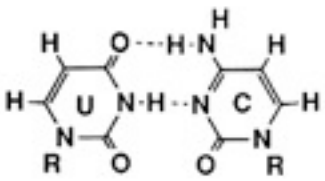
C·U N3-N3, 2-carbonyl-amino



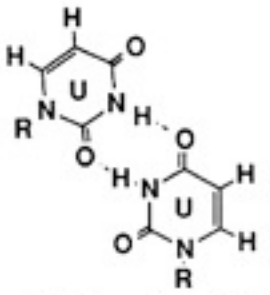
U·U 4-carbonyl-N3, symmetric



U·U 2-carbonyl-N3, symmetric

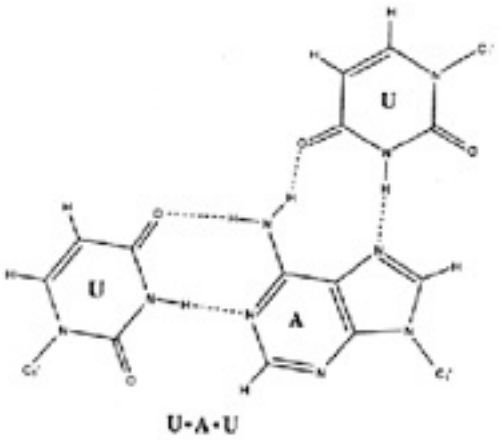


U·C N3-N3, 4-carbonyl-amino

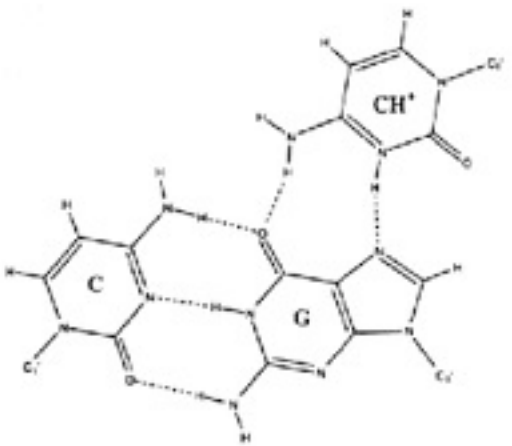


U·U 2-carbonyl-N3, 4-carbonyl-N3

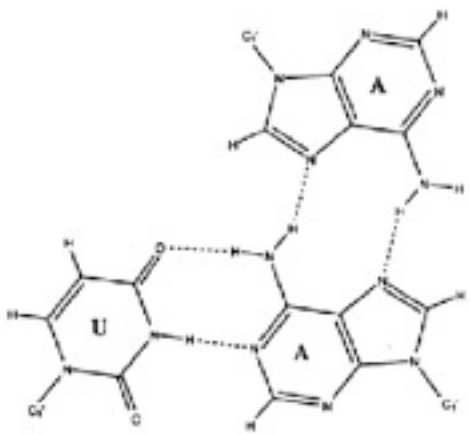
Base triples



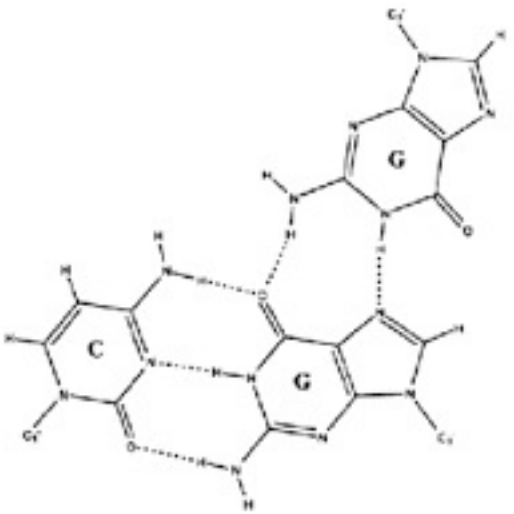
U•A•U



C•G•CH'

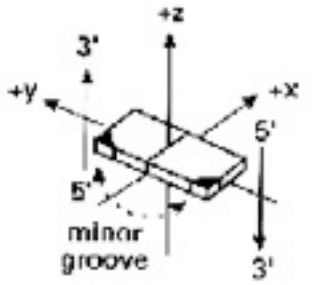


U•A•A

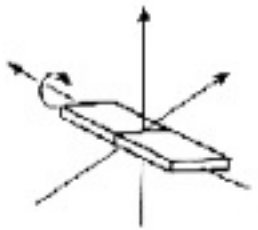


C•G•G

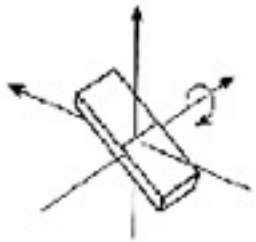
Movements of base pairs



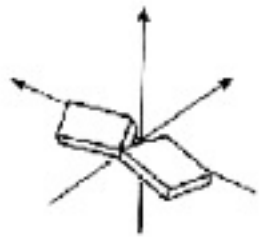
co-ordinate frame



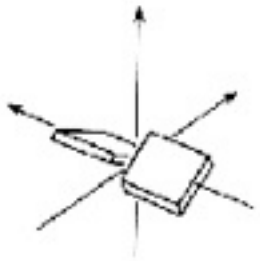
tip (θ)



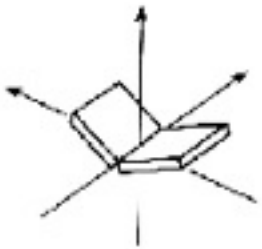
inclination (η)



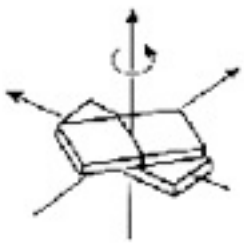
opening (σ)



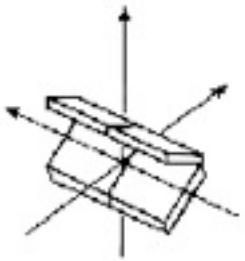
propeller (π)



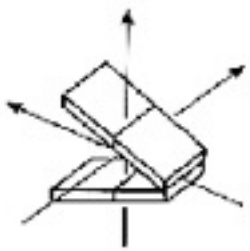
buckle (κ)



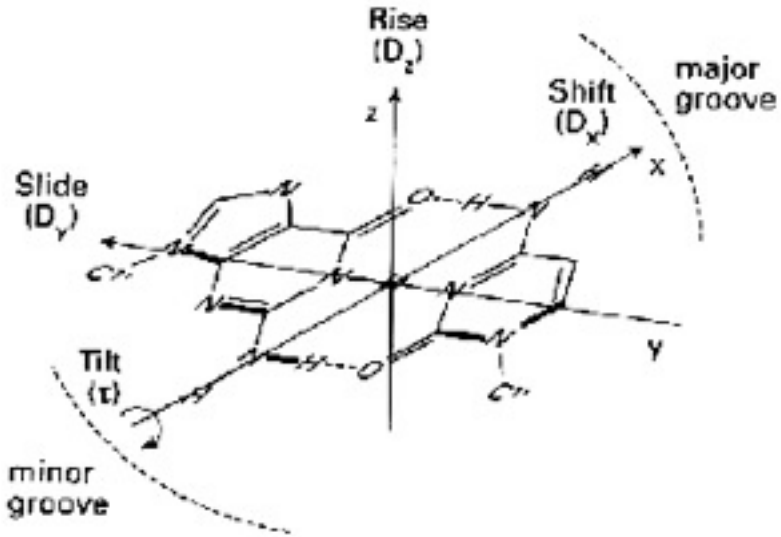
twist (Ω)



roll (P)



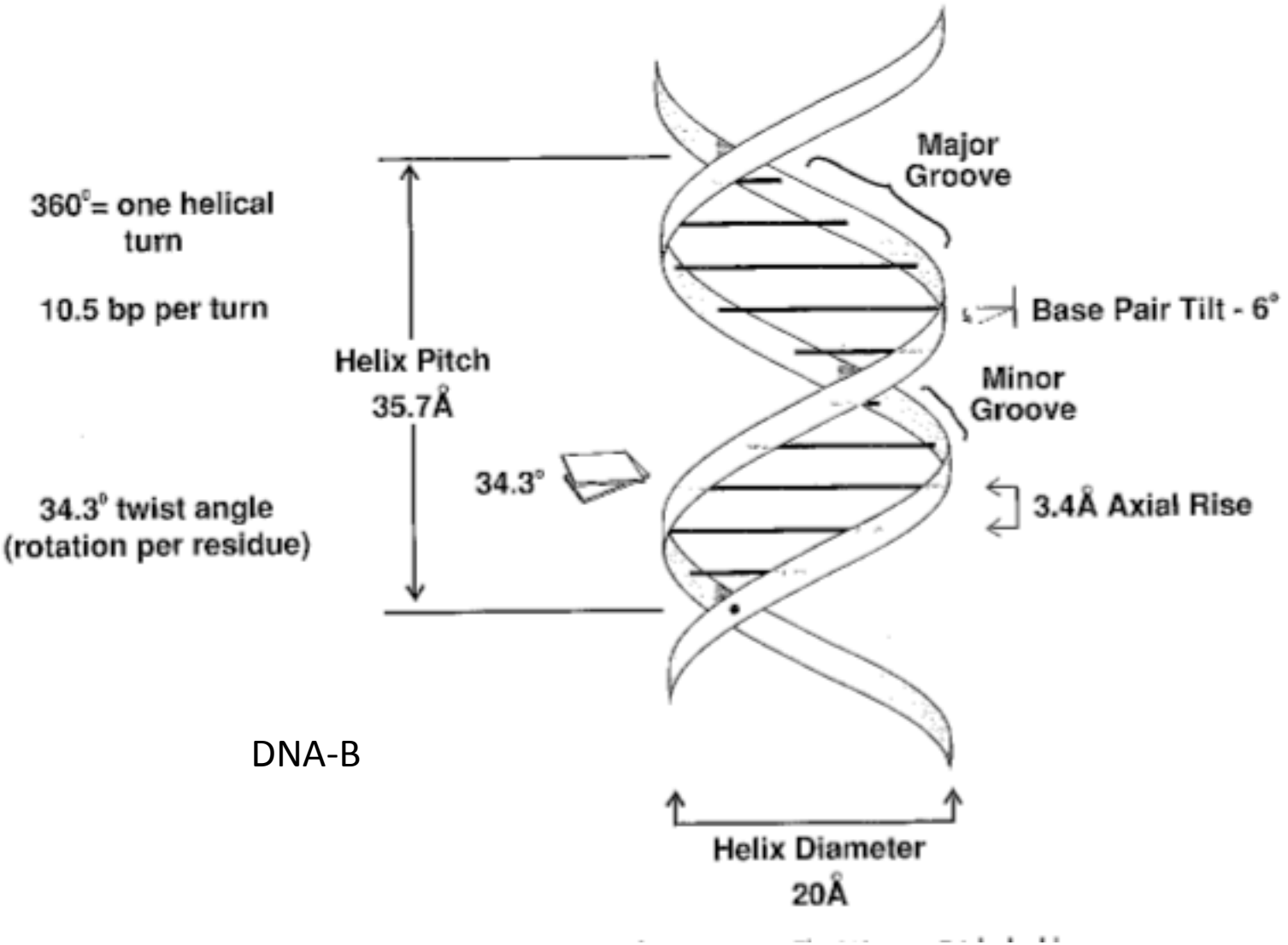
tilt (τ)



Helical parameters

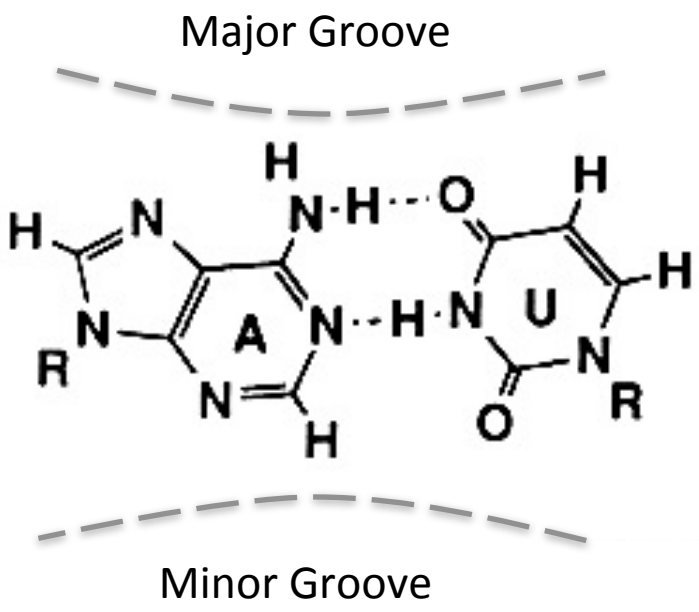
- Sense. Helical rotation of the double helix. Clock- or anticklockwise
- Residues per turn. Number of residues in one helical turn.
- Axial rise. Distance between adjacent planar bases.
- Helix pitch. Length of one helical turn.
- Diameter of the helix. Width across the helix.
- Rotation per residue or Twist angle. Angle between two adjacent base pairs.

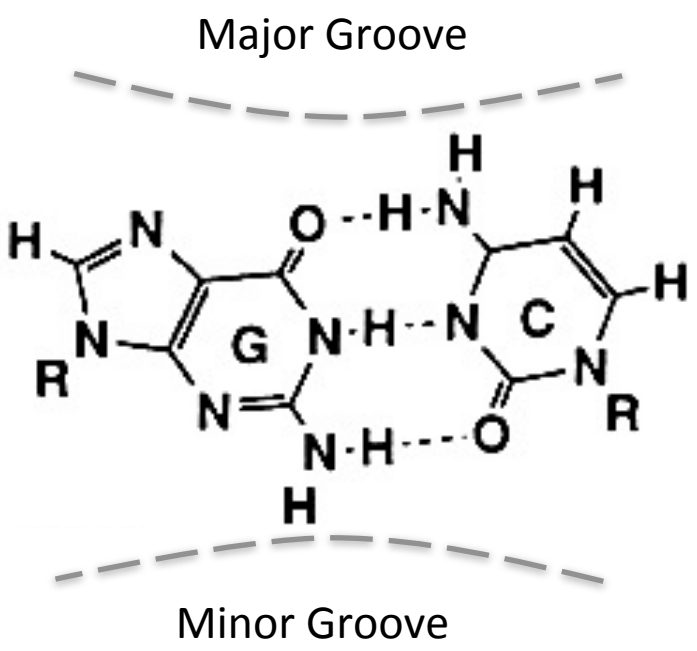
Helical parameters



DNA-B

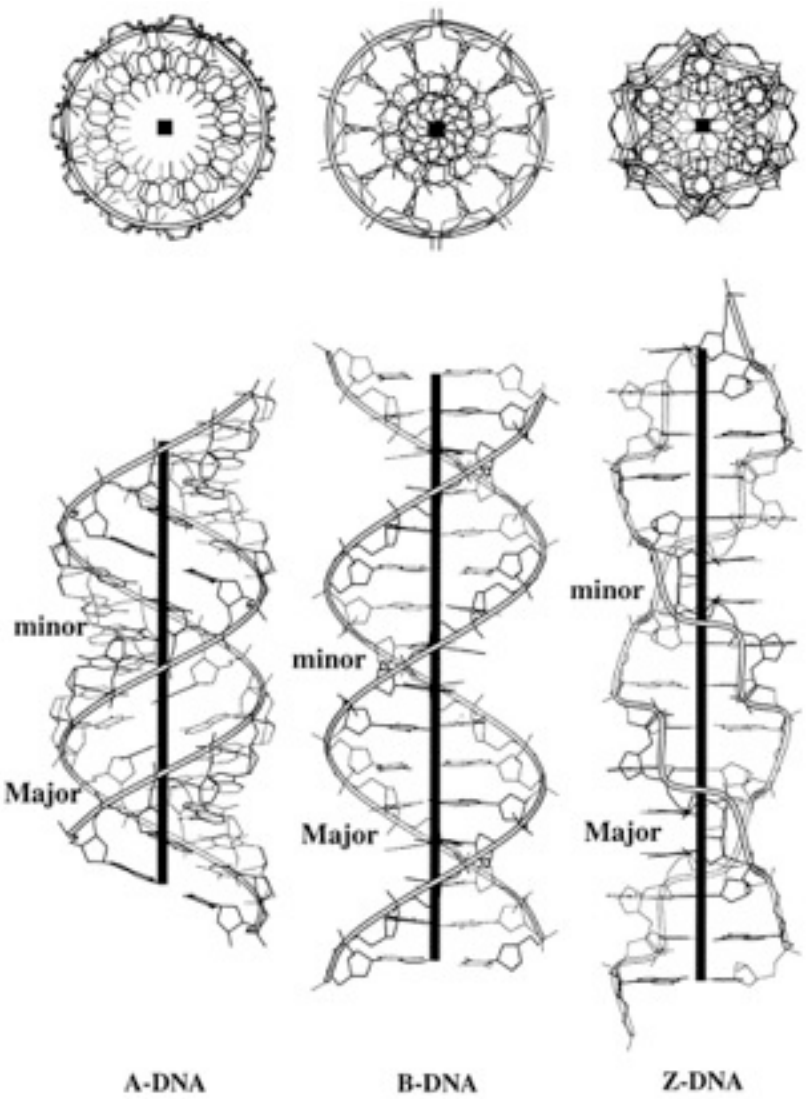
Major VS Minor Groove





Nucleic Acid Helical Structures

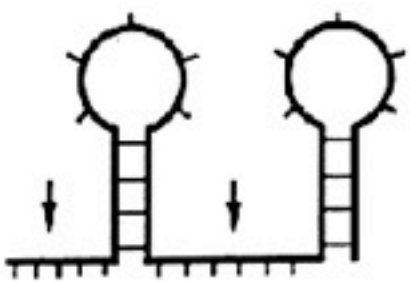
Geometry attribute:	A-form	B-form	Z-form
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	33.6°	35.9°	60°/2
Mean bp/ turn	11	10.5	12
Inclination of bp to axis	+19°	−1.2°	−9°
Rise/bp along axis	2.4 Å (0.24 nm)	3.4 Å (0.34 nm)	3.7 Å (0.37 nm)
Rise/turn of helix	24.6 Å (2.46 nm)	33.2 Å (3.32 nm)	45.6 Å (4.56 nm)
Mean propeller twist	+18°	+16°	0°
Glycosyl angle	anti	anti	pyrimidine: anti,
			purine: syn
Sugar pucker	C3'-endo	C2'-endo	C: C2'-endo,
			G: C2'-exo
Diameter	23 Å (2.3 nm)	20 Å (2.0 nm)	18 Å (1.8 nm)



Secondary structures in RNA

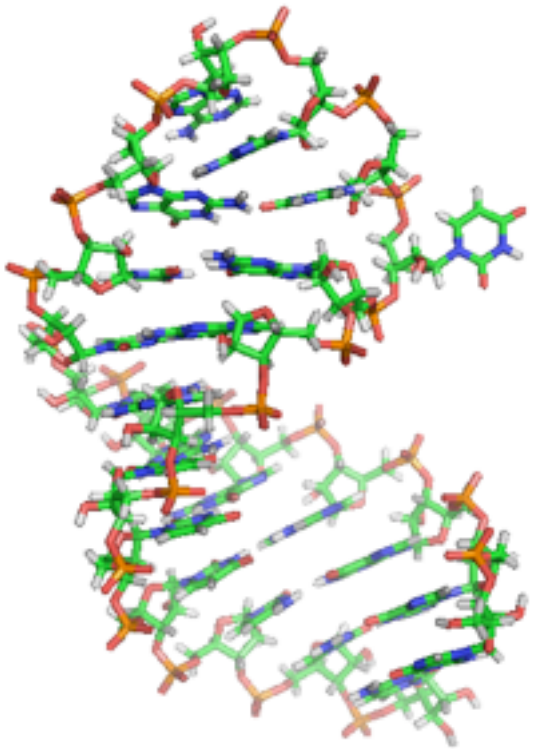
a. DUPLEXES

b. SINGLE STRANDED REGIONS



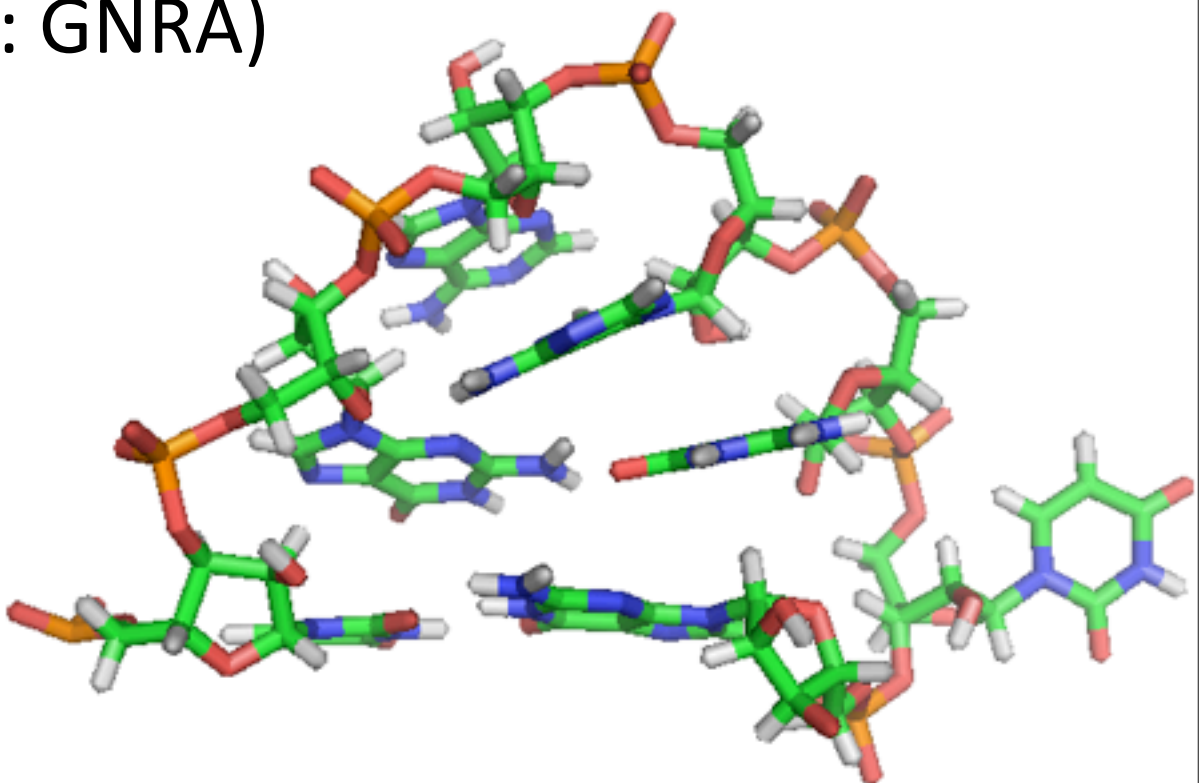
Apical loops (hairpins)

c. HAIRPINS

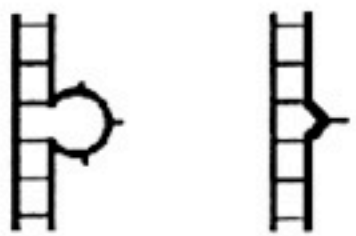


Several kinds of apical loops

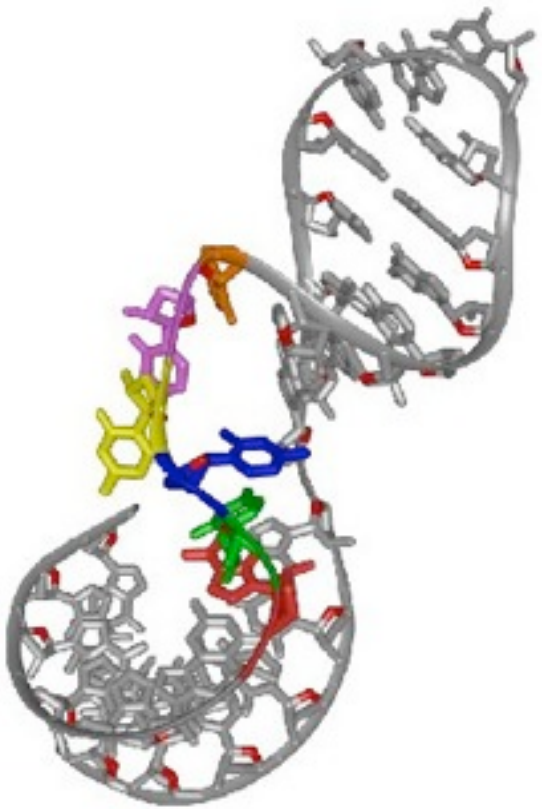
- Minimum: triloops
- Tetraloops (e.g.: GNRA)
- Pentaloops
- Hexaloops
- .
- .
- .
- whatever loops



d. BULGES

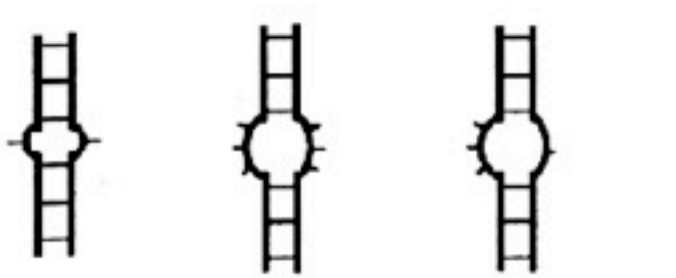


BULGE SINGLE-BASE BULGE



e. INTERNAL LOOPS

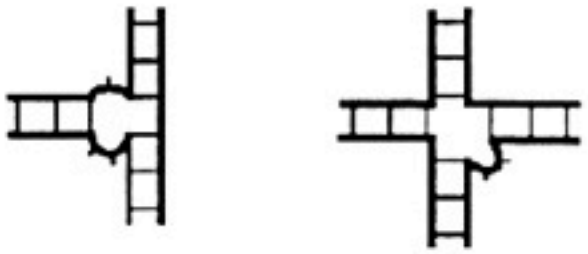
f. JUNCTIONS



MISMATCH

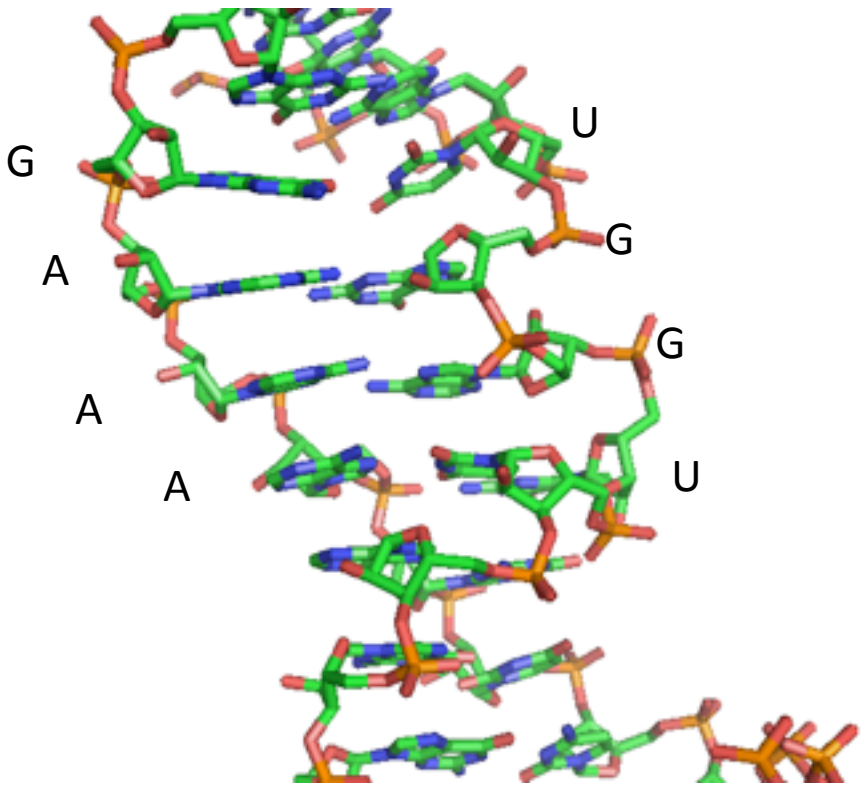
SYMMETRIC INTERNAL LOOP

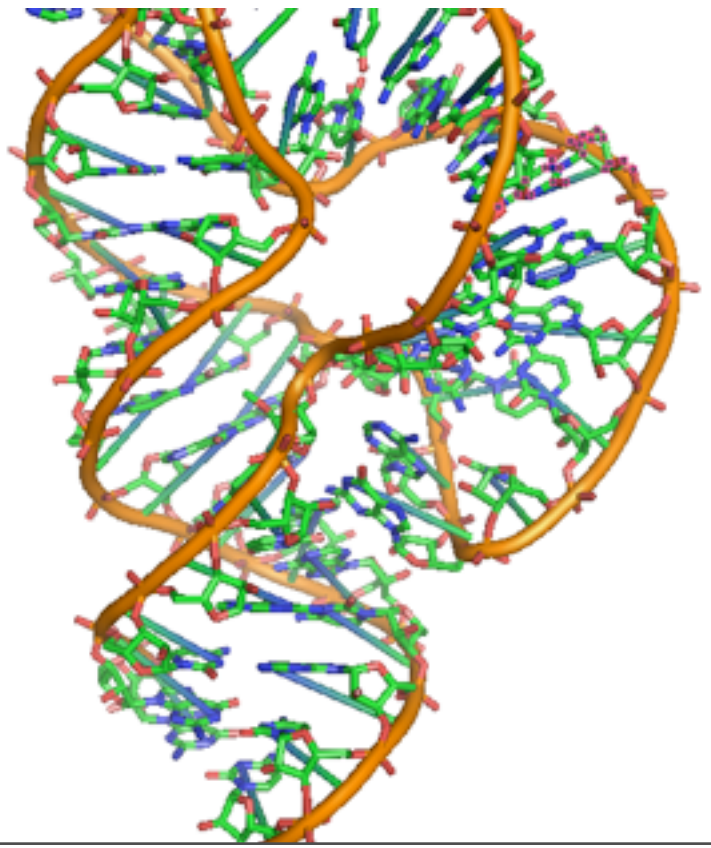
ASYMMETRIC INTERNAL LOOP



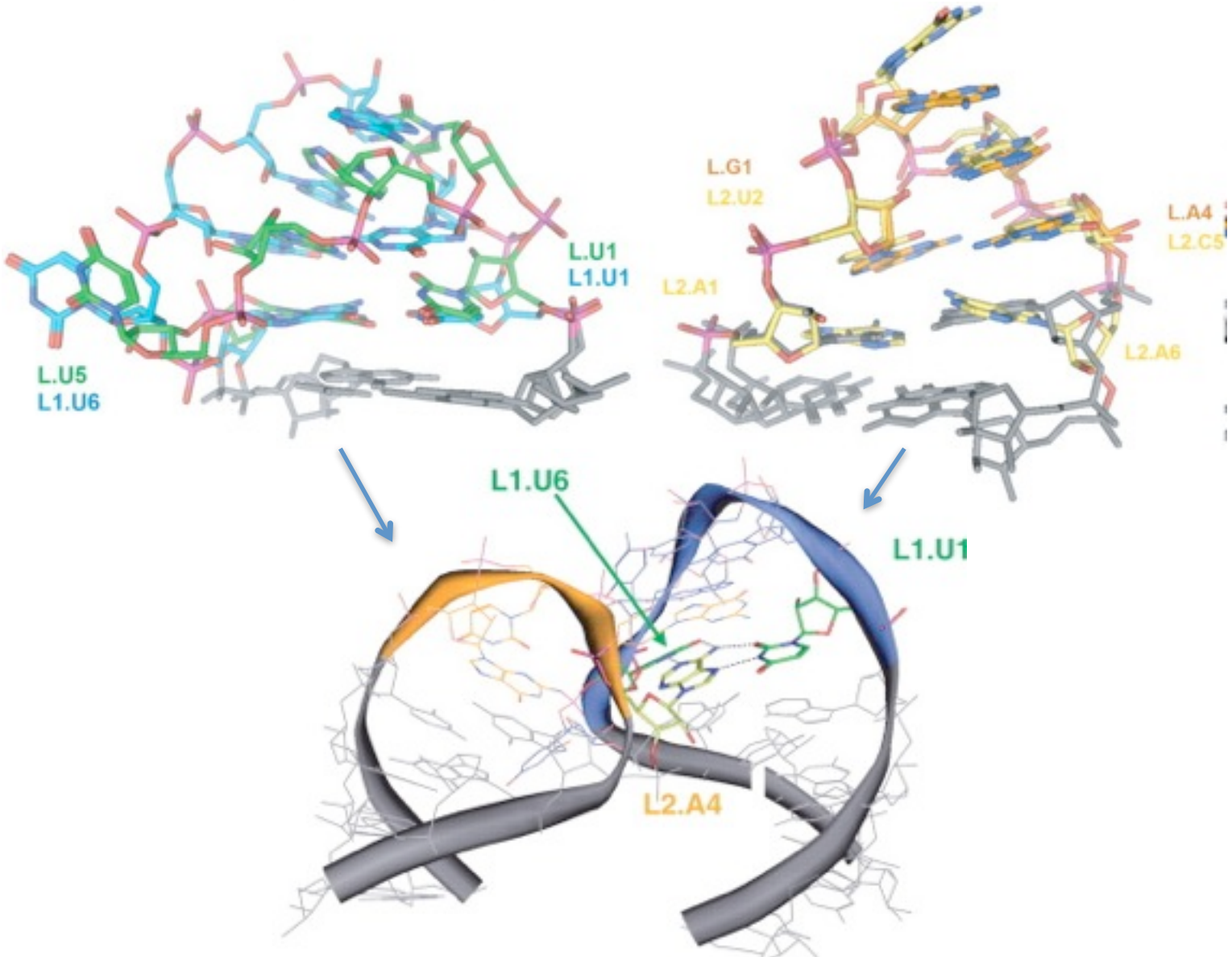
THREE STEM

FOUR STEM

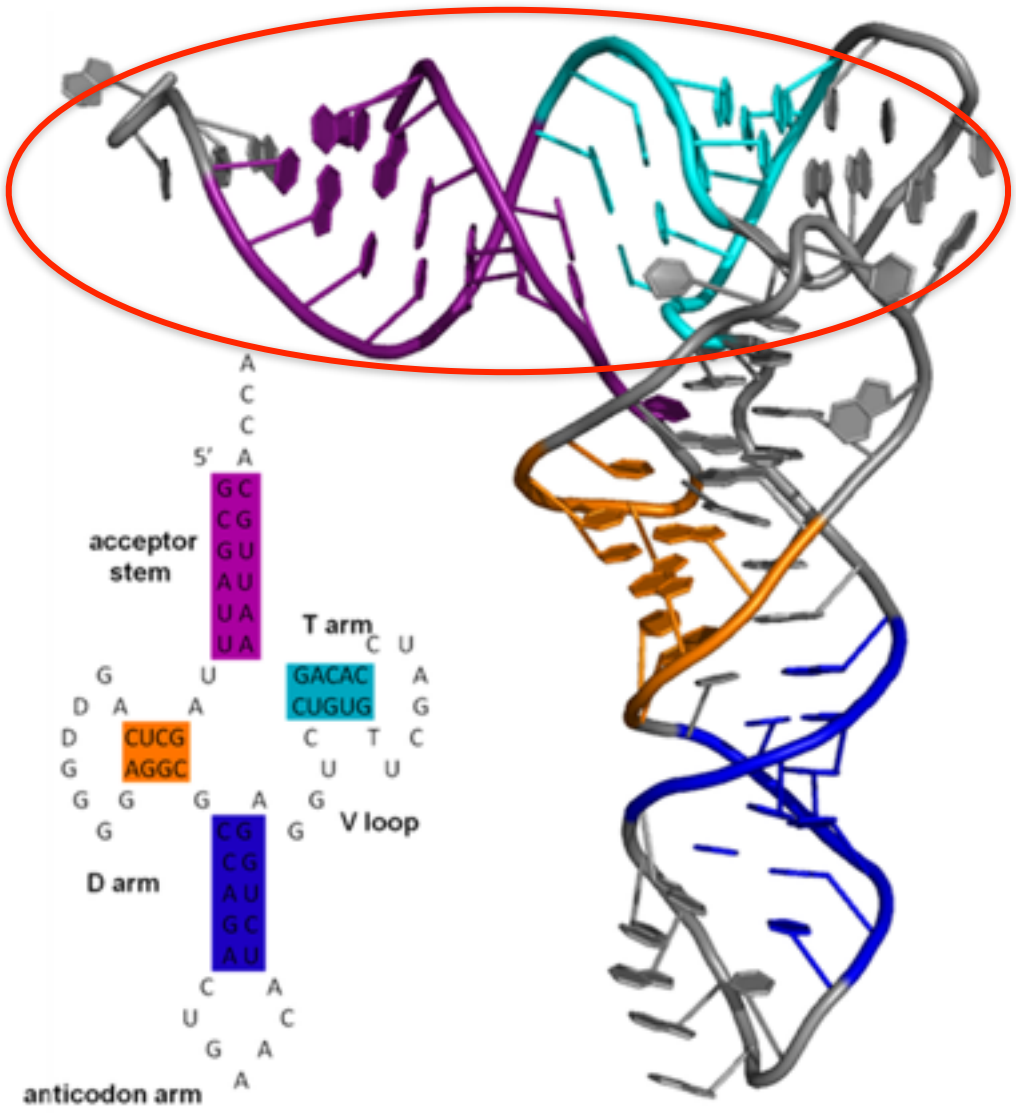




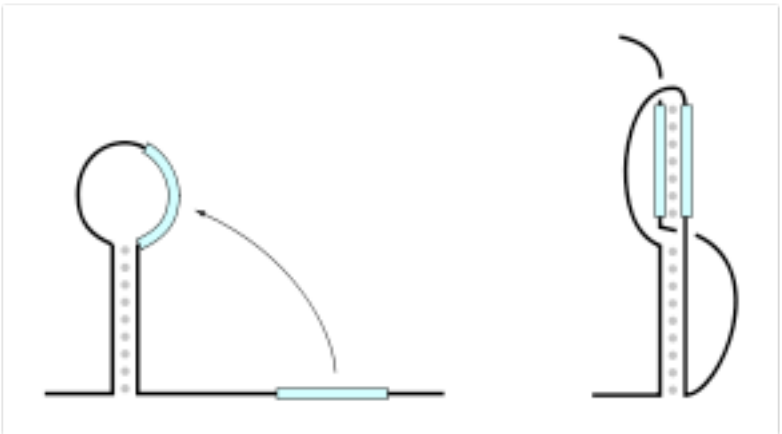
Loop-loop interactions

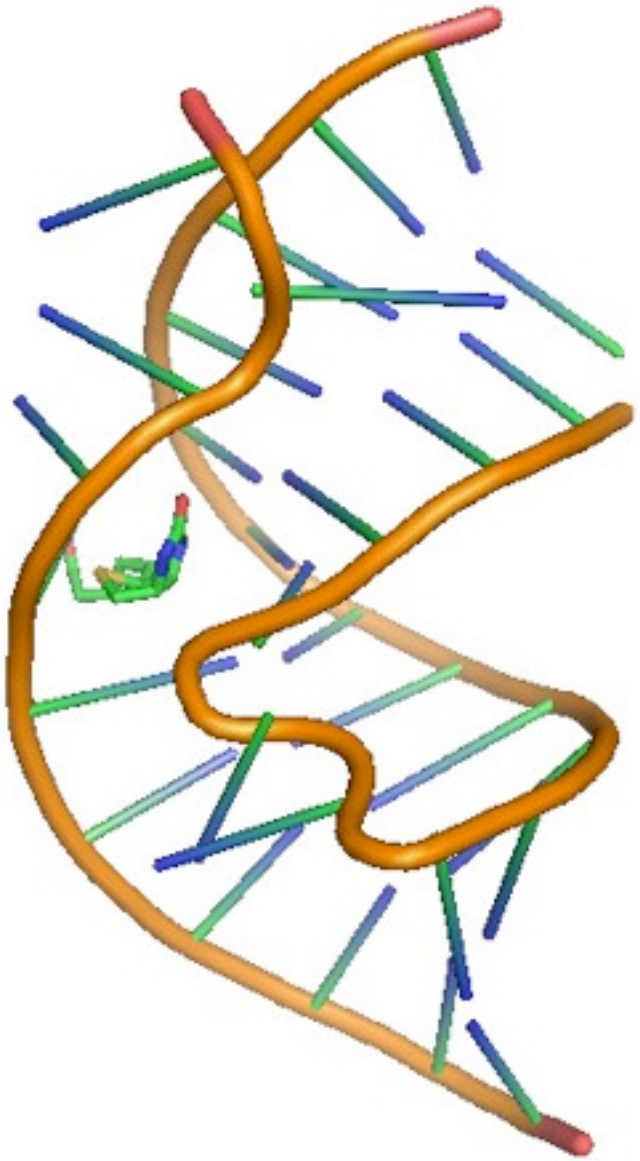


Coaxial stacking



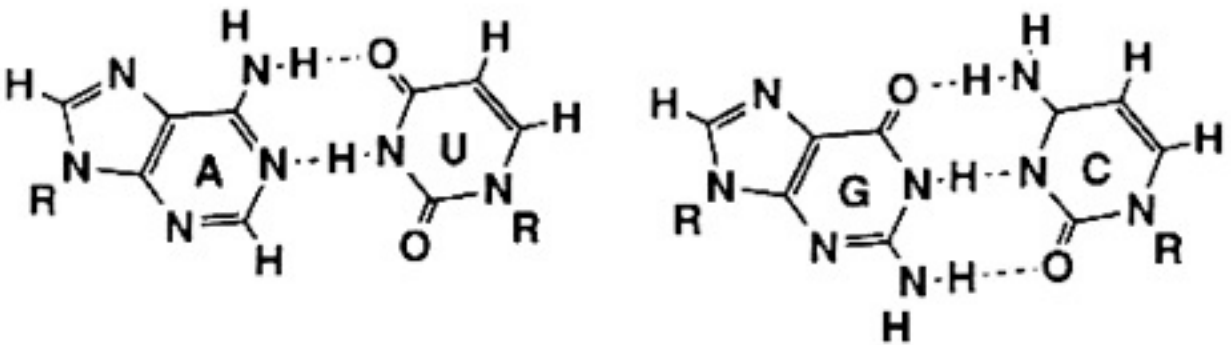
Pseudoknots





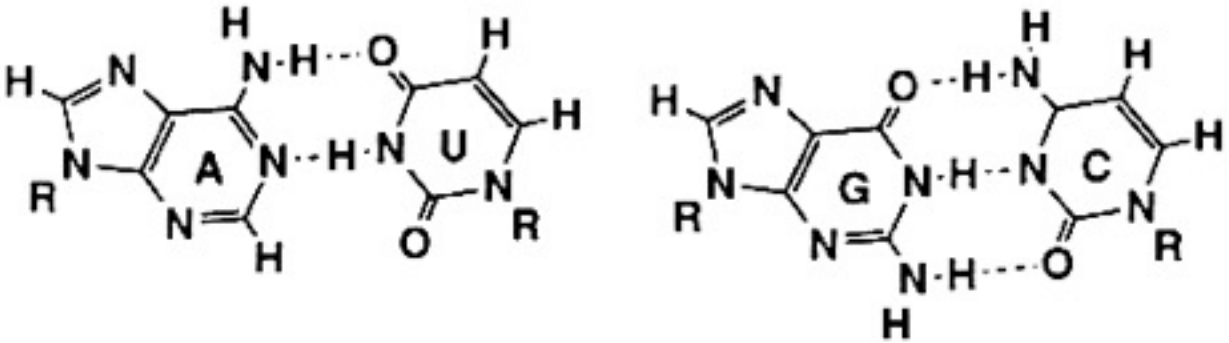
Forces that drive RNA folding

- 1) Hydrogen bonds

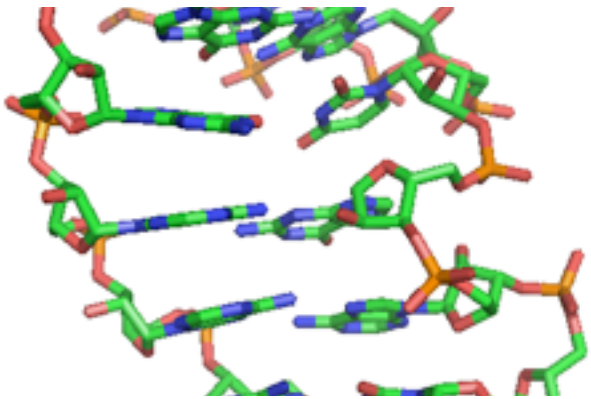


Forces that drive RNA folding

- 1) Hydrogen bonds

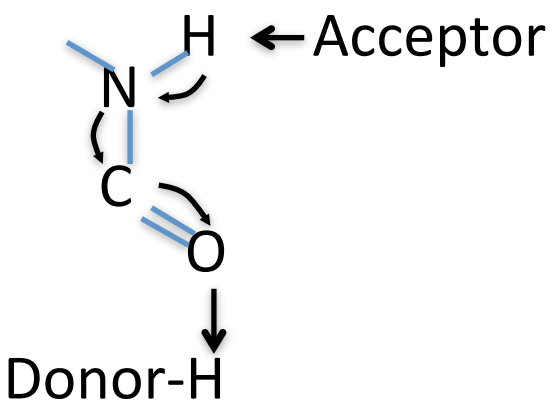


- 2) Stacking interactions



Hydrogen Bonding

- Short, noncovalent, highly directional between an electronegative atom (-C=O, -N:) and a H atom bound to an electropositive atom (-N-H).
- 20-30 times weaker compared to covalent bonds (3-7 kcal/mol VS 80-100 kcal/mol)
- Additive and cooperative



Base Stacking

- Base stacking = Van der Waals forces + Hydrophobic interactions
- 4-15 kcal/dinucleotide
- Van der Waals = dipole-dipole interactions + London dispersion forces

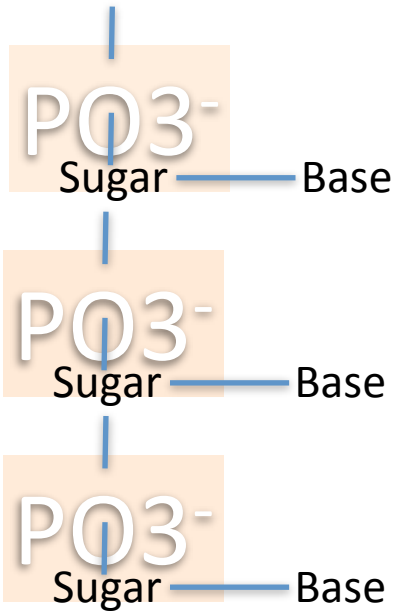
Dinucleotide base pairs	Stacking energies (kcal/mol/stacked pair)
GC · GC	-14.59
AC · GT	-10.51
TC · GA	-9.81
CG · CG	-9.69
GG · CC	-8.26
AT · AT	-6.57
TG · CA	-6.57
AG · CT	-6.78
AA · TT	-5.37
TA · TA	-3.82

Base Stacking

- Isodesmic reaction
- Additive
- Diffusion controlled reaction
- Weak force controlled process
- $E_{tot} = E_d + E_p + E_{el}$
- E_{tot} = Total energy
- E_d = Dispersion energy
- E_p = Polarization energy

Other interactions

- RNA is a polianion



- Metal ion coordination ($Mg\ 2^{+}$)
  - Diffusion controlled
  - Though water or direct contact
  - $PO3^{-}$ or bases

NDB

http://ndbserver.rutgers.edu/