

Struktura, dynamika a molekulové
interakce v DNA a RNA.
Moderní počítačové metody.

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a

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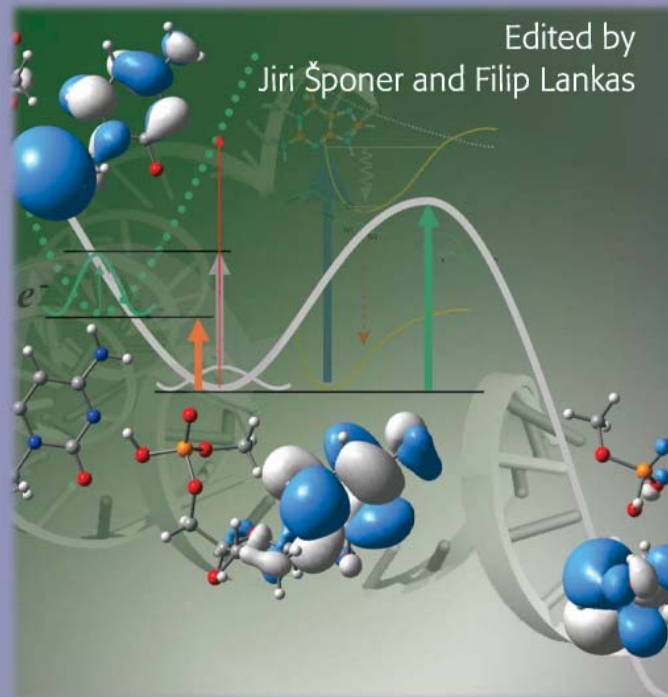
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CHALLENGES AND ADVANCES IN
COMPUTATIONAL CHEMISTRY AND PHYSICS

Computational Studies of RNA and DNA

Edited by
Jiri Šponer and Filip Lankas



 Springer

Cíl přednášky

Ukázat počítačové techniky jako
moderní metodiku strukturní
biologie.

Hlavní techniky

1. Přesné kvantově-chemické výpočty *ab initio* .
Schroedingerova rovnice, MO=LCAO
2. Nanosekundové simulace
klasická molekulová dynamika s explicitním
zahrnutím vody a iontů.

Tyto metody jsou dostupné od r. 1995.

Cíl

přispět ke kvalitativnímu pochopení molekulových interakcí

doplnit experimenty

provádět předpovědi jdoucí za rámec experimentů

Vztah mezi strukturou a funkcí biopolymerů

Jak biomolekuly fungují?

Biomolekuly se vyznačují **nesmírnou variabilitou svého prostorového spořádání**. **Digitální informace** kódovaná v sekvenci bází nukleových kyselin nebo aminokyselin vede ke konkrétní trojrozměrné architektuře a ta vstupuje do procesu **molekulového rozpoznávání**, vlastně ve formě **informace analogové**.

Sekvence (digitalní informace)



struktura (energie)



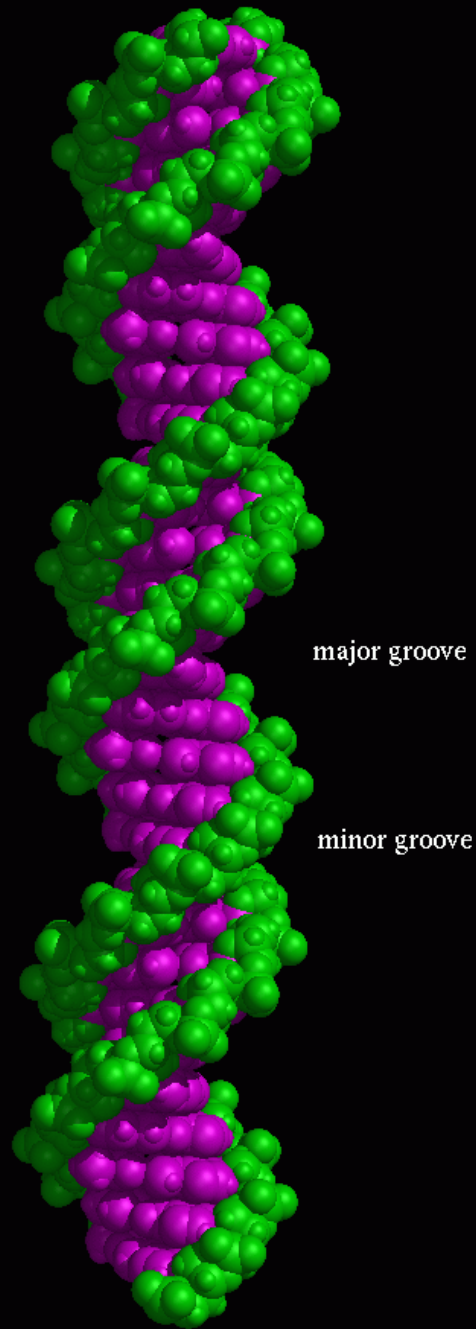
funkce

Nalezení vztahu mezi primární sekvencí bází/aminokyselin a trojrozměrnou strukturou biomolekul patří mezi klíčové úkoly soudobé molekulární biologie a biofyziky.

Molekulová dynamika

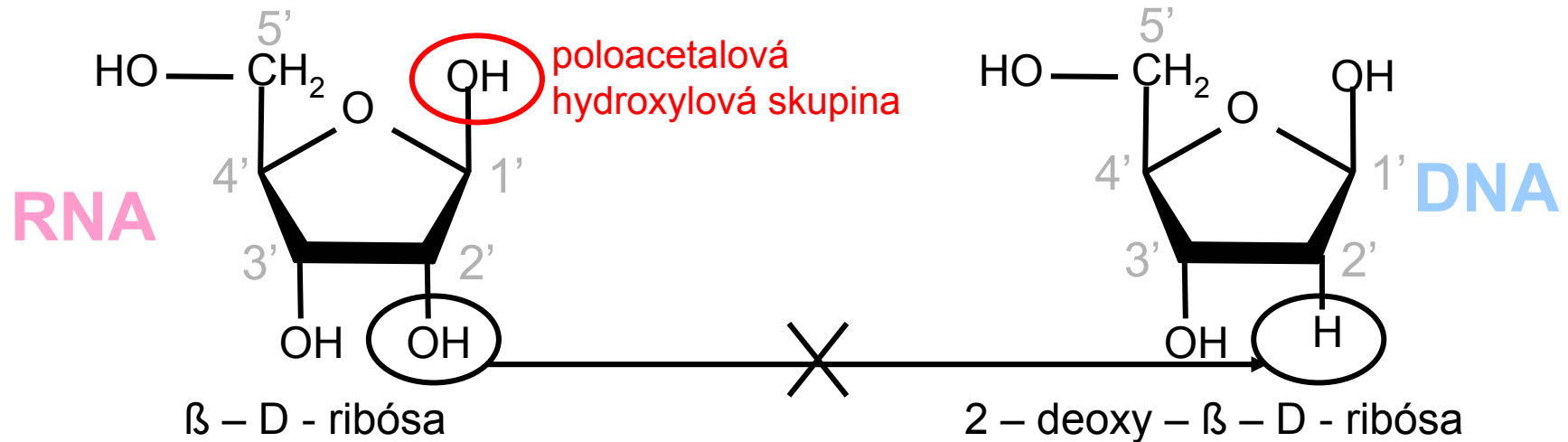
- jednoduchý analytický force field
- explicitní zahrnutí vody
- dnes 100 a více nukleotidů
- simulační časy 100+ nanosekund (krok dvě femtosekundy).
- modelování reálné dynamiky za pokojové teploty

B-DNA



backbone
base

Cukr - pentóza



poloacetalová hydroxylová skupina

+ báze

N-glykosidová vazba

nukleosid

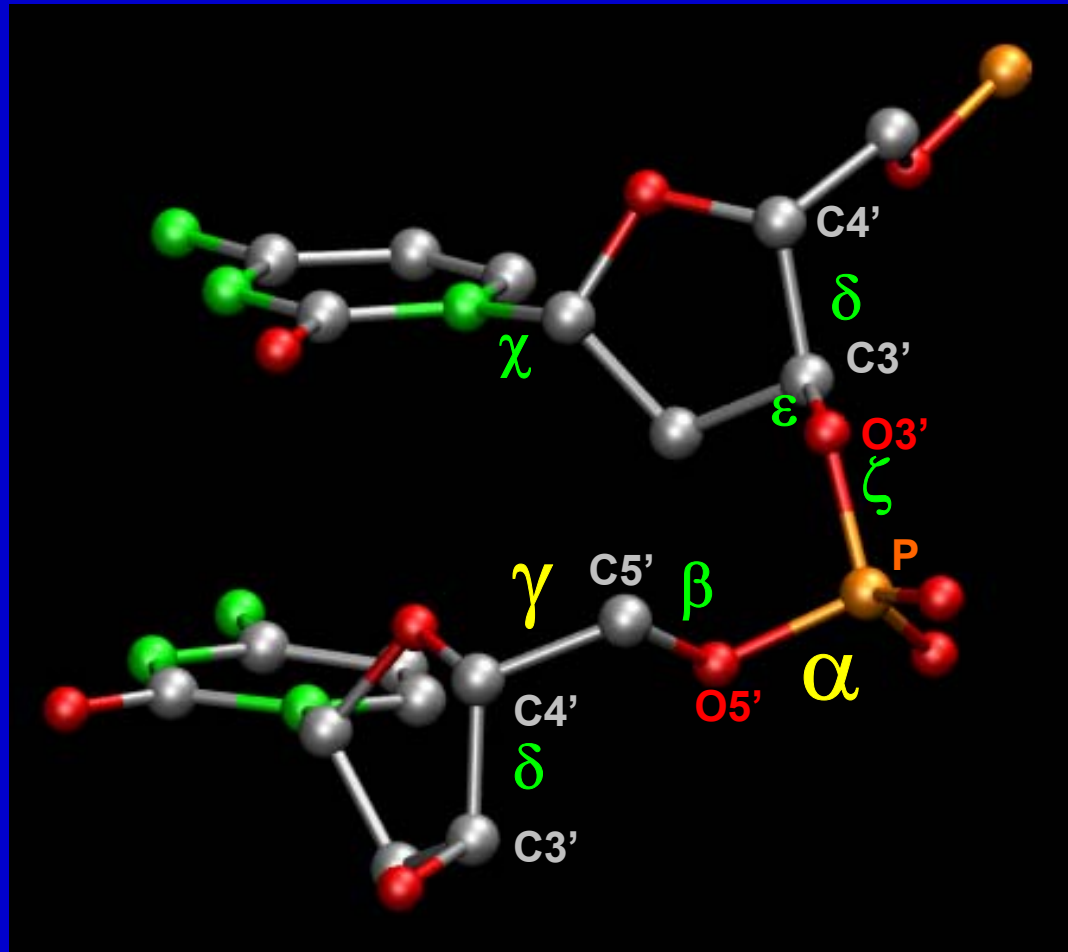
C1' - N1

pyrimidiny

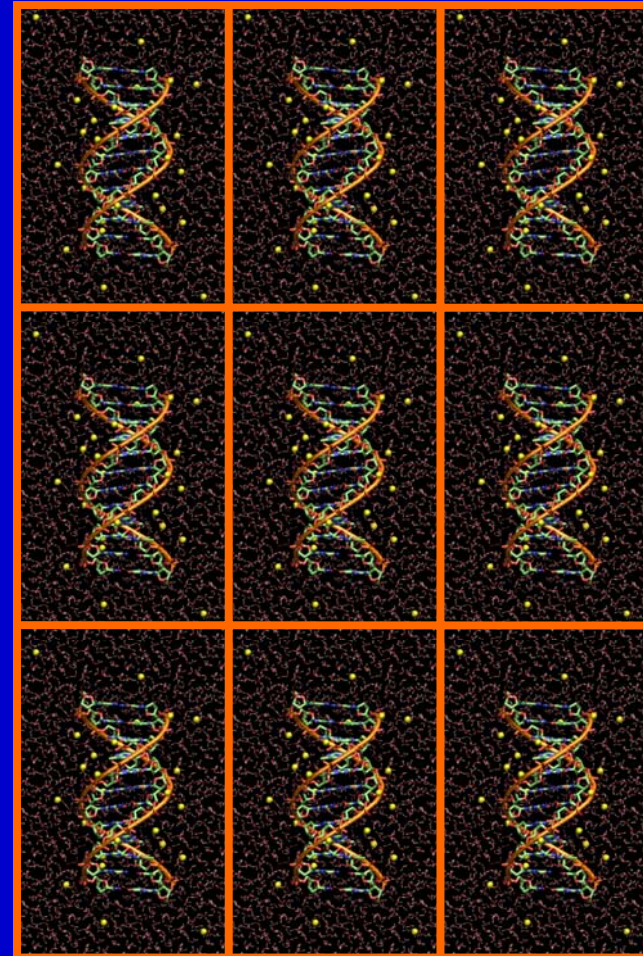
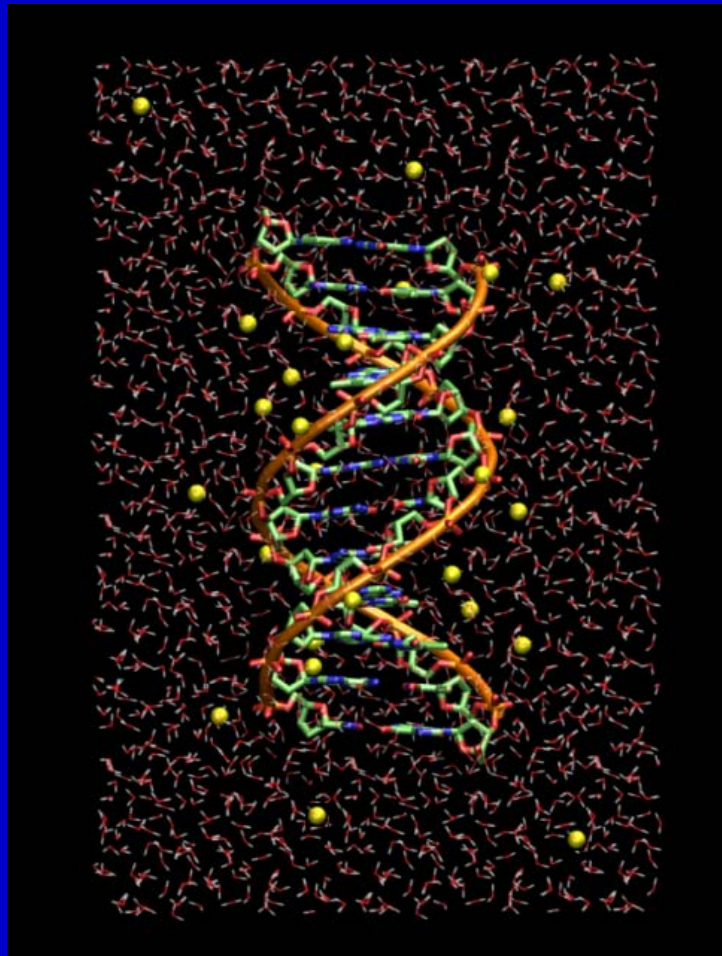
C1' - N9

puriny

Backbone torsion angles

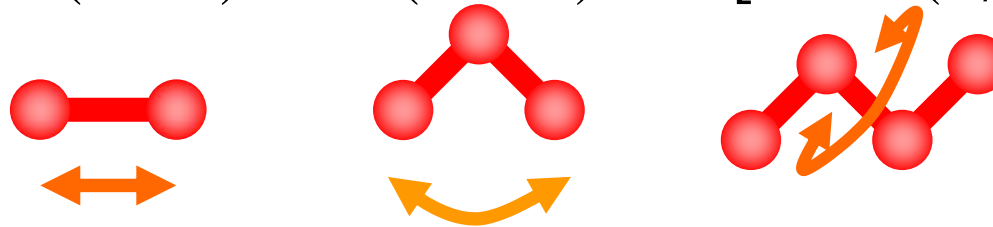


DNA molecule in a periodic box of water molecules



$$E_{\text{celková}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}}$$

$$K_r(r - r_0)^2 + K_\theta(\theta - \theta_0)^2 + K[1 + \cos(n\varphi - \gamma)]$$



$$+ E_{\text{VDW}} + E_{\text{elstat}}$$

$$\left(\frac{A}{R_{ij}^{12}} - \frac{B}{R_{ij}^6} \right) + \frac{q_i q_j}{R_{ij}}$$

$$\begin{aligned}
E_{total} = & \sum_{bonds} K_r (r - r_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \\
& \sum_{dihed} \frac{V_n}{k} [1 + \cos(n\varphi - \gamma)] + \sum_{vdw} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} \right) + \sum_{elstat} \frac{q_i q_j}{R_{ij}}
\end{aligned}$$

Struktura a funkce ribosomální RNA

Primární genetická informace se přepisuje do mRNA. tRNA (adaptor) přiřadí správnému kodonu mRNA správnou aminokyselinu.

Syntézu proteinu dle sekvence mRNA zabezpečují obří molekulární továrny zvané ribosomy.

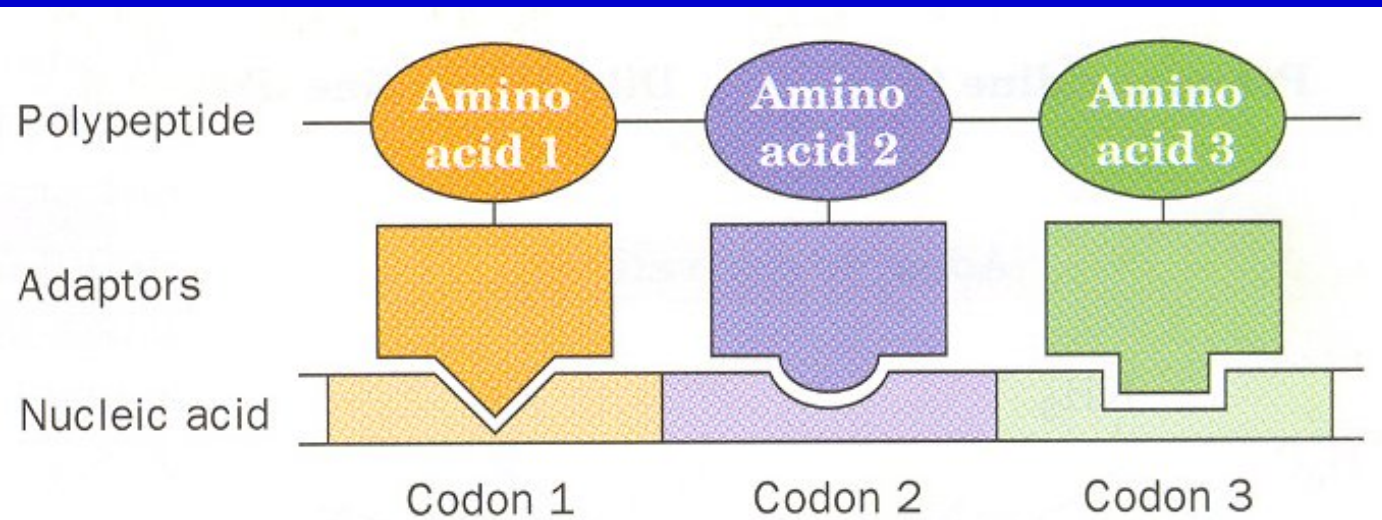
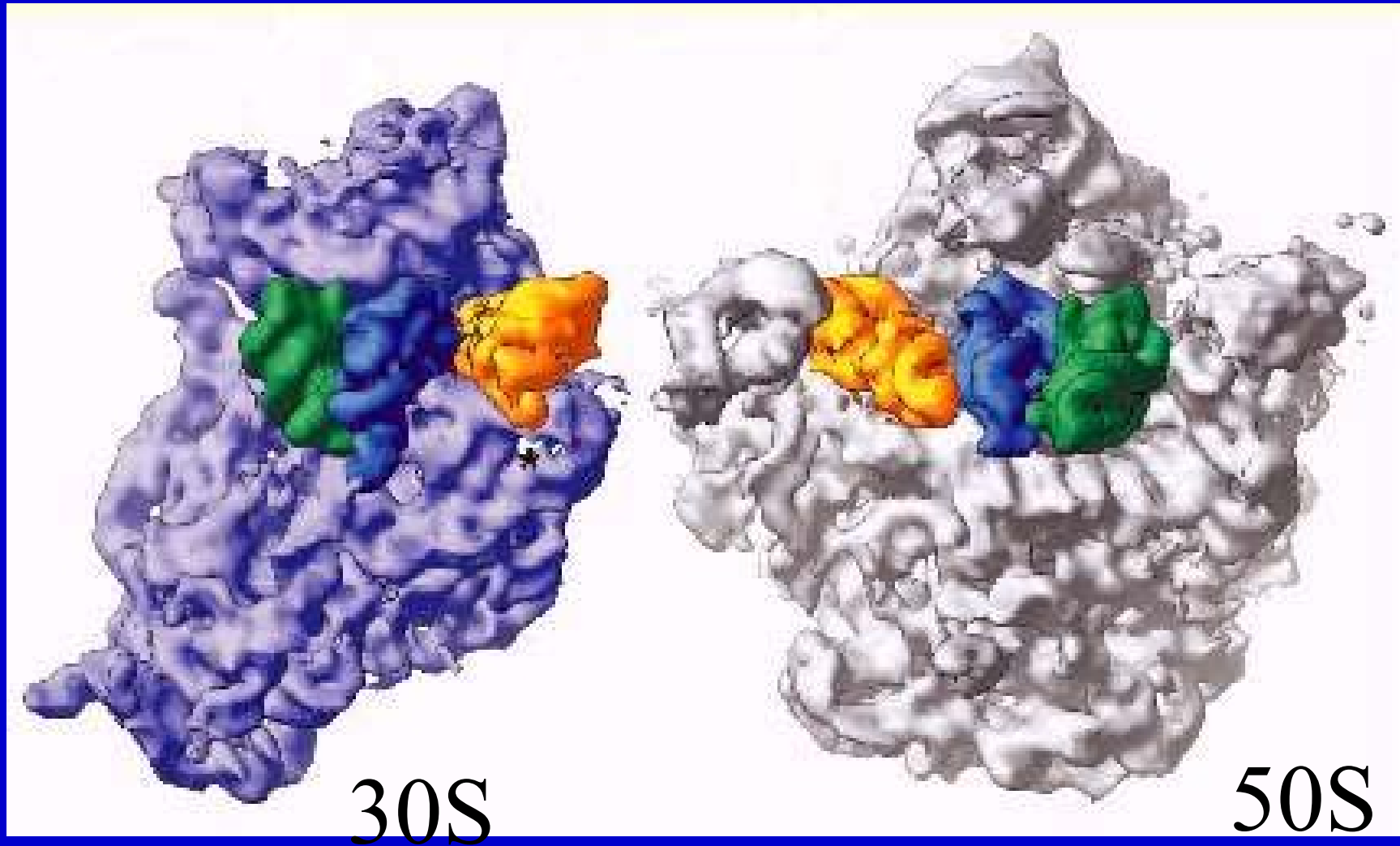


Figure 26-3. The adaptor hypothesis. This hypothesis postulates that the genetic code is read by molecules that recognize a particular codon and carry the corresponding amino acid.

Ribosome:

Small (30S) + large (50S) subunit = 70S



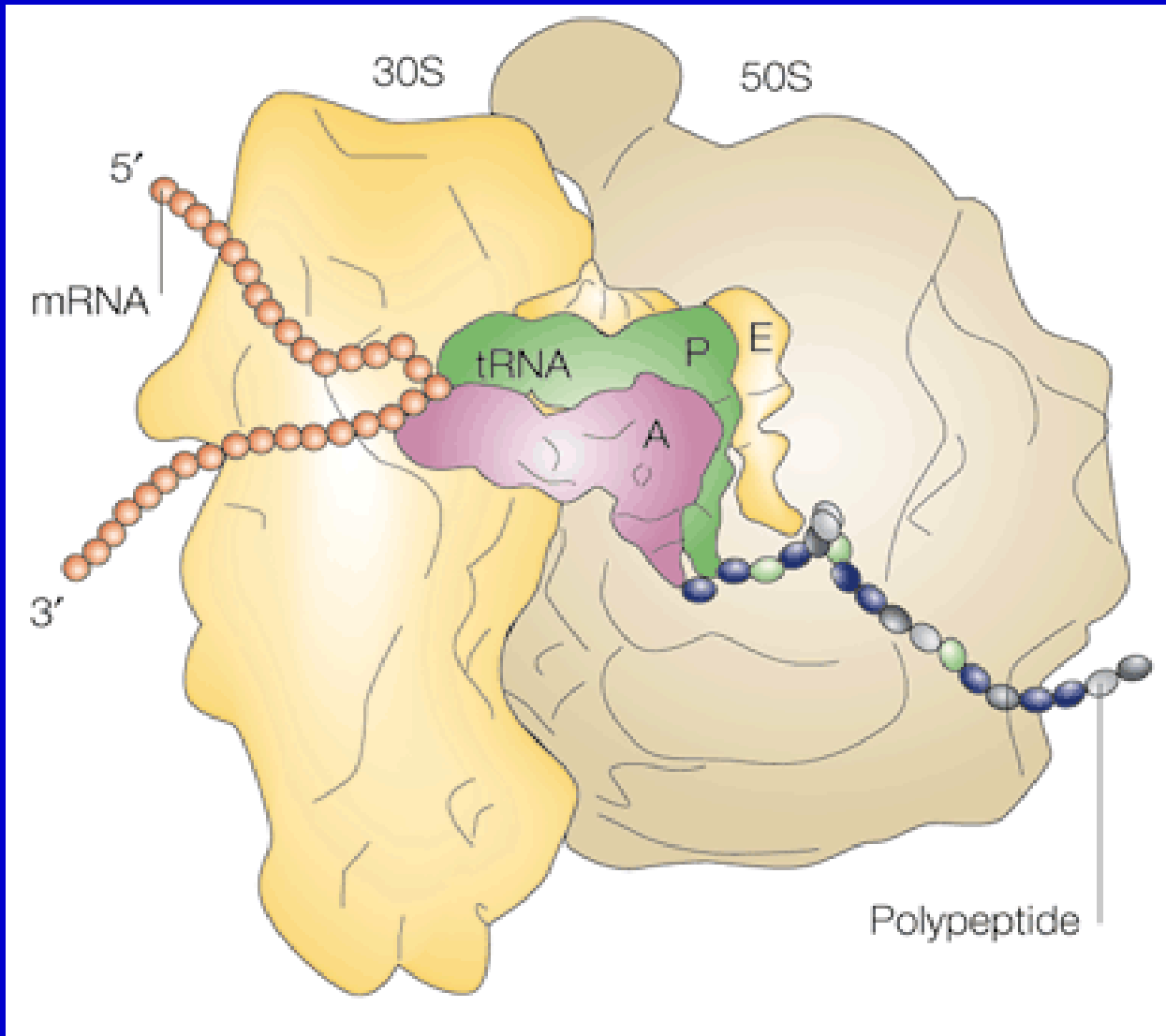
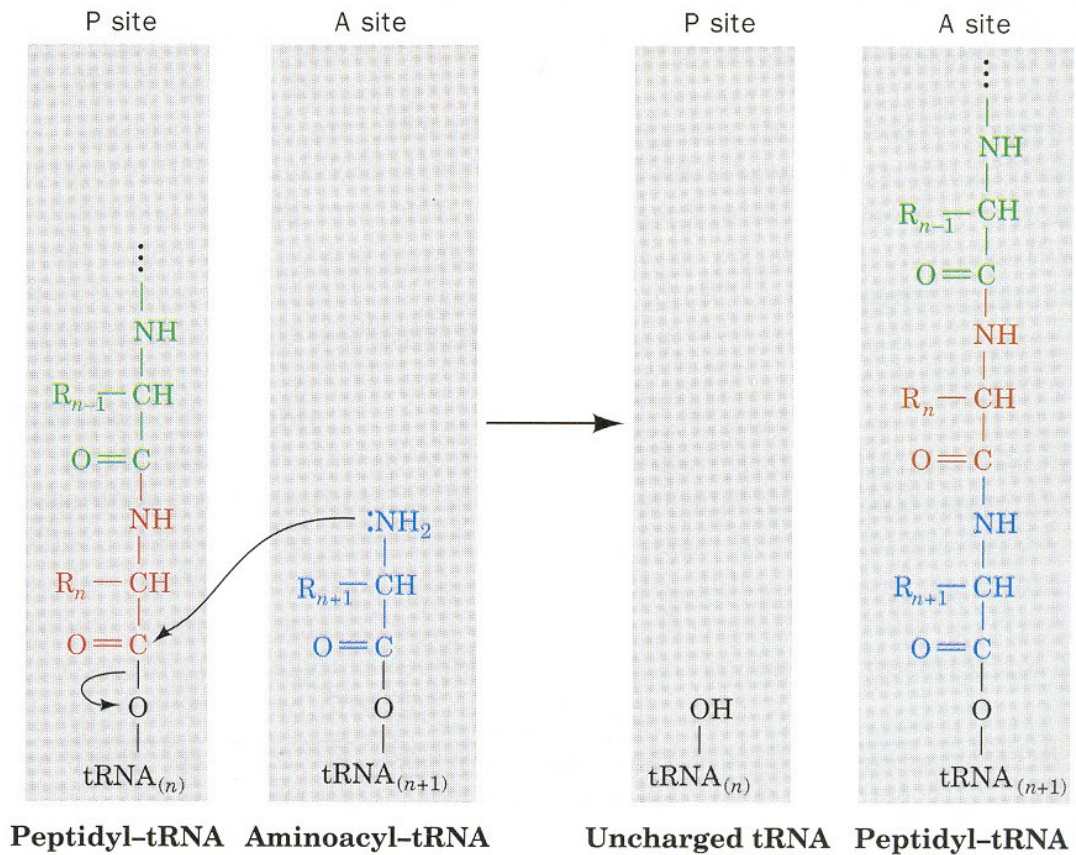


Figure 26-23. The ribosomal peptidyl transferase reaction forming a peptide bond. The amino group of the aminoacyl-tRNA in the A site nucleophilically displaces the tRNA of the peptidyl-tRNA ester in the P site, thereby forming a new peptide bond and transferring the nascent polypeptide to the A-site tRNA.



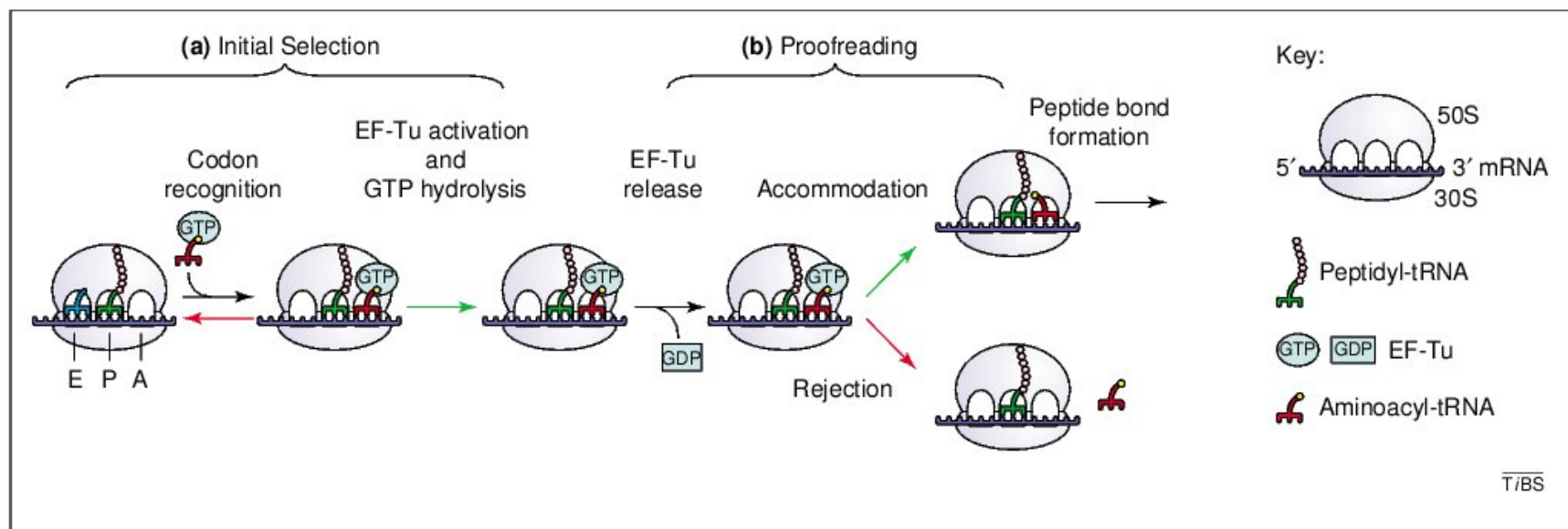
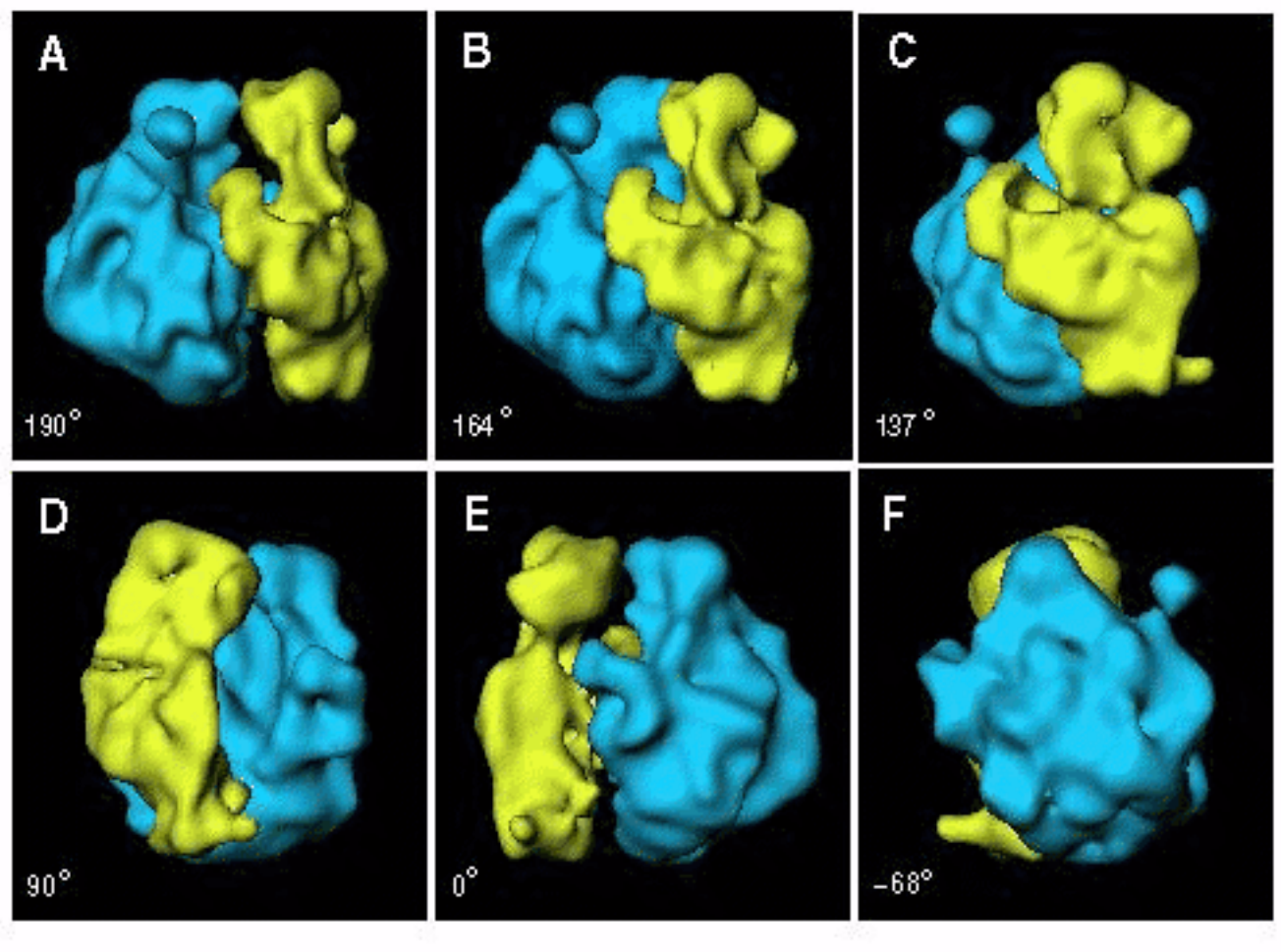
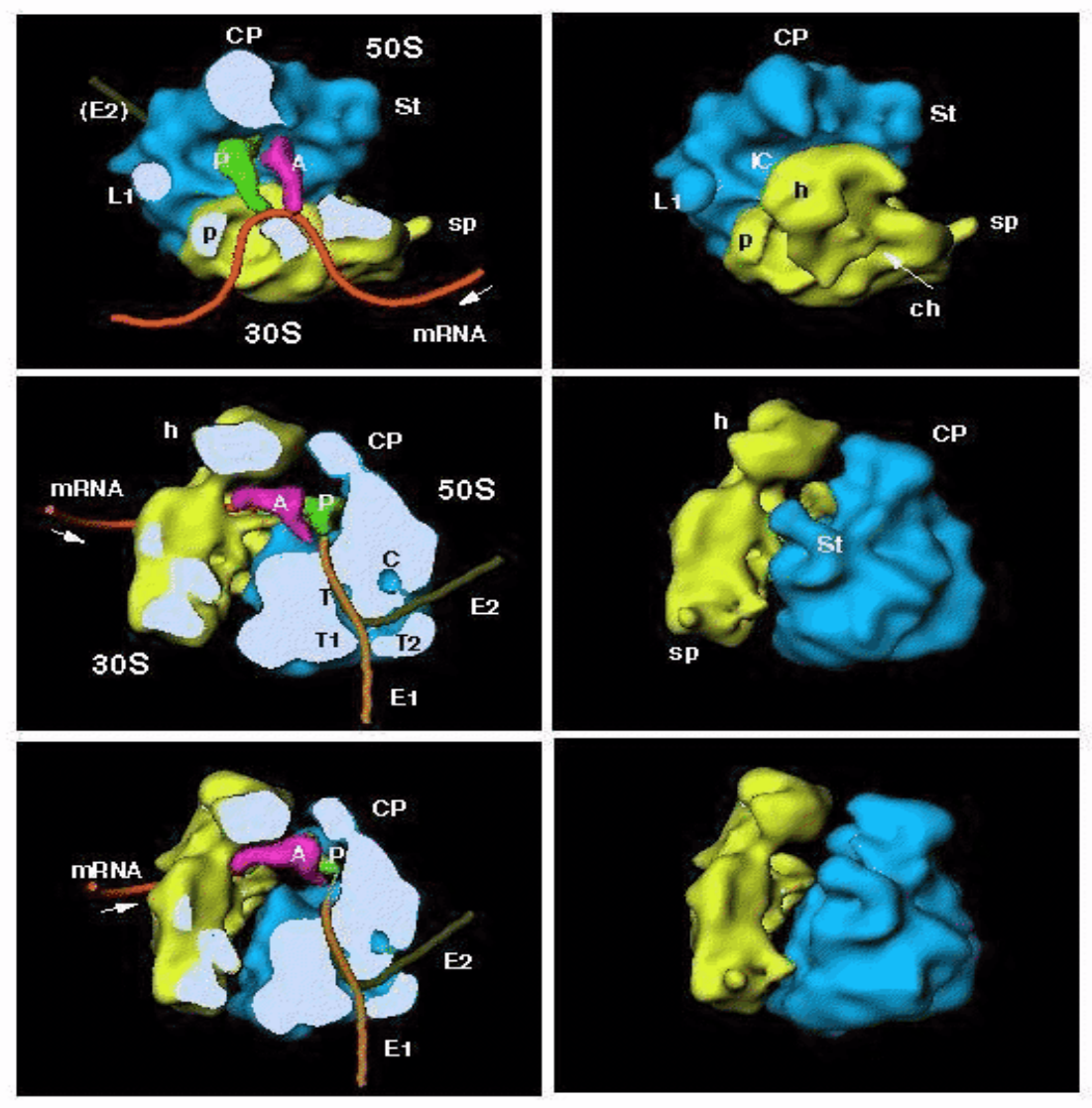
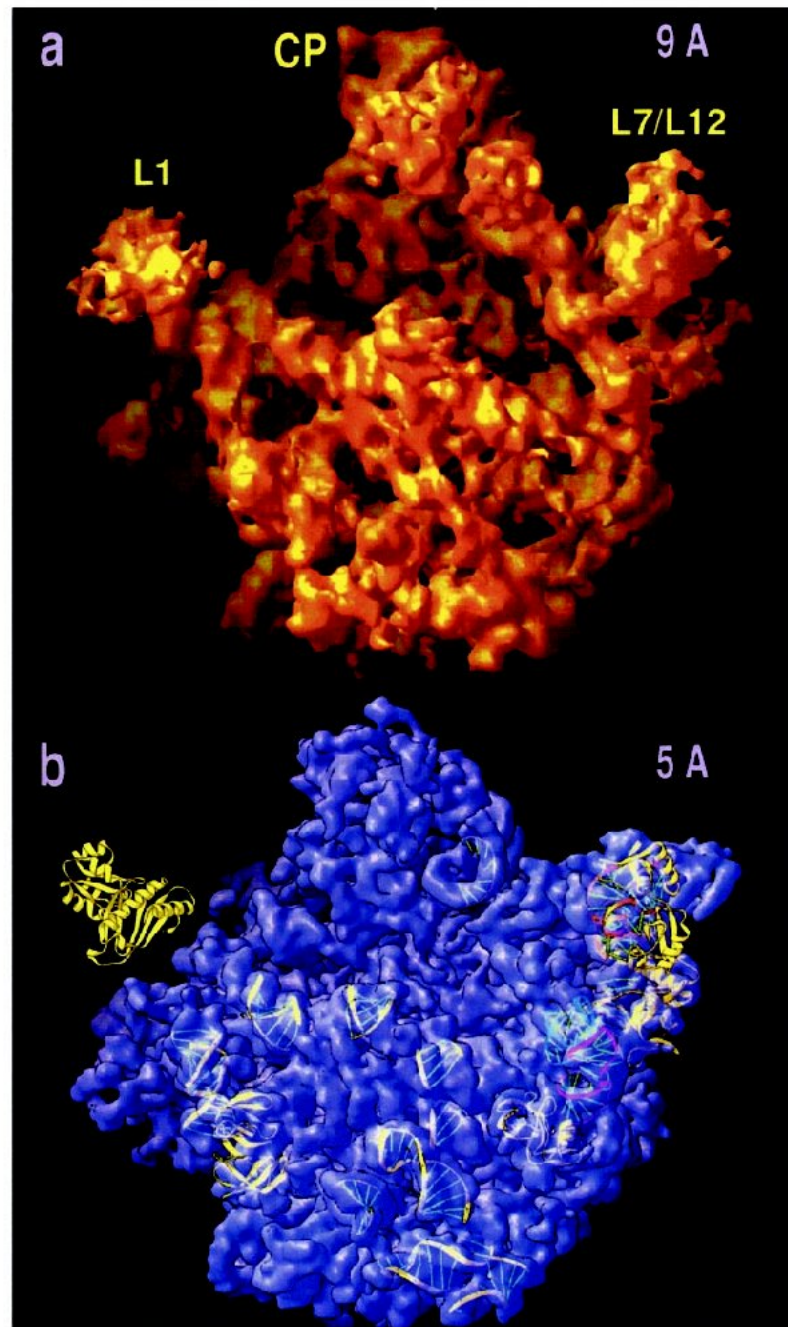


Fig. 2. The aminoacyl-tRNA (aa-tRNA) selection pathway. Ternary complexes of aa-tRNA, EF-Tu and GTP bind reversibly to the ribosome. The anticodon can access mRNA codon in the 30S A site, and if the codon is recognized as correct, the EF-Tu GTPase is activated. After GTP hydrolysis, the GDP form of EF-Tu dissociates, whereupon the aminoacyl end of cognate aa-tRNA moves into the peptidyl transferase site on the 50S (accommodation). Red arrows indicate steps at which non- or near-cognate aa-tRNA are rejected, either during initial selection before GTP hydrolysis or in a proofreading step thereafter. With near-cognate ternary complex, steps represented by green arrows are slower than in the cognate case, but are accelerated by paromomycin or streptomycin [7,8,11].

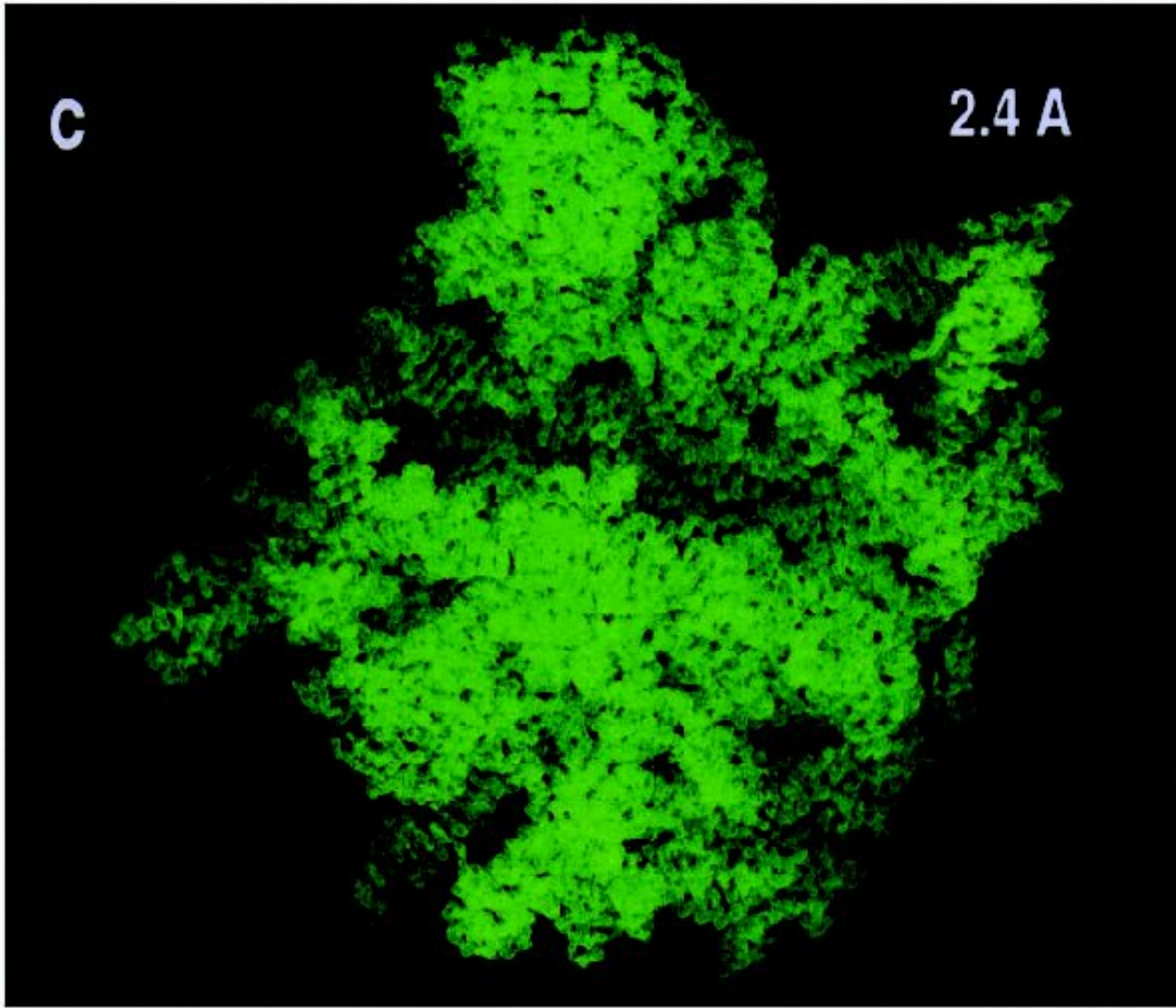




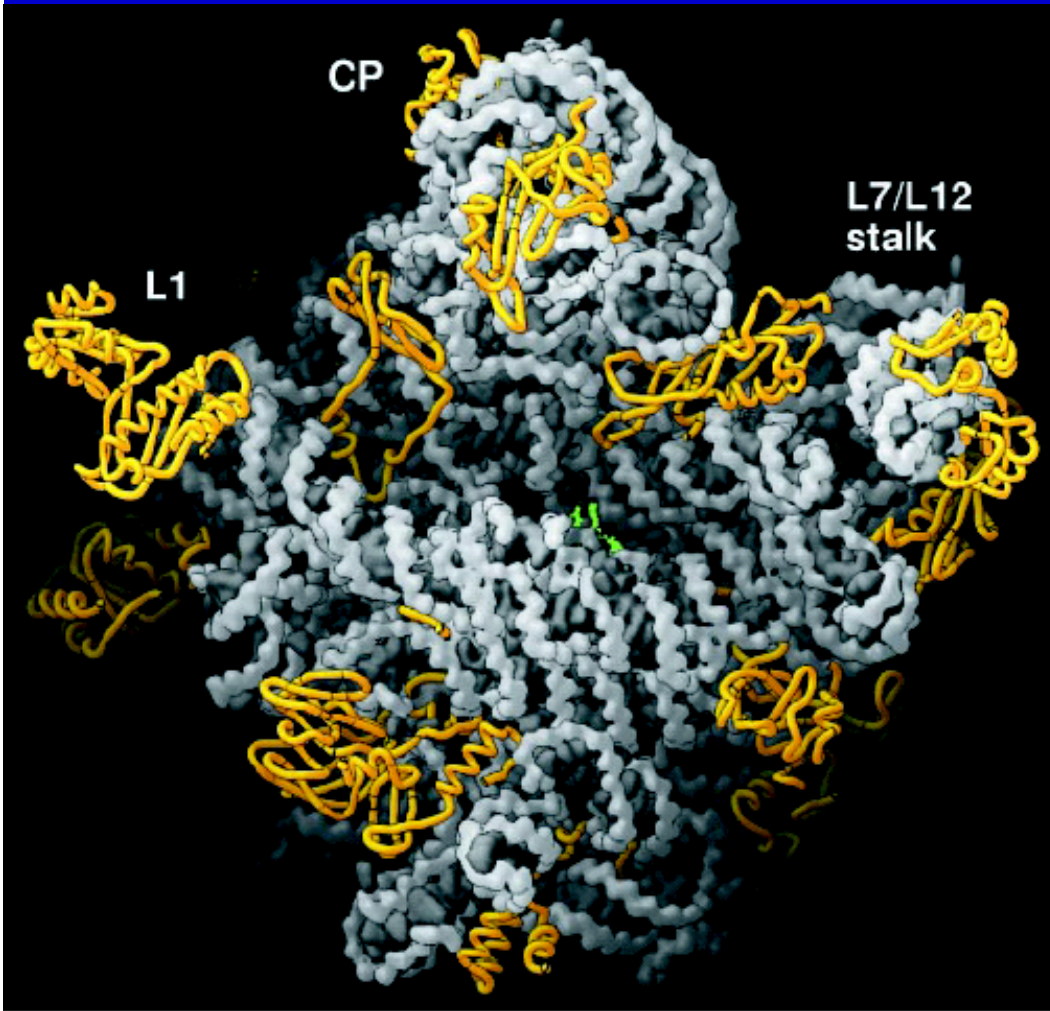


C

2.4 Å



50S Ribosomal Subunit – X-ray



MW $\sim 1.7 \times 10^6$ daltons

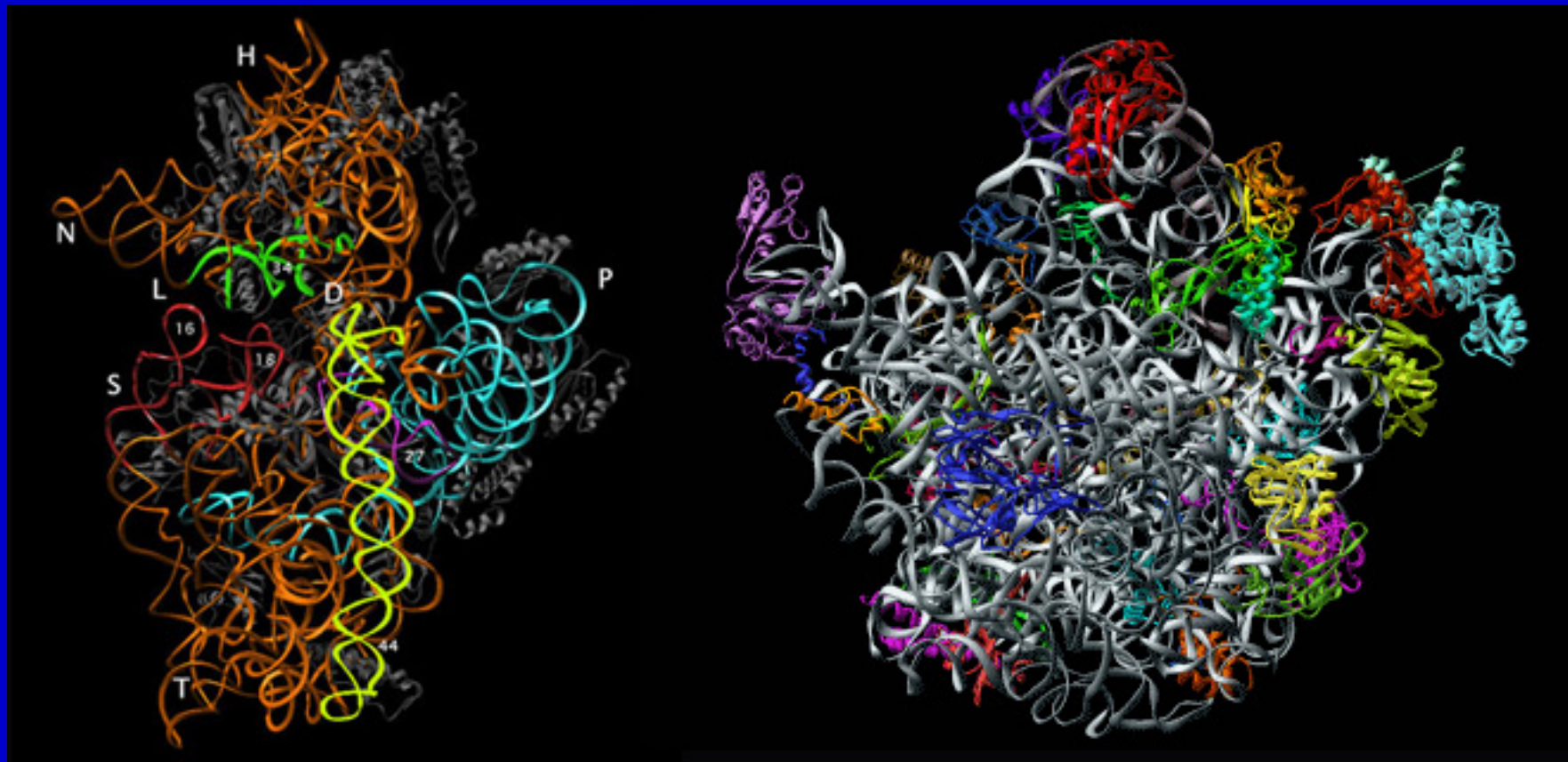
23S RNA (~ 2900 nt)

5S RNA (~ 120 nt)

31 proteins
(1/3 of the MW)

Computations on ribosome

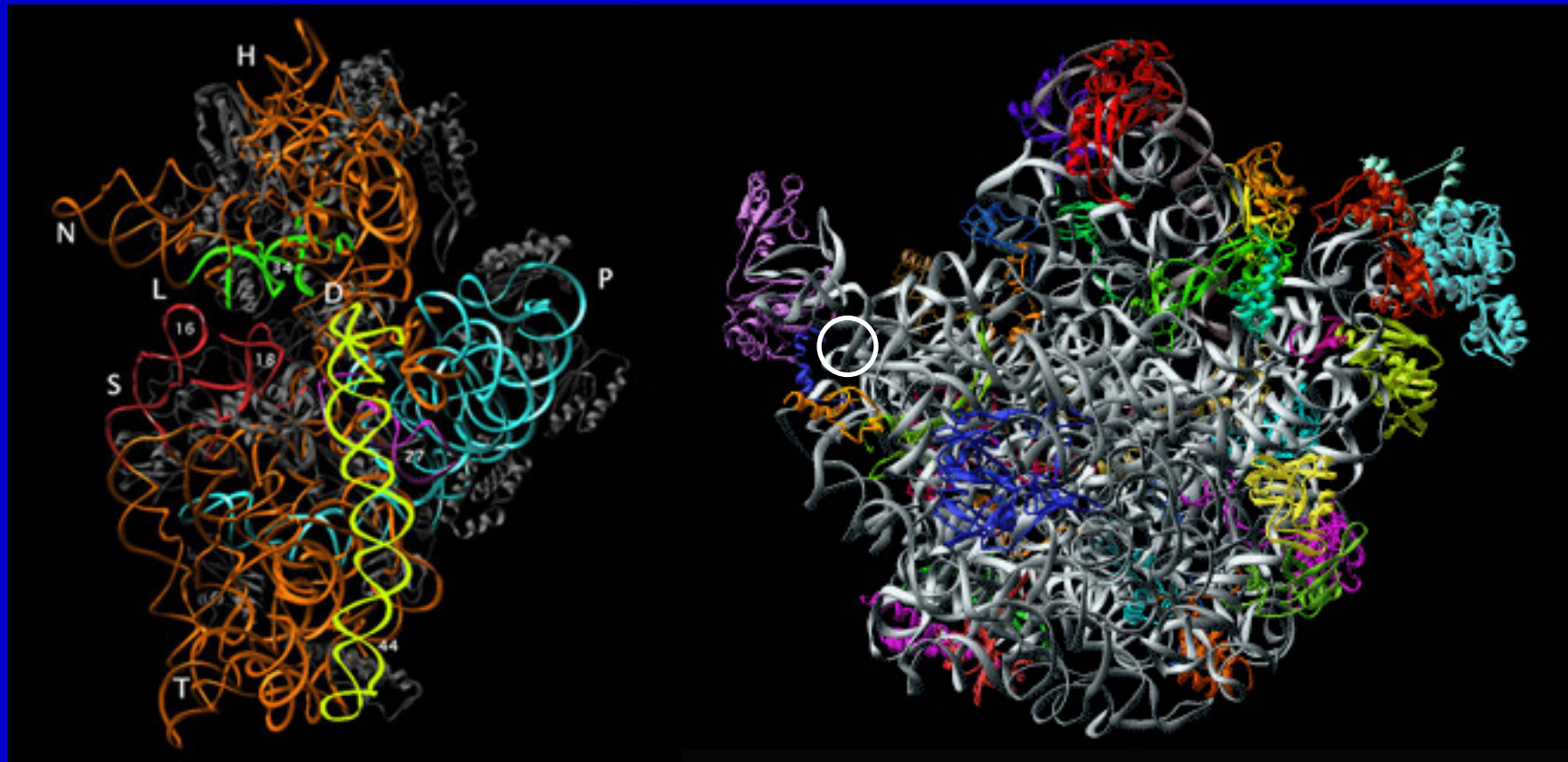
Ribosome → 50 S large subunit → 23 S rRNA → select rRNA segments for computations.



30 S - small subunit

50 S - large subunit

Ribosome → 50 S large subunit → 23 S rRNA → K-turn motifs

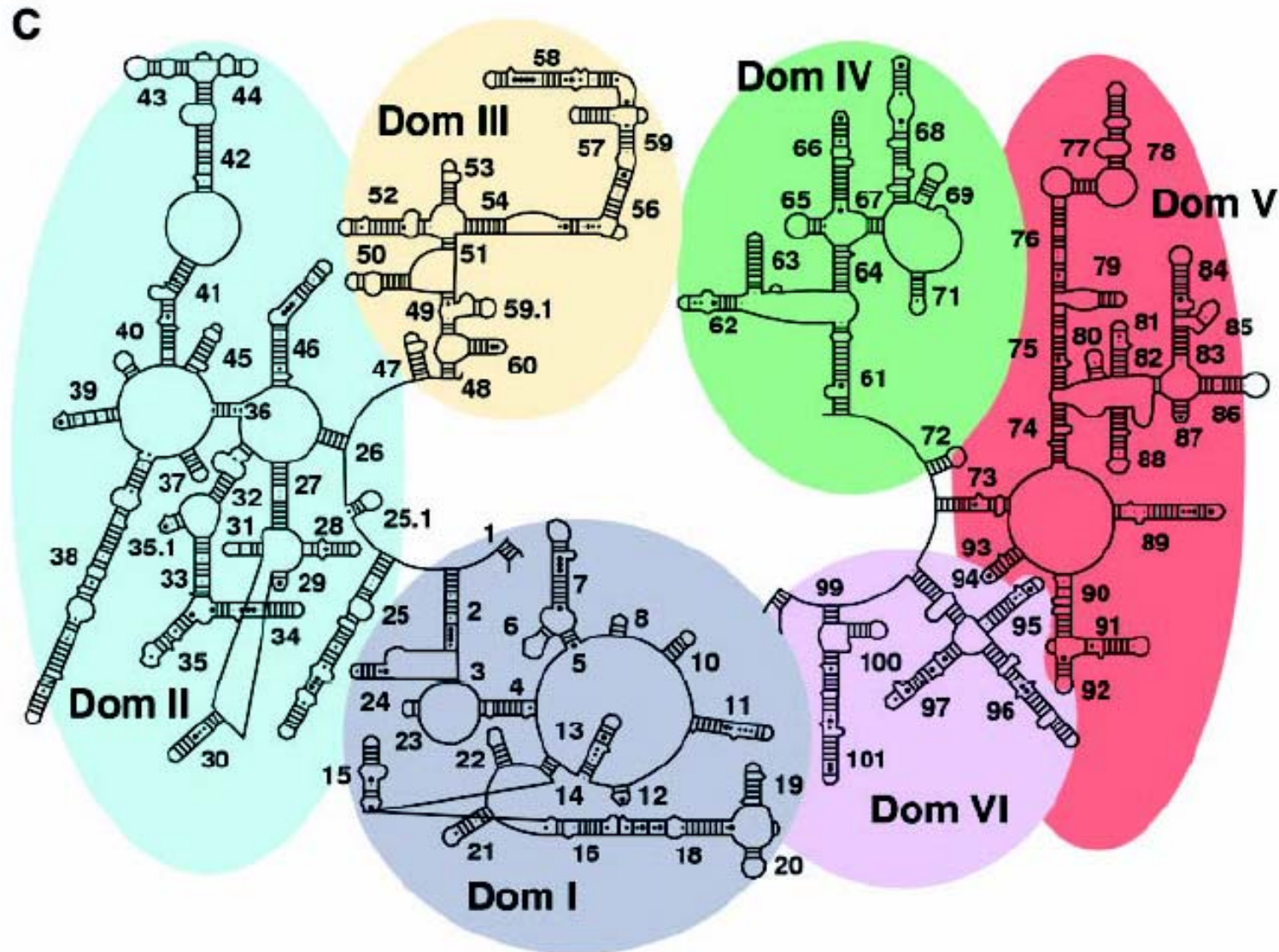


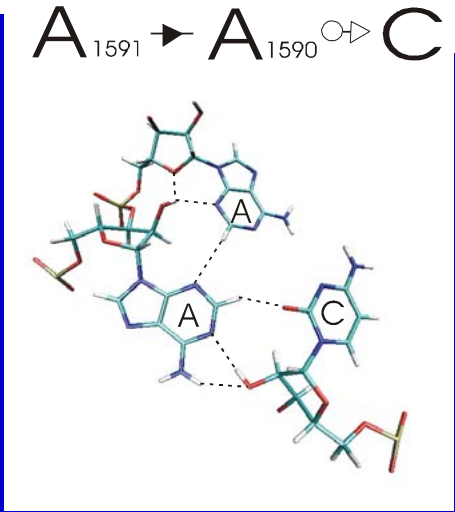
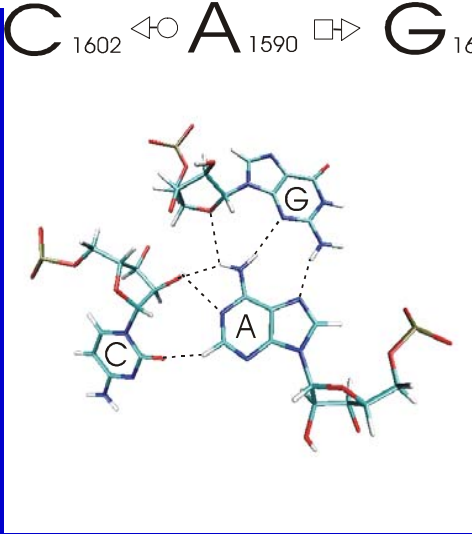
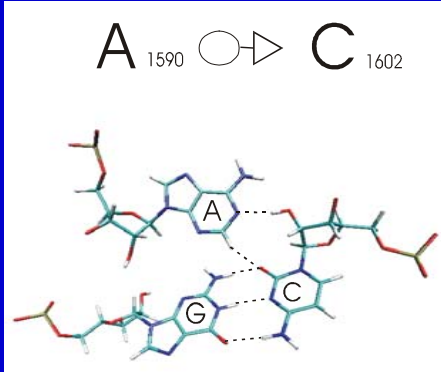
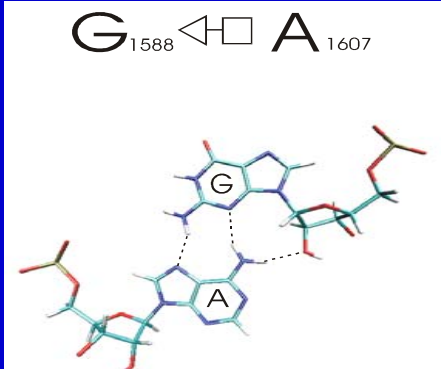
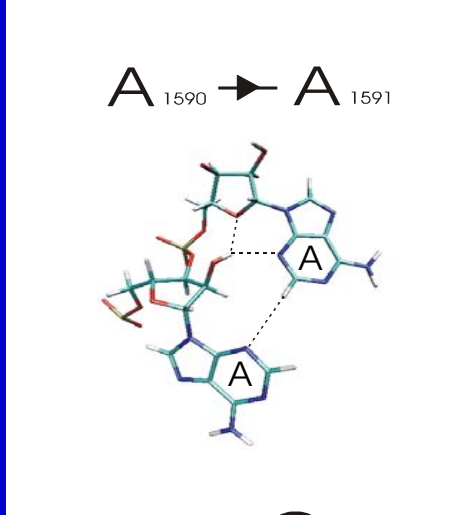
30 S - small subunit

50 S - large subunit

23S rRNA Domains.

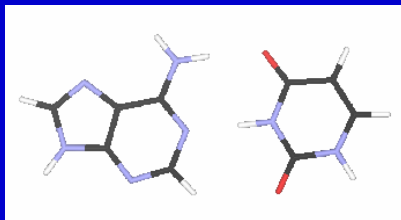
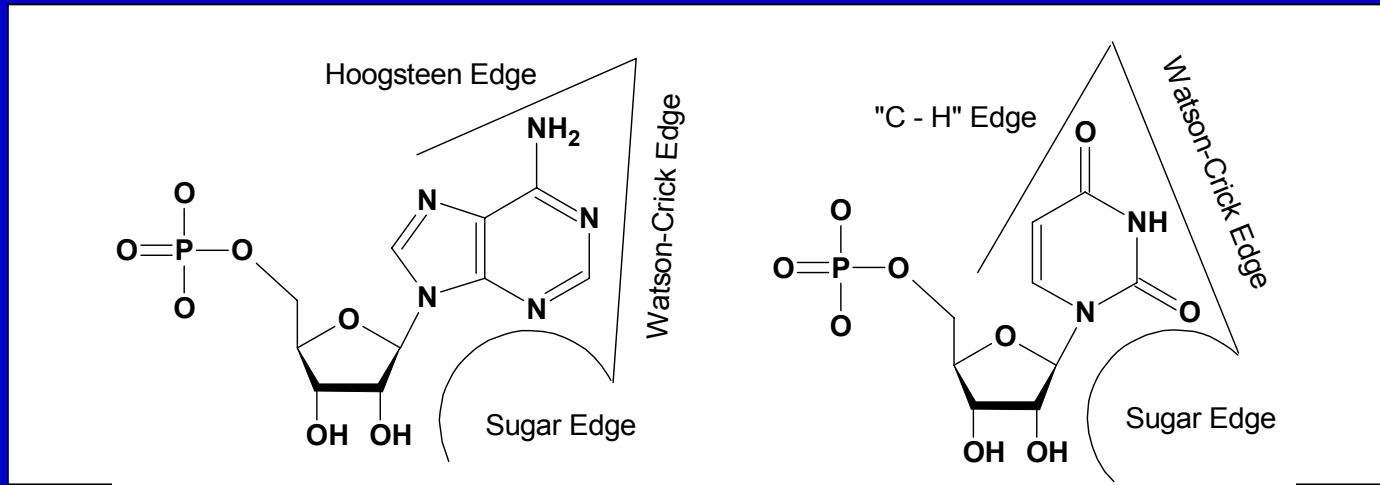
Proč není WC až tak moc zajímavé??



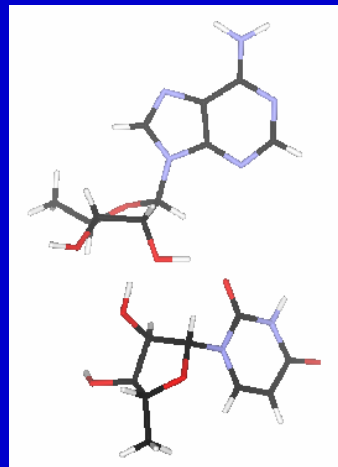


Příklady ne-Watson-Crickových párů. Klíč k pochopení funkční RNA.

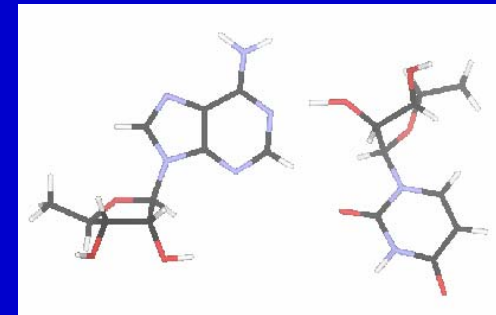
Nomenklatura RNA párů bází, 150 – 200 principiálně možných kombinací.



WC/WC AU



cis SE/SE rA/rU



trans SE/SE rA/rU

Ribosomální RNA je kombinací krátkých Watson-Crick helixů a krátkých nekanonických segmentů zvaných RNA motifs, propojených terciárními interakcemi, proteiny.....

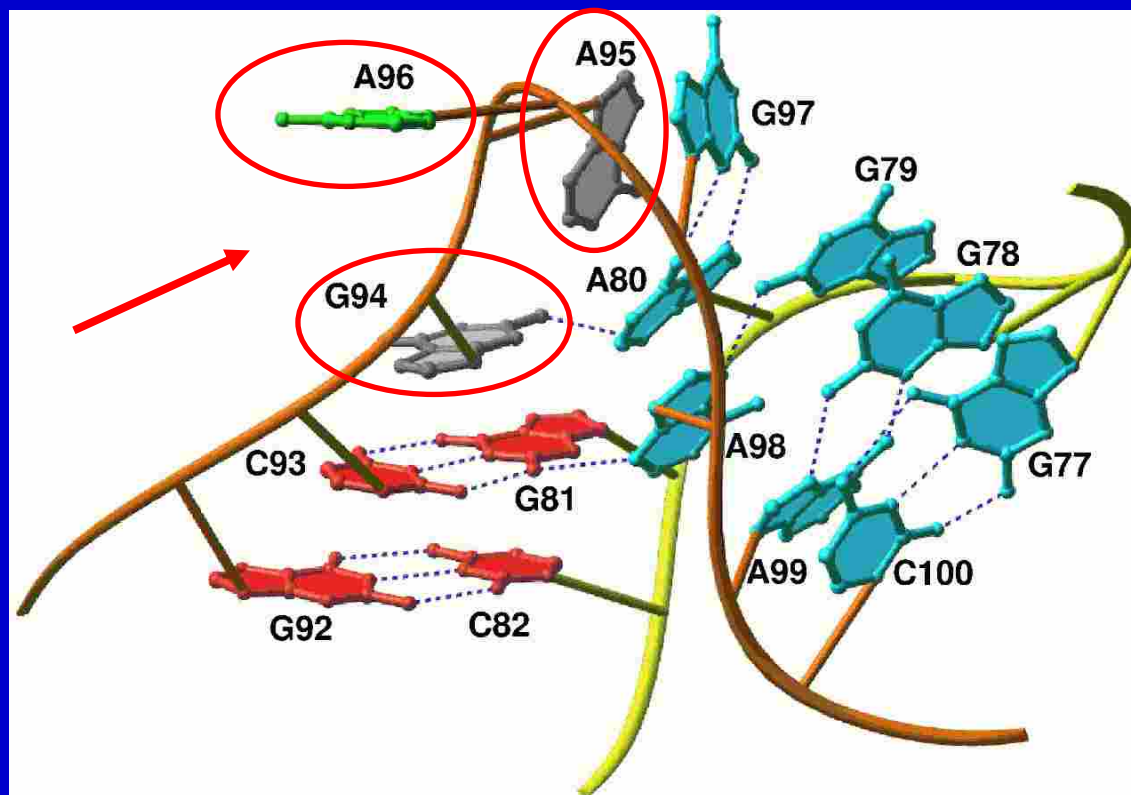
Je to jako LEGO, opakující se universální stavební jednotky a rozsáhlá dynamika.

Studujeme systematicky všechny základní komponenty a terciární interakce v ribosomu.

Studium ribosomálního lega pomocí MD
Kink-turn jako molekulární kloub

Consensus of K-turn

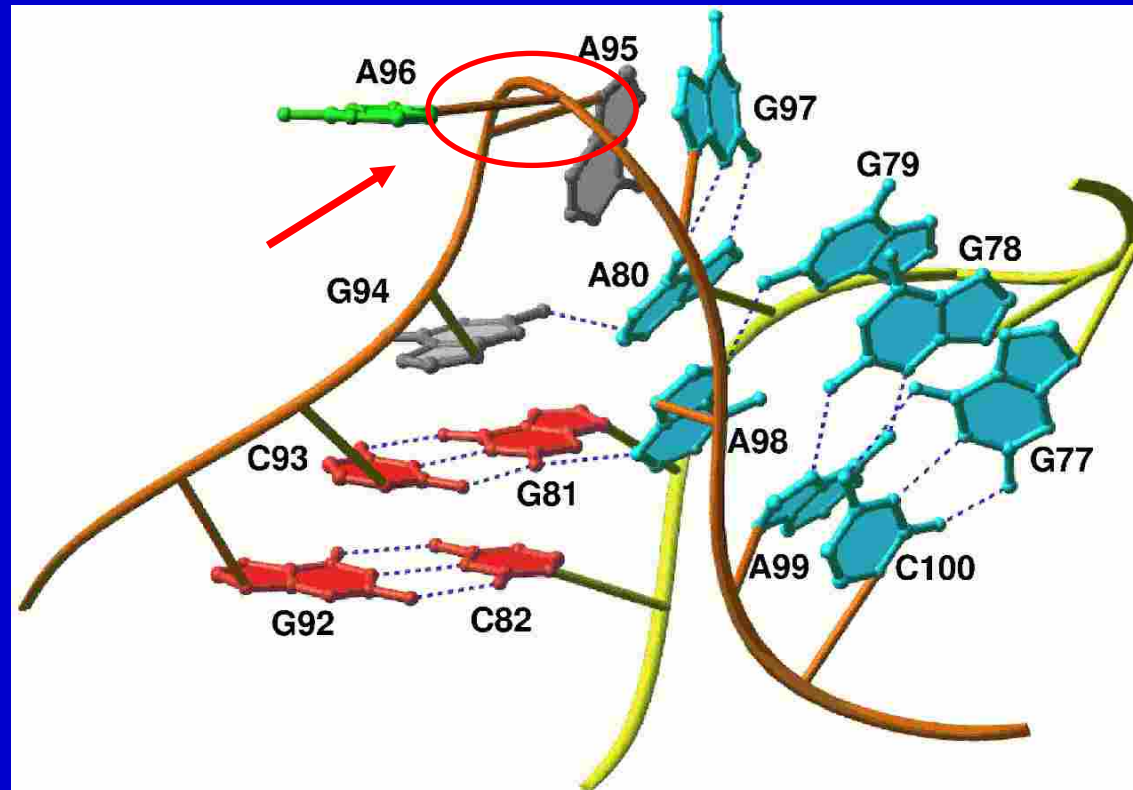
K-turn 7 (Haloarcula marismortui)



asymetrická smyčka se 3 nespárovanými nukleotidy v jednom řetězci

Consensus of K-turn

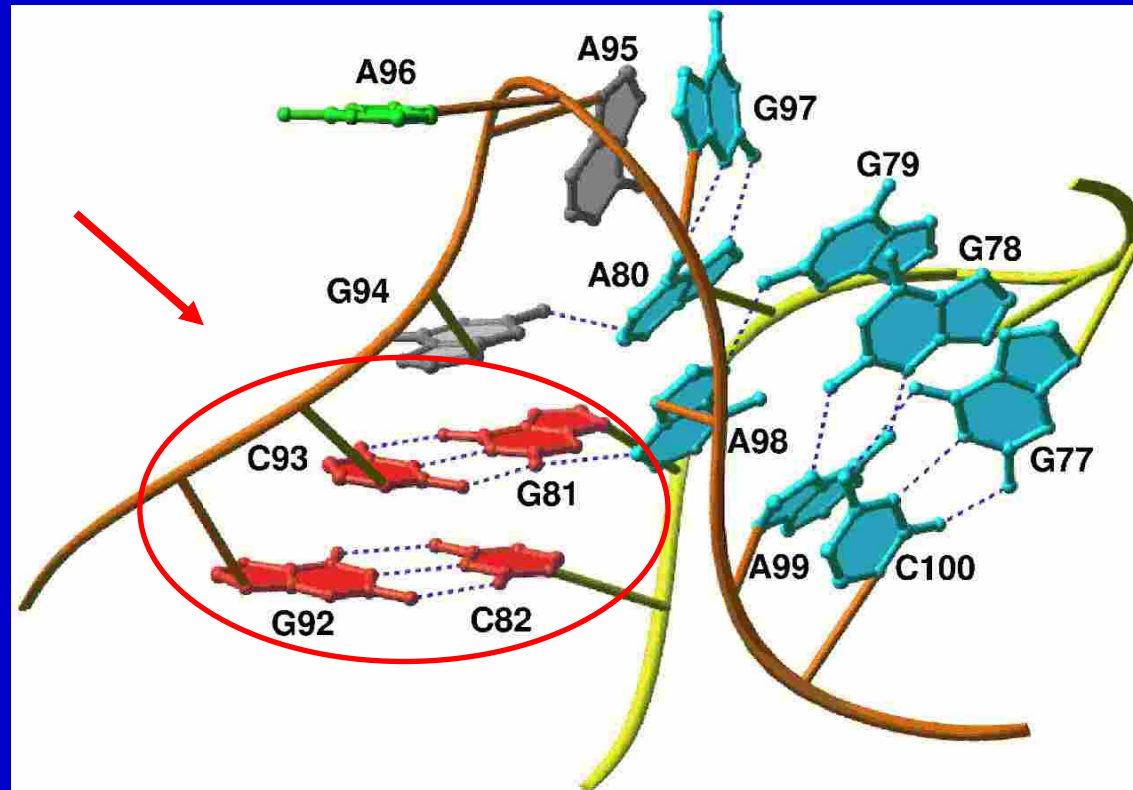
K-turn 7 (Haloarcula marismortui)



ostrý zlom páteře o 120°
„V“ shaped structure

Consensus of K-turn

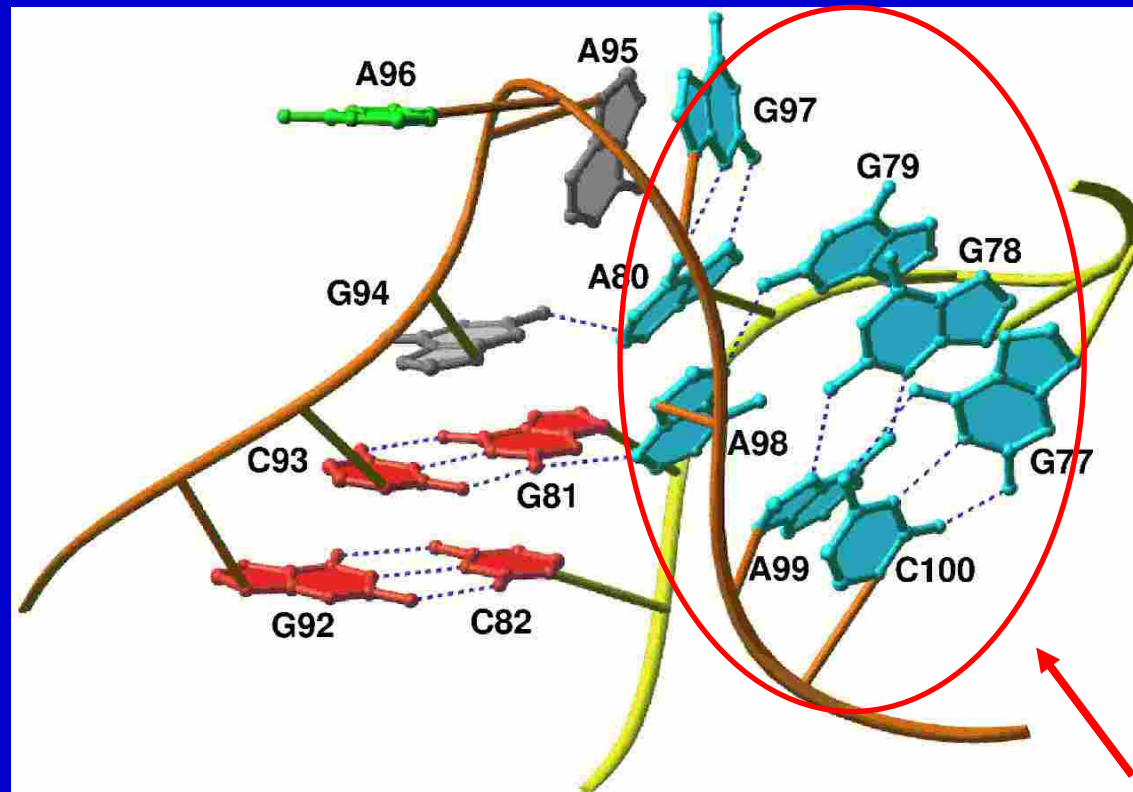
K-turn 7 (Haloarcula marismortui)



C-stem - Watson-Crickovy páry

Consensus of K-turn

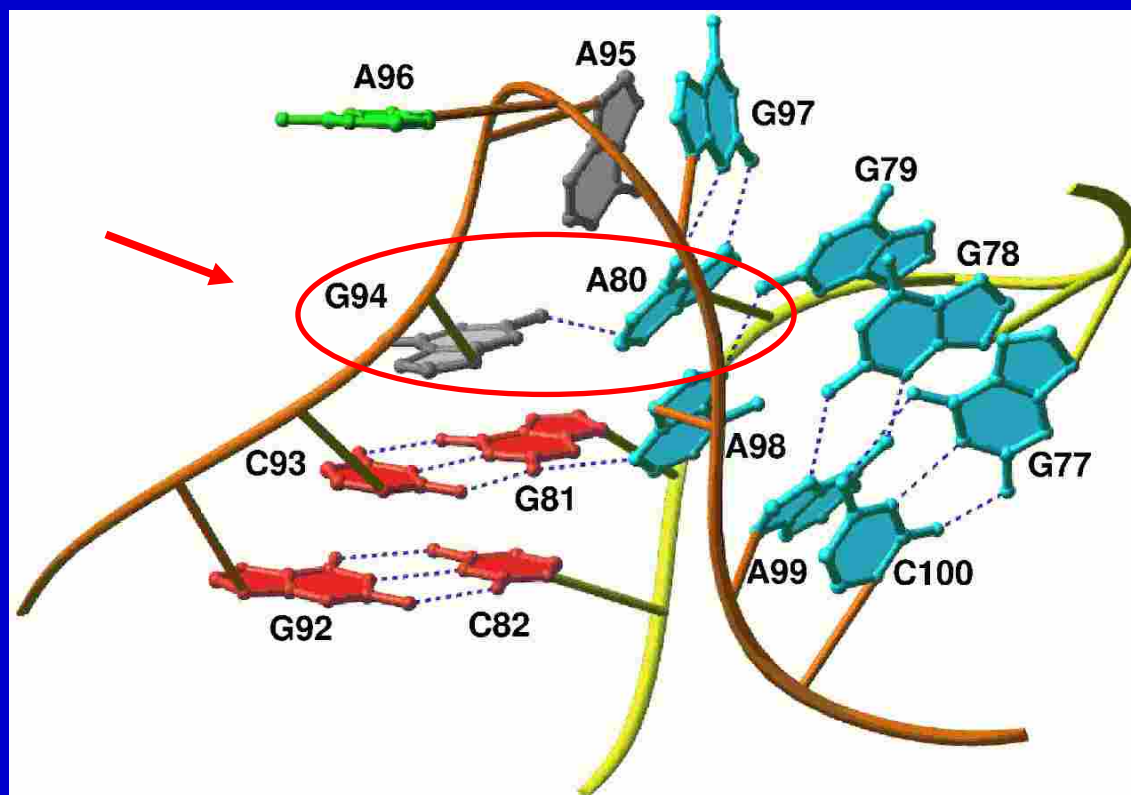
K-turn 7 (Haloarcula marismortui)



NC-stem - A/G trans Hoogsteen/Sugar edge páry

Consensus of K-turn

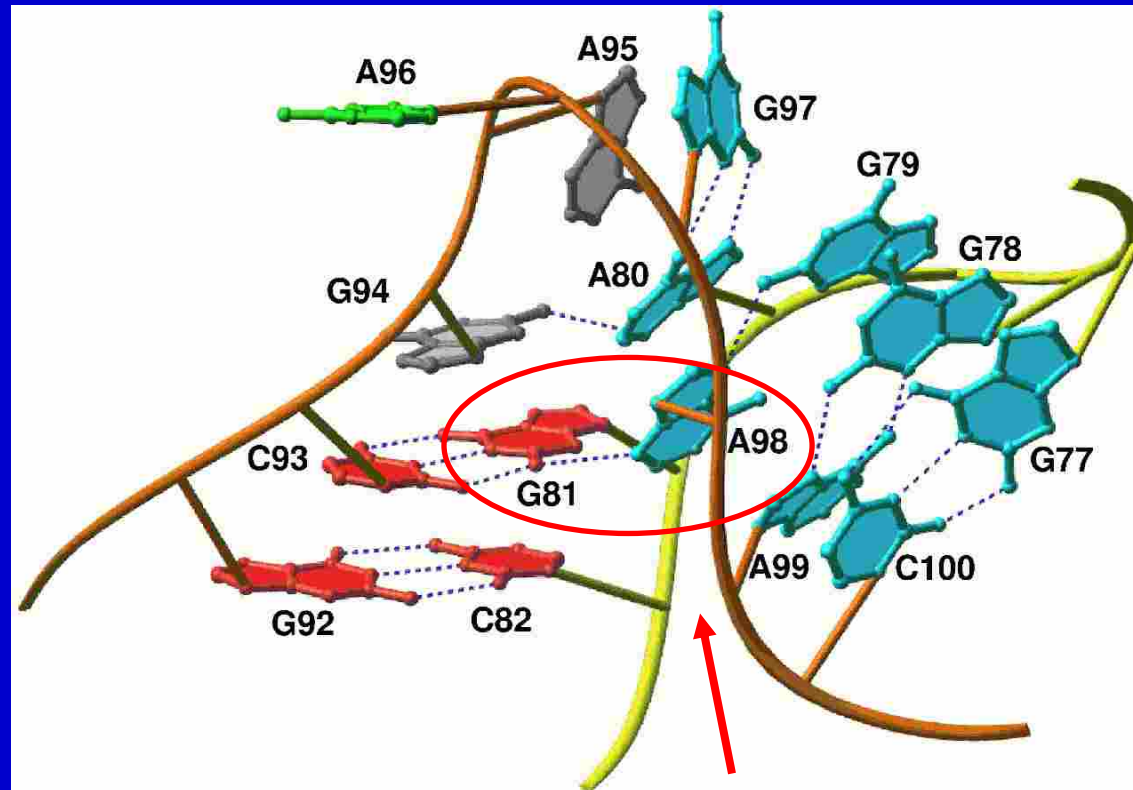
K-turn 7 (*Haloarcula marismortui*)



konservovaný adenin tvoří trans Sugar edge pár s prvním nespárovaným nukleotidem na druhé straně interní smyčky. ***A-minor motif***.

Consensus of K-turn

K-turn 7 (Haloarcula marismortui)



A druhá taková interakce (*A-minor motif*)

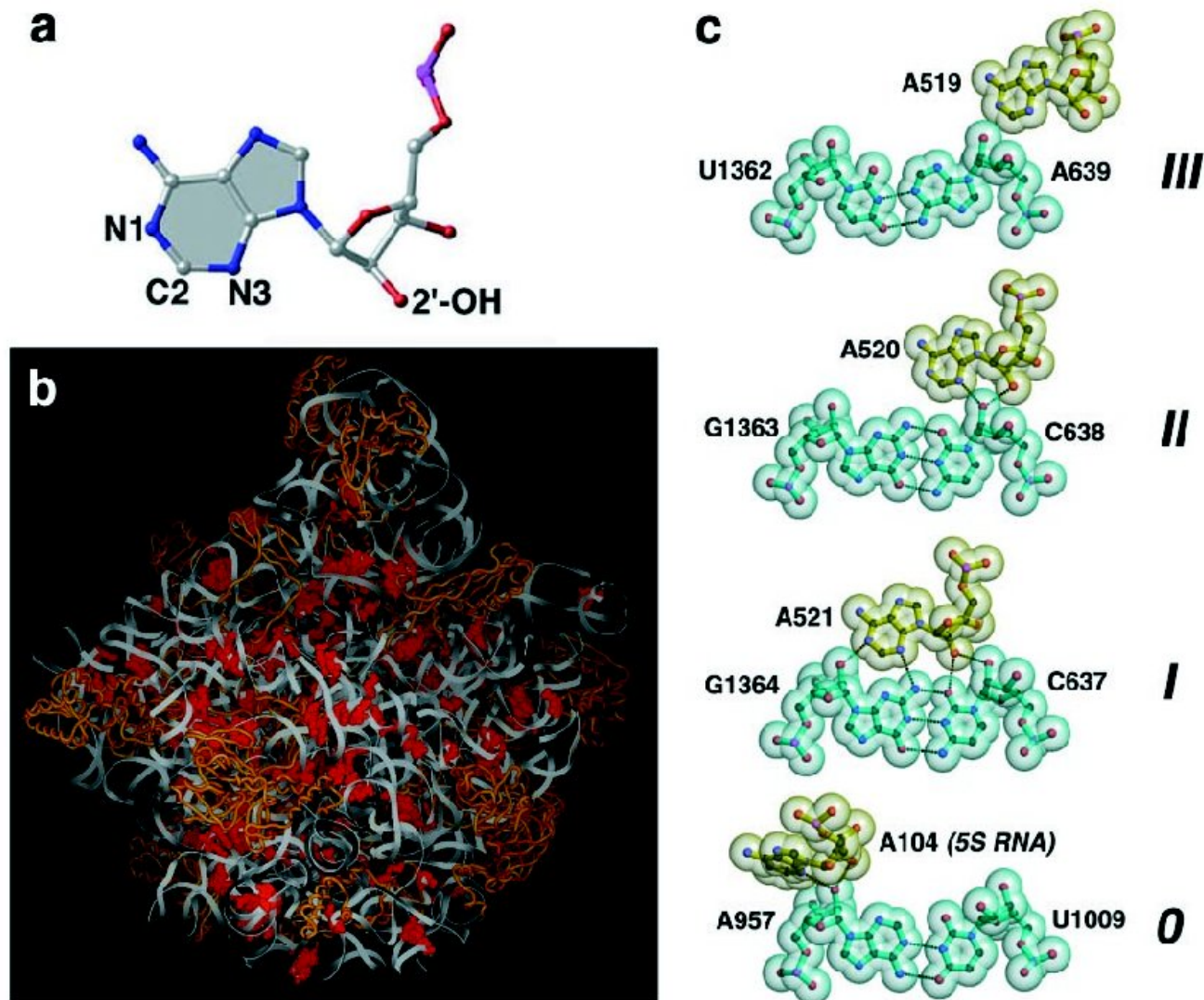
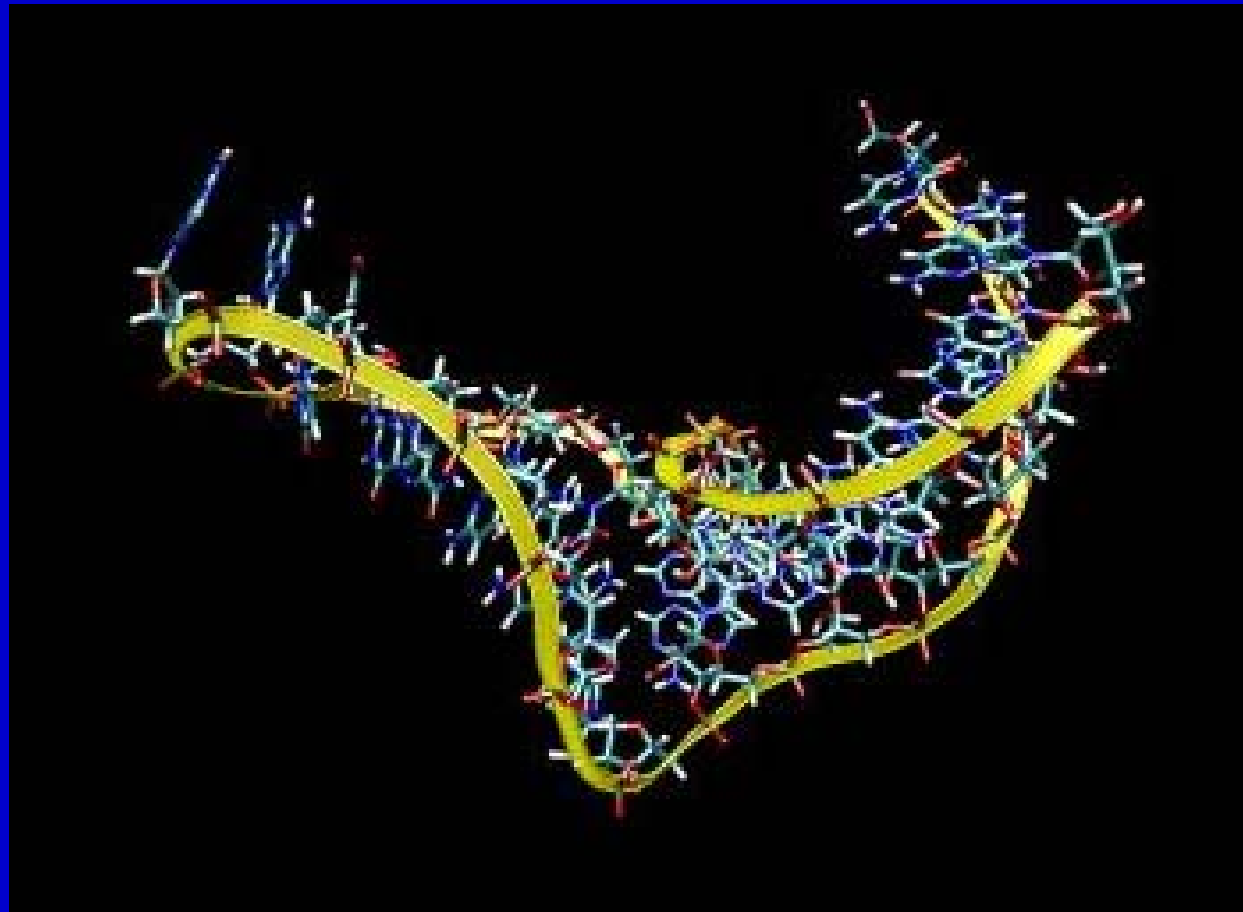
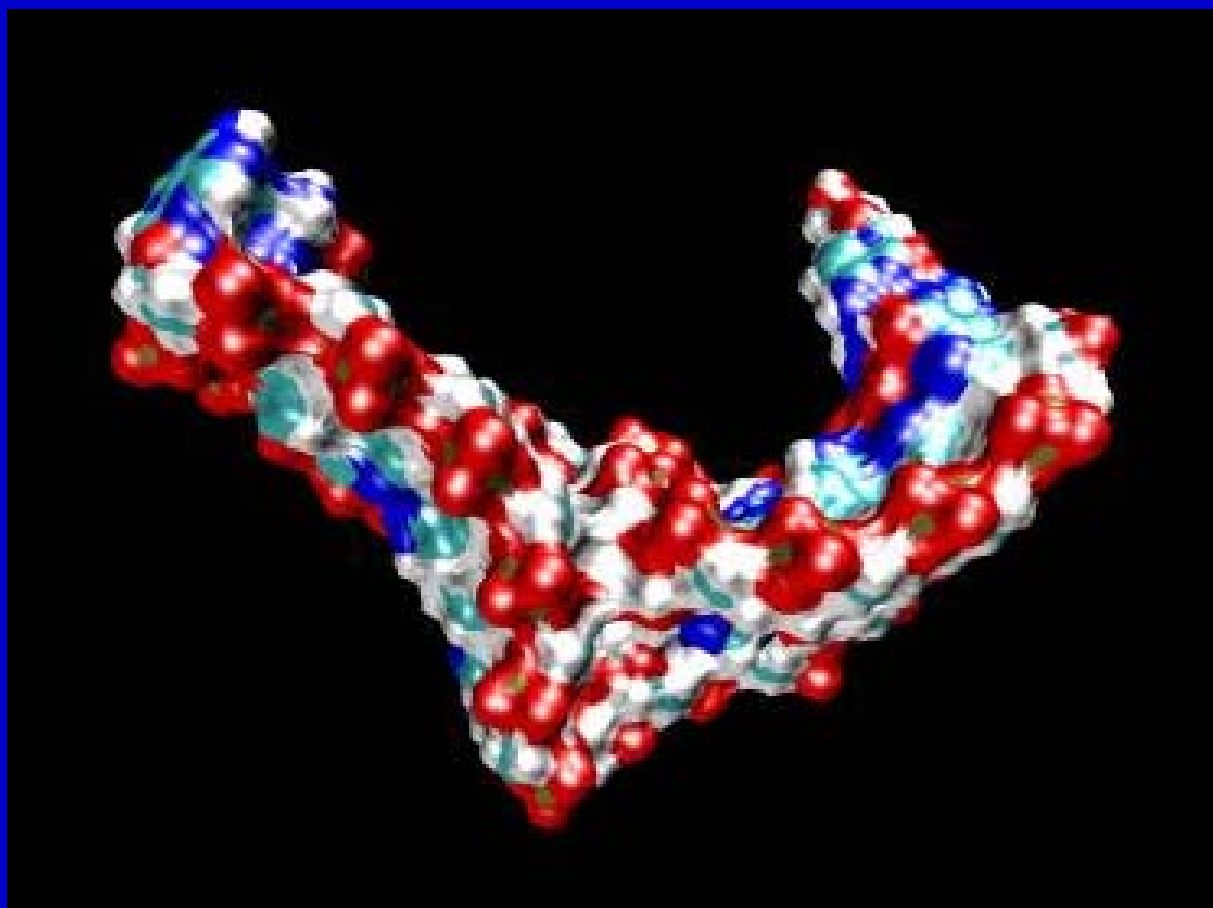
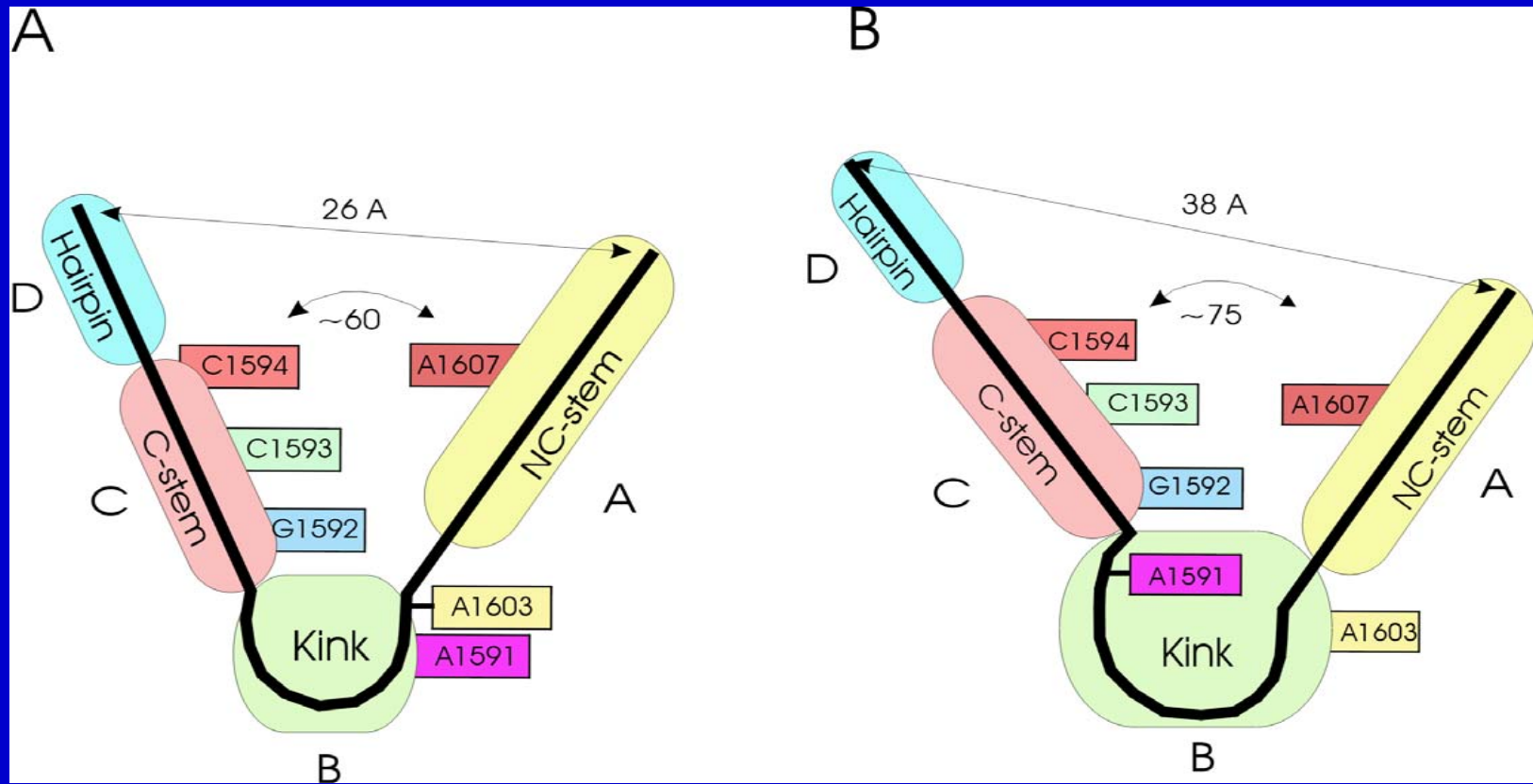


Fig. 1. (a) The smooth minor groove face of the adenosine nucleotide allows the base to pack tightly into the minor groove of an RNA helix. Its N1, N3, and 2'-OH atoms are available for hydrogen-bonding interactions. (b) Ribbon drawing of the overall structure of the 50S ribosomal subunit from *H. marismortui* highlighting the 186 adenosines (shown in red spheres) that make A-minor interactions based on distance and geometric criteria (see text). (c) Examples of the four major types of A-minor interactions found in *H. marismortui* 50S shown in surface representation. Each type is defined by the position of the 2'-OH group of the interacting adenosine relative to the positions of the two 2'-OH groups of the receptor base pair. Whereas type I and type II interactions are A-specific, type 0 and type III also are observed for other bases even though As are still preferred when the base packs against the ribose backbone.

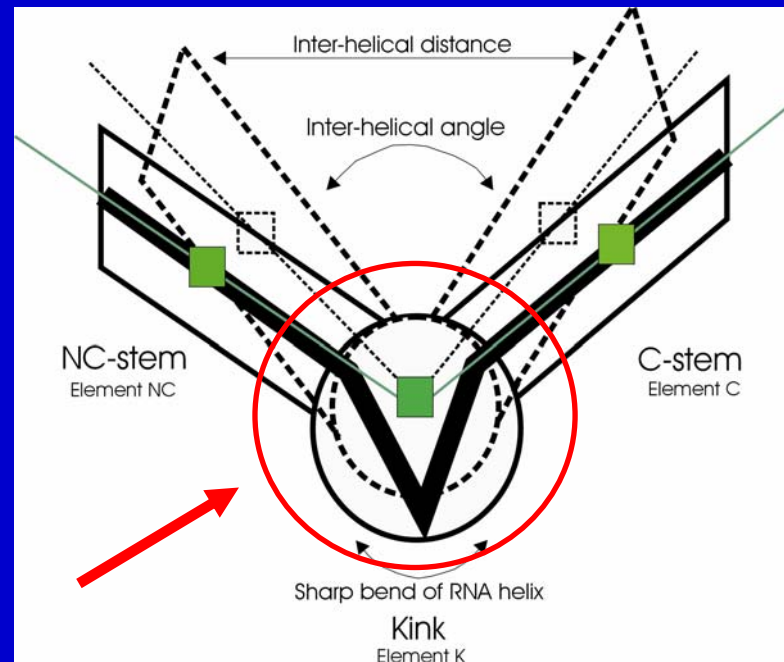






Chová se to v simulacích jako bezprecedentní flexibilní kloub.

Local geometrical changes and global motion



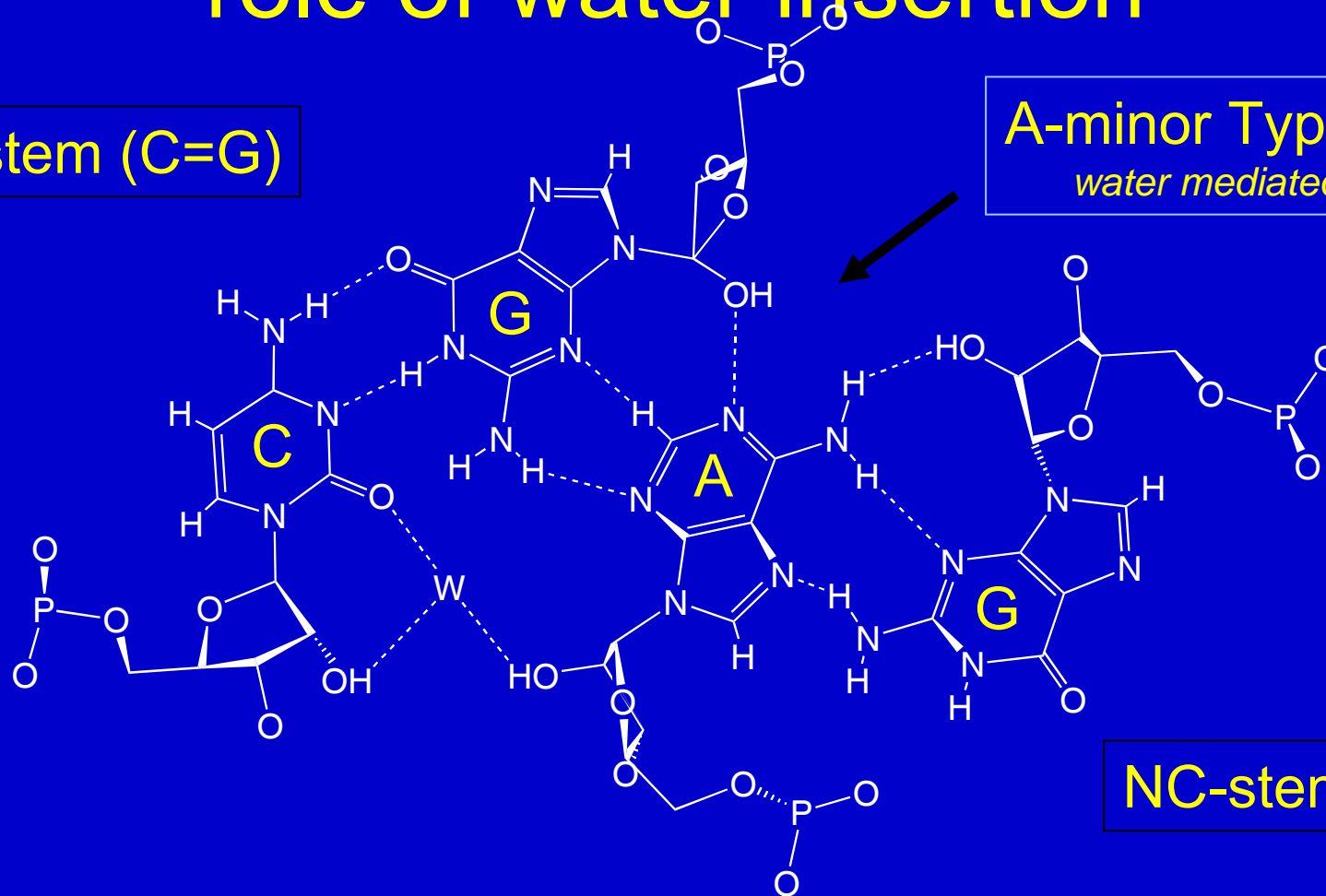
Motion of unpaired nucleotides (Kt-58 - permanent change)

Dynamics of A-minor submotif (Kt-38, Kt-42 - oscillatory changes)

Dynamics of A-minor submotif – key role of water insertion

C-stem (C=G)

A-minor Type I
water mediated

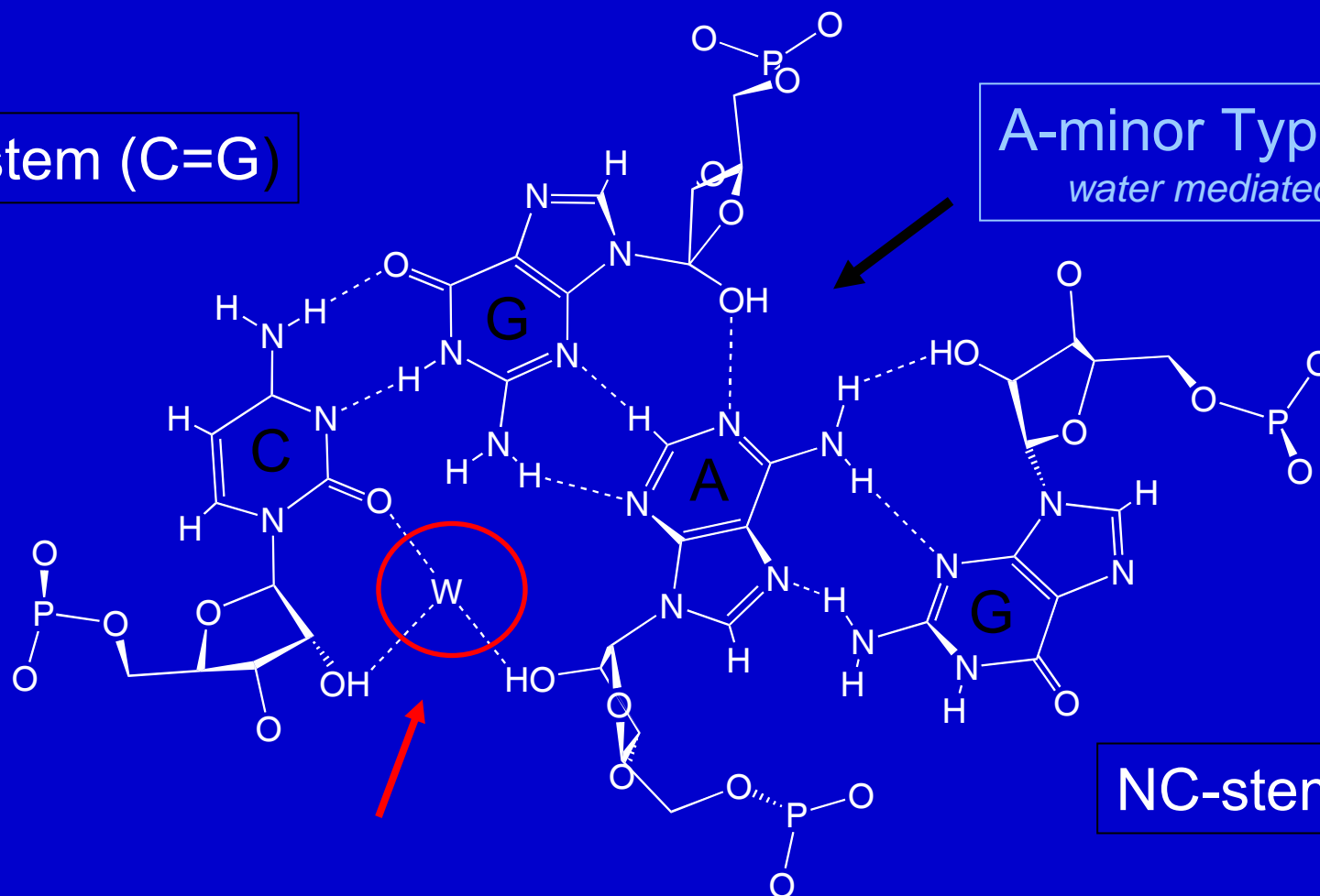


A-minor type I submotif mediates the interaction between the rigid C- and NC-stems of Kt-38 and Kt-42

Dynamics of A-minor submotif

C-stem (C=G)

A-minor Type I
water mediated



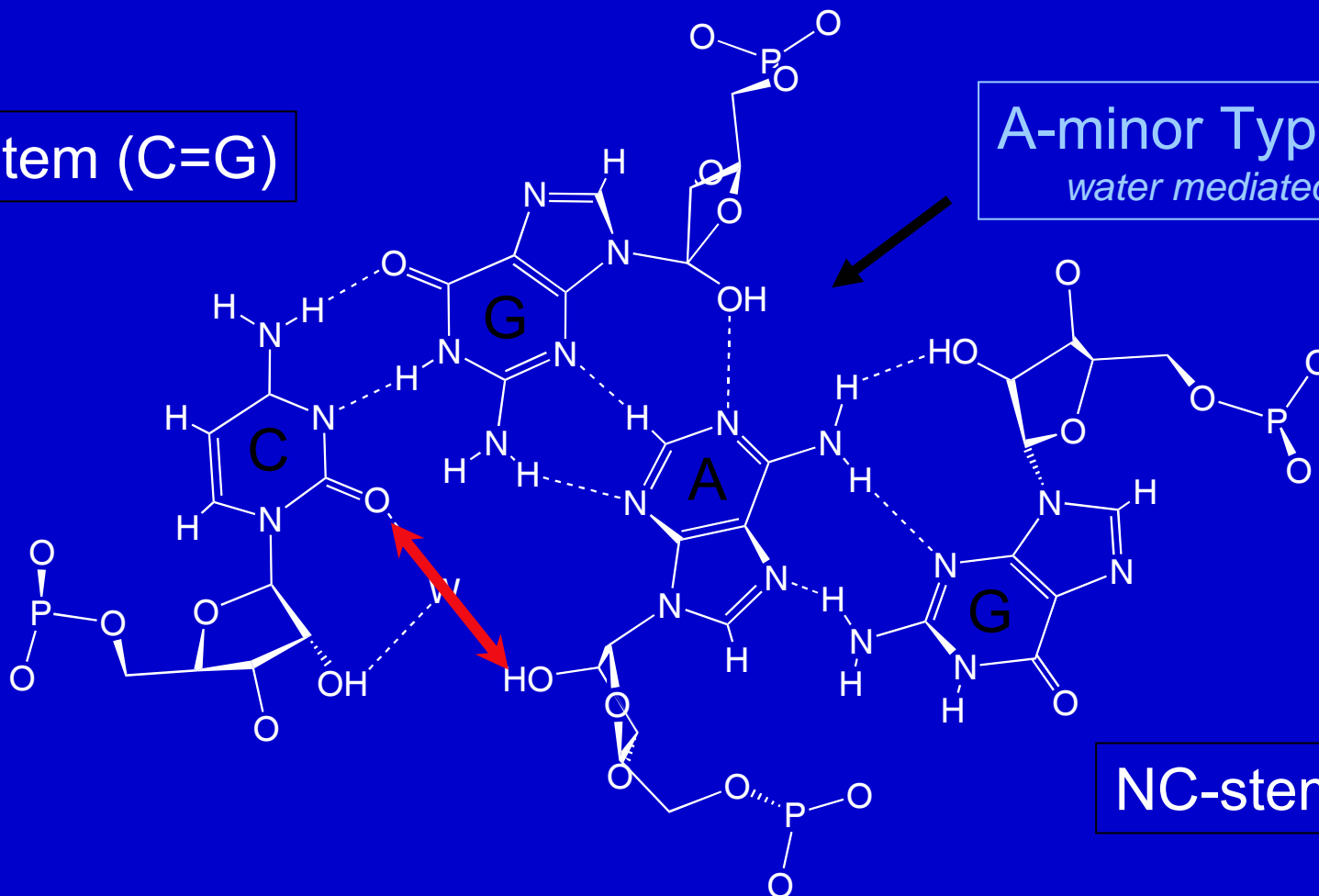
NC-stem (A/G)

Insertion of water molecules into this A/C pair regulates the global motion of Kt-38 and Kt-42

Dynamics of A-minor submotif

C-stem (C=G)

A-minor Type I
water mediated



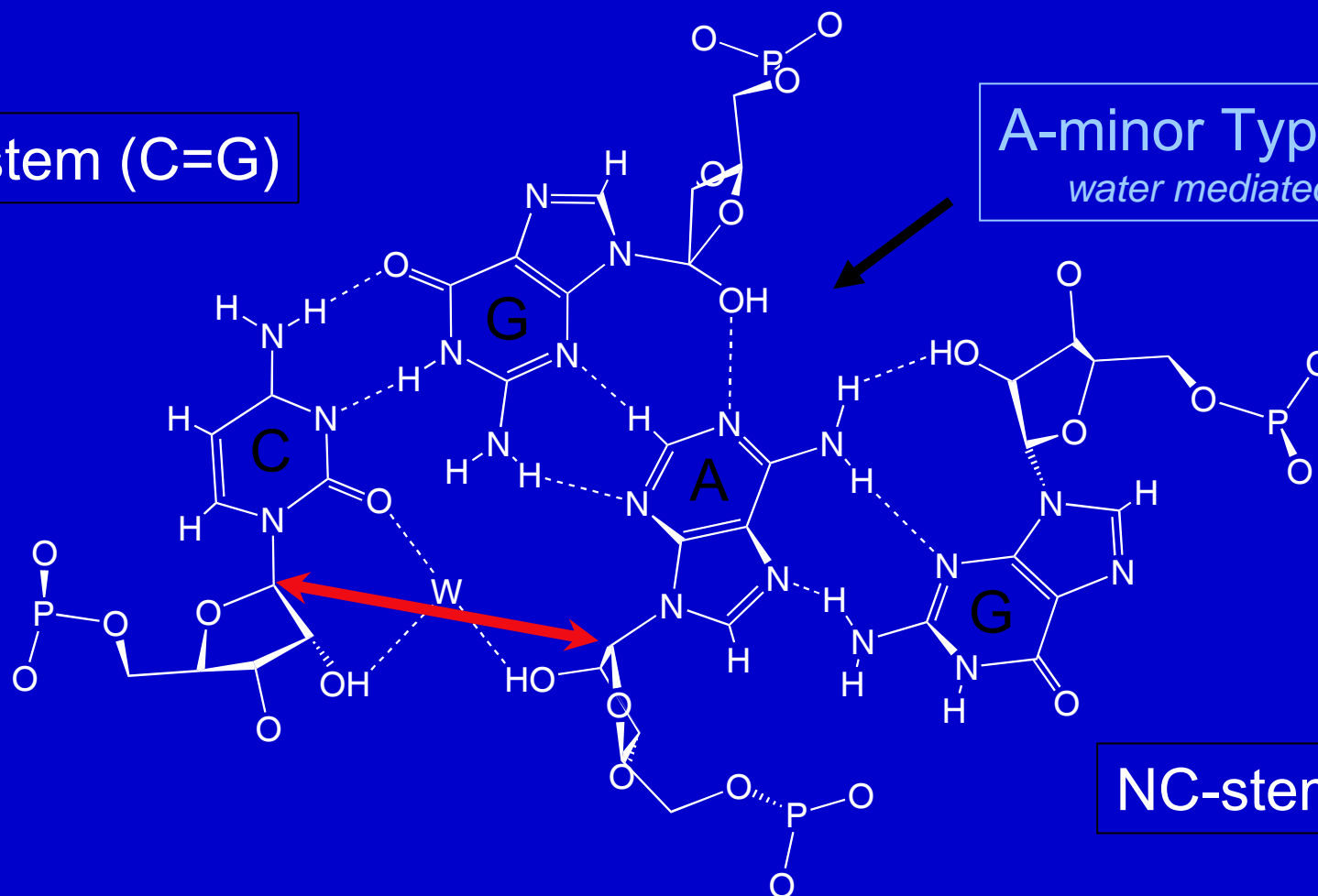
NC-stem (A/G)

Insertion of water molecules into this A/C pair regulates the global motion of Kt-38 and Kt-42

Dynamics of A-minor submotif

C-stem (C=G)

A-minor Type I
water mediated

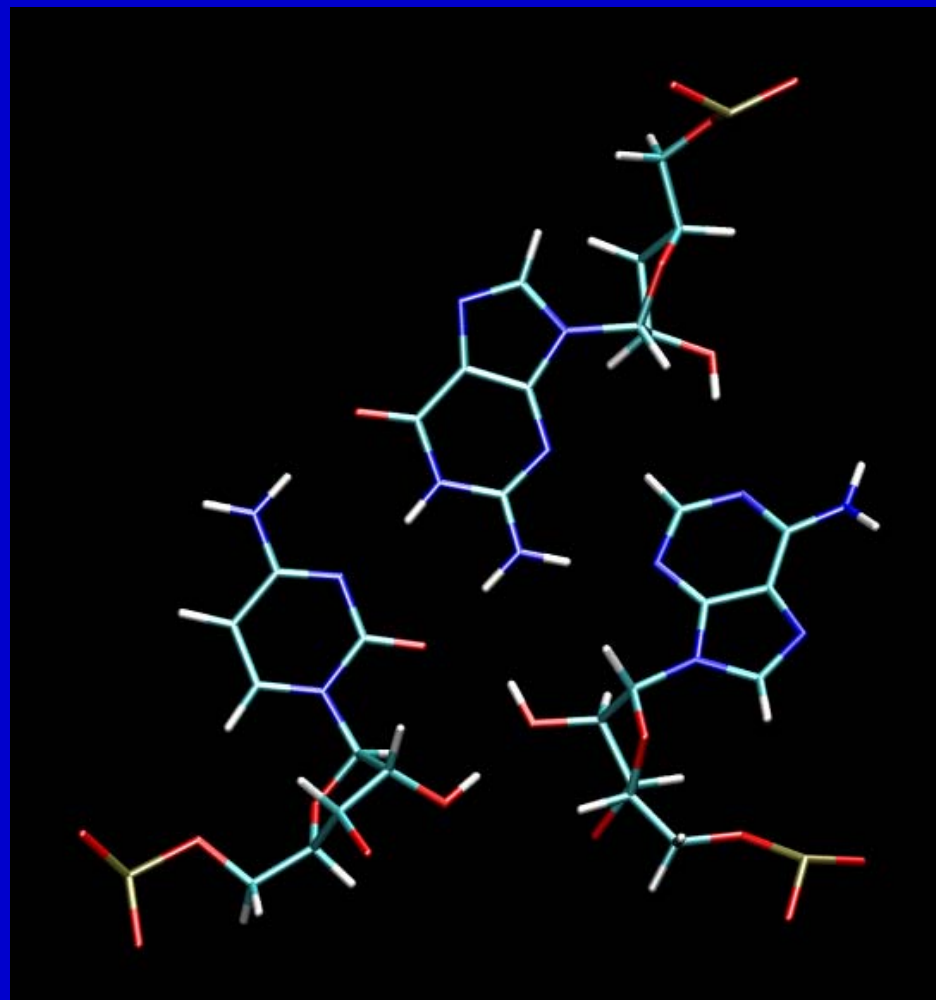


NC-stem (A/G)

Insertion of water molecules into this A/C pair regulates the global motion of Kt-38 and Kt-42

Dynamics of A-minor type I

Closed

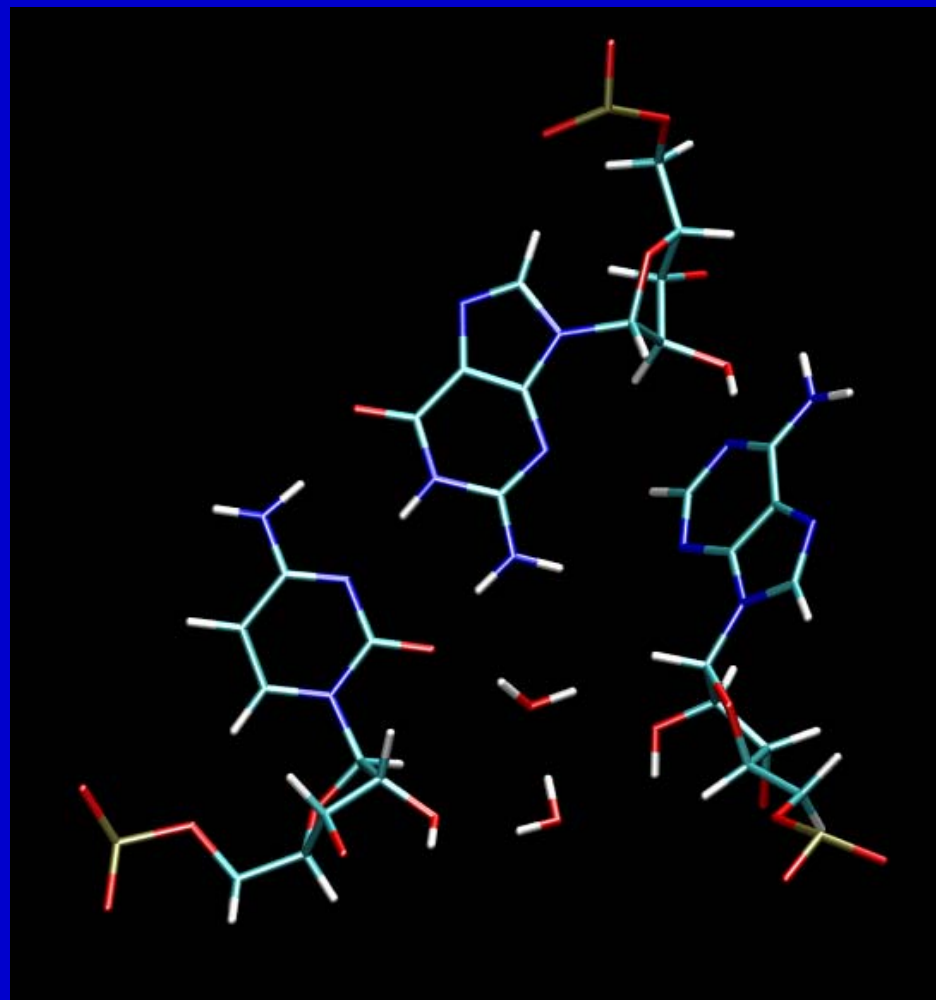


Closed substate: direct H-bonds between A/C (Kt-42 in crystal)

Open substate: water molecule inserted between A/C (Kt-38 in crystal)

Dynamics of A-minor type I

Open

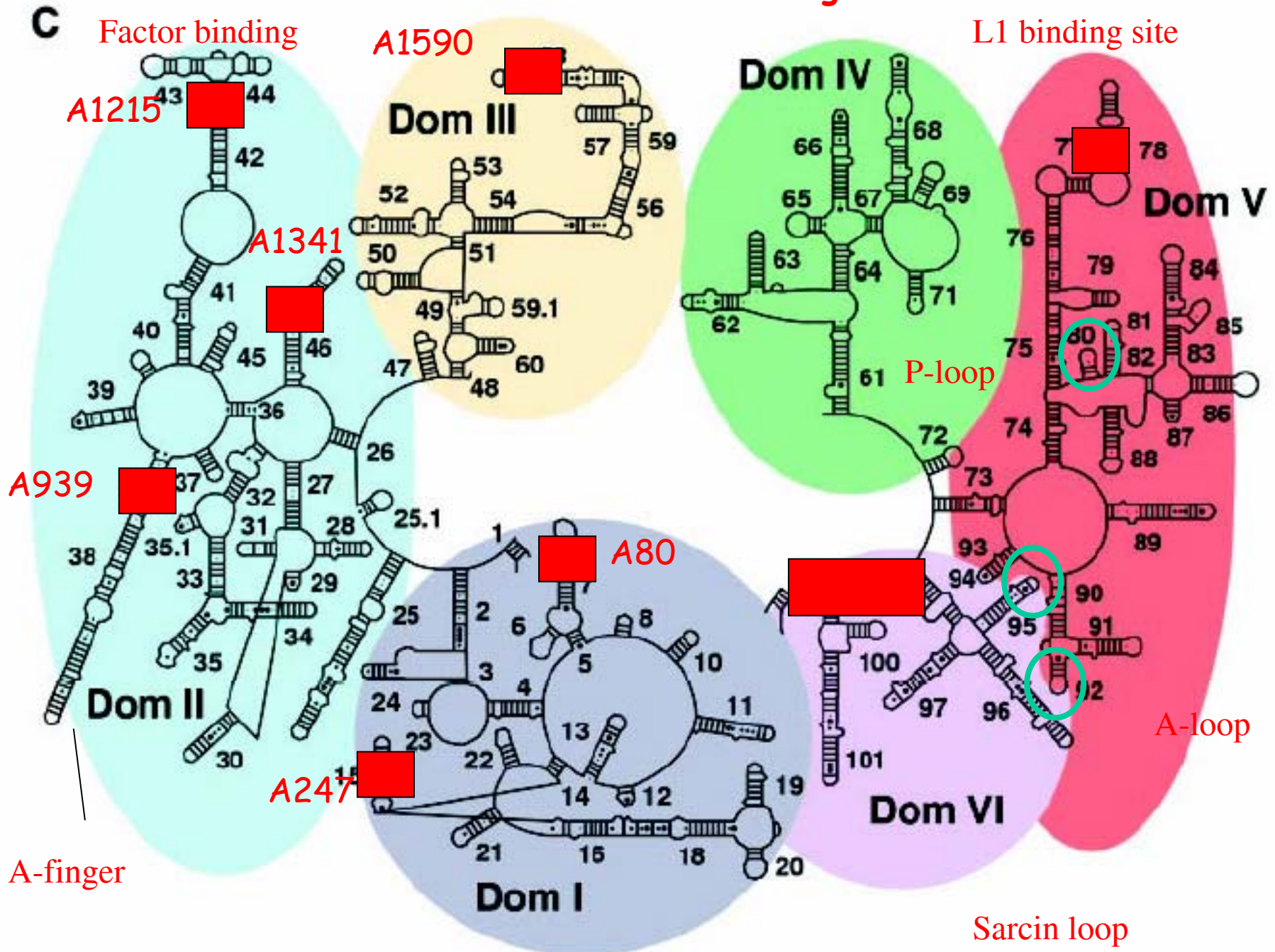


Closed substate: direct H-bonds between A/C (Kt-42 in crystal)

Open substate: water molecule inserted between A/C (Kt-38 in crystal)

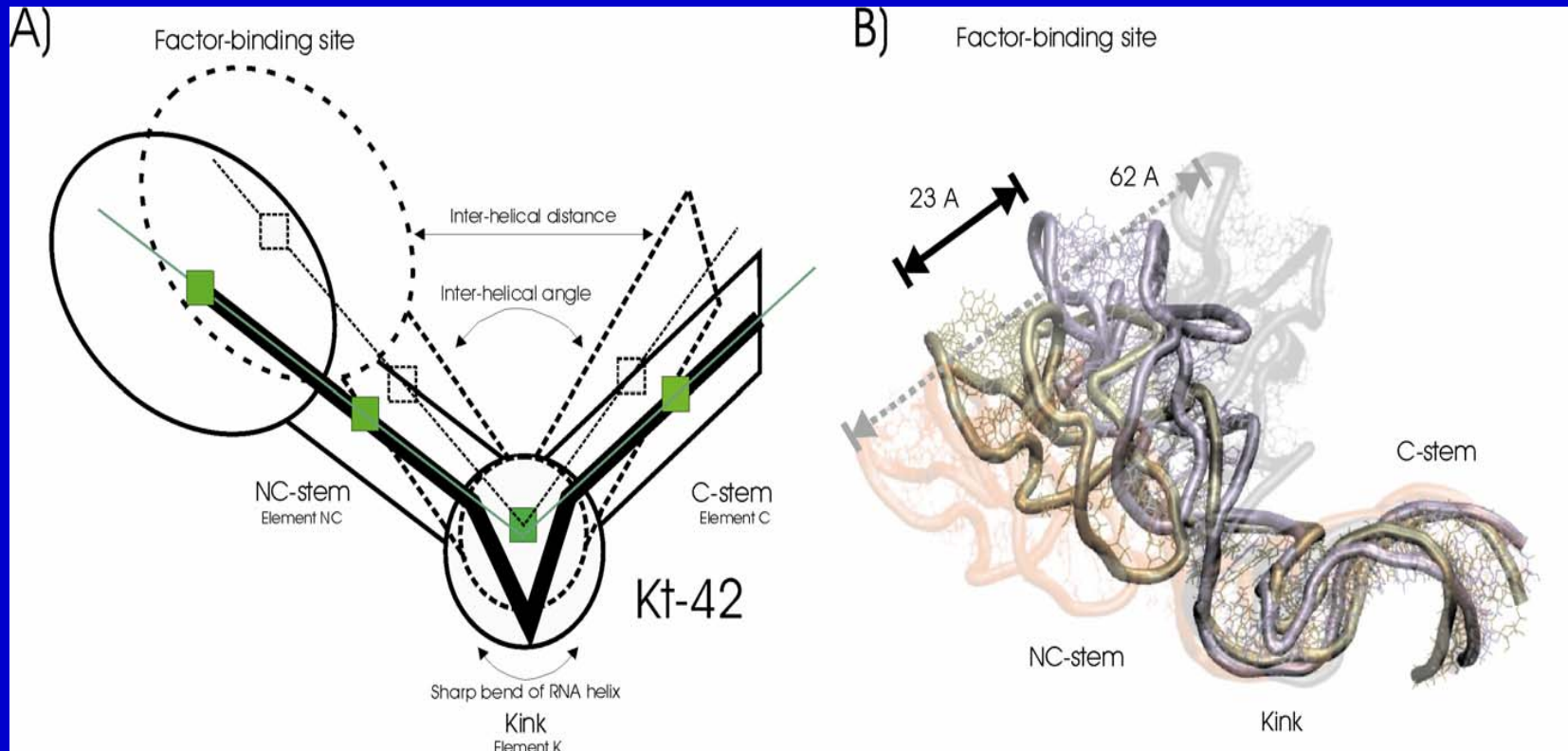
K-turny jsou flexibilní klouby, které mohou umožnit dynamické pohyby v ribosomu během proteosyntézy.

K-turns in 23S rRNA of the large subunit

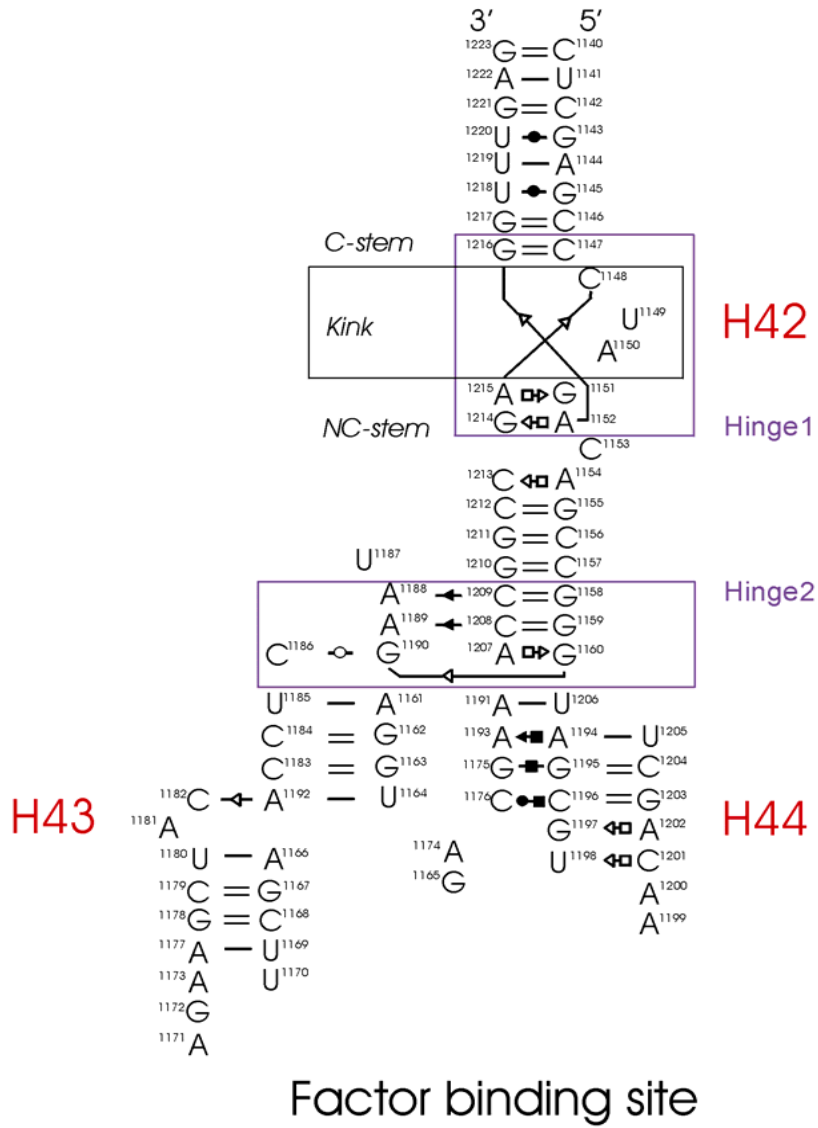


MD simulation of the factor binding site

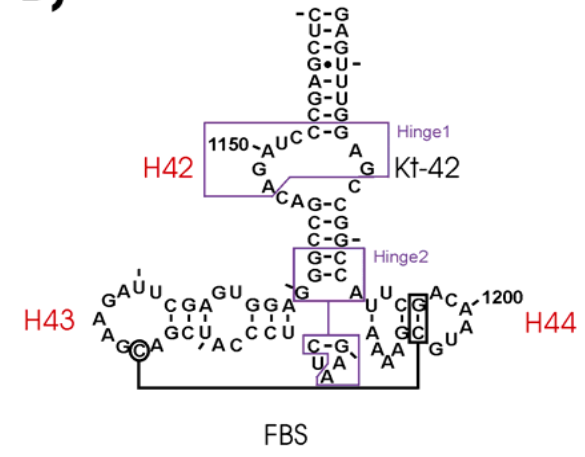
Kt-42 dynamics propagates to large-scale motions of the whole factor-binding site



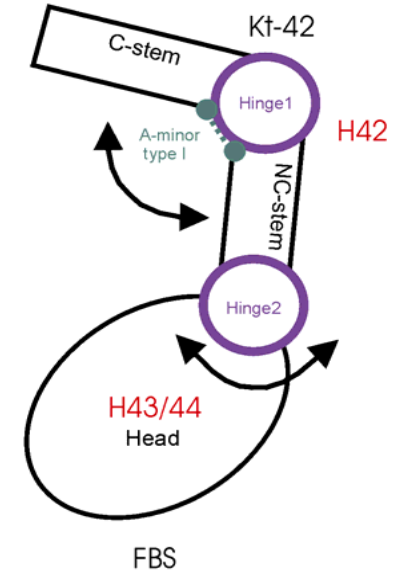
A)

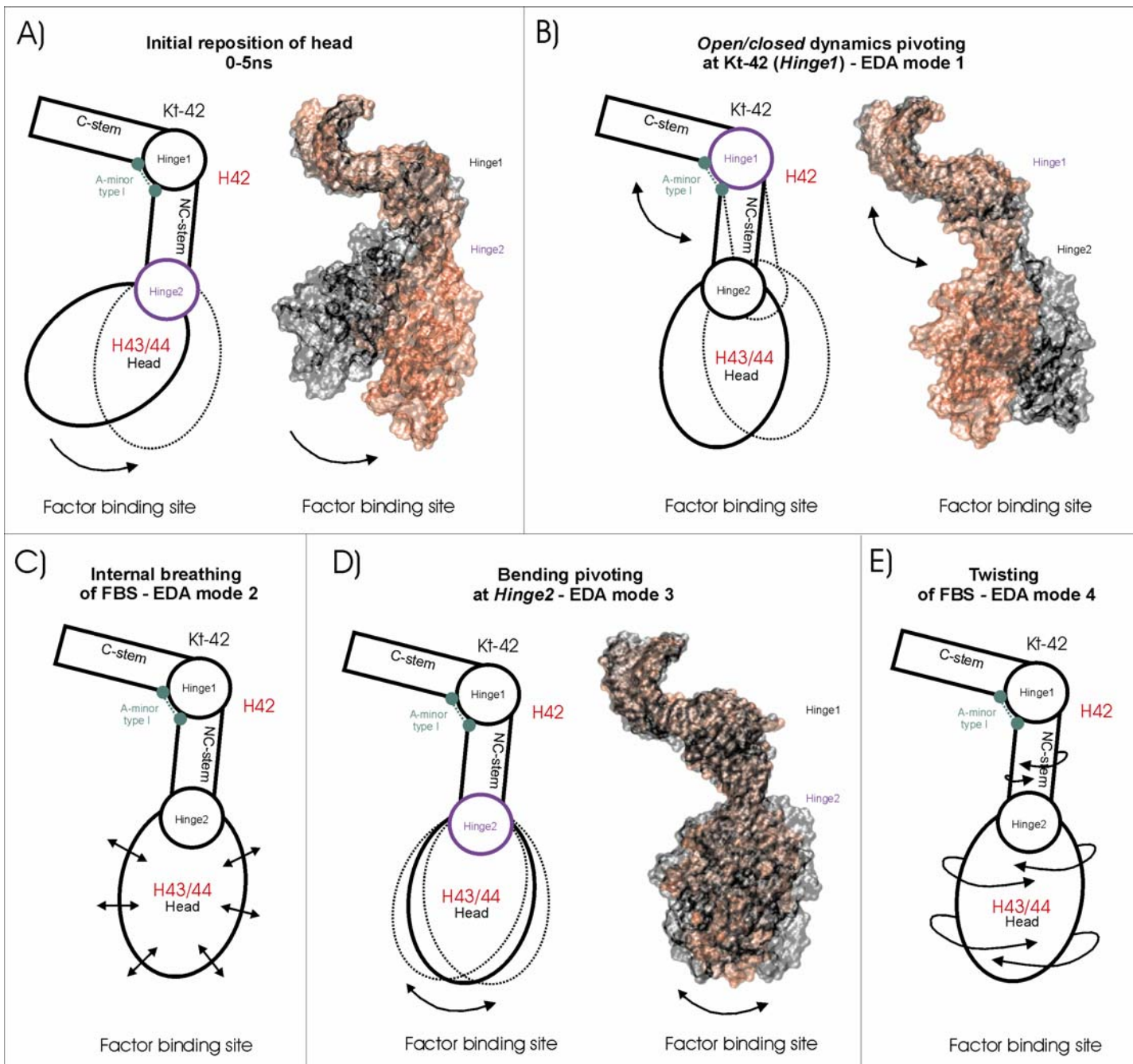


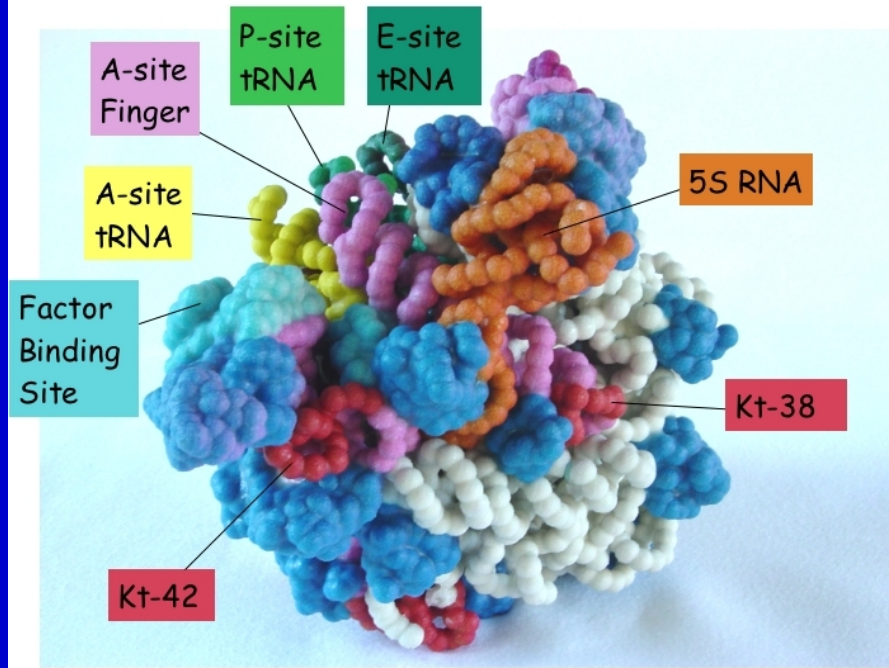
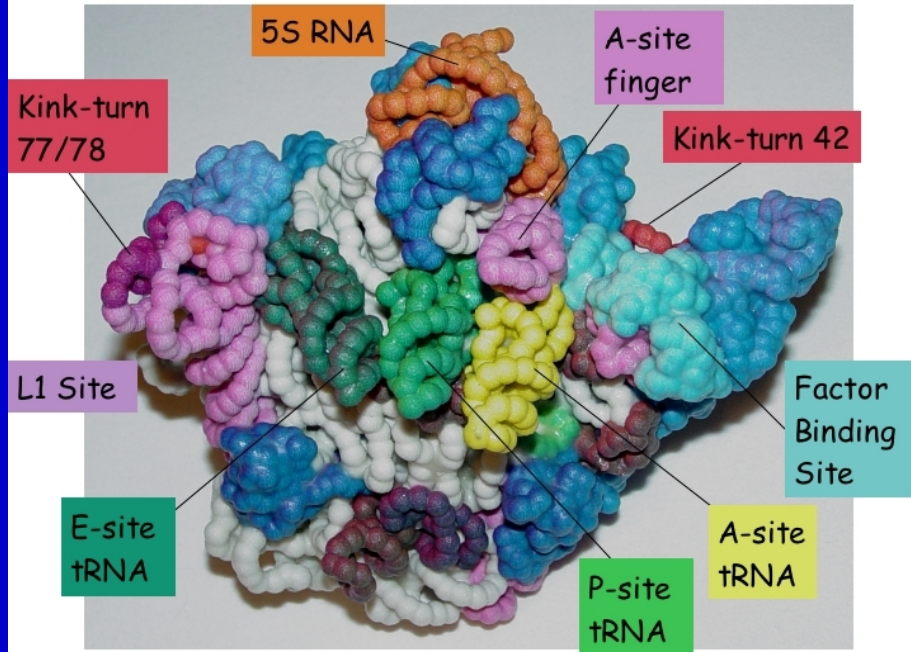
B)



C)



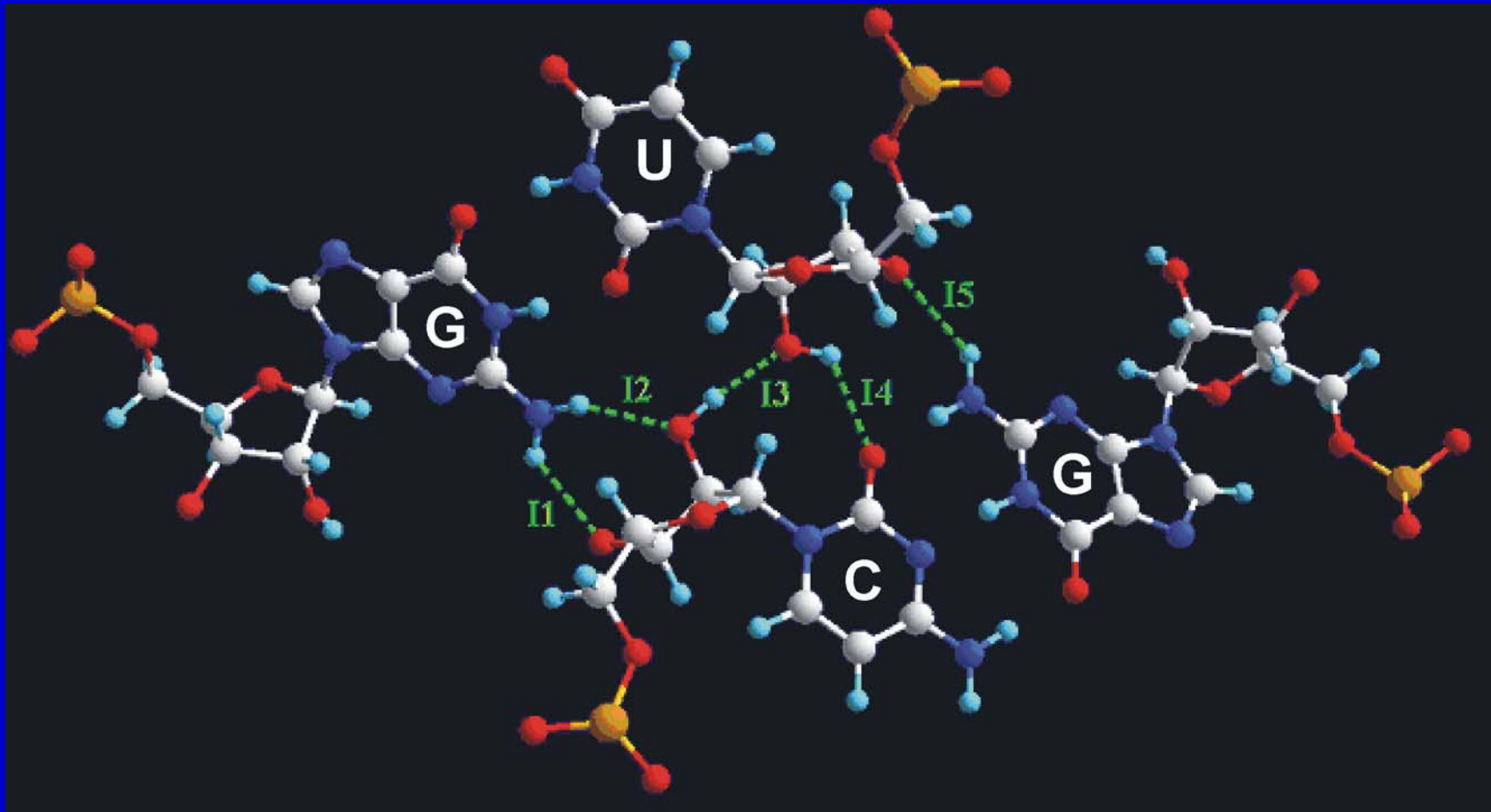




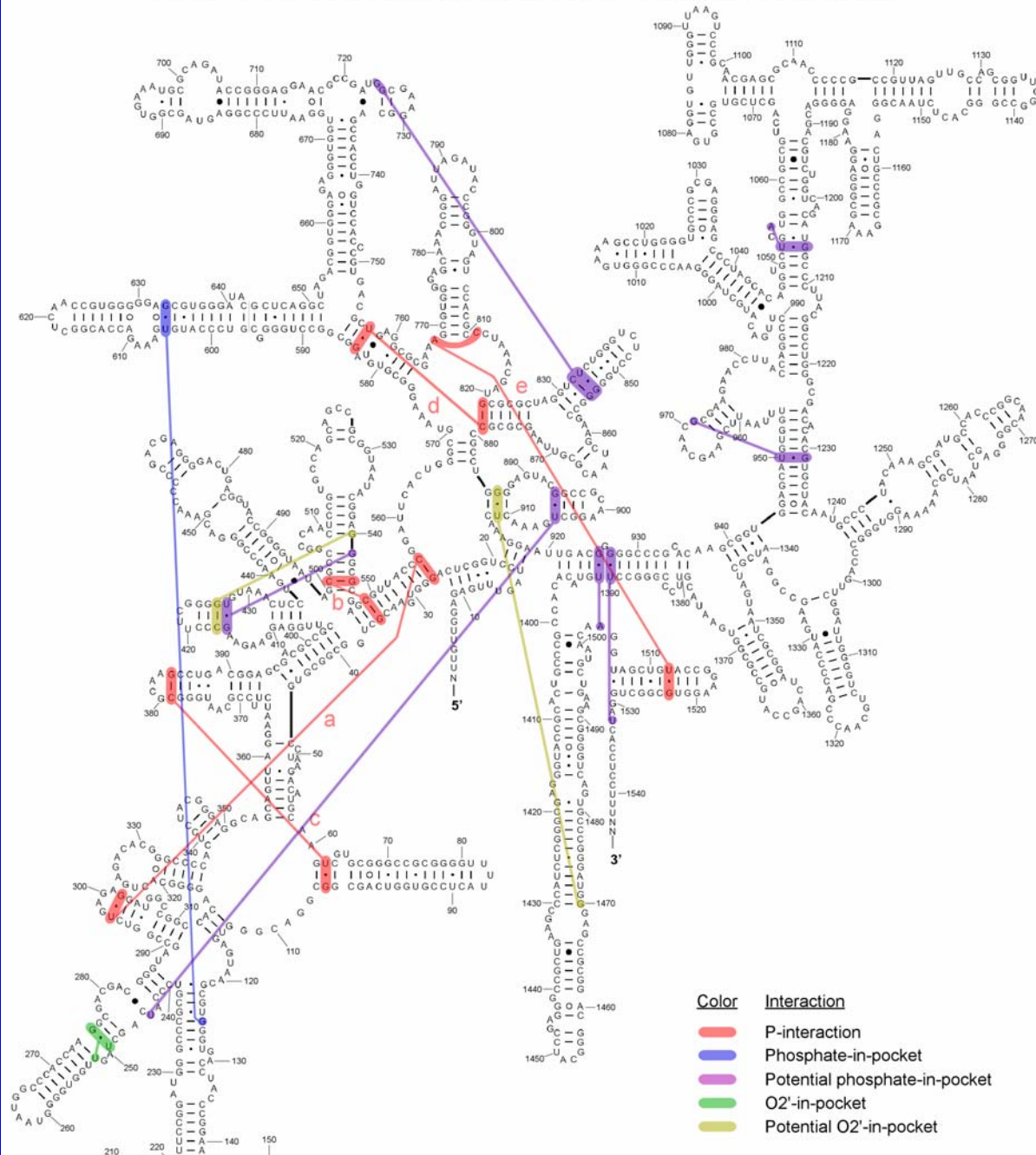
Princip isostericity – diktatura 3D struktury nad sekvencí

Pokud dojde k takové isosterické mutaci, která umožní vytvořit pár bází stejného tvaru jako byl pár původní, tak tato mutace většinou zachovává funkci a je dovolená.

P – interaction – ribose zipper type of interaction that brings together a GU wobble from one helix and GC canonical pair from another helix.

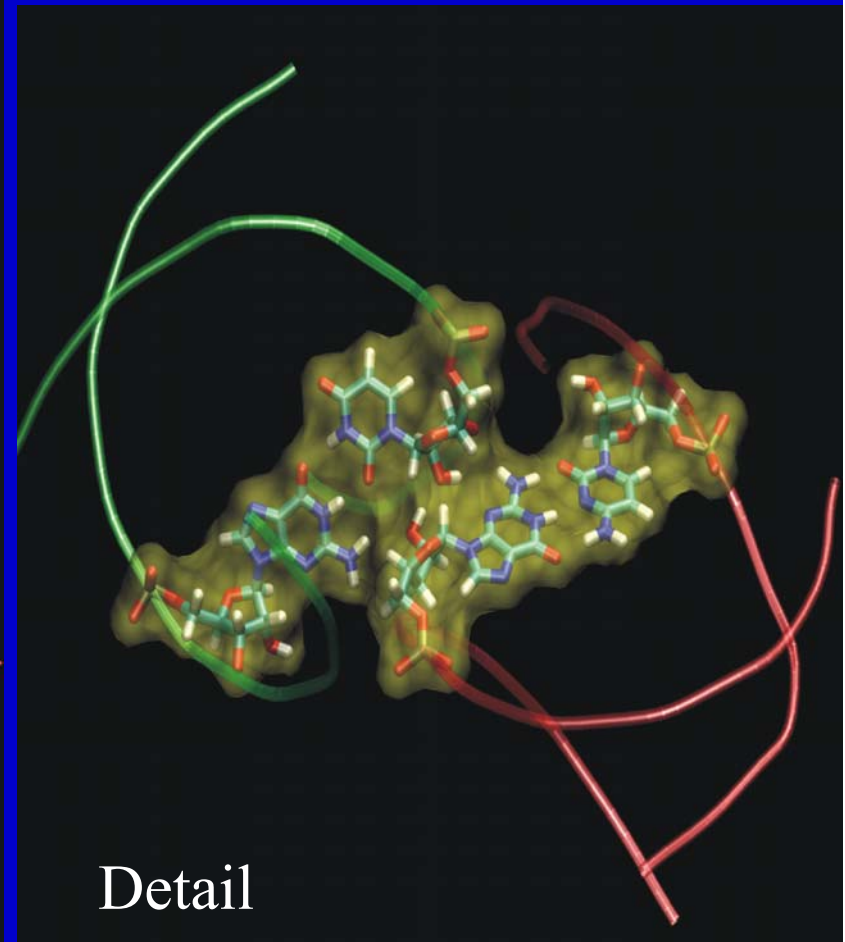
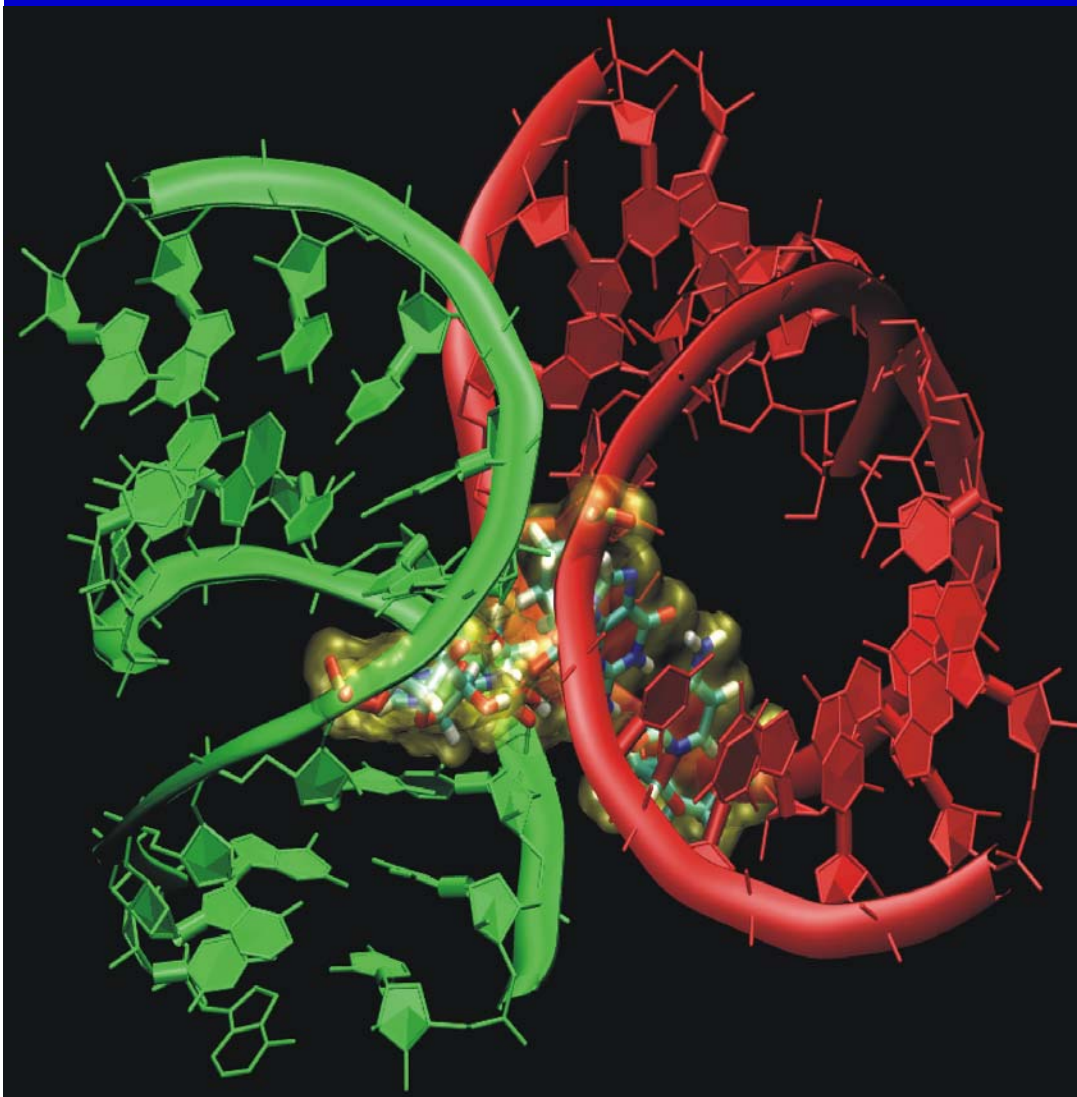


Shallow groove pocket interactions (or potential interactions) in
Thermus thermophilus 16S rRNA (numbers are based on *Escherichia coli*)

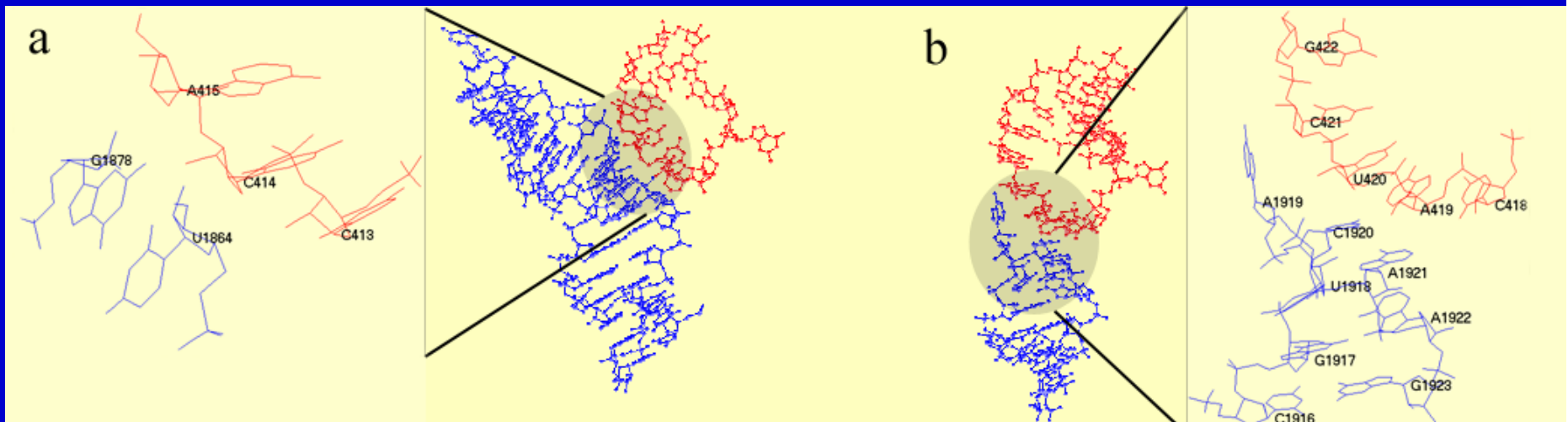


P-interaction, a unique ribosomal quartet interaction that causes an unprecedented simultaneous **covariation of four bases in the genom**:

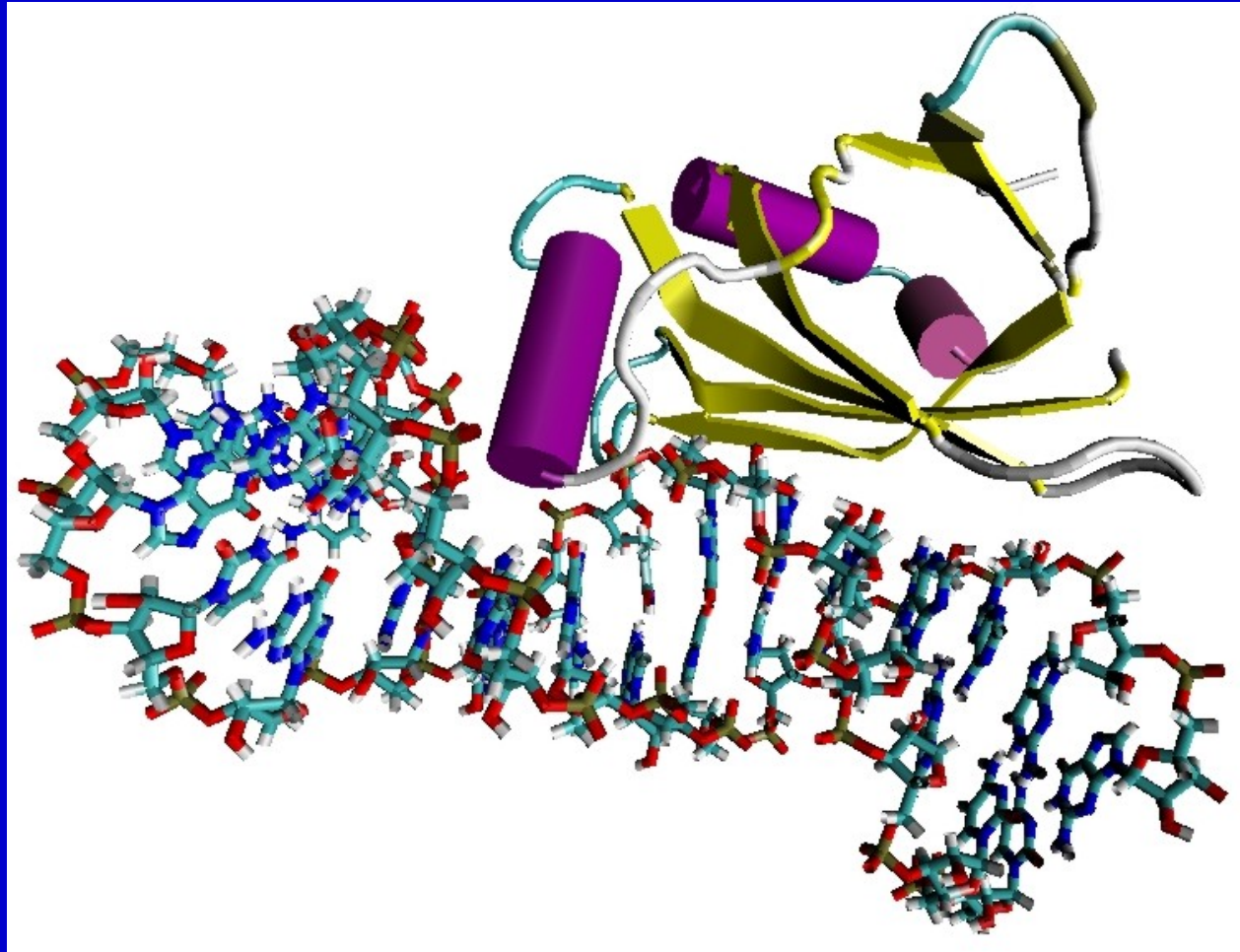
-GU-...-CG- mutates to **-GC-...-UG-**



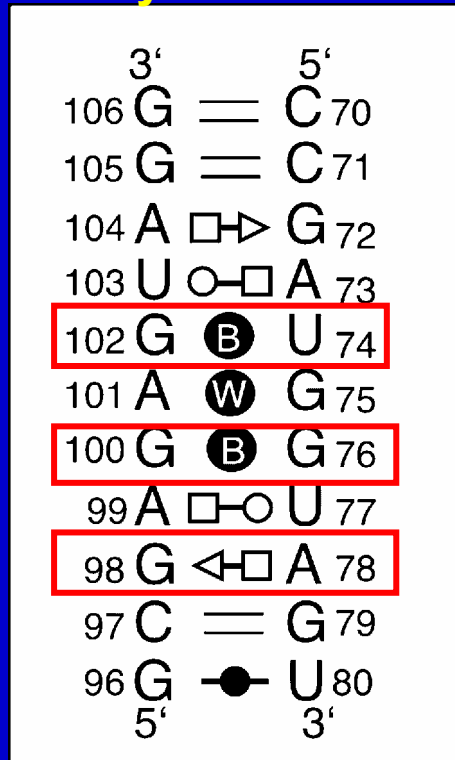
Motif swap – helix v jednom ribosomu je evolucí
zaměněn za smyčku, ale lokální kontakt se
nezmění.



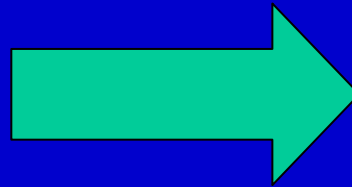
E coli loop E/Helix IV RNA - protein L25 complex.
Loop E is a rigid RNA docking segment with unique metal binding capability. 7 consecutive non-WC pairs!



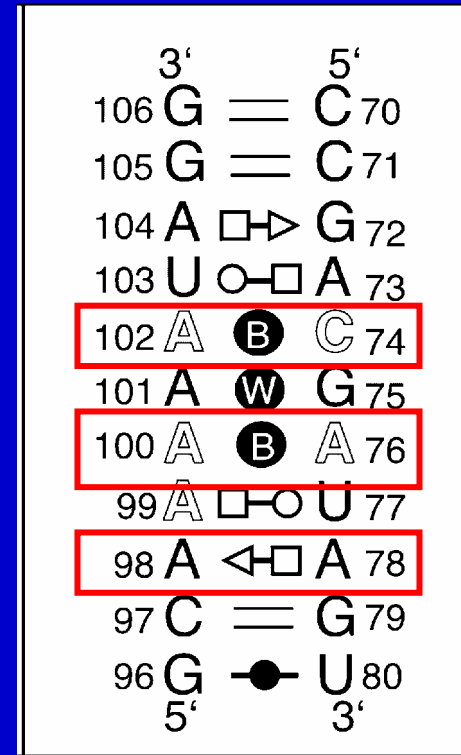
Bacterial Loop E X-ray structure



?



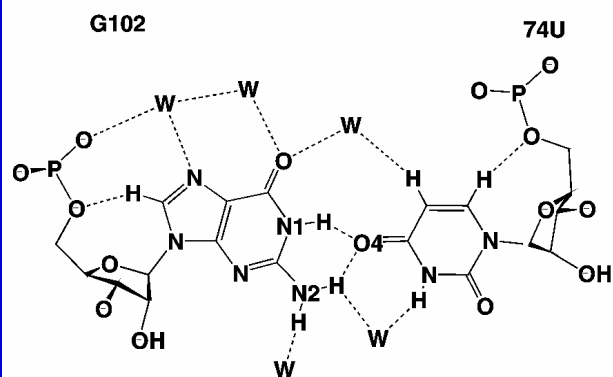
Spinach Chloroplast Hypothetical structure - isosteric pairing



Circles - Watson-Crick edges, squares - Hoogsteen edges, triangles – Sugar edges. Open symbols represent *trans* and filled symbols *cis* base pairs.

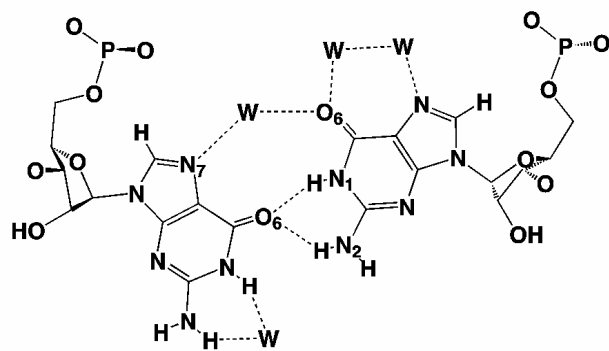
B indicates *cis* bifurcated pairs and W water-inserted pairs

Bacterial Loop E



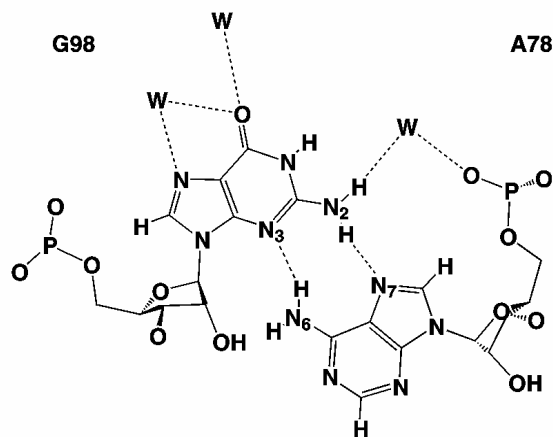
G100

G76

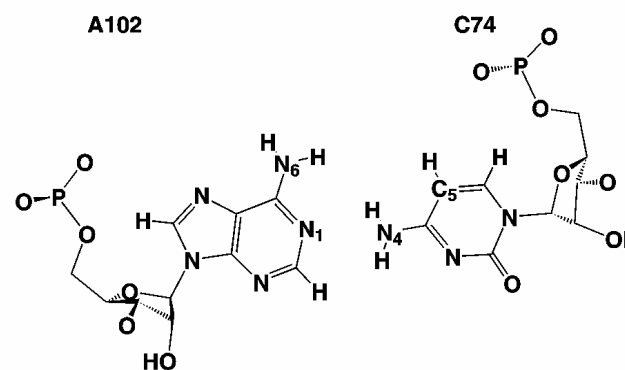


G98

A78

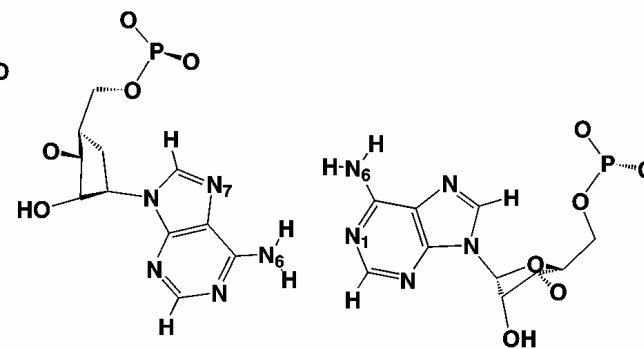


Chloroplast Loop E



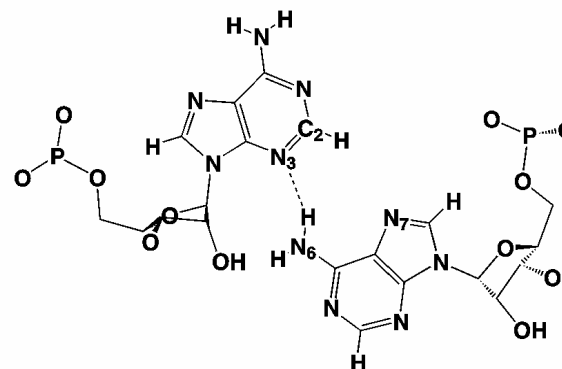
A100

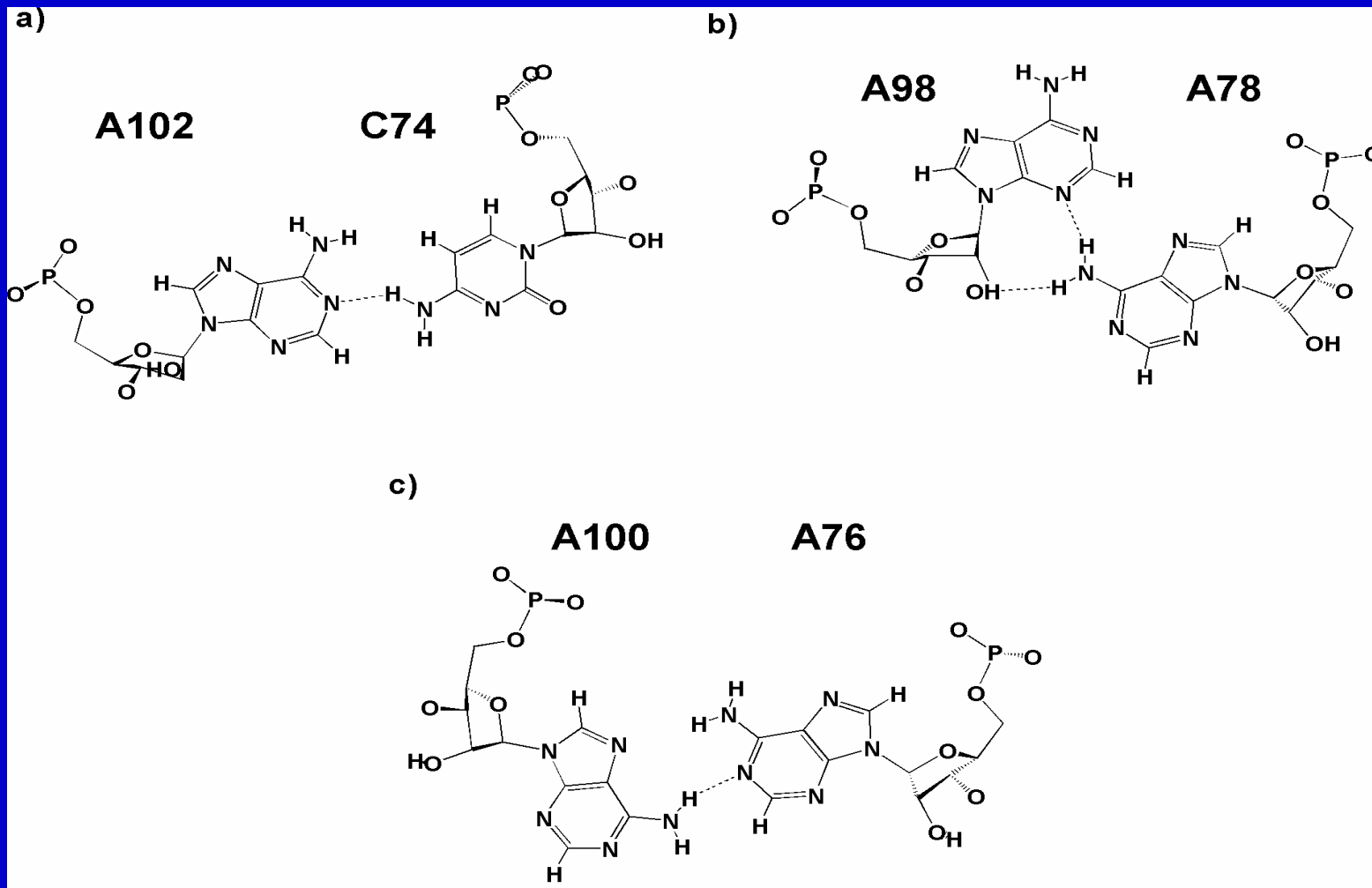
A76



A98

A78



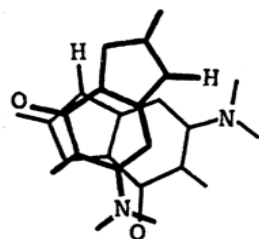


Average geometries new base pairs in chloroplast Loop E that differ from the consensus bacterial Loop E. (a) Bifurcated A102/C74, (b) A98/A78 and (c) A100/A76.

Pokročilé kvantově-chemické metody

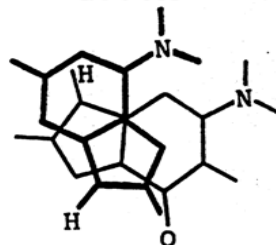
Cíl – přesné výpočty malých systémů, referenční, fyzikálně kompletní metoda. Přímý vztah mezi strukturou a energií.

G...G



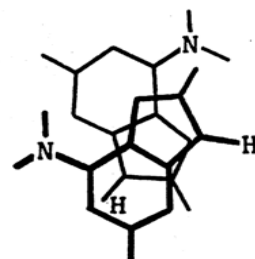
-11.3

G...A



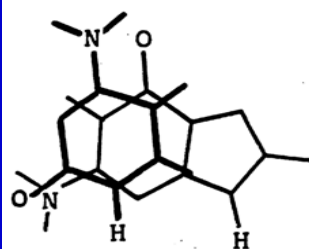
-11.2

A...A



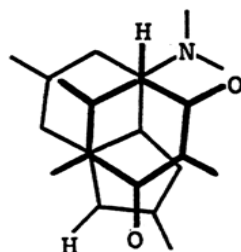
-8.8

G...C



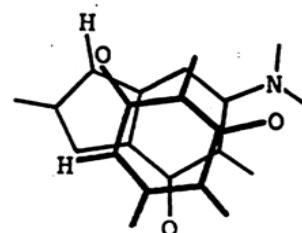
-9.3

A...U



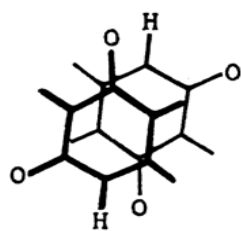
-9.1

G...U



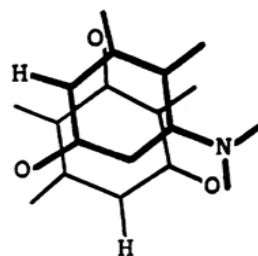
-10.6

U...U



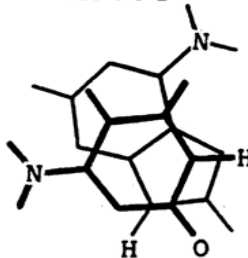
-6.5

C...U



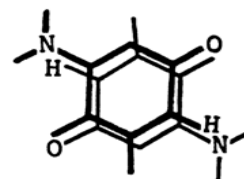
-8.5

A...C



-9.5

C...C



-8.3

Interakční energie

$$\Delta E^{A,B} = E^{A,B} - E^A - E^B$$

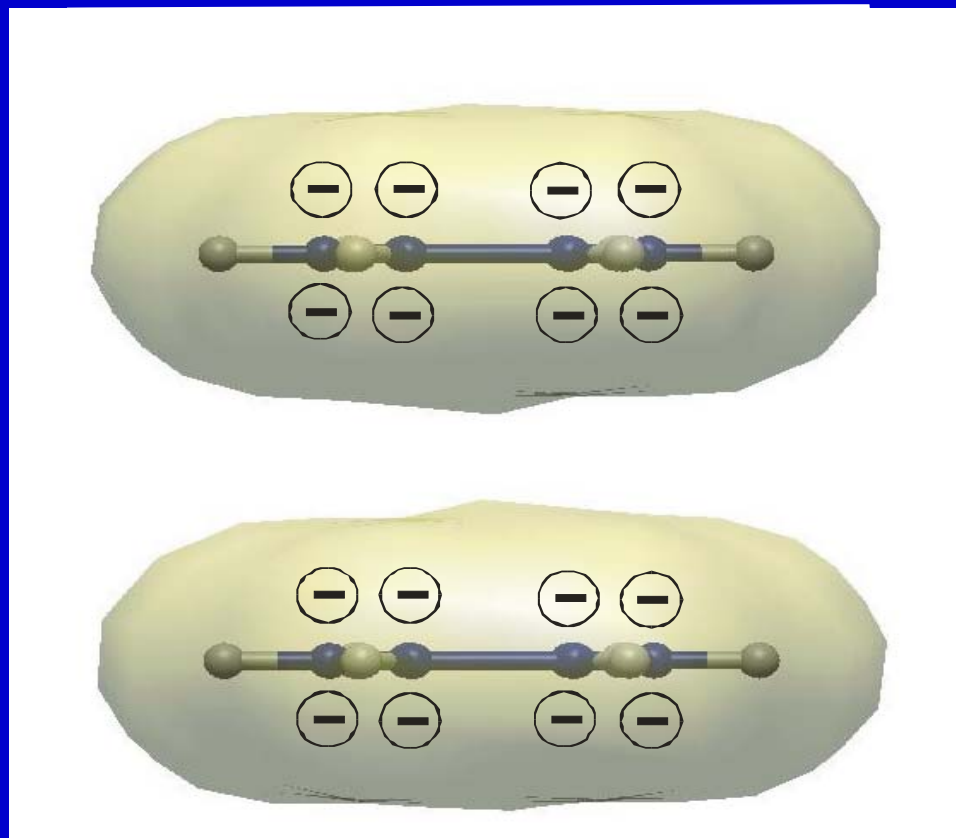
O fyzikálním původu vertikálních interakcí bází

Base stacking je překvapivě jednoduchou kombinací Londonovy dispersní energie, krátkodosahové repulse, a běžné elektrostatiky. Nic jiného podstatného tam není.

Specifické "aromatické" příspěvky byly vyloučeny.

π - π MODEL – tak takhle našťestí ne

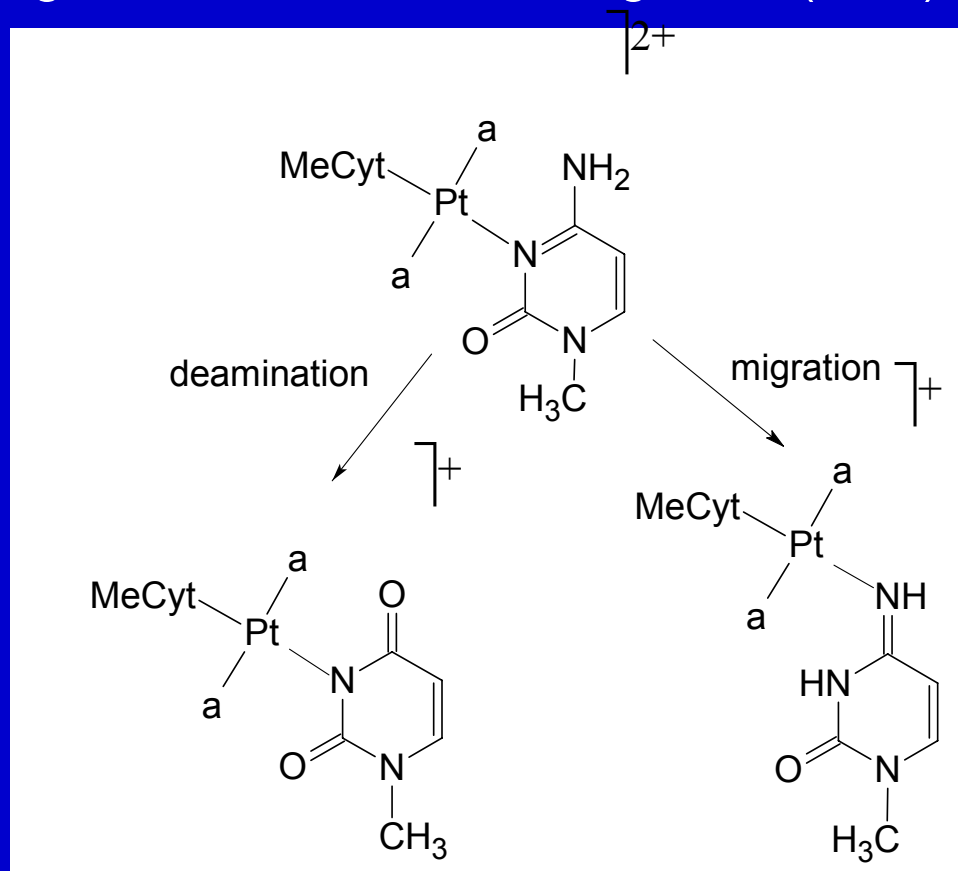
Out-of-plane $\pi \cdots \pi$ interactions **DO NOT** exist!



Deamination of cytosine to uracil

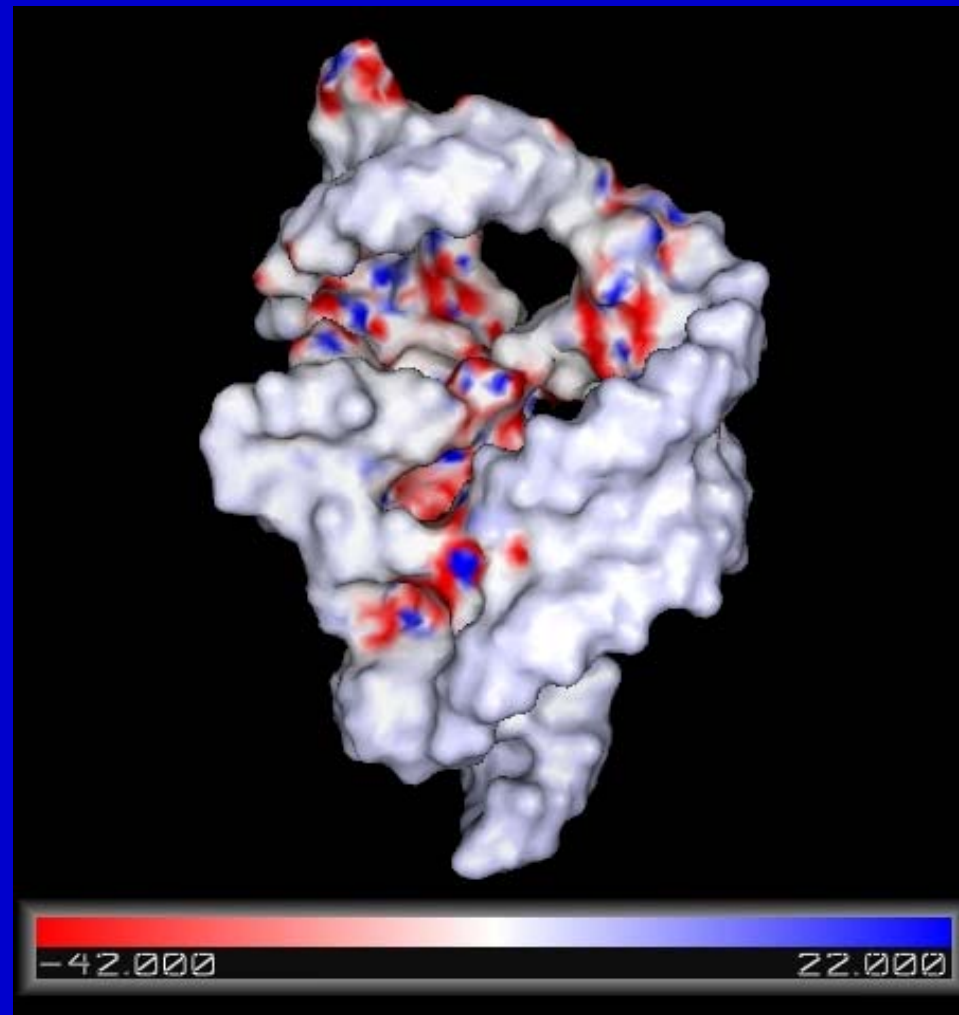
In N3-platinated cytosines the deamination is the decisive scenario (73%)

Competing reaction – 1,4-metal migration (27%)

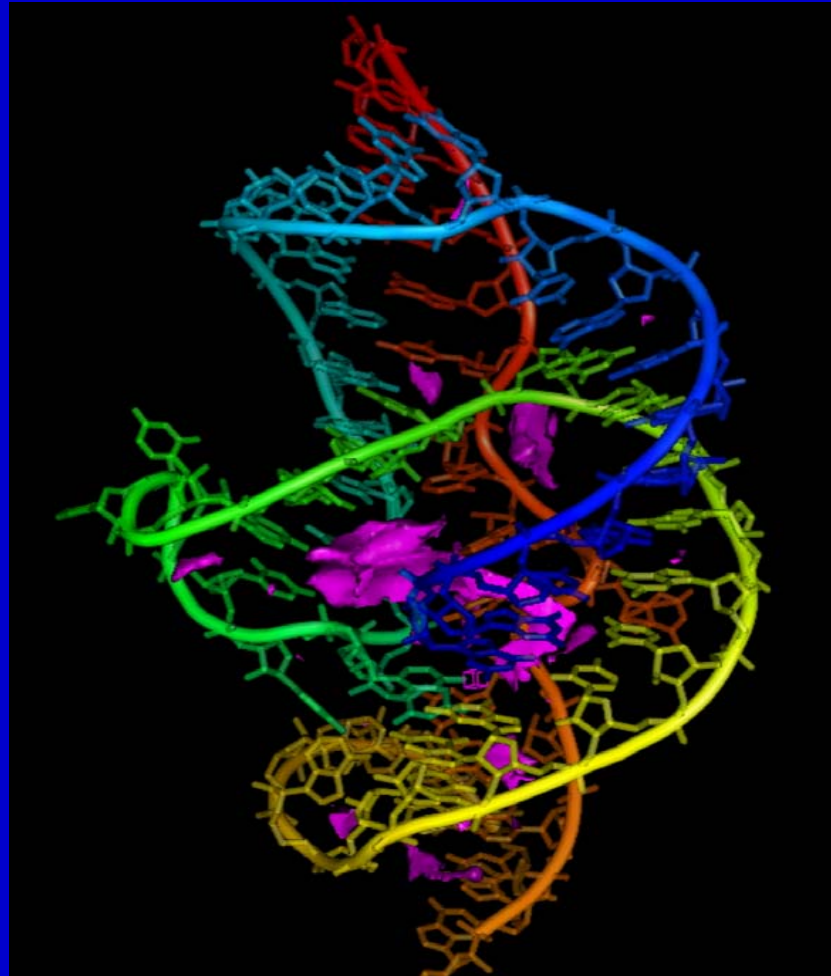


Potřeba hybridních kvantově-
chemických molekulárně
mechanických metod – katalýza
RNA.

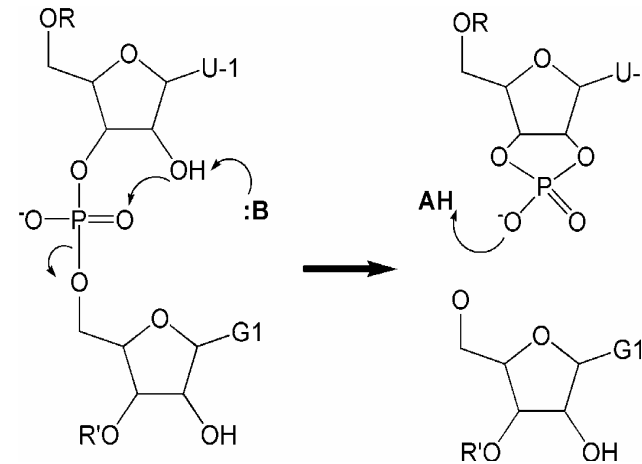
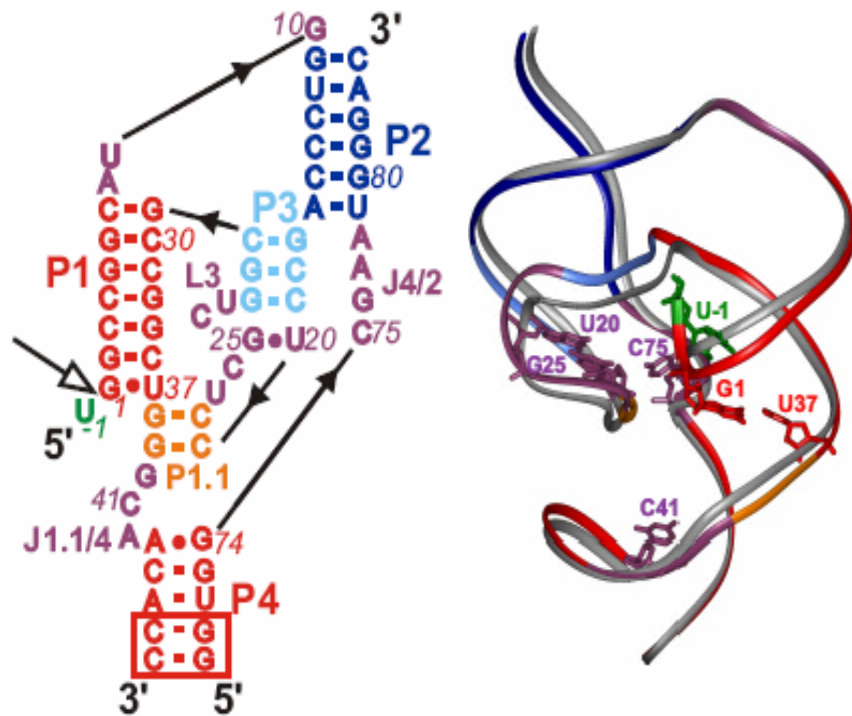
Hepatitis Delta Virus ribozyme Surface electrostatic potential



HDV ribozyme



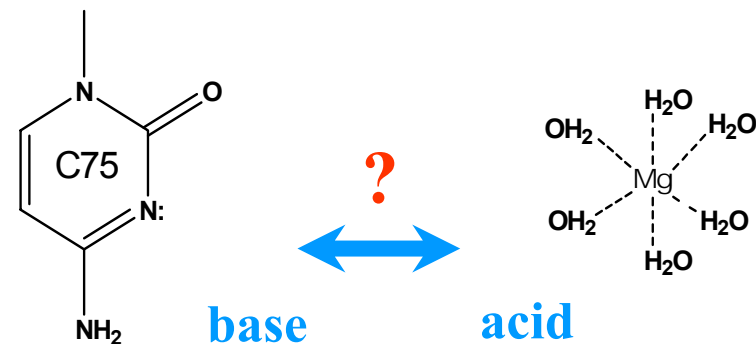
Introduction



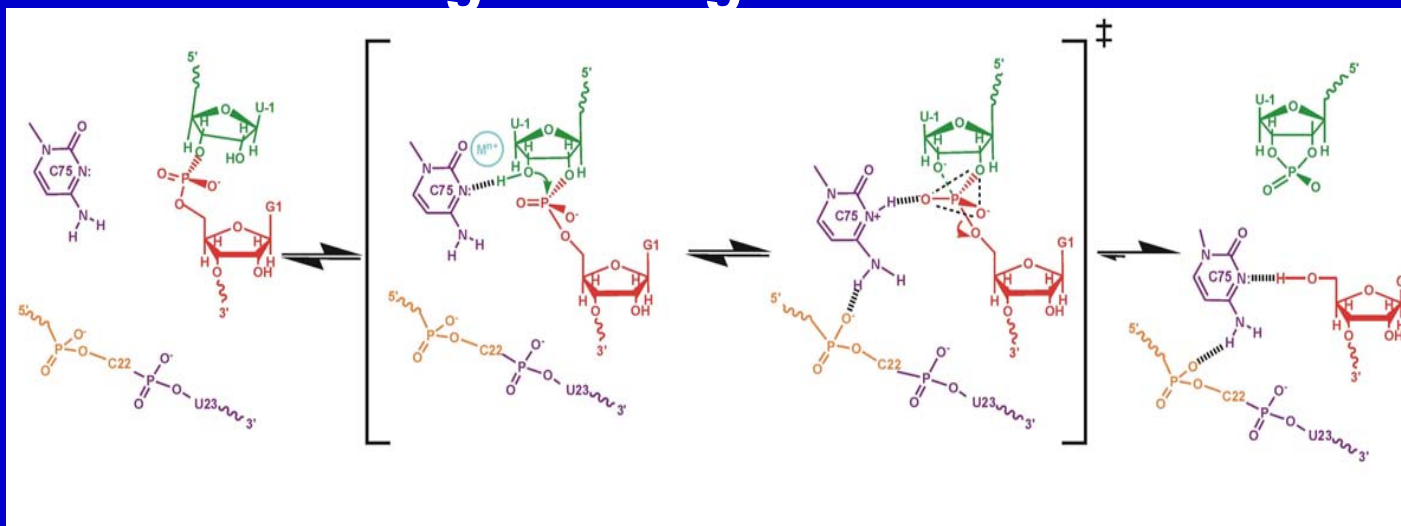
The self-cleavage reaction catalyzed by HDV ribozyme is a transesterification reaction. Based on experimental data, general acid-base catalysis is suggested with either Mg^{2+} or C75 being general base or acid.

Secondary structure

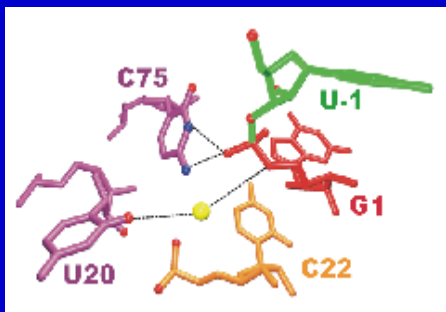
The HDV ribozyme folds into a compact structure comprising five helical segments joined by five strand-crossovers connected as a nested, double pseudoknot. Right -overlay of product (grey) and precursor (colour) x-ray structures.



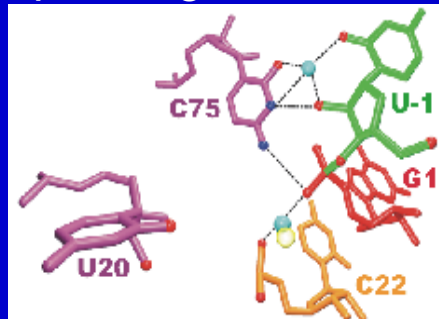
MD simulations are consistent with C75 acting as the general base



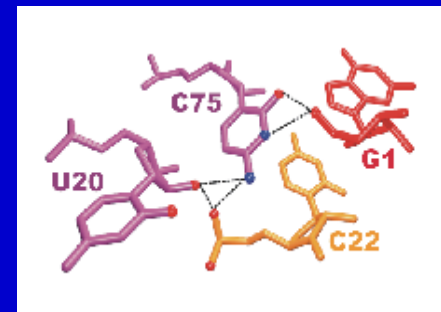
Schematic reaction mechanism (above)
and corresponding stick models (below)



**Precursor
crystal structure**



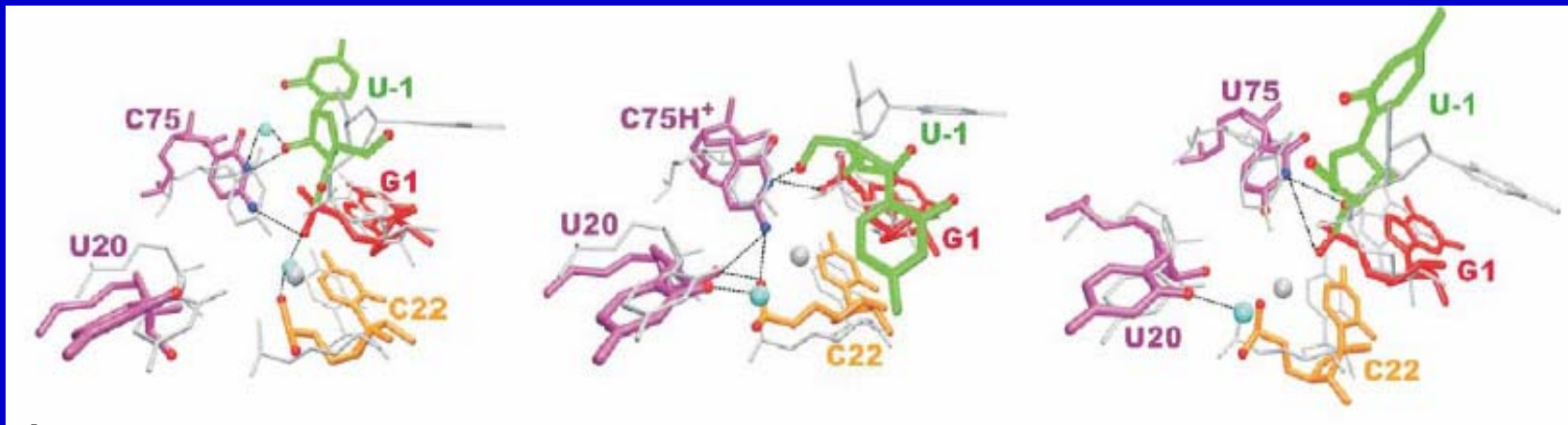
**C75
simulation snapshot**



**Product
crystal structure**

Blue spheres represent Na⁺ cation, yellow sphere represents Mg²⁺ cation

The Active Site of Precursor Ribozyme: Dynamics and Permanent Cation Binding



C75 simulation:
dynamical binding of C75 at the active site with a temporary formation of “transition-state” C75(N3)-U-1(HO2') H-bond.

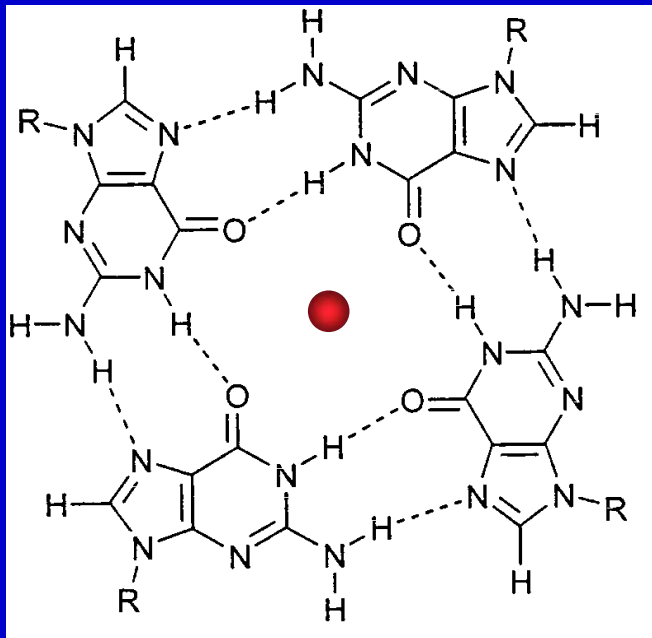
C75+ simulation:
strong product-like binding of C75+ in the active site, inconsistent with C75+ acting as general acid.

U75 simulation:
directly corresponds to the precursor x-ray structure. Very good agreement with the x-ray structure.

Overlay of the precursor crystal structure (grey) and three simulated precursor structures (colour). Blue sphere represents Na⁺ cation.

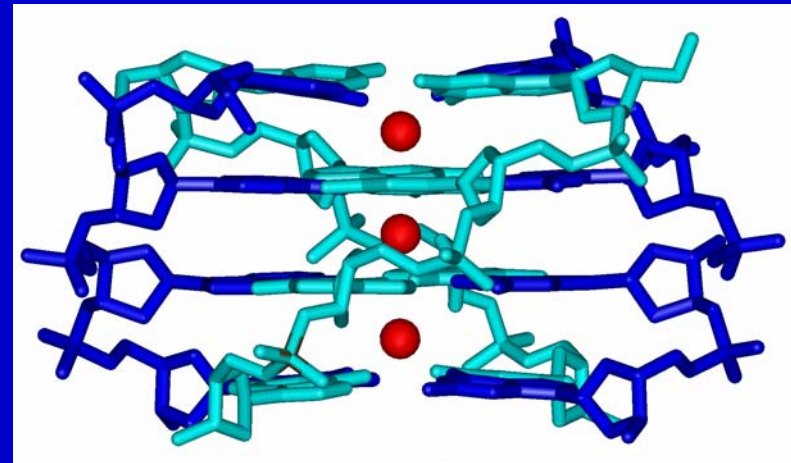
Příklad - Modelování guaninového kvadruplexu

Guanine quadruplex – G-DNA



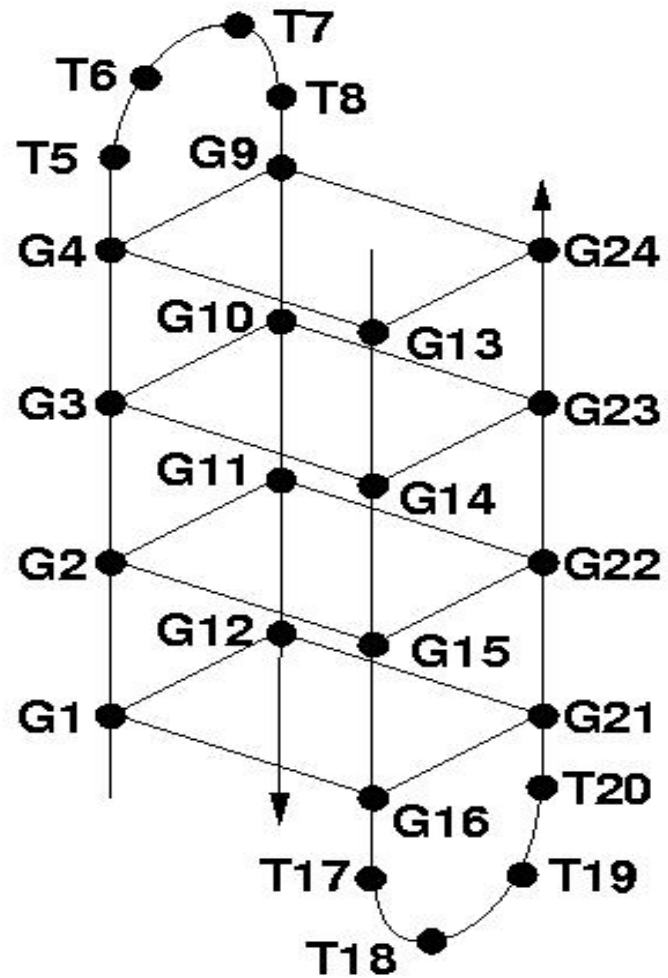
guanine quartet
with cation

$d(\text{GGGG})_4$



guanine quadruplex with a
fully occupied central channel

G-DNA loops

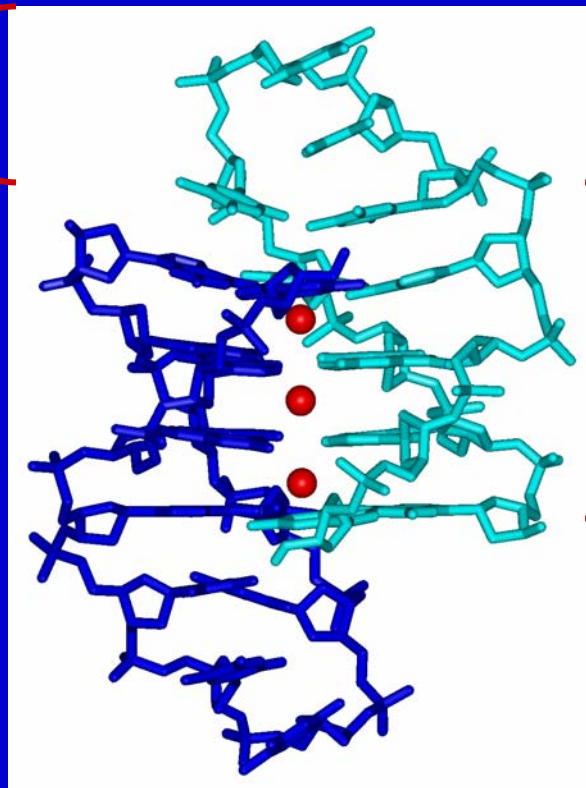


Guanine quadruplexes – a unique combination of mechanical rigidity (stem) and flexibility (loops)

thymidine loops



high flexibility



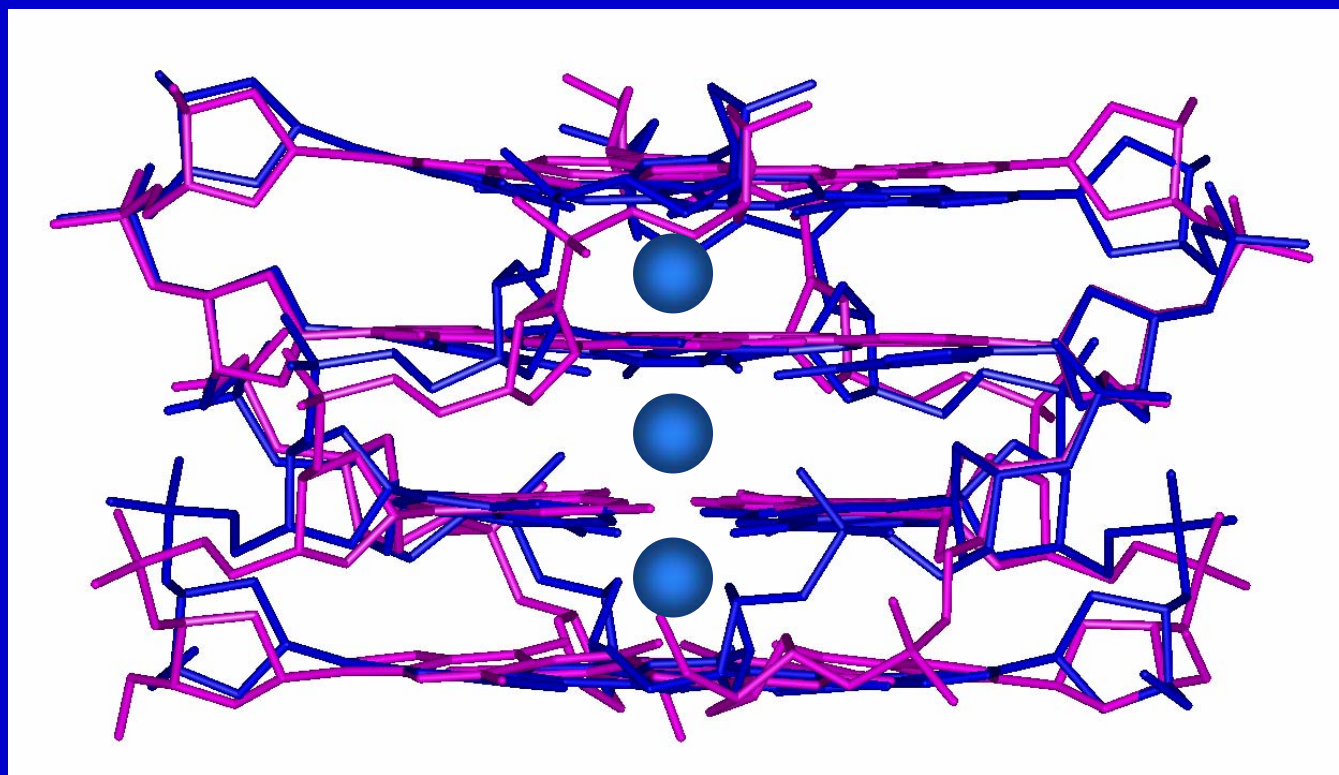
guanine stem



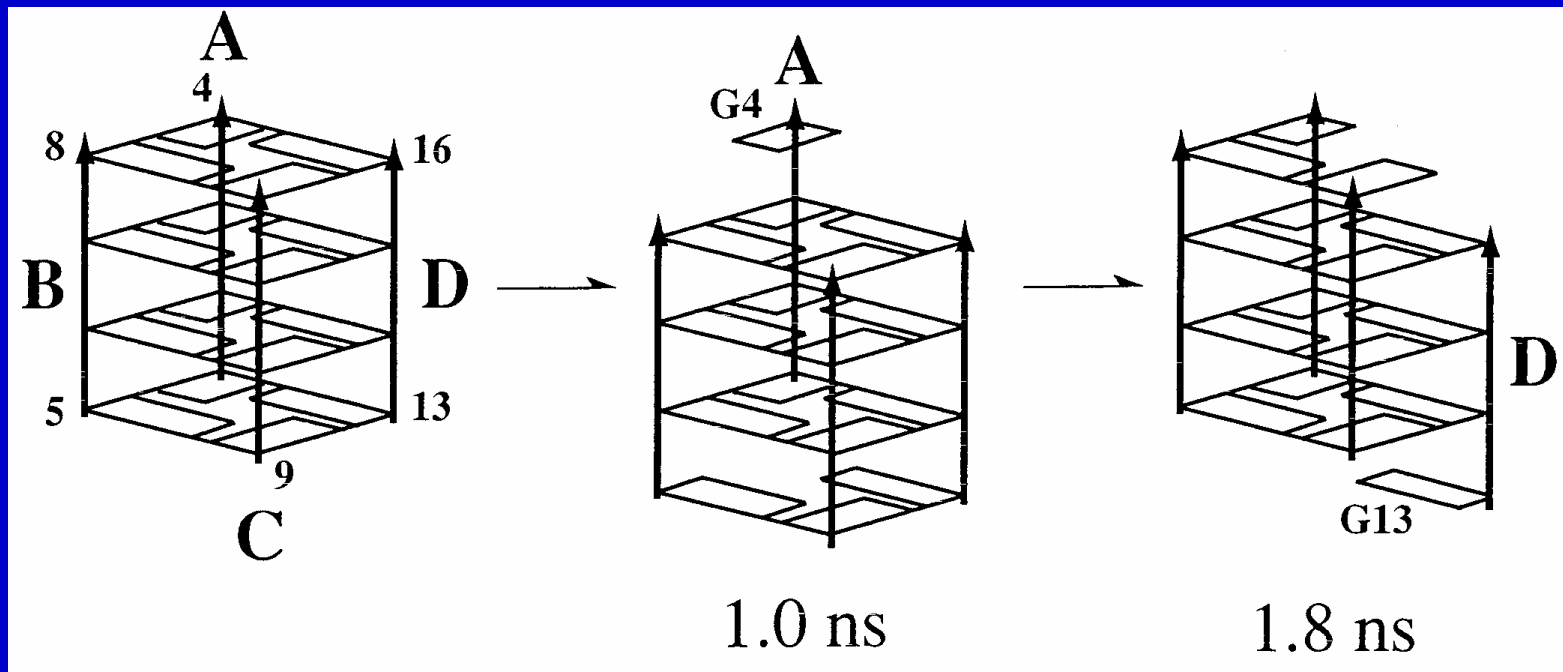
rigidity

Sekvence schopné tvořit
kvadruplexy jsou v genomu běžné,
nejdůležitější z nich je zřejmě
telomerní DNA na úplném konci
chromozomu – d(GGGTAA)_n

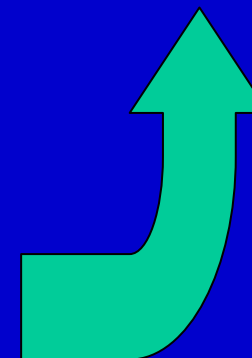
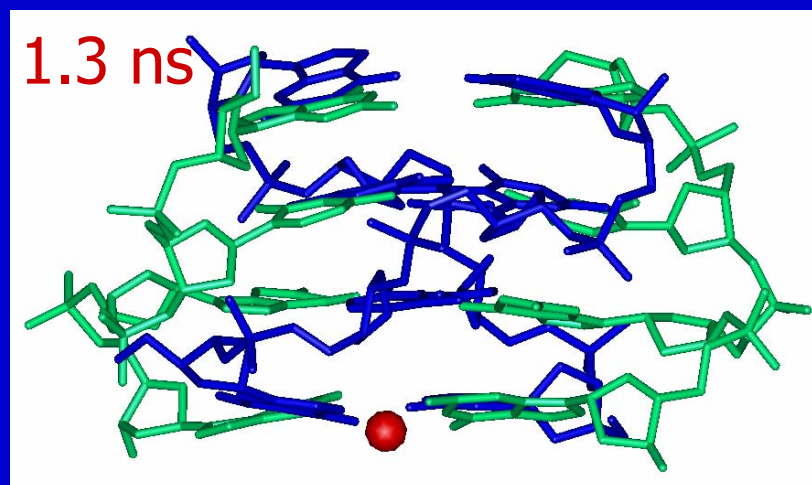
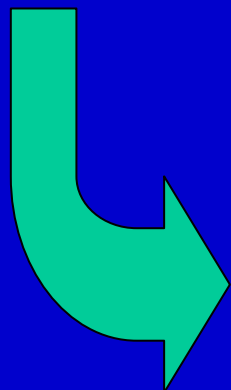
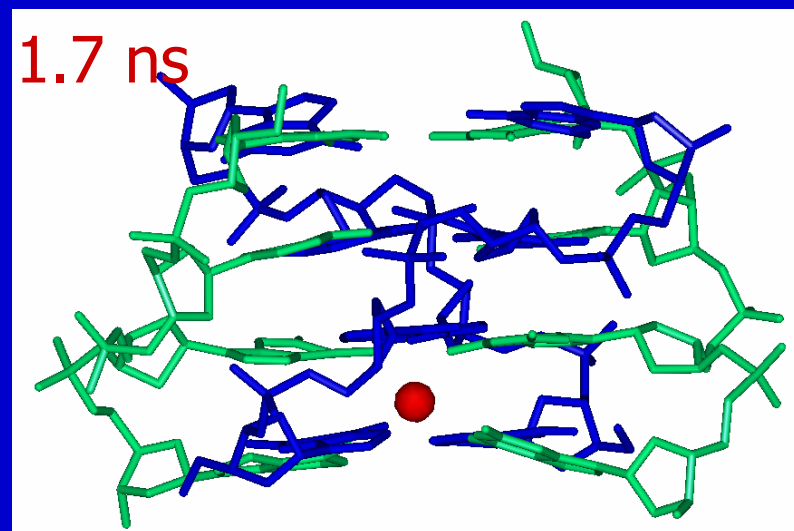
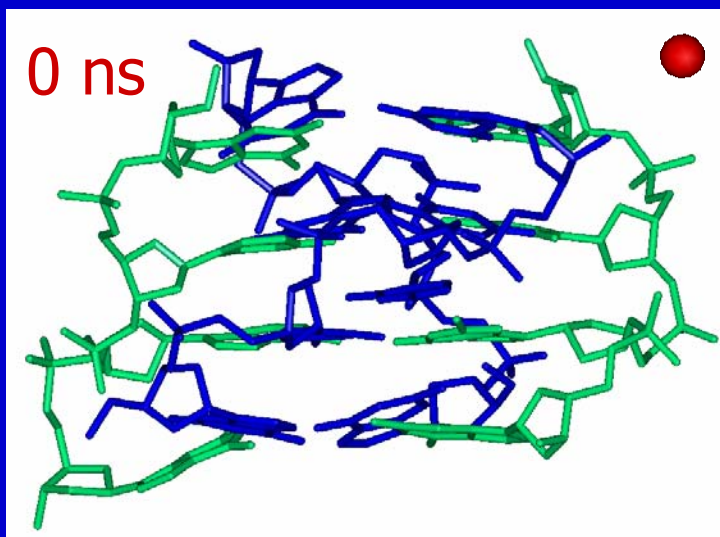
Shoda mezi X-ray (modrá) a MD (růžová)



A tohle udělá kvadruplex, když mu na počítači vytáhneme z kanálu jeho ionty.....

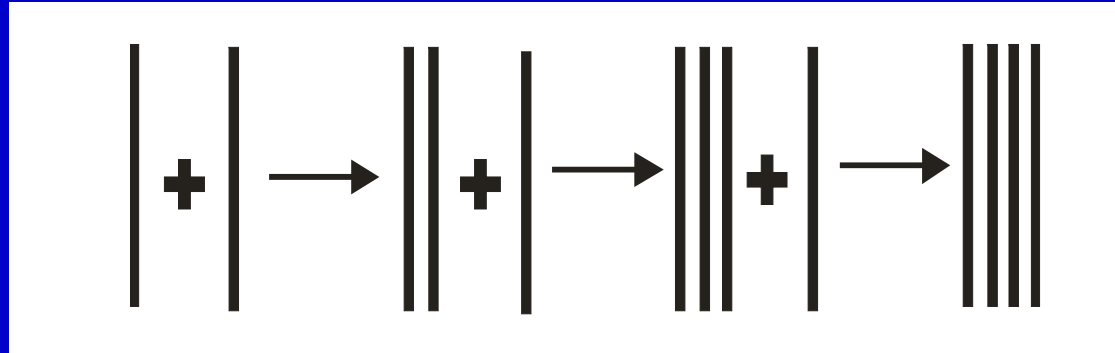


Prázdný kvadruplex ulovil iont během
stochastické simulace.....

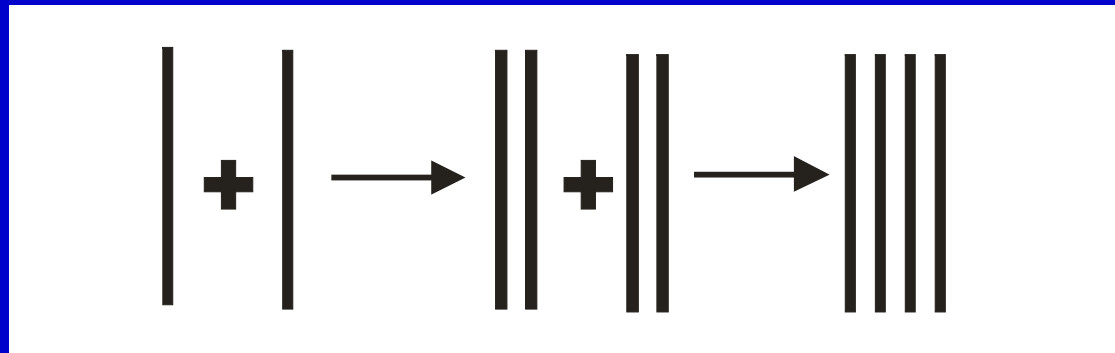


Jak takový kvadruplex vůbec může vzniknout....

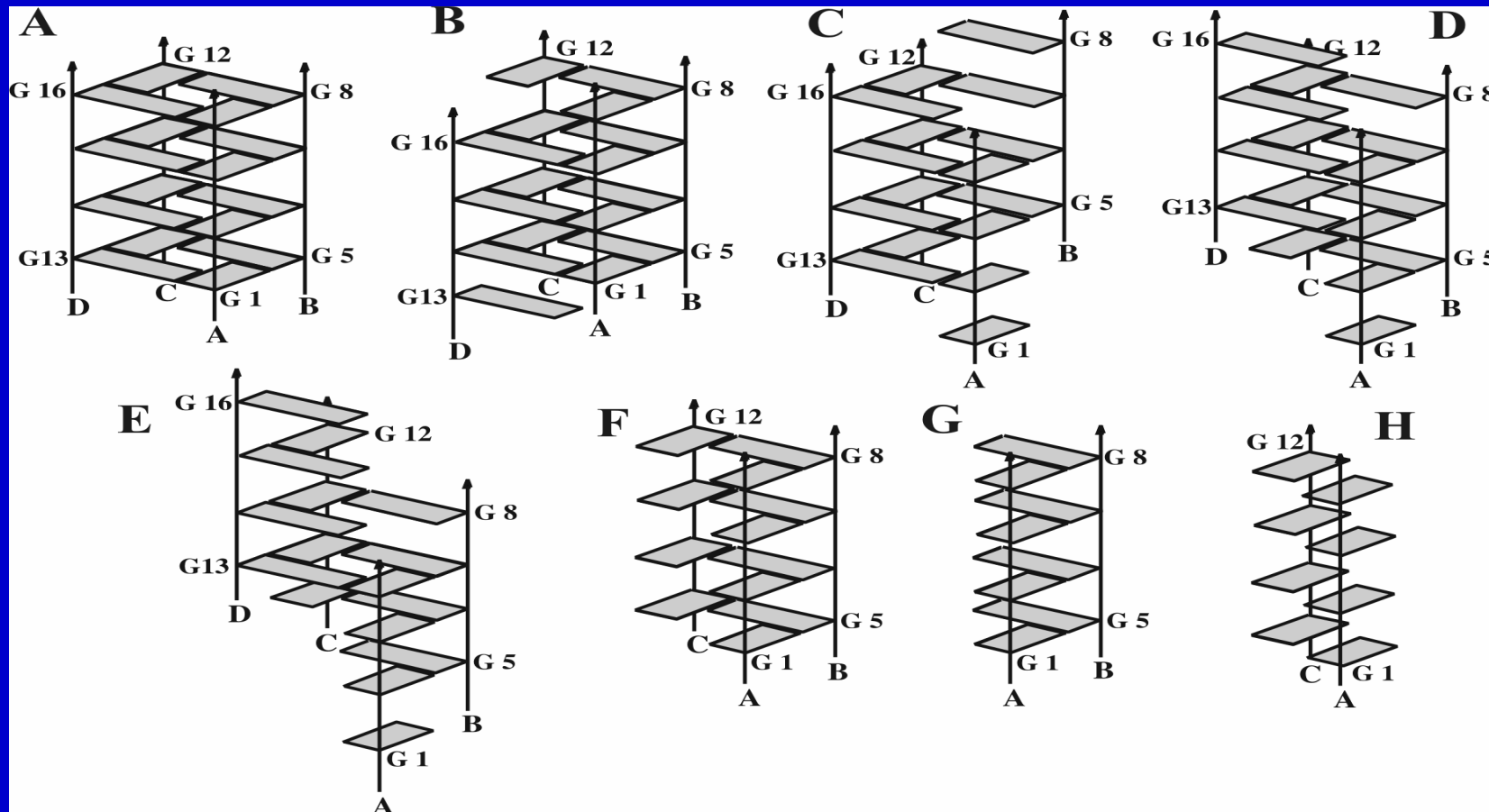
- Stepwise strand addition:



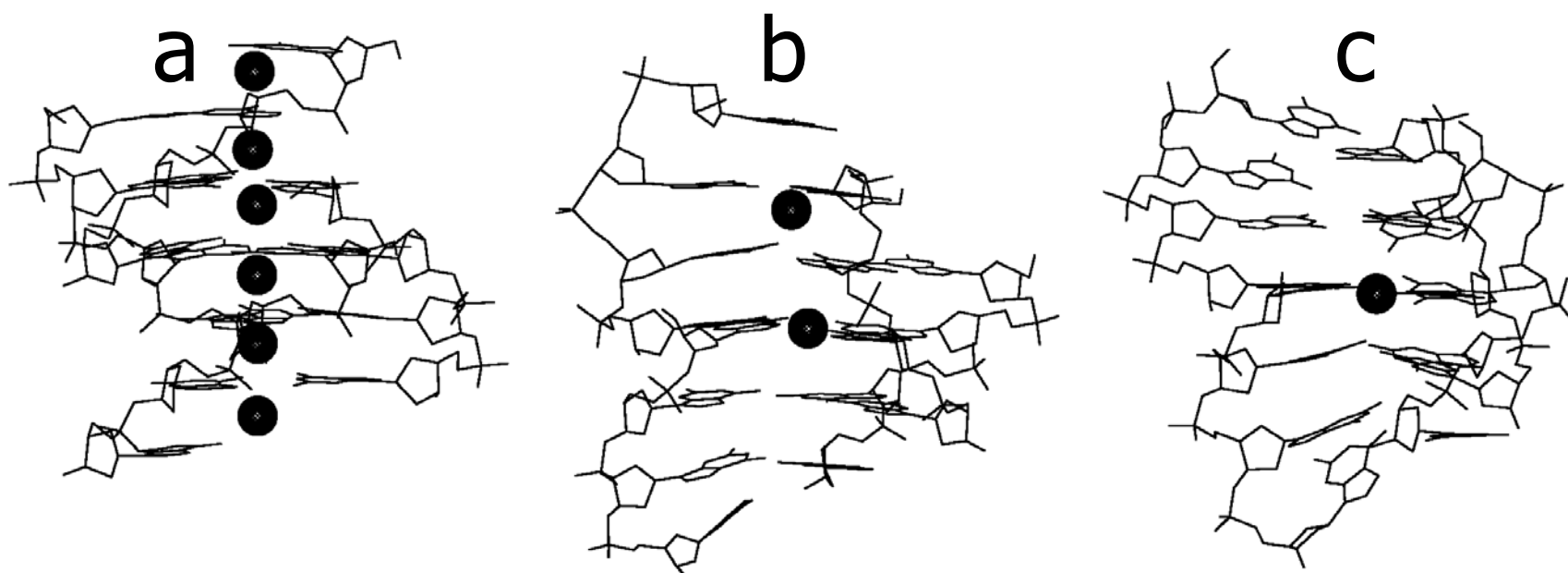
- • Duplex dimerization:



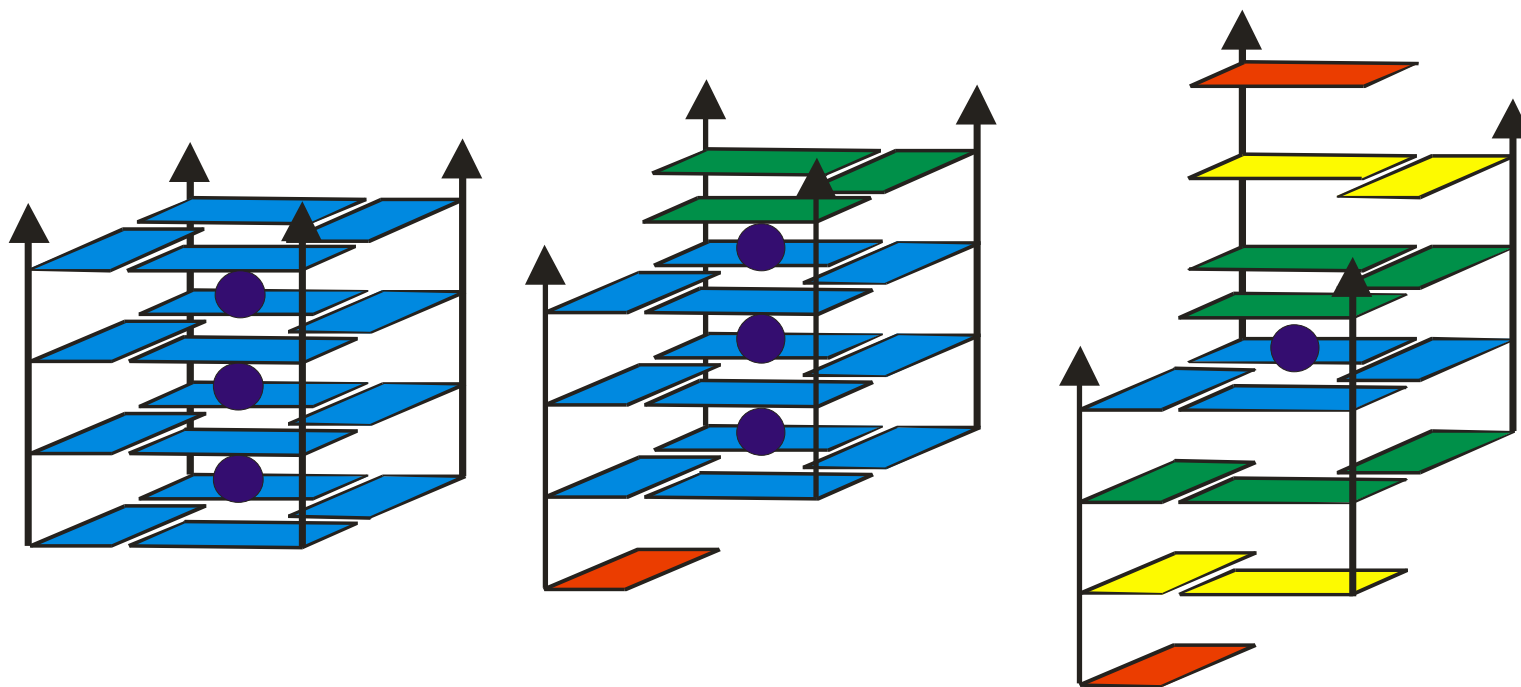
Navrhli jsme si alternativní topologie $d(\text{GGGG})_4$ a podívali se, jak se budou chovat.



Spiral stem: (a) startovací model, (b) průměrná struktura 7–9 ns a (c) výsledek.



Alternativní konformace stemu kvadruplexu studované MD.



$\Delta\Delta G = 0 \text{ kcal/mol}$

$\Delta\Delta G = +10 \text{ kcal/mol}$

$\Delta\Delta G = +22 \text{ kcal/mol}$

- **Publikace 2005-zaří 2006**
- **116** J.E. Sponer, N. Spackova, P. Kulhanek, J. Leszczynski, **J. Sponer** Non-Watson-Crick base pairing in RNA. Quantum chemical analysis of the cis Watson-Crick/sugar edge base pair family. **Journal of Physical Chemistry B** **109**, **2005**, **2292-2301**
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- 119 J.E. Sponer, N. Spackova, J. Leszczynski, **J. Sponer**: Principles of RNA base pairing: Structures and energies of the trans Watson-Crick/sugar edge base Paris. **Journal of Physical Chemistry B** **109**, **11399-11410**, **2005**
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- 124 Flavia Barone, Filip Lankas, Nada Spackova, Jiri Sponer, Peter Karran, Margherita Bignami and Filomena Mazzei. Structural and dynamic effects of single 7-hydro-8-oxoguanine bases located in a frameshift target DNA sequence. **Biophysical Chemistry**, 118, 31-41, 2005
- 125. Naďa Špačková, Jiří Šponer: Molecular Dynamics simulations of Sarcin Ricin rRNA motif. **Nucleic Acids Research** 34, 697-708, 2006
- 126. Jiří Šponer, Petr Jurečka, Pavel Hobza, Ivan Marchan, F. Javier Luque, Modesto Orozco: Nature of base stacking. Reference quantum chemical stacking energies in ten unique B-DNA base pair steps. **Chemistry - A European Journal** 12, 2854-2865, 2006
- 127. M. Pavelka, M. Simanek, J. Sponer, J.V. Burda: Copper cations interactions with biologically essential types of ligands: a computational DFT study: **Journal of Physical Chemistry A** 110, 4795-4809, 2006
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- 131 F. Rázga, M. Zacharias, K. Réblová, J. Koča, J. Šponer: RNA Kink-turns as molecular elbows: hydration, cation-binding and large-scale dynamics. *Structure* 14, 2006, 825-835

- 132. M. V. Krasovska, J. Sefcikova, K. Réblová, B. Schneider, N. G. Walter, J. Šponer: Cations and hydration in catalytic RNA: Molecular dynamics of the hepatitis delta virus ribozyme. *Biophysical Journal* 91, 2006, 626-638.
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- 135. J. Šponer, P. Jurečka, P. Hobza: Base stacking and base pairing. In: *Computational studies of RNA and DNA*. J. Šponer, F. Lankaš, Eds., Computational studies of RNA and DNA. Dordrecht: Springer, 2006, pp. 343-388.
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