

MCSS Update

biomolecular fragments

solvent models, scoring functions, ... and application
examples to oligonucleotides

Fabrice Leclerc

Institute for Integrative Biology of the Cell (I2BC)

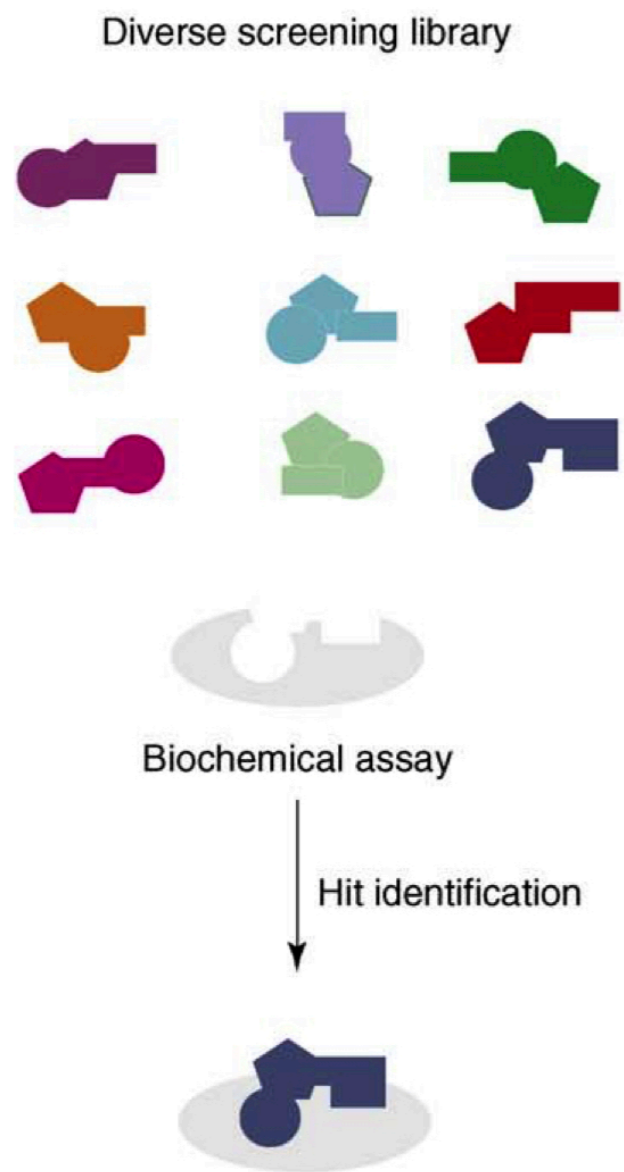
CNRS-CEA-Univ. Paris Sud, Univ. Paris Saclay

fabrice.leclerc@u-psud.fr

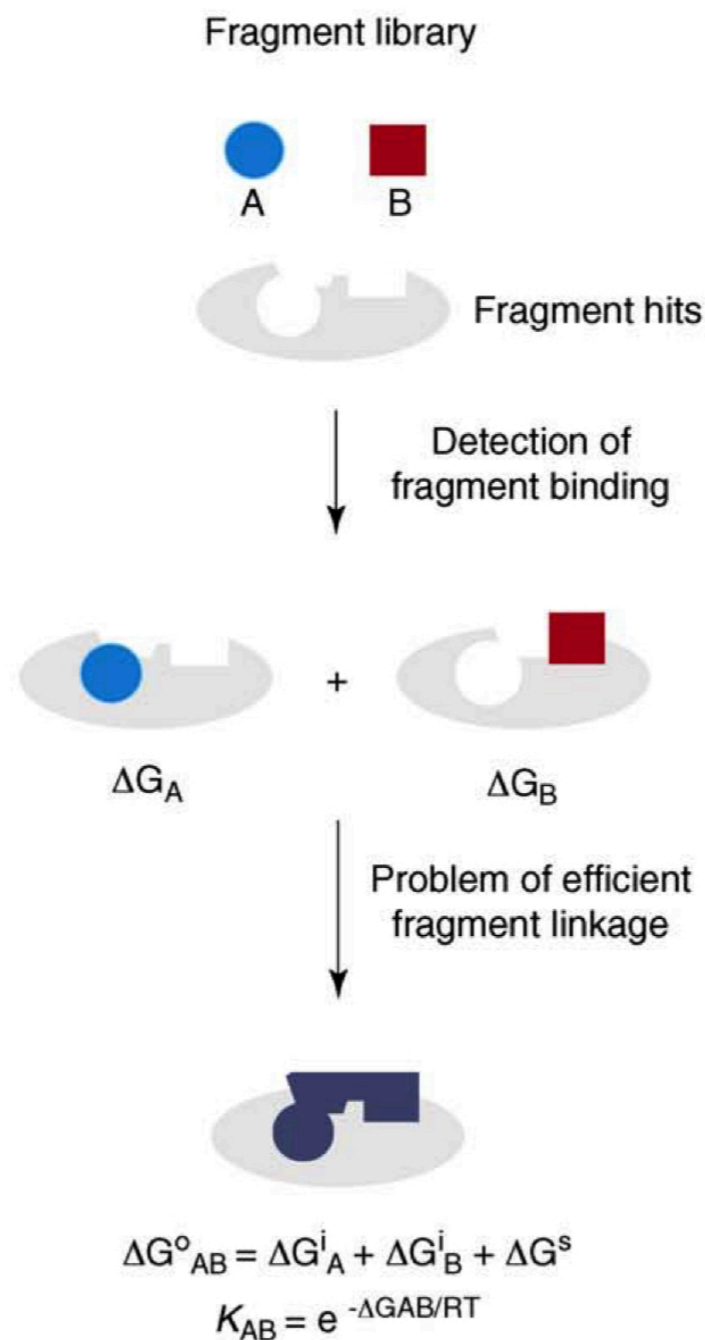


Fragment-Based Ligand Design

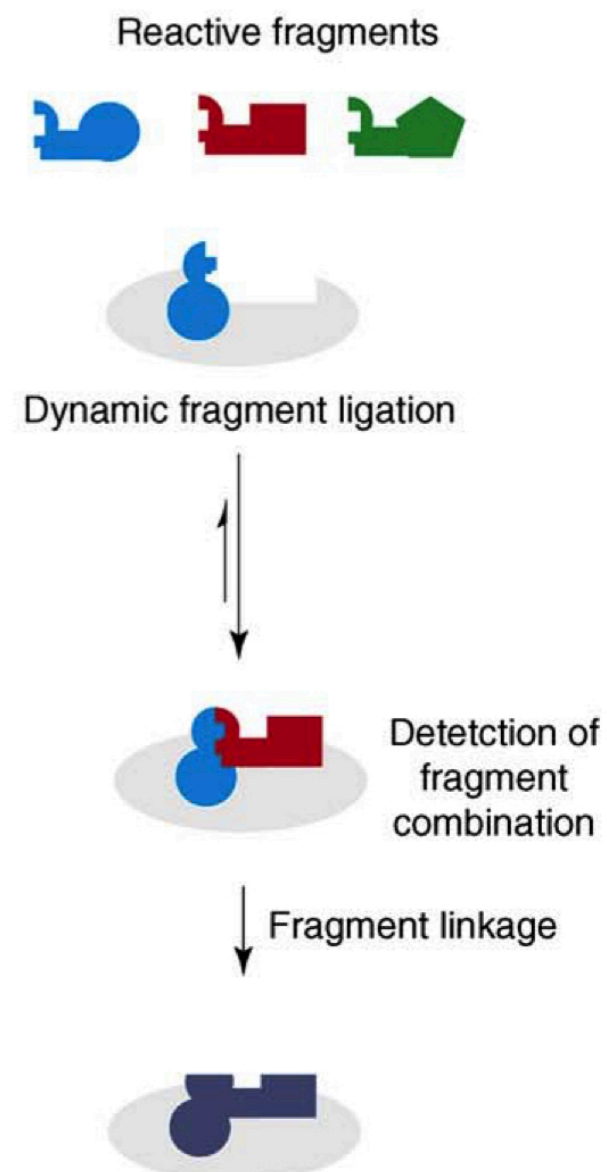
(a) High-throughput screening



(b) Fragment-based drug discovery



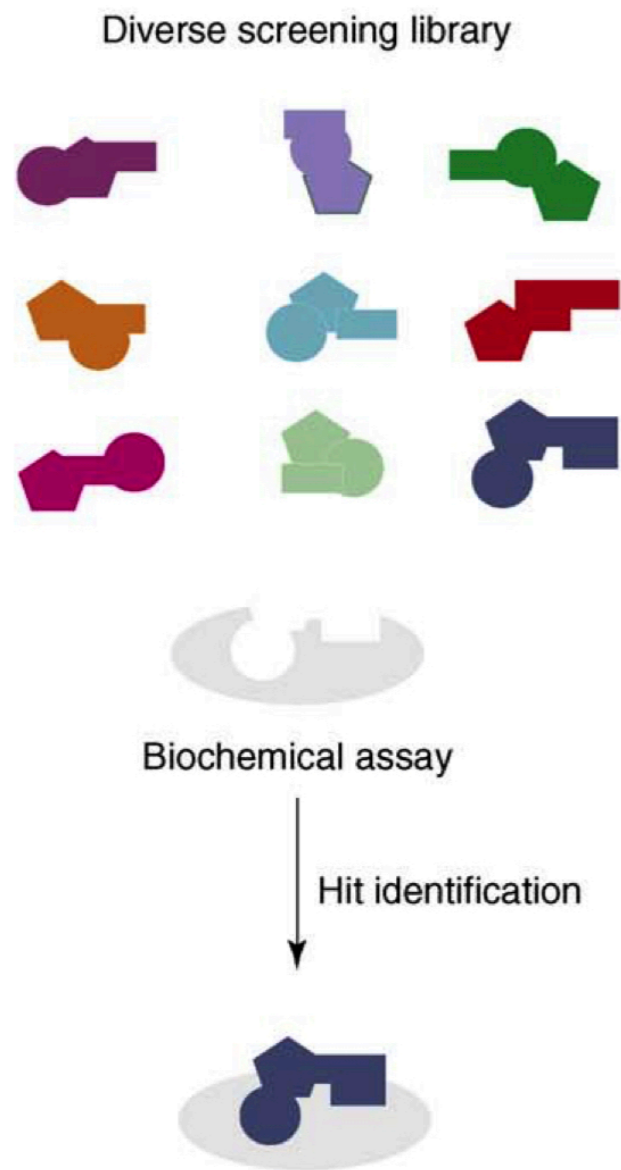
(c) Dynamic, template-assisted drug discovery



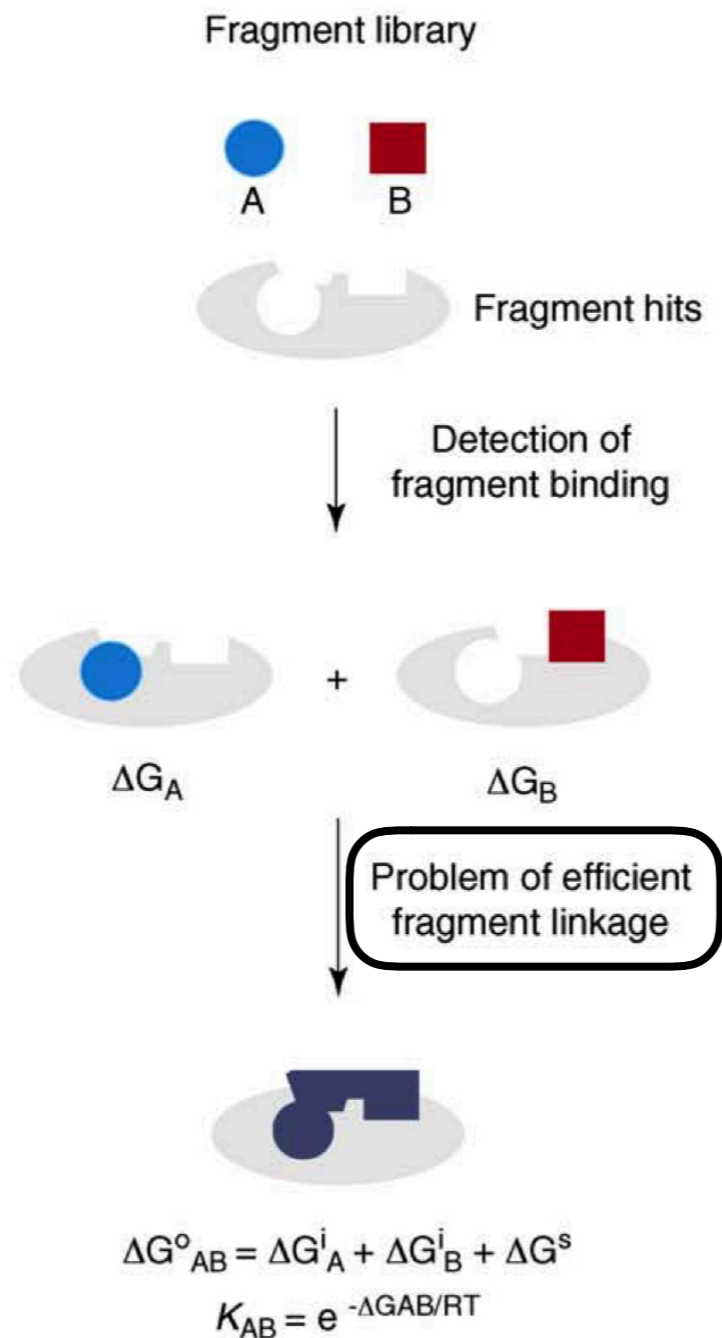


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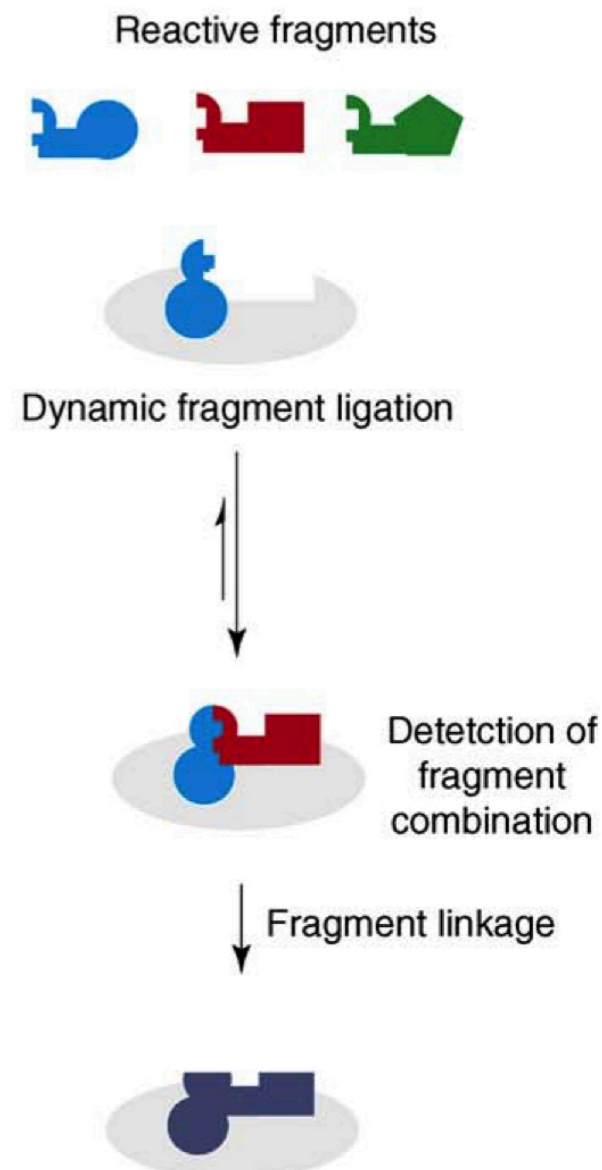
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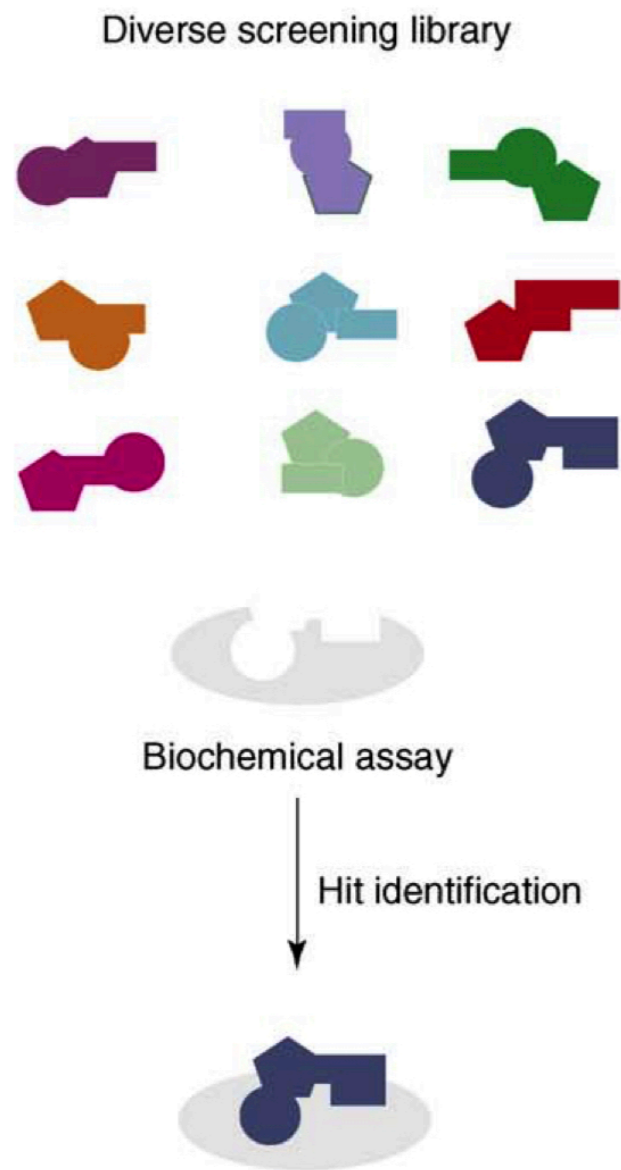
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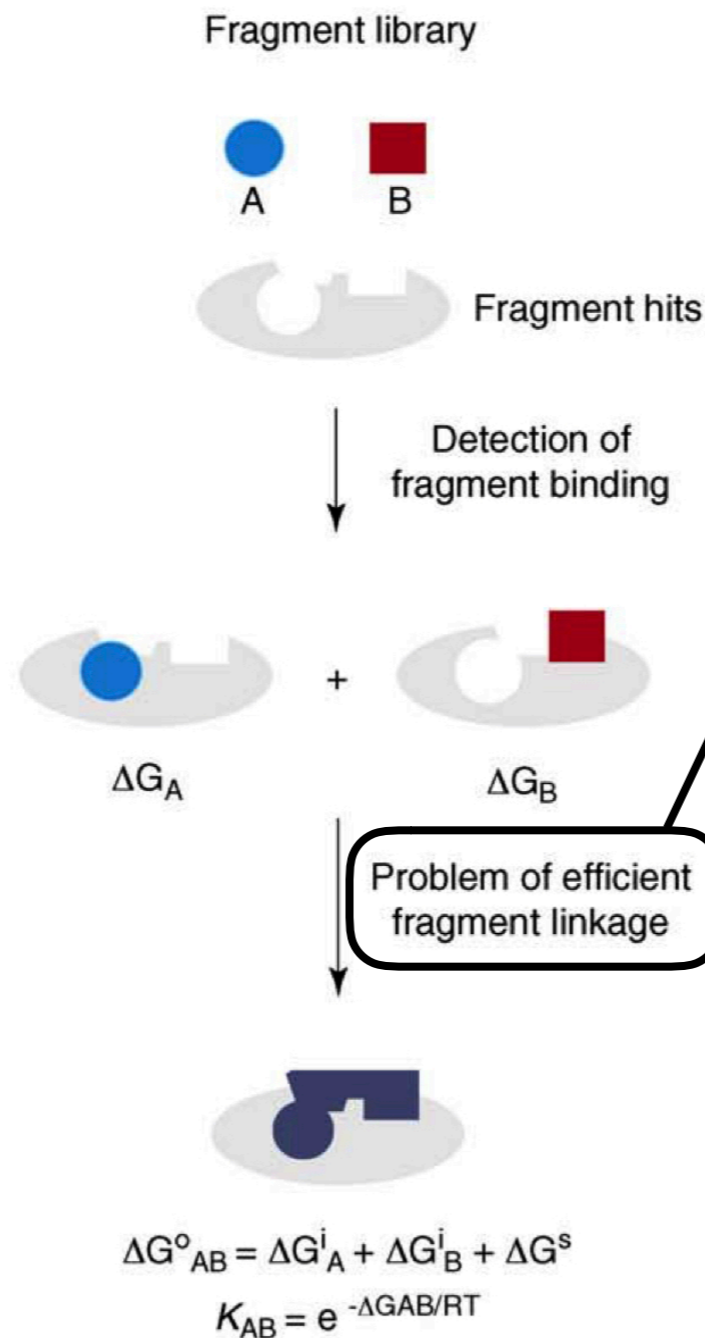


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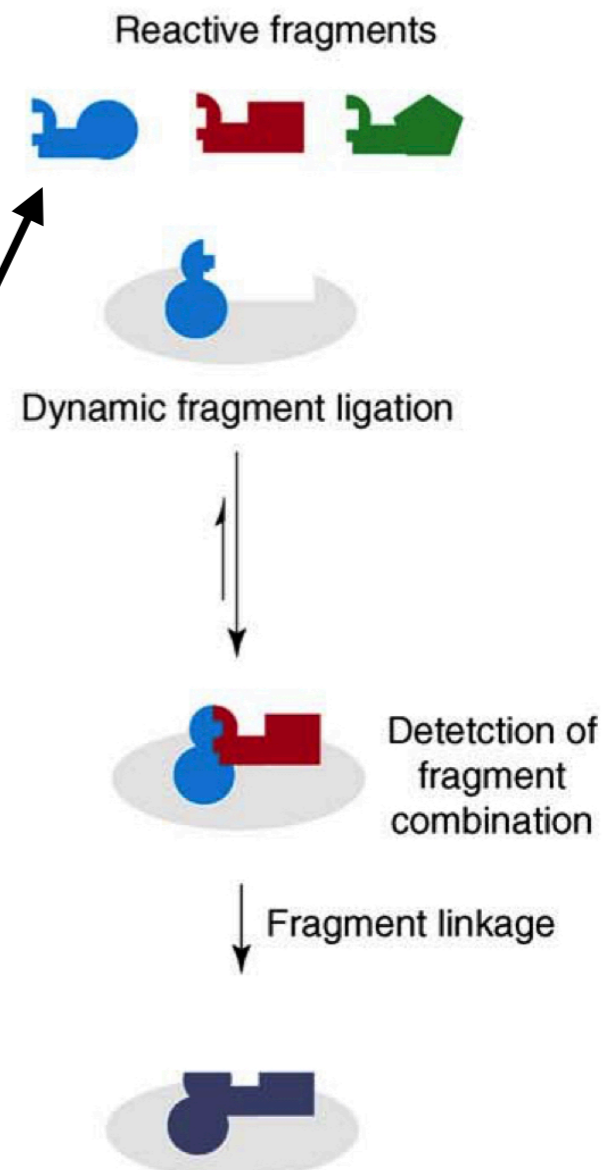
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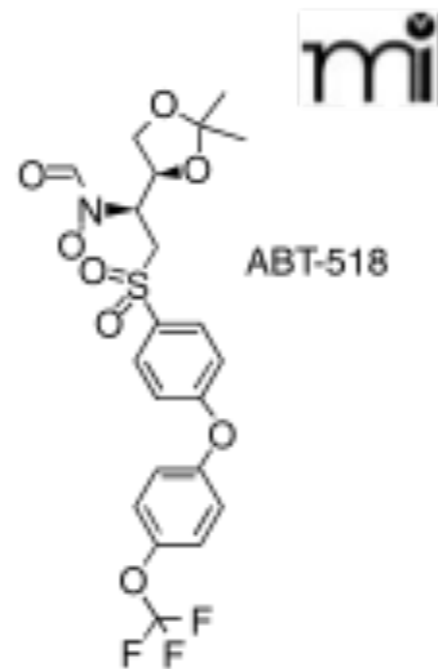
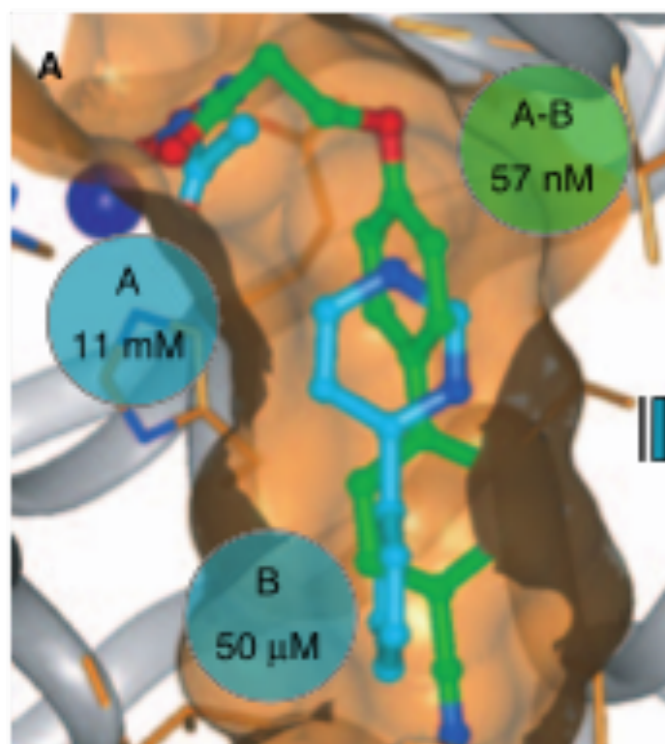
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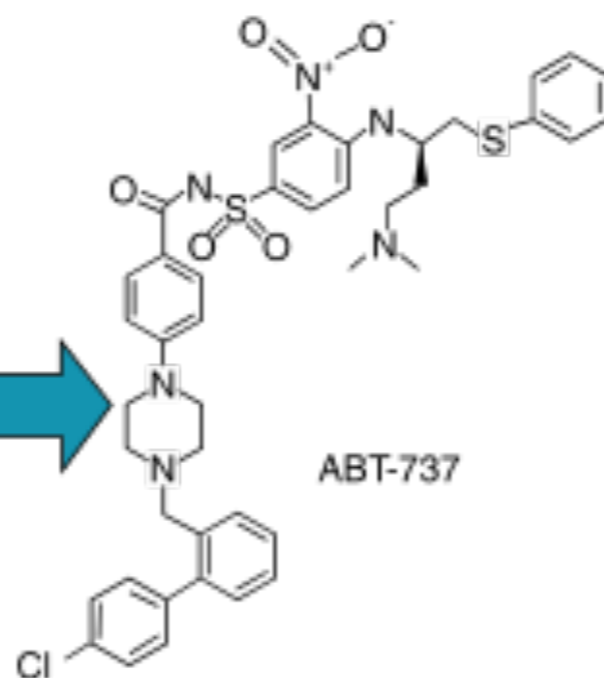
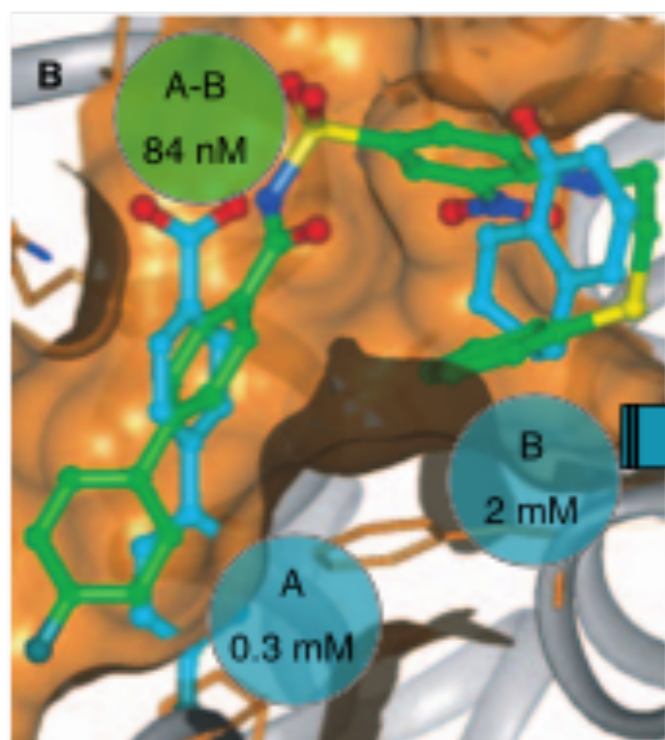
Success stories in FBLD



“SAR by NMR”

Shuker *et al.*, 1996

Metalloproteinases (MMP-3)
(arthritis and tumor metastasis)

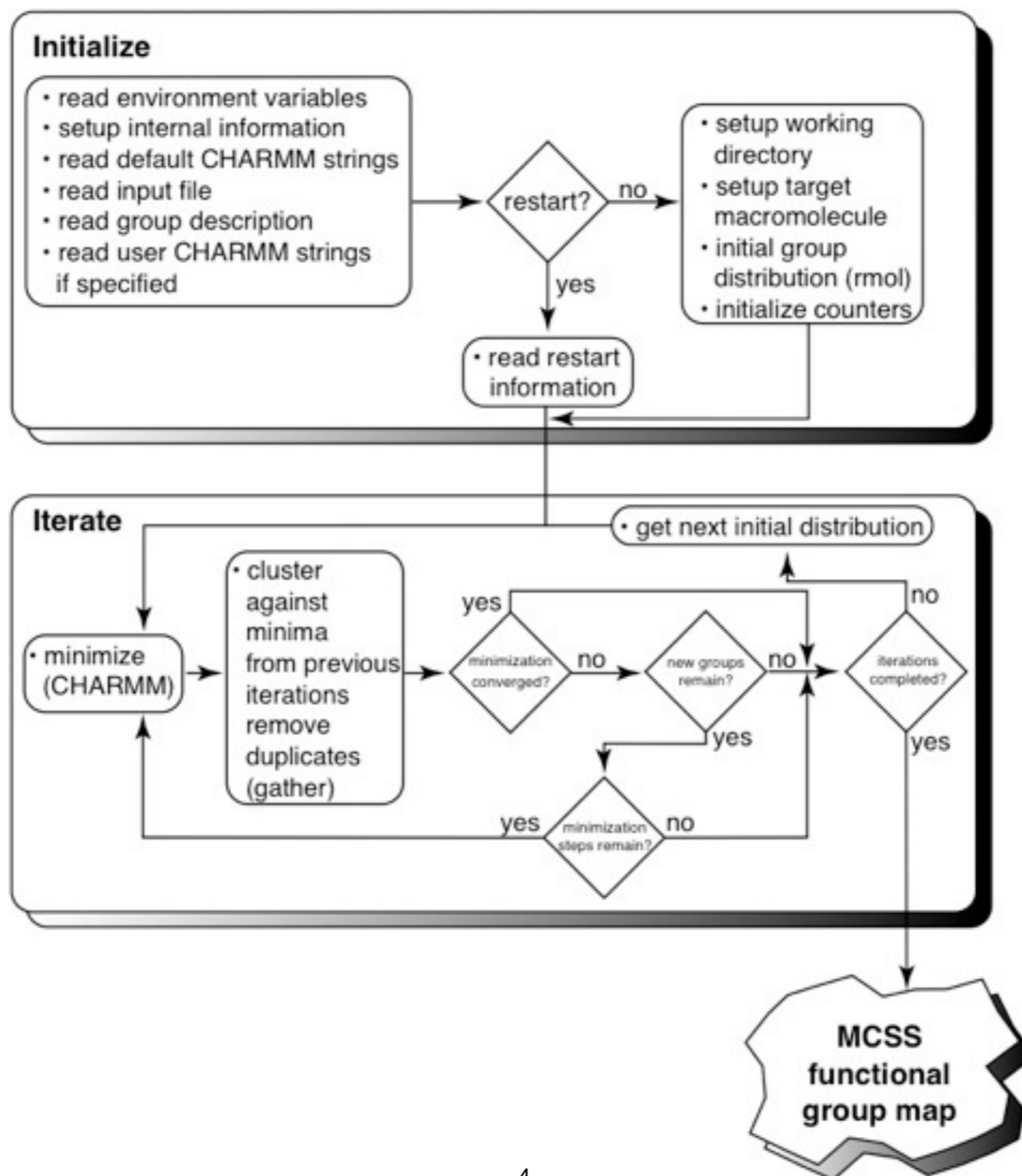


Bcl-2

(pro- and anti-apoptotic)

Hadjuk, *Mol. Interv.*, 2006

MCSS Workflow



MCSS Updates & Integrations

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- CHARMM-GUI & CHARMMING integrations

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MCSS Updates & Integrations

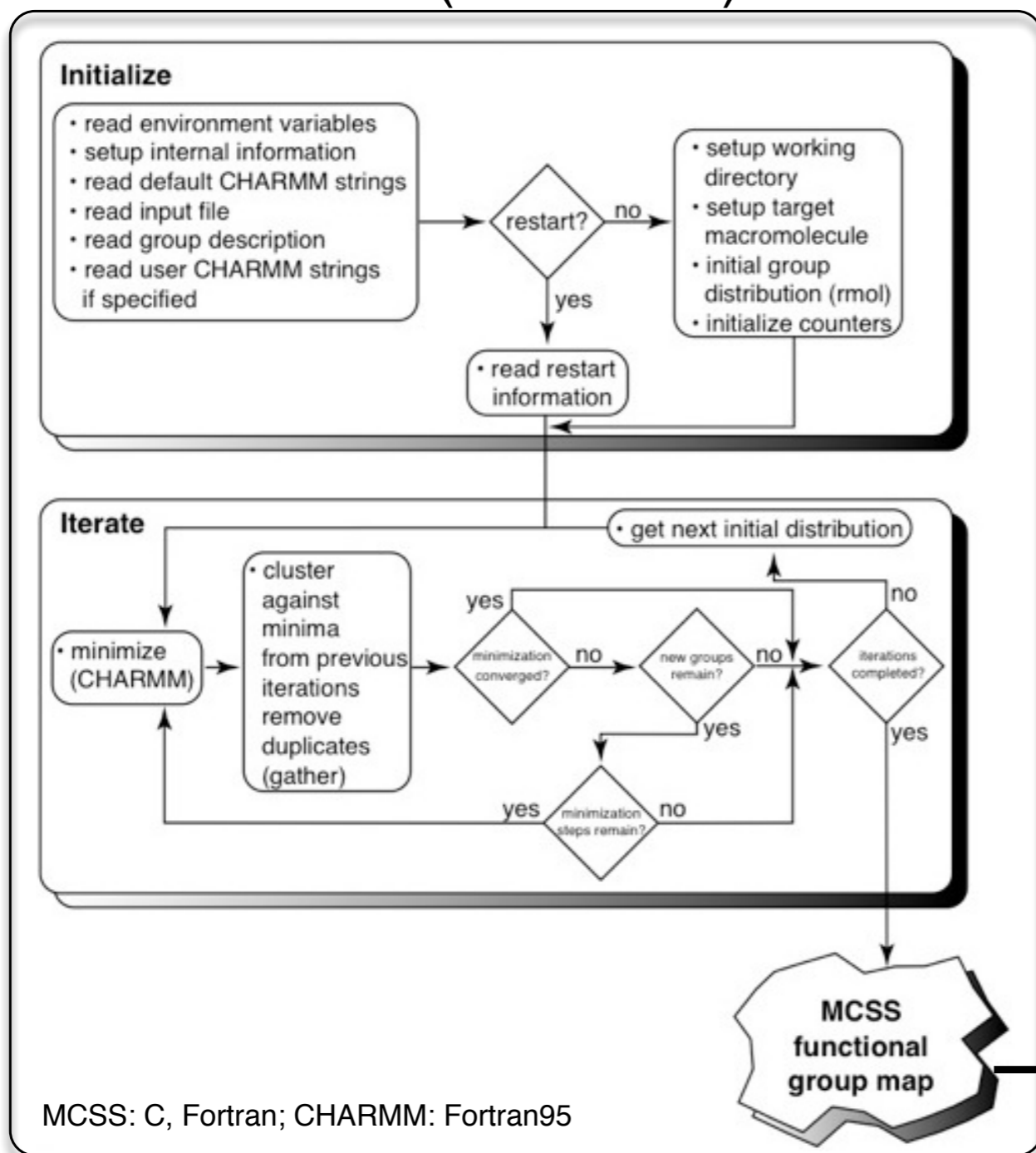
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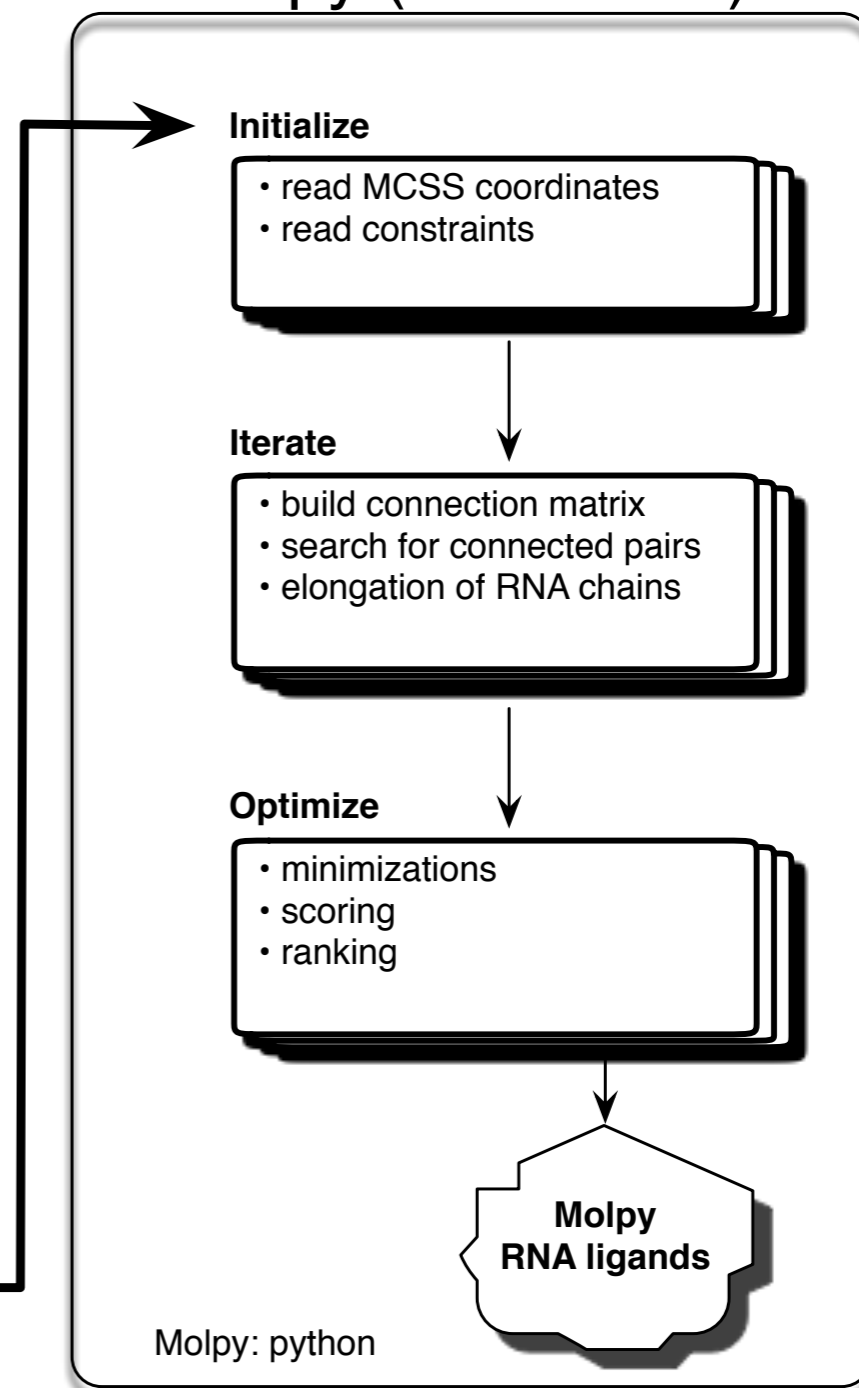
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- automatic generation of fragments

MCSS+Molpy Workflow

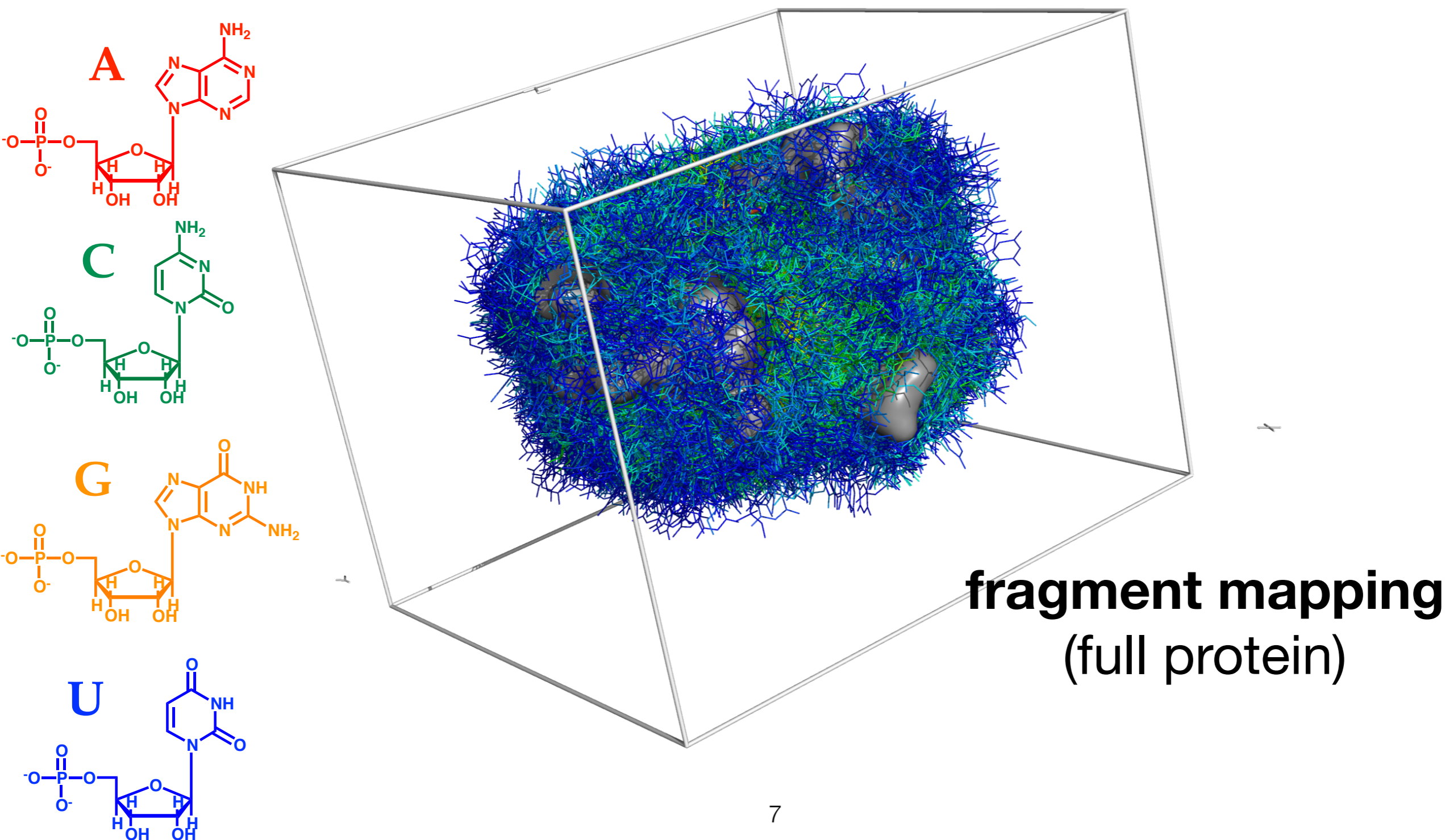
MCSS (CHARMM)



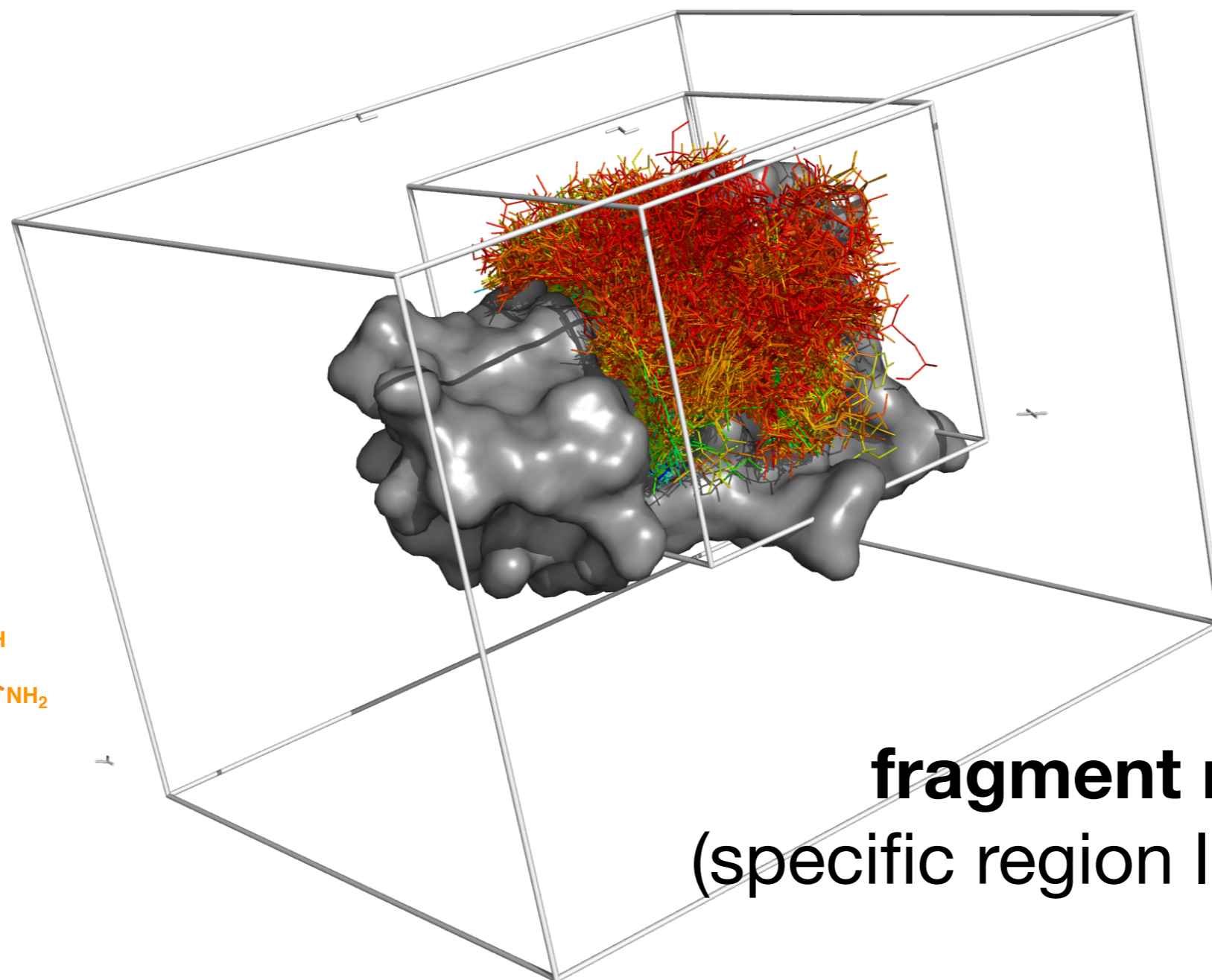
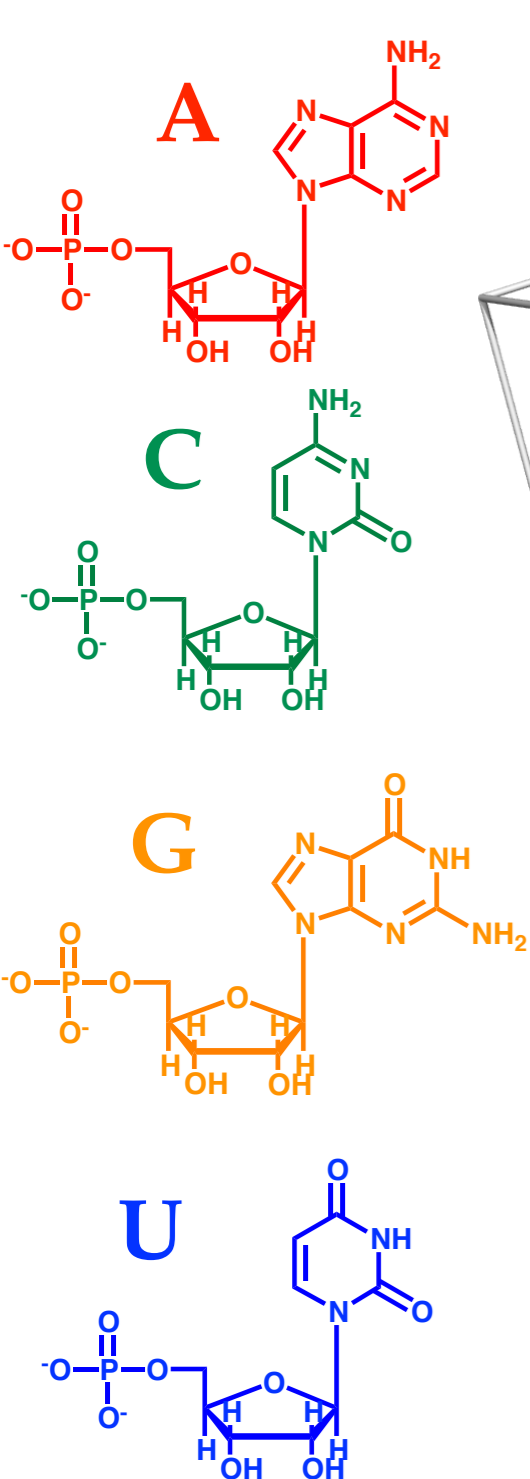
Molpy (CHARMM)



MCSS in Practice (1)



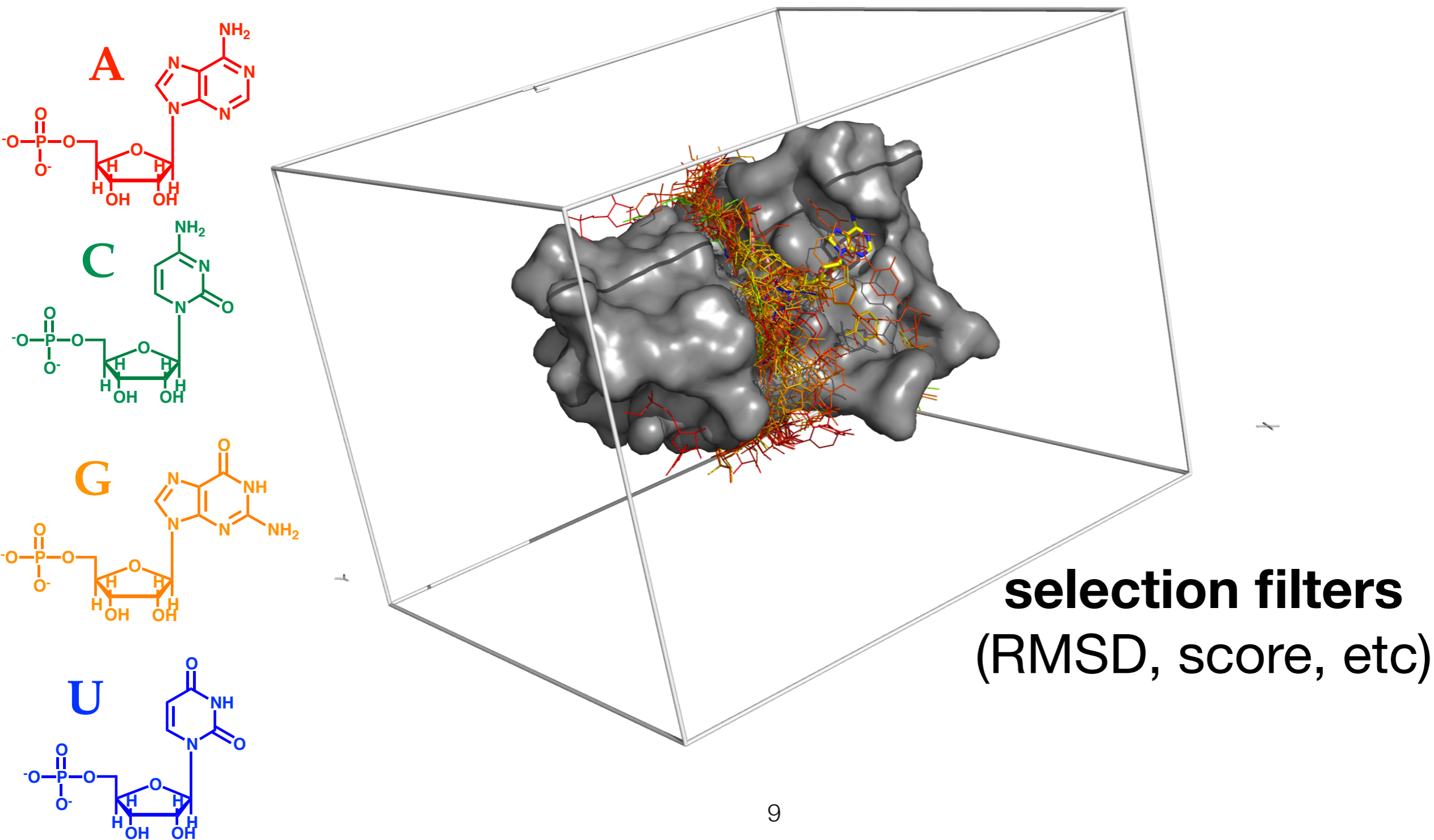
MCSS in Practice (2)



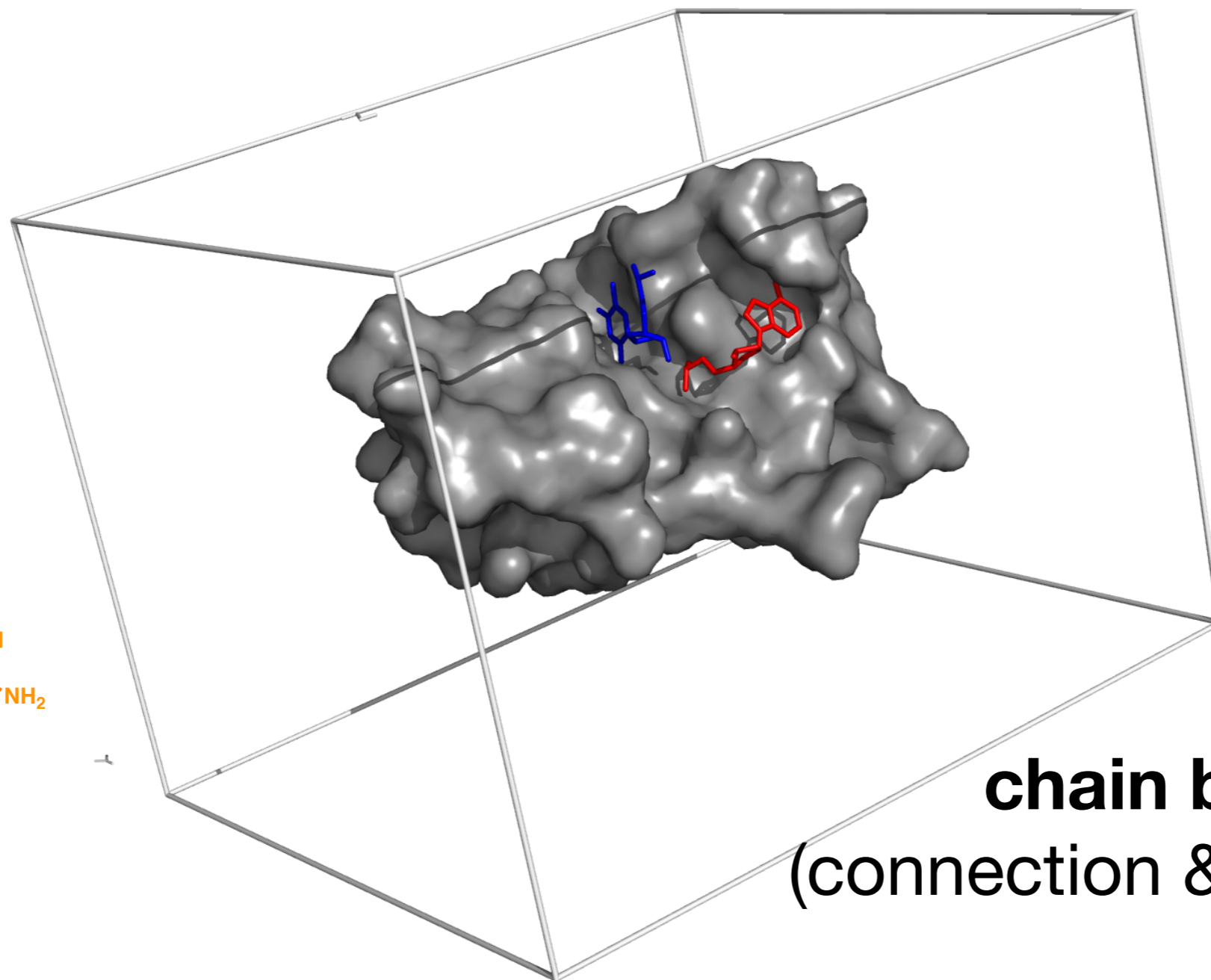
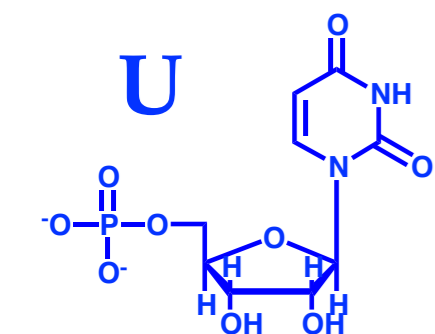
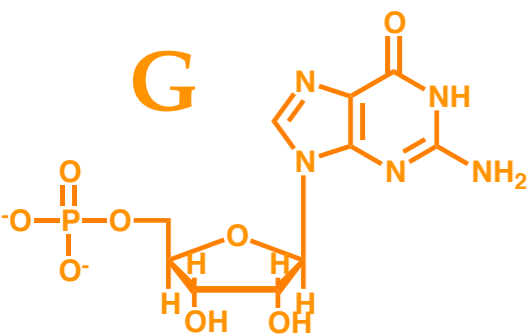
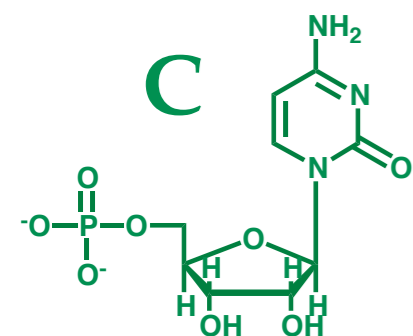
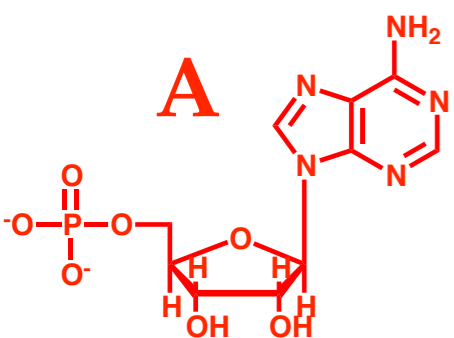
fragment mapping
(specific region like “hotspots”)



MCSS in Practice (3)

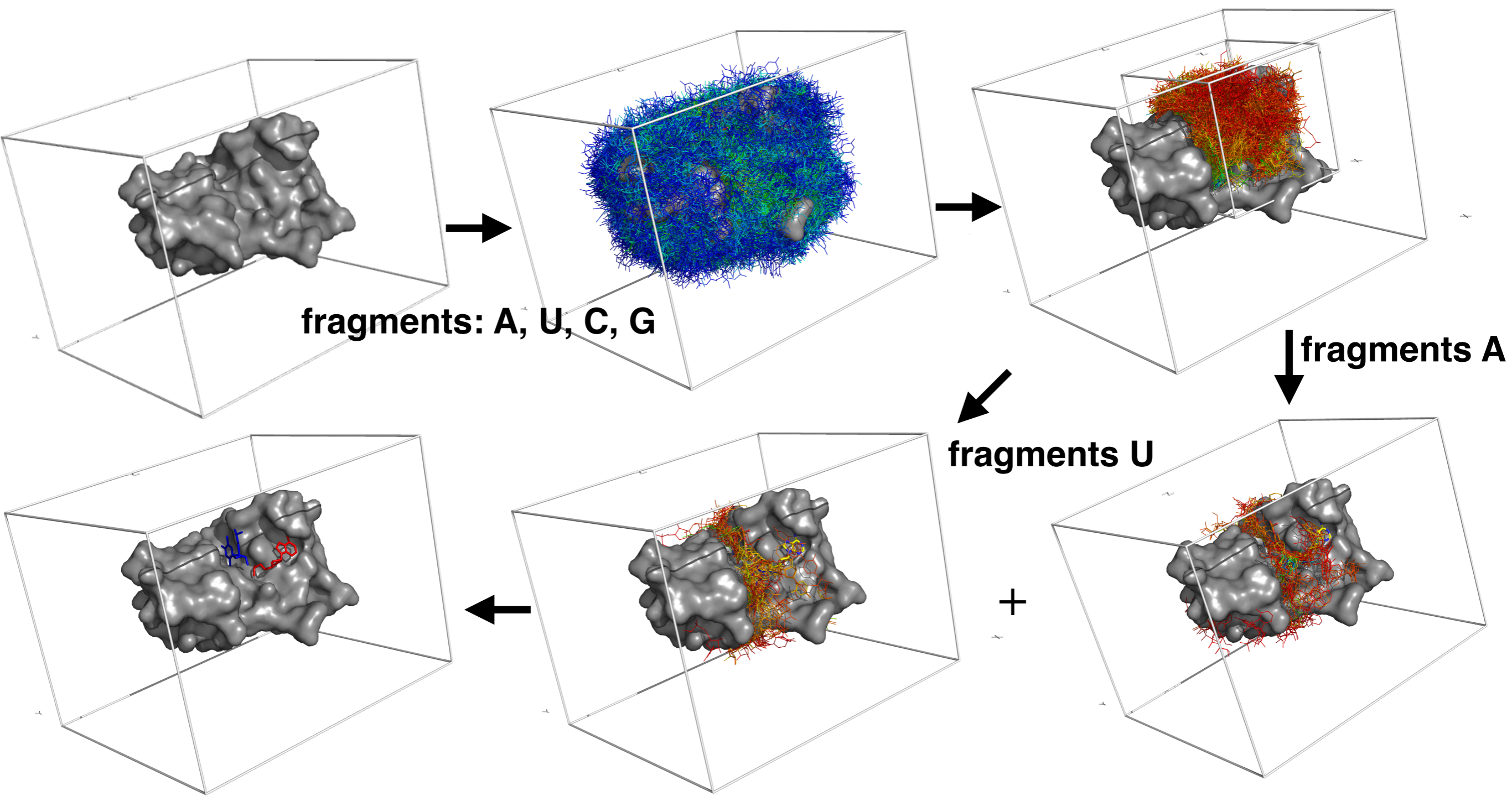


MCSS+Molpy in Practice



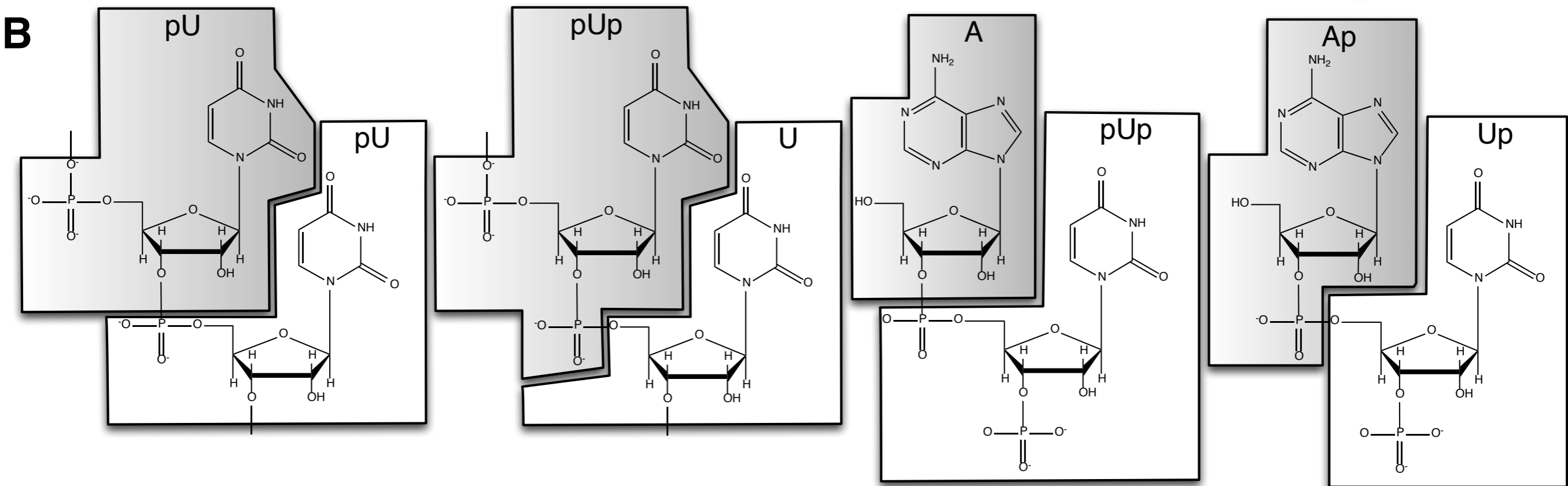
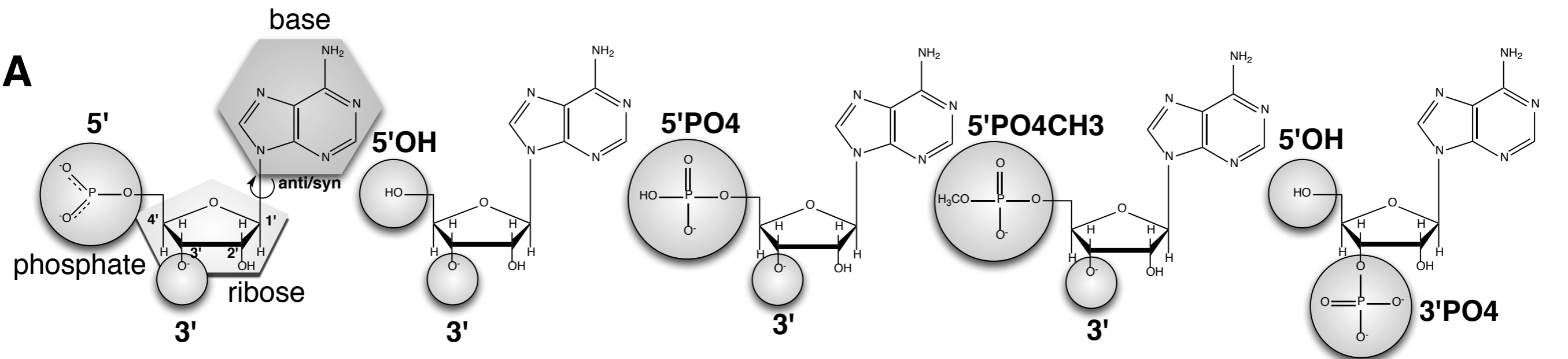
chain building
(connection & optimization)

MCSS+Molpy in Practice

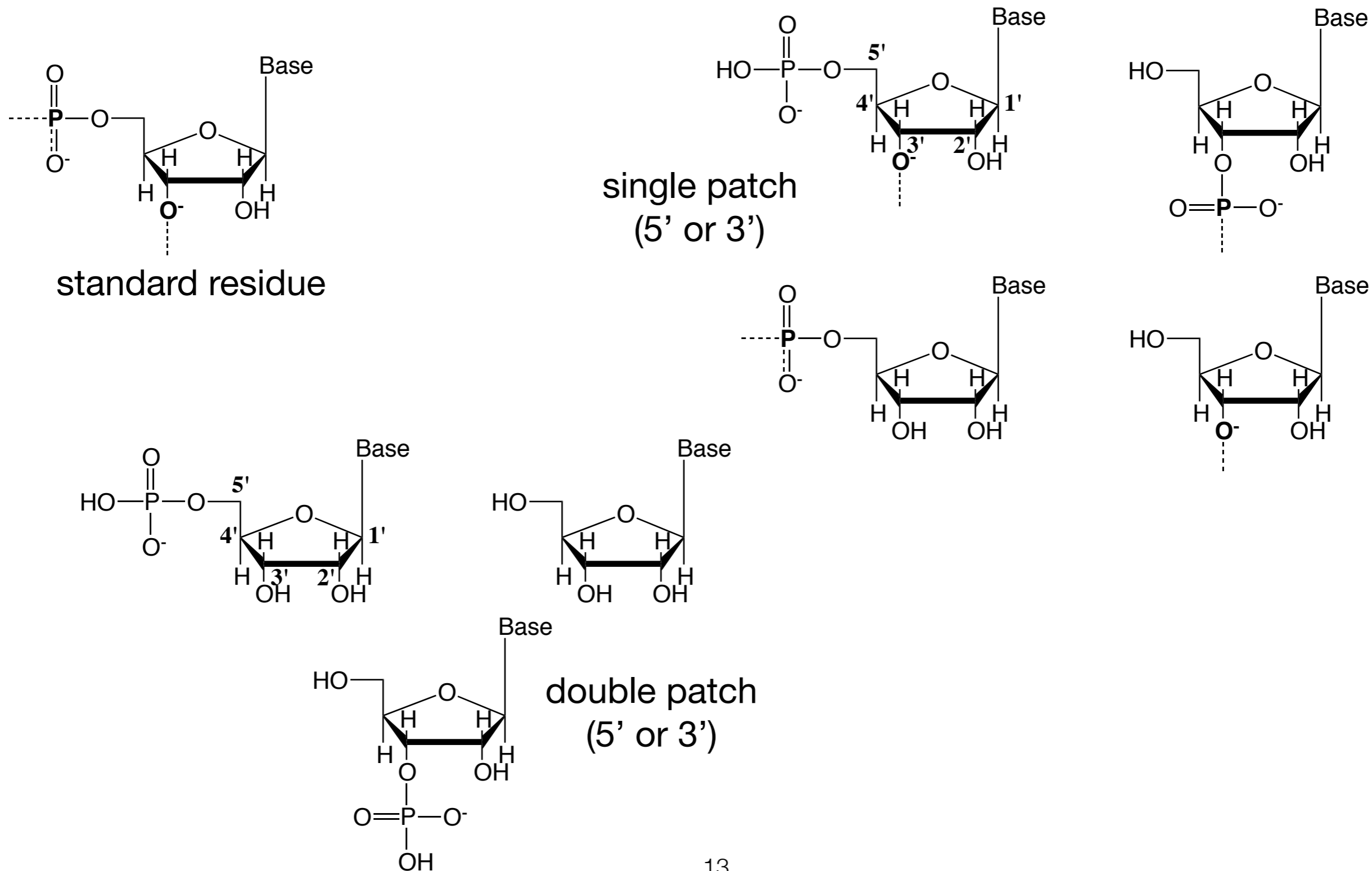




Fragments & Partition Schemes



Nucleic fragments library



Conformational & Connection library

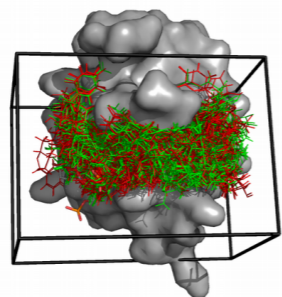
Structure of Nucleotides	0	A	E	1	1	0	0	1	1	0	1	1	0	1	2	0	0	2	0	1	2
Nucleobases, Ex :	0	A	E																		
Mono-nucleotide, Ex :	D	A	X	N	1	1	0														
Di-nucleotide, Ex :	R	T	Y	S	1	0	1	R	T	Y	S	0	1	1							
Tri-nucleotide, Ex :	R	C	X	N	1	0	2	R	C	X	N	0	0	2	R	C	X	N	0	1	2

Type	Patches	Orientation	Pucker
0 None	E Ethyl	X Anti-Trans	N North
D Deoxyribonucleic	H Hydrogen	Y Syn-Cis	S South
R Ribonucleic	M Methyl		

Base	5' Patch	3' Patch	Connection
0 None	0 None	0 None	0 None
A ADES	1 5Ter	1 3Ter	1 3 - 5
C CYTS	2 5Pho	2 3Po3	2 2 - 5
G GUAS	3 5Pom	3 3Pho	
I INOS		4 3Pom	
P PSUS		5 2Ter	
T THYS		6 2Po3	
U URAS		7 2Pho	
		8 2Pom	

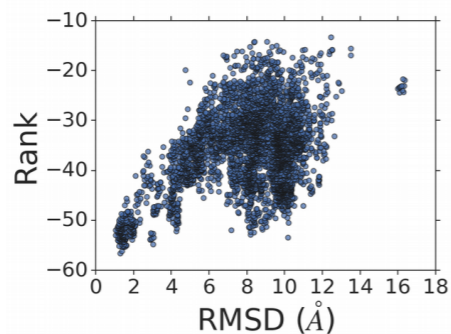
RNA-Binding Proteins Testcases

200U & 200C
2XNR

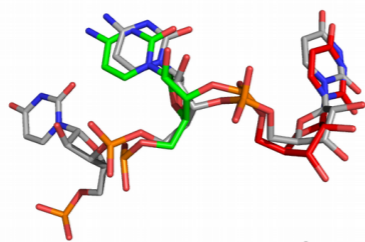


Chain search
for CU

4670 chains

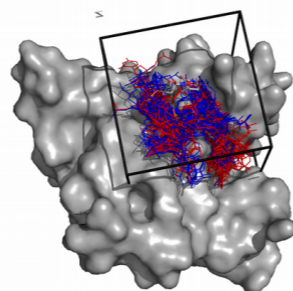


Top 1 chain



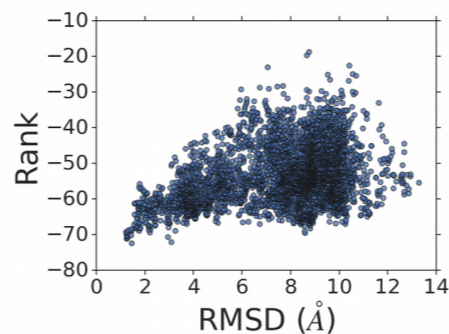
RMSD = 1,3 Å

200U & 200A
5ELH

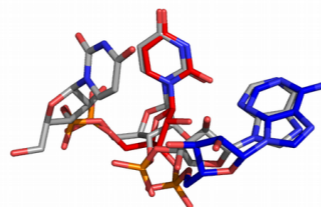


Chain search
for UA

5550 chains

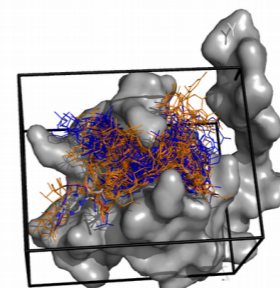


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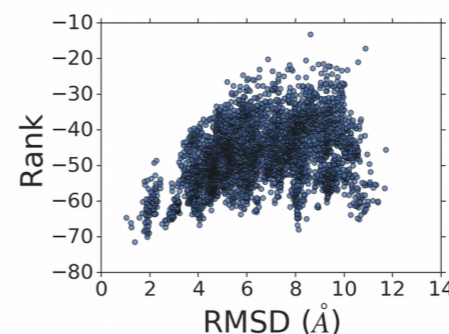
RMSD = 1,36 Å
15

200A & 200G
5WWX

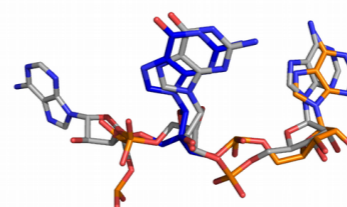


Chain search
for AG

5151 chains



Top 1 chain

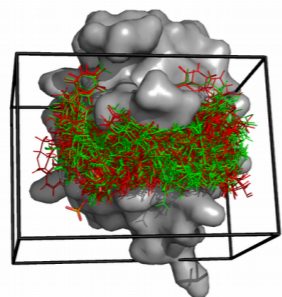


RMSD = 1,45 Å

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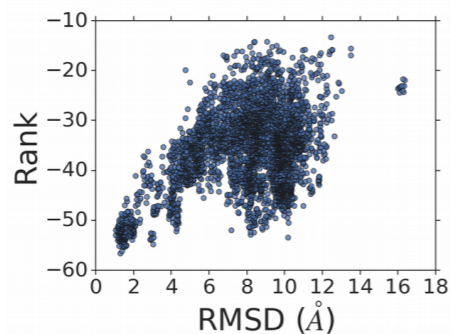
200 initial poses

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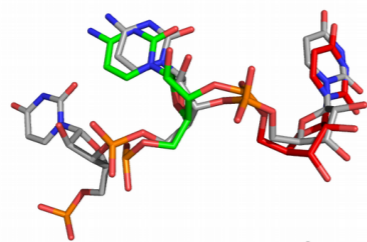


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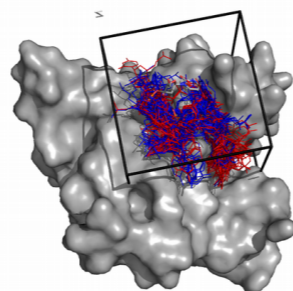


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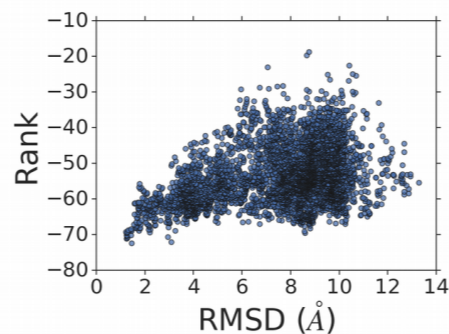
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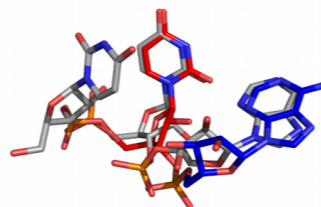


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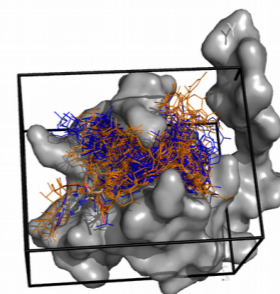


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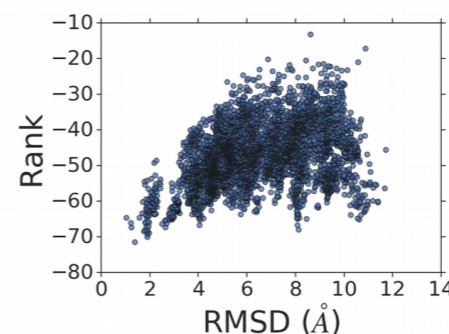
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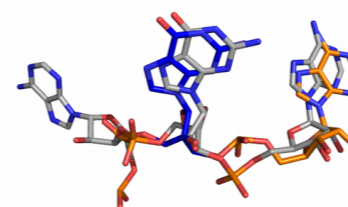


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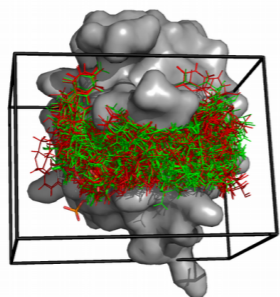


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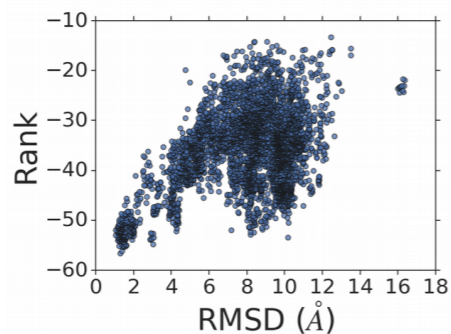
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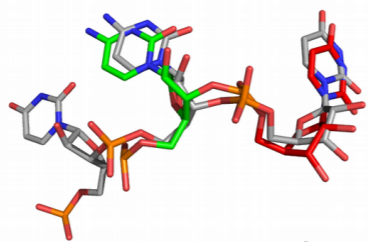


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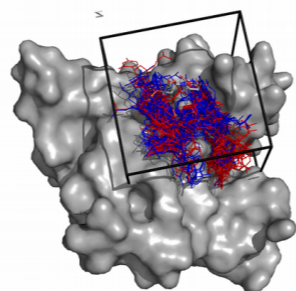


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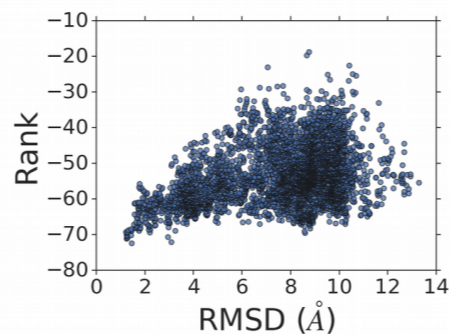
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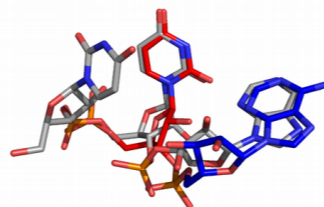


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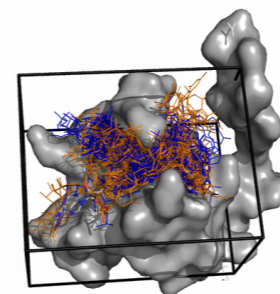


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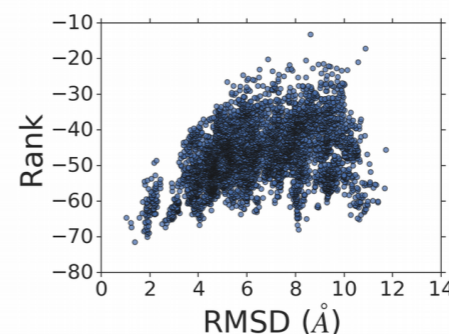
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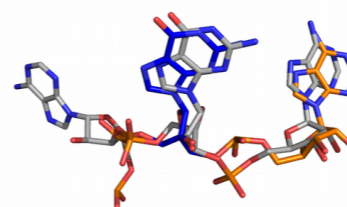


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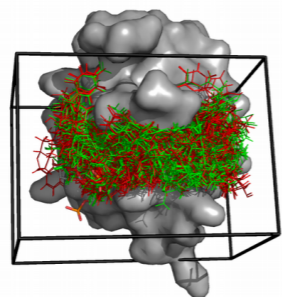
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~ 5000 3-mers

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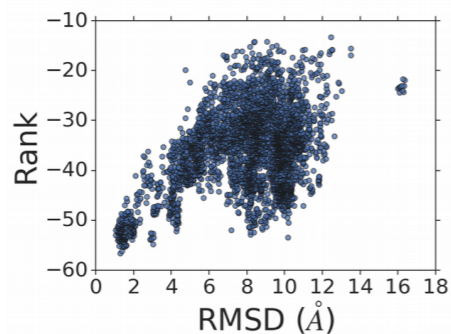
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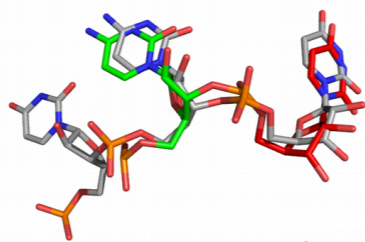


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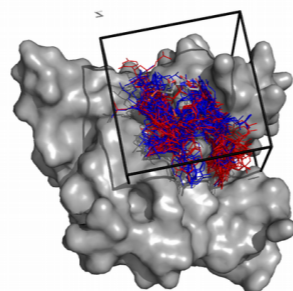


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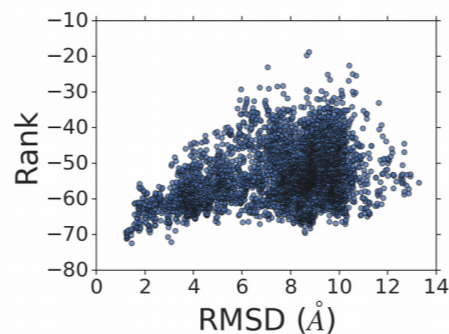
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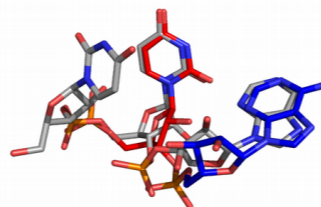


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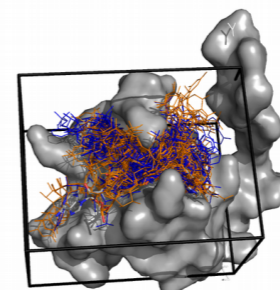


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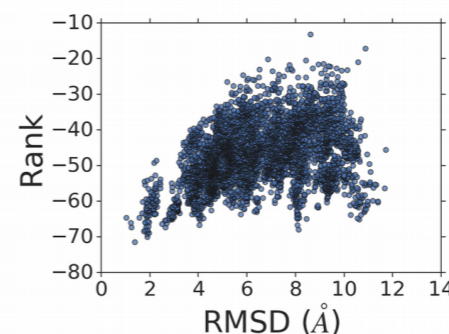
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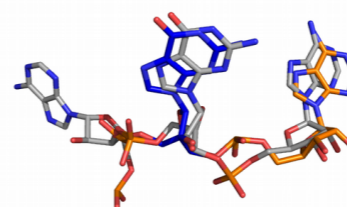


Chain search
for AG

5151 chains



Top 1 chain

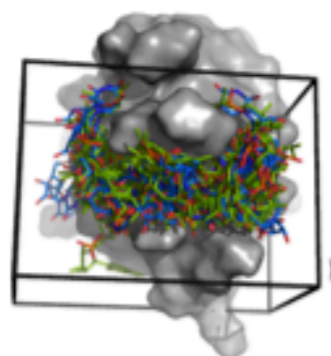


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~ 5000 3-mers

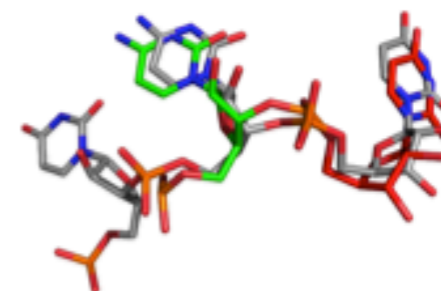
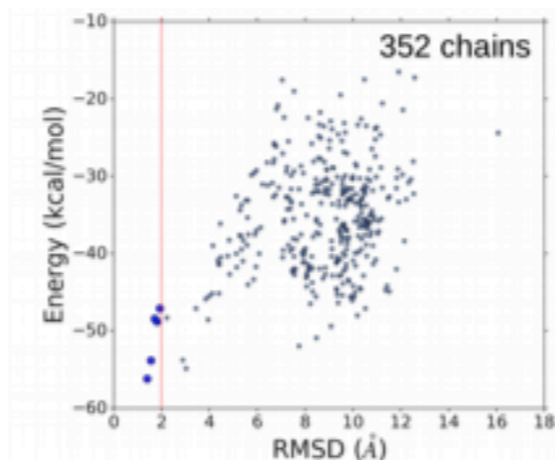
Top1 for 2-mers

Clustering of initial poses

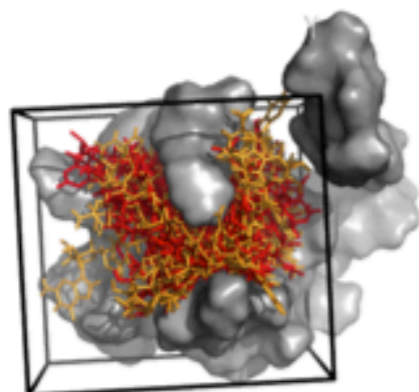


RRM (top 60 U&C)

chain search
sequence: CU

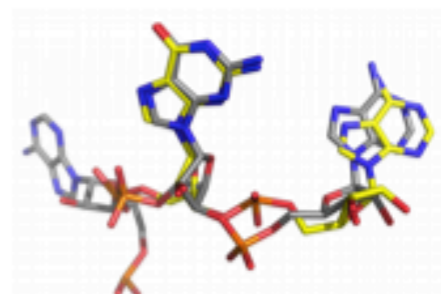
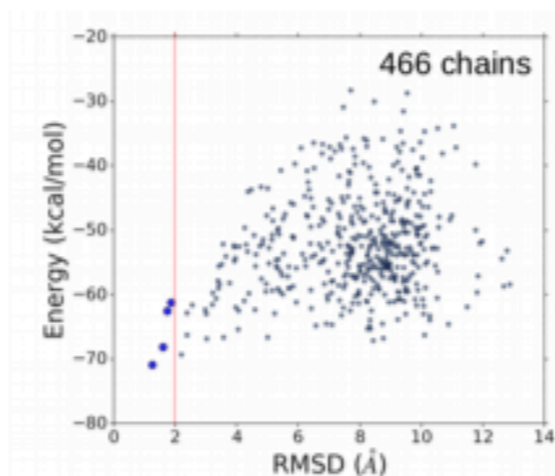


Best scored chain (1,3 Å)

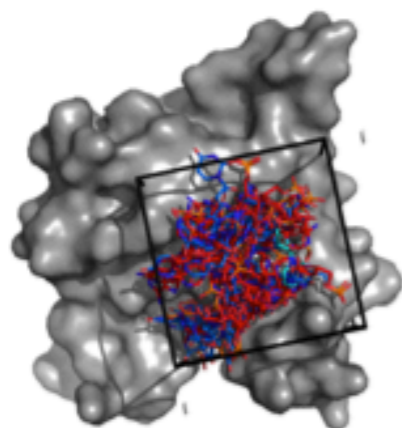


KH (top 60 A&G)

chain search
sequence: GA

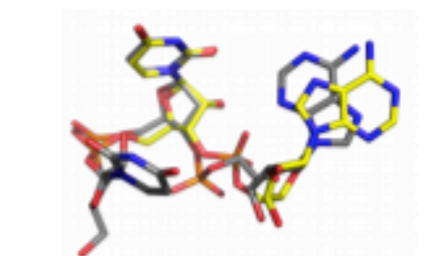
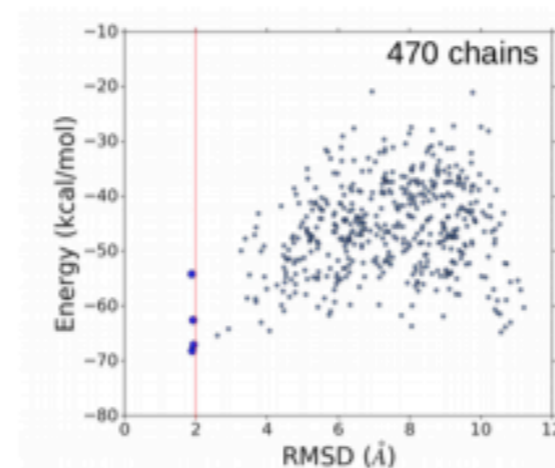


Best scored chain (1,2 Å)



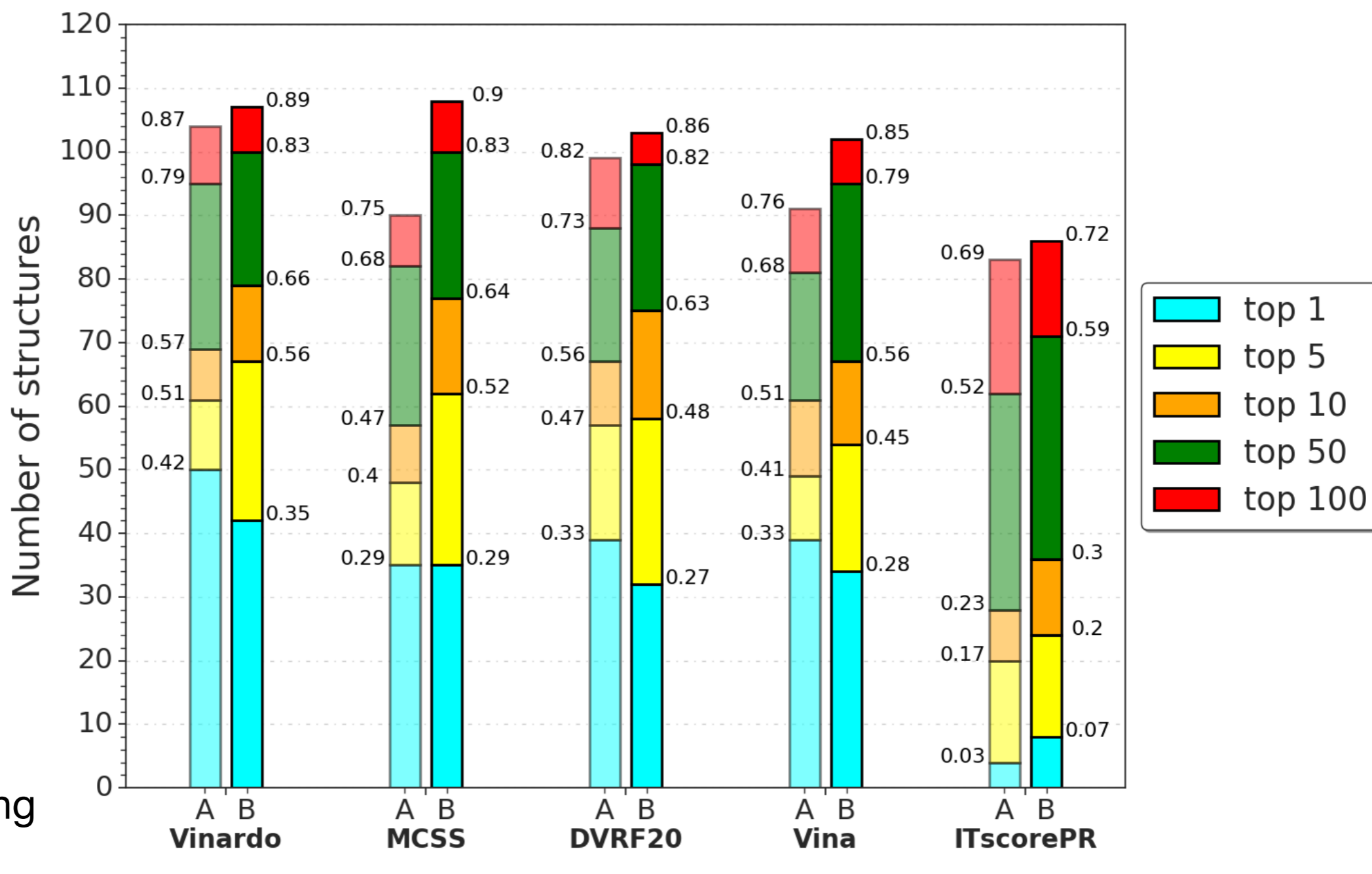
Zf-CCCH (top 60 U&A)

chain search
sequence: UA



Best scored chain (1,9 Å)

Scoring functions: nucleotide-protein interactions



Other biomolecules

- amino acids
- sugars
- lipids
- etc

Other biomolecules

- amino acids
- sugars
- lipids
- etc

You're welcome to join and contribute ...

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