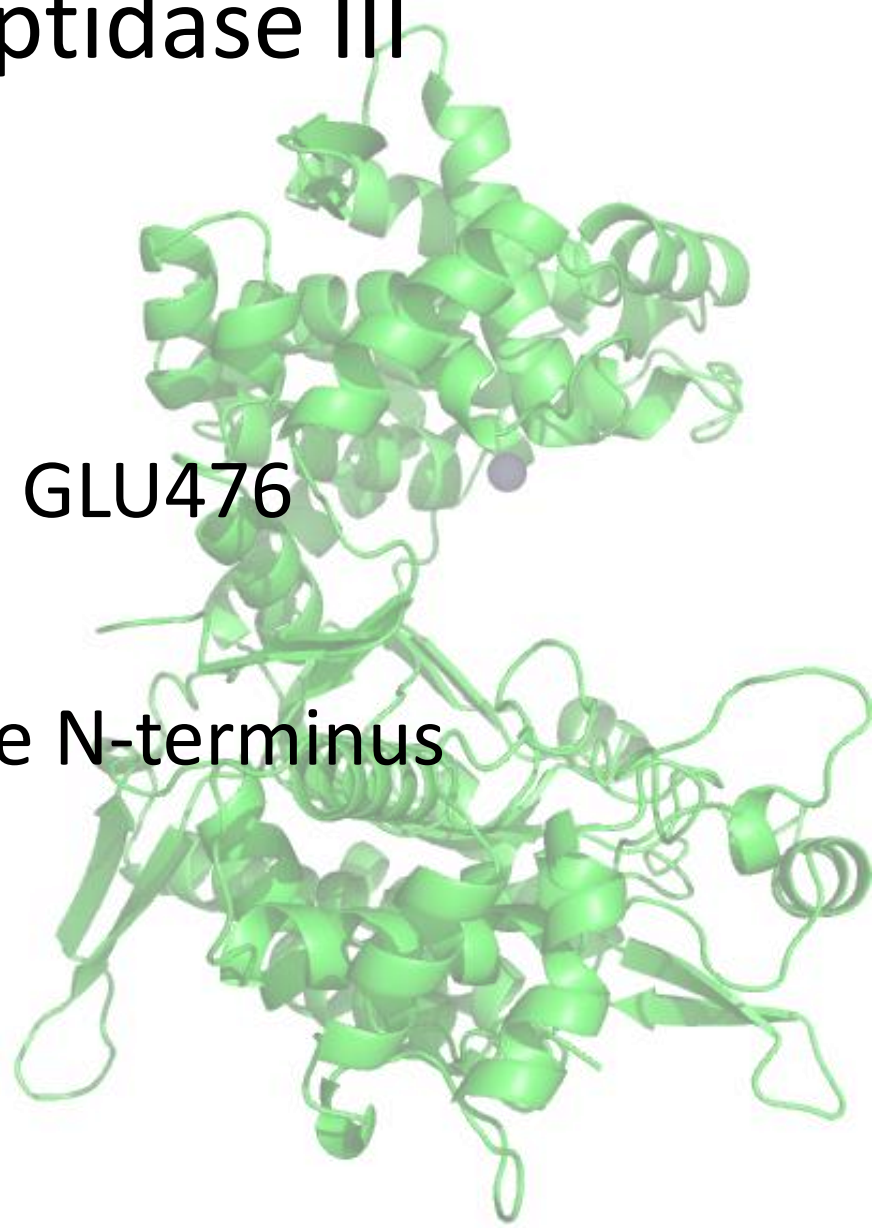
Conformational study of DPP III from *Bacteroides thetaiotaomicron*

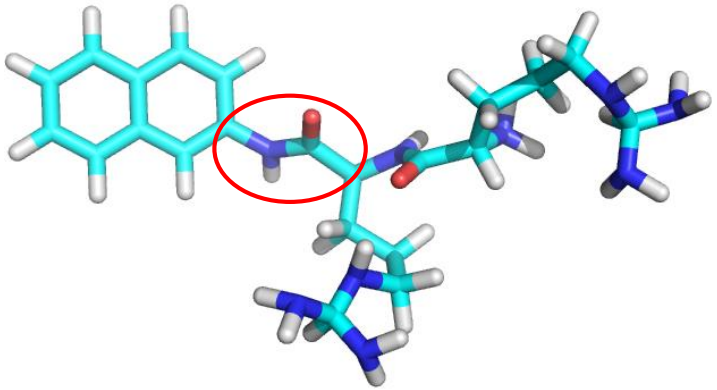
Marko Tomin, mag. chem.

Dipeptidyl peptidase III

- 2 domains
- Zn^{2+}
- HIS448, GLU449, HIS453, GLU476

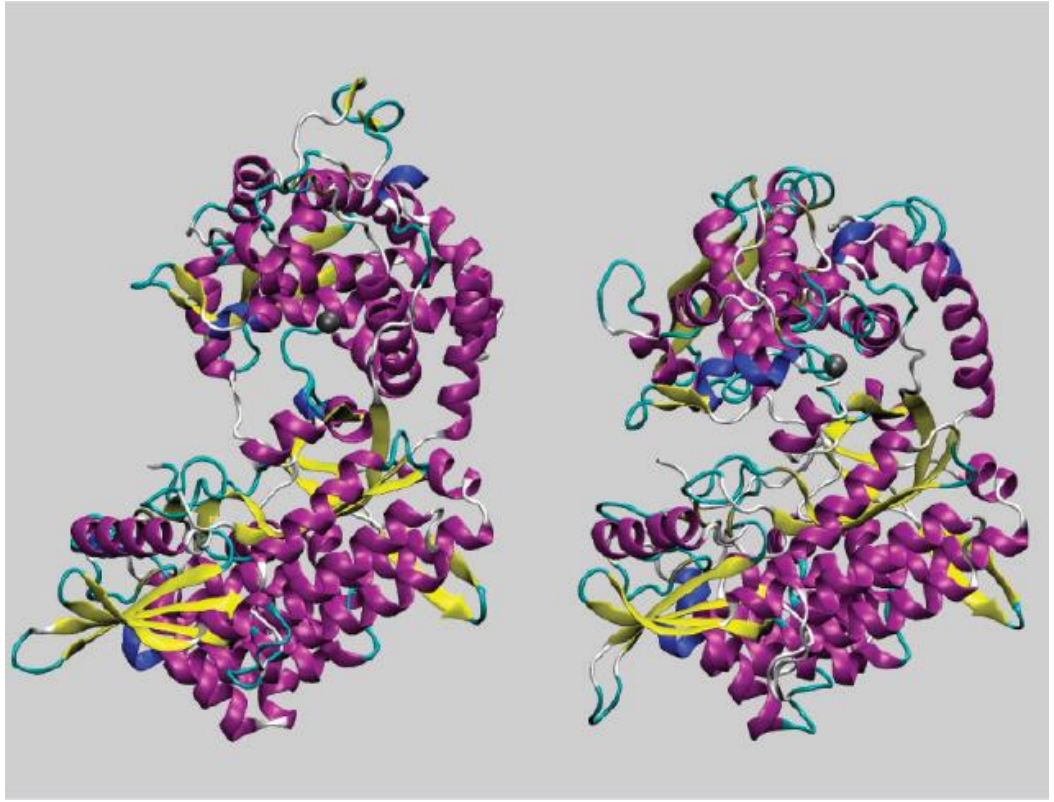


Cleaves dipeptides from the N-terminus



Human DPPIII

- Sequence identity ≈23%
- RMSD: 4,3 Å

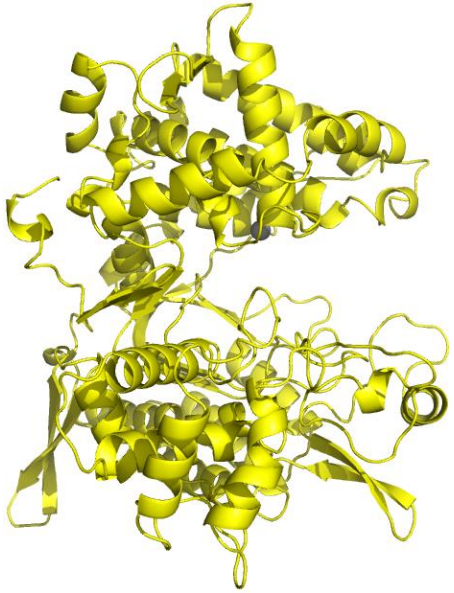


Open and closed forms of the human DPPIII[1]

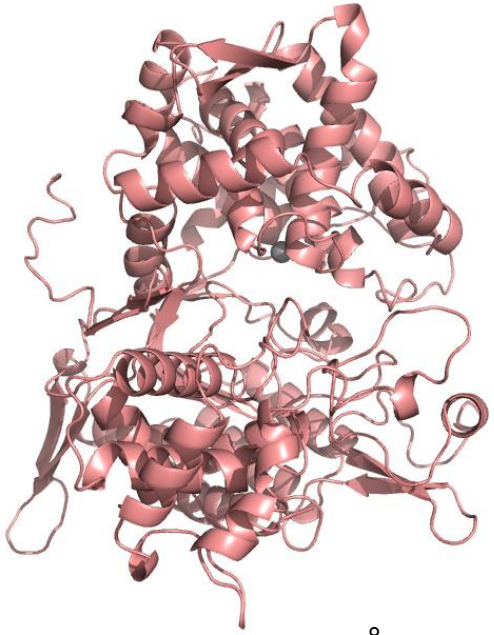
1. A. Tomić, M. González, S. Tomić, *J. Chem. Inf. Model.* **52** (2012) 1583-1594

Approaches used

RMSD: 3,244 Å

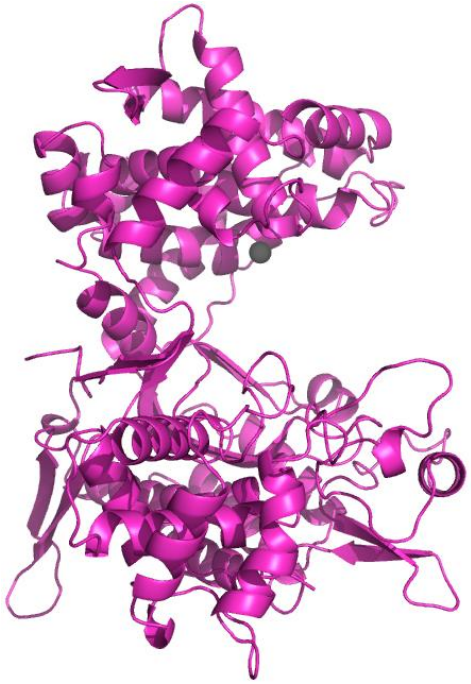


ff03

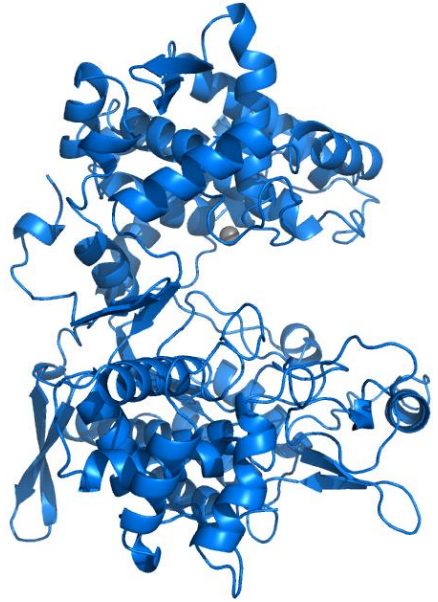


RMSD: 4,862 Å

ff12sb

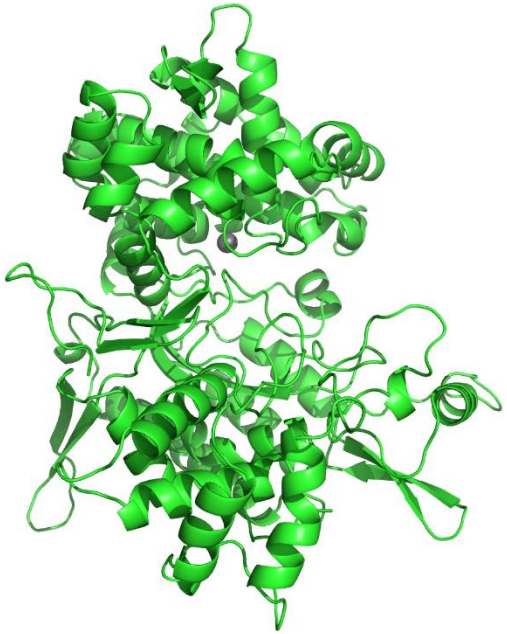


ff14sb



RMSD: 2,035 Å

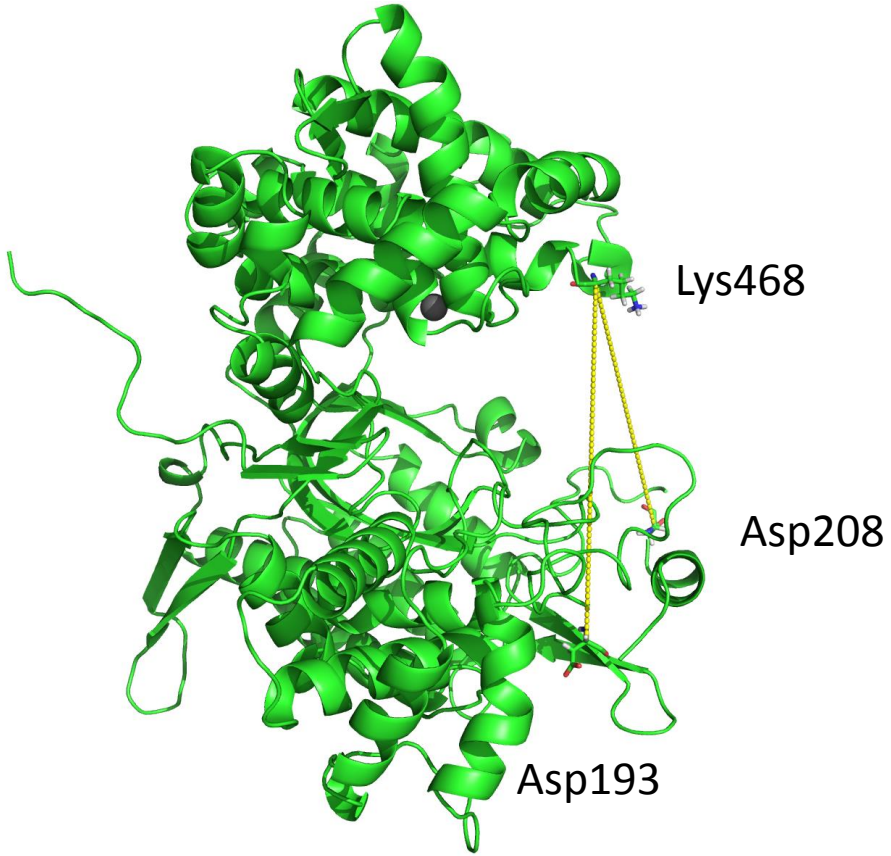
ff14sb aMD



RMSD: 3,501 Å

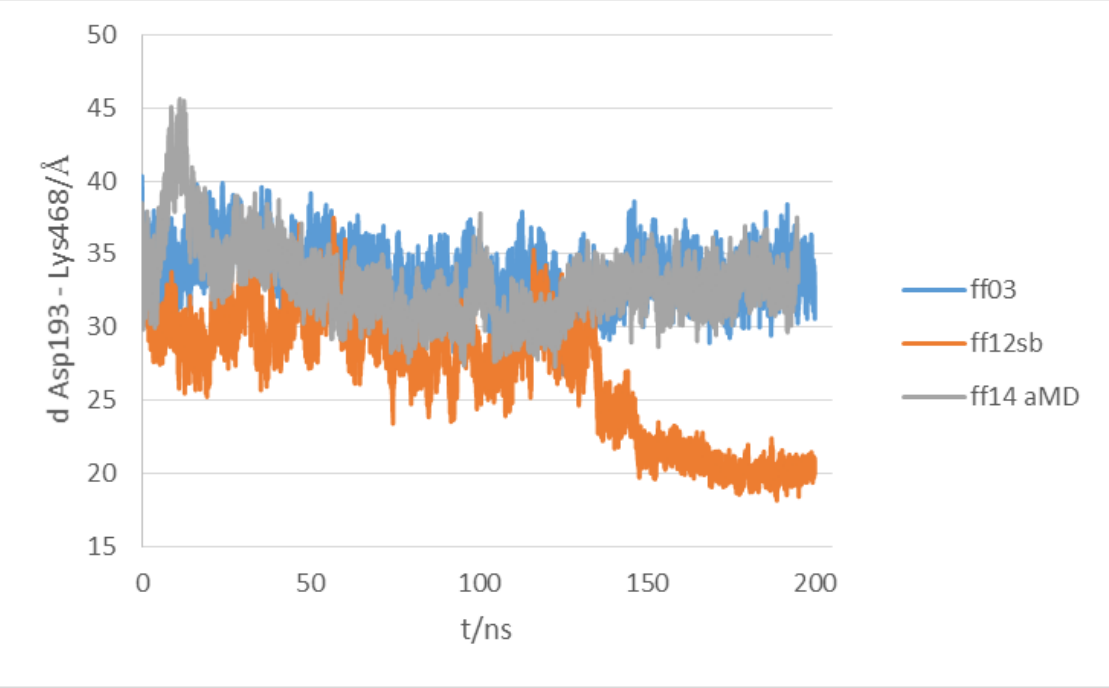
Geometric parameters

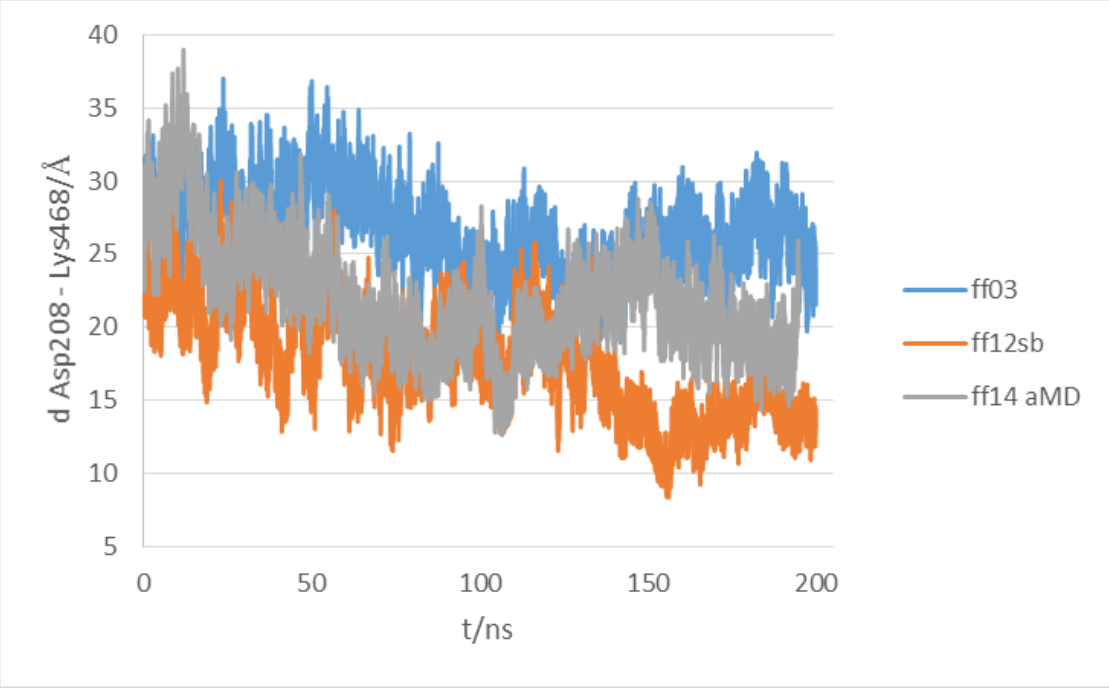
- RMSD and radii of gyration are not good descriptors
- Two distances used due to the lack of secondary structure



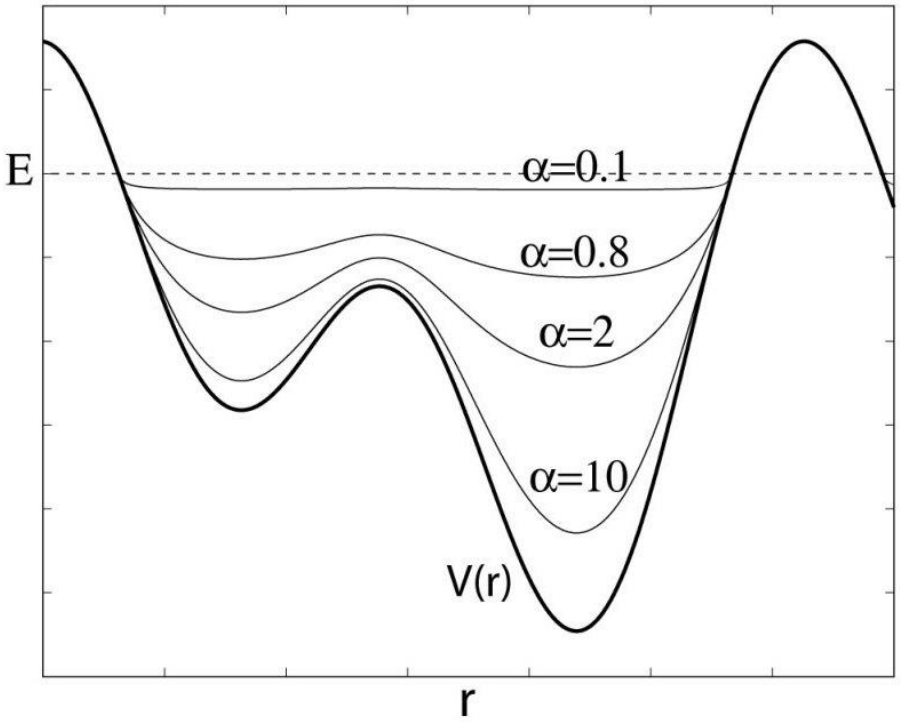
Geometric parameters

- High oscillations due to the nature of aMD



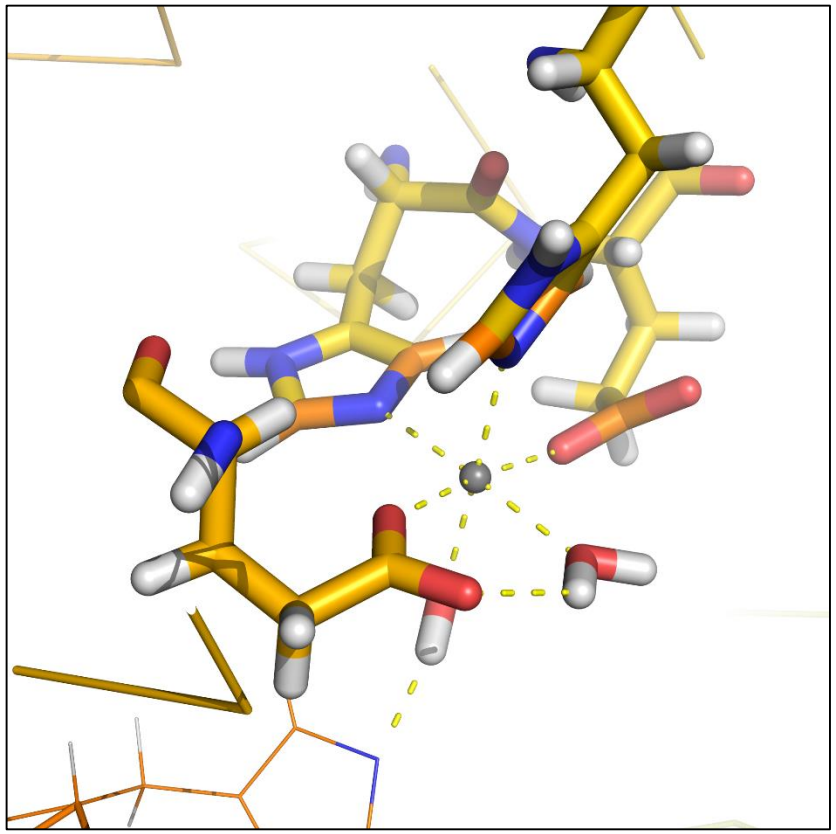


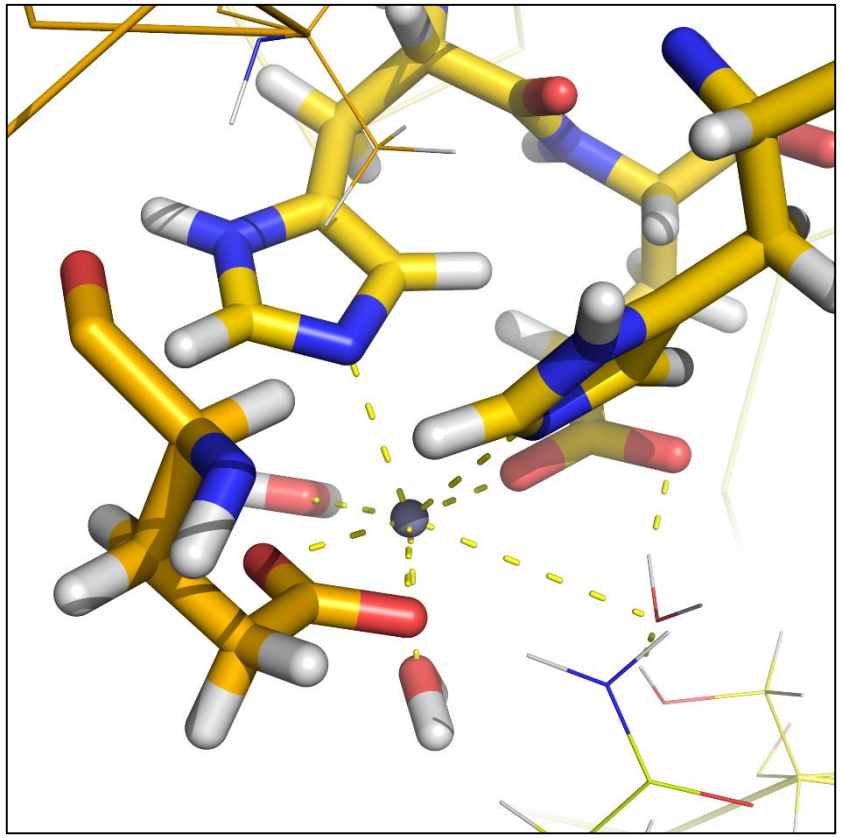
Accelerated molecular dynamics



$$\Delta U(r) = \begin{cases} 0, & U(r) \geq E \\ \dfrac{\left(E - U(r)\right)^2}{\alpha + (E - U(r))}, & U(r) < E \end{cases}$$

Zn^{2+} coordination

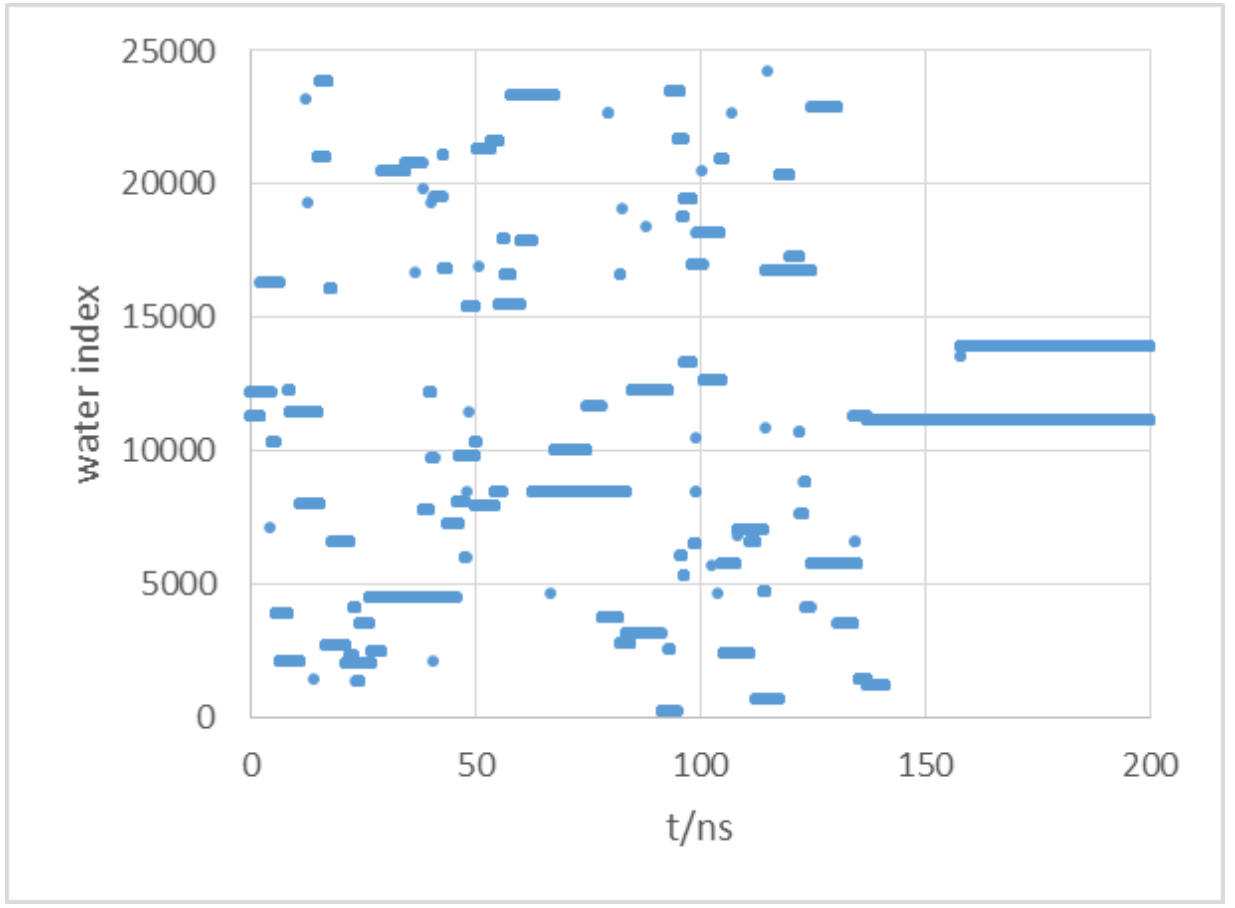




- High plasticity seen in human DPPIII[2] not observed in Bt-DPPIII

2. A. Tomić, S. Tomić, *Dalton trans.* **43** (2014) 15503-15514.

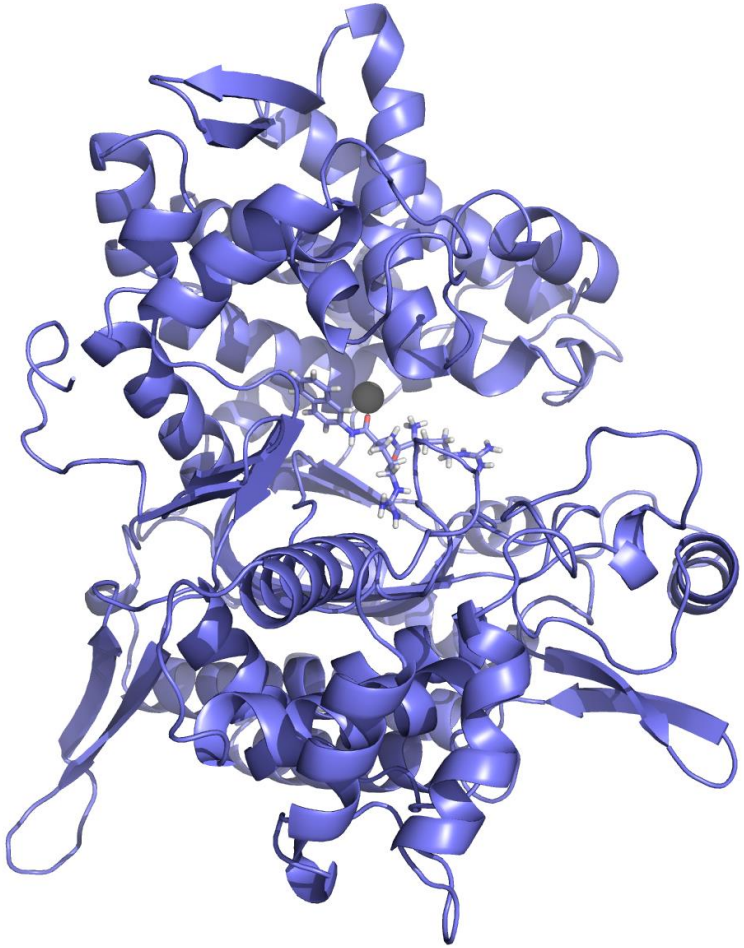
Zn^{2+} coordination sphere

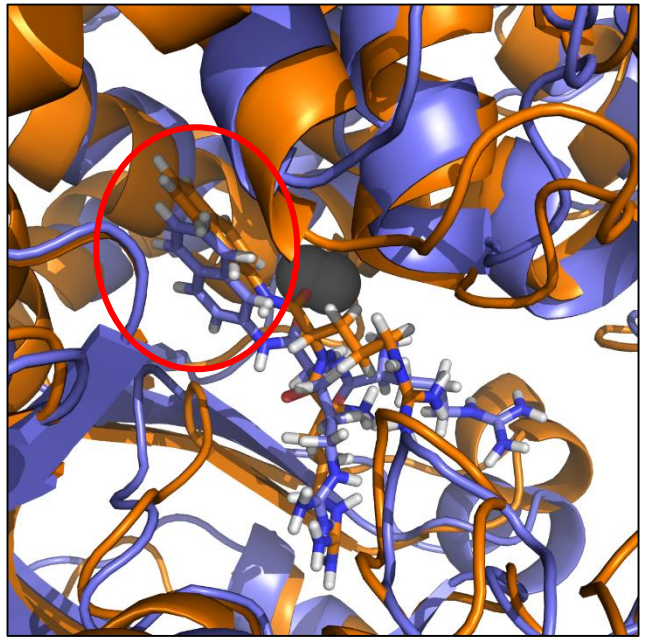


Water retention time for 200 ns of MD simulations with ff12SB

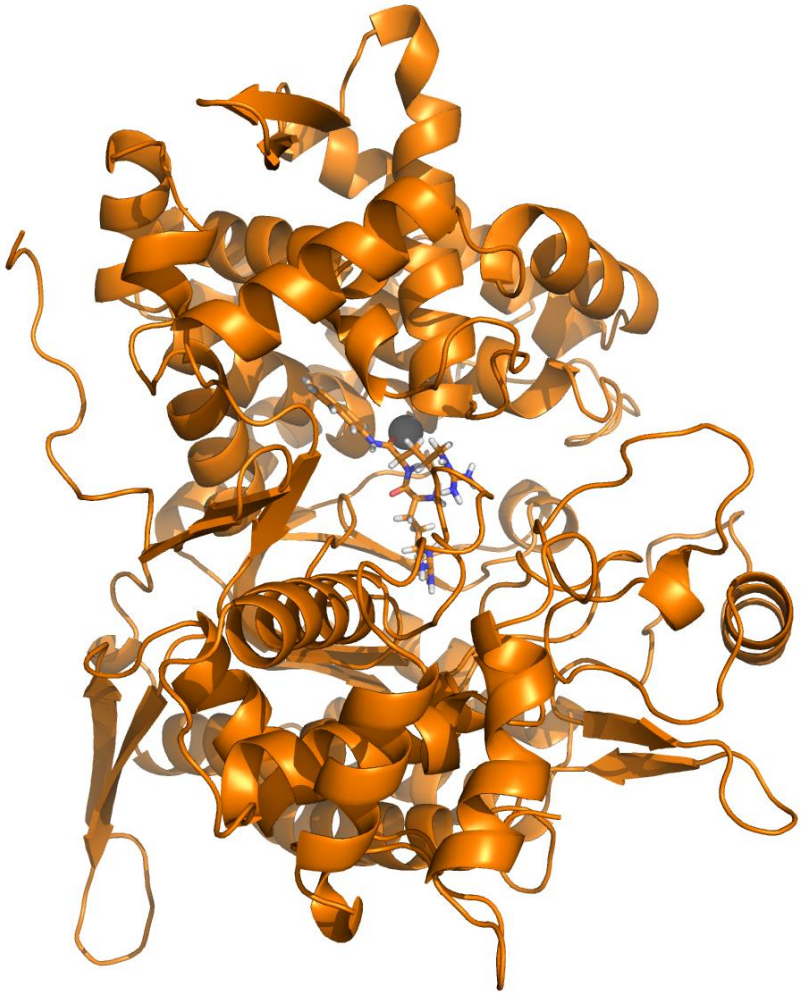
RRNA docking

cMD ff12sb





aMD ff14sb



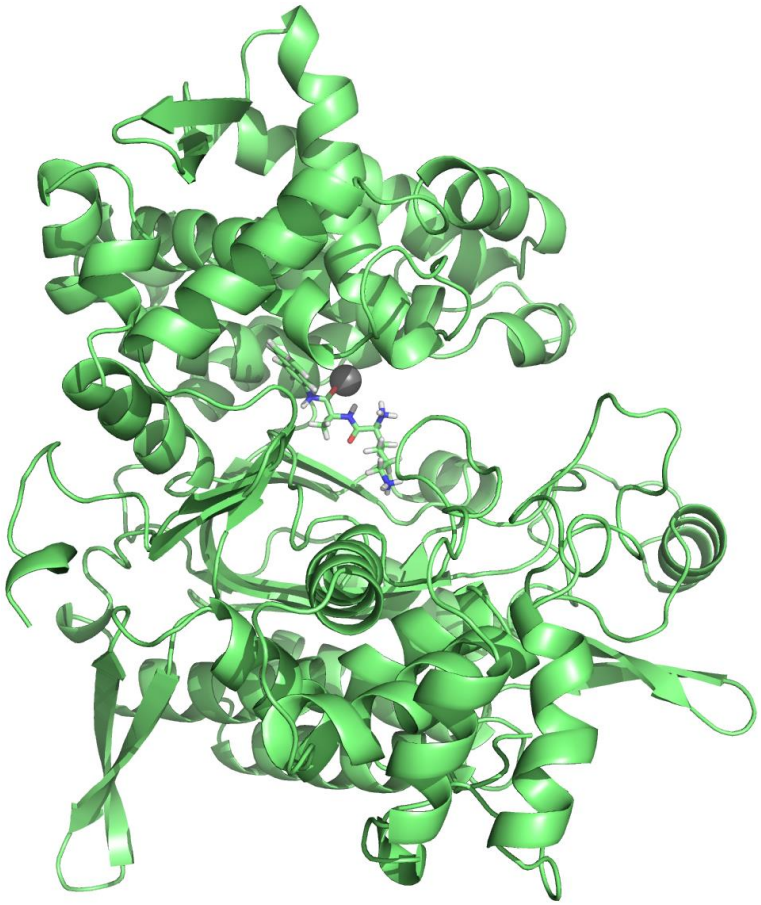
Energetics of RRNA docking

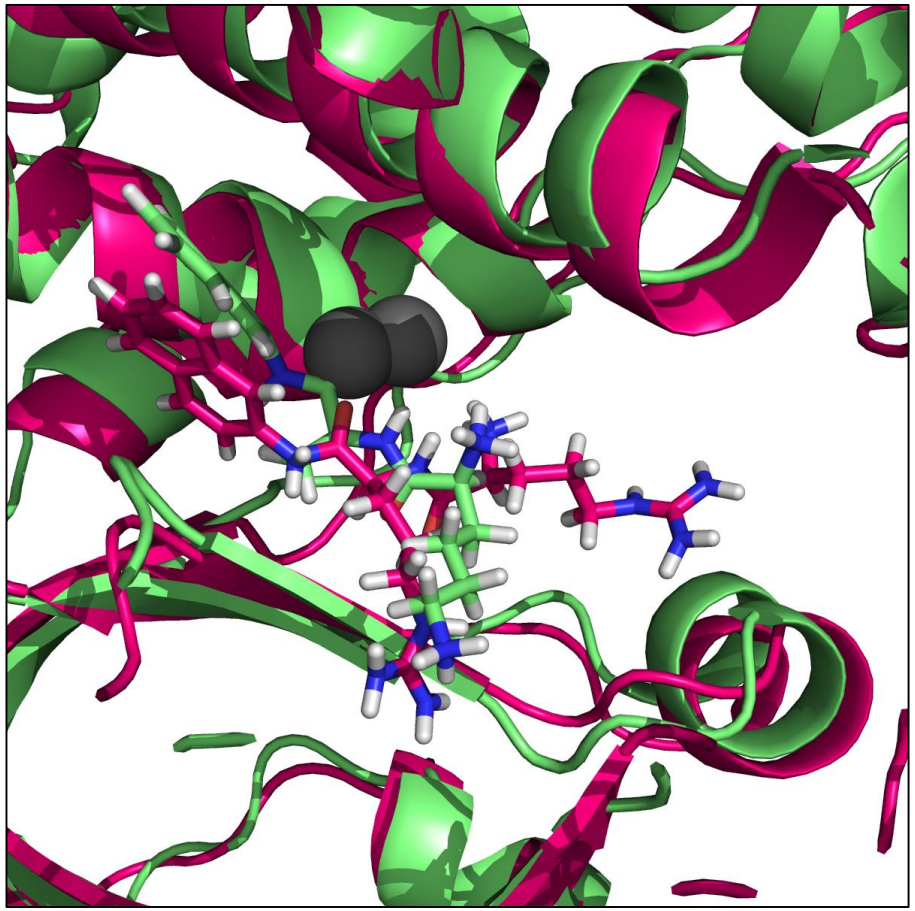
Method	ΔE_{GB}/kcalmol^{-1}	ΔE_{PB}/kcalmol^{-1}
cMD/ff12SB	-32.46	-49.76
aMD/ff14SB	-53.8	-63.2

- Structure obtained by aMD/ff14SB used as starting point for cMD ff12SB simulations

- aMD/ff14SB produced a more stable complex conformation

KANA docking

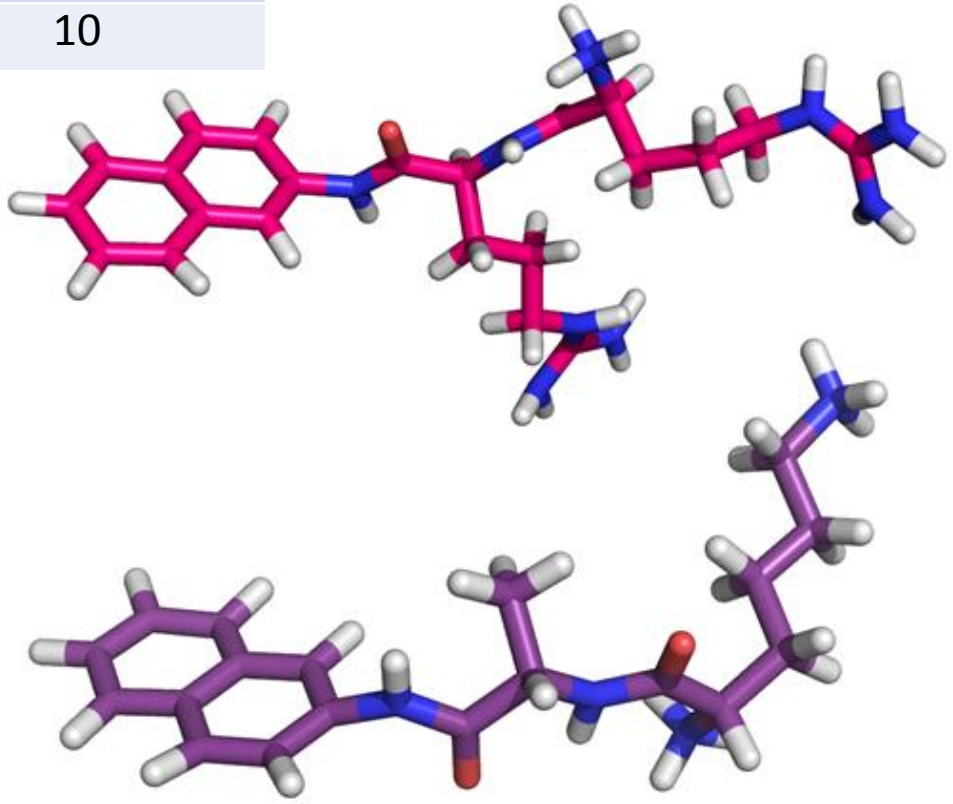




RRNA and KANA energetics

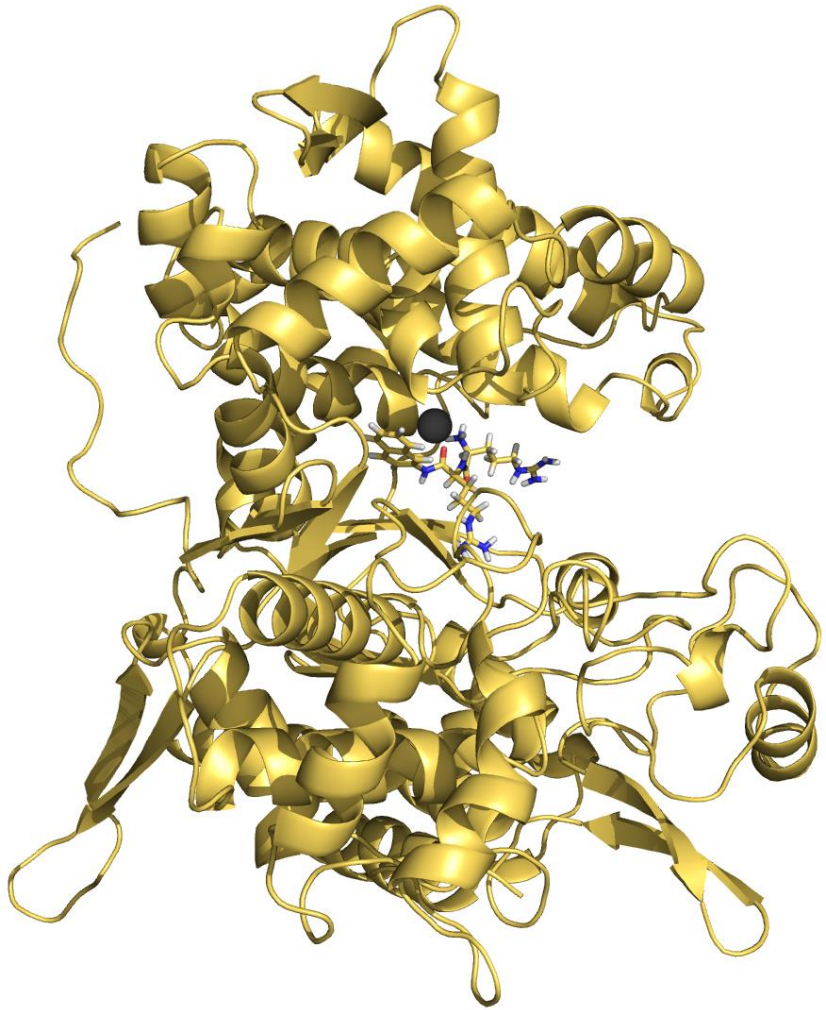
Complex	ΔE_{GB}/kcalmol^{-1}	ΔE_{PB}/kcalmol^{-1}	RHR (%)[3]
DPPIII - RRNA	-32.46	-49.76	100
DPPIII - KANA	-29.74	-41.41	10

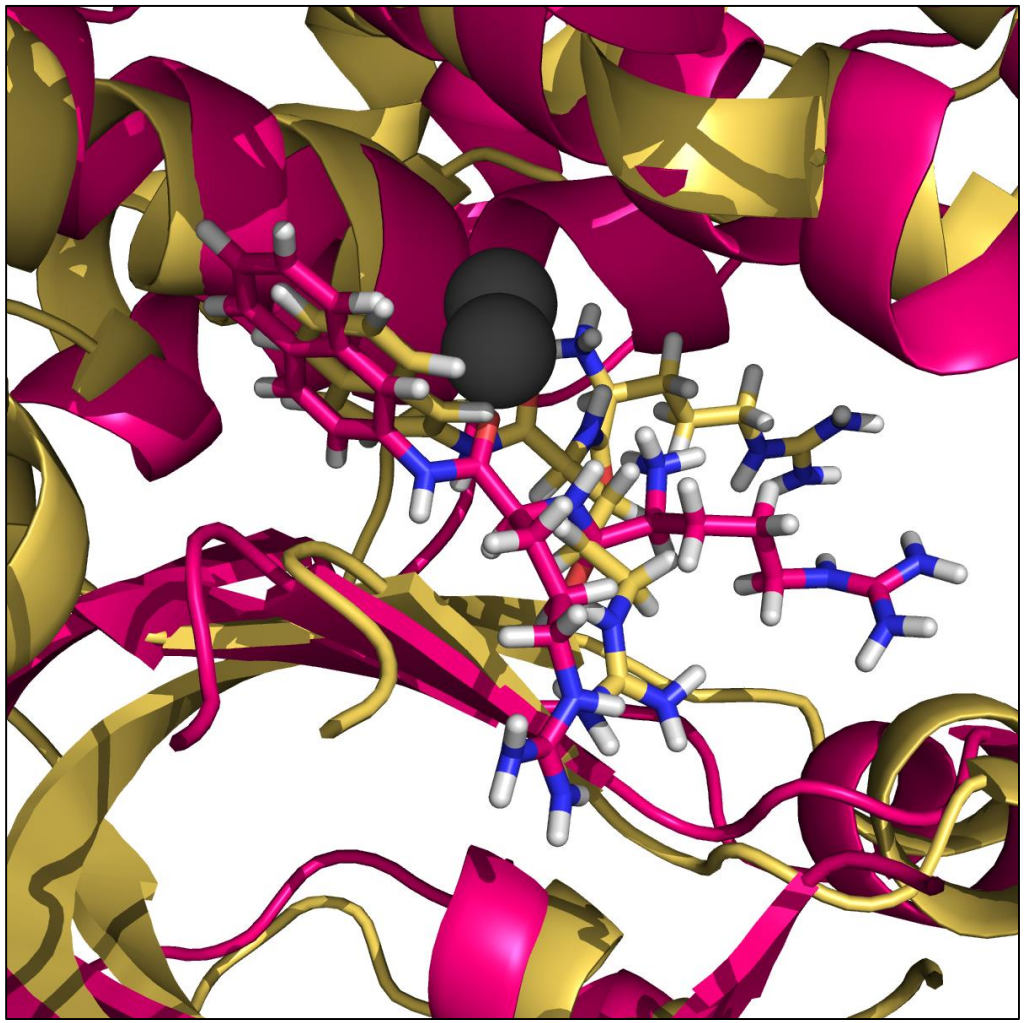
Acceptor	% of frames RRNA	% of frames KANA
Glu475 (I)	98.72	66.76
Gly383	71.84	-
Glu320	70.88	-
Glu475 (II)	33.36	55.84
Glu307	31.08	47.48
Asp375	-	38.88
Glu475 (III)	-	31.28



3. B. Vukelić, B. Salopek-Sondi, J. Špoljarić, I. Sabljić, N. Meštrović, D. Agić, M. Abramić, *Biol. Chem.* **393** (2012) 37-46

C450S mutant





C450S mutant energetics

Complex	ΔE_{GB}/kcalmol^{-1}	ΔE_{PB}/kcalmol^{-1}	k_{cat} (s^{-1})[3]
wt-DPPIII	-32.46	-49.76	5.0
c450s DPPIII	-22.46	-44.24	0.6

Acceptor	% of frames Wt-DPPIII	% of frames C450S-DPPIII
Glu475 (I)	98.72	99.00
Gly383	71.84	14.44
Glu320	70.88	-
Glu475 (II)	33.36	21.60
Glu307	31.08	-
Glu449	-	77.84

3. B. Vukelić, B. Salopek-Sondi, J. Špoljarić, I. Sabljić, N. Meštrović, D. Agić, M. Abramić, *Biol. Chem.* **393** (2012) 37-46

To-do list

- Dock again with aMD/ff14SB
- Start on DPPIII from *P. Gingivalis* – homology modelling
- QM/MM calculations to unveil the mechanism

That’s all, folks!