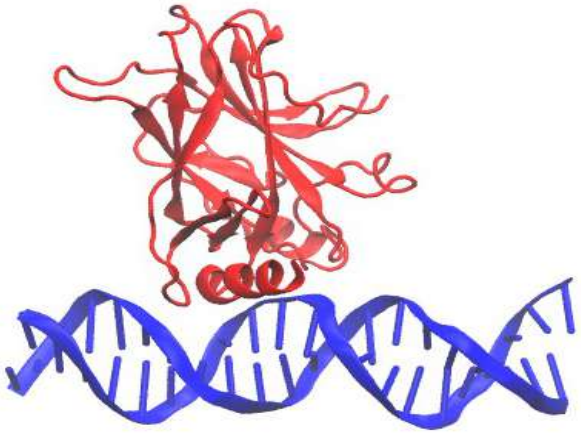
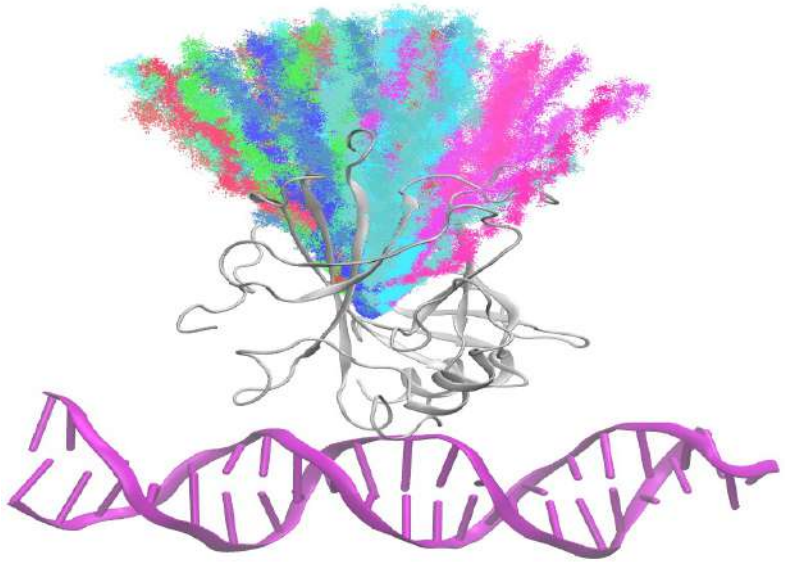
Investigating the dissociation process and binding free energy of the p53-DBD/DNA complex by PaCS-MD and MSM





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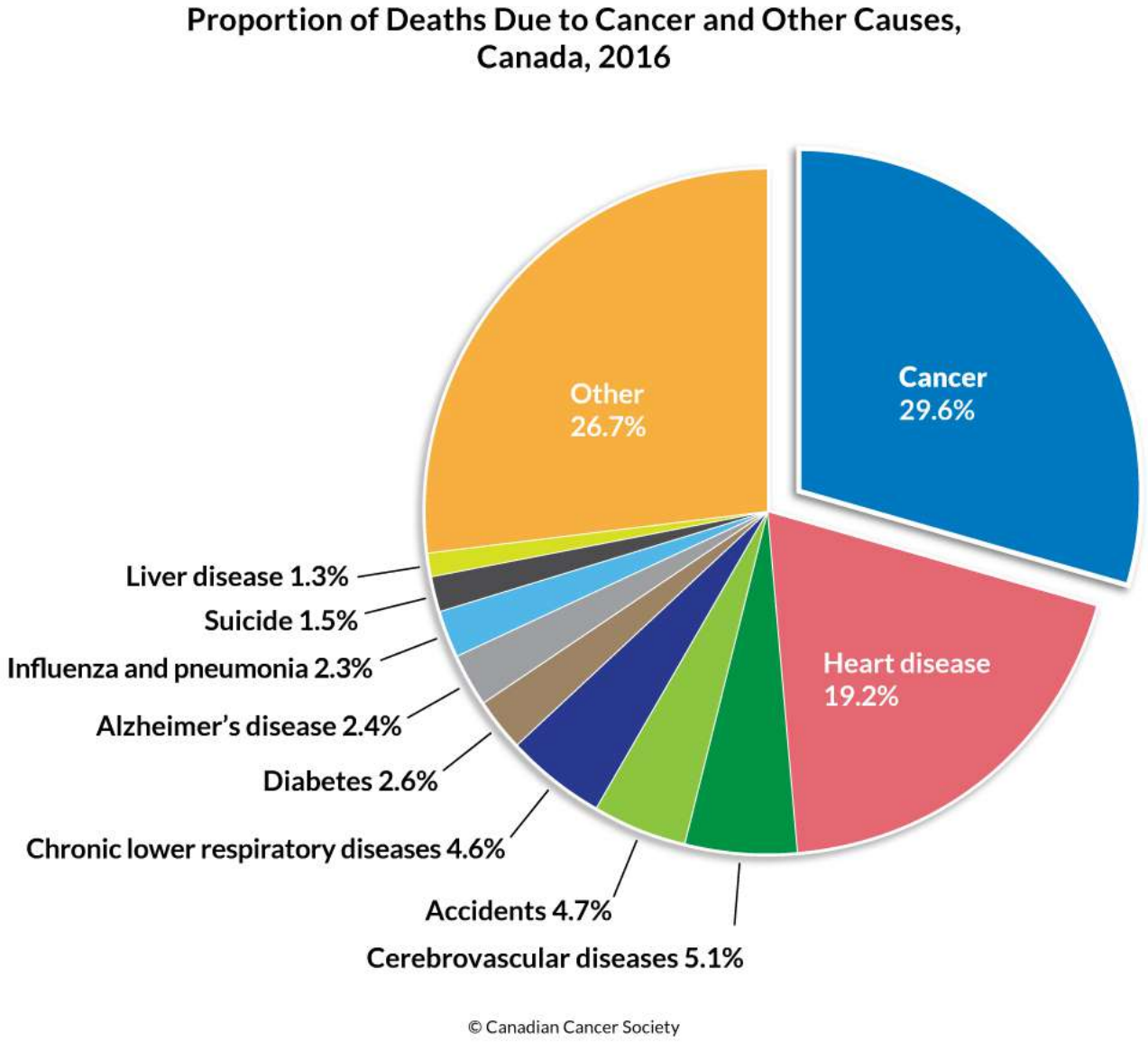
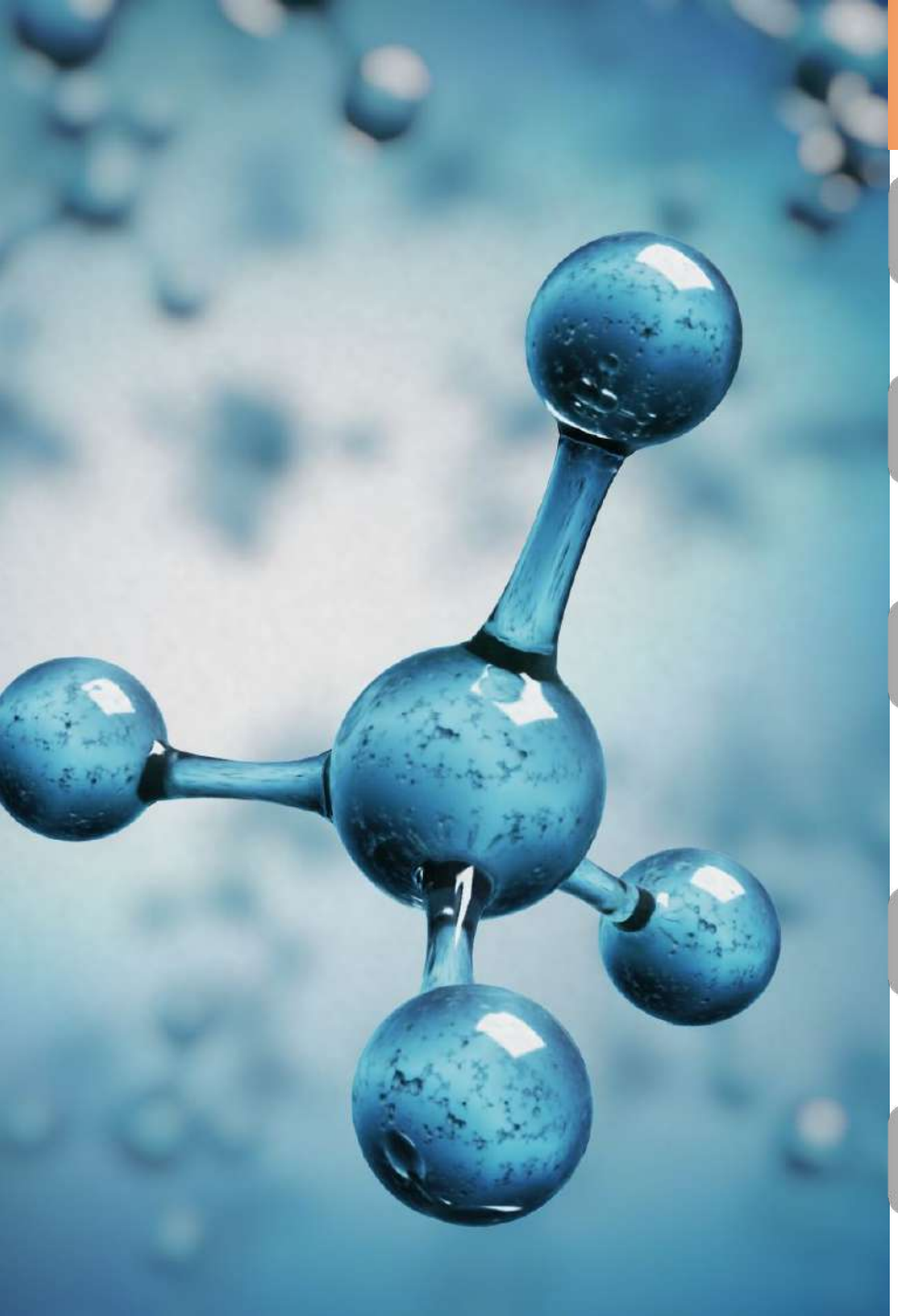
Third International Online Conference on Molecular Modeling and Spectroscopy.

15-16 September 2021

Motivation

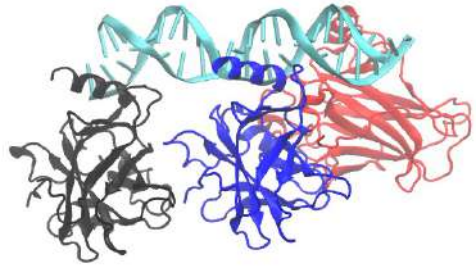


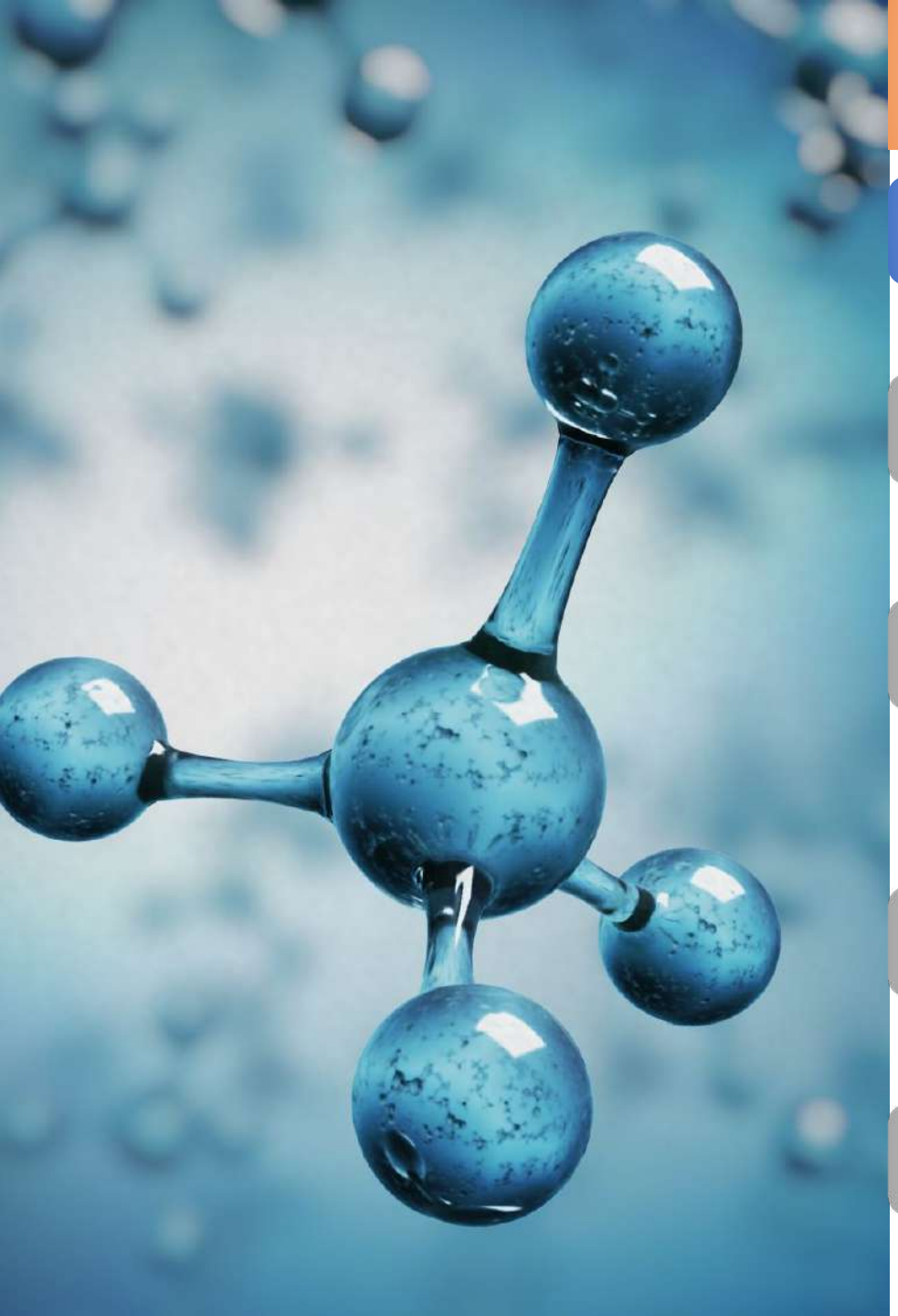
https://www.cancer.ca/en/



Outlines

- Introduction
- Stability of p53/DNA complex
- Dissociation simulation
- Free energy analysis
- Conclusion





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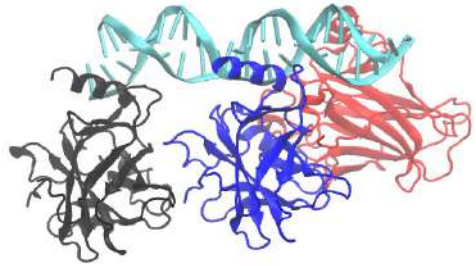
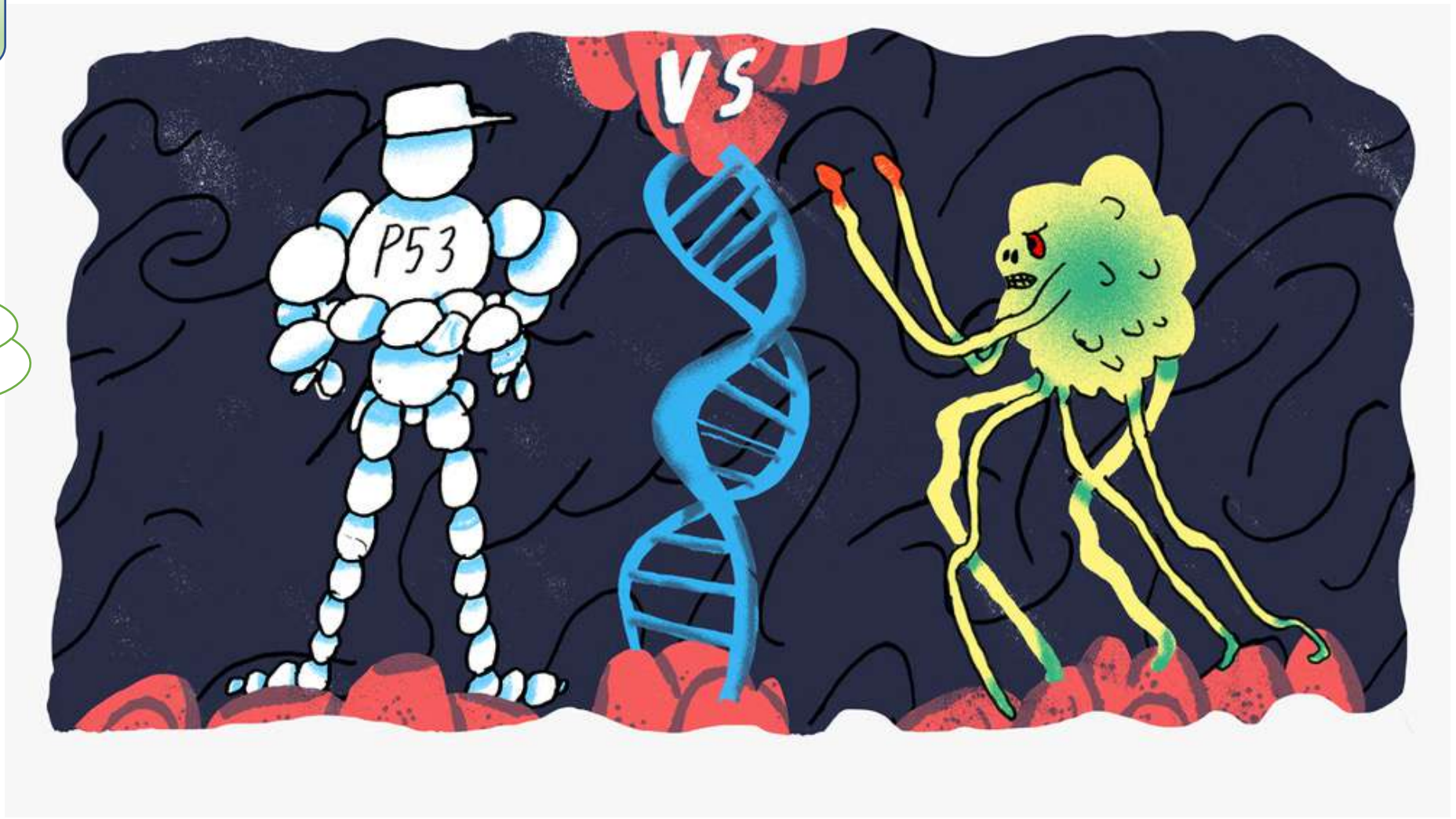


P53 main roles

The guardian of the genome

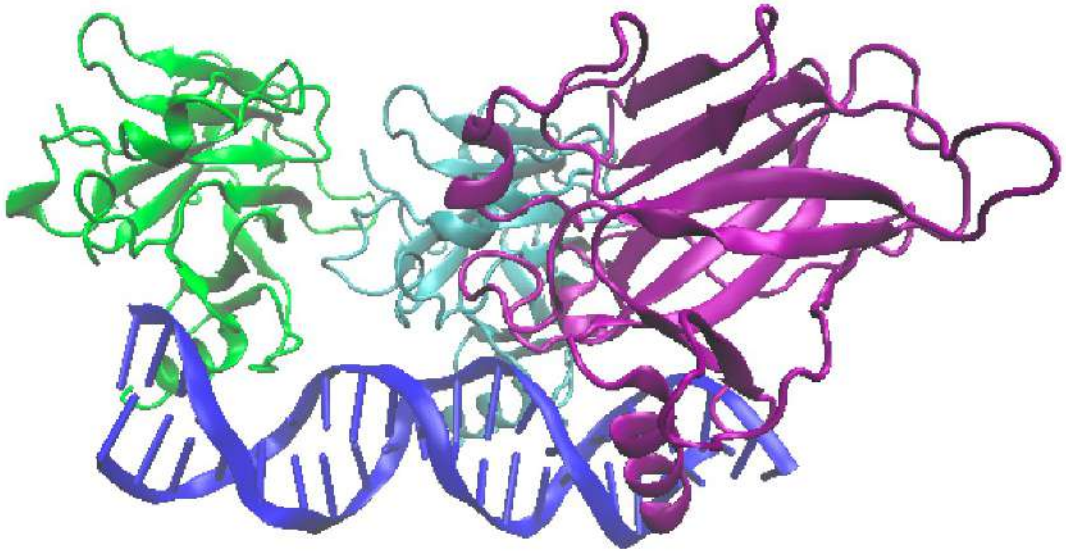


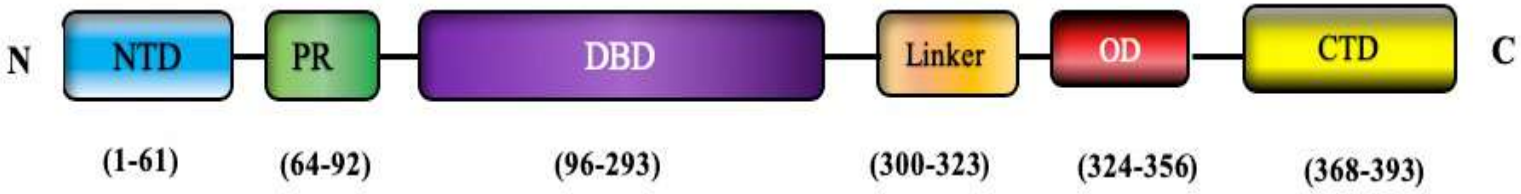
“If you define the problem correctly, you almost have the solution.”

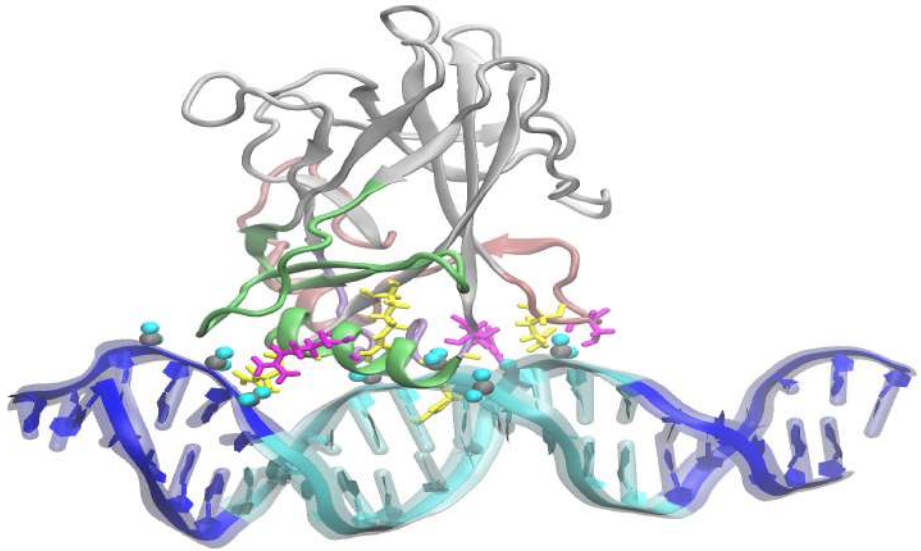
Steve Jobs

https://mosaicscience.com/story/brazils-cancer-curse/

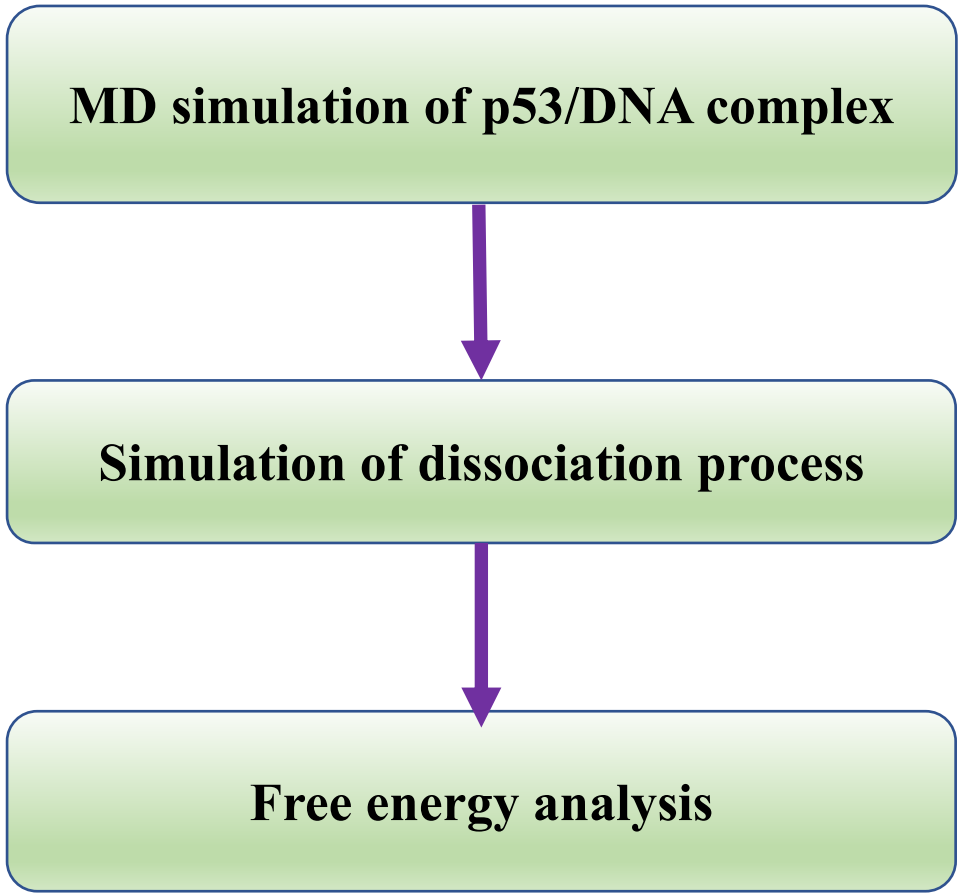
P53 structure







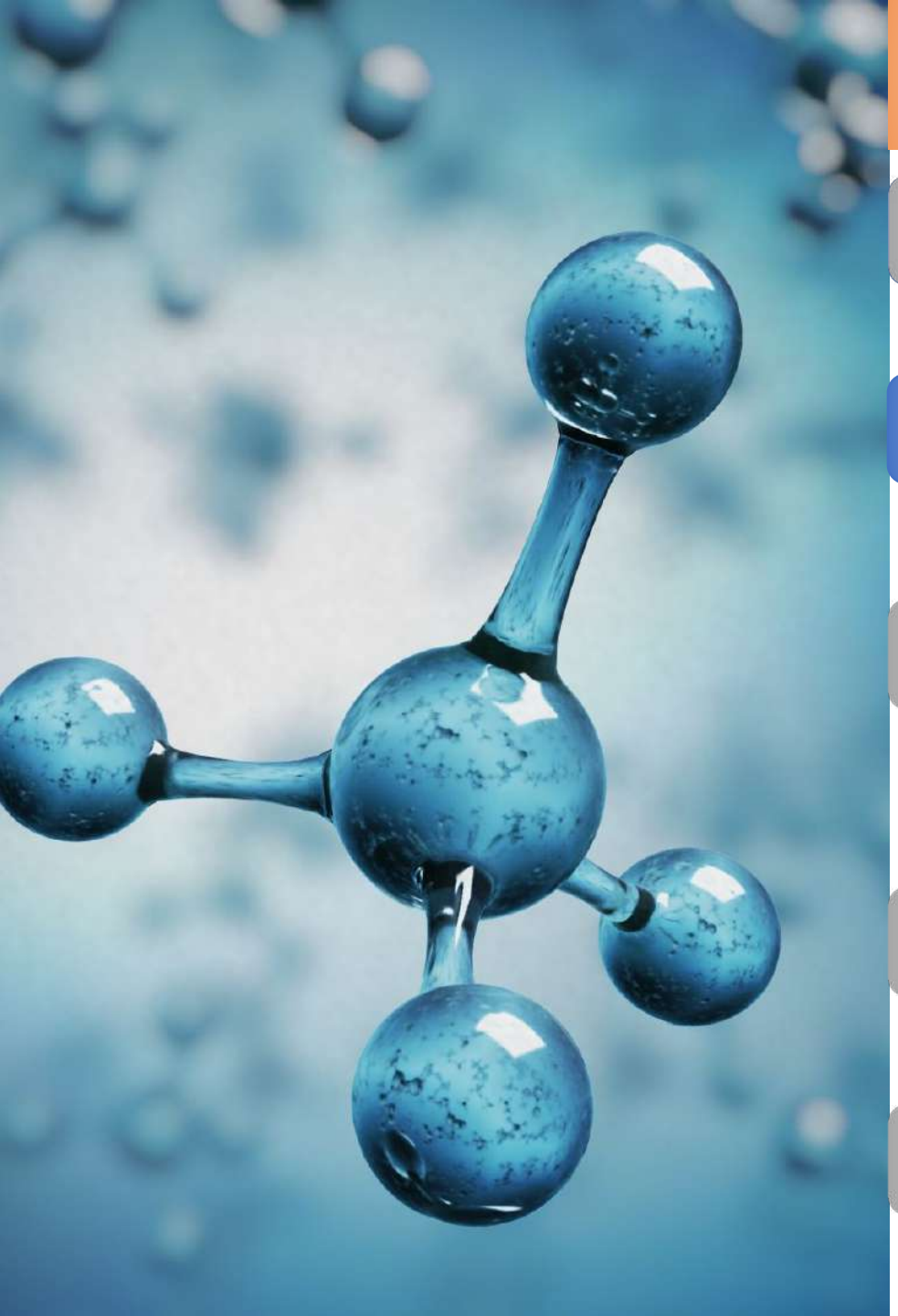
Overview of research steps



Examining the stability of the complex structure

Observing dissociation process at atomic resolution

Understanding the dissociation mechanism



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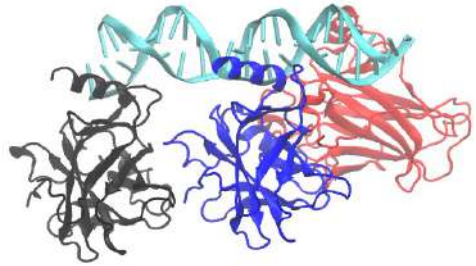
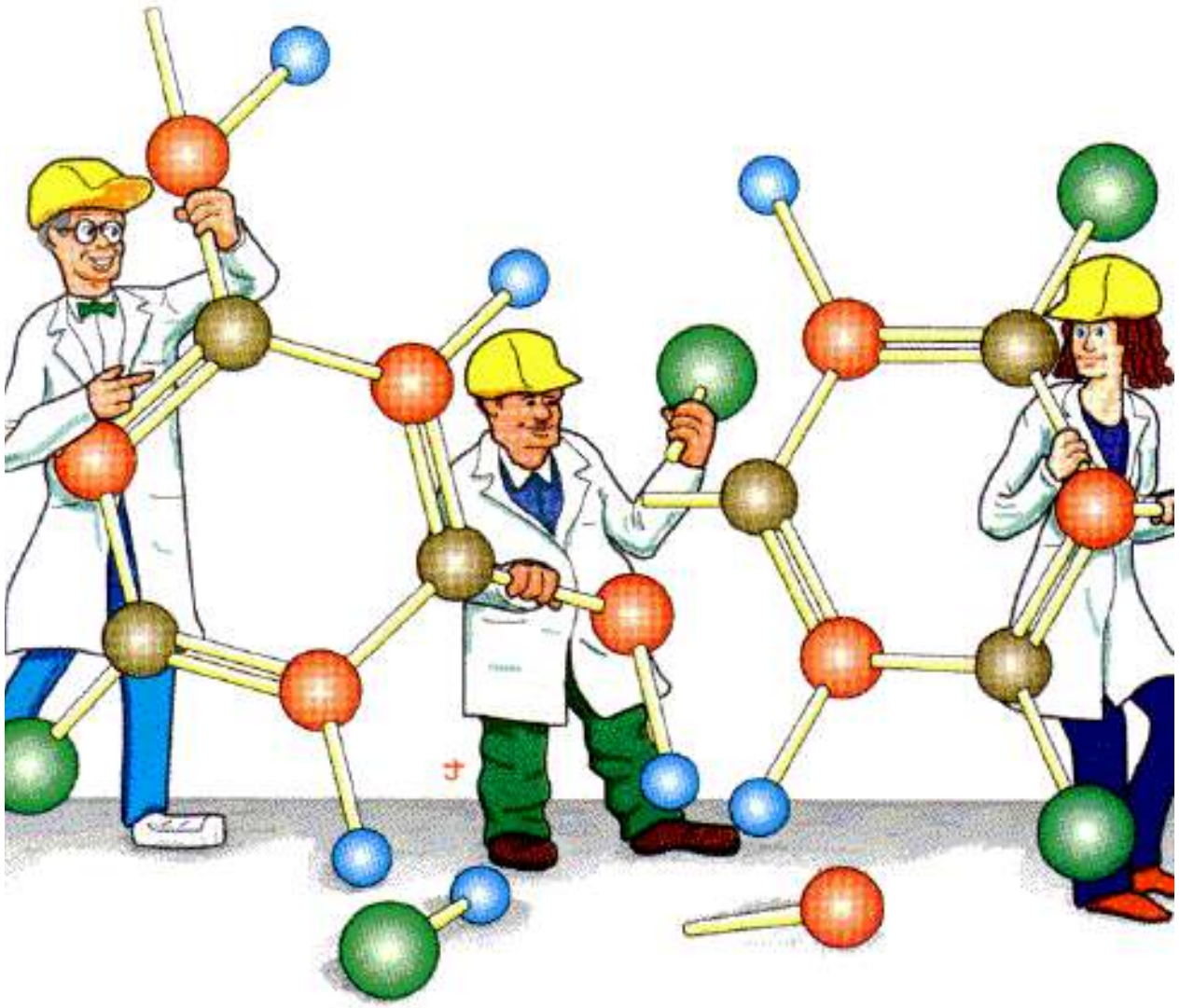


What is Molecular Dynamics (MD) Simulation?



https://dasher.wustl.edu/tinker/

MD Simulation

- The force is given by the negative gradient of the potential energy.

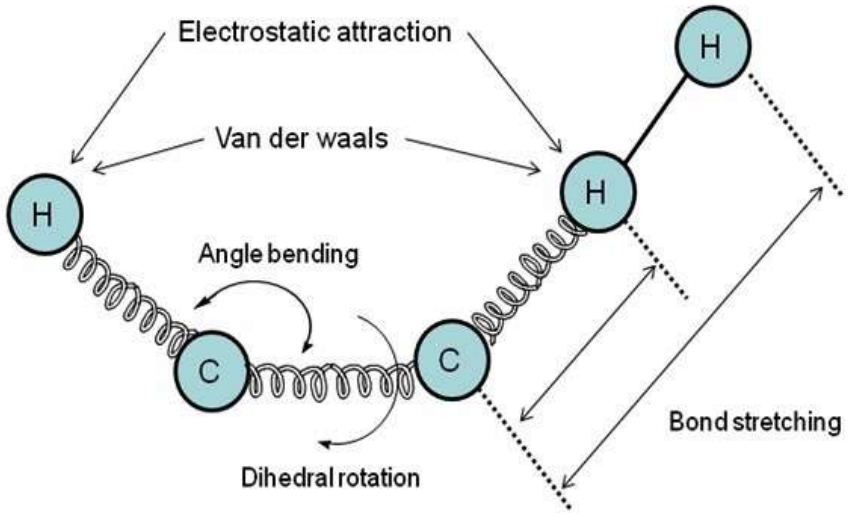
$$F = -\nabla V(r)$$

- Knowing the force allows us to accelerate the atoms in the direction of the force.

$$\vec{F} = m\vec{a} = m\frac{d\vec{v}}{dt}$$

- Interactions between atoms (energy) are described by **Force Fields**

$$V_{AMBER} = \sum_{bonds} k(r-r_{eq})^2 + \sum_{angles} k(\theta-\theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1+cos(n\phi-\gamma)] / \\ +\sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right] + \sum_{i<j}\left[\frac{q_i q_j}{\varepsilon R_{ij}}\right]$$



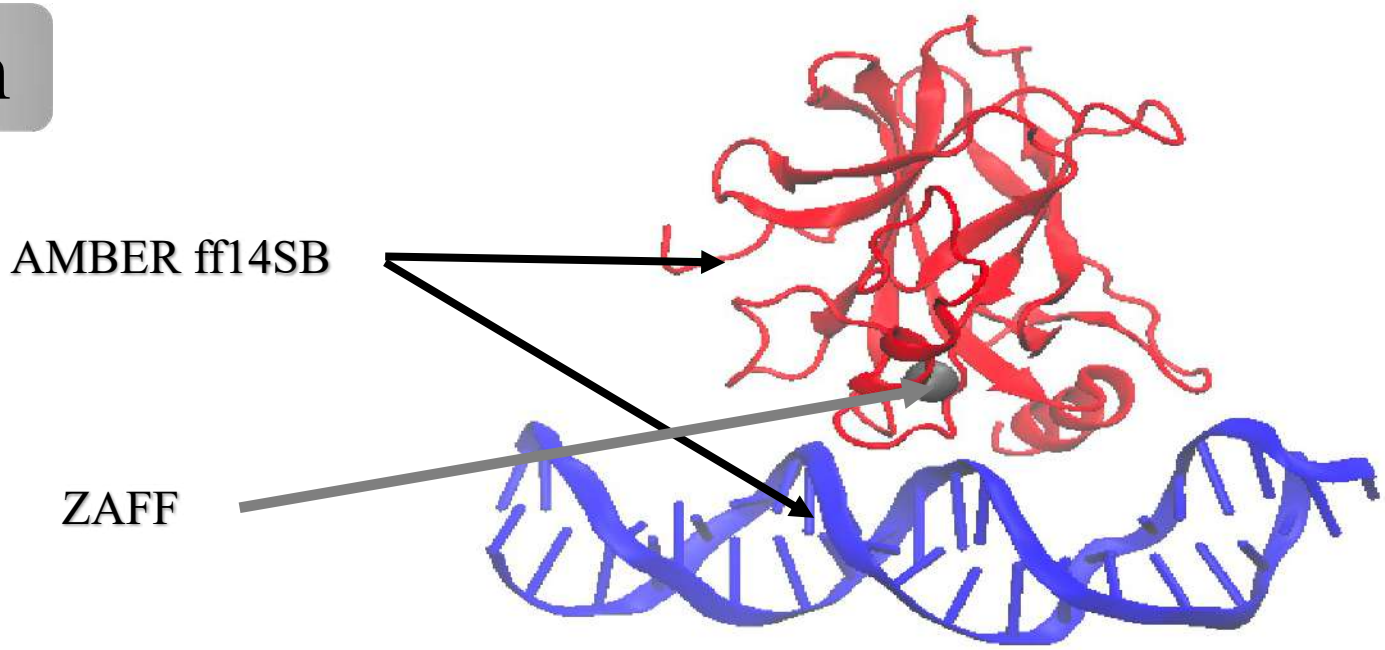
- **However,** MD simulations are limited by the fastest degree of freedom(bond vibration) ≈10 fs.

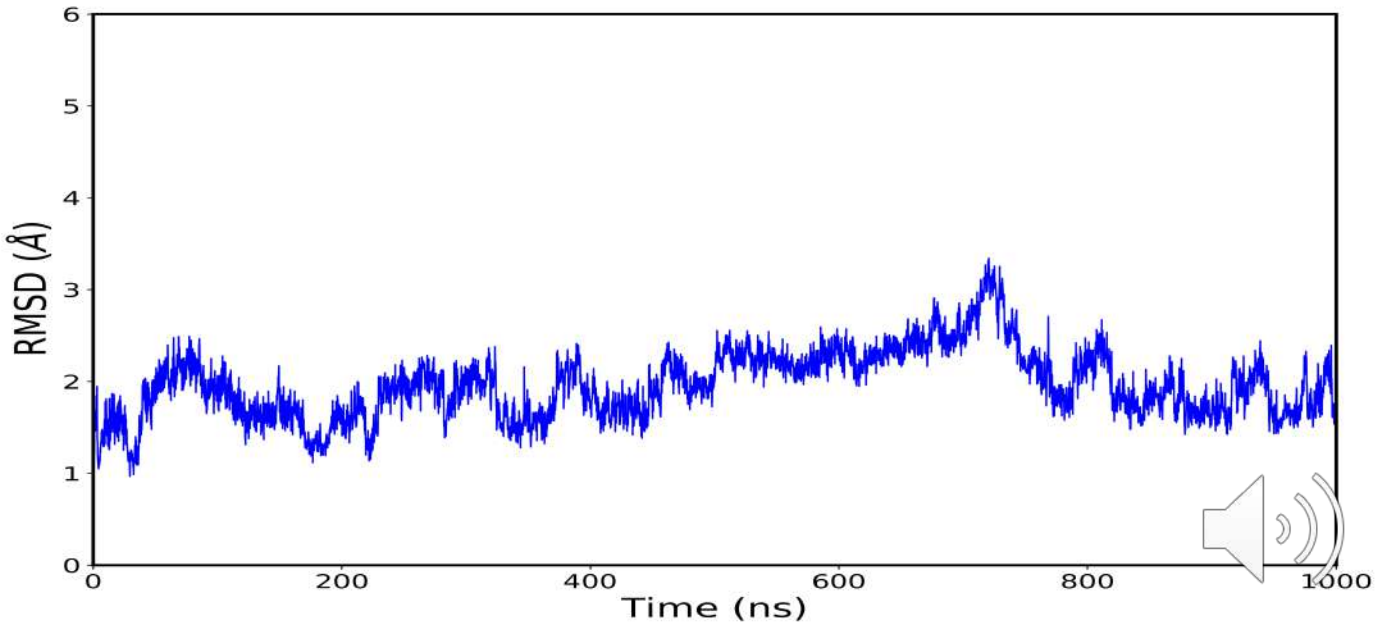
- Typically, timestep during simulation ≈ 1- 4 fs.

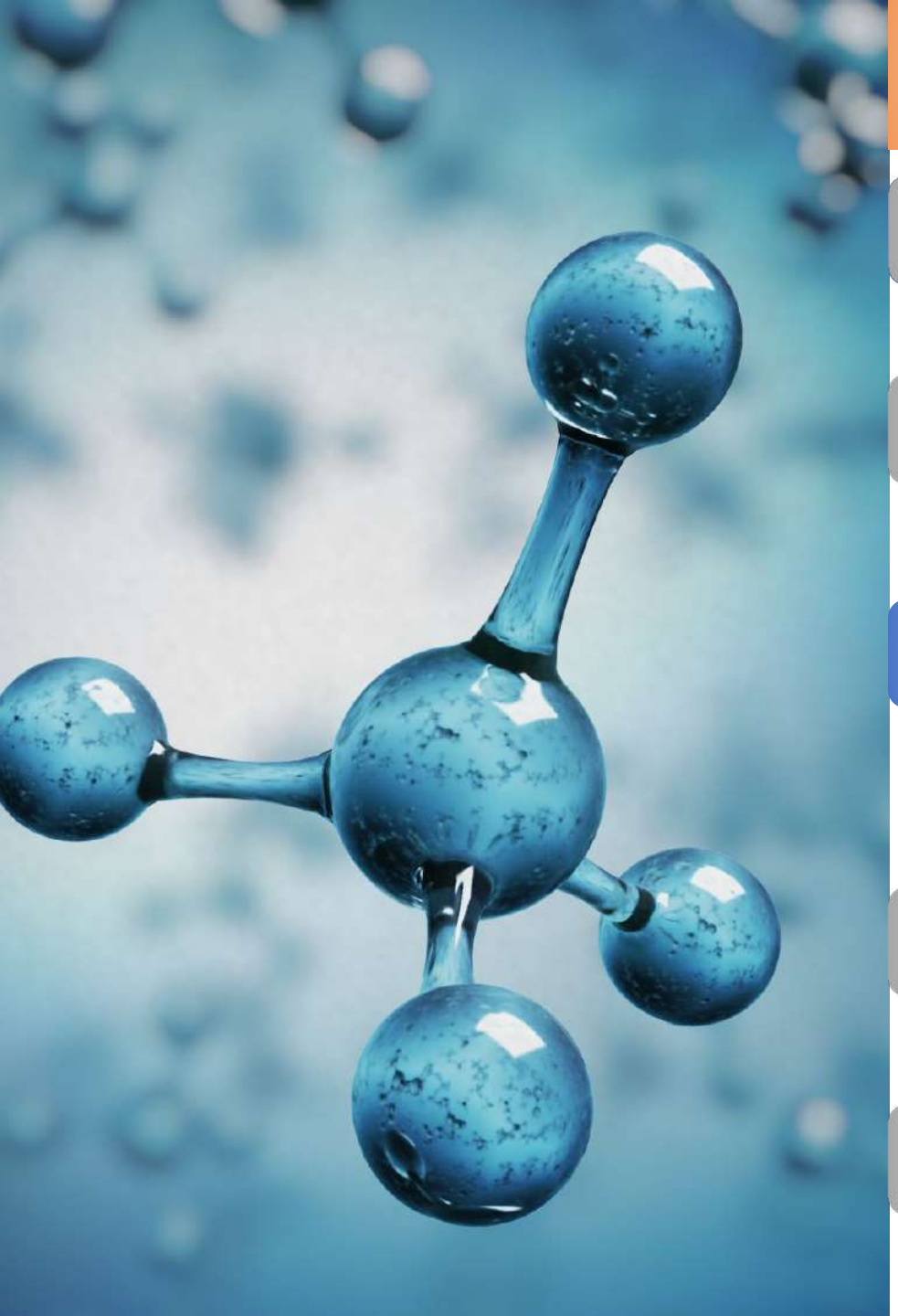
p53/DNA complex simulation

Simulation setup

- PDB ID: 1TSR
- Force field: AMBER ff14SB
- Zinc AMBER Force Field (ZAFF).
- Water model: TIP3P
- Ion: KCl 144 mM
- Temperature: 300 K
- Pressure: 1 bar
- No. of residues: 242 residues
- No. of protein residues: 200
- No. of DNA bp : 21
- No. of atoms the whole system : 107665 atoms
- Simulation time: 1 μs







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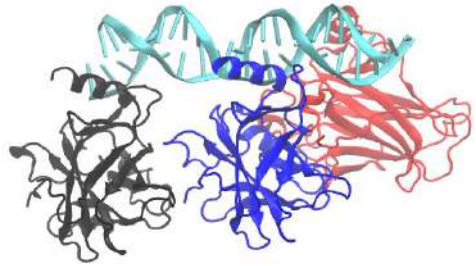
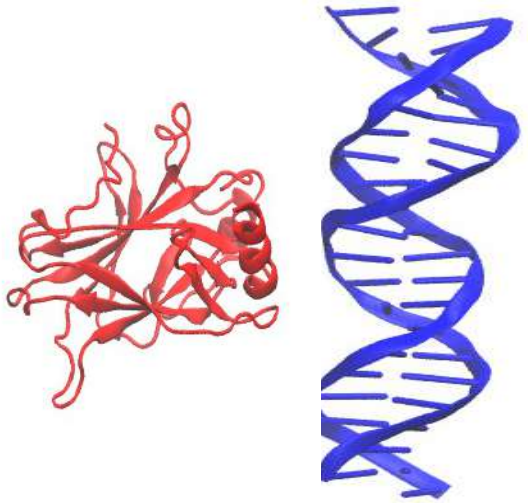
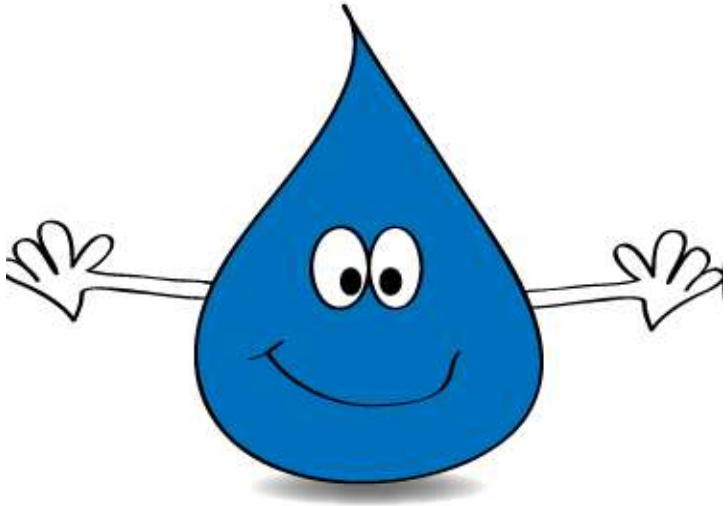


Dissociation simulation

The Idea

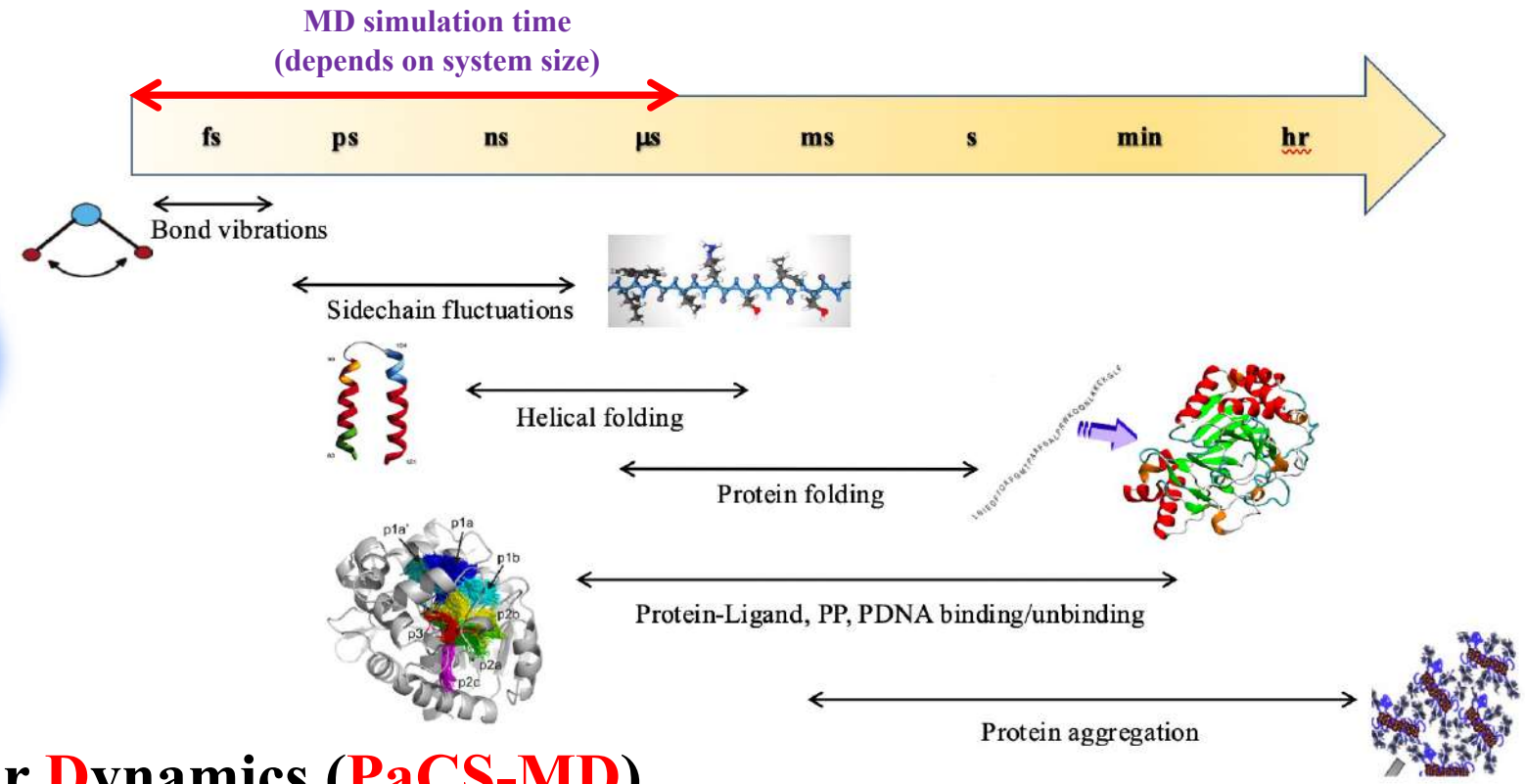




Can we do this using classical MD?

Dissociation simulation

Protein dynamics timescale



Enhanced sampling technique

Parallel Cascade Selection Molecular Dynamics (PaCS-MD)

Harada, Kitao. J. Chem. Phys. **139**, 035103 (2013).

Example :

For large systems (221413 atoms): for simulation step 2 fs , to reach 1 second in simulation ≈ 100 years

TSUBAME supercomputer with 1 GPU NVIDIA P100

Applications of PaCS-MD

Our group successfully dissociated

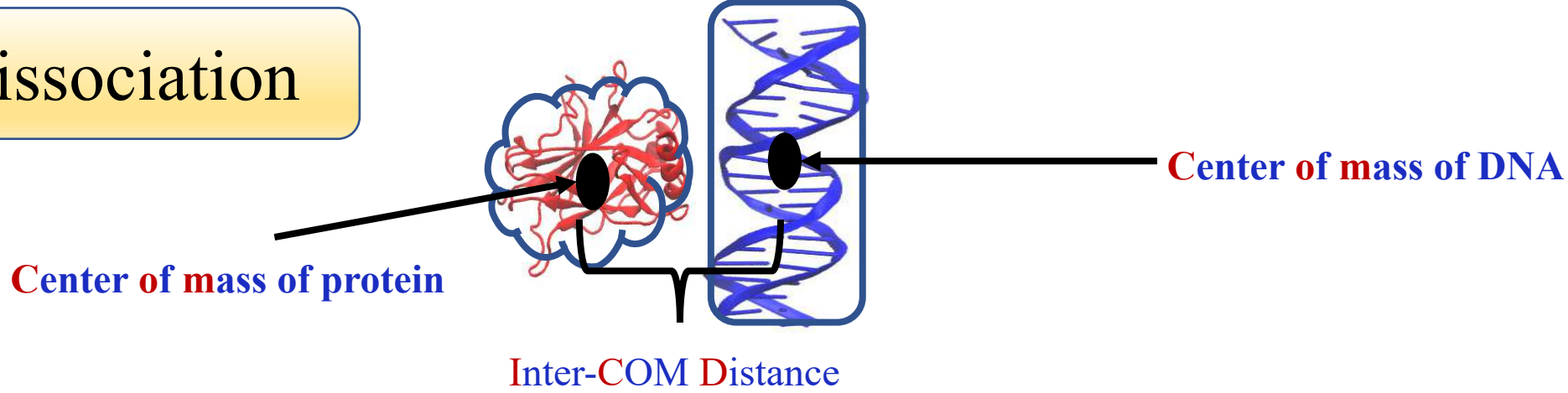
- Protein/ligand by Duy-san
- Protein/protein by Hata, Miyazawa & Ogawa-san
- Protein/DNA … currently

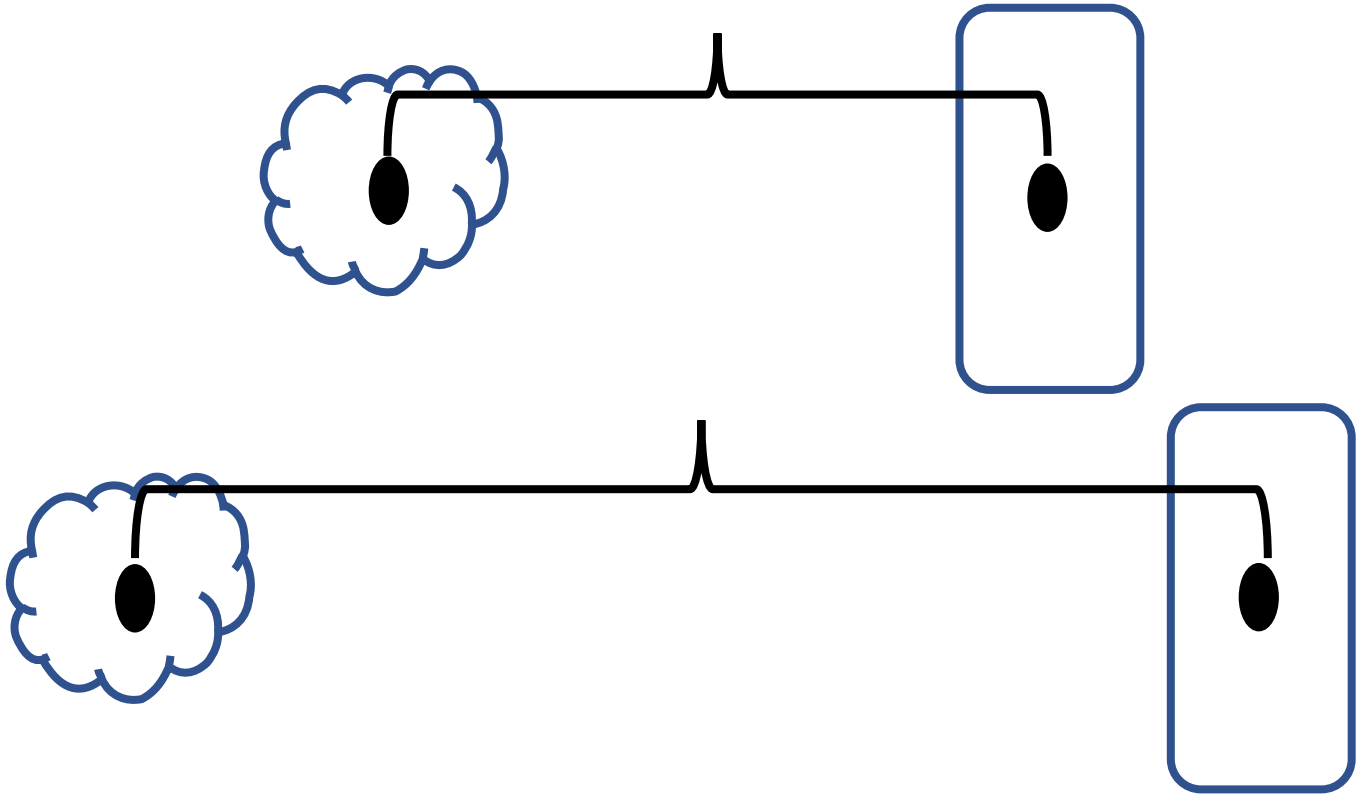
Tran & Kitao, A. *J. Phys. Chem. B* **123**, 2469–2478 (2019).

"Binding Free Energy of Protein/Ligand Complexes Calculated using Dissociation Parallel Cascade Selection Molecular Dynamics and Markov State Model"

Hiroaki Hata, Duy Phuoc Tran, Mohamed Marzouk, Akio Kitao, Chem Archive.

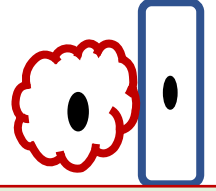
The Idea of Dissociation



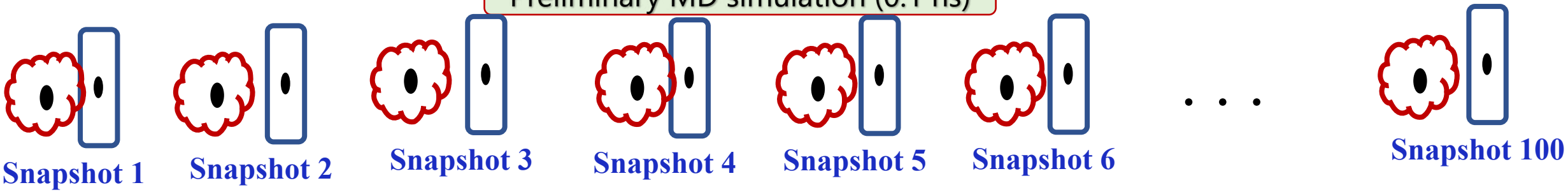


PaCS-MD

Parallel Cascade Selection Molecular Dynamics



Preliminary MD simulation (0.1 ns)



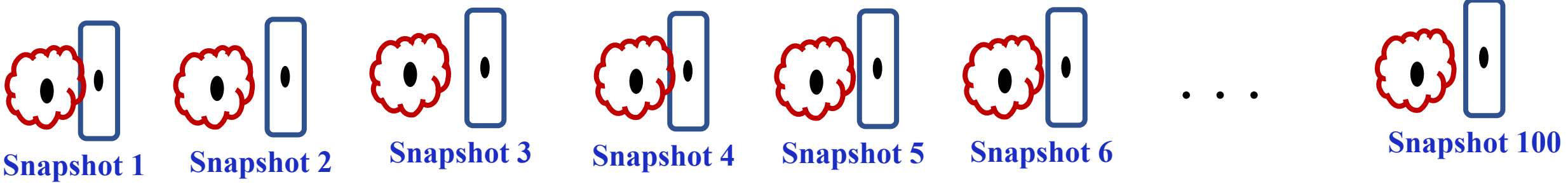
Structural ranking

Top 10 snapshots with higher inter-COM distance chosen for the first cycle.

Rank No.1 | Rank No.2 | Rank No.3 | . . . | Rank No.10

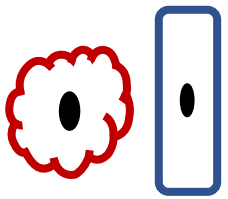
10 parallel MD simulation (0.1 ns)

Structural ranking



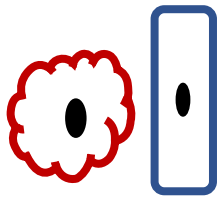
Structural ranking

Rank No.1



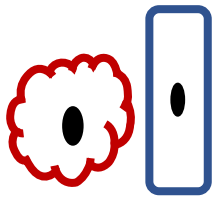
Snapshot 3

Rank No.2



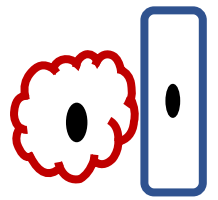
Snapshot 2

Rank No.3



Snapshot 100

Rank No.10

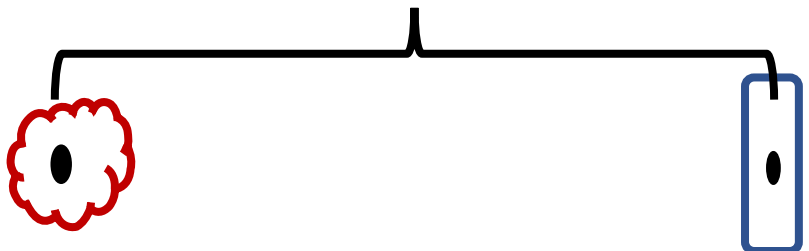


Snapshot 5

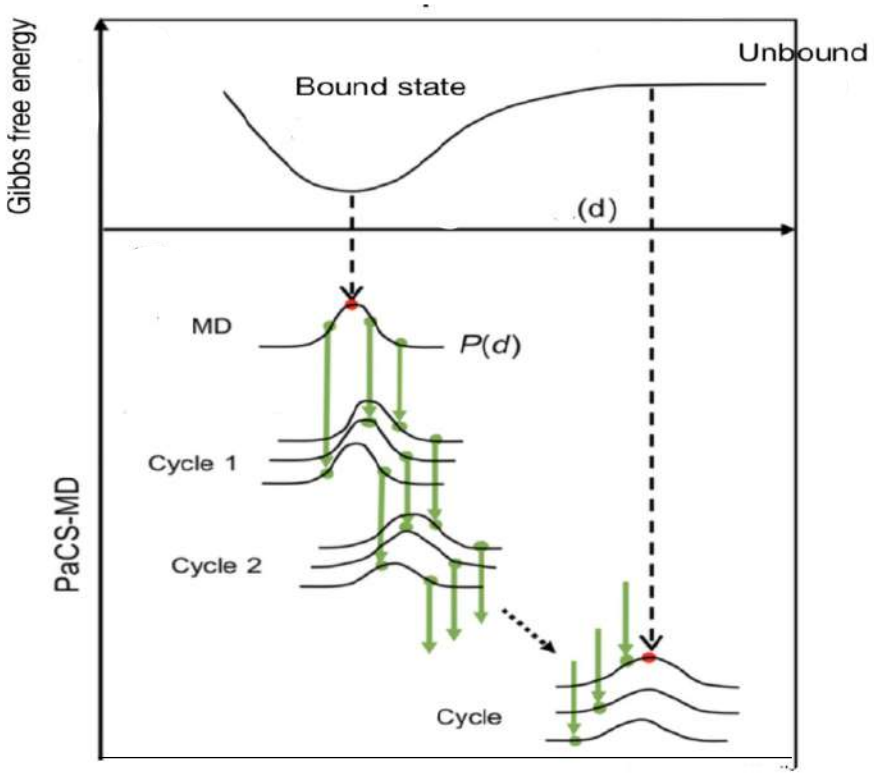
10 parallel MD simulation (0.1 ns)

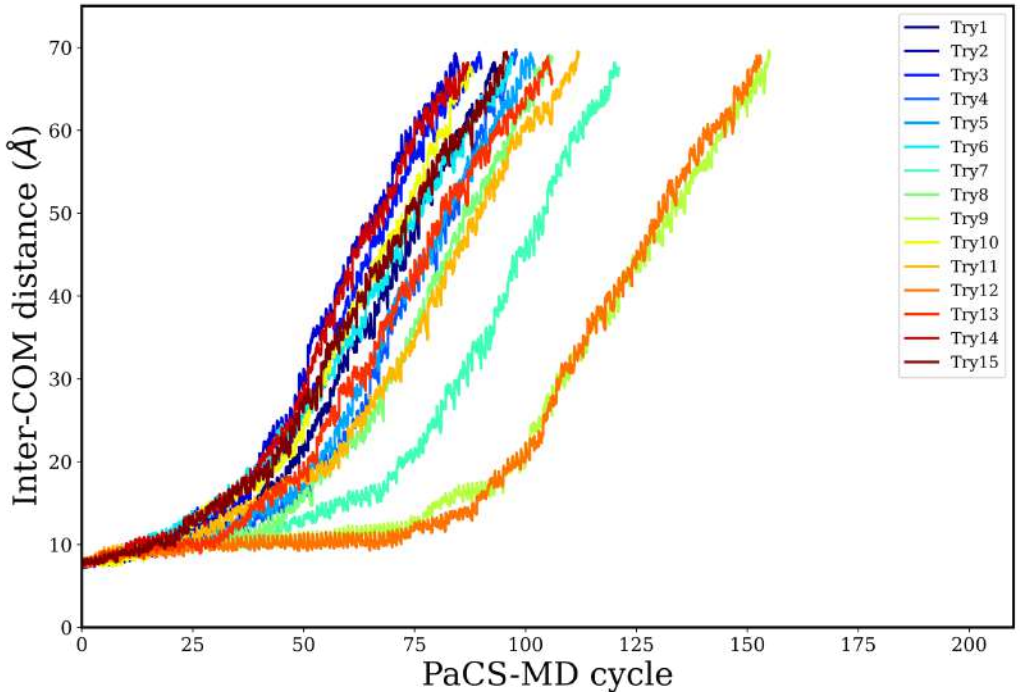
Structural ranking

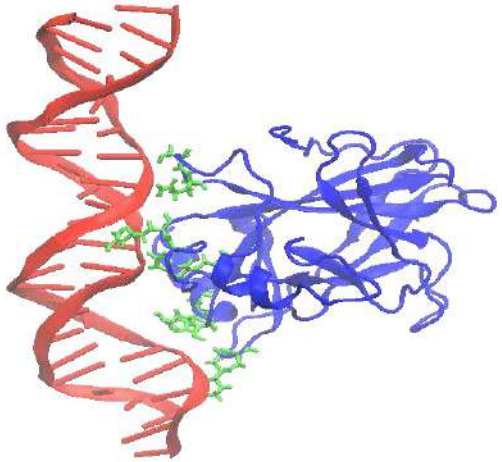
Inter-COM = 70 Å



p53/DNA complex dissociation by PaCS-MD

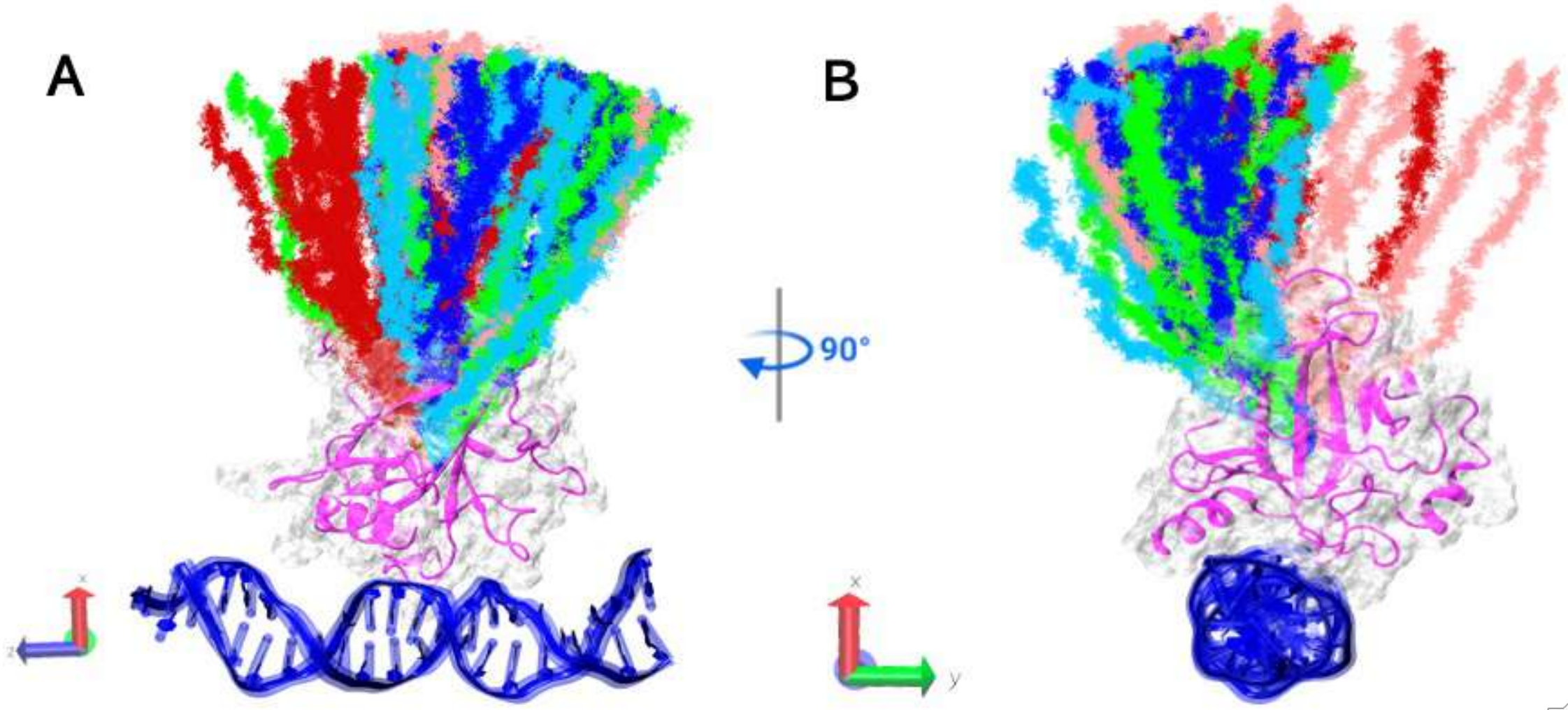


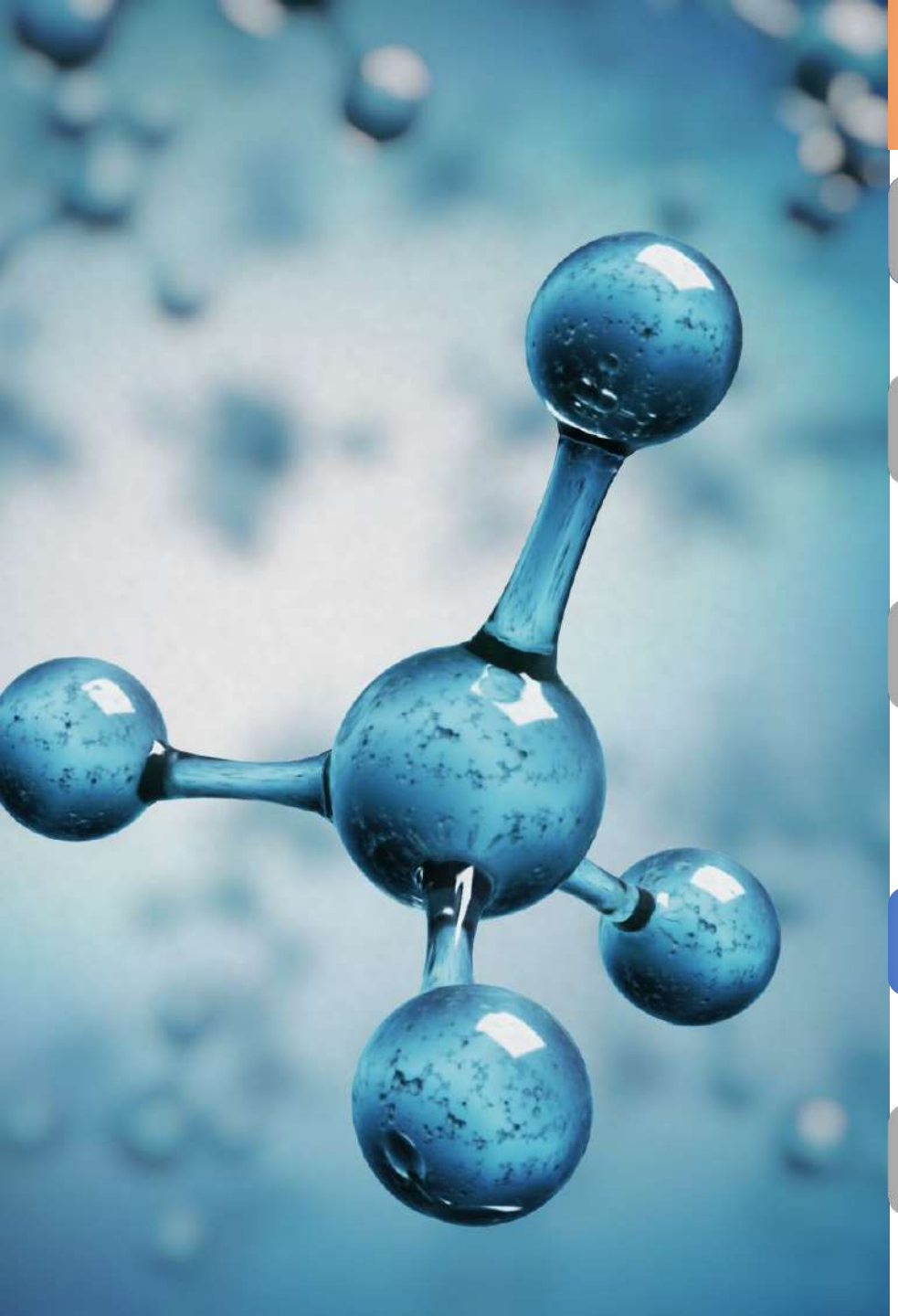




https://www.jstage.jst.go.jp/article/butsuri/74/8/74_533/_pdf/-char/ja

Dissociation pathways





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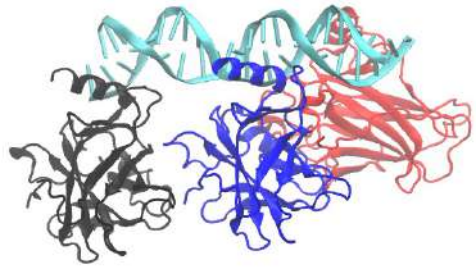
Conclusion



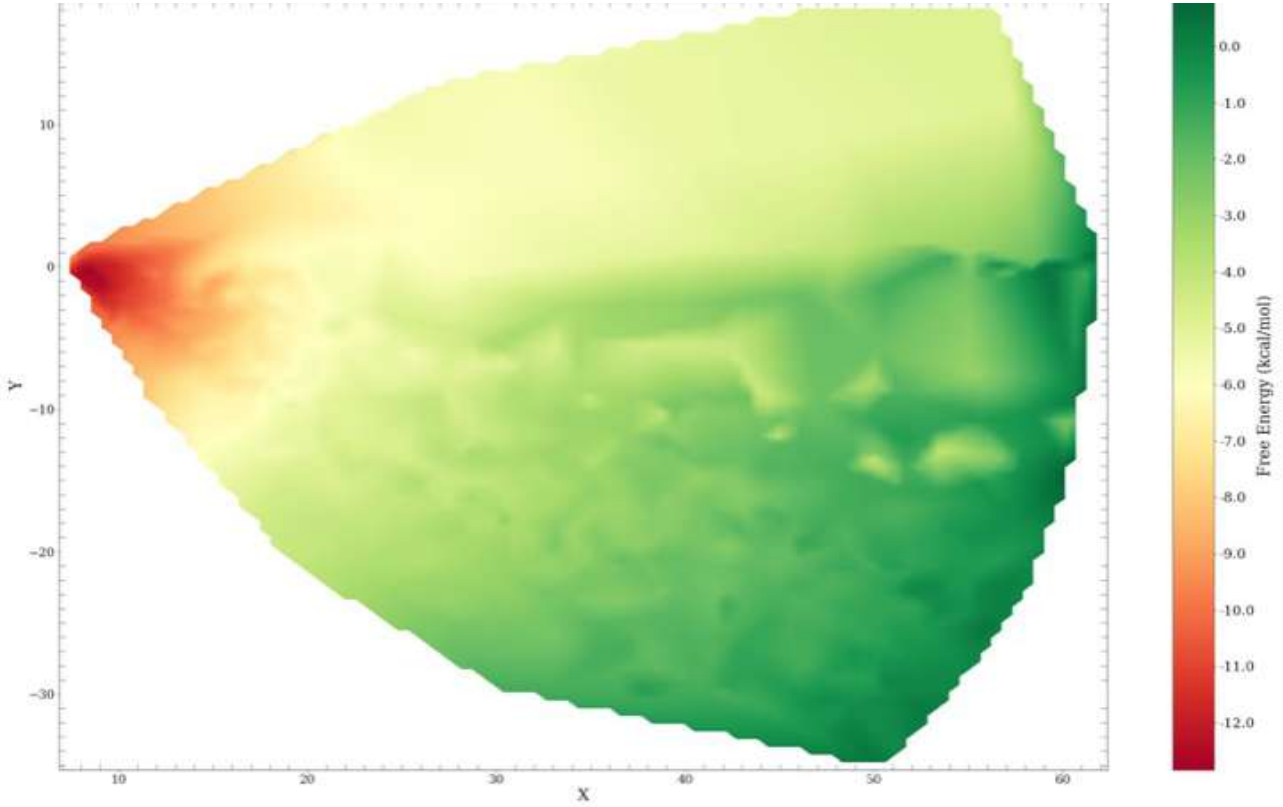
Free energy analysis

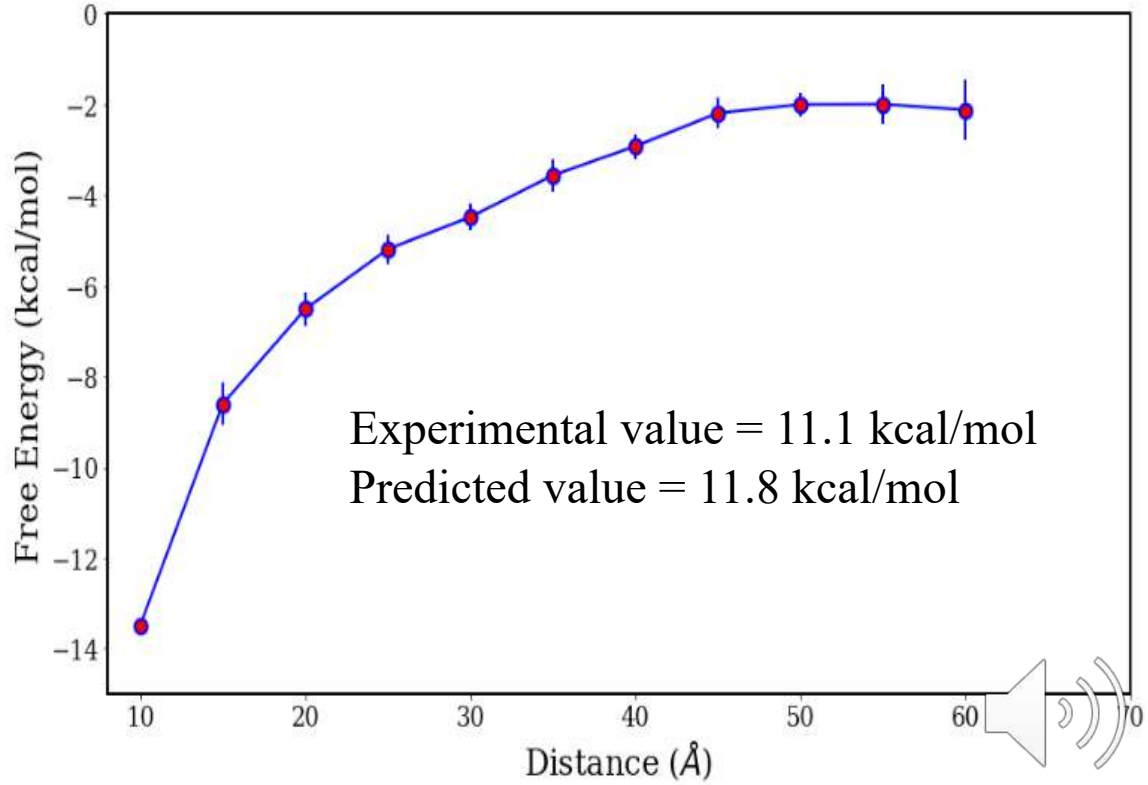
Markov State Model(MSM)

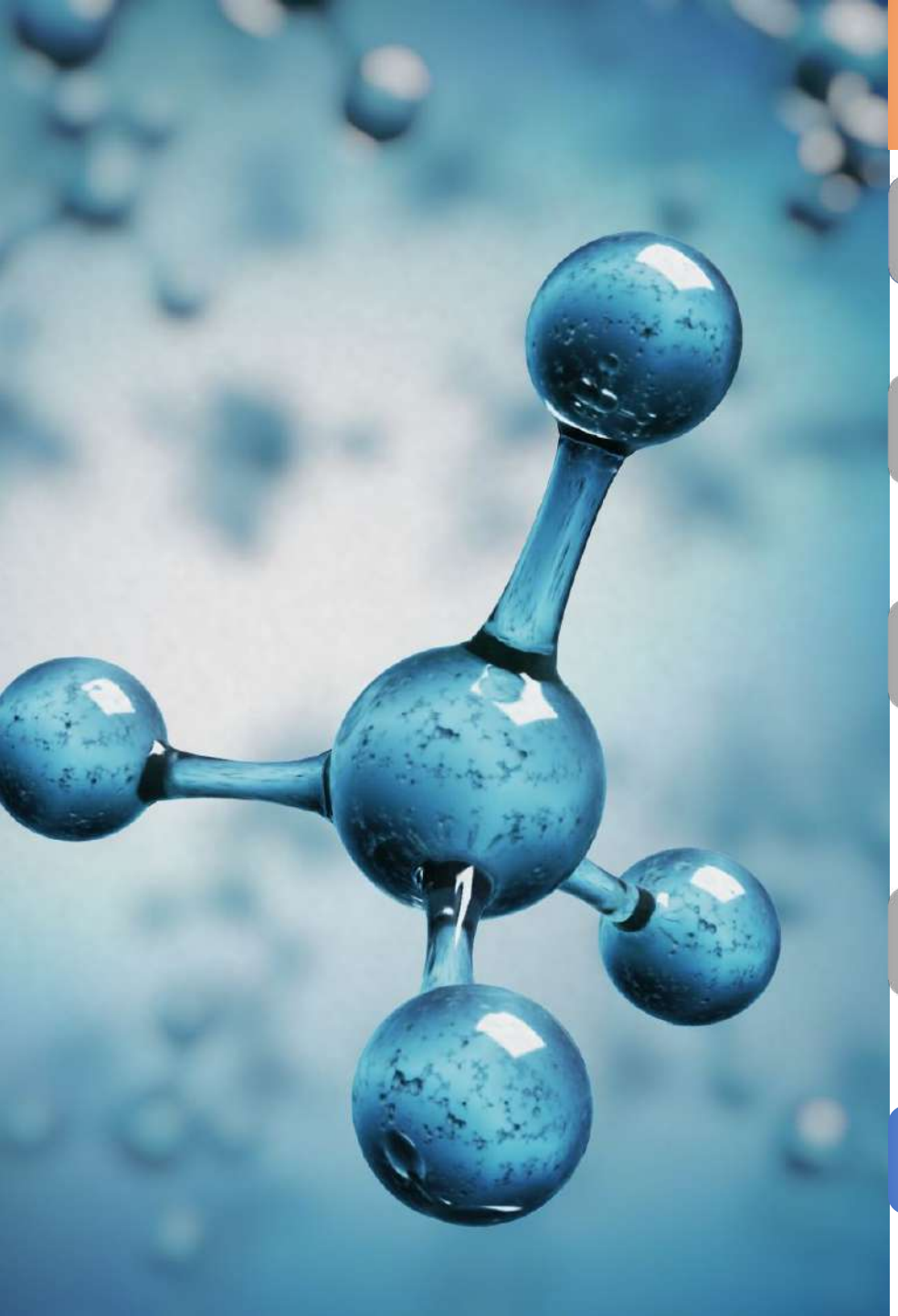
2.5.7

3.8

$$\Delta G_{bind} = -k_B T \ln \frac{P_b}{P_u}$$







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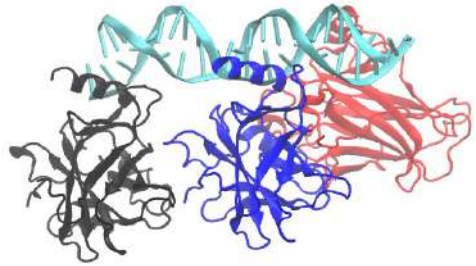

Conclusion

The combination of PaCS-MD/MSM was shown to be useful in the investigation of dissociation pathways of a large protein/DNA complex and can assist to obtain the free energy landscape and profile as well.

Plan

Study the effect of mutations of one of key residues during dissociation on the binding free energy.

Using PaCS-MD/MSM to do association/dissociation simulation for p53 and DNA.

Thank you