Universiteit van Amsterdam

Biomolecular Simulations

Exploring the Conformational Space of SARS-CoV-2 Spike Protein

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Abstract

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1 Introduction

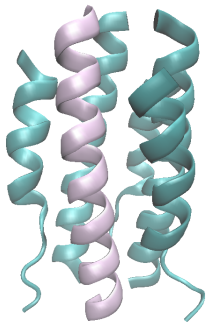

Figure 1: Protein. Pink - chain A.

The project is layed out in two parts: molecular dynamics and metadynamics simulations.

2 Methods

2.1 Molecular dynamics

Molecular dynamics (MD) is a simulation technique that allows conformational space exploration of a molecular system. The main principle behind the simulation is integration of Newton's laws of motion equations (Leach [2007]). To investigate the stability of spike protein complex two simulations were carried out at a temperature of 310 K and one at 400 K. Two simulations at 310 K were conducted to account for the stochastic nature of the molecular dynamics simulations with each simulation drawing a different sample of velocities assigned to the atoms based on the Boltzmann distribution at 310 K. All simulation were carried out using `gromacs` software package.

System preparation The protein complex was placed into a box filled with 6407 water molecules. The resulting size of the box - 216.52 nm^3. This was then followed by energy minimisation to mitigate unwanted interactions between atoms. 43

Table 1: Parameters used for molecular dynamics simulations.

Simulation	310 K	400 K
Force field	AMBER99SB-ILDN	AMBER99SB-ILDN
Water model	TIP3P	TIP3P
Reference pressure (bar)	1	1
Barostat	Parrinello-Rahman	None
Thermostat	V-rescale	V-rescale
Time (ns)	100	100
Integration algorithm	leap-frog	leap-frog
Coulomb method	PME	PME
Van der Waals method	cut-off (1.1 nm)	cut-off (1.1 nm)

water molecules were replaced with 23 NA and 20 CL ions and again followed by energy minimisation. Finally, an equilibration step was applied on the system. After this, the molecular dynamics simulations were started. Parameters used for system preparation and simulations are displayed in Table 1.

2.2 Metadynamics

Metadynamics (metaD) simulations were used to investigate the free energy profile of the spike protein complex. By adding bias potential to make the most visited states unfavourable, metaD allows better sampling of rare events and thus better exploration of the conformational space (Liao [2020]). The simulations were performed using the `plumed` plugin for `gromacs`. The same `gromacs` files as prepared with the procedure laid out in Section 2.1 were used for metadynamics simulations (at a temperature of 310 K). In total, 3 simulations were performed - specifications can be found in Table 2.

Simulations 1 and 3 (Table 2) were set up to explore the free energy profile of the unfolding process of chain A. The main difference between the two simulations lay in the hill height parameter - it is 2 times higher for simulation 3. This was done to investigate whether increasing the hill height accelerates the exploration of the free energy surface. Simulation 2 explores the free energy profile of the chain A detachment from the rest of the complex.

Table 2: Parameters and collective variables used for metadynamics simulations

Simulation	1	2	3
Collective variable (CV)	Distance between atoms 1-19 and atoms 369-388	Distance between atoms 1-388 and atoms 389-2046	Distance between atoms 1-19 and atoms 369-388
CV description	Distance between mass centers of N and C-terminus in chain A	Distance between mass center of chain A and mass center of the rest of the complex	Distance between mass centers of N and C-terminus in chain A
Hill height (kJ/mol)	0.01	0.01	0.02
Hill width (nm)	0.35	0.35	0.35
Hill step size	500	500	500

2.3 Analysis

A number of measurements were extracted from the simulations to quantify the processes observed in simulations. Visual investigation was done using `VMD` software.

Physical properties Temperature, pressure and volume progressions during MD simulations were extracted via `gromacs`' `energy` module.

RMS Root mean square deviation of the whole complex was calculated over time via `gromacs`' `rms` module.

Distances Two distances were calculated from the MD simulations: between C and N-terminus of chain A and between chain A and the rest of the complex. The distances were calculated between the centers of mass - analogous to *Collective variable (CV)* in Table 2.

Free energy profile The bias potential every 500 deposited hills was calculated via `plumed`'s `sum_hills` module for the metaD simulations.

3 Results and Discussion

3.1 Molecular dynamics

3.1.1 Physical properties

3.1.2 Stability of chain A

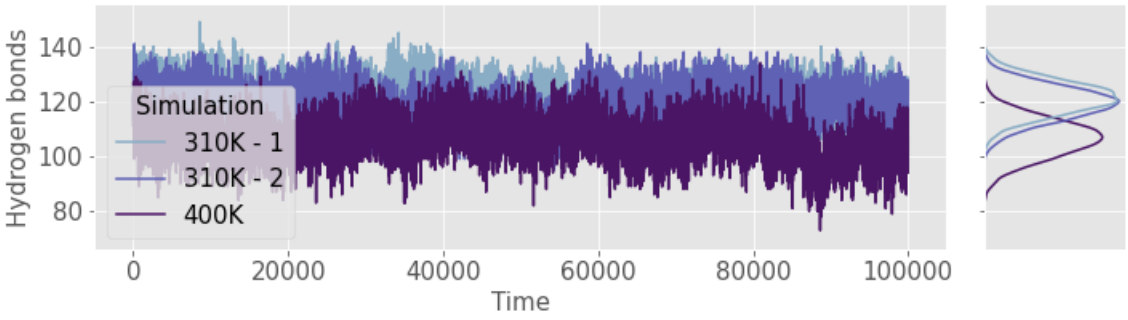

Figure 2: Number of hydrogen bonds in the system over time.

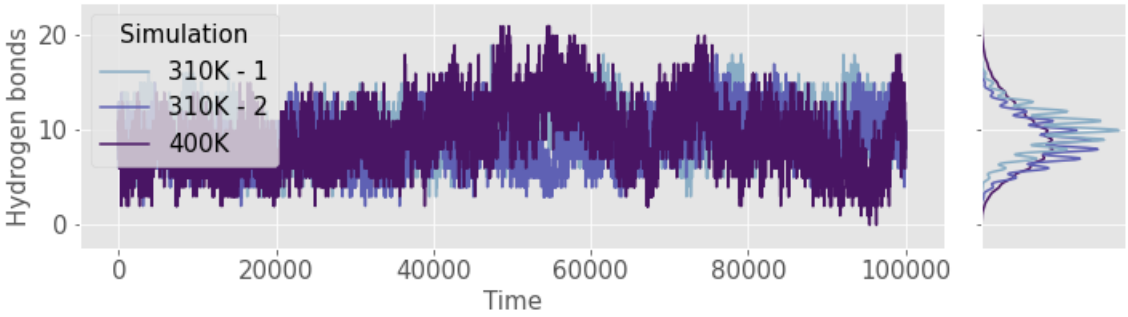

Figure 3: Number of hydrogen between chain A and the rest of the protein over time.

3.1.3 Distances

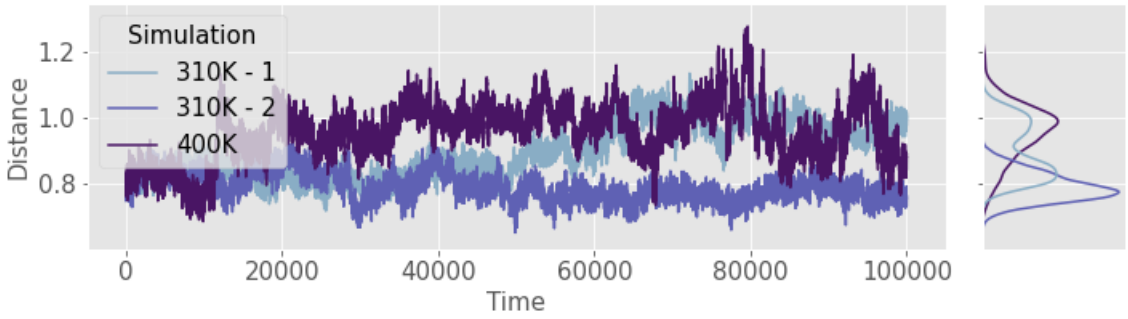

Figure 4: Distance between chain A and rest of the complex over time.

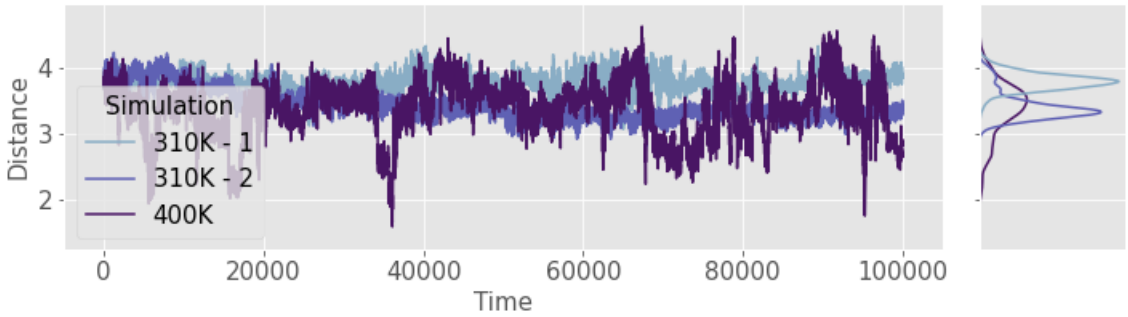

Figure 5: Distance between C-terminus and N-terminus in chain A over time.

3.2 Metadynamics

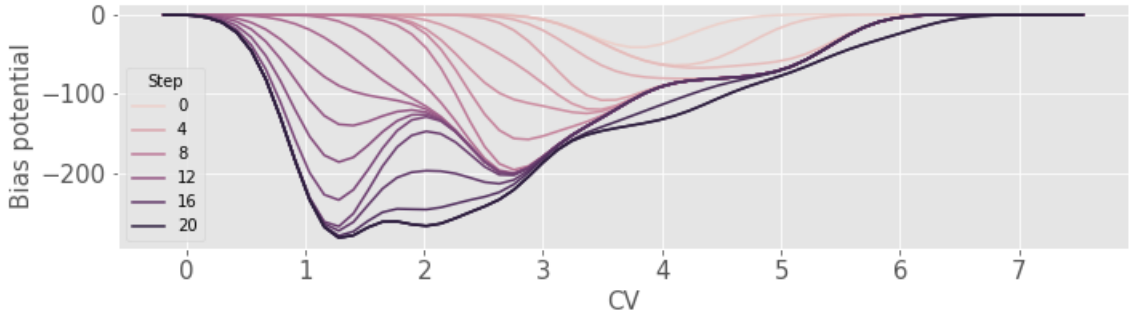

Figure 6: Distance between C-terminus and N-terminus in chain A over time.

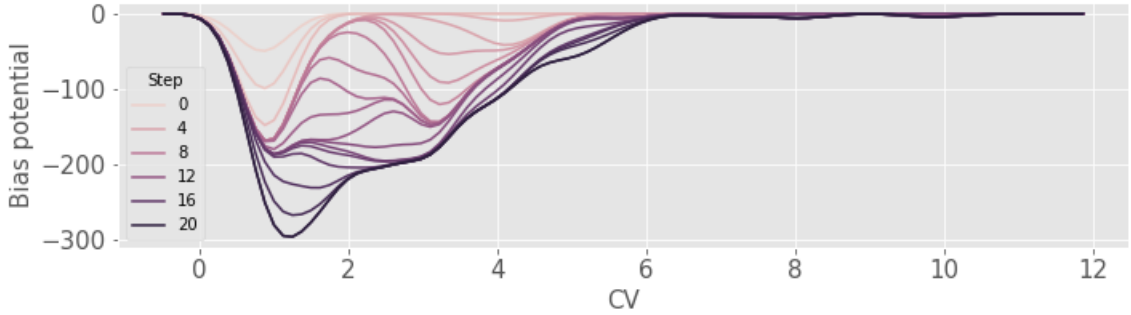

Figure 7: Distance between C-terminus and N-terminus in chain A over time.

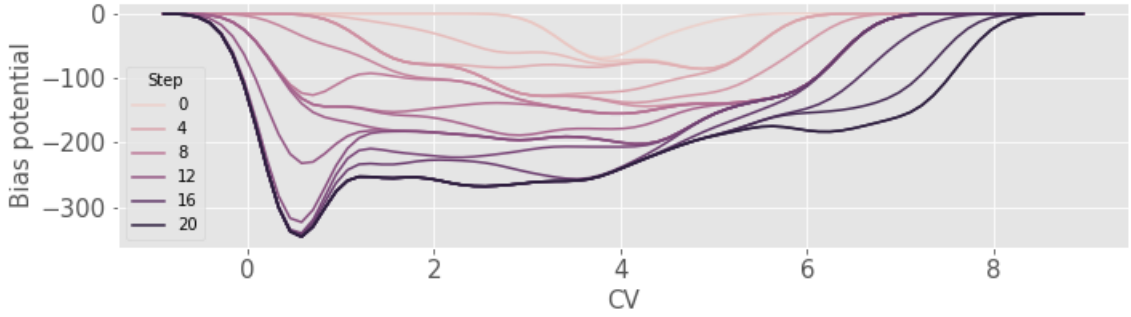

Figure 8: Distance between C-terminus and N-terminus in chain A over time.

4 Conclusions

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References

A.R. Leach. 4.05 - ligand-based approaches: Core molecular modeling. In John B. Taylor and David J. Triggle, editors, *Comprehensive Medicinal Chemistry II*, pages 87–118. Elsevier, Oxford, 2007. ISBN 978-0-08-045044-5. doi: https://doi.org/10.1016/B0-08-045044-X/00246-7. URL `https://www.sciencedirect.com/science/article/pii/B008045044X002467`.

Qinghua Liao. Chapter four - enhanced sampling and free energy calculations for protein simulations. In Birgit Strodel and Bogdan Barz, editors, *Computational Approaches for Understanding Dynamical Systems: Protein Folding and Assembly*, volume 170 of *Progress in Molecular Biology and Translational Science*, pages 177–213. Academic Press, 2020. doi: https://doi.org/10.1016/bs.pmbts.2020.01.006. URL `https://www.sciencedirect.com/science/article/pii/S187711732030017X`.

A Physical properties

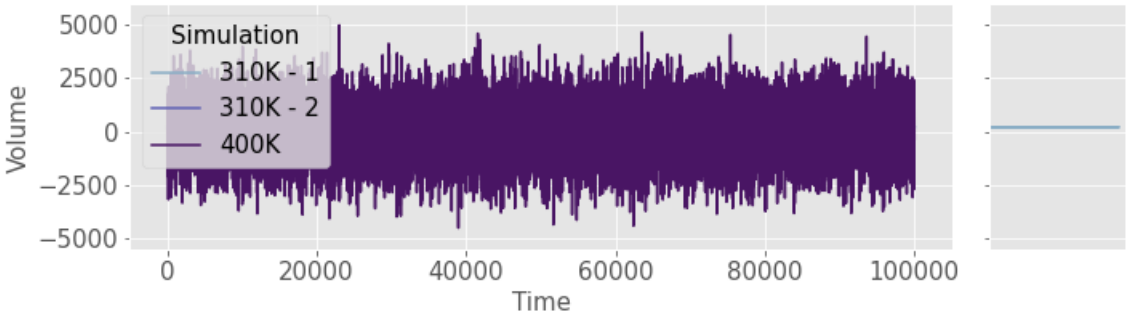

Figure 9: Volume over time.

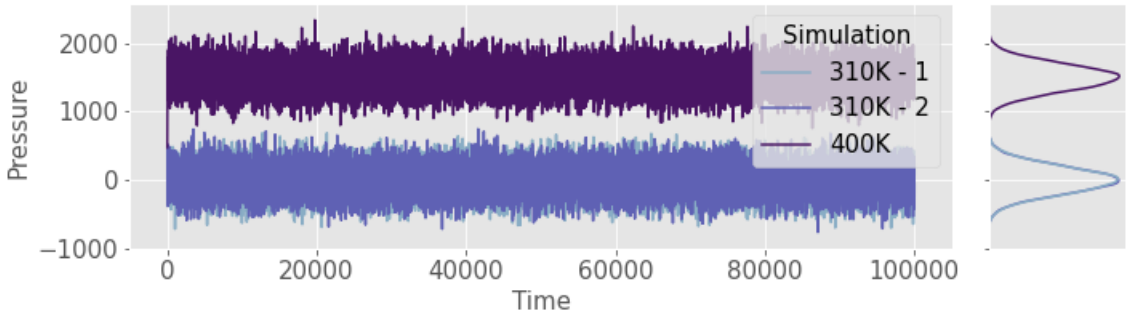

Figure 10: Pressure over time.

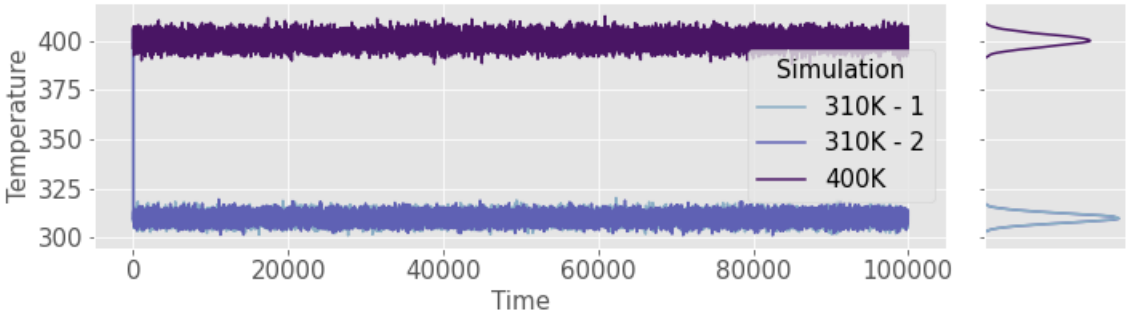

Figure 11: Temperature over time.