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Molecular Dynamics Simulation of Prion Protein

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Sory1:
Perfomance evaluation and tuning AMBER9

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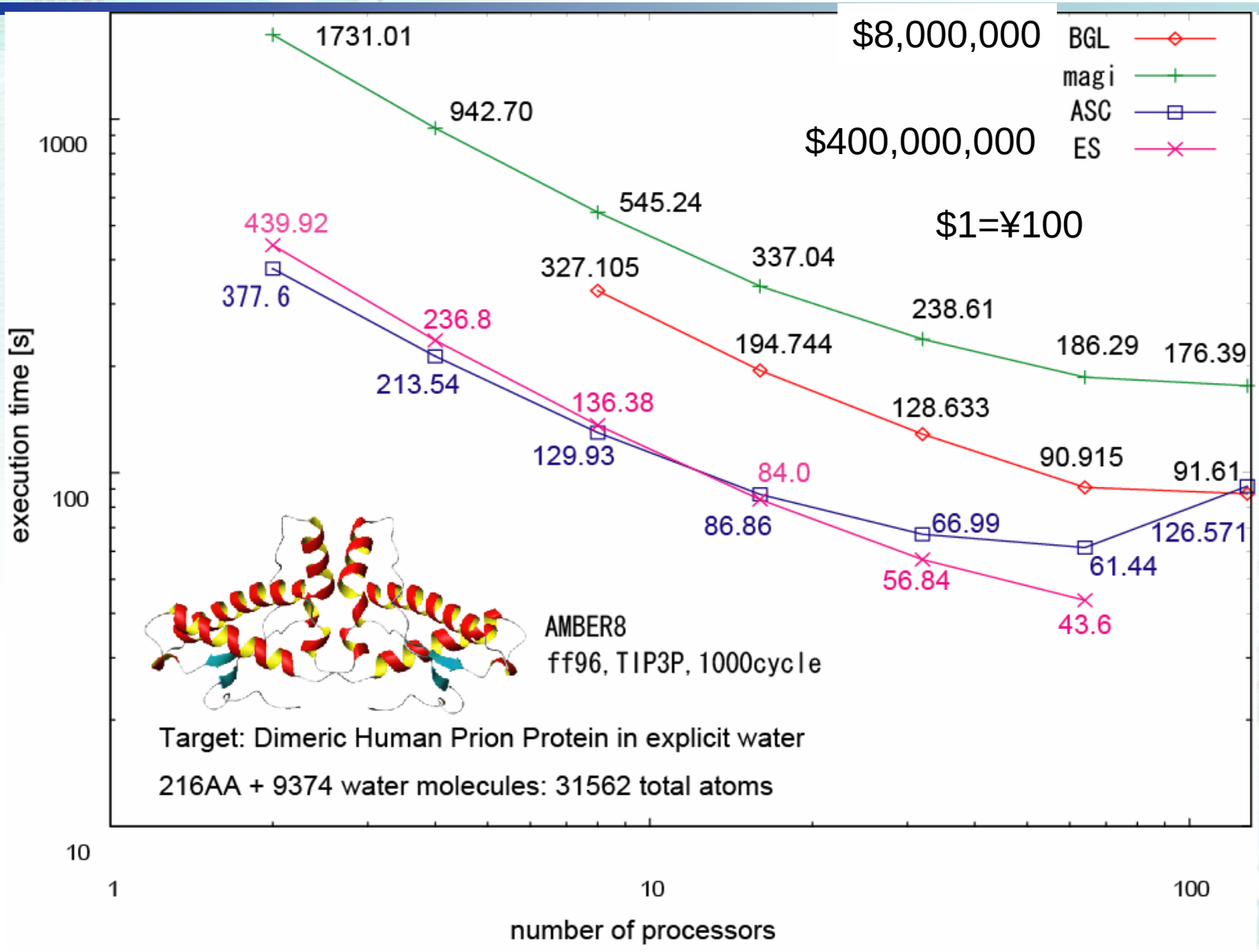
Performance Comparison



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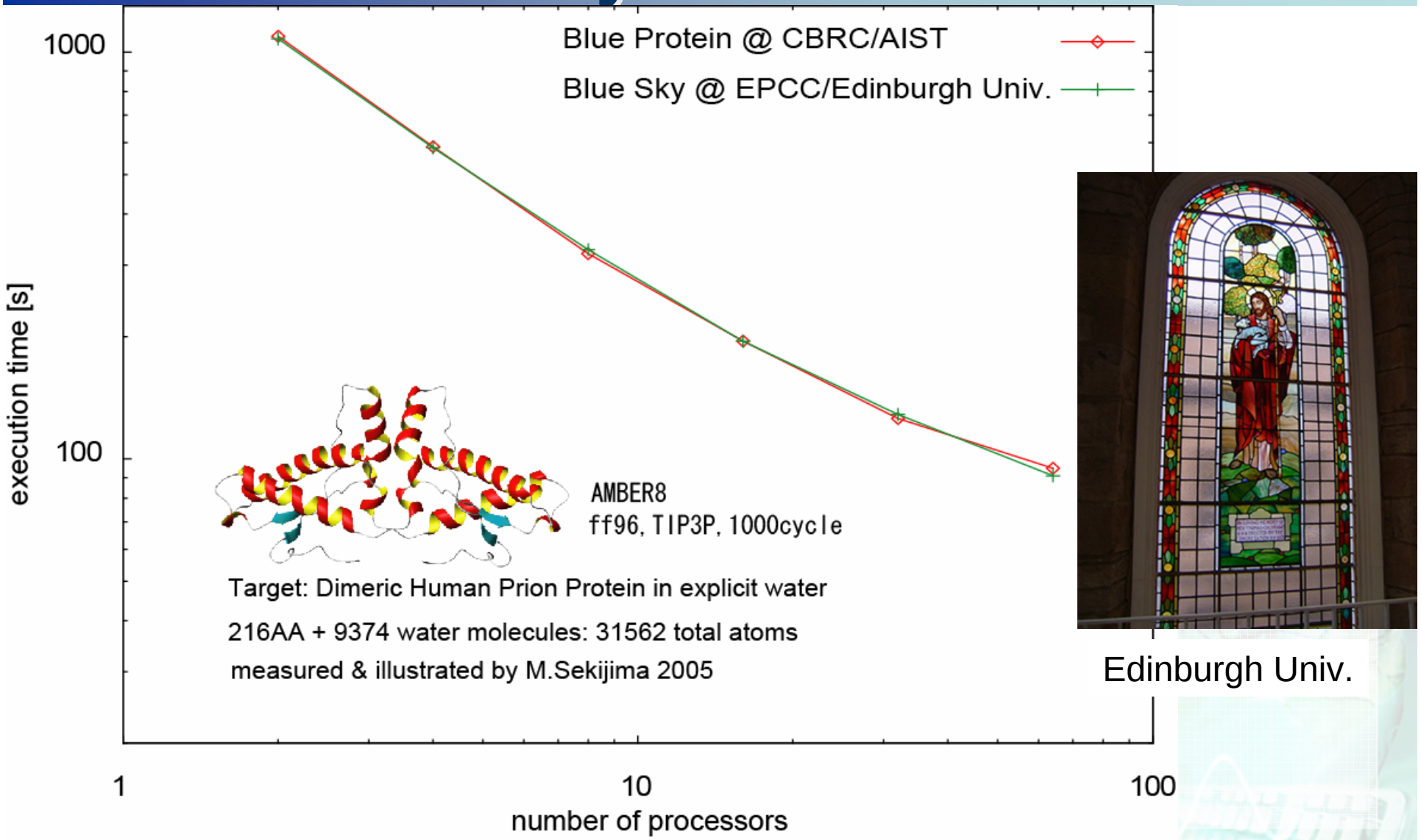
Performance Comparison between Blue Sky and Blue Protein ☺



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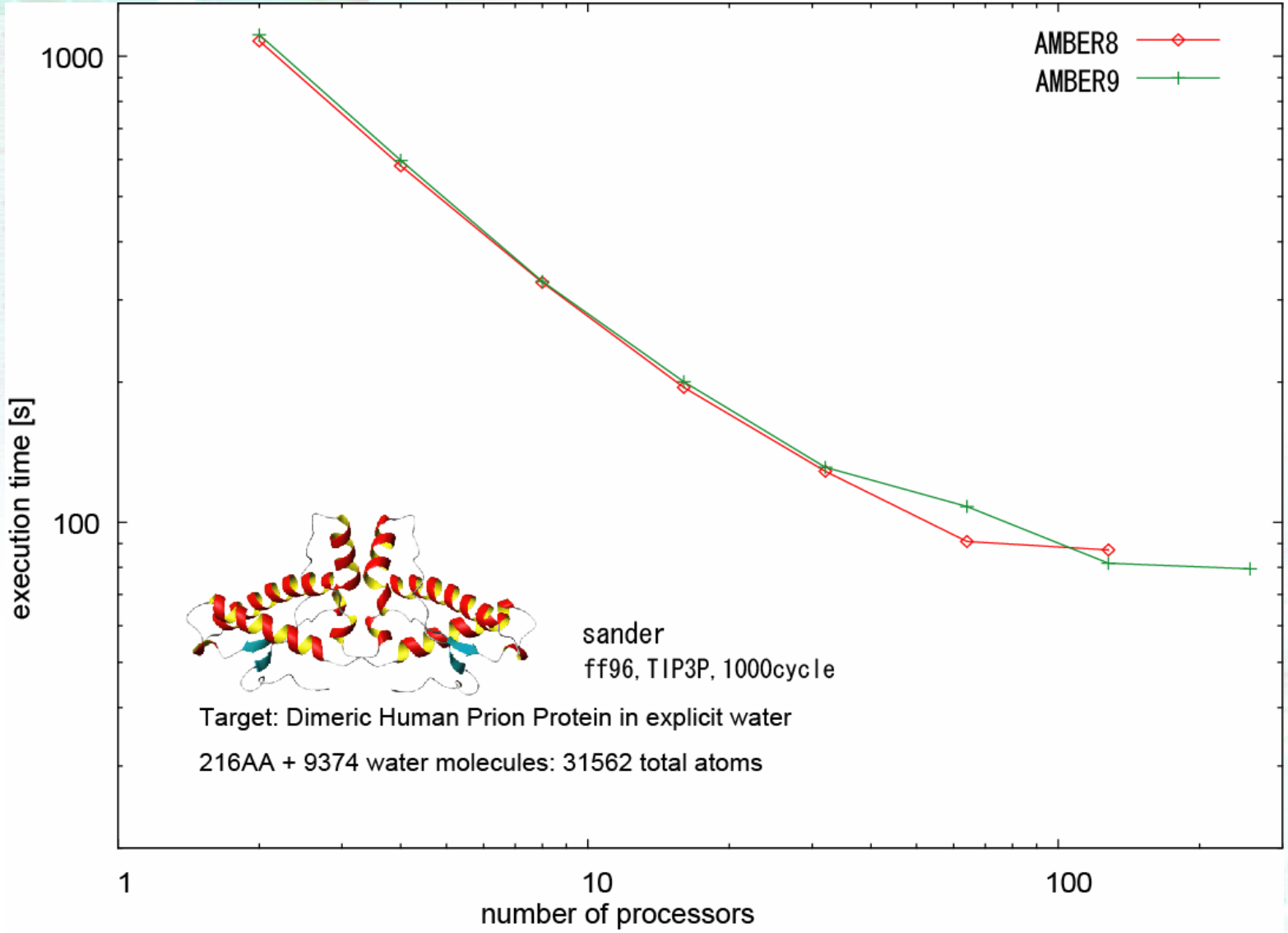
Performance comparison between AMBER8 and 9



Five presentation sheets are eliminated by author.

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Story2: Molecular Dynamics Simulation of Wild-Type and Mutant Human Prion Protein: Effect of Pro102Leu

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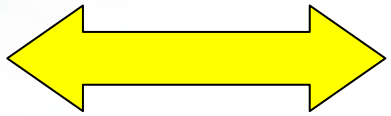
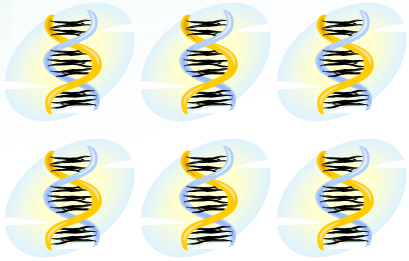
Mystery of Prion Diseases

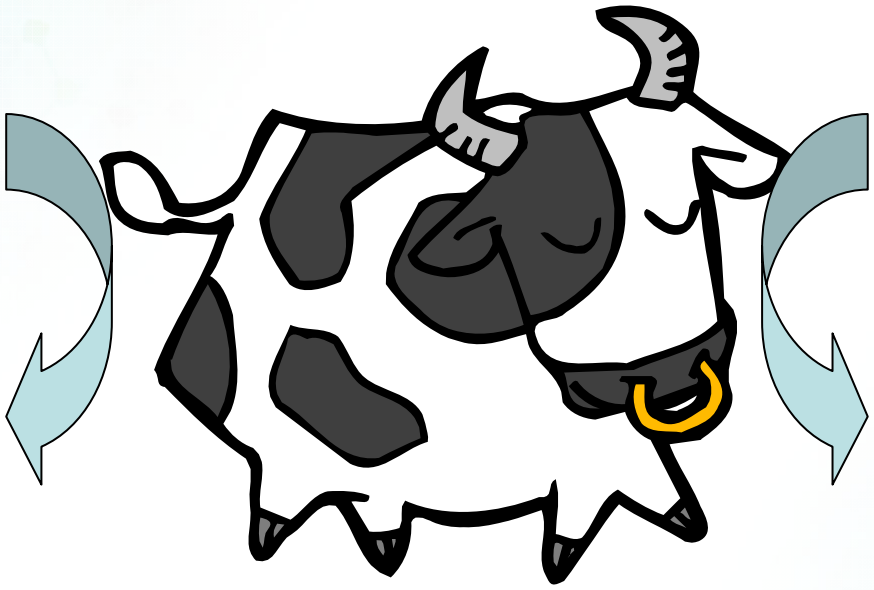
Virus



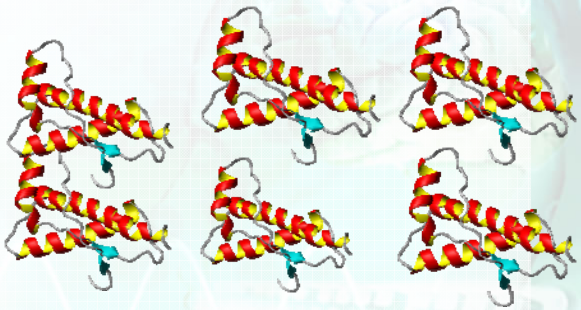
Prion Diseases

nucleic acid to infectious





Only Protein？



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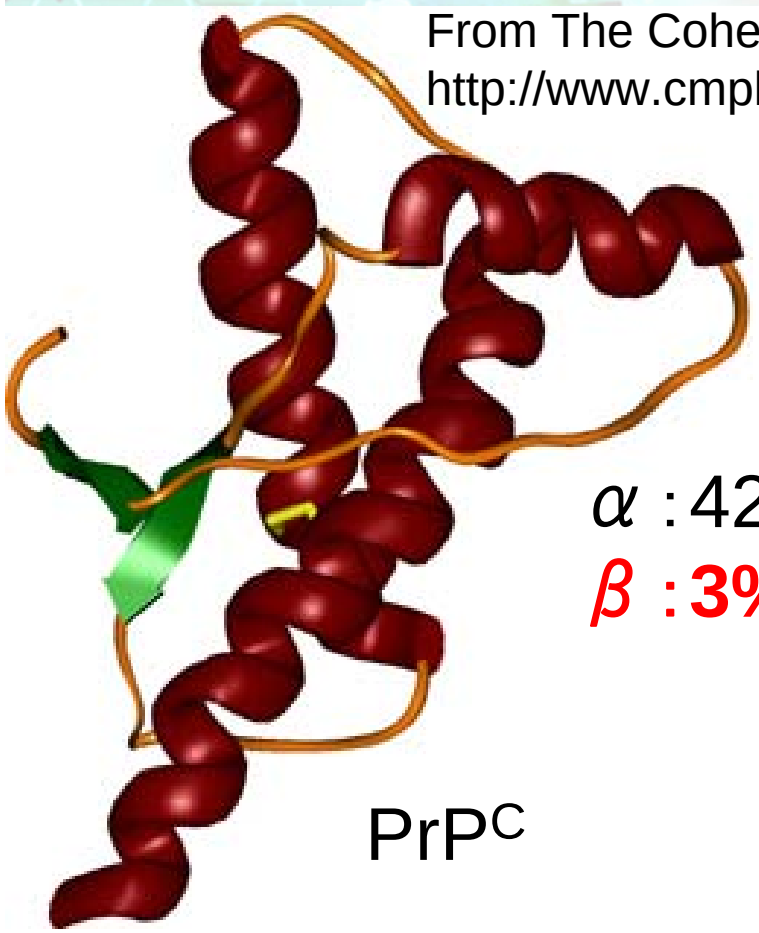
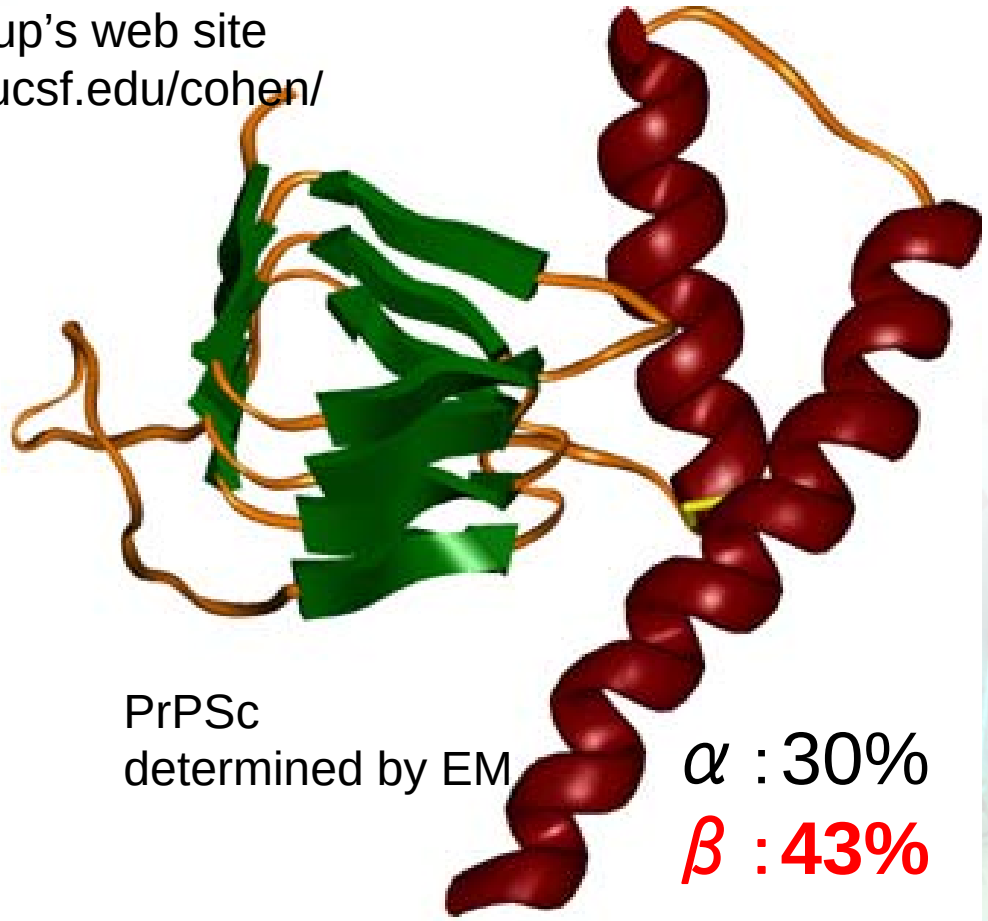
Amino acid sequences of PrPC and PrPSc are identical.

From The Cohen Group's web site
http://www.cmpharm.ucsf.edu/cohen/



α : 42%
β : 3%

PrP^{C}



PrPSc
determined by EM

α : 30%
β : 43%

A central theme in prion protein research is the detection of the process that underlies the conformational transition from the normal cellular form (PrPC) to its pathogenic isoform, PrPSc.

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Molecular Dynamics (MD) Simulation

Molecular Dynamics simulations are widely used for simulating the motion of molecules in order to gain a deeper understanding of

- chemical reactions
- fluid flow
- phase transitions
- and other physical phenomena due to molecular interactions.

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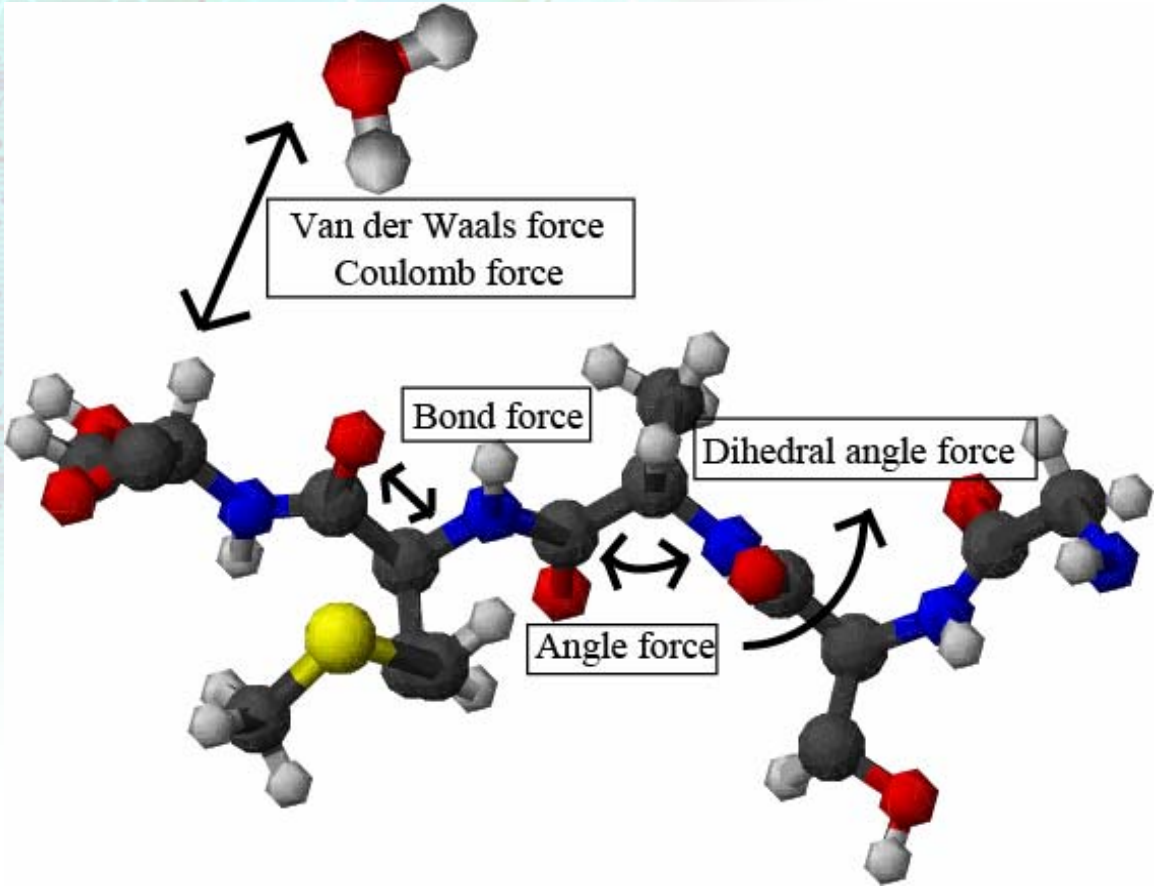
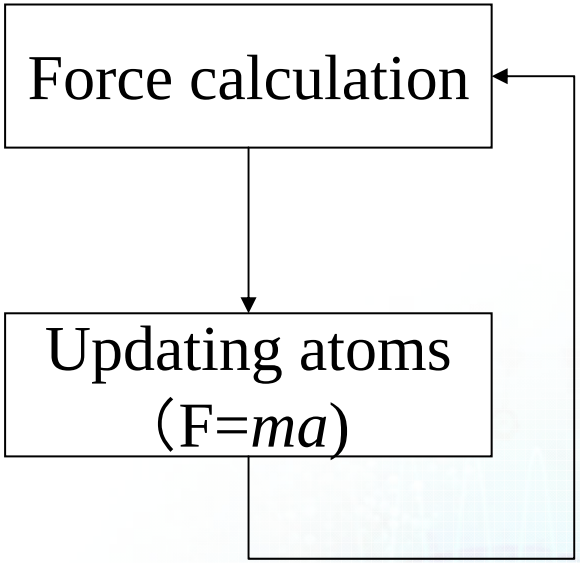
Molecular Dynamics (MD) Simulation



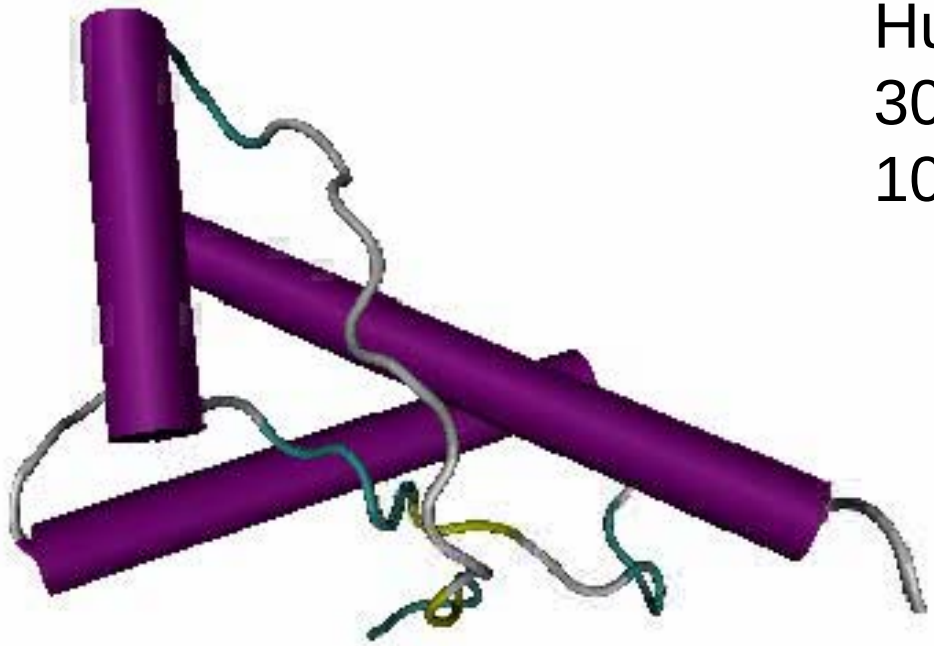


the continuous process is broken down into discrete small timesteps each of which is an iteration and has two parts:

force calculation and atom update

Molecular dynamics similation on Prion Protein monomer at 300K

purple : Helix
Yellow : Strand



Human PrPC
300K
10ns

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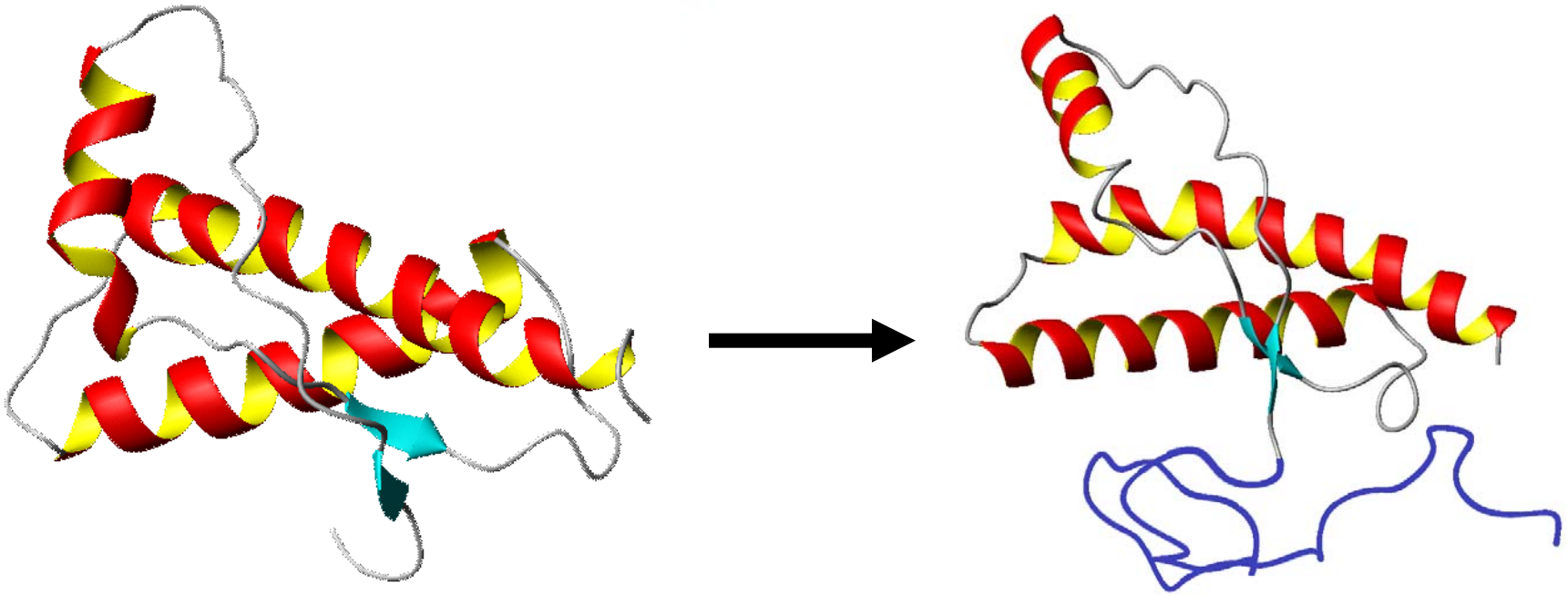
Simulation target



(a) PrPC structure determined by NMR

(b) Blue colored residues were modeled by this study

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Simulation Condition

- Wild Type (102Pro): 20619 atoms
- Mutant (102Leu): 20626 atoms
  - ↳ difference is only one reside!
- Package: AMBER7
- Potential function: ff96
- TIP3P water
- 20ns at 300K

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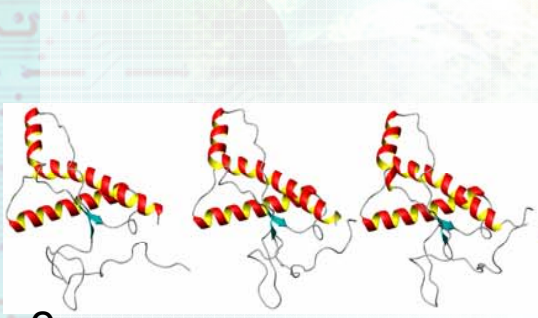
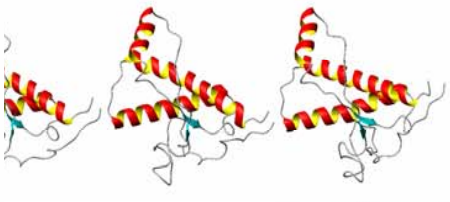
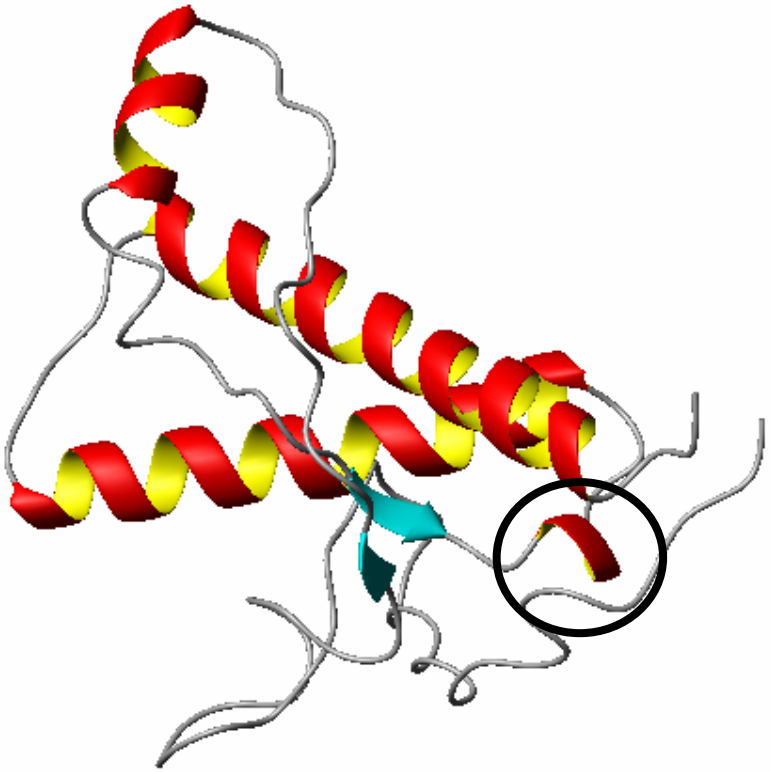
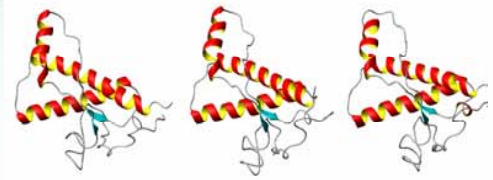
Simulation Results
Wild Type 300K



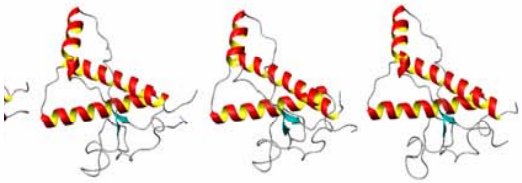
0ns







10ns



20ns

Helix was observed at residues which predicted as Helix.

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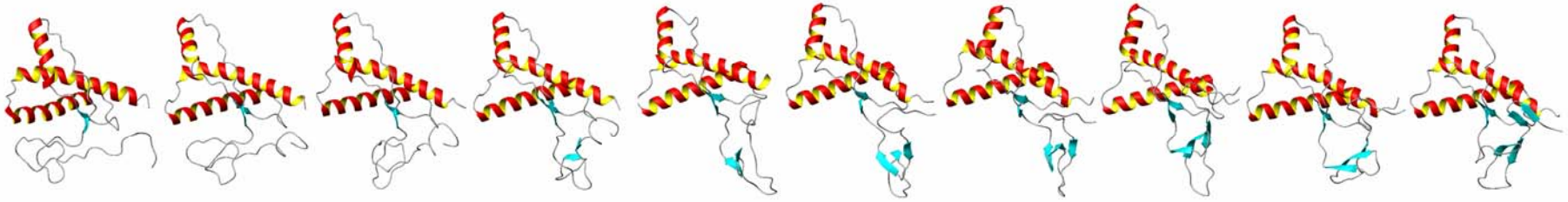
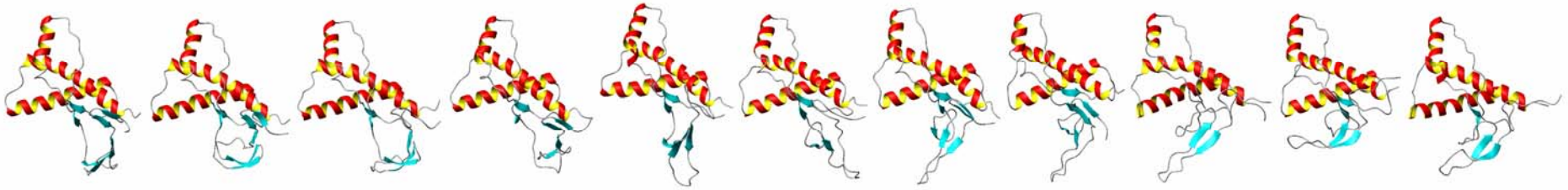
Simulation Results Mutant (P102L) 300K



0ns

5ns



10ns

15ns

20ns

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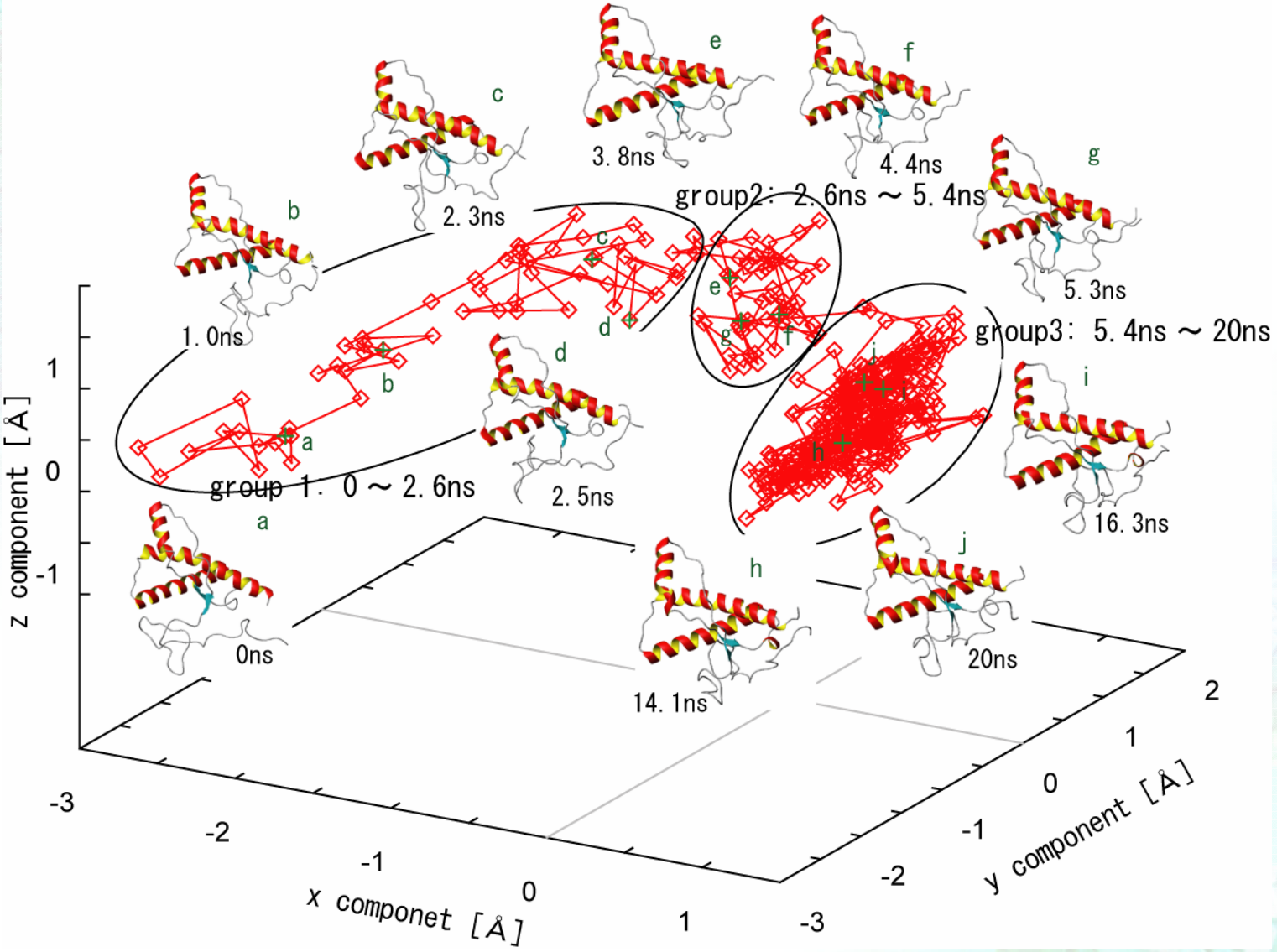
Conformational distribution of Wild type in 3D PCA Space



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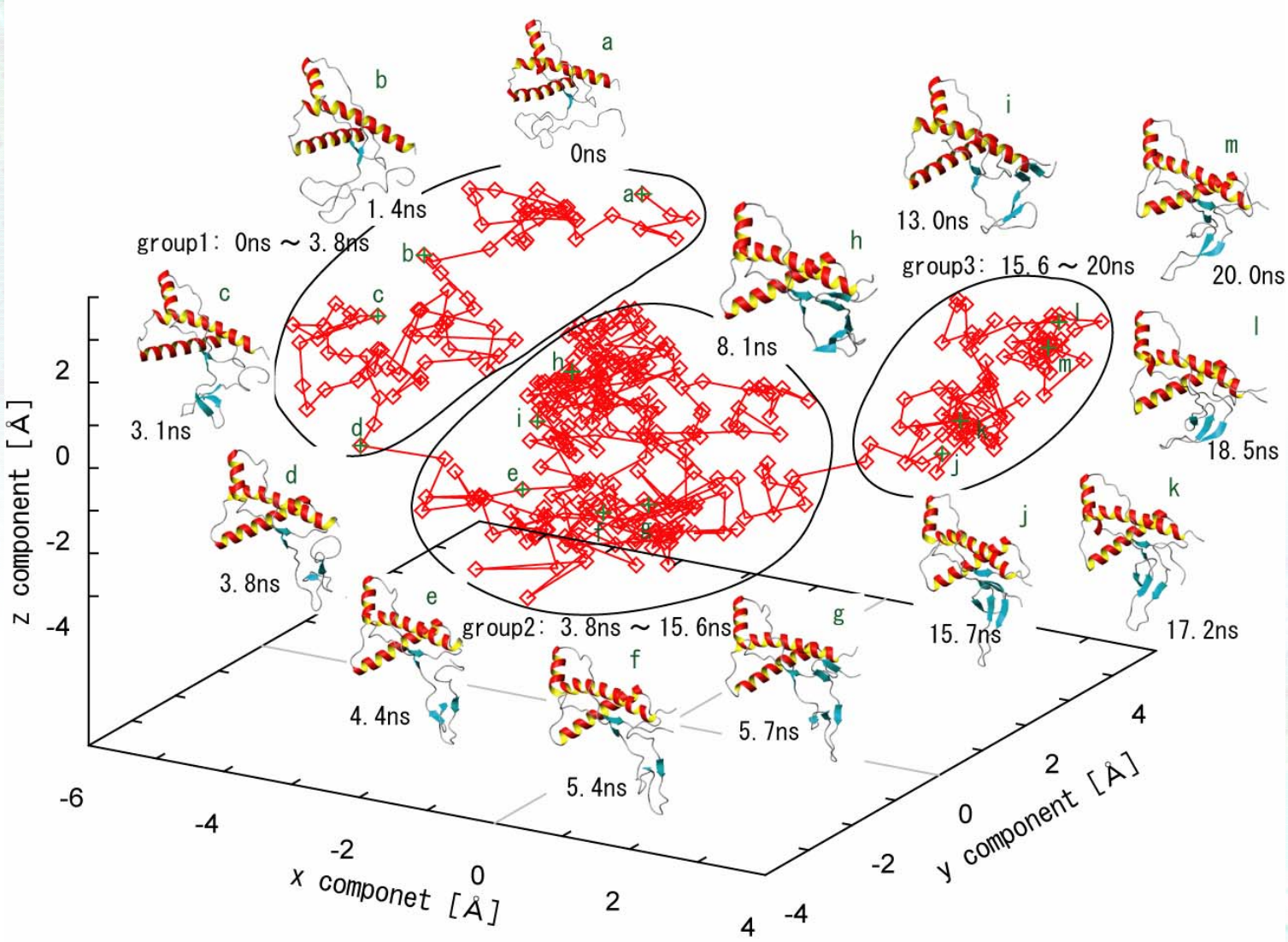
Conformational distribution of Mutant in 3D PCA Space



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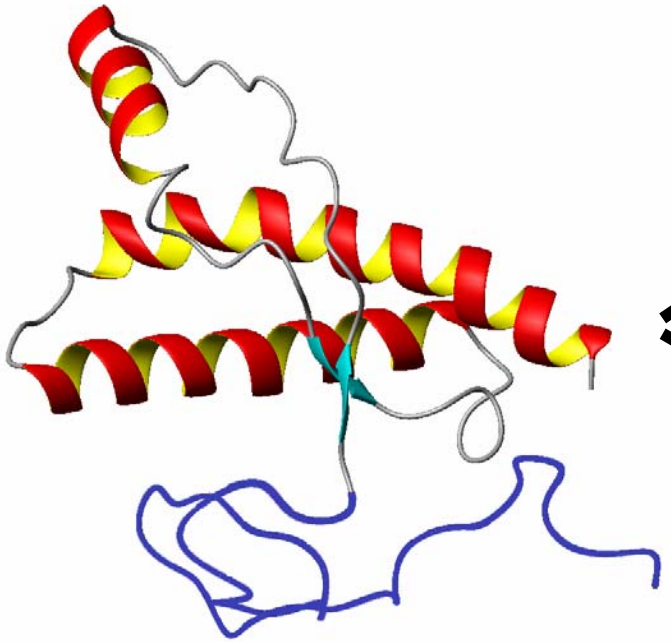
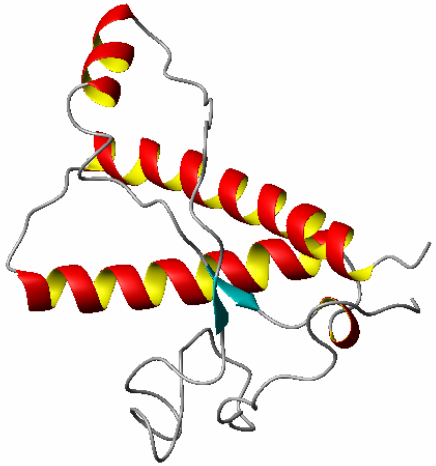
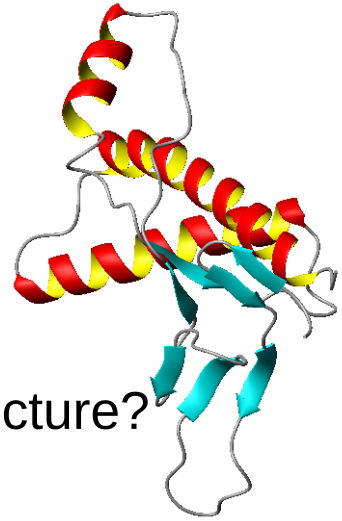
Our interests



WildType



Mutant
(P102L)



Why did one point mutation make different final structure?

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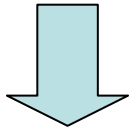
Conclusion

- Pro102's dihedral phi value was very stable, remaining within a small range throughout our simulation.
- Leu102's dihedral phi value varied considerably, allowing the possibility of interacting with other residues to form secondary structures, such as a beta sheet.



- This suggests that Pro102 is critical to prevent the transition from random structure to beta sheet structure in the wild type form.