Electronic Supplementary Information

Impact of Cu(II) and Al(III) on the conformational landscape of Amyloidβ_{1-42}

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1. *Initial Conformation and PCA analysis*

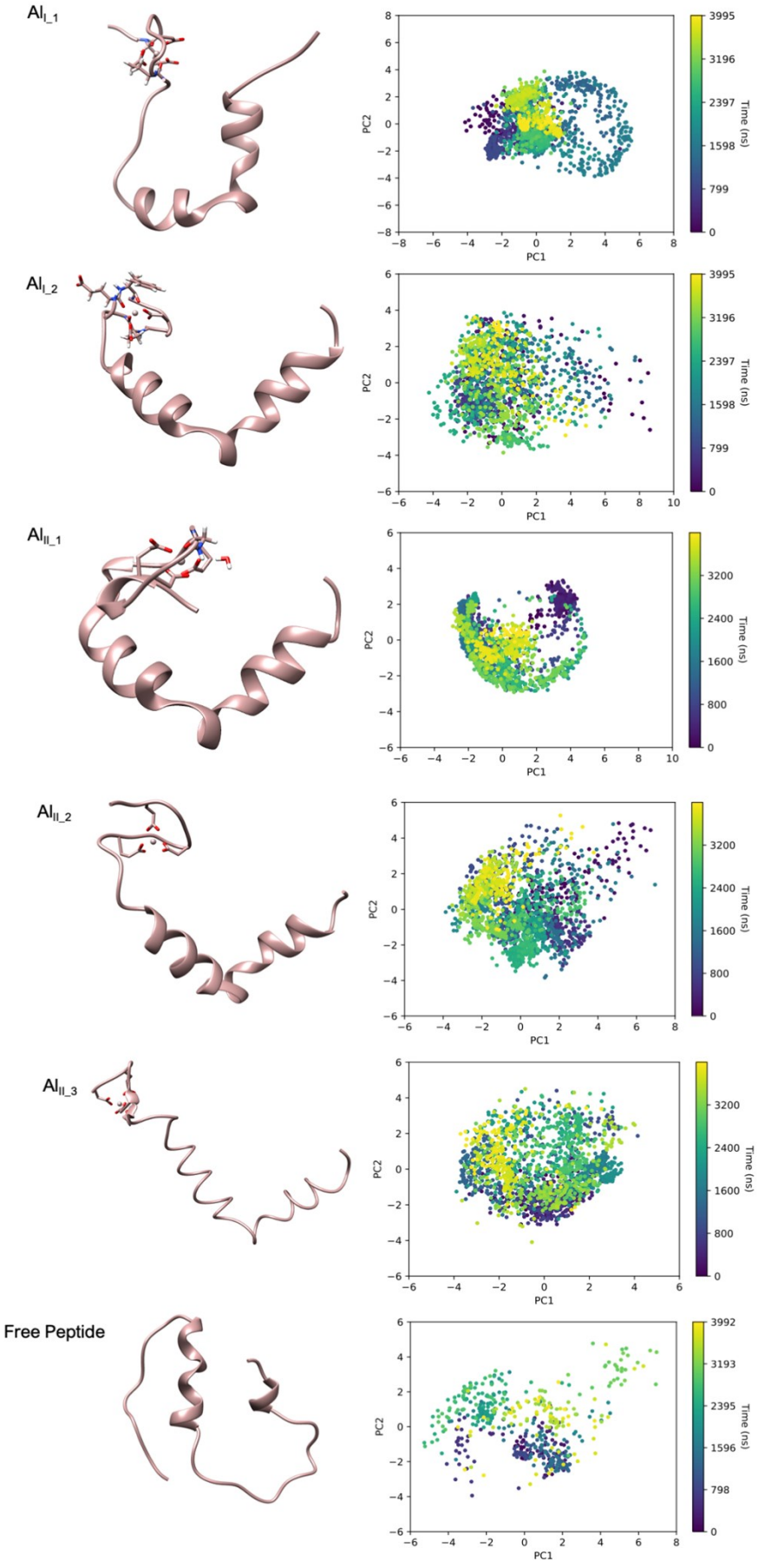


Figure S1. Initial conformation of each system and PCA analysis of the whole simulation.

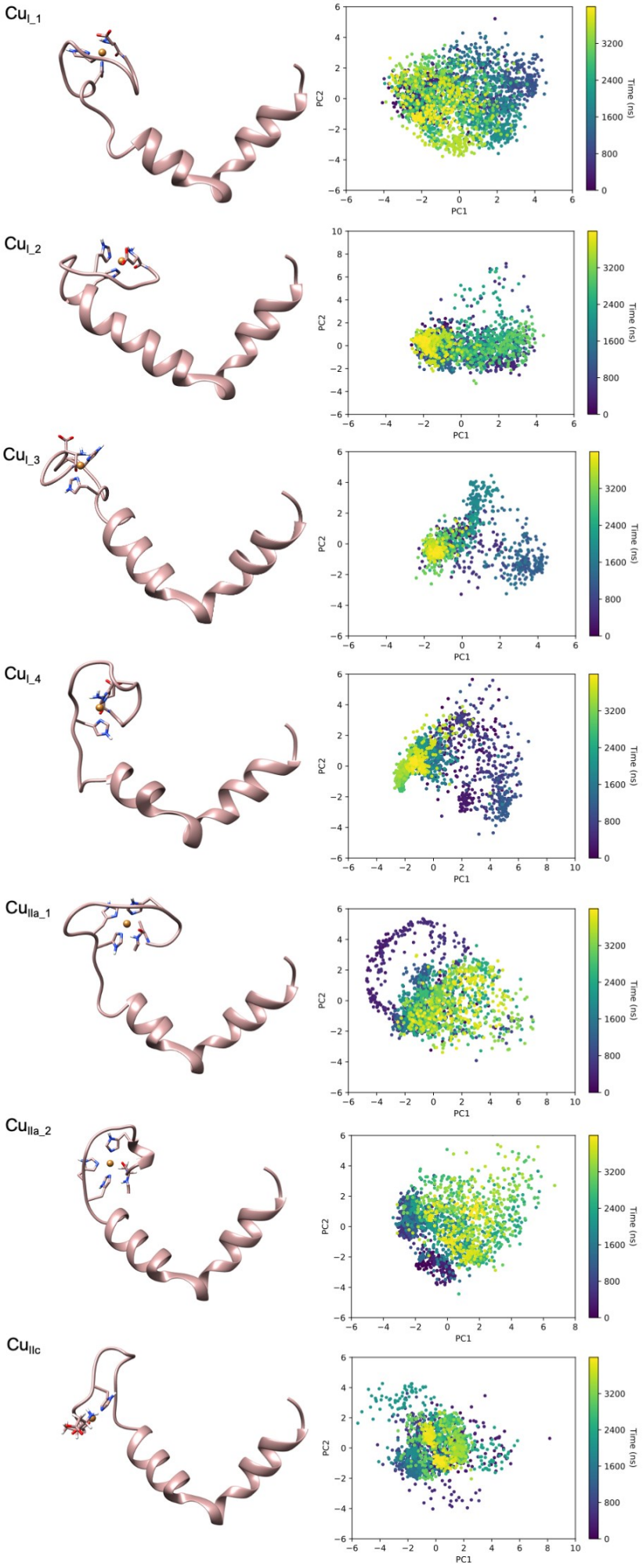


Figure S1. Continued.

2. *Aluminium systems*

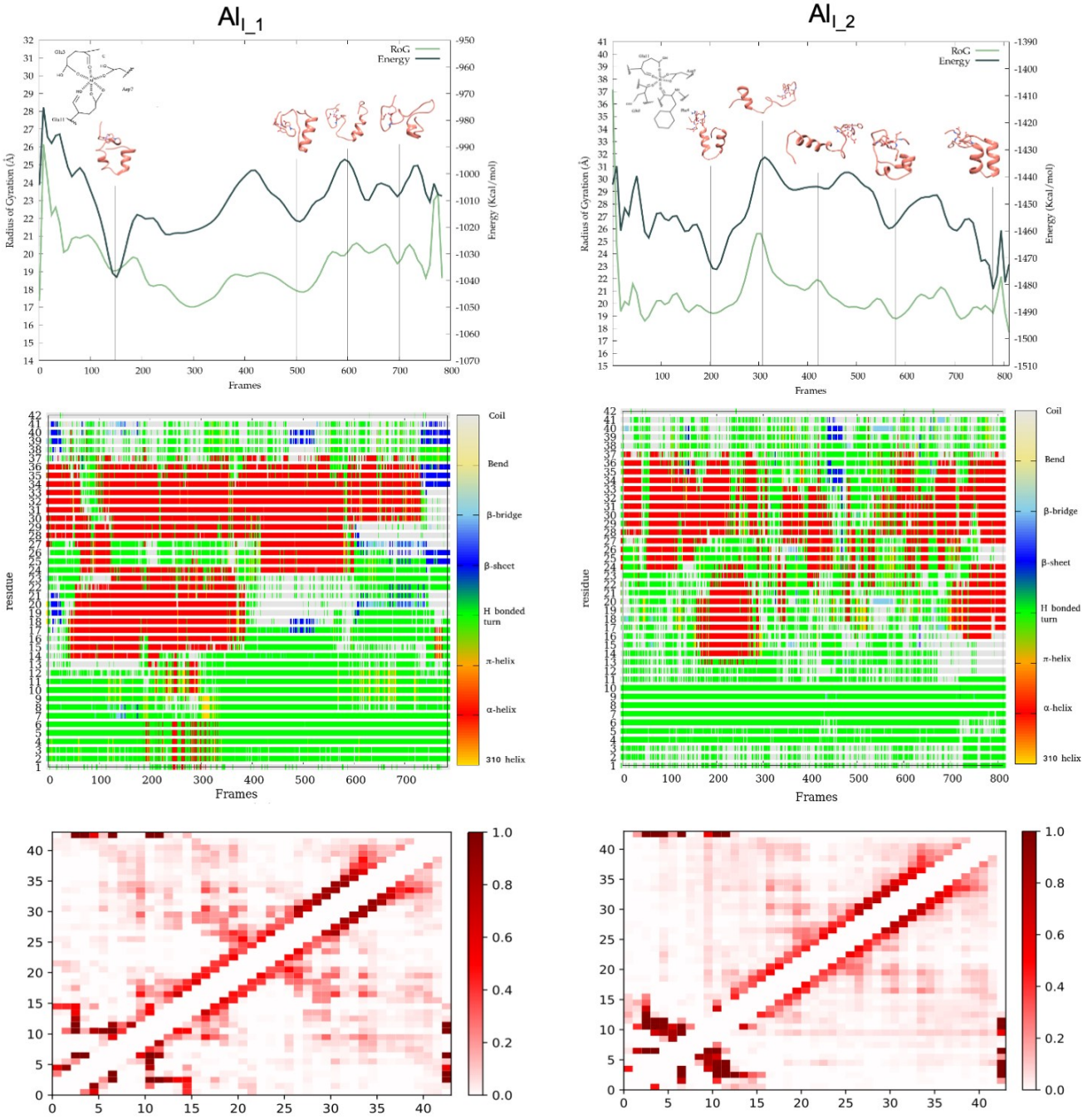


Figure S2. Energy profile with Radius of Gyration and representative frames, Timeline and Frequency Contact Map for Al(III) complexes and Free Peptide.

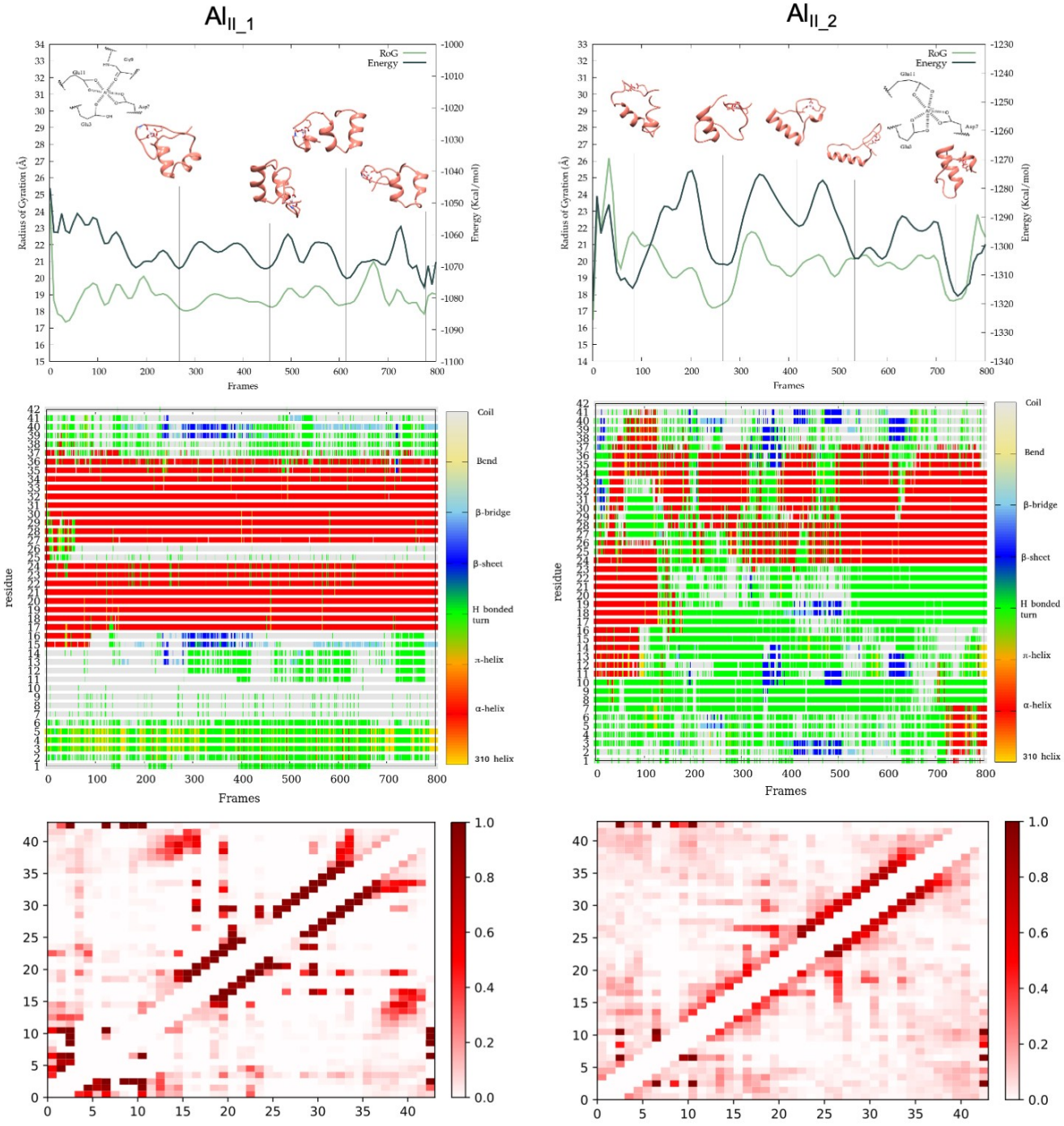


Figure S2. Continued.

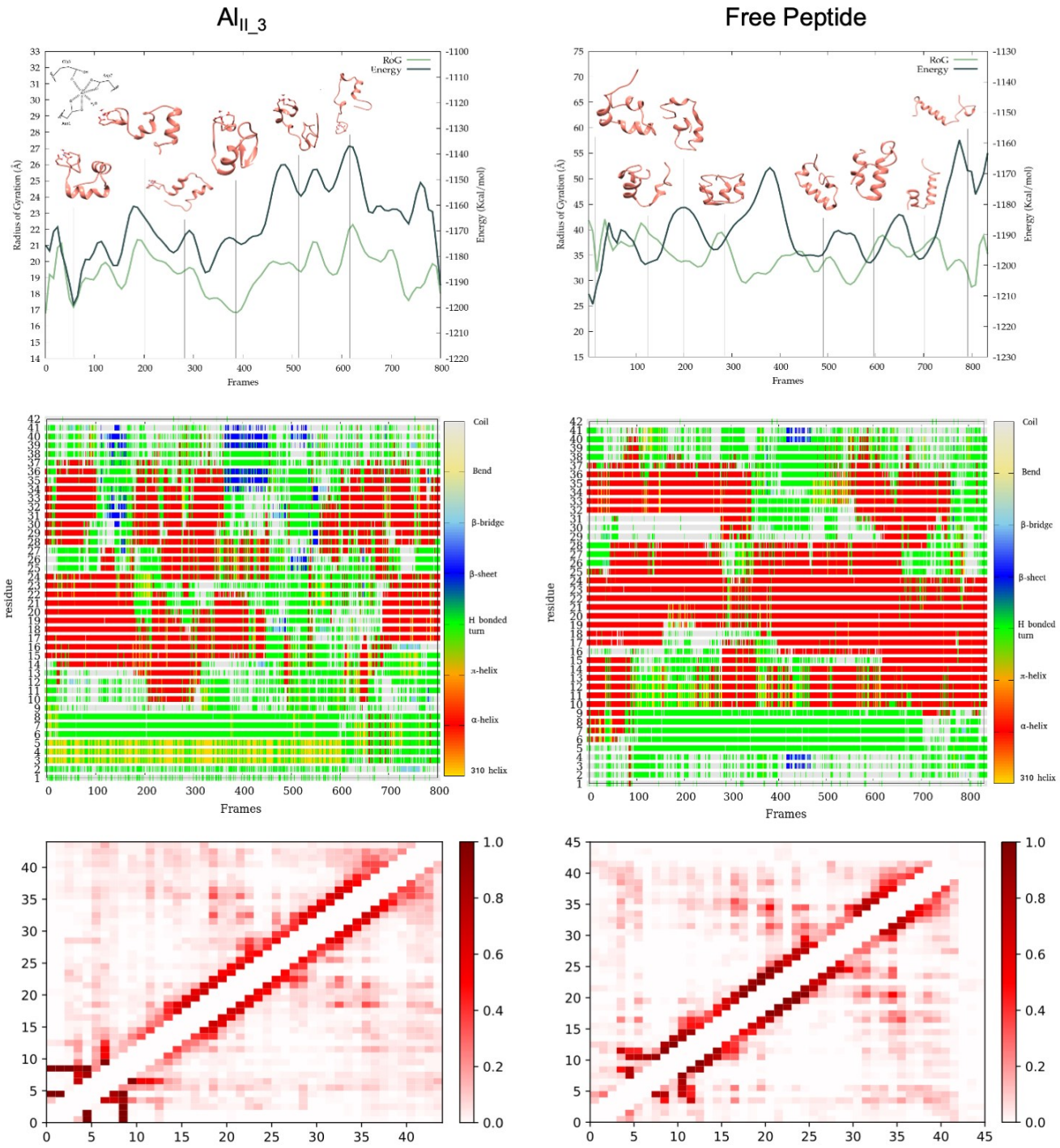
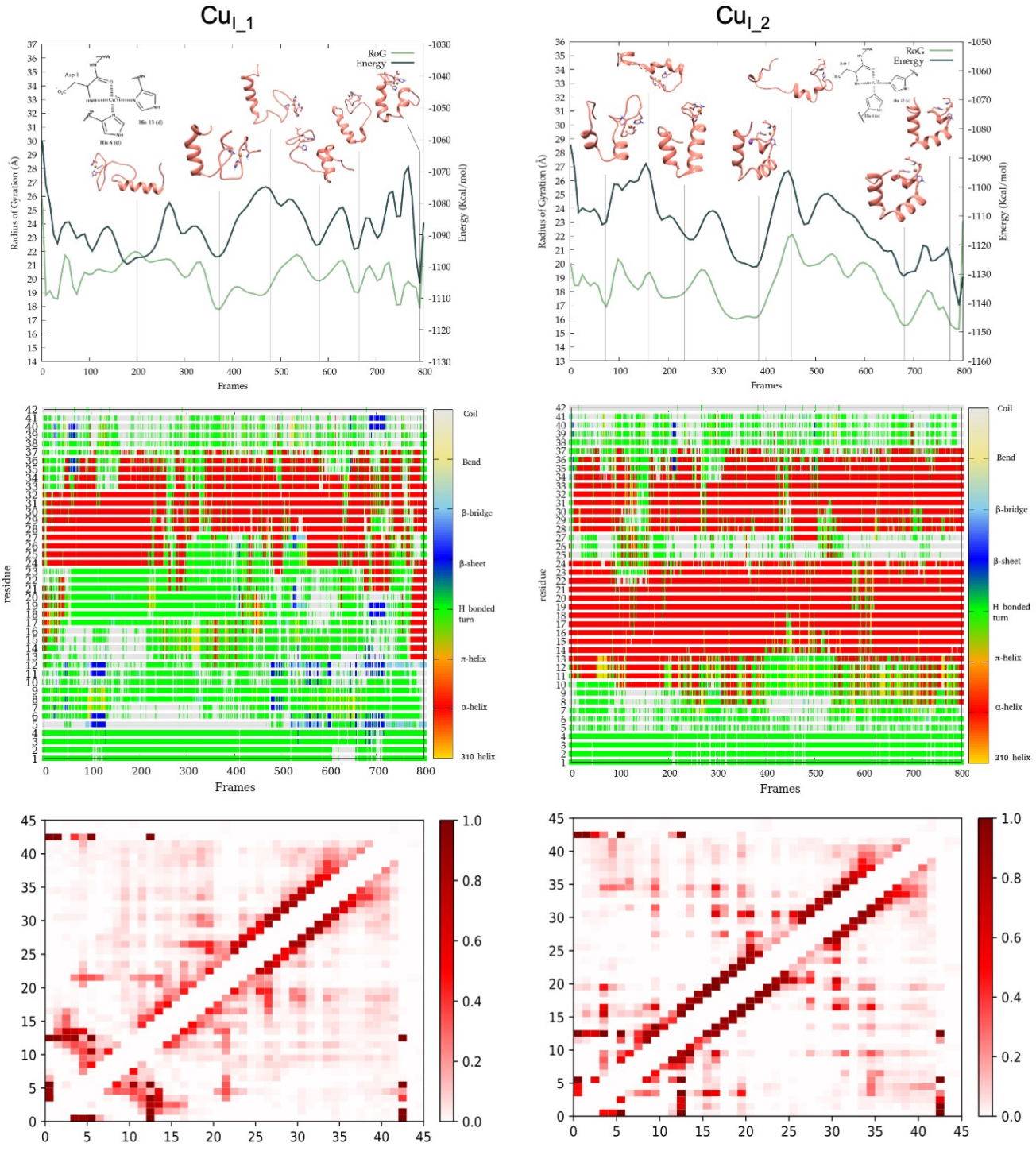


Figure S2. Continued.



3. *Copper Systems*

Figure S3. Energy profile with Radius of Gyration and representative frames, Timeline and Frequency Contact Map for Cu(II) complexes.

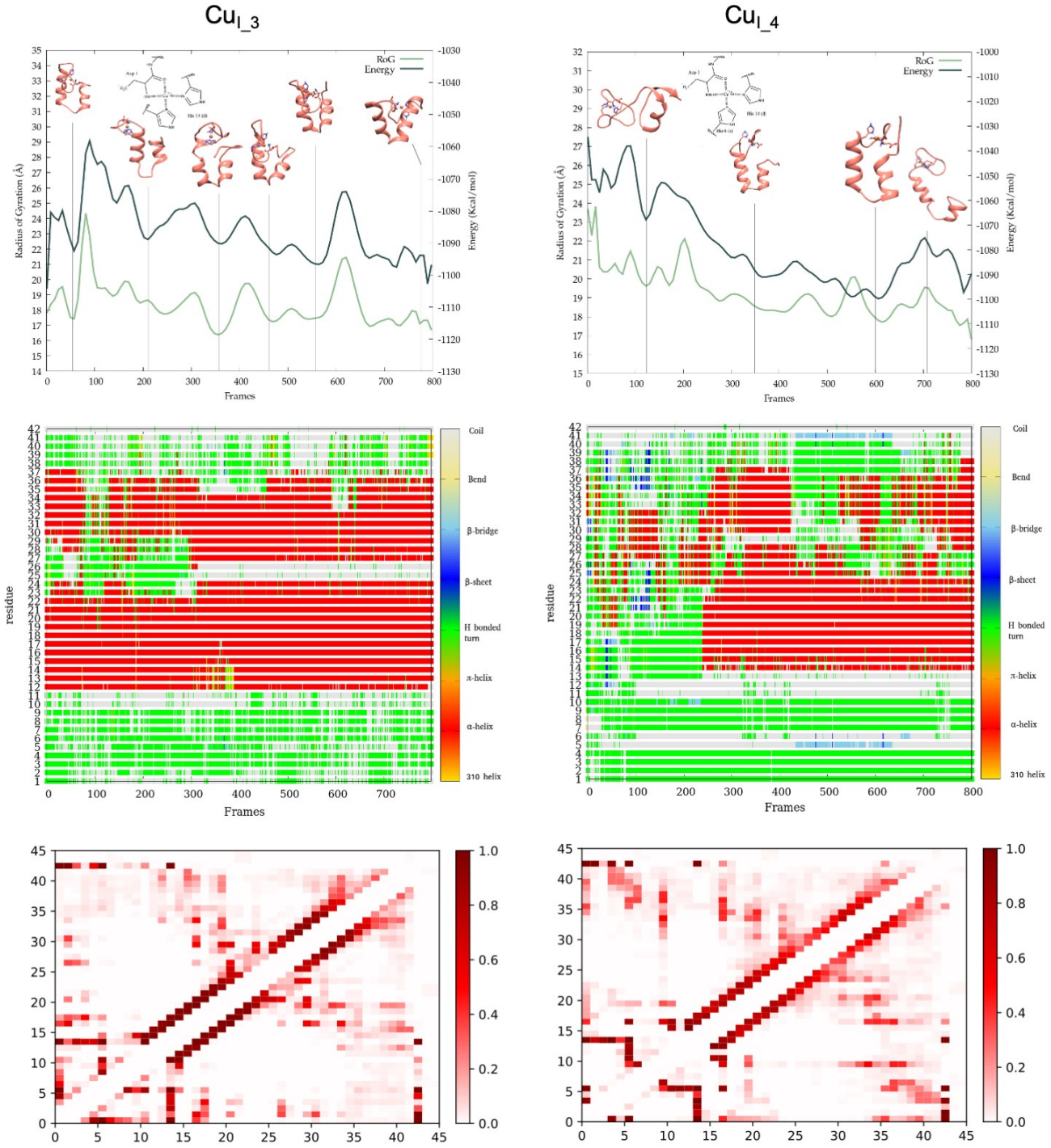


Figure S3. Continued.

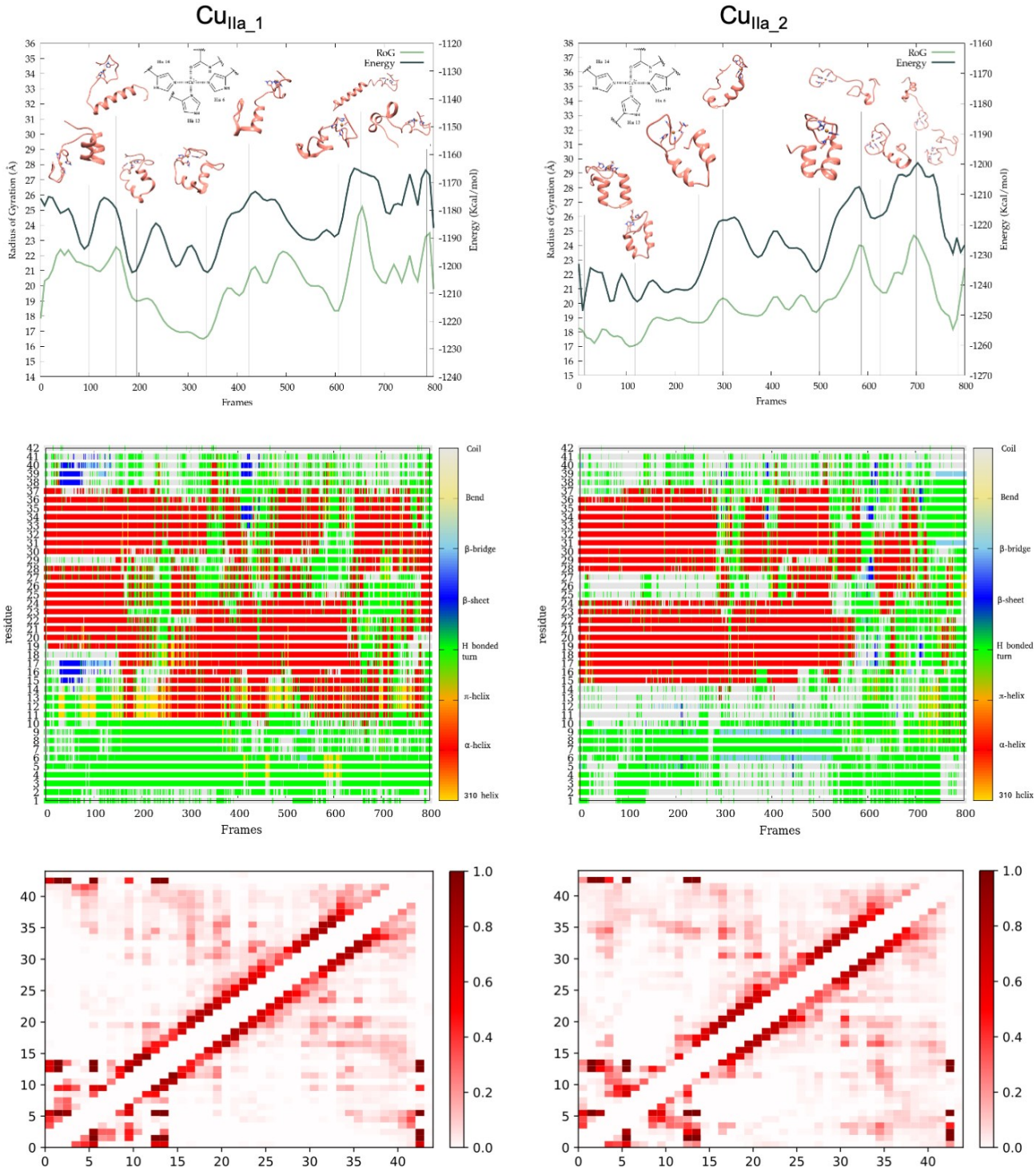


Figure S3. Continued.

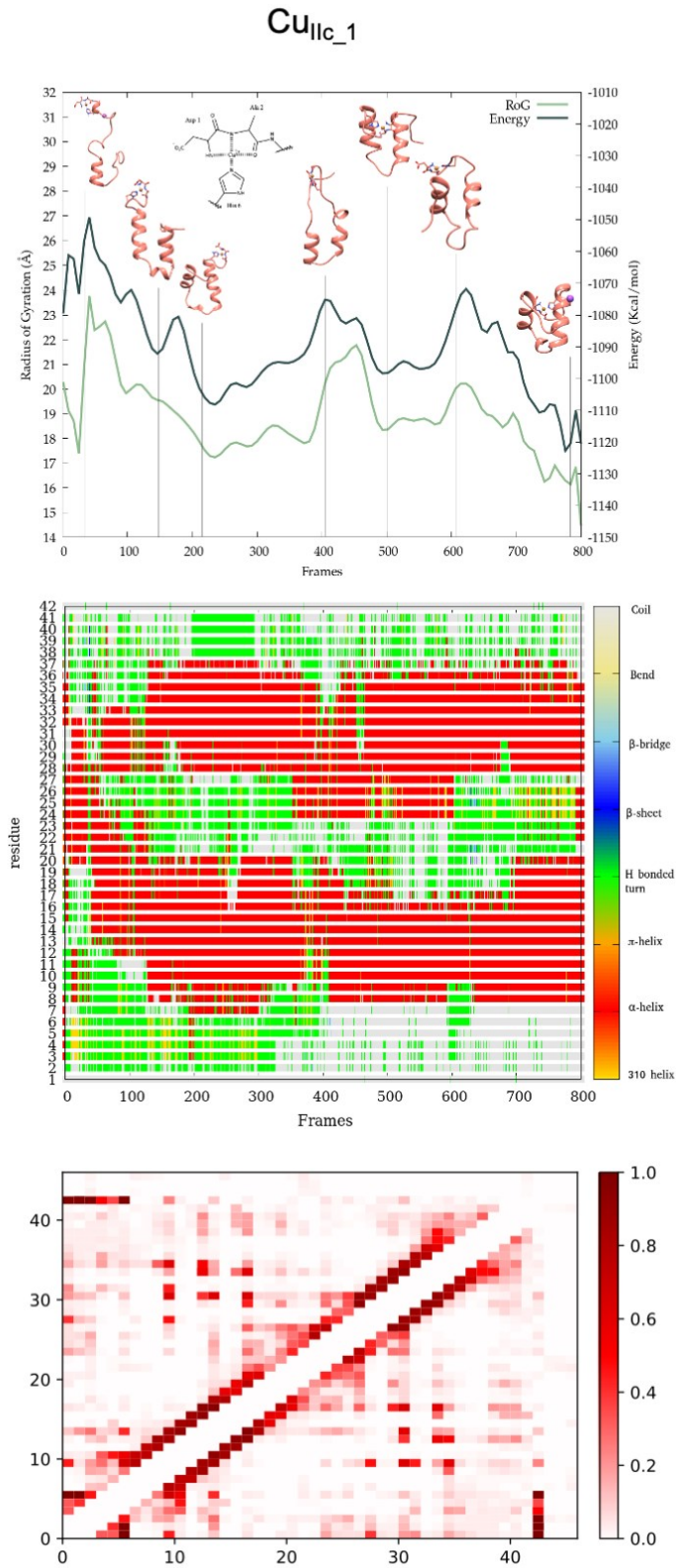


Figure S3. Continued.

4. *Phe19 and Phe20 exposure in U-Shape structures*

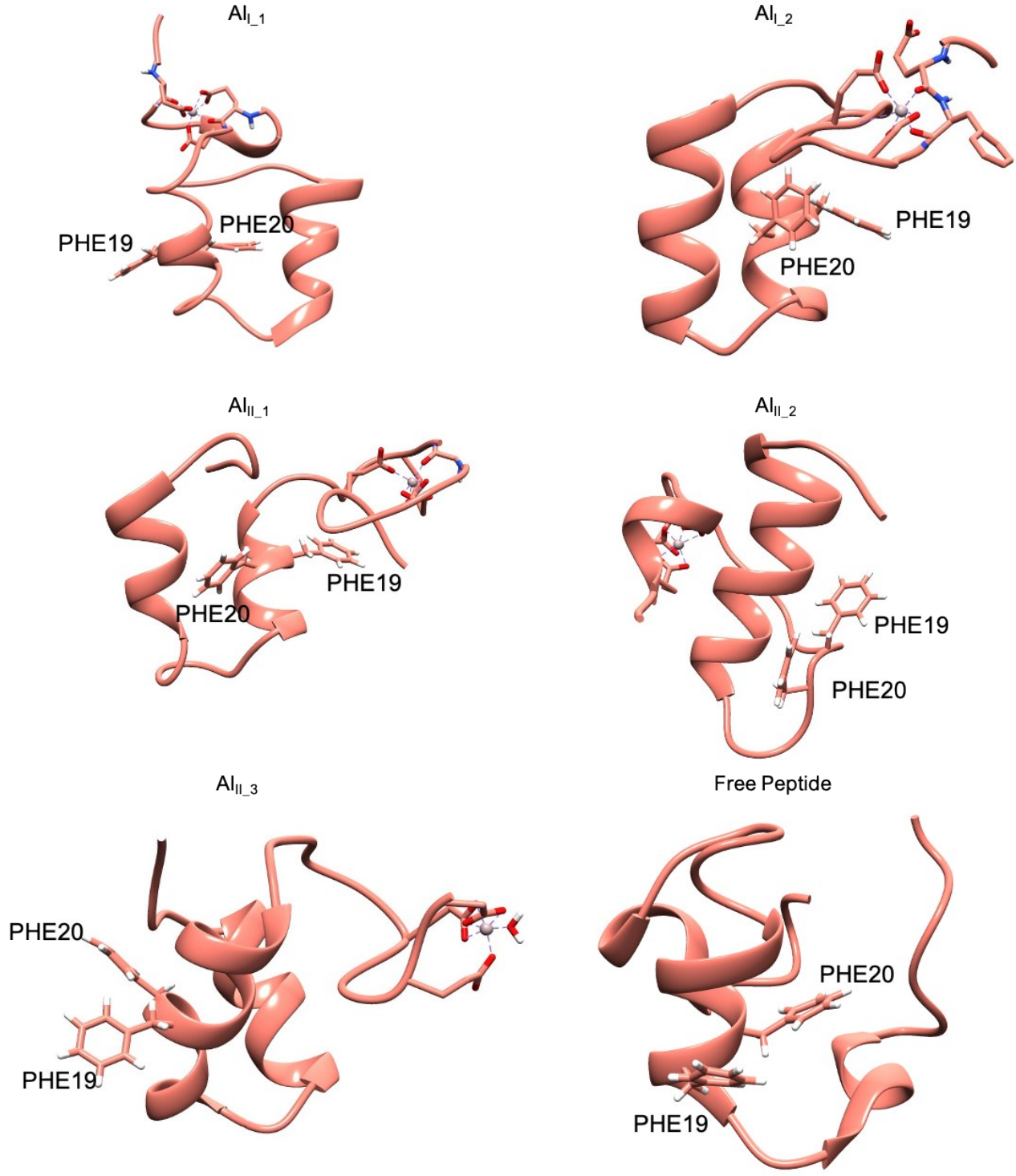


Figure S4.1. Exposure of residues Phe19 and Phe20 in the lowest energy well of Al(III)-Aβ complexes and free peptide.

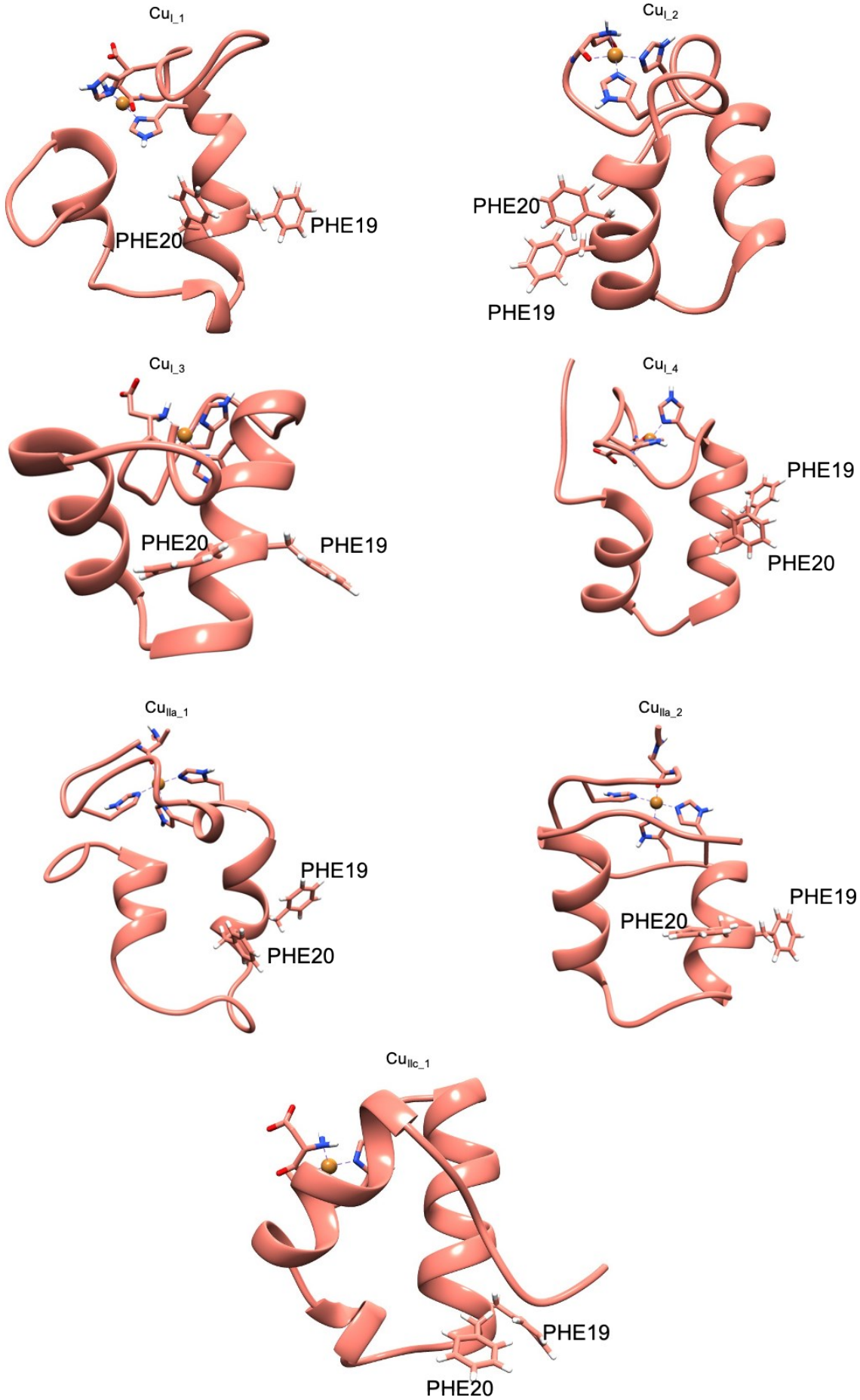


Figure S4.2. Exposure of residues Phe19 and Phe20 in the lowest energy well of Cu(II)-Aβ complexes.

5. Computational Information for Docking studies

BioMetAll version 1.0.0 was used for the preliminary metal-binding regions search on the β-amyloid fibril (PDB code: 2MXU). All possible binding areas were found restricting to the already known binding residues ASP, GLU, GLN, HIS, TYR and backbone coordinators, with a cutoff of 1.5 from the backbone. The results were analyzed with the UCSF Chimera Software,[1] identifying the most likely metal-binding zones and the residues involved.

Once the possible binding areas were delimited, the metal coordination was tested with GOLD software[2] with the updated GoldScore scoring functions accounting for metal coordination.[3,4] The protein structures were prepared with Chimera, generating *.mol2* files with the proper protonation state. Metal moieties have been prepared replacing the H_2O ligands of the optimized aquocomplexes with fictitious hydrogens as reported following the published method.[3,4] An evaluation sphere of 8 Å radius, centered in the BioMetAll found area, was set. The protein side chains flexibility was taken into account including GOLD libraries. All the parameters were set to default, with the genetic algorithm (GA) set to 50 GA runs and a minimum of 100,000 operations.

[1] Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. UCSF Chimera - A Visualization System for Exploratory Research and Analysis. *J. Comput. Chem.* **2004**, *25*, 1605–1612.

[2] Verdonk, M. L.; Cole, J. C.; Hartshorn, M. J.; Murray, C. W.; Taylor, R. D. Improved Protein–Ligand Docking Using GOLD. *Proteins Struct. Funct. Bioinforma.* **2003**, *52*, 609–623.

[3] Sciortino, G.; Rodríguez-Guerra Pedregal, J.; Lledós, A.; Garribba, E.; Maréchal, JD. Prediction of the interaction of metallic moieties with proteins: An update for protein-ligand docking techniques. *J. Comput. Chem*. **2017**, *39*, 42-51.

[4] Sciortino, G.; Garribba, E.; Maréchal, JD. Validation and Applications of Protein–Ligand Docking Approaches Improved for Metalloligands with Multiple Vacant Sites. *Inorganic Chemistry*, **2019**, *58*, 294-306.