A Computational Model Predicting How DNMT3A Is Recruited by PRC2 to Catalyze Epigenetic Modifications Associated with the Progression of Aging

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1 BACKGROUND

- It is theorized that one of the central causes of aging is the deterioration of the epigenome [1].
- The epigenome is a collection of chemical modifications to the DNA which control gene expression [1].
- The epigenetic pattern within a cell is controlled by epigenetic modifier proteins such as DNA Methyltransferase 3A (DNMT3A) and the Polycomb Repressive Complex 2 (PRC2) [2].
- DNMT3A is known to catalyze de novo DNA methylation [3].
- PRC2 is known to catalyze methylation on histone H3 at lysine 27 [3].
- Previous experimental evidence indicates PRC2 physically recruits DNMT3A to specific areas throughout the genome [3].
- This reported interaction is relevant to the aging process as it has been found that 90% of age dependent DNA methylation gain occurs at PRC2 target sites [4].
- This suggests that the malfunction of this recruitment process is related to the progression of aging.
- The goal of this project is to develop a computational model predicting the recruitment interaction between DNMT3A and PRC2.
- Characterizing this interaction is important as it will further our understanding of how the epigenetic landscape is maintained. This will in turn hopefully lead to insight on how to support the epigenome's maintenance and prevent its decay.

2 METHODS

1. Computational models of DNMT3A and PRC2 were developed from the PDB files 4UT7 and 5HYN respectively.
2. Docked models of the two complexes were generated using the program HDOCK. The top 3 structures were selected: model 2, model 5, and model 10. These models were selected for having interaction sites aligning with the experimental data, and not physically interfering with the catalytic sites [3].
3. 3 250 ns molecular dynamics (MD) simulations were run for each of the models using the software NAMD. MD simulations can create predictions on how two proteins will interact with each other over time.

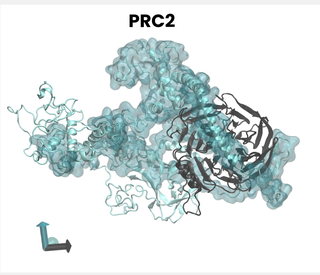


Figure 1. This image presents the PRC2 model. This PRC2 model includes the EED subunit (black) and the EZH2 subunit (light blue). The experimentally reported area of interaction is EZH2 amino acids 1 to 340 [3], which is highlighted here in blue.

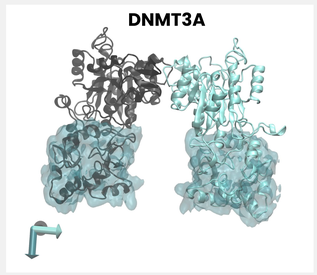
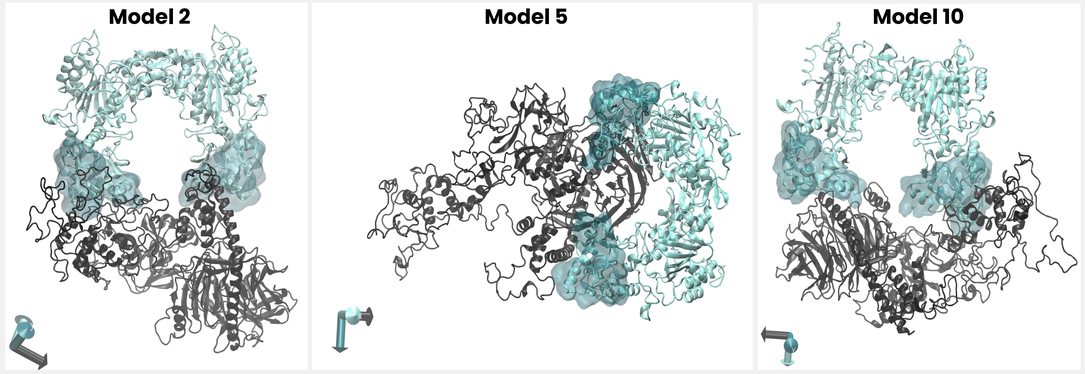


Figure 2. This image presents the DNMT3A model, which is composed of a homodimer of DNMT3A proteins (light blue and black). The experimentally reported area of interaction is highlighted in blue [3]. This region spans amino acids 476 to 600 and is known as the ADD domain.

3 RESULTS



Figures 3-5. These images present the top docked models of DNMT3A and PRC2 in ascending order. PRC2 is represented in black while DNMT3A is represented in light blue. The area of interaction is highlighted in blue.

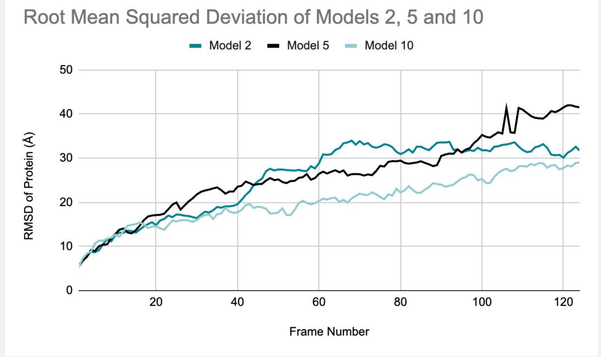


Figure 6. This graph presents the average RMSD of models 2, 5 and 10 from 3 simulations. All the models appear to be approaching equilibrium, meaning the complexes are becoming stable.

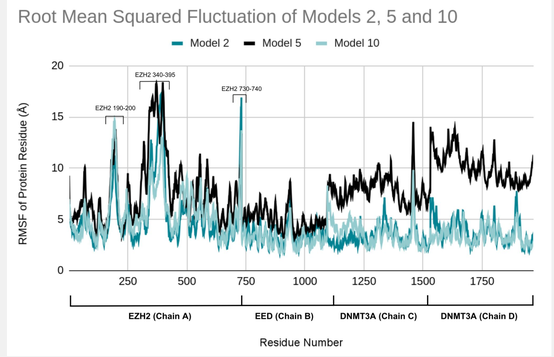


Figure 7. This graph presents the average RMSF of models 2, 5 and 10 from 3 simulations. EZH2 amino acids 190-200, 340-395, and 730-740 appear to be the most dynamically active.

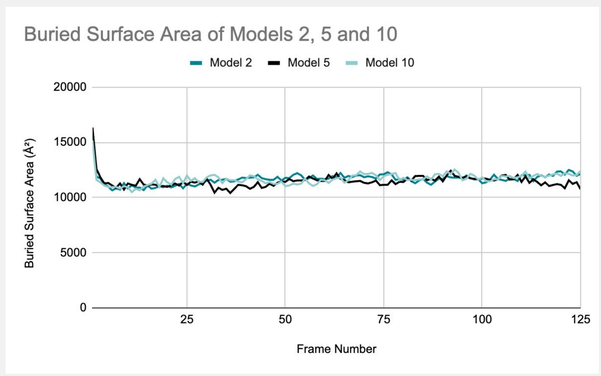


Figure 8. This graph presents the average BSA of models 2, 5 and 10 from 3 simulations. The BSA of all the models drops steeply in the beginning, but then seems to plateau for the remainder of the simulation. This suggests all the models interact in a similar manner and that their interaction remains stable over time.

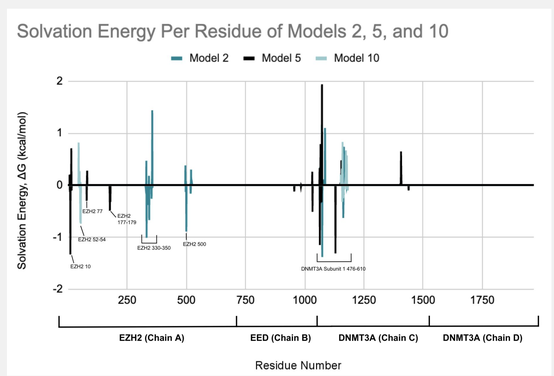


Figure 9. This graph presents the solvation energy per residue of models 2, 5 and 10. A negative solvation energy suggests the binding interaction is energetically favorable for that residue. This means that residues with negative solvation energy are likely important in facilitating the recruitment interaction between DNMT3A and PRC2.

4 DISCUSSION

- In conclusion, these models suggest possible mechanisms of the recruitment interaction between DNMT3A and PRC2.
- All 3 models appear to present stable interactions based on the RMSD and BSA plots.
- Additionally, the regions experimentally reported to be apart of the recruitment interaction, EZH2 1-340 and DNMT3A 476-600, appear to be the most dynamically and energetically involved in the interaction based on the RMSF and Solvation Energy plots.
- This work provides a starting point to understanding the intricate recruitment interactions between large epigenetic regulatory protein complexes at an atomic level.
- The next step would be to examine this recruitment interaction in the wet lab using a method such as cryogenic electron microscopy, which would provide further experimental evidence to shape additional models.

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6 REFERENCES

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