Evaluation of the unbinding kinetics of Mineralocorticoid (MR) receptor steroid agonist Cortisol (COL) , Aldosterone (AS4), and Progesteron (STR) ligands using Molecular Dynamics (MD) and Monte Carlo (MC) simulations

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April 14, 2023

Abstract

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I Introduction

Why MR and these ligands

II Methods

Selection of the best method to simulate the system, description of the simulation methods and how are we analyzing the date, since the MD simulations have a sense of time while the MC simulations does not, pyEMMA.

III Results and Discussion

Select images of interest and explain them

IV Conclusion

What is possible to conclude from each simulation and how can it be explain from chemistry and physics

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References

[1] Sebastian Aguilera Novoa and Alessandro S. Nascimento. Evaluation of the unbinding kinetics of mineralocorticoid (mr) receptor steroid agonist cortisol (col) , aldosterone (as4), and progesteron (str) ligands.

[2] Chantal Hellal-Levy, Jérôme Fagart, Anny Souque, and Marie-Edith Rafestin-Oblin. Mechanistic aspects of mineralocorticoid receptor activation. *Kidney International*, 57(4):1250–1255, 2000.

[3] Marie-Edith Rafestin-Oblin, Anny Souque, Brigitte Bocchi, Gregory Pinon, Jerome Fagart, and Alain Vandewalle. The Severe Form of Hypertension Caused by the Activating S810L Mutation in the Mineralocorticoid Receptor Is Cortisone Related. *Endocrinology*, 144(2):528–533, 02 2003.

[4] David S. Geller, Anita Farhi, Nikki Pinkerton, Michael Fradley, Michael Moritz, Adrian Spitzer, Gretchen Meinke, Francis T. F. Tsai, Paul B. Sigler, and Richard P. Lifton. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science*, 289(5476):119–123, 2000.

[5] Jéróme Fagart, Jessica Huyet, Grégory M. Pinon, Marina Rochel, Claudine Mayer, and Marie-Edith Rafestin-Oblin. Crystal structure of a mutant mineralocorticoid receptor responsible for hypertension. *Nature Structural & Molecular Biology*, 12(6):554–555, Jun 2005.

[6] John W. Funder. Aldosterone and mineralocorticoid receptors: Orphan questions. *Kidney International*, 57(4):1358–1363, 2000.

[7] K. Belfon I.Y. Ben-Shalom J.T. Berryman S.R. Brozell D.S. Cerutti T.E. Cheatham III G.A. Cisneros V.W.D. Cruzeiro T.A. Darden R.E. Duke G. Giambasu M.K. Gilson H. Gohlke A.W. Goetz R. Harris S. Izadi S.A. Izmailov K. Kasavajhala M.C. Kaymak E. King A. Ko-valenko T. Kurtzman T.S. Lee S. LeGrand P. Li C. Lin J. Liu T. Luchko R. Luo M. Machado V. Man M. Manathunga K.M. Merz Y. Miao O. Mikhailovskii G. Monard H. Nguyen K.A. O'Hearn A. Onufriev F. Pan S. Pantano R. Qi A. Rahnamoun D.R. Roe A. Roitberg C. Sagui S. Schott-Verdugo A. Shajan J. Shen C.L. Simmerling N.R. Skrynnikov J. Smith J. Swails R.C. Walker J. Wang J. Wang H. Wei R.M. Wolf X. Wu Y. Xiong Y. Xue D.M. York S. Zhao D.A. Case, H.M. Aktulga and P.A. Kollman (2022). *Amber 2022*. University of California, San Francisco.

[8] Yinglong Miao, Apurba Bhattarai, and Jinan Wang. Ligand gaussian accelerated molecular dynamics (ligamd): Characterization of ligand binding thermodynamics and kinetics. *Journal of Chemical Theory and Computation*, 16(9):5526–5547, 2020. PMID: 32692556.

[9] Yinglong Miao, Apurba Bhattarai, and Jinan Wang. Ligand gaussian accelerated molecular dynamics (ligamd): Characterization of ligand binding thermodynamics and kinetics. *bioRxiv*, 2020.

[10] Yinglong Miao, Apurba Bhattarai, and Jinan Wang. Ligand gaussian accelerated molecular dynamics (ligamd): Characterization of ligand binding thermodynamics and kinetics. *Journal of Chemical Theory and Computation*, 16(9):5526–5547, 2020. PMID: 32692556.

[11] Heloisa dos Santos Muniz and Alessandro S. Nascimento. Ligand- and receptor-based docking with libela. *Journal of Computer-Aided Molecular Design*, 29(8):713–723, Aug 2015.

[12]

[13] Martin K. Scherer, Benjamin Trendelkamp-Schroer, Fabian Paul, Guillermo Pérez-Hernández, Moritz Hoffmann, Nuria Plattner, Christoph Wehmeyer, Jan-Hendrik Prinz, and Frank Noé. PyEMMA 2: A Software Package for Estimation, Validation, and Analysis of Markov Models. *Journal of Chemical Theory and Computation*, 11:5525–5542, October 2015.

[14] Matthew M. Copeland, Hung N. Do, Lane Votapka, Keya Joshi, Jinan Wang, Rommie E. Amaro, and Yinglong Miao. Gaussian accelerated molecular dynamics in openmm. *The Journal of Physical Chemistry B*, 126(31):5810–5820, 2022. PMID: 35895977.

[15] Jinan Wang, Pablo R. Arantes, Apurba Bhattarai, Rohaine V. Hsu, Shristi Pawnikar, Yu-ming M. Huang, Giulia Palermo, and Yinglong Miao. Gaussian accelerated molecular dynamics: Principles and applications. *WIREs Computational Molecular Science*, 11(5):e1521, 2021.

[16] Geraldo Rodrigues Sartori and Alessandro S. Nascimento. Comparative analysis of electrostatic models for ligand docking. *Frontiers in Molecular Biosciences*, 6, 2019.

[17] Heloisa S. Muniz and Alessandro S. Nascimento. Towards a critical evaluation of an empirical and volume-based solvation function for ligand docking. *PLOS ONE*, 12(3):1–19, 03 2017.

[18] Tamar Schlick. *Molecular Modeling and Simulation: An Interdisciplinary Guide*, volume 21 of *Interdisciplinary Applied Mathematics*. Springer New York, NY, Berlin, Heidelberg, 2 edition, August 2010.

[19] A.R. Leach. *Molecular Modelling: Principles and Applications*. Prentice Hall, 2 edition, 2001.