Sheila Sarkar, Muhammad Tanveer, Lauren Wickstrom
June 2022
CUNY Research Scholars Program Report

Large-scale Binding Affinity Calculations of ER-Ligand Complexes: Assessment of the Predictive Power of Autodock Vina

Abstract

Estrogens are steroid molecules that promote and regulate cell and tissue growth. This growth becomes an issue when cells malfunction as seen in cancerous outcomes. Xenoestrogens also bind to the estrogen receptor (ER) and serve as key ingredients in widespread products. Experimental assays demonstrate that many xenoestrogens bind weakly to the ER; however, it is often unknown as to whether these compounds mimic the magnitude of the estrogen's response. In our previous study, we used Autodock Vina to predict the binding affinity and poses of estradiol, triclosan and methylparaben in the ER binding pocket, which were in reasonable agreement with experiment. As a continuation of this work, we performed a large scale binding affinity survey of 171 xenoestrogens using Autodock Vina to assess the reliability of our computational predictions on a more diverse groups of ligands with different chemical function groups. The parabens produced the best results while the antiestrogens produced the worst results relative to experiment. Future work will focus on linking the chemical nature of these ligands to the accuracy of their computational models.

Introduction

Estrogenic chemicals in the environment have generated public concerns over potential cancerous effects and other endocrine-dependent outcomes. Xenoestrogens are synthetic compounds that simulate the effect of estrogen. Experimental studies identify various xenoestrogens for their potential role in cancer development. However, these studies do not always focus on structural models of the binding process of compounds to the estrogen receptor. Our goal is to address this gap of knowledge and to learn more about the endocrine disruption and risk.

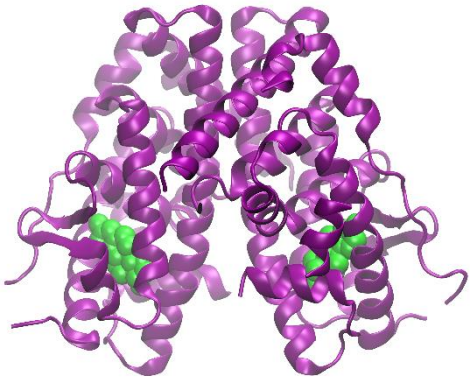

Figure 1. 3D Protein Structure of the Estrogen Binding Domain (PDB ID: 1GWR). Protein Backbone – purple Estradiol -- green

As a first step, we completed the binding analysis of estradiol, triclosan, and various parabens such as methyparaben because limited modeling work existed to explain the binding mechanism of these compounds. AutoDock Vina accurately predicted the native pose of ligands to the ER based on the estradiol docking experiment, estradiol was predicted to have a more favorable binding affinity than the other ligands which reproduced the experimental trend, and hydrogen bonding, hydrophobic packing, and electrostatic repulsion appeared to play a role in the binding process. For triclosan, we focused on the role of chlorine and benzene rings in the chemical structure. For parabens, we examined the role of phenyl rings and lengthening alkyl chains that impact binding affinity. From those studies, we expanded our approach to a wider survey of xenoestrogens to assess whether the binding of various compounds can still be accurately assessed with designated software and whether the binding is similar to other compounds with similar chemical structures. This step was required to establish the reliability of software testing and to promote future experiments to build structural and energetic interpretations of the binding affinities.

Methods

In this work, we used the computational docking tool, Autodock Vina, to predict the binding affinity and the most favorable binding pose of different ligands in the ER binding pocket. This software involves a conformational search process where the ligand searches for the best place to bind in or around the ER binding pocket. Binding pose takes into account the (1) orientation of the ligand or the way it positions itself in the pocket and the (2) conformation of the ligand or how atoms are positioned differently in space without breaking bonds. Binding affinity takes into account the strength of binding. The binding affinity is expressed as a free energy (ΔG°_b). Strong binders have a more negative affinity. Docking is performed on a rigid protein structure where only the ligand is allowed to move during the search. Charge and shape complementarity along with favorable types of chemical bonding play a role in the overall scoring process.

We performed the docking experiments on an agonist structure of the ER alpha receptor (PDB ID: 1GWR). 171 ligands from 12 compound categories noted in the Blair et al. study were docked into the ER pocket.

Results

Table 1. Docking results for 171 ER-ligand complexes

Compound Group	Number of Ligands	Average Absolute Error	Correlation Coefficient	Compound Group	Number of Ligands	Average Absolute Error	Correlation Coefficient
Steroidal Estrogens	11	2.00	-0.03	Organochlorides	20	1.86	0.23
Synthetic Estrogens	16	2.74	0.21	Pesticides	19	1.62	-0.24
Antiestrogens	6	3.90	-0.94	Parabens	7	1.11	0.79
Miscellaneous Steroids	12	2.64	0.39	Phthalates	5	2.50	0.00
Alkylphenolic Compounds	15	1.26	-0.09	Benzophenone Compounds	5	2.29	0.75
Diphenyl Derivatives	16	1.85	0.34	Miscellaneous Compounds	39	1.94	0.57

We docked 171 ligands to the ER-binding pocket using Autodock Vina (Table 1). These ligands were subdivided into 12 groups based on their chemical functional groups. Overall, the average absolute error and correlation coefficient of the calculated binding affinities (excluding anti-estrogens) relative to the experimental binding affinities were 1.95 kcal/mol and 0.36, respectively. Of the 12 chemical groups, the computational model was the most accurate for the parabens (absolute error = 1.11 kcal/mol and correlation coefficient = 0.79). The group demonstrating the worst results was the antiestrogens (absolute error = 3.90 kcal/mol and correlation coefficient = -0.94).

Discussion

Overall, the computational predictions demonstrated an excellent absolute error but a poor correlation coefficient based on the overall results. It appears that the best agreement relative to experiment is achieved when the ligand contains a chemical template of an aromatic ring, a hydroxyl group, and a long alkyl chain as observed with some of the parabens and alkylphenolic compounds (Figure 2). The non-polar hydrophobic chain helps secure it deep in the ER cavity. Antiestrogens were the poorest predicted because these antagonist ligands are large molecules that are too bulky to fit securely in the binding pocket of our current ER model, which was built from an ER agonist conformation of the protein.

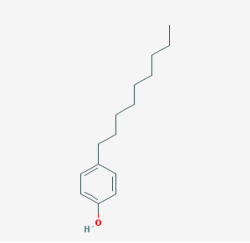

Figure 2. Example of Alkyphenolic Alkyl Chain in 4-Nonylphenol

Conclusions

In this work, we report the results of 171 docking experiments of ER-ligand complexes. This work demonstrates that Autodock Vina has limitations as a computational tool for binding affinity predictions. Future work will focus on further examination of these results to understand the predictive power of Autodock Vina.

References

1) Blair, R. M., Fang, H., Branham W. S., Hass, B. S., Dial, S. L., Moland, C. L., Tong, W., Shi, L., Perkins, R., and Sheenan, D., M. (2000). The Estrogen Receptor Relative Binding Affinities of 188 Natural and Xenochemicals: Structural Diversity of Ligands. *Society of Toxicology*, *54*, 138-153.

2) Trott, O., Olson, A.J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *Journal of Computational Chemistry*, *31*, 455-461.