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Binding free energy of small molecule/GLP-1R complexes calculations with funnel metadynamics

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Motivation and Aim: The glucagon-like peptide-1 (GLP-1) hormone is released following food intake [1] and plays a pivotal role in regulating glucose levels within the body. Upon secretion, GLP-1 interacts with its receptor, GLP-1 receptor (GLP-1R), triggering a cascade of events that includes the stimulation of insulin secretion and the inhibition of glucagon release [2]. This hormonal pathway not only aids in maintaining glucose homeostasis but also influences other metabolic processes. Activation of GLP-1R by GLP-1 leads to various physiological responses, including the delay of gastric emptying [3], heightened feelings of satiety [4], suppression of food intake, and consequent weight reduction [5]. Consequently, harnessing the effects of GLP-1 and its receptor has emerged as a promising therapeutic strategy for managing conditions such as Type 2 Diabetes Mellitus (T2DM) and obesity.

Currently, multiple peptidic GLP-1R agonists, including semaglutide and liraglutide, have received approval for the treatment of T2DM [6, 7, 8]. However, the administration of them via subcutaneous injection poses challenges in patient adherence and convenience, highlighting the need for more accessible delivery methods. Oral administration emerges as a preferable alternative, offering improved compliance and convenience [9]. Moreover, emerging evidence suggests that GLP-1R agonists not only address metabolic dysregulation but also confer cardiovascular benefits by reducing blood pressure [10] and enhancing microvascular function. However, the development of small molecule drugs targeting GLP-1R activation poses significant challenges [11].

The exploration of ligand-receptor interactions often relies on assessing binding free energy. However, common methods for this analysis are resource-intensive and time-consuming, limiting their practicality for precise results. We propose utilizing funnel metadynamics [12], a computational technique that enhances sampling efficiency by employing a funnel-shaped restraint potential. This approach guides ligands through relevant conformational space, reducing unnecessary exploration of irrelevant regions.

Our aim is to investigate the binding free energy of small molecules with the GLP-1R using funnel metadynamics. We aim to validate this method's accuracy using molecules with known binding free energies as ground truth. Furthermore, we seek to explore novel molecules as potential candidates for developing therapeutics targeting T2DM and obesity.

Methods and Algorithms: Atomic partial charges were calculated using PsiRESP [13], which employs the Psi4 quantum chemistry engine. Molecular topologies were generated using ACPYPE, incorporating charges obtained from PsiRESP and the GAFF2 force field.

Molecular dynamics simulations were employed to analyze the temporal movements of atoms and molecules. Additionally, funnel metadynamics was utilized to restrict available space during simulation. This technique also enabled enhanced sampling of binding free energy space by employing collective variables, specifically the distance along the cone axis and the distance from the cone axis.

Results: Our study has yielded results demonstrating close agreement between the calculated values of free binding energy and experimental data, validating the accuracy of used approach. Furthermore, we have determined free binding energies for novel small molecules interacting with the GLP-1R, offering valuable insights into their potential as therapeutic candidates. The results will be used further in the ongoing development of drugs that activate GLP-1R.

Conclusion: Our study has shown that the funnel metadynamics method is effective. By using a funnel-shaped restraint potential, we were able to focus more precisely on exploring the binding site of the receptor and ligand, improving our understanding of their interaction. This suggests that funnel metadynamics could be valuable for future research aimed at identifying potential agonist molecules for the receptor we studied. This approach could lead to better ways of studying how drugs interact with their targets, which is crucial for discovering new treatments in the field of molecular pharmacology. Further investigation using funnel metadynamics may help us uncover complex molecular interactions and develop new drugs that are more effective and specific in their actions.

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