
XXIV National Meeting in Medicinal Chemistry
10th Young Medicinal Chemists' Symposium
Nuove prospettive in Chimica Farmaceutica
7N 15P 6C 9F 10
Società Chimica Italiana
Divisione di Chimica Farmaceutica
UNIVERSITÀ DEGLI STUDI DI PERUGIA
dsf
DIPARTIMENTO SCIENZE FARMACEUTICHE
With the patronage of:
Regione Umbria
Comune di Perugia
CAPITALE ITALIANA DEI GIOVANI
PERUGIA 2016
EFMC
Perugia, Hotel Giò
September 11-14, 2016
Abstract eBook

PC-120

MOLECULAR DYNAMICS - MULTIPLE RECEPTOR CONFORMATIONS APPROACH TO ENHANCE STRUCTURE-BASED VIRTUAL SCREENING ON PPAR-ALPHA RECEPTORS

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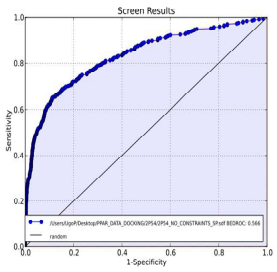
Structure-based approach is commonly used to study molecular interactions in drug discovery. Most computational studies consider proteins as rigid, decreasing the accuracy of predicted ligand poses because of a reduced space of likely side chains conformations that can be explored. Therefore, Molecular Dynamics simulations (MD) can be used prior to virtual screening to add flexibility to proteins[1-2]. Furthermore, the use of multiple receptor conformations (MRC) approach, using multiple protein crystals of the same protein with different ligands, can help to elucidate the role of the ligand on protein active conformation and then on common interactions between small molecules and the receptor[3]. In this work, we evaluated the contribution of the combined use of MD together with MRC to examine the crucial ligand-protein interactions within the complex. These findings were then exploited as constraints for the docking grid generation used in a virtual screening study on human PPAR-alpha, a well-studied protein involved in metabolic diseases. Using DESMOND for dynamics simulations and Glide molecular docking program, we found that information derived from short MD simulations, carried out on different protein crystals, can improve molecular docking results in terms of early enrichment of active ligands. Our results, expressed as the area under the receiver operating characteristic (ROC) curves (**Fig.1**) and Robust Initial Enrichment, showed an increase in the ability to discriminate active from inactive compounds, referred to the early recognition, when docking is performed using MD-MRC approach. In **Fig.2** we report the docking pose of the best ranked active molecule and the 2D interactions map showing the most common interaction pattern retrieved from the MD-MRC protocol and used as constraints in the docking protocol. This knowledge-based technique for docking grid generation could be very useful as demonstrated by the significant improvement of specificity and sensitivity of the screening capability. We aim to extend this approach to other systems in order to better evaluate the real applicability of the protocol.



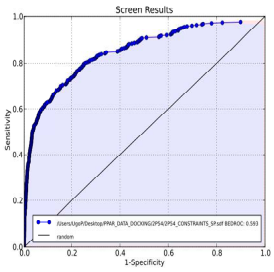
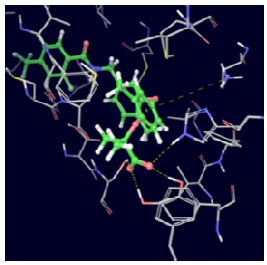


Fig1. ROC curve of the Virtual Screening using default docking grid (left) and MD-MRC derived docking grid (right)



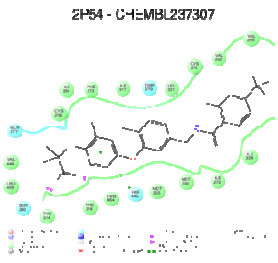


Fig2. Best ranked Active molecule in 3D binding pose (left) and in 2D interaction map (right)

References

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