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Ligand-based pharmacophore modeling using novel 3D pharmacophore signatures

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Abstract

© 2018 by the authors. Pharmacophore modeling is a widely used strategy for finding new hit molecules. Since not all protein targets have available 3D structures, ligand-based approaches are still useful. Currently, there are just a few free ligand-based pharmacophore modeling tools, and these have a lot of restrictions, e.g., using a template molecule for alignment. We developed a new approach to 3D pharmacophore representation and matching which does not require pharmacophore alignment. This representation can be used to quickly find identical pharmacophores in a given set. Based on this representation, a 3D pharmacophore ligand-based modeling approach to search for pharmacophores which preferably match active compounds and do not match inactive ones was developed. The approach searches for 3D pharmacophore models starting from 2D structures of available active and inactive compounds. The implemented approach was successfully applied for several retrospective studies. The results were compared to a 2D similarity search, demonstrating some of the advantages of the developed 3D pharmacophore models. Also, the generated 3D pharmacophore models were able to match the 3D poses of known ligands from their protein-ligand complexes, confirming the validity of the models. The developed approach is available as an open-source software tool: http://www.qsar4u.com/pages/pmapper.php and https://github.com/meddwl/psearch.

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Keywords

3D pharmacophore hash, 3D pharmacophore signatures, Ligand-based modeling, Pharmacophore modeling

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