Using consensus molecular docking for the discovery of Wee1 inhibitors in the context of cancer

Jochem Nelen[1], Miguel Carmena-Bargueño[1], Carlos Martínez-Cortés[1], Alejandro Rodríguez-Martínez[2], Jose Manuel Villalgordo-Soto[3] and Horacio Pérez-Sánchez[1]

[1] Structural Bioinformatics and High Performance Computing Research Group (BIO-HPC), Computer Engineering Department, UCAM Universidad Católica de Murcia, Murcia, Spain
[2] Departamento de Química Física, Instituto de Biotecnología y Unidad de Excelencia de Química aplicada a Biomedicina y Medioambiente Universidad de Granada. Campus Fuentenueva s/n 18071 Granada, Spain
[3] Eurofins Villapharma Research, Murcia, Spain

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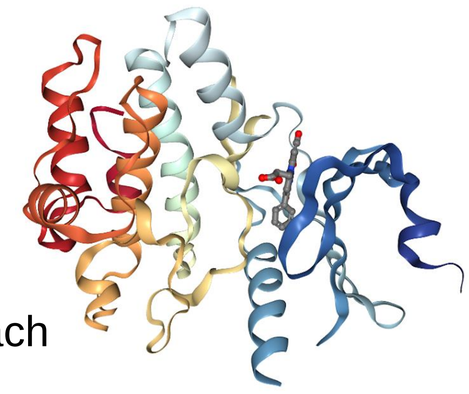
Abstract

- Structural drug discovery methods such as molecular docking can have quite variable results
- Consensus docking can lower this variability, leading to less false positives
- In this study, consensus docking was successfully utilized to perform a virtual screening of the DrugBank library for Wee1

Wee1

- Important regulator during cell division checkpoint
- Target for inhibition as a cancer treatment
- Case study target for the consensus docking approach



Workflow Overview

DRUGBANK

~10000 compounds
8 compounds listed as active against **Wee1**

Molecular Docking **AutoDock Vina** using **MetaScreener**

Molecular Docking **LeadFinder** using **MetaScreener**

Consensus Script

Residue Interaction Table

Residue Interaction JSON

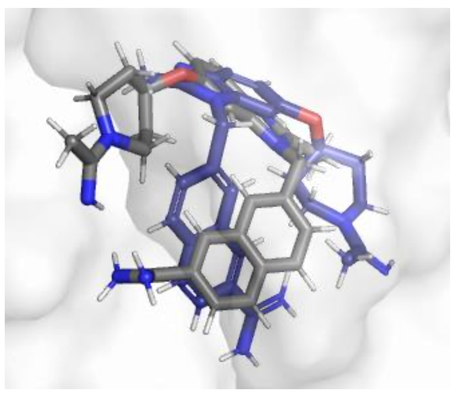
Table containing top **50** compounds sorted by Mean Binding Energy

4 active compounds scattered in top **50** (ranks **24**, **31**, **36** and **44**)

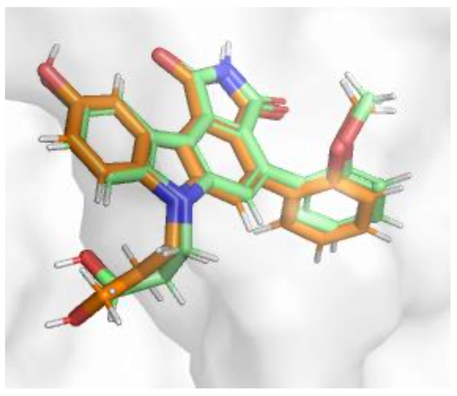
Compare docking poses by calculating and sorting by **RMSD**

4 active compounds scattered in top **10** (ranks **1**, **2**, **3** and **9**)

Consensus of predicted binding poses



- DB03373
- RMSD ~ 6,5 Å
- Bad consensus
- Lower confidence result



- DB07006
- RMSD ~ 0,5 Å
- Good consensus
- Higher Confidence result

Consensus Script Output

	GLU303	ILE305	SER307	GLU309	PHE310	VAL313
DB11847_AD	0	1	0	0	1	0
DB11847_LF	0	2	2	0	1	2
DB12892_AD	0	2	0	0	1	1
DB12892_LF	0	1	0	0	0	1
DB12678_AD	0	2	0	0	2	2
DB12678_LF	0	0	0	0	1	2


```
"DB11847": {
    "AD": {
        "HydrophobicInteractions": [
            "ILE305",
            "ALA326",
            "LYS328",
            "PHE433"
        ],
        "HydrogenBonds": [
            "LYS328",
            "GLU346",
            "CYS379",
            "SER430"
        ],
        "piStacking": [
            "PHE310",
            "PHE433",
            "PHE433"
        ]
    },
```


Mixed Rank	Ligand Name	Mean Binding Energy	Mean Rank	RMSD	AD Rank	AD Binding Energy	LF Rank	LF Binding energy
CL_1	DB11847	-11.705	49	1.2369	78	-10.9	20	-12.51
CL_2	DB12892	-11.645	93.5	4.26647	179	-10.64	8	-12.65
CL_3	DB12678	-11.555	43.5	7.75356	32	-11.1	55	-12.01
CL_4	DB15426	-11.485	52	10.502	19	-11.15	85	-11.82

Conclusions

- As demonstrated here for Wee1, using RMSD as a consensus metric can be used to enrich for higher confidence results
- Using this workflow, additional useful information like predicted residue interactions can be generated
- Workflow of postprocessing after MetaScreener is still in development, but already used extensively in-house

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Villapharma research
sigma2
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References

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(2) AutoDock Vina: https://doi.org/10.1002/jcc.21334
(3) LeadFinder: https://doi.org/10.1021/ci800166p
(4) MetaScreener: https://github.com/bio-hpc/metascreener

Contact: jnelen@ucam.edu

BIO-HPC Structural Bioinformatics and High Performance Computing Research Group

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