



SimulationsPlus

MIDD+22

Model Informed Drug Development

AIDD with External Models

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.



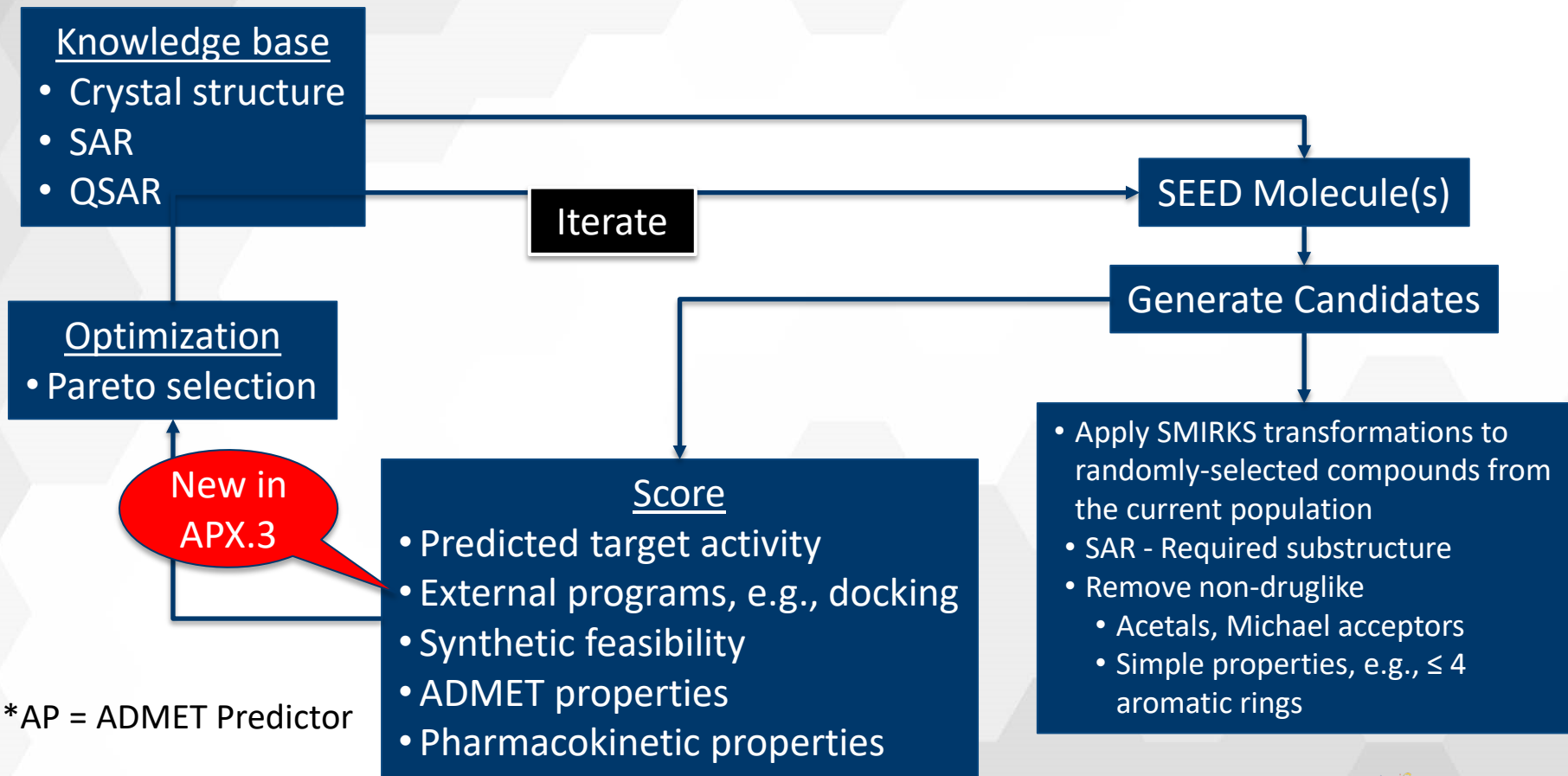
AIDD Module

Goal – design compounds that have:

- High potency at the primary target
- High synthetic feasibility
- Good ADMET and pharmacokinetic (PK) properties

Can be used for hit finding, lead optimization,
and scaffold hopping e.g., patent busting

AIDD Workflow



AIDD External Application File

The screenshot displays the 'Compound optimization' window. A dialog box is open, prompting the user to 'Compute objectives using external application'. The dialog includes a text field for the 'Parameter file for external application' with the path 'C:\Users\mlawless\AppData\Local\Simulati' and a 'Browse' button. The background window shows a list of 'Available properties' with checkboxes for various metrics like '<Synthetic_Difficulty+>', '<Fraction absorbed (%Fa)>', and '<Fraction bioavailable (%Fb)>'. It also features a 'Properties to optimize' table and a 'Parameters for selected properties' section with input fields for values like 1, 10, and 7.4.

Compound optimization

Available properties

- <Synthetic_Difficulty+>
- <Fraction absorbed (%Fa)>
- <Fraction bioavailable (%Fb)>

Compute objectives using external application

Parameter file for external application

C:\Users\mlawless\AppData\Local\Simulati

Properties to optimize

Name	Direction	Capping Value
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Modify Selected Remove Selected Remove All

Parameters for selected properties

1 Out-of-scope factor for risk models

10 Out-of-scope penalty for standard models

7.4 pH for pH-dependent properties

Uncheck All

Compute objectives using external application

Parameter file for external application

C:\Users\mlawless\AppData\Local\Simulati

Cancel Next >

External File Parameters

filePathAlias – working directory

- Defines [PATH] variable
- Can be set to AIDD output directory

structureFile – name of file containing AIDD generated structures

- SDF or SMILES file

outputFile – name of temporary file containing 1 or more objective functions

- Created by external program

commandLine – script or executable program

- BAT or bash shell script

InputAttributes – comma separated list of AP attributes, e.g., S+logP, to be written to structure file

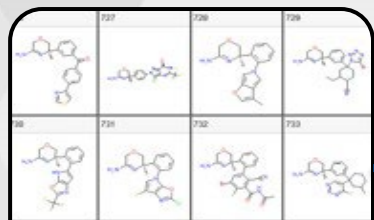
objectivesList – names of objective functions from external program

objectiveMaximize – 0 if minimum is preferred and 1 if maximum is preferred

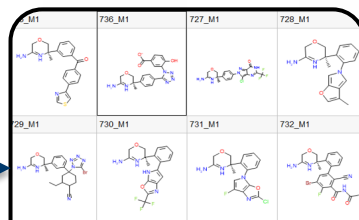
Acknowledgements

- **AutoDock** – Ravindranath PA, Forli S, Goodsell DS, Olson AJ, and Sanner MF. AutoDockFR: Advances in Protein-Ligand Docking with Explicitly Specified Binding Site Flexibility, *PLoS Computational Biology* **2015**, 11(12): e1004586.
- **YASARA** – Krieger E and Vriend G. YASARA View-molecular graphics for all devices-from smartphones to workstations, *Bioinformatics*, **2014**, 30(20), 2981-2982.
- **Babel** - O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. *J. Cheminf.* **2011**, 3, 33.

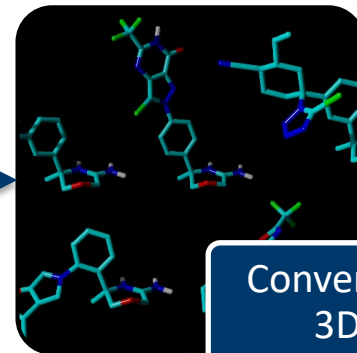
Workflow for AutoDock AIDD Example



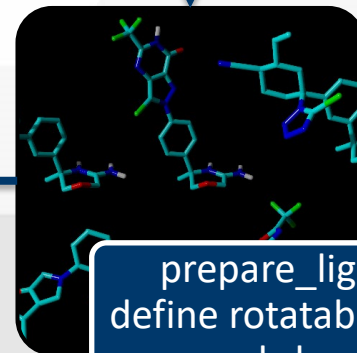
Candidate molecules
from AIDD



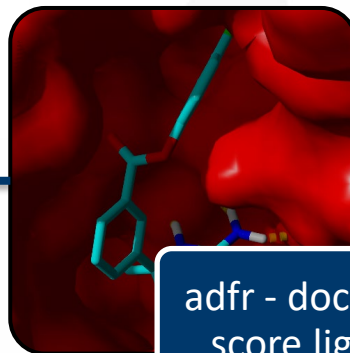
Convert to dominant
microstate



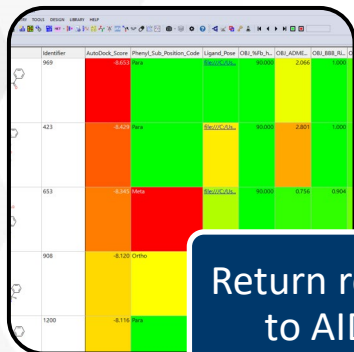
Convert to
3D



prepare_ligand –
define rotatable bonds
and charges



adfr - dock and
score ligand



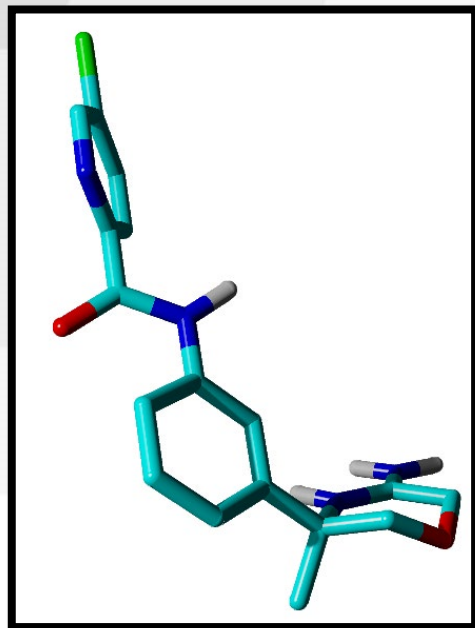
Identifier	AutoDock Score	Phenyl Substitution Code	Ligand Flex	Clk	SH N	N	Clk	ADME	Clk	SH	Clk
969	-6.881	0000	0000	0000	0000	0000	0000	2.060	0.000	0.000	0.000
423	-4.493	0000	0000	0000	0000	0000	0000	2.807	1.000	0.000	0.000
653	-4.183	0000	0000	0000	0000	0000	0000	0.750	0.000	0.000	0.000
908	-4.120	0000	0000	0000	0000	0000	0000	0.000	0.000	0.000	0.000
1200	-4.116	0000	0000	0000	0000	0000	0000	0.000	0.000	0.000	0.000

Return results
to AIDD

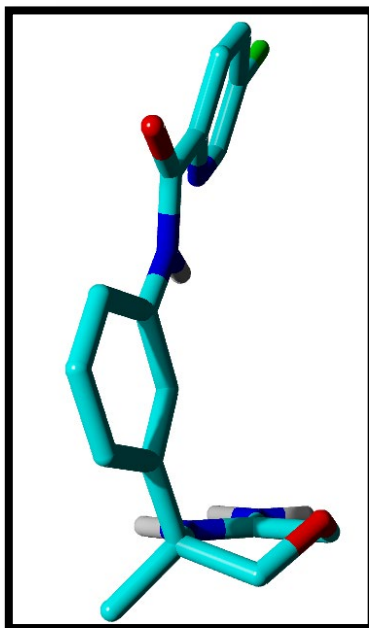
More on 3D Structure Generator

- Parameter file is first argument and parameters can be specified on the command line:
 - ADMET_Predictor.exe ms_generate_3d.txt –structureFile m.sdf –outputFile c_3D.sdf
- Multithreaded
- Multiple conformer generator
- MMFF94s force-field can be used to minimize structures
- 3D coordinates of ring systems can be specified in order to generate a specific ring conformation

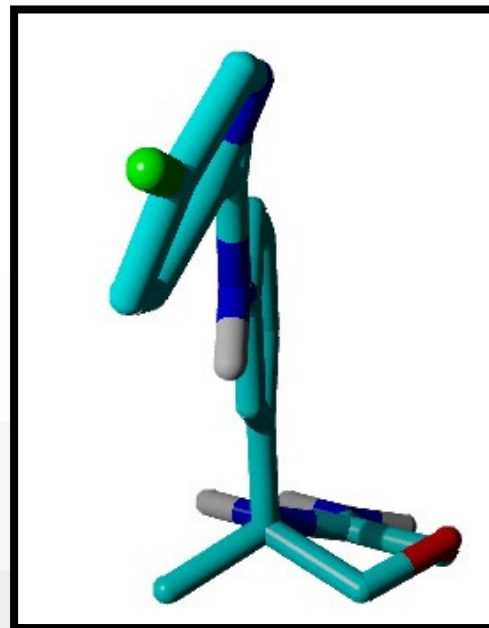
Dihydro-oxazine Conformation



Dihydro-oxazine oxygen is typically pointing “down” from 3D structure generators



Dihydro-oxazine oxygen points “up” in 6FGY and other oxazine crystal structures

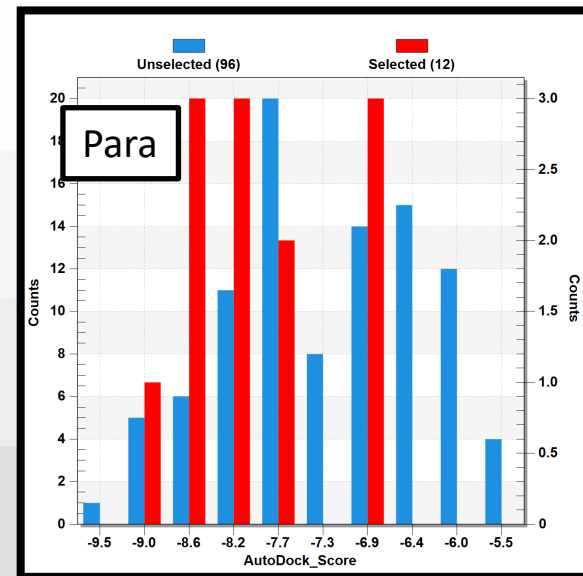
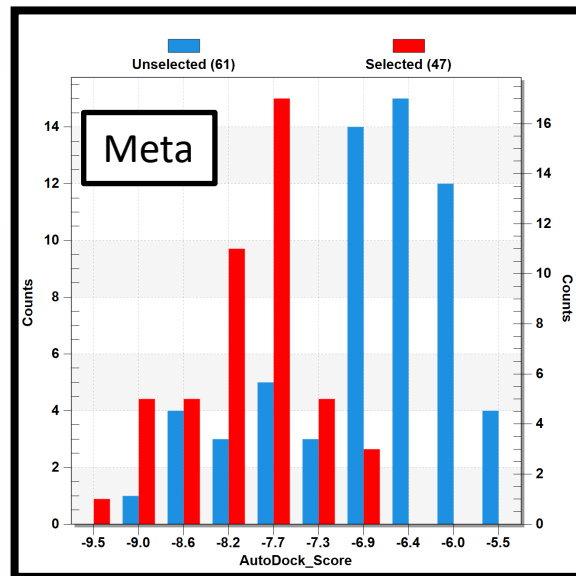
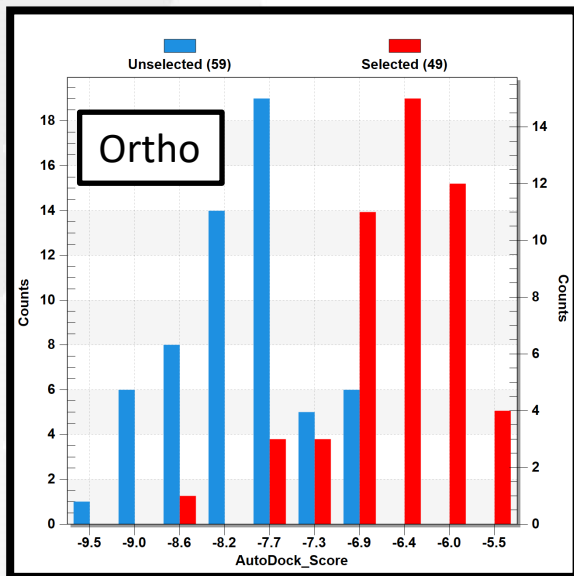


AP generated structure using dihydro-oxazine ring template

Docking Score Statistics

Phenyl substituent	Number	Best	Worst	Ave
Ortho	49	-8.5	-5.5	-6.5
Meta	47	-9.5	-7.0	-8.0
Para	12	-9.0	-6.8	-7.9

Meta substituents have best docking scores followed by molecules with substituents in the para position



AIDD with External Models

- The capabilities of the AIDD module have been expanded to include objective functions from external programs
- SDF or SMILES file of candidates from AIDD is written each generation
 - AP attributes can also be included
- AIDD External BAT or shell is called to execute other programs
- File containing results from external program is read into AIDD and included in Pareto optimization
- AIDD candidates were docked into a BACE1 crystal structure, and the scores were used as an objective function



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Q&A

Questions & Answers

