Docking with GOLD

CCDC

G. Marcou, E. Kellenberger

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GOLD Suite

- GOLD - Protein-Ligand docking using Genetic Algorithm
- HERMES - Structure visualisation
- GoldMine - SGDB based post-docking management

GOLD

Genetic **O**ptimisation for **L**igand **D**ocking (GOLD)
Chromosoms: two binary string encoding rotatable bonds for both ligand and protein.
Fitness function: adaptative across GA
Genetic Operators: crossover, mutation and migration (island model)

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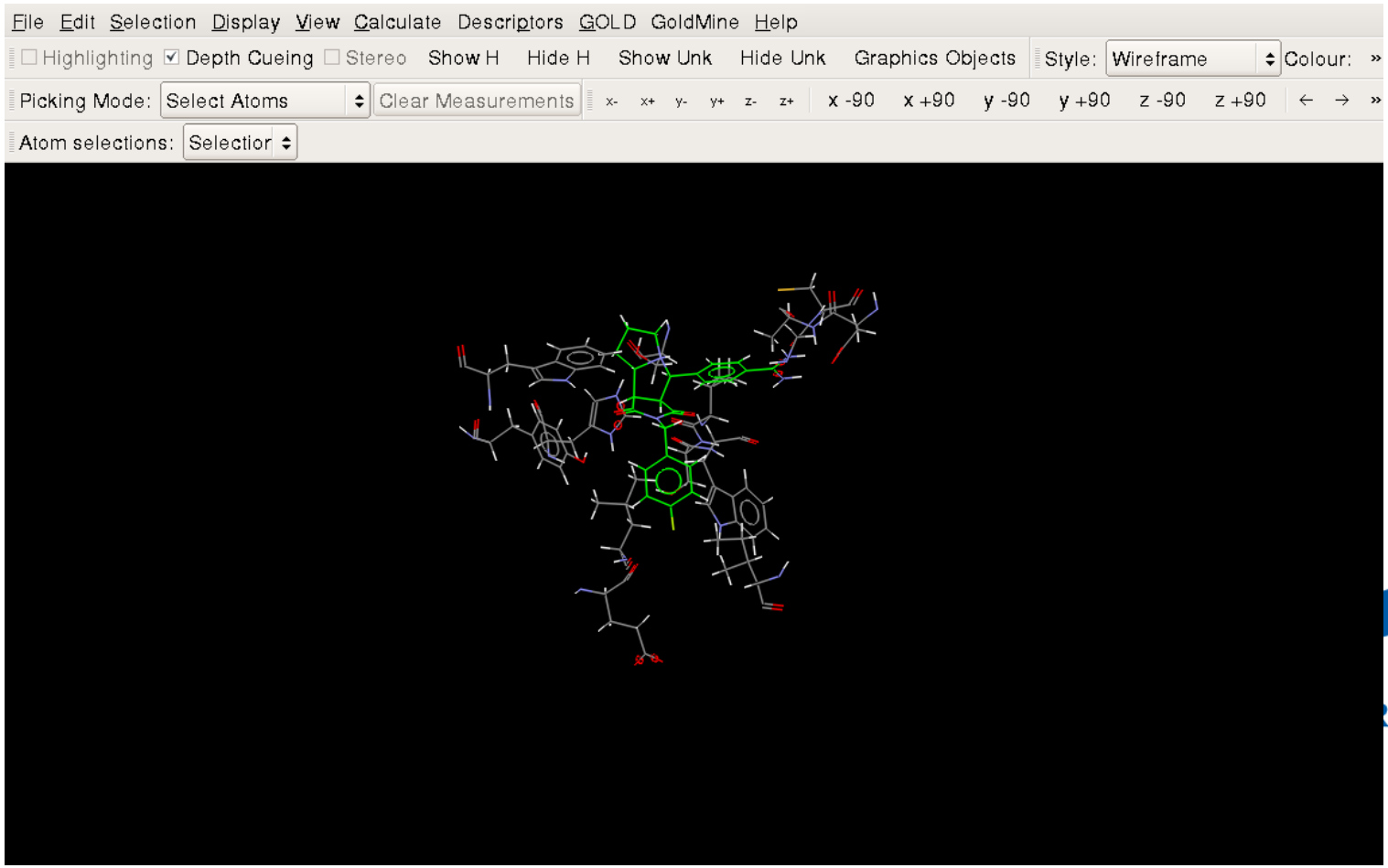
HERMES

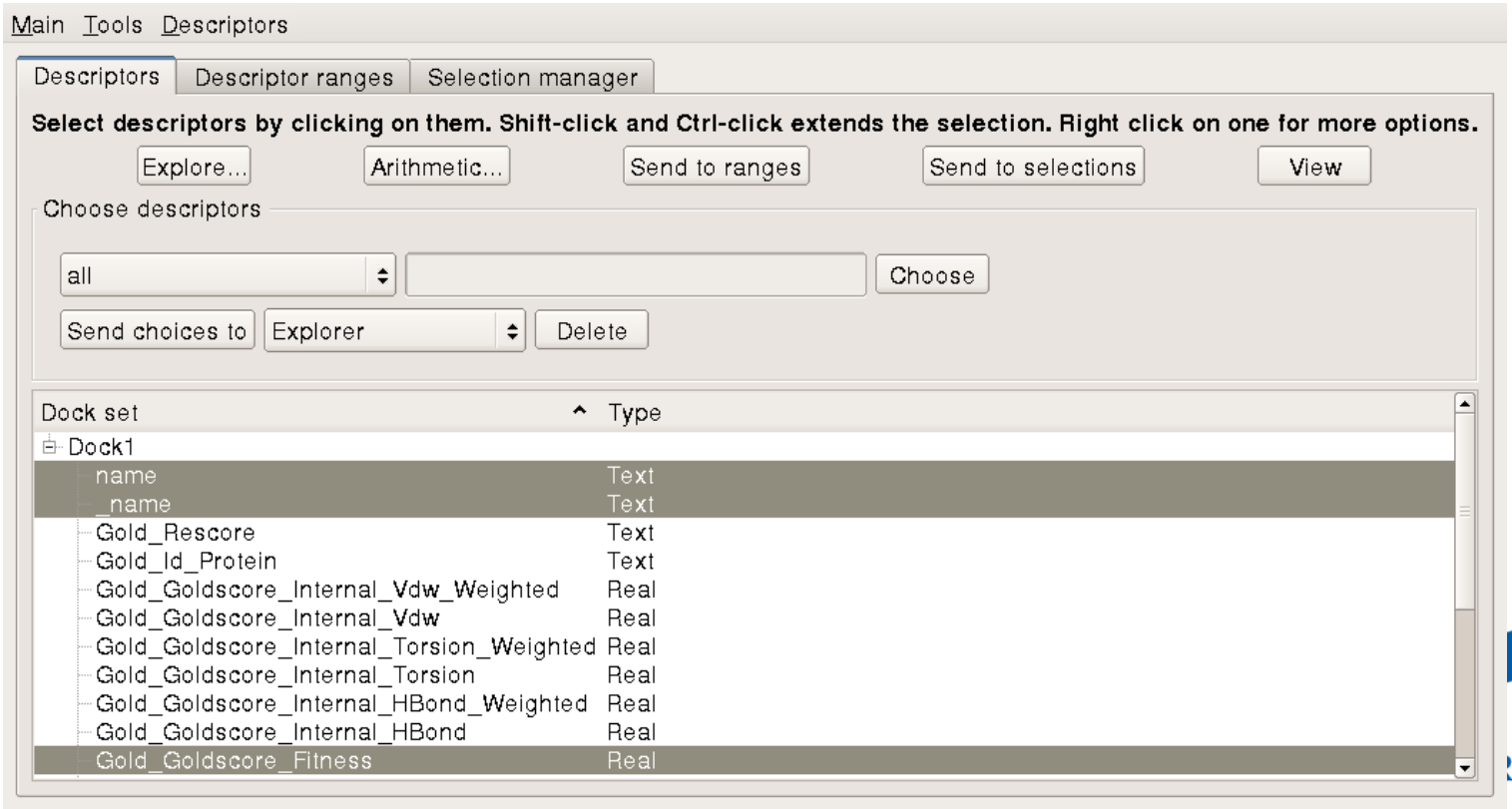
Structure visualization

Interface with GOLD, Mogul and IsoStar



GoldMine

Post-Docking manipulations



Hermes

1. Launch `Hermes` in `CCDC->GOLD Suite`
2. In the top menu, select `GOLD->Wizard`

Wizard Step 1

Click on `Load` and choose the file `1oyt_protein.mol2`.

Beware!

- Atom types
- Residues
- Protonation and charges
- Water

Wizard Step 2

Do nothing. The protein was already prepared.

Protein setup

- Protonation
- Water deletion
- Ligand deletion

Wizard Step 3

Define the active site.

1. Click on `List of Atoms or Residues`
2. Click the file selection button
3. Select the file `ListOfResidue.txt`
4. Click on the button `Add definition as a Selection`

Notice that

- The cavity is highlighted into `Hermes`
- A `Selection` is a shortcut to a relevant user defined set of atoms

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Wizard Step 4

A template is a set of GOLD parameters optimized for a particular targets.
The Thrombin is one of the target of the template `gold_serine_protease_VS`

1. Click on `gold_serine_protease_VS`
2. Click on `Load Template`

Wizard Step 5 -Redocking

Select the small molecules to dock.
For the **redocking** experiment:

1. Click the `Add` button
2. Choose the file `1oyt_ligand.mol2`.
3. Click on the file selection button of the `Reference ligand` textbox
4. Choose the file `1oyt_ligand.mol2`.

Pay attention to:

- The number of docking experiment performed by ligand (default 10)
- A subset of a library can be selected
- The ligands structures must be carefully prepared. Check the manual for help.

Wizard Step 5 -Virtual Screening

Select the small molecules to dock.
For a **Virtual Screening**:

1. Click the `Add` button
2. Choose the file `database100.sdf`.

Pay attention to:

- The number of docking experiment performed by ligand (default 10)
- A subset of a library can be selected
- The ligands structures must be carefully prepared. Check the manual for help.

Wizard Step 6

The predifined settings for the **scoring protocol** is fine.

Available scoring in GOLD

- *GoldScore* An empirical scoring aiming at accurate poses
- *ChemScore* An molecular mechanic scoring aiming reproduction ΔG
- *ASP* A knowledge based scoring aiming at maximizing geometric expectations of interactions
- *PLP* A computationaly efficient empirical scoring aiming at accurate poses

Wizard Step 7

Genetic Algorithm settings. Keep the default settings

Automatics settings

- *Library Screening* Fast and dirty conformation sampling for 10^6 compounds
- *Virtual Screening* Still fast but inaccurate conformation sampling for 10^4 compounds
- *Default* Slow but accurate conformation sampling for 10^2 compounds
- *Very Flexible* Very slow but very accurate sampling for 1 compound

All parameters of the Genetic Algorithm can be modified.

Wizard Step 8 - Redocking

Advanced settings.

Click on the bottom `Advanced` button to access advanced settings.

- Protein and small molecule treatments
- Add constraints
- Perform covalent docking
- Add Interaction motifs
- Save the configuration file and set the output parameters
- Interface with GoldMine and parallel architectures

Select `Output` and set `Output directory` as `OUTPUT/Redock`

Set `Save solutions to one file` named `Redock.sd`

Click on Save and call your configuration file `gold_loytredock.conf`.

Wizard Step 8 - Virtual Screening

Advanced settings.

Click on the bottom `Advanced` button to access advanced settings.

- Protein and small molecule treatments
- Add constraints
- Perform covalent docking
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- Save the configuration file and set the output parameters
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Select `Output` and set `Output directory` as `OUTPUT/VS`
Set `Save solutions to one file` named `VS.sd`
Click on Save and call your configuration file `gold_db100VS.conf`

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Wizard Step 8 - Virtual Screening

Click `Run GOLD`

Vizualize the reference ligand

1. Click on `File->Open`
2. Select the file `1oyt_ligand.mol2`
3. Choose in the `Selection` menu `Select Molecules...`
4. While the radio button of `Whole Molecules` is on, click on an atom of the ligand
5. Right click on the display area and in the pop-up menu, select `Colours->Custom Carbons...`
6. Select a pale blue.

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Vizualize the pocket

1. Click on `File->Load GOLD Results`
2. Select the configuration file of the redocking `gold_1oytredock.conf`.
3. Choose `cavity_atoms` as `Atom Selection`
4. In the `Selection` menu, choose `Invert Selection`
5. In the `Display` menu, choose `Show/Hide->Atoms...` and select `Hide`.

Analyze docking poses

1. Click on the left side on any pose to display it in the drawing area
2. It is possible to overlay several poses
3. In the `View` menu, choose `Contacts...`
4. Display hydrogen bonds and short contacts

GOLD Virtual Screening

Perform a virtual screening using the file `database100.sdf`
If it is too long, a virtual screening was performed in advance. Results are in the directory `VS`

Create a GoldMine

1. In the `GoldMine` menu, choose `Create...`
2. A wizard opens. While the `Gold run` radio button is on, select the file `gold_db100VS.conf`
3. Next, choose to import a New GoldMine and give it the name db100VS.db
4. Finaly, name your new dock set as db100

Simple plots

1. In the main `GoldMine Controller` Window, select simultaneously `Gold_GoldScore_Fitness` and `Gold_ASP_Fitness`
2. Click on the button `Explore...`
3. In the `Explore` window, select `Gold_GoldScore_Fitness` then clik on the histogram button
4. Repeat with `Gold_ASP_Fitness`
5. Select simultaneously `Gold_GoldScore_Fitness` and `Gold_ASP_Fitness` then right click on them and select `Scatter Plot`

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Enrichment

1. In the main `GoldMine Controller` Window, select simultaneously `Gold_GoldScore_Fitness`, `Gold_ASP_Fitness` and `_name`
2. Click on the button `Send to ranges`
3. In the `Descriptor ranges` tab, click on the `Option...` button of `Gold_GoldScore_Fitness`
4. Click on `Set by %` and require 10%
5. Do the same for the `Gold_ASP_Fitness`
6. Click on `Send to selections`
7. In the `Selection manager` drag and drop `Gold_GoldScore_Fitness` and `_name` in the `AND` area, then click the button `Count`
8. Do the same for `Gold_ASP_Fitness`

Conclusion

This conclude the presentation of this docking tool.

- Genetic Algorithm
- Combines of pose scoring and binding free energy scoring
- Advanced configuration to perform covalent docking or constrained docking
- Powerfull post-docking tools