DockingServer: GUI-based molecular docking on the web using Chemaxon tools

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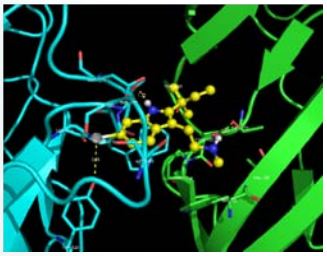
Molecular Docking

Docking calculation:

Predicts the orientation and binding energy of a small molecule to a protein when forming a complex.

Requirements:

- Knowledge of the protein structure and binding site
- Knowledge of the structure of the ligand



Goal:

Docking calculation is used to predict the activity and effect of a drug candidate (ligand-protein complex geometry)

Steps of docking calculation

1. Ligand set up
calculate geometry, pH and charges, identify rotatable bonds

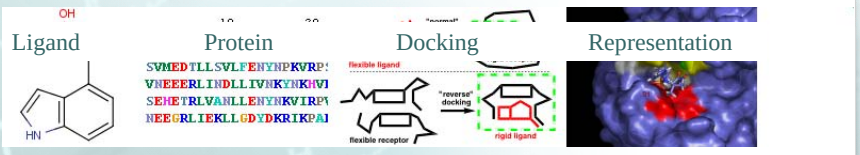
2. Protein set up
calculate electrostatic properties of the protein of interest
and define the ligand-binding region if possible

3. Docking calculation
the ligand-protein interaction is then calculated by a scoring function
that includes terms and equations that describe the intermolecular energies.

4. Results evaluation, representation of complex geometry

Problem definition

Integration of software carrying out the different steps of docking calculation is needed



Goal

User-friendly integrated software that allow **reasonable control** of the whole docking procedure, but can be **highly automated** as well.

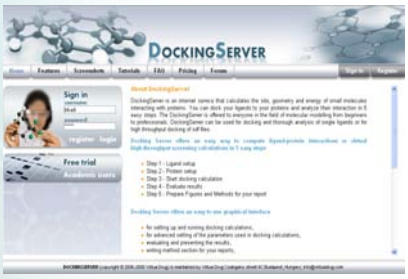
Solution: www.dockingserver.com

Web service that handles all aspects of molecular docking calculation, **free access for academic users, integrating software available on cd.**

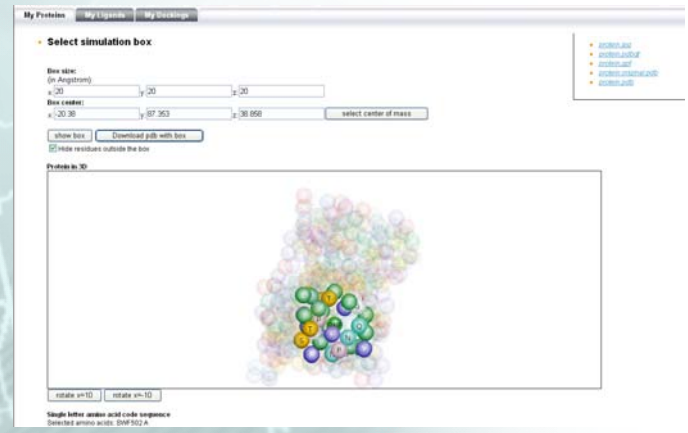
Following software are integrated in a php framework:

- Docking calculations: Autodock
- Ligand geometry optimization: MOPAC
- Visualization of ligand-protein complex: VMD

- Ligand preparation and visualization: **ChemAxon tools**



Protein set up



Docking results

ChemAxon software used in DockingServer I: Ligand set up

- cxcalc calculates the protonation state of the ligands at a given pH

```
if ($params["ligand_parameters"][0]["ph"]) {
     $input=$input_mol;
     $output = $HOMOKOZO."ligand_0h.mol";
     $command = $chemaxon."cxcalc ".$input." majorms -H
".strval($params["ligand_parameters"][0]["ph"])." -f mol >
".$output;
     echo "\r\n".$command."\r\n";
     $ret_value = exec($command);
     echo $ret_value."\r\n..end\r\n";
}
```

ChemAxon software in DockingServer I: Ligand set up

- cxcalc is used to achieve rough geometry optimization of the ligands

```
$input = $HOMOKOZO."ligand_0h.mol";
$output = $HOMOKOZO."ligand_0hopt.mol";
if ($params["ligand_parameters"][0]["optimize"])
      $command = $chemaxon."molconvert -3:c30[hydrogenize] mol ".$input." -o
".$output." >> ".$error;
else
      $command = $chemaxon."molconvert -3:c2[hydrogenize] mol ".$input." -o
".$output." >> ".$error;
echo "\r\n".$command."\r\n";
$ret_value = exec($command);
echo $ret_value."\r\n..end\r\n";
```

- to calculate IUPAC names for the ligands

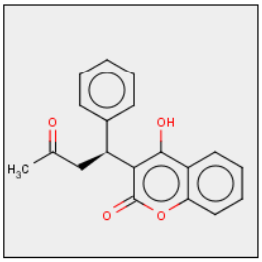
Results of ligand set up

SWF A

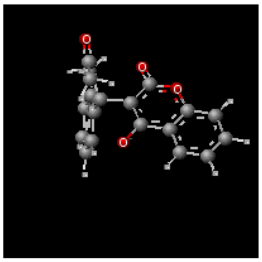
2-oxo-3-[(1S)-3-oxo-1-phenylbutyl]-2H-chromen-4-olate

Main | Modify | Partial Charges

Ligand in 2D



Ligand in 3D



ChemAxon software used in DockingServer II

- file conversion tasks, such as sdf conversion to multiple ligands using molconvert command
- generate smiles from 3D input

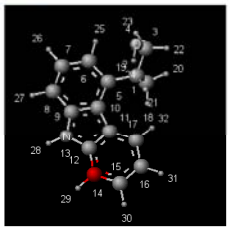
  $command = $chemaxon."molconvert smiles:a ".$input." -o ".$output." > ".$log;
- generate mol and PDB files

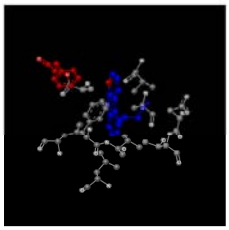
  $command = $chemaxon."molconvert mol ".$input." -o ".$output." > $command = $chemaxon."molconvert pdb ".$input." -o ".$output." > ".$log;

Chemaxon software used in DockingServer III

Visualization and input of the ligands in 2D and 3D, visualization of the binding site-ligand interaction is achieved by using MarvinSketch and MarvinView.

Interaction Table





hydrogen bonds	polar	hydrophobic	pi-pi	cation-pi	other
none	*none*	C11 (12) – ALA113 (*CB*)	C12 (14) – PHE114 (*CE2*)	*none*	N1 (13) – ALA113 (*CB*)
		C12 (14) – ALA113 (*CB*)	C13 (15) – PHE114 (*CE1*)		H11 (28) – ALA113 (*CB*)

Future tasks

- identify rotatable bonds with ChemAxon tools
- identify atom types with ChemAxon tools
- mol2 files with partial charges
- Cleaned, accelerated applets
- MarvinSpace integration (command line rendering, „light” version”)
- identify hydrogen bonds (pi-pi interactions, cation-pi interactions, etc.)