# DockAFM

v1.0

http://biodev.cea.fr/DockAFM

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DockAFM is an online computational tool for scoring the agreement between 3D atomic structures and experimental envelopes obtained by Atomic Force Microscopy (AFM).

## Quick Start Manual

Start by uploading the **structure** (in PDB format) to be docked. Then the **AFM** topograph (saved in ASCII format using for instance Gwyddion, http://gwyddion.net/, and including the header option). For the AFM image indicate the **z threshold**: the region to be considered during docking.

Optionally, the image can be eroded assuming a conical tip ending by a sphere (height **h**, radius **r** and angle **a**).

Docking the structure requires the definition of docking layers. Under the AFM topograph will be defined a **favorable** region for interaction energy calculation: only the atoms inside this region will be considered. To constraint the docking under the AFM topograph, define a **forbidden** region above the AFM surface.

The docking **grid size** (16 - 256) should correspond to the dimension of the image in pixels, i.e. for an image side of 32 px use a grid of 32. The **resolutionXY** (Å/px) is the pixel dimension of the AFM image; the **resolution Z** can be smaller if desired. The **rotation step** defines the minimum rotation of the PDB molecule on the grid (values range from very fine step 6° to very large step 90°).

Upon completion of the calculation, the server generates and returns the lowest energy conformation in a PDB file and a ranked list of 10 000 docking possibilities which can be received either by email or by downloading the results in a zip file (*.e6d).

## Remarks

### 1. AFM image preparation

The AFM image should be treated for noise reduction, for that we recommend a frequency-based method without averaging such as DeStripe: http://biodev.cea.fr/destripe
During erosion, note that the height of the tip used should be higher than the taller feature on the AFM topograph.

DockAFM can erode the AFM image to correct for tip shape artifact but the user must enter appropriate tip shape values (usually taken from the manufacturer).
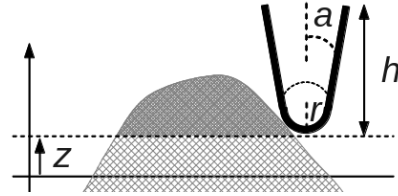
### 2. Docking grid size dimension

The docking grid dimension is established by the size of the image and the thicknesses of the favorable and forbidden layers, can be found by

$$\textbf{grid size} = \max(\dim_{XY}, \dim_Z), \text{ where}$$

$\dim_{XY}$ = image lateral size / resolution$_{XY}$, and
$\dim_Z$ = (image z range + favorable + forbidden) / resolution$_Z$.

For instance, a grid size of $32^3$ with resolution 5 Å/px in XY, means that the region in the image processed will be 160x160 Å$^2$. And the available z range for a resolution in Z of 2.5 Å/px is 40 Å (using favorable + forbidden = 40 Å). Consequently, the forbidden layer should be adapted not to extend beyond the grid size and if still required select the next larger grid dimension (e.g. 64-cubic grid).

### 3. Docking by DOT 2.0

The AFM image is transformed into favorable and forbidden layers. The docking is performed at a constant null electrostatic potential so that only van der Waals interactions is counted for atoms residing inside the favorable region. Thus, the top ranking solution has the minimum energy which corresponds to the maximum number of atoms located within the favorable layer beneath the AFM surface.

The most important input parameter is the thickness of the favorable layer. The favorable thickness must be optimized for the structure tested. As the thickness of the favorable layer is increased the weight of the topographic information is minimized. As a rule of thumb: for spherical protein shapes a thicker layer is fine where as for ellipsoidal (flatten shape) proteins a thinner layer is necessary. For example, a decreased thickness is more suitable for distended molecules such an antibody (12 Å) on the other hand a globular molecule such as the blood coagulation factor V activated requires a thicker layer (20 Å).

A commonly accepted successfully docking should cluster top solutions very close to one another.

4. Interpretation of results

The output consists in:
   - Two PDB files (topographic image provided, and top docking solution);
   - Docking energy value of the top solution;
   - Offset of the top docking solution regarding the center of the topographic image;
   - List of all docking solutions, a .e6d file, containing the energy and translation/rotation operations of the first 10 000 solutions.

Single test:
   The two PDBs contain atomic coordinates (absolute referential) allowing the visualization of the top docking solution.

Benchmarking:
   In the case of multiple tests, where different structures are tested on the same image and under the same docking conditions, the evaluation of the solution and the selection of the best fit can be done numerically.
   First, make sure the different structures used have the same number of atoms, to guarantee the normalization of the energy values for the same fit.
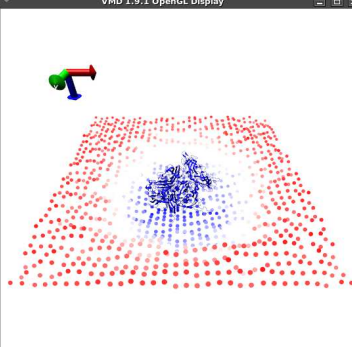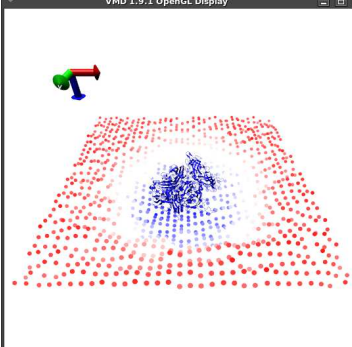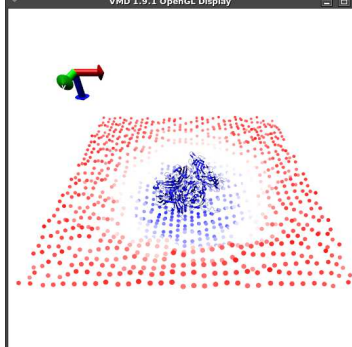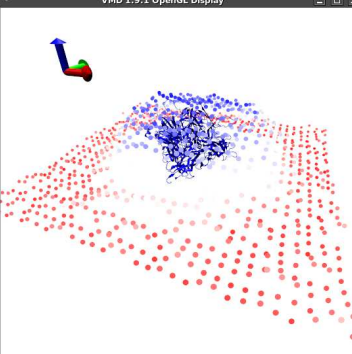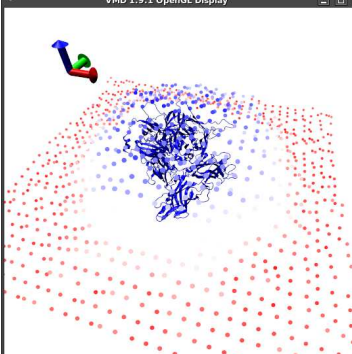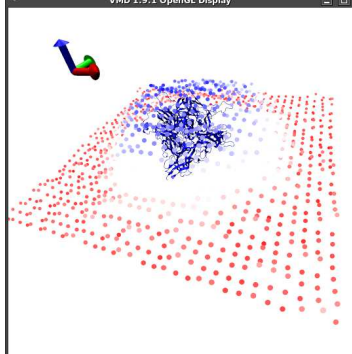   After a run, the docking must be validated: is the topograph a valid image? The cases where the image does not allow the fitting of the structure (either due to low resolution or no shape-compatibility) need to be not taken in consideration.
   For low resolution, the precision of the docking (how good is the scoring) can be verified in the list of energy values (the .e6d file): if the energy values are too similar or even the same, the resolution used is not enough. This can be solved by either decreasing the docking grid steps size or using a topograph with higher resolution.
   In the cases where the topographic volume does not allow the fitting of the structure, the result is the positioning of the structure in the flat region of the topography; this situation can be numerically identified by checking the offset value. For instance if the cropped image contains a flat region margin like half of the diameter of the topographic volume, the solutions with an offset larger than 25% could be discarded.
   Finally, for the runs respecting the previous rules (in particular within the offset threshold), the energy value can be used to select which is the structure that best fits the image.

# Examples

| a) image not eroded | b) image eroded | c) image eroded by DockAFM |
|---|---|---|
| image = **image.txt** | image = **image_erode.txt** | image = **image.txt** |
| z = **0.0**Å | z = **0.0**Å | z = **0.0**Å |
| erosion = no | erosion = no | erosion = yes |
|  |  | tip: h = **84**Å\| r = **8.0**Å\| a = **15.0**° |
| favorable = **20.0**Å | favorable = **20.0**Å | favorable = **20.0**Å |
| forbidden = **20.0**Å | forbidden = **20.0**Å | forbidden = **20.0**Å |
| grid = **32** | grid = **32** | grid = **32** |
| resolution = **10.0**Å,  **10.0**Å | resolution = **10.0**Å,  **10.0**Å | resolution = **10.0**Å,  **10.0**Å |
| **rotation = 12°** | **rotation = 12°** | rotation = **12°** |
| Expected output: | | |
| Energy (kcal.mol$^{-1}$) = **-12.1000** | Energy (kcal.mol$^{-1}$) = **-12.4000** | Energy (kcal.mol$^{-1}$) = **-12.4000** |
| offset (Å) = (**1.375**,**-15.457**, **46.364**) | offset (Å) = (**1.375**,**-15.457**, **46.364**) | offset (Å) = (**1.375**,**-15.457**, **46.364**) |
|  |  |  |
|  |  |  |

The docking solutions provided by DockAFM in PDB format can be visualized for instance with VMD (http://www.ks.uiuc.edu/Research/vmd/).