MEET-U - Scoring Group1

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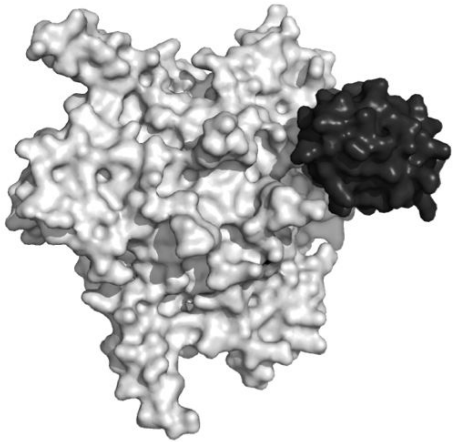


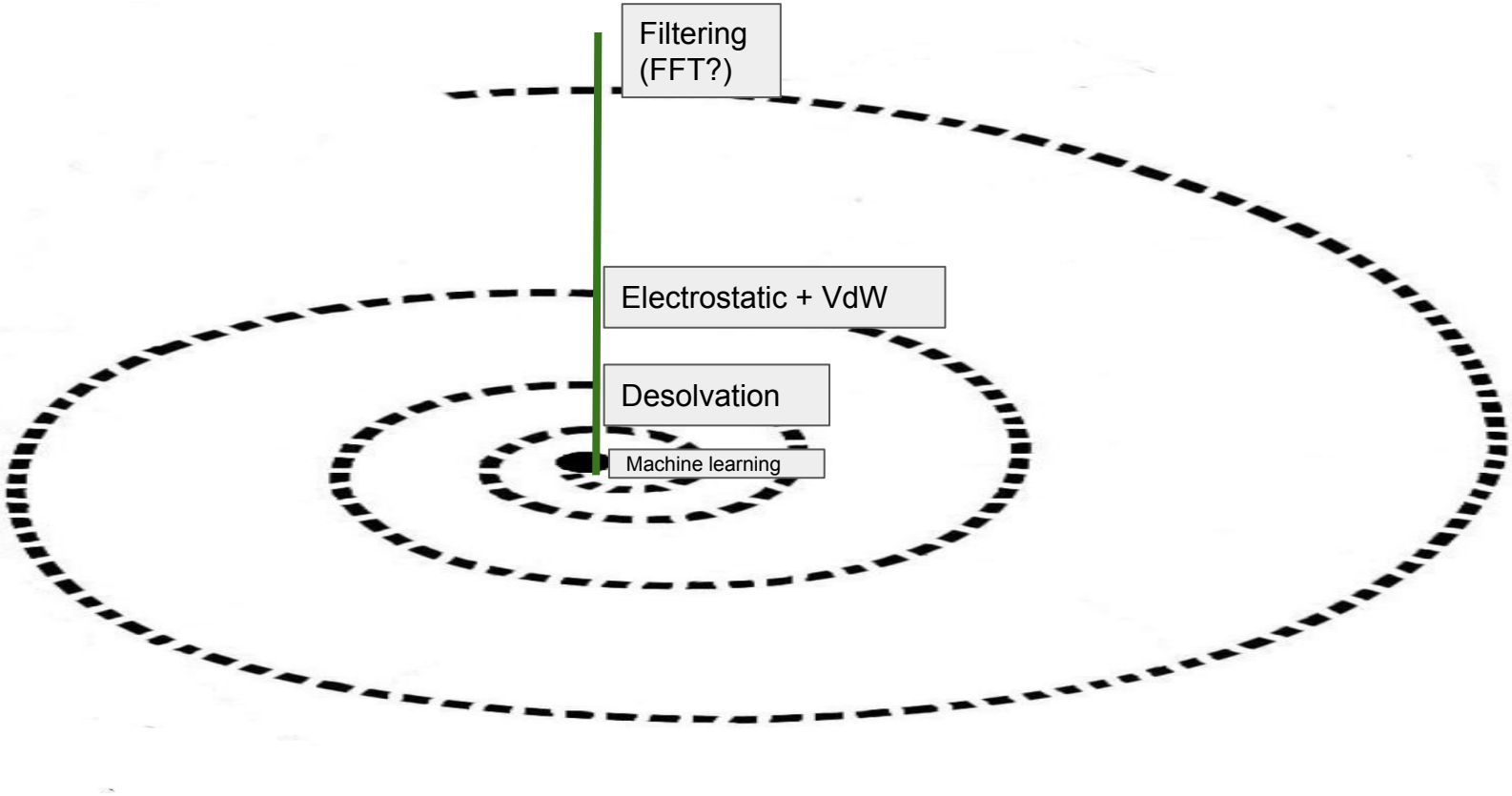
Meet-U

PROJET COLLABORATIF
PARIS 6 - PARIS 7 - PARIS 11 - EVRY

édition 2018

université PARIS DIDEROT PARIS 7

To implement



Shape Complementarity (SC) with FT

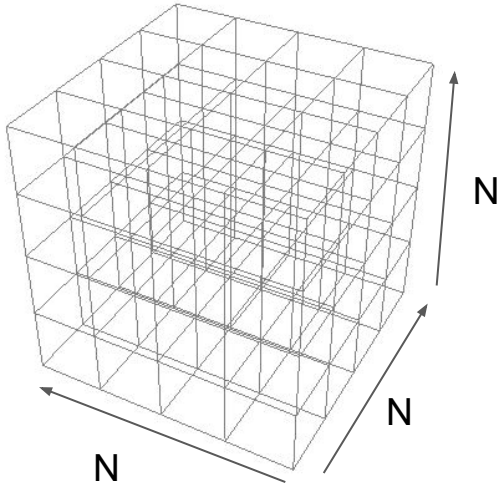
- **N** x **N** x **N** grid
- grid point (**l**, **m**, **n** = 1, 2, ... **N**)
- **grid spacing** 1.2 Å
- **N** large enough for **R** and **L**

$$R_{SC}(l,m,n) = \begin{cases} 1 & \text{surface of } R \\ \rho i & \text{core} \\ 0 & \text{open space} \end{cases}$$

$$L_{SC}(l,m,n) = \begin{cases} 1 & \text{surface of } L \\ \rho i & \text{core} \\ 0 & \text{open space} \end{cases}$$

$i = \sqrt{-1} \qquad \rho = 9$

- Sample rotational (360*360*360/15^3), if angle step = 15°
- N^3 translations (x,y,z)



$$S_{SC} = \mathrm{Re}\left[\frac{1}{N^3}\,\mathrm{IFT}(\mathrm{IFT}(R_{SC}) \cdot \mathrm{DFT}(L_{SC}))\right] - \mathrm{Im}\left[\frac{1}{N^3}\,\mathrm{IFT}(\mathrm{IFT}(R_{SC}) \cdot \mathrm{DFT}(L_{SC}))\right]$$

(Zdock, Chen and Weng, 2002)

Protein-Protein Interface Size

Defining macromolecular interfaces based on solvant accessibility

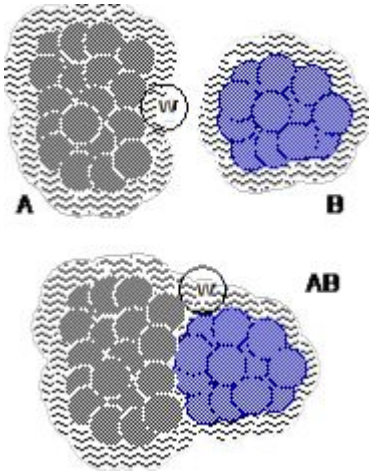
ASA accessible surface area
measures molecule-solvent contacts
with the
rolling ball algorithm
Lee & Richards, JMB,1971

BSA buried surface area
measures molecule-molecule contacts
Chothia & Janin, Nature, 1975

Interface atoms or residues
are all atoms or residues that
contribute to the
BSA. On average, each interface atom
contributes ≈ 10 Å²

Hydrophobic effect

$$BSA = ASA_A + ASA_B - ASA_{AB}$$



Electrostatic and Van Der Walls

Electrostatic forces:

-Easy to compute
-Per residue (considered as points)
→ Charges in tables
-Cutoff to determine
-Only with closest residues within the interaction zone

$$\overrightarrow{F_1}(2) = q_2 \frac{q_1 \overrightarrow{e_r}}{4\pi\varepsilon r_{12}^2} = q_2 \frac{q_1 \overrightarrow{r_{12}}}{4\pi\varepsilon r_{12}^3} = -q_1 \frac{q_2 \overrightarrow{r_{21}}}{4\pi\varepsilon r_{21}^3} = -\overrightarrow{F_2}(1)$$

Van der Walls:

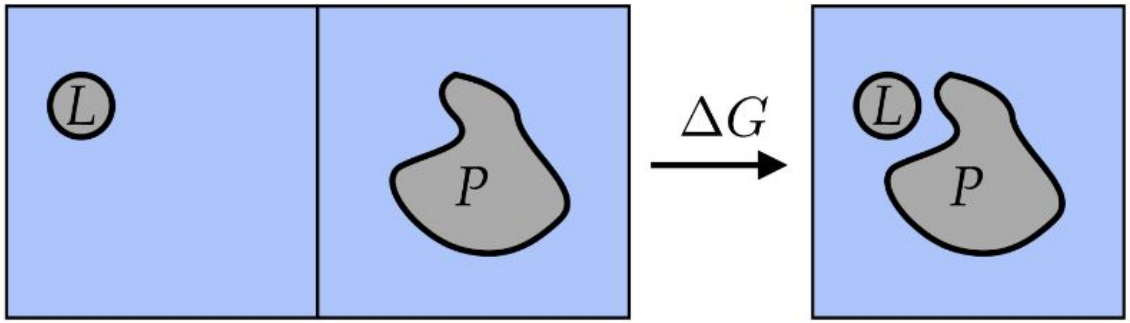
More complex computation due to induced dipole mechanism

$$E_{\text{van der Waals}} = -\frac{1}{r^6}\left[\underbrace{\frac{\mu_1^2 \cdot \mu_2^2}{3(4\pi \cdot \epsilon_0 \cdot \epsilon)^2 \cdot k_B \cdot T}}_{E_{\text{Keesom}}} + \underbrace{\frac{\mu_1^2 \cdot \alpha_2 + \mu_2^2 \cdot \alpha_1}{(4\pi \cdot \epsilon_0 \cdot \epsilon)^2}}_{E_{\text{Debye}}} + \underbrace{\frac{3}{4} \cdot \frac{h \cdot \nu \cdot \alpha_1 \cdot \alpha_2}{(4 \cdot \pi \cdot \epsilon_0)^2}}_{E_{\text{London}}}\right]$$

-Hydrogen Bonds ++ (gmx_hbond)
-PyPLIF (Other VDW)
-PPICP

Desolvation energy

No easy way: LIE / Umbrella / Alchemical ...



$$\frac{p_A}{p_B} = \exp\frac{F_B - F_A}{k_B T}$$

Short MD simulations needed → To do once only for separated L and P

*Reasonable computational cost if we first filtered the samples

*Pipeline (GROMACS / LOMAP - Alchemical setup)

Or implicit water models

*More complex to implement

*No shown benefit in our case

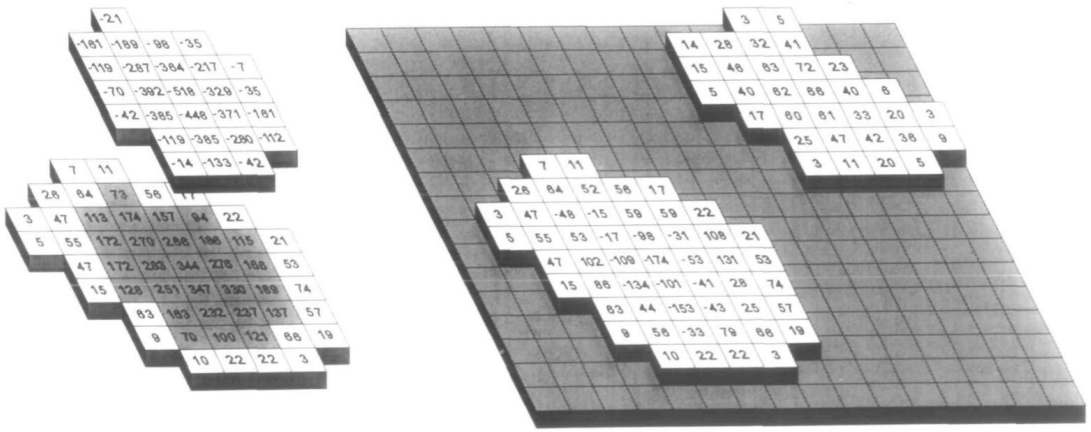
Machine learning

Score = a x Desolvation + b x Electrostatic + c x VDW + d x CFT [...]

→ How to combine our parameters to build a score function ?

Which kind of machine learning hasn’t been determined yet

Image negative



(Vakser, 1995)

- Compute surface with ASA
- Encode surface height in image with colors/grey levels
- Ideal docking site is negative
- Compute MSE

- Encode chemical/physical properties with colors
- Machine Learning (NN?) on images for docking site recognition