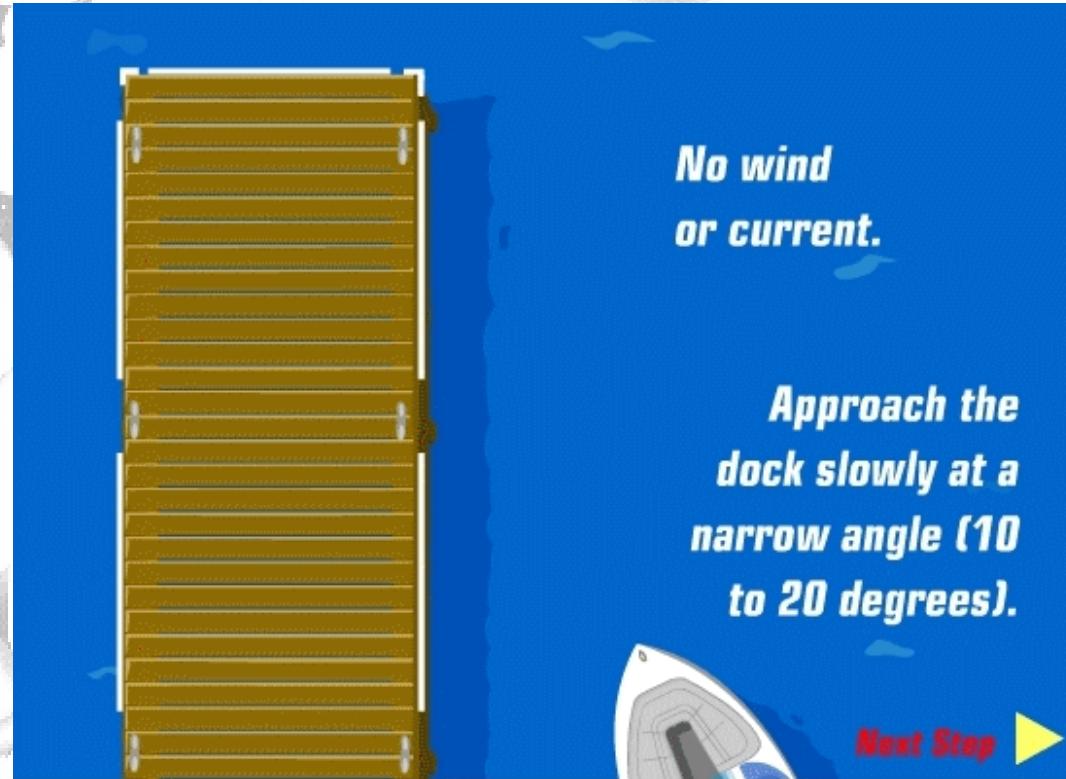
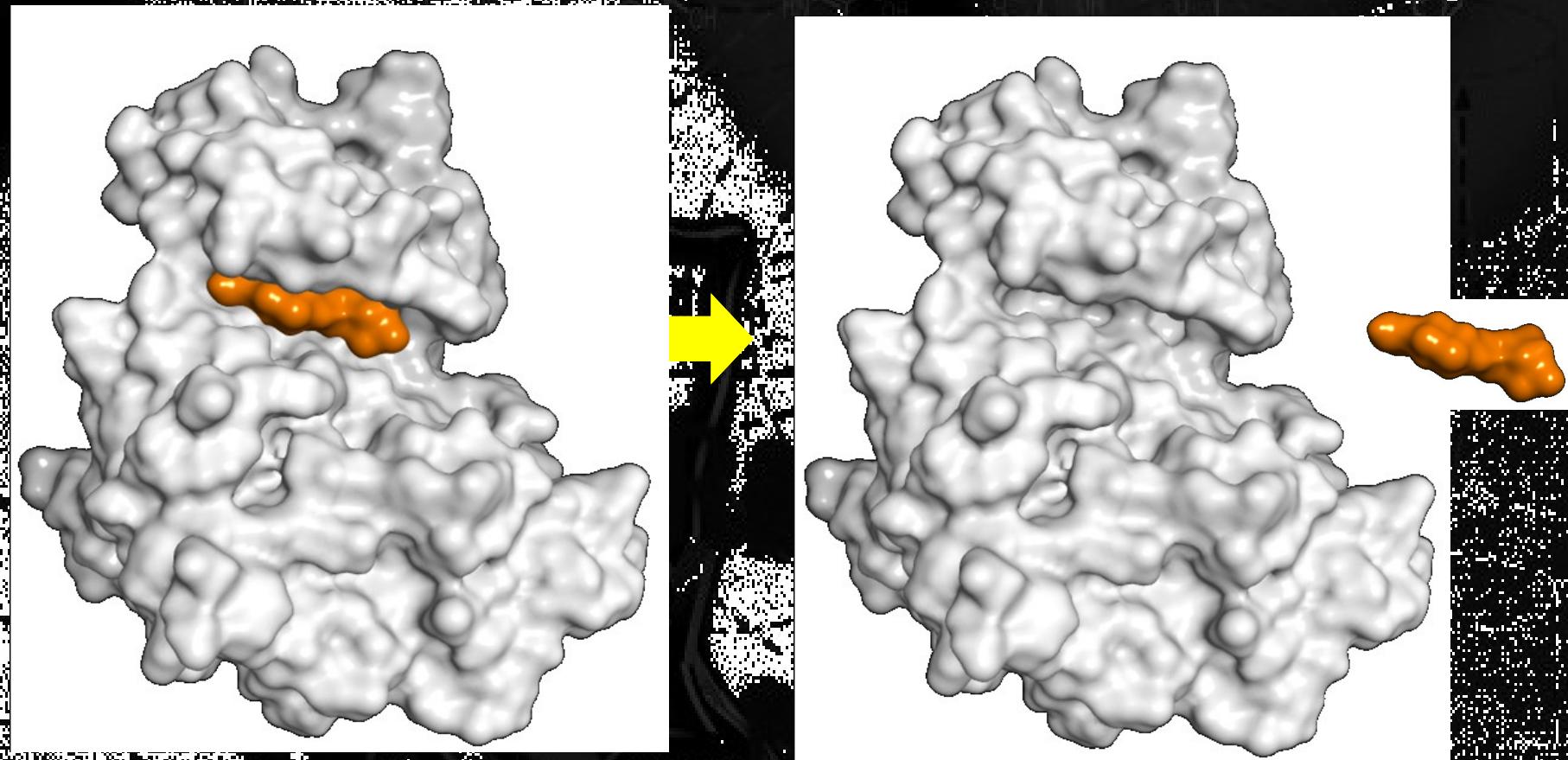


Docking... and Scoring





You have now a wonderful tool to estimate
the topological complementarity between a
cavity and its ligand:



Complementarity \propto Vol_{cavity} – Vol_{ligand}

Do you remember?



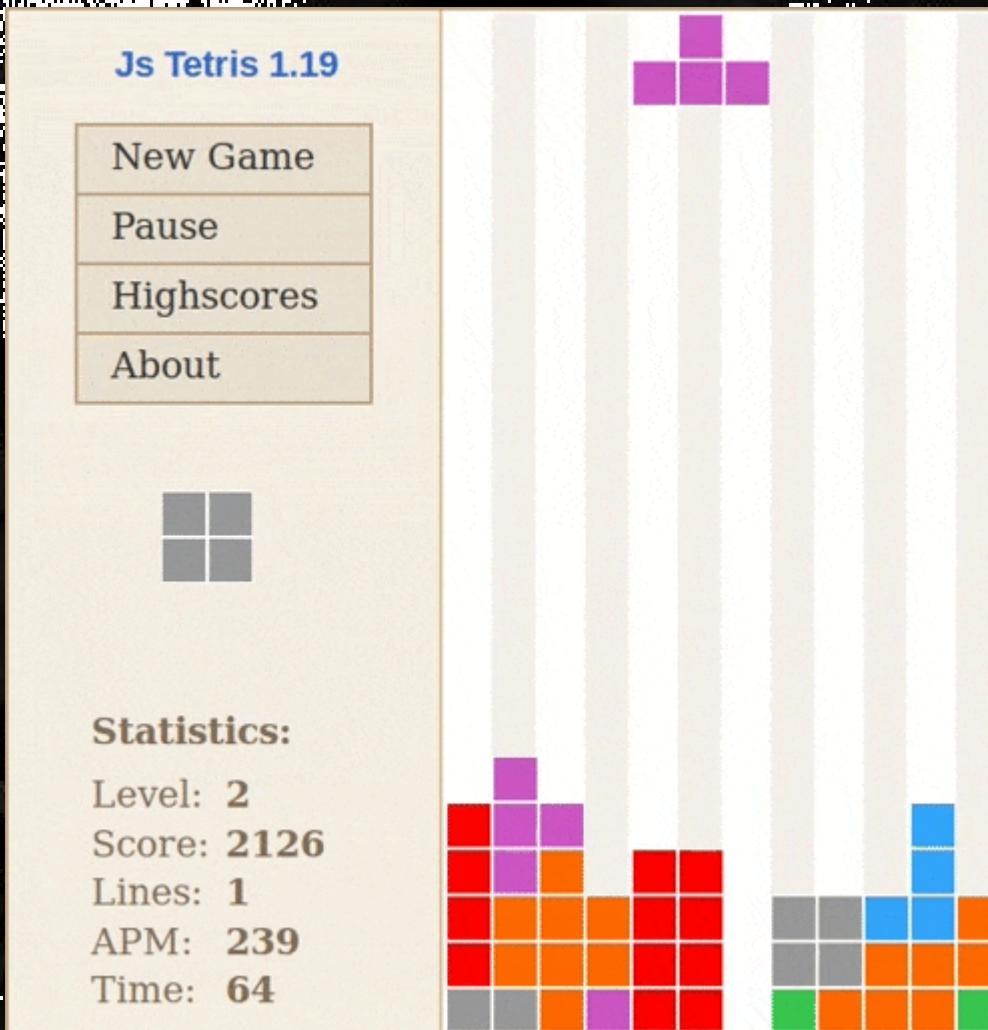
Js Tetris 1.19

New Game
Pause
Highscores
About

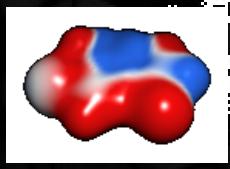


Statistics:

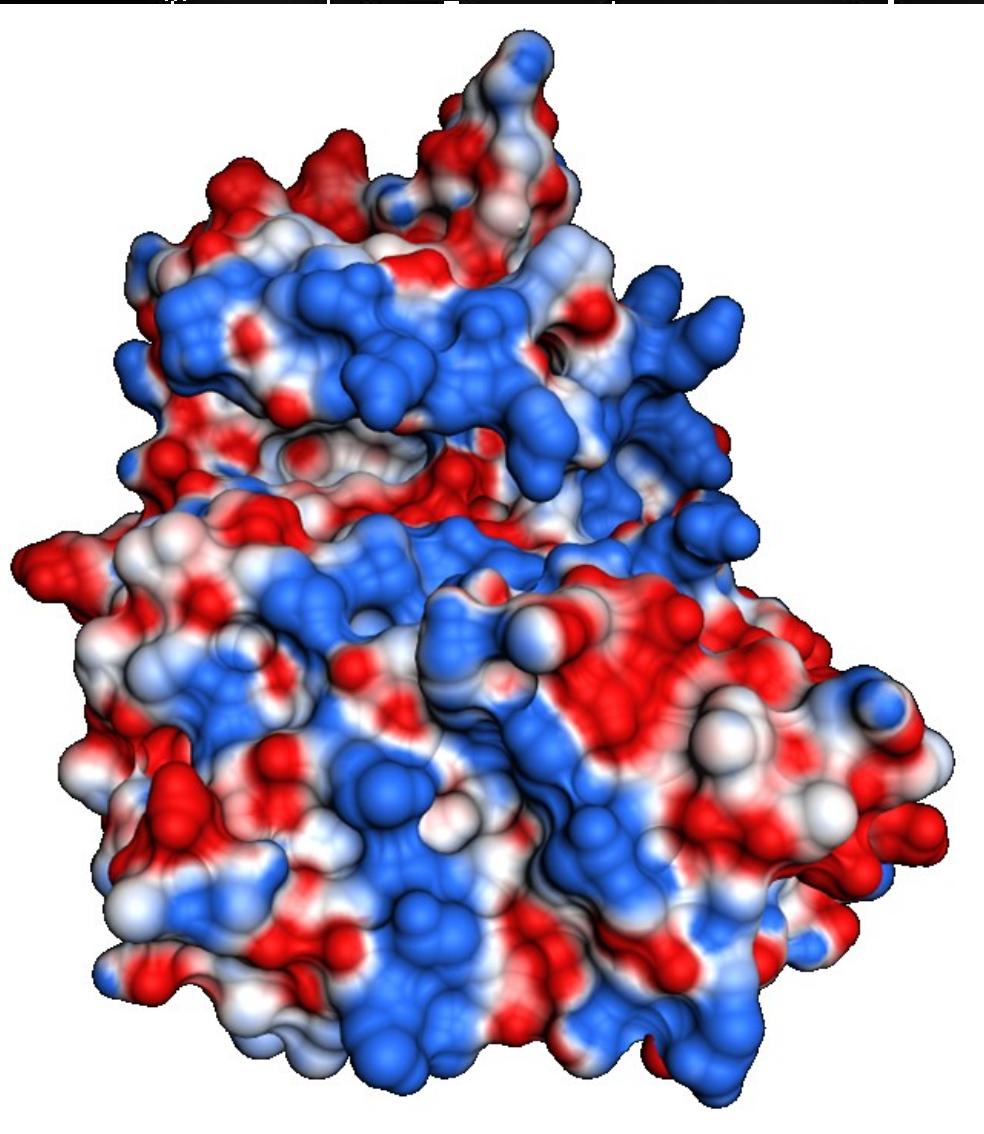
Level: 2
Score: 2126
Lines: 1
APM: 239
Time: 64



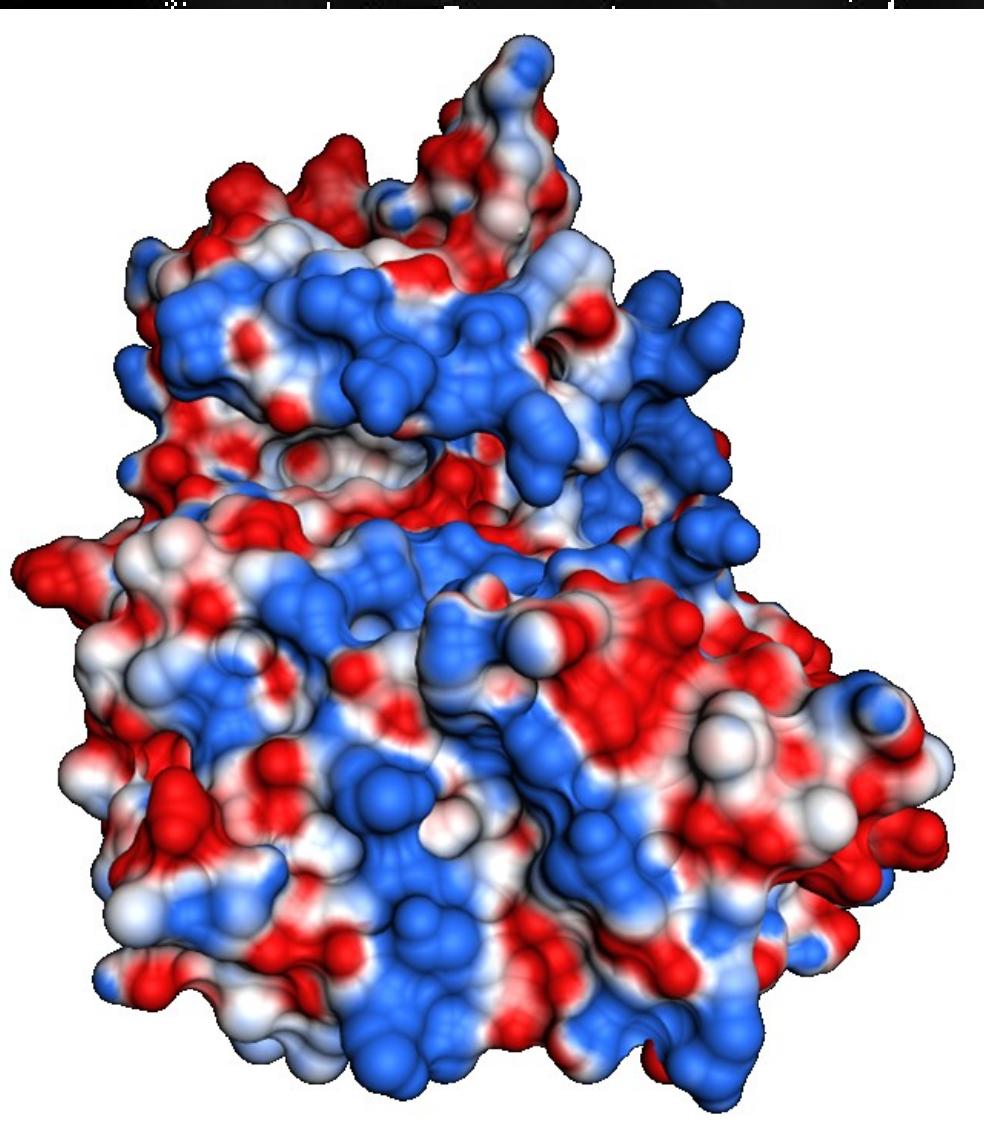
Mix all together to solve this problem...



where?
how?
how long?

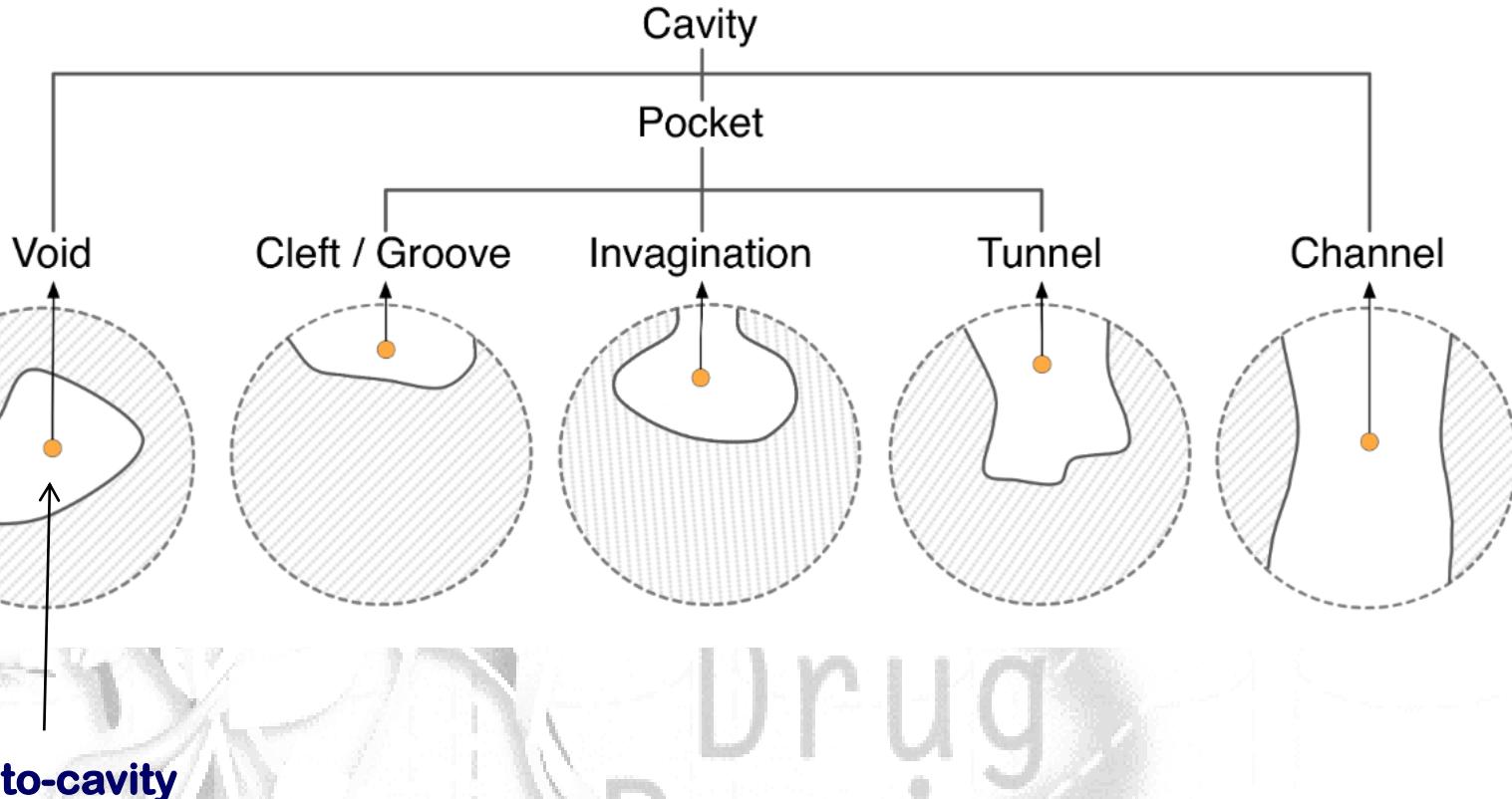


Virtualize docking and scoring...





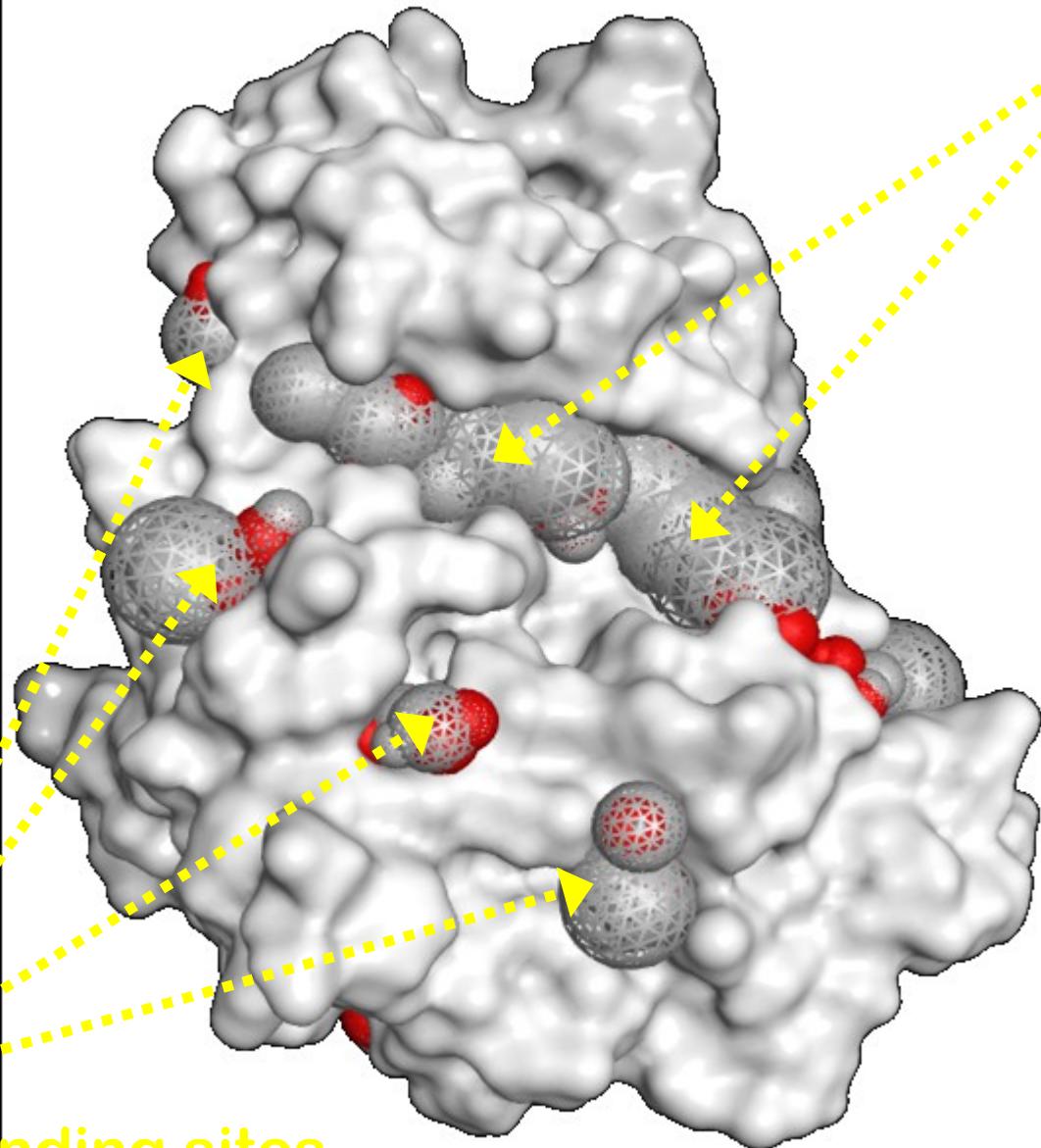
Some geometrical definitions...



Drug
Design

credits: <https://pdfs.semanticscholar.org/3082/da45a9ae986f8df40f572230cd28df98e3bd.pdf>

Principal binding sites



Alternative binding sites



From predicted binding site(s)... to *druggable* binding site(s)

Analysis of 5600 protein-ligand structures from the PDB:

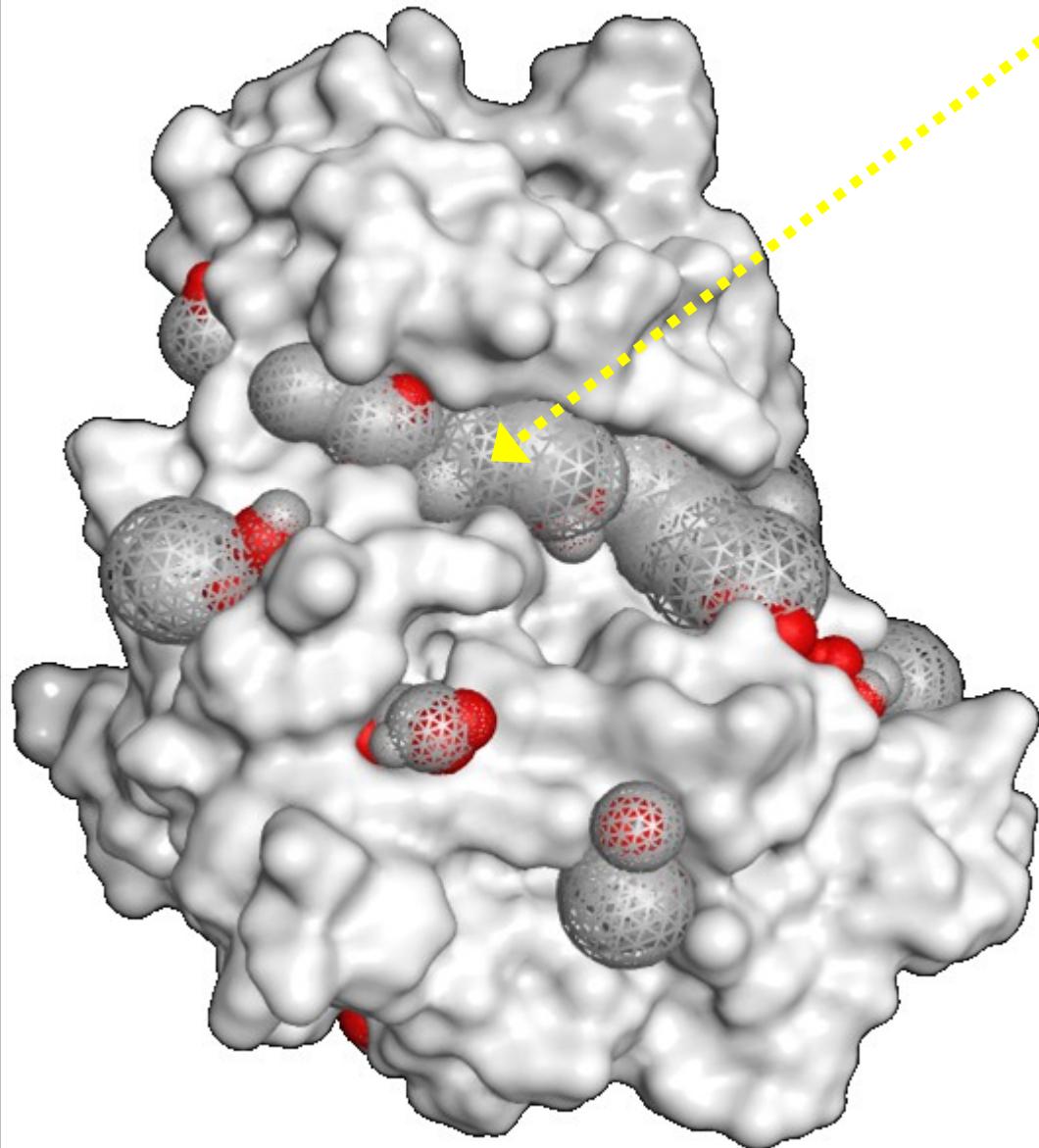


Table 1. Properties of druggable protein pockets.

pocket property	observed value
depth	7–11 Å [33]
volume	500–1000 Å ³ [33,37]
surface area	300–600 Å ² [30,38,39]
compactness	low radius of curvature [30]; volume : surface area ratio of approximately 0.4 [40]
surface complexity	rough [40]
hydrophobicity	20–40% polar surface area [41]

credits: <https://royalsocietypublishing.org/doi/10.1098/rsif.2011.0843>

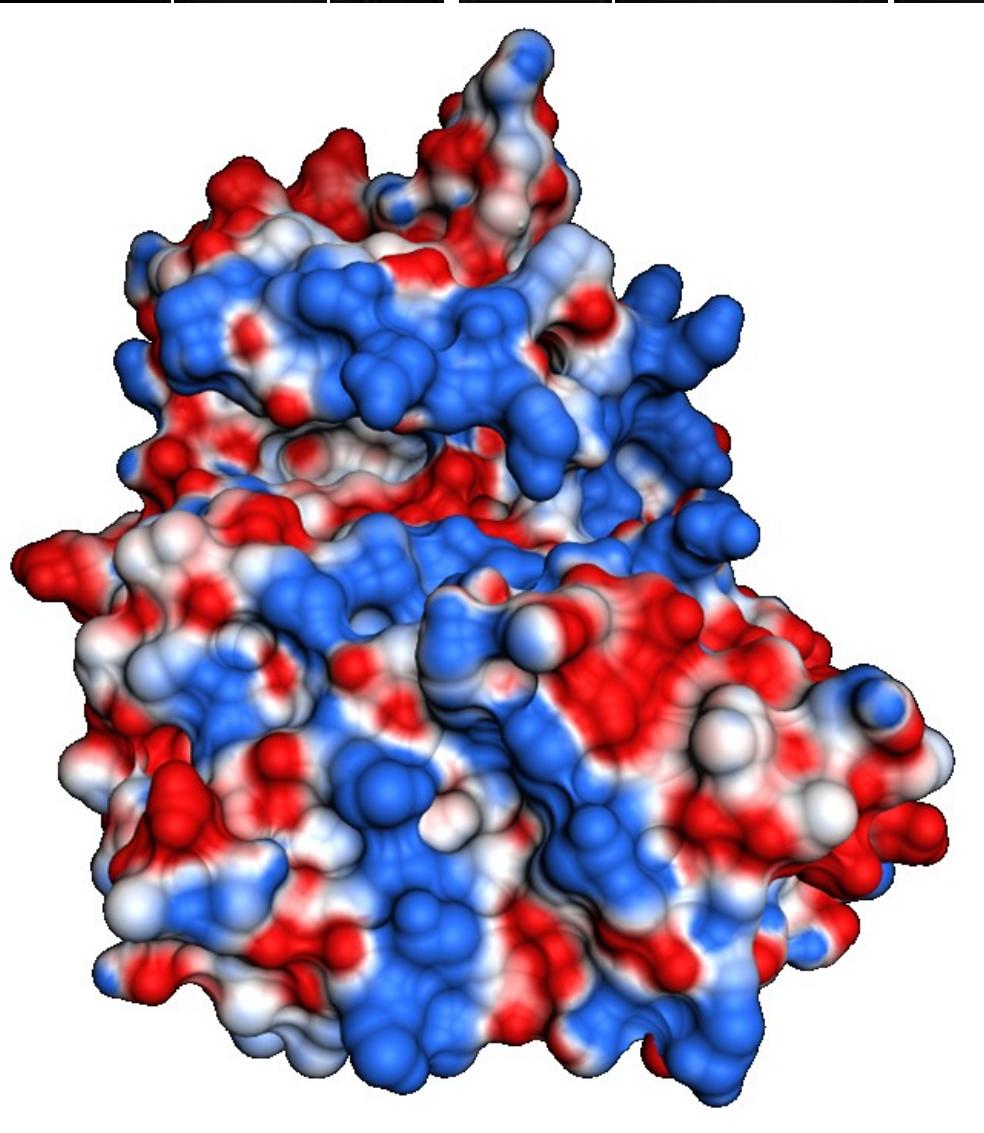
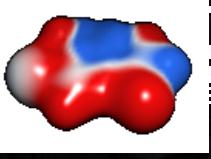
Druggable binding site



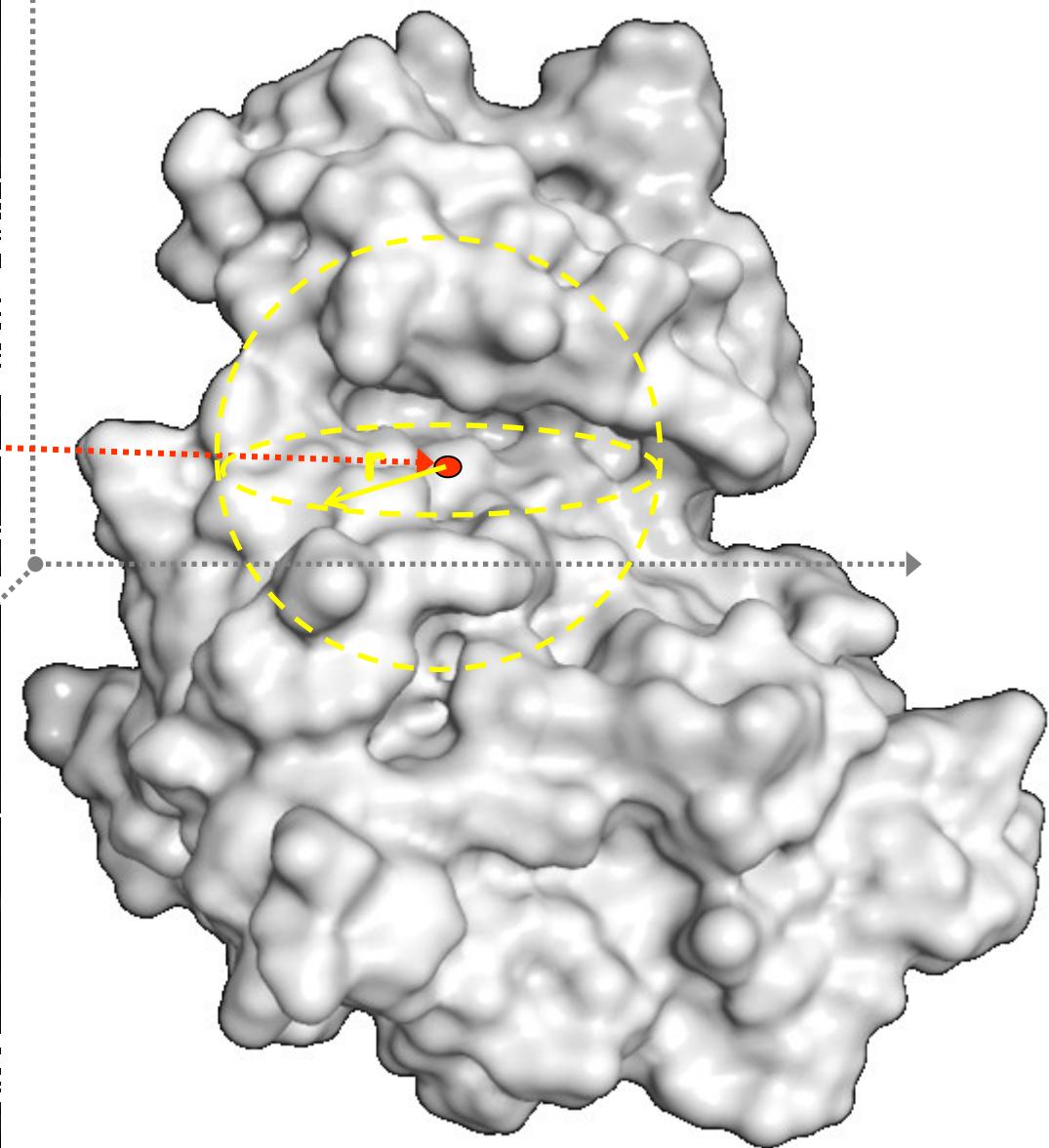
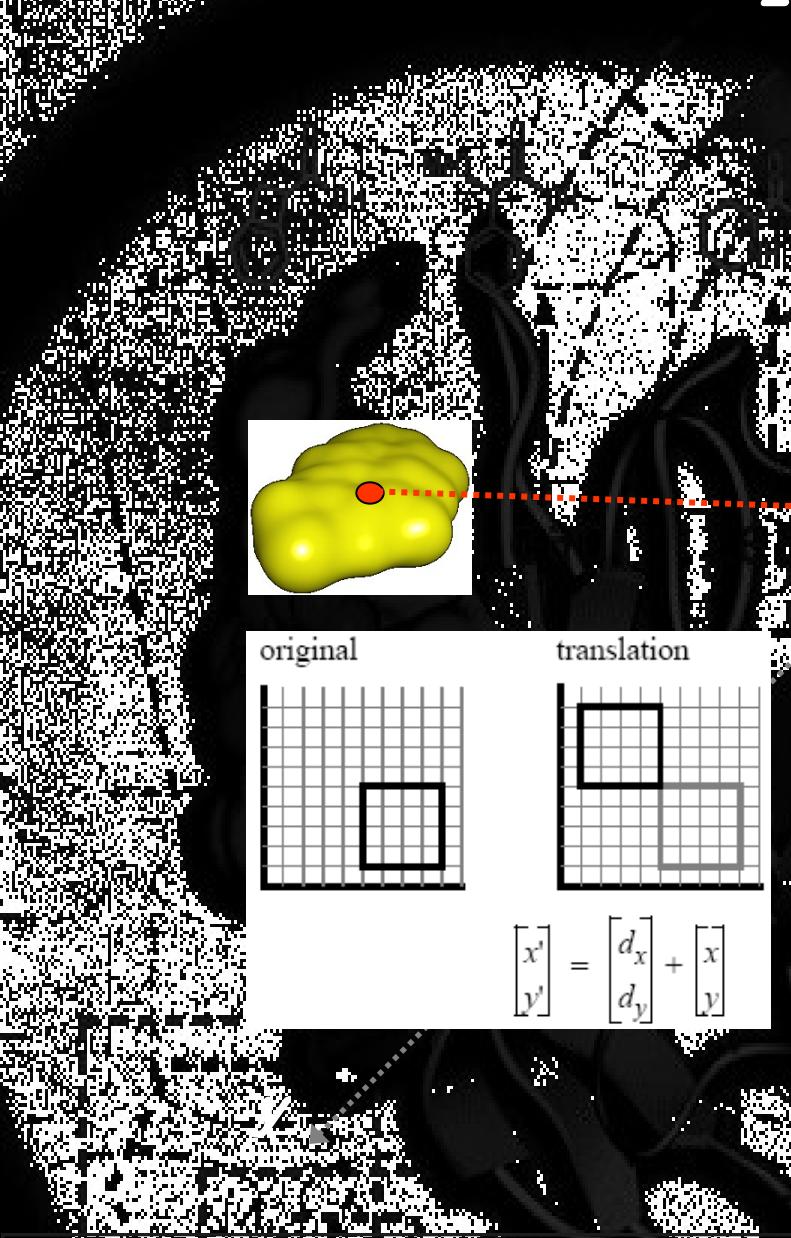
Virtualize docking...



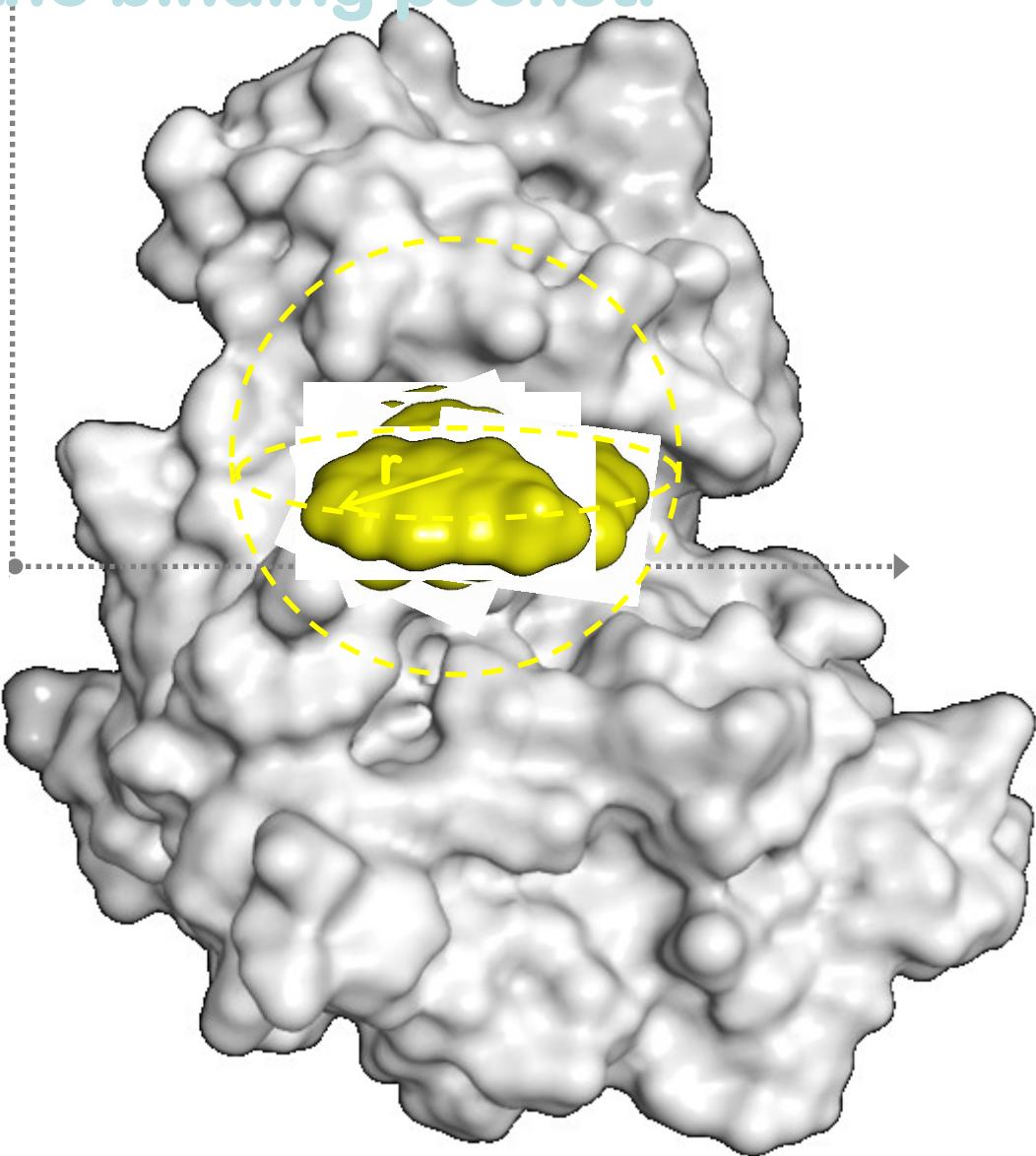
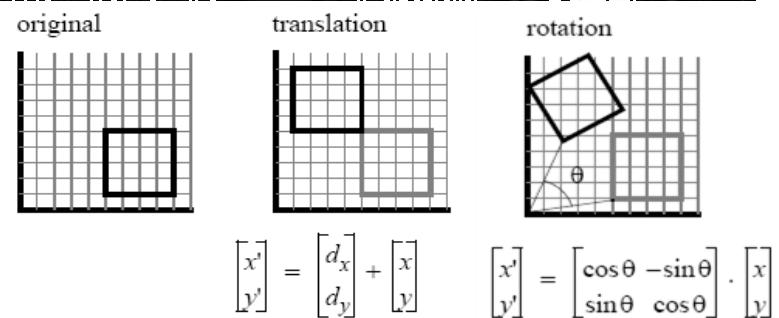
1. where?
2. how?



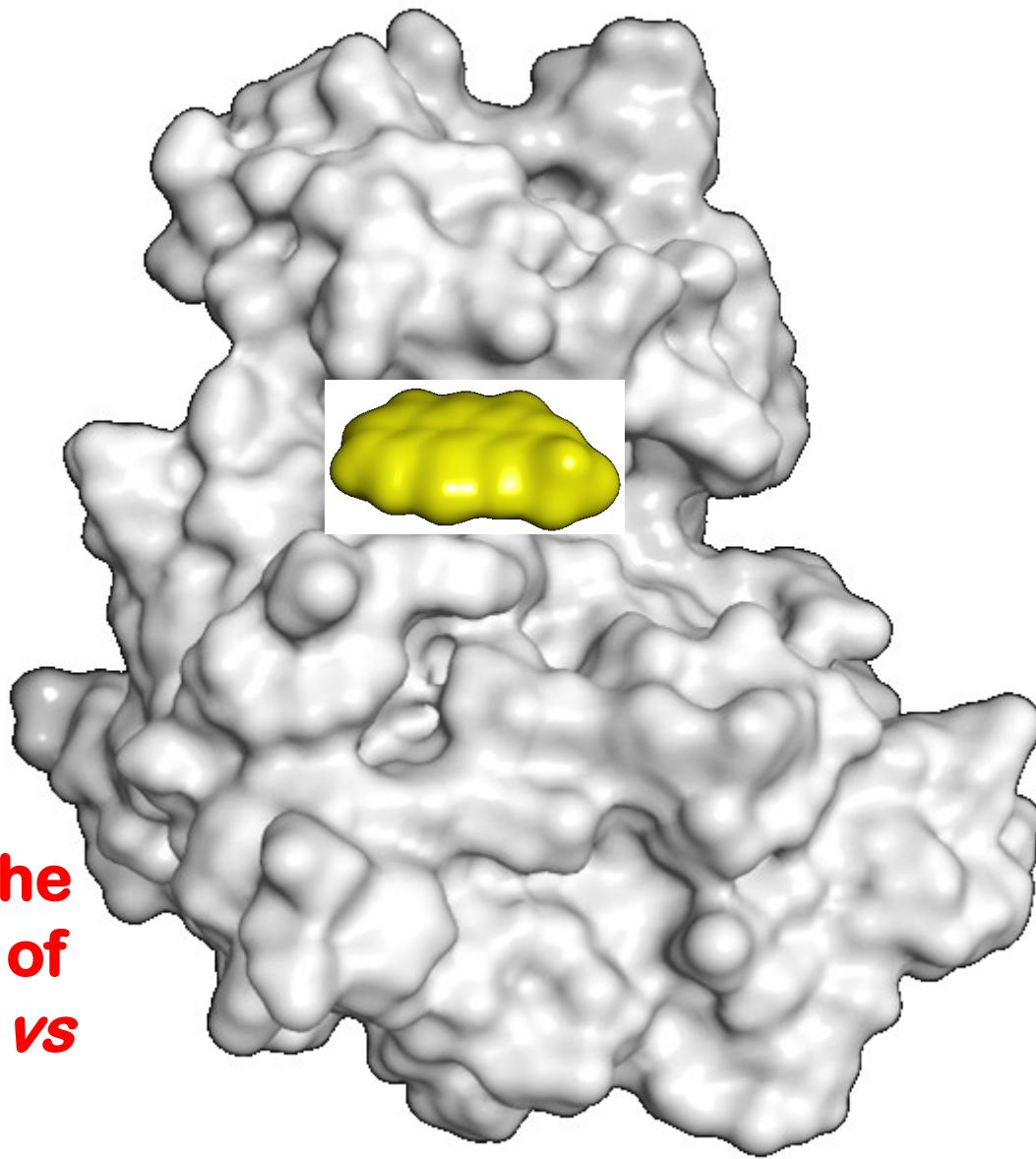
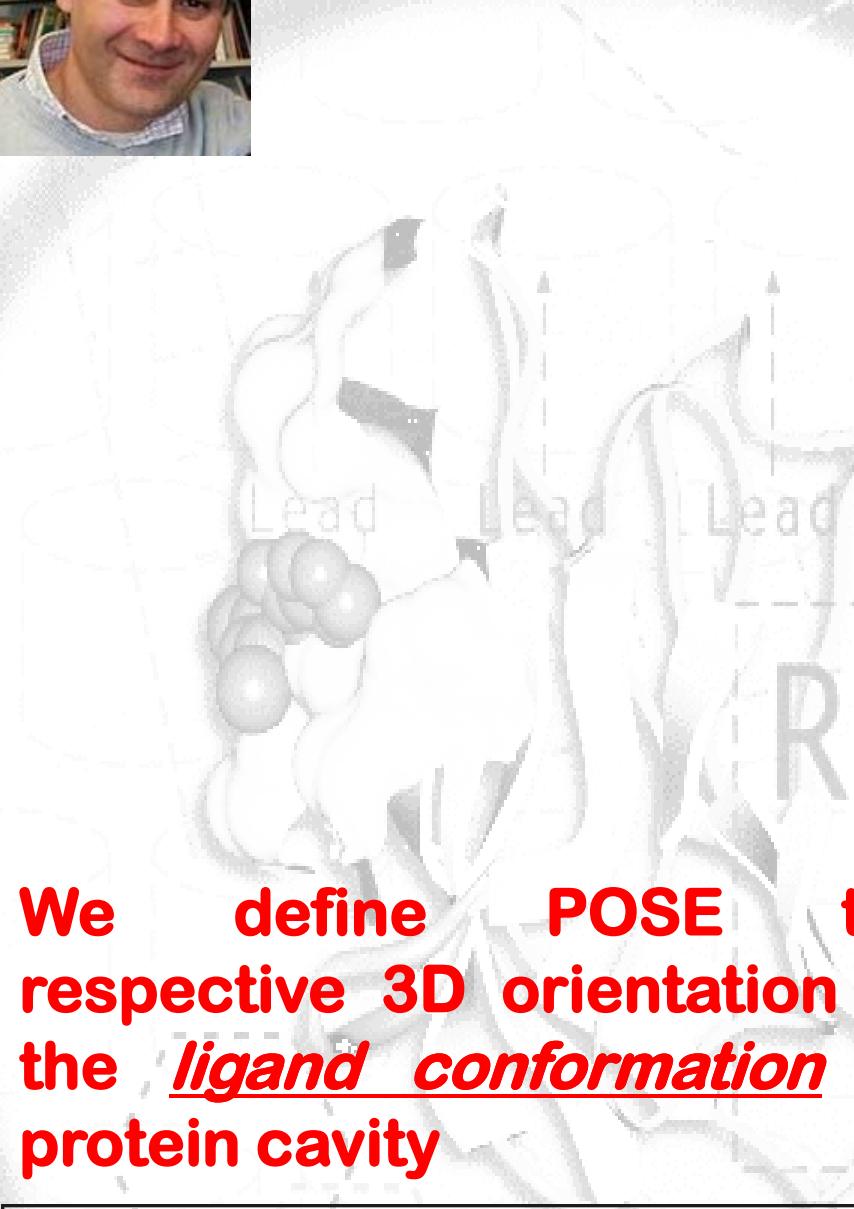
1. Positioning the ligand into binding pocket:



2. Docking: translate, rotate of the ligand conformation inside the binding pocket:



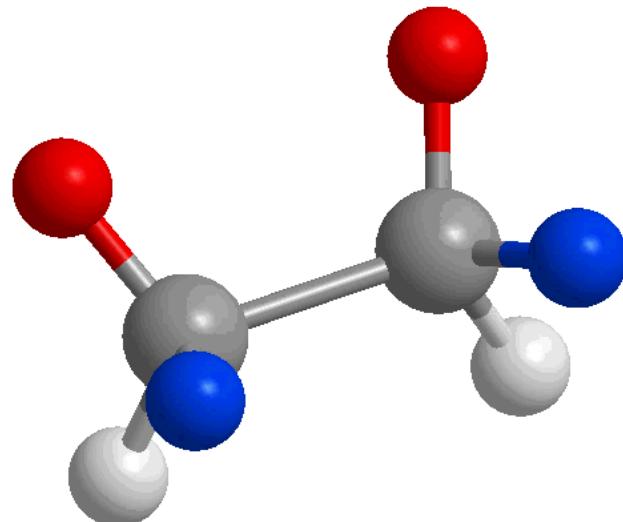
Pose: a geometrical definition...



We define POSE the
respective 3D orientation of
the ligand conformation vs
protein cavity



Ligand conformation... at this point we must open an important parenthesis

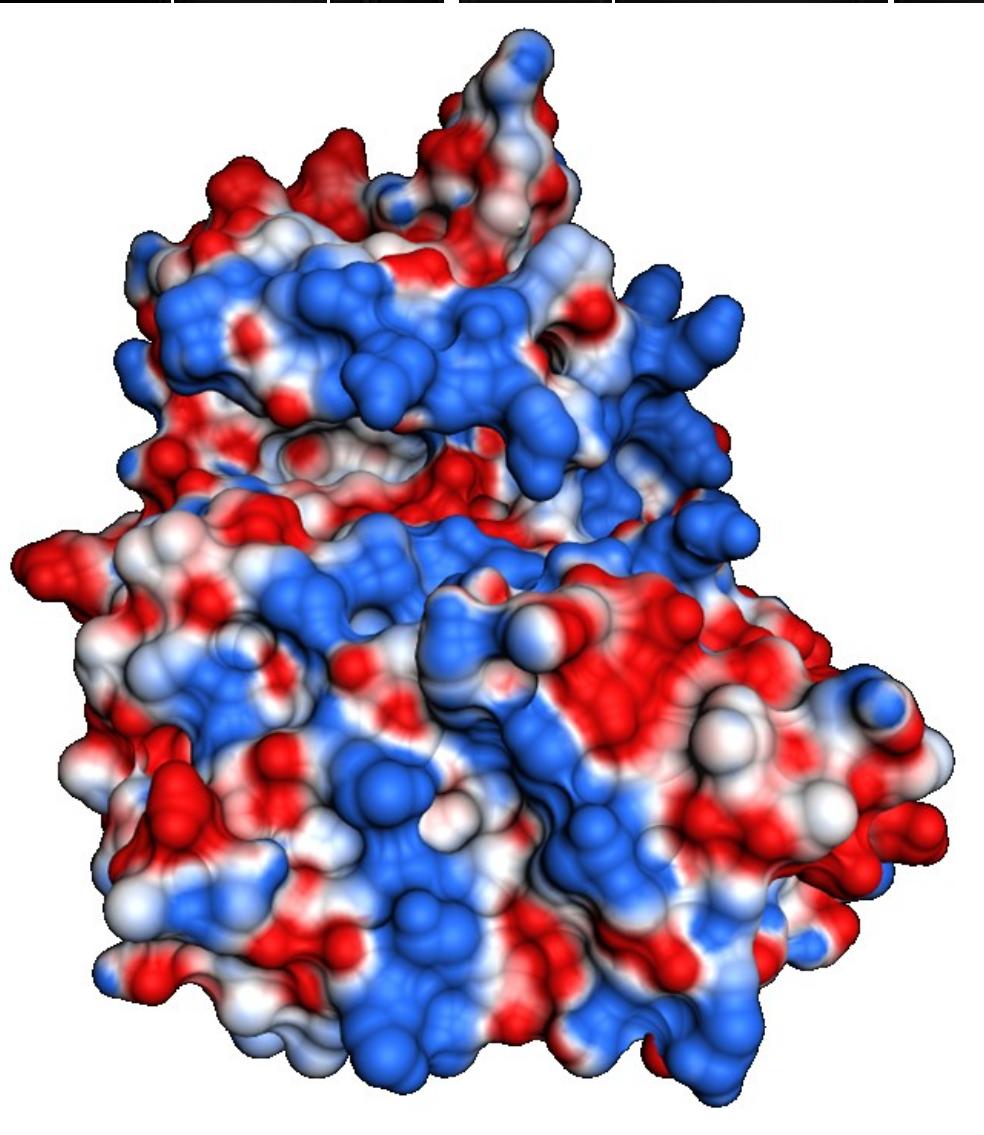
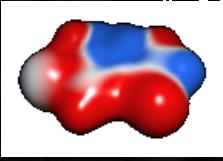


... back to SBDD_1 file

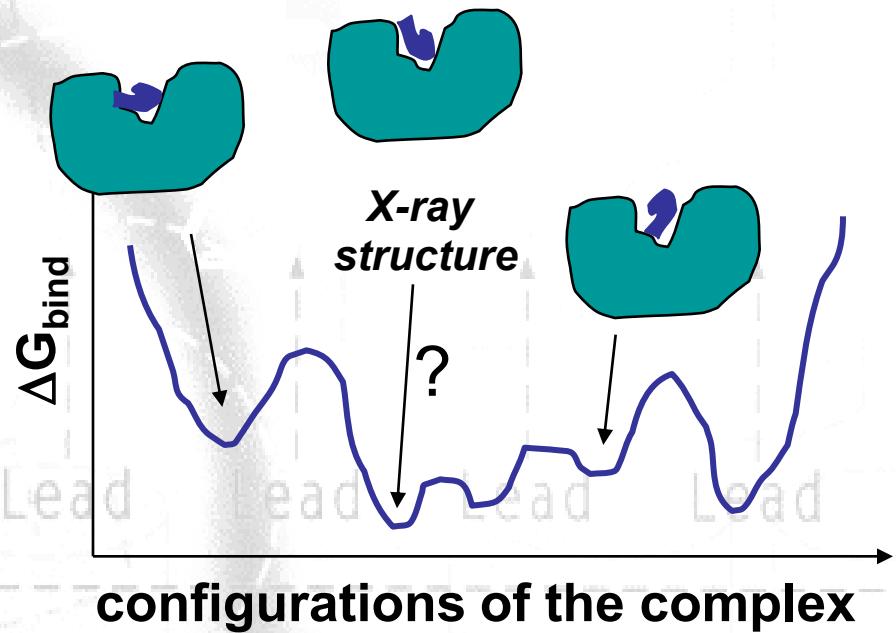
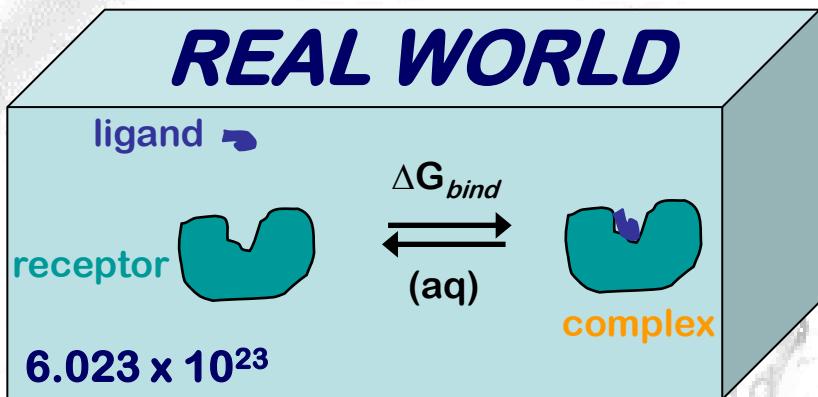
and now scoring...



1. where?
2. how?
3. how long?



REAL WORLD

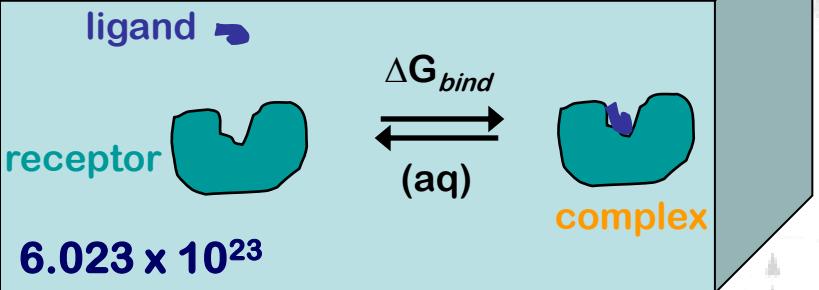


$$\Delta G_{binding} = -RT \ln(K_{affinity})$$

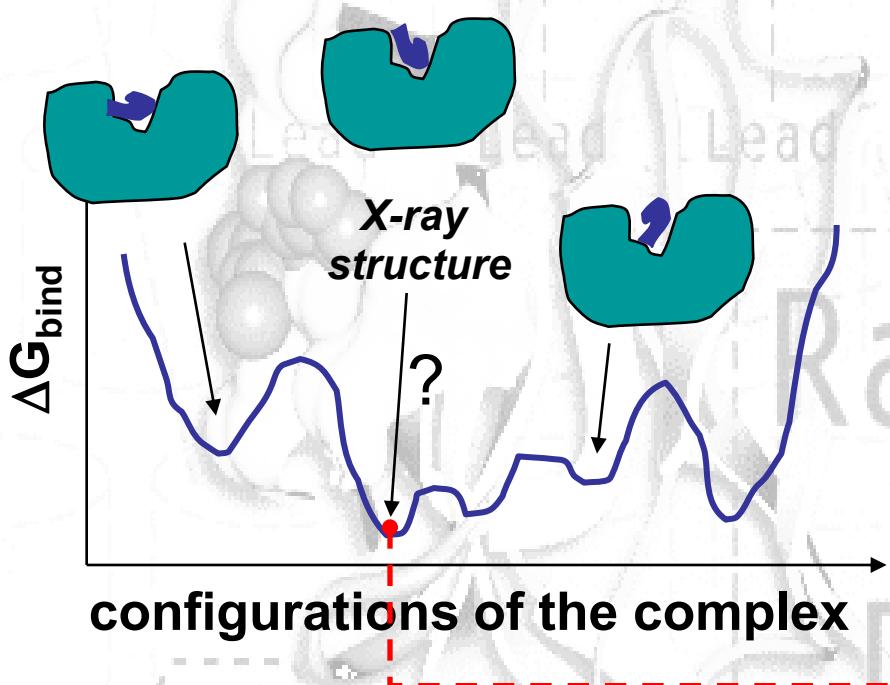
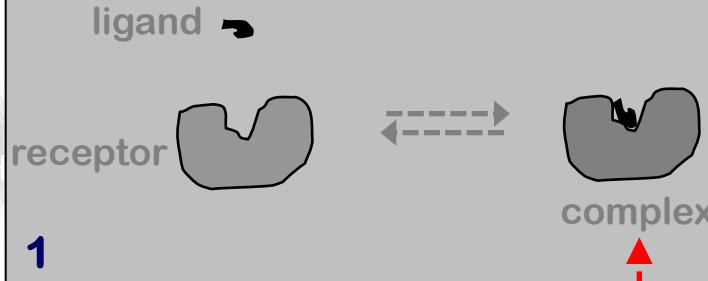
$$= \sum_1^n \Delta G_{complex/solv} - \Delta G_{ligand/solv} - \Delta G_{protein/solv}$$

Remember Avogadro!

REAL WORLD



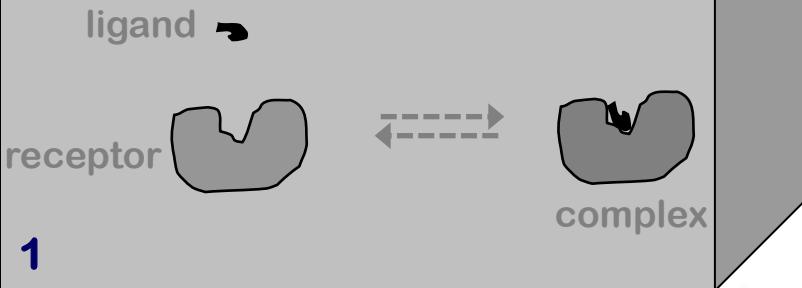
VIRTUAL WORLD



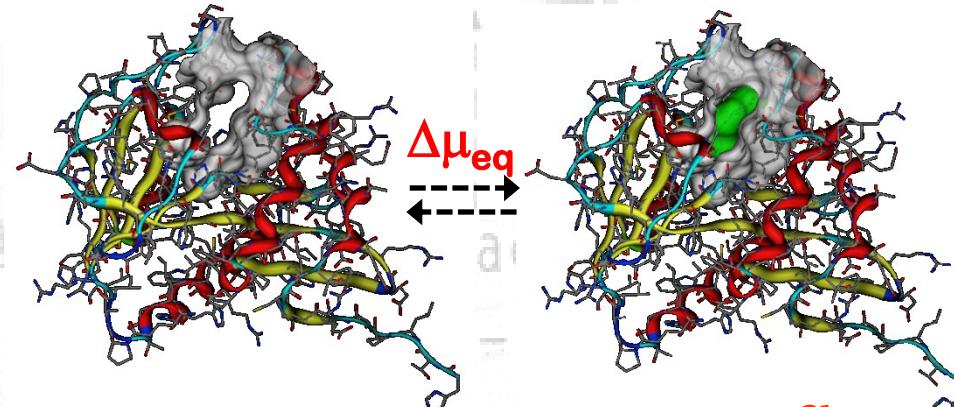
$$\frac{\Delta G_{eq}}{N} \simeq \Delta \mu_{eq}$$

Bye bye Avogadro!

VIRTUAL WORLD



In a time-independent contest



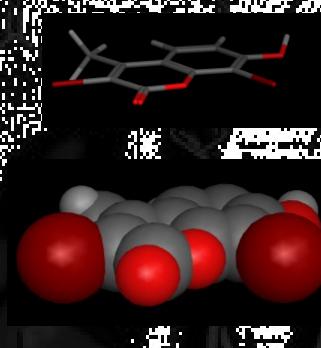
$$\Delta\mu = \mu_0 - kT \ln \frac{a_{LR}}{a_L a_R}$$

if $T = 0$

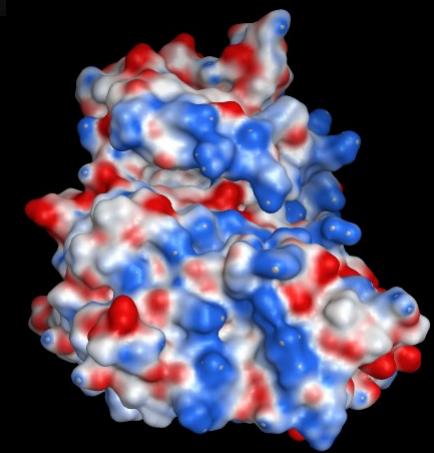
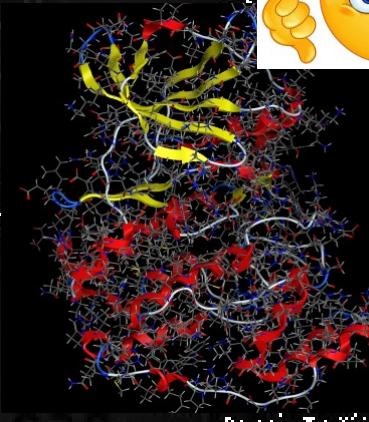
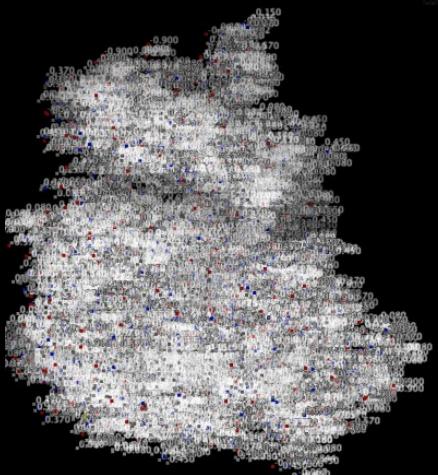
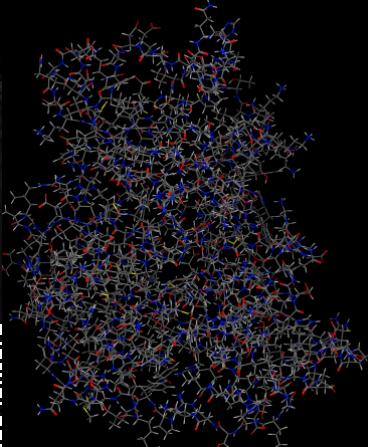
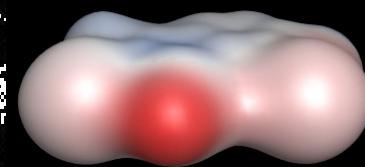
$$\Delta\mu_{eq} \approx \Delta E_{p_{eq}}$$

A

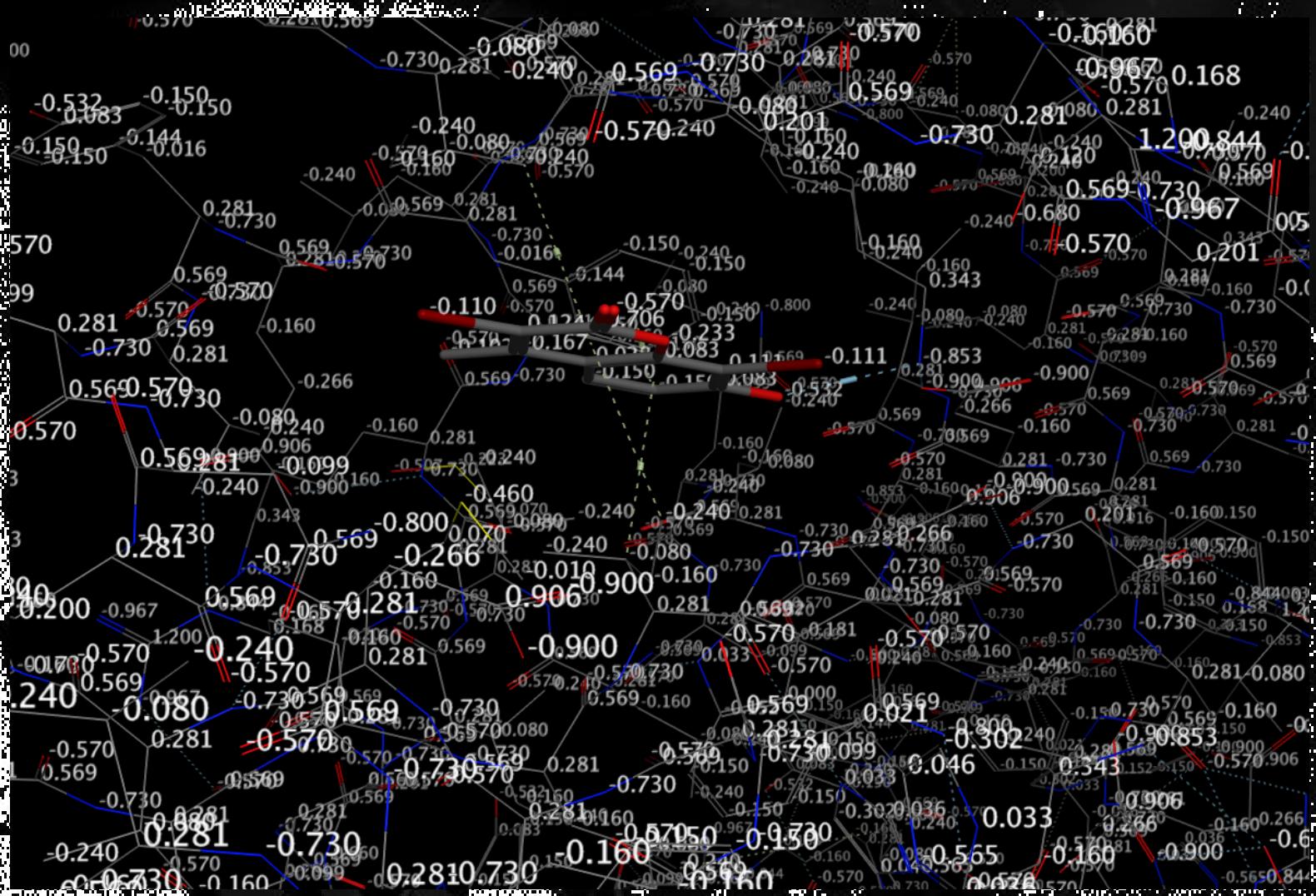
+

B

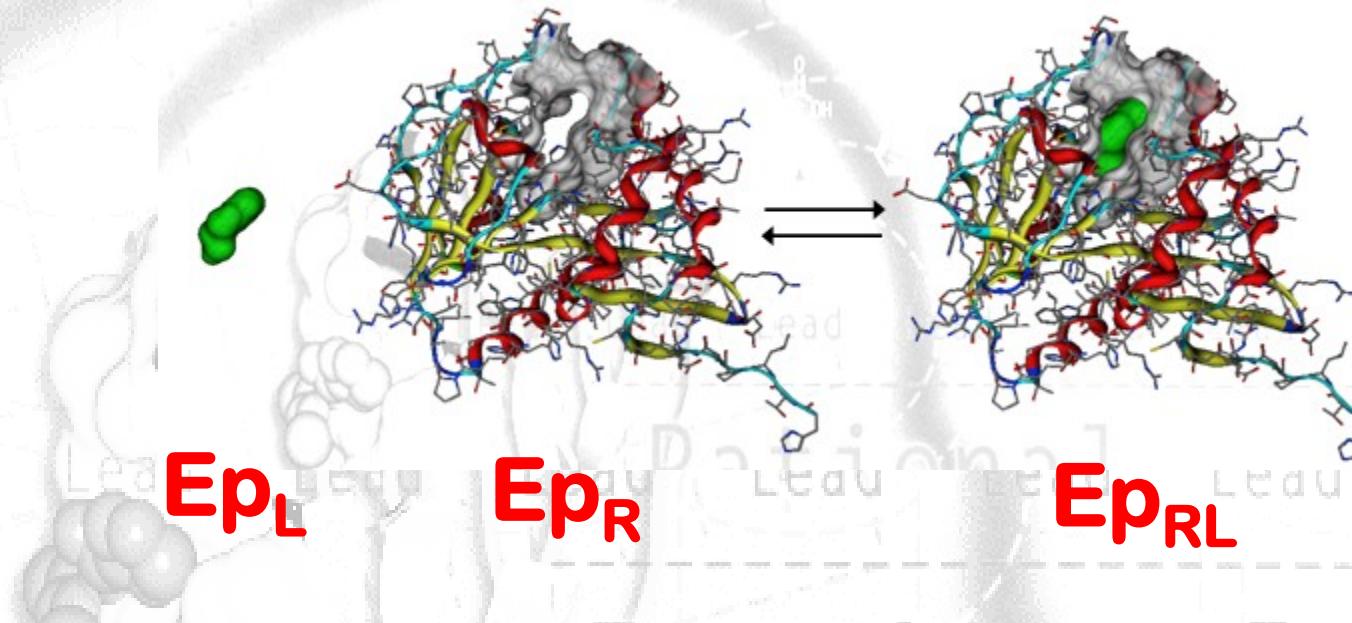
.080 .080 .150 .150 .150 .450
.102 -.167 .028 .083 .011 .532
.1180 .124 .083 .111 -.233 -.111
.570 .706 .233 -.111



A-B

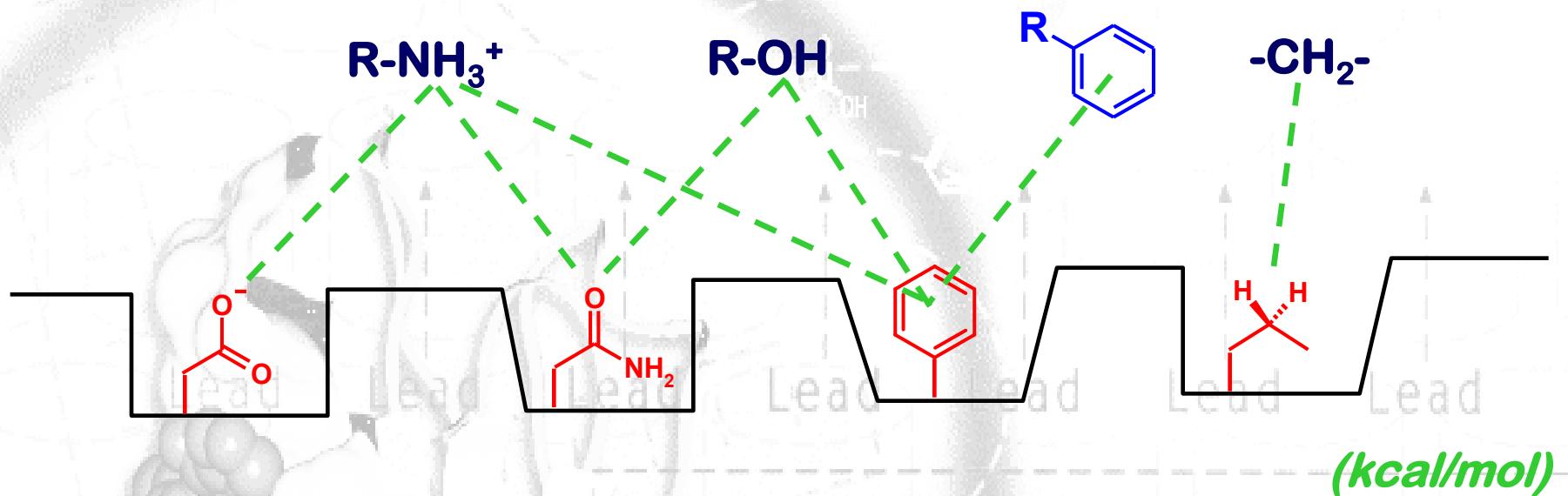


Force Field Based Scoring Functions



$$\Delta E_p = \sum_{\text{nonbonded pairs}} \frac{q_i q_k}{4\pi\epsilon_0 r_{ik}}$$

Empirical Scoring Functions



charge-charge interaction (*ionic bond*):

charge-dipole interaction:

charge- π interaction:

hydrogen bond:

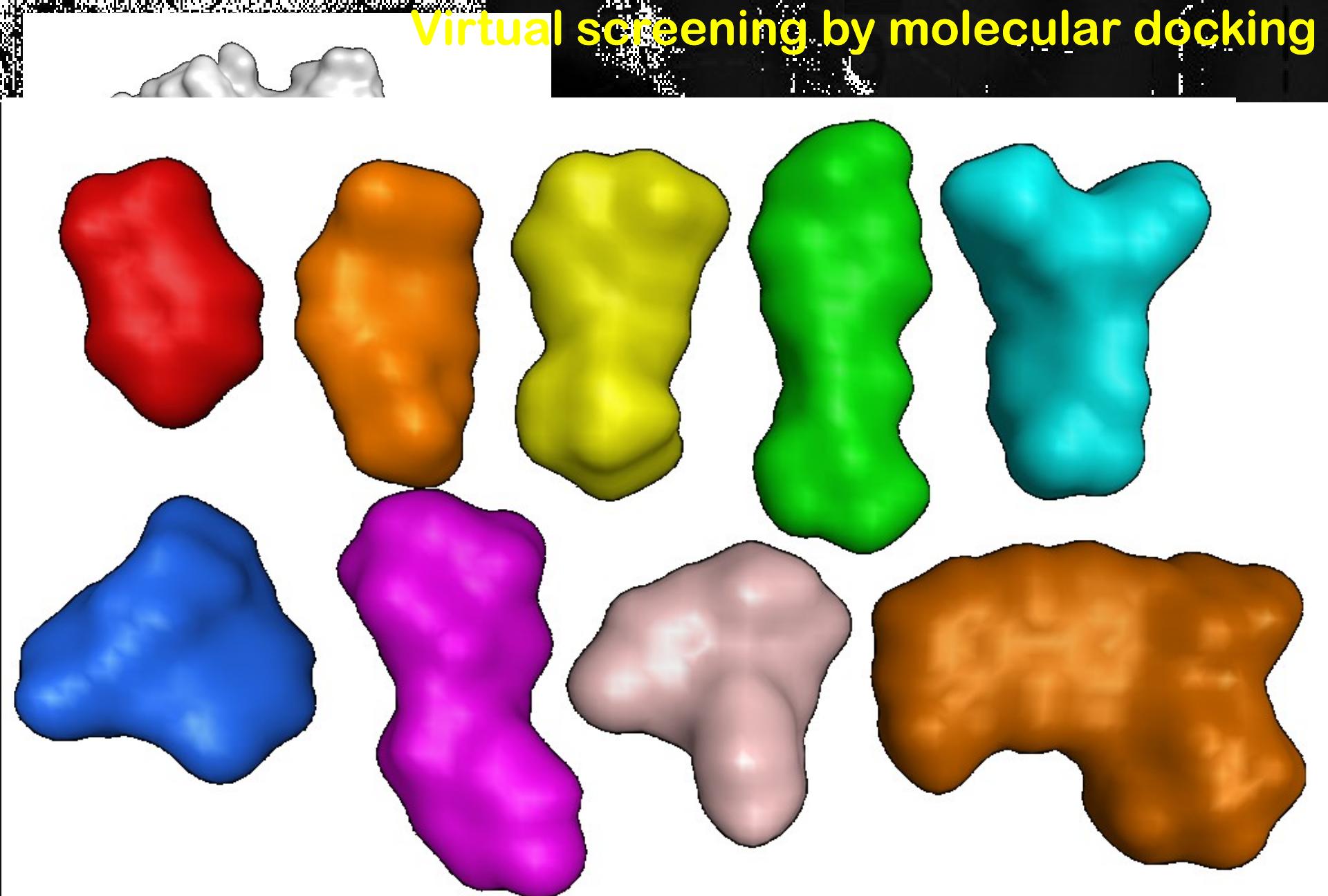
charge transfer interaction:

π - π interaction:

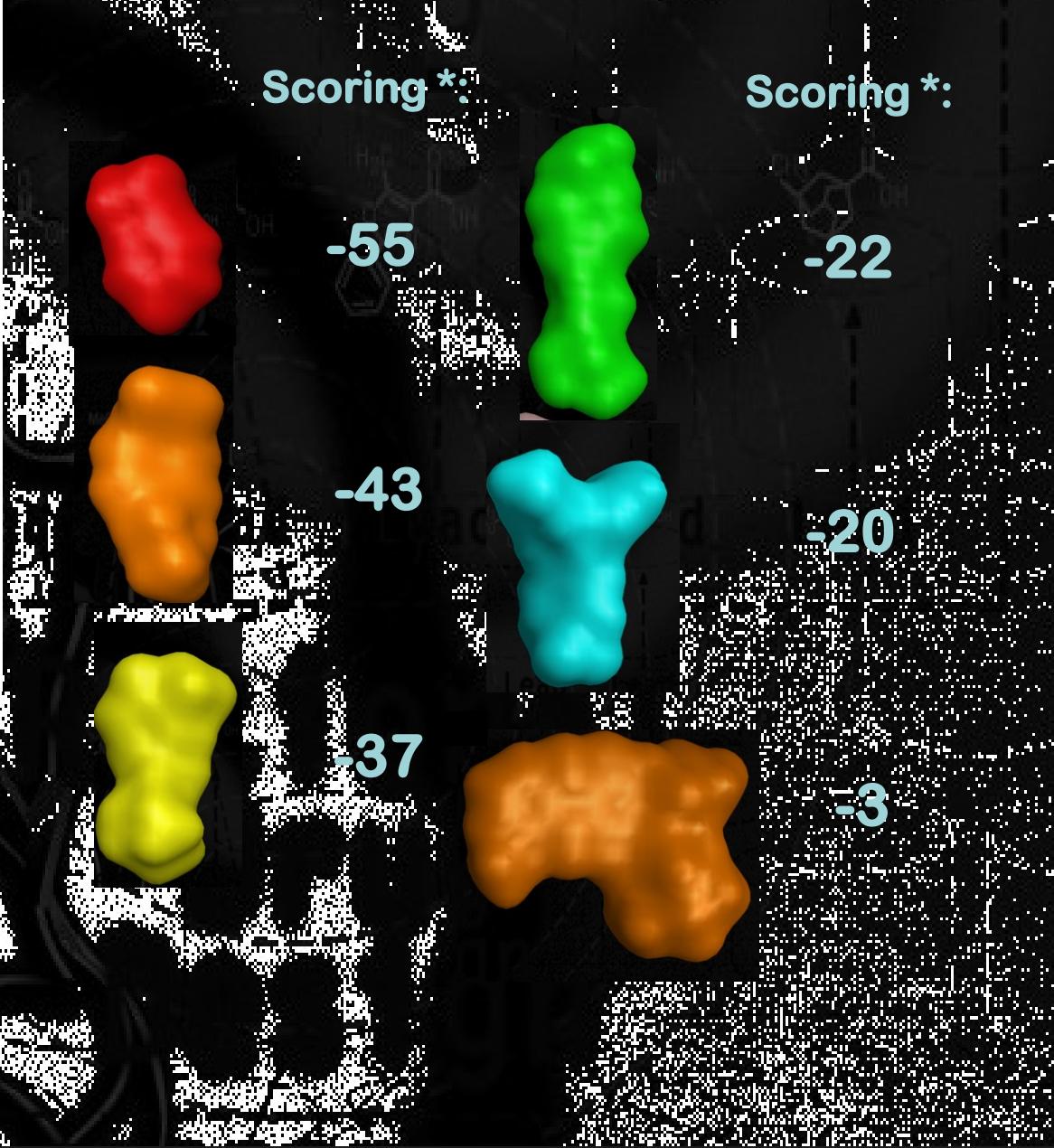
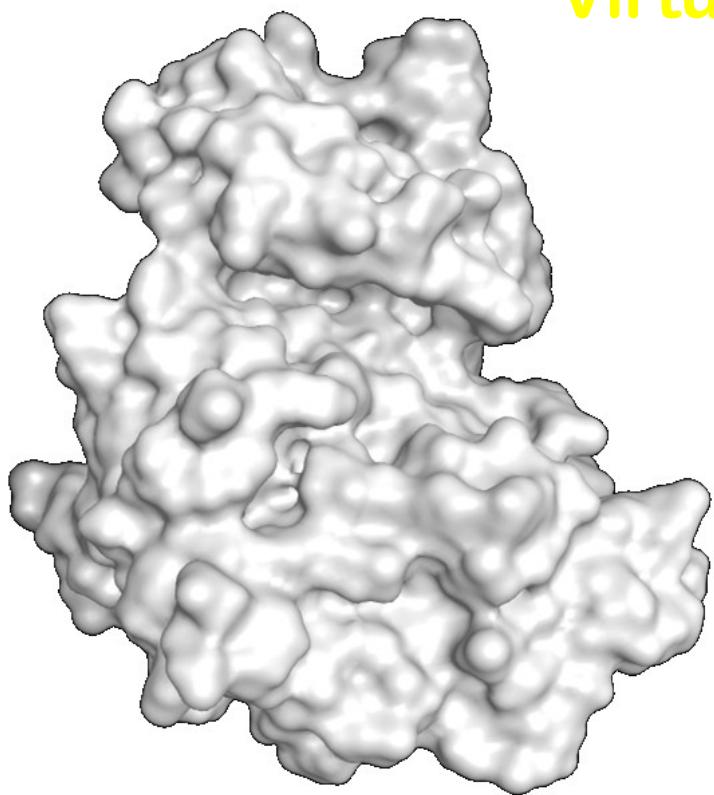
dipole-dipole interaction (van der Waals):

$-\Delta G^0 \approx$	$5 \div 10$
$-\Delta G^0 \approx$	$1 \div 7$
$-\Delta G^0 \approx$	$8 \div 10$
$-\Delta G^0 \approx$	$1 \div 7$
$-\Delta G^0 \approx$	$1 \div 6$
$-\Delta G^0 \approx$	$1 \div 2$
$-\Delta G^0 \approx$	$0.5 \div 1$

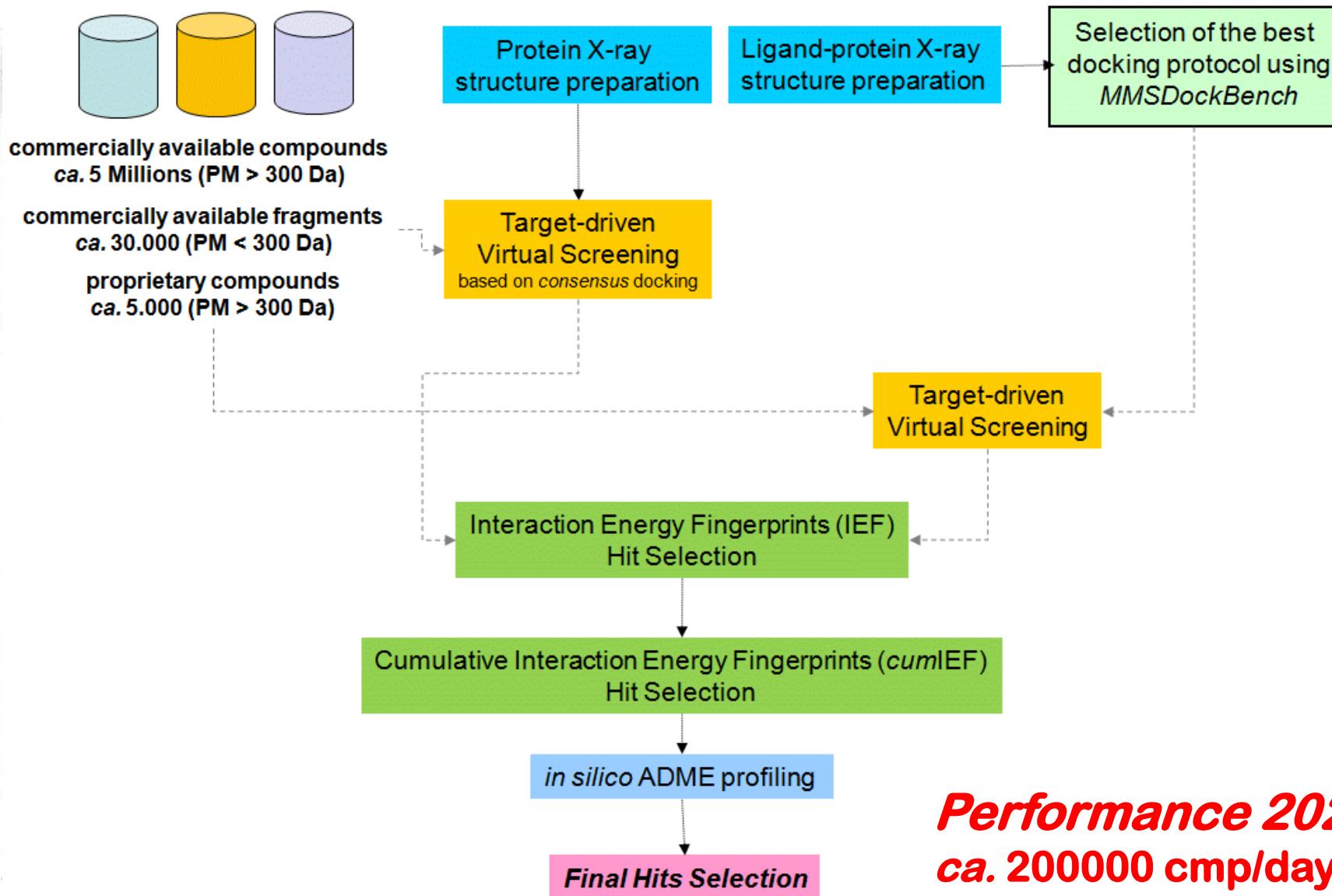
Virtual screening by molecular docking



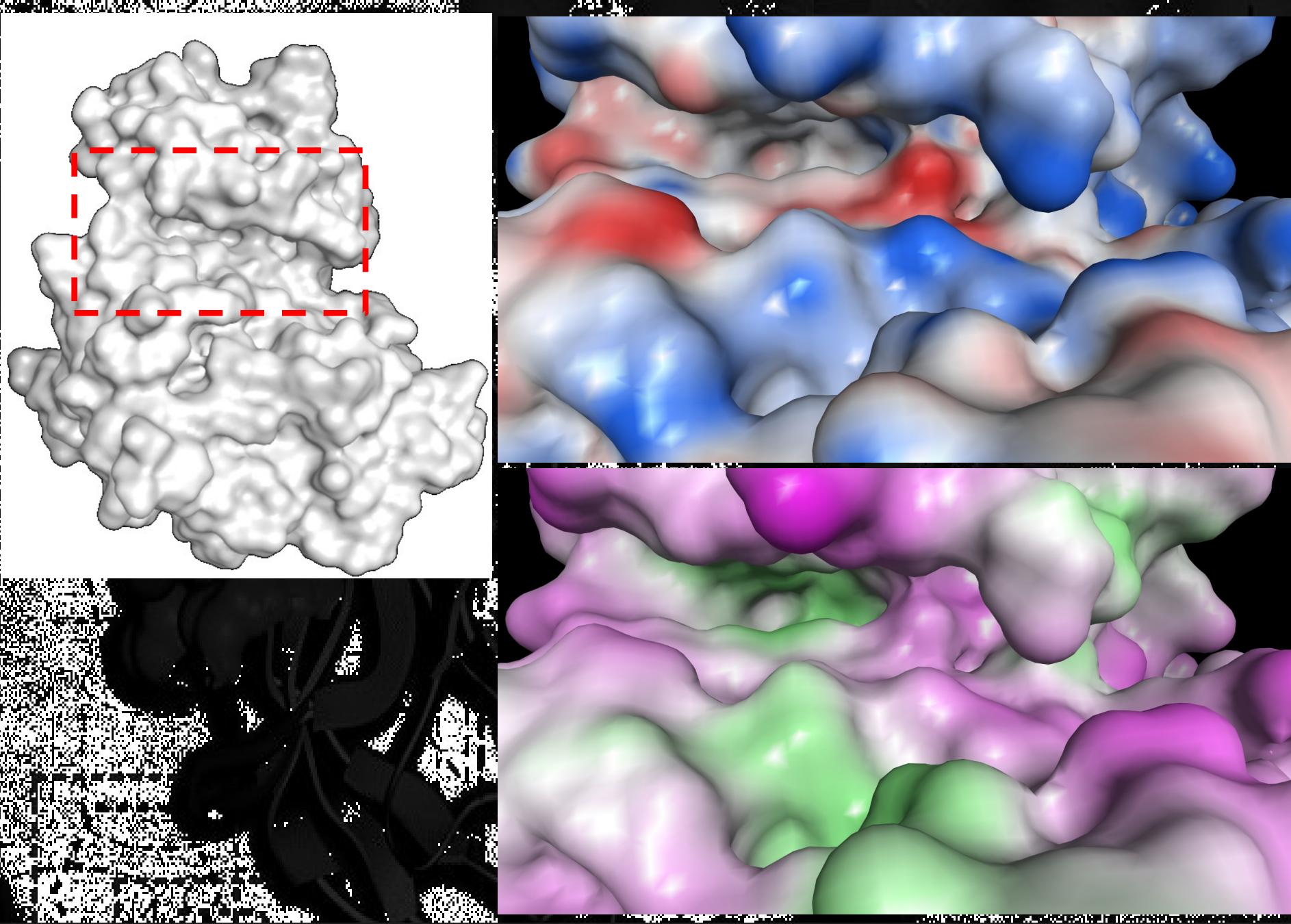
Virtual screening by molecular docking



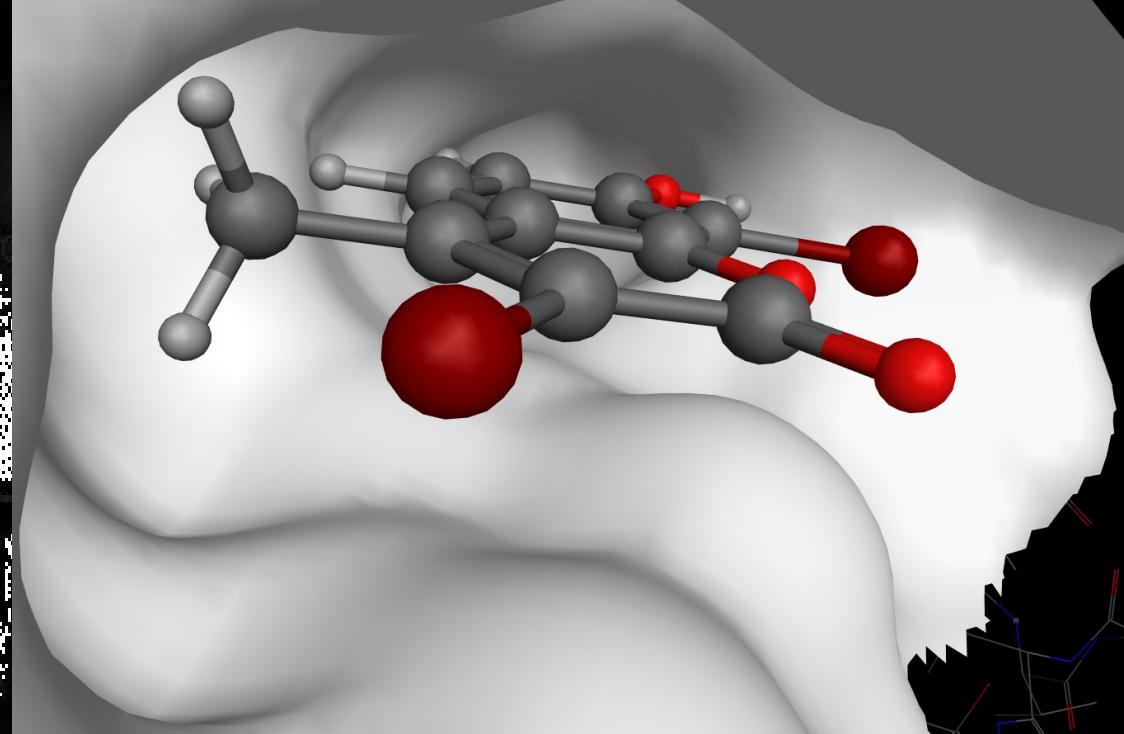
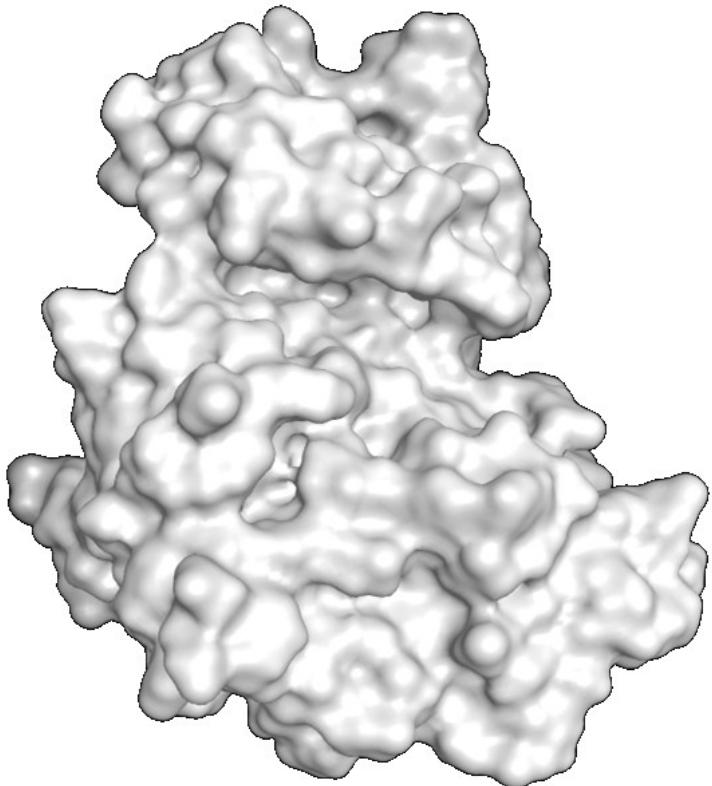
VS@MMS Platform



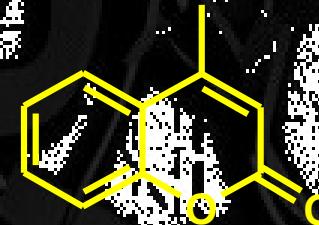
Performance 2023:
ca. 200000 cmp/day



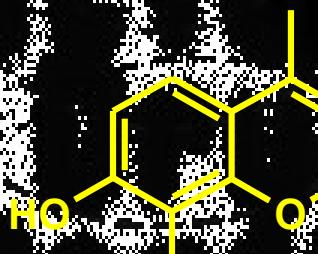
Hit optimization



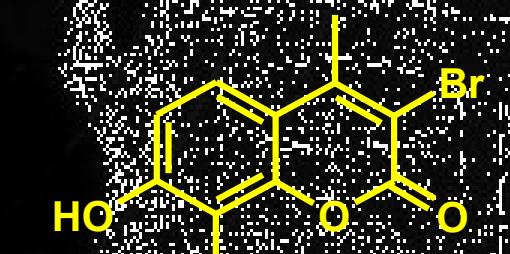
$K_i = 254.0 \mu\text{M}$



$K_i = 115.6 \mu\text{M}$



$K_i = 0.60 \mu\text{M}$



DBHC: $K_i = 0.05 \mu\text{M}$



Gr Stefan R.

National Drug Design