Introduction to Molecular Docking

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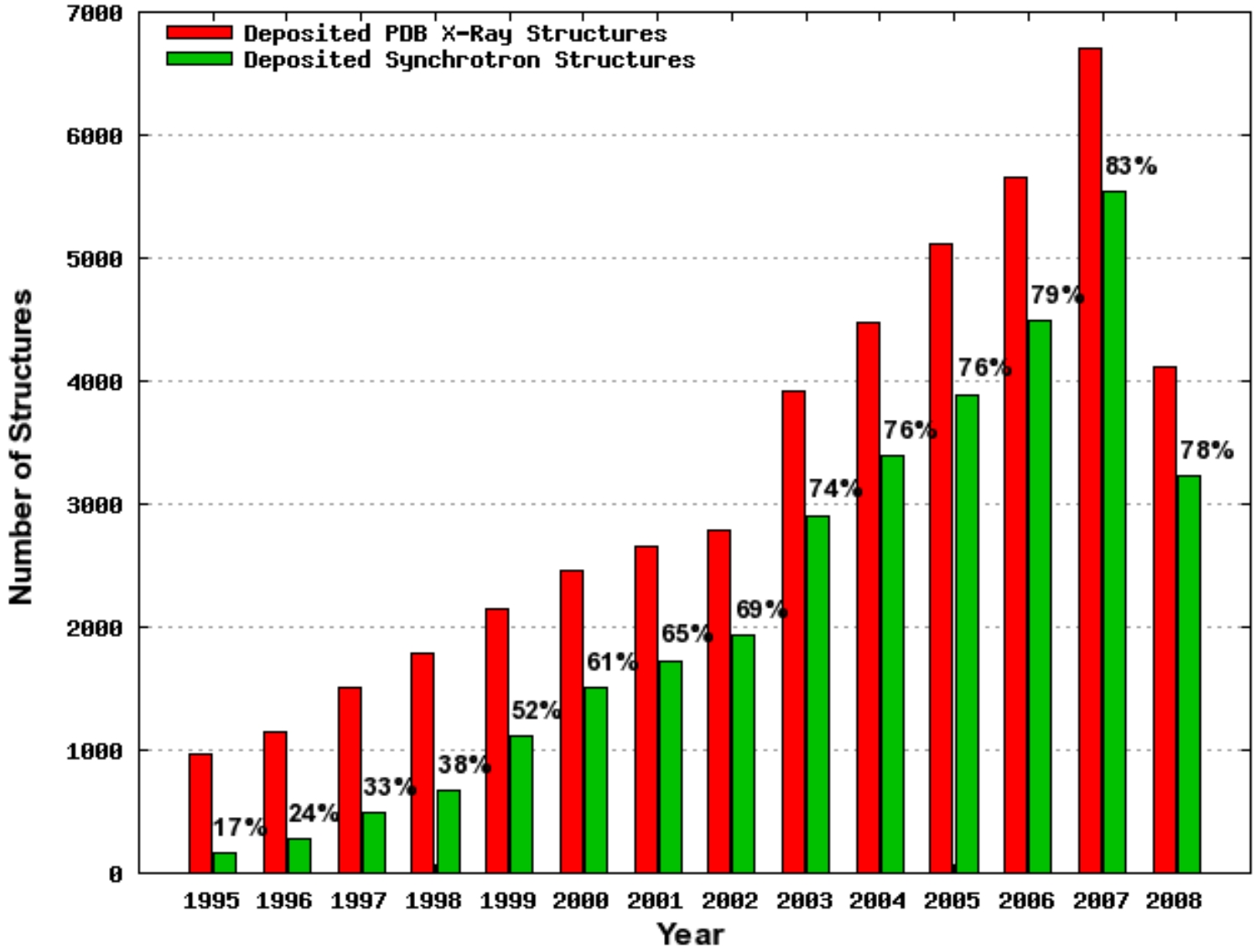
DEFINITION

Molecular docking tries to predict the structure of the intermolecular complex formed between two or more constituent molecules.

APPLICATIONS

- **Virtual screening (hit identification)**
- **Drug Discovery (lead optimisation)**
- **Prediction of K_A (biological activity ?)**
- **Binding-site identification (blind docking)**
- **De-orphaning of a receptor**
- **Protein – Protein (or Protein – Nucleic Acid) interactions**
- **Structure-function studies**
- **Enzymatic reactions mechanisms**
- **Protein engineering**

The Protein Data Bank (PDB)



http://www.rcsb.org/

Most typical case: **Protein - Ligand docking**

● The final goal uses to be to predict the biological activity of a given ligand

Two different problems:

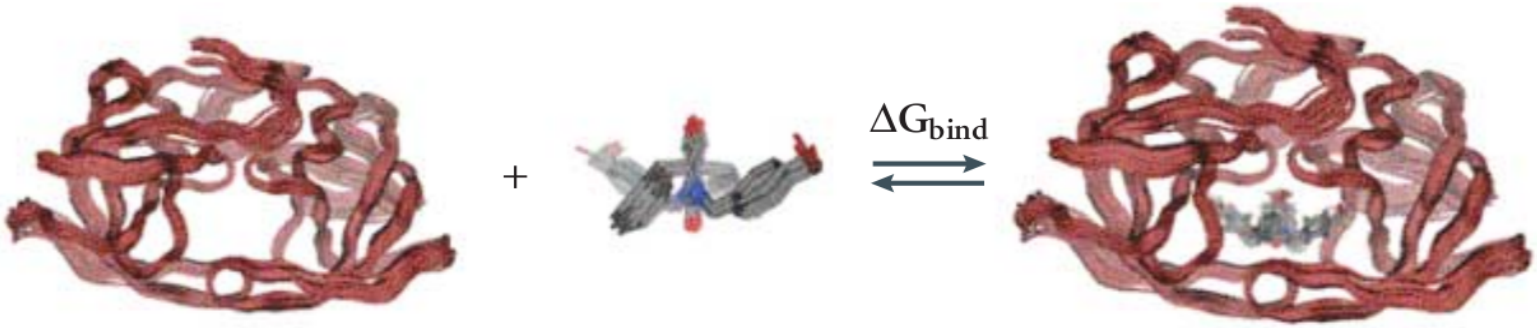
POSING

The process of determining whether a given conformation and orientation of a ligand fits the active site. This is usually a fuzzy procedure that returns many alternative results.

SCORING

The pose score is a measure of the fit of a ligand into the active site. Scoring during the posing phase usually involves simple energy calculations (electrostatic, van der Waals, ligand strain). Further re-scoring might attempt to estimate more accurately the free energy of binding (ΔG, and therefore K_A) perhaps including properties such as entropy and solvation.

$$[EI]_{aq} \rightleftharpoons [E]_{aq} + [I]_{aq} \qquad (1)$$



The free energy of binding (ΔG) is related to binding affinity by equations 2 and 3:

$$\Delta G = -RT\ln K_A \qquad K_A = K_i^{-1} = \frac{[EI]}{[E][I]} \qquad (2,3)$$

Prediction of the correct structure (posing) of the [E+I] complex does not require information about K_A. However, prediction of biological activity (ranking) requires this information; scoring terms can therefore be divided in the following fashion. When considering the term [EI], the following factors are important: steric, electrostatic, hydrogen bonding, inhibitor strain (if flexible) and enzyme strain. When considering the equilibrium shown in equation 1, the following factors are also important: desolvation, rotational entropy and translational entropy.

Nature Reviews Drug Discovery, **2004**, *3*, 935

$$\Delta G = \Delta G_{\text{vdW}} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + \Delta G_{\text{hbond}} \sum_{i,j} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} + E_{\text{hbond}} \right) + \Delta G_{\text{elec}} \sum_{i,j} \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} + \Delta G_{\text{tor}} N_{\text{tor}} + \Delta G_{\text{sol}} \sum_{i_C,j} S_i V_j e^{(-r_{ij}^2/2\sigma^2)}$$

SCORING FUNCTION IN AUTODOCK

Molecular Mechanics Terms

van der Waals $\Delta G_{vdW} = W_{vdW} \sum_{i,j} (A_{ij} / r_{ij}^{12} - B_{ij} / r_{ij}^{6})$

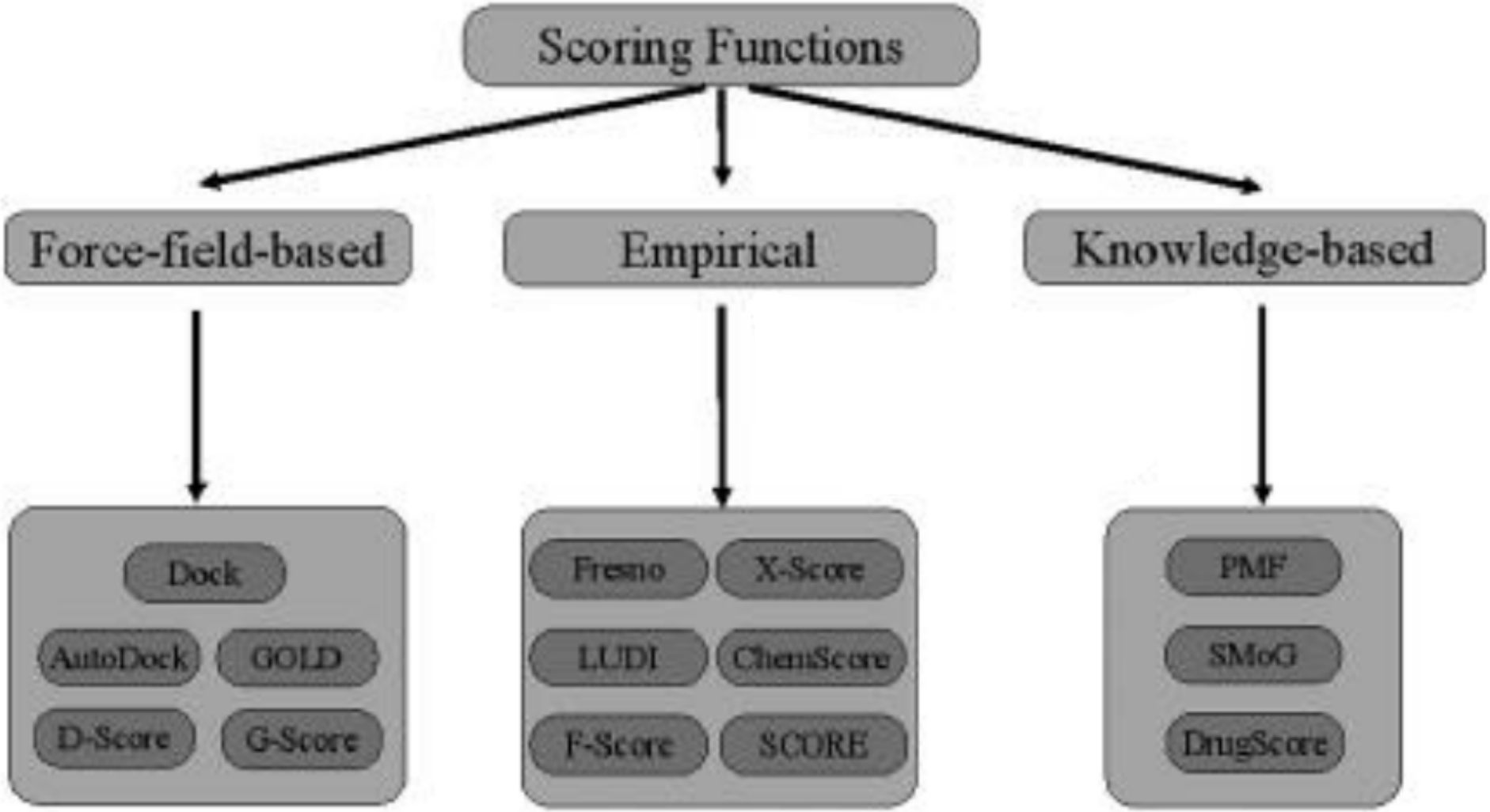
Hydrogen Bonding $\Delta G_{H\text{-}bond} = W_{H\text{-}bond} \sum_{i,j} E(t) * (C_{ij} / r_{ij}^{12} - D_{ij} / r_{ij}^{10} + E_{hbond})$

Electrostatics $\Delta G_{elec} = W_{elec} \sum_{i,j} (q_i * q_j) / (\varepsilon(r_{ij}) * r_{ij})$

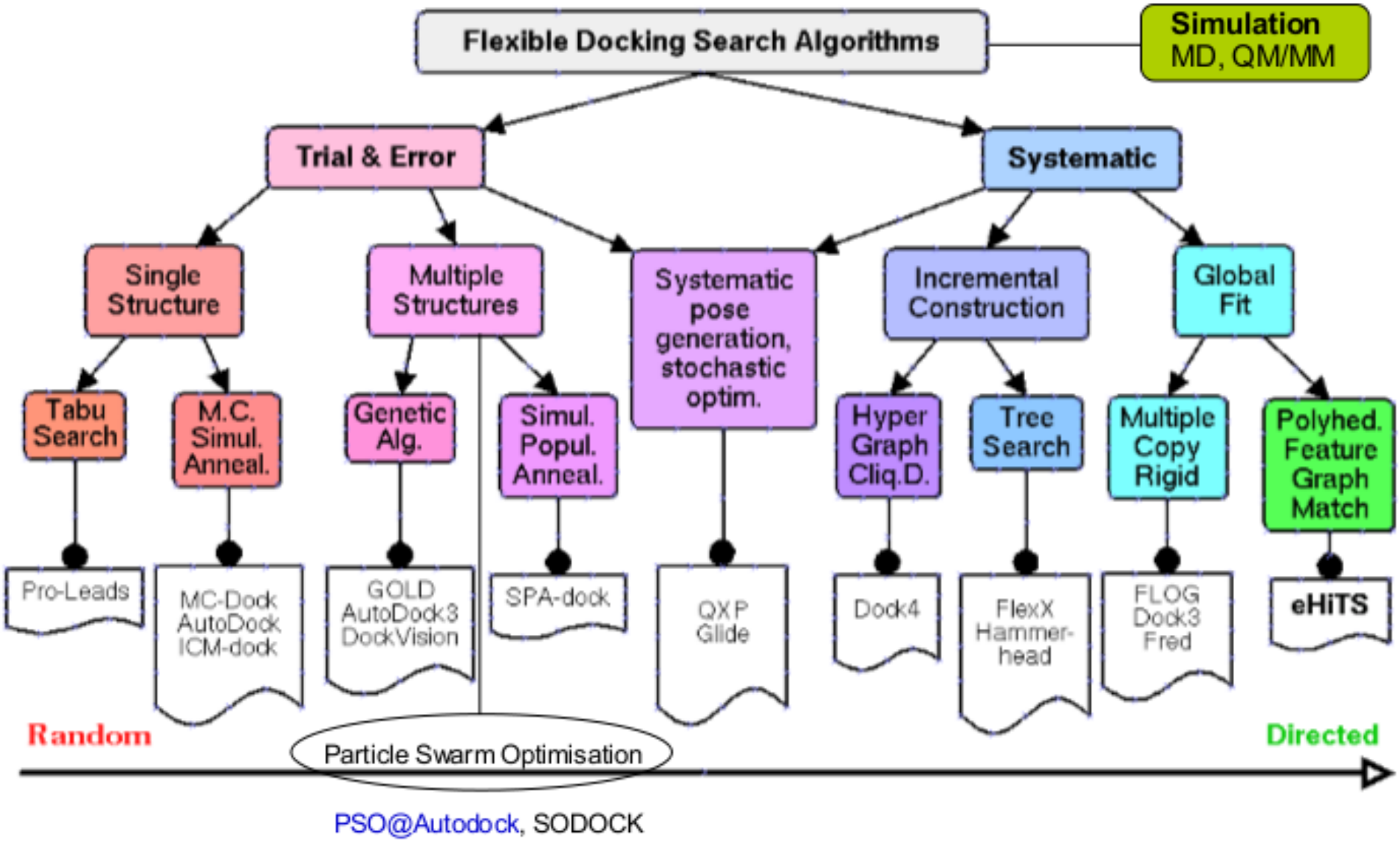
Desolvation $\Delta G_{desolv} = W_{desolv} \sum_{i\,(C),j} (S_i * V_j * \exp (-r_{ij}^2 / (2 * \sigma^2)))$

Change in Torsional Free Energy when the Ligand goes from Unbound to Bound

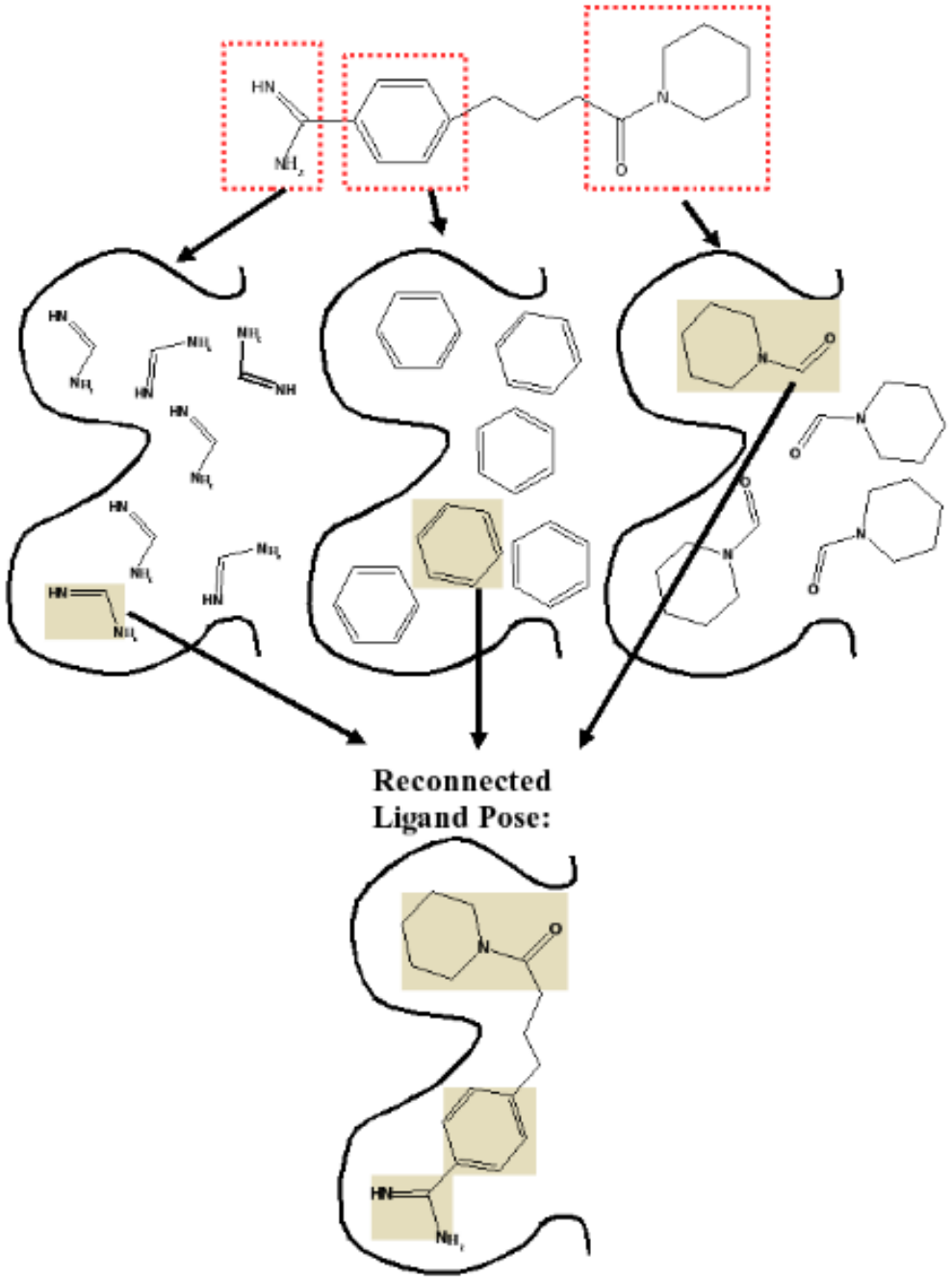
Torsional $\Delta G_{tor} = W_{tor} N_{tor}$


Scoring Functions
Force-field-based
Empirical
Knowledge-based
Dock
AutoDock
GOLD
D-Score
G-Score
Fresno
X-Score
LUDI
ChemScore
F-Score
SCORE
PMF
SMoG
DrugScore

Posing and Scoring: Flexible docking algorithms

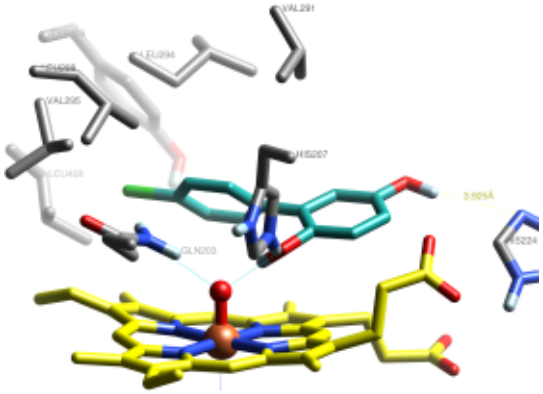


J. Mol. Graph. Model. **2007**, *26*, 198

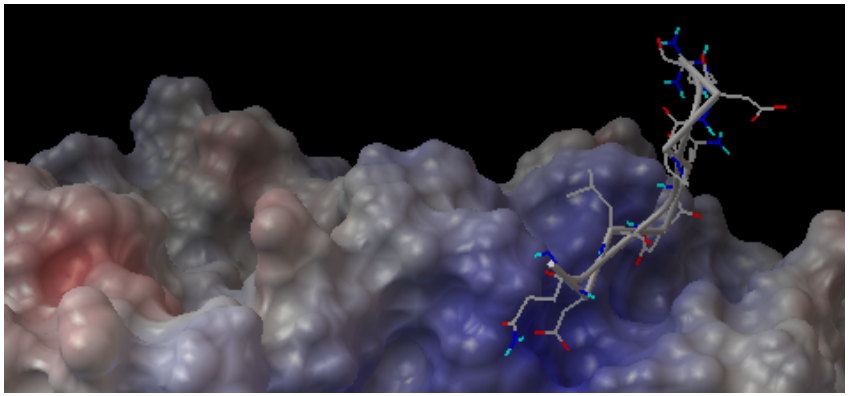

Reconnected
Ligand Pose:

MOLECULAR REPRESENTATIONS

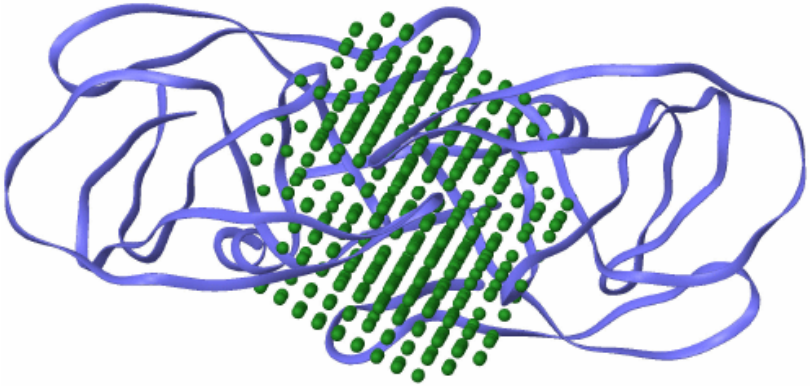
Atomic



Surfaces



Grid



PROTEIN FLEXIBILITY

- **Molecular Dynamics**
- **Energy Minimisation**

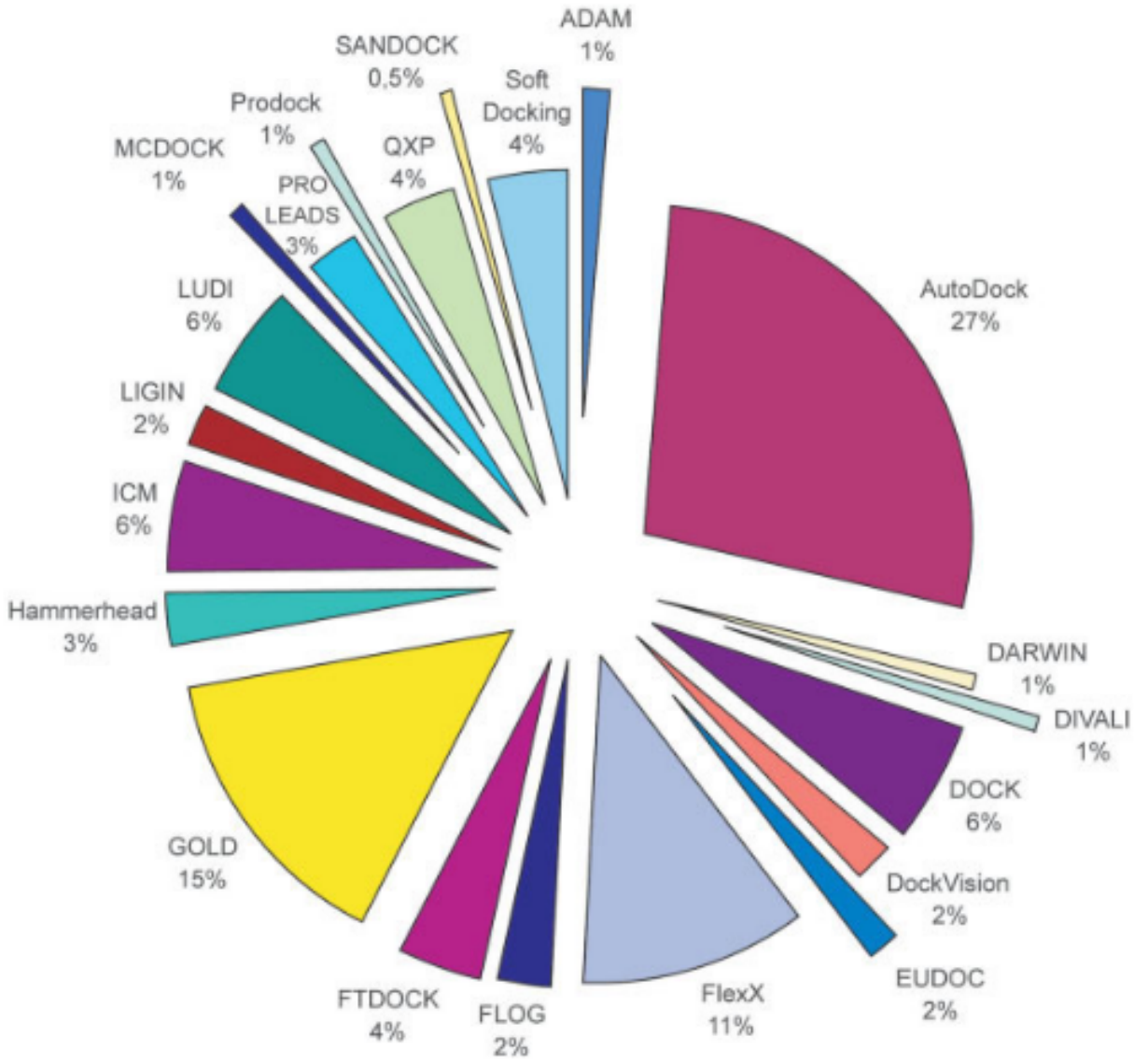
} Usually in combination with other methods

- **Monte Carlo**
- **Normal Modes**
- **Rotamer Libraries**
- **Protein Ensembles** (NMR, MD, NMA) **/ Protein Ensemble Grids**
- **Soft Potentials**

LIMITATIONS OF CURRENT DOCKING METHODOLOGIES

- **Flexible ligands → Rotatable bonds → Combinatorial explosion**
- **Entropic effects → Rotatable bonds**
- **Solvation / desolvation → Accurate computation is expensive**
- **Water molecules** (and ions)
- **Tautomers**
- **Protein flexibility → Induced fit**
- **Specificity of binding → Understanding important interactions**
  (currently larger ligands are favoured by the scoring functions)
- Pharmacokinetic effects, allosteric effects, biomolecule-biomolecule interactions (molcecular context), etc.

DOCKING SOFTWARE



Proteins: Structure, Function and Bioinformatics **2006**, *65*, 15.

RESOURCES:

- Protein – Protein Interaction Website (docking software):

http://www.imb-jena.de/jcb/ppi/jcb_ppi_software.html

- Structural Biology Software Database:

http://www.ks.uiuc.edu/Development/biosoftdb/biosoft.cgi

- Molecular Docking Web:

http://mgl.scripps.edu/people/gmm/

- Molecular Docking Servers:

http://www.dockingserver.com/web

http://bioinfo3d.cs.tau.ac.il/PatchDock/

- My Website:

http://www.edelmiromoman.eu/

- AutoDock GUIs: AutoDockTools (ADT), BDT, DOVIS

CONCLUDING REMARKS

- **Molecular modelling is about READING !!!**
- **Inspect all available structures of your protein: check for alternative conformations, R factors, ligands; become familiar with your binding site**
- **Carefully consider tautomerism, protonation, waters, X-ray resolution, etc.**
- **Also look to proteins of the same or related families / functions**
- **Collect all the relevant empirical data: site-directed mutagenesis, ligands, affinity / inhibition constants, etc.**
- **Critically analyse all this stuff in view of existing (and your own) hypotheses**
- **You are ready for modelling !** (docking is just the beginning)
- **Find the right balance between simulations and experiments**

MAY THE FORCE BE WITH YOU