

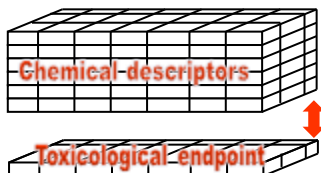
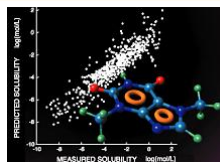
Post-processing of docked protein: rank-ordering of ligands in structure-based drug design

Arianna Bassan, Elena Fioravanzo

S-IN, Soluzioni Informatiche
L'Aquila, 21-23 Novembre 2011

- S-IN, Soluzioni Informatiche
- Binding affinities
 - Overview of methods
 - MM-GB/SA
 - Watermap
- Conclusions and acknowledgements

Molecular Modeling and (Q)SAR



Computational Toxicology

Data storage and management



Enterprise Solutions



Quality by Design

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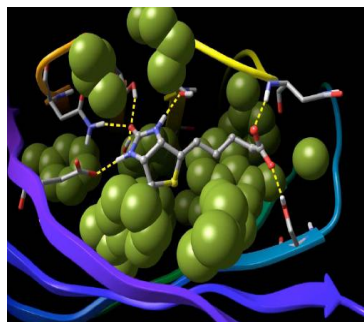
- Consulting Services
- Contracted Research
- Training Activities
- In silico Predictions
- Software Solutions



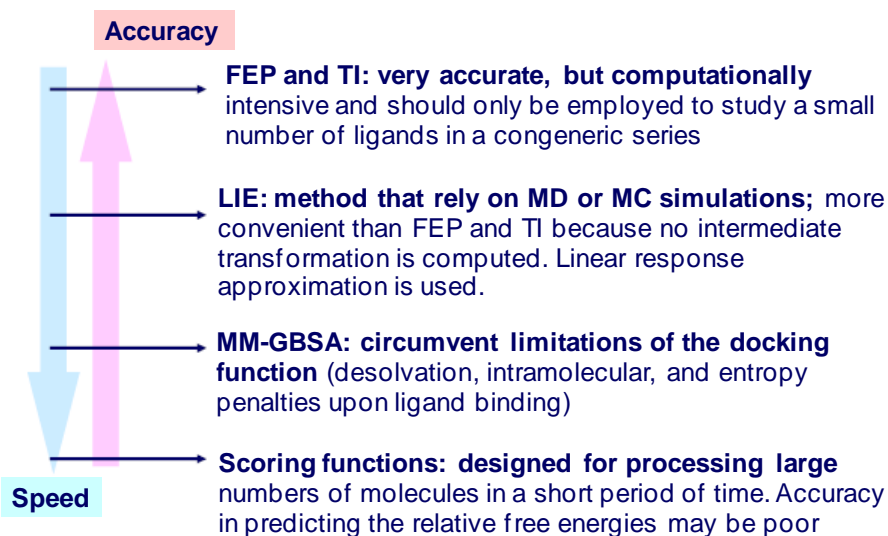
- **Cosmetics** - Innovative chemistry approaches for toxicity predictions - EU and Colipa funded project - Partners: JRC, Liverpool University, FDA, Molecular Networks ...
- **Database** – European Food Safety Authority (EFSA)
- **In silico predictions** for regulatory use – Chemsafe
- **Molecular modelling** – Industry

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- Binding energies: challenging task
 - Active area of research in the scientific community
- **Docking** is primarily concerned with:
 - Generating an accurate pose for each ligand
 - Generating good enrichment
- **Docking score** (e.g. GlideScore):
 - Estimate of the binding affinity, but it is only accurate to a few kcal/mol.
 - limited to distinguishing actives from inactives (e.g. nanomolar from micromolar).



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- **Fitting a scoring model to experimental binding data:**
 - Liason
 - MCPRO+
 - Strike
 - Canvas

- **MM-GB/SA**
 - Prime-MMGB/SA
 - MM-GB/SA protocol (from the literature)

- **Watermap**

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- Decomposition of binding free energy between a ligand (L) and a receptor (R) to form a complex (RL):

$$\Delta G_{\text{BIND}} = \Delta H - T\Delta S \approx \Delta E_{\text{MM}} + \Delta G_{\text{SOLV}} - T\Delta S$$

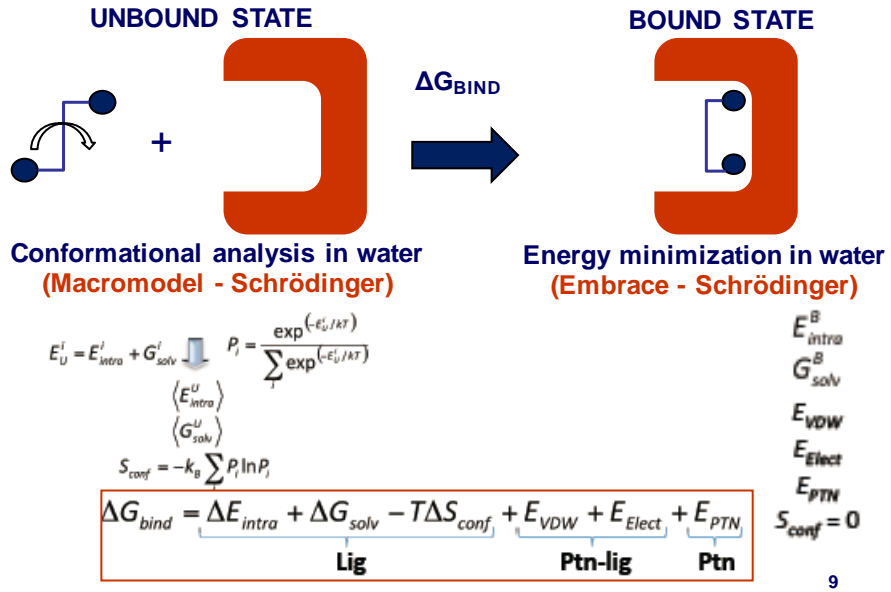
$$\Delta E_{\text{MM}} = \Delta E_{\text{internal}} + \Delta E_{\text{electrostatic}} + \Delta E_{\text{vdW}}$$

$$\Delta G_{\text{SOLV}} = \Delta G_{\text{GB}} + \Delta G_{\text{SA}}$$

- Different MM-GB/SA flavours
 - Prime MM-GB/SA
 - Protocol described by Guimarães
 - Guimarães CR, Mathiowetz AM. Addressing limitations with the MM-GB/SA scoring procedure using the WaterMap method and free energy perturbation calculations. *J Chem Inf Model.* **2010** Apr 26;50(4):547-59.
 - Guimarães CR, Cardozo M. MM-GB/SA rescoring of docking poses in structure-based lead optimization. *J Chem Inf Model.* **2008** May;48(5):958-70.

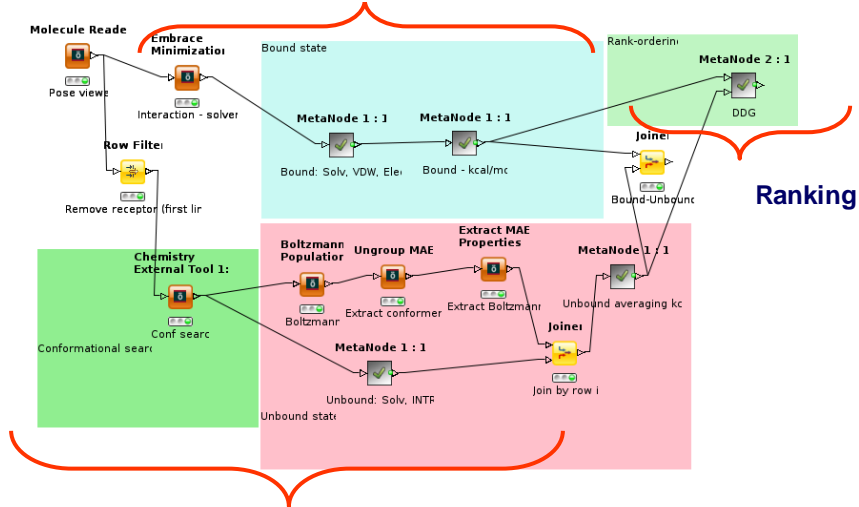
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S-IN MM-GB/SA scoring protocol (Guimarães)

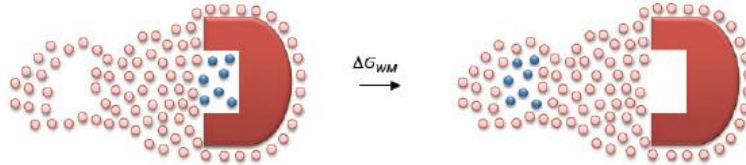


S-IN KNIME WORKFLOW – MM-GB/SA

MACROMODEL (EMBRACE) – minimization in water (bound state)



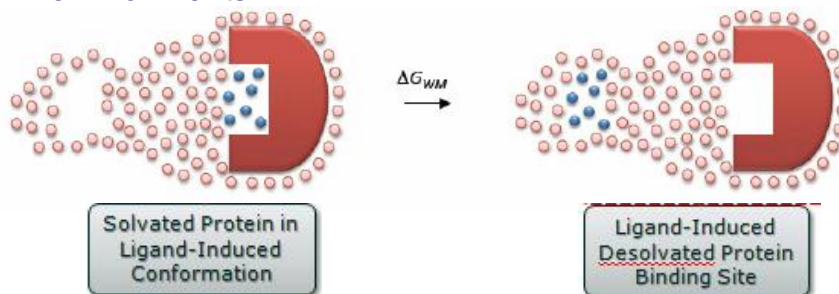
- Ligand binding to the protein: solvent (water) is displaced from the active site into the bulk fluid



- WaterMap scoring function:**
binding free energy of a ligand = sum of the free energies associated with the displacement of water
 - Removing water from sites that are comparatively less favorable than bulk contributes favorably to binding
 - Removing water from hydration sites that are more favorable than bulk opposes binding

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- ΔG_{WM} = Free energy liberation for the binding site waters into bulk solution upon cavity transfer between the two environments



- Reference states:
 - Assumed-to-preexist cavity in solution formed to accommodate the ligand
 - Binding site waters get displaced to the cavity leaving a cavity of identical size in the protein

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- Watermap scoring function includes only one component of the binding free energy (= the water displacement)
 - It does not provide a complete picture of binding when ligands differ in ways beyond simple hydrophobic modifications that fit into the binding site.
- Terms from an **MM-GB/SA** calculation, (e.g., protein–ligand van der Waals contacts, electrostatic interactions, ligand desolvation, and internal strain) + **WM**
 - Guimaraes protocol + WM scoring function
 - Guimarães J Chem Inf Model. **2010**.
 - Prime MM-GB/SA + WM scoring function
 - Abel, R., et al. (2011) Chem Med Chem

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- Calculation of accurate binding affinities: many methods need careful tuning of the calculation depending on the system of interest
- FEP calculations are too slow and accounts for small changes
- Fitting: acceptable results but need training set
- MM-GB/SA: interesting approach
- Watermap + MM-GB/SA: promising approach

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Acknowledgements

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 - Anna Maria Capelli
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- **Pfizer**
 - Cris Guimaraes

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THANKS

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- Combines MD simulation and trajectory analysis
 - ~2 ns simulation with explicit waters and restrained protein
 - Waters are spatially clustered and analyzed
 - Chemical potential (entropy and enthalpy) are computed for each hydration site
 - Energy terms are relative to bulk water
- Based on inhomogeneous solvation theory
 - Lazaridis T (1998) J Phys Chem B 102:3531-3541
 - $\langle E \rangle$ is taken directly from nonbonded interactions
 - S_e from a local expansion of spatial and orientational correlation functions

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WaterMap Extensively Validated

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