CESGA HPCN Workshop 2010

Santiago de Compostela, 25 November 2010

Cribado computacional de compuestos mediante técnicas de dinámica molecular

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Virtual screening

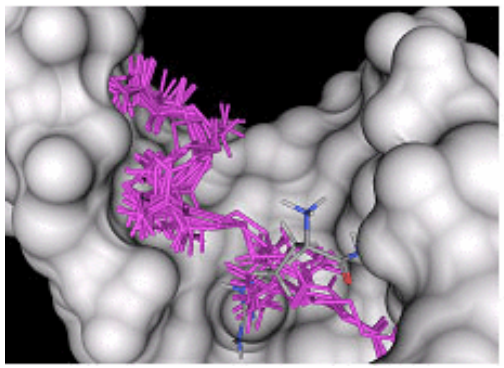
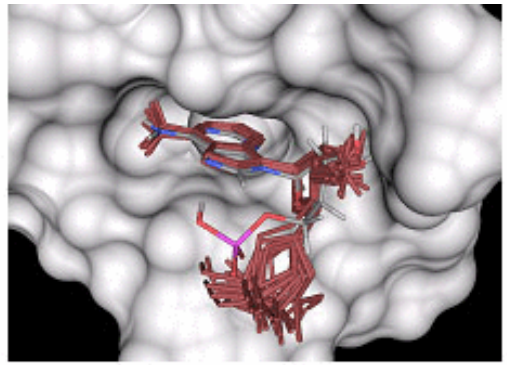
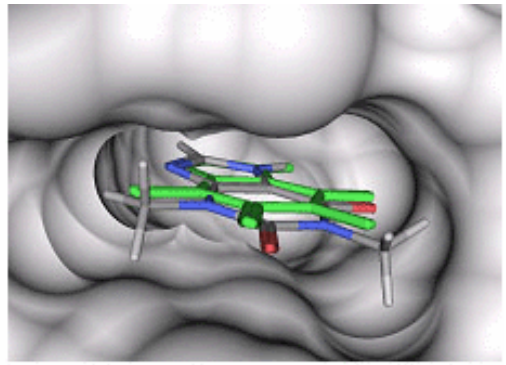
Automatic scanning of a large library of chemical compounds, in terms of binding to a protein target, using computational (prediction) algorithms

Commonly used as first (cheap and fast) filter in drug discovery projects

- Ligand-based methods
- Structure-based methods

Docking: prediction of the conformation, position and orientation of the ligand in the protein's binding site

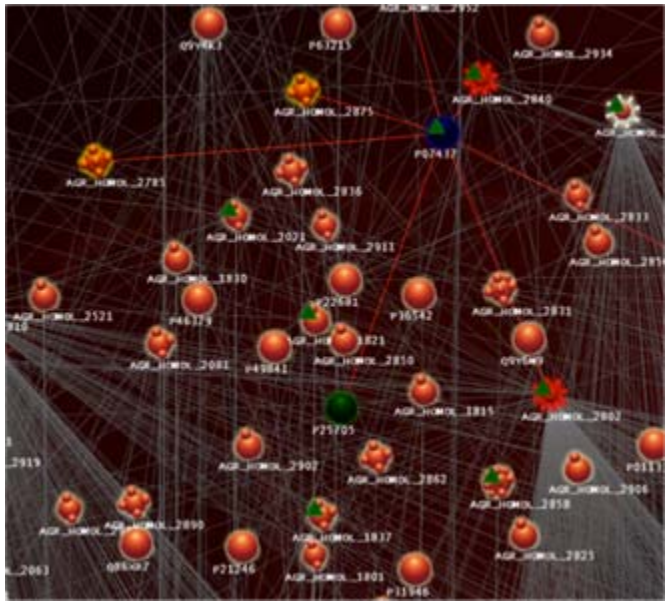
Success is limited by several factors, originating in the empirical character of the scoring functions and aggravated by flexibility issues

The DrugsForAgeing project

Collaborative project, Subprograma de Proyectos Singulares y Estratégicos, Programa Nacional de Cooperación Público-Privada, Ministerio de Ciencia e Innovación

Main objective: identification of new drug targets for combating Alzheimer's disease, as well as hit compounds against these targets



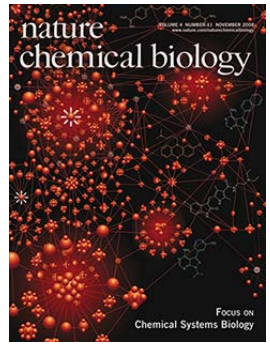
PPI-based target discovery

structure determination

virtual screening

experimental validation

current knowledge
extension (comp & exp)
modelling (AI) & query



Our virtual screening approach

Library of compounds

Chemical DataBase Manager (CDBM), Xavier Barril, UB

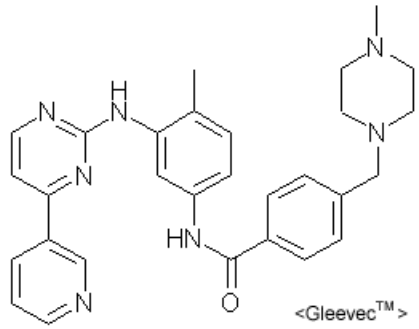
Compounds commercially available from different vendors

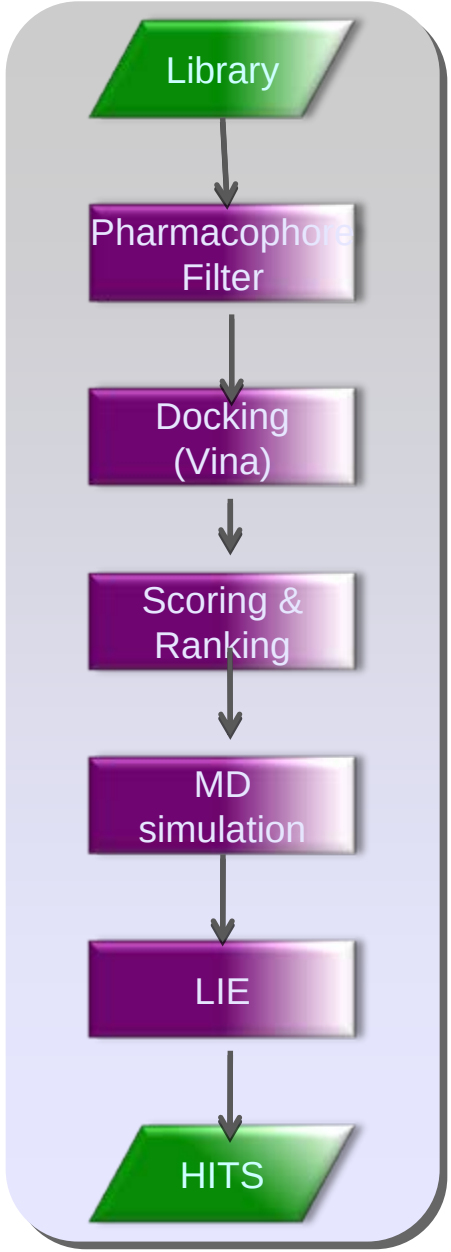
Molecular states and three-dimensional conformations generated with LigPrep, which enumerates tautomers, ionization states and, when the chirality is not specified, stereo-isomers

3D structure energy-minimized with the OPLS force-field

Filtered according to availability in the collections, Lipinski and Veber rules, no reactive moieties (toxicity) and a maximum of 4 conformational states considered

Over $2x10^6$ compounds

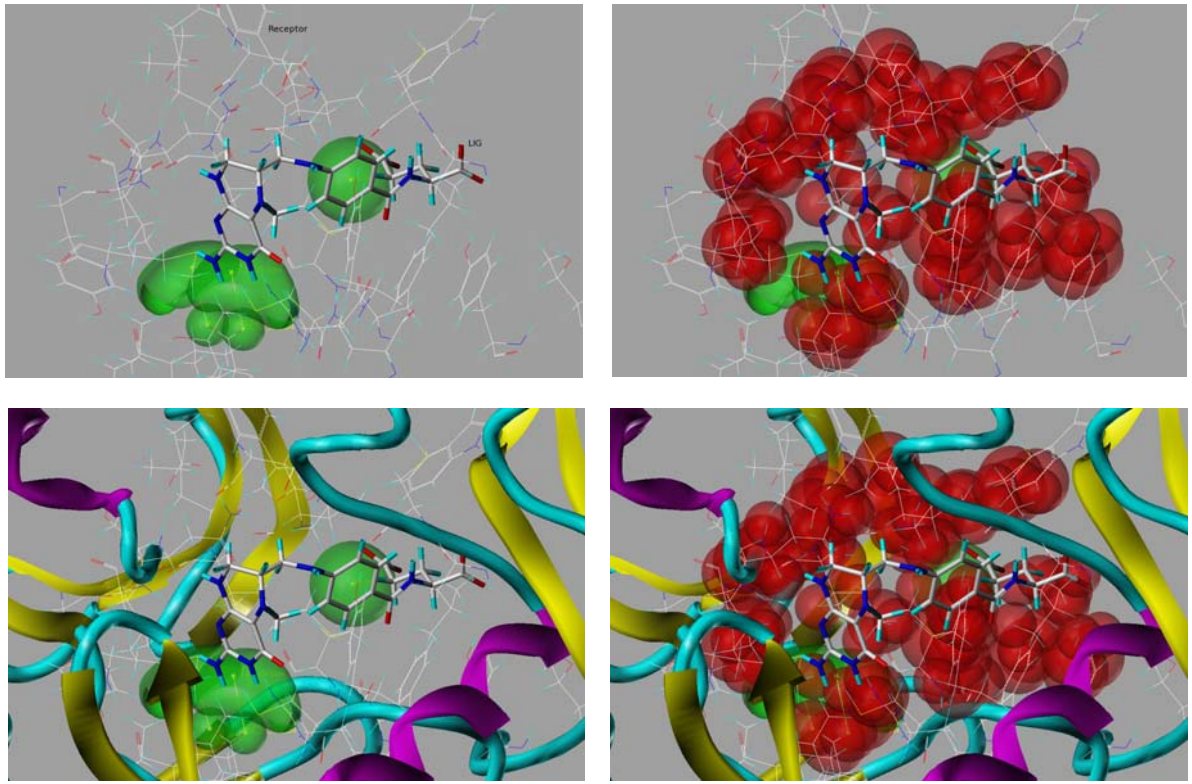


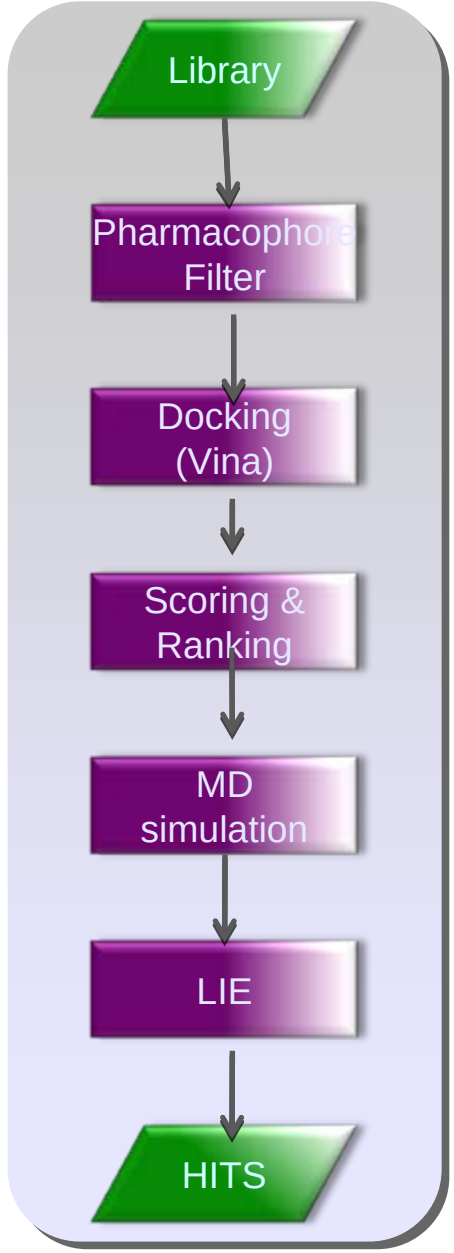


Our virtual screening approach

Pharmacophore

Ensemble of steric and electronic features that are necessary to ensure the optimal molecular interactions with a specific biological target and to trigger (or block) its biological response



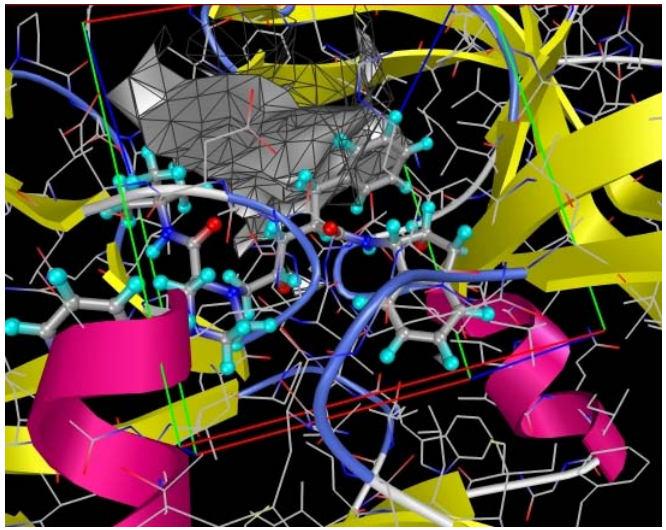


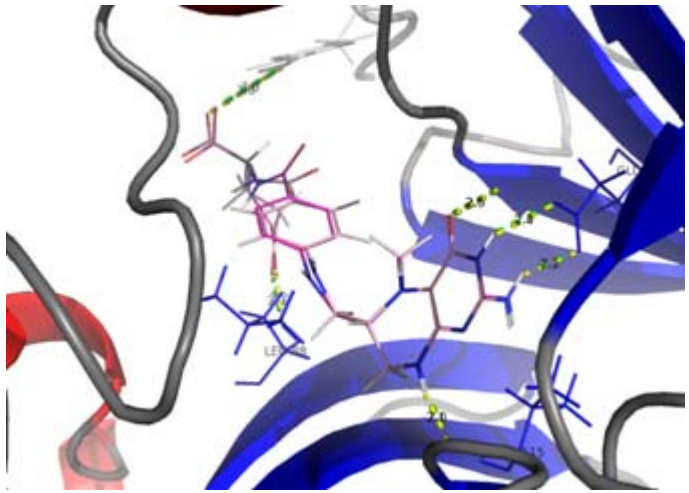
Our virtual screening approach

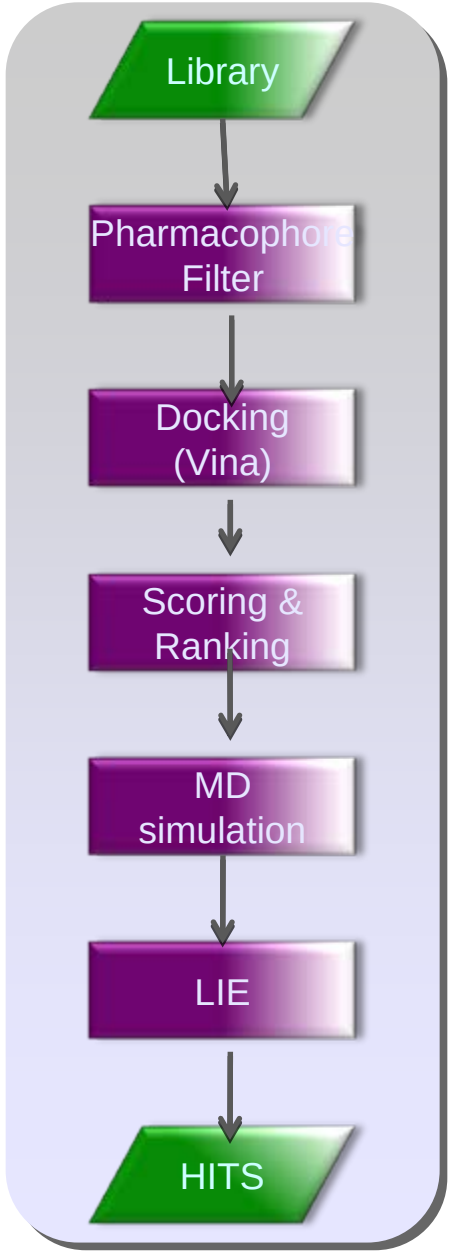
Docking with AutoDock Vina

Scoring with Vina + CSCORE (G-Score, PMF-Score, D-Score and ChemScore)

Ranking and selection of the best 5000

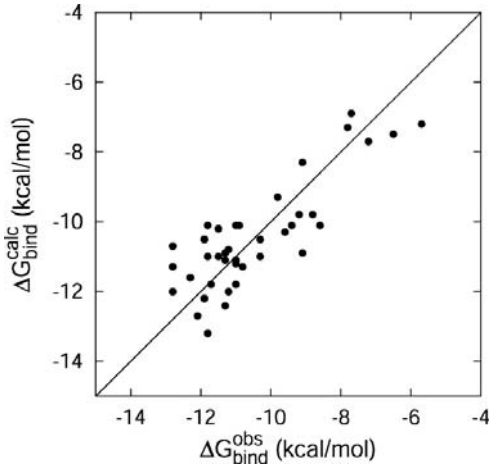






AutoDock Vina: Trott & Olson. J Comput Chem 2010, 31: 455

The Linear Interaction Energy (LIE) approach



$$\Delta G_{bind}^{LIE} = \alpha\Delta\left\langle U_{l-s}^{vdW}\right\rangle + \underbrace{\beta\Delta\left\langle U_{l-s}^{el}\right\rangle}_{\text{linear response approximation}} + \gamma$$

$$\left.\begin{aligned}\Delta\Delta G_{sol}^{np} &= a\sigma + b\\ \Delta\left\langle U_{l-s}^{vdW}\right\rangle &= c\sigma + d\end{aligned}\right\} \Delta\Delta G_{sol}^{np} = \frac{a}{c}\left(\Delta\left\langle U_{l-s}^{vdW}\right\rangle - d\right) + b = \alpha\Delta\left\langle U_{l-s}^{vdW}\right\rangle + \gamma$$

Parameterisation based on experimental binding free energies:

α = 0.18 : "universal", includes all size-dependent contributions to ligand binding

γ : protein dependent, correlates with the hydrophobicity of the binding-site pocket

β = 0.5 : derived from linear response approximation (but dependent on the chemical nature of the ligand)

Hansson T, et al. J Comput-Aided Mol Design 1998, 12: 27
Carlsson et al. J Med Chem 2008, 51: 2648

Molecular dynamics simulation

Principle: Δt : time step in the simulation (typically $2 \times 10^{-15} s$)

$\mathbf{r}_{i,n}$: coordinates of atom i at time $t_n = n\Delta t$

$\mathbf{v}_{i,n}$: velocity of atom i at time $t_n = n\Delta t$

$$\mathbf{r}_{i,n}, \mathbf{v}_{i,n} \xrightarrow{\Delta t} \mathbf{r}_{i,n+1}, \mathbf{v}_{i,n+1}$$

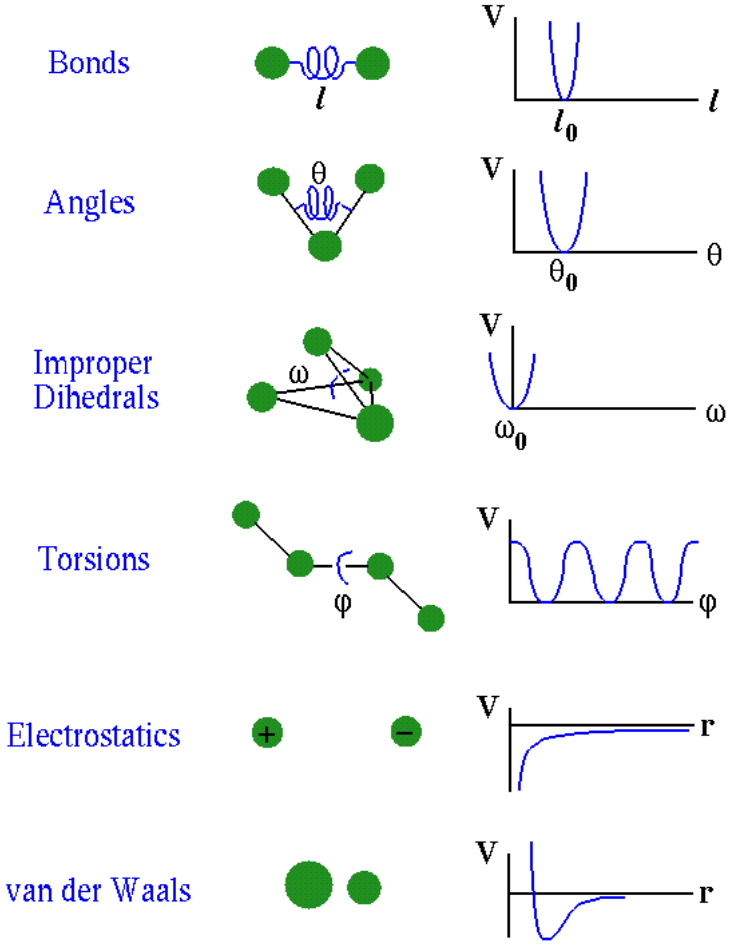
$$\left.\begin{aligned} \frac{d\mathbf{r}_i}{dt} &= \mathbf{v}_i \\ \frac{d^2\mathbf{r}_i}{dt^2} &= \frac{\mathbf{F}_i}{m_i} \end{aligned}\right\}$$ Newton's equations of motion

$$\mathbf{F}_i = -\frac{\partial V}{\partial \mathbf{r}_i}$$

$\left(\mathbf{r}_0, \mathbf{v}_0, t = 0\right), \left(\mathbf{r}_1, \mathbf{v}_1, t = \Delta t\right), \text{K}, \left(\mathbf{r}_m, \mathbf{v}_m, t = m\Delta t\right) \rightarrow$ trajectory of the system

Biomolecular simulation: $m\Delta t = 10^{-8} - 10^{-5} s$

Biomolecular model and force field



$$V(\mathbf{r}) =$$

$$V^{\text{bonds}}(\mathbf{r}) + V^{\text{angles}}(\mathbf{r}) +$$

$$V^{\text{improper dihedrals}}(\mathbf{r}) + V^{\text{torsional dihedrals}}(\mathbf{r}) +$$

$$V^{\text{van der Waals}}(\mathbf{r}) + V^{\text{electrostatic}}(\mathbf{r}) =$$

$$\sum_{n=1}^{N_b} \frac{1}{2} K_n^b \left[b_n - b_n^0 \right]^2 + \sum_{n=1}^{N_\theta} \frac{1}{2} K_n^\theta \left[\theta_n - \theta_n^0 \right]^2 +$$

$$\sum_{n=1}^{N_\xi} \frac{1}{2} K_n^\xi \left[\xi_n - \xi_n^0 \right]^2 + \sum_{n=1}^{N_\phi} k_n^\phi \left[1 + \cos\left(m_n \phi_n - \delta_n \right) \right] +$$

$$\sum_{i<j} \left[\frac{C12_{ij}}{r_{ij}^{12}} - \frac{C6_{ij}}{r_{ij}^{6}} + \frac{1}{4\pi\varepsilon_0\varepsilon_r} \frac{q_i q_j}{r_{ij}} \right]$$

Our virtual screening approach

5000 compounds per target protein
2 proteins
2 simulations per compound ($2x10^4$ simulations):
- ligand-protein + water
- ligand + water

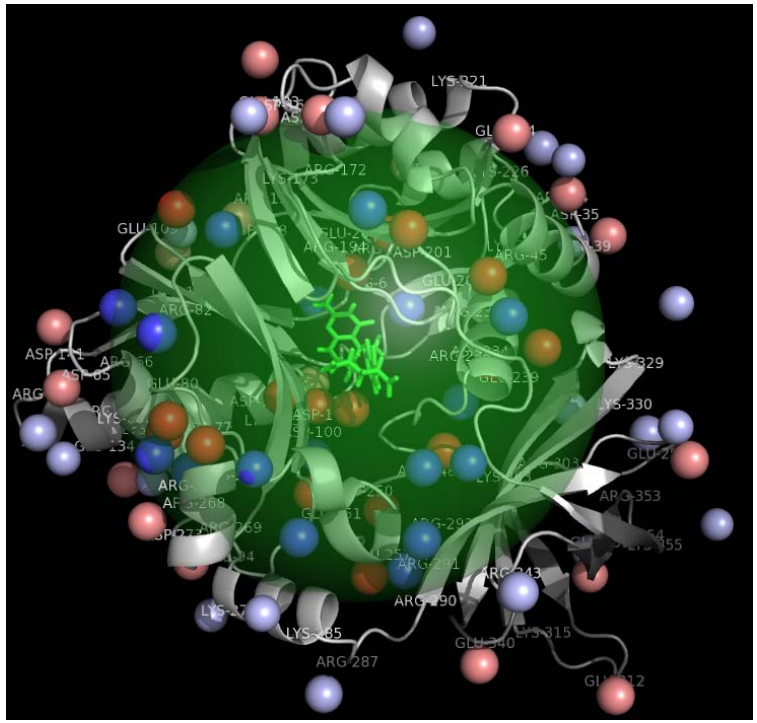
1CPU: 50h / compound

ICTS-CESGA

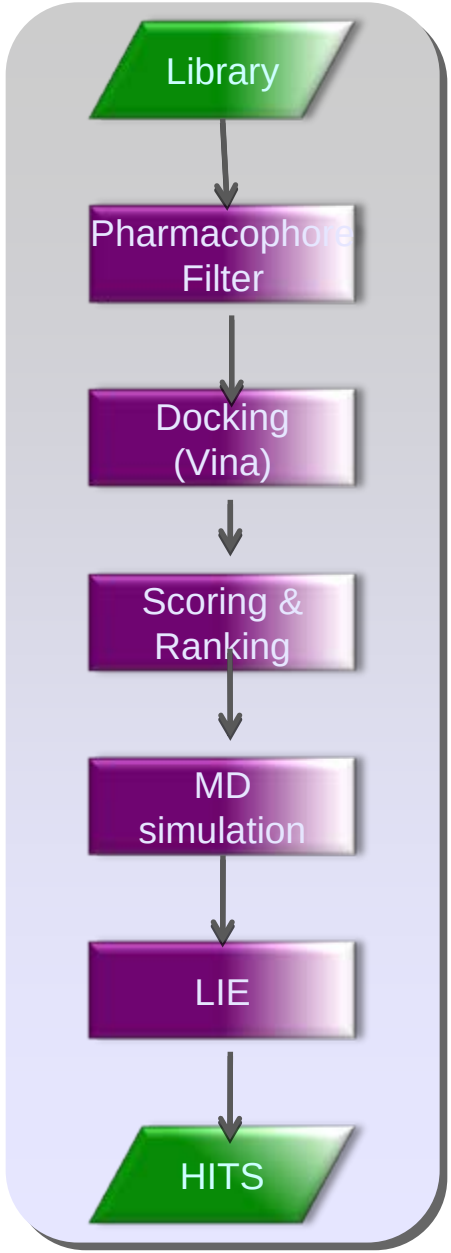
Simulations with Q
OPLS-AA force field
Spherical boundary conditions
T = 310 K
500 ps per simulation

Current status:
1st target: done
2nd target: 3000 compounds

1st HTS with MD



Q: Marelius et al. J Mol Graph Model 1998, 16: 213
OPLS: Jorgensen et al. JACS 1996, 118: 11225



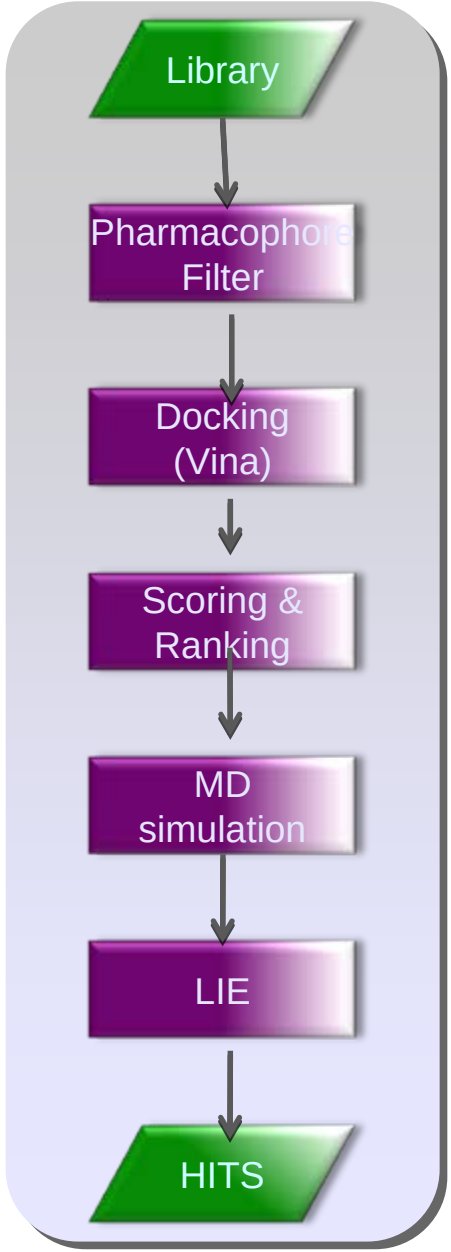
Our virtual screening approach

$$\Delta G_{bind}^{LIE} - \gamma = \alpha\left[\left\langle U_{l-p+w}^{vdW}\right\rangle - \left\langle U_{l+w}^{vdW}\right\rangle\right] + \beta\left[\left\langle U_{l-p+w}^{el}\right\rangle - \left\langle U_{l+w}^{el}\right\rangle\right]$$

Ranking of the $\Delta G_{bind}^{LIE} - \gamma$ calculated for the 5000 compounds

Clustering according to chemical and structural similarity

Experimental testing of 50-100 compounds



Acknowledgements

Oscar Conchillo (UAB)
Hugo Gutiérrez de Terán (USC)

Xavier Barril (UB)

José Manuel Mas (RPS Research Iberica)
Patrick Aloy (IRB)
Baldomero Oliva (UPF)
Xavier Gomis-Rüth (CSIC)

Personal de soporte de CESGA (Aurelio, Alejandro, Pablo, ...)