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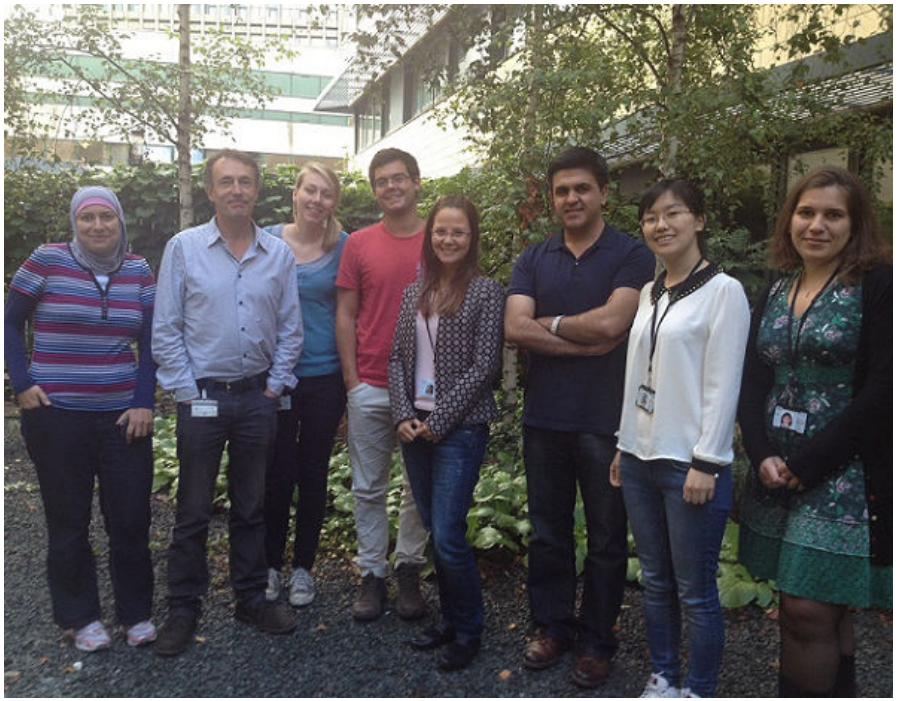
Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Receptor Sampling with dpEDMD for Virtual Screening

Ramon Goñi, PhD

SO Mobility Grant

The University of Nottingham



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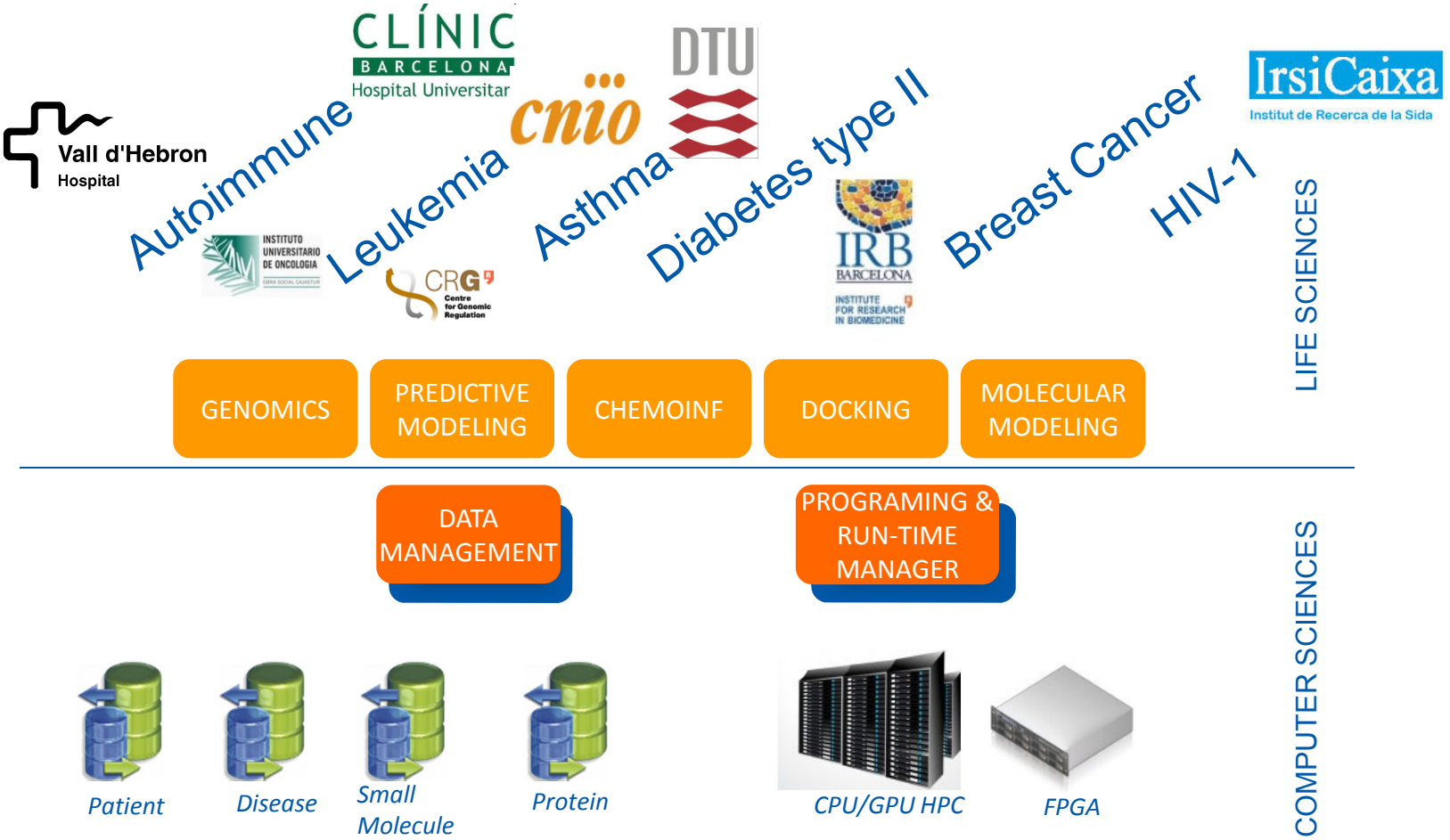
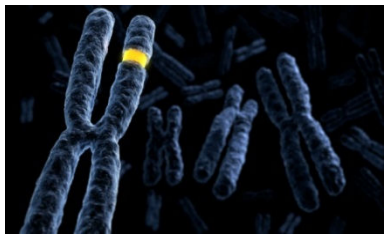
Severo Ochoa - Personalized medicine

- A new framework oriented to support research on personalized medicine has been designed



APPLICATION Workflows



Genotype

Phenotype

SNP Association

Predictive Modeling

Diagnosticate/ Prognosticate

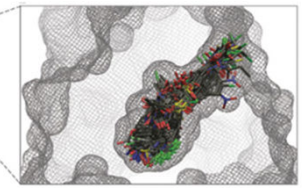
Predict Drug Resistance

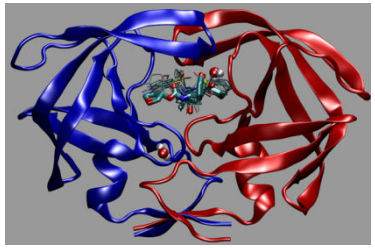
QSAR* Model

Prepare Screening Library

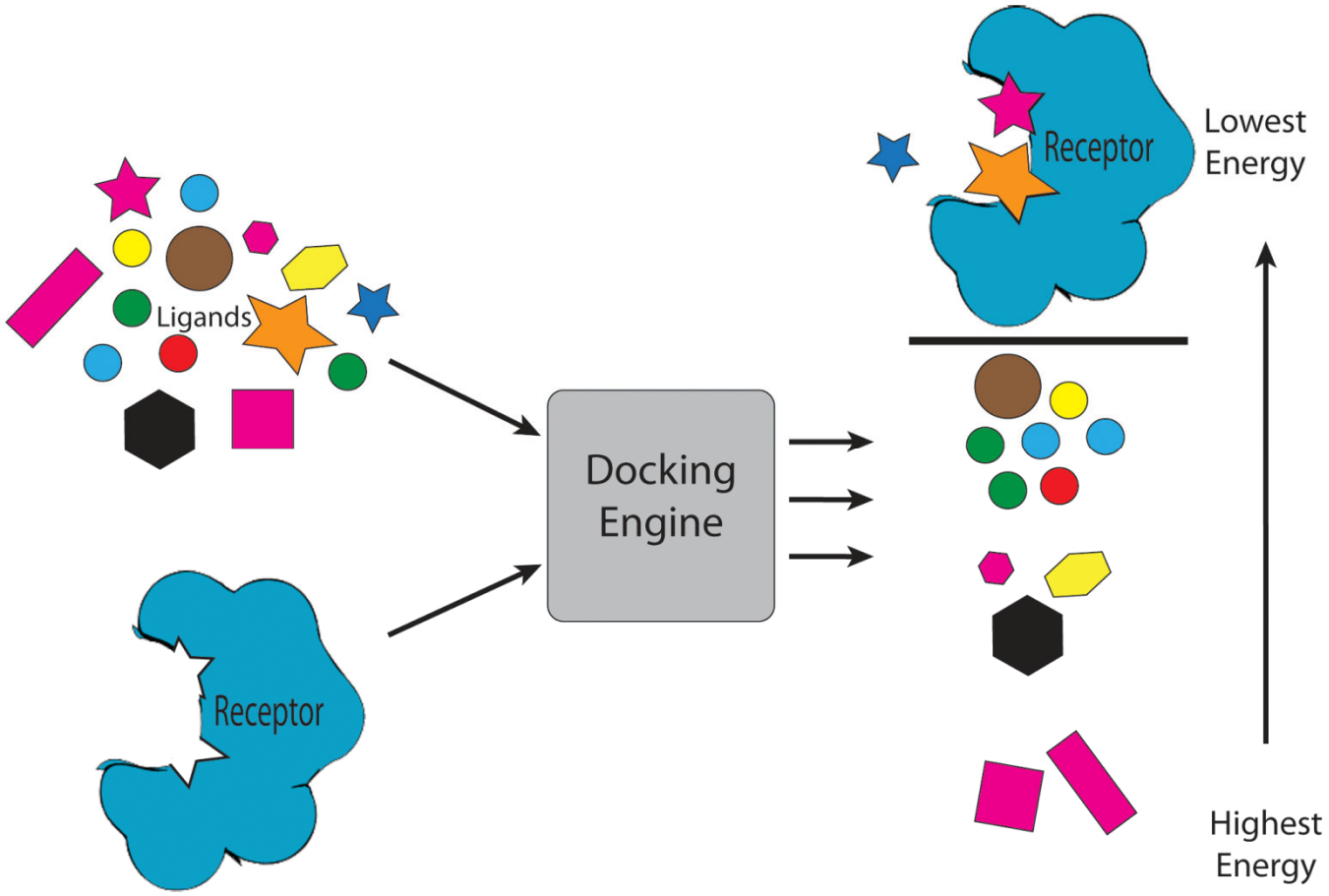
Lead Discovery

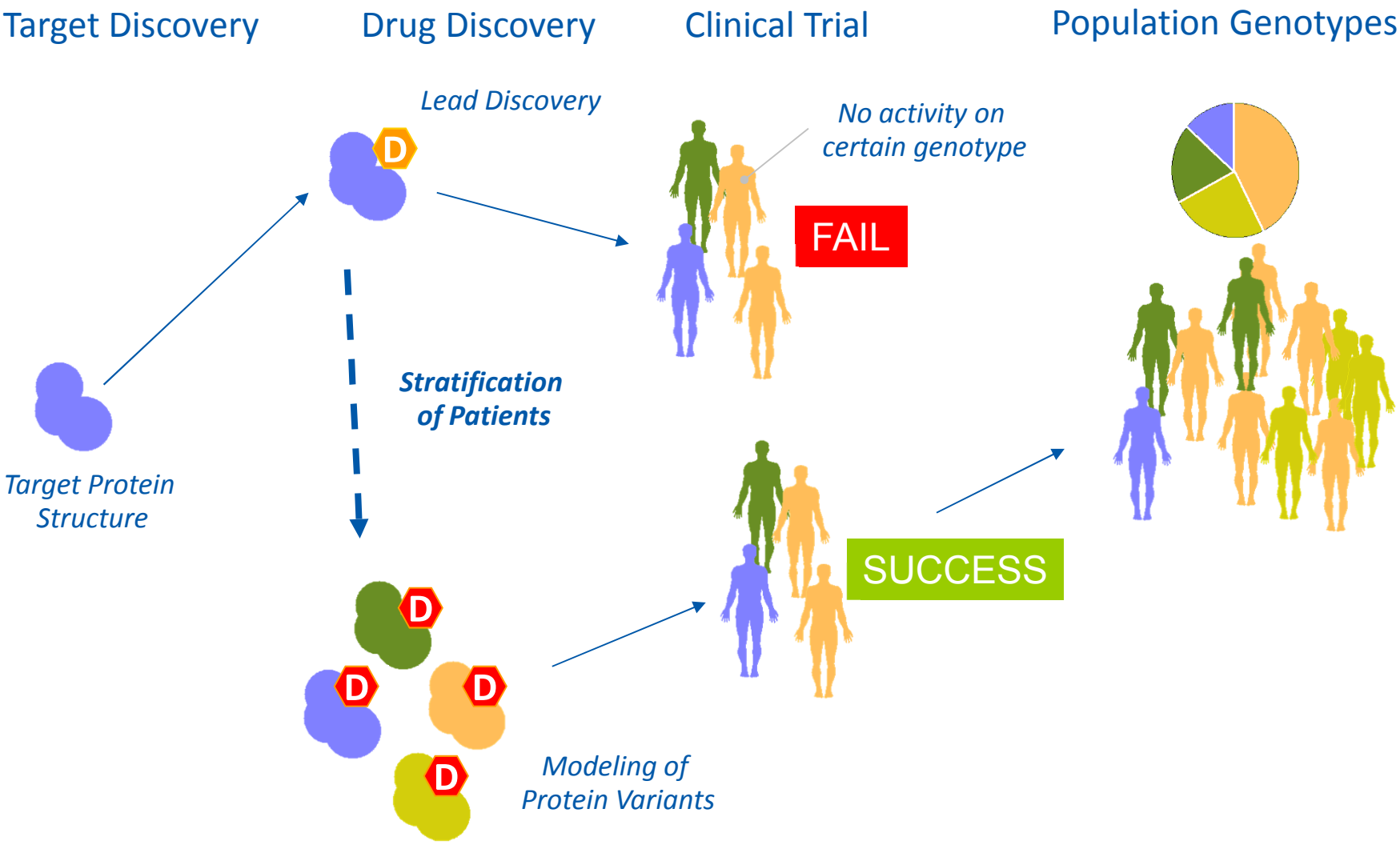
Drug Repositioning





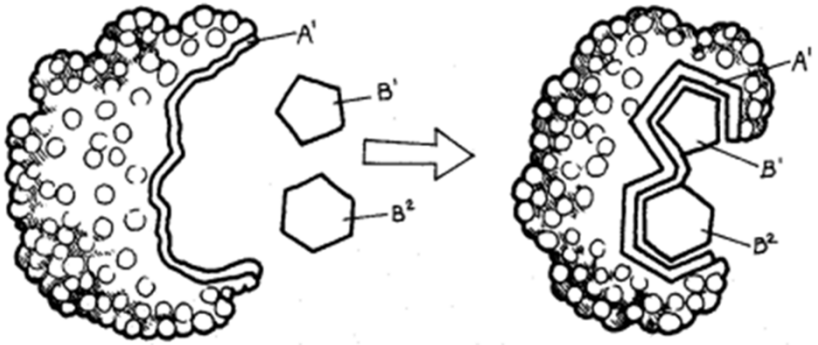
Structure-based Drug Design




Target Discovery
Drug Discovery
Clinical Trial
Population Genotypes
Lead Discovery
No activity on certain genotype
FAIL
Stratification of Patients
Target Protein Structure
SUCCESS
Modeling of Protein Variants

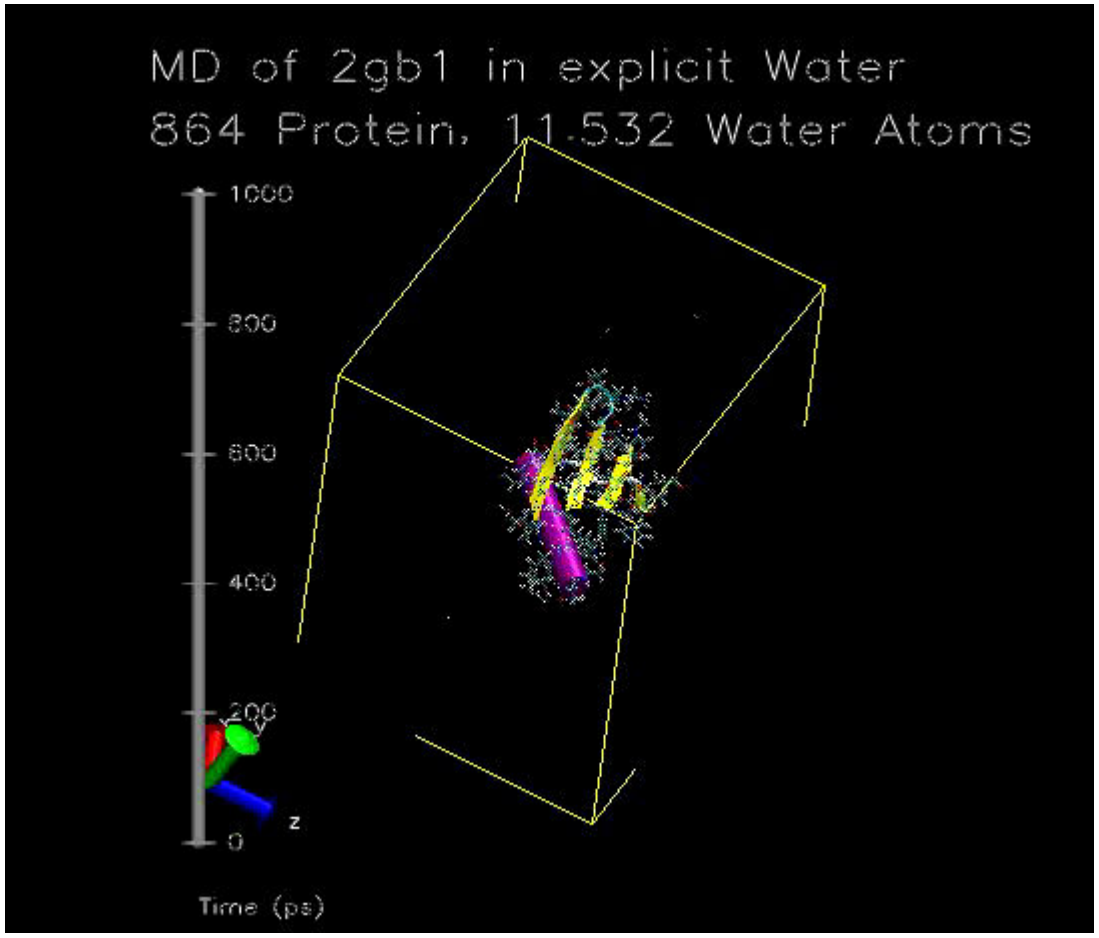
Flexible docking

- Receptors are not rigid structures and we need their flexibility and deformation patterns



- There are numerous techniques that can be applied, amongst which molecular dynamics (MD) is widely regarded as the most rigorous and powerful one

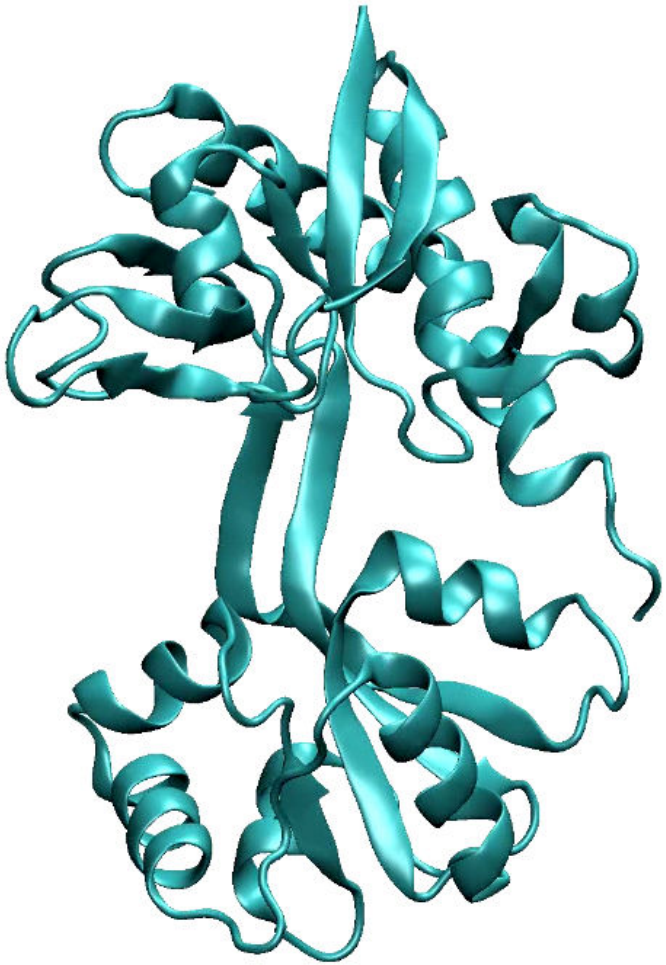
Molecular Dynamics of Solvated Protein



- Step every femtosecond (10^{-15}s)
- System of 10^4 atoms (small)
- 100 operations per atom pair-mate
- Size of the system
  - Typically: 10^4 - 10^5 particles
  - Flagship: 10^7
- Simulation length (10^4 particles)
  - Typically: 10^2 ns
  - Using HPC: μs
  - Using Anthon: ms

Unfortunately MD computational cost is not affordable to explore more few compounds

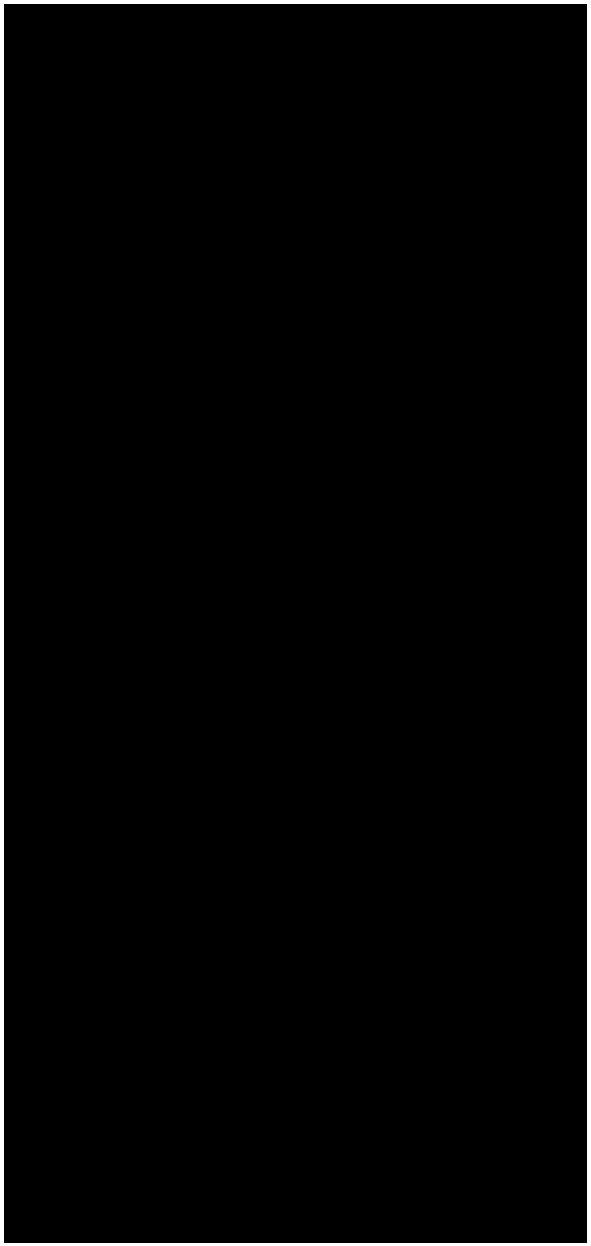
Essential Dynamics / Molecular Dynamics



eigenvector1

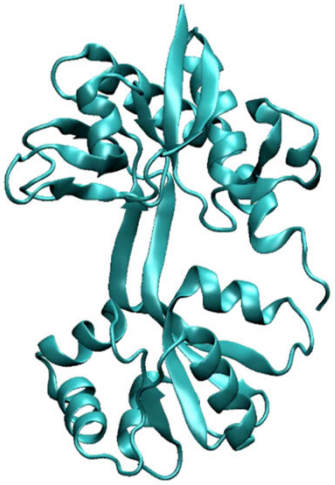
eigenvector2

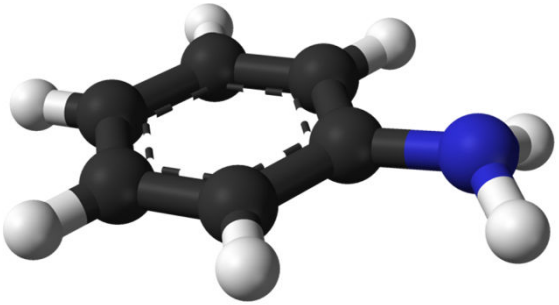
eigenvector3



Drug perturbed EDMD (dpEDMD)

- User has full control of the desired level of resolution of the trajectory



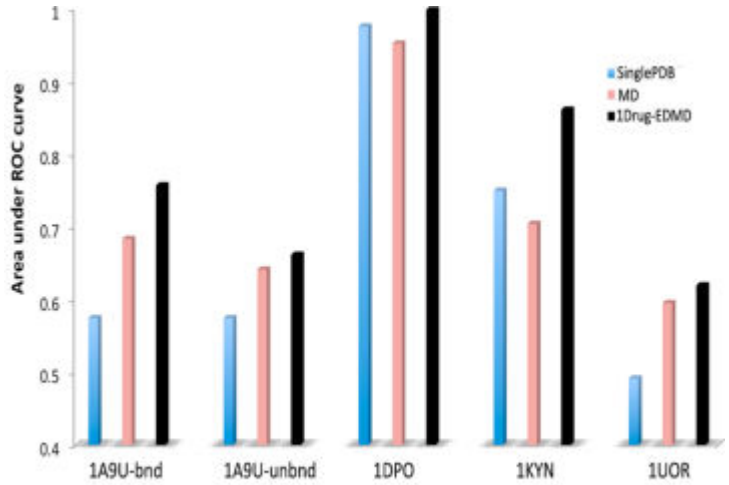


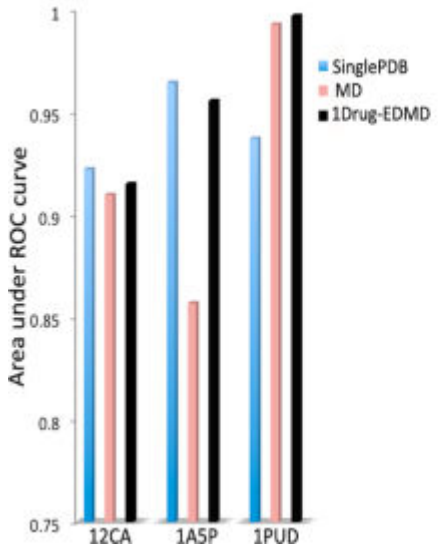
$$\vec{F}_i^{(M)} = -\sum_{k=1}^{M} \frac{k_B T e_k^i}{\lambda_k} \left(\Delta\vec{r} \cdot \hat{e}_i\right) + \vec{F}_i^*$$

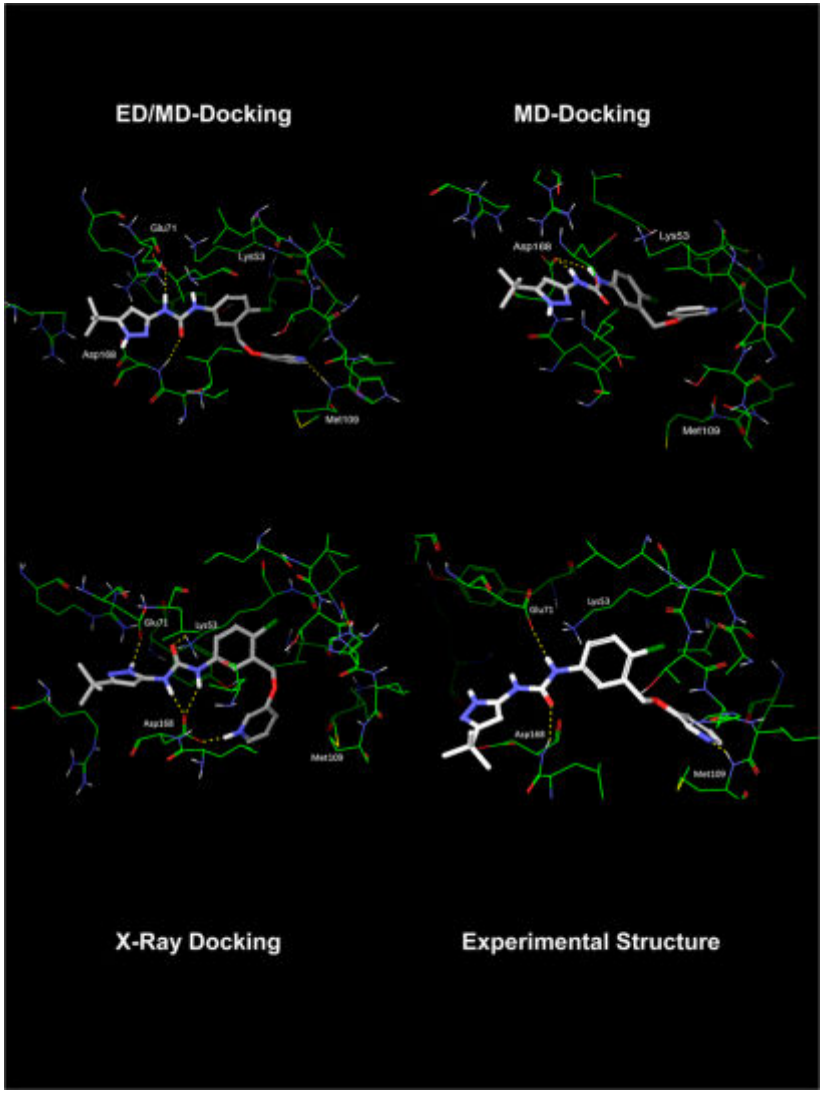
Carrillo et al. 2012 JCTC

- Hybrid Hamiltonian, partly projected in the essential dynamics space and partly in normal Cartesian space, allowing a very fast calculation of the dynamics of macromolecules and complexes.

Virtual Screening using dpED/MD

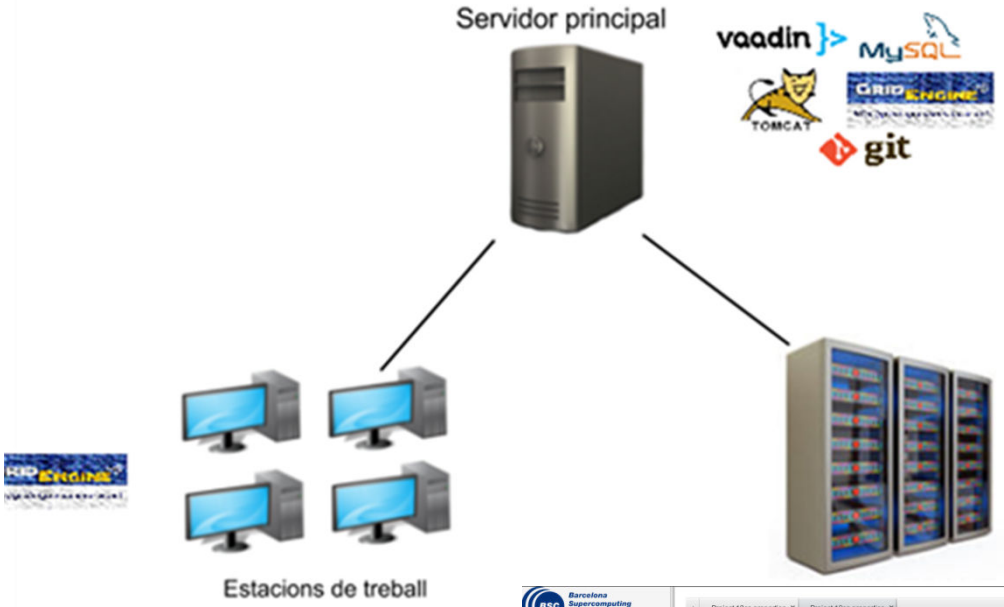




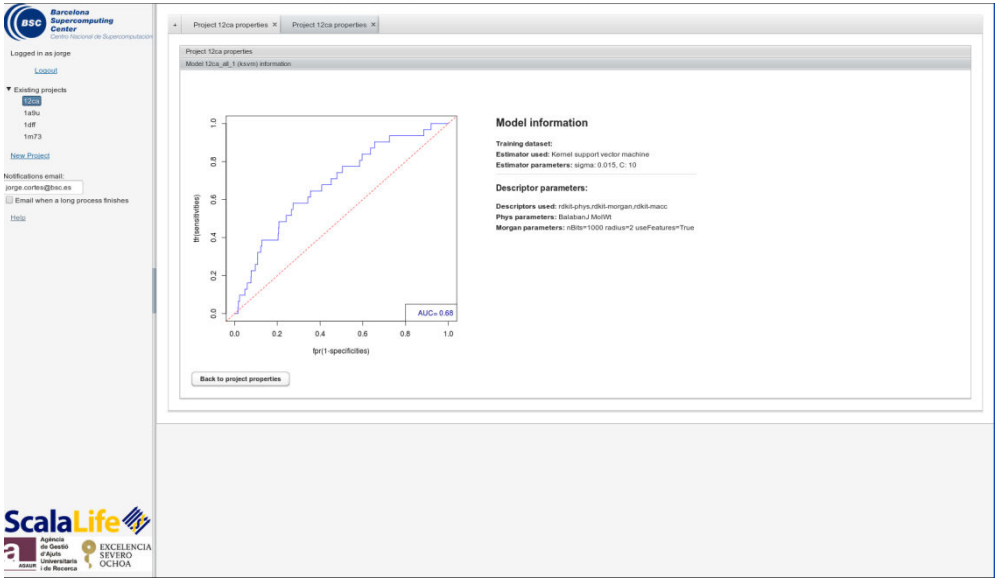


Chaudhuri et al. 2012 JCTC

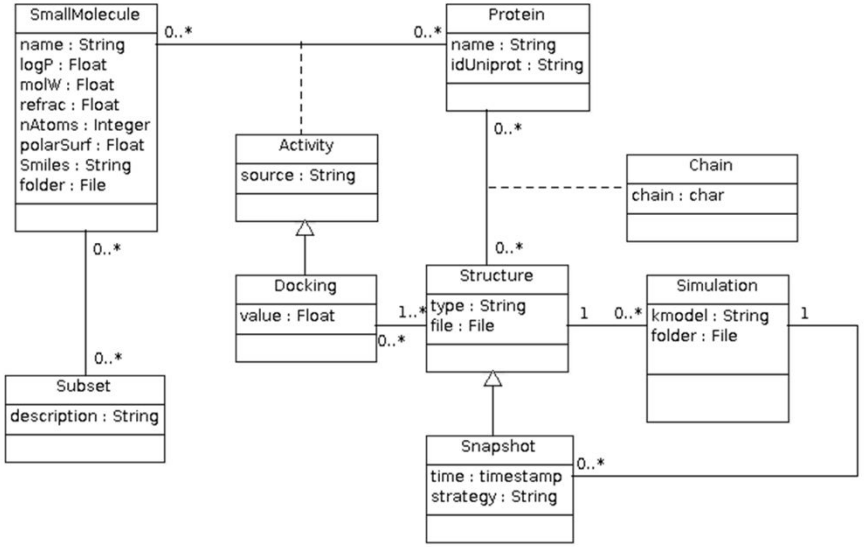
Automatic set-up for Virtual Screening with dpED/MD



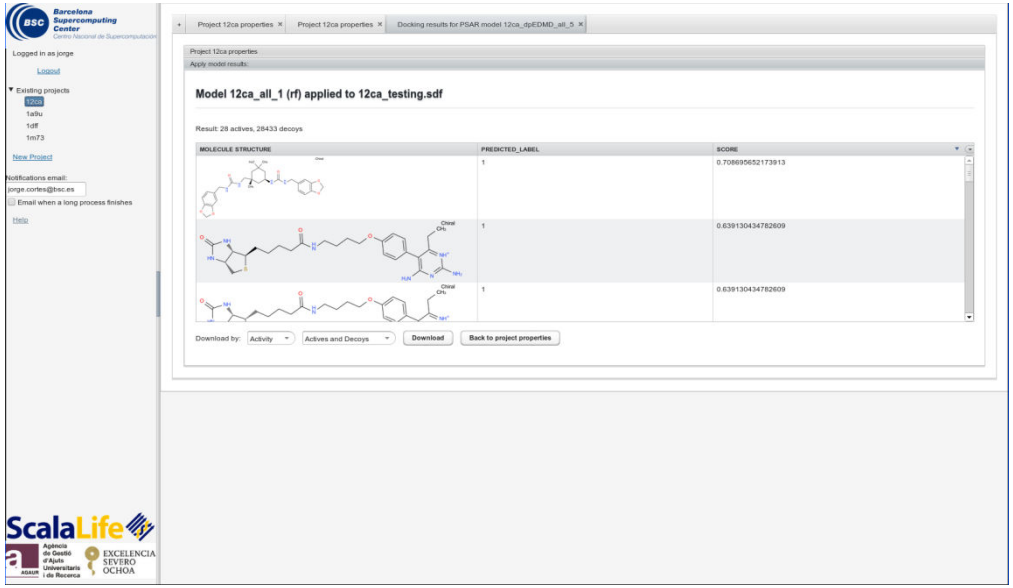
Python APIs
Wrappers for 3rd party code
Reengineering
x10 dpEDMD code
(not parallelized)



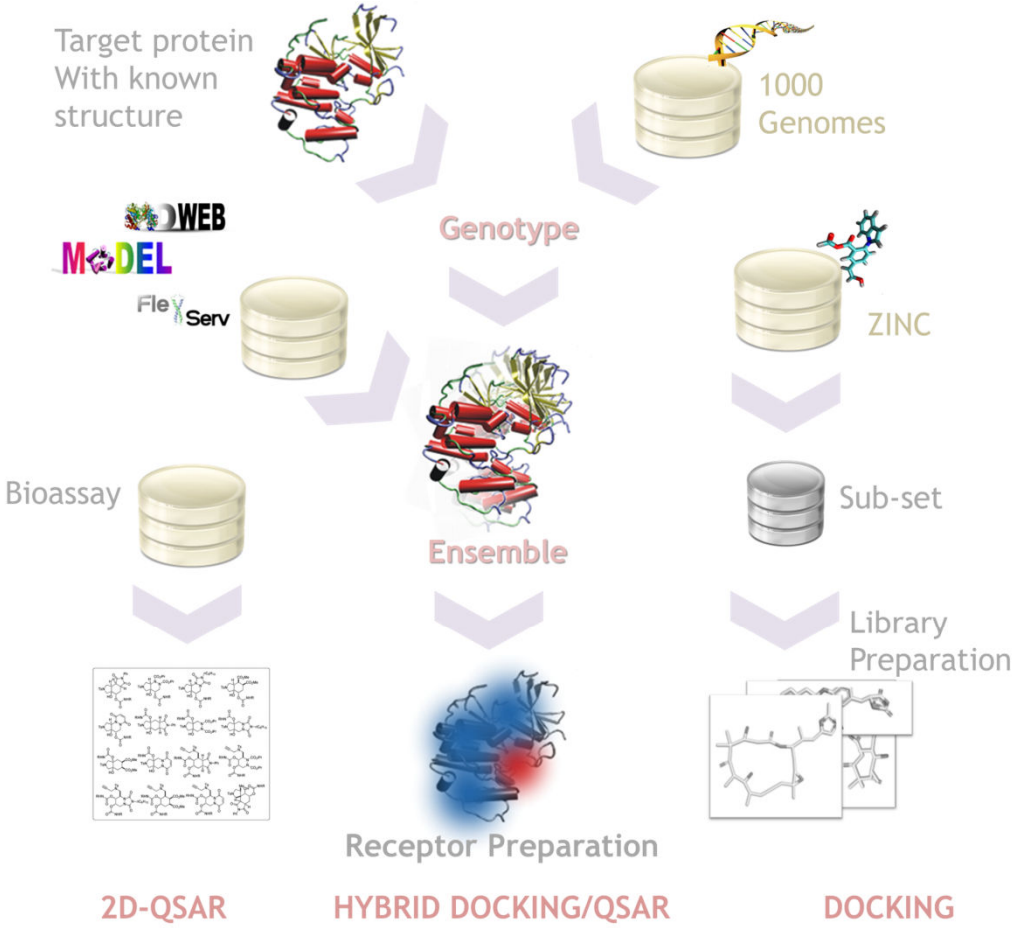
Data Handling

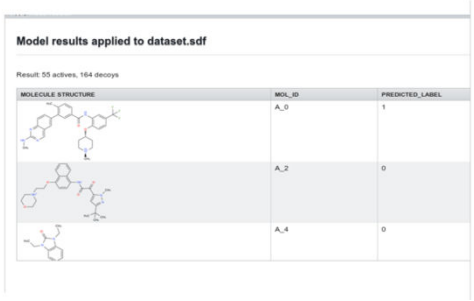


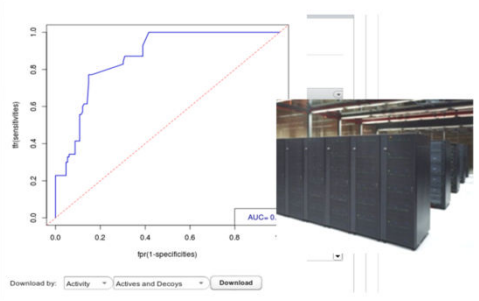
SQL Diagram (Trajectories in file system)



Hybrid structure-based / ligand-based VS







Acknowledgements

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