Grid-enabled drug discovery to address neglected diseases

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WISDOM : Wide In Silico Docking On Malaria

Scientific objectives

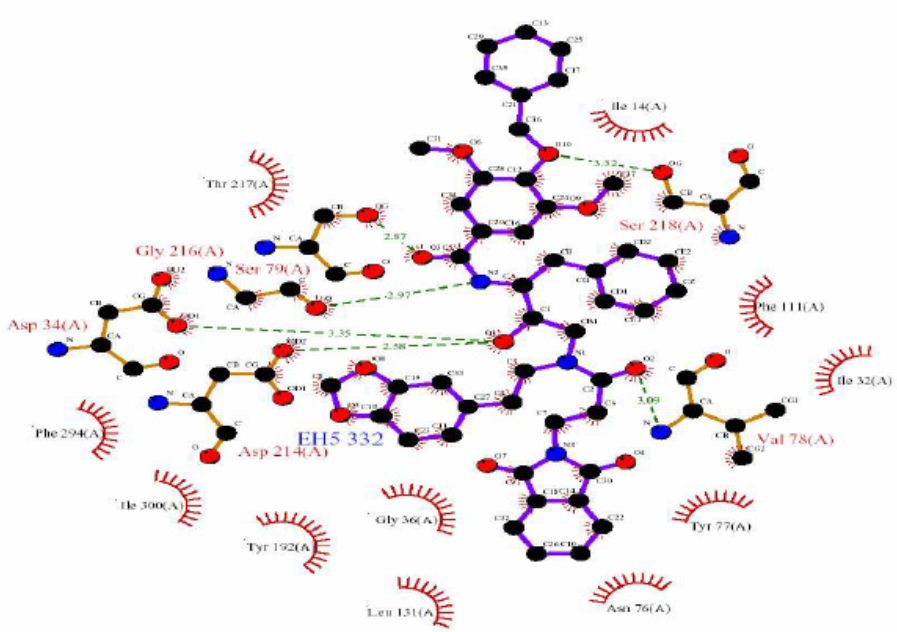
Demonstrate to the research communities active in the area of drug discovery the relevance of grid infrastructures

Deployment of a CPU consuming application generating large data flows to test the grid infrastructure and services of the BioMed VO.

Method

- Large scale molecular docking on malaria target
  to test million of compounds with
  several docking softwares.

- Docking is about scoring the potential binding
  of a protein target to a library of
  compounds



Goals of the Data Challenge (DC) on *in silico* drug discovery

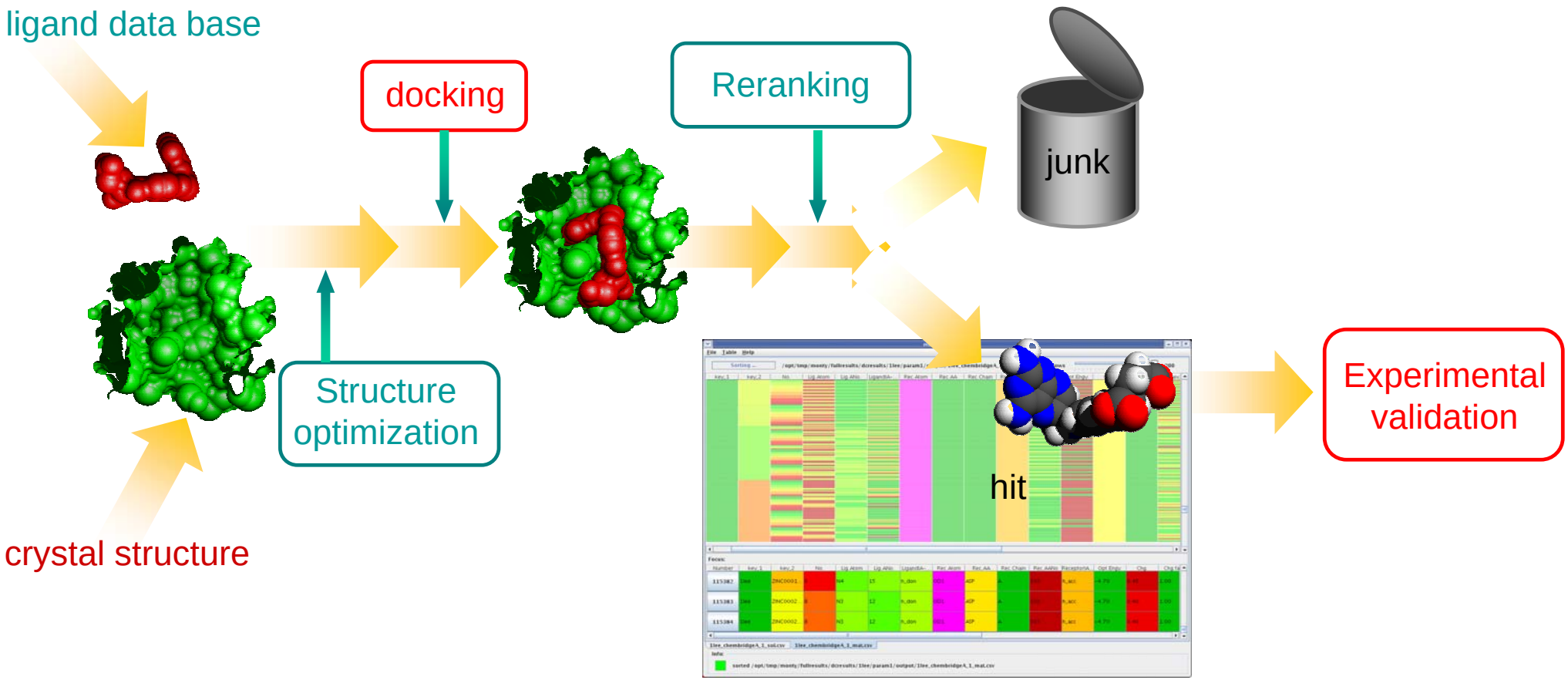
Biological Goal : proposition of new drug candidates addressed to neglected diseases

- The target : *Plasmepsin* is a promising aspartic protease target involved in the hemoglobin degradation of *P. falciparum*. 5 different structures are prepared
- The compounds database : *ZINC* is an open source library of 3,3 millions selected compounds. They are made available by chemistry companies

Biomedical informatics goal : deployment of *in silico* virtual screening on the grid

- The software : *Autodock* is an open source algorithm, *FlexX* is a commercial algorithm available for this data challenge during 3 weeks

Dataflow and workflow in a virtual screening



Success with virtual screening

Dihydrofolate reductase inhibitor (1992)

HIV-protease (1992)

Phospholypase A2 (1994)

FKBP-12 (1995)

Thrombine (1996)

Abl-SH3 (1996)

Trypsine, streptavidine, phosphrylase nucleotid

ex : virtual screening of the trypsine, 2h of computing : 153 compounds, 2 inhibitors

Overview on neglected diseases

Infectious diseases kill 14 million people each year, more than 90% of whom are in the developing world.

Access to treatment is problematic

- the medicines are unaffordable,
- some have become ineffective due to drug resistance,
- and others are not appropriately adapted to specific local conditions and constraints.

Drug discovery for a neglected disease

Lack of ongoing or well coordinated R&D

- Research often takes place in university or government labs
- Development is almost exclusively done by the pharmaceutical and biotech industry
- Critical point is the launching of clinical trials for promising candidate drugs.

Producing more drugs for neglected diseases requires

- building a focussed, disease-specific R&D agenda including short-, mid- and long-term projects.
- a public-private partnership through efficient, secure and trusted collaborations that aim to improve access to drugs and stimulate discovery of easy-to-use, affordable, effective drugs.

Virtual organisation

Motivate and gather together :

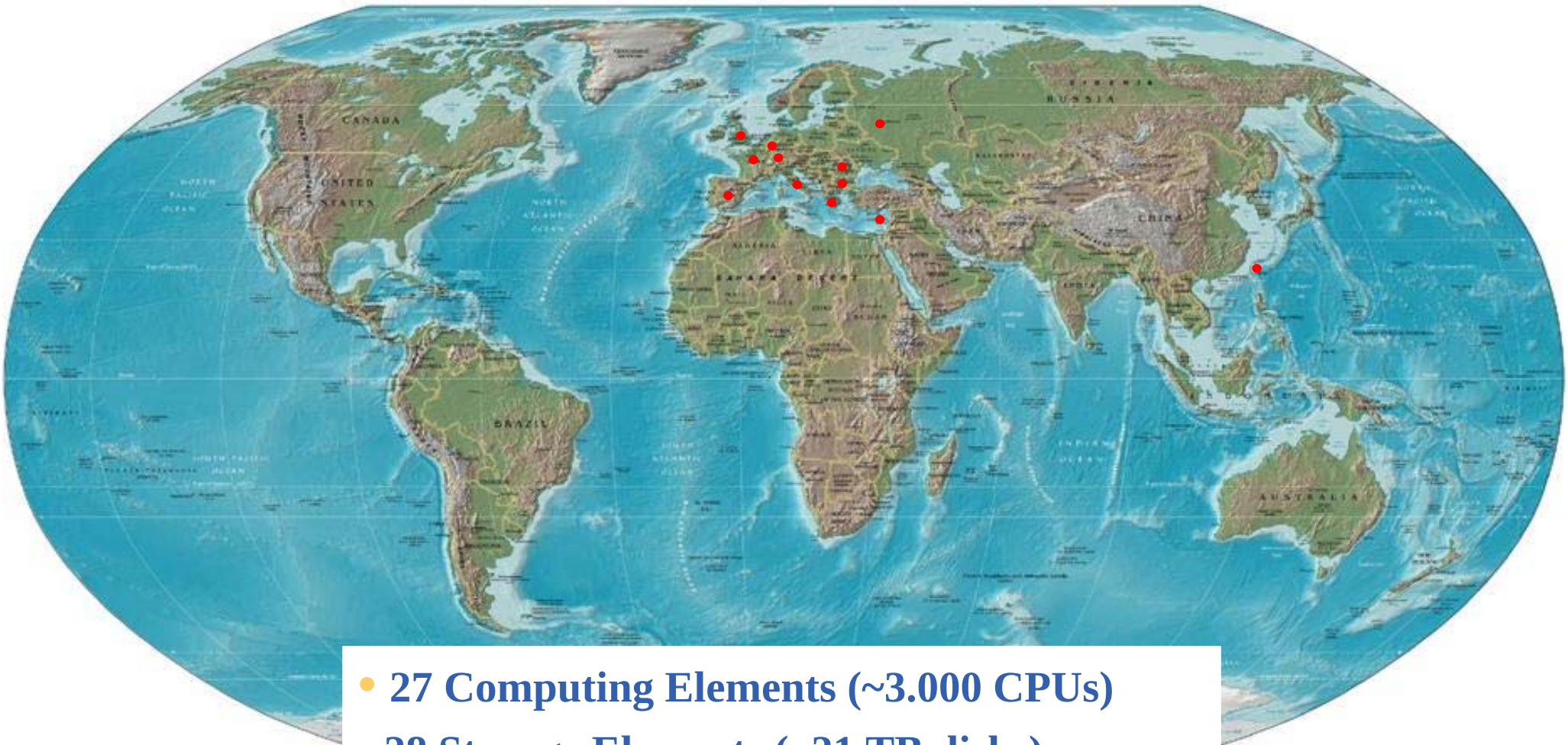
- drug designers to identify new targets and drugs
- healthcare centers involved in clinical tests and collecting patent information
- healthcare centers collecting patent information
- organizations involved in distributing existing treatments
- informatics technology developers
- computing and computer science centers
- biomedical laboratories working on vaccines, genomes of the virus and/or the parasite and/or the parasite vector

Collaborative environment

A PharmaGrid will support such processes as:

- search of new drug targets through post-genomics requiring data management and computing
- massive docking to search for new drugs requiring high performance computing and data storage
- handling of clinical tests and patient data requiring data storage and management
- overseeing the distribution of the existing drugs requiring data storage and management
- trusted exchange of IP, possibly auction-mediated

The BioMed VO at a glance



- 27 Computing Elements (~3.000 CPUs)
- 28 Storage Elements (~21 TB disks)
- in 12 countries

Selection criteria of potential drugs

Potential drugs

- 28 million compounds currently known
- Drug company biologists screen up to 1 million compounds against target using ultra-high throughput technology

- Chemists select 50-100 compounds for follow-up
- Chemists work on these compounds, developing new, more potent compounds

- Pharmacologists test compounds for pharmacokinetic and toxicological profiles
- 1-2 compounds are selected as potential drugs

Target

- Well known organism
- Multiple crystal structures
- Multiple bound inhibitors
- Structural similarity between
- multiple species

Inhibitors

- The one more selective
- Acts on multiple targets
- The one with active in low quantities
- Shows good pharmacokinetics properties
- Good pharmacodynamic properties

Data challenge scenario

	Scenario
Duration	28 days
CPU time	11 years CPU
Grid performance	50%
Max number of CPU used	1,008
Number of grid jobs (20h)	12,215
Storage	2*6 TB
Docking workflow description	
Number of software / targets / compounds / parameters settings	2 / 5+3 / 500,000 / 4 = **32 mio dockings**
Objective	Selection of the best hits with short analysis

FlexX running time : 1 mn
F. output size : 1MB
F. job output size : 1.2GB
F. job compressed output size : 250MB

Autodock running time : 2.5 mn
A. output size : 1MB
A. job output size : 0,5GB
A. job compressed output size : 100MB

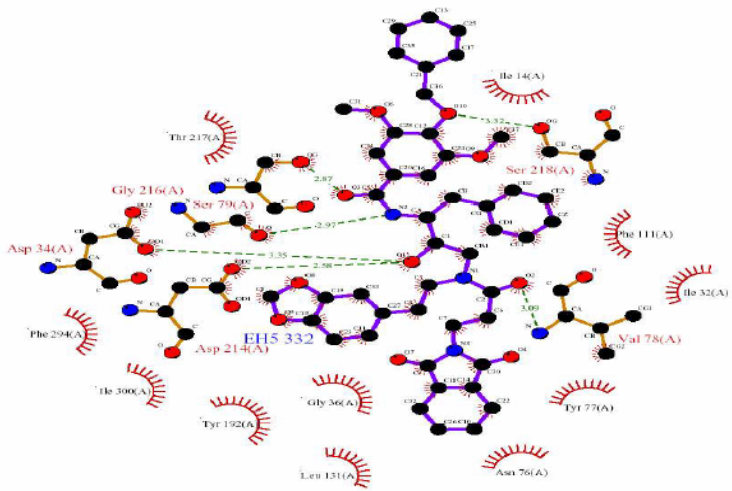
Output analysis

Ranked scoring lists:

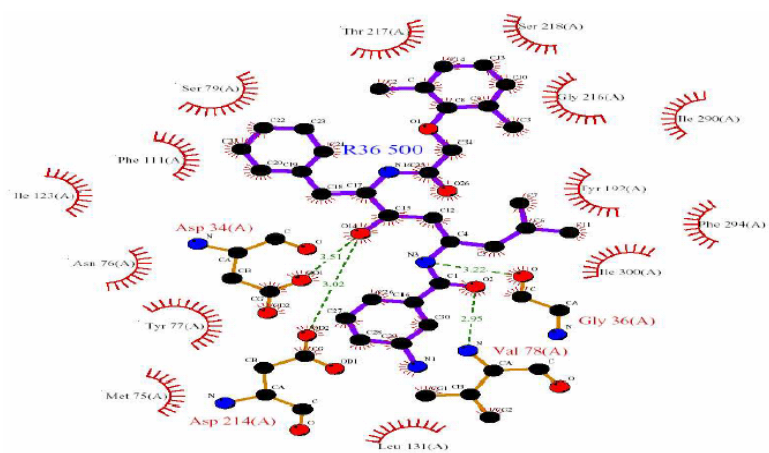
- Sorting and assembly of data from the Grid
- Offline post filtering
- Clustering of similar conformations
- Doing statistics on the score distribution
- Checking pharmacophoric points of each conformation
- Re-ranking for interesting compounds

Comparing:

- Tools
- Parameters
- Targets (and water molecules)
- Ligand scaffolds

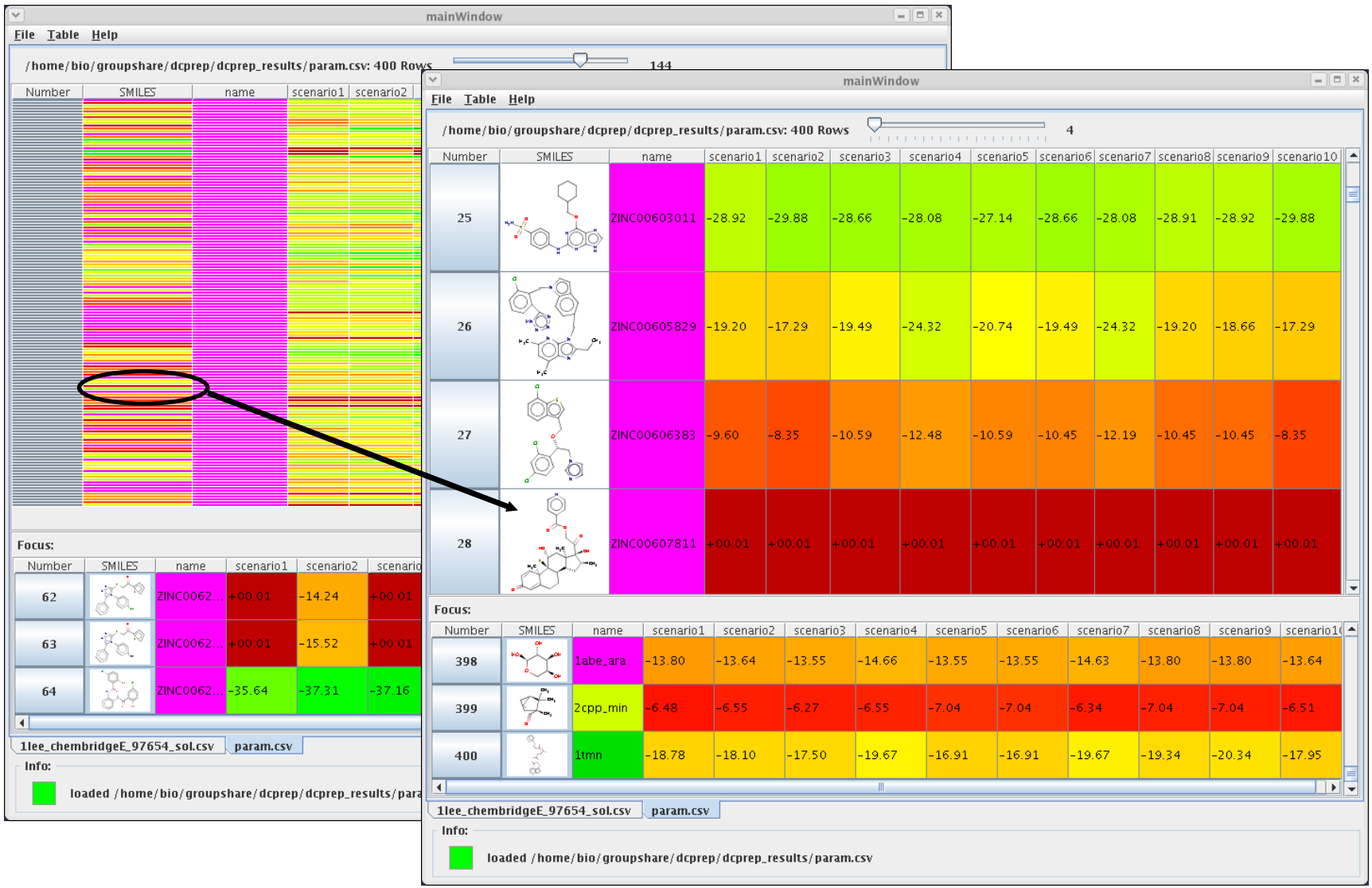


Ligand plot of 1LF3 with inhibitor EH5 332



Ligand plot of 1LEE with inhibitor R36 500

VS Explorer as tool for gridscale ranking lists



Follow-up of the DC

The best hits found by post-treatment will be published and available on a permanent grid storage via a portal

A knowledge space will be progressively build around these results
- to extract and process the most interesting information
- to enrich the data with the results found later by other *in silico* drug discovery processes

Next scenarios will be able to use the gLite middleware

The *in silico* drug discovery will be further extend
- to include more precise molecular dynamics computations using quantum chemistry software like NAMD

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