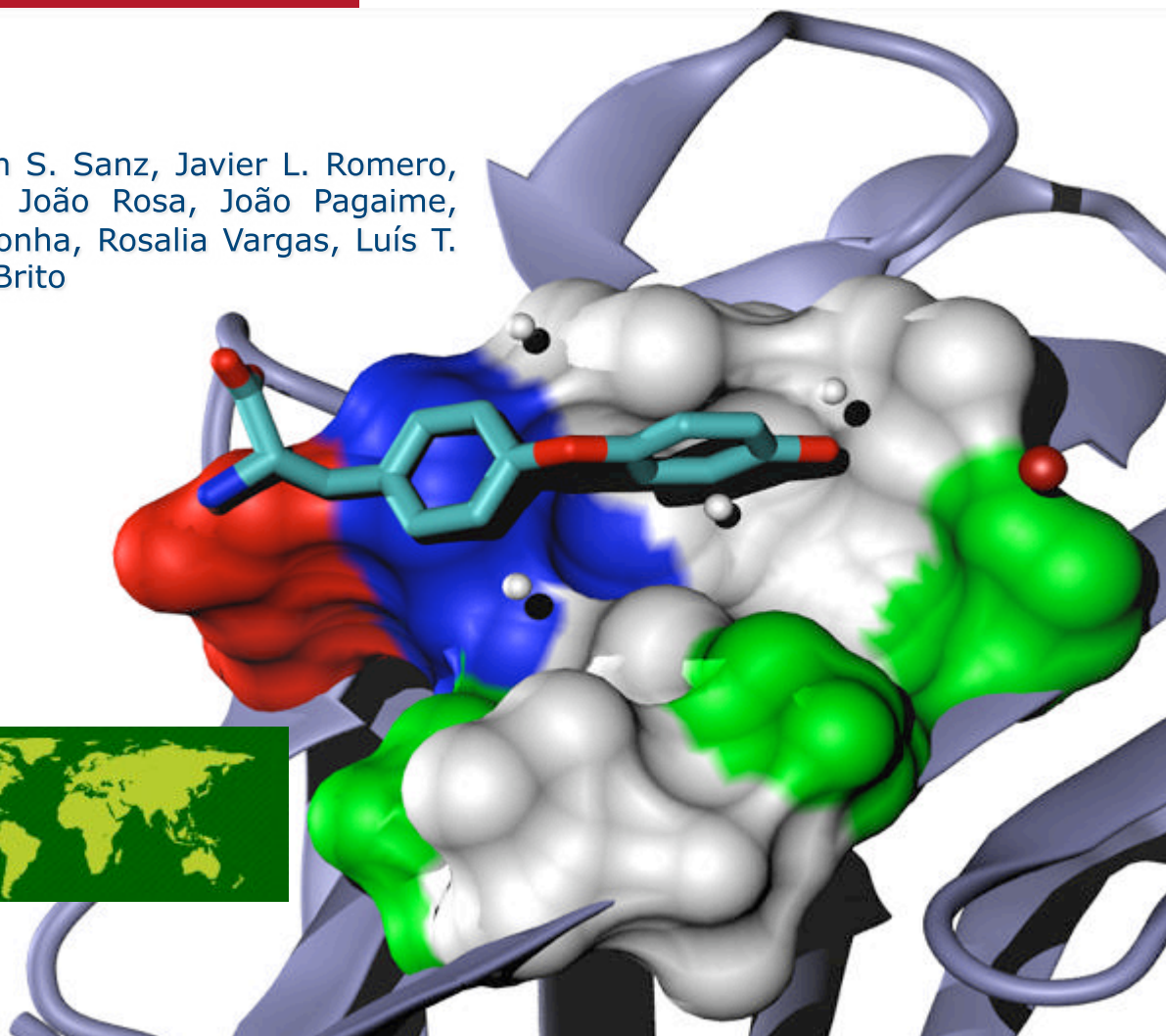


Running faster and further together: The AMILOIDE project, the onset of the Portuguese participation on the IBERCIVIS volunteer computing network

Carlos J. V. Simões

Alejandro Rivero, Alfonso Tarancón, Fermín S. Sanz, Javier L. Romero, Pedro Abreu, Carlos Manuel, Rui Durão, João Rosa, João Pagaime, Pedro Veiga, Richard M. Jackson, Ana Noronha, Rosalia Vargas, Luís T. Magalhães, Gaspar Barreira and Rui M. M. Brito



Running faster and further together

A volunteer computing network for the Iberian peninsula and beyond

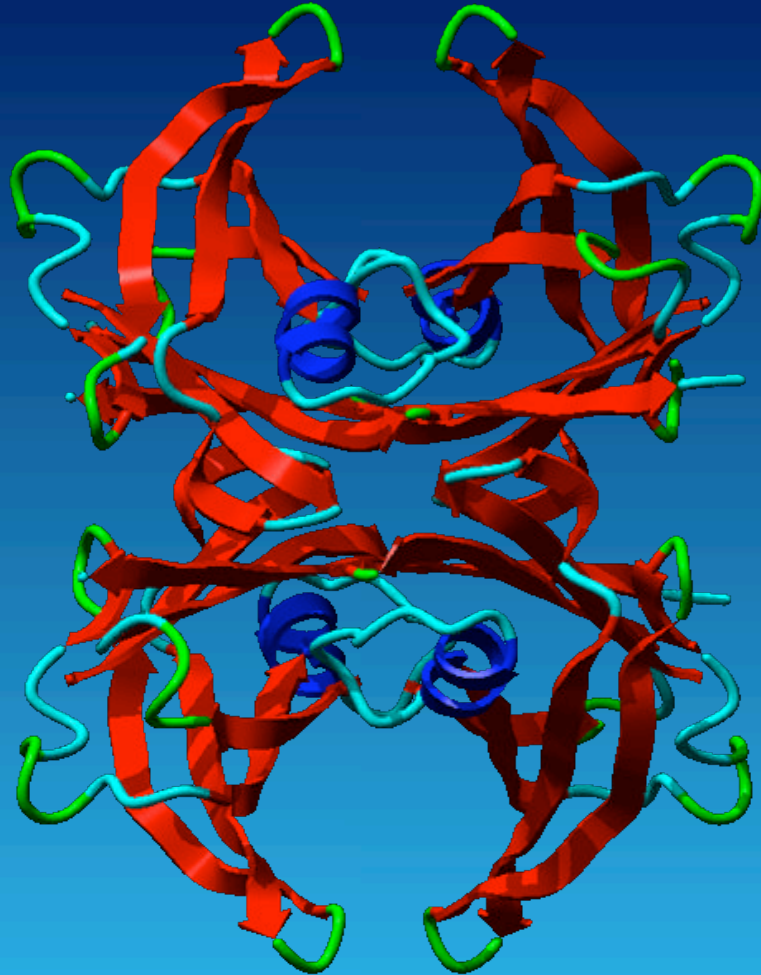
Amyloid Research and Virtual Screening: the Science behind the Tech

AMILOIDE: the onset of the Portuguese participation on IBERCIVIS

Science and Society: mind the gap

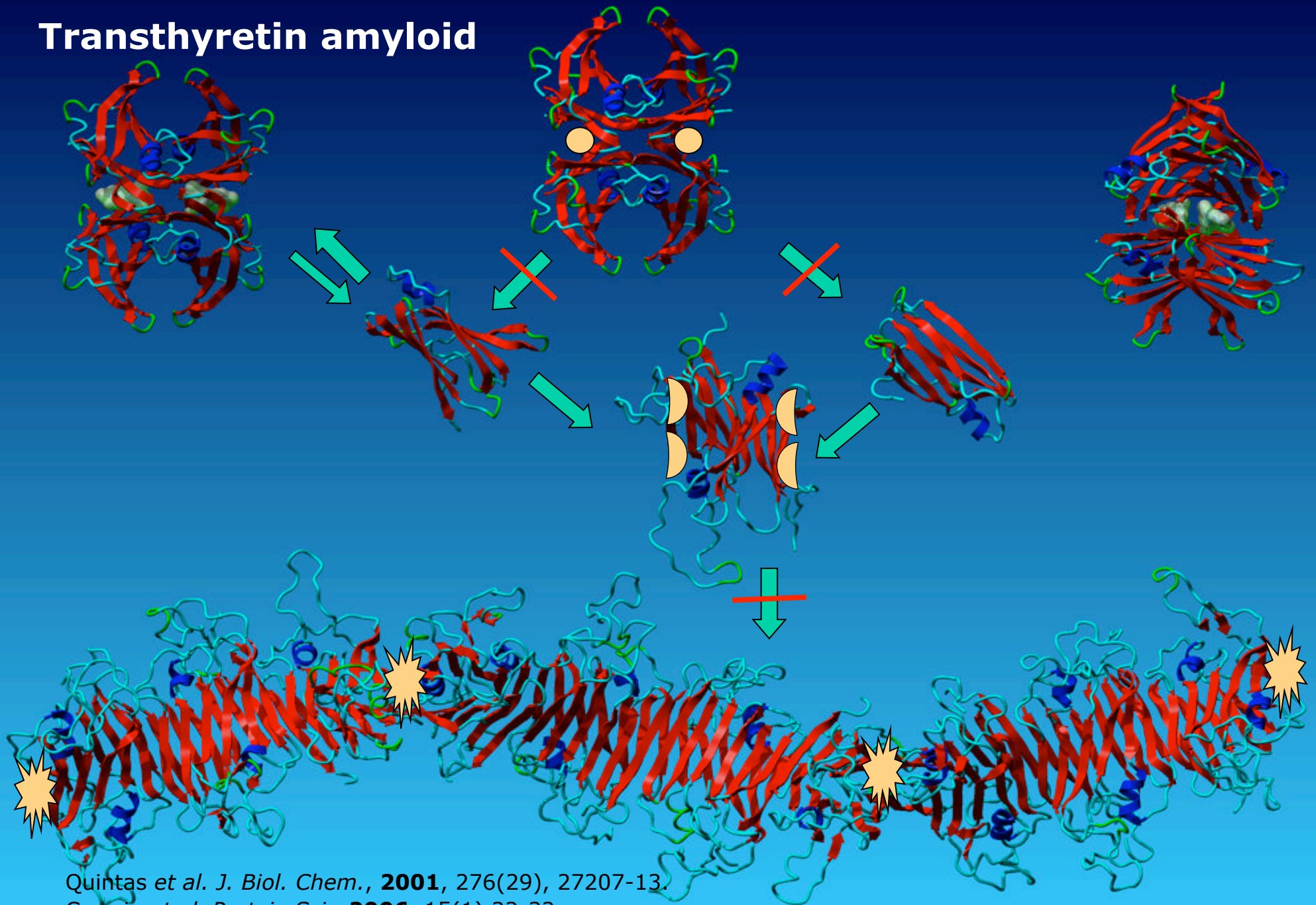
Transthyretin (TTR)

A case study



- ✧ **Production sites**
 - ✦ Liver
 - ✦ Brain choroid plexus
 - ✦ Eye
- ✧ **Pathological involvement**
 - ✦ Familial Amyloid Polyneuropathy
 - ✦ Senile Systemic Amyloidosis
- ✧ **Structural features**
 - ✦ Homotetrameric protein
 - ✦ MW 55 kDa
 - ✦ 127 amino acids per monomer
 - ✦ 2 binding pockets
 - ✦ Mostly beta-sheet
- ✧ **Structural information**
 - ✦ > 100 PDB entries for "Transthyretin"
 - ✦ > 42 complexes
 - ✦ 35 complexes with resolution < 2 Å
 - ✦ 28 complexes for "Human"

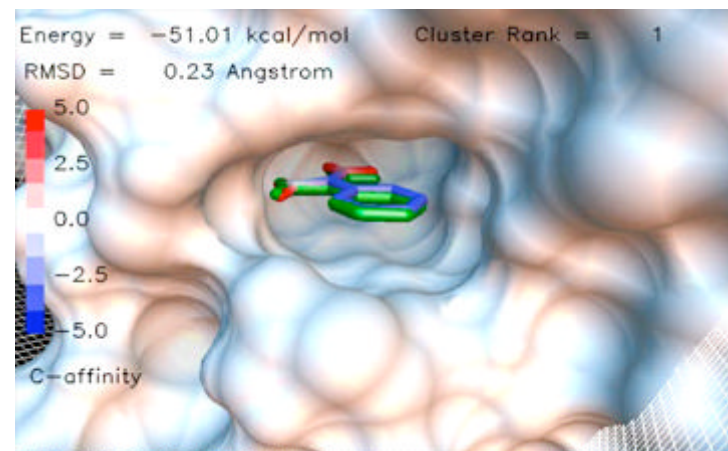
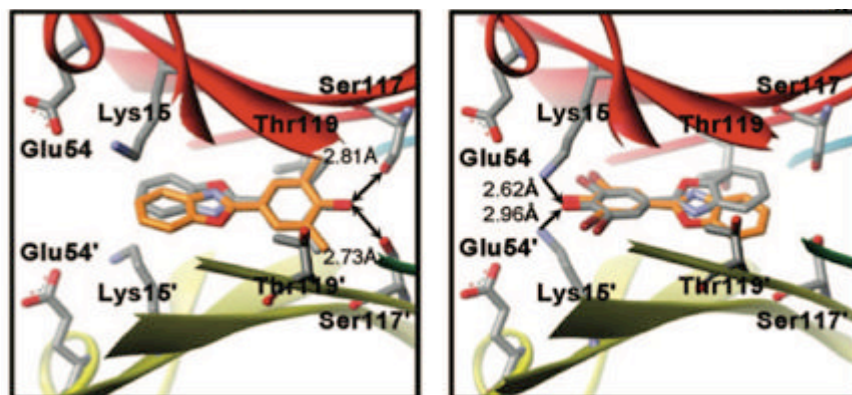
Transthyretin amyloid



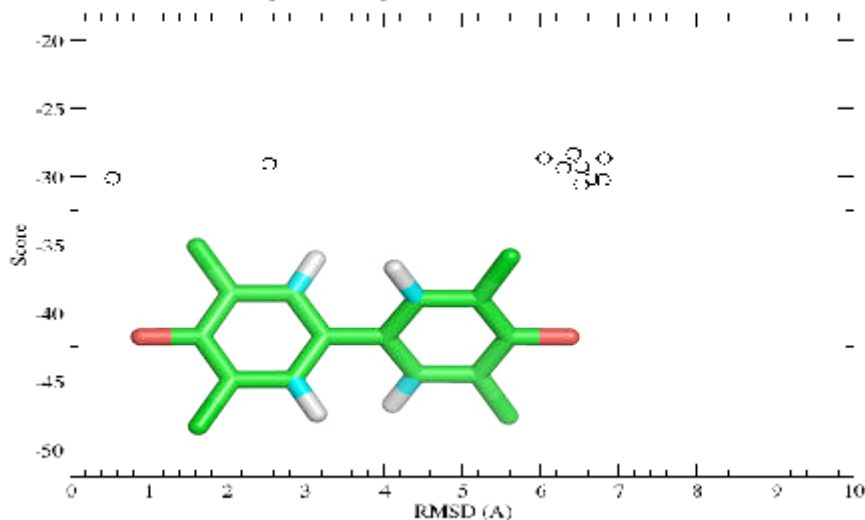
Quintas *et al.* *J. Biol. Chem.*, **2001**, 276(29), 27207-13.
Correia *et al.* *Protein Sci.*, **2006**, 15(1), 22-32.

Docking and Scoring assessments

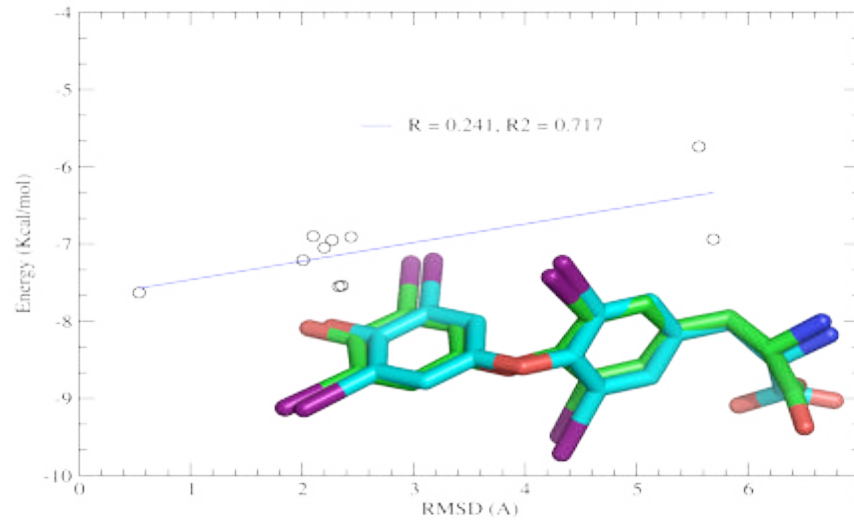
“All that glitters is not gold”



TTR redocking: 2g9k_pocketAC
Docking and Scoring results with GOLD v3.2 /ChemScore



Redocking of T4 to TTR (2ROX)
Docking and Scoring results with AutoDock4



Correct pose – Crystal structure
Predicted pose – by Molecular Docking

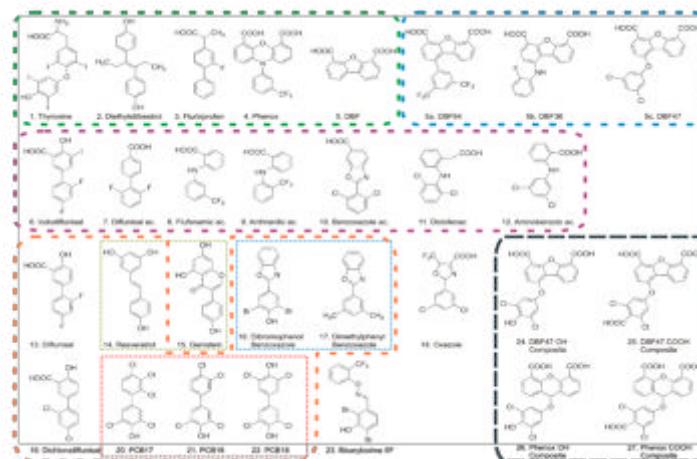
$$\text{RMSD} = \sqrt{\frac{1}{n} \sum_{i=1}^n (v_{ix} - w_{ix})^2 + (v_{iy} - w_{iy})^2 + (v_{iz} - w_{iz})^2}$$

Evaluation of Virtual Screening performance

Enrichment studies

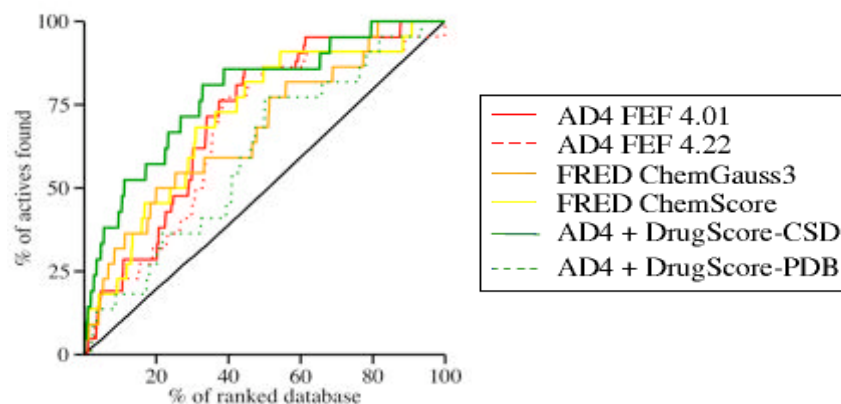
Virtual screening (VS) is like a police line-up

1. inactive
2. active
3. inactive
4. active
5. inactive
6. active
7. inactive
8. inactive
9. inactive
10. inactive
- (...)



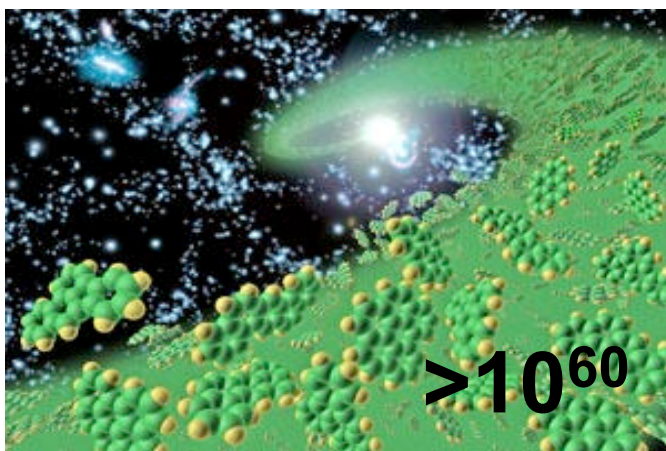
The innocents
should resemble
the guilty

ROC curves to evaluate VS performance

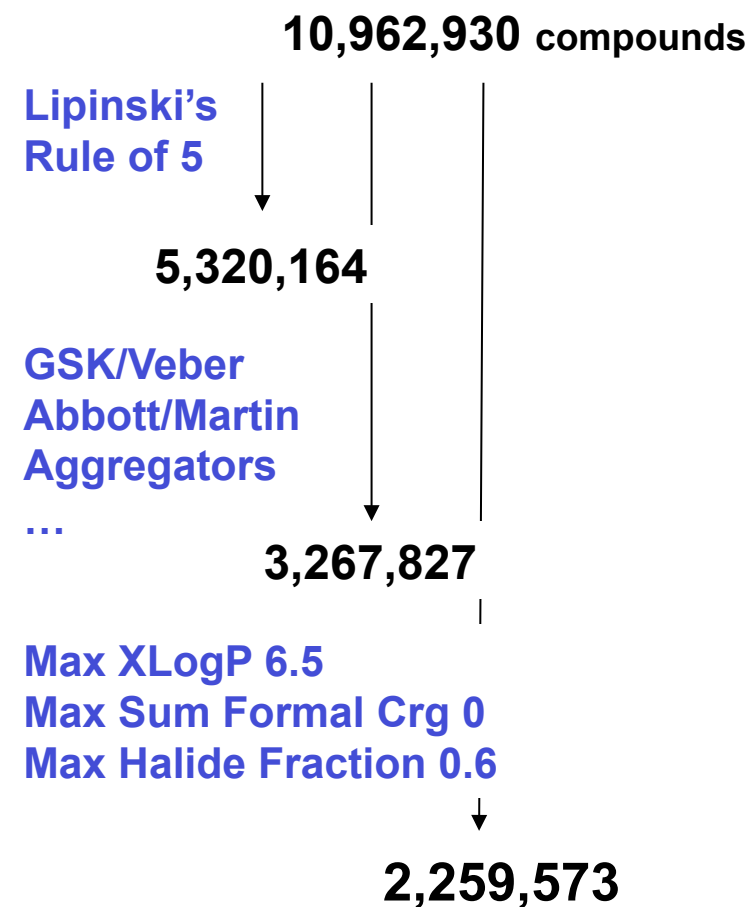


A tailored library of molecules for virtual screening

Chemical space



Docking 2.3 million molecules would still take ~43 years on a single CPU!!



Volunteer/Distributed Computing

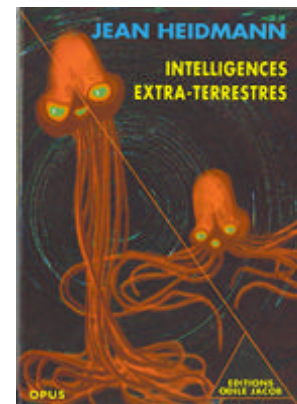
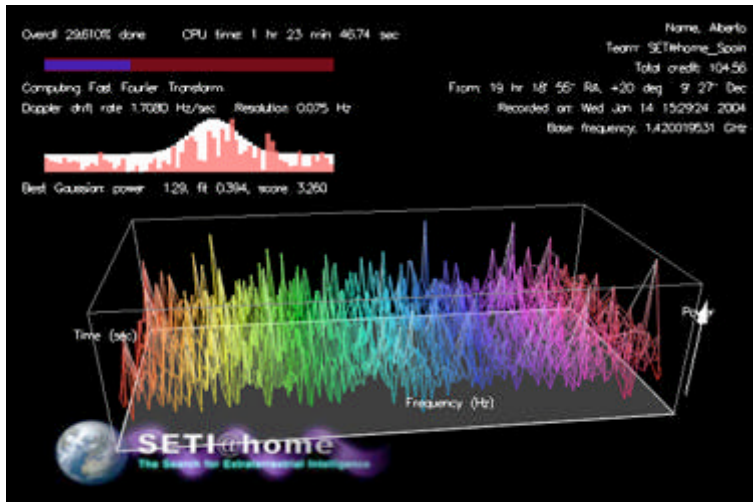


Onset in 1999

Comprising >50 projects nowadays

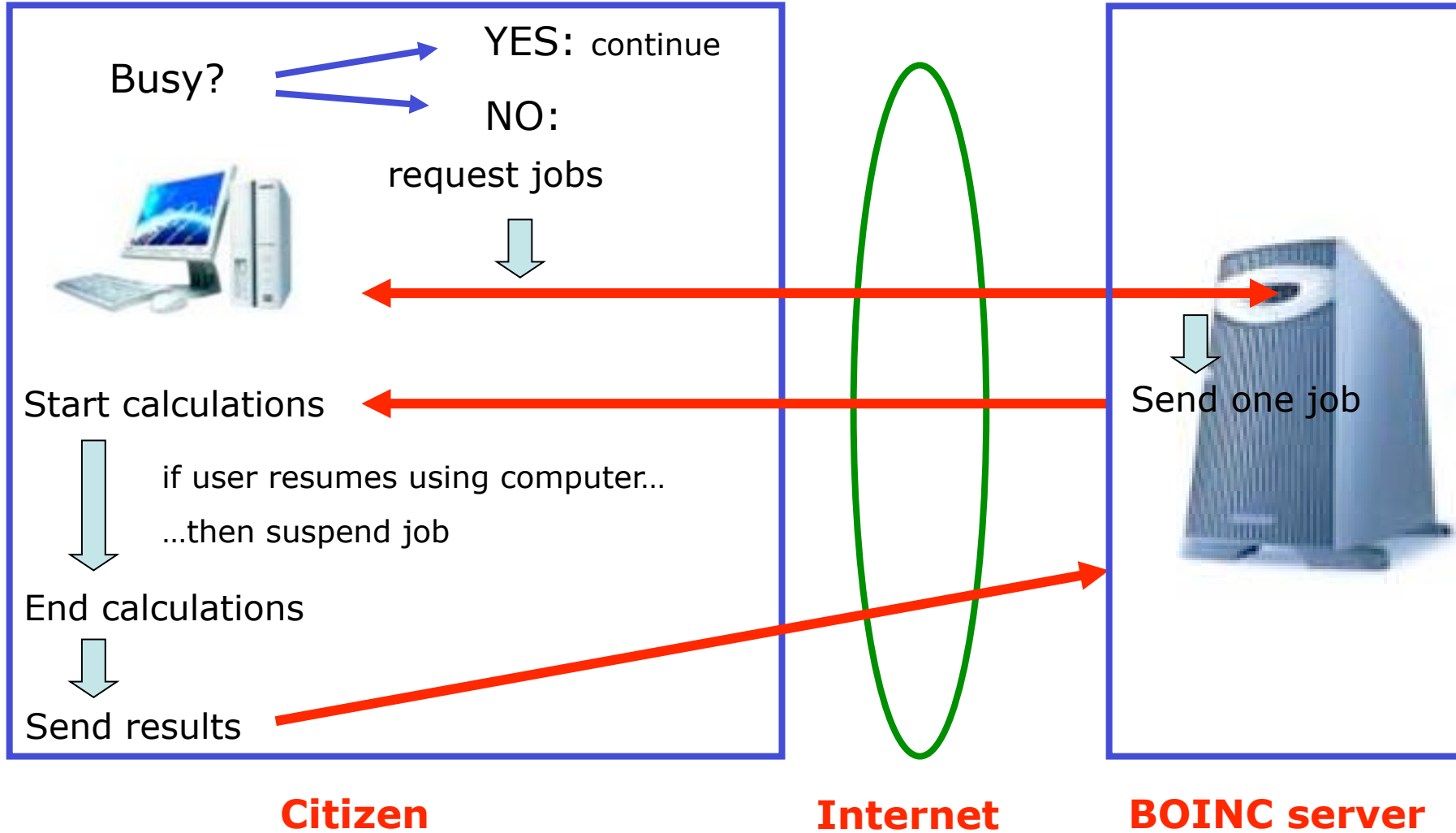
> 500,000 active computers

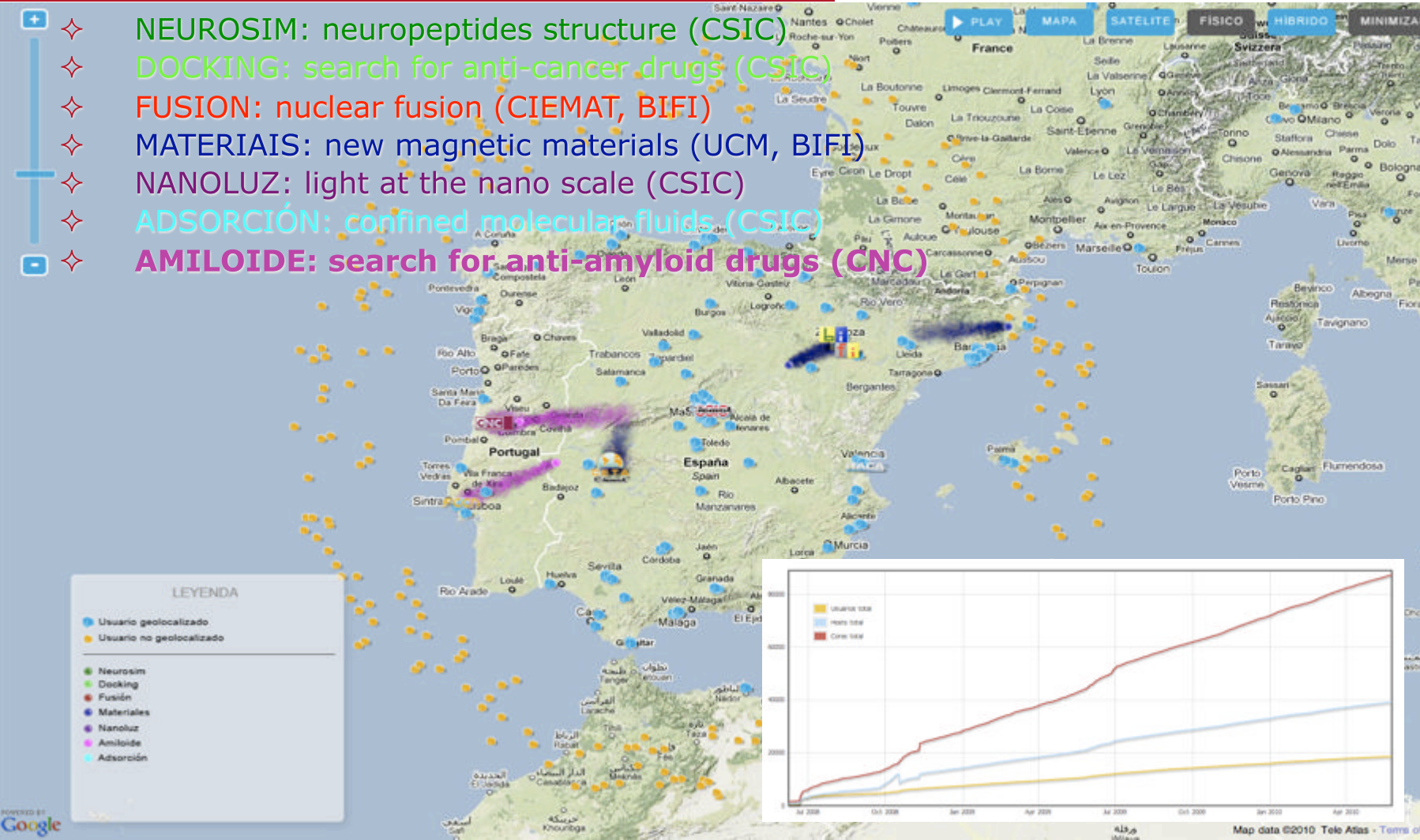
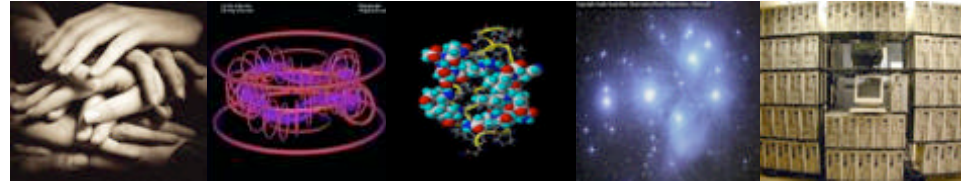
Performance of 5.128 Pflops (Apr 2010)



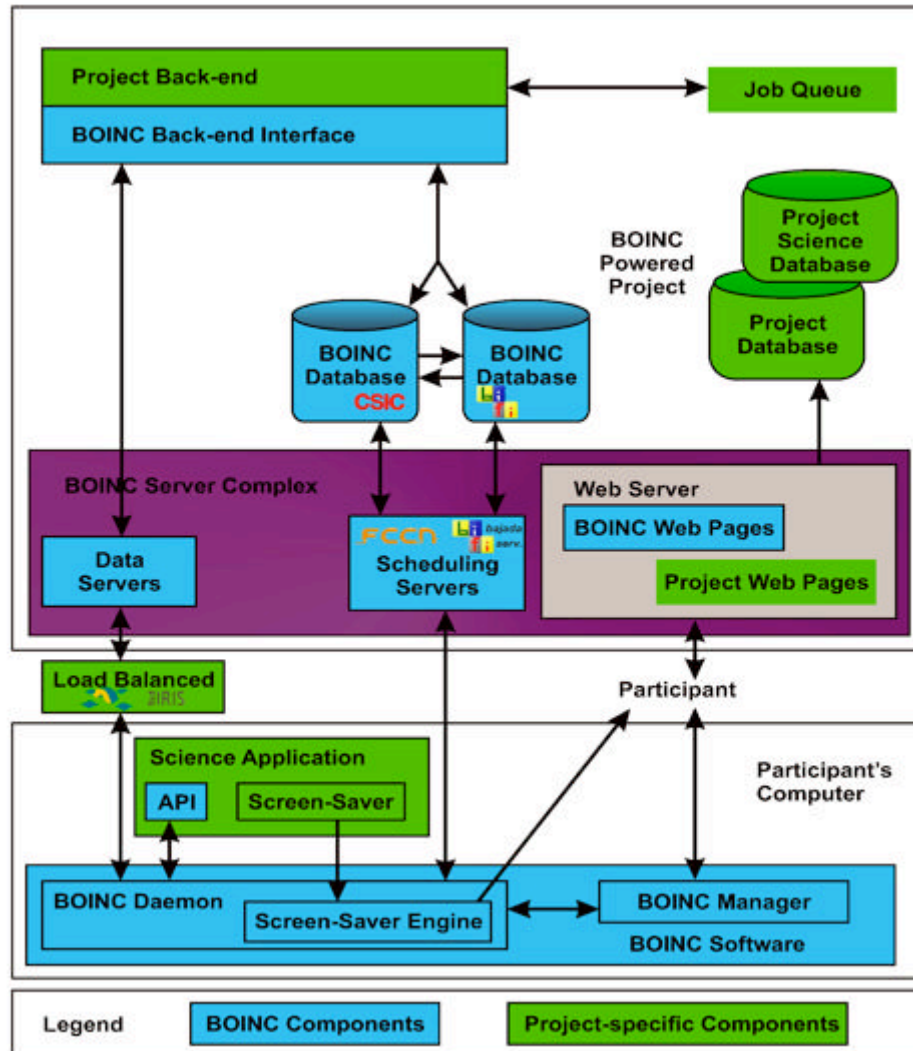
<http://setiathome.ssl.berkeley.edu/>

The BOINC middleware





The new Ibercivis architecture



✧ Expansion of the backbone

- ✦ A new scheduler
- ✦ A new website

✧ Application development

- ✦ Local support group
- ✦ Application hosting

✧ New infrastructures in PT

- ✦ 2 blade systems
- ✦ HP BL680c G5 CTO Blade
- ✦ 4 Xeon E7430 CPUs
- ✦ 16 GB RAM and 10 TB ROM
- ✦ Linux OpenSUSE 11.1

Simões et al. *IBERGRID Conf. Proc.*, **2010**, S3, 404-16.

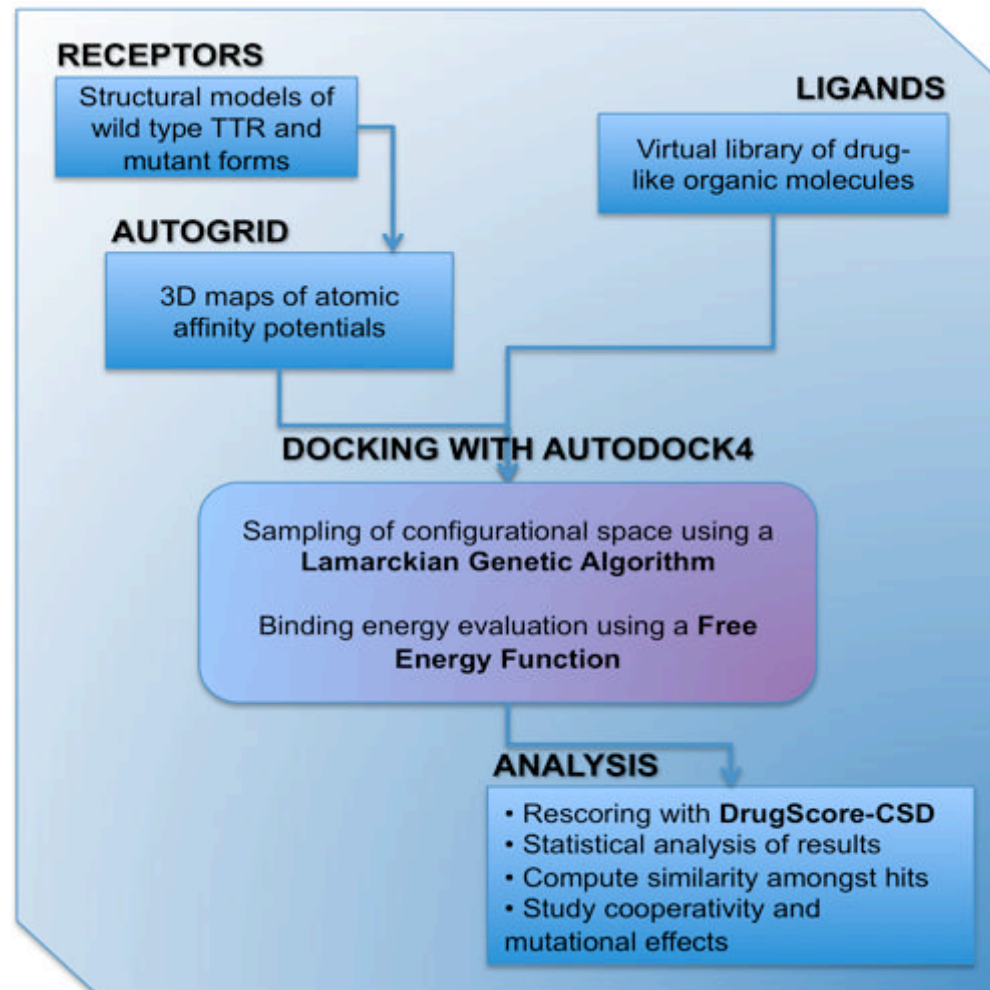
www.ibercivis.pt

Integration of the AMILOIDE application

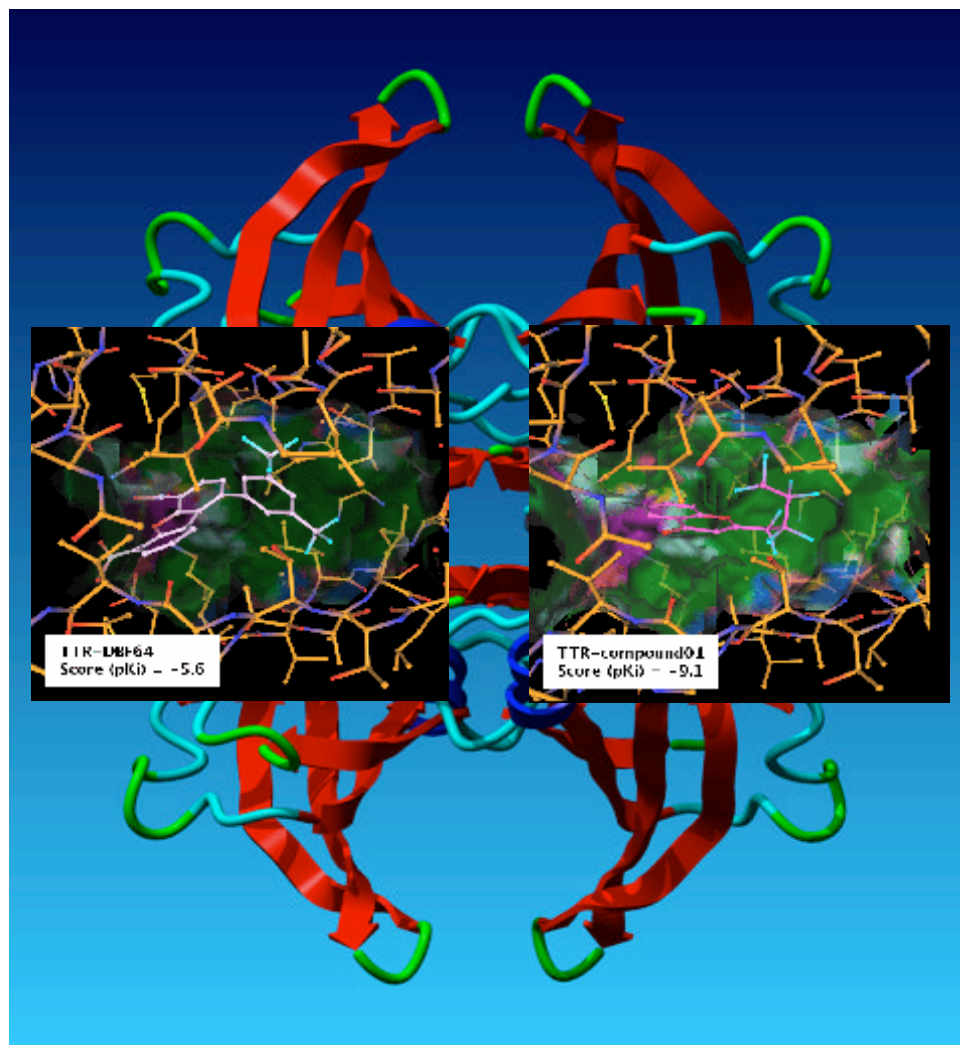
- ✧ **Application wrapper**
 - ★ Runs “any” application as sub-process
 - ★ Controls communication with the core client

- ✧ **System interface (bash)**
 - ★ 1st *Scripts of commands*
 - ★ 2nd *The minishell*
 - ★ 3rd *Daemons*

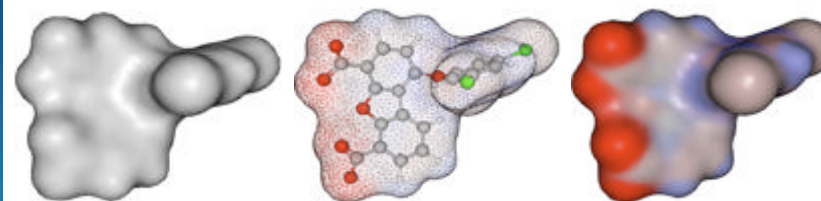
- ✧ **Virtual screening protocol**
 - ★ Preliminary steps (local)
 - ★ *Docking with AutoDock4*
 - ★ Post-processing (local)



AMILOIDE: preliminary results



- ✧ **AMILOIDE, the figures**
- ✦ First production WorkUnit sent in October 2009
- ✦ All 2,259,573 WorkUnits sent (as of May 2010)
- ✦ Approximately 80% reported as *successful* results



- ✧ **AMILOIDE, the outcomes**
- ✦ Retrieval of compounds with appropriate shape, chemistry and/or electrostatics
- ✦ Better combined pocket affinities
- ✦ Better physicochemical props
- ✦ Potential drug candidates for biological evaluation

Science Communication

- ✧ **Narrowing the gap between Science and Society**
 - ✦ Encontro Nacional de Ciência 2009, Fundação Gulbenkian, Lisbon
 - ✦ Presentations at secondary schools
 - ✦ Promulgation by *Ciência Viva* and UMIC
 - ✦ Dissemination across the media (press, radio, television and Internet)
 - ✦ Websites managing all information and project contents (requirements for participation, personal statistics, teaching units for secondary schools, leaflets and podcasts of the scientific research)

- ✧ **The growth of Ibercivis and future research**
 - ✦ Growth of interest of Portuguese citizens will translate into growth of the network
 - ✦ Incorporation of new projects
 - ✦ Further developments to the AMILOIDE project



Acknowledgements

✧ Portugal

- ✧ UMIC
- ✧ CNC
- ✧ LIP
- ✧ FCCN
- ✧ Ciência Viva



✧ Spain

- ✧ BIFI
- ✧ CIEMAT
- ✧ CSIC
- ✧ RedIRIS



✧ RMBlab task force

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- ✧ Catarina Jesus
- ✧ Daniela C. Vaz
- ✧ Elsa S. Henriques
- ✧ Nuno Loureiro-Ferreira
- ✧ Pedro Cruz
- ✧ **Rui M. M. Brito**

✧ BIFI task force

- ✧ **Alejandro Rivero**
- ✧ Alfonso Tarancón
- ✧ Fermin Sanz
- ✧ Javier Romero

✧ **YOU!**