# Molecular dynamics of proteins in the cloud

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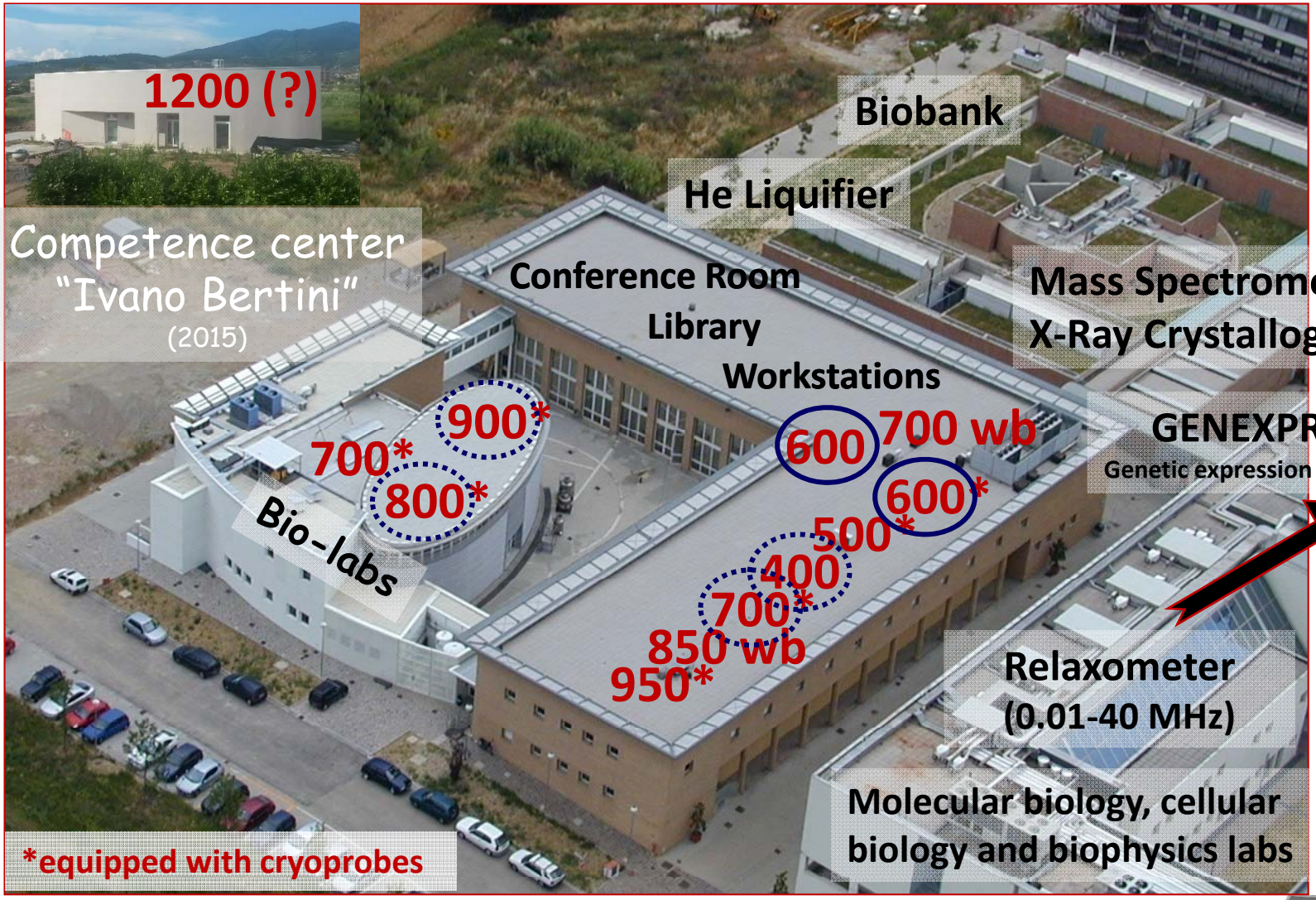
# CERM/CIRMMP

## Magnetic Resonance Center

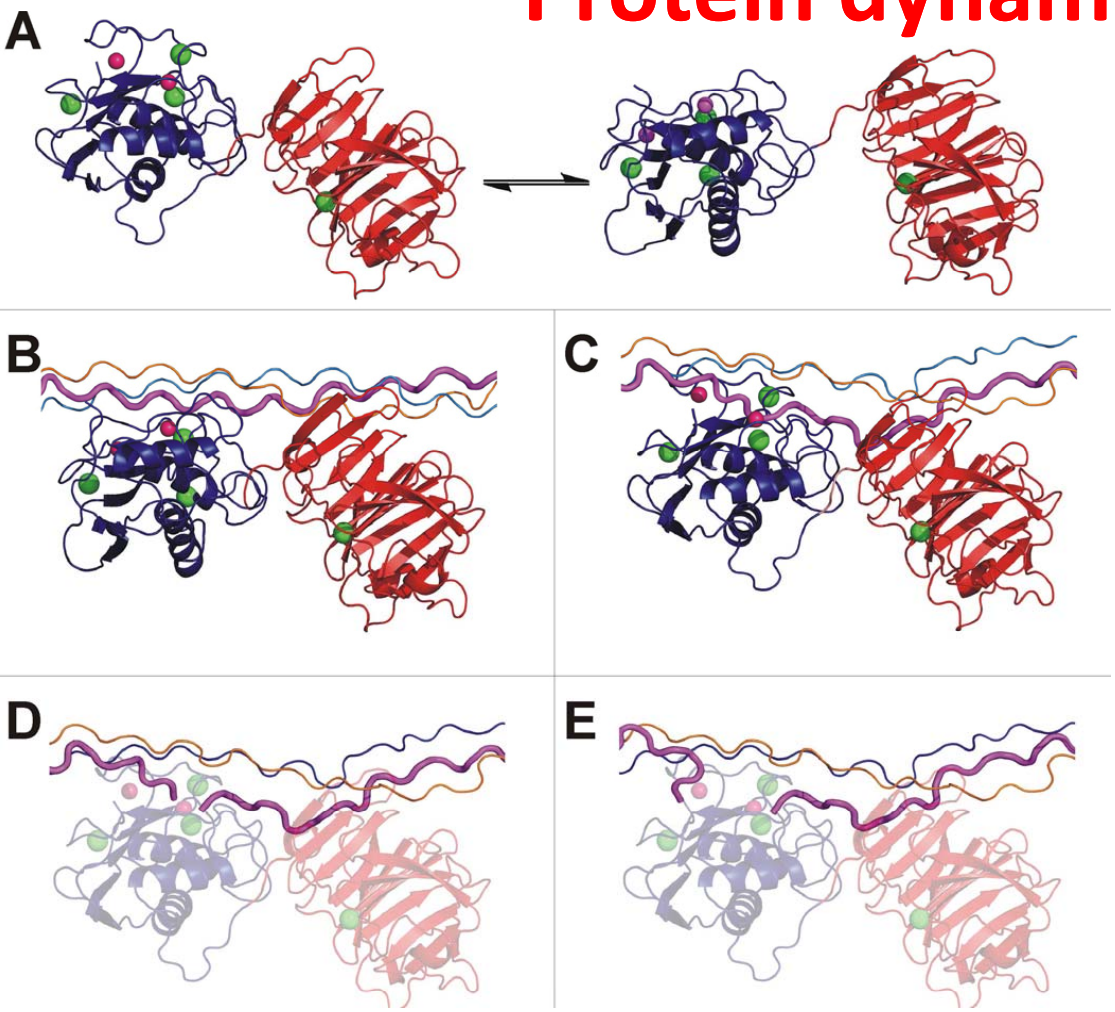
## An INSTRUCT Core Center




**www.cerm.unifi.it**

*for metabolomics*

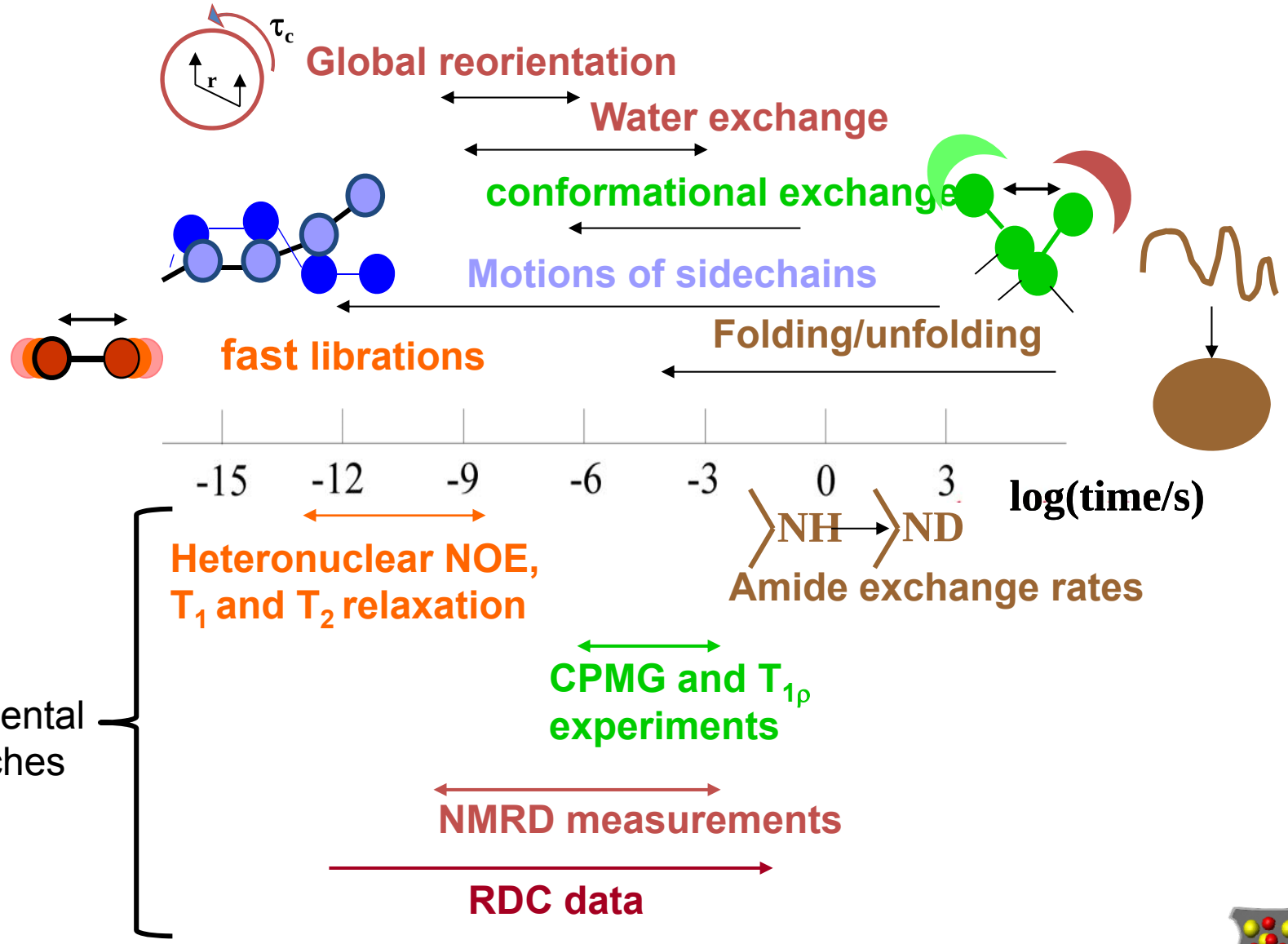
# Protein dynamics





The initial steps of collagenolysis. (**A**) Closed (left) and open/extended (right) forms of FL-MMP-1 in equilibrium. (**B**) The extended protein binds THP chains 1T-2T at Val23-Leu26 with the HPX domain and the residues around the cleavage site with the CAT domain. The THP is still in a compact conformation. (**C**) Closed FL-MMP-1 interacting with the released 1T chain (in magenta). (**D**) After hydrolysis, both peptide fragments (*C*- and *N*-terminal) are initially bound to the active site. (**E**) The *C*-terminal region of the *N*-terminal peptide fragment is released.

# Timescales of protein dynamics



# Molecular dynamics simulations

Because no experimental technique can be applied to the investigation of all atoms/groups in a protein, **computer simulations are needed** to obtain a complete picture

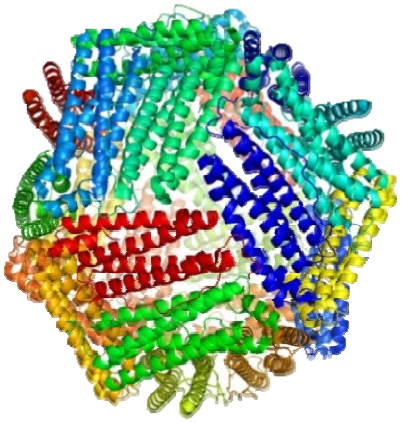
MD simulations are based on the integration of classical equations of motion (variation of position, velocity and acceleration) over small intervals of time $\Delta t$ (constant acceleration, linear motion). At each time step the system energy and forces over atoms are re-evaluated.

For protein MD simulations $\Delta t$ = 1-2 fs. So for **1 μs of simulation, 1 billion steps** are needed.

Calculations require several days and generate 10's Gb

MD simulations on GPGPUs

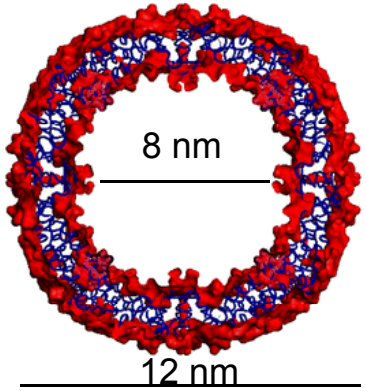
# The ferritin homopolymer



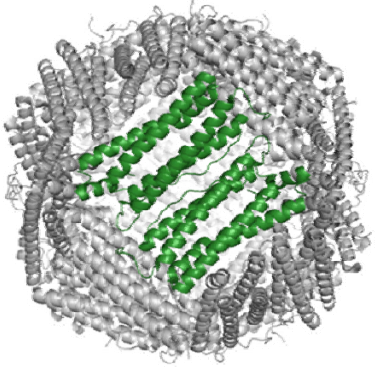
TOTAL MW 480 kDa

24 subunits 175 aa each

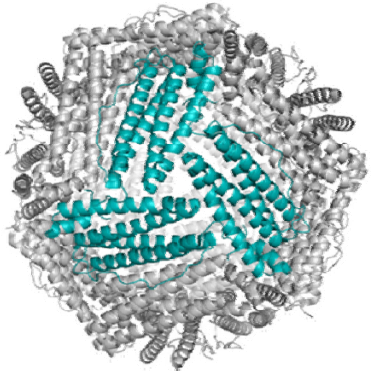
Octahedral (432) symmetry



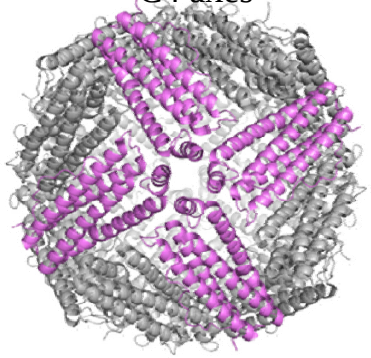

C2 axes



C3 axes



C4 axes



**Ferritin plus solvent: 178910 atoms**

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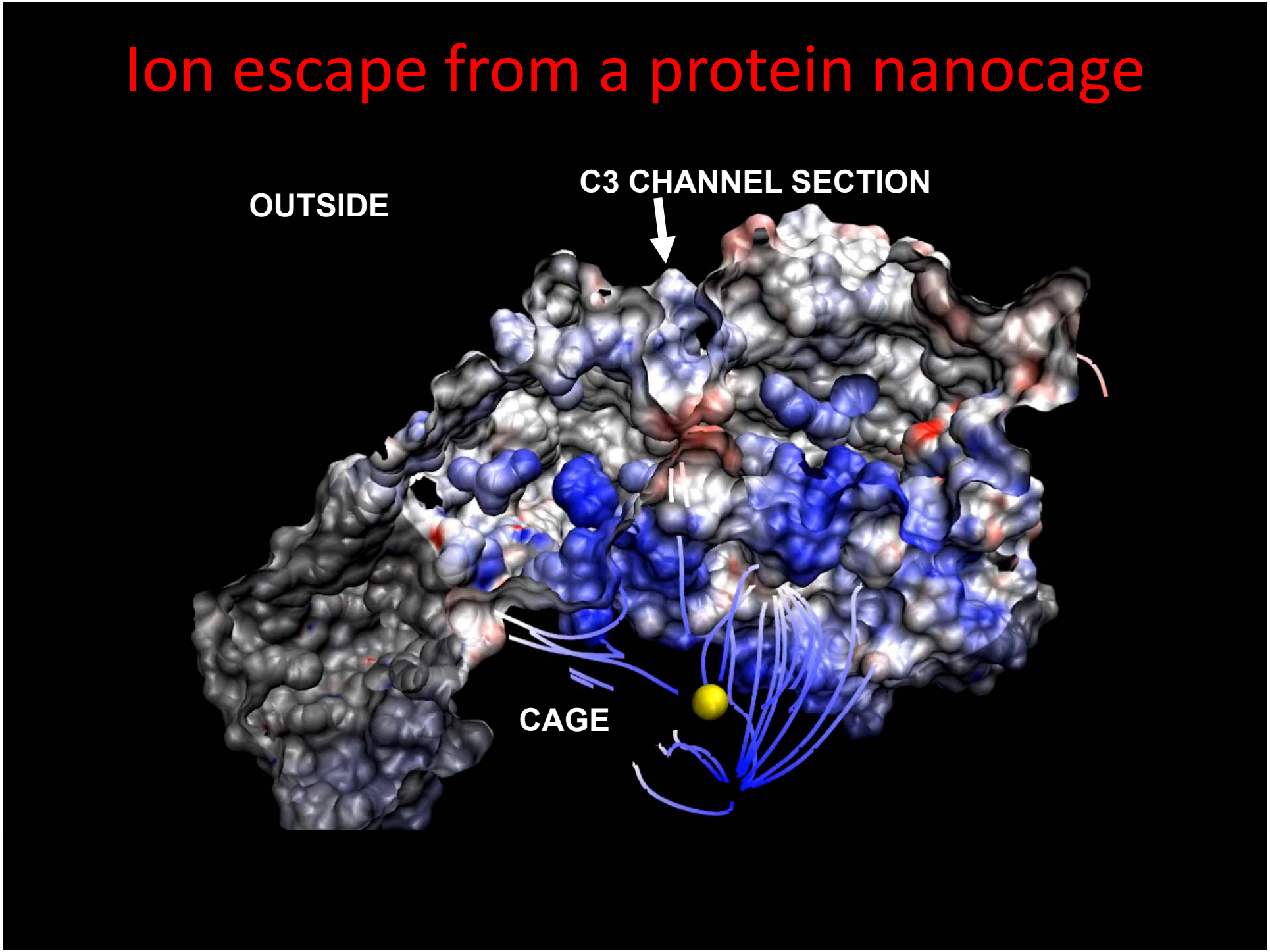
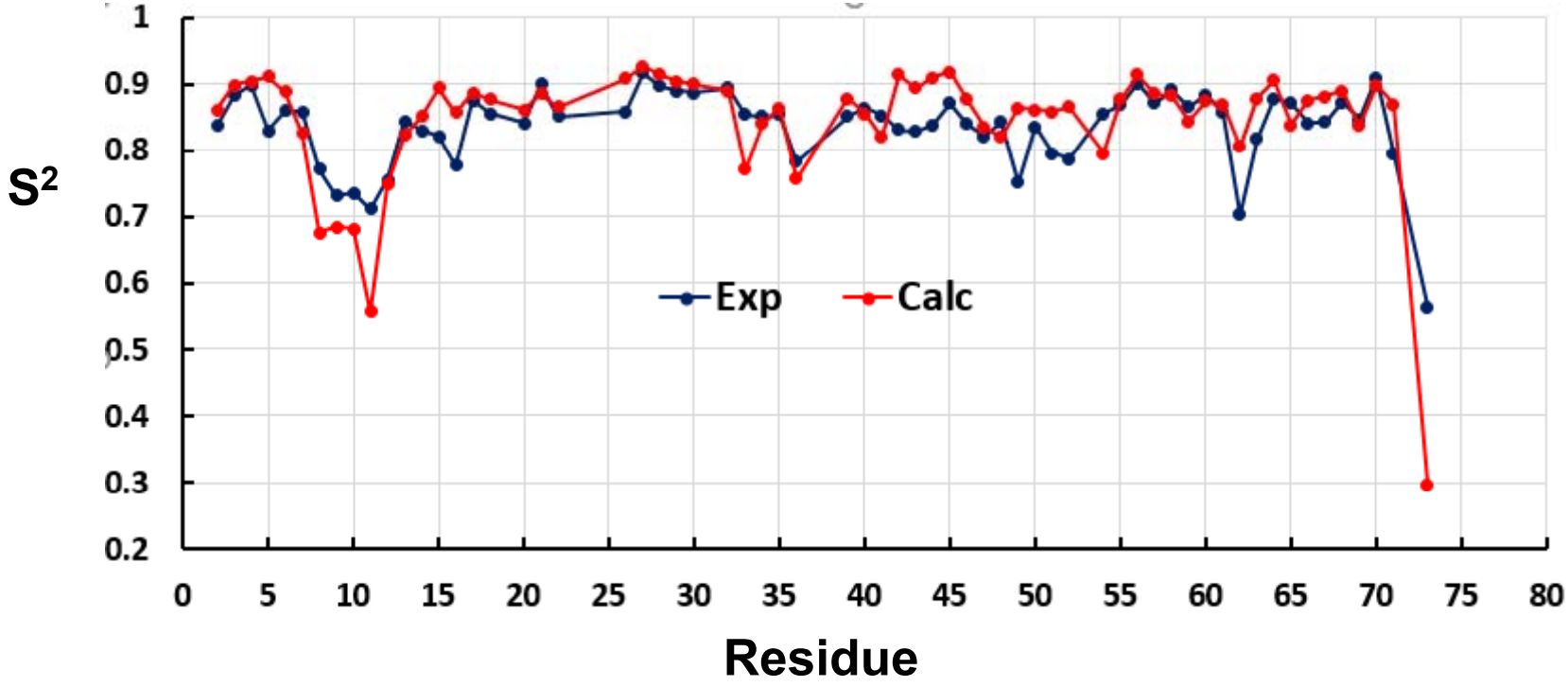
# Ion escape from a protein nanocage



# MD vs. NMR-derived dynamics

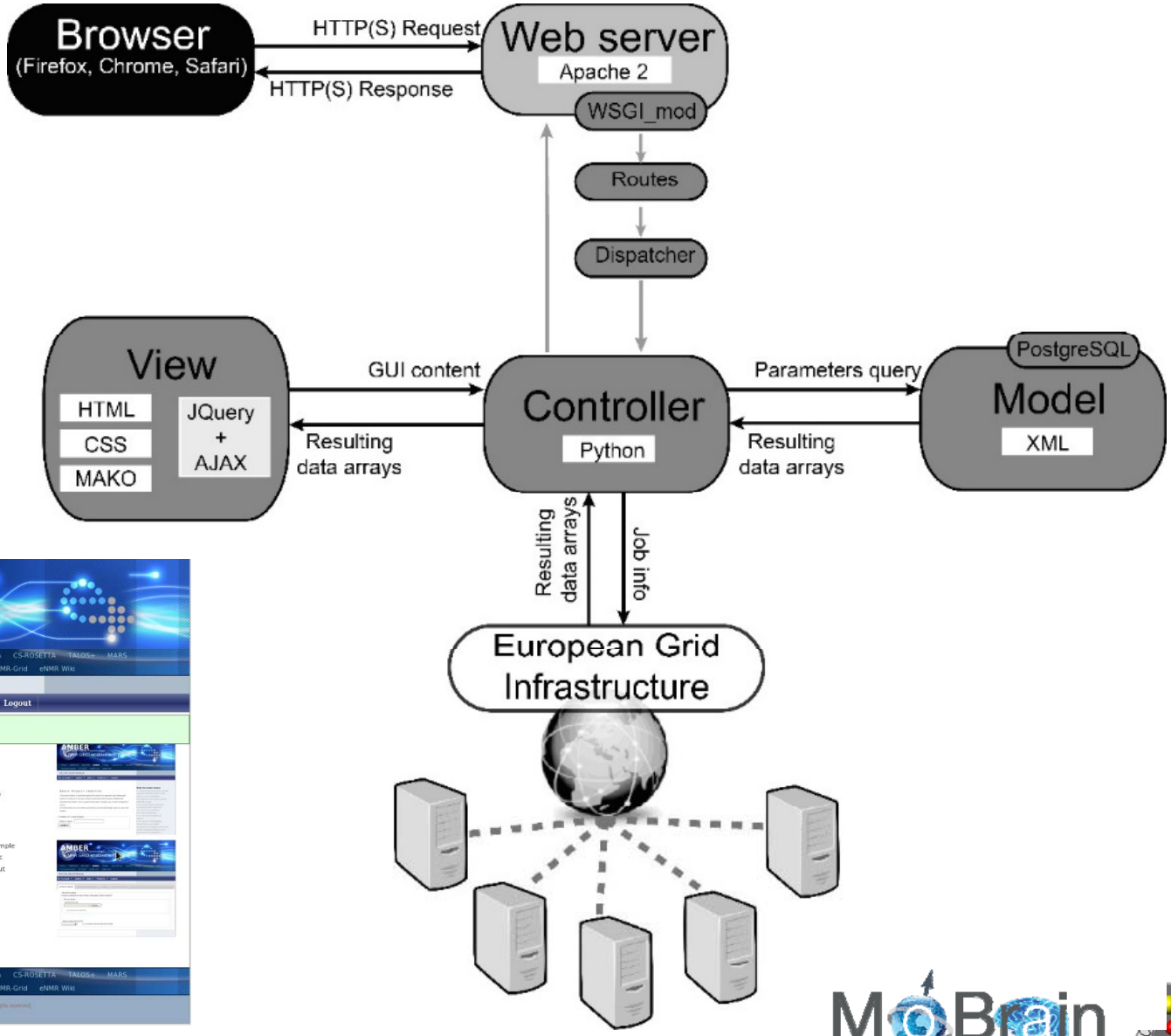
IRED analysis of a 1 μs simulation of ubiquitin, compared to order parameters derived from experimental data




**Pearson coefficient Exp-Calc = 0.82**


Prompers, J. J., & Bruschweiler, R., 2002, *J. Am. Chem. Soc.*, 124(16), 4522–4534.
Tjandra *et al.*, *J. Am. Chem. Soc.*, 1995, *117* (50), pp 12562–12566

# Structure of our current portal for short MD calculations



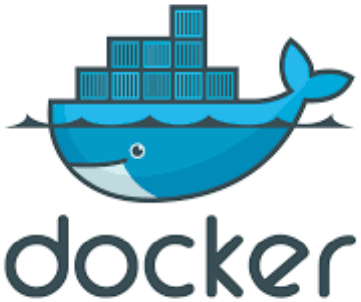


Bioinformatics, 27, 2384-2390 (2011). *A Grid-enabled web portal for NMR structure refinement with AMBER*.
Bertini I, Case DA, Ferella L, Giachetti A, Rosato A.

# Building a cloud-based web server for MD analysis

We used solutions developed by the **INDIGO-DataCloud** project (https://www.indigo-datacloud.eu/)

The AmberTools software package for MD was implemented as a container for Docker




We additionally implemented the **Oneclient** application in the Docker image

ONEDATA

**Onedata** is a Dropbox-style cloud storage solution. Its Oneclient component allows mounting your Onedata space in the local file system tree


# In the Dockerfile

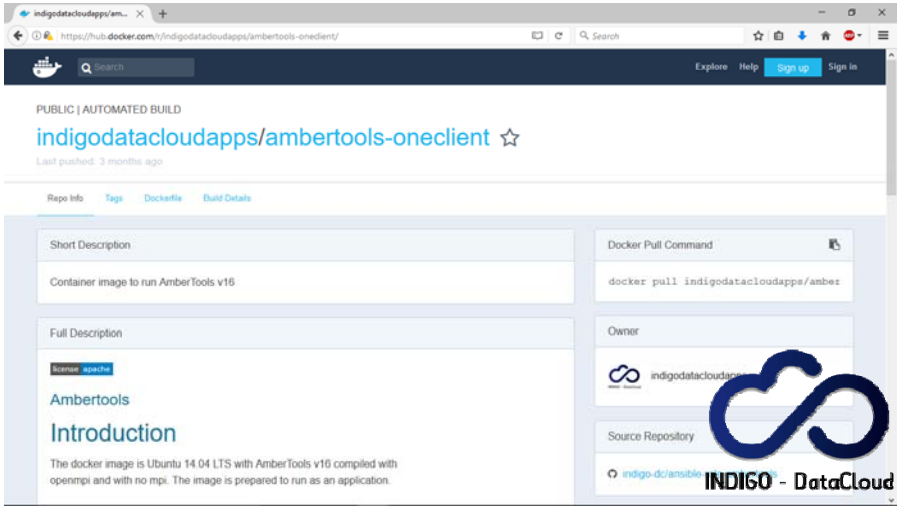
```
[…]
ENV PROVIDER_HOSTNAME=oneprovider.cloud.cnaf.infn.it
ENV ONECLIENT_AUTHORIZATION_TOKEN='AADDFF.....'
ENV MOUNT_POINT=/tmp/onedata
RUN mkdir /tmp/onedata

[…]
EXPOSE 8080
CMD oneclient --authentication token $MOUNT_POINT --no-check-
        certificate && mvn jetty:run
```

can be accessed via POSIX

Web server

Based on https://hub.docker.com/r/indigodatacloudapps/ambertools-oneclient/



# Building a cloud-based web server for MD analysis

The container further includes

- A data browser, so the container can be accessed via your web browser (i.e. no need to use the Onedata web interface in another tab).
- A viewer for macromolecular structures (NGL, a highly memory-efficient and scalable WebGL-based viewer)

We then instantiate the VM using Ansible with specifications in YAML

This is compatible with the **PaaS Orchestrator** of INDIGO


# To instantiate the VM

**YAML file**

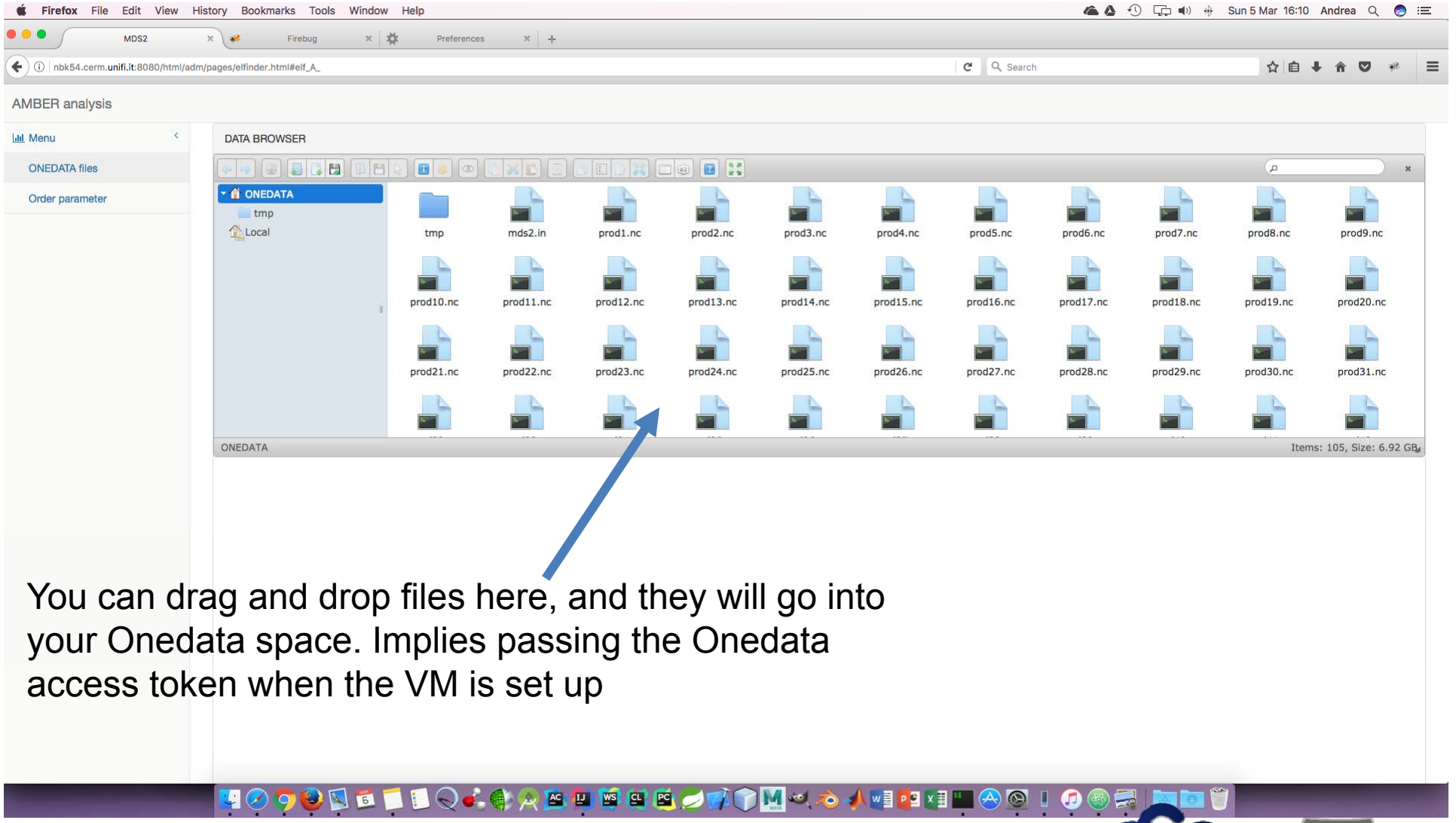
```
[…]
   - name: build the image
     docker_image:
       path: /tmp/site
       name: cirmmp/mds2


   - name: run the site in a docker container
     docker_container:
       name: mds2
       privileged: True
       image: "cirmmp/mds2"
       dns_servers: 150.217.1.32
       published_ports: 8080
```

As we are in dev, the container is stored locally

INDIGO - DataCloud

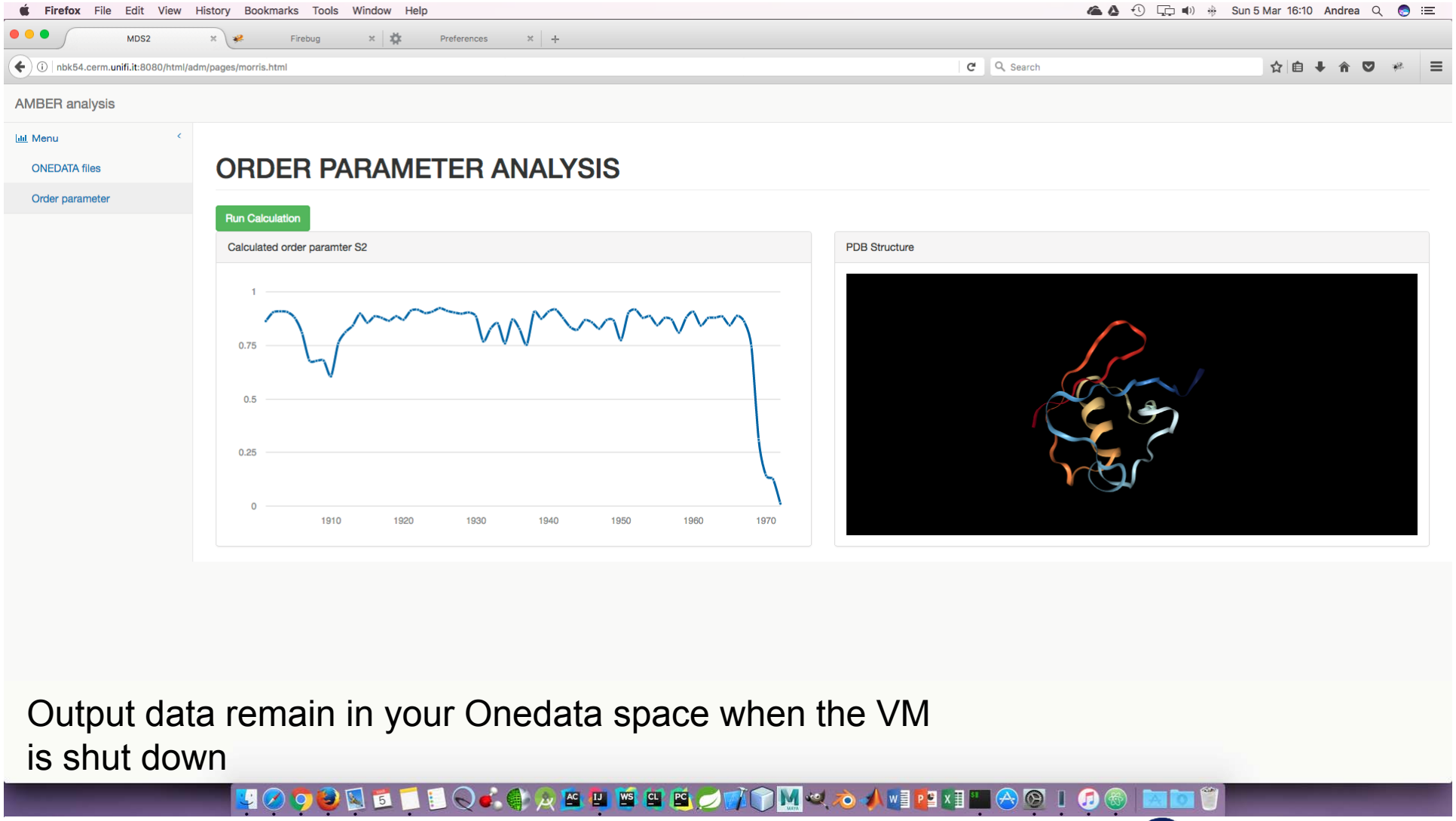
# How it looks




You can drag and drop files here, and they will go into your Onedata space. Implies passing the Onedata access token when the VM is set up

INDIGO - DataCloud

# Display of the results of MD analysis




Output data remain in your Onedata space when the VM is shut down

INDIGO - DataCloud

# Infrastructure to compute MD simulations

Presently:

- GPGPU-based using the HTC infrastructure of EGI

Next

- Dockerized version for GPGPU VMs

Computing MD simulations is much more efficient on GPGPUs: see https://documents.egi.eu/public/ShowDocument?docid=2774
Instead, MD analysis does not require GPGPUs

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# Next steps

Integrate this with the INDIGO **IAM** (Identification and Authorization Mechanism), to simplify management of the access token

Adapt to check running calculations on the fly

Improve the design of the web interface

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# Thank you for your attention!

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- Andrea Giachetti

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Regione Toscana

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INDIGO - DataCloud

we-nmr

MoBrain

CERM Firenze

# R1 relaxation parameters of Menkes protein

MD simulations of the WT- and A629P-MNK6 domain in the apo-form.

After 0.5 μs of simulation the IRED analysis was performed

**R1 correlations**
(Exp-Calc)

**A629P = 0.50**

**WT = Sample partly aggregated**