

# Atomistic Molecular Dynamics Setup with MDWeb

BioExcel Educational Webinar Series

Presenter: Adam Hospital

Host: Adam Carter

25 May, 2016

## Partners



## Funding





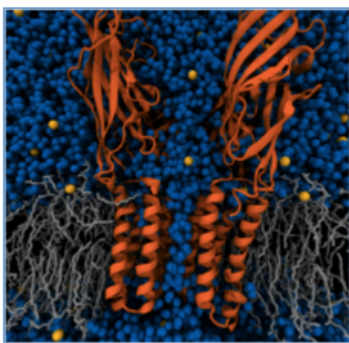
This webinar is being recorded

# Objectives of BioExcel

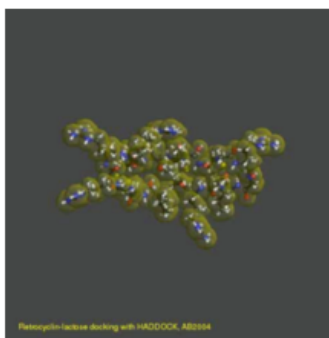
## Excellence in Biomolecular Software

Improve the performance, efficiency and scalability of key codes

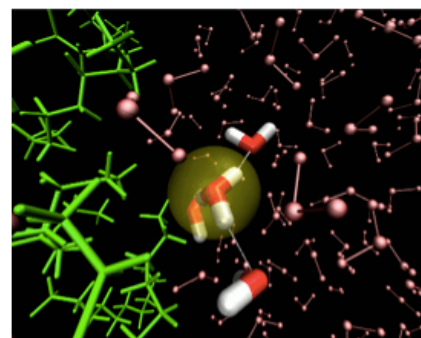
- GROMACS (Molecular Dynamics Simulations)
- HADDOCK (Integrative modeling of macro-assemblies)
- CPMD (hybrid QM/MM code for enzymatic reactions, photochemistry and electron transfer processes)



MD simulations  
/GROMACS/



Docking  
/HADDOCK/

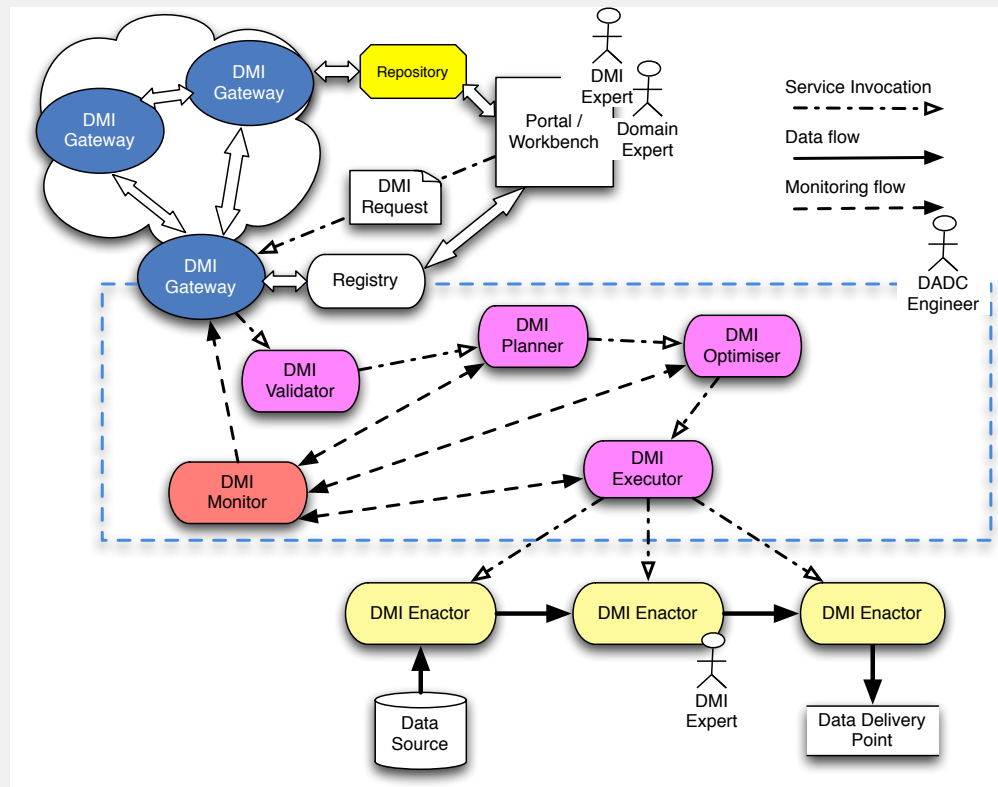


QM/MM  
/CPMD/

# Objectives of BioExcel

## Excellence in Usability

- Make ICT technologies easier to use by biomolecular researchers, both in academia and industry
- Devise efficient workflow environments with associated data integration





# Objectives of BioExcel

## Competence-building among academia and industry

Promote best practices and train end users to make best use of both software and computational infrastructure

- academic and non-profit users
- industrial users
- independent software vendors (ISVs) and academic code providers of related software
- academic and commercial resource providers



# Interest Groups

- Integrative Modeling
- Free Energy Calculations
- Best practices for performance tuning
- Hybrid methods for biomolecular systems
- Biomolecular simulations entry level users
- Practical applications for industry

## Support platforms

<http://bioexcel.eu/contact>



Forums



Code Repositories



Chat channel



Video Channel

# The presenter

Adam Hospital is a Postdoctoral fellow in **Molecular Modeling and Bioinformatics Unit (MMB)** hosted by **Institute for Research in Biomedicine** in Barcelona (**IRB-Barcelona**) and computer technician for the **Spanish National Institute of Bioinformatics (INB)**.

From a computer science background, he jumped to the bioinformatics world and got trapped by the fascinating field of structural bioinformatics. After 2 years, he joined **INB**, where he has been working for more than 10 years. INB has recently joined **Elixir**, which is building a sustainable European infrastructure for biological information. He has been involved in projects developed at **IRB** and also at the **Barcelona Supercomputing Center (BSC)**.

While working as a bioinformatician, he got his PhD in Biotechnology from the **University of Barcelona** with his thesis *“High Throughput Computational Studies of Macromolecular Structure Flexibility”*. At INB he has developed a set of public web servers and databases related to macromolecular structure flexibility, including MDWeb.



# Atomistic Molecular Dynamics Setup with



**BioExcel Webinar, 25/05/2016**

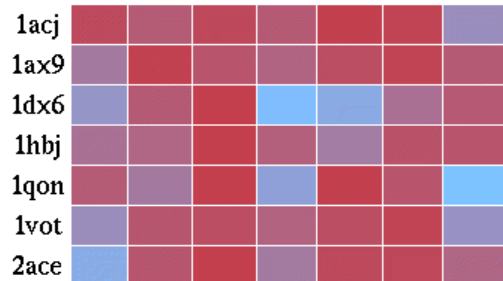
**Adam Hospital Gasch, IRB-Barcelona**

- **Introduction.**
  - *Molecular Flexibility: importance.*
  - *Molecular Dynamics: use limitations.*
  - *MoDEL, MDMoby & MDWeb.*
- *Molecular Dynamics on Web (MDWeb).*
  - *MDWeb Setup: Structure Checking, Workflows & Operations, MD Run.*
  - *MDWeb Analysis: Basic Analysis & FlexServ.*
- *IRB Web Servers.*
  - *MD & Flexibility: FlexServ, NAFlex.*
  - *MD Databases: MoDEL, BigNASim.*

Protein

Ligand

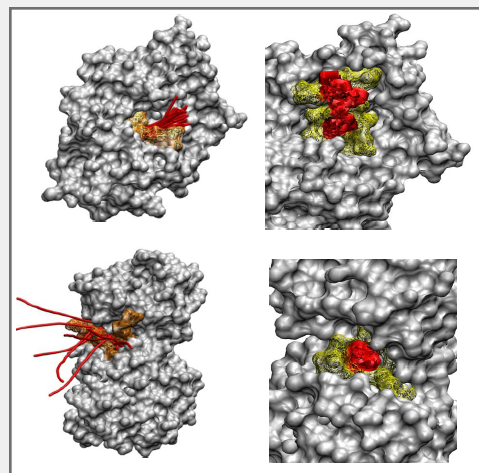
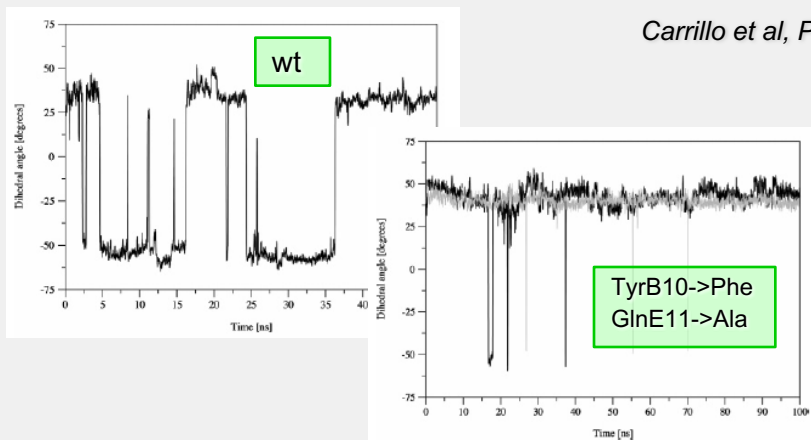
1acj 1ax9 1dx6 1hbj 1qon 1vot 2ace



0 5

RMSd docking solutions

Hospital et al, Adv Appl Bioinform Chem, 2015, 10:37-47



Protein Channels, Drug Cavities  
MDGrid

Carrillo et al, Proteins 2008, 70, 892-899

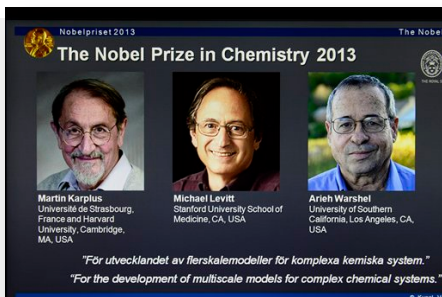
RCSB PDB  
PROTEIN DATA BANK



Gate Opening Molecular  
Switch.

Bidon-Chanal et al, JACS  
2007, 129, 6782-6788

# Introduction: Molecular Dynamics



$$\vec{f}_i = - \frac{\partial E_i}{\partial \vec{r}_i}$$

$$E_{pot} = E_{bond} + E_{angle} + E_{dihedral} + E_{elec} + E_{vdw}$$

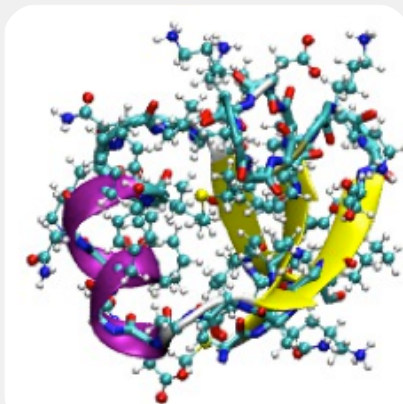
$$E_{bond} = \sum_{bonds} K_r (r - r_0)^2$$

$$E_{angle} = \sum_{angles} K_\theta (\theta - \theta_0)^2$$

$$E_{dihedral} = \sum_{diheds} \sum_n \frac{V_n}{2} (1 + \cos(n\Phi - \gamma))$$

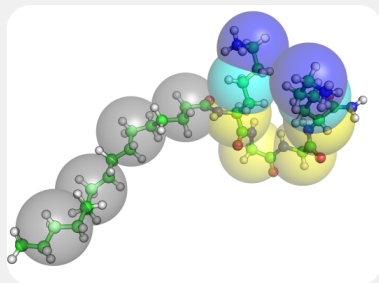
$$E_{vdw} = \sum_i \sum_{j>i} (A_{ij} r_{ij}^{-12} - B_{ij} r_{ij}^{-6})$$

$$E_{elec} = \sum_i \sum_{j>i} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$



Time Scale: ps -  $\mu$ s

RCSB PDB  
PROTEIN DATA BANK



Time Scale:  $\mu$ s - ms



# Introduction: Molecular Dynamics Limitations



Large Computational Resources

$$\begin{aligned}
 V(\mathbf{r}) &= \sum_{\text{bonds}} K_b (b - b_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 \\
 &+ \sum_{\text{dihedrals}} K_\chi (1 + \cos(n\chi - \delta)) \\
 &+ \sum_{\text{nonbonded-pairs}, i, j} \left[ \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} - \epsilon_{ij} \left\{ \left( \frac{R_{\text{min}, ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min}, ij}}{r_{ij}} \right)^6 \right\} \right]
 \end{aligned}$$

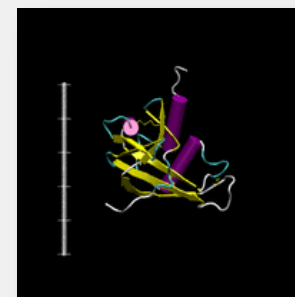
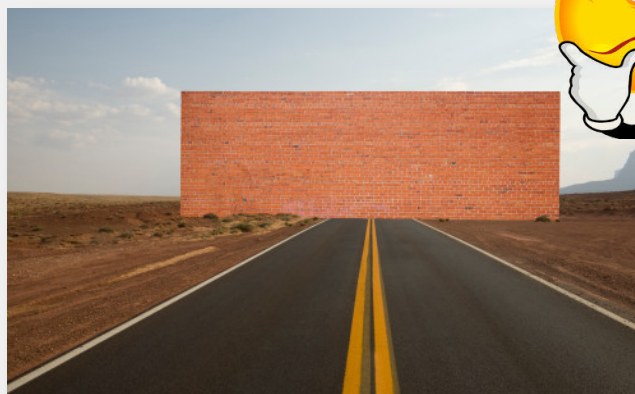
Energy dependencies on:

1. Bond length
2. Bond valence angle
3. Bond dihedral angle
4. Non-bonded electrostatic interactions
5. Non-bonded van-der Waals interactions

Force Fields Uncertainties



High level of expertise needed







*BSC Marenostrum Supercomputer*



*ANTON Supercomputer*



*Graphical Processing Units (GPUs)*

## • Reparameterization of amber force-field.

- Keeping  $\alpha/\gamma$  **ParmBSC0** (2007) corrections.
- Reparameterizing **sugar puckering**,  $\epsilon$ ,  $\zeta$  and  $\chi$  torsions.



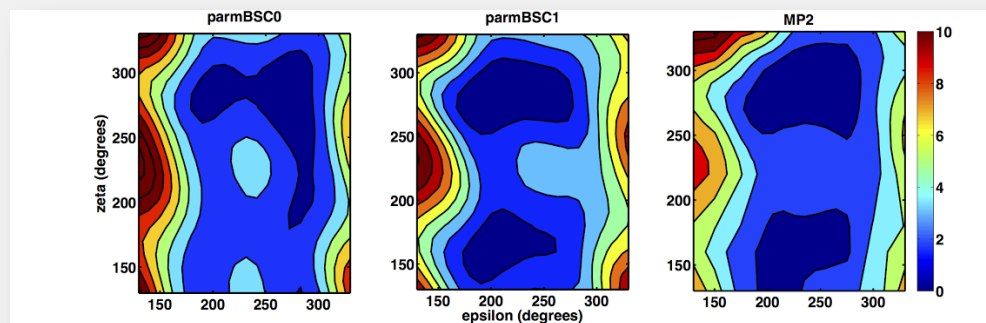
$$E_{bond} = \sum_{bonds} K_r (r - r_0)^2$$

$$E_{angle} = \sum_{angles} K_\theta (\theta - \theta_0)^2$$

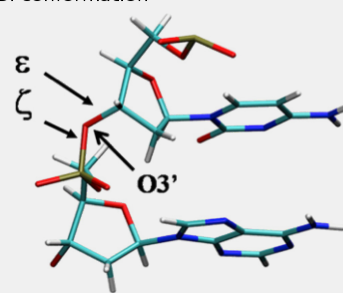
$$E_{dihedral} = \sum_{diheds} \sum_n \frac{V_n}{2} (1 + \cos(n\Phi - \gamma))$$

$$E_{vdw} = \sum_i \sum_{j>i} (A_{ij} r_{ij}^{-12} - B_{ij} r_{ij}^{-6})$$

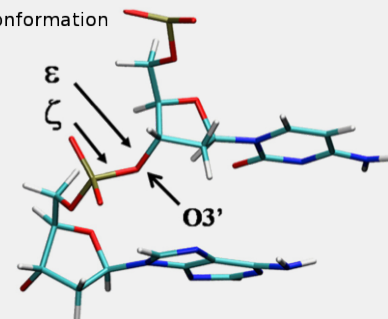
$$E_{elec} = \sum_i \sum_{j>i} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$



BI conformation

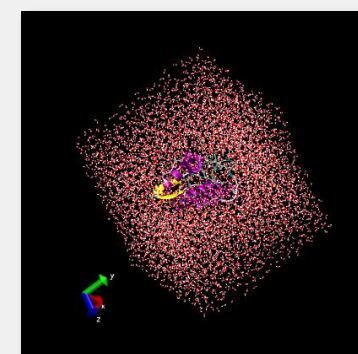
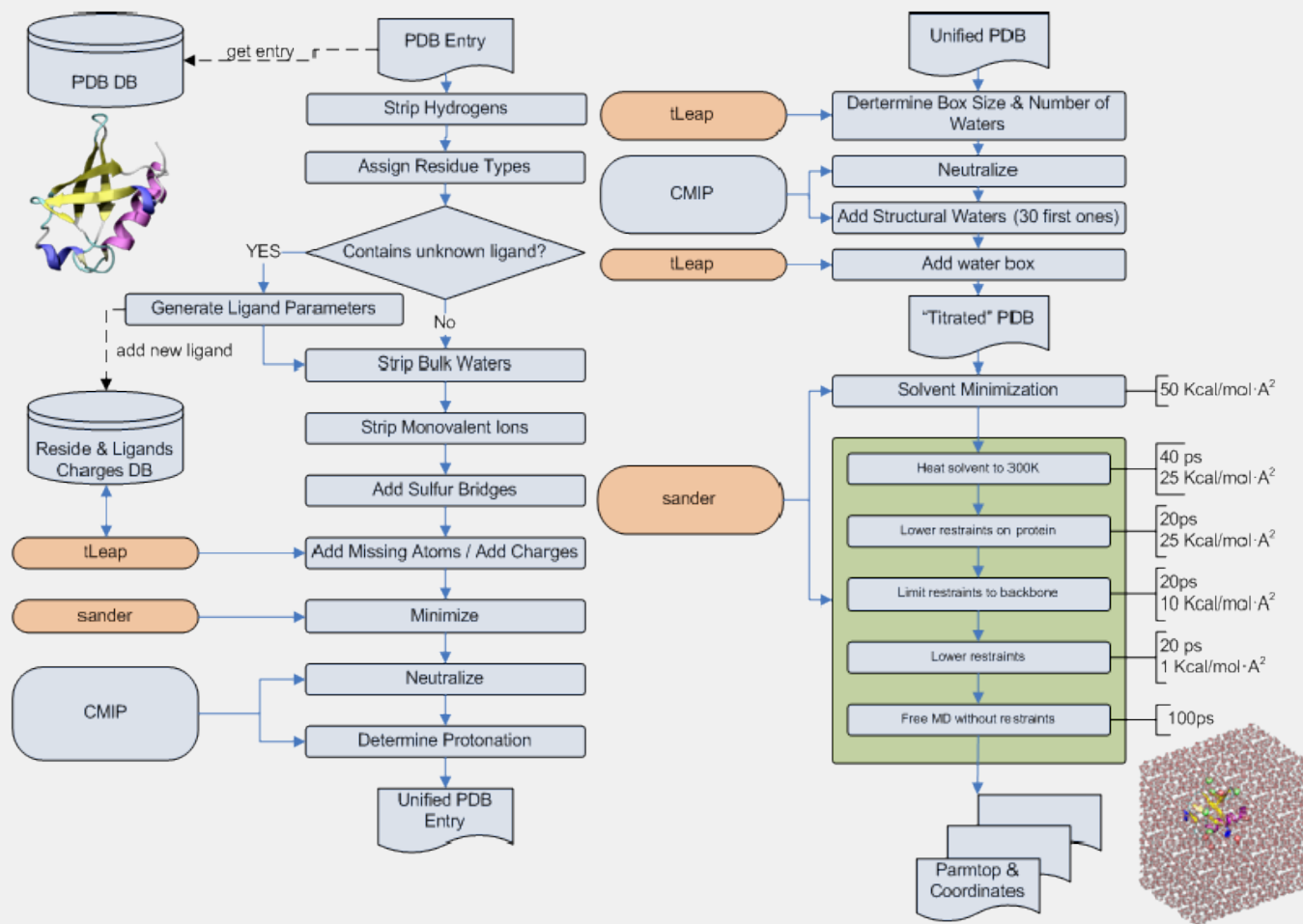


BII conformation



**ParmBSC0:** A. Pérez et al. *Biophys J.* (2007) 92 (11), 3817-3829.

**ParmBSC1:** I. Ivani et al. *Nature Methods* (2016), 13 (1), 55-58.

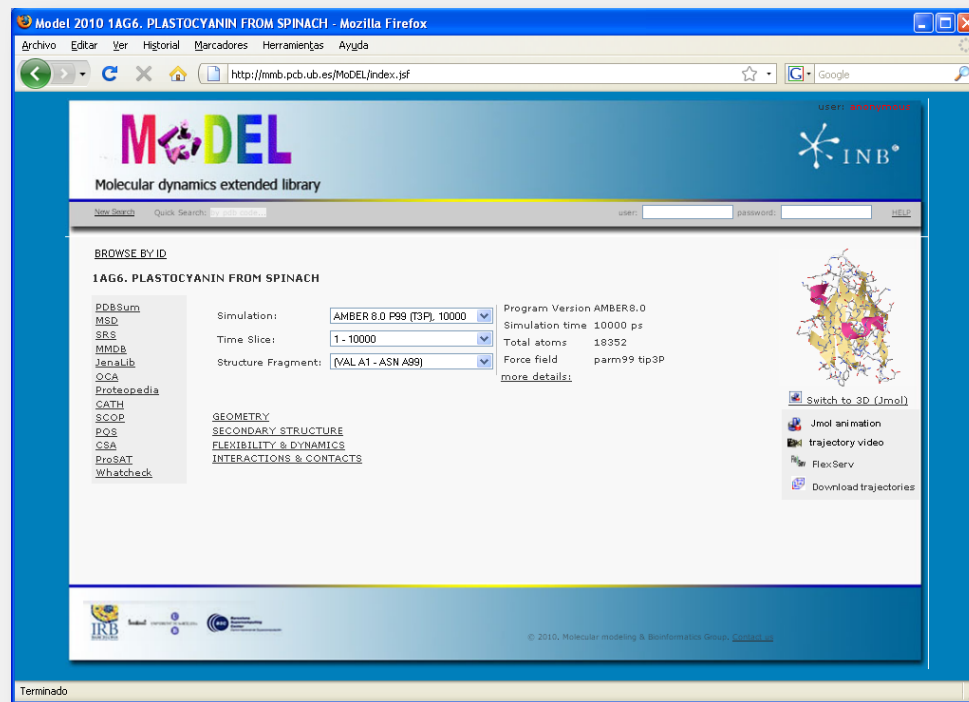




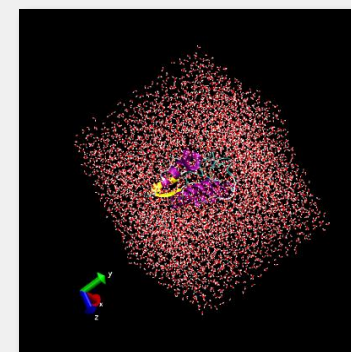
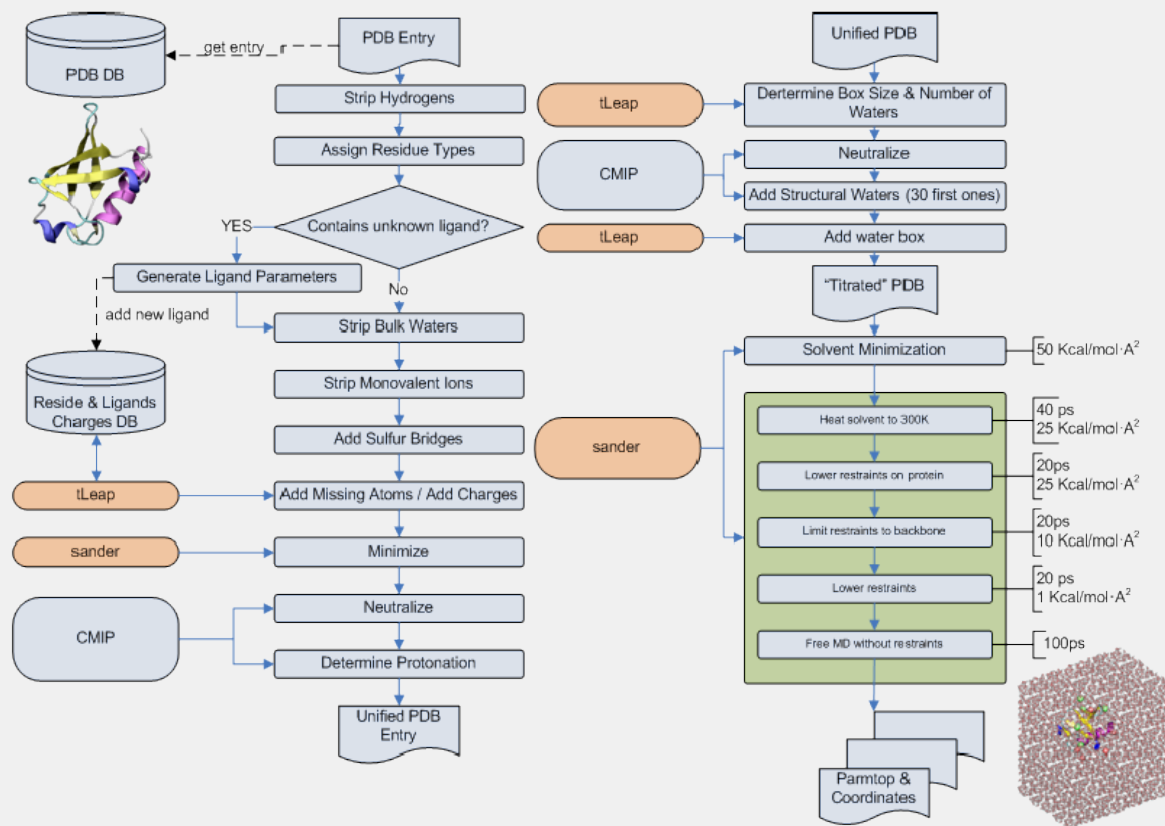
## Molecular Dynamics Extended Library.

<http://mmb.irbbarcelona.org/MoDEL>

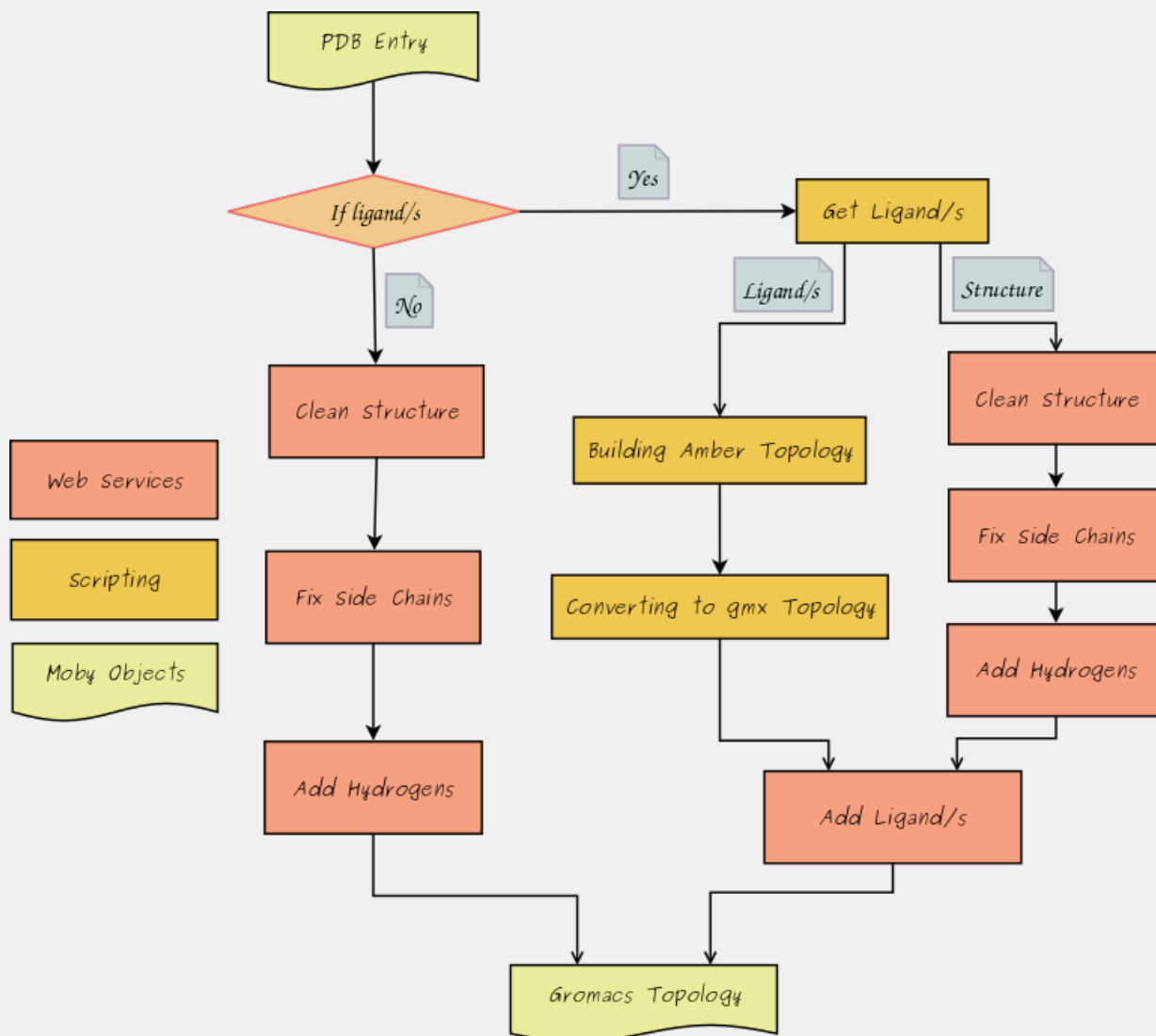
- **1875 Simulations** (~1600 structures).
- **Amber, Namd, Gromacs.**
- **Charmm22, Charmm27, Parm99, Parm99SB, Parm03, OPLS, etc.**
- **Web interface connected to a Relational Database.**
- **Automatic MD Setup, Run & Analysis.**



*Meyer et al, Structure 2010, 18 (11), 1399-1409.*



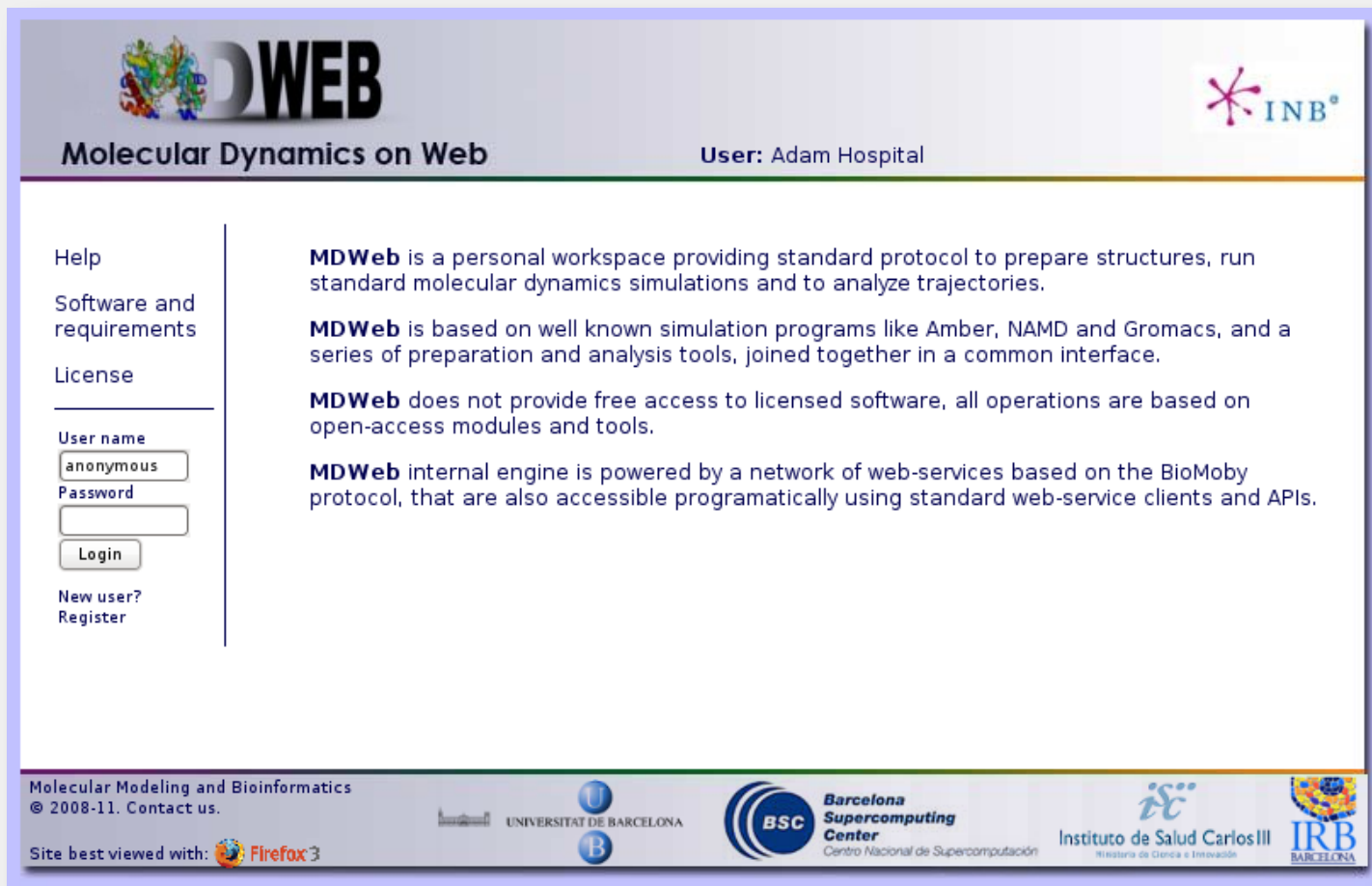
- Workflow Example:
- Generate Topology for Gromacs with amberff.
- Mixing web services with scripting.
- Others (Amber/Namd/Gromacs):
  - Generate Topology.
  - Setup.
  - Setup with Solvation.
  - Complete Setup (with eq).





## ***MDWeb & MDMoby: an integrated web-based platform for molecular dynamics simulations.***

*A. Hospital et al, Bioinformatics 2012, 28 (9), 1278-1279.*

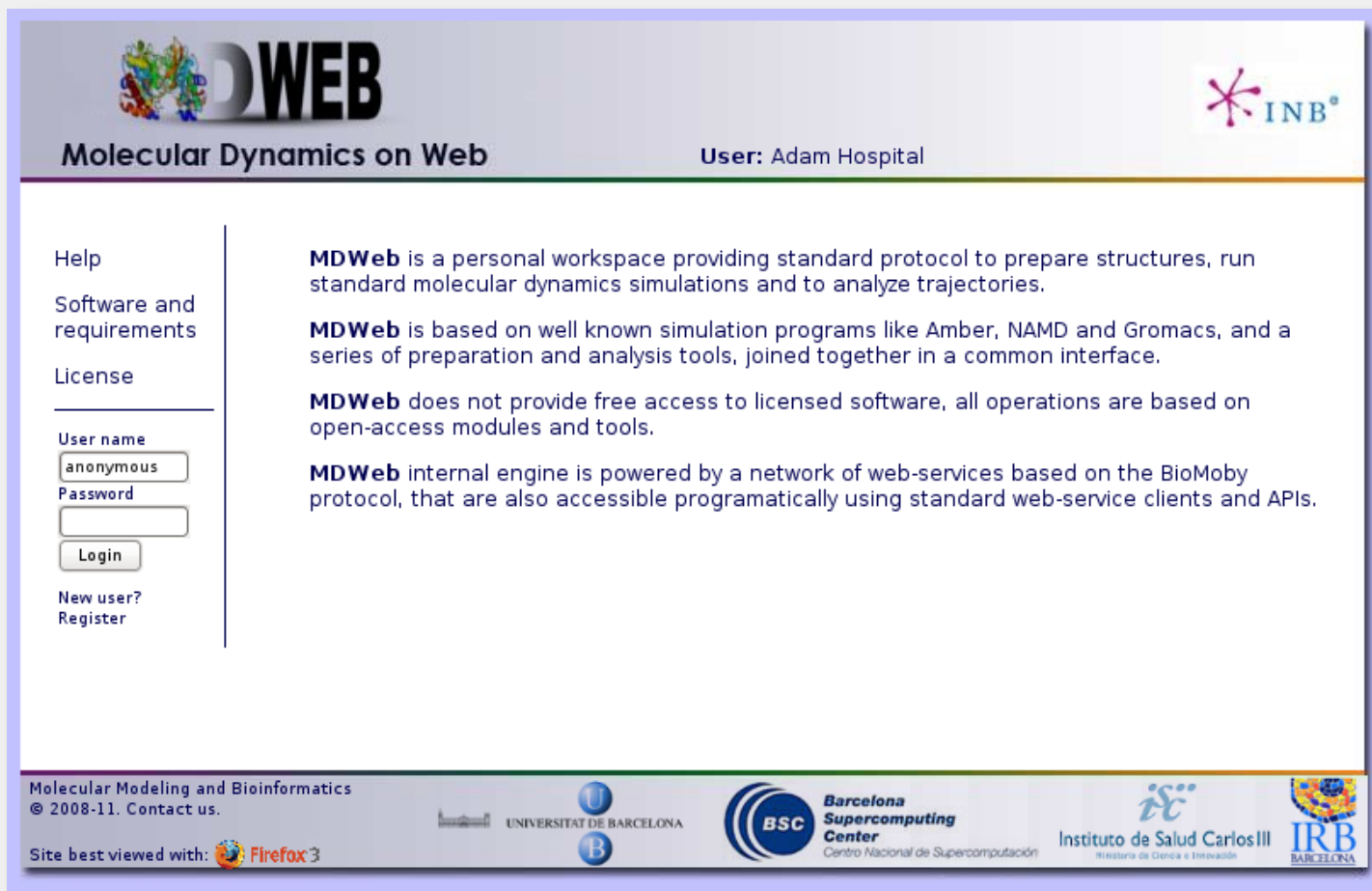


The screenshot shows the MDWeb website interface. At the top, there is a logo for MDWeb (Molecular Dynamics on Web) and the INB logo. Below the logo, the text "Molecular Dynamics on Web" is displayed. To the right, the user name "User: Adam Hospital" is shown. On the left side, there is a navigation menu with links: "Help", "Software and requirements", "License", "User name" (with a text input field containing "anonymous"), "Password" (with a text input field), "Login" (a button), "New user?", and "Register". The main content area contains three paragraphs of text: "MDWeb is a personal workspace providing standard protocol to prepare structures, run standard molecular dynamics simulations and to analyze trajectories.", "MDWeb is based on well known simulation programs like Amber, NAMD and Gromacs, and a series of preparation and analysis tools, joined together in a common interface.", and "MDWeb does not provide free access to licensed software, all operations are based on open-access modules and tools." Below this, it states: "MDWeb internal engine is powered by a network of web-services based on the BioMoby protocol, that are also accessible programatically using standard web-service clients and APIs." At the bottom, there is a footer with logos for "Molecular Modeling and Bioinformatics", "© 2008-11. Contact us.", "UNIVERSITAT DE BARCELONA", "BSC Barcelona Supercomputing Center", "Instituto de Salud Carlos III", and "IRB BARCELONA". A note at the bottom left says "Site best viewed with: Firefox 3".

- *Introduction.*
  - *Molecular Flexibility: importance.*
  - *Molecular Dynamics: use limitations.*
  - *MoDEL, MDMoby & MDWeb.*
- **Molecular Dynamics on Web (MDWeb).**
  - *MDWeb Setup: Structure Checking, Workflows & Operations, MD Run.*
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- *IRB Web Servers.*
  - *MD & Flexibility: FlexServ, NAFlex.*
  - *MD Databases: MoDEL, BigNASim.*



<http://mmb.irbbarcelona.org/MDWeb>



The screenshot shows the MDWeb web interface. At the top, there is a logo for MDWeb and the text "Molecular Dynamics on Web". To the right, it says "User: Adam Hospital". Below the header, there is a sidebar on the left with links: "Help", "Software and requirements", "License", "User name", "Password", "Login", "New user?", and "Register". The main content area contains three paragraphs of text about MDWeb. The footer includes logos for the University of Barcelona, BSC (Barcelona Supercomputing Center), Instituto de Salud Carlos III, and IRB Barcelona.

**MDWeb**

Molecular Dynamics on Web

User: Adam Hospital

Help

Software and requirements

License

User name

anonymous

Password

Login

New user?

Register


**MDWeb** is a personal workspace providing standard protocol to prepare structures, run standard molecular dynamics simulations and to analyze trajectories.

**MDWeb** is based on well known simulation programs like Amber, NAMD and Gromacs, and a series of preparation and analysis tools, joined together in a common interface.

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Molecular Modeling and Bioinformatics  
© 2008-11. Contact us.

Site best viewed with:  Firefox 3

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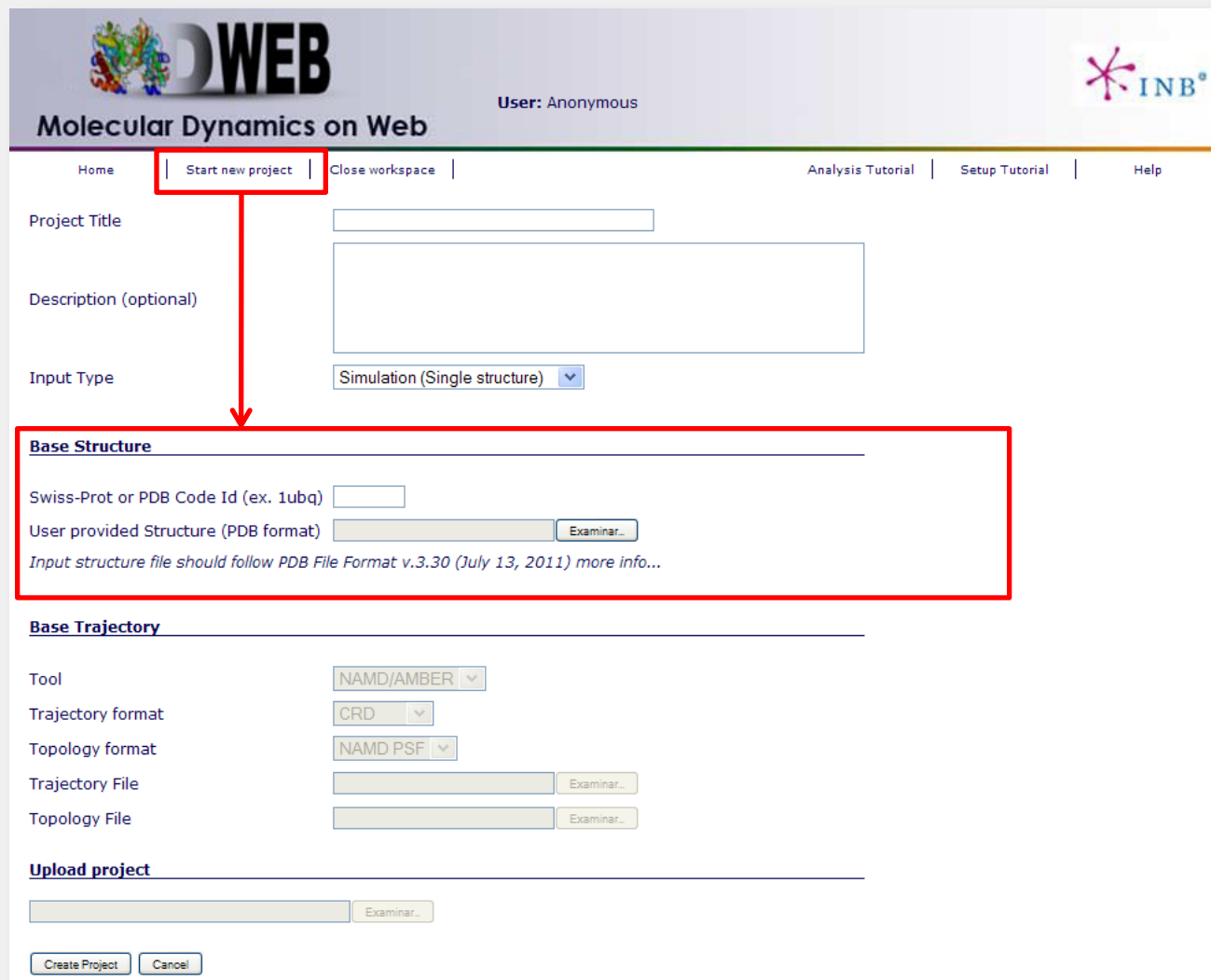
BSC  
Barcelona Supercomputing Center  
Centro Nacional de Supercomputación

Instituto de Salud Carlos III  
Ministerio de Ciencia e Innovación

IRB  
BARCELONA

## Start New Project:

- Base Structure.
  - *Str. checking.*
- Base Trajectory.



**MDWEB**  
Molecular Dynamics on Web

User: Anonymous

Home | **Start new project** | Close workspace | Analysis Tutorial | Setup Tutorial | Help

Project Title

Description (optional)

Input Type

**Base Structure**

Swiss-Prot or PDB Code Id (ex. 1ubq)

User provided Structure (PDB format)

Input structure file should follow PDB File Format v.3.30 (July 13, 2011) more info...

**Base Trajectory**

Tool

Trajectory format

Topology format

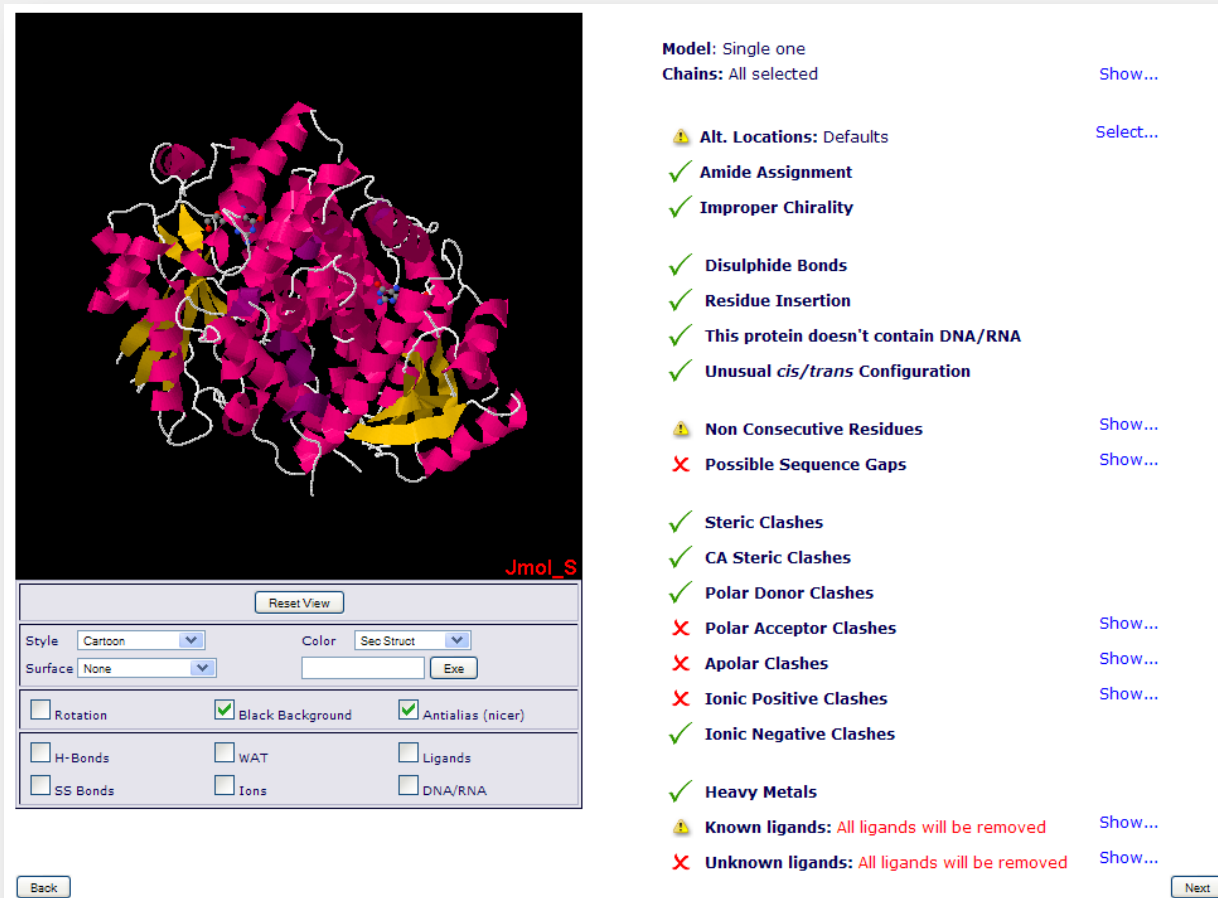
Trajectory File

Topology File

**Upload project**

## Initial Structure Checking:

- Models/Chains.
- Atom Alt. Location.
- Amide Assignments.
- Missing atoms/residues.
- Clashes.
- Ligands (known/unknown).



**Model:** Single one  
**Chains:** All selected [Show...](#)

**Alt. Locations:** Defaults [Select...](#)

- ✓ Amide Assignment
- ✓ Improper Chirality
- ✓ Disulphide Bonds
- ✓ Residue Insertion
- ✓ This protein doesn't contain DNA/RNA
- ✓ Unusual *cis/trans* Configuration
- ⚠ Non Consecutive Residues [Show...](#)
- ✗ Possible Sequence Gaps [Show...](#)
- ✓ Steric Clashes
- ✓ CA Steric Clashes
- ✓ Polar Donor Clashes
- ✗ Polar Acceptor Clashes [Show...](#)
- ✗ Apolar Clashes [Show...](#)
- ✗ Ionic Positive Clashes [Show...](#)
- ✓ Ionic Negative Clashes
- ✓ Heavy Metals
- ⚠ Known ligands: All ligands will be removed [Show...](#)
- ✗ Unknown ligands: All ligands will be removed [Show...](#)

[Back](#) [Next](#)



**MDWEB**  
Molecular Dynamics on Web

User: Anonymous

Home | Start new project | Close workspace | Help

**1a32 (MDWeb4db7444d5700b)**

Last modification on: 27/04/2011 00:16  
Disk Usage: 804 kB

**Stored structures**

Click on structure title to deploy the toolbox.

• PDB Base structure (86.3 kB) [Icons]

Select the desired operation.

Title: \_00 Comment:

List of Operations:

- Check for disulphide bonds
- Clean PDB
- Fix Side Chains
- Mutate residue
- Amber FULL MD Setup
- Amber MD Setup
- Amber MD Setup with Solvation
- Generate Topology for Amber
- Generate Topology for Gromacs
- Generate Topology for Namd
- Gromacs FULL MD Setup
- Gromacs MD Setup
- Gromacs MD Setup with Solvation
- Namd FULL MD Setup
- Namd MD Setup
- Namd MD Setup with Solvation

**Operations**

[Icons]

**Operations**

- Perform a new setup operation on the selected structure.
- Perform a new simulation/optimization.
- Perform a new analysis.
- Visualize structure using Rasmol compatibles viewers (plug-in required).
- Visualize structure using JMol.
- View log file.
- Download results in a compressed tgz file.
- Delete item from the workspace.

Molecular M...  
© 2008-11...  
Site best vie...

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BSC  
Barcelona Supercomputing Center  
Centro Nacional de Supercomputación

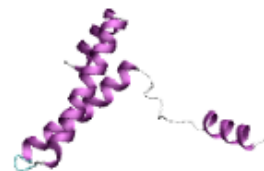
Instituto de Salud Carlos III  
Instituto de Salud Carlos III

IRB  
BARCELONA

## 1a32 (MDWeb4d5d3df62d0da)

Last modification on: 22/04/2011 13:12

Disk Usage: 59.4 MB



### Stored structures

Click on structure title to deploy the toolbox.

Base structure (86 kB)

Select the desired operation.

Title:  Comment:

Forcefield:

Cleaned Structure\_10 (57 kB)

Structure with hydrogens added (GROMACS)\_00 (592 kB)

#### Generate top and itp Topology Files for Gromacs.

- Program: pdb2gmx from Gromacs Package.
- Crystallographic waters will be removed.
- Side chain missing atoms will be added with Leap from AmberTools package.
- Hydrogens will be added with pdb2gmx from Gromacs Package if needed.

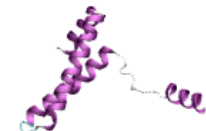
[Click for more information](#)

# MDWeb: Workflow progress report

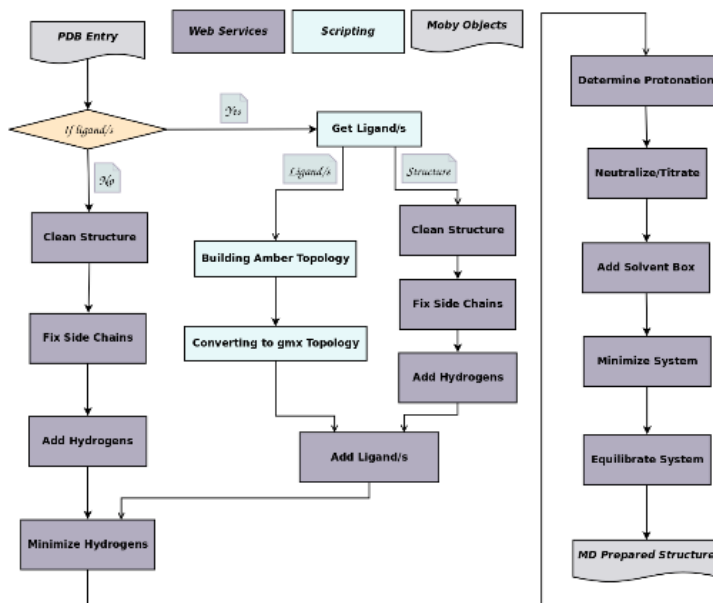
**1a32 (MDWeb507e85d99fbf0)**

Last modification on: 17/10/2012 12:19



Disk Usage: 700 kB



## Running Workflow: GROMACS FULL Setup



- 1.- Checking If ligand/s ... Done
- 2.- No Ligand/s found! Done
- 3.- Cleaning Structure ... Done
- 4.- Fixing Side Chains ... Done
- 5.- Adding Hydrogens ... Done
- 6.- Minimizing Hydrogens ... Done
- 7.- Determining Protonation ... Running
- 8.- Neutralizing / Titrating ... Waiting
- 9.- Adding Solvent Box ... Waiting
- 10.- Minimizing System ... Waiting
- Equilibrating system:
- 11.- Heating solvent to 300K ... Waiting
- 12.- Lowering Protein Restraints ... Waiting
- 13.- Reducing Restraints to just Protein Backbone ... Waiting
- 14.- Lowering Restraints to just 100 KJ/Mol-nm2 ... Waiting
- 15.- Free MD, without restraints ... Waiting

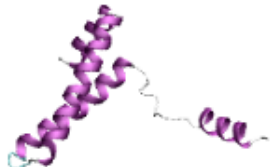
**Molecular Dynamics on Web**
User: Adam Hospital

[Home](#) | [Start new project](#) | [Close workspace](#) | [Help](#)

## 1a32 (MDWeb4d5d3df62d0da)





















Last modification on: 22/04/2011 13:12

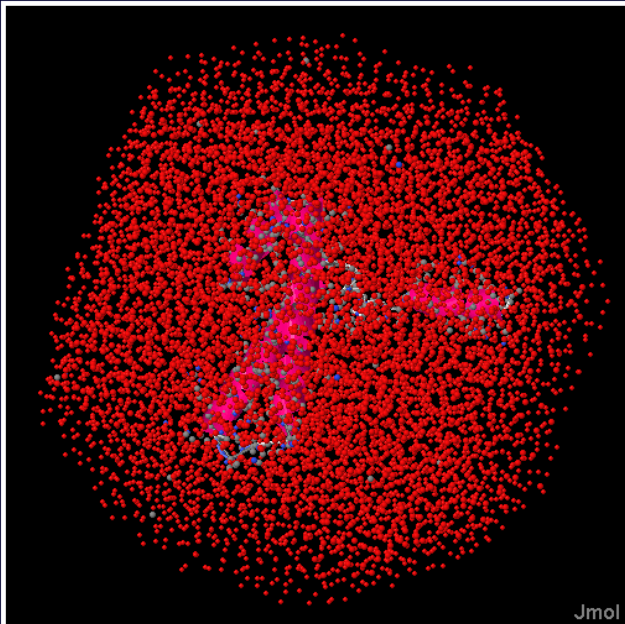
Disk Usage: 59.4 MB



### Stored structures

Click on structure title to deploy the toolbox.

- [-]  Base structure (86 kB) 
- [-]  Cleaned Structure\_10 (57 kB) 
- [-]  Structure with hydrogens added (GROMACS)\_00 (592 kB) 
- [-]  Energetically minimized hydrogens\_01 (636 kB) 
- [-]  Energetically minimized structure\_02 (520 kB) 
- [-]  Solvated system (GROMACS)\_03 (3.6 MB) 
- [-]  Energetically minimized system\_07 (3.7 MB) 
- [-]  Equilibrated System (NVE)\_56 (MD Config Files) 
- [-]  Equilibrated System (NVE)\_58 (63.1 MB) 
- [-]  Trajectory snapshot\_59 (17.5 kB) 



**Structure**

- ☒ Atoms
- ☒ Ligands
- ☐ Wireframe
- ☒ Cartoon
- ☐ Show hydrogen bonds

**Cartoon color**

☒ Structure ☐ Chain

☒ Hide Hydrogens

[Reset view](#)



## 1a32 (MDWeb50657024cc97e)


Last modification on: 28/09/2012 16:49

Disk Usage: 24.9 MB

### Stored structures

Click on structure title to deploy the toolbox.


 Base structure (88 kB) 


•  Prepared Amber Structure (Setup + Solvation + Equilibration)


Select the desired operation.

Title:

Comment:

Simple Box Solvent Molecular Dynamics (NPT) 

 Click for more information

**Only return Configuration Files (without running simulation) **

Time step (fs)

Temperature (K)

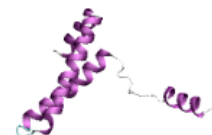
Total Time (ps)

Output freq. (steps)

Total Snapshots: 10000

### System Molecular Dynamics Simulation in Water Box:

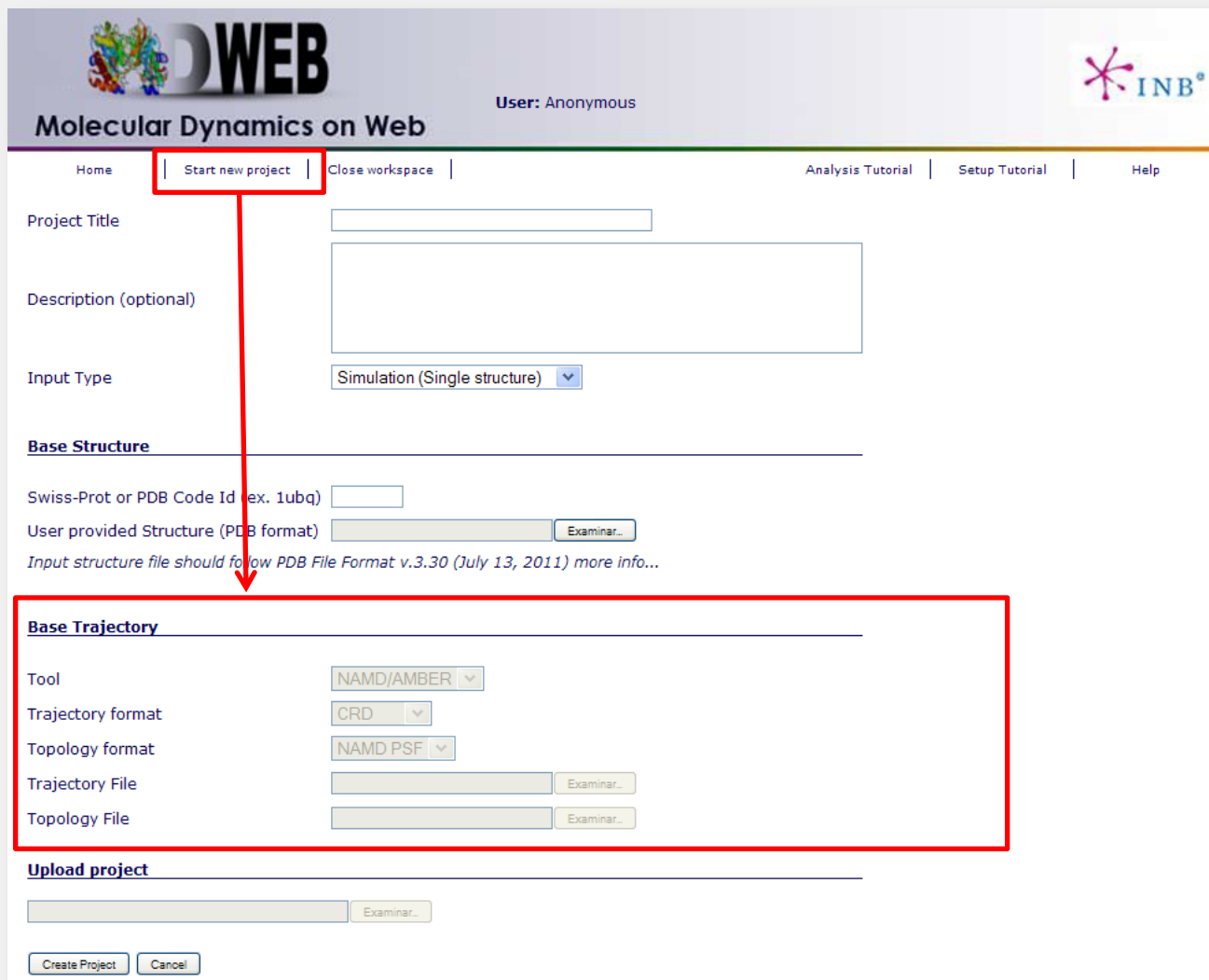
- Program: namd2 from NAMD package.
- Simulation done in NPT ensemble with Periodic Boundary Conditions.
- Particle Mesh Ewald (PME) for full-system periodic electrostatics.
- Constant temperature dynamics via Langevin Dynamics.
- Constant pressure dynamics via Nose-Hoover Langevin piston.
- SHAKE was used to maintain all bonds involving hydrogen atoms at their equilibrium values.





## Start New Project:

- Base Structure.
  - *Str. checking.*
- Base Trajectory.



**MDWEB**  
Molecular Dynamics on Web

User: Anonymous

Home | **Start new project** | Close workspace | Analysis Tutorial | Setup Tutorial | Help

Project Title

Description (optional)

Input Type

**Base Structure**

Swiss-Prot or PDB Code Id (ex. 1ubq)

User provided Structure (PDB format)

*Input structure file should follow PDB File Format v.3.30 (July 13, 2011) more info...*

**Base Trajectory**

Tool



Trajectory format

Topology format

Trajectory File

Topology File

**Upload project**

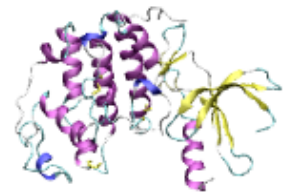
**Molecular Dynamics on Web**
User: Adam Hospital

[Home](#) | [Start new project](#) | [Close workspace](#) | [Help](#)

## 1aq1 (MDWeb4db16d2e4c55f)



Last modification on: 22/04/2011 13:59



Disk Usage: 28.4 MB



### Stored structures

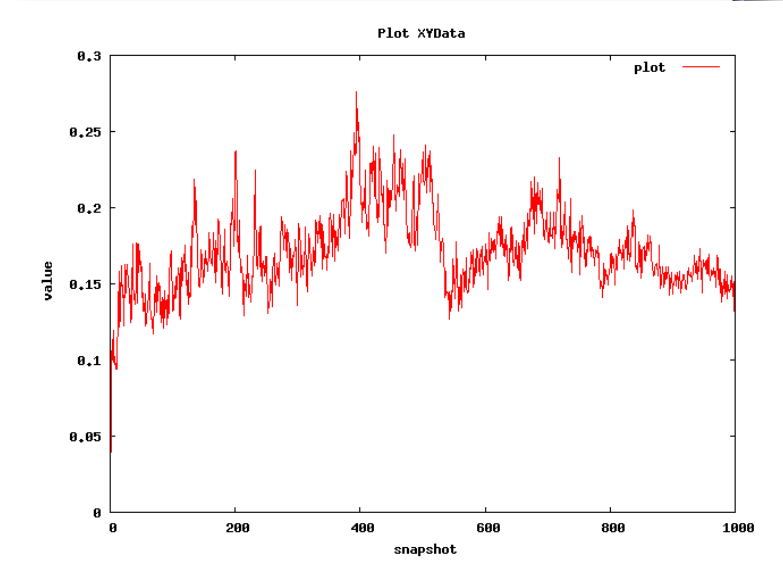
Click on structure title to deploy the toolbox.

☒  Base trajectory (23.7 MB) 

☒  Trajectory RMSd\_00 (2.2 MB) 

List of Operations:

- Compress trajectory to PCZ
- Converts trajectory to a set of PDB Files
- Converts trajectory to BINPOS Format
- Converts trajectory to CRD Format
- Converts trajectory to DCD Format
- Flexibility Analysis
- Get a trajectory fragment
- Get a trajectory snapshot
- Get Average Structure
- Plot BFactor per residue
- Plot Radius of Gyration along the trajectory
- Plot RMSd along the trajectory
- Plot RMSd x Residue
- Remove Water molecules and ions from trajectory
- Return trajectory for a set of atoms



Plot XYData

value

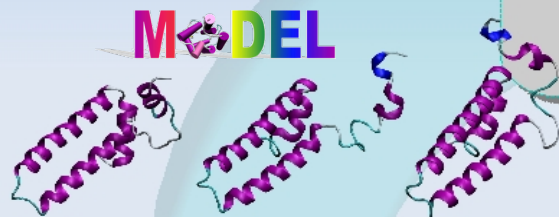
snapshot

plot

*FlexServ: Protein Flexibility Analysis from Coarse-Grained Simulations.*

**FlexServ**

**MODEL**



Brownian Dynamics  
Discrete Molecular Dynamics  
Normal Mode Analysis

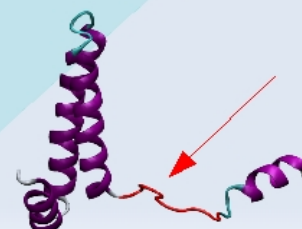
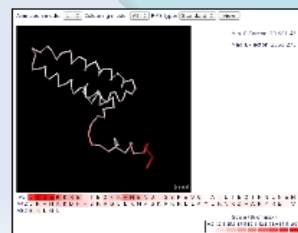
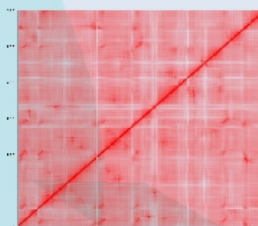
Coarse-Grained Dynamics

RCSB **PDB**  
PROTEIN DATA BANK



Principal Components  
Variance Profile  
B-factors Landscape  
Lindemann Coefficients  
Apparent Stiffness  
Hinge Point Predictions  
Residue Correlations  
Collectivity Indexes

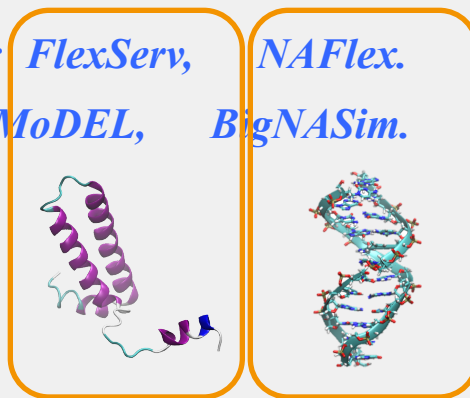
**Analysis**



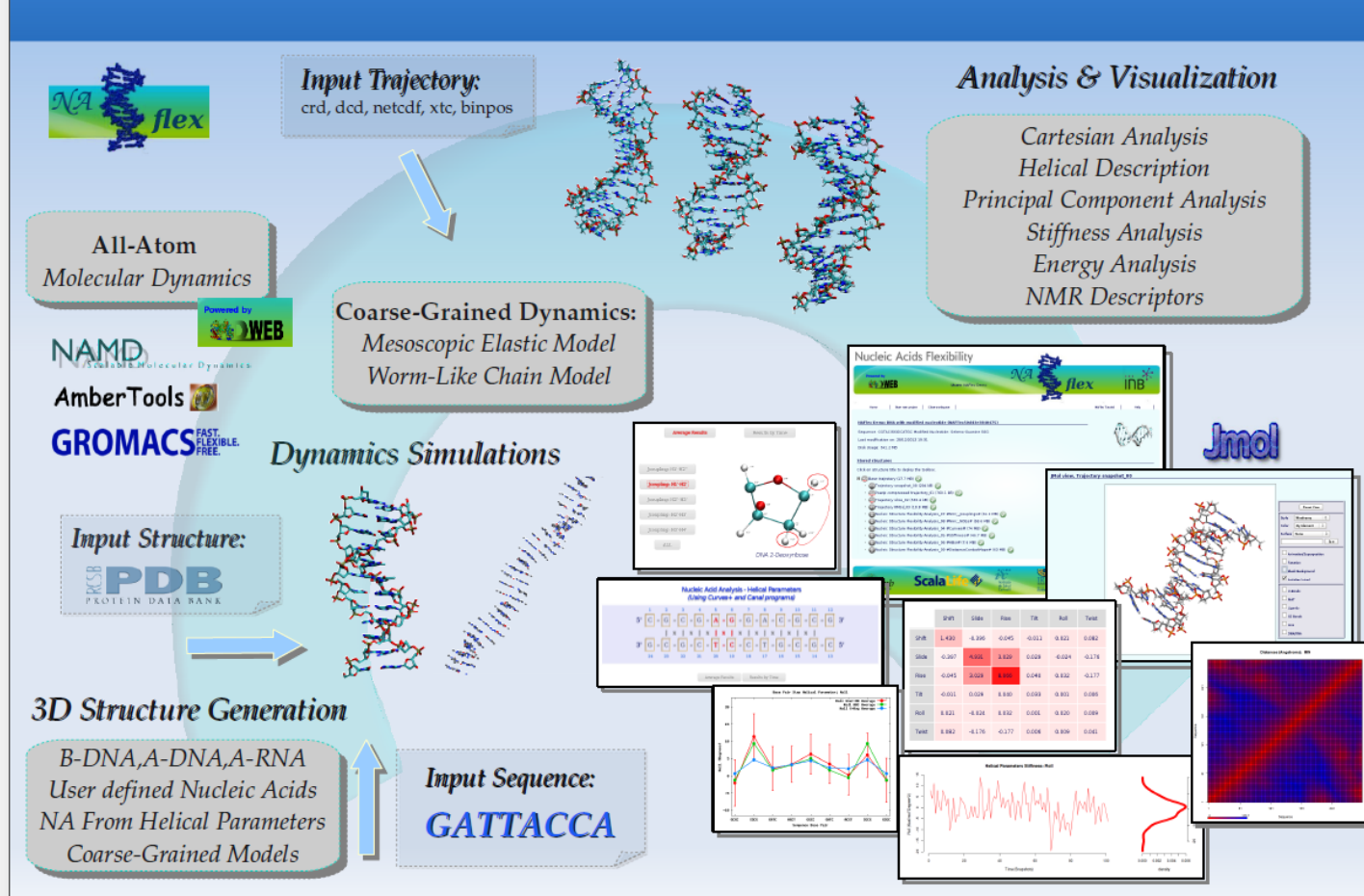
<http://mmb.irbbarcelona.org/FlexServ>

J. Camps et al, *Bioinformatics* 2009, 25(13):1709-10.

- *Introduction.*
  - *Molecular Flexibility: importance.*
  - *Molecular Dynamics: use limitations.*
  - *MoDEL, MDMoby & MDWeb.*
- *Molecular Dynamics on Web (MDWeb).*
  - *MDWeb Setup: Structure Checking, Workflows & Operations, MD Run.*
  - *MDWeb Analysis: Basic Analysis & FlexServ.*
- **IRB Web Servers.**
  - *MD & Flexibility: FlexServ, NAFlex.*
  - *MD Databases: MoDEL, BigNASim.*

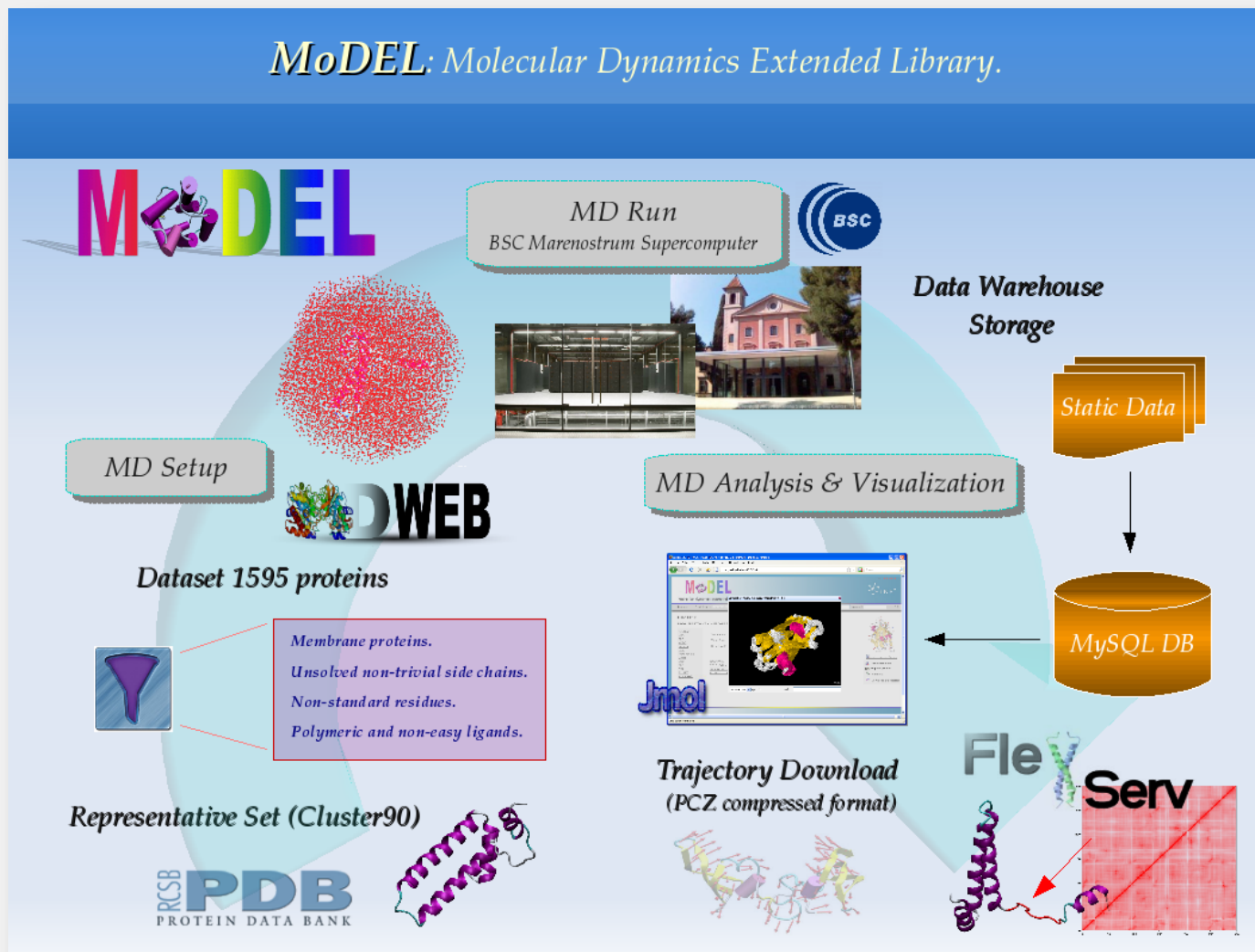


*NAFlex: A web server for the study of Nucleic Acids Flexibility.*



<http://mmb.irbbarcelona.org/NAFlex>

A. Hospital et al, Nucleic Acids Research, 2013, 41(W1):W47-W55.

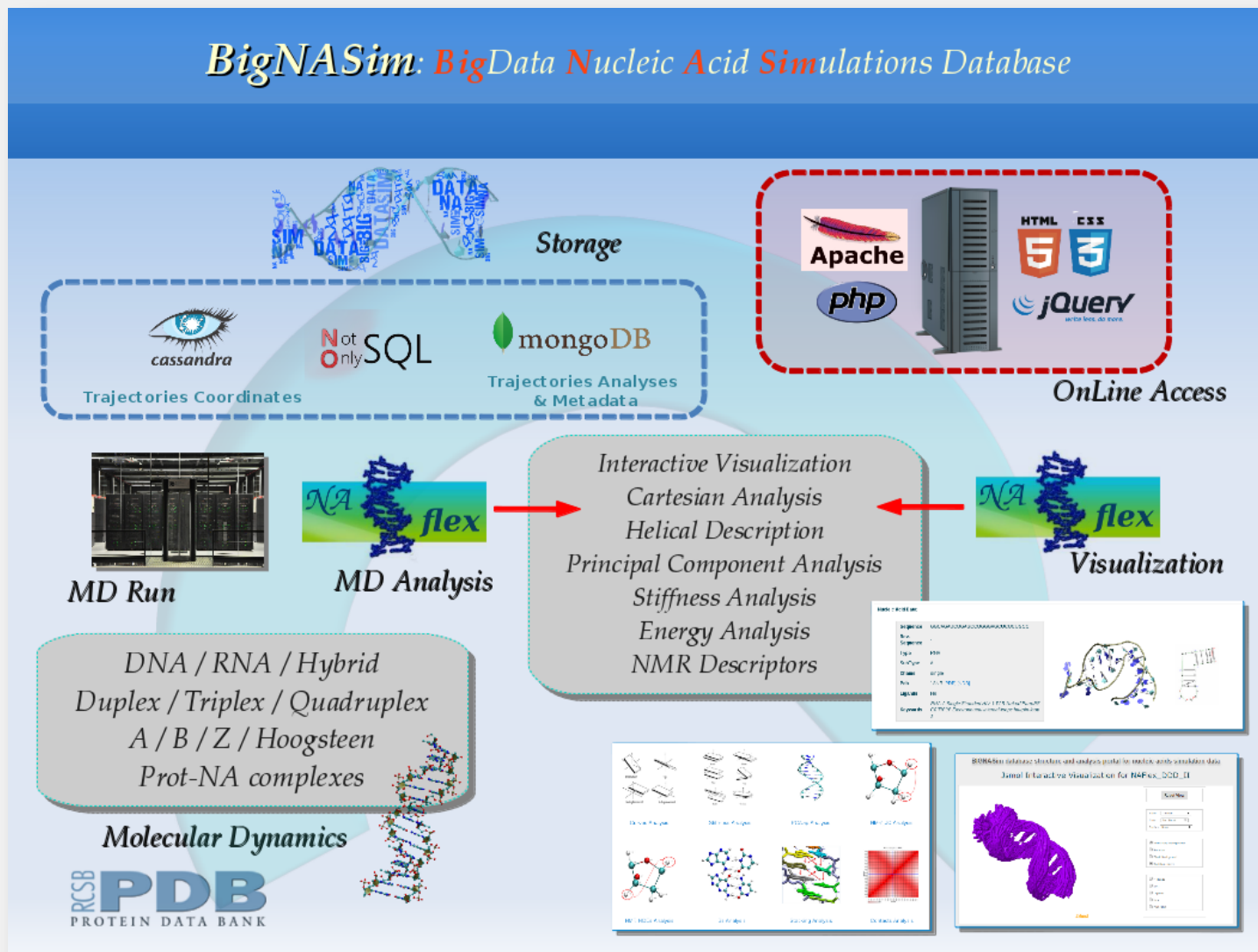


<http://mmb.irbbarcelona.org/MoDEL>

Meyer, D'Abramo & Hospital et al, Structure 2010, 18(11), 1399-1409



## BigNASim: *Big*Data *N*ucleic *A*cid *S*imulations Database



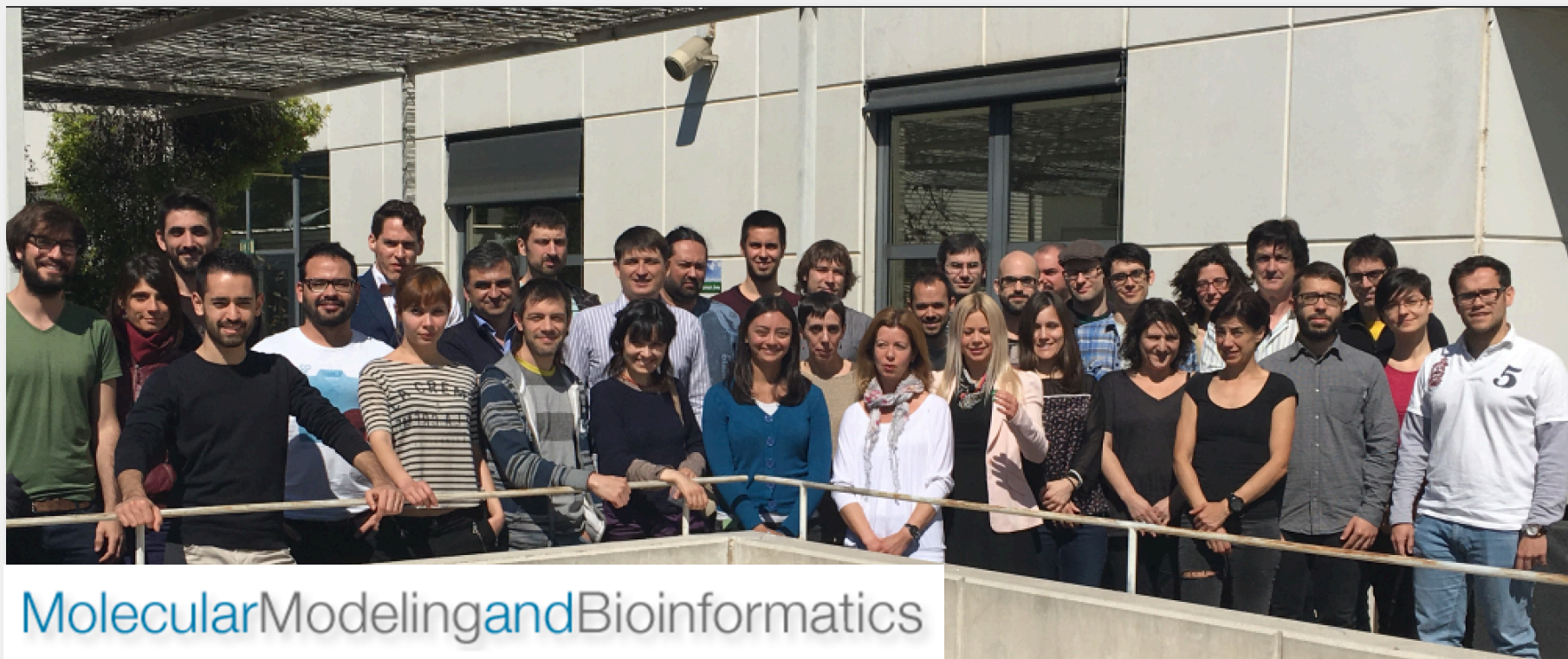
<http://mmb.irbbarcelona.org/BigNASim>

Hospital et al, Nucleic Acid Research 2016, 44(D1), 272-278.

- **BioExcel center of Excellence for Computational Biomolecular Research**
  - <http://www.bioexcel.eu>
- **MMB - IRB Barcelona Web Servers:**
  - <http://mmb.irbbarcelona.org/MDWeb> <http://mmb.irbbarcelona.org/MDWeb2>
  - <http://mmb.irbbarcelona.org/FlexServ>
  - <http://mmb.irbbarcelona.org/NAFlex>
  - <http://mmb.irbbarcelona.org/MoDEL>
  - <http://mmb.irbbarcelona.org/BigNASim>
- **Molecular Dynamics Packages:**
  - <http://www.gromacs.org>
  - <http://ambermd.org>
  - <http://www.ks.uiuc.edu/Research/namd/>







- <http://mmb.irbbarcelona.org>
- **Josep Lluís Gelpí & Modesto Orozco**



# Audience Q&A session

Please use the **Questions** function in GoToWebinar

## NEXT WEBINAR

**“Mutation free energy calculations with pmx”**  
with Bert de Groot

*10 June 2016*

*16:00-17:00 CEST*

[www.bioexcel.eu/contact](http://www.bioexcel.eu/contact)