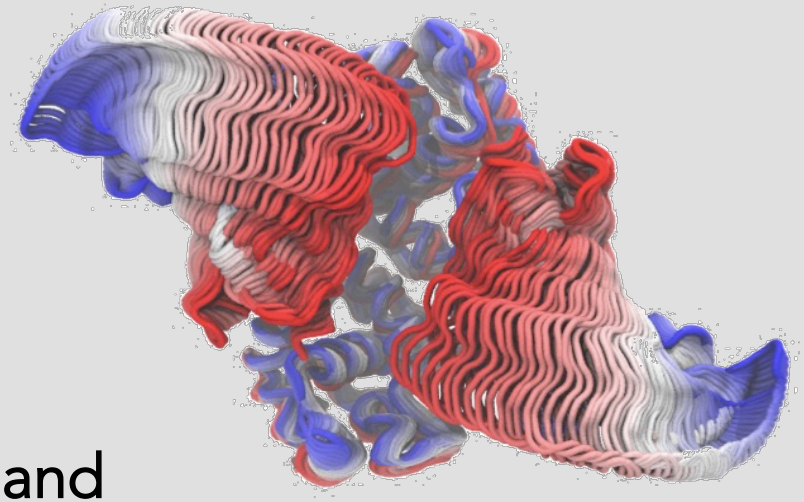
eBDIMS

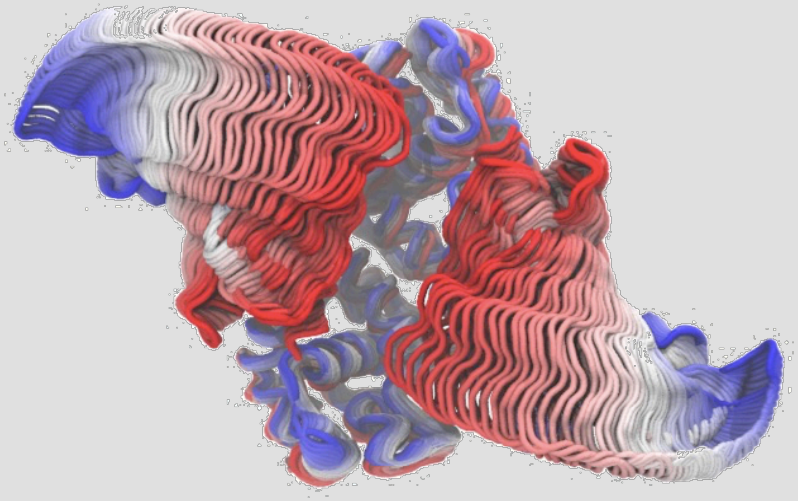
elastic-network driven Brownian Dynamics Importance Sampling



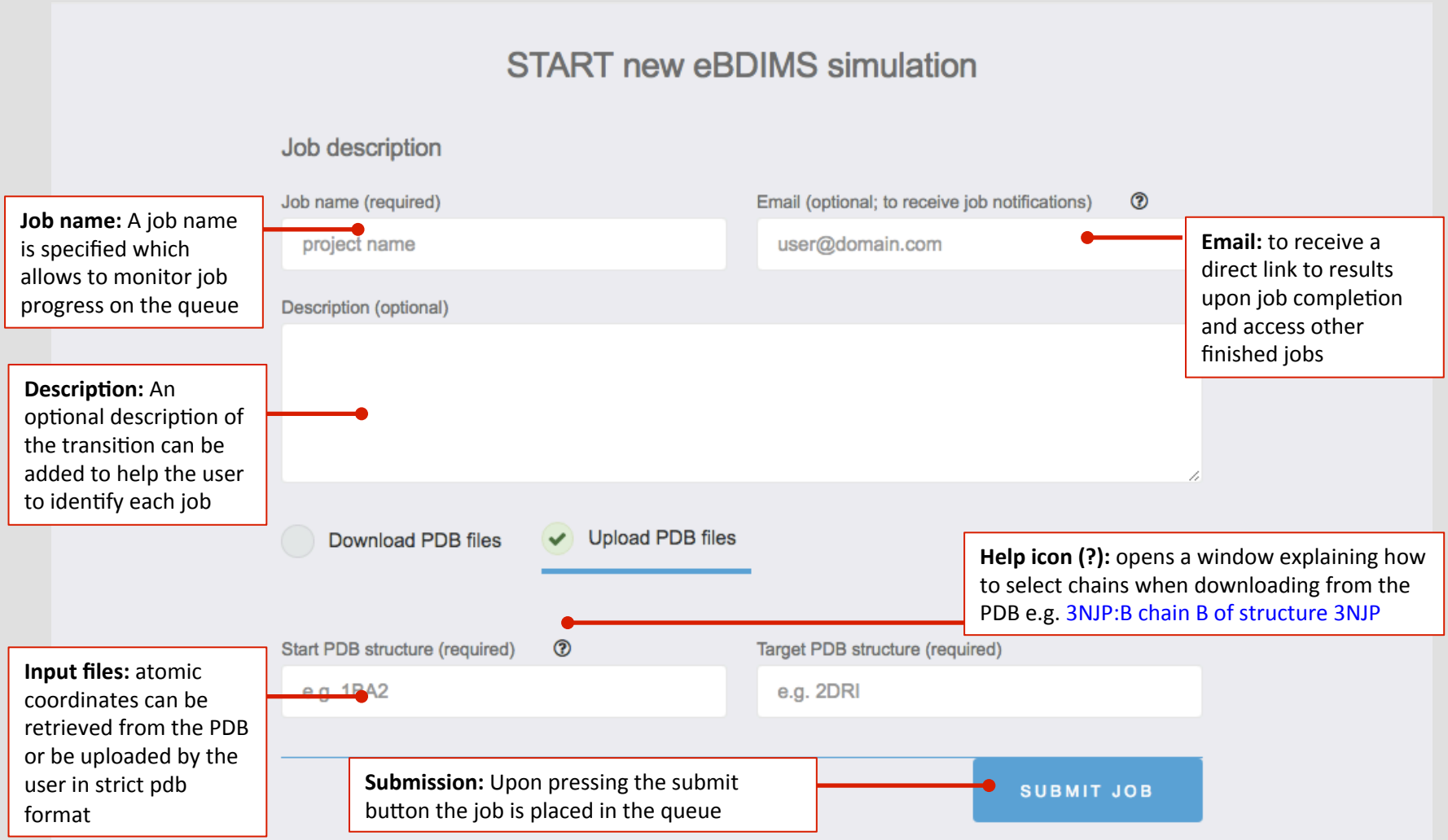
Step-by-step quick guide and tutorial

eBDIMS

User Interface



Job submission interface



Job name: A job name is specified which allows to monitor job progress on the queue

Email: to receive a direct link to results upon job completion and access other finished jobs

Description: An optional description of the transition can be added to help the user to identify each job

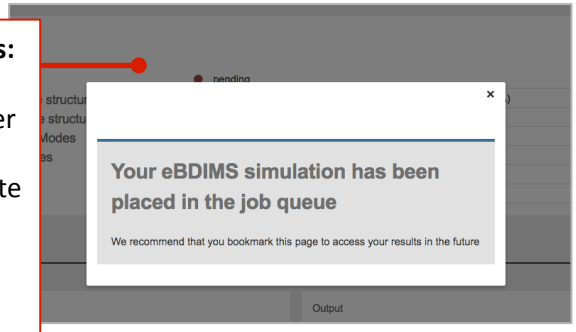
Help icon (?): opens a window explaining how to select chains when downloading from the PDB e.g. 3NJP:B chain B of structure 3NJP

Input files: atomic coordinates can be retrieved from the PDB or be uploaded by the user in strict pdb format

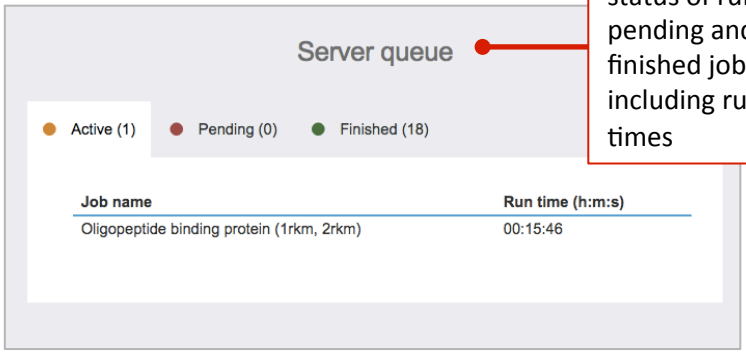
Submission: Upon pressing the submit button the job is placed in the queue

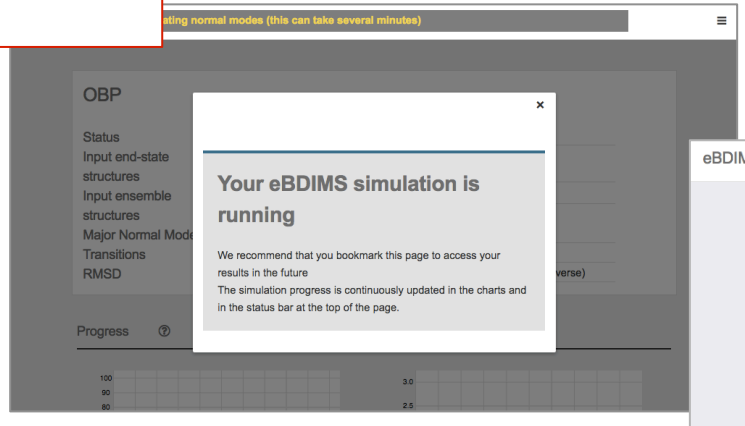
Real time updates upon submission

Job submission status: After clicking the submit button the user is redirected to a webpage with a private link to results, including job status, description and real-time updates on progress



Public queue tab: status of running, pending and finished jobs including running times

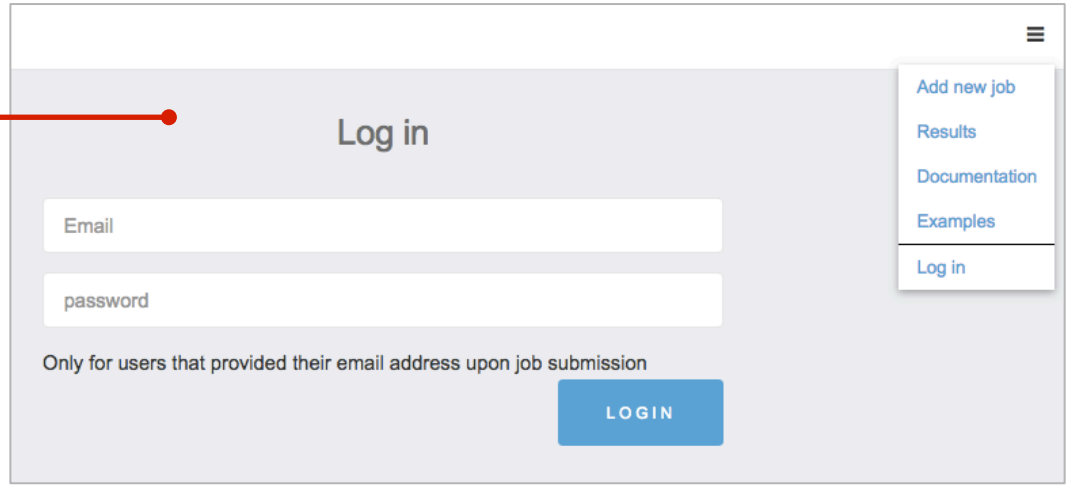




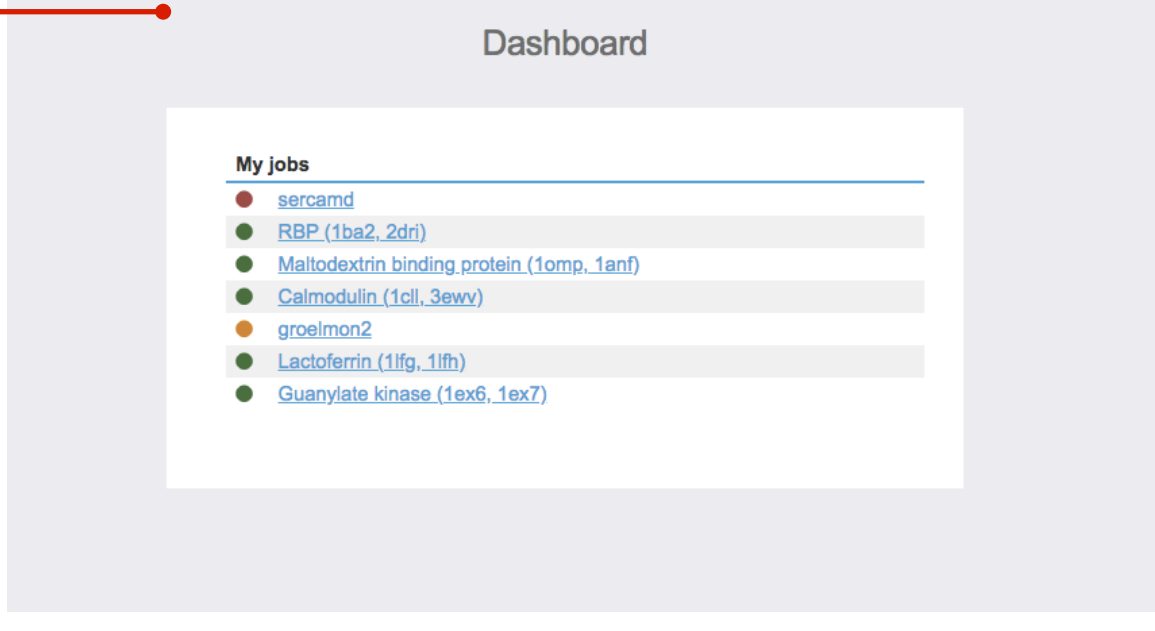
Real-time updates: as transitions advance, the progress and rMSD are plotted in real-time

Access to user jobs

Login to access stored results: If the user has provided an email, he/she will receive a password to log in by clicking on a menu at the upper right corner of the page.



Private user dashboard: upon login, the user can see the status of all his/her jobs (finished/running/queued) and access the results



Results interface

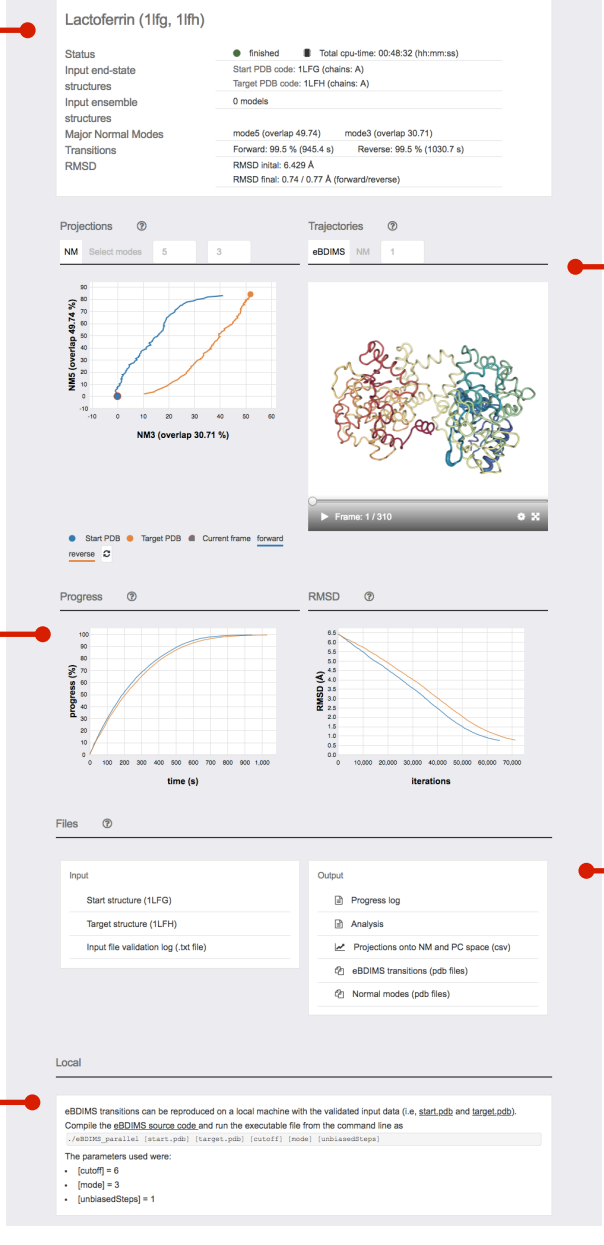
General information on the transition:
- initial and final rMSD
- run time, etc

NM/PC 2D-projections linked to 3D-Movies:
- Default modes
- Explore within the 10-subspace

Transition progress and rMSD versus time:
- Convergence
- Final rMSD reached

Links to download results files:
- Trajectories
- Projections

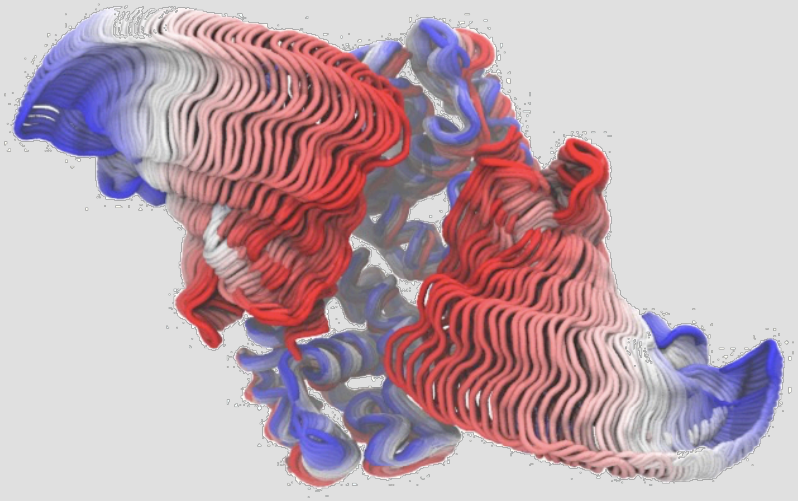
Commands to run the job in a local machine



eBDIMS

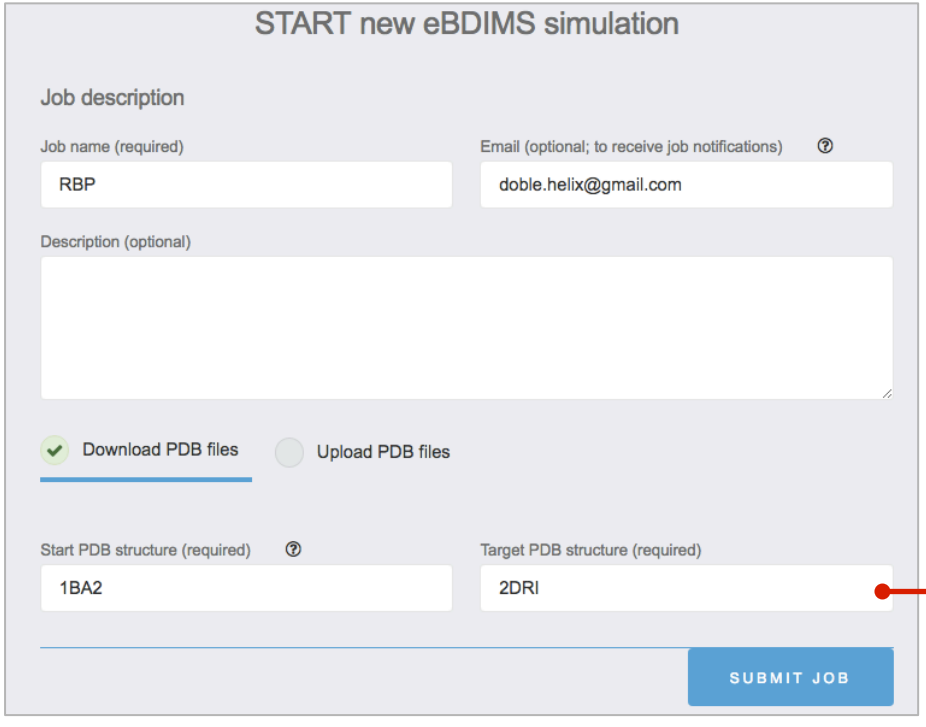
Example 1: Simple simulation from PDB codes

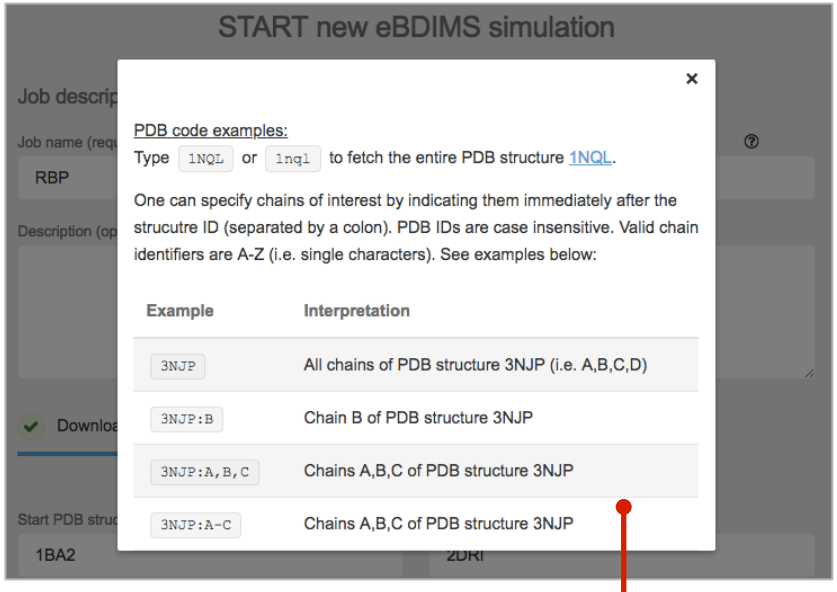
Example 2: Running eBDIMS uploading files



Running from PDB codes- Step 1 Chain Selection

In this tutorial we will show how to use the eBDIMS server by computing the transition pathways connecting the open (1BA2) and closed (2DRI) conformations of the *E.coli* Ribose Binding Protein (RBP):

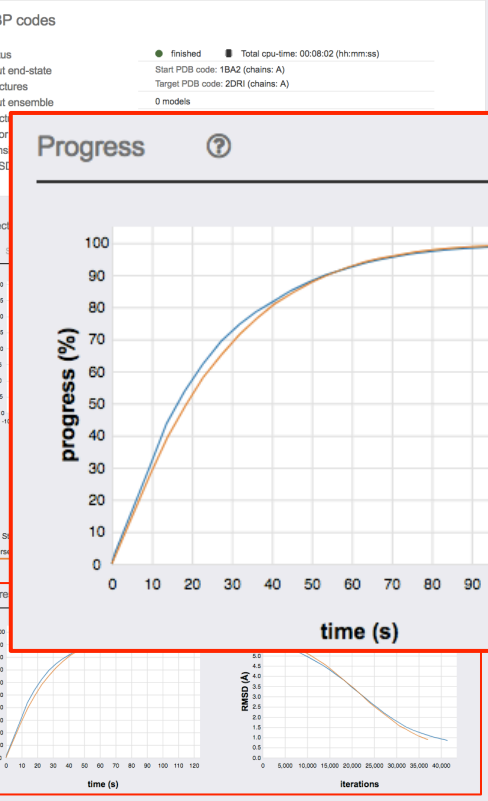




PDB codes and chains: since 1BA2 has two chains (A,B) and 2DRI only one (A), by default the server will take chain A which is common to both

Chain selection: For PDBs with the same chains, all are taken unless specified otherwise.
Click on the help icon to visualize the syntax for chain selection

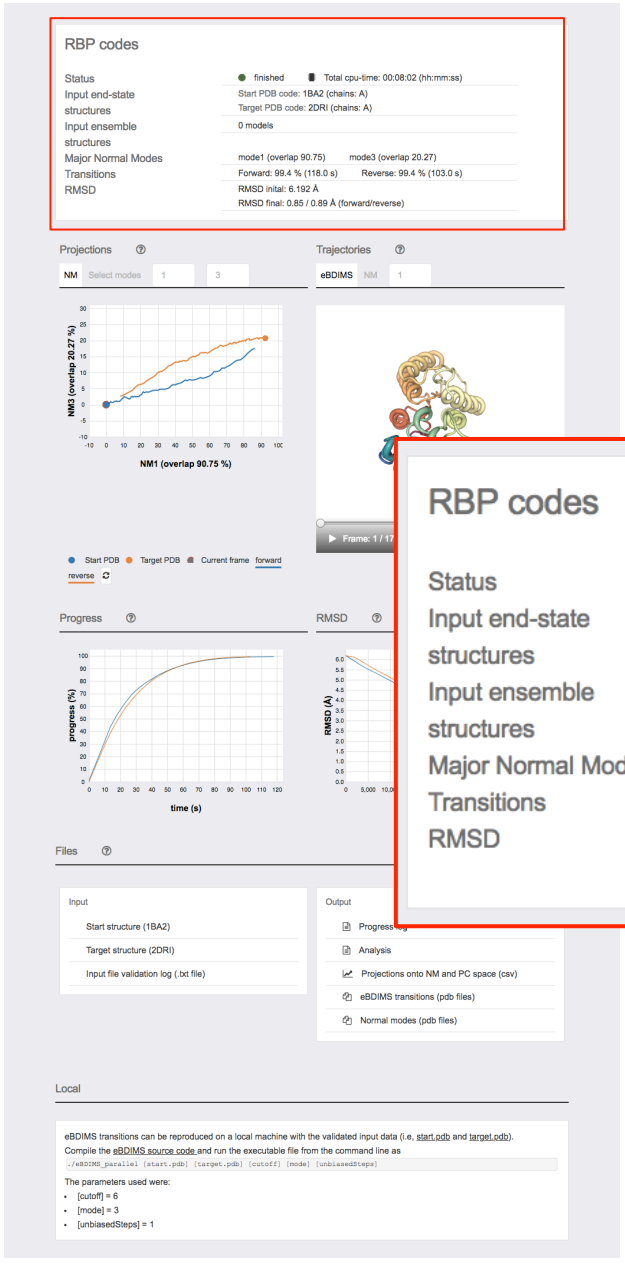
Running from PDB codes- Step 2 Transition Progress



Transition Progress: as the transitions run (first in the forward and then in the reverse direction), the evolution of the rMSD versus their target structure is reported.

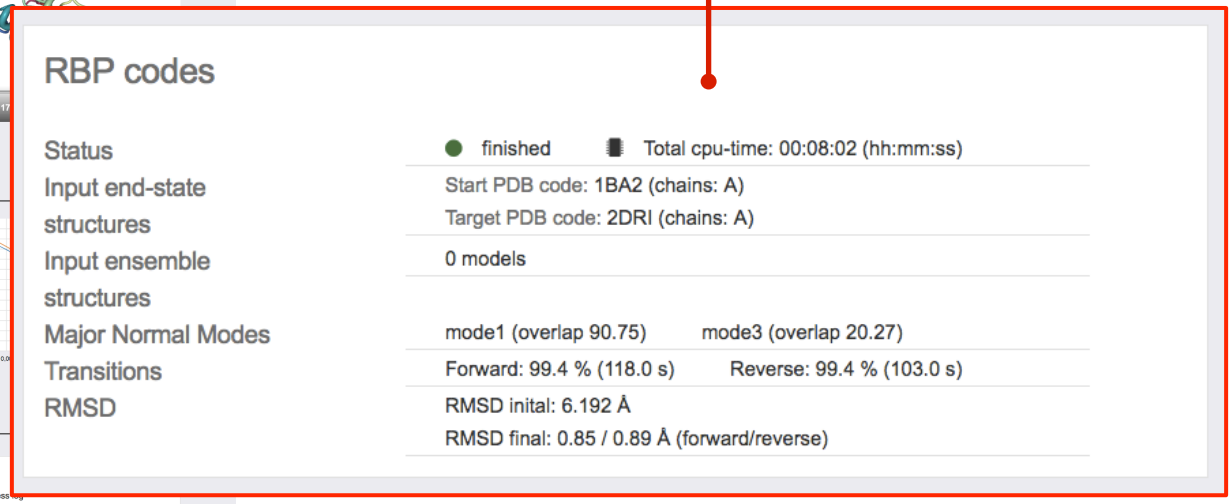
Each direction is completed > 95.5% or after 4h.

Running from PDB codes – Step 3 Checking results



General information: at the top of the results page, the final rMSD achieved in each direction is reported along with running time

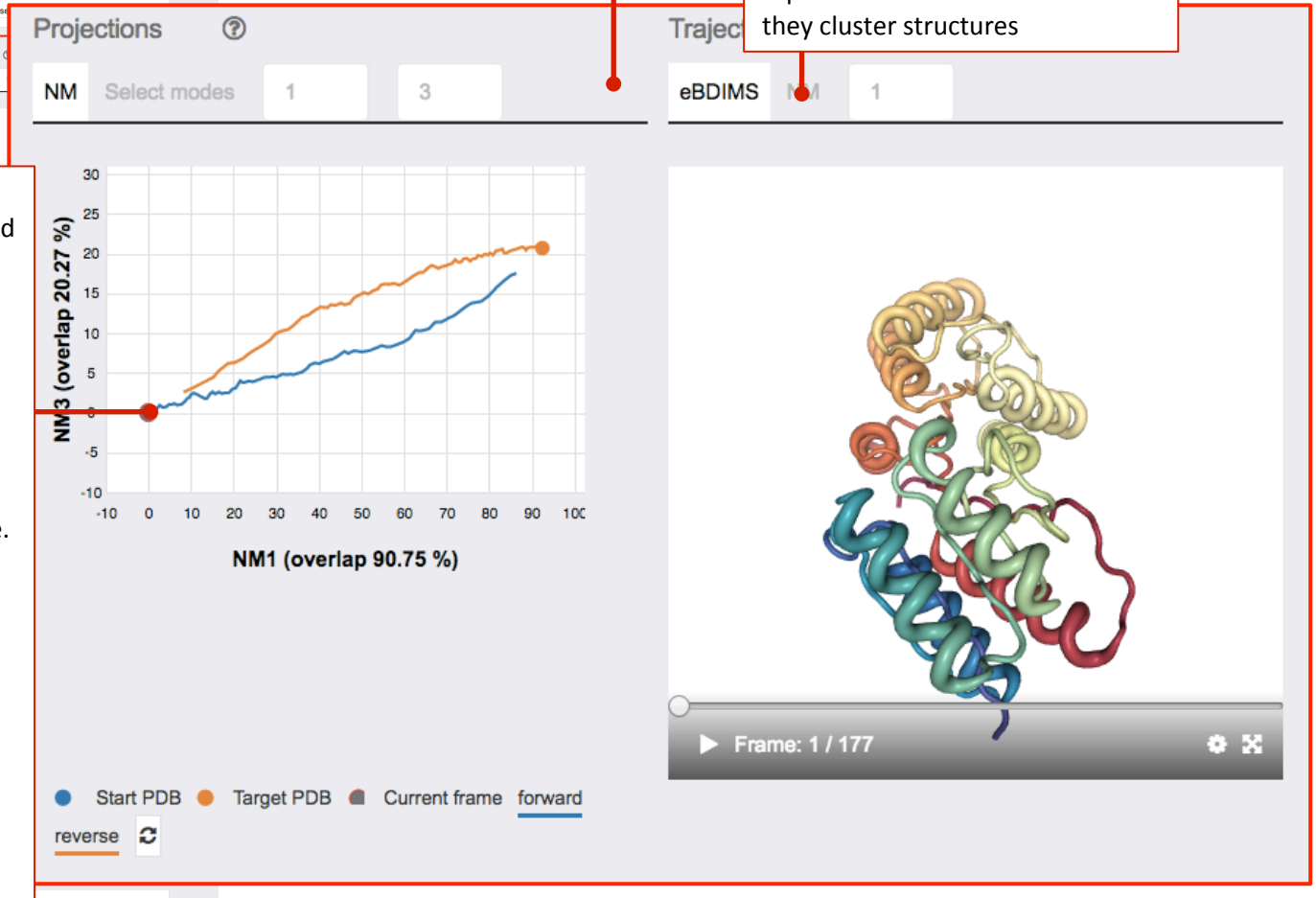
In general transitions proceed until completion (>99%), but in the case of very large proteins or small-scale complex rearrangements they may not be completed in the maximal allowed running time (8h), thus requiring several consecutive runs.



Running from PDB codes - Step 3 Checking results

Transition 3D-Movies: forward and reverse movie transitions are coupled to the projections onto NMs.

Normal Modes 3D-Movies: All NMs within the first 10-modes subspace can be visualized to better grasp which motions represent the 2D-axes and how they cluster structures



NM-Projections: forward and reverse trajectories are projected by default onto the two better overlapped NMs from the structure defined as “start”, which will appear at (0,0).

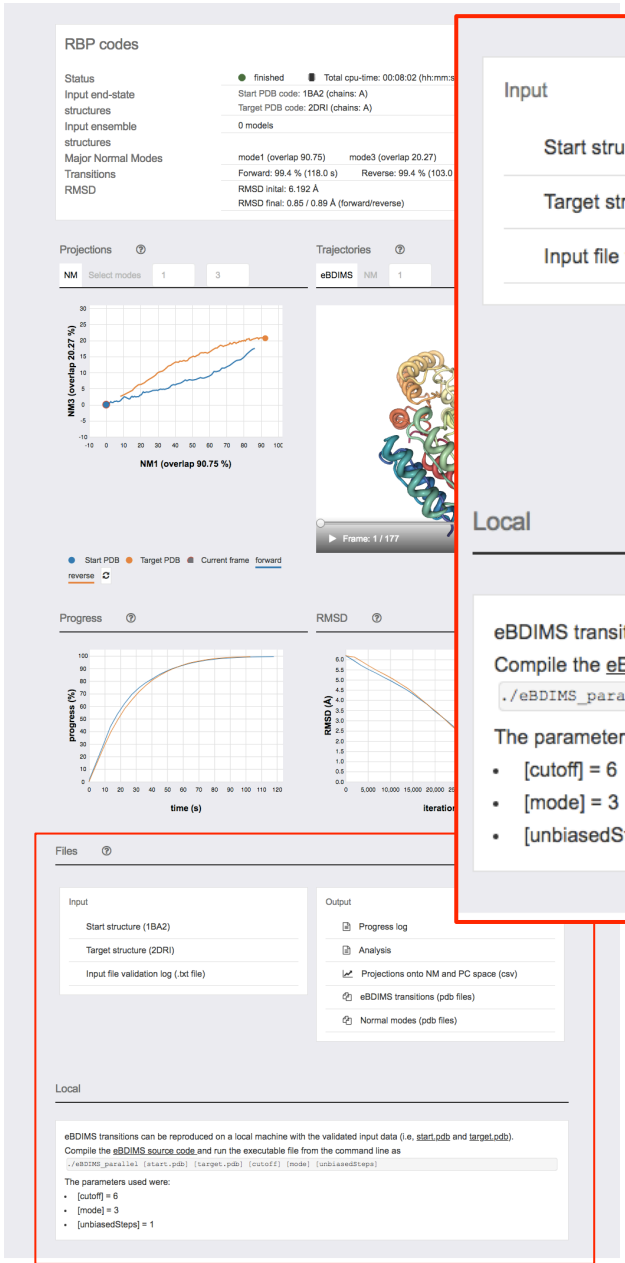
Structures with a “open” configuration render NMs with better overlaps with transitions and should be used as reference.

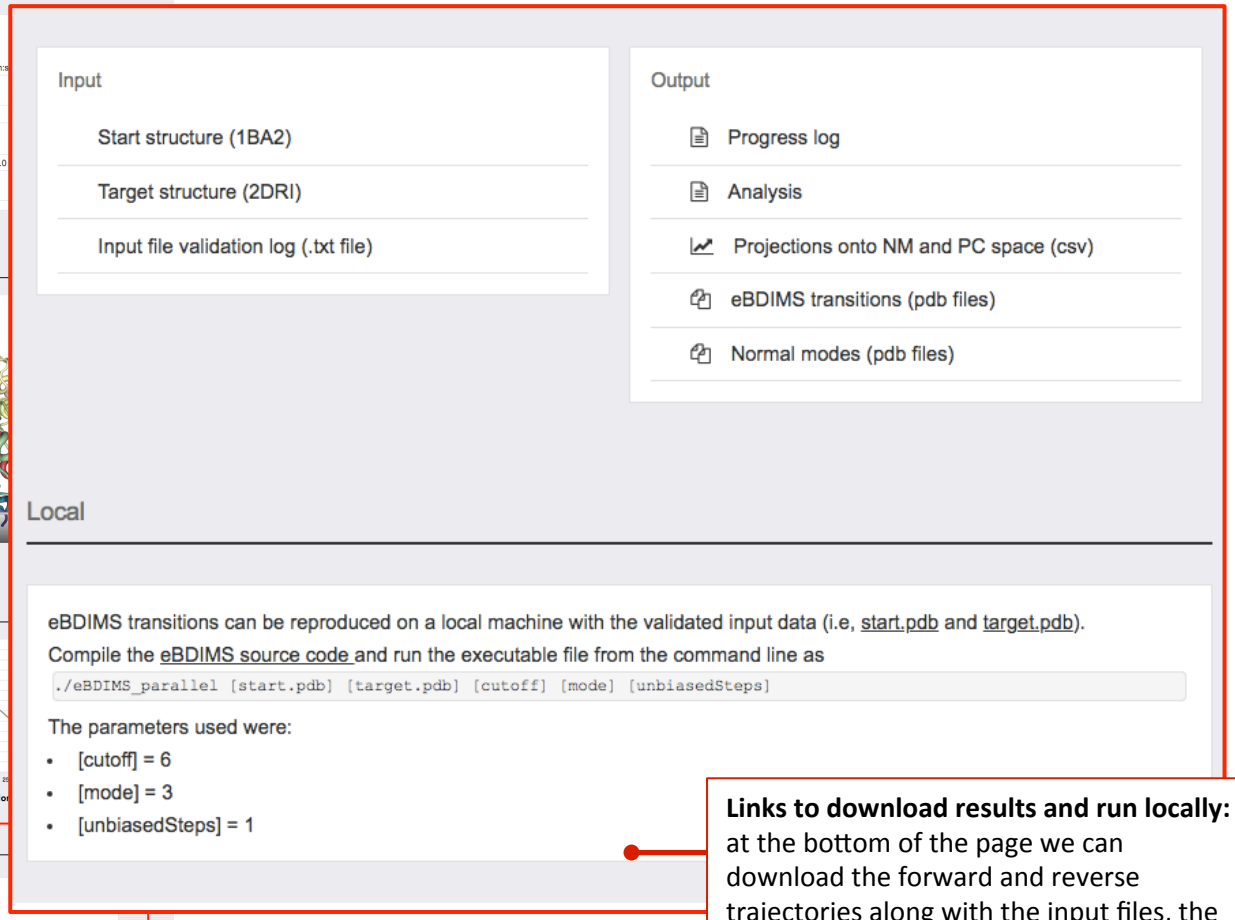
NMs within the 10-lowest frequency modes subspace can be explored.

Significant projections must be:
- Smooth
- Cluster different conformations separately

If projections do not fulfill these conditions, we recommend using the target structure as reference.

Running from PDB codes – Step 4 Downloading results



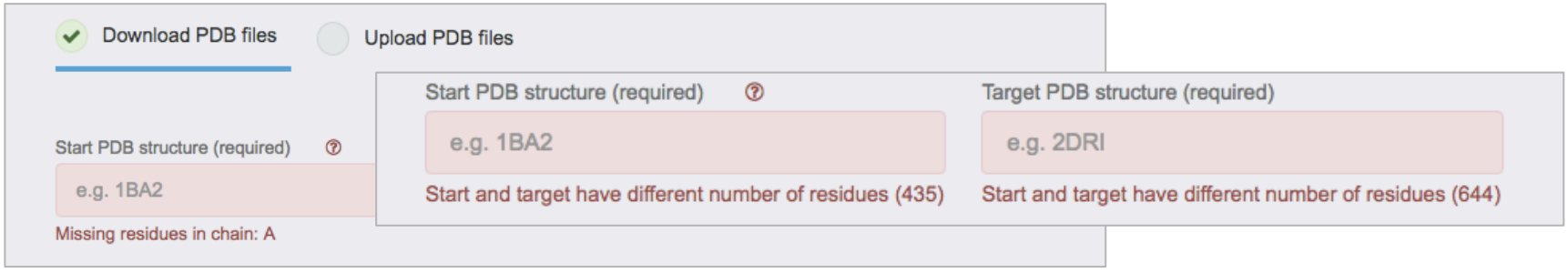


Links to download results and run locally: at the bottom of the page we can download the forward and reverse trajectories along with the input files, the NM movies in pdb format and the 2D-projections.

We recommend to download the projections and plot them coloring the points versus structure descriptors such as rMSD, key interresidue distances, etc

Running from PDB codes- Issues

1. Incomplete/Inconsistent PDBs: PDB files retrieved from the Protein Data Bank can have missing residues, gaps, chimeric constructs, etc:



2. Fixing and uploading your own PDB files:

- Fixing PDB files for eBDIMS can be as simple as cutting N- or C-terminal residues, or relabeling a broken chain as two separate chains

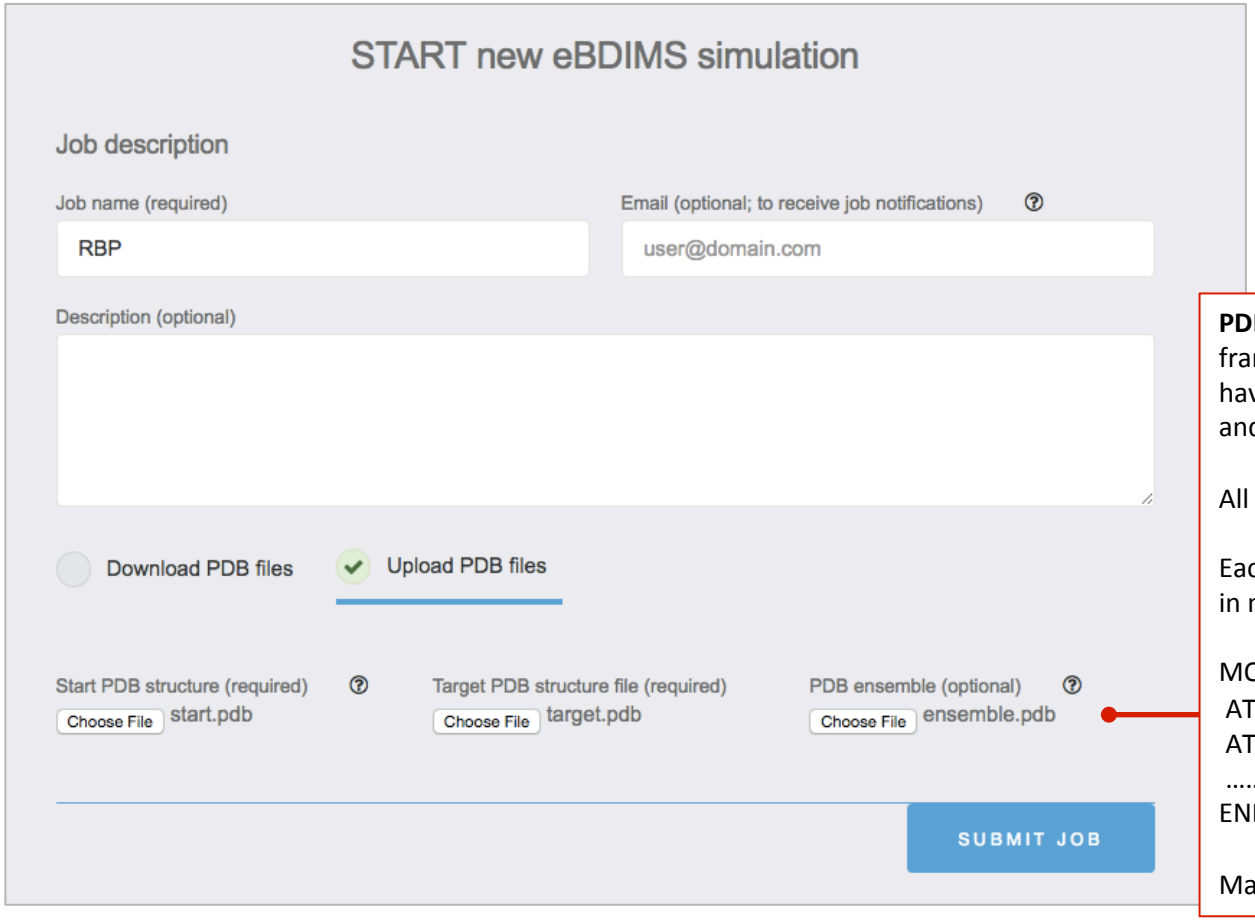
- Another alternative is to download a special eBDIMS version to run incomplete structures locally (https://github.com/laura-orellana/eBDIMS)

You can also use tools as *modeller* to reconstruct full-length structures.

If you want to build an ensemble, you can try our tutorial for ensemble preparation with pdbParser (https://github.com/ozyo/pdbParser) or tools such as *Bio3D* or *ProDy*.

Running from PDB files- Step 1 Uploading files

Now we imagine our RBP files were “broken” so we took the time to fix them and curate an 11-mer ensemble from the Protein Data Bank. In this case we don’t need to worry about specifying chains since we have prepared our files to be perfectly consistent (otherwise we will get an error message!):



PDB file format: start, target and all frames in the ensemble need to have the same number of chains and residues.

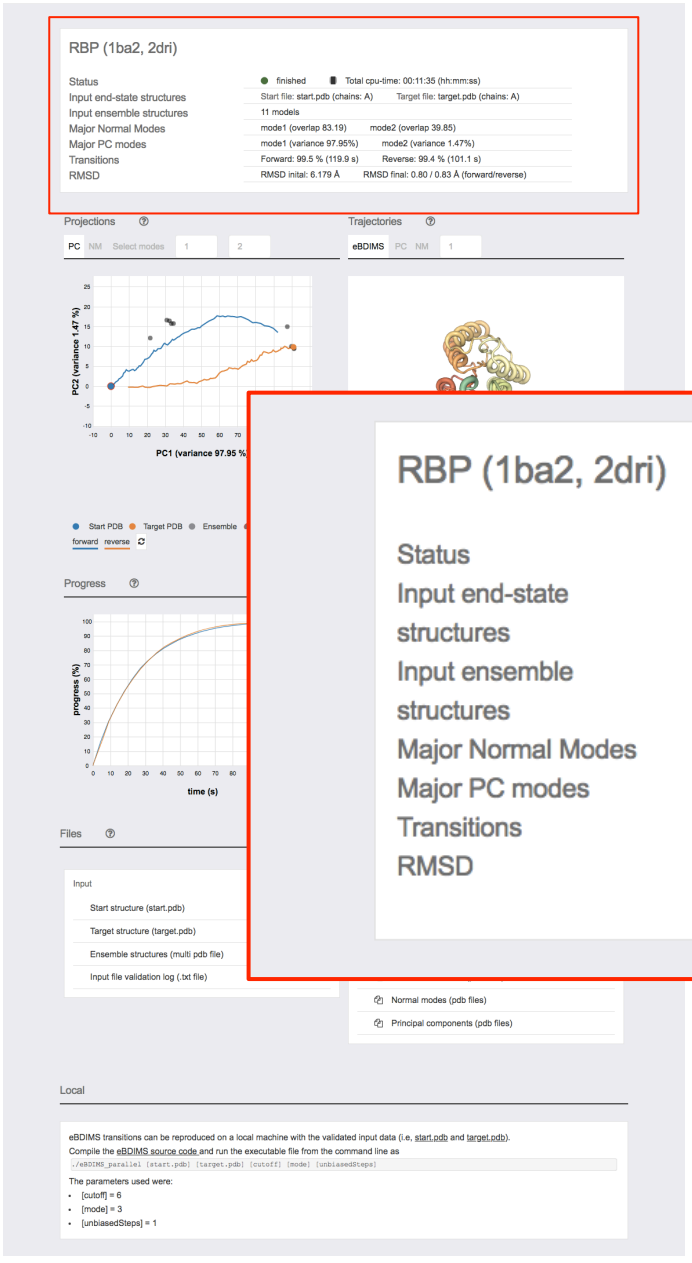
All chains are processed.

Each coordinate set is delimited as in multipdb files:

MODEL
ATOM 1
ATOM 2
…….
ENDMDL

Maximal File size should be <15Mb.

Running from PDB codes - Step 2 Checking results



General information:

Apart from NMS, information from the two major PCs (capturing the most collective motions of largest variance) is now reported.

The first two PCs typically accumulate > 70-80% of the total ensemble variance.

RBP (1ba2, 2dri)

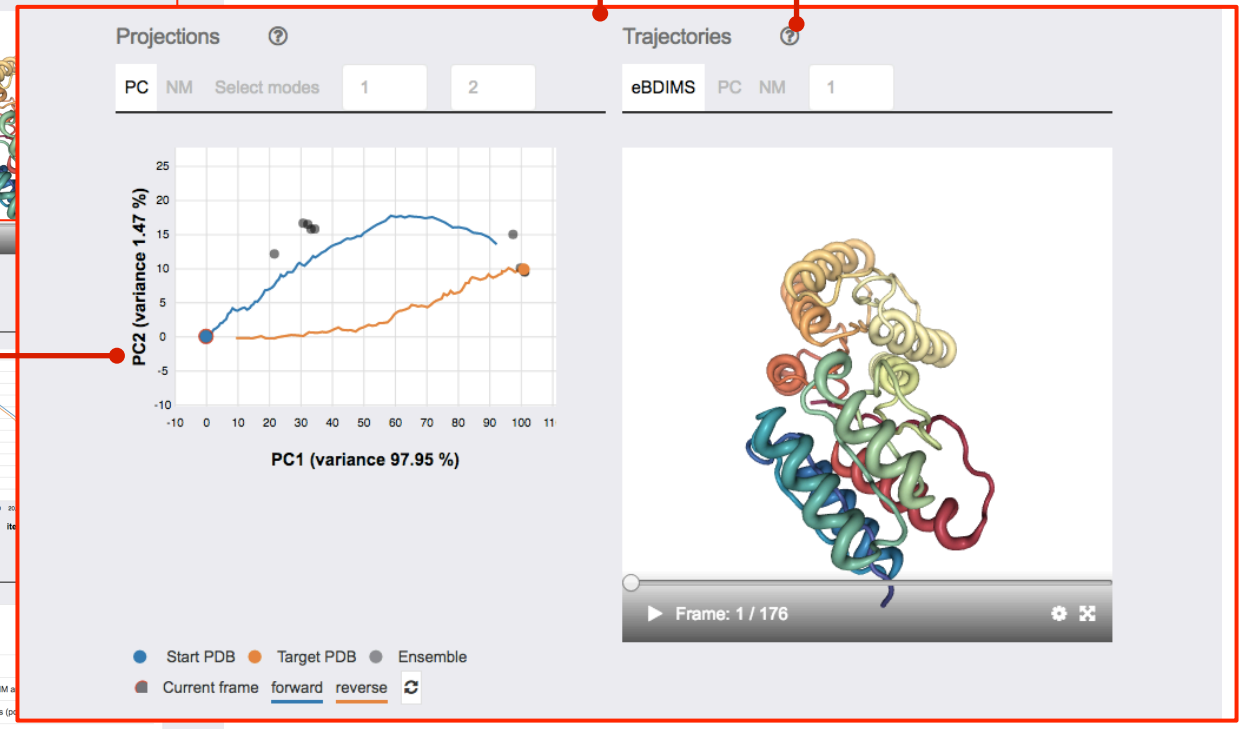
Status
Input end-state structures
Input ensemble structures
Major Normal Modes
Major PC modes
Transitions
RMSD

finished
Total cpu-time: 00:11:35 (hh:mm:ss)
Start file: start.pdb (chains: A)
Target file: target.pdb (chains: A)
11 models
mode1 (overlap 83.19)
mode2 (overlap 39.85)
mode1 (variance 97.95%)
mode2 (variance 1.47%)
Forward: 99.5 % (119.9 s)
Reverse: 99.4 % (101.1 s)
RMSD inital: 6.179 Å
RMSD final: 0.80 / 0.83 Å (forward/reverse)

Running from PDB codes - Step 2 Checking results

Transition 3D-Movies: forward and reverse movie transitions are coupled to the projections onto NMs and also PCs.

Principal Components 3D-Movies: All PCs within the first 10-modes subspace can be visualized to better grasp which motions represent the 2D-axes and how they cluster structures



PC-Projections: apart from projections onto the best NMs from the reference structure, projections onto the two largest-variance PCs of the ensemble are presented.

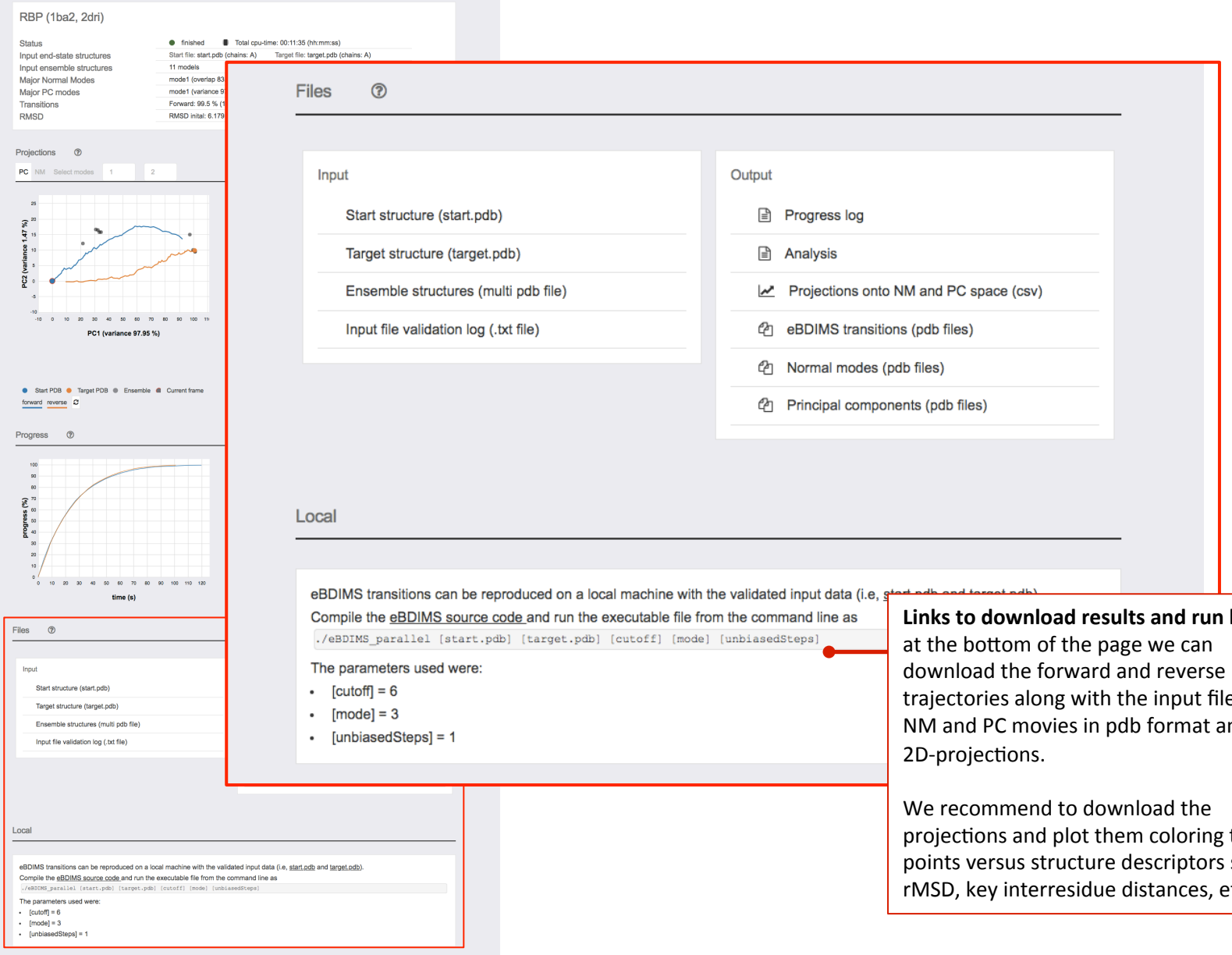
Intermediates appear as clusters near any of forward/reverse transitions, clearly separated from the end-states.

Remember that significant projections must be:

- Smooth
- Cluster different conformations separately

If PC-projections do not fulfill these conditions, we recommend carefully analyzing the ensemble composition and which kind of motions are represented.

Running from PDB codes - Step 4 Downloading results



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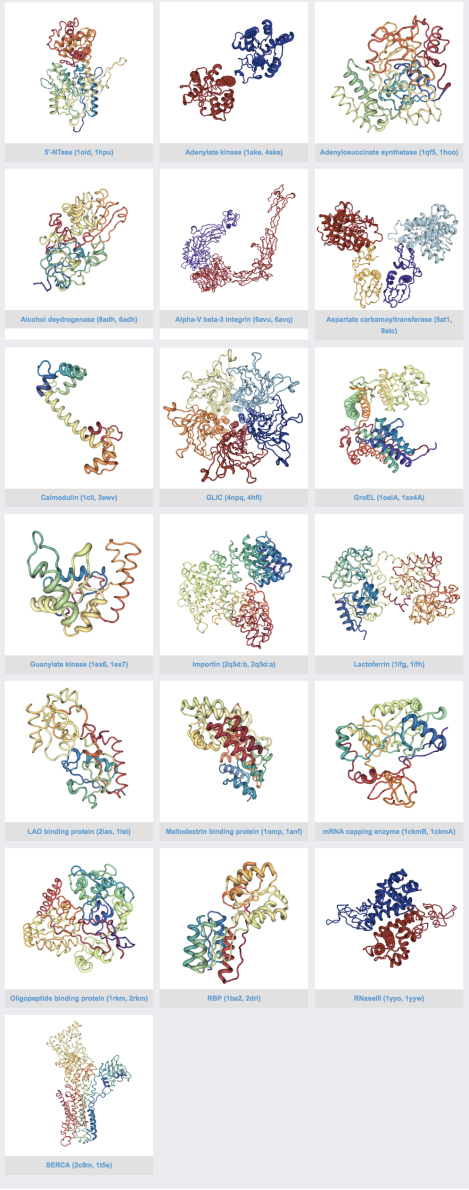
Further examples and contact



- All the examples of the eBDIMS benchmark (with input and output files) are publicly available in the server website, including those discussed in the original publication of the method (Orellana et al, 2016).

- For any questions or comments, contact us at:

ebdimserver@gmail.com

FUNCTION COMPUTATION STRUCTURE

MOLECULAR BIOPHYSICS STOCKHOLM

- To download eBDIMS source codes and related software:

https://github.com/laura-orellana/eBDIMS

https://github.com/cabergh/eBDIMS

https://github.com/ozyo/pdbParser