3dRS; a Web-Based Tool to Share Interactive Representations of 3D Biomolecular Structures and Molecular Dynamics Trajectories

BioExcel Webinar, 2021-10-26

Adam Hospital

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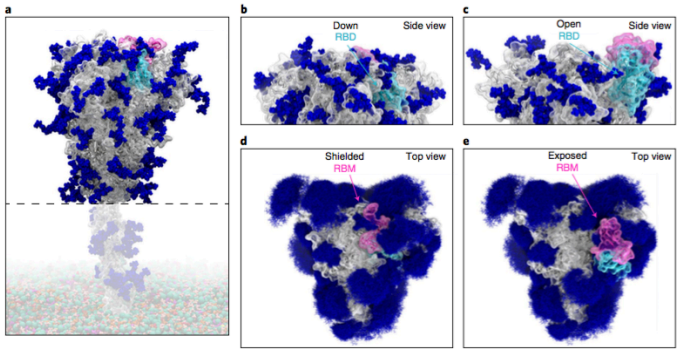

Fig. 1 | Glycosylated spike RBD 'down' and 'open' conformations. a, The SARS-CoV-2 spike head (grey) with glycans (dark blue) as simulated, with the stalk domain and membrane (not simulated here, but shown as transparent for completeness). RBD shown in cyan, RBM in pink. **b**,**c**, Side view of the RBD_{down} (shielded, **b**) and RBD_{open} (exposed, **c**). **d**,**e**, Top view of the RBM_{closed} (shielded, **d**) and RBM_{open} (exposed, **e**). Composite image of glycans (dark blue lines) shows many overlapping snapshots of the glycans over the microsecond simulations.

trajectories provides an unbiased characterization of the system's time-dependent ensemble properties[13]. The WE strategy therefore generates continuous pathways with unbiased dynamics, yielding the most direct, atomistic views for analysing the mechanism of functional transitions, including elucidation of transient states that are too fleeting to be captured by laboratory experiments. Furthermore, while the strategy requires a progress coordinate towards the target state, the definition of this target state need not be fixed in advance when applied under equilibrium conditions[21], enabling us to refine the definition of the target 'open' state of the spike protein on the basis of the probability distribution of protein conformations sampled by the simulation.

Our work characterizes a series of transition pathways of the spike opening, in agreement with conformations detected in the cryo-EM dataset by ManifoldEM[22], and identifies key residues, including a glycan at position N343, that participate in the opening mechanism. Our simulation findings are corroborated by biolayer interferometry (BLI) experiments, which show a reduction in the ability of the spike to interact with ACE2 after mutation of these key residues.

Results and discussion

WE simulations of spike opening. As mentioned above, simulations of the spike-opening process require an enhanced sampling strategy as the process occurs beyond the microsecond timescale (that is, the seconds timescale[7]). We therefore used the WE path-sampling strategy, which enabled the generation of continuous, atomistic pathways for the spike-opening process with unbiased dynamics (Fig. 2a–e and Supplementary Video 1); these pathways were hundreds of nanoseconds long, excluding the waiting times in the initial 'down' state. The protein model was based on the head region (residues 16 to 1,140) of the glycosylated SARS-CoV-2 spike from Casalino et al.[8] (Fig. 1), which in turn was built on the cryo-EM structure of the three-RBD-down spike (Protein Data Bank (PDB) ID, 6VXX (ref. [3])). The entire simulation system, including explicit water and salt ions, reaches almost half a million atoms. We focused sampling along a two-dimensional progress coordinate to track RBD opening: the difference in the centre of mass of the spike core to the RBD and the root-mean-square deviation of the RBD from the RBD_{up} state (Fig. 2f,g). On the San Diego Supercomputer Center (SDSC) Comet and Texas Advanced Computing Center (TACC) Longhorn supercomputers, 100 graphics processing units (GPUs) ran the WE simulations in parallel for over a month, generating over 130 μs of glycosylated spike trajectories and more than 200 TB of trajectory data. We simulated a total of 310 independent pathways, including 204 pathways from the RBD_{down} conformation (PDB ID, 6VXX (ref. [3])) to the RBD_{up} conformation (PDB ID, 6VSB (ref. [4])) and 106 pathways from the RBD_{down} to the RBD_{open} state, in which the RBD twists open beyond the 6VSB (ref. [4]) cryo-EM structure. Remarkably, the RBD_{open} state that we sampled includes conformations that align closely with the ACE2-bound spike cryo-EM structure (PDB ID, 7A95 (ref. [4])) even though this structure was not a target state of our progress coordinate (Fig. 2f,g, Supplementary Video 1 and Supplementary Figs. 2 and 3). This result underscores the value of using (1) equilibrium WE simulations that do not require a fixed definition of the target state and (2) a two-dimensional progress coordinate that allows the simulations to sample unexpected conformational space along multiple degrees of freedom. The ACE2-bound spike conformation has also been sampled by the Folding@home-distributed computing project[11], and RBD rotation has been detected in cryo-EM experiments[6].

Comparison with spike conformations detected by ManifoldEM. To validate our simulated RBD_{down} to RBD_{up} pathway, the ManifoldEM framework[22] was applied using the cryo-EM dataset of PDB 6VSB from McLellan and colleagues[4]. The ManifoldEM method allows characterization of conformational variations as obtained from a single-particle cryo-EM ensemble of a molecule in thermal equilibrium. Two conformational coordinates (that is, collective motion coordinates) CC1 and CC2 were discovered from this dataset, and observed from several exemplary projection directions (PDs) showing a (1) RBD_{down} to RBD_{up} pathway and (2) RBD outward opening pathway (Supplementary Fig. 4 and Supplementary Videos 2 and 3).

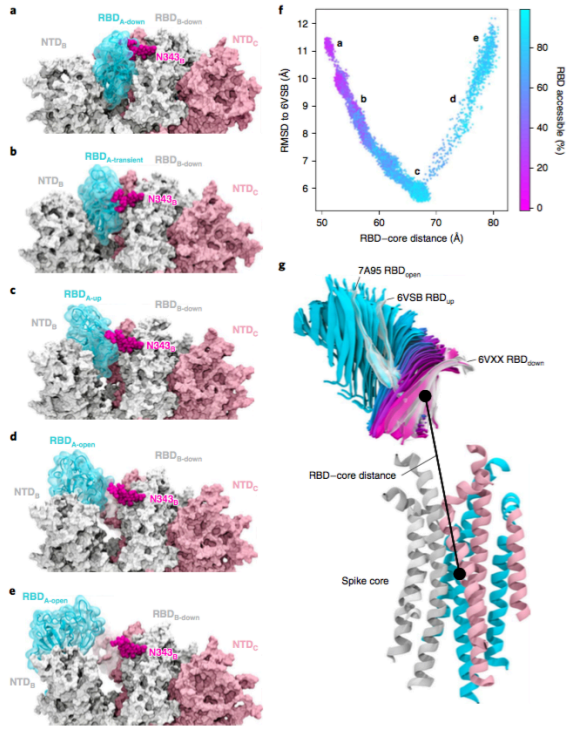

Fig. 2 | Atomically detailed pathways of spike opening. a–**e**, Snapshot configurations along the opening pathway with chain A shown in cyan, chain B in grey, chain C in pink and the glycan at position N343 in magenta. Each RBD and N-terminal domain (NTD) are subscripted with their chain ID (A, B or C). RBDs are also subscripted with their conformation from initial conformation with all three RBDs in the 'down' state (6VXX) (**a**), RBD_A in a 'transient' state in between the 'down' and 'up' state (6VSB) (**b**) RBD_A in the 'up' state (**c**), RBD_A in the 'open' state (beyond 6VSB) (**d**) and RBD_A in the furthest open state sampled (**e**). **f**, Scatter plot of data from the 310 continuous pathways with the Cα-root-mean-square deviation (RMSD) of the RBD from the RBD– state plotted against the RBD–core distance. Data points are coloured on t RBD_{down} state. The locations of the snapshots shown in **a**–**e** are labell The spike core is composed of three central helices per trimer, colou beta-sheets, and an overlay of snapshots from a continuous WE sim cryo-EM structures are highlighted and labelled including the initial

These projections were next aligned to correspondir dimensional projections of coulomb potential maps ge with frames from the WE simulation (Supplementary Fig Supplementary Videos 2 and 3). Overall, there was ver agreement between the ManifoldEM conformational coo and the WE trajectory, aside from two discrepancies. Fi CC2 observed in the ManifoldEM included concerted ope all three RBDs, while the WE focused sampling on the

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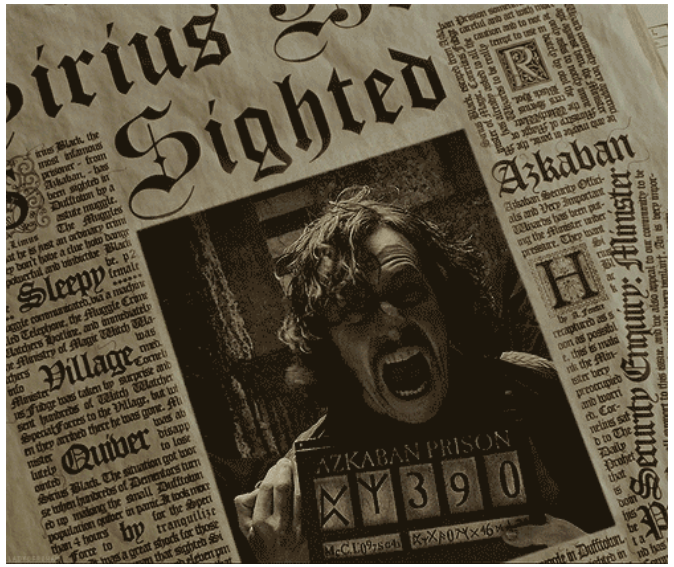

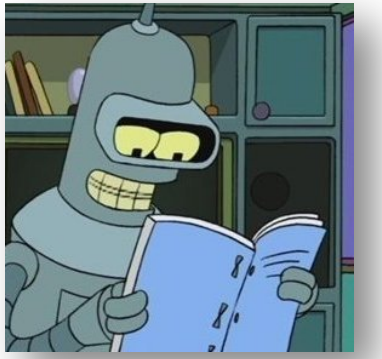

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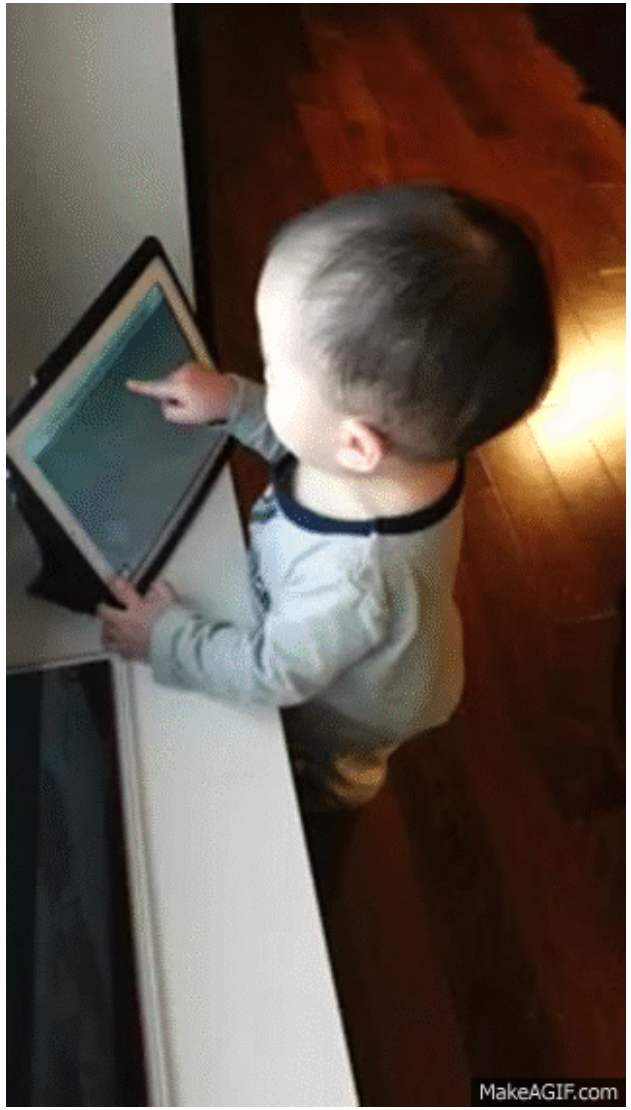

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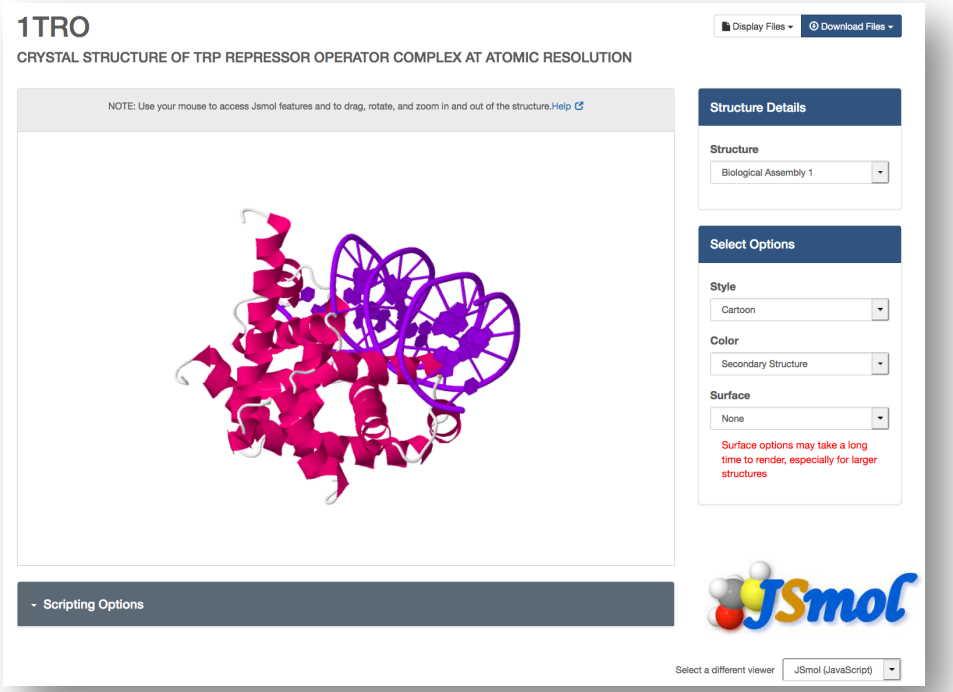

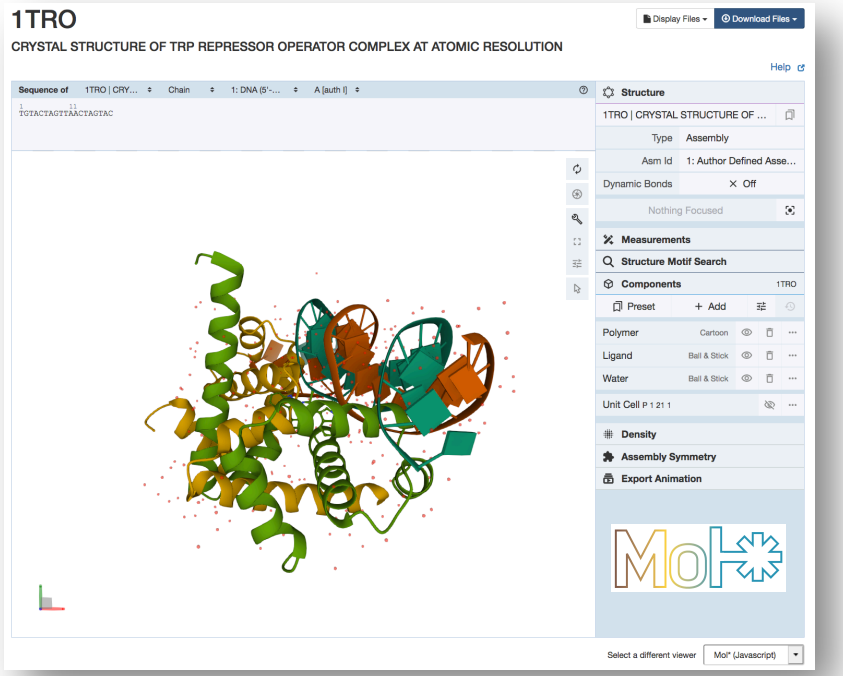

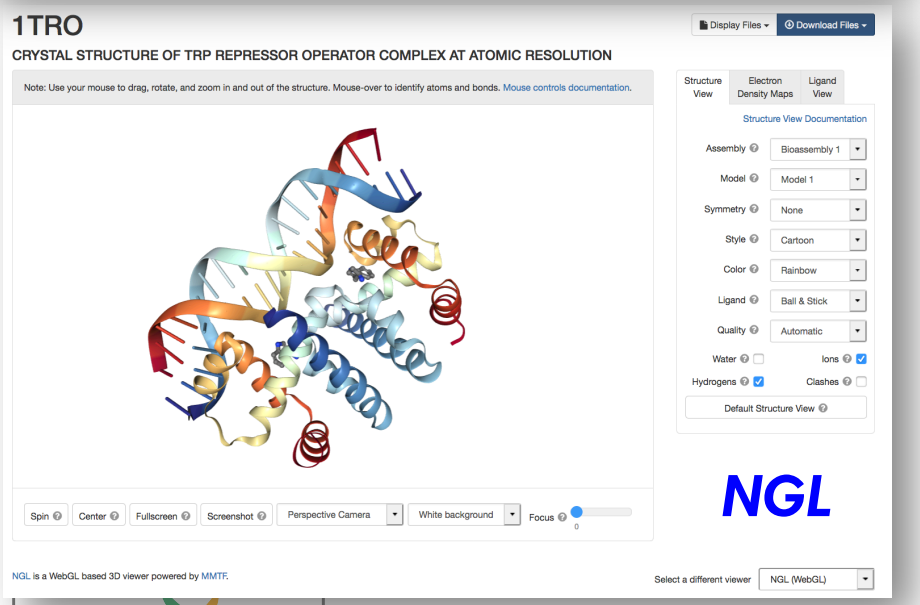

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- ***Protein Viewer***
- ***…***

Interactivity

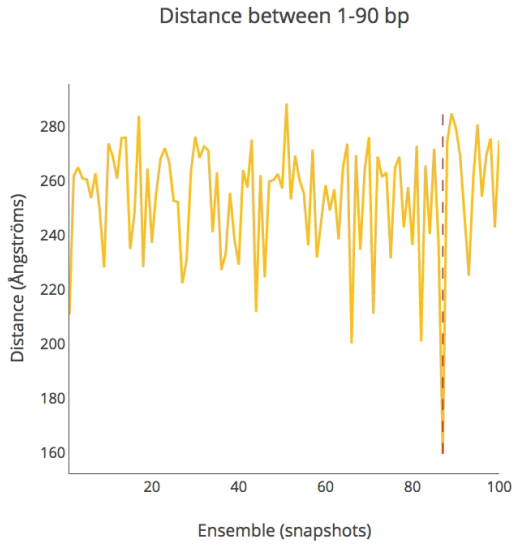
Curves | Stiffness | Contacts | Bending | End-to-end

DISTANCES SELECTOR

159.68Å 288.41Å

159.68 211.18 225.09 229.17 233.29 236.43 238.78 242.85 249.05 253.15 255.54 257.46 260.24 260.83 262 263.03 264.48 265.61 268.78 269.18 271.46 272.86 274.83 275.81 280.71

END-TO-END DISTANCES PLOT



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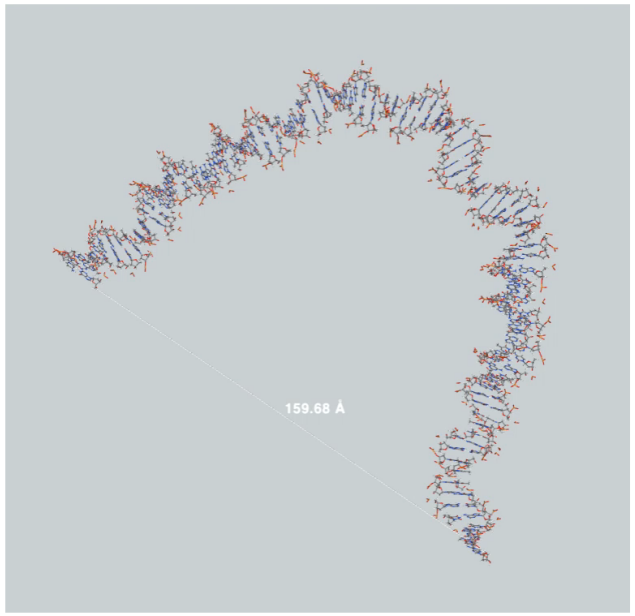

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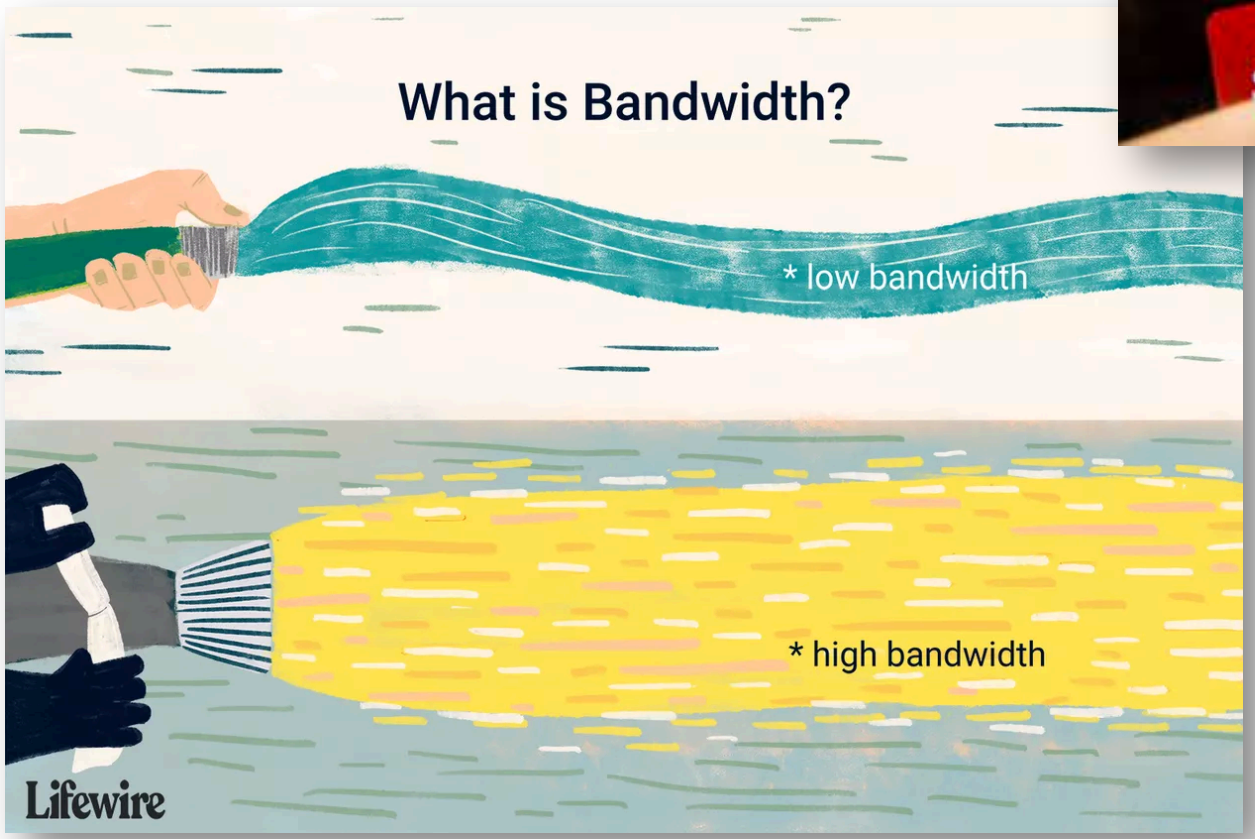

- ✓ WebGL tools
- ✓ Interactivity
- ✓ Network Bandwidths

Add Interactivity

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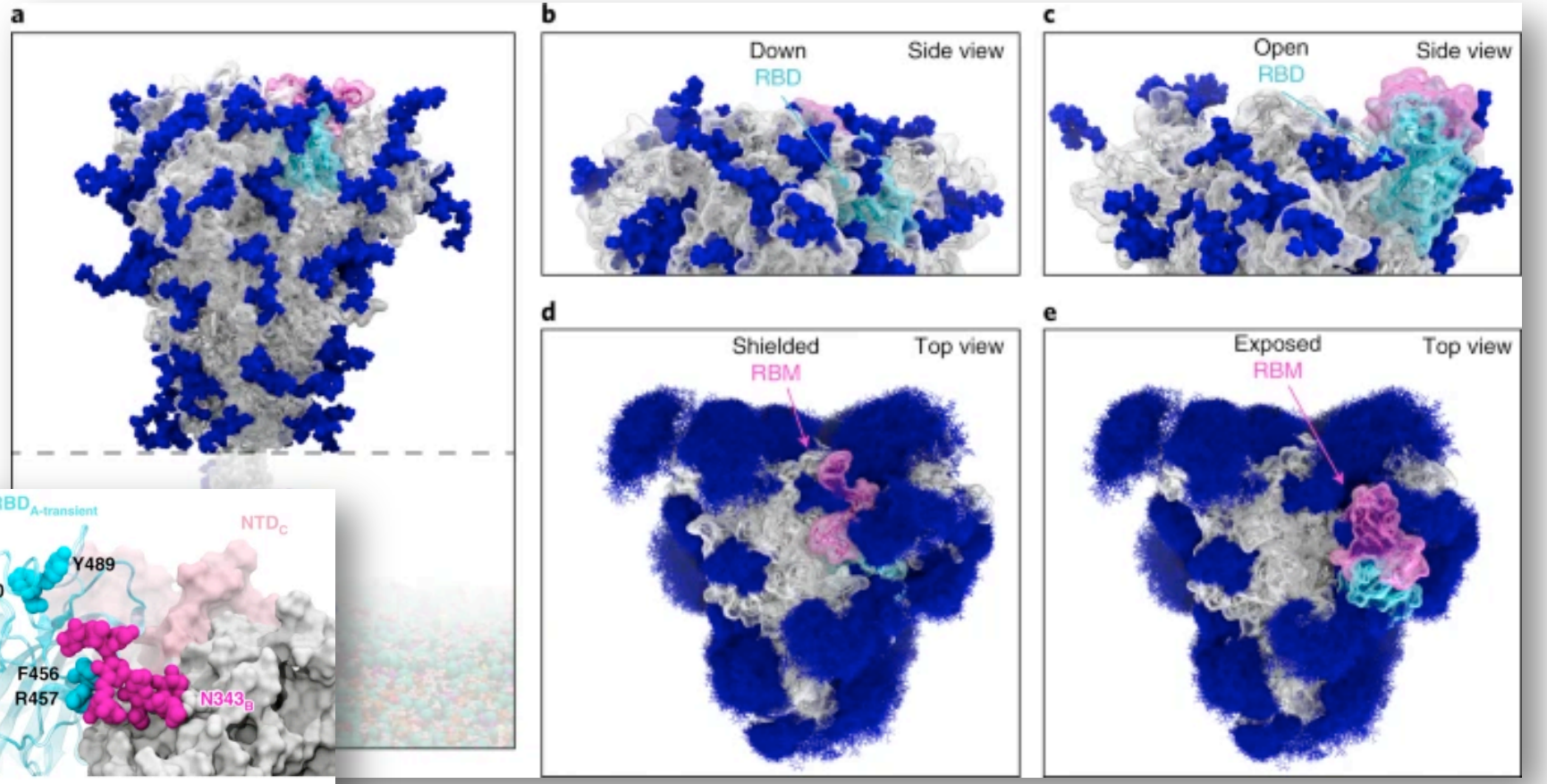

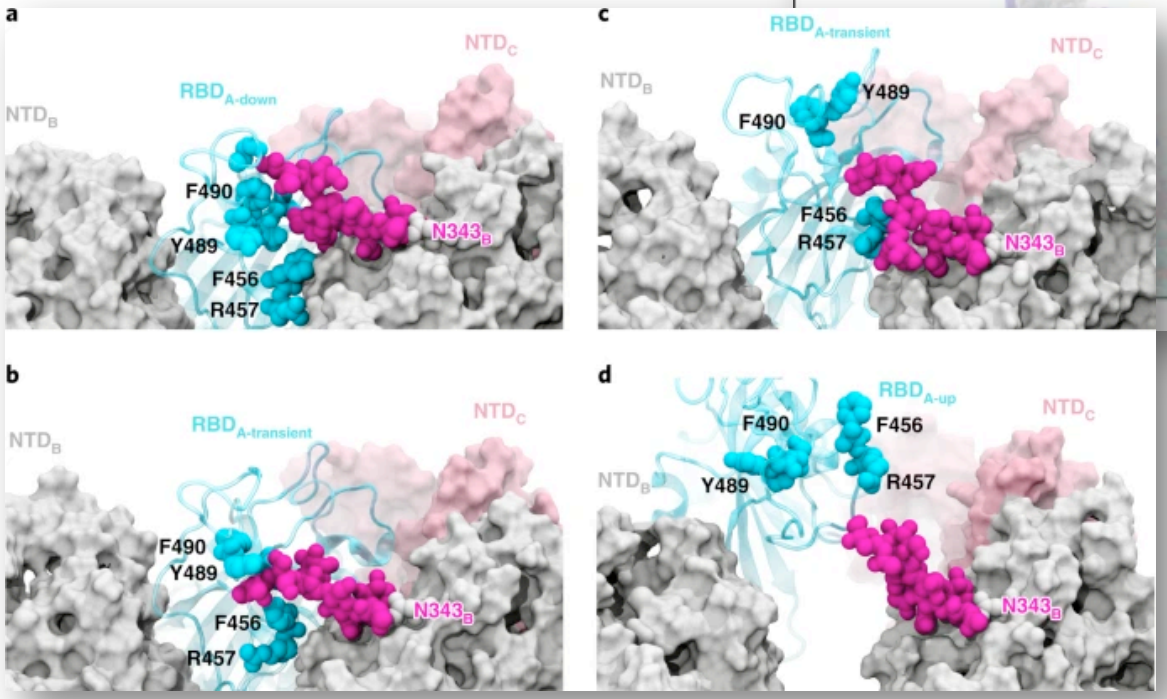

Sztain, T., Ahn, SH., Bogetti, A.T. et al. A glycan gate controls opening of the SARS-CoV-2 spike protein. Nat. Chem. 13, 963–968 (2021). https://doi.org/10.1038/s41557-021-00758-3

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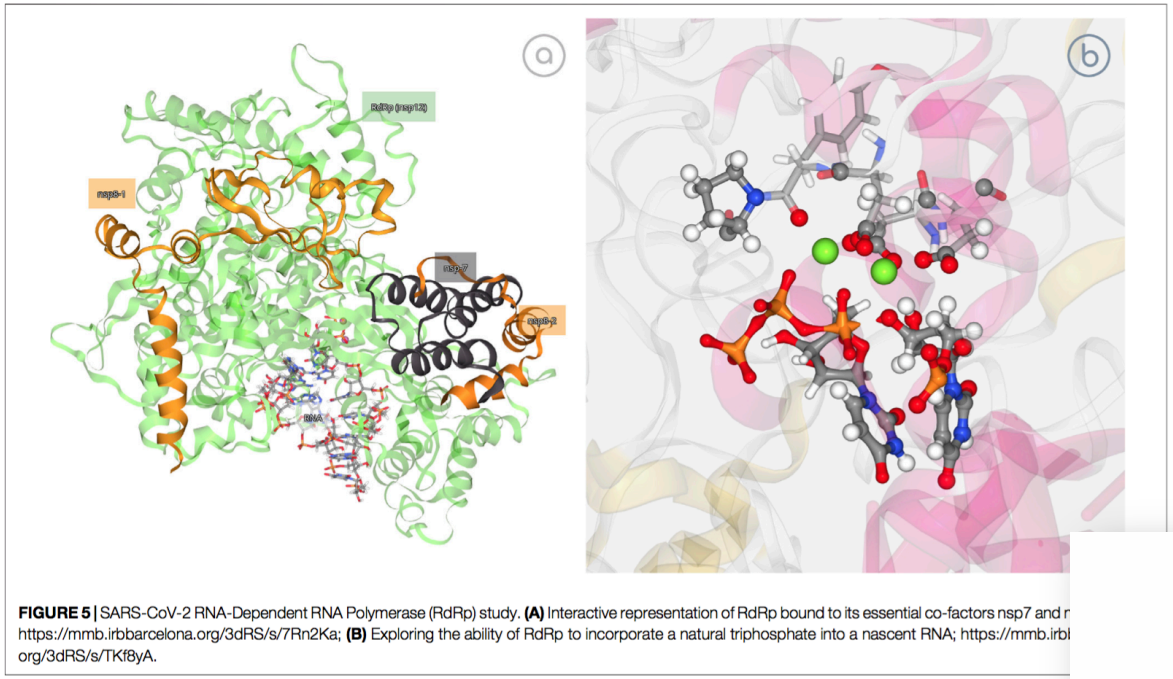

FIGURE 5 | SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) study. **(A)** Interactive representation of RdRp bound to its essential co-factors nsp7 and r
https://mmb.irbbarcelona.org/3dRS/s/7Rn2Ka; **(B)** Exploring the ability of RdRp to incorporate a natural triphosphate into a nascent RNA; https://mmb.irbb
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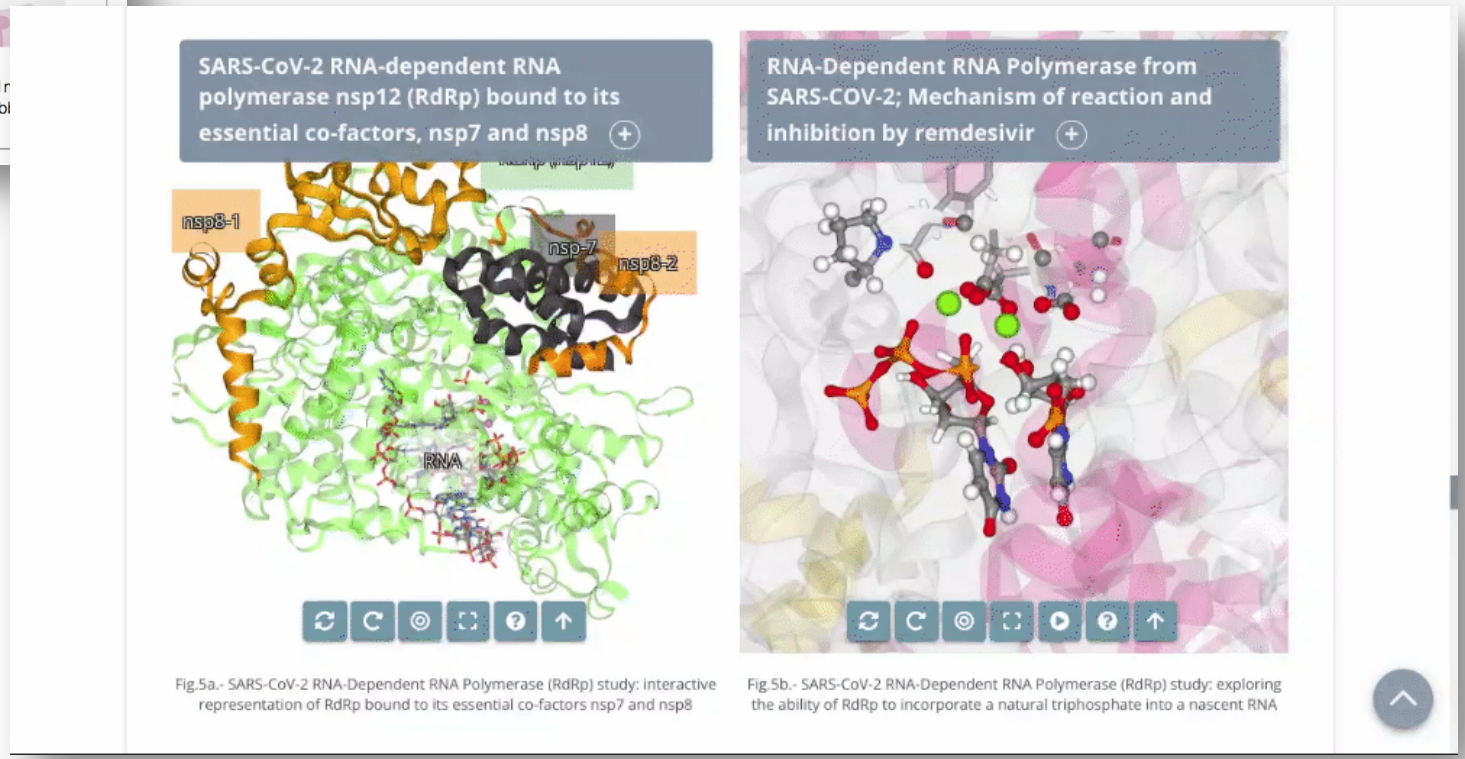

Fig.5a.- SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) study: interactive representation of RdRp bound to its essential co-factors nsp7 and nsp8

Fig.5b.- SARS-CoV-2 RNA-Dependent RNA Polymerase (RdRp) study: exploring the ability of RdRp to incorporate a natural triphosphate into a nascent RNA

Introduction: Why?

- **Live Figures**
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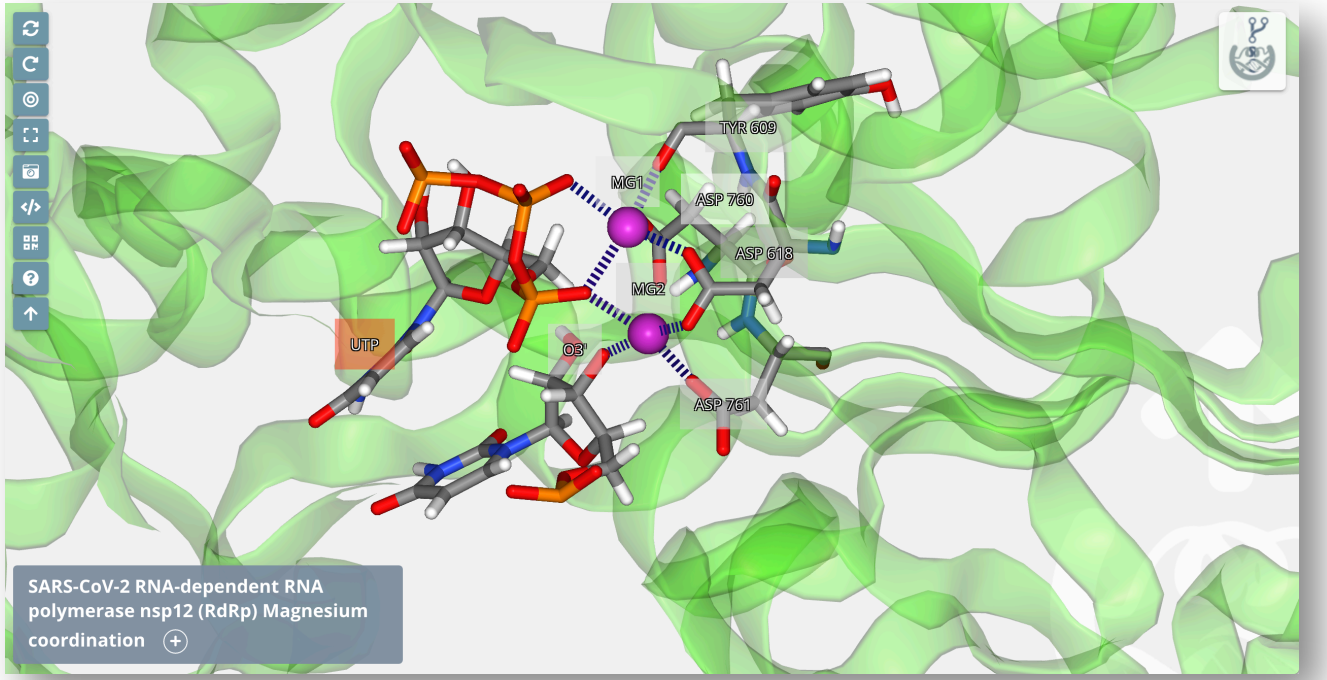
- **Presentations** - show + share



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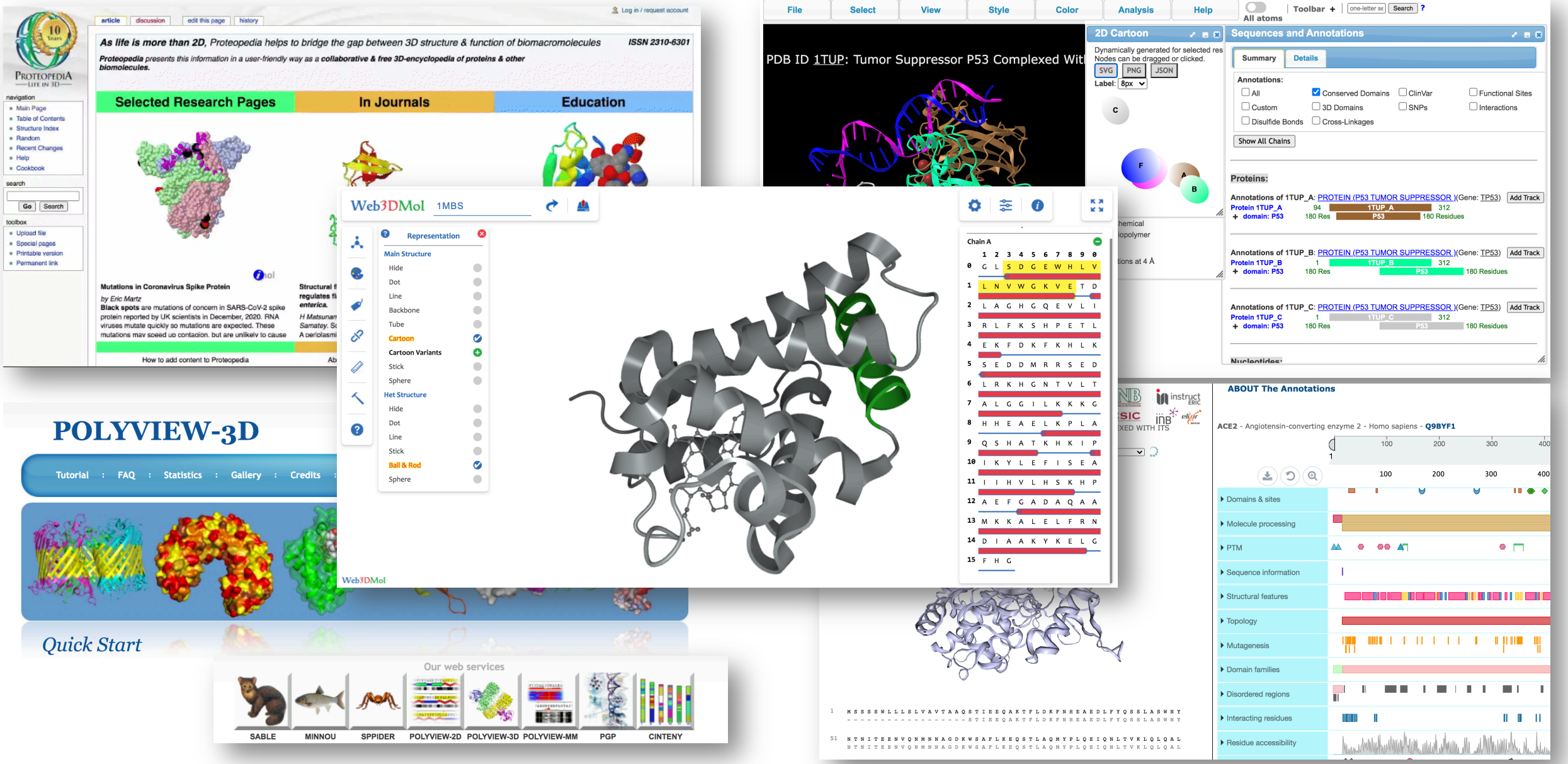
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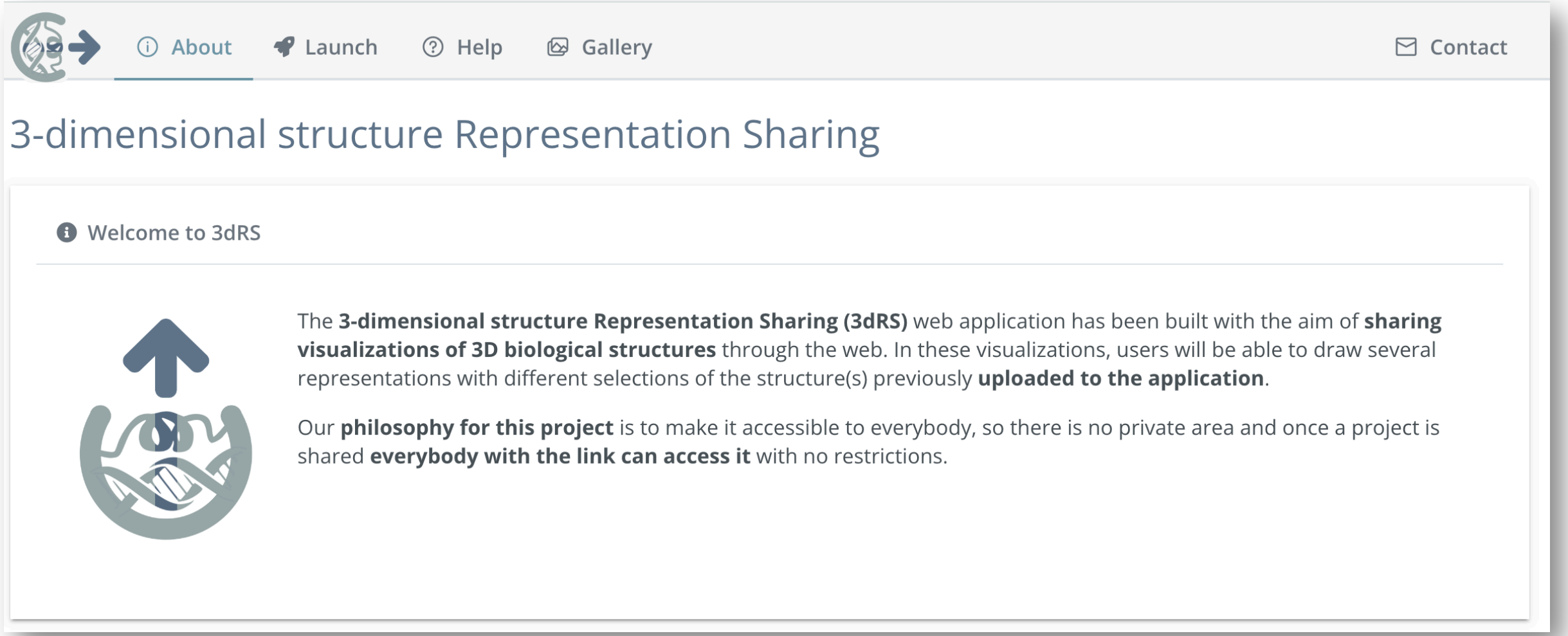

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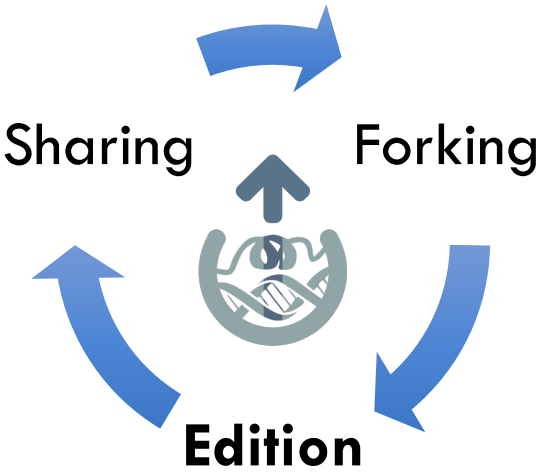
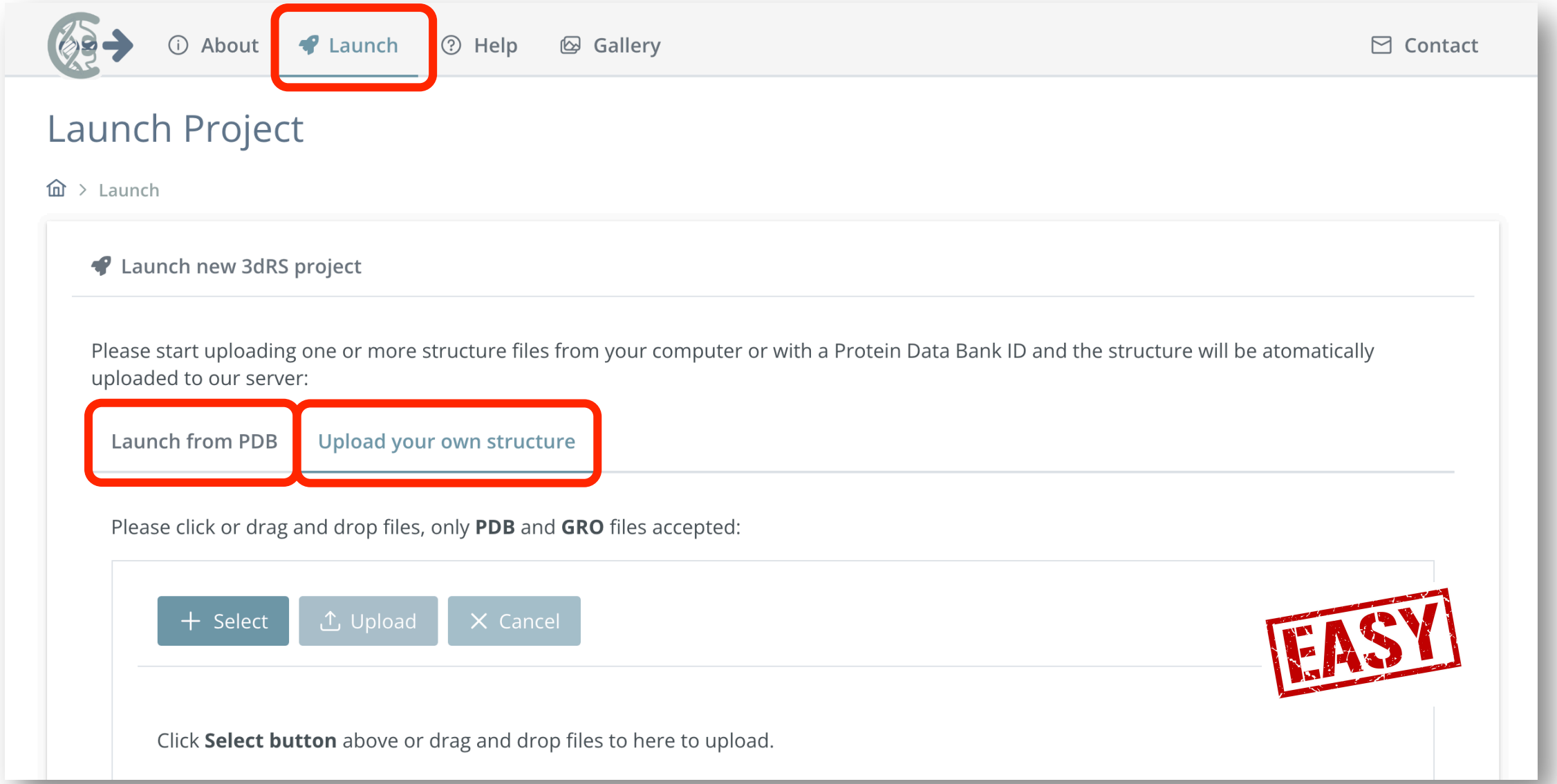
- **Easy generation of 3D/4D biomolecular representations**
  - Single Page Application (SPA) Web-based Graphical user interface (GUI)
  - Seamless user experience, mimicking a native, standalone program (no reloads or saving buttons)
  - VMD-like selections + representations

- **Molecular Dynamics Trajectories** (using MDSrv)
- **Multiple structure representation**

- **Persistent URL to share the biomolecular representation** (e.g. https://mmb.irbbarcelona.org/3dRS/s/TVVSQ2)

- **Representation Forking** (GitHub-like)

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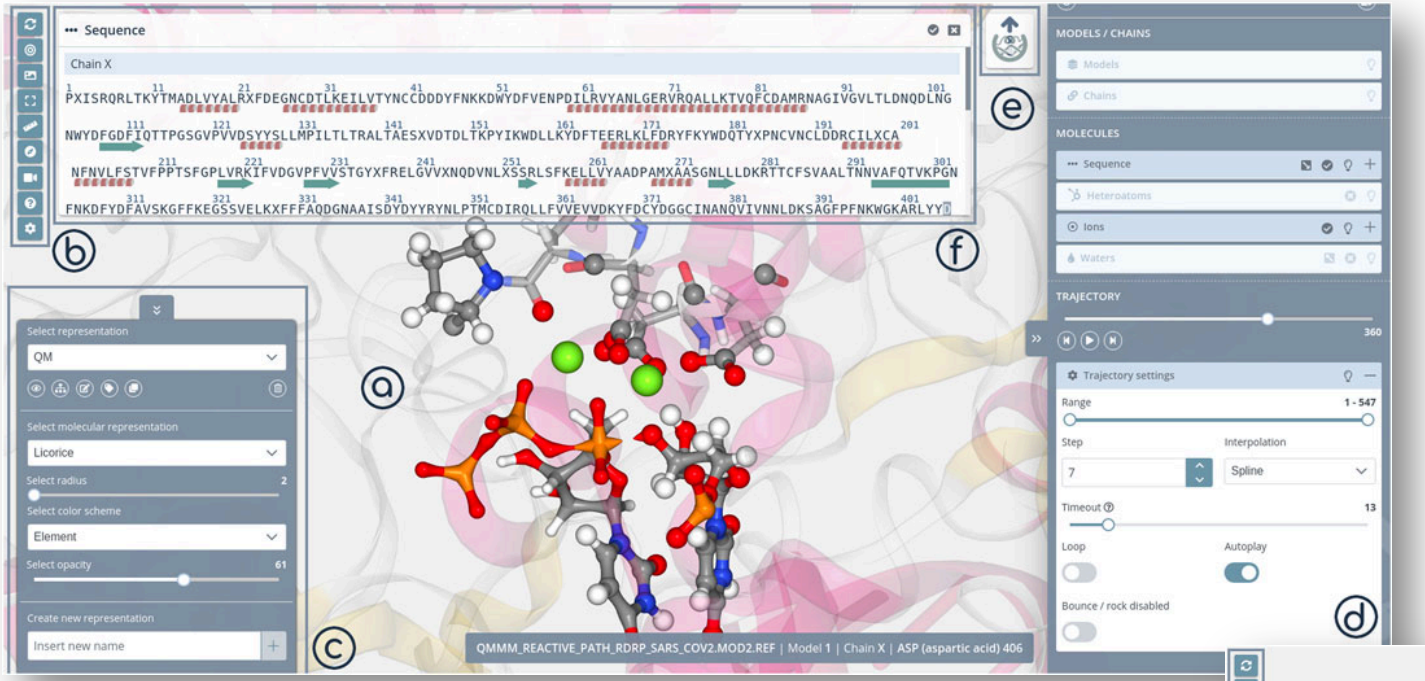

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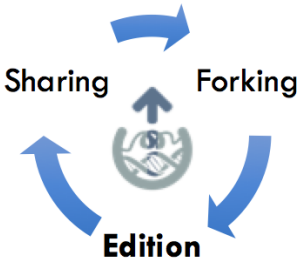

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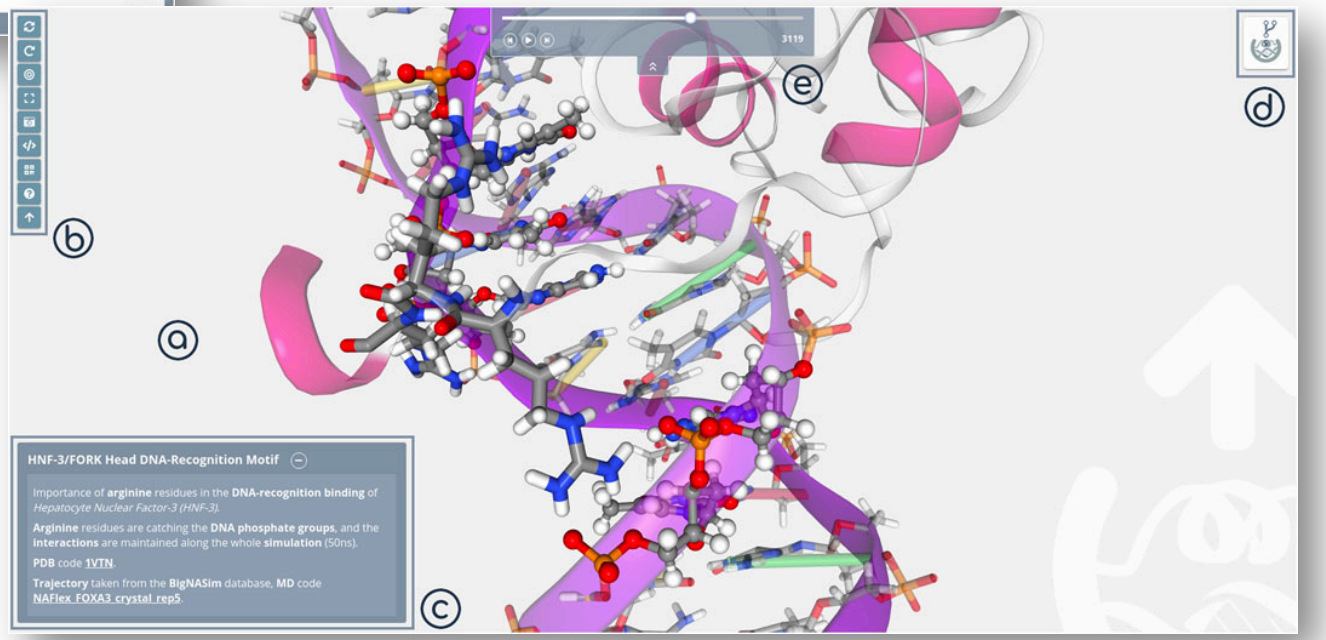

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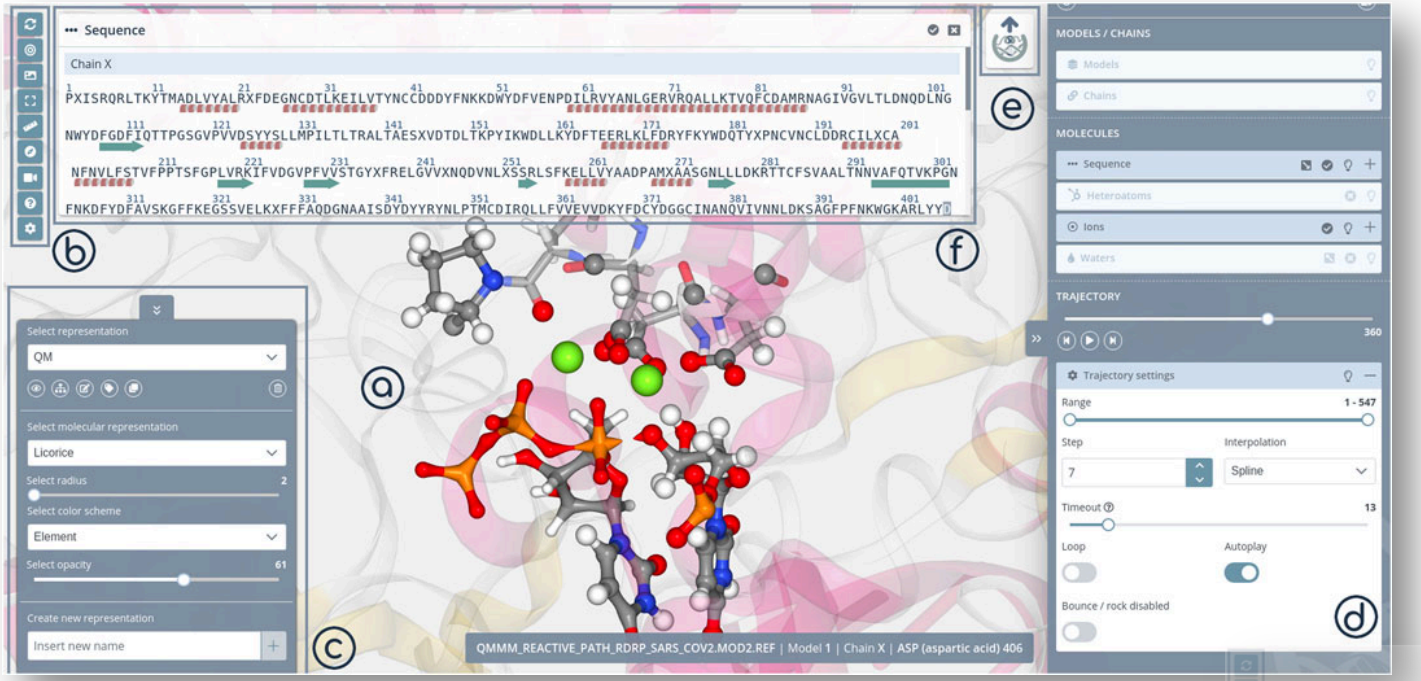

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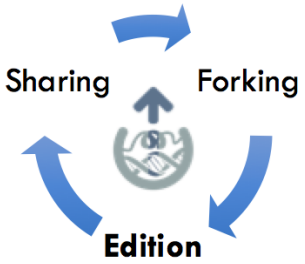

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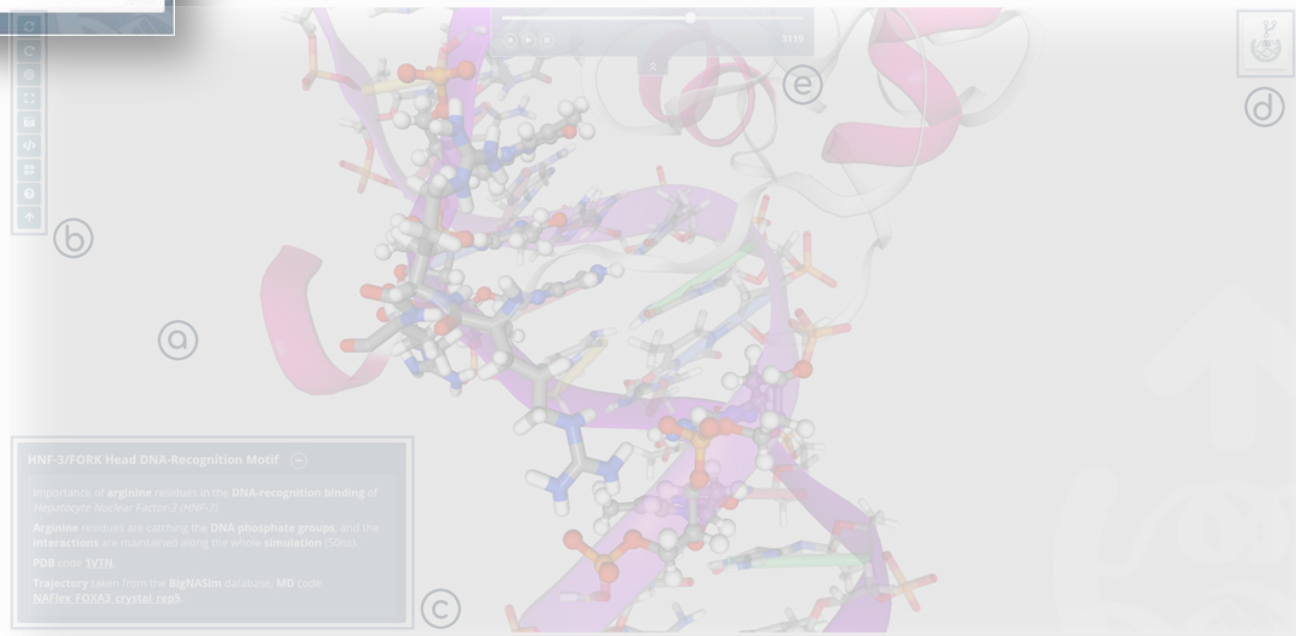

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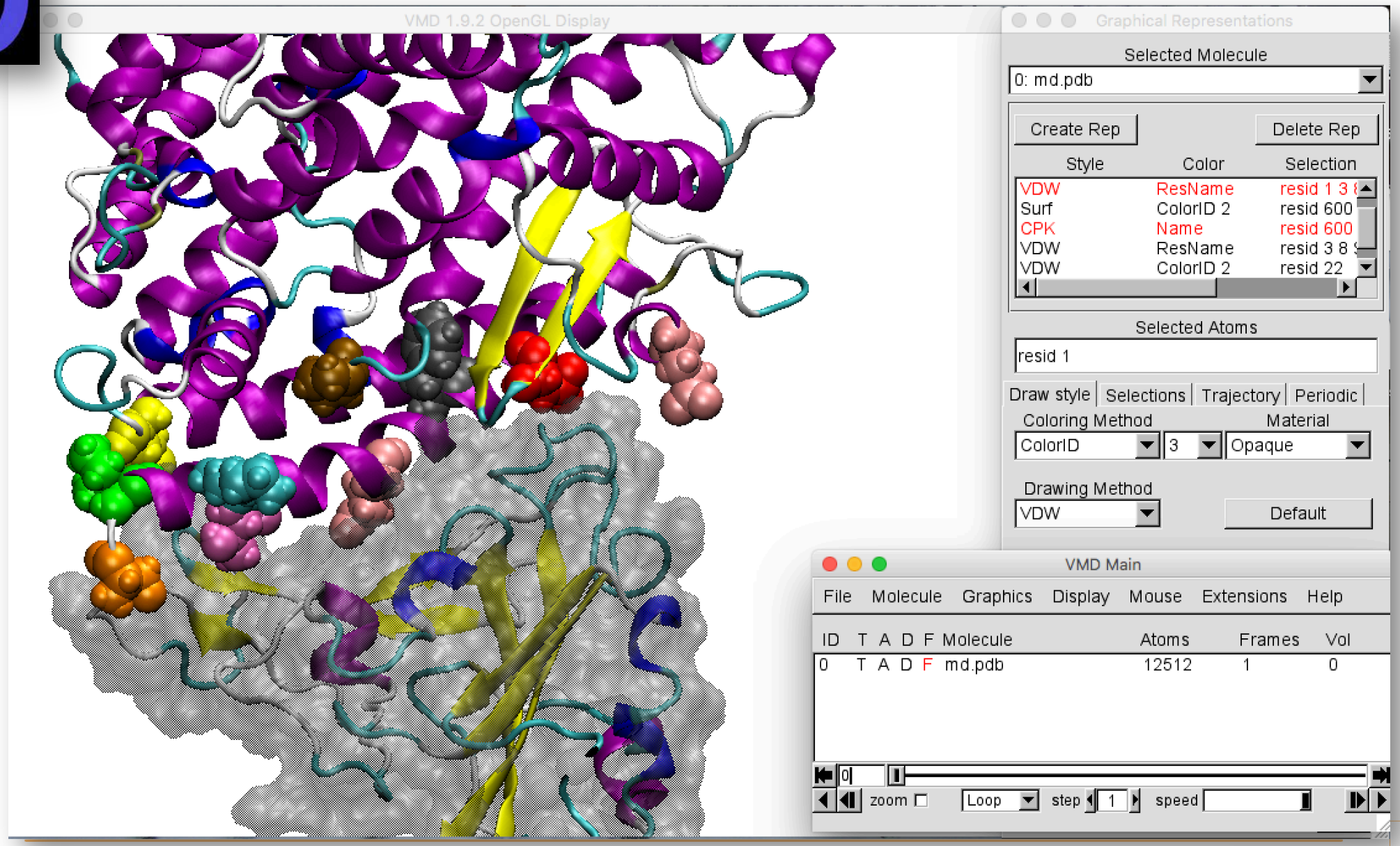

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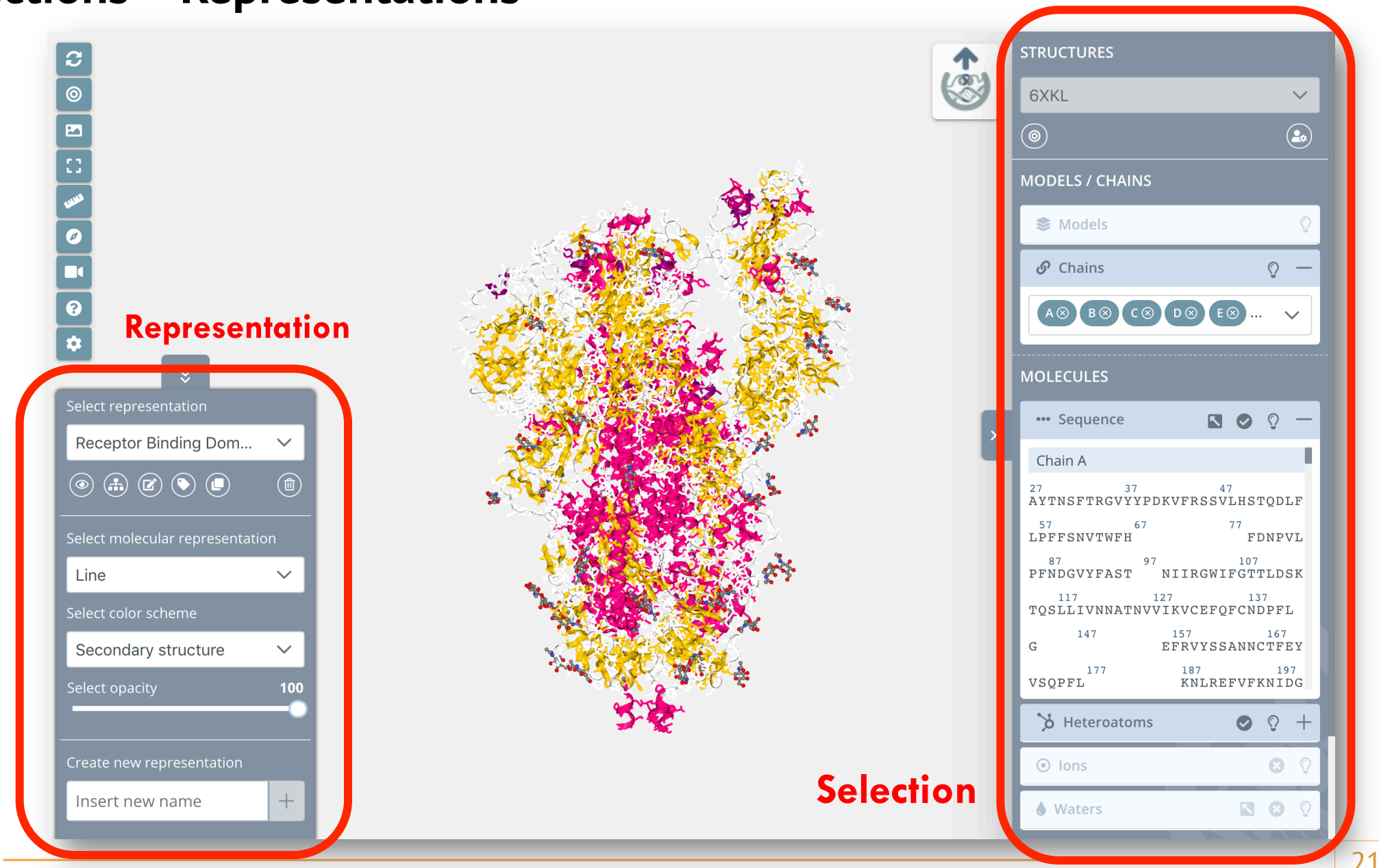

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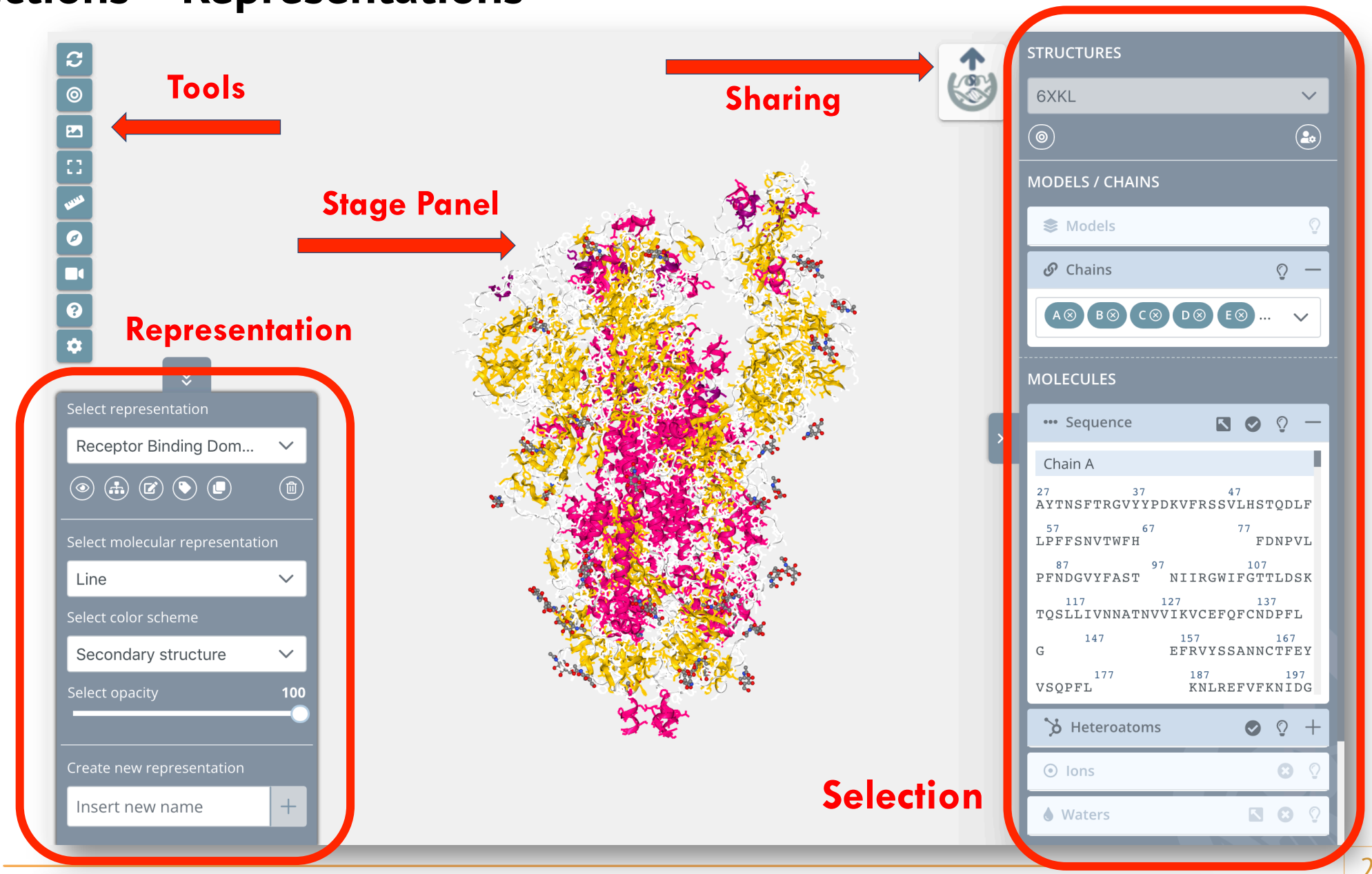

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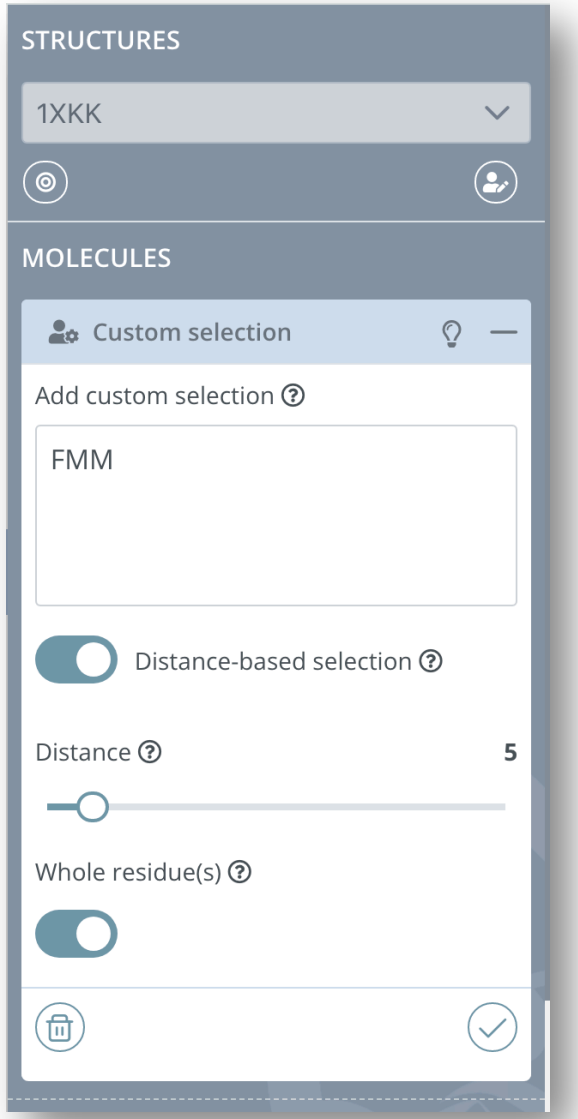

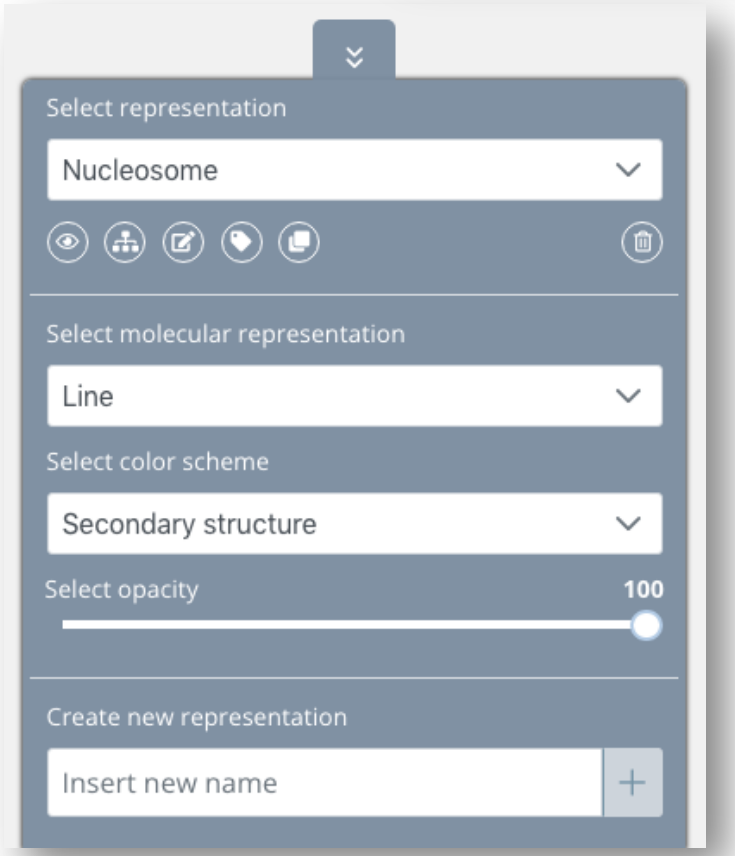

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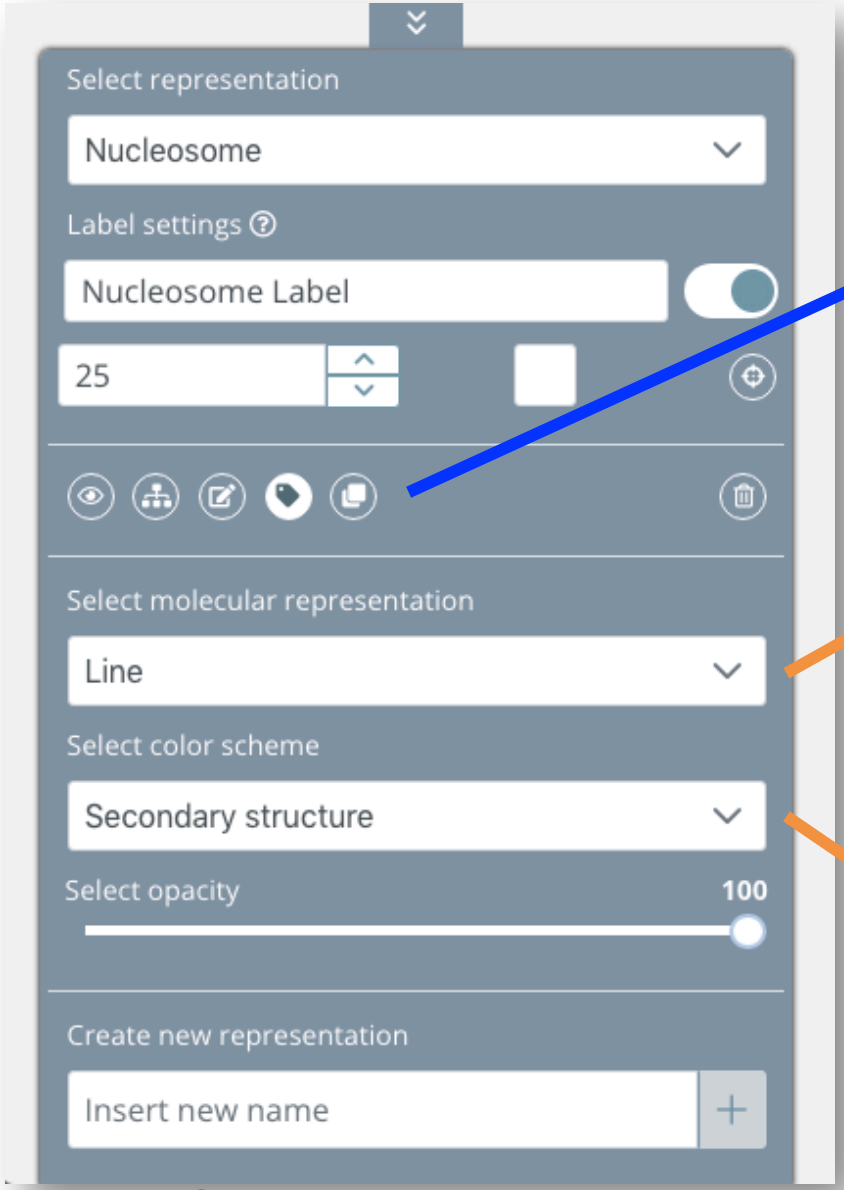

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- *Atom index*
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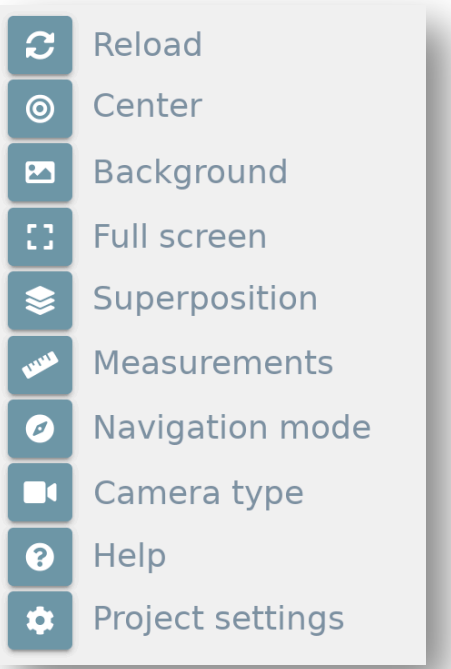

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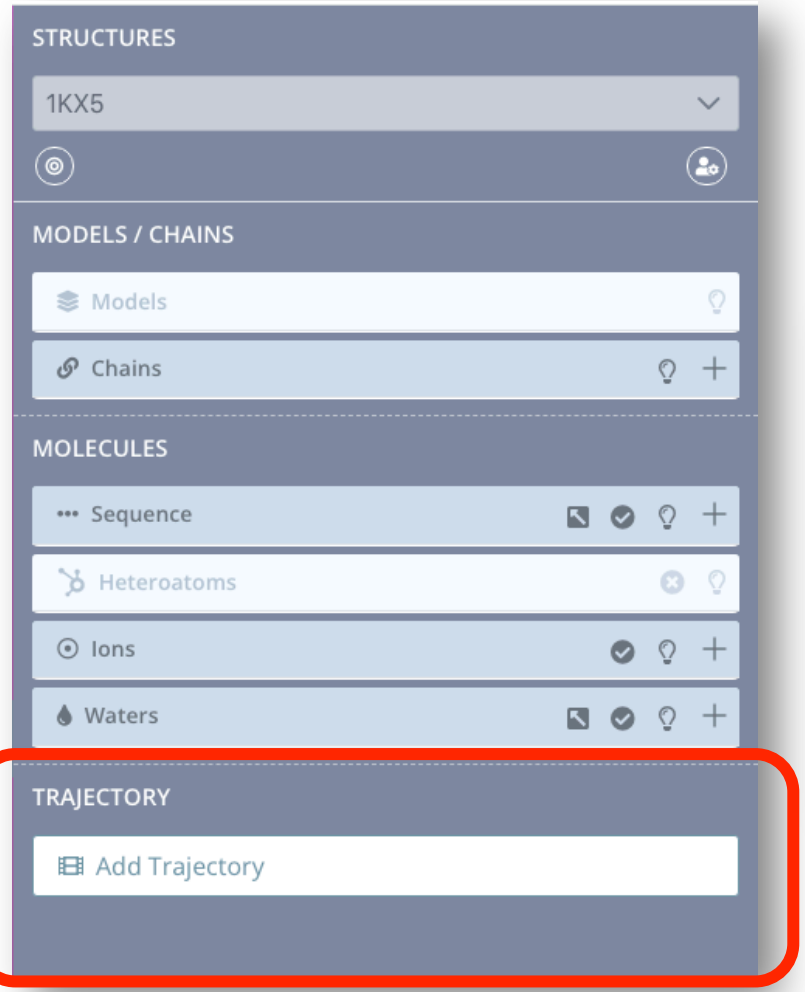

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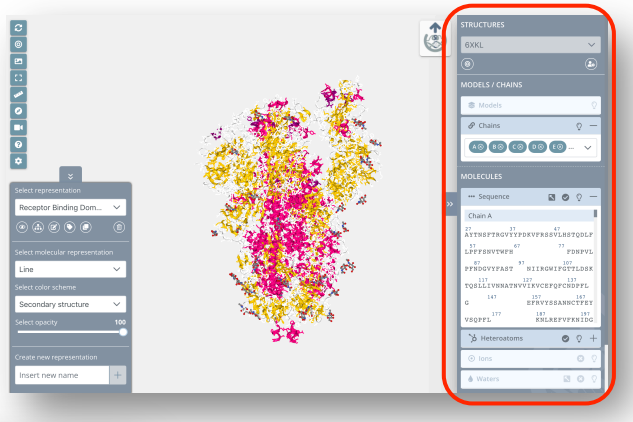
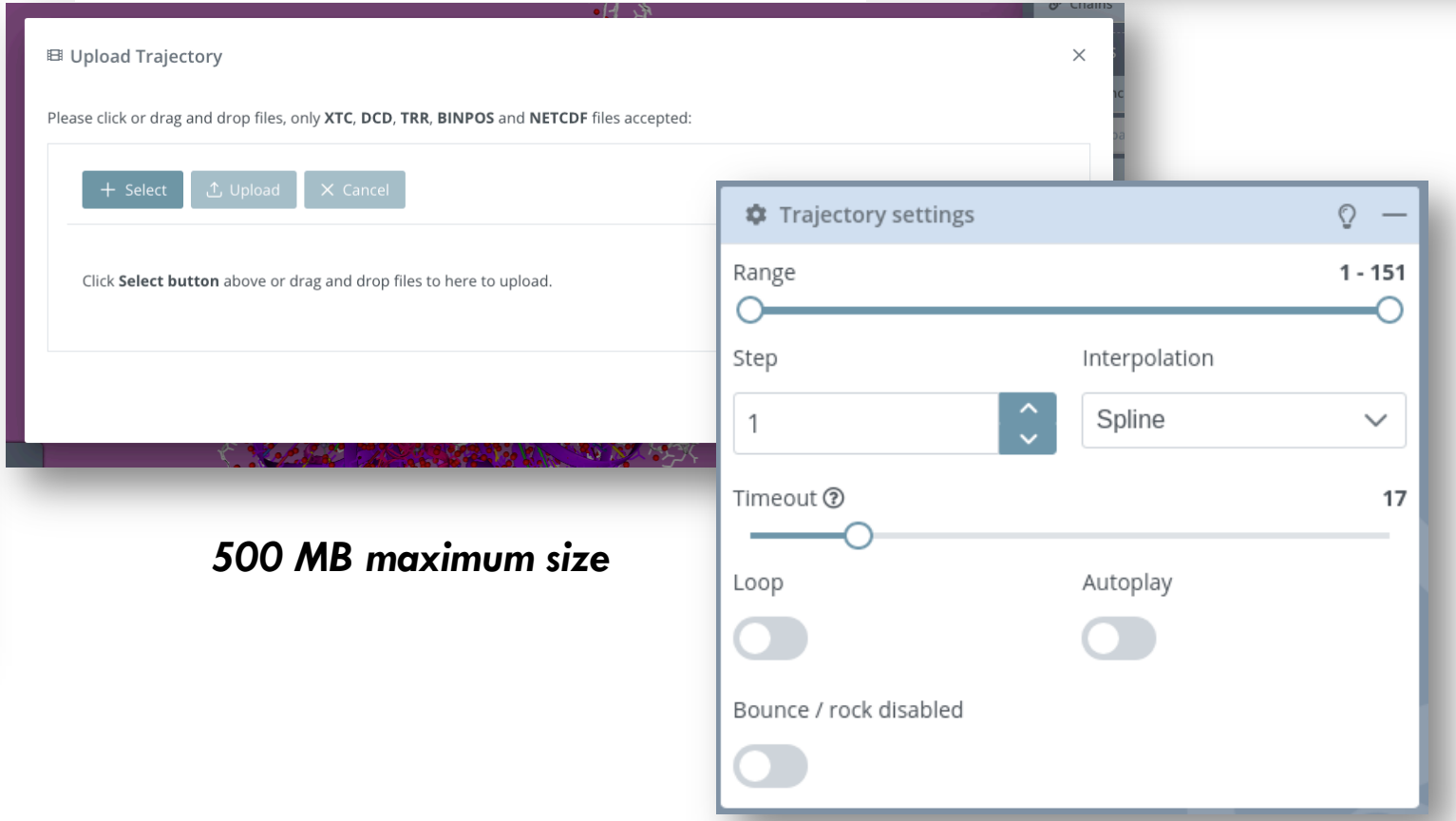
nglviewer/**mdsrv**

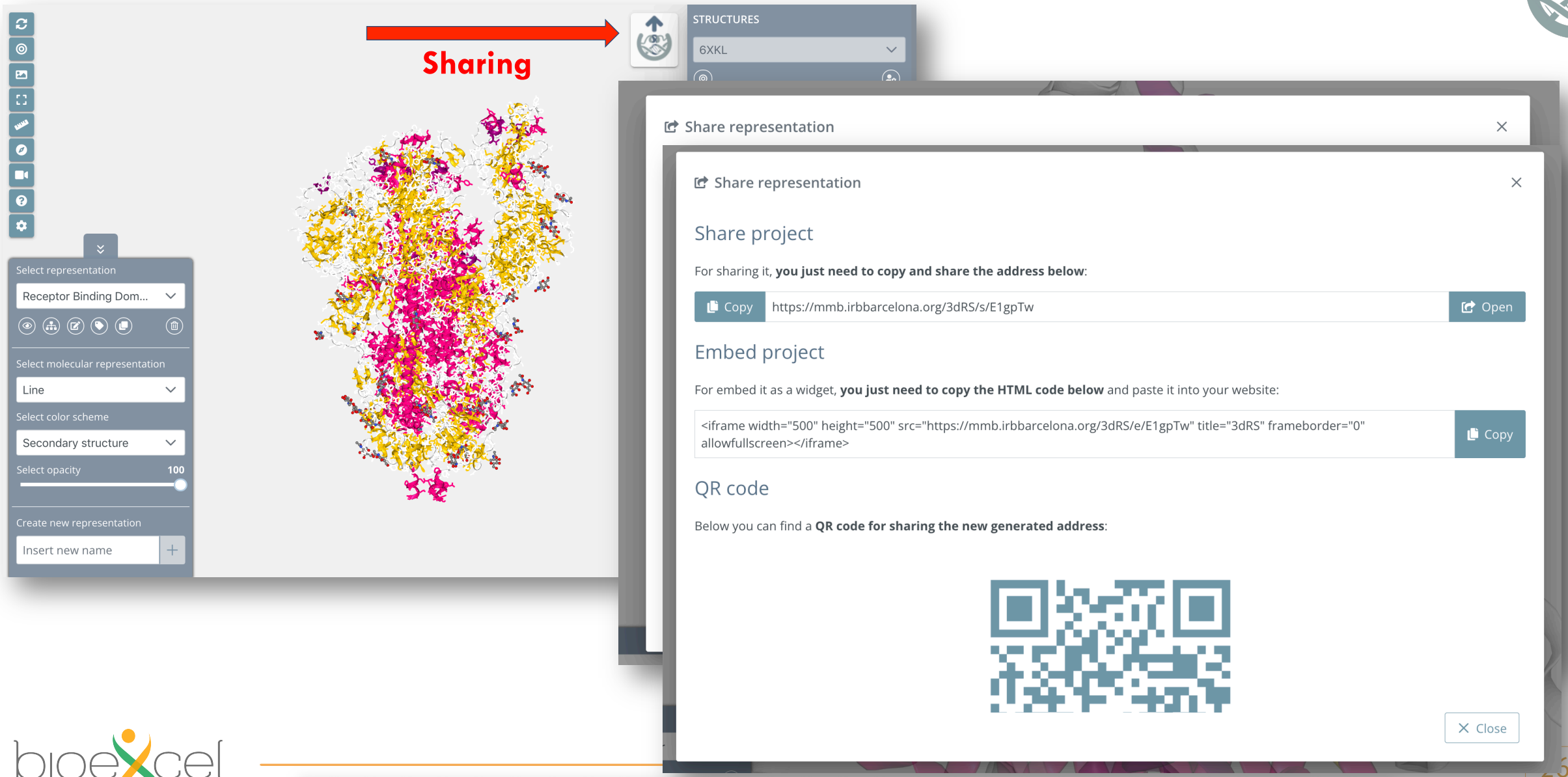
MD trajectory server

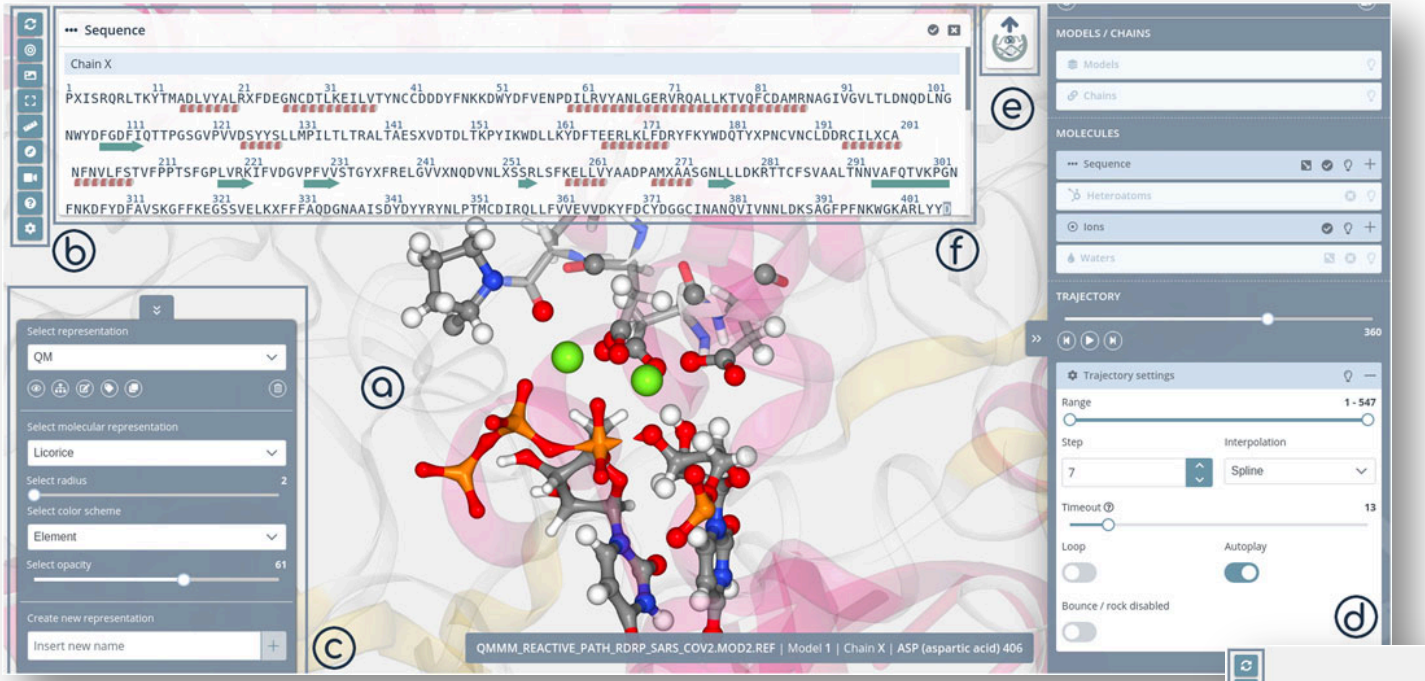




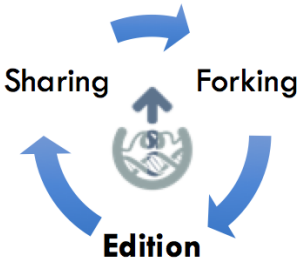
500 MB maximum size

3dRS: Sharing

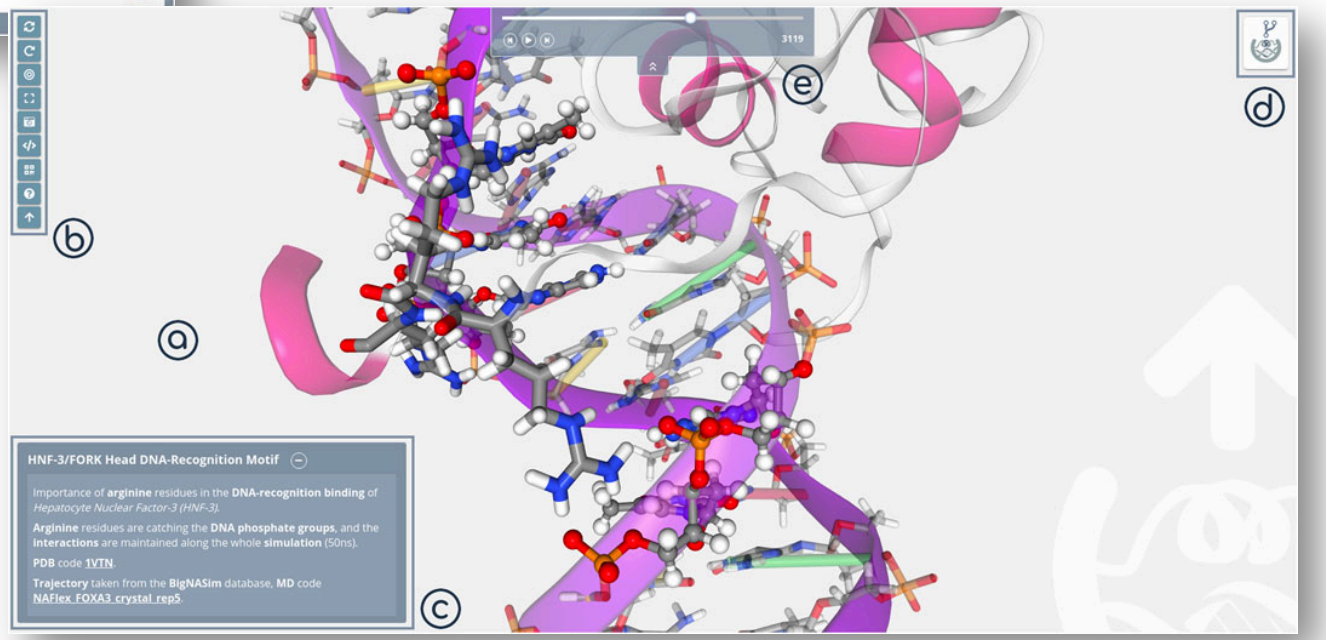




Share



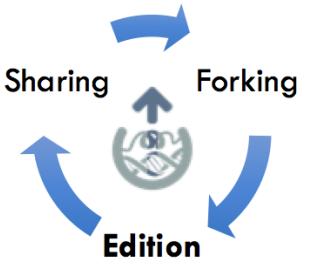
Shared Mode
Persistent Link



Edition Mode

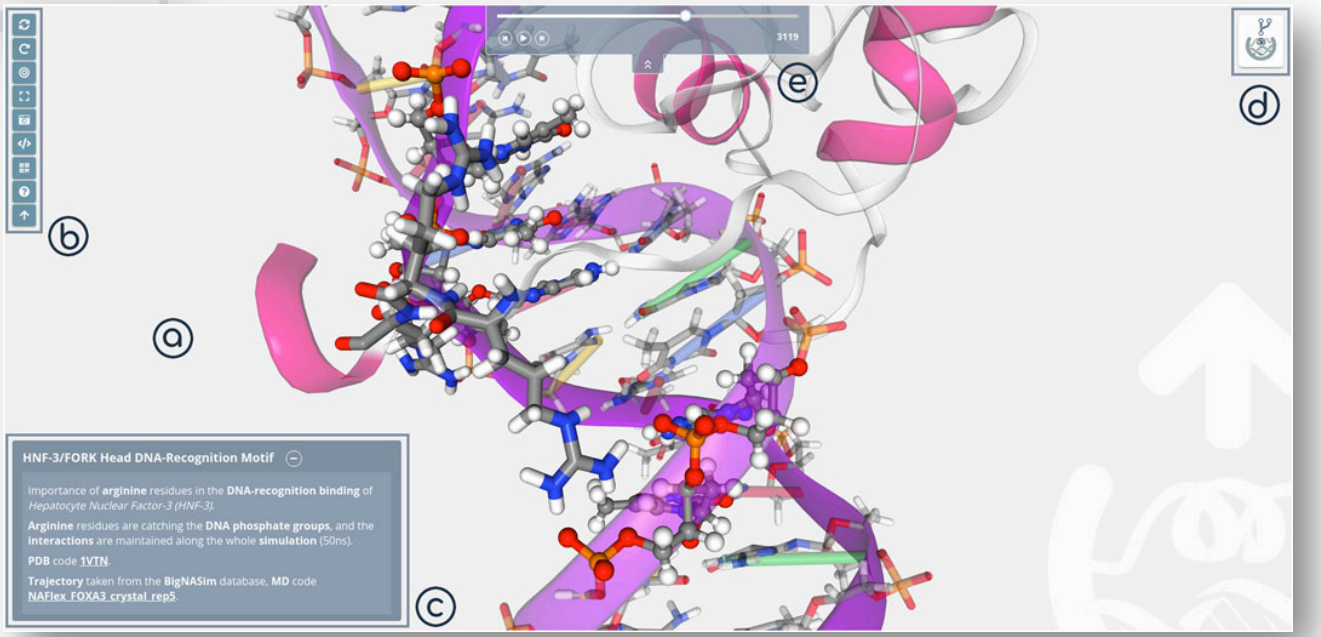
Fork

Share

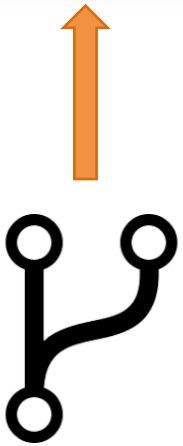


Shared Mode

Persistent Link



Edition Mode



Fork

Main differences between Edition and Shared Mode

- No modification
  - *Selection / representation*
  - *Labels / Measurements*
  - *Background color / Perspective*

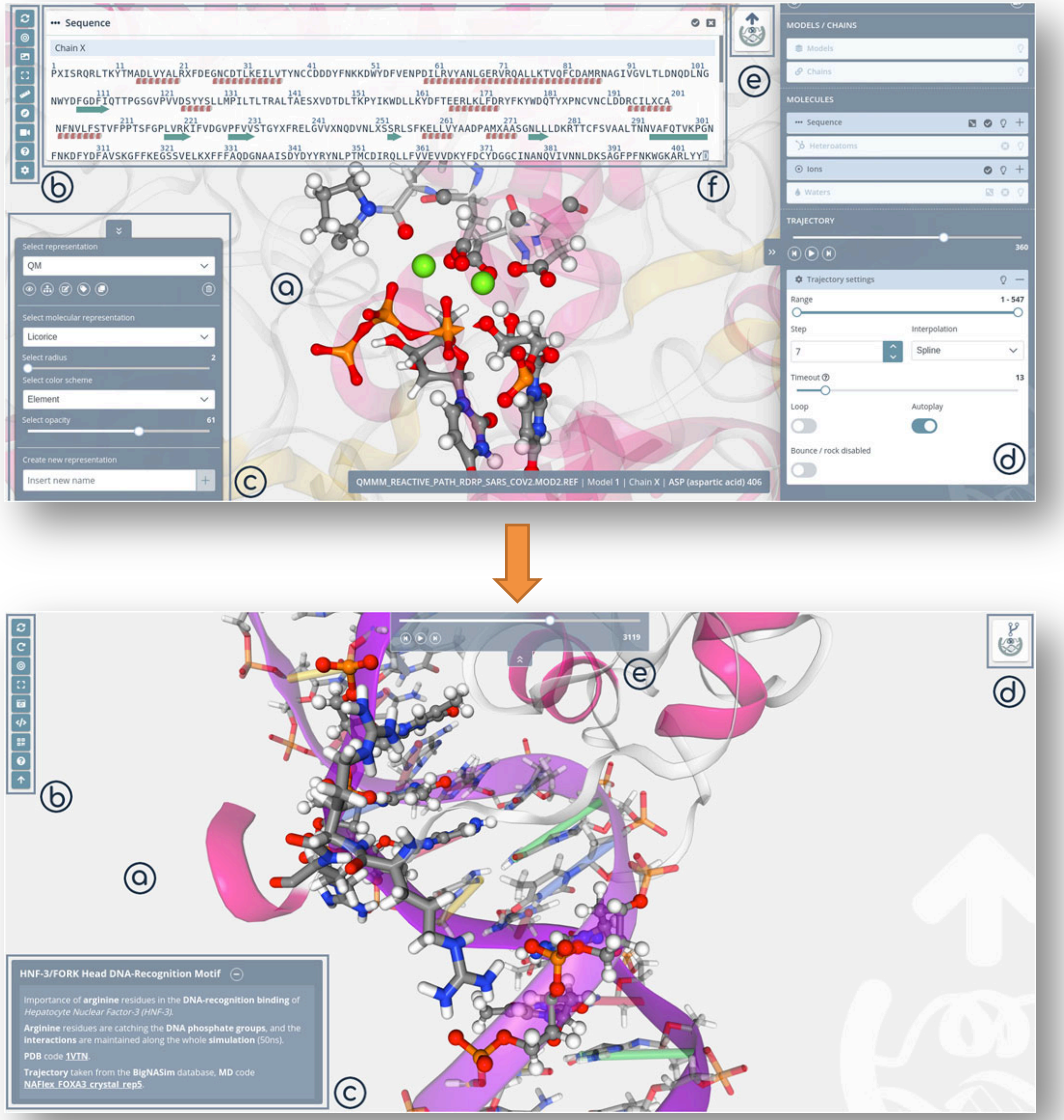
OUT

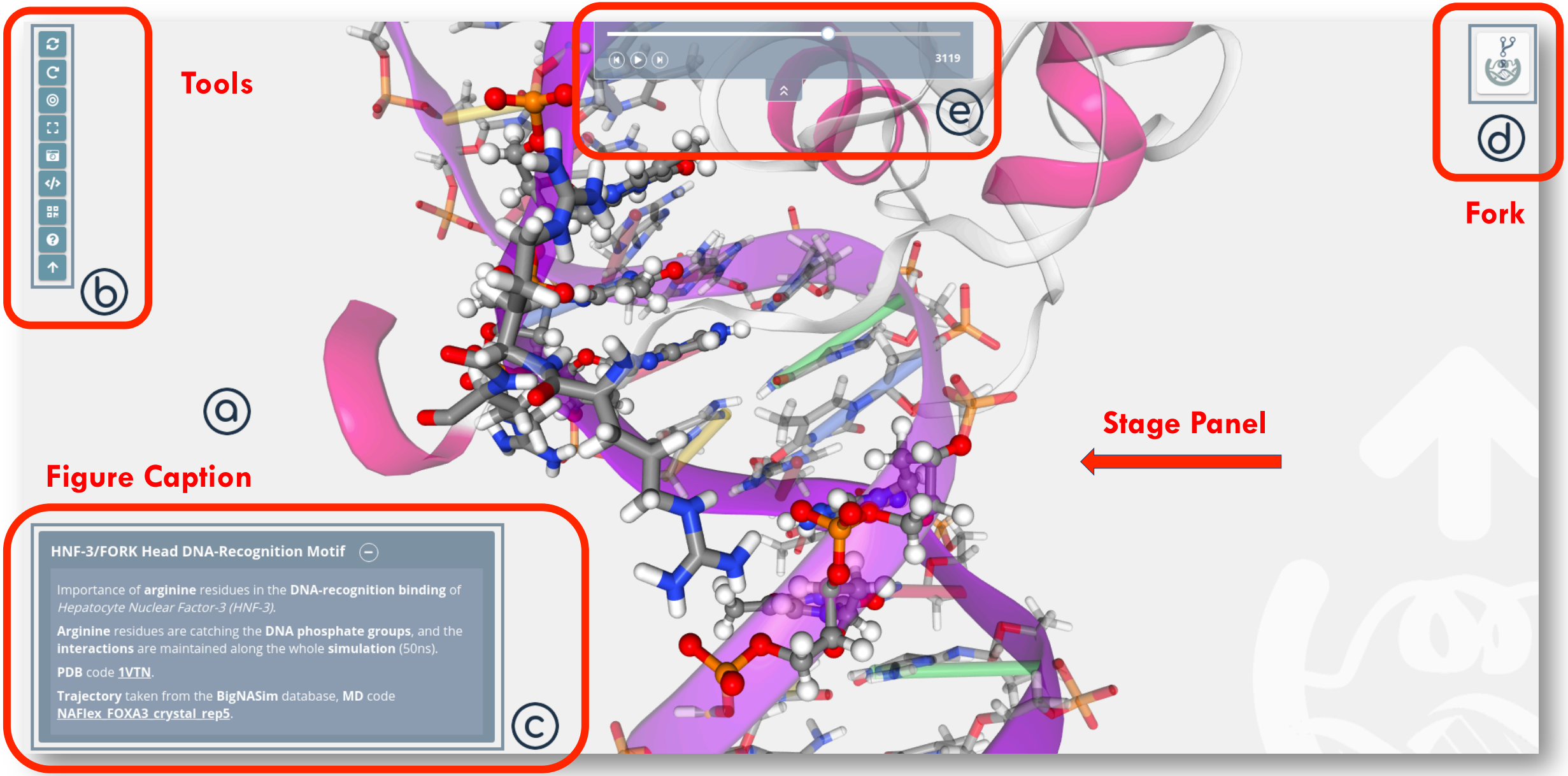
- Zoom / Rotation
- Atom-Residue information

=

- Figure Caption
- Trajectory Player
- Specific Tools
- Forking process

NEW




Trajectory Player
3119
e
Tools
b
d
Fork
a
Stage Panel
Figure Caption
HNF-3/FORK Head DNA-Recognition Motif
Importance of arginine residues in the DNA-recognition binding of Hepatocyte Nuclear Factor-3 (HNF-3).
Arginine residues are catching the DNA phosphate groups, and the interactions are maintained along the whole simulation (50ns).
PDB code 1VTN.
Trajectory taken from the BigNASim database, MD code NAFlex_FOXA3_crystal_rep5.
c

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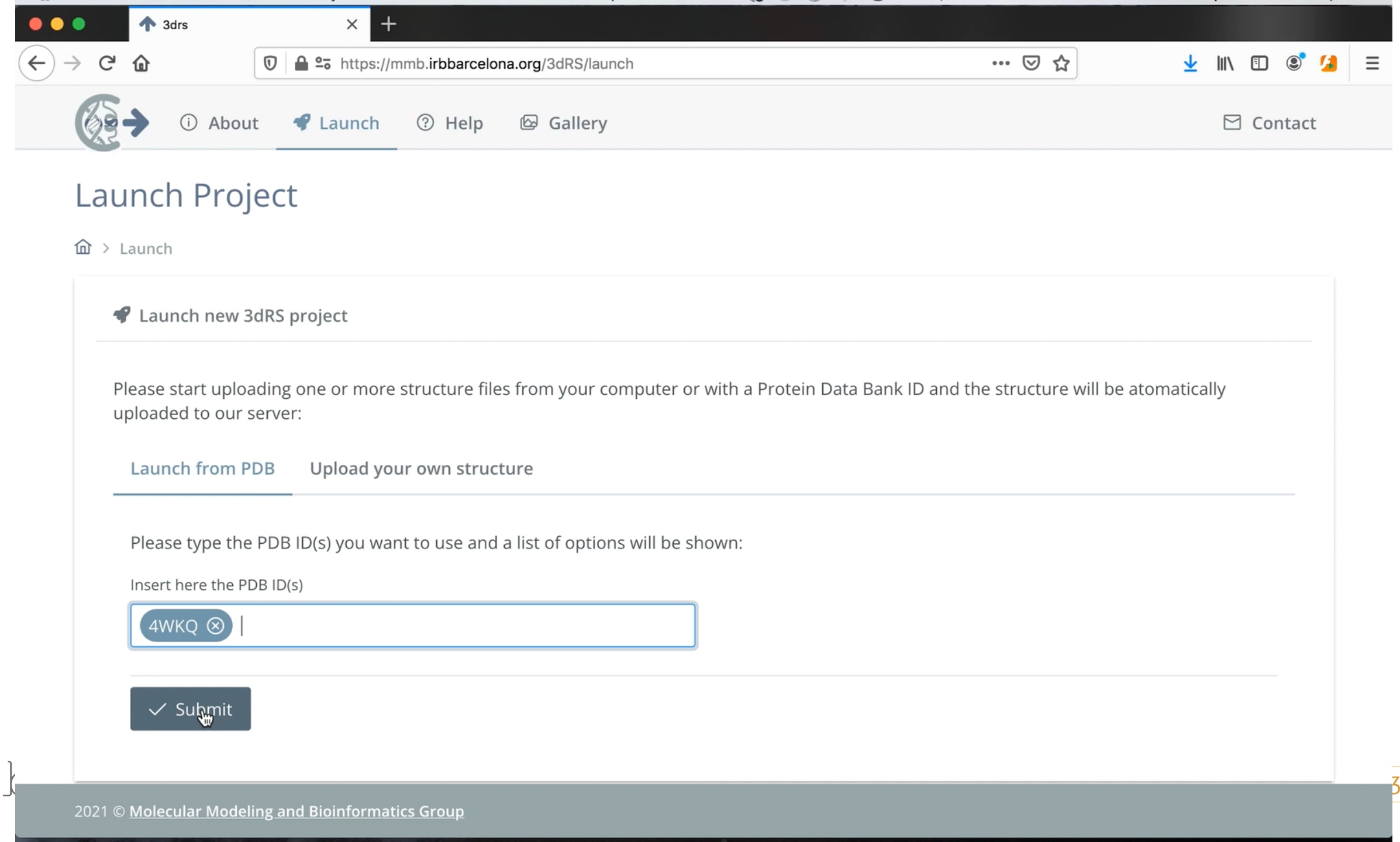
Demo | Input | Edit | Share | Fork


3drs
https://mmb.irbbarcelona.org/3dRS/launch
About
Launch
Help
Gallery
Contact
Launch Project
Launch
Launch new 3dRS project
Please start uploading one or more structure files from your computer or with a Protein Data Bank ID and the structure will be atomatically uploaded to our server:
Launch from PDB
Upload your own structure
Please type the PDB ID(s) you want to use and a list of options will be shown:
Insert here the PDB ID(s)
4WKQ
Submit
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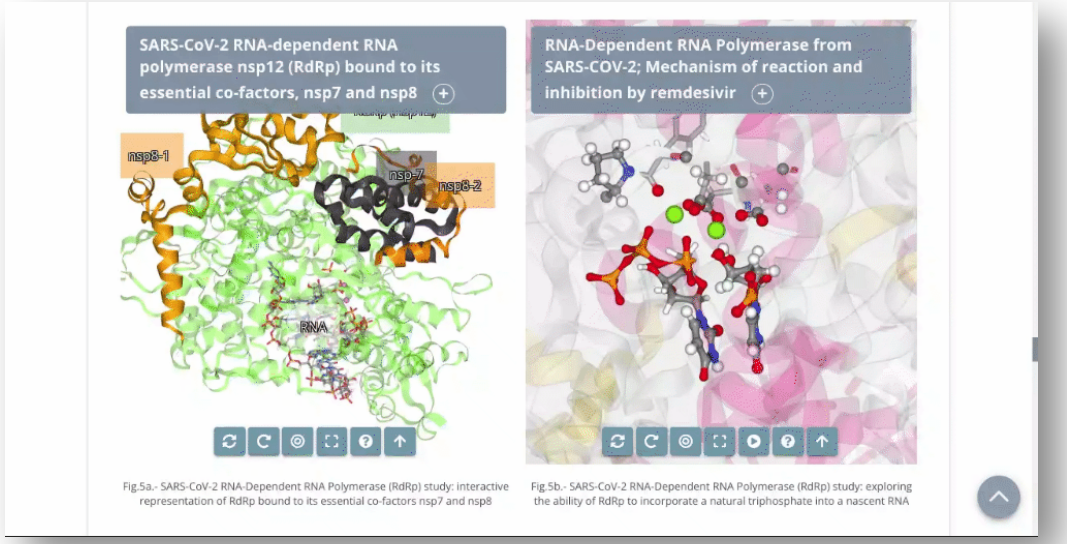
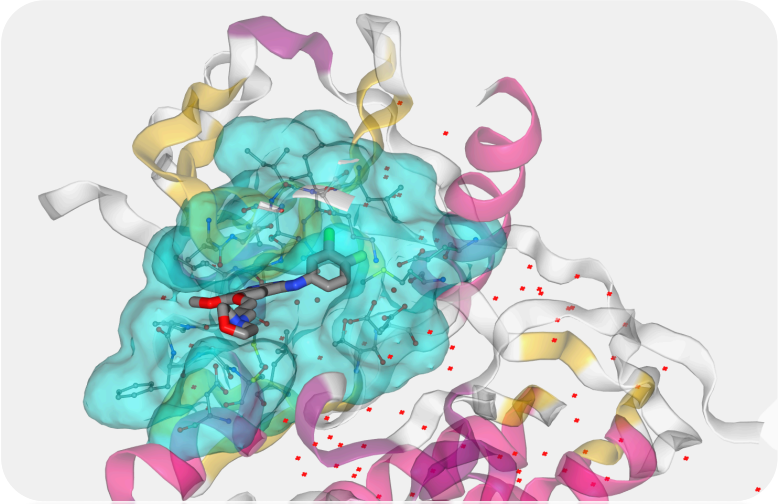
Summary

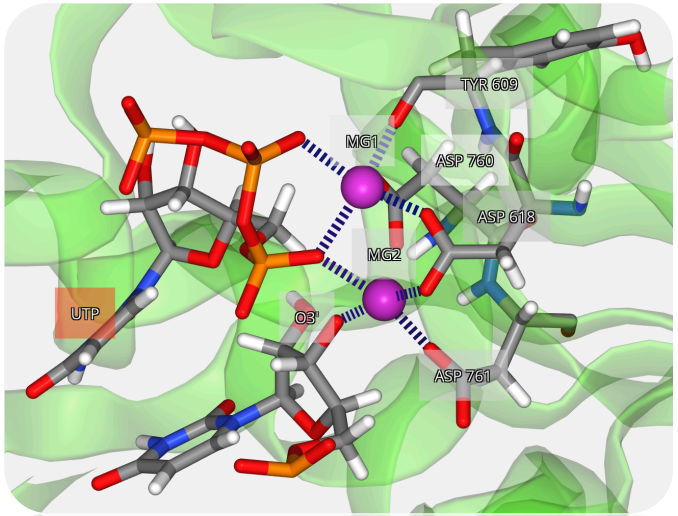
EASY

- **Generation** and **sharing** of **living**, **interactive**, **3D/4D custom representations**
  - **SPA** designed web page (*VueJS*, *MongoDB*)
  - **VMD-like** Selections and Representations
  - **NGL** to efficiently show 3D macromolecular representations
  - **MDsrv** to efficiently stream MD data

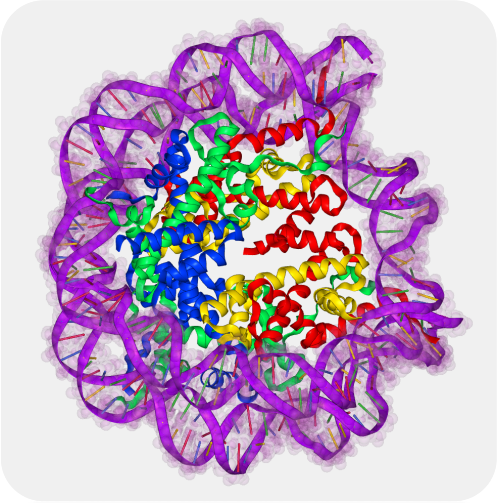




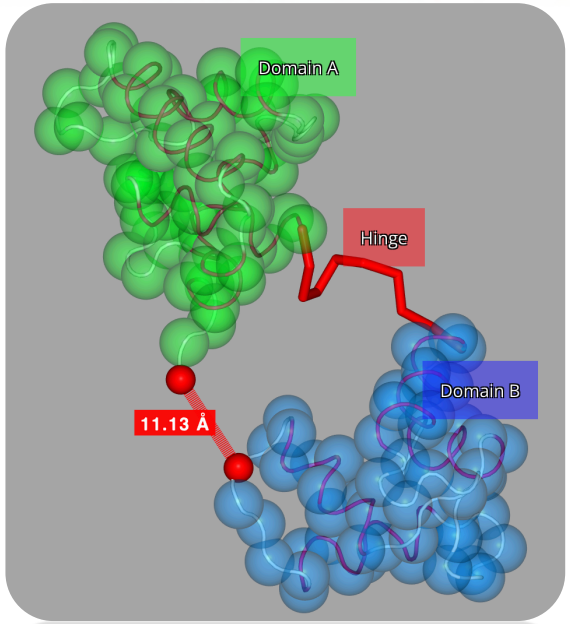
EGFR kinase domain complexed with gefitinib



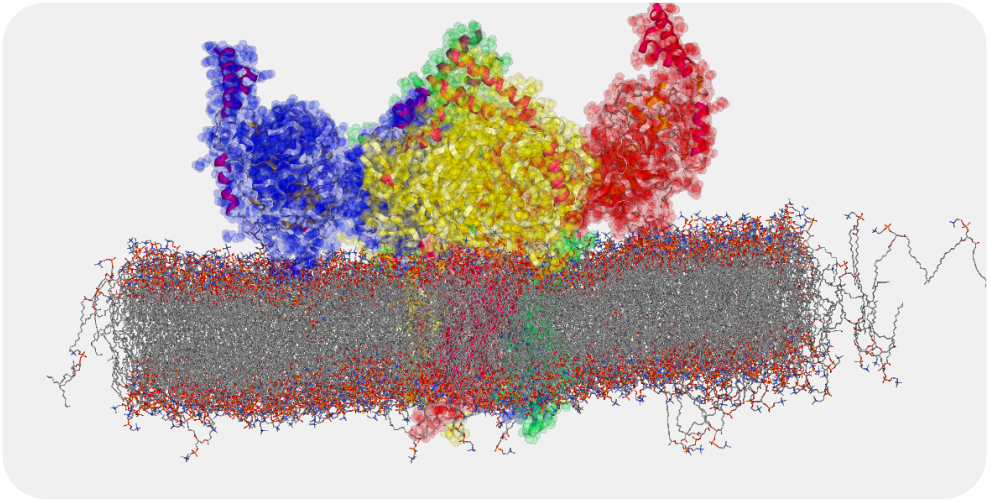
SARS-CoV-2 polymerase Magnesium coordination



Nucleosome Core Particle

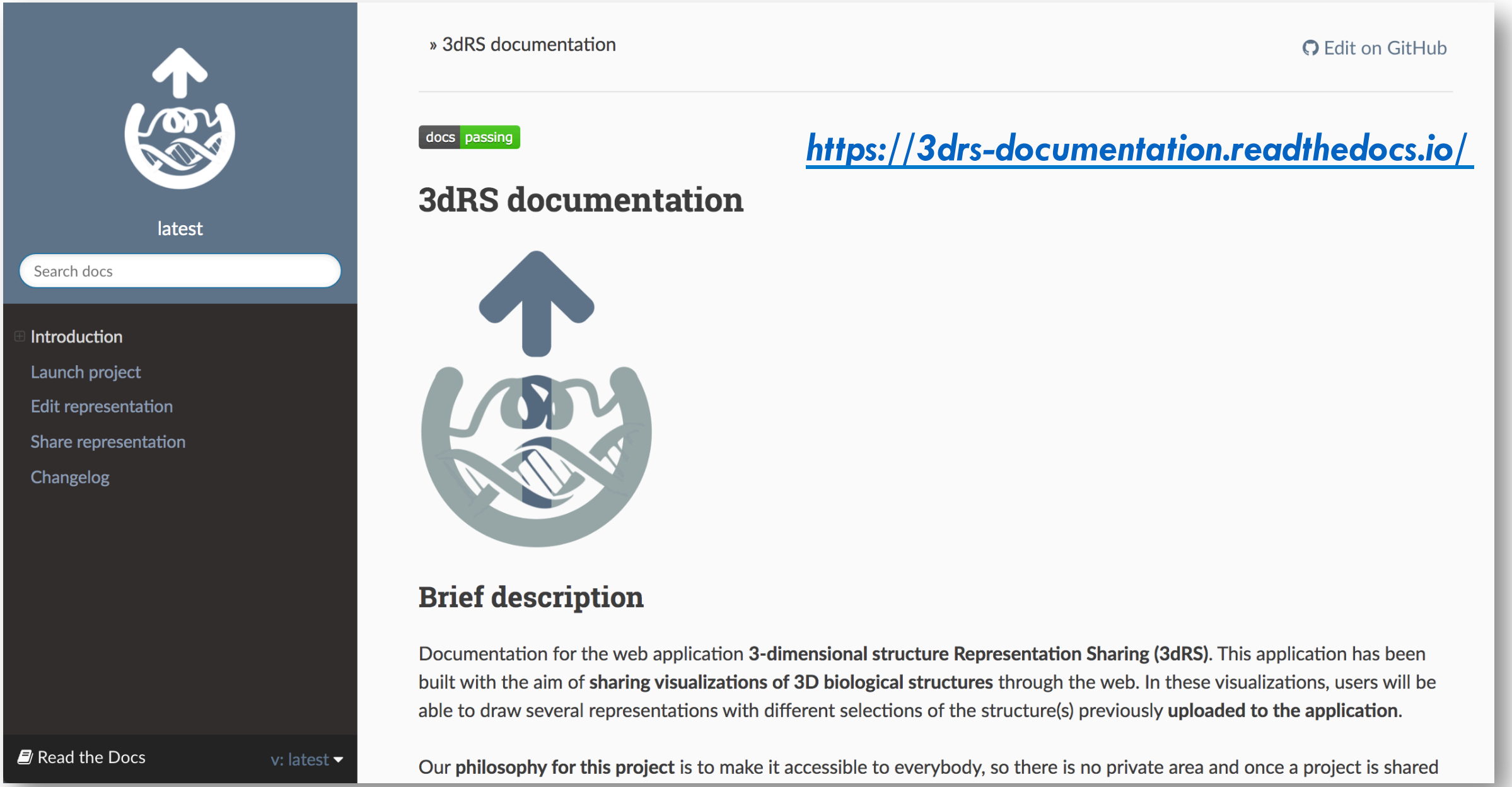


Conformational Changes (Calcium Saturated Cardiac Troponin C)



G Protein-Gated K+ Ion Channel

https://mmb.irbbarcelona.org/3dRS/gallery


latest
Search docs
Introduction
Launch project
Edit representation
Share representation
Changelog
Read the Docs
v: latest
» 3dRS documentation
Edit on GitHub
docs passing
https://3drs-documentation.readthedocs.io/
3dRS documentation
Brief description
Documentation for the web application 3-dimensional structure Representation Sharing (3dRS). This application has been built with the aim of sharing visualizations of 3D biological structures through the web. In these visualizations, users will be able to draw several representations with different selections of the structure(s) previously uploaded to the application.
Our philosophy for this project is to make it accessible to everybody, so there is no private area and once a project is shared

Share representation

Sharing instructions

If your project is ready for sharing, **please follow the next steps**:

1) First off, **take a look to the project draft**. It will show you the project the same way the final users will see it. Take into account that **this address shouldn't be shared**, because until you **generate a shared project**, the current one will be **expirable**.

View draft

2) Be sure that you agree with the **fork permissions** for this project. You can allow or not other users to **fork this project** once it is shared:

Fork enabled

3) Allow or not to **make this project public** and **available to other users** throughout the home page:

Project is private

4) Finally, clicking the button below **the shared project will be you want**, but once a project is shared, the subsequent update projects.

Share project

Last projects

List with the last projects developed by our users:

Name	Date	Link
EGFR kinase domain comple...	02/08/2021 15:19:00	Open
AppA BLUF domain	02/08/2021 09:35:44	Open
SARS-CoV-2 glycosylated S...	30/07/2021 09:32:23	Open
Nucleosome core Particle,...	30/07/2021 08:40:34	Open
G protein-gated inward re...	29/07/2021 17:14:10	Open

Acknowledgments

Prof. Modesto Orozco

RESEARCH GROUP

Molecular Modelling and Bioinformatics

Mechanisms of Disease

IRB BARCELONA

INSTITUTE FOR RESEARCH IN BIOMEDICINE

Genís Bayarri

Questions

TECHNOLOGY AND CODE article

Front. Mol. Biosci., 13 August 2021 | https://doi.org/10.3389/fmolb.2021.726232

3dRS, a Web-Based Tool to Share Interactive Representations of 3D Biomolecular Structures and Molecular Dynamics Trajectories

Genís Bayarri[1], Adam Hospital[1]* and Modesto Orozco[1,2]*

[1]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology (BIST), Barcelona, Spain

[2]Departament de Bioquímica i Biomedicina, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain

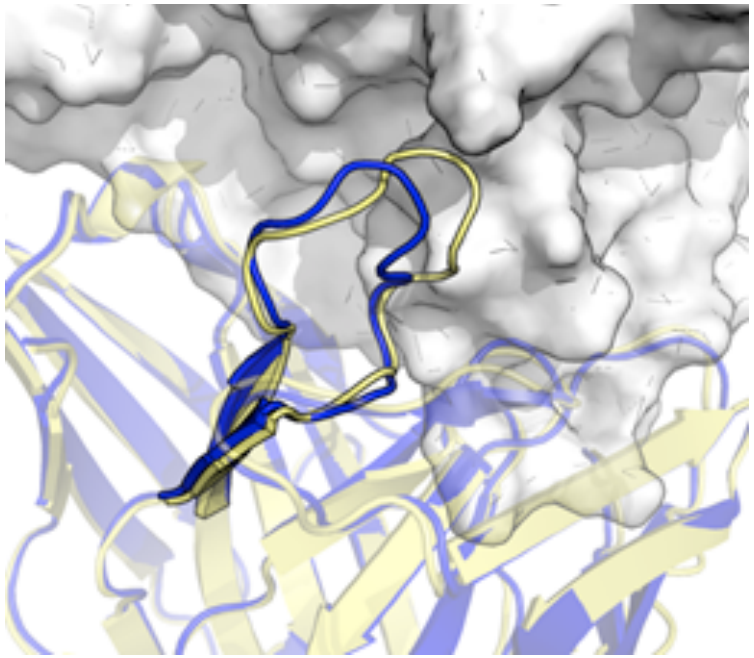
Audience Q&A session

- Please use the Q&A function at the bottom of **Zoom** application

  - If you *can't use your microphone*, write ***no micro*** and we will read the question for you

- Any other questions or points to discuss after the live webinar? Join the discussions at http://ask.bioexcel.eu.

Next BioExcel webinar



Webinar: Computationally designing therapeutic antibodies - combining immune repertoire data and structural information. (2021-11-09)

By Charlotte Deane

3dRS infrastructure scheme