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

BioExcel Webinar, 2021-10-26

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A glycan gate controls opening of the SARS-CoV-2 spike protein

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Nature Chemistry 13, 963–968 (2021) | Cite this article

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**Introduction - Idea**

Transcutaneous provides an unbiased characterization of the current time-dependent ensemble properties. The 9S strategy therefore facilitates the generation of data-based dynamics, yielding the most direct, atomistic views for analyzing the mechanisms of functional transitions, including elucidation of transient states that are not being captured by laboratory experiments. Furthermore, while the strategy requires a precise coordinate towards the target state, the definition of that target state need not be fixed in advance when applied under ‘adaptive conditions’, 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 data by MaxiIMM. Conformations in the 9S ensemble sample a range of possible structural states of the spike C-terminus and are identified as key residues, including a glycan at position N154A that participates in the opening mechanism. Our simulation findings are corroborated by biosensor structural (HGK) experiments, which show a reduction in the ability of the spike to interact with ACE2 after mutation of the glycan.

**Results and discussion**

WS simulations of spike opening. An animated view above shows the conformational space along multiple degrees of freedom. The 9S-based spike conformation has also been sampled by the Foldit/handling-distributed computing project, and 9S results have been detected in cryo-EM experiments.

Comparisons with spike conformations detected by MaxiIMM. To validate our simulated RBD- ACE2 complex, we structure at N154A of the glycan (134) of the glycerol 9S-C2G-2f spike from Casalino et al. (Fig. 1c), which is a test was used to sample the conformational space of the three-state model. In this study, the three-state model was used to sample the conformational space along multiple degrees of freedom. The 9S-based spike conformation has also been sampled by the Foldit/handling-distributed computing project, and 9S results have been detected in cryo-EM experiments.

These projections were not aligned to corresponding directional projections of clinical potential glycoproteins with 9S from the MaxiIMM framework. The 9S framework was applied using the cryo-EM dataset of 9S-C2G from McLellan and colleagues. The MaxiIMM framework method allows characterization of conformational variations obtained from a single-particle cryo-EM ensemble of a molecule in thermal equilibrium. Two conformational coordinates or a collective rotation coordinate C1 and a collective axis coordinate C2 were involved from the dataset. The latter, we averaged between the MaxiIMM conformational space along multiple degrees of freedom. The 9S-based spike conformation has also been sampled by the Foldit/handling-distributed computing project, and 9S results have been detected in cryo-EM experiments.
Future Journals

Harry Potter – Daily Prophet (2001)
Minority Report – USA Today (2002)
nature chemistry

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Article  Published: 19 August 2021

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Abstract

Introduction - Idea
Introduction - Idea

- HTMol
- MolMil
- 3DMol.js
- LiteMol
- Protein Viewer
- …
Interactivity
Introduction - Idea

- WebGL tools
- Interactivity
- Network Bandwidths
Add Interactivity
Add Movement?

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
https://mmb.irbbarcelona.org/3dRS/help/integration
Introduction: Why?

- **Live Figures**
- **Internal meetings** - same room
- **Collaborative projects** - not in the same room (e.g. BioExcel CoE partners)
- **Presentations** - show + share

https://mmb.irbbarcelona.org/3dRS/s/TVVSQ2
Introduction – Similar tools
The 3-dimensional structure Representation Sharing (3dRS) web 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 everybody with the link can access it with no restrictions.
How it works

Main Functionalities

Input

Edition Mode

Shared Mode
3dRS: Main functionalities

- **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)
Launch Project

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 automatically uploaded to our server:

- Launch from PDB
- Upload your own structure

Please click or drag and drop files, only **PDB** and **GRO** files accepted:

Click **Select button** above or drag and drop files to here to upload.

How it works – Input
How it works – Main Functionalities

Edition Mode

Fork

Share

Shared Mode

Persistent Link

BioExcel
How it works – Edition Mode

Edition Mode

Fork

Share

Sharing

Forking

Shared Mode

Persistent Link
VMD-like: Selections + Representations

How it works – Edition Mode
3dRS: Selections + Representations

How it works – Edition Mode

Selection

Representation
3dRS: Selections + Representations

How it works – Edition Mode

Tools

Stage Panel

Representation

Selection

Sharing
3dRS: Selections + Representations

How it works – Edition Mode
3dRS: Representations

- Hide Representation
- Edit Representation Name
- Clone Representation
- Open Label Settings

Select representation
- Nucleosome

Label settings
- Nucleosome Label

Select molecular representation
- Line

Select color scheme
- Secondary structure

Select opacity
- 100

Create new representation
- Insert new name

Menu:
- Reload
- Center
- Background
- Full screen
- Superposition
- Measurements
- Navigation mode
- Camera type
- Help
- Project settings

How it works – Edition Mode
3dRS: Trajectories

**Powered by…**

nglviewer/mdsrv

MD trajectory server

**500 MB maximum size**

How it works – Edition Mode
3dRS: Sharing

How it works – Edition Mode

**Sharing**

**Share representation**

**Share project**

For sharing it, **you just need to copy and share the address below**:

- **Copy**
  - https://mmb.irbbarcelona.org/3dRS/s/E1gptw

**Embed project**

For embed it as a widget, **you just need to copy the HTML code below** and paste it into your website:

```html
<iframe width="500" height="500" src="https://mmb.irbbarcelona.org/3dRS/s/E1gptw" title="3dRS" frameborder="0" allowfullscreen></iframe>
```

**QR code**

Below you can find a **QR code for sharing the new generated address**:
How it works – Main Functionalities

Edition Mode

Fork

Share

Shared Mode
Persistent Link
How it works – Shared Mode

Fork

Edition Mode

Shared Mode

Persistent Link
Main differences between Edition and Shared Mode

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

- Zoom / Rotation
- Atom-Residue information

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

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
Conclusions  Summary  Acknowledgements  Questions
Summary

- **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
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...
Conclusions – Feedback

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.

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:

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

4) Finally, clicking the button below the shared project will be useful to you, but once a project is shared, the subsequent updates are only for the shared 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

RESEARCH GROUP
Molecular Modelling and Bioinformatics
Mechanisms of Disease

Prof. Modesto Orozco

Genís Bayarri
Questions

TECHNOLOGY AND CODE article
Front. Mol. Biosci., 13 August 2021 | https://doi.org/10.3389/fmoib.2021.726232

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

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Conclusions – Questions
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