Interactive MD in Virtual Reality to Explore Macromolecular Landscapes

Ludovica Aisa

StatPhys29 Satellite Meeting

INTANGIBLE REALITIES LABORATORY

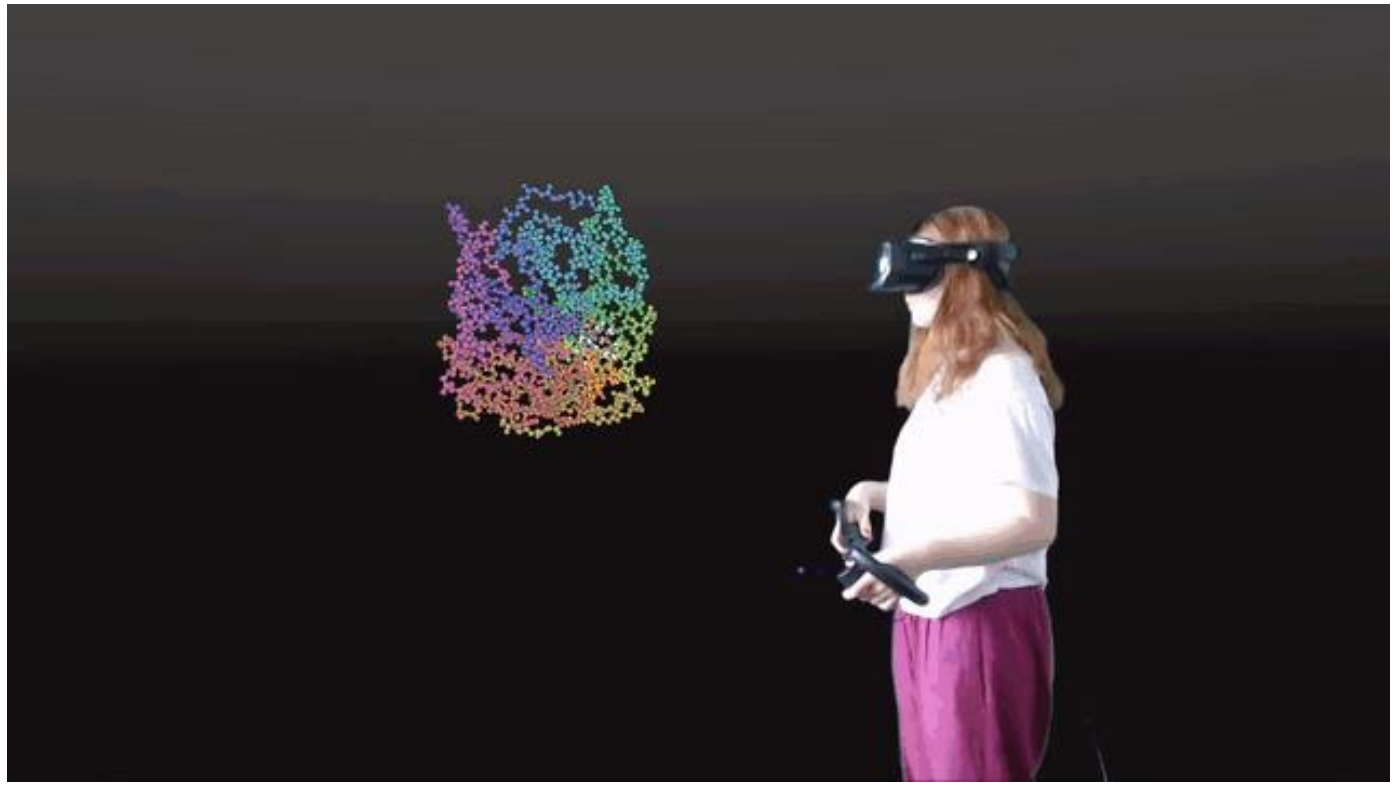
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

CiTiUS Centro Singular de Investigación en Tecnoloxías Intelixentes

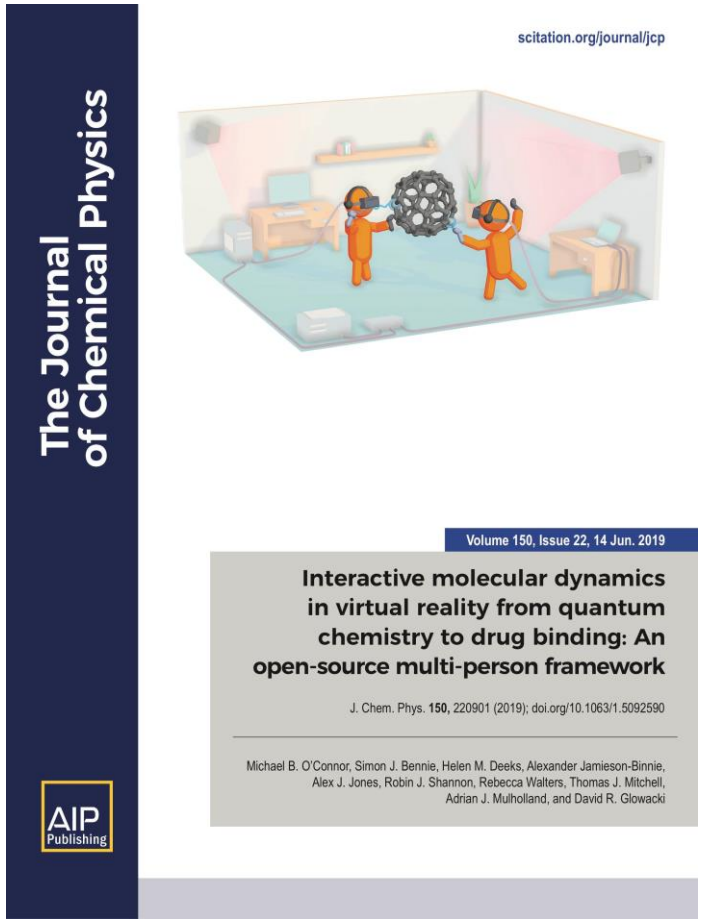
09/07/25

Outline:

- NANOVR project
- Interactive Molecular Dynamics in Virtual Reality (iMD-VR)
- NanoVer software
- An iMD-VR case study: GluHUT, a macroreceptor of glucose
- Free energy profiles from human-sampled paths of unbinding sugar-receptor complexes



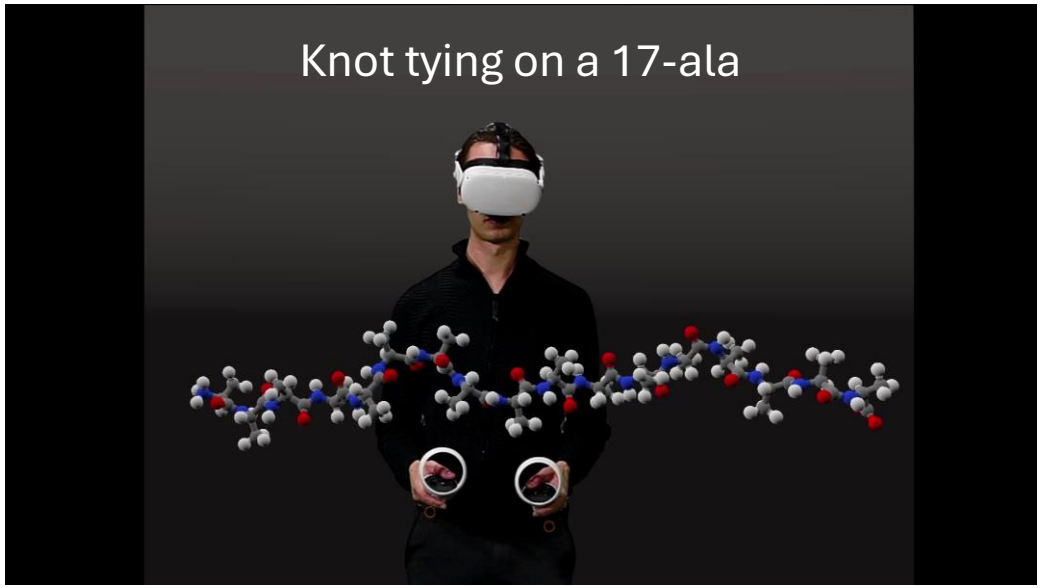
NANOVR

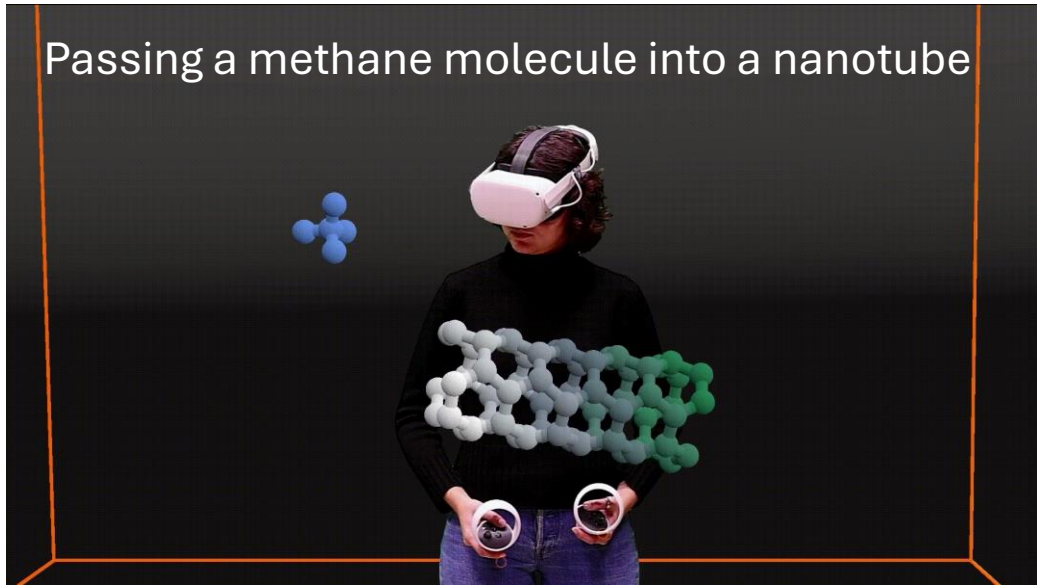


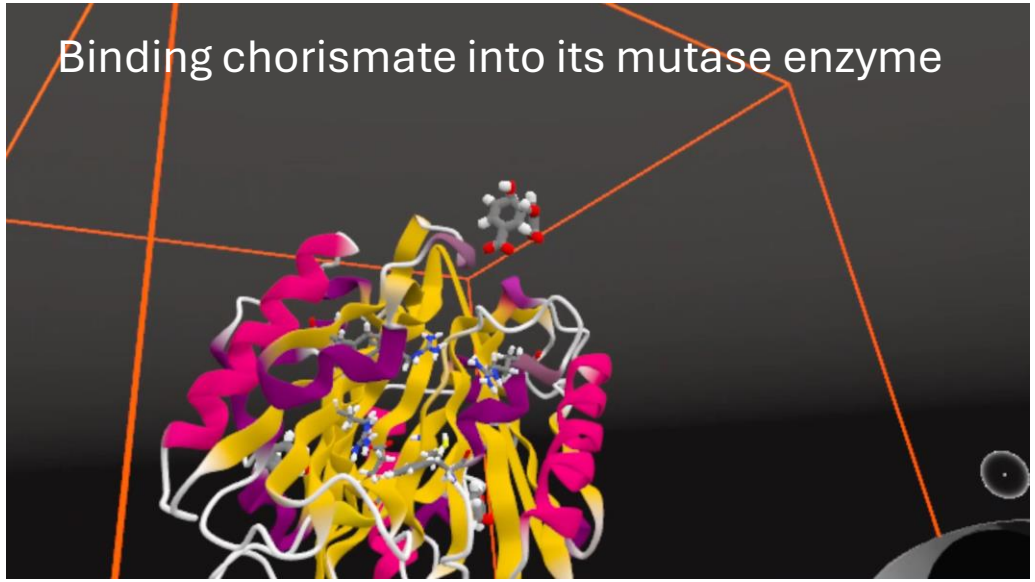
- Virtual Reality for visualising and understanding the dynamics of complex high-dimensional systems.
- iMD-VR facilitates molecular science and education
- Researchers and citizens can 'reach out and touch' real-time Molecular Simulation

iMD-VR is a nonequilibrium enhanced sampling method:

The user adaptively biases molecular simulations on-the-fly in real time







NanoVer's Architecture

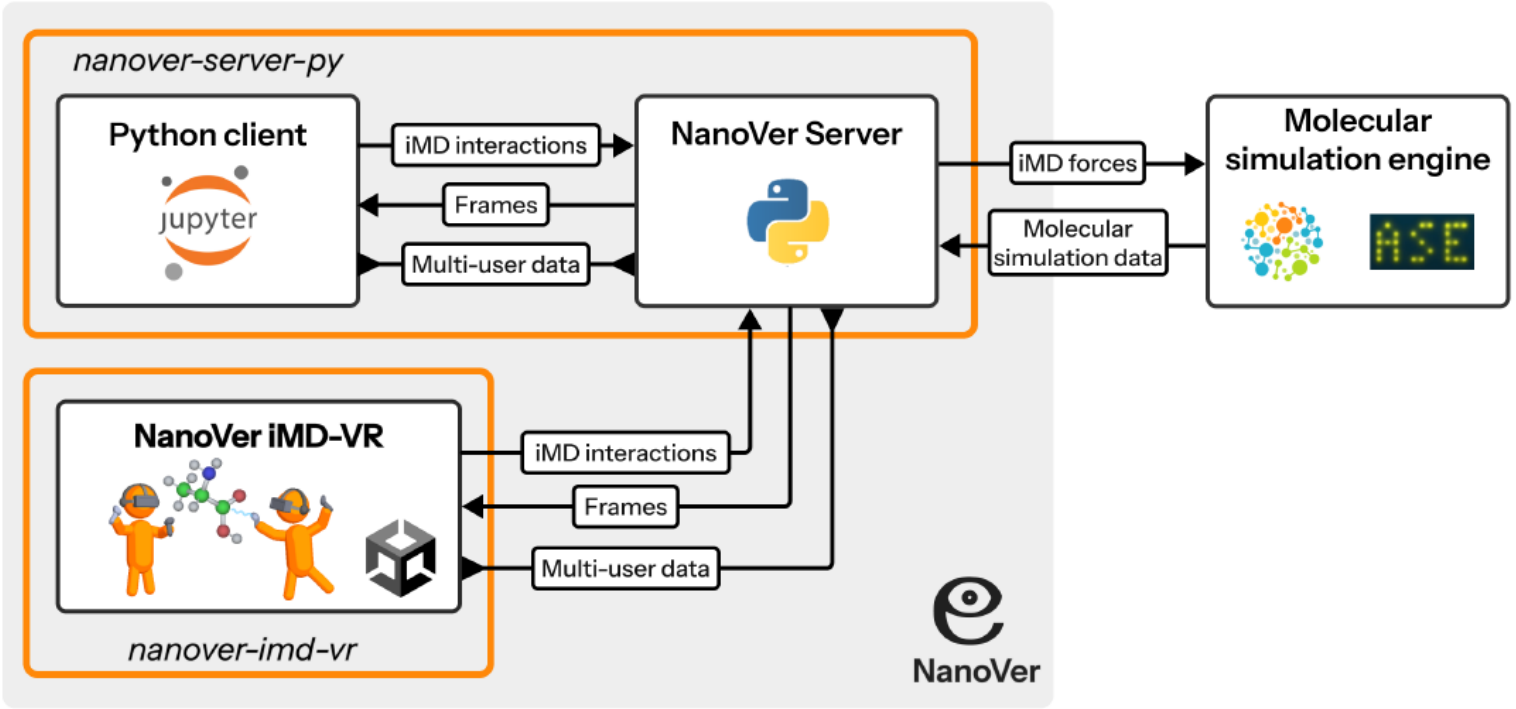
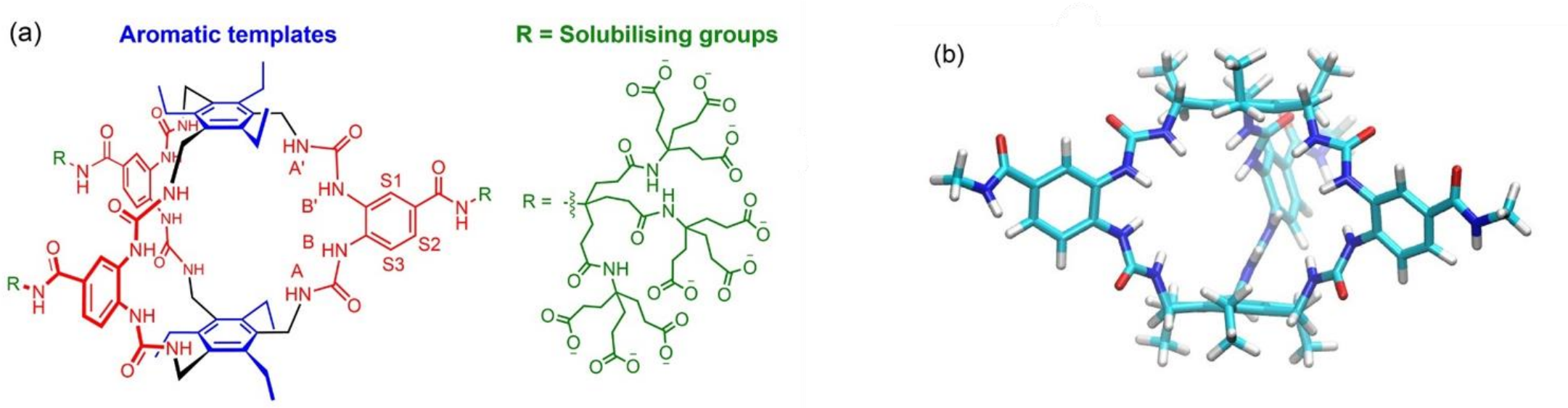


Figure 1: Systems diagram of the NanoVer ecosystem for iMD (displayed within the grey box) that illustrates how NanoVer Server communicates data between the molecular simulation engine and connected clients, and between clients themselves. The orange boxes indicate the contents of the GitHub repositories for NanoVer Server (nanover-server-py) and NanoVer iMD-VR (nanover-imd-vr).

*Stroud, H. J. et al. NanoVer Server: A Python Package for Serving Real-Time Multi-User Interactive Molecular Dynamics in Virtual Reality. Journal of Open Source Software **10**, 8118 (2025).*

iMD-VR case study: GluHUT



- "**GluHUT**" (**Glu**cose-binding **H**exa**U**rea **T**emple) is a synthetic receptor for glucose;
- Structure: the cavity is formed by the roof and floor of aromatic rings connected by three NH-urea linkages.

Figures:

(a) Chemical structure: polar and hydrophobic regions with water-solubilising groups.

(b) Structure of the truncated model used in this work.

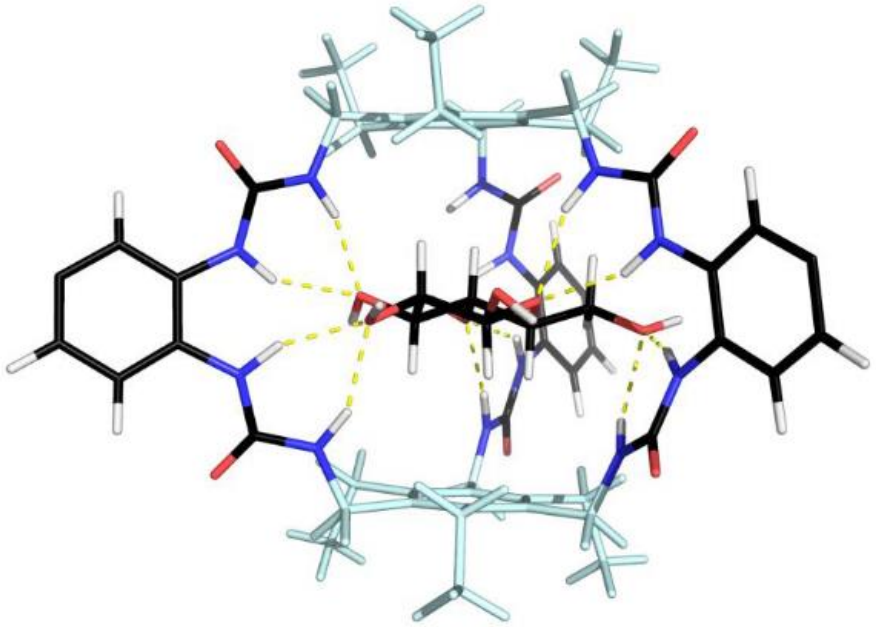
Tromans, R. A. *et al.* A biomimetic receptor for glucose. *Nature Chem* **11**, 52–56 (2019).

GluHUT and glucose: binding pose

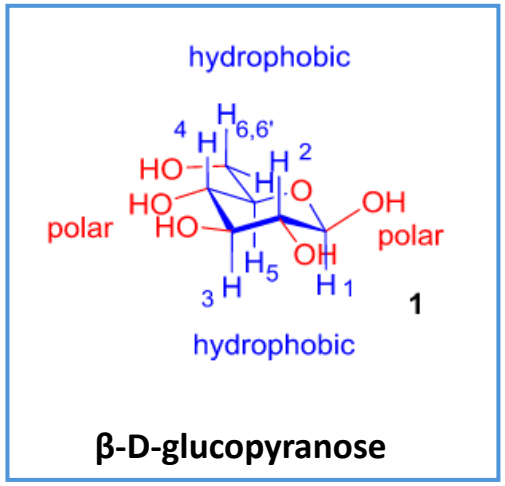
It was designed to maximise the number of hydrogen bonds with the receptor.

- Glucose OH groups bind with the NH-urea groups of the “arms”

The aromatic rings form CH-π interactions with the CH groups of the sugar.



10 hydrogen bonds predicted by MC simulation



Tromans, R. A. *et al*. A biomimetic receptor for glucose. *Nature Chem* **11**, 52–56 (2019).

GluHUT-Sugars binding affinities

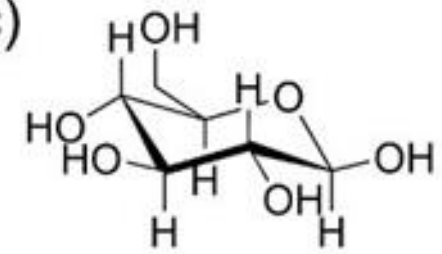
Glucose shows the strongest affinity.

Galactose Minor conformational differences from it weaken the binding by a factor of ~100.

Fructose shows the lowest binding affinity.

.

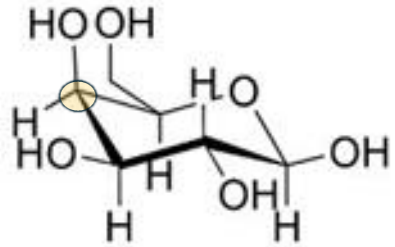
(c)



β-D-glucopyranose

K_a = 18,300 M^{-1}

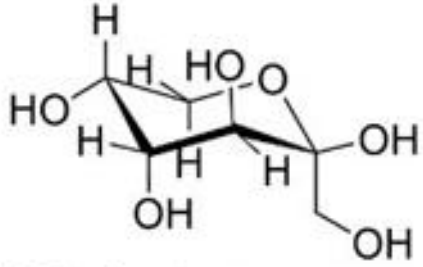
ΔG_{bind} = -5.85 kcal mol^{-1}



β-D-galactopyranose

K_a = 180 M^{-1}

ΔG_{bind} = -3.10 kcal mol^{-1}



β-D-fructopyranose

K_a = 60 M^{-1}

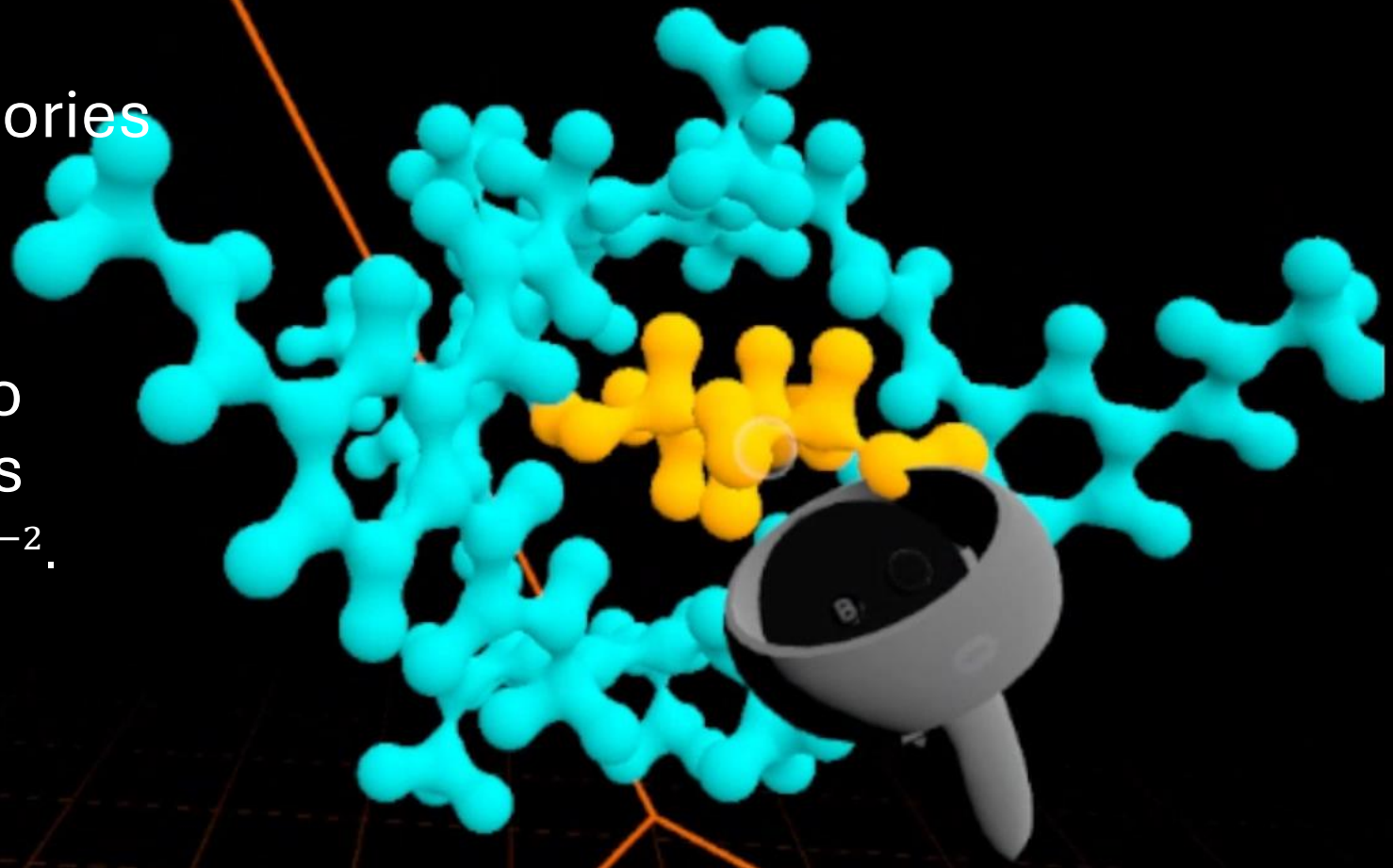
ΔG_{bind} = -2.44 kcal mol^{-1}

Tromans, R. A. *et al*. A biomimetic receptor for glucose. *Nature Chem* **11**, 52–56 (2019).

iMD-VR simulations:

- Human-driven trajectories of sugars unbinding

- Spring force applied to sugar's centre of mass (cm), $k = 2000\ kJ\ mol^{-1}\ nm^{-2}$.

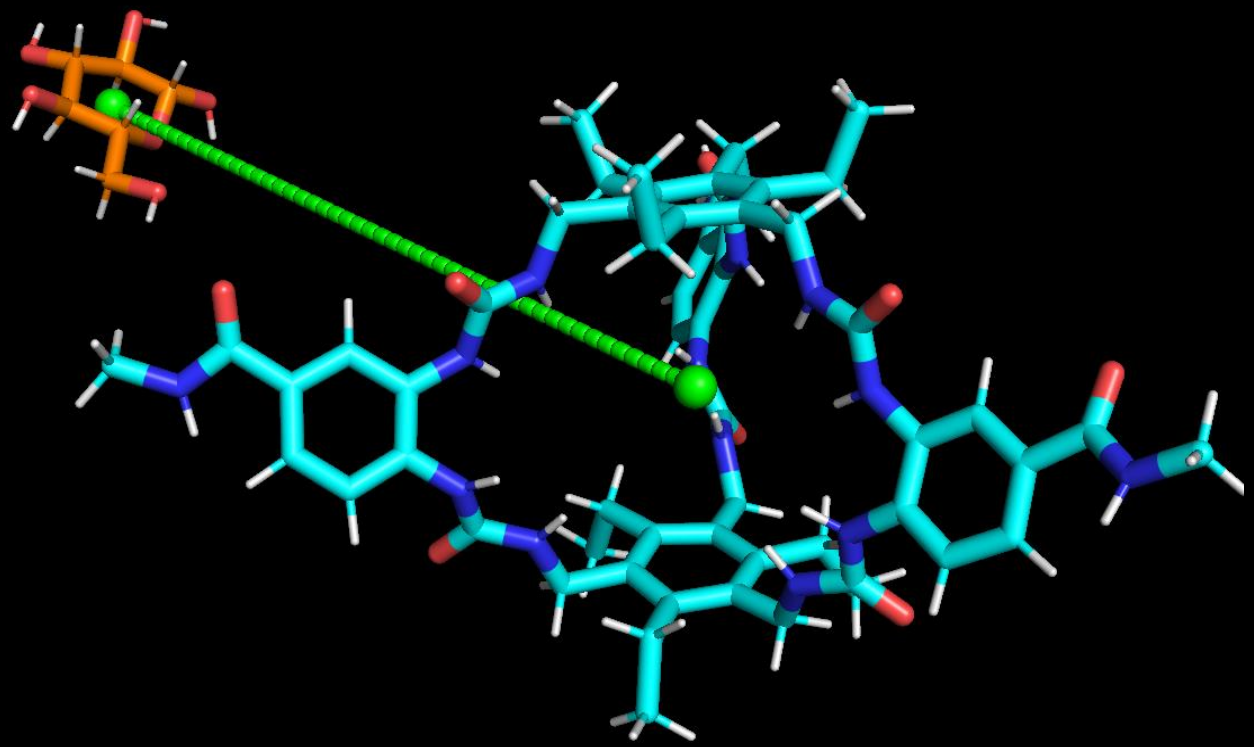


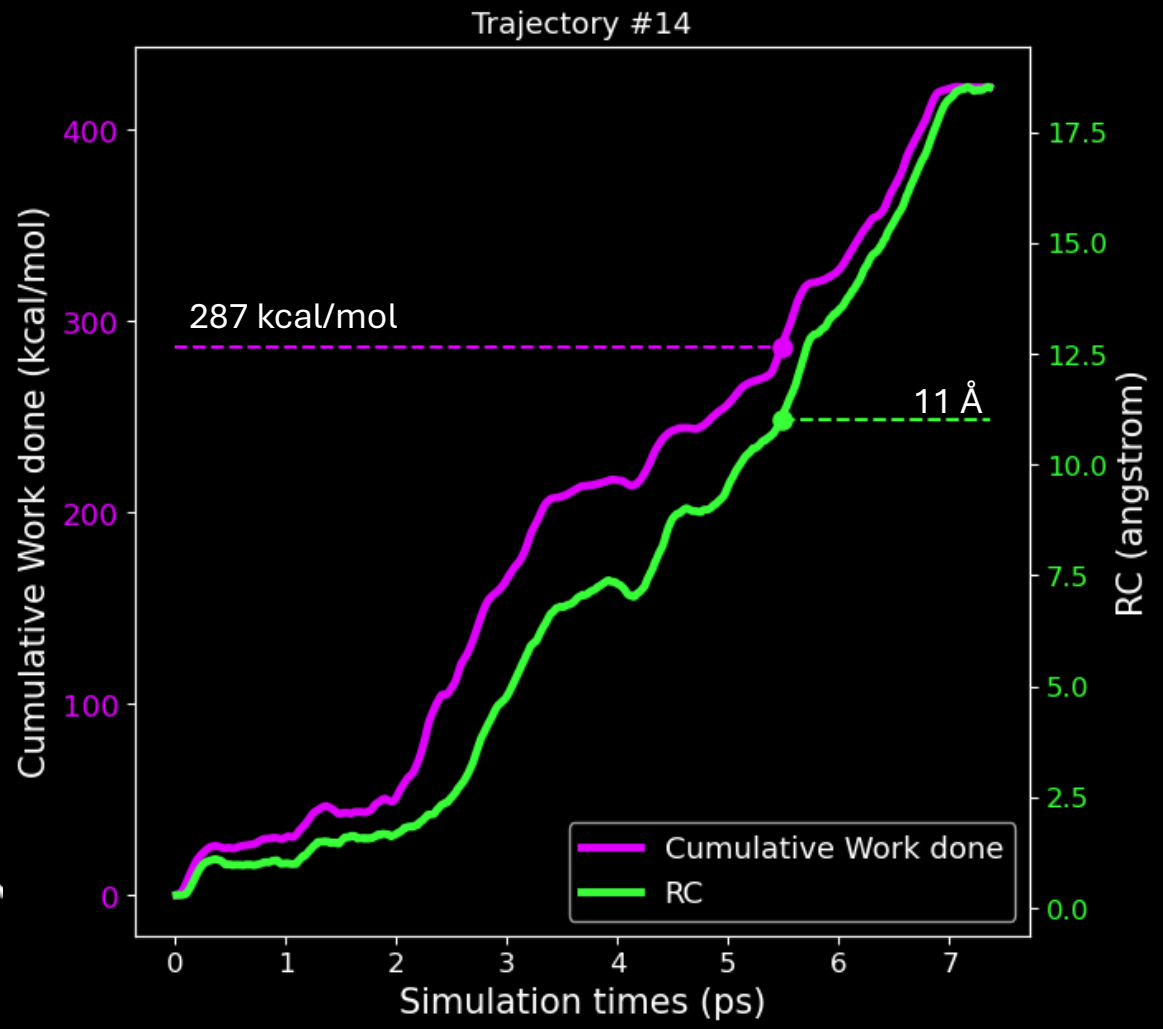
Park, S. & Schulten, K. Calculating potentials of mean force from steered molecular dynamics simulations. *The Journal of Chemical Physics* **120**, 5946–5961 (2004).

Cumulative work done:

$$W = \int_a^b F_{user} ds_{cm} \cong \sum_i F_i \cdot \Delta s_i$$

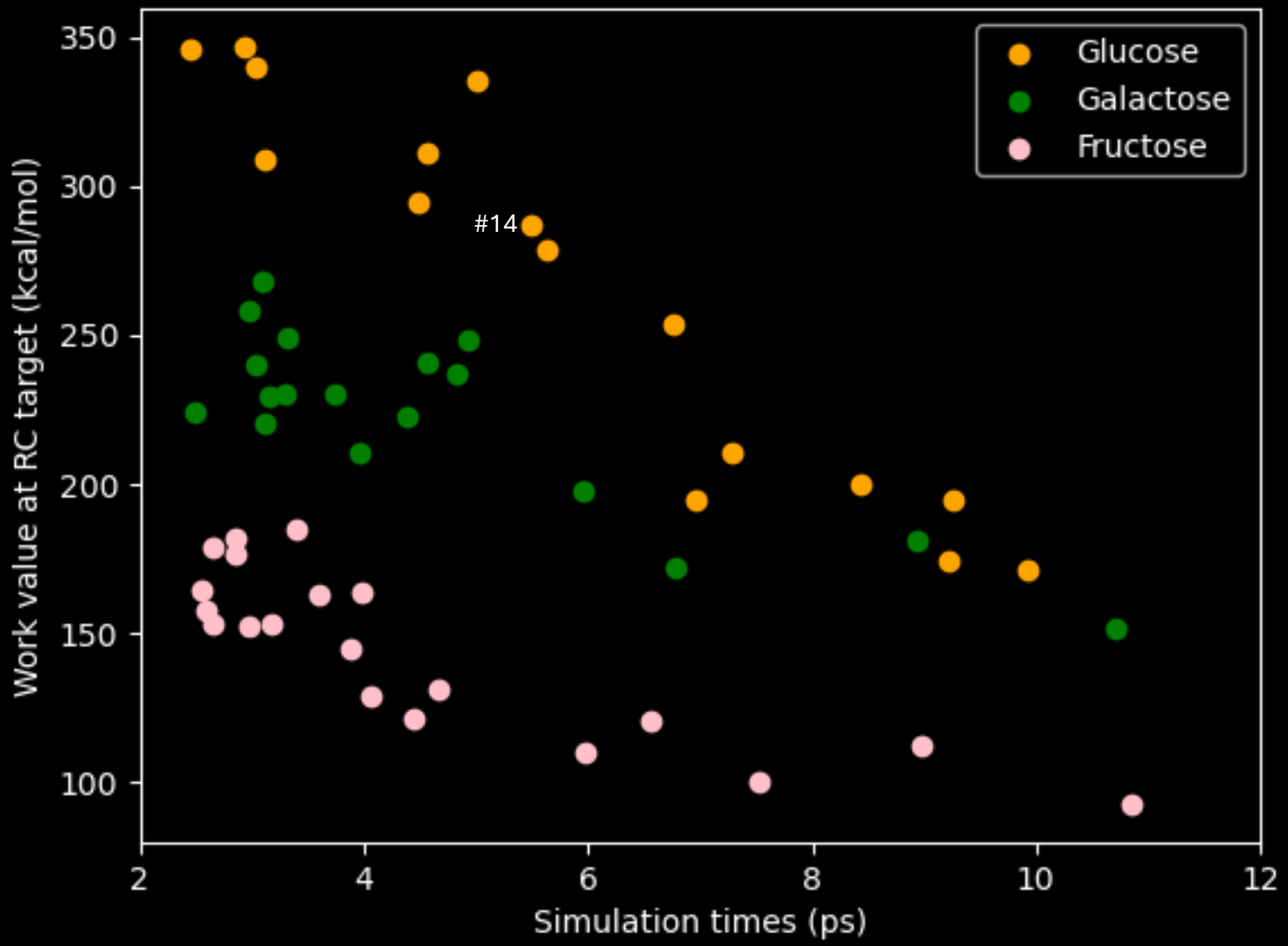
Reaction coordinate:





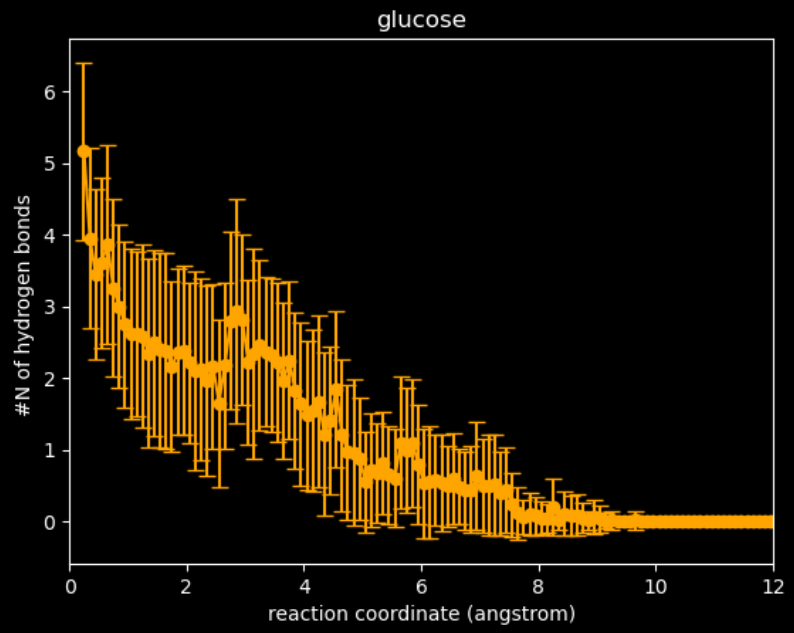
Cumulative work values at RC target

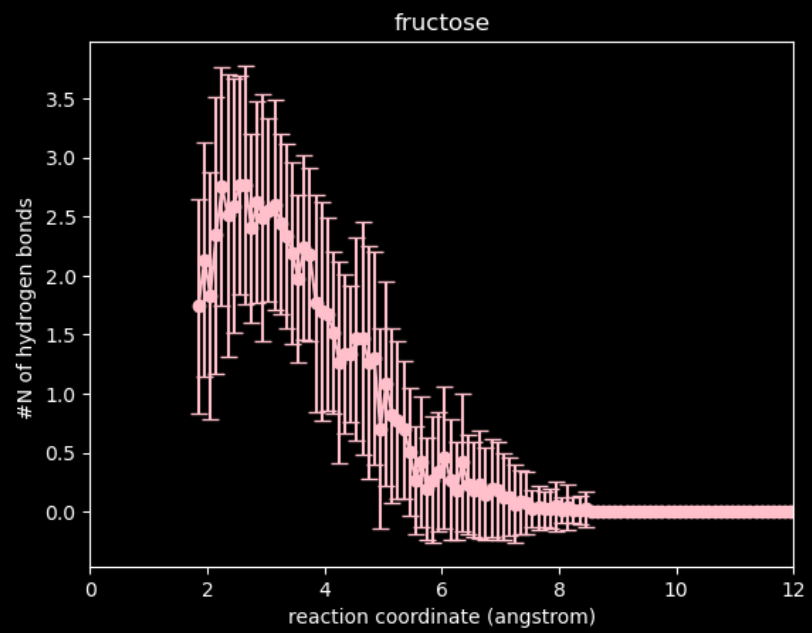
- The values occupy three different ranges
- Qualitatively, the order of magnitude is consistent with the sugars' affinities to GluHUT
- The reason is probably due to the breaking of hydrogen bonds.

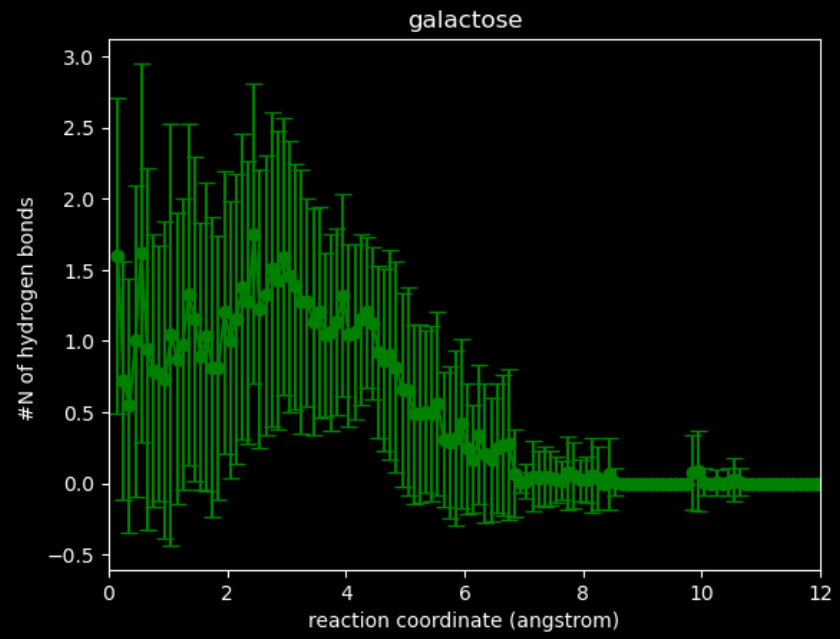


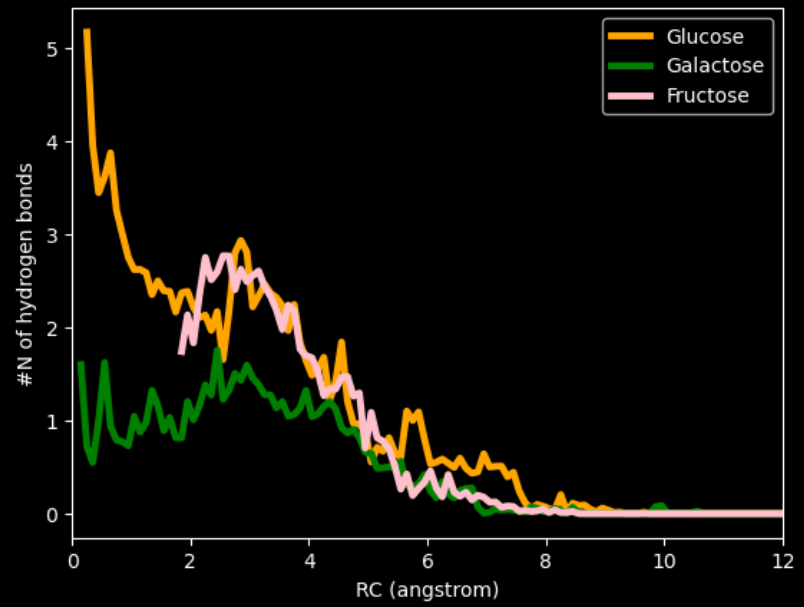
Hydrogen bonds

- Glucose shows a higher number of hydrogen bonds along the RC.
- Fructose tends to partially enter the cavity (< 2Å).
- Galactose enters the cavity, but it shows a lower number of HB.
- All the sugars form HB with the “arms” of the receptor (2-8Å).









PathCV and Umbrella Sampling

Workflow:

1) Human-sampled trajectory in IMD-VR;

2) Path CV definition;

3) US along the pathCV to obtain free energy profile.

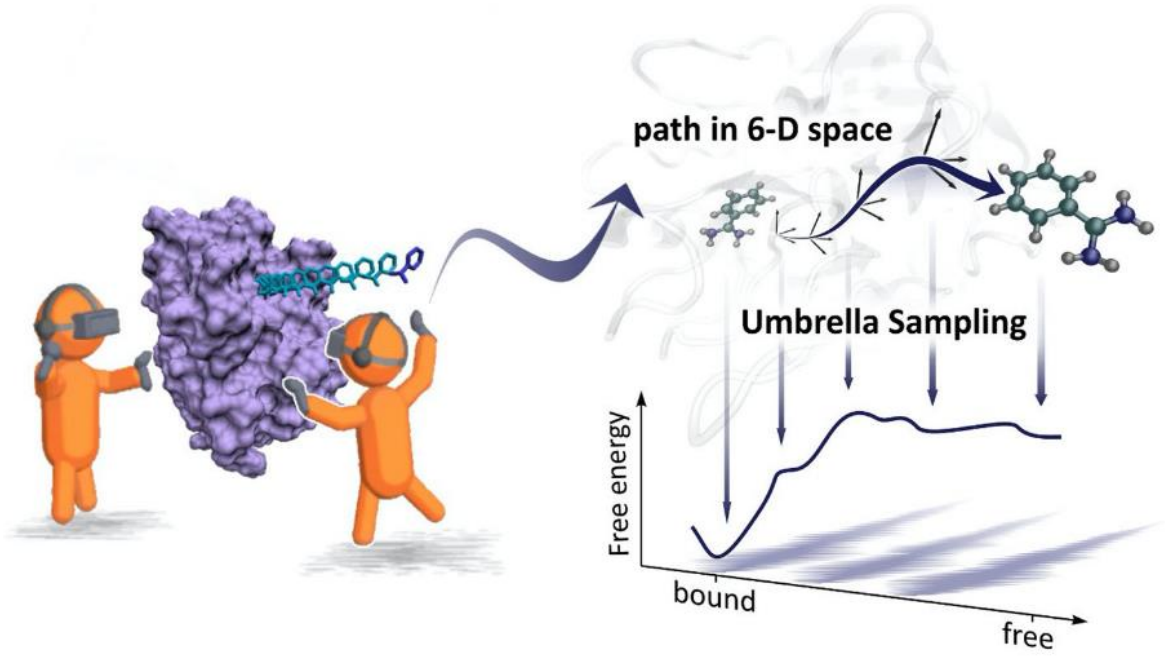
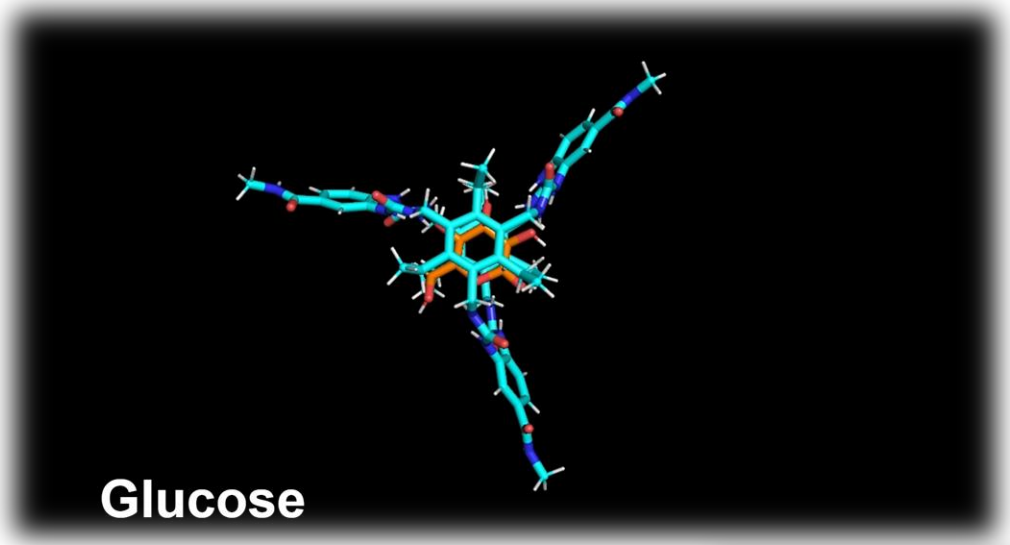


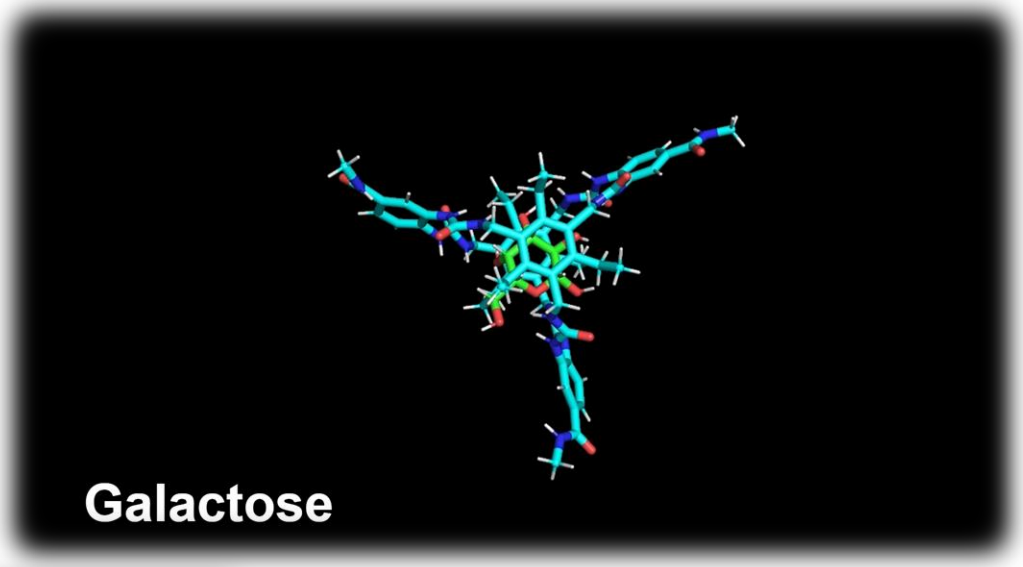
Figure 1. Workflow used to obtain free energy profiles for benzamidine unbinding from trypsin. First, users in iMD-VR model the dissociation of the ligand, by 'pulling' it out in an interactive MD simulation (left). Snapshots of the unbinding trajectory are used as input for umbrella sampling along a 6-D path collective variable (right) to obtain the free energy profile along the path.

Deeks, H. M. *et al.* Free energy along drug-protein binding pathways interactively sampled in virtual reality. *Sci Rep* **13**, 16665 (2023).

Step one:

Human-sampled paths in iMD-VR





Step two:

path CV

$$r = distance(P_1L_1);$$

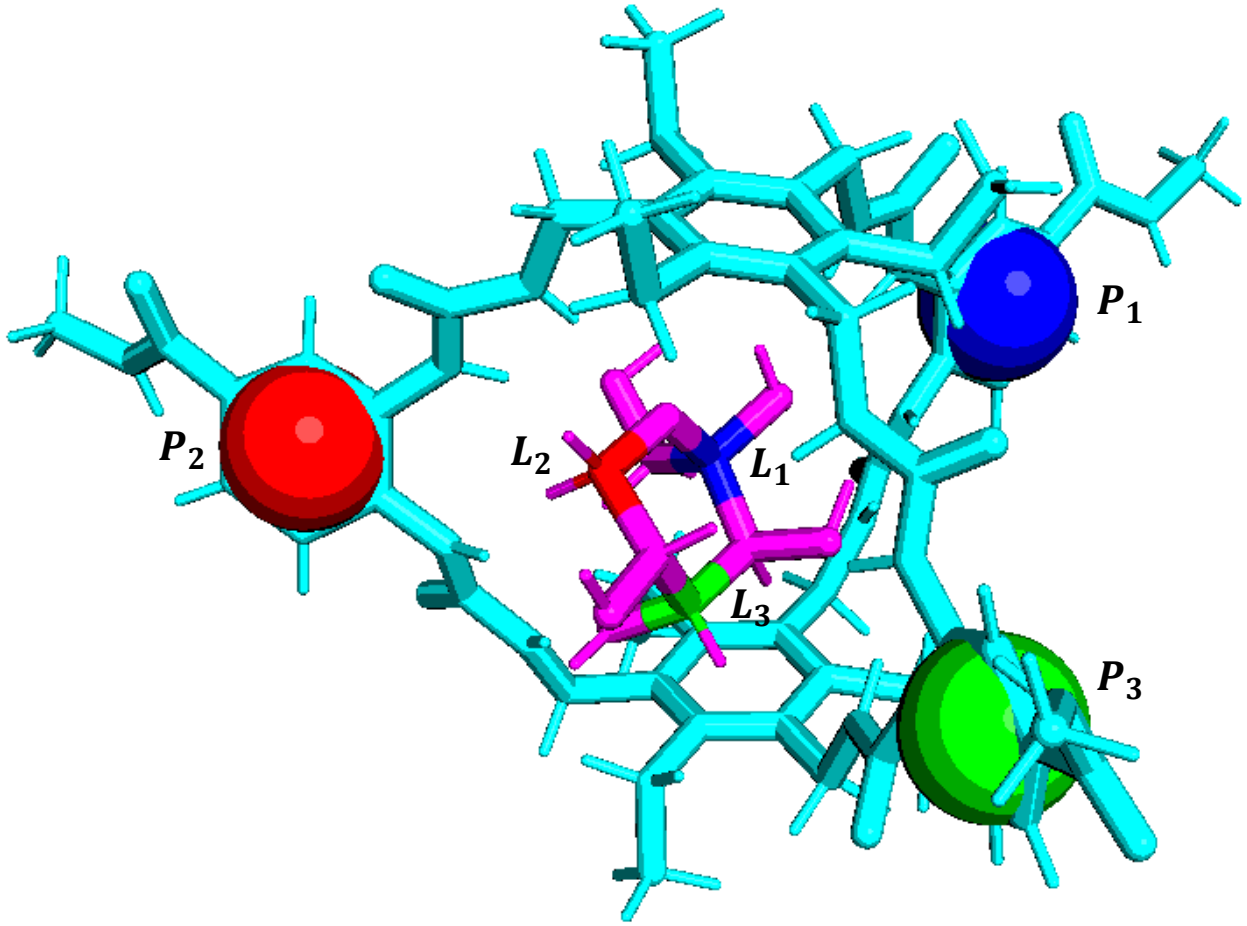
$$\theta = angle(P_1L_1L_2);$$

$$\phi = dihedral(P_1L_1L_2L_3);$$

$$\Theta = angle(P_2P_1L_1);$$

$$\Phi = dihedral\ (P_2P_1L_1L_2);$$

$$\Psi = dihedral(P_3P_2P_1L_1)$$

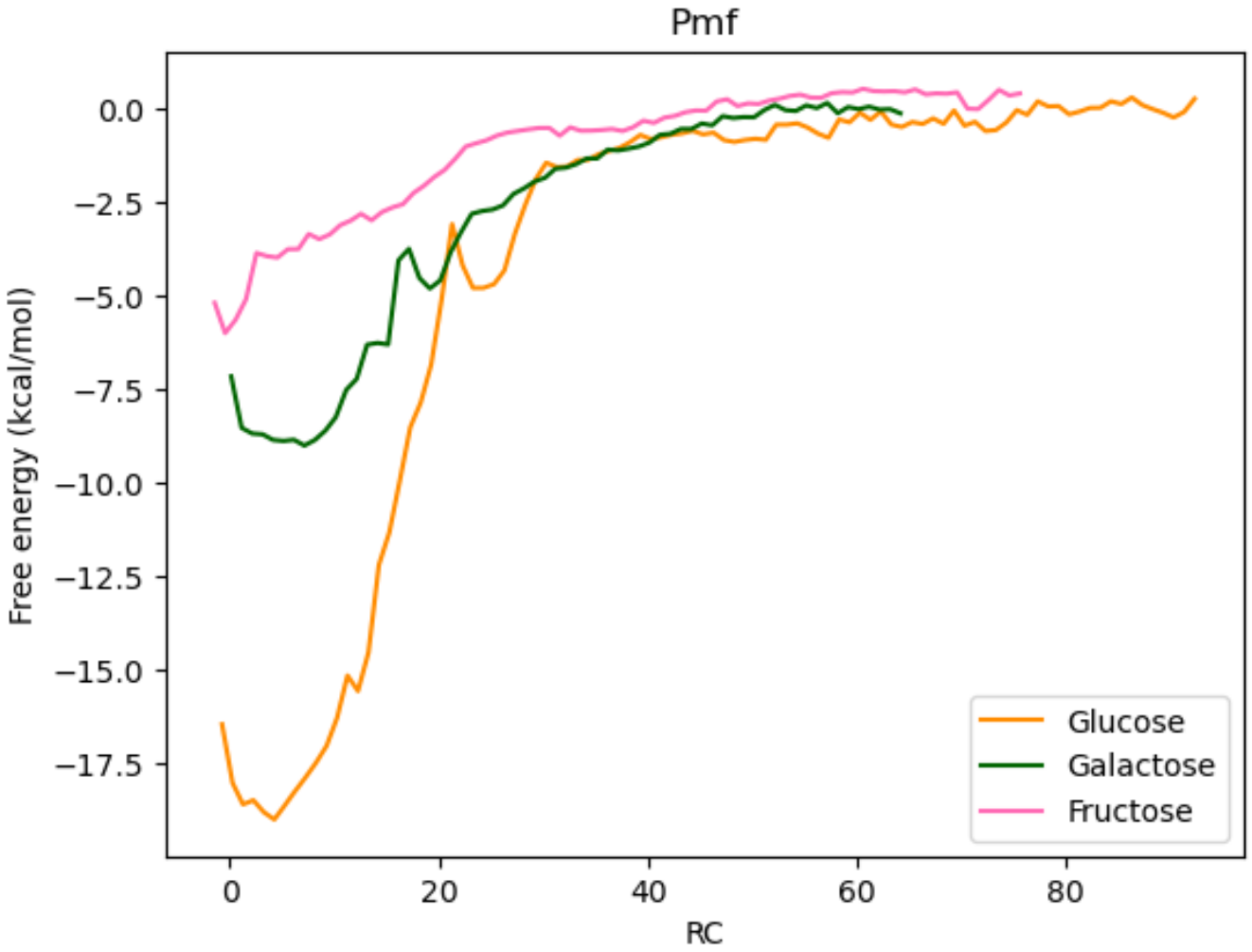


$$s(\boldsymbol{r}) = \frac{\sum_{i=1}^{n} t_i e^{-\lambda d(\boldsymbol{\theta}(\boldsymbol{r}),\boldsymbol{z}(t_i))}}{\sum_{i=1}^{n} e^{-\lambda d(\boldsymbol{\theta}(\boldsymbol{r}),\boldsymbol{z}(t_i))}}; \qquad z(\boldsymbol{r}) = -\lambda^{-1} \ln \sum_{i=1}^{n} e^{-\lambda d(\boldsymbol{\theta}(\boldsymbol{r}),\boldsymbol{z}(t_i))}; \qquad t_i = \frac{i-1}{n-1} L$$

- Zinovjev, K. & Tuñón, I. Exploring chemical reactivity of complex systems with path-based coordinates: Role of the distance metric. *Journal of Computational Chemistry* **35**, 1672–1681 (2014).

Step three:

Umbrella Sampling



Potential Mean Force profiles with US of 60 windows and 30 ps production.

The results show a coherent trend with the experimental values.
17.75 kcal mol^{-1} for glucose;
9.4 kcal mol^{-1} for galactose;
6.5 kcal mol^{-1} for fructose;

Conclusions and future plans

- Quantitative data from iMD-VR can detect molecular mechanistic details among different ligands bound to the receptor.
- Improving the quality of the iMD-VR data: path drawing in VR, followed by SMD calculations.
- Longer sampling for the PMF profiles and explore other trajectories.
- Compare with FE from MD methods (Metadynamics).

Acknowledgments

IRL team:
David Glowacki
Mark Wonnacott
Rhoslyn R. Williams
Luis Toledo
Mohamed Dhouioui
Harry Stroud
Denis Protopopov
Sila Sobrado
Catherine Andreu

Collaborators:
Kirill Zinovjev (UV)
Adrian Mulholland's team (UOB)

European Research Council
Established by the European Commission

XUNTA DE GALICIA

NanoVer