Using MDAnalysis to squeeze simulation trajectories of ABC efflux transporters to get scientific insights

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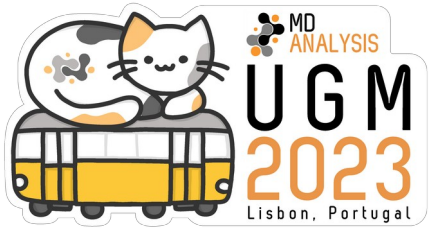

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cbios
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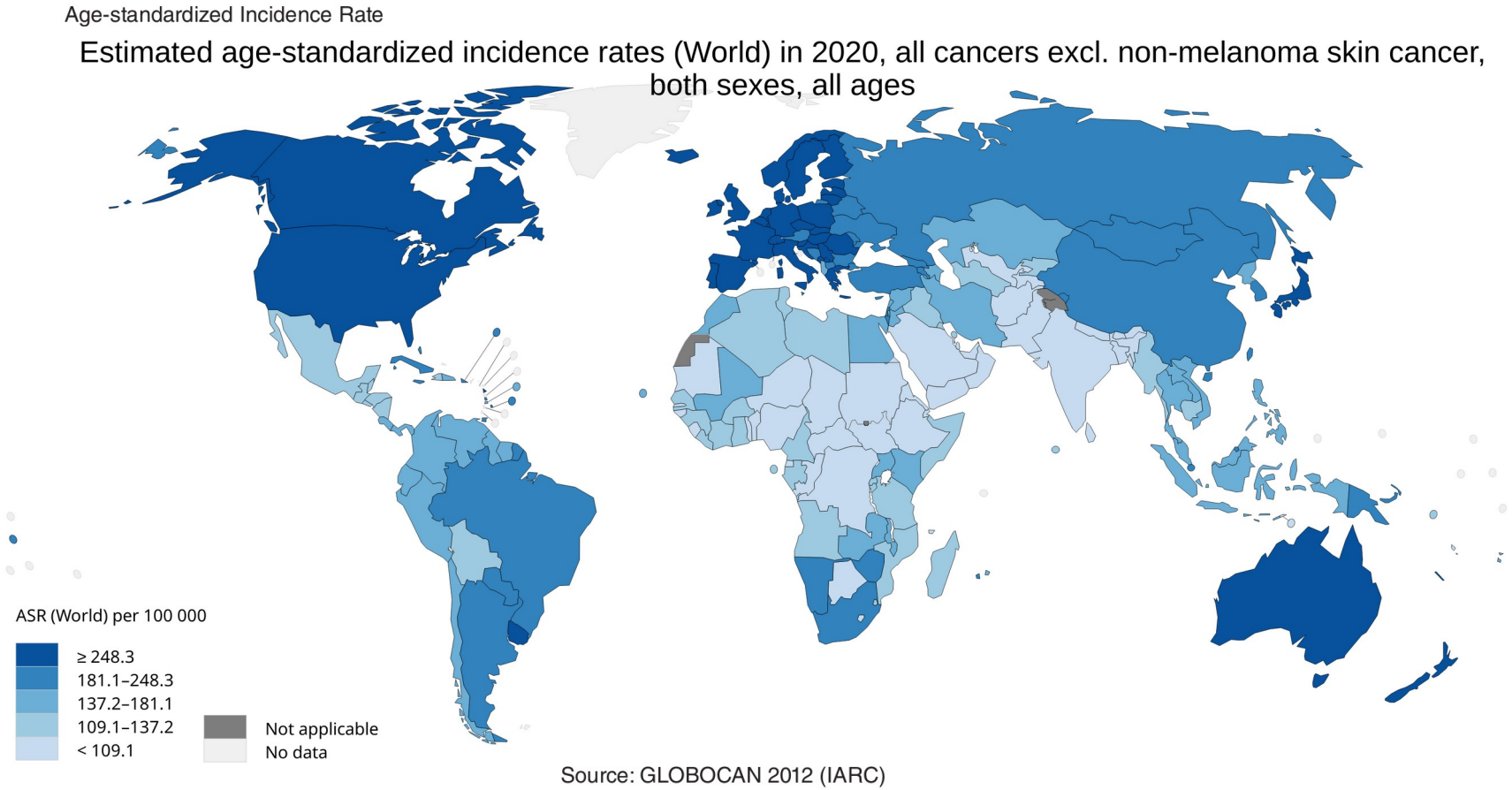
RESEARCH CENTER FOR BIOSCIENCES & HEALTH TECHNOLOGIES

“Using Computational Tools to...”

Outline

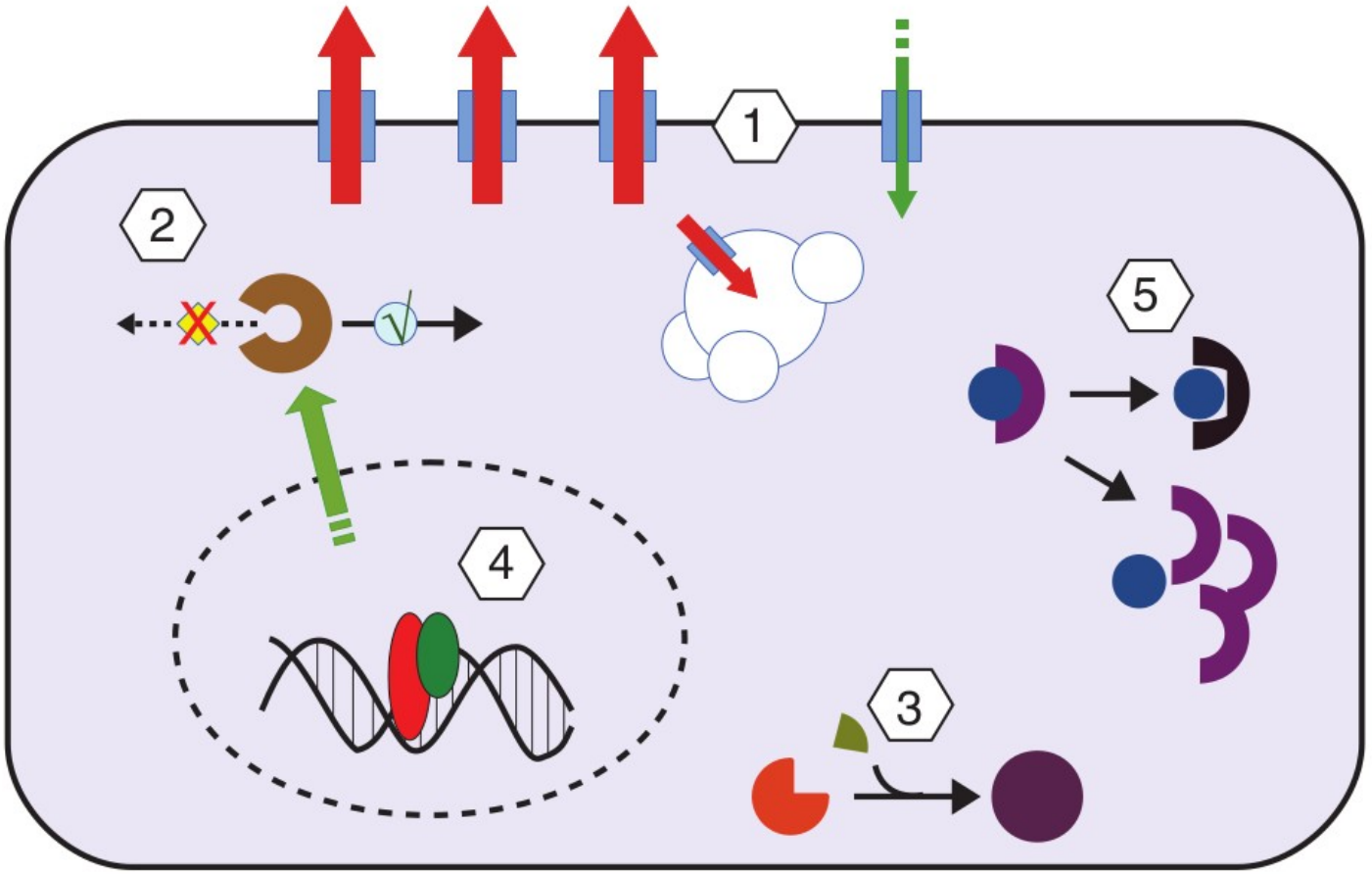
1. Short introduction: cancer and multidrug resistance
2. ABC transporters
3. My way to MDAnalysis: from every now and then to being the analysis core

Cancer incidence



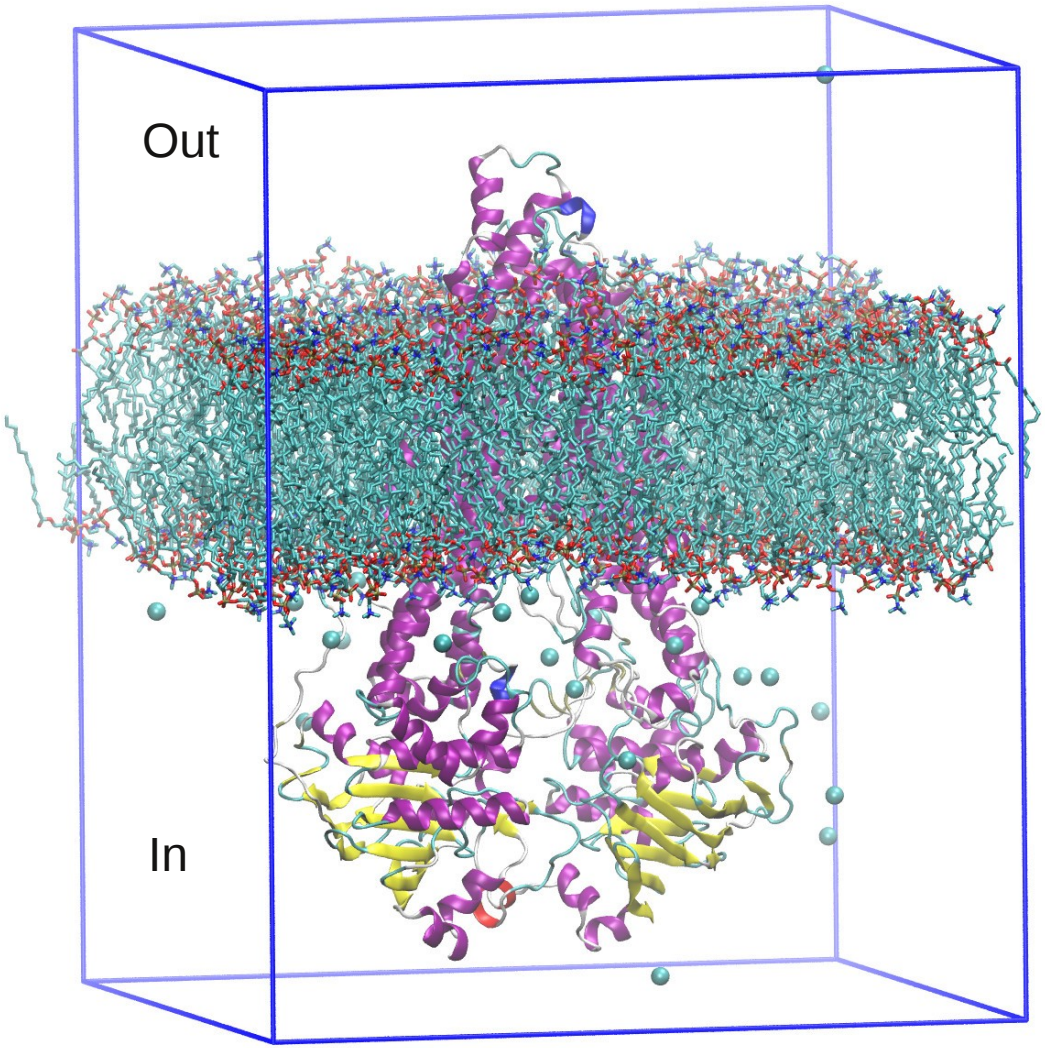
World cancer incidence in 2020

Resistance pathways



Resistance to drugs: (1) decreased influx or increased efflux/sequestration, (2) disruption of apoptosis or alterations in cell cycle checkpoints, (3) activation of drug metabolism, (4) increase in DNA repair, or (5) mutations in cellular targets.

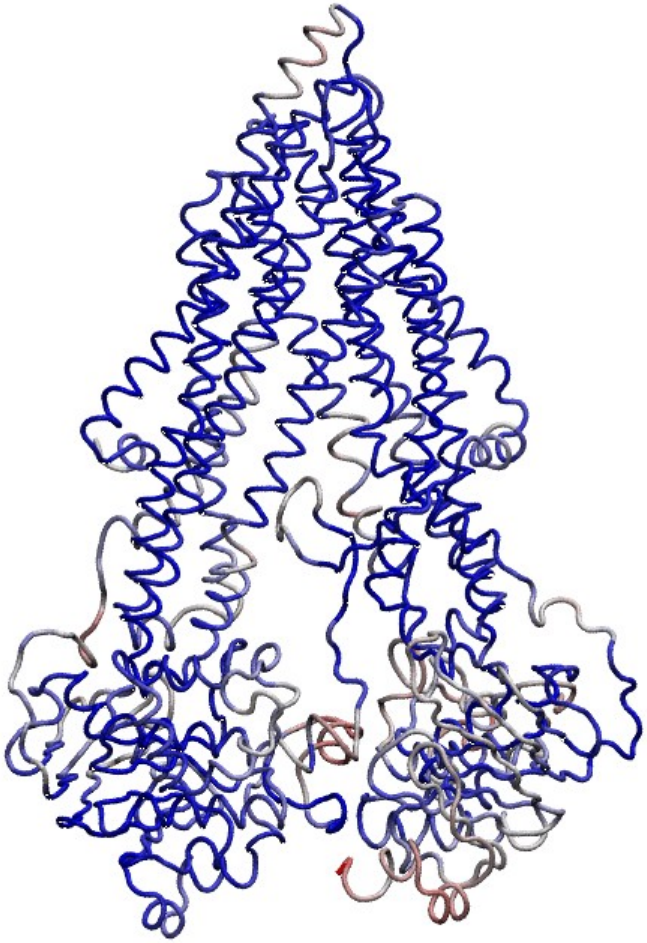
Trajectory production



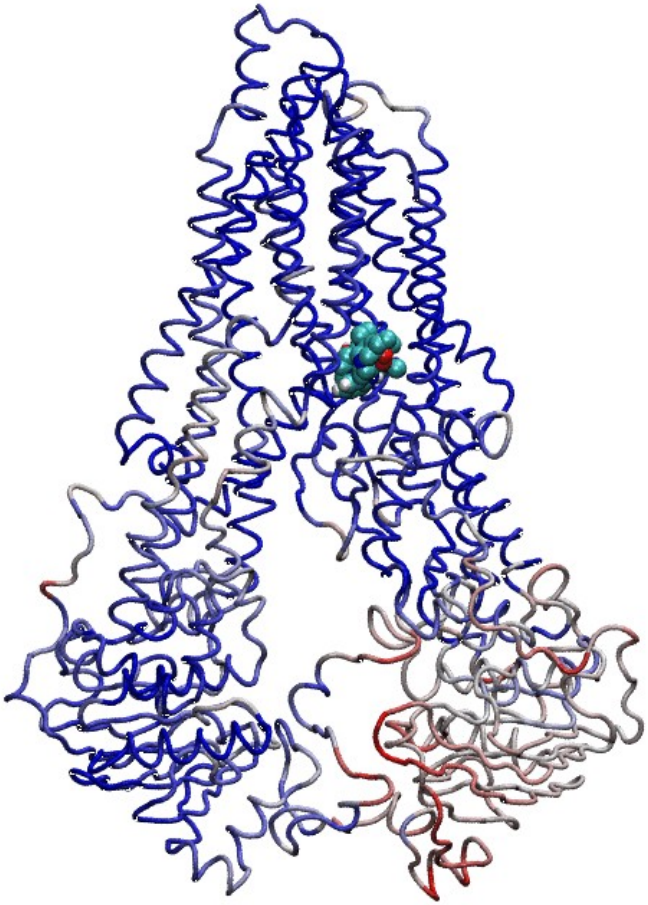
Ferreira, R. J.; Ferreira, M.-J. U.; dos Santos, D. J. V. A. Insights on P-Glycoprotein's Efflux Mechanism Obtained by Molecular Dynamics Simulations. J. Chem. Theory Comput. 2012, 8 (6), 1853–1864. https://doi.org/10.1021/ct300083m.

Trajectory analysis: motion patterns

Normal motion patterns

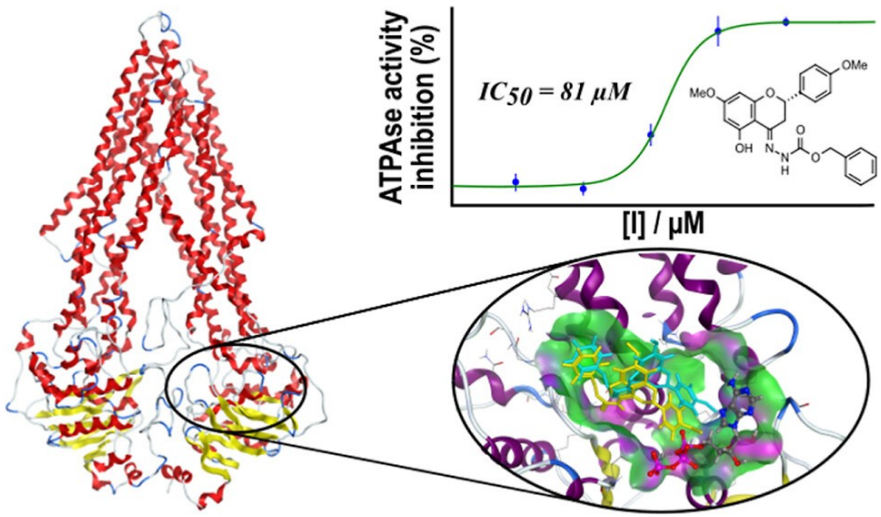


Gate-induced motion patterns



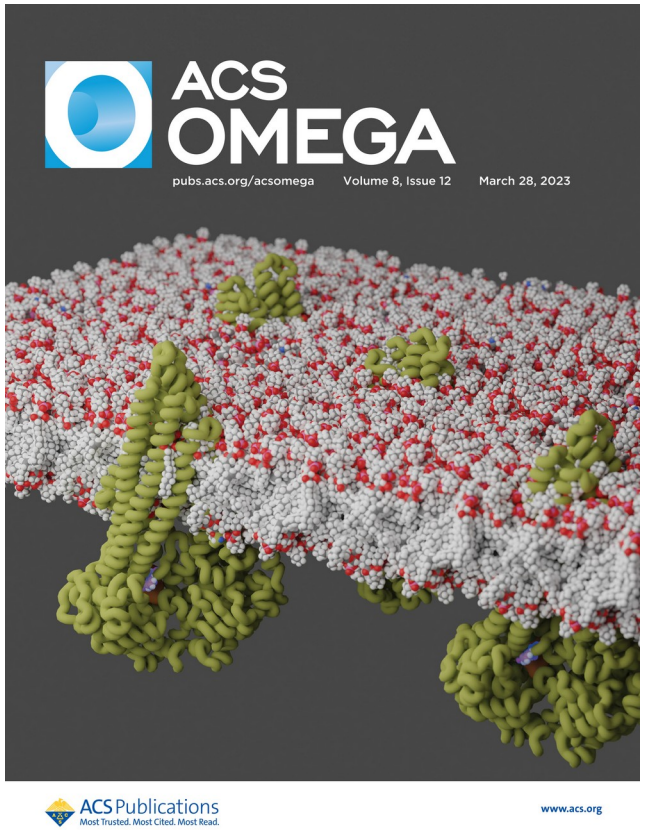
Ferreira, R. J.; Ferreira, M.-J. U.; dos Santos, D. J. V. A. Insights on P-Glycoprotein's Efflux Mechanism Obtained by Molecular Dynamics Simulations. J. Chem. Theory Comput. 2012, 8 (6), 1853–1864. https://doi.org/10.1021/ct300083m.

Trajectory analysis



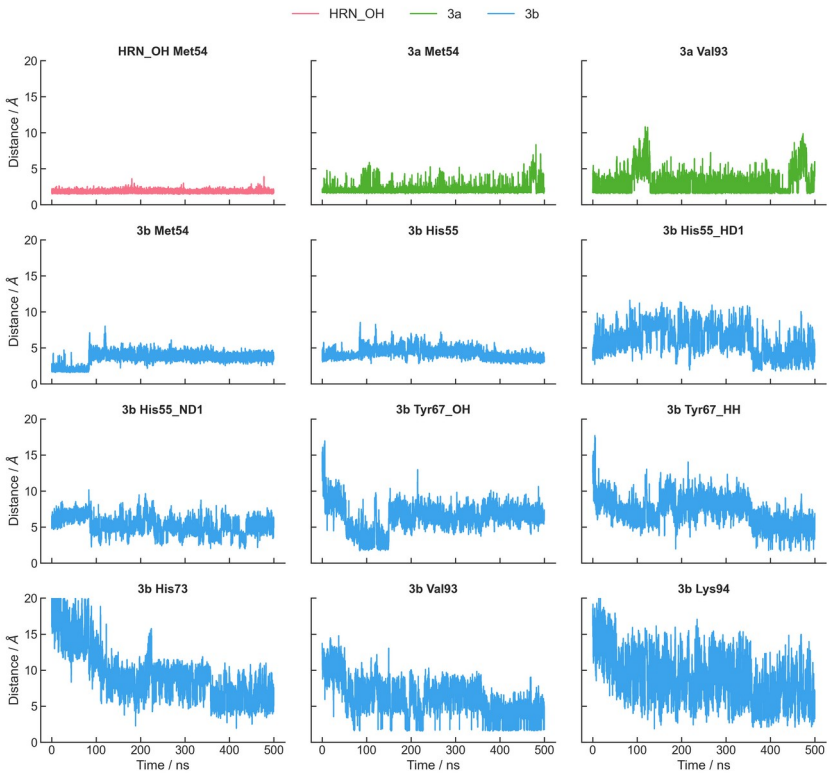
Binding site, and interactions description

Blender generated picture



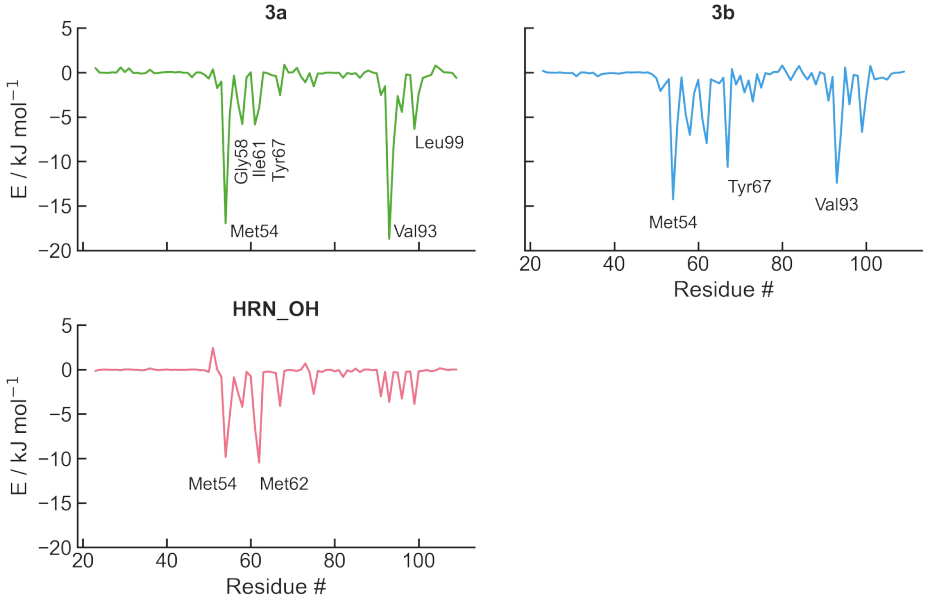
Bonito, C. A.; Ferreira, R. J.; Ferreira, M.-José. U.; Durães, F.; Sousa, E.; Gillet, J.-P.; Cordeiro, M. N. D. S.; dos Santos, D. J. V. A. Probing the Allosteric Modulation of P-Glycoprotein: A Medicinal Chemistry Approach Toward the Identification of Noncompetitive P-Gp Inhibitors. ACS Omega 2023, 8 (12), 11281–11287. https://doi.org/10.1021/acsomega.2c08273.

Trajectory analysis



Hydrogen bonds and relevant interaction contacts along the 500 ns production run

Estimation of the residues contribution to the binding energy



Espadinha, M.; Lopes, E. A.; Marques, V.; Amaral, J. D.; dos Santos, D. J. V. A.; Mori, M.; Daniele, S.; Piccarducci, R.; Zappelli, E.; Martini, C.; Rodrigues, C. M. P.; Santos, M. M. M. Discovery of MDM2-P53 and MDM4-P53 Protein-Protein Interactions Small Molecule Dual Inhibitors. European Journal of Medicinal Chemistry 2022, 241, 114637. https://doi.org/10.1016/j.ejmech.2022.114637.

Our way to MDAnalysis

from every now and then

to

being part of the analysis core

Before and after MDAnalysis

- Use a combination of different tools:
  - Blend of package programs related do the MD program (gromacs)
  - Other programs specific for a property calculation
  - Not unified interface: **plot programs** like gnuplot or xmgrace, with tweaks for better looking.

- Not really satisfied...
  - In 2006, around gromacs version 3.x, I built my analysis program to use the C++ libmd and libgmx API
  - Read trajectories, implement definitions for atoms, molecules, interactions, and properties...
  - implemented calculation of specific properties namely of systems with interfaces/bilayers
  - Needed updated after major gromacs changes (3 to 4 and so on)
  - Met a colleague in last July conference still using the code :-)
  - I don’t use it anymore :-)

Before and after MDAnalysis

- Still not really satisfied...
  - Searching for Principal Components analysis program I found MDAnalysis
  - Using it since…whenever deeper detailed analysis is needed

- Huge step forward:
  - PhD Students just need to **learn python**
  - Some are already **acquainted at Bsc level**
  - Analysis friendly interfaces (e.g. jupyter notebooks) with output *in situ*
  - All the python data architecture and manipulation readily available
  - Interface with **statistical methods** and analysis: hypothesis testing, p-values, ANOVA, bootstrap method, ...
  - Interface with **high level data visualization methods** with beautiful state-of-the-art plots (e.g. seaborn)
  - Possibility to display trajectories...

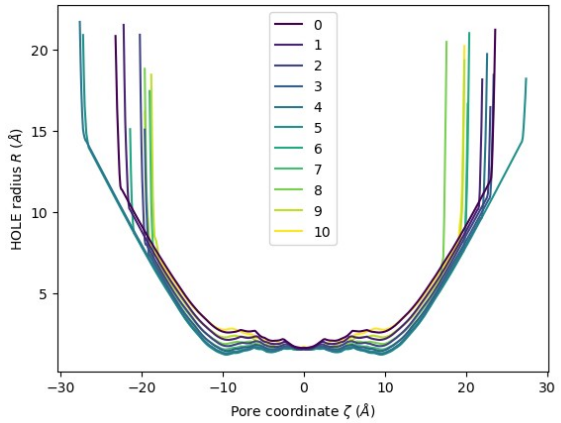
dos Santos, DJVA et al. *J. Chem. Inf. Model.* **2013**, *53*, 1747–1760 (doi: 10.1021/ci400195v)

Before and after MDAnalysis

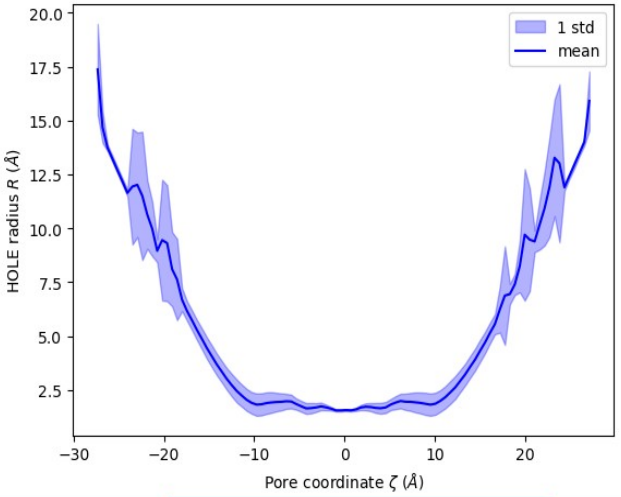
```
In [14]: u = mda.Universe(MULTIPDB_HOLE)

         with hole2.HoleAnalysis(u, executable='/opt/bin/hole') as h2:
             h2.run()
```

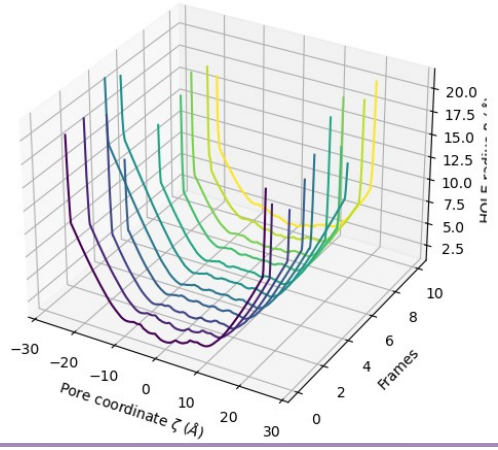
```
In [15]: hole2.HoleAnalysis.plot(h2, frames=None)
Out[15]: <AxesSubplot: xlabel='Pore coordinate $\\zeta$ ($\\AA$)', ylabel='HOLE radius $R$ ($\\AA$)'>
```




```
In [17]: hole2.HoleAnalysis.plot_mean_profile(h2)
Out[17]: <AxesSubplot: xlabel='Pore coordinate $\\zeta$ ($\\AA$)', ylabel='HOLE radius $R$ ($\\AA$)'>
```




```
In [16]: hole2.HoleAnalysis.plot3D(h2, frames=None)
Out[16]: <Axes3DSubplot: xlabel='Pore coordinate $\\zeta$ ($\\AA$)', ylabel='Frames', zlabel='HOLE radius $R$ ($\\AA$)'>
```



Projects, grants,...

Just finished projects:

- **Pgp & BCRP**
  with Prof. Maria José U. Ferreira / iMed-FFUL
- **Cystic Fibrosis**
  with Prof. Margarida Amaral / BioISI-FCUL
- **MCAD deficiency**
  with Prof. Fátima Ventura / iMed-FFUL
- **P53-MDM2/X interactions**
  with Dr. Maria Santos / iMed-FFUL
- **LOXL2 inhibitors**
  With Profs. Patrícia Rijo & Ana Fernandes / CBIOS

Just starting project:

- **Resistance in BRCA-deficient cancers**
  with Prof. Maria José U. Ferreira / iMed-FFUL

PhD Grants:

FCT PhD grant to **Ricardo Ferreira**
PhD-program grant to **David Cardoso**
FCT PhD grant to **Cátia Bonito**
FCT PhD grant to **Jéssica Matos**: **P-gp Activation**

Work, work, work... Visit: **www.chemistrybits.com**

Ricardo Ferreira
Project researcher: mFAOD disorder

Marta Carrasco
Project researcher: Cystic Fibrosis, iMed/FFUL

Michael González-Durruthy
Project researcher: Cystic Fibrosis, LAQV@REQUIMTE

Cátia Bonito
PhD: Human P-glycoprotein
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David Cardoso
PhD: Dual inhibitors Pgp/BCRP, iMed/FFUL

Bruno Gonçalves
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