

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

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# “Using Computational Tools to...”

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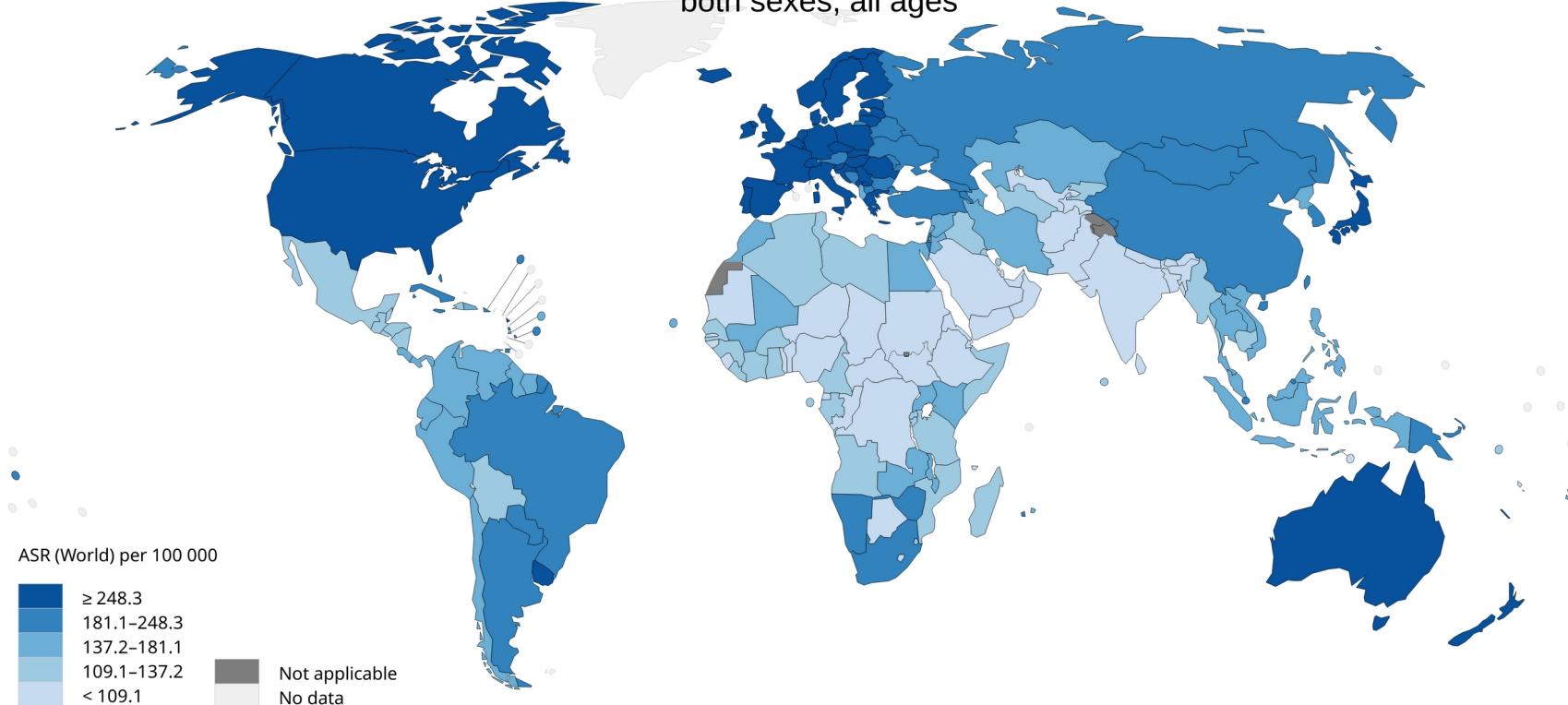
## Outline

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

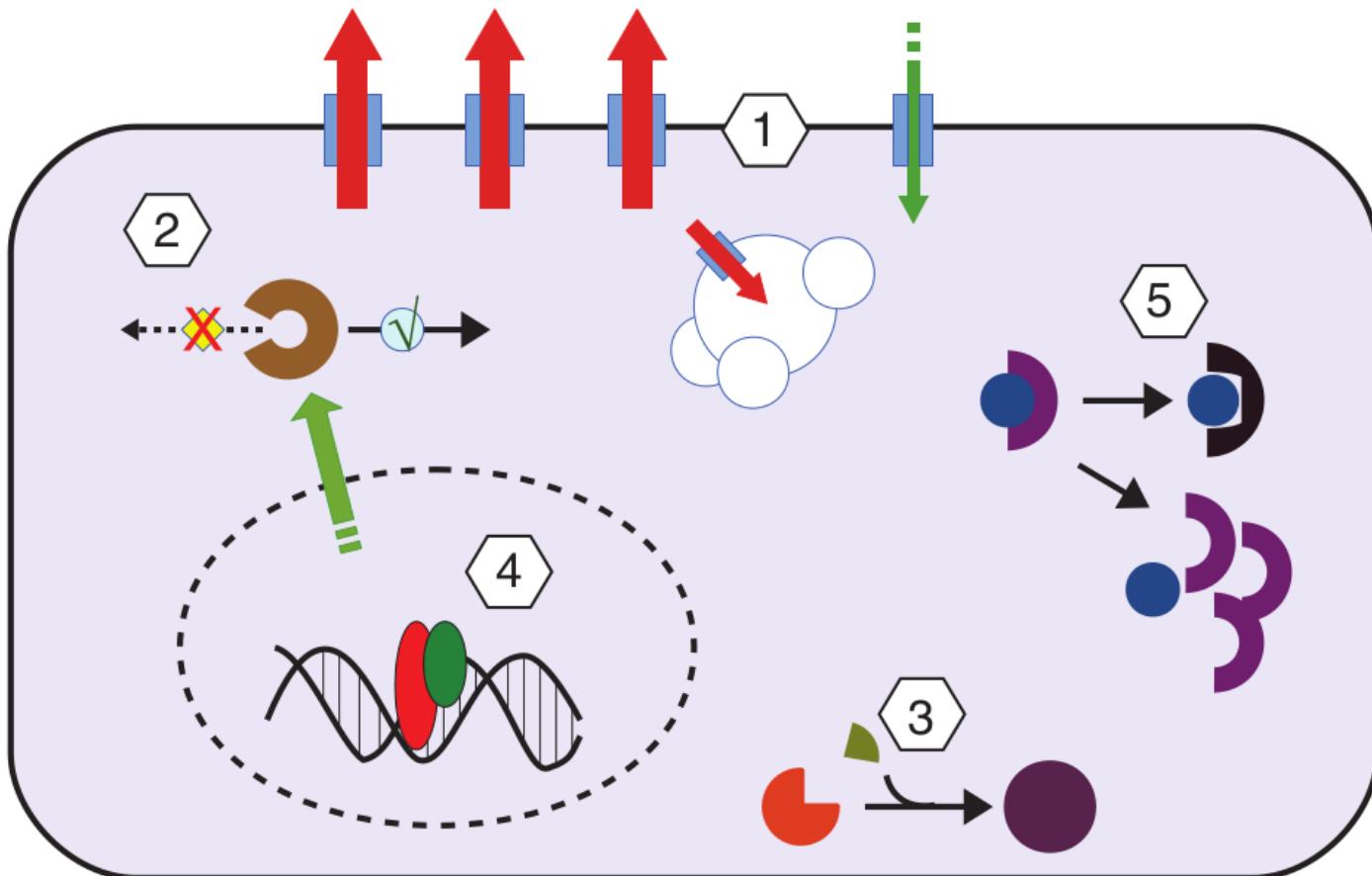
Age-standardized Incidence Rate

Estimated age-standardized incidence rates (World) in 2020, all cancers excl. non-melanoma skin cancer, both sexes, all ages



World cancer incidence in 2020

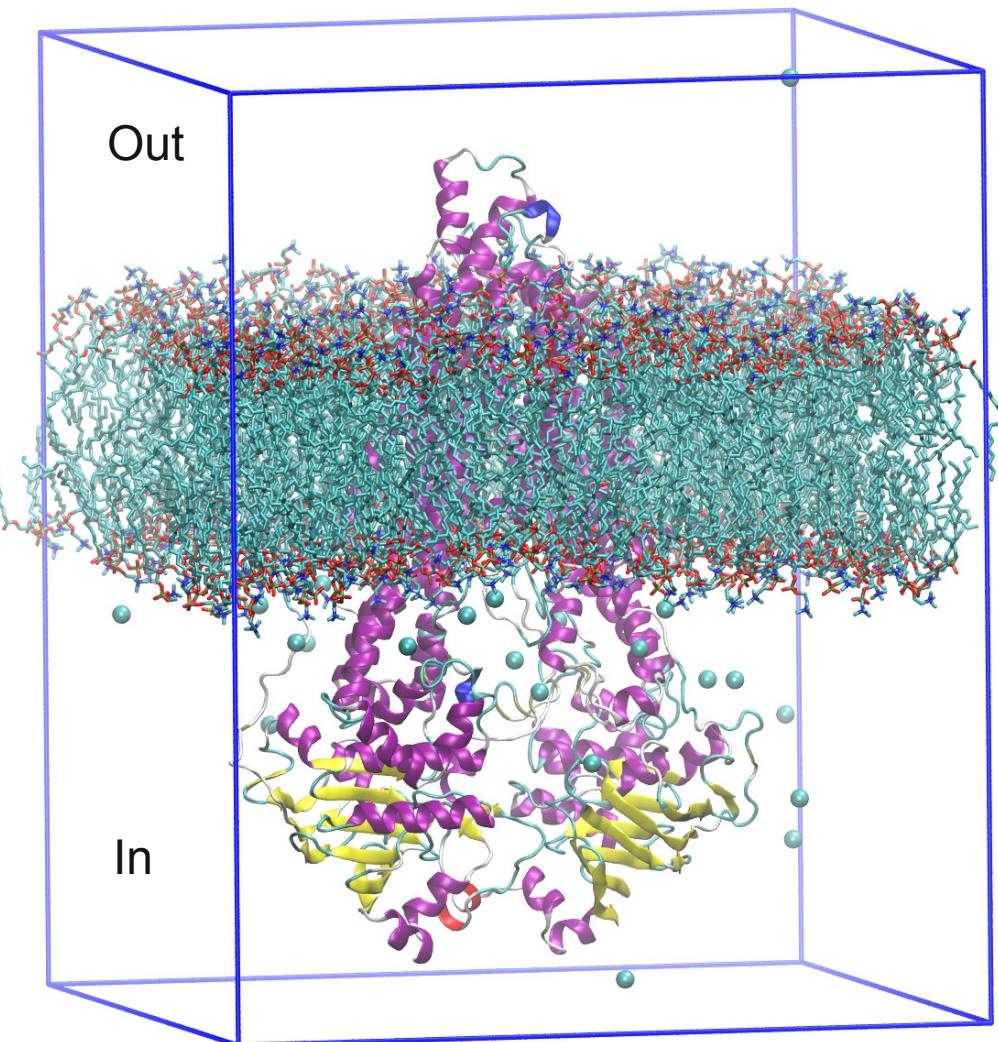
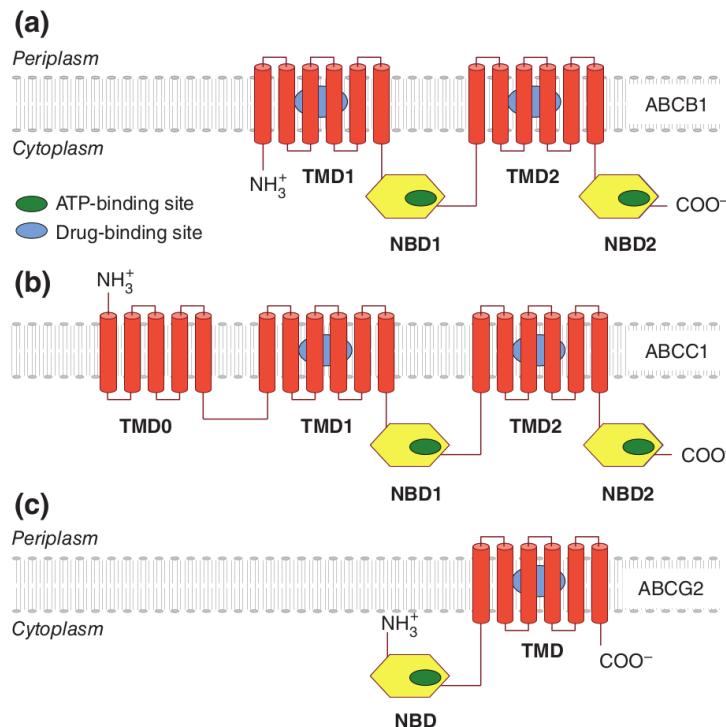
# Resistance pathways



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

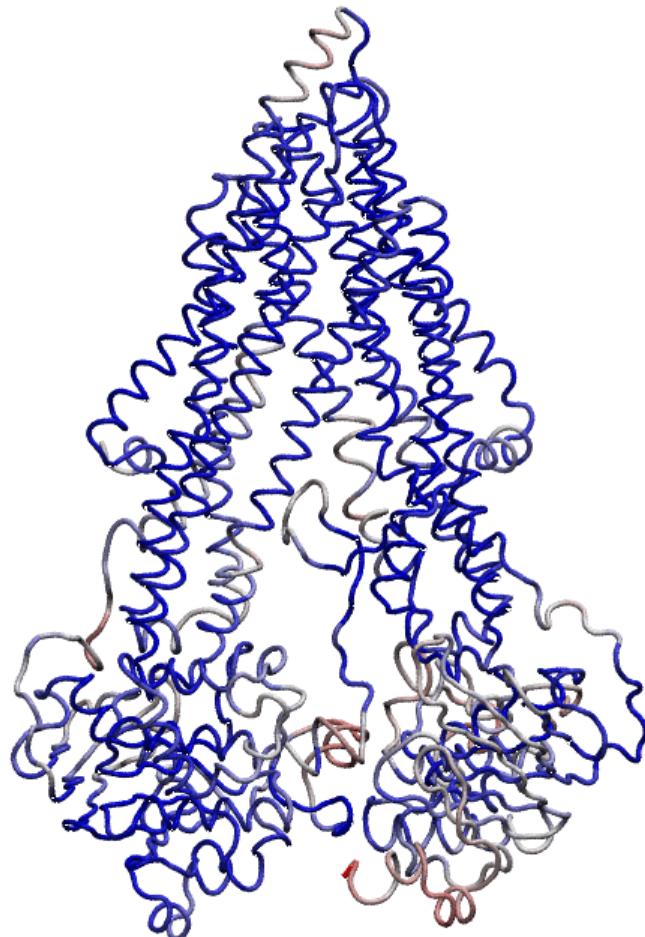
Membrane topology models of  
(a) P-gp, (b) MRP1, and (c)  
BCRP



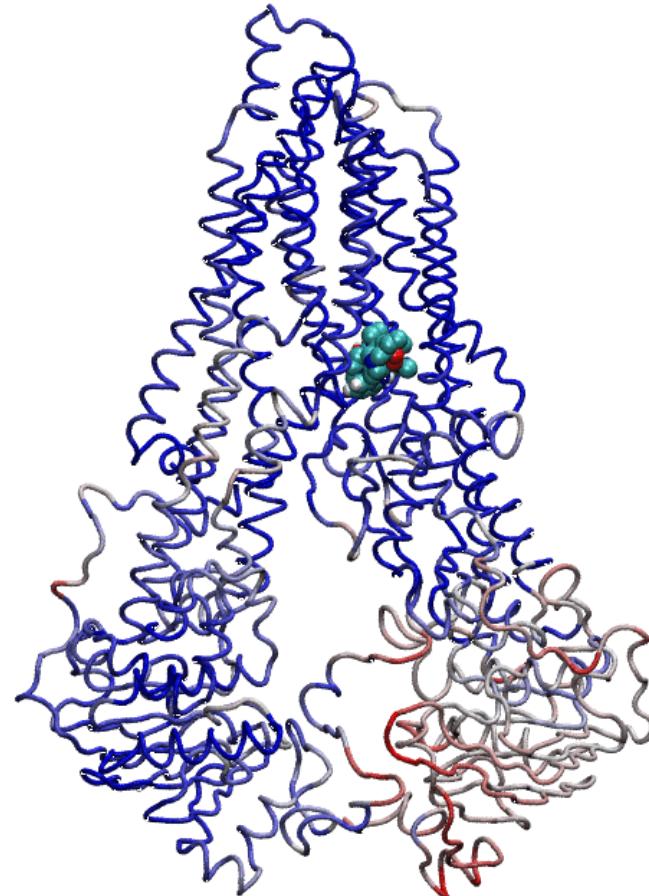
Ferreira, R. J.; Ferreira, M.-J. U.; dos Santos, D. J. V. A. Insights on P-Glycoprotein's Efflux Mechanism Obtained by Molecular Dynamics Simulations. *J. Chem. Theory Comput.* 2012, 8 (6), 1853–1864. <https://doi.org/10.1021/ct300083m>.

# Trajectory analysis: motion patterns

Normal motion patterns

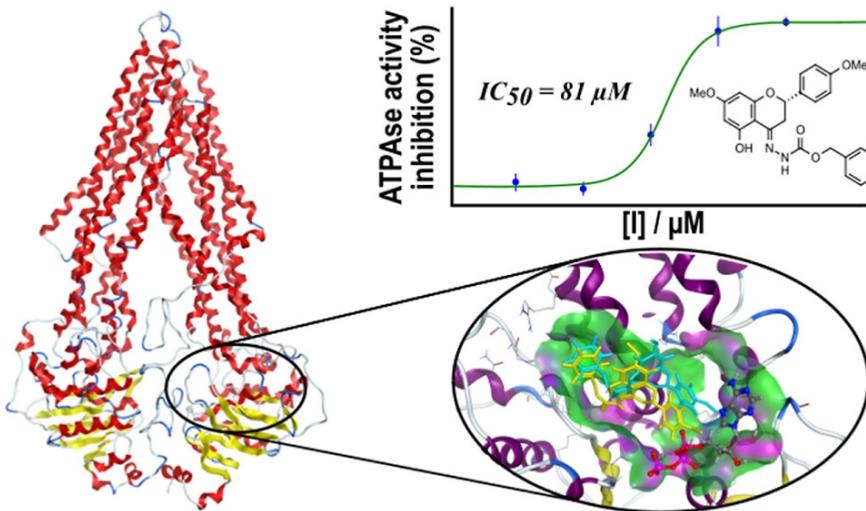


Gate-induced motion patterns



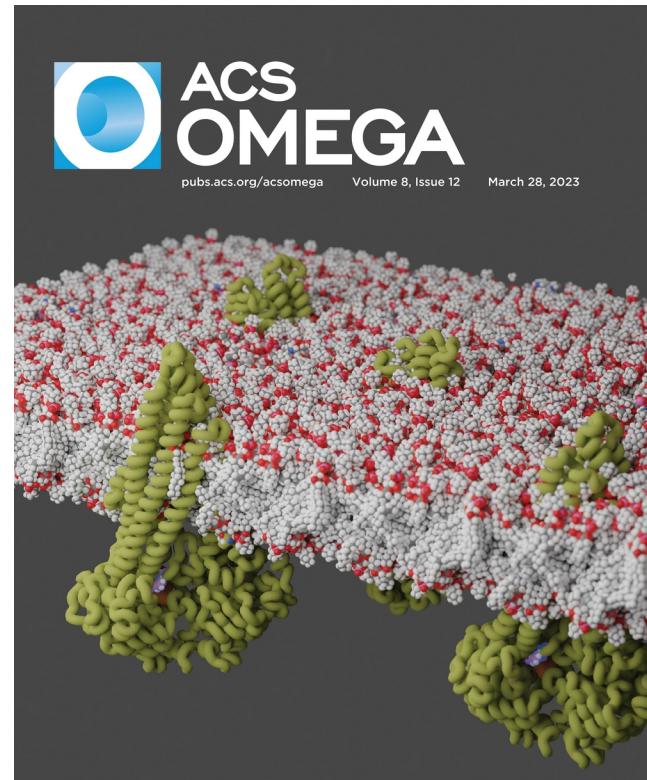
Ferreira, R. J.; Ferreira, M.-J. U.; dos Santos, D. J. V. A. Insights on P-Glycoprotein's Efflux Mechanism Obtained by Molecular Dynamics Simulations. *J. Chem. Theory Comput.* 2012, 8 (6), 1853–1864. <https://doi.org/10.1021/ct300083m>.

# Trajectory analysis



Binding site, and interactions description

Blender generated picture

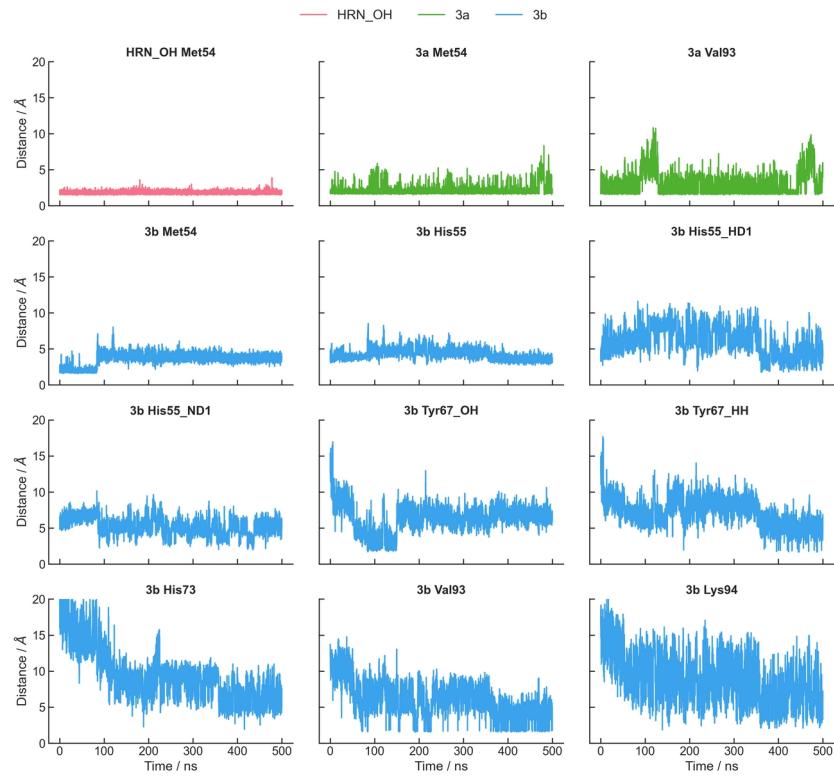


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Bonito, C. A.; Ferreira, R. J.; Ferreira, M.-José. U.; Durães, F.; Sousa, E.; Gillet, J.-P.; Cordeiro, M. N. D. S.; dos Santos, D. J. V. A. Probing the Allosteric Modulation of P-Glycoprotein: A Medicinal Chemistry Approach Toward the Identification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

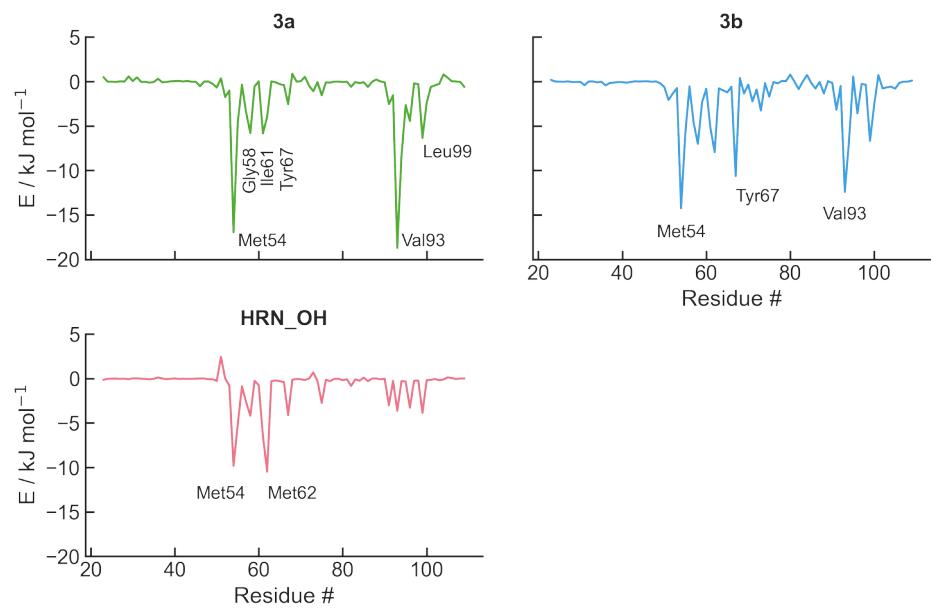
# Trajectory analysis



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

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>.

Estimation of the residues contribution to the binding energy



# Our way to MDAnalysis

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from every now and then  
to  
being part of the analysis core

# Before and after MDAnalysis

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- 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

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- 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* for fast visualization
  - 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...

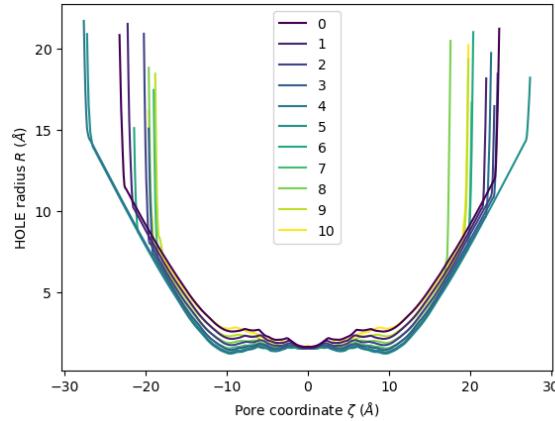
# Before and after MDAnalysis

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

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

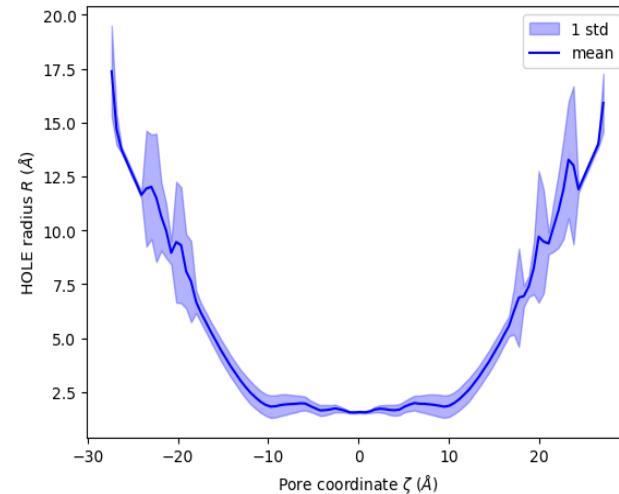
```
In [15]: hole2.HoleAnalysis.plot(h2, frames=None)
```

```
Out[15]: <AxesSubplot: xlabel='Pore coordinate $\zeta$ ($\AA$)', ylabel='HOLE radius $R$ ($\AA$)'
```



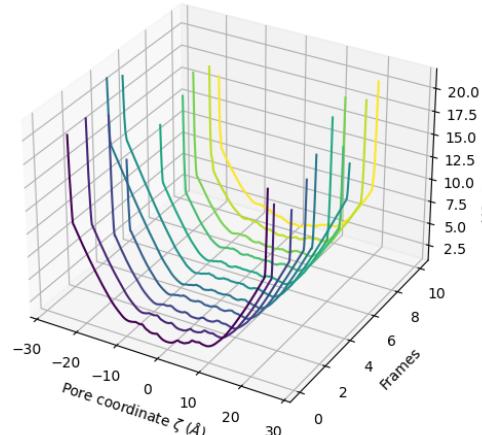
```
In [17]: hole2.HoleAnalysis.plot_mean_profile(h2)
```

```
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



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## 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**



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**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  
LAQV@REQUIMTE



**David Cardoso**  
PhD: Dual inhibitors  
Pgp/BCRP, iMed/FFUL



**Bruno Gonçalves**  
Project researcher: Dual inhibitors  
Pgp/BCRP, iMed/FFUL

# Contribute: section 'Drug Discov. & Develop.'

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