



# Running molecular dynamics simulation to understand proteins

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Analyzing the transport pathway and regulation of the ABCG2 transmembrane protein with MD simulations

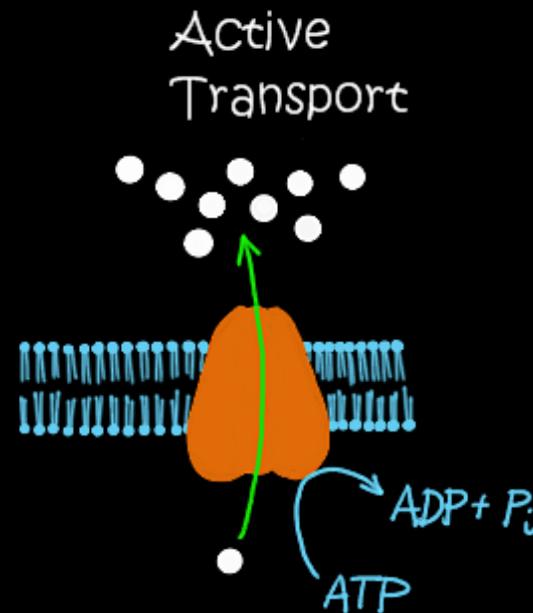
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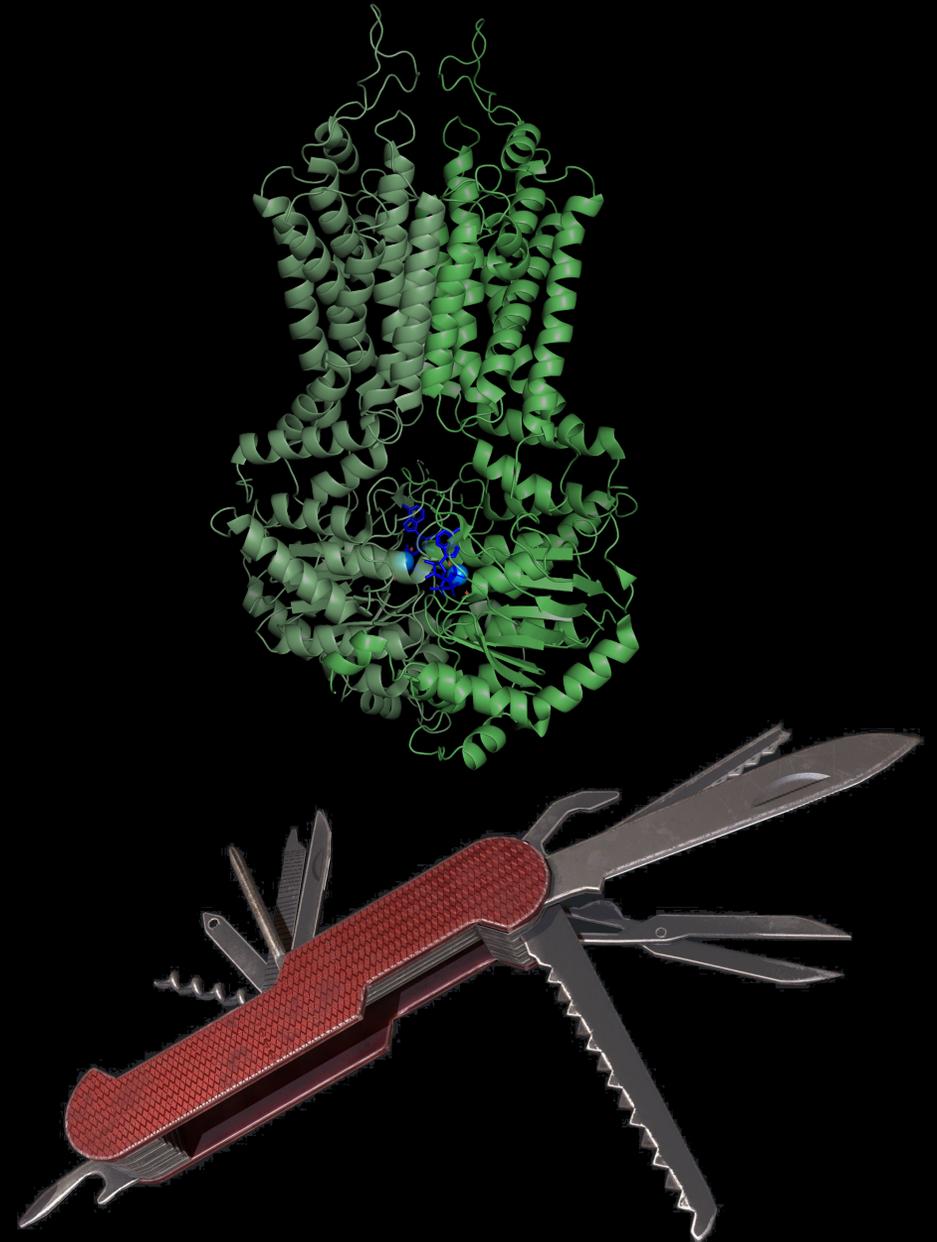
# “What? Why?”

- Cells have membranes and they metabolize
- Membranes separate intracellular space from environment
- The cell should carefully choose what goes in and what goes out
- Many ways of transport, two main categories
  - Passive – along electrochemical gradient
  - Active – needs energy
    - ABC – ATP Binding Cassette super-family

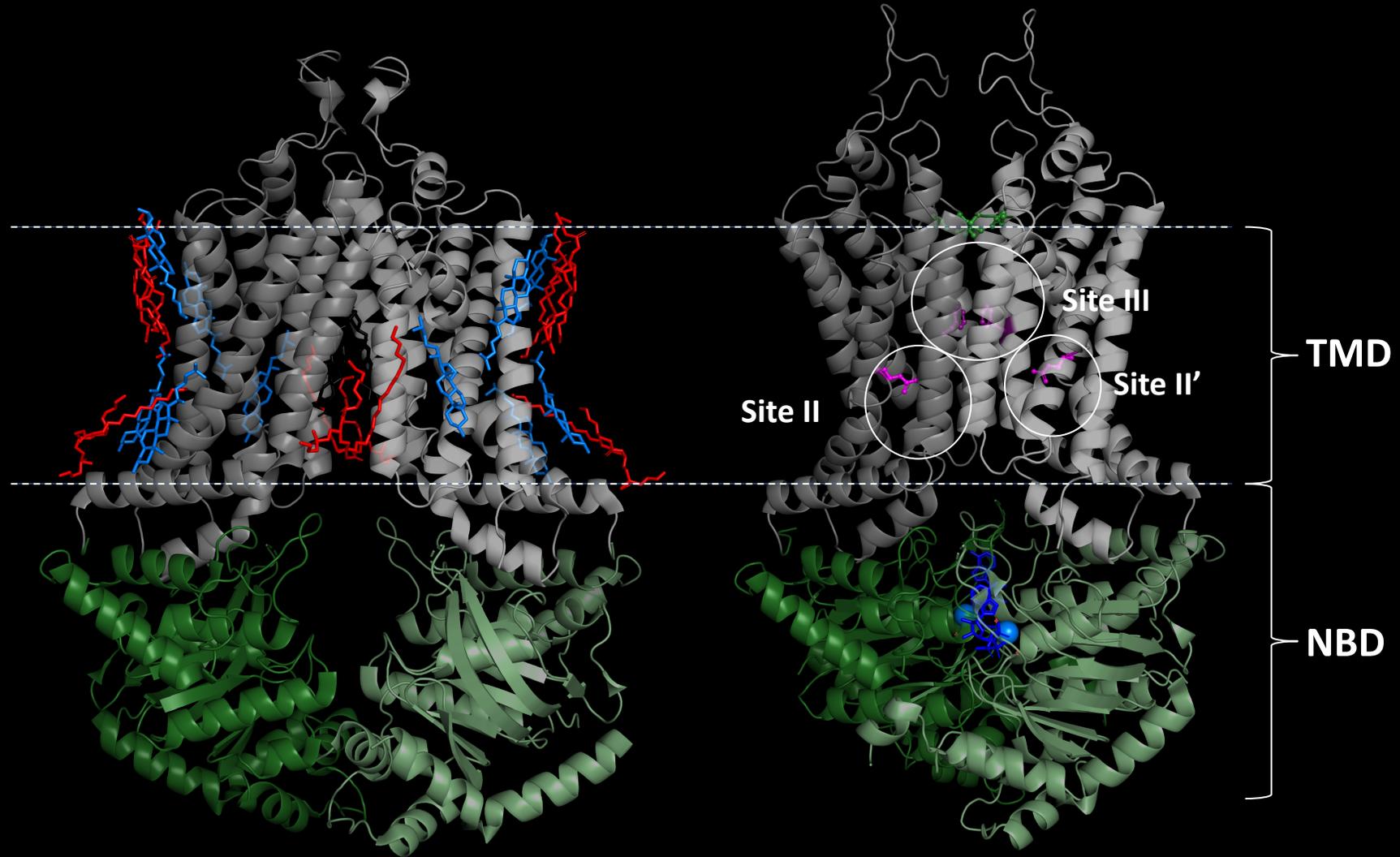


# ABCG2

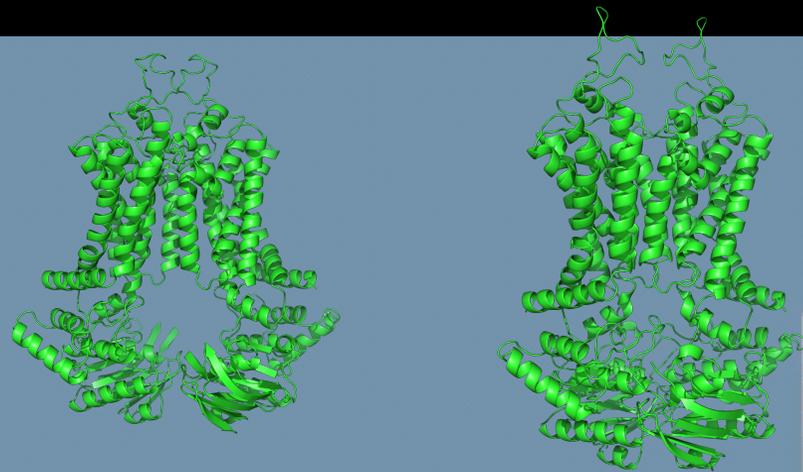
- The 2<sup>nd</sup> member of the G sub-family
- Multi drug transport
  - Exports a wide variety of cytotoxic molecules
  - BBB, placenta, breast
  - Cancer cells can develop Multi Drug Resistance (MDR)
- Uric-acid transport
  - A specific mutation is linked to gout (“köszvény”)



# ABCG2 - structure



Rack & Pinion  
Gear  
(controls  
emptying/holding  
valve)



Upper  
Gate

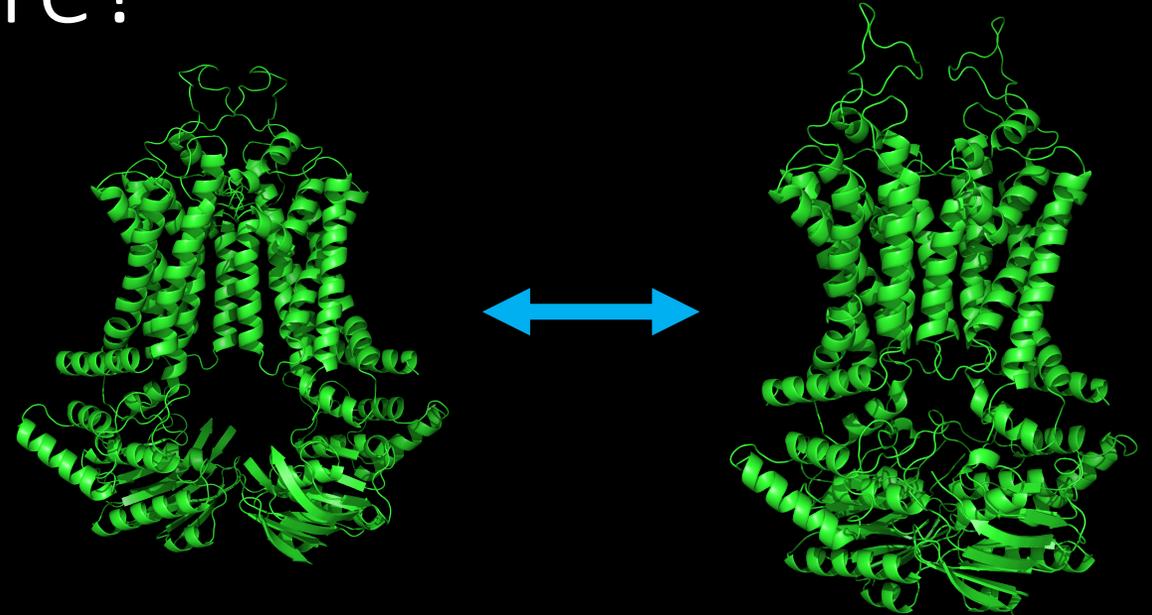


Filling  
Valve

Lower  
Gate

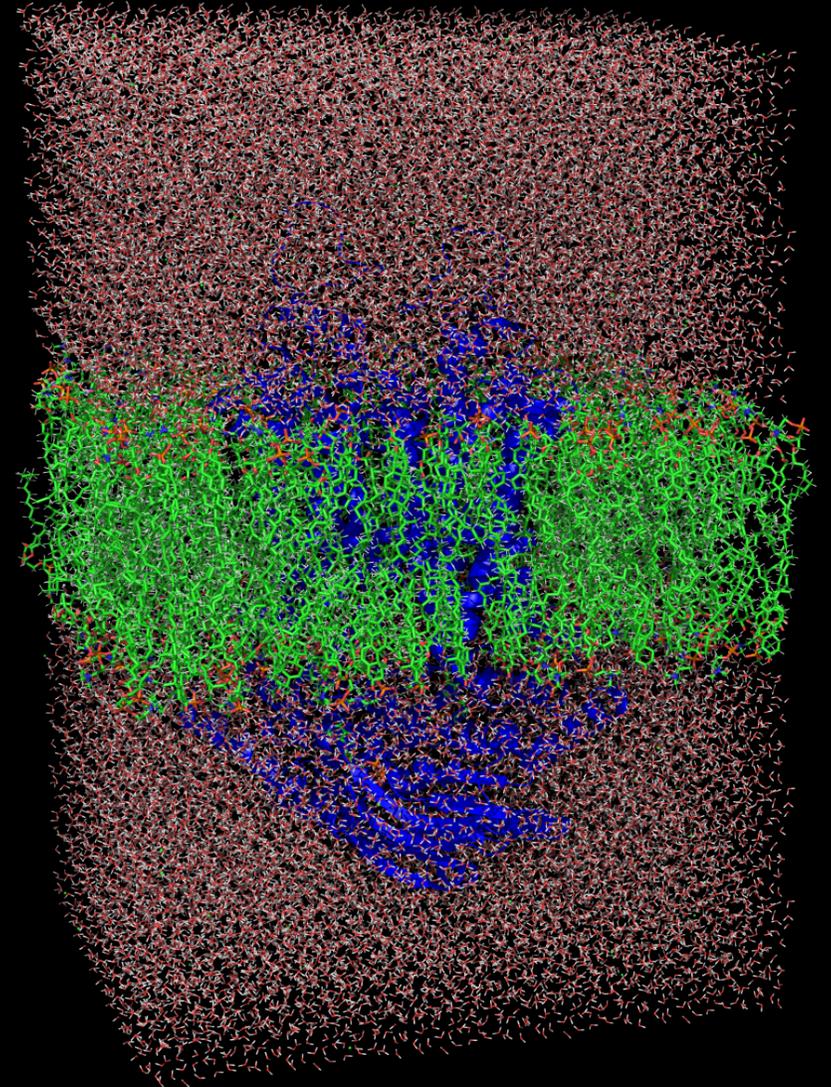
# “OK, but why are you here?”

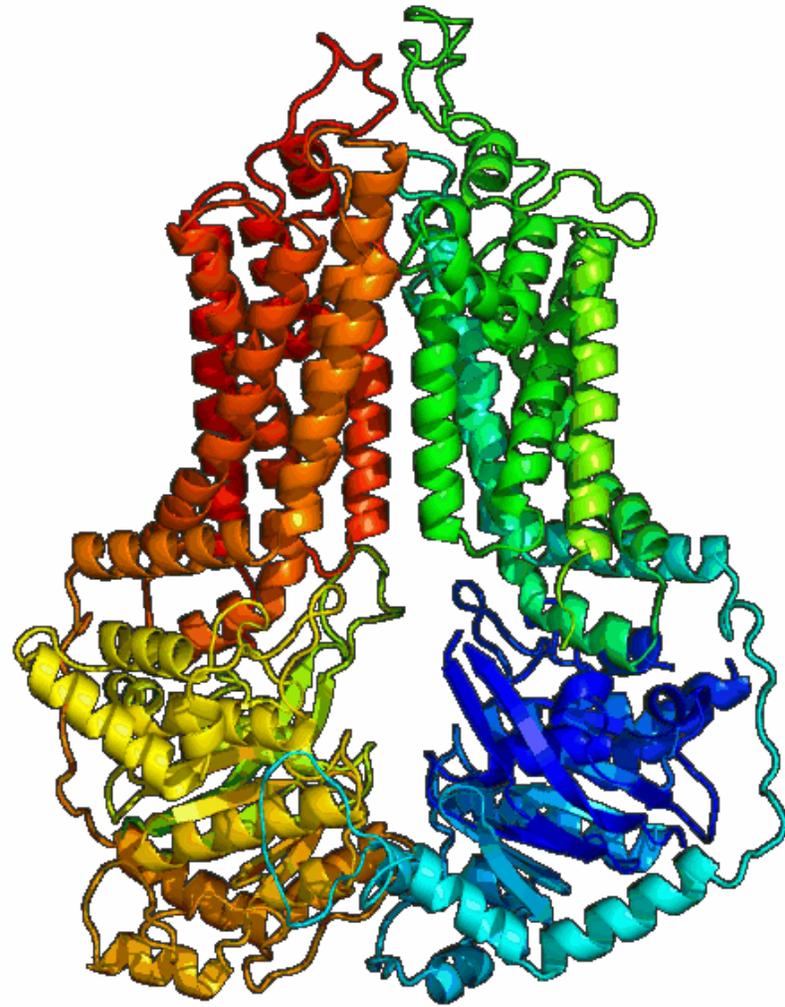
- Organic macromolecules
- Dynamic behavior, atomic level
- Most experimental methods are not suitable to observe dynamics
  - Cryo EM creates static images



# Molecular Dynamics Simulations

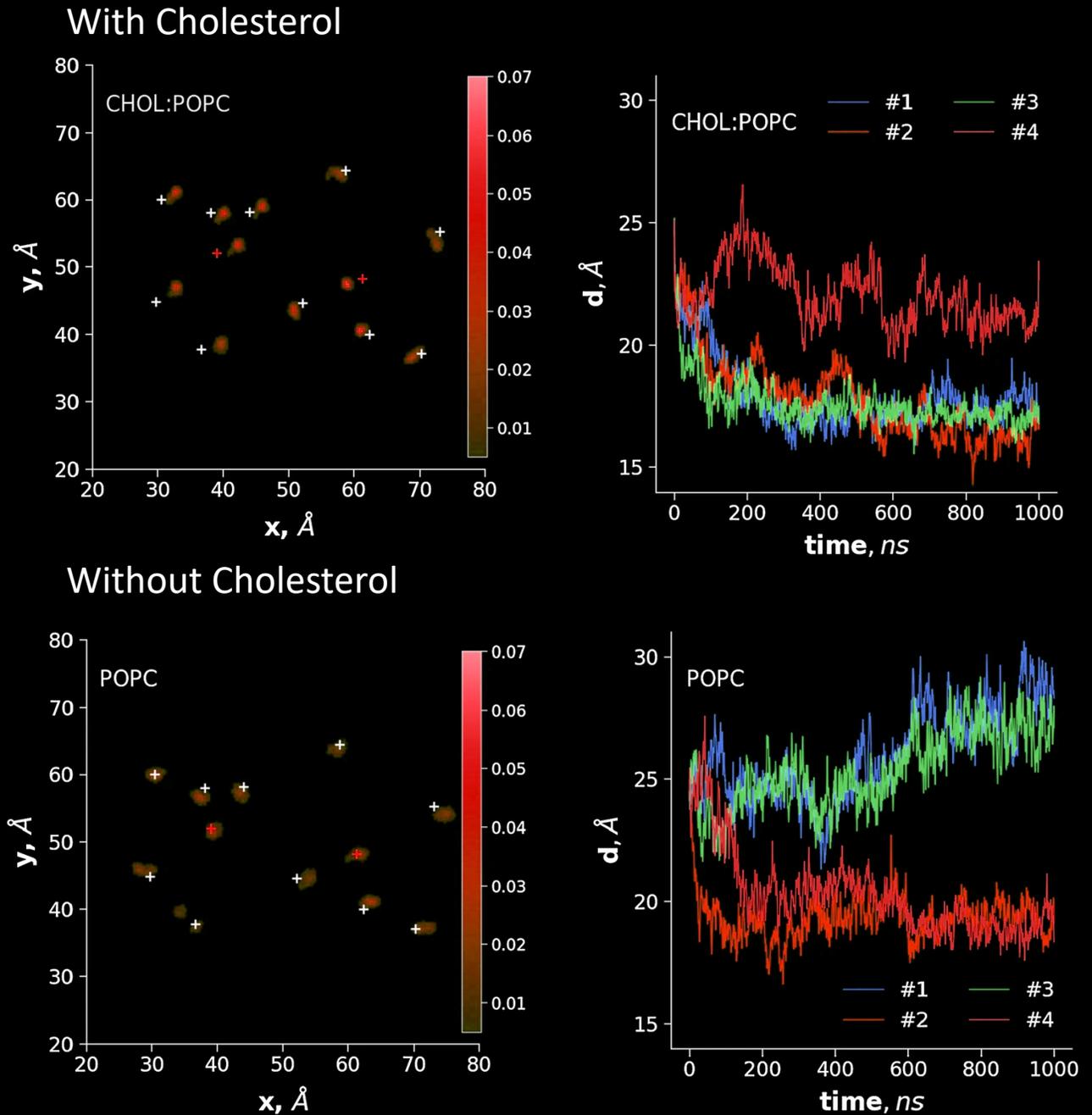
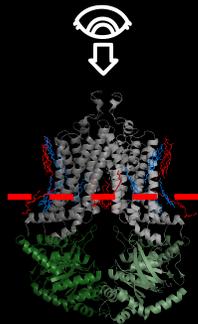
- Our system of approx. 200 000 atoms
- Solving Newton's equations of motion
- 500 ns took 3 weeks with 4 high-end GPUs

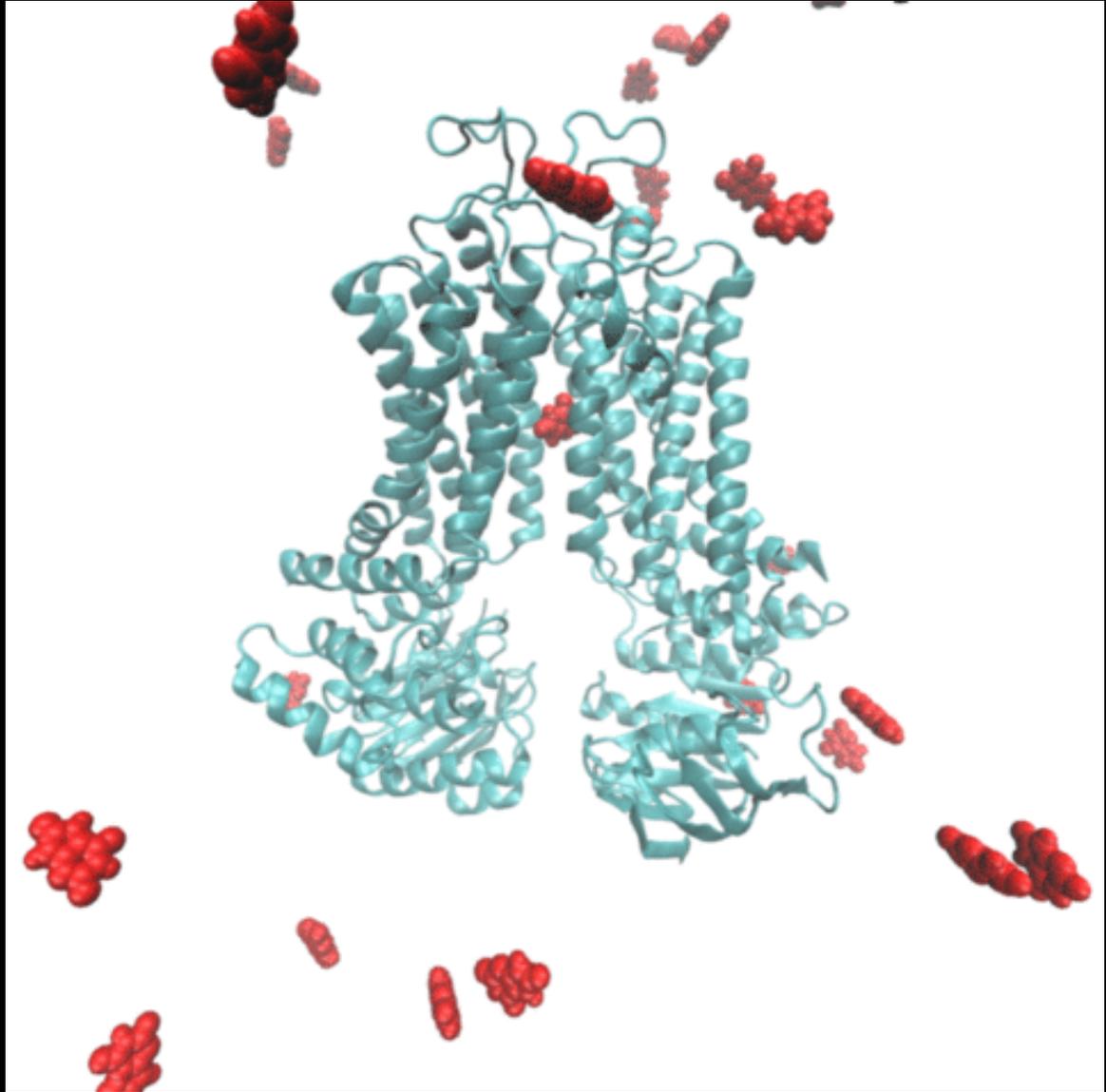




# Regulation via cholesterol

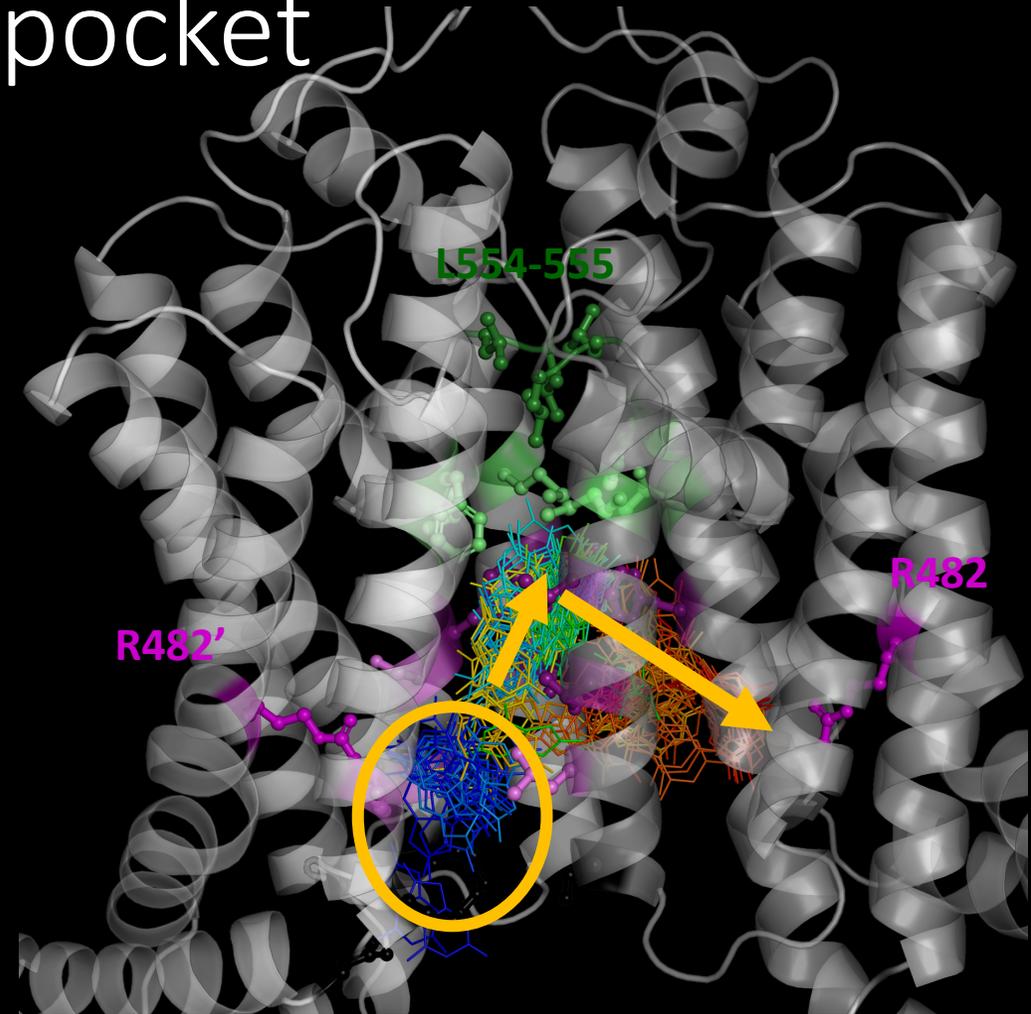
- Experimental data of cholesterol's regulatory effect
- Result: central helices are more likely to close





# Uric acid in the binding pocket

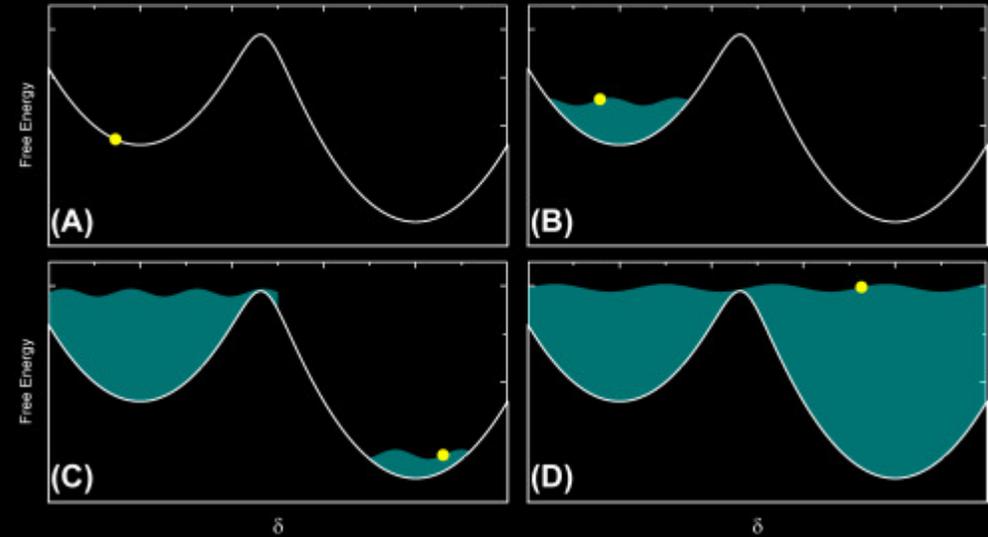
- Passes through Site II
- Interacts with Site III
  - The energy boundary of exit is too high
- Exits through the other side's Site II



TIME →

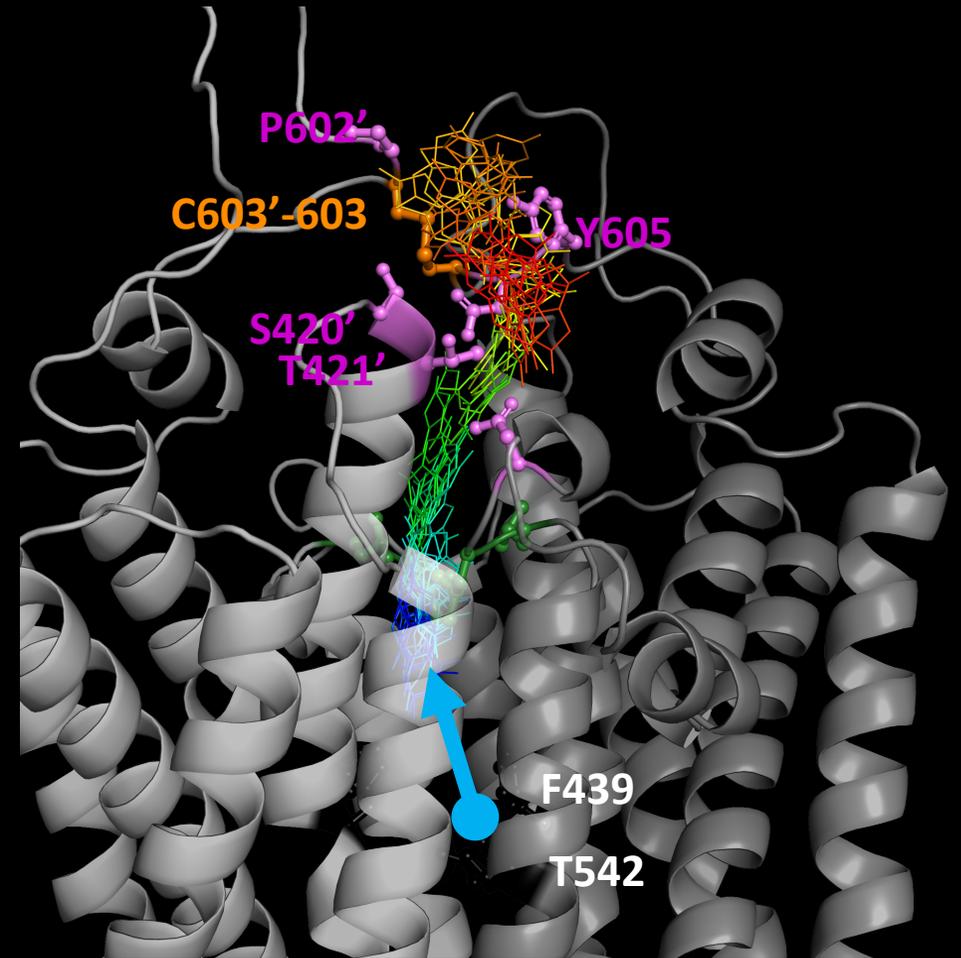
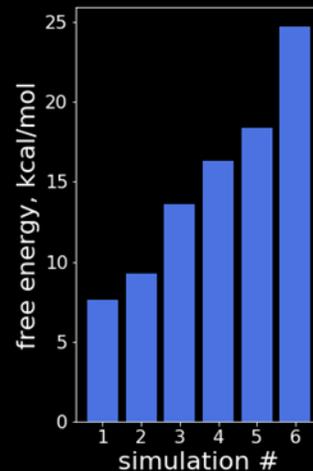
# Metadynamic simulations

- RC - Reaction Coordinate (e.g. distance)
- if RC value does not change in  $n$  simulation steps then energy is artificially increased at that point of the RC
- We can measure how much energy is needed to get over energy boundaries



# Uric acid exits

- Bottom-closed conformation
- Reaction coordinate:
  - distance between substrate and specific amino acids
- Free energy
  - in the range of ATP hydrolysis (7-14 kcal/mol)



# Summary

- ABCG2
  - Mechanism of cholesterol regulation
  - Binding pockets along the translocational pathway
- Large amount of computing capacity is required for MD simulations



Special thanks to Wigner GPU Laboratory for providing computational capacity



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## The transport pathway in the ABCG2 protein and its regulation revealed by molecular dynamics simulations

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<https://link.springer.com/article/10.1007/s00018-020-03651-3>

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# Thank you!