# *Understanding the Mechanisms of Multidrug Transport Proteins*

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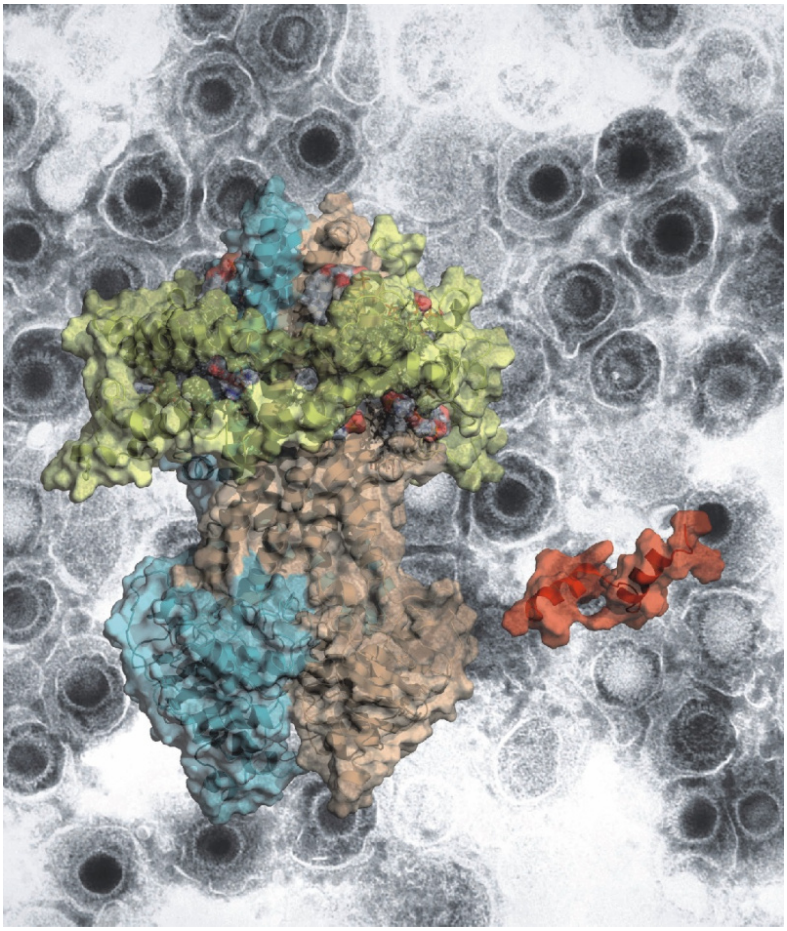

Fig. 1: Snapshot from MD simulation of transporter associated with antigen processing (TAP) embedded in a lipid anodisc. TAP is shown in cyan and orange, whereas the nanodisc proteins and lipids are colored yellow and grey, respectively. The red molecule at the right is the ICP47 protein from herpes simplex virus, a high-affinity inhibitor of TAP. The transmission micrograph in the background shows the preparation of herpes simplex virus.

## Introduction

The Schäfer group is driven by the aim to understand life at the molecular level: can we describe biomolecular systems from the basic principles of chemistry and physicsfi Molecular dynamics (MD) computer simulations can provide a deep and causal understanding of the structural dynamics and energetics underlying biomolecular processes, and are thus one of the most powerful tools to achieve this goal.

## Methods

One of the major bottlenecks of conventional all-atom MD is the huge computational effort involved, which limits the time- and length-scales that are accessible by simulation. Therefore, the group is active in the development and application of computationally efficient methods for describing large biomolecular assemblies on long time scales. This requires efficient classical molecular dynamics (MD) type simulations, in which Newton's equations of motion are iteratively solved in small time steps and empirical potentials (force fields) are employed for describing the interatomic interactions. In addition to using conventional all-atom MD simulations, the group also contributes to improving the accuracy of efficient coarse-grained approaches, and to the development of hybrid multiscale methods that combine different levels of resolution.

The following case study highlights the application of MD to membrane proteins. These nano-machines are not only of great interest due to their intriguing chemical and biophysical principles, but also because of their pharmaceutical importance: about half of all current drugs target membrane proteins. We use MD simulations to probe their structure, dynamics, and the driving forces behind their working mechanisms at the molecular level. Recent work focused on the ATP binding cassette transporter TAP (transporter associated with antigen processing), in collaboration with Robert Tampé at Goethe-University Frankfurt [1].

## Results

To enable experimental characterization, TAP was embedded in a special nanodisc environment (see Figure 1). Intriguingly, biochemical experiments indicated that as little as 22 lipid molecules (grey) were surrounding the TAP protein (cyan and orange). This small number raised the question whether these suffice to isolate TAP from the scaffold proteins of the nanodisc, which wrap around the disc in a double-belt fashion (yellow). The detailed atomic-level structure of this protein/nanodisc complex, as shown in the Figure, could not be obtained by experiment, but only from the MD simulations. Since the overall simulation system is very large (ca. 200.000 atoms, including explicit water), these simulations were only possible through the HPC resources available at CSC.

## Outlook

In summary, the MD simulations show how computational techniques can synergistically complement experiments by probing the interactions between the different components (proteins, lipids, water molecules) that govern the structure and dynamics – and hence the function – of proteins. Fostered by the continuous increase in HPC development, in the near future, detailed MD simulations of even larger protein complexes will become feasible, which are abundant in the cell and steer numerous processes of life.

## Reference

[1] S. Eggensperger, O. Fisette, D. Parcej, L.V. Schäfer, and R. Tampé (2014), An annular lipid belt is essential for allosteric coupling and viral inhibition of the antigen translocation complex TAP, J. Biol. Chem., 289(48): 33098-33108. https://doi.org/10.1074%2Fjbc.M114.592832

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