Influenza is a respiratory system disease that humanity has been facing since ancient times. Nowadays, influenza is estimated to affect 10-20% of the world's population annually and despite relatively low mortality, it results in a large number of deaths (up to 650.000 per year). Moreover, due to a high mutation rate, influenza possess a constant pandemic threat. Influenza virus enters a host cell in order to replicate. This event is owing to the fusion of viral and host cell membranes. In spite years of studies, the details of this important event in the virus life cycle remain elusive. Its understanding is of high value both from scientific standpoint as well as for practical purposes, as a necessary step to develop novel therapies targeted at highly conserved fusion machinery. The promising new influenza treatment is to obtain inhibitors that will slow down or completely block lipid membrane fusion and prevent the viral genetic material from entering into the host cell.

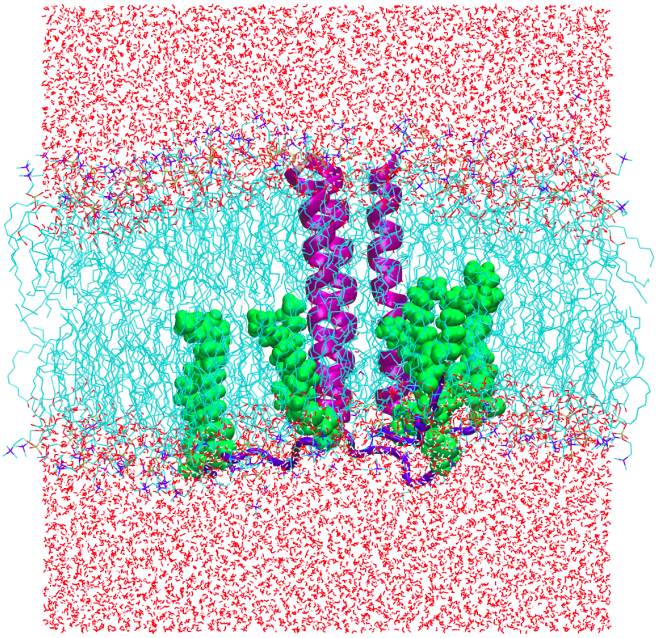

Figure 1: Simulation snapshot of TMD-CT in trimeric state. The TMD configuration (purple) depends on subtle interplay between its intermolecular forces and membrane interaction. The cytoplasmic tail possess S-acylated cysteines (green), and is presented as blue line.

The fusion process is mediated by viral surface protein hemagglutinin (HA). HA is a homotrimeric protein, which inserts its N-terminal fragments, known as fusion peptides, into the target membrane. By undergoing a conformational change, in a jackknife motion, it drags viral and host membranes to close proximity, enabling membrane fusion. Although most of the work to date has focused on fusion peptides, the role of viral membrane HA anchor is increasingly important. It consists of a transmembrane domain (TMD) and a cytoplasmic tail (CT), which is anchored at internal side of viral membrane. Supposedly, they participate in cholesterol dependent HA partitioning and support HA tilting with respect to viral membrane. While the 3-D structure of the external part of HA has been resolved using experimental methods, the secondary and 3-D structures of viral part of HA are entirely unknown. Particularly little is known about CT. The CT is short, highly conserved, and exposed to the viral cytosol peptide. It possess five residues that are invariant in all HA types and two or three cysteines, which are post-translationally palmitoylated and stearated. Intriguingly, the high conservation of those amino acids suggests functional importance but still its details and its actual role in the fusion process remains elusive since no experimental method can reveal reliable membrane anchor structure due to strong tendency of CT to aggregate within membrane mimetic environments. The possibility to bridge the gaps in experimental knowledge is offered by increasingly reliable computational approaches that benefit from tremendous technological and methodological advances in recent years.

In this project, we will conduct extensive computer simulations of HA-membrane anchor in fully atomistic resolution. We will characterise transitions between suggested by experiment TMD geometries that support HA tilting with respect to viral membrane. Our particular attention will be focused on the effect of cholesterol concentration on these TMD transitions. The second part of this project will be devoted to the structural characterisation of CT and putative reasons for its high sequence conservation. Finally, we will consider complete TMD-CT structure (Fig. 1) and by comparison with results obtained for TMD alone, we will determine the likely functional role of CT, in particular, its participation in cholesterol sensing by HA. By completing this project and filling the gaps inaccessible to the experimental studies, we will significantly contribute to the present knowledge concerning structural and functional characteristics of HA viral membrane anchor.