

Membrane fusion and the S



Utilizing DEISA computing resources, Marc Baaden, his research team in Paris, France, and colleagues from France, the United Kingdom

and Austria, have modeled a protein complex that acts as a catalyst in the fusion of two membranes. This exceptionally complex model could not have been constructed without the distributed European computation capacity offered by DEISA. Understanding the functioning of proteins will open up new opportunities for pharmaceutical development.

Pirkko Soininen

“Basic research is essential, since there are several aspects concerning the functioning of proteins and cell membranes that are not yet fully understood. A better understanding of these mechanisms will facilitate, for example, the development of new pharmaceutical agents”, explains Marc Baaden who took part in the DEISA training session.

In medicine, the membrane-embedded proteins are of particular interest, as many of them are potential target sites for pharmaceuticals.

“By examining a phenomenon at the atomic level, we can gain insight into the behavior of cell membranes and proteins in general and on a larger scale”, says the French researcher.

“Researchers often describe molecule-level events by sketching schematic models on paper. This kind of ‘cartoon biology’ is, however, easily misleading, because such schematic models are rarely consistent with the actual physical properties of the proteins, such as their size or form”, says Baaden.

“Computational molecular modeling, or simulation, takes the physical properties into account in a more realistic manner. A good molecular model enables us to examine the smallest details of the system in a controlled fashion and under the desired circumstances. We can also easily change any of the properties of the model to test different hypotheses”, explains Baaden.

Experimentally determined molecular structures provide a static picture of the phenomena at the atomic level; they lack the dynamics and motion that are a central part of

the functioning of, say, proteins. Simulation, on the other hand, facilitates the examination of dynamic events.

Challenging accuracy in modeling

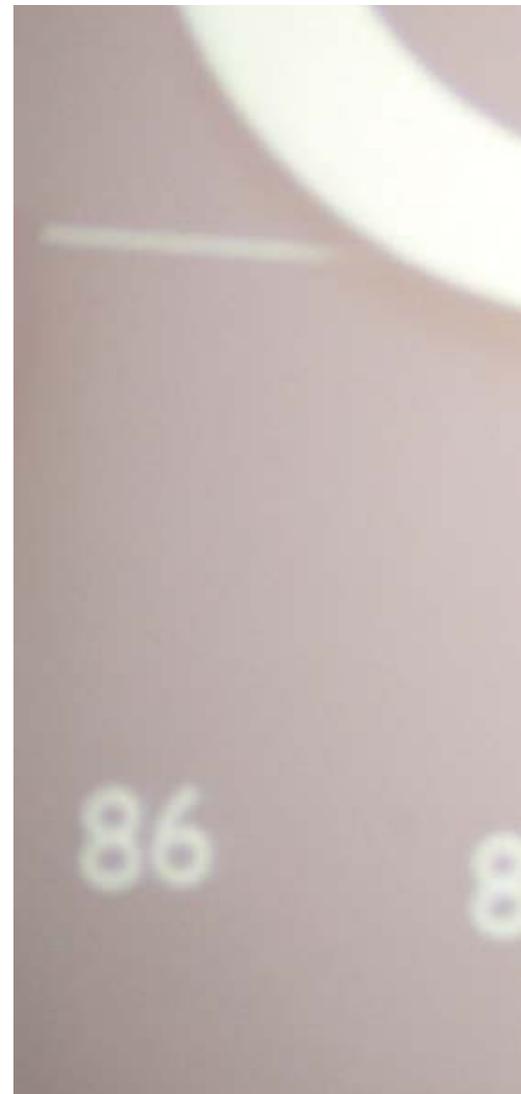
Marc Baaden and his team have modeled the SNARE protein complex that contributes to membrane fusion in cells.

“Traditionally, computational modeling has been applied to simulate a single membrane – this is already a very challenging task. We, however, simulated two lipid membranes held together by a protein complex, so our challenge was even greater”, Baaden says.

In his experiments, Baaden has constructed a functioning simulation environment. While examining the SNARE complex, he has also tested various future methods for modeling cell membranes. The new model has also facilitated the testing of the accuracy of the existing models and theories.

“We have been able to glimpse into the very finest details of a biological system to actually see what happens at the molecular level. This would not have been possible with any other method.”

“I believe that, in the future, those methods will succeed that combine highly accurate atomic level modeling with coarse-grained models simulating a more extensive event. Communication between the simulations on various levels is important. This will allow us to simulate a detail of particular significance more accurately, and larger



entities by means of a coarse-grained model”, Baaden concludes.

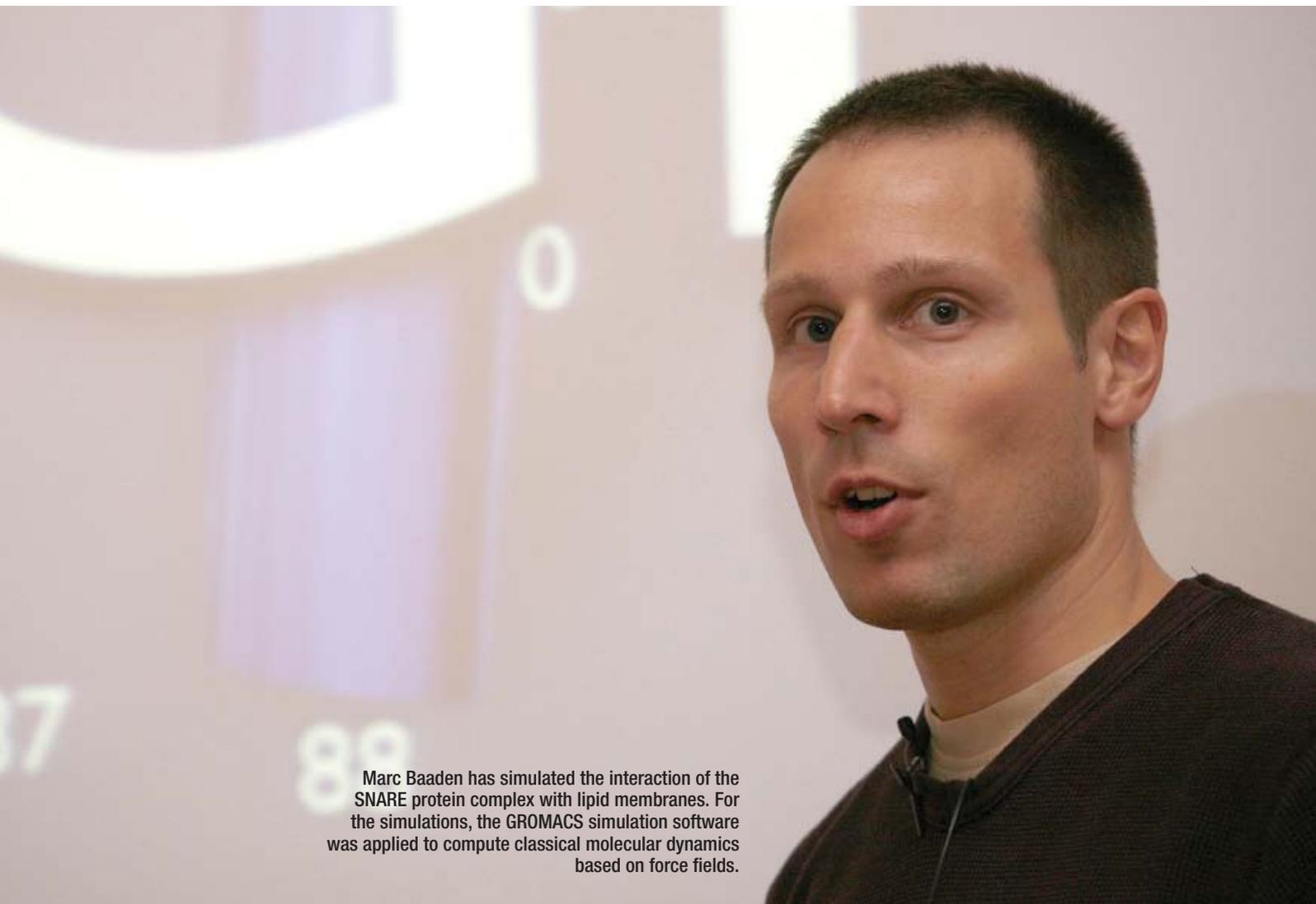
Complex modeling demands high computation capacity

Marc Baaden has striven for high accuracy in the modeling. The team used standard molecular modeling methods in their work, but the system subject to simulation was exceptionally extensive and complex. The total number of atoms to simulate in the model was 340 000. And yet, on the cellular scale, the area to be simulated was extremely small.

“Our greatest challenge concerned the construction of the computational model. We ran several trial tests on different models without success until we managed to make the system work. There was a stage when I was about to give

SNARE protein complex

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Marc Baaden has simulated the interaction of the SNARE protein complex with lipid membranes. For the simulations, the GROMACS simulation software was applied to compute classical molecular dynamics based on force fields.

up, since it seemed that the model simply would not work. Luckily, an Austrian colleague, who loves challenging cases, came to my aid. Together we were able to construct a model that could be run using GROMACS”, Baaden remembers.

“DEISA has helped us greatly. In Paris, we did not have sufficient computation capacity, but the DEISA infrastructure was an optimal suit for our purposes. The only drawback was that the computing hours reserved for us coincided with the start of the academic year, so it was quite hard to recruit students”, Baaden says.

First steps toward future applications

The functional disorders of cell membranes are known to be associated with many diseases. The fusion of membrane structures, which

is catalyzed by the protein complex studied by Baaden, may be disturbed in two ways: either the membranes do not fuse at all, or they fuse too heavily.

“At present, we do not sufficiently understand the details of the cell membrane mechanisms. By modeling these events, we may, in the future, be able to develop more efficacious drugs that are conveyed directly to the target site”, says Baaden.

“It is important for a researcher carrying out basic research to be able to visualize the goal. We are contributing to a long process, even if we are only taking the first steps in the track. We may imagine potential future applications, but it is equally possible that once we learn to better understand the cell functions, the applications will be something completely different”, he says.

Apart from medical science, the cosmetics industry and nanotechnology will benefit from a better understanding of protein functioning.

“Knowledge of the functioning of cell membranes will open up opportunities in the field of nanotechnology as well. In technical terms, the proteins we study are clever machines that perform their intended tasks excellently, that is, to fuse two lipid membranes firmly together”, Baaden points out.

For more information

<http://www.baaden.ibpc.fr/projects/snaredeci/>

www.deisa.org/applications/projects2005-2006/snare.php

SNARE proteins in cell membrane fusion

Tommi Kutilainen

SNARE proteins are a large protein superfamily. Their primary role is to control membrane fusion of cellular transport vesicles with cell membranes or with target compartment membranes. Such fusion activities are essential for the normal function of the cell.

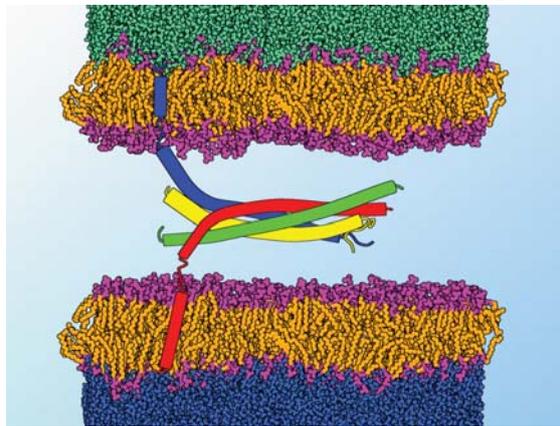
A vesicle is a compartment separated from the cytoplasm by at least one lipid bilayer. Vesicles transport, store, and digest products or waste produced within the cell. The vesicle membrane enclosing the vesicle is similar to that of the cell membrane. SNARE proteins inside the cell assist in the fusion of the vesicle membrane and the cell membrane. The membrane fusion plays an active role in the vesicle-mediated transport of materials inside the cell and through the cell membrane.

For example, when a particle is removed from a cell in exocytosis, the particle is encapsulated by a vesicle that migrates to the cell surface and anchors to the cell membrane with its inside facing the outside of the cell, thus secreting the particle out of the cell. In a similar way, vesicles transport proteins and lipids to the Golgi apparatus, which is responsible for processing and packaging of proteins and lipids.

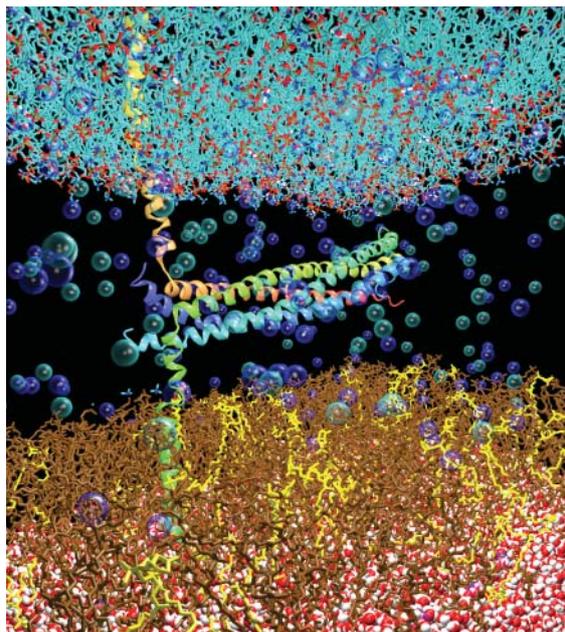
Mutual identification of SNARE proteins precedes the fusion of the vesicle and target cell membranes. A receptor (v-SNARE, synaptobrevin) protein anchored on the vesicle membrane and a corresponding receptor (t-SNARE, syntaxin) on the target membrane are wound with two SNAP-25 proteins creating a SNARE protein complex in the form of a four- α -helix bundle. This four-protein complex is a necessary, but probably not sufficient, condition for cell membrane fusion to take place.

The scope of SNARE research is not limited to adding to the understanding of normal cellular activities. For example, disturbed functioning of SNARE proteins may initiate the adult-onset diabetes (type 2 diabetes). Hence, understanding the SNARE function may facilitate development of new therapeutic treatments. It is essential to develop new therapies, as diabetes is one of the most significant national diseases in Finland. According to the current WHO figures, approximately three percent of people in Finland develop diabetes, but the number is constantly growing.

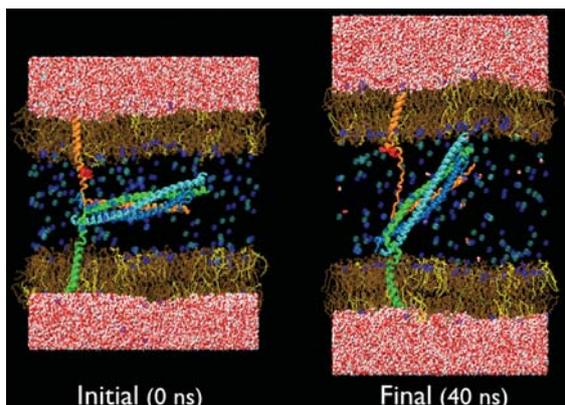
© Marc Baaden



A structural image of a SNARE protein complex embedded between two protein bilayers. The upper membrane structure depicts the membrane encapsulating the vesicle. The lower one represents the cell membrane, on which the vesicle is about to fuse. The SNARE protein, essentially a four- α -helix bundle, is between the cell membranes. Synaptobrevin (blue) is partly inside the vesicle and syntaxin (red) is partly within the cell membrane. SNAP-25, a third SNARE complex protein, is shown in green and yellow. For the sake of clarity, water molecules between the cell membranes are not presented.



A SNARE system bound onto cell membranes. The counterions Na^+ and Cl^- are shown as spheres. They are needed to neutralize the highly charged POPC and POPS lipids of the lower cell membrane. POPC is marked with brown and POPS with yellow.



On the left, the initial structure of a SNARE complex bound a cell membrane and the simulated final structure on the right. Synaptobrevin is marked in orange and tryptophans that may possibly be essential in the cell membrane fusion process (89 and 90) are marked in red. The composition of the cell membrane is illustrated by marking the neutral POPC in brown and the charged POPS in yellow.