Usage Report for Fiscal Year 2017

Project Title:

Protein-Ligand and Protein-Lipid Interaction

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1. Background and purpose

Biological membranes are the most important borders in the biological world. Not only do they provide a barrier towards the outside world, and protect the function of life inside each cell, but they also separate different areas within a cell and thus giving rise to specialized cellular compartments. While the membrane contains proteins, its main constituents are lipids. Lipids are not only capable to form these protective barriers spontaneously, but also to seal off holes.

Naturally each barrier or wall requires windows and doors to allow the exchange of nutrients and information between the two sides. This task is conducted by proteins, embedded in the lipid membranes of cells, such as receptors to convey signals or transporters, capable to transport nutrients or ions across this barrier.

While the structural information of proteins can be deduced in many cases by x-ray crystallography, the structural flexibility of lipids defies resolving individual lipids with currently available physical or biophysical methods. To overcome this shortcoming, molecular dynamics simulations have proven a highly useful tool, bridging the gap between frozen x-ray cryptographica data and bulk dynamics measured established biophysical methods.

To study the detailed interaction between lipids as well as lipids and proteins in cellular membranes it is essential to establish sufficiently accurate biophysical models of lipids and proteins. To achieve this goal, quantum mechanics simulations are used to devise a limited set of parameters describing the behavior of a specific lipid species, small molecule, also known as metabolite, or protein.

2. Usage status and calculation methods

Primarily quantum mechanics (QM) simulations utilizing the Gaussian 09 software package have been performed. Additionally the NAMD software package has been employed for molecular dynamics (MD) simulations.

2. Results

Suitable force field parameters (CHARMM) for a non-protonated and thus neutral terminal amino function of the phosphatidylethanolamine head group has been developed. This enabled the creation of hydrated membrane patches containing the novel lipid molecule and dynamics simulations are currently ongoing. Additionally, lipid-protein interaction has being probed utilizing the NAMD package and a homology model of a GPRC embedded in a fully hydrated lipid membrane.

3. Conclusion

Based on our previously established experimental data in combination with the preliminary MD simulations we are characterizing the ligand binding pocket of a to–date not crystallized GPCR from a molecular point of view. Additionally, we are on our way to probe the lipid-lipid interaction of charged and neutral phosphatidylethanolamine head groups in lipid bilayers, to better highlight the importance of head group to head group interaction and their influence on lipid phase behaviour.

4. Schedule and prospect for the future including aims for the next usage term

The focus of the next usage period will be set on QM simulations (Gaussian software package) of phosphatidylethanolamine analogues at different protonation states, to complete the establishment of suitable CHRAMM force field parameters for the whole series..

Additionally, QM simulation of small molecules will be conducted to understand the energy difference between their isomers. The QM results will be corroborated with our experiment result and provide a novel route to detect specific small molecules in urine samples.

Fiscal Year 2017 List of Publications Resulting from the Use of the supercomputer

[Oral presentation at an international symposium]

1. "Lyso-Phosphatidyl-β-D-glucoside Analogues as GPR55 Agonists: Synthesis and Modality-Specific Repulsive Guidance of Nociceptive Neurons"; 19th European Carbohydrate Symposium, Barcelona, Span, July 2nd-6th
2. "Synthesis and Modality-Specific Repulsive Guidance of Nociceptive Neurons by Novel GPR55 Agonists"; 36th Japanese Society for Carbohydrate Research Meeting, Asahikawa, Japan, July 19th–21th.

[Others (Press release, Science lecture for the public)]

Invited oral presentations:

1. "GPR55 Ligands: From Endocanabinoids to Lysolipids"; RIKEN Symposium, Japan, January 26th, 2018.
2. "Probing Lipid-Cholesterol Interaction"; International Membrane Seminar, Osaka, Japan, October 9th-10th, 2017.
3. "Recent Progress Toward BMP Structure and Biosynthesis and

the Dynamics of Sphingolipid-Toxin Interaction"; IMBL-UMR1060 – CarMeN_15, Lyone, France, June 30th.