An attempt to clean up the sweet chaos

Exploring the conformational phase space of N-linked glycans using enhanced molecular dynamics and sketch-map analysis

***I. L. Grothaus, M. Delle Piane, L. Colombi Ciacchi**, Hybrid Materials Interfaces Group, Faculty of Production Engineering and Bremen Center of Computational Materials Science, University of Bremen*

In Short

- N-linked glycans are carbohydrate chains, covalently attached to proteins as post-translational modifications.
- Due to their flexible rotation around bonds, many different conformations can be adapted by the glycan tree.
- Glycans follow the same lock and key model as proteins, but represent several keys at ones due to their many different conformations.
- Exploring this hugh conformational phase space is important as well as the facilitated representation for comparison of different structures.
- This project will sample glycan conformers extensively via enhanced MD and visualize their distribution using the dimensionality reduction algorithm sketch-map.

The covalent attachment of glycans to the polypeptide chain of proteins is a form of post-translational modification that occurs for over 50% of mammalian proteins [1]. Over the years, different biological functions have been assigned to glycosylations like involvement in folding and stability of proteins or as target structures for lectins and antibodies, illustrating their importance for proteins' structure and functions [2]. The study of glycans itself is extremely important, as they serve similarly to proteins as keys to a lock, where one glycan represents several keys due to its many conformations. Dealing with glycan structures, one is facing the problem of a high dimensional space that is required to describe the conformations explored by the sugar trees. This is due to their diversity depending on composition, linkage type and branching, giving rise to such flexible behaviours. Unfortunately, structural motives like α-helices and β-sheets for proteins are not applicable to glycans, rather classical description using torsion angles or spherical coordinates have been used [3].

As a consequence thereof, describing conformer populations of one single glycan tree unambiguously are depended on many torsion angles (Figure 1) and cumbersome to describe in a 2D map. Therefore, the aim of this project is to greatly push forward the ability to visualize glycan conformers of high dimensional space in a low dimensional representation. This is thought to be achieved by applying the dimensionality-reduction algorithm sketch-map, which transforms data of a high-dimensional space (e.g. many torsion angles) into a 2D map (low-dimensional space)[4]. This map comprises points where each point corresponds to one conformation that was recorded during a molecular dynamics run. Conformations are clustered by the algorithm depending on their similarities and can be coloured using either free energies or variables differentiating found clusters.

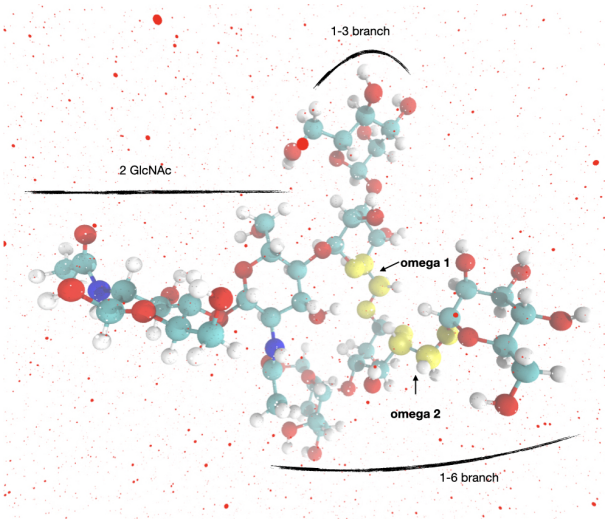

***Figure 1:** Oligomannose glycan with important structural features like the two omega angles, found to have a high energy barrier of around 12 $k_b T$.*

To achieve a sufficient sampling of all relevant torsion angles, enhanced molecular dynamics simulations are required. We therefore plan to use the approach replica exchange with solute scaling combined with metadynamics (RESTmetaD) for which HPC infrastructure is greatly required.

The employment of this tool is thought to facilitate the study of a large number of differently sized glycans to easily map their free energy landscape and corresponding conformer population for comparison by simple 2D maps. As an application, we aim at sampling the conformation of a N-glycan when attached to a model glycoprotein, to investigate the difference in adapted conformations due to interactions with the protein surface and other glycan trees.

WWW

http://www.hmi.uni-bremen.de

More Information

[1] R Apweiler, H Hermjakob, and N Sharon. *Biochimica et biophysica acta* **1999** 1473(1):48. doi:10.1016/s0304-4165(99)00165-8

[2] Ajit Varki. *Essentials of Glycobiology* **2009**.

[3] Wataru Nishima, Naoyuki Miyashita, Yoshiki Yamaguchi, Yuji Sugita, and Suyong Re. *The journal of physical chemistry*. **2012** 116(29):8504-12. doi:10.1021/jp212550z

[4] Michele Ceriotti, Gareth A Tribello, and Michele Parrinello. *PNAS* **2011** 108(32):13023-8. doi:10.1073/pnas.1108486108