Conformational Dynamics of Glycoproteins

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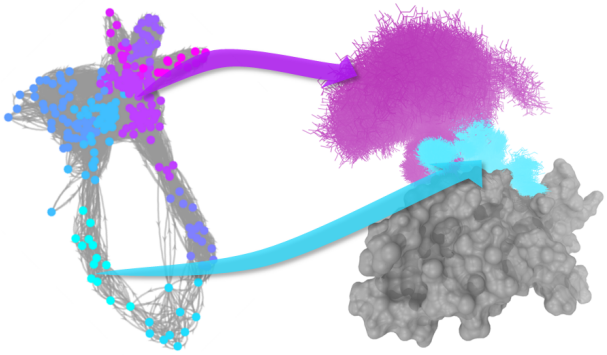

Site, number, type and the degree of branching of N-linked glycosylations modify biophysical attributes of glycoproteins in a hardly predictable manner. Structural studies can provide insight on fundamental protein-glycan interactions, but pose a challenge to crystallography due to the glycan's tremendous conformational flexibility. Molecular simulation techniques have proven their ability to accurately reproduce both free energy landscapes of glycosidic linkage torsion angles and intramolecular hydrogen bonds in a number of oligosaccharides [1].

In this research, we utilize molecular dynamics (MD) simulation to investigate structure and dynamics of various glyco-isoforms of human erythropoietin (EPO). In particular, sialylated, complex-type, biantennary N-glycans at positions ASN^{24}, ASN^{38} and/or ASN^{83} were modeled and simulated in explicit solvation for at least 100 ns each. Glycosidic linkage torsion angles were monitored and used for an initial conformational clustering into hundreds of microstates. Markov modelling involves computation of microstate transition probabilities and a spectral clustering via PCCA+ [2]. Finally, this allows us to reduce the conformational variance into a comprehensible number of distinct, kinetically relevant macrostates (see figure).

Extensive knowledge about conformational states allows us the identification of concealed patterns in noisy MD data and reduces the computational expense of calculating free energies, electrostatic potentials, hydrodynamic properties or protein-protein association rates. Additionally, Markov modelling serves as an enhanced sampling method in a way that kinetically unfavorable states are appropriate initial configurations for subsequent MD simulations to sample otherwise barely accessible states.

[1] O. Guvench, et al., JCTC, **2011**, *vol. 7*, no. 10, pp. 3162-3180
[2] S. Röblitz and M. Weber, ADAC, **2013**, *vol. 7*, no. 2, pp. 147-179