VUB SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Structural Biology Brussels

has the honor to invite you to the public defence of the PhD thesis of

Bhawna Dixit

to obtain the degree of Doctor of Bioengineering Sciences, Joint PhD with UGent

Investigating Protein Flexibility: Using Molecular Dynamics Simulations of α-1 Acid Glycoprotein and Large-Scale Normal Mode Analysis of AlphaFold Models

Tuesday **February 25th**, 2025, **2:30 pm**

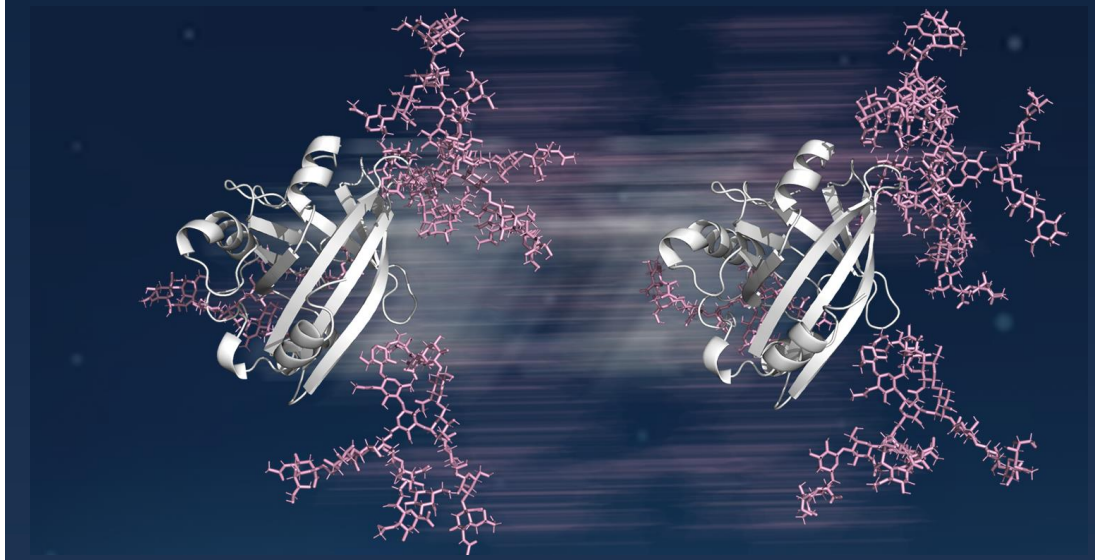
Auditorium P Jozef Plateau, ground floor, Jozef Plateaustraat 22, 9000 Gent

Online participation: MSTeams

Following the defense, you are kindly invited to a reception at the same venue, starting at 5:00 pm

Please confirm your attendance at the defense before **February 18th** via the email address bhawna.dixit@ugent.be, or bhawna.dixit@vub.be or via google forms

Best regards Bhawna Dixit



Examination Committee

Prof. Dr. ir. Joris Degroote, Ghent University, Belgium (chair)

Prof. Dr. Dominique Maes, Vrije Universiteit Brussel, Belgium

Prof. Dr. Janez Konc, National Institute of Chemistry, Slovenia

Prof. Dr. Savvas Savvides, Ghent University, Belgium

Prof. Dr. Kathleen Marchal, Ghent University, Belgium

Prof. Dr. Karine Breckpot,Vrije Universiteit Brussel, Belgium

Prof. Dr. Vera Van Noort, KU Leuven, Belgium

Supervisors

Prof. Dr. ir. An Ghysels, Ghent University, Belgium

Prof. Dr. Wim Vranken, Vrije Universiteit Brussel, Belgium

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Investigating Protein Flexibility: Using Molecular Dynamics Simulations of α-1 Acid Glycoprotein and Large-Scale Normal Mode Analysis of AlphaFold Models

Summary

Proteins are inherently dynamic entities, exhibiting conformational flexibility that is essential for various biological functions. This flexibility spans a spectrum, from complete structural disorder to the motion of specific protein fragments, including various intermediate conformational states. These dynamic behaviours arise from atomic coordinate fluctuations driven by thermal motion and influenced by factors such as temperature, forces, and vibrations. Despite this intrinsic flexibility, traditional models have often relied on static representations, failing to capture the true dynamics of proteins. To address this limitation, this thesis explores protein flexibility using two complementary approaches: a "close-up" perspective and a "panoramic" perspective, offering deeper insights into protein conformational dynamics and flexibility.

The close-up perspective focuses on α-1 acid glycoprotein and its mutants how mutations and glycosylation, individually and in combination, affect the conformational dynamics and flexibility of a (glyco)protein, α-1 acid glycoprotein (AGP) through Molecular Dynamics (MD) simulations. The panoramic perspective integrates computational and experimental methods to analyze protein flexibility on a large scale. This includes using AlphaFold2's pLDDT scores, experimental data from Nuclear Magnetic Resonance (NMR), MD simulations, and Normal Mode Analysis (NMA) to investigate the relationship between computational predictions and experimentally observed protein flexibility. By combining these perspectives, the thesis provides a more nuanced understanding of protein flexibility, addressing the challenges of capturing flexibility on a large scale and improving the understanding of a protein's biophysical behaviour, especially in the context of glycosylation. The results of this thesis could serve as a framework for integrating protein dynamics into routine protein structure prediction methodologies, paving the way for moving beyond static models.

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