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Report on Ph.D. thesis "Deciphering the Molecular Basis of Specificity in Protein-Glycosaminoglycan Interactions: form All-atom to Coarse-Grained Models" by MSc. Annemarie Danielsson, University of Gdansk

Dear Faculty Council of Chemical Sciences of the University of Gdansk,

This dissertation presents an original and carefully executed contribution to the field of computational glycobiology and biomolecular simulation. Through the application of multiscale computational methods, systematic validation against experimental data, and the development of new methodological tools, the candidate advances the mechanistic understanding of interactions between proteins and glycosaminoglycans. The thesis provides insight into the determinants of binding specificity and introduces computational approaches that broaden the available methodology for studying structurally complex and conformationally flexible carbohydrate polymers. The clarity of presentation, coherence of argumentation, and consistency of scientific reasoning reflect a high standard of scholarly work.

Glycosaminoglycans are central to biological recognition processes, extracellular matrix organization, inflammation, coagulation, viral entry, and diverse cellular signaling pathways. Their interactions with proteins depend on a combination of sulfation patterns, conformational variability, electrostatic influences, and environmental context. These characteristics limit the applicability of many experimental techniques, which makes computational chemistry an essential complement to experimental studies. The thesis addresses these challenges through a coordinated use of electrostatic modeling, all-atom molecular dynamics simulations, coarse-grained modeling, free energy calculations, and machine-learning methodologies. Particular emphasis is placed on validating computational results with experimental measurements, including NMR spectroscopy, electrophoretic methods, and glycan microarray assays.

The work is organized into several interconnected research studies, each corresponding to a published or submitted work. Collectively, they form a coherent and comprehensive investigation of the physical principles that underlie protein–glycosaminoglycan interactions.

The first study quantifies the near-surface electrostatic potentials of proteins and protein–glycosaminoglycan complexes using Poisson–Boltzmann level calculations, together with validation by a paramagnetic-probe NMR method. This combined approach allows the identification of likely binding regions and enables an assessment of how ligand binding modifies the electrostatic environment of the protein. In their system highly sulfated glycosaminoglycans produce substantial alterations in the local electrostatic potential, whereas ligands with lower charge density induce more limited changes. These findings contribute to a clearer understanding of chemokine recognition of glycosaminoglycans.

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The second study examines the relative contributions of electrostatic interactions, conformational entropy, and hydrogen bonding through molecular docking, atomistic molecular dynamics simulations, free-energy analysis, and NMR validation. The observation that isocharged acidic peptides bind to IL-8 far less strongly than heparin demonstrates that charge alone does not account for the known high binding affinity of the complex and that geometric and chemical features specific to involved glycosaminoglycans play an important role. This work clarifies the balance between electrostatic and structural determinants in chemokine–glycosaminoglycan recognition.

A significant methodological contribution of the thesis is the extension of the physics-based SUGRES-1P coarse-grained model to heparin in the third study. This required detailed parameterization of bead representation, charge distribution, electrostatic screening, and bonded interactions. Benchmarking against experimental end-to-end distances, radii of gyration, and known structural features shows that the model is able to reproduce characteristic properties of heparin across a range of chain lengths. The resulting coarse-grained model permits simulations of long glycosaminoglycan chains with substantially reduced computational cost.

In the fourth study, the candidate integrates the extended SUGRES-1P model of heparin with the UNRES coarse-grained force field for proteins. This integration creates a computational platform capable of simulating protein–heparin complexes over timescales that are difficult to reach with fully atomistic methods. Applications to basic fibroblast growth factor, acidic fibroblast growth factor, and the NK1 splice variant of hepatocyte growth factor show that the combined model reproduces known binding residues, maintains stable complexes in repeated simulations, reflects the effect of chain length on dimer stability, and captures principal dynamical features consistent with structural data. This constitutes the first validated unified coarse-grained framework for simulating protein–heparin systems of this size and flexibility.

Finally, the thesis presents a study based on a library of twenty-seven synthetic heparan sulfate hexasaccharides. The candidate performs atomistic simulations of unbound ligands, extracts a diverse set of physicochemical descriptors, and applies principal component analysis, regression, and clustering to identify relationships between these descriptors and protein binding preferences. The results show that different proteins display preferences for distinct structural features, that 3-O-sulfation-dependent flexibility correlates with binding in several cases, and that a subset of molecular descriptors can serve as predictors of binding specificity. This constitutes a structured approach for linking the conformational behavior of unbound ligands to their binding properties and has potential relevance for the rational design of glycosaminoglycan mimetics.

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The dissertation is clearly organized, beginning with a detailed introduction, followed by explicit research aims, a chapter summarizing the studies linked to publications. The figures and tables are numerous and well prepared, and the writing maintains a consistently formal and precise scientific style. The bibliography is extensive and contextualizes the presented research within the relevant literature in glycobiology, computational chemistry, and structural biology.

The end of last chapter includes a set of future research directions that are coherent and aligned with current developments in the field. These include the extension of coarse-grained models to additional glycosaminoglycan classes and assemblies, the integration of protein descriptors into simulation frameworks, and the scaling of simulations to extracellular networks using advanced computational resources.

In summary, this dissertation presents a coherent and substantial body of research that contributes meaningfully to the understanding of protein–glycosaminoglycan interactions. It demonstrates advanced competence in multiscale simulation methodologies, detailed knowledge of glycobiology, and the ability to integrate theoretical, computational, and experimental perspectives. Consequently, I conclude that the doctoral dissertation by MSc. Annemarie Danielsson, entitled "Deciphering the Molecular Basis of Specificity in Protein-Glycosaminoglycan Interactions: from All-atom to Coarse-Grained Models," meets the requirement set forth in the Act – Law on Higher Education and Science (Article 187, paragraphs 1–3) of 2018, as amended. Therefore, I submit to the Council of the Discipline of Chemical Sciences of the University of Gdansk a recommendation to allow Annemarie Danielsson to proceed to the subsequent stages of the procedure for awarding the academic degree of Doctor.

Kind regards,

Hector Martinez-Seara

Signed by: Hector Martinez-Seara
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