Report Thesis Mateusz Marcisz

To whom it may concern

Mateusz Macrcisz submits an essay entitled "*Development of novel computational approaches for Glycosaminoglycans*" in partial fulfilment of the degree of Doctor of Science of the University of Gdansk, Faculty of Chemistry. The work was carried out under the supervision of Dr Sergey Samsonov in the Molecular Modeling Laboratory of the Department of Theoretical Chemistry.

The goal of the work underlying Mateusz Marcisz's research is to develop computational tools to assess some of the 3D features characterizing the structures and interactions of a complex class of polysaccharides: the glycosaminoglycans (GAGs). Among their compositions, GAGs belong to the large and challenging family of complex carbohydrates. Moreover, their polyelectrolyte character and polymeric composition give them a special status, making GAGs one of the most complicated macromolecules to characterize. These difficulties are at several levels, from the isolation, synthesis of GAGs oligosaccharides to build large and diverse libraries, sequencing and analysis by mass spectrometry, to biophysical methods to study the binding interface. The development of molecular modeling methods is also required to characterize the structures and dynamics of GAGs per se and to assess the unique features that characterize their interaction with proteins. Computer simulations are not a standalone method for studying GAGs and their interactions with proteins but a complementary tool that can be used with experimental methods and other computational methods to gain a deeper understanding.

The construction of the thesis follows a presentation based on interrelated sections covering the introduction, a presentation of the methods of structural glycobiology, the inclusion of seven research articles, and a conclusion.

The seven articles provide the backbone of the narrative presentation of the thesis. These articles have been published in international peer-reviewed scientific journals, with Mateusz Marcisz

as the first author. Their publications warrant the quality and soundness of the reported findings in the context of the collaborative efforts of the associated co-authors.

Therefore, the introduction, discussion and conclusion sections, which cover 60 pages of the thesis manuscript, provide a way to evaluate the personal soundness and mastering of the concepts.

After a general and concise presentation of GAGs, an overall description of the main methods used in GAG-related studies is given. It illustrates the contribution of computational methods to unravel the complexity of interactions between GAGs, proteins and surrounding media in addition to experimental methods. The presentations follow a classical description of the methods: the general way to perform molecular docking and the strategies and applications of GAG molecular docking. The principles and applications of molecular dynamics are described in extenso in the all-atom and coarse-grained approximation, with appropriate illustration to GAGs. The thermodynamic properties of receptor-ligand binding are conveniently described throughout a presentation of free energy calculations. The analysis of the role of water in the computational studies of GAGs completes the diversity of methods and issues addressed by Mateusz Marcisz.

A brief introduction to the seven published articles helps the reader appreciate Mateusz's contributions to developing novel approaches to GAGs, their analysis with proteins, and the analysis of the role of water in GAD computational studies. A very comprehensive reference section with 484 entries completes the presentation.

Overall the integrative expertise acquired by the candidate is unique. The work highlights the power of integrating computational methods such as molecular dynamics simulations to understand and predict crucial three-dimensional features. Such features drive and amplify how to assess and build a rationale for integrating molecular modelling results within the range of methods required to decipher the complexity of the features that underline the properties and the physiological role of GAGs.

The quality and quantity of results summarized in the reviewed document "*Development of novel computational approaches for Glycosaminoglycans*" fulfil the PhD thesis criteria.

The extension of these results can be the source of novel interrogations and questions that will be formulated during the oral defence.

Point 1. The thesis lacks an informed presentation of the ExtraCellularMatrix (ECM), the non-cellular component in all connective tissues, and has a specific composition for each tissue. It comprises a complex and highly organized three-dimensional macromolecular network of biomolecules. These include fibrous proteins (such as collagens, elastins, and laminins), proteoglycans and glycosaminoglycans, hyaluronan, and their cell receptors, such as CD44 and integrins. The ECM is constantly remodeled by the balance between the synthesis and degradation of its components.

Do you have any idea about the density of the ECM ? How can some of the results assembled in the thesis be transposed to deal with such a dense environment?

Point 2. The model which has dominated our scientific minds is that a unique biological function of a protein is defined by its specific highly structured state determined by the amino-acid sequence. However, many protein functions do not require a unique structure, the so-called Intrinsically Disordered Proteins occur in all proteomes of organisms in all kingdoms of life, and the abundance of the disorder increases proportionally with organism complexity. There are pieces of evidence of the occurrence of such highly disordered proteins in the ExtraCellularMatrix, for example, CD44, to which Hyaluronic Acid is the primary ligand. CD44 displays both ordered and disordered regions. The disordered region is an Intrinsically Disordered protein that plays a crucial role in the function of the receptor.

How do you foresee the role of computational modeling in dealing with this new level of complexity?

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