Annex 7: Habilitation thesis reviewer's report

Masaryk university	
Faculty	Faculty of Science MU
Habilitation field	Biomolecular chemistry
Applicant	RNDr. Radka Svobodová Vařeková, Ph.D.
Unit	National Centre for Biomolecular Research, PřF MU, Brno
Habilitation thesis	Analysis of Biomacromolecular Structural Fragments
Reviewer	Doc. Mgr. Daniel Svozil, Ph.D.
Unit	Laboratory of Informatics and Chemistry, Faculty of Chemical Technology, University of Chemistry and Technology Prague

Reviewer's report

Dr. Svobodová Vařeková works in the field of structural bioinformatics and cheminformatics. Though her thesis is entitled ‚Analysis of Biomacromolecular Structural Fragments', it actually covers a wide range of diverse topics only a fraction of which concerns biomacromolecular fragments. The thesis consists of two parts: 50 pages of an introduction and commentary and the collection of 16 peer-reviewed journal articles. The articles cover four major topics: small molecule structure validation, the detection and characterization of biomolecular channels, biomolecular structure comparison and partial atomic charge calculation. Formally, the work is well designed, tables and figures are adequate and informative and references are representative. However, some facts are described ambiguously which makes reading and understanding the manuscript a bit harder. For example, at page 4, methods for 3D comparison of organic molecules are categorized into implicit and sequence alignment-based approaches. Nevertheless, this distinction applies to atom pairing identification that is only a part of 3D comparison. In addition, though a term 'organic molecules' is used in the text, sequence alignment-based approaches can, probably, be used only for biomacromolecules. Fortunately, these small slip-ups can't conceal undeniable scientific novelty Dr. Svobodová Vařeková contributed to each of her areas of expertise, as is documented by papers from high-quality peer reviewed scientific journals. In addition, I'd like to also point out to Dr. Svobodová Vařeková complex qualification. In her habilitation thesis, she proved familiarity not only with many bioinformatics and cheminformatics methods, but also with various approaches of computational chemistry. In conclusion, the thesis clearly demonstrates Dr. Svobodová Vařeková ability to perform an independent research using a sound scientific methodology.

Reviewer's questions for habilitation thesis defense

1. At page 13, four different classes of algorithms (grid-based, sphere-filling, slice and optimize, and Voronoi-based) for tunnel detection in biomacromolecules are briefly described. What are advantages and disadvantages of these approaches? Why Voronoi-based method was chosen to be implemented in MOLE?
2. MOLE, CAVER and MolAxis are listed as three existing Voronoi-based methods. Two (MOLE and CAVER) of these three approaches come from the same country, city and university. What are the differences between latest versions of MOLE and CAVER? Are there any plans to unite these two into one package?

3. Biomolecular structural comparison is one the most important tasks in structural biology and bioinformatics. Thus, many different approaches were developed and published. However, chapter 2.3.1., describing the state of the art in biomolecular structural comparison, fails to give an overview of existing algorithms. What was the motivation for the development of a new approach (SiteBinder) and how does SiteBinder compare to already existing methods?
4. SiteBinder uses a combinatorial and subgraph matching approach to identify individual atom pairings. Both approaches are computationally demanding, subgraph isomorphism is, for example, NP-complete. What are complexities of these algorithms, as implemented in SiteBinder, in Big O notation? Do there exist any alternative, faster methods?
5. OpenBabel is certainly an important cheminformatics toolbox. However, RDKit seems to be at the cutting edge at the moment. The inclusion of EEM charges into RDKit, that offers only Gesteiger charges, would certainly be beneficial for a wide cheminformatics community. Are there any plans to do so and if not, I personally would urge you to do so.
6. The applicability of EEM charges in proteins was demonstrated on docking glycerol into ubiquitin. In this experiment, EEM poses were compared to a QM pose that is considered to be ideal. Why a QM pose, and not an experimentally derived structure of the glycerol-ubiquitin complex (or any other ligand-protein complex), is taken as a benchmark?
7. Models for the prediction of pKa are derived only for uniprotic compounds and predicted pKa is, thus, macrostate. How would you predict microstate pKa in multiprotic compounds?
8. Approximately, how much faster are EEM charge calculations than QM charge calculations?

Conclusion

The habilitation thesis ‘Analysis of Biomacromolecular Structural Fragments’ submitted by Radka Svobodová Vařeková meets the requirements applicable to habilitation theses in the field of Biomolecular chemistry.

Prague, 12.8. 2016

Doc. Daniel Svozil, Ph.D.