Habilitation Commission
Charles University, Prague, Albertov 6, 12843 Prague 2
Czech Republic

Prof. RNDr. Tomas Obsil, PhD
Head of Habilitation Commission
Charles University, Prague, Albertov 6, 12843 Prague 2
Czech Republic

RE: habilitation thesis review for RNDr. Jiri Vondrasek, CSc.

Vienna, September 18th 2018

Dear prof. Obsil, dear members of the Charles University Habilitation Commission, dear Sir or Madam,

it is with enthusiasm and pleasure that I write this letter of review assessing the habilitation thesis of RNDr Jiri Vondrasek submitted at Charles University in Prague. The thesis is a comprised of a series of original, peer-reviewed articles by Dr. Vondrasek that were published in reputable journals in the area of physical chemistry and/or biochemistry including some of the top journals in the field as well as several leading interdisciplinary journals. The principal topic of the thesis is the usage of advanced computational approaches to study the key stabilizing features in globular proteins. The question of what stabilizes proteins at the atomistic level is an extremely important scientific question with implications extending to diverse fields ranging from molecular biology to biomedicine to nanotechnology. The habilitation thesis by Dr. Vondrasek provides a timely, original, methodologically advanced contribution to this question as further explained below.

The positive qualities of Dr. Vondrasek's thesis extended in three principal directions. First, the work presented in the thesis fills in an important gap in our understanding of proteins stability by focusing on the pairwise interactions of the fundamental building blocks in proteins, amino-acid residues. This problem has, of course, been studied before and in different contexts, but Dr. Vondrasek's thesis raises our understanding of the key open questions involved to a completely new level and, as a whole, provides one of the most compelling arguments that many key aspects

concerning proteins stability can indeed be understood by a careful dissection of the pairwise interactions of individual residues. Moreover, the work by Dr. Vondrasek also provides a detailed analysis of the open problems and challenges in the field and, in this sense, also serves as a stimulating foundation for the future work to come. The second principal quality of the presented work is its comprehensive nature. Specifically, the biologically relevant contributions to protein stability are studied in a systematic, quantitative fashion from different directions, including importantly quantum-mechanical description at different levels. What is important to mention here is that the work of Dr. Vondrasek and coworkers provides, on the one hand, a detailed analysis of several select types of specific interactions in proteins but, on the other hand, also give a panoptic, systematic dissection of such interactions at a level of, for example, all amino-acid types. It is precisely this expert treatment of key interactions from both local/specific and global/general standpoints that makes this thesis a standout contribution. Finally, the third strength of the thesis is that it presents an openly-accessible, web-based tool for the community, the INTAA server, which provides the calculation of the residue interaction energy matrix for a protein structure of interest, but also gives a detailed analysis of interfaces in protein-DNA complexes. As a service to the community and an important resource in-and-of-itself, the server is likely to become a widely-used tool in the analysis of the fundamental properties of proteins and nucleic acids alike.

While the work by Dr. Vondrasek, as presented in the thesis, focuses predominantly on the enthalpic part of the pairwise interaction energies in proteins, a potentially important, open area also involves the entropic part of the interactions involved. Entropy, of course, enters implicitly in the analysis of known protein structures, but is not necessarily central in all of the treatments presented in the thesis, especially those based on quantum-mechanical approaches. On the one hand, it may be that the enthalpic contributions are indeed the dominant part of the interaction energy, as Dr. Vondrasek and co-workers argue in multiple places. On the other hand, I personally find a more comprehensive comparison of the enthalpic contributions with the entropy-containing free energy of interactions as an important future direction to explore. This should not in any way be taken as a criticism of the thesis, but rather a stimulation for future work.

Overall, and for the reasons stated above, I find the submitted thesis to be fully adequate in quality and scope and I wholeheartedly and without any reservations recommend RNDr. Jiri Vondrasek for the title of Docent/Associate Professor at Charles University in Prague. Should you have any questions or concerns, please do not hesitate to contact me directly.

Sincerely,

Bojan Zagrovic, PhD

Professor of Molecular Biophysics

Department of Structural and Computational Biology
Max F. Perutz Laboratories, University of Vienna
Campus Vienna Biocenter 5, A-1030 Vienna, Austria
email: bojan.zagrovic@univie.ac.at
http://www.mfpl.ac.at/groups/mfpl-group/group-info/zagrovic.html
Tel: +43-1-4277-52271
Fax: +43-1-4277-9522