***D**ynamique des **S**tructures et **I**nteractions des **M**acromolécules **B**iologiques*
INSERM UMR_S 1134 – Univ. Paris – Univ de la Réunion - INTS - Laboratoire d'Excellence GR-Ex

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Paris, 2nd April 2020

Object: Habilitation Dissertation of Dr Hoksza

To whom is concerned,

To be the opponent (or external examiner) for the Habilitation Dissertation of young researcher is always a difficult and sometimes exquisite exercise. The evaluation must be honest, equilibrated and scientifically flawless. The researcher during the last years must have shown his/her abilities to do good collaborations, to drive as Principal Investigator pertinent researches, and to publish good papers in recognized journals. Reading the manuscript presented by Dr. Hoksza allows us to respond more than positively to all these points and even goes beyond it.

An essential point of scientific work is the valorisation by the publication of articles in recognized journals of the field, in significant number and in positions that shows the major participation in these work. On this point no problem, Dr. Hoksza has 9 articles on the period selected, including 2 first and 6 last author. Journals are at the forefront with *Bioinformatics* (1), *Nucleic Acid Research* (2), *BMC Bioinformatics* (3), *Journal of Cheminformatics* (2) and *IEEE / ACM transactions on computational biology and bioinformatics* (1), already demonstrating all the quality of the research done.

Another point which the reading of the document shows is the educational quality of Dr Hoksza. Presented in 3 balanced parts, it first brings the bases of knowledge on biological macromolecules with the essential concepts that it has addressed in recent years. Then, he proposes to follow his major research axes: (i) RNA functional analysis and (ii) protein interactions with protein-ligand and protein-protein binding sites.

Concerning the RNA functional analysis, Dr Hoksza had focussed on the arduous question of comparison of RNA structures His approach named SETTER for SEcondary sTructure-based TERtiary Structure Similarity Algorithm. The methodological interest of SETTER is to decrease the number of elements to be compared by representing each RNA structure by a set of non-overlapping generalized secondary structure units. Interestingly, it was as good or better than existing approach with (i) several times lower runtime and (ii) allows the superimposition of largest structures which cannot be handle by other approaches. He extended the approach to multiple structure superimpositions with MultiSETTER by adapting the well-known ClustalW algorithm. It was the first 3D structure-based solution at the time of publication. Both approaches were rigorously evaluated. Importantly, the methods were provided to the scientific community as

efficient webservers, but also as binaries and raw codes. This point is essential and shows the quality of the research done by Dr Hoksza.

We can notice the interesting new developments on secondary structure visualization. The idea behind Traveller software is to use already know representations of templates that shares good 'homology' with the query and do –with a minimal number of operations- a homology construction of the new representation. The result is very well made, and is made available to the scientific community in the form of containers.

Dr. Hoksza then extended his research to the competitive world of binding sites. The change does not just affect the type of macromolecules but also the description of these macromolecules as well as the methodologies used. For protein-ligand sites, it uses classic and robust descriptors linked to random forest approaches to improve pocket scores. These are often done with a single methodology. Here, a fine combination is made by this machine learning approach, and above all is strictly evaluated with several data sets. The approach named PRANK for Protein RANKing, is still made available in the form of a website. Improvements have been made with the following approaches, namely PRANK2, such as conservation and a wide range of pocket detection have been tested. A dedicated webserver named PrankWeb provided a large set of information both as text and visual rendering useful for the specialist and the non-specialist.

Finally, he prolonged this research on the protein – protein interaction site, a competitive area. Coarsely, the main idea was to use the neighbour amino acid information encoded as fingerprints (to improve storage and informatics efficiency) with graph comparison to provide with large dataset efficient results. The software is currently developed and accessible at a GitHub repository.

Hence, these recent works show clearly an excellent quality in the design of the research, of the development and usage of efficient methodologies to answer to complex bio/chemical questions, extensive and rigorous evaluation of the results to ensure the absence of bias, a very good level in computer science with quite different languages, valorisation in terms of papers evaluated in recognized peer-reviewed journals and, an essential point, a systematic providing of the methodologies developed to the scientific community in the form of webservers and / or software. Moreover, he had showed his abilities to adapt to new scientific areas and new methodologies with great efficiency. He is obviously an international recognized expert; his excellent papers in top Bioinformatics and Cheminformatics journals undoubtedly underlined it.

To conclude, I have the highest opinion on the works presented by Dr Hoksza, showing clearly all the quality of researcher needed for an Associate Professor in a world class University.

Yours sincerely,

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