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Review report on the doctoral dissertation by Selvaraj Sengottiyan
„From organic molecules to the nanoscale: The computational framework to design and improve functional materials"

The dissertation by Mr. Selvaraj Sengottiyan supervised by Prof Tomasz Puzyn and Dr Alicja Mikołajczyk presents a methodology and examples of computer-aided materials design for biomedical applications. It is a computational work combining molecular simulations at different resolutions, statistical modelling, and machine learning. The topic of the work is in the area of active interest of the research community and has numerous practical applications.

The development of sensors and drug nanocarriers in medicine is currently experiencing an unprecedented rise for multiple reasons: the progress in the synthesis and characterisation of nanoscale entities, the progress in visualisation and imaging of these in live tissues, and the progress in information technologies including computational techniques and machine learning. The latter greatly benefit from the increasing amounts of good quality data generated and collected in digital formats. The thesis by Mr Sengottiyan convincingly illustrates these developments and the new possibilities arising from a combination of computational chemistry with data science and machine learning.

The thesis is structured around four examples of computational studies of biomedical applications. It starts with a literature review and justification of the study. Chapter 1 also contains a description of the methodology used later in the case studies. The molecular modelling component of the thesis includes several advanced techniques: electronic structure calculations using density functional theory (DFT), atomistic molecular dynamics, and docking. A short Chapter 2 presents the subject of the study, while Chapter 3 formulates its main hypotheses. Chapter 4 provides summaries of the four case studies and their main results. Finally, Chapter 5 presents the conclusions and outlook. The four case studies include: (i) a computer-aided molecular design of pyrene-based antimicrobial substances using quantum chemistry and docking, (ii) an atomistic molecular dynamics study of nanoparticle uptake into cells depending on the nanoparticle charge at different pH conditions using advanced sampling techniques; (iii) a development of novel descriptors and a nano-QSPR model to predict the zeta potential of coated nanoparticles; (iv) a computer-aided optimisation of rapid colourimetric detection of CN- ions.

The computational techniques and the analyses selected in this work seem adequate in each case, which is confirmed by the successful completion of the case studies. The literature review is exhaustive and contains the most important papers on the topics and shows the familiarity of the candidate with modern scientific literature. In all the published papers, the studies are carefully and thoughtfully designed and the predictions of computational models are validated either by more accurate simulations or experimental data. The high quality of the numerical work is certified by peer-reviewed publications in high-impact international journals. I would like to specially emphasise the importance of one of the main results: a description of the nanoparticle-protein corona complexes using novel descriptors. This part of the dissertation contributes to the development of a novel paradigm in nanomaterials design and safety assessment. The challenges in the materials design are related to the complexity of the bionano interactions and the variability of the nanoparticle properties in biological media. This variability is reflected in extrinsic properties on nanoparticles such as surface charge and zeta potential. The possibility to predict those from more basic descriptors will make a major impact on the field.

Overall, the thesis is well structured and delivers the main messages well. The language of the thesis, however, is often imprecise and inconsistent. I give some examples below.

In the text of the dissertation, two quantities are used as full synonyms: nanoparticle surface charge and zeta potentials. For example, on page 16: “process of agglomeration mainly depends on the surface charge (zeta potential (ζ)) of the nanoparticle”. Surface charge and zeta potential of a colloidal particle are different quantities that are related to each other in a complex and non-unique way. Can the candidate explain the difference between these two? How does each of them depend on the external conditions? Finally, at what conditions and in what sense one can synonymise these two quantities?

Further, on page 26: “The agglomeration process depends mainly on the zeta potential…”. Zeta potential does not appear in any theory of dispersion stability I know of. Can the candidate explain the meaning of zeta potential and how it is related to particle aggregation?

Some sentences have logical problems. On page 16:

“This is directly related to the degree of cellular absorptivity of the nanoparticle, which leads to the measurement of the risk assessment of the materials so that the development of new nanomaterials is always based on a comprehensive risk factor.” – Can the candidate clarify what is meant here?

On page 19: “the structural features of nanoparticles present significant difficulties in the development of functional materials.” – If the structural features of nanoparticles are a problem, why would one use them at all? How are these features different from the features of bulk materials?

On page 20: “to evaluate density functional theory calculations (DFT)” What is actually evaluated?

On page 23: “modeling usually uses pure/pristine materials, which leads to problems with accuracy.” – I suppose, the problem is not with the accuracy but with something else. What is the actual problem with the modelling?

On page 28: “The application of computational models based on MD and MD” – What is actually meant here?

On page 31: “The Hamiltonian of the single-electron system is as follows...” - Equation 2 is not a Hamiltonian but a Schroedinger equation. The equation itself is misformed.

On page 32: “To obtain the molecular dynamics simulations of the BSA–PS complex, the first confirmation was extracted from the docking studies.” – What exactly was aimed to be obtained?

On page 32: “The second term is a directed H-bond term with a potential of 10/12.” – In the equation itself, the second term labelled “hbond” is 6/12. Which of these is correct?

On page 33: “BS-APS complex was initially energetically reduced” – In what sense is the complex reduced?

On page 33, equation 5: The Coulomb term is lacking 1/r factor.

On page 33, equation 5: What is the meaning of “improper” term in the force field?

On page 34: What are the “inappropriate” interactions?

On page 34: “Equation (9) describes the molecular mechanism.” – What is the meaning of that equation?

On page 40: “all h-bonds with atoms were subjected to the limitation technique LINCS” – What is the meaning of the “limitation technique”?

On page 40: “A cut-off value of 10 Å was used for the application of the Lennard–Jones interactions, which was then reduced to 12 Å.” – Reduced or increased?

On page 42: “This discovery leads us to conclude that the drug transport mechanism begins when the dihedral angle (ϕ) of the pterin ring becomes linear, while cell uptake is more favorable when it is perpendicular to the drug molecule.” – What is perpendicular to the drug molecule? How can the angle become linear?

On page 44: “both nanoparticles on the left side of the curve have a greater energy barrier due to the characterization of the permeation of nanoparticles into the hydrophobic tail of the bilayer core.” – The sentence sounds confusing. Can the candidate explain the origin of the energy barrier?

On page 46: “it is clear why there is a higher solubility and nanoparticle distance ratio with the head groups of the membrane.” – This sentence is confusing. Can the candidate clarify it?

On page 46: “free solvation energy” – What is the meaning of this term?

On page 48: “Therefore, it is possible to maximize the scale of the model, which better predicts the prediction error of the most influential sample of compounds.” – What does the model actually predict?

On page 54: “I hypothesize that these two compounds are likely to absorb cells.” – Can the candidate clarify what is meant here?

On page 54: “However, the idea of a negative zeta potential (-4 for PS_CF1), which can adsorb proteins that occasionally have very little or no absorption and are still a mystery in our situation, is controversial.” – Can the candidate clarify what is meant here?

On page 61: “we focused on the proteins covered by the nanoparticles” – No such systems are discussed in the text.

The above issues, however, do not detract from the merit of this tremendous work. Given the amount and quality of presented research (4 papers as a first author and 8 additional co-authored papers in top international journals) and the diversity and complexity of the used research methods, I do not doubt that the candidate achieved the required qualification. He has convincingly demonstrated his mastery of physical and theoretical chemistry as well as computational techniques and data analysis. The presented thesis meets the requirements specified in the regulations of awards of the Faculty of Chemistry of UG. I am happy to recommend awarding a doctoral degree to Mr Selvaraj Sengottiyan.

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