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Recenzja rozprawy doktorskiej magistra Selvaraja Sengottiyana pt. „From organic molecules to the nanoscale: The computational framework to design and improve functional materials"

The results presented in the thesis relate to the research topics of the dissertation's supervisor Prof. Tomasz Puzyn and the co-supervisor Dr. Alicja Mikołajczyk. The topics of these works relate to nanotechnology, especially to nanoeffects modeling in silico. In the most general terms, the goal is the modeling and design of functional nanomaterials and their in silico effects. The design and synthesis of molecules with specific biological properties is a fundamental objective of chemistry and chemical synthesis. One of the most prominent modern chemists, Barry Sharpless, notes after Hammond that the most fundamental goal of chemistry is not to create new chemical compounds but to generate or "produce properties." However, property production is also the biggest problem of modern chemistry, for mapping the structure of chemical molecules into properties is a complex issue. As a rule in drug design, in silico models are based on molecules as simplified models of chemical systems. Materials, usually cannot be so easy represented by molecules. Let us take metals, typical materials used, for example, for making swords or knives. Their bonding extends into large distances formally into the super-molecule-like structure. Such structures need unique representations. Also, drugs can need material type representation to analyze a modified-release tablet or nanosystems for modifying drug substance release or transport, or even to describe molecular aggregates. Modeling materials requires considering their complete structure determined by the ordering of atoms which can generally represent many molecules and many different atoms.

Comparing drugs vs. materials helps to understand the methods engaged in their development. Modeling drugs involves small organic chemical compounds typically structured by the C and H atoms, while materials are formed also by different atom types. The ligand-receptor moiety (for drugs) is a highly complicated molecular scale system. We need sophisticated chemical or biophysical experiments to observe this system. Still, many phenomena are too complex for an easy explanation. In turn, the material's structure is assembled beyond the single-molecule scale. We need complex descriptors for the proper representation of these structures. The larger scale decides, however, that we can often examine materials and their interaction with the environment more quickly in bench chemistry. At the same time, in silico simulations of larger systems can cause problems. Materials informatics is the term used recently to organize materials discovery, forming an extension of chemoinformatics to materials.

This brief introduction will allow us to understand and describe the subject of the current research quickly. In the briefest terms, the thesis title fragment, "from organic molecules to the nanoscale" reflects this well. The author simulates systems of different molecular scales. The design of drugs and materials of different types is the common topic of the investigations broadly covering basically unrelated molecular objects. The thesis is a collection of four publications: (i) **Sengottiyan, Selvaraj,** Kakoli Malakar, Arunkumar Kathiravan, Marappan Velusamy, Alicja Mikolajczyk, and Tomasz Puzyn. Integrated Approach to Interaction Studies of Pyrene Derivatives with Bovine Serum Albumin: Insights from Theory and Experiment. *J. Phys. Chem. B* 2022, 126, 3831−3843. [IF 2021 = 3.466; MNiSW 2021 =140]; (ii) **Selvaraj**

Sengottiyan, Alicja Mikolajczyk, Tomasz Puzyn. How does the study MD of pH-dependent exposure of nanoparticles affect cellular uptake of anticancer drugs? *Int. J. Mol. Sci.* 2023, [IF 2022 = 6.208; MNiSW 2022 =140]; (iii) **Selvaraj Sengottiyan,** Alicja Mikolajczyk, Karolina Jagiełło, Marta Swirog, and Tomasz Puzyn. Core, coating, or corona? The importance of considering protein coronas in nano-QSPR modeling of zeta potential. *ACS Nano.* 2023, [IF 2022 = 18.027; MNiSW 2022 =200]; (iv) Kathiravan, Arunkumar, **Selvaraj Sengottiyan,** Tomasz Puzyn, Pushparathinam Gopinath, Kanagachidambaresan Ramasubramanian, Praveen Ayyappan Susila, and Mariadoss Asha Jhonsi. Rapid colorimetric discrimination of cyanide ions–mechanistic insights and applications. *Analytical Methods.* 2022, 14, 518-525. [IF 2022 = 3.532; MNiSW 2022 =70].

Publications i-iv involve various molecular modeling methods covering the title regions "from the molecule to the nanoscale" of the molecules and materials. What deserves to be emphasized is the neatly constructed introduction, which, on the one hand, provides an excellent introduction to the theoretical basis of the work's problems, and, on the other hand, allows the reader to understand the common denominator for the atomic models described by the thesis. In a similar manner, the author formulates the four hypotheses on pages 29-30.

Paper (i) describes a study of the simulation of pyrene derivatives with bovine serum albumin by molecular docking and molecular dynamics methods. In the doctoral commentary, the author discusses in detail the technical issues of the methodology of his calculations, which yield results that correlate in terms of the trend with experimental binding energy studies conducted for two pyrene derivatives synthesized in the laboratory by a team of cooperating synthesists.

Paper (ii) describes simulations of the effect of pH on the transport of nanoparticle drugs in areas affected by cancerous lesions. Nanoparticle uptake to cancer cells are limited by a variety of factors involving nanoparticle physicochemical properties, protein-particle interactions, and subsequent agglomeration, diffusion, and sedimentation. Publication (ii) is a molecular modeling study addressing these mechanisms for the series of drug-loaded nanoparticles extracted from the literature, including methotrexate. The author research is an MD study to understand how the charge, geometry, and energetics of drug-loaded functionalized nanoparticles affect cellular uptake at three different pH levels: neutral pH, tumor pH, and stomach pH of 7.0, 6.4, and 2.0. According to this analysis, the tumor pH has a high dipole moment compared to other models, which ultimately affects the penetration forces within the cell membrane. The study is of potential interest for practical nanodrug candidate design. However, the publication lacks experimental attempts to prove the performed simulations.

Publication (iii) defines a machine learning-based model based on the nanoparticles' structure (core and coating descriptors), their PC fingerprints in the biological medium defined by the so-called corona descriptors, and the nano-QSPR model with a value of zeta potential (ζ)-value nano-QSPR model. The author studies seven types of polymers and seven functional groups. The study models the behavior of 80 different proteins absorbed on the surface of nanoparticles. Descriptors were calculated using the Dragon software. The author correctly applies the QSAR modeling methodology, modeling the zeta potential and showing the importance of specific interactions (core and coating features) for nanoparticle transport in real environments, which determines, for example, the toxicity of such nanoparticles.

The publication (iv) involves experimental studies and computer simulations. In silico methods aim to clarify the results of colorimetric tests using a cyanide ion probe. Detection of such ions is a fundamental analytical problem. In the experimental part, the research is based on a spectroscopic test. The co-authors also constructed a 3D-printed portable accessory for the smartphone and an open-source android application. The simulations performed by the author help explain the observed probe response. "The malononitrile-functionalized DMN probe prevents intramolecular charge transfer when cyanide ions are added, leading to the

development of a Michael adduct at the site where the dicyanovinyl group is cyanide β-conjugated." Technically, in silico modeling is the DFT study.

The thesis has a form typical for a dissertation of a new type, i.e., a commentary on a collection of co-authored publications. The thesis also includes "co-author statements" to the publications. The commentary is 80 pages long. It consists of a summary of the research conducted, an introduction, a section discussing the literature, the author's research methodology (in silico simulation), the research hypotheses and objectives (statement of the research project), and a commentary on the publications i-iv (A-D). The author cites 175 literature items.

The thesis discusses molecular modeling problems in the literature section, neatly finding a common topic for the vast research subjects. The paper is written in English. Mature scientific language and correct wording are confirmations of a high level. A great asset of the thesis is the outstanding journals in which the publications i-iv were published, e.g., ACS NANO or J. Phys. Chem. B.; the total IF is about 31 (550 points MEiN). Publications in such prestigious journals would not have been possible if it were not for the other strengths, which are the very timely and important research topics and the combination of experimental results and computer simulations, especially in publications A and D.

The author correctly applies the broad methodology of molecular design research. The scope of the research conducted must be highly respected. The author is proficient in QSAR modeling, DFT and MD calculations and correctly applies their methodologies.

However, as a rule, the results of in silico simulations often depend heavily on the parameterization, differences in the software used, etc. For example, in publication (ii), the author observes a correlation between calculated and experimental binding energies, but the absolute values of calculated and experimental parameters differ significantly. A pragmatic solution is to use docking and MD methods in the so-called consensus voting version, i.e., using several different programs and then selecting the most frequently occurring, e.g., (J. Chem. Inf. Model. 2022, 62, 14, 3415-3425). The inclusion of water molecules, e.g., in MD simulations, e.g., (J. Chem. Inf. Model. 2019, 59, 6, 2818-2829), plays a similarly important role in simulating interactions with proteins. I wonder why the author did not use consensus modeling methods. Were the protein structures supplemented with water molecules?

The next issue considers the problem of the differences between drug and materials discovery. How would we differentiate between these areas, and how would the Doctoral candidate classify his investigations? This issue relates to the title "from the molecules to the nanoscale. Can the performed simulations explore uncharted materials space? What should we target in the most general sense in the materials discovery (compare: JACS, 2022, 144, 18730).

In general, the thesis is written clearly. What deserves to be emphasized is the mature way of describing the results. After all, the results were published in articles in outstanding scientific journals. Of course, I am finding some minor errors in the text. e.g.:

str.7 The future of European industry requires advances in the development and characterization of advanced chemicals and organic compound chemicals in combination with nanoforms of the substance (…)

Almost true, but imprecise. After all, the author means:

The future of industry requires(...), which is also a priority for EU.

str. 29 The cell membrane itself is a major barrier that drug molecules cannot easily penetrate, which is why many drugs fail in the clinical trial phase.

We should say more accurately: many *drug candidates* fail in the clinical trial phase.

I wonder how much the organic chemistry definition (p. 11) "*everything but CO*" (page 11) is correct. What about, for example, carbonic acid salts, etc.

The more general remark is that the commentary may include a short, more general description of the publications, including the experimental part, which could provide the reader better insight into the investigations. To look inside this part, we should go directly to the publications themselves, while the author only focuses on the computer simulation part.

The Doctoral Student co-authors twelve scientific publications with a total IF of 62 and a MEiN score of over 1,000. This record is an outstanding achievement at the doctoral level. He is the first author of all the publications in the series (A-D). Summing up this part, the output far exceeds the requirements for a doctoral thesis. Therefore, considering the substantive value of the results, it is worth considering awarding Mr Selvaraj Sengottiyan a pass with distinction. The high level of the research, significantly contributing to in silico nanochemistry, describing methods for simulating such systems with various chemoinformatics methods justifies the request for an this award. The research scope and maturity indicate that the Doctoral Student has significantly exceeded the required level of the doctoral dissertation. Also, the manner of preparation of the dissertation deserves appreciation. The language of the commentary is correct. It reads with pleasure and interest. The thesis results were published in prestigious chemical journals with high scientific parameters. The thesis meets the requirements specified in the regulations of awards of the Faculty of Chemistry of UG. Therefore, with conviction, I suggest awarding the work of Mr. Selvaraj Sengottiyan, MSc.

For a formal reason below are short final conclusions in Polish:

Doktorant jest współautorem dwunastu publikacji naukowych o łącznym IF 62 i liczbie punktów MEiN ponad 1000. To bardzo dobry dorobek na etapie dorobku doktorskiego. We wszystkich pracach serii doktorskiej (A-D) jest pierwszym autorem. Podsumowując ten fragment, dorobek Doktoranta znacznie przekracza wymogi określone dla pracy doktorskiej. Biorąc zaś pod uwagę merytoryczną wartość pracy, sądzę, że warto rozważyć wyróżnienie przygotowanej przez Doktoranta rozprawy. Wniosek o wyróżnienie uzasadniania wysoki poziom merytoryczny pracy, która wnosi istotny wkład w nanochemię *in silico*, opisując metody symulacji takich układów różnymi metodami chemoinformatyki. Zarówno zakres przeprowadzonych badań, ich dojrzałość wskazują, że Doktorant znacznie przekroczył wymagany poziom pracy doktorskiej. Także sposób przygotowania rozprawy zasługuje na docenienie. Praca napisana jest bardzo poprawnym językiem. Czyta się ją z przyjemnością i zainteresowaniem. Wyniki pracy opublikowane zostały w prestiżowych czasopismach chemicznych o wysokich parametrach naukometrycznych. Formalnie praca spełnia wymogi określone regulaminem wyróżnień Wydziału Chemicznego UG. Z przekonaniem wnoszę więc o wyróżnienia pracy pana magistra Selvaraja Sengottiyana.

Podsumowując, uważam, że przedstawiona mi do recenzji praca doktorska spełnia wymogi stawiane rozprawom doktorskim przez ustawę Prawo o szkolnictwie wyższym i nauce, w związku z czym wnoszę o dopuszczenie pana Selvaraja Sengottiyana do dalszych etapów przewodu doktorskiego.

Jarosław Polański