

Opponent's Review of Dissertation Thesis

Title: „Application of Electronic Continuum Correction to Molecular Simulations of Nano/Bio Interfaces“

Author: MSc. Denys Biriukov

Opponent: doc. RNDr. Marek Malý, Ph.D.

Author deals with the inclusion of electronic polarization of water molecules in MD simulations of selected solvated solid surfaces (titanium dioxide, silicon dioxide, gold), in order to obtain the most accurate detailed information about the interaction of water molecules and other components of the studied aqueous solutions (ions, oxalic acid or selected amino acids) with these surfaces, including the effect of solution pH (in cases of TiO_2 , SiO_2) on these interactions, using classical force fields with constant charges. In his work, the author takes into account the electronic polarization of solvent molecules, which is the part of their response to solvated charges, by suitable scaling of the original charges of solvated ions or charged molecular groups. Author demonstrates the benefit of this innovative approach on simulations of above mentioned systems, where he achieved more realistic description of interaction processes at the studied interfaces, in comparison with simulations performed with original (non-scaled) charges as confirmed by experimental results or ab initio calculations.

The work is divided into four main chapters. The introductory chapter explains the motivation and summarizes the scope of work, including a clear description of all presented molecular systems. The second chapter contains an explanation of the methodologies used both for the simulations themselves and those used for the analysis of simulated systems. The third chapter then forms the main part of the work, which describes the content and conclusions of the author's already published studies which are part of the work, but also those not yet published. The final chapter then briefly summarizes all the results of the work. Then follows a list of references and 6 enclosed professional publications DB1-DB6, of which DB1-DB5 have already been published and DB6 was submitted to the Journal of Physical Chemistry. The author also refers to manuscripts DB7 and DB8, which are not part of the work. In three cases author appears in the first place in the list of authors (DB1, DB2, DB5), in two cases he is listed second in order (DB6, DB7), in the works DB3 and DB8 he appears in the 3rd position and in DB4 he is listed as 4. co-author. The author's contribution to all of the above publications is considerable and consists in the preparation of all simulated systems, the realization of all MD simulations and consequent analyzes, including the use of his own routines. In connection with the publication DB5, the author even implemented the method of prediction the zeta potential from nonequilibrium molecular dynamics simulations into LAMMPS software. Last but not least, the author always significantly contributed to the text preparation of individual publications. All already published works were published in prestigious scientific journals with a high IF (around 4 in all cases).

The work is is very current and useful, both in terms of studied systems as well as the efforts to improve methodology of their simulation, especially if this improvement lies in only small modifications of commonly used force fields and therefore do not increase the time required for simulations.

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Author states that this work presents pioneering studies in application of Electronic Continuum Correction theory in MD simulations of solid / liquid interfaces. The text of the thesis is comprehensible and suitably supplemented by pictures of simulated systems, key graphs and tables that present the results of individual studies. The author often refers to the attached articles as well as other publications, whose list occupies a respectable 23 pages.

Here I would have only a small critical remark regarding the form of used links to this literature, where I would welcome the numbering (both in the links and in the list) and in the electronic version of the work an active links, redirecting readers after clicking automatically on the list page, which contains complete specification of the given reference.

Discussion topics for the defense

1) In work (page 26) author mentioned, that used water models for presented simulations were SPC/E ($\epsilon_r = 71$), TIP3P ($\epsilon_r = 82$) and TIP4P/2005 ($\epsilon_r = 60$) and that any water parameters were not changed for ECC simulations. So in ECC simulations where original solvated charges Q_i and Q_j are scaled by $1/\sqrt{\epsilon_r^e}$ where $\epsilon_r^e = 1.78$ (relative electronic permittivity of water), their electrostatic potential energy in the water model from the macroscopic point of view is $E_{ij} = \frac{1}{4\pi\epsilon_r^m\epsilon_r^e\epsilon_0} \frac{Q_iQ_j}{r_{ij}}$ where ϵ_r^m is the relative permittivity of the given water model. So it corresponds to solvation in solvent with the total relative permittivity $\epsilon_r^m\epsilon_r^e$ which is 126 in SPC/E, 146 in TIP3P, 107 in TIP4P/2005 so the values significantly higher than is the relative permittivity of water (ca 80). Would not be better to use within water-ECC simulations the water model, whose relative permittivity is as close as possible to $80/1.78 = 44.9$ and so the total relative permittivity $\epsilon_r^m\epsilon_r^e$ close to 80? What about the TIP4P water model ($\epsilon_r = 53$), whose total rel. permittivity (after inclusion of the electronic polarisation) is $1.78 * 53 = 94$?

2) Discuss the use of scaling charges of ions or charged molecular groups in a solvent by $1/\sqrt{\epsilon_r^e}$ in the context of their possible partial or complete desolvation as the result of attractive intermolecular interactions and formation of molecular complexes during simulation (protein-protein, protein-surface, ion- [lipid bilayer] ...) and compare to simulations without charge scaling.

3) Do you have any explanation for your result in the study devoted to the interaction of selected amino acids with the gold surface and simultaneous comparison of full-charge and ECC-charge amino acid models, that Arg behaves in the opposite way to the remaining charged amino acids (Lys, Asp, Glu), ie. that in the full-charge version, where its binding to the surface is more disturbed by interactions with water, similarly to the remaining charged amino acids, it has a stronger binding to the surface than in the ECC-charge version (i.e. with reduced charges)?

The author has demonstrated a very good ability of independent creative work consisting in obtaining a number of original results, as well as in their processing and interpretation. In my opinion, the work is above standard and its value and quality is evident from the publication of the most of the presented results in prestigious scientific journals, and therefore, of course, I recommend it for defense.

In Ústí nad Labem, 12.6. 2020

doc. RNDr. Marek Malý, Ph.D.



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Oponentský posudek disertační práce

Denys BIRIUKOV: Application of Electronic Continuum Correction to Molecular Simulations of Nano/Bio Interfaces

In his PhD thesis, by means of molecular dynamics simulations, Denys Biriukov, investigated the solution structure in the vicinity of rutile, quartz, or gold, which serve as a model nanoparticle surfaces. More specifically, this thesis presents a systematic study of a role of pH, surface charge density, and counterion quality (from simple to molecular ions and to charged amino acids) on the water structure, ion and amino acid distribution, and surface binding motives.

In order to gain an accurate and detailed insight in these interfacial processes, the candidate had to first develop novel generation of force-fields (introducing Electronic Continuum Correction) for rutile and silica surfaces as well as for oxalate anions and for amino acids. Importantly, the candidate was also involved in the development of NEMD framework, which allows for in-silico zeta potential determination. These accurate models&techniques were then employed to gather the microscopic insight and interpretation of experimental 'surface' data from collaborating experimental laboratories. This was the case of thermodynamic study of oxalate adsorption. The real-world molecular detail was then gathered via angle-resolved second harmonic scattering within the cooperation with the Laboratory for Fundamental BioPhotonics (Prof. Roke). In both studies, it was only the joint experimental-theoretical approach, which provided the consistent and reliable picture. Published work, the thesis, and the unpublished data demonstrate that the candidate and his supervisor are step-by-step approaching their ultimate goal, i.e., the quantitative molecular modelling of biomaterials on nano-interfaces.

Overall, the thesis is well build, chapters are systematically ordered, and the text, which well complements the already published results, is clearly written. Though, I would appreciate, if the thesis itself contains the Table with e.g. rutile parameters (or at least full and ECCR charges), which are currently in DB1-Table 4. It would help the reader, when reading and trying to understand the origin of observed differences between some systems, e.g. in part 3.2.

The candidate, who gathered solid background in MD simulations of nano/bio systems, benefits from being part of the research team of 2 GAČR projects, collaborating with quantum chemists, as well as from scientific exchanges with experimental collaborators.

Backed by 6 directly related publications in peer-reviewed journals (*Physical Chemistry Chemical Physics*, *Langmuir*, *Journal of Physical Chemistry C*), the PhD thesis of the candidate summarizes focused work on model Nano/Bio interfaces, with all the needed care and detail.



To summarize, I must clearly state that Denys Biriukov conducted independently very good theoretical research. His thesis and scientific work fulfils all criteria for obtaining PhD degree. Thus, I am happy to recommend Denys Biriukov being awarded the PhD degree.

Prague, June 11, 2020

RNDr. Mgr. Jan Heyda, Ph.D.

Questions for the defence that should be addressed by the candidate:

1. The deficiencies of LJ+full charge force-fields are known for a long time. However, variants, which very accurately reproduce hydration thermodynamics at infinite dilution (M. Fyta, JCP 132, 024911 (2010)), or solution thermodynamics (P.E.Smith, JCTC 2011, 7, 1369-1380) were derived. As the multivalent ion parametrization is more challenging, it is tempting to pragmatically follow the ECC approach. However, there are also other approaches in the literature, e.g., where the cross ion-water LJ parameters are readjusted (R.R. Netz, JCP 138, 024505 (2013)). Could the candidate comment on this alternative directions towards more accurate description of ions in solutions and potential applicability of such approach for the parametrization of rutile or silica surfaces?

2. The naive (or also pragmatic) understanding of the ECC approach is the scaling of all charges (or partial charges in case of molecular ions) by 0.75 factor. When reading through *DBI PCCP 2018*, I found that the ECCR partial charges for rutile are often in absolute value higher than those of full charges FF. I would like to ask the candidate to describe in more detail (for non-expert reader), how was the refitting of rutile partial charges performed. What were the target macroscopic/microscopic observable benchmarks used in the parametrization? Could the candidate comment on the transferability of his approach towards parametrization of soft bio-interfaces, e.g., in the direction of more realistic systems (e.g., Chandler, doi.org/10.1073/pnas.1110703108).

3. I like the Gouy-Chapman-Stern model way of description of ion-distribution near the 2D planar surfaces, where the tightly bound counterions and diffuse layer are introduced. Qualitatively correct and mechanistically easy to understand. I have a question to ion-affinity to 2D surfaces:

Motivated by ion-specific effects, Prof. Netz group published series of papers (R.R.Netz et al., Langmuir 2013, 29, 2602-2614) on affinity of simple-monovalent ions to surfaces of varying quality (from hydrophobic to charged). Would be such multi-scale approach applicable also in case of candidate's work with quartz, rutile, or gold surfaces?

4. In the context of polyelectrolytes (1D-chains), based on simple arguments, Gerald Manning, proposed so called counterion-condensation to occur, when line-charge density is sufficiently high (G.S.Manning, doi.org/10.1080/07391102.1998.10508261). Moreover, the fraction of condensed counterions can be calculated. Manning-condensation attracted a lot of experimental, theoretical and computational research (Smiatek, Soft Matter, 2018,14, 6243; Deserno, Macromolecules 2000, 33, 199-206).

Could the candidate comment on, whether analogous qualitative-theory, which would allow for the prediction of counterion condensation and its extent, is available for 2D surfaces?

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Report on Ph.D. thesis
of
MSc. Denys Biriukov

**“Application of Electronic Continuum Correction
to Molecular Simulations of Nano/Bio Interfaces”**

The dissertation of MSc. Denys Biriukov is a valuable contribution to studies of interactions of three different nanosurfaces (titania - titanium dioxide - TiO_2 , silica - silicon dioxide - SiO_2 and gold - Au) with water, ions, small organic molecules and amino acids. These studies are relevant to the design of nanodevices, which can be used in many areas from biotechnological applications to medicine (biocompatible implants, biosensors, drug delivery vehicles, antibacterial and antiviral nanoparticles etc.).

The thesis document consists of ~54 pages organized in four main chapters. Both published and unpublished data are combined to give an overall picture of author's achievements. The first chapter - Introduction - familiarizes reader with studied nanosurfaces, summarizes many open questions in this field and clarifies motivation, strategy and novelty of the work. The second chapter describes methods including Electronic Continuum Model (ECC) and advanced topics – biased (US) and non-equilibrium MD simulations (used for Zeta potential calculations). Next chapter presents main results, which are as follows.

a) The behavior of water molecules at TiO_2 and SiO_2 surfaces showed that ionic adsorption does not lead to any visible changes in density profiles of water. However, the preferred water orientation changes owing to this adsorption.

b) Further, it was shown that cations adsorb to quartz surfaces substantially weaker than to rutile. Interestingly, the shape of the Zeta-potential curves over pH is completely different. The behavior is rather trivial for quartz. Nevertheless, the sodium adsorption to rutile is so strong that a surface charge is overcompensated and Zeta-potential is always positive. This anomalous behavior could affect functioning of titania based nanoparticles in biological environment.

c) Another part of this work was devoted to the adsorption of the simplest dicarboxylic acid. Presented results clearly contradict with a common opinion that strong adsorption implies inner sphere adsorption, while outer sphere coordination means a weak adsorption.

d) Finally, unpublished results shed some light on the adsorption of amino acids to gold and rutile surfaces.

Then conclusions follow.

The dissertation itself, as far as I can judge, is written in good and understandable English. Its graphical lay-out is appended with nice instructive pictures. The thesis text is comprehensive and well-organized. The storyline is easy to follow and understand.

However, the individual chapters are always based on results from several papers (DB1-DB6), which are attached as appendices in chronological order rather than grouped thematically. Therefore, I would appreciate more clues in the main text as those provided on p. 43 (see Figure 2 in DB2, Figure 5 in DB2 etc.).

The whole work represents very suitable combination of various computational methods used to shed light on studied subject. It is evident without any doubts that MSc. Denys Biriukov masters wide range of advanced modeling techniques – including free energy calculations (US) and Zeta potential computation by means of NEMD using several different software packages (GROMACS, LAMMPS). Apparently, MSc. Denys Biriukov knows to suitably apply them to get valuable data.

The scientific results are of major interest and substantially contribute to the knowledge of interactions between molecules and nanosurfaces. There are enclosed six papers (with IF > 3.5). Two other manuscripts were submitted. Other papers could appear soon, if we take into account the amount of unpublished data.

In my opinion, the work certainly fulfils the requirements for Ph.D. thesis, and I recommend it for the defense.

Prague 11th June 2020

3amrk
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Questions:

- 1) Did you produce MD simulations using just a workstation or some powerful Linux clusters in a supercomputing center were needed? Exclusively CPU or even GPU were used?
- 2) Some "MUSIC-CD" data are included in Figure 3-7. Explain briefly essence of this "MultiSite Complexation – Charge Distribution" method.
- 3) As for amino acids and the widely used force fields AMBER and CHARMM. When parameterizing partial charges, it is taken into account - in different ways - that these molecules are in water.

A basis set for deriving AMBER partial charges, 6-31G*, uniformly overestimates molecular polarity. It leads to excellent relative free energies of solvation (Cornell et al., A Second Generation Force Field for the Simulation of Proteins, Nucleic Acids, and Organic Molecules, J. Am. Chem. Soc. 117 (1995) 5179-5197).

In contrast, the CHARMM force field emphasizes reproducing QM interactions with a TIP3P water molecule (Mayne et al., Rapid Parametrization of Small Molecules Using the Force Field Toolkit, J. Comp. Chem. 34 (2013) 2757-2770).

Resulting partial charges are quite different. Therefore, shouldn't the ECC scaling parameter be somehow force-field dependent?

- 4) For future MD simulations of interactions of nanosurfaces with amino acids, peptides and proteins, it would probably be good for their partial charges to be calculated using the same methodology.

As regards Quartz surface, for example, partial atomic charges were derived using the Natural Bond Orbital method (Kroutil et al., J. Phys. Chem. 119 (2015) 9274-9286).

Are you thinking about some alternative approaches that would bring parametrization of nanosurfaces closer to the way how force fields for biomolecules were derived?

For example, existing force constants for Silica (Lopes et al., J. Phys. Chem. B 110 (2006) 2782-2792) could be used as a starting point and forcefield CHARMM could be extended

using the Force Field Toolkit (Mayne et al., *J. Comp. Chem.* 34 (2013) 2757-2770), which enables creation of input files for QM calculations as well as subsequent fitting of all force constants.

5) Regarding adsorption of amino acids. It was stated in your thesis that there are no reference data that can validate your results. Maybe, as a first step, it would be interesting to compare solvation free energies of amino acids with full and ECC-scaled charges? (See Ngo et al., *Comparative Analysis of Protein Hydration from MD simulations with Additive and Polarizable Force Fields*, *Adv. Theory Simul.* 2 (2019) 1800106)

6) Charts in Figure 3-9 indicate a little bit counterintuitive adsorption of negatively charged amino acids on negatively charged rutile surfaces. These findings are precisely described and explained in the text. Yet it puts too high demands on my imagination. Please, show explicit pictures of atomic models illustrating water mediated anchoring of negatively charged amino acids to negatively charged surfaces.

7) Manuscripts DB7, DB8 were not attached to the dissertation. What are the main results of these papers?