Opponent report for a doctoral thesis

Name and surname of the doctoral candidate: Ing. Kryštof Březina

Title: Ab initio and path integral molecular dynamics methodology for hydrogen-bonded systems in the condensed phase

I have read the doctoral dissertation of the candidate with a great interest as my own expertise modestly overlap with the topics presented in it. It was a very pleasant read, as the dissertation uses not only correct and clear academic language, despite being occasionally a bit flowery (e.g., page 48 "non-negotiable"), and conveys the information in a very concise and "fresh" way allowing a rather deep understanding of complex topics in the span of only a few paragraphs. This applies to most of the thesis, with a few exceptions being the sections 2.3.3.3 or 2.2.4 (on modelling reaction rates and on GW approximation), which were more difficult to parse and properly understand, however, a very advanced character of these sections could represent an extenuating circumstance. Also, I very much value candidate's striving to motivate adopted approximations or explain the reported observations by resorting to simplified physical models and interpretations (e.g., as in section 4.2.3.2). The dissertation contains a minimum of typographic or grammar errors (but some could be still found, e.g., on page 108 - "Reference93" or on page 139 "which is has"). Also, the dissertation is well organized into sections, with the text being supported with numerous visually attractive figures described in great detail. I value, that the contributions of the candidate are, with a few omissions (Paper II and section 6 - first author publication though), explicitly described at the beginning of each section devoted to the results and that the candidate honestly describes both his contribution to other related publications (on which he is a secondary author and which he has not included in the dissertation) and the limitations and strengths of the proposed methods (e.g., of the TTS method in section 3.4.3.) as well as of the application-level observations made (e.g., in section 4.2.2. discussing difficulties in establishing correspondence to experiments).

The candidate covers a broad range of methodologies (a spectrum of static and dynamical ab initio methods including highly advanced ones as GW, machine learning potentials, methods for treating nuclear quantum effects, etc.) at the edge of the current state-of-the-art and both develops some of them further (Papers I & II - particularly the TTS method but also the query-by-committee workflow) or at least applies them for a range of challenging specific systems/problems (sections 4-6), with the common thread being them featuring important and sometimes non-standard (π-bonding in section 5) hydrogen-bonding patterns. The extent of this effort is admirable with the methodology mostly described more than appropriately with respect to its importance for the dissertation and/or to the

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degree of how much the current contribution extend the state-of-the-art. Nevertheless, to be a bit picky, I would still appreciate a bit more thorough and more balanced description of the methodology related to the development of the neural network potentials and to the (hybrid dispersion-corrected) density functionals, which are the workhorses of most of the application work described in Papers III-IV in particular but also Paper V. The practical motivation for properly describing various types of hydrogen-bonding including NQEs is very comprehensively provided in the Introduction section, however, the current contribution still represents rather fundamental research highlighting general concepts or experimental misconceptions (e.g., as alluded to by the candidate in the closing section 7) with the particular model systems being still rather removed from the real-world set-up and application. The research data (both of applied and methodological nature) are of high interest/importance, in particular, I see the TTS method representing an extremely important addition to a now very broad and topical field of "active learning" of machine learning potentials, with an overlooked importance of a need of sampling an extended configuration space in the context of the nuclear quantum effects. I can also concur with the stance of the candidate provided in Conclusions that the whole topic of accelerating ab initio simulations via machine learning (e.g., via neural network potentials as showcased in this work) is probably the hottest topic in the field currently and one with the great capacity to upend the status-quo in the field becoming a completely standard approach within a few years (now, I would claim, it is still in the "early adopter" stage). In addition, the application results described in Papers III-V represent, in my opinion, extremely solid research utilizing the state-of-the-art approaches (e.g., hybrid AIMD accompanied by G_0W_0 calculation of electron binding energies) for as-of-yet not properly understood systems and trying hard to understand the problem deeply not shying away from the problems encountered (e.g., section 4.2.1. on why solvent stabilizes benzene anion or section 5.2.2. on the complex character of vibrational spectra and why it does not matter that much) - such an approach is, unfortunately, becoming nowadays, at least in our scientific field (computational chemistry/physics), less common.
In summary, my overall rating of the thesis very high, it **clearly demonstrates the candidate's capacity for independent creative work** and with pleasure **I recommend the dissertation for the defence.**

I have a lot of questions/remarks, however, I tried to limit them to only a few below:
1. The candidate utilizes an approximative ring polymer instanton rate theory to evaluate the rates of proton-transfer. As alluded by the candidate, one can directly evaluating the average in formula (2.112) from a set of trajectories started at the separatrix - such approach has been seemingly taken by other groups (e.g., 10.1038/s41467-023-36666-y). What are the advantages and disadvantages of these two approaches? Has the alternative approach been tested on candidate's systems?
2. It appears that the validity of following statement (without a reference) on page 54 is pivotal to relevance of many of the results presented in the thesis: "Despite this limitation, it was proposed that given a reasonable choice of replica masses, the auxiliary PIMD dynamics can, in fact, be used, at least

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in an approximate way, to capture real-time dynamics". It would be appreciated, if candidate could discuss this issue in more detail than done anecdotally at the end of page 54.
3. As illustrated in Figure 3.2 (page 73) the quantum probability distributions (QPDs) are rather different from the classical ones and the TTS is a nice way of how to sample particularly those QPDs. Still, I'd be interested in how important is the inclusion of those data for the robustness/stability of the trained NNPs? Could be the similar aim be achieved by training on classical distributions but just sampled at increased temperatures (as is often done in practice to sample structures for training NNPs for reactive events, e.g., in 10.1038/s41467-024-45840-9 or here 10.1038/s41467-023-36666-y)?
4. The candidate mentions the high importance of using high-level simulations (e.g., hybrid level DFT for AIMD) and of inclusion of NQEs. However, I am missing a bit the comparison between predictions on a such level and the lower more standard level (e.g., GGA DFT w/o NQEs) and I would welcome more of such comparisons being showcased. For example, I would be interested whether a qualitatively similar results as presented in section 5 (π-hydrogen bonding of benzene in neat water and ammonia) could be also achieved with standard GGA DFT w/o inclusion of NEQs.
5. Using committees of models for uncertainty prediction is still a "golden" standard, however, there has been a push towards alternative approaches for uncertainty predictions, e.g., using only a single model for this task, which are few-fold less costly in the production mode. Has alternatives to QbC been tested/considered in your work?

Lastly, on a bit of a philosophical note (before more tests from the community come in), indeed as mentioned by the candidate, the foundational models could represent a game-changer in the field, however, aren't they a bit too general and despite being stable their PES could be too different from a real-one to make them a reasonable choice for generating good training structures for their refinement or generation of a new NNP for a problem of interest (i.e., them becoming an improved version of the analytical universal force field - UFF).

In Prague, 02.08.2024

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