Final summary report

Project: **Computation of Nuclear Magnetic Relaxation in Paramagnetic Systems**
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Nuclear Magnetic Resonance (NMR) of paramagnetic systems (pNMR) is recognized as an important tool for investigation of the atomic and electronic structure of molecules in a range of scientific disciplines within physics, chemistry and biology. The significance of the fundamental research is apparent from applications in material research, structural biology and drug research as well as medicine, particularly in the field of magnetic resonance imaging (MRI) contrast agents. The purpose of this research was the development and application of theoretical methods as well as a first principles modeling paradigm for *in silico* investigation of pNMR relaxation. The aqueous solution of a Ni^{2+}-ion has been used as a model system throughout the time course of the project.

Structure and dynamics of the Ni^{2+}(*aqua*)-complex. A highly accurate molecular dynamics (MD) trajectory was required for the subsequent quantum mechanical (QM) calculations. Since no sufficiently accurate empirical forcefield was available for the Ni^{2+}(*aq*) simulation, First-principles MD (FPMD) as implemented in the QUICKSTEP module of CP2K programme was selected for production of the necessary MD trajectory. Since any equivalent calculation has not been published before, we proceeded with a thorough analysis of structural and dynamical parameters, for which development of new software tools for the analysis was necessary. The results were critically compared with available experimental data as well as with relevant computational works and published. As a main conclusion, the FMPD method proved to be accurate for structural parameters, however insufficient for dynamical properties.

ESR parameters and nuclear shielding. The next goal was the Curie-type pNMR relaxation, which is related to the nuclear shielding interaction. The state-of-the-art theory to obtain pNMR shieldings requires calculation of electron paramagnetic resonance (EPR) parameters, the hyperfine coupling, zero-field splitting (ZFS) and g-tensors. The best applicable level of theory was selected to do these calculations. Software tools for automatic setup and processing of the QM calculations of thousands of MD snapshots were developed. These included calculation of nuclear shielding tensors and their breakdown into contributions of the different underlying physical mechanisms. The results were compared with available experimental results and compiled into a publication.

Empirical forcefield development. To further proceed with Curie-type pNMR relaxation, it was necessary to obtain a new MD trajectory because of the mentioned shortcomings of FPMD for the dynamical parameters. This time, a highly-accurate empirical polarizable forcefield method was selected. The Ni^{2+}-H_2O potential in the AMOEBA forcefield was parameterized against high-level QM calculations. Unfortunately even this state-of-the-art forcefield proved to need empirical adjustments for the notoriously difficult case of Ni^{2+}-H_2O (anticipated also for other transition metals, TMs), however structural and dynamical parameters in excellent agreement with experimental results were finally obtained. The results summarizing the Ni^{2+}(*aq*) MD simulation are complete and a manuscript for a scientific publication is currently in preparation.

Spin-dynamical calculations. At the same time, the project proceeded to spin-dynamics (SD) simulation of the simplest unit of Ni^{2+}(*aq*), consisting of the first solvation shell – the $Ni(H_2O)_6^{2+}$ complex. In these calculations the spin density matrix evolves under the influence of EPR-NMR Hamiltonians, for which the parameters are supplied from the above-mentioned MD snapshots. From these, fully QM calculations, relaxation rates of both electronic and nuclear spins can be obtained without resorting to simplifications such as the Redfield theory. For this part of the project, cooperation with the group of Malcolm Levitt (Southampton) was established. This part is mainly pursued by a M.Sc. student, Jyrki Rantaharju, co-supervised by the Fellow and the Scientist in

Charge. The SD calculations have so far given results for the EPR relaxation, which are close to be ready for the first publication. The procedures needed to accomplish the SD simulations are made available to the author of the programme SpinDynamica for free distribution.

Zero-field splitting calculations. At this point, the progress became hindered by the fact that the available methods to calculate ZFS turned out to be too unreliable for our purposes. Unfortunately, the electronic SD (including relaxation) and therefore the coupled electronic-nuclear SD is crucially dependent on this parameter unlike isotropic nuclear shielding values, which are influenced only very modestly. *At the moment, the biggest effort is being invested in a method, which would for our system supply accurate ZFS.* Very likely, the currently obtained ZFS values can be *ad-hoc* corrected by a multiplicative factor and the relaxation calculations can be then promptly finalized.

Curie-type relaxation. Software for calculation of the Curie-type relaxation based on Redfield theory was developed and applied. Curie relaxation also suffers from the inferior quality of ZFS, since the relevant 2^{nd}-rank part of the shielding tensor is appreciably affected, however ignoring this fact can be in this case still justified as the effect remains minor. These results are now ready for publication and are being composed into a manuscript. As a conclusion, these results for the first time directly address the efficiency of Curie relaxation, which is experimentally masked by the electronic mechanism for Ni^{2+}(*aq*) in the nowadays available NMR fields.

Solomon-Bloemberger-Morgan relaxation. A dominant contribution to the pNMR relaxation can be obtained by the second-order perturbational Solomon-Bloemberger-Morgan theory. The calculation can be readily pursued and give parallel, low-level relaxation rate theory, which will later be otherwise obtained by the SD calculation. Also for this point, accurate ZFSs are crucially needed.

Conclusions. Despite the delay caused by the unexpected shortcomings in FPMD and ZFS calculations for a TM such as Ni, the project has progressed to the most advanced stage of the pNMR relaxation calculation on the model system. Realising the time constraints we chose in the course of the project to focus entirely on the basic methodology, and the application of the methodology to other examples (Gd systems including nanostructures relevant for MRI) requires continuing effort. The project is being continued on local funding, and has so far laid the background for a computational study of pNMR relaxation at a hitherto unseen level.

Potential socio-economic impact of the project. The MD learnings for systems containing a TM ion can benefit a wide society of applied scientists, particularly in structural biology and drug research, since TM parametrization in the *a priori* appealing AMOEBA forcefield has been missing despite the importance of TM-containing catalytic centers.

The calculation of EPR-NMR parameters showed capabilities of currently available tools and theories in the field of open-shell molecules. In this, experimental spectroscopists are aided in assignments of the signals based on calculated positions and widths. The combination of modern QM methods with older theories of NMR relaxation (Redfield, Solomon-Bloembergen) show the validity of such approaches. The work also reveals shortcomings of widely used DFT calculations, and suggest the development of spectroscopy-oriented DFT functionals. Problems and overall sparsity of code implementations for ZFS should stimulate efforts in this field.

The eventual mature outcome of the project will be beneficial in the development of MRI contrast agents in the field of human-health targeted diagnostics and research methods. On the other hand, our efforts on SD simulations already stimulated improvements in the unique software written by M. Levitt, which is becoming widely recognized as a general tool for an in-depth analysis of NMR (EPR) experiments.