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Historical Perspective

SIMPSON – An important driver for numerical simulations in solid-state NMR spectroscopy

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ABSTRACT

We present a historical recollection on the development of the software package SIMPSON (SIMulation Package for SOlid-state Nmr). This covers a brief description of the underlying ideas and events leading to creation of SIMPSON and numerous auxiliary programs as well as comments on its impact on the development and application of solid-state NMR in research laboratories world-wide.

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Interview with the author(s).

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Since it is release in 2000, the SIMPSON software package [1] has been the most extensively and most widespread used piece of general-purpose software in the solid-state NMR community. It has been cited around 650 times, there has been numerous follow-up papers with demonstrations and new contributions in terms of embedded or auxiliary software [2–9], and there have been an uncountable number of training events and presentations at conferences. Overall a very large fraction of active solid-state NMR researchers including students at all levels have used SIMPSON either directly or indirectly in their research, that being for method development or pure applications.

These facts are not listed to set a special status neither set ignorance to other equally important contributions in the area, but rather establish focus on the very positive appreciation from the NMR community and some of the ingredients leading to its development. The latter includes the effect of apparent long-standing need in the community, some luck and coincidences, and the everlasting need of timely assembly of teams with the right resources and spirits to make something like a large software package effective in a short period of time.

SIMPSON (simulation program for solid-state NMR) was developed primarily over the years of 1998 and 1999 – not from scratch as for most research contributions it was based on strong fundamental developed previously – but notably it did not take more than a couple of years from idea to release. The acceptance from the NMR community came immediately after release. The initial ingredients of SIMPSON was (i) existing knowledge on the theory of solid-state NMR and hundreds of pieces of less structured software made in FORTRAN-77 for simulation of solid-state NMR experiments (Niels Chr. Nielsen), (ii) a Ph.D. student with excellent capabilities in programming in essentially all languages (Mads Bak), and (iii) a very talented M.Sc. student with strong programming skills and very good ideas on how to make simulations efficient (Jimmy Tønners Rasmussen).

In 1998, I (Niels Chr. Nielsen) had the pleasure teaching a young student (Mads Bak) in a computer course and later in an advanced course in solid-state NMR spectroscopy. In both courses there was focus on programming, coding programs for Fourier transforms, and later solid-state NMR simulations along with introduction to the basic theory required for this. Short after Mads Bak, on his CV saying that he was an autodidact programmer (despite I thought we learned him a few tricks in the programming course – but clearly, as became very visible later, not nearly enough to meet his standards) joined the newly established BioNMR group at Aarhus University to participate in the development of solid-state NMR methods, in addition to biological liquid-state NMR studies of bioactive peptides and ^{31}P solid-state NMR on casein micelles – a quite diverse project which also here puts credibility to the capability of good students (or the lack of focus of

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supervisors). In relation to the solid-state methodology projects, Mads Bak was introduced to my software package containing a large number of subroutines assembled in custom-made fashion to each project, triggering the comment: It should be possible to this smarter! The first claim was that existing broadly-oriented software packages such as GAMMA [10] would be a good entry as most of the framework of object-oriented programming, fundamental matrices, Hamiltonians, etc. were present there already – we just needed to add powder averaging and spinning. It turned out, however, in his implementations the code was even longer than my present custom-made software and it in the relevant implementation was substantially slower. The combination of these observations, lead to the decision that Mads Bak would try to establish a user-friendly software package for simulation of any solid-state NMR experiment with a user-programming effort comparable to or less complicated than setting up a pulse sequence on a commercial NMR instrument. I had no problems supporting this idea knowing the programming skill of Mads Bak from previous courses and our present knowledge on the fundamentals of solid-state NMR. We should note that numerous other NMR software packages were present at this time including ANTIOPE [11], STARS [12,13], and QUASAR [14], which, however, did not meet the desire of being sufficiently general or flexible.

To meet the requests of a program generally applicable for solid-state NMR simulations, the required theory was assembled based on existing solid-state NMR teaching notes [15], numerous previous projects and coding initialized using earlier software as inspiration, but here build in the language C to form the computationally efficient core shell of SIMPSON. The user interface was established using the at that time very widespread Tcl scripting language [16] as a base to form input files with easier programming load and a high degree of flexibility (including the possibility to interface with other programs and ability to perform independent evaluations, establish useful output, etc.) while providing transparent input files with similar coding ease as typically encountered on spectrometer interfaces. With the aim of conducting fast simulations, we in parallel carried out projects on important elements of solid-state NMR calculations including for example development of the widely used REPULSION powder averaging scheme [17] and the so-called γ-COMPUTE [18] algorithm efficiently exploiting the analogy between one of the three powder Euler angles (γ_{CR}) and the rotor rotation angle ($\omega_r t$). In this work, Jimmy Tønners Rasmussen entered the project with strong expertise from previous studies on solid-state NMR homonuclear decoupling sequences and simulations of solid-state NMR spectra from his M.Sc. projects. Among many other contributions to SIMPSON, he designed smart procedures to efficiently reuse propagators for fast calculation of spectra for static as well as rotating solids. Jimmy Tønners Rasmussen was central in the work with many of the key matrix operations and assembly of the program together with Mads Bak.

After setting up the main elements of the program, the team tested it very extensively against previous simulations and experiments in essentially all areas of solid-state NMR to provide widely-oriented challenges to the setup (triggering numerous revisions) and very importantly a voluminous catalog of examples later forming a major ingredient in the SIMPSON paper [1]. This paper still constitutes the major manual to the program – and has inspired descriptions in many languages, including Chinese. We believe this careful work of testing formed a very important element in the later success of SIMPSON in the sense that it had very few errors and surprises relative to the big task of making a program being sufficiently flexible to simulate essentially all types of NMR experiments. Fair to say, we also learned a lot about solid-state NMR in this process.

With the SIMPSON program up running, we had to make a serious choice. A well-functioning program would set our research group in a good position to make strong moves within the field exploiting the advantage of having a tool not available to others. Another option could be to establish a commercial platform harvesting income from selling the software, partly for own benefit and partly to ensure funding to maintain the program. A third option would be to release it as open-source software. The latter became the choice, and we are convinced – in retrospect – that this was the only real choice and that it has been extremely important for the success of SIMPSON. Free release of the program immediately gave an enormous expressed respect and gratitude from the solid-state NMR community, including the many students immediately having access to a tool that could simulate experiments prior to and after the experimental work to test ideas, confirm theories, and extract parameters from experimental spectra. Not least, access to the code – although for the vast majority not used for direct changes despite existing possibility – provided the researchers visible information on the underlying theory, thereby inducing trustworthiness relative to a "black-box" approach often seen in commercial programs.

SIMPSON was indeed very well received by the NMR community, as mentioned it is heavily cited and had a steady use in and citations from the solid-state NMR community in the past decade, witnessing a long-standing impact. It has been followed up by further development of procedures, including most notably the SIMMOL program [2] (and its predecessor PDB2SIMPSON [19]), offering possibilities to establish large spin systems with reliable tensorial interactions, and optimal control procedures enabling automated numerical design of NMR experiments [8,20]. These and other supplementary packages demonstrate that SIMPSON – although less intensive than we wanted due to funding issues – is still being developed to fulfill the ever increasing need for a fast and versatile tool for simulations of solid-state NMR experiments. In combination with recent developments leading to substantially faster operation, SIMPSON and its further developments has certainly made an impact on the field of solid-state NMR as expressed to us by many colleagues over the years. Mostly through private communication, but also through statements as the one made by H. Eckert (Westfälische Wilhelms-Universität Münster) in a overview paper on solid-state NMR in the Bunsen Magazine: "The design of new pulse sequences is greatly aided by the availability of program packages that calculate the behavior of the spins under the influence of the external and internal interaction Hamiltonians using standard time-dependent perturbation theory. Especially noteworthy is the program package "SIMPSON", which enables the simulation of complex NMR experiments under the precise conditions used at the spectrometer [22]. This freeware has proven invaluable in the analysis of complex experiments and profoundly influenced NMR research in many laboratories." [21].

In addition to its direct impact, we also believe that SIMPSON has made an indirect impact to the solid-state NMR community through stating the worth and necessity of efficient software packages as an important ingredient in experiment design and data interpretation. Such needs have since the release of SIMPSON lead to the development of numerous numerical and more analytically based software packages for experiment evaluation in solid-state NMR spectroscopy [22–30]. Development of new software packages as well as running up-date of existing packages is in our opinion extremely important for the steady development and application of solid-state NMR spectroscopy fully exploiting the enormously rich source of information about molecular structure and dynamics through isotropic as well as anisotropic nuclear spin interactions.

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