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ABSTRACT

Nuclear Magnetic Resonance (NMR) is a powerful tool for observing the motion of biomolecules at the atomic level. One technique, the analysis of relaxation dispersion phenomenon, is highly suited for studying the kinetics and thermodynamics of biological processes. Built on top of the relax computational environment for NMR dynamics is a new dispersion analysis designed to be comprehensive, accurate and easy to use. The software supports more models, both numeric and analytic, than current solutions. An automated protocol, available for scripting and driving the GUI, is designed to simplify the analysis of dispersion data for NMR spectroscopists. Decreases in optimisation time are granted by parallelisation for running on computer clusters and by skipping an initial grid search by using parameters from one solution as the starting point for another – using analytic model results for the numeric models, taking advantage of model nesting, and using averaged non-clustered results for the clustered analysis.

Availability: The software relax is written in Python with C modules and is released under the GPLv3+ licence. Source code and precompiled binaries for all major operating systems are available from http://www.nmr-relax.com.

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Biological macromolecules are intricate machines and their functions are closely related to their motions. These motions can be studied experimentally at the atomic level by NMR spectroscopy. Many important biological processes occur on the $\mu$s to ms timescale and, for atoms exchanging between different states, NMR relaxation dispersion can be observed. By studying this exchange process, kinetic and thermodynamic information can be obtained.

For exchanging atoms, their nuclear spin magnetisation is described by the Bloch-McConnell equations (McConnell, 1958), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
The number of dispersion models supported by relax is extensive (Table 1). This allows for detailed comparisons between modern numeric and traditional analytic approaches. Different user interfaces (UIs) can be employed to analyse dispersion data including the prompt, scripting, and graphical user interface (GUI). The scripting UI enables the greatest flexibility and allows for most analysis protocols to be replicated. By implementing a novel automated analysis and providing an easy to use GUI based on this auto-analysis, the study of dispersion data is much simplified.

The setup of the auto-analysis includes defining the molecular system, loading the dispersion data directly from peak lists, clustering atoms with the same kinetics, modifying the list of dispersion models, and setting up Monte Carlo (MC) simulations for error propagation. Execution involves sequential optimisation of the models, fixed model elimination rules to remove failed models and failed MC simulations increasing both parameter reliability and accuracy (d’Auvergne and Gooley, 2006), and a final run whereby AIC model selection is used to judge statistical significance (Akaike, 1973; d’Auvergne and Gooley, 2003). The optimisation is designed for absolute accuracy and robustness but, as this can take time, it has been parallelised at the spin cluster and MC simulation level to run on computer clusters using OpenMPI. Three additional methods are used to speed up calculations, all designed to skip the computationally expensive grid search. The first is model nesting – the more complex model starts with the optimised parameters of the simpler. The second is model equivalence – when two models have the same parameters. For example the CR72 model parameters are used as the starting point for the CPMG numeric models resulting in a huge computational win. The third is for spin clustering – the analysis starts with the averaged parameter values from a completed non-clustered analysis.

The dispersion analysis in relax is implemented in Python using NumPy and the GUI using wxPython. Optimisation using the Nelder-Mead simplex and log-barrier constraint algorithms from the minfx library (https://gna.org/projects/minfx/) removes the need for numerical gradient approximations which add a second numeric layer to the NS models. Data visualisation is via the software Grace.

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REFERENCES


