Chemical Simulations Group

Providing solutions that connect chemistry and biology…

url: http://www.chemicalsimulations.com
email: solutions@chemicalsimulations.com

Chemical Simulations Group (CSG) provides consulting services and software to the pharmaceutical, biotechnology, and chemical industries. Our mission is to deliver solutions that connect chemistry and biology.

One such application area is Nuclear Magnetic Resonance Spectroscopy (NMR). NMR spectroscopy is an important and well-known tool for biopharmaceutical, chemical, and medical applications. Chemical Simulations Group has developed CSG-NMR, a software system for the interpretation of one-dimensional proton NMR spectra. Chemical Simulation Group's capability to fit complex splitting patterns accelerates the process of natural or synthetic compound identification, structure elucidation, and the determination of relative concentrations in mixtures. Figure 1 shows a region from an NMR spectrum containing strongly coupled and overlapping spin systems for a mixture of two isomers. Experiment and simulation are compared and the difference is shown.

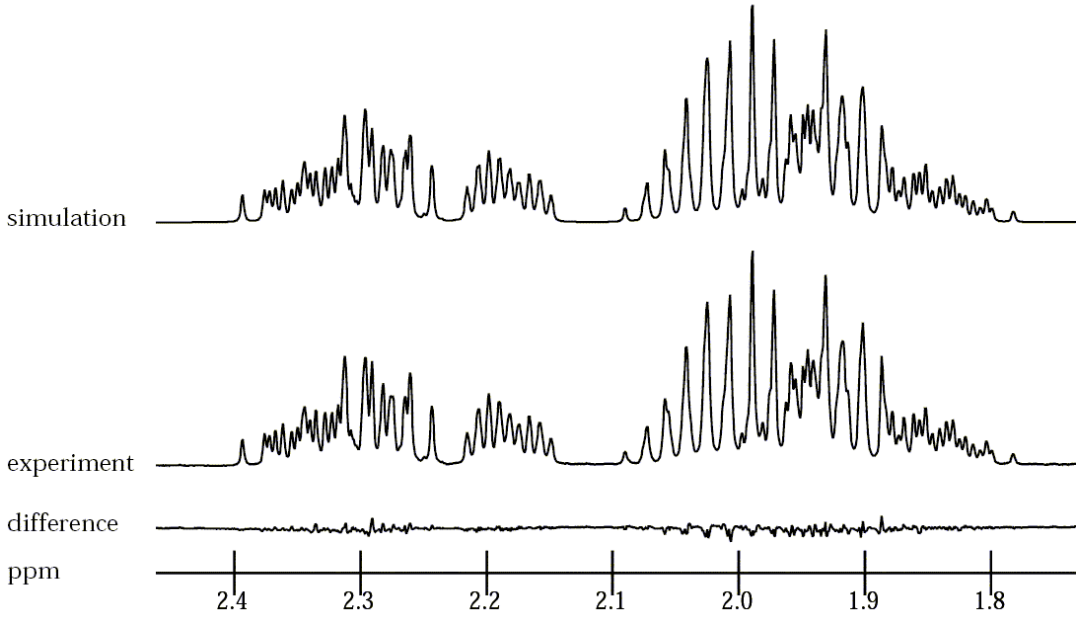

Figure 1 - Comparison of experimental and computed NMR spectra for strongly coupled and overlapping spin systems

Instead of using *ab initio* estimates for chemical shifts and coupling constants to predict splitting patterns within spectra, CSG-NMR iteratively fits computed spectra to the target experimental spectrum until the scoring function is optimized. This is accomplished by treating the chemical shifts and coupling constants as physical parameters that are varied in the Hamiltonian matrix. The accuracy of the resulting chemical shifts and coupling constants are limited only by the quality of the experimental spectrum.

Whether using traditional or high throughput NMR methods, it is important to collect good spectra. The better the spectra, the better the fit between experiment and theory. This results in the extraction of higher quality information. For example - suppression of the water peak if present, a long enough pulse delay to allow the system to relax, proper shimming using high digital resolution, setting the dead time to minimize linear phase correction, and a good number of free induction decays (FIDs) with a large number of points, are all important factors. It is also important

to process the NMR spectra with proper apodization, zero filling, and phase correction. Chemical Simulations Group can work with you to optimize data collection parameters and processing protocols.

Input to CSG-NMR is the processed experimental spectrum, the number of spin systems, the number of spins per system including magnetic equivalence, and initial guesses for the chemical shifts and coupling constants. The software then generates basis states and Hamiltonian matrix representations for the spin systems. Magnetic equivalence factoring is applied using spin angular momentum. Isolated spin systems within a compound share the same concentration parameter, enabling the treatment of mixtures. The chemical shifts and coupling constants in the Hamiltonian matrices are treated as physical parameters that are varied until the optimal fit to experiment is achieved. The result is the accurate extraction of chemical shifts and coupling constants from experimental data and the fit for complex and overlapping splitting patterns

Given a list of putative structural isomers for a compound, each proposed isomer can be simulated and iteratively fit to the experimental spectrum. The results can then be ranked and the correct structure selected based upon goodness of fit. It is well known that different spin systems give rise to different splitting patterns. CSG-NMR is designed to annotate these signatures. This is also applicable to mixtures of different compounds, mixtures of structural isomers, and mixtures of stable conformational isomers. Such mixtures are simulated by defining all component spin systems at initialization together with a single weighting factor per chemical entity. This is followed by simultaneous optimization of the weighting factors and the parameters in the Hamiltonian representations. The fit shown in Figure 1 is an example of two stable conformational isomers with tightly coupled and overlapping splitting patterns.

Figure 2 - Fully solvated model of the human estrogen receptor with bound estradiol.

Other offerings from Chemical Simulations Group include protein structure prediction (Figure 2), sequence and small molecule database design, high throughput computing systems design, and customer requested software and services. Future offerings will include chemical registration systems, predictive pharmacology, and quantum chemistry applications. These current and future offerings will be the topics of forthcoming articles in this series. All services and software are available exclusively from Chemical Simulations Group.

Telephone: 1-781-278-0082 Fax: 1-781-278-0083
email: solutions@chemicalsimulations.com
url: http://www.chemicalsimulations.com