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שילוב טכניקות באופטימיזציה ובהסקה בייסיאנית על מנת לכמת חילוף כימי
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Combining global optimization and Bayesian inference to
quantify chemical exchange from Z-spectral data.

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Abstract

Chemical exchange saturation transfer (CEST) is a technique in NMR spectroscopy and imaging to study the effect that exchanging nuclei in different chemical environments have on their respective NMR signals, when the system is exposed to pulses of radio-frequency irradiation. This technique allows to indirectly probe species in solution that are otherwise barely detectable in traditional NMR spectroscopy. CEST experiments typically report the NMR signal reduction of the abundant specie for varying irradiation pulse frequency. The resulted profile is called a "Z-spectrum", and its numerical analysis poses a difficult challenge due to lack of a tractable, analytical solution to the set of equations that model the system's behavior. We wish to contribute to the ongoing effort of fitting Z-spectra, while exploiting recent computational advancements to reduce assumptions and analytical approximations to a minimum, so that a wider range of systems may be accessible for CEST studies.

Introduction

Nuclear induction is a phenomenon in physics where a precessing nuclear magnetic moment in an external magnetic field induces observable voltages when exposed to irradiation at its Larmor frequency [1, 2]. Local magnetic fields around a nucleus, caused partially by its chemical environment, change the effective magnetic field the nucleus experiences and shift its resonance frequency. This gives atoms in functional groups a magnetic fingerprint that can be characterized via nuclear magnetic resonance (NMR) spectroscopy [2].

Bloch equations, which describe the time evolution of the magnetization that causes nuclear induction, form the basis for analysis of NMR spectra, which, when applied in-vivo, allows one to obtain noninvasively biochemical data on metabolites and probe physiological parameters [3]. Furthermore, it has been shown that, when two NMR-active species undergo reversible chemical exchange, there is a quantitative relation between the species' NMR line shapes and their rate of exchange [4]. The discovery of this relation, which has been mathematically derived by H. McConnell in 1958 [5], has created fruitful opportunities to use NMR techniques to study kinetic processes.

NMR line shape dynamics induced by chemical exchange, as modeled by Bloch-McConnell equations, do not only provide information on the back and forward exchange rates, but also on the exchanging species' concentrations. This seemingly minor technicality should not be overlooked, as it enables one to potentially overcome one of the most problematic caveats of NMR spectroscopy—low sensitivity—which is caused by the small population difference between the nuclear spin states that form the magnetic moment [6]. Essentially, NMR-active species in low concentrations are barely detectable due to low signal-to-noise ratio. However, by using a technique termed chemical exchange saturation transfer (CEST), one may indirectly probe a dilute solute via its interaction with an abundant specie, such as the solvent.

The CEST mechanism is illustrated in Figure 1. Let there be a dilute solute in water than has an exchangeable proton that resonates at a frequency different from the bulk water protons. A pulse of radio-frequency irradiation "saturates" the solute protons, that is, in the case of a spin-1/2 system, drives the system to equal population of spin up and spin down states [3]. This temporary saturation increases the chance that nuclear spins that are

aligned against the external magnetic field exchange with bulk water protons with spins that are aligned with the magnetic field. As a result, the difference in the population of the spins states of the bulk water protons is slightly reduced. Continuous irradiation at the dilute protons' resonance frequency causes observable attenuation of the bulk water NMR signal [7]. Profiling the NMR signal reduction at different saturation frequencies produces a "Z-spectrum", which may be numerically analysed via Bloch-McConnell equations [8].

Considering the far-reaching applications of NMR spectroscopy in physics, chemistry, and medicine [6], overcoming the technique's low sensitivity via CEST has peaked the interest of the scientific community [9, 8]. One major effort in the study of the CEST mechanism is numerical analysis of Z-spectra [10].
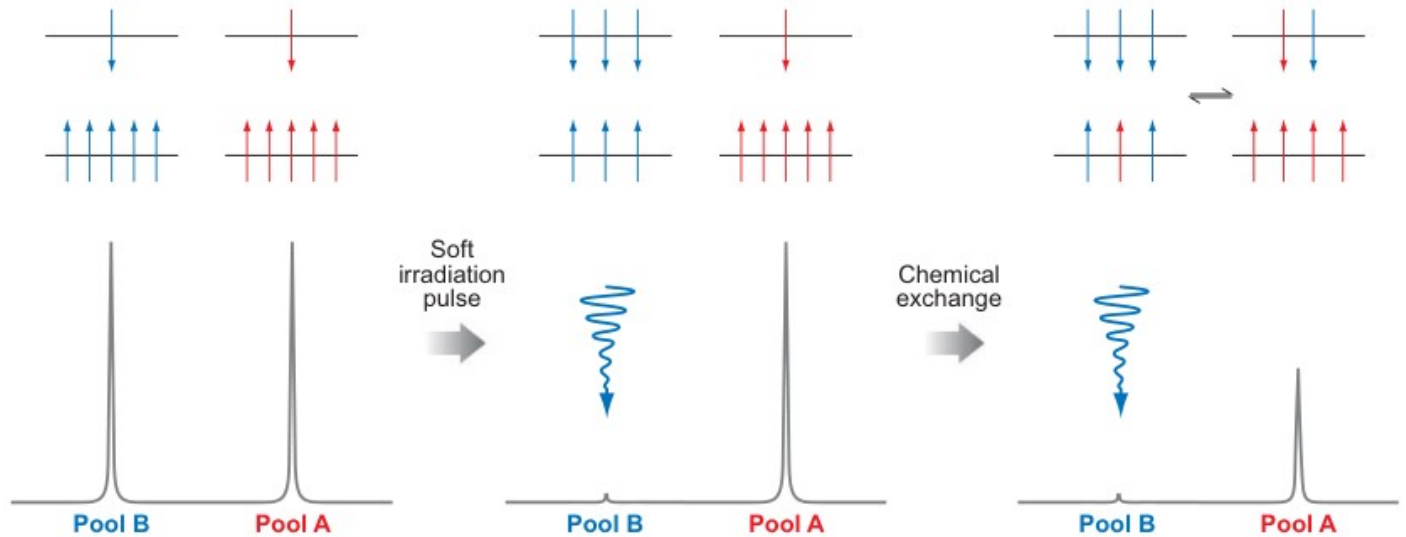

Figure 1: Illustration of the CEST mechanism for too pools. Adapted from *Sherry AD, Woods M. Chemical exchange saturation transfer contrast agents for magnetic resonance imaging* [11].

The most empirically prominent methods to successfully tackle fitting of Z-spectra are based on Bloch-McConnell equations [12, 10]. These are a set of coupled differential equations of at least 6th order, that, even in the most simple case, do not have a closed-form analytical solution that is derived without system-specific approximations, due to Abel-Ruffini theorem [13]. Eigenvalue analysis of Bloch-McConnell equations contributed to a simplified set of equations, which have been shown to successfully predict Z-spectra in a moderately large range of varying systems, including exchangeable lithium [14], fluorine [9], and hydrogen [3]. This method, however, relies on approximations that limit analysis of CEST-capable systems to a confined set [10].

Goals

1. Develop an algorithm to numerically fit Z-spectra to Bloch-McConnell equations without limiting approximations.

2. Be able to fit multiple Z-spectra at once with varying saturation pulse amplitude.

3. Validate the algorithm against well explored systems found in the literature.

Work Plan

- The study will focus on systems that have at most two distinguished exchangeable species.

- Bloch-McConnell equations shall be solved unmodified, using matrix exponentiation.

- The algorithm shall be based on a Bayesian paradigm. Bayesian inference is a method in statistics that is primarily suited to deal with limited data availability, and is relatively robust to noise [15].

- Priors for Bayesian inference, which encapsulate prior information on the fitting parameters behavior, shall be chosen with assumptions set to a minimum. This is to maximize the influence of experimental data on decision making.

- The algorithm shall be tested against a multitude of hydrogen CEST systems from the literature, as well as some lithium CEST from Leskes et al. [14]

Preliminary Results

Example Z-spectra were taken from Li-CEST experiments conducted by Leskes et al [14], as seen in Figure 2a. A fitting algorithm based on Normally distributed priors using the No-U-Turn sampler [16] for Bayesian analysis was employed in the Stan programming language. Figure 2b shows the fitting result of the spectrum with saturation amplitude of 500Hz:
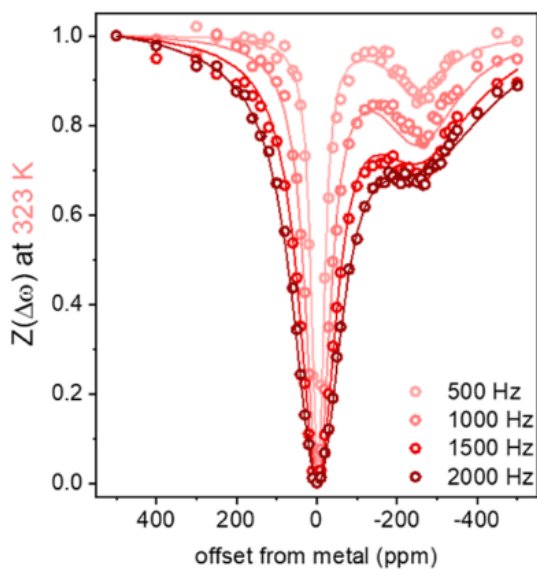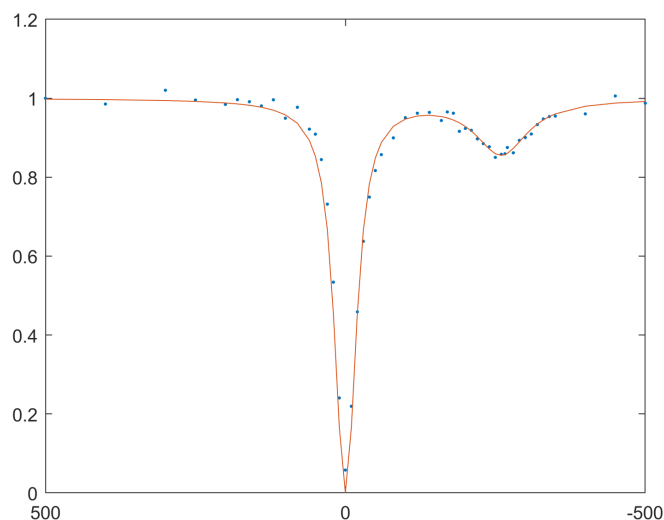
| (a) | (b) |

Figure 2: (a) Experimental Z-spectra (circles) acquired from dendrites grown and immersed in LP30 as a function of saturation amplitude with a 0.2 seconds saturation pulse, at 323K. Solid lines represent fit conducted using Zaiss's algorithm [10]. (b) Fit of the 500Hz spectrum, using an alpha version of the Bayesian fitting algorithm. The abscissa represents the offset from the metal's resonance frequency in ppm, and the ordinate represents the NMR signal attenuation.

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