Brute Force Search Program Overview

This program was developed to simplify the analysis of kinetic data obtained from nuclear magnetic resonance (NMR). It can process data in either a simple text file with whitespace-separated values or a clipboard copy from MestReNova. The reactant and product species do not need to be specified; the program automatically surveys the data to select initial starting values. It then uses a search algorithm to fit the best least-squares solution for seven parameters by individually varying each and repeating the search until a minimum error is found for the ensemble of variables.

Given that the system is in equilibrium, an exact equation defining the forward and reverse rates is not possible under magnetic relaxation conditions. To address this, the program maintains a running calculation every 1 millisecond time interval, starting from an initial state and ending at a final state, while computing the error at each data point by comparing predicted fits to observed data.

Key Parameters

The Brute Force Search program models the exchange system using seven key parameters, which are initially set to specific values based on the NMR data:

$M_A\infty$ – Magnitude of the reactant at equilibrium
$M_B\infty$ – Magnitude of the product at equilibrium
M_A0 – Magnitude of the reactant after perturbation
M_B0 – Magnitude of the product after perturbation
T_1A – Longitudinal nuclear relaxation time of the reactant nucleus
T_1B – Longitudinal nuclear relaxation time of the product nucleus
k – First-order exchange rate from reactant to product

Calculation Process

The program begins by setting the initial magnetization values, **M_A0** and **M_B0**, based on the equilibrium magnitudes of species A and B, assuming all spins are aligned with the magnetic field at equilibrium approximated by **$M_A\infty$** and **$M_B\infty$**. The calculation is simplified by considering the difference between the spin-up and spin-down states as the net magnetization at equilibrium. The equilibrium magnetization values are also used to calculate the equilibrium distribution between species A and B.

Next, the program calculates the relaxation for species A and B using their respective longitudinal relaxation times. The number of spins in each state is updated after every relaxation cycle, and exchange between species A and B is applied. The program repeats this process for every 1 millisecond until all time points are covered.

Data Acquisition and Exchange Rate Constraints

The time required to collect an NMR Free Induction Decay (FID) is typically 1–2 seconds. When the exchange rate exceeds 1 second, fitting the data becomes challenging because multiple exchanges occur during the FID collection, limiting the ability to accurately determine the true exchange rate. Conversely, for very slow exchange (**k** > 0.01 sec), the number of exchanges is too small to detect accurately due to magnetic relaxation. This issue can be mitigated by increasing the number of averages or data points, although this will extend the total acquisition time.

Initial Guesses for Parameters

The initial guesses for $\mathbf{M_A\infty}$ and $\mathbf{M_B\infty}$ are based on experimental data, specifically the magnetization values at the longest mixing time, which best represent the equilibrium values. $\mathbf{M_A0}$ and $\mathbf{M_B0}$ are set to the magnetization values at the shortest mixing times.

The initial guesses for $\mathbf{T_1A}$, $\mathbf{T_1B}$, and **k** are determined by testing a range of values:

$\mathbf{T_1}$ values range from 0.1 to 10 sec

k values range from 0.01 to 10 1/sec

The program chooses the optimal values for these parameters by performing a least-squares fit to the data, minimizing the error between predicted and observed values.

Fitting Algorithm

The fitting algorithm adjusts each parameter individually, either increasing or decreasing the value, until the sum of squared errors (the difference between predicted and observed values) is minimized. The program iterates through each parameter, repeating the process until no further reduction in error is achieved.

Data Fitting Approach

Rather than fitting the data to a predefined equation, the program uses a predictive approach. The expected values are determined by applying the Bloch equation for magnetic relaxation over a 1 millisecond time period, considering the exchange of nuclei between the reactant and product species. This is repeated for each time step, generating a dataset spanning the longest mixing time in the experiment.

This method does not assume a specific direction of exchange, nor does it depend on which species (A or B) is being excited. Additionally, the level of nuclear inversion (flip angle of the spins) is important for the accuracy of the fit. Without inversion, the fitted values may be inaccurate, and maximum accuracy is achieved when near-perfect inversion of one species (via a 180-degree pulse) is performed.

Error Estimation and Confidence Intervals

Currently, the Brute Force Search program provides approximate error estimates based on the importance of each parameter in the accuracy of the fit. These estimates were validated using **CIFIT**[1], which has been used in prior kinetic publications. The authors are working on developing a method to calculate the standard deviation of the fit, which may allow for the determination of a 95% confidence interval for the errors.

[1] https://chemistry.mcmaster.ca/bain/

Download Windows and MacOS programs

The program is an executable with a clickable app that runs in the terminal. Download the zip file and extract in the location you would like to run the program from. In the same folder you should place the text files (.txt) for the data. The program will provide the option to input which file you would like to use from the folder. If only one file is present that file will be selected. When inputting the file name an autocomplete is provided and the tab button will finish the file name.

Windows –

MacOS –

MacOS recommend terminal settings: