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Predictive modeling of the reduced partition function ratio for organic isotopologues

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Chemical reaction pathways and conditions (e.g., temperature) can generate distinctive isotopic signatures in their products. It is now possible to measure numerous site-specific singly and multiply substituted isotopologue distributions for many compounds, with the accuracy required for reconstructing the reaction pathways. However, interpretation of these data requires the ability to model intramolecular chemical isotope effects with unprecedented diversity and complexity. Here we present new advances in numerical tools for predicting and interpreting such isotopic data.

Interpretations of isotopic measurements from (bio)geochemically relevant molecules are partly constrained by our ability to predict the isotopic fractionation in the reaction pathways for the molecule. A common approach to computing equilibrium and kinetic isotope effects combines Density Functional Theory (DFT) calculation of structures of reactants, products, and transition states with Urey-Beigelsen-Mayer (UBM) theoretical models of vibrational isotope effects. However, since the number of possible isotopologues grows exponentially with the size of a molecule, this method is prohibitively computationally expensive and time-consuming for most isotopologues of most compounds.

Our study explores the feasibility of building an empirical model for the reduced partition function ratio (RPFR) that is fit to RPFR's calculated by DFT and UBM-predicted. We have compiled a dataset of RPFR for C1-C10 alkanes and up to C5 amino acids using DFT/b3lyp/6-31G* level of theory. Then, we constructed a multivariate exponential regression model with the moiety where isotopic substitution occurred as input. With this approach, we have achieved a mean predictive relative error towards the DFT data of 1.4‰ (permille) for a single 13C substitution in amino acids and 0.4‰ for alkanes. This study also quantitatively assessed the clumping effect for larger molecules and found that the effect is generally consistent for adjacent heavy isotope clumping, independent of molecular bonding environment, and negligible for non-adjacent clumping of heavier nuclei. These results demonstrate the possibility of predicting the RPFR of singly and multiply substituted isotopologues to an accuracy within the required range for helping interpret mass-spectrometry data, using an empirical function that entails negligible computational cost.