Prediction and interpretation of comprehensive molecular isotopic structures

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Innovations in NMR, mass spectrometry, spectroscopy and on-line reaction and chromatography have given us broad capabilities for measuring intramolecular isotopic distributions, including site-specific and 'clumped' isotope effects. A generalized ability to measure nearly any moderately abundant isotopologue of nearly any compound is in sight.

Our community's technological progress presents us with another, greater challenge: Can we predict and systematically interpret the things we can now measure? If so, we will marshall these remarkable capabilities to engage in rigorous hypothesis-driven research. If not, we can only explore, guided by hunches and resorting to *post hoc* interpretations.

We will present the first stages of an integrated model that turns hypothesized chemical reaction networks into predictions of the time-varying isotopic structures and mass spectra of all participating reactants and products, including dozens to hundreds of isotopologues per chemical species. Key model components include: An algoritm for defining time-varying or steady-state networks of elementary reactions; a parameterization of reduced partition function ratios that provides self-consistent descriptions of a large number of isotopologues and compounds, and is usefully (though variably) accurate for compounds outside its calibration set; a treatment of kinetic isotope effects based on semi-classical transition state theory, including idealized descriptions of transition state structure, and capable of providing first-order descriptions of inverse KIE's, secondary isotope effects, quantum tunneling, and other complex behaviors; and explicit prediction of mass spectra, permitting one to design measurements tailored to a model, and modify a model in direct response to measurements.

Full implementation of this model will unfold over several years, but key data bases and procedures are operational. We will outline the structure and assumptions of this model and illustrate its applications to significant chemical species and reactions, including metabolic reactions, the Diels-Alder chemistry, and cases of general reaction types (e.g., homolytic cleavage, beta scission, elimination).