

## Fundamentals Interest Group Workshop

ASMS 2024, Anaheim

**Title:** "Isotopocules": Frontiers & Limitations

**Organizers:** Cajetan Neubauer and Yury Tsybin

**Date:** Tuesday, June 4, 2024

Attendance: 50-60.

The 2024 workshop was devoted to the emerging field of "Isotopocule" analysis with mass spectrometry, focusing on the growing importance and challenges of detecting and quantifying isotopically-substituted molecules with high accuracy and precision.

To introduce the topics and to maximize the breadth and depth of discussion, a very versatile panel of speakers formed by **Tom Brenna**, **Alexander Makarov**, **Xia Gao**, and **Huiming Bao**, was also acting as a panel of experts for the follow up discussions with the audience.

The retiring presider **Yury Tsybin** opened by inviting participants and initiating the exchange on the past, present, and future of the Fundamentals Interest Group. The six Fundamentals-centered sessions in the 2024 ASMS program included:

1. Beyond Mass Analysis: Isomers
2. Unconventional Approaches in MS
3. Ion Structures, Energetics, and Reactions
4. Native MS and Structures of Large Ions
5. Ion Activation and Dissociation
6. Ionization Methods

In a comparison with the prior ASMS content (which included up to 7 related sessions), there is a clear shift toward topic-based sessions that include applications. A general survey was conducted with the audience to understand the needs of the community and to search for new topics for the workshop. The response of the audience was in favor of continuing with the Fundamentals Interest Group workshop. The audience was encouraged to make suggestions for the topics of the next workshops (hydrogen-deuterium exchange MS was suggested) and to act as a co-presider.

Yury then passed the baton to the new presider **Cajetan Neubauer** who then moderated the discussion.

**Tom Brenna** (University of Texas Austin) initiated the panel session by highlighting the significance of isotopocules, and natural variations in isotopes within (bio)molecules. He emphasized the vast potential of this information for understanding biological systems. He highlighted the historical attempts associated with utilizing magnetic sector-based isotope ratio mass spectrometry (IRMS) for this purpose, proof of concept data on the utility of isotopocule data and the lack of follow up work due to technical limitations. He concluded with a positive outlook, emphasizing the ongoing advancements and immense potential of isotopocule analysis in biological research.

The next speaker, **Alexander Makarov** of Thermo Fisher Scientific, focused on the performance characteristics of state-of-the-art mass analyzers in comparison to traditional magnetic sector instruments for IRMS applications. This overview provided a basis for discussions on factors that fundamentally limit current instrumentation for the study of isotopocules, and opportunities to specifically improve their performance towards improved novel isotope research in areas such as metabolomics and proteomics.

The next speaker, **Xia Gao** (Baylor College of Medicine) emphasized promising frontiers of isotope tracing in human health research. Her presentation highlighted the potential of natural molecular isotopic signatures in understanding human nutrition, disease risk factors, and metabolic processes during cell differentiation in health and disease. In the future, naturally occurring molecular isotope signatures could thus be used to gain insights into metabolic pathways and dietary patterns, particularly in patient and biobank samples that are not amenable to isotope labeling techniques.

As the final speaker, the isotope geochemist **Huiming Bao** (Nanjing University) concluded the panel introduction by exploring the cutting-edge applications of molecular isotope analysis in geo- and environmental sciences. He explained the fundamental physical principles that govern the formation of molecular isotopic patterns and their expected utility in geosciences. Dr. Bao highlighted the transformative role of soft-ionization mass spectrometry in isotope geochemistry, opening new ways to deepen the understanding of natural processes such as major Earth history transitions, climate change, and anthropogenic environmental pollution.

The short panel presentations sparked a lively discussion on the “isotopocule” nomenclature and on the future of isotopocule analysis as a bridge between environmental and health research. Panelists acknowledged challenges in fostering collaboration between experts in IRMS and bioanalytical mass spectrometry. These challenges stem from decades of independent development, leading to differences in training, funding, terminology, and research focus. A key theme emphasized by the audience was the need for meticulous standardization of emerging IRMS methodologies to facilitate collaboration. Towards the end of the discussion, a senior mass spectrometry developer highlighted the crucial role of isotope chemists in pioneering the use of isotopocules within biomedical research. Their deep understanding of isotope effects and measurements is invaluable. To bridge this gap, fostering a larger presence of isotope ratio mass spectrometrists within the ASMS community would certainly be helpful.

The presidors thank all the speakers and the audience for a fruitful and active workshop! The floor remains open for questions, future topic suggestions, and new presidors proposals!



**Figures:** Impressions from the 2024 ASMS Workshop: (left) Yury Tsybin activating the audience in the beginning of the workshop and (right) the “Isotopocules” after a wave of the questions and debates: (left to right) Cajetan Neubauer, Alexander Makarov, Tom Brenna, Xia Gao, and Huiming Bao.