

FRONTIERS IN METABOLOMICS

AUGUST 5-8TH 2024



Organisers:

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TSRC office

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Location of the meeting and breakfast: Telluride Science & Innovation Center, 300 S Townsend Street, Garden Level Workshop Room.

Participants

1. Art Edison, University of Georgia (USA)
2. Clary Clish, Broad Institute (USA)
3. Corey Broeckling, Colorado State University (USA)
4. Dan Raftery, University of Washington (USA)
5. Dajana Vuckovic, Concordia University (USA)
6. David Wishart, University of Alberta (Canada)
7. Elizabeth Want, Imperial College (United Kingdom)
8. Ewy Mathe, National Center for Advancing Translational Sciences (USA)
9. Ian Lewis, University of Calgary (Canada)
10. Nichole Reisdorph, University of Colorado, Anschutz Medical Campus (USA)
11. Rafael Brüscheiler, The Ohio State University (USA)
12. Robert Powers, University of Nebraska (USA)
13. Timothy Ebbels, Imperial College (United Kingdom)
14. Tracey Schock, National Institute of Standards and Technology (USA)
15. Ulrich Günther, Universität zu Lübeck (Germany)
16. Valerie Copie, Montana State University (USA)
17. Vanessa Phelan, University of Colorado, Anschutz Medical Campus (USA)
18. Min Zhang, Purdue University (USA)

Program Notes:

- The length of each talk is 45 min, with ~30-35 min to present and ~10-15 min for discussion.
- There is an LCD projector in the classroom, but please bring your own laptop to connect to the projector.
- Please include a few slides that briefly explain the main techniques you use plus strengths/weaknesses, as we have a diverse array of expertise attending
- One of the best outcomes from previous meetings was robust discussion of common challenges/opportunities in the field with ideas to improve moving forward. Feel free to include a slide toward the end which captures these ideas, faced by your specific metabolomics domain, to facilitate this kind of discussion
- There will be a fair amount of time for discussions and activities outside of the formal lectures. For those interested in hiking, keep a close eye on the weather especially at higher altitudes (risk of lightning). Also, bring a rain jacket in anticipation of possible thunderstorms, especially in the afternoon.
- Nichole and Liz will organize a WhatsApp group on Day 1 for communicating about group activities and informal meals. If you'd like to participate, you'll just need to have WhatsApp installed and provide your phone number on Day 1.
- The old mining town of Telluride is at 8750 feet above sea level with low humidity. This may require some physiological adjustment, especially during the first couple of days. Staying hydrated usually helps.
- Evenings can be chilly, thus a sweater or fleece will be useful.
- Family members are welcome to participate in the optional lunches, informal events, and the final evening meal at Talay. Payment is to be made through TSRC; please contact Cindy Fusting cindy@telluridescience.org.

Meeting Description:

Synopsis:

Metabolomics is a rapidly evolving field that studies the metabolism of a living system in relationship to its phenotype, including health and disease states. The two primary analytical techniques used are nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), which provide both qualitative and quantitative high-resolution information concerning the metabolites present in a cell, tissue, or biofluid. Rapid progress is being made in method development and their application to complex biological systems. Advances in statistical methods, including big data approaches and rapidly growing databases, are also impacting the field. The purpose of this workshop is to bring together metabolomics experts in NMR, MS, and bioinformatics to discuss recent successes and challenges in their research.

Expanded narrative:

In recent years, metabolomics (sometimes also called metabonomics) has made great strides in the analysis of complex metabolite molecular mixtures encountered in many different areas of the life sciences ranging from food to biomedicine. Many powerful applications have emerged for rapid screening, biomarker identification, diagnostics, and the identification of biochemical pathways and their fluxes. In the human body alone, it has been estimated that more than 150,000 different metabolites exist, most of which are still unknown. There is a clear need for the development of new tools for the identification of unknowns and their assignment to new biochemical pathways.

The two main analytical techniques in metabolomics are mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. Both techniques are very powerful on their own, but in the past their high complementarity has impeded their synergistic use. As a consequence, and due to cost and expertise needed to run these instruments, many research labs predominantly use one of the techniques over the other. When both techniques are used, they are often applied independently rather than as a hyphenated system, and comparison of the results can be inconclusive.

This TSRC workshop has the goal to bring together leading scientists in both NMR- and MS-based metabolomics to spur constructive discussions about current successes and challenges of both MS and NMR. Particularly how to optimize the integration of these two methods to produce new and better science. We also invite speakers who are at the forefront of metabolomics applications to inspire new metabolomics tools in terms of sample preparation, quality control, hardware, software, databases, and reproducibility.

Sunday, August 4th

17:00-18:30 TSRC sponsored Meet & Greet, [Alibi](#) – 157 S. Fir Street
TSRC staff will be on hand to welcome you and distribute badges. You will find Nichole and Liz and many other participants here. We hope you can join us!

18:45-21:00 Dinner + drinks/cocktails and snacks for Frontiers in Metabolomics Attendees who wish to partake. Location: TBC. Please talk to Liz at the Meet & Greet for more information.

Monday, August 5th

8:00-8:30 Breakfast at Telluride Science & Innovation Center, 300 S Townsend Street
***Breakfast is available here every morning from 7:30 onward

8:40-9:10 Welcome Remarks, Liz and Nichole, Telluride Science & Innovation Center, 300 S Townsend Street, Garden Level Workshop Room
Introductions (<3 min each please)

Session 1: Pipeline Improvement

Session Chair: Liz Want

Day 1 Scribe: Nichole Reisdorph

9:10-9:55 Clary Clish, Integration of nontargeted metabolomics datasets from human cohorts for replication analyses and other purposes: Approaches and challenges

9:55-10:40 Dan Raftery, Anomalous Dynamics of Plasma Metabolites: Should We Change Our Collection Procedures?

20 minute break

11:00-11:45 Min Zhang, Modeling blood metabolite homeostasis to minimize sample heterogeneity across cohorts

11:45- 12:30 Corey Broeckling, Benchmark Metabolomics Data: A description of the resource and evaluation of an R-based processing workflow

Lunch Break

Afternoon: Free discussions amid hiking, biking, or other activities

Tuesday, August 6th

7.30-8.30 Breakfast at Telluride Science & Innovation Center, 300 S Townsend Street

Session 2: Machine Learning

Session Chair: Corey Broeckling

Day 2 Scribe: TBD

- 08:30-09:15 Tim Ebbels, Getting more out of metabolomic NMR data with deep and shallow learning
- 09:15-10:00 Rafael Brüscheiler, New Experimental and Computational Approaches for Studying Knowns and Unknowns in Metabolomics Mixtures

20 minute break

- 10:20-11:05 Dave Wishart, Deep Learning for Deeper Metabolome Coverage
- 11:30-12:30 Organized optional lunch at Depot (RSVP and pay prior to meeting)

Free discussions amid hiking, biking, or other activities

Session 3: Microbiome meets Metabolome

Session Chair: Dan Raftery

Scribe: TBC

- 15:00- 15:45 Vanessa Phelan, Harnessing metabolic boundary fluxes to map the evolution of human pathogens: new insights into the role metabolism plays in speciation, phylodynamics, and ecology
- 15:45-16:30 Ian Lewis, Deconvoluting Metabolic Exchange within Synthetic Microbial Communities
- 16:30-17:15 Nichole Reisdorph, Microbiome-mediated effects of natural products on neurotransmitter-related molecular networks and the metabolome
- 17:15 – 18:00 White Paper Discussion, Facilitators: TBD
- 18:30-19:30 Telluride Science Town Talk
Location: Telluride Conference Center in Mountain Village, Cash Bar, Doors Open at 6:00pm
Topic: Chromatin: Your DNA in a package

Wednesday, August 7th

- 7.30-8.30 Breakfast at Telluride Science & Innovation Center, 300 S Townsend Street

Morning: Free discussions amid hiking, biking, or other activities

**Headcount for dinner together on Thursday evening at Talay Restaurant. This was pre-paid as part of your registration. Family members can be added in advance.*

**Reminder of need to schedule shuttle to Montrose Airport for return on Friday*

Session 4: Advances in Data Quality

Session Chair: Tim Ebbels

Scribe: TBD

- 13:30-14:15 Ewy Mathe, Increasing in trust in our data generation and analysis pipelines

14:15-15:00 Robert Powers, Metabolomics Best Practices: some updates, progress, and problems

20 minute break

15:20-16:05 Tracey Schock, NIST SRM 1950 Metabolites in Frozen Human Plasma: Community Engagements and What's Next

16:05-16:50 Dajana Vuckovic, Improving data quality and harmonization of untargeted lipidomics studies

17:30-19:30 All Telluride Science Picnic

Free BBQ, Beer, Wine, and Non-Alcoholic Beverages. Friends and Family are invited free of charge.

Location: Telluride Science & Innovation Center, 300 S. Townsend St.

Thursday, August 8th

7.30-8.30 Breakfast at Telluride Science & Innovation Center, 300 S Townsend Street

Morning: Free discussions amid hiking, biking, or other activities

Session 5: Next Generation Technology

Session Chair: Clary Clish

Day 4 Scribe: TBD

11:30-13:00 Organized optional lunch at Dept (RSVP and pay prior to meeting)

13:00-13:45 Art Edison, Functional Metabolomics using NMR

13:45-14:30 Liz Want, Multi-omics approaches in Glioblastoma and Brain Injury

20 minute Break

Session 6: Clinical Applications

Session Chair: Nichole Reisdorph

Day 4 Scribe: TBD

14:50-15:35 Valerie Copie, Can we employ metabolomics to redress metabolic dysfunctions associated with neuronal degeneration?

15:35-16:20 Ulrich Günther, NMR Glycomics: From method development to clinical applications

16:20 – 16:50 White Paper Discussion, Facilitators: TBD

16:50- 17:20 Business Meeting - Feedback on current meeting, discuss the next meeting, vote on conference chairs. All attendees are asked to participate.

Closing Remarks Nichole and Liz

18:00 Dinner to celebrate last evening together at Talay

Speakers, Titles and Topics

Clary Clish: Integration of nontargeted metabolomics datasets from human cohorts for replication analyses and other purposes: Approaches and challenges

- Our approach to aligning nontargeted datasets to enable replication analyses or feature annotation
- Filling gaps for features that are not consistently extracted among sample batches or cohorts using unsupervised software
- Some examples from recent projects

Dan Raftery: Anomalous Dynamics of Plasma Metabolites: Should We Change Our Collection Procedures

- Labile metabolites don't behave as you'd expect when blood is stored on ice.
- Some of these metabolites appear to be early indicators of sample quality and storage conditions.
- We may need to rethink blood sampling methods for metabolomics going forward.

Min Zhang: Modeling blood metabolite homeostasis to minimize sample heterogeneity across cohorts

- Majority of the variations between metabolite levels are due to cohorts;
- Modeling metabolite levels can reduce cross-cohort variations;
- Metabolites can capture most of the variations across cohorts;
- Additional cohorts can further improve homeostatic model;

Corey Broeckling: Benchmark Metabolomics Data: A description of the resource and evaluation of an R-based processing workflow.

- Development of an benchmark dataset designed specifically for metabolomics informatics evaluation
- Evaluation of an XCMS/RAMClustR based workflow for processing data
- Discussion of evaluation criteria to enable robust comparisons of software performance

Tim Ebbels: "Getting more out of metabolomic NMR data with deep and shallow learning"

- Application of Generative Adversarial Networks for resolution enhancement in metabolomic 2D NMR
- 1D NMR spectral annotation by feature extraction and recovery (SAFER)

Rafael Brüsweiler: New Experimental and Computational Approaches for Studying Knowns and Unknowns in Metabolomics Mixtures

- Deep neural networks for accurate deconvolution of overlapped spectra
- Pros and cons of 1D vs 2D NMR-based metabolomics with COLMARq and COLMAR1d
- B0-field independent metabolite query
- A streamlined platform for unknown determination with NMR and MS
- Application to infections caused by *Pseudomonas aeruginosa*

Dave Wishart: Deep Learning for Deeper Metabolome Coverage

- Explaining some basic deep learning concepts
- Showing examples of how deep learning can identify novel metabolites in MS-based metabolomics
- Explaining how deep learning can enhance NMR spectra for broader coverage
- Illustrating how deep learning and LLMs can mine novel metabolites from the literature

Vanessa Phelan: Deconvoluting Metabolic Exchange within Synthetic Microbial Communities

- Relevance of SynComs to understanding the role of the microbiota in mediating health and disease
- Use of metabolomics to capture the metabolic exchange within SynComs
- Integrating structure-driven and statistical approaches to generate metabolite and microbe-specific hypotheses

Ian Lewis: Harnessing metabolic boundary fluxes to map the evolution of human pathogens: new insights into the role metabolism plays in speciation, phylodynamics, and ecology

- Why measuring boundary fluxes is a useful orthogonal strategy
- How metabolic preferences of organism can be used to reconstruct phylogenies
- Surprising lineage-specific insights that manifest through boundary flux analysis

Nichole Reisdorph: Microbiome-mediated effects of natural products on neurotransmitter-related molecular networks and the metabolome

- Experimental and computational strategies for associating microbial species with food related compounds following dietary interventions.
- Expansion of our use of a step-wise, “food first” approach to reduce complex datasets to compounds that are of relevance to dietary interventions.
- Includes update to previous talk on Nutrimetabolomics, including validation of our strategy/biomarkers in a new cohort. Will also discuss the use of Biotransformer to predict metabolites of food compounds and detect them in biosamples.

Ewy Mathe: Increasing in trust in our data generation and analysis pipelines”

- Metabolomic and lipidomic profiling at scale
- Building a FAIR data analysis infrastructure
- Standardizing data reporting for linking metabolism with other information on diseases, targets and drugs

Robert Powers: Metabolomics Best Practices: some updates, progress, and problems.

- Meta-analysis of cancer clinical metabolomics studies identifies a reproducibility problem.
- A simulated LC-MS metabolomics data set identified variable and inconsistent results from three different software packages.
- Systematic assessment of NMR acquisition and processing parameters.
- Optimization of NMR sample preparation and software parameters.
- Further assessment of ¹H and ¹³C chemical shift variability due to sample conditions (i.e., field strength, temperature, pH, ionic strength, and mixture composition).
- New capabilities with our MVAPACK software and MVAPACK Online webserver.

Tracey Schock, NIST SRM 1950 Metabolites in Frozen Human Plasma: Community Engagements and What’s Next

- A community survey of existing and potential users on use, practices and certified values
- Metabolomics Quality Assurance and Quality Control Consortium (mQACC) initiative on community characterization of NIST SRM 1950.
- Plans for the successive material

Dajana Vuckovic: Improving data quality and harmonization of untargeted lipidomics studies

- Microsampling and in vivo microextraction: opportunities and challenges
- Analytical factors contributing to data quality and issues with data harmonization: internal standard selection, adduct formation, sample stability during sampling and sample preparation
- Need for stability markers and stability databases
- Metabolomics Quality Assurance and Quality Control Consortium (mQACC) Living Guidance

Art Edison: Functional Metabolomics using NMR

- Chromatography can improve annotation and open up new opportunities for functional testing of metabolites.
- Improved ¹³C detection facilitates flux studies.

Liz Want: Multi-omics approaches in Glioblastoma

- Targeted DESI imaging of brain tissue
- Proteomics analysis of regions of interest
- How small can we go?
- How can we ensure maximum protein recovery?

Valerie Copie: Can we employ metabolomics to redress metabolic dysfunctions associated with neuronal degeneration?

Ulrich Günther: NMR Glycomics: From method development to clinical applications

- Glycosylations and clinical diagnostics - what is already known?
- Cleaning up old errors in glycoprotein assignments
- New fast NMR methods for glycoprotein analysis
- Looking at first disease populations
- Outlook: What is needed to get this method clinically used?