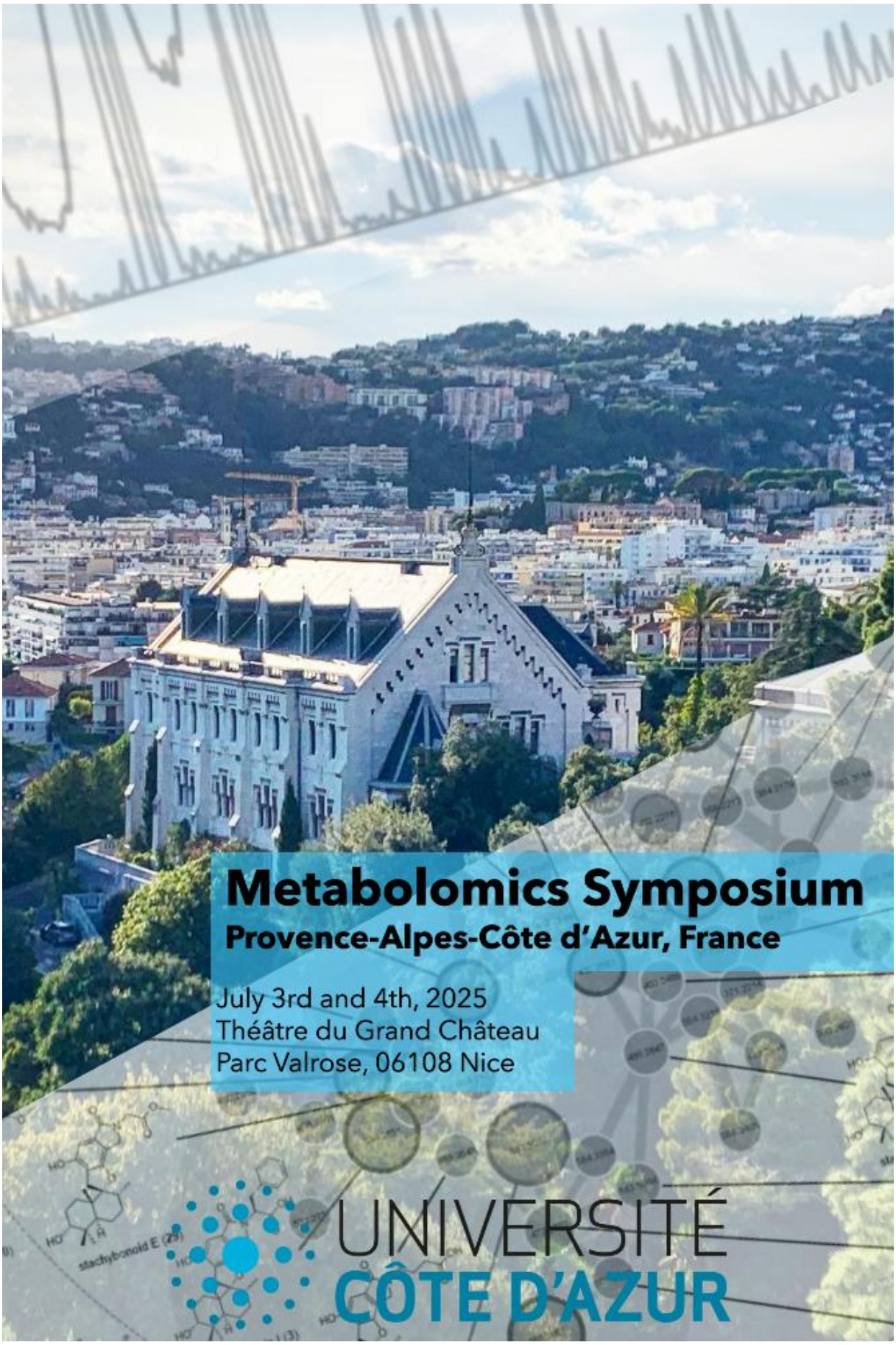
Metabolomics Symposium
Provence-Alpes-Côte d'Azur, France
July 3rd and 4th, 2025
Théâtre du Grand Château
Parc Valrose, 06108 Nice
UNIVERSITÉ
CÔTE D'AZUR

Program

Metabolomics Symposium
Provence-Alpes-Côte d'Azur, France

3rd July 2025

Théâtre du Grand Château, Campus VALROSE, Université Côte d'Azur, 28 avenue de Valrose, 06108, Nice

08:30 - 09:00: Welcome and Registration

09:00 - 09:30: Opening Speech

- Pr. Laurent COUNILLON
Vice President of Research, Université Côte d'Azur

- Local Organizing Committee
Pr. Mohamed MEHIRI, ICN, CNRS, Université Côte d'Azur
Dr. Delphine DEBAYLE, IPMC, CNRS, Université Côte d'Azur
Aurélie SEASSAU, ISA, INRAE, Université Côte d'Azur
Dr. Fabien FONTAINE-VIVE, ICN, CNRS, Université Côte d'Azur
Dr. Louis-Félix NOTHIAS, ICN, CNRS, Université Côte d'Azur

Session 1

09:30 - 10:00: Can internal exposome signatures predict lung cancer risk beyond smoking? Evidence from metabolomics and multi-omics studies
Pr. Sonia DAGNINO, UMR 4320 PHEN-X, CEA, Université Côte d'Azur

10:00 - 10:15: Search for metabolomic signatures to determine the exposome of honey bees (Apis mellifera), a colony health indicator
Safae OUALI, UMR 4320 PHEN-X, CEA, Université Côte d'Azur

10:15 - 10:30:The Role of Epigenetic and Metabolic Biomarkers in Predictive and Preventive Medicine
Dr. Mohamed BEN AHMED, TechInCare

10:30 – 11:00: Coffee Break, Posters, and Discussions

Session 2

11:00 - 11:45: Leveraging metabolomics to reveal how metabolic alterations drive colorectal cancer progression and enable patient stratification.
Dr. Nathalie LEGRAVE, Luxembourg Institute of Health, Department of Cancer Research

11:45 - 12:00: Use of a metabolomics approach by Py-GC/MS for archaeometric purposes
Pr. Gérald CULIOLI, IMBE, Avignon Université

12:00 - 12:15: The Latest Innovations in Mass Spectrometry: The Orbitrap Astral
Marie-Pierre PAVAGEAU, Thermo Fisher Scientific

12:15 - 13:45: Lunch Break and Poster Session

Session 3

13:45 - 14:15: Presentation of a Software for the Interpretation of Metabolomic and Multi-Omics Data Based on Multi-Block Data Segmentation Methods
Dr. Jean-Charles MARTIN, C2VN, INRAE, Aix-Marseille Université

14:15 - 14:45: High-Throughput Metabolomics and Lipidomics Workflows for Rare Disease and Cancer Research
Dr. Djawed BENNOUNA, NIH, NCATS/DPI, USA

14:45 - 15:00: Perspicacité-AI: An LLM-Powered Platform for Accelerating Scientific Research and Education
Lucas PRADI, ICN, CNRS, Université Côte d'Azur

15:00 - 15:30: Coffee Break and Discussions

Session 4 – Workshop on Data Analysis

15:30 - 17:30: Data Processing and Spectral Annotation of LC-HRMS/MS Metabolomics Data
Dr. Corinna BRUNGS, University of Vienna, Austria
Dr. Robin SCHMID, mzio GmbH, Bremen, Germany

17:30: Symposium Closing Session

Program

Metabolomics Symposium
Provence-Alpes-Côte d'Azur, France

4th July 2025

Théâtre du Grand Château, Campus VALROSE, Université Côte d'Azur, 28 avenue de Valrose, 06108, Nice

08:30 - 09:00: Welcome and Registration

Session 5

09:00 - 9:45: Bioactive Natural Products: From Discovery to Chemo-diversification
Dr. Emerson F. QUEIROZ, University of Geneva, Switzerland

09:45 - 10:15: New Strategy in the Discovery of Natural Antituberculosis Agents from French Guiana Flora
Dr. Elnur GARAYEV, IMBE, Aix-Marseille Université

10:15 - 10:30: Exploration of the Antitubercular Potential of French Guiana's Flora through a Metabolomic Study
Célia BREAUD, IMBE, Aix-Marseille Université

10:30 - 10:45: Development of Innovative Natural Cosmetic Ingredients
Dr. Camille DUBOIS, ICN, CNRS, Université Côte d'Azur

10:45 - 11:00: UHPLC-DAD-nano ESI-HRMS/MS-DPPH/ABTS-VIS On-Line coupling for the detection of antioxidant compounds: a novel analytical approach applied to Provence flora species
Clémentine ACHARD-BACCATI, Aix-Marseille Université

11:00 – 11:15: Coffee Break, Posters, and Discussions

Session 6

11:15 - 11:45 : Discovery and quantification of lipoamino acids in bacteria: new partners in microbiote studies?
Dr. Justine BERTRAND MICHEL, MTH_MetaToul, I2M, Toulouse

11:45- 12:15: Lipidomics with a broad coverage of lipid isomers
Dr. Takeshi HARAYAMA, IPMC, CNRS, Université Côte d'Azur

12:15 - 12:30: Lipid Analysis by High Performance Thin Layer Chromatography Coupled to Mass Spectrometry
Dr. Rita ARAUJO, IPMC, CNRS, Université Côte d'Azur

12:30 - 12:45: Latest Sciex Advances in Metabolomics and Lipidomics
Heather CHASSAING, Sciex

12:45 - 14:00: Lunch Break and Poster Session

Session 7

14:00 - 14:30: Characterizing marine benthic exometabolites from species to ecosystems
Dr. Charlotte SIMMLER, IMBE, CNRS, IRD, Aix Marseille Université

14:30 – 15:15: Multi-Omics Analysis of Plants: Uncovering Metabolic Defense Mechanisms
Dr. Raphael LUGAN, INRAE, Avignon Université

15:15 - 15:30: Coffee Break and Discussions

Session 8 – Workshop on Data Analysis

15:30 - 17:00: Comprehensive Analysis of Small Molecule MS/MS Data with SIRIUS
Dr. Kai DÜHRKOP, Bright Giant GmbH

17:00 - 17:30: Symposium Closing Session

Can internal exposome signatures predict lung cancer risk beyond smoking? Evidence from metabolomics and multi-omics studies

Prof. Sonia DAGNINO
UMR 4320 PHEN-X PHysiopathologie, ENvironnement & eXposome
Team EARTH, Directrice Scientifique de la Multi-Omiques, B. Rossi
Université Côte d'Azur, CEA. Nice, France.

Lung cancer is the leading cause of cancer-related mortality worldwide, with over 1.8 million deaths annually. While tobacco smoking remains the main recognized risk factor, a significant proportion of lung cancer cases occur in non-smokers, especially among women. Environmental exposures beyond smoking remain insufficiently characterized, and internal exposome profiling offers a novel approach to detect early biological responses to environmental insults. In this work we investigate whether molecular signatures of internal exposome (proteomic, metabolomic, adductomics and epigenomic markers) are associated with lung cancer risk independently of smoking, and whether these signatures can serve as early biomarkers for precision prevention strategies. This work integrates data from two nested case-control studies within large prospective cohorts. Blood samples were analyzed using: (i) an inflammatory proteomics panel (92 proteins), (ii) genome-wide DNA methylation (485,512 CpG sites), and (iii) untargeted metabolomics (16,778 features). Multi-omics data were analyzed using univariate models, directed acyclic graphs (DAGs), and integrated network-based approaches to disentangle the contribution of smoking-mediated and independent molecular alterations.

We identified multiple omics markers significantly associated with lung cancer risk years before diagnosis. Only a subset of these biomarkers were associated with smoking, suggesting distinct exposome-driven pathways. Our findings support the presence of robust, early molecular fingerprints of environmental exposure linked to lung cancer development, independent of tobacco use. These exposome-informed biomarkers offer promising avenues for early detection and prevention, particularly in non-smokers.

Search for metabolomic signatures to determine the exposome of honey bees *(Apis mellifera*), a colony health indicator

Safae OUALI
PhD in bioinformatics,
Université Cote d'Azur (PHEN-X UMR 4320, Team EARTH)
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&
Anses (Honeybee pathology unit)
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Bees play a fundamental role in the balance of ecosystems, contributing to biodiversity and serving as bioindicators of environmental quality. However, in recent years, a worrying decline in bee populations has been observed worldwide. This phenomenon is attributed to various stress factors likely to weaken colonies and increase their mortality, including pesticides and pathogens. The links between these factors and the deterioration in bee health have been established, but the underlying molecular mechanisms remain poorly understood. Metabolomics offers great potential for the discovery of biomarkers and for enhancing our understanding of physiological disruptions at the molecular level. To better characterize the effects of pesticides exposure, controlled laboratory experiments and field exposures under natural conditions have been carried out. The aim of these studies is to identify biomarkers of bee metabolome capable of specifically signaling the cause of mortality, thereby adding to the targeted analyses. To achieve this, an analytical approach based on high-resolution mass spectrometry (HRMS) is being developed. Statistical analyses, including univariate and multivariate methods, revealed distinct metabolic signatures associated with pesticide exposure. Several biological pathways were significantly altered, highlighting key molecular disruptions linked to chemical stress. The results highlight the utility of metabolomics in identifying candidate biomarkers indicative of pesticide-induced stress in bees. This approach not only contributes to monitor and protect bee populations, but also to take advantage of their role as sentinel species, providing valuable information on the health of the ecosystem.

Leveraging metabolomics to reveal how metabolic alterations drive colorectal cancer progression and enable patient stratification

Dr. Nathalie LEGRAVE
Head of Metabolomics Platform, Metabolomics Platform
Luxembourg Institute of Health
Department of Cancer Research
1A-B, rue Thomas Edison, L-1445 Strassen
Luxembourg

Colorectal cancer (CRC) is projected to have the highest global incidence and mortality by 2040, with rising rates of therapy resistance and an alarming increase among younger individuals. Despite advances in targeted and immune therapies, CRC's heterogeneity continues to limit universal treatment strategies. To address this, a deeper understanding of the mechanisms driving CRC progression is essential for improving patient stratification and enabling personalised care. Our recent work highlights metabolic rewiring as a key driver of disease evolution, with formate emerging as a metabolite of particular interest. Here, we present the implementation of a robust metabolomics strategy for large-scale cohort analysis applied to a well-characterised CRC cohort. This includes tumour and matched normal tissues, as well as longitudinal plasma samples from CRC patients and healthy controls. Our ongoing approach integrates clinical data, transcriptomic analysis and cytokine profiling with in-depth metabolomic and lipidomic analyses, with a particular focus on formate metabolism. This comprehensive multi-omics workflow is currently being developed to minimise technical variability, enhance analytical sensitivity, and uncover meaningful biological trends beyond statistical significance—particularly in longitudinal data. Additionally, our approach enables a multi-compartment analysis that expands biomarker discovery and provides mechanistic insight into metabolic reprogramming in cancer. With this strategy, we aim to demonstrate that the observable metabolic reprogramming in CRC, and the dysregulated formate metabolism, can serve as a powerful tool for patient stratification, predicting disease trajectories, and discovering novel therapeutic targets and strategies. We are also working toward developing predictive models based on combined molecular and metabolic features. The workflow we are developing in the context of CRC is broadly applicable to other disease cohorts, and we believe it holds real potential for advancing precision medicine.

Use of a metabolomics approach by Py-GC/MS for archaeometric purposes

Lou Spanneut[2,4], Manon Zgajnar[1], Céline Joliot[1], Océane Pollet[2,3], Gwenaëlle Goude[4], Edouard Bard[2], Thibaut Devièse[2] & Gérald Culioli[1]

1 Institut Méditerranéen de Biodiversité et d'Ecologie marine et continentale (IMBE), Aix-Marseille Université, Avignon Université, CNRS, IRD, Avignon, France
2 Centre de Recherche et d'Enseignement en Géosciences de l'Environnement (CEREGE), Aix-Marseille Université, CNRS, IRD, INRAE, Collège de France, Aix-en-Provence, France
3 Physique des Interactions Ioniques et Moléculaires (PIIM), Aix-Marseille Université, CNRS, Marseille, France
4 Laboratoire Méditerranéen de Préhistoire Europe Afrique (LAMPEA), Aix-Marseille Université, Ministère de la Culture, CNRS, Ministère de la Culture, Aix-en-Provence, France

Archaeological bones, which are often analysed for chronological and dietary reconstructions, are vulnerable to contamination from the burial environment and/or the conservation materials applied, which can compromise the integrity of the analytical data thus obtained. In this context, this study examines the use of pyrolysis coupled with gas chromatography and mass spectrometry (Py-GC/MS) to improve the analysis of collagen extracted from archaeological bones. Py-GC/MS is a particularly effective analytical technique for archaeometric studies. It requires no sample preparation and can be used to characterise a wide range of organic molecules, in particular by degrading the macromolecules present. As a result, it produces chromatograms of pyrolysates, known as pyrograms, which reflect both native products (thermostable low molecular weight molecules) and degradation products (thermosensitive and/or high molecular weight molecules). One drawback is that these pyrograms are often complex and difficult to interpret. This is where metabolomics comes in, a powerful approach to analytical chemistry that enables large, complex datasets to be analysed.

In this study, a panel of archaeological collagen samples of good and poor quality (notably due to the presence of contaminants) were analysed by Py-GC/MS. The results obtained showed that this technique is highly effective in detecting poor quality samples, enabling the most appropriate processing protocol to be chosen for the subsequent step of carbon-14 dating.

Perspicacité-AI: An AI-Pipeline for Accelerating Scientific Education and Research

Lucas Pradi[1], Tao Jiang[1,2], Matthieu Ferraud[1,2], Madina Bekbergenova[1,2], Louis-Félix Nothias[1,2]*

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2 — Interdisciplinary Institute for Artificial Intelligence (3iA) Côte d'Azur, Nice
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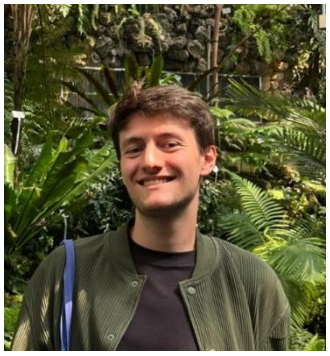


Recently, emerging tools such as LLM have gained attention in scientific research and education. However, their limitations — notably outdated knowledge and untraceable provenance — hinder their ability to keep pace with rapid advancements in scientific fields, like metabolomics. Some of these challenges can be addressed by coupling LLM with Retrieval-Augmented Generation (RAG) techniques, which combine relevant data retrieval with generative AI. Here, we developed Perspicacité-AI, a free and open-source agentic literature assistant with advanced RAG capabilities designed for scientific research and education.

Perspicacité-AI required the development of the Bibt2KB python package, which seamlessly transforms open-access bibliographic references into a structured and searchable Facebook AI Similarity Search (FAISS) knowledge base (KB). The KB generated is used by the pipeline's framework to deploy an AI-assistant enhanced by RAG, ensuring that each question asked is grounded in relevant literature and documents. The framework features different advanced modes of document search and question-answering, including Perspicacité-Profound, an iterative, structured reasoning workflow suitable for answering complex scientific questions with the trackable facts and sources. Furthermore, the pipeline supports major open source and proprietary LLM providers, broadening access for different users.

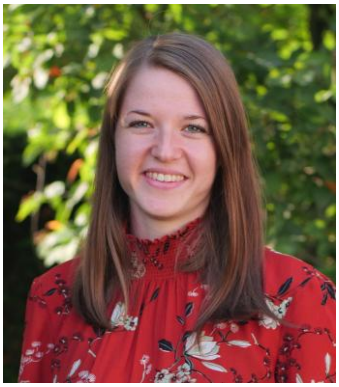
Perspicacité-AI also incorporates a novel reranking function for document selection, Sigmoid Weighted RRF (SW-RRF). The benchmarking of SW-RRF showed improvement over the traditional Reciprocal Reranking Function (RRF) for all tested metrics: Recall, Precision, F1, Mean Reciprocal Rank (MRR), Average Precision (AP) and Normalized Discounted Cumulative Gain (NDCG) at 1, 3, 5 and 10 documents retrieved ($p < 0.05$) at no computational expenses.

Initial applications of Perspicacité-AI in computational metabolomics [metaboguide.holobiomicslab.eu] demonstrated effective chatbot responses with accurate citations, and while still ongoing, initial evaluations of the pipeline show promising results, not only mitigating some of the limitations of standalone LLMs but empowering scientific literature with generative AI.

Acknowledgement:

This work was supported by the French government through the France 2030 investment plan managed by the National Research Agency (ANR), as part of the Initiative of Excellence Université Côte d'Azur under reference number ANR-15-IDEX-01. **Lucas Pradi** is Supported by the Fonds National de la Recherche, Luxembourg, project **17994255**.

Computational Mass Spectrometry in mzmine - Hands-on Training



Dr. Corinna BRUNGS, University of Vienna, Austria
Pharmacist and Analytical Chemist focused on reference data and plant metabolism
Reference Data Project Lead cbrungs1789@gmail.com
GitHub | Twitter | LinkedIn

Dr. Robin SCHMID, mzio GmbH, Bremen, Germany
Food Chemist and Analytical Chemist focused on computational mass spectrometry
Lead Architect of mzmine https://robinschmid.github.io

This workshop will introduce non-target LC-MS^2 data processing workflows in mzmine. You will integrate feature detection, compound annotation, molecular networking, and statistical analysis. The new interactive molecular networking in mzmine clusters MS^2 fragmentation spectra by similarity reflecting the structural similarity of their underlying compounds. All the results from these workflows can be exported for downstream analysis in other popular tools like GNPS, SIRIUS, and statistical pipelines. The mzwizard aids in setting up workflows for various instruments and methods, e.g., for mass spectral reference library generation. We encourage you to bring your laptops for the best hands-on experience, but you can also take it as a live demo. Please download the provided dataset and install mzmine before the workshop.

Dataset

The dataset is constituted of HRMS/MS data acquired over *Pseudomonas* strains. It contains wild type or mutant strains together with medium blanks and QCs. More background on the dataset is available at https://doi.org/10.1111/1462-2920.15139.

Downloads

- Download the **dataset zip** file ~500 MB and unpack it. https://drive.google.com/drive/folders/12X1fGBcTpkcfSAijlpNXQxjU484xFL6Y?usp=sharing

- Open mzmine and register a **new user** for free or download the workshop user: https://drive.google.com/file/d/1H03wfwFCZEvlFSRiBggcvfFkUlYNTrSy/view?usp=sharing
- **Spectral library**:
  The Google Drive dataset **already** contains the MoNA (LC-MS^2 pos) library Alternative link if downloading from MassIVE

Installation

- **mzmine:** Download and install the latest version - Current **mzmine 4.2.0**. https://github.com/mzmine/mzmine/releases/latest
  There are platform-specific installers for Windows, Mac, and Linux. There is **NO** need to install any other tool or Java Virtual Machine (JVM): Refer to the documentation for installation instructions and post issues on GitHub: https://mzmine.org/documentation/

1. **mzmine paper**: https://www.nature.com/articles/s41587-023-01690-2
2. Development: https://github.com/mzmine/mzmine/
3. Documentation: https://mzmine.org/documentation/
4. Protocol: https://doi.org/10.26434/chemrxiv-2023-98n6q-v2
5. YouTube: https://www.youtube.com/@mzmineproject/playlists

Bioactive Natural Products: From Discovery to Chemo-diversification

Plinio Scapozza[1,2], Marion Zwingelstein,[3] Robin Huber[1,2], Laurence Marcourt[1,2], Emilie Michellod[3], Jean-Luc Wolfender[1,2], Katia Gindro[3], and **Emerson F. Queiroz**[1,2]

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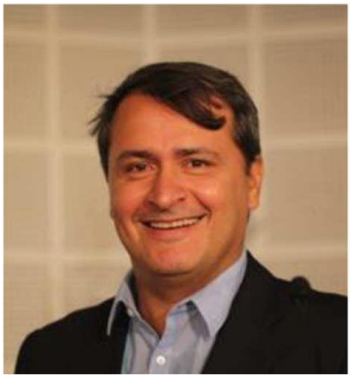
[2] Institute of Pharmaceutical Sciences of Western Switzerland (ISPSO), University of Geneva, CMU – Rue Michel Servet 1, 1211 Geneva 4, Switzerland.
[3] Agroscope, Plant Protection Research Division, Route de Duillier 50, P.O. Box 1012, 1260 Nyon, Switzerland



Over the past decade, we have witnessed a revolution in the methodologies applied to natural product research. Current approaches combine powerful metabolite profiling methods for compound annotation and prioritization. Targeted isolation is performed using high-resolution chromatographic methods that closely match those obtained for analytical profiling [1]. Thanks to these tools, minor bioactive compounds were identified. However, in plant extracts, the major compounds are generally common structures, apparently irrelevant for drug discovery. In this context, biotransformation could be an alternative to valorize them. For this proposal, we employ two biotech approaches: reactions using fungal secretomes (mixture of enzymes), and biotransformation using living organisms (whole-cell biotransformation). Saprophytic fungi, such as *Bothyis cinerea* and *Trametes versicolor*, were used as a source of enzymes [2]. Stilbenes, chalcones, phenylpropanoids, and terpenes from the Swiss flora were used as substrates. Biotransformations were first conducted at an analytical scale and monitored by UHPLC-PDA-ELSD-HRMS for the detection of unusual features. Promising reactions were scale-up at the gram scale, and high-resolution preparative chromatography combined with dryload was used for their purification [1]. Enantiomers were purified by chiral chromatography. HRMS, 2D NMR, and ECD were used for structural elucidation. Compounds were evaluated for their antibacterial and antiviral activity against relevant targets. A library of over 280 compounds was generated at the mg scale from common NPs. Some of the compounds obtained presented unique scaffolds and potent biological activities [3]. In most cases, it was possible to propose the enzymes and mechanisms involved in the synthesis of each compound [4]. The applications, possibilities, and limitations of these latest technologies will be illustrated with recent investigations carried out in our laboratory.

[1] Queiroz EF, Guillarme D, Wolfender JL. Advanced high-resolution chromatographic strategies for efficient isolation of natural products from complex biological matrices: from metabolite profiling to pure chemical entities. Phytochem Rev 2024; 23: 1415-1442; DOI; 10.1007/s11101-024-09928-w.

[2] Huber R, Marcourt L, Koval A, Schnee S, Righi D, Michellod E, Katanaev VL, Wolfender JL, Gindro K, Queiroz EF. Chemoenzymatic synthesis of complex phenylpropanoid derivatives by the *Botrytis cinerea* secretome and evaluation of their wnt inhibition activity. Frontiers in Plant Science 2021; 12: 805610; DOI; 10.3389/fpls.2021.805610.

[3] Huber R, Marcourt L, Heritier M, Luscher A, Guebey L, Schnee S, Michellod E, Guerrier S, Wolfender JL, Scapozza L, Kohler T, Gindro K, Queiroz EF. Generation of potent antibacterial compounds through enzymatic and chemical modifications of the *trans*-delta-viniferin scaffold. Scientific Reports 2023; 13,: DOI; 10.1038/s41598-023-43000-5.

[4] Huber R, Marcourt L, Félix F, Tardy S, Michellod E, Scapozza L, Wolfender JL, Gindro K, Queiroz EF. Study of phenoxy radical couplings using the enzymatic secretome of *Botrytis cinerea*. Front Chem 2024; 12: DOI; 10.3389/fchem.2024.1390066.

New Strategy in the Discovery of Natural Antituberculosis Agents from French Guiana Flora

Elnur Garayev
Associate Professor
Aix Marseille Univ, CNRS 7263, IRD 237, Avignon Université, IMBE, 27 Blvd Jean Moulin, Service of Pharmacognosy, Faculty of Pharmacy, 13385 Marseille, France

Nowadays, approximately 60% of the world's population uses herbal medicines, and plants are recognized as a source of therapeutically effective drugs. Natural products are an important source of new structural scaffolds and historically have always been a privileged source of inspiration in drug discovery. Tuberculosis (TB) is one of the top 10 world's leading causes of death despite 100 years of vaccination and 60 years of antibiotherapy. The region the most affected of France is French Guiana with 3-times more notification rate compared to the whole country. As French Guiana is also one of the world's biodiversity spots, the local people in French Guiana have long used plants to treat the TB symptoms.

In this context, combination of the traditional ethnopharmacology with new metabolomics and bio/chemoinformatics approaches are used to foster the detection of bioactive compounds and select the appropriate samples from which further isolation/purification will be performed.

The ethnopharmacological approach represents the first filtering step, focusing only on the plants with already reported anti Mycobacterium tuberculosis activity and/or used in traditional medicine in the treatment of TB symptoms. Bio/cheminformatics approaches by molecular network and *in silico* pharmacophore screening represent the second and the third filtering steps, allowing to decrease the number of compounds to purify and avoid unnecessary and time-wasting purification.

Exploration of the Antitubercular Potential of French Guiana's Flora through a Metabolomic Study

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PhD student in Natural Products Chemistry
Aix Marseille Univ, CNRS 7263, IRD 237, Avignon Université, IMBE, 27 Blvd Jean Moulin, Service of Pharmacognosy, Faculty of Pharmacy, 13385 Marseille, France

Tuberculosis, a bacterial infection caused by *Mycobacterium tuberculosis*, is still one of the world's deadliest infectious diseases. With the rise of multidrug-resistant strains, the need for new therapeutic options is more urgent than ever. Natural products remain a key source of bioactive molecules, but their chemical complexity often makes it difficult to identify the compounds responsible for biological activity.

In this work, we applied an integrative metabolomics strategy, to explore the chemical composition and antitubercular properties from 80 extracts and fractions, obtained from seven medicinal plants collected in French Guiana. We combined high-resolution LC-MS/MS, bioactivity-guided Feature-Based Molecular Networking, and *in vitro* screening against *Mycobacterium tuberculosis* H37Ra. The most active samples were non polar extracts from *Zingiber zerumbet*, *Tetradenia riparia*, and *Indigofera suffruticosa*. By integrating spectral data, taxonomic information, and antitubercular screening results into a single molecular network, we could quickly associate specific metabolite families with the observed bioactivity. Methoxylated flavonoids and one sesquiterpene emerged as the main contributors, and their predicted activity was validated with commercial standards, showing micromolar MICs (Minimum inhibitory concentration).

This approach allowed us to distinguish active compounds from structurally similar, inactive analogues, thus saving time and avoiding redundant isolations. This study highlights the power of combining untargeted metabolomics with molecular networking to accelerate the discovery of natural antitubercular agents.

Lipidomics with a broad coverage of lipid isomers

Dr. Takeshi HARAYAMA
Institut de Pharmacologie Moléculaire et Cellulaire,
Université Côte d'Azur – CNRS – Inserm

Lipidomics is used to detect and quantify lipids comprehensively. It is an essential tool for fundamental lipid biology as well as applied research to find biomarkers or novel disease mechanisms. Lipidomics remains a method that requires a high degree of expertise, as the interpretation of chromatographic peaks and MS/MS spectra done by lipidomics software contains multiple errors that require extensive data curation. Via the extensive analysis of lipid standards artificially generated in live cells, we are proposing approaches to solve existing issues, improving the accuracy of lipidomics for a broader usership. I will describe the current developments of our approaches, as well as its future directions.

UHPLC-DAD-nano ESI-HRMS/MS-DPPH/ABTS-VIS On-Line coupling for the detection of antioxidant compounds: a novel analytical approach applied to Provence flora species

Clémentine ACHARD-BACCATI (PhD student)
Aix Marseille Univ, CNRS 7263, IRD 237, Avignon Université, IMBE, 27 Blvd Jean Moulin, Service of Pharmacognosy, Faculty of Pharmacy, 13385 Marseille, France

Conventional antioxidant screening methods, such as well-plates assays using DPPH or ABTS reagents, provide a global evaluation of antioxidant activity through IC_{50} determination, but do not allow the identification of individual bioactive compounds. This study presents an on-line coupling methodology that integrates UHPLC-DAD-HRMS/MS with real-time DPPH/ABTS-VIS detection, enabling simultaneous chromatographic separation, high-resolution mass spectrometric compound identification, and antioxidant activity profiling, within a single run. By eliminating the need for time-consuming fractionation and post-fractionation bioassays, this method enhances the efficiency to identify antioxidant components in a complex mixture, and considerably reduces analysis time.

This approach was applied in a comparative study of antioxidant properties and phytochemical profiles of three pairs of plant species, each composed of a widely used medicinal plant and its regional counterparts from Provence with the same traditional indications:

- *Arnica montana* with *Pentanema montanum* (formerly known as *Inula montana)*
- *Helichrysum italicum* with *Helichrysum stoechas*
- *Satureja hortensis* with *Satureja montana*.

Phytochemical characterization using UHPLC-HRMS/MS and molecular networking revealed chemical profiles dominated by phenylpropanoids and flavonoids. According to DPPH and ABTS well-plate assays, all three Provence species demonstrated antioxidant activities comparable or even superior to their conventional counterparts. The on-line system successfully mapped antioxidants activities to 34 individual phenolic compounds, especially mono- and di-caffeoylquinic acid derivatives.

This work—recently published as *“Can Provence Flora Offer Effective Alternatives to Widely Used Medicinal Plants?”*- establishes this on-line coupling technique as a powerful tool for high-throughput bioactive compound discovery and demonstrates the potential of Provence flora as sustainable alternative to over-harvested medicinal plants for cosmetic of pharmaceutic applications.

Multi-Omics Analysis of Plants: Uncovering Metabolic Defense Mechanisms

Dr. Raphaël LUGAN

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Plants defend themselves against environmental aggressions by adapting their metabolism. Thanks to omics analyses, it is possible to explore these adaptations on a large scale, including a large number of biological functions: modulation of growth and development, allocation of resources, synthesis of cellular structures and defense metabolites, *etc*. The potential of metabolomics and of combined metabolomics/transcriptomics is illustrated here in chili pepper and peach responses to water stress and green aphid infestation respectively.

We treated chili pepper plants with UV-C flashes before imposing a progressive drought stress. In the absence of drought, plants treated with UV-C showed phenotypes similar to control plants. Leaf metabolic fingerprints, covering large portions of central and secondary metabolism, revealed a very limited effect of UV-C treatment on the metabolome, including notably the accumulation of pipecolate. In contrast, when subjected to drought, plants treated with UV-C exhibited enhanced water retention in leaves and significant changes in the metabolome. Variations in major water stress markers were significantly mitigated by UV-C pretreatment and overall, the results suggest that UV-C treatments induce priming, based on the activation of systemic defense effectors and the absence of harmful symptoms, resulting in partial but significant avoidance of dehydration.

The transcriptomic and metabolomic responses to green peach aphid infestation were studied in Rubira, a peach accession carrying the major resistance gene Rm2, causing antixenosis, as well as in GF305, a susceptible accession. Transcriptome and metabolome displayed both a massive reconfiguration in Rubira 48 hours after infestation, while GF305 displayed very limited changes. The Rubira immune system was massively stimulated, with simultaneous activation of genes encoding cell surface receptors involved in pattern-triggered immunity and cytoplasmic NLRs (nucleotide-binding domain, leucine-rich repeat containing proteins) involved in effector-triggered immunity. Hypersensitive reaction featured by necrotic lesions surrounding stylet punctures was supported by the induction of cell death stimulating NLRs/helpers couples, as well as the activation of H2O2-generating glyoxylate biosynthesis. The triggering of systemic acquired resistance was revealed by the activation of the pipecolate pathway and accumulation of this defense hormone together with salicylate. Important reduction in carbon, nitrogen and sulphur metabolic pools and the repression of many genes related to cell division and growth, consistent with reduced apices elongation, suggested a downregulation of apices growth and a strong decline in their nutritional value.

Characterizing marine benthic exometabolites from species to ecosystems

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Sponges are aquatic sessile invertebrates known to produce a wide range of specialized metabolites, which are extensively explored in drug discovery contexts.[1] These metabolites are also thought to be part of the sponge's defense and communication toolkit. However, in contrast to their pharmacological activities, the ecological functions of these specialized metabolites are generally more difficult to assess and therefore remain less well understood.[2] One way to address this challenge is to further study the metabolic or chemical output of sponges within their ecosystems. Through filter-feeding and metabolic processes, sponges recycle organic matter and subsequently release various metabolites (*i.e* exometabolites), including their specialized ones. These exometabolites may participate to the cycle of energy and nutrients in the benthos, and could also act as chemical cues involved in species interactions, thereby influencing the structure of marine biodiversity.[3] This presentation will showcase MS-based metabolomic results obtained from exometabolite captures performed with I-SMEL (In situ Marine moleculE logger)[4] in sponge-dominated Mediterranean ecosystems.

References:

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Comprehensive Analysis of Small Molecule MS/MS Data with SIRIUS

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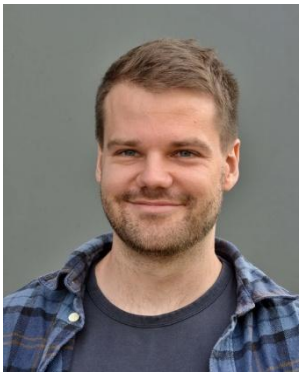

SIRIUS is a powerful tool for the automated analysis of tandem mass spectrometry (MS/MS) data, enabling the identification and annotation of small molecules with high confidence. In this workshop, we will guide participants through the entire SIRIUS data analysis pipeline, from loading LC-MS/MS data to feature detection, alignment, and molecular formula annotation. We will demonstrate how to search structure databases efficiently and validate results by integrating in-silico annotations, analog spectral library searches, and combinatorial fragmentation techniques. Additionally, we will explore strategies for processing large datasets, including classifying thousands of metabolites by chemical class and leveraging confidence scores to identify relevant compound annotations. This hands-on session will equip participants with practical skills for enhancing their MS/MS data analysis workflows.