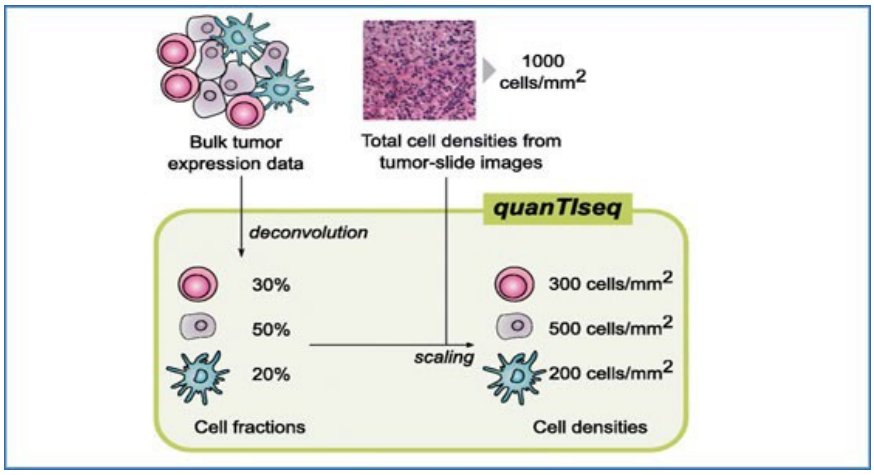
Toulouse **25 - 28 Juin, 2024**

1ère édition

JOBIM
Journées Ouvertes en Biologie Informatique et Mathématiques

Nouvelles approches computationelles pour la déconvolution cellulaire d'échantillons biologiques à partir de données transcriptomiques.



JOBIM
Journées Ouvertes en Biologie Informatique et Mathématiques

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StatOmique

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LIP6

INCEPTION

Pourquoi ce symposium ?

Bien que les analyses transcriptomiques aient grandement contribué à une meilleure compréhension de la complexité des maladies, leur précision est généralement affectée par l'hétérogénéité de la composition cellulaire de la plupart des échantillons biologiques. D'autre part, les analyses RNASeq de type "single-cell" sont expérimentalement lourdes et coûteuses, et subissent certaines limites statistiques intrinsèques, notamment en terme de profondeur de séquençage et de couverture des génomes étudiés.

Pour faire face à ces limites, une vaste gamme de méthodes bioinformatiques de déconvolution a été conçue pour déduire automatiquement les caractéristiques des compositions des tissus. L'approche la plus courante consiste à déduire les abondances relatives des populations cellulaires en s'appuyant sur des échantillons de référence de populations cellulaires purifiées. Ainsi, les algorithmes de déconvolution supposent une relation linéaire entre les expressions cumulées des transcrits quantifiés par RNASeq massif et l'expression spécifique des transcrits à chaque population cellulaire étudiée. Les ratios cellulaires inconnus à estimer sont les contributions individuelles des sous-populations au "pool de transcrits" dans chaque échantillon.

Cependant, les algorithmes de déconvolution de référence souffrent d'une série de limitations communes. Bien qu'une cinquantaine de méthodes ait été proposée, il n'y a pas de véritable consensus ni de solution pratique pour résoudre les problèmes suivants : leurs performances insuffisantes pour différencier des populations de cellules rares ou étroitement liées ; le manque de cohérence des résultats renvoyés par ces méthodes, par exemple l'écart observé dans des conditions réelles entre les ratios estimés par ces approches numériques et ceux mesurés à l'aide de méthodes expérimentales, telles que les expériences de cytométrie de masse.

L'enjeu de la recherche de solutions à ces problèmes méthodologiques est de favoriser de nouvelles avancées dont l'impact sera direct sur la recherche de maladies telles que le cancer ou les maladies auto-immunes. En effet, en améliorant la caractérisation des tissus, tels que le micro-environnement tumoral, d'une manière non destructive, ces modèles de pointe permettraient de mieux comprendre les interactions qui se produisent au sein d'une variété de populations cellulaires, essentielles au maintien de l'homéostasie des systèmes biologiques.

Timetable

1st symposium on deconvolution algorithms applied to bulk RNA-Seq

27 June, 2024 (hours are in CEST zone)

1st symposium on deconvolution algorithms applied to bulk RNA-Seq 27 June, 2024 (hours are in CEST zone)		
14:00 14:10	Opening of the symposium and brief introduction to deconvolution	Emeline Perthame et Bastien Chassagnol
14:10 14:40	Deconvolution for clinical applications: a quest to make sense of reference-based deconvolution on tumour tissue samples	Vera Pancaldi
14:40 15:00	Statistical inference of cellular heterogeneity using multi-omic prior biological knowledge	Hugo Barbot
15:00 15:15	Next-generation cell-type deconvolution of transcriptomic data	Francesca Finotello
15:15 15:30	Benchmarking second-generation deconvolution tools with omnideconv	Lorenzo Merotto
15:30 15:50	CDState for unsupervised deconvolution of malignant cell transcriptional states	Kraft Agnieszka
15:50 16:00	Conclusion of the symposium	Emeline Perthame et Bastien Chassagnol

Deconvolution for clinical applications: a quest to make sense of reference-based deconvolution on tumour tissue samples

Vera Pancaldi

CRCT, INSERM – Université de Toulouse - France

Abstract: *Despite the increasing popularity of single-cell technologies, their price, complicated protocols and uncertain biases make it an unlikely option to be applied routinely in clinical practice. Especially when confronted with tumour samples, capturing cellular heterogeneity as well as the presence of specific subtypes is key to correctly stratify patients and personalise their treatment.*

Deconvolution of cell type proportions offers an interesting solution that has been widely explored in the last few years. Despite the large and growing number of methods and signatures generated, it remains very hard to define consensus between them and benchmarks are abundant but not trivial. In our lab we are interested in practical applications of these methods in immuno-oncology and we have therefore strived to perform benchmarks and generate data that would help us find some order in the sea of methods and signatures that exist.

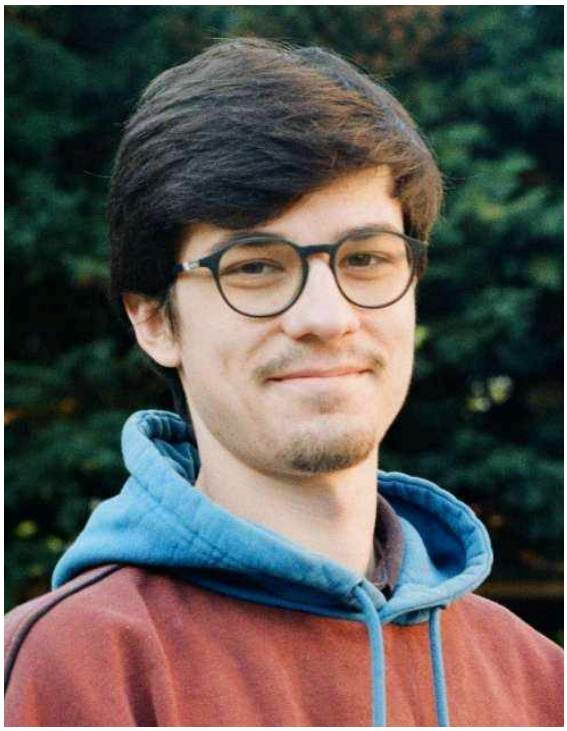
In particular, we have generated in-vitro data to generate some of the phenotypes that we aim to identify in patients under controlled conditions. Meanwhile, we have strived to develop methods that deconvolve the presence of specific cell-states, rather than cell-types, rarely captures by in-vitro or in-silico benchmark datasets.

Bio:

Vera Pancaldi was trained as a physicist at Imperial College London and has 14 years experience in computational biology. Since 2018 she leads the Network Biology for Immuno-Oncology team at the Cancer Research Center of Toulouse (CRCT) as the recipient of the Chair for bioinformatics in Oncology of the CRCT, working on modelling cancer and, in particular, cellular interactions in the tumour microenvironment. She also holds a joint part-time appointment at the Barcelona Supercomputing Center through the Bioinfo4Women programme. In particular, she applies network theory to study chromatin structure and epigenomics, cellular networks in tumoral tissues and disease relationships in a personalised medicine framework.

Multi-omic statistical inference of cellular heterogenetity Hugo Barbot

IRMAR – Université de Rennes - France



Abstract:

Cellular heterogeneity in biological tissues reflects progression of disease state and is therefore useful for improved diagnostic and prognosis. Cell deconvolution is a common approach to unravel the heterogeneous molecular profiles observed in bulk tissues. So far, cellular deconvolution assumes that bulk omic profiles result from weighted sums of so-called signature cell-specific omic profiles, weights being the unknown proportions of those cell types. Consistently, most statistical methods used for cellular deconvolution are based on extensions of the Ordinary Least Squares (OLS) optimization algorithm, under nonnegativity and sum-to-one constraints on those unknown mixing coefficients. Using OLS make implicit assumptions which are highly questionable when applied to bulk molecular profile. Indeed, strong violations of those assumptions may be due to the instrinsic nature of omics data or to the dependence structure induced by the gene regulatory network. The goal of this work is to provide a well defined statistical framework that respects the inherent characteristics of biological data for deconvolution, using multi-omic data.

Multi-omic data integration for cellular deconvolution aims at leveraging complementary viewpoints on cellular heterogeneity. Many simultaneous optimization strategies are considered, either based on constrained and weighted maximum likelihood or on gene selection. An extensive comparative study of cell deconvolution performance with leading single or multi-omic methods is conducted on benchmark data and using nine cell types commonly found in PDAC (pancreatic cancer). Results confirm both the gain in a multi-omic integration approach and in the use of ad-hoc probability distributions for each -omic data type.

Bio:

I'm a PhD student in statistics applied to biology at the institut de recherche mathématique de Rennes (IRMAR) directed by David Causeur, Yuna Blum and Magali Richard. My PhD is part of the M4DI project involved in the Digital Health PEPR. I am working on the design of a new multi-omic cellular deconvolution method with a well-defined statistical framework. I am interested in the links between omics data and their integration, non-normal regression models and high-dimensional inference.

Next-generation cell-type deconvolution of transcriptomic data

FFrancesca FFinotello

Institute of Molecular Biology – Université d'Innsbruck, Autriche

Abstract:

The investigation of the cellular composition and architecture of tissues is key to understanding mechanisms that underlie tissue function and its disruption during disease. Deconvolution is a computational technique used to quantify the cellular composition of complex tissues profiled with transcriptomics technologies.

While first-generation deconvolution methods could disentangle only a handful of cell types (mainly human immune cells), second-generation methods can be trained using single-cell transcriptomics data to learn the transcriptional "fingerprints" of any cell type, thereby possibly extending deconvolution to any tissue, disease context, and organism of interest. Moreover, these approaches can now be applied to spatial transcriptomics data, revealing the architecture of tissues and the spatial distribution of their cellular constituents.

In this talk, I will show how different types of transcriptomic data can be analyzed deconvoluted to chart the cellular organization of complex tissues in health and disease, with a special focus on next-generation deconvolution techniques.

Bio:

Francesca Finotello earned her PhD in Bioengineering in 2014 at the University of Padova, Italy. She is an Assistant Professor at the Institute of Molecular Biology and Digital Science Center (DiSC) of the University of Innsbruck, Austria, where she leads the Computational Biomedicine group. Her research focuses on the bioinformatic analysis of bulk and single-cell multiomics data and on the development of computational methods to inform precision and personalized medicine, with a special focus on cancer immunology.

Benchmarking second-generation deconvolution tools with omnideconv

Lorenzo Merotto

Institute of Molecular Biology – Université d'Innsbruck, Autriche

Abstract:

Deconvolution methods are computational techniques that infer cell-type fractions from bulk RNA sequencing data leveraging cell-type-specific transcriptomic signatures. Second-generation tools, in particular, learn how to quantify different cell types by training their models with an annotated single-cell RNA-seq atlas, extending the applicability of deconvolution to a much broader panel of cell types, tissues, and organisms. This flexibility, however, poses major challenges in their usage and evaluation.

Therefore, we developed omnideconv (omnideconv.org), an ecosystem of resources that simplifies the usage and benchmarking of second-generation deconvolution tools. These include a dedicated R package to access several deconvolution tools in a unified and simplified manner; an interactive web app for the exploration of deconvolution signatures and results; a curated compendium of validation datasets from different organisms; 4) a simulator of artificial RNA-seq datasets with controlled composition; and a reusable pipeline for the systematic benchmarking of second-generation deconvolution tools. Building upon these unique methodologies, we extensively benchmarked eight state-of-the-art deconvolution methods under various scenarios that reproduce real-life applications, shedding light on methods' strengths, weaknesses, and complementarities.

In this talk, I will introduce the omnideconv collection of tools and present the framework and results of our benchmarking study.

Bio:

Lorenzo Merotto is a PhD candidate at the Institute of Molecular Biology of the University of Innsbruck, Austria. His research revolves around single cell data, with a double focus on the integration of multimodal omics and their usage to inform the dissection of bulk sequencing.

Unsupervised Deciphering of Malignant Cell Heterogeneity in Bulk Tumor RNA-Sequencing Data with CDState

Agnieszka Kraft

Computational Cancer Genomics Lab - ETH Zürich - Switzerland

Abstract:

Intratumor transcriptional heterogeneity poses a significant challenge in cancer treatment due to limited understanding of tumor cell types, states, and their implications for therapy resistance. While single-cell sequencing has offered insights into tumor composition across various cancer types, its routine clinical application remains impractical. In contrast, bulk RNA sequencing is more feasible but lacks effective methods for identifying subpopulations of malignant cells without relying on marker genes or reference single-cell data. The effectiveness of these methods heavily depends on the availability of an appropriate reference, which continues to pose a significant challenge.

To address these limitations, we introduce CDState: an unsupervised method for predicting and enumerating malignant cell subpopulations using bulk tumor data. CDState employs a Nonnegative Matrix Factorization model extended with a sum-to-one constraint on weights and kurtosis-based optimization of source gene expression, to disentangle bulk data into distinct cell states.

Validation of CDState using simulated and "bulkified" data from publicly available single-cell RNA sequencing datasets showcases its reliability and accuracy in recovering previously discovered cancer cell states. Based on these results, we apply CDState to 29 TCGA datasets to provide a comprehensive overview of malignant cells' transcriptional profiles on a pan-cancer scale.

Bio:

Agnieszka Kraft is a PhD candidate at the Computational Cancer Genomics Lab at ETH Zurich. Her research focuses on studying intratumor heterogeneity, particularly on developing a method for the unsupervised identification of transcriptional cell states from bulk RNA-seq tumor data. She collaborates closely with the Department of Thoracic Surgery at University Hospital Zurich, where she is involved in translational research for cancer biomarker discovery.