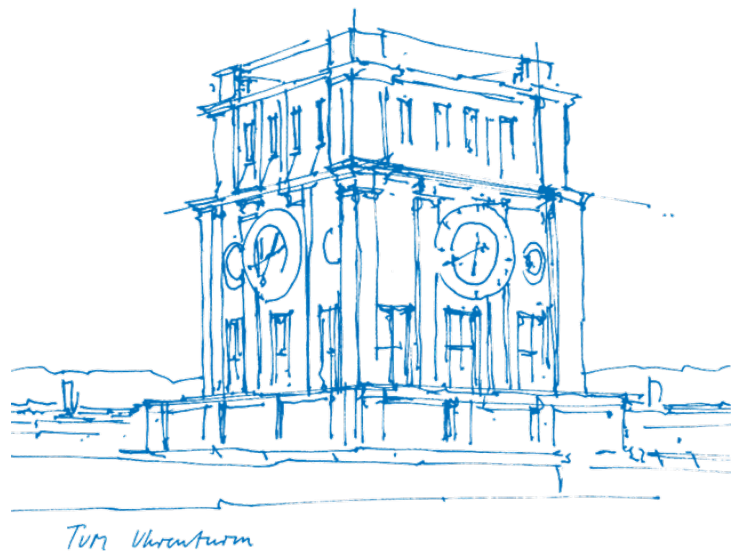


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Vollständiger Abdruck der von der Fakultät für Elektrotechnik und Informationstechnik der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktor-Ingenieurs (Dr.-Ing.)

genehmigten Dissertation.

Vorsitzende(r):

Prof. Franz X. Gabelsberger

Prüfer der Dissertation:

1. Prof. Dr. Georg Simon Ohm
2. Prof. James Clerk Maxwell

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To Franz X. Gabelsberger, inventor of the street named after him.

Abstract

The abstract of your thesis goes here.

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1 Introduction

This is the introduction of the thesis.

1.1 Pathophysiology of chronical lung diseases

1.1.1 Bronchopulmonary Dysplasia (BPD)

1.1.2 Asthma

1.1.3 Chronic Obstructive Pulmonary Disease (COPD)

1.1.4 Idiopathic Pulmonary Fibrosis (IPF)

1.2 Computational biology and chronic lung diseases

1.2.1 Multi-omics data integration

1.2.2 Clinical prediction

1.2.3 Systems biology

1.3 Aims

2 Methodology

This is the methodology of the thesis.

2.1 Data gathering

2.1.1 Mice data

Transcriptomics

2.1.2 Human data

Transcriptomics

Metabolomics

2.1.3 Public data

Multi-omics bulk data

Neonatal single-cell transcriptomics

2.2 Preprocessing

2.2.1 Normalization

DESeq2

Pareto scaling

Size-effect

2.2.2 Data imputation

Random-forest

knn-Imputation

2.2.3 Batch-effect detection

Principal component analysis (PCA)

Hierarchical clustering

K-BET

2.3 Differential expression analysis

2.3.1 Limma

2.3.2 DESeq2

2.4 Enrichment analysis

2.4.1 Gene list functional enrichment analysis

2.5 Multi-omics factor analysis (MOFA)

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2.6 Clinical data correlation

2.6.1 Linear regression

2.6.2 Binomial regression

2.6.3 Ordinal regression

2.6.4 Multinomial logistic regression

2.6.5 Dirichlet regression

2.7 Benchmarking of Lasso models dealing with missing values

2.7.1 Knowledge guided multi-level network inference

2.7.2 Two-steps based models

Grouped adaptive Lasso (GALasso)

Stacked adaptive Lasso (SALasso)

2.7.3 Inverse covariance based methods

Convexed conditioned Lasso (CoCoLasso)

Lasso with high missing rate (HMLasso)

2.8 Adult data correlation

2.8.1 Random forest

Imbalanced random forest

Nested cross-validation in random forest

2.8.2 t-test, manova, log-reg

3 Summary of publications

1. Juan Henao, Alida Kindt, Tanja Seegmüller, Kai Foerster, Andreas Flemmer³, Juergen Behr⁴, Nikolaus Kneidinger, Marion Frankenberger, Fabian Theis, Benjamin Schubert, Markus List, Anne Hilgendorff. Multi-omic signatures relate to the severity of pulmonary outcome in neonates traced into adult disease.

Summary: This project focused on the detection of endotypes behind Bronchopulmonary Dysplasia (BPD) by proteomics, metabolomics, and clinical data integration using a cohort of 55 neonates with and without BPD. The endotypes were detected using Multi-Omics Latent Factor Analysis (MOFA) REF with sensitivity selection. We caught seven latent factors. However, none showed a sign of endotyping discrimination given the combined distribution of latent scores between no BPD and BPD patients in each latent factor. Nevertheless, the biological interpretation of each latent factor allowed us to discover a persistent inflammatory disease component in BPD.

We expanded our analysis by looking for individual molecular features with the potential to be biomarkers of severity using ANOVA with a t-test as a post-hoc method comparing no BPD, mild BPD, and moderate/severe BPD. Acknowledging the clinical heterogeneity signal of BPD cases, we reclassified them into no or moderate/severe BPD using a random forest model trained using oxygen supplementation and mechanical ventilation days (clinical variables used to diagnose BPD). We applied a t-test to identify significant molecular features between no BPD and moderate/severe BPD. We complement our analysis by training different random forest models combining significant molecular features and sets of increasing BPD characterization:

- a) **BPD descriptors:** Oxygen supplementation and mechanical ventilation days.
- b) **Main risk variables:** Gestational age and birth weight.
- c) **Deep clinical phenotyping:** *Main risk variables* and a compendium of clinical measurements encompassing comorbidities, medical interventions, and previously defined MRI-based scores.

The metabolite PC(O-36:5) was detected in both significant analyses and, combined with deep clinical phenotyping, improves the BPD classification along with PC(O-44:5) and gestational age. The protein CCL22 was detected in both significant analyses and improved the BPD classification according to random forest when combined with the main risk variables. Besides, SCGF-alpha, SCGF-beta, and KIR3DL2 were significantly different by ANOVA analysis of no, mild, and moderate/severe BPD comparison.

We traced our significant proteins in an adult chronic lung disease cohort composed of Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), and healthy donors by ANOVA analysis comparing the three conditions. CCL22 and KIR3DL2 were detected in COPD, while SCGF-beta was significant in COPD and IPF. Those results support the hypothesis regarding the susceptibility of neonates with a BPD diagnosis to develop chronic lung diseases in adulthood.

2. Erika Gonzalez Rodriguez¹, Juan Henao², Motaharehsadat Heydarian¹, Tina Pritzke¹, Alida Kindt³, Anna M. Dmitrieva¹, Heiko Adler^{4, 5}, Melanie Markmann⁶, Valeria Viteri-Alvarez¹, Prajakta Oak¹, Markus Koschlig¹, Xin Zhang¹, Kai M. Foerster⁷, Andreas Flemmer⁷, Hamid Hossain^{6,8}, Xavier Pastor², Holger Kirsten⁹, Peter Ahnert⁹, Juergen Behr¹⁰, Tushar J. Desai¹¹, Benjamin Schubert², Anne Hilgendorff^{1,12}. Hyperoxia-induced cell cycle arrest drives long-term impairment of lung development and DNA repair in neonates.

3. Juan David Henao Sanchez^{3,14}, Mustafa Abdo^{1,2}, MD, MSc, Benjamin Schubert^{3,14}, PhD, Markus List⁴, PhD, Henrik Watz^{2,14}, MD, Frauke Pedersen^{1,2,14}, PhD, Alina Bauer^{3,15}, MSc, Dominik Thiele^{5,14}, MSc, Adam M. Chaker^{6,7}, MD, Constanze A. Jakwerth^{7,15}, PhD, Benjamin Waschki^{1,8,14}, MD, Anne Kirsten^{2,14}, MD, Markus Weckmann^{9,14}, PhD, Oliver Fuchs^{9,10,14}, MD, PhD, Gesine Hansen^{11,16}, MD, Matthias V. Kopp^{9,14}, MD, Erika v. Mutius^{12,13,15}, MD, MSc, Inke R. König^{4,14}, PhD, Klaus F. Rabe^{1,14}, MD, PhD, Thomas Bahmer^{1,14}, MD, Carsten B. Schmidt-Weber^{7,15}, PhD, Ulrich M. Zissler^{7,15}, PhD, and the ALLIANCE Study Group*. Cytokines Derived from Nasal Epithelial Lining Fluid in Patients with Asthma.
4. Henao, J. D., Lauber, M., Azevedo, M., Grekova, A., Theis, F., List, M., ... & Schubert, B. (2023). Multi-omics regulatory network inference in the presence of missing data. *Briefings in Bioinformatics*, 24(5), bbad309.

4 Discussion

This is the discussion of the thesis.

A Appendix

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