Keynote Talks:

Applications of Data Science in Drug R&D

Prof. Andreas Raue

Institution: Chair of Modeling and Simulation of Biological Processes. Department of Computer Science, Augsburg University, Germany

Abstract:

Data science analyses play a crucial role in drug research and development across various stages. Computational models have become an integral part of the drug development process, addressing a range of challenges. There are two main types of approaches used in these applications: 1) Machine learning and statistical models are employed for larger-scale data analysis. 2) Mechanistic models are utilized to address smaller scale biology and engineering related questions. They help optimize drug design, target engagement, dosing, and PK/PD (pharmacokinetics/pharmacodynamics). They aid in identifying and characterizing targets, selecting patient populations, and understanding biomarkers of response or resistance. This presentation will showcase recent examples in both areas and explore potential future opportunities for AI in drug research and development.

Title [tba]

Prof. Fabian Theis

Institution: Director of Helmholtz Munich Computational Health Center and Scientific Director of the Helmholtz Artificial Intelligence Cooperation Unit, Munich, Germany

The working principles of modern AI and where it is still lacking

Prof. Thomas Brox

Institution: Head of the Computer Vision Group, Department of Computer Science, University of Freiburg, Germany

Project Talks:

Integrating Single-Cell Variability into ODE Models with L1-Based Parameter Learning

Speaker: Dr. Marcus Rosenblatt

Institution: Institute of Physics, University of Freiburg

Abstract:

Ordinary Differential Equation (ODE) models for biological signaling pathways typically rely on population-level data, which aggregate cellular responses and overlook single-cell variability. However, advanced measurement techniques such as Fluorescence-Activated Cell Sorting (FACS), live-cell imaging, and single-cell RNA sequencing (scRNA-Seq) now provide time-resolved, quantitative data at the single-cell level, presenting new opportunities and challenges for model integration. We propose a data-driven approach leveraging clustering and regularization techniques to address the high-dimensional parameter space that arises when modeling single-cell dynamics. Single cells are clustered based on their signaling behavior, and cluster-specific parameters are identified using L1 regularization, a sparsity-promoting method commonly used in machine learning. This framework significantly reduces the parameter space and enables accurate ODE model fitting across cell clusters. Our approach demonstrates its utility on data from a published study on TGFβ signaling [Strasen et al., 2018], highlighting its potential for scalable modeling of single-cell dynamics in complex biological systems.

CytoVI: Deep Generative Modeling of Antibody-based Single Cell Technologies

Speaker: Dr. Florian Ingelfinger

Institution: Weizmann Institute of Science & University Medical Center Freiburg

Abstract:

Florian Ingelfinger[1, 2], Nathan Levy[1], Can Ergen[3], Artemy Bakulin[1], Pierre Boyeau[3], Martin Kim[3], Alexander Becker[3], Jonas Maaskola[1], Robert Zeiser[2], Corinne Widmer[4], Ido Amit[1, #] & Nir Yosef[1, 3, #]

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Abstract:

Flow cytometry was historically the first single cell technology to measure millions of cellular states within minutes. Due to its robustness and scalability flow cytometry and related antibody-based single cell technologies have become an irreplaceable part of routine clinics and evolved to a powerful tool for exploratory research. Opposed to the intrinsically noisy and sparse data characteristics of most genomic single cell technologies, antibody-based cytometry technologies offer high-resolution measurements of millions of cells across a wide dynamic range facilitating the analysis of large patient cohorts. However, the analysis of multi-cohort studies is often obstructed by batch effects and differences in antibody panels or technology platforms utilized to analyze samples. Here, we present CytoVI, a deep generative model designed for the integration across antibody-based technologies. CytoVI removes technical variation in flow cytometry, CyTOF or CITE-seq data and embeds cells into a meaningful low-dimensional representation corresponding to a cells intrinsic state. CytoVI performs favourable compared to existing tools in data integration tasks, imputes missing markers in experiments with overlapping antibody panels and predicts a cells transcriptome if paired with CITE-seq data. We utilized CytoVI to generate an integrated B cell maturation atlas across 350 proteins from conventional mass cytometry data and automatically detect T cell states associated with disease in a large cohort of Non-hodgkin B cell lymphoma patient measured by flow cytometry. Beyond its applicability for preclinical research, we showcased that CytoVI can automatically identify tumor cells in chronic lymphatic leukemia patients via transfer learning and predict a patient's diagnosis in a fully automated fashion. Therefore, CytoVI represents

a powerful deep learning tool for preclinical research and enables an accurate automated analysis of immunophenotypes in patient samples in clinical settings.

Prioritizing biomarkers from DNA methylation data using graph neural networks and explainable AI

Dr. Anup Kumar

Institution: Bioinformatics group, Department of Computer Science, University of Freiburg

Abstract:

Prioritization of biomarkers from DNA methylation data using graph neural networks and explainable AI

Anup Kumar1*(Presenting), Ton Anh Do2, Jörg Hagmann3, Heiko Becker2, Rolf Backofen1

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Abstract:

Acute myeloid leukaemia (AML) is a complex disease characterized by aberrant DNA methylation. This study uses DNA methylation profiles and machine learning approaches to predict novel biomarkers in AML patients undergoing Decitabine (DAC) treatment. A publicly available DNA methylation dataset from Gabriele Greve et al. [1], comprising methylation profiles of AML patients pre- and post-decitabine (DAC) treatment is utilised for developing a computation approach for biomarker detection. The 450 K methylation array dataset includes over 450,000 CpG sites, with approximately 1,500 differentially methylated CpG sites identified as a "positive" (seed) set. Positive-unlabeled (PU) learning [2] approach is utilized to explore novel "likely positive" CpG sites from a highly variable selected set of 10,000 CpG sites. A protein-protein interaction network is constructed by calculating Pearson correlation coefficients between CpG site methylation profiles and establishing similarity thresholds to create a network graph. Using heat diffusion techniques, soft labels are assigned to unknown CpG sites based on their association with known positive ones. These soft labels classify CpG sites as positive, likely positive, weakly negative, likely negative, and negative. A graph neural network (GNN) further refines these classifications by incorporating DNA methylation profiles and learned features from PU learning, achieving a high level of accuracy. The study highlights "likely positive" CpG sites, such as the combination "cg01550473_HSPA6," which, through network analysis, shows strong connectivity with other positive markers. This CpG site was subsequently validated as a potential biomarker by Flotho et al. [3], demonstrating the effectiveness of the GNN-based classifier in identifying novel biomarkers. The integrative approach combining DNA methylation data, PU learning, and GNN provides a robust framework for discovering potential biomarkers for AML paving the way for further investigation into therapeutic targets for different diseases. To investigate the utility of the above approach on a different dataset, it is applied to the Illumina Infinium 850k Human DNA methylation Beadchip dataset [4] containing DNA methylation

profiles for 50 breast cancer patients and 30 normal controls. A protein-protein interaction network is created using the similarity of DNA methylation profiles of CpG sites and genes. Using this network and positive-unlabeled learning, features of a few known and 10,000 highly variable sites are extracted. These sets of features are combined with the DNA methylation profiles to obtain the final feature set of CpG sites. Using these features and soft labels for a few seed markers and mostly unknown markers, a graph neural network is trained. Using the trained model, labels are predicted for the unseen CpG sites. From the predicted CpGs which form the set closest to the known marker, a few novel markers such as PAX6 [5] and FZD6 [6] genes are identified which are known to be associated with breast cancer.

References:

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[2] Paola Stolfi, Andrea Mastropietro, Giuseppe Pasculli, Paolo Tieri, Davide Vergni, NIAPU: network-informed adaptive positive-unlabeled learning for disease gene identification, Bioinformatics, Volume 39, Issue 2, February 2023, btac848, https://doi.org/10.1093/bioinformatics/btac848

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[5] Xia, X., Yin, W., Zhang, X., Yu, X., Wang, C., Xu, S., Feng, W., & Yang, H. (2015). PAX6 overexpression is associated with the poor prognosis of invasive ductal breast cancer. Oncology letters, 10(3), 1501–1506. https://doi.org/10.3892/ol.2015.3434

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Enhancement of network architecture alignment in comparative single-cell studies

Speaker: Clemens Schächter

Institution: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Germany

Abstract:

Animal models can provide meaningful context for human single-cell data. To transfer information between species, we propose a deep learning approach that pretrains a conditional variational autoencoder on animal data and reuses its last encoder layers in the human network architecture during fine-tuning. This unifies latent spaces and enables information transfer across species, even when gene sets differ. When applied to cross-species pairs of liver, adipose tissue, and glioblastoma datasets, our method learns an aligned representation that can be used for label transfer. Thus, we reliably uncover and exploit similarities between species to provide context for human single-cell data

Physics-informed Machine Learning for Quality Inspection in Solar Cell Production

Speaker: Dr. Matthias Demant

Institution: Fraunhofer ISE, Freiburg

Abstract:

The transfer of deep learning technology into solar cell production is a promising but challenging process. Early models are capable of quantifying defects and properties in measurement images, such as cracks in electroluminescence images. Typically, human annotations are required which depend on experts, leading to cumbersome analysis of the single measurements. On the other hand, simulation methods allow for the derivation of physical information but require special samples and measurements or extensive computation time. The latest approaches combine physics- and data-driven models making the models interpretable. We present two examples of our work on physics-informed DL applications for quality inspection during solar cell production.

In the first application, we introduce surrogate models for the fast prediction of thin film thickness based onmultispectral images. HJT solar cells contain a stack of thin layers with a Transparent Conductive Oxide (TCO) on top of an amorphous silicon layer. Physical models allow to derive the thickness of the TCO layer from reflection data, which is necessary for process optimization. DL models can be used to train a surrogate model which can calculate TCO layer thickness spatially resolved on full area within microseconds based on visual inspection images at only three wavelengths. Our quality inspection can be used to optimize the deposition process or sort out solar cells at early stages.

In the second application, we introduce a hybrid model to derive a physics-informed digital twin for solar cell analysis. While the amount of data measured during PV manufacturing is growing, the various analysis methods result in parameters that are difficult to interpret, reproduce and compare. Even DL techniques can fail when driven by human annotations. Since human struggle to process the image data space, explainable and theory-guided data analysis techniques are the next scientific step to constrain and support machine learning models. In practice, the presented method allows an efficient reduction of the data to meaningful physical quantities. Therefore, the inline measurement data are correlated with *IV* parameters. Since the hybrid model is a DL-encoder combined with a simulation-model as decoder, the model learns to predict valid physical inputs for the simulation model. The latent representation in the bottle neck is our digital twin that contains hidden cell properties, which can be interpreted by solar cell experts to explain losses and potentials of the manufacturing process.

Posters

Machine Learning-Based Imputation of Deep Mutational Scanning (DMS) Scores Using ESM-1v Embeddings and Pathogenicity Features

Presenter: Polina Polunina
Institution: University of Freiburg, Bioinformatics Lab

Abstract:

Deep mutational scanning (DMS) enables high-throughput measurement of protein variant effects, yet missing data within DMS score sets limits their utility in many applications. To address this challenge, we present a machine learning framework for imputing missing DMS scores, leveraging rich feature sets derived from both biological and deep learning-based models.
Our approach incorporates embeddings from ESM-1v, capturing the sequence context of wild-type and variant amino acids, pathogenicity scores from the EVE predictor, physico-chemical properties, and substitution matrices such as BLOSUM62 and Grantham. Using a LightGBM model, we achieve competitive performance across diverse datasets, demonstrating strong R^2 and RMSE values.
This work showcases the utility of integrating deep learning-derived features with domain-specific knowledge for accurate DMS score imputation. The proposed approach holds promise for improving protein function prediction and expanding the applicability of DMS datasets in research and therapeutic development.

Aligning Text and Omics Modalities: Challenges and Opportunities in Contrastive Learning for RNA Sequencing Data

Presenter: Jonatan Menger
Institution: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Germany

Abstract:

Integrating RNA sequencing data with textual context presents new opportunities for improving the interpretability and accessibility of omics datasets. We introduce a contrastive learning framework based on Hugging Face sentence-transformers and datasets, designed to embed both modalities into a shared latent space. This approach enables natural language queries of omics datasets and serves as a foundation for future generative models. However, aligning text and omics data poses significant challenges, particularly due to batch effects in language annotations. Our work-in-progress explores strategies to mitigate these issues, highlighting both the potential and the current limitations of this approach. We discuss open questions and key areas for improvement, aiming to refine cross-modal embeddings for more robust and meaningful biological insights.

Machine Learning-Driven Prediction of Epitope Overlaps Using Deep Mutational Scanning (DMS) Profiles

Presenter: Schama zannou

Institution: Nantes Université, Nantes

Abstract:

The accurate prediction of antibody-epitope interactions is essential for therapeutic antibody discovery. Traditional sequence-based clustering methods often fail to capture the **functional relationships between antibodies and their target epitopes**, especially when mutations affect antigen binding and escape. To address this, we developed a **machine learning model that leverages Deep Mutational Scanning (DMS) data** to improve the prediction of epitope overlaps based on paratope features. This approach allows for the functional characterization of antibodies without requiring experimental structural data.

Assessing to what extent manifold learning can reveal structure across single-cell RNA-sequencing measurements

Presenter: Laia Canal Guitart

Institution: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Germany

Abstract:

Various manifold learning techniques are used to visually inspect the underlying dynamical patterns present in time-series single-cell RNA-sequencing (scRNA-seq) data, as there is no one-to-one correspondence between cells at different timepoints. Focusing on a single representation implicitly assumes that this technique has correctly modelled the manifold in which the dynamical patterns occur. As a result, the use of different techniques can lead to discrepancies in the representation of these patterns, and there is typically no benchmark dataset that can be used to reason about these discrepancies. To investigate this issue, we generate artificial time-series scRNA-seq data using a variational autoencoder based simulation design. This design introduces synthetic dynamical patterns using vector fields in a low-dimensional manifold, allowing for the transformation of the low-dimensional representation according to biologically meaningful temporal patterns, such as dividing cell clusters during a differentiation process. We consider manifolds obtained from different techniques such as Principal Component Analysis (PCA), t-Stochastic Neighbour Embedding (t-SNE), Uniform Manifold Approximation and Projection (UMAP) and single-cell Variational Inference (scVI). Our simulation design provides a tool for reasoning about the sensitivity of different techniques to different dynamical patterns, and demonstrates that while the dynamics of interest may be present in any of the several plausible manifolds, these techniques, when used in isolation, may not be sufficient to reliably represent them.

Sparse dimensionality reduction for constructing easy-to-assess representations and visualizations of gene expression data

Niklas Brunn[12*], Maren Hackenberg[12], Tanja Vogel[3], Harald Binder[124]

Institution: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Germany

*Presenting author

Abstract:

Several approaches have been proposed to reconstruct interactions between groups of cells or individual cells from single-cell transcriptomics data, using prior information about known ligand-receptor interactions. At the single-cell level, the large volume and complexity of interaction data obscures patterns that cannot be detected through visual inspection, highlighting the need for pattern recognition tools.

To improve downstream analyses, we present an end-to-end dimensionality reduction workflow, specifically tailored for single-cell cell-cell interaction data. In particular, we demonstrate that sparse dimensionality reduction can pinpoint specific ligand-receptor interactions in relation to clusters of cell pairs. For sparse dimensionality reduction, we focus on the Boosting Autoencoder (BAE), which combines unsupervised deep learning with componentwise boosting. Specifically, the approach identifies small sets of ligand-receptor interactions during optimization that explain the patterns in latent dimensions. The integration of a soft clustering component further allows the assignment of cell pairs to clusters and helps to improve the disentanglement of the latent patterns.

Overall, we provide a comprehensive workflow, including visualization of results, that simplifies the analysis of interaction patterns in cell pairs. This is supported by a Jupyter notebook that can readily be adapted to different datasets.

From Genes to Images: Leveraging Spatial Transcriptomics for Histological Image Generation

Frederieke Lohmann[1], Alberto Valdeolivas[1], Jelica Vasiljevic[1]
[1]Roche Pharma Research and Early Development, Data and Analytics, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Presenter: Frederieke Lohmann

Institution: Roche, Basel

Abstract:

Introduction

Spatial Transcriptomics (ST) is a groundbreaking technology that enables the capture of gene expression within the native tissue context. Platforms such as 10x Visium and Visium HD facilitate

the integration of gene expression data with histological images, providing a comprehensive, multi-dimensional understanding of tissue organization and cellular function. Considering their complementary aspects, we examine whether gene expression can act as a descriptor of morphology. Motivated by generative models utilised in computer vision and natural language processing, this project aims to explore the generation of histological images from gene expression profiles.

Material and methods

We utilise a VisiumHD mouse kidney sample to generate a large dataset of paired histological images and gene expression profiles. By applying a 10-micron stride and binning gene expression data from 27×27 2-micron bins, we create a dataset consisting of over 300,000 paired samples. We adopt the StyleGAN-T architecture to synthesise histological patches conditioned on gene expression to model the relationship between morphology and gene expression. For this purpose, we modified the original architecture to incorporate a foundational digital pathology model into the discriminator and designed a specialised gene expression module as a conditioning mechanism for image generation. We validate our results using standard 10x Visium mouse kidney samples.

Results

The proposed generative model successfully produces histological images that appear morphologically plausible, as confirmed by visual inspections from both pathologists and non-experts. Furthermore, integrating gene expression conditioning enables the model to infer certain morphological features from gene expressions, such as global cell counts, suggesting that gene expression reflects aspects of tissue structure,

Conclusion

The obtained results suggest the feasibility of generating histological images from gene expression data. The successful integration of gene expression as a conditioning factor implies that transcriptomic profiles may encapsulate certain morphological information. However, the comprehensive nature of this relationship requires further examination. While these preliminary findings are encouraging, additional validation is essential to establish biological interpretability and to explore potential applications in digital pathology and computational histology.

Contrasting Global and Patient-Specific Regression Models via a Neural Network Representation

Presenter: Max Behrens

Institution: Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Germany

Abstract:

When developing clinical prediction models, it can be challenging to balance between global models that are valid for all patients and personalized models tailored to individuals or potentially unknown subgroups. To aid such decisions, we propose an approach that contrasts potential global and local models, including quantities and visualizations for evaluating when a global model is adequate and when personalized models offer a better fit for specific patients. We focus on regression models and specifically suggest a localized regression approach that identifies regions in predictor space where patients are not well represented by the global model. As localization becomes challenging when dealing with many predictors, we propose modeling in a dimension-reduced latent representation obtained from an autoencoder. Using such a neural network architecture for dimension reduction enables end-to-end training, where the latent representation is optimized with respect to reconstruction of original data as well as local prediction of the clinical outcome. We illustrate the proposed approach with a clinical study involving patients with chronic obstructive pulmonary disease. Our findings indicate that the global model is adequate for most patients but that indeed specific subgroups benefit from personalized models. We also demonstrate how to map these subgroup models back to the original predictors, providing insight into why the global model falls short for these groups. Thus, our approach complements analysis results from a global regression model by evaluating its validity and identifying when personalized models are more appropriate for specific patients.

Deep Neural Operators for Real-time Inference of Stochastic Reaction Networks

Presenter: Nicolo' Rossi

Institution: D-BSSE, ETH Zürich, Basel

Abstract:

In isogenic cell populations, stochastic gene expression significantly influences phenotypic diversity, impacting cellular decision-making and gene expression stability. Technological advancements, such as time-lapse microscopy, have advanced our understanding of single-cell dynamics, highlighting the complexity of intracellular processes.
Disentangling such complexity requires tracking multiple biochemical species, however, this is limited by the availability of measurable reporters.
We frame this limitation as an on-line stochastic filtering problem, where we seek estimates of the full system from noise-corrupted discrete-time partial observations of the biological species. Considered the challenges due to the nonlinearity of chemical interactions and the high dimensionality of the state-space of chemical networks, we tackle this task with deep neural operators, in a framework specifically tailored to chemical reaction networks.
This results in the estimation of a martingale that adheres to an almost-sure relationship, yielding

fast and simulation-free estimates of the real-time behavior of the full system for new observation trajectories.

Un-Freezing Time: Electron Microscopy-Based Reconstructions of Cardiomyocyte Contraction Dynamics Enabled by Deep Learning

Presenter: Dr Eva Rog-Zielinska

Institution: Institute for Experimental Cardiovascular Medicine, University of Freiburg, Freiburg

Abstract:

Cardiomyocyte function is profoundly linked to its ultrastructure, which undergoes significant mechanical deformation during each heartbeat. Characterization of these dynamics is crucial for understanding cardiac function in health and disease. Conventional methods for this characterization rely on light microscopy, which lacks spatial resolution to resolve nanoscopic detail. Electron microscopy offers orders of magnitude higher resolution but lacks temporal information. Here, we overcome the latter limitation by combining action potential-synchronized high-pressure freezing to capture defined time-points during the cardiomyocyte contraction and relaxation cycle (effectively adding 1 ms-resolved temporal resolution) with electron tomography-based reconstructions (offering ~1 nm3 spatial resolution). Deep learning-enabled processing not only massively accelerates analyses of these images, but it also uncovers information that would remain inaccessible with conventional methods. Using this approach, we characterize the nanoscopic structure and dynamics of cardiomyocytes, focusing on key organelles involved in excitation-contraction coupling.

Cardiomyocytes were isolated from vibratome-cut living left-ventricular rabbit tissue and treated with pharmacological agents to modulate microtubule stability: colchicine for destabilization (12.5 µM and 1.25 mM) or paclitaxel for stabilization (1.2 µM), using untreated cells as controls. Cells were high-pressure frozen at prescribed intervals post-electrical stimulation, freeze-substituted, heavy metal-stained, resin-embedded, and cut into 300 nm sections. Dual- and single-axis electron tomography resulted in ~850 ultrastructural reconstructions with an average reconstructed volume of ~2.5×2.5×0.2 µm3. Detailed 3D models were created with neural networks and custom semi-automatic segmentation tools. We created an accessible web-based visualization interface to manage, explore, and share the extensive datasets. Finally, we used neural networks to generate electron microscopy ‘movies’, synthesizing nanoscopic visualizations of virtual cells during contraction and relaxation. Our evaluation of the segmented volumes revealed that contraction is associated with an increase in cross-sectional axis ratio (eccentricity) of transverse tubules in control cells. While we observed a similar effect in paclitaxel-treated cells, we could not observe a significant change in cross-sectional axis ratio in colchicine-treated cells. These observations

indicate a microtubule-dependent contribution to transverse tubular deformation, facilitating advection-assisted exchange of transverse tubules' luminal content. At the same time, there was a remarkable absence of significant effects of contractile activity or microtubule modulations on dyadic distances. This suggests that the tight control of dyadic distances is not acutely affected by microtubule integrity.

In conclusion, our study presents an innovative framework that combines action potential-synchronized high-pressure freezing, electron tomography, and deep learning-enabled processing, providing unique insights into the nanoscopic dynamics of cardiomyocytes and their modulation due to microtubules. We believe that understanding cardiac nanoscopic dynamics is key to advancing our knowledge of the ultrastructural foundations of cardiac health and disease.