**TMDU-Humboldt University Symposium on Disease Systems Biology**
14:00-18:00, September 9, 2024
Conference Room, 2nd F, 22nd Building, Surugadai Campus, TMDU

Disease Systems Biology aims at systemic understanding of diseases and contributing to improvement of treatments by combining network biology based on multi-omics data and clinical information from healthcare. This symposium is organized by Humboldt-Universität zu Berlin Theoretical Biophysics and TMDU M&D Data Science Center. All speakers are invited.

Program
14:00-14:05
Opening: Satoru Miyano (Director of M&D Data Science Center, TMDU)

14:05-14:45
**Edda Klipp (Theoretical Biophysics, Humboldt-Universität zu Berlin)**
Signaling in Time and Space

14:45-15:25
**Rune Linding (Theoretical Biophysics, Humboldt-Universität zu Berlin)**
Systematic Discovery of Mechanistic Cell Signaling Networks in Cancers with Theory Informed Machine Learning

Break 15:25-15:55

15:55-16:35
**Heewon Park (Sungshin Women's University & TMDU M&D Data Science Center)**
Computational Network Biology Analysis for COVID-19 Severity Marker Identification

16:35-17:15
**Hideyuki Shimizu (M&D Data Science Center, TMDU)**
Toward Systematic Discovery of Therapeutic Molecules for Nnmet Medical Needs

17:15-17:55
**Takanori Hasegawa (M&D Data Science Center, TMDU)**
Computational Approaches to Neoepitope Selection and Immunogenicity Prediction

17:55-18:00
Closing: Kunihiko Takahashi (Vice Director of M&D Data Science Center, TMDU)

Open Discussion 18:00-

**Speakers and Abstracts**

**Edda Klip** (Humboldt-Universität zu Berlin)

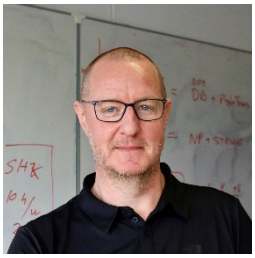
**Signaling in Time and Space**

Signaling within eukaryotic cells is organized in space and time. It is mainly realized by proteins binding each other or lipid membranes, typically in the vicinity of a membrane-located receptor. Protein states can be modified through binding and post-translational modifications such as phosphorylation. Signal transmission in the resulting signaling networks is highly complex and dynamic. Because of their importance in cancer development, cellular signaling pathways have attracted quite some modeling effort in order to understand the wiring of the network, to conceptualize the modes of signal transmission and to integrate and analyze different types of data.

Cell shape is important for the dynamics of cellular signaling. We investigated the time and space dependency of cellular signaling on the cell shape by combining experimental time-resolved data for the activation of cell signaling with image analysis of the affected cells during a wound-healing experiments and spatio-temporal agent-based modeling. We performed systematic stochastic simulations and analyzed the resulting temporal behavior and spatial distribution of different signaling compounds for different cell shapes. As an input for the simulation pipeline, we adapted a method to create meshes for the surfaces of arbitrary cell shapes that subsequently can take real image data as input. Systematic simulation of the network (here exemplified for the ERK signaling pathway) in different cell shapes and under different conditions led to following insights: (i) Shape influences the dynamics of signaling molecules in the cytoplasm. (ii) The distribution of receptor molecules at the surface was not found to be affected by cell shape. (iii) The time needed by phosphorylated ERK to reach the nucleus is dependent on cell shape, where elongated cell shapes lead to longer delay between first signal and signal output reaching nucleus. (iv) Small sub-volumes such cell protrusions can restrict the diffusion of signaling molecules affecting signal transduction and creating locally different concentrations of signaling molecules.
We have combined the different analysis steps into a prototypical pipeline. This will in future allow to investigate the spatio-temporal dynamics of signaling pathways in specific cell shapes typical for different conditions such as cells in a confluent cell layer, cells invading empty space, single cells under microscope or migrating tumor cells. This will allow for a deeper understanding of the mutual dependence of cell shape and signaling.

Short Bio
Edda Klipp is full professor for Theoretical Biophysics at Humboldt-Universität zu Berlin. She has a doctoral degree in theoretical biophysics. In 2009 she was awarded an honorary doctor of Göteborg University. 2015 she was awarded the Caroline-von-Humboldt professorship at Humboldt-Universität zu Berlin. Klipp carries out multi-disciplinary research projects to understand cellular organization, dynamics of cellular processes and stress response. Her group has long-standing experience in computational systems biology with focus on dynamic modeling of regulatory processes including signaling, cell cycle, metabolism, transcriptional regulation and growth control.

**Rune Linding** (Humboldt-Universität zu Berlin)



**Systematic Discovery of Mechanistic Cell Signaling Networks in Cancers with Theory Informed Machine Learning**

Signaling systems in multicellular organisms are vital for cell-cell communication, tissue organization and disease. Cancer genomics has unraveled a surprisingly large set of novel gene lesions from tumors. Our previous studies have globally explored the rewiring of cell signaling networks underlying malignant transformation caused by kinases and other signaling proteins. We are now working to employ Sci-ML (Scientific ML) and BPINNs (Biophysics Informed Neural Networks) based machine learning with big data to discover the underlying causal and mechanistic systems structure and dynamics (e.g. ODEs with partially unknown functions and/or parameters). We aim to use such models to predict novel treatment and diagnostic strategies for tumors harboring different genetic lesions. To this end our lab has generated systems-scale quantitative time- and state-series multi-omics data and subsequently used these as input for computational algorithms aiming to model the principal changes in the genome, cell signaling and phenotypes of cells harboring cancer mutations. We have validated this approach by forward prediction of experimentally observed phenotypic responses to drug and genetic perturbations. We are currently attempting to deploy biophysics-informed Sci-ML models to forecast how cell signaling networks are mechanistically, dynamically and differentially utilized in TNBC (Triple Negative Breast Cancer) cells during metastasis. Our studies aim to unravel the fundamental rewiring of cell signaling networks in cancer and its impact on the disease, paving the way for future clinical applications and tumor specific cancer therapy.

Selected References:

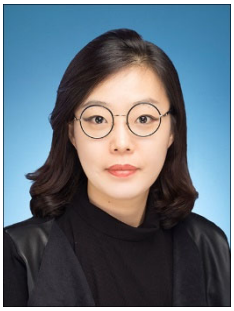
1. Linding et al., Cell 2007.
2. Bakal et al., Science 2008.
3. Jørgensen et al., Science 2009.
1. Miller et al., Science Signaling 2008.
2. Tan et al., Science Signaling 2009.
3. Tan et al., Science 2009.
4. Tan et al., Science 2011.
5. Creixell et al., Nature Biotechnology 2012.
9. Creixell et al., CELL 2015 I & II
10. Koplev et al., CELL Reports 2017.
11. Van de Kooij et al., Elife 2019.
12. Miller et al. PLoS Biology 2019.
13. Longden et al. CELL Reports 2021.
14. Seeger et al. Curr Genomics 2021.
15. Klipp & Linding Current Opinion in Systems Biology 2021.
16. Johnson et al. Nature 2023.

Short Bio

Dr. Linding completed his Ph.D. at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, followed by postdoctoral training at EMBL. He then jointly trained with professors Tony Pawson and Mike Yaffe at the Lunenfeld at Mount Sinai Hospital in Toronto, Canada, and the Massachusetts Institute of Technology (MIT) in Cambridge, US, respectively. Dr. Linding then established his own laboratory of Cellular & Molecular Logic at the Institute of Cancer Research (ICR) in London, UK, before returning to Denmark to take a position as professor of cell signaling, currently at the Biotech Research and Innovation Centre (BRIC) at the University of Copenhagen. His research group focuses on big data network biology, exploring biological systems by developing and deploying algorithms aimed to predict cell behavior, in particular looking at cellular signal processing and decision making. A strategic focus is to continue to develop computational tools (such as KinomeXplorer, ReKINect, NetworKIN, and NetPhorest) and to deploy these on genome-scale quantitative data obtained by, for example, mass spectrometry, genomic, and phenotypic screens to understand the principles of how spatio and temporal assembly of mammalian signaling networks transmit and process information at a systems level in order to alter cell behavior. His overarching aim is to advance network medicine by identifying and targeting signaling networks associated with complex diseases. To this end Dr. Linding is leading high-level, strategic, multidisciplinary studies of signaling network dynamics driving cancer metastasis in collaboration with other labs at Harvard, Yale, Memorial Sloan Kettering Cancer Center and MIT. Dr. Linding is based and employed at HU-Berlin since 2019 as co-PI for the Klipp-Linding laboratory.

**Heewon Park** (Sungshin Women's University & TMDU M&D Data Science Center)

**Computational Network Biology Analysis for COVID-19 Severity Marker Identification**



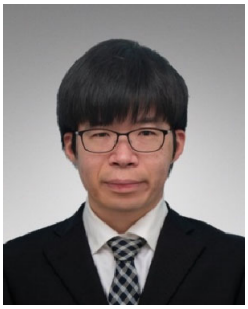
Coronavirus disease 2019 (COVID-19) rapidly spread worldwide. Severe and critical patients are expected to rapidly deteriorate. Although various studies have attempted to uncover the mechanisms underlying COVID-19 severity, most have focused on the abnormalities in single genes. However, the complex mechanism of COVID-19 involves numerous perturbed genes in a molecular network rather than a single abnormal gene. We aimed to identify COVID-19 severity-specific markers in the Japanese population using gene network analysis and developed a novel computational network biology strategy to identify differentially regulated gene networks between severe and non-severe COVID-19 samples. Our strategy was applied to whole blood RNA-seq data from 465 genotyped samples from the Japan COVID-19 Task Force consisting of 108 medical institutions and revealed the COVID-19 severity-specific molecular interplay. Our findings from computational network biology analysis with literatures suggests that suppression and activation of the molecular interplay between HLA class II, CIITA, and CD74 provide crucial clues to reveal the mechanisms of COVID-19 severity.

Short Bio

Heewon Park is currently an Associate Professor of School of Mathematics, Statistics and Data Science, Sungshin Women's University, Republic of Korea. She received the PhD degree in mathematics from Chuo University in 2013, where she studied on information criterion for model evaluation. Her current research interests cover computational network biology, e.g., gene network estimation and interpretation of the estimated huge amount of gigantic gene network. She is a guest professor of TMDU M&D Data Science Center.

**Hideyuki Shimizu** (TMDU M&D Data Science Center)

**Toward Systematic Discovery of Therapeutic Molecules for Unmet Medical Needs**



The quest to address unmet medical needs has driven significant advancements in drug discovery. In this talk, I will begin with the Warburg effect, a century-old enigma in cancer metabolism. Through comprehensive proteomic and metabolomic measurements, combined with integrative analysis of data from over 10,000 cancer patients, we have identified a novel therapeutic target molecule, PPAT. This discovery opens new avenues for cancer treatment.
To expedite the development of PPAT inhibitors, we have created an AI-based drug discovery platform capable of identifying inhibitors solely from amino acid sequences. LIGHTHOUSE has not only facilitated the discovery of PPAT inhibitors but has also been instrumental in finding treatments for bacterial infections and COVID-19.

Furthermore, we are leveraging AI for genome mining of microorganisms to discover new antibiotics and antimicrobial peptides. This approach holds promise for addressing the growing threat of antibiotic resistance.

Additionally, a large-scale project has been initiated to find treatments for glioblastoma, a notoriously difficult-to-treat cancer. This project employs organ transparency techniques, large-scale imaging technologies, and AI to uncover potential therapeutic agents.
In this talk, I will share some of our ongoing endeavors and discuss the potential of systems medicine to revolutionize drug discovery, ultimately aiming to meet the pressing medical needs of our time.

Short Bio

Hideyuki Shimizu, M.D., Ph.D. Professor. Department of AI Systems Medicine, M&D Data Science Center, TMDU. Hideyuki Shimizu was born in JAPAN and earned his M.D. from Tohoku University School of Medicine in 2012. From 2012 to 2014, he completed his initial residency at Iwate Prefectural Chubu Hospital. He then pursued Ph.D. at Kyushu University Graduate School of Medical Sciences under the supervision of Professor Keiichi Nakayama from 2014 to 2018, studying molecular and cellular biology and bioinformatics. From 2018 to 2020, Dr. Shimizu worked as an Academic Researcher at the Medical Institute of Bioregulation, Kyushu University, studying systems biology and AI. He then moved to the United States, where he was a Research Associate at the Department of Systems Biology, Harvard Medical School, and the Wyss Institute for Biologically Inspired Engineering at Harvard/MIT, working with Professor Pamela Silver from 2021 to January 2022. Since February 2022, Dr. Shimizu has been a Principal Investigator at TMDU. Additionally, he has been a PRESTO Researcher at the Japan Science and Technology Agency (JST) since October 2022.

**Takanori Hasegawa** (TMDU M&D Data Science Center)

**Computational Approaches to Neoepitope Selection and Immunogenicity Prediction**

Tumor cells may express tumor-specific or tumor-associated antigens (TSA/TSS). Some of these peptides may bind to major histocompatibility molecules (MHC) and be recognized by T cells, eliciting an anti-tumor immune response in the patient. These peptides are called neoantigens. Neoantigens are expected to become new targets for personalized immunotherapy and can be applied as predictive indicators of patient survival, prognosis, and responsiveness to immune checkpoint inhibitors. Prediction of neoantigens involves many steps, but in particular, T cell receptor (TCR)-peptide/MHC binding prediction has been the focus of recent research. Although prediction accuracy has improved with the development of computational techniques, including deep learning, it is almost impossible to obtain sufficient data sets, and prediction for unlearned data sets is still low. In response, advanced methods using structural information are being proposed.

Short Bio

Takanori Hasegawa received a BS in Engineering from Waseda University, an MS in Information Science and Technology from The University of Tokyo, and a PhD in Informatics from Kyoto University in 2010, 2012, and 2015, respectively. He is an Associate Professor at the Department of Integrated Analytics, M&D Data Science Center, Tokyo Medical and Dental University. His focus is computational immunogenomics on tumor immunity, senescent cell elimination, and multi-omics analysis of emerging infectious diseases, including COVID-19 and associated sepsis.