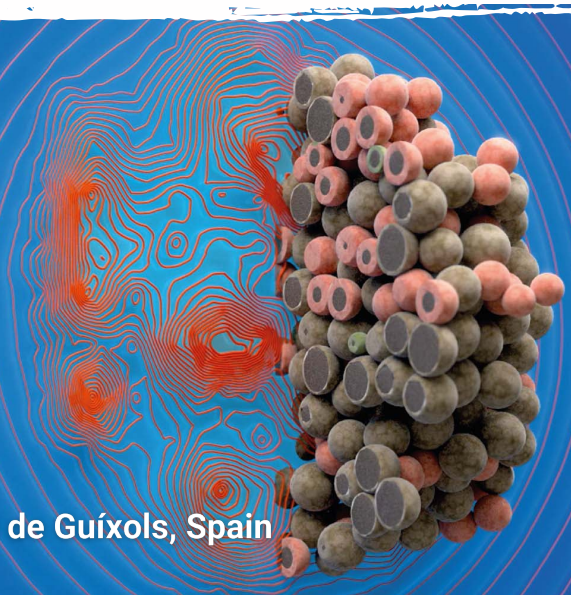
EMBO Workshop

Computational models of life: From molecular biology to digital twins



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Book of abstracts

EMBO Workshop:
Computational models of life:
From molecular biology to digitla twins

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Speakers

Rossen Apostolov
KTH Royal Institute of Technology, SE
Title of the talk: Advanced methods for extreme-scale biomolecular simulations & Community Impact

Alexandre Bonvin
Utrecht University, NL
Title of the talk: Solving 3D bimolecular puzzles by integrative modelling

Lukas Breitwieser
ETH Zurich, CH
Title of the talk: Reducing Time-to-Insight: Accelerating Agent-Based Simulation with BioDynaMo

Marta Cascante
University Barcelona, ES
Title of the talk: Metabolic phenotyping from cells to tumour biopsies: towards the design of personalized therapies

Javier Conejero
Barcelona Supercomputing Center (BSC), ES
Title of the talk: Programming workflows with PyCOMPSs and PerMedCoE's Building Blocks

Dirk Drasdo
INRIA Saclay Île-de-France, FR
Title of the talk: Towards a full digital liver twin: drug injury, regeneration and disease progression

Liesbet Geris
University de Liège, BE; KU Leuven, BE; VPH Institute
Title of the talk: Building the virtual human twin: an ecosystem approach

Nikos Giatrakos
Technical University of Crete, GR
Title of the talk: Extreme Scale Big Data Analytics Towards Battling Cancer (online)

Alberto Gómez
Barcelona Supercomputing Center (BSC), ES; Red Española de Supercomputación (RES), ES
Title of the talk: How to access HPC resources in Europe with RES and EuroHPC (online)

Tomas Helikar
Department of Biochemistry, University of Nebraska-Lincoln, US
Title of the talk: Digital Twin Innovation Hub: Towards a General-Purpose Immune Digital Twin

Olga Ivanova
University Heidelberg, DE
Title of the talk: Logic models and their application for personalised medicine

Adrianne Jenner
Queensland University of Technology, AU
Title of the talk: Virtual clinical trials provide insight into therapeutic targets for oncolytic viruses

Luana Licata
University Roma Tor Vergata, IT
Title of the talk: Contextualizing molecular networks for human diseases

Vinicius Maracaja-Coutinho
University of Chile, CL
Title of the talk: The Human Cell Atlas and the cell map of Latin America diversity

Anna Niarakis
University of Toulouse III-Paul Sabatier, FR; INRIA Saclay, FR
Title of the talk: A Digital twin for Rheumatoid Arthritis: Science or science fiction?

Saran Pankaew
Institut Curie, FR
Title of the talk: The power of logic: Modelling cancer across scale, with the help of omics data

Francis Planes
University Navarra, ES
Title of the talk: Network-based algorithms for the prediction of metabolic vulnerabilities in cancer

Osbaldo Resendis-Antonio
UNAM/INMEGEN, MX
Title of the talk: Modeling heterogeneous metabolism at the community level: From microbiome data to cancer heterogeneity

Genevieve Stein-O'Brien
Johns Hopkins University, US
Title of the talk: Encoding biology: Mechanism informed algorithms for high dimensional molecular and single cell data

Mariano Vazquez
Barcelona Supercomputing Center (BSC), ES; ELEM Biotech, ES
Title of the talk: Supercomputer-based in-silico clinical trials on Virtual Human Twins

Abstracts

Aetiology-specific global metabolic alterations in hepatocellular carcinoma

Authors:

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Nagasuma Chandra, (Department of Biochemistry, Indian Institute of Science)

Abstract: Primary tumours with liver tissue as origins are known as hepatocellular carcinoma (HCC) or liver cancer. According to GLOBOCAN2020, liver cancers account for 4.5 % of new cases identified and 8.3 % of global cancer-related mortalities. As the most active metabolic organ, liver plays a significant role in whole-body homeostasis. Liver cancer has many known aetiologies such as viral infections (Hepatitis viruses HBV, HCV and HDV), genetic disorders (hereditary hemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease), metabolic syndrome (diabetes, obesity), Fatty liver and carcinogens (Aflatoxin B1). According to a 2020 US NCI Surveillance, Epidemiology, and End Results (SEER) study, non-viral aetiology-related liver cancers have higher mortality than viral-related liver cancers. This study emphasizes understanding the differences between aetiology to develop targeted therapies. Many studies have focused on pan-liver cancer analysis without aetiology information for identifying diagnostic progression biomarkers or pharmacological drug targeting. The current targeted therapies for liver cancer do not consider the underlying aetiology.

To understand the differences across various liver cancer aetiologies, we have designed this study to analyze publicly available liver cancer patient transcriptomics data with matched adjacent normal tissue and underlying aetiology determined at diagnosis. Upon comparison of differential gene expression analysis between tumour and matched adjacent normal tissues, we found a small number of common differentially expressed genes and pathways but many unique differential genes and pathways mapped to each aetiology. Further, we performed Genome-scale metabolic modelling to understand the transcriptome-inferred metabolism changes among the aetiologies. Our preliminary analysis revealed a few pathways like glycolysis, pyruvate and fatty acid metabolism to be shared among aetiologies and many pathways are uniquely enriched in each aetiology, such as pyrimidine metabolism in viral aetiologies and aromatic amino acid metabolism in non-viral aetiologies. This shows the possibility of aetiology-preferred reaction routes leading to liver cancer progression. This knowledge can help us design aetiology-specific diagnostic and therapeutic interventions for HCC.

Prediction of cancer-selective drug combinations for acute myeloid leukemia (AML) with single-cell RNA sequencing and drug-target networks

Authors:

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Liye He, (Institute for Molecular Medicine Finland (FIMM))

Tero Aittokallio, (Institute for Molecular Medicine Finland (FIMM))

Abstract: The development of high-throughput technologies has promoted a rapid accumulation of the large-scale patient data, such as clinical information, functional data, and epi/genomics profiles of patient samples. Powerful machine learning (ML) or artificial intelligence (AI) techniques have been used to translate the big data in cancer into discovering tailored therapies for each individual patients. In this study, we developed a functional precision medicine pipeline to integrate the multi-omics profiling data and clinical data to identify effective and safe drug combinations for patients with acute myeloid leukemia (AML). The pipeline combines ex vivo patient-derived drug sensitivity profiles, compound-target interaction networks and single-cell RNA sequencing (scRNA-seq) data separately from each patient sample. Based on the integrated high-dimensional data, an ensemble machine learning model, Extreme Gradient Boosting (XGBoost), was constructed to make drug combination predictions targeting specific cell subpopulations deconvolved by scRNA-seq cell type annotation tools. 5-fold cross validation (CV) was used to optimize the model parameters and select the most predictive model. We further developed a target-based standardized single-cell expression (TSSE) score to quantify the enriched expression of drug targets in each cell type. The TSSE score supports the association of the drug responses across different cells with target expression levels of the drugs in heterogenous AML patient samples via the integration of compound-target interaction networks and scRNA-seq data. The proposed pipeline offers possibilities to identify patient-specific combinations with high synergy and potency in co-inhibiting AML cells that show non-synergistic effects in the non-malignant cells. With the implementation of Shapley Additive exPlanations (SHAP) techniques, the interpretable ML model identifies also polypharmacological mechanisms for patient-specific drug combination effects, via compound-target interaction networks, and suggests predictive biomarkers toward clinical translation of the selective combinatorial therapies.

Deciphering cellular interactions through gene regulatory network inference

Authors:

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Abstract: Gene regulatory networks (GRNs) are critical for understanding the complex regulatory mechanisms that underlie cancer development and progression, providing insights into the molecular mechanisms that drive cancer, including the identification of key driver genes and molecular pathways, and the identification of novel therapeutic targets. In the context of the tumor microenvironment (TME), the complex interactions between immune and cancer cells give rise to a cascade of regulatory processes at different levels, defining the cellular behavior and response to external stimuli and to treatments. We aimed to obtain a detailed molecular description of cancer cell behavior and state transitions during interactions with immune cells. This project aims to investigate how regulatory interactions between genes characterize cellular behavior. We use an in vitro model of Chronic Lymphocytic Leukemia (CLL) to study the functional processes determining the CLL cellular interactions at the molecular level. CLL is a blood tumor characterized by progressive proliferation and accumulation of malignant B lymphocytes. In the lymph node, the CLL cells interact with monocytes that differentiate into macrophages that can promote CLL cells' survival, a process which is recapitulated in our in-vitro cultures and is often at the origin of resistance to treatments also in solid tumors.

To investigate how the presence of immune cells, including macrophages, determines CLL behavior, we performed experiments in three conditions (CLL patient blood including a mix of immune cells and a majority of CLL cells, monocytes from healthy people and CLL cells, CLL cells alone) and obtained 14-day gene expression time-course bulk RNAseq of CLL cells. We then performed GRN inference for each experimental condition, revealing substantial structural and functional differences between the GRNs inferred from the three conditions. Additionally, differential gene expression analysis and Gene Set Enrichment analysis highlighted important gene modules and the biological processes in common or specific to the three cultures, allowing us to dissect the main regulators of interactions between macrophages and cancer cells. It is likely that we identified novel transcription factors involved in CLL cellular crosstalk, thus better understanding their behavior and response to external stimuli.

Modelling of MEG3v1-p53 complex

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Abstract: Long non-coding RNAs (lncRNAs) are functionally RNAs longer than 200nt. These have a regulatory role in several cellular processes, from chromatin remodeling to protein regulation, directly or through miRNAs, for example. These molecules are usually very long, from 1500 nt to 6-10k, and their function is strictly related to their structure. Unfortunately, the structure prediction of so long molecules, with few conserved secondary structural elements, is challenge.

Human maternally expressed gene 3 (MEG3) is an highly expressed, imprinted, alternatively-spliced lncRNA, with tumor suppressor function, directly or indirectly mediated by p53. MEG3 is downregulated in tumor cells, reducing its stabilizing effect on p53. This function is related to expressed MEG3 splicing variants as well as to its structure.

Here we predict the tridimensional structure of MEG3v1, one of the active isoforms for p53, starting from experimentally determined 2D structure, in order to obtain the complex conformation with p53.

The tridimensional conformation of MEG3v1 was obtained with SimRNA using dot-brackets of secondary structure obtained from Uroda et. al. Obtained conformation was optimized with 4 replicas of REMC. Clustering of the lowest total energy conformations returns three main clusters. Several tools, KYG, NucleicNet, aaRNA, PST-PRNA, NucBind and DRNApred were employed to predict residues interacting with RNA and RBPmap for nucleotides interacting with protein; residues or nucleotides common to at least three tools are considered for the interaction surface. The central structure of each cluster was divided into three “domains” of about 500nt each one, according to the conformation, and to reduce the dimensionality. Each domain in the three clusters conformation and the full length p53 model obtained from AlphaFold2 (Uniprot ID: P04637), were employed for Protein-RNA docking with HADDOCK using previously identified interaction surface as active residues. Then, best Haddock score results, one for each domain, were undergone to classical MD simulation to obtain equilibrated complexes.

Tackling oncogenic drivers and differentiation blocks in blood cancers by computational modelling

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Oleksii Rukhlenko (Systems Biology Ireland, School of Medicine, University College Dublin)

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Walter Kolch (Systems Biology Ireland, School of Medicine, University College Dublin | Conway Institute of Biomolecular and Biomedical Research, University College Dublin)

Abstract: Childhood leukemia, while increasingly curable, still relies on non-specific chemotherapy, resulting in severe long-term side effects for patients. To improve treatment strategies, my project will explore the molecular intricacies driving aberrant cell states, specifically looking at impaired hematopoietic differentiation and altered kinase signaling pathways governing cellular proliferation and survival.

Drawing inspiration from existing examples of successful differentiation therapy such as acute promyelocytic leukemia (APML), the aim is to shift the malignant cell state towards differentiation or apoptosis. APML's remarkable transformation, from a poor prognosis to high cure rates with 'chemo-free' regimens, is evidence for the promise of precision medicine. Focused on moving away from non-specific chemotherapy, this project centres on the precise mapping and control of cell state transitions along the hematopoietic lineage, thus enabling us to accurately pinpoint the key molecular networks that underpin blood cell differentiation block in leukaemia. To achieve this, the project integrates various methods, including computational modeling, experimental analysis, and machine learning. One of the project's core methodologies used to map state transitions is the newly developed cell state transition assessment and regulation (cSTAR) method that was developed in our institute (Rukhlenko et al. Nature 609, 975–985, 2022, DOI: https://doi.org/10.1038/s41586-022-05194-y). This approach harnesses high-throughput omics data and applies machine learning to classify cell states. It identifies the pivotal core signaling network dictating cell fate transitions and mechanistically models how cells navigate Waddington's landscape, determining their chosen cell fate.

The project combines multiple data sources, including publicly accessible datasets on cancer genomes, gene expressions, and proteomics, combined with in-house data including phosphoproteomic data from mutant leukemia cell lines. Importantly, this project will also integrate real-time clinical genomic information from leukaemia samples in paediatric patients treated in our partner hospital. My project will feed into a wider group project within my institution with the vision to build a digital twin. Digital twins, traditionally in engineering, involve creating virtual replicas of physical systems. In this context, a "digital twin" represents a patient's leukemia cell population in a virtual environment which will capture dynamic cell behavior and responses to therapies.

Computational Models in Cancer Research: Advancing Molecular Biology Insights

Authors:

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Abstract: Cancer research has witnessed a dynamic shift in recent years with the incorporation of computational models within the realm of molecular biology. This abstract provides an overview of the pivotal role that computational models play in advancing our understanding of cancer and its therapeutic strategies.

The complex nature of cancer, involving intricate genetic and molecular alterations, necessitates a multifaceted approach to unravel its mechanisms. Computational models, ranging from mathematical simulations of intracellular processes to machine learning-driven analyses of large-scale omics data, offer a means to dissect the underlying intricacies of cancer biology. Molecular modeling and structural biology simulations are instrumental in elucidating the three-dimensional structures of cancer-related proteins and predicting their interactions with potential therapeutic agents. These techniques aid in the rational design of targeted therapies, contributing to the development of precision medicine approaches. Systems biology models have enabled a systems-level view of cancer by integrating diverse biological data types, including genomics, transcriptomics, and proteomics. These models provide insights into the dynamic behavior of cancer networks, paving the way for the identification of key regulatory elements and potential drug targets.

Furthermore, machine learning and artificial intelligence approaches have been leveraged to mine vast datasets, enabling the discovery of novel biomarkers, patient stratification, and drug repurposing opportunities. These computational tools enhance the efficiency of biomarker discovery and the personalization of cancer treatment strategies.

This abstract emphasizes the pivotal role of computational models in shaping the landscape of cancer research within the domain of molecular biology. The integration of these models has not only deepened our understanding of cancer but has also expedited the translation of research findings into clinical applications. As the synergy between computational sciences and molecular biology in cancer research continues to evolve, it holds the promise of accelerating the development of more effective cancer therapies and improving patient outcomes.

Mechanistic insights into vaccine-induced immune responses gained from a data-enhanced Boolean modelling approach

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Anne-Sophie Beignon (Université Paris-Saclay)

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Marine Ciantar (Dassault Systèmes BIOVIA)

Laurent Naudin (Dassault Systèmes BIOVIA)

Abstract: The growing volume and complexity of omics data has opened the door to a system-wide understanding of biological processes. Popular approaches to exploit the ensuing datasets include differential expression and co-expression network analyses. While both yield interesting insights about the biological entities and pathways involved in those processes, they often fail to capture the underlying mechanisms.

We developed a workflow to extract information from both existing knowledge and experimental data, and build a dynamic network of binary variables, called Boolean network, to elucidate the modus operandi of Modified Vaccinia Ankara (MVA), a vaccine approved against monkeypox and smallpox. The resulting model was calibrated, using an original algorithm leveraging the Zhegalkin polynomial form of Boolean expressions combined with a SAT-solver, to mimic the measured gene expressions and cell abundances in three immunized animals.

Despite the approximation inherent to the Boolean formalism and the stringent statistical filtering operated on the microarray transcriptomic and flow cytometry data, the network built from four immune pathways and eleven cell populations successfully recapitulated the observed dynamics of those populations following immunization (reported in Rosenbaum et al., Front. Immunol. 2018). More importantly, it gave insights about the interacting genes responsible for these dynamics, including the underlined shared behavior of the granulocytes and monocytes subsets on one hand, and lymphocytes on the other. This model will allow us to make new mechanistic hypotheses for MVA-induced inflammatory responses to be validated experimentally in a 3R-motivated approach.

French Center for 3Rs : 3Rs & Digital tools

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Abstract: The French Center for 3R (FC3R) has for a mission to encourage and implement the Replacement, Reduction, and Refinement (3Rs principle) of animal experimentation in France through the promotion of responsible and innovative research, education and transparent communication. The FC3R's dedication to promote and advance alternative methods in life sciences research results in a great interest in computational biology and digital approaches.

One of the FC3R's core missions is the provision of research funding : our first two calls for projects - on "Collaborative initiatives" and "Replacement" respectively - , already bolstered the development and application of computational models in life sciences with a high-impact for the 3R. We launch this year a new call specifically for "Digital tools", in order to provide financial support for innovative projects that develop or democratize a new strategy, method or digital technology that advances Replacement, Reduction and/or Refinement in the life sciences.

Considering the importance of knowledge dissemination in offering researchers access to the latest digital tools and methodologies, the FC3R intensively communicates about innovation, grants, awards, evolution of practices and regulations ; and recognizes through interviews, conferences and awards researchers whose accomplishments lead forward the 3Rs in France. In order to map the scientific knowledge and facilitate scientific collaborations, the FC3R is currently conducting a survey on the use of alternative methods – including in silico approaches – in France.

The FC3R also advocates for open science and collaborative efforts by providing a platform for unpublished-data sharing, and a catalogue of international training offers. Moreover, the FC3R is willing to accompany researchers with their experimental design through project engineering support, in order to empower scientists to harness computational models for scientific breakthroughs while ensuring that funded research projects are effectively executed and translated into impactful outcomes.

A community benchmark of multiscale modelling tools serves as beacon for the construction of digital twins

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Alfonso Valencia (Barcelona Supercomputing Centre | ICREA)

Arnau Montagud (Barcelona Supercomputing Centre) & benchmarking tools developers

Abstract: To help map the field of agent-based modelling for digital twins, at PerMedCoE we gathered different developer teams and organised a community-driven benchmark. The tools that participate in this benchmark were PhysiCell (Ghaffarizadeh et al., 2018), Chaste (Cooper et al., 2020), BioDynaMo (Breitwieser et al., 2021) and TiSim/CellSys (Hoehme and Drasdo, 2010).

The goal of the benchmark was to agree on a set of reference datasets, metrics and scope of the scientific questions addressed by the tests and run these in all the tools in a common computing cluster. Even the simple unit tests yielded different results among the tools, but the tools fitted well a set of experimental growth values of a 2D monolayer growing in vitro.

From the results of these, it was decided that the next steps were to carefully study the simulation results of each tool, their code implementation and their underlying mathematics to be sure that the benchmark is comparing tools that simulate exactly the same behaviour using the same equations.

These outcomes will be disseminated in a community paper with a global picture of where we stand, identifying gaps and obstacles that need addressing if we are to deliver digital twins in the future.

Insights into NLRP3 inflammasome activation using MD simulation

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Abstract: NLRP3 (NOD-, LRR- and pyrin domain containing 3) inflammasome is a cytoplasmic protein complex that regulates the activation of inflammatory cytokines. Given its implication in a range of diseases, NLRP3 is an important therapeutic target [1]. The cofactor ATP and the centrosomal kinase NEK7 are important for NLRP3 activation. We have constructed and simulated computational models of full-length monomeric NLRP3 to shed light on the importance of NEK7 and cofactor interactions for its conformation and dynamics in aqueous solution. These computed dynamical trajectories of NLRP3 provide insight into coordinates of deformation that may be key for cofactor binding and inflammasome activation [2].

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2. El-Sayed, S.; Freeman, S. and Bryce, R. A., Prot. Sci. 2022, 31, e4420. DOI: 10.1002/pro.4420 and 10.1002/pro.4493.

3. Sharif, H.; Wang, L.; Wang, W. L.; Magupalli, V. G.; Andreeva, L.; Qiao, Q.; Hauenstein, A. V.; Wu, Z.; Nunez, G. and Mao, Y., Nature 2019, 570, 338-343. DOI: 10.1038/s41586-019-1295-z.

Optimized Finite Volume Methods solver allows for real-sized tumor simulations

Authors:

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Abstract: Multi-scale cell simulators are among the most computationally demanding bioinformatics applications and are a source of daunting challenges for supercomputing. Human digital twins require extremely massive simulations that the state-of-the-art is not able to model. Physics-based multiscale cell simulator, PhysiCell, sets the basis of a community-built software that helps researchers bridge the intracellular mechanisms to tissue-level biomedical solutions. PhysiCell uses a Finite Volume Method to model the diffusion equation. If we aim at simulating real-sized tissues and as these tools are memory-bound, we need to incorporate MPI into the software. By doing so, the diffusion-decay solver cannot solve the Tridiagonal matrix algorithm in a scalable manner.

This work presents a scalable solution, called BioFVM-B, for the diffusion-decay solver in three dimensions that is decomposed through Locally One-Dimensional method that accelerates the solution by a first-order splitting in the x-, y- and z-directions. BioFVM-B is presented as a scalable distributed library to model microenvironment evolution with optimized methods for High Performance platforms. It is a performance upgrade of the cutting-edge BioFVM's distributed version, BioFVM-X. The solution included in BioFVM-B involves lightweight microenvironment data structures that enhance memory usage and a new computation workflow to solve a massive number of large tridiagonal equations systems. Tridiagonal matrix algorithm resolution serialization is concealed by enabling concurrent communication and computation of the different subsets of large tridiagonal systems. Furthermore, Auto-fitter is proposed as a pipeline to assess cluster-specific optimal number of subsets that the optimization processes in parallel. The tool uses empirical data from performance tests to select an energy efficient number of steps and nodes for a determined problem size.

BioFVM-B allows simulating microenvironments able to contain a real-size tumor by efficiently using up to 4608 cores as a further step towards reaching the virtual digital twins goal.

Systems Modelling and Analysis of Signaling Pathways in Hepatocellular Carcinoma

Authors:

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Akilan M (National Institute of Technology Warangal)

Anbumathi Palanisamy (National Institute of Technology Warangal)

Abstract: Hepatocellular carcinoma (HCC) is a highly aggressive primary liver cancer associated with significant morbidity and mortality. The development and progression of HCC involves several genetic mutations, alterations in signaling pathways leading to dysregulation of cellular processes such as growth, proliferation, apoptosis, and invasiveness. Several investigations have demonstrated the participation of diverse regulators and their complex signaling cascades in the advancement and progression of HCC. Understanding these crucial signaling pathways, including receptor tyrosine pathways, PI3K/AKT/GSK3□/mTOR, Wnt/β-catenin, Ras/Raf/MAPK, TGF-β, Hedgehog, JAK/STAT, and Hippo signaling, offers potential openings for the development of targeted therapeutic interventions. The current study aims to construct a comprehensive molecular map of the signaling pathways involved in the development and progression of HCC using network editor Cell Designer. The assembled network consisting of 193 distinct species and 362 reactions, provides a holistic representation of HCC-associated pathways and adheres to standard SMBL (Systems Biology Markup Language) format. Through subsequent analyses, including biological and functional processes ontology term analysis, subnetwork extraction, and survival analysis, the pivotal roles of regulators such as PTK2, GSK3β, β-catenin, in driving HCC progression were illuminated. Such studies may provide insights into the key molecular targets of HCC and further guide studies exploring combinatorial drug targets towards improving treatment outcomes.

Integrating stochastic Boolean and agent-based modeling frameworks for in-silico gastric cancer drug screening experiments with PhysiBoSS 2.0

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Abstract: Gastric cancer (GC) is considered to be a world-wide health issue. It is one of the most common and deadly cancer types, with over 1 million new cases in 2020. This poor prognosis is only accentuated by the resistance to chemotherapeutic drugs. There is an urgent need for more research on the mechanisms that confer GC this resistance to develop novel therapeutic strategies. Computational systems biology offers the tools and methodologies to create models of specific components of cancer systems while incorporating knowledge regarding the biology of cancer at different scales. An example is the modeling of cancer signaling pathways through Boolean networks, as Flobak et al., 2014 [1] did with the Gastric Adenocarcinoma (AGS) cell line to predict and discover drug synergies in gastric cancer, which were further validated experimentally. In this context, our work is a proof-of-concept that aims to develop a multiscale, agent-based model of AGS that serves as an in silico template for discovering novel therapies against gastric cancer. To do so, we build on top of the work of Flobak et al., 2014: First, integrating their Boolean model, their experimental setup information and drug synergy data, we build a multiscale, ABM model with the PhysiBoSS modeling framework, by combining the mechanistic modeling and multiple timescales of PhysiCell, along with the Boolean cancer signaling networks of MaBoSS. Then, with the experimental drug synergy data as a ground truth, we employ an optimization-via-simulation approach to obtain a personalized, biologically realistic model. Lastly, through this model we are able to study mechanisms of multidrug resistance in AGS by modeling efflux pumps and mutations in the signaling pathways, key players in drug resistance emergence. This digital twin can then be used for discovering and predicting novel therapeutic approaches that help overcoming the ever-increasing drug resistance issue in gastric cancer. For this reason, I am eager to attend to the talks by Olga Ivanova: “Logic models and their application for personalised medicine”, Logic models and their application for personalised medicine, Saran Pankaew: “The power of logic: Modelling cancer across scale, with the help of omics data”.

[1] Flobak, Å., Baudot, A., Remy, E., Thommesen, L., Thieffry, D., Kuiper, M., & Lægreid, A. (2015). Discovery of Drug Synergies in Gastric Cancer Cells Predicted by Logical Modeling. PLOS Computational Biology, 11(8), e1004426. https://doi.org/10.1371/journal.pcbi.1004426

Boolean modelling highlights different regulatory modules during complex disease progression and therapeutics

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Reinhard Schneider (Luxembourg university)

Marek Ostaszewski (Luxembourg university)

Abstract: Our research introduces a robust methodology for elucidating the molecular mechanism underlying Parkinson's Disease (PD) using Boolean Modeling (BMs). Utilising the PD-map, disease specific molecular interaction diagram, complex pathways were converted into a form that can be analysed computationally. This transformation facilitates in silico experiments that not only corroborate existing scientific understanding but also unveil new regulatory elements crucial for the progression and management of PD.

Our approach stands out for its inherent flexibility and scalability, particularly when detailed kinetic parameters are lacking. Boolean Models allow us to conduct qualitative assessments that are both resilient and adaptable, thereby addressing a notable gap in the existing landscape of computational modelling. We have demonstrated the wide-ranging utility of this methodology by applying it to diverse biological systems, from canonical metabolic pathways like the TCA cycle to intricate signalling networks such as the Wnt-PI3K/AKT.

A cornerstone of our research is the incorporation of high-throughput omics data, sourced from the Parkinson's Progression Markers Initiative (PPMI) and other heterogeneous cohorts. This rich data layer enables a comprehensive exploration of PD's molecular diversity, shedding light on how molecular dysregulation can impact therapeutic efficacy. By parameterizing our models based on this omics data, we are laying the groundwork for more individualised treatment strategies in PD management.

Furthermore, our work transcends mere theoretical constructs by pinpointing prospective drug targets and simulating the outcomes of various therapeutic interventions. This has direct effect for the development of treatment modalities, rendering our research not only theoretically noteworthy but also of immediate clinical importance.

To sum up, our research signifies a shift in the utilisation of computational modelling for the study of complex diseases. It provides a robust, and flexible framework for understanding the molecular intricacies of PD, and offers substantial promise for the advancement of targeted therapeutic interventions. Given its groundbreaking nature and clinical applicability, our study establishes a robust benchmark for cross-disciplinary research in systems biomedicine.

Mechanisms of FITC-MBP induced Cytotoxicity: Cell Cycle Arrest, Mitochondrial Apoptosis, and Microtubule Disruption

Authors:

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Abstract: Our study investigates the cytotoxic effects of FITC-MBP on human lung epithelial cells (A549) and human peripheral blood mononuclear cells (PBMC). The results showed that treatment with FITC-MBP caused disruption of the microtubule network in A549 cells in a time and concentration-dependent manner. It also led to cell cycle arrest in the G2/M phase and induced apoptosis. The half-maximal inhibitory concentration (IC50) for FITC-MBP -induced cell death was approximately 40 µM after 24 hours and approximately 24 µM after 48 hours in A549 cells. In PBMC cells, the IC50 was around 25 µM after 24 hours of treatment.

The study observed up-regulation of cyclin B1 and down-regulation of cyclin D1, which are proteins involved in cell cycle regulation, leading to G2/M arrest in the treated cells. Furthermore, we found increased expression of pro-apoptotic proteins such as p53 and Bax, along with decreased expression of the anti-apoptotic protein Bcl-2 in FITC-MBP treated A549 cells. Loss of mitochondrial membrane potential, activation of caspase-3, and release of mitochondrial cytochrome c were also observed, indicating the involvement of mitochondrial apoptosis pathways.

In addition, FITC-MBP was found to inhibit tubulin polymerization in a cell-free system, suggesting a direct interaction with microtubules. The binding of FITC-MBP to purified tubulin exhibited a stoichiometry of nearly 1:1 and a dissociation constant of 14.0 ± 0.6 µM at 25 °C. The interaction between FITC-MBP and tubulin induced conformational changes in tubulin, as evidenced by experiments measuring fluorescence, binding of colchicine and ANS (an indicator of hydrophobicity), and circular dichroism (CD).

An agent-based model of tumor-associated macrophage differentiation in chronic lymphocytic leukemia

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Abstract: In the tumor microenvironment, tumor-associated macrophages are known to play a critical role in the survival and chemoresistance of cancer cells. In the case of chronic lymphocytic leukemia (CLL), these tumor-associated macrophages are called Nurse-Like Cells (NLCs) and reside mainly in the lymph nodes, where they are able to protect leukemic B cells (B-CLL) from spontaneous apoptosis and contribute to their chemoresistance, hindering the efficacy of immunotherapy in many patients. NLCs are differentiated from monocytes through cytokines signaling and physical contact with the cancer cells [1], however, the precise mechanisms by which B-CLL cells influence this differentiation are still unknown. We used an in vitro model of leukemia, in which we can closely follow the production of NLCs from monocytes in the presence of leukemic B cells from CLL patients. Building on experimental observations of cancer cells in these cultures of patients' blood, we propose here a two-dimensional agent-based model simulating the monocyte-to-macrophage differentiation and intercellular interactions in the spatial context of this in vitro co-culture of monocytes and cancer B-CLL cells. Using our time-course measurements of B-CLL cell viability and concentration to optimize the model parameters, we were able to reproduce the experimentally observed dynamics. We further tested the model's predictive power by simulating specific NLC production features in relation to varying measured proportions of monocytes in each patient in the co-cultures. Our results suggest that this model could be made patient-specific using their blood monocytes counts, which is a routinely measured variable. Finally, we performed a sensitivity analysis of the different parameters and suggest a strong role for phagocytosis from monocytes and NLCs to ensure the survival of cancer cells in this in vitro CLL model, especially in the initial phases of the time course. Additionally, we show that the protective anti-apoptotic signals provided by NLCs to the cancer cells are most important towards the later stages of the culture. This finding suggests that monitoring and potentially modulating phagocytosis could play a role in the control of NLCs polarization in CLL and also help understanding tumor-associated macrophages formation even in solid tumors [2].

Towards the creation of a digital kidney twin through multi-omics profiling of urinary extracellular vesicles in ADTKD-MUC1 patients and healthy controls

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Abstract: Introduction. Autosomal Dominant Tubulointerstitial Kidney Disease caused by mutations in MUC1 (ADTKD-MUC1), is a rare genetic disease presenting with non-specific tubulointerstitial fibrosis, bland urinary sediment, progressive chronic kidney disease, and variable age of onset of end-stage renal disease (ESRD) due to yet undefined reasons. The aim of this study is to generate a digital representation of normal and diseased kidney substructures, assisted by multi-omics profiling of extracellular vesicles (EVs) released in the urine by relevant cell types to create a digital microenvironment that mimics disease progression states. Methods. Through an ongoing observational study, longitudinal clinical and biochemical data and samples were collected by 46 participating individuals diagnosed with ADTKD-MUC1 and analyzed for disease progression patterns. Biomarker discovery efforts included the profiling of urinary EVs using high-throughput small RNA sequencing and mass spectrometry (MS)-based proteomics, metabolomics and lipidomics. Differential expression (DE) analysis was performed to identify deregulations in the expression patterns of patients compared to controls, as well as between patients with different progression rates. To gain deep understanding on disease pathobiology and eventually design better therapeutics, we plan to consider EV multi-omics data as surrogates for cell disease states and generate a digital twin of cellular identity and interactions between tubular cells that are affected by the disease. Results. Comparative analysis resulted in the identification of distinct expression signatures between patient groups demonstrating different disease progression rates. Subsequently, publicly-accessible repositories, such as the Kidney Tissue Atlas, Single-Cell Expression Atlas, Protein Atlas and Genotype-Tissue Expression (GTEx) Portal, will be used to map the expression signatures of the uEVs. Given the disease's heterogeneous clinical and molecular presentation, our analysis will expand beyond DE. A personalized approach will be adopted, by horizontally integrating multi-omics expression data to generate individualized digital biopsies, that will accurately profile the disease characteristics of each patient, and which will serve as tools towards the development of personalized medicine. Discussion. This study performs a multileveled exploitation of the uEV cargo in ADTKD-MUC1 patients and healthy individuals, for the creation of a realistic and scalable digital kidney twin that will revolutionize and redirect global kidney research and drug discovery efforts.

Synergy between mechanics and biochemical signalling hinges on mitochondrial dynamics during mesoderm emergence in human pluripotent stem cell colonies

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Abstract: Micropatterned human pluripotent stem cell (hPSC) colonies display signatures of gastrulation upon exposure to BMP4. The exposure yields internalising WNT3 waves in these colonies resulting in mesoderm-like cells in the annular locus between the colony centre and edge. Both biochemical signals and mechanical cues have been shown to mediate the emergence of mesoderm-like cells in this system. How these orthogonal modules synchronise activity during this process remains poorly understood. To address this, we developed a phenomenological model to describe the active mechanical behaviour of the colony based on neo-Hookean mechanics. This model considered interplay between growth (modelled as volumetric thermal expansion) and contractile cytoskeletal forces (modelled via radial compaction). It predicted that the colony locus with mesoderm-like cells will display higher stiffness (Young's modulus), which was validated in vitro by conducting atomic force microscopy on hPSC colonies. The computational model also predicted the locus with mesoderm-like cells will display higher strain energy (i.e. mitochondrial demand). This was validated in vitro by imaging TOM20 (mitochondrial membrane marker), OPA1 and MFN2 (mitochondrial fusion proteins), and FIS1 and DRP1 (mitochondrial fission proteins). In vitro, both fusion proteins and TOM20 were expressed more significantly in the locus with mesoderm-like cells vs neighbours ($p<0.01$). To understand how biochemical signals, mechanics, and mitochondrial dynamics co-regulate cell fate, we used GARMEN, a multiscale framework, to integrate gene regulatory networks (GRNs) capturing transition from pluripotency to germ-layer fates, mitochondrial dynamics, and actin polymerisation. GARMEN captured cell activity via agent-based modelling and signal gradients via reaction-diffusion. GARMEN predicted that areas with high actin intensity will result in increased mitochondrial fission that will eventually inhibit WNT activity. It also predicted that disrupting cytoskeletal activity and/or mitochondrial dynamics will restrict mesoderm-like cells to colony edge (instead of the inner annulus). We confirmed these observations by exposing hPSCs to blebbistatin (cytoskeletal activity inhibitor) and mdivi1 (mitochondrial fission inhibitor). We, thus, show how cellular mechanics and signalling are connected via mitochondrial activity during the emergence of mesoderm-like cells in hPSCs. We anticipate that our approach that combines signalling, energetics, and mechanics will help systematic investigations into how signalling and mechanics synergise during morphogenesis.

Mathematical Modeling of the Effects of Anaesthetic Drug Dosing on Postoperative Outcomes

Authors:

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Abstract: Anesthesia is commonly induced and maintained using a combination of a hypnotic drug to cause unconsciousness and an analgesic drug to prevent responses to painful stimuli during interventions. In clinical practice, anesthesiologists are faced with the complex task of finding the correct dose of these two interacting types of drugs, as underdosing of either drug can lead to intraoperative stress responses and associated worse patient outcomes while overdosing may be associated with postoperative nausea, prolonged time to emergence from anesthesia with associated higher risks of infection and postoperative delirium. This study aims to investigate the optimal individual drug dosage of the hypnotic drug Propofol and the analgesic drug Remifentanil to prevent detrimental effects of both under- and overdosing.

We aim to create non-linear-mixed effect pharmacokinetic/pharmacodynamic (PK/PD) models of Propofol and Remifentanil accounting for individual-based covariates like sex, age, and BMI to model the response to different types of stimuli (verbal, shaking, and incision). These models will be the basis for the implementation of digital twins, which will be used to conduct a virtual clinical trial to estimate optimal individual drug dosages that are as low as possible but sufficient to prevent neurophysiological responses to painful stimuli during surgery.

Identification of genome-wide expression differences between patient-matched intra- and extracranial melanoma metastasis pairs using Hidden Markov Models

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Abstract: Overcoming the therapy resistance of melanoma brain metastases (intracranial metastases) is a crucial step to improve therapy response of affected patients. Therefore, key molecular mechanisms that distinguish treatment-resistant intracranial from treatable extracranial metastases need to be determined. Melanoma metastases from the same patient are more similar to each other than to metastases in the same tissue from other patients. This strengthens the need for a personalized analysis. Thus, we compared RNA-sequencing data of 16 intracranial metastases with 21 patient-matched extracranial metastases in a personalized way using a three-state Hidden Markov Model (HMM) with state-specific Gaussian emission densities to identify altered genes for each individual metastasis pair. Training and optimization of hyperparameters of the model was performed using a HPC. An in-depth analysis of the predicted gene expression alterations across all patients led to three major findings: (i) especially cytokine signaling, calcium signaling and ECM-receptor interaction were most frequently altered, (ii) immune-relevant genes showed most frequently decreased expression in intra- compared to patient-matched extracranial metastases, and (iii) intracranial metastases were associated with a brain-like phenotype expression program. These general findings are in good accordance with other studies comparing intra- and extracranial melanoma metastases. Moreover, a candidate gene set was identified that includes 103 genes that were differentially expressed in the same manner in 69% (11 of 16) of all patients. This gene set contains known immune-relevant genes (e.g. CCL19, CLEC10A, CD8B, CD79A) and potential cancer therapy targets (e.g. CLEC10A, CXCL11, GPR68). We want to find out which cells exactly express these candidate genes and if spatial arrangement to other types of cells plays an important role. For this purpose, we need to analyze melanoma metastases on a single-cell level. In future, we will also build a model-based prediction of potential therapy targets for melanoma brain metastases using public data. Overall, our study contributes to a better characterization of key pathways and genes that could play a role in therapy resistance of melanoma brain metastases.

Bodylight.js – toolchain for in-browser simulation of simple and complex mathematical models

Authors:

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Abstract: Web-based simulators of models in biomedical engineering have seen significant advancements. The evolution of web standards has made web-based simulations more accessible across various platforms, including mobile devices, thanks to the comprehensive HTML, JavaScript and related standard APIs offered by contemporary web browsers. A platform for interactive models as web application was introduced by Tiller et al. [1].

We introduce an open-source Bodylight.js (https://bodylight.physiome.cz) toolchain – which is combination of tools, scripts and libraries to compile simple or complex mathematical models (written in standard Modelica language) into WebAssembly and present them as a static server-less web application. Model simulation have near native performance on any device that has a modern web browser able to execute WebAssembly and other related standards [2][3].

Sample models related to human physiology from cellular level to organ and complete human physiology level is demonstrated as various web simulators enriched with interactive text, graphics and visualisation at https://egolem.online/demo

Simulators based on the Bodylight.js toolchain are appropriate for interactive documents like educational materials, technical reports and digital appendices. Such simulators might bridge the gap between scientific-oriented models, methods,tools and end-user-oriented applications where scientific accuracy is hidden behind user-friendly design and carefully selected and identified subset of parameters. Such simulators can be used by experts in other domains or by patient consulting his calibrated "digital twin" for feedback.

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Multiscale Modeling and Data Assimilation: A Path to Personalized Medicine

Author:

Heber Lima da Rocha [Presenter], (Indiana University)

Abstract: In recent years, the rise of personalized medicine has been fueled by remarkable advancements in biology, data science, and computational modeling. An emerging concept capturing attention within the scientific community is that of the patient digital twin (DT). This innovative approach seeks to construct comprehensive computational models, allowing clinicians to systematically analyze patient complexity, simulate treatment outcomes, and make informed decisions regarding optimal treatments. Developing a patient digital twin involves creating a detailed computational model capable of capturing an individual's unique characteristics. This model should encompass their medical history, current health status, genetic makeup, and other pertinent variables that influence treatment outcomes. Yet, assembling this information poses a challenge, as obtaining complete clinical data on individual patients is often constrained. To address this limitation, researchers turn to mechanistic models, which replicate observed phenomena across various scenarios. Formulating accurate predictive computational models is a complex endeavor, necessitating calibration and validation steps. The intricacy of this task arises primarily from the diverse sources of uncertainty inherent in observational data, model parameters, and formulation. Uncertainty in observational data stems from experimental or clinical design, while model uncertainty originates from hypotheses formulated to describe underlying dynamics and parameter values. To tackle these challenges, my strategies incorporate model selection to mitigate bias in hypothesis formulation and Bayesian inference to estimate parameter uncertainty. Specifically, the implementation of multiscale models like agent-based models, with their extensive cell populations, demands significant high-performance computing resources. This factor can render the calibration of such models challenging. In this workshop, I intend to elucidate the challenges involved in uncertainty quantification in agent-based models, discussing the strategies we have devised to create a digital twin framework. By sharing my experiences, I hope to contribute to a broader understanding of uncertainty management and its role in advancing patient-specific computational models.

A novel multi-omics data analysis to reveal dose-dependent and temporal changes in chemical perturbation: a case study on caffeine

Author:

Yufan Liu, [Presenter], (The University of Surrey)

Abstract: Comprehensive analysis of multi-omics data can reveal alterations in regulatory pathways induced by cellular exposure to chemicals by characterizing biological processes at the molecular level. Data-driven omics analysis, conducted in a dose-dependent or dynamic manner, can facilitate comprehending toxicity mechanisms. This study introduces a novel multi-omics data analysis designed to concurrently examine dose-dependent and temporal patterns of cellular responses to chemical perturbations. This analysis, encompassing preliminary exploration, pattern deconstruction, and network reconstruction of multi-omics data, provides a comprehensive perspective on the dynamic behaviors of cells exposed to varying levels of chemical stimuli. Importantly, this analysis is adaptable to any number of any omics layers, including site-specific phosphoproteomics. We implemented this analysis on multi-omics data obtained from HepG2 cells exposed to a range of caffeine doses over varying durations and identified six response patterns, along with their associated biomolecules and pathways. Our study demonstrates the effectiveness of the proposed multi-omics data analysis in capturing multi-dimensional patterns of cellular response to chemical perturbation, enhancing understanding of pathway regulation for chemical risk assessment.

Unveiling metabolic vulnerabilities associated to chemotherapy resistance in colorectal cancer using a systems biology approach

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Abstract: Metabolic reprogramming is a sensitive target for cancer therapy. FOLFOX chemotherapy is used in the treatment of colorectal cancer (CRC), but its effectiveness is limited by chemoresistance. Our group investigates the impact of FOLFOX on the metabolic reprogramming of CRC cells using transcriptomics and metabolomics techniques. The experimentally obtained metabolomic and transcriptomic data, as well as mitochondrial respiration rates, for control and FOLFOX treated cells, will be integrated into Genome-Scale Metabolic Models (GSMM) using Phyton and the COBRApy toolbox. Furthermore, our group has developed a new metabolomics-based classification of different CRC cell lines, which can refine the current consensus molecular subtypes (CMS)-based classification and facilitate the design of new combination therapies to overcome FOLFOX resistance. All these findings will provide insights into the metabolic landscape of CRC and suggest new strategies to improve the efficacy of FOLFOX chemotherapy.

Spatially-resolved multiscale models shed light into personalized drug treatments

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Abstract: Multiscale models have been very helpful in tissue biology by providing novel hypotheses to uncover mechanisms and novel treatments that tackle diseases of interest. PhysiBoSS is an open-source software which combines intracellular signalling using Boolean modelling (MaBoSS) and multicellular behaviour using agent-based modelling (PhysiCell). Since 2018, it has been successfully used in tissue simulation of diseases such as cancer and COVID. PhysiBoSS can use Boolean models personalized using bulk omics data and its simulation can be set-up using manually- designed 3Dal architectures defining an extracellular matrix (ECM). In spite of these advances, current simulations use rather simplistic 3Dal set-ups and much remains to be done to have a simulation that accurately produces results that can seem like the real tissue. To have spatially-resolved personalized multiscale models, we have taken advantage of a novel technique: single cell spatial transcriptomics. This new technique allows to have the spatial information of unique cells combined with its transcriptomic state. We hereby present a user-friendly workflow called “PhysiBoSS-spatial” for setting up PhysiBoSS simulations using spatial transcriptomics data. This workflow enables the translation of a slice of spatial transcriptomics in the initial disposition of the multiscale model. Users can modulate the the number of cell types to be captured (and which), the resolution of the clustering and the cell-type annotation. To showcase the use of this workflow, we hereby present the set-up of the simulations using breast cancer spatial omics datasets and their simulation with different drugs treatments and architectures.

Metabolic modelling of pro-inflammatory human macrophages

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Abstract: The cytokine storm observed in COVID-19 patients has emerged as a significant contributor to the severity of the disease and its associated mortality. This study seeks to unravel the intricate metabolic alterations that macrophages undergo in response to cytokine storms, thereby shedding light on the underlying mechanisms driving the exacerbated immune response. Through the integration of genomic-scale data and metabolic experimental measurements, a comprehensive workflow was developed using the COBRApy module. Our study's primary objectives were two-fold: first, to establish a robust methodology for probing macrophage metabolic flux reprogramming under environmental challenges or therapeutic interventions; and second, to apply this innovative workflow to identify the metabolic alterations occurring in macrophages during SARS-CoV-2-triggered cytokine storms. Key methods employed encompass Genome-Scale Metabolic Models (GSMMs) for metabolic pathway representation, Flux Balance Analysis (FBA) and Flux Variability Analysis for predicting flux distributions, and the Gene Inactivation Moderated by Metabolism (GIM3E) algorithm to model the complex interplay between gene expression and cellular metabolism. To simulate targeted metabolic changes, the Metabolic Transformation Algorithm (MTA) was applied in driving macrophages from pre- to post-cytokine storm states. This research offers insights into the metabolic reprogramming of macrophages, providing a deeper comprehension of their role in the pathogenesis of cytokine storms. Moreover, the developed workflow that integrates transcriptomic genomic-scale data, and metabolic experimental

measurements serves as a template for studying cellular responses to different environments and/or therapeutic interventions.

Functional Analysis of Childhood Cancer Genomes

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Abstract: Cancer's genetic complexity remains a challenge, but whole genome sequencing (WGS) has improved our understanding of the underlying mechanisms of cancer, but much is still unknown. Childhood cancers lack the mutational burden of adult cancers, and therefore provide the most simple level at which we can study cancers. In addition, the functional roles of most mutations, including those in known cancer driver genes, remain obscure. Meanwhile, despite evidence emerging of the symbiotic relationships between mutated oncogenes and supportive normal genes, these interactions largely remain a mystery. With this project I aim to identify the minimum genetic mutations needed for cancer initiation, to explore the functions of these minimal gene sets, to probe for emergent biochemical and biological functions and investigate how normal genes bolster the functions of mutated oncogenes. Addressing these questions could change our understanding of cancer mechanisms and inspire innovative therapies targeting not just oncogenes but also their normal gene support network.

AI methods will help to unearth patterns in omics data of paediatric and childhood cancers linked to driver mutations, encompassing gene expression and mutation patterns. Various neural networks will be employed, such as graph convolutional neural networks and autoencoders. Patterns will be mapped to potential signalling pathways, unlocking new therapeutic targets and enabling mechanistic dynamic models for pathway simulations. The project builds upon previous work in extracting ordinary differential equation (ODE) models from network reconstructions, aiming for refinement. In addition this work will feed into a project aimed towards creating digital twin models, initially for neuroblastoma but other cancer types. Publicly available data of of paediatric cancers, artificially generated data and newly generated data from selected childhood cancer cell lines and patients through an Irish childhood cancer sequencing project, will all be utilised to carry out the investigations involved in this work. This research seeks to decode childhood cancer genetics via advanced computational biology techniques. Its potential to improve our understanding of cancer biology and inspire targeted therapies makes it a promising avenue in the fight against cancer.

Unveiling Microanatomical Domains in Inflammatory Bowel Disease (IBD) Tissue through Spatial Transcriptomics Analysis

Authors:

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Abstract: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD) marked by chronic gastrointestinal inflammation. The precise causes remain elusive; nonetheless, it is understood that the disease is influenced by environmental, genetic, and immunological factors. Clinical practices often witness significant variability in disease severity, treatment response, and progression. Unfortunately, no established clinical or biological markers reliably explain or predict this variability. (Garrido-Trigo et al., 2023)

Omics techniques, including spatial and single-cell transcriptomics, are beginning to be implemented to comprehensively explore gut mucosa cells and their role in IBD pathogenesis (Lloyd-Price et al., 2019). Spatial transcriptomics enables simultaneous visualization of cellular organization, tissue structure and cell communication, helping discover and understand microanatomical domains that are formed in CD and UC. And therefore, could explain the state, severity, and variability of the disease.

We employed Nanostring's CosMx technology for spatial transcriptional analysis on nine samples: three from healthy individuals and six from IBD patients. This dataset encompasses 996 genes and a staggering 551,959 individual cells in total. The data curation details for the CosMx analysis can be also found in our published paper by Garrido-Trigo et al, 2023. Here we used the UTAG algorithm (Kim et al., 2022), which integrates cellular phenotypic information and spatial proximity to precisely identify microanatomical domains within both healthy and diseased tissues. This algorithm identified discrete clusters within the spatial context, enabling the delineation of microanatomical domains for subsequent in-depth analysis. Microdomain composition was dramatically changed in both UC and CD samples compared to healthy samples. Importantly we could also observe marked differences across patient samples which support the use of spatial transcriptomics to unravel the cellular and molecular features that could explain patient-to-patient variability.

In conclusion, microanatomical domains can help us understand the complex heterogeneity of the tissues in this complex disease. In addition, it can provide a better insight into how the tissue behaves in IBD patients, and how this intricate cell-to-cell communications cause different states of the disease.

Integrating Spatial Transcriptomics and Image-based Proteomics Using Graph Neural Networks for Multi-omics Alignment

Authors:

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Asier Antoranz (Laboratory for Translational Cell and Tissue Research, Department of Imaging and Pathology)

Abstract: The advent of single-cell multi-omics technologies has ushered in a new era of biological exploration, enabling the simultaneous interrogation of spatially resolved transcriptomics and image-based proteomics data. In our study, we tackle the challenge of integrating these diverse data modalities, with a primary focus on Glioblastoma and Melanoma tissues.

Obtaining spatially resolved multi-omics data from different sections of tissues introduces inherent deformations and misalignments. Traditional rigid registration methods are ill-suited for handling these complexities, as they assume a one-to-one correspondence between cells across omics layers. In reality, the same cells do not necessarily appear in both omics datasets, making direct alignment unfeasible.

To address this issue, we propose a novel approach leveraging phenotypic and morphological features, as well as the spatial topology of cells within each omics layer. Our method involves constructing graphs where individual cells serve as nodes, and their phenotypic and molecular characteristics form node attributes. Importantly, we account for the spatial distances between nodes, capturing the spatial context crucial for understanding tissue organization.

Graph Neural Networks (GNNs) play a pivotal role in our methodology. We employ GNNs to align the two omics datasets by identifying similar subgraphs within the graphs. This alignment process involves combining the features of neighboring nodes, allowing us to uncover shared spatial patterns between the datasets. By doing so, we achieve a data-driven integration that transcends the limitations of traditional alignment methods.

Our proof of concept demonstrates the potential of this approach to harmonize spatial transcriptomics and image-based proteomics data, shedding light on the intricate relationships between gene expression and protein localization within the tumor microenvironment. We believe that our method opens new avenues for exploring the molecular underpinnings of complex biological processes, providing insights into diseases such as Glioblastoma and Melanoma.

Quantifying mutational synergy using computational models predicts survival in haematological cancers

Authors:

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Simon Mitchell, (Brighton and Sussex Medical School)

Abstract: Genetic heterogeneity and co-occurring driver mutations contribute to poor clinical outcomes in cancer. However, the impact of multiple mutations on complex signalling networks is not easily predicted. We found that, by placing mutations into their cellular context, multi-scale agent- based mathematical models could predict how genetic events combine in haematological malignancies. Simulations of lymphoma and myeloma predicted co-occurring mutations synergised to increase tumour cell expansion beyond what would be expected from the impact of the individual mutations alone. Mutational synergy between MYC and BCL2 was consistent with the more aggressive disease course of patients with double-hit lymphoma, and mutational synergy between MCL1 and CKS1B was predictive of outcome in patients with gain 1q multiple myeloma. Incorporating patient-specific mutational profiles into personalised models of lymphoma patients with the worst clinical outcomes revealed a correlation between simulated mutational synergy and overall survival, which outperformed widely used classifications of lymphoma informed by gene expression or mutational data alone. Our results demonstrated that mutational synergy scores enabled prediction of the impact of co-occurring mutations and may improve personalised prognostic predictions.

Machine Learning Approaches for the Characterization of COPD

Authors:

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a complex and heterogeneous disease, comprising a wide range of nonidentical patient profiles. Its diagnosis is not straightforward - it is underdiagnosed, especially in women - usually appearing with severe airflow obstruction profiles, leading to a need for improved strategies to identify individuals who are at greater risk of developing COPD or who have early-stage.

Understanding the diversity of the disease is important for diagnosing and treating COPD, enabling the implementation of more individualized therapies. Here, we aim to enhance the binary patient classification of COPD using gene expression data from the Lung Tissue Research Consortium. To achieve this, we employ various feature selection criteria to identify the most relevant genes. These filtering approaches include knowledge extracted from intrinsic data characteristics (data-driven), external information from DisGeNET of genes associated with COPD (curated COPD-related genes), and their respective biological expansions based on physical interaction partners (OmniPath) and network-based prioritization algorithms (GUILDify). Subsequently, we evaluate the performance of different classifiers: Random Forest, Support Vector Machines - polynomial and radial kernel, k-Nearest Neighbors, Generalized Linear Models, and XGBoost.

Our results show that the data-driven and curated COPD-related expansion gene selection approaches yield the highest cross-validation and independent test data performances, respectively. Our techniques demonstrate their ability to accurately classify COPD patients, outperforming previous studies with accuracies up to 84,8%, and the selected genes represent relevant biomarkers for disease prediction.

Dynamic Modelling when ODEs are not applicable

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Abstract: A major goal of systems biology is the establishment of mathematical models that describe the dynamics of signalling in living cells at the molecular level. Such models are frequently realised as mechanistic ordinary differential equation (ODE) models, where each dynamic variable and model parameter has its counterpart in the biological process, facilitating the interpretation and prediction of the system's behaviour.

However, ODE models suffer from several drawbacks, including the requirement of large and comprehensive amounts of experimental data for the calibration of the unknown model parameters. Furthermore, ODE models fail to provide analytical solutions of the ODEs and the dynamics they describe are nonlinear, which impedes numerical approaches and statistically valid reasoning.

Thus, we introduce the retarded transient function (RTF) [1], a curve fitting approach which is tailored to typical dynamic response curves observed in cellular signalling. As it provides accurate estimates of the underlying dynamics and facilitates intuitive interpretations of its parameters (response time, amplitudes, time constants of a transient and a sustained part of the response), the RTF is a valuable complement to the traditional ODE-based modelling for the analysis of time-course data.

We recently also extended the RTF approach, specifically focusing on modelling dose dependencies. This advancement enables time- and dose-dependent predictions and offers an intuitive means to investigate and characterize signalling differences between biological conditions or cell types. The RTF approach is available within the MATLAB-based Data2Dynamics modelling toolbox on https://github.com/Data2Dynamics and as R package (under development).

Development and implementation of mechanistic modelling approaches for the analysis and functional interpretation of omics data

Authors:

Kinza Rian, [Presenter], (Computational Medicine Platform, Andalusian Public Foundation Progress and Health-FPS)

Joaquín Dopazo (Computational Medicine Platform, Andalusian Public Foundation Progress and Health-FPS)

Abstract: Extensive amounts of omics data has been generated in different settings, describing human pathophysiology. This requires advanced computational techniques to unearth the complexities generated by these data. Genome-scale mechanistic models are gaining importance for genomic data interpretation. Mechanistic models provide a natural link between genotype measurements (transcriptomics or genomics data) and the phenotype of the cell (its functional behaviour). Further, such models can be used to predict the potential effect of interventions, including drug inhibitions. My objective is to utilise the revolutionary advances of computational modelling approaches to perform personalised analysis and functional interpretation of omics data. My specific role is to democratise the use of mechanistic modelling approaches for entry-level users, developing web-based tools and packages such as Hipathia and CyPathia. Such tools offer a realistic framework to understand how signal transduction depends on changes in the expression of genes involved in signalling pathway circuits (See my CV). My research intersects profoundly with the domain of digital twins technology. Utilising mechanistic models is instrumental in elucidating the qualitative aspects of signalling cascades. These models are particularly invaluable when navigating the complex nature of molecular interactions. The premise of my research facilitates a critical knowledge sparseness, specially when the available kinetic molecular parameters are not known within the context of digital twins. This research supplements the existing data and galvanises the necessary analytical framework for dissecting the complexities of molecular mechanisms. Further, the model scalability is an important feature that reaffirms their capacity to evolve in tandem with the escalating complexity of biological systems and computational demands. I believe that my research landscape aligns cohesively with the workshop, especially network to model, and signalling modelling sessions. I am excited about the opportunity to collaborate with peers and experts alike, gaining insights and experience that will enhance my future research.

Deciphering Inflammatory Bowel Disease Patients' Heterogeneity Using Single-Cell Transcriptomics Data

Authors:

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Abstract: Ulcerative colitis (UC) and Crohn's disease (CD) are a set of inflammatory bowel diseases (IBD) characterized by chronic inflammation of the patient's gastrointestinal system. Traditional patient stratification is based on disease severity, however, IBD patients exhibit significant variability not only in symptoms but also in their response to clinical treatment. Given this heterogeneity, there is a need for a new classification approach that considers patients' variability at a molecular level (Lai, L. et al., 2022). In this way, single-cell transcriptomics offers an unprecedented level of resolution to address this heterogeneity by deciphering IBD's molecular profiles. In this way, we used consensus non-negative matrix factorization (cNMF) (Kotliat., D, 2019) to decipher gene expression programs (GEP), which are sets of co-regulated genes that function together to carry out a particular biological function. cNMF provides an activity score of these GEPs across individual cells, providing more granularity of the data obtained. In this project, we analyzed 50 IBD single-cell samples (both UC and CD) having an active state of the disease using our own-curated pipeline as published in Garrido-Trigo, A., 2023. Then, we performed cNMF into each of the five major subsets found in the gut's mucosa: myeloid, plasmas, epithelial, stromal and T cells. From there, we calculated the mean usage of GEPs per program and patient, obtaining a final matrix with all the usages per patient. Then, the samples were stratified using the hierarchical k-means unsupervised clustering algorithm, whose clustering was validated using the Random Forest supervised algorithm. As a result, we obtained two clusters, one of them is mostly composed of UC patients, while the other one is a mixture of UC and CD patients. Also, we obtained that the top variables that contributed to this classification were mainly GEPs from the stromal and myeloid subset, making them of the upmost importance to understand the hetereogenity of the groups of patients. Future studies should focus on optimization of the analysis and understanding the clinical relevance of these results.

Study of the molecular pathways, gene regulatory networks and cellular heterogeneity governing biological processes in the context of disease through the development of integrated bioinformatic analysis framework of multimodal next-generation sequencing data

Authors:

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Abstract: Cutaneous squamous cell carcinoma (cSCC) is a prevalent keratinocyte carcinoma, with increasing occurrence, that can arise from actinic keratosis (AK) or de novo. It is usually treated with surgical excision, however, recurrence and metastasis of cSCC are challenging to treat and in many cases lead to death. Given the high incidence of cSCC, identifying the pathogenic tracks that drive SCC initiation and progression as well as dissecting the therapy resistance mechanisms is of utmost importance. Furthermore, there is significant research potential in the field, as cSCC remains one of the least explored cancer types.

For this study, I am developing a computational pipeline for the bioinformatic analysis and integration of multimodal single cell (sc) and spatial transcriptomics data to examine the transcriptomic, epigenetic and spatial heterogeneity between non-cancerous and cancerous cells from cSCC biopsies of various stages (AK, in situ cSCC, and infiltrative (invasive) cSCC). The pipeline will focus on cell population characterisation, gene regulatory networks, trajectory inference, cell-to-cell communication, and developing predictive models for biomarkers.

At present, the analysis focuses on the integration of publicly accessible scRNA-seq and scATAC-seq datasets obtained from the studies conducted by Ji et al, Zou et al, and Schutz et al. Our first objectives are to create a cSCC atlas that will enrich the data (scRNA-seq, scATAC-seq, spatial transcriptomics) produced in our lab and develop a robust and scalable pipeline to study cancer studies.

Our aim is to locate novel cell clusters and features that characterise the disease consistently among cancerous samples of different patients, predictive/diagnostic biomarkers from healthy tissue or early stages samples, as well as identifying cell populations, genes, and enhancer regions that could be targeted for therapeutic approaches. Successful completion of this project will provide an integrative view of the different molecular aspects underlying cSCC pathogenesis and may contribute to diagnostic and therapeutic breakthroughs.

Proteomic and phosphoproteomic characterization of the role of Cdk4 in early adipogenesis

Authors:

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Abstract: Cyclin-dependent kinase 4 (CDK4) is conventionally known as a cell cycle regulator, however it has also been reported to play an important role in promoting adipogenesis in mice (Abella et al. 2005 Cell Metab 2: 239–249). Our recent studies have revealed that in accordance with the mouse model, CDK4 inhibition effectively inhibits adipogenic differentiation in human cells, too. However, the precise targets for CDK4 kinase activity during adipogenesis are completely unknown. To address this, we have performed proteomics and phosphoproteomics analyses of stem cell cultures during early adipocyte differentiation process in the presence and absence of CDK4 inhibitor. In 3 different timepoints during differentiation, we quantified altogether 7661 proteins and 23562 phosphorylation sites of 4617 proteins to get temporal information on the mechanism of the defective adipogenesis when CDK4 is inhibited. Standard proteomic data analysis including log-median normalization, principal component, differential expression and Reactome and Kegg pathway enrichment analysis were performed in R.

As expected, PCA identified the differentiation process as a major axis of variation in the data. This was independent of the presence/absence of the inhibitor. Nevertheless, both differential expression and phosphoproteomic analysis revealed alterations in the process upon CDK4 inhibition. As an example, adipogenesis regulatory factor ADIRF/C10orf116 is strongly downregulated upon CDK4 inhibition early in the differentiation process. Regarding changes in phosphorylation, CDK4 inhibition perturbed e.g., the phosphorylation of Cavin-1/PTRF, whose mutations are associated with congenital generalized lipodystrophy type 4 (Hayashi et al. 2009 J Clin Invest 119:2623–33).

Our long-term aim is to understand and model the effects of CDK4 and its targets in the early differentiation process of fat tissue. Creating digital, customizable models with the aid of pathway databases, especially protein phosphorylation cascades, may accelerate the introduction of personalized treatments for obesity and associated metabolic diseases. As CDK4 is also associated with cancer, it is an already druggable target, providing an attractive avenue for novel treatment possibilities in adipose tissue related diseases.

Towards a computational model of adaptive immunity

Authors:

Munetomo Takahashi, [Presenter], (Medical Research Council Toxicology Unit, University of Cambridge | Graduate School and Faculty of Medicine, The University of Tokyo)

Abstract:

Our adaptive immune system orchestrates a dynamic response to protect us from viruses, bacteria and tumours. While technological advances have enabled us to dissect adaptive immune responses at single-cell level, we lack a model to explain how these components combine and determine immune response success.

Here, by utilizing mouse models that enable us to temporally track immune responses against tumors, we develop computational methods to reconstruct immune dynamics from single timepoint data. We show how molecular insights from transcriptomic single cell data predicts CD8+ T cell dynamics, which in turn predicts rates of tumour regression. Together, by combining computational modelling of cellular dynamics with single cell omics, we demonstrate a model of CD8+ T cell immunity that predicts immune response success.

Mapping the therapeutic potential of Ag5 and its effects on the TME using a multi-omics approach in GBM patient-derived models

Authors:

Jayesh Telang, [Presenter], (KU Leuven)

Abstract: Glioblastoma (GBM) is a formidable and highly aggressive grade 4 cancer in the cerebral cortex. It has a high relapse and recurrence rate with a median survival of just 12-16 months. Despite intense research towards GBM treatment, a definite therapeutic strategy to improve the prognosis of GBM has not yet been discovered. Recently, Ag5, a novel drug classified as a therapeutic molecular cluster composed of a few silver atoms covalently bonded in a specific conformation, harbours therapeutic potential for GBM. Ag5 can easily cross the BBB and damage mitochondrial function via elevating ROS levels above the threshold, leading to cancer cell death. Oxidative stress-mediated cancer cell death due to Ag5 administration is further enhanced when combined with radiotherapy. Considering the favourable toxicology profile of Ag5, investigating its therapeutic activity across GBM tumour microenvironment (TME) subtypes using in vitro and in vivo model systems combined with state-of-the-art (spatial) single-cell profiling becomes essential. We seek to unveil the transcriptomic and proteomic shifts occurring at the single-cell level, spatially influenced by Ag5 treatment, by utilising cutting-edge techniques like single-cell RNA sequencing, cytometry by time-of-flight (CyTOF), and multiplexed immunohistochemistry (IHC). The project involves utilizing patient-derived cell lines (PDCLs) and patient-derived xenograft (PDX) mice models to elucidate a combinatorial therapeutic approach and the potential of Ag5 across multiple GBM TME subtypes. We hope that this multidimensional approach will illuminate new pathways, enhancing our understanding of glioblastoma's vulnerabilities and moving us closer to a breakthrough in its treatment.

Computational simulations of yeast models of neurodegenerative diseases

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Abstract: Neurodegenerative disease is an umbrella term, encompassing a wide range of illnesses that all lead to the gradual degradation and death of neurons. Since these are usually late-onset diseases they pose an even greater and greater burden on the aging populations of developed countries. However, to this day, no effective treatment options are known for these diseases, most probably due to our missing knowledge of their exact molecular mechanisms.

Here, we have examined how four neurodegenerative diseases - namely amyotrophic lateral sclerosis (ALS), Alzheimer's, Parkinson's, and Huntington's diseases can be modelled in yeast through computational whole-cell simulations.This is done by the the Cytocast Cell Simulator, a stochastic, agent-based quantitative complexome simulation software developed by Cytocast Hungary Ltd. It can simulate the complexation and decomplexation events of protein complex formation through protein interactions. The analysis of simulation results is done through multiple modalities. We use statistical methods to evaluate which protein complexes had a significantly changed abundance distribution. In most cases, a two-sided Anderson-Darling test. Our approach also tries to quantify changes in the composition of the simulated complexes through their internal protein-protein interaction, and an evaluation of the global interaction network of the simulation. Furthermore, we also examine the transient protein-protein interactions of our computations. These do not lead to complex formation, but can encode information on various signaling pathways. By using this approach of simulating human diseases through computational models of either human cells, or cells stemming from a different model organism (in this example, yeast), and examining the results of the complexome of these simulated cells, we hope to find hitherto unknown molecular mechanisms that play a role in these illnesses. Finding such altered mechanisms may bring us closer to developing effective and available treatment options for these disorders.

Differentiable Information Imbalance identifies automatically sets of optimally weighted collective variables from MD simulations of RNA tetraloops

Authors:

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Alessandro Laio (Scuola Internazionale Superiore di Studi Avanzati (SISSA))

Abstract: Many databases, especially biological databases, are wider than they are long. In these cases, it is desirable to find a reduced set of features that retains all the information about the system. In biological modeling, one such case is the selection of collective variables from MD simulations. The complete information of the system is encoded in the space of all atomic coordinates in Euclidean 3D space at each point of the trajectory. For most systems, this space is very large, making it necessary to find collective variables.

We have developed a differentiable version of a novel statistic called "Information Imbalance," which identifies combinations of features that are maximally informative for a given purpose. This differentiable information imbalance can be optimized with standard approaches like gradient descent and can automatically identify the maximally informative set of variables, the optimal set size, and the best weights for the features. We apply this method to RNA tetraloops to identify the variables that contain the most information about their folding state. The optimal number of features turns out to be on the order of 10 and can be used for enhanced sampling and interpretable data analyses.

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