

Vortragszusammenfassungen

Ian Dirk Fichtner – 3404046

aus Heidelberg

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Heidelberg 22/11/2023

gez.:

A handwritten signature in black ink, appearing to read "Jan Zilkther".

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What's left to learn? Extracellular vesicles (EV) biodistribution, pharmacokinetics and immunogenecity

2023/08/09

Dr. Kenneth Witwer

DKFZ

BioMedX Lunchtalk series

Extracellular vesicles (EVs) are heterogeneous lipid-bilayer-delimited particles that are released by eucaryotic cells and bacteria and cannot replicate. They have been found to participate in intercellular communication and are involved in multiple cellular processes through the transfer of biological matter and genetic information. They transport molecules such as RNA originating from their parental cell and consequently, the number of EV subtypes is posited to be as high as the number of different cell states. Their specific biological functions and the possibility for cell-type-specific targeting are not yet clearly understood. Their research holds great clinical potential as they have been linked to diseases such as cancer, viral infections and neurodegenerative diseases. Especially, since they have been recently shown to carry viral particles.

Viruses which are reported to use EVs as a shuttling system are EBV, HHV6, hAV2, hAV5, Rheovirus, KSHV, the dengue virus, HCV, influenza A, HIV, GBV-C, SFV and the picornavirus. Only retroviruses were not shown to use EVs for viral infection as no simultaneous retroviral RNA and reverse transcriptase cargo was found, although this occurrence may still be possible. Since the EV envelope is coated in the organism's native cell membrane, infectious EVs have been shown to elicit a diminished immune response. However, specific cases of plasmacytoid dendritic cells were shown to capture hAVs with increased frequency.

Cell-type-specific targeting of EVs has been hindered by experimental

limitations. While empty EVs were promiscuous concerning the receiving cell type, there has not yet been found a way to discriminate and isolate different biologically meaningful EV subpopulations. Consequently, there is a large gap in the literature due to the lack of a method to pursue this line of study.

In the context of Alzheimer's disease (AD), when EVs isolated from mice models of AD were implanted into healthy rat cortical neuronal tissue, destabilization of neuronal Ca²⁺ homeostasis, impairment of mitochondrial function and increased sensitivity of neurons to excitotoxicity was observed. The isolated EVs contained a low amount of A β but an increased A β 42/ A β 40 ratio. These findings suggest a mechanism by which pathogenic A β is spread to surrounding cells via EV shuttling.

Computational modeling: prime time for clinics

2023/09/15

Prof. Steven Niederer Mathematikon Healthy AI conference: AI meets medicine

Within the context of heart disease, computer simulations and artificial intelligence (AI) have demonstrated potential in the effort to understand the underlying causes and providing patient-specific treatment strategies.

Currently, leadless pacemakers (LP) are used to prevent heart failure and to treat certain kinds of arrhythmias such as bradycardia, heart block and atrial fibrillation. Leadless pacemakers' advantages over transvenous pacemakers include a lower probability of lead failure and pocket infection. However, the optimal implant site for atrial LPs is unknown. Prof. Niederer's research aimed to find optimal implant sites by leveraging complementary analytic 3D simulations and anatomical analysis. Gross anatomy, magnetic resonance imaging (MRI) and computer simulations were integrated to yield a possible optimal location: the right atrial appendage (RAA) base, the anteromedial recess of the RAA apex and lateral wall are alternate sites. On the anatomical evaluation side, ex-vivo human heart specimens were analyzed for wall thickness, right atrial, and right atrial appendage dimensions. Anatomic structures were further analyzed using one hundred MRI heart scans in which the dimensions of the RAA ostium and depth, the distance from the crista terminalis (CT) to the relevant other anatomical structures, and the proximity of the right pulmonary pleura to the lateral RA wall were measured. Finally, 3D simulation of the LP implant to analyze potential mechanical interactions of the atrial LP within the RA.

Another focus of Prof. Niedersen's research lies in computer models

of human cardiomyocyte action potential (AP). To reduce computational computing requirements when interfacing these models with experimental data, neural networks (NN) were used to emulate the AP for given maximum conductances of selected ion channels, pumps, and exchangers. A speed-up of 10^4 and the forward problem was solved on a synthetic dataset with average root mean square errors (RMSE) of 0.47 mV in normal APs and of 13.6 mV in abnormal APs.

Old dogmas revisited (and reshaped): A new view of the landscape of bacterial coupled transcription-translation

2023/09/18

Mikel Irastortza-Olaziregi

EMBL

EMBL seminar

Coupled transcription-translation (CTT) is a hallmark of prokaryotic gene expression. This phenomenon is depicted in most modern biology textbooks with the famous Miller et al. electron microscopy image showing how nascent mRNAs are coupled with multiple concatenated ribosomes forming the polysome. It has been shown that transcription and translation rates in *Escherichia coli* are generally well-matched suggesting that CTT may have an important role in this process and gene expression regulation. Furthermore, CTT inhibition leads to cell-viability problems stemming from the relationship between CTT and Rho-mediated premature transcription termination (PTT). The current hypothesis sustains that ribosomes and Rho compete for the same binding interface of NusG and CTT prevents Rho-mediated PTT. Uncoupled transcription-translation (UTT) has also shown regulatory effects. For example, during low tryptophan concentrations, the leader ribosome lags behind the RNA polymerase (RNAP) which causes the formation of an antitermination structure which further inhibits the attenuation structure.

Transcription and translation rates are affected by environmental factors such as nitrogen scarcity and oxidative stress. In such cases, the translation elongation is slowed down with respect to transcription elongation leading to a lagging ribosome. As a response, (p)ppGpp concentrations rise and induce an RNAP translation rate reduction. It has also been shown, that when transcription elongation slows down as a consequence of car-

bon limitation, the leading ribosome reaches the transcription elongation complex (TEC) and physically pushes the complex forward to match the transcription and translation rates.

Ribo-seq, also known as CTT-seq, was developed to map the location of ribosomes on the mRNA. Lowly coupled genes such as LPP and RPSA-C were ribosomal genes. Notably, the cell-division-involved FtsK gene was found highly coupled. 25% of all *E. coli* genes were shown to be uncoupled which defies current consensus on CTT prokaryotic gene expression and indicates a coexistence and interplay between CTT and UTT.

Different bacteria were also shown to present different transcription and translation rates. While *E. coli* has similar rates, *B. subtilis* shows less coupling and *C. crescentus* present higher coupling rates.

Power to the protein: analyse, signal, protect with bacterial su- perglues

2023/09/19

Prof. Mark Howarth

MPI

Rudolf Mößbauer Colloquium

The engineering of protein-protein and protein-peptide interactions is essential for many biotechnological methods and processes. For example, peptides are commonly used as tags for protein purification, immobilization and detection. Using peptides as tags is a widespread methodology. However, antibodies and other peptides bind probe-peptides with very low affinity and mechanical strength.

In search for a more stable bond for peptides, the Horwath lab isolated the fibronectin-binding protein FbaB of invasive *S. pyogenes* strains. FbaB contains a second immunoglobulin-like collagen adhesin domain (CnaB2). Upon crystallography and NMR analysis, it was shown, that CnaB2 forms a spontaneous and covalent intramolecular isopeptide bond. Next, Horwath and colleagues optimized a splitting point in the CnaB2 domain to create an interacting protein-peptide pair: the *S. pyogenes* catcher (SpyCatcher) and the cognate peptide, SpyTag. The covalent bond was confirmed via electrospray ionization mass spectrometry. 40% of SpyCatcher and SpyTag covalent bond reaction occurred within minutes of mixing the reactants. The second-order rate constant was $1.4 \times 10^3 M^{-1}s^{-1}$ and the reaction half-time was 74 s. Conducting a reversibility analysis over time, the SpyCatcher-SpyTag bond remained covalent over days.

Furthermore, the SpyCatcher-SpyTag bond was found highly efficient from 25 - 100 °C and, albeit at a slower reaction speed, still occurring at 4 °C. The bond was stable at pH 5-7. Furthermore, single-molecule dynamic force spectroscopy confirmed the high mechanical stability of Spy-

Tag, which did not separate from SpyCatcher until the force exceeded 1 nN, the threshold where covalent bonds break.

The specificity of the bond was investigated by genetically fusing the SpyTag to green fluorescent protein-labeled Intercellular Adhesion Molecule-1 and tagging the SpyCatcher with a fluorescent dye. Adding the SpyCatcher to SpyTag-recombinant HeLa cells showed the colocalization of both fluorescent signals, indicating high specificity.

Due to its high stability, affinity and irreversibility, the SpyTag-SpyCatcher system holds great potential for peptide probing and other methods based on a strong peptide-protein interaction.

The Epstein-Bar virus: friend or foe?

2023/10/04

Prof. Henri-Jacques Delecluse DKFZ Science @ DKFZ seminar series

The Epstein-Barr virus (EBV), which pertains to the human herpes family, is transmitted via saliva, and it is estimated that 95

Upon infection of mainly B cells, the double-stranded EBV virus integrates into the host genome and replicates generating an adaptive immune response. Three days after infection the infected B cells establish permanently growing cell lines which have been shown to induce cancer in immunocompromised patients. The virus remains latent for potentially years.

The specific tumour-inducing driving factor of EBV in non-immunocompromised patients has been elusive and is one of the main areas of research of Prof. Delecluse's lab. In their recent finding, they showed that when a mitotic cell comes in contact with the viral particle BNRF1, the cell develops an excessive number of centrosomes leading to chromosomal instability. This was replicated with virus-like particles lacking EBV DNA. In contrast, BNRF1-devoid cells did not show any abnormal aneuploidy nor other chromosomal instabilities. This event could happen during the short and sporadic lytic phase of the virus, which releases large amounts of viral particles that interact with neighbouring cells. This demonstrates that lytic replication of EBV is a cancer risk factor. Other risk factors include the consumption of nitrosamines or phorbol esters in food or smoking.

Additionally, the Delecluse lab found that the EBV non-coding RNA gene EBER2 accelerates cell proliferation by inducing the over-expression of UCHL1 deubiquitinase which enhances cyclin B1 and of Aurora kinase expression.

Image denoising and the generative accumulation of photons

2023/10/16

Dr. Alexander Krull

Online

NCT/ELLIS - Data science seminar

Poisson shot noise is one of microscopy's main challenges which originates from the particle nature of light. It is especially present in fluorescence microscopy due to the low-light imaging conditions but it is also present in confocal and brightfield microscopy. In recent years, machine learning (ML) and deep learning (DL) have proven increasingly efficient in noise removal by learning from existing image data of low and high-noise images.

The need for high quality and quantity of training data for each new denoising condition makes supervised ML very unpractical. Self-supervised learning, in which the image to de-noise itself is used to train the model, poses a way to circumvent this problem. A novel approach of this kind views shot noise as the sequential accumulation of photos in the detector grid and poses the learning task of predicting the possible locations of the next photon to hit the detector. It has been shown that this generative accumulation of photons (GAP) approach is equivalent to solving the minimum square error denoising task.

The method consists of the iterative prediction of the distribution of the next photon and sampling of photons from this distribution. This method is generative and depending on the amount of initial photons will produce predictions with less variation when more photon counts are available. On fluorescence microscopy datasets which include the Conv-PC and Neuro-PC datasets, GAP-based U-Net convolutional neural network (CNN) models showed similar or better performance than many of the supervised ML de-

noising methods such as CARE, Noise2Void and HDN256.

The probabilistic approach of GAP hints that viewing denoising as the task of predicting posterior probabilities of clear images is more promising than the common regression approach.

New ways to look through nanopores

2023/10/17

Dr. Nils Klughammer

EMBL

EMBL seminars

Current knowledge about specific nuclear pore transport selectivity and mechanism has been challenged by the finding of nuclear pore complex (NPC) inner diameter variability from 40 nm to 70 nm. To better understand the influence of NPC diameter size on molecule transport and selectivity, the Dekker lab established a protocol to create nanopores on metal films that block light propagation of wavelengths above the nanopore's diameter but allowing molecules to pass through (so-called zero-mode waveguides). Specifically, blocking the 485 nm to 640 nm spectrum allowed for fluorophore-labeled molecules to pass the nanopore from the "dark side" to the "bright side" where excitation by a focused laser beam and emission probing with a confocal fluorescence microscope allowed for multiplexed molecule translocation detection on a single-molecule level with a high signal-to-noise ratio.

NPCs were mimicked by functionalizing the solid-state palladium film with FG-nucleoporin Nsp1 to create Nsp1 meshes at pore locations (< 200 nm). Nuclear transport receptor KAP95 translocation rate - which is responsible for the protein import to the nucleus in yeast - was compared to inert BSA transport rate across the above-mentioned pores. High selectivity was shown for pores smaller than 55 nm with increasing unspecific transport at 55 nm as increasing levels of BSA leak through the pore. The translocation rates scaled in a quadratic fashion as a function of diameter size. No specificity was observed for non-functionalized pores.

Furthermore, coarse-grained molecule dynamics simulations were per-

formed modeling Nsp1 meshes within the pores at different diameter sizes. Nsp1 density and void formations suggest that BSA leaks through transient openings in the mesh.

Finally, the dependence of transport rate on Kap95 concentration was investigated. Below 50 nm increased selectivity was observed with increased Kap95 concentration and BSA leakage for large pores increased with higher Kap95 concentration.

A non-equilibrium view of cellular information processing

2023/10/24

Dr. Jeremy Gunawardena

Bioquant

Bioquant seminar

With increasing biological data being generated, machine learning models allow the inference of many variables and states. However, they usually are not informative about the mechanism that underlies the prediction. Low-level modeling of mechanisms can conceptually be approached from an information or energy perspective. To approach the energetic modeling of mechanisms, steady-states are often used, for example, the Michaelis-Menten equation in enzyme kinetics. Steady-states can be modeled in two forms: (1) equilibrium thermodynamics and (2) non-equilibrium thermodynamics. Thermodynamic equilibrium assumes no change in time and only two states, an initial and a final state. It assumes homogeneous variable distribution and a smooth mathematical passage along a continuous path of states of thermodynamic equilibrium. The latter allows it to accept large deviations from the thermodynamic equilibrium. This is not possible with non-equilibrium thermodynamics. Non-equilibrium thermodynamics describes time-courses using detailed state variables which are closely connected to states of thermodynamic equilibrium. This constraint limits the amplitude of modeled states and also causes a high computational burden on the model. Non-thermodynamic equilibrium poses the difficulty of describing entropy at a certain time point in macroscopic terms. Recently, non-equilibrium thermodynamics steady-state models have shown progress by describing macroscopic entropy via many local thermodynamic equilibria.

Systems in nature such as signal transduction, cell motility and life

forms themselves are subjected to non-thermodynamic equilibria since cells and organisms change with time, transform energy and exchange matter. John Hopkin demonstrated that certain information processing processes in biological systems can improve by exceeding the equilibrium limit at the cost of energetic expense. However, with equilibrium thermodynamics which cannot model time, space and directionality, the mechanism cannot be modeled. Non-equilibrium information-processing models were achieved by using graph Markovian processes, where steady-state probabilities are modeled as rational functions of transition states. However, the algebraic complexity hinders empirical calculations. By reorganizing the complexity in a linear framework, it was shown, that at non-equilibrium, the steady-state probability of a specific node is equal to an average of the exponential of the minimal path entropies from node 1 to i, where the average is taken over a probability distribution on the spanning trees of the graph rooted at 1.

Exploring new frontiers in MS-based proteomics: spatial and visual phenotypic insights into cellular heterogeneity

2023/11/02

Prof. Matthias Mann

Online

IMPRS Lecture Series

Mass spectrometry is currently the golden standard for proteomics analysis. Mann's research group focuses on the development of novel mass spectrometric and proteomic methods for application in biology. Applied areas of focus are signal transduction, biomarker discovery and metabolic diseases.

Recently, Mann and colleagues developed a workflow for ultra-high sensitivity mass spectrometry quantification by single-cell proteome changes upon perturbation. A combination of miniaturized sample preparation, very low flow-rate liquid chromatography, and a novel trapped ion mobility mass spectrometer yielded a 10-fold sensitivity improvement in comparison to previous protocols. When applied to 430 HeLa single-cells, they found a perturbation-resistant core proteome whilst the transcriptome seemed to vary stochastically.

Additionally, Mann's lab develops algorithms and software for the identification and quantification of peptides and further downstream systems biology and clinical knowledge mining. "Deep Visual Proteomics" (DVP) is a protocol that combines automated single-cell or single-nucleus laser microdissection and ultra-high-sensitivity mass spectrometry with machine learning analysis of cellular phenotypes to link the protein abundance to the cellular phenotypes while preserving the spatial location of cells. In a primary melanoma tissue sample, DVP identified proteome changes in melanocytes during their transition to malignant melanoma. Furthermore,

they maintain and augment the AlphaX packages. Notably, the AlphaPept-Stats package was developed to allow automated and scalable statistical analysis of mass spectrometry-based proteomics.

In a short review of machine learning in mass-spectrometry proteomics, Mann highlights the potential to predict experimental peptide measurements from amino acid sequences and to surpass the biomarker discovery performance of existing best-in-class assays.

2023/11/03

Prof. Hanns Ulrich Zeilhofer Online UCAM Pharmacology department seminar series

Benzodiazepines enhance the action of GABA neurotransmitters resulting in the inhibition of action potential transmission. They mainly target the alpha-1,2,3,5 GABA-A receptor subunits. Benzodiazepines are mainly used for their anxiolytic properties. However, side effects such as sedation, motor impairment and muscle relaxation preclude their extended use. Previous studies hint towards the potential of selective benzodiazepines for specific alpha-subunits of the GABA-A receptor to avoid undesired effects.

There is a consensus that the activation of the alpha-1 subunit should be avoided due to its related sedation, addiction and motor dys-coordination effects. The alpha-5 subunit has shown cognitive impairment effects whilst the activation of alpha2 and alpha-3 lead to the sought anxiolytic and muscle relaxant effect without a clear distinction of effect-specificity between the two.

The spinal dorsal horn secretes GABA and glycine neurotransmitters and is enriched for alpha-1,2,3,4 GABA-A receptors. The spinal origin of chronic itch (pruritus) made benzodiazepines and drugs targeting the same region of GABA receptors medically relevant for anti-pruritus treatment. Electrophysiological experiments showed the anti-pruritic effect of alpha-1 and alpha-2 subunit activation by TPA023 via binding with the benzodiazepine site. TPA023 was found to alleviate chronic itch in mice models of atopic dermatitis and in dogs sensitized to house mites while avoiding sedation, motor dysfunction and loss of antipruritic activity after prolonged

treatment.

Single-cell and spatial dissection of plant-microbe interactions

2023/11/06

Dr. Tatsuya Nobori Online Sainsbury Laboratory Seminars series

Plant immune response against pathogens like *Pseudomonas syringae* has extensively been studied at the bulk tissue level. However, pathogenic attack characteristically occurs in a heterogeneous fashion which indicates the necessity for plants to have a single-cell independent immune response.

The Nobori lab tackled this gap in the literature by scRNA-seq and scATAC multiome analysis which showed a broad number of mesophyll cell subpopulations. Based on immunity-gene expression, these mesophyll subpopulations were confirmed to be distinct cell states spanning from immunity to susceptibility cell states in response to infection. Further pseudo-time analysis of mesophyll cells revealed a linear trajectory with clear clusters for different pathogen infection phases and respective immune-gene expression profiles for each cluster. The pseudo-time predictions were validated via transgenic reporter lines allowing for visualization of selected genes such as FRK1 and CBP60g, whose increased expression upon infection was consistent with the pseudo-time prediction.

Furthermore, the spatial omics technique MERFISH was applied to investigate spatial RNA expression trends. 500 manually-curated genes were selected for the task showing sprouting expression increase at different time points for immune-response genes such as ALD1. Via cell segmentation, the multiome transcriptome and chromatin accessibility data were mapped to the MERFISH data allowing for label transfer and modality integration.

To expand the spatial information dimension, the Nobori lab developed

a spatial transcriptomics protocol named PHYTOMap which allowed for multiplexed single-cell 3D spatial gene expression analysis in whole-mount plant tissue. This technique is based on bar-coded rolling-circle amplification, comes at a relatively cheap cost and prevents the disrupting section preparation step of other spatial transcriptomics protocols.

Additionally, the Nobori lab made available a time-resolved single-cell and spatial gene regulatory atlas of *Arabidopsis thaliana* under *Pseudomonas syringae* attack based on the integration of scRNA-seq and scATAC-seq. Distinct immune-gene-expression profiles were characterized at different stages of the pathogen attack.

Drosophila axis extension is robust to an orthogonal pull by invaginating mesoderm

2023/11/07

Dr. Claire Lye

Online

UCAM Morphogenesis seminar series

During embryogenesis, embryo shaping is driven and influenced by cell-intrinsic forces like genetic patterning and cell-extrinsic forces. The latter was studied in *Drosophila* embryo models. Specifically, the effects of mesoderm and endoderm invagination on germband extension (GBE) were studied using light sheet microscopy for cell tracking and particle image velocimetry to track Myosin II flow.

GBE occurs during stages 6 to 8 of embryogenesis and refers to the elongation of the germband ventral cells along the anterior-posterior (AP) axis. The deformation of the apical germband was hypothesized to be linked to the above-mentioned invaginations. By tracking germband cell shape deformation, a gradient along the AP axis with a tensile force propagating from the posterior pole cells was observed. Additionally, the GBE onset originated synchronously with the mesoderm and endoderm invaginations.

Twist mutants, which lack mesoderm invagination, showed no impact in GBE in the AP axis of the anterior and posterior views whereas a lack of extension of the dorso-ventral (DV) axis in the anterior view was found. This suggested that DV and AP cell elongation was produced by two independent tensile forces, the mesoderm being responsible for the DV cell elongation in the germband but not for the elongation along the AP axis.

Furthermore, tracking the GBE of folded gastrulation and torso-like mutants (which hinder the ectoderm invagination), showed that the gradient of AP cell elongation was dependent on ectoderm invagination. Finally, by analyzing the flow of cortical Myosin II meshwork, constriction of the

apical surface of the posterior endoderm primordium in acellular embryos was found to be the culprit of the AP-axis tensile force. Myosin II flowed towards the contracting posterior endoderm region causing increased tension in the posterior cells.

2023/11/07

Dr. Anaïs Baudot

Online

Bioquant seminars

The increasing availability of multimodal omics data poses the opportunity for the joint analysis. Multi-modal data integration methods hold the potential to leverage complementary information of the individual modalities, reduce the joint noise and increase interpretability amongst many advantages.

The Baudot lab focuses on the development of network-based data integration methods to investigate rare disease genotype-phenotype relationships.

Multiomics integration can be useful for multi-layer network mining. MutliXrank leverages the graph-theory method named random walk with restart (RWR) which is an iterative diffusion process which determines initial probability distributions to investigate multiplex network topology for node-prioritization, sub-network community detection, node embedding and supervised classification. MultiXrank was applied to protein-protein interaction (PPI) and gene co-expression integrated networks yielding improved performance in extracting communities than monoplexed networks. MultiXrank was additionally extended to multiplexed heterogeneous networks and showed improved performances in community detection using additional disease-disease similarity networks.

Investigating Hutchinson-Gilford progeria syndrome and other progeroid syndromes, which are mainly hypothesized to stem from dysregulated DNA repair mechanisms, MutliXrank found 6 defined network clusters enriched for genes implicated in DNA repair, mitosis, transcription, signal transduc-

tion, cell adhesion and vesicle-mediated transport.

MOGAMUN is a method implementing a network-based genetic algorithm which identifies active modules in multiplexed networks by iteratively mixing the nodes and edges of parent sub-networks, ranking the child networks and selecting the top-ranked child-networks for new iterations. Studying Facio Scalpulo Humeral Dystrophy disease, MOGAMUN found a D4Z4 hypomethylation active module.

Finally, multiple omics can be integrated via joint matrix factorization. The Baudot lab also focuses on benchmarking existing methods such as MOFA, JIVE and scikit-fusion for reproducibility and standardized benchmarking approaches.

2023/11/08

Dr. Ruth Baker Online Kirk lecture series - Isaac Newton Institute

Modeling collective cell motility is essential to understand complex biological phenomena such as development, repair and disease progression. In the present work, the Baker lab attempts to quantify the behaviour of motile and proliferative cells when filling a limited local environment and model the mechanism using quantitative data from two sets of experimental design choices.

The first experimental design is the well-established growth-to-confluence assay where a 2-dimensional lattice is initially seeded with cells at low density and the cell population is observed as they move and proliferate until they fill the entire area. The second experiment, the scratch assay, involves perturbing an already confluent population of 2-dimensionally distributed cells by scratching off an area and observing the cell's capability of filling the area anew.

To model the cell behaviour a probabilistic Bayesian approach was taken to be able to infer uncertainty of predictions. Specifically, an ABC approach was taken to generate an approximate posterior distribution. The cell growth rate P_p and the cell motility rate P_m were of primary interest for prediction. Several single summary statistics that were considered most informative were analyzed for the predictive performance of P_p and P_m . For the growth-to-confluence assay, it was found that only the P_p or P_m could be individually predicted with certainty, but no single summary statistic was able to predict both parameters simultaneously. However, the one-dimensional correlation function summary statistic, C_Y was able to predict

both P_p and P_m with a good degree of confidence in a scratch assay but not in a growth-to-confluence assay. Investigating the number of cells used for model initiation, it was shown, that with an increasing number of cells, a better predictive performance was achieved which was probably due to a lower variance of the summary statistics. Furthermore, the growth-to-confluence assays require cell trajectory tracking for accurate parameter inference.

Due to the experimental bottleneck that cell tracking often poses, the results indicate that the scratch assay is a preferable experimental design choice for mechanistic cell proliferation and motility models. An additional experiment to model single tissue expansion showed distinct cell density parameter profiles for different cell cycle stages as a function of distance from the tissue centre. This enabled the probabilistic quantification of cell cycle phase duration based on cell density and the identification of checkpoints.

Tracking pathogens in space and time: something old, something new

2023/11/09

Dr. Lucy van Dorp

Online

UCAM - Genetics seminar series

Zoonotic pathogenic diseases are prevalent in humans, with 250 diseases with accounted for animal origin and 450 with to-date unknown animal origin. To investigate the precise relationship between these bacterial and viral pathogens across time and diversification innovative approaches are needed, especially since collected genomic data is biased to modern times (genomic sequencing of samples started 100-50 years ago).

Common childhood dsDNA viruses Herpes Simplex Virus (HSV) and human adenovirus (HAdV) are characterized by low mutation rates and virulence leading to the hypothesis of a long co-evolutionary association and co-divergence with their homidine host. However, the age of their association and diversity in early modern humans is largely unknown since current knowledge of ancient pathogen genomics is restricted to the Holocene (11,500 years ago); the oldest recovered viral genome being of the Hepatitis C virus 7,000 years ago.

Recently, an archeological excavation site in Yana, Northern Siberia, found two 31,600-year-old human milk teeth. DNA sequence isolation recovered four partial genomes of human herpes viruses and two complete genomes of HAdV-C. This finding pushes back the oldest zoonotic human-virus association to the Pleistocene and reinforces the hypothesis of long-term associations of common childhood infections with human hosts. Upon analysis of the HAdV-C genomes and comparison with known genomes, genotypic markers and the viral backbone were shown to be conserved across long time scales with most changes taking place in the capsid genes.

Hierarchical clustering showed 7 distinct genotype clusters. The Yana samples clustered mostly together. Phylogenetic analysis of the evolutionary history of HAdV-C showed coinciding divergence for the aforementioned genotype clusters with the Yana cluster occurring during the age of out-of-africa migration, suggesting 2 major historical genotypes and the co-evolution of the virus with humans. An alternative hypothesis would be the development of the found virus with another hominin species.

The endogenous and neoplastic response to immunotherapies in cutaneous T-cell lymphoma

2023/11/09

Dr. David R Glass

DKFZ

DKFZ presentation

The increasing availability of different omics technologies and datasets allows for a more comprehensive profiling of the human immune system. Bioinformatical analysis of the observation data is key. Glass et al. characterized the immune-cell landscape of cutaneous T-cell lymphoma patients undergoing monotherapy with anti-PD1 treatment and the combination therapy of anti-PD1 and IFN-g treatment by collecting mass-spectrometry, TCR-seq, serum proteomics, bulk transcriptomics and CODEX imaging data over a span of three weeks.

Via dimensionality reduction and embedding using UMAP, neoplastic T-cell showed a unique phenotype for each patient while clustering separately from healthy T-cells. Neoplastic T-cells showed increased FOXP3 and CTLA-4 expression but did not display regulatory T-cell phenotype. Additionally, neoplastic T-cells express significantly high PD1 ligand but lack activation during anti-PD1 therapy.

Furthermore, analyzing the transcriptomics and proteomics data of the combination therapy with anti-PD1 and IFN-g showed no expression of PD1-ligands nor any expression of IFN-g response genes in tumour or serum samples. Also, in contrast to healthy control patients, CTCL patients were less responsive to IFN-g.

Under the assumption that PD1-ligand expression correlates with anti-PD1 response, a classifier for responsive and non-responsive patients was trained. The features with the highest weights were clustered into immune modules which were related to immune response in high dimensional

multi-omics data. Responders showed higher levels of cytotoxic molecules while non-responders had greater activation in CLA+CD39+ T-regulatory cells. Finally, the input data features were condensed to 15 features which yielded a well-performing classification.

2023/11/13

Dr. Virginie Uhlmann

Online

UCAM morphogenesis series

In the biological context, microscopy images can be regarded as the most direct source of information about cell structure, shape and texture. They allow for the investigation of cell function, motility and development at 2D, 3D levels, time series and different resolutions. Dr. Uhlmann's lab investigates how cell morphological data can be represented as vectors in a mathematical expression and develops methods for cell shape quantification in a modality-agnostic manner.

One such method is SplineDist, a supervised geometrical modeling pipeline of 2D contours. SplineDist applies a U-net machine learning model to extract cell shapes from microscopy images. The geometrical cell shape representations are defined by using spline interpolation to construct continuous object curves from discrete image points. Given the difficulty of defining a single ground truth label for the image shapes for training, Uhlmann and colleagues defined the ground truth as one of the possible continuous spline approximations that yields the manually annotated segmentation mask at the pixel level.

SplineDist performs well on cell segmentation tasks generating cell outlines as spline approximations. These cell outlines can be used to effectively measure hand-crafted metrics such as cell perimeter, diameter, area etc. The outline data also allows for unsupervised feature learning such as using autoencoders to learn a low-dimensional latent representation of the cells. Applied to the MNIST numbers dataset, a UMAP representation of the data shows the qualitative proximity of numbers similar in shape (e.g.

1 and 7). This approach was applied to a *Platynereis dumerilii* seaworm whole-body electron-microscopy and gene expression dataset. The learned "morphofeatures" obtained with the autoencoder were able to recover features indicative of cell shape, context and texture. However, the feature vector obtained by this method comes at the cost of loss of interpretability of the features. Further clustering of the data yielded clusters with a clear overlap with tissue location defined by gene expression. Notably, the anatomical lateral symmetry which characterizes the *Platynereis* worm was maintained in these clusters.

Towards accurate antibody-antigen complex prediction from sequence using AI and integrative modeling

2023/11/14

Prof. Alexandre Bonvin

Online

EMBL seminar

Molecular docking is an emerging field within structural biology that allows the prediction of the preferred orientation of one molecule to another forming a stable complex. Typically used for ligand-receptor binding affinity and protein-protein interactions (PPI), molecular docking samples the conformational landscape of the molecules' interactions producing an interaction score which is used as a proxy for the binding affinity. The global minimum usually represents the stable form of the interaction. However, given a broad conformational landscape, global search approaches can be computationally intensive. Hence, the computational tool HADDOCK was designed to integrate experimental and predictive information to allow for an information-driven search approach to reduce computational burden and increase modeling accuracy.

HADDOCK incorporates even ambiguous and low-resolution data of information sources such as NMR titrations, cross-saturation, mutagenesis and cross-linking experiments, bioinformatics predictions etc while allowing for integrative flexibility and leveraging symmetries. Furthermore, it can handle up to 20 molecule interactions of proteins, peptides, nucleic acids, glycans, glycosilated proteins, small molecules etc. HADDOCK includes optional Martinin coarse graining and multiple restraint types such as NMR residual dipolar couplings, NMR relaxation anisotropy, cryo-EM and unambiguous distances amongst many others. HADDOCK calculates the energies (HS) as as the sum of the electrostatic, van der Waals, desol-

vation and air energy terms.

$$HS = E_{elev} + E_{vdw} + E_{desolv} + E_{AIR}$$

By default, no molecule dynamics are performed and no solvent interactions are included.

DeepRank-GNN-esm is another tool which uses graph neural networks (GNNs) to model protein-protein interactions. It predicts the 3D structure using meta's ESM large language model and defines protein atoms as graph nodes and atom distances as graph edges. DeepRank-GNN-esm performs well on scoring PPIs scoring and classification of biological vs crystallographic interfaces with low computation times.

Recent applications of HADDOCK and DeepRank include pathogen-sugar interaction studies and antibiotic-bacterium interactions. A very promising field of application is antibody-antigen modeling where HADDOCK has shown comparable results to state-of-the-art methods in docking prediction.

Quantifying metabolic interactions between the gut microbiota and the host

2023/11/14

Dr. Maria Zimmermann-Kogadeeva

Online

EMBL seminar

The patient-unique gut microbiome is hypothesized to contribute to the high variability of drug efficacy, toxicity and pharmacokinetics in patients. One possible source of this phenomenon is the ability of microbiome bacteria to metabolize drugs analogously to the human host.

To investigate the possible contribution of gut bacteria on brivudine (BRV), which is biotransformed by humans and mice to hepatotoxic bromovinyluracil (BVU), first, an in-vitro liver fraction assay was conducted for humans and S9 mice livers showing the decrease of BRV levels and increase of BVU levels over time. In a gut contents assay, the same changes in BRV and BVU levels were observed for humans and mice. Germ-free mice did not convert BRV to BVU. After establishing the dual host and microbiome metabolism of the drug, thousands of *Bacteroides thetaiotaomicron* strains with random mutations were assayed for BRV metabolism. The knockout of gene bt4554 was found to suppress the aforementioned metabolism.

Model mice were generated via colonizing germ-free mice with wild-type (WT) or bt4554 (MUT) cultures. Upon BRV administration, no effect on BRV bioavailability in the mice serum was observed while BVU increased significantly in serum and liver. While BRV levels in the cecum were depleted in WT mice, they remained high in MUT which were also found high in feces of MUT whilst not in WT. BVU levels were also found higher in the cecum of WT than MUT mice. These findings suggest the lack of effect of BRV transformation on BRV availability in serum by WT *Bacteroides*

thetaiotaomicron. On the other hand, BRV is metabolized in the cecum by WT bacteria influencing the levels of BRV and BVU in the gastro-intestinal tract and BVU levels in serum.

Furthermore, a physiologically-based host-microbiome pharmacokinetic model was established using ordinary differential equations to combine the absorption, distribution, metabolism and elimination of the drug by the host and microbiome simultaneously. The model was tested on the drugs sorivudine and clonazepam enabling the quantification of microbiome and host contributions to serum drug metabolites.

Highly multiplexed imaging of *in situ* tumour ecosystems towards precision medicine

2023/11/14

Prof. Bernd Bodenmiller DKFZ DKFZ 77th Grand Tour Dissecting
Cancer Histopathology with Spatial Omics

Spatial omics grant access to the spatial coordinates of omics data which can be very useful in precision oncology. Specifically, spatial omics allow for an in-depth analysis of the tumour micro-environment to, for example, identify and understand metastatic cells or the tumour-immune border.

One protocol to obtain spatial proteomics data is imaging mass cytometry (IMC). In IMC, pathology slides are incubated in rare-metal-tagged antibodies which are used as marker stains targeting specific proteins, mRNA, metabolites or post-translational modifications. Next, laser ablation coupled to a mass cytometer by time of fight quantifies the number of metals detected for a specific section region to finally generate an image with sub-cellular resolution. IMC is very robust and reproducible in comparison to other fluorescence-based techniques as it does not face autofluorescence noise.

Recently, IMC proteomics has been improved in several aspects with novel protocols allowing for 3D image generation by Z-stack sectioning, increasing the sensitivity and increasing the plexity (up to 50-plex) by using DNA-based signal amplification by exchange reaction (immuno-SABER). IMC's versatility, protocol simplicity, ease of integration into existing medical histo-pathological workflows and low-time requirement make it ideal for clinical use. The Bodenmiller lab develops algorithms and software for the analysis of spatial omics data such as 'Steinbock', 'Cytomapper' and 'imcRtools'.

The Tumor Profiler Study (TuPro) is currently being conducted to assess the importance of in-depth tumour profiling by gathering many complementary patient data modalities and allowing the tumour board to make treatment decisions based on the integration of the aforementioned data. Collected datatypes include IMC, CyTOF, scDNA, scRNA, bulk-RNA, targeted NGS, digital pathology, health record and pharmacoscopy. Despite the elevated costs of multi-modal data collection, the TuPro infrastructure could pioneer the next step in clinical precision oncology.

Cross-technology spatio-molecular profiling of breast cancer metastases

2023/11/14

Prof. Johanna Klughammer DKFZ 77th Grand Tour Dissecting Cancer Histopathology with Spatial Omics

To investigate the tumour microenvironment and metastatic properties of breast cancer a study was conducted on 15 breast-cancer-positive patients where two tumour biopsies were extracted per patient. On the first biopsy sample, 10x single cell?nucleus RNA sequencing was performed. On the second, five different and simultaneous protocols were applied to extract spatio-molecular information of 4 consecutive sections: (1) H&E stain, (2) Slide-seq, (3) CODEX, (4) MERFISH and (5) ExSeq.

This metastatic breast cancer (MBC) dataset showed significant differences between malignant cells of different patients on the UMAP embedding. Genomic heterogeneity between patients was shown where malignant cells had different copy numbers. Technical consistency was shown between patients and experiments and biological consistency was observed within patient samples at different time points. The latter was achieved via pairwise correlation of malignant pseudo-bulk expression profiles showing a high correlation between samples of the same patient.

Furthermore, TACCO was developed to transfer cell type and cell state annotations from the single-cell dataset to the complementary spatially-resolved omics datasets. TACCO is based on an optimal transport model extended with different wrappers to annotate a wide variety of data. Two TACCO modalities were compared: (1) RCTD, RObust Cell Type Decomposition and (2) OT, unbalanced Optimal Transport. RCTD explicitly models RNA counts and showed good results for count-based data while showing

worse results for non-count-based data like CODEX. OT on the other hand matched the expression value distribution well without any explicit modeling and performed decently for all data modalities.

Finally, cell type composition quality was compared between spatial methods and single-cell and single-nucleus RNAseq. The latter two were considered to be the ground truth. A correlation comparison yielded slightly favorable results towards the spatial single-cell RNAseq.

Fingerprinting your RNA - one molecule at a time

2023/11/16

Dr. Adrian Chan Mathematikon Machine learning galore conference

The development of nanopore-based third-generation sequencing methods allows for genome-length reads and the identification of RNA modifications such as N6-methyladenosine (m6A), 5-methylcytosine (m5C) and pseudouridine (ψ).

Nanopore sequencing consists of a biological or synthetic membrane with biological trans-membrane pore proteins such as alpha hemolysin. A difference in electric potential is established via an electrolyte solution and single-molecule identification is achieved by measuring the voltage measurement during the passing of molecules through the pore. This allows for DNA and RNA sequencing.

Experimentally, epitranscriptomic modifications could be identified via antibody-based protocols. In Illumina-based protocols, this evolved to antibody-free methods such as the treatment of RNA with a methylation-sensitive RNA restriction enzyme (MazF) and DART-seq complemented protocols. In nanopore-based methods, the in-depth analysis of previously considered noise in the fluctuation of electric-current has led to the development of computational methods directly inferring RNA modifications without the need for extended protocols. JACUSA2 identifies m6A sites using the comparison of read-errors between wild-type and KO experiments. JACUSA2 can also use non-negative matrix factorization to identify m6A patterns.

In their current research, the Dietrich lab works on further computational methods to identify the 140+ known RNA modifications. A notable approach is an artificial neural network trained on labeled data generated

by synthetic RNAs with and without m6A modifications. The current model can accurately identify m6A modifications and infers repetitive transcriptomic RNA locations with this modification. Current challenges are the small labeled sample size due to elevated RNA synthesis costs and limited labels. In addition, it is unknown whether the methylated carbon atom is being discriminated. The goal is to generate comprehensive epitranscriptomic signature profiles.

Probabilistic factor models for subcellular spatial transcriptomics

2023/11/16

Florin Walter Mathematikon Machine learning galore conference

Factor analysis is a commonly used unsupervised learning approach to disentangle sources of variation in highly dimensional datasets. This is achieved via non-negative matrix factorization (NMF) where a samples-by-features count matrix is decomposed into the inner product of a samples-by-factors and a factors-by-features matrix by minimizing a loss function. When the arbitrary factor number is set to a much lower number than the genes, this achieves a dimensionality reduction. Existing implementations include MOFA+, which uses Bayesian factor analysis while accounting for sparse datasets to integrate several modalities and infer the common latent factors. MEFISTO extends the approach of MOFA+ to datasets whose temporal and spatial relationships between samples are known.

FISHFactor, the latest implementation of a factor model, tackles the unsuited format of spatial transcriptomics data like MERFISH which detects single mRNAs on a spatial-coordinate level. FISHFactor models spatial location data using a probabilistic factor model with a Poisson point process likelihood. A common weight matrix is calculated for all cells and as such allows for the investigation of sources of variation common to all cells within a sample.

FISHFactor was benchmarked against other models such as NMF and non-negative spatial factorization (NSF), which rely on binning data from individual molecules. First, spatial data consisting of 20 cells, 50 genes per cell and 3 latent factors was simulated using a spatial Poisson point process by thinning approach. The 3 latent variables were effectively recovered by

FISHFactor while NMF and NSF performed worse with binning. Furthermore, applied on cultured mouse embryonic fibroblasts (NIH/3T3) from a seqFISH+ experiment, FISHFactor revealed major gene clusters and sub-cellular expression patterns with factor 1 showing a high contribution by genes involved in cell protrusion.

2023/11/20

Dr. Yohanns Bellaiche

Online

UCAM morphogenesis series

The effect of gene expression and patterning on morphogenesis has been broadly studied. However, the phenomenon where animal embryos of different sizes generally retain cell identity proportions remains unresolved. The Bellaiche lab studies the possible mechanisms that underlie the embryo size scaling in *Drosophila* with invariant cell type proportions. More specifically, they study how in-plane cell morphogenesis is affected by cell size.

First, timelapse fluorescence microscopy in combination with laser ablation was used to determine apical epithelial cell outlines, actomyosin stress fibre (aSF) formation and tensile force direction experienced in dorsal thorax morphogenesis. A correlation between increased tissue stress anisotropy over time and the number of aSFs per cell was found. This indicates that stress fibres are created along the tension axis as a response to tensile stress.

Simulation of cell shape distortion under uniaxial tensile stress, where cells are modeled to retain their shape with increasing size predicted higher aSF numbers to retain cell shape and resist mechanical stress. The proportional scaling of aSF number per cell with cell apical area was confirmed in vitro which indicated that morphogenesis is regulated by cell size and the number of stress fibres formed.

Furthermore, it was hypothesized that the mechanism by which the cell senses its area to ensure scaling is linked to tricellular junctions (TCJ). aSFs were observed to nucleate from TCJ and bigger cells showed a higher

number of TCJs per cell. Using *tbl* upregulated cells to induce cell cycle arrest and thereby the number of TCJs, it was shown that TCJ number per cell increases at constant cell size and SF lifetime.

Finally, cell-size based regulation of apoptosis via Hippo/YAP pathway was also shown. Hippo showed activation levels were proportional to cell apical area and SFs clustered Hippo/YAP components at the adherens junction.

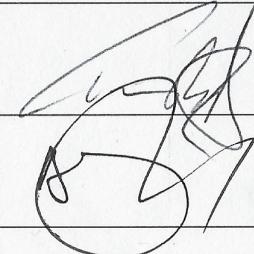
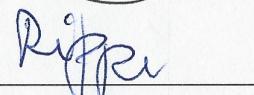
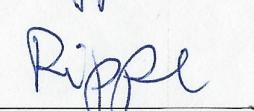
**Laufzettel für die wissenschaftlichen Vorträge im Masterstudiengang Molekulare Biotechnologie
der Universität Heidelberg**

Fichtner, Jan Dirk

Name, Vorname des Studierenden

3404046

Matr. Nr.

Lfd. Nr.	Datum	Titel des Vortrags	Dozent	Ort (z.B. DKFZ)	Name der Veranstaltung (z.B. Symposium xy)	Unterschrift Gastgeber o. Dozent	Wife Biogrant R2r
1	08/11/2022	Nothing but noise? Quantifying intracellular mechanics from fluctuations	Timo (Prof.) Betz	Biogrant	Seminar Biogrant		x
2	11/11/2022	Stem cell models of mammalian embryogenesis - hype or hope?	Alfonso (Prof.) Martinez Arias	COS	Seminar COS: Bertalanffy lecture series		x
3	08/12/2022	Cellular drivers of heart regeneration in zebra fish - origin and function	Phillip Junker (Dr.)	Biogrant	Seminar Biogrant		x
4	08/12/2022	Modeling single-cell data with (complex) experimental designs	Harald Vöhringer	Biogrant	Seminar Biogrant		x
5	16/01/2023	Slimming down through frustration: Understanding fibrous protein self-assembly	Dr. Martin Lenz	Biogrant	Colloquium - Engineering molecular systems		x

Es sind 45 wissenschaftliche Vortragsbesuche nachzuweisen, davon müssen 30 Vorträge in einseitigen Abstracts zusammengefasst werden
Nach der alten PRO: 39 Vorträge hören u. zusammenfassen. Weitere Hinweise finden Sie in den Leitlinien.

Laufzettel für die wissenschaftlichen Vorträge im Masterstudiengang Molekulare Biotechnologie der Universität Heidelberg

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							Wifo Bio- info BPC
6	14.07.2023	TMEM 55B - A missing link between lysosomal dysfunction and LRRK2 signaling	Dr. Piessenjit Pal	INF 306	Eigenständiger Vortrag / Special lecture Mol. Biotechnology and Neurosciences	Piessenjit Pal	X
7	25.07.2023	Rewriting the ubiquitin code by linear chains	PD Dr. med Konstanze F. Winkelhofer	BZH	BZH lecture	SJ	X
8	26.07.2023	Polygenic risk score and risk-adapted breast cancer screening: Ready for clinical use?	PD Dr. med Anna Quant	Univ Klinikum Heidelberg	Institut für Humangenetik Kolloquium	A. Quant	X
9	09.08.2023	What's left to learn? EV biodistribution, pharmacokinetics and immunogenicity	Dr. Kenneth Witwer	DKFZ	BioMedX: dunchtalk presentation series	K. Witwer	X
10	06.09.2023	An introduction to protecting software-based innovations with Patents	Dipl. Phys. LL.M Peter Bittner	Mathematikon	IWR Heidelberg: Patent course	P. Bittner	X
11	06.09.2023	Investigation of KCNQ1 junction in human neurons	Dr. Simone Beikel	Univ Klinikum Heidelberg	Institut für Humangenetik: Kolloquium	S. Beikel	X
12	07.09.2023	A novel role of IL-10 in preventing T-cell exhaustion and maintaining anti-tumour immunity	Dr. Martina Seiffert	DKFZ	BioMedX: dunchtalk presentation series	M. Seiffert	X
13	07.09.2023	Publishing oncology research in Nature Medicine	Dr. Ulrike Haries	DKFZ	DKFZ: Immunology, infection and inflammation seminar series	U. Haries	X

Es sind 45 wissenschaftliche Vortragsbesuche nachzuweisen, davon müssen mind. 23 Vorträge in Präsenz gehört werden.
Weitere Hinweise finden Sie in den Leitlinien.

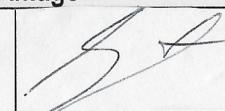
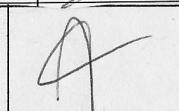
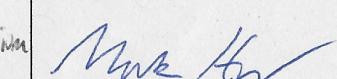
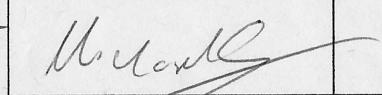
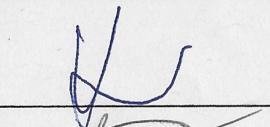
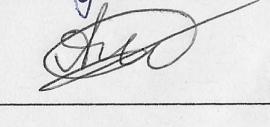
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							Wifo	Bio-info	BPC
14	15.09.2023	Computational modeling: Prime time for clinics	Prof. Steven Niederer	Mathematik	Healthy AI conference AI meets medicine		X		
15	18.09.2023	old dogmas revisited (and reshaped) A new view of the landscape of bacterial coupled transcription-translation	Mikel (Dr.) Iastorza- Olazigeri	EMBL	EMBL seminars		X		
16	19.09.2023	Power to the protein: analyse, signal, protect with bacterial superglues	Mark (Prof.) Howarth	MPG	Rudolf Mößbauer Colloquium			X	
17	21.09.2023	Exploring the complexity and potential of large language models (LLMs)	Prof. Michael Gertz	Mathematik	Big PyData Congress #5		X		
18	26.09.2023	DEAD-box ATPase Dbp2 acts late during transcription and is required for efficient 3'-end formation and RNA release from cleavage	Dr. Cornelia Kilchert	BZH	BZH: Guest seminar series		X		
19	28.09.2023	Exploring chemical reactivity in ^{bodies} the age of automation and ML	Prof. Fernanda Duarte	HITS	HITS - SIMPLAIX joint colloquium			X	
20	04.10.2023	The Epstein-Barr Virus: friend or foe?	Prof. Henri-Jagès Delecluse	DKFZ	Science @ DKFZ Seminar series		X		
21	12.10.2023	Energy of chemical bonds as a driving force for organic reactions: molecule spinners, stereo-electric frustration and electron upconversion	Prof. Igor V. Alabugin	Anorganisch-chemisches Institut ACI	SFB Kolloquium		X		

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							Wifo Bio- info BPC
22	16.10.2023	Molecular cross-talk between cell fate determination and orientation in epithelial cell divisions	Prof. Marina Mapelli	Massilius Kolleg	Massilius Kolleg: Wnt seminar	<u>Mapelli</u>	X
23	16.10.2023	Chemical design of functional protein assemblies	Prof. Alain Tchern	Biognant	FI EMS Kolloquium	<u>A. Tchern</u>	X
24	17.10.2023	New ways to look through nanopores	Dr. Nils Klughammer	EMBL	EMBL seminar	<u>N. Klughammer</u>	X
25	24.10.2023	A non-equilibrium view of cellular information processing	Dr. Jeremy Gunawardena	Biognant	Biognant seminar	<u>J. Gunawardena</u>	X
26	09.11.2023	The endogenous and neoplastic response to immunotherapies in cutaneous T-cell lymphoma (CTCL)	Dr. David R Glass	DKFZ	DKFZ presentation	<u>D. R. Glass</u>	X
27	14.11.2023	Highly multiplexed imaging of in-situ tumour ecosystems towards precision medicine	Prof. Bernd Bodenmüller	DKFZ	DKFZ seminar series	<u>B. Bodenmüller</u>	X
28	14.11.2023	Cross-technology spatio-molecular profiling of breast cancer metastases	Prof. Johanna Klughammer	DKFZ	DKFZ 77 th Grand Tour Dissecting Cancer Histopathology with spatial omics	<u>J. Klughammer</u>	X

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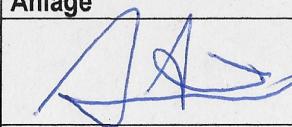
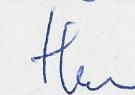
Laufzettel für die wissenschaftlichen Vorträge im Masterstudiengang Molekulare Biotechnologie der Universität Heidelberg

Fichtner, Jan Dirk

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29	16.11.23	Fingerprinting your RNA- one molecule at a time	Dr. Adrian Chan	Mathematikum	Machine learning galore!			X		
30	16.11.23	Probabilistic factor models for subcellular spatial transcriptomics	Florian Walter	Mathematikum	Machine learning galore!			X		

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Table 24.1: Table of online visited talks, adapted from the “Laufzettel”.

Lfd. Nr.	Date	Title of presentation	Speaker	Place (e.g. DKFZ)	Event name	URL	Fachbereich		
							Wifo	Bioinfo	BPC
1	07/09/2023	Molecular mechanisms and therapeutic targets in bone and soft-tissue sarcoma	Dr. Priya Chudasama	Online	Progress in Cancer Research - DKFZ	https://us02web.zoom.us/j/89906876234?pwd=WX1TOHZXenVLMFMvUUZTQ1ZzRUo4Zz09	X		
2	14/09/2023	Immune escape mechanisms in cancer	Dr. Martina Seiffert	Online	Progress in Cancer Research - DKFZ	https://us02web.zoom.us/j/89906876234?pwd=WX1TOHZXenVLMFMvUUZTQ1ZzRUo4Zz09	X		
3	16/10/2023	Image denoising and the generative accumulation of photons	Dr. Alexander Krull	Online	NCT ELLIS data science seminar	https://dkfz-de.zoom.us/meeting/register/u5Urd-iopjMvE9M_jv-90Vi5zZFbcIaX0LLs		X	
4	24/10/2023	A RNA-centric perspective on respiratory RNA viruses	Prof. Volker Lohmann	Online	CIID seminars	https://ukhd.webex.com/ukhd/j.php?MTID=mfd5bf231839de8bab49e15b5818b8656	X		
5	02/11/2023	Exploring new frontiers in MS-based proteomics: spatial and visual phenotypic insights into cellular heterogeneity	Dr. Matthias Mann	Online	IMPRS lecture series	https://mpi-biochemistry.zoom-x.de/j/64180753743	X		
6	03/11/2023	GABA-A receptor subtypes controlling pain and itch	Prof. Hanns Ulrich Zeilhofer	Online	UCAM Department of Pharmacology seminar series	https://cam-ac-uk.zoom.us/j/98809937536?pwd=T3BpN0E2UUwvV1R0ejdodFVhYVpqdz09	X		

Continued on next page

Table 24.1 – continued from previous page

Lfd. Nr.	Date	Title of presentation	Speaker	Place (e.g. DKFZ)	Event name	URL	Fachbereich		
							Wifo	Bioinfo	BPC
7	06/11/2023	Single-cell and spatial dissection of plant-microbe interactions	Dr. Tatsuya Nobori	Online	UCAM Sainsbury Laboratory seminar series	https://cam-ac-uk.zoom.us/j/89243392445?pwd=SXJ1YS9yK0h3Uj1SRXc5V1ZUT00wUT09		X	
8	07/11/2023	Drosophila axis extension is robust to an orthogonal pull by invaginating mesoderm	Dr. Claire Lye	Online	UCAM Morphogenesis series	https://us06web.zoom.us/j/82089026611?pwd=L2Fyc1JFL21YR0J3SFBDbHQyUFp6UT09			X
9	07/11/2023	Multimodal data integration for rare genetic diseases	Dr. Anaïs Baudot	Online	Bioquant seminar	(https://eu02web.zoom-x.de/j/63868989793?pwd=RFRSR253Q1N6T2xIajIzRE0xMUc1Zz09		X	
10	08/11/2023	Data-driven modelling of collective cell motility	Dr. Ruth Baker	Online -stream	Isaac Newton Institute - Kirk lecture series	https://www.newton.ac.uk/seminar/40542/			X
11	09/11/2023	Tracking pathogens in space and time: something old, something new	Dr. Lucy van Dorp	Online	UCAM Genetics seminar series	https://zoom.us/j/97819373964?pwd=NHJZRD1VL1A3MWFxWnBUWGVSSF1Mdz09		X	
12	13/11/2023	Turning biological morphology into numbers	Dr. Virginie Uhlmann	Online	UCAM Morphogenesis series	https://us06web.zoom.us/j/82089026611?pwd=L2Fyc1JFL21YR0J3SFBDbHQyUFp6UT09		X	
13	14/11/2023	Towards accurate antibody-antigen complex prediction from sequence using AI and integrative modeling	Prof. Alexandre Bonvin	Online	EMBL seminars	https://embl-org.zoom.us/j/93252044294?pwd=ZF1JQ1VnTGdVektTaktLRGNpbHU4QT09			X

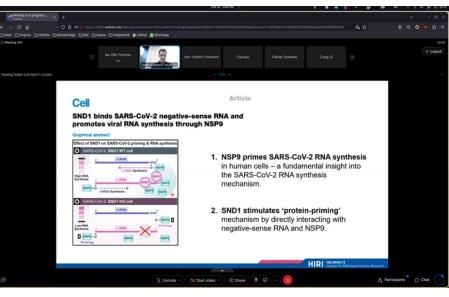
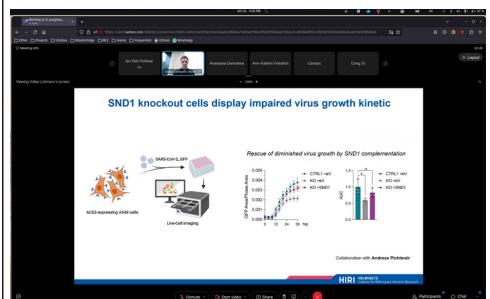
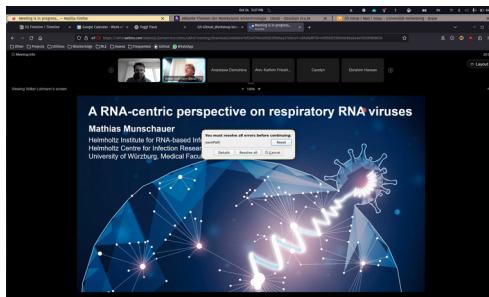
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Table 24.1 – continued from previous page

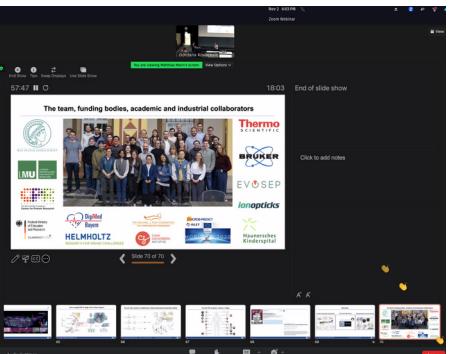
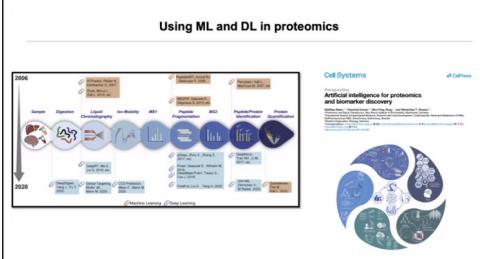
Lfd. Nr.	Date	Title of presentation	Speaker	Place (e.g. DKFZ)	Event name	URL	Fachbereich		
							Wifo	Bioinfo	BPC
14	14/11/2023	Quantifying metabolic interactions between the gut microbiota and the host	Dr. Maria Zimmermann-Kogadeeva	Online	EMBL seminar	https://us02web.zoom.us/j/83129558871?pwd=NmFOdUlMV0xGRWRaQTlVaC9WSTV6Zz09		X	
15	20/11/2023	How cell and tissue morphology influences morphogenesis	Dr. Yohanns Bellaiche	Online	UCAM morphogenesis series	https://ucammorphogenesisseries.com/program/			X

Lfd. Nr. (Online)	Screenshot beginning	Screenshot middle	Screenshot end	Screenshot announcement
1	<p>Screenshot beginning</p>	<p>Screenshot middle</p>	<p>Screenshot end</p>	<p>Screenshot announcement</p>
2	<p>Screenshot beginning</p>	<p>Screenshot middle</p>	<p>Screenshot end</p>	<p>Screenshot announcement</p>
3	<p>Screenshot beginning</p>	<p>Screenshot middle</p>	<p>Screenshot end</p>	<p>Screenshot announcement</p>

4



5



6

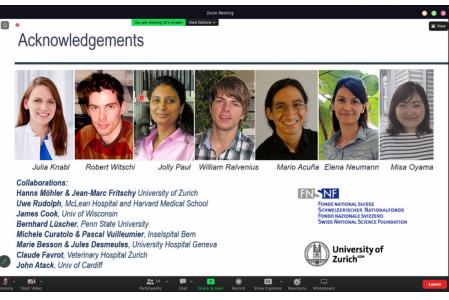
Benzodiazepine-Site Agonists Induced Analgesia?

You are only looking at hyperalgesia. What about the aversive component of pain?

Are you sure, your "analgesia" is not a reversal of anxiety-induced hyperalgesia?

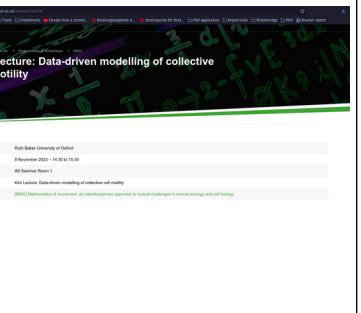
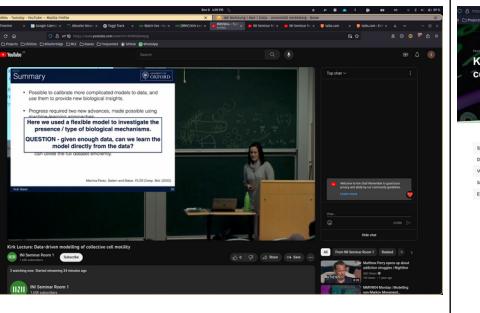
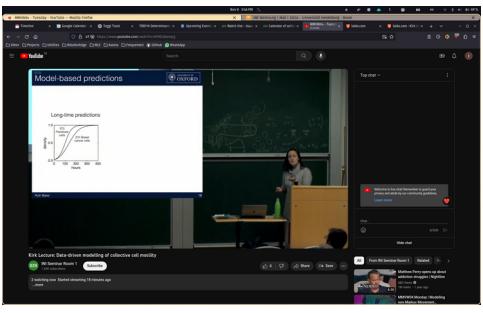
Aren't you just shutting down any somatosensory input to the cord?

OK, fine, you get less side-effects with a more selective drug, but why should subtype-selective benzodiazepines be analgesic if non-selective ones are not?

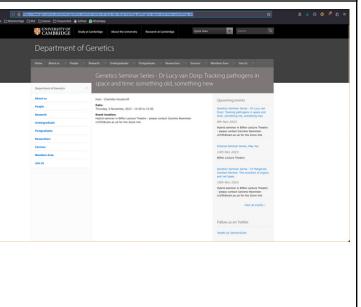
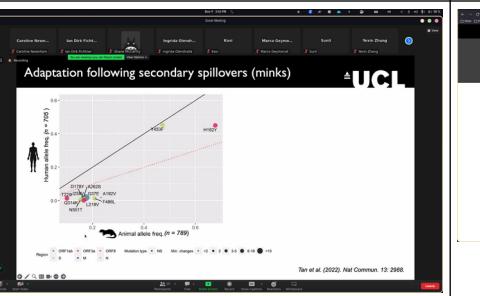
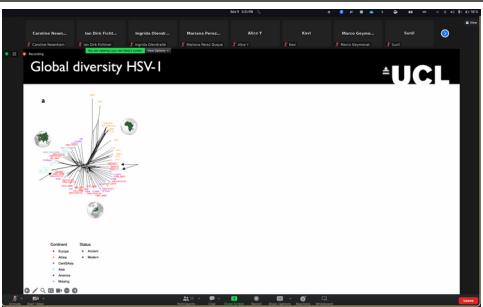
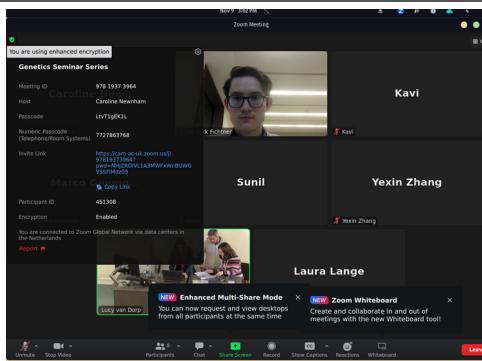


7	<p>Noboru seminar Meeting ID: 992 4399 2445 Host: Elisabeth Burmeister Passcode: N0b0r0 Invite Link: https://cam.ac.uk.zoom.us/j/99243992445?pwd=U19XK0NURyRkSVZUT0FzQWJtOT09</p> <p>Participant ID: 58870 Encryption: Enabled Copy Link You are connected to Zoom Global Network via data centers in Cambridge, UK. Report</p> <p>Enhanced Multi-Share View Zoom Whiteboard Create and collaborate in and out of meetings with the new Whiteboard tool!</p> <p>Leave</p>	<p>Future perspectives: Exploring the new dimensions of plant-microbe interactions</p> <p>Single-cell multiome atlas</p>	<p>Single-cell and spatiotemporal gene regulatory map of plant immune responses</p>
8	<p>Morphogenesis Seminar Cambridge's Zoom Meeting Meeting ID: 981 9661 9844 Passcode: 65847 Invite Link: https://cam.ac.uk/zoom/meeting.php?w=10&id=98196619844&pw=65847</p> <p>Drosophila axis extension is robust to an orthogonal pull by the invaginating mesoderm</p> <p>Claire M Lye, Guy B. Blanchard, Jenny Evans, Alexander Nestor-Bergmann, Bénédicte Sanson</p> <p>Preprint available on BioRxiv, under revision</p>	<p>Overall effect on tissue extension</p> <ul style="list-style-type: none"> Increased rate of tissue extension in twist, mainly due to increased cell shape change Therefore, mesoderm recognition acts to increase cell intercalation 	<p>Thank you</p> <p>Bénédicte Sanson Jenny Evans Guy Blanchard Alex Nestor-Bergmann</p> <p>Preprint available on BioRxiv Published online 2 December 2023 Funded by Wellcome</p>
9	<p>Talk by Anais Baudot Meeting ID: 638 6899 9793 Host: BioQuant Passcode: 377210 Invite Link: https://camweb.zoom.us/j/63868999793?pwd=UFR5d1QmQHETZnajR0dMU12209</p> <p>You are connected to Zoom Global Network via data centers in Cambridge, UK. Report</p> <p>Enhanced Multi-Share View Zoom Whiteboard Create and collaborate in and out of meetings with the new Whiteboard tool!</p> <p>Leave</p>	<p>3 frameworks for multimomics integration</p> <ul style="list-style-type: none"> Multi-Layer Network Mining Active Module identification Joint Dimensionality Reduction 	<p>Multimodal data integration for rare genetic diseases Anais Baudot BioQuant Systems Biology, Marseille Medical Genetics, Aix-Marseille University, France Nov 07, 2023 Hosted by Carl Hermann</p> <p>Abstract Multimodal integration and the growing availability of molecular datasets offer unprecedented opportunities to better understand human disease. However, it is often not clear how to best integrate heterogeneous sets of these data into meaningful insights, nor how to process complex datasets. In this talk, I will present three different frameworks for multimodal integration that have been developed to address these challenges. These frameworks can be used to identify the relationships between different types of data and to predict disease risk or progression.</p> <p>Short Bio Anais Baudot is a postdoctoral researcher at the Institut Curie in Paris. Her main interests are to develop computational approaches to study human diseases, with a particular emphasis on rare genetic diseases. She has a background in bioinformatics and machine learning, and has experience in the analysis of complex biological systems.</p> <p>Affiliations Institut Curie, Paris, France Aix-Marseille Université, Marseille, France Marseille Medical Genetics, Marseille, France anr*, AFM TELETHON*</p>

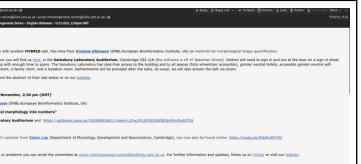
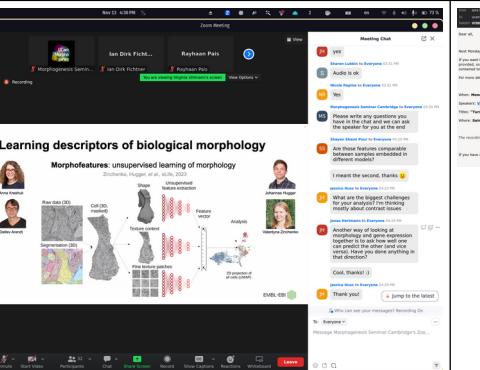
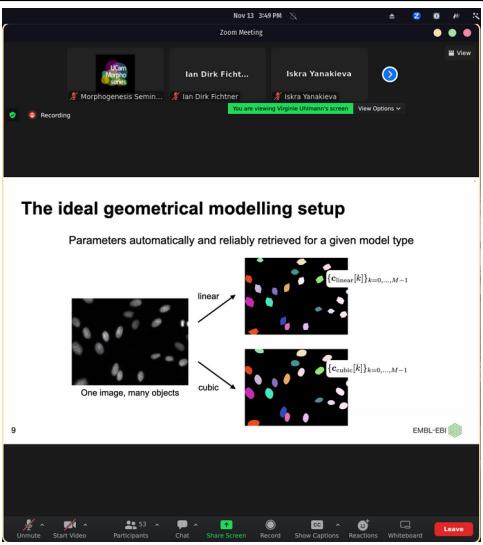
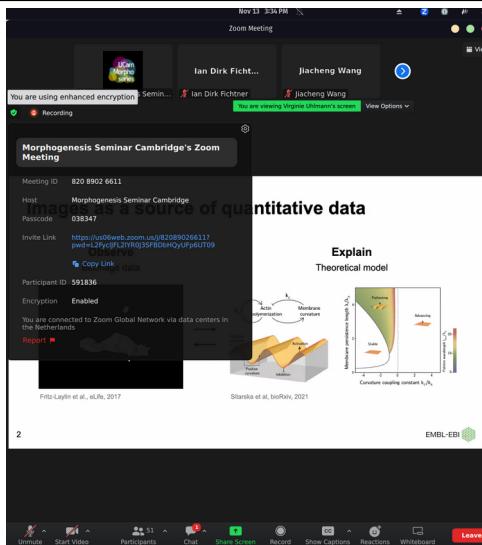
10



11



12



13

Nov 14, 2023 PM Zoom Meeting

Ian Dirk Fichtner, Lena Gottschalk, Lubov Makarova

You are viewing enhanced encryption

External Faculty Speaker - Alexandre Bonvin

Meeting ID: 932 5204 4294
Host: EMBL Grenoble Unit
Passcode: 395411
Invite Link: <https://zoom.us/j/93252044294?pwd=VHJzUmltZWZwZWxkZWxkQGJ0T09>

Participant ID: 456888
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Integrative modeling of biomolecular complexes
Towards accurate antibody-antigen complex prediction from sequence using AI and integrative modeling

EMBL Grenoble November 14, 2023

Nov 14, 21:25 PM Zoom Meeting

Ian Dirk Fichtner, Lubov Makarova

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Recent application examples

Pathogen-sugar interactions revealed by universal saturation transfer analysis

A universal saturation transfer analysis (USTA) workflow for the identification of sugar residues in glycoproteins and glycolipids. The workflow involves labeling with a biotin-conjugated lectin, followed by a series of steps including reduction, alkylation, and labeling with a biotin-conjugated lectin. The labeled samples are then analyzed by mass spectrometry to identify the presence of specific sugars.

B protein-protein binding

C protein-glycan binding

D protein-carbohydrate binding

E protein-peptide binding

F protein-lipid binding

G protein-nucleic acid binding

H protein-oligosaccharide binding

I protein-oligosaccharide binding

J protein-oligosaccharide binding

K protein-oligosaccharide binding

L protein-oligosaccharide binding

M protein-oligosaccharide binding

N protein-oligosaccharide binding

O protein-oligosaccharide binding

P protein-oligosaccharide binding

Q protein-oligosaccharide binding

R protein-oligosaccharide binding

S protein-oligosaccharide binding

T protein-oligosaccharide binding

U protein-oligosaccharide binding

V protein-oligosaccharide binding

W protein-oligosaccharide binding

X protein-oligosaccharide binding

Y protein-oligosaccharide binding

Z protein-oligosaccharide binding

An antibiotic from an uncultured bacterium binds to a host cell

Science

Experimental knowledge

Call for targets

http://www.capri-docking.org

- We welcome all types of protein complexes. We are particularly interested in (but not limited to):
 - Protein complexes without templates
 - Conformational change
 - Weak binding
 - Complexes involving antibodies or nanobodies
 - Protein-glycan complexes
- For additional information see: <http://www.capri-docking.org/contribute/>
- Contribute a target by emailing to targets@capri-docking.org

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QR code

About the speaker

Ian Dirk Fichtner studied Chemistry at a German university, graduated and obtained his PhD at Princeton University, USA, after two years of postdoctoral work at the University of California Berkeley, USA. In 1996 he was appointed as a research scientist at EMBL.

14

Nov 14, 3:04 PM Zoom Meeting

Adriana Vieira, Yulin

SyNNet / SGC Tuesday Seminar - 14 Nov 14H WET / 15H CET

Meeting ID: 831 2995 8871 Host: SyNNet Project Passcode: 220333 Invite Link: <https://zoom.us/j/83129958871?pwd=N2lhdUJnZWZmRWhvTWVzV2d09>

Participant ID: 30767 Encryption Enabled

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Maria Zimmermann-Kosadeeva, PhD
EMBL Heidelberg IGC seminar 14. November 2023

Quantifying metabolic interactions between the gut microbiota and the host

Nov 14, 3:08 PM Zoom Meeting

Ian Dirk Fichtner, Indra Almada Correia, Ana Raquel Cruz

Novelty

Factors affecting drug and metabolite in serum

Brivudine (BRV) Serum

Bromo-uridine (BUD) Serum

Concentration

Time, h

WT - colonized mice MDT - colonized mice

EMBL

Nov 14, 3:04 PM Zoom Meeting

Ian Dirk Fichtner, Indra Almada Correia, Ana Raquel Cruz

Recording

Model describes metabolite profiles in the GIT

Model assumptions:

- Metabolic pseudo-steady state
- Intestinal flow f equal across conditions
- Host metabolism in small intestine is diet-specific
- Host metabolism in large intestine is diet-specific
- Microbiome metabolism in large intestine is diet-specific

Duodenum (D), Jejunum (J), Ileum (I), Colon (C), Rectum (R), Feces (F)

Brivudine (BRV) Serum

Bromo-uridine (BUD) Serum

Concentration

Time, h

WT - colonized mice MDT - colonized mice

EMBL

Nov 14, 3:04 PM Zoom Meeting

Ian Dirk Fichtner, Indra Almada Correia, Ana Raquel Cruz

Abstract

In the gut microbiome, the community of microorganisms residing in our gastrointestinal tract, it is involved in different aspects of host health and disease. One of the main ways they interact with the host is through metabolites. To quantify these metabolite-host metabolite interactions, we developed a mathematical model that describes the concentration of metabolites based on the measured diet, host metabolism, and microbiome metabolism. With this model, we can predict how different sources of chain-drugs will affect the metabolite concentrations in the host. After this, we can analyze how different metabolite concentrations affect the host.

About the speaker

What the speaker

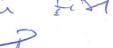
What the speaker

The image consists of four side-by-side screenshots from a Zoom meeting.
 - The first screenshot shows a participant's video feed, with a small thumbnail of the speaker in the top right corner. The interface includes standard Zoom controls like 'Start Video', 'Participants', 'Chat', 'Share Screen', 'Record', 'Show Captions', 'Reactions', and 'Whiteboard'.
 - The second screenshot shows a presentation slide titled 'Scaling of cell mechanosensitivity with cell apical area'. It features a microscopy image of cells with green and purple staining, and text explaining that the number of apical actomyoain stress fibers (SF) scales with apical cell size to prevent elongation of large cells, and that the scaling between SF number and cell size depends on tricellular junctions. The slide is attributed to Lopez-Gay et al., Science, 2020.
 - The third screenshot shows another presentation slide titled 'Large Fold formation during epithelial morphogenesis'. It displays a microscopy image of tissue folds and text about '10.07 hr APF' and 'ubiquitin-DE-Cad-GFP'. The slide is attributed to Boswell et al., 2012.
 - The fourth screenshot shows a slide titled 'How cell and tissue morphology influences morphogenesis'. It includes a bioRxiv preprint link: 20.11.2023 Yohann Bellaläche (Institute Curie, Paris). The slide discusses shape as a fundamental property of biological systems and how cell and tissue geometry influences morphogenesis. It also mentions that our understanding of the mechanics of morphogenesis lags behind and poses two questions: how cell size influences cell stiffness and tissue elongation, and how tissue curvature modulates tissue folding.

Attendance list

Git/Github workshop 9th October 2023

Held by Ian Dirk Fichtner

Name Surname	Email	Signature
Nazli Aybike Boldemir	aybike.boldemir@stud.uni-heidelberg.de	
Steiner, Lydia Matte Hermes	lydia.steiner@stud.uni-heidelberg.de hermes@stud.uni-heidelberg.de	 
Eisl Michael	eisl.michael@wes.de	
Reimers, Alexandra	a.reimers@stud.uni-heidelberg.de	
Fichtner, Franziska	franziska.fichtner@stud.uni-heidelberg.de	

Attendance list

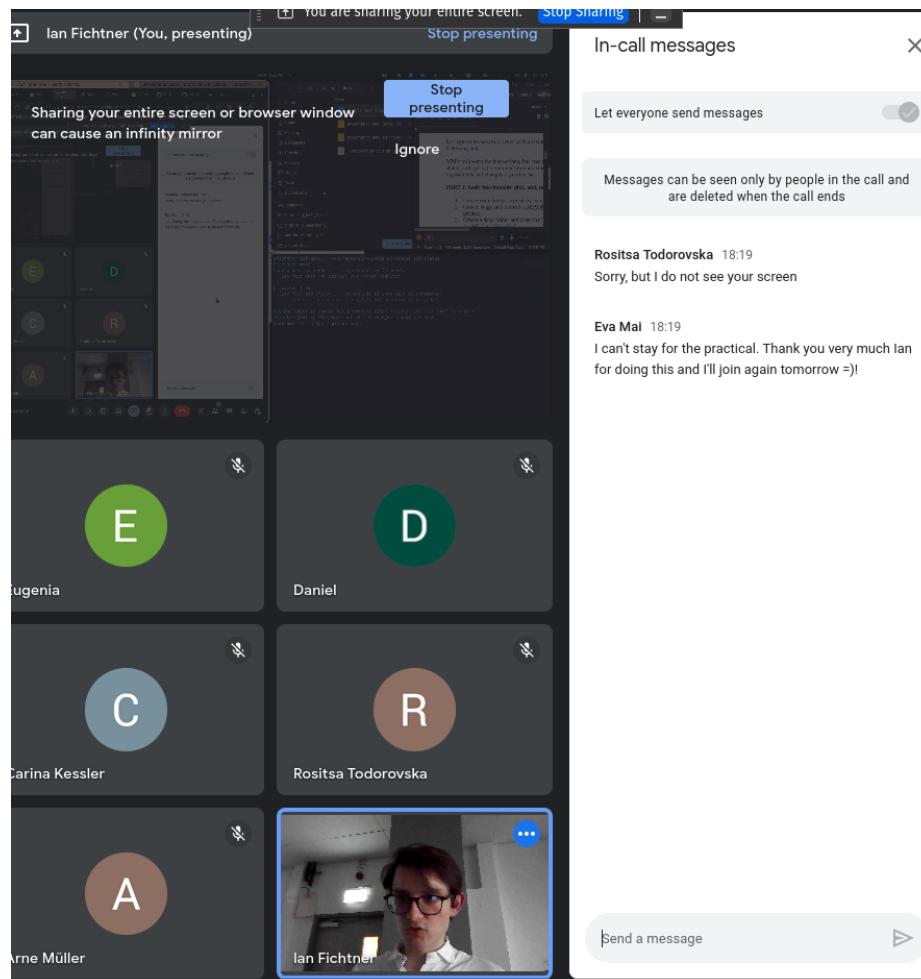
Git/Github workshop 10th October 2023

Held by Ian Dirk Fichtner

Name Surname	Email	Signature
Lydia Steiner	lydia.steiner@stud.uni-heidelberg.de	
Nazli Aybike Boldemir	aybike.boldemir@stud.uni-heidelberg.de	
Franziska Fichtner	franziska.fichtner@stud.uni-heidelberg.de	
Michael Eisl	eisl.michael@wes.de	
Alexandra Reimers	a.reimers@stud.uni-heidelberg.de	
Matte Hermes	hermes@stud.uni-heidelberg.de	

Attendance list – Online

09.10.2023



10.10.2023

