AI Health Innovation Cluster

- an initiative of the Innovation Campus Heidelberg Mannheim Health & Life Sciences

Funded Projects in the 2022 Calls

Second Call Funded Projects

AIH1: COmorbidity modeling IN spinal Cord Injury and DEpression (**COINCIDE**)

Abstract: Depression is a highly frequent and severely disabling condition affecting approximately 40% to 60% of patients with traumatic spinal cord injury (SCI). It has serious consequences for the short- and long-term rehabilitation of individuals with SCI, and is associated with an increased suicide risk. However, the biology of depression in SCI is poorly understood and no biological tools exist that could aid in identifying at-risk patients. COINCIDE, an interdisciplinary project focusing the development and application of artificial intelligence methods to characterize the mechanisms underlying depression in SCI, aims to address this and provide the basis for the development of novel diagnostic and predictive tools. The project will develop and apply multi-task machine learning approaches to characterize the link between neurological SCI deficits and depression-relevant brain function. The project builds on already available data from SCI patients, as well as large-scale brain-functional data acquired in healthy controls, as well as patients with major depressive disorders. COINCIDE will then determine genetic and epigenetic associations in the same individuals, to characterize the biology of depression in SCI, and provide the basis for the development of novel diagnostic and predictive tools.

	Coordinator	Partner 1
PI	Emanuel Schwarz, PhD	Prof. Dr. Norbert Weidner
Institution	Central Institute of Mental Health (CIMH) Department of Psychiatry and Psychotherapy Mannheim	Heidelberg University Hospital (HD) Spinal Cord Injury Center Heidelberg

AIH4: Never split the difference – Machine Learning approaches to full-length transcript isoforms (ONT-SPLiT-seq) deconvolution.

Abstract: Mutations in the cardiac splice factor *RBM20* cause severe dilated cardiomyopathy (DCM) however, due to technological limitations, its regulatory network is only partially understood. SPLiT-seq is one of the few single-cell sequencing methods for the analysis of cardiomyocytes. In several split-pool rounds, fixed cells are randomly distributed into wells and transcripts are labelled with well-specific barcodes. The Steinmetz Lab (EMBL/Stanford) and Dieterich Lab (U. Heidelberg) combine their expertise on Bioinformatics, long-read Nanopore sequencing, RNA splicing and systems cardiology to rethink SPLiT-seq completely new. While conventional SPLiT-seq uses short Illumina sequencing, we will propel SPLiT-seq into the era of long-read, single-molecule Nanopore sequencing without compromising on accuracy and speed. We have recently established a combined protocol for SPLiT-seq and long-read sequencing (ONT-SPLiT-seq), which we propose to employ for the generation of a single cell isoform atlas of the murine heart. Next, we will identify cell populations that are prone to mis-splicing in mice with patient-relevant mutations in *RBM20*. Finally, we will integrate for the first time CRISPR-mediated perturbations with single-cell long read analysis to associate gene function to splicing in a high-throughput fashion. Combined, this approach

will provide crucial insights into the *RBM20*-mediated splice network and its perturbation in DCM.

	Coordinator	Partner 1
PI	Prof. Dr. Christoph Dieterich	Prof. Dr. Lars Steinmetz
Institution	Bioinformatics and System Cardiology, Klaus Tschira Institute for Integrative Computational Cardiology and Department of Internal Medicine III, Medical Faculty Heidelberg, Universität Heidelberg	Genome Biology Unit - Steinmetz Group European Molecular Biology Laboratory (EMBL)

AIH6: Computational models of social interactions as a basis for adaptive gamified treatment approaches

Abstract: Social interactions form a key aspect of our everyday life. Through cooperative exchanges with our fellow human beings, we obtain behaviorally relevant information, as well as emotional support and protection. Disturbed or altered interaction behavior is a core feature in multiple psychiatric disorders, and is perceived as extremely burdensome and stressful, both by the affected individuals as well as by those in their immediate surroundings. Here, we propose to adopt modern Machine Learning (ML) algorithms from the reinforcement learning (RL) domain to model and emulate (alterations in) social interaction behavior in healthy and diseased individuals. Highly predictive models will then be applied to develop model-based adaptive gamified treatment approaches to modify individuals' behavior, as well as to gain mechanistic insights into the pathogenic processes that underlie maladaptive social interactions and their neural substrates. By encouraging positive social learning experiences, the proposed approach is hypothesized to promote learning of more advantageous interaction strategies, enhance cooperation, and strengthen core social competences. We expect that the development and validation of this ML approach will have strong clinical implications and could be integrated into treatment approaches for psychiatric disorders.

	Coordinator	Partner 1
PI	Dr. Georgia Koppe	Jun.-Prof. Dr. Christoph Korn
Institution	ZI	University Hospital Heidelberg

AIH9: Estimating the health and economic burden induced by heatwaves in Germany using machine learning methods

Abstract: Climate change represents a major threat to human health, for instance due to heatwaves and other extreme weather events. In 2003 alone, about 70.000 excess deaths were attributed to heat within few weeks in Europe. The Lancet Countdown on health and climate change estimates the economic burden of heat induced excess mortality to correspond to 0.28% of the gross world product, with the greatest economic burden occurring in Europe. However, these costs are likely underestimated since very limited evidence is available as to what costs heat imposes on the health system, due to increased health service utilisation, and on society at large, due to reduced productivity and premature mortality. Our study addresses this knowledge gap by combining economic evaluation methods with machine learning methods, to estimate the societal cost of heatwaves in Germany for 2011-2021. To achieve

our objective, we examine how machine learning approaches perform compared to the state-of-the-art time series regression approaches to estimate the impact and predict costs by linking nationally representative insurance data with historic temperature data. This represents a unique attempt to reconcile different disciplinary approaches to produce more valid and credible results than those derived by standard approaches and to promote methodological advances.

	Coordinator	Partner 1	Partner 2
PI	Prof. Dr. Manuela De Allegri	Prof. Dr. Joacim Rocklöv	Dr. Alina Hermann
Institution	Heidelberg Institute of Global Health, UKHD, Health Economic and Financing Unit, Hosting institution	Interdisciplinary Center for Scientific Computing, Heidelberg University	Heidelberg Institute of Global Health, UKHD, Climate Change, Nutrition, and Health Group

AIH19: Combining Multiplexed Imaging and Computational Frameworks to Reveal Cellular Metabolic Interactions in the Human Tumor Microenvironment

Abstract: Significant transition points in human cancer span tumor initiation, expansion, metastasis, and therapeutic resistance. Importantly, these transitions involve complex interactions between cells within the tumor microenvironment (TME). Novel spatial-omics technologies now provide an opportunity to interrogate this complexity at unprecedented resolution. In this project, we will combine a novel proteomic imaging platform (multiplexed ion beam imaging: MIBI) with machine learning frameworks to extract clinically significant cellular interactions from human melanoma tissue. MIBI visualizes the expression and spatial distributions of up to 40 proteins and thus enables deep analysis of the TME. Extracting knowledge from multiplexed spatial data requires the development of scalable computational methods that can leverage the availability of the spatial context. We have recently developed such approaches, with an emphasis on leveraging prior biological knowledge to extract mechanistic insights. Bringing together this novel cutting-edge imaging technology with AI-supported data analysis frameworks will advance our understanding of cellular interactions and their functional consequences and may thus lead to novel biomarkers and potential therapeutic targets for human cancer.

	Coordinator	Partner 1
PI	Dr. Felix J. Hartmann	Prof. Dr. Julio Saez-Rodriguez
Institution	German Cancer Research Center (DKFZ)	University of Heidelberg

AIH21: Automated detection and molecular characterization of micronuclei in cancer cell lines and tumor tissues.

Abstract: Chromosomal instability (CIN) is a hallmark of cancer and manifests as structural or numerical alterations in the chromosomes. CIN is associated with widespread therapeutic resistance, immune evasion, and metastasis. Despite its prominent role, no druggable

molecular targets are currently known. To enable a systematic assessment of CIN, we will leverage genetic constructs of members of the kinesin family to generate various levels of chromosomally unstable cell lines. The most common way to assess CIN is by micronucleus scoring, which is usually performed manually by counting micronuclei or abnormalities under a microscope. Here we propose to (i) create a computational approach to automatically count micronuclei and associated abnormalities in immunofluorescence images. Next, (ii) we will perform spatial omics analysis on those cell lines to create a molecular profile of CIN. Finally, (iii) we will apply the here developed computational methods to human tissue samples (connected to clinical information) to uncover potential druggable molecular targets for CIN. The spatial omics technologies and single cell analysis pipelines created by AG Schapiro combined with the image analysis and machine learning capabilities by AG Hamprecht provide a unique setup for this interdisciplinary project.

	Coordinator	Partner 1
PI	Denis Schapiro	Fred Hamprecht
Institution	Institute for Computational Biomedicine and Institute of Pathology, Heidelberg University Hospital	Heidelberg Collaboratory for Image Processing (HCI), Interdisciplinary Center for Scientific Computing (IWR) and Department of Physics and Astronomy, Heidelberg University

AIH24: Building a framework for the integrative analysis of clinical parameters and multi-omics data in cancer care

Abstract: The increasing availability of high-dimensional biomedical data creates the opportunity to optimize cancer care towards better individualized treatment, including prevention of complications after surgery. Simultaneous characterization of tumours and patient constitution may help to identify individuals at high risk of severe post-surgical complications, often excluded from prospective studies. While multi-omics data is informative on tumour aggressiveness and evolutionary plasticity, it could be combined with clinical data to improve assessment of patient fragility and prediction of post-surgical complications such as sepsis.

This pilot study will initialize a strategic partnership between the UMM and the DKFZ to integrate these data levels into a holistic approach for patient stratification. Several thousand digital health records and multi-omics datasets of cancer patients will be analysed using supervised and unsupervised machine learning techniques to identify relevant features for short-term and mid-term outcomes. The candidate will address fundamental questions including the integration of longitudinal clinical and laboratory parameters into the training of AI algorithms, the implementation of efficient transfer learning for different cancer entities and feature selection of prospective studies.

The upcoming decade will shape how AI will be integrated into clinical care, and this project is an opportunity to promote this development.

	Coordinator	Partner 1	Partner 2
PI	Feuerbach	Schneider-Lindner	Westermann
Institution	DKFZ	UMM / Medical faculty Mannheim	KITZ/DKFZ

AIH26: AI-guided design of functional RNA origami structures

Abstract: Bottom-up synthetic biology and DNA/RNA nanotechnology are two distinct frontier fields. What unites them is their rational engineering mindset, their common understanding that precise function needs precise components – with the aim to either build a cell or to repurpose nucleic acids for nanoscale construction. Here, we will explore how AI-guided evolutionary approaches can lead to a step change in the functional complexity of DNA/RNA-based nanomachines and synthetic cells alike because they allow us to explore a large design space. In particular we will probe RNA-lipid interactions with AI-accelerated multi-scale simulations. This alone will provide insights on the potential role of RNA-lipid interactions at the origins of life. Moreover the simulations yield design instructions for functional RNA origami structures, in particular (i) RNA nanopores and (ii) vesicle division inducing RNA structures. These structures will be implemented experimentally and tested in lipid vesicles as synthetic cellular compartments. We thereby envision an interdisciplinary contribution to the field of bottom-up synthetic biology as well as applicable RNA origami-based tools for nanopore sensing and as genetically encoded biophysical probes in cell biology.

	Coordinator	Partner 1
PI	Kerstin Göpfrich	Frauke Gräter
Institution	Max Planck Institute for Medical Research	HITS

AIH28: Gut microbiome profile as a diagnostic marker in eating disorders.

Abstract: The gut microbiota is essential in the regulation of appetite and body weight and has been found to be altered in eating disorders. Previous research has identified gut microbiota dysbiosis as a potential pathognomonic aspect of Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. Changes in microbiota composition and production of bioactive metabolites may contribute to the development and/or maintenance of eating disorders. In this project, we plan to longitudinally assess gut microbiota composition and function in patients with eating disorders during in-house treatment to gain a better understanding of microbiome changes associated with progression or remission of eating disorders. In line with similar investigations in obesity, where variations in the gut microbiome allow classification of individuals according to their risk of further weight gain, we aim to establish an AI-based diagnostic procedure for the classification of patients into different profiles of disease progression.

	Coordinator	Partner 1
PI	Prof. Dr. Hans-Christoph Friederich	Dr. Georg Zeller
Institution	Centre for Psychosocial Medicine Department of General Internal Medicine and Psychosomatics, University Hospital Heidelberg.	Structural and Computational Biology Unit, EMBL Heidelberg

AIHII: Surgical AI platform – a core facility fostering translational research and clinical innovation for decision support in surgical oncology.

Abstract: Our AI innovation is to provide a platform for clinical translation of data driven decision support in surgical oncology. We aim to link data from the medical data integration center at UKHD with novel surgical data science algorithms developed at the DKFZ to be used by surgeon scientists in the labs and operating rooms of the surgical department.
In particular, the requested staff scientist will maintain and further develop the Kaapana platform that has been developed at DKFZ within the NCT-DSDSO-project to meet the crucial need for a platform within the surgical department of UKHD. Firstly, the platform will be used to extract multimodal surgical data from their primary sources and integrate it into the semantic data model of the MEDIC-environment of UKHD in order to obtain semantically enriched structured data in a standardized format (FHIR, OpenEHR, ODM). Secondly, algorithms developed at DKFZ will be integrated into the real-time environment of the operating rooms within the surgical department. Finally, in order to facilitate surgical AI innovation for a larger community we will establish a core facility within the surgical department to support both, other clinician AI scientists at UKHD and basic scientist inside and outside DKFZ and UKHD.

	Coordinator	Partner 1	Partner 2
PI	Prof. Dr. Dugas	Dr. Wagner	Prof. Dr. L. Maier-Hein
Institution	Heidelberg University Hospital	Heidelberg University Hospital	DKFZ

AIHIV: AI for serological analysis of COVID-19 patients using multiplex microscopy assay

Abstract: The emergence of the novel pathogenic coronavirus SARS-CoV-2 and its rapid pandemic spread had dramatic consequences on human society across the globe. Continuous evolution of new viral variants affecting infectivity, disease severity and immune evasion has challenged the society's efforts to contain the virus. Mutations in the viral spike protein are of special interest, as all currently licensed vaccines against SARS-CoV-2 are based on the immune response to the spike. Early in the pandemic, we have established a microscopy-based assay which allowed for studies of population immunity to the original strain of the virus. We will now extend this work to simultaneously measure the levels of patient serum antibodies against different spike mutants and determine the patient’s susceptibility to emerging variants. The assay will also detect auto-recognizing antibodies as major determinants of Long COVID. The approach relies heavily on the analysis of very large microscopy images. The aim of this project is to develop an image analysis pipeline based on state-of-the-art AI-based methods for segmentation and classification of complex cellular staining patterns. The pipeline needs to be implemented as a flexible solution to be employed in other clinically relevant projects within the Center for Integrative Infectious Disease Research and beyond.

	Coordinator	Partner 1	Partner 2
PI	Vibor Laketa	Anna Kreshuk	Constantin Pape
Institution	University Hospital Heidelberg	EMBL	University of Göttingen

AIHV: Generation of multiplex data and integration with electronic medical records for dimension reduction towards prediction of complications in critical illness

Abstract: The immune response to severe injury (trauma, infection, cancer…) and its treatment critically determines the risk of acute and difficult-to-predict clinical complications. Among these, sepsis and organ dysfunction predominate. New prognostic and diagnostic classifiers are urgently sought to improve patient outcomes. Electronic medical records (EMRs) in the intensive care unit (ICU) capture clinical courses at high resolution. Their integration with large-scale longitudinal immunophenotyping has potential to significantly advance classifier discovery by AI. To this end, the staff scientist will direct medium-throughput multiplex analyses of blood markers of immunity in 1100 available blood samples collected from 100 ICU patients and leverage expertise in processing EMR data at UMM and in application of AI for nonlinear dimensionality-reduction at DKFZ. Multiplex data will be integrated with EMR data from same patients and time points and analysed by uniform manifold approximation and projection (UMAP). Ground truth labels on sepsis and organ dysfunction will be projected onto resulting UMAP embeddings. We seek clusters associated with the onset of clinical complications and afferent trajectories of patient time for analyses of the clinical features/blood markers that essentially define them. We expect these features/markers to inform future patient stratification strategies and to represent potential classifiers for further investigations.

	Coordinator	Partner 1
PI	Lindner	Feuerbach
Institution	UMM / Medical Faculty Mannheim	DKFZ

First Call Funded Projects

AIH01: Anonymous Synthesizer for Health Data (ASyH)

Christoph Dietrich, Heidelberg University
Martin Lablans, DKFZ

Motivation: Our ASyH proposal aims to remove barriers between rapid developments in the machine learning community and the inert world of hospital information management concepts and systems. On one hand, any AI-based machine learning approach requires adequate data. On the other hand, all data originating in the health sector are rightfully protected from uncontrolled use and access.
Approach: For this specific situation in the health community, we propose to generate suitable data sets through AI-based anonymization as well as data synthetization methods. We take up the challenge of generating non-identifiable data according to GDPR regulations. To this end, we use available data in the university hospitals of Mannheim and Heidelberg to build on our own and use existing AI models for data de-identification and data synthesis. These models preserve the underlying statistical properties of the original data. Another important aspect in ML is data augmentation as sufficient data is oftentimes scarce.
Expected outcome: Our proposal has a clear service-oriented character as it caters AI-ready data from local hospitals to the machine learning community. Herein, we use our own and

existing software solutions and local infrastructure (including MII DICs). We will also evaluate a very relevant question: To what extent are data generated at both partner sites actually comparable?

AIH03: Digital ~~Twin~~ Cousins Generator for Radiotherapy Research

Oliver Jäkel, DKFZ
Kristina Giske, DKFZ
Jens Fleckenstein, UMM

With AI on the rise in radiotherapy, our research community is facing an increasing challenge to source enough patient scans for scrutinizing deep learning models for segmentation, registration, image synthesis, and dose prediction along adaptive treatment courses. Specifically, pilot-phase projects suffer from delays due to ethics vote application, volunteer recruitment, and missing secure transfer channels from clinical systems to research teams. Sharing these medical data is even more challenging. Open access datasets seldom provide all necessary scan types to investigate adaptive radiotherapy research questions. Especially in radiotherapy, scans from multiple modalities acquired over a month-long treatment course are needed to assess accumulated dosimetric effects. The aim of the proposed project is to establish a hybrid - AI and rule-based - computational infrastructure able to generate artificial anatomies mimicking radiotherapy patients. GAN-like random anatomy generators shall be combined with rule-based biomechanical motion models and imaging simulators to create representative artificial patient cohorts for development of technical AI prototypes in the radiotherapy community. With this, also research teams around the world without access to clinical databases could progress scientific insight by publishing proposed developments alongside the utilized artificial data or by benchmarking their proposed solutions to earlier approaches on the same artificial data cohorts.

AIH07: Machine learning-assisted detection of microsatellite instability

Matthias Kloor, UKHD
Fruzsina Molnár-Gábor, Heidelberg University

Microsatellite instability (MSI) is one of the two major types of genomic instability drivi ng
human cancers. Cancers with MSI develop because of a functional defect in their DNA mismatch repair system and occur in the colorectum (15% of colorectal cancers), the endometrium (25-30%) and a broad variety of other malignancies. The clinical impact of MSI is wide-ranging: MSI tumor patients (1) show limited benefit from standard chemotherapy, (2) have a better prognosis, and (3) are generally highly responsive to immunotherapy. Therefore, immune checkpoint blockade has been approved by the FDA for all MSI cancers irrespective of tumor origin, representing the first basket admission entirely based on a molecular marker. Despite the high and rapidly increasing significance of MSI testing, the high costs, technical hurdles and complexity of the analysis hampers implementation of MSI reflex testing in routine

diagnostic procedures. Recent independent studies have demonstrated that prediction of the MSI phenotype by machine learning-assisted classification of histopathology images is highly promising. The present project intends (1) to establish the data life cycle for a multi-center initiative compliant with data protection law to optimize machine learning-assisted prediction of MSI and (2) to prepare roll-out of AI classification algorithms to clinical application in diagnostics.

AIH11: Inferring dynamics of clinically-relevant lipid markers of NASH and their master regulators from single-cell data

Theodore Alexandrov, EMBL
Julio Saez-Rodriguez, Heidelberg University/UKHD

Non-alcoholic steatohepatitis (NASH) is an inflammatory stage of the non-alcoholic fatty liver disease (NAFLD) and is a key factor of liver fibrosis, irreversible damage, and cancer. Novel molecular analyses of NASH are critically needed since no drugs are currently approved. Lipids were shown to be clinically-relevant markers discriminating healthy liver from NAFLD and NASH. However, interpretation of these markers is challenging in particular due to the limited understanding of their dynamics along the disease progression. Here, we will address this challenge by developing and applying new computational strategies for single-cell lipidomics. We will use these to investigate the in vitro model of NASH, recently obtained by the host team together with the Heikenwalder group at DKFZ. First, we will perform network analysis of lipids detected in the single-cell data and create a hypergraph linking co-detected lipids with the regulating enzymes. Next, we will infer dynamics of the clinically-known lipid markers of NASHin the single-cell data. Finally, we will find clusters of lipids co-regulated with the markers along the pseudo-time trajectory and infer dynamics of their master regulatory enzymes. Overall, this project will create a novel methodology with a potential to elucidate mechanisms of the reprogramming of lipid metabolism upon NASH and to yield novel targets for NASH therapies.

AIH12: Predicting tipping points toward sepsis in ICU patients using deep dynamical systems reconstruction

Daniel Durstewitz, ZI
Verena Schneider-Lindner, UMM
Holger Lindner, UMM

Sepsis is the leading cause of death in the intensive care unit (ICU). Empirically, sepsis requires rapid and specific therapy, but its bedside diagnosis still largely relies on patient assessment by clinical experts. Building on a large ground truth database of ICU patients that we have been collecting since 2016, we aim to develop novel AI approaches based on interpretable recurrent neural networks designed for nonlinear dynamical systems (DS) reconstruction. These methods yield subject-specific DS models which can be mathematically analyzed using DS theory tools, and can be simulated under different scenarios. Such models will hence not only enable onsite running forward predictions of individual patient trajectories, but will also allow for advanced identification of future tipping points, crucial transitions

(bifurcations) in the underlying disease dynamics toward sepsis. Moreover, through their interpretability from a DS perspective, we will gain mechanistic insight into the pathogenic processes that could be harvested for better tailored clinical interventions. It is therefore expected that the development and validation of this approach will have major clinical implications and could be integrated into clinical decision support systems. The planned studies crucially rely on the complementary medical-statistical and AI & DS expertise of the collaborating groups.

AIH20: Computational integration of cellular circuits and immune cell repertoires in health and disease

Julio Saez-Rodriguez, Heidelberg University / UKHD
Hedda Wardemann, DKFZ
Lucas Schirmer, Heidelberg University / UMM

Understanding the functioning and regulation of the immune system is key to treating a range of conditions from autoimmune diseases to cancer, as well as improving vaccinations. Recent advances in single-cell technologies provide molecular data with unprecedented detail, including with spatial or time resolution, that is information on where individual cells are placed in a tissue or when they develop over time, respectively. This project aims to link two currently decoupled areas in computational biology, analysis of immune repertoire and characterization of molecular circuits, and apply them to single-cell resolved data to study the effect of immune repertoires on intra-and inter-cellular signaling. Using as illustrative cases own spatially-resolved data sets obtained in the context of chronic inflammation in tissue of patients and time-resolved data following vaccine responses, we expect to improve our understanding of the deregulation of the immune system, paving the way for improved treatments of a variety of conditions.

AIH21: Integration of Thermal Proteome Profiling and phospho-proteomics within network models to dissect disease mechanisms and drugs' mode of action

Mikhail Savitski, EMBL
Julio Saez-Rodriguez, Heidelberg University/UKHD

Understanding the mode of action of drugs as well as the molecular underpinnings of disease states is essential for developing new therapeutic strategies. Powerful proteomics technologies such as phosphoproteomics as well as the recently developed thermal proteome profiling (TPP) hold the potential for deciphering and understanding cellular processes that are modulated by drug treatment and altered in disease. Currently, there are no adequate tools for comprehensively extracting the relevant information from TPP experiments alone or in combination with phosphoproteomics. We propose to leverage the expertise present in our labs and to develop powerful new tools that will be capable of mining these datasets thus elucidating drug mode of action, as well as assessing cellular changes specific to cell lines that represent different disease states. We are convinced that this computational framework will become instrumental in multiple efforts within the Alliance. All tools developed in the

context of this project will be released as free, easy-to-use open software and become available to the scientific community.

AIH23: Detection and validation of somatic mosaicism of variants in amyotrophic lateral sclerosis

Lena Voith von Voithenberg, DKFZ
Benedikt Brors, DKFZ
Rosanna Parlato & Jochen Weishaupt, UMM

Amyotrophic lateral sclerosis (ALS) is a fatal degenerative disease of the nervous system. Only few percent of ALS cases are familial with a known underlying germline mutation, whereas 90% of the cases occur spontaneously. In this project, we will investigate the hypothesis that somatic mutations in few cells (somatic mosaicism) play a role in the development of sporadic ALS. To this end, we will analyse somatic variants by targeted sequencing in a panel of known risk genes in post-mortem tissue of the motor cortex and spinal cord of ALS patients. To determine whether somatic mosaicism of variants exists, we will differentiate between low frequency variants and sequencing artefacts by using error correction based on unique molecular identifiers. We will further establish and implement combinations of AI-supported variant calling and filtering strategies with differing feature selection strategies and will validate candidate genes by using amplicon sequencing and mutation-specific in situ hybridization approaches.

AIH28: Explainable Deep Neural Network-based Coronary Artery Disease Characterization via Photon-Counting Computed Tomography

Sandy Engelhardt, UKHD
Stefan Schönberg, UMM

Photon counting Computed Tomography (CT) is a major technological advancement in the field of radiology. It allows for significantly better resolved images by reduced radiation at the same time. While this is an already existing development, especially for imaging small scale structures like coronary plaque, tissue characterization might become feasible with other contrast agents at high resolution. This will have a disruptive impact in the field of cardiovascular diseases, where 3D image interpretation is mostly hampered by high MRI slice thicknesses (e.g. short axis acquisitions of 8 mm voxel length). As part of the PC3 consortium (www.pc3.eu) UMM has one of the first photon counting CT machines in Germany installed.
In this proposal, based on our previous work and available infrastructure, we form a novel collaboration and aim to address two issues: We aim to develop novel deep learning based methods for plaque characterization and assessment of severity of stenosis. This combined With the concept of explainability and quantitative and qualitative quality control, as supervised learning techniques require highly standardized annotations and rigorous testing. Furthermore, the novel tissue resolving capabilities of gadolinium-enhanced CT will be investigated and correlated withMRI to assess fibrosis and myocardial scar formation.

AIH31: PepAISim: Combining AI and molecular simulation for anticancer peptide and peptidomimetic design

Rebecca Wade, Heidelberg University
Elke Burgermeister, UMM

The goal of this project is to leverage significant recent advances in AI methods for the design and mechanistic characterization of peptides and peptidomimetics for therapeutic purposes with a focus on cancer. As a case study, we will focus on the potential for treating gastrointestinal cancers with peptides that mimic the effects of the tumor suppressor “myotubularin-related protein 7” (MTMR7). Computational approaches, combining machine learning with molecular simulation, will be used to investigate the protein-protein interactions of MTMR7, design peptides, and predict their molecular mechanisms. State-of-the-art methods employing deep learning and invertible neural networks that are being developed in Heidelberg and elsewhere will be applied. Computations will guide experiments to functionally characterize the interaction candidates and the experiments will inform further computations in a tight, iterative process. Peptides will be assessed for anti-tumor efficacy in patient-derived tumor organoid models and their molecular mechanisms of action will be explored in human gastrointestinal cancer cells using in vitro protein interaction assays. We expect this project to advance AI methods for drug discovery and their practical application to the discovery of therapeutic peptides, and to lead to the discovery of specific molecular mechanisms and therapeutics against gastrointestinal cancers.

AIH36: Model-based Artificial Intelligence in Surgical Data Science

Lena Maier-Hein, DKFZ
Beat Müller, UKHD

Death within 30 days after surgery is the third-leading cause of death worldwide, with research suggesting that a large proportion of these deaths are due to surgical error. The newly established domain of Surgical Data Science (SDS) aims to improve the quality and outcome of interventional healthcare through the capturing, organizing, analyzing and modeling of data. However, clinical translation of data science methods proves difficult.
A large international consortium of experts recently attributed the lack of clinical success stories to the lack of large annotated databases. Data sparsity can thus be regarded as the main roadblock in the field of SDS. Previous approaches have addressed this roadblock with a diverse set of methods including crowdsourcing, self-supervised learning, active learning and synthetic data generation. In this project, we investigate an entirely complementary approach based on integrating existing medical knowledge in neural network-based analysis. Specifically, we propose the integration of prior knowledge encoded in ontologies in a Graph Neural Network (GNN) based-approach to surgical decision support. The method will be validated based on a data set from the TIGER study, an international effort to include 5000 patients with esophageal cancer, and two in-house data sets on esophageal cancer and intrahepatic Cholangioma.

Funded Clinician Scientist Projects Second Call

Xeno-Learning for Spectral Image Interpretation Surgery

Death within 30 days after surgery has been found to be the third-leading cause of death worldwide[1]. One of the major challenges faced by the surgeons is the visual discrimination and evaluation of tissues. To overcome the limitations of visual perception, hyperspectral imaging (HSI) might present a solution. While conventional medical cameras are limited by "imitating" the human eye; hyperspectral cameras remove this arbitrary restriction. Instead, they capture multiple bands of light that decode relevant information on tissue type and perfusion.

The bottleneck related to converting the potential of this novel imaging technique into patient benefit is related to the lack of large annotated human data sets. Consequently, this project aims to address this issue based on a new concept that we refer to as *Xeno-Learning*. The core idea is to address the shortage of data by transferring knowledge from one species (specifically porcine) to another (here: human). The core methodological data science challenge is to develop a data representation that enables the generalization not only to new individuals but also to other species. To this end, we can leverage a huge data set consisting of HSI data comprising several thousand images of animals and humans.

	Coordinator	Partner 1
PI	PD Dr. Felix Nickel, MME	Prof. Dr.-Ing. Lena Maier-Hein
Institution	Department of General, Visceral and Transplantation Surgery Heidelberg University Hospital Im Neuenheimer Feld 420 69120 Heidelberg	Computer Assisted Medical Interventions German Cancer Research Center (DKFZ) Im Neuenheimer Feld 223 69120 Heidelberg

Deep-learning based prediction of clinical outcome after endovascular therapy in acute ischemic stroke using topographic information of CT perfusion maps

Stroke is a leading cause of mortality and disability worldwide, with a global lifetime risk of approximately 25%. A major factor determining where patient might benefit from interventional recanalization is the ischemic infarction that may already present at the timepoint of treatment selection. Perfusion imaging is well suited to delineate permanently infarcted areas from tissue-at-risk, which can possibly be saved with successful treatment. However, this approach only accounts for the volume of the tissue-and-risk, but not for the function of the damaged or endangered tissue. In our project, we aim to overcome this limitation by applying a deep-learning based approach, that will not only consider the volume of ischemic tissue and tissue-at-risk, but also the topographic distribution, the severity of ischemia and the specific symptoms of patients who have been successfully treated with an endovascular technique in our institution. The findings of this project will be used to improve selection of patients who would benefit from endovascular therapy for acute ischemic stroke.

	Coordinator	Partner 1
PI	PD Dr. Ulf Neuberger	Prof. Dr. David Bonekamp
Institution	University Hospital Heidelberg, Department of Neuroradiology	DKFZ

AI-based risk prediction and diagnosis for heart failure and cardiomyopathy patients

Cardiovascular diseases are one of the leading causes of death in industrialized nations. In Germany, heart failure (HF) is also the most common reason for hospitalization in adults. This cardiovascular pandemic not only burdens the patients and their families, but also strains the resources of the health system. In view of the increasingly aging population, this burden will continue to increase in the future. We propose an AI-based risk prediction for heart failure and cardiomyopathy patients to address this problem with a scalable approach. AI can serve cardiologists through a clinical decision support system (CDSS) and even enhance diagnosis and risk prediction by evaluating complex patterns. In this project, we aim to combine clinical data from multimodal sources, routinely acquired in the current standard patient workup in the clinics, to create a comprehensive AI model for everyday clinical practice in cardiology.

	Coordinator	Partner 1
PI	Prof. Dr. med. Benjamin Meder	Prof. Dr. Klaus Maier-Hein
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Robust Deep Learning for CT-based Pedicle Screw Planning in Navigated Spinal Instrumentation

Navigation and robotic systems have been increasingly applied in spine surgery but dedicated screw planning is a time-consuming prerequisite to tap the full potential of these guidance techniques. We recently described a deep-learning (DL)-based approach to automatic lumbar screw planning which produced robust results that were non-inferior to manual planning by spine experts holding great potential to improve time-efficacy in surgical workflows when converted into fully equipped surgical planning tool. Our goal is to extend the applicability of the DL-approach to thoracic spine segments requiring additional training of the algorithm and refinement of the model as thoracic vertebrae differ critically in size and pedicular anatomy from previously leveraged lumbar vertebras. An iterative learning approach is sought enable a constant improvement of the algorithm incorporating expert-based corrections of screw suggestions prior to implantation during surgery. Lastly, maximization of screw dimensions

and consideration of local bone quality for adjustment of screw trajectories according to maximized screw fastening strength can contribute to a reduction of implant failures due to poor bone quality and osteoporosis in a constantly aging patient population requiring spine surgery nowadays.

	Coordinator	Partner 1
PI	PD Dr. med. Moritz Scherer	Prof. Klaus Maier-Hein
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Funded Clinician Scientist Projects First Call

Creation of a standard dataset for laparoscopic Roux-en-Y gastric bypass procedures

PI: Prof. Dr. Christoph Reissfelder /Prof. Dr. Jürgen Hesser, UMM
Co-PI: Prof. Dr. Lena Maier-Hein, DKFZ

The application of data science in surgery has been far less successful than in other fields of science. An international consortium of experts has identified missing datasets as the major hurdle in enabling Surgical Data Science (SDS)1. To create high-quality datasets, data needs to be collected according to strict acquisition protocols and annotated by trained personnel following strict annotation protocols. This requires significant effort and the access to expert knowledge represents a major bottleneck. By creating, curating and publishing a dataset for laparoscopic Roux-en-Y gastric bypass, an operation that requires performing intestinal anastomosis, we aim to facilitate the use of SDS methods in training and during operations. The collected data will be two-fold, consisting of (1) data deriving from training sessions and (2) real-life procedures in operating rooms (OR). Care will be taken to systematically capture and annotate perioperative data (Surgical team, skill level, patient data from the Electronic Health Record (EHR)), video clips of surgeons using standardized protocols that will be published together with the dataset. Modern tools will be used for annotation2, and algorithm specific metadata (Implementation, Version, Uncertainty, Training data used, etc.) will be collected and included in the dataset.

Machine Learning assisted early diagnosis of sepsis based on microcirculatory alterations in ICU patients

PI: Univ. Prof. Dr. med. Markus A. Weigand, UKHD
Co-PI: Prof. Dr.-Ing. Lena Maier-Hein, DKFZ
Co-PI: Prof. Dr. rer. nat. Annette Kopp-Schneider, DKFZ

Sepsis is a life-threatening systemic response to infection leading to organ failure, with an associated 8% increase in mortality per hour of delay of therapy. Microcirculatory alterations

are a fundamental component of septic organ failure. Currently, no objective microcirculatory monitoring is established in the clinical routine of the intensive care unit (ICU). Hyperspectral imaging (HSI) is an innovative technique which allows for fast and non-invasive microcirculatory measurements, without risk or relevant burden to the patient. In a first pilot study, HSI of skin microcirculation has shown potential for sepsis detection. However, to date, no data from larger cohorts of patients with microcirculatory abnormalities measured with HSI is available.
As the worldwide first ICU, we will establish microcirculatory HSI measurements as routine monitoring. Furthermore, we aim to implement a registry of all ICU patients with subsequent development and validation of a machine learning algorithm for automated sepsis diagnosis based on the acquired data. We expect machine learning assisted evaluation of HSI to open up new opportunities in early diagnosis and initiation of sepsis therapy, thus improving survival.

In All Beginnings Dwells a Magic Force: How Deep Learning Can Transform State of the Art Head and Neck Cancer Radiation Therapy

PI: Prof. Dr. S. Adeberg, UKHD
Co-PI: Prof. Dr. K. Maier-Hein, DKFZ

Due to technical advances, the outcome has improved significantly in head and neck cancer radiation therapy. But local tumor recurrence occurs often and the quality of life of patients is impaired by treatment toxicities. Moreover, treatment planning remains complex and time-consuming.
Thus, the two main research aims of the project are (I) to reduce treatment planning time and target volume variability using autosegmentation to create consistent, high-quality target volumes and (II) to determine tumor control probabilities to enhance outcome prediction and clinical decision making.
The work program will be based on training and cross-validation data sets derived from retrospective cohorts that will be further evaluated as part of prospective clinical trials. All data will be made available in the radiation oncology and data science communities according to common open science principles.
By reducing the time required for treatment planning, the efficiency and flexibility of current clinical workflows can be transformed, thereby saving costs and improving consistency and treatment quality. By modeling of tumor control and normal tissue complication probabilities, patient selection, treatment plan optimization and personalized radiation treatments will be enhanced. Thereby, the current developments can improve the oncological outcome and reduce treatment toxicities for the benefit of the patients.

Abbreviations:
DKFZ: German Cancer Research Center, Heidelberg; EMBL: European Molecular Biology, Heidelberg Laboratory; UKHD: Universitätsklinikum Heidelberg; UMM: Universitätsmedizin Mannheim; ZI: Central Institute for Mental Health, Mannheim