

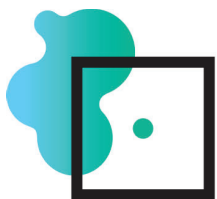
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Poster Abstracts



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Spatial multiomics analysis demonstrate lipid metabolism alterations in prostate cancer tissue

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Key-words: multiomics, prostate patient tissue, spatial transcriptomics, mass spectrometry imaging

Altered lipid levels and metabolism is commonly observed during prostate cancer (PCa) progression. However, analysis of PCa tissue can be challenging as it typically displays a heterogeneous composition. *Ex vivo* molecular imaging therefore pose a significant advantage to bulk analysis by conserving the spatial location of molecules. Furthermore, combining multiple -omics technologies together, such as metabolomics, lipidomics, proteomics and transcriptomics, is powerful approach to model the mechanism of lipid metabolism in human prostate tissue. We aimed to map lipid metabolism in PCa through spatial multiomics.

Serial fresh frozen tissue sections (10 μ m, \varnothing 3mm) from 32 samples, arising from PCa 8 patients, were analyzed through spatial transcriptomics (ST) for mRNA gene expression (GE) and mass spectrometry imaging (MSI) for metabolites and lipids (phospholipids and sterols). Approximately 2500 GEs and 73 metabolites and lipids were detected and identified. The same analyzed sections were stained with H&E and annotated as either cancer (grade group (GG) 1-5), normal glands, stroma or lymphocytes. For this study, normal gland was compared to cancer glands.

Our spatial multiomics approach revealed several lipid metabolic pathways to be altered in PCa both the GE and metabolic level. The GE of fatty acid synthesis enzymes, such as ACACA and FASN were elevated in cancer compared to normal glands. This was further supported by higher levels of several classes of phospholipids, as well as higher levels of phospholipid building block metabolites. In contrast, all detected genes related to cholesterol synthesis were downregulated in cancer. This was despite higher cholesterol levels in cancer samples. CrAT, an enzyme involved in β -oxidation (production of energy from fatty acids), also had higher levels in cancer areas. This finding, which was further supported by elevated carnitine levels (a crucial metabolite for β -oxidation), may demonstrate higher use of lipids for energy production in PCa.

Seeing the whole molecular picture is crucial for understanding lipid metabolism in PCa. Here, spatial detection of mRNA, metabolites and lipids already reveal valuable molecular insights, of which several would have been masked with bulk analysis.

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Modelling H3K27M-mutant diffuse midline glioma in zebrafish (zDMG)

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Diffuse midline glioma (DMG) is a devastating pediatric-type glioma. Although, DMG patients face a very poor median overall survival of just 9-11 months, currently available chemotherapy is ineffective in treating these patients. Approximately 85% of DMG contains the somatic gain-of-function p.K27M mutation in the H3 histone genes. Genomic analyses revealed intra- and intra-tumour heterogeneity, which is however insufficient to explain clinical outcomes. So far, the cell of origin (COO) of H3K27M-mutant DMGs is poorly understood and not considered in precision medicine trials. This project aims to use a lineage tracing system to establish and characterize genetically engineered DMG zebrafish models (zDMGs).

Impact of charge in disordered peptide tails on PAMAM- DNA binding

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Biocompatible Poly(amidoamine) (PAMAM) dendrimers are positively charged and interact nonspecifically with DNA and other nucleic acids. This makes them promising candidates for nucleic acid delivery [1], as they both have the ability to condense and thus decrease the size of the nucleic acids and protect them from enzymatic degradation [2].

However, due to the high charge as the generation of dendrimers increases, their biocompatibility decreases. Adding polyethylene glycol or other polymers might decrease cytotoxicity, however it also decreases the ability of PAMAM to condense DNA.

In this work, we investigated the conjugation of PAMAM dendrimers with peptide tails, in order to increase their biocompatibility and potential as delivery vectors for nucleic acids. Using both Monte Carlo simulations and experimental techniques such as gel electrophoresis and dye exclusion assays, we found an increase of DNA compaction with PAMAM conjugated to positively charged peptide tails compared to PAMAM alone.

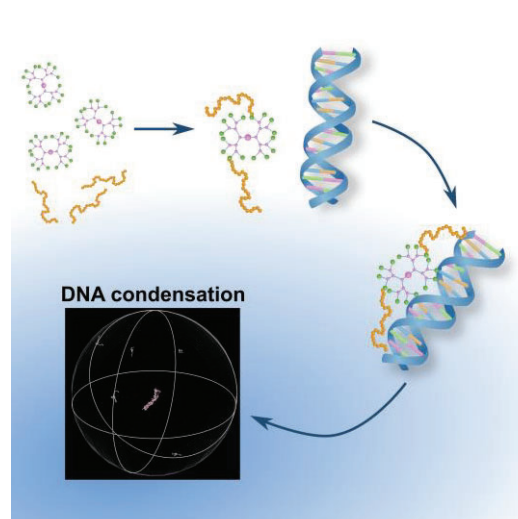


Figure 1. PAMAM dendrimers conjugated to peptide tails can increase DNA condensation.

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AI IN PROSTATE CANCER DIAGNOSTICS

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Diagnostic precision is a major challenge in the field of prostate cancer (PCa), and scientists are currently developing artificial intelligence (AI) systems to improve today's diagnostic systems. The venture point for our study is that diagnostic methods for PCa are complex and contested, and can potentially lead to overdiagnosis and overtreatment. MRI is applied increasingly in the diagnostic process, due to its high level of precision in identifying clinically relevant tumors. We are part of a research project that aims to further improve diagnostic precision and reduce radiologists' workload, by creating AI systems in image analysis. However, implementing AI in PCa diagnostics poses several ethical, societal, and scientific issues for a range of different actors. This part of the research project is a qualitative study investigating these matters. Our research question is: How is a new AI system in MRI technology for PCa diagnostics received, understood, and developed, by scientists, medical professionals and lay people? Our main methods are qualitative focus group interviews, semi-structured interviews, and participant observation.

Automated Lymphoma Cancer Detection and Ann-Arbor Staging Using Deep Learning with 18F-FDG PET/MR Images

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Abstract

Background: Lymphoma cancer develops in the lymphatic system and can affect organs throughout the body. Lymphoma cancer is assigned an anatomic stage using the Ann Arbor system which relies on segmentation and localization of affected lymph nodes.

Objective: Widespread lymphoma makes manual segmentation of metastatic lymph nodes a tedious task. We aim to develop a method for automated segmentation and localization of lymph nodes.

Methods: We present a deep learning framework for automated detection and Ann-Arbor based staging of Lymphoma patients using FDG PET/MR in two phases. In the first phase, we trained a U-Net model using PET/MR images in lymphoma patients to automatically segment the metastatic lymph nodes. The second phase is training the nnU-Net model for automated multi-organ segmentation using PET/MR images along with manual segmentations for lesion localization. As lymphoma Ann-Arbor Staging is based on lymph nodes localization above or below the diaphragm, we propose using the location of nearby organs as prior information to guide the lymphoma stage classification. Our model is based on nnU-Net, a validated model for multi-organ segmentation using CT images. We used the transfer learning technique and initially trained our model on the dataset provided by nnU-Net developers. Furthermore, we used in-house dataset comprised of PET and MR images of 20 lymphoma patients, with manual segmentations of multiple anatomical landmarks (lungs, heart, liver, spleen, urinary bladder, pelvic bone, abdomen, kidneys, teeth, cervical vertebrae, aorta, mediastinum) validated by a radiologist. Firstly, we trained nnU-Net with no change to provide a baseline for further modifications using MR images including T1, DWI, and T2W images. Secondly, we ran the nnU-Net with some modifications. For our training model, we used binary cross-entropy instead of using cross-entropy loss which optimized each of the regions independently. In addition to the nnU-Net original data-augmentation methods, we increased scaling range, rotation probability, and brightness augmentation for enhanced data-augmentation. We also increased the batch size from 2 to 3 for improving model accuracy, but due to the relatively smaller dataset, this resulted in overfitting. All experiments were run as nine-fold cross-validation. Resampling of PET, MRI (T1, DWI, T2W), predicted lesion segmentations, and predicted organ segmentations was done using affine transformation, nearest neighbor, and B-spline interpolation. The distance of each lesion was calculated from organs segmentation to estimate the lymph nodes' location with respect to the diaphragm. We clustered the lymph nodes which have similar distances from the main organs (heart, lung, liver, and spleen). The lesion clusters corresponding to the organs located above and below the diaphragm were counted for predicting the lymphoma cancer stage.

Results: We carried out experiments for 10 organs segmentation, and compared results with the ground-truth, leading to promising results. We aimed to investigate the accuracy of the computer-aided segmentation using Dice Similarity Coefficient (DSC) and Intersection over Union (IoU) parameter for the evaluation of 12 organs delineation in the testing cohort. nnU-Net achieved 0.5145 mean DSCs and IoU 0.3162 whereas nnU-Net model with modifications achieved 0.8313 mean DSCs and IoU of 0.659. Owing to the small cohort, the low IoU value of 0.659 was observed in our experiment. These preliminary results highlight the potential of nnU-Net for automated multi-organ segmentation. The lymphoma cancer stage predicted by the automated Ann-Arbor staging method was compared with the cancer stage diagnosed by the clinician. Our proposed automated Ann-Arbor staging method yielded an accuracy of 0.6335, sensitivity of 0.6105, and F1 score of 0.511 when compared with the stage diagnosed by the physician.

Conclusion: Using a large dataset with a wide range of variations in terms of lymph nodes location, shape or contrast uptake will be used for further evaluation of our fully automated system for Ann-Arbor staging.

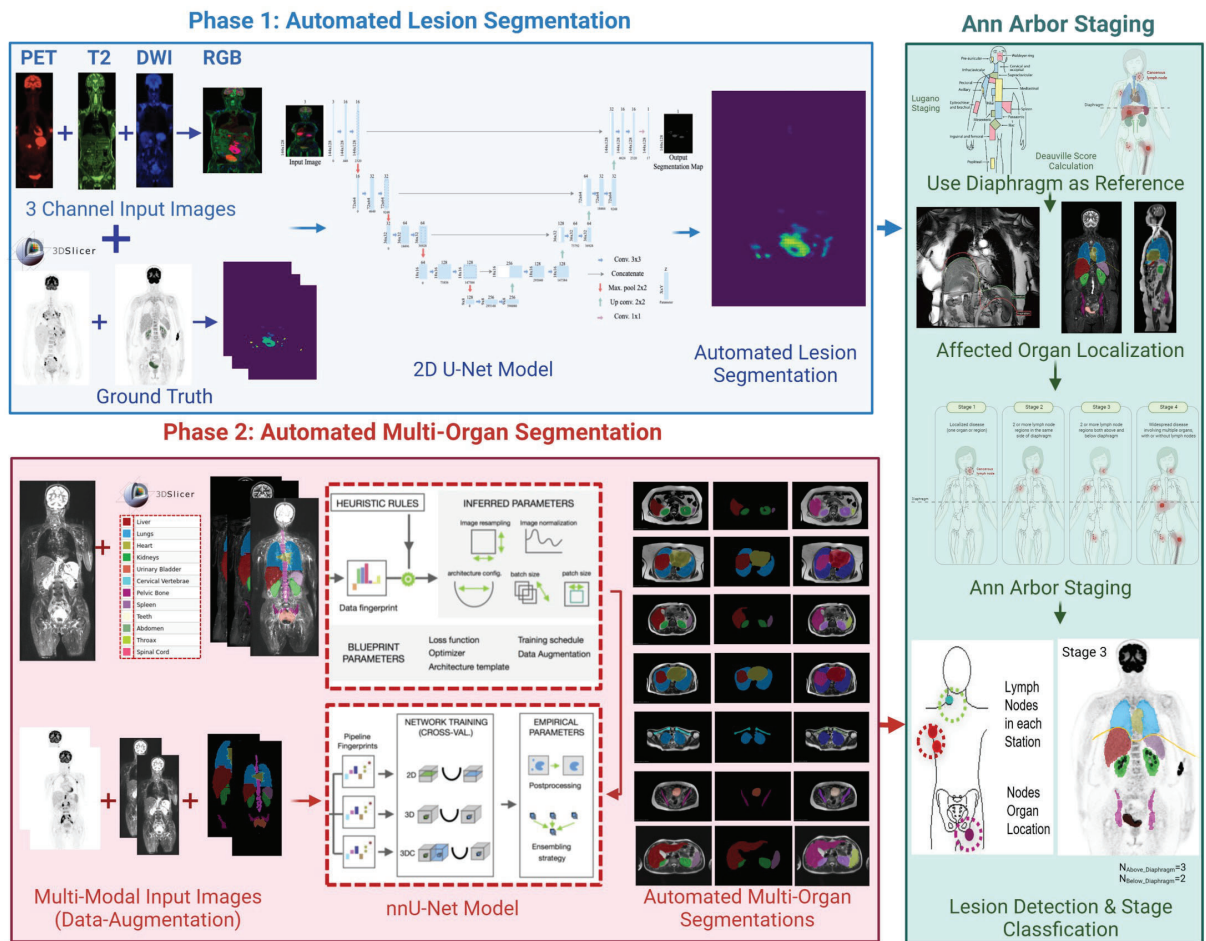


Figure 1: Proposed end-to-end framework for automated lymphoma detection and staging pipeline. Our two-phase model relies on a U-Net architecture for automated lesion segmentation and nnU-Net model for automated organ segmentation. Final output produces lymph nodes segmentation, location above or below the diaphragm and the Ann-Arbor based lymphoma stage classification.

Non-invasive technique of assessing the stiffness of the carotid artery

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Key words: model validation, FSI, cardiovascular biomechanics

Abstract

Stiffening of arteries is associated with various diseases and aging, but, despite its acknowledged value as a biomarker, a gold standard for assessment of local arterial stiffness does not yet exist. Stiffened vasculature is less able to expand as the heart ejects fluid into the arteries, which results in steep and amplified forward pressure waves that penetrate into smaller vascular beds and promote damage to organs such as the kidneys and brain. Cardiovascular diseases can lead to strong spatial variations of material properties in the arteries' walls. Therefore, local properties of an artery's wall are of interest since they give a closer insight into the current status of an individual's cardiovascular system. The goal of the ENTHRAL project is to develop an in vivo technique for estimating the local stiffness of arteries based on inverse modelling. To develop and validate this approach, we created experimental rig with a phantom artery to generate data for development and validation of a 1D and 3D Fluid-Structure Interaction models which will be employed in an inverse solver. Model input uncertainties are introduced to the numerical model, therefore it is necessary to quantify the model output variability (Uncertainty Quantification, UQ). The contribution of each parameter's uncertainty to the model's total variance is quantified through Sensitivity Analysis (SA). The results of the UQ and SA will be used to determine the reliability of the developed numerical models and to improve the experimental set-up and the inverse solver.

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CellFit: T cells fit to fight cancer

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The use of T lymphocytes in adoptive cell therapy (ACT) shows great promise for treatment of cancers otherwise incurable. However, one of the largest challenges faced in cell-based cancer therapy is to provide an efficient and scalable production. The use of “living drugs” leads to the development of promising therapy but requires precise logistics at all stages of cell life: development, manufacturing, transport and finally the infusion to the patient.

Presently, only five T-cell products have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for clinical use. Whilst the main focus of development has been on finding tumour targets and improving the genetic modifications of the immune cells in ACT, less effort has been made to efficiently produce the optimal subset of immune cells, which ideally is more **homogenous** and **stem-cell like**, for treatment. Indeed, it is now clear that the **quality, efficacy, and longevity** of T-cell immunity depend on the differentiation of naïve T cells (T_N) into phenotypically distinct subsets with specific roles in protective immunity. These include memory stem-like (T_{SCM}), central memory (T_{CM}), effector memory (T_{EM}), and highly differentiated effector (T_E) T cells. Less differentiated cells like T_{CM} and T_{SCM} were shown to respond more persistently against cancer cells^{1,2}. Now, the present *ex vivo* T-cell manufacturing is very different from physiological T-cell expansions occurring *in vivo* when T cells encounter antigen and does not generate the T-cell subsets that provide long-term therapeutic efficacy in solid cancers. To realise broader clinical applications for efficacious ACT and enhance the current therapeutic approach, the immunotherapy field has a great need to further improve therapeutic T-cell manufacturing methods.

With the CellFit project, we aim to define optimal growth conditions for improved manufacturing of adapted therapeutic T cells required for solid tumour treatment. The T-cell culture methods will be translated from manual to robotic set-ups where all pipetting, cell culturing and assay read-outs will be performed in 96-well plate formats with robots coupled to incubators, spectrophotometer and high-content confocal microscope. Moreover, we will test a panel of phenotypic markers using state-of-the-art technologies such as mass cytometry (CyTOF) and cellular metabolism (Seahorse analysis) to be able to compare different culture conditions and characterise the heterogeneity of the T-cell population. Then, data acquired by these high-throughput systems will be analysed with a custom pipeline especially designed for this project and including various modern computational cytometry techniques. We will present the pipeline of the project to establish an optimal T cell product and a high throughput screening platform for cellular therapies.

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Mechanical Characterization and in-depth Collagen Structure Quantification of Human Degenerative Mitral Valve Leaflets

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Introduction

Mitral valve ensures a unidirectional blood flow from the left atrium to the left ventricle. Mitral regurgitation (MR), with a prevalence of more than 0.4% in Europe, is a common valvular heart disease with frequent complications. The main cause of primary MR is the degenerative mitral valve (DMV). This study explores the material and microstructure characterization of DMV. This material model can improve numerical simulation used in surgical planning and assessment.

Methods

The tissues are acquired from patients, diagnosed with DMV diseases. The tissue is snap frozen upon excision and stored in a biobank. It is then shipped in Liquid Nitrogen to the testing facility. Before the test, it is thawed in PBS at room temperature. The mechanical behavior is investigated using planar mechanical tension tests in PBS at 37°C. Immediately after the mechanical tests, the tissue is chemically fixed and cleared. The cleared tissue is imaged throughout the entire thickness using Second Harmonic Imaging microscopy. The collagen fiber structure is quantified using image analysis based on Fourier analysis.

Results

SHG revealed that the DMV leaflets have multiple distinct groups of collagen fibers at most of the layers through the thickness. The quantified relative amplitude of collagen fiber orientations shows two distinct families of fiber. Additionally, relative amplitude of collagen fibers across the entire thickness, reveals several distinct main orientations through the thickness. This information can be used in an informed constitutive modeling. This will enhance the numerical modeling of DMV apparatus, enabling a better assessment of the postoperative outcome.

Analyzing the Biomass composition of an organism

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A prerequisite for accurate predictions using genome-scale metabolic models (GEMs) is an accurate representation of the biomolecular composition of the cell necessary for replication and growth. This is implemented in GEMs as the so-called biomass objective function (BOF). The BOF contains metabolic precursors required for the synthesis of cellular macro- and micromolecular constituents (e.g. protein, RNA, DNA), and its composition is highly dependent on the particulars of the organism, strain, and growth conditions.

Despite its critical role, the BOF is rarely constructed using specific measurements of the modeled organism, drawing the validity of this approach into question. Thus, there is a need to establish robust and reliable protocols for experimental condition-specific biomass determination.

Here, we address this challenge by presenting a general pipeline for biomass quantification, evaluating its performance on *Escherichia coli* K-12 MG1655 sampled during balanced exponential growth under controlled conditions in a batch-fermentor set-up. We significantly improve both the coverage and molecular resolution compared to other published workflows, quantifying up to 91.6% of the biomass. Our measurements display great correspondence with previously reported measurements, and we were also able to detect subtle characteristics specific to the particular *E. coli* strain. Using the modified *E. coli* GEM *i*ML1515a, we compare the feasible flux ranges of our experimentally determined BOF with the original BOF, finding that the changes in BOF coefficients considerably affect the attainable fluxes at the genome-scale.

We are further developing and broadening the scope of this experimental biomass quantification pipeline and associated protocols, studying *Saccharomyces*, *Pseudomonas*, and *Bacillus* to name a few. We employ bioreactor and chemostat experiments to determine growth-, uptake-, and excretion rates in specified nutrient environments and growth phases of the organisms.

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Poster

We are unique – age and sex dependent cardiovascular model parameters

Friederike Schäfer, Jacob Sturdy, Leif Rune Hellevik

Biological variations in a human's cardiovascular system are due to many factors like genetics, age, sex, and lifestyle. The existence of these variations are known, however, most studies consider homogeneous populations during the development of in silico diagnostics and treatment. By combining a numerical model and non-invasive measurements, we seek to estimate local arterial stiffness, an acknowledged biomarker of cardiovascular health, with an inverse methodology. In formulating the inverse problem, some parameters that vary across the population must be assumed. Certain sub-populations may have distinct distributions of these parameter values, which may in turn result in varying model robustness when applying the method to different groups. To investigate the necessity of considering different age and sex groups during the development of a 1D-common carotid artery model, we conducted a structured literature review to compile distributions of the model parameters for a total of eight age and sex groups. Model sensitivity was investigated through a global sensitivity analysis. Results show that the sensitivity structure changes for different age groups, whereas sex differences are less pronounced within each age group. Further, model output variability can be attributed to the variability in the Young's modulus and geometric parameters, regardless of age and sex. These results suggest that age groups need to be considered during the numerical model development though distinguishing between sexes are of minor importance. High sensitivity of the Young's modulus strengthens the feasibility of inferring arterial stiffness through an inverse problem.

Investigation of transcriptional changes underlying calcification of aortic valve

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Introduction Aortic valve stenosis due to calcification of valve cusps is the most common valve disease in the world today. The main feature of this condition is a progressive mineralization of valve tissue. The mechanisms underlying this process is still unknown, but in recent years it has become clear that pathological mineralization of heart and blood vessels has some similarities with the physiological process of bone formation. It has been suggested that interstitial cells (VICs) are the main functional units in the valve that undergo calcification. However, the early initiating mechanisms that trigger osteogenic transformation of cells remain unclear.

Purpose The aim of the present study was to elucidate the most responsive time point of osteogenic differentiation induction and to identify the main osteogenic markers that mediate pathological calcification in human aortic valve.

Methods VICs were obtained from patients with aortic valve calcification and from healthy aortic valves. The effectiveness of cell cultures osteogenic differentiation was estimated by Alizarin Red staining. Investigation of gene expression changes upon osteogenic differentiation was performed by qPCR and RNA sequencing.

Results We found that 48 hours after the induction of osteogenic differentiation is the most relevant time point to identify the early regulators of osteogenic transformation of the cells. That is the time when the most intensive response from osteogenic markers takes place – *BGLAP*, *OPG*, *OGN*, *RUNX2* – in comparison to 24, 72 and 96 hours of differentiation in both patient's and healthy cells. We found out that induction of osteogenic differentiation on early stages initiates transcriptional program that serve to induce the next molecular events which recruit phenotype-specific osteogenes. We revealed that 558 and 232 genes which were up and down regulated during differentiation were the same for healthy and patient's cells. However, there was a number of genes which was specific for either patient's or healthy cells.

Conclusions We presume that a great amount of the main molecular participants of osteogenic differentiation is shared between different types of cells which are prone to differentiation. However, we perform the results about specificity and difference between the mechanisms of osteogenic differentiation of patient's and healthy cells.

Establishing robust 2D cultures of killer whale primary cells: an optimization study

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Abstract

Persistent organic pollutants (POPs) pose a threat to marine mammals in the Arctic by inducing toxic effects on cells. Top predators, such as killer whales, are especially vulnerable to POPs due to the chemicals' ability to resist degradation, bioaccumulate in adipose tissue and bio-magnify along the food chain. This study aims to establish a robust cell culture with primary fibroblasts from Killer whale skin biopsies through optimization of the cell culturing conditions. This could potentially enable the study of the relationship between contamination by POPs and the biochemical responses in the killer whale cells. The cells used in this study originated from one adult and one juvenile killer whale, sampled outside of Tromsø in Northern Norway. Primary fibroblasts were isolated from biopsies and cultivated with different chemical and physical conditions. Microscopic imaging, counting of cells and metabolite analysis were used to measure cellular growth and determine which conditions increased cell viability and proliferation. The most efficient parameters were combined to test how many cell passages could be accomplished with the killer whale fibroblasts.

MIXED-EFFECTS MODELING FOR ANALYSIS OF PRESSURE AND FLOW DATA

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Key words: Mixed-Effects Modeling, Linear Regression, ANOVA

Abstract

Experimental data is essential for verifying and validating computational-model based estimation of physiological parameters, such as local arterial stiffness. In the ENTHRAL project, we have developed an experimental model of the common carotid artery and collected data on the pressure, flow and deformation of experimental specimens. This data will be used to validate a method of estimating the stiffness of the artery, and the accuracy and reproducibility of the experimental data must be assessed. The analysis of uncertainty and reproducibility of fluid flows and material deformation lab experiments typically focuses on simple descriptive statistics and sometimes fixed-effects ANOVA. The limited analysis is somewhat justified by a high level of control and direct measurements, but mixed-effects modelling can provide more insight to experimental variability. In particular mixed effects modelling provides a natural approach to assess variability in different groupings of data such as repeated experimental conditions over distinct specimens, material samples, etc. This approach is widely applied in fields such as ecology, medicine and psychology. We applied mixed-effects modeling to assess the uncertainty and reproducibility of pressures, flows and deformations generated to mimic various physiological conditions in the experimental setup. In particular, we investigated the variation of the mean values over cardiac cycles both within experiments and across experiments.

The ENTHRAL project is financed from Norway Grants 2014-2021 under contract UMO-2019/34/H/ST8/00624.

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A method for representation of spatially distributed uncertainties about vascular anatomy
Jacob Sturdy

Digitalization and computational modeling offer exciting possibilities to support and improve clinical care by reducing the need for invasive measurements, automating the processing and interpretation of data, and improving the rationale and effectiveness of clinical decisions by integrating various data and knowledge through computational and mathematical models. The ENTHRAL project aims to develop a method for non-invasively measuring the stiffness of human arteries in order to provide a clinically usable method to enable further research about the clinical significance of local arterial stiffness. The approach focuses on using an inverse model of arterial deformation, consequently the anatomy of the artery must be modeled, however, imaging methods and subsequent segmentation of arteries have a limited resolution and thus there will be errors or uncertainties about the anatomy. To translate model based methods to the clinic it is essential to assess the impact of uncertainties on model derived predictions. A particular challenge is to represent spatially varying uncertainty as due to increased computationally burden and difficulties in characterizing the correlation of variations. We present an approach that may be used to represent this uncertainty in a relatively efficient way and compare this method against variations observed in a data-set of segmented arteries.

Development of aortic valve calcification pharmacological treatment (Calinhib)

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Aortic valve stenosis and calcification is the third leading cardiovascular disease. Today the only therapeutic option is heart surgery with implantation of an aortic valve prosthesis. The heart valve prostheses are either based on biological material, which will degenerate and calcify after 10-15 years, or mechanical valves, requiring life-long anticoagulation treatment which leads to complications such as major bleedings including strokes. We aim to replace the burden of the aortic valve replacement surgery with a pill that will prevent the development of aortic valve calcification and stenosis. Avoiding surgery and usage of mechanical valves will lead to a significant patient's life quality improvement and cost reduction.

We employed our group's expertise in the cellular and molecular mechanisms of aortic valve calcification and we have developed an advanced in vitro model of the aortic valve calcification using human valve interstitial cells which are known to be crucial for calcification. Valve interstitial cells in culture are regarded as a standard in vitro model of heart valve calcification. Healthy and calcified aortic valves are obtained from heart transplant recipients and patients undergoing aortic valve replacement due to calcific valve disease, respectively. VIC are isolated and stored in biobank until used.

We have detected inhibitor of aortic valve calcification from a pool of FDA-approved drugs. The drug was able to stop the development of aortic valve calcification in a dose-dependent manner in our model. The lead compound is safe and known to be well tolerated in prolonged use in patients. These findings may develop into a promising future pharmacological therapy to treat heart valve calcification. The repurposing route will allow a short-term development of the therapy to reach patients.

Growing Anisotropic Gold Nanoparticles for Biosensing Applications

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Anisotropic gold nanoparticles exhibit several absorption bands, of which the NIR absorption can be tuned by the AuNP shape. As living tissue has a minimum in absorption in this range, these particles are ideal candidates for bio-medical applications, especially in theranostics^[1,2].

The gold nanoparticle shape can be tuned through the experimental conditions during the seed-mediated growth process. This exploits the decoupling of nucleation and growth phase during the synthesis, which enables the fine-tuning of supersaturation. By tracking the influence of several reaction parameters and introducing a novel weak reducing agent, a wide range of shapes and sizes of gold nanoparticles were obtained. These colloids are promising candidates as transducers for optical fiber based biosensing.

References

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