UNIVERSITÄT BERN

Bern University of Applied Sciences

Master Biomedical Engineering

Annual Report 2021

MASTER OF SCIENCE IN BIOMEDICAL ENGINEERING

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Master's Program Biomedical Engineering

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Photo front page
Class of 2021 in front of the Institute of Anatomy on the occasion of our annual First Semester Information Event in event. To show the faces in Corona times, the picture was taken outdoors.

Photo back page
The same students in the lecture hall, wearing masks according to the Corona regulations.

(Photos cover: Adrian Moser).

Introduction

What a relief! After a year and a half of the coronavirus pandemic and online education, we were allowed to return to the lecture halls in the fall. Finally, we were able to benefit from face-to-face interactions again and explore the relevance of hybrid and fully virtual solutions in a more detached mindset. In all options, our students appreciated the possibility of reviewing the lectures' contents, watching the available podcasts.
From a personnel point of view, Ms. Ulla Jakob was promoted head of the study coordination team. This is a highly deserved career step and I wish to acknowledge here her exceptional dedication to ensure optimal learning conditions, complete information, and fair treatment to all students of the program. My thanks extend to all members of the study coordination who support Ms. Jakob, especially for the additional tasks generated by the pandemic.
This year, a resized Biomedical Engineering Day was organized online for the first time. After the display of the new master's program in Artificial Intelligence in Medicine, eight companies presented themselves and a live surgery was retransmitted from the department of thoracic surgery. I would like to thank Gregor Kocher and Patrick Dorn for presenting an impressive intervention that generated a broad flow of questions. My special thanks go to Julia Spyra for the seamless organization and the Musculoskeletal Biomechanics team of ARTORG for technical support.
At this same occasion, the RMS award for the best average grade during the entire program was attributed to Adrian Ruckli, while the best master's thesis awards were awarded to Giuditta Thoma for basic science and Maxime Chiarelli for innovation. The best PhD thesis was attributed to Serife Kucur for her work "Exploration and Exploitation of Visual Fields: from Acquisition to Prediction of Glaucoma". Congratulations to all of them.
Despite the reduced number of events, the master's program exhibits a healthy condition with 38 alumni and 70 new students. The list of courses was revised, and a new study plan was approved by the medical faculty for the upcoming academic years. The degree of our students' satisfaction, as reflected in the independent evaluation of the University of Bern, remains stable despite the frequent alternation of teaching and examination modes.
Once again, I wish to express my appreciation to the lecturers for their constant involvement in the program and their personal efforts to deliver the best possible education to our graduate students. With this recognition in mind, I am very glad to present our yearly report in the next pages. I wish you an enjoyable reading.

Philippe Zysset

Organization

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Ph. Büchler
Master Thesis Coordinator, University of Bern

Structure of Courses in the Master's Program

Since the start of the Master's Program Biomedical Engineering in March 2006, the constant effort to improve the quality of our curriculum has resulted in substantial changes of the course structure over the past years. The first curriculum consisted of a number of individual courses that were either mandatory or elective, but their coherence with regards to contents was in most cases not expressed by a defined structure. However, two major modules (formerly called "focus areas") already existed.

As of Fall Semester 2009, all courses were grouped in a strictly modular way in order to enhance both the clarity and the flexibility of the curricular structure. A main idea was to guide the students through their studies in a better way by adding an elective part to the major modules, which formerly had consisted exclusively of mandatory courses. Besides, the curriculum was expanded by a number of new specialized courses as well as an additional major module called "Image-Guided Therapy".

Adaptations in the legal framework of the master's program are now offering more flexibility in the design of courses and modules, thus providing the basis for a second fundamental restructuration of the curriculum as of Fall Semester 2013. In particular, a module called "Complementary Skills" was introduced. In addition, the list of mandatory courses in both basic and major modules was revised. More recently, in Fall Semester 2017, a module "preparation courses" was created. The courses in this module are intended to fill gaps regarding prerequisites for basic and advanced courses in the master's program Biomedical Engineering.

After intensive preparation, the curriculum was again restructured as of fall semester 2021. The focus is now on a more practice-oriented education, which is achieved primarily through the newly created "BME Laboratories". These will be conducted in the second semester in the research groups of the University of Bern, the Bern University of Applied Sciences (BFH) as well as our partner institutions Bern University Hospital (Inselspital) and Empa, the Swiss Laboratories for Materials Science and Technology . In addition, thanks to the great commitment of the Institute of Biochemistry and Molecular Medicine, practical laboratories were now included in the course "Biological Principles of Human Medicine", which illustrate and complement the theoretical lectures.

The Curriculum

Duration of Studies and Part-Time Professional Occupation

The full-time study program takes 4 semesters, which corresponds to 120 ECTS credits, one ECTS credit being defined as 25-30 hours of student workload. It can be extended to a maximum of 6 semesters. When a student decides to complete the studies in parallel to a part-time professional occupation, further extension is possible on request. To support regular part-time work, mandatory courses take place (with rare exceptions) on only 3 days per week.

Preparation Courses

Owing to the interdisciplinary nature of the BME master's program, our students come from various fields of study. Especially students with a non-engineering background – for example in medicine – do not fulfill all prerequisites for the courses of the master's program. Therefore, introductory courses in MATLAB, C++ programming, Electrical Engineering, Engineering Mechanics and Material Science as well as the tutorial-based course "Selected Chapters in Mathematics" were introduced and allow to create a tailor-made curriculum for these students. Students with a background in engineering, on the other hand, have the possibility to select these courses freely if they feel the need to refresh some of the knowledge provided.

Basic Modules

The basic modules provide the students with the necessary background to be able to fully understand the complex subject matter in the specialized courses. All students have to complete all courses in the Basic Modules Human Medicine, Applied Mathematics, and Biomedical Engineering. In the first semester, all mandatory courses belong to this group, whereas in the second semester, the courses from the basic modules make up for approximately 20%.

Major Modules

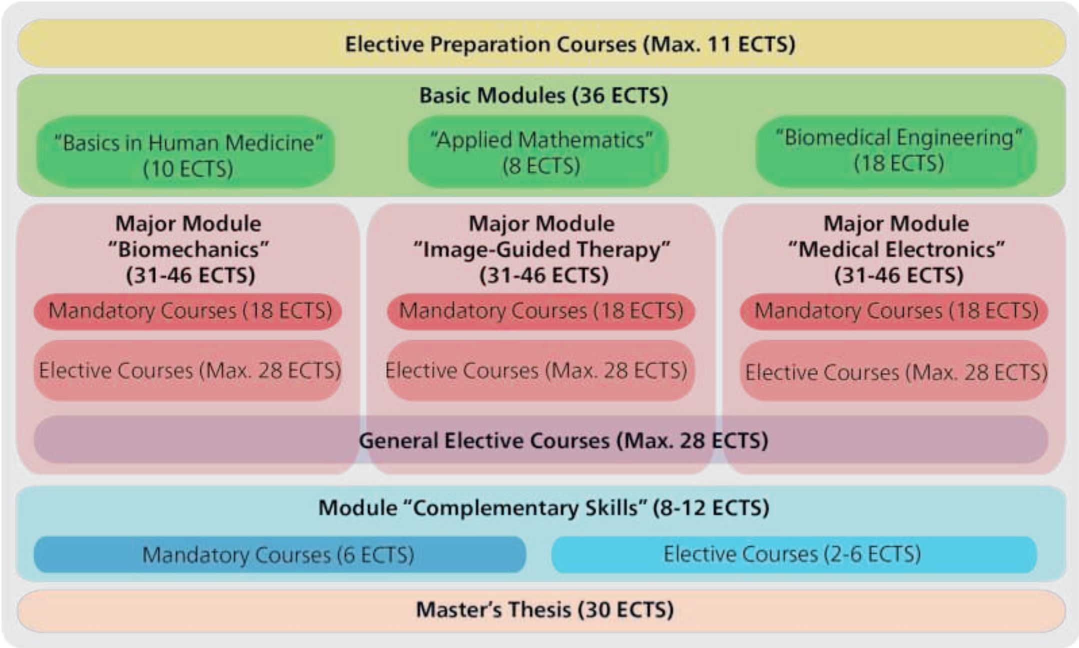
The choice of one of three major modules Biomechanical Systems, Electronic Implants, or Image-Guided Therapy after the first semester constitutes the first opportunity for specialization.

Approximately one third of the major modules consist of mandatory courses. In the elective part of the major module, the student is allowed to select every course from the list of courses in the master's program, giving rise to a high degree of diversity and flexibility and allowing for numerous course combinations. However, this freedom makes it somewhat difficult for the student to make reasonable choices regarding professional prospects.

This is why the responsible lecturers developed a recommended study plan to guide the students through the course selection process and to avoid organizational problems such as overlapping courses. If a student follows the recommended path, he or she can be sure to establish a sound professional profile.

Module "Complementary Skills"

Apart from the rapid development of technology itself, today's biomedical engineers are increasingly challenged by complementary issues like ethical aspects, project planning, quality assurance and product safety, legal regulations and intellectual property rights, as well as marketing aspects. Language competence in English is of paramount importance both in an industrial and academic environment. This situation has been accounted for by the module called "Complementary Skills" where students are required to complete two mandatory courses (Innovation Management; Fundamentals of Quality Management and Regulatory Affairs) as well as 2-6 ECTS from the electives courses (Ethics in Biomedical Engineering; Scientific Writing in Biomedical Engineering; Clinical Epidemiology and Health Technology Assessment.)



Master's Thesis

The last semester is dedicated to a master's thesis project on an individually suited topic in an academic research group at the University of Bern or the Bern University of Applied Sciences or, for particular cases, in an industrial research and development environment. As a rule, all 90 ECTS credits from the course program have to be completed, thus ensuring that the student is able to fully concentrate on the challenges imposed by exciting research activities. The master's thesis includes the thesis paper, a thesis presentation and defense as well as a one-page abstract for publication in the Annual Report of the master's program.

List of Courses

- Advanced Topics in Machine Learning
- Applied Biomaterials
- Basics in Physiology for Biomedical Engineering
- Biological Principles of Human Medicine
- (Bio)Materials
- Biomedical Acoustics and Audiology
- Biomedical Instrumentation
- Biomedical Laser Applications
- Biomedical Sensors
- Biomedical Signal Processing and Analysis
- BioMicrofluidics
- C++ Programming I
- C++ Programming II
- Cardiovascular Technology
- Clinical Applications of Image-Guided Therapy
- Clinical Epidemiology and Health Technology Assessment
- Computer-Assisted Surgery
- Computer Graphics
- Computer Vision
- Continuum Mechanics
- Design of Biomechanical Systems
- Dynamical Models: Analysis, Conception and Simulation
- Ethics in Biomedical Engineering
- Finite Element Analysis I
- Finite Element Analysis II
- Fluid Mechanics
- Functional Anatomy of the Locomotor Apparatus
- Fundamentals of Quality Management and Regulatory Affairs
- Image-Guided Therapy Lab
- Innovation Management
- Intelligent Implants and Surgical Instruments
- Introduction to Artificial Intelligence
- Introduction to Biomechanics
- Introduction to Digital Logic
- Introduction to Digital Signal Processing
- Introduction to Electrical Engineering
- Introduction to Engineering Mechanics
- Introduction to Engineering Mechanics
- Introduction to Material Science
- Introduction to Programming
- Introduction to Signal and Image Processing
- Introductory Anatomy and Histology for Biomedical Engineers
- Lecture Series on Advanced Microscopy
- Low Power Microelectronics
- Machine Learning
- Medical Image Analysis
- Medical Image Analysis Lab
- Medical Informatics
- Medical Robotics
- Microsystems Engineering
- Numerical Methods
- Ophthalmic Technologies
- Osteology
- Principles of Medical Imaging
- Programming of Microcontrollers
- Regenerative Dentistry for Biomedical Engineering
- Rehabilitation Technology I
- Rehabilitation Technology II
- Scientific Writing in Biomedical Engineering
- Selected Chapters in Mathematics
- Short Introduction to MATLAB
- Technology and Diabetes Management
- Tissue Biomechanics
- Tissue Biomechanics Lab
- Tissue Engineering
- Wireless Communication for Medical Devices

Major Modules

Biomechanical Systems

Prof. Dr. Philippe Zysset

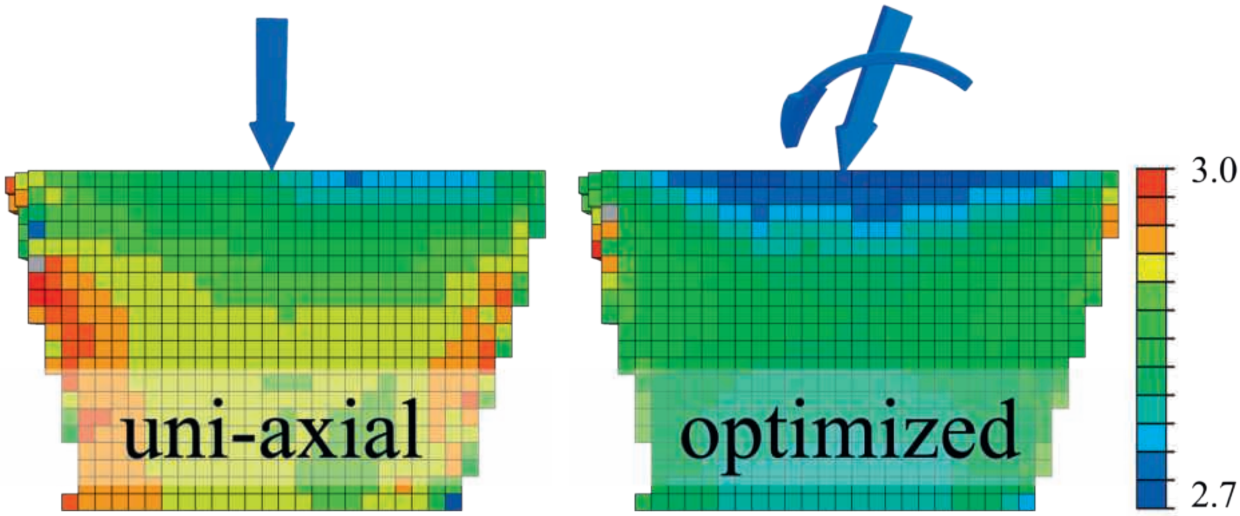
The respiratory, cardiovascular and musculoskeletal systems are the transport and structural bases for our physical activities and their health have a profound influence on our quality of life. Lung diseases, cardiovascular diseases, musculoskeletal injuries and pathologies are costly ailments facing our health care systems, both in terms of direct medical costs and compensation payments related to loss-of-work.

In this module, students will gain a comprehensive understanding of the multi-scale organisation of the respiratory, cardiovascular and musculoskeletal systems, combining knowledge from the cell, tissue, organ to the body level. They will learn how to apply engineering, biological and medical theory and methods to resolve complex problems in biomechanics and mechano-biology. Students will learn to draw connections between tissue morphology and mechanical response, and vice versa. Students will also gain the required expertise to apply their knowledge in relevant, practice-oriented problem solving in the fields of pneumology, cardiology, cardiovascular surgery, orthopaedics, dentistry, rehabilitation and sports sciences.

The mandatory courses in this module provide the student with fundamental knowledge of fluid and solid mechanics, tissue engineering, tissue biomechanics and finite element analysis. This provides an overview of the functional adaptation of the respiratory, cardiovascular or musculoskeletal system to the demands of daily living, and the necessary conditions for its repair and regeneration. This major module requires a prior knowledge of mechanics, numerical methods and related engineering sciences, as many of the mandatory and elective courses build upon these foundations. Elective courses allow the students to extend their competence in a chosen direction, gaining knowledge in analytical methodologies, medical device design, minimally invasive surgery or rehabilitation.

Knowledge gained during the coursework highlights the multidisciplinary nature of this study focus area, encompassing the cell to body, the idea to application and the lab benchtop to the hospital bedside. This knowledge is applied during the final thesis project, a project often with a link to a final diagnostic or therapeutic application. Examples of recent master thesis projects include lung alveoli array on chip, development of an in-vitro model of the lower urinary tract, personalized prediction of percutaneous coronary interventions, setup and analysis of a hop test and development of a device for sensorimotor hand training.

Career prospects are numerous. Many students proceed to further post-graduate education and research, pursuing doctoral research in the fields of biomechanics, tissue engineering, lab on chip or development of biomaterials. Most of the major companies in the fields of cardiovascular technology, orthopaedics, dentistry, rehabilitation engineering and pharmaceuticals are strongly represented within the Swiss Medtech industry and have an ongoing demand for graduates of this major module. At the interface between biomedical engineering and clinical applications, graduates may also pursue careers related to the evaluation and validation of contemporary health technology, a cornerstone for future policies on the adoption of these new methods in the highly competitive health care domain.



Patient-specific loading for high-resolution peripheral quantitative computed tomography (HR-pQCT) based homogenized FE analysis of the distal radius (Illustration: Denis Schenk)

Major Modules

Electronic Implants

Prof. Dr. Volker M. Koch

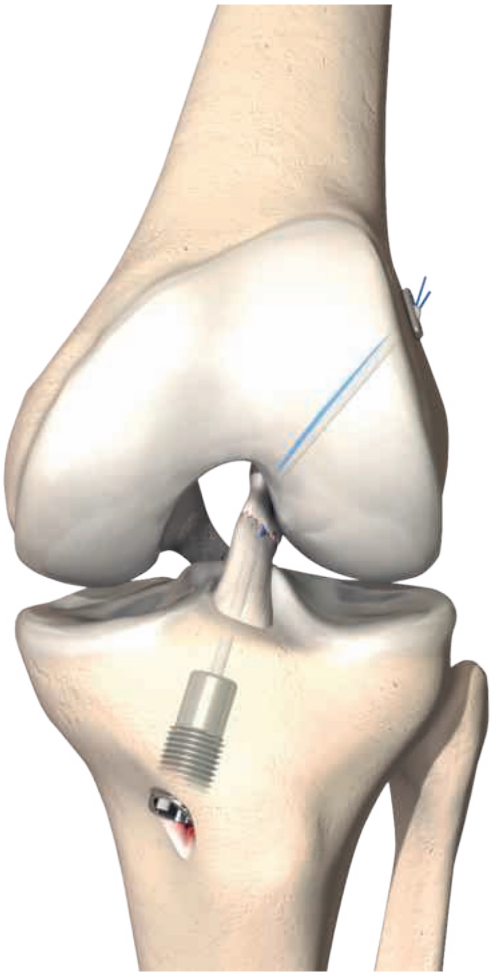
Electronic implants are devices like cardiac pacemakers and cochlear implants. Due to miniaturization and other developments, many new applications become feasible and this exciting area is growing rapidly. For example, cochlear implants provide people a sense of sound. These people were previously profoundly deaf or severely hard of hearing. Recently, researchers demonstrated that electronic retinal implants allow the blind to read large words. There are many more applications for electronic implants beyond treating heart problems, hearing loss or blindness. For example, there are electronic implants that treat Parkinson's disease, obesity, depression, incontinence, hydrocephalus, pain, paraplegia, and joint diseases.

In this module, students will gain a comprehensive technical and application-oriented understanding that will allow them to select, use, design, and optimize electronic implants and similar biomedical systems. Since the work on such complex systems is usually done in interdisciplinary groups, another important goal is that graduates are able to work and communicate in teams consisting of, e.g., engineers, scientists, and medical doctors.

Specifically, students will learn about technology basics including intelligent implants and surgical instruments, biomedical signal processing and analysis, low-power microelectronics, wireless communications for medical devices, biomedical sensors and microsystems engineering including MEMS technology. Application-oriented elective courses are also taught, e.g., cardiovascular technology, biomedical acoustics, biomedical laser applications, ophthalmic technologies, and diabetes management.

Students may already apply their knowledge as a part-time assistant in an institute and/or during their master's projects. After finishing the degree program, a wide variety of career paths are available, ranging from research and development to project and product management. Many companies in Switzerland work in this field and "traditional" implants manufacturers have recently become interested in electronic implants, e.g., to measure forces in knee implants.

This major is open to all students of our master's program. However, typically, students have an engineering-related background, for example, electrical engineering, microtechnology engineering, systems engineering, mechatronics engineering, mechanical engineering, or computer science.



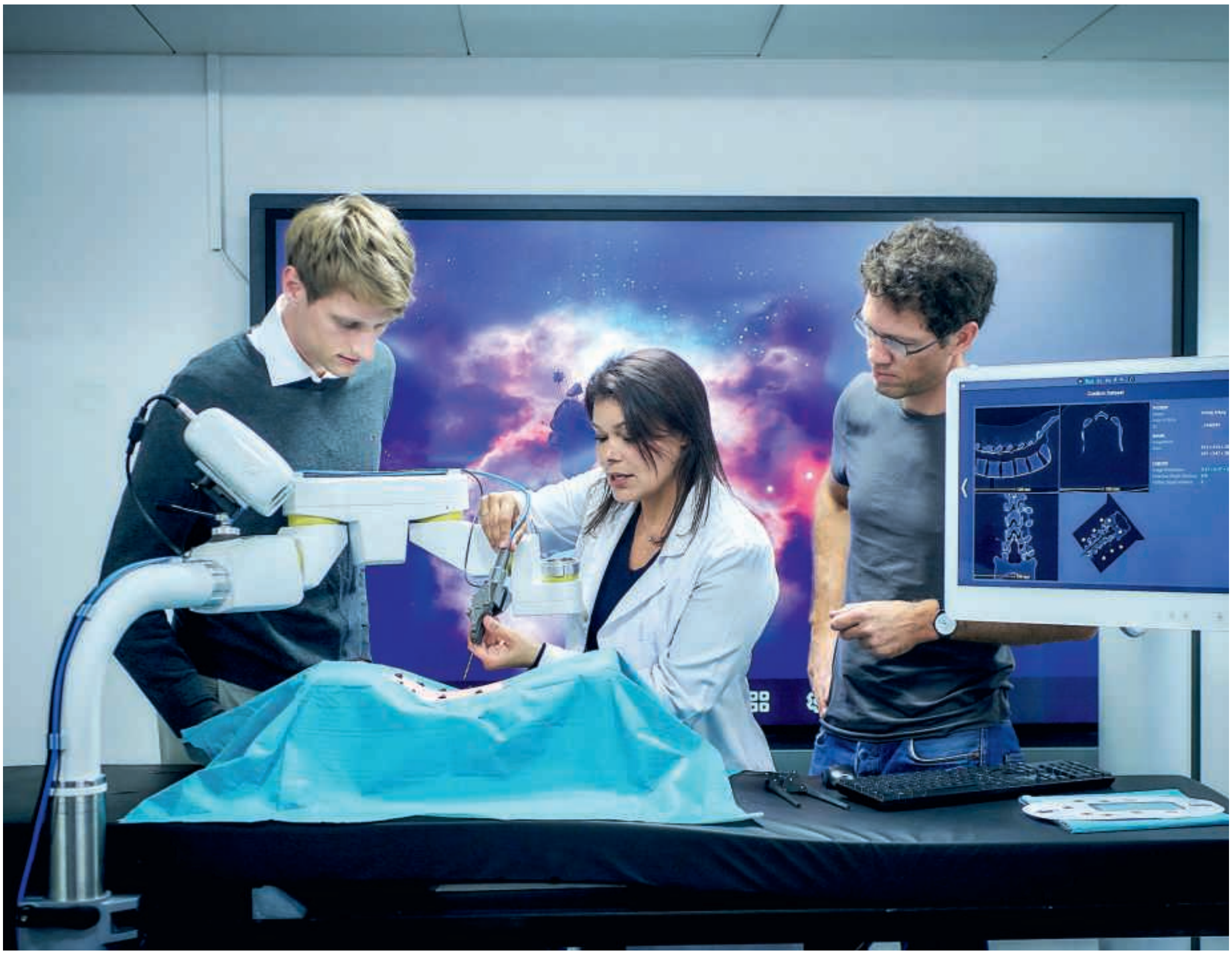
The Ligamys implant used for anterior cruciate ligament (ACL) rupture healing has been instrumented to be able to measure in-vivo loads wirelessly. This work was part of an Innosuisse project. The BFH (HUCE-SensorLab) together with the Swiss Innovation Park Biel and the HAFL were involved in the development of this innovative solution.

Major Modules

Image-Guided Therapy

Prof. Dr. Stefan Weber

Image-Guided Therapy refers to the concept of guiding medical procedures and interventions through perceiving and viewing of medical image data, possibly extended by using stereotactic tracking systems. Medical imaging typically relates to a great variety of modalities ranging from 2D fluoroscopy and ultrasound to 3D computed tomography and magnet-resonance imaging, possibly extended to complex 4D time series and enhanced with functional information (PET, SPECT). Guidance is realized by determination of the spatial instrument-to-patient relationship and by suitable visualization of tracking and medical image data. Image guidance is very often accompanied by other surgical technologies such as surgical robotics, sensor enhanced instrument systems as well as information and communication technology.
Students of the IGT module will study the clinical and technical fundamentals of image-guided therapy systems. They will develop an understanding of currently applied clinical standards as well as an overview of latest advancements in research. Successful students will be enabled to develop novel clinic-technological applications for complex medical procedures as well as improve existing approaches. This will be the basement for successful careers both in the industrial and academic sector.
Mandatory courses of this module are concerned with the fundamentals of Signal and Image Processing and Medical Image Analysis. Furthermore, fundamental aspects of stereotactic image guidance, tracking, patient-to-image registration and basic clinical applications are taught in the course Computer-Assisted Surgery. Recent trends and fundamental aspects in surgical robot technology, minimally invasive procedures and its applications within IGT are introduced in the course Medical Robotics. Additional elective courses extend students competencies in related areas such as computer graphics, pattern recognition, machine learning, and regulatory affairs.



Demonstrator for robotic spinal surgery (© ARTORG Center, 2021)

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New Courses

Introduction to Digital Signal Processing

PD Dr. Wilhelm Wimmer

Digital signal processing (DSP) is the cornerstone of applications in audio and speech processing, sonar, radar, digital image processing, data compression, telecommunications, control systems, biomedical engineering, and many other fields.
The goal of this course is to provide a basic introduction and refresher on DSP theory. Important concepts such as complex amplitudes, spectral representation, Fourier series, sampling and aliasing, interpolation, filtering, and the discrete (time) Fourier transform will be introduced. Practical examples using MATLAB in the laboratory are performed to support the theory. The course material is based on the book "DSP First, 2nd edition" by James McClellan, Ronald Schafer, and Mark Yoder.

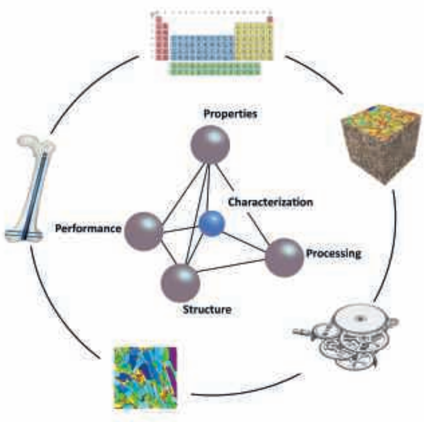
After completing the course students will:
- be able to describe and discuss how continuous-time signals are sampled and reconstructed
- have an intuition about the frequency spectrum of a signal and the Fourier transform
- be able to implement simple MATLAB scripts to simulate and analyze problems in signal processing

Head and torso simulator for electroacoustics tests of audio devices, microphones, headphones, hearing aids, hearing protectors and smart speakers.

Introduction to Materials Science

Prof. Dr. Alex Dommann
Dr. Reto Luginbuehl
PD Dr. Annapaola Parrilli

This lecture provides the basic knowledge about materials. The aim is to convey the basic material classes and principles about the material-structure relationship.
Today, the development of medical devices requires an in-depth understanding of materials. Although many tables on material properties are available, the engineer must be able to evaluate them and convert the properties into the design concept for a medical device with appropriate materials. And this is not possible without knowledge of materials science.
This lecture covers the fundamentals of the chemical, physical, and mechanical properties of metals, ceramics, and polymers as fundamental classes of materials. To start, the atomic structure, properties that favor interatomic bonding, or the various bonding defining material classes are discussed.
Since crystal structure is the key to most physical properties, the most important crystal structures, the concepts of crystallographic points, directions, and planes, the imperfection of solids, and phase diagrams are introduced by using metallic materials as examples. With this knowledge, more complex materials such as ceramics or polymers are explained.
The second part of the lecture focuses on material surfaces, material interface and material interphases. The material surface is of utmost importance for medical devices because it is only the surface that interfaces with the biological system of an organism and thus determines the nature of interactions and reactions. The modulation of surface properties by soft and hard coatings will be addressed, as well as the appropriate analytical methods to measure these properties.
The lecture "Introduction to Materials Science" will be followed in the next semester by the lecture (Bio-)Materials, where the specific material properties and the interaction of materials with biology will be discussed in more detail. The lecture series is largely based on the book "Fundamentals of Materials Science and Engineering" by William D. Callister, David G. Rethwisch, Wiley 10 edition, which offers additional in-depth topics.



New Courses

Introduction to Artificial Intelligence

Prof. Dr. Raphael Sznitman

Artificial Intelligence (AI) has become an essential element in many areas of technology and society. With a rich development history, the domain has undergone radical shifts in thinking. Therefore, this course provides a broad overview of the topic of AI. As an introductory course, a historical overview of the subject is given and a number of technical frameworks and concepts are introduced. Topics covered include:

- Knowledge-based systems
- Search methods including heuristic-based search, A* etc.
- Information theory
- Sampling methods including MCMC, importance sampling, MCTS etc.
- Representations, knowledge, planning and agents
- Uncertainty reasoning

At the end of the semester, students have developed a general understanding of different kinds of AI systems and methods. They have also gained experience in the implementation of a small number of AI systems in a medical context.

Radiological preparation for neurosurgical treatment training with a realistic simulator: Fredrick Johnson built the 3D files he is touching from the software for the patient-specific simulation training as part of his PhD thesis at the ARTORG Center.

Photo: Adrian Moser

New Study Program

MSc in Artificial Intelligence in Medicine

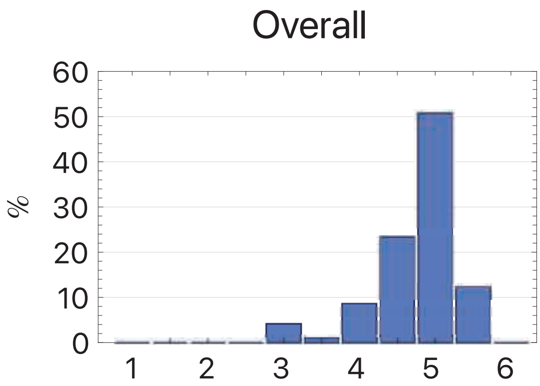
In spring 2021, the master's program Artificial Intelligence in Medicine (MSc AIM) was launched, starting in September 2021 with the first group of highly motivated students. The program is part of the newly established Center for Artificial Intelligence in Medicine (CAIM) which was founded by the University of Bern and the Bern University Hospital (Inselspital) in January 2021.
The new MSc AIM runs in close cooperation with the well-established MSc BME program to the mutual benefit of students from both programs. AIM and BME students, for example, are allowed to register for courses from both programs.
One of the new courses designed for the master's program Artificial Intelligence in Medicine is the course "Introduction to Artificial Intelligence". Being mandatory for AIM students, it was much frequented in the fall semester 2021 (as an elective) by BME students as well.
For details visit www.caim.unibe.ch/msc_aim

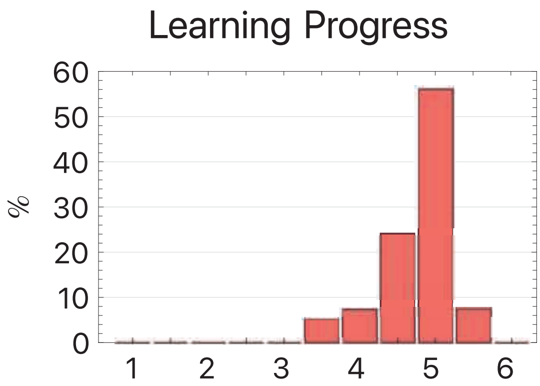
Professor Dr. med. Lukas Ebner, radiologist at the University Cancer Center Inselspital, and Matthias Fontanellaz, PhD student in the AI in Health and Nutrition group at the ARTORG Center for Biomedical Engineering Research, discuss AI-based interpretations of lung X-rays.

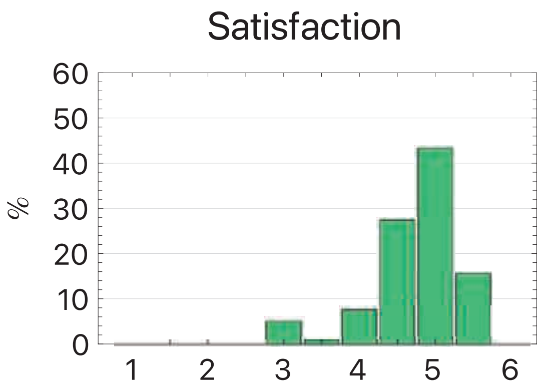
Photo: Adrian Moser

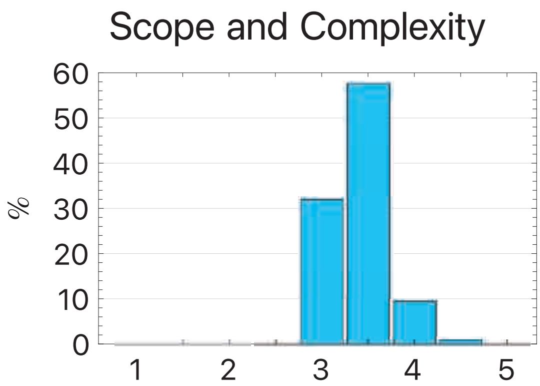
Evaluation of Courses in the Year 2021

Like in the previous years, a centralized online evaluation was performed in the master's program in Spring and Fall Semester 2021 according to the guidelines of the University of Bern. Both semesters were considered leading to 54 course evaluations involving 877 forms in total. The results regarding all forms (see below) reveal that the students are generally satisfied with the program and that the courses are interesting and promote the acquisition of skills.



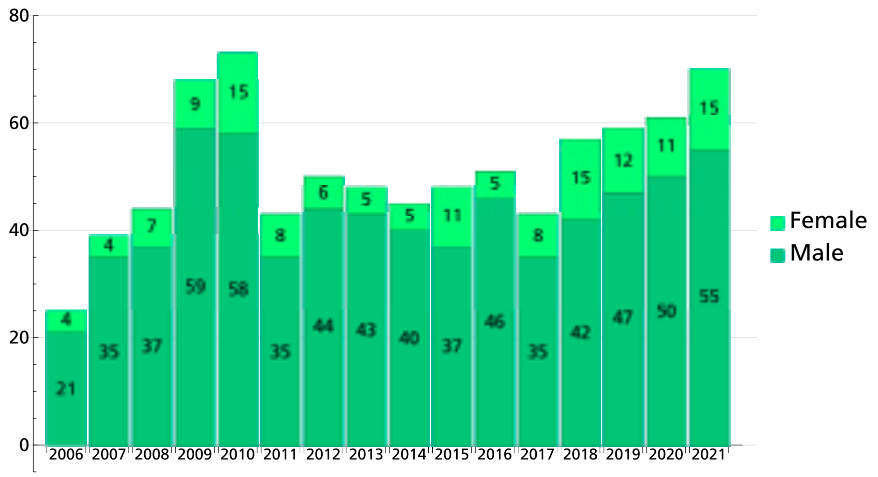


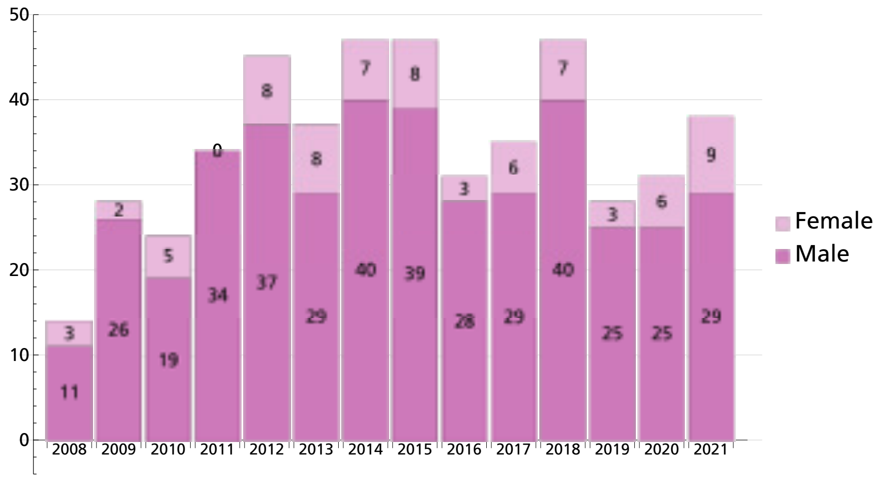




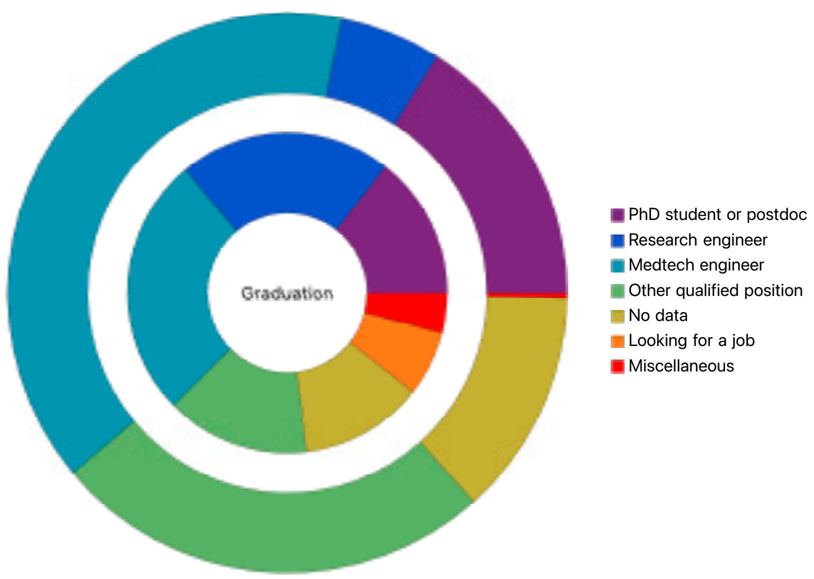
Statistics

Number of New Students (above) and Graduates (below)





Profession after Graduation: Activity after 1 (inner circle) and 5 years



Graduations

Congratulations to our 2021 graduates! We wish you all the best for your future private and professional life:

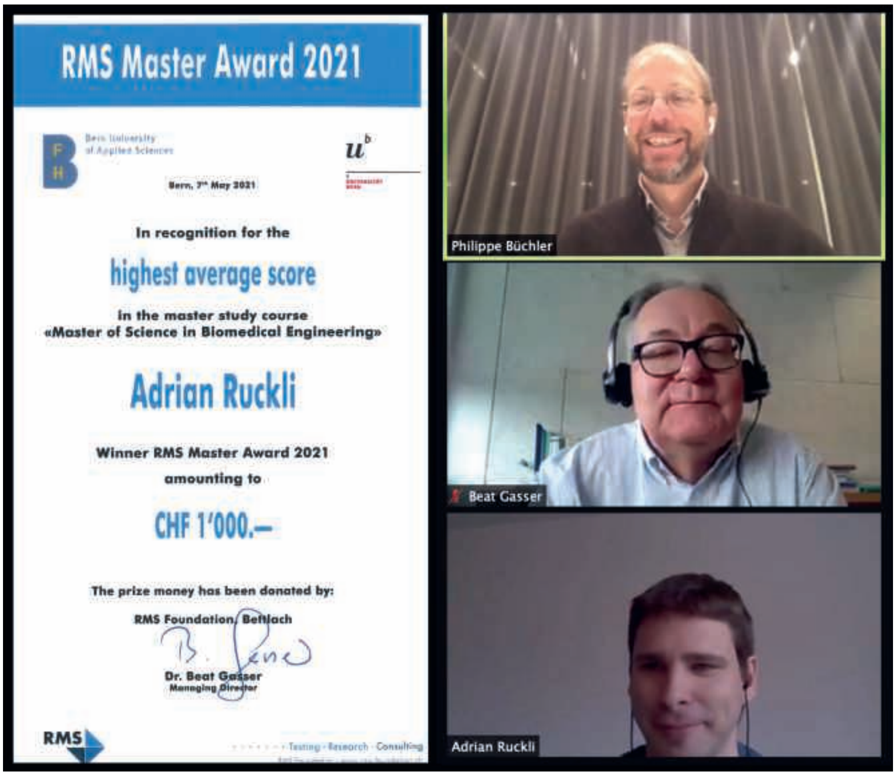
Graduates with Major Module Biomechanical Systems
Muriel Caroline Bischof
Katrin Anita Gfeller
Rafael Gfeller
Marc Sascha Ilic
Camille Léonard Kaufmann
Christian Werner Kündig
Caleb Michael Leichty
Remo Pascal Muri
Lara Piers
Barbara Schläpfer

Graduates with Major Module Electronic Implants
Eylem Akalp
Raphael Raschid Andonie
Martin Bertsch
Benjamin Bircher
Pavel Bouduban
Nina Chatelain
Lukas Geisshüsler
Ece Su Ildiz
Simon Krebs
Ajith Manimala
Rafael Philippe Morand
Rémy Minh-An Nguyen
Ralph Hans Rechsteiner

Graduates with Major Module Image-Guided Therapy
Cyril Dominic Albrecht
Thomas Buchegger
Linard Büchler
Carolina Duran
Michael Herren
Nalet Julian Meinen
Killian André Paul Monnin
Robert Armando Münger
Basil Finn Peterhans
Christian Gabriel Piguet
Adrian Josef Rechsteiner
Simon Adrian Salzmann
Leonardo Pietro Emanuele Sartori
Jana Stárková
Stefan Tobias Weber

RMS Award

In 2021, the RMS Award went to Adrian Ruckli for his excellent grade point average (GPA) of 5.77/6.0.
The RMS Award is an award of excellence. Each year, the Robert Mathys Stiftung (RMS), an independent service laboratory and research institute, gives it to the best BME student for his/her outstanding achievements.
The award of 1000 CHF honors the student who receives the best grade point average over the course of the two-year BME master's program. In 2021, the prize was awarded during the virtual BME Day.
The program management wishes to thank Dr. Beat Gasser and the executive board of the Robert Mathys Foundation for this contribution to the excellence and visibility of our biomedical engineering field.



Adrian Ruckli (bottom) receives the award from Beat Gasser (center), managing director of the RMS foundation. Philippe Büchler (top) is chairman of the video session.

Graduate Profile

Muriel Bischof, BME Alumna 2021

Q: What was your academic and professional background prior to your BME Master's studies?
A: After the Swiss Matura (high school diploma), I completed a bachelor's and a master's degree in civil engineering at the Lucerne University of Applied Sciences.

Q: How did you get interested in biomedical engineering?
A: During my master's studies, I worked part-time and realized that civil engineering didn't suit me one hundred percent. On the other hand, I knew I wanted to stay in engineering. I have always had a strong interest in medicine but was aware that being a doctor would not be the right profession for me. Professional career counseling reinforced my idea that biomedical engineering would be the right thing for me.

Q: How did you come to know about the BME Master's program? Why did you choose this program among others?
A: At first, I only knew the study program at ETH Zurich, but I found out that I would have to fulfill additional requirements of 60 ECTS, which meant that my study time would be at least three years. Since I already had a master's degree, this was not an option for me. I came across the BME program at the University of Bern through an internet search. The fact that I was accepted without requirements was a big plus for me.

Q: Did you work part-time during your studies?
A: When I started the BME master's program, I decided to concentrate on my studies. I had done a part-time job during my master's in civil engineering. Although this was a good experience, I wanted to focus exclusively on my studies. In addition, I am very involved in climbing and endurance sports and didn't want to make any compromises here.

Q: How would you describe your time as a student in Bern in retrospect?
A: Actually, I was astonished to see that many students – like myself – did not have a background in Biomedical Engineering. They came from different disciplines, which made interactions and exchange very interesting. In fact, I have never experienced such a good spirit between students in my previous courses of study. We were a group of around 10 people and met regularly not only for learning, but also for leisure activities and cooking. Many good friendships were created, and we are still in contact.

Q: How did you experience the Corona Lockdown?
A: I started my studies in the fall semester of 2018. Therefore, unlike students who started in fall 2019 or 2020, I had three semesters of face-to-face courses and therefore enough time to socialize. But from one day to the next, in spring 2020, all courses and exams were online only. Most students then returned home; my group kept in daily contact, and in the beginning, we found the regular Teams "coffee" meetings quite amusing, but over time it became very monotonous to pursue studies just sitting alone in a room. Luckily, I could return to Bern after one semester and work on my master's thesis in the lab.

Q: What was your career plan after graduation? Where do you work now and in which position?
A: I had chosen the specialization "Biomechanical Systems" and wanted to work in the field of joint replacement development. That's why I applied to companies in this field and finally found a job as a development engineer at Mathys in the hip development team. Amazingly, two other graduates from my year started in the same team after me, and another alumnus who graduated some years ago holds a senior position here.

Q: Which competences did you gain during your studies that are useful for your present professional position?
A: I found the course "Design of Biomechanical Systems" very interesting and instructive, as lecturers from industry presented their implants. The practical experience in anatomy that I was able to acquire in the course "Functional Anatomy of the Locomotor Apparatus" and watching orthopedic surgical procedures in "Orthopaedic Surgery – Practical Course" also proved to be very useful. The courses Tissue Biomechanics, Biomaterials and Applied Biomaterials also provided valuable knowledge for my current work, as did actually all the courses in biomechanics.

Q: What is your personal conclusion? Were your expectations of your studies and your new job fulfilled?
A: To make it short: Yes, I am very happy with both.

Biomedical Engineering Day 2021

The first virtual BME Day was a great success

On May 7, 2021, the first virtual Biomedical Engineering Day in 13 years took place. The master's program in Biomedical Engineering of the University of Bern organized this event for the 12th time.

The event is an efficient platform in Switzerland for networking of Master and PhD graduates and Swiss and international medical technology companies. This year's companies introduced themselves through oral presentations in a zoom webinar and gave insight into their commercial activities and their company philosophies as well as showed their demands on junior employees. Students thus had the opportunity to get to know potential future employers and contact them directly during the virtual coffee break organized in the virtual town "gather city".

The BME Day offered great opportunities for the Bernese biomedical researchers, too. The ARTORG Center for Biomedical Engineering Research and the Bern University of Applied Sciences, a partner within the master's program, used the possibility of presenting current research projects to more than 200 virtual participants. Interestingly, master and PhD students play an important role in many of these projects. Thereby, this event was a demonstration of scientific achievements, too.

Besides company representatives, scientists, researchers, and young academics, medical doctors participated in this year's event as well.

For the first time, young researchers presented their projects in a humorous way during a "my thesis in 180 seconds" session. One highlight of the morning was definitely the successful live surgery by Gregor Kocher and Patrick Dorn, Department of Thorarcic Surgery, University Hospital Bern (Inselspital). Many students asked questions in the live chat during the lung surgery.

Awards

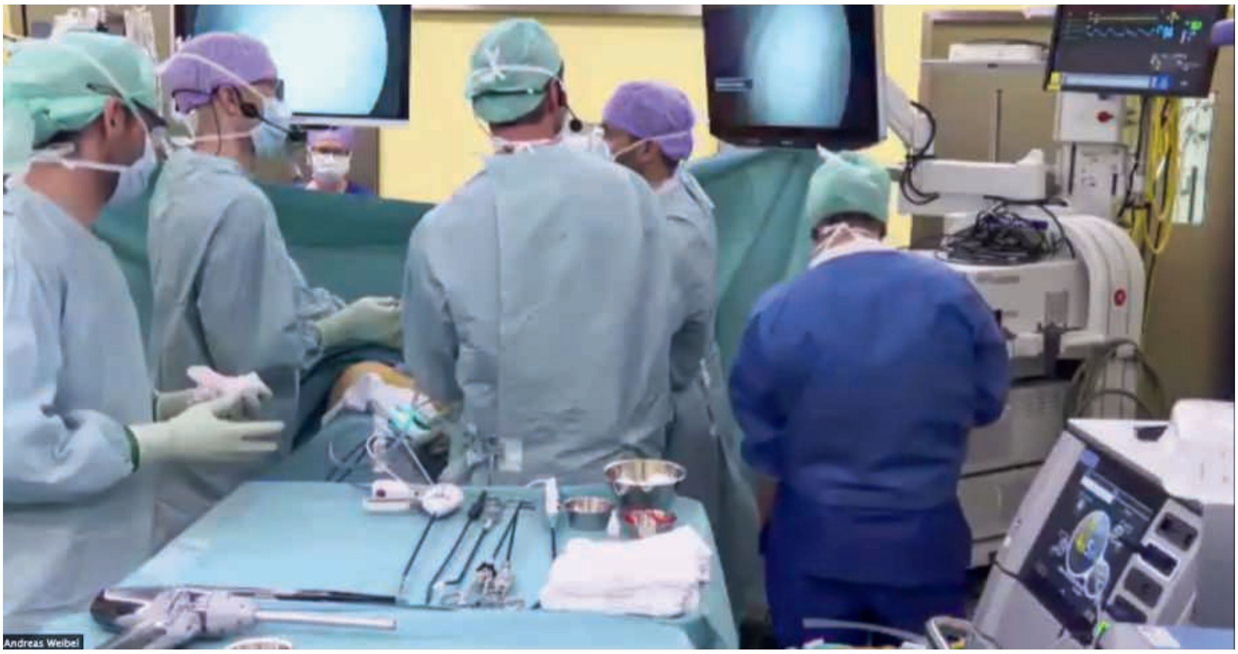
The following awards for excellent academic achievements in the field of Biomedical Engineering at the University of Bern were presented:

- Swiss Engineering Award for the best master's thesis (innovation): Maxime Chiarelli (Estimation of the Energy Loss through Turbulence in an Aortic Stenosis Model Using Backlight Particle Tracking Velocimetry in a Silicone Ascending Aorta Phantom)
- Swiss Engineering Award for the best master's thesis (basic science): Giuditta Thoma (Lung-Alveoli-on-Chip: Mechanical Characterization of a New Biological Membrane)
- CCMT Award for the best PhD thesis: Serife Kucur (Exploration and Exploitation of Visual Fields: from Acquisition to Prediction of Glaucoma)
- BME Club Awards for the best master's thesis abstract:
  1st place: Simone Poncioni (Optomechanical Simulations of Laser Refractive Surgeries)
  2nd place: Nathan Gyger (Contacless Detection of Gait and Gait Abnormalities)
  3rd place: Martin Bertsch (Targeted Drug Delivery in Glioblastoma Mouse Models)
- RMS Award for the best GPA in the MSc Biomedical Engineering: Adrian Ruckli (GPA 5.77)

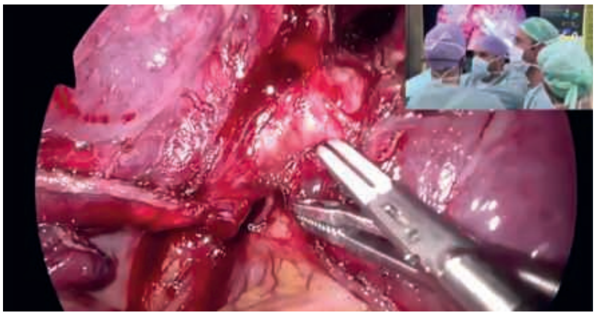
From left to right: Maxime Chiarelli, Giuditta Thoma, Serife Kucur, Simone Poncioni, Adrian Ruckli

122 people (left) visit the company room in gather city

The virtual research groups of BFH and ARTORG



The surgical team at the operating table



Live surgery (lung resection due to cancer)

Chairman Philippe Büchler (top) awards the prizes to Giuditta Thoma, Maxime Chiarelli and Serife Kucur

We thank our sponsors and exhibitors

The Biomedical Engineering Club

The BME Club and its Mission

The Biomedical Engineering (BME) Club is a non-profit Alumni organisation from the University of Bern that aims to provide and promote networking events among its interdisciplinary members. We are a constantly growing group of biomedical engineers, scientists, past and present students and medical technology corporate eager to bring together the fields of engineering, biology, and clinical medicine. The BME-Club accomplishes these goals by networking and hosting events, in particular, information sessions to learn about cutting-edge research fields of bioengineering, attendance of national/international conferences, and visit plans to industries and laboratories. The BME Club has been recognized as an official Alumni association of the University of Bern under the umbrella organization – Alumni UniBE. A dedicated executive committee within the BME-Club follows the principles of our constitution. We are an enthusiastic and versatile group that performs diverse activities including:

- Regular visits to Swiss medical and engineering companies
- Organization of the annual MEDICA trip
- Information on career opportunities for Masters levels
- Organization of the annual Welcome event for new students of the BME Master program
- Organization of an annual Alumni gathering for networking purposes
- Sponsorship of the best, Master thesis award at the annual BME day
- Sponsorship of 2 Travel Grants to International conferences
- Joint membership for former students of the University of Bern
- Offering (optional) joint membership with Swiss Society for Biomedical Engineering

Taken together, the BME club represents a unique platform for professional, lifelong communication and networking events.
Further details on the BME-Club are available on our website http://www.bmeclub.ch.

How to Join

Becoming a BME member is easy! Simply join at any BME Club event or sign in at our website. We are looking forward to seeing you.

BME Club on pause

Due to the current pandemic situation in Switzerland and Worldwide, we had to adapt our planned events.
We were very happy to be able to award the three best master thesis abstract awards during the first virtual BME Day in May – for details, see the article "Biomedical Engineering Day" on page 16.
Furthermore, we finally could see each other again in person at a small gathering during the Alumni BBQ in September. We hope for more visits possibilities and networking events for 2022.

Further improvements

As we could not offer the number of events we would have liked to, we improved our online presence. We have updated our website with a new compelling design, changed our LinkedIn appearance (https://www.linkedin.com/company/biomedical-engineering-club/) and frequently add posts to the Instagram profile of the BME-Master course (https://www.instagram.com/bme_unibe/). Follow us if you want to be informed about events, meetings, or other activities of the club.

The BME Club executive Board members in 2021

Samuel Knobel
President
M.Sc. class 2016

Tamara Melle
Secretary, Treasurer
M.Sc. class 2017

Adel Tekari
Alumni Representative
M.Sc. class 2007

Mark Keller
Corporate Representative
M.Sc. class 2007

Tobias Imfeld
Webmaster
M.Sc. class 2009

Fredrick Joseph
PhD Student Representative

Arina Auchlin
Student Representative
M.Sc. class 2020

BME club alumni barbecue, September 2021

Success Story

Nicolas Bouduban, BME Alumnus 2008

Q: What was your academic and professional background prior to your BME Master's studies?

A: I had finished a diploma in Microtechnology at the Bern University of Applied Sciences (BFH).

Q: How did you come to know about the BME Master's program?

A.: After graduating from BFH in 2005, I stayed at BFH as an assistant in Jürgen Burger's lab, working on a medtech project. Jürgen was strongly involved in setting up the BME master's program, and so I learned about this opportunity first-hand. I was very interested in the field of medical technology, and the prospect of obtaining a master's degree – which at the time was not possible at Swiss universities of applied sciences – was very appealing to me. So finally, when the master's program started in 2006, I was one of the first students and continued to work at BFH part-time.

Q: What was your first career step after completing the master's degree?

A: I had already conducted my master's thesis on the topic of osteosynthesis as part of a project with the Synthes company. After my thesis, I started right away as a development engineer in the innovation team of Synthes, which was headed by Robert Frigg at the time. I spent at least one day per week at Balgrist University Hospital in Zurich. My job was to follow orthopaedic surgeries in the operating room in order to identify opportunities for improvement and innovation. I found this very exciting, and I would not have been able to do this work without my previous knowledge from my BME studies, especially in anatomy of the musculoskeletal system.

Q: How did your career continue after that?

A: After the acquisition of Synthes by Johnson & Johnson (J&J), I moved to the development department of DePuy Mitek (later Mitek Sports Medicine), a subsidiary of J&J active in the field of sports medicine. There I worked very internationally, first in Europe and then for several months each in Boston and Philadelphia. When Robert Frigg, my former boss at Synthes, built the company 41medical together with long-time colleagues in 2016, I joined his company as Head of Marketing and Sales. My work included project acquisition and project development from new ideas to CE marking in the fields of sports medicine, orthopaedics, traumatology, dental medicine and a little cardiology. In 2019, I was given the opportunity to take on the CEO position at Swiss M4M center.

Q: Can you describe the center and its activity?

A: The company is a technology transfer center for additive manufacturing in the field of medical technology, initiated and promoted by the federal government under the Innovation Act. Empa, the Swiss center for materials science and technology, had been pursuing the plan for a center in this field for a long time and was then able to realize it in collaboration with the industry where Pierangelo Gröning from Empa and Robert Frigg from 41medical played a major role. The purpose of the center is to ensure the accessibility of additive manufacturing in the market, i.e., to give companies the chance to get in touch with this technology, learn know-how, make projects and then implement them.

Q: Nowadays, you are a teacher in the master's program yourself. How did that come about?

A: Prabitha Urwyler, like me one of the first students in this program, is now coordinator of the course "Design of Biomechanical Systems". When she asked me in 2021 whether I would take over two lectures on additive manufacturing in medical technology, I gladly accepted. I am excited about sharing my knowledge in my field of expertise and teaching in a course that I took myself as a student.

Q: Which competences did you gain during your studies that were useful for your career?

A: The program included many topics that are very important for entering the medtech industry, especially the medical subjects, but also e.g. imaging or engineering mechanics. An understanding of regulatory affairs and quality aspects is also very valuable. Over the years, many exciting topics were added to the program, but the basis was already laid when I was a student. What makes the program unique in my view is the proximity to the hospitals, which gives you insight into the needs of medical professionals.

Q: Would you study the BME master's program again?

A: Yes, and I can fully recommend it.

Nicolas Bouduban (right) in Swiss M4M's certified production for high-tech 3D printing













MASTER'S THESES 2021



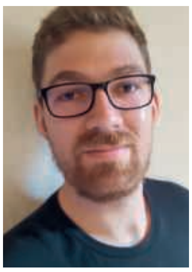

















Modality Dependent Accuracy Analysis of Patient-Specific 3D Anatomy Modelling

Eylem Akalp

Supervisors: Dr. Kate Gerber, MSc Hanspeter Hess
Institutions: University of Bern, Sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: Dr. Kate Gerber, Dr. Guodong Zeng

Introduction

The stability of the shoulder joint is mainly ensured by four muscles of the rotator cuff. If some of these muscles are torn, less invasive arthroscopic rotator cuff repair (RCR) surgeries have been attributed to significant short- and long-term improvements in pain score, function, and strength, compared to complete shoulder arthroplasty. To date, still a incidence rate of 39% - 89% of rotator cuff retears exists for RCR [1]. Various anatomical shoulder parameters exist which have a significant influence on the development of an rotator cuff tear (RCT) or a retear. This includes parameters like the glenoid version and inclination, the critical shoulder angle (CSA), the glenoid cavity, and the muscle atrophy. These parameters are typically measured on 2D images or on CT-based surface models. The main disadvantage, which cannot be neglected, is the harmful ionizing radiation which is necessary for the CT-imaging. In such cases, a good alternative would be the new MRI Dixon sequences with his properties. In today's clinical routine, the T1-weighted MRI sequence is still used for the diagnosis of most shoulder diseases. Therefore, the aim of this thesis is to test the usability of the T1-weighted MRI sequence to quantify the morphological parameters.

Materials and Methods

To validate the parameters from the T1 images, the Dixon sequence was used as ground truth, and the parameters of both modalities were compared with each other. The parameters were measured on Dixon- and T1-based surface models (see Figure 1), which were created with manually segmented images. On the surface of these models, landmarks were placed for automatic calculation of the morpheological parameters. Dataset consisted of 17 shoulders, imaged with isotropic two-Point-Dixon MRI sequence. The same procedure was carried out with a second dataset with T1- weighted images from the same patients. The error of the models was represented with a surface distance map (see Figure 1). Additionally, a non-inferiority test was used to demonstrate if the difference of the parameter from both modalities does not exceed a predetermined inferiority threshold. The segmentations of the four largest outliers between the comparison of Dixon and T1 images were improved by considering the area of the cartilage on the glenoid rim and the mean squared errors between Dixon and T1 transversal was calculated.

Results

The non-inferiority test showed that the CSA parameter obtained with the T1 based 3D models was showing non-inferiority. The statistical analysis of the other morphological parameters showed a large spread between the Dixon and T1 transversal models. A significant improvement in all landmark based parameters was achieved by correcting the segmentation on the glenoid rim with the knowledge of the cartilage area.

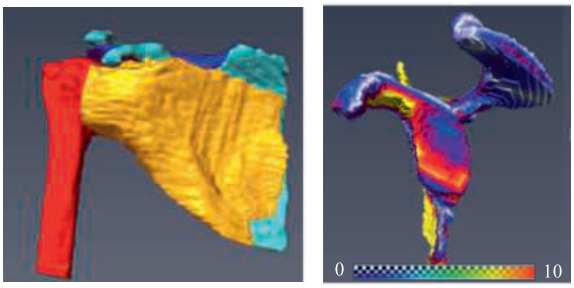


Figure 1: Left: Dixon based 3D model of the shoulder, Right: Surface distance model of the scapula, where red represents a distance of 10 voxels and blue of 0 voxel.

Discussion

We demonstrated the usability of T1 sequences to measure the morphological parameter CSA that significantly influence the development of an RCT. This was verified against the Dixon sequence, which was used as ground truth and has a similar isotropic property as CT. In this way, the findings of this work combined with enhanced segmented images and the automated segmentations can be used to make better outcome prediction for several shoulder treatments with routinely used MRI protocols. This would reduce the incidence rate of a rotator cuff retear (39% - 89% of all RCR patient cases [1]).

Reference

[1] Chillemi, C. et al. (2011): Rotator cuff re-tear or non-healing: histopathological aspects and predictive factors. In: Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 19 (9), S. 1588–1596. DOI: 10.1007/s00167-011-1521-1.

Acknowledgement

We would like to thank our clinical partner Prof. Dr. med. Matthias Zumstein for providing the clincal perspective to this endeavour.

Trajectory Planning for Robotic Thermal Ablation with overlapping Volumes

Cyril Albrecht

Supervisors: Milica Bulatović, Dr. Iwan Paolucci
Institution: ARTORG Center for Biomedical Engineering Research, University of Bern
Examiners: Prof. Dr.-Ing. Stefan Weber, Milica Bulatović

Introduction

Liver cancer is a common type of cancer with low survival rate. Current curative treatments include liver resection, transplantation and thermal ablation (radiofrequency or microwave). Thermal ablation is usually used for small tumors (<3 cm in diameter), but can also be applied to larger tumors with multiple needle insertions. Bale demonstrated this with manual planning in 2010 [1]. The aim of this thesis is to develop a trajectory planning algorithm for large and irregularly shaped tumors.

Methods

The algorithm is fed with a CT-scan and the segmented volumes of interest: liver, tumors, skin, and the obstacles (bone, major blood vessels, etc). The users sets the main parameters to create an ablation plan: the discretization distance (discrete space between entry points), the safety margin around the tumor, and the weights for the weighted sum of the soft constraints. The target point inside the tumor is defined with measurements of the tumor obtained with PCA decomposition. Hard and soft constraints are used to select the best fitting entry point on the skin to reach the target point. The ablation volume is simulated with a spheroid model given by the ablation device manifacturer. This process is repeated until no more tumor voxels are present. To evaluate the performance of the implemented algorithm, 6 patient cases of the 3D-*IRCADb 01* database were used. A clinical expert assessed 7 aspects the computed ablation plans and commented on them.

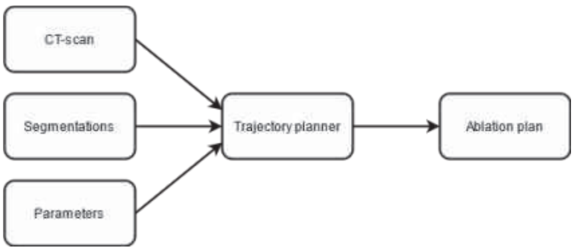


Fig. 1 Concept of the trajectory planning algorithm.

Results

The trajectory planning algorithm has successfully been implemented. The computation time for a single ablation plan is 2 to 3 minutes. However, the plan quality does not reach clinical standards. Most of the plans were considered unsafe, had suboptimal tumor coverage, and an excessive number of ablations. In some cases, the ablation needles even did go through the lung or the stomach, which would lead to major complications.

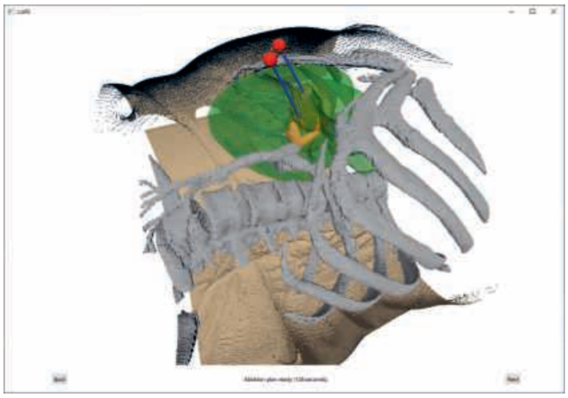


Fig. 2 Ablation plan computed with the implemented trajectory planning algorithm.

Discussion

The algorithm still needs some revision and refinements before getting a chance in clinical suite. Implementing additional hard and soft constraints would benefit the algorithm in the future. Splitting the tumor volume into subvolumes with the *K-means* algorithm and combining the soft constraints with Pareto optimization are potential improvements. Adding user interaction to choose between the optimal entry point on the skin and make minor corrections of the plan would greatly benefit the ablation plans quality.

References

[1] Bale R, Widmann G, Stoffner DI, *Stereotaxy: breaking the limits of current radiofrequency ablation techniques*, European Journal of Radiology, volume 75, issue 1, pages 32-36, 2010, https://doi.org/10.1016/j.ejrad.2010.04.013

Acknowledgements

Dr. med. Anja Lachenmayer (University Hospital Bern), Marcel Schoch (ARTORG Center)

Time-Adaptive Algorithms for Low-Power Medical Devices

Raphael Andonie

Supervisors: Prof. Dr. sc. ETH, Dr. med. Reto Wildhaber, MSc Christof Baeriswyl
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: Prof. Dr. Marcel Jacomet, Prof. Dr. sc. ETH, Dr. med. Reto Wildhaber

Introduction

Conventional surface electrocardiography (ECG) shows some major limitations regarding the investigation of rhythmological questions related to the analysis of the atrial regions. An alternative technology to examine atrial activity in more detail is the esophageal electrocardiography (EsoECG). The Institute for Human Centered Engineering HuCE is working towards an implantable EsoECG device, capable of real-time data processing at a restricted power budget. The present work improves signal processing methods based on Autonomous Linear State Space Models (ALSSMs).

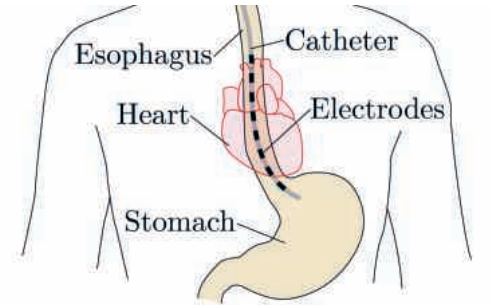


Fig. 1 Posterior placement of the EsoECG catheter. The electrodes reside in close proximity to the heart, especially to the atria, allowing for high-resolution electrophysiological measurements.

Materials and Methods

In a first part of this work, we increased the numerical stability of recursive linear state space computations. In such systems, numerical issues occur with increased complexity of linear state space models and get worse when the numerical precision is reduced, e.g. when fixed-point computations are used.

In a second part of this work, we derived a method to robustly detect P wave onsets in multichannel EsoECG signals, applying ALSSMs as our signal model. Our approach splits up in two steps: first, edge detection algorithms (EDAs) are applied to all channels independently, generating discrete events (edge locations) on each channel. Therefore several existing ALSSM based EDAs as well as new ideas to improve them (e.g. using L2-regularization) are presented and applied to real signals. In the second step, temporally and spatially located models are fitted to the obtained events. The models are scored to decide on the presence of a multi-channel onset at a given point in time.

Results

Given signal denoising applications, which broke at order 5 polynomial models (PM) ran with the numerical stabilization of the first part robustly with models up to order 13.

The single-channel EDA architecture showed a maximum sensitivity of 97% with a rather modest positive predictive value of 66%.

Our multi-channel approach finally significantly increased the sensitivity and positive predictive value. Figure 2. shows some detection examples.

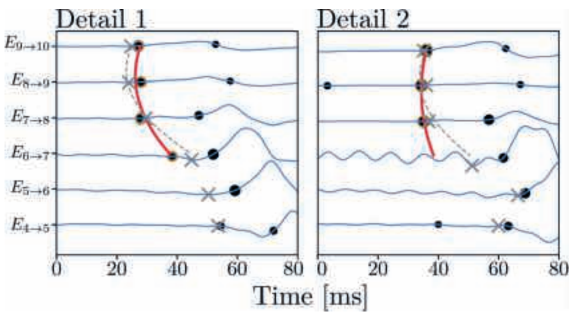


Fig. 2 Automatically detected p-wave onsets with localized propagation models. Blue: EsoECG observation, Black: EDA output, Yellow: active set, Red: found propagation model. Grey: Hand labeled events with corresponding propagation model (ground truth).

Discussion

We have shown that the evaluation of polynomial models with ALSSMs is also possible on hardware platforms with restricted numerical resolution such as fixed-point computations.

The proof of concept of the multi-channel onset detection was successfull. By using multi-channel information, the robustness was improved compared to single channel onset detection by fitlering out the noise or artefact induced false positive events of the particular channels.

References

R. Wildhaber et al., "Signal Analysis Using Local Polynomial Approximations," in 2020 European Signal Processing Conference (EUSIPCO), pp. 2223, Sep. 2020.

Acknowledgements

I would like to express my special thanks to Prof. Dr. Reto Wildhaber, Prof. Dr. Marcel Jacomet, Christof Baeriswyl and Frédéric Waldmann for their support throughout the project.

Targeted Drug Delivery in Glioblastoma Mouse Models

Martin Bertsch

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Institution: University of Bern, Institute for Biochemistry and Molecular Medicine
Examiners: Prof. Dr. Roch-Philippe Charles, MSc Javier Pareja

Introduction

Cancer is an omnipresent and dreaded disease, on a worldwide scale. In many countries it is the foremost or second ranked cause for premature death. Brain tumors account for 2.5% of cancer deaths, often affecting young adults. The most aggressive form of malignant brain cancer, glioblastoma multiforme, is also the most common. Less than 5% of patients diagnosed with this uncurable disease survive beyond 5 years [1]. Treatment usually involves chemotherapy, however, the blood-brain barrier functions to protect the brain from xenobiotics and consequently reduces the entry of the chemotherapeutic into the tumor-infested parenchyma of the brain. Nanocarriers might facilitate the delivery of therapeutics across this biological barrier and thereby increase the bioavailability in brain tumors. In this study, a liposomal carrier containing an approved chemotherapeutic drug was tested in glioblastoma xenografts using a mouse model.

Materials and Methods

A human-derived luciferase-expressing glioblastoma cell line was cultured and implanted into the brains of immunocompromised mice in a surgical procedure. Tumor growth was examined by bioluminescence imaging.

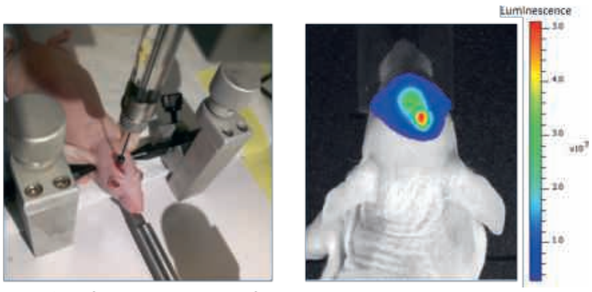

Fig. 1 Left: Implantation of cancer cells into a mouse brain. Right: Bioluminescence imaging of a mouse with an orthotopic brain xenograft of lusiferase-expressing cancer cells.

When the implanted tumors reached sufficient sizes, the mice were divided into three groups and treated by weekly intravenous injections either with the liposomal carrier, or directly with the same chemotherapeutic agent without the nanocarrier. The third group was used as control and was injected with a placebo. Following treatment end, the mice were euthanized, brains were recovered and stained for histological examination.

Results

All mice developed brain tumors, as confirmed by hematoxylin and eosin stained coronal brain sections. Cancer cell proliferation was reduced by 50% when treated with the drug-containing liposomal formulation compared to the other groups. Likewise, an increase in apoptosis index was observed in the group treated with the liposomal formulation of the drug compared to the control group of mice.

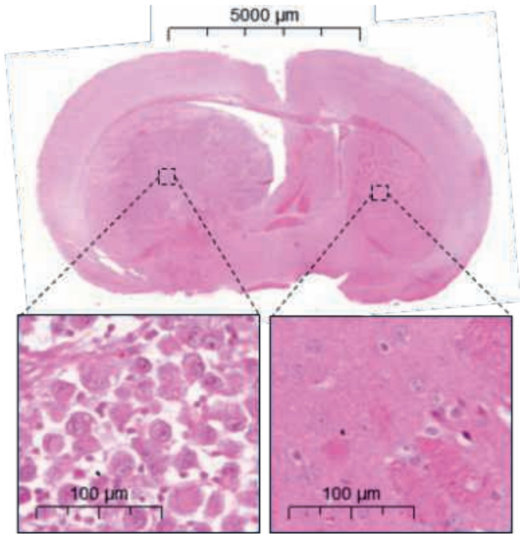

Fig. 2 Hematoxylin and eosin stained coronal brain section with a xenografted tumor (visible on the left side). The magnified section shows cancerous tissue (left) compared to normal nervous tissue (right).

Discussion

Although not statistically significant due to small sample sizes and differences in tumor morphology, the reduction in cancer cell proliferation and increase in apoptosis points towards a higher efficacy of the liposomal formulation, which might be due to a higher bioavailability. This would indicate a higher ability of the liposomal formulation to cross the blood-brain barrier than the free-drug formulation. However, further studies need to be conducted to determine this with certainty.

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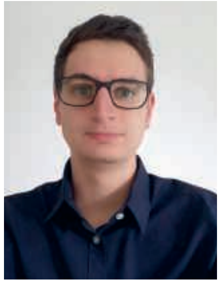
Middle Ear Laser Doppler Vibrometry Assessment for improved Electrocochleography

Benjamin Bircher



Supervisors: Prof. Dr. Bertrand Dutoit, Klaus Schürch
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University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: PD Dr. Wilhelm Wimmer, Prof. Dr. Bertrand Dutoit

Introduction

Electrocochleography (ECochG) records electrical potentials generated in the inner ear in response to acoustic stimulation. ECochG is a promising monitoring tool to improve preservation of residual hearing during cochlear implantation. However, the success rates of ECochG are highly affected by measurement-specific, patient-specific, or surgery-specific factors [1]. The aim of this project was to investigate surgery-specific factors by analyzing vibrations of the middle ear ossicles using Laser Doppler Vibrometry (LDV).

Materials and Methods

In our study, the velocity of the incus short process of a whole head cadaver specimen was measured through a transmastoid posterior tympanotomy using LDV. Three effects were analyzed: (1) the effect of opening the middle ear cavity (partially or completely), (2) the effect of cerumen or liquids in the ear canal, and finally (3) the effect of inserting a cochlear implant array. A middle ear circuit model was used to validate the experimental results.

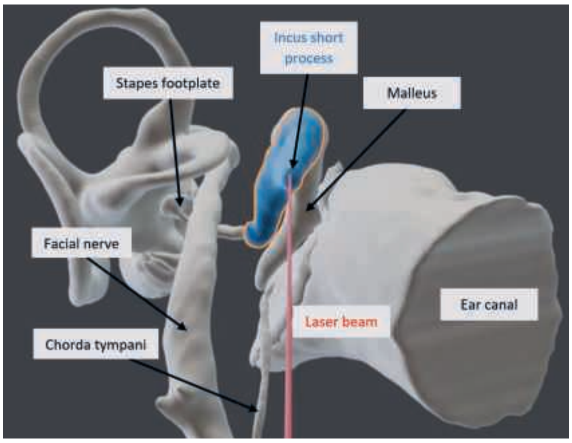

Fig. 1 3D view of the human ear. LDV measurements of the incus short process were taken through a transmastoid posterior tympanotomy (Ear model source [2]).

Results

Complete or partial opening of the middle ear cavity resulted in an increase in admittance of the incus short process, except around 2 kHz. The presence of cerumen in the ear canal caused a decrease in middle ear admittance.

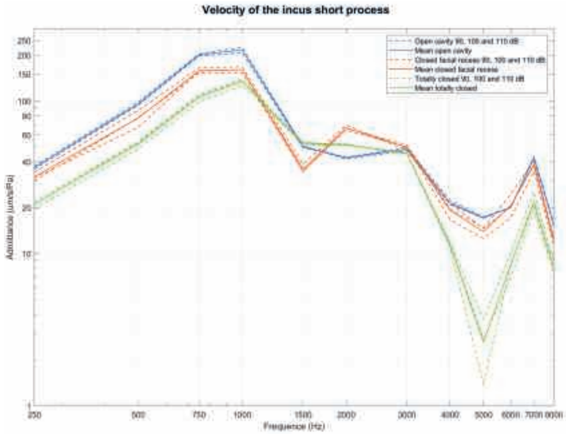

Fig. 2 Admittances of the incus short process with an open middle ear cavity (blue), a partially closed cavity (red), and a totally closed cavity. The curves were normalized by the ear canal sound level pressure.

Discussion

Measurements made with a probe microphone inserted into the ear canal are not sufficient to analyze the effects of surgery-specific factors on the middle ear. The opening of the middle ear cavity mainly leads to an increase in the compliance of the tympanic membrane. This leads to a decrease in middle ear impedance which results in an increase in ossicle velocity.

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Acknowledgements

I would like to express my special thanks to Klaus Schürch, Prof. Dr. Bertrand Dutoit, PD Dr. Wilhelm Wimmer, and PD Dr. med Stefan Weder for their support throughout the thesis.

Effect of Angiopoietin-1 and Angiopoietin-2 on Human IVD Progenitor Cells

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Examiners: Prof. Dr. Benjamin Gantenbein, Dr. Julien Guerrero

Introduction

Low back pain (LBP) is a musculoskeletal disorder leading to severe social and economic burden. It has been shown that LBP is mainly associated with intervertebral disc (IVD) degeneration. In contrast to healthy IVDs, degenerate IVDs become vascularized. In this context, Angiopoietin (Ang), a vascular growth factors involved in embryonic and postnatal angiogenesis plays a crucial role. Initial investigation in nucleus pulposus (NP) tissue from IVDs revealed that Ang-1 and Ang-2 were expressed by native NP cells. Furthermore, Ang-2 expression was significantly increased in infiltrated and degenerated tissue samples compared to healthy tissue. Moreover, the ratio Ang-2/Ang-1 in tissues from patients markedly increased with increasing age and level of degeneration of the IVD. Although, previous studies have shown that Ang-1 is crucial for the survival of nucleus NP cells. This study aimed to investigate the influence of Ang-1 and Ang-2 on NP progenitor cells (aka. NP Tie2$^+$ cells) a subpopulation of NP resident cells (Fig. 1), in a context of regenerative medicine.

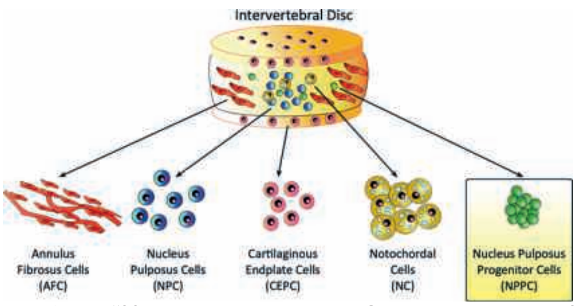

Fig. 1 The "fifth element" in the IVD: Schematic drawing of the four major cell types for the IVD tissue that were known for a longer time: (1) AFC, (2) NPC, (3) CEPC, (4) NC, and very recently (5) NPPC [1].

Materials and Methods

NP cells were isolated after digestion of human NP tissue from trauma patients. Following NP cells isolation, a Fluorescence-Activated Cell Sorting (FACS) was performed to sort out cells for positivity against Tie2 receptor. The resulting NP cells (Tie2+, Tie2- or mixed population) were cultured on 12-well plates in presence or absence of different concentration of Ang-1 and Ang-2 during 7 days in normoxia (21% O_2) or hypoxia (≤5% O_2). At the end of the process, samples were analysed by Alamar Blue assay to quantify metabolic activity and by Hoechst DNA assay to measure cell proliferation. Additionally, relative gene expression of NP related markers was evaluated via qPCR to study NP cells phenotype and behaviour.

Results

The study shows with statistical relevance differences between cells cultured in normoxia and hypoxia concerning NP cell's (Tie2$^+$, Tie2$^-$ or mixed population) metabolism after 7 days of culture. However, no significant differences in cells cultured within normoxia and hypoxia could be shown on the amount of DNA measured. Besides, the relative gene expression (hypoxia vs normoxia) some genes presented trends comparable to the one observed for metabolism and DNA measurement.
However, our study cannot provide evidence that either stimulation upon Ang-1 or Ang-2 or their dose-dependent administration have an influence on NP cell's metabolism and proliferation, as well as their relative gene expression.

Discussion

Our study can confirm previous findings, which demonstrated that hypoxia enhances NP cells phenotype which results in greater ECM components production, and indeed a higher metabolism. Regarding the differences in NP Tie2$^+$ cell's proliferation upon normoxia and hypoxia, our results are in accordance with previous studies performed on NP cells, showing that hypoxia can inhibit proliferation and induce apoptosis but might also promote the chondrogenic differentiation of IVD progenitor cells. Despite our results for the effect of Ang-1 and Ang-2 on NP Tie2$^+$ cells, recent studies prompt to continue our project with an improved experimental design as NP Tie2$^+$ cells (aka. NP progenitor cells) may constitute a novel therapeutic target for the treatment of IVD degeneration.

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Acknowledgements

This thesis was fulfilled in the Tissue Engineering for Orthopaedics and Mechanobiology (TOM) Laboratory. The important contribution of the TOM group is gratefully acknowledged. The project was financially supported by the Horizon 2020 project „iPSpine" under the grant agreement #825925.

Ex Vivo Validation of an Implantable Continuous Cardiac Monitor

Pavel Bouduban

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Institute for Human Centered Engineering HuCE
Examiners: PD. Dr. Thomas Niederhauser, PD. Dr. Andreas Häberlin

Introduction

Cardiovascular diseases are a major cause of mortality. Among them, arrhythmias are an electrical disorders causing irregularities in heartbeats, either bradycardia or tachycardia, potentialy leading to severs pathologies like stroke, syncope or thrombo-embolism. With ageing population, the prevalence of arrhythmias increases causing a significant demand for diagnostic tools. External Holter monitors are widely used to record electro-physiological activity of the heart, but long time measurement are not possible due to electrode-skin contact irritation and daily movements hindrance. Implantable loop recorder are subcutaneously implanted and record unregular and/or distorted ECG event, restraining the capability to detect asymptomatic arrhythmias like paroxysmal atrial fibrillation. To overcome these limitations, a new implantable continuous cardiac monitor (ICCM) has been developed, based on previous feability study realized by Sven Krause. The device is able to record continuously 3-leads ECG signal and transmit it through Bluetooth low power communication. It is powered by a 3.7 (v) Lithium battery being rechargeable via Wireless Power Transfer.

Materials and Methods

A SemiLunar shaped implant reproducing the triangle of Eithoven was built. Miniaturization, development of an integrated Bluetooth circuit and interaction between the different units of the implant were intensively studied. The setup was built to integrate easily removable user interfaces for programming and signal simulation purposes.
The implant was hermitically sealed with a PDMS encapsulation before undergoing an ex-vivo trial.

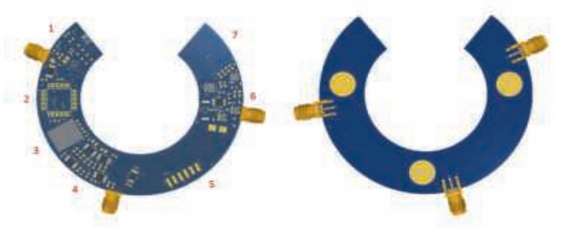

Fig. 1 SemiLunar ICCM Front (left) and Back (right) side developed for In-Vivo validation of an implantable cardiac monitor.

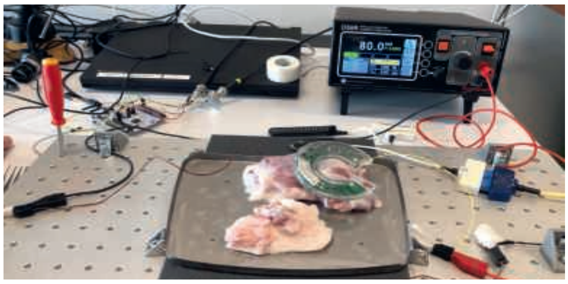

Fig. 2 Ex-Vivo trial with stimulated action potential detection

Results

The battery is effectively rechargeable through built-in 3-layer antenna. The new implemented Bluetooth circuit with free-clearance chip antenna is able to transmit data with a stable connection. Analog-front-end is able to acquire and filter signals. The components are interacting with each other as expected. The action potentials were read and transmitted to a remote smartphone.

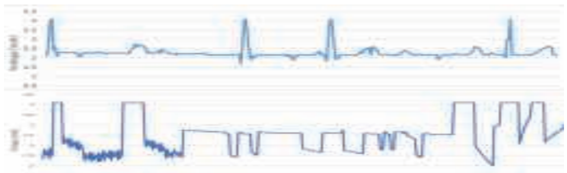

Fig. 3 (Top) ECG with MCI Simulator through electrodes, (Bottom) ex-vivo trial action potential recording,

Discussion

A functional rechargeable implantable continuous cardiac was developed and tested in a ex vivo trial. The device is able to record and send data via Bluetooth low energy. Further investigation has to be done concerning data flow security to avoid data loss. The encapsulation procedure has to be improved with additional coating and encapsulation to avoid any liquid leakage.

Acknowledgements

I would like to thank my two supervisors, Prof. Dr. Thomas Niederhauser and Sven Krause, for their expertise and knowledge. Also, I would like to thank all my colleagues from the HuCE-microLab for their help and support during my thesis.

Speech Recognition for Parkinson Patients in an Instrumented Apartment

Thomas Buchegger

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Examiners: Prof. Dr. Tobias Nef, Dr. Stephan Gerber

Introduction

Parkinson's Disease (PD) is a neurodegenerative disease characterised by tremors, rigidity, and bradykinesia that affects 15'000 patients in Switzerland. Currently, there is no cure for PD, but treatments, such as drugs or surgery, are available to help reduce symptoms and keep the quality of life. The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is often used in a clinical environment to evaluate PD symptoms. However, continuous monitoring using wearable devices in a familiar environment is desired because there is a discrepancy between a patient's performance in clinical assessment and activities of daily living. One way to assess Parkinson is by analysing emotional speech. It has been proven that there is a strong correlation between the severity of speech impairment and how PD speech sounds. The more the speech is impaired, the sadder its emotion sounds [1]. The “NeuroTec Loft” is an instrumented apartment [2] that aims to monitor human behaviour and how neurological disorders influence daily life. This thesis aimed to complement the current sensors in the NeuroTec Loft with the addition of new microphones that record patient’s voice in activities of daily living to enable the analysis of emotional speech.

Materials and Methods

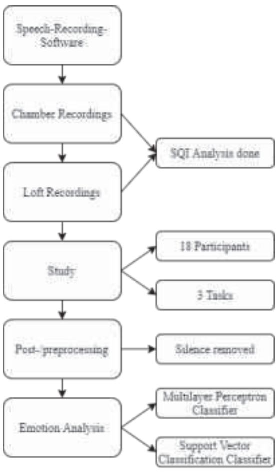

Fig. 1 Overview of methods steps

The goals of this thesis were to find the optimal microphones positions in the NeuroTec Loft and gather emotional speech data for a dataset. For this, experiments in the ARTORG sound chamber were first conducted to better understand the behaviour of different speech quality indices (SQI) under different conditions. Those findings were later used to evaluate the speech quality of the recorded audio signals. To find optimal positions of the microphones in the NeuroTec Loft, test recordings were performed at several locations under different conditions. The best position was derived by analysing the SQIs. Then a study was conducted, made up of three tasks – free speech, image description and sentence repetition. After that, a labelled dataset with positive, neutral and negative emotional speech audio signals was created with the recordings from the study. Finally, a first analysis was conducted on the dataset to determine if emotions could be extracted from the recordings with the help of speech emotion recognition.

Results

A Neural Network trained with recordings containing only positive and negative emotions was used to analyse the data and correctly predicted the emotions in the given recordings with an accuracy of 63.85%. Training the model also with recordings with a neutral emotion reduced the overall accuracy to 40.56%.

Predicted value

Fig. 2 Confusion Matrix of correctly predicted positive (pos) and negative (neg) emotions for the complete dataset

Discussion

It was proven that evaluation of speech audio signals with multiple SQIs can be used to determine the optimal microphone position in an apartment. Furthermore, it was concluded that detecting positive emotions in speech is easier than negative.
To further improve emotion recognition results, several preprocessing methods could be applied to the audio files and the NN model could be trained with a bigger dataset.

References

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[2] Schindler et al. “NeuroTec Sitem-Insel Bern: Closing the Last Mile in Neurology”, 2021

Acknowledgements

I would like to thank my two supervisors Dr. Stephan Gerber and Pascal Reuse for their enthusiasm, support, encouragement, and guidance throughout this project.

Assessment of Cell Viability and Metabolic State using Autofluorescence Spectroscopy inside Cell Bulk

Linard Büchler

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Bern University of Applied Sciences, Institute for Human Centered Engineering
University of Bern, Institute of Cell Biology
Examiners: Karl-Heinz Selbmann, Prof. Christopher Meier

Introduction

Monitoring of cell cultures represent a wide and promising field of research. From culture medium feed to cell internal activities, multiple monitoring parameters have been investigated and are been used in various control loops in order to guarantee optimal cell growth. The metabolic activity of cell bulks is mostly monitored using metabolites such as CO_2 rejection or O_2 consumption by the cells. In this study we investigated a novel in-line monitoring method for the redox ratio (RR) in cell cultures using autofluorecence (AF) spectroscopy. Two biomarkers were used, flavin adenine dinucleotide (FAD/H) and β-nicotinamide adenine dinucleotide (NAD/H), that are two co-enzymes, which act as electron carrier during cell respiration.

Materials and Methods

The oxidised form NADH has an AF property (Ex:360 [nm], Em:460 [nm]) and the reduced form FAD (Ex:450 [nm], Em:530 [nm]). A measuring device was build and characterized. It is able to exite samples at the specific wavelength of 360 [nm] and 450 [nm]. The spontaneous emitted light spectra are collected and integrated by a CCD spectrometer. The setup is design to measure transmission and emission of light from samples containing different mixed concentration of NADH and FAD.

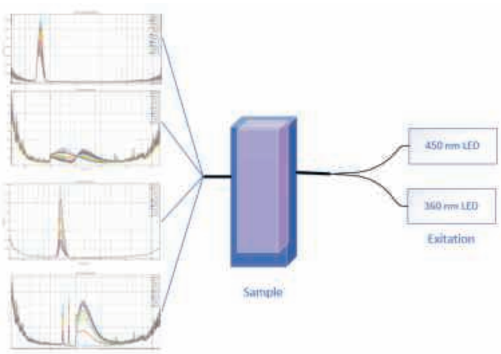

Fig. 1: Representaiton of the measure setup. With the two light sources on the right and the four spectral measures done on each sample on the left.

Qualitative and quantitative models were generated using Principal Component Analyses (PCA) to reduce the data set dimentionality and to generate predictive Partial Least Square (PLS) regression models for molecule concentrations.

Results

The predictive models are able to compute the concentration out of several mixed samples. With the coefficient of determination of $R^2 = 0.980$ for NADH and $R^2 = 0.986$ for the FAD models, respectively.

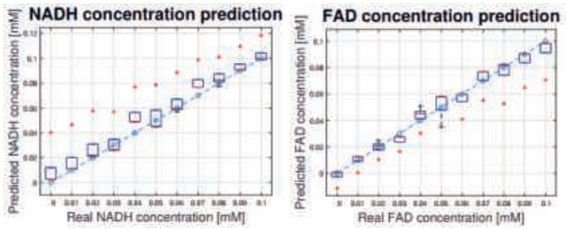

Fig. 2 Results from the trained models over the rest of the spectral data from unknown concentrations. (Left) predicted NADH concentration, (Right) predicted FAD concentration.

It was possible to demonstrate a trending behavior on the first two Principal Component (PC1/PC2) which is correlated with the evolution of RR.

Discussion

These results are consistent with the findings presented in other studies regarding the spectrometric behavior of NADH and FAD in spectroscopy. Multivariable analysing methods in form of the PCA and PLS models show promising capacities on samples containing different molecule concentrations.

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Acknowledgements

The project was supported by Bern University of Applied Sciences by allocating budget to build the entire experience setup.

Mechanical and Biological Validation of a Novel Microvasculature-on-Chip Device

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Examiners: Prof. Dr. Olivier T. Guenat, MSc Dario Ferrari

Introduction

Organ-on-chip (OOC) models aim to bridge the gap between the complexity of in vivo models and the simplicity of in vitro models. It is an interdisciplinary research field involving microfluidic systems and cell cultures. OOC aims to reproduce a key functional unit of an organ. Microvasculature-on-chip (MOC) is intended to reproduce the function of microvessels on a microfluidic chip. Vascular networks facilitate nutrient and oxygen transport in the body. They are a key component for many tissues [1,2]. The establishing of vasculature-on-chip is essential for future developments within the field. The aim of this novel MOC is to create a microvascular network within a hydrogel membrane.

Materials and Methods

In this thesis, a novel microvasculature-on-chip device was mechanically and biologically characterized. Two different chip designs were fabricated with polydimethylsiloxane (PDMS) and validated. The first part was the filling of the chip with fibrin gel, as only one of three interconnected channels needs to be filled. PDMS is hydrophobic which complicated the filling, therefore two hydrophilic surface treatments were applied on the channels of the chip. Second, the chip was biologically characterized by culturing HUVECs on the chip. The viability of the cells was observed as well as their self-assembly with fibrin gel and collagen hydrogel, during set time periods. The analysis was done using fluorescence microscopy and Fiji/ImageJ.

Results

Filling the untreated first chip design with fibrin gel was not possible. Whereas, the filling of the chip was successful with surface treatments. However, all channels were filled and the fibrin gel did not stick to PDMS. The second chip design shows a successful filling when the channel is already wet (Fig.1). HUVECs cultured on fibrin gel on both chip designs result in cell viability (~85%) coherent with the literature [3]. Self-assembly of HUVECs has been observed on fibrin gel and collagen. The cells already started to self-assemble after 4 days in culture and at 12 days a network was taking shape inside fibrin gel, minium sample number n=5. As a preliminary result, after 4 days in culture, more cells seem to self-assemble in collagen than in fibrin. The collagen membrane was thinner than the fibrin gel membrane.

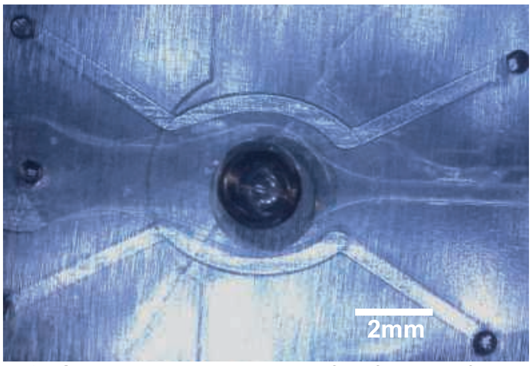

Fig. 1 – Second chip design successfully filled with fibrin gel.

Discussion

Thin hydrogel membranes were successfully created in the chip although further improvements can be made to optimize the filling of the chip. Surface treatments considerably facilitated the filling of the chip with fibrin gel. However, they can not be used due to adhesion issues. On the other hand, updating the design has shown an improvement for the filling via only one channel. The surface conditions of channels are not ideal which can be a major limiting factor of the filling. The results validate that HUVECs are viable and able to self-assemble on the two chip designs. Collagen is a more physiological microenvironment for cells than fibrin gel [1]. In addition, for the collagen to attach to PDMS a surface treatment (hydrophilic) is anyways required. For these reasons, collagen is an excellent candidate to culture cells on this chip.

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Acknowledgements

I would like to thank the Organ-on-chip research group which was a resourceful, supportive and amazing group.

Master's Thesis in Biomedical Engineering

Confounder-Free Deep Learning Training for Brain Tumour Segmentation

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Examiners: Prof. Dr. Mauricio Reyes, Dr. John Anderson Garcia Henao

Introduction

When extracting MRI imaging features with calculation algorithms it is of great advantage to obtain one general model for MRI images of different MR scanners. Inter- and intra-vendor biases occur in MRI images. These biases can cause differences in the performance of a model. It is desirable to obtain a confounder-free deep learning network. The scope of this thesis was to evaluate and erode the impact of biases caused by inter-vendor differences when accomplishing a glioma segmentation task.

Materials and Methods

A confounder-free deep learning segmentation network (ConfNet) was developed similar to a Generative Adversarial Network. The min-max game consisted in minimizing the confounder biases (two vendors), while maximizing the confusion of the classifier model. The classifier model recognises features associated to the confounder biases (two vendors). These were removed by applying an adjusted loss function which extincts these biases in the segmentation task. In Figure 1 ConfNet is shown. Raw classification and segmentation models were developed to compare its results to ConfNet.
These three models have been trained on a training dataset with two vendors and tested on the testing dataset of a third vendor. The vendors have been synthetically generated by applying three different filters to the same MRI images of glioma patients.

The results were compared by their accuracy, box plots, the Dice Similarity Coefficient (DSC) and the 95th-percentile Hausdorff Distance (HD95).

Results

The accuracy of the raw classifier was 91.89%, while ConfNet achieved only 50%. The difference in DSC between the raw segmentation model and ConfNet was 0.50%. The difference in HD95 between the latter was 47%.

Discussion

ConfNet is not impacted by the confounder bias any more. The difference in DSC is negligible. The HD95 shows a larger difference between the models than the DSC. The box plot shows that the segmentation model has a smaller discrepancy in the HD95 results than ConfNet. These results are encouraging and show that ConfNet is no longer affected by confounder biases and does not lose performance accuracy.

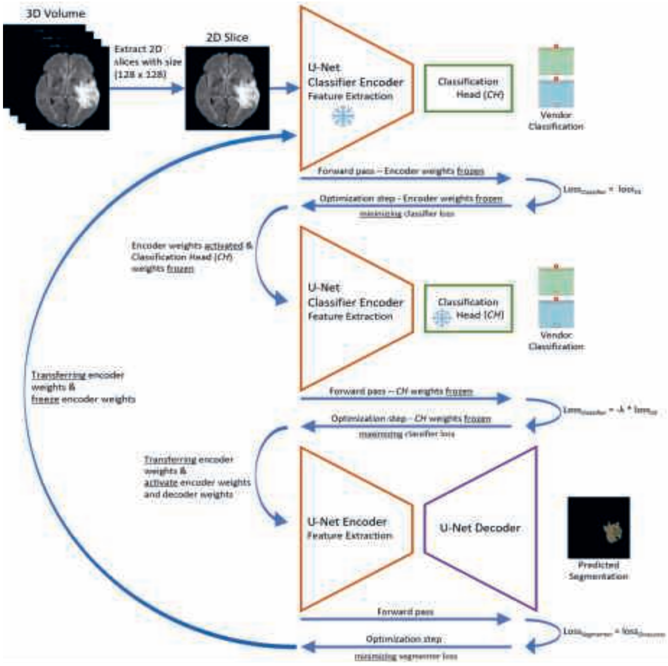

Figure 1: Training and Testing Network of ConfNet model

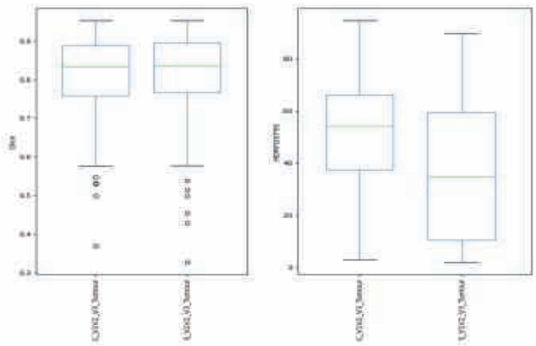

Fig. 2 DSC and HD95 of ConfNet (left) compared to raw segmentation model.

References

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In Vitro Setup for Temporal Interference Stimulation

Lukas Geisshüsler

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Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering HuCE
Examiners: Prof. Dr. Thomas Niederhauser, PD Dr. Andreas Häberlin

Introduction

Conventional electrical stimulation has some significant limitations in terms of its ability to reach deeper structures without stimulating structures closer to the electrodes. In addition, the spatial resolution of stimulation is very limited. A promising technique to overcome these limitations is temporal interference (TI) stimulation. TI stimulation takes advantage of the low-pass filtering property of nerves to use the low-frequency envelope of two interfering signals for stimulation, rather than being stimulated directly by the high-frequency carriers. The location of maximum interference can be controlled by adjusting the amplitude ratios of the stimulation current and electrode pair placement. To further investigate the applications of TI stimulation, a sophisticated stimulation setup was designed and characterized. It allows to study and verify the influence of the specific stimulation frequency, stimulation waveform and electrode design on the stimulation efficiency for the desired application.

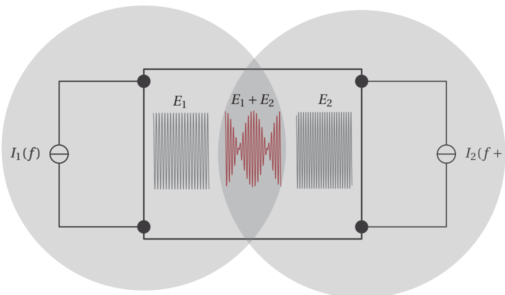

Fig. 1 Example of two interfering electrical fields. The interference has an envelope oscillating with Δf.

Materials and Methods

The high voltage power amplifier is the most critical part of the stimulator design. To achieve the best performing solution, four different prototypes of voltage-controlled constant current sources were stimulated using SPICE model-based simulation tools. Based on the simulation results, a prototype of each circuit was designed and its performance was evaluated. The constant current source with the best performance was then used in a stimulator prototype.

Results

The final design is based on a Howland current pump in bridge configuration us- ing two high voltage operational amplifiers. The design allows unipolar and bipolar stimulation with an output voltage amplitude of up to 375 V and an output current range of 1 mA up to 100 mA. The stimulator allows driving currents of 10 mA at load impedances up to 35 kΩ at 10 kHz. For higher frequencies up to 100 kHz, the stimulator can drive currents up to 10mA in load impedances up to 3kΩ. To test a hypothesized way to reduce current crosstalk between stimulator channels by temporal separation the stimulation signals, a high-frequency AC switch was added to the stimulator. Based on high-voltage, high-speed gallium nitride (GaN) transistors, it can switch an output signal of up to 400 V with rise times of 20 ns and fall times of up to 40 ns.

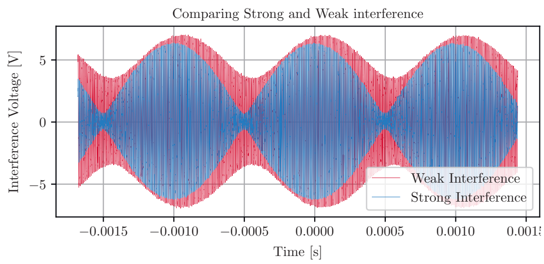

Fig. 2 Interferences of a 100kHz and a 101kHz carrier signal. Interference envelope has a frequency of 1kHz. Note the difference of the envelope amplitude based in the location.

Discussion

The stimulator setup designed within this work is the first that has been proposed specifically for TI stimulation. Because of its high frequency range in combination with a large range of output currents and a large voltage compliance the setup allows testing a large variety of application specific stimulation protocols. By using a specially designed stimulator in combination with commercially available high voltage power supplies and arbitrary waveform generators, rapid changes to the stimulation signal can be done and the necessary signal precision is ensured.

References

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Acknowledgements

I would like to express my special thanks to Prof. Dr. Thomas Niederhauser, PD. Dr. Dr. med. Andreas Häberlin and MSc Elisa Maria Kaufmann for their support throughout the project.

Design of an End-Effector Based Arm-Swing-Device for Gait Training

Katrin Gfeller

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Examiners: Prof. Dr. Kenneth Hunt, Dr. Juan Fang

Introduction

Rehabilitation robots offer high-dosage and high-intensity training. This makes them a promising novel treatment for patients with motor disorders caused by stroke or spinal cord disease. Robots that are currently used in gait rehabilitation only move the lower limbs. However, to achieve a higher task specificity, the arms should simultaneously be moved. The aim of this thesis was to modify an existing gait trainer by adding functionality for moving the arms. This is accomplished by following embodiment principles which state that control and process tasks should be distributed as much as possible across all components of a robot.

Materials and Methods

The Lyra, a gait trainer which is characterized by its sophisticated mechanical design, serves as the basis for this thesis. Its mechanical design offers possible extension points for integrated arm movements that can be synchronized with movements of the lower limbs.

In a first step, the arm movements observed in natural gait were analysed in order to determine the movement the arm swing mechanism (ASM) should assist. For this purpose, existing recordings were analysed with a dedicated Matlab script. The analysis showed that arm movement during gait is characterized by a high variability and an pronounced movement in walking direction.
In a second step, a mechanism was devised that assists the pronounced movement in the walking direction but does not further impede with the natural movement of the arm. To address the great variability of natural arm swing, amplitude and direction of the assisted movement are individually adjustable. This is achieved with a crank-drive that converts the rotational movement of the installed motor to a longitudinal movement and a cable with some pullies that transmits the motion of the drive to the arm of the patient. The amplitude of the motion can be adjusted at the crank-drive and the direction can be adjusted with the position of the pullies that lead the cable.
In order to evaluate the function of the newly developed system the angular trajectories of the joints as induced by the ASM were measured and compared with the angular trajectories of the natural gait.

Fig. 1 CAD-Modell of the complete System

Results and Discussion

The newly developed ASM is characterized by its plain but functional mechanics. As the movement is predetermined by the mechanics, no additional control technology is needed. The light weight construction allows for fast movements up to a cadence of 100 steps per minute. The movement transmission by means of ropes supports the arm swing but does not restrict the arm movement any further. The arm movements induced by ASM correspond well with those of natural gait.

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I would like to thank my supervisors Dr. Juan Fang and Prof. Dr. Kenneth Hunt for their constant motivation and scientific guidance throughout this study. I would also like to thank the workshop team at BFH for their great assistance and for manufacturing all the components for this thesis.

A Bioactive Transplantation Device for Reduction of Complications after Pressure Injury Surgery

Rafael Gfeller

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Examiners: Prof. Dr. Jivko Stoyanov Ph.D., Prof. Dr. Benjamin Gantenbein Ph.D.

Introduction

Pressure injuries (PI) occure due to high contact pressure of the skin and/or the underlying tissue over a prolonged period of time. They are one of the most frequently occurring complications during a hospital stay. The treatment of PIs is very care intensive with a high complication rate in wound healing after surgery and therefore connected to a high number of needed re-operations. A promising future direction to reduce complications and re-operations is the combination of tissue engineering techniques with autologous adipose-derived stem cells (ADSC) to augment the subcutaneous tissue after plastic surgery. Previous studies suggest that ADSC could have an important role in wound healing. Furthermore, the combination of ADSC with autologous platelet rich plasma (PRP) could additionally improve the healing process. This study aimed to test and optimize in vitro various combinations of ADSC, PRP and collagen scaffolds in order to promote faster PI recovery after surgical intervention and possibly reduce the steps required to translate ADSC use to clinical practice (Fig. 1). Another objective was to evaluate mechanical fat isolation techniques yielding different adipose tissue fractions, compare it with enzymatic digestion, and to replace FBS with PRP to promote cell proliferation, both potentially in conflict with regulatory agencies.

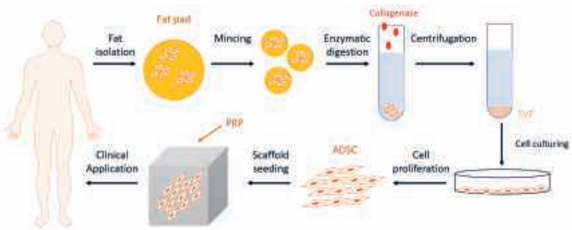

Fig. 1 Steps required to get autologous ADSC to the clinical application.

Materials and Methods

A number of monolayer (2D) experiments and scaffold based (3D) experiments were conducted. ADSC were isolated from four donors and cultured as 2D monolayers in 6- and 24-well plates, or as 3D cell-construct using a medical device collagen sponge (BIOPAD). 2D Monolayers were proliferated for 5, 7, or 12 days in medium supplemented with either FBS or PRP. 2D monolayer and 3D cell-constructs were differentiated for 14 days towards adipogenic lineage using adipogenic medium supplemented with either FBS or PRP. Outcome measures included cell proliferation, lipid quantification, DNA quantification and the expression of adipogenic genes, evaluated via qRT-PCR.

Results

The study showed that ADSC harvested with mechanical isolation techniques without enzymatic digestion required 12 days to reach 80-95% confluence while ADSC harvested with enzymatic digestion only needed 5 days. However, no significant differences in the differentiation potential were detected between the two groups. Furthermore, increased proliferation could be observed in ADSC cultured in medium supplemented with PRP compared to ADSC cultured in DMEM/Ham's F12 with 10% FBS (Control). In addition, 3D cell constructs showed a significant increase in lipid accumulation when differentiated in adipogenic medium with FBS compared to the Control group. No significant differences for lipid accumulation could be observed for the differentiation in adipogenic medium with PRP compared to the Control group.

Discussion

Besides slower expansion, our study demonstrated promising results to consider mechanical isolation techniques to avoid the use of enzymatic digestion. ADSC could be successfully differentiated towards adipogenic lineage more effectively on the 3D cell-constructs compared to monolayer. Regarding the effects of PRP on the proliferation of ADSC, our results showed enhancement of cell proliferation, however it had an inhibitory effect on adipogenesis. Altogether, these results demonstrate the potential suitability of ADSC-constructs for PI healing, however PRP would have a role in promoting host cell regrowth and vessel formation rather than supporting ADSC adipogenesis.

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Acknowledgements

This thesis was conducted in the SCI population biobanking & translational medicine unit. The important contribution of the group is gratefully acknowledged. The project was supported from the Swiss Paraplegic Research.

Deep Learning based Segmentation and Fat Fraction Analysis of the Shoulder Muscles using quantitative MRI

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Examiners: Dr. Kate Gerber, Dr. Nicolas Gerber

Introduction

Stability of the shoulder joint is mainly provided by four rotator cuff muscles. If some of these muscles are torn, arthroscopic rotator cuff repair (ARCR) surgeries have been related to significant short- and long-term improvements in pain score, function, and strength, providing a less invasive alternative to complete shoulder arthroplasty. However, various anatomical shoulder parameters can impair the success rate of ARCR surgeries. One crucial influencing factor for a successful repair is the fatty infiltration of the torn muscle, which is typically estimated within five discrete stages using the Goutallier classification. The measurement is visually estimated on an oblique sagittal T1 weighted shoulder MRI slice on a defined anatomical position (Y-view), which limits its reliability and greatly depends on the reader's experience. While specialized MR sequences, such as two-point Dixon (2PD), allow fat fraction (FF) analysis on a volume and have been shown to be more reliable than the Goutallier grade (Horiuchi et al.), the time-consuming manual work required to extract such a metric has limited their use in clinical routine. To our knowledge, no automated system for such an analysis on rotator cuff muscles exists. We, therefore, propose a fully automated end-to-end pipeline to allow quantitative FF analysis on 2PD data, which includes data alignment and Y-view slice detection for result validation.

Materials and Methods

We developed a complete web-based application for FF calculation and morphological analysis of patient specific shoulder anatomy from 2PD data, which includes automatic: client side anonymization of DICOM data; muscle and bony anatomy segmentation; Y-view detection; and calculation of the FF of the supraspinatus (SSP) muscle. To segment the SSP muscle and the humerus and scapula bones, we employed nnU-Net, a state-of-the-art convolutional neural network for medical image segmentation. The network was trained on 23 2PD images of non-tear patients and the mask ground truths. Similarly, a landmark detection algorithm was developed and trained on 30 2PD images. The detected landmarks were used to automatically identify the Y-view slice along the scapular wing. For the SSP, we extracted the average FF over the complete volume and the Y-view slice. Fivefold cross-validation was used to compute the segmentation accuracy compared to the ground truth manual segmentation. For efficient computation and easy accessibility, the workflow was integrated into a web application and deployed to the cloud. A fully interactive 3D volume viewer was integrated to allow inspection of the MRI data and segmentation results.

Results

The SSP was detected with a Dice coefficient of 90%. The average FF over the complete SSP volume differed approximately 1.5% from the ground truth on the evaluated cases. The detected landmarks allowed axial scapula alignment and Y-slice detection. With the currently employed hardware, the automatic analysis takes approximately 10 minutes.

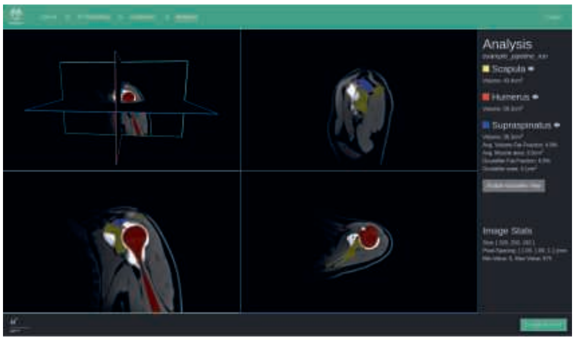

Fig. 1 Main window of the web-based application with fully interactive 3D viewer and analysis results on the right side.

Discussion

We could demonstrate that a fully automated quantitative fat fraction analysis of the supraspinatus on non-tear 2PD data is feasible. The deployment in a cloud environment grants flexible scaling of the infrastructure and allows clinicians to perform analysis of a patient's shoulder within 10 minutes and is, therefore, potentially applicable in clinical settings. This work builds the basis for further automated quantitative analysis on larger datasets which might lead to better surgical outcome predictions in the future.

References

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Acknowledgments

We would like to thank our clinical partners Prof. Dr. med. Matthias Zumstein, Dr. med. Michael Schär and Dr. med. Lukas Dommer for providing the clinical perspective to this endeavour.

Lack of Endothelial PECAM-1 Enhances Extravasation of Brain Seeking Melanoma Cells Across the Blood-Brain Barrier *in vitro*

Ece Su Ildız

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Institution: University of Bern, Theodor Kocher Institute
Examiners: Prof. Dr. Ruth Lyck, Dr. Giuseppe Locatelli

Introduction

Melanoma is the most aggressive type of skin cancer in humans. Main cause of melanoma fatalities is due to formation of melanoma brain metastasis, which requires extravasation of melanoma cells across the tight blood-brain barrier (BBB). Here, we investigated the effect of compromised barrier properties caused by the absence of PECAM-1 on two separate steps of extravasation: the shear resistant arrest and diapedesis of the melanoma cells. In addition, we compared two different melanoma cell lines: The YUMM1.1 (Yale University Mouse Melanoma) melanoma cell line and a brain seeking daughter cell line YUMM1.1-BrM4. Overall, this project is one building block in the understanding of the role of BBB integrity on metastasis formation by aggressive brain seeking melanoma cells.

Materials and Methods

Primary mouse brain microvascular endothelial cells (pMBMECs) isolated from the PECAM-1$^{+/+}$ or PECAM-1$^{-/-}$ C57BL/6 mice were used to model the BBB in vitro. A flow chamber setup combined with in vitro live cell imaging was employed to study shear resistant arrest and sustained adhesion. A multi-well chamber setup was used to determine melanoma cell firm adhesion under static condition with multiple samples in parallel. Melanoma cell diapedesis was assessed in a two-chamber based Transwell® assay (Figure 1). Diapedesed melanoma cells remained adherent on the underside of the filter insert (Figure 1) and were counted after immune fluorescence staining and image acquisition at the confocal microscope (Figure 2). Images were processed using FIJI software and melanoma cells were automatically counted.

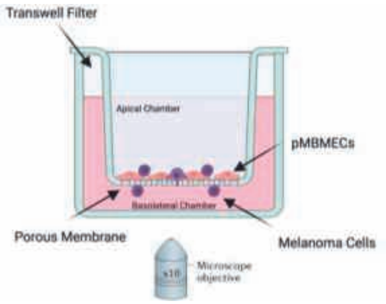

Fig. 1 In vitro diapedesis experiment setup with Transwell filter insert with 8 μm pore size, pMBMECs monolayer and melanoma cells.

Results

pMBMECs formed a confluent monolayer with a strong junctional VE-cadherin signal irrespective of the presence of absence of PECAM-1. Shear resistant arrest and sustained adhesion of YUMM1.1 and YUMM1.1-BrM4 to PECAM-1$^{+/+}$ and PECAM-1$^{-/-}$ were comparable. In contrast, YUMM1.1-BrM4 cells presented a drastic increase in diapedesis across both cohorts of pMBMECs compared to YUMM1.1. Moreover, YUMM1.1-BrM4 diapedesis across PECAM-1$^{-/-}$ pMBMECs strongly exceeded diapedesis across PECAM-1$^{+/+}$ pMBMECs. Taken together, the compromised PECAM-1 deficient BBB favored diapedesis of the brain seeking YUMM1.1-BrM4 melanoma cells.

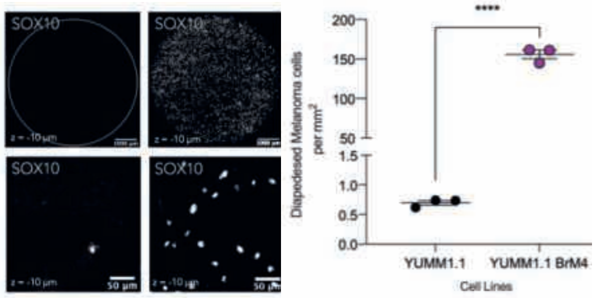

Fig. 2 Confocal microscopy imaging of a Transwell filter insert with 8 μm pore size with PECAM-1$^{+/+}$ pMBMECs demonstrating the diapedesis event of YUMM1.1 (left) and YUMM1.1-BrM4 (middle) cells shows the underside of the filter. Diapedesed number of YUMM1.1 and YUMM1.1 BrM4 cells across PECAM-1$^{+/+}$ pMBMECs per mm^2 (right).

Discussion

Based on our findings, we hypothesize that the adaptations of the brain seeking YUMM1.1-BrM4 melanoma cells are independent of adhesive interaction with the BBB but promote diapedesis across the BBB. We further conclude that the complex cell-cell junctions of the BBB are important to limit melanoma extravasation. Taken together, it will be important to further reveal the mechanism by which the brain seeking melanoma cells can benefit from compromised barrier properties. One possibility would be that diapedesis of melanoma cells requires proteases and that the brain seeking variant harbours increased proteolytic activity compared to its parental cell line. As a next step, RNA-sequencing and comparison of gene expression between the two YUMM1.1 cell lines could help elucidating the molecular mechanism of melanoma cell extravasation across the BBB.

Acknowledgements

I would like to thank my supervisor Prof. Dr. Ruth Lyck and MSc. Federico Saltarin for their great support, help and motivation throughout this project.

Devlopment of Stenosed Coronary Arterial Phantom for a Coronary Artery bench Simulator

Marc Ilic

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Institution: University of Bern, sitem Center for Translational Medicine and Biomedical Entrepreneurship
Examiners: Prof. Dr. Jürgen Burger, MSc Cornelia Amstutz

Introduction

Development of newly designed devices for cardiac catherization, such as balloons or stents, requires an adapted and realistic testing environment. This project focuses on creating stenosed coronary vessel phantoms, which feature physiologic properties.

Materials and Methods

Different approaches were used to create stenosed coronary vessel phantoms, including multilayer casting methods, which allows for regulation of the mechanical properties along the arterial phantom. The main components used for the manufacturing of the phantoms are silicone and gypsum.

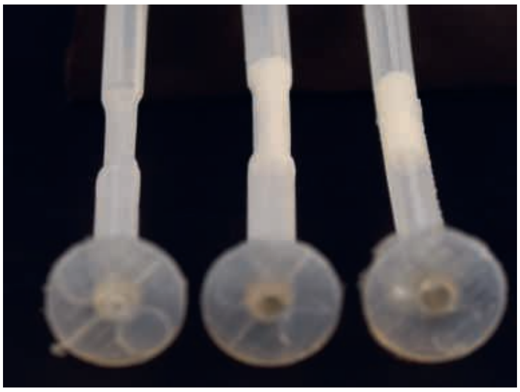

Fig. 1 Different stenosed arterial phantoms based on a generalized geometry

Mechanical properties were determined through tensile tests and compliance measurements, which were performed using optical coherence tomography (OCT). Microscopic evaluation was performed to investigate the layer structure of the test specimens.

Results

Experimental compliance values for stenosed phantoms were in the range of 10.8 to 16.0 $mm^2/mmHg \times 10^3$, which is comparable to data reported in literature. Additionally, significant differences were seen in phantoms with healthy versus stenosed segments. Individual layer thickness of 0.6 mm was measured during the microscopic evaluation; however, significant eccentricity was observed for more than 30 % of the stenosed specimen.

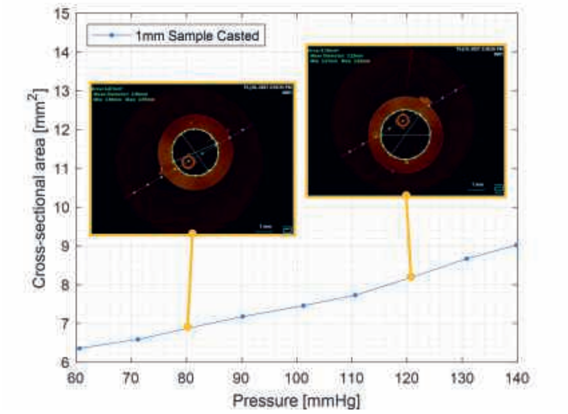

Fig. 2 Cross-sectional change of stenosed coronary arterial phantom due to the increase in pressure, including two OCT images at 80 mmHg and 120 mmHg.

Discussion

The chosen methodology seems suitable for the creation of stenosed coronary vessel phantoms with changing mechanical properties along the vessel. Additionally, a significant amount of data for further processing has been gathered. A remaining challenge is to deduce the exact tuning of parameters to achieve the desired properties. Furthermore, the precision of the procured phantom must be improved to accomplish higher reproducibility with smaller variances.

References

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Acknowledgements

I would like to thank the members of the Cardiac Technology and Implantable Devices group for their contribution and inputs throughout my thesis work.

Development of an Ultrasonic Scaler for Dental Calculus Removal

Camille Kaufmann

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Examiners: Prof. Dr. Juergen Burger, Martin Hofmann

Introduction

Periodontal diseases are inflammatory conditions affecting the periodontum. Ultrasonic scalers are used by dental hygienists to remove dental biofilm and calculus to reduce inflammatory reactions and thus the risk of associated systemic diseases such as atherosclerotic cardiovascular disease and diabetes. A typical piezoelectric transducer, the so-called Langevin transducer, consists of a piezoelectric disc stack, a mechanical wave amplifier and a tip. The aim of this work is to develop a novel planar ultrasonic piezoelectric transducer to improve efficiency, weight, and controllability; thus, making the procedure more comfortable for the patient and operator. This new transducer is composed of two piezoelectric rectangular plates adhesively-bonded to each side of a titanium horn.

Materials and Methods

Finite element method (FEM) was used to simulate the new design and has been continuously extended and optimized. The model initially comprised a single piezoceramic plate, was then expanded to a symmetrical transducer and finally extended with the amplifying section and a tip. At each step, the simulation has been compared and verified with electric impedance and mechanical vibration measurements of fabricated prototypes. Based on the calibrated simulation of a coarse design, the transducer has been optimized with the objective of achieving a proper longitudinal resonance at 28 kHz with a in-plane tip displacement amplitude >50 µm. Thereby, the out-of-plane flexural and torsional vibration should be less than 10 % of the in-plane vibration to prevent damage to the tooth surface.

Fig. 1 Three-dimensional FEM simulation using COMSOL Multiphysics 5.5 to identify longitudinal eigenmodes around 28 kHz. Left: in-plane vibrations and right: out-of-plane vibrations.

Results

The simulation configurations (plate, symmetrical and coarse design) were successfully modelled and matched the measurements carried out on the prototypes. By optimising the simulation model, a final design was developed to meet the target values. The performances of the optimized prototypes were in line with the expectations of the simulation and attained the objectives. The tip displacement amplitude at a supply voltage of 50 V_p reaches 65 µm .

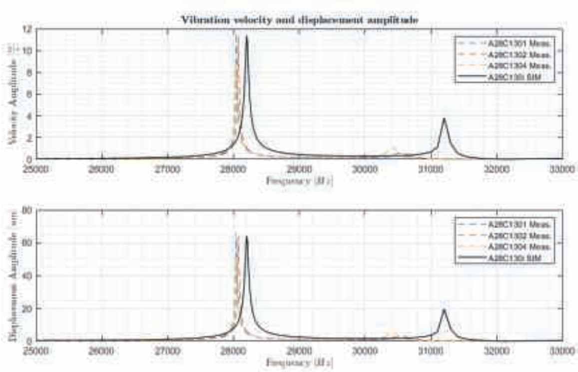

Fig. 2 Frequency response of the vibration intensity with velocity and displacement amplitudes of the tip extremity. Laser Doppler vibrometry measurements performed on three identical prototypes of the optimized design in comparison to the corresponding simulation results.

Discussion

The performance objectives of the freely vibrating transducer have been achieved. Thus, the feasibility of a planar ultrasonic transducer for dental applications could be demonstrated. However, the efficiency of the transducer still needs to be evaluated in real conditions in which the instrument tip is in contact with biofilm and calculus.

References

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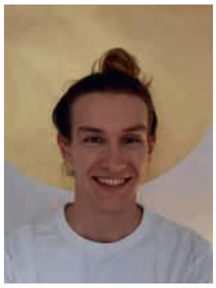
A Novel Device to Measure Applied Forces During Minimal Invasive Coronary Interventions

Simon Krebs



Supervisors: Dr. Adrian Zurbuchen, MSc Cornelia Amstutz, PD Dr. Andreas Haeberlin
Institutions: University of Bern, sitem Center for Translational Medicine and Biomedical Entrpreneurship
University Hospital Bern (Inselspital), Department of Cardiology
Examiners: Dr. Adrian Zurbuchen, Prof. Dr. Rolf Vogel

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a surgical technique used to open blocked or narrowed coronary arteries in the human heart. The main component of the PTCA system is an inflatable balloon catheter. To do a quantitative performance analysis of such catheters and to study the interaction of the physician with the catheter a novel device has been developed in this work. This device should be able to measure forces as well as movements applied by the physician on the catheter in order to quantify the catheter qualities.

Materials and Methods

The development has been initiated by investigating a framework of general conditions which the device should respect. For the device, a morphological box was developed, and different sensor technologies were compared. To evaluate the feasibility of different force transducer designs finite element (FE) simulations (Fig. 1) were done in COMSOL Multiphysics 5.5 and occurring strains and deformations were compared. A control circuit to acquire and process the signals from the force sensor was established.

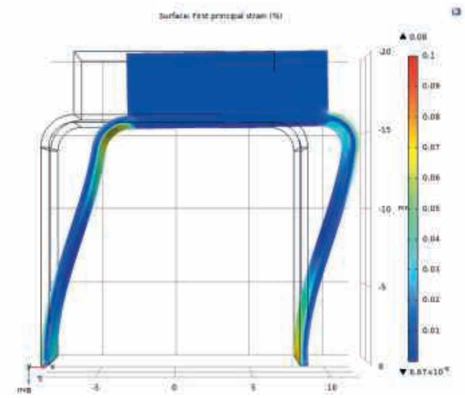


Fig. 1 Result of the FE-Simulation of a possible force transducer design with a applied force of 6N.

Validation of the force measurement unit was done by measuring its static and dynamic behavior and precision. For the clamping unit, the achievable clamping force was examined, the friction properties of different coatings were evaluated, and the catheter compatibility was checked.

Results

The developed handheld device is small, lightweight, and consists of 3D printed components. The catheter gets clamped using a spring-loaded clamping unit which generates a maximal clamping force of 24.9 N. To increase friction, the contact surface between the clamps and the catheter is coated with a nitrile rubber. The clamping unit was tested to work with a catheter diameter between 2 and 6 French. The maximal achieved retention force in these tests was 4.76 N ± 0.30 N. To measure the force, a prefabricated force transducer (TAL221), that indicates the forces with an accuracy smaller than the required 0.01 N, was used. Inside the device, a BNO055 orientation sensor can record the orientation of the device in time. The data is stored on a 16 GB SD card, controlled by a battery powered Arduino Nano. Interaction with the device is enabled via a push button and acoustic feedback.

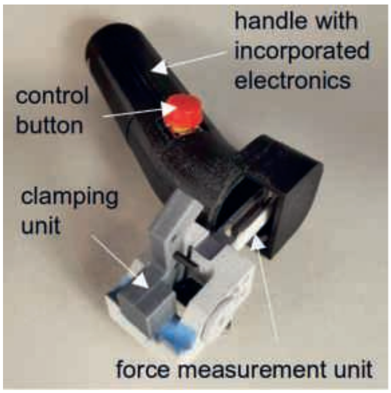


Fig. 2 The Prototype of the developed device.

Discussion

Our results have shown that the device is able to measure forces applied by the physician on the catheter. The remaining challenge is the increase in retention force to prevent the catheter from slipping during an intervention.

Acknowledgements

The expertise and support of Corneli Amstutz, Ardian Zurbuchen and the whole team of the Cardiac Technology and Implantable Device group is gratefully acknowledged.

Lung Alveoli Array on Chip: Reproduction of Alveolar Structure with *in Vivo* Stiffness Gradient

Christian Kündig

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Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Olivier T. Guenat, MSc Dario Ferrari

Introduction

Standard lung alveoli in vitro models poorly reproduce the microenvironment of the distal airways. In recent years, researchers worked on the development of more relevant in vitro models called organs-on-chip (OOC). OOC are microfluidic cell culture devices able to mimic a functional unit of an organ. They are expected to become the next generation in vitro tool that will help to better understand human biology in health and disease, as well as to efficiently test new drug candidates and ultimately to reduce animal testing [1,2]. To reproduce the remodelisation of the alveoli during pathologies, such as idopatic pulmonary fibrosis IPF or chronic obstructive pulmonary diseases COPD, it is crucial to develop a new lung-on-chip with an ultrasoft membrane. Additionally it is of interest to replace the reported gold mesh in [1] with a softer material to reproduce the stiffness of alveolar walls.
The aim of this project was to develop and characterize a soft PDMS membrane and combine it with a PDMS mesh to form a bilayer. The novel lung-on-chip should then be used for the cultivation of lung fibroblasts.

Materials and Methods

During the thesis a new soft and flexible PDMS mesh was developed to mimic the alveolar walls. Further on, a hypersoft thin PDMS membrane was developed and characterized. Different compositions were used to reach a physiological stiffness The Young's modulus was assessed via bulge test.. Afterwards, the PDMS mesh and the hypersoft membrane were integrated on a lung-on-chip device. The lung-on-chip was then used for the culture of normal human lung fibroblasts (NHLF). The adherence of the cells to the PDMS was improved subsequently with different coatings.

Results

Reproducible protocols for the fabrication of the mesh and the membrane were established. The integration into a lung-on-chip device and cell culturing were successful. Stiffness measurements on the membrane showed a strong dependence on production parameters and a high batch-to-batch variability. It was shown that membranes with a Young's modulus 100kPa are producible. Four different designs of lung-on-chips were developed. Differences are the diameter of the hexagons in the mesh being either 400/500µm and the mesh being freestanding or combined with the membrane to form a bilayer

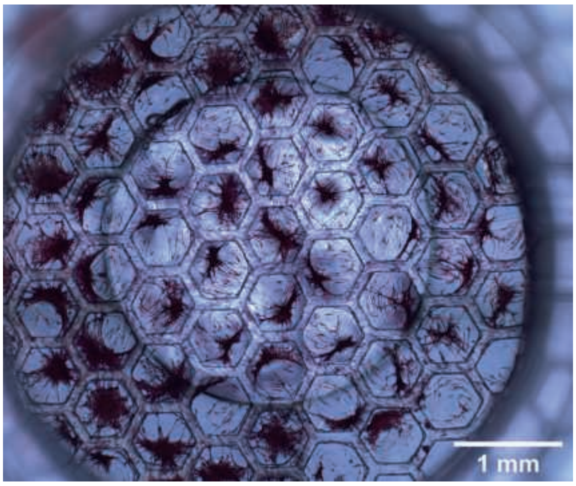

Fig. 1 NHLF cells are cultured on a bilayer built of a hypersoft thin PDMS membrane and a hexagonal PDMS mesh. The cells were culitvated with TGF-β and afterwards stained with Direct Red to make the collagen deposition visible.

Discussion

The results showed that it is possible to produce PDMS membranes in a physiological range of stiffness. The extensive bulge testing showed the importance of controlling all parameters during fabrication and storage. It was possible to add the PDMS mesh on this membrane, allowing for compartmentalization. This will allow to apply deflection testing of the mesh more easily in the future. It was also shown, that the mesh itself is currently too stiff and the fibroblasts were not able to deform the hexagonal structures. Further research is necessary on the PDMS parts and coating to improve cell attachment. The foundation for more in-depth cell culturing on this lung-on-chip device however has been laid. The results can also be transferred to other OOC researching fibrosis or organoid culturing.

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Master's Thesis in Biomedical Engineering

Development of High-Throughput Platform for IPF-on-Chip Model

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Introduction

New advanced lung *in vitro* models, called lung-on-chips (LOCs), are able to reproduce the cellular microenvironment of the lung parenchyma [1,2,3]. Even though over the last decade LOCs have grown in popularity, several challenges still need to be tackled. In fact, the development of a high-throughput platform, the standardization of protocols and the automation of read-out are required to make the LOCs a reference for pharmaceutical laboratories. Additionally, most of these models include a stretchable membrane made of polydimethylsiloxane (PDMS) as cell culture support [1, 2]. This synthetic material poorly mimics the chemical and physical properties of the extracellular matrix (ECM). We report here about the development of a high-throughput platform equipped with a freestanding thin biological membrane. The platform has been used to evaluate the secretion of collagen of normal and fibrotic cells.

Materials and Methods

The fabrication of the biological membrane has been adapted from the previously published methods [3]. Briefly, a collagen-elastin (CE) solution was pipetted on top of polyester film (Melinex). After a gelation and a drying step, the membrane was integrated onto a newly designed 24-well polycarbonate (PC) chip. The dimensions were based on those of a 96-well plate. Additionally, a placeholder was designed to be used in a standard flat plate for microscopy (Fig 1). For cell culture, normal human lung fibroblast (NHLF, Lonza) have been used. NHLF treated with TGF-β at 10 ng/mL were used to induce a fibrotic phenotype.

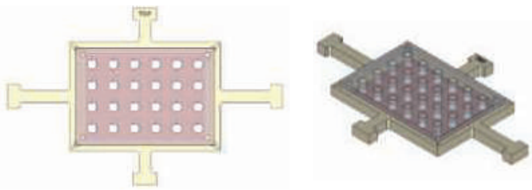

Fig. 1 24-Well PC chip with the placeholder. Freestanding vitrified CE-membrane was integrated on the chip and attached via double tape(red). Pins on either side of the chip were used to properly align the membranes.

Results

The developed platform allows for the automation of imaging with EVOS microscope. The freestanding membrane was thin (8µm in average) and stable for at least 1 week. It offers a good support for cells (Fig. 2a). Additionally, it has been shown that fibroblasts treated with TGF-β secreted more collagen than those without treatment (Fig. 2b). However, no difference was observed in terms of permeability.

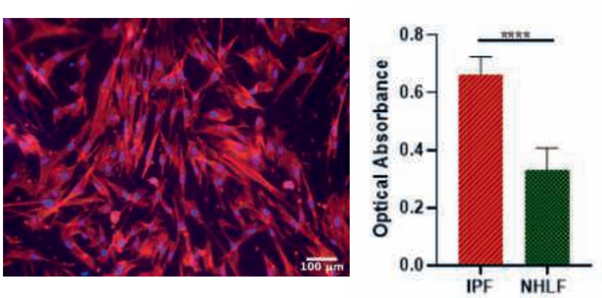

Fig. 2 (a) NHLF on CE-membrane stained with actin (red) and hoechst (blue). (b) Measurement of the difference of collagen secretion via optical absorbance between NHLF treated with 10ng/mL of TGF-β (IPF) and without treatment (NHLF).

Discussion

The high-throughput design, standard dimensions, as well as the absence of PDMS, make this new platform a promising tool for toxicological assays. Additionally, the biological nature of the cell support makes it a relevant tool to investigate lung disease such as in IPF. Further investigation can be led on the impact of IPF patient's cells on the membrane composition and stiffness. Then the effect of anti-fibrotic drugs such as pirfenidone and nintedanib, could be studied.

Reference

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Acknowledgements

The OOC group members at ARTORG center were a great resource during my thesis and their help is gratefully acknowledged.

Development of an In-Vitro Model of the Lower Urinary Tract with Physiological Mechanical Properties

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Examiners: Dr. Lukas Bereuter, PD Dr. Francesco Clavica

Introduction

Urinary retention is a pathological condition characterized by the inability to empty the bladder completely. It can include symtomps such as a weak stream, feeling of incomplete bladder emptying and urinary tract infections. The UGE group of ARTORG Center is developing a novel non-invasive medical device to aid bladder emptying in urinary retention patients. The device relies on the impedance pumping principle: applying cyclic compression to a fluid-filled tube (in this case to the urethra) leads to a complex pattern of non-linear wave interference, which can cause a net flow. Hence, urine is actively pumped out of the bladder. The aim of this thesis was to investigate the impedance pumping principle in in-vitro models mimicking physiological mechanical propreties of the lower urinary tract.

Materials and Methods

Three main bench tests were designed and implemented. All setups were developed to simulate the lower urinary tract. The bladder was simulated either by a reservoir or a urinary bag and the urethra was simulated by a PDMS urethra in-vitro model (Fig. 1).

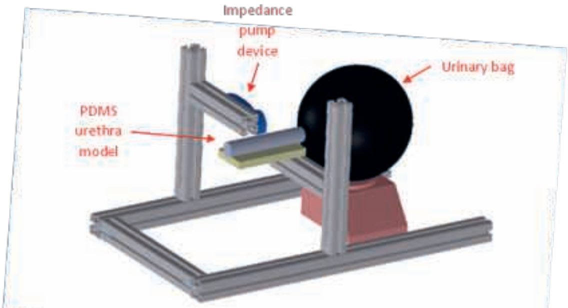

Fig. 1 Bench test including a urethra and bladder model

The behavior of wave propagation and reflection inside the urethra was studied by recording pressure waveforms after compression and release of the urethra. Flow measurements and complete emptying tests were conducted by varying parameters of compression frequency, position and compression width of the stimulator.

Results

The mechanical properties of the manufactured urethra matched physiological values. The measured wave propagation velocity was ~3.5 m/s. The pressure wave experienced attenuation of 80-100 dB/m, showing a higher attenuation for higher pressure amplitudes. The wave reflection behavior at the urethra outlet and bladder interface was studied, showing a reflection polarity as expected by theory. An initial wave may be reflected several times and change polarity, depending on the characteristics of the the reflection interface (Fig. 2).

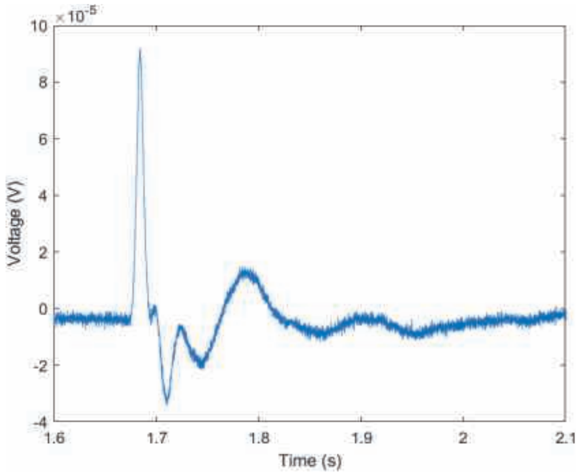

Fig. 2 Measured signal of a compression wave followed by several reflected waves

Discussion

The impedance pump is a complex phenomena. The generated net flow is dependent on many parameters. In this thesis, some of the basics of wave propagation and reflection could be demonstrated on an in-vitro model of the lower urinary tract. These insights serve to better understand the principle and pave the way towards an optimization of the medical device. When applying a cyclic compression to generate a net flow, the reproducibility of the results was limited, pointing out some improvement possibilities of the setup and at the same time showing the sensitivity of the principle to e.g. positioning and boundary conditions.

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Acknowledgements

I would like to thank my two supervisors Dr. Lukas Bereuter and PD. Dr. Francesco Clavica for their support, encourgements, enthusiasm and guidance throughout this thesis.

Motion Classification in Video Recordings

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Introduction

No matter what humans do, they move. From movement, one can differentiate different behaviors initiated by a person. Injuries related to sports or diseases can impact how people move. Diagnostics can be used to assess the level of impairment by evaluating the movement [1]. However, these techniques rely on how humans recognize movements and classify them. With current machine learning techniques, it is possible to classify everyday movements, like watering plants, with very high accuracy [2]. However, research regarding movement detection applied when sitting or lying in bed is lacking. Therefore, the aim of this thesis was to develop a system to monitor and classify movements typically occurring while in a bed.

This work hypothesizes that it is possible to develop such a system which is able to monitor and differentiate the movements of a person in the bed. If someone were to interact with an individual lying in a bed (e.g., nurse tending to patient in a bed), the system should recognize such interaction. It is also hypothesized that this classification task can be made with high accuracy.

Materials and Methods

This work aimed to develop a system that allows continuous recording of a bed to capture movement while lying down and interactions around the bed. A study was conducted to capture 32 individual movements, detect interactions at the bed, and detect movement differentiated by the pose (e.g., supine, prone, back, and supine fowler). A total of 43 healthy subjects were recruited for this study. The age range was 44 ± 16 [22-76].

The study simulated someone lying in a bed. Participants were asked to do different movements while laying in different positions. Two cameras from different angles, at the head of the bed and looking down on the bed, were recording those movements continuously.

The labeled dataset of the recorded movements was used for analysis with neuronal networks. Three different neuronal networks – a simple convolutional network (CNN), a 3D ResNet, an X3D Net – were used to train the model for movement recognition.

Results

The neuronal networks differentiated the 32 different movements with an overall accuracy of <10%. Interaction classification resulted in an overall accuracy of over >95% with the 3D ResNet and the X3D network. The position classification task was performed with an accuracy of over >50%. Table 1 shows the performance of every training with network and used dataset.

Table 1 results of accuracy in % on the test set

	Dataset both cameras	Dataset camera 1	Dataset camera 2
All classes			
Simple CNN	2.70	6.06	1.58
3D ResNet	27.71	14.39	19.84
X3D	11.19	6.81	7.93
Interaction classes			
Simple CNN	50.89	46.48	46.12
3D ResNet	96.20	98.43	99.18
X3D	95.60	95.31	98.77
Position classes			
Simple CNN	36.96	25.00	33.98
3D ResNet	62.08	64.81	59.22
X3D	55.92	55.55	53.39

Discussion and Conclusion

This work showed that it is possible to use a camera setup to differentiate movements while lying in a bed. This work is relevant for work related to bed-bound individuals, for example, in nursing homes or hospital settings. More specifically, this could be useful for determining if a patient in a hospital is self-initiating a movement or if the nurse at the bedside is initiating the movement. Some movements, namely the interaction with patients from medical staff at a bed, can be separated with high accuracy. The results found here are comparable to those found in the literature on other classification tasks. Based on these results, we can conclude that our results are successful. However, it also showed that separating 32 different movements with low sample size is challenging.

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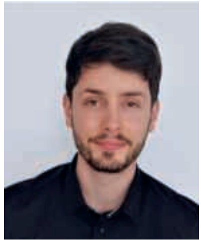
I would like to thank my two supervisors Dr. Stephan Gerber and Aileen Naef, for their enthusiasm, support, encouragement, and guidance throughout this project.

Detection of Disease and Conditions in Optomap imaging

Killian Monnin



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Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila

Introduction

Retinal detachment(RD) is a condition in which the retina at the back of the eye detaches from his position and may lead to permanent loss of vision if not treated. With the last advances in fundus imaging technology, the identification of that type of retinal condition has become easier with the ultra-widefield imaging technology which allows to capture a 200° picture of the retina in only one shot. While manual inspection of ultra-widefield images can be performed by a doctor, an automated detection of retinal conditions and disease in these images could be useful to assist experts in their work. Then the aim of this study was to build a deep learning system to detect non-healthy retina and then propose a method to classify the different types of non-healthy retinas.

Materials and Methods

A data set of 1445 Optomap images was used to train and evaluate some pre-trained ResNet-50 models. The data set was composed of 4 different classes of retinas: healthy, with breaks, with RD or with breaks+RD. Then a cascade of binary classification models was proposed to classify the images into these 4 categories.

Results

The accuracy of the system was evaluated with cross validation to characterise its general performance. The F1 score was used to measure the accuracy of the system. The system was first evaluated with predictions of the models per image and then with average predictions per patient.

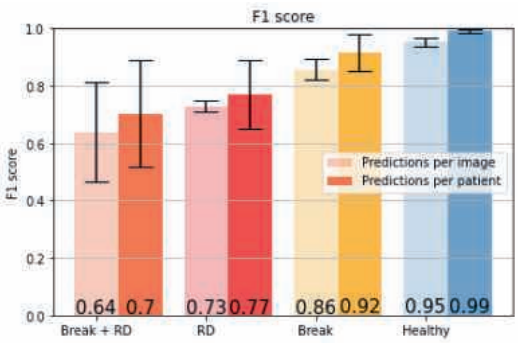

Fig. 1 Mean F1 scores of the predictions of the system

The system achieved high accuracy at detecting healthy retinas with an F1 score of 0.99. Thus the system performed worse at detecting the different types of retinal conditions but the results are still encouraging. The use of a mean prediction per patient tends to increase the mean F1 score of the class detection but also increase the standard deviation around the means. The grad-CAM of the different detectors showed that in most cases the detectors are focusing on the region of interest when they make a correct prediction.

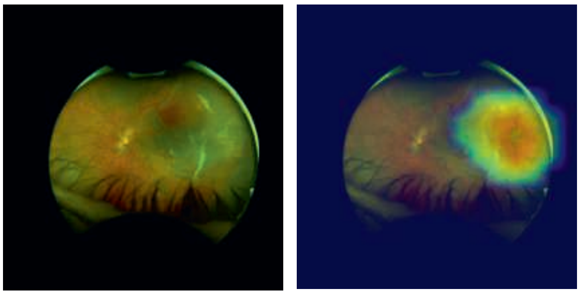

Fig. 2 Left: Optomap with a retinal detachment and breaks, Right: Optomap with grad-CAM of a ResNet-50 model trained at detecting non-healthy retinas.

Discussion

These results correspond to the findings of similar studies performed at detecting retinal breaks and retinal detachments although a lack of data is limiting the results obtained in this study. Deep learning models show a high potential for detection of healthy and non-healthy retinas. These results are then very encouraging for screening purposes and might help experts in their clinical settings routine. However, the effective high level of accuracy should be critically evaluated with more data.

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I would like to thank my supervisors Dr. Andrés Marafioti and Prof. Dr. Raphael Snitzman and the medical student Merlin Christ who provided the data set for their support throughout the project.

Denoising Inertial Measurement Units with Deep Learning for Human Gait Analysis

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Examiners: Prof. Dr. Volker M. Koch, MSc Thomas Wren

Introduction

Thorough gait analysis allows to detect and quantify gait disorders. The gold standard by VICON© is an optical motion tracking system with a usually fixed installation in a gait lab. The system allows for high precision measurements but cannot be used for long-term monitoring of everyday activities. A more flexible method is gait analysis with inertial measurement units (IMU), which in turn suffers from drift. The drift originates from the integration of noisy and biased IMU readings, which is why those readings must be filtered first. We propose two new methods for denoising IMUs. The proposed methods were tested as stand-alone filters on standard datasets and on actual gait data in the pipeline of a newly developed IMU based gait analysis tool.

Materials and Methods

The gyroscope and the accelerometer of the IMU were filtered with individual temporal convolutional networks, GyroNet and AccNet. Both networks were trained and tested on a proprietary dataset (panIMU), where the IMU was strapped to a robotic arm that recorded the ground truth orientation and position.
GyroNet was introduced by Brossard in 2020 (GyroNet-B) and we propose changes in the architecture (GyroNet-M). We evaluated the performance of either GyroNet on the original EuRoC dataset (IMU strapped to a drone) and panIMU. AccNet is a novel approach and was compared against an IIR high-pass filter.
Furthermore, a gait analysis tool (GAT) was developed using IMUs only. The IMUs were first calibrated and initialized w.r.t to a common coordinate system. Then, the IMU data was optionally filtered by GyroNet-M before being passed to a Kalman filter. Lastly, the joint angles were extracted as the quaternion distances between two IMUs. The GAT pipeline was eventually compared against VICON© with one voluntary participant as a preliminary test before clinical testing in a future step.

Results

AccNet showed better filtering behaviour at low frequencies than the IIR filter with 25 % less error. When filtering high frequencies it had a 9 % higher error compared to the IIR, underestimating peaks.
The proposed GyroNet-M competed with the extended version of GyroNet-B and outperformed the basic version under similar conditions.
The preliminary trials of the GAT resulted in RMS errors lower than 5 degrees for five of the nine joints and axes and no RMS error above 10 degrees for the standard pipeline. With GyroNet-M in the pipeline, the RMS error was higher in seven out of nine cases and topped 10 degrees RMS error in the ankle flexion.

Tab. 1 Average RMS relative orientation error in degrees of Brossard's GyroNet-B and the proposed GyroNet-M. The error was calculated for $t \in \{1,4,7\}$ minutes on the panIMU dataset.

test \ train		GyroNet-B extended EuRoC	GyroNet-B extended panIMU	GyroNet-B basic EuRoC	GyroNet-B basic panIMU	GyroNet-M EuRoC	GyroNet-M panIMU
EuRoC		**0.59**	564	1.42	642	0.73	434
panIMU	1	490	2.19	2312	9.78	2373	**1.87**
	4	1327	5.36	2071	10.43	2109	**5.20**
	7	1817	7.61	1943	19.66	2024	**6.32**

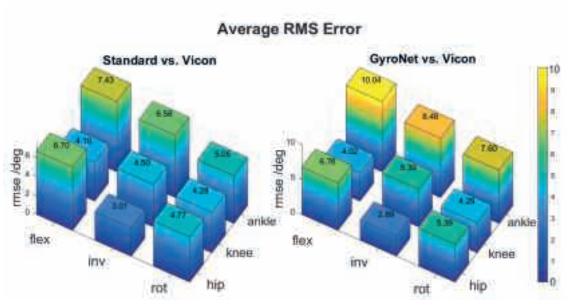

Fig. 1 Average RMS error in degrees of the standard pipeline (left) and the pipeline with GyroNet-M (right) depending on the joint and axis.

Discussion

AccNet has desirable properties with good DC-block while preserving sharp edges. However, future work must retrain AccNet to allow short peaks. GyroNet-M is performing well on the known datasets but failed the deployment to the GAT. Most notably, the error was highest at the ankle joint where the most change in IMU readings is expected to happen. Nevertheless, the GAT suggested acceptable results in the standard pipeline. Thus, the basis for a new IMU based GAT is laid with this project.

References

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Acknowledgements

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Evaluation and Application of Alternative Segmentation using Gaussian Process and Deep-Learning models

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Examiners: Prof. Dr. Mauricio Reyes, Prof. Dr. med Nicolaus Andraschtke

Introduction

A precise medical image segmentation is needed, since an ill-posed problem may have a significant impact in e.g. radiation therapy planning. Experts often disagree about the exact position of the target tissue which needs to be segmented. In this work, current segmentation methods in terms of qualitative rating, Dice similarity score and radiation dosimetry were evaluated.

Materials and Methods

The alternative segmentation methods Gaussian Process for Sampling Segmentation of Images (GPSSI)[1] and Stochastic Segmentation Networks (SSN)[2] were used. The SSN is an additional algorithm, which in this work was applied over the Deep-learning Network Deepmedic. The qualitative evaluation was done by analysing answers of 3 different experts to a questionnaire. The quantitative evaluation was done next to the Dice similarity score with a prediction of a radiation therapy planning software.(Overview in figure 1)

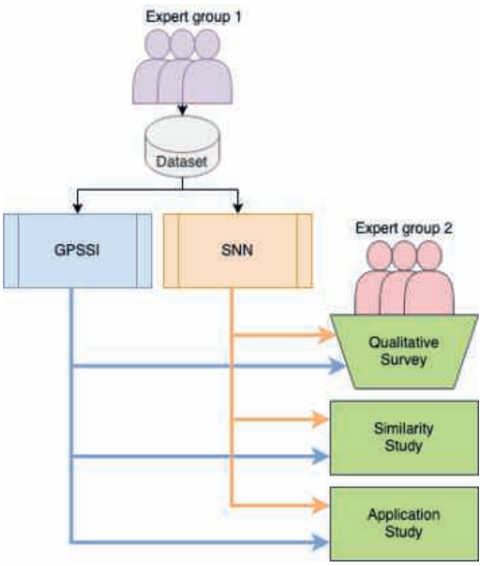

Fig. 1 Work structure: Dataset segmented by 3 experts. 2 alternative segmentation method used. Results evaluated qualitatively by 3 other experts. Metrics compared by DSC score and the application RT-Planning.

Results

The qualitative result is shown in figure 3 by the overlay of ten samples. Figure 2 highlights that even a small variation show an impact to the radiation dosimetry in a high dose region.

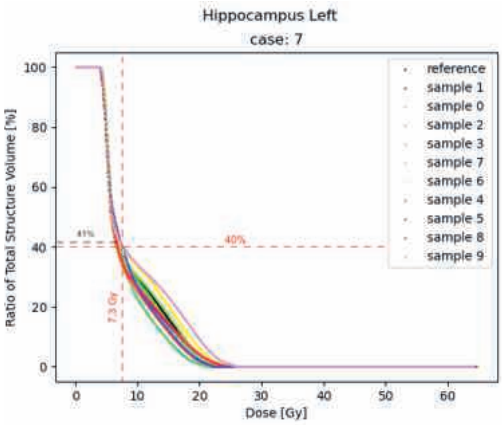

Fig. 2 Dose per Volume histogram of the left hippocampus. The dose limit according to clinical standart is 40% of the hippocampi volume < 7.3 Gy. Here the dose of 40 % of the volume fits this limit but the range of 20% volume is between 11 Gy and 16 Gy. Which shows the influence of the marginal sample variations.

Fig. 3 Ten samples of alternative segmentations for the brainstem and hippocampi. Since the brainstem has clear borders, the variations are not as noticeable as the variations of the hippocampi.

Discussion

Additional to the influence of small variations towards similarity and dosimetry study, an outlier study showed the effect of the commonly occurrence of miss-clicks on a manual segmentation tool. For small but noticeable outliers this study showed no effect on each evaluation method used in this work.

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Personalized Prediction of the Outcome of Percutaneous Coronary Interventions

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Introduction
Cardiovascular disease is a global public health problem and contributes to approximately nine million deaths worldwide each year [1]. One of the most common causes of coronary heart disease is myocardial infraction, which can be caused by stenosed coronary arteries that restrict blood supply to the heart. The aim of percutaneous coronary interventions (PCI) is to restore blood flow. However, severely calcified lesions are increasingly encountered in routine clinical practise due to the increasing age and complexity of patients referred for PCI. If inadequately prepared, these calcified lesions can lead to under-expansion of the stent with its associated complications. Predicting the outcome of PCI would help physicians to decide if a more aggressive technique is required to prepare the artery before stenting. This project aimed at combining intra-arterial imaging and mechanical simulations to determine the outcome of PCI in patients with calcification and comparing the simulations with post-operative data.

Materials and Methods
Five patient-specific arteries were reconstructed from OCT images. The constitutive models accounted for the tissue non-linear and anisotropic behaviour as well as damages induced by the intervention. Finite element analyses were conducted to mimic the different steps of the clinical procedure: percutaneous transluminal angioplasty (PTA), stent deployment and post-dilation (*Fig. 1*), according to the patient's interventional information.

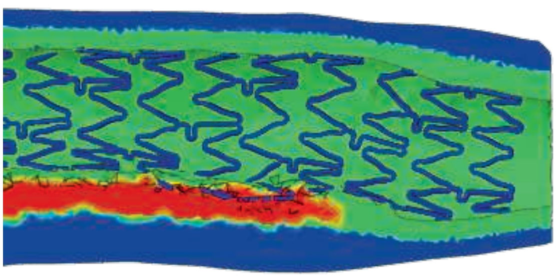

Fig. 1 Finite element simulation of a personalized artery for prediction of the interventional outcome, calcification (red), media (green) and adventitia (blue) after post-dilation.

During post-processing, geometrical features of the simulation were compared to post-surgical clinical data after PTA and post-dilation.

Results
The behaviour of the media, adventitia and calcifications were in good agreement with previously published experimental tests [2]. The simulation results showed a lumen gain similar to the one measured in clinics (*Fig. 2*). In regions with many calcifications, the lumen area was correctly predicted. However, the simulations failed to reproduce the clinical lumen gain in the highly stenosed regions where no calcifications were identified. In these sections of the artery, the simulation predicted under-expansion of the stent, which was not observed after surgery.

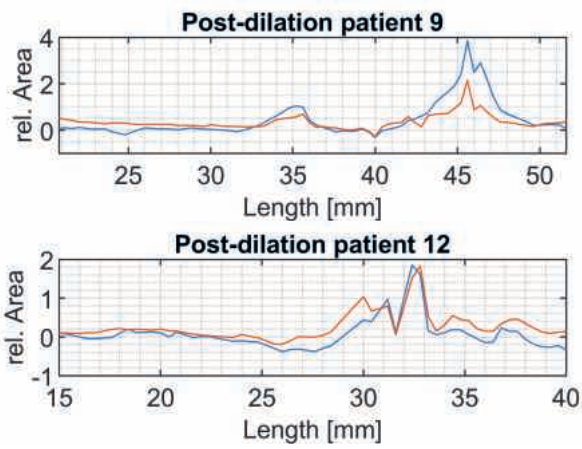

Fig. 2 Relative lumen gain after the intervention (blue) and after the simulation (red) for two patients.

Discussion
A numerical framework was set up based on in-vivo data. The arterial geometries and the simulated procedure were patient-specific. This work was the first to compare mechanical simulations of PCI with patient-specific clinical outcomes. Simulations performed well when calcified plaque was identified on OCT images. However, predictions were inaccurate for stenosed areas that did not have calcification, likely due to other plaque components that were not identified on the OCT images. Nevertheless, these other types of softer plaques appear to be less prone to under-expansion of the stent and could therefore be ignored to focus predictions on the calcified regions of the artery.

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Development of a Hybrid Bone Conduction Implant Demonstrator

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Examiners: PD Dr. Wilhelm Wimmer, Emile Talon

Introduction

Bone conduction (BC) hearing aids are primarily used for hearing losses where air conduction (AC) hearing aids are not possible. With the bone conduction devices, hearing is perceived with the vibrations through the skull which are transmitted to the cochlea. The most common transducers used to create vibrations are mainly electromagnetic. In recent years, piezoelectric transducers have been implemented. Piezoelectric transducers and electromagnetic transducers have their own advantage. It was shown how piezoelectric transducers have better performances in the high frequencies domain (f > 2 kHz) compared to the electromagnetic floating mass transducers. However, in the lower frequencies (f < 1,5 kHz), the electromagnetic transducers perform better. Combining these two technologies in a single bone conduction implant would represent a new approach that could eventually improve hearing of the patient in a larger frequencies domain.

Materials and Methods

A demonstrator for the bone conduction implant using two different transducer types: piezoelectric and electromagnetic transducers was developed. The frequency splitting between the transducers at a selected frequency was developed in the Raspberry pi hardware. The Artificial Mastoid Type 4930 from Brüel & Kjær which allowed stable and reproducible simulation of the mechanical characteristics of the human head's was used for the measurements.

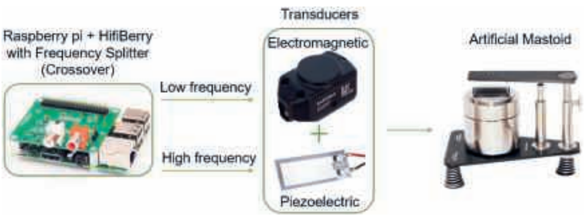

Fig. 1 Schematic of the Hybrid Bone Conduction Implant Demonstrator

Crossover's designs with FIR filters, Butterworth (IIR) filters and Linkwitz-Riley design were implemented and their measurements were compared to find the best option.

Results

First, the results were obtained with the output force level of each transducers without the crossover filter. Using a Butterworth crossover design, the Hybrid bone implant followed both transducers' curves accurately with respect to the cutoff frequency set at 4900Hz and without attenuation. The cross-talk's effect was insignificant.

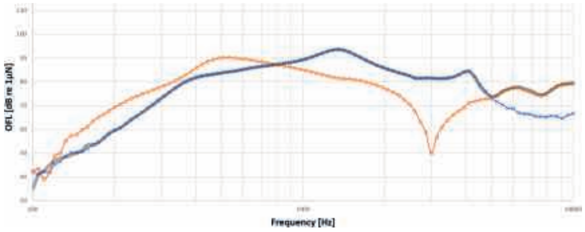

Fig. 2 Electromagnetic and piezoelectric transducers with a classic Butterworth crossover. Output Force Level from the Mastoid. Blue: Electromagnetic transducer as Low frequencies. Red: piezoelectric transducer as High frequencies. Grey: Hybrid bone conduction implant with a classic Butterworth crossover at 4900Hz.

Discussion

Existing bone conduction devices on the market or in development incorporate only one transducer's type. The developed Hybrid Bone Conduction Implant combining the best of each transducer's type is a new approach to enlarge the frequency's domain with a high hearing level.

References

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Acknowledgements

I would like to express my gratitude to my supervisors PD Dr. Wilhelm Wimmer and Emile Talon for their precious ideas and continuous support during the master thesis.

Multi-Angle Optical Coherence Tomography Data Reconstruction

Basil Peterhans

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Examiners: Prof. Dr. Patrik Arnold, Dr. Silvano Balemi

Introduction

For quality control of extruded plastic profiles, e.g., medical tubing, optical coherence tomography (OCT) was introduced as it features an improved resolution and no hazardous radiation compared to currently used methods. However, a major problem with OCT measurements is that they suffer significantly from image distortions such as refraction at the interfaces of different optical media. Refraction causes spatial distortion of the data, so that the image does not correspond to the actual geometry of the sample. Another limitation of OCT measurements is the limited measurement depth and light attenuation in the samples, which leads to a limitation of the visible range. The goal of this study was to overcome these limitations. Sample-related attenuation was accounted for by using multi-angle OCT data, since information from different directions complements each other. To correct refraction, a sophisticated distortion correction algorithm was developed based on the implementation of Zhou et.al.[1].

Materials and Methods

A set of 14 extruded, semi-transparent plastic specimens ranging from simple tubes to specimens with 28 internal chambers were examined. Cross-sectional OCT data were acquired from 12 angles using a sophisticated method that establishes a spatial relationship between the acquired images. This relationship is important later because it facilitates the merging of the images. To correct for refraction in these images, the behavior of light in the sample must be simulated. To perform this simulation, rays are propagated on a reference geometry of the sample, as shown in Fig.1 (center). This ray propagation requires the refractive index (RI) of the sample, the geometry (RI map) and the spatial relationship between the OCT scan and the RI map. All of these requirements had to be established manually. Then, the OCT data in Fig.1 (left) are projected onto the propagated rays, resulting in a refraction-corrected image, as shown in Fig.1 (right). Finally, the corrected images from 12 view angles are merged together.

Fig. 1 From left to right: Original OCT image, RI-map with propagated rays laid over, refraction corrected OCT image.

Results

The refraction-corrected multi-angle reconstructions can be seen in the center images of Fig.2. Compared to the uncorrected merge image on the left, the internal structures are clearly visible and the wall thicknesses are much thinner. On the right side, the real microscope images of the samples are shown as a geometric reference for the reconstruction. Note that the microscope images have been scaled down to match the dimensions of the reconstruction.

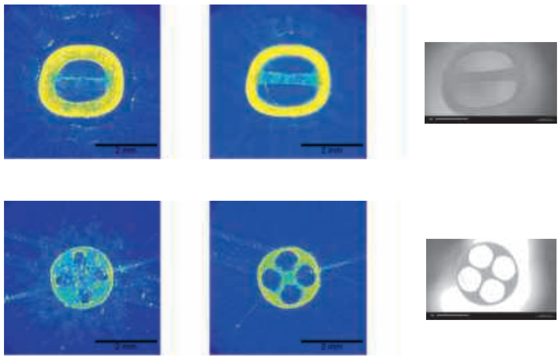

Fig. 2 reconstruction process for 12 angles. From left to right: merged images without correction, corrected merge images, microscope images.

Discussion

The results indicate that OCT with a sophisticated measurement setup and image processing algorithm may be suitable for the inspection of samples with complex internal geometry. Visual evaluation, based on reconstructions of the selected sample set, implies a reconstruction feasibility of 75%. The advantage of multi-angle data has been successfully demonstrated, as the original data shown in Fig.1 (left) depicts only about half of the specimen, while the merge view in Fig.2 shows an all-around view. It has been demonstrated that the internal structures can only be realistically reproduced if an algorithm is used to correct for refraction. Future work in this area could investigate a more sophisticated method for generating the spatial relationship between the OCT scans and the reference RI-map.

References

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Towards Gait Analysis with 6D Tags and 2D Cameras: Setup and Analysis of a Hop Test

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Examiners: Dr. Patric Eichelberger, Prof. Dr. Gabriel Gruener

Introduction

Three-dimentional Motion Capture (MoCap) can be useful in various stages of the rehabilitation process, as well as in diagnostics and sport sciences. Gait assessment is the most widely used application. MoCap also allows for objective, more informed decision making. High costs are the primary factors preventing a broader application in clinical routine. Therefore, it is desirable to develop more affordable alternatives. The aim of this work was to develop an affordable application capable of analysing a hop-test and to evaluate this solution against a state-of-the-art 3D MoCap system.

Materials and Methods

The solution is based on the detection of 3D-printed 6D tags, called CCTags and seen on fig. 1, on 2D camera frames. The outputs of the detection software permit the calculation of the 3D pose of these 6D tags. Three experiments were conducted in a controlled environment using an industrial robot. Then, the quantitative data extracted during three real-life movement tasks, i.e. flexion/extension while sitting on a chair, a squat and a hop-test for distance, were compared with the measurements taken by the state-of-the-art MoCap installation from the company Vicon. The experimental setup can be seen in fig. 2.

Fig. 1 CCTag.

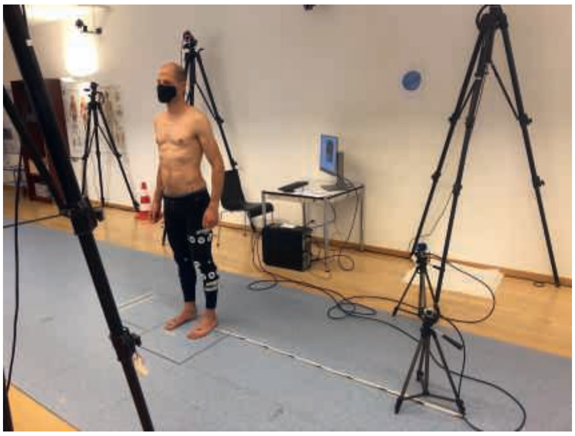

Fig. 2 Experimental setup for the comparison of the developed solution with Vicon.

Outcome measures include 3D tag positions and orientations, 3D knee angles and patella trajectories.

Results

The in-plane knee angle and the tags' positions exhibited high stability and precision when compared to the "ground truth". In the controlled environment of the robot with known orientations, the other knee angles showed a maximum error of 12.1°. When applied to real-life movement tasks, the average absolute error increased to up to 28.1° for the hop-test. Fig. 3 shows the results of a squat.

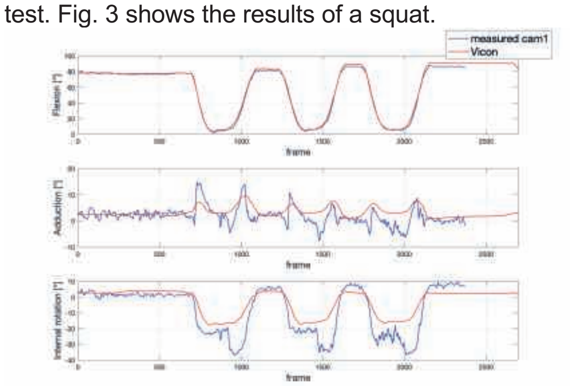

Fig. 3 Comparison of the knee angles measured with the solution vs. Vicon during a flexion/extension experiment performed by a subject ditting on a chair .

Discussion

The out-of-plane knee angles show a substantial error compared to the current high-end technologies. The main reason for that is the ambiguity in the out-of-plane orientation of the tags. The low camera resolution and limited redundancy restrict the accuracy of the solution. However, the measurements resulting from the robot experiments and from the in-plane knee angles show promising results for the analysis of larger movements and trajectories of points of interest. While the use of CCTags with 2D cameras remains an attractive possibility for gait analysis, the ambiguity problem needs to be addressed with a systematic approach.

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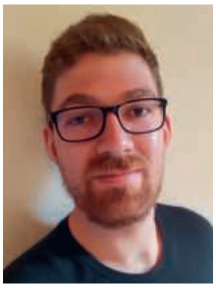
M. Eltoukhy, A. Kelly, C. Kim, H. Jun, R. Campbell, and C. Kuenze. Validation of theMicrosoft Kinect® camera system for measurement of lower extremity jump landingand squatting kinematics. Sportsbiomechanics, 15(1):89–102, 2016

Acknowledgements

This project was enabled by CSEM SA, who supplied the CCTags and the recognition software.

Positive-Unlabeled Learning for Segmentation from Sparse Annotations

Christian Piguet



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Examiners: Prof. Dr. Raphael Sznitman, Dr. Pablo Márquez Neila

Introduction
The segmentation is now a task of high importance for medical image analysis. Its ability to provide a fast and reliable delimitation of structure of interest has made it particularly useful in multiple domains.
Unfortunately, deep learning methods that perform well requires a large amount of annotated data. Theses data are costly and requires a lot of time to be produced.
The aim of this study is to experiment the effectiveness of segmentation based on weakly annotated data. The use of a Positive-Unlabeled approach is used.

Materials and Methods
The first step was to implement the non-negative loss estimator which allows the use of deep learning methods with a Positive-Unlabeled (PU)approach.
The segmentation model used was a standard U-Net. The model was trained on volumetric MRI scan, which was converted into 2D for the experiment.
The whole tumor of the ground-truth image is considered with the Positive label and the rest of the image is considered with the Negative label.
In order to simulate low annotated data, each ground-truth has been stripped of 95% of their original label. More precisely, 95% of the Positive label in ground-truth image has been set as Unlabeled during the training.

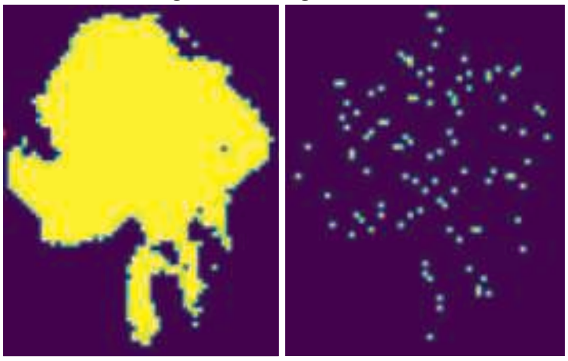

Fig. 1 Original ground-truth image on the left and the one that has been striped of 95% of its Positive label on the right..

Two experiments were conducted with identical parameters except for the positive prior parameter of the non-negative loss function. One was conducted with extracted from the data with a value of 0.02. The other was simply set with a value of 0.5. A standard Positive-Negative (PN) configuration with unmodified ground-truth was used as reference to compare the results.This comparative model is trained with unmodified ground-truth image and use the Binary Cross Entropy (BCE) loss. The Dice coefficient metric is used to evaluate the segmentation. The models are trained on 200 epoch.

Results
Both experiment with the varying positive prior produce identical results. The defined prior requires less training before providing significant results. For example, the Dice coefficient at the middle of the training is 0.45 for the defined prior and 0.2 for the extracted prior.
The results are similar to the results of the comparative model BCE. This could conclude that it is possible to train efficient segmentation models with low annotated data.

Methods	Dice coefficient WT
PU : $\pi_p = 0.5$	0.5003
PU: $\pi_p = 0.02$	0.5000
PN: BCE	0.5300

Fig. 2 Dice coefficient results for the whole tumor (WT) for both PU experiment with both positive prior experiment and with PN experiment as comparison.

Discussion
These results unfortunately doesn't compete with the state of the art on such dataset which reach a dice coefficient a minimum of 0.8. The next step would be to reproduce the experiment with a unmodified 3D BraTS2020 dataset and compare it again with the state of the the art. Finally, an analysis of the state of the art methods to observe which would be applicable to Positive-Unlabeled learning would be most interesting an could improve the results.

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Acknowledgements
I would like to thank, Prof. Dr. Raphael Sznitman and Dr. Pablo Márquez Neila for their guidance through the thesis. And I would like to thank Mr. Fei Hugo Wu for his support and help during the whole project.

Positional Accuracy Evaluation of a Robotic System for Spinal Surgery

Adrian Rechsteiner

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Examiners: Prof. Dr. Stefan Weber, MSc Fabian Müller

Introduction

In robotic spine surgery, sufficient geometric accuracy when delivering pedicle screws is crucial. As part of a research project aiming at providing foundations to the next generation of robotic solutiosn, this project aimed at introducing a reliable and volatile accuracy benchmark system and method.

Materials and Methods

The factors potentially contributing to geometric inaccuracy were identified. Subsequently, several phantom benchmarks were conceptionalized to assess registration and drilling errors. Requirements include CT scanability, rigidity, durability and resembling of relevant anatomy. A first phantom was designed and manufactured that allows studying imaging effects, fiducial localization and simple pointing accuracy (Fig. 1).

Fig. 1: Registration Performance phantom

The second phantom was designed and manufactured to study robotic drilling performance under rigid conditions (ie. the target does not move during drilling Fig. 2).

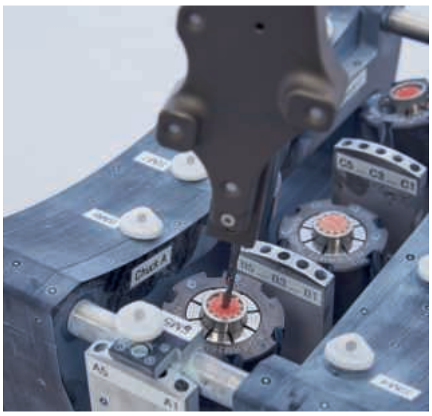

Fig. 2: Study of drilling performance in rigid conditions

It integrates up to three chucks that can hold drill samples (artificial bone material) and interfaces for the attachment of segment markers to allow emulation of tracking individual spine segments.

The third phantom was designed and manufactured to study robotic drilling performance under moving conditions (ie. the target does move during drilling. It integrates two chucks that can hold drill samples (artificial bone material) and interfaces for the attachment of segment markers to allow emulation of tracking individual spine segments. (Fig. 3). The phantom provides freedom of motion around the cranial-caudal axis (rotation) and along the anterior-posterior axis (translation), as they are assumed to be the most relevant in vertebral motion.

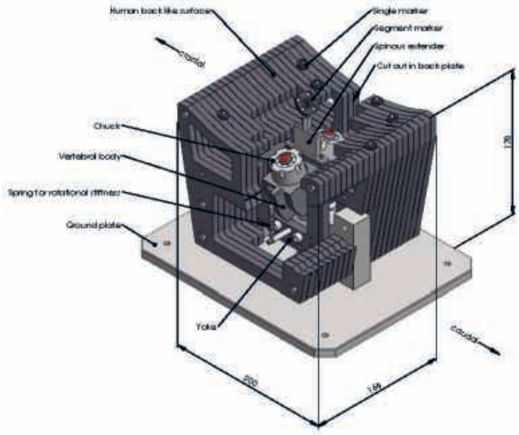

Fig. 3: Phantom to study drilling performance in non-rigid conditions.

For all produced phantoms geometric ground truth was produced using a coordinate measurement machine.

Results

All phantoms were designed, two are already produced and measured for ground truth.

References

ASTM International, F2554 Standard Practice for Measurement of Positional accuracy of Computer Assisted Surgical Systems, 2018

Acknowledgements

The project was supported by a Bridge SNF grant of the Swiss national science foundation (SNF). The important contribution of the ARTORG machine shop (Urs Rohrer) during construction and production is gratefully acknowledged.

High-Level Synthesis of an Edge Detector Using Windowed State Space Filters in 180nm CMOS

Ralph Rechsteiner

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Examiners: Prof. Dr. Marcel Jacomet, Prof Dr. Reto Wildhaber

Introduction

For the 3-D Esophageal ECG Project [1] a versatile and robust set of signal processing algorithms was developed. These algorithms heavily rely on autonomous linear state space models (ALSSMs) that allow recursive computations of squared error cost functions. Despite their advantageous features and power saving potential, the implementation of these methods in electronic hardware like an FPGA (Field Programmable Gate Arrray) or an ASIC (Application Specific Integrated Circuit) has not yet been realized [1]. In this work, the feasibility of hardware implementations of ALSSMs was studied and a simple yet powerful algorithm was integrated in 180nm CMOS. The chip was optimized with various architectural power techniques for low power consumption. In order to design and simulate models with fast iterations on architectural level, High-Level Synthesis (HLS) is used [2].

Materials and Methods

We are interested to implement an edge detection or change point detection algorithm in hardware, which is a widely used method, e.g. to detect onsets of QRS waves in ECG signals (Fig. 1).

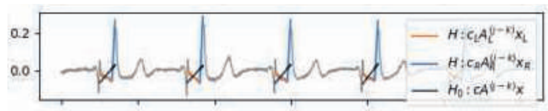

Fig. 1: Edge Detection Algorithm using Autonomous Linear State Space Models (ALSSMs)

As a first step, a high level Simulink model including a test framework has been created, which served as a golden reference. Next, four major and five minor hardware models with word lengths of 8, 12 and 16 bits are designed. The new models are assessed in their edge detection quality measuring the sensitivity and specificity. If sufficient, VHDL code is generated using a HDL-Coder and transferred to the ASIC toolchain. The VHDL files are first checked in a dynamic timing simulation before an RTL synthesis is performed. The standard logic cells are then placed and routed according to the gate-level netlist and optimized for power, performance and area (PPA), while ensuring that no timing violations occur. The final chip has to undergo carefully testing before manufacturing.

Results

The performance of the edge detector highly depends on the chosen word length. 8 bit data resolution has shown to be the absolute minimum. Good detection is achieved with 12 bits and above, while real esophageal ECG signals need a minimum resolution of 16 bit. The developed nested fixed-point conversion method reduced the power consumption by 46 % and the core area by 37%.
This lead to a minimum chip size of 1.037 mm x 1.408 mm with a total power consumption of 1.02 µW at 0.80 V and 8 bit data resolution (Fig. 2).

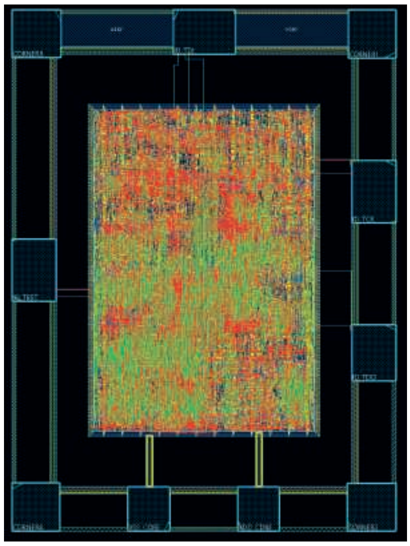

Fig. 2: Layout of an 8 bit Edge Detector in 180nm CMOS measuring 1.037 mm x 1.408 mm

Discussion

We successfully demonstrated that efficient implementations of autonomous linear state space models in hardware are possible. Methodologies to relax the fixed-point parameter restriction are very desirable to extend hardware ALSSM capabilities to more complex signal filtering.

References

[1] R. A. Wildhaber. Localized Sate Space and Polynomial Filters with Applications in Electrocardiography. PhD thesis, ETH Zurich, 2019.
[2] S. Mohanty et. al.. Low-power High-Level Synthesis for Nanoscale CMOS Circuits.

Acknowledgements

A special thanks goes to Christof Baeriswyl who provided me a lot of his knowledge in the digital ASIC design and to Frédéric Waldmann who helped obtaining the desired results from the Imlib library. I want to thank Reto Wildhaber and Marcel Jacomet for the good guidance during the course of this work.

Bern University of Applied Sciences

Master's Thesis in Biomedical Engineering

UNIVERSITÄT BERN

Optical Coherence Tomography Assisted Laser Treatment of Retinal Detachments

Simon Salzmann

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University Hospital Münster, Department of Ophthalmology
Knappschaftsklinikum Saar, Eye Clinic Sulzbach
Examiners: Prof. Christoph Meier, MSc Christian Burri

Introduction

Retinal detachment (RD) is a severe eye condition in which the neurosensory retina (NSR) detaches from the underlying retinal pigment epithelium (RPE), often leading to profound loss of vision. The prevalent form is rhegmatogenous RD, where a full-thickness retinal break allows fluid from the vitreous cavity to enter the subretinal space. To prevent progression of RD, laser photocoagulation (LPC) lesions are placed immediately around the break in clinical practice to seal the tissue, referred to as laser retinopexy. The treatment is usually performed under indirect ophthalmoscopy, and a successful outcome requires an experienced operator. Complementary optical coherence tomography (OCT) is used to determine disease progression, but not as a treatment planning tool. Therefore, this master's thesis was conducted using a diagnostic OCT imaging system with integrated navigated treatment laser (Spectralis Centaurus, Bern University of Applied Sciences, Biel, CH) to extend its functionality with a semi-automatic OCT-guided treatment of retinal breaks for facilitated prophylaxis of RD.

Materials and Methods

The elaborated concept for retinal break treatment includes volumetric OCT scanning of the affected area, OCT-based treatment planning, and subsequent LPC treatment execution. To reliably seal the break, LPC lesions must be applied in regions of still attached NSR. Therefore, OCT scans were used to manually mark the boundary of the RD, which allowed to compute optimally placed treatment points in an elliptical shape around the detachment.

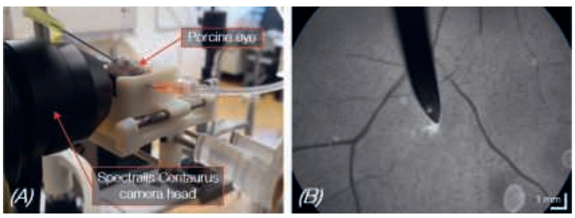

Fig. 1 (A) setup for ex-vivo porcine eye experiments. (B) Artificial provoking of retinal break for subsequent treatment.

To evaluate the proposed method, artificially provoked retinal breaks in 10 ex-vivo porcine eyes were treated accordingly (Fig. 1). Fundus photography and OCT imaging were used to evaluate the treatment outcome.

Results

The implementation of the concept provided a simplified OCT-based treatment planning in combination with a navigated LPC application for prophylactic treatment of retinal breaks. Fundus photography of the porcine eyes revealed the typical tissue whitening at the planned treatment locations. The required ruptures of the retina at the LPC application sites were verified in OCT cross-sectional scans (Fig. 2).

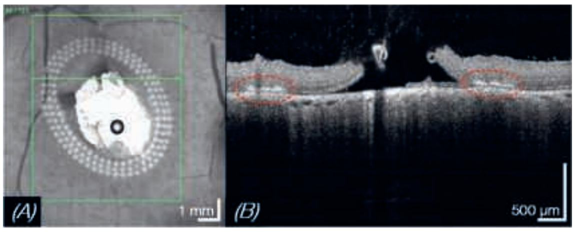

Fig. 2 Tissue whitening in the fundus image (A) and retinal ruptures (red markings) in the corresponding OCT scan (B) indicate a successful treatment.

Discussion

The successful ex-vivo experiments demonstrated the capability of the novel method and indicated improved applicability and accuracy compared to conventional laserretinopexy. However, clinical OCT data from one patient who had suffered a retinal break revealed potential difficulties because retinal breaks are often located far in the periphery and are therefore difficult to reach with the standard 30° field of view lens. This issue might be solved by using a wide-angle lens or a three-mirror contact lens. Furthermore, integration of the existing tracking and follow-up capabilities of the SPECTRALIS platform (Heidelberg Engineering, Heidelberg, DE) would further enhance and facilitate the treatment.

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I would like to thank Dr. med. Sami Al-Nawaiseh and Dr. med. Philip Wakili for the clinical perspective and suggestions, Heidelberg Engineering and Meridian Medical for the helpful support, and the optoLab group for the guidance and constructive feedback.

Interpretability-Driven Failure Modes Investigation of Deep Learning Segmentation Models

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Examiners: Prof. Dr. Mauricio Reyes, Dr. Alain Jungo

Introduction

In the medical domain it is of paramount importance to provide reliable information on the decision process of a deep-learning model for it to be used in the clinical practice. Interpretation algorithms are currently developed and investigated to enhance interpretability of models. In this study we present a new framework for improving medical image segmentation models interpretability using a state of the art model and a simple interpretation algorithm to study model's failure modes. Moreover, we introduce *decision similarity maps* that show the degree of confusion of a model when repeating wrong decisions.

Materials and Methods

A state of the art modified U-Net architecture was trained and used to predict segmentation masks out of 2D axial slices from the Medical Segmentation Decathlon Prostate dataset. The Neuron-Gradient interpretation algorithm was applied to selected pixels of interest for corresponding neurons in the two output channels of the model resulting in a pair of saliency maps for each pixel of interest. For each pixel of interest, both saliency maps were again processed by the model and their bottleneck representation was compared by means of the cosine similarity function resulting in what we call *decision similarity*. The same process was repeated for different perturbed versions of the input images and the corresponding pixel-wise *decision similarity* was studied along with their Dice score.

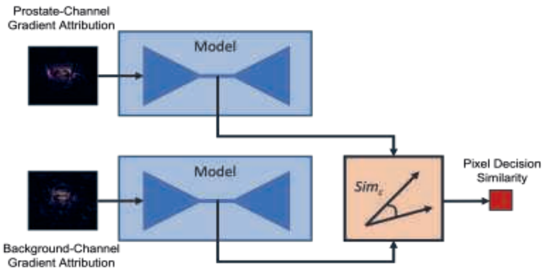

Fig. 1 Scheme used to compute pixel's decision similarity from its per-channel Neuron-Gradient attributions.

Fig. 2 Example of similarity maps for different perturbations.

Results

We observe a substantial increase in *decision similarity* and decrease in Dice score when applying our framework to original and perturbed images. Moreover, clear patterns in the coupled variation of both variables can be identified.

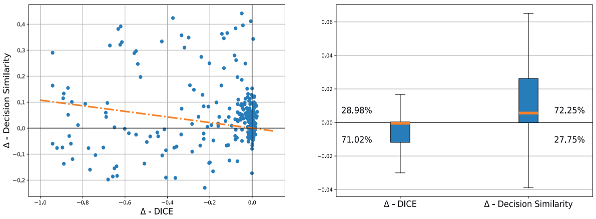

Fig. 3 Left: Correlation plot of Dice score and decision similarity variations. Right: Boxplot of variation of Dice score and decision similarity.

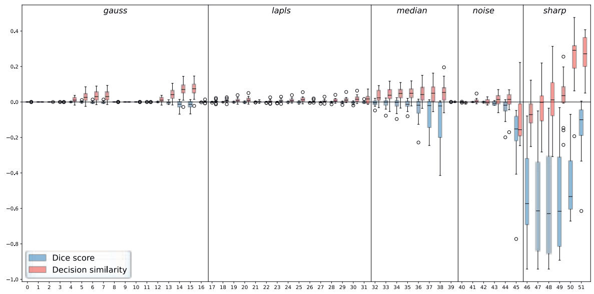

Fig. 4 Dice score and decision similarity coupled results for all perturbations applied to the samples.

Discussion

An increase in *decision similarity* is coupled with a decrease of Dice score. This demonstrates that *decision similarity* can be used as a proxy for the performance of a model, while measuring how similarly the model takes decisions for perturbed versions of the same images. Hence, it measures the degree of confusion of the model.

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I would like to thank Prof. Dr. Mauricio Reyes and the entire Medical Image Analysis group for the support and precious contributions to this work.

Quantification of the Energy Loss through Turbulence in an Aortic Stenosis Model using Particle Tracking Velocimetry and Doppler Echocardiography in a Silicone Ascending Aorta Phantom

Barbara Schläpfer

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University Hospital Bern (Inselspital), Department of Cardiology
Examiners: Prof. Dr. Dominik Obrist, Dr. med. Eric Buffle

Introduction
The main cause for aortic stenosis (AS) is the degenerative calcification of the aortic valve which leads to an increase in leaflet stiffness and a reduced valve orifice area associated. A consequence of that is an increased transvalvular pressure gradient. The gold standard to assess aortic stenosis is echocardiography. In several studies, an increase of turbulent kinetic energy (TKE) loss in combination with aortic stenosis was demonstrated. To compensate for this loss, there is an increase of work by the left ventricle. However, the measurement of turbulence intensity with echocardiography is not yet validated for clinical evaluations for AS. The aim of this project is to quantify the energy loss associated with turbulent flow in a silicone aortic phantom, continuing on the foundations laid in a previous master thesis.

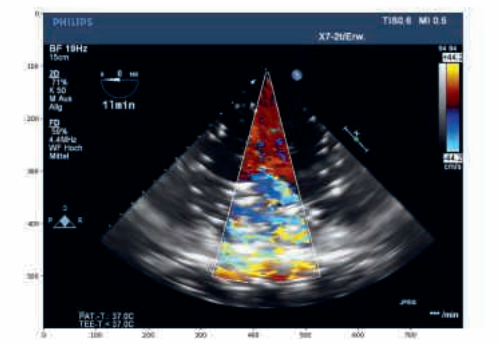

Fig. 1 A color Doppler images used to extract the velocity

Materials and Methods
A blood mimicking fluid had to be found which complies with optical, rheological constraints and does not cause the valve tissue to shrink. Five porcine aortic valves were tested in a flow loop that replicates the pulsatile flow of the heart. The flow was recorded by a high-speed camera and color Doppler ultrasound images. Three different flow rates were applied (1, 2.5, and 4 l/min). To achieve a stiffening of the valve and therefore be able to test three different stiffness grades (a, b, c), the valves were submerged into formaldehyde. The successful stiffening was measured by computing the left ventricular myocardial work. The gold standard quantification of turbulence was performed with backlight Particle Tracking Velocimetry (PTV). The ascending aorta phantom was modified to include an ultrasound probe and reduce the retrograde flow. The ultrasound images were analyzed with custom-made software to quantify the TKE.

Results
The valve shrinking could be reduced with the used blood mimicking fluid. The ultrasound was successfully integrated into the experimental setup. The velocity field was extracted from the PTV data as well as the color Doppler images and the TKE computed. The fluctuation of TKE at different points of the cardiac cycle could be shown. Trends toward an increase in TKE both PTV and Doppler data could be found but were inconsistent across valve and flow rate.

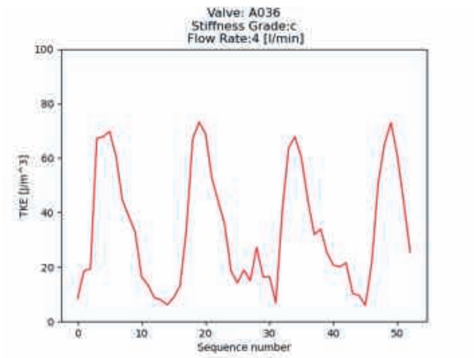

Fig. 2 Shows the turbulent kinetic energy fluctuation over the sequences extracted from the color Doppler images.

Discussion
Descriptive analysis of the results shows a trend increase in TKE with PTV data and to a lesser extent in the Doppler data. Further development of the Doppler analysis algorithm is needed. Rigorous statistical analysis of the change in TKE in the PTV and Doppler data analyses needs to be done as well as the correlation between the TKE with both measurement methods.

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Bern University of Applied Sciences

Master’s Thesis in Biomedical Engineering

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Retinal Images and Meta-Data Verification to Ensure Data Consistency and Anonymity

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Introduction
To avoid bias in clinical studies, the assessment of medical data is performed by an independent organisation, usually called a reading centre. However, in the evaluation process, meta-data mismatches and data inconsistencies are observed in approx. 10% of data. The aim of this thesis is to design and evaluate a set of algorithms that would work on OCT volumes and fundus photographs to solve two main tasks. The first task is to detect data inconsistencies regarding eye laterality and the presence of patient information in the images. The second task is to detect whether two samples come from the same patient.

Materials and Methods
For each task, we defined one dataset per imaging modality and preprocessed the data. The preprocessing techniques used were resizing, greyscale conversion and normalisation. We defined two models using modified ResNet-50 architecture. Our first model was a binary classifier that we used for eye laterality and anonymity verification. It was based on previous research. For the task of patient similarity recognition, we combined two models in a siamese architecture which served as a feature extractor from a pair of input samples.

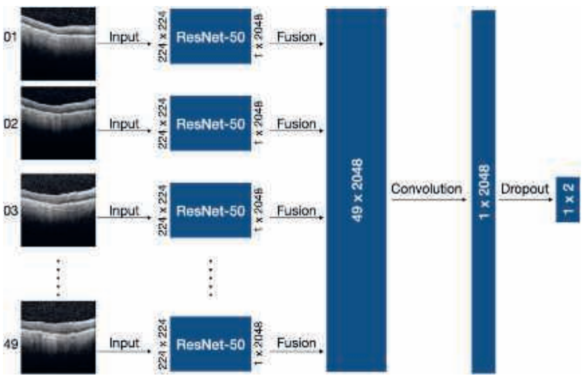

Fig. 1 The scheme of the model used in this work. In the case of the Fundus dataset, there was only one input image which was processed by one ResNet-50. The feature vector was also of shape [1x2048], we skipped the fusion step and the convolution step did not have any effect. The output was in the shape of [1x2] to predict for 2 output classes.

Results
This work brings the following key contributions. Firstly, we introduce a model architecture that extends previous work to classify eye laterality from both fundus photographs and OCT volumes with great performance (ROC AUC >0.99). Secondly, we present a pipeline of algorithms with the potential of reducing the need for manual corrections by at least 87%. And lastly, we present novel work in recurring patient recognition from fundus photographs and OCT volumes with promising results.

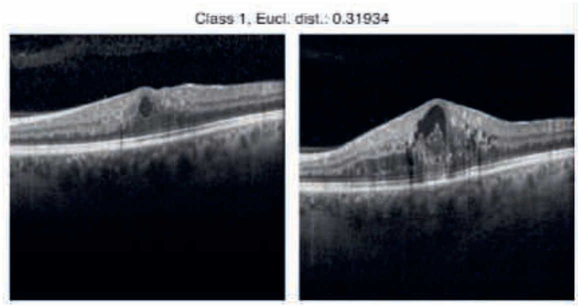

Fig. 2 Example of a pair of OCT BScans from one patient. The scans were acquired during visits more than 3 years apart. Our model considers these samples very similar (small Euclidean distance) despite evolved retinal pathology between samples. Visualisation of BScans n.24.

Discussion
The analysis of manual corrections reduction showed great opportunity for the eye laterality task. However, the problem of anonymisation was found to be more complex and would require a text recognition approach rather than classification. Our approach to patient similarity recognition brought promising initial results, although we believe that the model performance could be increased by redefining the datasets used. Additionally, it could be useful to visualise pair similarities using similarity maps.

References
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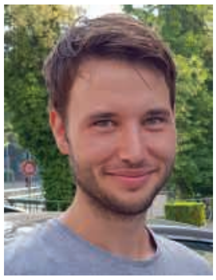
Deep Learning based Fully Automatic Quantification of Rotator Cuff Tears from MRI

Stefan Weber



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Introduction

Rotator cuff tears are the most common source of shoulder pain. Many factors can be considered to choose the right surgical treatment procedure. The most important factors are tear thickness (partial vs. full), tear size, tear shape, and muscle quality. The aim of this work was the fully automated quantification and classification of a full-thickness posterosuperior rotator cuff tear from MR images using a deep learning based approach.

Materials and Methods

A complete new approach to automatically quantify and classify a rotator cuff tear, based on the segmentation of the tear from MR images, was developed and validated. A neural network was trained to segment the rotator cuff tear from an MR image and automatic methods for calculating tear width and retraction and for classifying the tear according to pattern, extension and retraction were implemented.

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Fig. 1: All steps of the developed fully automatic quantifiaction pipeline for rotator cuff tears.

The results were also evaluated clinically by intraoperative measurements of the rotator cuff tear performed on a separate dataset of six patients.

Results

The accuracy of the tear retraction calculation based on the developed automatic tear segmentation was 6.56 mm ± 6.48 mm in comparison to the interrater variability of tear retraction calculation based on manual segmentations of 3.77 mm ± 3.58 mm.

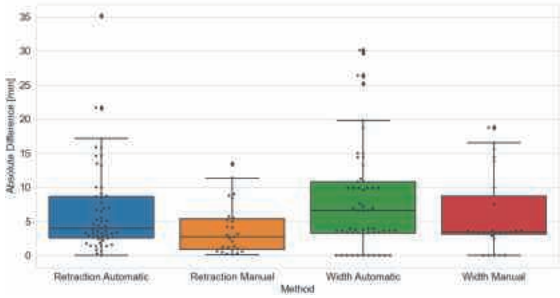

Fig. 2: Absolute errors of the extracted measurements (retraction and tear width) when measured manually and automatically.

Discussion

These results show that an automatic quantification of a rotator cuff tear is possible. The achieved accuracies of the quantification pipeline for rotator cuff tears need to be improved to make them clinically useable. The large interrater variability of manual segmentation based measurements, highlights the difficulty of the tear segmentations task in general. To improve the accuracy of an automated segmentation, a larger dataset for training may be required or a semi-automatic approach could be used.

References

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