Bern University
of Applied Sciences

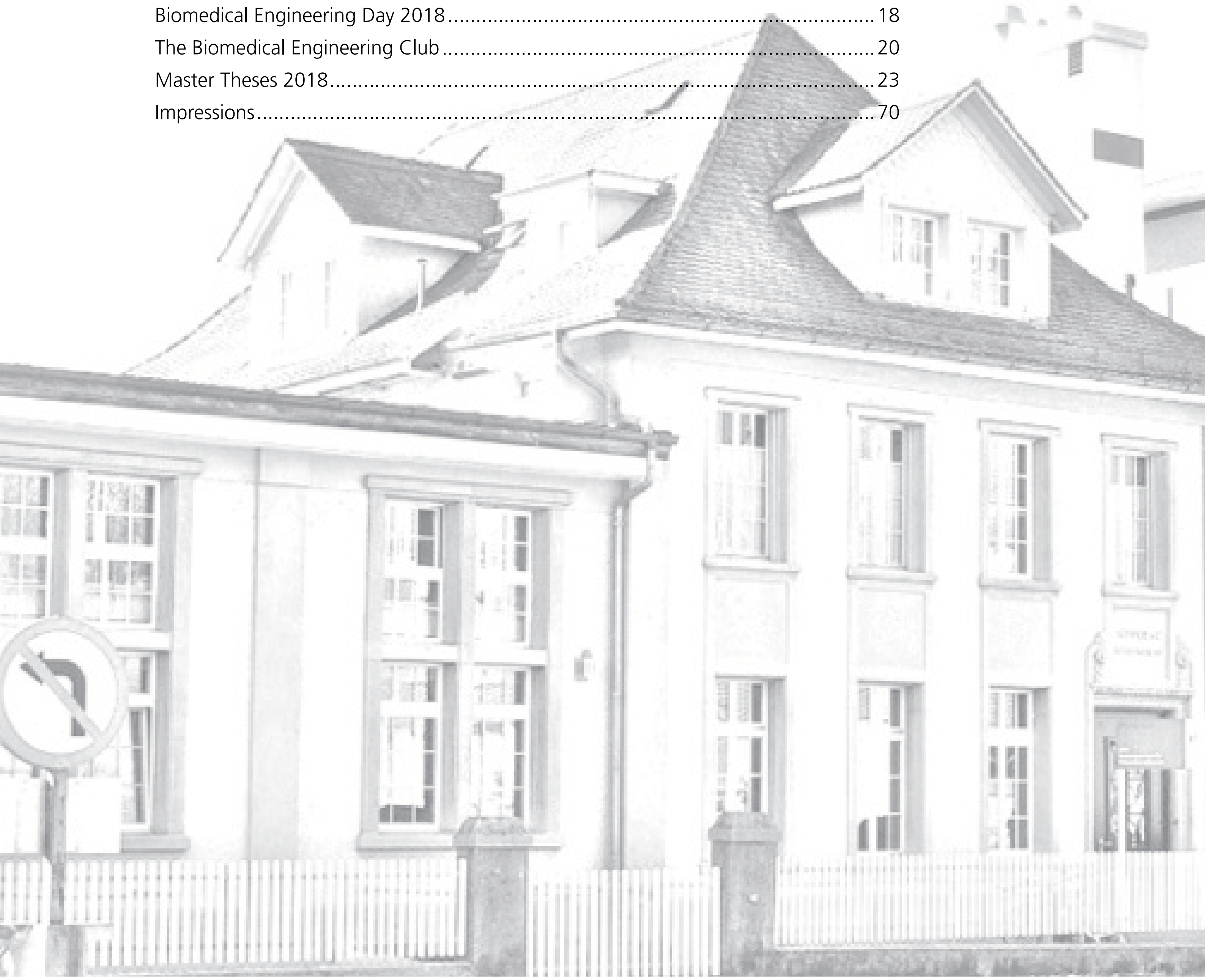
UNIVERSITÄT
BERN

Master Biomedical Engineering

Annual Report 2018

MASTER OF SCIENCE IN BIOMEDICAL ENGINEERING

Contents



Introduction

In the era of digitalisation, the expectations on the form but even more on the content of a Master's program at the intersection between biomedical and engineering sciences are increasing markedly. Our Master's program in Biomedical Engineering at the University of Bern (BME) seeks to meet both expectations and to deliver a globally competitive academic program.
On the form, our master's program leverages the capabilities of the central course management system (KSL) of the University of Bern. KSL brings transparency on grade transfer and proper accounting of credits with the use of the European Credit Transfer System (ECTS), allowing students to track their progress towards graduation.
On the content, we initiate continuously new courses to better cover fundamentals in biomedical engineering but also to introduce more advanced, research-driven subjects such as medical informatics and machine learning. A further preparation course in engineering mechanics was introduced that completes the former ones in mathematics, electrical engineering or programming in order to help students with other backgrounds to follow the compulsory courses of the basic modules in mathematics and biomedical engineering. A novel laboratory course in biomechanics was initiated to illustrate the lectures with technical/clinical experimentation in groups and to train students in scientific writing by presenting, analysing and discussing the obtained results in a short technical report.
Our master's program in BME represents a remarkable opportunity for students with a variety of academic qualifications and disciplines to achieve a university level master's degree and go on to carry out doctoral studies at an internationally recognised university or join industry as a highly qualified biomedical engineer. Further hallmarks of our program are the full integration of the program with the Bern University Hospital (Inselspital), the application-oriented clinical research projects, the International footprint with all mandatory courses in English, the flexible study calendar that can accommodate students with a part-time employment and the central geography of the Bern area.
The annual Biomedical Engineering Day 2018 attracted numerous students, alumni and larger and small to medium medtech companies from the Bern region and beyond. Like in previous years, we received a very positive feedback for our efforts in cultivating a strong relationship between students, research institutes and industrial partners. As a clinical highlight, the Department of Otorhinolaryngology, Head and Neck Surgery presented a live intervention of the removal of nasal polyps executed by Prof. Marco Caversaccio in the operating room of the Inselspital and kindly moderated by Dr. Mantokoudis, in the auditorium. The BME Day keynote lecture was given by Prof. Osman Ratib, from the Department of Radiology and Medical Informatics of the University of Geneva, with pertinent insights into big data analytics and personalised medicine. I would like to thank all the participants for this 10th successful edition of the BME Day!
Finally, we are delighted to report that forty-three master's degrees were conferred in 2018 and 57 regular students were admitted to the Master's program in the fall. Another 2 students were admitted through an exchange program.
A notable number of Master's thesis projects that investigated broad medical applications were submitted and successfully defended by viva voce. One-page summaries of the 2018 projects can be found in the second part of this report.
I wish to conclude by expressing my appreciation to the internal but also the external teachers, who deliver year after year, the knowledge and skills that make the core value of our master's program. I would also like to thank the study coordination, Mrs Ulla Jakob, Alexandra Neuenschwander-Salazar and Julia Spyra for providing the best possible support to the students and lecturers of the program and for organizing events such as the BME Day with professionalism and enthusiasm.

Philippe Zysset
Program Director

Organization

Management

Ph. Zysset
Program Director

V. M. Koch
Deputy Program Director

Administration

U. Jakob-Burger
Study Coordinator

A. Neuenschwander Salazar
Study Coordinator

J. Spyra
Study Coordinator

M. Reyes
Master Thesis Coordinator

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 complexity 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. In 2018, the basic module "Biomedical Engineering" was re-structured and augmented by new courses in "Medical Informatics" and "Introduction to Biomechanics".

The Curriculum

Duration of Studies and Part-Time Professional Occupation

The full-time study program takes 4 semesters, which corresponds to 120 ECTS points, one ECTS point 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, biology or related fields, do not fulfill all prerequisites for the courses of the master's program. Therefore, introductory courses in MATLAB, C++ programming, Electrical Engineering and Engineering Mechanics 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 highly complex subject matter in the specialized courses. All students with an engineering background (for other students, individual study plans are set up which may contain certain variations) 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 and third semester, the courses from the basic modules make up for approximately 30%.

Major Modules

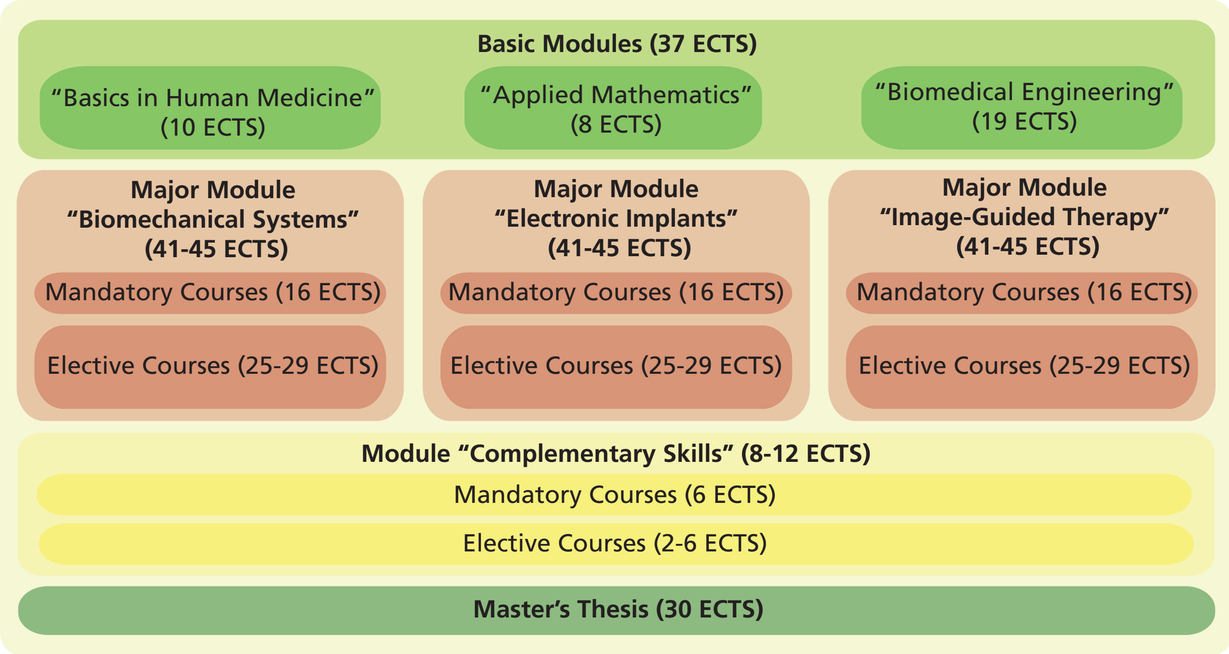
After the first semester, the choice of one of three major modules Biomechanical Systems, Electronic Implants, or Image-Guided Therapy constitutes the first opportunity for specialization.

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 introduction of a new module called "Complementary Skills" where students are required to complete two mandatory courses (Innovation Management; Regulatory Affairs and Patents) as well as 2 ECTS from the electives courses (Ethics in Biomedical Engineering; Scientific Writing in Biomedical Engineering; Introduction to Epidemiology and Health Technology Assessment). If a student selects more than 2 ECTS from the elective part, the additional points can be credited in the student's major module.



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 points 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
- Biomechanics Labs
- Biomedical Acoustics
- 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
- Cutting Edge Microscopy
- 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
- Image-Guided Therapy Lab
- Innovation Management
- Intelligent Implants and Surgical Instruments
- Introduction to Biomechanics
- Introduction to Digital Logic
- Introduction to Electrical Engineering
- Introduction to Engineering Mechanics
- Introduction to Medical Statistics
- Introduction to Programming
- Introduction to Signal and Image Processing
- Introductory Anatomy and Histology for Biomedical Engineers
- Low Power Microelectronics
- Machine Learning
- Medical Image Analysis
- Medical Image Analysis Lab
- Medical Informatics
- Medical Robotics
- Microsystems Engineering
- Molecular and Cellular Biology Practical
- Numerical Methods
- Ophthalmic Technologies
- Orthopaedic Surgery – Practical Course
- Osteology
- Principles of Medical Imaging
- Programming of Microcontrollers
- Regenerative Dentistry for Biomedical Engineering
- Regulatory Affairs and Patents
- Rehabilitation Technology
- Scientific Writing in Biomedical Engineering
- Selected Chapters in Mathematics
- Short Introduction to MATLAB
- Technology and Diabetes Management
- Tissue Biomechanics
- Tissue Biomechanics Lab
- Tissue Engineering
- Tissue Engineering - Practical Course
- 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, vessel 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 bench top 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 evaluation of the frictional behaviour of biomaterials on articular cartilage, development of new breathable lung alveoli on a chip, characterization of an ultrasonic microscalpel and finite element analysis of human bones, diastolic blood flow or tissue-mimicking biomaterials.

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 engineering, orthopaedics, dentistry, rehabilitation engineering and pharmaceuticals are strongly represented within the Swiss Medical Technology industry and, despite the strong Swiss franc, 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.

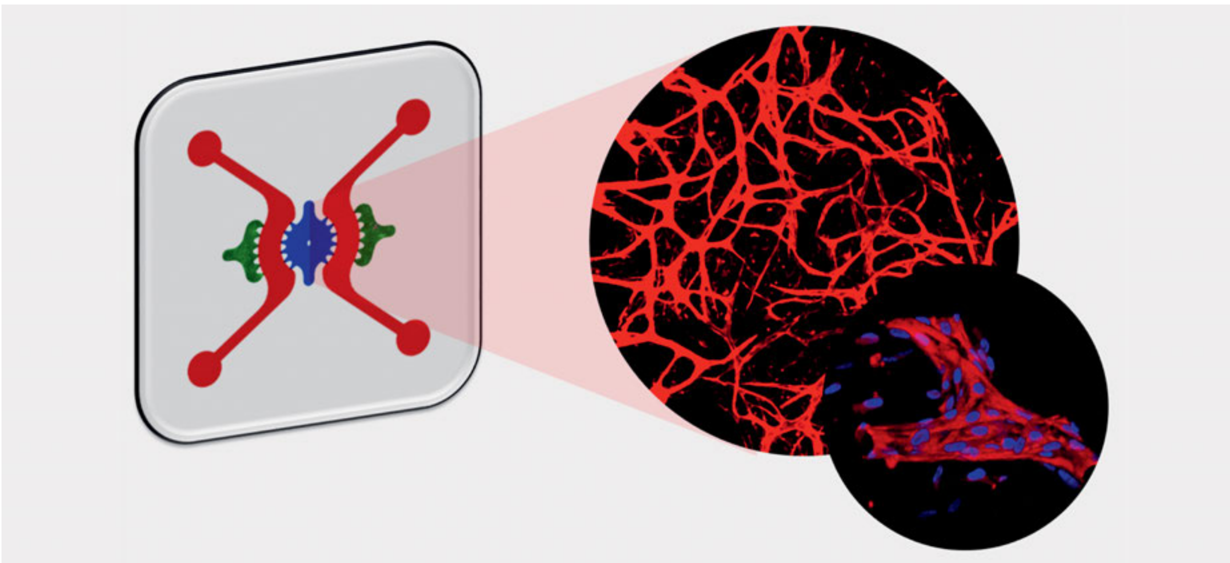


Fig 1 Microfluidic chip of in vitro perfusable microvasculature network. Microvasculature network immuno-stained for endothelial cell marker PECAM-1.

Major Modules

Electronic Implants

Prof. Dr. Volker M. Koch

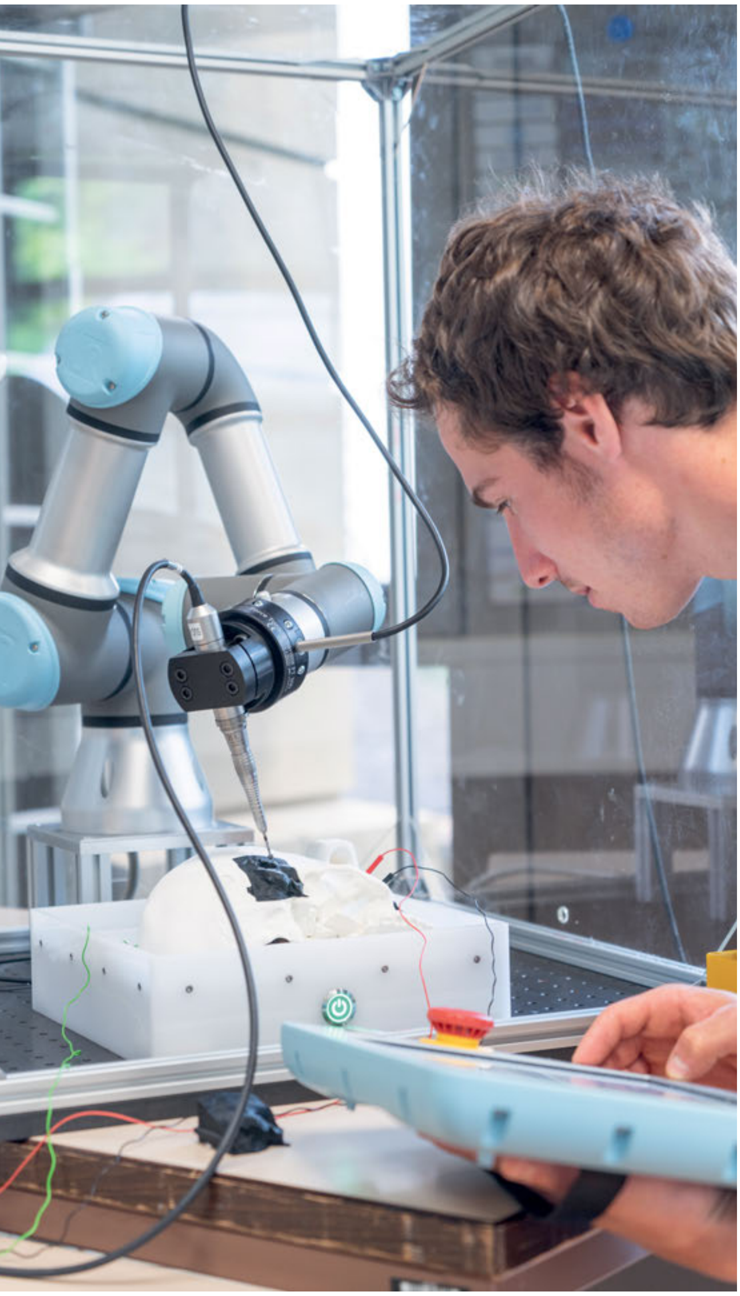
Electronic implants are devices like cardiac pacemakers and cochlear implants. Due to miniaturization and other developments, many new applications become feasible and this exciting area is growing rapidly. For example, cochlear implants provide already approximately more than 320’000 people worldwide 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, and microsystems engineering including MEMS technology. Application-oriented elective courses are also taught, e.g., cardiovascular technology, biomedical sensors, 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.



Cochlear implant surgery requires drilling near the facial nerve. The goal of the DrillMon project is to develop, optimize and characterize a system that combines a surgical drilling device with an electrical nerve stimulation probe. This allows surgeons to continuously monitor nerves while drilling with up to 80’000 rpm.

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 and machine learning.

Robotic cochlear implantation, Inselspital Bern (© ARTORG Center, 2017)

New Courses

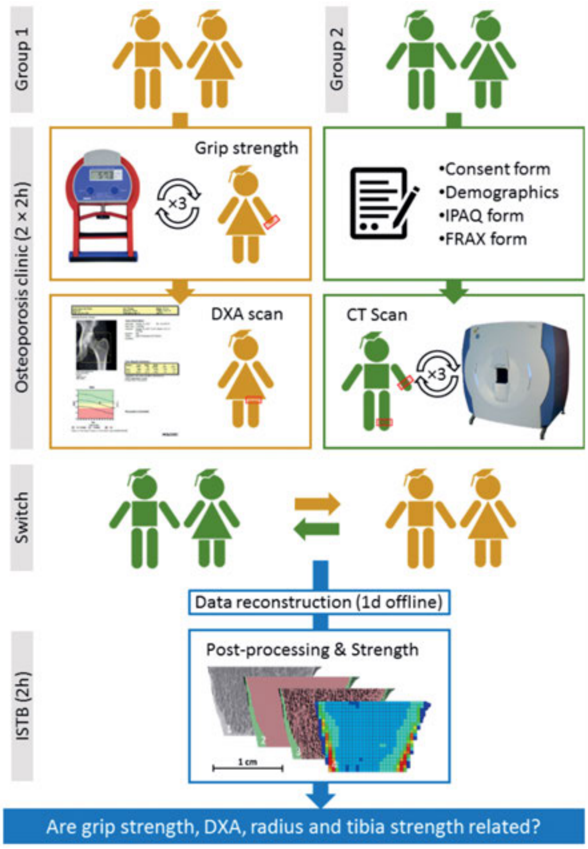
Biomechanics Labs

Prof. Daniel Baumgartner
Prof. Heiner Baur
Prof. Bernd Heinlein
Prof. Kurt Lippuner
Prof. Dominik Obrist
Prof. Philippe Zysset

The course consists of a collection of experiments in biomechanical engineering based on diverse methodologies used in the contributing research institutes and clinics of the program.
The aim is to acquire and train the practical skills necessary for the acquisition of data, statistical analysis, interpretation of the results and identification of the key limitations of the methods. Finally, the preparation of the reports represents an opportunity to train the scientific writing skills needed for the redaction of a master thesis.

The titles of the proposed laboratories are

- Performance assessment of prosthetic heart valves
- X-ray microtomography and material testing of bone
- Gait and movement analysis
- HR-pQCT-based radius and tibia strength and their relationships with DXA and clinical factors
- The human shoulder - kinematic assessment and experimental simulation
- Musculoskeletal simulation - inverse dynamics of the knee joint



Flow chart of the biomechanics lab entitled "HR-pQCT-based radius and tibia strength and their relationships with DXA and clinical factors".

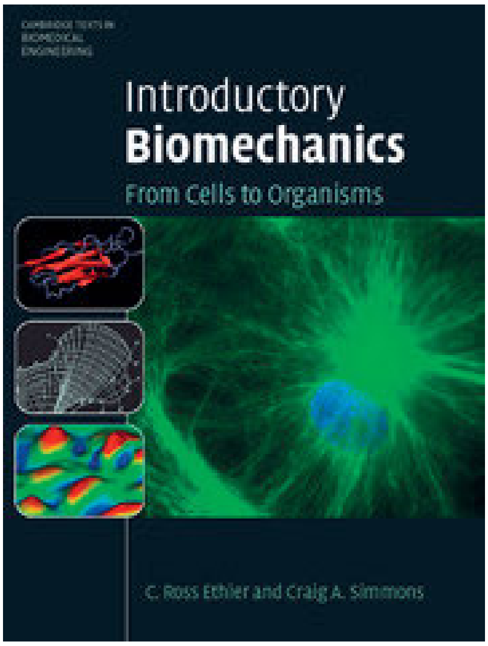
Introduction to Biomechanics

Prof. Dominik Obrist
Dr. Jakob Schwiedrzik
MSc. Soheila Zeinali

Biomechanics is the mechanics of living systems and plays an important role not only in the pathogenesis but also in the diagnosis and treatment of multiple diseases affecting humans.
This course is an introduction to biomechanics for engineers and follows the spirit of the book "Introductory Biomechanics" of R. Ethier and C. Simmons. It relies on essential notions of fluid and solid mechanics as well as their interaction to better understand human physiology from cells to organisms. The cells, tissues and the major biomechanical systems of the human body, namely the respiratory, cardio-vascular and musculoskeletal systems, are presented in the context of health and disease. Finally, the concepts of structural adaptation and mechanobiology are introduced.

The learning outcome of this course are

- Know the relevant concepts in
  - kinematics, dynamics and energetics
  - fluid and solid behaviour
  - transport phenomena
- Understand the biomechanical function and adaptation of the
  - respiratory system
  - cardiovascular system
  - musculoskeletal system
- Resolve simple biomechanical problems



Reference: "Introductory Biomechanics – From Cells to Organisms", C. Ross Ethier and Craig A. Simmons, University of Toronto, Cambridge University Press, 2007 (https://doi.org/10.1017/CBO9780511809217).

Introduction to Engineering Mechanics

MSc. Marzieh Ovesy
Prof. Philippe Zysset

Mechanics stems from the Greek "amkan", which means "machine" and burgeoned as the oldest branch of physics during the scientific revolution. As Theodor von Karman (1881-1963) claimed, science studies what already exists and engineering creates what never existed before. Today, mechanics is the science of motion of solid bodies, the forces that animate them, the energy stored and dissipated in them, the laws that govern them and of the behaviour of solid matter.

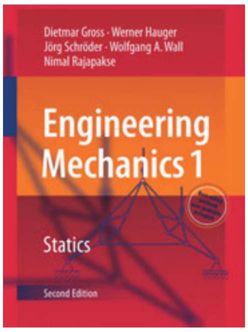
This course is a so-called preparation course devoted to students in the first semester with no background in mechanics or mechanical engineering.

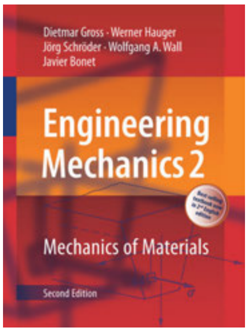
Introduction to engineering mechanics focusses on the needs of the practicing biomedical engineer, who analyses biological structures, biomedical devices or biomaterials at various length scales to determine whether they are able to perform certain motions or sustain certain loads.

The course introduces the basic concepts of mechanics with the aim to solve problems of growing complexity. Accordingly, half of the credits are dedicated to the theory and the other half to exercises.

In the first part on statics, the concepts of force and moments are presented and drawing of free-body diagrams is trained to determine if structures such as rigid bodies, trusses or beams are statically determinate or not. In the former case, the equilibrium equations are exploited to calculate the unknown forces and moments. Following the appearance of motion at joints, the notion of work and power are exposed in the context of duality between translations/rotations and forces/moments.

In the second part on the mechanics of materials, the concepts of strain and stresses are derived for infinitesimal volume elements. The ubiquitous Hooke's law relating strains to stresses is then exploited to resolve the equilibrium equations of deforming bars and beams.





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"Engineering Mechanics I - Statics" by Gross D., Hauger, W, Schröder J, Wall W. and Rajapakse N, Second edition, Springer Verlag, 2013.
"Engineering Mechanics II - Mechanics of Materials" by Gross D., Hauger, W, Schröder J, Wall W. and Bonet J., Second Edition, Springer Verlag, 2018.

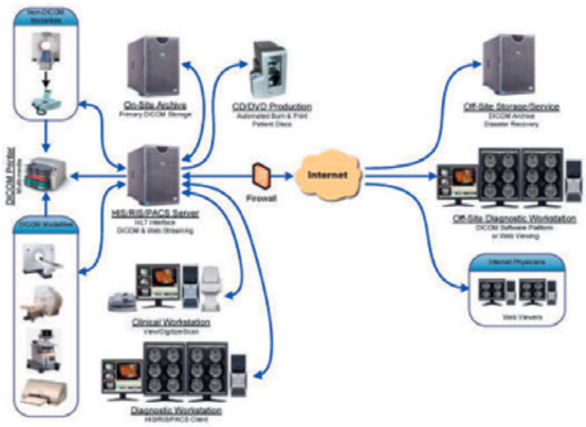
Medical informatics

Prof. Dr. Raphael Sznitman
Dr. Waldo Valenzuela

This course presents key fundamentals in computer science, with a focus on both theoretical and practical concepts, which form the basis of computer systems and networks in medicine. With a growing desire to digitalize data from hospital workflows and clinical trials, this course lays a broad foundation of knowledge in what it means to handle and automate processes related to data for the purpose of security, robustness and reliability.

In a first instance, the course outlines standard algorithms and formalism central to algorithms, their evaluation and comparison. Traditional approaches in sorting, searching of data of various types are explored while highlighting the advantages and disadvantages of different methods. Fundamentals in graph-based algorithms and hashing are also explored so to solve problems related to structured data such as images and text.

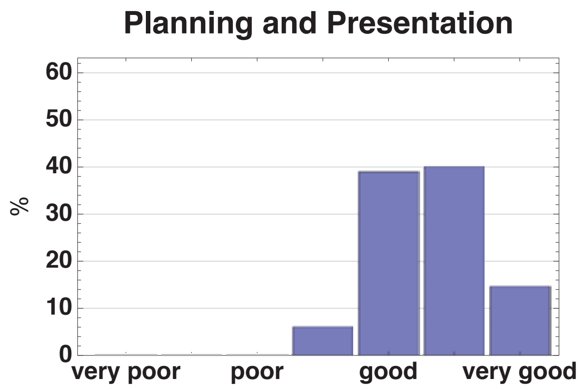
The second part of the course dives into the basics of computer network systems, scripting, and a step-by-step analysis of common computer network systems. Exploration and examination of standard or common digital imaging communication systems in medicine are highlighted to provide a hands-on experience of such tools. In general, standard protocols in medicine and medical information systems are highlighted so to pave the way for more in-depth courses in the Biomedical Engineering master's program.

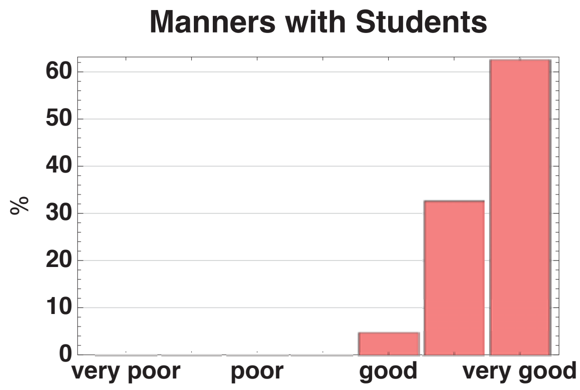


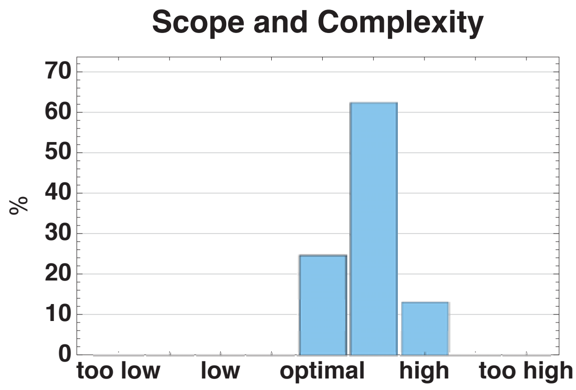
Hospital computer network system with connections to imaging devices and PACS systems.

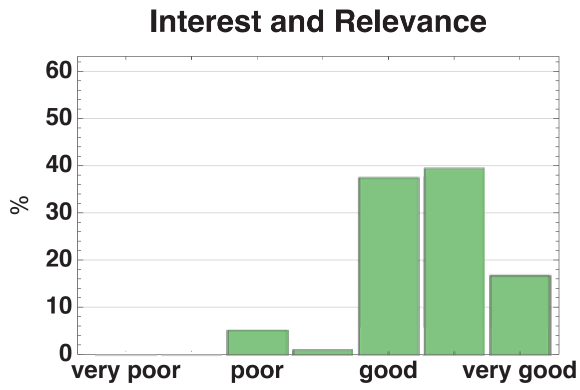
Evaluation of Courses in the Academic Year 2017/2018

Like in the previous years, a centralized evaluation was performed in the master's program in Fall Semester 2017 and Spring Semester 2018 according to the guidelines of the University of Bern. Both semesters were considered leading to 50 course evaluations involving almost 900 forms in total. The results regarding all forms (see below) reveal that the students are satisfied with the course program and that the courses are interesting and demanding at the same time.









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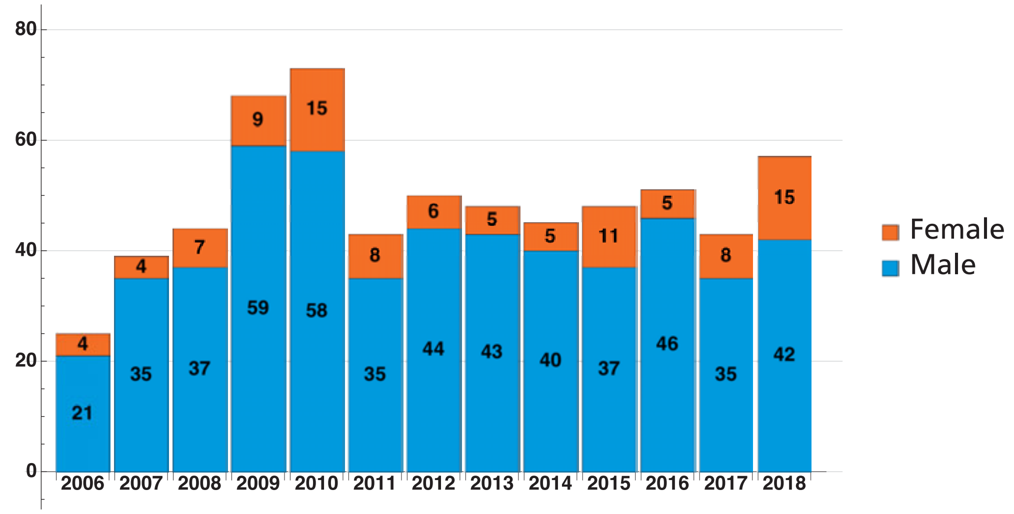
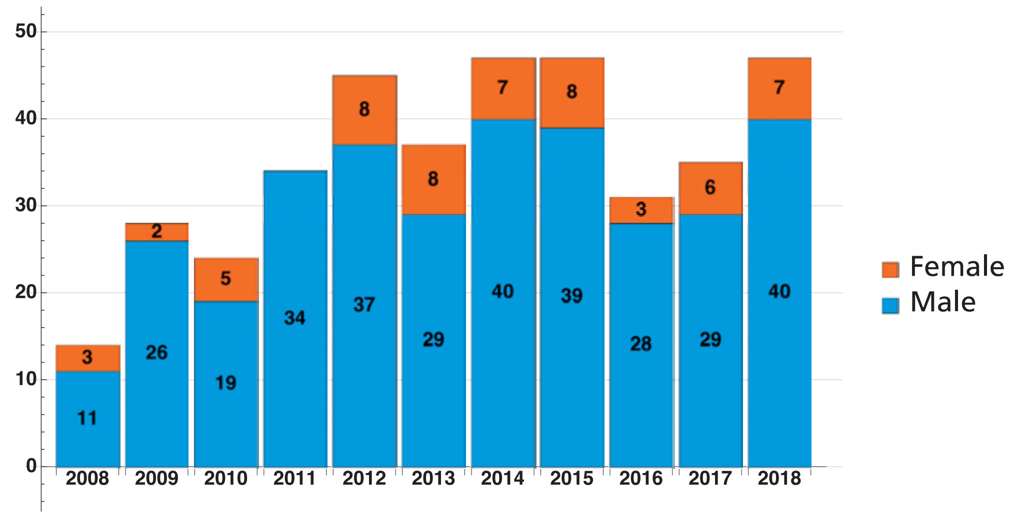
Janosch Häberli, Dr.
Daniel Haschtmann, PD Dr.
Bernd Heinlein, Prof. Dr.
Philipp Henle, Dr.
Roman Heuberger, Dr.
Ulrich Hofer, Dr.
Thomas Imwinkelried, Dr.
Björn Jensen, Dr.
Herbert Keppner, Prof. Dr.
Marc Kleinschmidt, Dr.
Jens Kowal, PD Dr.
Beat Lechmann
Reto Lerf, Dr.
Reto Luginbühl, Dr.
Katharina Maniura, Dr.
Simon Milligan, Dr.
Walter Moser, Dr.
Richard Nyffeler, PD Dr.
Jean Pascal Pfister, Prof. Dr.
Benjamin Pippenger, Dr.
Felix Reinert, Dr.
Barbara Rothen-Rutishauser, Prof. Dr.
Jorge Sague, Dr.
Birgit Schäfer, PD Dr.
Matthias Schwenkglenks, Prof. Dr.
Jivko Stoyanov, PD Dr.
Peter Varga, Dr.
Jürgen Vogt, Dr.
Bruno Wägli
André Weber, Dr.
Tobias Wyss, Dr.
Andeas Zumbühl, Prof. Dr.

Statistics

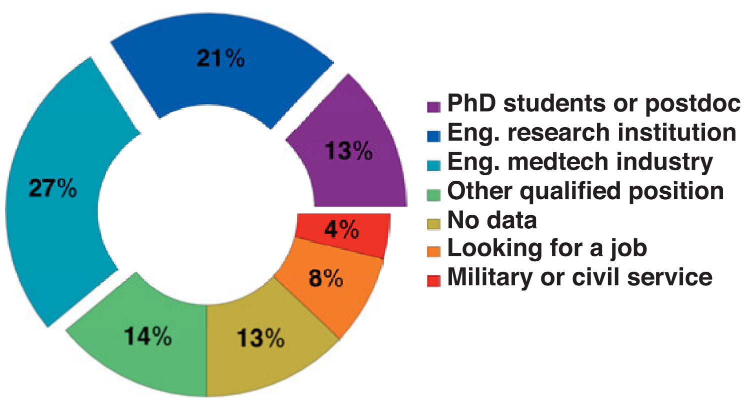
Number of New Students (above) and Graduates (below) per Year



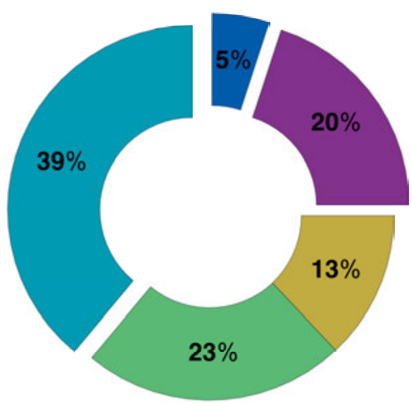


Profession after Graduation

Activity after 1 year



Activity after 5 years



Graduate Profile

Charlotte Voutat, BME Alumna 2018

Q: What was your academic and professional background prior to your BME studies?
A: After one preparation year for "future engineers" at the HEIG-VD in Yverdon, I got my bachelor's degree in mechanical engineering at the He-Arc, Neuchâtel. I did not have any engineering professional experience prior to this master's degeree, except for a few students' jobs.

Q: Why did you choose to pursue your master's studies in the master's program Biomedical Engineering?
A: I have always wanted to work in the medical field, to help people and have a positive impact on our society. During my bachelor's studies, I had the opportunity to work on a few projects related to this field and they reinforced this idea. One of my professors, who also taught in the biomedical engineering master's program, recommended it to me. The program was very suitable for my interests and skills.

Q: Did you continue to work during your studies?
A: No, I did not work during my master's studies. I wanted to dedicate all my time to my studies, to ensure the best possible results.

Q: What was your career plan after the completion of your degree?
A: I wanted to find a job in the medtech industry, if possible in the research and development field. I also thought that later, I would maybe build my own start-up company. For this, a first work experience was indispensable from my point of view.

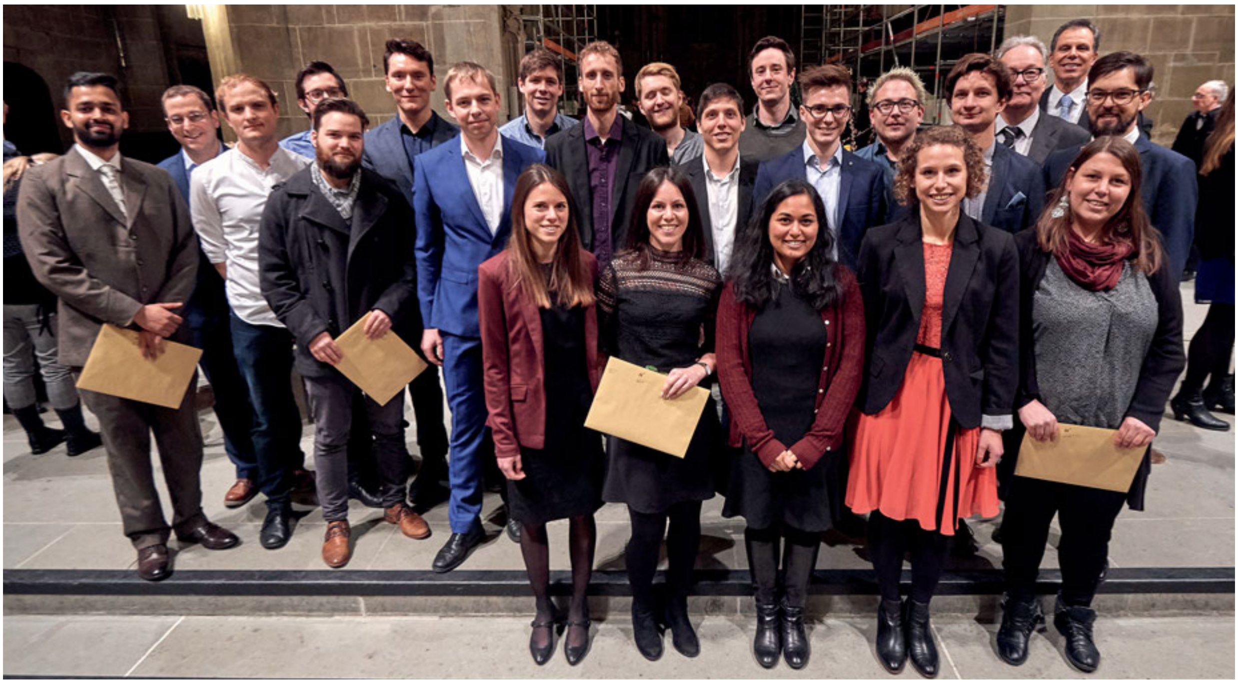
Q: What is the benefit of the master's studies with regard to your current professional activity?
A: I had the chance to find a job that perfectly fitted my expectations. I work in the R&D department of a company which manufactures knee and hip prostheses. I daily use a large part of the knowledge I gained during my master's studies. On the one hand, theory and knowledge are always helpful to find solutions and to develop products, and on the other hand, all the group projects helped me with communication and project management.

Charlotte Voutat receives her diploma from Philippe Zysset. (Photo: Adrian Moser)

Graduation Ceremony

Graduation ceremonies are usually thought of as special occasions – the culmination of years of hard work, a moment of celebration shared with classmates, friends and family. This year's ceremony was certainly all of that, but it was special in other ways too. To begin with, there was a bomb scare in the Heiliggeistkirche, just outside of the train station. So when we arrived in Bern, we found that the roads around there were closed and public transport rerouted, changing our excitement from happy to slightly nervous, as it was not altogether clear that we would make it to the ceremony in time. This was an unfounded fear, as the Bernese police have very efficient systems in place in case of such a disruption; we were on time.

The graduation venue was also special; instead of the festive grand hall of the Kultur Casino (closed for renovation) where the Medical Faculty of the University of Bern usually holds the ceremony, we were in the rather more solemn Berner Münster: beautiful, calm and busy-quiet. That last attribute was due to the prevailing moods of delight and excitement in the cathedral, as people greeted one another whilst looking for their seats. The central aisle was mainly reserved for soon-to-be graduates, starting with the medics, then the dentists, and eventually, the biomedical engineers – you have to put the engineers at the back, so they can properly support the first two groups – it is known. Behind us, and to either side, were those who supported and encouraged all of us graduates during our studies: our friends and loved ones, there to share our joy at our successful completion of this phase in our lives. Beautiful, if somewhat melancholic, orchestral music marked the start of the ceremony, and the one-time congregation settled into a still-excited-but-more-reflective mood as we waited for Prof. Dr. Hans-Uwe Simon, the dean of the Medical Faculty, to begin speaking. What he said must have been very inspirational, because my German-speaking classmates had shining, smiling eyes. This was followed by a more upbeat moment of orchestral music. The next speaker, Prof. em. Dr. Daniel H. Scheidegger, I understood, was a country doctor, as well as the president of the Swiss Academy of Medical Sciences. His speech sounded warm, and people's smiles spread throughout the audience, even to the non-German speakers. This was followed by the diploma-giving part of the ceremony, sending a wavelet of anxious anticipation through the assembled almost-graduates: how does it work? Do I follow the last person of the row in front? Wasn't there something we had to do with our name tags?… Luckily, we had a good half-hour of medics and dentists to observe before us, so when our turn to collect our handshake and diploma arrived, we were primed and ready.



Front row: Karin Tschan, Desirée Biedermann, Aarati Chacko, Marie Larraillet, Charlotte Voutat
Upper row from left to right: Sidartha Gupta, Yannick Suter, Mirco Gysin, Samuel Stucky, Michael Müller, Christian Fröhlicher, David Schmidlin, Jan Grossrieder, Rens Janssens, Klaus Schürch, Pierre-André Friedrich, Christopher Lenherr, Remo Odoni, Alian Reimann, Michael Indermaur, Iwan Paolucci

Our diplomas were presented to us by Prof. Dr. Philippe Zysset, our MSc Program Director, who was also the head of the Biomechanical Systems section that I was in. In a sense, he is an epitome of what the master's program meant to me; his courses were incredibly challenging, but also, incredibly rewarding, when at last I understood and could use what we learnt. It is with a sense of pride and gratitude that I received my diploma.
After a few more speeches, the ceremony ended, and we gathered for a last group picture. Then it was over; we headed out into a frozen, winter-wonderland-apéro prepared for us in front of the Münster (Bern was snow-covered that day, and cold). Already, graduate-guest aggregates where making their way into the future, the graduates no longer students, but equipped with the skills and knowledge that will serve them in the next stages of their careers.

Aarati Chacko, BME Alumna 2018

RMS Award

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.
The study direction 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.

RMS Award 2018
Iwan Paolucci receives the RMS Award 2018 from Dr. Beat Gasser, managing director of the RMS Foundation and Prof. Dr. Philippe Zysset, Program Director Master Program Biomedical Engineering.

Biomedical Engineering Day 2018

The industry, medical doctors, and engineers meet for the Biomedical Engineering Day at the Inselspital in Bern with great success.

On May 4, 2018, the Biomedical Engineering Day took place in the auditorium Ettore Rossi at the Inselspital in Bern. The Master in Biomedical Engineering program of the University of Bern organized this event for the ninth 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 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. This was made possible between the sessions in personal conversations and at the exhibitors' booths.

The BME Day offered great opportunities for the Bernese biomedical researchers, too. The ARTORG Center for Biomedical Engineering Research and the Institute for Surgical Technologies and Biomechanics as well as the Bern University of Applied Sciences, a partner within the Master's program, used the possibility of presenting current research projects to more than 250 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 they had the chance for intensive communication with the biomedical engineers.

One highlight of the day was the successful live surgery by Marco Caversaccio, Department of ENT, Head & Neck Surgery, University Hospital Bern (Inselspital). Illustrative explanations in the auditorium were given by Georgios Mantokoudis, from the same department.

The talk by Berhard Pulver, President of the Bernese government at the time, "Importance of the medical sector for the development of the canton of Bern" was another highlight of the event.

Students check out a new software. Photo: Adrian Moser

Participants in the auditorium. Photo: Adrian Moser

Research exhibition. Photo: Adrian Moser

Participants testing the 3D technology used in the OR.
Photo: Gianni Pauciello

Bernhard Pulver, Regierungspräsident, Kanton Bern
Photo: Adrian Moser

Awards

At the end of the day, seven awards for excellent academic achievements in the field of Biomedical Engineering at the University of Bern were presented:

1. Swiss Engineering Award for the best master's thesis (innovation):
   Samuel Stucky - Building online mosaics for low-cost intra-ocular imaging
2. Swiss Engineering Award for the best master's thesis (innovation):
   Gerhard Kuert - Next generation of cardiovascular catheters based on flex-print technology
3. Swiss Engineering Award for the best master's thesis (basic science):
   Emily Thompson - Development of an in silico and in vitro dynamic lung microvasculature model
4. SICAS Award for the best PhD thesis:
   Arne Feldmann - Thermal and drilling properties of bone
5. BME Club Award for the best poster:
   Can Gökgöl - The effects of nitinol stent oversizing in patients undergoing femoropopliteal artery revascularization: a finite element study
6. BME Club Award for the best master's thesis abstract:
   Christopher Lenherr - Indentation properties of metastatic vertebral bone
7. BME Club travel grant:
   Stephan Gerber - Virtual reality for activities of daily living training in neurorehabilitation: a usability and feasibility study in healthy participants (ECMB 2019, Hawaii)

Emily Thompson, Arne Feldmann, Samuel Stucky, Gerhard Kuert (all photos: Adrian Moser)

Can Cökgöl and Stephan Gerber

We thank our sponsors and exhibitors

Anton Paar · Biomedical Engineering Club · CAScination · csem · DePuy Synthes (Companies of Johnson & Johnson) · Haag-Streit Diagnostics · Nobel Biocare · nowak engineering · RMS (Testing · Research · Consulting, www.rms-foundation.ch) · sicas Swiss Institute for Computer Assisted Surgery · stryker · Swiss Engineering STV UTS ATS · Switzerland Innovation Park Biel/Bienne · ziemer Ophthalmology

The Biomedical Engineering Club

The BME Club and Its Mission

The BME Club is an alumni club with the mission to provide and promote networking among its interdisciplinary members. We are a constantly growing group of biomedical engineers, scientists, past and present students and medical technology corporates eager to bring together the principles of engineering, biology, and clinical medicine. The club accomplishes these goals by hosting events such as information sessions on the latest cutting edge research in different fields of biomedical engineering, attendance of international conferences and organizing visits of various industrial plants and laboratories. The BME Club is recognized as an official alumni association of the University of Bern under the umbrella organization – Alumni UniBE. A dedicated executive committee follows the principles of our constitution.

We are an enthusiastic and versatile group with diverse activities:

- bi-annual "Stammtisch" in a local restaurant as an amiable platform to exchange, discuss, brainstorm or simply chat
- visits to Swiss medical and engineering companies
- organization of the annual MEDICA trip
- information on career opportunities (incl. job offers)
- organization of the annual welcome event for new students of the BME Master program
- organization of an annual alumni gathering
- sponsorship of the poster and abstract awards at the annual BME day
- sponsorship of conference Travel Grants
- provide access to the Medical Cluster events
- automatic joint membership with Alumni UniBE
- offer joint membership with SSBE (Swiss Society for Biomedical Engineering)

In short, the BME club represents a unique platform for professional, lifelong communication and networking. For further details, look up our website at http://www.bmeclub.ch.

How to Join

Becoming a member is easy! Simply sign up at any BME Club event or visit us at http://www.bmeclub.ch. We are looking forward to seeing you

The BME Club Board in 2018


Prabitha Urwyler
President & PR


Andrea Nienhaus
Secretary & Treasurer


Tobias Imfeld
Webmaster


Fatih Toy
Alumni


Stephan Gerber
PhD Students


Tamara Melle
Master Students


The GP Bern as usually motivates more members year by year. The runners from May 2018 also pose amidst a gloomy day.


BME students test an innovative message table.
Photo: Pierre Cuony


Seniors and juniors exchange experienes at the alumni BBQ, August 2018.

The sudden downpour towards the end of the GP Bern didn't dampen our spirits.

Welcome day for the new students ends in the old city of Bern. Thanks to our dynamic student representative Tamara Melle!

BME Club goes Medica – Medtech wonderland

Around 30 people sitting together in a bar having a chat, some laughter here and there. This is the spirit of the BME Club; bring people together and create a network of dynamic, unique people who are interested in the Medtech industry. We are ready for the MEDICA 2018 in Düsseldorf! Our journey started late in the evening around midnight when our bus arrived at Bern to pick us up. While everybody was sleeping we had a great bus driver who drove us safely to our hostel in Düsseldorf. After a nice breakfast we drove into the city jungle of unknown public transport but we found our way to the place which I personally would call "Medtech wonderland".

Medica exhibition

In many halls visitors are able to see the latest inventions of the Medtech industry. Sometimes you could just watch but why not trying out from time to time some endoscopes, 3D vision glasses for surgery or enjoy a nice massage in a hydrojet massage pot? The representatives from different companies all around the world are highly interested to have a conversation with you explaining their new technology or application. Everything is possible at MEDICA!
Finally, back in the hostel you might feel tired but after a nice shower you feel refreshed and energetic again to join the delicious BBQ. The party people went out for a drink, others just had a nice chat till midnight. Having a look on your fitbit or step counter will tell you to just relax because around 20'000 steps for one day should have been enough. Sleep well and recover for the second day in Düsseldorf.
Visiting MEDICA again or walk around in the city and enjoy some sightseeing. You have all the opportunities you would like to have. In the famous brewery "Füchschen" delicious traditional German food is waiting in the evening for you. But take care the waiters never miss the chance to replace your empty glass of beer with a new one. ;)
With our filled stomachs we are now ready to ride home and you all now, you always sleep better after a nice dinner with a nice beer.
With a lot of new impressions, we arrive safely back home in Bern and everybody starts their way back home or some of the warriors are already talking about the next lecture of the day.

See you all next year and let's discover together the Medtech-World in Düsseldorf!
Tamara Melle, BME student

Düsseldorf by night

MASTER'S THESES

2018

Signal Processing on 2- and 3 Dimensional EECG Data Sets From Clinical Trial

Hector Alvarez

Supervisors: Dr. med. Reto Wildhaber, Dr. Med Romy Sweda
Institutions: Bern University of Applied Sciences, Institute for Human Centered Engineering
University of Bern, University Hospital Bern (Inselspital)
Examiners: Prof. Dr. Marcel Jacomet, Prof Dr. Josef Goette

Introduction

Cardiac disorders represent high threats that are associated with fatal consequences. Its early detection is crucial before aggravation of the conditions. Current biomedical signal processing techniques have been proven to be inefficient for evaluation, and prediction of atrial disorders due to the low resolution provided by the clinical standard twelve lead. Additionally, heart beat detection algorithms are based only on the information of the QRS complex information. Invasive recordings from the atria, provide good resolution but involve a minor surgery. Esophageal ECG recorder is a semi-invasive device that provides ECG records with good atrial and ventricular activity resolution. The aim of this project was to develop a computational model to detect, and classify atrial, and ventricular contractions using EECG records from clinical trial.

Materials and Methods

The computational model is subdivided into function-oriented processes. Statistical analysis of the power spectrum and the standard deviation were implemented to suppress non-active and high energy segments to minimize sensitivity to artifacts. Two bandpass filters comprised of sinusoid filters were used to extract frequencies describing the atrial and ventricular contractile activity. A variation of Pan-Tompkins QRS detection was used to detect contractile periods. The signal was converted in a low frequency sinusoid representing the cardiac rhythm to extract parameters and perform unsupervised clustering with K-means. Finally, the clusters were labeled.

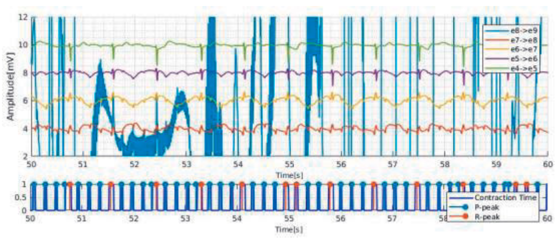


Fig. 1 P-R detection-classification algorithm results for an atrial flutter with strong artifact interference in the time interval 50-80s using five EECG channels. Contractions correctly filtered, detected, clustered, and classified

Results

Pan-Tompkins et al. QRS algorithm has an accuracy and sensitivity of about 99%, but there is no algorithm capable of detecting both the QRS complex, and the P-wave in the ECG. The results after first tests indicate a sensitivity and accuracy of about 99% for detecting atrial and ventricular contraction for a subject with a normal heart beat (HB). The algorithm identified atrial flutter; however, labeling P and R was inversed. Premature ventricular contractions are detected but wrong clustered.

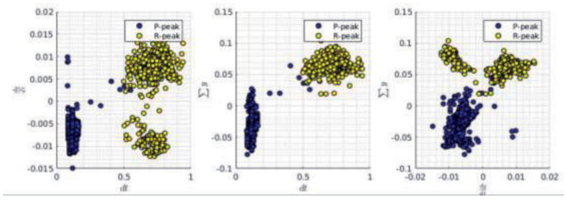


Fig. 2 P-R detection-classification results for a normal heart beat using a data set from five EECG channels evaluated in a period of 0-500s.

Discussion

Considering this is the first version of the algorithm, the results are outstanding. The algorithm has shown its efficiency for artifact suppression, and its accuracy for P-R detection, which are the main weaknesses in current ECG analysis. There are opportunity areas in the segmentation and labeling processes, but its performance is optimal due to complexity of the biomedical signal analysis.

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Acknowledgements

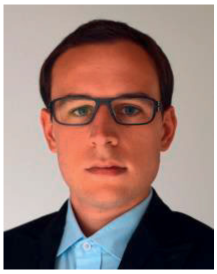
The author would like to thank HuCE-microLab.

Bern University of Applied Sciences

Master's Thesis in Biomedical Engineering

UNIVERSITÄT BERN

Design of an Electrospray Device for Targeted Drug and Gene Delivery



Bruno Bahnmüller

Supervisors: Dr. med. Amiq Gazdhar, Prof. Dr. David Hradetzky
Institutions: University Hospital Bern (Inselspital), Department of Pulmonary Medicine
University of Applied Sciences and Arts Northwestern Switzerland, Institute for Medical Engineering and Medical Informatics
Examiners: Prof. Dr. Dominik Obrist, Dr. med. Amiq Gazdhar

Introduction
Targeted drug delivery is important to improve the effect of the drug and reduce the side effects. Also important is the safe and controlled gene delivery. There are viral or non-viral approaches. Viral is effective but potentially dangerous and non-viral approaches are not efficient. For the drug as well as for the gene a specific volume has to be addressed. Electrospray method is feasible to deliver the drug or gene locally and specifically in a defined volume. An electric field produced by high voltage accelerates fluid droplets which penetrate the tissue. On one hand a new device which can be potentially used in medical environment, for oral applications was designed and on the other hand the effectiveness as well as the penetration depth evaluated.

Materials and Methods
For the design a standard development approach was applied. First the user needs were evaluated, including an insight into an operation where the electrospray potentially could be used in future. Before the design of the device could be tackled, the requirement specifications were derived. At the end, a risk analysis was carried out and proved that the designed device meets the essential requirements according MDR as far as possible.
For the effectiveness-tests an in vitro experiment was done. Squamous cell carcinoma cells (EBS-2) were grown in in wells. Cells were grown in collagen coated 24 well plates, when cells reaches confluence electrospraying was performed. A fluid with Cisplatin was sprayed on the cells with a large working chamber, 3 kV, a flow rate of 20 µl/min the amount in each well was 3x25 µl. After 24 hours incubation the cells were analyzed by flow cytometry “BD bioscience LSR II”. The goal was to reduce the healthy cells since they stand for tumor cells.
To measure the penetration depth of the electrospray, ex vivo experiments on tissue explants were performed. Therefore mice subcutaneous tumors were used. On the tumors water resistant visible ink was sprayed with a large working chamber, 3 kV, 20 µl/min, and 4x25 µl to increase the visibility. After a drying period of 5 minutes the tissue was cut and analyzed by eye.

Fig. 1: Electrospray device with the large working chamber

Results
The design of the electrospray is small and lightweight, see fig. 1. It addresses the user needs, and risk assessment showed what still has to be done to meet the rest of the MDR.
The use of an electrospray leads to a reduced number of healthy cells, see fig 2.

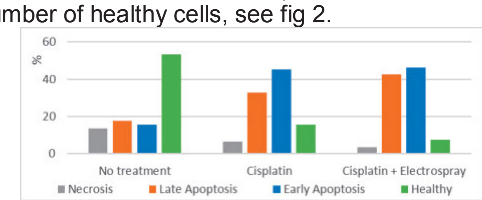


Fig. 2: Results of the in vitro tests with the EBS-2 cells

Electrospraying on a hard tumor leads to a penetration depth of 3-4 mm and even deeper on soft tumors. No penetration was observed if just delivered without electric electrospray, see fig. 3.

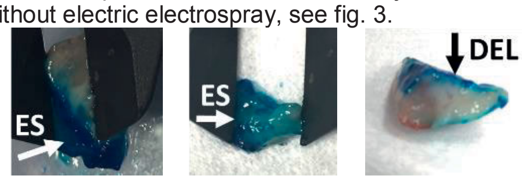


Fig. 3 left: Result of electrospray on hard tumors in ES direction, the caliper is on 3.6 mm. Middle: Full penetration of soft tumor with a depth of an 5.7 mm. Right: Only ink at the surface where the delivery (Del) took place.

Discussion
The device works well in research environment, but for the clinical use some improvements must be done. On one hand to improve handling. Mainly to facilitate the loading of the drug. On the other hand, to reduce the risk of short circuits due to undesired fluid.
In “in vivo” tests the performance of electrospray shows that it leads to an increased effect of the Cisplatin.
The penetration depth shows, efficiency of the electrospray device.

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Acknowledgements

Many thanks to PD Dr. Roland Giger, University Hospital Bern (Inselspital) for the support to capture the user needs as well as to Georg Hasler, FHNW for the manufacturing of the parts of the electrospray.

Optical Coherence Tomography Controlled Selective Retina Therapy for In-vivo Treatment

Christian Burri

Supervisors: Prof. Christoph Meier, MSc Daniel Kaufmann
Institution: Bern University of Applied Sciences, Institute for Human Centered Engineering
Examiners: Prof. Christoph Meier, Dr. Boris Považay

Introduction

Conventional laser photocoagulation (LPC) is a widely used treatment method for retinal diseases that unfortunately leads to collateral damage of all retinal layers including healthy, non-regenerative photoreceptors. An alternative approach is selective retina therapy (SRT), in which finely dosed laser pulses in the sub-microsecond range cause selective cell death limited to the retinal pigment epithelium (RPE) [1].
However, the complexity of radiant exposure control in variable absorbing tissue prevented wider uptake of the technology. Recent literature shows that optical coherence tomography (OCT) can provide reliable dosimetry control in parallel with SRT because RPE lesions can be predicted indirectly as a change of OCT signal strength in M-scans [2]. This master's thesis investigated OCT-controlled SRT in ex-vivo porcine test series and built the base for an upcoming human in vivo study.

Materials and Methods

For the experiments the Spectralis Centaurus system (Fig. 1) was built, adapted and tested for controlled treatment of excised porcine eyes. This device provides OCT in parallel to SRT and uses a laser that was built for the thesis according to parameters that are mostly chosen in recent SRT studies.

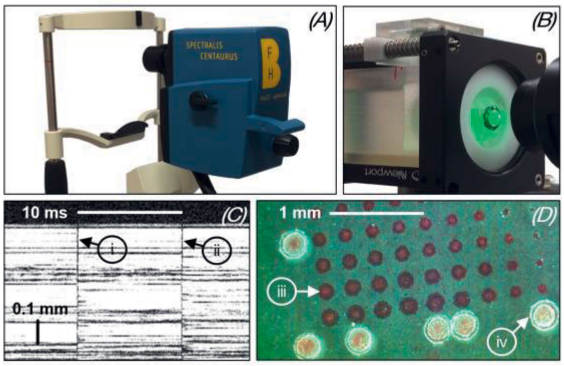

Fig. 1 (A) HuCE-optoLab Spectralis Centaurus system. (B) artificial eye used for porcine RPE explant measurements. (C) presents a M-scan with two so called signal washouts showing a change of OCT signal strength (i,ii). (D) RPE sample evaluated under a fluoerescence microscope with typical SRT (iii) and LPC marker lesion (iv).

To verify the laser's capability for SRT, experiments with different laser pulse durations in the microsecond range were carried out. Therefore, entire porcine eyes or porcine RPE explants were treated. Evaluation of the samples took place by using a live/dead staining kit (EthD-1, Calcein AM) and visualization by a fluorescence microscope and histological sections (Fig. 2) with hematoxylin and eosin (H&E) staining. Furthermore, the clinical potential of the system's OCT M-scans dosimetry was evaluated at the Medical Laser Center Lübeck.

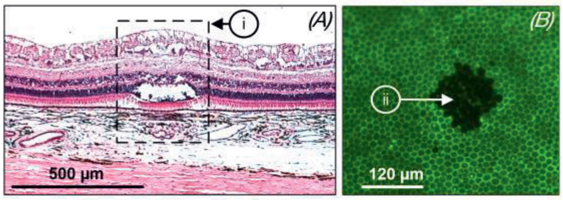

Fig. 2 (A) histological sections with H&E stain of porcine retina at a LPC marker lesion (i). (B) RPE sample with rectangular SRT lesion (ii) evaluated under a fluoerescence microscope.

Results

Histological sections with H&E stain showed LPC marker lesions but SRT lesions were not found. For the applied treatment parameters, changes of OCT signal strength in M-scans were observed when the Spectralis Centaurus system and the laser were able to create SRT lesions in porcine RPE. Recent efforts, in negotiation with the University Hospital Bern (Inselspital) pointed out that an in-vivo patient study could be requested in January 2019.

Discussion

The novel Spectralis Centaurus system and the laser fulfill the requirements for OCT-controlled SRT. However, the sensitivity of the signal washout detection in OCT M-scans has to be improved.
Furthermore, additional ex-vivo porcine eye measurements with histological evaluation are needed to prove that healthy photoreceptors are not destroyed during SRT. Regarding the experiments with different laser pulse durations, the results obtained correspond to the findings of similar studies. In general, OCT as real-time dosimetry has the potential to establish SRT as standard therapy for RPE-related retinal pathologies.

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Definition of Personalized Load Cases for the Human Distal Radius

Alberto Cerutti

Supervisors: Prof. Dr. Philippe Zysset, MSc Denis Schenk, Dr. Patrik Christen
Institutions: University of Bern, Institute for Surgical Technology and Biomechanics
ETH Zurich, Institute for Biomechanics
Examiners: Prof. Dr. Philippe Zysset, Dr. Patrik Christen

Introduction

Among all the osteoporotic fractures, the one involving the distal part of the radius occurs early in life. The advent of high-resolution peripheral quantitative computed tomography (HR-pQCT) allows the detailed evaluation of bone's cortices and trabecular microarchitecture at peripheral skeletal sites. Patient-specific bone stiffness and strength can be estimated by micro- or homogenized finite element (uFE or hFE) analysis for a standardized, axial compression load case. This study aims at exploring an alternative, personalized load case for homogenized FE that minimizes the heterogeneity of bone tissue strains in the spirit of a bone adaptation paradigm.

Materials and Methods

A set of 21 double sections (20 mm) human distal radii were converted in hFE models. Three displacements and three rotations were applied to the rigidly coupled upper surface, whereas, the lower surface was fixed in all degrees of freedom (Fig. 1). An optimization equation provided a linear combination of scaling factors for the individual load cases that minimized the deviation of the strain tensor with respect to a homogenized reference compressive strain. To reduce the effect of the kinematically coupled boundary conditions, one or multiple element layers on each face were excluded from the optimization domain. The influence of voxel size (1 and 2 mm) and remaining region of interest (0 to 4 layers removed) on the optimal scaling factors was investigated .

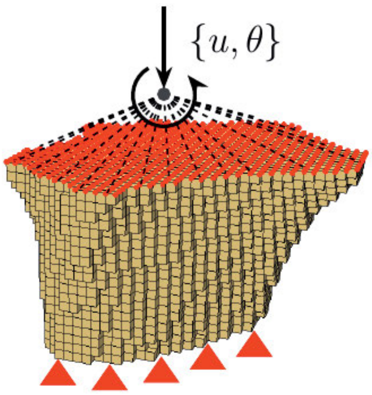

Fig. 1) Radius hFE model with a schematic representation of the boundary conditions and the load application.

Results

The six hFE simulations combined with the optimization equations delivered a unique set of 6 scaling factors linked to a load case (ux, uy, uz, θx, θy, θz). In 100% of the cases, the dominating scaling factor refered to a displacement in the z-direction. The means of the normalized scaling factors for the 21 models were: α_1=0.0165, α_2=0.0372, α_3=0.967, α_4=0.0088, α_5=-0.0001 and α_6=-0.0020.The influence of the regions of interest on the scaling factors is shown in Fig 2 for 1 mm voxel hFE models.

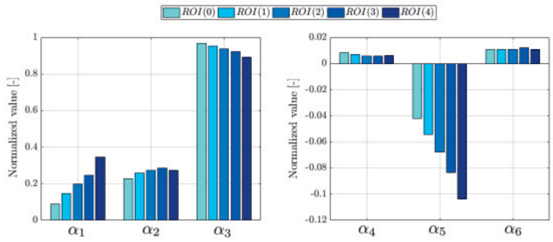

Fig. 2) Bar plots representing the normalized scaling factors, for different regions of interest (ROI), obtained in a particular radius section.

Discussion

A methodology for the calculation of a patient-specific load case based on a combination of 6 hFE simulations and the resolution of an optimality condition was implemented. The results provided the set of displacements and rotations that minimized the strain heterogeneity within a region of interest. The solution is expected to maximize the strain energy density and especially the strength of the bone structure for that set of boundary conditions. It remains to be shown that for a given region of interest, the solution converges as the number of layers to the rigid faces increases.

This personalized loading approach may well deliver a more reproducible and meaningful evaluation of radial strength for clinical applications.

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Acknowledgements

The author sincerely thanks all persons involved in the realization of this research.

Frictional Behaviour of Polycarbonate-Urethane to Cartilage – an Experimental Study

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Introduction

Approximately 5% of the human population and 80 % of people above 65 years suffer from osteoarthritis (OA) [2]. Nowadays total shoulder replacements are performed to treat severe cases of OA. Although the glenoid is not affected by OA in 30 to 40% of cases, the glenoid is often replaced because humeral head prostheses are known for wearing off cartilage relatively fast. Wear testing experiments showed good sliding properties for polycarbonate-urethane (PCU) against cartilage and indicate that PCU might be a promising coating for hemiprostheses [1]. The aim of this thesis is to develop a pin-on-disc test apparatus and test the usability of PCU as a coating for hemiprostheses.

Materials and Methods

Cartilage pins were extracted from bovine knees and were tested against 3 different biomaterials: zirconia toughed alumina (ZTA), cobalt chrome alloy (CoCr ISO 5832-12) and PCU. Tests were conducted with above-physiological loads (test 1: pressure 2.5 MPa) to see differences in wear and surface structure, as well as with physiological loads (test 2: pressure 0.63 MPa) to see the reaction of the living tissue. For test 2, only ZTA and PCU were tested. For the tests, a pin-on-disc test apparatus was developed, which allows the testing with different materials, variable loads, variable sliding velocities, and different two-dimensional test paths. The surface morphology of the articular cartilage was analysed under the microscope after testing. Further the loss of cartilage height was measured (test 1). Safranin-o (SAF-O) and lactate dehydrogenase (LDH) staining were performed to show the viability of the chondrocytes after the tests (test 2).

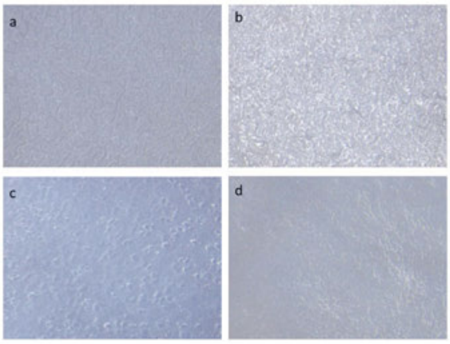

Fig. 1 Surface morphology after above-physiological testing with a) PCU, b) ZTA, c) CoCr and surface structure of the d) control group

Results

Microscopic images showed striking differences in cartilage surface morphology after testing (test 1) against the different biomaterials (Fig. 1).
Cartilage tested against ZTA showed a significantly greater decrease in height compared to the PCU group (Fig. 2). There was no significant difference in decreased height between the samples tested with CoCr and PCU.
The SAF-O staining showed increased fibrillation on the articulating surface in both tested groups compared to the control group. The LDH staining showed a very high viability in all tested samples and the control group.

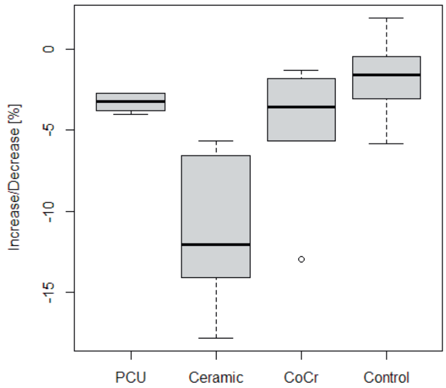

Fig. 2 Boxplot of decrease in cartilage height after testing with above-physiological loading (n=6 for each group).

Discussion

Although there was a significant reduction in loss of cartilage height compared to ZTA, the histological assessment did not find significant differences between treatments. Thus it remains uncertain whether PCU would be a better choice for hemiprostheses coating than CoCr and ZTA.
To validate the results, further tests (test 2) with longer test time and greater sample number needs to be performed.

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Detection and Removal of Pacing Artifacts in Multi-Channel Esophageal ECG Signals

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Introduction

Cardiovascular diseases (CVDs) lead the overall global mortality statistics. Cardiac arrhythmias are a major group of CVDs; mostly diagnosed by standard 12-lead surface electrocardiogram recordings. Esophageal electrocardiograms (EECGs) provide in comparison to standard ECGs a higher atrial sensitivity due to operation in close proximity to the atrias and have better long-term properties as a result of insertion in the moist and collapsed esophagus. The clinical trial esoECG-3D has been conducted by the Institute for Human Centered Engineering in Biel (HuCe) in co-operation with the Department of Cardiology, Bern University Hospital. The trial includes patients, who suffer from arrhythmias and aims to improve arrhythmia diagnostics using an advanced electrical mapping system based on esoECG-3D, a novel esophageal catheter. During the clinical trial, the hearts of the patients are paced in a controlled manner.
The aim of this thesis was to develop an offline algorithm to identify and remove applied pacing artifacts in a multi-channel EECG obtained by the esoECG-3D catheter, while introducing only minimal filter artifacts.

Materials and Methods

An algorithm working in the time domain has been designed using linear state space models. To discriminate between baseline artifacts and pacing artifacts. Sophisticated decision layers have been added, which take advantage of pacing artifacts periodic and multi-channel appearance.

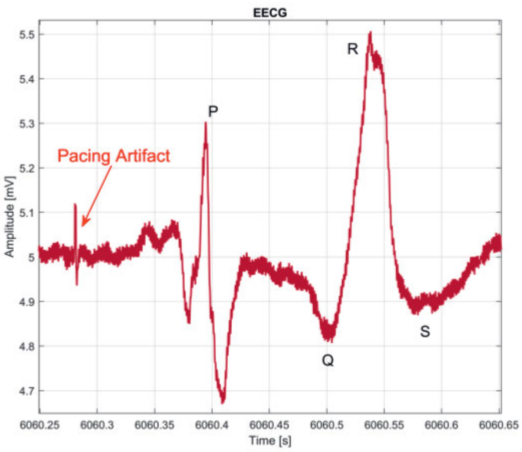

Fig. 1 EECG recorded during clinical trial, performed at Department of Cardiology, Bern University Hospital. Pacing artifact, Atrial signal (P), Ventricular signal (QRS).

Results

Our algorithm was applied to multiple sets of patient data. Best results were achieved by an exponentially decaying pulse model. The consecutive decision layers discriminate successfully pacing artifacts from other baseline artifacts. The removal of identified pacing artifacts is finally accomplished either by interpolation using a local baseline estimation or by subtracting the parameterized pulse model. While first method is more robust, second preserves the baseline noise.

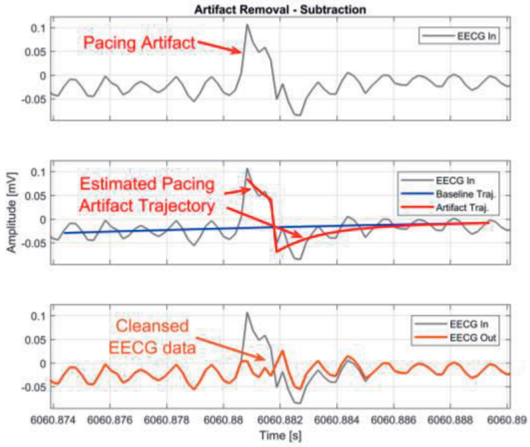

Fig. 2 Pacing artifact removal by subtracting parameterized pulse model from EECG.

Discussion

Provided that the pulse width of applied pacing artifacts is known, the algorithm shows excellent detection rates and is tolerant to interferences such as random noise or baseline artifacts. Automatic detection of pacing artifacts pulse widths would be desirable.

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Acknowledgements

I would like to express my deep gratitude to my first supervisor Dr. Reto Wildhaber, for his immense support, patient guidance and constructive suggestions during this thesis. All members of the HuCE microLab, Biel are thankfully acknowledged.

Bern University of Applied Sciences

Master's Thesis in Biomedical Engineering

UNIVERSITÄT BERN

Mimicking and Investigation of the In-Vivo Stiffness of the Lung Alveolar Milieu

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Examiners: Prof. Dr. Olivier Guenat, Dr. Janick Stucki

Introduction

Cells of the human body sense their environment and its mechanical properties, such as the stiffness. To investigate this, polyacrylamide hydrogels with varying stiffness were created and seeded with normal human lung fibroblasts, A549 cells (holoclone type 1.5) and primary human alveolar epithelial cells. Further, a pour-on method was established to incorporate the polyacrylamide hydrogel into a microfluidic Lung-on-Chip model.

Materials and Methods

To create the polyacrylamide gel, 40 % Acrylamide solution and 2 % N,N'-Methylene-bis-Acrylamide solution were mixed at different ratios in phosphate buffered saline solution and degassed. Then ammonium persulfate as a thermoinitiator and N,N,N',N'-tetramethylethylene-diamine as a cross-linking accelerator were added. The linking of the hydrogel onto polydimethylsiloxane was done with benzophenone and UV-initiation. Coating of the polyacrylamide with extracellular matrix proteins, namely collagen I and fribronectin, was achieved with the cross-linker sulfosuccinimidyl-6-(4-ayido-2-nitrophenylamino)-hexanoate in 1 M HEPES buffer and UV-initiation. After cell seeding, immunostaining was conducted.

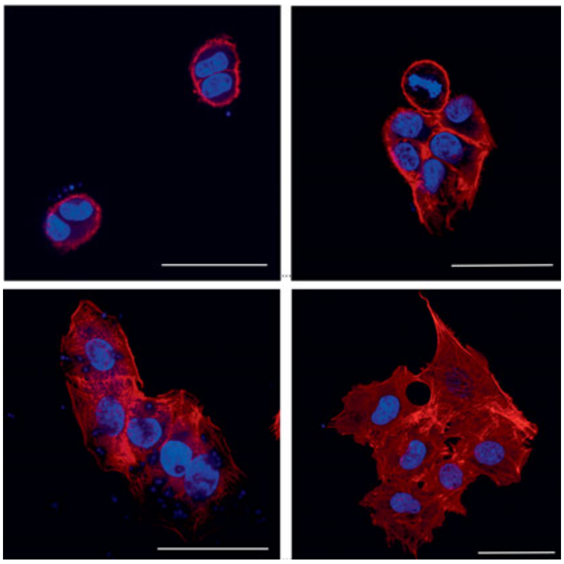

Fig. 1 Morphological comparison of A549 cells, seeded on substrates of different stiffness. Top row: ~1 kPa and ~10 kPa polyacrylamide hydrogels, bottom row: ~35 kPa polyacrylamide hydrogel and ~1 MPa polydimethylsiloxan. Blue = Hoechst staining, Red = phalloidin staining.

Results

Morphological evaluation of the A549 resulted in a description of rounder, smaller cells in smaller colonies on softer hydrogels in contrast to flattened, larger cells in bigger colonies on stiffer hydrogels. Comparing the cell area of the nuclei and bodies of the A549 cells of 1200 cells per polyacrylamide gel stiffness, a statistically significant (one-way ANOVA, Tukey's post hoc test) increase in spreading could be shown.

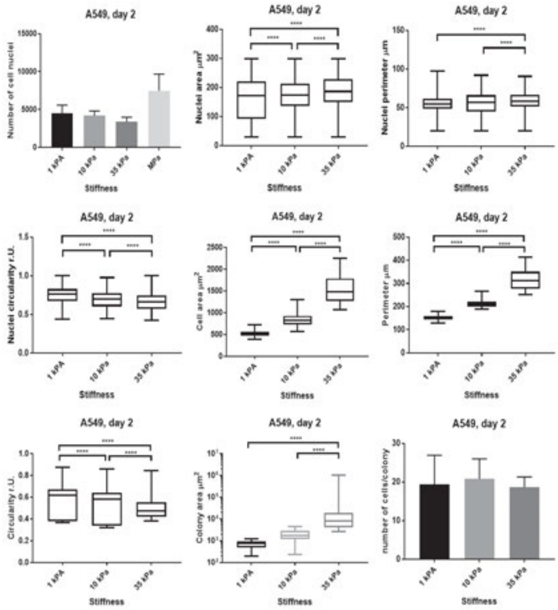

Fig. 2 Quantitative measurements of A549 cell shape and seeded on polyacrylamide hydrogels of varying stiffness, increase of cell nuclei and body area and perimeter on stiffer polyacrylamide hydrogels is statistically significant.

Discussion

The novel pour-on method that was established could not only be successfully included into the Lung-on-Chip through a top-down approach, but regarding the results from the A549 cell experiment, it was also shown that this method yields working polyacrylamid hydrogels for cell culture.

References

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Predicting Glaucoma Progression via Long Short-Term Memory Networks

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Examiners: Prof. Dr. Raphael Sznitman, Dr. Carlos Ciller

Introduction

Glaucoma is the leading cause of blindness after cataracts, affecting more than 61 million people worldwide. Early detection of glaucoma is crucial in order to choose a proper treatment for the patient and therefore, prevent irrevocable defects. The goal of this work is to study the progression of glaucoma and predict the disease condition at a future point in time.

Materials and Methods

We use visual field data collected from automated static perimetry since it provides quantitative measurements of the visual function represented as a two-dimensional map (see *Fig. 1*). This technique has become by far the most important tool used for both glaucoma diagnosis and follow-up. Concretely, we work with sequences showing glaucoma progression through 1 up to 3.5 years.

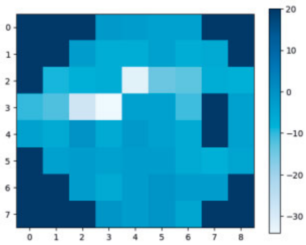

Fig. 1 Visual field image representation.

Current state-of-the-art methods for predicting glaucoma progression rely on clinical judgement and conventional statistical models. However, such approaches have limited prediction capability given the complexity of visual field structures and the disability to capture non-linearities of the data. Accordingly, we propose a method that uses deep learning schemes based on Long Short-Term Memory (LSTM) networks. We explore different architectures to capture the temporal and spatio-temporal information of the disease progression. In order to evaluate the accuracy of the predicted estimation, we compared it to the corresponding ground truth by means of mean absolute error. On the other hand, we create a baseline so as to assess the performance of the model itself. The baseline consists of weighting each of the input frames in the sequence, by giving more emphasis to the recent ones.

Results

The results show that the obtained error values are within the acceptable dB range, which implies a potential use of the method in the clinics. Regarding the model architecture, we found that those models involving the spatio-temporal features of the progression worked better than the ones only considering the temporal information.

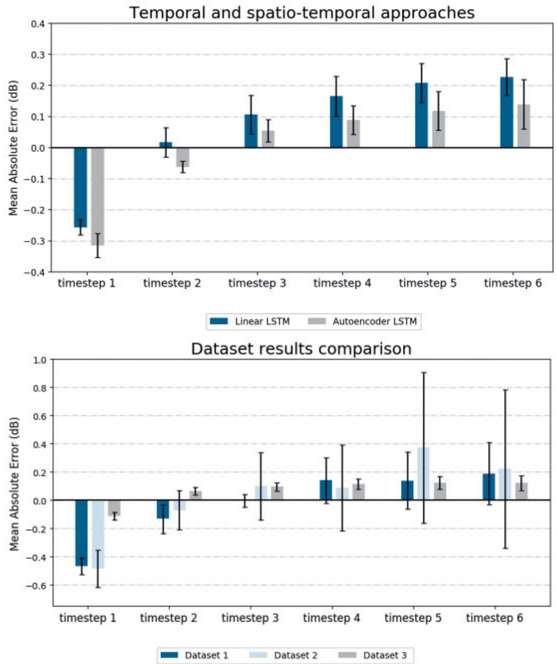

Fig 2. On the top, results were given for the comparison of the temporal and spatio-temporal architectures. On the bottom, results were given for the comparison of different datasets. Time steps refers to the number of preceding visual fields from patient history. The prediction error is compared to the baseline such that negative bars implies the proposed model is better compared to the baseline.

Discussion

Taking into account all the experiments carried out we can demonstrate our model outperforms the baseline when considering only few measurements. Nonetheless, the performance gets poorer when more measurements from patient history were considered.

Acknowledgements

The author thanks to Prof. Dr. Raphael Sznitman and all the OTL team for their support, and specially to Serife.

Master's Thesis in Biomedical Engineering

Tricking the Human Brain: Does Human Visual Self-Perception Bias Motor Planning?

Luca Ferriroli

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Examiners: Prof. Dr. Laura Marchal-Crespo, MSc Joaquín Á. Peñalver-Andrés

Introduction

Researchers investigating human multi-sensory integration have shown that perception of the material qualities of human self-bodies can be artificially distorted. For example, in the Marble Hand Illusion (MHI) paradigm, the neural perception of the hand's material information is updated through congruent audio-tactile feedback (Senna et al., 2014). In this cited study, the hand of the participants was gently hit with a hammer, while the sound of this tool hitting a marble surface was reproduced. This intervention induced the feeling of having a heavier and stiffer hand. Within this project, we aim to revisit the Marble Hand Illusion. We hypothesized that multimodal (i.e. audio-visuo-tactile) stimuli induce a stronger illusion than simpler stimulation paradigms (e.g. only visuo-tactile). We believe that the MHI might cause a behavioral change, reflected on a change in movement parameters (e.g. hand's speed and reaching height).

Materials and Methods

Thirty-six participants (mean age = 25.72, SD = 3.89) took part in the experiment. The study had two experimental conditions: Audio-Visual Feedback (AVF) and Visual Feedback (VF); and one control condition (No Feedback, NF). All participants were immersed in a virtual reality environment, using a head mounted display, and controlled a virtual avatar. During both interventions, congruent visuo-tactile stimulation was provided (i.e. subjects saw and felt a hammer slightly hitting their right arm). In both the experimental conditions the virtual arm's skin transmuted from skin to stone, during the intervention; while in the control condition the skin appearance remained human. In AVF the tactile feedback was synchronized with the sound of a hammer hitting a stone. Participants performed an arm lifting task and answered questions about the sensations of the arm pre/post stimulation. The scale of questionnaires ranged from - 3 to 3. Movement features and questionnaire's scores were analyzed. Mann-Whitney U tests results are reported.

Results

Participants rated their arm as been significantly colder, after the stimulation, in AVF ($z = -2.11$, $p = 0.034$) and VF ($z = -2.28$, $p = 0.022$) compared to NF (fig 1.a). Furthermore, participants in AVF felt their arm heavier compared to NF, although the difference did not reach significance ($z = 1.59$, $p = 0.109$). The kinematic measures revealed that subjects in the

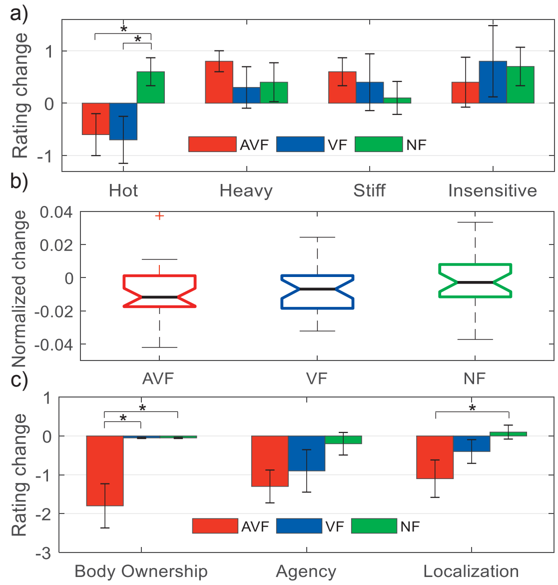

Fig. 1 All graphs relate to the difference before and after the stimulation. Whiskers represent standard error. a) Rating change in the arm questionnaire. b) Normalized relative change in maximum height of the hand during the lifting task. c) Change in embodiment scores after intervention.

AVF group reduced the lifting height after the intervention compared to the control group, although the difference did not reach significance ($z = -1.75$, $p = 0.079$). During baseline, embodiment was high for all conditions. The intervention also affected the body ownership, being significantly smaller in AVF than VF ($z = -3.01$, $p = 0.0027$) and NF ($z = -2.85$, $p = 0.0044$; fig. 1c).

Discussion

This study partially confirmed the MHI study results. Visual feedback strengthened the effect of perceived coldness and stiffness of the arm. We also found a non-significant effect of the illusion on the kinematic measures. These findings support the possibility of inducing behavioral changes in subjects training immersed in a virtual environment. The induced illusion investigated in this study could be potentially employed to promote successful goal-directed movements targeted during a session of motor neuro-rehabilitation.

References

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Bern University of Applied Sciences

Master's Thesis in Biomedical Engineering

UNIVERSITÄT BERN

A Novel Lead- and Batteryless Pacemaker driven by an Endocardial Mass-Imbalance Oscillation Generator

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Examiners: Dr. med. Andreas Häberlin, Dr. Adrian Zurbuchen

Introduction

Conduction diseases impair the ability of the cardiac conduction to correctly regulate the ace heart rate. Thus, pacemakers are implanted to improve patient's life expectancy. Two main disadvantages motivate ongoing research in the field of cardiac pacemakers. First, depletion of the energy source implies pacemaker replacements, increasing the risk of complications. Second, traditional pacemakers suffer from a risk of complications directly related to the leads transmitting the stimuli to the myocardium. The global goal of this project is to develop a lead- and batteryless pacemaker driven by an endocardial mass-imbalance oscillation Generator MIOG, i.e. driven by the movement of the heart, implanted in the right ventricle.

Materials and Methods

The harvester retrieves energy from the movement of the heart. Unlike conventional batteries, the voltage amplitude harvested is very small and oscillating between positive and negative potentials (fig. 1). Therefore, it must be rectified and boosted to be used to power the pacing circuit.

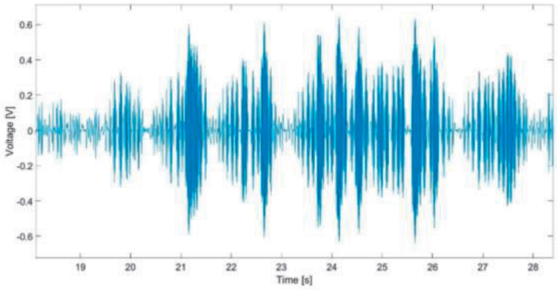

Fig. 1 Sample of the measured output of the MIOG.

An electrical device composed of two stages has been developed. The first stage rectifies the signal, whereas the second stage boost the voltage to supply the pacing circuit. Based on the analysis performed on the MIOG signal and on the electrical characteristics of the pacing circuit, the main criteria were to reach a total power efficiency conversion of 41% and an output voltage supply of 1.8V.

Results

The concept of a full wave rectifier able to extract energy from the MIOG signal as low as 100mV and was successfully simulated and tested. However, the power harvested was not enough to supply a pacing circuit (fig. 2+3.), due to an hardware issue that impaired the rectification of the negative part of the MIOG output voltage.

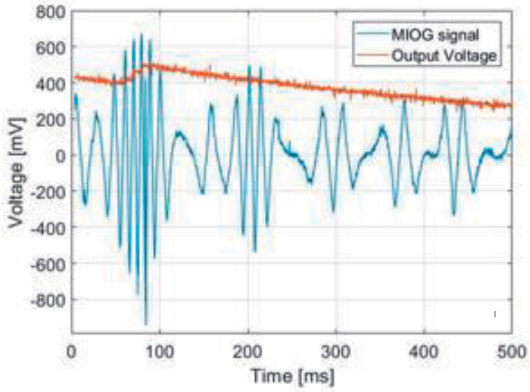

Fig. 2 MIOG signal rectified by the prototype developed in thin

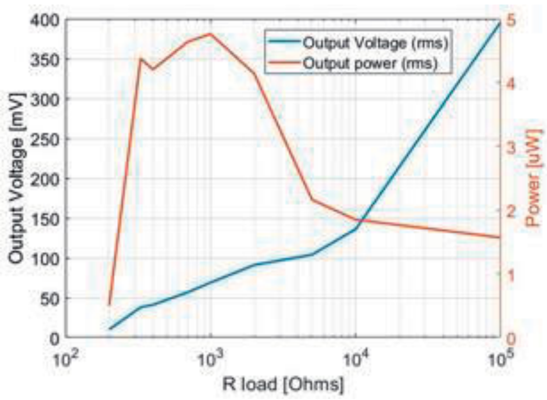

Fig. 3. Output power and voltage potentials for different loads

Discussion

Based on the simulations performed, we believe that the new concept developed in this thesis would be able to supply a pacing circuit.
The results obtained in this project are preliminary but promising, supporting the possibility to develop a new generation of pacemaker, solving the problem of battery exhaustion and lead complications.

References

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Visual Surveying for Automated Needle Injection System

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Examiners: Prof. Dr. Raphael Sznitman, MSc Lino Schüpbach

Introduction

In the course of development of fully automatic robotic systems within the medical field, patient safety and efficacy of treatment are crucial factors for successful implementation, deployment and marketing of said systems. Recent advances in the fields of computer vision and machine learning made vision-based guidance and surveillance a valuable option for control and safety in robotic systems. This work presents four different approaches to real-time vision-based 3D needle tracking as a safety control framework for a fully automatic intraocular injection system.

Figure 1: Conceptual design for a fully automatic intraocular injection system. (Figure taken from ophtorobotics.com)

Materials and Methods

For our tracking algorithms, we use a stereoscopic camera system in combination with convolutional neural networks (CNN) and 3D reconstruction techniques to obtain 3D position information about the surgical needle solely from raw image data. We examine four different processing pipelines (full scale and two-stage detectors) and evaluate the tracking accuracy first in 2D against our annotated ground truth and then also in 3D against a ground truth from a modified Phantom Omni haptic device. Furthermore we conduct a study on the impact of the geometric relation between the tool and the camera system on the tracking accuracy. Our tracking algorithms were trained on a custom dataset that was acquired and annotated exclusively for this work.

Figure 2: The Ensenso N10 infrared stereo camera system used throughout the course of this work. (Figure taken from ensenso.com)

Results

Our results show that real-time 3D tool tracking is feasible with the setup used for this work and accurate within the error ranges in both our 2D and 3D ground truths. Our most accurate tracking algorithm achieves an average deviation of 2.42 pixels from the annotation ground truth. Our fastest pipeline processes the input stream at an inference rate of 54 FPS. Furthermore we show in our study that the tracking accuracy is dependent on the angle of the tool axis with respect to the optical axis of the stereo camera system.

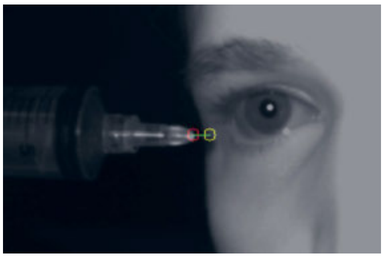

Figure 3: Example output image of our tracking pipelines. We track the tip of the plastic hub piece (red) and the tip of the cannula (yellow). The cannula is visualized in green.

Discussion

In this work we have shown that given our camera system, it is possible to develop and implement a tool tracking system for surgical needles that works in real-time. We demonstrated that our two-stage detectors provide a dramatic increase in processing speed compared to their full scale counterparts. We have also shown that with our current setup, we are limited to a certain range of tool angles with respect to the optical axis of the camera system, in order to have the best performance of our detectors.

Acknowledgements

This project was supported by OphtoRobotics, a Swiss company with the aim of developing robotic intraocular injection systems. Their contribution to this work is kindly acknowledged.

Ultrasonic Microscalpel for High-Precision Surgery

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Examiners: Prof. Dr. Jürgen Burger, Prof. Dr. Andreas Stahel

Introduction

Ultrasonic cutting instruments are used in a wide range of surgical fields such as plastic, pediatric, gynecologic, orthopedic and other open and endoscopic procedures. The ultrasonic dissection device is intended for soft tissue incisions when bleeding control and minimal thermal lesions are desired. The device can be used as a supplement or alternative to electrosurgical, laser or steel scalpels. However, due to the size, weight and cost of the current systems, their usage is limited to a few fields of intervention. The aim of this work is to develop a new generation of ultrasonic microscalpels for high-precision surgery. A unique planar, titanium-based scalpel has been designed that is much smaller and more precise than conventional instruments.

Materials and Methods

The transverse displacement of the piezoelectric actuators is coupled into the titanium horn through an adhesive layer and amplified by the tapered horn geometry. A reproducible manufacturing process was developed and various materials for the bonding layer (epoxies, solder pastes) as well as different heat treatments of the metallic horn were evaluated. With the help of finite element modeling (Fig. 1), impedance analysis and experimental displacement and velocity data, as well as cutting tests and temperature measurements, important design parameters were identified that directly affect the performance and robustness of the device and its controllability in resonance operation.

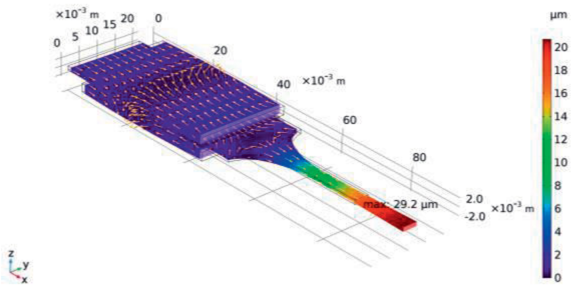

Fig. 1 The COMSOL Multiphysics simulation indicates the peak displacement of the scalpel tip when operating at the λ/2-decoupled resonant frequency f_{res} = 48.15 kHz.

Results

The performance of the microfabricated titanium scalpels is slightly lower compared to existing commercial ultrasound scalpels. However, performance indicators such as scalpel peak displacement of up to 29 µm and velocities up to 8.5 m/s indicate that the devices are suitable for dissection of tissue and coagulation for hemostasis in surgical operations. The operating frequency is in the range of 40-50 kHz, depending on the transversal operating mode. The maximum recorded temperature is 56°C, measured on the titanium horn after 10 minutes of loaded operation. The cutting ability of the scalpels has been successfully demonstrated on chicken tissue (Fig. 2) and synthetic muscular tissue.

Fig. 2 Dissection test with ultrasonic microscalpel prototype on a chicken breast.

Discussion and Outlook

The obtained results correspond to the findings of similar studies performed with silicon-based micro scalpels. The influence of the different bonding materials is minimal which indicates a good manufacturing process and therefore the adhesive with the most favorable fabrication properties may be used for further prototypes. No significant influence on the performance of the scalpel could be determined by heat treatments of the titanium horn. However, very stiff materials such as nitriding stainless steel remain as an alternative. Finally, it turned out that the tip shape has a major impact on the cutting power. Although cutting ability has been proven, coagulation has not yet been tested on living tissue.

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Experimental Modelling of Calcified Native Aortic Valves in a Transcatheter Aortic Valve Intervention

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Introduction

More and more patients have an aortic stenosis (ASt) of the aortic valve, which is treated with a transcatheter aortic valve intervention (TAVI). During TAVI an artificial valve is implanted into the native valve. The influence of the remaining native valve on the hemodynamics in the aortic root is not yet fully understood. To further investigate this, an aortic root (AR) phantom for an experimental setup is needed. The aim of this Master Thesis was to develop, and manufacture, AR phantoms, that are transparent and compliant, including the valve, with adjustable leaflet stiffness and embedded calcifications.

Materials and Methods

The AR geometry was obtained from literature, and two possible manufacturing processes were developed to be able to manufacture AR phantoms. The first approach was to direct 3D-print the phantoms on a fused deposition modelling (FDM) printer with flexible filament. Different filaments were therefore evaluated for their transparency and their compliance. The second approach, was to cast the phantoms in silicone. A casting procedure which had to be adjustable to different AR geometries, leaflet thickness and leaflets topologies were developed. The resulting casting forms were supposed to have the possibility to embed solid calcifications into the leaflets (Fig. 1). The casting forms were printed on a FDM printer, and the phantoms were manufactured by silicone casting, using these forms.

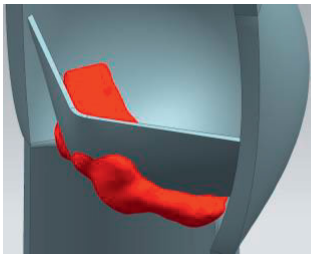

Fig. 1 CAD of an AR phantom with leaflets with calcifications from a patients CT segmentation.

In addition to AR phantoms with leaflets, reference phantoms without leaflets were created. An experimental hemodynamic test was performed to investigate the impact of the leaflets on the para-valvular leakage after TAVI (Fig.2) (CoreValve, Evolut R, Medtronic, Minneapolis Minesota, USA), compared to the situation without native leaflets. The leak was measured with a flow probe and visualized using dye and an highspeed camera.

Results

The 3D-printed casting forms were used to manufacture AR phantoms with different sizes, leaflet thicknesses and embedded calcifications. The para-valvular leakage was measured to increase from 20% to 40% for an AR phantom with leaflets compared to without for an identical cardiac output and aortic pressure. The pictures from the high speed camera support this finding. The direct 3D-printing approach was stopped after the first promising phantom test prints with the best suited filament (Ninjaflex, Manheim, USA) of the evaluation.

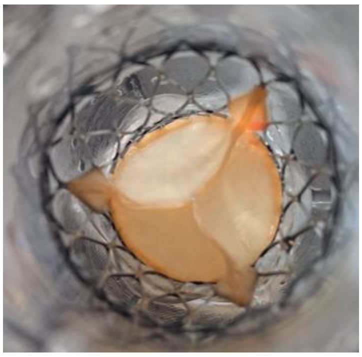

Fig. 2 AR phantom with leaflets and implanted TAVI

Discussion

The AR phantoms created by casting are promising and can be used to further investigate the influence of the native valve on the AR hemodynamics after TAVI. The increase of para-valvular leakage, due to the native valve correspond to the findings in post-TAVI patients and other studies [1]. The advantage of being able to rapidly and directly print patient-specific phantoms with leaflets from CT segmentations, should be further investigated, as this could be a future tool for pre-TAVI planning.

References

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Acknowledgements

The large support from the CVE group, especially Prof. Dr Dominik Obrist and Silje Jahren is gratefully acknowledged. I would also like to thank Dr. med. Paul Phillip Heinisch, Dr. med. Andreas Häberlin and Prof. Dr. med. Thomas Pilgrim for their insight into the world of cardiology.

Low Cost Robotic Prosthesis for Children and Adolescents

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Introduction

According to the World Health Organization, about 30 million people in Africa, Asia and Latin America do not have access to adequate prostheses or orthotics. Commercial myoelectric prosthesis cost between 20'000 and 100'000 CHF. In developed countries, insurance companies usually limit contributions to prosthetic services to 500 to 3'000 CHF per year and 10'000 CHF to prosthetic devices during a person's lifetime [1]. While a hand prosthesis may be a one-time investment for an adult, children and adolescents need to replace their prostheses often as they grow.

The aim of this work is to design and build a low-cost prosthesis for children and adolescents, that is able to support daily activities. An analysis of these activities yields a set of hand configurations.

To reduce costs, the expensive components of the prosthesis are planned to be reusable as the child grows. A functional prototype has been realized to prove the concepts behind the development.

Materials and Methods

The prosthesis is intuively controlled by an eight-electrodes EMG sensor placed on the forearm of the patient.

Machine learning based on a neural network acquires the sensor signal and recognizes the pattern. A controller then commands the six degrees of freedom of the prosthesis to achieve the desired hand configuration. The system is implemented in python and runs on a Raspberry Pi.

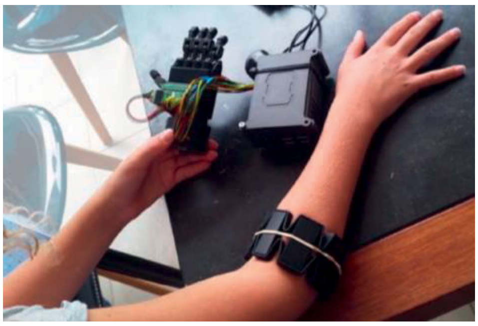

Fig. 1 Size comparison between the hand of a 9 year-old and the prosthesis. The prosthesis is controlled by the EMG sensor placed near the elbow.

Results

A robotic prosthesis has been developed. Its size is in the range of the target population. The plug-and-play design allows to re-use the most expensive part. To reduce even more the cost the mechanical structure has been 3D-printed with PLA. The price of less than 500 CHF for a prosthesis has been achieved.

The prosthesis is able to recognize six hand configurations with an accuracy greater than 90% in most cases.

Reco. / Perf.	PinchIT	Power grip	Rest	Finger spreading	Index pointing	Side grip
PinchIT	99.9	0.1	0	0	0	0
Power grip	3.78	93.17	0.5	0	1.2	1.35
Rest	0	0.23	99.62	0	0.15	0
Finger spreading	0	0	0	97.54	2.46	0
Index pointing	0	16.83	2.16	10.89	70.12	0
Side grip	0	0.2	0	0	0	99.8

Fig. 2 Occurrence Table with a healthy 9-year-old child. Reco: recognized pattern. Perf: performed configuration.

Discussion

This project's main innovation is the achievement of several hand configurations and intuitive control in a very small size and extremely low cost.

Future work shall miniaturize the computation unit and power supply. Usability tests with patients will provide important end-user feedback.

Finally, the device shall be further developed into a commercial product in developed countries and for humanitarian use in developing countries.

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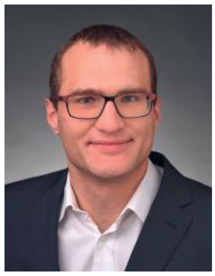
Impedance Spectroscopy to Assess Facial Nerve Proximity during Robotic Drilling in the Mastoid

Yves Jegge



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Examiners: Prof. Dr. Stefan Weber, Dr. Juan Ansó

Introduction

Today robotic surgery is used in different surgical domains to enhance the surgeon's tool kit. However, robotic interventions are not free of errors, for instance inaccurate positioning of the surgical tool. Thus, safety mechanisms are required to ensure preservation of delicate structures proximal to the tool path. Several groups have investigated electrical impedance as an *in situ* tissue discrimination method. *Kalvøy and Sauter* [1] evaluated the accuracy of impedance spectroscopy during needle guidance for discrimination between muscle and neural tissue. The aim of this study was to assess if bio-impedance spectroscopy enables accurate assessment of facial nerve proximity during image-guided robotic drilling in the mastoid.

Materials and Methods

Bio-impedance spectroscopy was evaluated *in vivo* using a robotic surgical platform for cochlear implantation. In each of three subjects, eight trajectories were drilled. Per trajectory, five predefined measurement points near the facial nerve (<1mm) were accessed and electrical impedance spectroscopy carried out (100Hz to 1MHz) using a multipolar electrode probe. Micro-computed tomography scans of the extracted temporal bones were evaluated postoperatively to measure the distances from the drilled tunnels to the facial nerve. Histopathology was realized to evaluate the type of tissue at the final position of the trajectory and additionally assess structural FN preservation.

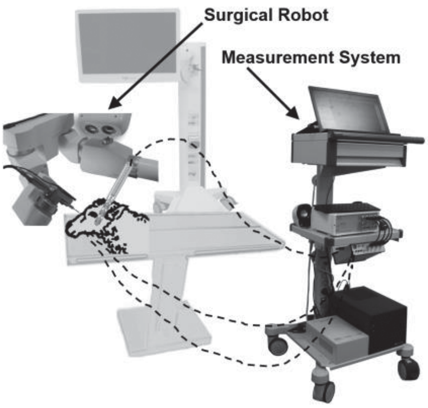

Figure 1: Schematic of in-vivo setup. The image-guided surgical robot and the impedance measurement system are depicted.

Results

From 18 trajectories, bone presented 2 to 3 times higher magnitude than nerve tissue (frequencies <100 kHz); and nerve resulted in lower phase shift than bone tissue (>30 kHz). A combined function (magnitude/phase) resulted in the highest sensitivity (100%) and specificity (67%) to discriminate *safe* and *unsafe* trajectories. A representative example of an *unsafe* trajectory approaching the facial nerve is depicted in Figure 2. The impedance measurement (magnitude, phase) detected a transition from bone into the nerve via thresholding.

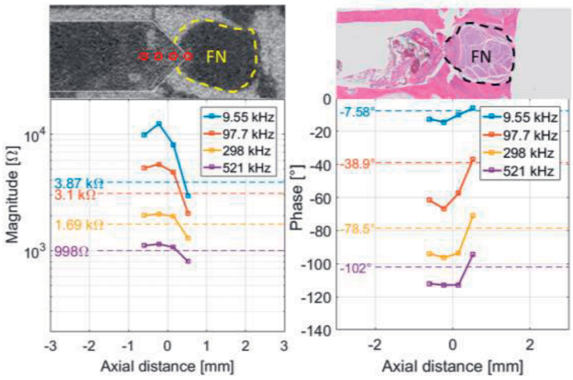

Figure 2: Magnitude (right) and phase (left) curves of one unsafe trajectory approaching the facial nerve (FN).

Discussion

Impedance spectroscopy enabled assessment of facial nerve proximity (100% sensitivity) during robotically drilled trajectories in the mastoid bone. However, the specificity of the approach (67%) was lower than an existing neuromonitoring method (>95%). In the future, impedance spectroscopy could be further investigated to calibrate and ultimately enhance the accuracy of nerve monitoring during robotic cochlear implantation.

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Acknowledgment

The project would not have been possible without the support of the animal hospital of Bern, the Oslo University Hospital and CAScinaction AG. Thanks to my supervisor Dr. Juan Ansó for his guidance

Development of a Reproducible 3D In Vitro Microvasculature Architecture

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Examiners: Prof. Dr. Olivier Guenat, Soheila Zeinali

Introduction

Diseases of the lung are a burden on society in form of sorrow of the affected individuals and ever rising insurance rates. High hopes are placed in microfluidic models of healthy and diseased lung to facilitate fundamental research of this organ works, as well as accelerating pharmacological drug studies and reduced animal testing.

Most of the currently available lung models focus mainly on the epithelial cells sitting of the air side of the alveolar/blood barrier. The few capillary models that exist are not actuated because they are not dedicated to the lung.

Due to the breathing motion the lung tissue is constantly stretched and relaxed. A suitable substrate for seeding with endothelial cells has been looked into.

Researching how cells adapt to external stressors and investigating the vessel formation in cell scaffolds was the goal of this thesis.

Materials and Methods

To create such a 3D cell scaffold many manufacturing technics and different materials were investigated to fulfill the demanding requirements. The stiffness of PDMS was adjusted and then tested to be brought into the desired shape. When PDMS was mixed with precise polystyrene beads the resulting form was additionally modified to enhance the perfusability to the later created scaffold. After curing the PDMS, the PS beads needed to be selectively removed without damaging the fragile scaffold filaments. The dissolving of the PS beads proved to be very challenging, so the Alvetex scaffold (Fig.1) was utilized for the chip design and their cell experiments.

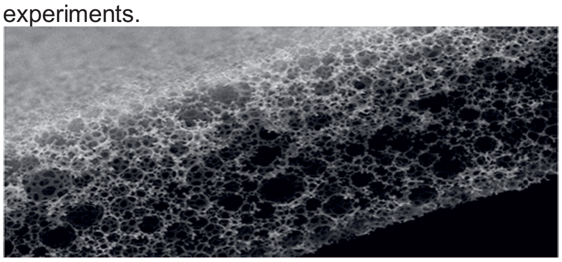

Fig. 1 Scanning electron micrograph of Alvetex Strata in transverse section. Thickness: 200 µm [Ref].

In order to mechanically actuate the Alvetex scaffold, it was bonded with a thin membrane and built inside a microfluidic chip. The scaffold was exposed to physiological levels of deformation to simulate the in vivo environment.

Endothelial cells were mixed with fibrinogen, then seeded on top of the Alvetex scaffold on the chips and in some cases deformed during the incubation. After immunofluorescent staining the cells were analyzed using confocal microscopy.

Results

Deformation measurements showed unequal deformation of the neighboring structures of the Alvetex scaffold.

In the cell culture experiments, endothelial cells formed a thin layer on top of the scaffold (Fig. 2) despite multiple attempts to enhance their ingrowth. Cells showed elongated morphology and created lumen-like cell structures in the thin cell layer.

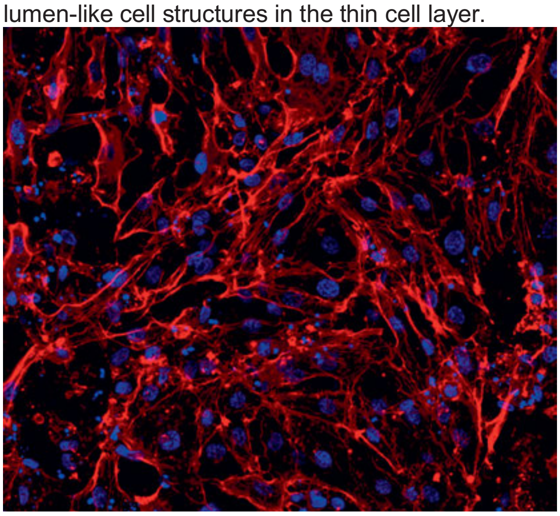

Fig. 2 Cell layer on top of the scaffold imaged with 20x magnification. The endothelial cells have formed lumen that span multiple cells. Immunostaining + confocal microscopy.

Disscussion

The production of the scaffold with the help of porogen is highly dependent on the methods to remove them. They have served their purpose after the scaffold material has solidified. Further investigation is required to finally bring the cell culture experiment as close to the situation in humans as possible.

References

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Head-Mounted Display VR-Training for Hemi-Spatial Neglect Patients: A Usability and Acceptance Study

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

Introduction

Each year approximately 16'000 people in Switzerland suffer from stroke, whereas 25% of post-stroke patients experience cognitive impairment called unilateral spatial neglect (USN). USN is an attention disorder, where subjects are not able to respond correctly to visual stimuli appearing on the contralesional side. As a consequence, USN leads to a reduction of quality of life and performance in activities of daily living (ADL).

Currently, research has mainly focused on stroke patient's rehabilitation of the upper and lower limb functionality, whereas there is less consensus how to improve the cognitive functioning and thus the performance in ADL. A promising new cognitive rehabilitation strategy is the training in a 3D virtual environment by using visual search tasks.

Materials and Methods

The VR system consisted out of two main parts, a head-mounted display to present the virtual environment to the user and a controller for interaction. Two constitutive applications have been developed and tested.

The first application intended to assess the feasibility of a visual work task based on the principle of the two-dimensional diagnostic pencil and paper cancellation task, whereas instead of two-dimensional objects, three dimensional objects were presented. The usability and acceptance of the game as well as the performance was tested in patients with unilateral spatial neglect (n=5, 63 ± 8.6) and healthy subjects (n = 10, 66 ± 8.2).

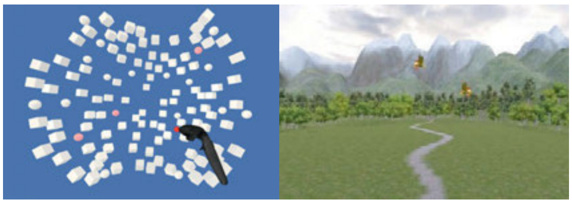

Fig. 1 Left: visual search task (Study 1), Right: visual exploration task (Study 2).

The second application, a first step towards rehabilitation training, was a gamified, dynamic, visual exploration task based on the design of Crazy Chicken with self-adapting difficulty scaling. The applications main goal was to explore the visual space and shooting moving targets. The training was tested in 21 healthy (28 ± 6.0) subjects.

Results

Based on results (Table 1) usability of the games (System Usability Scale) were close to the maximum (i.e. user highly appreciated the game), whereas sickness (Simulator Sickness Questionnaire) was close to the minimum (i.e. symptoms negligible) of the score scale.

The second application was highly entertaining and accepted (Questionnaire of Game Perception) by users. Motivation was significantly higher than the middle of the score scale, whereas frustration was significant lower (Table 2).

	SUS [10 - 100] (Mean ± SD)	**SSQ [0 - 80] (Mean ± SD)**
Healthy, 1. application	93.5 ± 7.2	1.50 ± 4.7
Stroke, 1. application	92.5 ± 4.3	0.00 ± 0.0
Healthy, 2. application	85.5± 12.2	12.1 ±11.8

Tab. 1 SUS and SSQ results of the first and the second application.

Item	**Mean ± Std**	**t-value(df)**	**p-value**
Entertainmet	4.52±0.17	18.7(20)	<0.001
Challenging	3.19±0.27	1.45(20)	0.162
Frustration	2.05±0.46	-4.36(20)	<0.001
Motivation	4.59±0.34	9.77(20)	<0.001

Tab. 2 The game experience of the second application. Score ranges [1 7].

Conclusion

The VR based search tasks were highly accepted and did not evoke any negative reactions. In addition, the new rehabilitation tool can be tailored to the patients need and promotes exploration in space to potentially lower subjects impairments.

From these findings, we conclude that the developed VR training is feasible and has a great potential in neurorehabilitation for patients with stroke and USN.

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Design and Development of a Miniaturized ECG Front-End for Dry Electrodes

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Examiners: Dr. Thomas Niederhauser, Prof. Dr. Marcel Jacomet

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is an independent risk factor for ischemic stroke which has a continuously increasing prevalence [1]. One type of AF named paroxysmal AF occurs suddenly over the timespan of months and terminates spontaneously. Long-term ECG monitoring is the gold standard for the detection of paroxysmal AF. Guidelines for the management of ischemic stroke recommend 24 h ECG monitoring after the event or an even longer recording time of up to 30 days for patients with cryptogenic stroke, where the etiology is not known.

Holter monitors, which use wet electrodes, are the state-of-the-art technology for clinical long-term ECG monitoring of up to 24 h. Electrode cable motion artifacts and low patient comfort are system-related drawbacks. Longer duration of monitoring shows a higher rate of AF detection. However, Holter monitoring imposes electrode-related limitations during prolonged application, such as drying out of the conductive gel, adhesive altering, and skin irritations, which lowers the signal quality and the patient compliance.

Dry electrodes eliminate the major limitations of wet electrodes, but manifest a higher contact impedance, which increases the susceptibility of the amplifier to contact pressure variations, especially when the electrode is included in garments.
Thus, electrode motion artifacts are more frequent and power-line interference rises.

This study aims a flexible tiny ECG recorder to improve the signal quality during prolonged recording.
The goals for the skin mounted device are to increase electrode contact pressure, reduce motion artifacts and cope with anatomical constraints.

Materials and Methods

A novel flex print material is used as substrate for the amplifier. This allows to create a flexible structure which is compliant with the patient's skin.

Results

Due to the flexibility of the amplifier structure, a more stable baseline is achieved as seen in Fig. 1. The amplifier especially designed for dry electrodes showed a promising performance, resulting in a lower interference level.

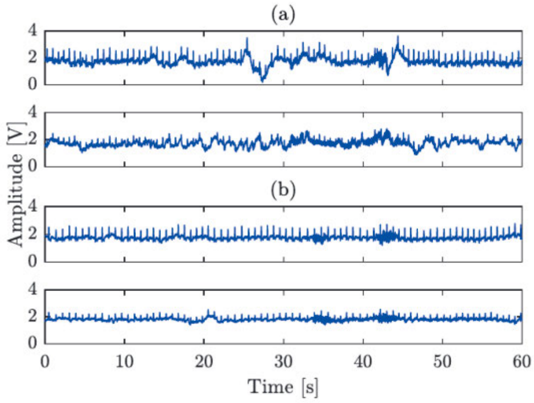

Fig. 1 Unfiltered ECG signal recordings of a subject at rest. (a) Using conventional rigid electrodes. (b) Using flexible electrodes.

Discussion

Challenges introduced by dry electrodes are successfully mitigated by the electrical design of the amplifier as well as by the mechanical structure.

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no. 12 Pt 2, pp. e391–e398, Dec. 2016.

Acknowledgements

The author would like to thank the members of the HuCE-microLab at BFH for their inputs and support.

Next Generation of Cardiovascular Catheters based on Flex-Print Technology

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Introduction

Flexible printed circuit boards (FPCB) have become more wide spread for applications were electronic systems are required to have an intrinsic bendability. In some instances a FPCB made out of biocompatible polymeric materials can be used for a catheter to convey signals in an active or passive way. Today's manufacturing processes for catheters are expensive and labor intensive. In order to facilitate an easier production a FPCB is adhered to a thermoplastic polyurethane (TPU) elastomer catheter tube whereby an expensive assembly process can be circumvented. This particular catheter was configured to be used as esophageal diagnostic device for the detection of paroxysmal arrhythmias as shown in [1].

Materials and Methods

The FPCB had multiple electrodes distributed on a length of 120mm. A small connector with various leads was used on the proximal end of the catheter. Different methods were developed to attach the FPCB on the catheter and standardized tests were conducted in order to characterize the peel and tensile strength.

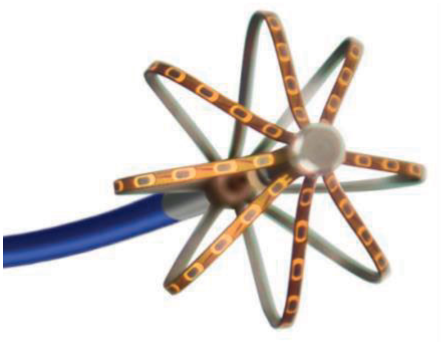

Fig. 1 Intravascular catheter using an expanded FPCB on the distal end of a catheter tube [2].

Result

The adhesion promoting process resulted in a measureable amount of peel and tensile strength. The overall costs and work hours required for the process were significantly reduced compared to the existing method. The FPCB was not mechanically or electronically impaired during the process.

Discussion

The process exceeded the requirements in terms of peel strength, flexibility and surface roughness. To further improve the applicability of this method, different process parameters and overall cleanroom compatibility issues have to be further examined.

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Fully Automatic Planning of Total Shoulder Arthroplasty without Segmentation: A Deep Learning Based Approach

Paul Kulyk

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Examiners: Prof. Dr. Guoyan Zheng, Guodong Zeng

Introduction

Anatomic total shoulder arthroplasty (aTSA) is a surgical procedure used to treat glenohumeral arthritis. Rates of implantation are steadily increasing. The goal of current aTSA systems is to restore the native anatomic dimensions with the implanted devices. One of the key steps in aTSA is resection of the humeral head along the articular marginal plane (AMP). This must be performed accurately to achieve good biomechanical function. While automated preoperative planning tools are in use for the glenoid component, the humeral component has not seen as much attention. Current manual planning techniques require fitting templates over images. These are time-consuming and subject to operator errors. Recent work has been done by Tschannen *et al.* to apply random-forest regression methods to predict the AMP. A positional error of 2.4 ± 1.2mm and an angular error of 6.51 ± 3.43° were reported by Tschannen *et al.* In this thesis, we propose a completely automated process utilizing a deep learning method.

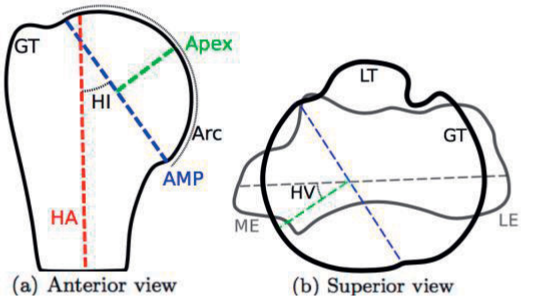

Figure 1: Proximal humerus anatomy, showing AMP in blue.

Materials and Methods

We present a method for automatically determining the position and orientation of the AMP of the proximal humerus in CT images without segmentation or hand-crafted features. The process is broken down into 3 stages; each comprised of an indepedent Fully Convolutional Network (FCN). Stage 1 determines a coarse regression of the AMP center by sampling patches over the entire image and combining predictions with a novel kernel density estimation (KDE) method. Stage 2 utilizes the estimate from stage 1 to focus on a smaller sampling region and operates on a higher image resolution to obtain a refined prediction of the AMP center. Stage 3 focuses patch sampling on the region around the stage 2 estimate and regresses the tip of a vector normal to the AMP which yields the orientation of the plane. The system was trained and evaluated on 27 right upper arm CTs with associated manual definitions in a 4-fold cross-validation.

Results

We took the manual definitions as the ground truth to validate the present method. The mean error in estimating the center of the AMP was 1.30 ± 0.65mm. The mean angular error in estimating the orientation of the plane was 4.68 ± 2.84°.

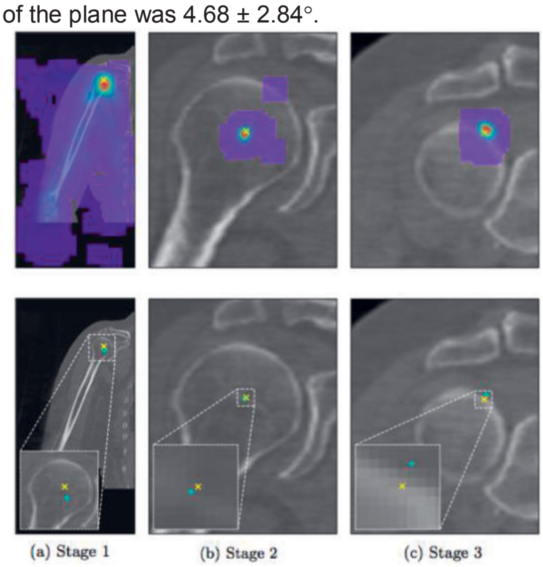

Figure 2: Example of KDE results. Yellow '×' is the ground truth and blue '+' is the prediction

Conclusion

Predicting the AMP using a 3-stage cascaded FCNs with progressively focused patch sampling and a novel KDE we achieved a better result than those reported in previous studies. Integration with other techniques has the potential to fully automate aTSA planning.

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Acknowledgements

Thank you to Drs. Vlachopoulos and Fürnstahl for providing the CT images and ground truth labeling and the IPMI group for guidance on the design.

Erythrocyte-Based Nanotechnology for Personalized Drug Delivery Systems

Vikas Mathew

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Institution: Swiss Paraplegic Research, Nottwil
Examiners: Prof. Dr. Benjamin Gantenbein, PD Dr. Jivko Stoyanov

Introduction

Nanoerythrosomes (NEs) are erythrocyte derived drug delivery systems which blend the unique drug carrying characteristics of erythrocyte membranes with the enhanced pharmacokinetics and bio distribution of nano-sized particles. They are usually generated from hemoglobin free erythrocyte membranes either by physical extrusion or sonication methods. Both methods have low efficiency if processing concentrated samples and raise concerns regarding process sterility and sample recovery. This thesis aims to address these challenges by establishing a new method for the fabrication of NEs from erythrocyte ghosts using shear force. The novelty is to use a mechanical approach, which involves physical disruption of erythrocyte membrane using shear forces produced by a rotor and stator based tissue homogenizer.

Materials and Methods

Different batches of NEs loaded with Fluorescein Isothiocynate conjugated Dextran (FITC Dextran) were fabricated using two different methods: first with the newly proposed shear force method and secondly with extrusion method, which is considered as the gold standard method for NE fabrication [1]. The various characteristics such as morphology, particle size distribution, yield, colloidal stability and encapsulation efficiency of the NEs produced using shear force based approach was compared and validated with the ones produced based on the standard extrusion method. The total count, particle size distribution and loading patterns of the produced NEs were analyzed using flow cytometry.

Results

The increased fluorescence response of the loaded nanoerythrosomes compared to the empty control samples confirmed the successful encapsulation of FITC Dextran within them (Fig. 1). The fluorescence response of the loaded NEs had similar intensities as that of standard fluorescent beads of similar sizes. In the transmission electron microscopy images, the NEs appeared as spherical closed vesicles with thin intact shells, irrespective of the fabrication method employed. The particle size distribution was in the range 100-150 nm for both shear force and extrusion based samples. The samples also showed high colloidal stability with zeta potential values between -40 to -60 mV. The shear force based samples had better encapsulation efficiency when compared to extrusion based samples. About 30 % increase in yield in terms of final NE count was observed for shear force based approach while processing erythrocyte ghosts with high concentration (~150 million ghosts/ml).

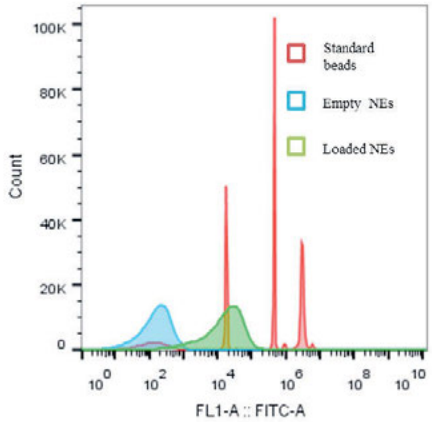

Fig. 1 A significant increase in fluorescence response is observed in FITC Dextran loaded NEs compared to empty control samples, confirming the encapsulation of fluorescent material.

Discussion

The characteristics of NEs produced using the newly proposed shear force method were equivalent to that of extrusion based method both in morphological and functional aspects. The NEs produced were intact and possessed high colloidal stability. The novel shear force method is strongly recommended for processing high concentration erythrocyte ghost samples for which the currently used methods are less efficient. The main limitation of the shear force approach is its low yield in terms of nanoerythrosome count while processing ghost suspension with low concentrations.

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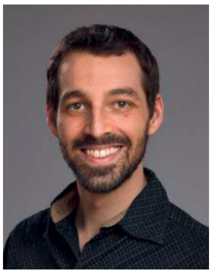
Acknowledgements

I would like to thank Dr. Jivko Stoyanov and MSc Simona Capossela for their valuable guidance and support during the course of the thesis.

Innovative Multilayer Deposition for Biomedical Devices

Jonas Maturo



Supervisors: Prof. Dr. Juergen Burger, Dr. Jérôme Steinhauser
Institutions: University of Bern
Coat-X SA (La Chaux-de-Fonds)
Examiners: Prof. Dr. Juergen Burger, Dr. Jérôme Steinhauser

Introduction

Outstanding reliability of implant encapsulation is a requirement in the biomedical industry to guarantee low diffusion of undesirable species over prolonged implantation times. The impermeable and biocompatible polymer parylene-C is already used but reaches limits in term of permeability for thicknesses inferior to 10µm. Composite stacks such as multilayers of silicon oxide and parylene, developed and commercialized by Coat-X, allow to reach lower diffusion than parylene alone by combining the conformity and the elasticity of parylene with the very low permeability of ceramics.
This work investigates the surface modification techniques and their impact on the adhesion of the multilayer stack as well as the formation of film defects in different ageing environments.

Materials and Methods

The contact angle of a water droplet is measured to qualify the hydrophilic nature of surfaces after they have undergone surface modification by different cleaning methods, different plasma activations, and exposition to a silane coupling agent in various configurations.
The adhesion of the multilayer stack is characterized by means of the scotch test. The adhesion of a stack composed of one parylene layer and one SiO_x layer has been quantified using different surface-activation methods for soda-lime glass and silicon wafer substrates. In addition, the adhesion and the defect formation have been investigated for different ageing environment exposures.

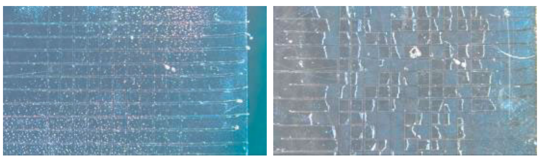


Fig. 1 Scotch test procedure to force the parylene and SiO_x film delamination after ageing in an aggressive environment. Left: before scotch test. Right: after scotch test.

Results

The plasma activation of surfaces impacts the adsorption of the silane coupling agent applied by evaporation. It was shown that the adsorption of the silane is time-dependent and pressure-dependent.

This work showed that the contact angle can be used as a predictor for the adhesion performance. Poor adhesion performance of the parylene/SiO_x composite layers has been observed on surfaces with a low contact angle value and good adhesion has been observed on surfaces with a high contact angle value.
The ageing environment has a significant impact on the formation of film defects and on the stability toward mechanical stress.

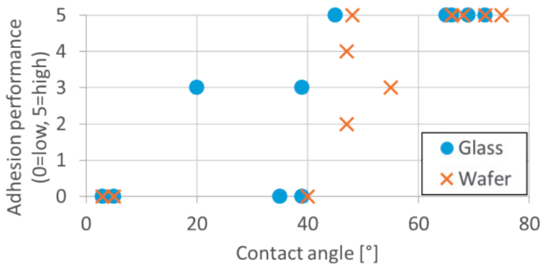


Fig. 2 The contact angle of a water droplet on treated glass and silicon wafer substrates gives an indication on the affinity of the surface to bind with parylene. The adhesion performance is obtained using the scotch test.

Discussion

This work quantitatively showed the impact of surface activation on the silane adsorption and thereby on the contact angle which subsequently improved the adhesion performance. These results are in accordance to theoretical models.
Good adhesion performance could be obtained but the long-term stability of the films could not systematically be guaranteed for all ageing environments.
In order to reach similar adsorption coverage within short duration and thereby decrease the process cycle time, further investigations have to be continued.

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Acknowledgements

The project was performed among the company Coat-X SA, in La Chaux-de-Fonds.

Diabetic Retinopathy Classification from Fundus Photography

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

Introduction

Diabetic retinopathy is a secondary disease of diabetic mellitus. It undergoes four stages and can lead to complete blindness of the patient. The number of patients is increasing, and the diagnosis is time consuming because of the manual evaluation. Therefore, it is even more relevant to automatize this process. One possible solution to do so could be to use classification algorithms, which are able to diagnose the different stages. In 2015, Kaggle.com started a competition with the aim to improve the detection of diabetic retinopathy. Worldwide, 661 teams participated at this contest. They developed several promising solutions, but the question is:" What is the performance of those algorithms in real environment circumstances?"

Materials and Methods

This master thesis focused on that question. Several architectures were tested. The two best solutions are based on ResNet50 and InceptionV3. For this purpose, Python 3.6 with a Keras-Tensorflow back-end was used. The Kaggle.com training set was used for training and validation of the convolutional neural networks.

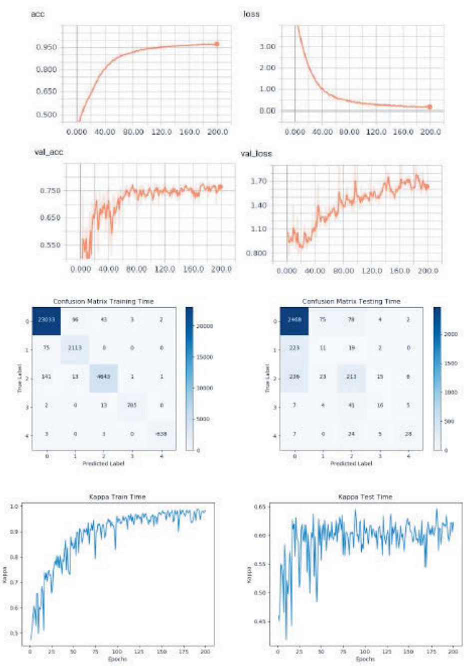

Fig. 1: Training and validation results of the best solution. It is based on the InceptionV3 architecture.

Results

The best working neural network was based on the InceptionV3. Pretrained weights form ImageNet were used to train. This network reached a training accuracy of 97.5%, whereas the validation accuracy was 77.9%. Interestingly, the validation loss is increasing during the training, which is caused by low probabilities of the right class, which leads to high loss values (categorical crossentropy loss).

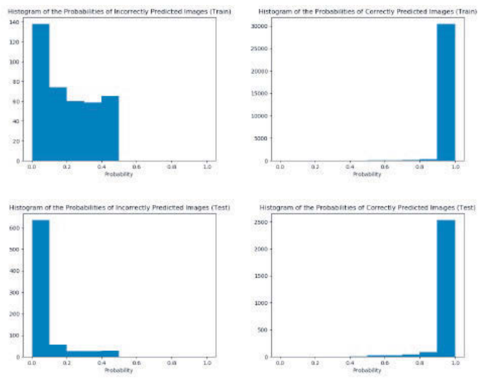

Fig. 2 Probabilities distribution of the training (top) and validation (bottom). The probabilies of the correct class were very hight, where the classification were right, and nearly 0, where it was wrong.

Discussion

To solve the low probability problem is the next step to improve the training further. If we look at the best Kaggle.com solutions, they have input resolutions between 512x512x3 and 900x900x3. Therefore, the next step could be to train the InceptionV3-network with images with higher resolution. For both networks 224x224x3 images were used for training. For ResNet50 this is already the maximal input size, but for InceptionV3 it could be increased to 299x299x3. If this increase is not enough, other architectures could be used.

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Acknowledgements

My thanks go to Prof. Dr. Sznitman and his team for the good support during this master thesis.

Patient-to-image Registration for Lateral Skull Base Surgery Utilizing the Patient Tracker Attachment: Concept, Design and Evaluation

Camilo Mendez Schneider

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Examiners: Prof. Dr. Stefan Weber, Dr. Kate Gerber

Introduction

Due to the geometric scale and proximity of important anatomical structures, image guidance on the lateral skull base requires accuracies of less than 0.5mm, which commercially available systems cannot provide (Labadie et al. 2005). However, it was shown that by using suitable tracking technology, registration with bone anchored fiducial screws and a bone anchored patient tracker, image guidance of approximately 0.2 mm can be achieved (Weber et al. 2017). To reduce complexity (placement of fiducials, placement of patient tracker, tools for retraction of soft tissue) in the small surgical site, invasiveness and setup time, this thesis aims to integrate the two functionalities of registration and patient tracking into one registration device. It was hypothesized that such a device could remove the neeed for invasive fiducials whilst maintaining navigation accuracy and providing additional intraoperative error checking capabilities.

Materials and Methods

A bone anchored patient tracker attachment (tripod) made of polyetheretherketon (PEEK) with integrated titanium fiducials for paired point matching was developed, allowing for registration and patient tracking during lateral skull base procedures. Finite element simulations were used to ensure minimal deflection of the fiducials under the attachment force. Automatic model based detection of the fiducials was added to an exisiting surgical planning software. The precision of the fiducial localization in the image data was assessed in computer tomography images. In an ex-vivo study the feasibility of the tripod was tested by performing 18 registrations with an intraoperative cone-beam CT imaging system..

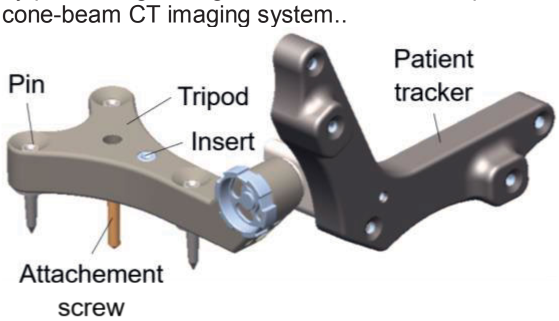

Fig. 1 CAD model of the developed tripod including registration fiducials (pins, insert) and attached patient tracker.

Furthermore, a tripod was designed for the use in robotic cochlear implantation (RCI). The design was adopted to enable the retraction of surrounding soft tissue, from the drilling workspace in a RCI procedure. Placement instructions were defined to prevent collision with the robotic system. In 20 drill simulations, the placement instructions were validated.

Results

A tripod with integrated fiducials for registration and enabling tracking of the patient was developed and manufactured. Finite element analysis showed deflection of the registration fiducials of less than 0.05 mm, allowing for accurate fiducial detection and intraoperative error checking relative to the devices known geometry. Fiducial localization precision of the registration fiducials in CT image data, relative to CMM measuremnts, was below 0.05 mm. Furthermore, 18 registrations were successfully be performed in an ex-vivo study. Fiducial registration errors of 0,042 ± 0,012 showed no significant difference to bone anchored fiducial screws (p-value = 0.3940). Furthermore, a tripod specifically for RCI was designed. Simulations of the RCI tripod placement instruction revealed potential collisions between the tripod RCI and the planned drill trajectory in one of 20 cases.

Conclusion

A patient tracker attachment with integrated registration fiducials was designed and manufactured. Accuracy evaluations demonstrate that the device achieves equivalent registration accuracies to previously reported fiducial screws alowing for navigation with reduced invasiveness and time and increased safety checking. In furure work, an optimized device for RCI will be developed and the devices will be tested within clinical trials of image guided proceudres on the lateral skull base.

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I would like to thank CAScination AG, the members of the Image-guided Therapy group at the ARTORG Center and the department of ENT surgery at Inselspital for their their support and contribution.

Smartphone Based Cataract Screening

Slaviša Obradović

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Institution: University of Bern, ARTORG Center for Biomedical Engineering Research
Examiners: Prof. Dr. Raphael Sznitman, Dr. Sandro De Zanet

Introduction

Nowadays, a smartphone represents a multi-functional electronic device. Technological progress and improvement with increasing number of accessible applications, as well as reduced costs, led it to an extensive use. There is also a significant increase of smartphone users among health professionals because it can be combined with many commonly used tools for clinical evaluation and education. In ophthalmology, there are already several applications available assessing the visual acuity using either the Snellen visual acuity test or modern interactive visual acuity tests. Some of the applications have tests for color vision, astigmatism, pupil size, oculomotor reflexes, and red desaturation. [1]
Our goal was to develop smartphone-based, automatic cataract level identification software that can be used by non-clinicians in the field. The aim was to have a simple protocol for non-clinical users to collect an image of a subject's eye and automatically determine whether or not the subject has an early or extensive cataract that warrants referral to a specialist.

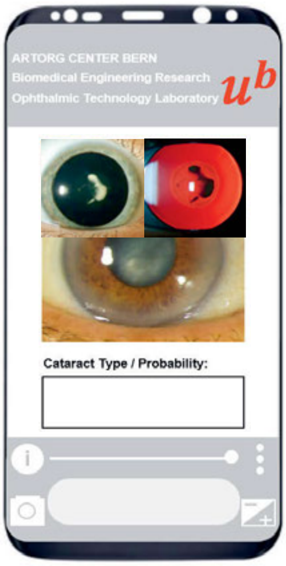

Fig. 1 The layout of the camera-based app.

Materials and Methods

The workflow of the project was divided into four major steps: developing of a camera-based application, data collection, training of the received dataset according to machine learning algorithm and developing a trainable application.
The target of the first phase was to develop a competitive Android application with exclusively determined camera features and parameters which promised cataract detection. These features are comprised of the exposure compensation, flash modus, manual- and autofocus, zoom, white balance, canvas and bitmap-based optical aid, score table, and finally the capture button.
For the second phase, a clinician from Inselspital has examined our application by taking pictures of cataract-affected patients. The third phase was launched by training an external database on a pre-trained convolution neural network (CNN). At the moment the fourth phase is in progress.

Results

During the data collection, the smartphone has shown some weaknesses. Main adversities are the reflectance of objects on the lens and the focus.

Discussion

For the further procedure, it is suggestable to collect solely red reflex images. Fig. 1 depicts a congenital nuclear cataract which has been taken by slit-lamps, in which the contrast of the red reflex eye is clearly highlighted. Even small spots, which could lead to an early-stage cataract, are well detectable.
In addition, the camera may be extended by more camera features, like a focus lock and a gyroscope display. [2]

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I would like to thank Dr. Raphael Sznitman for giving me the opportunity to be a part of his team and PD Dr. Christoph Tappeiner for supporting us during the project.

Effects of Low Oxygen Pressure on Iron Metabolism in Osteoclasts

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Institution: University of Bern, Department for BioMedical Research
Examiners: Prof. Dr. Willy Hofstetter, PD Dr. Benjamin Gantenbein

Introduction

Iron is an important trace metal in cells, which is used for numerous biological processes and is required for efficient ATP production by mitochondria. Osteoclastic bone resorption is an energy consuming process. Consequentially, osteoclasts (OC) possess a lot of mitochondria and transferrin receptor (Tfrc), required for iron uptake, which is upregulated during differentiation. In this study, the effects of hypoxia on osteoclast development and activity were investigating, since oxygen is essential for cellular energy production.

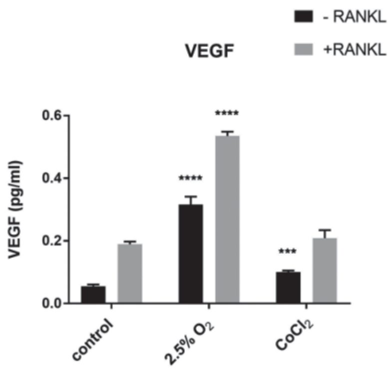

*Fig. 1. **ELISA for VEGF**. VEGF was measured in conditioned media after OPC were exposed to 2.5 % O_2 and 100 uM of $CoCl_2$, respectively, for 24h.*

Materials and Methods

Osteoclast precursors (OPC) were exposed to either cobalt (Co^{2+}) or low oxygen environment (0.5 % or 2.5 % O_2). To assess the hypoxic condition of the cells, the level of vascular endothelial growth factor (VEGF) in the culture medium was quantified by ELISA. Cell viability and osteoclasts differentiation were evaluated by XTT assays and quantitative RT-PCR. Mature OC have been seeded onto amorphous calcium phosphate (CaP), spiked with ^{45}Ca, to assess the dependence of the resorptive activity on oxygen.

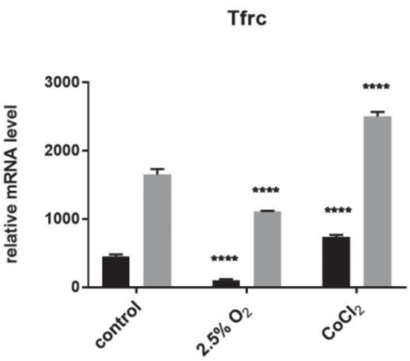

*Figure 2. **Levels of Tfrc transcripts**. Level of transcripts encoding Tfrc relative to the housekeeping gene GUSB were increased in cells treated with 100 μM $CoCl_2$.*

Results

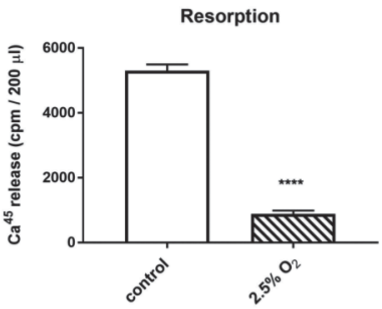

*Fig. 1. **Mineral dissolution by OC**. The capacity of OC to dissolve amorphous CaP was fully blocked when the cells were grown with 2.5% O_2.*

Cultivation of OPC for 24h in 2.5% O_2 lead to a significant increase of VEGF in the culture media (control: 19.7±1.1; low O_2 treatment: 65.5±1.6) (Fig. 1). Treatment of the cells with Co^{2+} induced the up-regulation of transcripts encoding Tfrc (Fig. 2). The resorptive activity of the osteoclasts was fully blocked when the cells were cultured in 2.5 % O_2, (Fig. 3), while levels of mRNA encoding OC specific proteins were unchanged after 24h of 2.5% O_2.

Discussion

The data demonstrates that energy balance in OC is critical for the correct function of the cells. Challenges to this balance activate corrective mechanisms and interfere with cell function.

References

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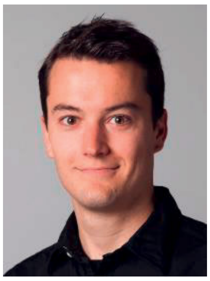
Acknowledgements

The project was support by the NCCR Platform “TransCure” which has been set up “To apply excellence in membrane transporter research to the treatment of human diseases”.

Feasibility of large scale Machine Learning based Ballistocardiography

Jacob Rasmussen



Supervisors: MSc Narayan Schütz, MSc Angela Botros
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Examiners: Prof. Dr. Tobias Nef, MSc Narayan Schütz

Introduction

Our society is constantly aging. Heart diseases are the main cause of death and disability in old age. Methods for early detection and prevention are therefore very important. Electrocardiography (ECG) is used as a standard for assessing heart function. Ballistocardiography (BCG) is an alternative method. It uses pressure sensors to measure the ballistic forces generated by the heart as blood ejects into the major vessels. Unlike the ECG, no electrodes or other devices are attached directly to the person recorded. Modern piezoelectric sensors can measure the heart's activity through a mattress, which makes this method suitable for unobtrusive long-term heart monitoring.

In this feasibility study, I have investigated whether it is possible to detect the heartbeat in the BCG signal using machine learning (ML) techniques. Because of the complexity and variability of the BCG signal, classic signal processing becomes increasingly difficult. ML however, leverages data to learn complex relationships without the need for additional manual instructions. Different ML methods were examined for their suitability.

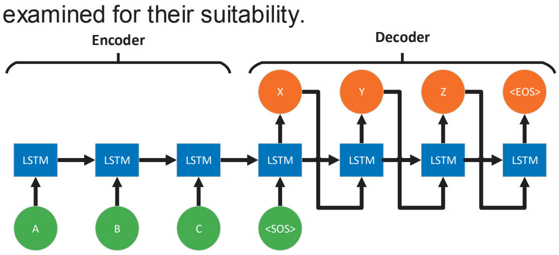

Figure 1 A schematic representation of a Seq2Seq model with encoder and decoder consisting of LSTM cells. It shows the translation from "ABC" into "XYZ".

Materials and Methods

BCG signals and simultaneously recorded ECG signals were recorded in a non-clinical environment (944 hours). Due to a time shift between these signals, they were aligned using cross-correlation. In a next step, artefacts were removed from both signals. Additionally, the ECG signal was resampled. Linear regression, support vector machine (SVM), convolutional neural network (CNN), standard long short-term memory (LSTM) and Seq2Seq (Sutskever *et al., 2014*) (Fig. 1) models were examined. The BCG signal was used as input. The simultaneously recorded ECG signal was used as ground-truth. Models were tested on an unseen data set.

Results

The Seq2Seq model predicted peaks were in proximate to the original peaks. The number of heartbeats in the predicted segments matched the number in the original ECG signal. Two segments with the predicted and original ECG signal can be seen in Fig. 2. Linear regression, SVM and CNN models predicted a straight line. The standard LSTM model predicted a signal randomly oscillating around zero.

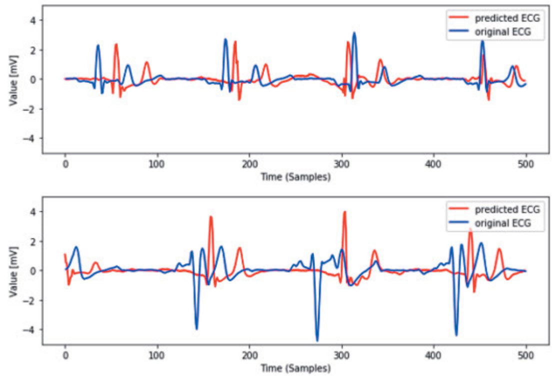

Figure 2 Example of two translated segments from the same subject. The red line is the predicted ECG signal and blue line is the original ECG signal. The predicted ECG signal shows some ECG characteristics.

Discussion

The Seq2Seq model produced the best results from all investigated ML methods. A drawback was the time shift, which could not be easily removed using cross-correlation. Better aligned data could lead to improved results. Furthermore, it might be advantageous to have higher quality ECG data. As seen in Figure 2, the QRS complexes in the original ECG signal are sometimes inverted. This inconsistency makes the learning task more difficult.

References

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I would like to thank Prof. Dr. Tobias Nef and the Gerontechnology and Rehabilitation Research group for their support and continuous encouragement throughout this thesis.

Fast and Accurate Human Brain Morphometry Estimation with Deep Learning

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Examiners: Prof. Dr. Mauricio Reyes, Dr. Christian Rummel

Introduction

Neurodegenerative and other neurological disorders like Alzheimer's disease, multiple sclerosis or epilepsy are often associated with structural changes in the brain. Magnetic resonance imaging (MRI) allows non-invasive assessment of brain structures. Brain morphometry, which is concerned with the measurement and analysis of brain structures, is about to become an essential clinical biomarker for the diagnosis and monitoring of such diseases. While manual measurements from MRI are too labor-intensive and error-prone, automated tools often come with a high computational burden (approx. 10h with FreeSurfer [1]), making them hard to use in clinical routine, where time is often an issue.
Recent advances in deep learning for image analysis motivates us to propose a deep learning-based approach for direct estimation (regression) of brain morphometry from MRI. We hypothesize that a neural network can directly predict the volumes of anatomically delineated subcortical regions of interest, and mean thicknesses and curvatures of cortical parcellations. Advantages are the near-time availability of results while maintaining a clinically relevant accuracy.

Materials and Methods

We propose a deep learning-based approach to directly estimate brain morphometry from T1-weighted MR images. An anonymized dataset of 574 subjects (443 healthy controls and 131 patients with epilepsy) is used for the supervised training of a convolutional neural network (CNN). A "silver-standard" ground truth is generated with FreeSurfer 6.0.

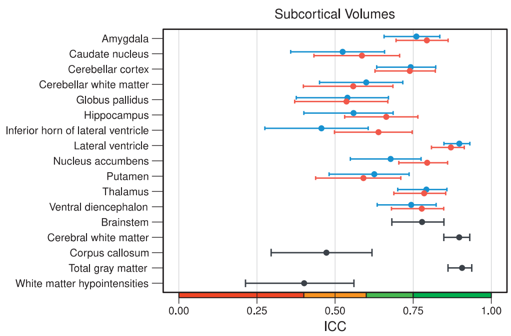

Fig. 1 Intraclass correlation coefficients (ICC) with 95% confidence intervals for all subcortical volumes. Blue: right hemisphere, red: left hemisphere. Color scale indicates poor (red), fair (orange), good (light-green), excellent (green) ICC.

Results

The CNN predicts a total of 165 morphometric parameters directly from raw MR images, without the need of prior image registration nor segmentation, enabling results to be available within seconds. Analysis of the results using intraclass correlation coefficients (ICC) and Bland-Altman plots showed, in general, good correlation with FreeSurfer generated ground truth data (Fig. 1). Although the CNN model was not able to capture the full variance of the assumed ground truth samples, some of the regions nearly reached human inter-observer performance (ICC > 0.75).

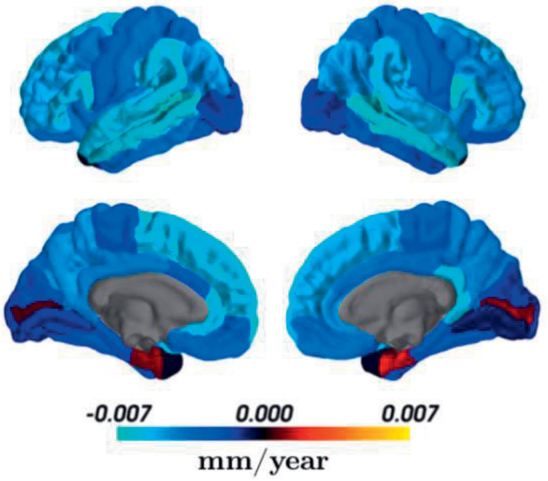

Fig. 2 Regional age-related gray matter atrophy rates. Regression maps based on the predictions from the CNN superimposed on a standard brain. Color scale indicates change of cortical thickness in mm/year (blue for reductions and red for increases).

Discussion

We have shown the general feasibility of using deep learning to estimate human brain morphometry directly from MRI. A comparison of the results to other publications shows accuracies of comparable magnitudes for the subcortical volumes and cortical thicknesses. The hypothesis of reaching an accuracy to be clinically relevant is supported by a replication of the findings from an epilepsy study and of cross-sectional annual age-related gray matter atrophy rates (Fig. 2).

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Development of an *In Vitro* Platform for Investigating Biofilm Formation and Testing Novel Devices in the Lower Urinary Tract

Joy Roth

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University Hospital Bern (Inselspital), Department of Urology
Examiners: Prof. Dominik Obrist, Prof. Fiona Burkhard

Introduction

Bladder underactivity is a highly incommodious urological condition. Patients suffering from it have difficulty to empty their bladder completely, because of reduced function of detrusor muscle (which either has less strength, or is unable to contract during a sufficient time period). This pathology causes a reduced quality of life, and frequent infections (due to urine remaining continuously in the bladder, called post-void residual). Medical solutions existing to treat this condition are currently insufficient because they cannot prevent infections, or induce strong side-effects. The aim of this study is to develop an experimental setup to test novel medical devices and solutions against bladder underactivity, and to quantify the performances in terms of flow and pressure under different conditions.

Materials and Methods

Both *in vitro* and *ex vivo* tests are performed to characterise the efficiency of possible new devices and solutions against bladder underactivity. Fresh female pigs' bladders and urethras are used for *ex vivo* experiments. These bladders are collected form a local slaughterhouse. The flow rate is measured using a weighting-scale able to measure weight variations in continuous mode. Pressure inside the bladders was also measured.

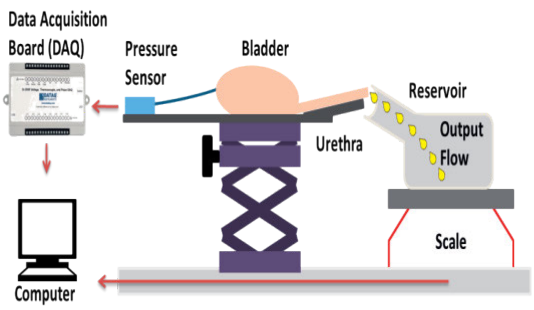

Fig. 1 Bench test to investigate new solution against bladder underactivity

These measurements are aimed at assessing the tested devices in terms of: i) increase of 'urine' flow rate (compared to a normal situation of 'natural urine flow coming out of the urethra, without any assist device), and ii) capability to completely empty a bladder. Pressure measurements are performed to ensure that the pressure inside the bladder stays in a safe range (<30-40cmH_2O) during the testing.

Results

The developed bench test is able to continuously measure the main useful urodynamic variables (flow, volume and pressure). Thus derived characteristics such as average flow rate, maximal flow rate, or total emptying time can be evaluated. Fig. 2 presents an example of internal pressure evolution during the voiding of a bladder initialy filled with 122ml of water. The voiding of this bladder is assisted by one of the novel medical devices tested.

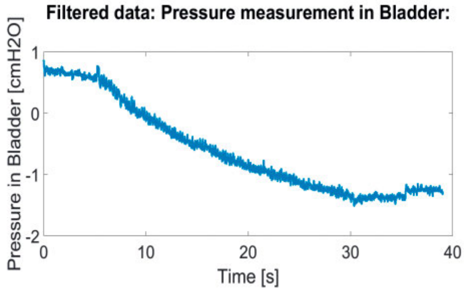

Fig. 2 Internal pressure evolution of an ex-vivo bladder during an assisted voiding sequence, with a new medical device..

Discussion

The developed bench test is ready for a quantitative testing of new devices and solutions against bladder underactivity.

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Acknowledgements

Bladders used for the *ex vivo* experiments were provided by the slaughterhouse of Les Ponts-de-Martel (NE).

Modality Crawler: Using Deep Learning for Automated Brain MRI Sequence Classification

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Introduction

In brain tumor treatment, clinical experts combine information from multiple MRI sequences to monitor tumor progression. Automated approaches to improve brain tumor volumetry have been developed to assist this process (e.g. [1]). The unstandardized naming of MRI sequences however, makes it difficult to deploy automated techniques in clinics. It also complicates research since manual data annotation by clinical experts is required in order to populate data sets for machine learning. This project aimed to improve this situation for both clinical partners and research, by implementing a crawler application that allows automated retrieval, verification and machine learning based classification of brain MRI image data.

Materials and Methods

A Convolutional Neural Network (CNN) based on the AlexNet [2] architecture was trained to classify the four main MRI sequence types used in brain tumor image analysis (T1, T2, T1-Contrast, FLAIR). The problem was approached with a two-dimensional strategy, by extracting axial key-slices from the scan volumes. Established brain tumor data sets (i.a. BRATS, TCGA-GBM) have been used to train and evaluate the model. During experimentation, a number of influences have been studied (i.e. skull-stripping, pre- and postoperative imaging, absence of pathology, other sequence types).

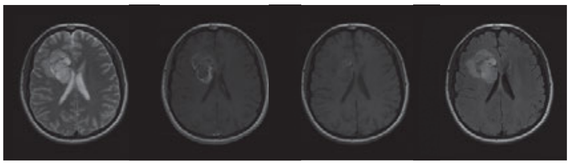

Fig. 1: The four main MRI sequence types used in brain tumor imaging (left-to-right: T2, T1-Contrast, T1, FLAIR) - image data from TCGA-GBM data set

A final model was trained based on the findings from the experiments and incorporated in a software prototype. The prototype, containing additional mechanisms for data validation, was evaluated in a blinded experiment setting.

Results

We concluded that for an optimal classification performance, models should be trained with a balanced mix of both preprocessed and unprocessed data, including both postoperative and preoperative images. Furthermore, models trained solely on scans of brain tumor patients showed no significant performance decrease when evaluated on healthy patients. The final model showed a volume accuracy of 98.4% on the validation set and an average volume accuracy of 99.3% over all involved sets.

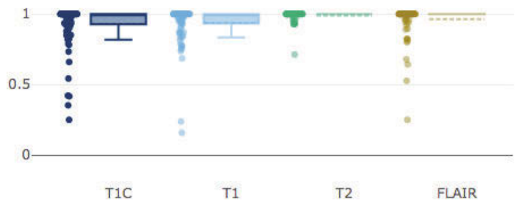

Fig. 2 : Average slice accuracy per volume (>0.5 indicating a correct volume classification) - performance of the final model on the validation set

During the manual outlier analysis over 20 volumes (0.6% of all volumes) from the utilized data sets have been identified to be mislabeled, including volumes from the established data sets BRATS and TCGA-GBM.

Discussion

The results show that a regular CNN is able to classify the most common sequences used in brain tumor imaging with reasonable accuracy. Due to the 2D approach of the model, the region of interest selection has shown to have a high influence on the outcome of the classification. The mislabeled samples found in the course of this project underline the importance of quality assurance mechanisms in research. Automated software such as our proposed Modality Crawler could contribute to improving this situation.

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Development of a 3D Virtual Urban Environment to Stimulate Critically Ill Patients

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Examiners: Prof. Dr. Tobias Nef, Stephan Gerber

Introduction

A growing incidence between critically ill patients and cognitive impairments (CI) has been observed in the past few years. The cause of these CIs is suggested to be due to the stressful environment in the intensive care unit (ICU), together with a sensory overload and sensory deprivation. A possible treatment to prevent these problems is exposure therapy to a nature scene. Since the patients cannot leave the ICU, the idea is to bring the nature to them using Virtual Reality (VR). A promising study using VR nature has already been conducted showing positive results. To now show that those positive effects are due to the nature environment and not just the VR treatment, a 3D urban environment has been designed to conduct a study, evaluating possible differences in the outcome between the environments.

Materials and Methods

The designed urban environment consists of a walk through a busy downtown, followed by a more relaxed old town.

The study has been conducted in the ICU of the University Hospital of Bern and the setup is depicted in Figure 1. 24 healthy participants were recruited and exposed to three different environ-ments in a cross-validation experiment: VR urban, VR nature and the ICU TV as the gold standard. The order of the environments has been randomized at the start of the experiment.

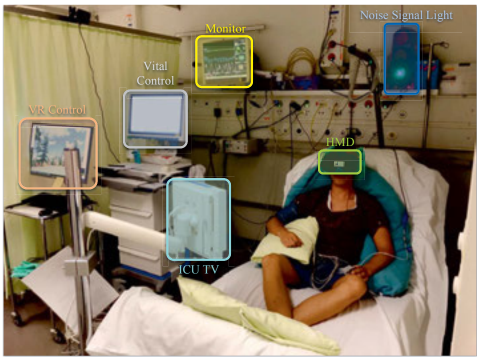

Fig. 1 Study setup in the ICU of the University Hospital of Bern

During the experiment, data has been recorded with questionnaires, vital signs (e.g. blood pressure, respiratory rate and heart rate) and eye-tracking to evaluate the effect of the different environments on the state of the test subjects.

Results

Compared to the other environments, the results from the nature environment show significantly more relaxing effects. This is especially shown in a higher positive effect on the emotional state together with a lower negative effect. The nature scene has also been perceived the most restorative by far. In the vital signs the participants showed a lower respiratory rate (see Figure 2), lower mean arterial pressure and higher heart rate variability compared to the urban scene and the TV.

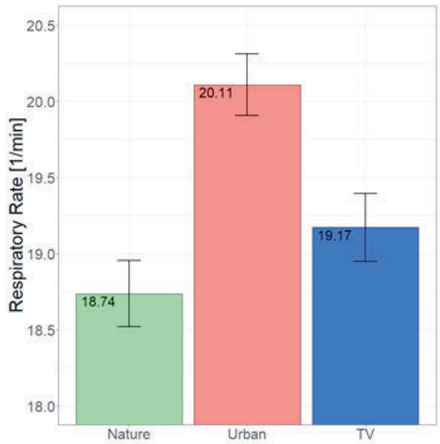

Fig. 2 Sample means of the respiratory rate with error bars representing the 95% confidence interval.

Discussion

These findings are in line with the suggestion from similar studies, promoting the positive effect of nature environments on the overall health of people. Although the participant count was rather low and not all the measured parameters were evaluated yet, the result of this work proposes that the beneficial effects result from the composition of the environment rather than just the distraction using a VR environment.

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Acknowledgements

I would like to thank the members of the Geron-technology and Rehabilitation Research Group for the opportunity the write my thesis and for their support and contributions.

Intraoperative 3D Ultrasound-Based Planning for Surgical Resection of Liver Tumors

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Introduction

Patients with liver cancer are only curatively treated by surgery. Liver resection surgeries are the gold standard to treat these patients. Image guided navigation approaches are not regularly used in this kind of surgery because the involved registration of preoperative imaging data to the surgical site leads to difficulties with deformations. The aim of this thesis is to conceptualize, implement and evaluate a new approach to navigate in tissue sparing resections without registration. This method would instead intraoperatively reconstruct the liver and create a surgical plan to resect tumors near the liver surface.

Methods

Liver reconstruction is done in two steps. First, the surface is reconstructed from a sample of points which were acquired from tracked ultrasound. Only points corresponding to ultrasound images arising from the liver surface are added to the sample. Secondly, the tumor is reconstructed as a sphere. The location and diameter of this sphere are determined from the tracked ultrasound images. After freezing an ultrasound image which shows the largest diameter of the tumor, it is semi-automatically segmented. The center of the segmentation is the tumor center and the diameter is estimated from the segmentation contour. Using the created 3D liver model, a plan to resect the tumor is created by fitting a resection shape which respects the safety margin around it.

Fig. 1 The setup in the operating room: Red the surgeon; Yellow the tracking camera; Green the ultrasound probe; Dark blue the 3D screen; Light blue the 2D screen.

Finally, to test the resulting approach, two experiments are performed on a liver phantom. The first one was executed to evaluate the accuracy of the reconstructed surface. The second one was an usability test conducted with three surgeons to evaluate the software applicability in the operating room.

Results

The accuracy experiment of the reconstructed liver surface shows a median error of 2.57 mm. Most of the accessible liver surface has been reconstructed exactly, but large errors (up to 50 mm) are visible at the edge of the reconstructed surface.
The usability test shows that the surgeons find the software useful and that they could imagine to use such a system in the operating room.

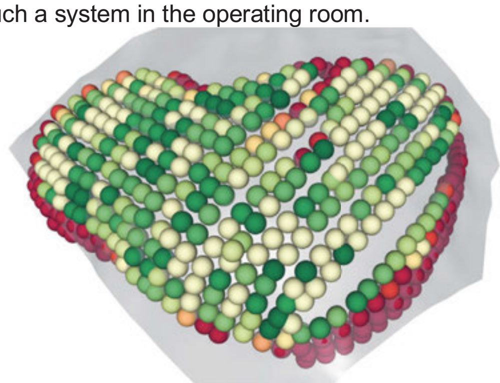


Fig. 2 The mean distance (in mm) of each reference point visualized by colors. All points with a mean distance of over 5 mm to the surface are colored dark red. Points with a mean distacne below 1.5 mm are colored dark green.

Conclusion

A method to create an intraoperative model of the liver which can be used to plan resections of tumors near the surface was developed. The proposed method works without registration and a first experiment to evaluate its reconstruction accuracy shows promising results for a method in such an early prototype state. Another experiment shows that surgeons would like to use a system with the proposed workflow. However, it has to be further tested if such an approach is applicable in clinics.

Acknowledgements

I would like to thank the members of the Image-guided Therapy group at the ARTORG Center and the surgeons who participated in the phantom experiments.

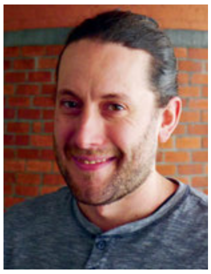
Bern University of Applied Sciences

Master's Thesis in Biomedical Engineering

UNIVERSITÄT BERN

Finite-Element Simulation and Characterization on Tissue-Mimicking Gelatin Phantom of Focused Ultrasound Stimulation

Yann Schaeffer



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Institution: BFH TI, Creaholic SA, Biel
Examiners: Prof. Dr. Andreas Stahel, Prof. Dr. Philippe Büchler

Introduction

Focused ultrasound mediated brain stimulation (FUS) is a non-invasive technology that has a higher spatial specificity with superior penetrations depth compared to transcranial magnetic stimulation. Studies have shown that ultrasound stimulation can enhance mood states of chronic pain patients. Furthermore, FUS potentially could be used as non-invasive computer-to-brain interface. A deep understanding of how the focus is influenced is crucial for a successful stimulation of specific brain areas. Therefore, FEM models could help to gain understanding of the influencing parameters. To prove that numerical results are correct, it is of high interest to validate them on a real-world model. The aim of this study was to simulate focused ultrasound using FEM and to validate the obtained results on an experimental head model using tissue mimic phantom materials.

Materials and Methods

An experimental setup was built that included a focused ultrasound transducer, the brain model, and a 3D-positioning system for the hydrophone. Furthermore, a characterization setup was built that was used to characterize ultrasound properties of used tissue phantoms. The final experimental brain model was built out of tissue mimic gelatin (scalp, meninges, and brain) and a 3D-printed epoxy skull. Each tissue phantom layer was added successively to the model. For each layer the ultrasound field was measured and compared to the corresponding FEM simulation.

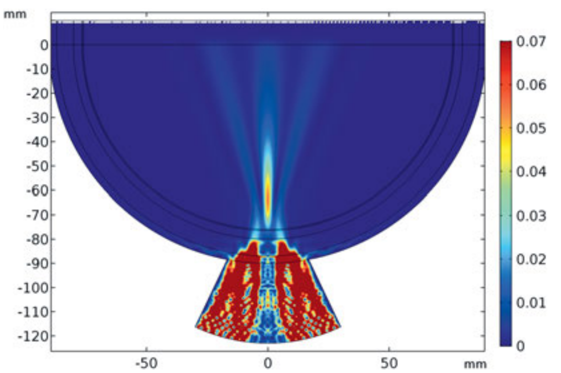

Fig. 1 COMSOL simulations of focused ultrasound showed a cigar shaped focus as described in the literature.

Results

Three out of five experiments showed similar focal lengths and penetration depths as simulated. The simulated focus radius showed an error of 12 - 16 % compared to the measured once.

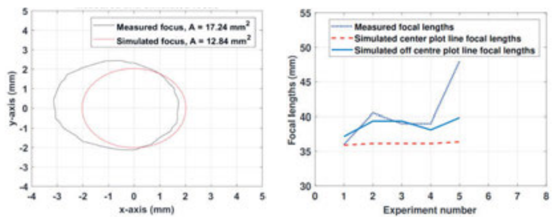

Fig. 2 Left: contour of the measured and simulated focus. Right: comparison of simulated and measured focal lengths.

Discussion

Although three results showed similar focal lengths and penetration depths, those results need to be questioned. Unfortunately, an electric failure caused unpredictable changing transducer supply voltages. Because of that, some experiments were conducted with higher ultrasound intensities. Furthermore, the acquisition system limited the number of data points that could be acquired with reasonable effort. On one side, the actual setup should be improved with an automated data acquisition system. On the other side, such study is a solid base for further investigations.

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Acknowledgements

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Optimization and Validation of a Fall Detection System through Trial

Simon Patrick Scheurer

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Examiners: Prof. Martin Kucera, Dr. Prabitha Urwyler

Introduction

Falls are one of the main reasons for accidents of elderly people [1]. From the age of 65, one in three people fall at least once a year [2]. Therefore falls are a current threat for health and quality of life [2]. An important factor for the severity of the consequences is the time period during which people lie on the ground [3]. To minimize the consequences of a fall through a short reaction time the motion sensor "AIDE-MOI" was developed. "AIDE-MOI" senses acceleration data and analyzes if a fall has occurred. In the case of a fall the sensor requests help automatically. The existing fall detection algorithm was developed by using motion data of young subjects. The aim of this study was first of all to improve and validate the existing fall detection algorithm and second of all to optimize the entire system through a trial with elderly people.

Materials and Methods

Twenty subjects (Mean: 86.25 years, SD: 6.656 years) with a high risk of fall (Morse > 65 points) were recruited from eight different elderly care homes. The trial consisted of recording the subjects' motion in their daily life over two months by using the system "AIDE-MOI". As shown in Fig. 1 the sensor is attached to the body and measures the acceleration (3-axis accelerometer, 100Hz, +/- 8g, 10 bit resolution). In case of a fall, the sensor sends out an alarm. The collected data was used to optimize the existing fall detection algorithm. The trial was then repeated with the revised algorithm and sensor. The second trial made it possible to evaluate the new algorithm. To improve the entire system, additional data which are wearing acceptance and the sensor's energy consumption was collected.

Fig. 1 [4] *The sensor was attached to the participant's body with an adhesive. The sensor was worn under the clothes, so it was not visible to third parties.*

Results

In a total of 140 weeks (Mean: 6, SD: 4.026 per subject) of daily motion data and 31 real falls of elderly people were recorded. Overall the sensitivity of the algorithm of fall detection improved from 27.3% to 80.0%. The specificity has been increased from 99.9957% to 99.9984%. This corresponds to an improvement from 0.43 false alarm per week and subject to 0.17 false alarms per week and subject. The sensitivity (p = .006) as well the specificity (p = 0.003) of the new algorithm was significant better compared to the old algorithm. The runtime of the sensor was improved from ten days to over twenty days and the saving of motion data during two and a half weeks was enabled.

	1.trial phase	2.trial phas
Trial duration in days	59	66
Number of participants	11*	18*
Number of collected data in weeks	67	73
Recorded falls	11	20
Recorded Non-Falls	29	12
TP (correctly classified falls)	3	16
TN (correctly classified non-falls)	675,350	735,840
FP (wrongly classified non-falls)	29	12
FN (wrongly classified falls)	8	4
Sensitivity	27.3%	80.0%
Specificity	99.9957%	99.9984%
Accuracy	99.9943%	99.9978%

** Several subjects were participating in the trial in the first and second phase. The total participation was limited to two months.*

Table. 1 Results of the trial phase one and two

Conclution

The algorithm could be significantly improved by using real recorded motion data of elderly people. The current state of development already allows the usage of the sensor in elderly care homes and in old age settlements. The system can be an important support especially for people with dementia, because they cannot use conventional emergency call system, which are buttons. The collected data can be analyzed further to improve the system "AIDE-MOI" and other fall detection devices.

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Computational Assessment of Blood Trauma due to Diastolic Flow through the Leaflet Clearance in the Lapeyre-Triflo Valve

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Introduction

Blood damage in the mechanical heart valves is believed to be correlated to non-physiological fluid stresses, which mandates anti-coagulation therapy for the recipients of such prostheses [1]. For the case of novel Lapeyre trileaflet valve, diastolic reverse flows through the clearance are likely to induce elevated levels of viscous shear stress, which can lead to chronic platelet activation and formation of blood clots. It remains unclear, however, what effect the leaflet clearance design may have on blood damage.

Methods

Herein, diastolic blood flows through different leaflet clearance designs are investigated by the means of computational fluid dynamics (CFD). Lagrangian particle trajectories are integrated within the Eulerian computed fields, to account for the stress history of several thousand particles which were seeded in regurgitating flow fields. The linear activation model of Bluestein et al. [2] is deployed to quantify the blood trauma in the leakage flow, which favors a cumulative representation of instantaneous shear stresses acting on the blood cells.

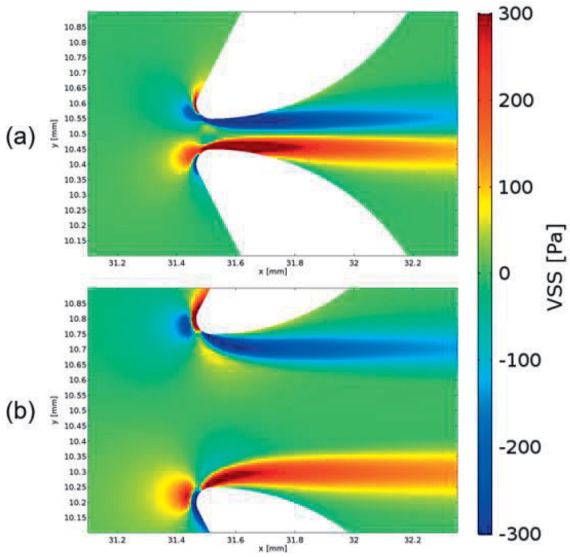

Fig. 1 Simulations demonstrate a critical viscous shear stress zone in the proximity of the leaflet clearance. (a) narrower clearance of 0.1 mm (b) wider clearance of 0.5 mm.

Results

Numerical simulations have shown that narrower clearances lead to higher shear stresses in the vicinity of the gap, when compared to larger designs (Fig. 1). Since fluid acceleration through the gap corresponds to less exposure times, averaged blood damage indices (BDI) are less critical than wider gap designs despite higher shear stresses (Fig. 2).

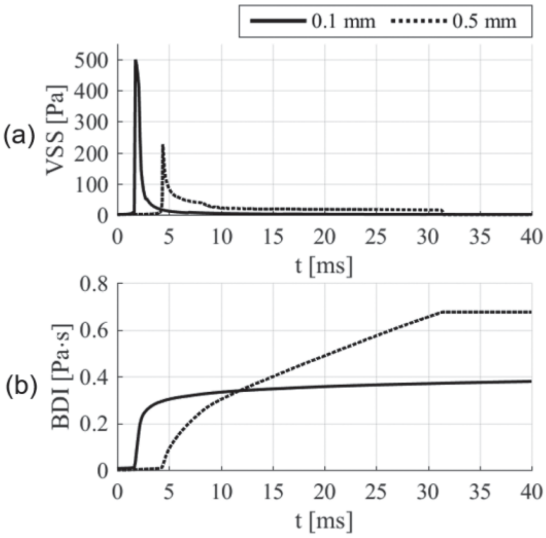

Fig. 2 (a) Shear stress history of the highest stressed Lagrangian particles and (b) the resulting blood damage index (BDI). The narrowest and widest clearances are in solid black and dotted black respectively.

Discussion

The cumulative blood damage is more dominating behind the valve, prior to the onset of jet instabilities and eventual breakdown. It is also illustrated, that the flow rate for smaller leaflet clearances is lower, compared to larger gaps, for the case of pressure-driven flow which was investigated in this study. The lower flow rate in the gap is found to contribute positively, in terms of blood damage indices, in reducing blood trauma.

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Segmentation of Peripheral Nerves in Thigh Magnetic Resonance Neurography Using Deep Learning

Yannick Soom

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University Hospital Bern (Inselspital), Institute of Diagnostic and Interventional Neuroradiology
Examiners: Prof. Dr. Mauricio Reyes, Dr. Olivier Scheidegger

Introduction

The peripheral nervous system (PNS) is susceptible to be affected by peripheral neuropathies, which are prevalent with 2.4 up to 14.8 %, rising with age, and can result in deficiencies or restrictions of sensory or motor abilities. Magnetic resonance neurography (MRN) has recently gained popularity as a complementary diagnostic tool for peripheral neuropathies. A problem, however, is that as of today MRN is qualitative because it is subjectively assessed by the radiologists. The use of MRN images to extract potential quantitative biomarkers, such as cross-sectional area and fascicular-to-nerve volume ratio has recently been proposed [1, 2]. However, a prerequisite for calculation of such biomarkers is the segmentation of the PNS, which is expensive and tedious work for radiologists, has reproducibility issues, and is not always clinically feasible. These issues motivated us to develop a fully-automatic deep learning-based approach to segment the sciatic nerve from thigh MRN images and to investigate the impact of 3-D context on the segmentation performance.

Materials and Methods

We retrospectively selected 52 thigh MRN cases separated into a patient cohort with diagnosed neuropathy and a healthy volunteer cohort. Furthermore, three ground truth segmentations of the sciatic nerve, manually delineated by experts, were available per MRN case. We developed and trained fully-convolutional neural networks (FCNN) with varying access to the 3-D context of the MRN images, and studied the impact of the 3-D context on the performance. Additionally, we developed and applied a post-processing method to reduce the false positive rates of the segmentations. Finally, we compared the performance of our best performing method to the human inter-rater variability obtained from the three manual ground truth segmentations.

Results

Tab. 1: Mean and standard deviation for the Dice coefficient (DICE) and 95th percentile Hausdorff distance (HD95) for our method (FCNN-GT) compared to the inter-rater performance (R-R).

Cohort	Comparison	DICE	HD95 (mm)
Patient	FCNN-GT	0.78 ± 0.12	**6.69 ± 10.33**
	R-R	**0.78 ± 0.09**	11.25 ± 19.01
Volunteer	FCNN-GT	**0.89 ± 0.04**	**0.66 ± 0.36**
	R-R	0.87 ± 0.03	0.70 ± 0.67

Access to 3-D context allowed for better segmentation performance. However, given the properties of our MRN images (4.40 mm slice distance, the most proximal and distal slices contain peripheral nerve), we obtained the best results with a mainly 2-D driven approach with some 3-D context. The applied post-processing removed false positive segmentations, which resulted in both a quantitative and qualitative better segmentation.

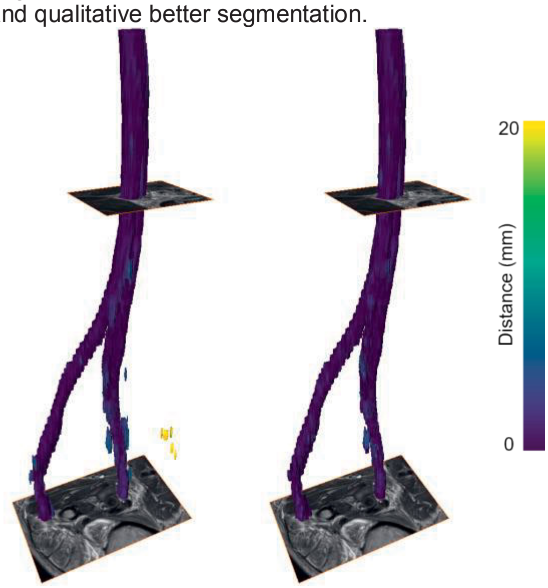

Fig. 1: 3-D segmentation renderings of the sciatic nerve of a patient subject before (left) and after (right) post-processing. The color indicates the surface-to-surface distance of the segmentation to the ground truth. Dice coefficients of 0.83 and 0.85 for the unprocessed and post-processed segmentation, respectively.

Discussion

Our method is an important step towards computer-assisted quantification of peripheral nerves. From a statistical and quantitative point of view, our proposed method achieves, or in the case of the Dice coefficient for the volunteer cohort surpasses, human-level segmentation performances. Moreover, our method comes with significant time gains compared to manual segmentation.

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Smartphone-based Perimetry for Fast and Low-cost Visual Field Acquisition

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Examiners: Prof. Dr. Raphael Sznitman, Serife S. Kucur

Introduction

Automated perimetry is widely used for the assessment of the visual function of the human eye. The high cost and size of perimetry machines restricts their access in developing countries. Further, there is a need for fast and accurate visual field (VF) testing algorithms. The aim of this thesis is to prove the concept of a smartphone-based perimetry system that performs fast and accurate VF measurements at an accessible price.

Materials and Methods

To acquire the goal of a low-cost system a smartphone application that runs perimetry tests was developed. Controlled testing conditions are established using a Google Daydream VR headset that keeps the phone display at a fixed distance to the tested eye.

Fast visual field acquisition is performed with the conventional testing strategy tendency-oriented perimetry (TOP). TOP is able to reduce testing time significantly but lacks of inaccuracies due to spatial interpolation of neighboring test locations. A deep learning approach was implemented to improve the results obtained with TOP in a postprocessing step. A denoising autoencoder is trained to reconstruct the spatial inaccuracies of TOP acquired visual fields.

Fig. 1 Hardware components of the new perimetry system: Samsung S8, Google Daydream VR headset and a wireless clicker. The latter is used for patient feedback during the visual field examination.

Results

The smartphone-based perimeter was validated by comparing VF measurements to data acquired with the Octopus900 perimeter. Small-scale trials show correlating results of both systems. Furthermore, the performance of the new strategy TOP+autoencoder was evaluated. The neural network was able to reconstruct details of the VF acquired with TOP in most cases. (Fig. 2).

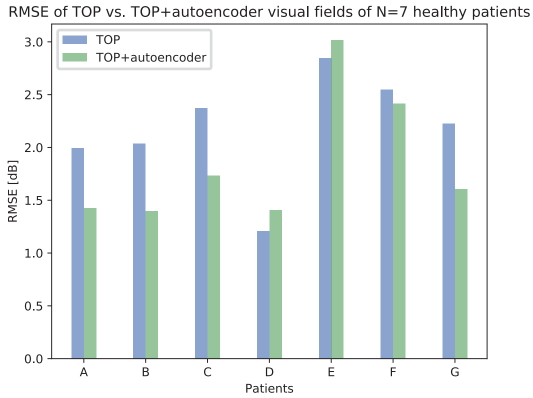

Fig. 2 Comparing root mean squared errors (RMSE) of both TOP and TOP+autoencoder strategies compared to acquired VFs using normal strategy approach (groundtruth). The accuracy of the VF could be improved with the autoencoder in most cases.

Discussion

The hardware components used in this project lower cost substantially compared to conventional perimeters. First results indicate that the TOP+autoencoder strategy may improve the quality of noisy VF measurements acquired with TOP.

The system may offer new possibilities in perimetry diagnosis and disease monitoring of patients with visual field loss.

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Sensor-Connected Glove for Hand Mobility Improvement

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Introduction

Hand injuries are frequent and can induce a loss of hand mobility. A reduction of the hand mobility has a direct impact on daily life. Tasks that were quickly and simply performed can become complicated or even impossible to achieve. Consistent and regular rehabilitation exercises are an easy and non-invasive way to improve the hand mobility [1].
Patient exercises are defined by specialists such as physiotherapists or occupational therapists. To improve their effectiveness, the exercises are personalized according to each patient's injury. The specialists regularly evaluate the progress of their patients and adapt the exercise according to the results. The aim of this work was to develop and characterize a prototype of a sensor-connected glove that automatically monitors the finger positions and movement and can thus support specialists and patients in the evaluations.

Materials and Methods

Specialists were interviewed to collect professionals requirements. An absolute orientation sensor using inertial movement units (IMU) was characterized to find out if it fits the requirements. An electronic system with a software was developed to handle sensors data. Multiple fixation systems were tested to create a wearable prototype and finally, a graphical user interface (GUI) was conceived to collect data and display them intuitively.

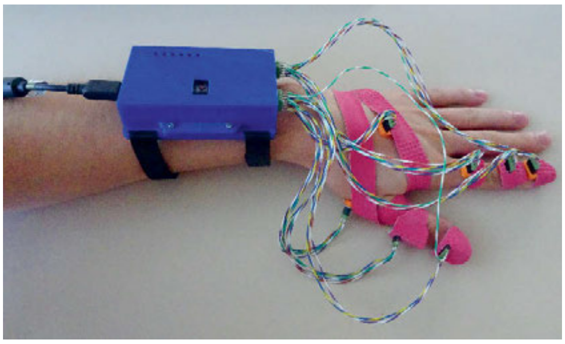

Fig. 1 Measurement system on the hand. The main electronic part is placed on the forearm where small auxiliary electrical modules are connected. The system shown on this figure can track the wrist, the thumb, and the index joints.

Results

The sensor was characterized and the error found of ±3° corresponds to similar results obtained by other users [2]. The final prototype allows to handle multiple sensors data and display them on the GUI in various formats. With appropriate conditions, the error on the measure of the joint angles lies in the error of the sensors.

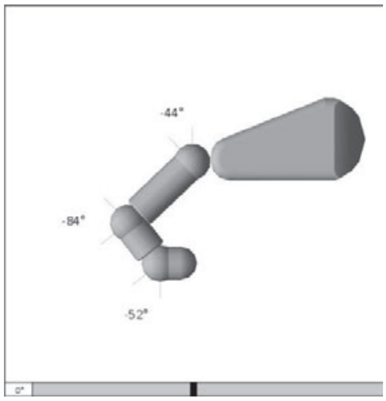

Fig. 2 Side view of the index taken from the graphical user interface. The 3D models and the values of the joints angles are displayed in real-time.

Discussion and Outlook

The results show the potential for hand joint tracking system using IMU sensors. The combination of the IMU technology and software allows the development of a lightweight and modular system. The graphical user interface demonstrates multiple functionalities to handle and display the patient's data. The fixation system works properly but the design should be reviewed as it is not convenient to put on. Moreover, additional work is needed to facilitate the necessary initial calibration and thus to improve the workflow which is indispensable for the use in practical routine.

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Development of an in silico and in vitro Dynamic Lung Microvasculature Model

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Introduction

The microvasculature of the lung is subject to both shear stress from blood flow and the rhythmic tensile forces associated with respiration. Endothelial cells transduce mechanical signals into a biological response, however the mechanisms by which this occurs remain widely unknown. Current state-of-the-art vascular models either ignore the influence cyclic stretch altogether or assume only a planar deformation, which are not physiologically representative of the lung. Towards this understanding, this project studies the effects of cyclic, three-dimensional stretch induced by respiration on the lung microvasculature remodeling within an in vitro microfluidic platform.

Materials and Methods

In vitro experiments were performed using a microfluidic platform fabricated by PDMS soft lithography. The platform is a multilayer system consisting of a PDMS membrane, pneumatic respiration chamber, and actuator well containing microvasculature in a fibrin gel. In vitro model parameters, such as membrane thickness and fibrin stiffness to obtain 8-10% linear strain, were optimized by mathematical simulation of the system in COMSOL Multiphysics 5.2.

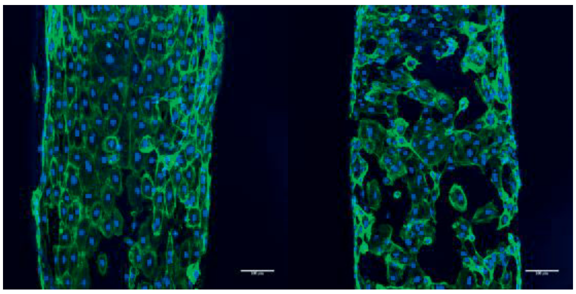

Fig. 1 Microvasculature imaged at 10x magnification, highlighting the increased cellular alignment and smaller gap sizes for CS samples. Left: Microvasculature after 72 hours of cyclic stretch. Right: Microvasculature cultured in static conditions. Actin shown in green and nuclei in blue.

Effect of three-dimensional cyclic stretch on cell viability, microvasculature shape changes, morphology (Fig. 1), and permeability were examined via immunostaining and fluorescent dye perfusion.

Results

Compared to static conditions, samples exposed to cyclic stretch (CS) resulted in significant differences in the structure of the microvasculature. CS microvasculature had significantly lower permeability coefficients, as shown in Fig. 2, which were supported by correspondingly smaller gap sizes in the vessel walls. Microvasculature under CS also experienced a distinct alignment of cells along the length of the vessels, as well as a permanent enlargement of the channel shape.

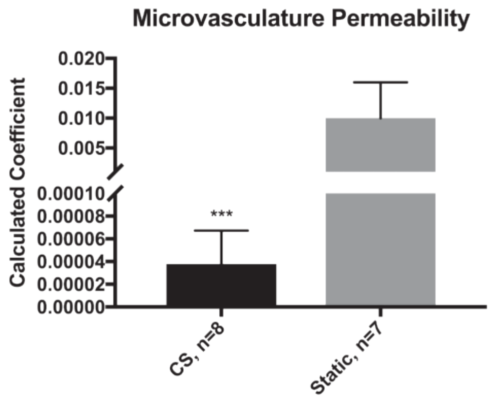

Fig. 2 Permeability coefficients for microvasculature cultured in static or cyclic stretch conditions. Coefficients were calculated by loading RITC dye into the microvasculature and measuring changes in fluorescent intensity over time.

Discussion

The results of this thesis suggest the novel platform provides an environment closer to physiological conditions for studying the formation of lung microvasculature. The model demonstrated the ability to culture perfusable microvasculature in vitro, while incorporating the cyclic stretch of the lung environment.

Future investigation with this model may lead to deeper knowledge on the physiological and pathological mechanisms of mechantransduction, as well as to novel therapeutic developments in the treatment of lung related disease.

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Signal Fusion for the Determination of Higher Neurological Functions in Preterm Infants

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Introduction

Worldwide approximately 15 million babies are born preterm and this number is increasing each year, leading to strong needs of improvement in the Neonatal Intensive Care Unit (NICU). First of all, preterm infants suffer from immature physiological functions, such as the inability to swallow and breath at the same time. Being able to detect the moment of coordination between swallowing and respiration would be a crucial indicator to release preterm infants from the NICU, thus allowing nurses to take care of patients in need. Esophageal ECG (eECG) recording is a novel approach which would allow to recognize the ability from the preterm infant to coordinate swallowing and breathing correctly. Furthermore, actual acquisition of ECG data and respiration rate are made via electrodes placed on the small body surface of neonates, which can cause irritation when the preterm infant is already fragile. Since a gastric tube is often needed in preterm infant, advantage of eECG data acquisition out of the gastric tube would be to stop the acquisition of ECG data from the body surface in near future. The aim of this project is to extract respiration waves and to detect peristalsis waves out of the recorded esophageal signals from a previous clinical trial study.

Materials and Methods

Respiration extraction

The method of principal component analysis (PCA) with singular value decomposition (SVD) is used in order to extract respiration waves from esophageal signals. The signal extracted $\hat{d}_k$ is computed such that

$$\{\hat{d}_k, \chi\} = \underset{d_k, \chi}{\operatorname{argmin}} \sum_{k=1}^{K} \sum_{m=1}^{M} (y_k^{(m)} - \chi^{(m)} d_k)^2,$$

Which, based on experience, is highly related to the respiration movements.

Peristalsis wave detection

The method of the state space models [1] was used to detect the beginning of the peristalsis waves. The idea is to local fit two continuous line segments to each channel, whereof the left sided line is forced to be horizontal, while the slope of the right sided signal model line is free. This is based on observation that it corresponds better to the pattern of a peristalsis wave.

Results

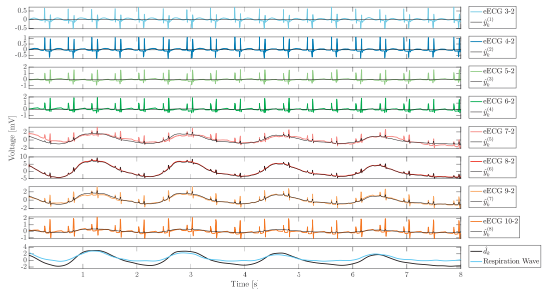

Fig. 1 Application of the extraction of the respiration wave with PCA. 8 esophageal signals, the extracted signal $\hat{d}_k$ and, in addition, respiration wave from standard monitoring as reference

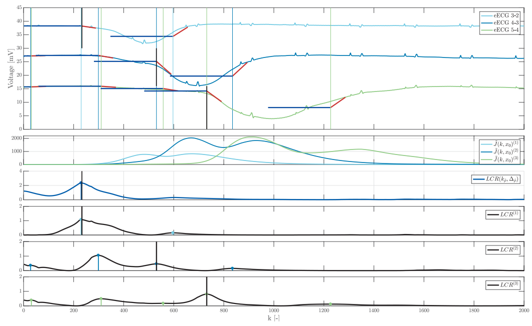

Fig. 2 Application of the state space model in real data where the vertical thick black lines indicate the beginning of the peristalsis wave.

Discussion

The extraction of the respiration wave from 8 esophageal channels is possible, but primarily during a non-feeding period. Concerning the detection of the peristalsis waves, obtaining acceptable results was challenging du to the significant variance of the shape of the pertistalsis wave over different period of time. Overlaping of respiration waves and EMG signal with peristalsis waves make the task of the detection even harder.

References

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Motor Learning Studies with Novel Error Modulating Strategies

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Introduction

The modern paradigm in motor rehabilitation following impairment due to brain injury (e.g. stroke), is the use of robotic devices along with manual therapy. However, how a robot should intervene physically with subjects in order to maximize motor learning and recovery is still an open question. A recently developed approach, amplifying errors, has been proposed to have a great potential to enhance learning, effort, and attention; but may also reduce satisfaction and motivation [1]. Within this project, we aim to explore adaptive controllers that can modulate errors inside a manifold to make experienced errors more consistent, while keeping the motivation high in order to increase the learning rate. We hypothesize that the way the error is modulated affects the rate and the amount of motor learning.

Materials and Methods

A motor task that consisted on swinging a pendulum through obstacles was developed using Unity (v2018.1, Unity Technologies) (Fig. 1). The aim of the game was to move the pendulum to reduce errors defined as distance between the pendulum's red ball and red lines on obstacles upon passing. An end-effector robot (Delta.3, Force Dimension) was employed as haptic interface to control the position of the pendulum (blue ball in Fig. 1). Two control strategies that haptically or visually modulate errors were developed, and a feasibility study was performed with the purpose of testing the efficacy of the control strategies at modulating errors and comparing their effects on learning. The first control strategy makes a haptic intervention on the pendulum by applying forces generated by a model predictive control (MPC) algorithm. The second strategy applies a visual intervention on the pendulum that reduces errors, leaving the haptic feedback unchanged.

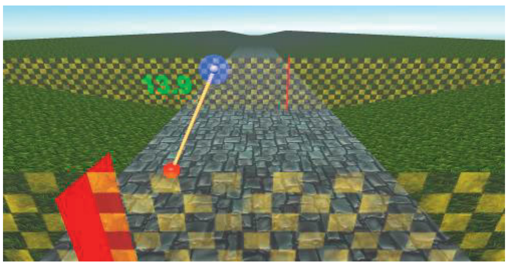

Figure 1. The pendulum task. The environment moves with constant speed. There are obstacles on the path (yellow horizontal walls). The robotic end-effector is matched to the blue extremity of the pendulum, while the opposite red extremity is free to swing. The error related to the last obstacle crossed is shown in green.

Seven healthy participants (mean age 26, SD=3.4) took part in the feasibility study. They were randomly assigned to one of the two strategies. The experimental protocol was divided into baseline, training (with control strategies active but for catch trials disabled), and retention. A linearly decreasing manifold was selected for the study to maintain subjects' motivation. Outcome measures include learning amount (i.e. error reduction after training) and self-reported motivation.

Results

The two developed control strategies constrained errors inside the selected manifold with a average accuracy of 11mm. All participants reduced errors significantly after training, (one-sided sign-rank test, p=0.039). No significant differences were observed for outcome error measures between groups, neither in motivation. For both groups, a stable motivation level was observed over time.

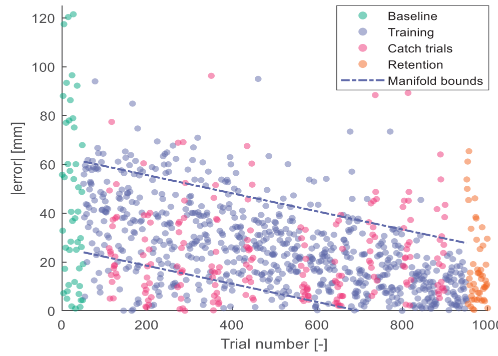

Figure 2. Performance of a participant assigned to the MPC haptic group. Dots represent errors done during baseline (green), training in purple (with catch trials in pink), and retention (orange). Error during training is constrained to a linear decreasing function (purple dotted lines show 80% confidence interval bounds).

Discussion

Learning to reduce errors by swinging a pendulum is a complex yet entertaining motor task. The linear decreasing manifold was able to maintain motivation throughout the task, and successfully enforced errors during the training phase. However, which shape the manifold should have, and how it should adapt based on subject's performance and motivation needs to be further investigated.

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In Vitro Investigation of Mechanical and Bioprosthetic Aortic Valve Leaflet Kinematics with Dual-Camera Stereo Photogrammetry

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Examiners: Prof. Dr. Dominik Obrist, MSc Leonardo Pietrasanta

Introduction

Beside heart attacks and strokes, valvular heart diseases (VHD), are an important cause of increasing morbidity and mortality in our society. If needed, diseased aortic heart valves are replaced with a aortic heart valve prosthesis. The structural valve deterioration and the haemodynamic performance of artificial aortic valves are strictly linked to the valve kinematics. Thus, understanding the valve kinematics, would help to improve their long-term performance.

Materials and Methods

The objective of this master thesis was to develop a method to investigate the three-dimensional (3D) leaflet kinematics of a mechanical Lapeyre-Triflo FURTIVA valve (LTV) and a bioprosthetic Edwards INTUITY valve (EIV) with dual-camera stereo photogrammetry. Therefore, an experimental setup was designed, which enabled simultaneous image acquisition of a marked valve leaflet during one heartbeat through the usage of two high speed cameras. Following the image acquisition, image processing was performed in order to conduct the triangulation, where the 3D coordinates were computed, based on matching points in the stereo images. Based on the 3D coordinates, the leaflet was reconstructed and the kinematics analysed. This processing was done using the open source image processing program Fiji (ImageJ) and MATLAB. To prove the working principle of the developed method, experiments were performed, using an in vitro heart duplicator (Figure 1). Furthermore, an error estimation was conducted to access the overall accuracy of the method.

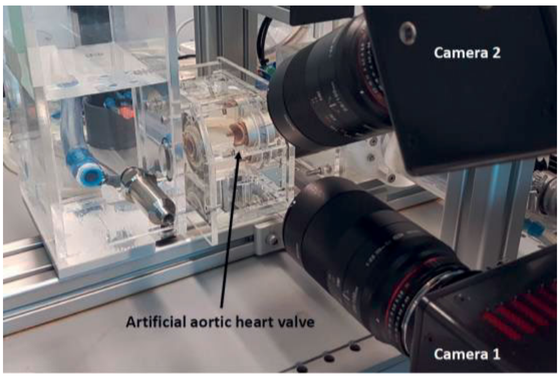

Fig. 1 Experimental setup with two high speed cameras (Photron Fastcam Mini AX100) and the bioprosthetic Edwards INTUITY valve (EIV).

Results

Based on the stereo images, the leaflets of both valves were reconstructed in 3D (Figure 2). Thus, a quantitative analysis of the leaflet kinematics could be performed by computing the position, velocity, and acceleration magnitude. The estimated overall error of the method was 0.0185 mm.

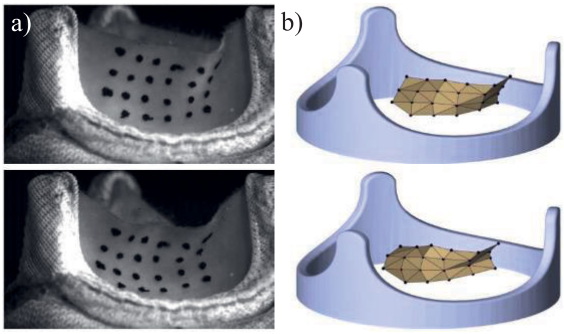

Fig. 2 3D reconstructed leaflet of the EIV at the onset of valve closure. (a) Acquired raw images of camera 1. (b) Corresponding 3D leaflet reconstructions.

Discussion

The developed dual-camera stereo photogrammetry method enabled an accurate 3D leaflet reconstruction and kinematic analysis for both valves. However, the 3D reconstruction depended on the markers applied to the leaflet surface. Disappearing markers therefore led to a gap in the 3D reconstruction and a loss of kinematic information. Marker disappearance occurred for the EIV during valve opening, where the leaflet bent strongly and a few markers vanished for approximately 5 ms. Nevertheless, the reconstructed 3D movement of the leaflet, revealed explicable and realistic kinematic results, when compared to raw images and literature. Furthermore, the limiting factor in terms of error, was the camera resolution.

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Acknowledgements

I thank the Cardiovascular Engineering group, especially Leonardo Pietrasanta and Prof. Dr. Dominik Obrist for their support.

Mutual Validation of a 3D Bone Damage Label with MicroFE Analysis

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Introduction

The occurrence of microdamage in trabecular bone is essential for understanding vertebral fractures and may become helpful for improving treatment of patients with osteoporosis [1]. Therefore, the aim of this thesis is a mutual validation of microdamage localization and intensity between a novel staining protocol and non-linear micro-finite element analysis (mFEA). For this purpose, an overloading experiment of bone sections with a trabecular core was conducted and microdamage evaluated with both experimental and computational methods.

Materials and Methods

Twelve porcine costal sections of 4 mm thickness with an outer cortical shell for proper load transfer, and an inner trabecular core were prepared. Existing and induced bone matrix microdamage was stained under vacuum with a $BaSO_4$ solution before and after mechanical overloading in order to account for preexisting damage and non-damage specific staining. A three-step microCT scanning procedure was applied to assess the intact morphology and the $BaSO_4$ distributions in the samples before and after mechanical overloading. Ten out of twelve samples were successfully compressed under displacement control along a diameter of the bone section until maximal force was reached. The apparent strain was tracked along the loading axis with a video extensometer. The intact CT scans were segmented to generate a non-linear microFE model with homogeneous tissue properties and boundary conditions reproducing the experiment. Reaction force and microdamage distribution were computed up to the experimental displacement at maximal force with the parFEAP software. Qualitative and quantitative analyses of the experimental and computed spatial distributions of damage were performed. The respective images depicting microdamage were compared side to side and the spatial correlation was quantified with a confusion matrix. Finally, the microdamage intensities were investigated by a direct voxel to voxel comparison.

Results

Qualitatively, microdamage location identified by $BaSO_4$ staining coincided only partially with the microdamage location computed by mFEA. However, the spatial correspondence of micro-damage was significantly improved with respect to previous studies. AUC values of up to 0.72 were reached, which indicates a fair categorization for predicted damage/no damage regions. In agreement with the qualitative analysis, the direct comparison between the measured and the computed microdamage intensity showed a weak but positive and significant correlation ($p < 0.001$) for all the tested samples (Fig. 1).

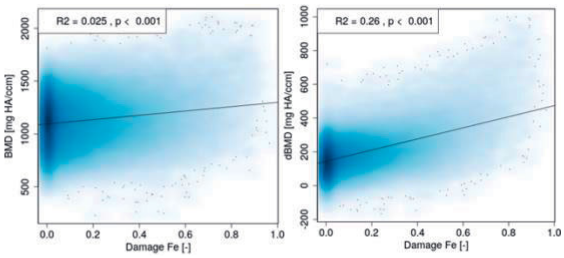

Fig.1 Direct voxel-wise comparison of the microFE and stained-compression-test BMD (left) and to the subtraction image dBMD (right).

Discussion

Significant improvements were achieved for the experimental versus computational microdamage correspondence by accounting for preexisting damage and non-damage specific staining. The current method could be further improved by increasing the staining time and reducing boundary effects during mechanical testing. Finally, noise of the image registration seems to affect the final outcome as well and should be minimized in future work.

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Acknowledgements

I am grateful for the support of Philippe Zysset, Benjamin Voumard, Michael Indermaur and Urs Rohrer.

Inkjet 3D Printing of Polycaprolactone for Tissue Engineered Vascular Grafts

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Examiners: PD Dr. Marie-Noelle Giraud, Prof. Dr. Olivier Guenat

Introduction

Synthetic vascular grafts are an option in the treatment of vascular disease cases where no healthy autologous grafts are available, but their thrombogenicity and low patency rate, especially for vessels with diameters inferior to 6 mm, remain a challenge. Alternatives, such as tissue-engineered blood grafts (TEBGs) and their fabrication through 3D printing have gained increasing interest. Recently, the feasibility of a novel approach for polymer deposition, by jetting solvent-based polycaprolactone (PCL) inks, a biodegradable material that withstands large deformations, through a 16-nozzle inkjet printhead, was demonstrated. This thesis aimed to enable the manufacturing of TEBGs out of PCL through an industrial inkjet featuring hundreds of nozzles in parallel.

Materials and Methods

The first specific goal was to develop an inkjet 3D printer and optimize the ink formulation as well as the printing parameters and process to enable the engineering of TEBGs. The second specific goal was to investigate the chemical composition and biocompatibility of PCL, after dissolution in 1,4-dioxane and urea treatment. Biocompatibility experiments were led by evaluating the proliferation of HUVECs in culture medium-based polymer supernatants and measuring the viability through LIVE/DEAD fluorescent assays on polymer patches. The chemical composition of the polymer and supernatants was analyzed through DSC and FTIR.

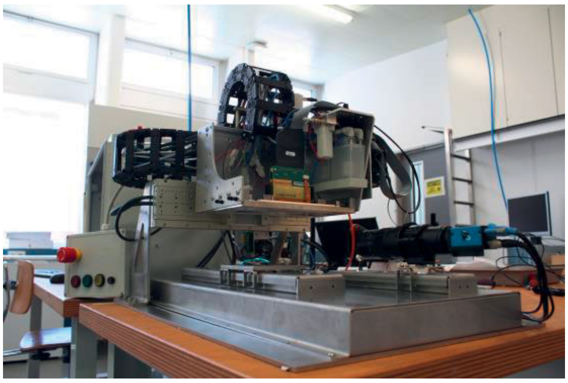

Fig. 1 Inkjet printing platform with dropwatching and a 256-nozzle industrial inkjet printhead implemented

A 3D printer equipped with a 256-nozzle industrial inkjet printhead and suitable for work in sterile conditions was developed. Dropwatching was implemented for drop formation visualization and enabled the computation of drop volume and velocity. Stable jetting was achieved by increasing the polymer concentration in the ink and tuning the waveform applied to the printhead. The printing resolution was increased from 100dpi to 400dpi by multi-pass to achieve the deposition of continuous polymer films, and an automated cleaning process was implemented.

Results

No traces of chemical contamination of the PCL were found through DSC and FTIR analyzes. The use of dioxane as a solvent for PCL did not induce a biological response while enabling the formulation of inks optimal for drop formation. Up to 30 layers of polymer were printed on top of each other in a single process, for a total thickness of 112µm, with structures as thin as one drop.

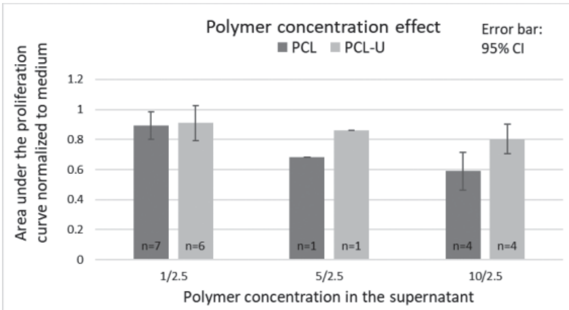

Fig. 2 Effect of the urea treatment of PCL on HUVEC proliferation as a function of the polymer concentration in the supernatant.

Discussion

The feasibility of PCL 3D printing with high-throughput industrial inkjet was demonstrated, but further improvements on the stability of the printing process are needed to achieve dimensions relevant to TEBGs. The biocompatibility of PCL was improved by urea treatment and prolonged exposure to culture medium prior to cell seeding.

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Optimized Path Planning to enable Robotic Surgical Milling Operations

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Introduction

Surgical milling is one of the most frequent tasks during lateral skull base surgery. Today, surgeons execute this with a handheld tool, using anatomical landmarks for navigation. This bone removal process during surgeries takes multiple hours, because of the vicinity to vital anatomical structures, which have an essential function, and must not be injured under any circumstances. Robotic milling of access cavities and implant beds is proposed to alleviate the surgeons' workloads, such that they can concentrate on more critical parts of the surgery. Additional benefits include provision of safety margins to vital anatomical structures through an image-guided approach and smaller milled volumes because landmarks are not necessarily exposed. A surgical robot requires information on the milling path, the type and size of the used burr, the allowed velocities and more to be able to perform the milling work. Before robotic milling can be started, the surgery has to be planned with preoperative medical images, which involves defining general anatomical areas to be removed and/or positioning device beds relative to the patient's anatomy. Hence this work focuses on the computer based planning of robotic surgical milling operations.

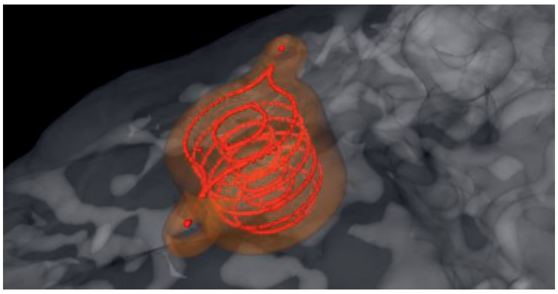

Fig. 1 3D generated milling path for a Bonebridge implant in the human mastoid bone

Materials and Methods

A software was developed to allow for planning of cavity milling for bone conduction hearing aids. This includes annotation and 3D reconstruction of relevant anatomical structures, the virtual placement of an implant using an intuitive 3D approach and the generation of robot's mill path using a custom-developed path-planning algorithm, based on a contour-parallel approach (Vatti 1992 and Minetto et al. 2017).

Results

In an experiment, the whole process of a robotic milling task was executed. The procedure started by planning the intervention using the developed software, which generated the desired milling path and ended with the successful milling of the implant socket.

Fig. 2 The robot performs the milling task based on the planning with the developed software.

Conclusion

A software was developed that surgeons can use for the planning of robotic milling surgeries, which was tested in an experiment where the generated milling path was successfully milled into a temporal bone phantom. However, the current status is only usable for milling implant but can be further extended for other implants.

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Development of a New Breathable Lung Alveoli on a Chip Based on a Biological Membrane

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Examiners: Prof. Dr. Olivier Guenat, Pauline Zamprogno

Introduction

One of the major challenges in pharmaceutical industry consists to predict the effects of a drug on humans based on data acquired from in vitro systems and in vivo animal models.

If animal models are physiological relevant, the interspecies differences make difficult to draw a conclusion adapted for human. Standard in vitro models, on the other hand, fail to mimic the complexity of a human organ, notably its cellular microenvironment. Therefore, more complex human in vitro models were developed – so called organs on chip. They are microsystems which tend to reproduce a human organ at reduce scale. In this field, the OOC-Technologies group have developed a new static lung alveoli in vitro model based on a biological membrane. They reproduce the extracellular matrix composition thanks to a membrane made of collagen and elastin (CE-membrane).

The aims of this master thesis were to further develop the model by mimicking the dynamic microenvironment of the air-blood barrier. In order to achieve this goal, a new chip was designed to cyclically stretch the membrane at a physiological level. Moreover, the mechanical properties of the membrane and the impact of long term breathing were investigated. Finally, a first dynamic cellular model was developed.

Materials and Methods

The collagen-elastin membrane was supported by a gold mesh in order to mimic the structure and the dimension of the alveoli (figure 1). Several production and assembling techniques were used. The deflection measurement was based on the height difference generated by the injection of negative pressure to the system. Primary human alveolar epithelial cells (hAEpC) were seeded on the chips to reproduce the composition of the lung alveoli epithelium. The biocompatibility of the membrane and the cells behavior were analyzed by immunofluorescence.

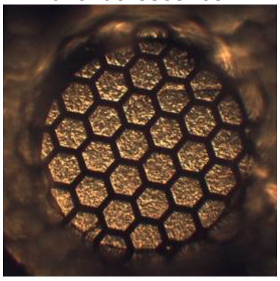

Figure 1: Reproduction of an array of lung extracellular matrix with a collagen-elastin membrane supported by a gold mesh.

Results

The redesign of the chip was successful. The thickness of the CE membrane was 8.6 ± 3.5 um. It's lower than the 10 um membrane used for most of the standard in vitro model. The new fabrication technique is easy, reproducible and reliable. Henceforth, all chips produced are sealed while only half of them were usable with the old production method. The model was able to breath for eight hours without any membrane rupture or leakage. The membrane could be deflected with a linear strain of 10.2 ± 2.0 %. This stress could be adapted with the pressure (figure 2a). Human primary cells were successfully cultured. After five days, a confluent layer was formed and they were deflected. Some cells still express tight junction marker after the breathing (figure 2b).

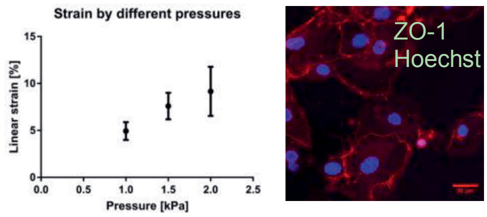

Figure 2: Dynamic air-blood barrier model. (a) Impact of pressure on biological membrane (without cells); (b) Tight junction of hAEpC (red: tight junctions, blue: nuclei), after 8h of breathing, day 6.

Discussion

The model developed make possible to deflect a biological membrane with a linear strain of 10.2 ± 2.0 %. This value is physiologically relevant as, according to the literature, the linear strain in the alveoli ranges from 4 to 12% [1]. As far as we know, it is the first biological membrane in a lung on chip which is able to mimic this 3D cyclic dynamic microenvironment.

References

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In Vitro Diagnostic / Interventional Method for Assessing and Quantifying the Effects of No-Reflow Phenomenon in Coronary Models

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Introduction

The Controlled Flow Infusion (CoFI™) system (CorFlow Therapeutics AG, Baar, Switzerland) is the first combined diagnostic and therapeutic medical device for diagnosing and treating microvascular obstruction (MVO[1]) after the revascularization of the coronary arteries. The aim of this thesis was to develop and optimize an in-vitro setup of a coronary artery network with MVO and to test the CoFI devices in this model.

Materials and Methods

A lumped coronary model (LCM) imitating the pressure and flow conditions in the left anterior descending (LAD) coronary artery with and without MVO was established. It consists of several elements, namely a hydraulic resistance, an element for the pumping effect of the intramyocardial blood vessels, a component for the effect of cross-section adaption of blood vessels by pressure change and the elasticity of the blood vessels. Collaterals which bypass the CoFI device can be added. By connecting an existing left heart flow loop, the pressure conditions present in the aortic root are introduced as boundary conditions to the setup. Additionally, a micro fluidic chip (MCM), which gives the possibility to microscopically examine the flow in the coronary arteries was added to the LCM.

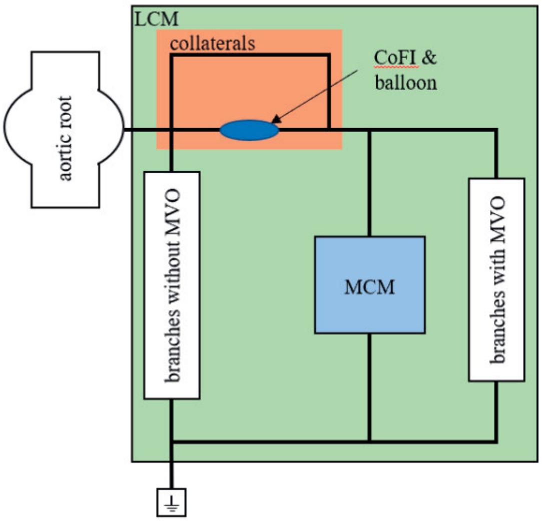

Fig 1 Entire setup with LCM, MCM, collateral and the CoFI device

The CoFI device itself consists of a catheter which is placed in the coronary artery proximal to the possibly affected area. The blood stream is interrupted with an integrated inflatable balloon. A peristaltic pump is used to induce a constant flow distal to the balloon. The pressure response of this infusion is measured with a low-drift optical pressure guidewire which is placed distal to the balloon.

Results

In-vitro pressure-flow relationships were acquired with the CoFI device and compared to animal data. The presence of MVOs strongly changes the dependence of coronary pressure on flow rates. This effect is dependent on the severity of the obstruction. The presence of collateral connections bypassing the balloon also influences the quantities extracted from diagnostic sequences.

Discussion

The coronary benchtop model successfully reproduces the hemodynamic behavior observed in porcine pre-clinical models. The model was used to test the CoFI device sensitivity to different degrees of MVO and assess the influence of collaterals. First observations in the MCM showed the feasibility of the method to test the therapeutic stage of the CoFI system and further optimization is necessary.

References

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