Bern University
of Applied Sciences

UNIVERSITÄT
BERN

Master Biomedical Engineering

Annual Report 2014

MASTER OF SCIENCE IN BIOMEDICAL ENGINEERING

Contents

Introduction

This year has seen the highest number of graduations (47) in the history of this Master's Program in Biomedical Engineering. I would like to acknowledge here Prof. Lutz Nolte who had the vision and launched this study program in 2006 within the Faculty of Medicine of our University in cooperation with the University of Applied Sciences of Bern, a unique configuration in Switzerland.

The new curriculum designed and accepted by the faculty in the previous year was put into practice and well received by the students since a majority of them switched from the old to the new one in March. In particular, a new course in Ethics in Biomedical Engineering represents a valuable addition to the complementary skills.

The Master in Biomedical Engineering was modeled into the Kernsystem Lehre (KSL), the university-wide study administration software that allows the study coordination to manage all course and exam registrations and gives the students permanent access to their credit status. Despite a few delays and preliminary difficulties, the software proves to be user friendly, fits our needs, and helps improve our internal processes.

The BME day offered a brilliant microsurgical demonstration by the clinic of neurosurgery of the Inselspital and was again a success confirmed by the participants from industry, clinics and academia. I would also like to thank here the companies that have supported us over the years and the study coordination for the seamless organization.

The improvements of the new curriculum confirmed by the independent student evaluation brings the program to an unreached level in selection of the themes, quality of the training and manner with students. It suggests also that the degree of complexity of the material is adequate. This enjoyable state of affairs will not prevent us from continuously questioning our materials or methods and keep our eyes on the evolution of the field as well as the potential of new learning technologies.

Finally, I would like to express my full recognition to the teachers of the program who are the ones who spend the numerous preparation hours to realize our updated mission statement: "train multidisciplinary engineers to deliver scientifically-founded and sustainable solutions for biomedical problems in research and industry".

Please find enclosed a glance into the substance and outcome of our daily work!

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

BME First Year Students 2014, University of Bern.
Photo: Adrian Moser

Structure of Courses in the Master's Program

The Curriculum
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 the clarity and reduce 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 new module called "Complementary Skills" is replacing the former module "Unrestricted Electives". In addition, the list of mandatory courses in both basic and major modules was revised.

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.

Basic Modules
The basic modules provide the students with the necessary background to be able to fully understand the complex subject matter in the specialized courses. All students with an engineering background (for all 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 courses belong to this group, whereas in the second and third semester, the courses from the basic modules make up for approximately 30% of the credits.

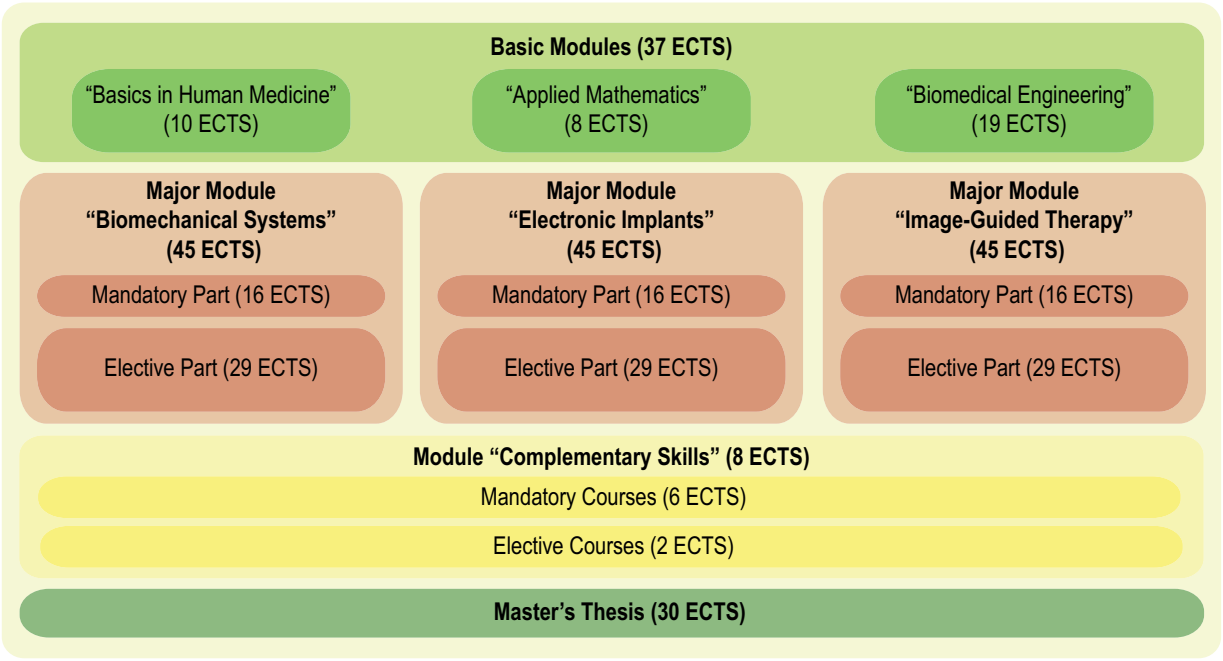
Major Modules
The choice of one of three major modules Biomechanical Systems, Electronic Implants, or Image-Guided Therapy after the first semester constitutes the first opportunity for specialization. The former major module "Musculoskeletal System" has been adapted and renamed "Biomechanical Systems".

Approximately one third of the major modules consists of mandatory courses. In the elective part of the major module, the student is allowed to select any course from the list of courses in the master's program, providing 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 is 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 report, 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

- Biological Principles of Human Medicine
- Biomedical Sensors
- Biomedical Acoustics
- Biomedical Instrumentation
- Biomedical Laser Applications
- Biomedical Signal Processing and Analysis
- BioMicrofluidics
- Cardiovascular Technology
- Clinical Applications of Image-Guided Therapy
- Computer Assisted Surgery
- Computer Graphics
- Computer Vision
- Continuum Mechanics
- Cutting Edge Microscopy
- Design of Biomechanical Systems
- Engineering Mechanics
- Ethics in Biomedical Engineering
- Fluid Mechanics
- Finite Element Analysis I
- Finite Element Analysis II
- Functional Anatomy of the Locomotor Apparatus
- Image-Guided Therapy Lab
- Innovation Management
- Intelligent Implants and Surgical Instruments
- Introduction to Clinical Epidemiology and Health Technology Assessment
- Introduction to Digital Logic
- Introduction to Medical Statistics
- 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 Robotics
- Microsystems Engineering
- Modeling and Simulation
- Numerical Methods
- Ophthalmic Technologies
- Osteology
- Physiology (German)
- Principles of Medical Imaging
- Programming in C++
- Programming of Microcontrollers
- Regenerative Dentistry for Biomedical Engineering
- Regulatory Affairs and Patents
- Rehabilitation Technology
- Scientific Writing in Biomedical Engineering
- Technology and Diabetes Management
- Tissue Biomechanics
- Tissue Biomechanics Lab
- Tissue Engineering
- Tissue Engineering - Practical Course
- Wireless Communication for Medical Devices

Major Modules

Biomechanical Systems

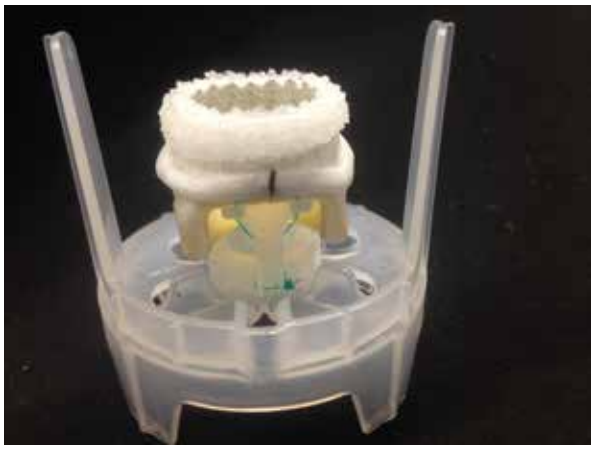
Prof. Dr. Philippe Zysset

The 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. Cardiovascular diseases, musculoskeletal injuries and pathologies are the most 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 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 mechanobiology. 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 cardiology, vessel surgery, orthopaedics, dentistry, rehabilitation and sports sciences.

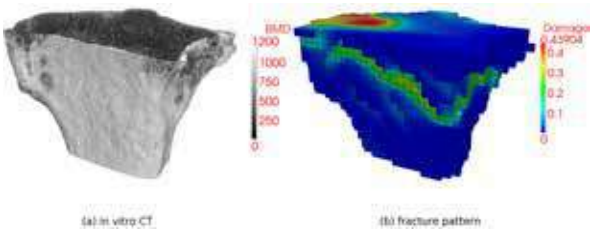
The mandatory courses in this module provide the student with fundamental knowledge of fluid and solid mechanics, tissue engineering, tissue biomechanics and finite element analysis. This provides an overview of the functional adaptation of the cardiovascular or musculoskeletal system to the demands 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 thesis projects include the analysis of rotodynamic blood pumps, the development of a monitoring tool for screw insertion in bone or the investigation of collagen scaffolds towards anterior cruciate ligament repair.

Career prospects are numerous. Many students proceed to further post-graduate education and research, pursuing doctoral research in the fields of biomechanics, tissue engineering 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 continue to experience growth, therefore driving a 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.



Edwards Intuity bioprosthetic valve system for aortic valve replacement.



Homogenized non-linear finite element analysis of the distal radius (right) based on high resolution peripheral computed tomography (left).

Electronic Implants

Prof. Dr. Volker M. Koch

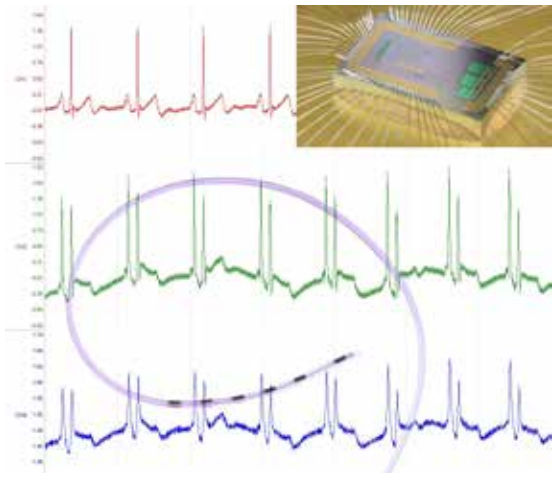
Electronic implants are devices like cardiac pacemakers and cochlear implants. Due to miniaturization and other developments, many new applications become feasible and this exciting area is growing rapidly. For example, cochlear implants provide already approximately more than 320'000 people worldwide 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 obesity, depression, incontinence, hydrocephalus, pain, paraplegia, and joint diseases.

In this module, students will learn about the basics of electronic implants. This includes: signal processing and analysis, low-power microelectronics, wireless communications, and MEMS technology. Application-oriented elective courses are also taught, e.g., diabetes management, biomedical acoustics, and biomedical sensors.

Since the development and manufacturing of electronic implants is highly complex and since it involves many different disciplines, it is not the goal of this major that students are able to develop an electronic implant on their own but rather to be able to work successfully in a project team that develops electronic implants.

Students may already apply their knowledge as a part-time assistant in a laboratory 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.



Long-term esophageal ECG research project at HuCE-microLab: surface and esophageal ECG signals in comparison, low-power esophageal recording chip to be integrated into catheter.

Major Modules

Image-Guided Therapy

Prof. Dr. Stefan Weber

Image-Guided Therapy refers to the concept of guiding medical procedures and interventions through perceiving and viewing of medical image data, possibly extended by using stereotactic tracking systems. Medical imaging typically relates to a great variety of modalities ranging from 2D fluoroscopy and ultrasound to 3D computed tomography and magnet-resonance imaging, possibly extended to complex 4D time series and enhanced with functional information (PET, SPECT). Guidance is realized by various means of determination of the spatial instrument-to-patient relationship and by suitable visualizations. 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 be introduced to the fundamentals of the above-mentioned clinical and technical aspects of image-guided therapy. They will receive an overview of currently applied clinical standards as well as an overview of latest advancements in research (check out the recently introduced course on Clinical applications of IGT as well as the IGT Lab). Successful students will be able to develop novel clinic-technological applications for complex medical procedures as well as improve existing approaches to IGT. This will enable further careers both in the industrial and academic sector.

Mandatory courses of this module are concerned with the fundamentals of Signal and Image Processing and Medical Image Analysis. Furthermore, fundamental aspects of stereotactic image guidance, tracking, patient-to-image registration and basic clinical applications are taught in the course Computer-Assisted Surgery. Recent trends and fundamental aspects in surgical robot technology, minimally invasive procedures and its applications within IGT are introduced in the course Medical Robotics. Additional elective courses extend students competencies in related areas such as computer graphics, pattern recognition, machine learning, and regulatory affairs.

Laparoscopic liver surgery guided by endoscopic visualisation (middle screen) and co-registered 3D model of the liver anatomy (right screen) (Photo © ARTORG Center Bern and Inselspital Bern).

New Courses

Cardiovascular Technology

Prof. Dr. Dominik Obrist

Cardiovascular diseases are the leading cause of morbidity and mortality in industrialized countries and lead to high socioeconomic costs. Contemporary diagnostic and therapeutic management of cardiovascular diseases relies on medical technology. It is the goal of the course on "Cardiovascular Technology" to give students of all backgrounds a detailed overview on the wide range of technologies used in this field.

A typical lecture in cardiovascular technology starts with the discussion of a specific patient case (e.g. a stroke patient) including some background information on this pathology and anatomy. This is followed by a technical introduction to the diagnostic and therapeutic technology used in the context of the underlying disease. Then a guest lecturer (a clinician from the Inselspital) provides his or her view on the technological challenges encountered in clinical practice. Usually the lecture is completed by a lab visit (e.g. to the electrophysiology lab) or by a hands-on visit to a clinic where the students can try out some clinical tools (e.g. echocardiography).

The lectures are organized with respect to the different clinical specializations: There are three lectures on aspects of rythmology and electrophysiology (e.g. pacemakers and ECG), three lectures on interventional cardiology (e.g. balloon angioplasty and stents), three lectures on heart surgery (e.g. heart valve replacement), two lectures on angiology (e.g. endovascular aneurysm repair) and two lectures on interventional neuroradiology (e.g. treatment of strokes).

The multi-disciplinary aspect of this course is reflected by the different academic backgrounds of the three lecturers: Prof. Dr. Dominik Obrist is a mechanical engineer, Dr. Dr. med. Andreas Häberlin is a cardiologist with an MD/PhD in biomedical engineering and Dr. Thomas Niederhauser is an electrical/biomedical engineer. Each lecturer focuses his lectures on his specific field of expertise such that this course provides a concise view at cardiovascular technology from different angles of science and engineering.

This course is addressed to all students of biomedical engineering regardless of their specific background . It is an overview course which does not go too deep into particular aspects of a certain field and there are no homework assignments. However, the students are expected to attend at least 80% of the lectures.

Students who complete this course will have obtained an overview on the different technologies which are applied in daily clinical routine and they will have obtained first-hand accounts of the technological problems encountered by clinicians.

MitraClip device for the percutaneous repair of mitral valves (from www.abbottvascular.com).

New Courses

Introductory Anatomy and Histology for Biomedical Engineers

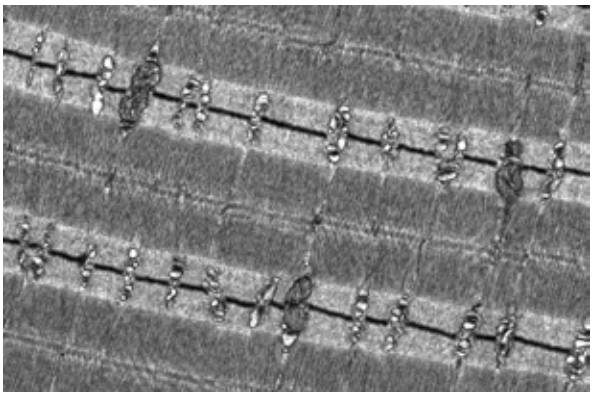
Dr. Glenn Lurman

This was the first year that the students within the Master of Biomedical Engineering programme had an introductory anatomy and histology course tailored specifically for them, in English, after it being separated from the German language Functional Anatomy and Histology course for the students of Pharmacy. A basic understanding of human anatomy is essential to any field of biomedical and bioengineering research. As a consequence, this is a compulsory first semester course which introduces students to most aspects of human anatomy and histology. This ranges from the anatomy of a single cell, through to tissues, organs, organ systems and the body as a whole. This course outlines the four basic tissue types: muscle, epithelial, connective and nervous tissues, together with the main organ systems: cardiovascular, respiratory, digestive, urinary, immune, reproductive, as well as the nervous system and the associated sensory organs. The musculoskeletal system is covered in extensive detail in subsequent two-semester course starting in the students' second semester.

The aims of the course are to gain:
- Knowledge of the anatomy and histology of the human body;
- Knowledge of the anatomical and histological vocabulary;
- An understanding of the correlation between the anatomical/histological structures and their functions.

While a traditional approach to anatomy involves lots of rote learning of names and structures, this course preferentially places a greater emphasis on structure-function relationships. It is expected that students exit the course with an elementary proficiency in, and understand of anatomy. More importantly however, this course is designed to complement the compulsory first semester course in physiology, so that students exit the course understanding why cells, tissues, organs, etc are constructed the way they are, what the function of the different cellular, tissue and organ components are and how these work together. They are encouraged to derive such structure-function relationships themselves, for example, by thinking about the mechanical forces exerted on different types of connective tissues, why they have a corresponding construction, and where these are likely to be found in the body. Where possible, links are also made to current medical technologies, for example, imaging, instrumentation, sensory implants, tissue and organ engineering.

This integrated, functional approach means that no strict division is made between micro and macroscopic anatomy, with lectures freely moving between all levels of anatomical organisation. An effort has also been made to include a hands-on aspect by including four practical lectures. In the Institute for Anatomy's histology teaching room, students are given a series of histological preparations which they can examine themselves with a microscope during the lecture. This practical aspect was received very well, and it is hoped that this practical aspect may be expanded to some of the lectures about macro-anatomical structures.



Light and electron micrographic images of pectoral muscle. In the light micrographic image, different muscle fibre types are indicated as small and large, with arrow heads pointing to individual blood capillaries.

Biomedical Sensors

Prof. Dr. Bernard Dutoit

Biomedical sensors allow measuring the main physiological parameters of human beings and comparing them with standards. They have a key role to help the physician, all medical personal and even patients to take the right decisions to improve their health. Body temperature sensors, blood pressure sensors and acoustic auscultation with stethoscopes are used since a long time. However, several innovations appeared during the last few years.

• The first one is the miniaturization of sensors due to microsystems technologies. Sensors have the same functionality, often associated with an increased reliability with a size approaching a cubic mm. The power consumption has also been reduced which is a considerable advantage for invasive investigation. Typical examples of such devices are pressure sensors used in intracranial or intraocular pressure monitoring. We could also mention several sensors around the pacemaker (such as the accelerometer) helping people suffering from chronotropic incompetence by pacing their heart at a speed reflecting their activity.

• Microsystems produced in volume cost less than 1$. Sensors are so inexpensive that they can be inserted in many devices, adding them new functionality. In the 90th, appeared the first one axis accelerometers. You can now find combo sensors including 3 accelerometers, 3 gyroscopes and 3 compasses. This has opened the large consumer market in body activity sensors. It allows everyone to precisely measure its daily activity. More generally, you also find complete systems allowing the remote surveillance of elderly people, tracking their activities and alarm if anything looks unusual.

• The large scale development of diabetes has pushed pharmaceutical companies to find convenient solutions to monitor the glucose level. In the last few years continuous monitoring solution appeared on the market. This is a first step in the direction of the artificial pancreas.

During this course, we also review some other commercial sensors such as: pulse oximeter, to monitor arterial saturation of oxygen or immunoassay, to learn how blood analyses have been considerably speeded up in recent years. These are just a few examples of how biomedical sensors have changed our world. Biomedical sensors are largely interdisciplinary and therefore represent a fascinating topic.

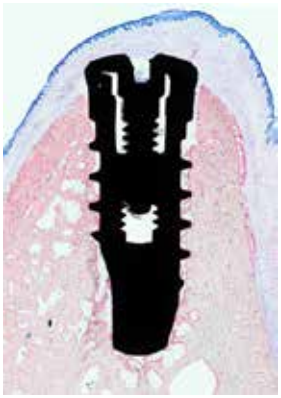
Wrist-oximeter allowing O2 saturation measurements.
Photo courtesy of Konica Minolta, Inc. All rights reserved.

New Courses

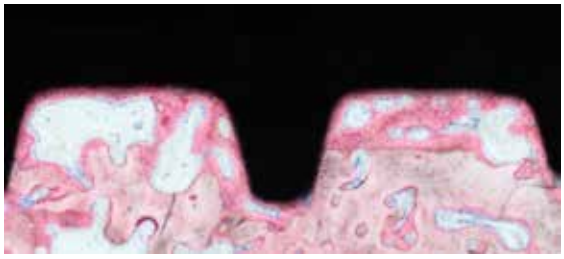
Regenerative Dentistry

Prof. Dr. Reinhard Gruber, Tommy Baumann, Dieter Bosshardt (without picture), Thiago Carvalho, Vivianne Chappuis, Simon Flury, Pjotr Fudalej, Tim Joda, Joannis Katsoulis, Klaus Neuhaus, Christoph Ramseier.

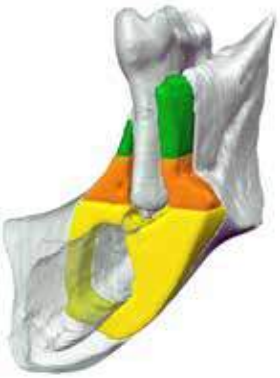
The course „Regenerative Dentistry" was established with the overall goal to introduce biomechanical engineers to the clinical aspects of dentistry, how dental materials and tools are applied, and to provide insights into the ongoing research. „Regenerative Dentistry" was based on the compelling understanding that advancing today's field of dentistry requires a multidisciplinary approach linking universities and industry, particularily in Switzerland where global players in dental medtech industry are located. We agreed that future biomechanical engineers have to understand the basic of clinical dentistry, dental materials and the tools to be prepared for working in R&D. We have therefore chosen the technical term "Regenerative Dentistry" to underline the importance to the interdisciplinary work of dentists and biomechanical engineers to improve the field. The course „Regenerative Dentistry" provides an overview on the clinical aspects of dentistry, basics about dental materials, on the tools and instruments in dentistry, and some clinically oriented laboratory research. The faculty represented all specialties such as endodontics, periodontics, orthodontics, prosthodontics and oral surgery, each operating with dental materials and tools including fillings, implants, bone substitutes, membranes, braces, crowns, and bridges.



Early phase of osseointegration of idental implant (survey) in minipig model.



Early phase of osseointegration of dental implant (detail) in minipig model.



3D illustration of a mouse's tooth and jawbone.

3D illustration of a mouse's tooth without jawbone.

Wireless Communication for Medical Devices

Prof. Martin Kucera

Wireless communication became an ubiquitous technology in the past decade: applications are numerous and growing virtually daily and it is common practice to access data or to control devices by means of a radio frequency wireless communication.

Medical devices and applications are no exception, although for very good reasons their proliferation is somehow lagging behind the developments of consumer electronic devices: The requirements and specifications for medical devices are often severe and require solutions which became either only recently achievable or economically viable. Furthermore there are issues with wireless communication for medical devices, like for instance security, which cannot be neglected and require a thorough and detailed review of existing practices and solutions.

Despite those interesting challenges, wireless communication for medical devices, either by means of inductive links or radio frequency communication has many very compelling advantages which make this the technology of choice: Especially implanted devices, with no other possibility to transfer information to the outside of the body are a very convincing example demonstrating the advantages and the potential.

But even body worn devices, which can be designed, tested and implemented much faster, can provide tremendous benefits.

This new course provides students with the required competence and knowledge to assess the possibilities and limitations of wireless communication for medical devices. The subject is addressed by case studies of four existing use cases, being hearing aids, pacemakers, cochlear implants as well as general body worn medical devices. These four well known medical devices serve as demonstrators for the different challenges, issues and possible solutions. Their shortcoming and limitations in terms of their wireless connectivity are elaborated and possible improvements discussed. The required theoretical knowledge and background is also detailed in this course such that students get a thorough understanding of the specific basic problems when medical devices are expected to communicate through wireless connections.

New Courses

Ethics in Biomedical Engineering

Prof. Dr. med. Kurt Laederach

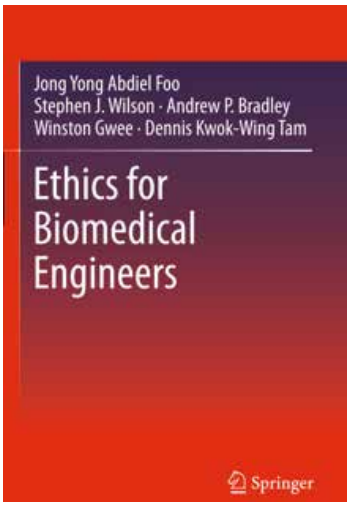
Towards the end of 2013, Prof. Ph. Zysset contacted me in order to discuss the options of establishing a specific ethics module in Biomedical Engineering. After a planning period of half a year, the course could be held for the first time in fall 2014. Like all courses in BME, this one was also given in English.

The course contents included:

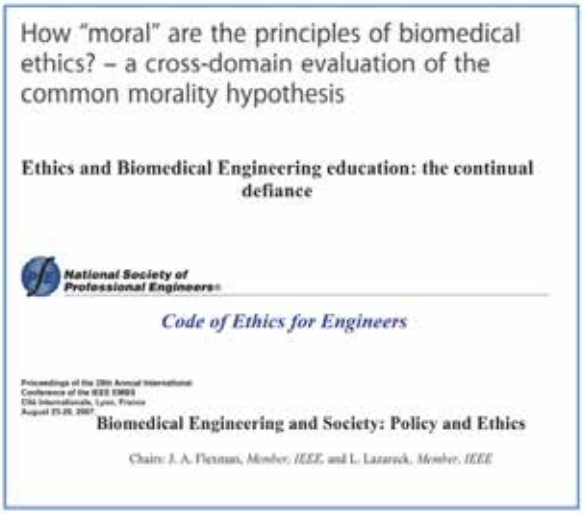
- Basics of medical ethics (Biomedical Ethics)
- Technical ethics, including the questions of material safety
- Animal and human trials
- Risk assessment tools and their function
- Ethical guidelines of BME worldwide
- History of ethical frauds
- Whistleblowing, e-health and newer information technologies
- Ethical codices (Nuremberg, Geneva, Helsinki) and BME regulatives (IEEE)
- Legal issues of BME in Switzerland, the EU and the US

Each lecture was subsequently followed by case exercises where students had the opportunity to directly apply their knowledge to specific case situations.
After completion of the first half of the course, a first assessment exam was performed, followed by a final assessment written towards the end of the course. In addition, students had to pass an exam to obtain the necessary ECTS.

As a new and somehow unusual course it could draw interest of about a dozen students. The success of the first realization of the ethics course enables us to include it in next year's agenda as well.



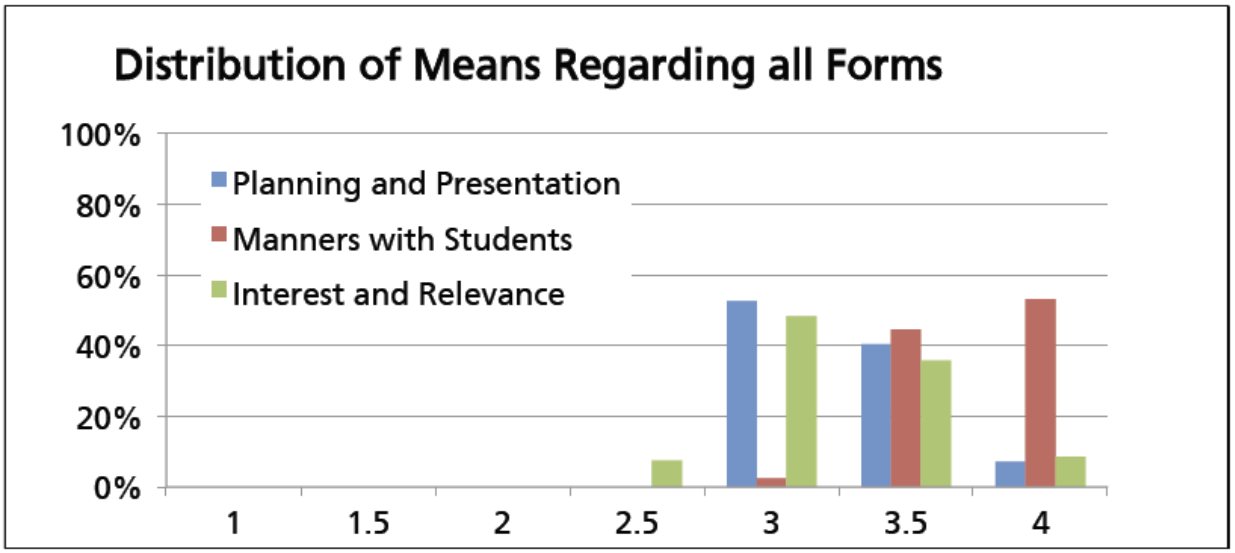
Suggested literature for students.



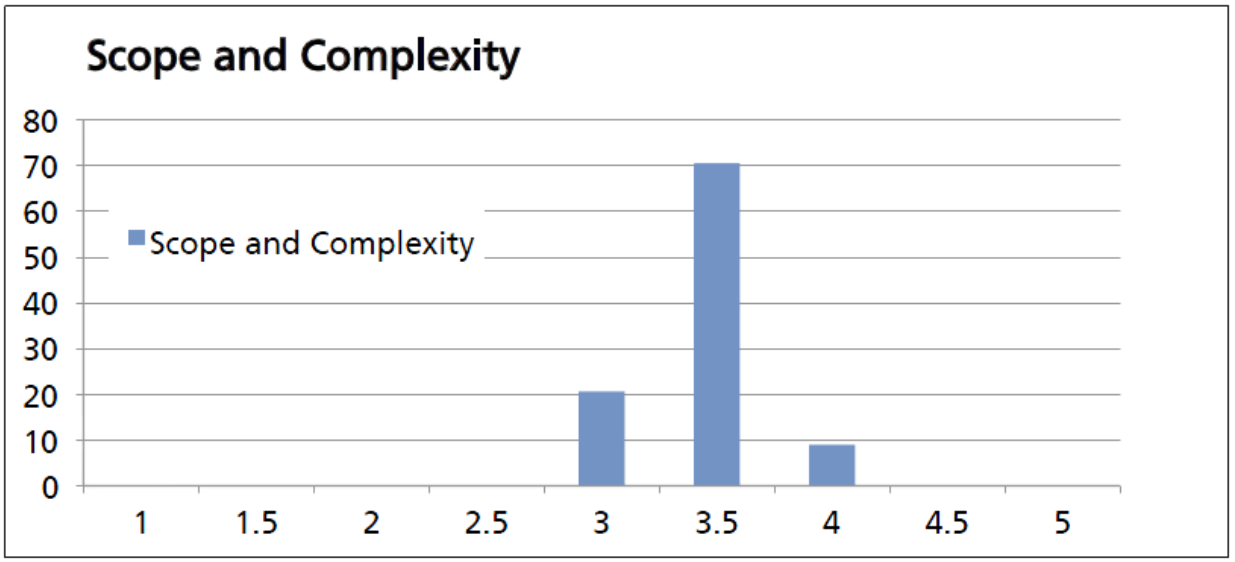
Some of the most discussed issues by title.

Evaluation of Courses in 2014

Like in the previous year, a centralized evaluation was performed in the Master's program in 2014 according to the guidelines of the University of Bern. Both spring and fall semester were considered leading to 45 course evaluations involving more than 1000 forms in total. The results regarding all forms (see below) reveal that the students are well treated, satisfied with the planning and presentation, and find that the courses are interesting and demanding at the same time.



1: very poor 2: poor 3: good 4: excellent



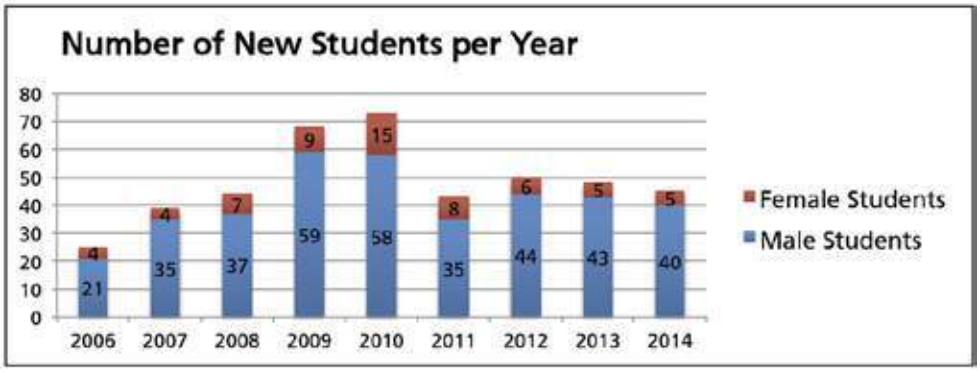
1: far too narrow/narrow 3: just right 5: far too high/wide

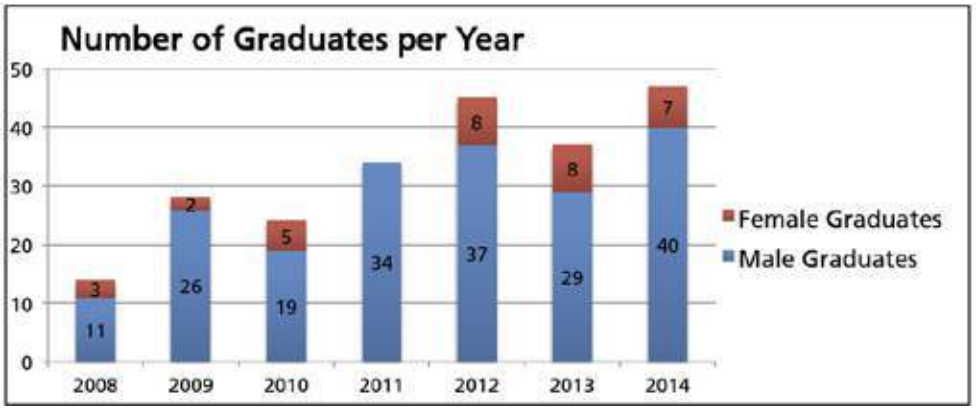
Faculty

Ahmad Dr., Sufian S
Albrecht Prof. Dr., Christiane
Baier Prof. Dr., Norman
Baumann Dr., Tommy
Bell Dr., Brett
Bosshard Prof. Dr., Dieter
Büchler PD Dr., Philippe
Burger Prof. Dr., Jürgen
Cattin Prof. Dr., Philippe
Caversaccio Prof. Dr., Marco-Domenico
Chan Dr., Samantha
Chappuis Dr., Vivianne
Charles Prof. Dr., Roch-Philippe
Da Costa Dr., Bruno
Debrunner Prof., Daniel
De Haller Dr., Emmanuel
Diehm Prof. Dr., Nicolas
Diem Prof. Dr., Peter
Dommann Dr., Alex
Dutoit Prof. Dr., Bertrand
Ecker Dr., Timo
Egger Prof. Dr., Marcel
Eglin Dr., David
Favaro Prof. Dr., Paolo
Fichtner Dr., Jens
Fix PD Dr., Michael
Flury Dr., Simon
Frenz Prof. Dr., Martin
Fudalej PD Dr., Pjotr
Gantenbein PD Dr., Benjamin
Gerber Dr., Kate
Gerber Dr., Nicolas
Gicquel Dr., Pierre-Yves
Giraud PD Dr., Marie-Noëlle
Götte Prof. Dr., Josef
Gralla Prof. Dr., Jan
Gruber Prof. Dr., Reinhard
Guenat Prof. Dr., Olivier
Häberlin Dr., Andreas
Haschtmann Dr., Daniel
Hofer Dr., Ulrich
Hofstetter Prof. Dr., Wilhelm
Hoppeler Prof. Dr., Hans-Heinrich
Hunt Prof. Dr., Kenneth
Hüsler Prof. Dr., Jürg
Iff Dr., Samuel
Jacomet Prof. Dr., Marcel
Jensen Prof. Dr., Björn
Joda Dr., Tim
Jüni Prof. Dr., Peter
Justiz Prof. Dr., Jörn
Katsoulis PD Dr., Joannis
Keppner Prof. Dr., Herbert
Kleinlogel Dr., Sonja
Kluter Prof. Dr., Theo
Koch Prof. Dr., Volker
Kompis Prof. Dr., Martin
Kopp, Doris
Kowal PD Dr., Jens
Kucera Prof. Dr., Jan
Kucera Prof. Dr., Martin
Laederach Prof. Dr., Kurt
Lechmann, Beat
Lerf Dr., Reto
Lu Dr., Huanxiang
Luginbühl Dr., Reto
Lurman Dr., Glenn
Mack Dr., Alexander
Meier Prof., Christoph
Milligan Dr., Simon
Minder, Beatrice
Moser Dr., Walter
Mougiakakou PD Dr., Stavroula
Nef Prof. Dr., Tobias
Nesic PD Dr., Dobrila
Neuhaus Dr., Klaus
Nevian Prof. Dr., Thomas
Niederhauser Thomas, Dr.
Niggli Prof. Dr., Ernst
Nolte Prof. Dr., Lutz-Peter
Nyffeler PD Dr., Richard
Obrist Prof. Dr., Dominik
Peterhans Dr., Matthias
Porz Dr., Rouven
Ramseier Dr., Christoph Andreas
Reyes Prof. Dr., Mauricio
Rothen-Rutishauser Prof. Dr., Barbara
Rutjes Dr., Anne
Saads Carvalho Dr., Thiago
Schäfer PD Dr., Birgit
Schenk, Samuel
Schwarzenbach Prof., Heinrich
Schwenkglenks PD Dr., Matthias
Senn Prof. Dr., Walter Martin
Stahel Prof. Dr., Andreas
Stoyanov Dr., Jivko
Streit Prof. Dr., Jürg
Tschanz Dr., Stefan
Von Garnier PD Dr., Christophe
Weber Dr., André
Weber Prof. Dr.-Ing., Stefan
Wolfram Dr., Uwe
Zheng PD Dr., Guoyan
Zimmermann Prof. Dr., Heinz
Zwicker Prof. Dr., Matthias
Zysset Prof. Dr., Philippe

Statistics

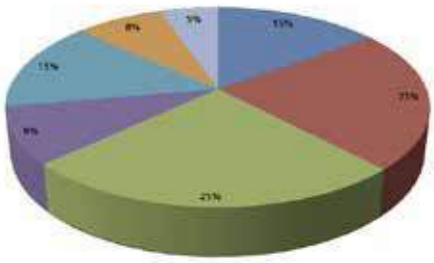
Number of Students and Graduates per Year



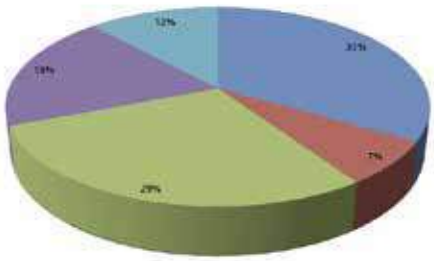


BME Alumni: Career Directions

Profession after Graduation



Profession 5 Years after Graduation



Biomedical Engineering Day 2014

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

On May 16 2014, 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 sixth time.

Attentive participants in the auditorium.
Photo: Tom de Bruyne

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.

An Erasmus student from the ARTORG Center and a PhD student from the ISTB discuss a current research project.
Photo: Tom de Bruyne

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, our 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.

Two students try out a planning system for cochlear implants.
Photo: Tom de Bruyne

Besides company representatives, scientists, researchers, and young academics, many 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 neurosurgical surgery by Jürgen Beck, Department of Neurosurgery, Inselspital Bern. In the auditorium, Christian Fung from the same department gave illustrative explanations.

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

Steven Balestra received the SICAS Award 2014 for the best Master thesis for his work "Statistical Shape Model-Based Articulated 2D-3D Reconstruction".

Steven Balestra received the SICAS Award 2014 for the best Master thesis in the Biomedical Engineering Program from Mauricio Reyes (left; ISTB, University of Bern) And Bernhard Reber (right; Director of the SICAS Foundation).
Photo: Tom de Bruyne

The SICAS Award 2014 for the best PhD thesis was given to Aloïs Pfenniger for his work "Intracorporeal Energy Harvesting with a Focus on the Human Cardiovascular System".

Aloïs Pfenniger received the SICAS Award 2014 for the best PhD thesis in the field of Biomedical Engineering, the University of Bern from Mauricio Reyes ((left; ISTB, University of Bern) And Bernhard REber (right; Director of the SICAS Foundation).
Photo: Tom de Bruyne

Raphael Meier received the BME Club Award for the best Master Thesis Abstract for his work "Decision Forest for Multimodal Brain Tumor Segmentation".

Raphael Meier received the BME Club Award 2014 for the best Master Thesis Abstract from Prabitha Urwyler (right; President of the BME Club) and Philippe Cattin (right; University of Basel and BME Club member).
Photo: Tom de Bruyne

We thank our sponsors and exhibitors

- BME Club
- CCMT
- Congrex
- CSEM
- Haag-Streit
- Medical Cluster
- Nobel Biocare
- RMS Foundation
- SICAS Foundation
- Stryker Trauma
- Carl Zeiss

The BME Club Poster Award 2014 was given to Janine Ruppen. Her poster "Increased Perfusion-Induced Chemoresistance in Multicellular Pleural Cancer Spheroids Cultured in a Microfluidic Chip" convinced the jury.

Janine Ruppen received the BME Club Poster Award 2014 from Prabitha Urwyler (right; President of the BME Club) and Philippe Cattin (right; University of Basel and BME Club member).
Photo: Tom de Bruyne

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. BME 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. 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-monthly "Stammtisch" in a local restaurant as an amiable platform to exchange, discuss, brainstorm or simply chat
- visits to Swiss medical and engineering companies
- information on career opportunities (including job offers)
- organization of the annual welcome event for new stu dents 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 Travel award to master students
- publish annual BME club Newsletter
- provide access to the Medical Cluster events
- offer joint membership with SSBE (Swiss Society for Biomedical Engineering)

BME alumni who join us automatically become a member of Alumni UniBe, the alumni association of the University of Bern. Among other benefits this includes receiving a lifelong UniBe email address facilitating staying in touch with your peers.

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 welcoming you!

The BME Club Board in 2014

Prabitha Urwyler
President

Matteo Fusaglia
PhD Students

Dobrila Nesic
Faculty

Tom de Bruyne
Vice President

Tobias Imfeld
Webmaster

Alejandro Juarez Robles
Master Students

Julia Spyra
Back Office

Carlos Ciller
Treasurer

Lukas Bösch
Alumni

Christian Güder
Public Relations

MEDICA 2014

MEDICA – the 'World Forum for Medicine' – is the world's largest professional trade fair for the medical sector. Every year around 130'000 visitors flock to Düsseldorf's Messe conference centre (where it is held) to discover, trade and discuss the very latest in health technology. This year, over 4'800 exhibitors filled the 116'000 m2 of hall space. More than half of these were companies specialised in electro-medicine & medical-technology (everything and anything from neurostimulators to imaging systems). Additionally, entire halls were dedicated to diagnostics & lab equipment, physiotherapy & orthopaedics, commodities & consumables (e.g. bandages, gloves and syringes), IT & communication technologies to name a few.

COMPAMED is a trade fair for suppliers of the med-tech sector. Here were presented the new materials and technologies that will one day change the way we live and practice medicine.

… The fuss? Well simply put – MEDICA in and of it-self is awesome. As a budding Biomedical Engineering MSc student, the convention is an opportunity to 'see what's out there', discover devices or technologies you've never heard of, touch them, try them, figure out how they were made and how they are different from other solutions. It is a chance to ask a million questions and gain insight into fields you've haven't worked in or perhaps, never came to know or think of. It is an opportunity to meet (as sometimes happens) the lead developers of a device or a product. They are always interesting people to talk to. What you discover at the trade fare may well widen your view of what comprises the medical sector. It might help you imagine applications for what we learn during our studies.

So MEDICA is awesome, but the trip as organised by the BME club, made the experience beyond amazing. 31 of us participated in this event. Here is roughly what our schedule looked like:

Thursday 13th of November 2014
20:00 Dinner at TRAMWAY in Bern (optional)
23:45 Meet at the bus outside the Kunstmuseum (departure at 24:00)
---- go to sleep in Bern, wake up in Düsseldorf ----
Friday 14th of November 2014
08:00 Arrive at the youth hostel, check-in, breakfast, head over to MEDICA
10:00 MEDICA / COMPAMED !!!
18:30 Leave the Messe, head back to the hostel
19:00 Dinner (BBQ)
21:00 Düsseldorf by night (optional)
Saturday 15th of November 2014
02:30 Walk back to the hostel (optional)
03:00 Arrive at hostel (optional)
08:30 Wake up, breakfast (optional)
09:30 Check-out (not optional)
10:00 MEDICA !!!
14:00 Düsseldorf by day (optional)
19:00 Dinner at UERIGE – the best brewery-restaurant in town (shouldn't be optional)
23:00 Bus departs from youth hostel.
---- go to sleep in Düsseldorf, wake up in Bern ----
Sunday 16th of November 2014
06:30 Arrive at the Hauptbahnhof in Bern

… okay, so we didn't really sleep all that much, but checking out the town and trading stories with fellow BME-ers was well worth it.

Would I do it again? DEFINITELY – because like they said, 'MEDICA is huge' and I feel like I haven't seen half of what there is to see. So next time, I will make a list of the companies I want to visit (being now a MEDICA veteran and able to navigate the website). I might even include more halls on my list. But more than anything, I'd do it again with a group from the BME club. You learn more when you're with like-minded others and it's a lot more fun. Enough said – see you next time!

The group is having dinner at one of the famous breweries in Düsseldorf, the "Uerige".

Just steps away from the ultimate MEDICA experience: Ping, Alejandro and Gleow.

Graduation Ceremony

"The Glorious Graduation Ceremony 2014"
3 years ago, at the beginning of 2011, I had just started my master studies in Biomedical Engineering at the University of Bern. Besides my studies, I started working in a research group of the faculty. At that time, I had no clue of German, and did not even know that "Bärn" has its own "Dialekt".
Last Saturday (March 8, 2014), at "Grosser Saal" in the Kultur Casino "vo Bärn", the newly graduated students and the new doctors in Medicine, Dentistry, Biomedical Sciences and Biomedical Engineering, were invited to an incredible "Diplomfeier". I was very proud of finally receiving the result of my master studies; and I was nicely impressed by the incredible room, the fine classical concert and the very interesting and stimulating talks.
My "take-home" message was that being a professional in the field of medicine, the sciences and technology, is not just a standard job. It requires professionals who are enthusiasts, able to devote passion to a very high degree, with the final goal of improving diagnosis and treatments of diseases of any kind of patients, at the most inexpensive cost to society. Probably not easy, eh? Indeed quite challenging; but I am quite certain that this will be, and already is, a very interesting and stimulating working field for me and for many other colleagues of the faculty.
Today, I am quite excited to continue extending my scientific skills and contribute to the new generation of biomedical engineers and scientists towards my PhD studies at the ARTORG Center. It was never easy to do a master and work part time as a researcher; nor will it be to pursue the doctorate during the next 3 years. Nevertheless, I think this experience has been to date the most interesting working time since I started my career in 2006. I would encourage those who are starting the BME master's to maintain their motivation high, accept the difficulties, as there will be many, and really believe in themselves until the end of their studies; just push hard, be respectful and work in a team… the rest will work out! Just needs time… and then will pay off!

Best wishes,
Juan Ansó

RMS Master Award
In 2013, the RMS Foundation established the RMS Master Award for students graduating from the Master in Biomedical Engineering program at the University of Bern. The annual award is bestowed in recognition of excellent academic achievements. It is presented to the student with the highest grade point average.
This year, Raphael Meier won the award. The laureate was honored at the graduation ceremony of the Medical Faculty in March 2014.

Our alumni and alumnae.
Bottom (from left to right): Christoph Strub, Juan Anso, Marc Stadelmann, Salman Alaraibi, Diana Pena Bello, Bergdis Sigurdardottir, Steven Balestra, Andreas Hugi.
Top (from left to right): Mohammad Shamsollahi, Michael Rieger, Kaspar Steiner, Benedikt Thelen, Ishan Shah, Agnes Imhof, Stefan Brun, Michael Muster, David Morgenthaler, Raphael Meier, Roger Infanger, Pietro Bottani, Matthias Hutter, Thomas Wyss, Philippe Zysset (Program Director).

RMS Award
From left to right: Philippe Zysset (Program Director, Master Biomedical Engineering) and Raphael Meier.

Graduation Profile

Michael Muster

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

A: After primary and secondary school, I did an apprenticeship as a biology lab assistant at the Federal Office of Public Health. During an internship as a mechanic, I decided to study Mechanical Engineering at the Bern University of Applied Sciences in Burgdorf. However, my interest in biology persisted, so I decided to do my Master's in Biomedical Engineering. This study course combines my main interests: biology and mechanical engineering.

Q: Why did you choose to pursue your Master's studies at the University of Bern / Bern University of Applied Sciences?

A: Bern is the perfect location to study for me, a beautiful city and not far away from my hometown. Due to the fact that the course is concentrated on three days per week, I had the chance to continue working at the Institute for Rehabilitation and Performance Technology (IRPT) at the Bern University of Applied Sciences (BUAS). For me it was never a matter of discussion to study at another university.

Q: You continued to work during your studies. How was this experience?

A: I had a 50% part time job as a research assistant at the IRPT in Burgdorf. It was a very good and intensive experience, because I worked in a slightly different research field compared to my study curriculum. Due to that I had the chance to expand my knowledge of medical devices. Sometimes, I was able to directly apply the skills to the job which I acquired at the universities and vice versa.

Q: What was your career plan after the completion of your degree?

A: First I tried to get a specific PhD position in an interesting field of biology. Unfortunately I did not get the approval. Then I tried to catch a job in the industry as a development engineer combined with applied research. I am work now in an industrial group.

Q: What is the benefit of the Master studies with regard to your current professional activity?

A: At the moment I am involved in several very interesting projects. Sometimes in strongly multidisciplinary fields. In general, the largest benefit is to have the capability to work and think in an interdisciplinary way. It is not possible to highlight just one specific part of the Master Studies.

Q: You had won the "Burgdorfer Innopreis 2014". What kind of award is this and with which project did you get the award?

A: The main idea behind the "Burgdorfer Innopreis" is to give to a general public the chance to see how fascinating the study at the BUAS is. For this purpose, the five most innovative projects are selected to compete against each other in a presentation competition. This means my master thesis "Foot-Stimulation Module for a Robotic Tilt-Table" had to be presented as simply as possible and within ten minutes. The preparation of such a presentation is labor-intensive but a very exciting and instructive task. I was surprised and very happy to win this price, this would not have been possible without the great help from my colleagues.

BZ Berner Zeitung, March 7, 2014, page 1.

Master's Theses 2014

Please visit our website at http://www.bme.master.unibe.ch for an online version with full page Master Theses Summaries

Novel stretchable strain sensor for biomedical applications

Mohammed Oluremi Adagunodo

Supervisors: Prof. Dr. János Vörös and Vincent Martinez
Institutions: Laboratory of Biosensors and Bioelectronics, ETH Zurich
Faculty of Medicine, Universität Bern
Examiners: Prof. Dr. Herbert Keppner and Prof. Dr. János Vörös

Introduction

The goal of this project is to fabricate a flexible strain sensor which can be used for strain measurements in soft body tissues. To achieve this, conformal devices or instruments are required to mimic these dynamics and be able to detect the changes. Stretchable electronics is a promising tool for monitoring these functions. Emergence of stretchable electronics has led to the need for composite materials which present high elastic properties with optimal electrical properties. To realize our strain sensor we used PDMS and silver nanowires. However, high resolution patterns are difficult to achieve on PDMS because of its low surface energy does not allow the adhesion of photoresist to the surface. Here, we present a wafer scale solution to the issue.

Materials and Methods

In this project, a photolithography compatible process was developed to pattern thin films made out of silver nanowires on PDMS substrate with a finest resolution of 10µm.

Thin films of nanowires were realized from silver nanowires deposition by either by centrifugation or sedimentation. The silver nanowires deposition was characterized using the optical transmittance and sheet resistance. To achieve a high resolution pattern, we designed two approaches using photolithography techniques. The first approach was patterning the silver nanowire deposition on glass and embedding them into PDMS after the lithography process. In the second approach, we deposited and patterned the silver nanowires directly on PDMS. Using these approaches, we were able to realize the strain gauge fabrication.

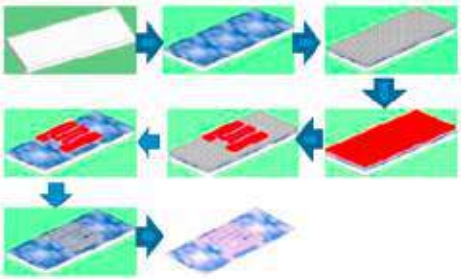


Fig 1: Photolithography process on PDMS (following the step sequence in the diagram): glass preparation, PDMS pouring, chromium adhesion layer + silver nanowires deposition, photoresist coating, UV exposure and development, photoresist removal and PDMS stripping

Results

Highest resolution achieved with both approaches was 10µm. Two techniques of microfabrication and deposition were realized. The transmittance was defined as a function sheet resistance. Low gauge factor of around 1 was realized over large deformations for large samples. Photo-patterned samples showed high gauge factor.

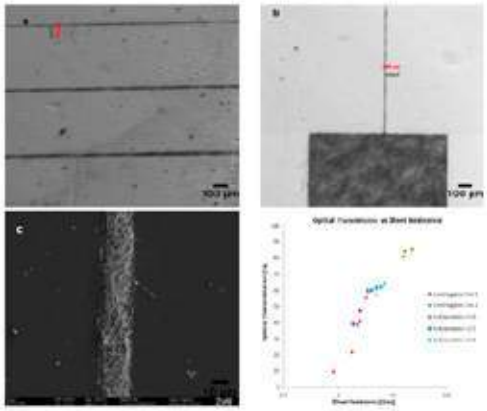


Fig. 2 shows the highest resolution achieved on PDMS (a) and on glass (b), (c)is the SEM image of the patterned silver nanowires (d) is the optical transmittance measurements Vs sheet resistance.

Discussion

Result from the characterization of our Silver nanowire thin film showed two regions which is described by percolation and bulk material characteristics. This corresponds with previous studies. High resolution patterns were realized on PDMS using photolithography using our novel approach. Initial results show that the gauge factor is not significantly influenced by concentration changes. Preliminary results of the photolithography pattern samples present high gauge factors of up to 17 for 60% strain rate. However, it needs further investigation.

References

De, S., et al., *Size effects and the problem with percolation in nanostructured transparent conductors.* ACS nano, 2010. **4**(12): p. 7064-7072.

Xu, F. and Y. Zhu, *Highly conductive and stretchable silver nanowire conductors.* Adv Mater, 2012. **24**(37): p. 5117-22

Adaptive Real-Time Ultrasound Image Segmentation for Patient Registration in Image-Guided Liver Surgery

Andreas Arnold

Supervisors: Delphine Ribes and Prof. Dr.-Ing. Stephan Weber
Institutions: ARTORG Center for Biomedical Engineering Research, University of Bern
CAScination AG, Bern
Examiners: Prof. Dr.-Ing. Stephan Weber and Dr. Matthias Peterhans

Introduction

Liver cancer is one of the most prevalent cancers in the world. The treatment of choice is resection, but it is only available to 10% - 20% of all patients. CAS-One Liver is a system for computer assisted liver surgery (CALS), relying on intra-operatively acquired ultrasound images to register the patient's liver to a pre-operatively acquired and segmented CT or MR model. In this thesis the effects of improved image segmentation and integration of a new ultrasound system as well as better user guidance towards an improved registration process were investigated.

Materials and Methods

In the first part of this thesis, current segmentation deficiencies were assessed using a set of qualitative and quantitative metrics, such as sensitivity, specificity, vessel detection rate, and average registration error. The segmentation algorithms under evaluation were a Difference of Gaussian (DOG) algorithm and a fixed thresholding approach. Both were tested with and without shadow removal, Gaussian kernel edge compensation, gradient artifact removal and level sets. The improvements were tested on 97 images acquired during 15 surgeries for the integrated ultrasound system and on 70 images acquired during 4 surgeries from a BK Flex 800 Ultrasound system.

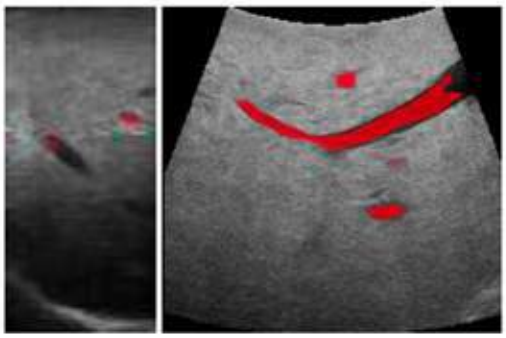


Fig. 1 US images and results of automatic vessel segmentation of liver from integrated (left) and BK Flex 800 ultrasound system.

The current ultrasound acquisition interface was evaluated and a new scheme proposed and evaluated in a lab settings. The new scheme was developed to minimize deformation artifacts and improve the ease of use during surgeries.

Results

Gradient artifacts, loss of information on the image edge and low signal to noise ratio were identified as the most prominent error cases. To improve the registration outcome, a gradient artifact removal algorithm and optimized segmentation parameters were added to the framework. Compared to the former algorithm the new registration algorithm increased the average accuracy from 4.8 mm to 2.5 mm ($n = 3$, $p = 0.50$). The integration of the BK ultrasound system was successfully tested during open liver surgeries at the Inselspital Bern.

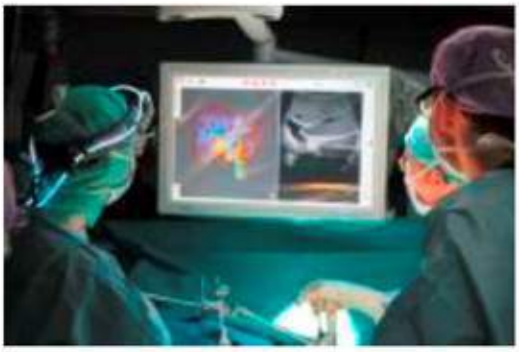


Fig. 2 CAS-One Liver used during a surgery at the Inselspital Bern.

Discussion

The registration process was improved through inclusion of the gradient artifact removal algorithm and with the use of optimized parameters. The new ultrasound system was successfully used during open liver surgeries, but further clinical tests are needed. The new guidance interface was implemented and preliminary tests performed. Further testing is still required.

References

Peterhans M. et al., A navigation system for open liver surgery: design, workflow and first clinical applications, The International Journal of Medical Robotics and Computer Assisted Surgery 7(1): 7-16, 2011.

Acknowledgements

The project was accomplished with technical and logistical support of CAScination AG.

Unipolar Amplifier Design for True Bipolar Long-term ECG Leads

Daniel Bär

Supervisors: Thomas Niederhauser and Dr. med. et phil. Andreas Haberlin
Institutions: HuCE Microlab, University of Applied Sciences Biel
Artorg Center for Biomedical Engineering Research, University of Bern
Examiners: Prof. Dr. med. et phil. nat. Rolf Vogel and Prof. Dr. Josef Götte

Introduction

Today, long-term ECG recordings are done with Holter monitoring devices, which require various wet electrodes placed on different positions on the limps and the chest. Cables are used to connect all these electrodes to the monitoring device. The aim of this thesis is to investigate a novel unipolar amplifier circuit, found in literature, for its capability to measure long-term ECG signals. In particular it shall be investigated if this novel circuit is capable to measure ECG signals at specific surface positions of the human body using two electrodes in close vicinity to each other. Thereby reducing the amount of wires currently needed to measure biopotential differences like the ECG signals.

Materials and Methods

An evaluation board, containing the mentioned unipolar front-end, is developed to measure biopotentials (Fig.1). The sensing electrode is connected to the non-inverting input of an instrumental amplifier and a low-pass filtered copy of it to the inverting input. With the result that the signal present at the electrode is high-pass filtered and amplified. A bootstrap summing amplifier creates a common-mode potential from the potentials of the sensing and grounding electrode, which is used as the reference potential of the instrumental amplifier.

Fig. 1: Evaluation board containing the unipolar analog front-end and a microcontroller to measure a surface biopotential.

Measurements done with the evaluation board are compared to simultaneously measured, fully differential ECG signals derived with a conventional, monitoring device (BioRadio 150). Additionally, the influence of the placement of the grounding electrode is investigated.

Measurement Results

The results derived with the evaluation board confirm that leads I, II and III can be reproduced with this circuit and they closely match the ECG measured with a standard recorder (Fig.2). The correlation coefficient was 0.95 or higher. However, potentials are highly dependent on the positioning of the grounding electrode.

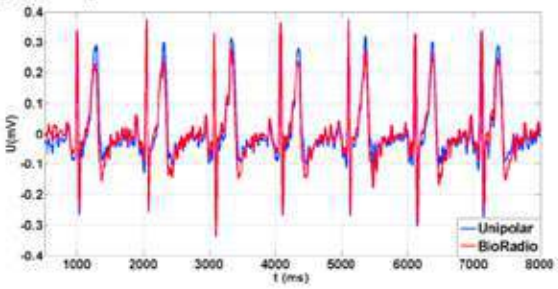


Fig. 2: Comparison of lead I between unipolar (blue) and standard differential circuit (red).

Discussion

Independent unipolar measurements cannot be conducted with this circuit if both, sensing and grounding electrode, are positioned in close vicinity to each other. They lie on the same iso-potential line of the electric field, which is created by the electric activity of the heart. The physical principles governing measurements including electrodes also apply to this circuit.

Two-electrode circuits still hold advantages as no grounding electrode must be connected to the leg. Measurements indicate that there are locations on the human arm where a potential difference can be measured, with the electrode distance still close enough to be integrated into a single measurement unit.

References

G. D. Gargiulo, A. L. McEwan, P. Bifulco, M. Cesarelli, G. Jin, J. Tapson, A. Thiagalingam and A. vanSchaik, Towards true unipolar bio-potential recording: a preliminary result for ECG, Physiological Measurement, vol. 34, pp. N1-N7, 2013.

A Novel Lead- and Batteryless Pacemaker

Lukas Bereuter

Supervisors: Dr. med. et phil. Andreas Häberlin and MSc Adrian Zurbuchen
Institutions: ARTORG Center for Biomedical Engineering Research, Universität Bern
Examiners: Prof. Dr. med. et phil. Rolf Vogel and Prof. Dr. Marcel Jacomet

Introduction

Today's cardiac pacemakers have two major disadvantages. First, they use primary batteries as their energy source. And second, they use leads to deliver the electrical stimulus to heart. The amount of energy storable by the batteries is a limiting factor of implanted devices. Hence, some patients need several device replacements during their lifetime. This procedure is unpleasant for the patient and bears the risk of complications. The leads are exposed to repetitive mechanical stress and are prone to fracture. To overcome these limitations, a lead- and batteryless pacemaker is desirable. The aim of this study was to evaluate the feasibility of leadless and batteryless pacing by developing miniaturized and low power consuming pacemaker circuits.

Materials and Methods

Towards a lead- and batteryless pacemaker, low power consumption and miniaturization are the major criteria. A development board was created to evaluate electronics for two pacemaker types. First, an endocardial pacemaker which is based on a microcontroller. The design was miniaturized for transvenous implantation. And second, an epicardial pacemaker, which is based on an analog circuit. This type is supplied by an energy harvester which is based on the clockwork of a commercially available automatic wristwatch. The design of the epicardial pacemaker features all components (i.e. the energy harvester, the energy management system and the pacemaker circuit) in one housing.

Fig. 1 Development board with microcontroller based circuits for an endocardial pacemaker and an analog circuit for a lead-and batteryless epicardial pacemaker

Results

Prototypes of both pacemaker types, which feature asynchronous pacing were built and tested. At the lowest supply voltage (1.8 V), the housekeeping power consumption of the microcontroller based endocardial prototype is as low as 1.9 µW. The epicardial pacemaker prototype is leadless and batteryless and was successfully tested in an in-vivo study. By performing asynchronous pacing under typical conditions, the overall power consumption of this prototype is 14 µW out of which 3.65 µW correspond to housekeeping power.

Fig. 2 PCB of the microcontroller based endocardial pacemaker. The dimensions are 8x4.7x1 mm

Discussion

The design of the epicardial prototype was validated by the in-vivo study. Considering that commercial pacemakers provide additional functions which are not implemented in the prototype, the housekeeping power consumption of the endocardial pacemaker was reduced (1.9 µW) compared to the commercial devices (~10 µW).

References

Deterre M., Toward an Energy Harvester for Leadless Pacemakers, PhD Thesis, Université Paris-Sud, 2013.

Acknowledgements

I would like to acknowledge the ARTORG Cardiovascular Engineering group, the BFH Biel microLab and all the people involved in this project.

Master's Thesis in Biomedical Engineering

Anchoring and Housing System for an Esophageal ECG Recorder

Angelo Blank

Supervisors: Dr. med. et phil. Andreas Häberlin and M.Sc. Thomas Niederhauser
Institutions: ARTORG Center for Biomedical Engineering Research, Universität Bern
Institute for Human Centered Engineering (HuCE), Bern University of Applied Sciences
Examiners: Dr. Dipl. lic. phil. nat. Reto Luginbühl and Prof. Dr. med. et phil. nat. Rolf Vogel

Introduction

Heart diseases are in many countries, besides cancer, the second major death reason. To diagnose specific heart diseases like heart rhythm disorders (arrhythmias), electrocardiography (ECG) is used. Paroxysmal arrhythmias in particular require long-term ECGs to detect rare events. The signal quality of the todays used long-term ECGs is low and the electrodes, which are stuck to the patient's chest or limbs, can lead to skin irritations. As an alternative, the esophageal ECG provides a method to avoid these inconveniences.
The aim of this master thesis was to develop a housing which allows to stow all the necessary electronic components of the esophageal ECG recorder in the nose. To prevent the housing from swallowing or shift outwards, it has to be fixated. It is important to ensure that the fixation doesn't harm the patient nor lead to complications.

Materials and Methods

To evaluate the prototypes for the anchoring and housing system, a 3D model of the human nose has been developed. This model was built by using the "Carleton Civic standardized nasal cavity model" [1] and various other patient data.

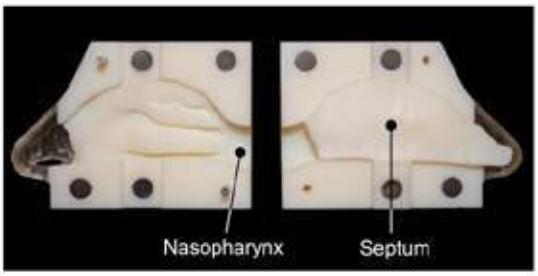


Fig. 1: 3D model of an average human nose (used for the evaluation of the anchoring and housing system)

Different variants have been developed for the housing and its fixation. Moreover, an insertion device for the system has been produced to guide the implantation. These concepts were systematically evaluated to choose the concept which best reaches the set requirements. With tests on the nose model and various meetings with ENT specialists, the decision was made to produce a housing which will be placed behind the septum in the nasopharynx.

The required energy for the electronics is provided by zinc-air batteries, which are widely used in hearing aids. These batteries need oxygen to work, but since they are placed behind the septum, they must be sealed against water. Therefore a method was developed to seal the batteries against water and allow the oxygen to access them. This was done by a hydrophobic membrane.

Results

The housing behind the septum is fixated by a thread which surrounds the nasal septum and is knotted over the nose bridge. To guide the implantation of the system, an insertion device has been developed. This device is used for the insertion and removal of the housing as well as for the insertion of the fixation thread.
Tests with the hydrophobic membrane proved, that it is possible to seal the batteries against water, while having normal ambient conditions.

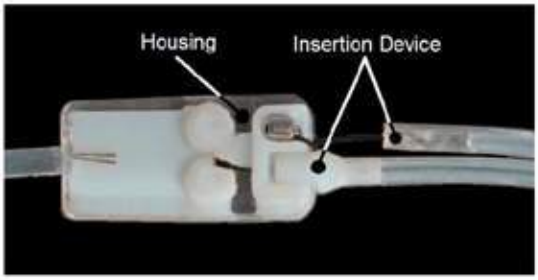


Fig. 2. Anchoring and housing system with insertion device

Discussion

Tests with the nose model confirmed the method of inserting the developed housing behind the septum. However, the system volume needs to be reduced. For a reliable insertion of the anchoring and housing system, further improvements towards the miniaturization of the device are required.

References

[1] Liu et al., Creation of a standardized geometry of the human nasal cavity, Journal of Applied Physiology, 2009

Acknowledgements

I would like to give my gratitude to the ARTORG Cardiovascular group, the microLab at the BFH and to all the persons involved in this project.

Deployment System for the World's First Lead- and Batteryless Pacemaker

Simon Bosshard

Supervisors: MSc Adrian Zurbuchen and Dr. med. et phil. Andreas Haberlin
Institutions: Department of Cardiology, Inselspital, Bern University Hospital
ARTORG Cardiovascular Engineering, University of Bern
Department of Cardiology, Bürgerspital Solothurn
Examiners: PD Dr. Jürgen Burger and Prof. Dr. med. et phil. Rolf Vogel

Introduction

Cardiac pacemakers are among the oldest and well established electrical implants and are used to treat various cardiac arrhythmias. However, today's pacemakers have some disadvantages, among which are battery replacements after 6 to 10 years by surgical intervention, possible fractures caused by the lead wire and alterations of the tricuspid valve.

The aim of this study was to develop a deployment system to implant a first prototype of a novel lead- and batteryless pacemaker. This included the designing of a miniaturized housing for encapsulating the pacemaker electronics, the linear energy harvester, and acceleration sensors. Furthermore, an intervention catheter system for a minimal invasive transvenous device implantation had to be developed. Finally, the deployment system had to be tested and evaluated on the bench and in vivo in an animal trial.

Materials and Methods

The study was divided into four phases: an analysis phase, a conception phase, a design and finalization phase and a testing phase. In the analysis phase, anatomical and technical boundaries for the development of the housing and the intervention catheter as well as already existing comparable systems were discussed. In the conception phase, different concepts for the final components of the deployment system were developed. This included possible solutions for the shape of the housing as well as the setup of the distal catheter. After evaluating all concepts, the best concepts were chosen to form an overall concept of the deployment system. In the design and finalization phase, the overall concept of the deployment system was used for the construction of the housing and the intervention catheter. Finally, a first prototype was produced. The last phase addressed the testing of the developed prototype. Bench tests as well as an in vivo test were used to evaluate the prototype. With the help of these tests, it was possible to assess important conclusions to improve the prototype.

Results

An intervention catheter and two housing versions, A and B, were developed. The housing version A is used for the installation of the pacemaker electronics. This version has two electrodes, which allow a stimulation of the heart muscle cells. Version B of the housing was developed as a carrier for an energy harvester and acceleration sensors. In contrast to version A, version B does not have electrodes and therefore exhibits more installation space. The catheter was designed as an interventional right-heart-catheter and can be used for implantation and explantation of the housing in or from the right ventricle of the heart.

Fig. 1 Overview of the overall system with the housing (1), the distal catheter end (2), the medial catheter (3), the proximal catheter end (4), and the retract needle (5).

Discussion

After the development and manufacturing, the deployment system was tested and evaluated on the bench and in vivo in a swine. During these tests, the housing was successfully anchored in the tissue, the intervention movements were effectively transmitted from proximal to distal, and the handling of the proximal catheter end worked properly. However, the tractability of the distal catheter end and the proximal front-end of the housing need to be improved.

Acknowledgements

I would like to thank the ARTORG Cardiovascular Engineering Group and all who were involved in this project.

Development and Evaluation of an Algorithm to Detect Gaze Position

Pietro Bottani

Supervisors: Prof. Dr. Tobias Nef and PhD Student Giuseppe Zito
Institutions: ARTORG Center for Biomedical Engineering Research of the University Bern.
Division of Cognitive and Restorative Neurology Department of Neurology Inselspital Bern
Department of Old Age Psychiatry Universitäre Psychiatrische Dienste Inselspital Bern
Examiners: Prof. Dr. med. René Müri

Introduction

A large research project is focusing on different aspects of driving and vision in the elderly. In this context a screening tool for the Octopus 900 perimeter to measure the visual exploration behaviour that will support and enhance "fitness-to-drive" assessments and decisions was developed. The Gerontechnology and Rehabilitation Research Group is also developing a new battery of tests to measure higher visual functions. In both cases the use of an eye-tracking technology is needed. The first objective, in this project, is the development of an algorithm to detect the point of gaze, in a 3D environment and to precisely evaluate the gaze behaviour during the visual exploration test. The second objective is the implementation of a real time fixation control to guarantee a high man-machine interaction during higher visual functions tests. Since most available remote eye gaze trackers have low tolerance for head movements and require the users to hold their heads unnaturally still, the third objective is to study and implement a possible solution to compensate head movements. All the three developed features are integrated into the Octopus 900.

Materials and Methods

Three versions of the algorithm are developed. The first one assumes that the head of the patient is still in a certain position and work only with the images returned by the Octopus 900. The second version also assume that the head of the patient is still in a certain position, but works with a wide range of images. The last one allows to determine the point of gaze under natural head movement, but work only with Octopus 900 images.

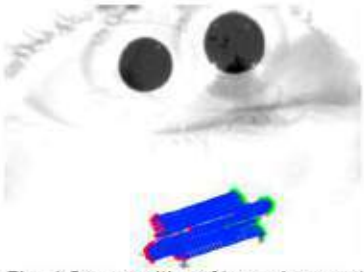
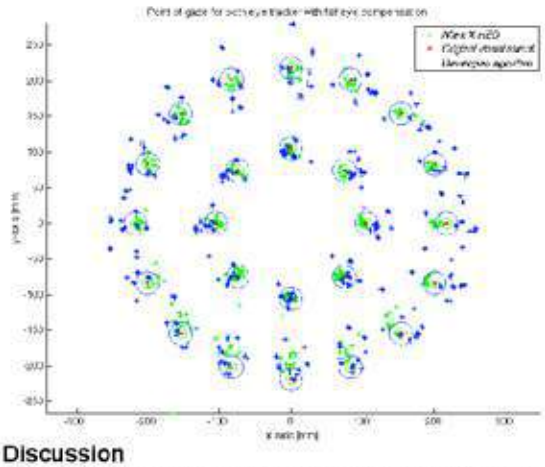


Fig. 1 Superposition of two subsequent frames with the inlying matches

Once the eye-tracker is developed it is important to validate it. A comparison with a commercial device (iView X HED produced by SensoMotoric Instruments (SMI)) is used to validate the developed eye-tracker.

Results

The validation process of the developed algorithm shows that, this type of model is very sensible and can lead to errors. However if the basic information, the pupil center, is precisely gathered, the gaze position can be determined with a relevant precision. More specifically, the developed eye-tracker reports a median absolute deviation on the x and y-axis of 1.5582° and 1.5013°, respectively, while the mean accuracy for the image based techniques is normally between 0.5° and 2°.



Discussion

This new eye-tracker uses an alternative approach that does not require, like most of modern eye-trackers, the glint. Therefore it is particularly suited for eyeglass wearers where IR reflections overlap with pupil region and interfere in the gaze estimation. The developed system is especially suited to work with the setup of the Octopus 900. In this context it was used to measure the gaze position of a series of participant during a clinical study Gruber, Müri et al.[1].

References

1. Gruber, N., et al., Effects of age and eccentricity on visual target detection. Frontiers in Aging Neuroscience, 2014. 5.

Multi-Model Data Fusion to Improve an Early Warning System for Hypo-/Hyperglycemic Events

Ransford Henry Botwey

Supervisors: Dr.-Eng. Stavroula Mougiakakou and Dr.-Eng. Elena Daskalaki
Institutions: ARTORG Center for Biomedical Engineering
Diabetes Technology Research Group, University of Bern
Examiners: Dr.-Eng. Stavroula Mougiakakou and Prof. Dr. Med P. Diem

Introduction

Prevention of hypo- and hyperglycemic events is of high importance for individuals with Type 1 Diabetes (T1D). Recently, the use of data from Continuous Glucose Monitoring (CGM) devices along with data-driven modeling techniques have been proposed for predicting glucose profile and for generating alerts whenever these events are forecasted. Individuals with T1D are thus enabled to take appropriate actions (e.g. carbohydrate intake, suspension of insulin infusion in case of a hypoglycemic event; additional insulin, or physical activity in case of a hyperglycemic event) in order to prevent the onset of the event. Different data-driven models such as autoregressive (ARX) [1], artificial neural networks [2] and support vector machines [3] have been proposed for glucose profile prediction. Each modeling method has its strengths and limitations. It is expected that a combination of two or more modeling methods to take advantage of their complementary prediction performances may lead to i) accurate prediction of hypo-/hyperglycemic events, ii) less false alarms, and iii) improved detection times.

Aim of this study is to improve, enhance and evaluate an early warning system (EWS) for hypo-/ hyperglycemic event prediction [4]. The EWS is based on the combined use of two adaptive models (an ARX with corrected output – cARX and a recurrent neural network - RNN). Within the MSc Thesis three different model fusion techniques have been developed. Their effect in the EWS has been systematically investigated using data from individuals with T1D.

Materials and Methods

To merge the complimentary performances of the cARX and RNN prediction models used in [4], data fusion techniques based on i) Dempster-Shafer evidential theory (DST), ii) genetic algorithms (GA) and iii) genetic programming (GP) were developed. Data from 23 individuals with T1D under sensor-augmented pump (SAP) therapy were used. **Figure 1** shows the steps involved in the enhanced EWS.

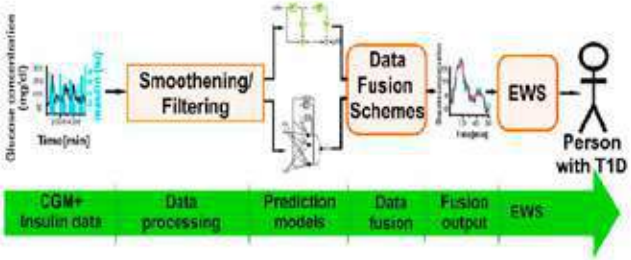


Fig. 1: Early warning system for hypo-/hyperglycemic events based on fusion of blood glucose prediction models.

Results

The performances of the EWS using the proposed fusion schemes (EWS-DST; EWS-GA; EWS-GP) were analyzed and comparatively accessed with the original EWS. The results are summarized in **Table 1**.

Table.1: Performance of the EWS and the EWS based on DST (EWS-DST), GA (EWS-GA) and GP (EWS-GP) fusion schemes in median (5th - 95th Percentiles). [CA: Correct Alarms, DT: Detection Time, DFA: Daily False Alarms]

Criteria	EWS	EWS-DST	EWS-GA	EWS-GP
(A) Hypoglycemia				
CA (%)	100 (100-100)	100 (100-100)	100 (93-100)	100 (94-100)
DT (min)	16.7 (10.-25)	18.4 (10-31)	13.0 (10-25)	12.3 (9-20.0)
DFA	0.8 (0.0-1.2)	1.0 (0.17-3.4)	0.25 (0 -0.65)	0.17 (0 - 0.8)
(B) Hyperglycemia				
CA (%)	100 (95-100)	100 (92-100)	100 (93-100)	100 (92-100)
DT (min)	14.7 (5.1.-19)	11.6 (7.2-18)	12.1 (8-16.1)	12.0 (8 -16.2)
DFA	0.8 (0.0-1.4)	0.73 (0.3-1.7)	0.25 (0 -0.98)	0.33 (0.0 -1.2)

Discussion and Conclusion

Among the three proposed fusion schemes the evolutionary based (GA and GP) were the most efficient. Furthermore, the EWS-GA and EWS-GP outperformed the initially proposed EWS in terms of daily false alarm. However the detection time of hypo- and hyperglycemic events was slightly reduced. In terms of prediction accuracy an equal performance of 100% was obtained.

From the results, it can be seen that the fusion schemes permit higher detection accuracy with much lower false alarm rates. Further investigation is needed in order to improve the detection time. Concluding, the proposed EWS system might be a useful tool for hypoglycemic unawareness, while it can be used as a safety module in insulin pumps and controllers for an artificial pancreas.

References

[1] Eren-Oruklu et al, Automatica (Oxf). 2012 Aug;48(8):1892-1897.
[2] Daskalaki et al, Diabetes Technol. Ther. 2012 Feb;14(2):168-74
[3] Georga et al, IEEE J Biomed Health Inform. 2013 Jan;17(1):71-81.
[4] Daskalaki et al, J Diabetes Sci Technol. 2013 May 1;7(3):689-98.

Wireless Functional Electrical Stimulation

Manuel Jonas Bracher

Supervisor: Prof. Dr. Kenneth James Hunt
Institution: Institute for Rehabilitation and Performance Technology, Bern University of Applied Sciences
Examiners: Prof. Dr. Kenneth J. Hunt and Prof. Dr. Volker M. Koch

Introduction

The loss of voluntary function in limbs and other body parts, also known as paralysis, is caused by disease or injury to the neuromuscular system. However, in an upper motor neurone lesion, the muscles themselves retain their ability to contract and produce force. By applying appropriate electrical fields to the lower motor neurons, action potentials are provoked artificially. Functional Electrical Stimulation (FES) is used to restore body functions. Mobile and dynamic applications, such as cycling or walking, require powerful, portable devices of small size, which allow the patient to move freely and without disruption by long wires. Most currently available devices for FES come in a bulky design and thus are restricted in portability.

The aim of this project was to develop a novel wireless controlled FES system, which provides functionality for cycling applications and fulfils output performance requirements for the activation of large human muscles.

Materials and Methods

The proposed FES system consists of three major sub-units.

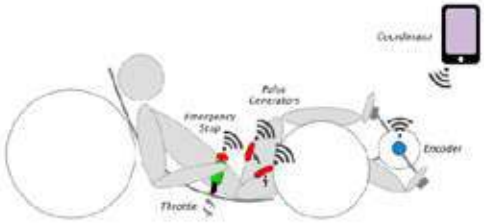


Fig. 1 Concept for wireless controlled FES-cycling.

The first one is the coordination unit, which serves as a user interface and manages the overall process. It interacts wirelessly with stimulation units, which form the second major sub-unit. Each stimulation unit generates electrical pulses on four channels simultaneously. In cycling applications two stimulators are required – one per leg. A sensor system, including a data transmitter, is placed directly on a recumbent tricycle and forms the third sub-unit of the system. It logs sensor data, and sends it wirelessly to the stimulators. Depending on the pedal position, measured by an encoder, specific leg muscles are triggered phase-wise in order to obtain cyclic motion of the legs. Using a throttle, the user can change the stimulation intensity, resulting in changing cycling speed. An emergency stop button enables the rider to terminate the muscle stimulation immediately.

The hardware and software for the stimulators and the data transmitter, as well as the application code for the smartphone-based coordinator (Android OS), were developed within this thesis.

Results

The described system has been implemented and tested. Stimulation parameters can be set individually for each channel on each unit (current amplitude: 10-150 mA, pulse width: 15-500 µs, frequency: 5-100 Hz). The accuracy of stimulation pulse modulation is of the order of 1 µs with regard to timing and 0.5 mA in amplitude.

Fig. 2 Newly developed FES-system in cycling use.

Textile leg pockets allow installation of the stimulation units directly on a patient's legs in order to keep the distance to the surface electrodes as short as possible. In order to set up a flexible and low power network ANT technology was selected. Its determined range is ~30 m.

Discussion

Tests have shown that all specifications were met, and performance requirements were fulfilled. Pulse modulation can be rated as very accurate. The wireless range is sufficient for the proposed applications. Due to its aspect ratio, minimal wire length and ease of operation, this novel system has substantially improved functionality when compared to existing FES devices.

Acknowledgements

I'd like to offer my special thanks to Prof. Dr. Kenneth J. Hunt, who introduced me to the interesting field of FES. Further, all the support received from IRPT members and my family is gratefully acknowledged.

Development, Production and Validation of a Needle Guide for Percutaneous Ablation Therapy

Boris Brun

Supervisor: Dr. Matthias Peterhans
Institution: CAScination AG
Examiners: Prof. Dr. Stefan Weber and Dr. Matthias Peterhans

Introduction

Percutaneous ablation therapy required accurate placement of applicator needles into tumors to be treated. Recent research at ARTORG center has shown that the use of a mechanical needle guide leads to a significant improvement in needle placement accuracy when compared to free-hand needle insertion [1]. The research was performed using commercially available devices for needle guidance such as the Atlas Needle Guide (Elekta, Stockholm, SE) and iSys1 neelde Guide (iSys, Kitzbühel, AT). Both function with the CAS-One IR system, but have several disadvantages in terms of usability and accuracy of calibration/tracking as none of them has been developed for navigated needle insertion. Therefore, there is a large potential for improvements towards a dedicated product for navigated percutaneous interventions.
The aim of this thesis is the development and production of a customized needle guidance device for navigated needle insertion with CAS-One IR (CAScination, Bern, CH).

Materials and Methods

After an analysis of existing products on the market, a two-axis needle, self-blocked alignment mechanism with adaptable needle guide is selected. Based on this choice, a first prototype is designed and manufactured using 3D printing on a Z-Corp Z510 printer using zp131 plaster powder (3D Systems, Rock Hill SC, USA). The prototype is then used to verify if usability and workspace requirements for the clinical application on the liver are fulfilled. Three optimization iterations are done. Especially the fixation to a 3D arm, the alignment of the rotational axes and the marker visibility are evaluated and quantified with a benchmark. Finally, the production of a fully clinically applicable prototype is started based on guidelines for medical devices and production documents.

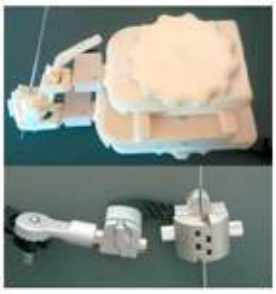


Fig. 1 iSys1 (top), Atlas needle guide (bottom)

Results

The produced aiming device has two rotational axis with a working range of +/- 26° and a resolution for fine adjustment of 0.2°. A usability test composed of representative trajectories defined by a radiologist shows that the device could be aligned with the trajectory in 8/9 cases while the markershield was visible by the IR camera. Targeting accuracy was tested on a rigid wooden phantom and shows a needle placement error of <2mm for 3 different trajectories with an average length of 12cm. Furthermore, the device covers the range of clinically used needles with diameters 0 to 5mm.

Fig. 2 Customized needle guidance

Discussion

The result of the thesis is a customized needle guidance, which was successful integrated in the CAS-One IR framework. Produced out of biocompatible materials, the device is expected to be compatible with standard sterilization process. The proposed geometry allows to reach most clinically relevant needle trajectories and to guide all types of applicators/needles used in percutaneous interventions. Future work could optimize the geometry to reach strongly inclined lateral trajectories.

References

[1] D Wallach, et al. (2013) Comparison of free-hand navigated and aiming device navigated targeting of liver lesions, International Journal of Medical Robotics and Computer Assisted Surgery: MRCAS Jul

Stereovision using a Biprism in the Anterior and Posterior Eye

Adrian Büchi

Supervisors: PD Dr. Jens Kowal and PhD candidate Sandro De Zanet
Institutions: ARTORG Center for Biomedical Engineering Research, Universität Bern
Universitätsklinik für Augenheilkunde, Universität Bern
Examiners: PD Dr. Jens Kowal and PD Dr. Mauricio Reyes

Introduction

Accurate diagnosis and therapy are crucial to minimize retinal disorders and consequently impairment of vision. Current diagnosis of eye diseases such as retinoblastoma or diabetic retinopathy, rely heavily on the experience of the ophthalmologist. In the scope of this thesis the potential of 3D stereo-vision of visible parts of the eye is explored using a biprism. In such a system a single-lens camera results in two virtual cameras providing binocular vision. Compared to a conventional stereo-camera system, this has numerous advantages for stereo reconstruction (e.g. correspondence search).

Materials and Methods

Images of test objects and the iris were acquired with a custom designed camera setup and the integration of a biprism into a fundus camera was examined.

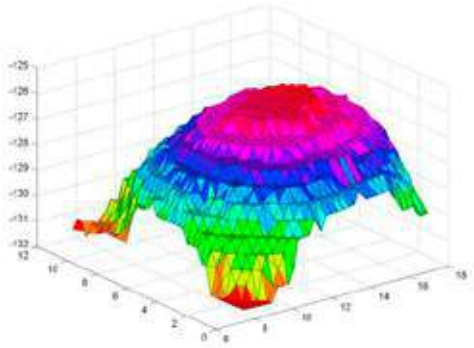


Fig. 1 3D Reconstruction of a Spherical Object that was used for Radius Estimation by the Means of Least-Squares

As an initial step, stereo images are preprocessed and rectified by basically rotating the image frame captured with the camera. Scale-invariant feature transform (SIFT) descriptors are matched in both images. For every matching pair the angle to the horizontal axis is calculated. The average angel is then taken to rotate the image. The result is a stereo plane with epipolar lines horizontally aligned. Different dense correspondence algorithms were implemented. In a hierarchical approach disparity search is performed on a downsized image used as initial estimate of the disparity map that is refined with disparity searches on higher-level image layers.

Results

Visual inspection showed anatomically correct reconstructions. To support the visual assessment, a numeric evaluation of the models was done. Two concepts were used, comparing the radius of a spherical object to the one estimated with reconstructed 3D points and comparing found dense correspondences against SIFT descriptor matches. The radius of the sphere is reliably estimated (7.69mm) compared to the measured radius (7.9mm). For the same object 96.70% of the dense correspondences differed by maximal one disparity compared to the SIFT descriptor matches.

Fig. 2 3D Reconstruction of the Iris using a Hierarchical Approach of a Dense Reconstruction Algorithm

Discussion

A great advantage of a biprism system is that a single camera can be used for 3D vision. A drawback is that less than half of the camera sensor is used for each stereo view. This should not pose a problem considering the high resolution of CCD cameras. Surprisingly high accuracy was accomplished for such a simple system and it was shown that stereo views of the fundus can be acquired using a biprism.

Reference

L. DooHyun, A novel stereo camera system by a biprism, Robotics and Automation, IEEE Transactions on 16(5), 528-541, 2000

Master's Thesis in Biomedical Engineering

Development and Evaluation of Algorithms to Detect and Analyze Activities of Daily Living in Patient's Homes

Marcel Büchler

Supervisors: Prof. Dr. sc. Tobias Nef and M.Sc. Reto Stucki
Institutions: Gerontechnology and Rehabilitation Research Group, Universität Bern
ARTORG Center for Biomedical Engineering Research, Universität Bern
Examiners: Prof. Dr. sc. Tobias Nef and Prof. Dr. med. Urs P. Mosimann

Introduction

Dementia is an age-associated disease with a growing number of patients. Despite cognitive impairments, most dementia patients wish to live independently in their own home as long as possible. Doctors and caregivers have a variety of possibilities to assess the patient's cognitive status, but they often lack knowledge about how well the patients cope with activities of daily living (ADL). To provide good and effective care, information about how good patients cope with ADL is important. It would be interesting to determine the ADLs directly in patient's homes. A possible technical solution are non-intrusive sensor networks to monitor patient's activities.

Materials and Methods

Prior to this master thesis, a non-intrusive sensor system has been developed, and verified in a pilot study with ten healthy subjects [1]. The systems sensors measure ambient values such as motion, temperature, luminescence and humidity. They are set up in every room of a subject's flat to capture ambient values. The measured data is transferred via a wireless protocol to a laptop, which stores it for later analysis. Furthermore the subjects were given a protocol device, with the aid of which they logged the performed ADL.

Fig. 1 Non-invasive wireless sensor network consisting of ten sensor boxes and a laptop. The sensors measure ambient values and transfer them via a wireless protocol to the laptop, which stores the data.

Based on existing classification algorithms, a combined clustering-classification algorithm was developed to determine ADLs. The evaluation of the classification performance was done with a cross-validation on the data measured during the pilot study. Furthermore a data viewer was implemented, which provides a convenient way to view the ADLs the subject performed by the subject.

Results

After developing an initial clustering, three classification algorithms were evaluated.

Performance comparison of tested classifiers		
Classifier	***Sensitivity***	***Specificity***
Naïve Bayes	26.72%	89.89%
Support Vector Machine	41.68%	92.34%
Random Forest	81.23%	99.09%

Fig. 2 Comparison of classifier performance (mean performance over all ADLs) in cross-validation.

After improving the clustering algorithm, a mean sensitivity of 81.23% and a mean specificity of 99.09% was achieved using Random Forest. Classification results were visualized in the implemented data-viewer.

Fig. 3 Two visualization examples of the classification results. The top image shows, that sometimes motionless activities (like watching TV) can be missed. The bottom image illustrates, that visitors not only can be detected, but that also their ADLs are determined.

Discussion

Of the tested classification algorithms Random Forest was found to have the best classification performance. Furthermore it could be shown, that clustering can be used to improve classification performance.

References

[1] Stucki R. et al., A webbased non-intrusive ambient system to measure and classify activities of daily living, Journal of Medical Internet Research, 16(7):e175, 2014.

Development of a Device Suitable for the Acute Assessment of Stretch Activated Ion Channels During Patch Clamp Experiments

Etienne de Coulon

Supervisors: Prof. Dr. Stephan Rohr and Prof. Dr. Olivier Guenat
Institutions: Department of Physiology, University of Bern & ARTORG Center, Lung Generation Technologies

Examiners: Prof. Dr. Olivier Guenat and Prof. Dr. Stephan Rohr

Introduction

Mechanosensitive ion channels (MSCs) incorporated into cell membranes react to the application of strain by changing their conductance. They play important roles under physiological conditions where they act as sensing elements in many regulatory feedback systems. So far, experimental systems permitting a linear stretch/relaxation of mechanosensitive cells with dynamics comparable to the in vivo situation are not available. Moreover, systems that would allow to perform patch clamp experiments on single cells undergoing linear stretch are not available. This is most likely due to the fact that such a system needs to keep positional stability at the site of the patch electrode during stretch with a precision in space < 1 µm.

Materials and Methods

Following initial design and simulation studies, the system ultimately implemented consists of a flexible cell culture dish (FCCD) that is actuated by stretching kinematics based on voice coil actuators. The design of the FCCD was inspired by a honeycomb structure which was modified to obtain a strain fields as uniform and unidirectional as possible. The FCCD is realized by a polydimethylsiloxan casting process, whereby the mechanical interfaces are part of the mold to avoid clamping stress and alignment problems. Voice coil actuators were chosen because they offer very high dynamics, low vibration and high force-to-size ratio.

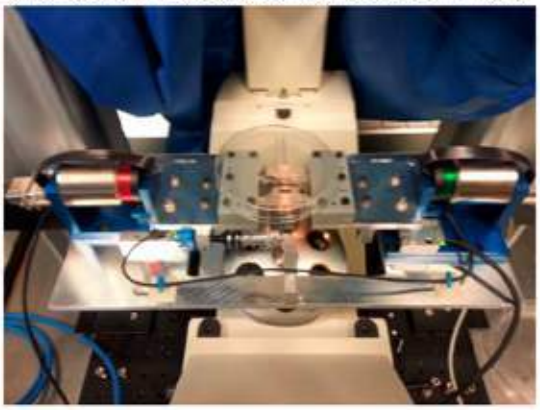


Fig. 1 Cell stretching kinematics with mounted flexible cell culture dish, integrated into an inverted microscope.

Results

Whereas the system designed met all the requirements in regard to the dynamics and size of stretch, the positional stability did ultimately not reach the goals set forward. In-plane displacements during stretch are shown in Fig. 2 and reached, in the center, 11 µm. Displacements in z-direction as estimated by focus adjustments of the microscope amounted to < 4 µm during application of 10% strain.

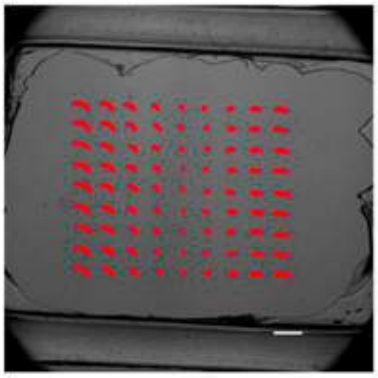


Fig. 2 in-plane displacement of the central membrane of the FCCD as a result of 12% principal strain. The white bars correspond to 500 µm.

Discussion

While the systems offers unprecedented dynamics for investigating stretch dependent activation of mechanosensitive channels, it falls short of producing the positional stability required for patch clamp experiments. As is, it will permit for the first time optical measurements of impulse conduction in cardiac cell strands subjected to precisely timed changes of strain of defined magnitudes and dynamics.

References

Vishal Nayyar, K. Ravi-Chandar, Rui Huang Stretch-induced stress patterns and wrinkles in hyperelastic thin sheets The University of Texas at Austin

Acknowledgements

The study was supported by the Department of Physiology.

Experimental Validation of an HR-pQCT-based Homogenized Finite Element Analysis of Human Distal Radius Sections

Andreas Dünki

Supervisors: Dr. Hadi Seyed Hosseini and Prof. Dr. Philippe Zysset
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Examiners: Prof. Dr. Philippe Zysset and Dr. Hadi Seyed Hosseini

Introduction

Osteoporosis is a disease that reduces bone mass and consequently increases the risk of fracture. A typical location of an osteoporotic fracture is the distal radius. Bone mass and its micro-architecture can be measured in the distal radius using high-resolution peripheral quantitative computed tomography (HR-pQCT). Based on the obtained images, a linear micro finite element (μFE) analysis can be performed to estimate fracture load. This computation takes currently from 30 minutes to half a day. A new generation of HR-pQCT scanner was recently released, namely the XCT2, providing higher resolution or reduced scan time. The aim of this project was to validate experimentally a non-linear XCT2-based homogenized FE (hFE) model to quantify stiffness and strength of the human distal radius at a reduced computational cost.

Materials and Methods

A compressive testing device for bone sections was designed that could be adapted on a servo-hydraulic testing machine. A ball joint system allowed rotation of the compression plate around all axes and an optical tracking system provided the actual position of the plate. Twelve pairs of cadaveric forearms were obtained from human donors (mean age = 77.2 ± 8.5 years). All arms were scanned intact to replicate *in vivo* conditions. Both a slow, high resolution and a fast, low resolution scanning protocol were applied. A 20mm bone section was then dissected out of each forearm and subjected to axial compression using the developed device (Fig. 1). Stiffness and strength were extracted from the resulting load-displacement curves. Voxel-based hFE models of the sections were then generated from the two types of XCT2 images.

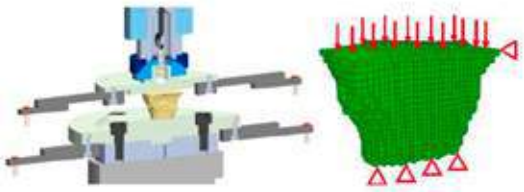


Fig. 1 Experimental compression setup (left) and voxel-based hFE model of the same section (right).

The hFE models used a calibrated bone volume fraction (BV/TV) and fabric-based non-linear material model to account for heterogeneity and anisotropy of the bone. A simplified axial compression without rotation was applied to compute stiffness and ultimate load of each sample (Fig. 1). Finally, validation was performed by a one-to-one comparison of the experimental stiffness and ultimate load with their numerically predicted values using linear regression analyses.

Results

Strong correlations between hFE and experimental results were obtained for stiffness and ultimate load for both protocols. However, the hFE simulations predicted higher values for stiffness and ultimate load, especially for the high-resolution protocol (Fig. 2).

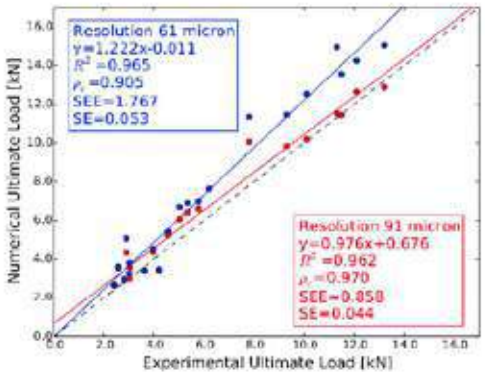


Fig. 2 Experimental validation analysis after excluding 3 specimens (2 outliers and 1 incomplete image).

Discussion

The results of this study confirm that the XCT2-based hFE models are reliable tools to predict the ultimate load of the human distal radius. In fact, the correlation between experimental and numerical strength obtained here is slightly better than the one from a previous validation study using XCT1-based non-linear hFE with smooth meshes (R^2=0.935) [1]. This may be attributed to the wider range in radial strength measured in this study and to the higher quality of the XCT2 reconstructions.

The predictions of the hFE simulations may be further improved by inclusion of the rotation of the loading plate during compression and an extended calibration function to cover the full range of bone volume fraction. The results and computing time of the hFE models remain also to be compared to the ones of the standard μFE models.

References

[1] Varga P. PhD Dissertation, TU-Wien 2009.

Acknowledgements

Thanks to ISTB team members and our industrial partner SCANCO Medical AG for their support.

Master's Thesis in Biomedical Engineering

Quantification of Insulin Sensitivity in Type 1 Diabetic Patients on Sensor Augmented Insulin Pump Therapy

Aurélie Drapela

Supervisors: Prof. Dr. Eng. Stavroula G. Mougiakakou and Dr. Eng. Elena Daskalaki
Institutions: ARTORG Center for Biomedical Engineering Research, University of Bern
Department of Endocrinology, Diabetes and Clinical Nutrition, University of Bern
Examiners: Prof. Dr. Eng. Stavroula Mougiakakou and Prof. Dr. med. Peter Diem

Introduction

People suffering from Type 1 Diabetes (T1D) need multiple daily insulin injections to control their blood glucose. The dose should be adapted for each meal in order to avoid hypo- or hyperglycemic events, which can lead to dangerous situations for the patient. Each individual with T1D reacts differently to insulin. Within a day a person can show varying insulin sensitivity (S_I), and thus the calculation of the right insulin dose is a challenging task. Insulin sensitivity defines by how much the blood glucose will be lowered after injection of one unit of insulin. It is an important element for individuals with T1D as an indication of how the body responds to insulin and will be useful to optimize insulin therapy.

Materials and Methods

Insulin sensitivity in individuals with T1D is estimated from clamp test or an intravenous glucose tolerance test, which is interpreted with the minimal model of Bergman [1]. This is a mathematical model describing the behavior of the glucose-insulin system. The acquired during the test glucose and insulin concentrations yield a value of insulin sensitivity, S_I(oral). Both methods are expensive and inconvenient for the patient. Therefore, indirect methods based on continuous glucose monitor (CGM) and the insulin pump data are being developed. With these methods, intra-day variability can be assessed without requiring blood sampling, which constitutes a considerable benefit for the patient. One of these methods uses transfer entropy (TE), which is the transfer of information between glucose and insulin, named S_I^{TE} [2]. TE is based on probabilities and assesses causality between glucose and delayed active insulin time series. A second method, named S_I^{SP}, is an adaptation of the minimal model of Bergman [3]. Using the adult population of the UVa/Padova T1DM simulator the two new methods were compared to the minimal model estimation considered here as reference value. Different meal scenarios, having varying carbohydrate (CHO) content, were used to test the three implementations. Insulin was administered with a pump according to a fixed insulin to CHO ratio (IC ratio) and the amount of CHO in the meal and the glucose concentration was measured by an *in silico* CGM.

Results

All subjects had good glucose control. Correlation analysis showed that for the adult population the three methods correlate positively with significant p-values (p<0.01). The details are shown in *Table 1*. Of note, S_I^{TE} needs four days of data to reliably estimate one value of insulin sensitivity but does not need information about the meals consumed. S_I^{SP} is able to estimate a value for each meal, but requires that the blood glucose concentration is lower than 150 mg/dl at the end of the observed period. This is problematic when several meals are ingested in a short period of time, as the glycemic responses add up and this condition is not fulfilled anymore.

Table 1 The correlation coefficients of the analyzed meal scenarios

	thee equal meals	complex scenario
S_I(oral) vs. S_I^{SP}	0.54597*	0.62160*
S_I(oral) vs. S_I^{TE}	0.51811*	0.41494*
S_I^{SP} vs. S_I^{TE}	0.49850*	0.30346*

* p<0.01

Discussion

The newly presented methods are able to estimate insulin sensitivity reliably under given circumstances. The good correlation of S_I^{SP} with the reference method S_I(oral) could be expected, as the latter serves as a basis to the new method. To determine which method is better at quantifying insulin sensitivity, further investigations have to be performed e.g. with individuals with T1D. As insulin sensitivity is, along with the amount of CHO in the meal, an important parameter for the estimation of the insulin dose, it is conceivable that S_I might play a role in bolus calculators and artificial pancreas algorithms in the future. Furthermore, current studies are investigating the effect of physical activity on insulin sensitivity with the goal to include this information in artificial pancreas algorithms as well.

References

[1] R. Bergman, et al., Am J Physiol. 1979 Jun;236(6):E667-77.
[2] E. Daskalaki, et al., Conf Proc IEEE Eng Med Biol Soc. 2013, 2013: 3487–90.
[3] M. Schiavon, et al., Diabetes Care. 2014 May; 37(5):1216-23.

Calibration and Reproducibility of an HR-pQCT based hFE Method to assess Strength of the Distal Radius

Jonas Fabech

Supervisors: Dr. Hadi S. Hosseini and Prof. Dr. Philippe K. Zysset
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Examiners: Prof. Dr. Philippe K. Zysset and Dr. Hadi S. Hosseini

Introduction

Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD) and increased fracture risk. High Resolution peripheral Quantitative Computed Tomography (HR-pQCT) allows *in vivo* assessment not only of BMD, but also of the 3D microarchitecture suitable for computing radial strength with micro finite element (μFE) models. A second generation HR-pQCT, the XCT2, recently emerged on the market with reduced measurement time and higher image resolution.

The aims of this study were 1) the establishment of the calibration functions for BMD and fabric necessary for an alternative, faster homogenized FE (hFE) approach 2) Measurement of the reproducibility errors of BMD and the mechanical variables calculated by hFE using XCT2

Materials and Methods

Fourteen pairs of human forearms were scanned three times on the XCT2 with high (HR=61μm) and low resolution (LR=91μm). The most distal radius sections of 20mm were dissected and scanned with an *in vitro* scanner μCT100 (Scanco Med. AG) with a resolution of 16.4 μm isotropic voxel size. Using rigid image registration all XCT2 scans of each sample were registered to the reference images of the μCT100. Registered cubical regions of interest (n=133) were selected to calculate bone volume fraction (BV/TV) and fabric eigenvalues in the XCT2 and μCT100 images. Following hFE analyses of the radial sections, the short-term reproducibility precision errors of BMD, stiffness and ultimate load were evaluated for both HR and LR imaging protocols [1].

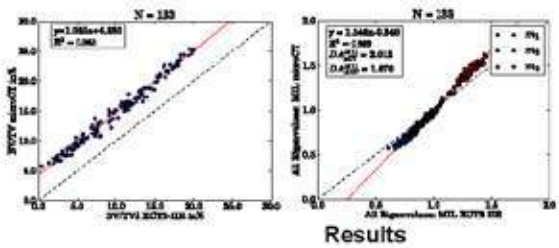


Fig. 1 Calibration functions for BV/TVd (left) and fabric eigenvalues (right). Evaluated based for XCT2-HR images.

The calibration functions for BV/TV and fabric eigenvalues are shown in Fig. 1, while the precision errors of BMD and the hFE variables are shown in Fig.2 for the two XCT2 measurement protocols.

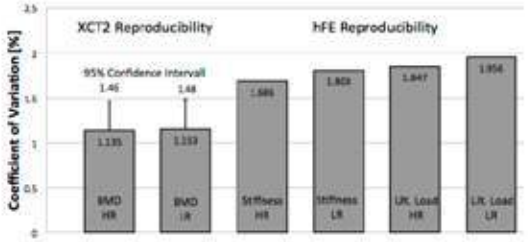


Fig. 2 Measured precision errors for XCT2 derived BMD and hFE based stiffness and ultimate load. (HR=61μm, LR=91μm isometric voxel size).

Discussion

The calibration functions based on the XCT2 for BV/TV (HR R^2=0.983; LR R^2=0.978) and MIL (HR R^2=0.989; LR R^2=0.968) (Fig. 2) showed better correlation compared to the results obtained in a previous study [2] where the first generation XCT1 scanner was used (BV/TV R^2=0.952; MIL R^2= 0.978). The reproducibility error of the XCT1 (82μm isometric voxel size) was evaluated in Mueller et al. and showed a precision error between 0.78-1.33% [3]. The achievements of the current work can be exploited in *in vivo* measurements of the XCT2 scanner to predict stiffness and strength of the human distal radius using the HR-pQCT-based hFE analysis. Several limitations must be mentioned. First the range of BV/TVd has a maximum of 20% and the extracted cubes are limited to trabecular bone. Second image registration included a rigid rotation and interpolation of the image, which may potentially reduce the image quality. Last BV/TVd calibration for hFE was based on the segmentation of the μCT images with a global threshold.

References

[1] C.-C. Glüer et al. Osteoporosis International 5:262-270, 1995.
[2] P. Varga and P.K. Zysset. Bone 45: 99-917, 2009.
[3] T.L. Mueller et al. Bone 44: 364-371, 2009

Acknowledgements

The project was supported by CTI grant no 14.311.1 PFLS-LS and the important support of Scanco Med. AG is gratefully acknowledged.

Diagnosing Phrenicus Paresis

Christian Fässler

Supervisors: Prof. Dr. Philippe Cattin
Institutions: Medical Image Analysis Center, University of Basel
Examiners: Prof. Dr. Philippe Cattin and Prof. Dr. Mauricio Reyes

Introduction

Impairment of the phrenic nerve causes partial or full paralyzation of the most important muscle for respiration, *i.e.* the diaphragm. To diagnose phrenicus paresis, the movements of the diaphragm have to be analyzed. Nowadays this is done with ultrasound or fluoroscopy examinations. A more sensitive and qualitative examination method could reduce the need of surgical treatment, which usually is necessary in the absence of recovery (spontaneous or due to other treatment techniques). Moreover, it would allow quantifying treatment success restricted to functional units of the diaphragm more precisely.

Currently applied radiological techniques analyze the diaphragm in maximal three dimensions (*e.g.* two spatial dimensions plus time). The developed program is supposed to improve examinations of diaphragm movements by analyzing the diaphragm in 4D automatically. Instead of analyzing points or lines of the diaphragm only, the dynamic behavior of the whole diaphragm as well as of functional units of the diaphragm can be evaluated.

Materials and Methods

3D MR images are analyzed sequentially to reconstruct the shape and movement of the diaphragm. First, a region of interest is determined to roughly localize the diaphragm in the volume. Then the images are enhanced and a modified Canny edge detection algorithm extracts the edge between the abdominal and thoracic cavities. The edges are used to calculate a Gradient Vector Flow field, which in turn is used as the external force field of a 3D snake (active contour). The final positions of the snake are used to reconstruct a 3D shape of the diaphragm. Concatenating the reconstructed diaphragms over time allows analyzing the movements of the diaphragm in 4D. Measures to quantify and qualify the reconstruction of the diaphragm and the movability of the diaphragm were introduced. Ground Truth was created for two breathing cycles of five healthy subjects, and used for a leave-one-out cross-validation.

Results

The mean Euclidean distance between voxels of the reconstructed diaphragms and the Ground Truth was between 1.81 mm and 3.53 mm for all subjects.

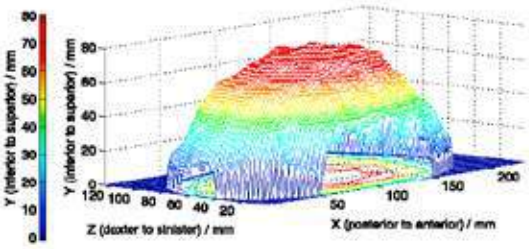


Fig. 1 3D reconstruction of the dexter hemidiaphragm

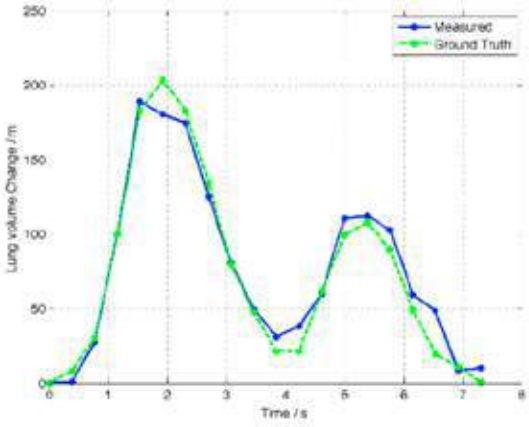


Fig. 2 Lung volume change of two breathing cycles of a healthy subject caused by diaphragm movement

Discussion

The results depend directly on the quality of the analyzed MR data but encourage further developments of the program and clinical routines using automatic 4D analyses nevertheless. Although the developed program is not ready for clinical use yet, it might be a valuable tool for research.

The developed program could also be used to create models of the diaphragm and for motion tracking of other organs, which could be registered to the diaphragm *e.g.* motion tracking of lung tumors for radiation therapy.

Designing and Building a Low Cost Strain-Controlled Dynamic Mechanical Stimulation Bioreactor

Christian Geissberger

Supervisors: PD Dr. Benjamin Gantenbein-Ritter
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Universitätsklinik für Orthopedie und Traumatologie, Universität Bern
Examiners: PD Dr. Benjamin Gantenbein-Ritter and Alexander Bürki

Introduction

Tendon and ligament injury is a major health problem worldwide, with only few treatment options. Partial tears or total ruptures of tendon and ligaments occur through sudden, excessive strain or repetitive loadings over long periods of time. Common treatments of partial or total ruptures range from physiotherapy to auto- or allograft replacement surgeries. Repairs using autografts bear the risk of damage to the donor site, whereas allografts pose the potential risk of immune reactions. An approach to repair injured or degenerated tendon/ligament lies in tissue engineered autologous grafts produced by dedicated bioreactors, applying dynamical mechanical stimulation to the tissue.

Materials, Methods and Requirements

Using an existing prototype device and a mechanical testing and sensing machine, three mechanical failure tests were conducted using human anterior cruciate ligament (ACL) samples. A displacement rate of 0.5mm/s was used and ACL properties, prototype concept and different fixation methods were tested. With this data, a strain-controlled mechanical stimulation bioreactor was developed and built. Basic requirements for the device included guaranteed sterility, controllable conditions of the sample chamber (pH, temperature, humidity, CO_2), secure fixation of different sample types (tendon, ligament, artificial grafts), continuous dynamic stimulation, exact strain control and force measurement.

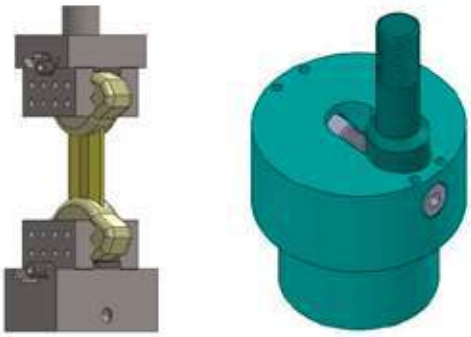


Fig. 1 a) CAD drawing of clamps with zigzag profile for sample fixation. Clamps feature holes for soft tissue samples or artificial grafts otherwise damaged by fixation. b) Strain adjustment wheel with ex-center. Radius up to 10mm, resulting in 20mm maximal displacement.

Results

The failure test results confirmed the literature and failure at the ligament ingrowth site was observed. The device fulfilled all vital requirements. Two secondary points, the space requirement (too wide to fit four in a row) and maximal possible frequency (4.56Hz instead of 5Hz) were not fulfilled.

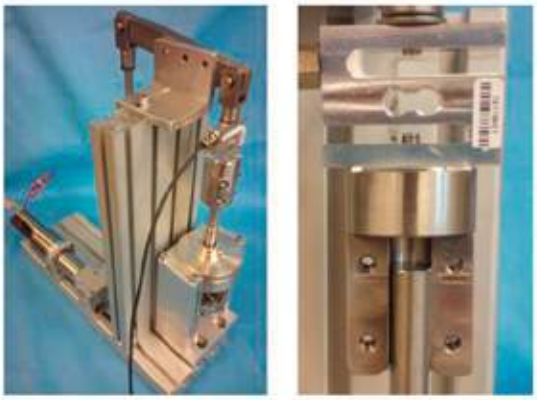


Fig. 2 a) Assembled device with motor block in back, sample chamber in front, force measurement adjacent to sample to minimize errors. b) Force measurement load-cell with open insertion mechanism, flexible height depending on sample geometry.

Discussion

The device fulfilled the main requirements and is able to mimic physiological mechanical tensile forces for different types of samples. A maximal displacement of 20mm is possible with a frequency of 4.56Hz and continuous torque of 2.5Nm. Compression and stretch forces are measured with 0.1% accuracy in the range of +/-100N. The fixation mechanism minimizes tissue damage and can secure a wide range of geometries. The cost of parts and labor was 3.5 times lower than commercially available products of similar capability. Final optimization and testing of the device was not possible due to time constraints.

References

Vavken, M.M.M.P. and B.C. Fleming, *The ACL Handbook*. Knee Biology, Mechanics, and Treatment. 2013: Springer.
Zhong, J.J., *Bioreactor Engineering*. 2011: p. 165-177.

Acknowledgements

The project was supported by a grant of the Swiss Orthopaedics Society (SGOT).

Master's Thesis in Biomedical Engineering

Female Turbo Cells: During *in vitro* Differentiation, Female IVD Cells of Degenerated Discs Produce Faster Proteoglycans

Marco Christian Gruber

Supervisor: Dr. Jivko Stoyanov
Institutions: Swiss Paraplegic Research, Spinal Injury Research, Nottwil
Examiners: Prof. Dr. Benjamin Ganterbein and Dr. Jivko Stoyanov

Introduction

Low back pain (LBP) is a pervasive problem that affects two thirds of adults at some point in their lives. There is a body of evidence suggesting that disc degeneration is associated with LBP. However, degenerative changes do not develop at the same rates in females as compared to males. In elderly subjects 55 years and older, females tend to have more severe disc degeneration than males [1]. Interestingly, the roles are switched at younger ages - young men are more inclined to have intervertebral disc (IVD) degeneration rather than age-matched women [2].

The aim of the thesis was to find a sex difference in cells harvested from degenerated discs. To accomplish this, IVD cells were taken from female and male donors aged 44 years and younger and differentiated to chondrogenic lineage on gelatin scaffolds, in both normoxia and hypoxia environments.

Materials and Methods

Chondrogenic differentiation of female and male IVD cells was investigated in donors who had a lumbar discectomy. Cells derived from Annulus Fibrosus (AF) and Nucleus Pulposus (NP) samples from pre-menopausal female donors under the age of 45 were used and compared to samples from age-matched male donors (aged 44 and younger). IVD cells were seeded on gelatin scaffolds and cultured for chondrogenic differentiation for 7, 14, and 28 days in normoxia, and 7, and 21 days in hypoxia. Chondrogenesis was assessed by cell viability, by measuring gene expression using quantitative polymerase chain reaction and extracellular matrix (ECM) accumulation with immunoblotting, immunohistochemical (Fig 1), and biochemical methods.

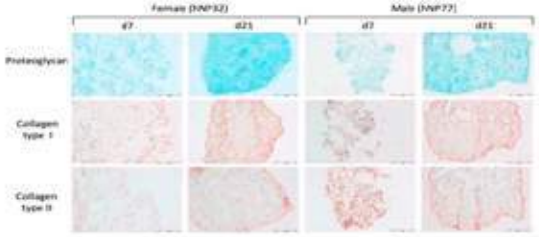


Fig. 1 immunohistochemistry microphotographs of female (h32) and male (h77) AF and NP cell constructs cultured in chondrogenic media for 7 and 21 days in 37° hypoxia. The figure illustrates the ECM staining of NP cells (entire scale bar is 500 µm).

Results

We could demonstrate through glycosaminoglycan (GAG) and DNA determination that female IVD cells produced faster proteoglycans than male IVD cells after 7 days in hypoxia cultivation. These results were in agreement with previous unpublished findings (Dr. Bertolo, personal communication) of an existing gender differences in ECM gene expression of IVD cells after 7 days of cultivation in normoxia.

In addition, we observed a significant difference in collagen type II mRNA expression between male AF and NP cells after 21 days of hypoxia cultivation. This result confirms those of others that collagen type II is re-expressed in alginate cultures.

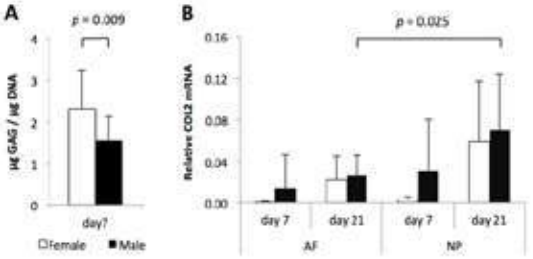


Fig. 2 A) Analysis of IVD cells cultured in chondrogenic media for 7 days at 37°C hypoxia. A) GAG/DNA Ratio, B) gene expression of collagen type II. Values indicate average result (n=12) and the error bar represents the standard deviation.

Discussion

This study, on gene expression, found no differences between sexes of other key ECM components of the disc, namely aggrecan and collagen type I and type II. Interestingly, aggrecan mRNA expression did not reflect the GAG accumulation of IVD constructs after 7 days. This can be explained by the fact that GAGs are not only attached to aggrecan but also to other proteoglycan types or that the peak of aggrecan mRNA production occurred at a time point before the sampling. However, more work on sex differences in IVD cells needs to be done, as chondrogenic differentiation was only tested in an ill-defined cell population. Thus, in further studies, IVD cells from healthy donors should also be tested.

References

[1] de Schepper, E.I., et al., Spine (Phila Pa 1976), 2010. 35(5): p. 531-536.
[2] Miller, J.A., C. Schmatz, and A.B. Schultz, Spine (Phila Pa 1976), 1988. 13(2): p. 173-8.

Random Forest based Fully Automatic Brain Tumor Segmentation from Multiple MRI Sequences

Simon Habegger

Supervisor: Raphael Meier, MSc Biomedical Engineering
Institution: Institute for Surgical Technology & Biomechanics, University of Bern
Examiners: Prof. Dr. Mauricio Reyes and PD Dr. Johannes Slotboom

Introduction

Automatic brain tumor segmentation is important to establish an accurate diagnosis and to assess treatment success. The current model is based on the structural T_1-, T_{1c}-, T_2- and FLAIR-weighted MRI sequences. In a first step, a number of different image features are extracted from the images. These features contain information on which the assignment of a tissue label via a random forest is based on. To take spatial relations into account, the random forest output is regularized with a conditional random field. The first part of the thesis was concerned with extending the structural image set with the functional ADC map. An ADC map is calculated from diffusion weighted images and is used in clinics for diagnosis and treatment assessment of brain tumors. The second part of the thesis focused on novel Riesz texture features and their use for automatic brain tumor segmentation. In a last part, the employed weak learner was replaced with two alternative models. The influence of these models with respect to segmentation performance was evaluated.

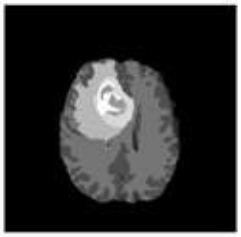


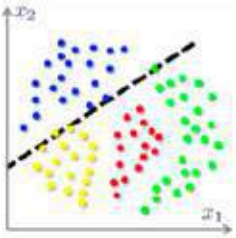
Fig. 1: Classification output of random forest and subsequent regularization step. Labels for healthy tissue (gray matter, white matter, cerebrospinal fluid) and tumor (necrosis, edema, enhancing and non-enhancing tumor).

Materials and Methods

The work of this thesis was based on the fully automatic brain tumor segmentation model first proposed in [1]. As a result of subsequent work described in [2], 237 image features were extracted from the structural image set. The performance of this feature set was used as base for comparison during this thesis. For the evaluation of the ADC map two experiments were performed. The first experiment was conducted to evaluate if the performance of the segmentation model can be increased with the additional ADC features. The second experiment was performed to investigate whether the ADC map and the T_2-weighted sequence contain redundant information. The Riesz features, obtained from the Riesz transform, are rotation and scale covariant. These features and derivations thereof (bag-of-words, energy) were evaluated in a similar manner as the ADC features.

The alternative weak learner model consisted of an oblique splitting hyperplane. In a first experiment, the hyperplane was computed based on ridge regression (RR) and in a second experiment principal component analysis (PCA) was used.

Fig. 2: Oblique splitting hyperplane as weak learner model. The orientation of the hyperplane is obtained from ridge regression and principal component analysis. (Source: Criminisi et al., Decision forests for computer vision and medical image analysis)



Results

Qualitatively, one could observe performance differences in all three parts of this work compared to the performance based on the feature set from [2]. The largest impact could be seen for the alternative weak learner models. However, a quantitative analysis revealed that no statistically significant performance improvement could be achieved with neither the ADC nor the Riesz features or the alternative weak learner models.

Discussion

Although ADC maps appear to be valuable with respect to brain tumors in clinics, the knowledge transfer from clinics to the current technical segmentation approach is rather challenging. The Riesz texture features seem to have promising properties for extracting image information. Nevertheless, at this point it remains unclear whether the current segmentation pipeline can take full advantage thereof. The experiment with alternative weak learner models has revealed that it is important to understand the data arrangement in the high dimensional feature space to choose a reasonable weak learner. In summary, this thesis has given an important insight into three different aspects of the current segmentation model.

References

[1] Bauer et al., MICCAI BraTS, 2012
[2] Meier, Master Thesis 2013

Acknowledgements

I would like to thank my supervisor Raphael Meier and my first examiner Mauricio Reyes for their support and for letting me pursue my own ideas.

Master's Thesis in Biomedical Engineering

Characterization of Electrode-Tissue Impedance and Reduction of Baseline Wander in Esophageal ECG Recordings

Martin Heller

Supervisors: Prof. Dr. Josef Goette, Dr. med. Reto Wildhaber and Dr. Thomas Niederhauser
Institutions: Institute for Human Centered Engineering HuCE, Bern University of Applied Sciences
Examiners: Prof. Dr. Marcel Jacomet and Prof. Dr. Josef Goette

Introduction

Over many decades, the electrocardiogram (ECG) has become an important diagnostic tool for diseases of the heart muscle or the heart's electrical conductivity system. Unfortunately, the important signals from the atria are much weaker (than the QRS) and are not always easily recognizable.

The esophageal ECG (eECG) plays an important role in long-term measurements. The position of the esophagus near the heart is a great advantage in recording the signals from the atria. In the eECG, however, motion artefacts (called baseline wanders BLW) can be caused by swallowing or breathing, or even by the patient's heart contraction itself.

Since the ECG has frequencies similar to the BLW, motion artefacts are not easy to filter out. For this reason, a new technique must be used to differentiate these signals.

An electrochemical model of the electrode-skin interface was developed by Webster. A similar model for the electrode-esophagus interface has to be worked out. An Electrical Impedance Spectroscopy (EIS) must be used to determine the different impedances of the interface. Since the various electrical sources are connected by different impedances, they should react differently on load variations.

Measurements and Results

In Vivo: Several measurements were made at a pig's esophagus. Since the conditions changed during the measurements (movement of the catheter, gastric acid has surged up into the esophagus), only a part of the measurements were then used to build up a second order model.

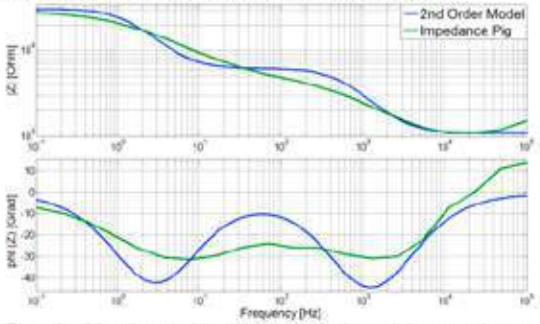


Fig. 1: Measured impedance of the pig's esophagus (green) compared with the second order model (blue).

In Vitro: Measurements were obtained because measurements with a low frequency in the range of mHz (expected low pole frequency) are not possible to cover in an in vivo setup. Therefore we imitated the electrolyte (mucus/saliva) in vitro and measured in four different sodium chloride solutions (NaCl).

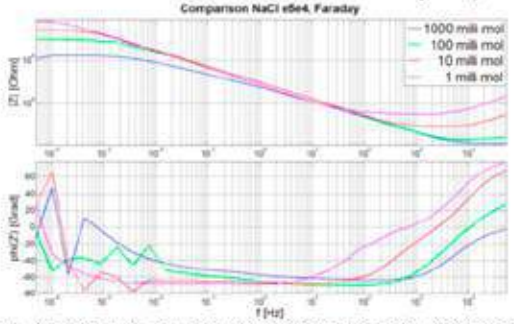


Fig. 2: EIS with several NaCl concentrations (milli mol). The impedances rise and cutoff frequencies move to lower frequencies as the NaCl concentration decreases.

Discussion

The data which we collected from the pig's esophagus are not transferable one-on-one since the pig was under general anesthetic and conditions were not stable during the measurements. Nevertheless, the in vivo measurement shows that the esophagus-electrode interface behaves like a model higher order than two.

The in vitro measurement explains how the system influenced by NaCl: The impedance falls and the possibility of electrochemical corrosion and disruptive breakdown of the electrode increases along with the increased NaCl concentration.

Since gastric acid (HCl) may rise up into the esophagus, measurements with HCl should be included to enhance the quality of the model of the esophagus-electrode interface.

References

R. Wildhaber, Removing ECG Motion Artifacts by Adaptive Signal Decomposition, 2014.

J. Goette, Biomedical Signal Processing and Analysis, 2014.

J. G. Webster, Biopotential Electrodes, Medical Instrumentation: Application and Design. 2009.

Acknowledgements

I would like to express my gratitude to the HuCE Institute of the BFH, especially to my supervisors Reto Wildhaber, Josef Goette and Thomas Niederhauser who have supported me throughout the work on my master's thesis.

Investigation into the Suitability of Collagen Scaffolds for Use in Anterior Cruciate Ligament Repair

Rachel Horovitz

Supervisors: PD Dr. Benjamin Gantenbein and Dr. med. Sandro Kohl
Institutions: Institute for Surgical Technology & Biomechanics, University of Bern, Switzerland
Department of Orthopaedic Surgery and Traumatology, Inselspital, University of Bern, Switzerland
Examiners: PD Dr. Benjamin Gantenbein and Dr. med. Sandro Kohl

Introduction

Anterior cruciate ligament (ACL) injuries are very common; in Germany incidence of ACL ruptures is estimated at 32 per 100,000 in the general population and in the sports community this rate more than doubles. Current gold standard for anterior cruciate ligament repair is reconstruction using an autograft. However, this approach has shown some limitations. A new method has been heralded by the Knee Team at the Bern University Hospital (Inselspital) and the Sonnenhof clinic called Dynamic Intraligamentary Stabilization (DIS) which keeps ACL remnants in place in order to promote biological healing and makes use of a dynamic screw system. The aim of this study was to investigate the use of collagen patches in combination with DIS to support ACL regeneration.

Materials and Methods

Tenocytes (TCs) and human bone marrow derived mesenchymal stem cells (MSCs) were seeded on two types of three dimensional carriers currently approved for cartilage repair, Novocart (NC) and Chondro-Gide (CG). These scaffolds comprise collagen structures with interconnecting pores originally developed for seeding of chondrocytes. Cells were cultured on these patches for up to 7 days.

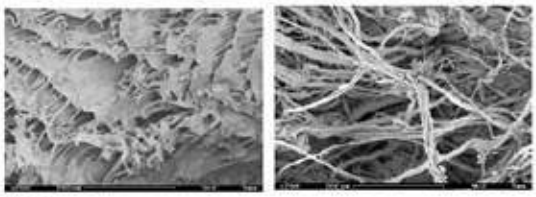


Fig. 1 Scanning electron microscopy (SEM) images of Novocart (left) and Chondro-Gide patches (right) 200x magnification.

Cells were also seeded in mono layers and on culture inserts to evaluate the effect of co-culturing the two types of cells. We were interested in assessing whether the patches provide a suitable environment for TCs and for MSCs and as such would enable proliferation and adherence. Further, we wanted to test the potential of MSCs to differentiate into a TC phenotype. Outcome measures included metabolic cell activity and proliferation, DNA, glycosaminoglycan and hydroxyproline levels, as well as relative gene expression. Microscopic imaging techniques were used to complement quantitative analyses.

Results

Adherence and proliferation of cells was confirmed with the metabolic cell activity assay as well as with confocal and scanning electron microscopy as can be seen in Figures 2 and 3. Relative gene expression analysis suggests an up-regulation of ligament markers as well as a down-regulation of Aggrecan for TCs.

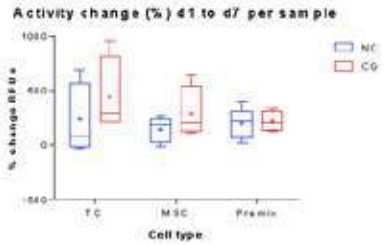


Fig. 2 Relative change in metabolic cell activity from day 2 to day 7 by cell type seeded.

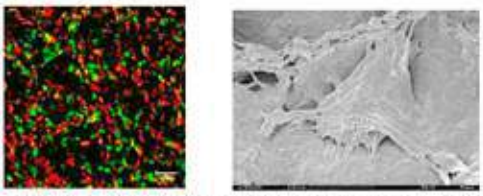


Fig. 3 Confocal laser microscopy image of a mix of MSCs and TCs cultured on NC patch for 7 days (left) and SEM image of an MSC on NC patch after 7 days (right).

Discussion

The results of these experiments illustrate the potential of collagen patches seeded with cells for use in ACL repair alongside DIS. To provide more conclusive results with regards to differentiation potential of the MSCs, longer experiment durations may be necessary.

References

[1] Voigt C., Schönaich M., Lill H. Anterior Cruciate Ligament Reconstruction: State of the Art. Eur J Trauma.32:332–9, 2006.
[2] Kohl, S. Vordere Kreuzband-OP-Technik: "State of the Art" und Zukunft. Schweizerische Zeitschrift für Sportmedizin und Sporttraumatologie 61 (2), 25–30, 2013.

Acknowledgements

The support of Dr. med. vet. Kathrin Kühni and Prof. Dr. med vet. Michael Stoffel, division of Veterinary Anatomy University of Bern, in SEM image acquisition, as well as of Dr. Samantha Chan in biochemical analyses is gratefully acknowledged.

Master's Thesis in Biomedical Engineering

Development of a microfluidic pump system for the recirculation of cell culture media

Andreas Hugi

Supervisors: Prof. Dr. Olivier T. Guenat and Janick Stucki
Institutions: ARTORG Center for Biomedical Engineering Research, University of Bern
Examiners: Prof. Dr. Olivier Guenat and Dr. Thomas Marti

Introduction

In-vitro microfluidic systems are ideally suited for high throughput screening assays and are expected to play a crucial role in the development of biomimetic organs. However, the transition from macro- to microscale implies a significant reduction of oxygen and nutrients availability for the cells cultured on chip. Therefore, the perfusion of the cells via automated pumping systems would be ideal to circumvent this limitation. In addition, by integrating a microfluidic pump in a cell culture system on chip, one eliminates connection problems, in particular the generation of air bubbles by leaking connections.

In this study, we present a new microfluidic pumping system, which can be easily integrated in existing microfluidic cell culture devices.

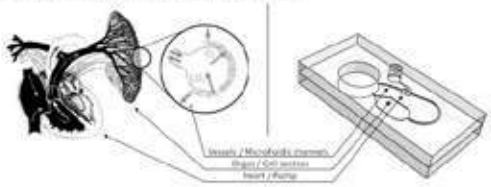


Fig. 1: Comparison between heart-lung system and a biomimetic system(left picture adapted from [1] and [2]).

Materials and Methods

The microfluidic pumping system was fabricated in polydimethylsiloxane (PDMS) using soft lithography. The molds to create the microfluidic chip were produced using stereolithography processes and the actuation membrane of the micropump was fabricated by spin coating.

The chip comprises a 50µm thin membrane sandwiched between two PDMS layers. The upper layer consists of fluidic circuits housing the pumping chamber and the lower layer includes the pneumatic circuit for the actuation of the pumping membrane. The pumping system is based on fluid displacement due to membrane deflection, which is controlled by an external electronic and pneumatic setup.

Fig. 2: Fabricated PDMS microfluidic chip including the new pumping system. One fluid channel is colored with blue food dye.

Results

A new on chip microfluidic single stroke pump was developed and fabricated. The microfluidic pumping system was characterized in terms of flow rate, pump head and by a long term experiment to test the stability in function of the time. It was possible to engender with this newly developed micropump, a flow rate of 2µL/min at 10Hz and 1.5bar over a long period of time. Further it is possible to generate a positive flow rate until a pressure head of 200Pa respectively a 20mm high reservoir. Additionally lung-epithelial cells(A549) were successfully cultured, on a integrated polycarbonate membrane, to confluence with high viability and tight junction expressions.

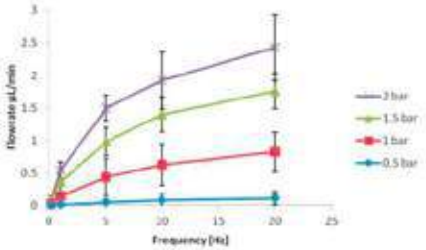


Fig. 3 Flow rate measurement as a function of frequency at different actuation pressures

Discussion

This newly developed microfluidic pumping system, for the integration in cell culture devices, is able to generate a more accurate flow rate compared to already existing single stroke systems. This is possible due to its new and unique three dimensional design of the pump chamber. Additionally, it was possible to generate a constant flow rate over a long period of time. Furthermore it was shown, that by integrating a polycarbonate membrane in the chip, a functional cell monolayer can be created, which is the basic for further biological assays on chip.

To enhance the performance of the produced microfluidic pump it is the idea to refine the geometry of the pumping chamber in order to improve the deflection of the membrane into the fluid layer. Further, the influences of the pump to an on chip cultured cell monolayer needs to be investigated.

References

[1] Understanding heart disease/A. Selzer/1992
[2] GSCE Double Science Biology/R. Parsons/2004

Control of an Unstable Platform for Strength and Coordination Exercise

Silvio Käppeli

Supervisors: Patric Eichelberger and Prof. Dr. Kenneth J. Hunt
Institutions: Institute for Rehabilitation and Performance Technology, BFH-TI
Movement Laboratory, aR&D Physiotherapy, BFH Health
Examiners: Prof. Dr. Kenneth J. Hunt and Prof. Dr. Slavko Rogan

Introduction

Strength training on vibrating plates as well as balance exercises on different types of unstable platforms are commonly used for practice and rehabilitation purposes. On the other hand the effect of stochastic vibration impulses in strength and coordination training is an innovative research field. Stochastic motion is characterized by an inconstant time and direction behaviour.

The assumption for this project is that a device with a combination of stochastic motion impulses and balance exercise would be an effective application which combines the benefits of both principles.

Furthermore most balance training devices do not have an adjustable level of difficulty.

The aim of this thesis is to implement position and force control for fluidic muscles, which are the actuators of a prototype of an active balance board. Another aim is to describe the existing kinematics and to implement a control system where the therapist can control the device via a tablet computer. The costs of the device should be kept low as it is intended to enter the market of therapeutic devices in the future.

The prototype included the mechanical part of the device and a first control system. The concept of the mechanics is shown in Fig. 1. The idea was that the platform performs a defined motion by moving the node (red dot) in plane.

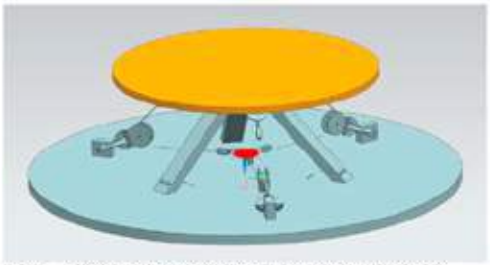


Fig. 1. Original concept of the foregoing prototype.

Materials and Methods

The actuators are three fluidic muscles by FESTO. Force and position sensors were evaluated and integrated into the application for every muscle to be able to set up the closed-loop controllers for the position and the force.

The control system consists of an Arduino Due microcontroller board and an Android App. These two components communicate over Bluetooth. An electrical circuit allows the pressure of the three muscles to be set and amplifies the force sensor signal to be read in by the microcontroller. The closed-loop controls were implemented on the microcontroller using an interrupt timer loop and PI-controllers.

Results

The original mechanical concept was disproved after a proper mathematical investigation. The problem is that the upper platform position is not uniquely defined by the node position.

The new mechanical system has a well defined kinematics. The final outcome of this thesis is a prototype with a properly functioning mechanical concept and a control system which enables the communication via a tablet computer and which has the required closed-loop controllers implemented.

Discussion

The aim of implementing the closed-loop controllers could be met. The required description of the kinematics led to a new mechanical construction. Further a cost-effective and user-friendly control and sensor system which is independent of expensive software was realized.

Tests are required to characterize the acceleration abilities and limitations of the system. It is also a task for the future to implement functionalities like impedance-control of the system, a human-in-the-loop-mode with biofeedback and stochastic motion; however the whole framework is now available.

Acknowledgements

I would like to offer my special thanks to Patric Eichelberger, Prof. Dr. Kenneth J. Hunt and the team of the Institute for Rehabilitation and Performance Technology for their support.

Inertial Sensors for Myocardial Wall Motion Quantification

Micha Kernen

Supervisors: Adrian Zurbuchen MSc BME and Dr. med. et phil. Andreas Häberlin
Institutions: Department of Cardiology, Inselspital, Bern University Hospital and Bürgerspital Solothurn
ARTORG Cardiovascular Engineering, University of Bern
HuCE – Microlab, Bern University of Applied Sciences, Biel
Examiners: Prof. Dr. Josef Götte and Prof Dr. med. et phil. Rolf Vogel

Introduction

Nowadays, an increasing amount of medical devices comprise electronics and therefore rely on internal primary batteries. Due to limited energy storage capacity, batteries have to be replaced after a certain period of time. Continuous energy harvesting from the human body is desirable to overcome this issue.

The heart seems to be the ideal energy donor: It performs a cyclic and repetitive motion for 24 hours a day, which makes it an enduring and reliable energy source. For the development of energy harvesting devices it is crucial to know the retrievable energy from the heart.

Myocardial contractions can be analyzed by different modalities such as MRI, ultra sonic or optical tracking systems (invasive). Since an energy harvester would be placed at a single point in the hearts wall, it is desirable to have an intra ventricular measurement in the myocardium.

Materials and Methods

Currently, a new device is being developed to harvest energy. The design of this harvester depends on the heart wall's accelerations. To determine the accelerations, a sensor probe for measuring in the right ventricle was developed, small enough for transvenous deployment. The measuring probe consists of an inertial measurement unit to measures the occurring linear and rotational accelerations in the beating heart.

Fig. 1 The device sutured onto a pig's heart

The electronic is encapsulated in a titanium housing and can be deployed with a custom-made intravascular delivery system. The design allows screwing the probe into the myocardium. Issues with the current deployment system did not allow an intravascular device implantation. Instead, measurements on the top of the heart were made as shown in Figure 1.

To collect the measured data, a microcontroller board was connected to the measuring probe which saves the data to a memory card. Two different displacement algorithms for post-processing were developed to estimate the linear motion of the sensor probe from the collected acceleration data. An additional algorithm for angular position and movement estimation was introduced.

Results

The blue graph in Figure 2 shows the measured acceleration on a pig's heart.

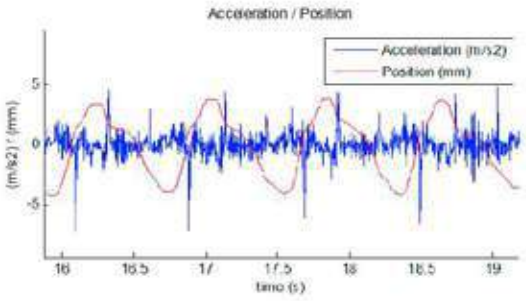


Fig. 2 Measured acceleration and calculated position on the heart.

The red graph indicates the drift-corrected displacement with amplitude of 8 mm. The cyclic motion fulfilled by the heart is well visible with approximately 80 beats per minute.

Discussion

The developed measuring probe gives a closer look of what's happening inside of the heart while it is moving. Through the measured acceleration the concise frequencies can be found which are eminent for designing an energy harvester. The calculated displacement is important to see the linear and rotational motion which is fulfilled by such a harvester.

References

Hoff L. et al., Measurements of Heart motion using Accelerometer, Vestfold University College, Horten, Norway, 2004

Acknowledgements

I'd like to give acknowledgement to the ARTORG Cardiovascular Engineering group, to the BFH in Biel and all persons involved in the project that have helped and supported me throughout my thesis.

The Role of Microarchitecture beyond Volume Fraction and Fabric in the Mechanical Properties of Human Trabecular Bone

Sarah Khadri

Supervisors: Dr. Ghislain Maquer and Prof. Philippe Zysset
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Examiners: Prof. Philippe Zysset and Dr. Ghislain Maquer

Introduction

Osteoporosis is a metabolic bone disease affecting the elderly by decreasing bone strength and increasing the risk of bone fractures. Beside loss of bone mass, degradation of trabecular microarchitecture belongs to most definitions of osteoporosis and it is therefore essential to understand how the morphological and mechanical properties are related. Morphology-elasticity relationships including bone volume fraction (BV/TV) and fabric [1] can predict 98% of the variation in elastic properties computed using micro-finite element analysis (µFE). Yet, other classical morphological variables such as structure model index (SMI), individual trabeculae segmentation (ITS) or trabecular bone score (TBS), are constantly discussed in the literature as surrogates of bone mechanical properties. Accordingly the aim of this work was to quantify the contribution of these alternative morphological variables in determining elasticity of trabecular bone with appropriate statistical methods.

Materials and Methods

The analyzed trabecular bone data consist of 869 microCT reconstructions (18^{-3} m) of 4-5.3mm cubic samples extracted from four anatomical sites: proximal femur, distal radius, lumbar/thoracic vertebral bodies and iliac crest. Their morphology was assessed using published methods and their full stiffness tensors were computed in two previous studies with 6 independent load cases (3 uni-axial and 3 shear cases). The correlation matrix between 25 morphological variables was evaluated to identify their dependence. The variance inflation factors (VIF) were then calculated to decide upon their valid inclusion in multi-linear regression models for prediction of the elastic constants. The coefficient of determination (r^2), the standard residual error (SEE), and the 95% confidence interval (CI) of statistically admissible multi-linear models were then compared. The contribution of each variable was evaluated using ANOVA and the parameters of the regression were computed.

Results

No morphological variables correlate with fabric. On the other hand, all but TBS show high correlations with volume fraction leading to exceedingly high VIFs and cannot be combined in multi-linear models. Among all dependent variables, volume fraction remains the best predictor of elastic properties with and without fabric. Despite its independency, inclusion of TBS in the original Zysset-Curnier model based on volume fraction and fabric leads to no substantial improvements (Table 1).

		Femur	*Radius*	*Vertebra*	*Iliac*	*Combined*
Zysset-Curnier model	r^2	0.983	0.965	0.955	0.974	0.968
	SEE	0.161	0.155	0.209	0.11	0.199
Zysset-Curnier model+TBS	r^2	0.983	0.967	0.957	0.974	0.969
	SEE	0.16	0.151	0.206	0.109	0.195

Table 1: r^2 and SEE of the two models.

Significant but small differences were found between anatomical sites. Volume fraction has the highest contribution to the variation in elastic properties (~90%), followed by fabric (~8%) and the residuals (~3%). The contribution of TBS was less than 1%. Despite the high correlations, prediction of the elastic constants by the Zysset-Curnier model involves errors with a CI of [–26% and +46%].

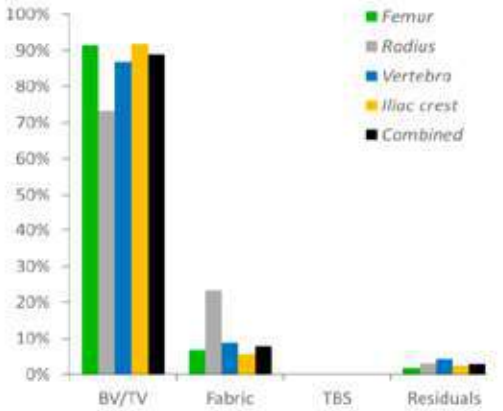


Fig. 1: Relative contribution of each parameter in explaining the variance in elastic constants.

Discussion

The results show that volume fraction and fabric are the best determinants for prediction of human trabecular bone elastic properties and the inclusion of other morphological parameters does not further explain changes in bone stiffness.

Similar studies need to be conducted to verify if those findings remain valid for specific metabolic diseases and post-elastic properties.

References

[1] Zysset P.K., J Biomech 36: 1469-1485, 2003.
[2] Gross T. et al., Biomech Model Mechanobiol 12:793-800, 2013.

Spheroids Viability Detection on a Microfluidic Chip Based on the SlipChip Technique and a Plate Reader

Thomas Kranz

Supervisors: Prof. Dr. Olivier T. Guenat and Janine Ruppen
Institutions: ARTORG Center for Biomedical Engineering Research, University of Bern
Division of General Thoracic Surgery, University Hospital of Bern
Department of Clinical Research, University of Bern
Examiners: Prof. Dr. Olivier T. Guenat and Dr. Thomas M. Marti

Introduction

In cancer research, three dimensional cell culture systems using spheroid models are developed as tool for innovative drug testing. The use of microfluidic systems allow perfused cell cultures, sample loading and precise transport as well as manipulation of tiny amounts of fluids on chip. These perfused spheroid systems better mimic *in vivo* conditions than standard *in vitro* systems as they mimic the continuous transport of nutrients and oxygen [1]. The aim of this project is to integrate the analytical part on an existing microfluidic platform, which already achieves cell loading, homogeneous cell distribution and spheroid formation. Therefore, precise mixing of supernatant and a viability assay needs to be done on chip prior to be analyzed on a plate reader. Dimensions adapted to standard well plate formats allow automated read-out with microplate readers. This further integration helps to overcome handling and contamination issues.

Materials and Methods

The SlipChip technique was developed in the group of Ismagilov [2] for fast and accurate mixing of very small volumes of reagent and samples for PCR applications. Here, we used this technique for larger volumes (supernatant and reagent on chip) to enable an accurate sample preparation on chip. The SlipChip consists of two polystyrene (PS) plates containing microfluidic channels and wells, which were manufactured by milling. Different slipping positions were designed to achieve cell loading, chip perfusion and assay loading. The SlipChip was integrated on the existing chip, produced by soft lithography technique, for cell loading and spheroid formation. A case designed according to well plate format allows compatibility with microplate readers.

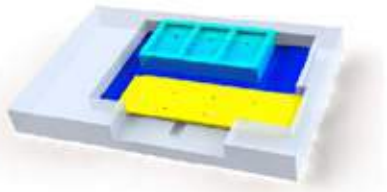


Fig. 1 Overview of the microfluidic platform; yellow: SlipChip / dark blue: PDMS chip for spheroid culture / grey: case in well plate format / light blue: reservoir for cell culture medium

A luminescence based assay was used for calibration purpose of the samples prepared on chip and compared to samples prepared on well plates. Further, cells from the H2052 mesothelioma cell line were seeded in 96-well plates and treated with different concentrations of cisplatin over 24 and 48h, respectively. Measurements with the luminescent Caspase-Glo 3/7 assay and different volumes of supernatant were done on 96-, 384-, 1536-well plates and on chip.

Results

The microfluidic platform was successfully produced and assembled. The proof of concept using the SlipChip technique with volumes in the microliter range was done. The concentration curve showed a linear correlation over three orders of magnitude of ATP concentrations on 1536-well plate and on chip. Therefore, assays reliably tested on 1536-well plate can also be used on chip. Tests with the Caspase-Glo 3/7 assay showed a signal peak using 32 µM cisplatin concentration and 48h treatment time. This signal pattern was observed on well plates and on chip, so measurements with small volumes on chip are possible.

Fig. 2 Proof of concept of the SlipChip using blue and red food dye as supernatant and reagent

Discussion

We present a microfluidic platform for spheroid culture and sample preparation on chip. The sample preparation part is successfully integrated on the existing chip. We demonstrate the proof of concept of the SlipChip technique in the microliter scale and calibrate the system with luminescence measurements using the ATP Kit. Finally, we show that reliable detection on chip using the Caspase Glo 3/7 assay with small volumes of supernatant is possible.

References

[1] J. Ruppen et al. - A microfluidic platform for chemoresistive testing of multicellular pleural cancer spheroid.
Lab Chip, 21;14(6):1198-205, 2014.
[2] W. Du et al. - SlipChip.
Lab Chip, 21;9(16):2286-92, 2009

On-Chip Impedance Analysis to Monitor Epithelial Barrier Integrity

Yves Mermoud

Supervisors: Prof. Dr. Olivier Guenat and Marcel Felder
Institution: ARTORG Lung Regeneration Technologies, University of Bern
Examiners: Prof. Dr. Olivier Guenat and Prof. Dr. Thomas Geiser

Introduction

With every breath taken, the respiratory epithelium is challenged by a wide range of airborne substances. A disruption of this critical barrier can initiate or further aggravate a variety of severe pulmonary diseases such as asthma, acute respiratory distress syndrome (ARDS) or pulmonary fibrosis (PF). The study of the epithelial repair mechanisms upon wounding has therefore become increasingly an important aspect of pulmonary research. Recently developed lung-on-chip (LOC) microsystems have the potential to provide new insights into these mechanisms. However, their power is currently limited by the lack of adequate sensors for monitoring the integrity of epithelial barriers. The aim of this thesis is the development and the integration of an electrical impedance sensor into an existing LOC, to monitor epithelial barrier integrity upon wounding.

Materials and Methods

A novel electrode arrangement combining the advantages of coplanar and tetrapolar systems has been developed and fabricated with the standard technology of flexible printed circuit board (PCB). A miniaturized impedance meter which can be placed into a cell culture incubator has been fabricated. The developed impedance sensor has been tested for performance in various cell-free scenarios, and ultimately in the permeabilization of an epithelial monolayer.

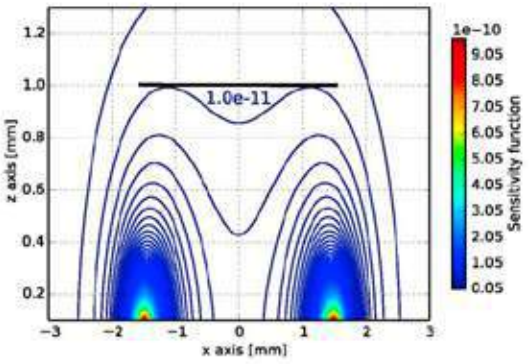


Fig. 1 The sensitivity field of the developed coplanar electrode arrangement. In contrast to conventional arrangement, there is no region of negative sensitivity and the homogeneity of the field in the cell culture region (thick line) is improved.

Results

The cell-free testing revealed that the coplanar arrangement is equally sensitive than conventional techniques. The permeabilization assay validated the ability of the impedance sensor to register the loss of barrier integrity of an epithelial monolayer. Despite these promising results, further testing of the impedance sensor is required.

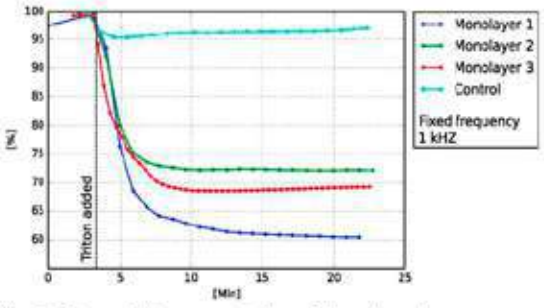


Fig. 2 The relative magnitude of the impedance upon treatment with triton X-100. The three monolayers showed a similar exponential decay, whereas the control remained essentially constant.

Discussion

In the frame of the work on a LOC mimicking the lung alveolar epithelial barrier, an on-chip barrier integrity sensor based on electrical impedance analysis is developed. Unlike existing impedance based techniques, this sensor relies on integrated coplanar microelectrodes and thus eliminates the need of electrodes on the apical side of the barrier. This design provides the combined advantages of simplified fabrication and handling, while keeping the same real-time, label-free and convenient monitoring capabilities as traditional techniques. Additionally, it has also the potential to allow the monitoring of epithelial barriers exposed to an air-liquid interface.

References

Stucki *et al.*, Mimicking respiration in an advanced in-vitro lung alveolus, MicroTas 2014

Acknowledgements

Prof Dr. Olivier Guenat
Prof Dr. Thomas Geiser
Dr. Pascal Olivier Gaggero
Marcel Felder
Betina Trueeb
Sarah Borcard

Complex Principal Component Analysis on Near Infrared Spectroscopy Data

Hanieh Mohammadi

Supervisors: Dr. Christian Rummel and Prof. Dr Josef Goette.
Institutions: University of Bern, Support Center for Advanced Neuroimaging (SCAN), University institute of Diagnostic and Interventional Neuroradiology and University of Bern Applied Science, School of Engineering and Information Technology.
Examiners: Prof. Dr. Josef Goette and Dr. Christian Rummel.

Introduction

In order to reduce brain cell damage, during adverse events like stroke or carotid artery disease, monitoring of brain oxygenation has an important role. In addition, in healthy subjects and patients, it allows acquiring knowledge about brain activities. Near infrared spectroscopy (fNIRS) is a portable, non-invasive, rather low cost, few constrain and safe tool that can be used for continuous assessment of brain hemodynamics. Contamination of the brain hemodynamic signal by scalp or systemic hemodynamic signal and systemic signals has been reported as a major problem of the NIRS technology. The aim of present study was quantitative evaluation of NIRS signals measured on the scalp in order to reconstruct brain and scalp oxygenation signals from mixture of multiple sources.

Materials and Methods

In order to simulate the oxy- and deoxyhemoglobin hemodynamic response to blood flow changes, Buxton's balloon model was used [1]. For quantification of the absorption changes of near infrared light in brain and scalp tissue, a method using multi distance optode (30 mm and 42 mm) of continuous wave near infrared spectroscopy (CW-NIRS) was used. Data was collected using the FORIE -3000 system (SHIMADZU, Japan) and principal component (PCA) was used. It was assumed that both scalp and brain signals are linearly combined with multiple signal sources. Furthermore, it was assumed that partial optical path length of scalp layer does not change whereas partial optical path length of brain tissue layer linearly increases with source detector (S-D) distance. The capability of source separation was examined. Changes of oxy- and deoxyhemoglobin are not independent. To account for the mutual influence, oxy- and deoxyhemoglobin were interpreted as real and imaginary part of a complex signal. Thus, complex independent component analysis (cICA) was employed with a technique introduced by Funane et al [2]. Using real valued ICA was generalized to complex calculus.
weighted by brain and scalp contribution ratio based on a technique that introduced by Funane et al. [1]l

Results

Results showed that using PCA, is not always possible to reconstruct brain and scalp signal. In contrast using real valued ICA level of accuracy can be achieved. Highest level of accuracy can be obtained using cICA.

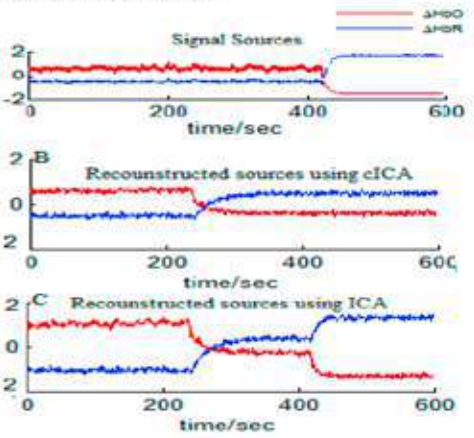


Fig. Comparison between ICA and cICA with SNR of 12.5 dB. A) Model of oxyhemoglobin and deoxhemoglobin sources during simulated artery occlusion. B,C) In contrast to real valued ICA, cICA is able to reconstruct the original sources.

Discussion

We proposed a new method for quantitative separation of the brain and scalp tissue contribution on CW-fNIRS, using dependence of complex independent component's weight on S-D distance. This is a robust method since drastical level of data enhancement based on using mutual information was used.

References

Buxton, Richard B and Wong., Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magnetic Resonance in Medicine. 39(6):855-864,1998.
Funane et al., Quantitative evaluation of deep and shallow tissue layers' contribution to fNIRS signal using multi-distance optodes and independent component analysis, Neuroimage 85:150-165, 2014.

Acknowledgements

The project was carried out at the Support Center for Advance Neuroimageing (SCAN) , Institute of Diagnostic and Interventional Nuerorasdology, Inselspital, Bern, Switzerland.

ASIC Low-Power Signal Processing Circuitry for Esophageal ECG

Michael Nydegger

Supervisors: Lukas Bösch and Thanks Marisa
Institutions: Institute of Human Centered Engineering - microLab, Bern University of Applied Sciences
Examiners: Prof. Dr. Marcel Jacomet and Prof. Dr. Josef Götte

Introduction

The E2corder is a new concept of a long-term ECG recorder suited for an outpatient investigation up to 30 days. The device records ECG signals from a catheter placed into the esophagus in close proximity to the heart. The high demand for the patient's comfort requires miniaturization of the microelectronics to capture, process and store a large amount of data generated during the investigation. For the miniaturization, new concepts of power efficient analogue designs, such as a novel asynchronous analogue to digital converter (ADC) are needed. The aim of this thesis was the realization of a low-power integrated voltage reference and the development of circuit concepts for a signal conversion, required to drive the asynchronous ADC.

Fig. 1 Concept of the esophageal ECG recorder E2corder

Method

The development of the voltage reference was accompanied by a study of reported integrated voltage references as well as fundamental models and concepts used in the design of low-power analogue integrated circuits. During the work, two similar voltage reference designs have been developed, simulated and integrated on an application-specific integrated circuit (ASIC) to verify the simulation results and to demonstrate the feasibility of the circuits.

The conceptual studies done on the driving circuit for the ADC implied the compilation and formulation of the design requirements to identify problems and possible solutions. High attention has been paid to a special type of analogue filters to perform a signal reconstruction from the preceding filtering blocks.

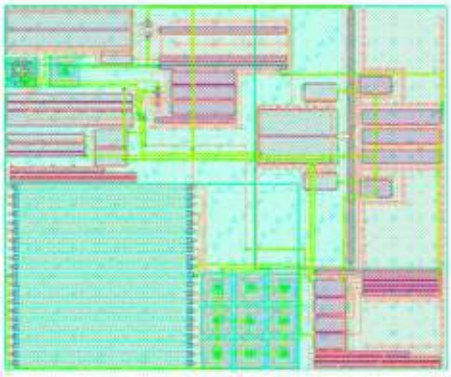


Fig. 2 Layout view of the second voltage reference design (Physical size: 147µm x 116µm)

Results and Discussion

The voltage reference designs developed during the thesis operate with a power consumption of less than 10µW with a high immunity against power supply noise, process- and temperature variations. The simulated performance ratings (especially for the second design) are comparable to other reported voltage references and an appropriate output interface for the interconnection with the asynchronous ADC is given. During the work on the driving circuit of the ADC, problems and possible solutions of the demanding interface between signal preconditioning filters and the ADC were evaluated and discussed. The filtering technique studied in this context was found to be suited for continuous time analogue filtering of low amplitude biomedical signals.

References

Marisa et al., Asynchronous ECG Time Sampling: Saving Bits with Golomb-Rice Encoding, Computing in Cardiology (CinC), 61-64, 2012.

Quantifying Myopic Changes with OCT

Michael Peyer

Supervisors: Prof. Christoph Meier and Dr. Boris Považay
Institutions: OptoLab, Institute of Human Centered Engineering, Bern University of Applied Sciences
ARTORG Center for Biomedical Engineering Research, Universität Bern
Examiners: Prof. Christoph Meier and PD Dr. Jens Kowal

Introduction

Deeper insight into dynamic changes of ocular microstructures during natural eye growth can support the development of new preventive treatments for myopia. Optical coherence tomography (OCT), with its ability to acquire fast, *in vivo* retinal cross-sectional images, is an almost ideal detection method. Extending a commercial 800nm OCT-system with a second wavelength band at 1075nm allows for detailed imaging of layers beneath the retinal pigment epithelium (RPE) such as the choroid (CH) and the sclera [1].

Method

To benefit from the sophisticated eye-tracking device of the commercial system, synchronized frame acquisition has been implemented. In corporation with the manufacturer (Heidelberg Engineering) hard– and software synchronization between the individual components was developed. Real-time protocol communication allows for scan parameter and mode exchange.

For patient specific correction of axial blur, a dispersion finder has been implemented for high speed processing on a GPU (graphic processing unit). It evaluates an entropy based sharpness measure on a region of interest and uses grid search to optimize dispersion.

Multi-frame averaging is used to increase signal to noise ratio (SNR) in the OCT scans. This requires precise correction of motion distortion between consecutive frames. An intensity-based registration frame-work has been implemented to correct for similarity– and affine motion models. The optimization is based on a variation of a steepest descent method combined with an image pyramid for multi-resolution registration. An additional phase correlation based initialization is used to further reduce failure rate.

Results

System synchronization has been shown on several patient examinations and reduces handling complexity which allows the use of the system for extensive clinical trials. Evaluation of the registration method by different sharpness measures (entropy, image acutance) showed good performance for similarity models. Registration quality is underlined by the high resolution of the averaged scan in Fig. 1a with dispersion corrected for up to the sixth order. Increasing dispersion order (e.g. from 2 to 6) showed to better separate adjacent peaks (e.g. Bruch's membrane (BM) and choriocapillaris (CC) from the RPE). Registration for a 1024x500 pixel frame computes in 0.5s on a standard machine (CPU-i5-2400).

Discussion

The use of the commercial eye tracking system in combination with the developed registration method allows for clinical high resolution imaging at 1075nm. Slow convergence of the optimizer could be improved by using more sophisticated methods (e.g. Levenberg-Marquardt). Parallelizing of the registration method on a GPU might further reduce computation time and enable real-time registration.

References

[1] Dr. Boris Považay et al., Enhanced visualization of choroidal vessels using ultrahigh resolution ophthalmic oct at 1050 nm, Opt. Express, 11(17) 43-52, 2003.

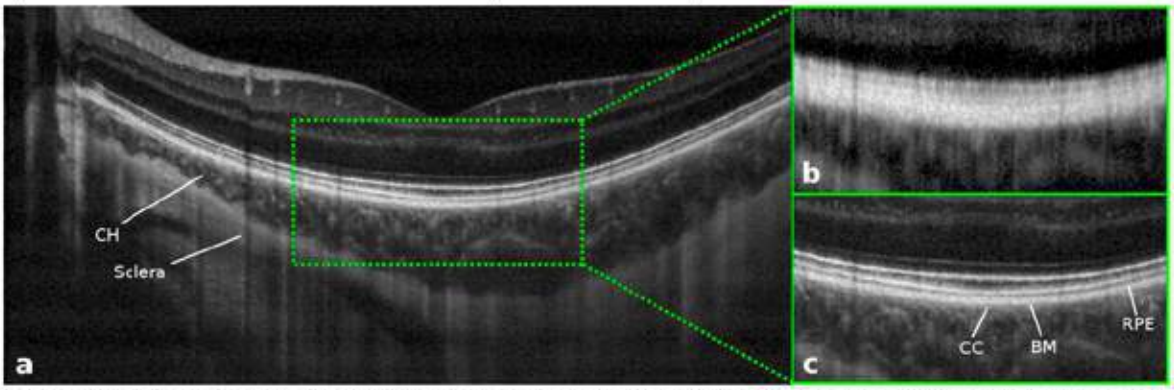


Fig. 1 1075nm-System OCT-scan with synchronized acquisition, dispersion finder and image registration method. a) shows the full B-Scan averaged over 100 Frames. Dispersion was corrected for five dimensions (a_2 - a_6) automatically on the region of interest marked by the green dashed rectangle and shown in c). In b) the ROI is shown without dispersion compensation.

Signal Processing of Asynchronous Sampled ECG Signals

Andreas Renggli

Supervisors: Thomas Niederhauser and Dr. med. Andreas Häberlin
Institutions: Institute for Human Centered Engineering (HuCE), Bern University of Applied Sciences
ARTORG Center for Biomedical Engineering Research, University of Bern
Examiners: Prof. Dr. Josef Götte and Prof. Dr. med. et phil. nat. Rolf Vogel

Introduction

Heart arrhythmias are conditions, where the heartbeat is irregular, either too slow, or too fast. Not all arrhythmias are life threatening, but they can decrease the quality of life of the patient. To diagnose rare occurring arrhythmias, such as paroxysmal atrial fibrillation, the monitoring of the heart rhythm over a longer time period is essential. This is done by long-term surface electrocardiography (sECG).

Long-term measurements with a duration of several days/weeks increase the possibility to detect rare occurring arrhythmias. Unfortunately, the sECG has some disadvantages which shorten the maximum recording time.

A potential ECG recording method for long-term measurement is oesophageal ECG (eECG).

The main challenge for developing a long-term implant, is the implementation of a power- and memory-efficient recorder.

Materials and Methods

The focus of this master-thesis is to emulate and investigate the proposed recorder in MATLAB. The recording method is divided into two main steps: the asynchronous sampling of the input signal, and the compression of the asynchronous samples. The asynchronous sampling method is based on a level-crossing analogue-to-digital converter. Samples are generated only when the input signal difference crosses a certain threshold value. A sample consists of the elapsed time since the previous sample and the direction in which the threshold value is crossed (either up or down).

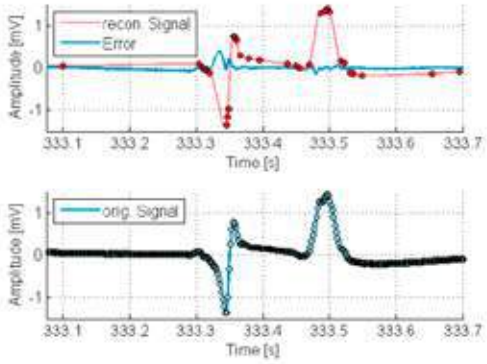


Fig. 1 MATLAB simulations with an asynchronous sampling resolution of 5 Bits/mV. (TOP): samples left after compression (red dots), reconstructed signal (red line), and error signal (blue line). (BOTTOM): samples of the original Signal (blue dots), and original signal (blue line)

The Compression method relies on different slope properties within an ECG signal. Depending on the similarity of asynchronous samples, samples within slopes (e.g. QRS-complex) can be accumulated. This approach leads to a more memory-efficient, and less power consuming recording method compared to a conventional recorder with a fixed sampling rate.

Results

The widely used MIT/BIH Arrhythmia Database, containing 48 sECG records, and an eECG Dataset with 13 records were used as test datasets. Different asynchronous sampling resolutions were evaluated. We can show that with an asynchronous sampling resolution of 5.5 Bits/mV a good compromise between signal reconstruction quality, peak detection performance, and compression ratio is achieved. This resolution leads to a compression ratio of more than 10:1 compared to conventional sampling methods. A recording time of more than 42 days with 1 GByte flash memory, and two eECG channels is possible. We can also show that an eECG signal generates less asynchronous samples. This is because eECG signals are less sensitive to high frequency noise. However, the effect is marginal since, the P-waves in the eECG signal generate more samples compared to the sECG signal.

Discussion

This is the first time that the whole MIT/BIH Arrhythmia Database, and 13 eECG records were analysed with a MATLAB framework emulating the asynchronous and compression algorithm. Prior to this work, this was done by a PYTHON script which took several hours for only a few minutes of an ECG signal. It is now possible to analyse different parameter settings on a wide range of ECG signals in a feasible time (≈50 ms/Beat).

References

T. Marisa, T. Niederhauser, A. Häberlin, R. A. Wildhaber, R. Vogel, M. Jacomet, and J. Götte, "Hermitian Basis Supported Online Compression of Asynchronous Time Encoded ECG Signals", Bern University of Applied Sciences, HuCE-microLab 2014.

Acknowledgment

This master thesis is part of a bigger project with the aim to develop an outpatient eECG recording implant, called E2Coder. I would like to acknowledge all the person involved in this project and who supported my work.

Master's Thesis in Biomedical Engineering

Hidden-Markov-Model for Esophageal ECG Wave Detection

Raphael Schertenleib

Supervisors: Dr. Thomas Niederhauser and Dr. med. et phil. Andreas Häberlin
Institutions: Institute for Human Centered Engineering, University of Applied Sciences
Department of Cardiology, Inselspital, Bern University Hospital
ARTORG Center - Cardiovascular Engineering, University of Bern
Examiners: Prof. Dr. Josef Götte and Prof. Dr. med. et phil. nat. Rolf Vogel

Introduction

To detect paroxysmal heart rhythm disorders (arrhythmias), long-term surface electrocardiograms (sECG) are recorded. As these signals suffer from low atrial sensitivity and the electromechanical contact properties limits the signal quality, automatic P wave detection is cumbersome. Alternatively, signals derived from the esophageal mucosa (eECG), containing more detailed information on the atrial activity, may be used. However, to take advantage of the increased signal quality, the atrial and ventricular waves need to be detected and separated automatically. This is difficult because these waves might have very similar properties. Therefore, an automatic classifier using Hidden-Markov-Models (HMM) is investigated.

Signal Synchronization and Annotation

To evaluate such a HMM classification, adequate data sets have to be defined. Since no annctated eECGs are available, an own patient database containing annotations from simultaneously recorded sECGs are used. However, the sECG and eECG recorders used in this database feature different oscillators with different sampling frequencies that alter with temperature. Consequently, the two signals need to be synchronized in segments individually. To align the signals and to calculate an initial resampling factor, two manually labeled arrhythmias are used. By minimization of the mean square error of the two filtered signals, the optimal resampling factor for each segment is found.

In this way the signals divided into segments of 3 min duration were synchronized with an accuracy of below ±10 ms (example: see Fig. 1). Thus, the annotations can be taken over without confusion of P and R waves.

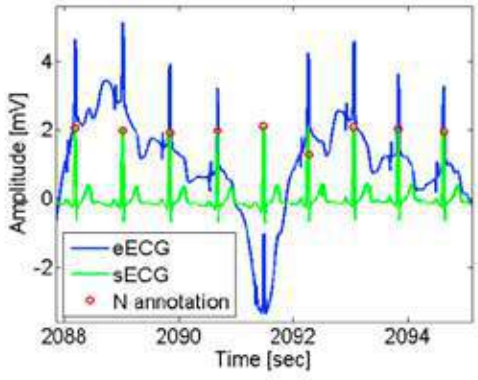


Fig. 1 Synchronized eECG and sECG signals.

HMM Classification

With sECG data derived from the MIT-BIH arrhythmia database a multidimensional HMM classifier for normal (N) and VES beats was designed and statistically quantified. For this purpose, different feature vectors for the HMM were investigated and evaluated. Most dedicated feature vector used the normalized slopes and normalized areas calculated from signal slices. These feature vectors, extracted from the whole signal, are fed to multiple HMM's to calculate the probability curves for each beat type (Fig. 2).

While both beat types were classified with a sensitivity of 95.3 %, positive predictive values of 96.4 % for N beats, and 87.1 % for VES beats, respectively, have been achieved.

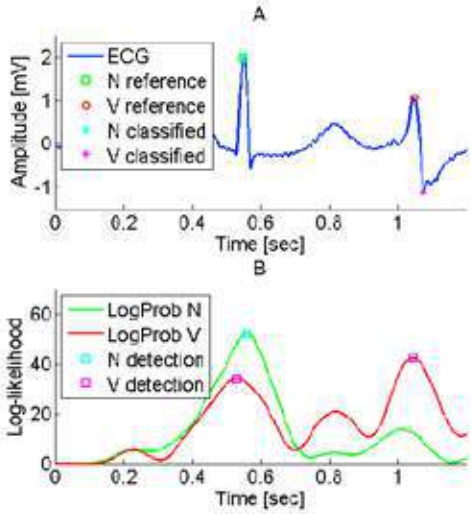


Fig. 2 Classified beats (A) resulting from the higher probability of the particular beat types (B).

Conclusion

The HMM approach achieved promising results with respect to N and VES classification in sECGs. To classify P and R waves, however, the HMM classification process have to be improved further.

References

R. Mark and G. Moody, MIT-BIH Arrhythmia Database, [Online], May 1997, Available: http://ecg.mit.edu/dbinfo.html.

Acknowledgements

The project was kindly supported by Dr. Thomas Niederhauser of the HuCE institute. I am very grateful for his helpful advices and his engagement through the process of this master thesis.

Development and Evaluation of a New Clinical Test to Investigate Higher Visual Functions

Theresa Sujata Maria Senti

Supervisors: Prof. Dr. sc. Tobias Nef and M.Sc. Giuseppe Angelo Zito
Institutions: ARTORG Center for Biomedical Engineering Research, University Bern, Division of Cognitive and Restorative Neurology, Department of Neurology, Inselspital Bern.
University Hospital of Old Age Psychiatry, Bern
Examiners: Prof. Dr. sc. Tobias Nef and Prof. Dr. med. Urs P. Mosimann

Introduction

Higher visual functions (HVF) can be defined as a series of cognitive processes responsible for object and pattern recognition, color and shape perception, and motion detection. People with impaired higher visual functions after unilateral brain lesion are often tested with paper pencil tests, but such tests do not assess the degree of interaction between the healthy brain hemisphere and the impaired one. Hence, visual functions are not tested separately in the contralesional and ipsilesional visual hemifield. Moreover, these tests do not take into account whether the central or peripheral visual field is more affected. HVF can be modulated with transcranial direct current stimulation (tDCS), which is a neurostimulation method. It modulates the excitability of the stimulated region of the brain using direct current, which is delivered by two or more electrodes. It is non-invasive, not painful, and there are no long-lasting effects. HD-tDCS stands for high definition tDCS. In this technique, several small electrodes are used to increase the focality of the stimulation.

Materials and Methods

In the first part of the thesis, two versions of a new HVF test battery to test higher visual functions (perception of shape, spatial orientation, direction, and speed) were developed and evaluated in terms of reliability and consistency. Additionally, the implementation of these tests in two different hardware setups, a flat screen and a hemispherical screen, was compared. The best setup together with the best test version was used for the non-invasive brain stimulation study.

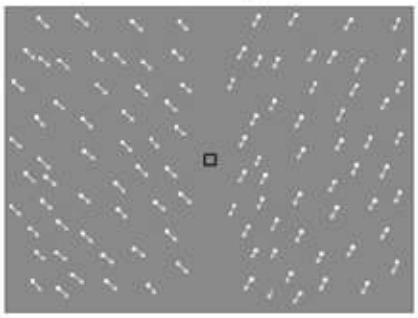


Fig. 1 Direction task as an example of one of the tasks from the HVF test battery

The aim was to investigate the influence of HD-tDCS of the extrastirate cortex on HVF. The study was designed as a sham-controlled cross-over study, in which 22 healthy subjects participated. The subjects first took the HVF test battery, followed by a reaction time test. Then, half of the participants received a cathodal HD-tDCS stimulation of the right visual cortex with the central electrode over V5 while the other half received a sham stimulation. After that, the tests were done again. After at least one week, the same subjects repeated the protocol, but this time the subject who had the real stimulation the week before got the sham stimulation and vice versa. It was assumed that there is no difference in performance pre/post sham and a change in performance in pre/post real. The results were analyzed using standardized pre-post differences.

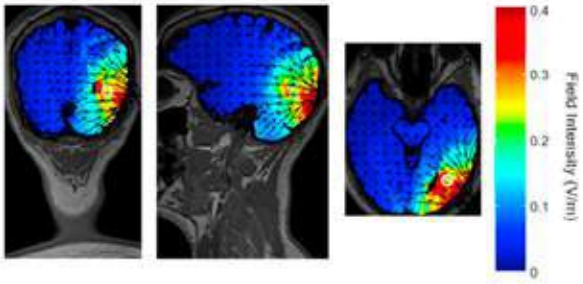


Fig. 2 Electrode montage and distribution of the electrical field in the brain

Results

Significant differences were found for one of the tasks of the HVF test battery, which assesses the perception of speed (sham = -0.009 ± 0.257, real = -0.219 ± 0.298, $p = 0.014$). As expected, the performance changed only after receiving the real stimulation.

Discussion and Conclusion

The results show that the subject became significantly more precise in solving the speed task after the stimulation. This allows for the conclusion that cathodal HD-tDCS over the V5 region enhances the perception of speed. This might be explained by the Bienenstock-Cooper-Munro (BCM) rule which states, that previous overall inhibition of cortical activity enhances synaptic strength of active neuronal connections.

Development of a measuring tool for the assessment of bone specific mechanical properties while inserting surgical screws

M.Javad Shamsollahi

Supervisors: Felix Wipf, Dr. Stefano Brianza, Prof. Daniel Debrunner, Prof. Dr. Andreas Stahel
Institutions: R&D Biomechanics, Stryker Trauma.
Human Centered Engineering, Science Lab, Bern University of Applied Sciences
Examiners: Prof.Daniel Debrunner and Prof. Dr. Andreas Stahel

Introduction

Annually, millions of bone screws are used for treatment of bone fractures worldwide. Commonly, functionality evaluation of bone screws is done by the bone simulation materials. This delivers more consistent results than testing in real bone; however it can result in different absolute values as if performed in real bone.
Thus, a novel sterilizable, portable device, in order to measure insertion torque and axial force while inserting bone screws in human bone (Cadaver Lab) is developed.

Materials and Methods

The aim of this project was to develop a portable, sterilizable device that can be used for measuring the insertion torque and applied axial force of a wide range of bone screws during the screw insertion in the cadaver lab. The design is divided in three parts: screwdriver handle, measurement part and the screw driver blade. In order to protect the measurement part of the device from the contamination, a capsule made of composite is designed around this part and the data acquisition is done wireless. The calibration of first prototype and experimental test by it on the bone simulation material and animal bone are done.

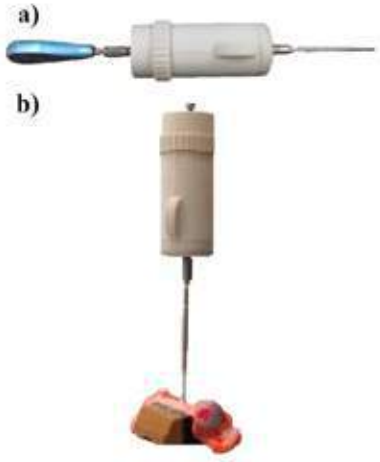


Fig.1. a) First prototype, b) Experimental test on a porcine femur

Results

The uncertainty of ±0.035N.m for measuring insertion torque (measuring range: 0.1-5.1 N.m) and ±1.793N for measuring applied axial force (measuring range: 1-200 N) for the confidence interval of 95% are achieved by the calibration procedure. All the principal requirements of the device are met. Ten samples of two different sizes of ISO standard Stryker cortex bone screws are inserted in a porcine femur and bone simulation material by the device and the insertion torque and axial force are recorded and monitored real-time, wireless.

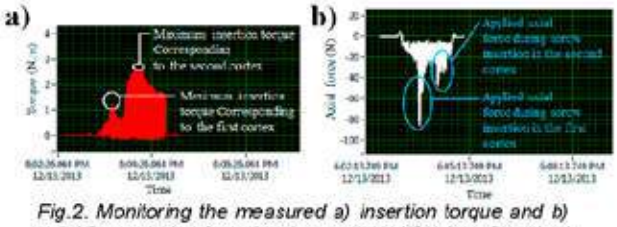


Fig.2. Monitoring the measured a) insertion torque and b) axial force during inserting bone screw (Stryker, Standard ISO cortex, Ø4.5 × 50mm stainless steel screw) in a porcine femur

Discussion & outlook

Further bone screw insertions by the device in bone simulation materials, animal bones and particularly human bones (Cadaver experiments) are needed for a sophisticated evaluation.
The assessment of the local bone quality may be performed by measuring the insertion torque. For this purpose, functionality of the real-time measuring of the bone screw insertion depth can be added to the device which would allow for a more detailed assessment of local bone quality.

References

Suhm, N., Haenni, M., Schwyn, R., Hirschmann, M., & Müller, A. M. Quantification of bone strength by intraoperative torque measurement: a technical note. Archives of orthopaedic and trauma surgery, 128(6), 613-620. 2008

Acknowledgements

The support of the Stryker Trauma, R&D team is gratefully acknowledged.

Design, Manufacturing, and Validation of a Sterile End-Effector for a Surgical Robot

Manuel Stebinger

Supervisor: Dr. Brett Bell
Institution: ARTORG Center for Biomedical Engineering Research, Universität Bern
Examiners: Prof. Dr.-Ing. Stefan Weber and Dr. Brett Bell

Introduction

A surgical robot system, developed at the ARTORG Center, for Direct Cochlear Access (DCA) has proven its ability to precisely and accurately drill a minimally invasive tunnel for electrode insertion. To integrate the system in the clinical environment for the first in-human experiment, deficits regarding the integration of surgical instruments in the operating room (OR) must be solved. The aim of this thesis is to develop a sterilizable end-effector, which focuses on surgical aspects such as sterility, usability and emergency release function.

Fig. 1: Existing robotic device for microsurgical DCA

Materials and Methods

Existing mounting concepts (quick release tool changers) in medical and industrial applications were evaluated. Specific focus was placed on clinical devices regarding the use of sterile drapes. Advantages and drawbacks of these devices in the context of robotic cochlear implantation was performed. Requirements & specifications of the sterile end-effector and robot mount with a sterile barrier were defined based on the experience from the literature and the medical device directory MDD 93/42/EEC. These requirements were classified by mechanical properties, dimensions, interface properties, material properties, workflow and reprocessing / sterilization. Requirements within each of these categories were then implemented into the design using the commercial CAD software SolidWorks. Additionally, the mechanical function of the tool adapter was modeled mathematically using scripting in MatLab. Once the design was proven mechanically stable a prototype of the mount was manufactured.

Results

A new sterilizable end-effector for a surgical robot was designed for use in Direct Cochlear Access (DCA) interventions. More precisely a surgical drill with a reduced diameter could be realized. The drill chuck was optimized such that tool's attachment and release could be performed by one person. Furthermore an emergency release function was also implemented to allow the tool to be removed in an axial direction, should the robot fail during drilling. Moreover method for attaching a sterile barrier between the non-sterile robot arm and the sterilizable end-effector was established. The new mounting concept also implicated an increased usability for the surgeon and the OR team, in terms of simplified installation of the end-effector.

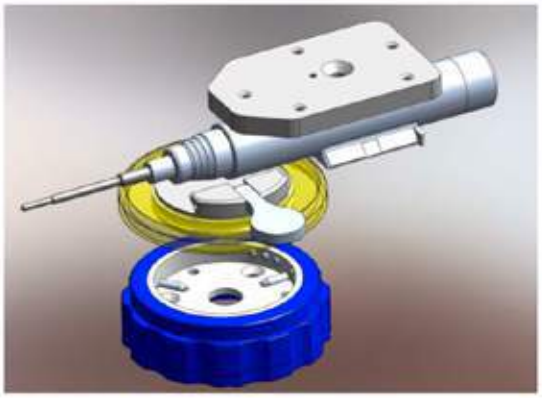


Fig. 2: Computer Aided design (CAD) model of the attachment interface, the surgical end-effector including a microsurgical tool with emergency release function (bottom) and rubber ring for sterile interface (yellow).

Discussion

The design and development of an end-effector which could be used in a surgical scenario was shown. A concept for instrument sterilization and attachment onto the robotic arm was also proposed. The design has fulfilled all of the priority level I and II requirements and should simplify the surgical workflow while also reducing the risk of human error due to the presence of built in safety features, which only allow the correct tool to be mounted in the correct configuration.

References

B. Bell, N. Gerber, T. Williamson, K. Gavaghan, W. Wimmer, M. Caversaccio, and S. Weber, "In vitro accuracy evaluation of image-guided robot system for direct cochlear access.," Otol. Neurotol., vol. 34, no. 7, pp. 1284–90, Sep. 2013.

Master's Thesis in Biomedical Engineering

Segmentation of Multiple Sclerosis Lesions in the Brain

Sandro Steffen

Supervisors: Dr. Stefan Bauer
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Examiners: Prof. Dr. Mauricio Reyes and Prof. Dr. med. Roland Wiest

Introduction

Multiple sclerosis is an inflammatory disease where the insulating covers of the nerve cells in the brain are damaged. The resulting lesions that are visible on the different MRI sequences are considered for diagnosis and treatment.

There are often a high number of small lesions to segment while the borders of the lesions are often not clearly visible. This makes an accurate manual segmentation very time-consuming and difficult.

In this thesis, the sequences T_1, $T_{1contrast}$, T_2 and FLAIR are used as input images for a fully automatic segmentation into the different classes of healthy tissues (CSF, GM and WM) and lesions (T_1 black holes, $T_{1contrast}$ acute lesions, T_2/FLAIR lesions). This subdivision offers important diagnostic advantages, but is not possible with other state-of-the-art fully automatic segmentation approaches for multiple sclerosis.

For this task, an algorithm previously developed for automatic segmentation of brain tumors [1] was adapted.

Methods

The segmentation process starts with pre-processing (registration, skull-stripping, denoising, bias-field correction, rescaling, histogram matching) of the input images. After the subsequent feature extraction, first a voxel-wise classification into healthy and non-healthy is performed using a decision forest. This is followed by a refinement step using a conditional random field. After this coarse segmentation, a separate finer classification step of the healthy tissue and the lesions is performed. The segmentation process is then finished by a slice-wise refinement of the fine classification.

The main work of this thesis was, apart from the adaption to MS lesions, to investigate into a larger feature set, the handling of the imbalance between the healthy- and non-healthy class and to handle mislabeled training data.

Results

The segmentation was evaluated with a data set from the Inselspital Bern consisting of 36 patients using 6-fold cross-validation. For each patient there was a manually segmented ground truth available.

The current state of the algorithm showed encouraging results for the overall lesion detection, despite a general tendency to over-segment in the coarse segmentation step. The accuracy of the fine segmentation of the different classes of the lesions was not yet satisfactory, in particular due to difficulties in distinguishing T_1 black holes from T_2/FLAIR lesions at unclear borders between the classes. The computation time for segmenting one patient was approximately 5 minutes.

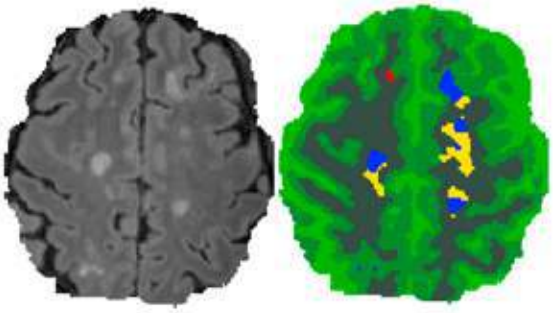


Fig. 1: Example of a skull-stripped FLAIR image and the resulting segmentation (green: healthy tissues; blue: T_1 black holes, red: $T_{1contrast}$ acute lesions; yellow: T_2 lesions)

Discussion

Although the overall accuracy of the current state of the method is not yet high enough for reliably distinguishing the different classes of lesions, the obtained results look promising, especially when considering the advantages in segmentation speed compared to manual segmentation. While a manual segmentation of MS lesions often suffers from high intra- and inter-rater variability, a fully automatic approach will always lead to the same result on the same input images. This is an important property for evaluating disease progression in terms of lesion count and volume.

References

[1] Bauer et al., Segmentation of Brain Tumor Images Based on Integrated Hierarchical Classification and Regularization, MICCAI BraTS, 2012.

Low Latency Video Processing System based on FPGA and DSP

Kaspar Steiner

Supervisor: PD Dr. Jens H. Kowal
Institution: Ophthalmic Technology Lab, ARTORG Center, Universität Bern
Examiners: Prof. Dr. Marcel Jacomet and PD Dr. Jens H. Kowal

Introduction

Cameras are widely used in today's health care. They showed up first in clinics in 1896 with the first clinical x-ray, and have nowadays established their position in the daily business with countless computer tomography devices, video endoscopes and various documentary applications. The number of publications related to "medical imaging" has increased four-fold in the last 30 years.
With diversity comes divergence. The choice of a modern digital camera means, besides sensor and optics, choosing an interface. Firewire (1394), USB 2.0 or 3.0, Gigabit Ethernet or Camera Link are just the available physical connections to a camera, not taking into account the built-on protocols. Having chosen one type of camera in the past, the threshold is raised to go for another type in the future, it would require, amongst others, additional cables, computer interface cards and software.

Materials and Methods

An abstraction layer is provided between the image processing algorithm and the camera access. A Field Programmable Gate Array (FPGA) is capable of reading data from cameras with different interfaces and provides it to two Digital Signal Processors (DSP) for further processing. In addition, three general purpose input/output ports are available; two of them might be used as analogue outputs. This is all combined in an embedded platform.

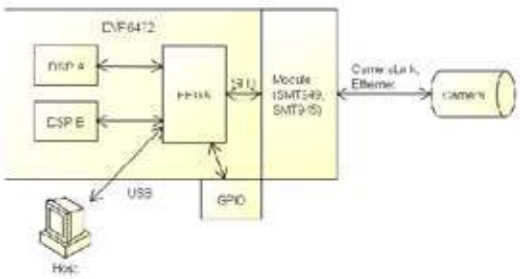


Fig. 1 The system overview shows the main components. The FPGA acts as a pivot and manages different interfaces, such as Ethernet, USB, Camera Link and proprietary ones.

Two use cases have been defined as guide lines for the development. These are a high-speed low-cost Optical Coherence Tomography (OCT) device and a general purpose Gigabit Ethernet camera.

Results

Line rates of up to 40.193kAscans/s have been obtained for the OCT device; this is 98.94% of the available internal transmission bandwidth. The latencies vary from 25µs for integration times t_{int} smaller than 40µs to 96µs for t_{int} larger than 80µs. Ethernet frame latencies are 280µs, therefore the quota of frame size and exposure time is much more considerable regarding frame rates.

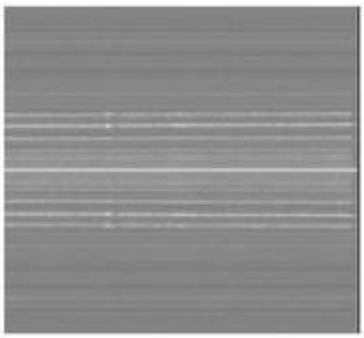


Fig. 2 OCT Bscan of a glass plate with scotch tape layers on top. The three layers are clearly distinguishable. The data has been processed on the embedded platform.

Discussion

The OCT application, to which this thesis contributed, has well evolved. The results of first tests with the whole system are comparable to the existing devices. Further development should improve the delivery optics and the transmission speed of the processed data to a host computer. The Ethernet camera control is less advanced. The proof of concept for very small frames has been done; but the transmission of larger images breaks down for a yet unknown reason. An architectural decision has to be taken prior to further development.

References

Fercher A. F., Drexler W., Hitzenberger C. K. and Lasser T., Optical Coherence Tomography – Principles and Applictions, Reports on Progress in Physics 66: 239-303, 2003.

Investigation of Silk Electro-Spinning for Intervertebral Disc Engineering

Thomas Paul Studer

Supervisors: PD Dr. Benjamin Gantenbein and Dr. René Rossi
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
EMPA – Swiss Federal Laboratories for Materials Science and Technology
Examiners: PD Dr. Benjamin Gantenbein and Dr. René Rossi

Introduction

Low back pain linked to intervertebral disc (IVD) degeneration is a highly abundant problem in the aging modern society. Until today there is no biological solution available based on the patient's autologous cells to restore or repair the IVD. We hypothesized that electrospun silk and salt leached scaffolds can mimic the extracellular matrix of the IVD cells: i) a random orientation of the fibres and a highly porous salt leached scaffold would be ideal for nucleus pulposus cells (NPC) and ii) an alignment of the fibres would be favourable for annulus fibrosus cells (AFC).

Methods

Silk liquefaction: Silk fibres from Bombyx mori (Swiss Silk) were cut in small pieces and boiled in 0.2M Na_2CO_3 for 30 min to remove the sericine. Then, the silk fibres were rinsed three times in ultrapure water (UPW) and dried overnight. The dry silk was then dissolved in 9.3 M LiBr solution and dialysed against UPW for 48 h and purified by high speed centrifugation.[1] Electrospinning: Silk was mixed with 5% (wt/vol) 900kDa-PEO to generate a solution of 6.4% silk and 1 % (wt/vol) PEO. This solution was electrospun on a flat collector for randomly oriented fibres and on a rotating mandrel for aligned fibres. Of each electrospun mat N=40 samples of 6mm diameter were punched out. N=20 of the randomly aligned samples were ultra-sonicated for 1 min at 80 Watts to increase their porosity.[2] Salt leaching: Salt particles were poured in 8% aqueous silk solution. After 24 hours of gelation at room temperature the salt was leached out by immersing the scaffold in UPW for three days. After cutting out a slice of a height of 3mm, samples of 6mm diameter were punched out.[3] Cyto-compatibility: Human derived NPC, AFC, TC and MSC (ethically approved) were seeded per carrier and grown for 7 days. On day 1 and 7 cell spreading (LIVE/DEAD® and confocal laser scanning microscopy), cell activity (DMMB) and DNA content (PicoGreen®) was monitored.

Results

The electro-spinning process revealed two completely different scaffold and micro environments for cells as confirmed by SEM (Fig 1 A and B). Live/dead stain of IVD cells confirmed their alignment in the direction of the parallel-oriented fibres(Fig 1 C). or nonoriented fibers (Fig 1 D). AFC, NPC, MSC and T cells adhered and proliferated on all scaffolds. Generally, it was noted that cells adhered and proliferated better on ultra-sonicated non-oriented and on salt leached scaffolds than on aligned and un-sonicated. scaffolds.

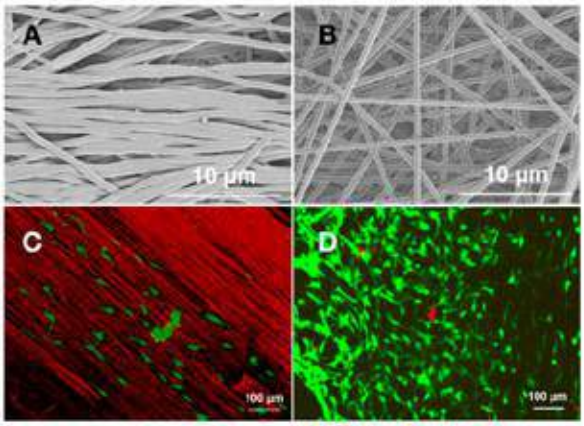


Fig 1: A-B) Scanning electron microscopy images of scaffolds A) Aligned silk fibres (mandrel speed=30Hz) B) Randomly distributed silk fibres C-D) Human IVD cells on scaffolds C) AFC aligned in the direction of silk fibres (red) D) NPC randomly oriented in ramdomly aligned silk nano fibres.

Discussion & Conclusions

By modification of the silk composition and the electro-spinning parameters the 3D environment of a scaffold can be controlled. This is crucial for cell adhesion and proliferation of primary cells. The general direction of cell growth can be controlled by the arrangement of the silk nanofibers. Future research will focus on the control of porosity and integration of adhesion molecules to tailor the IVD cell specific niche.

Acknowledgments

This research was financed by the Gebert-Rüf Foundation project # GRS-X028/13. LM Benneker provided the IVD specimen from Trauma Spinal Surgery.

References

1D N Rockwood (2011) Materials fabrication from Bombyx mori silk fibroin Nat. Protoc. 6 1612-31 2J B Lee (2011) Highly Porous Electrospun Nanofibers Enhanced by Ultrasonication for Improved Cellular Infiltration Tissue Engineering 17 2695-2702

Evaluation of new Polymers for Organ on Chip Applications

Issarawan Taoyuwapan

Supervisors: Assist. Prof. Dr. Olivier Guenat, Janick Stucki and Andreas Stucki
Institutions: ARTORG Center for Biomedical Engineering Research
Faculty of Medicine, University of Bern
Examiners: Assist. Prof. Dr. Olivier Guenat and Dr. med. Manuela Funke-Chambour

Introduction

Most organs-on-chips used in microfluidics and biomedical engineering research are fabricated from poly(dimethylsiloxane) (PDMS). PDMS has very good optical and mechanical properties and is well suited for the production of devices using soft lithography techniques. However, PDMS releases cytotoxic monomers over time, which makes it challenging to use for long-term cell experiments [1]. Furthermore, the strong absorption and adsorption of small molecules in and on the PDMS, makes it unsuitable for toxicological studies and drug analyses. The aim of this master thesis was to evaluate new polymers for organs on chip applications [2].

Materials and Methods

Three commercially available polyurethanes Tecoflex SG-80A, Tecoflex EG-80A, and Tecothane were evaluated in terms of microfabrication and cell culture capacities. The materials were prepared as a solution with different concentrations in either dimethylacetamide (DMAC) or tetrahydrofuran (THF). Three different fabrication techniques were compared: casting in a mold, spin coating, and dip coating. The characterization of ab- and adsorption of the fabricated PU bulks was done using 3 fluorescent dyes: rhodamine B (Rho B), FITC and Hoechst. The PU thin films fabricated using the spin coating technique were evaluated in terms of their biological capacity to culture lung epithelial cells (A549).

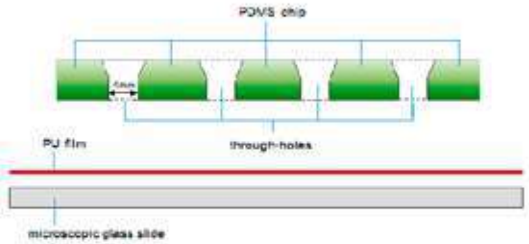


Fig. 1 The PU-PDMS cell culture system.

O_2-plasma was used to modify the surface of PU films, by covalently-linking fibronectin to it. The alamarBlue assay was chosen as method to determine the cell metabolic activity. At the end of cell culture, immunofluorescence staining was performed.

Experimental Results

The PU thin films used in the biological experiments are 25 µm thin. PU SG-80A as bulk showed less absorption and adsorption of Rho B than PDMS. PU EG-80A showed the highest absorption and adsorption of Rho B. PU SG-80A does adsorb Hoechst slightly and no adsorption of FITC was seen. Further, the A549 cells started to adhere on the PU thin films within 2 hours after cell seeding. The metabolic activity and the proliferation of the cells cultured on PUs for 5 days are not lower than the cell cultured on PDMS. The cells showed better adhesion on PU thin films than on PDMS.

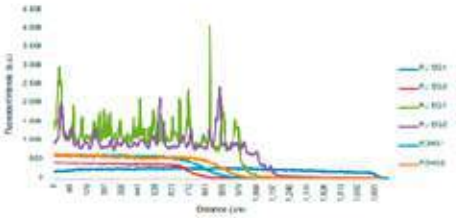


Fig. 2 Comparison of Rho B adsorption profile on different substrates. PU SG-80A showed the lowest fluorescence intensity, suggesting there was very little amount of Rho B adsorption on the PU surface.

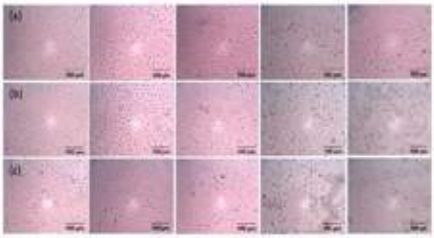


Fig. 3 A549 cells culture on PU thin film (a), PDMS (b), and microscopic glass slide (c).

Discussion

Spin coating and dip coating are suitable for the fabrication of PU thin films. PU SG-80A adsorbs less hydrophobic molecules than PDMS, but it adsorbs a bit of water-soluble molecule. The results of biological experiments of PUs showed that PU is a biocompatible material, which can be used as cell culture substrate. Therefore, PU SG-80A can be used as alternative material for organs-on-chips applications.

References

[1] Regehr, KJ et al. *Lab on a chip*, 2009, 9(15), 2132-39.
[2]. Domansky,K et al. *Lab Chip*, 2013, 13(19), 3956-64.

Motion Artefacts Correction in Optical Coherence Tomography Volumes based on Scan Patterns

Dominik Täschler

Supervisors: Prof. Christoph Meier
Institutions: OptoLab, Institute of Human Centered Engineering, Bern University of Applied Sciences
Examiners: PD Dr. Jens Kowal and Dr. Boris Považay

Introduction

Optical coherence tomography (OCT) is an imaging technology providing high resolution, cross sectional images of the human retina. however, one of the major problems in retinal OCT imaging are motion artifacts caused by heart beating, breathing and eye motion. In recent years, several hardware and software based motion trackers were developed to overcome this problem. Hardware based trackers require additional imaging modalities resulting in higher costs whereas software based methods use the acquired image to correct for motion. Recently published software based methods require multiple volume scans for motion detection [1]. The aim of this thesis is to develop a simple software based method which detects motion on a B-scan basis.

Materials and Methods

The idea of the proposed method is to scan a retinal region containing strong features like the vessels around the optical nerve head (ONH) followed by scanning the region of interest. The absolute position of the acquired scans can then be estimated by segmenting the vessels from the reference scan and matching them to a previously acquired map of the ONH. The whole vessel matching process can be divided into an image acquisition, a vessel segmenting and a vessel matching task.

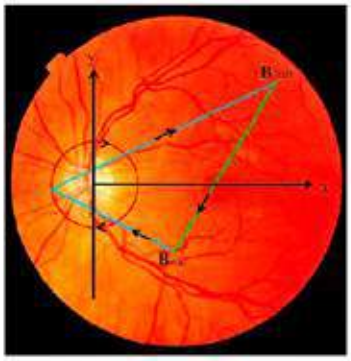


Fig. 1 Fundus image and the chosen scan pattern. The red circle indicates the reference scan around the ONH and the green line the B-scan at the desired position. The blue line denotes the connection between the reference and the B-scan.

In order to generate the desired reference scans and a map of the ONH, a simple retinal scanner was developed and an existing OCT processing LabView software was extended to create the desired scan pattern and save the acquired scans. The vessels of the reference scans were segmented and had to be matched to the corresponding fundus vessels in the map. Aligning the OCT vessels to the fundus vessels and minimizing the distance between them was achieved with an expectation maximization algorithm [2]. The algorithm estimates the probabilities if an OCT vessel belongs to a fundus vessel and minimizes the distances between corresponding vessels according to the previously calculated probabilities.

Results

The algorithm was implemented in Matlab and tested on artificial data and OCT scans from healthy subjects. Simulations with artificial data demonstrated a theoretical B-scan aligning accuracy of +/-15µm in x and y direction if the OCT vessels are segmented with an accuracy of +/- 7µm and no axial movement occurs. The patient data was assessed by measuring the normalized cross correlation of B-scans that were assumed to originate from the same position. Adjacent B-scans showed correlation values of >0.7.

Discussion

Results show that with the proposed algorithm tracking of OCT scans can be achieved without the need for additional complex and expensive hardware. However, results demonstrate an accuracy which is approximately three times lower then state of the art hardware based motion tracker. The results from living subjects only showed sufficient correlation when acquired consecutively. The reason for this can be inaccurate vessel segmentation but also axial movement of the eye during acquisition.

References

[1] M. F. Kraus et. al., *Biomedical optics express*, vol. 3, no. 6, pp. 1182-1199, 2012.
[2] H. Zhu et al., *Medical Imaging, IEEE Transactions on*, vol. 30, no. 6, pp. 1228-1238, 2011

Effect of Age on the Micromechanical Properties of Wet Human Femoral Bone

Suwanwadee Thaiwichai

Supervisors: Jakob Schwiedrzik
Institutions: Institute for Surgical Technology & Biomechanics, Universität Bern
Examiners: Prof. Dr. Philippe Zysset and Jakob Schwiedrzik

Introduction

Osteoporosis is an age-related metabolic disease characterized by low bone mass leading to bone fragility. The current methods for osteoporosis diagnosis, bone mineral density measurements or CT-based finite element analyses, can only explain 75-90% of the variation of bone strength, which may be due to alterations in bone tissue quality. The aim of this study is to examine the micromechanical properties of wet cortical bone of the femoral diaphysis by indentation in axial direction as a function of (1) age, (2) gender (3) microstructure, and (4) their interactions.

Materials and Methods

Cortical bone samples were extracted from the mid-diaphysis of the left femur of 41 donors (22 females and 19 males) with age ranging from 46 to 99 years old. An indentation technique [1] was used for simultaneously measuring force and displacement of a diamond Berkovich tip pressed 1000 nm into the rehydrated bone with a trapezoidal load profile including a 30s holding time. The plane strain modulus, indentation hardness, plastic work and total work were computed from the force-displacement curves.

Results

No relationship between plane strain modulus, hardness, plastic work, total work, the ratio of plane strain modulus to hardness, and the ratio of plastic to total work was found with age, with gender, with interaction of age and microstructure, with interaction of age and gender, or with interaction of age, gender, and microstructure at the confidence level of 0.05. However, the effect of microstructure (osteonal and interstitial lamellae) on the plane strain modulus, the indentation hardness, the ratio of hardness to plane strain modulus, and the ratio of plastic to total work was found to be statistically significant (p-value of 3.96e-08, 1.46e-09, 2.21e-07, and 3.93e-04, respectively). The interstitial bone had a greater plane strain modulus (20.08 ±3.16 GPa), hardness (0.50 ±0.14 GPa), and the ratio of hardness on plane strain modulus (0.025 ±0.004) than osteonal bone (18.09 ±3.14 GPa, 0.41 ±0.13 GPa, and 0.022 ±0.004, respectively). Only the ratio of plastic to total work in osteonal lamellae (0.76 ±0.028) was slightly higher than in interstitial lamellae (0.75±0.026).

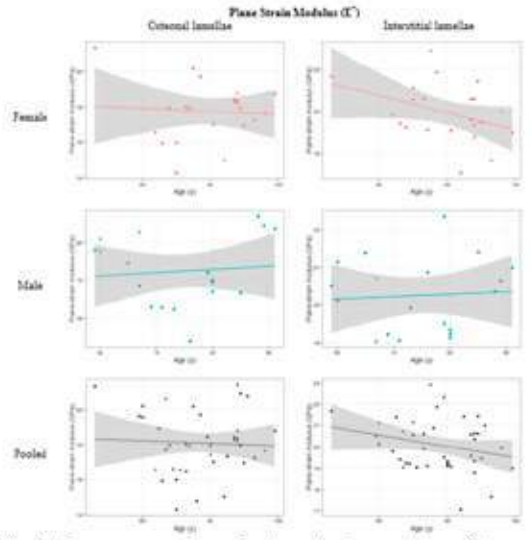


Fig. 1 Linear regressions of plane strain modulus with age for both gender and microstructures. The slopes were not statistically different from zero.

Discussion

This is the first wet indentation study on diaphyseal femoral bone including as many as 41 patients. The main finding that elastic modulus and other indentation variables are independent of age and gender confirms the outcome of two former studies: a first one using an alternative irrigation technique with 27 samples from the femoral neck [2] and a second one with dry and wet vertebral trabecular bone samples [3]. The observed difference in indentation properties between microstructures was also reported in previous studies and reflects the higher mineralization of the older interstitial lamellae.. In conclusion, these results suggest that the declining mechanical properties of aging bone tissue may be the result of factors such as porosity or distribution of micro-cracks rather than material properties at the lamellar level.

References

[1] Oliver, W. C. & Pharr, G. M., 2004. J Mater Res, 19(1), 3-20.
[2] Hoffler, C. E. et al., 2000. J Orthop Res, 18(3), 432-437.
[3] Wolfram, U et al., 2010, Bone 46, 348-354.

Near-Infrared Illumination System for Retinal Tracking

Andreas Vollenweider

Supervisors: Dr. Raphael Sznitman
Institutions: ARTORG Center for Biomedical Engineering Research, Universität Bern
Examiners: Dr. Raphael Sznitman, and Prof. Christoph Meier

Introduction

Slit lamps are one of the most used and available ophthalmic instruments. They have been adapted and upgraded to some of the newer technologies available like Optic Coherence Tomography (OCT) in recent years. OCTs do profit greatly from integrated tracking of their target. This has however not been done with an easy-to-use, cost-efficient system up until now. Employing near-infrared (NIR) light to capture a video of the retina during OCT acquisition with a slit lamp could fill this gap. This approach has to overcome a number of challenges including reduction of glare within the confines of static lens positioning and optimization of the video stream with regard to contrast and irradiance.

Evaluation of Lighting Solution

In a first step three possible solution ideas were evaluated in regards to their theoretical performance in NIR light video acquisition. For this assessment a list of required properties was developed based on the theoretical background presented in the chapters before. The three alternatives included a ring-illumination system, a moving-slit system and a solution utilizing polarization filters. Of these three, the ring-illumination system proved most promising and was therefore selected to be developed further.

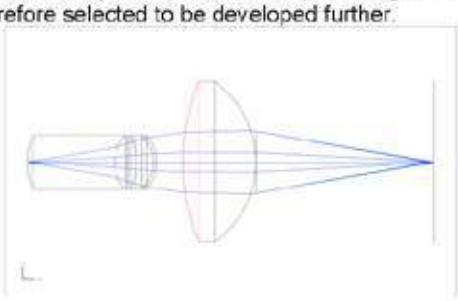


Fig. 1 Simulation of the optical path of a light source (right) through a 90 diopter lens into a Gullstrand-LeGrand schematic eye. Every light ray within the blue confines hits the center of the retina.

Materials and Methods

For the ring-illumination system a complete holder for a normally hand-held lens was developed. This holder included a number of different NIR light emitting diodes (LEDs) and was positioned at a predetermined location between the binoculars of the slit lamp and the patient's eye. To test the capabilities of this newly developed piece, a holding device for a mock eye was constructed and employed to record video sequences of controlled rotational and translational movements. A video sequence showcasing the system with a real eye was acquired as well.

Results

First tests with the newly developed ring-illumination system did show great promise regarding both the ability to provide video sequences with sufficient information content for tracking as well as being easily integrated into an existing slit lamp system. An increase in illuminated area of about 240% was achieved. The test videos did also show that microsaccades of up to 2 degree amplitude between frames should be trackable.

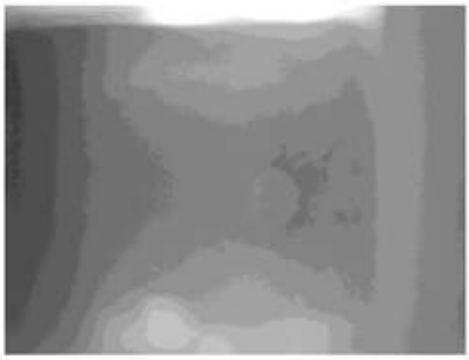


Fig. 2 Picture acquired with the finished prototype. Visible features include the optic disc (center) and surrounding vasculature. There is only minimal glare at the border of the image.

Discussion

The video sequences taken with the newly constructed device show great promise. There are however areas of optimization, namely the use of LEDs with a narrower opening angle for more focused light application as well as possibly better contrast. Exchanging the camera currently employed in the slit lamp setup could also increase the light sensitivity of the setup and thereby the possible information content of the videos.

References

M. Sheehan and A. Goncharov. Unwanted reflections during slit lamp assisted binocular indirect ophthalmoscopy. Journal of Modern Optics, 58(19-20):1848-1856, September 2011.

Interictal Epileptic Activity and its Impact on Driving Ability

Andreas von Allmen

Supervisors: PD Dr. Arto Nirkko and Dr. Heinz Krestel
Institutions: Universitätsklinik für Neurologie, Universität Bern
Examiners: Prof. Dr. Josef Goette and PD Dr. Arto Nirkko

Introduction

Epilepsy is a common disease affecting ~ 3 % of the population in the course of life. Epileptic seizures are caused by excessive electrical brain discharge and may lead to shaking of limbs or loss of consciousness. Due to seizures while driving, epilepsy patients have a higher risk of traffic accidents. Interictal epileptic activity (IEA) is not defined as an overt seizure and is not realized by patients but can be observed in the electro-encephalogram (EEG). Typically IEA lasts only a few seconds and can lead to transient cognitive impairment, but its impact on driving is unclear [1, 2].

IEA can be investigated by measuring reaction times (RT). To achieve this, 1) IEA has to be detected in real time, so that the stimulus can be delivered to the patient during the short period of IEA. This is normally done by visual analysis, but the need for real time requires development of automatic IEA detection. 2) The time when the stimulus is visible on the screen and can effectively be seen by the patient has to be known, but the digital device cascade between trigger and effective display on the screen has unknown and variable cumulative latencies, so that the effective appearance of the stimulus on the screen has to be actually measured. 3) The time of the braking response of the patient hast to be determined. This thesis aimed at solving these problems.

Materials and Methods

In the developed device named "iRT" (Fig 1A), a single-board computer running Linux (Raspberry Pi), acquires EEG data in real time through a serial port from an amplifier (Trackit). Each channel is automatically processed by the own developed IEA detection software. Upon detection of IEA, a trigger is sent to the driving simulator, resulting in the display of a stop sign in front of the patient (Fig. 1B). The stop sign can also be manually triggered during normal EEG to obtain reference RTs without IEA. A RGB-color sensor (Fig. 1C) measures the reflected light from a selected area of the screen. The RGB signals are processed by software on a microcontroller to detect the on-screen stop sign. Together with the brake signal, this yields the effective RT (eRT).

Results

Measurements were done to assess: a) the internal timing of the developed system, which used 5.4 ms for sampling and filtering the stop sign signal, and 520 us for registration of the braking signal; b) to assess the delays of several digital systems, including the driving simulator which showed a median latency between stop sign triggering and on-screen display of 234 ms (range: 189 - 611 ms; Fig. 1D); c) to assess the feasibility of IEA detection and determination of eRT in 6 healthy subjects and one patient with epilepsy: the average reaction times of controls were 871.4 ± 20.2 ms. Reaction times of the patient were 846.7 ± 123.9 ms (n = 38) during normal EEG and were prolonged by 113 ms (p = 0.004) to 960.4 ± 126.1 ms during IEA (n = 16).

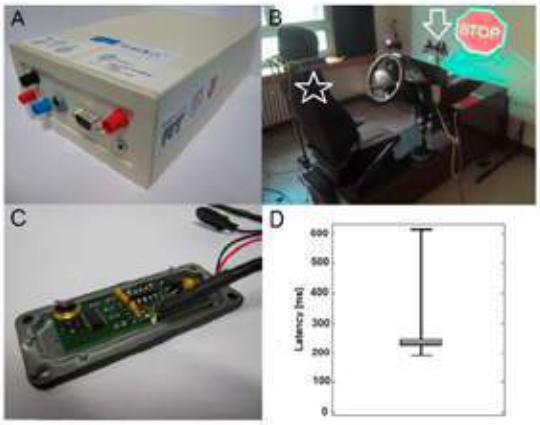


Fig. 1: Reaction time measurement units. A) iRT unit (Raspberry Pi & microcontroller). B) Foerst driving simulator with EEG registration (, Trackit; arrow, sensor unit). C) Sensor unit. D) Latency between stop sign triggering and registration.*

Discussion and Conclusion

The developed iRT system allowed automatic IEA detection. The digital delays between triggering and on-screen display have been measured for various digital systems including the driving simulator. The driving simulator latencies and variability (189 - 611 ms) are large. For the first time, IAE detection and reliable measurements of effective RTs are possible.

References

[1] Krestel H et al. Epilepsia 2011;52:126-129
[2] Yang L et al. Epilepsy Behav 2010;18:238–246.

Development of a Sunlight-Powered Cardiac Pacemaker

Sébastien Walpen

Supervisors: Dr. med. Andreas Häberlin, Thomas Niederhauser MSc BME
Institutions: ARTORG Cardiovascular Engineering, University of Bern, Department of Cardiology, Inselspital, Bern University Hospital
Photovoltaic Laboratory, Bern University of Applied Sciences, Burgdorf
HuCE – Microlab, Bern University of Applied Sciences, Biel
Examiners: Prof. Dr. Josef Götte, Prof. Dr. Dr. Rolf Vogel

Introduction

Today, the lifetime of an implantable cardiac pacemaker is primarily limited by the battery. A contemporary cardiac pacemaker needs to be replaced after approximately 10 years. This exposes the patient to an increased risk of medical complications (e. g. infections, bleedings) and also increases health costs due to multiple surgical interventions.

To allow an implantable device autonomously working over long term and avoid repeated device replacements, intracorporeal energy harvesting systems are desired. Sunlight is a virtually unlimited ubiquitous energy source and partially penetrates the skin. This means, that some of the sun's energy may be harvested and converted into electrical energy by subcutaneously implanted photovoltaics cells.

Materials and Methods

The aim of this project was the development of a sunlight-powered cardiac pacemaker which is made out of a photovoltaic module, an energy management system, a storage element and finally a pacing circuit. First, different solar cells were compared theoretically and experimentally.

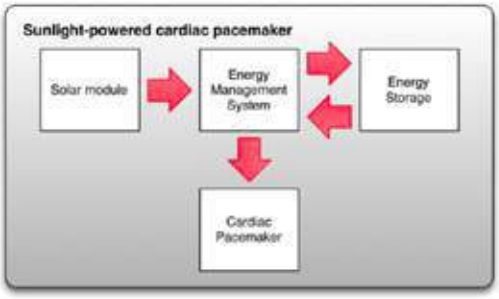


Fig. 1 Block diagram sunlight-powered cardiac pacemaker

Then, the energy management system was designed according to the choice of photovoltaic cells. The pacing circuit was devloped to be a SOO pacemaker which paced at a rate of 125 bpm. Afterwards an storage element was selected to supply the system during one month without energy harvesting. A mathematical simulation based on meteorological data was set up to calculate the harvestable energy in function of lifestyle and weather. Finally prototypes were build in order to implant them and validate the system in vivo.

Results and discussions

The solar module was finally composed of three photovoltaics cells in series with an efficency of 22% and a total area of 22 x 22 mm. Its output power reaches aroud 20mW under optimal sunlight conditions (1'000 W/m2) under 3.5 mm of skin. The power consumption was estimated to be 23.7 µW. Thus, per month, 61.43 J are needed. The energy management system was based on a dedicated chip, which allows to harvest more than 80 % of the available power provided by the solar module under the skin. A Li-Ion battery dedicated for medical implants was selected in agreement with previous results. Two of them fully charged and mounted in parallel reach a capacity of 6 mAh and allow powering the system during more than on month without additional power.

The simulation showed, that the energy harvested during 30 minutes each day in ambient sunlight during wintertime in Bern (80 W/m^2) is sufficient to harvest an average of 69 J during the whole month. Thus, even in winter subcutaneous solar cells may provide enough energy to power a pacemaker.

Finally, two fully integrated pacemaker prototypes (figure 2) were designed and built to be implanted in vivo in a domestic pig. Both pacemakers were set to have a pacing rate of 125bmp in S00 mode. The first prototype was powered with a capacitor to allow implanting without stored energy (the capacitor can be emptied with a magnet). The second prototype (Fig. 2) was powered by a Lithium-Polymer battery of 9 mAh. Both prototypes were implanted and successfully paced after irradiation.

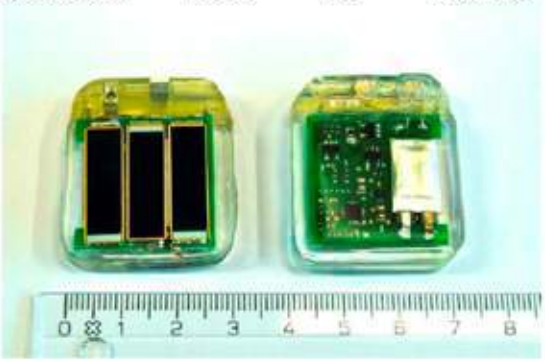


Fig. 2 Fully integrated sunlight-powered cardiac pacemaker

Integration of quantitative EEG analysis into clinical workup of epilepsy surgery candidates

Manuel Weibel

Supervisors: Dr. Christian Rummel
Institutions: Support Center for Advanced Neuroimaging (SCAN)
Institute of Diagnostic and Interventional Neuroradiology, Inselspital Bern
Examiners: Prof. Dr. Volker M. Koch

Introduction

In clinical evaluation of electroencephalographic signals (EEG) visual analysis by clinical experts remains the gold standard. To assist observers, different quantitative EEG (qEEG) analysis methods were developed in the last 20 years, which offer more objective criteria for assessment and may indicate subtle signal changes.

Examples are high frequency components, signal interactions, nonlinear properties or driver-responder relationships. With regard to the EEG of epilepsy patients, two key applications of qEEG analysis methods are early detection or even prediction of seizures and the localisation of ictogenic tissue, which can be targeted by epilepsy surgery.

Although qEEG is more objective and often more sensitive than visual EEG analysis, it is still only little used in clinical routine. The reason is that current qEEG tools require profound programming skills, which only few clinical experts have.

Materials and Methods

The present master thesis provides a tool to integrate qEEG methods into clinical routine workup of candidates for epilepsy surgery. In the thesis proposal it was requested to assort algorithms that highlight complementary diagnostic information in a routine way. The aim is to maximise the added value of qEEG and promote the acceptance of these modern methods by clinicians.

Results

EEGLAB is an interactive MATLAB toolbox for processing continuous and event-related EEG, which is widely spread among clinical experts. To be able to benefit from the full functionality of EEGLAB, an add-on for this toolbox was developed in the present master thesis, which was called "qEEGsuite". It gives clinical experts with limited or even without programming skills access to different qEEG algorithms. qEEG results are always displayed together with the raw data, clinicians are familiar with. For advanced programmers qEEGsuite provides a structure that allows straight forward inclusion of additional algorithms. qEEGsuite is developed in an object oriented structure to allow straightforward enhancement.

Discussion

After a literature research a concept of the program was built. In expert interviews this concept was refined, to develop the program afterwards. The program qEEGsuite defines a base to create new qEEG methods. After a test phase in a selected board the program can be published and further augmented.

References

C. Rummel, R. G. Andrzejak, and K. Schindler. Quantitative analysis of peri-ictal multi-channel EEG. Epileptologie 2012, 29:99–113, 2012.

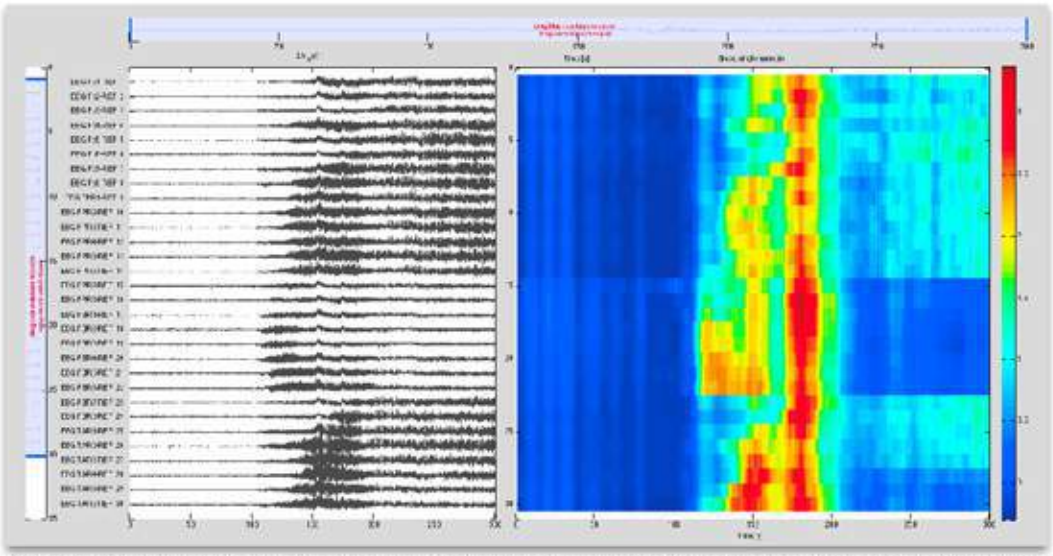


Fig. 1 The scroll plot shows on the left side a peri-ictal EEG signal. On the right side the absolute slop of the EEG signals. The scroll bars on top and very left enable to scroll and zoom in simultaneously original EEG signal and the qEEG result.

Master's Thesis in Biomedical Engineering

Optimisation of Stimulation Patterns for Fes Cycling

Jeremias Max Wolfensberger

Supervisor: Prof. Dr. Kenneth J. Hunt
Institutions: Institute for Rehabilitation and Performance Technology of BFH-TI, University of Bern
Examiners: Prof. Dr. Kenneth J. Hunt and Dr. Volker M. Koch

Introduction

Functional electrical cycling is an alternative way of cycling for paraplegics who have lost motion control of their legs. FES works by creating an electrical field through muscle tissue thus depolarizing nerve cells which in turn contract muscles and cause motion. FES for rehabilitation purposes has been around for about thirty years and has been studied extensively. Regardless of the efforts made in the field, the efficiency of FES is still low and muscles stimulated by FES generate less power and fatigue faster than voluntarily contracted muscles. Through novel stimulation patterns a more physiological and efficient way to contract a muscle might be found.
The aim of the thesis was to improve an existing recumbent FES tricycle test bed to measure power output generated by riders and to conduct a validation study to investigate two different muscle stimulation patterns to determinate changes in power output.

Fig. 1 FES tricycle test bed in use

Materials and Methods

The base of the test bed was an Adventure tricycle by ICE. It was equipped with a Maxon motor and motor controller to turn the pedals, to simulate cycling movement in passive riders and a brake chopper to turn excessive energy, generated by stimulated riders, to heat. The chain drive of the bike was replaced by a belt drive by Mädler to reduce play and friction. The belt drive was connected to the motor. An analogue X-Cell RT torque and position sensor by Thun AG was used to measure power output. FES stimulation was applied through a RehaStim stimulator by Hasomed. Communication with the sensors and actuators as well as design of the user interface was done using Matlab and Simulink. Stimulation algorithms were written in Simulink to either stimulate with a constant frequency of 35 Hertz or with a stochastic time delay between stimulation pulses from 1/50-1/20 seconds. Test cases for short-term (4 times 2.5 min stimulation pattern) and long-term (40min, one stimulation pattern) stimulation were implemented to find differences in stimulation algorithms regarding power output.

Results

The existing test bed was improved. The torque of the left leg was measured with a resolution of 10 mV/Nm in a 5 Volt range with zero Nm at 2.5 Volts. The power output can be extrapolated to total power output by assuming symmetry of both legs. Pedal position tracking was done with a precision of ±3° and a pedal play of 1.5°, allowing high stimulation timing precision. Further a GUI was implemented in Matlab to communicate with the sensors and effectors on the test bed and to control electrical stimulation as well as display the current measurement parameters of the system. Differences in power output by different stimulation patterns were investigated in a technical validation study conducted on the 4 members of the FES cycling project team. A mean power output increase per leg of 0.88 watt for constantly pulsed stimulation and 0.64 watt for stochastic pulsed stimulation compared to unstimulated power output was found in short-term measurements.

Discussion

The goal of setting up a cycling test bed to apply FES stimulation to a person and measure generated power output was reached. A novel stimulation pattern was implemented and applied successfully. The technical validation study showed that the test cases could be run and that the test bed works aside from issues with computational power of the PC used causing timing errors in stimulation pulses. Furthermore electrode placement must be revised to gain better results in terms of power output. Power output was additionally limited by pain experienced by riders caused by the stimulation. This limitation is not applicable to people with spinal cord injury which are the end users of the test bed. Overall the test bed implemented is a good basis for further research as it is simple in handling, measures power with high precision and can easily be adapted to new tasks thanks to its modular design.

Acknowledgements

I would like to offer my special thanks to Prof. Dr. Kenneth J. Hunt, Marco Laubacher, Anil Aksöz and the team of the Institute for Rehabilitation and Performance Technology for their support.

Imprint

Master's Program Biomedical Engineering Annual Report 2014
Editor: University of Bern, Master's Program Biomedical Engineering
Layout: Weimin Yu, ISTB, University of Bern
Print: Druckerei Varicolor, 3053 Münchenbuchsee
Photo Cover: Adrian Moser

University of Bern
Master's Program Biomedical Engineering
Stauffacherstrasse 78
3014 Bern
Switzerland

Phone +41 31 631 59 05
Fax +41 31 631 59 60
Email BME@istb.unibe.ch

www.bme.master.unibe.ch