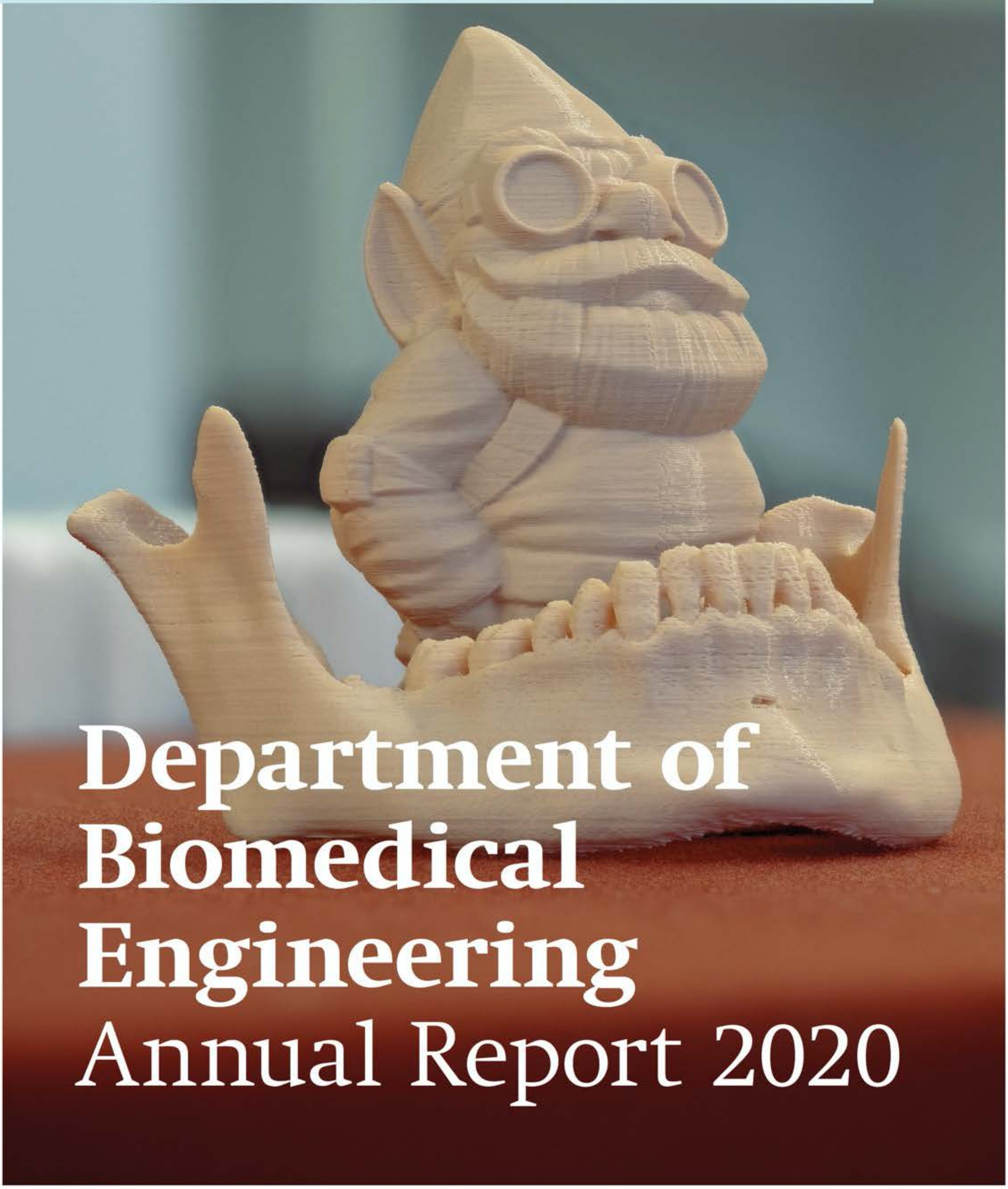
Universität Basel

Departement of
Biomedical Engineering



Department of Biomedical Engineering
Annual Report 2020

Guiding Principles

We contribute to a world where health care needs are met
by innovative biomedical research and engineering solutions.

We translate basic science and engineering
into medical knowledge and healthcare innovations.

We provide high-quality education and capacity building
for academics, clinicians, and industrial partners.

We adhere to the policy of the University of Basel
and promote an interdisciplinary culture of dialog,
appreciation, respect, honesty, and tolerance.

We are committed to scientific integrity, reliability,
transparency, and good scientific practice.

We value and foster enthusiasm and passion for science.

The success of our mission is based on the support of our founding institutions:

University of Basel

Universitätsspital Basel

UKBB

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Highlights of 2020

Creativity in the Age of Covid-19

The human brain imagined as a planetary surface (Picture: R. Wendler/DBE).

Creativity is a delicate plant. Surrounded by too much work and stress, it does not grow, does not form blossoms and does not bear fruit. Creativity needs time, freedom and a playful attitude. Therefore, one would assume that Covid-19 and all the restrictions it came with have stifled the creativity of the researchers at the DBE. But this was not the case.

Indeed, researchers at the DBE were not able to exchange ideas with the clinicians of our partner hospitals in a casual and – precisely for that reason – fruitful manner. Since we depend on this exchange, we have missed many opportunities for new ideas and collaborations here, some of them forever. But at the same time, we have succeeded in taking and using inconvenient necessities as fresh opportunities to leave old ways.

One example for this are the virtual lab tours, which initially were born out of sheer necessity but were so well received by our audiences that we decided to produce more of them even after Corona. Necessity is the mother of invention, so they say, and the virtual lab tours prove that.

The lesson here is that we can take something positive from even a disaster if we are willing to accept it as a challenge. The review of 2020 shows that the DBE succeeded in this and that we have every reason to believe that it will do so in 2021. Creativity in the age of Covid-19, we may therefore conclude, means simply not letting any burden prevent us from inventing and realizing a better future.

Philippe Cattin

A look back on 2020

The DBE: Robust success due to collaboration (Picture: R. Wendler/DBE).

If we look back on the year 2020 and only consider the enormous successes of the researchers at the DBE, the difficulties that the pandemic brought seem to have passed without a trace. Never before, so many master's and doctoral theses were completed at the DBE, so many new projects started, so many papers published, and so much research funding acquired. These are the fruits of the enthusiasm for translational research coupled with an iron will to achieve the ambitious goals as well as the excellent collaborations of the research groups with each other and with the physicians in the clinics.

In order to further strengthen this unique, successful constellation and to open up all channels that enable and support the optimal translation between research and clinic, a strategy group from all areas of the DBE set out last year to define the common strategic goals and to set out on the paths to achieve them with targeted actions. In doing so, we hope that each of the coming years will continue to surpass its predecessor in terms of successes, even if, on closer inspection, Corona has also put the brakes on some of our projects.

In this report, we show you how the DBE did evolve in the past, how it wants to develop in the future and we turn the spotlight on some of the successes of 2020 mentioned above. I hope you will enjoy reading it and that the enthusiasm of our researchers will spread to you.

Daniela Vavrecka

How to Keep Growing

Figure 1: Members of the strategy group at work (Picture: D. Vavrecka).

To maintain and even further expand its excellent position and to define its strategic goals, also with regard to its move to the GRID in 2023, DBE group leaders defined the following aims in four fields of action:

In research, the DBE focuses on problem-solving and providing practical, innovative biomedical engineering solutions to clinical challenges. It aims at covering the entire translational process from bench to bedside by developing and validating clinical applications and supporting regulatory approval processes.

The organizational setting and the multidisciplinary network of the DBE is unique, as it is a research institution integrated in the clinical environment and embedded in an ecosystem of med-tech spin-offs and strong connections to the industry. The visibility of this unique network must be enhanced to provide a continuous flow of translational projects.

To attract the best talents the DBE offers and promotes a most desirable MSc in Biomedical Engineering and directly engages its interdisciplinary students in ongoing research activities. We aim to be able to choose from twice as many applicants as places are available.

The DBE must be backed by solid structural funding from the medical faculty to cover its core facilities, research IT, security, administration, and at least one structural university professorship in each research cluster. To substantiate this legitimate request, the DBE continues to attract substantial third-party research funding, and at the same time, increases the number of translational projects with clinical partners.

The still young and comparatively small DBE does deliberately not restrict itself to narrow and specific research fields but is open to developing in every direction of biomedical engineering in its research clusters.

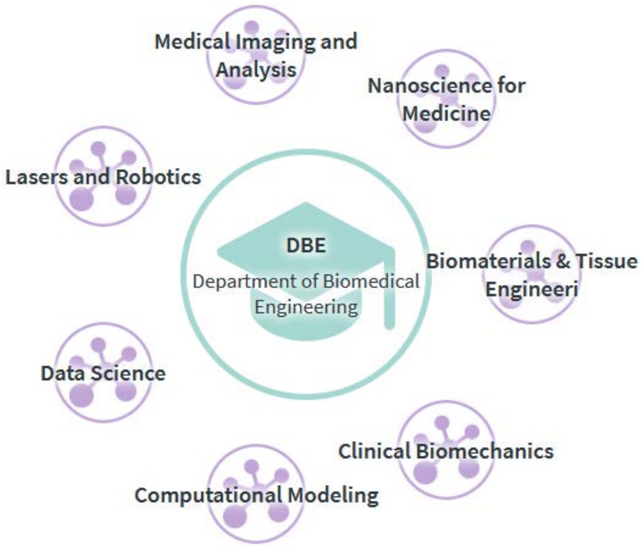

Figure 2: The Research Clusters of the DBE in its circle of expertise (Picture: N. Zentai).

The members of the strategy group:
- Philippe Cattin
- Oliver Bieri (deputy: F. Santini)
- Olivier Braissant
- Reinald Brunner
- Edgar Delgado
- Cristina Granziera
- Ludwig Kappos
- Srinivas Madduri
- Bert Müller (deputy: G. Schulz)
- Anne Mündermann
- Georg Rauter (deputy: N. Gerig)
- Najat Salameh
- Arnaud Scherberich
- Pablo Sinues (deputy: G. Oser)

Retreat organization and consulting:
- Sandra Jauslin, University of Basel, Personal- und Organisationsentwicklung

Strategy project coordinator:
- Daniela Vavrecka-Sidler, DBE

Read more:
https://dbe.unibas.ch/en/about-us/mission-success-positions

Nominations, Awards & Distinctions

Figure 1: Award Ceremony for Tino Töpper at the Swiss Medtech Day (Picture: B. Osmani).

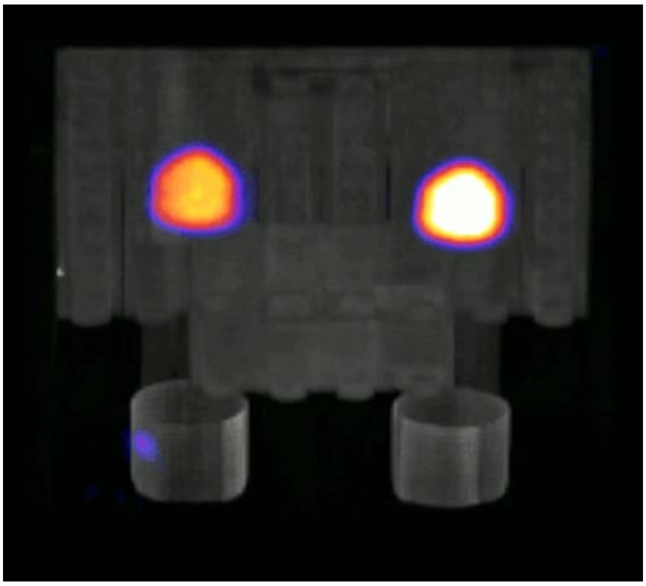

Figure 2: Still from the victorious contribution of P. von Niederhäusern for the SNSF Scientific Image Competion (Picture: P. von Niederhäusern).

In 2020, members of the DBE have received a number of prizes and awards, have been appointed to positions of responsibility, or have received their Venia Docendi. These honors reflect the increasing innovative appeal of the DBE. We are very happy to congratulate the following people:

- Cordula Netzer, Florian Thieringer and Srinivas Madduri have been granted the Venia Docendi.
- Georg Rauter has been appointed associate member of the NCCR Robotics and was appointed chair of the Swiss Branch of the International Federation for the Promotion of Mechanism and Machine Science (IFToMM).
- Pablo Sinues was honored with the 4thSGMS Award by the Swiss Group for Mass Spectrometry, acknowledging his cross-disciplinary expertise, his highly innovative and productive work and his key contributions to the analysis of exhaled breath by ambient mass spectrometry. Pablo Sinues has additionally been re-elected as Innosuisse Expert.
- Bert Müller and group members co-authored a publication in SMALL for which they provided unique µCT data that was used to produce an image that won the 1st prize in the SNC Nano Image Award.
- Peter von Niederhäusern has won the 1st prize at the SNSF Scientific Image Competition with an entry called "Transparency in Science“, submitted in the category 4 "Video Loop".
- Tino Töpper has won the Science Slam Awards 2020 at the Swiss Medtech Day.

New Spin-Offs, Network Expansions, Patents

Spin-offs:
With so many innovative research projects at the DBE, it is not surprising that new spin-offs are constantly being founded. For the ones in 2020, see below Acthera and Bottmedical. The spin-off AOT (Advanced Osteotomy Tools) successfully completed its "first-in-man" clinical trial.

- Acthera develops mechano-responsive, Hard-Shelled Liposomes (HSLs) for targeted drug release (ex Biomaterials Science Center).

- Bottmedical AG develops and produces bio-based polymer splints to correct teeth positioning – the NaturAligner® (ex Biomaterials Science Center).

- The Swiss AOT successfully completed the first-in-man clinical study and demonstrated the performance and safety of its proprietary system CARLO® (Cold Ablation Robot-guided Laser Osteotome), a surgical robotic platform, which cuts bones through cold laser ablation.

Networks:
Since this success is heavily based on networks, the DBE expanded its network further and became a member of the Swiss Society for Biomedical Engineering and the NCCR Robotics. The latter thanks to Prof. G. Rauter, who is also the new head of the Swiss organization of IFToMM (International Federation for the Promotion of Mechanism and Machine Science).

Patent applications:
EP20186274 Breath-based therapeutic drug monitoring method (Research group of Pablo Sinues).

Funding Through Grants and Foundations

Foundations at the Root of the DBE

The old "Frauenspital Basel" (Picture: University of Basel)

Those who forget the past
are condemned to repeat it.

George Santayana, The Life of Reason, 1905

The Department of Biomedical Engineering has its roots in several private foundations and trusts. Without these benefactors who endowed chairs, supported education or funded visionary projects, we would hardly flourish as we do now. Let's turn the spotlight on the most influential ones.

The support of the "Hardy und Otto Frey-Zünd-Stiftung" for the "Laboratory of Orthopedic Biomechanics" (LOB[1]) could be considered the nucleus for the DBE. The LOB was founded in 1990 and mainly established by Prof. Erwin Morscher, head of Orthopedic Surgery at the University Hospital Basel. Prof. Morscher was additionally able to convince his close friend Dr. h.c. Zaeslin to contribute to education – what he does to this day!

In April 2005, the LOB and the "Hightech Research Center of Cranio-Maxillofacial Surgery" (HFZ[2]) were merged in the faculty focal area "Clinical Morphology and Biomedical Engineering" (CMBE) and moved together into rooms of the old abandoned "Frauenspital" at Schanzenstrasse. Subsequently, two privately endowed professorships were established and included in CMBE: 2006 the "Biomaterials Science Center" (BMC[3]) sponsored by Thomas Straumann, and 2007 the "Center for medical Image Analysis & Navigation" (CIAN[4]) sponsored by Hansjörg Wyss.

In 2014, the "Werner Siemens Foundation" granted 15.2 million SFR for the project MIRACLE, led by Prof. Hans-Florian Zeilhofer (HFZ) and Prof. Philippe Cattin (CIAN).The following year the strengthened CMBE moved to Allschwil, installed two additional professorships for "Medical Robotics and Mechatronics" and for "Medical Laser Physics and Optics" and was reborn as the "Department of Biomedical Engineering". The DBE's growth through foundations continues as Werner Siemens Foundation granted a further 12 million SFR for MIRACLE II.

Links:

https://dbe.unibas.ch/en/about-us/

https://www.unibas.ch/de/Aktuell/Uni-Nova/Uni-Nova-126/Uni-Nova-126-Mit-Ingenieurskunst-zu-neuen-Loesungen-in-der-Medizin.html

https://geschichte.medizin.unibas.ch/de/die-ordinarien/n-o/orthopaedie/fakultaet/orthopaedie

Links:

[1]formerly LOB today COB. Head: Prof. Niklaus Friederich
[2]HFZ Head: Prof. Hans-Florian Zeilhofer
[3]BMC Head: Prof. Bert Müller
[4] CIAN Head: Prof. Philippe Cattin

Research Funding

Figure 1: Georg Rauter, Niklaus Friederich, Manuela Eugster, and the tiny MIRACLE endoscope tip (Picture: R. Wendler/DBE).

Figure 2: PhD candidate Murali Karnam with a virtualized prototype of the MIRACLE-system (Picture: R. Wendler/DBE).

Third-party and SNSF research funding granted in 2020 peaked again, mainly due to the generous support for the second phase of MIRACLE by the Werner Siemens Foundation.

Considered "Excellent Junior Researchers", several young researchers at the DBE received support from the Research Fund of the University of Basel (Dr. C. Lenz, Dr. I. Schulz, Dr. Ch. Tsagkas) and others from SNSF for their innovative projects (Prof. N. Salameh, Prof. Ph. Cattin, Dr. F. Santini). Researchers received funding for collaborations in Innosuisse projects with industrial partners (Dr. B. Göpfert, Prof. A. Zam) or with medical partners in a BRCCH project (Dr. Stübinger). On European level Prof. L. Kappos and Prof. C. Granziera are involved in a major Eurostars project. Additionally, various collaborations are funded by industrial partners (Prof. Cattin, Dr. C. Jud, Dr. O. Braissant). Not known to many are two long-time "secret" benefactors of the DBE: Hans-Heiner Zaeslin, supporting teaching and the Merian Iselin Stiftung, sustaining the micro-calorimetry lab.

Undoubtedly, the funding highlight of 2020 is the support for MIRACLE II (Minimally Invasive Robot-Assisted Computer-guided LaserosteotomE) of 12 million SFR by the Werner Siemens Foundation. The successful MIRACLE team aims to teach a modular robot (RG Prof. G. Rauter) not only to perform osteotomy by laser (RG Prof. A. Zam), but also to print personalized bio-implants directly in the patient if possible (RG PD Dr. F. Thieringer). This completely novel procedure will be planned with virtual reality (RG Prof. Ph. Cattin).

University of Basel
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Klinik für Orthopädie und Chirurgie
Innosuisse - Swiss Innovation Agency
Schweizerische Eidgenossenschaft
Confédération suisse
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WSS
WERNER SIEMENS-STIFTUNG
fondation
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Dr. h.c. Hans-Heiner Zaeslin Supporting Education

Figure 1: The couple Hans-Heiner and Claudine Zaeslin during the opening ceremony for the Zaeslin Guest House (Picture: D. Plüss).

Figure 2: If your invited professor stays for some time in Basel, he/she might stay at the Zaeslin Guest House of the University Basel at the Nonnenstrasse. This guest house – funded also by Dr. Zaeslin – opened in fall 2020 (Picture: D. Plüss).

In the last twenty years, Dr. h.c. Hans-Heiner Zaeslin and his wife Claudine have been very strong supporters of biomechanics at the University of Basel, where especially teaching benefited from their generous donations.

Teaching had always been a very strong interest of Dr. Zaeslin. Through his trust and funded with personal money, he supported summer schools and teaching programs at the Faculty of Business and Economics and at the Medical Faculty since the late 1990's. Honoring his long-time active and generous support, in 2007 the University of Basel awarded him the title of a 'Doctor honoris causae' (Dr. h.c.).

After their time as classmates, Dr. Zaeslin remained a very close friend to Prof. Erwin Morscher (1929 – 2008), former head of Orthopedic Surgery at the University of Basel – a reason why Dr. Zaeslin specifically supported the LOB (Laboratory for Orthopedic Biomechanics). Since 2003 parts of the grant from the Zaeslin trust were dedicated to fund the teaching activities of the heads of the LOB (later named COB, Center of Biomechanics): Prof. A.U. Daniels and – after his retirement – Prof. Niklaus F. Friederich.

However, and even more important: The annual funds from the Zaeslin trust are utilized to invite the best and most outstanding researchers in biomedical engineering from North America to teach our students in Basel. As 'Erwin Morscher Visiting Professors' and/or as visiting professors to the summer and winter schools of the DBE, those researchers brought the best knowledge to Basel and strengthened collaborations between top research groups in US, Canada and Basel.

Without this long-time and most generous support from Dr. Zaeslin, neither we at the COB nor at the DBE would be where we are today. Thank you very much.

Author:
Niklaus F. Friederich, MD
Adjunct Professor of Orthopedic Surgery

MIRACLE II

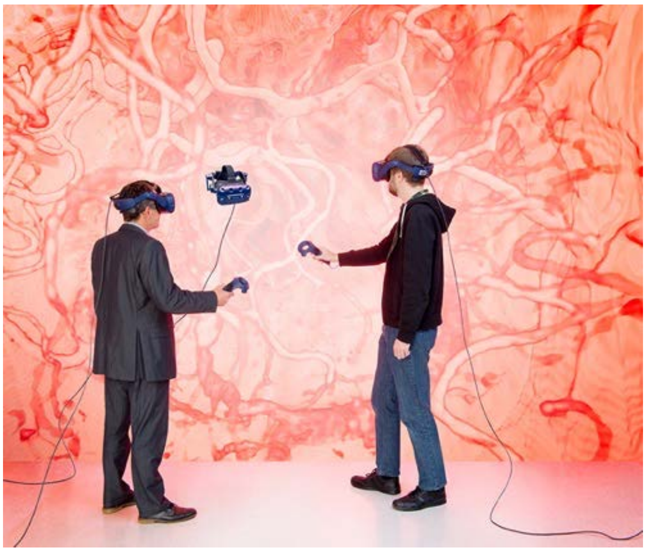

Figure 1: Surgery planning in the VR with remote participant (Picture: F. Brüderli/WSS).

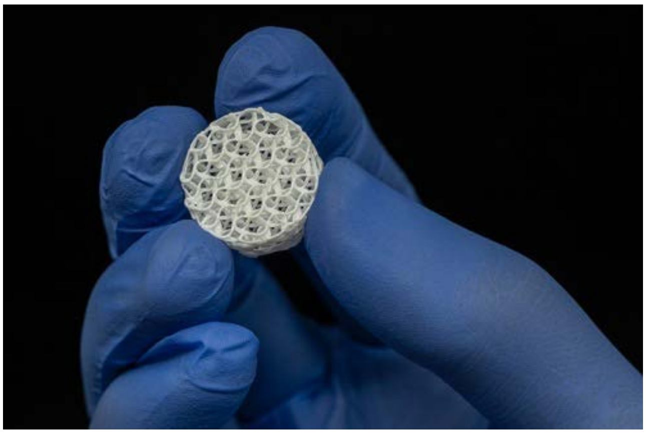

Figure 2: 3D-printed scaffolds for guided bone regeneration (Picture: R. Wendler/DBE).

Building on the achievements of the MIRACLE Project, the researchers at the Department of Biomedical Engineering are about to enter a second project phase. Generously supported by the Werner Siemens Foundation with 12 million CHF, the team around Prof. Philippe Cattin (DBE) and PD Dr. Florian M. Thieringer (University Hospital Basel, successor of Prof. Hans-Florian Zeilhofer) aims at teaching a modular robot to print personalized bio-implants.

These completely novel interventions are supposed to be planned in virtual reality. The resulting designs will be produced in 3D printing, perhaps one day even directly in the body of the patient. In contrast to older, primarily manual methods, this approach aims to enable faster and more precise designs. The MIRACLE-project will remain composed of the following four groups:

- The Planning and Navigation Group creates the Virtual Reality environment.
- The Bio-Inspired RObots for MEDicine-Lab develops bio-inspired robotic and mechatronic systems for medical applications.
- The Biomedical Laser and Optics Group develops laser- and optical-based systems for medical applications.
- The Smart Implants Group develops a novel Minimal-Invasive Modular Implant System.

The first phase, which started in 2016, has been funded by the Werner Siemens-Stiftung with 15 million CHF. The second phase will begin in mid 2022, with the exception of the Smart Implants II team, which has already started its work.

Funding:

WSS
WERNER SIEMENS-STIFTUNG

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Project coordinator:
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More:
https://dbe.unibas.ch/en/research/flagship-project-miracle/miracle-ii/

Our Research is Funded by

University of Basel

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MERIAN ISELIN
Klinik für Orthopädie und Chirurgie

WISSENSCHAFT. BEWEGEN
GEBERT RÜF STIFTUNG

Osteology Foundation

Horizon 2020
European Union Funding
for Research & Innovation

FH
Berner Fachhochschule
Haute école spécialisée bernoise
Bern University of Applied Sciences

HMZ

propatient
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Universitätsspital Basel

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Schweizerische Eidgenossenschaft
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Bundesamt für Gesundheit BAG

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Swiss Confederation
Federal Department of Economic Affairs,
Education and Research EAER
State Secretariat for Education,
Research and Innovation SERI
Swiss Space Office

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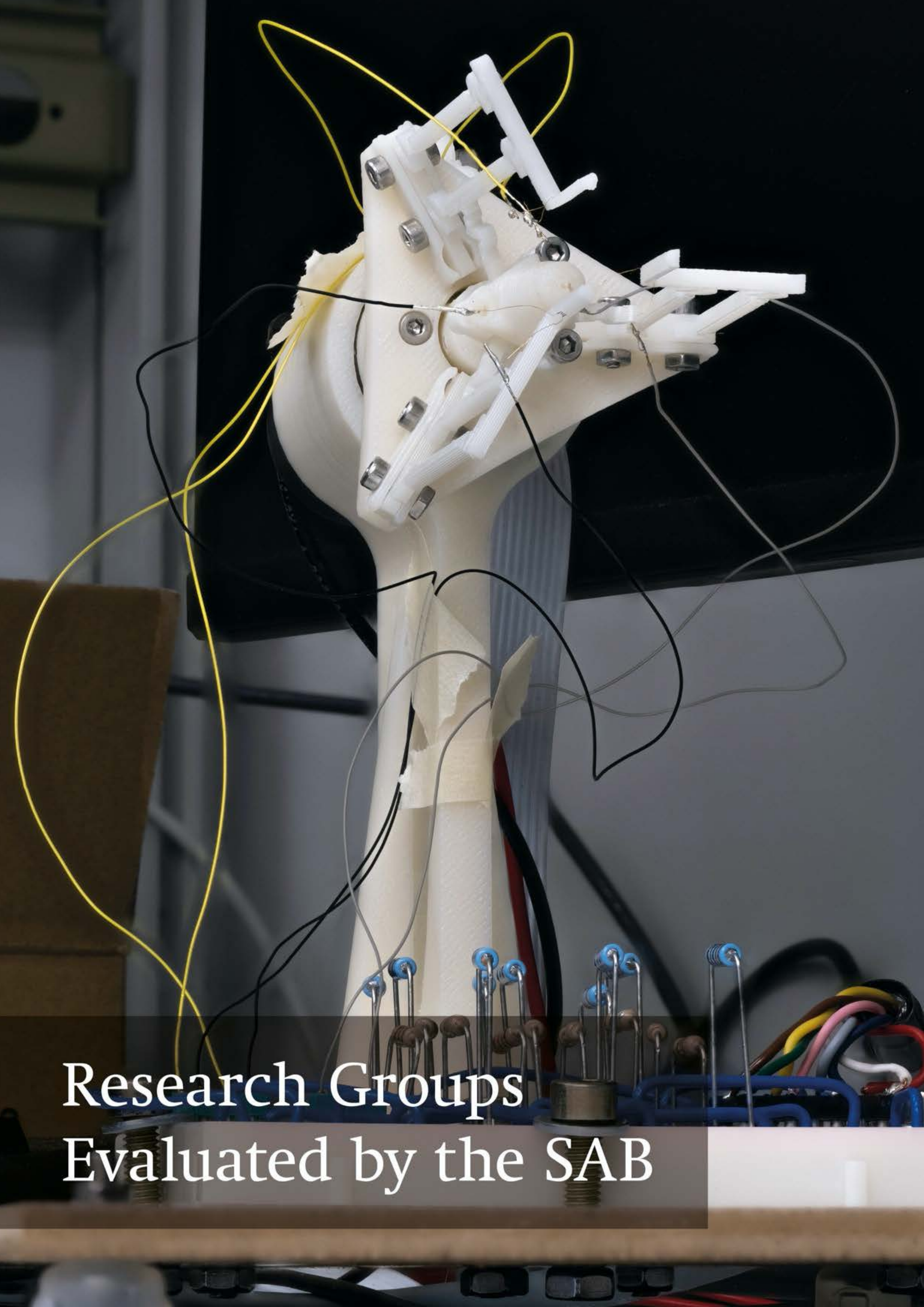

Research Groups Evaluated by the SAB

Bio-Inspired RObots for MEDicine-Laboratory

Figure 1: Force-sensitive endoscopic tip prototype (Picture: I. Sušić/DBE)

Figure 2: Team photo 2019 (Picture: T. Schürch/DBE).

The BIROMED-Lab develops bio-inspired robotic and mechatronic systems for medical applications. The main research focus of the BIROMED-Lab is minimal invasive semi-autonomous robotic surgery for laser ablation of hard tissue (bone). Our portfolio includes know-how in mechatronics, mechanical design, micromachining, robotics, control, and real-time data processing. Due to our expertise, we also maintain strong collaborations in the fields of robot-assisted gait and arm rehabilitation.

We are developing an entire surgical platform that will consist of several dedicated subsystems for the positioning and stabilization of the robotic endoscope, flexible robotic endoscopes for single port surgery, new technologies in force sensing for endoscopes, intuitive telemanipulation interfaces, highly integrated optics, and spray systems for endoscopic laser surgery. To achieve repeatable high precision cuts in minimally invasive procedures, our endoscope tip attaches to the target tissue and decouples mechanically from the endoscope, thus avoiding disturbances. Cutting will be performed in a semi-autonomous procedure, where the robotic endoscope tip moves the laser along pre-planned trajectories, while the surgeon surveys the cutting process and can intervene at any time. We investigate novel teleoperation interfaces and control modes to enable intuitive, novel surgical procedures for robotic laserosteotomy.

The BIROMED-lab was founded in May 2016 as part of project MIRACLE. We employ eight PhD-students and collaborate with ETH Zurich (Sensory-Motor Systems Lab), University of Zurich (Paralab), Technical University of Innsbruck, MCI Innsbruck, Reha-Stim Medtec AG (Schlieren), and AOT AG (Basel).

Funding:

WSS
WERNER SIEMENS-STIFTUNG

Group Leader:
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Selected Publications:

G. Rauter, N. Gerig, R. Sigrist, R. Riener, and P. Wolf, “When a robot teaches humans: Automated feedback selection accelerates motor learning,” *Science Robotics*, vol. 4, no. 27, p. eaav1560, Feb. 2019.

M. Eugster, P. Cattin, A. Zam, and G. Rauter, “A Parallel Robotic Mechanism for the Stabilization and Guidance of an Endoscope Tip in Laser Osteotomy,” in *IEEE Conference on Intelligent Robots and Systems (IROS),* pp.1306-1311, 2018.

Biomedical Laser and Optics Group (BLOG)

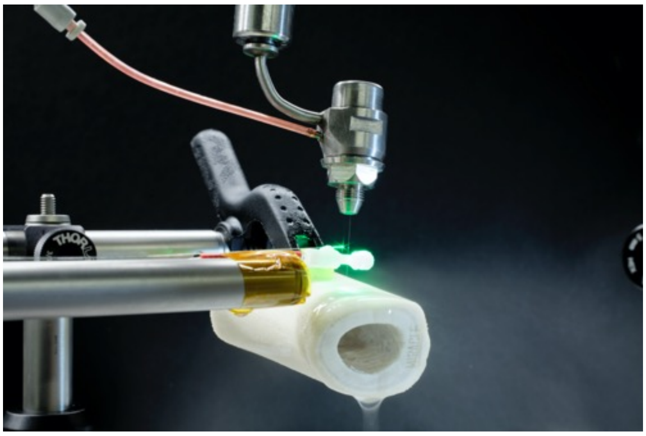

Figure 1: Fiber-based Smart Laser Surgery (Picture: O. Lang/WSS).

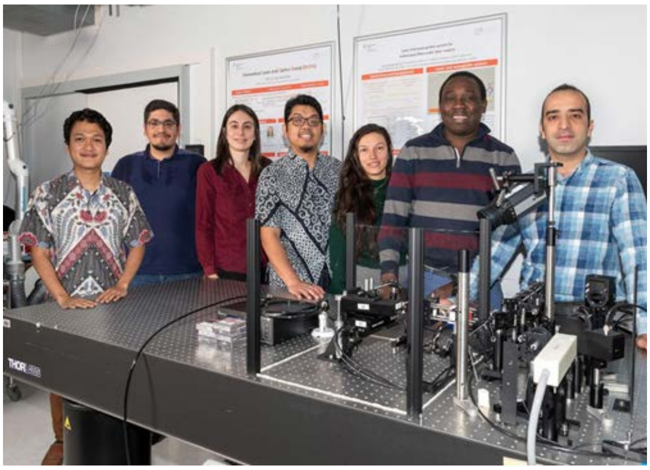

Figure 2: The BLOG team (Picture: T. Schürch/DBE).

BLOG develops smart devices for medical therapy, diagnostics and monitoring using novel optical technologies. The main research focus of BLOG is to develop a fiber-based laser with feedback systems that guarantee exact cuts of almost all shapes in minimally invasive surgery. The laser and the feedback system will detect the tissue type in front of the tip. To achieve this, an opto-acoustical- and optical coherence tomography-based feedback sensors have been integrated. Depending on the information obtained from the real-time feedback system, the laser continues cutting or immediately stops to avoid damaging collateral damage to surrounding tissues. The combined system will be applied in Smart Laser Surgery.

The main projects under development in the BLOG group are:

A) Fiberoptic delivery system
B) Optical feedback system
C) Acoustical feedback system
D) Optics-based imaging system

A: The fiberoptic delivery method will be used to send the laser beam along with the endoscope. Since a flexible endoscope design is needed, sequential mirror systems cannot be used.

B-C: Optical and an acoustic feedback system will be used to differentiate the tissue types. Depending on the feedback, the cutting laser will continue cutting or immediately stop.

D: During laser ablation, depth control, and tissue differentiation will be provided using optical coherence tomography (OCT), a high-resolution imaging system. By using OCT not only depth control but also temperature increase in the surrounding tissue can be measured.

Funding:

WSS
WERNER SIEMENS-STIFTUNG

Group Leader:
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Selected Publications:

H. N. Kenhagho et al., "Miniaturized opto-acoustic feedback sensor for smart laser osteotome: Fiber-coupled Fabry-Pérot etalon sensor." *Sensors and Actuators A: Physical* 2021, *317*, 112394.

L. Beltrán et al., "Optimizing deep bone ablation by means of a microsecond Er: YAG laser and a novel water microjet irrigation system ", Biomedical Optics Express, 2020, 11, Nr. 12, 7253-7272.

H. Abbasi et al., "Laser-induced breakdown spectroscopy as a potential tool for autocarbonization detection in laserosteotomy", Journal of Biomedical Optics, Vol. 23, No. 7, p. 071206 (2018).

Translational Medicine Breath Research

Figure 1: Real-time breath analysis platform at the lab (Picture: Translational Medicine Breath Research).

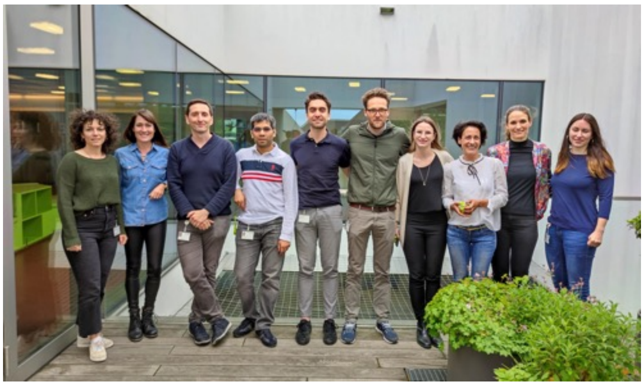

Figure 2: Translational Medicine Breath Research group at the University Children's Hospital Basel (Picture: Translational Medicine Breath Research).

Breath is a diagnostically underexploited body fluid, which contains valuable bio-chemical information about health status. For example, the sense of smell was used by clinicians already in ancient Greece and China to retrieve information about their patients. However, nowadays, very few diagnostic tests rely on expired breath. We work to reverse this situation by uncapping the full potential that breath analysis holds as a non-invasive method to assist in clinical decision making (1). To achieve this goal, we use modern analytical platforms combined with sophisticated computational tools.

The Translational Medicine Breath Research group is part of the Department of Biomedical Engineering and is located at the University Children's Hospital Basel (UKBB). It was established in June 2017 and is led by Prof. Dr. Pablo Sinues (Botnar Professor).

Our mission is to develop novel diagnostic methods, with a special focus on breath analysis, which holds great potential as a non-invasive method to assist in clinical decision making.

Our vision is to improve disease diagnosis, to better characterize complex pathophysiological processes, as well as to personalize therapy. Our primary research lines include rapid diagnosis of pneumonia and therapeutic drug monitoring guided by breath analysis.

Funding:

Swiss National Science Foundation (FNSNF)

fondation BOTNAR

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Patent:
EP20186274
Breath-based therapeutic drug monitoring method

Selected Publication:

Singh, K. D.; Del Miguel, G. V.; Gaugg, M. T.; Ibanez, A. J.; Zenobi, R.; Kohler, M.; Frey, U.; Sinues, P., Translating secondary electrospray ionization-high-resolution mass spectrometry to the clinical environment. *J. Breath Res.* 2018, *12* (2), 027113.

New Research Groups at the DBE

Neurosurgery

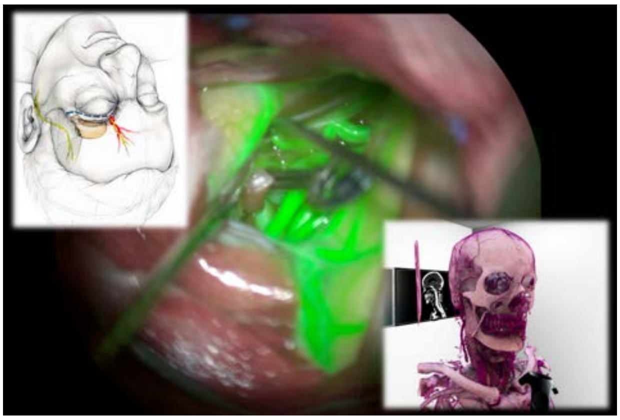

Figure 1: VR in **brain** aneurysm **surgery** (Picture: R. Guzman/Neurosurgery Group)

Figure 2: Experimental setup for a neurosurgical endoscope (Picture: R. Wendler)

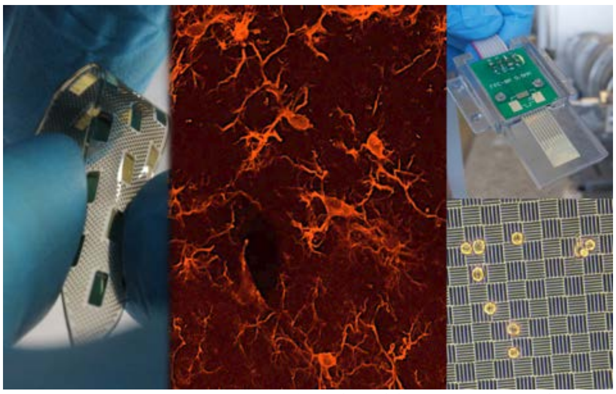

Figure 3: Nano-engineered neural interfaces (NENI) (Picture: R. Guzman/B. Osmani).

The Neurosurgery Group develops new methods and technologies for the use of SpectoVR in the planning of neurosurgical interventions in a collaboration with CIAN's Prof. Philippe Cattin.

VR is used in the planning of minimally invasive approaches for Brain Aneurysm surgery. In conjunction with Augmented Reality fluorescence guided surgery this becomes a very powerful package. Currently, the focus lies on new visualization tools inside the VR and a robot-based haptic feedback to enhance surgery simulation. SpectoVR is also used to prepare patients for surgery and to introduce medical students to surgical practice.

Together with Prof. Georg Rauter from the BIROMED-Lab, the Neurosurgery group is developing novel optical systems for neurosurgical endoscopes which are to be used in the minimally invasive laser robot of the MIRACLE team, but which could also be of great benefit for neuro-endoscopic procedures. In the same project context, Prof. Guzman is working with Prof. Azhar Zam (BLOG) on systems providing measurements of the depth of cutting and tissue recognition beyond the bone – essential safety features for this technology.

Prof. Guzman's Lab also works with Dr. Bekim Osmani and Prof. Bert Müller on the development of ultra-thin electrodes for application in neuromodulatory therapies for brain and spinal cord diseases. These Nano Engineered Neural Interfaces (NENI) are about 10'000 times softer than currently used electrodes. In Prof. Guzman's Lab they investigate the effect of neuromodulation on neuroinflammation, which is an important pathophysiological mechanism in central nervous system diseases. BottNeuro, a spinoff of the University of Basel was established in 2021.

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Facial & Cranial Anomalies

Figure 1: Research Group working on the project of Burden Reduced Cleft Care and Healing (Picture: BRCCH – Botnar Research Centre for Child Health).

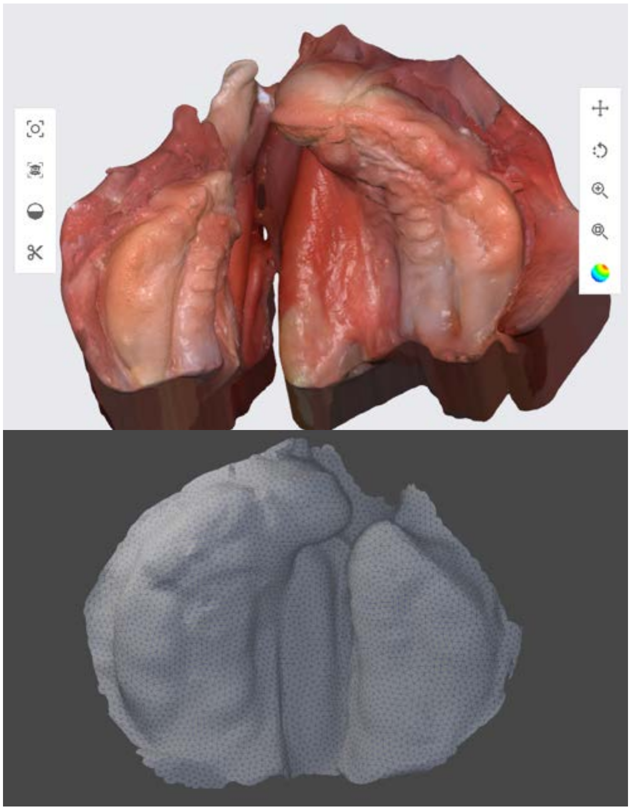

Figure 2: Digitized intraoral shape in infants with cleft lip and palate (Picture: USB / ETHZ).

Orofacial clefts are the most common facial & cranial abnormalities associated with a heavy burden on children and their families. The newborns suffer from an incomplete tissue fusion along natural embryological lines in the face and oral cavity. This leads to a number of disturbances in terms of lip and tongue movement, speech, hearing, swallowing, nasal breathing, chewing, as well as craniofacial and dental development.

Our research topics include the spectrum of biological, technical and clinical assessments to deepen the understanding of the anomaly and to build thereupon optimized treatment strategies with optimal outcome and minimal burden of therapy.

Current ongoing projects involve:

- Machine learning-based approach for image-based palatal shape recognition in cleft patients, with partners at ETH Zurich, Disney research Zurich and clinical partners in Poland and India (BRCCH).
- In vivo three-dimensional volume stability of regenerative material enhanced bone grafting and action on tooth eruption.
- In-silico test of next-generation treatment strategies using magnet transmitted periosteal distraction for the generation of mucosa and bone (with UZB).
- Intraoperative vascular anatomy and microcirculation measurement in cleft palate repair.
- Assessment of the first-in-man performance and safety of Cold Ablation Robot-guided Laser Osteotomy (CARLO®) for midfacial corrections.
- Hands-on open-source surgical simulation and training model for cleft repair with partners in Chile.
- Applying standardized digital patient-reported outcome measurements according to the ICHOM standards.

Funding:

BRCCH Botnar Research Centre for Child Health

Centro Latinoamericano-Suizo Universität St.Gallen

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Details:
https://dbe.unibas.ch/en/research/regenerative-surgery/facial-and-cranial-anomalies/

https://mueller.medizin.unibas.ch

Smart Implants

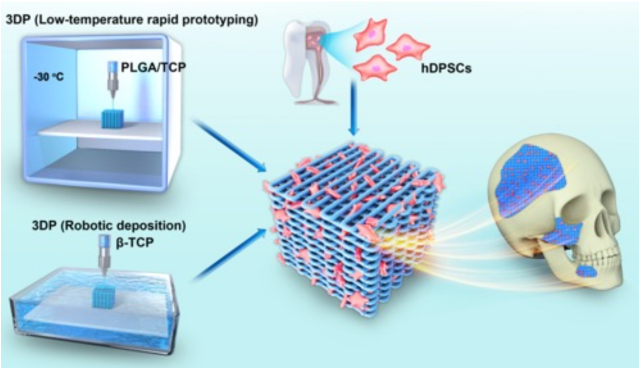

Figure 1: Overview of applying two types of 3DP technologies used to fabricate scaffold incorporated with hDPSCs for oral and maxillofacial bone reconstruction (Picture: S. Cao/USB).

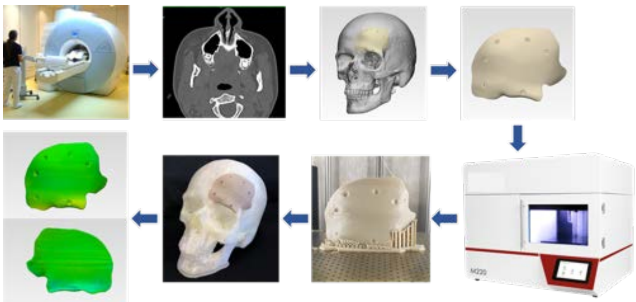

Figure 2: Schematic representation of a digital workflow for the in-hospital fabrication of PEEK patient-specific cranial implants (Picture: N. Sharma/DBE).

Figure 3: Team members of the new Smart Implants group (MIRACLE II) (Picture: T. Schürch/DBE).

In regenerative and reconstructive surgery, the healthy human anatomy is the best blueprint for our planning. Smart implants allow us to take a step further into the future. They are personalized bio-implants that feature customized shapes, special functions such as sensor technology or shape memory in combination with flexible and durable biomaterials. Additionally, smart implants can be biological implants consisting of different cell types and biomaterials. Ideally, smart implants can be produced quickly and cost-effectively at the point-of-care. This is what we are working on at the 3D Print Lab of the University Hospital Basel in the field of high-performance polymers and resorbable biomaterials. The Smart Implants group focuses on developing novel and minimally invasive implant and device technologies within the flagship project MIRACLE II.

The Smart Implants Group is, together with the 3D Print Lab (Core Facility at the DBE), a part of the Medical Additive Manufacturing Research Group (Swiss MAM). In 2020 we were allowed to take over the Smart Implants Group from Hans-Florian Zeilhofer, who developed and patented an innovative modular implant system. We build on his excellent work, refining and reinventing patient-specific high-performance implants. The Smart Implants team aims to grow the implants in bioreactors or create them using robot-supported organic printing technology outside and even inside the human body through an innovative 3D printing process.

Main projects under development in the Smart Implants Group:

A) Models & Implant Topology Optimization
B) Robot Guided Additive Manufacturing
C) High-performance 3D-printed Surgical Implants
D) Bio-resorbable 3D-printable Materials
E) Bio-Inks, Biomaterials and Bioprinting Technologies for Regenerative Surgery

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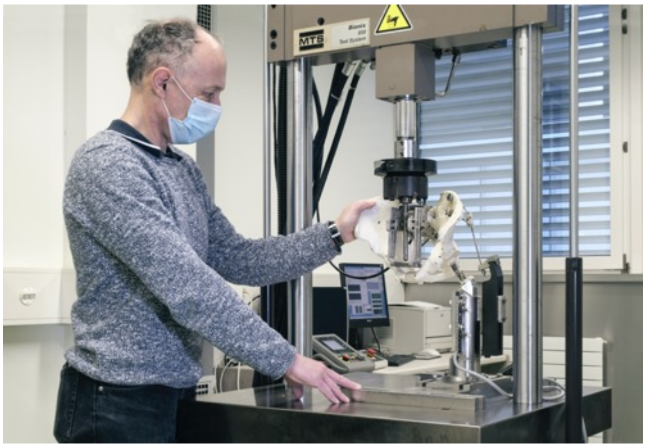
https://dbe.unibas.ch/en/research/core-facility-3d-print-lab/

https://dbe.unibas.ch/en/research/flagship-project-miracle/miracle-ii/

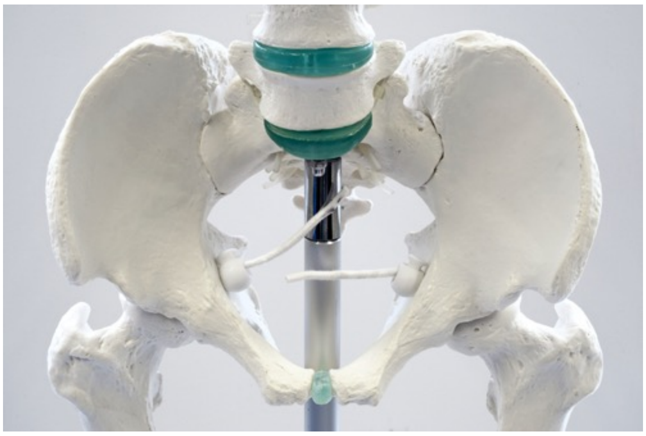
References / publications:
http://bit.ly/FTpubmed

Collaborations

An Example: Development and Testing of a New Pelvis-Fracture Implant



Beat Göpfert at the servo-hydraulic material testing machine of the DBE. (Picture: R. Wendler/DBE)



The human pelvis looks like a ring structure (Picture: R. Wendler/DBE).

The structure and mechanical function of the human pelvis is complex. Therefore, after a fracture, it needs adapted implants currently developed at the clinic for Orthopedics and Traumatology, University Hospital Basel, and tested at the DBE.

The human pelvis looks like a ring structure with three elastic interfaces between the two sides of the pelvic bones and the sacrum, connected to the spine. In action, the pelvis transmits the internal forces of the upper body to the legs and hence has to endure different loading conditions while maintaining its geometry.

After a pelvic fracture, an implant has to stabilize the broken bone so it can heal. Due to the elastic interfaces, as mentioned above, the fixation needs some 'built-in' elasticity. Furthermore, it is quite demanding for a surgeon to place an implant in a mechanically stable way because access to the bone is obstructed by surrounding muscles, nerves, blood vessels and internal organs. However, today's engineering tools and 3D-printing of metal allow the design of very specific implants. Beyond the question of design and production, new implants also have to 'work' under real conditions, be it in the operating room or under load in the body of the patient. To get more mechanical information about a newly designed 3D-printed implant, which has been developed in the University Hospital Basel, some classical mechanical tests were done with the servo-hydraulic material testing machine at the DBE. First tests showed that some improvements were still necessary. Still, after the design was adapted, considering the demanding anatomy of the human pelvis, further tests showed that this development is on the right track. We prepare a long-term test series with more than one million loading cycles and then give the involved surgeons new ways to treat a pelvis fracture with a biomechanically optimized implant.

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We Collaborate with

3devo

3D SYSTEMS

Ad Mirabiles
mesmerizing implants

additiveflow

AGA
Gesellschaft für Arthro
und Gelenkchirurgie

Amsterdam UMC
University Medical Centers

AO
CMF

AO
Research Institute Davos

AOT
Advanced Osteotomy Tools

Apium
Additive Technologies GmbH

axial3D
Patient data made real

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CELLEC BIOTEK AG

chondrometrics

medartis
CMX

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deep breath initiative

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FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

山东大学齐鲁医院
QILU HOSPITAL OF SHANDONG UNIVERSITY

GLOOR INSTRUMENTS

HEIDELBERG ENGINEERING

HOCHSCHULE FURTWANGEN UNIVERSITY HFU

Hochschule Offenburg
University of Applied Sciences

HAAG-STREIT

IFToMM

interreg
Oberrhein
Rhin Supérieur

暨南大學
1906
JINAN UNIVERSITY

暨南大學
JINAN UNIVERSITY

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REGEMAT 3D

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PARK BASEL AREA

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GOETHE UNIVERSITY

UPPSALA UNIVERSITET

SWISS LIGHT SOURCE
SLS

Universitätsklinikum Erlangen

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EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

Unil
UNIL | Université de Lausanne

University Hospital Basel

UNIVERSITY OF LEEDS

USZ Universitäts Spital Zürich

SOLEIL SYNCHROTRON

UNIST
ULSAN NATIONAL INSTITUTE OF SCIENCE AND TECHNOLOGY

UZB Universitäres Zentrum für Zahnmedizin Basel

Education & Completed MSc and PhD Theses

Teaching in the Master of Science in Biomedical Engineering in 2020

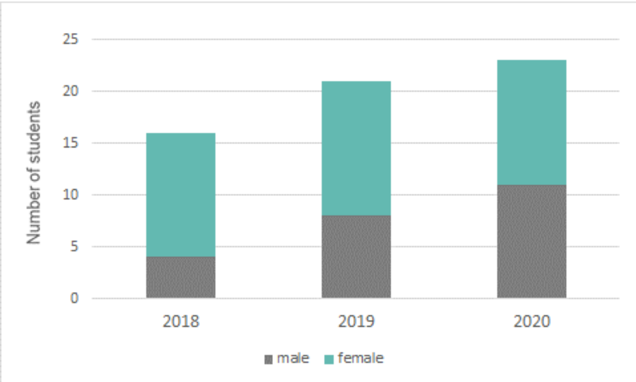

Figure 1: Master student numbers starting the year 2018, 2019 and 2020.

Figure 2: Master students in the large lecture hall at the Alte Univerität during the exam session of autumn 2020; due to COVID-19 only large lecture rooms could be used. The students sit only on indicated seats with at least 1.5 meter of distance and wear facial masks (Picture: G. Oser-Duss).

In the light of the Master program the year 2020 was again very successful: the first students finished their Master's degree and again, we had slightly increasing numbers of new Master students.

In spring 2020, after three semesters of study, the first Master's student finished the Master of Science in Biomedical Engineering at the University of Basel. Within the year 2020 six further Master's students accomplished their degree. With the completion of the Master's degree in 2020 all steps of this Master program have now been established and implemented. In the next years, we will carefully observe, evaluate and improve all steps to optimize the workflow.

In autumn 2020, the Master's program started with 23 new Master students. Despite compromising conditions due to the current pandemic, the student numbers again increased slightly. While most of the master students in 2018 were male, in 2020, we have almost equal numbers of female and male students (Figure 1).

The teaching for the students in the spring and autumn semester 2020 was substantially influenced by the COVID-19 pandemic. In spring of 2020, 11 of the 14 weeks had to be taught in an online format; practical classes had to be cancelled or replaced by an online format, while a few practical parts could be shifted to summer of 2020. In autumn of 2020, 7 of the 14 weeks had to be held in an online format.
At the beginning of the autumn semester and in contrast to many other study programs, our program's lecturers could still give face-to-face lectures as the student numbers were rather low (Figure 2). The Master's students greatly appreciated this commitment of the lecturers.

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Manipulating the Micro-World - Design and Fabrication of a Small-Scale Force-Sensitive Gripping Device

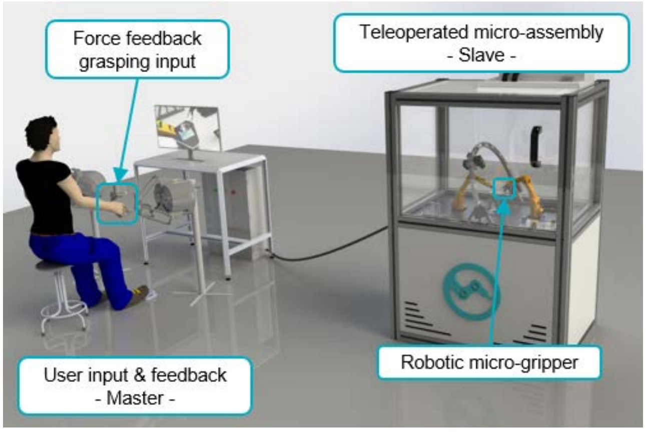

Figure 1: Representation of the future intended teleoperated micro-assembly station (Picture C. Duverney)

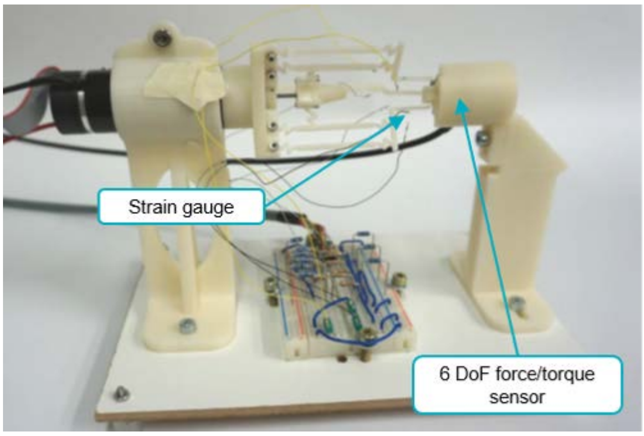

Figure 2: Prototype robotic micro-gripper with three strain gauges for grasping force measurement mounted in a test bench with a 6 DoF force/torque sensor for strain gauge calibration and performance evaluation (Picture: C. Duverney)

Master's Thesis by Mohamed Ali El Bahi (National School of Engineers of Monastir – ENIM) at BIROMED-Lab.

The trend towards increased miniaturization of devices has been driving developments in various industry sectors in the past decades, such as telecommunication, medical technology, or even watchmaking. Assembling such miniature devices remains a challenge to this day, especially in unique prototypes that cannot be assembled by pre-programmed, high-performance production lines. One way to address this issue is to rely on a teleoperated micro-assembly system. These typically include one or several micro-grippers on the slave slide controlled by a suitable input device on the master side (1). To increase the intuitiveness of the assembly process for the user and reduce the risk of damaging the fragile micro-parts, the micro-grippers may be fit with force-sensing capabilities, which allow the grasping forces to be fed back to the user for instance by means of a haptic grasping input handle. A lack of suitable force-sensitive micro-grippers motivates the developments carried out in this thesis. After careful analysis of the given system requirements, various micro-gripper concepts have been designed and evaluated. A first prototype of the most promising structure has then been manufactured. It relies on a flexure-based mechanism to largely reduce mechanical play, which represents one of the predominant issues when handling micro-parts. The flexure-based structure further allows for straightforward and cost-efficient force-sensing by means of strain gauges directly affixed to the gripper tips. A test stand including a high-precision 6 degrees of freedom (DoFs) force/torque sensor has been built to calibrate and evaluate the micro-gripper. A series of experiments demonstrated the functionality of the proposed concept. The next steps will include miniaturization and precise characterization of the micro-gripper.

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References:
(1) J. Cecil et al. "A Review of Gripping and Manipulation Techniques for Micro-Assembly Applications." *Int. J. of ProductionResearch*, vol. 43, no. 4, pp. 819-828, Feb. 2005. doi.org/10.1080/00207540512331311813

Structural Analysis of a Miniature Parallel Robot for Precise Milling in Surgery

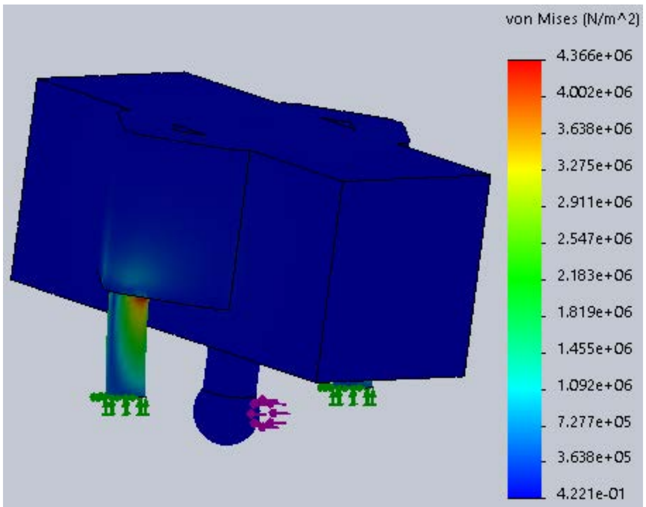

Figure 1: Finite element results of a model with a fixation structure in steel with a 1.5 mm diameter and a force along the endoscope axis - the Von Mises stress (Pa) is indicated with the colorbar (Picture: L. Aribi).

Master's Thesis by Lina Aribi at BIROMED-Lab.

A study of the fixation design of the robot during bone milling.

In a current project carried out in the BIROMED-Lab, the robot cuts the bone with laser technology. Another possible alternative is to cut the bone by milling. In contrast to laser ablation, milling involves reaction forces transmitted to the robot during surgery. The tip of the endoscope (end–effector) is mechanically attached to the bone while milling. This project aimed to study the fixation design of the robot during bone milling by using finite element simulation.

Several models with different materials, different geometrical parameters of the fixation structure and different milling force directions were simulated. It could be shown that steel, 1.5 mm in diameter, and a force along the endoscope axis are preferred to avoid damaging the fixation structure.

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Post-Mortem Temperature and its Effect on Quantitative Magnetic Resonance Imaging

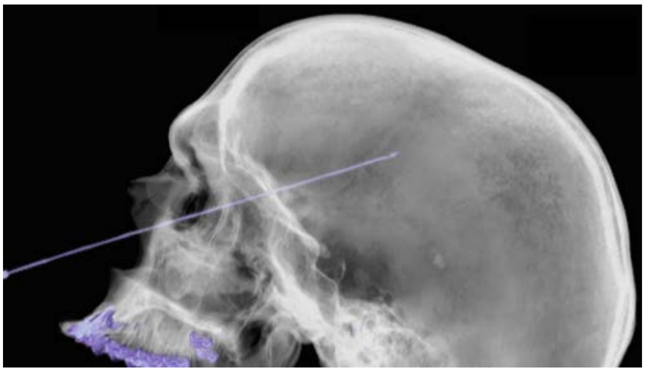

Figure 1: The skull presented with the osseous transparent metal mode of the console software (Siemens Healthineers Syngo CT 2014 A VB42B) of subject 9 represented in the sagittal with the temperature probe along the longitudinal fissure (Picture: C. Berger/Institute of Forensic Medicine).

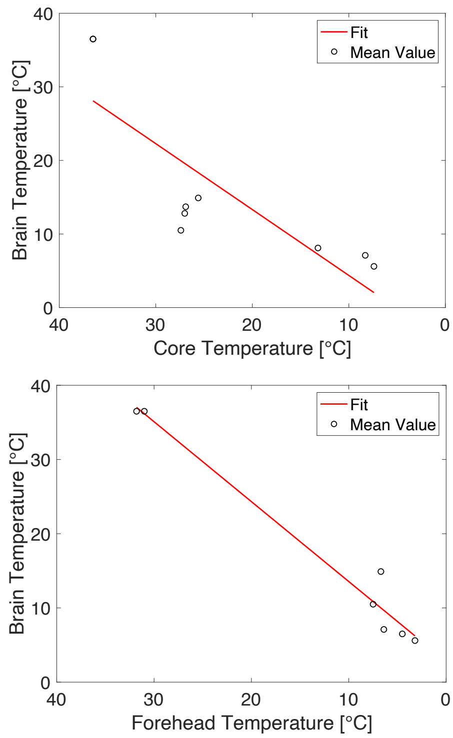

Figure 2: The brain temperature as a function of the core temperature and as a function of the forehead temperature measured at the same moment prior to the MR scan. A linear model was fitted to the data. Note that the x-axis is inversely (40-0) plotted (Picture: C. Berger/Institute of Forensic Medicine).

Master's Thesis by Celine Berger at the Institute of Forensic Medicine).

The purpose of this study was to determine the relations between the post-mortem temperature and the magnetic resonance (MR) parameters T_1 T_2, T_3*, MD, and FA. These relations would allow the correction of the MR parameters for the temperature in post-mortem magnetic resonance imaging (PMMR). Further, the forehead, brain, and rectal temperature profiles were recorded to find a correlation that would allow a non-invasive determination of the brain temperature [1-3].

The post-mortem MRI parameters of the brain were measured in situ of nine deceased. The temperature profiles were recorded in situ with temperature probes placed on the forehead, in the rectum, and in the brain (see Figure 1).

In this thesis, a significant linear correlation was observed between the brain and the forehead temperature, while the brain and the core temperature revealed no linear correlation (see Figure 2). Further, a significant linear relationship between the brain temperature and the relaxation parameter T_1 of the gray matter was observed.

In conclusion, the observed results suggest the need for correction regarding different brain temperatures, particularly that of T1, to avoid brain tissue contrast loss caused by post-mortem temperature decreases.

Funding:

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References:

[1] C. Birkl et al., 2014, "Temperature-Induced Changes of Magnetic Resonance Relaxation Times in the Human Brain: A Postmortem Study", *Magnetic Resonance in Medicine*

[2] W. Zech et al., 2016, "Post-mortem 1.5T MR quantification of regular anatomical brain structure", *Int J Legal Med*

[3] C. Bartgis et al., 2016, "Determination of time of death in forensic science via a 3-D whole body heat transfer model", *Journal of Thermal Biology*

Augmenting a Custom Haptic Input Device Handle with Force Feedback for Intuitive Grasping

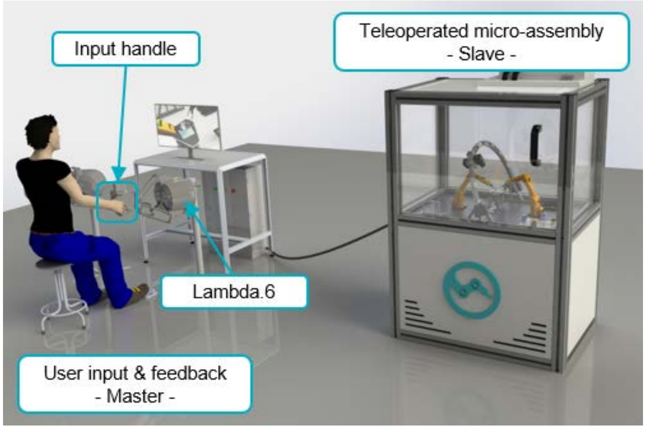

Figure 1: Representation of the future intended teleoperated micro-assembly station (Picture: C. Duverney)

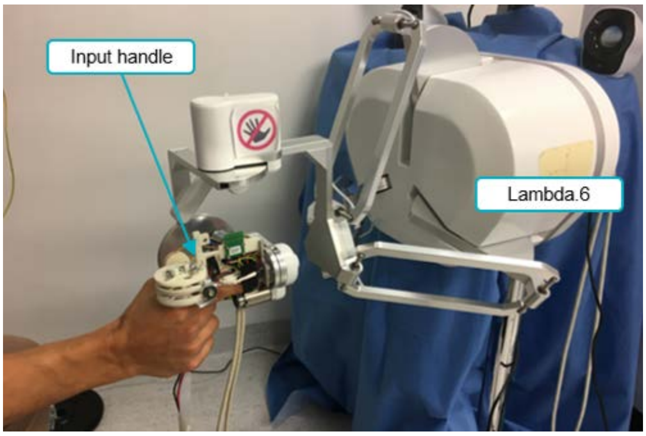

Figure 2: Prototype input handle with grasping DoF attached to the 6 DoF Force Dimension lambda.6 haptic device (Picture: C. Duverney)

Master's Thesis by Nicolás Candia (Eidgenössische Technische Hochschule Zürich – ETHZ) at BIROMED-Lab.

There is a trend towards miniaturization and automation in several domains. One of them is the MIRACLE project, that aims at developing robotic endoscopic devices for minimally invasive surgery. Here, to develop prototypes, components with dimensions in the millimeter and even micrometer range need to be assembled. Human-controlled, teleoperated robotic micro-assembly stations with haptic interfaces are a way to tackle this challenge (1). Due to the lack of a convenient input handle, this master thesis pursued the goal of extending the six degrees of freedom (DoFs) of a commercial force-reflecting interface with a seventh grasping DoF for an intuitive force feedback control of a robotic gripper, including input channels to operate system settings and tool selections. During the development process, the needs of the target application as well as affected human movement and sensing capabilities were investigated. The resulting system requirements allowed identifying system features and possible solutions and their evaluation to define the desired system. An extensive mechanical and electronic design process yielded a first prototype input handle. It combines an index-finger controlled, force-reflecting grasping DoF with a torque-reflecting scroll wheel for the control of rotational tools and settings, tactile feedback channels, and inputs for menu navigation. The handle can be easily modified to fit different hand sizes and offers the possibility to connect further components to increase the number of input and output channels. A first evaluation study demonstrated the well-functioning of all prototype features and their usability and revealed the potential for improvements. The developed prototype offers a good platform for further experimental evaluations to investigate different input and feedback channels for an intuitive teleoperated micro-assembly and improve the handle's ergonomics.

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References:

(1) A. Bolopion and S. Régnier. "A Review of Haptic Feedback Teleoperation Systems for Micromanipulation and Microassembly." *IEEE Trans. Automation Sc. and Eng.*, vol. 10, no. 3, pp. 496-502, Jul. 2013. doi.org/10.1109/TASE.2013.2245122

Development and Design of a Multi-Functional Laparoscopic Instrument

Figure 1: Laparoscopic equipment in the OR (Photo source: https://byrlmed.com/product/byrl-laparoscopic-dissecting-grasping-forceps/, accessed 7 February 2021).

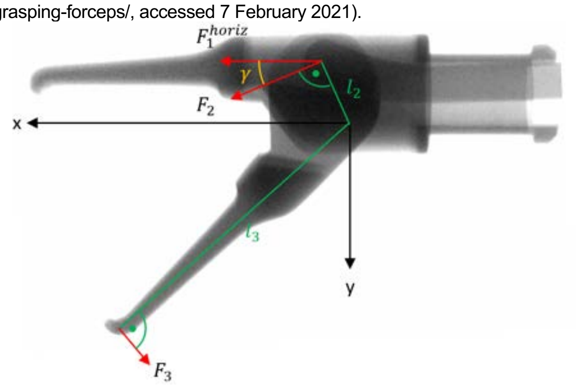

Figure 2: CT scan of a laparoscopic tool to analyze the kinematic relations of the gripper (Picture: L. Eggenberger).

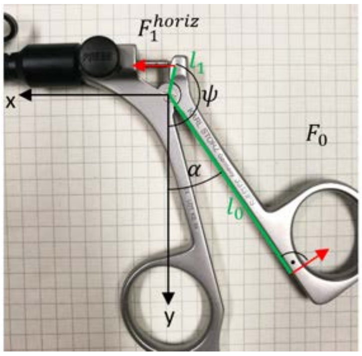

Figure 3: Kinematic analysis of a photo of the handgrip of a laparoscopic tool (Picture: L. Eggenberger).

Master's Thesis by Lukas Eggenberger (ETH Zurich) at BIROMED-Lab.

The medical technology market is one of the most innovative sectors of the international economy. In this exciting field, big players work alongside small businesses to design top-notch medical devices to improve and save the lives of thousands of patients [1, 2, 3].

This project resulted from first-hand experiences of surgeons during their work with laparoscopic devices in the OR. While using the existing laparoscopic tools, we have discovered so far untouched improvements to the current functional principles. Most of todays existing tools have exactly one function and are single-use devices. Therefore, we conceptualized a multifunctional, multiuse laparoscopic device.

This thesis aims at developing basic technical functionalities for a new multifunctional laparoscopic instrument. It will allow the surgeon to perform one-handed tool-tip changes without extracting and reinserting the laparoscopic instrument. Thereby, the surgeon creates less risk for infections through repeated device insertion and extraction, and the surgeon can keep the focus on the surgical site and saves overall time. For the patient, shorter intervention times (5-15 minutes) lead to less application of anesthesia and therefore, a faster recovery.

As a first step towards developing device functions for the multifunctional laparoscopic instrument, the requirements for different functionalities of the tool were derived. In particular for the tool-tip extraction and reinsertion, the requirement list was found to be challenging to fulfil: a lightweight mechanism that allows robust, one-handed tool-tip exchange by pressing one button, while the haptic connection between hand grip and tool-tip should remain.

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3T Surface-Based Quantitative Susceptibility Mapping and T1 Relaxometry in Relapse-Remitting and Progressive Multiple Sclerosis Patients

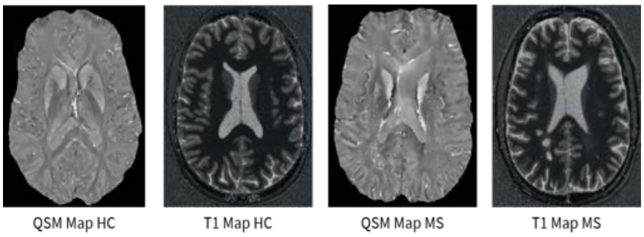

Figure 1: Exemplary QSM and T1 maps for one HC and one MS patient. (Picture: N. Eichner/ThINk)

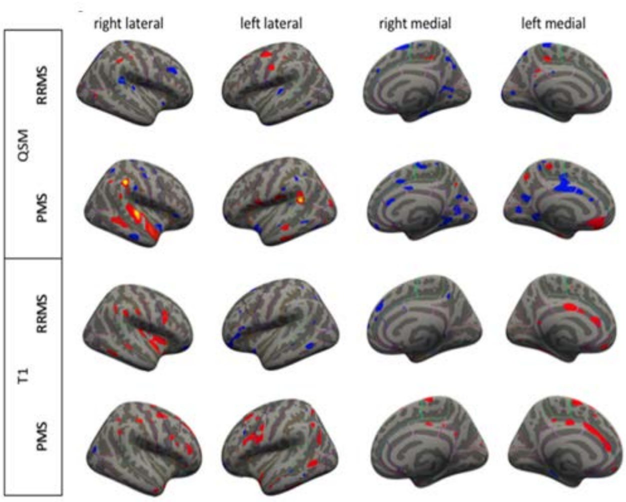

Figure 2: T1 and QSM Significance Maps of PMS and RRMS (Picture: N. Eichner/ThINk).

Master's Thesis by Nicholas Eichner at Translational Imaging in Neurology.

Multiple sclerosis (MS) is an incurable inflammatory disease of the central nervous system (CNS) characterized by multifocal and diffuse inflammation and degeneration in both cortical grey and white matter, affecting roughly 2.3 million people worldwide [1-3]. The experienced symptoms are due to the area(s) of inflammation and scarring (sclerosis) in the different parts of the CNS. There is currently limited knowledge about the extent and distribution of diffuse cortical damage across different MS subtypes.

This study was performed to investigate whether patients with relapsing-remitting MS and progressive MS show different QSM/T1 relaxometry characteristics of the cortical surface than a group of healthy controls and to help assess and understand the cortical pathology in MS patients.

Quantitative susceptibility mapping (QSM) provides maps sensitive to iron deposition and demyelination, two major standard pathologic features in MS.

T1 relaxometry provides an assessment of tissue microstructural integrity and has shown to be highly sensitive to diffuse white matter pathology in MS patients.

The results showed that QSM and T1 maps acquired at 3T MRI are sensitive to cortical damage in MS patients. Additionally, both methods revealed more extensive areas of alterations in progressive than in relapsing-remitting MS.

Overall, this study using QSM and T1 relaxometry surface mapping by 3T MRI shows patterns compatible with cortical demyelination and possibly iron accumulation, which predominate in progressive MS to relapsing remitting MS patients.

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Retrieval Optimization in Magnetic Resonance Fingerprinting

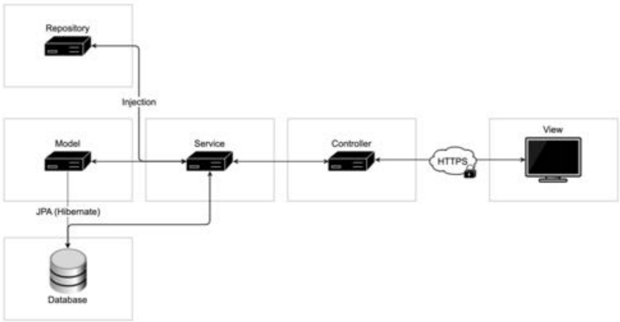

Figure 1: Architecture of *Dactyloquant (*Picture: M. Hürbin).

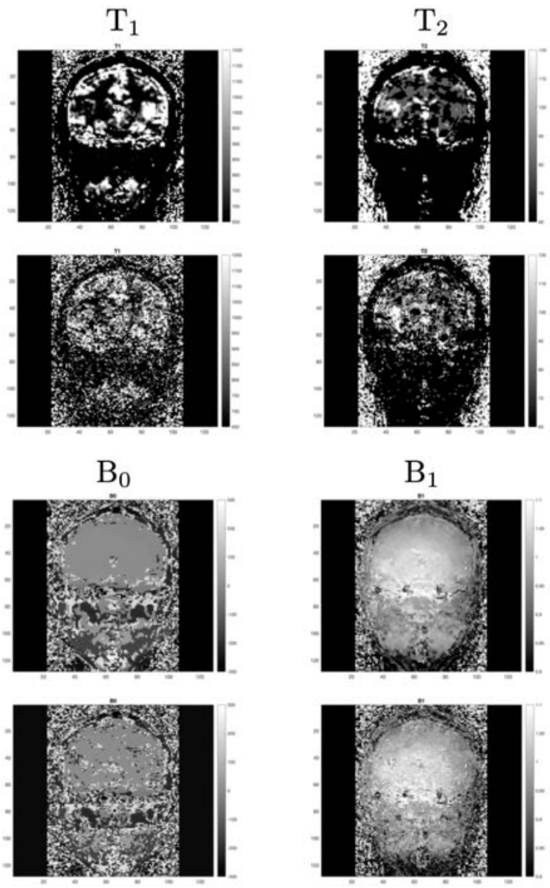

Figure 2: Proof of concept reconstruction of different MRI parameters (Relaxation times T1,T2, magnetic field homogeneity B0, and radiofrequency transmit field B1) using brute-force (top rows) and SB-LSH (Picture: M. Hürbin).

Master's Thesis by Manuel Hürbin at AMT-Center.

Quantitative approaches in MRI are crucially needed to provide comparable metrics across patients and pathology types. Model-based approaches, such as MR Fingerprinting (MRF) proposed in 2013[1] have brought an original formalism where the complexity inherent to quantitative measurements with magnetic resonance is shifted towards a pattern-matching problem *in silico*. As such, a custom-built MR dataset is matched to a large, pre-computed database to retrieve quantified properties of interest. The best match then yields the required information for a proper reconstruction of the image. Considering databases with over 250.000.000 entries, the time to find the best match becomes critical. Additionally, such large amounts of data require adequate processes to store and access data. This work introduces *Dactyloquant*, a software client treating the aforementioned matching pipeline as a nearest neighbor search problem as typically seen in multimedia retrieval. Dactyloquant uses and extends *Cottontail DB* – a specialized database for multimedia retrieval queries – for storage and data access. This newly developed system does not only enable scalability since it uses on-disk storage, but it also introduces modern index structures, such as Super-Bit Locality-Sensitive Hashing (SB-LSH)[2] or the Vector-Approximation+ File [3], that speed up the look up significantly and thus provide a valid alternative in current MRF data reconstruction research.

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Intuitive Surgeon-Robot-Interface to Control Macro-Robots Hands-On

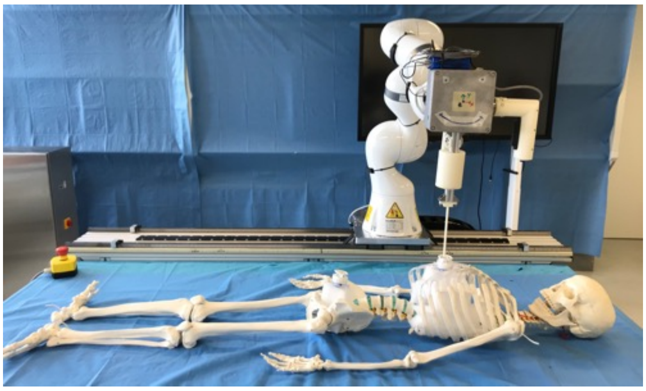

Figure 1: The user study setup with the macro-robot (7-DoF Kuka LBR iiwa) fixed via rails to the table and the mock-up skeleton with two trocars in front of it. Here the robot has two handles mounted that allow surgeons to move the tool as desired.

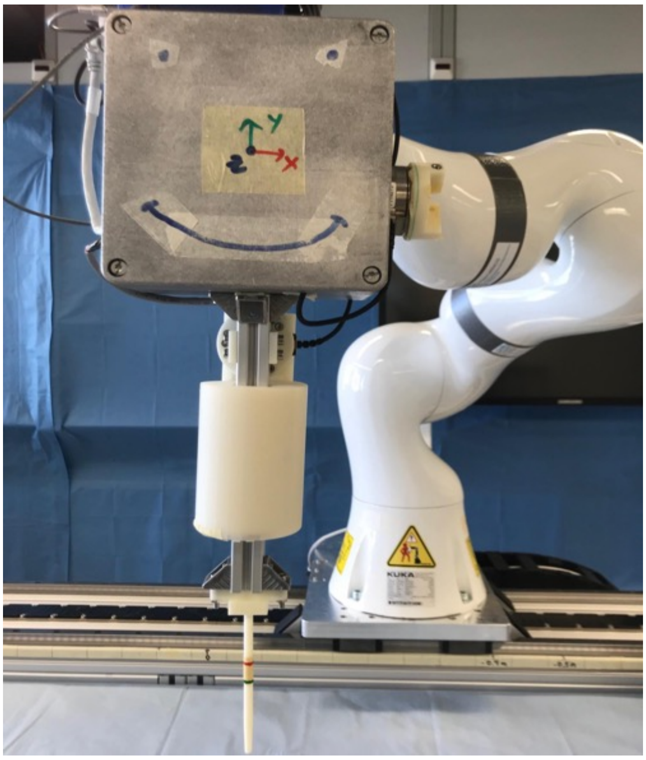

Figure 2: First prototype of handle aligned with the tool. This seems the most intuitve interface among the three that were tested.

Master's Thesis by Aleksandra Ivanovic at BIROMED-Lab.

Typically, robots are rigid, and it is not safe for humans to work with them collaboratively. With the development of lightweight robots [1-3] and the introduction of force/torque sensors, users can now accomplish these tasks. We suggest that hands-on control could be beneficial in the medical environment, where the advantages of a robot can be combined with the surgeon's expertise. Only a few hands-on controlled medical robots are on the market by now. To the best of our knowledge, no studies have investigated the requirements of intuitive user-interfaces for hands-on control of macro-robots.

We assume that the mounting location and orientation of the user-interface (handle) is crucial to intuitively move macro-robots hands-on. We designed and prototyped three different handles, which have a cylindrical shape but differ in size and mounting location. We compared them qualitatively with the help of a questionnaire in a user study, in which the participants moved a mock-up endoscope attached to the robot between two trocars using the built-in KUKA hand guidance mode (see Figure 1). We compared the time needed to complete the task, the end position accuracy, and the forces applied to the handle. The qualitative results indicated that a user-interface aligned with the tool (see Figure 2) seemed most intuitive for the participants. However, our quantitative results suggested that the combination of user-interface and controller was not suitable for small and subtle movements, but usable for large motions with low accuracy. In future work, we will employ a user-interface aligned with the tool with an admittance control mode that is currently being developed.

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Motion Planning Framework for Insertion of a Robotic Endoscope in the Human Knee

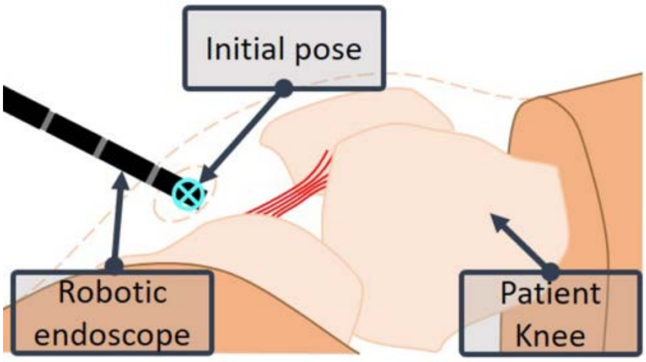

Figure 1: Human knee with a robotic endoscope at the initial pose directly in front of the anteromedial portal (Picture: G. König).

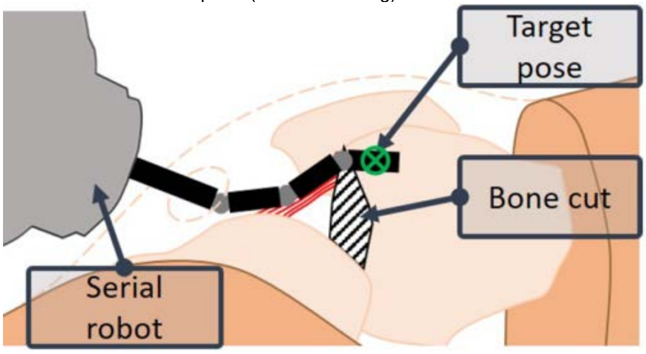

Figure 2: The approach path of the endoscope respecting the anatomical constraints and the surgeon's preferences is computed for a specific target pose, using motion planning algorithms (Picture: G. König).

Master's Thesis by Gabriel König (ETH Zürich) at BIROMED-Lab.

To perform minimally invasive knee surgery with a robotic instrument, the instrument's motion starting from its initial pose at the surgical portal for incision to its final target pose inside the knee needs to be planned carefully. This motion planning is a challenging task due to the complexity of the robotic instrument (13 degrees of freedom) and the constraints based on the anatomy of the patient (hard and soft structures) and input from the surgeon (desired motion).

After a thorough evaluation of different software environments for motion planning, we selected MoveIt as the development platform with the Open Motion Planning Library (OMPL) as the underlying planning library and the Flexible Collision Library (FCL) as the collision detection library.

We successfully developed a test scenario and a user interface that allows planning a feasible motion of the robotic instrument currently being developed at the BIROMED-Lab within the scope of the MIRACLE project based on the desired initial and target poses while respecting anatomical and user-defined constraints.

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Dielectric Elastomer Sensors For the Tongue-Computer Interface

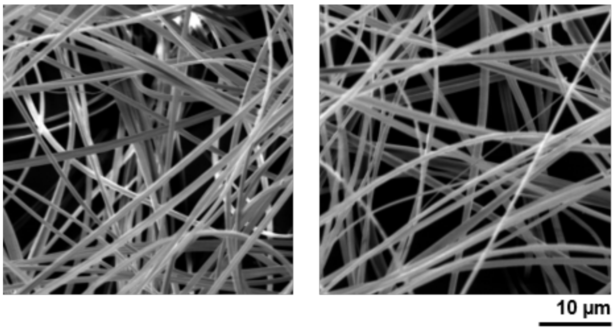

Figure 1: Electrospun fiber network visualized by electron microscopy (Picture: L. Luchsinger).

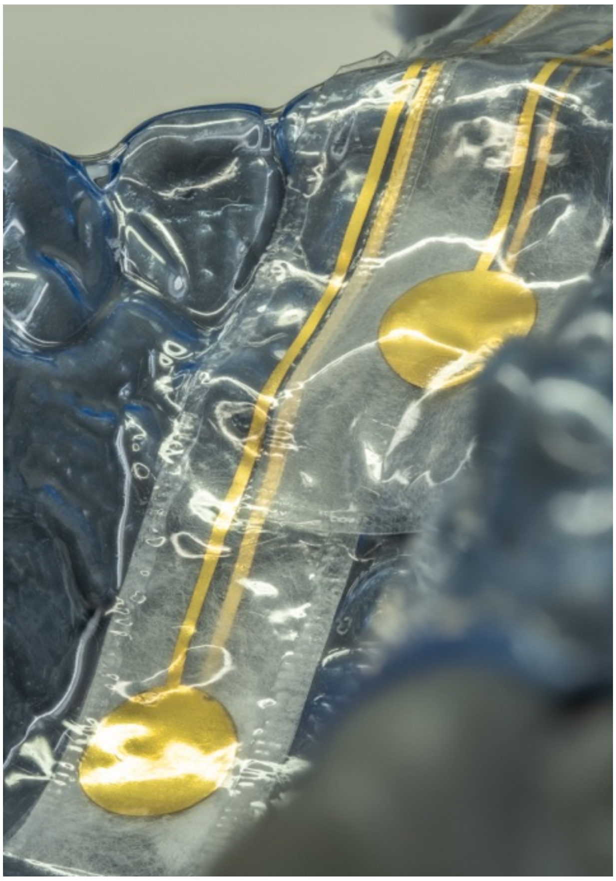

Figure 2: Two dielectric elastomer sensors embedded between two molded substrates for their integration/implementation into a personalized dental splint. (Picture: R. Wendler/DBE)

Master's Thesis by Carina Luchsinger Salinas at the Biomaterials Science Center.

This thesis project pursued the development and comprehensive characterization of a sensor prototype for the tongue-computer interface. These dielectric elastomer sensors are micrometer-thin and highly flexible and thus well suited for intraoral tongue-machine interface applied to treat sleep apnea and snoring problems through digitalized myofunctional therapy.

The elastically deformable pressure sensors consist of elastomer films sandwiched between compliant electrodes [1]. The application of a force changes the capacitance of the device. Such sensors are attractive for various applications in wearable electronic devices, soft robotics and touch-sensitive electronic products [2].
To guarantee softness and flexibility, the sensor prototype contains a nonwoven porous network of polymer fibers. The micro- and nanometer-thin fibers were fabricated employing an electrospinning technique [3].

The pressure sensors can operate in the range between 1 kPa and more than 10 MPa. Its sensitivity at the characteristic tongue pressure of 100 kPa reached about 0.15 pF/kPa. Therefore, the prototype was functioning in the oral cavity to detect the tongue forces at predefined locations. Partners at Empa provided the electronics and the Zurich University of the Arts contributed to the software for the demonstrator device.

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Vision-Based Registration of a Robotic Endoscope

Figure 1: A miniature camera mounted to the endoscope's tip was used to estimate the pose of the endoscope relative to a knee phantom (Picture: M. Meyer).

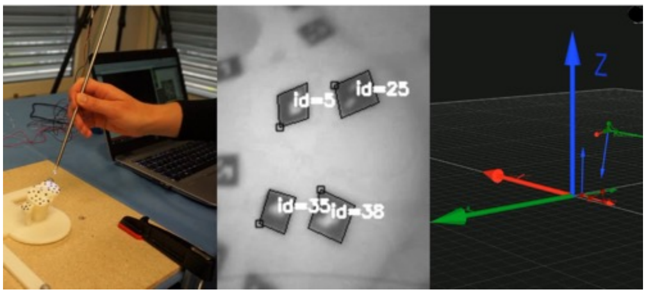

Figure 2: Pose estimation process (left to right): 1. acquire endoscopic images, 2. process the images to find the location of image markers, 3. estimate the pose of the endoscope relative to the anatomy (Picture: M. Meyer).

Master's Thesis by Mia Meyer (ETH Zürich) at BIROMED-Lab.

Advances in minimally invasive surgery come with enormous advantages for the patient, such as fewer skin incisions, faster recovery, and shorter hospitalization time. On the other hand, minimally invasive surgery introduces challenges for surgeons, such as restricted vision on the surgical scene, less freedom of movement with the surgical instruments, and limited haptic feedback. Robot-assisted surgery tries to overcome these challenges and to support the surgeons. To automate and optimize several surgical tasks, robot-assisted surgery requires localizing the surgical robot relative to its environment.

In this thesis, a vision-based method was introduced to localize an endoscope with a miniature camera relative to the patient's anatomy. Markers with a previously known location relative to some coordinate system were tracked. The known location of the markers and their corresponding image coordinates were used to estimate the pose of the camera. Three different feature trackers and three different pose estimation approaches were employed to achieve continuous and robust endoscope localization.

The proposed localization method was validated on a 3D-printed human knee phantom. We could show that our method outperformed existing vision-based localization approaches resulting in a smaller pose error of the endoscope. We achieved a Euclidean distance error of 14.52 mm and an angular error of 26.64 degrees.

Even though the developed localization method is not yet robust enough to use in real surgery, the results are promising, considering that only one camera with a low resolution was used for the localization. We anticipate that our localization method could be the starting point of localizing an endoscope autonomously in the patient, enabling us to automate specific surgical tasks.

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Integrated Sensor Insole Systems for Application in Knee Osteoarthritis: FeetMe® versus Moticon®

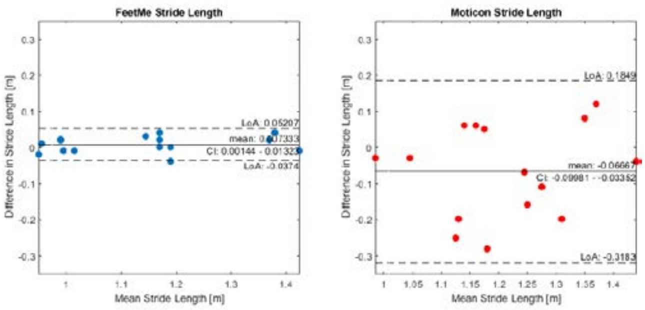

Figure 1: Bland Altman plots showing the difference in stride length of FeetMe and Moticon compared to the instrumented treadmill (Picture: T. Oshima).

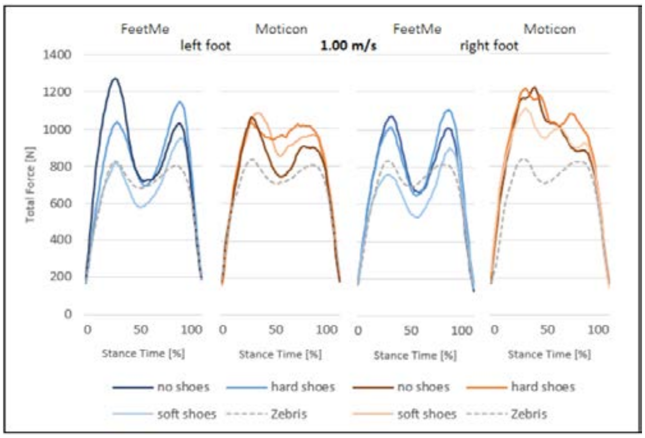

Figure 2: Vertical GRF for the individual insoles with different footwear (soft shoe, hard shoe, and without shoe where the insole was worn and fixed inside a sock) at medium gait speed. The reference curve from the instrumented treadmill represents the mean of all footwear measurements since the difference was negligible (Picture: T. Oshima).

Master's Thesis by Takanobu Oshima at Functional Biomechanics.

Wearable sensors have become more advanced and offer a solution for gait analysis outside of the laboratory. Their recent advances determine a significant impact on the healthcare monitoring system and may overcome classical measurement systems' limits [1]. With gait assessment being a potential exploratory for objectively measuring benefits of a drug in pain and function of knee osteoarthritis (OA), the purpose of the study was to compare the integrated sensor insole systems from FeetMe® and Moticon® with each other. System differences were shown with an overview in technical specifications, a usability review for clinical application, and a validation regarding spatiotemporal gait parameters and the vertical component of the ground reaction force (GRF) with an instrumented treadmill (Zebris) as reference.

The FeetMe® insole had advantages in technical specifications with a better resolution and a higher sampling frequency. For the usability aspect, FeetMe® showed benefits regarding data transfer and Moticon® regarding battery replacement. Only FeetMe® comes into question if a certified medical device is required.

Similar sensor performances were observed in gait cycle time and cadence. Superior results were acquired by FeetMe® for the spatial parameters stride length (Figure 1) and walking speed. FeetMe® had a better accuracy in mean double support phase, while Moticon® showed a systematic offset but with higher precision.

The FeetMe® insole combined with the soft running shoe, showed the best results regarding vertical GRF calculation when compared to the reference system (Figure 2).

In conclusion, this study allows for selecting the appropriate insole system if its application is known and carefully planned. The results suggest the FeetMe® insole to have many advantages over Moticon®.

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Feasibility Study on Using Supervised Deep-Learning to Model Edge-FBG Shape Sensors

Figure 1: The experimental setup used for training data collection .The sensor's real shape and the edge-FBG spectrum were measured using a motion capture system and a fast spectrometer respectively (Picture: T. Renna).

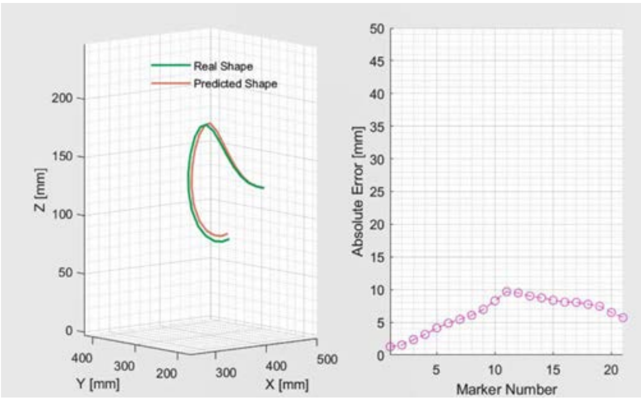

Figure 2: An example of the predicted shape with less than 10 mm tip error (Picture: T. Renna).

Master's Thesis by Tatiana Renna at Planning and Navigation Group.

In minimally invasive surgeries, it is often required to use non-rigid instruments to maximize accessible regions. However, the main drawback of using flexible tools is the higher risk of damaging non-target tissues as there is uncertainty about their shape. Fiber shape sensors are suitable for tracking these tools inside the patient's body as they are small, biocompatible, immune to electromagnetic interference, and require no line-of-sight. One of the most recent types of fiber shape sensors is based on edge fiber Bragg gratings (edge-FBG), a single-mode fiber with Bragg gratings around the edge of its core. The amplitude of the Bragg peaks in such sensors contains the strain information. However, undesired bending-related phenomena affect the spectrum profile of the gratings in an unpredictable way making the classical approach insufficient in shape estimation.

This project aimed to study the feasibility of modeling edge-FBG sensors with deep learning. We showed that neural networks can be trained to predict the sensor's shape, given the edge-FBG spectrum. The implemented architecture can detect medium to large deflections in a 300 mm sensor with an average tip positioning error of 17 mm.

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A Deep-Learning Based Automatic Dental Assessment for OPTs

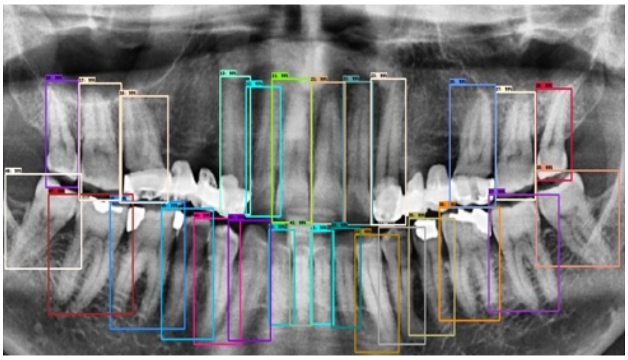

Figure 1: Automatic teeth FDI numbering in an OPT with several missing teeth (Picture: N. Sahraei Winkler).

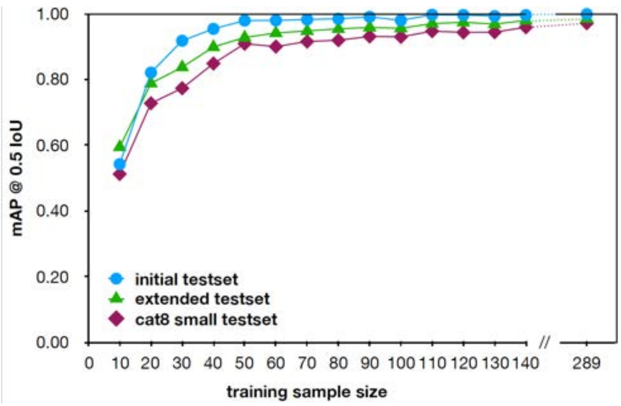

Figure 2: Variation of the mAP @0.5 IoU on three different test sets based on the number of OPTs used for training the object detector (Picture: N. Sahraei Winkler).

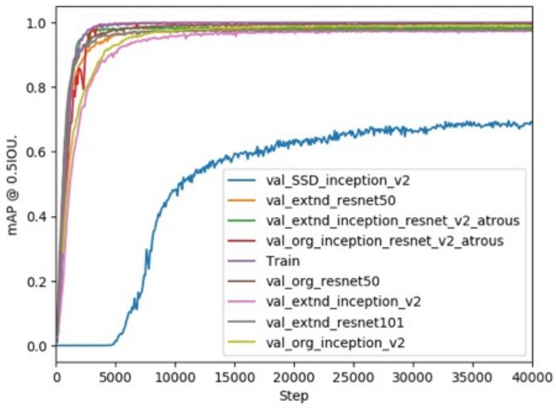

Figure 3: Difference of the mAP @0.5 IoU on a validation set for different SSD and Faster-RCNN based models (Picture: N. Sahraei Winkler).

Master's Thesis by Negin Sahraei Winkler at CIAN.

X-ray imaging plays a vital role in dentistry and can be adopted in both diagnosis and treatment phases. Teeth characterization and diagnosis of different pathologies using X-ray panoramic images (OPTs) are both time-intensive and error-prone. As a solution, using an automatic diagnosis system for such purposes can be of great assistance to dentists by reducing detection time and providing a second opinion. In this thesis, a deep learning-based automatic teeth detection and classification tool for OPTs has been developed.

For this purpose, initially, a dataset of 234 panoramic images and their corresponding ground-truth labels consisting of information on the bounding box and Federation Dentaire Internationale (FDI) notation of each tooth has been created. Due to small initial labeled OPT images for training, a technique called transfer-learning was used. An object detector using different pre-trained CNNs from the TensorFlow object detection API was trained based on these images. For initial training, different architectures based on SSD and Faster RCNN meta-architectures were adopted. Among all models trained on our dataset, the Faster R-CNN inception ResNet v2 baseline training showed the best performance. A mean Average Precision (mAP) of approximately 98% was achieved on the test dataset. The baseline results have been studied thoroughly and used to extend the dataset to 482 images to have a better-generalized object detector. The models were then trained using these 482 images dataset and a mAP of approximately 99% was achieved on a test dataset consisting of over 150 random OPTs, including the ones with missing teeth. This thesis's promising results suggest that the adopted method has very high accuracy even once trained on a very small dataset and can be developed further for computer-aided diagnosis (CAD) purposes.

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Injectable Hydrogel with Nasal Chondrocytes for Intraoperative Articular Cartilage Repair

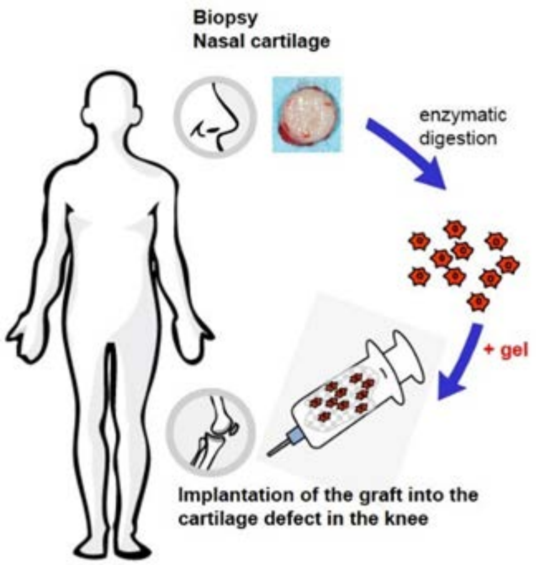

Figure 1: Project overview: freshly isolated nasal chondrocytes embedded in a hydrogel are implanted arthroscopically into the knee cartilage defect in the same day (Picture: A. Barbero).

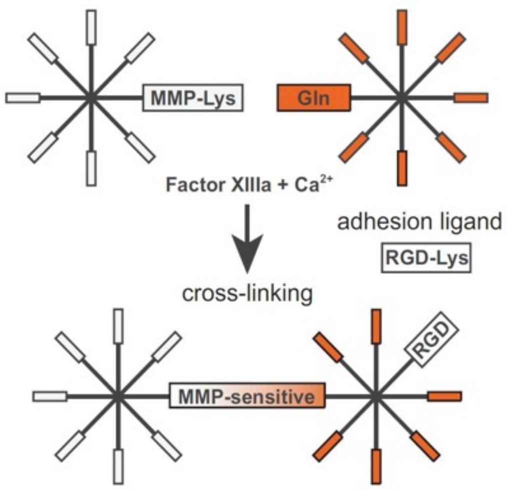

Figure 2: Schematic representation of degradable PEG hydrogels polymerization containing the MMP-sensitive sites and optionally the integrin adhesion ligand RGD, crosslinked by FXIIIa in the presence of calcium ions (Picture: EhrbarLab, University Hospital Zurich).

Master's Thesis by Raluca Trofin at Tissue Engineering research group at DBM.

Articular cartilage has a very limited self-repair capacity and, once damaged, undergoes irreversible degenerative changes. Current treatments are not capable to fully restore the properties of this hyaline cartilage regarding the quality, durability and reproducibility of the formed tissues. Recent studies demonstrated that nasal chondrocytes represent an alternative cell source for the treatment of cartilage lesions due to their superior and more reproducible regenerative capacity as compared to articular chondrocytes that are currently used. Moreover, once embedded into a degradable Poly (ethylene glycol/PEG) hydrogel containing platelet lysate and RGD peptide, they efficiently proliferate and produce a cartilage matrix.

This project primarily aimed at improving the polymerization kinetics by reducing the gelation point of the hydrogel to guarantee a proper intraoperative injection of the graft. Secondly, the simplification of the hydrogel formulation was evaluated by removing the RGD adhesion peptide while maintaining the proliferation and cartilaginous properties of the embedded cells. The gelation time was reduced from 4 minutes to approx. 1 minute by increasing the crosslinker (FXIII) concentration while maintaining the therapeutic effect of the graft. The experiments also showed that RGD peptide can be removed from the gel formulation without affecting the cells` biological functions.

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Deep Neural Networks for Automated Choroidal Tumor Segmentation in OCT Data

Figure 1: Ocular fundus photography of a choroidal tumor [1].

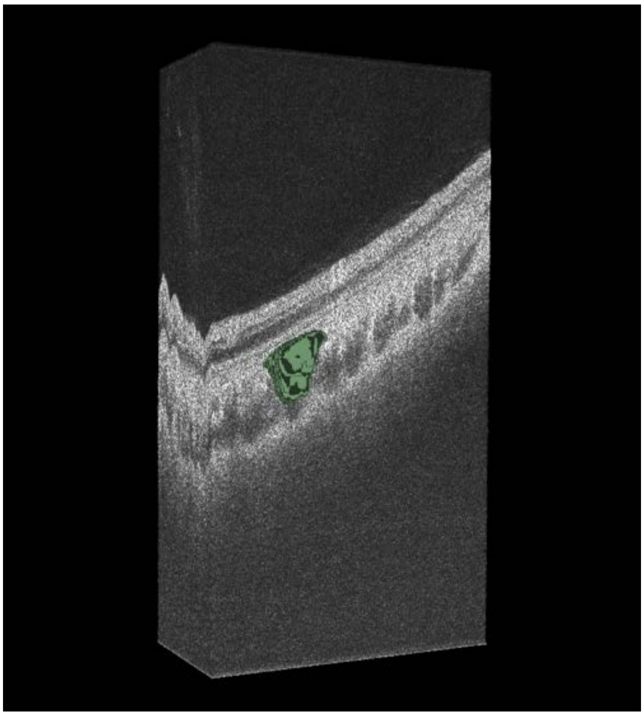

Figure 2: Tumor prediction (green overlay) with the MDGRU-3D_touchdown model in a 3D volume rendered OCT [2].

Master's thesis by Philippe Valmaggia at CIAN.

Machine Learning algorithms have improved a vast number of medical image analysis applications, such as the segmentation of anatomical structures. This thesis's purpose was the application, comparison, and optimization of different segmentation algorithms with regard to choroidal tumors in Optical Coherence Tomography (OCT) images.

For this purpose, a binary pixelwise annotation for tumor and background was made for 121 OCT image stacks. The dataset consisted of 21 eyes with and 100 eyes without tumors and was split into training, validation and testing sets. Two deep neural network architectures were applied to the data; one is a Multidimensional Gated Recurrent Unit marked or MD-GRU, the other is a Convolutional Neural Network denominated as U-Net. Both networks were applied to the OCT data in 2D and 3D.

Segmentations of choroidal tumors were generated in 2D and 3D. The overall best performing network was the MD-GRU model denominated as MDGRU-3D_touchdown and achieved a DICE score of 0.76 on the testing set. This model relied on extensive data augmentation, loading a patch containing a tumor for every training step and downsampling of the original data to half the size in each dimension. The evaluation for a downsampled volume with a size of 128x496x256 pixels takes 4.5 minutes with the MDGRU-3D_touchdown.

This thesis presents the first automated segmentation of choroidal tumors in 3D compared to previous 2D segmentations. It could serve as proof of principle for segmentations of other pathologies in volumetric OCT data. Improvements on the used models are conceivable to meet clinical demands for the diagnosis and follow-up of choroidal tumors.

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Assessment of Different Grasp Type Handles to Improve the Usability of Surgical Teleoperation

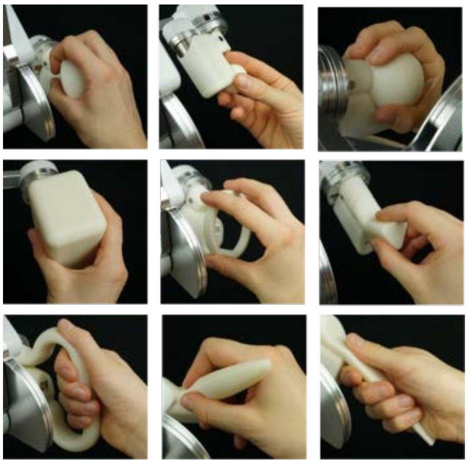

Figure 1: Nine different grasp type handles that can be mounted on the lambda.6 haptic device (Picture: E. Zoller).

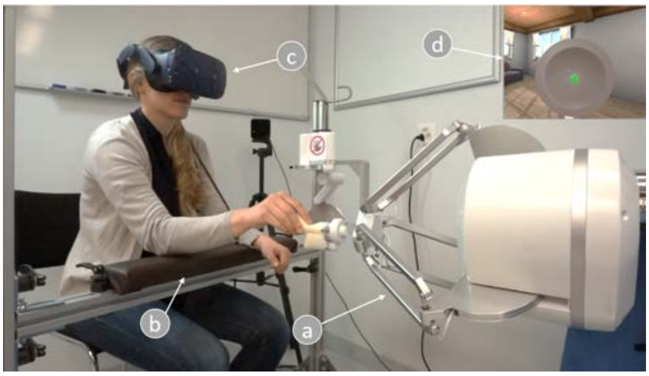

Figure 2: Experimental setup for the peg-in-hole task: a) lambda.6 haptic device (Force Dimension, Nyon, Switzerland), b) armrest, c) head-mounted display (HMD, HTC, New Taipei City, Taiwan), and d) the virtual environment that is displayed on the HMD to the participant (Picture: S. von Ballmoos).

Master's Thesis by Sibylle von Ballmoos (ETH Zurich) at BIROMED-Lab.

Surgical teleoperation systems offer benefits like fine manipulation capabilities, repeatability, and high accuracy [1]. Literature indicates that an ideal teleoperation setup allows the user to reach all necessary orientational motions and includes a handle with an ergonomic and task specific design [2,3].

To understand the features of an efficient and ergonomic handle design for teleoperation, a user study has been conducted comparing the performance of different grasp type handles (Fig. 1) in a placement task. Four performance metrics, namely the task completion time, movement smoothness, collision forces, and perceived cognitive workload, have been investigated for a peg-in-hole task. In total 27 participants have conducted the task by controlling a virtual object with a 6 degrees-of-freedom haptic device (Fig. 2). Linear mixed-effects models were used to statistically investigate if the performance metrics differed among the investigated grasp type handles.

Very high evidence was found that the grasp type influences all of the metrics of interest. Further pairwise comparisons were performed for all metrics. With the reported results, suggestions for handle designs were made to improve teleoperation interfaces' design process.

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Comparing Intraoral Scanners Using Advanced Micro Computed Tomography

Figure 1: PEEK model on the rotation stage of the CT-system nanotom® m (Picture: M. Sacher).

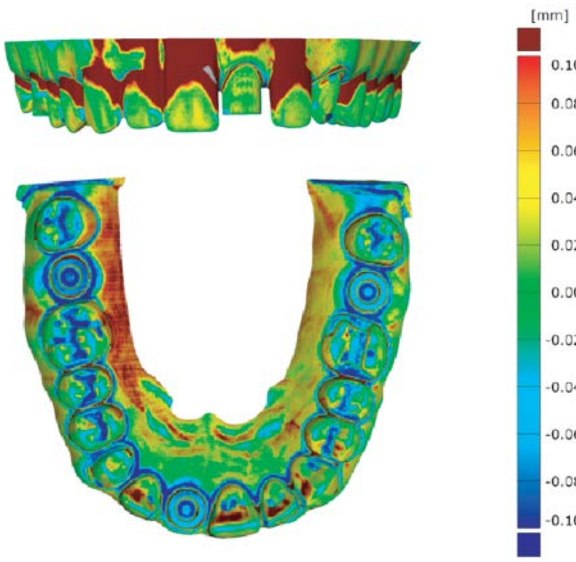

Figure 2: Three-dimensional representation of the deviations between the data of the intraoral scanner TRIOS 3® and the design (Picture: M. Sacher).

MD Thesis by Mattia Sacher at the Biomaterials Science Center.

Intraoral scanners play an increasingly important role in today's dental offices. The technology has become a valuable and economically reasonable alternative to conventional silicone impressions and plaster casts, which are still considered as the gold standard [1].
To determine the precision of a range of commercially available scanners, a clinically relevant polyetheretherketone (PEEK) model of a full arch upper jaw was designed and fabricated. This model was three-dimensionally visualized with an isotropic voxel length of 35 µm using the nanotom® m (phoenix|x-ray, GE Sensing & Inspection Technologies GmbH, Wunstorf, Germany). These reference data were compared with multiple scans of the five commercially available systems, i.e. PlanScan® (Planmeca Oy, Helsinki, Finland), TRIOS® 3 (3shape, Copenhagen, Denmark), CS 3600 (Carestream, Atlanta, GA, USA), Medit i500 (Medit corp., Seongbuk-gu, South Korea) and 3M™ True Definition Scanner (3M Espe, Rüschlikon, Switzerland) [2].

Non-rigid registration of the scans with the reference tomography data demonstrated that the intraoral scanners can be grouped: The more precise instruments gave rise to deviations of 35 µm (TRIOS® 3), 43 µm (CS 3600) and 46 µm (3M™ True Definition Scanner) and the less precise systems yielded 93 µm (Medit i500) and 97 µm (Emerald™) [2]. This means that we can recommend all scanners for the preparation of reconstructions with two to three teeth, but only the one's of the first group for treating larger defects.

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The PhD-Program in Biomedical Engineering 2020

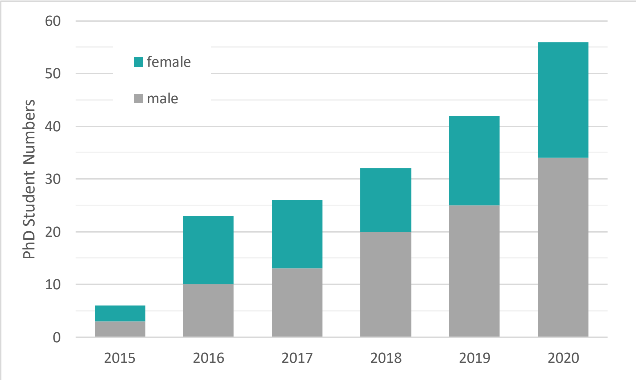

Figure 1: PhD Student numbers in the PhD Program in Biomedical Engineerig are constantly rising.

Figure 2: Posters of the HS 2020 Seminar Series on medically relevant experiments with synchrotron radiation. Speakers were (in order of appearance) Hans M. Hertz (Royal Institute of Technology, Stockholm, SE), Timm Weitkamp (Synchrotron SOLEIL, Gif-sur-Yvette, FR), Marianne Liebi (Empa, St. Gallen, CH/Chalmers University of Technology, Gothenburg, SE), Alexandra Pacureanu (ESRF -The European Synchrotron, Grenoble, FR), Christoph Rau (Diamond Light Source, Didcot, UK), Alexander Rack (ESRF -The European Synchrotron, Grenoble, FR), Felix Beckmann (Institute of Materials Research, Helmholtz-Zentrum Geesthacht, GER), Ana Diaz (Paul Scherrer Institute, Villigen, CH), Alberto Bravin (ESRF - The European Synchrotron, Grenoble, FR), Benjamin Hornberger (Lyncean Technologies Inc. Fremont CA, USA), and Julia Herzen (Technical University of Munich, GER).

The PhD-Program in Biomedical Engineering started its activities and offers in the 2015. Since then, the PhD-Program has a steady increase in student numbers. (Figure 1). 40 % of the PhD-students are female, showing that the PhD Program is diverse and balanced.

In 2020, eleven PhD-students started a thesis project and registered with the PhD-Program in Biomedical Engineering. Six PhD-students of the program graduated in 2020. Unfortunately, the majority of the related defences were online only. Hence, the well-deserved celebrations and good-bye apéros had to be postponed.

The current pandemic greatly influenced the PhD-Program in 2020. The social events were cancelled. The Summer School, planned to happen in the Black Forrest this year, had to be shifted to summer 2021.

Fortunately, the seminar series in the spring and autumn semesters were a success. Due to the flexibility of the invited experts, 70 % of the presentations were given in an online format or in a hybrid format (online and face-to-face). The online format resulted in an increase of audience, because participation from abroad became possible. Even scientists and students from Australia and US raised their questions despite the time differences. The experts who gave their presentations via zoom will be re-invited to Allschwil with the aim to scientifically exchange knowledge with the PhD-students. Figure 2 gives an impression of the posters, which have been prepared to advertise the event among the members of the department and their partners around the world.

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Optical Feedback System for Smart Laserosteotome

Figure 1: LIBS (short for Laser-Induced Breakdown Spectroscopy) setup. A high peak power nanosecond Nd:YAG laser pulse is used to create plasma from the specimen. The collected plasma emission is transferred to the spectrometer for spectrochemical analysis (Picture: H. Abbasi).

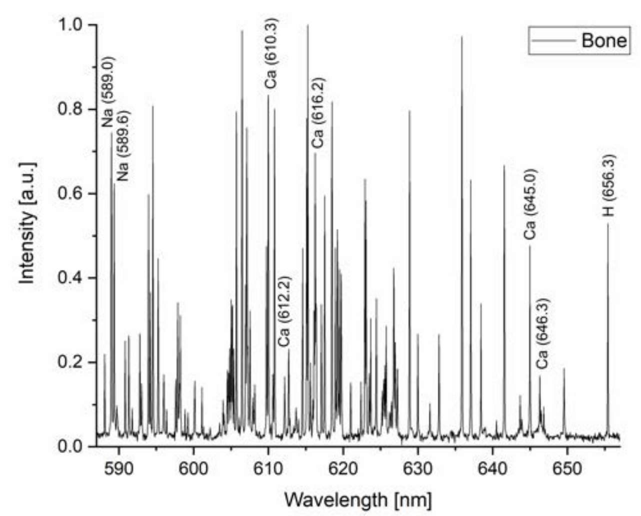

Figure: Typical LIBS spectrum collected from a bone sample. By comparing the wavelength of the observed peaks with reference wavelengths, the presence of specific elements in the material can be concluded (Picture: H. Abbasi).

PhD Thesis by Hamed Abbasi at BLOG.

Compared to traditional mechanical tools for bone cutting (osteotomy), laser offers several benefits, including functional cutting geometry (high axial and lateral resolution), contactless interaction, reduced trauma, and, subsequently, accelerated healing. Lack of real-time feedback about the type of tissue being cut risks iatrogenic damage due to body/laser movement or any other unexpected error. Therefore, real-time feedback during laserosteotomy is essential to avoid damage to adjacent soft tissues. Equally vital is the ability to monitor laser-induced thermal damage to control the irrigation system used for rehydrating and cooling down the tissue during laserosteotomy. Laser-induced thermal damage (e.g., carbonization) can slow down the cutting procedure and prolong the healing process. Therefore, an optical feedback mechanism based on laser-induced breakdown spectroscopy (LIBS) was developed to serve as a powerful label-free method for elemental analysis.
For this purpose, a custom-made, high-resolution, broadband Echelle spectrometer with high optical throughput was developed. The portable LIBS system, coupled with multivariate spectrochemical analysis, was able to differentiate bone from its surrounding soft tissue and to detect laser-induced thermal damage — both with high accuracy in a single-shot measurement without any sample preparation. The feedback system was integrated into an efficient bone cutting system and was tested in a real-time closed-loop manner, to stop the ablation laser in situ when it encountered the adjacent soft tissues that should be preserved. In the end, the system was miniaturized by delivering the high peak power laser beam through a highly flexible bend-insensitive fiber system with a tiny half-ball lens at the tip, suitable for intraoperative tissue characterization in a minimally invasive endoscopic procedure.

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New Therapeutic Approaches for Peripheral Compression Neuropathies

Figure 1: Chronic sciatic nerve compression model with controlled features: Rat sciatic nerve was entrapped using a hemostatic clip that we designed to have a defined lumen size postoperatively (Picture: L. Degrugillier).

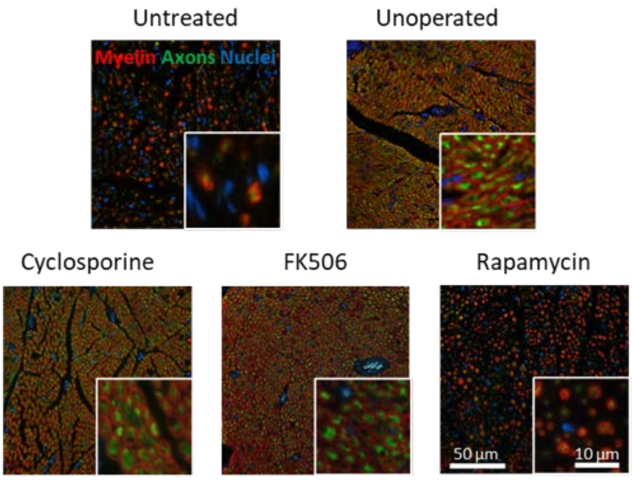

Figure 2: Immuniphilin ligands holds great potential for repair regeneration of chronic nerve compression injury: Systemic drug delivery resulted in functional and anatomical amelioration. This figure shows representative cross sections of the nerves of each treatment group after chronic compression where we can observe that animals treated with Cyclosporine and FK506 show an improved nerve structure preservation (Picture: L. Degrugillier).

PhD-Thesis of Lucas Degrugillier at the Center for Bioengineering and Regenerative Medicine.

Chronic peripheral nerve compressions are a type of neuropathies that can cause paresthesia, pain, numbness and tingling. These neuropathies are caused by the entrapment or the compression of a nerve or its root. Existing treatments are showing limitations and are regularly followed by a surgery to release the injured nerve from compression. Unfortunately, these surgeries are not always successful in curing the symptoms and are also showing some detrimental outcomes. Therefore, the thesis aimed to develop new and effective therapeutic approaches for treating chronic nerve compression neuropathies.

The first part of the thesis covers the development of a new nerve compression model that was achieved by the controlled entrapment of the rat sciatic nerve using a modified hemostatic clip (1). Thus, the chronic injury model with differential injury inputs resulted in different sensory-motor pathophysiological outcome as evidenced by electrophysiological, behavioral and anatomical impairments. The resulting nerve compression model was further employed for drug screening for neuro-muscular protection. Thus, the second part of the thesis covers drug-screening studies in vivo. For this, three FDA-approved drugs, cyclosporine, FK506 and rapamycin, were first evaluated *in vitro* for their neurotrophic activity and further *in vivo* as described earlier. The resulting data and knowledge (2), i.e., histological and functional markers appeared to be promising and provides a strong basis for further clinical development (3). The third part of the thesis covers the studies on the two novel synthetic molecules inspired from the natural product, paecilomycine A, *in vitro* and *in vivo* (4). The resulting data and knowledge revealed the beneficial effects for neuro-muscular regeneration and hold promise for treating peripheral neuropathies.

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Ultrasound-based Motion Modelling for the Lungs in Scanned Proton Therapy

Figure 1: Maximum intensity projection of a 3D MRI scan of the lungs (Picture: A. Giger).

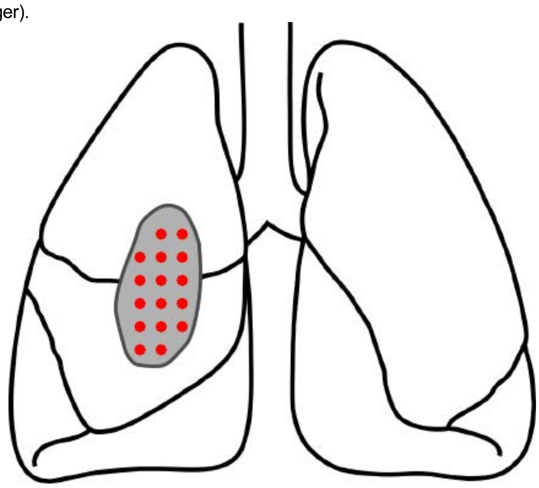

Figure 2: The priniciple of pencil beam scanning proton therapy: In spot scanning, the treatment beam is steered to scan the target volume spot by spot (Picture: A. Giger).

PhD Thesis by Alina Giger at CIAN.

According to the WHO's World Cancer Report 2020, lung cancer ranks first both in terms of incidence and mortality compared to other common sites of cancer. The aim of this project is to investigate the use of ultrasound-based respiratory motion models for their application in pencil beam scanned proton therapy.

Due to the physical properties of protons and the resulting high dose conformation, pencil beam scanned (PBS) proton therapy holds the potential to significantly improve cancer treatment when compared to conventional radiotherapy. However, respiratory organ motion hampers the clinical application of abdominal and thoracic proton therapy. For tumor tracking in the lung, the delivered beams are steered to follow the tumor in the presence of respiratory motion to ensure the best combination of target coverage and dose conformation. Precise tumor tracking requires accurate methods to determine in real-time tumor position and shape of the lungs. Ultrasound (US) imaging offers an interesting surrogate signal as it provides internal organ motion information at a high temporal resolution while being non-invasive, relatively inexpensive and without providing additional radiation dose. Unfortunately, however, it is not possible to image lung tumors directly using US imaging due to physical constraints.

In this project, we developed methods to use US imaging of the upper abdomen to predict three-dimensional motions in the lungs. With the indirect prediction scheme, surrogate structures in the liver and on the diaphragm are used in combination with a patient-specific motion model of the lung to predict the respiratory motion and to allow accurate tumor tracking.

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Opto-Acoustical Feedback System for Smart Laser Surgery

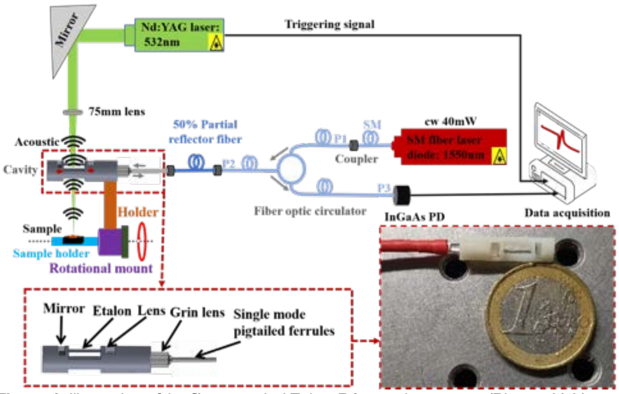

Figure 1: Illustration of the fiber-coupled Fabry-Pérot etalon system (Picture: H. Nguendon Kenhago).

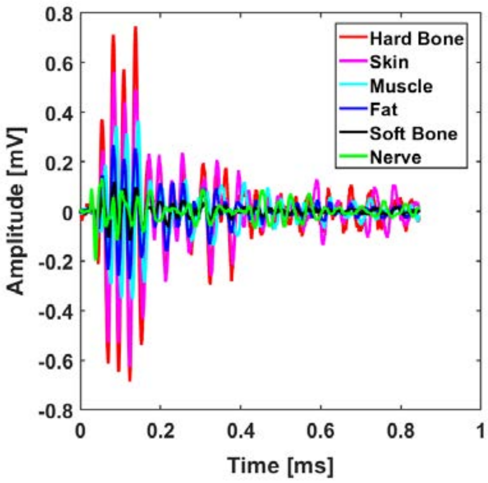

Figure 2: Acoustic shock waves in the time domain (Picture: H. Nguendon Kenhago).

PhD Thesis by Hervé Nguendon Kenhagho at BLOG.

Laser surgery requires efficient tissue classification to reduce the probability of undesirable or unwanted tissue damage. The aim of this study was to investigate acoustic shock wave spectroscopy as a means of classifying sciatic nerve tissue.

In this study, we classified sciatic nerve tissue against other tissue types — hard bone, soft bone, fat, muscle, and skin extracted from two proximal and distal fresh porcine femurs — using the acoustic shock waves (ASWs) generated by a laser. A nanosecond frequency-doubled Nd:YAG laser at 532nm was used to create ten craters on the surface of each tissue type. We used a fiber-coupled Fabry-Pérot sensor to measure the ASWs. The amplitude of the spectrum from each ASW frequency band measured was used as input for principal component analysis (PCA). PCA was combined with an artificial neural network to classify the tissue types. A confusion matrix and receiver operating characteristic (ROC) analysis was used to calculate the accuracy of the testing-data-based scores from the sciatic nerve and the area under the ROC curve (AUC) with a 95% confidence-level interval. Based on the confusion matrix and ROC analysis of the model's tissue classification results (leave-one-out cross validation), nerve tissue could be classified with an average accuracy rate and AUC result of 95.78± 1.3% and 99.58± 0.6%, respectively.
This work demonstrates the opportunity acoustic shock wave spectroscopy presents for remote classification of nerve and other types of tissue. The technique can serve as the basis of a feedback control system to detect and preserve sciatic nerves in femur laser surgery.

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2) H. N. Kenhagho, F. Canbaz, R. Guzman, P. Cattin, and A. Zam, "Miniaturized Optoacoustic Feedback Sensor for Smart Laser Osteotome: Fiber-Coupled Fabry-Pérot Etalon Sensor," *Sensors and Actuators A: Physical,* p. 112394, 2020.

Novel Quality Controls for Nasal Chondrocyte-Derived Tissue Engineered Cartilage

Figure 1: Identity and purity assays were developed to characterize the starting nasal cartilage biopsy tissues and cells. A final potency assay assessed the maturity of the engineered cartilage after four weeks of culture (Picture: L. Power).

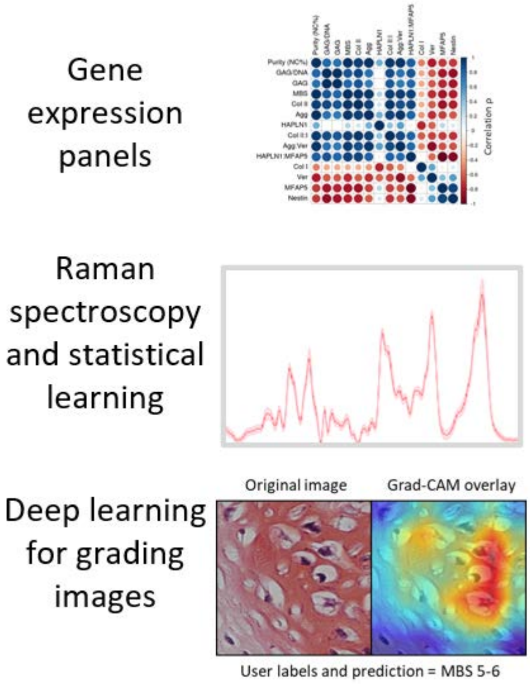

Figure 2: Various methods were investigated for the developent of characterization assays (Picture: L. Power).

PhD Thesis by Laura Power at Tissue Engineering research group at DBM.

Cartilage defects are caused by injury, can be painful if left untreated, and may lead to degenerative joint diseases. Currently available treatments have not shown long-term predictable and durable results. Nasal chondrocytes have been investigated as an alternative to articular chondrocytes for engineering cartilage grafts due to their ability to produce high-quality engineered tissues and reduce harm to patients' knees. Thus, we are conducting a phase II clinical trial (1), for which novel quality controls must be developed. The starting materials, i.e., nasal septal biopsy and the cells within, must be evaluated with identity and purity assays. Potency assays must also be based on the product's hypothesized mode of action, i.e., the filling of cartilage defects with mature cartilaginous cells and matrix.

For the development of identity, purity, and potency assays, gene expression panels (2) as well as Raman spectroscopy (3) were investigated. Moreover, the automated grading of histological images was implemented using deep learning (4).

Prospectively, when two- and five-year follow-up results from the patients become available, the assays developed in this thesis should be reevaluated and related to good clinical outcomes.

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Hydrogel Assisted Stem Cell Delivery for Peripheral Nerve Repair and Regeneration

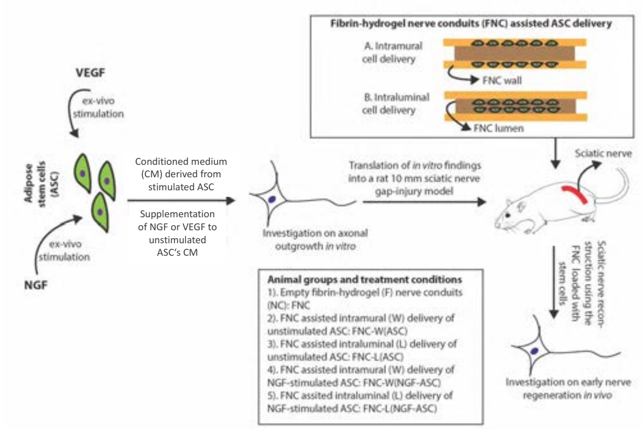

Figure 1: Ex-vivo stimulation of adipose stem cells using growth factors and fibrin-hydrogel nerve conduits assisted stem cell delivery strategies (Picture K. Prautsch).

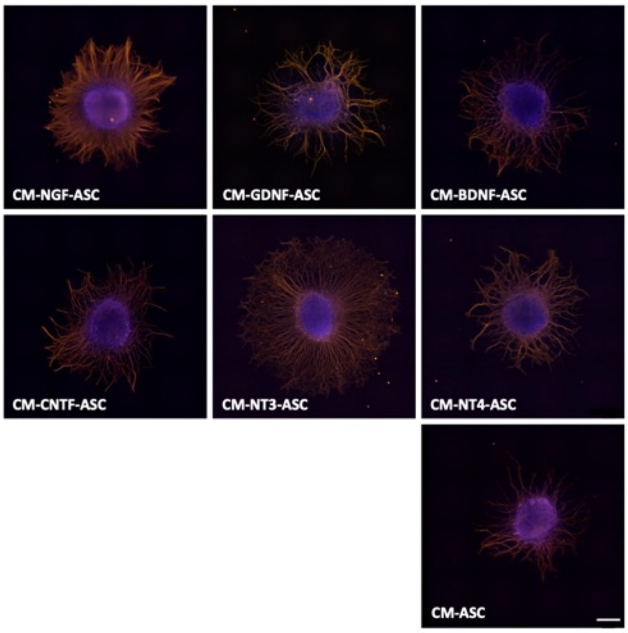

Figure 2: Neurotrophic potency of conditioned medium (CM) derived from NTF-stimulated ASC for supporting axonal regeneration. Microphotographs of dorsal root ganglion explants treated with CM derived from different NTF-stimulated ASC (Picture K. Prautsch).

MD PhD Thesis of Katharina Prautsch at the Center for Bioengineering and Regenerative Medicine.

Injuries to the peripheral nerve system are a common clinical problem that affect primarily young individuals. Standard treatment methods are well established but are associated with several undeniable disadvantages that may have a long-lasting impact on the patients' quality of life.

My thesis aimed to investigate a multidisciplinary, translational approach for enhancing peripheral nerve regeneration and surgical nerve repair.
The first and second manuscript[1,2] of this thesis focused on the neurotrophic potency of adipose derived stem cells (ASC) in response to neurotrophic factors (NTF) stimuli, i.e. NGF, BDNF, NT3, NT4, GDNF, CNTF and VEGF *in vitro* and *in vivo*. The neuroregenerative events taking place in ASC and sensory neuronal cells upon stimulation and the impact of two different stem cell delivery strategies, i.e. intramural versus intraluminal loading, in fibrin nerve conduits (FNC) on early nerve regeneration were investigated. In the third manuscript, a *prospective, randomized clinical trial* was conducted comparing the outcome of digital nerve injuries with or without nerve gap after experimental treatment with the fibrin nerve conduit (FNC) or the epineural suture with fibrin sealant versus the standard treatment with the autologous nerve graft or the epineural suture over a period of 12 months.

Ex-vivo stimulation of ASC by NTF and FNC-assisted intramural delivery may offer new options for developing effective stem cell-based therapies. At the same time, the FNC and the fibrin sealant might already present viable clinical treatment alternatives for the repair of short-gap nerve injuries.

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Detecting Early Choroidal Thickness Changes using Piecewise Rigid Image Registration and Eye-Shape Adherent Regularization

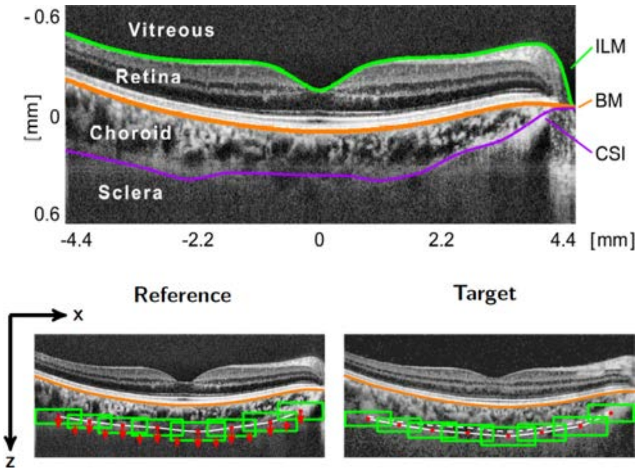

Figure 1: Above: OCT B-scan with segmented layers: inner limiting membrane (ILM), Bruch's membrane (BM) and choroid-sclera interface (CSI). Below: Simulation of choroidal growth. Left: The continuous white line serves as a reference for the deformation. Right: After blockwise transformation, the reference line is shifted (white dotted line). As the images are aligned to BM, the displacement corresponds to the CSI shifts (Picture: T. Ronchetti).

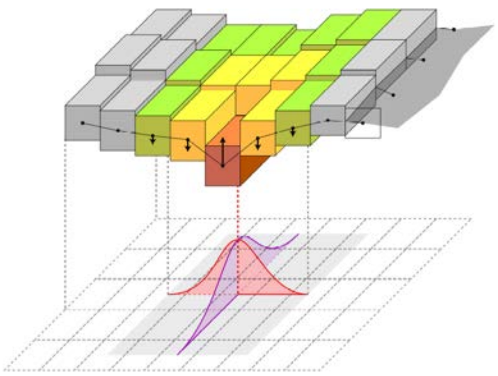

Figure 2: The eye-shape adherent regularization used in the developed method CRAR (Picture: T. Ronchetti).

PhD Thesis of Tiziano Ronchetti at CIAN.

This research work focuses on developing an automatic algorithm to detect subtle changes in the human choroid area. This is relevant because choroidal thickness changes could be among the first signs of, for example, myopia or glaucoma and must therefore be monitored.

Image acquisition with optical coherence tomography (OCT) allows 2- and 3-dimensional images with micrometer resolution. However, segmenting the choroid is often challenging because of low contrast, loss of signal and the presence of artifacts. In particular, in vivo imaging of the choroid-sclera interface (CSI, see Fig. 1), the border separating the choroid from the sclera, is problematic.

CRAR [1] is a novel method for the early detection of **C**horoidal changes based on piecewise rigid image **R**egistration using eye-shape **A**dherent **R**egularization. It focuses on the changes of the entire choroid-sclera border, for which an exact recognition of the CSI is not required (see Fig. 1 and 2).

Since a ground truth for comparison with the in-vivo situation is lacking, we combined a self-developed statistical validation framework with an exhaustive power analysis [2]. We then applied CRAR to macular telangiectasia type 2 (MacTel2). Follow-up images of this disease suggest a correlation between changes in the choroidal thickness and the further development of MacTel2 [3].

We see great potential in expanding CRAR in other medical imaging fields, especially with low SNR, reproducible environments and potentially disease-related minute changes in tissues.

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Registration and Analysis of Dynamic MRI Image Series

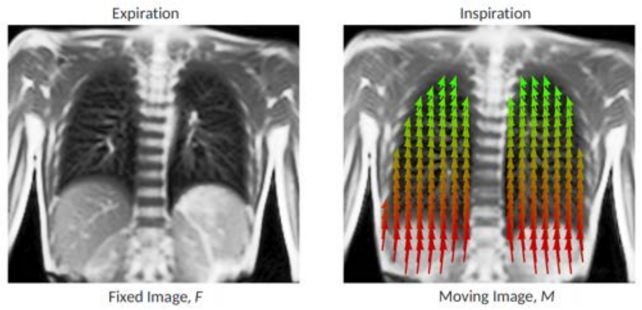

Figure 1: MR images of the lung during expiration and inspiration. Overlayed vector field shows the lung motion between inspiration and expiration (Picture: R. Sandkühler).

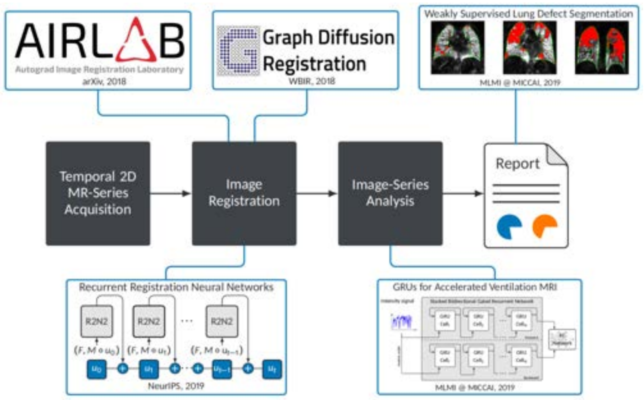

Figure 2: Overview of the different developed methods to improve CF patients' monitoring process (Picture: R. Sandkühler).

PhD Thesis of Robin Sandkühler at CIAN

This work aimed to develop new image registration and analysis methods for dynamic MR image series of the lungs.

Cystic fibrosis (CF) is an autosomal-recessive inherited metabolic disorder that affects all organs in the human body. Patients affected with CF suffer particularly from chronic inflammation and obstruction of the airways. Through early detection, continuous monitoring methods, and new treatments, the life expectancy of patients with CF has been increased drastically. Through the development of new MRI sequences and evaluation methods [2], MRI is able to measure physiological changes in the lungs. The process to create physiological maps, i.e., ventilation and perfusion maps, of the lungs using MRI can be split up into three parts: MR-acquisition, image registration, and image analysis.

In this work [1], we present different image registration parts and the image analysis part. We developed a graph-based registration method for 2D dynamic MR image series of the lungs to overcome the problem of sliding motion at organ boundaries. Furthermore, we developed a human-inspired learning-based registration method [3]. We also developed a general registration framework called Autograd Image Registration Laboratory (AIRLab) for rapid prototyping registration algorithms.

For the image analysis part, we developed a deep-learning approach based on GRUs that can calculate ventilation maps with less than a third of the current method's number of images. Automatic defect detection in the estimated MRI ventilation and perfusion maps is essential for the clinical routine to evaluate the treatment progression automatically. We developed a weakly supervised method that can infer a pixel-wise defect segmentation by using only a continuous global label during training.

Funding:

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Quantitative Measurement of the Cornea by OCT

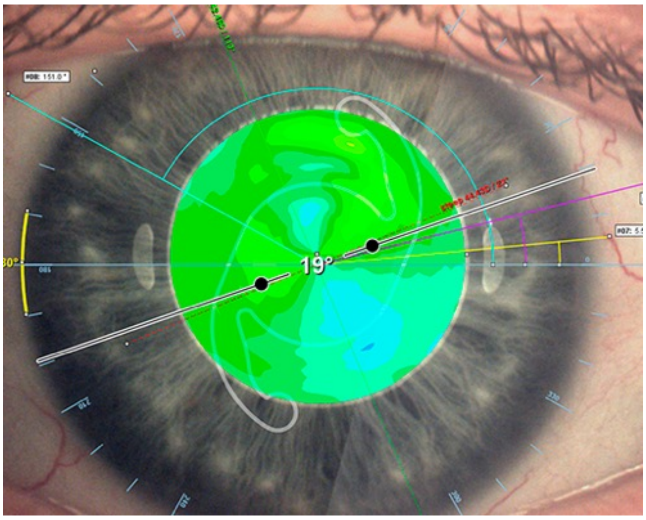

Figure 1: Topography map in a surgical planning tool shown as overlay on the cornea. The color encodes the refractive power of the cornea at this point (Picture: J. Wagner).

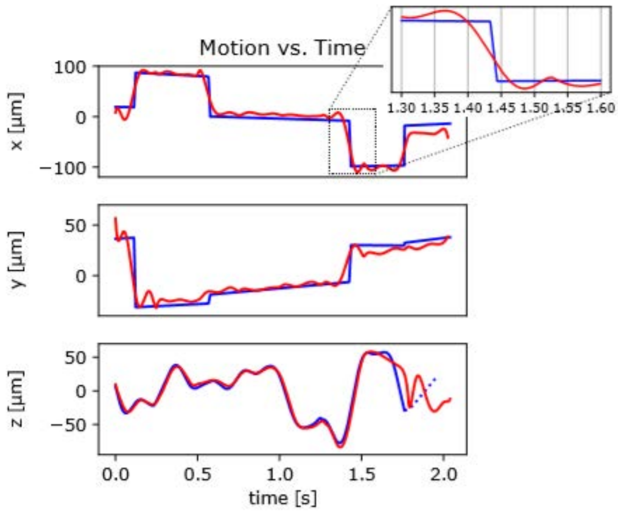

Figure 2: Comparison of the motion detected by our motion compensation (red) and the ground truth (blue) (Picture: J. Wagner).

PhD Thesis of Jörg Wagner at CIAN.

The accurate measurement of the corneal shape and refractive power is essential for diagnostics and the planning of surgeries. Keratometry and corneal topography are clinically established measures for the quantitative description of the corneal shape and refractive power. In our work (1), we present solutions to enable keratometry and topography based on optical coherence tomography (OCT).

One major application of keratometry and topography is the planning of cataract surgeries, where the natural lens gets replaced by an intraocular lens (IOL). OCT potentially enables the three-dimensional measurement of all optically relevant structures of the eye at once. However, the use of OCT for corneal topography and keratometry is still limited. One limitation is the sensitivity of beam-scanning OCT to eye motion. This sensitivity can be decreased by increasing the scan speed. Nevertheless, there is a trade-off between axial resolution, scan range, scan speed, signal-to-noise ratio (SNR), and the system's cost. To take full advantage of OCT – measuring the full depth of the eye at once – one has to make compromises regarding the resolution and speed of the system. In our work, we present solutions for OCT-based keratometry and topography, using a system with limited axial resolution and speed, which is, in return, able to measure the full depth of the eye. We propose new scanning techniques with two-dimensional scan trajectories, enabling robust reconstruction and accurate motion compensation with high temporal resolution. The motion compensation features model-based motion compensation in three dimensions. Because current segmentation methods do not apply to these new scanning techniques, we further present a novel method for model-based segmentation.

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Biological Therapy and Tissue Engineering Approaches for the Treatment of Osteoarthritis

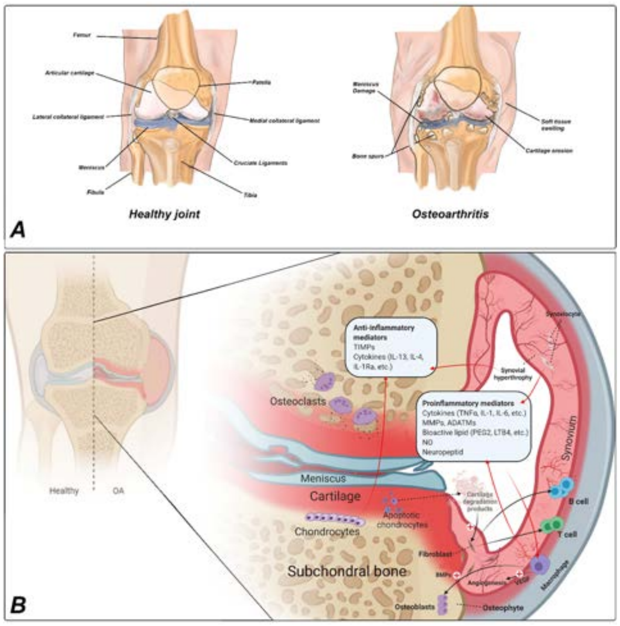

Figure 1. (A) Schematic representation of a healthy and osteoarthritic knee joint. (B) Biochemical environment of an osteoarthritic joint showing the pro- and anti-inflammatory mediators involved in OA (Picture: R. Ziadlou).

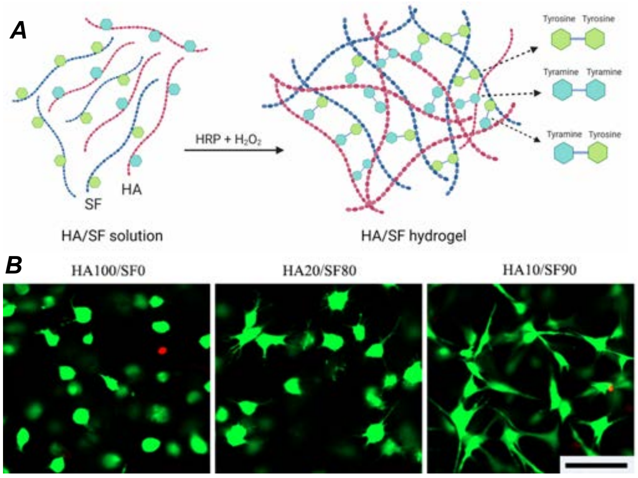

Figure 2. (A) Schematic illustration representing the potential covalent crosslinking in HA-SF composite hydrogels which can occur between tyramine residues of HA and tyrosine in the silk after enzymatic crosslinking. (B) Cell viability for the cell-laden hydrogels with live-dead assay representing the morphology of the cells in the hydrogels at day 7 of culture in chondrogenic medium. Scale bar: 100 µm (Picture: R. Ziadlou).

PhD-Thesis by Reihane Ziadlou at Tissue Engineering research group at DBM.

In this thesis, we aimed to find an effective biological therapy to treat or impede osteoarthritis (OA) and to regenerate damaged articular cartilage. To achieve this goal, inhibition of pro-inflammatory cytokines that are excessively abundant in OA joints is necessary (Figure 1). Furthermore, for the regeneration of damaged cartilage, it is essential to increase the chondrocytes anabolism for cartilage tissue to recover. Pharmacological therapy and tissue engineering approaches are the two most promising strategies towards cartilage regeneration.

There is currently no effective pharmacotherapy featuring anti-inflammatory and anabolic effects to restore the degenerated cartilage in OA or other degenerative joint diseases. Therefore, we used an inflammatory model of human OA chondrocytes microtissues, in which after screening of 34 herbal compounds with potential anti-inflammatory and anabolic effects, VA, Epi C, PS, PCA, 4-HBA and 5-HMF were selected for further studies (1). We selectively identified the mechanism of action of Vanilic acid (VA) and Epimedin C (Epi C). Our results indicated that VA had significant anti-inflammatory effects through inhibition of IKK complex in NF-κB signaling and Epi C showed a significant anabolic effect by increasing the expression of collagenous and non-collagenous matrix proteins (2). Additionally, we developed a tunable and injectable hydrogel for drug delivery and cartilage tissue engineering by crosslinking different concentrations of HA-Tyramine (HA) with aqueous Silk-fibroin (SF) solutions (3). HA20/SF80 composite hydrogel showed the longest and the most sustained release profile for VA and Epi C over time, which is necessary for the long treatment duration for OA joints. Also, we showed superior ECM production in HA20/SF80 chondrocyte-laden constructs (Figure 2). For future studies, to achieve a successful therapy, the combination of all mentioned approaches in an *ex vivo* cartilage organ culture model and in animal models is envisioned.

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Publications & Circle of Expertise

Selected Publications 2020

*Peer-reviewed, first author (45) or last author (70) at DBE, impact factor >2.

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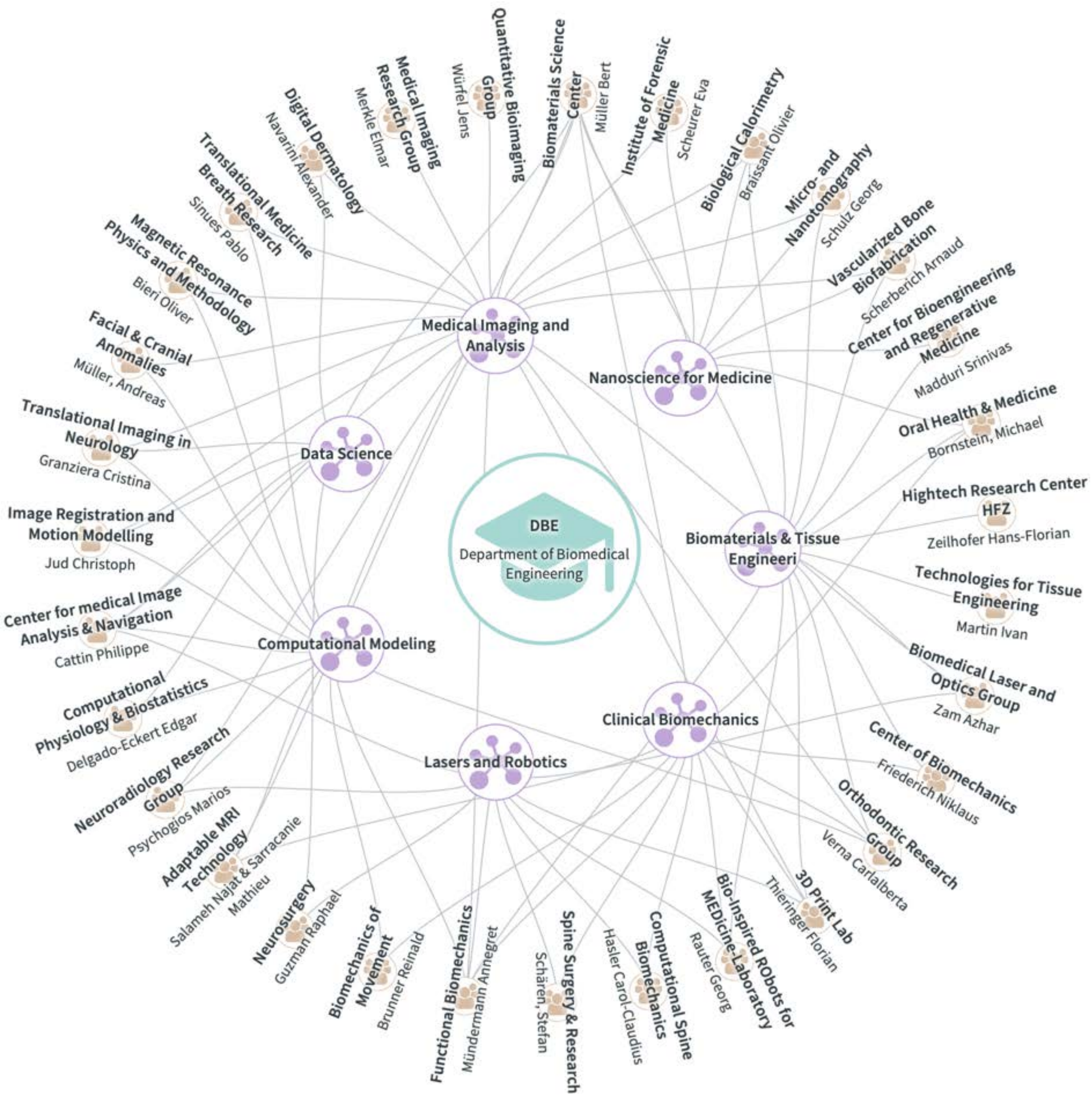

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