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Medical Faculty
Justus-Liebig University of Giessen (Germany)

2019 Proceedings of the 2nd International Conference on Trauma Surgery Technology in Giessen

11 to 13 October 2019

Funded by the Deutsche Forschungsgemeinschaft

University Medical Faculty
Giessen (Germany)

2019 Proceedings of the 2nd International Conference on Trauma Surgery Technology in Giessen
Editors: WA Bosbach, A Presas, A Mieczakowski, C Heiss

Conference Organisation at JLU Giessen

WA Bosbach, S Drahorad, M Hofacker, M Ebeling, KE Bosbach, C Bosbach, M Otto

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Summer 2020
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2nd conference: Vibration in oncological and antibacterial therapy
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11 - 13 Oct 2019
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Preface

Dear Colleagues

It is now for a 2nd time that we can invite researchers to come to Giessen for an international exchange of latest research and a discussion of ideas. This year again, the Deutsche Forschungsgemeinschaft (DFG) is sponsoring the event.

The main topic for **2019** is **vibration in antibacterial and oncological therapy**. Many effects of mechanical vibration on tissue have been discovered so far. Clinical applications relying on vibration exist for a variety of conditions. The intracellular processes however are still largely not understood. And reproducibility remains a matter of potential for improvement.

During the last year, we have worked on building **vibration bioreactor prototypes** for the controlled exposure of *in-vitro* cell cultures to resonance vibration. We see great potential for piezoelectric patches (PZTp) as mechanical actuators. Compared to ultrasound, the controllability of vibration frequency and local vibration energy density is an important advantage. With the support from the **DFG and the Justus-Liebig Fellowship**, we have been able to collaborate with the **Grandfield Lab at McMaster University** in Ontario (Canada) for the performing of cell vibration experiments on Saos-2 cells. The analyses of the exposed cell cultures are still going on and we are working on their submission for publication (see p 9-11).

Figure: Bosco, Joe, Kathryn, Alex, and Bryan during lunchbreak at McMaster University (Canada) on 07 Sept 2019. Results from the cell vibration experiments are being prepared for submission for publication (see p 9-11).

In Giessen, day 1 will be used for hosting the talks of the participants. Day 2 will be again as in the previous year an interactive session with the possibility for exchanging ideas for future work and also an osteosynthesis workshop.

DFG funds for the **3rd conference in 2020** have already been approved. Anna, Bosco, and Wolfram will host next year the event with a focus on **multifunctional trauma surgery implants**.

Welcome to Giessen, your scientific committee

Press statement by host institute Justus-Liebig University of Giessen

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Vibrationen als Therapie in der Unfallchirurgie
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Vibrationen als Therapie in der Unfallchirurgie

Internationale Tagung an der Justus-Liebig-Universität Gießen am 12. und 13. Oktober 2019

Nr. 201 • 9. Oktober 2019

Mechanische Vibration kann vielfältige Auswirkungen in menschlichen und auch in tierischen Zellen entfalten. Möglichkeiten für neue Therapiekonzepte basierend auf Vibration gegen bakterielle Infekte nach Operationen und gegen Knochentumore stehen im Fokus einer internationalen Tagung zur Unfallchirurgie an der Justus-Liebig-Universität Gießen (JLU). Unter dem Thema „Vibration in der neuartigen onkologischen und antibakteriellen Therapie" tauschen sich am 12. und 13. Oktober 2019 Wissenschaftlerinnen und Wissenschaftler aus dem In- und Ausland zu neuesten Forschungsergebnissen und Entwicklungen bei der klinischen Anwendung von Vibration aus. Zudem gibt es interaktive Workshops zu chirurgischen Techniken, aber auch zu den Hürden beim Transfer von Technologie in die klinische Anwendung.

Die englischsprachige Tagung wird gefördert durch die Deutsche Forschungsgemeinschaft (DFG). Die Mittel wurden eingeworben von Wolfram A. Bosbach, PhD (JLU) in Kooperation mit Dr. Alexandre Presas von der Universitat Politècnica de Catalunya in Barcelona (Spanien). DFG-Mittel für die Folgeveranstaltung im Sommer 2020 sind bereits bewilligt im Rahmen einer Einreichung mit Dr. Anna Mieczakowski von der University of Cambridge (Großbritannien) und Dr. Bosco Yu der McMaster University (Kanada).

- Termin

12. und 13. Oktober 2019
Auftakt: 12. Oktober 2019, 9 Uhr
Medizinisches Lehrzentrum – Lehrgebäude und Dekanat, Klinikstraße 29, 35390 Gießen

- Weitere Informationen

www.uni-giessen.de/fbz/fb11/institute/klinik/chirurgie/uch/forschung/trauma-surgery-technology-conference-2019/

- Kontakt

Wolfram A. Bosbach, PhD
Experimentelle Unfallchirurgie
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Web link: http://www.uni-giessen.de/ueber-uns/pressestelle/pm/201-19vibrationentherapieinderunfallchirugrie (issued on 09 Oct 2019)

Programme overview

Friday, 11 Oct 2019

- Lunch meeting for early arrivals from Toronto, Cambridge, Freiburg, Bremen
- Hotel check-in
- Get-together at the Giessen Old Brewery

Day 1 - Saturday, 12 Oct 2019

- Registration, presentations with lunch break
- Dinner party at the Giessen Boat House

Day 2 - Sunday, 13 Oct 2019

- Interactive morning session:
  Osteosynthesis workshop (Dr Biehl)
  Workshop on technology transfer into clinical application (Dr Mieczakowski)
- Lunch break
- Departure by shuttle to Frankfurt airport for 5 pm flight connections or by train

Overview of presented abstracts

2019 Proceedings of the 2nd International Conference on Trauma Surgery Technology in Giessen
Editors: WA Bosbach, A Presas, A Mieczakowski, C Heiss

Energy density in vibration bioreactors and bovine vibration modelling

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In this work, we validate a numerical simulation of a vibrating plate by experimental results. We show the suitability of resonance vibration for the design of vibration bioreactors and we investigate vibration energy density in those, as well as in a bovine model.

Introduction The osteosarcoma is the most common malignant bone cancer, which mostly occurs in childhood and often shows only unspecific symptoms [1]: It is important to constantly expand the possibilities of curative therapy. It is known that vibrations have an influence on osteoblasts [2]–[4] and also are used in cancer therapies [5]–[7]. The aim of this work was to construct a vibrating plate with the help of numerical simulation using Finite Element Method (FEM). The assembly was extended by a fluid filled petri dish and local vibration energy quantified. Results are being compared to the vibration response of a gross anatomical bovine model.

Method and materials With the Abaqus 2017 software from Dassault Systems the numerical simulation was implemented. For this purpose, a bronze vibrating plate was simulated. A modal analysis from 0 to 100 kHz and a harmonic analysis were performed. The results of the simulations were compared with experimental results which were performed at the Center for Industrial Diagnostics and Fluid Dynamics (CDIF) of the Polytechnic University of Catalonia (UPC) [8]. There also the experimental measurements of bovine vibration response was done.

Results and discussion In the validation, the modal analysis results from the simulation are compared to experimental results. For the frequencies from 0 to 22 kHz, the average deviation between simulation and experiment is only 2.6%.

The harmonic analysis results from the simulation are also compared to experimental results. First, an offset correction and amplitude normalisation is necessary to compensate the difference in the frequency position and the amplitude of the modes. With this compensation it is easier to compare the shapes of the curves. The normalised amplitudes of the acceleration from the simulation and experiment which we have performed indicate good agreement. So the numerical simulation is validated for further work.

In the extended assembly, we analysed to what extent the natural frequencies of the disk change after adding the petri dish with the culture medium. Numerical and also experimental analyses are being performed. It can already be seen in our preliminary results that the natural frequency values decrease when adding the petri dish with the culture medium, however the difference is minimal.

Our preliminary results about bovine femur vibration show that the first bending mode shape has similarities with beam beanding and maximum amplitude in the middle of the bone shaft. Higher mode shapes allow varying this location of the maximum amplitude.

Conclusions and future work The numerical model is validated as a prototype of the bioreactor and suitable for further experiments and design steps for an experimental setup. Energy densities which we can observe are within the useful range, reported in [2]–[4], or greater.

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2019 Proceedings of the 2nd International Conference on Trauma Surgery Technology in Giessen
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A mechanical assembly for experiments of Saos-2 cells under vibration actuation

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Our current experimental work investigates the influence of mechanical vibration on Saos-2 cells. We impose the vibration by using piezoelectric patches and we measure vibration response by a Laser Doppler Vibrometer. We use the effect of resonance for the experiments. Our work has shown so far the adequacy of our experimental approach. Cell culture analyses for the quantification of cell response are still on going.

Introduction In our present collaboration, we are researching the effects of mechanical vibration on cell cultures. It has been known since the 1980s that bone tissue can be stimulated so that enhanced bone growth is observable [1]. Other tissues similarly react, such as the endothelium [2]. Vibration theory is today a well established concept within the field of mechanics [3]. We have used it in the past for work on submerged or non-submerged systems [4], [5], as well for the design of a vibration bioreactor [6]. In the work which we are presenting herein, we investigate the effects which are observable in Saos-2 cells attached to flat surfaces or 3d scaffolds [7]. The greater aim of our work is to make the effects accessible for therapeutic clinical application.

Method and materials We excite a stainless steel plate with a Piezoelectric Transducer (PZT patch). Firstly, a Modal Analysis of the plate is performed in order to determine the Natural Frequencies and mode shapes of the plate. For further experiments the first Natural Frequency is excited with the PZT. In this way, the stainless steel plate is vibrating under resonance conditions with high vibration amplitudes. Velocity of vibration is measured by means of the Laser Doppler Vibrometer and an accelerometer glued on the plate. The accelerometer measures directly the vibration of the plate which drives and controls the vibrations of the well plate.

The well plate consists of 18 wells, in a 24-well plate, filled with cell culture media and a scaffold. Only in 6 of these tubes cells are introduced for the study purpose. The LDV is moved in order to measure the axial vibration of these 6 scaffolds during the excitation of the PZT, which lasts 10 minutes with a constant frequency and force. The whole experimental apparatus is shown in Figure 1.

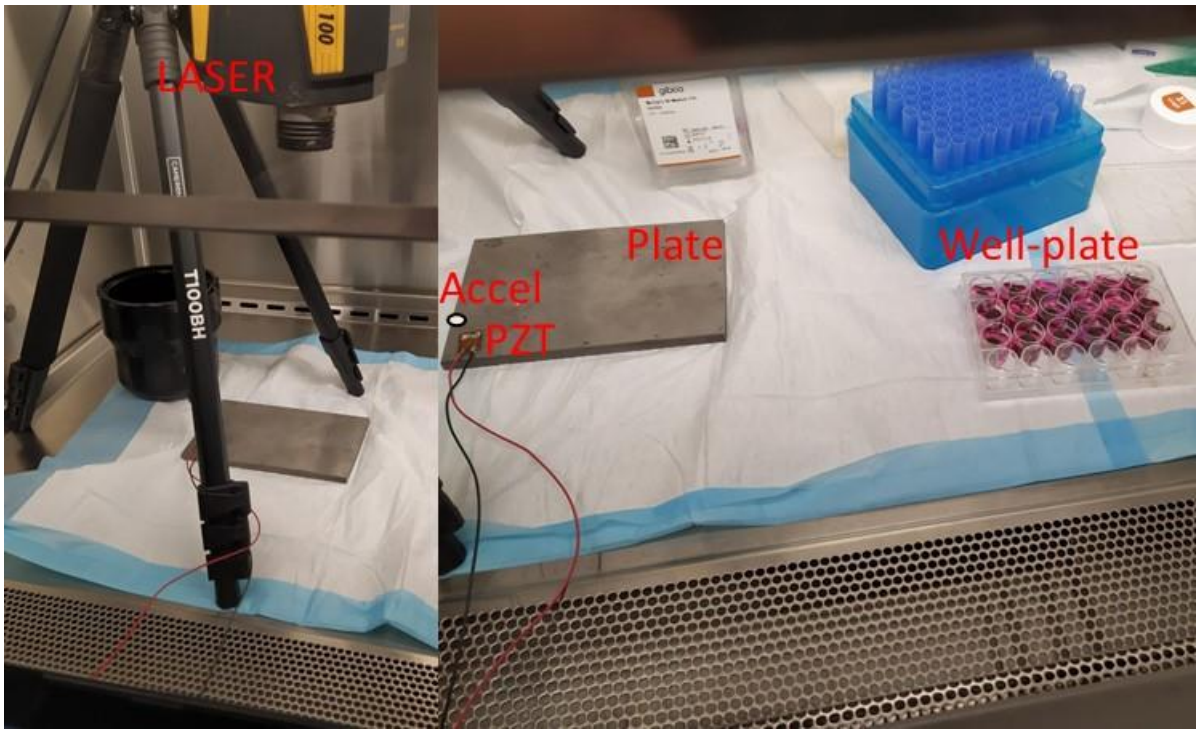

Figure 1: Sensors& actuators used: Laser Doppler Vibrometer and Accelerometer for measuring velocity. PZT exciting the plate.

Twelve different well-plates are excited in this study. Half of them contain cells which are cultured for 1 day and half of them which are cultured for 3 days. In order to analyse the effect of having a scaffold on the well, in half of the plates there was no scaffold (control plates). For checking the reproducibility of the results, 3 identical plates are excited in every case. This is summarised in Table 1.

Table 1: Well-plates excited during the experiments

Cultured time	Configuration	Repetitions	Total Plates
1day/ 3 days (2)	With scaffold /without scaffold (control case) (2)	3	2*2*3=12

Preliminary results and discussion The amplitude of vibrations and the vibration energy transmitted to every scaffold is properly measured with the LDV. It has been shown that the following system driven by the PZT and the stainless steel plate can excite the scaffolds with different amplitudes. Maximum amplitudes achieved are greater than 1 mm/s at a frequency of 1,280 Hz (first natural frequency of the plate). Therefore, the feasibility of using this system to excite cell systems at a high frequency and very high amplitudes is proven. Effects of these vibrations on the cells will be discussed in future papers.

Conclusions and future work Overall the experiments have been so far successful .The analyses of cell cultures are a still ongoing

matter. In the future, we plan to investigate further the intracellular metabolic response, as well effects on signalling pathways. Another objective of our future work are experiments to show the mechanical feasibility for the effects observed *in-vitro* on the gross anatomical scale. Therapeutic concepts which rely on vibration and where resonance vibration could increase the patient benefit are the stimulation of bone growth for the treatment eg of osteoporosis [1], [8], oncological treatments [9], or antibacterial measures [10].

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The effect of BDNF-functionalised PEC-NP on the vitality and proliferation of an osteocyte-neuron-coculture

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In this study, we investigate the effect of BDNF, bound to polyelectrolyte complex nanoparticles (PEC-NP), on MLO-Y4 in monoculture and in a coculture with DRG-neurons. We showed a highly significant influence of BDNF without nanoparticles on the proliferation of MLO-Y4 in mono- and coculture, measured by BrdU proliferation assay. PEC-NP seem to show biocompatibility on MLO-Y4 and DRG-neurons. BDNF expression was shown for the first time in an osteocyte-like cell line.

Introduction Although the variety of drugs for treating osteoporosis is increasing, there is still need for improvement of the treatment of osteoporotic fractures. Brain-derived neurotrophic factor (BDNF), known as a neurotrophin to support neuronal development [1], was found to play a role in fracture healing [2]. When added exogenously, BDNF promoted fracture healing after osteotomy of non-osteoporotic bone [3]. One option to apply drugs directly to the required location in fractured bone, is to bind them to bone substitute materials via polyelectrolyte complex-nanoparticles (PEC-NP) [4]. This study was performed to investigate the effect of BDNF and PEC-NP on osteocytes. DRG neurons were used as an endogenous source of BDNF [5].

Method and materials A murine osteocyte-like cell line, called MLO-Y4 and murine DRG-neurons, isolated previously, were cultured as monocultures and as a coculture. Cells were observed using a light-microscope after adding either BDNF (40 ng/mL), PEC-NP or BDNF-functionalised PEC-NP. Proliferation rate of MLO-Y4 was measured by a BrdU proliferation assay after 8, 24 and 32 hours (h) and mRNA expression by real-time reverse transcriptase polymerase chain reaction (real-time RT-PCR).

Results and discussion BDNF had a highly significant positive effect on the proliferation rate of MLO-Y4 in monoculture and in coculture with DRG-neurons after 24 h of incubation time (Figure 1). In contrast, neither BDNF-functionalised PEC-NP nor pure PEC-NP or DRG-neurons showed any significant influence. We suppose that the BDNF release rate from PEC-NP was too low. Furthermore, there was no significant difference in gene expression of receptor activator of nuclear factor-κ B ligand (RANKL) and osteoprotegerin (OPG) after 24 h of incubation time with BDNF (40 ng/mL) This result

suggests that BDNF does not affect bone remodelling or proliferation through induction or inhibition of these key proteins. In this study, BDNF expression was detected in MLO-Y4 for the first time, TrkB expression, however, was not detectable, although TrkB expression was found in previous studies in osteocytes [3].

Conclusions and future work Our results showed that BDNF stimulated the proliferation of MLO-Y4. Additionally, the PEC-NP showed a good biocompatibility. Thus, we suppose that PEC-NP are a suitable drug-delivery system and BDNF a promising medication for bone pathologies..

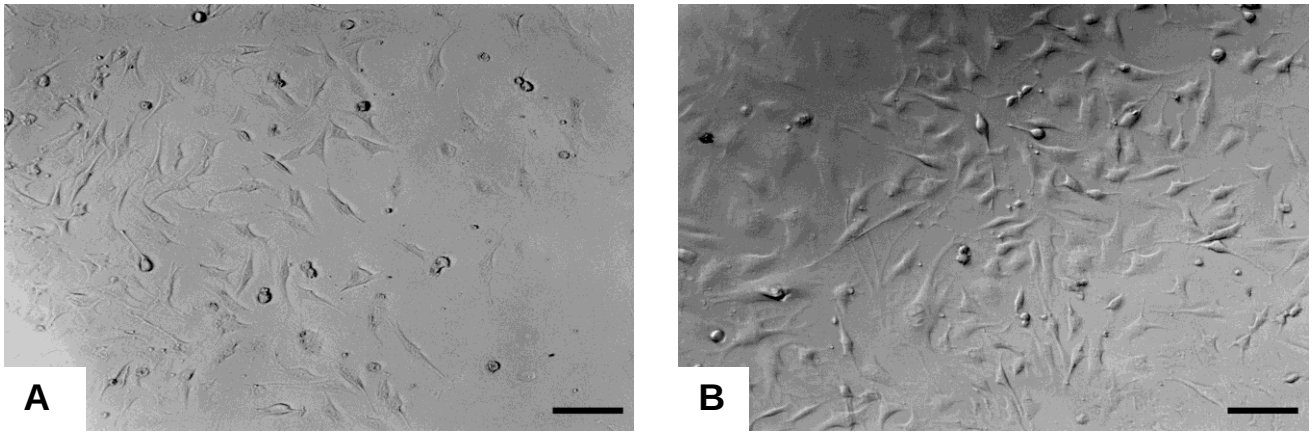

Figure 1: MLO-Y4 monoculture. (A) Control and (B) after addition of BDNF after 24 hours (h) of incubation time. The number of cells was increased in B. Scale bar 100 µm

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Electrical charge in bone – a mechanism for bone adaptation

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The overall goal of our work is to understand the role that electrical charge plays in bone adaptation. We are exploring electrical stimulation from three approaches: 1) We characterized mechanically induced electrical potentials in *ex vivo* cortical bone samples. 2) We electrically stimulated the knee in ovariectomized rats *in vivo* and found partial mitigation of bone loss. 3) We are stimulating bone cells *in vitro* to understand the effects of electrical potential at the cellular level.

Introduction The knowledge that electrical charge is induced in bone by mechanical loading is not new [1, 2], but it is poorly understood, and the relationship between mechanical loading and electrical charge is not well characterized. Though electrical charge is thought to play a role in bone adaptation, current clinical applications of electrical stimulation are focussed primarily on improving fracture repair [3] (an endochondral process) but not at bone remodelling processes associated with bone adaptation. Our overall goal is to determine if wearable electrical stimulation (e.g., by capacitive coupling) can be used to enhance bone formation or prevent bone loss.

Method and materials All protocols were approved by the institutional Animal Research Ethics Board in accordance with guidelines from the Canadian Council on Animal Care. Our research on electrical charge in bone has followed three experimental approaches. In the first experiment, we performed mechanical bending tests on *ex vivo* samples of bovine cortical bone machined into rectangular beams (50 x 20 x 3mm). We measured strain and surface electrical charge in response to increasing load magnitude and loading rate. Exponential decay curves were fit to two-term exponential functions to characterize the temporal mechanical and electrical responses. In the second experiment, we electrically stimulated (15 Hz AC, 250 μA amplitude) the right femur of ovariectomized (OVX) rats and rats that had undergone an OVX sham surgery as controls. We stimulated the right knee for 1 hr per day for six weeks (5 days / wk). Measures of bone properties in the right and left femurs and tibias were characterized using 3D microCT scans. In the third experimental approach, we are developing a protocol to electrically stimulate bone cells. In our initial work, we have been working to ensure that electrical charge in the cell media does not degrade over time or cause changes in the cell media that affect the cell environment. Our goal is to stimulate osteocyte-like cells in co-culture with osteoblast-like cells to determine how electrical stimulation affects bone cell signalling.

Results and discussion Results of the *ex vivo* loading tests showed stress generated electrical potentials in cortical bone had greater magnitude with larger applied load magnitude and decayed more rapidly with higher displacement rates. These repeatable stress-generated electrical potentials diminished and became inconsistent when the samples were dried, suggesting that they were caused by ionic fluid-flow in the bone rather than piezoelectrical effects. The *in vivo* electrical stimulation of OVX rat knees caused a small but significant mitigation of bone loss in the stimulated (right) femur compared to the non-stimulated (left) femur, but there was no significant effect on the tibia. The OVX rat is a model of human post-menopausal osteoporosis and the results suggest that a wearable capacitive coupling device could help to prevent bone loss. The *in vitro* work to explore electrical stimulation of bone cells in culture is work in progress. We will use the relationship that we characterized between mechanical loading and electrical stimulation to guide how we stimulate the cells *in vitro*.

Conclusions and future work The characterization between mechanical loading and electrical charge supports that mechanically induced electrical potentials in cortical bone are caused by fluid flow. The mitigation of bone loss in the femurs of OVX rats suggests that electrical stimulation could be used clinically to prevent bone loss. We have more work to do with the cell culture model and future studies to understand the optimal parameters for electrical stimulation of bone.

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Composite nanofibrous architectures: towards electroactive scaffolds for tissue engineering

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Here, research on composite materials based on electrospun fibres is presented. The final goal is to create electroactive scaffolds that can recreate natural electromechanical conditions *in vitro*.

Introduction Conventional materials for tissue engineering fail to provide the optimal environment for tissue regeneration, mainly due to lack of bioactivity and ability to respond to the external environment. Advanced and more effective materials are therefore required to create medical devices to facilitate tissue growth and improve patient quality of life.

This research focuses on the development of scaffolds based on composite nanofibres that can actively stimulate tissue regeneration [1-3]. The scaffolds possess a hierarchical structure obtained by combining micro- and nanofabrication approaches for biomaterials: biomimetic layers of nanofibres produced by electrospinning to promote cell attachment and proliferation; porous 3D structures to provide mechanical support.

Method and materials The electrospinning technique (extrusion of polymeric nanofibres by the application of an electric

field) is used to produce scaffolds with antibacterial or piezoelectric properties. Polymers of interest are polylactic acid (PLA), polycaprolactone (PCL), polyvinylidene fluoride (PVDF) and zein. Active materials, such as antibacterial agents or piezoelectric nanoparticles, are added to the polymer matrix to provide functionalities. The electrospinning process is conducted by loading a plastic syringe with the polymeric solutions containing the active materials. The syringe is connected to a syringe pump that works at a flow rate of 0.7-2.0 ml/hour. A 23G needle is connected to the syringe and clamped to the positive electrode of a high voltage power supply, generating a voltage in the range of 10-18 kV. The ground electrode is connected to an aluminium collector (air gap distance of 12-15 cm). All experiments are conducted in normal environmental conditions. The morphology of the samples prepared was analysed by Field Emission Gun Scanning Electron Microscopy (FEGSEM). Prior to observation, the samples are stuck on aluminium stubs by carbon adhesive tapes and then coated using a palladium/gold sputter coater for 90 s to produce a conductive surface.

Results and discussion Polymeric fibres incorporating antibacterial nanoparticles, such as ZnO, or piezoelectric materials, such as $BaTiO_3$, are produced by electrospinning.

For example, ZnO nanoparticles have been generated in zein/polyethyleneimine fibres [3]. Zein is found in the endosperm of corn and belongs to the group of storage proteins

known as prolamins. This protein is a "generally recognized as safe" (GRAS) excipient by the United States Food and Drug Administration (FDA) and for tissue engineering and drug delivery applications. The mats containing ZnO nanoparticles exhibit antibacterial properties, manifest by the inhibition of the growth of E. coli colonies.

In another study, fibres of fluorine-capped PCL (synthesised in the laboratory) have been manufactured with a high level of surface porosity using an optimised concentration of solvent [4]. The porous electrospun mats consistently show absorption values of therapeutic essential oils up to three times higher than those of commercial PCL samples, as well as increased hydrophobicity. The results of this work suggest that PCL fibres with desired porosity and functionalities can be successfully produced without the need of additional post-processing.

Conclusions and future work In conclusion, the research here presented aims to develop novel micro- and nanostructured materials with controlled absorption/delivery of bioactive agents and tuneable porosity. The final applications include scaffolds for tissue engineering and devices for controlled drug delivery.

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Slippery surfaces for anti-fouling application

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An easy 'one-pot' synthesis of polydimethylsiloxane (PDMS) surfaces with tethered PDMS chains shows potential bacterial anti-fouling properties. In comparison with coatings of similar chemistry but without tethered chains, these surfaces offer a better resistance against fouling of *E. Coli*. Though similar effect can be achieved by traditional polymer brushes, the ease of fabrication of this material represents an advantage for applications requiring a large coating area.

The undesirable accumulation of material, biologic or not, is a common problem in most applications where fluids are in contact with surfaces; this includes applications such as medical devices, industrial pipelines and marine shipping. This implies a significant economic and environmental impact, particularly in shipping where the increasing drag force generated by the fouling from marine species attached to the hulls of the ships demands increasing fuel consumption which in turn generates higher emissions. Recently, Zhang et al. [1] proposed an easy 'one-pot' synthesis, where divinyl- terminated (^{Vi}PDMS^{Vi}) and monovinyl-terminated (^{Vi}PDMS) polydimethylsiloxane are crosslinked with polymethylhydrosiloxane (PMHS) via hydrosilylation reaction producing a crosslinked PDMS matrix with tethered PDMS molecules. In this material the liquid-like PDMS tethered molecules are covalently bond to the crosslinked PDMS matrix. Based on this methodology we prepared coatings which were exposed to an E. coli solution overnight at 37 °C. The surfaces with tethered chains demonstrated superior resistance to bacterial fouling in comparison to the surfaces with same chemistry but without tethered chains.

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Treatment alternatives for secondary infections after pilon fractures

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Introduction Fractures involving the joint surfaces require increased effort for reconstruction in order not to induce an arthrosis. In most injuries the soft tissue is additionally prolonged damaged, especially in open injury. At the extremities, the joints with low soft tissue coverage are, particularly at risk. This also increases the risk of necrosis of the affected tissue and infection of deeper structures. However pilon fractures represent a particular challenge for surgeons and therapists. The number of these fractures at an advanced age has been increasing for years. In addition to the local problematic situation, generalized concomitant diseases such as diabetes mellitus must be considered as an additional source of danger for the risk of complications.

Method and materials We analysed pilon fractures in our clinic of the last 5 years. 5 patients had an additional extended soft tissue trauma leading to complications. All patients required several operations to treat the osteomyelitis and to restore the skin defect plastically. The bone defect could be treated after the skin had been repaired.

Results and discussion Pilon fractures with an additional soft tissue trauma show an increase risk of osteomyelitis in problematic soft tissue conditions. Open fractures did not show a significantly higher rate of osteomyelitis compared to secondary necrosis. The extent of soft tissue damage was crucial for long-term healing. Patients seem to benefit more from short lying times and avoidance of hospitalization than from preservation of the limb with long-term limitations and reduced leg resilience. Differential therapy options are discussed based on exemplary progressions.

Conclusions and future work Intact skin is a basic prerequisite for the treatment of osteomyelitis and thus determines the long-term preservation of the limb. Which procedure has the greatest gain in quality of life for patients can only be decided based on individual considerations. The results of long-term studies on quality of life, independence, handicap, and social acceptance have to be taken into account when making recommendations for or against therapy. The collection and evaluation of relevant data link gait analysis are reserved for (multicentre -) studies in the future.

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Development and first evaluation of a biomimetic rasping tool: An opportunity for facilitated hip surgery?

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Introduction Hip surgery is among the most common inpatient surgeries [1]. In order to introduce and anchor the implant in the femur, an implant fitting cavity is created, mostly manually, utilizing a set of differently sized rasps [2, 3], which can be time consuming. A simple tool that creates cavities in final size fast and reproducible in an easy to handle process without inflicting high forces to the patient would be desirable. Due to the cavity's shape, rotatory methods (drilling) are not applicable. The Fraunhofer Institute for Manufacturing Engineering and Automation (IPA) is working on tools designated for the creation of non-round holes in various substrates, possibly also suitable for the creation of cavities in bone. In the development of such a tool a biomimetic approach was chosen, which is presented together with first evaluation tests in the following sections.

Method and materials Ovipositors of different Hymenoptera were examined using a reflected-light microscope (Expert-Serie, Müller Germany, Germany). Pictures were taken, lengths and heights of the ovipositor's structures as well as distances in between them were analysed (Fig. 1). Available videos of the rasping process of a wood wasp were investigated in order to extract upstroke distances and time depending sequences of the ovipositor's single parts movement. The determined sequence as well as geometric ratios were abstracted in a technical handheld demonstrator (Fig. 2), consisting of a gear and three rasping elements.

The demonstrator's ability to create holes in different substrates (drywall, Medium-density

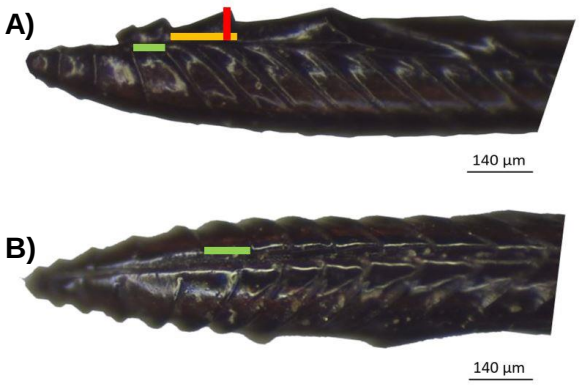


Figure 1: Ovipositor tip of Xeris spectrum. A) Lateral view with length (orange) and height (red) of structures on the ventral part of the Ovipositor and the lateral distance (green) between two structures on the dorsal part of the Ovipositor. B) Dorsal view with dorsal distance (green) between two structures on the dorsal part of the Ovipositor.

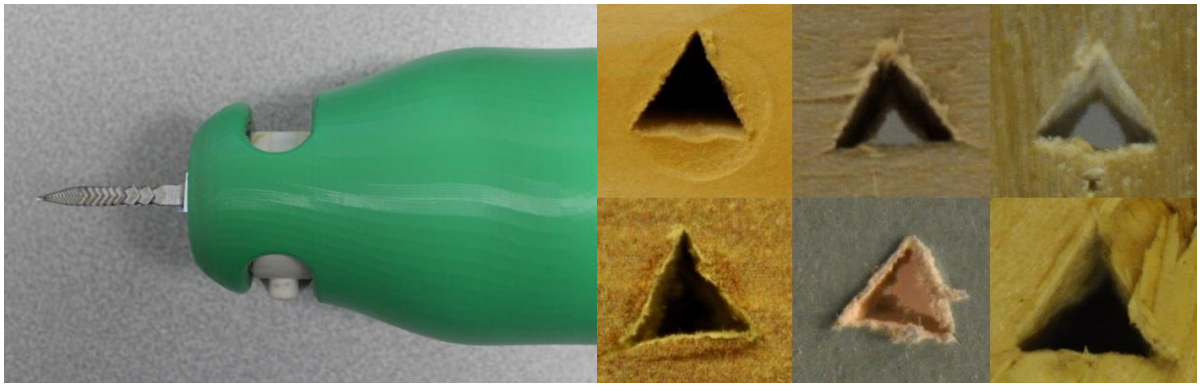
fibreboard (MDF), spruce, pressboard with mixed woods, pine plywood, birch multiplex plate) was evaluated. Also, the perceived effort to create those holes in different substrates as well as in prebored substrates (completely drilled through the substrate using a regular drilling bit for wood with a diameter of 5 mm) was qualitatively rated by the experimenter in the categories very easy, easy, moderately demanding, demanding, exhausting.

Results and discussion Our experiments could show the feasibility to create holes with the demonstrator (Fig. 2) in all tested scenarios. The perceived effort for each substrate (prebored and bulk material) is shown in table 1. Not surprisingly, the results show facilitated cavity creation in all prebored substrates. Since all tested substrates in these first trials showed not only different mechanical properties but also different geometries, performance in those substrates is not yet comparable. Nevertheless, drilling in all prebored substrates was rated very easy, easy, or moderately demanding.

Table 1: Perceived effort to create a non-round hole in different substrates with the developed demonstrator. The substrate materials were differently sized. Tests were carried out in bulk material and in material with prebored holes.

Substrate	Width [mm]	Prebored (ø5 mm)	Bulk Material
Drywall	12	Very Easy	Easy
Molding (MDF)	10-15	Very Easy	Moderately Demanding
Square Timber (Spruce)	44	Moderately Demanding	Demanding
Press Board (Mixed)	12	Easy	Moderately Demanding
Plywood (Pine)	9	Easy	Demanding
Multiplex (Birch)	15	Moderately Demanding	Demanding

Figure 2: Demonstrator (left) and examples of holes rasped into different substrates (I) spruce, II) birch Multiplex plate III) pine plywood plate, IV) MDF molding, V) drywall, VI) press board) with the demonstrator.



Conclusions and future work A better understanding of the drilling process of Hymenoptera led to the realization of a handheld biomimetic demonstrator that allows for the creation of non-round cavities in different construction materials. Perceived easiness of hole-creation in prebored substrates is promising for future developments of tools for industry applications and in surgery. Next steps will therefore not only focus on enhanced performance of the technique in construction materials but also in biological tissues and especially bone. As a first proof of concept for surgery applications, we will therefore utilize the technique to create femoral stem shaped cavities in cadaver

femurs. If successful, a new tool for easier cavity creation during hip surgery will be developed.

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Interpretation of 'stiffness' in biological networks

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It is commonly argued that the existence of a continuous force chain in random networks ensures that the mode of network deformation is affine. This assumption has formed the basis of several analytical models of biological short fibre networks such as the actin microstructure in cytosketelon, for example. The affine assumption is also reasonably valid in the case of engineering composites with long fibres such as a quasi-isotropic layup of carbon fibre/epoxy laminae which do not delaminate. But is the deformation of all long fibre networks (and their composites) always affine?

We show via a systematic numerical study, the transition from a structural non-affine response to a material affine response, as the constraint between the overlapping fibres in a domain is varied. It is shown that the addition of a weak matrix to a network of disconnected fibres mimics the constraint between fibres that ultimately provides the network its high stiffness. This synergy between soft matrix and stiff fibres has deep implications on the response of biological tissue networks (such as collagen in water), as well as in the design of engineering composites such as CNT/epoxy and carbon fibre/epoxy systems.

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Persistence-based kernel methods for topological data analysis

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A major role for the performance of machine learning models is a suitable feature representation which can reduce the data complexity and characterize the intrinsic of the data. Persistent homology as the main tool of Topological Data Analysis strikes a balance between data simplification and preservation of the underlying information. The goal of this research is to combine persistent homology with kernel methods from machine learning by proposing new kernels as well as examine existing kernels in this setting.

Topological Data Analysis (TDA) has emerged recently [1] and introduced topological and geometric methods to data science to infer relevant features and capture the shape of data in a multi-scale way. Most tools are based on persistence homology introduced in [2]. Using these methods, successful applications of TDA can be found in many different scientific areas including computational biology [3] and brain science [4] among others. In this research techniques from Machine learning, namely kernels [5], are combined with persistent homology for the sake of analysing certain data sets as, for example, MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight) mass spectrometry [6].

A tool in algebraic topology for the analysis of the connectivity of spaces is homology. This algebraic invariant captures some of the information of the space, but it is scale dependent. Persistent homology, on the other hand, uses a filtration procedure to encode the topology of a space at all scales simultaneously. Its main output is the persistence diagram. To apply machine learning techniques to these persistence diagrams the two main approaches are an explicit vector representation for the persistence diagrams by, for example, computing and sampling functions constructed from these diagrams like persistence landscape [7], and an implicit representation using kernels such as the Persistence Weighted Gaussian kernel [8].

Following the second approach, challenges for the construction of kernels between persistence diagrams are presented as well as their desired properties and recent proposed kernels are discussed. In addition to the theoretical analysis of the kernels, they are evaluated with support vector machines on several datasets. One of the datasets is from MALDI-TOF mass spectrometry and pose particular challenging to be used for persistent homology in the first place.

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Opportunities for the Development of Additive Manufactured Parts in Health and Trauma Applications

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The research network at McMaster University has been focusing on the development of advanced manufacturing for health care application in the past years. Our past investigations showed that medical parts made from additive manufacturing are attractive in health and trauma applications where devices that have complex geometries, have tunable material properties, and that is patient specific are particularly desirable. In this study, we will first discuss our recent efforts to produce (i) surgical implants as well as (ii) brain-protective sports helmets using additive manufacturing. We will also discuss future research directions in developing functionally grade materials/composites for health and trauma applications.

Introduction As an emerging technology, additive manufacturing is a particularly attractive fabrication process for health care applications. Compare to traditional casted materials, 3D printed metal parts can have much more complicated geometries. This additional degree of freedom allows us to create (i) rapid prototype parts, and (ii) structures with tunable multifunctional properties [1-4]. In health care and trauma applications, devices and implants often need to be patient-specific; in these low quantity manufacturing cases, additive manufactured parts can be more economical than those made from traditional methods (e.g. casting, CNC machined). In surgical applications, the internal porosity/architecture of the implant can be designed specifically to withstand the unique loading condition the patient; furthermore, the surface roughness of 3D printed implants can also be modified by changing 3D printing parameters to promote bone growth. Meanwhile, in trauma application such as the design of a brain-protective helmet, the internal structure of the helmet can be rapidly prototyped and redesign so that they can have higher crushability that EPS foams in both out-of-plane and oblique loading conditions. The objective of the current study is to explore to what degree can we utilize additive manufacturing to manipulate structural complexity (surface roughness, strut thickness gradient, and cell architectures) to enhance the performance of implants and helmets.

Method and materials Metal bio-scaffolds and polymer crushable materials were fabricated using a 3D printing method, commonly known as selective laser melting (SLM). Both metal and polymer parts were fabricated using commercially available powders provided by the EOS manufacture. The mechanical parts were then manufactured using industrial EOS 200series 3D printer using EOS certified printing specifications.

In terms of the 3D printed scaffolds, different cellular structures such as BBC lattice and gyroids structures were designed with different surface roughness and strut thickness gradient. The porosity and the surface roughness of the 3D printed parts were inspected using CT-tomography. Mechanical testing was performed onto the cellular scaffolds. Furthermore, biological cells were also introduced to growth inside select scaffolds to determine their osteoblast adhesion.

In terms of the 3D printed helmet, the objective is to determine the effect an architectural mis-shaped defect on the energy absorption ability of the cellular materials. To this end, different types of cellular structure with different distributions cell mis-shape defects were compared in terms of their crushability. All three honeycomb designs were then compared under in-plane, out-of-plane, and inclined compression tests. Finite element simulations were also performed to obtain more insights.

Results and discussion In terms of the 3D printed scaffolds, it was observed that a high level of reduction in compressive stiffness was achieved be introduced 3D printed porosity into the scaffolds. Furthermore, we have successfully demonstrated that SLM can introduce topography and surface roughness that cells are favourable to interact with.

In terms of the 3D printed helmet, it was observed that the misshaped defect can induce a structure stress asymmetry inside the materials. It was determined that depending on its arrangement misshaped cell can provide benefits to energy absorption in cellular materials.

Conclusions and future work We have demonstrated that additive manufacturing has great potential in improving the mechanical properties of various types of parts and device in health care and trauma applications. In future, materials properties heterogeneity may also be introduced into the above parts to further improve their properties by design structure and microstructure at multiple lengthscales.

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New Generation Nano Sensor for Improved Wound Healing

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Introduction Seventy-six million people worldwide suffer from acute and chronic wounds annually due to complications from diabetes (15% of which lead to leg ulcers), obesity and cardiovascular disease. Moreover, there are approximately 312.9 million surgically-induced incisions performed annually around the world [1]. Chronic, hard-to-heal wounds are worryingly increasing in numbers and impose a significant and often underappreciated burden to the individual, the healthcare system and the society as a whole (e.g. 3% of the health budget in most developed countries).

Currently, medical practitioners (predominantly nurses) evaluate wound-status through a visual inspection based on experience (not on data), routinely changing dressings every 2 days, which in more severe cases requires anaesthetic and costly theatre time. 30% of wounds lack an accurate diagnosis due to treatment by non-specialist clinicians and 85% of dressings are changed too early, hampering healing [2]. Thus, a wound dressing equipped with a point-of-care, real-time sensor could significantly optimise and improve wound management and therapy.

Method and materials Together with a sensor development company, an academic institution and a Hospitals Foundation Trust based in the UK, the author is working on a project developing a miniature, cheap and non-invasive graphene-based sensor for detecting the healing state of acute and chronic wounds by monitoring oxygen, moisture and infection-inducing gases in the different healing zones of the wound. Wound healing is highly oxygen-dependent due to the increased energy demand for tissue reparative processes, response to infections and collagen synthesis, and damaged tissue deprived of adequate blood flow has a decreased ability to heal. While moist wounds accelerate healing, too much moisture leads to damaging maceration, while too little results in wound drying out and scaring. Moreover, bacterial infections pose a big threat to wound healing and one of the most prevalent, gas gangrene (made up of hydrogen, carbon dioxide, nitrogen and oxygen), which is hard to detect early, leads to gas build up inside the tissues.

The project is analysing the sensor's high specificity for the target wound-related gas/vapour analytes, sensitivity in the relevant concentration-range and stability overtime. It is also aimed at investigating the wound oxygenation, moisture and infection-inducing gases under different therapeutic wound dressings. The project aims to contribute to cost-effectiveness and improve the quality of life of the affected patients.

Results and discussion While the project is currently underway, it has already evaluated the potential impact of the sensor in the thermal wounds' area – the project's first intended use case. For example, a patient with burns covering 30-40% of body surface area, treated for over 42 days, incurs a wound dressing cost of approximately £3,500 (roughly £84 per day). Currently, the UK's health system primarily relies on the following burn treatment products (estimated for a 10x10cm burn and changed every 2 days): Jelonet primary dressing (10x10cm) = £0.41; BioBrane biosynthetic wound dressing (5x15cm) = £32; DuoDerm hydroactive gel = £10 for a 15g tube; Primafix adhesive tape (20cm) = £4.24. Based on this, the total estimated cost per one routine dressing change on a 10x10cm wound is £46.65 every 2 days, regardless of the level of oxygen, moisture levels and infection gases, amounting to a weekly cost of £163.275 per patient. The nanotech sensor under investigation, costing £5-10 per use, would roughly halve this weekly cost by informing the clinicians to change the dressing only when the target gases are out-of-range.

Conclusions and future work Despite that this work is currently underway, it already demonstrates the significant potential of the sensor for improving the quality of life for patients as they will be better informed about the trajectory of their wound healing process, will not have to be so frequently subjected to unnecessary and painful dressing changes, often requiring costly anaesthetic. With infections, such as gas gangrene, being a major treat to patients' wound healing and life, and the foot ulcers often leading to amputations and untimely death, and in the absence of reliable preventative solutions, the proposed nanotech sensor offers an effective and emphatic solution. Another benefit is that the sensor is planned to be inexpensive (£5-10 per use) to apply in dressings and the aim is to also provide it for use in non-clinical settings.

Bibliography

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Disclosure The author is owner of the consulting business Ameliot which is part of a consortium of organisations developing this New Generation Nano Sensor.

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Detailed programme

Friday, 11 Oct 2019

12.00 pm Midday lunch and lunch meeting (faculty room 311)
at Giessen Medical Faculty
for early arrivals from Toronto, Cambridge, Bremen, Freiburg

From 02.00 pm Hotel check-in at Hotel Kübel possible

From 08.00 pm Evening get-together at the Giessen Old Brewery

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Day 1 - Saturday, 12 Oct 2019

08.00 am Breakfast at Hotel Kübel
Due to a water damage, continental breakfast will be served across the road in **Café Zeitlos**.
Reception can show directions.

From 09.00 am Registration
09.30 am Introductory session (lecture theatre 307/308)

- Bosbach, WA: Workshop Structure
- Heiss, C: *Trends in Modern Trauma Surgery*
- Presas, A: *Vibration Theory*

10.30 am Coffee break

10.45 am Session 1 - Chair: Mele, E (lecture theatre 307/308)

- Roehr, C: *Numerical Design Study for the Development of a Resonance Mechanics Bioreactor for Osteosarcoma Cell Experiments*
- Bosbach, WA: *Vibration energy in bioreactors and bovine models for antibacterial and oncological experiments*
- Presas, A: *A mechanical assembly for experiments of Saos-2 cells under vibration actuation*
- Loy, LT: *The effect of BDNF-functionalised PEC-NP on the vitality and proliferation of an osteocyte-neuron-coculture*

12.30 pm Lunch break & group photo

01.15 pm Session 2 - Chair: Bosbach, WA (lecture theatre 307/308)

- Wohl, G: *Electrical charge in bone – a mechanism for bone adaptation*
- Mele, E: *Composite nanofibrous architectures: towards electroactive scaffolds for tissue engineering*
- Prieto-Lopez, L: *Slippery surfaces for anti-fouling application*
- Biehl, C: *Treatment alternatives for secondary infections after pilon fractures*
- Schiebl, J: *Development and first evaluation of a biomimetic rasping tool: An opportunity for facilitated hip surgery?*

03.15 pm Coffee break

03.30 pm Session 3 - Chair: Wohl, G (lecture theatre 307/308)

- Tankasala, H: *Interpretation of 'stiffness' in biological networks*
- Senge, FJ: *Persistence-based kernel methods for topological data analysis*
- Yu, B: *Opportunities for the Development of Additive Manufactured Parts in Health and Trauma Applications*
- Mieczakowski, A: *New Generation Nano Sensor for Improved Wound Healing*

08.00 pm Dinner party at the Giessen Boat House

Day 2 - Sunday, 13 Oct 2019

08.00 am Breakfast at Hotel Kübel

Due to a water damage, continental breakfast will be served across the road in **Café Zeitlos**.
Reception can show directions.

09.30 am Interactive morning session:

- **Osteosynthesis workshop** (faculty room 244)
  Instructor: Dr Biehl, Mr Otto
- **Workshop on technology transfer into clinical application** (lecture theatre 307/308)
  Instructor: Dr Mieczakowski

	Osteosynthesis workshop (Dr Biehl)	Technology transfer into clinical application (Dr Mieczakowski)
10.00 am – 11.00 am	Group 1	Group 2
11.00 am – 11.30 am	Coffee break	
11.30 am – 12.30 pm	Group 2	Group 1
12.30 pm – 01.00 pm	Evaluation round and award for the winning pair	

01.00 pm Lunch break

From 02.00 pm Departure by shuttle to Frankfurt airport for 5 pm flight connections or departure by train from Giessen train station

Friday, 11 Oct 2019

2020 steering committee and evening get-together

Day 1 - Saturday, 12 Oct 2019 – Introductory session

Day 1 - Saturday, 12 Oct 2019 – Session 1

Day 1 - Saturday, 12 Oct 2019 – Session 2

Day 1 - Saturday, 12 Oct 2019 – Session 3

Day 1 - Saturday, 12 Oct 2019 – Dinner party

Day 2 - Sunday, 13 Oct 2019 – Interactive sessions

2019 Group photo – 12 Oct 2019

2018 Group photo – 17 Nov 2018

Conference venue: Giessen University Medical Faculty

29, Klinikstrasse

Giessen 35390

Germany

Image source: by friendly permission of Landesbetrieb Bau und Immobilien Hessen, Mr Hoffmann on 27 Sept 2018 by email.

Hotel: Hotel Kübel

20, Westanlage

Giessen 35390

Germany

Restaurant 11 Oct 2019: Old Brewery Giessen

30-32, Westanlage

Giessen 35390

Germany

Restaurant 12 Oct 2019: Boat House Giessen

12, Bootshausstraße

Giessen 35390

Germany

Source: www.bing.com/maps, date accessed 27 April 2019

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