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A microfluidic-based toolkit for automated analyses of *C. elegans* nematodes as models for mitochondrial and neurodegenerative human diseases

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The nematode *Caenorhabditis elegans* represents one of the best model organisms for longitudinal analyses, mainly because of its fast life cycle and the ease of its genetic manipulation. Complex biological processes related to human dysfunctions developing throughout years – e.g. neurodegenerative diseases – could be investigated in *C. elegans* within a few days or even hours[1]. Because of its small size (hundreds of microns), however, high-magnification imaging is needed to extract relevant biological information, while microtechnology-based solutions for gentle and precise worm manipulation are becoming highly desirable tools in the field[2].
Here we present a toolkit of microfluidic solutions tailored for the automated analysis of *C. elegans* at each precise developmental stage. First, we introduce a device for on-chip nematode culture and creation of synchronized *C. elegans* embryo micro-arrays[3]. Long-term multi-dimensional imaging in this device allows systematic phenotyping studies at single-embryo resolution. Specifically, we demonstrate unprecedented accuracy in the analysis of embryonic developmental variations and successfully investigate the impact of perturbations of the mitochondrial functions on worm's embryogenesis. A second device is then presented, enabling long-term automated studies on *C. elegans* at single-nematode resolution and over its whole embryonic and larval development, up to adulthood. Our third device then features: a microfluidic design tailored for the isolation of larvae at a desired developmental stage and for their successive culture and treatment; a method for reversible worm immobilization, enabling long-term high-resolution imaging of adult worms[4]. We successfully employ this platform to analyze protein aggregation in *C. elegans* models for human neurodegenerative diseases. The device allows precisely localizing protein aggregates within the nematodes' tissues, and monitoring the evolution of single aggregates over consecutive days at sub-cellular level. We believe that this toolkit will open new possibilities in terms of worm handling and analysis, paving the way for more accurate and efficient *C. elegans* research.

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Monitoring the effectiveness of the vacuum bell during the treatment of pectus excavatum: technical innovation

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The vacuum bell (VB) is the only non-invasive treatment for PE, and represents a valid alternative to surgery. So far, no suitable tool was available for assessing objectively the efficiency of the VB. In collaboration with the University of Applied Sciences and Arts of Northwestern Switzerland, we developed a new measurement system, providing the pressure inside the VB and the related elevation of the sternum during the application of the VB. The system is mounted on the conventional VB, and is available for the different sizes of the VB. 67 patients were included in the study. A correlation between the patient's age and the pressure related to the sternal elevation has been proven. As younger the patient, as lower is the pressure to lift the sternum to 1 cm. For the first time, we are enabled to gather pressure related elevation information in a clinical scenario. The relationship between the patient's age, the depth of the pectus, the sternal elevation, and the pressure inside the VB, give an idea of the flexibility of the chest. With this information, we expect to

- Predict the duration of treatment, which is supposed to be function of the age of the patient and its deformity (form, length and deepest point of the PE)
- Set up a therapeutical algorithm
  - in case of an elastic/flexible chest (low pressure): VB as first therapeutical approach
  - in case of a stiff chest (high pressure): VB to soften the chest wall in preparation of the surgery

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Development of a pneumo-tactile vibrissae stimulator for freely behaving rodents

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Bidirectional brain-machine interfacing requires some type of feedback loop into the subject/patient in order to establish a robust transmission channel. As we are currently developing such an interface, we chose to find ways to stimulate the somatosensory system of awake and freely roaming animals. The vibrissae-system of a rat is thought to be close enough to the human haptic system as to serve as a model region. Consequently, the following study reports on the development of a rat-portable, untethered whisker stimulating device by directed puffs of compressed air.
At the core of the device lies a steady source of compressed air, either supplied by a custom designed peristaltic pump (3D printed, PLA, about 15g, pressure about 40000 Pa) controlled by an Arduino Mini Pro (Arduino LCC, Italy) or by a CO2 cartridge (filled with liquid CO2 12g, total weight 35g, Zefal, Germany) thread-connected to the air tube system of the device. CO2 cartridge fit via a custom-designed pressure reducer to a 3D printed air guide. This guiding structure with Arduino controlled valves (5-volt solenoid valve, 5g) is custom-fitted to a circular socket implanted onto the rodents skull [1] extending to adjustable, small diameter pipes (about 2mm inner diameter) running along the animal's nose center and ending in back-bending arcs pointing towards the whisker aimed at. Power for the whole device is supplied by two 3-volt button cells connected in series (CR2025). It is currently remote controlled by a commercial IR and the device is fixed on a body harness for rodents.
Bilateral air puffs are produced with a pulse width of 500 ms, with an air pressure of 40000 Pa. Frontends of working tubes can be exchanged to adjust for wider or narrower target regions on the rat's whisker area.
Experimental validation with preceding extensive habituation of animals to carry the device on the harness is under way and results will be presented.

[1] Pinnell R C, Almajidy R K, Hofmann U G: Versatile 3D-Printed Headstage Implant for Group Housing of Rodents. Journal of Neuroscience Methods 2015.

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Microwave evaluation of prostate tissue from transurethral resection

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Prostate tissue obtained by transurethral resection is evaluated using two different microwave methods in the frequency range of 1 to 10GHz. We developed a coplanar waveguide sensor for measuring the spectral transmission and reflection characteristics depending on the dielectric properties of the incorporated prostate tissue. Furthermore an open ended coaxial probe is applied for surficial analysis of resectate tissue and complete prostate organ. The prostate tissue samples are measured within a few minutes after being extracted to avoid changes in the dielectric properties due to drying or other decomposition effects. The microwave results are compared with histologic examination results. Both measurement techniques are evaluated in matters of their ability to differentiate between levels of tissue degeneration (inflammation, neoplasia). The dielectric tissue properties in terms of the complex relative permittivity are derived by simulation calculations and probe calibration using reference fluids. The prospect of this work is an apparatus for fast peri-operative characterisation of malign and benign prostate tissue.

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CTCelect: fully automated singularization of circulating tumor cells from human blood for personalized cancer immunotherapy

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Liquid Biopsy is expected to be a future standard in cancer diagnostics and patient monitoring. Currently three groups of blood based biomarkers are intensively investigated to understand their prognostic value and potential for personalized medicine: (1) circulating tumor cells (CTCs), (2) cancer cell derived exosomes, and (3) cell-free DNA.
CTCelect is fully automated process for enrichment, detection and isolation of single CTCs. It combines large volume liquid handling and an advanced microfluidic disposable in one platform. The process starts directly from 7.5 mL of human whole blood in a standard tube and ultimately delivers single CTCs in wells of a standard microtiter plate.
The core steps of the fully automated process are: (1) Immunomagnetic enrichment in a pipetting station (e.g. based on EpCAM). (2) CTC labelling using a secondary cancer cell specific antibody. (3) Transfer of the pre-enriched suspension to a disposable microfluidic cartridge. (4) Detection and counting of CTCs with a miniaturized flow cytometry module. (4) Selective dispensing of CTCs directly into wells of a standard microtiter plate. This comprehensive process is currently unique in the field of automated Liquid Biopsy systems and enables downstream single cell analysis by next generation sequencing and/or (reverse transcriptase) quantative PCR.
The entire process has been extensively tested with human blood spiked with 20 model cells (MCF7) and yields a cell recovery of 70% on a regular basis. The probability for finding one background lymphocyte per well is below 10%.
The talk will introduce into system strategy and design, will describe new solutions found to overcome crucial technological hurdles, and will present experiential results gained on human blood.

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Modular measuring systems for individual treatment and care of dementia patients (PYRAMID)

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PYRAMID addresses consequently the holistic development of a miniaturized, modular, extendable measurement systems which allow both personnel identification, monitoring of medical parameters and a continuous interpretation of measured results of various functional parameters. The collection and compilation of this occurring, complex data and their interpretation on the basis of clinical pathways and guidelines in dealing with dementia will allow for a high level of acceptance for people with dementia and the caregiver. These measuring systems should not cause a foreign body sensation. This will minimize the risk of immediate removal of the measurement system and the actual measurement procedure for dementia related parameters is not perceived. Possible solutions already exist through use of measurement on the skin, in which the measuring system is very light and thin, and adheres to the body surface of the patient only due to adhesive forces. This offers to the greatest possible extent the requirement for "imperceptible" sensors. Furthermore, it can be placed e.g., on the patient´s back as an unobtrusive patch, making it "difficult to remove" simultaneously not interfering with the patient in his comfort. Possible metrics like temperature, electrophysiological data and increased acceleration after a fall could be detected. From the perspective of the health care personnel following challenges have been identified as essential: 1.Easy identification of the patient prior to evaluation of the measured values ("ID"), 2. Automated measurement of the most important health data, such as blood pressure, heart rate, hydration, food intake and excretion, sweat, blood sugar, pressure load in bedridden patients, drug delivery, etc. ("automation"), 3. Electronic data consolidation and evaluation of complex medical data in information system documentation ("Automatic data transfer and processing"), 4. Information about significant deviations of measurement data and adjustment of the existing knowledge (guidelines, clinical pathways) ("ICU management")