OrChESTRA

International Workshop on Emerging Organ-on-Chip Technologies

Thursday, June 27
Hybrid (in-person & online)
Venue: ICMS, Ceres 0.31, TU Eindhoven

Contents

OrChESTRA

Timetable June 27 - Morning

9:00	**Arrival and coffee**		
9:20	**Welcome & Opening remarks**		
9:30	IS	**Jaap M.J. den Toonder** Microsystems, TU/e	*"Microfluidic technology enables lumen-based Organ-on-a-Chip"*
10:00	Short talks 1	Guillem Monso	*"Brain-on-chip for AI Computing"*
		Oksana Savchak	*"Exploring digital microfluidics platforms for biomedical research"*
		Ali Can Atik	*"Modelling of Villi Differentiation in a Gut-on-a-Chip Platform Integrated with Interdigitated TEER Sensor"*
10:30	IS	**H. Cumhur Tekin** Izmir Institute of Technology	*"Magnetic Levitation for 3D Cell Culture in Miniaturized Platforms"*
11:00	**Coffee**		
11:30	IS	**Ender Yildirim** METU MEMS, Ankara, Turkey	*"Capillary pressure barriers for spatial confinement in organ-on-a-chip devices and their fabrication"*
12:00	Short talks 2	Ana Carina Baeta Manjua	*"Designing an electromagnetic microchip for cardiovascular studies"*
		Gülden Akçay	*"Brain-on-Chip: A New Approach for Studying Brain Microenvironment"*
12:20	**Lunch**		

OrChESTRA

Timetable June 27 - Afternoon

13:30	IS	**Burcu Gumuscu** Biomedical Engineering, TU/e	*"Exploring the Potential of Microfluidics for Automating Cell Experiments"*
14:00	Short talks 3	Seren Kecili	*"Magnetic levitation-based formation and dynamic rotation of 3D clusters of microspheres and HUVEC cells in a microfluidic chip"*
		Mohammad JouyBar	*"Tubular microchannels influence endothelial orientation: modeling cancer metastasis on a chip"*
		Meltem Okan Aydin	*"Synthetic Receptors: Harnessing Molecularly Imprinted Polymers for Advanced Sensing Platforms"*
14:30	IS	**Andries van der Meer** Twente University, Enschede	*"Organs-on-Chips: From Platform Technology to Applications in Drug Development"*
15:00	**Coffee**		
15:30	IS	**Haluk Külah** METU MEMS, Ankara, Turkey	*"A Fully Implantable Artificial Ear"*
16:00	Short talks 4	Jia-Jun Yeh	*"In-line biocompatible micropumping chip module for a standardized and modular organ-on-chip platform"*
		Pan Zuo	*"3D-Oxygen Gradient Chip for Cancer Cell Migration Research"*
16:20	IS	**Ozlem Yesil Celiktas** Ege University, Izmir, Turkey	*"The promise of engineered multicellular systems-on-chip"*
16:50	**Drinks and networking**		
18:00	**Dinner in town**		

List of Abstracts

“Microfluidic technology enables lumen-based Organ-on-a-Chip”

Jaap M.J. den Toonder IS

Microsystems, Department of Mechanical Engineering, TU Eindhoven

Organ-on-a-Chip (OoC) is a game-changing technology in which human cells are cultured in microfluidic chips simulating and predicting the response of healthy and diseased human tissues. In this lecture, after a general overview on OoC, I will focus on our new technology based on 3D sugar printing, which enables to create tubular structures with circular cross sections down to small scales. I will discuss the benefit of such tubular structures over usual rectangular channels that are present in conventional OoC devices, in terms of physiological representation. I will demonstrate applications of the technology to emulate blood vessels, nephrons, and cancer metastasis. Finally, I will touch upon the topic of upscaling OoC towards adoption.

“Brain-on-chip for AI Computing”

Guillem Monso Short talks session 1

Microsystems, Department of Mechanical Engineering, TU Eindhoven

Standard Machine Learning (ML) architectures have extremely high energy requirements, are prone to biases, high noise sensitivity and struggle to learn and adapt in real time. As an alternative, are emerging new models based on Active Inference, algorithms that mimic some of the information processing capabilities of the brain. However, they still require high amounts of computing power compared to it, which consumes as little as a 20W light-bulb. Although, despite of its many advantages, the brain has very limited programmability compared to ML models.
As a solution, the BayesBrain research project is aiming to create a new computing paradigm by building a hybrid computer that exploits the energy efficiency of biological neural networks, derived from human-induced pluripotent stem-cells, and the programmability of Active Inference agents, by connecting them both through a Micro-Electrode Array neural interface. In this way leveraging their advantages without their disadvantages.

“Exploring digital microfluidics platforms for biomedical research”

Oksana Savchak Short talks session 1

Department of Biomedical Engineering, TU Eindhoven

Digital microfluidics (DMF) platforms have gained significant attention over the past decade for their ability to handle individual droplets, which has enabled the automation of various assays. However, the use of DMF chips for long-term cell studies has been hindered by high humidity conditions in cell-culture incubators, leading to dielectric breakdown, current leakage, and compromised assay accuracy. To address this, a new fabrication process was developed using photoresist as a dielectric material to create a water-impenetrable barrier, and a second dielectric material to prevent degradation and current leakage at high voltages. While single dielectric materials showed either low resistance to high voltages (SU-8 3005, current leakage at $\sim$140V), or high current output at the application voltages (Polyvinylidene fluoride, 100 μA at 70V), combining these materials created a stable dielectric layer with minimal current leakage (<20 nA current) up to 200V. Compared to commercial chips, which showed significant breakdown and current leakage, the demonstrated chips maintained stable performance over 7 days. This work allows for the adaptation of DMF to long-term cell studies, enabling semi-automated on-chip cell cultures for at least 7 days while preserving chip integrity and functionality for subsequent assays up to 60 days.

“Modelling of Villi Differentiation in a Gut-on-a-Chip Platform Integrated with Interdigitated TEER Sensor”

Ali Can Atik Short talks session 1

METU MEMS Center, Ankara, Turkey

We present the numerical modelling of transepithelial electrical resistance (TEER) sensor with interdigitated electrodes (IDEs) for real-time monitoring of the integrity and villi-like differentiation of intestinal epithelial cell monolayer within a microfluidic organ platform. The electrode configuration and placements should ensure a uniform current density field, thereby a uniform sensitivity, across the entire cell layer as possible to prevent misestimation of impedance when cells aggregate or disintegrate in a high-sensitivity area. The finite element method (FEM) analysis has been performed to evaluate the electrical impedance along the cell barrier by utilizing COMSOL Multiphysics® v5.6. In accordance with the reciprocity theorem, the normalized sensitivity is calculated, where the current density distribution from the applied current in the excitation electrodes and from the identical current in the readout electrodes are superimposed over entire cell layer of the cross-sectional area. The IDE structure achieves improved sensitivity without altering the electrode-occupied area, thus allowing for microscopic visualization. Electrical simulations were conducted with varying villi heights (25-175 μm) while maintaining the input TEER at 750 Ωcm^2. The modeled impedance spectra predicts that villi formation increases capacitance due to the larger surface area of the villus epithelium, as an indicator of villi differentiation.

“Magnetic Levitation for 3D Cell Culture in Miniaturized Platforms”

H. Cumhur Tekin IS

Izmir Institute of Technology & METU MEMS Center

Traditional two-dimensional (2D) cell cultures, which consist of monolayers of cells, are commonly used in in vitro studies but fall short in replicating essential cell-cell and cell-extracellular matrix (ECM) interactions. In contrast, three-dimensional (3D) cell cultures more accurately simulate the cellular microenvironment, fostering realistic cell-cell and cell-ECM interactions. Moreover, 3D cultures ensure the uniform distribution of nutrients, gases, and metabolites, which is crucial for proper cellular function. Magnetic forces have emerged as powerful tools for cellular organization, facilitating the formation of spheroids and cell sheets. In 3D cell culture, positive and negative magnetophoresis enable the aggregation of cells within a magnetic field generated by permanent magnets, resulting in the formation of cellular clusters. The principle of magnetic levitation, based on negative magnetophoresis, allows for precise cell manipulation by leveraging differences in cell densities. This enables cells to be levitated at points where the magnetic force balances the buoyancy force. This talk will delve into the innovative use of magnetic levitation techniques in cell culture studies, highlighting their applications and benefits for advancing cellular research without the use of labels.

“Capillary pressure barriers for spatial confinement in organ-on-a-chip devices and their fabrication”

Ender Yıldırım IS

Middle East Technical University, ODTÜ MEMS Center

Organ-on-a-chip systems have been investigated for more than a decade and are becoming more pronounced especially as potential alternatives to animal testing in drug development.
Fundamentally the devices are composed of microfluidic channels to provide perfusion of the culture medium and compartment in which the cells can be cultured. The compartment can either be separated from the perfusion channel via a membrane so that the cells can be directly cultured on the membrane, or via pillars so that the cells suspended in a matrix are confined in the chamber on one side of the pillar. In the second arrangement, the pillars act as capillary pressure barriers preventing overflow of the cell-laden matrix through the perfusion channel. In this work, numerical and experimental investigation of different capillary pressure barriers and their fabrication are presented.

“Designing an electromagnetic microchip for cardiovascular studies”

Ana Carina Baeta Manjua Short talks session 2

Department of Biomedical Engineering, TU Eindhoven

This work reports a novel stimuli-responsive cardiovascular microdevice with electromagnetic properties to mimic the native cardiac microenvironment and investigate cardiovascular tissue regeneration on-chip.
With the increasing incidence and severity of cardiac diseases worldwide, the research in translational regenerative medicine demands for better understanding of the underlying biological mechanisms involved in cardiac tissue remodeling and repair. Our microdevice is the first to combine electrical, mechanical, and chemical inputs into a single microchip. By combining the smart electromagnetic membranes with an external magnetic field, we apply electrostatic forces within the cell culture media, propagating the electrical signals through cell-cell communication to produce synchronous contractions. To achieve this effect, membranes with electromagnetic fibers were developed by coaxial electrospinning. Matured cardiomyocytes showed high affinity to the coaxial fibers after 8 days. The electromagnetic stimulation also showed significant improvement in cell adherence. During the experimental setup, it was possible to observe an increased cell density of living cardiomyocytes in the different regions of the microchip after 24h of electromagnetic stimulation in comparison to the non-stimulated control condition. The initial results of this electroconductive microchip show great promise for the next studies focusing on cardiac tissue remodeling and repair.

“Brain-on-Chip: A New Approach for Studying Brain Microenvironment”

Gülden Akçay Short talks session 2

Microsystems, Department of Mechanical Engineering, TU Eindhoven

The brain, a mechanically delicate organ, is influenced by internal forces such as cerebrovascular blood flow, which can displace brain tissue by tens of micrometers with each heartbeat. Recognizing the importance of mechanical cues in brain function, innovative Brain-on-Chip (BoC) concepts have emerged, offering physiologically relevant settings for neural research. Building on previous studies using hydrogel and PDMS-based chips to mimic brain stiffness and apply mechanical stimuli, we have enhanced our BoC chip by using glass shaped with FEMTOprint technology. This BoC features microfluidic channels in a fused silica glass substrate and a PDMS membrane, allowing precise local actuation and time-dependent mechanical stimuli to brain cells. We cultured neurons from human-induced pluripotent stem cells on the BoC and confirmed neuronal formation and maturation through immunostaining. We then applied mechanical stimulation and observed neuronal activity using calcium live imaging. This advanced BoC model enhances the device’s capabilities and holds significant promise for advancing neuroscience research.

“Exploring the Potential of Microfluidics for Automating Cell Experiments”

Burcu Gumuscu IS

Department of Biomedical Engineering, TU Eindhoven

Digital microfluidics (DMF) chips have garnered increasing attention over the past decade thanks to their ability to address individual droplets. These chips consist of an array of mm-sized electrodes to manipulate liquid-based, individually addressable droplets through applied voltages. Programmed sub-microliter scale droplets performing basic pipetting operations paved the way for the automation of laborious assays. Automated biological assays are an exciting application of DMF, including DNA-based analysis, electroanalysis, and short-term cell culture experiments. However, there are still limitations to be overcome. DMF chips.

“Magnetic levitation-based formation and dynamic rotation of 3D clusters of microspheres and HUVEC cells in a microfluidic chip”

Seren Keçili Short talks session 3

İzmir Institute of Technology, Bioengineering Department

The viability control in cell spheroids is enabled by rotation. In this study, we aimed formation of 3D-clusters by trapping and inducing rotation of microspheres and cells using magnetic levitation in microfluidic chip. For the rotation, a PDMS-based chip was placed on a 3D-printed platform including two axial ring magnets. The microspheres, or HUVEC cells with 100 mM of Gadavist were introduced inside the chip and the washing was applied on them at different flow rates. After introducing, microspheres were collected in the middle of magnets, but at three different locations at stationary. The size of 20-27 µm microspheres under 6 μL/min flow rate, firstly, got closer to magnet and began to rotate. The size of 35-48 µm microspheres got closer to magnet and rotated under both 4 and 6 μL/min flow rates. Also, HUVEC with a concentration of 4×105 cells/mL and a size of 15 $\pm$ 1.9 µm were given to the channel. The clusters maintained their integrity until 20 μL/min flow rate. Our proposed method based on magnetic levitation enables both efficient formation of 3D-clusters of microsphere and cell and inducing rotation for 3D-cluster. This approach holds promise for characterization and viability analysis of spheroids in tissue engineering.

“Tubular microchannels influence endothelial orientation: modeling cancer metastasis on a chip”

Mohammad JouyBar Short talks session 3

Microsystems, Department of Mechanical Engineering, TU Eindhoven

Metastasis is a complex process that remains poorly understood due to limitations of current in-vitro models. Our research models cancer metastasis on a chip, incorporating relevant physiological factors of the tumor microenvironment (TME). We femtosecond laser (FSL) technology to fabricate round luminal channels mimicking microvessels and breast ducts. The FSL beam modifies glass, which is then etched to create precise lumens, enabling the creation of curved structures for chip master-molds. We developed a multi-compartmental chip, “Lumina-Chip,” with two 300 μm lumens connected by 800 μm channel, integrating breast ductal lumen (MCF10a) and blood micro-vessel (HUVECs). Using this model, we could mimic breast cancer cells (MDA-MB-231 and MCF-7) invasion from epithelium and intravasation into the vessel. We compared EC morphology under static, bidirectional, continuous, and pulsatile flow conditions, finding that cell orientation depends on both flow conditions and channel geometry. Morphological tests showed that endothelial cells (ECs) in round luminal channels aligned circumferentially, unlike the random orientation in rectangular cross-section channels. We compared EC morphology under static, bidirectional, continuous, and pulsatile flow conditions, finding that cell orientation depends on both flow conditions and channel geometry. These findings underscore the importance of physiologic morphology in Cancer-on-Chip models.

“Synthetic Receptors: Harnessing Molecularly Imprinted Polymers for Advanced Sensing Platforms”

Meltem Okan Aydın Short talks session 3

METU MEMS Center, Ankara, Turkey

Molecularly imprinted polymers (MIPs) represent a class of synthetic receptors tailored with high specificity and selectivity towards target molecules. These polymers are fabricated through a template-assisted polymerization process, where the template molecule’s shape and functional groups dictate the polymer’s structure and recognition capabilities. The inherent stability and cost-effectiveness of MIPs make them attractive candidates for various sensing platforms. The employment of MIPs is explored across cutting-edge sensor technologies, including surface plasmon resonance (SPR), quartz crystal microbalance (QCM), microcantilever mass sensors, and organ-on-a-chip platforms. In SPR, MIPs are utilized as recognition elements integrated into the sensor’s surface, enabling real-time detection of target analytes based on changes in refractive index. Similarly, in QCM systems, MIP-coated electrodes enhance the sensitivity and specificity of mass detection through frequency shifts caused by analyte binding. Microcantilever mass sensors leverage MIPs to detect minute mass changes, offering high sensitivity suitable for biomolecular detection. Furthermore, the integration of MIPs into organ-on-a-chip platforms facilitates precise molecular recognition within complex biological environments, mimicking physiological conditions for drug testing and disease modeling. Here, the versatile and promising applications of MIPs in advancing sensor technologies are highlighted, underscoring their pivotal role in enhancing detection capabilities across diverse analytical and biomedical fields.

“Organs-on-Chips: From Platform Technology to Applications in Drug Development”

Andries van der Meer IS

University of Twente, Enschede, the Netherlands

Organs-on-chips are advanced tissue culture models that can mimic organ-level functionality in a controlled, dynamic microsystem. They differ from other cell culture models in that they use microenvironment engineering to capture increasingly complex physiological functions. In the past years it has been shown that organs-on-chips can provide accurate and relevant data for preclinical studies, thereby potentially reducing the time and cost of drug development and clinical trials. Moreover, with their unique combination of person-specific human cells and high-level tissue function, organs-on-chips challenge the strong reliance on animal models in life sciences.
In this talk, Prof. Van der Meer of the University of Twente will provide examples of how organs-on-chips can be used to study drugs, taken from his group’s work on vessels-on-chips, heart-on-chip and retina-on-chip. Moreover, he will address the central challenge in the field: how can we upscale, standardize and miniaturize organ-on-chip models in the near future?

“A Fully Implantable Artificial Ear”

Haluk Külah IS

METU MEMS Center, Ankara, Turkey

Today, congenital or acquired hearing loss affects around 5% of the world population and presents a significant impact on people’s social, emotional, and economic wellbeing. Sensorineural impairment is caused by irreversible damage to cochlear hair cells rendering them non-functional/missing. It can be restored using CIs, which are used to bypass the damaged hair cells and directly stimulate the auditory nerve by means of a cochlear electrode to repair hearing in people with severe-to-profound sensorineural hearing loss. However, conventional CIs have major drawbacks In this presentation, a new generation CI system eliminating these drawbacks with ultra-low-power, fully implantable approach will be presented. The presented system is the first fully implantable CI mimicking the natural hearing mechanism. As the most unique feature, the proposed CI benefits eardrum or ossicular vibrations through frequency selective piezoelectric cantilevers to generate the signals for neural stimulation, mimicking the natural hearing mechanism, and extract energy from this vibration. This approach eliminates most of the power hungry electronics, such as microphones and active bandpass filters, while keeping the healthy portions of the middle ear functional. This feature creates a paradigm shift in the operation principle of the conventional CIs.

“In-line biocompatible micropumping chip module for a standardized and modular organ-on-chip platform”

Jia-Jun Yeh Short talks session 4

Microsystems, Department of Mechanical Engineering, TU Eindhoven

Fluid flow in Organ-on-Chip (OoC) devices is usually achieved using external peripheral equipment, which is bulky and not user friendly. Here, we present a novel miniaturized actuation setup for actuating biocompatible magnetic artificial cilia (MAC) integrated in a microfluidic chip module which generates fluid flow within the modular Translational OoC Platform (TOP). We present an additional module containing round cross-section microchannels mimicking breast ducts. Combining these modules on the TOP, the micropumping chip module generates perfusion in the breast duct module.
The actuation of the MAC in the micropumping module induced fluid flow throughout the TOP microfluidic channel network, including the breast duct module, of velocities up to 100 mm/s. Furthermore, the successful cultivation of MCF10A in the circular channel emphasizes the platform’s suitability for cell culture. Compared to other micropumping methods, this solution does not require tubing or electrical connections, which opens a wide range of possibilities for OoC-applications.

“3D-Oxygen Gradient Chip for Cancer Cell Migration Research”

Pan Zuo Short talks session 4

Microsystems, Department of Mechanical Engineering, TU Eindhoven

Most breast cancer related deaths are caused by secondary tumors formed through metastasis to other organs. The first step of metastasis, invasion, is determined to a large extent by properties of the tumor microenvironment, and hypoxia is reported to be an important factor. Usually, an oxygen level below 3% is recognized as hypoxia, and oxygen concentrations in physioxic organs range from 4% to 12%. Previously, we made a 2D-oxygen gradient chip to study the effect of hypoxia on cancer cell migration in 2D culture conditions. Here, we introduce a novel 3D-oxygen gradient chip to study the effect of hypoxia on the migration of cancer cells in 3D. The chip is made of PDMS and can maintain a linear oxygen gradient ranging from 1% to 11% along the chip. Human breast cancer cells (MDA-MB-231, MCF-7, CAMA-1) in Collagen I are seeded in the chips for 48 hours. Then the viability and morphology of the cells are studied. Also, spheroids of the cancer cells can be seeded in Collagen I in the chips to study the collective behavior of the cancer cells.

“The promise of engineered multicellular systems-on-chip”

Ozlem Yesil Celiktas IS

Ege University, Izmir, Turkey & METU MEMS, Ankara, Turkey

Engineered multicellular systems-on-chip represent a transformative advancement in bioengineering, merging the principles of microfabrication and cellular biology to create intricate, functional biological models on microchips. These systems emulate the complex interactions and behaviors of living tissues and organs, providing a high-fidelity platform for biological research, drug discovery, and personalized medicine. By incorporating multiple cell types and mimicking the three-dimensional architecture and microenvironment of native tissues, on-chip platforms offer unprecedented insights into cellular dynamics and tissue physiology. In this talk, a number of use cases developed in our Biomimetic Microsystems Research group will be presented, highlighting the possibilities to accelerate preclinical testing by improving the predictive accuracy of disease models and reducing the reliance on animal testing. Despite the challenges in standardization, scalability, and integration with existing biomedical workflows, the advancements in materials science, microfluidics, and stem cell technology continue to drive the rapid progress of this field. As the research arena evolves, engineered multicellular systems-on-chip are poised to become an indispensable tool in both fundamental research and clinical applications, heralding a new era of precision medicine and innovative therapeutic strategies.

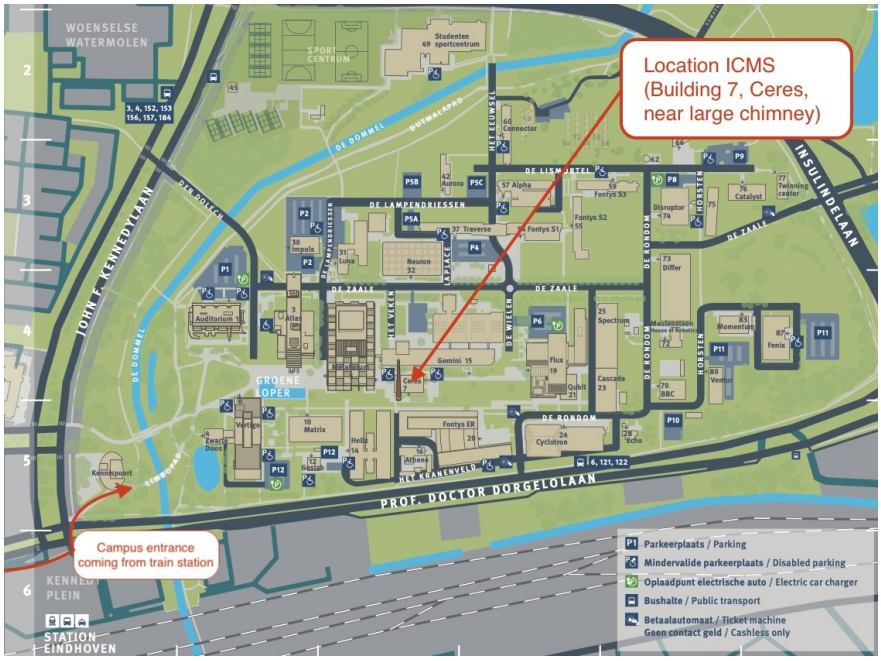
Acknowledgement: Financial support provided by TUBITAK under grant number 123M406

Useful Information

Venue (Talks, Lunch & Dinner)

- **Talks** will be held in the main lecture room of the **Institute for Complex Molecular Systems (ICMS)** at TU Eindhoven. The building name is Ceres, room number is **Ceres 0.31**.
- **Coffee Breaks and Lunches** will be offered in the ICMS common area in the center of the ICMS building.
- The **Conference Dinner** will be held at the "Sizzling" restaurant, Stationsplein 3A, 5611 AB Eindhoven

How to get to TU/e and the ICMS?



Funding

This workshop is organized in the context of the **OrChESTRA consortium**, which brings together European research organisations with synergistic scientific and innovative expertise, establishing a long-term, strategic and productive partnership.

OrChESTRA

Funded by
the European Union

This Project has received funding from the European Union's Horizon Europe Programme under grant agreement nr. 101079473.