DigiTwin4Health 2024

First International Symposium

Digital Twins 4 Healthcare

May 16-17, 2024, Ayia Napa, Cyprus

Enabling a revolution in personalized and precision healthcare

DIGIPREDICT

OPTOMICS

neurotwin®

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101017915 (DIGIPREDICT).

https://digitaltwin4health2024.eu

https://www.digipredict.eu

https://www.linkedin.com/company/digipredict-project

Welcome Message

With the aim to materialize a transformational vision, with extraordinary technological depth, an exquisite collaborative partnership model, and a true commitment to benefit all sectors of society, the DIGIPREDICT FET Proactive Consortium, in collaboration with OPTOMICS and NEUROTWIN FET Proactive and EDITH CSA announces the First International Symposium on Digital Twins in Healthcare.

Digital Twins are making possible a revolution in human model development by leveraging data from multi-omics analyses, medical and imaging data, environmental and life style big data that are continuously updated by a multitude of biosensors at an unprecedented scale. With these complex data sets, first of their kind(s) Human Digital Twins can be personalized and used to prevent and cure each one's own disease(s). The Symposium is calling for contributions across the following scientific, translational and policy-making pillars:

- Emerging technologies for Digital Twins
- Designing and building data and models repositories
- Development, testing and implementation of IT platform architectures combining computational advances, cybersecurity, cloud services and edge infrastructure
- Clinical Translation – Industrial Uptake, including standardization and interoperability
- Ethical considerations and Societal Adoption
- Transformational Vision – Policy Creation and Implementation towards Proactive Healthcare

World-class research and innovation will be presented at topic-oriented sessions and problem-driven workshops. High quality abstracts from enthusiastic students and young scientists will be presented in a specially designed, interactive poster session. As the Symposium's central activity, a specially designated forum with high level European Commission and European Parliament representation will provide the floor for productive dialogue and policy making.

The Symposium envisions contributions to Digital Twins Roadmaps towards exploitation of most technologies to realize, validate and use such personalized Human Digital Twins in advanced clinical setups.

We extend a warm welcome to you for this high-level multidisciplinary event, which we aim to organize systematically as an annual forum for the reporting and exchange of academic and industrial advancements in the field of Digital Twins for Healthcare!

Chairs

ANDREANI D. ODYSSEOS

(EPOS-Iasis, Cyprus)

ADRIAN IONESCU

(EPFL, Switzerland)

Agenda for Day 1

Thursday, May 16, 2024

	Registration
8:30	**Welcome from the Chairs - Opening Remarks.** Andreani Odysseos (EPOS, CY) Adrian Ionescu (EPFL, CH)
9:00	**Session 1: Emerging technologies for Digital Twins** Chair: Andreani Odysseos (EPOS, CY)
9:00	**Cyber-Physical Twins for Predicted Patient Care Pathways: Hope or Hype?** Costas Pitris (KOIOS CoE/UCY)
9:30	**Electrical Methods for Microfluidics, Labs- and Organs on Chips.** Albert van Den Berg (UTWENTE, NL)
10:00	**From Chips to Tissues: Combining in Silico and In Vitro Tools in Skeletal Tissue Engineering.** Liesbet Geris (VHP-i, BE)
10:30	Coffee Break
11:00	**Session 2: Designing and building data and model repositories** Chair: Constantine Dovrolis (CyI, CY)
11:00	**Translational genomics of complex disease.** Eleftheria Zeggini (Helmholtz, DE)
11:30	**From DNA to Digital Twins: Redefining Healthcare through Personal Genomics.** Gökhan Ertaylan (VITO, BE)
12:00	**Computational modeling of physiology for therapeutics development: from the virtual second species to in silico human trial passing by digital OoC.** Raphaëlle Lesage (EsqLab, DE)
12:30	**Standardization gaps for Virtual Human Twins.** Martin Golebiewski (HITS, DE)
13:00	Lunch Break
14:30	**Session 3: Democratized and Sustainable Healthcare with Digital Twins & Poster Highlights** Chair: Ivy Curren (TUM, DE)
14:30	**Digital Twins in Healthcare: a Look into the Future.** Adrian Ionescu (EPFL, CH)
15:00	**Driving the next generation of Digital Twins with wearable, ingestible and implantable sensor.** Wouter Van den Bosch (IMEC, BE)
15:30	**Poster Highlights**
16:00	Coffee break and Interactive poster session.
17:00	**Problem-Driven Panel Discussion** **The Transformational Potential of Digital Twins- Discovering the Building Blocks of Europe's Proactive Healthcare: Policy Creation and Implementation.** Moderator: Adrian Ionescu (EPFL, CH) Introduction Overview: Kyriacos Hatzaras (EC, DG CNECT) Panelists: Ivy Curren (TUM, DE), Liesbet Geris (VHP-I, BE), Koen Kas (HealthSkouts & UGhent, BE), Alexander Meyer (DHZC-Charité, DE), Andreani Odysseos (EPOS, CY), Wouter Van de Bosch (IMEC, BE),
20:30	The Symposium's Dinner & Performance by the University of Cyprus Dancing Group

Agenda for Day 2

Friday, May 17, 2024

8:30	**Session 4: Clinical Translation- Industrial Uptake, including Standardization and Interoperability – Ethical Consideration** Chair: Andrian Ionescu (EPFL, CH)
8:30	**Insight on the ethical considerations of Digital Twins: the OPTOMICS case** Anne Demoisy (RIZOME, BE)
09:00	**Challenges and opportunities for the deployment of Digital Twins in clinical settings** Alex Meyer (Charité, DE)
9:30	**An AI-enhanced digital twin for the prediction of stroke and cerebrovascular events through computational modelling of carotid artery disease** Demitrios Fotiades (FORTH, GR)
10:00	**A Clinician's Approach to the Cardiovascular Digital Twin** Anthony Mathur (QMUL, UK)
10:30	**Special Session: Presentation and Discussion on the Position Paper. Towards an European Roadmap of Digital Twins in Healthcare** Andreani Odysseos (EPOS, CY), Adrian Ionescu (EPFL, CH), Liesbet Geris (VHP-i, BE) Contribution by the Cyprus National Authority of Electronic Health
11:00	Coffee Break
11:30	**Session 5: Combining Computational Advances, Cybersecurity, Cloud Services and Edge Infrastructures** Chair: Constantinos Pattichis (CYENS&UCY - BERC, CY)
11:30	**Information Matters** Vasilis Ntziachristos (TUM, DE)
12:00	**Micro-scale tumor digital twins – the role of tumor microenvironment and how to model it** Igor Balaz (UNS, SR)
12:30	**Explainable Digital Twins** Antonis Kakas (UCY, CY)
13:00	**Diving Deeper into the Future: Harnessing the Synergy of Digital Twins and Triplets** Koen Kas (Healthskouts &UGhent, BE)
13:30	Lunch Break
14:30	**Session 6: Designing and building data and models repositories** Chair: Nataliya Yakymets (EPFL, CH)
14:30	**Continuous measures of cortisol in healthy individuals** Nelly Pitteloud (UNIL, CH)
15:00	**Digital twins for model-driven non-invasive brain stimulation in Alzheimer's Disease** Adrià Galan-Gadea (Neuroelectrics, ES)
15:30	**Personalized Brain Simulation** Petra Ritter (Charité, DE)
16:00	Coffee and Farewell

Abstracts of Invited Papers

Igor Balaz — Micro-scale tumor digital twins – the role of tumor microenvironment and how to model it

Abstract: The complex and ever-changing tumor microenvironment (TME) is a major obstacle to successful cancer treatment. This ecosystem of blood vessels, immune cells, and connective tissue protects tumors by reducing drug efficacy through resistance, immune modulation, and physical barriers. Modeling such multi-scale system is not straightforward. In our laboratory we are combining stochastic and agent-based simulations to develop a tumor model that includes malignant cells, TME components, such as blood vessels, cancer-associated fibroblasts, and tumor-associated macrophages, along with a complex network of microenvironmental interactions mediated by signaling molecules. In this talk we will give an overview of the model, the level of customization and what still needs to be done to call it a digital twin.

Bio: Igor Balaz's primary academic interests combine AI and modeling and analyzing the adaptability of complex biological systems. With his extensive background in leading international projects, funded with over 7.6 million euros, he led the development of a tumor digital twin simulator and modular framework for designing and producing biohybrid machines.

Anne Demoisy — Insight on the ethical considerations of Digital Twins: the OPTOMICS case

Abstract: Our session will highlight some ethical challenges supporting Horizon2020 research projects exploring Digital Twins by focusing on the OPTOMICS project coordinated by TUM, Technical University of Munich. OPTOMICS Digital Twin model combines molecular biomarkers with Raster Scan Optoacoustic Mesoscopy (RSOM), an optoacoustic technology using the skin as a window to the diabetes disease. Key ethical challenges relate to sensitive personal data collection in clinical settings (including omics), building solid study ethical protocols and patients' consent collection, use of Machine Learning methods or critical role of the project Ethics Board.

Bio: Anne Demoisy is a senior Ethics expert, Director of Rhizome s.a. Ethics and Technology, Brussels; she is a member of Ethics Boards in more than 15 European research projects and an evaluator for the European Commission, ERC and EUROSTARS. She is an independent Ethics Advisor in HORIZON funded projects such as OPTOMICS, (coord. TUM, Munich, Germany) developing Digital Twin technology to improve type-2 diabetes healthcare.

Gökhan Ertaylan — From DNA to Digital Twins: Redefining Healthcare through Personal Genomics

Abstract: In this talk, we'll explore the exciting journey towards creating the Human Virtual Human Twin— via digital twins applications from the perspective of personal genomes. We'll begin by examining the key changes needed in our healthcare system to make this future a reality. We'll then discuss the step-by-step integration of personal genomics into healthcare, leading to the development of Digital Twin applications. This progression represents a major leap towards customized healthcare solutions. To conclude, we'll highlight ongoing research enabling personal genomics applications and how they will be gradually integrating across the healthcare digital twins landscape.

Bio: Gökhan Ertaylan is the Principal Investigator of Digital Precision Health Group at the Flemish Institute for Technological Research (VITO). His research focuses on innovating and deploying data-driven, explainable and ethical precision health (Digital Twins) technologies in practice such as *Personal Genome Vaults*, *Pharmacogenomics Passports* and *Individual Reference Intervals*. He is coordinating and partnering in several European (REALM, EDITH, ONCOSCREEN, RAIDO), and National Projects.

Dimitrios I. Fotiadis — An AI-enhanced digital twin for the prediction of stroke and cerebrovascular events through computational modelling of carotid artery disease

Abstract: Patients with carotid artery stenosis (**CAS**) are at risk of chronically reduced cerebral blood flow and recurrent emboli to the brain and accounts for 15 – 20% of strokes. Digital twins can be used for the prediction of stroke caused by carotid artery disease (CAD). Such a digital twin has two pillars: i) Multi-scale and multi-level spatiotemporal mechanistic models which simulate the biological mechanisms and changes of carotid physiology, and ii) explainable AI models utilizing different sources of data. The digital twin acts as a decision support system which provides prediction of CAS evolution and cerebrovascular events.

Bio: Dimitrios I. Fotiadis is a Greek biomedical engineer and professor at the University of Ioannina where he is the director of the Unit of Medical Technology and Intelligent Information Systems. He is an affiliated member of the Foundation for Research and Technology Hellas. His research interests include multiscale modelling of human tissues and organs, intelligent wearable/implantable devices for automated diagnosis, processing of big medical data, machine learning, sensor informatics, image informatics, and bioinformatics.

Adrià Galan-Gadea — Digital twins for model-driven non-invasive brain stimulation in Alzheimer's Disease

Abstract: At Neuroelectrics, we are exploring the application of personalized digital twins to create tailored non-invasive stimulation protocols. In collaboration with various centers in the Neurotwin project, we are collecting data on brain responses to transcranial electrical stimulation in individuals suffering from Alzheimer's disease. This initiative involves developing models that blend physics and physiology to one day be able to predict the effects of stimulation before its application. The project holds the potential to transform treatment by providing safer, personalized solutions that incorporate insights from different experiments across multiple disciplines.

Bio: Adrià graduated in Biomedical Engineering at the University of Barcelona and later a pursued a master´s degree in Brain and Cognition in Pompeu Fabra University and a Master´s degree in Neuroengineering at the Technical University of Munich. He started working in neuroscience in 2014 with small world networks, and since then he worked in different projects, including how different single neuron dynamics can emerge from different network models and Brain-Computer Interfaces. He joined Neuroelectrics in 2020 to model how electric fields affect different neuron types and now he is in charge of the development of the modeling tools of the Brain Modeling department.

Liesbet Geris — From chips to tissues: combining in silico and in vitro tools in skeletal tissue engineering

Abstract: In silico and in vitro technologies are tools complementary to the traditional biomedical tools, allowing the study of multi-factorial processes under controlled conditions. In this talk, I will provide several examples related to bone and joint degeneration and regeneration where we combine computer modeling and simulation with microphysiological systems to gain understanding of the pathophysiological processes and design potential regenerative approaches. The first example will tackle the multiscale process of osteoarthritis, combining the multi-scale mechanics of the joint with inflammation and intricate intracellular regulation at the gene and protein level. The second example will focus on the initial phase of bone regeneration (inflammatory phase) where an agent-based model describes the actions of various cells of the immune system in response to inflammatory and mechanical stimuli. The final example combines information obtained from single cell RNA sequencing and experiments on microphysiolgical systems with agent-based modeling to study lymphangiogenesis in the context of inflammatory conditions such as those discussed in the first two examples. At the end of the talk I'll provide a broader perspective of this work in the light of the Virtual Human Twin, an initiative of the European Commission aimed at developing a public infrastructure bringing together the necessary resources (models, data, algorithms, compute infrastructure, enabling technologies) and expertise present in the ecosystem to facilitate the development, credibility assessment and deployment of integrated digital twins in healthcare.

Bio: Prof. Liesbet Geris is professor Biomechanics and Computational Tissue Engineering at the University Liège and KU Leuven (BE). Her research focusses on developing enabling technologies (in silico & in vitro) for skeletal tissue engineering. She received several ERC grants (1 StG, 2 CoG) and research awards. Liesbet is the Virtual Physiological Human Institute's executive director and coordinates the EDITH CSA.

Martin Golebiewski — The role of standards in defining an ecosystem for Virtual Human Twins (VHTs)

Abstract: The emerging European ecosystem for Virtual Human Twins (VHTs) requires interoperability of the diverse models and their data. We develop ISO standards for VHTs: ISO 20691 provides a guideline for interoperable (meta-)data standards in the life sciences with requirements and rules for development and application of standards for formatting, description (including terminologies), and documentation of data. ISO TS 9491-1 “Recommendations and requirements for predictive computational models in personalised medicine research” provides guidelines for the construction, validation, integration, and simulation of VHT components. ISO TS 9491-2 provides guidelines for implementing computational models in clinical integrated decision support systems. These ISO standards refer to a whole bunch of community standards, e.g. defined by the COMBINE network or ASME.

Bio: Martin Golebiewski, a biochemist at HITS, focuses on data & model standards in life sciences. They lead data standardization efforts in German & European health data infrastructure projects, ensuring FAIR data & facilitating personalized medicine advancements.

Adrian Ionescu — Digital Twins in Healthcare: a look into the future

Abstract: In this presentation, we delve into the landscape of data-driven Digital Twins within the realm of healthcare, exploring both present challenges and future horizons. At the heart of this discourse lies the relationship between Digital Twins and Artificial Intelligence (AI), seamlessly intertwined across Cloud and Edge platforms. We will spotlight the pivotal role played by some cutting-edge technologies; wearable devices, implantable sensors, and organ-on-chip technologies emerge as key examples, generating vast troves of data that serve as the lifeblood of Digital Twins. Drawing from the advancements of Digipredict and RealCare European projects, we showcase tangible examples that underscore the transformative potential of these innovations. From predictive analytics to real-time monitoring, these projects epitomize the fusion of technology and healthcare, propelling us towards a future characterized by personalized, preventive, and participatory medical interventions. By elucidating the challenges and opportunities inherent in this field, we foresse a path forward, where data-driven Digital Twins stand as beacons of progress, guiding us towards a future where healthcare is not merely reactive but anticipatory, paving the way for a healthier, more resilient society.

Bio: Adrian M. Ionescu, a professor of EPFL and IEEE Fellow, leads ground-breaking research in nanoelectronics and Digital Twin technologies, focusing on energy-efficient and emerging devices for sensing and computation. His work bridging theory and application is shaping the future of semiconductor technology and has been recognized by the IEEE Technical Field Cledo Brunetti Award in 2024.

Antonis C. Kakas — Explainable Digital Twins

Abstract: AI Machine Learning generates digital structures (or theories) that allow us to make useful predictions under some future circumstances. These learned structures can be understood as a Digital Twin for some cohort of physical systems, e.g., for the extended population cohort from which the data was collected for the purpose of learning some medical diagnostic theory. But such systems suffer from the fact that the learned theory is a one fits all model for any individual or subgroup of the physical cohort they are meant to represent. From the perspective of Digital Twins, these learned structures are too coarse with little if any ability to specialize or personalize their representation. One way to address this issue is to follow the approach of Explainable AI & ML and consider the explanation model of the learned structure as a basis for producing refined personalized digital twins. Our work aims to leverage on the integration of methods from the area of Explainable AI & ML to gradually refine and personalize the coarse one size fits all Digital Twin of a learned theory to increasingly more particular Digital Twins for individual elements of the cohort. Our study of this problem is based on the approach of Explainable ML through Argumentation (https://link.springer.com/chapter/10.1007/978-3-031-44070-0_19) where the learned structure is an argumentation theory which at the same time forms an explanation model. This can then be used to naturally partition the original prediction problem into subcases each one of which is uniquely identified by the explanation of the prediction. The corresponding digital twin for an individual is then the sub theory identified by the explanation that accounts for the prediction under the inputs of the individual. The approach has been applied and evaluated on several ML problems in Healthcare, including the prediction of stroke (https://link.springer.com/chapter/10.1007/978-3-031-44070-0_19) or malignant cancer image prediction (https://ceur-ws.org/Vol-3208/paper1.pdf). Our work establishes a fruitful connection between Explainability in AI and ML and personalized Digital Twins. Apart from the usual benefit provided by the explanations of the predictions of a Digital Twin, explanations can be used to specialize the use of DTs to individual cases. Based on this we can study how to further specialize ML learned structures to form useful and adaptable DTs.

Bio: Antonis C. Kakas is a Professor at the Department of Computer Science of the University of Cyprus. His current interests include the development of a new framework of Cognitive Programming aiming to offer an environment for developing Human-centric AI systems for developers and human users at large. He is co-founder of Argument Theory, offering solutions to real-life application decision taking problems based on AI Argumentation Technology.

Koen Kas — Diving Deeper into the Future: Harnessing the Synergy of Digital Twins and Triplets

Abstract: A digital triplet combines three elements: the real you, your digital twin that mimics your actions, and a smart assistant that learns from your digital twin to offer real-world advice. This virtual health assistant savours your health data, and anticipates and predicts potential health issues. This enables personalized advice for maintaining or improving health. Or to reach one's full potential. As generative AI advances, digital triplets will revolutionize healthcare being the heart of an emerging wave of novel robots. This is enabled by secure health data storage in Personal Online Datastores (PODs) on a new internet version, using SOLID technology. Get ready to welcome Baymax, from Big Hero 6, alive.

Bio: Prof. Dr. Koen Kas is a healthcare futurist & delight thinker, healthtech entrepreneur, professor of molecular oncology & digital health at the University of Ghent in Belgium, and renowned international keynote speaker. He published his vision in 2 books. 'Sick no more' describes how we will transition from reactive sickcare to proactive healthcare with omics and digital tools. 'Your guide to Delight' outlines health creation and our personal Digital Twin that – with the use of AI - will keep you, and your company, healthy, relevant and "young". His new book will take you beyond disease prevention and will describe how a new way to deal with personal data, on a novel version of the internet, help you to become epic. Koen developed a unique Delight Thinking methodology applicable throughout life and career. 400+ keynotes, incl. Fortune 500, underscore his expertise. Koen chairs the European Cancer Prevention Organisation, co-chairs the Digital Twin Consortium healthcare workgroup, advises the Digital Therapeutics Alliance, and is the ambassador of Health House. His team at Healthskouts curates the global database of digital health Apps and Software as a Medical Device AI tools. He's involved in VITO's We Are project on decentralised citizen-centric health data on Solid, and sits on 5 healthcare company and investor advisory boards.

Raphaëlle Lesage — Computational modeling of physiology for therapeutics development: from the virtual second species to in silico human trial passing by digital OoC

Abstract: Computational methods play an increasingly pivotal role in the landscape of therapeutic development. The imperative for their use in therapeutic development arises from the challenges posed by traditional in vitro and in vivo models. Issues such as cost, limited fidelity with respect to human health, and under-representation of diverse populations underscore the need for alternative approaches. Here, we explore the role of mechanistic physiology-based digital twins at various stages of drug development and reflect upon how artificial intelligence tools increasingly power those approaches. Diverse bio-simulation applications are showcased, including microfluidics assays, animal and pre-clinical studies, and human trials. Through the lens of physiology-based pharmacokinetics and pharmacodynamics, we illustrate how ADME properties, efficacy, and safety parameters are assessed, ensuring a better understanding of therapeutic outcomes and model-informed drug development. At the heart of these case studies lies the integration of (whole-body) Physiologically Based Pharmacokinetic (PBPK) and Quantitative Systems Pharmacology (QSP) modelling with the resources and software supported by the Open System Pharmacology community [1]. These mechanistic models, possibly augmented by artificial intelligence (AI), offer a multiscale perspective, encompassing organ, tissue, intracellular biochemistry, and genetic profiles.
As a first use case, the Virtual Second Species project aims at leveraging machine learning-aided multiscale modelling for toxicological endpoint predictions in dogsa. Secondly, the Organ-on-Chip Digital twin platformb showed the potency to bridge the gap between in vitro findings and their clinical relevance and to predict human physiological parameter values [2]. Finally, simulating human pathophysiology allowed the reproduction of thyroid hormone regulation and their disturbance by xenobiotics or to inform dose selection for an anti-tumoral compound. Moreover, we underscore the potential of AI along the process, whether for data curation and formatting or parameter prediction. In conclusion, the evolving landscape of therapeutic development and healthcare continues to be shaped by integrating computational methods and AI. As we head towards a future of personalized medicine and streamlined drug development processes, leveraging the whole compendium of available data, knowledge, and digital technologies remains paramount.

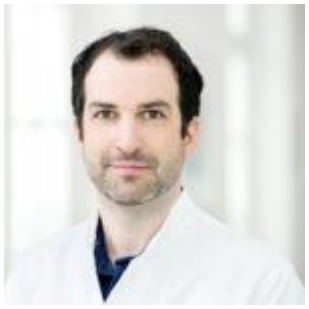
Bio: Engineer and Systems Pharmacologist at ESQlabs, Dr. Raphaëlle Lesage, specializes in physiology-based computational modeling for therapeutics (pre)clinical development. Formerly with the Virtual Physiological Human institute, she engaged in international consortia, advocating for digital twins in healthcare. She is particularly interested in enhancing bio-simulations with AI methods.

Anthony Mathur — A Clinician's Approach to the Cardiovascular Digital Twin

Abstract: In the forthcoming lecture, I will describe a methodology that applies specific clinical scenarios to create highly personalized digital replicas of patients' disease specific cardiovascular system. This method integrates real-time sensing, advanced programming, and robust output metrics to construct a dynamic model that mirrors the unique physiological features of an individual's heart and vascular system. I will examine the practical applications of these digital twins in real-world clinical settings, demonstrating how they can inform and enhance decision-making processes. The talk will highlight the transformative potential of these tools in providing precise, patient-tailored diagnoses and treatments, ushering in a new era of targeted and effective cardiac care.

Bio: Prof. Anthony Mathur is a cardiologist who balances clinical work with research on biologics for heart disease. As the Clinical Director at Barts Health, he manages complex cases of heart failure and angina. He also chairs the ESC's Stem Cell Task Force and led the UK's Cardiac Stem Cells Collaborative. Additionally, he leads the CVDHub, which supports innovation in cardiovascular devices and facilitates trials for SMEs.

Alexander Meyer — Challenges and opportunities for the deployment of Digital Twins in clinical settings



Abstract:

Bio: Alexander Meyer is Charité Professor of Clinical Applications of AI and Data Science, Chief Medical Information Officer at the German Heart Center of Charité (DHZC), group leader at DHZC‘s Clinical Data Science Group and senior resident in cardiothoracic surgery at the Clinic for Cardiac, Thoracic and Vascular Surgery at the German Heart Center of Charité.

Vasilis Ntziachristos — Information Matters

Abstract: Biological discovery is a driving force of biomedical progress. With rapidly advancing technology to collect and analyze information from cells and tissues, we generate biomedical knowledge at rates never before attainable to science. Nevertheless, conversion of this knowledge to patient benefits remains a slow process. To accelerate the process of reaching solutions for healthcare, it would be important to complement this culture of discovery with a culture of problem-solving in healthcare. The talk focuses on recent progress with optical and optoacoustic technologies that collect new streams of information and computationally process them in order to model disease processes and open new paths for solutions in biology and medicine. Particular attention is given on the use of these technologies for early detection and monitoring of disease evolution, as represented by digital twins. The talk further shows new classes of imaging systems and sensors for assessing biochemical and pathophysiological parameters of systemic diseases, complement knowledge from –omic analytics and drive integrated solutions for improving healthcare.

Bio: From electrical engineer to imaging pioneer, Prof. Ntziachristos' journey spans the globe. A Ph.D. from UPenn landed him at Harvard & Mass General, followed by a professorship at the Technical University of Munich, where he chairs Biological Imaging and directs the Institute for Biological and Medical Imaging. He also heads bioengineering at both institutions and the Helmholtz Pioneer Campus, showcasing his commitment to innovation in healthcare technology.

Costas Pitris — Cyber-Physical Twins for Predicted Patient Care Pathways: Hope or Hype?

Abstract: The rise of AI has also propelled the concept of Digital Twins (DTs) to the forefront of several fields, including healthcare. However, there is also an arbitrary rebranding and reuse of various technologies (e.g. prediction, simulation, and machine learning) as embodiments of DTs. Hype notwithstanding, DTs have great promise but the inherent variability in the human biology and physiology imposes significant limitations to their real-world performance. Although, for other applications DTs are used as tools to improve the performance of cyber-physical systems, physical models can be used to improve the performance of DTs in clinical practice.

Bio: Costas Pitris is a Professor at the KIOS Center of Excellence, University of Cyprus. Prof. Pitris has studied at the MIT (PhD 2000) and Harvard Medical School (MD 2002). His research interests include optical diagnostics, biomedical imaging, spectroscopy, signal/image analysis, and computational intelligence. He has coordinated research grants totaling over €8.5mil and participated in others worth over €2mil. He has published 57 peer reviewed journal publications, 146 conference proceedings, 5 book chapters, and 1 book. He also holds 12 US, European, and other patents. The citations to his work have reached > 15400 (h-index: 40) according to Google Scholar.

Nelly Pitteloud — Continuous measures of cortisol in healthy individuals

Abstract:

Bio: Prof. Nelly Pitteloud is a Professor of Medicine and Chief of Endocrinology at Lausanne University Hospital. After receiving her medical education at the University of Geneva Medical School, she trained and conducted research in endocrinology at Harvard Medical School and Massachusetts General Hospital. Her research focuses on the link between reproduction and metabolism. She founded the European Center for Reproductive Endocrinologys.

Petra Ritter — Personalized brain simulation

Abstract: Simulations of brain networks allow us to understand how different units in the brain interact to produce functions. In addition, such computational model simulations provide the opportunity to understand the principles of cognition and the causes of performance variability between individuals. Personalized brain network avatars have the potential for a variety of clinical applications to improve diagnostics, for in silico testing of interventions and for inferring disease mechanisms.

Bio: Prof. Petra Ritter, a medical doctor specializing in brain research, completed extensive international training before becoming a Professor for Brain Simulation. Leveraging her expertise in neural oscillations and brain imaging, she now leads research efforts in developing personalized brain simulations for medical applications.

Albert van Den Berg — Electrical methods for microfluidics, Labs and Organs on Chip

Abstract: Electrical methods play an important role in microfluidics and its applications in Labs- and Organs on Chip. First, a field effect method to control flows in microchannels will be presented using a so-called FlowFET. In a second example, direct energy conversion from hydraulic to electrical energy using charged microdroplets is discussed, where a high efficiency of close to 50% is obtained. The use of electrophoresis combined with impedance detection is used to realize an point of care lithium sensor to be used by patients suffering from mood disorders. Finally, a so-called Blood Brain Barrier chip is presented where Trans Epithelial Electrical Resistance (TEER) measurements are used to test the endothelial barrier integrity and correlate that to the effect of drugs.

Bio: Albert van den Berg is full professor on Labs- and Organs on Chips at the University of Twente. He received several awards (ERC, POC and EIC grants, Simon Stevin, Spinoza prize) and is member of the Royal Dutch Academy of Sciences (KNAW). From 2018-2024 he was (co)director of MESA+ institute for Nanotechnology and currently is quartermaster of the UT Climate Centre.

Wouter Van den Bosch — Driving the next generation of Digital Twins with wearable, ingestible and implantable sensors

Abstract: Key to the next generation of Digital Twins for Healthcare is an ever deeper understanding of the complex system that is our human biology and creating novel data needed for this. That is why imec is focused on developing new sensing technology that can measure our biology at higher resolutions & frequencies or more continuously than is possible today. We take a look at some of these technologies and on the way AI is paving the way for hardware/software co-design in this field.

Bio: Wouter Van den Bosch is R&D Program Manager “AI & Health” at imec. Together with a highly motivated and capable team of data scientists, developers, domain experts and project leads, his team aims to push the boundaries of datascience and AI applied to imec’s technological roadmaps in the domains of Health and Life Sciences. Before taking up this role, Wouter was Program Manager Public Health at Imec, helping to accelerate digital transformation and access to health data at scale in the Belgian health ecosystem & explore how technology can be used to create new insights in personalised and predictive health pathways. Wouter is a seasoned technologist with a passion for innovation, disruption, collaboration and new technology applied well.

Eleftheria Zeggini — Translational genomics of complex disease

Abstract: In this talk, I will give an overview of how we have used translational genomics approaches to enhance our understanding of complex diseases like type 2 diabetes, shed novel biological insights, and provide a stepping stone for bridging the gap between basic discovery and translation.

Bio: Prof. Eleftheria Zeggini, FMedSci Eleftheria Zeggini obtained a BSc in Biochemistry and a PhD in Immunogenetics of Juvenile Arthritis from the University of Manchester. Following a statistical genetics post doc at the Centre for Integrated Genomic and Medical Research in Manchester, she moved to the Wellcome Trust Centre for Human Genetics in Oxford to undertake a post doc in type 2 diabetes research. In 2008, she joined the Wellcome Sanger Institute Human Genetics Faculty where she built a programme of work to advance analytical genomics of complex traits. In 2018, she moved to Helmholtz Munich as founding Director of the Institute of Translational Genomics, and since May 2020 holds the TUM Liesel Beckmann Distinguished Professorship at the Technical University Munich School of Medicine. Her research aims to translate insights from genomics into mechanisms of disease development and progression, shortening the path to translation and empowering precision medicine.

The abstracts of posters

Chatbot based Digital Twin for Citizen access to Patient Summary.	Aliki Vasili, Eirini Schiza, Antonis Kakas, Constantinos Pattichis
Multimodal health patch for cardiopulmonary characterization.	Bernard Grundlehner
Novel micromesh multielectrode array sensor for organ-on-chip applications.	Mar Cóndor, Sohail F. Shaikh, Aaron Delahanty and Dries Braeken
Computational Modelling of (Bio) Interfaces via Atomistic and Continuum Models.	Hilal Reda, Panayiota Katsamba, Vangelis Harmandaris
Multimodal sensing platform for dual monitoring of lactate and pH.	L. De Schrijver, A. Saeidi, J. Longo, and A. M. Ionescu.
Collaborative Learning via Prediction Consensus.	Dongyang Fan, Celestine Mendler-Dünner, Martin Jaggi
Image-based Time Series Generation for Electronic Health Records.	Hojjat Karami, Anisoara Ionescu
inDISCO: Interpretable DIStributed COllaborative learning for biomedical images.	Klavdiia Naumova, Arnout Devos, Sai Praneeth Karimireddy, Martin Jaggi, Mary-Anne Hartley
Genetic drivers of heterogeneity in type 2 diabetes pathophysiology.	Konstantinos Hatzikotoulas, Ken Suzuki, Lorraine Southam, Henry J. Taylor, Xianyong Yin, Kim M. Lorenz, Ravi Mandla
Programmable graphic user interface-controlled multiplexed translation organ-on-a-chip platform integrated with microelectrode array.	Shao-Hsuan Kuo, Mariia Zakharova, Mar Condor Andries van der Meer, Dries Braeken, Loes Segerink.
Towards strain sensing with carbon nanotubes for monitoring respiratory activity and digital twins	Morten Vollmann, Mainak Basu, Cosmin Roman, Christofer Hierold
Non-Invasive Estimation of Pressure-Volume Loop of the Left Ventricle in the ICU Setting: A Digital-Twin Based Approach.	Rajagopalan G., Komarakshi R. Balakrishnan, Ramarathnam Krishna Kumar.
Sampling tool for interstitial fluid enables mining of biomarker data.	P. Rangsten, M. Hillmering, A. Engman, S. Grant, L. Kopp Fernandes, M. Renlund
Development of a multisensor patch for the clinical setting.	M. Renlund, N. Shi, A. Engman, M. Hillmering, S. Grant, J. Scheffel, P. Rangsten
Programmable graphic user interface-controlled multiplexed translation organ-on-a-chip platform integrated with microelectrode array.	Shao-Hsuan Kuo, Mariia Zakharova, Mar Condor, Andries van der Meer, Dries Braeken, Loes Segerink
iPSC-Derived Vasculature Organ-on-Chip Models for Digital Twin Construction.	Mariia Zakharova, Mar Cóndor, Sohail F. Shaikh, Aaron Delahanty, Dries Braeken, Albert van den Berg, Andries D. van der Meer and Loes I. Segerink.
Hybrid implantable optoelectronic sensor for fingerprinting of brain tumour evolution.	P. Giannakou, K. Faropoulos, T. Andreou, E. Tsitsou, E. Efthymiadou, C. Pitris, A. Odysseos
Towards the creation of a digital kidney twin through multi-omics profiling of urinary extracellular vesicles in ADTKD-MUC1 patients and healthy controls.	Andrea C. Kakouri, Maria Pozova, Apostolos Malatras, Panayiotis Savva, Yiolanda Englezou, Natasa Giallourou, Christoforos Stavrou, Constantinos Deltas, Gregory Papagregoriou.
Hardware accelerators for privacy-preserving biomedical AI on the Edge	Lara Orlandic, Benoît W. Denkinger, Miguel Peón-Quirós, Mario Konijnenburg, David Atienza, Francky Catthoor

Chatbot based Digital Twin for Citizen access to Patient Summary

Aliki Vasili[1], Eirini Schiza[2], Antonis Kakas[1], Constantinos Pattichis[1].

[1] Department of Computer Science and Biomedical Engineering Research Centre UCY.

[2] HealthXR CYENS.

vassili.aliki@ucy.ac.cy

Introduction: This study proposes a chatbot-based digital twin to enhance citizen access to Patient Summary, crucial for cross-border healthcare. Patient Summary contains vital health details such as allergies and lifestyle indicators, proving essential, particularly in addressing language barriers between health professionals and patients.

Objective: To develop a personalized chatbot based Patient Summary digital twin using machine learning to categorize user inputs, providing customized responses and reducing time-consuming searches.

Methods: This study leverages bioBert [https://doi.org/10.1093/bioinformatics/btz682], a pre-trained NLP model. The bioBert model is fine-tuned with a specific dataset for effective user input categorization. Integration with digital twin technology ensures continuous adaptation to each user.

Results: Initial findings indicate that the model efficiently categorizes user inputs, enabling the chatbot to retrieve Patient Summary information effectively.

Discussion: Despite promising results, limitations include reliance on data quality and challenges with ambiguous user text. Ongoing retraining, also, raises scalability and resource concerns.

Conclusion: The chatbot digital twin offers a promising solution for swift and accurate access to Patient Summary, enhancing healthcare information accessibility.

Keywords: *Digital twin, Chatbot, Healthcare, bioBert, Machine Learning.*

Multimodal health patch for cardiopulmonary characterization

Bernard Grundlehner[1].

[1] IMEC.

bernard.grundlehner@imec.nl

Introduction: Data is at the basis of any digital twin for healthcare. A wide variety of sensing modalities is required to create a proper model, capable of predicting disease progression and the best possible treatment. Among all options available nowadays, physiological sensing provides insightful information and is easily executed.

Objective: The objective of this work was to create a wearable sensor with novel and meaningful sensing modalities, and to make it available for clinical research studies. By making available both raw as well as processed data, the system will help establishing novel databases for training of digital twins.

Methods: In this work, modern electronic system design techniques are used to establish low-power and miniaturized system designs. For patch integration, a PET film was used on which tracks and Ag/AgCl electrodes are printed using screenprinting technology, with Hydrogel deposited to establish a good electrical skin contact. Photoplethysmographic (PPG) signals are used for the estimation of oxygen levels in blood (SpO2).

Results: A lightweight and low-power self-adhesive system was created, consisting of a disposable patch and reusable electronics module, with raw streaming of ECG, Impedance Pneumography, PPG (red and infrared) and skin temperature. Onboard processing is implemented to extract heart rate, respiration rate and blood oxygen concentration. An SpO2 measurement is triggered every time the user places his/her finger on top of the PPG window. With a fully charged battery, the system is capable of measuring these signals for 72 hours continuously. The systems was calibrated for SpO2 measurements through induced hypoxia, and validated for long-term monitoring on 10 healthy subjects.

Discussion: A novel vital sign monitoring patch was developed, that characterizes the pulmonary and cardiovascular systems, including cardiac activation (ECG), cardiac pumping function (PPG), breathing effort (Impedance Pneumography) and resulting blood oxygen concentration. The collection of raw data might enable additional functional characterization from the raw ECG, Bio-Impedance and Photoplethysmographic signal morphologies. Validation on healthy subjects has indicated that the device is capable of reliably measuring the signals for 72 hours continuously. Documentation is prepared to use the device in clinical research studies.

Conclusion: A novel multimodal health patch was developed, manufactured and validated for use in clinical research studies. Combined with other biomarkers, this will further strengthen the in creating digital twin models to predict disease progression and optimize treatment strategies.

Keywords: *cardiopulmonary characterization, multimodal health patch, data collection.*

Novel micromesh multielectrode array sensor for organ-on-chip applications

Mar Cóndor[1], Sohail F. Shaikh[1], Aaron Delahanty[1] and Dries Braeken[1].

[1]Life Science Technologies, Interuniversity Microelectronics Centre (IMEC), Leuven, Belgium.

mar.condor@imec.be

Introduction: Understanding cellular electrical phenomena, such as communication, ion channel activity, and tissue barrier function, is crucial for unravelling various biological processes. The advent of multi-electrode arrays (MEAs) has revolutionized this field, enabling researchers to record and stimulate cells grow on the surface of arrays of electrodes. This provides easy access to electrophysiological data (no difficult, time-consuming manipulations needed) and allows for non-invasive interfacing with cells. Recent advancements in human cell models, microfluidics, organ-on-a-chip (OoC) technology, and biosensors have enabled the development of more physiologically relevant in vitro models. However, today, few models out there have sensors incorporated and still rely on endpoint and label-based methods.

Objective: This work aims to pioneer a new sensor platform: a thin, mesh-like, MEA array. The novel micromesh MEA chip facilitates the growth of 3D tissues and organs in physiologically relevant microenvironments while enabling exploration of their electrophysiology in a non-invasive, label-free manner through integrated sensors.

Methods: The sensor-embedded porous membrane was fabricated using a custom 0.13 um CMOS process. The chip features 121 monolithically integrated electrodes sitting on islands interconnected by bridges, distributed in a 11 x 11 matrix, over a 1.4 x 1.4 mm cross-section. The membrane thickness in the center of the chip is 17 µm, based on silicon-on-insulator (SOI) wafers available. Various mesh designs were developed, adjusting the dimensions and distribution of electrode islands and bridges to meet the precise requirements of the intended application, notably the measurement of tissue barriers.

Results: Numerical simulations were employed to ascertain the optimal pore distribution across the silicon membranes and evaluate the total resistance of the resulting structures. These simulations unveiled an optimal mesh chip design with an electrode pitch equal to 100 µm, a pore diameter of 70 µm and with spacing between pores of +/- 100 µm. Subsequently, biocompatibility and toxicity using immortalized human epithelial Caco2 cells derived from a colon carcinoma. As a result of these tests, optimal sterilization and cell seeding procedures were established to ensure optimal cell growth, cell viability and the formation of correct monolayers on top of the mesh-MEA chips. The resultant Caco-2 cell monolayers demonstrated the expression of key barrier hallmarks, including tight junction formation (e.g. ZO-1). Further, cell barriers formed on top of the chip were assessed via permeability tests. These tests involved assessing the diffusion of a 10kDa dextran particle under various cell seeding conditions: Collagen coating, Collagen coating with Caco2 cells and Matrigel coating with Caco2 cells. The findings revealed a significant impairment in diffusion under the presence of Caco2 cells on top of the membrane chips for both protein coatings, indicative of functional Caco2 cellular barriers on top of the porous chip.

Conclusion: The micromesh MEA sensor presented in this work contributes to the state of the art for organ-on-chip applications, incorporating electrical readouts with high-spatial and temporal resolution for in vitro experimentation.

Keywords: *Organ-on-chip, Silicon manufacturing, MEA, Tissue barrier integrity.*

Computational Modelling of (Bio) Interfaces via Atomistic and Continuum Models

Hilal Reda[1], Panayiota Katsamba[1], Vangelis Harmandaris[1,2].

[1] Computation-based Science and Technology Research Center, The Cyprus Institute, Aglantzia 2121, Nicosia, Cyprus.

[2] Department of Applied Mathematics, University of Crete, Heraklion GR-71409, Crete, Greece.

v.harmandaris@cyi.ac.cy

Introduction: The continuum models describing an "effective polymer/nanoparticle interphase", obtained from micromechanical models, are well-founded and based on a combination of molecular dynamics (MD) simulations and multiscale methods. However, in such models, the effective interphases at the continuum level are usually not defined via a systematic, "bottom-up", approach and do not accurately describe the local stress transfer at the polymer/nanoparticle interphase region [1]. In general, a main challenge in the modeling and characterization of the mechanical properties at interphases is to directly describe the spatial distribution of stress/strain fields as a result of the mass density and polymer chain conformational heterogeneities in polymer-based nanostructured materials. Hence, a rigorous coupling between the atomistic and the continuum scales, which takes into account explicitly the mechanical properties at the interphase is currently missing. In addition, a detailed investigation of the spatial distribution of stress and strain fields for deformed PNCs has not been carried out so far [2-3].

Objective: The objective of this work is to extract the properties of effective interphases in the nanostructure through nanocontinuum bridged multiscale model that implicitly matches the strain energy at the interphase as well as its effective thickness through homogenization and deformation energy density matching processes.

Methods: We propose a hierarchical methodology that combines microscopic (molecular dynamics) simulations, mesoscopic (homogenization approaches, and continuum finite element models (FEM) that will be developed and applied using input from atomistic simulation on a system consisting of polymer nanocomposites (PNC) (Figure 1).

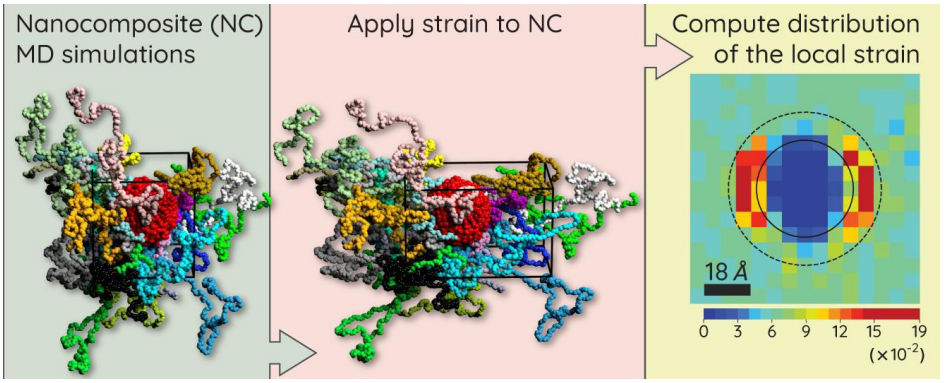


Fig.1 Multiscale approach combining finite element and atomistic simulation.

Taking into account the stochastic distribution of inclusion, we will implicitly solve for the size (geometrical) and mechanical properties of the effective local interphases, which have an equivalent deformation energy around the inclusion, as well as the global elastic stiffness of the PNC scale that is equivalent to the corresponding value from atomistic simulation (Figure 2).

Results: The methodology is then applied to tumor cell behaviour. Determining the properties of the interphase (micro-nanotube polymer) together with the properties, inclusion, and the matrix (through experiments) will allow us to solve the inverse problem to guide the production and the in silico design. The main finding of our work is summarised as follows:

- The interphase region is more rigid compared to the matrix region, as expected because of the higher potential interaction energy between the polymer atoms and the Si atoms averaged over a small area;
- The behaviour of the interphases are the same regardless of the volume percentage of the nanofiller (for the same diameter);
- Gradient in mechanical properties (Young modulus and Poisson ratio) within the polymer/NP interphase, ranging from the values of the silica spherical NP to those of the matrix polymer.
- The presence of such gradients is required to ensure the continuity of stress and strain within the interphase region.

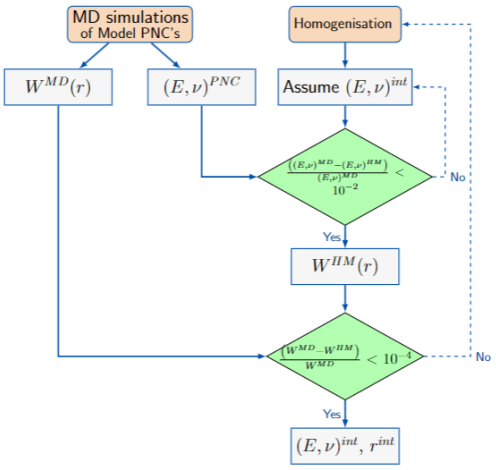


Fig.2 Flowchart for MD-HM bridged multiscale method which characterizes the thickness and strain energy density of the effective interphases of Si/PB and Si/PEO nanocomposites.

Discussion: Overall, determining the properties of the interphase (hollow-micro-nanotube) together with the properties the inclusion and the matrix (through experiments) will allow us to solve the inverse problem to guide the production and design of the required nano-devices for medical application. Promising mixing ratios are considered those that give rise to a material properties distribution with the desired mean target behaviour and variations away from it falling within the accepted. The desired homogenisation method will enable faster and higher fidelity exploration of new systems, as well as optimising conditions during the development of established nanodevices.

Conclusion: The suggested approach involves computational modelling across scales, from atomistic molecular dynamics (MD) up to continuum finite element simulations using homogenisation approaches, as well as Finite element and topology optimisation methods to provide structure-property relationships, acting at the same time as a decision-support tool for the in-silico design, for specific bio-materials.

***Keywords*:** Multiscale approach, Interphase characterization, in silico design.

1. G. M. Odegard, T. C. Clancy, T. S. Gates, Modeling of the mechanical properties of nanoparticle/polymer composites, Polymer 46 (2005) 553–562.

2. Reda, H.; Chazirakis, A.; Behbahani, A. F.; Savva, N.; Harmandaris, V. Revealing the Role of Chain Conformations on the Origin of the Mechanical Reinforcement in Glassy Polymer Nanocomposites. Nano Letters 2023, 24, 148–155.

3. Reda, H.; Chazirakis, A.; Behbahani, A. F.; Savva, N.; Harmandaris, V. Mechanical properties of glassy polymer nanocomposites via atomistic and continuum models: The role of interphases. Computer Methods in Applied Mechanics and Engineering 2022, 395, 114905.

Multimodal sensing platform for dual monitoring of lactate and pH

L. De Schrijver[1], A. Saeidi[2], J. Longo[2], and A. M. Ionescu[1].

[1]Nanoelectronic Devices Laboratory, EPFL, Lausanne, Switzerland.

[2]Xsensio SA, Lausanne, Switzerland.

lotte.deschrijver@epfl.ch, adrian.ionescu@epfl.ch

Clinical research shows that monitoring pH and lactate can improve patient prognosis and outcome. However, current blood pH and lactate sampling methods do not allow for a high frequency of measurements. As a solution, we have developed a dual sensing platform which can potentially be integrated with microneedles to provide non-invasive, continuous measurements of lactate and pH in interstitial fluid.

To measure pH, we fabricated junctionless ion-sensitive field-effect-transistors (ISFET) which have a pH sensitive gate oxide. Variations in hydrogen ion concentration modify the surface charge of the gate oxide, which alters the transistor's conductance. Moreover, Si nanowires (NWs) arrays are implemented because their larger surface to volume ratio enables enhanced sensitivity. Fig. 1a shows the output characteristics of the Si NWs for different pH levels, confirming their pH sensitivity. To measure lactate, a three Pt electrode platform is used where the enzyme 'lactate oxidase' is dropcasted on top of the working electrode. The enzyme converts lactate into hydrogen peroxide which subsequently oxidizes at the electrode surface. Fig. 1b presents the amperometric response of the lactate sensor, exhibiting a limit of detection of 0.17 mM and a working range up to 20 mM, corresponding to advanced requirements of ICU and ward patients in hospitals. The two sensors have been integrated onto a single chip measuring 1x1 cm^2, as depicted in Fig. 1c and Fig. 1d, with plans for future evaluation of multiplexed sensing. The proposed multimodal sensor platform holds promise to be integrated in a wearable device for continuous monitoring of patients.

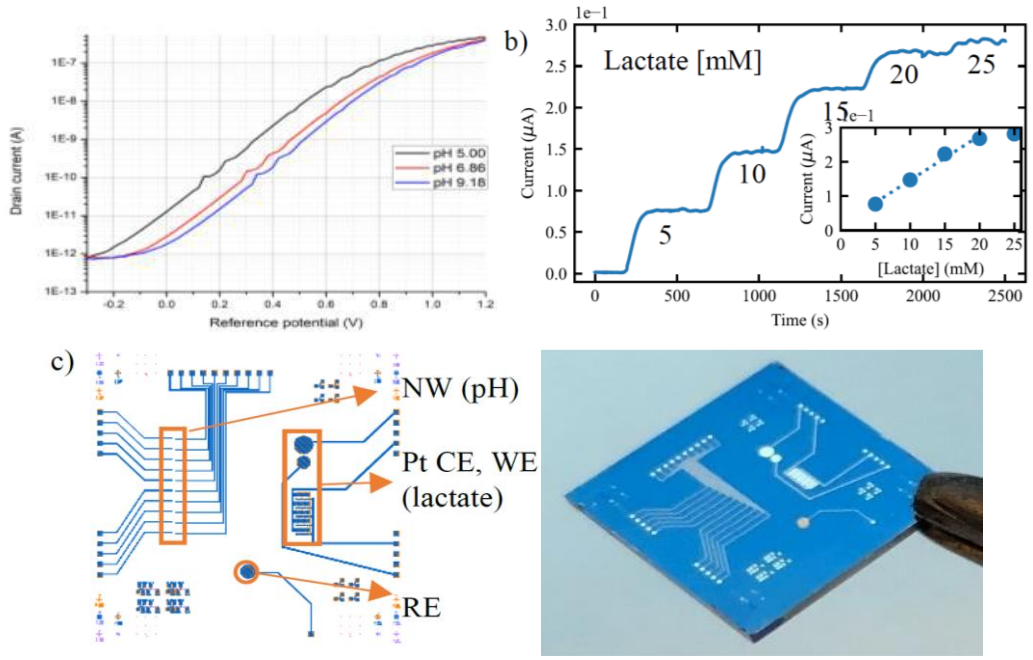


Figure 1. a) pH sensing; transfer characteristics of the NW FET device at different pH levels. b) Lactate sensing; amperometric response towards different lactate concentrations. c) Design layout of the dual sensing chip. d) Optical picture of the finished chip.

Keywords: *dual sensing, pH sensor, lactate sensor, amperometry, ISFET.*

Collaborative Learning via Prediction Consensus

Dongyang Fan[1], Celestine Mendler-Dünner[2], Martin Jaggi[1].

[1] EPFL.

[2] MPI Tübingen, ELLIS Institute Tübingen.

dongyang.fan@epfl.ch

Objective: We consider a collaborative learning setting where the goal of each agent is to improve their own model by leveraging the expertise of collaborators, in addition to their own training data.

Methods: We propose a distillation-based method leveraging shared unlabeled auxiliary data, which is pseudo-labeled by the collective. Central to our method is a trust weighting scheme that serves to adaptively weigh the influence of each collaborator on the pseudo-labels until a consensus on how to label the auxiliary data is reached.

Results: Our collaboration scheme is able to significantly boost the performance of individual models in the target domain. By design, our method adeptly accommodates heterogeneity in model architectures and substantially reduces communication overhead compared to typical collaborative learning methods. At the same time, it can probably mitigate the negative impact of bad models on the collective.

Discussion: Suitable scenarios 1) small to moderate number of clients; 2) clients communicates honestly, while they are allowed to have weak models or low-quality data.

Conclusion: We proposed a collaborative learning scheme that allows for model/data heterogeneity in local nodes, which is also robust to honest low-quality nodes. While only model predictions are shared, the method gives higher privacy guarantees than typical gradient or model parameter-based aggregation methods, which renders it more applicable for medical domain datasets.

Keywords: *Collaborative learning, consensus, trust.*

Image-based Time Series Generation for Electronic Health Records

Hojjat Karami[1], Anisoara Ionescu[1].

[1]EPFL.

hojjat.karami@epfl.ch

Introduction: Time series in Electronic Health Records (EHRs) present unique challenges for generative models, such as irregular sampling, missing values, and high dimensionality.

Objective: Generating clinical time series that can address these challenges could help generate more clinical data while preserving privacy, thus facilitating research for developing machine learning models.

Methods: We propose a novel generative adversarial network (GAN) model, TimEHR, to generate time series data from EHRs. In particular, TimEHR treats time series as images and is based on two conditional GANs. The first GAN generates missingness patterns, and the second GAN generates time series values based on the missingness pattern.

Results: Experimental results on three real-world EHR datasets show that TimEHR outperforms state-of-the-art methods in terms of fidelity, utility, and privacy metrics.

Discussion: Our findings hold significant implications for the advancement of digital twins in healthcare. By successfully generating clinical time series data with improved fidelity, utility, and privacy preservation, TimEHR lays a foundation for enhancing patient-specific modeling and personalized medicine.

Conclusion: Summarize the main conclusions drawn from your research. Clearly state the broader impact of your work on the advancement of digital twins in healthcare.

Keywords: *Electronic Health Records (EHRs), generative adversarial network (GAN), time series.*

inDISCO: Interpretable DIStributed Collaborative learning for biomedical images

Klavdiia Naumova[1], Arnout Devos[1], Sai Praneeth Karimireddy[2], Martin Jaggi[1], Mary-Anne Hartley[3].

[1]Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland.

[2]University of California Berkeley, CA, USA.

[3]Yale University, New Haven, CT, USA.

klavdiia.naumova@epfl.ch, +41 21 693 70 59

Introduction: DIStributed COllaborative learning (DISCO) is a promising approach for machine learning on privacy-sensitive data such as medical images. This method allows multiple data owners (clients) to train a joint model without sharing their data. However, this black-box data setting may conceal systematic biases, compromising the performance and fairness of the resulting model.

Objective: This work aims to create a visually interpretable and privacy-preserving approach to identify systematic bias in DISCO learning for biomedical images.

Methods: We adapt an inherently interpretable prototypical part learning network (ProtoPNet) to a DISCO setting enabling each client to visualize the differences in prototypes learned by other clients on its own local data. In our inDISCO framework, four clients collaborate to train two diagnostic classifiers on a benchmark chest X-ray dataset. We compare the model performance in an unbiased setting and under the strain of two distinct types of systematic visual bias, where one client's data has a misleading feature associated with the target label.

Results: In an unbiased setting, the global model reaches 74.14 % balanced accuracy for cardiomegaly and 74.08 % for pleural effusion classification, while in the biased setting, the performance of these models drops to near-random when evaluated on unbiased data. We demonstrate that differences between local and global prototypes can indicate the presence of bias and can be visualized on each client's data without compromising privacy.

Discussion: This study demonstrates an approach to address low data interoperability among the clients in DISCO learning which is crucial for developing efficient and generalizable models. Exploring the balance between privacy and inDISCO's capacity to detect bias, along with developing a method to remove the effect of bias on models, represent areas of potential future improvements.

Conclusion: inDISCO is an innovative approach leveraging ProtoPNet, which allows interpretable and privacy-preserving identification and attribution of data bias in DISCO learning for imaging data. By facilitating transparency from black-box data without compromising privacy, inDISCO holds the potential for medicine and can further scale to applications broadly in engineering, primarily in high-stakes privacy-sensitive domains.

Keywords: distributed collaborative learning, interpretability, data bias, data interoperability.

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

Konstantinos Hatzikotoulas [1], Ken Suzuki [2,3,4], Lorraine Southam [1], Henry J. Taylor [5,6,7], Xianyong Yin [8,9], Kim M. Lorenz [10,11,12], Ravi Mandla [13,14] on behalf of the Type 2 Diabetes Global Genomics Initiative (T2DGGI).

[1]Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.

[2]Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Manchester, UK.

[3]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

[4]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan.

[5]Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA.

[6]British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

[7]Heart and Lung Research Institute, University of Cambridge, Cambridge, UK.

[8]Department of Epidemiology, School of Public Health, Nanjing Medical University, Nanjing, China.

[9]Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA.

[10]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA.

[11]Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.

[12]Department of Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.

[13]Programs in Metabolism and Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA.

[14]Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA.

Konstantinos Hatzikotoulas: konstantinos.hatzikotoulas@helmholtz-munich.de ; 004915906143021

Introduction: Type 2 diabetes (T2D) is a heterogeneous complex disease that develops through diverse physiological pathways and molecular processes. The public health burden is huge, hence there is a clear need to better understand the underlying mechanisms of the disease which may offer a route to optimise global access to genetically-informed diabetes care across global populations.

Objective: Through the newly-established Type 2 Diabetes Global Genomics Initiative, we leverage the power afforded by big genetic and genomic data, to disentangle the aetiological heterogeneity of T2D across multiple ancestry groups.

Methods: We performed the largest, most ancestrally diverse T2D genome-wide association meta-analysis to date, including 428,452 cases and 2,107,149 controls of which 39.7% are non-European ancestry. We applied K-means clustering to define clusters of T2D signals characterised by distinct profiles of cardiometabolic

phenotypes. We integrated T2D association signals with single-cell data of 328 cell types and performed enrichment analysis. We used meta-regression to evaluate the extent of ancestry-correlated heterogeneity at T2D association signals. Finally, we constructed cluster-specific partitioned polygenic scores (PS) in up to 279,552 individuals to test their association with T2D-related vascular outcomes in multiple ancestries.

Results: We identified 1,289 independent association signals at genome-wide significance (P<5x10-8), mapping to 611 loci, of which 145 loci have not been previously reported. We classified these signals according to their profile of associations with 37 cardiometabolic phenotypes in eight non-overlapping clusters related to insulin production/processing in the pancreatic beta-cell and to mechanisms of insulin response. We found that these clusters are differentially enriched for cell-type specific regions of open chromatin, including pancreatic islets, adipocytes, endothelial, and enteroendocrine cells. 127 signals showed evidence (PHET<3.9x10-5) of ancestry-correlated heterogeneity. However, after adjustment for body mass index (BMI), this number was reduced to 24 loci. Finally, we observed significant association (P<0.0063) of cluster-specific partitioned PS with coronary artery disease, peripheral artery disease and end-stage diabetic nephropathy across ancestry groups.

Discussion: In this study, we assembled the largest collection of T2D GWAS to date for five major ancestry groups, increasing the effective sample size by almost three-fold compared to previous efforts. We leveraged the power afforded by this multi-ancestry increased sample size (39.7% non-Europeans) to identify 145 new risk T2D loci. However, larger collections of under-represented populations remain an urgent priority to better capture the global genetic diversity. We present eight mechanistic clusters of index SNVs for T2D association signals by using a “hard clustering” approach that assigns each index SNV to exactly one cluster. We observed evidence of ancestry-correlated heterogeneity, and highlight the importance of accounting for differences in the distributions of mean BMI in T2D cases and in controls between ancestry groups. For the first time across multiple ancestry groups, we demonstrated significant associations of vascular outcomes with cluster-specific components of the partitioned PS.

Conclusion: Our findings demonstrate the value of integrating multi-ancestry GWAS of T2D and cardiometabolic traits with single-cell epigenomics across diverse tissues to disentangle the aetiological heterogeneity driving the development and progression of T2D across population groups.

Keywords: *Type 2 Diabetes; Multi-ancestry genome-wide association meta-analysis; single-cell epigenomics; clustering; polygenic scores.*

Programmable graphic user interface-controlled multiplexed translation organ-on-a-chip platform integrated with microelectrode array

Shao-Hsuan Kuo[1], Mariia Zakharova[2], Mar Condor[3], Andries van der Meer[1], Dries Braeken[3], Loes Segerink[2].

[1]Department of Applied Stem Cell Technologies, University of Twente, the Netherlands.

[2]BIOS lab on a Chip group, MESA+ Institute and Technical Medical Centre, University of Twente, the Netherlands.

[3]Life Science Technologies, Interuniversity Microelectronics Centre, Belgium.

s.-h.kuo@utwente.nl

Introduction: Recently, organ-on-a-chip (OoC) technologies has demonstrated advantages in biotechnical and pharmacological research and development. Researchers and engineers in both academia and industries show they are eager to integrate the technology into their workflows. As alternatives to 2D cultures, OoCs provide higher similarity to real tissues while consuming fewer cells and reagents. The unique data on tissue function generated by organs-on-chips could be an important source of data-driven healthcare algorithms. However, the throughput of existing OoCs is too low to fit the demands of healthcare. Intensive operation, limited numbers of replicates, and prerequisite knowledge to microfluidics restrict the possibility of OoC implementation.

Objective: Here, we describe our development towards a sensor-integratable, multiplexed organ-on-a-chip platform for improved parallelization and automation. The platform is controlled by a self-coded LabVIEW graphic user interface (GUI), of which the algorithm supports real-time, manual and automatic, customized microfluidic valve control.

Methods: We designed a tissue-culturing microfluidic chip with integrated pneumatic valves that enable opening and closing of each culture compartment. We developed a user-friendly GUI to realize independent introduction of liquid to each culture compartment. Moreover, we developed a fabrication protocol to integrate the microfluidic chip with a microelectrode array (MEA), thereby enabling plate sensor integration. Finally, we cultured engineered heart tissues in the microfluidic MEA chip to demonstrate the feasibility of tissue maintenance.

Results: The chip is composed of two parts: the microfluidic network and the culture chambers. The microfluidic network regulates complex liquid manipulation with solenoid valves, which are directly controlled via the GUI. The layout enables direct integration of surface sensors to the culture chambers. The valve operation and the independency of chambers during operation are shown. The feasibility of tissue maintenance and sensor integration are demonstrated.

Discussion: In our initial studies, we have already demonstrated the user-friendliness of cell culture and liquid manipulation in the chips, as well as the feasibility of sensor integration. The specified GUI minimized the operation difficulty and allowed customization of experimental protocols.

Conclusion: In this work, we described our first steps towards a parallelized and automated microfluidic culture platform with integrated sensing. This platform will overcome the current limitations of throughput and handling of organ-on-a-chip models. As such, it may enable future systematic generation of large amounts of functional data for integration in healthcare algorithms.

Keywords: *multiplexed organ-on-a-chip, microfluidic large scale integration, microelectrode array, automatic programmable tissue experiment platform.*

Towards strain sensing with carbon nanotubes for monitoring respiratory activity and digital twins

Morten Vollmann[1], Mainak Basu[1], Cosmin Roman[1], Christofer Hierold[1].

[1]ETHZ.

mvollmann@ethz.ch

Introduction: This study demonstrates the high strain sensitivity and resolution of single-walled carbon nanotubes (SWCNTs). Using SWCNTs as sensing elements for strain on a patient's thorax, for example to measure respiration rate, can provide insightful data to digital twins for early detection of diseases.

Objective: This research demonstrates the feasibility of SWCNT strain sensing using the dry transfer process with a MEMS straining platform using thermal actuators in vitro. The integration onto suitable flexible PDMS patches for healthcare applications is investigated.

Methods: The MEMS straining platform consists of two thermal actuators in the device layer of the SOI connected to movable electrodes insulated by silicon nitride. The SWCNT is grown using CVD and placed with a dry transfer process.

Results: The SWCNT exhibits gauge factors over 1000 for applied strain levels between 0 and 0.8 mε with a resolution of 63 με.

Discussion: The small form factor of the device could reduce the influence of motional artifacts. The unmatched sensitivity in combination with multiple sensors on a patient's thorax can give access to new biomarkers for digital twins like asymmetry of thorax movement or the continuous long-term observation of reduction in breathing volume.

Conclusion: Strain sensing with SWCNTs has been demonstrated and high gauge factors (strain sensitivity) have been measured. Their integration on flexible PDMS patches has been explored and approaches have been presented.

Keywords: *carbon nanotube, strain sensing, flexible substrate, PDMS.*

Non-Invasive Estimation of Pressure-Volume Loop of the Left Ventricle in the ICU Setting: A Digital-Twin Based Approach

Rajagopalan G.[1], Komarakshi R. Balakrishnan[2], Ramarathnam Krishna Kumar[1].

[1]Indian Institute of Technology Madras, Chennai, India.

[2]MGM Healthcare Pvt Ltd, Chennai, India.

rajagopalang58@gmail.com

Introduction: The left ventricle's pressure-volume (PV) loop offers critical insights into heart failure diagnosis, but its invasive acquisition via conductance catheter limits its clinical use. Non-invasive methods employing cardiac magnetic resonance imaging for predicting PV loops have emerged recently, but their application in the ICU faces implementation challenges. Therefore, alternative approaches are necessary to overcome these limitations.

Objective: This study aimed to develop a methodology to predict the PV loop non-invasively in the ICU by creating digital twins. The resulting digital twin's PV loop mirrors the PV loop of the actual patient, offering a non-invasive means of assessing cardiac function and pathology.

Methods: We have developed a deep-learning algorithm to create a digital twin of heart failure patients by predicting the patient-specific model parameters using routine clinical measurements in the ICU and echocardiography: systolic and diastolic blood pressure, cardiac output, heart rate, right and left atrial pressures and left ventricular ejection fraction. The deep-learning algorithm is trained based on the in silico database of 3330 patients.

Results: Patient-specific model parameters used to create digital twins were predicted accurately (Figure 1). The PV loop of the digital twins matches accurately with the corresponding patients in the in silico database (Figure 2).

Discussion: This is the first time the digital twin approach has been used to predict the patient-specific PV loop, considering the various heart failure phenotypes, including systolic and diastolic dysfunction in the left ventricles alongside systemic and venous hypertension. Our methodology has demonstrated remarkable accuracy, as evidenced by the validation conducted using the in silico database. While these results are promising, future clinical trials are needed to confirm these findings in actual patients.

Conclusion: Digital twin-based methodology shows promising potential for non-invasively predicting the PV loop and highlights the importance of digital twins in advancing personalized health care.

Keywords: *Pressure-volume loop, Digital twins, Artificial intelligence.*

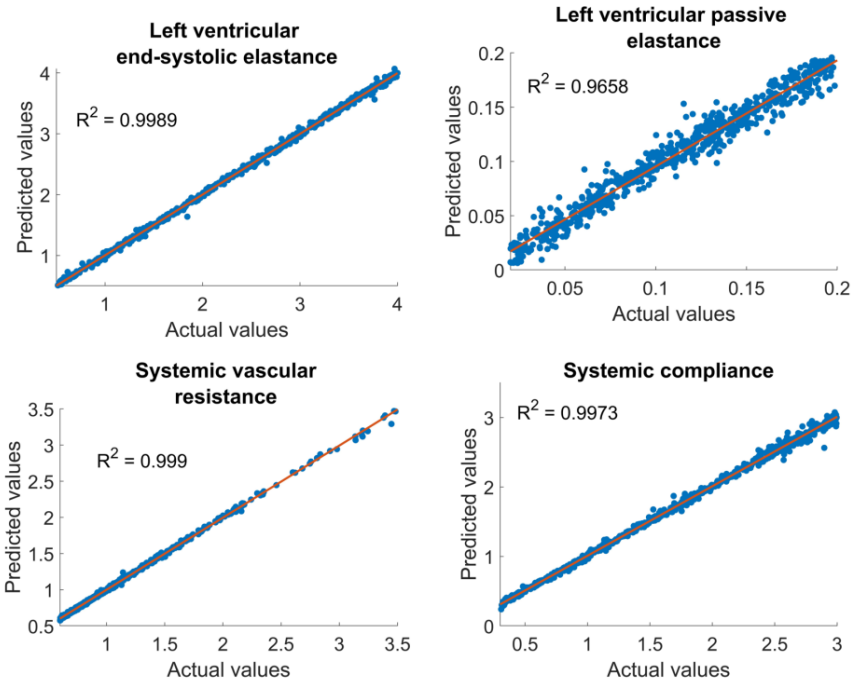


Figure 1. Predicted patient-specific cardiovascular parameters using deep learning.

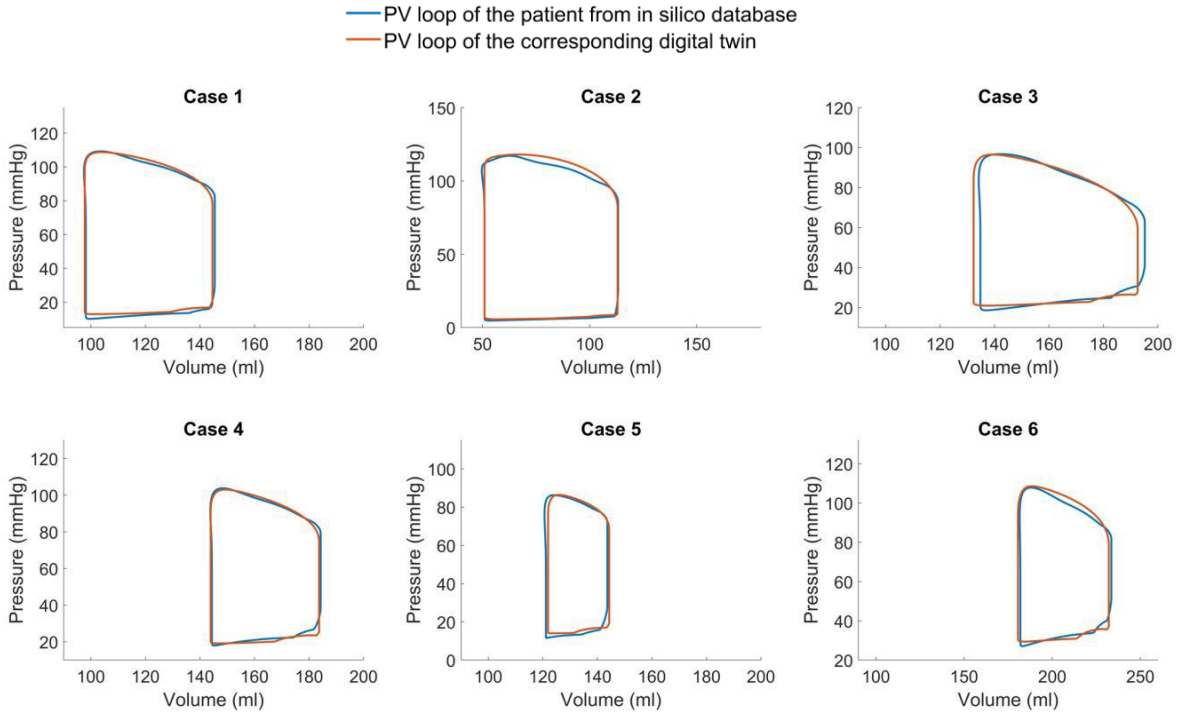


Figure 2. Predicted PV loop using digital twins.

Sampling tool for interstitial fluid enables mining of biomarker data

P. Rangsten[1], M. Hillmering[1], A. Engman[1], S. Grant[1], L. Kopp Fernandes[2,3], M. Renlund[1].

[1]Ascilion AB, Kista, Sweden.

[2]Deutsches Herzzentrum der Charité, Dept. Of Cardiothoracic and Vascular Surgery Germany.

[3]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Klinik/Centrum, Berlin, Germany.

info@ascilion.com

Introduction: Digital Twins need comprehensive data sets. To fully analyze physiological data, access to biomarkers is required. Today blood is the carrier of choice for biomarker quantification due to established sampling techniques. Other biofluids are considered and of those dermal interstitial fluid (dISF) has the substantial advantage of being closely related to blood plasma. dISF is however perhaps the least explored of the extravascular bodily fluids due to the lack of sampling tools. Convenient access to dISF is a prerequisite for development of new sensors as other accessible fluids contains too low concentrations or having too slow biomarker exchange to be meaningful in a clinical setting. Hollow microneedles represent one of the most promising platforms for access to pure dISF, enabling mining of biomarker information, hence enabling the creation of Digital Twins.

Objective: A specific challenge, apart from developing a tool and method tolerable for the patient being sampled, and a limiting factor for dISF sampling to be competitive with blood sampling, is the amount of fluid that can be collected and used for further analysis.

Methods: A miniaturized chip containing ultra-sharp hollow microneedles has been designed and manufactured using state-of-the-art micro-electro-mechanical-system (MEMS) technology. The chip is mounted in a customized system, using a negative pressure for improved sampling rates. Involving 20 heart failure patients, dISF and blood will be sampled and analyzed in the clinical study DIGIPREDICT-BIO (DIMDI 00014679). Analysis and correlation between dISF and blood will be performed at multiple sites for validation of new sensors. This represents a novel way of characterizing conditions ranging from skin diseases to heart failure.

Results: In addition to the hardware, two sampling systems including 120 sterilized needle units, a protocol has been developed for use in the upcoming clinical study of the project. In a small pilot on 10 healthy volunteers, where each subject was sampled six times. The average sampling rate for the tool was 1.0 µl/min (across several subjects and sampling sites), where each sampling lasted 15 minutes.

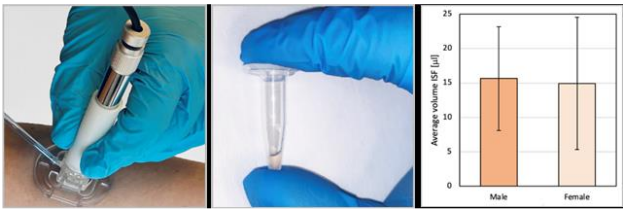


Figure 1. Sampling tool (left), 32 µl sampled dISF (middle), and comparison between sampled volumes (right).

Discussion: This work is an important steppingstone to continuous monitoring using wearables with integrated microneedles and sensors.

Conclusion: Here a non-stigmatic sampling tool is presented enabling access to a pure and not yet explored source of thousands of relevant biomarkers, which all could be used as valuable input to personalized medicine and Digital Twins.

Keywords: *Microneedle, MEMS, interstitial fluid, cytokines, DIGIPREDICT.*

Acknowledgments: *This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101017915 (DIGIPREDICT).*

Development of a multisensor patch for the clinical setting

M. Renlund[1], N. Shi[2,3], A. Engman[1], M. Hillmering[1], S. Grant[1], J. Scheffel[2,3], P. Rangsten[1].

[1]Ascilion AB, Kista, Sweden.

[2]Institute of Allergology, Charité – Universitätsmedizin Berlin, Germany.

[3]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany.

info@ascilion.com

Introduction: A minimal invasive device that detects multiple biomarkers in the dermis adds specificity and depth to the clinical data needed in the spawning of Digital Twins within healthcare. The scientific advantages include localized monitoring, real-time data collection, and minimally invasive procedures all of which contribute to a more accurate and personalized representation of an individual's health.

Objective: Patient friendly tools that don't require trained health care professionals or local anesthesia for real time monitoring of localized tissue biomarkers don't exist. Here we present the design concept of a minimal invasive device for detection of multiple biomarkers and a first study of water-soluble cytokines detected in dermal interstitial fluid (dISF) and serum with and without dermal provocation.

Methods: A prototype for multisensing of biomarkers in dISF has been designed. Sampling of dISF and detection has been performed using hollow microneedles from Ascilion and Olink Target 96 Inflammation (v.3024) panels in a collaboration study at Charité (Approval EA4/075/23). Codeine was used for skin provocation and comparison between markers found in dISF and plasma pre and post provocation was performed.

Results: Results suggest that cytokines associated with inflammation can be detected within dISF but not plasma as no up-regulation of cytokines could be detected in serum.

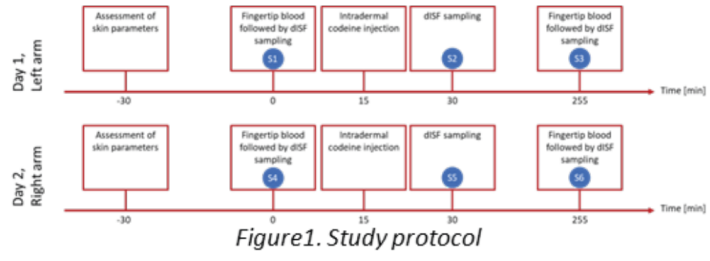


Figure1. Study protocol

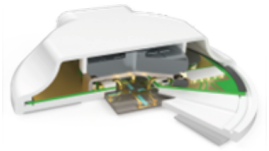


Figure 2. Device cross-section

Figure 3. Device Size comparison

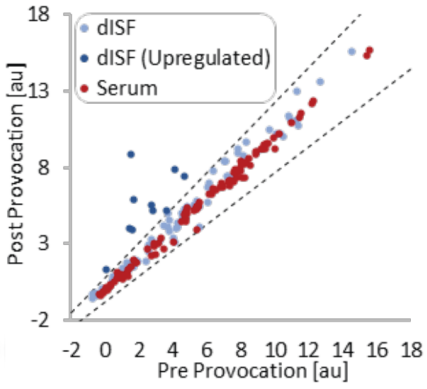


Figure 4. Cytokine data

Discussion: Biomarker detection in dISF could enable new insights into health as well as new opportunities for minimal invasive monitoring.

Conclusion: In summary, wearable sensors are instrumental in collecting real-time, comprehensive, and continuous biomarker information, which is vital for the development and effectiveness of Digital Twins in healthcare and beyond. They contribute to a more accurate, personalized, and dynamic representation of an individual's health status, fostering proactive healthcare and personalized interventions.

Keywords: *Cytokine detection, patch, real-time monitoring, dermal interstitial fluid, dISF, Digital twin.*

Programmable graphic user interface-controlled multiplexed translation organ-on-a-chip platform integrated with microelectrode array

Shao-Hsuan Kuo[1], Mariia Zakharova[2], Mar Condor[3], Andries van der Meer[1], Dries Braeken[3], Loes Segerink[2].

[1]Department of Applied Stem Cell Technologies, University of Twente, the Netherlands.

[2]BIOS lab on a Chip group, MESA+ Institute and Technical Medical Centre, University of Twente, the Netherlands.

[3]Life Science Technologies, Interuniversity Microelectronics Centre, Belgium.

s.-h.kuo@utwente.nl

Introduction: Recently, organ-on-a-chip (OoC) technologies has demonstrated advantages in biotechnical and pharmacological research and development. Researchers and engineers in both academia and industries show they are eager to integrate the technology into their workflows. As alternatives to 2D cultures, OoCs provide higher similarity to real tissues while consuming fewer cells and reagents. The unique data on tissue function generated by organs-on-chips could be an important source of data-driven healthcare algorithms. However, the throughput of existing OoCs is too low to fit the demands of healthcare. Intensive operation, limited numbers of replicates, and prerequisite knowledge to microfluidics restrict the possibility of OoC implementation.

Objective: Here, we describe our development towards a sensor-integratable, multiplexed organ-on-a-chip platform for improved parallelization and automation. The platform is controlled by a self-coded LabVIEW graphic user interface (GUI), of which the algorithm supports real-time, manual and automatic, customized microfluidic valve control.

Methods: We designed a tissue-culturing microfluidic chip with integrated pneumatic valves that enable opening and closing of each culture compartment. We developed a user-friendly GUI to realize independent introduction of liquid to each culture compartment. Moreover, we developed a fabrication protocol to integrate the microfluidic chip with a microelectrode array (MEA), thereby enabling plate sensor integration. Finally, we cultured engineered heart tissues in the microfluidic MEA chip to demonstrate the feasibility of tissue maintenance.

Results: The chip is composed of two parts: the microfluidic network and the culture chambers. The microfluidic network regulates complex liquid manipulation with solenoid valves, which are directly controlled via the GUI. The layout enables direct integration of surface sensors to the culture chambers. The valve operation and the independency of chambers during operation are shown. The feasibility of tissue maintenance and sensor integration are demonstrated.

Discussion: In our initial studies, we have already demonstrated the user-friendliness of cell culture and liquid manipulation in the chips, as well as the feasibility of sensor integration. The specified GUI minimized the operation difficulty and allowed customization of experimental protocols.

Conclusion: In this work, we described our first steps towards a parallelized and automated microfluidic culture platform with integrated sensing. This platform will overcome the current limitations of throughput and handling of organ-on-a-chip models. As such, it may enable future systematic generation of large amounts of functional data for integration in healthcare algorithms.

Keywords: *multiplexed organ-on-a-chip, microfluidic large scale integration, microelectrode array, automatic programmable tissue experiment platform.*

iPSC-Derived Vasculature Organ-on-Chip Models for Digital Twin Construction

Mariia Zakharova, Mar Cóndor, Sohail F. Shaikh, Aaron Delahanty, Dries Braeken, Albert van den Berg, Andries D. van der Meer and Loes I. Segerink.

[1]BIOS lab on a Chip group, MESA+ Institute and Technical Medical Centre, University of Twente, the Netherlands.

[2]Life Science Technologies, Interuniversity Microelectronics Centre, Belgium.

m.zakharova@utwente.nl

Introduction: The organ-on-chip (OOC) field holds significant promise for advancing digital twin applications in healthcare. OOC models replicate human organ functions, providing dynamic in-vitro platforms for drug development. Combining OOC models with digital twin technology enables the creation of predictive virtual replicas, essential for refining predictions and understanding organ responses. Our focus here is on recapitulating vasculature in-vitro models, laying the foundation for a digital tool to early predict severe complications in COVID-19 patients.

Objective: Ultimately, the goal is to bridge the gap between in-vitro experimentation and in-vivo human responses, providing a more accurate representation of COVID-19's impact on various organs. By utilizing human induced pluripotent stem cells (hiPSC) we develop personalized in-vitro models, specifically focusing on vascular structure, with the ultimate goal of constructing a comprehensive digital twin.

Methods: To mimic the vasculature, we used the 17 µm thick Si mesh membrane (SMM) with a 1.4×1.4 mm cross-section. Those membranes were integrated into well plates, Transwells, and OOC devices. These three in-vitro models are the most commonly used when studying organ functions. The hiPSC endothelial cells (EC) were seeded on the SMM with pores covered by collagen-I protein resembling the biological basement membrane (BM). The cells were cultured for 5 days.

Results: At the end of the experiment, the hiPSC-EC were immunostained for tight-junctional proteins, and an intact monolayer was observed, critical for the tight vasculature modeling. The optical visualization revealed that cells were viable over the cell culture period and organized themselves in the large pores of the SMM. Thus the fabricated SMM proved to be suitable for barrier formation in a variety of in-vitro models.

Discussion: Here we focused on modeling the vasculature on a chip employing the hiPSC-EC. To improve the physiological characteristics of the vasculature barrier, a novel SMM with a unique pore design and high porosity (>90%) was fabricated. Unlike standard cell supports represented by synthetic polymer membranes with low porosity and high thickness, the fabricated SMM allows clear visual inspections of the cells while minimizing cell-substrate contact. By integrating the biologically relevant BM we can closely mimic the intricate vascular dynamics.

Conclusion: In summary, our work makes the first steps in incorporating in-vitro vasculature models into the digital twin framework. Future integration of electrical readouts on Si-mesh islands holds the potential for real-time monitoring of cell layer dynamics. This comprehensive approach promises to enhance our understanding of COVID-19's impact on the vascular system, aiding in the prediction and management of patient outcomes. This synergistic strategy holds great promise for more targeted and effective treatment strategies.

Keywords: *organ-on-chip, vasculature in-vitro model, silicon mesh membrane.*

Hybrid implantable optoelectronic sensor for fingerprinting of brain tumour evolution

P. Giannakou[1], K. Faropoulos[2], T. Andreou[3], E. Tsitsou[3], E. Efthymiadou[4], C. Pitris[1], A. Odysseos[3].

[1]KOIOS CoE-University of Cyprus.

[2]Nicosia General Hospital.

[3]EPOS-Iasis, R&D.

[4]National and Kapodistrian University of Athens.

giannakou.pavlos@ucy.ac.cy

Introduction: Implantable sensors generate and deliver data from physical disease representations such as Organ-on-Chips, animal models and patients, enabling functional and predictive simulations. Developing sensors that can continuously record and quantify specific biomarkers of disease evolution or recurrence such as exosomes and their response to therapy, is a major prerequisite for data-driven decisions and interventions enabled by visualisation models and algorithms.

Objective: We aim to intercouple photocurrent measurements with image visualisation and processing and interfacing with disease pathways, specifically representing tumour evolution and progression and its response to therapy with longitudinal and in real time monitoring. Sensitivity and specificity are enhanced with integration of electronic & biological attributes by rationally designed, lanthanide-based smart optical nanoparticle probes, eliciting optical signals upon interaction with propagating tumour exosomes and intercoupled with the electronic components of the sensor. Multiparametric data are integrated towards disease simulation and prediction of the indicated interventions.

Methods: The hybrid sensor is comprised co-polymer, lanthanide- and aptamer- based nanoparticles in polymeric nanomembranes, integrated on a set of light emitting diodes (LEDs), a set of photodiodes (PDs) used for fluorescence detection, the related electronics for signal amplification and processing, and an ultrasonic transducer for non-invasive transfer of high-fidelity data in real-time, ensuring minimal signal degradation during transmission, circumventing traditional barriers in data communication. Glioblastoma organoid was developed on a hybrid scaffold of nanorods and hydrogel. For orthotopic mouse model tumour cell spheroids underwent stereotactic implantation and sensor was implanted through a cranial window. The processed data are consequently fed into computational frameworks including statistical, machine learning, artificial neural networks.

Results: In-vivo photocurrent measurements confirmed the ability of the hybrid sensors to monitor qualitatively and quantify the growth of glioblastoma. The advanced data processing pipeline has been conceptualized to employ machine learning techniques, which, although not yet fully implemented, is designed to transform multivariate sensor outputs into predictive insights, offering a forward-looking model for tumour growth trajectory and therapy efficacy assessment as well as patterns observations of the biomarkers over time.

Discussion: Albeit preliminary, these results provide insights into the multiscale and longitudinal prerequisites for a dynamic DT with the development of organoid and organism and implementation of continuous monitoring. The integration of nanobiotechnology with electronics in the same biocompatible deep sensor paves the way to a new generation of implantable sensors and more data sets for optimization of the prediction models

Conclusion: Rationally designed deep sensors and biomimetic models can support the evolution of digital twins with high clinical relevance.

Keywords: *Hybrid sensor, orthotopic models, ultrasound communication.*

Acknowledgments: *We thank EIC for HORIZON2020 Grants 828837 and 101017915.*

Towards the creation of a digital kidney twin through multi-omics profiling of urinary extracellular vesicles in ADTKD-MUC1 patients and healthy controls.

Andrea C. Kakouri[1], Maria Pozova[1], Apostolos Malatras[1], Panayiotis Savva[1], Yiolanda Englezou[2], Natasa Giallourou[1], Christoforos Stavrou[3], Constantinos Deltas[1,4], Gregory Papagregoriou[1].

[1] biobank.cy, Center of Excellence in Biobanking and Biomedical Research, University of Cyprus, Nicosia, Cyprus.

[2] KIOS Research and Innovation Center of Excellence, University of Cyprus, Nicosia, Cyprus.

[3] Evangelismos Hospital, Pafos, Cyprus.

[4] Medical School, University of Cyprus, Nicosia, Cyprus.

Papagregoriou.gregory@ucy.ac.cy

Kakouri.andrea@ucy.ac.cy

Introduction: Autosomal Dominant Tubulointerstitial Kidney Disease caused by mutations in MUC1 (ADTKD-MUC1), is a rare genetic disease presenting with non-specific tubulointerstitial fibrosis, bland urinary sediment, progressive chronic kidney disease, and variable age of onset of end-stage renal disease (ESRD) due to yet undefined reasons. There is an urgent need for advanced models that accurately reflect complex biological systems and disease states.

Objective: The aim of this study is to generate a digital representation of normal and diseased kidney substructures, assisted by multi-omics profiling of extracellular vesicles (EVs) released in the urine by relevant cell types to create a digital microenvironment that mimics disease progression states.

Methods: Through an ongoing observational study, longitudinal clinical and biochemical data and samples were collected by 46 participating individuals diagnosed with ADTKD-MUC1 and analyzed for disease progression patterns. Biomarker discovery efforts included the profiling of urinary EVs using high-throughput small RNA sequencing and mass spectrometry (MS)-based proteomics, metabolomics and lipidomics. Differential expression (DE) analysis was performed to identify deregulations in the expression patterns of patients compared to controls, as well as between patients with different progression rates. To gain deep understanding on disease pathobiology and eventually design better therapeutics, we plan to consider EV multi-omics data as surrogates for cell disease states and generate a digital twin of cellular identity and interactions between tubular cells that are affected by the disease.

Results: Comparative analysis resulted in the identification of distinct expression signatures between patient groups demonstrating different disease progression rates. Subsequently, publicly accessible repositories, such as the Kidney Tissue Atlas, Single-Cell Expression Atlas, Protein Atlas and GTEx Portal, will be used to map the expression signatures of the uEVs. Given the disease's heterogeneous clinical and molecular presentation, our analysis will expand beyond DE. A personalized approach will be adopted, by horizontally integrating multi-omics expression data to generate individualized digital biopsies, that will accurately profile the disease characteristics of each patient, and which will serve as tools towards the development of personalized medicine.

Discussion & Conclusion: This study performs a multileveled exploitation of the uEV cargo in ADTKD-MUC1 patients and healthy individuals, for the creation of a realistic and scalable digital kidney twin that will revolutionize and redirect global kidney research and drug discovery efforts.

Keywords: *kidney digital twin, tubular, multi-omics, extracellular vesicles*

Hardware accelerators for privacy-preserving biomedical AI on the Edge

Lara Orlandic[1], *Benoît W. Denkinger[1]*, *Miguel Peón-Quirós* [1], Mario Konijnenburg[2], David Atienza[1] and Francky Catthoor[2].

[1]EPFL

[2]IMEC

Lara.orlandic@epfl.ch

Introduction: Modeling humans as digital twins requires significant volumes of biomedical signal data. The sensor nodes at the edge of such Internet of Things systems must ensure that the data is processed accurately and efficiently while also protecting patients' privacy.

Objective: We have designed a hardware accelerator for biomedical AI that executes algorithms such that the raw data never leaves the edge device, thus ensuring secure Edge-AI execution.

Methods: We developed our accelerator, the VWR2A, using innovative processor architecture techniques, such as reconfigurable arrays and low-power memories, to speed up common biomedical functions (i.e. FIR filters, FFTs). We compare the VWR2A to a standard FFT accelerator.

***Results**:* The reconfigurability of the VWR2A allows it to accelerate many different parts of the biomedical algorithm while exhibiting a comparable FFT performance speed-up to the standard accelerator. Thus, the VWR2A enables a 9.9x performance increase and 2.9x energy savings overall.

Discussion: We have shown that reconfigurable, domain-specific architectures like the VWR2A execute biomedical applications more quickly and efficiently than standard accelerators.

Conclusion: The VWR2A architecture extracts meaningful biomedical data from digital twins directly on the edge devices themselves, thus preserving data privacy.

Keywords: *Edge Artificial Intelligence, Biomedical Signal Processing, Domain-Specific Integrated Processors, Internet of Things*

Acknowledgments: DIGIPREDICT, IMEC