DMD Europe 2017
Micro-fabrication for medical devices
14 – 15 November 2017
High Tech Campus - Eindhoven - The Netherlands

Editors:
Shivani Joshi
Angel Savov
Johan Klootwijk
Welcome

To this special edition of the Design of Medical Devices Europe conference that is jointly organized by the Delft University of Technology and Philips.

The central theme this year is “Microfabrication for Medical Devices,” and with a reason! In the ECSEL, INCITE and InForMed project initiatives, a European consortium developed the technology concepts as well as the manufacturing pilot line infrastructure to realize the next generation of smart catheters. This is the reason to organize the conference at the High Tech Campus, just opposite to the pilot line where the “brains” of these catheters will be manufactured.

The High Tech Campus is the heart of one of the most innovative regions in the world where some 11 000 researchers, developers and entrepreneurs employed by more than 150 companies and institutes work on innovative products and technologies.

In this book you will find information about the conference, the conference program, the key note and invited speakers, descriptions of important locations and all accepted abstracts.

The DMD-EU 2017 Organising Committee

Organizing Committee Members (left to right): Angel Savov, Folkert Morsheim, Ronald Dekker, Shivani Joshi, Sieger Swaving, Johan Klootwijk
Delft University of Technology is a modern university of science and technology. Its eight faculties are at the forefront of technological developments contributing to scientific advancement in the interests of society. The university’s excellent research and education standards are backed by outstanding facilities and research institutes.

Delft University of Technology is not only the oldest, but also the largest university of technology in the Netherlands. Its history dates back to 1842 when King Willem II founded the “Royal Academy for education of civilian engineers.”

The Delft University of Technology has close ties with Philips Electronics. In 1883 Gerard Philips, the founder of Philips Electronics graduated from the faculty of mechanical engineering. In 1917 Gerard Philips was awarded an honorary doctorate degree from the same university. By then, Philips was the largest employer in Holland with more than 3500 employees.

The group Electronic Components Technology and Materials (ECTM) of the faculty of Electrical Engineering, Mathematics and Computer Science, focuses on emerging materials, innovative microstructures and devices. Together with the state-of-the-art Else Kooi Lab (EKL) cleanroom facility, the group realizes novel integration concepts for health, energy, sensing & environmental applications.

Many PhD and master students have been involved in joint projects with Philips Research in the framework of national (STW, M2i, NanoNextNL) as well as international (H2020, ECSEL, ENIAC, PENTA) healthcare related projects. With the realization of the new polymer lab in the context of the ECSEL InForMed project, the capabilities of the EKL lab are now fully aligned with the pilot line of Philips in Eindhoven, enabling an even closer cooperation and a swift valorisation of research results.
The Philips Physics laboratory was founded in 1914 to support the production of lightbulbs and develop new products. In the ensuing century it grew into one of the most important industrial laboratories. Among the most well-known innovations it generated are: the compact cassette and compact disk, the pentode, ferroxcube, delta modulation and the plumbicon TV camera tube.

Today Philips Research is a global organization that helps Philips introduce meaningful innovations that improve people’s lives. We provide technology options for innovations in the area of health and well-being, targeted at both developed and emerging markets. Positioned at the front-end of the innovation process, we work on everything from spotting trends and ideation to proof of concept and – where needed – first-of-a-kind product development.

Philips Innovation Services is specialized in bringing innovations to the market, for customers inside and outside of Philips, from start-up to multinational. It is globally active with almost 1,000 specialized experts and 10,000 m² of high-tech infrastructure. This includes the “InForMed” pilot line for micro fabricated medical devices consisting of a 2600 m² medically qualified micro-fabrication cleanroom, a 3500 m² equally qualified assembly centre and a fully equipped catheter workshop.

Philips Research and Philips Innovation Services closely cooperate to bring new innovative healthcare products to the market thereby spanning the whole continuum from idea to product.
In INCITE, technology platforms were developed that will enable advanced ultra-sound imaging, sensing (pressure, force) and steering functions to be integrated into (sub)millimetre size in-body catheters and surgical instruments for emerging complex minimally invasive cardio-, neuro-, and peripheral vascular interventions.

The devices will accelerate the paradigm shift from costly, burdensome surgical treatments to cost-effective and patient-friendly minimally invasive interventions. They will also enable the creation of new advanced treatments for currently complex surgical procedures that will improve present therapies and increase the efficacy of treatments. These new technologies will improve patient outcome and by this lowering the tremendous economic and social cost of cardiovascular disease in society.

INCITE is an ENIAC JU project and is co-funded by grants from the Netherlands, Finland, Hungary, France, Ireland, Sweden, Spain, and Poland, grant number 621278-2. Start March 2014 – end Sept 2017.

www.incite-project.eu
In the InForMed project an integrated open pilot line for medical devices is being established, covering the complete innovation chain from technology concept to system qualification. It will include micro-fabrication, assembly and even the fabrication of smart catheters. The integrated pilot line is hosted by Philips, and is specifically targeted and equipped to bridge the gap in the landscape of micro-fabrication of medical devices between concept creation and full-scale production.

39 partners from 10 countries participate in the project to form manufacturing networks and build an eco-system where new medical devices can be seeded and nurtured to grow into new business opportunities for Europe, in a time when there is a paradigm shift from large expensive diagnostic equipment towards small, disposable, minimally invasive and un-obtrusive diagnostic and therapeutic instruments and tools.

The pilot line is demonstrated by six demonstrator products that cover traditional, emerging, and entirely new market segments, in the domains of "Hospital and Heuristic Care" as well as "Home Care and Well-being," and that demonstrate the trend towards "Smart Health" solutions.

InForMed is an ECSEL JU project and is co-funded by grants from Belgium, Finland, France, Germany, Great Britain, Ireland, the Netherlands, Spain, Sweden and Switzerland. Grant number 2014-2-662155. Start June 2015 – end September 2018.

www.informed-project.eu
Conference Floorplan

Ground Floor

- Einstein Auditorium
- Poster session
- Catering
  - Zeeman
  - Lorentz
  - Debye
- Catering
  - Röntgen
- Toilets
- Luggage area
- Back Entrance
- Main Entrance

First Floor

- Einstein Auditorium
- Parallel sessions
  - Ernst
- Toilets
- Vide

Venue

HIGH TECH CAMPUSS BINTSWAARD
T +31 (0) 60 330 57 00
E conferencecenter@hightechcampus.com
W www.hightechcampus.com/conferencerecenter
BY CAR
• Follow the signs for Eindhoven- centrum or Veldhoven/Randweg N2 (not highway A2) and leave the motorway at exit 32a High Tech Campus.
• When using a route planner or navigation system, please enter the address “High Tech Campus 1” at Eindhoven.
• Note: Not all route planner and navigation systems have updated software. You may find the Campus under its former address “Professor Holstlaan 4”.

PARKING
Visitors are advised to park in garage P0. All gates to Randweg N2 and Professor Holstlaan are open during weekdays, between 06.30 and 20.30 hours.

BY PUBLIC TRANSPORT
Easy access from NS railway station Eindhoven with bus connection and 407 (bus stop HTC/The Strip)
Dr. Pim Tonino

Presently leading a corporate start-up venture in the cardiology field within Philips’ Image Guided Therapy business. Before that created new medical device propositions in China and delivered the Allura X-ray cathlab product line for Philips Healthcare. Educated as a chemist and physicist, corporate entrepreneur by nature.

**Presentation Title:** Exploring the future of Image guided surgery with smart catheters

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Ron Kroon, PhD

Philips Healthcare

Presently leading a corporate start-up venture in the cardiology field within Philips’ Image Guided Therapy business. Before that created new medical device propositions in China and delivered the Allura X-ray cathlab product line for Philips Healthcare. Educated as a chemist and physicist, corporate entrepreneur by nature.

**Presentation Title:** Exploring the future of Image guided surgery with smart catheters

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Dr. Pim Tonino

Catharina Hospital, Eindhoven

Pim Tonino is an interventional cardiologist, working in the Catharina Hospital, Eindhoven, the Netherlands. The Catharina Hospital is well known for its supraregional, tertiary role in interventional cardiology, electrophysiology and cardiothoracic surgery. As head of the interventional catheterisation laboratory, the primary clinical focus of Pim is complex percutaneous coronary intervention (PCI), percutaneous valve therapies and training fellows in PCI techniques. In 2010 he obtained his PhD degree at the Technical University Eindhoven (TUE) on the subject of Fractional Flow Reserve (FFR) measurements. Intracoronary FFR measurements are performed with a micro-sensor that is integrated in a regular PCI wire. A large, randomized clinical trial (FAME study) was the core of his thesis, showing that a PCI strategy guided by FFR was superior to the, at that time, mainstream strategy guided by angiography. Nowadays, FFR plays a pivotal role in the international PCI guidelines (class 1A recommendation) and in all cath labs throughout the world. His current research activities include new developments in FFR, intracoronary temperature measurements, absolute coronary flow measurements and physiology based assessment and therapeutic clinical decision making in aortic and mitral valve disease. Many of these research projects are performed in collaboration with the Department of Biomedical Engineering of the TUE.

**Presentation Title:** FFR - 'less is more' - from innovative theory to golden standard
Prof. Thomas Stieglitz
University of Freiburg

Thomas Stieglitz received the Dipl.-Ing. degree in electrical engineering with the specialty in biomedical engineering from the University of Technology, Karlsruhe, Germany, in 1993. He received the Dr.-Ing. degree in electrical engineering from the University of Saarland, Germany, in 1998. In 1993, he joined the Fraunhofer-Institute for Biomedical Engineering, St. Ingbert (IBMT) Germany where established in 2002 the Neural Prosthesis Group and IBMT. Since October 2004, he is a full Professor of Biomedical Microtechnology with the Institute for Microsystem Technology (IMTEK), University of Freiburg, Germany. His research interests include biomedical microdevices, neural prostheses, neuromonitoring, functional electrical stimulation, and biohybrid systems. Prof. Stieglitz is member of the IEEE-EMBS, the International Society for Functional Electrical Stimulation (IFESS), the German Engineering Society (VDI), and the German Society for Biomedical Engineering (DGBMT).

Presentation Title: Miniaturized Neural Implants: Design, Development and Reliability

Prof. Albert van den Berg
University of Twente

Albert van den Berg received his MSc in applied physics in 1983, and his PhD in 1988 both at the University of Twente, the Netherlands. From 1988-1993 he worked in Neuchatel, Switzerland, at the CSEM and the University (IMT) on miniaturized chemical sensors. In 1998 he was appointed as part-time professor "Biochemical Analysis Systems", and later in 2000 as full professor on Miniaturized Systems for (Bio)Chemical Analysis in the faculty of Electrical Engineering and part of the MESA+ Institute for Nanotechnology. In 1994 he initiated together with Prof. Bergveld the international MicroTAS conference series.

Presentation Title: From Lab on Chip to Organ on Chip
Nicolaas (Klaas) Bom was born in 1937 in Velsen, The Netherlands and received his degree in electrical engineering from the Delft Technical University with a thesis on electromagnetic wave propagation. He became naval officer and subsequently worked for 6 years on SONAR research in Italy whereafter he moved in 1968 to the cardiology department at the Erasmus University Rotterdam starting diagnostic echo research. He obtained his PhD with work on echocardiography in 1972 and became head of bioengineering of the Thoraxcenter in Rotterdam.

In diagnostic ultrasound, he developed the first phased array catheter and the first linear array. This started worldwide electronic cross-sectional real time imaging in 1972 with linear array transducers. He developed a portable echo machine as early as 1976. His research group became well known in echo contrast, intravascular echo catheters and many other aspects of diagnostic ultrasound.

**Presentation Title:** Prehistory of IVUS 1971-1989 and beyond

Peter Dirksen obtained his PhD degree in physics at the Leiden University, Leiden, The Netherlands. In 1990 he joined Philips Research Eindhoven. Until 2006 he worked on optical lithography, including the field of alignment and exposure-tool characterization. Between 2001 and 2006 he was stationed at IMEC Leuven for Philips. Back in Eindhoven, he initiated the development of CMOS post-processing compatible MEMS (CMUT) ultra-sound transducers. Until today he remains the leading CMUT architect within a growing team of multidisciplinary experts, with disciplines ranging from physics-based modelling to medical application development. They succeeded in optimizing the performance of the CMUT transducers, so that they can compete with commercial piezo transducers available today. Furthermore, they have been able to demonstrate new application opportunities. In addition, he worked on integrated pressure sensors. Peter Dirksen is an inventor of 40 patents owned by Philips worldwide in the field of CMUT.

**Presentation Title:** CMUT - from research to product
Prof. Liesbet Lagae
KU Leuven/IMEC

Liesbet Lagae received her degree from the KU Leuven, Belgium for her work on Magnetic Random Access Memories in 2003. She has pioneered the field of molecular biochips based on magnetic, plasmonic and electrical sensing principles at IMEC, Belgium. She is currently research group leader and program manager of IMEC’s HUMAN++/Life sciences program. She has (co-)authored 72 peer reviewed papers in international journals and holds 12 patents in the field. She is also part-time professor in nanobiotechnology at KU Leuven/Physics department.

Presentation Title: *Life sciences go digital*

Prof. Stéphanie Lacour
Ecole Polytechnique Fédérale de Lausanne

Prof. Stéphanie P. Lacour holds the Bertarelli Foundation Chair in Neuroprosthetic Technology at the School of Engineering at the Ecole Polytechnique Fédérale de Lausanne. She received her PhD in Electrical Engineering from INSA de Lyon, France, and completed postdoctoral research at Princeton University (USA) and the University of Cambridge (UK). Her research focuses on the materials, technology and integration of soft bioelectronic interfaces including artificial skin, ultra-compliant neural electrodes for in vitro platforms as well as in vivo implants.

Presentation Title: *Soft bioelectronic interfaces*
Janny van den Eijnden-van Raaij is managing director and member of the board of the Institute for human organ and Disease Model Technologies (hDMT) in The Netherlands.

She studied biochemistry at the University of Nijmegen. At this University (faculty of mathematics and natural sciences) she obtained her PhD in 1985 on the thesis ‘Calcium-binding lens membrane proteins’. She pursued her career as a group leader at the Hubrecht Institute in Utrecht. Her research focused on the role of growth factor and growth factor receptors in embryonic development and tumor formation, using stem cell cultures as in vitro model system.

**Presentation Title:** hDMT Organ-on-Chip Consortium: Joining forces for the future in Europe

Maurits Butter is an expert in industrial innovation policy. He graduated at the faculty of chemical engineering at the Delft University of Technology and started his career as an environmental consultant with a Dutch consultancy firm. In 1994-1998 he worked for the Netherlands’ Ministry of Housing, Spatial Planning and Environment (VROM). In 1998 he joined TNO as senior advisor innovation policy. He is involved in the interface between technological innovation and policy, focusing on industrial innovation policy. He was the research leader for the TNO research program on “Renewal of Innovation” and now is expert in connecting research to industrial innovation. At Tebodin, he was involved in supporting companies in “prevention of waste disposal and emissions”. He took this practical experience with him to the Ministry and as a civil servant to develop industrial innovation policy, combining people, planet, profit. His present focus is understanding the development and financing of public private partnerships where sharing expertise and infrastructures are used to cross the valley of death.

**Presentation Title:** Sharing to reduce economic risks
Bert De Colvenaer was appointed Executive Director of the ECSEL Joint Undertaking as of January 1st 2016. ECSEL is a public-private partnership on nanoelectronics, embedded software and smart system integration established as an autonomous European Union body through the merger of ENIAC and ARTEMIS JUs.

As Executive Director, he is the legal representative of the ECSEL JU and is the chief executive responsible for its day-to-day management. Prior to his appointment he was Executive Director of the Fuel Cells and Hydrogen Joint Undertaking (FCH JU) mandated to bring the FCH technology to the point of market readiness. Bert De Colvenaer has been involved in the automotive industry for more than 20 years, in the field of power-train production engineering and advanced research. He has been working on fuel cell research from the early 90’s and was involved in high level group activities and major EU research projects. In 2002 he established and led the Advanced Technology Division of Toyota Europe, focusing on breakthrough research in the field of fuel cell and hydrogen, robotics and new automotive production technologies. Prior to Toyota, he worked for Volvo. His academic background is in mechanical engineering and in industrial management.

**Presentation Title:** Thinking together, Working together, Investing together
**CONFERENCE SCHEDULE**

**14th November 2017**

**Tuesday**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1</th>
<th>Session 2</th>
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</thead>
<tbody>
<tr>
<td>10:30 - 12:00</td>
<td>The next generation smart catheters</td>
<td>INCITE / InForMed pitch presentations</td>
</tr>
<tr>
<td>10:30</td>
<td>A Front-End ASIC with In-Probe Digitization for 3-D Forward-Looking Intravascular Ultrasound Imaging</td>
<td>Micro-fabrication of medical devices for Europe: Introduction to the INCITE and InForMed projects</td>
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<tr>
<td></td>
<td>Mingliang Tan</td>
<td>Sieger Swaving</td>
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<tr>
<td>10:45</td>
<td>Compressive Forward-Looking 3D Intravascular Ultrasound Imaging Using a Single Element Transducer</td>
<td>Speed presentations to pitch the project achievements</td>
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<tr>
<td></td>
<td>Jovana Janjic</td>
<td>INCITE &amp; InForMed demo leaders</td>
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<tr>
<td>11:00</td>
<td>RF ablation catheter for photoacoustic lesion monitoring</td>
<td>Meet the experts: Visit the INCITE/InForMed poster exhibition</td>
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<td></td>
<td>Sophinese Iskander-Rizk</td>
<td>INCITE &amp; InForMed demo leaders</td>
</tr>
<tr>
<td>11:15</td>
<td>Heartbeat OCT disposable catheter with distal microphone</td>
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<td></td>
<td>Leonardo Cecchetti</td>
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<tr>
<td>11:30</td>
<td>Improving bladder cancer diagnostics with an Optical Coherence Tomography imaging catheter</td>
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<td>Arjan Groenevelt Scinvivo</td>
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<table>
<thead>
<tr>
<th>Time</th>
<th>Session 4</th>
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<tbody>
<tr>
<td>13:50 - 16:00</td>
<td>Innovation in micro-fabricated medical devices</td>
</tr>
<tr>
<td>13:50</td>
<td>Bridging the Valley of Death for Microfabricated Medical Devices</td>
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<tr>
<td></td>
<td>Ronald Dekker</td>
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<tr>
<td>14:00</td>
<td>Thinking Together, Working Together, Investing Together</td>
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<tr>
<td></td>
<td>Bert de Colvenaar</td>
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<tr>
<td>14:20</td>
<td>Sharing to Reduce Economic Risks</td>
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<td></td>
<td>Maurits Butler</td>
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<tr>
<td>14:40</td>
<td>The Philips MEMS Foundry – a European Pilot Line for Medical Devices</td>
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<td></td>
<td>Robbert v.d. Waal</td>
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<tr>
<td>15:00</td>
<td>Design and Development of SureStim</td>
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<td></td>
<td>Hubert Martens</td>
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<tr>
<td>15:20</td>
<td>PhD+, from Lab to Fab</td>
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<td></td>
<td>Paul de Wit</td>
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<tr>
<td>15:35</td>
<td>UBORA: Euro-African Open Biomedical Engineering e-Platform</td>
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<td>Andrés Díaz Lantada</td>
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</table>

**Registration and Coffee**

<table>
<thead>
<tr>
<th>Time</th>
<th>Location</th>
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<tbody>
<tr>
<td>08:00 - 09:00</td>
<td>Röntgen</td>
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<tr>
<td>09:00 - 09:10</td>
<td>Einstein Auditorium</td>
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<tr>
<td>09:10 - 09:50</td>
<td>Einstein Auditorium</td>
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<tr>
<td>09:50 - 10:20</td>
<td>Einstein Auditorium</td>
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<tr>
<td>10:30 - 12:00</td>
<td>Röntgen</td>
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<tr>
<td>12:00 - 13:00</td>
<td>Röntgen</td>
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<tr>
<td>13:00 - 13:40</td>
<td>Einstein Auditorium</td>
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<tr>
<td>13:50 - 16:00</td>
<td>Ernst</td>
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<tr>
<td>16:00 - 16:15</td>
<td>Röntgen</td>
</tr>
<tr>
<td>16:15 - 17:30</td>
<td>High Tech Campus / Greenhouse</td>
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<tr>
<td>18:00 – 20:00</td>
<td>Philips Museum</td>
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## Conference Schedule

**15th November 2017**

### Wednesday

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30 - 09:00</td>
<td>Registration and Coffee</td>
<td>Röntgen</td>
</tr>
<tr>
<td>09:00 - 09:10</td>
<td>Welcome</td>
<td>Einstein Auditorium</td>
</tr>
<tr>
<td>09:10 - 09:40</td>
<td>Keynote: Miniaturized Neural Implants: Design, Development and Reliability</td>
<td>Einstein Auditorium</td>
</tr>
<tr>
<td>09:50</td>
<td>Invited: Life Sciences Go Digital</td>
<td>Einstein Auditorium</td>
</tr>
<tr>
<td>10:20</td>
<td>Invited: Soft Bioelectronic Interfaces</td>
<td>Ernst</td>
</tr>
<tr>
<td>10:20 - 12:00</td>
<td>Session 5: Smart Body Patches</td>
<td>Einstein Auditorium</td>
</tr>
<tr>
<td>12:00 - 13:00</td>
<td>Lunch</td>
<td>Röntgen</td>
</tr>
<tr>
<td>13:00 - 13:40</td>
<td>Keynote: From Lab on Chip to Organ on Chip</td>
<td>Einstein Auditorium</td>
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<tr>
<td>13:50 - 16:00</td>
<td>Session 6: Robotics and Miscellaneous</td>
<td>Ernst</td>
</tr>
<tr>
<td>16:00 - 16:15</td>
<td>Closure</td>
<td>Einstein Auditorium</td>
</tr>
<tr>
<td>16:15 - 17:30</td>
<td>Drinks &amp; Snacks</td>
<td>Röntgen</td>
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</tbody>
</table>

**Session 5: Smart Body Patches**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker(s)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:20</td>
<td>DermaTrax: Development of a Bluetooth-enabled Wound Dressing with onboard Temperature and Moisture sensing</td>
<td>Suzanne O'Callaghan</td>
<td>Tyndall</td>
</tr>
<tr>
<td>10:35</td>
<td>Smart Textiles for Health Monitoring</td>
<td>Marcin Meyer</td>
<td>KOB</td>
</tr>
<tr>
<td>10:50</td>
<td>Human Health Monitoring by Micro Gas Detectors</td>
<td>Johan Klootwijk</td>
<td>Philips Research</td>
</tr>
<tr>
<td>11:05</td>
<td>Breaking Barriers: Wearable Micro Transdermal Interface Platforms (MicroTIPs) for Transdermal Delivery and Diagnostics</td>
<td>Conor O'Mahony</td>
<td>Tyndall</td>
</tr>
<tr>
<td>11:20</td>
<td>Microneedle-based ECG Monitoring</td>
<td>Andrea Bocchino</td>
<td>Tyndall</td>
</tr>
<tr>
<td>11:40</td>
<td>Hybrid Printed Electronics in Health patches: the perfect match!</td>
<td>Frank Everaerts</td>
<td>Holst Centre</td>
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</tbody>
</table>

**Session 6: Bioelectronics**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker(s)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:20</td>
<td>Deep brain stimulation and sensing</td>
<td>Luc van Immerseel</td>
<td>Nexeon Medsystems</td>
</tr>
<tr>
<td>10:40</td>
<td>Advancing bioelectronics development</td>
<td>Rory Murphy</td>
<td>Intelligent Implants</td>
</tr>
<tr>
<td>11:00</td>
<td>Flexible implantable ultrathin chip encapsulation (FITEP) to fabricate neural CMOS-based probes for intra-fascicular implantation</td>
<td>Maaike Op de Beeck</td>
<td>IMEC</td>
</tr>
<tr>
<td>11:15</td>
<td>Miniaturized Electrodes and Catheter Tips with Integrated Functional Components based on LCP Substrates</td>
<td>Eckardt Bihler</td>
<td>Dyconex</td>
</tr>
<tr>
<td>11:30</td>
<td>Generic platform for the miniaturization of bioelectronics implants</td>
<td>Marta Kluba</td>
<td>TU Delft</td>
</tr>
<tr>
<td>11:45</td>
<td>Ultra-Low-Noise Signal-Recording Amplifier/MUX ASIC</td>
<td>Reza Lotfi</td>
<td>TU Delft</td>
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**Session 7: Organ-on-Chip**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker(s)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:20</td>
<td>Heart-in-a-Dish: Preclinical Drug Screening for Cardiotoxicity</td>
<td>Berend van Meer</td>
<td>Leiden MC</td>
</tr>
<tr>
<td>14:35</td>
<td>Heart-on-a-chip: a high-throughput, multimodal cardiotoxicity screening platform</td>
<td>Thomas Pauwelyn</td>
<td>IMEC</td>
</tr>
<tr>
<td>15:05</td>
<td>Cystostretch: A Multi-Well Plate Heart-on-Chip Device</td>
<td>Nikolas Gaio</td>
<td>TU Delft</td>
</tr>
<tr>
<td>15:05</td>
<td>Skin-on-chip: integration of skin tissue and microsystems engineering</td>
<td>Lambert Bergers</td>
<td>TU Delft</td>
</tr>
<tr>
<td>15:20</td>
<td>MEMS-Electronics Integration: A Smart Temperature Sensor for an Organ-on-a-chip Platform</td>
<td>Ronaldo Ponte</td>
<td>TU Delft</td>
</tr>
<tr>
<td>15:35</td>
<td>New polymer fabrication strategy for integrated microfluidic systems</td>
<td>Paola Fanzio</td>
<td>TU Delft</td>
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**Session 8: Robotics and miscellaneous**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker(s)</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
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<td>Force feedback and tactile sensing for Robin Heart Surgical Robot</td>
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With the expansion of Philips, Eindhoven grew to the 5th largest city in the Netherlands. For a long time Eindhoven was equivalent to Philips in Holland. Despite the fact that almost all production disappeared from Eindhoven, many landmarks in the city still remind us of the tight links between Philips and the city. Many historical industrial sites such as the White Lady and Strijp-S are now the centre of vibrant social activities.

Amidst all these changes the original factory where Gerard and Anton started their empire is still there, right in the centre of Eindhoven. It is now a preserved industrial building site. A number of years ago it was transformed into a small museum where you can experience Philips’ history in a number of ways. It offers a fascinating picture from the company’s origins in 1891 to the innovations of tomorrow. After the first day of the conference, on the 14th of November, we have appropriately selected this inspiring location to mingle with drinks and snack. Afterwards, you can dine in one of the many restaurants in Eindhoven and experience the amazing GLOW festival!
GLOW is a light and colour festival held every autumn in the centre of Eindhoven that every year reminds us of the long standing love affair between Eindhoven and electrical light. Artists and designers from Holland and abroad present light art and design applications by using new media technologies, such as computers, sensors, animations, and also the well-known projection techniques. GLOW was held for the first time in 2006. The festival is an outdoor exhibition that transforms the city into a work of art. The festival route changes every year to give attention to different areas and neighbourhoods of Eindhoven.
### The Next Generation Smart Catheters

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A Front-End ASIC with In-Probe Digitization for 3-D Forward-Looking Intravascular Ultrasound Imaging

Mingliang Tan¹, Chao Chen¹, Zhao Chen¹, Jovana Janjic²,Verya Daeichin³, Zu-yao Chang¹, Emile Noothout¹, Gijs van Soest², Martin D. Verweij³, Nico de Jong²,³, and Michiel A. P. Pertijs¹

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1. Introduction

Forward-looking intravascular ultrasound (FL-IVUS) is an important tool for the diagnosis of complex lesions inside the coronary arteries, such as chronic total occlusions (CTOs). In order to generate 3-D images, a 2-D transducer array needs to be integrated at the tip of an IVUS catheter. However, it is challenging to integrate the micro-coax cables needed to connect the elements to an imaging system within the limited catheter diameter (<2 mm). A front-end ASIC can be used to reduce the number of cables. Prior work has applied on-chip pulsers and analog receive multiplexers, but still requires at least 13 cables [1]. In this work, we present a front-end ASIC which requires only four micro-coax cables to interface with a total of 80 PZT elements. The ASIC is the first reported design capable of digitizing the received echo signals locally.

2. Methods

The block diagram of the front-end ASIC is shown in Figure 1. The ASIC contains three main parts: 1) a high-voltage (HV) switch array, 2) a receive signal chain, and 3) a clock and data recovery circuit. The HV switch array consists of 16 HV switches which are used to excite 16 transmit elements using HV pulses generated in the imaging system (HV TX PULSE). This implementation allows for a synthetic-aperture transmit scheme in which each of the 16 TX elements are successively pulsed, or, alternatively, a plane-wave transmit scheme in which multiple TX elements are pulsed simultaneously. The 64 RX elements are connected via a multiplexer to a receive signal chain. This allows for the realization of a synthetic-aperture receive scheme by amplifying and then digitizing the echo signals in 64 successive pulse-echo sequences. A SAR ADC is adopted to locally digitize the echo signals. The ADC’s output data is transmitted serially to the imaging system using a load-modulation data link (RX DATA). The clock and data recovery circuit is responsible for extracting a clock for the ADC and chip configuration data, including switch and gain settings, from a COMMAND signal generated by the imaging system. A fourth and final cable provides the ASIC with a supply voltage (VDD).

3. Results

The 10-mW ASIC has been realized in a 0.18 µm HV CMOS process. A transducer array (13 MHz center frequency, 100 µm pitch) was built on the ASIC using the approach described in [2] (Fig. 2). To show the imaging capability of the prototype, a 3D image of a 3-needle phantom has been generated (Fig. 3).

4. Discussion & Conclusion

The proposed front-end ASIC interfaces with 80 PZT elements using only four 1.5 m micro-coaxial cables. The local digitization of the received echo signal provides robust data transmission and paves the way towards further in-probe digital multiplexing and data reduction schemes.

References


Compressive Forward-Looking 3D Intravascular Ultrasound Imaging Using a Single Element Transducer

Jovana Janjic, Pieter Kruizinga, Pim van der Meulen, Geert Springeling, Johan G. Bosch, Geert Leus, Gijs van Soest, Antonius F. W. van der Steen

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1. Introduction

Imaging of coronary chronic total occlusions (CTOs) requires forward-looking intravascular ultrasound (FL-IVUS). Integration of transducer arrays at the tip of a catheter is challenging due to the limited space available. In this work, we explore an alternative strategy for FL-IVUS imaging, using a single element transducer and a coding mask that enables compressive imaging [1]. The coding mask in front of the transducer breaks the uniformity of the ultrasound (US) field and allows to uniquely address every voxel in 3D space. Steering the catheter within the vessel, allows additional measurements for image reconstruction. A specialised algorithm is developed to achieve compressive 3D FL-IVUS imaging.

2. Methods

The 3D coding mask (fabricated using stereolithography at Univ. of Leiden), comprising small pillars of different heights (1.5 mm diameter and 0.7 mm height), is glued on a single element piezoelectric ultrasound transducer (20 MHz, 1 mm outer diameter). See Fig. 1a and b. We compute the forward US field from a hydrophone recording using the angular spectrum approach method [2]. Auto convolution of the forward field provides the estimated pulse-echo signals which are stored (column-wise) in the imaging system matrix $A$. Translation of the US field in the 3D volume allows for additional rows in $A$, thereby increasing the imaging capability of the system. The actual pulse-echo measurements are stacked in the signal vector $y$. The image $x$ is then found by solving $y = Ax$ for $x$ using iterative least squares (LSQR) [3]. We test the imaging algorithm on a simulated imaging target (Fig. 1(e)).

3. Results

Fig. 1c and d show the US field after applying the mask demonstrating that the coded aperture scrambles the US field addressing every pixel with a unique signal. Moreover, the mask acts as a diverging lens, which allows for a better overlap between subsequent recordings. The reconstructed image of the simulated target with the mask is shown in Fig. 1f.

Figure 1: Top view of the coding mask (a), US transducer with coding mask (b), US energy projection in a 2D plane normal (c) and parallel (d) to the US propagation direction, simulated imaging target (e), image reconstruction with the proposed method (f).

4. Discussion & Conclusion

This study shows the feasibility of using compressive imaging for 3D FL-IVUS. This technique requires fewer measurements than classical scanning using a focused field. Future work entails imaging of realistic ex-vivo IVUS targets.

References

The Next Generation Smart Catheters

RF ablation catheter for photoacoustic lesion monitoring

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1. Introduction

Atrial fibrillation is a heart arrhythmia which affects 5.5% of the Dutch population aged 55 or above [1]. Atrial fibrillation patients suffer from fatigue and are at a higher risk of stroke and heart failure. One of the treatments for atrial fibrillation is catheter-based ablation. In that procedure, a catheter is inserted in the left atrium, and electrically active foci are ablated by applying RF current. However, the success rate of such intervention is only about 60-70%. One way to improve the procedure is by providing the cardiologist with a way to monitor lesion progression. We propose using photoacoustic (PA) signals generated from the ablation catheter tip and collected by an ICE (Intracardiac Echo) catheter to visualize the process. In this study, we describe an RF ablation catheter prototype with integrated fiber optic, and we demonstrate its imaging capability on ex vivo fresh porcine tissue.

2. Methods

Previously, we have shown that lesion progression and extent can be monitored and identified in contrast to untreated tissue by taking the PA image ratios at 790 nm and 930 nm. We study now the feasibility of robust lesion assessment, with an illumination source limited to fit within an ablation catheter. For that purpose we manufactured an ablation catheter compatible with the EPT 1000 XP APM ablation system (Boston Scientific, Marlborough, MA, USA) and we integrated a single fibre optic at its centre. We imaged fresh porcine left atrium specimen in a transmission mode photoacoustic setup. We positioned the prototype catheter (incorporating the light source) at the endocardium side and the transducer at the epicardium side. We used a linear array (192 channels, L12-3v, Verasonics, Redmond, Washington) connected to a Verasonics Vantage 256 research system to collect the photoacoustic signals. The laser source (Vibrant B-355II, Opotek, Santa Clara, CA, USA) was tuned from 710 to 1000 nm in steps of 2 nm.

3. Results

The ablation catheter fabricated was of 2.5 mm outer diameter and included a 400 µm fibre of NA 0.5 (Fig.1c). The fibre was positioned at the centre of the catheter, using one of the irrigation channels in some ablation catheter types. It could successfully create lesions and illuminate the tissue with a fluence of 120 mW/cm². The SNR was ~30 dB before ablation and ~35 dB after ablation. Clearly the tissue signal changes in response to ablation (Fig.1a). Prior to ablation both walls (endocardium and epicardium) generated signal; and post ablation we only see signal from the lesion. Applying a dual wavelength imaging method, taking the ratio of PA images at 790 and 930 nm, provides specific contrast for the presence and extent of the ablation lesion (Fig.1b).

4. Discussion & Conclusion

We have demonstrated an ablation catheter which provides sufficient optical power to obtain photoacoustic signal from fresh and ablated porcine tissue ex vivo. Future work targets improving the catheter design to improve the photoacoustic image capability of lesions as well as to keep space for a cooling tube.

References

Heartbeat OCT disposable catheter with distal micro-motor

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1. Introduction

The formation of atherosclerotic plaques on the walls of coronary arteries can lead to myocardial ischemia, a reduced oxygen supply to the cardiac muscle. The most severe and deadly form is an acute interruption of the flow in one of the major coronary arteries, a myocardial infarction (30,000 in the Netherlands every year).

Minimally invasive treatment by stent implantation in a procedure called percutaneous coronary intervention (PCI) is the current standard treatment in most countries. To guide the interventional cardiologist, imaging technologies are used. Greater accuracy in imaging guidance enables more precise treatment choices, which may lead to better outcomes.

Catheter-based optical coherence tomography (OCT) is the technology with the highest resolution. It provides 3D images of the coronary circulation, visualizing geometry and artery wall composition, based on broadband infrared interferometry. Some present limitations are: undersampling, cardiac motion artefacts and non-uniform rotation distortion (NURD).

We develop an ultrafast OCT system, called Heartbeat OCT, with higher sampling rate and acquisition speed to overcome these shortcomings. It employs a custom-built catheter that integrates a micro-motor in its distal end. This eliminates the NURD artefacts caused by a flexible rotating shaft and enables scan speeds up to a frame rate of 5.6 kHz.

2. Methods

The Heartbeat OCT system is based on a FDML laser unit with a 1.6 MHz sweep rate and a resolution of 12 μm in tissue.

The catheter that is inserted into the coronary artery has an outer diameter of 1.1 mm and contains the single mode optical fibre that carries the laser radiation and a two-phase synchronous micromotor with four copper wires that provide the driving current.

The micromotor, built by Kinetron BV, has a prism mounted on its shaft (figure 1) for reflecting the laser beam sideways, towards the vessel wall. In imaging configuration it spins at 3200 RPS, but it has been capable of up to 7000 RPS during testing.

The system can acquire a 3D image of 10 cm of artery in 1 s. By triggering the acquisition with the R peak of the ECG, the short acquisition time eliminates the cardiac motion artefacts.

![Figure 1: Schematic and photograph of the micromotor mounted in the Heartbeat OCT catheter.](image)

3. Results

An in vivo 3D porcine coronary artery OCT scan has been performed. The acquisition took 1 second to complete, thus eliminating the heart movement artefact by acquiring the image between two consecutive heart contractions.

![Figure 2: a) 3D reconstruction of Heartbeat OCT data b) section of the artery](image)

4. Discussion & Conclusion

The device shows promising results. The next step will be further miniaturization of the micromotor and consequently of the catheter, for an improved deliverability.

References


Improving bladder cancer diagnostics with an Optical Coherence Tomography imaging catheter

Maaike de Jong¹, Geert Claassen¹, Arjan Groenevelt¹

¹Scinvivo B.V., Eindhoven; arjan.groenevelt@scinvivo.com

1. Introduction

Worldwide there are 2.7 million people with (a history of) bladder cancer. Bladder cancer has high survival rates (up to 80%), but the recurrence rate of bladder cancer is very high (31%-78%). This means that a patient who is once diagnosed with bladder cancer needs regular check-ups for at least 5 years, and sometimes even lifelong. This makes bladder cancer one of the most costly cancers from diagnosis to death [1].

The treatment of bladder cancer depends on the stage and grade of the cancer. Current technologies to determine this stage and grade are cytology and cystoscopy to screen the bladder, followed by pathological staging after tissue removal. Especially the screening of the bladder with cytology and cystoscopy has its limitations, in the form of a 30% false positive rate. These false positives lead to a high number of unnecessary surgical interventions, which are costly and a burden for the patient as they are performed under full anaesthesia [2].

Optical coherence tomography (OCT) is a new imaging technology, which is analogous to ultrasound but uses light instead of sound. OCT is based on interferometry of light, and in that way allows to view up to 3 mm inside the tissue. With OCT real-time, high resolution (<50µm) cross sections of the tissue are provided. OCT is often described as an optical biopsy technology, which means that it provides instant information about tissue structures behind the surface, without actually taking an invasive biopsy [3].

2. Methods

Using OCT during bladder cancer diagnostics would provide the urologist with additional structural tissue information. Based on this information the urologist can determine more accurate if the tissue is cancerous or benign. Another benefit is that the urologist can determine the invasion depth of the tumour [4].

The challenge is to put this OCT technology in a catheter, that can be used in combination with a cystoscope. Important requirements for the catheter are that it fits in the 2.2 mm working channel of a cystoscope, is forward looking, is not harmful for the patient, and increases the sensitivity and specificity of current diagnostic technologies [4].

3. Results

The developed catheter consist of four main parts: 1) The optical fibre, that transports the light to the tissue and back; 2) Electronics, to actuate and control a MEMS-based laser scanner in the tip of the catheter; 3) A support structure to align and protect all elements in the catheter; 4) A catheter tube, that makes the catheter watertight and sterilisable. The integration of these parts into one OCT-catheter is proprietary technology owned by Scinvivo.

The developed catheter is a disposable, and can be used in combination with commercially available OCT-systems. Figure 1a shows the current product, Figure 1b shows the corresponding OCT scan.

![Figure 1](image)

Figure 1: a) Prototype catheter aimed at a finger; b) corresponding OCT image of a fingertip.

4. Discussion & Conclusion

A forward looking OCT catheter to improve the diagnostics of bladder cancer is developed. The next step to take are performing clinical trials, first ex vivo and then in vivo. Simultaneously a next generation catheter will be developed, which can image with a higher resolution and further miniaturization of the current prototype.

References

### Innovation in micro-fabricated medical devices

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1. Introduction

The InForMed project will establish an industrial pilot line for micro-fabricated medical devices. This pilot line will take up promising new technologies from university labs (Technology Transfer) and develop them to higher maturity levels.

Unfortunately, this Technology Transfer is a weak link in the innovation chain (“Valley of Death”). It often fails, or costs too much time and resources, if it is not abandoned before the start.

To support increase of the inflow of new technology to the pilot line, a methodology is therefore developed and validated as a part of InForMed.

2. Methods

First, we analysed the technology transfer process. We considered the organisational context of the transfer, and identified factors that influence the transfer efficiency and effectiveness. Based on the analysis we formulated principles and a framework that will contribute to improved technology transfer.

We used an iterative approach, in which intermediate results were discussed with InForMed participants whose feedback was then used to expand the analysis and improve the methodology.

3. Results

Technology Transfer from University to Industry is problematic because technologies developed at universities typically have low levels of applicability, manufacturability, and/or technology maturity, which decreases the technologies’ value and increases risks for industry. Also, much university know-how is embodied in persons as tacit knowledge, which is difficult to transfer. Moreover, universities may need to develop and use methods and techniques that are specific for their own labs, which also leads to lower transferability.

We developed an integrated methodology to arrive from new product initiative, via technology development at university, to industrial application. It integrates the main aspects of new product development, from market analysis to manufacturing, and includes a phase-gate model along the lines of H2020’s Technology Readiness Level framework, from TRL2 to TRL9.

Figure 1: PhD student with a wafer containing brain-stimulation probe prototypes.

For each phase, protocols specify what information needs to be produced for decision-making and transfer of explicit knowledge. Transfer of tacit knowledge takes place through working side-by-side in a University-Industry development team. Alignment of infrastructures, skills, and materials used, and best practices for experimental microfabrication, further improve transferability.

The methodology is compatible with new product development methodologies already in use at InForMed industrial partners. Although it contains domain-specific elements, the methodology is generally applicable to Key Enabling Technologies.

The methodology entails a new dynamic way of working for PhD students, which we call the PhD+ programme. Two PhD students are currently working in this way, on organ-on-chip technology and integration of electronics in brain-stimulation probes, respectively. Their research has already resulted in scientific publications, ideas for innovative products, solutions for micro-fabrication processes, a patent application, and a start-up company.

4. Discussion & Conclusion

We made an extensive overview of factors that affect technology transfer from university to industry, and developed a methodology for improved technology transfer. The proposed methodology shows great promise for industry, university, and PhD students.
Innovation in Micro-fabricated Medical Devices

UBORA: Euro-African Open Biomedical Engineering e- Platform

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1. Introduction
UBORA [1] ("excellence" in Swahili), a project funded by European Union, brings together European and African Universities and their associated technological hubs to create an e-infrastructure for the co-design of open source biomedical devices to address current and future global healthcare challenges with particular attention to local needs and constraints. The e-infrastructure is aimed at stimulating innovation in the field of BME through knowledge distribution, promoting harmonization of biomedical device requirements, provision of standardized methods for design control. The e-infrastructure allows peer-to-peer and expert review of all the design phases thus ensuring a higher level of compliance to technical, performance and regulatory requirements and a faster and more efficient transition from ideation to production.

2. Methods
The e-platform is developed by UBOA project participants, from the Academia and the Industry; technical solutions for the platform and implementation of its main functionality are aimed at obtaining a simple and lightweight responsive user-interface (UI), helping users to accomplish a given task as simply and efficiently as possible. The UBOA e-platform is developed to be a modern web standards compliant application: it will be reachable from any location over the internet, available to all common devices and platforms through a web browser. Users never have to worry about updating the UBOA on their devices. The e-platform is lightweight in page load for maximum accessibility.

3. Results
The running version of the e-platform is accessible at http://ubora-dev.azurewebsites.net/ , it is under continuous improvement by AgileWorks with the feedbacks from the UBOA partners. The UBOA platform is an integrated virtual ecosystem, which will lead engineers and healthcare workers through all the phases of innovative design, fabrication, development, testing and implementation of biomedical technology. It will ensure regulatory compliance to main international standards through control of regulatory inputs and verification of regulatory outputs. The platform will be composed of four sections, to fulfill specific tasks of a project:

- a needs identification section, open to everyone (general public, healthcare providers), aimed at identifying problems using forums and surveys, and also at generating disruptive new ideas;
- a project management part, open to accredited users and coordinated by Biomedical Engineers, using specific project management tools. This part is already available in its Alpha version;
- a repository, for free download of projects blueprints which have passed the development phase and have been certified as compliant with applicable international standards;
- a funding section, for supporting selected UBOA initiatives.

The project management UI allows following predefined steps in the design process. The steps have been chosen to mirror the most common design steps as described by ISO standard for quality management systems for the biomedical industry (ISO 13485:2016) and as also described in current GMPs. Predefined reviews will be performed by authorised “mentors”, between specifics steps..

4. Discussion & Conclusion
This e-infrastructure enables a peer-to-peer evaluation and a subsequent expert (by “mentor”) review of the design. This may be a great improvement in an open design process as it ensures higher compliance to industry standards without being a financial or temporal burden on designers. The platform structure also enables mentoring and tutoring during the whole process as opposed to auditing and inspecting the design when it is completed. Quality and safety guidelines for biomedical device, under the guidance of ISO standards and current European Medical Device Directive and upcoming Regulation, are at the foundation of the project, which will be spread to other institutions through partnerships and linkages embedded in the e-infrastructure ’s architecture. UBOA will help also the sharing of open data on devices’ statistics (performance, field tests, quality control), promoting the research on the highest priority medical devices backed with research on current disease burdens.

References
[1] This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 731053
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1. Introduction

Micromachined ultrasonic transducers (MUTs) are an emerging class of MEMS devices, which can be used in a wide variety of potential applications such as in gesture recognition and range finding, in medical applications and in personal healthcare as well as in different types of sensors based on ultrasonics such as gas sensors [1]. Miniaturization of ultrasonic transducers provide several advantages which can make them attractive even for mobile applications, these are low power consumption, small size and good coupling to the medium (air or liquid). MUTs are divided into two different categories, CMUTs (capacitive micromachined transducers) and PMUTs (piezoelectric micromachined transducers). Typically, PMUT devices are fabricated either with aluminum nitride (AlN) or lead zirconium titanate (PZT). We will present a novel type of device fabricated with scandium doped AlN (ScAlN) [2]. The main advantage of ScAlN is a stronger piezoelectric coupling than AlN, while it still has the same order of magnitude dielectric constant, and thus reduced parasitic capacitance of the device compared to e.g. PZT.

Methods

Our PMUT device consists of a released membrane with SiO$_2$/Mo/ScAlN/Mo stack, with SiO$_2$ and ScAlN layer thicknesses of 1 um and bottom and top Mo electrode thicknesses of 150 nm and 250 nm, respectively. ScAlN film was sputter deposited on top of the bottom electrode with Sc concentration of 26%.

In addition, we have also fabricated reference devices with AlN, which is a more conventional piezoelectric material. The reference AlN devices have the same stack thicknesses and electrode geometries as ScAlN devices allowing us to make a feasible comparison of the acoustic and electrical properties of the devices. Devices were fabricated on a 6” (150 mm) wafers containing membrane diameters from 130 µm to 240 µm. Electrical impedance and acoustic transmission characteristics are measured on selected dies on different locations of the wafer to determine the process uniformity.

2. Results

ScAlN PMUT transducers showed a typical Q factors of 1 – 250 in air depending on the membrane size. Typical electromechanical coupling $k^2$ for ScAlN samples was between 1 % and 4 %, while AlN devices showed an order of magnitude lower coupling.

3. Discussion & Conclusion

We have demonstrated operation of ScAlN based PMUT devices. The initial measurements of ScAlN show about an order of magnitude stronger electromechanical coupling $k^2$ than conventional AlN samples, showing that ScAlN is an attractive material for PMUTs.

References


First ever solid-state cMUT IVUS catheter through Flex-to-Rigid integration

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1. Introduction
The Flex-to-Rigid (F2R) technology platform is a wafer-level microfabrication method to realize arbitrary form factor silicon dies which are mechanically as well as electrically connected by flexible interconnects [1]. On these silicon dies, sensors such as capacitive ultrasound micromachined transducers (cMUTs) can be manufactured. In this paper, we present the first ever demonstrated functional solid-state cMUT IVUS catheter realized by means of integration using the F2R technology platform.

2. Methods
Intravascular ultrasound (IVUS) is a medical imaging method using a specially designed catheter having ultrasound functionality at its tip, by which cross-sectional images can be made of a blood vessel from the inside, in order to determine plaque volume and composition as well as the degree of stenosis of the vessel lumen. The two main categories of IVUS catheters are rotational and solid-state devices. Rotational catheters have a single transducer element, which is mechanically rotated to form the ultrasound image, whereas solid-state devices have a stationary array of transducer elements around the catheter circumference, which are electronically scanned to form the image. In the majority of the world, solid-state IVUS catheters are preferred over rotational catheters for their ease of use, however their image quality is lacking due to the limited number of piezo elements that can be diced and integrated in the small circumference of the device.

3. Results
In the ENIAC INCITE project, we have successfully realized the first cMUT based solid-state IVUS catheter as a first step towards a solid-state IVUS catheter combining the superior ease of use and image quality of both categories of catheters. The realized catheter contains 96 transducer elements inside a 1.2 mm diameter, which is a factor of 1.5 more than the commercially available catheters in the same form factor. The INCITE catheter can be operated at ultrasound center frequencies between 15-25 MHz (compared the 20 MHz fixed frequency of the commercial device), thus opening up possibilities for coded excitation schemes, being investigated by Erasmus Medical Center in Rotterdam, The Netherlands. First in-vivo images were successfully obtained at Erasmus Medical Center in Rotterdam (publication in preparation).

Figure 1: Collection of images showing various stages of the INCITE IVUS catheter integration.

4. Discussion & Conclusion
The F2R technology platform has allowed us to realize the tightly curved cMUT array to be wrapped around the circumference of the INCITE catheter, which was an essential element in successfully realizing the first ever demonstrated functional cMUT based solid-state IVUS catheter. We gratefully acknowledge Fraunhofer IZM in Berlin for their support in realizing the catheters, and Erasmus Medical Center in Rotterdam for their valuable input and support in evaluating the catheters. The research leading to these results is part of INCITE (grant #621278), an ENIAC Joint Undertaking project that is co-funded by grants from the Netherlands, Finland, Hungary, France, Ireland, Sweden, Spain, and Poland.

References
1. Introduction

Developers of ultrasound (US) arrays are often faced with questions that cannot be answered by (analytic) models that oversimplify the geometry. Finite element (FE) simulations can include the geometric details of the transducers, but a complete US array model easily becomes too large to solve.

Figure 1: An Intravascular ultrasound (IVUS) array

2. Methods

Within the INCITE project, Reden BV has developed a simulation method that can be used to characterize an US array with FE simulations; based on [1]. Each simulation is relatively small and contains just a single unit cell. The computation time increases linearly with the number of unit cells in the array and the memory usage is independent of it. This makes the method very efficient for large US arrays. The method can be used for 1D and 2D, planar and cylindrical arrays; for example as in figure 1. CMUT (capacitive) or PMUT (piezoelectric) US arrays can be modelled. The transducer geometry can be included in detail and anisotropic materials may be used.

3. Results

Figure 2 shows how a pulse on the central transducer spreads over the array. The reaction current is chosen as output in this example.

Figure 3 shows the same data as Figure 2 after a 2D FFT. This reveals that some crosstalk propagates as a Lamb wave, beside the acoustic propagation in water.

Figure 3: Crosstalk in the frequency/wavenumber domain.

Further processing gives the peak-peak crosstalk current as shown in Figure 4.

Figure 4: Peak-peak crosstalk current. Each dot represents a single transducer.

4. Discussion & Conclusion

The simulation method has two restrictions: the US array needs to be periodic (repetitive), and the response must be (approximated as) linear.

The simulation method is able to simulate radiation patterns and crosstalk of US arrays. We did not yet model incident waves.

Large periodic US arrays can be efficiently modelled using this method. This can help to answer questions (about geometric details) that may arise during the development phase and help to optimize the performance.

References

Electrifying Frequency-Tunable Ultrasound Catheters with Light

Martin Pekar1*, Martin B. van der Mark1


1. Introduction
Cardiovascular deaths represented 31% of all global deaths in 2015. Advances of medical technology, enabled minimally invasive procedures to be performed on the heart. Long, thin, flexible tubes called catheters are threaded through a blood vessel to diagnose and treat the heart from inside. Intracardiac echocardiography (ICE) is an established guidance tool for device closure of interatrial communications and electrophysiological ablation procedures. The exploitation of ICE for navigation during other cardiac interventions is, however, currently limited by its imaging performance at a distance and the restricted side-looking views it typically provides.

2. Methods
Enabled by novel technology called capacitive-micromachined ultrasound transducers (CMUTs), we have developed a new forward-looking ICE that has an advanced functionality of frequency-tunable ultrasound imaging.

The prototype, however, faces connectivity challenge because the signal transmission and supply of power at the distal end require many fragile wires. We have replaced these wires with optical fibers in a benchtop demonstrator that is scalable to catheter dimensions. A vertical-cavity surface-emitting laser is used for transfer of synthetic aperture ultrasound signals and a light-emitting diode is used in reverse as photovoltaic convertor to supply all electronics.

3. Results
The developed frequency-tunable probe prototype is tested ex vivo in a passive heart platform. Images of an aortic valve acquired in high penetration (6 MHz) and high-resolution (18 MHz) mode combine good image quality and penetration depth between 2.5 cm and 10 cm as shown in Fig. 1.

Synthetic aperture ultrasound images were taken at a frequency of 12 MHz with the ultrasound benchtop demonstrator electrified by light. System bandwidth, noise level and dynamic range provided good image quality as illustrated by the ultrasound image of a cyst phantom shown in Fig. 2.

4. Discussion & Conclusion
In conclusion, ex vivo experiment showed that combination of the forward-looking design and the frequency-tuning feature allows visualizing intracardiac structures of various sizes, e.g. leaflets of the heart valves and the ventricle at different distances relative to the probe, providing both wide overviews and detailed close-ups. Further, we have successfully demonstrated low-cost, scalable optical signal and power transmission for an ultrasound imaging system enjoying intrinsic radiofrequency and magnetic-resonance imaging compatibility as well as galvanic isolation.

This research received financial support from the Marie Curie Actions FP7 project OILTEBIA (317526) and ECSEL JU project InForMed (2014-2-662155).
Ultrathin MEMS pressure sensor and readout ASIC

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1. Introduction

We report a new capacitive pressure sensor and a read-out circuit to be integrated in a FFR catheter. The novelty presented in this work is based on two new components: (1) VTT ultra thin and narrow MEMS pressure sensor element and (2) a surface area optimized ASIC designed and implemented for pressure sensor readout and AD-Conversion. The laboratory measurement results of the MEMS pressure sensor with the ASIC correlate well with the calculated and simulated results.

2. Methods

The sensing element is a vacuum capacitor constructed of an ultrathin bending top polysilicon diaphragm and a flat bottom electrode. External pressure causes bending of the top diaphragm and thus varies the capacitance of the element proportional to the external pressure. These pressure sensor dies have extreme dimensions, demanded by the application requirements. The size of the sensor die outline dimensions is 2450 μm x 200 μm x 75 μm (LxWxT). Sensor and its integration concept are described in [1] more detail.

The pressure sensor chips were fabricated on 400-1-75 μm thick SOI -wafers. The SOI wafers are needed for simplifying the thinning of the process wafers down to 75 μm by removing the 400 μm thick handle of the SOI-wafers.

The ASIC (Application Specific Integrated Circuit) was designed and implemented for MEMS pressure sensor readout and AD-Conversion. An integrating/multi slope converter with multiplexed inputs for sensor, calibration and internal capacitor bank has been utilized. The ASIC was designed for 14- to 16-bit system level accuracy (utilizing a 24-bit counter). The die outline dimensions are 3570μm x 200μm x 75μm (LxWxT). The utilized process technology was the 0.35μm CMOS by Austria Microsystems (AMS) complying with the system speed, power and size requirements.

Both the static and dynamic pressure behaviour of the MEMS/ASIC sensor system were tested with addition to the environmental tests with silgel and saltwater applied on top of the sensor elements. An interface console utilizing a microcontroller board was developed for controlling and digital data readout of the ASIC.

3. Results

In the first phase the calibration data was measured, which are used for calculating the calibration coefficients for the specific assembly. In the second phase the active sensor data was measured at four static pressure values. The sensor assemblies were finally tested under a dynamic pressure: where a 125Kpa static pressure and a dynamic pressure pulse of approx. 1.5 Hz frequency have been applied. In Figure 1, a measurement data without any noise filtering is shown. The sensor system’s data output is changing according to the pressure changes and the data acquisition has been successfully synchronized. The dynamic measurements were carried out in an automatic probe station developed by Afore [2] in the Incite-project [3].

![Figure 1: A pressure chamber measurement with a 125Kpa static pressure and a dynamic pressure pulse of 1.5 Hz frequency have been applied.](image)

4. Discussion & Conclusion

In both the static and dynamic measurements the data acquisition was accomplished successfully. It can be concluded that both the MEMS and ASIC are meeting the system specification requirements.

References

Catheter integration for two flexible circuit based cardiovascular applications
Frank Stam
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1. Introduction
Two cardiovascular applications are presented which were enabled by miniaturisation of microelectronics and development of smart materials. In the one case, the catheter is used for electrical activation and as a delivery device for an expandable hydrogel implant to occlude an impaired or unwanted blood vessel. In the other case a capacitive pressure sensor is integrated in a catheter to carry out coronary artery Fractional Flow Reserve (FFR) measurements.

2. Methods
2.1 Blood vessel occlusion
The principal of this concept is based on using an Electro-Responsive Hydrogel (ERH). An electrical bias is applied to the ERH implant to keep it shrunk during the delivery phase. Upon delivery the electrical bias is removed, and the implant will then expand, and occlude the vessel in the presence of the liquid blood medium. Figure 1 below illustrates the concept.

![Figure 1: Schematic of how a bleeding (a) could be stopped by delivering a small sized EAH sample on the tip of a push bar to the treatment site (b). The electrical bias is removed by pushing the EAH sample from the push bar (c), followed by passive swelling. In (d) an electrode configuration is shown that surrounds the EAH sample, the electric field of which keeps it uns swollen.](image)

2.2 Pressure sensing
The target catheter for the FFR measurements had a 2 Fr (0.67mm) outer diameter. A thinned MEMS capacitive pressure sensor was used in combination with a thinned ASIC, with both dies mounted on a thin flexible circuit which was wrapped around the outside of a catheter with the dies being embedded in the catheter wall as indicated in Figure 2.

![Figure 2: Cross-section of MEMS pressure sensor and ASIC, integrated in FFR catheter with 0.43mm guidewire lumen.](image)

3. Results
3.1 Blood vessel occlusion
In vivo trials in sheep showed that average blood flow in the carotid artery of 245±7 ml/min could be inhibited by the swollen EAH. Furthermore, an ex vivo trial showed that the occlusion could withstand blood pressures of over 270 mmHg [1].

2.2 Pressure sensing
Initial assembly trials showed stress failures in circuit flex and component attachment, when manipulating it into the required tubular form factor. Changes to the flex design and use of gold stud bumps and solder laser jetting for the interconnects showed major improvements [2].

4. Discussion & Conclusion
It is necessary to further optimise the Pluronic based EAH in order to increase the expansion rate and a more efficient flexible electrode configuration is needed.

While assembling on a flat surface is achievable, the required curvature for catheter integration and kink test compliance appeared very challenging. A single die solution could be a good alternative.

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DermaTrax: Development of a Bluetooth-enabled Wound Dressing with onboard Temperature and Moisture sensing.
Suzanne O’Callaghan¹, Marco Belcastro², Brendan O’Flynn¹, Paul Galvin², Frank Everaerts², Jeroen Schram², Mark Fleming³, Ray O’Brien³, Conor O’Mahony³

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2) Holst Centre, Eindhoven, Netherlands 3) Fleming Medical, Limerick, Ireland

1. Introduction
Pressure wounds, diabetic foot ulcers and bed sores are examples of open wounds which are painful, difficult to heal and costly to treat. [1] In 2041 the 65+ age group is projected to make up 24% of the Irish population and in addition [2] the global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014. The prevalence of pressure wounds and diabetic foot ulcers amongst these two groups means improved monitoring and treatment of these wounds is fast becoming a priority. As part of the InForMed ECSEL JU Project, a wearable wound diagnostic device is being developed which will be integrated into a wound dressing for remote monitoring of wound and dressing parameters such as temperature, moisture, exudation rate, pressure and patient position.

2. Primary Requirements
The device will have on-board Bluetooth communication to facilitate both hospital ward monitoring as well as remote monitoring from patient’s homes via smartphone app. Due to the sensitive and painful nature of the wound, the flexible device must be undetectable from a patient’s perspective and yet robust enough to withstand a patient’s weight and applied shear forces of beds, bedding and seating. Temperature sensors will detect wound inflammation and moisture sensors the saturation levels of the dressing. In addition the rate of wound exudation will provide vital information regarding the stage of wound healing or regression. By enabling a clinician to evaluate the condition of both the wound and dressing, without disturbing the dressing, the wound environment remains undisturbed and bacterial balance is maintained. The entire dressing-device combination can be disposed of safely in line with hospital protocol and incineration policy.

3. Prototype Development
This poster outlines the development of a wound monitoring device from its conceptual phase to prototype development and progression to manufacturable design. Emphasis has been placed on miniaturisation of communications components and battery technology. The use of low profile components and flexible substrates enables the production of an ultrathin and conformal dressing module, with flexible batteries providing the necessary power supply.

Figure 1. First iteration of sensor and communications module.

Figure 2. Left: Prototype ‘smart dressing’. Right: Flexible sensor/communications module printed at the Holst Centre

4. References
1. Introduction

The human population, especially in Germany, is aging rapidly. One of the reasons for this is negative natural increase (Figure 1), which causes a shortage of manpower.

![Figure 1: Demographic changes in Germany. 2014 population (dark colors) and prediction for 2020 (light colors) [1]](image1)

A lack of staff in medical care centers and nursing homes can particularly be noticed. [1] People are living longer and would like to take care of theirself by their own as long as possible. In order to do so they need appropriate support in form of for example “intelligent” medical textiles.

2. Methods

The KOB group has been developing special elastic textiles for medical use for over 110 years. As a worldwide leading manufacturer KOB has production sites in Germany and India. The production of bandages and woven fabrics includes all production steps from spinning up to the finishing and packaging process (Figure 2).

![Figure 2: Production steps of the medical textiles by KOB.](image2)

As a private label manufacturer (OEM) KOB is delivering on the market the range of first-class tested source materials comprises bandages for compression, support and fixation as well as woven fabrics and carrier materials. Nowadays KOB is developing new smart textiles containing electronic sensors for medical applications.

3. Results

KOB has already developed for a German customer a textile pocket for electronic, which enables the monitoring of back movement. The textile has been coated with a biocompatible glue and can be placed on the back for over 48 hours and causes any irritation and doesn’t peel off by itself even after the shower. KOB is running couple of development projects and focusing on intelligent plaster for wound monitoring, smart textiles for the pressure measurement by the compression and sports medicine. All focus areas can be seen in Figure 3.

![Figure 3: KOB focus areas.](image3)

4. Discussion & Conclusion

KOB is developing smart textiles with integrated sensors for medical use. Some examples of current development projects as well as ideas and opportunities for potential cooperation partners will be part of the presentation.

References

Human health monitoring by micro gas detectors

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1. Introduction
Exhaled human breath contains thousands of volatile molecules that originate from human or microbiome metabolism, or from the outside environment [1]. Exhaled molecules have been linked to various diseases such as asthma [2], pneumonia [3], and acute respiratory distress syndrome (ARDS) [4]. Exhaled concentrations range from ppmV level for common molecules such as acetone and isoprene to low ppbV levels for some hydrocarbons such as octane. To accurately assess these low level molecules, laboratory based measurement equipment is needed. Gas chromatography combined with mass spectrometry (GC-MS) provides the gold standard in breath analyses. The gas chromatograph enables separation of the different molecule species, while the mass spectrometer allows detection and identification. For further advancements in the field of breath analysis, the GC-MS needs to be miniaturized to allow point-of-care applications. Therefore we have developed a micro gas chromatograph (μGC), initiated by a cooperation with WIMS² [5]. This is a simplified version of a normal GC-MS and is much smaller in size. To achieve this, the MS has been replaced by an ionization detector, removing the need for vacuum systems. The lack of MS identification power has been compensated by adaptive designs. Additionally, synthetic air is used as carrier gas instead of the commonly used helium, pre-empting the use of gas cylinders at the point-of-care. The current abstract aims to illustrate that μGC systems allow point-of-care testing at sensitivities comparable to laboratory based GC-MS systems.

2. Micro-Gas Chromatograph (μGC)

![Figure 1: schematic layout of μGC](image)

Basically our μGC comprises of four components: pump, preconcentator, separation column and a detector (Figure 1). The system can be realized through microfabrication in silicon, using commonly known processing equipment and steps (some realizations @ PInS shown in Figure 2). This enables easy adaptation of e.g. column dimensions and filling.

3. Results
In order to show the potential of our μGC we have compared its ability to detect octane compared to a GC-MS (down to 100ppt!). A good correlation is obtained (Figure 3).

![Figure 2: Photographs of columns and a preconcentator.](image)

![Figure 3: Graph showing correlation of octane detection between a GC-MS and a μGC.](image)

4. Discussion & Conclusion
In the development of a μGC we have shown a good performance, comparable to a professional GC-MS. This potentially allows for point-of-care testing, opening many other opportunities!

References
Breaking Barriers: Wearable Micro Transdermal Interface Platforms (MicroTIPs) for Transdermal Delivery and Diagnostics

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1. Introduction

The outer layer of the skin, the stratum corneum (SC), is only 10-20 μm thick but yet poses a major barrier to the transdermal passage of substances and electrical signals both into and out of the body. However, emerging microneedle-like structures can be used to painlessly create transient micro pores in the SC, thereby increasing skin permeability by several orders of magnitude.

Such microneedle technologies will form the basis for wearable, intelligent, patch-like systems, capable of independently diagnosing physiological conditions and autonomously delivering relevant therapeutic doses, while simultaneously relaying patient-centric information to clinical personnel and mhealth software platforms using wireless protocols [1].

These Micro Transdermal Interface Platforms (MicroTIPs), will have significant applications in areas such as diabetes management, Parkinson’s treatment and cardiac health, as well as in consumer-orientated areas such as sports nutrition.

2. Primary Requirements

MicroTIPs will require key ‘building blocks’ in the form of microneedle-based transdermal delivery and diagnostics modules that will be in direct contact with the body, as well as ancillary subsystems for data analysis and storage, power management, system validation and control, and wireless communications. All of these must be integrated and packaged in a patch-like form factor. Significant miniaturization of communications components and battery technology is required to achieve this goal, as are advancements in flexible interconnect, low profile packaging, heterogeneous system integration, micropump capabilities and secure adhesives. A concept system is shown in Fig. 1.

3. Recent Progress Towards MicroTIPs

This paper outlines progress towards various aspects of MicroTIPs technology, including microneedles for drug delivery and diagnostics, micropump integration, associated smartphone apps pressure/impedance/flowrate sensors for internal monitoring of the system performance, data management and storage, and customised modules for control and Bluetooth communications (Fig. 2).

Figure 1: Concept diagram of a future Micro Transdermal Interface Platform (MicroTIPs) constructed and packaged in a wearable ‘smart patch’ format.

Figure 2: Left - 500 μm tall microneedle. Right - control and communications module for micropump drug delivery.

Figure 3: Dye delivery to ex-vivo skin using microneedles.

References

Microneedle-based ECG Monitoring – Part 1: Dry Electrodes

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1. Introduction

Electrocardiography (ECG or EKG) procedures are used to monitor the electrical activity of the heart and to detect any form of cardiac abnormality. Wet electrodes – that use an electrolytic gel to ensure a low-impedance skin-electrode contact - are commonly used during these tests to collect the ECG signal.

Although wet electrodes usually require inconvenient skin preparation such as abrasion and/or shaving, they work very well for short term use. However, they are not ideal for long term measurements as the gel used at the interface between electrode and skin dries out over time, lowering the quality of the recorded ECG. Dry microneedles (MNs) based electrodes have been proved to be a valid solution to this problem [1] maintaining good quality signal recording even during long tests. Moreover, no skin preparation is required before the application of the MNs electrodes.

2. Methods

To compare the performances of dry and wet electrodes (Fig. 1), two sets of three electrodes were applied to the chest of a 28 years old Caucasian male in a lead II configuration. The ECG signals were recorded simultaneously and at the same sampling frequency.

![Figure 1: Dry and wet electrodes (A) and SEM image of a 500 μm tall microneedles.](image)

The recording system was built using an Arduino UNO interfaced with 2 Single Lead Heart Monitor (SLHRM) boards based on the Analog Devices AD8232 heart rate monitor front end.

Different types of electrodes were compared during several tests and the relative quality of the traces was evaluated by calculating the signal-to-noise Ratio (SNR) over a fixed number of cardiac cycles.

3. Results

The results (Fig. 2) showed that MNs based dry electrodes can be used to record ECG signals with a quality similar to those measured using commercially available wet electrodes. Typical data is shown in Figure 2; in this case, the SNR of the recording obtained using the dry electrodes is (23.39 ± 3.28) dB and the wet electrode equivalent is (23.32 ± 3.34) dB. The two signals are statistically similar.

![Figure 2: SNRs found during 10 tests performed using a set of wet (red) and dry (blue) electrodes.](image)

4. Discussion & Conclusion

While the data indicates that performance of these dry electrodes is similar to that of wet electrodes, the microneedle-based electrodes do not require advanced skin preparation and do not produce the unstable skin-electrode interface associated with wet gel. Tyndall is currently assessing the performance of several different types of electrodes, and our results indicate that MNs based dry electrodes will offer a valid alternative to the commonly used wet option.

References

Hybrid Printed Electronics in Health patches: the perfect match!

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1. Introduction

In the past years wearable technology sky-rocketed and many new products are released frequently. Obviously this is all based on advances made in micro-electronics and (wireless) communication technologies. Each generation of devices are smaller in footprint and an increased amount of sensors are combined with better computing techniques and algorithm. The comfort level of these products is one of the main factors that determines if the wearable is accepted by the general public.

In order to reach these goals new manufacturing and processing technologies had to be, and still are being developed. The presentation will focus on integration of flexible and stretchable electronics in health patches. An overview will be presented on the journey we started 5 years ago and includes information on design decisions made and lessons learned during testing and evaluation of the various prototypes that were created.

2. Methods

Traditionally electronic circuits are created by mounting of electronic components on a rigid board containing conductive traces – a Printed Circuit Board (PCB). Alternatively, if rigid PCB’s are replaced by flexible plastic substrates, so-called ‘flexible’ electronics is created. Electrical conductive traces on these substrates can be created by means of traditional etching processes but also by means of screen printing of silver or carbon circuits. Screen printing is a versatile and foremost cheap technique that allows for the deposition of relatively thick layers, depending on the type of ink between 1µm and 15µm per print step. Furthermore screen printing is an additive technology thus waste is minimized. A multi-layer circuit is created by printing conductive and non-conductive layers respectively.

One of the deliverables of the Healthpatch project that takes place at the Holst Centre is about the integration of flexible electronics into wearables. In the last 5 years we have been working on several demonstrators each focussed on different aspects: from water tightness to skin compliance and from disposable to refurbishable solutions.

3. Results

While initally we focused on the technology readiness and robustness of printed electronics, in later prototypes also ‘softer’ aspects like comfort and wearability were taken into account.

Evaluations of each prototype yielded in design guidelines that were integrated in the next prototype. We have demonstrated that flexible electronics are very suitable for wearables but one needs to consider that special precautions are needed in order to assure that the patch survives the harsh conditions while used in-vivo.

4. Discussion & Conclusion

We successfully matured the printed electronics technology to such an extent that it is suitable for wearables. One main aspect that needs to be taken into account is the balancing act between protection of the electronics and the skin of a subject versus comfort and wearability.
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Flexible implantable ultrathin chip encapsulation (FITEP) to fabricate neural CMOS-based probes for intra-fascicular implantation

Maaike Op de Beeck 1, 2, Rik Verplancke 3, David Schaubroeck 1, Dieter Cuypers 1, Maarten Cauwe 1, Bjorn Vandecasteele 1, John O’Callaghan 2, Dries Braeken 2, Marco Ballini 2, Rizwan Bashirullah 2, Johan De Baets 2

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1. Introduction

Miniaturization of the hermetic encapsulation of electronics for long term implantation is a challenge [1] which is addressed at IMEC/CMST by the development of a dedicated chip packaging platform called FITEP. A first demonstrator is fabricated: a recording and stimulating neural CMOS probe for intra-fascicular implantation in peripheral nerves.

2. Hermetic packaging concept

Single polymer barrier layers (polyimide, Parylene,..) will not protect electronic chips sufficiently to enable long term implantation. A superior diffusion barrier is essential. After detailed optimization [2], a multilayer stack of several polyimide and atomic layer deposition (ALD) films is selected as insulating bidirectional diffusion barrier. Since electrodes on the chip can't be covered by an insulator, platinum layers are locally used as conducting diffusion barrier.

3. Neural probe fabrication

A CMOS chip is designed containing recording and stimulation electrodes, logic for electrode selection, drivers and amplifiers. A dedicated post-CMOS-process prepares for the placement of 35 um thin chips, which are glued on a carrier substrate containing a multilayer polyimide/ALD stack, being the bottom hermetic shell of the chip encapsulation.

Next, the top multilayer stack is formed, again based on polyimide/ALD barrier films, but containing also the metallization, which consists of platinum on top of the chip and gold to connect the chip with control electronics (not yet packaged for implantation). Electrodes are finished with iridium oxide for optimum performance. Figure 1 shows the probe's encapsulation layers and metallization build-up.

4. Results and conclusion

As shown in Figure 2, the FITEP process results in a very thin and highly flexible neural probe. Tests performed in air and in fluid (PBS) proved full CMOS functionality. Acute in vivo stimulation tests in rats were successful. Extensive further testing is ongoing. It can be concluded that the FITEP platform is a promising encapsulation technology for the small, hermetic packaging of implantable electronics, although further testing is still needed.

Figure 2: final packaged CMOS probe ready for implantation. The FITEP-probe is only 75 um thick and highly flexible.

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References


Miniaturized Electrodes and Catheter Tips with Integrated Functional Components based on LCP Substrates

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Dyconex AG, Bassersdorf, Switzerland.

1. Introduction

Liquid Crystal Polymer (LCP), a biocompatible and bio-stable, thermoplastic dielectric film material is best suited as the base material for a novel substrate technology for implanted electrical interconnects, electrodes and electronic devices. Flexible, thin substrates made from Liquid Crystal Polymer (LCP) with embedded traces of either gold or copper are suitable to replace established biocompatible wire materials (MP35N or similar) in medical catheter and electrodes especially when more than 5 wires need to be wired into small catheters and electrodes with diameters of less than 3 mm. LCP is a biocompatible material with very low water absorption, high temperature stability and chemical inertness even for very acidic conditions. Active and passive components can be embedded in LCP and used to reduce the required wiring density (i.e. by embedding a multiplexer) or improve signal integrity (i.e. by embedding frontend amplification).

2. Methods

The traces on the LCP substrates, which replace the wires, have dimensions down to about 30 μm in width and up to 20 μm in thickness and are embedded between sheets of LCP with a thickness of 25 μm. The resulting flex cables are not thicker than about 60 μm and can also integrate thermocouples, thermistors, heaters or even thinned semiconductor components. Being a thermoplastic material, the substrate material can be thermoformed into any desired shape to support the application. The structures can be tailored such, that they are stretchable, even when embedded into a stretchable polymer, such as polyurethane or silicone. In areas where an electric signal needs to be passed to the tissue a surface coating with a low impedance, such as Platinum or Platinum/Iridium can be provided. Last but not least, complex structures covering a wide variety of requirements in different parts of the implant can be simplified by the use of a new hermetically sealed interconnect technology which allows connecting different substrates using only biocompatible materials. This includes sealed interconnect to MP35N wires.

3. Results

Long term soak tests in saline solution at elevated temperatures prove the usability of LCP to encapsulate conductors and active components for use in direct body contact.

4. Discussion & Conclusion

LCP substrates can provide hermetic sealed and bio-stable interconnect structures for catheters, electrodes and small microelectronics implants usable even for long term implantation.

5. References

Generic platform for the miniaturization of bioelectronic implants

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1. Introduction

The success of active bioelectronic implants such as pacemaker, cochlear implant (IC) or deep brain stimulator (DBS) initiated a research trend in the field of so called electroceuticals – devices that allow for intelligent and precise electrical stimulation of targeted region in the body. In contrast to the standard bioelectronics, electroceuticals require even further device miniaturization, for less invasive implantation procedures, and more precise stimulation, without sacrificing the patient’s safety and the long-term reliability of the device.

In this paper a platform for the miniaturization of long-term implantable bioelectronics is presented.

2. Methods

The miniaturization of already small-sized electronic implants is a challenge that can be achieved only by bringing together state-of-the-art technologies with biocompatible and biostable materials. The platform developed here combines widely used bioelectronics materials, such as Parylene C and platinum, with the off-the-shelf thin film technologies.

In the simplified manufacturing flow (Figure 1), the high performance safety capacitors (IPDs) [1] are fabricated on an SOI silicon wafer and precisely separated using the single-step trench technology [2]. Next, the Parylene-platinum based flexible interconnects and stimulation electrodes are fabricated, and the foldable structure is released using the Flex-2-Rigid (F2R) platform [3]. This allows for further chip (ASIC) integration (e.g. by flip-chip) and folding of the device into arbitrary shapes.

3. Results

The success of the newly developed platform greatly depends on merging of the single-step process with the F2R platform using biocompatible materials. As a proof of concept, a large mock-up device containing precisely separated silicon island connected with parylene flexible film was successfully fabricated and wrapped into a 1.3 mm diameter cylinder (Figure 2).

4. Discussion & Conclusion

In this paper we showed that with the developed platform it is possible to fabricate an implantable and foldable silicon-based structure enabling significant bioelectronics miniaturization by allowing for integration of passive (IPDs) and active devices (ASIC).

References


Ultra-Low-Noise Signal-Recording Amplifier/MUX ASIC

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1. Introduction

In several biomedical and pharmaceutical researches like cardiotoxicity, scientists and clinicians can simultaneously stimulate cells and record the biomedical signals in several spots, by the use of MEAs [1]. It is therefore, desired to have an ASIC in which a MUX connects the electrode pins to either a stimulation pin or the corresponding LNA for amplification and recording. The high-voltage (HV) feature of stimulation signals demands HV switches and the low amplitude signals from electrodes need ultra-low noise amplifiers. The desired amplifier must have an input-referred noise (rms) voltage of <1.5μV, a bandwidth of 8 kHz with no high-pass filtering, non-resistive input impedance with a supply voltage of 5V, and capable of driving the sampling capacitors of the succeeding ADCs in a 0.18-μm HV CMOS technology.

2. Methods

The instrumentation amplifier, shown in Fig.1, passes the DC component of the input signal and presents a non-resistive input impedance. Assuming a maximum input signal voltage swing of 400mVp-p with a 4-V output swing, the amplification gain cannot exceed 20dB. With such a low gain, noise contribution due to R1-R7 will be considerable if we select large resistances to minimize power consumption. A simple RC low-pass filter followed by a voltage buffer is used to drive the sampling capacitor of the ADC. The main challenge in designing the LNA is thus, optimally selecting the values of the size and the current of the transistors in OP1-2 to achieve the desired extremely small value of the input-referred noise voltage.

The desired HV switch, made up of MOSFETs with \( V_{GS,\text{max}}=5 \text{ V} \), must pass 20Vp-p (the first challenging issue), and have robust on-resistance insensitive to process and voltage variations. The other challenging feature of the desired switch is having a fast transition time because in some applications there is a need to switch to the recording mode immediately after the stimulation mode. The proposed switch, is inspired by the bootstrapped switch in [2], consisting two large transistors Q1-2 as the core of the switch to pass the stimulation signal, Q3-Q6, R1, C1 and S1 to turn off the switch and Q7-Q10, R2, C2, S2 and D1 to turn it on. The faster \( V_{GS,\text{op}} \) settles, the smaller the transition time becomes; but more \( I_{Q2} \) will be needed. Capacitors C1 and C2 are added to make a large amount of current at the beginning of the transition; so \( C_{G1,2} \) receive sufficient current to be charged much faster causing the transition time to be considerably smaller.

3. Results

Both the measurement results of the amplifier and the simulation results of the (2nd version of) HV switches are summarized below. It can be observed that the objectives are completely met.

Table 1: measurement results of the proposed LNA

<table>
<thead>
<tr>
<th>Input referred noise</th>
<th>Power (5V power supply)</th>
<th>Area*</th>
<th>Input capacitance</th>
<th>THD (4V swing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3μV</td>
<td>4.45mW</td>
<td>900×190 μm²</td>
<td>&lt; 4.5pF</td>
<td>~60dB</td>
</tr>
</tbody>
</table>

*The LF large capacitor is placed on top of the whole circuit using MIM capacitor

Table 2: simulation results of the proposed HV switch

<table>
<thead>
<tr>
<th>( R_{\text{on}} )</th>
<th>Off isolation</th>
<th>Static power consumption</th>
<th>Area</th>
<th>( T_{\text{on}} )</th>
<th>( T_{\text{off}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 Ω</td>
<td>-86dB</td>
<td>40μW</td>
<td>0.015mm²</td>
<td>50ns</td>
<td>10ns</td>
</tr>
</tbody>
</table>

* @ 20Vp-p, f=10 kHz, RL=10 kΩ

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Heart-in-a-Dish: Preclinical Drug Screening for Cardiotoxicity

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1. Introduction

Organ mimics in a dish entail the promise to revolutionize the drug development trajectory by capturing drug- and disease responses in human (stem) cell based cellular models [1]. Screening for changes in cardiac contraction is one of the primary focus areas since current models often fail to predict cardiotoxicity [2]. Several methods exist to measure cardiomyocyte contraction but these require customized hardware, often fabricated with polydimethylsiloxane (PDMS), and/or dedicated measurement methods, making it difficult to setup and to compare results between different models [3]. Here we have investigated the effect of PDMS in drug screening assays and developed a software tool adaptable for use with standard laboratory- and clinical imaging equipment that enables quantitative analysis of pharmacological responses across a vast range of models in vitro and in vivo, enabling translation studies.

2. Methods

High-performance liquid chromatography was used to determine the effect of PDMS on the free drug concentration in tissue culture wells. Cell culture friendly lipid coatings were used in attempt to reduce compound absorption by PDMS [4].

A computer animated model cell was developed to validate the contractility algorithm. Human stem cell derived cardiomyocytes (hPSC-CMs) in various cellular configurations (single cells, monolayers and 3D constructs) and adult cardiomyocytes isolated from rabbits were used to compare our algorithm to gold standards in the field and measure drug responses [5]. Recordings from zebrafish hearts and echoscopic data from human hearts were used to demonstrate in vivo applicability.

3. Results

PDMS was found to have a major potential impact on molecule absorption, depending on the drug. Measuring contraction with our algorithm was easy, fast and effective under different recording conditions and in different cellular setups (Figure 1). Outcomes highly correlated with the current gold standards for measuring contractility such as optical flow, pole deflection, edge-detection systems or manual analyses. Finally, we were able to measure pharmacological responses and measure contractility in vivo.

4. Discussion & Conclusion

When measuring drug response in PDMS based cell culture environments, compound absorption might affect the free drug concentration severely. The contraction algorithm presented here can measure cardiac and cardiomyocyte contractility in response to drugs without the need for specialized equipment in a wide range of in vitro and in vivo applications. This enables future translational contractility studies.

References


Heart-on-a-chip: a high-throughput, multimodal cardiotoxicity screening platform

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1. Introduction
The failure of current in vitro models to model the complexity of the human heart has led to high attrition rates in drug development. Traditionally, preclinical drug screening focuses on detecting the risk for torsades de Pointes through hERG blockage assays, but these models show low specificity [1]. Thus, there is a need for novel devices that assess the effects on both cardiac action potential and contractility. Here, we demonstrate a heart-on-a-chip device that simultaneously measures the intracellular electrical activity and contractility of in vitro cardiac cells as well as strategies to increase throughput.

2. Methods
(1) Packaging for high-throughput measurements: Two strategies for increasing the throughput of heart-on-chip devices were explored. Both approaches start from the same PCB with silicon chip lay-out and film-assisted epoxy molding to protect the wirebonding. In the first approach epoxy molding defines chambers on the silicon chip whereas in the second approach chambers are defined with a microfluidic interposer.
(2) Measurement modalities: electrophysiology and contractility measurements were optimized in parallel. A reflective lens-free imaging (RLFI) technique was developed to monitor the cellular deformation (RCD) and rate (RCDr) of in vitro cardiac monolayers. The RLFI device was then implemented on: (1) a fluorescence imaging microscope and (2) microelectrode arrays (MEA). In the latter setup, the drug-induced effects of blebbistatin and 1-octanol were investigated.

3. Results
Both packaging approaches for high-throughput measurements were evaluated on glass substrates. This allowed for cell culture testing of cell seeding protocols and cell viability analysis. Cardiac cultures were successfully seeded and grown in multiwell devices and microfluidic chambers. Both approaches are in progress of being transferred to silicon surfaces. Next, we explored the combination of electrophysiology and contractility measurements.

The RLFI device monitored RCD and RCDr of 448 clusters of cells (0.124 mm²) over a field-of-view of maximally 57 mm². The RCD had a clear temporal relationship with intracellular calcium concentration. The combined RLFI-MEA device was used to detect the unlinking of the electromechanical coupling (Fig. 1). The IC50 for contraction rate was 381 nM while for relaxation rate it was 612 nM. Furthermore, reductions in excitation propagation velocity were detected after addition of 1-octanol (IC50 of 45 μM).

Figure 1: Averaged intracellular action potential (blue traces, MEA) and RCD (red traces, LFI) under conditions of (A) cell medium, (B) cell medium containing 0.015% DMSO, and (C) cell medium containing 5 μM blebbistatin [2].

4. Discussion & Conclusion
Novel on-chip sensors were developed for multiparametric monitoring of in vitro cardiac cell contraction. The potential of RLFI was first validated by calcium imaging and then combined with MEAs to monitor both electrical and contractile parameters. These parameters were determined on both cellular level (RCD, RCDr, action potential duration) and monolayer level (propagation velocity). Additionally, increases in throughput for heart-on-a-chip devices were investigated by defining chambers in epoxy on the chip surface or by integrating microfluidic chambers onto the chip. The integration of these technologies has the potential to develop a new platform that gathers multi-content information on drug toxicity in a high-throughput fashion.

References
1. Introduction

Cystostretch is a modular platform that can be customized for different Organ-on-Chip (OOC) models [1]. Unlike other OOCs, Cystostretch is based on conventional semiconductor micro-fabrication processes, allowing for wafer-scale fabrication. The elimination of the manual fabrication steps required for the assembly of other OOC models enables high-volume fabrication.

An important application of Cystostretch is Heart-on-Chip [2], where it is used for safety pharmacology, and to study cardiac biology. The possibility to mechanically stimulate cardiomyocytes in-vitro is expected to improve the maturation of induced pluripotent stem cell (iPSC)-derived cardiomyocyte cultures [3]. Additionally, the Cystostretch device is equipped with a micro-electrode array (MEA) to record the electrical activity of the cells during static or dynamic stretching. Here we present the latest results towards industrialization of the Cystostretch technology. The production version allows for parallel screening, and is compatible with standard MCS readout systems. Fig.1b,c shows the chips and the embedded MEA, respectively. The molded wells on top of the Cystostretch chips were filled with phosphate buffered saline and placed in a biological incubator for seven days. During this period no leakage was detected, proving sufficient adhesion between the molded packaging and the Cystostretch chips.

3. Results

A picture of the final plate including four Cystostretch chips is shown in Fig.1.a The plate is compatible with standard MCS readout systems. Fig.1b,c shows the chips and the embedded MEA, respectively. The molded wells on top of the Cystostretch chips were filled with phosphate buffered saline and placed in a biological incubator for seven days. During this period no leakage was detected, proving sufficient adhesion between the molded packaging and the Cystostretch chips.

4. Discussion & Conclusion

The presented version for the Cystostretch device is a first step toward the commercialization of the device. The plate is compatible with parallel screening and standard routine followed by biologists on daily basis. The preliminary leakage test proved that the adhesion between the molded package and the chip is sufficient. The previously tested chip [2] and the achieved packaging reliability make the presented plate an important step forward toward high-throughput qualitative screening for OoCs.

References

Skin-on-chip: integration of skin tissue and microsystems engineering

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1. Introduction

All skin disease has an underlying immune component e.g. skin-cancer, fibrosis, allergy [1]. Animal models or simple petri-dish tissue cultures are inadequate for studying these complex human interactions. To study skin diseases an immune competent model is necessary. Existing models, like animal models or 2D in vitro cultures are inadequate because of the human-specific complexity. The exchange of immune cells between microvasculature and (epi)dermal layers is a critical aspect for next generation skin models. To realize this, the first step is to integrate a perfused microvasculature. The aim of this work is to create a full thickness skin equivalent in an endothelium-lined microfluidic device that mimics microvasculature.

2. Method

A microfluidic device is employed having a microchannel below a culture chamber. The flow conditions are designed to mimic microvasculature flow. The chamber and channel are separated by a micro-porous membrane of conventional Transwell-like type or PDMS-type. Primary human cells are employed. The skin equivalent cultured on top of the membrane consists of a fibroblast filled collagen-based gel onto which keratinocytes are cultured. The endothelial layer is cultured on the bottom of the membrane. This complete equivalent is exposed to 1-week perfusion flow in a microfluidic setup. Characterization of structure is subsequently performed through immunohistology of relevant markers (Vimentin, \(\alpha\)-SMA, CD31). Viability is characterized with LDH measurements during the flow while MTT-assay is used for end-point analysis. Lensless microscopy is explored as a label-free in-flow method for detecting differences between monocytic and dendritic immune cells.

3. Results

Results show that 1) a construct can be cultured having an endothelial barrier below a full thickness skin equivalent (Fig.1) in static conditions, while flow experiments reveal issues with long term bubble-formation. 2) Lensless microscopy of static immune cells allows for similar differentiating capability as conventional light microscopy (Fig.2).

4. Discussion & Conclusion

We created a full thickness skin equivalent augmented with an endothelial-barrier in static culture conditions, which is now suitable for incorporating into a microfluidics device.

5. References

MEMS-Electronics Integration: A Smart Temperature Sensor for an Organ-on-a-chip Platform
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1. Introduction
Incubators in cell cultures are used to grow and maintain cells under optimal temperature alongside with other key variables. As enzymatic activity and protein synthesis proceed optimally at 37 °C, a temperature rise can cause protein denaturation, whereas a drop can slow down catalysis and peptide initiation [1].

Inside the incubator, measurements nowadays are gauged via the temperature of the heating element which is not exactly the same of the cells. Apart from that, time spent outside the incubator can greatly impact cell health. In fact, out-of-incubator temperature and its evolution is an unknown variable to researchers. For a non-incubator temperature monitoring, besides a more accurate temperature measurement of the cell culture, in situ temperature sensing is of paramount importance. This also enables growth optimization of the cultured cells. To the authors' best knowledge, no fully integrated in situ temperature sensing for organ-on-a-chip (OOC) exists to date and this is the first time such integration is being reported using a custom-designed circuit fabricated on the same silicon substrate of the OOC.

Moreover, the simple, robust and flexible IC technology used for the sensor fabrication grants a very cost-effective integrated solution in virtue of the reduced cost per wafer along with the large silicon area available in the platform.

2. Methods
The temperature sensor circuit outputs a square-like waveform conveying a proportional to absolute temperature frequency information that can be post-processed with a microcontroller unit. Simulations of the circuit were run in Spectre from Cadence.

The fabrication used a “MEMS-last” process to avoid potential PDMS and other material contamination. A planar BiCMOS IC technology that requires only 7 masks steps is used to fabricate three main devices in the circuit: NPN, nMOS and pMOS transistors. The start material is a double-polished p-type silicon wafer. Mask 1 is used to define the n-well and the collector area of the NPN transistor, while masks 2 and 3 define, respectively, the n/p-type diffusion areas for the CMOS and the emitter/base area for the bipolar device. Contact openings are wet etched after the patterning of mask 4, while mask 5 is used to pattern the interconnect and gate material via deposition of AlSi (1%). Masks 6 and 7 are used to open vias and deposit the second layer of metal. This last step is also used to deposit the first metal layer of the OOC module. The process follows with the SiO2 deposition using PECVD on the front and back of the wafer. The SiO2 layer on the back is patterned by dry etching to define the membrane area. Then, PDMS is spun onto the front of the wafer and cured for 30 min at 90 °C. Finally, the membrane is released removing the Si and the SiO2 layers from underneath the membrane using DRIE and buffered hydrofluoric acid, respectively. The envisioned result of this process is shown in Figure 1.

![Figure 1: Envisioned MEMS-electronics integration of the smart temperature sensor and the OOC showing the PDMS membrane air-inflated at 10 kPa [2].](image)

3. Results
Simulation results of the circuit reveal a responsivity of 4766 ppm/°C ranging from 30 °C to 44 °C, with a frequency conversion of 1.25 kHz/°C and jitter of 600 ps. Total power consumption is about 75 mW at 15 V of power supply.

Measurements and more detailed pictures of the OOC platform with the integrated sensor will be presented in the conference.

4. Discussion & Conclusion
The in situ temperature sensor presented here will allow a more accurate measurement than methods in use nowadays and, for the first time, out-of-incubator temperature monitoring using a simple, robust and very cost-effective IC solution.

References
New polymer fabrication strategy for integrated microfluidic systems

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1. Introduction

The interest of the scientific and industrial communities in the development of wearable devices and Organ-on-Chip systems is pushing research to find new innovative manufacturing approaches that provide easier, cheaper, faster and innovative solutions for the integration of microfluidics with electrodes and sensing components. Moreover, the need for easy manufacturability and tunable mechanical properties requires the realization of fully-polymeric devices where conductive polymers can be used to create organic electrodes. In this context, we present the development and the characterization of a novel fully-polymeric wearable sensor for pH monitoring. Polymeric electrodes and microfluidics have been fabricated in a single step by means of a high-throughput soft-embossing process coupled with intermediate lithography.

2. Methods

Figure 1A shows the fabrication protocol. The substrate is a bi-layer made of Poly(3,4-thielenedioxythiophene) (PEDOT), a conductive polymer wildly used thanks to its high conductivity and transparency, spin coated on a flexible cyclic olefin copolymer (COC) foil. The soft-embossing process allows to transfer a pattern present on a soft mold (made of Polydimethylsiloxane PDMS) into the substrate creating electrodes and microfluidics. A Polyaniline (PANI) layer has been electrodeposited on the working electrode in order to make it pH sensitive. The layout of the device is shown in figure 1B.

3. Results

Patterning PEDOT is quite challenging since it is not a thermoplastic material. However, we have been able to pattern the PEDOT layer till 1µm dimensions thanks to the presence of the COC support acting as an intermediate layer. We have developed a protocol based on the use of Ethylene Glycol in order to increase the PEDOT conductivity and decrease its solubility in water making the device suitable for application in water-based environments. Moreover, we have demonstrated that the device can be used as a pH sensor via potentiometric measurements of the redox PANI reactions at different pHs, as shown in figure 1C.

4. Discussion & Conclusion

In conclusion, we propose a low cost and high throughput technique based on the coupling between soft embossing and intermediate layer lithography. The use of a soft mold instead of a silicon one allows to reduce breaking problems during embossing (lowering the costs) and stiction with the substrate. In a single step we have been able to create electrodes and microfluidic channels, avoiding alignment problems and reducing the process duration. The optimization of the PEDOT properties (conductivity and solubility) and the presence of the PANI layer make the sensor sensitive to sensitive to pH in the range between 4 and 7. Our results demonstrate that this approach is promising for the realization of organic electrodes that can be integrated into complex microfluidic systems such as Organ-on-Chip or wearable devices. Future developments will be focused on the possibility to create a mold with custom geometries by means of 3D printing via 2 photon polymerization.

Figure 1: A) scheme of the fabrication process. B) Layout of the sensor. C) pH response (Open current potential versus pH)

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Force feedback and tactile sensing for Robin Heart Surgical Robot

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1. Introduction

Minimally invasive robotic surgery (MIS) offers several advantages for the patients, although the lack of sensory feedback for the surgeon is one of the main barriers in its progress and widespread application. Gathering immediate multi-parametric information about the physical and anatomic conditions of tissues is crucial for the operator to precisely control the robotic actions. “Smart” laparoscopes with integrated MEMS sensors can provide such feedback and to improve the safety of these interventions.

Our goal was to develop a novel laparoscope for surgery robots with integrated 3D force sensors inside the grasper and also on the tip of the device to measure the gripping strength and to provide tactile information about the different organs and tissues touched.

2. Results

Silicon based piezoresistive vectorial force sensors were designed and manufactured by bulk micromachining techniques. The device geometry was modelled by coupled finite element simulation (FEM) to determine its expected performance. Flexible electronics was designed to integrate the force sensors, as well as the AD converters. The electronics accomplishes the analogue-digital conversion and I2C data transfer. I2C – CAN BUS converter was also designed to perform not only the communication with the robot control system but also for noise filtering, data collection and transfer.

According to the proposed medical application and functional requirements the sensors were electromechanically integrated into a metal laparoscope grasper and covered by biocompatible elastic polymer. (Fig. 1) The developed “smart” laparoscope device was integrated into the ROBIN HEART surgery robot system. The analogue-digital conversion and the communication between the pre-processing electronics and the robot control system were verified, and calibration functions were recorded. The assembled sensors were tested in different environmental parameters (in thermal chamber) and further packaging rules were defined.

Preliminary tests were accomplished to evaluate the force and tactile signals of the integrated sensors during interventions. The information was successfully applied to provide haptic feedback for the operator by a specific controller (Fig. 1). Tactile measurements were implemented on artificial and real animal tissues to prove the applicability of the device for biomechanical screening during MIS surgery.

3. Conclusions

Studies of the prototypes of “smart” sensory laparoscopes have verified their remarkable usefulness in real-time force feedback robotic systems to recognize the state of tissue and to determine the clamping force of the grasper of surgical system. By integration of this “smart” tool into the surgery robot system an advanced human-machine synergy was demonstrated applying two-directional haptic control.

References

Safe Puncture Tool for Retinal Vein Cannulation
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1. Introduction
Retinal vein occlusion (RVO) is a major cause of vision loss in patients over 50 years old. RVO can be treated by cannulation of the retinal vein to remove clots. However, cannulation of small retinal veins is challenging as the required puncture force (~10 mN) is well below human sensing capability [1]. In this paper, we introduce a passive compliant tool for retinal vein cannulation having predetermined stroke and threshold force which allows safe and precise puncturing independent of actuation input. Our tool can be utilized in either stand-alone mode or mounted onto a robotic system.

2. Concept and design
Our tool uses a bistable mechanism, i.e., having two stable states and one unstable state, which releases a constant amount of energy when it passes from its unstable state to a stable state [2], see Figure 1. It follows that a threshold force can be obtained by limiting the stroke of the mechanism. This ensures safe and precise cannulation of the retinal vein, assuming a very thin wall, with puncturing force lower than the threshold force, cannulation is guaranteed. The surgeon simply displaces the mechanism across its unstable state.

Figure 1: Strain energy and reaction force of a bistable mechanism

Figure 2 illustrates a puncture tool where bistability is realized by a buckled beam fixed on both sides by compliant pivots [3]. The beam is axially loaded on one end by a tuning stage and elastically driven by a spring loaded actuation stage. The other end is connected to a needle having an embedded micro-fluidic channel which cannulates the vein laterally. The dimensions of the mechanism are chosen so that maximum stroke is 500 µm and threshold force is 25mN with these parameters controlled by the position of the tuning stage.

Figure 2: Puncture tool

3. Fabrication
The tool is monolithically fabricated in fused silica using femto-laser printing-wet-etching [4], glass was used for its bio-compatibility and favorable elastic properties. Figures 3 and 4 illustrate the 3D pivot and the outlet of the micro-fluidic channel embedded in the needle of the tool, their monolithic fabrication is very challenging without femto-laser technology.

Figure 3: 3D cross pivot
Figure 4: Needle tip

3. Results & Discussion
We validated our design using FEM simulations and experimental measurements, see Figures 5-7. Our tool successfully cannulated pig eye retinal veins.

Figure 5: Puncture tool deformation using FEM
Figure 6: Measurement setup
Figure 7: Experimental and numerical values of stroke and puncturing force for different tuning displacements

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References
Modeling the behavior of guidewire inside the vascular system and comparing the trajectory and the applied forces

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1. Introduction

Guidewires are the basic tools used during interventions to access the place of interest [1]. Since the range of vascular geometries are extensive from one organ to another and from one patient to another, there is a variety of guidewires available. Therefore, the interventionalist needs to select an appropriate guidewire in each procedure. Despite the importance of this selection in the success rate of the procedure, it is mainly subjective and based on experience.

Knowledge of the guidewire's trajectory and applied forces prior to the procedure can support the interventionalist in selecting a guidewire with suitable mechanical properties for successful navigation. Therefore, we developed a 3D model, based on rigid multibody dynamics, to simulate the motion of the guidewire in vascular system. The force transmission between the instrument and the vascular wall was also determined.

2. Methods

In our model, the guidewire is considered as a discrete body: a number of interconnected rigid segments, each of which may translate and rotate. To account for the bending stiffness of the guidewire, joints with torsional springs and dampers are located at each interconnection [2]. A 3-point bending test is performed to obtain real data regarding the stiffness of guidewire. The left anterior descending (LAD) coronary artery is chosen as vascular geometry. Therefore, based on consultation with specialists, Pilot50 and Pilot200 are used as guidewires.

The developed model is based on the forward dynamic method, i.e. given initial conditions and applied forces and/or applied moments, over a given time interval to predict the motion. By applying a defined force to the proximal side of the guidewire, the guidewire moves by a constant speed of 2 mm/s. The model is developed in MATLAB/Simulink (The Math Works, Inc.) environment. To validate the accuracy of our method, a series of experiments on a phantom model were performed.

3. Results & Discussion

In this study, we have developed a 3D guidewire model and have endeavored to investigate its behavior in a specific vascular geometry and the importance of guidewire’s stiffness on the motion. Although we used LAD as the vascular geometry and Pilot50 and Pilot200 as guidewires, the model is generic and it is possible to adopt to any other geometry or guidewire.

The results show that the flexibility of a guidewire impacts its behavior during advancement: a higher flexibility, more fluctuation (see Figure 1). This can be explained by the fact that under the applied loads, the flexible tip deflects easier than the stiff one. Moreover, the stiff one (here, Pilot200) causes more applied forces to the vascular wall (see Figure 2).

Use of such simulations enables the user to assess the possible motions, and even to predict the success rate of the procedure. Moreover, this information might help instrument designers to predict the performance of a new guidewire before manufacturing.

ACKNOWLEDGMENT

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References

Automated Visualization of Steep Needles in 3D Ultrasound

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1. Introduction
Ultrasound (US) guided interventions are broadly applied in medical procedures, e.g. for regional anaesthesia or ablation. However, for a typical 2D US system, successful interventions are complicated, mainly due to the limited field of view and multi-fold coordination of the needle and US plane. Recent 3D US transducers can improve the quality of the image-guided intervention if an automated detection of the needle is used. An image-based detection technique is most interesting when the needle, signal generation and imaging devices remain unaltered, and yet the manual skills are significantly simplified after the system returns the best scan plane with respect to the needle [1]. However, an automated localization becomes challenging when the needle is inserted at higher angles with respect to the ultrasound probe. For very large insertion angles, the needle will be virtually invisible in the ultrasound data and medical specialists need to find the needle indirectly either from out-of-plane or in-plane views. In this study, we propose a novel method to automatically detect steep needles in 3D ultrasound data and visualize its 2D in-plane view to the medical specialist.

2. Methods
During acquisition of US images, the transmitted waves passing through the tissue around the needle are selectively attenuated, which results in a shadowed region below the needle. Our method exploits indirect information regarding the presence of a needle in the volume, by examining the form and strength of attenuated regions. In our proposed technique, after regularization of the shadow geometry and enhancing the contrast, the needle shadow plane is localized based on 3D Gabor transformation designed to be sensitive to dark planar structures oriented perpendicular to the coronal planes. Furthermore, computational complexity of our method is optimized by analysing 2D coronal cross-sections below the needle for localizing the needle plane.

3. Results
The proposed algorithm is evaluated on 3D US data of a chicken breast, acquired with a 5–13 MHz motorized linear array transducer (Philips, Bothell, WA). The dataset consists of 10 trials of a standard 17G needle inserted at various steepness angles (25°–70°). In 25 executions for each volume, our proposed method always successfully detects the needle plane with accuracy in the sub-millimeter domain. The average needle tip localization error is 0.37 mm, which indicates that the needle tip is always visible in the extracted scan plane, as their distance is much less than the thickness (~1 mm) of US planes (see Figure 1). Furthermore, the average tip localization error of applying 2D Gabor in coronal cross-sections is 0.47 mm, which is slightly higher than 3D Gabor. Nevertheless, by not processing the unnecessary and redundant information, the computational complexity is decreased by a factor of 12 fold (from ~12s to ~1) at the cost of slight increase in the position error.

Figure 1: Examples of detected needle planes at (a) 25°, (b) 40°, (c) 55°, and (d) 70° insertion angles.

4. Discussion & Conclusion
In this work, we presented a novel image processing system to efficiently and robustly visualize the in-plane view of a needle in 3D US volumes, while the insertion angle is very steep and the needle is virtually invisible in the acquired data. The proposed method is computationally efficient and achieves average tip localization accuracy of 0.35 mm, thereby strongly supporting the clinical intervention.

References
Automatic online layer separation for vessel enhancement in X-ray angiograms for percutaneous coronary interventions

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1. Introduction

Percutaneous coronary intervention is a minimally invasive procedure that is usually performed under image guidance using X-ray angiograms in which coronary arteries are opacified with contrast agent. In X-ray images, 3D objects are projected on a 2D plane, generating semi-transparent layers that overlap each other. The overlapping of structures makes robust automatic information processing of the X-ray images, such as vessel extraction which is highly relevant to support smart image guidance, challenging.

2. Methods

In this paper, we propose an automatic online layer separation approach that robustly separates interventional X-ray angiograms into three layers: a breathing layer, a quasi-static layer and a vessel layer that contains information of coronary arteries and medical instruments. The proposed method treats the intensity of an XA frame as the sum of the three layers. The method consists of two main steps: first, large-scale breathing structures, e.g. diaphragm, are separated and removed from the original XA frame, and second, smaller moving structures, e.g. vessels and guiding catheters, are separated from a quasi-static background using online robust PCA (OR-PCA). Figure 1 provides an overview of the complete method.

![Figure 1: The overview of online layer separation for an XA frame.](image)

3. Results

Using block-coordinate descent with the optimal parameter setting, an example of online layer separation of an XA sequence (512 × 512, 55 frames) is shown in Figure 2. Note that the layer separation result for the first frame shows strong artefacts (e.g. the vertebral shape in the vessel layer) due to random initialization of the subspace basis. As time proceeds, the layer separation improves quickly. The 10th frame already has a good layer separation.

![Figure 2: An example of online layer separation of an XA sequence using OR-PCA. Row 1-4 show the original frames, the quasi-static layer, the vessel layer and the breathing layer, respectively. Column 1-3 are 3 frames taken from the sequence in a chronological order and their layer separation outcomes. The frame ordinals from left to right are 1st, 10th, 20th.](image)

4. Discussion & Conclusion

The method is potentially applicable for clinical practice without the necessity of using advanced hardware, opening the way for relevant clinical applications, such as improving the vessel visibility under conditions of low contrast concentrations, so as to allow a reduced amount of contrast agent usage to prevent contrast-induced side effects.

References

New concept silicon microgripper: fabrication and biocompatibility assessment
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1. Introduction

In the last decade, a new concept mechanical microgripper has been designed and patented for the general purpose of manipulation, which gives rise to higher design flexibility and performance compared to previous ones (1,2). Due to its peculiar structure, this device is compatible with silicon microfabrication process, enabling the realization of sub millimeter gripper chips which include both the tweezer and the actuation in a single component. Such novel silicon microdevice requires a dedicated fabrication technology and needs a proper assessment about its biocompatibility. The present work reports the microgripper technology development, device fabrication and biocompatibility tests.

2. Methods

The work had two consequent experimental parts, the first being device fabrication process development, the second being biocompatibility assessment on fabricated devices.

- micro fabrication

Figure 1: process sequence – main steps

The microgripper fabrication process is summarized in figure 1. A standard silicon on insulator (SOI) wafer is used for the fabrication, which consists of a front DRIE (fig. 1b) to define the gripper structure, and a back DRIE (fig. 1c) to pattern the support structure. A final release stage will remove the silicon oxide from the layer between the device and the support, with the consequence of releasing the structures (fig. 1d).

The present microgripper design includes a wide range of feature sizes (from sub-micron to 100μm) to be fabricated using silicon deep reactive ion etching (DRIE). In order to do this, a very long etching time is required, which is usually obtained with thick mask layers. Thick masks have poor pattern transfer for submicron patterns, therefore a thin mask would be best suited. Thin masks for very long etching times means the mask etch rate in DRIE has to be near zero: to this purpose, a novel aluminium masking was developed, adopting titanium as protective layer to prevent aluminium re-sputter in the first DRIE etching phase (3).

To optimize the etching recipe, a series of tests were carried out by changing a single etching parameter at the time, and the resulting re-sputter was examined: the effect of each DRIE parameter on re-sputter density was measured.

- biocompatibility test

To assess the compatibility of microgrippers with their use in micro surgery, a test based on protein adsorption was selected. Protein adsorption is reckoned as the main problem when external objects contact body organs or tissues (4). Amongst proteins, serum albumin is the most abundant in human blood, accounting for more than 50% of total proteins (5). The presence of albumin in the extravascular compartment is also significant. For these reasons, a fluorescently-labelled albumin, i.e. BSA-TAMRA, was selected to evaluate the possible clogging effects on microgrippers and 0.2 to 10 mg/mL BSA-TAMRA were incubated on both sides of fully fabricated microgrippers. Incubation times ranged from 30 min to 64 h. The adsorption of BSA-TAMRA was imaged via confocal microscopy. Both sides of microgrippers were observed and the presence of BSA was quantified in terms of fluorescence intensity per surface area for all the experimental conditions tested.
3. Results

- Microgripper test devices

Thanks to the tuning of the resulting multilayer mask and the DRIE recipe parameters, the aluminium re-sputtering could be eliminated, enabling the etching of a wide range of feature sizes in a single DRIE step, with very high aspect ratio (>40). The fabrication method adopting multilayer aluminium-titanium mask was used to successfully fabricate a set of microgrippers. An example of completed structure is reported in figure 2.

![Figure 2: a microgripper device](image)

- Biocompatibility assessment

A complete protein adsorption has never been observed, both with long-term incubation and high BSA concentration. The BSA coating was indeed inhomogeneous also on the silicon side after short incubation time, as witnessed in Fig. 3. All samples have a modest propensity to adsorb proteins.

![Figure 3: a microgripper device](image)

4. Discussion & Conclusion

A complete fabrication process for novel microgripper devices was developed, based on aluminum masking and DRIE of SOI wafers. The new process method prevents aluminum re-sputter in the first stages of the etching by using a protective layer on top of the aluminum mask. Fully functional devices based on the novel microgripper design were fabricated, each with overall size of 2x2 mm. The microgrippers were tested to assess their biocompatibility, measuring the adsorption of serum albumin protein.

The protein adsorption was modest and inhomogeneous for all samples, independent on the protein concentration or time of incubation. No complete adsorption of the protein was observed. This first biocompatibility assessment of the microgripper surfaces is crucial towards future medical applications, such as mini-invasive surgery, where protein-mediated adsorption would lead to clogging.

References


Proximal Audio Measurement and Analysis - Information Enhancement for Interventional Device Guidance

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1. Introduction
Targeting and subsequent verification is one of the main issues when medical interventional devices (MIDs) such as needles, catheters and guide wires are used [1, 2]. In combination with the clinicians skills and experience accurate device placement is essential for a successful surgery. Visual feedback from a diagnostic imaging modality as computed tomography, ultrasound or magnetic resonance is helpful to achieve that. However, even with image guidance accurate placement cannot be guaranteed due to image artefacts. We propose a new approach for MID/tissue interaction data acquisition and processing that can provide additional MID guiding information. The main idea consist on processing audio signals acquired from the MID proximal end to extract dynamical characteristics of the interaction between the MID distal tip and the tissue.

2. Methods
For that two experimental setups (ES) for two different MIDs, a biopsy needle and a guide wire, were implemented. The main objective of the ES for the biopsy needle was to observe audio signal dynamical changes when the needle passes through different tissue layers. In contrast the guide wire ES intended to analyse signal dynamics of perforation in arteries. For both experiments a stethoscope was directly and firmly attached to the proximal end of the MID via a 3D printed adapter and connected to a smartphone (Figure 1).

A gelatine phantom filled with fruits has been used to insert the biopsy needle, while for the ES with the guide wire coronary arteries of pigs were used. Additional guide wire artefacts like friction and bumps were also generated to compare them to the perforation audio signal dynamics. A time-varying auto-regressive (TVAR) spectral analysis was used to characterize dynamical changes of the audio signals. From the TVAR model the maximal energy time-varying pole (METVP) was computed for extracting a trace in the audio signal that then can characterize patterns of the MID/tissue interaction.

3. Results
Figure 2 shows the obtained audio signal and the METVP signal for needle insertion in persimmon fruit and for guide wire coronary artery perforation. The METVP shows clearly the time instants when the needle enters and leaves the fruit. The obtained guidewire perforation pattern was significantly different to other observed sounds.

4. Discussion & Conclusion
In this work we have shown that audio signal acquired from the proximal part of an MID could be a powerful tool for providing additional guiding information to surgeons in minimally invasive procedures.

References
The posters will be on display both days in rooms Zeeman and Lorentz

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A steerable needle prototype for the TIPS procedure
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1. Introduction
The Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedure is a radiologic intervention in which a portosystemic tract is created between a branch of the hepatic vein and the portal vein (Fig. 1). It is one of the treatment methods to decrease portal venous hypertension caused by liver cirrhosis. During this procedure, access is obtained via the jugular vein in the neck. An instrument set, consisting of a needle, catheter, and guidewire, is used to create the shunt.

The TIPS procedure is considered to be one of the most challenging radiologic interventions, because: 1) the needle deflects upon insertion through the stiff, cirrhotic liver parenchyma, 2) the needle angle required to reach the portal vein cannot sufficiently be achieved. The aim of the present research is to design and validate a lockable steerable needle for the TIPS procedure, to overcome the aforementioned problems.

2. Methods
A steerable needle prototype, intended for single use, was designed and fabricated at TU Delft. The prototype was made by modifying the existing Rosh-Uchida TIPS needle set (Cook Medical). An exploded view of the handle design can be seen in Fig. 2. The threading in the original needle cap was preserved to guarantee its compatibility with the catheter.

A groove was made along the length of the needle, in which a cable was placed and secured with a shrink tube. The interventional radiologist holds the handle in one hand and turns the internally threaded wheel with his thumb. By rotating the wheel, the bolt translates, pulling the cable and therefore bending the needle tip in one direction. The steerable angle automatically locks in the selected position due to high friction in the threading.

The repeatability of needle steering was tested by puncturing (n=12) into porcine gelatin (5 and 15 m% to water) at 5mm/s for an insertion depth of 50mm. Repeatability error was defined as the distance in millimeters between the mean of all insertions and an individual insertion.

3. Results
The maximal steering angle that can be achieved with the prototype is 14.5°, as shown in Fig. 3. This range was maintained when puncturing in the gelatin phantoms. No significant differences in repeatability were found for the insertions into the different gelatin concentrations. The maximal repeatability error was found to be 1.6mm.

4. Discussion & Conclusion
In this study, a lockable steerable needle prototype for the TIPS procedure is developed and tested. With this needle, the ultimate goal is to decrease the number of punctures needed to create the tract between the hepatic and portal vein, and thus improving needle placement during the TIPS procedure.
Characterization of mechanical properties of thin non-flat membranes – a novel bulge test based methodology

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1. Introduction

The mechanical properties of thin membranes in microelectronic systems need to be characterized to be able to predict their performance, failure and reliability. The bulge test method is the current gold standard for freestanding thin film characterization with relatively simple sample handling and data post processing [1]. However, this method requires pre-stretched, flat samples, and cannot be applied for deformed membranes (as encountered in, e.g., ultrasound transducers or spectral purity filters). In particular, thin membranes have negligible bending stiffness and consequently, even small compressive stresses, usually arising from processing steps, can induce deformation of the membrane. A novel method is therefore introduced to characterize properties of non-flat, deformed, thin membranes. Buckled membranes (Fig.1a) are used as demonstrator samples to show the proof of principle.

2. Methods

Buckling results in locally varying, non-uniform displacement fields even when the membranes are pressurized [2]. Recently, we introduced a new technique, quasi-3D Digital Image Correlation (DIC) [3,4], with which local deformation and curvature fields can be measured accurately. The goal of this work is to investigate the possibility of extracting material properties from buckled membranes using quasi-3D DIC data. To this end, finite element analysis are employed to model the buckled membranes, while bypassing the buckling bifurcation point [2]. The resulting post-buckled regime is used to identify regions of simplified stress states to apply the bulge test methodology with certain modifications to extract mechanical properties from the membranes.

3. Results

The results show that the FE model is indeed able to accurately capture the complex buckled membrane shape (Fig.1b). Consequently, three regions are identified where modified bulge equations can be applied. The analysis for extracting material properties in the regions of interest is numerically validated in a virtual experiment, which shows that the proposed technique is indeed valid: Young’s modulus is extracted with an error of 1.4% while Poisson’s ratio is obtained with an error of 0.56%.

Figure 1: (a) Topview of the bulge test sample with a buckled membrane; (b) FE result of the meander-like buckled profile (c) Custom-built bulge test setup placed under confocal profilometer; (d) Topographical image of the rippled membrane at 10 kPa, obtained using optical profilometry.

4. Conclusion

A novel methodology for characterizing the mechanical behaviour of buckled thin films, which employs an enhanced bulge test methodology, was presented in this work. A proof of principle experiment was successfully performed while further in-depth experiments are currently being performed.

References

1. Introduction

Gynaecological brachytherapy involves the timely manipulation of radioactive sources in and near tumorous tissue. The treatment quality largely depends on the accuracy in source placement. In practice, this is realized by means of intracavitary applicators, occasionally supplemented with interstitial needles. However, in the case of lower (para)vaginal involvement or distal parametrial tumour extension, current instruments do not provide the freedom needed for an optimal radioactive dose delivery.

Custom-fit applicator designs, based on patient MRI data, were devised with the aid of 3-D printing techniques. It was expected that a custom-fit design improves the device position stability, which is crucial for an accurate source placement. Moreover, the attained freedom to customize needle channels results in a vast improvement of the treatment planning options. Practical path constraints were studied in relation to the rise in insertion force as the needle passes through the curved channels.

2. Methods

MRI scans were obtained from two patients with relevant cases of gynaecological cancer. The visibility of the vaginal cavity was enhanced with ultrasound gel. The outlines of the vaginal cavity and of the tumour were segmented by means of conventional treatment planning software (Oncentra, Elekta, SE), resulting in DICOM RT-struct files. The desired needle channels were made compatible with 6F catheters (Proguide, Nucletron BV, NL). The anatomy and the needle channels were converted to coordinate data (MiVisLab, Fraunhofer MEVIS, DE), imported in a CAD program (SolidWorks, Dassault Systèmes, US), and turned into a printable applicator design. The prototypes were made from PLA (Ultimaker 2 Extended+, Ultimaker, NL).

To study the path constraints caused by the intrinsic needle stiffness, a separate print contained needle channels with radii ranging from 20-75 mm. The print was suspended in a 10 m% gelatin phantom. A linear stage (PRO-115, Aerotech, US) was used to insert needles at a constant speed of 5 mm/s, through the channels and into the gelatin, while insertion forces were measured (LSB200, Futek, US).

3. Results

The maximum needle insertion force rapidly increased for radii of 35 mm and smaller (>14 N). As a result, the occurrence of needle buckling increased during the automated insertion series. In manual insertions, performed by a clinician (R.A.N.), radii smaller than 35 mm were also considered uncomfortable. For the used needle and prototyping method, a path radius of 35 mm was therefore considered to be a constraint that should be considered during treatment planning.

Two custom-fit 3-D printed needle applicators are shown in Fig. 1. The needles enter the applicator at the lower cylindrical part and exit through the holes at the top of the print. Exemplar needle paths are shown in the left image (red lines).

4. Discussion & Conclusion

Custom-fit 3-D printed needle applicators for intracavitary and interstitial brachytherapy were successfully constructed from MRI-scans of patients with vaginal cancer. Path planning constraints were studied and a minimal channel radius of 35 mm was advised for this needle type and printing quality. A continuation of this study should improve the acquisition of MRI scans of the vaginal cavity, the optimization of needle paths, and the transformation of medical images to printable models. Moreover, the true effects of these custom-fit applicators on the brachytherapy treatment quality should be further evaluated.
Ultra-stretchable interconnects for high-density stretchable electronics applications
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1. Introduction

The quest for integrating intrinsically stiff and brittle electronics with the human body has resulted in a new and exciting field of stretchable electronics (SE). The resulting ground breaking medical applications include surgical and diagnostic devices amongst others. These devices are of a hybrid nature, involving stiff Integrated Circuit (IC) islands such as detectors or actuators connected with stretchable (typically) metallic interconnects on top of a rubber substrate.

![Figure 1: Concept illustration of an inflatable catheter-tip ultrasound detector (top), CMUT array on a catheter tip produced using the F2R technology (bottom) [1].](image)

2. Methods

The goal of this project is to achieve ultra-stretchability i.e. interconnect stretchability beyond 1000%, which is required in high stretch applications such as balloon catheters (see fig. 1). Furthermore, the high stretchability can allow high IC areal coverage and also provide a high factor of safety highly needed in medical applications. The strategy adopted here is to make the interconnects freestanding as opposed to the conventional interconnects, which are embedded in the matrix. The freestanding nature of the interconnects allows them to use extra degrees of freedom such as out of plane buckling and subsequently bending and torsion, thus allowing much increased global stretchability. A new freestanding interconnect design was conceived and analysed using finite element (FE) simulations (see fig. 2). Furthermore, the flex-2-rigid (F2R) microfabrication routine [2] was adopted to allow routine microfabrication of miniature interconnects with footprint dimensions in the range of tens of microns.

3. Results

The performance and reproducibility of these freestanding structures is promising, with an elastic stretch beyond 2000% (see fig. 2) and ultimate (plastic) stretch beyond 3000%. 4-wire electrical resistance measurements show only minute (<0.3%) resistance change with stretch up to 3000%. Furthermore, the interconnects exhibit excellent performance in cyclic loading, with >10 million cycles at 1000% stretch with <1% resistance change.

![Figure 2: Comparison of experimental and numerical (FE) results for 100 μm interconnect, with loading and subsequent unloading to analyze the reversibility of deformation [1].](image)

4. Discussion & Conclusion

Further steps towards actual device fabrication involve application of an isolation layer (e.g. parylene) and steps to make the F2R process CMOS compatible to allow regular CMOS processing of highly stretchable SE devices.

References


Label-free interaction-triggered cell binding assay in autonomous microfluidic system for blood typing

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1. Introduction

Medical applications of microfluidics promises miniaturized and accelerated quantitative on-site (Point-of-Care) analysis of biomarkers. Besides the adaptation of classical assays, it could also enable to introduce novel principles utilizing physical phenomena dominating in micro scale. Since cells' dimensions are compatible with the micrometer range it seems advantageous to develop applications that utilize cells as components of the assay. We applied the cell-molecule interactions to significantly modify the flow characteristics in a self-driven microfluidic system in order to generate a simple but robust assay and readout system for Point-of-Care diagnostics. Here we provide the proof-of-concept of the system for human blood typing.

2. Methods

The applied microfluidic capillary systems were fabricated by standard soft-lithography techniques polydimethylsiloxane (PDMS – Dow Corning Sylgard 184) polymer as structural material. Autonomous flow of blood was achieved by adjustment of hydrophilic surface properties with embedding dimethylsiloxane ethylene oxide block copolymer (PDMS-b-PEO - Sigma-Aldrich) in the raw material. Appropriate surface areas of a hydrogel coated glass slide (Nexterion Slide H, Schott) were functionalized with the anti-A and anti-B blood typing reagents from Diagast. Blood was obtained by fingerprick and introduced into the adequately aligned microfluidic system. The whole blood entered a common capillary channel which diverted into two channels having similar geometric dimensions. (Figure 1.) As analytical signal the fluid movement was observed to differentiate the interactions between the functionalised channel walls and the Red Blood Cells (RBCs).

3. Results

Upon introduction into the microfluidic system blood autonomously started to fill up the device. RBCs reaching the area functionalised by relevant antigens were captured: type A RBC were bound to anti-A surface, type B RBC to the anti-B surface, respectively.

This binding decreased the progression of RBC's front due to collision of moving cells with stationary cells. Additionally, a plasma separation effect could be also observable. By monitoring this separation it was possible to identify the blood group of the sample, as shown in Fig. 1.

Figure 1: Development of plasma and RBC front in blood samples of different blood types (A, B, 0, AB).

4. Conclusion

We have identified strong interactions between blood cells and functionalized microfluidic channel surface resulting in significant change of capillary flow characteristics. We demonstrated the applicability of this principle for reliable blood typing [1] moreover the phenomenon can be exploited for further medical diagnostic applications utilizing simple autonomous microfluidic systems [2].

References

1. Introduction

The past ten years have seen tremendous improvement in minimally invasive surgeries and diagnostics, in areas such as cardiac, orthopedics and peripheral vascular. To drive quantum advances in resolution, noise, and enhanced definition it will be necessary to move sensing, conditioning and portions of the processing into the distal end of catheters to provide doctors deeper and clearer insights. To achieve this, advances in sensors, electronics and packaging have to be thought of as a system, and system engineering and domain knowledge applied to make tradeoffs, including size, integration, partitioning, power dissipation and noise. We will show work on high resolution EP smart catheter oriented devices able to provide high definition cardiac mapping, as well as work to provide distal tip ultrasound processing for IVUS (Intravascular ultrasound).

In the field of cardiac mapping, the catheters and system have evolved from 4 electrode HIS bundle catheters and 8-20 electrode duodecapolar catheters to baskets and other catheters with up to 64 electrodes, all in efforts to provide faster and higher definition construction of electro-anatomic maps to better inform the electrophysiologist and cardiac interventionist of the best targets for therapy. In order to provide higher definition and real time beat to beat diagnostics, catheters need to add more electrodes and splines. This however causes the catheter to suffer performance issues, both electrically (crosstalk, triboelectric effects, RFI, noise, etc) and responsiveness (thickness increases due to wires, lack of flexibility and feel for the surgeon). The challenge is to provide low noise, high channel count, detection, protection and conditioning distally without expanding the catheter lumen size, increasing stiffness and complying with heat dissipation limitations.

In IVUS, image quality and subsequent diagnostic utility are clearly related in order to assess plaque. Image quality is improved by increasing the ultrasound array channel count, while maintaining the agile frequency response and avoiding parasitics impacts, the degrade signal quality. Similar to the EP catheter case, higher channel count leads to larger catheter lumen sizes to accommodate the wiring.

Additionally, due to the high frequency nature of the signals (~20-60 MHz), parasitic impacts of the cabling impair the image quality. All this and other issues auger for a distal processing solutions to enhance channel count, improve signal quality and more agilely control beam steering.

2. Methods

We have funded advanced R&D efforts in these areas to address the issues of distal electronics to improve diagnostics and therapy.

3. Results

In order to achieve the end goals for these highly complex and high performance systems, with their extraordinary size and power limitations, we focused on first analysing the system, brainstorming and analysing alternate approaches from the system to the tip, from the electrodes and sensors, to the lumen and handles and electrical connections to the system and the algorithms and partitioning of the signal conditioning and processing, and finally the ICs (Protection, filtering, amplification, beam forming, data conversion, power and bus).

Figure 1: 7 Fr. Catheter lumen containing distal electronics servicing hundreds of electrodes in a high density EP catheter.

4. Discussion & Conclusion

A holistic, systems level approach yields the best results, with innovations coming not only on IC architecture, die size reduction, power reduction, and performance, but also in protection schemes, integration into ultrafine pitch flex assemblies, as well as architectural analysis and repartitioning of the functions of the system.
A B-Spline-Kalman framework for catheter shape estimation using tracked ultrasound imaging

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1. Introduction

Tracking the location of interventional devices in an image during minimally invasive interventions can greatly improve the success rates or in some cases be of critical importance. Interventional tool tracking in X-ray images has already been used during many catheter based interventions. A typical tracking approach involves detection and tracking. A guide-wire or catheter can be modelled using B-splines [1]. Our goal is to use ultrasound imaging for 3D tracking of interventional devices. In this study, we present a tracking scheme based on Kalman filtering with a B-spline framework for modeling the catheter shape.

2. Methods

The detection of the catheter on consecutive 2D frames was performed using a block matching (2x2mm kernel size) technique. The initial kernel was manually placed over the catheter cross section. The tracking scheme consisted of an unscented Kalman filter with a B-spline framework. The Kalman filter was initialized with a straight uniform B-spline curve fitted to two end point locations of the catheter. The Kalman state consisted of 5 B-spline control points, current 3D catheter location, 3D location and orientation of the 2D ultrasound frame. The control points of the B-spline curve were updated for any new 3D catheter location that was detected from the 2D ultrasound frame. The B-spline was fitted using a Levenberg-Marquardt [2] least squares optimizer by minimizing the sum of squared errors between the B-spline curve and the data points for 100 iterations. The B-spline was updated recursively for each new point.

The tracking accuracy was evaluated with an experimental setup consisting of an electromagnetic tracking system (3D Guidance trackSTAR, NDI, Canada), a static ablation catheter [Blazer Open Irrigated, Boston Scientific] with 2 sensors attached to its end points (Fig 1b). The whole catheter was tracked with a 2D ultrasound probe (SA4-2/24, SonixTouch, Ultrasonix) by sweeping between the end points. The catheter model is shown in Fig 1a. The 3D locations of the catheter detected by the block matching technique were taken as the ground truth and added with Gaussian noise (standard deviation = 0.8mm) as input to the tracking. The tracking was performed with 3 freehand sweeps.

3. Results

The tracking result after 3 sweeps is shown in Fig 1c. The root mean squared error between filtered curve and the ground truth was 1.24mm.

![Figure 1: a) B-spline catheter model with sensor locations and catheter cross section data points extracted from each ultrasound frame b) Experimental setup with a static catheter attached to a wire frame inside a water tank, c) B-spline tracked result.](image)

4. Discussion & Conclusion

A 3D tracking method using an unscented Kalman filter with a B-spline framework allowed updating the 3D catheter shape from each 2D ultrasound frame containing the cross section of the catheter. This seems to be a promising technique for real time update of catheter shape using freehand 2D ultrasound sweeps.

References


A Wireless Sensor for Monitoring Encapsulation Performance in Non-hermetic Implants

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1. Introduction

For years, medical devices have relied on the titanium housing to protect the inside electronic. Such devices, however, end up to be bulky and resu in low specificity when stimulating neuron: Miniaturization is essential to target more specific populations of neurons in order to develop precise bioelectronic medicines [1]. Polymer encapsulation is a type of non-hermetic encapsulation, which could greatly reduce packaging size while protecting the electronic circuitry. One main drawback, however, would be the loss of hermeticity and a method to predict lifetime reliability [2]. The lifetime reliability of such a package depends on the adhesion quality between the polymer and the substrate. Since all polymers are permeable to water moisture, water could condense at the polymer-substrate interface jeopardizing the adhesion quality. Such a phenomenon would eventually lead to corrosion and device failure by exposing the electronics to liquid water. In this work, we aim to detect the problem at its early stage: when water condenses at the interface. Fig.1 shows a system-level view of the proposed wireless sensor. When the sensor detects liquid water, a signal will be transmitted well before any corrosion has taken place.

2. Methods

So far, inter-digitated electrodes (IDE) have been used during long term soak tests to monitor and assess the substrate-to-encapsulant adhesion quality [3]. Fig.2(a) shows an IDE structure in which the adhesion quality is monitored by measuring the impedance between the comb structure. Such a method, however, shows adhesion failure in its final stages, when water condensation has accumulated, created a larger gap in the interface and led to leakage (Fig. 2b). The method proposed in this work is to use a sensitive micro-sensor that could detect liquid water forming at the interface and signaling the onset of failure well before any corrosion has taken place.

![Wireless sensor for monitoring adhesion quality in-vivo.](image1)

Figure 1: Wireless sensor for monitoring adhesion quality in-vivo.

![IDE encapsulated IDEA for monitoring adhesion quality.](image2)

Figure 2: (a) a polymer encapsulated IDE for monitoring adhesion quality, (b) water condensation at interface[2].

3. Discussion

Such a monitoring sensor could significantly shorten the duration of soak tests. Moreover, it could be used as a reliability sensor for future non-hermetic implants. Nevertheless, there are some technological challenges in the design and fabrication of such a unit. One main challenge is to design the sensor in a way that it could detect liquid water at the interface well before it has reached the electronics underneath. Another challenge would be to design and place the sensor on the implant in a way that it would detect condensation well before any condensation or corrosion takes place on other locations on the implant.

4. Conclusion

Polymer encapsulation as a packaging solution is a viable candidate for miniaturizing future implants. For such packages, however, no hermiticity check could be performed to predict lifetime reliability. In this work, we have brought forward the idea of using a surface monitoring sensor to detect water condensation at its very early stages. Such a sensor could ultimately be used in situ as a diagnostic self-check for future non-hermetic implants.

References

Silicon based microfluidic device with integrated electrodes for the assessment of cellular stiffness

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1. Introduction

Diseases such as atherosclerosis, malaria and cancer can alter the cellular stiffness [1]. Quantification of this value in a short time, effortlessly, will significantly improve the understanding of these diseases. Cellular stiffness can be derived from the velocity of a cell squeezed through a constriction channel. In this research, a microfluidic device with silicon-based integrated electrodes was fabricated to detect the cell within the constriction channel and to measure its velocity.

2. Methods

The device fabrication starts with a double side polished SOI wafer with a 40 μm thick device layer that is doped with high boron concentration (< 20 mΩ·cm).

First, 1.7 μm of PECVD SiO₂ was deposited on the wafer and patterned using a mask with a mesh of small rectangular openings (0.8 × 4.8 μm²) at the location of the microchannel and around the electrodes. Second, the single-step DRIE [2] was performed to etch trenches down to the BOX layer. Third, the remaining SiO₂ mesh was sealed by the deposition of 2.0 μm thick PECVD SiO₂ layer. Afterwards, via openings to the silicon-based electrodes were etched which was subsequently covered with 2.0 μm of aluminium and patterned to form the electrical interconnects and the bond pads. Finally, the microfluidic inlet/outlet were opened.

3. Results

Figure 1 shows the fabricated device (Left) with a close up image of the constriction channel and the electrodes (Right). Six pair of electrodes with different sizes were integrated next to the constriction channel. A continuous microfluidic flow of 2 hours was applied to the channel and no leakage occurred. Figure 2 shows the cross section of the device where we see that the electrodes are isolated from the rest of the bulk by the BOX layer and the void surrounding it. The electrical isolation of the electrode was also confirmed by measuring the impedance between the two electrodes which was infinite (> 12 GΩ).

4. Conclusion

Tightly sealed microchannel was integrated with silicon-based electrode using standard IC based fabrication process. This opens possibility for a mass producible lab-on-a-chip device to measure cellular stiffness at a high throughput, requiring very small effort from the users due to the electrical readout system. The fabrication method is scalable for further miniaturization which will lead to further integration of microfluidic technology with CMOS electronics.

References


Microneedle-based ECG Monitoring – Part 2: A Wearable System

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1. Introduction

Existing ambulatory electrocardiography (ECG) monitors can collect cardiac signals from a single set of electrodes. Although these systems can measure high quality ECG signals for diagnostic purposes, such systems are typically not able to accurately compare the ECG signals from various types of electrodes, which is a key requirement during the development of new electrodes. In order to facilitate performance assessment of different types of electrodes, we have therefore developed a wearable and compact system capable of acquiring and analyzing ECG signals from multiple sets of electrodes simultaneously. The system is being further developed to include wireless capability.

2. System Description

The wearable ECG system is intended for simultaneous acquisition/analysis of two input ECG signals, and a breadboard-level prototype is depicted in Figure 1. Key components include gold-plated Eptek 353ND microneedle electrodes, Analog Devices AD8232 single-lead ECG front-ends, a SparkFun nRF52832 Breakout board, and a coin cell battery. Using conventional snap fasteners, the ECG electrodes are attached to electrode cables which can be wired to the AD8232 front end that extracts and amplifies the low-voltage ECG signal and filters it from noise signals.

Figure 1: Prototype demonstrator of wearable ambulatory ECG monitor.

The amplified ECG peak signal amplitude is 3.3 volts, which is interfaced with the analog input of the SparkFun nRF52832 Breakout board. Application-specific embedded software was developed using the Arduino Integrated Development Environment (IDE) to stream the ECG signal data points at a rate of 56 data samples per second through a USB serial cable to a PC. In the experimental setup, two sets of three electrodes (viz. commercially-available Red Dot 2239 Monitoring Electrodes from 3M and Tyndall’s microneedle-based ‘dry’ electrodes) were attached to the subject’s chest in a Lead 2 configuration adjacent to each other.

3. Preliminary Results

A screenshot of four consecutive ECG cycles is shown in Figure 2. All of the ECG waves are visible and easily recognizable.

Figure 2: A plot of four ECG cycles for gel-based wet (red) vs. microneedle-based dry (blue) electrodes.

To compare the quality of the two signals, the signal-to-noise Ratio (SNR) is calculated for an ECG frame of 15 cycles. The results show that the SNR for dry electrodes is (20 ± 1.3) dB compared to that using a commercial wet electrode (21.5 ± 0.8) dB for ten sample regions. Statistical analysis shows that the two are statistically different on a paired t-test with a p-value of 0.0068.

4. Discussion

The developed system provides a cheap, compact and lightweight solution for the purpose of evaluating various types of ECG electrodes. The data reveals a small but statistically significant difference between the performances of the wet and dry electrodes. Current work is gathering further data in order to assess whether this is repeatable across multiple subjects, skin types and ages. Also, the developed wearable system is being further improved to include wireless communications utilising Bluetooth low-energy protocol.
Design, Evaluation, and Future Applications of a Multi-Steerable Catheter for Cardiac Interventions

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1. Introduction

To overcome the challenges presented by complex 3-dimensional shapes and tortuous vasculature in the cardiovascular environment, we developed a prototype of a multi-steerable catheter having 4 DOFs controlled by two joysticks [1]. However, it remains unknown whether the added steering possibilities are beneficial in the cardiovascular anatomy. With this research we aimed to investigate the effect of 0-DOF, 2-DOF, and 4-DOF catheter systems on surgical performance in a cardiovascular model.

2. Methods

Catheter Prototype – The catheter prototype was modified to compare 0-DOF (no steering), 2-DOF (multi-directional steering with a single segment), and 4-DOF steering (multi-directional steering with two segments).

Heart Model & Pathways – A transparent, rigid 3D-printed heart model was fabricated by Materialise (Leuven, Belgium) based on patient CT-data. Three pathways were defined for the experiment, differing in level of complexity:

1. Endo-myocardial biopsy route: starting in the jugular vein to reach a specified location on the intraventricular wall of the right ventricle.
2. Aortic valve implantation route: starting from the femoral artery to reach a specified location past the aortic valve.
3. Trans-septal mitral valve route: starting from the inferior vena cava to reach a specified location past the mitral valve.

Test Setup – The three pathways were visibly marked on the heart model and an electrode was placed at the start and end points of each pathway. The electrodes were connected to a National Instruments LabVIEW box to record the elapsed time between the start and end of each test.

Test Procedure – 18 novices (all students and employees at Delft University of Technology) between 18 and 30 years old, participated in the experiment. Each participant conducted three experimental sessions. In each session, one catheter type was used to manoeuvre along each of the three pathways. This resulted in nine tests per participant. Catheter order and pathway order were randomized.

Performance measures – Performance was assessed using the following objective measures: 1) completion time of each of the nine tests, and 2) number and locations of errors (wrong branch or chamber, retraction of the catheter, catheter blocking). Moreover, the following self-reported measured were used: 1) task performance, 2) usability, 3) workload, and 4) catheter preference.

3. Results

General Observations – General observations gave insight in the methods the users applied to overcome difficulties in steering. These methods included rotation of the shaft, fast push-pull movements of the catheter as a whole, shaking movements to direct the catheter in a specific region, and making use of the cardiac wall.

Preliminary Results – Four participants have been tested so far, yielding a total of 36 tests (4 x 9). For both the 0-DOF and the 2-DOF catheters, 4 out of 12 tests succeeded within 5 minutes. With the 4-DOF catheter, the task was completed within 5 minutes in 8 out of 12 tests. From the tasks that were completed within 5 minutes, the average completion time was measured as 102 s for 0-DOF, 126 s for 2-DOF, and 118 s for 4-DOF. Additionally, all four users reported that they preferred the 4-DOF catheter over the other two.

4. Discussion & Conclusion

The preliminary results indicated that the 4-DOF catheter is able to overcome the challenges of the cardiac pathways better than the 0-DOF and 2-DOF catheters. The remaining 14 participants must be tested before any clear conclusions can be drawn from the results.

References

Fabrication and transfer method of PDMS porous membranes for Organ-on-Chips

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1. Introduction

Organ-on-Chip (OOC) is an emerging technology aiming at creating dynamic cell culture microenvironments that reproduce activities, mechanics and physiological responses of human organs. Novel devices, such as the lung-on-chip developed in [1], comprise of a top and bottom PDMS substrate interfaced by a porous membrane that mimics a biological barrier. Although such technologies have allowed better understanding of numerous cell mechanisms, very often their fabrication and assembling methods are time consuming and depend strongly on manual handling. Moreover, the porous membranes fabricated with these methods provide limited features (pore size, thickness and porosity) to cover diverse biological questions. Here, we present a process to fabricate and transfer porous PDMS membranes in OOC devices in an easy and methodical way that is compatible with standard IC and MEMS fabrication technologies.

2. Methods

To expand the range of application to any OOC device, we included Poly (acrylic acid) (PAA) as a sacrificial layer to easily transfer porous PDMS membranes at chip level. The process developed reduces the need and risks of manual handling, allowing thinner functional membranes to be easily transferred into OOCs. Briefly, as sacrificial layer, Poly-acrylic acid (PAA) layer is initially deposited on a 100mm-Si wafer. The PDMS layer is patterned through our customized lithography process. The silicon substrate containing the porous layer is diced to match the dimensions of the targeted OOC device. The bottom layer and the porous membrane are treated with oxygen plasma to guarantee their mechanical bonding and brought together. Finally, the silicon substrate is detached from the PDMS chip by dissolving the PAA layer in an ultrasonic bath in water. The final device is completed by the top thick PDMS layer placement.

3. Results and Discussion

With the process, it is possible to tune the pores size from 2 µm to 10 µm (Fig.1). The minimum feature size achieved is 50% smaller than previously reported [2]. The membrane porosity ranges between 8-65%.

The biocompatibility of the process was assessed by transferring porous membranes on a PDMS-based OOC (Fig. 2a) and by seeding on Human Umbilical Vein Endothelial cells (Fig. 2b). Further experiments will address the influence of the porous size and porosity of the membranes on different cell lines.

References

Printing on thermoplastic polyurethane substrates: solutions for next generation wearables

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1. Introduction

Stretchable electronics have gained increased interest in the industrial and academic world. Recent developments provide routes to integrate stretchable electronics on textiles and thermoplastic materials, allowing novel applications in the medical, sports and apparel sector [1]. Thermoplastic polyurethanes (TPU) are a suitable substrate for integration of stretchable electronics, due to its high comfort level, biocompatibility, breathability, low price and robustness (washability).

The Holst Centre has developed demonstrators by direct printing of stretchable electronic pastes on TPU. Some examples of these demonstrators are multisensor health patches for vital monitoring (Figure 1), pressure-sensing shoe inlays and solar-powered shirts with LED integration.

2. Methods

The fabrication of these demonstrators can be summarized in a generic process flow as followed. First, as TPU is a highly tunable material by adjusting the chemical formulation, a suitable substrate material needs to be chosen based on the requirements. Next, the circuitry is printed in one or more layers using stretchable silver ink with the desired properties. The printing process can be either screen printing, inkjet printing or using the Laser-Induced-Forward-Transfer (LIFT) method [2]. Next, the components such as LEDs, SMDs and ASICs are pick-and-placed and interconnected. Optionally, additional layers such as another TPU, silicone or textile can be laser-cut, assembled and laminated to complete the demonstrator.

As short-loop experiments to demonstrate the mechanical and electrical properties of assemblies, the circuits are for instance evaluated on an Instron 5566 draw bench while the resistance in the circuit is monitored. An industrial washing machine is used to do wash-cycle tests.

3. Results

During cyclic loading on the draw bench an increase with cycle count in the inherent hysteresis of TPU is shown. Furthermore, residual strain, strain hardening and resistance increase when stretching (Figure 2) are just a few of the effects that have been observed.

Figure 1: Stretchable TPU substrate with screen printed interconnects made from stretchable ink for a health patch.

Figure 2: Measurements on a stretchable interconnect. In blue the force required to achieve the strain level, in red the resulting increase in resistance.

4. Discussion & Conclusion

TPU is an interesting material for wearable applications. However, its limitations should be taken into account when designing a demonstrator using this substrate. By smart design of the device, these short-comings can often be mitigated.

References


CMUT based IVUS Catheter

FFR Integrated Catheter

Robotic Steerable SMA-actuated Catheter System

Force Feedback for INCITE Surgical Robot Demo
Philips – cMUT based IVUS catheter

Technical Solution

First ever solid-state cMUT IVUS catheter
• Improved axial & lateral ultrasound resolution wrt state-of-art

Key attributes:
• Cylindrical cMUT based transducer
• 96 transducer elements
• Diameter 1.2 mm
• 20-30 MHz

Innovations

• High-frequency cMUTs (20-25 MHz)
• Successfully wrapped cMUT transducer (Ø1.2 mm)

Demonstrator

Achievements:
• Complete imaging system @ Erasmus MC
• Fully functional catheters
• Successful animal test June 2017
• First in-vivo images

Promising exploitation potential:
• Significant expected impact - addressing recognized clinical unmet need
• Excellent fit with Philips Business (Volcano)
Technical Solution

- VTT designed, fabricated and tested a FFR catheter system together with
- Murata Electronics
- Creganna
- Tyndall and
- Afore
- The system is intended to be used for measuring the fractional flow reserve (FFR) in coronary catheterization.

Innovations

- Ultra thin (75 μm) capacitive MEMS pressure sensor was designed, fabricated and tested
- ASIC for the capacitive pressure sensor was designed, fabricated in MPW and tested
- ASIC and MEMS were tested and calibrated using Afore test equipment
- Console interface electronics and measurement system software was developed and tested

Conclusions

- ASIC is starting up and running the measurement procedure autonomously and functioning as designed. The accuracy for the full-range output was roughly 15-bits, of the 24-bit output data.
- The measured maximum pressure error was 226 Pa, equivalent to 1.7 mmHg, well within the specification (3 mmHg).
- The system follows 1 Hz dynamic pressure changes well
- Further development needed in temporary abnormal behaviour of the ASIC and EMI noise filtering

Collaboration

- Murata: WP3 leader and concept design
- VTT: manufacturing
- Tyndall: bumping
- VTT: die thinning
- Creganna: Catheter specifications and integration
- Afore: wafer level calibration

System overview

- ASIC layout: 3570μm x 200μm x 75 μm
- ASIC functional block diagram

Demonstrator

- ASIC, MEMS and a calibration capacitor glued and wire-bonded into a ceramic DIL-24 package.
- Console box: MCU-board and interface circuit board as a shield with DIL-assembly attached.
Force Feedback for INCITE Surgical Robot Demo

Technical Solution

Functional requirements:
- 3D force sensing in MIS robotic surgery systems for tissue recognition and grasping function
- Force controlled endoscopic vision robot

Develoment chain

Electro-mechanical FEM modelling (MFA-BME)
MEMS design (MFA)
Micromachining technology (MFA)
Electro-mechanical Integration (BME)
Communication (MFA-FRK)
Signal processing (MFA-FRK)
Robot integration (FRK)

Results

Reliable microfabrication process for piezoresistive force sensors including 3D geometry of Si transducer, implanted piezoresistors and hybrid Si/glass bonding for mechanical and electrical connections

Low noise read-out algorithm and electronic circuit for complex architecture of multiple piezoresistive sensor element

Architecture and design of I2C-CAN BUS communication electronics

Detailed characterisation strategy for integrated sensors (calibration, overloading, thermal and biomechanical tests).

Design of flexPCB and chip assembling technology

Demonstrators and tests

“Smart” laparoscope
with integrated force sensors, electronics and display

ROBIN HEART Minimal Invasive Surgery robot
with real-time force feedback to provide tactile information to surgeons by display and haptic controller

Remote controlled robotic arm or surgery tool
(laparoscope camera) by force sensor based joystick

Biomechanical tests
measuring clamping force on (artificial) blood vessels between forceps (perpendicular component)

Testing tissue hardness
A robotic arm moves the laparoscope perpendicularly with constant speed. Measured forces (N) versus distance (mm) as the laparoscope approaches and touches chicken bone. After slipped the laparoscope started to press softer tissue.

Incite
Robotic Steerable SMA-actuated Catheter System

Current steerable catheters (mechanical pull wire systems)

- Directionally restricted
- Difficult to operate
- Limited shape control
- Physical limitation in miniaturization

Wanted: Electrical actuator with high stroke and extremely small \(\rightarrow\) Shape Memory Alloy

* The research leading to these results is part of INCITE (grant #621278), an EniAc Joint Undertaking project that is co-funded by grants from the Netherlands, Finland, Hungary, France, Ireland, Sweden, Spain, and Poland.
InForMed

Pilot Line: Micro-fabrication & Advanced Assembly

Technology Development Methodology bridges Valley of Death for Microfabricated Medical Devices

Smart Ablation Catheter with Optical Shape Sensing

Advanced Electrophysiology Devices

Minimally Invasive Bioelectronic Implants

AlphaSIP: Bacterial Platform

ECG Monitoring System

Foot Pressure Monitoring
**Pilot line: Micro-fabrication & Advanced assembly**

**New concepts**
- Flexibility
- Fast learning
- Feasibility studies
- New Competences
- Manufacturability insights
- ...

**Product to market**
- Stability
- Traceability
- ISO13485
- Verification & Validation
- Manufacturing ramp-up
- ...

**Micro-fabrication**
Starting point: Shared research facility

After Informed: Pilot fabrication facility, tailored towards the needs and requirements of present and future medical devices.

**Micro assembly**
Starting point: Facility with selected micro-assembly competences.

After Informed:
- Process development and Manufacturing facility for integrated Semiconductor / Electronics solutions.
- New capabilities include:
  - HPE assembly
  - Handling of extremely thin and small dies
  - Coating for protection

**Smart Catheters**
Starting point:
Prototyping for Catheter related activities

After Informed:
- Concept feasibility
- Catheter verification
- Build according DMR Competence center

New capabilities include:
- Optical fiber processing
- Guide wire processing

Manufacturing Process Development: approach with maturity gates
Document Management System for DHF and DMR
**Project InForMed will establish a pilot line for microfabrication of medical devices**

**Microfabrication of Medical Devices**

- Foldable sensors for catheter tip
- Sensors assembled on catheter
- Foldable sensors for catheter tip

**Valley of Death for Microfabricated Medical Devices**

Differences between university and industrial environment cause low transferability of technology.

- **Technology Transferability from University to Pilot Line is problematic**
  - Low (commercial) value
  - Low manufacturability
  - Low Technology Readiness
  - Adaptation delay & costs
  - Technology may work only in lab / only in pilot line
  - Barriers to learning
  - Uninformed decision-making

**Joint Technology Development Methodology improves University-Industry Technology Transfer**

- **Technology Readiness Levels used as gates for U-I cooperation**
  - Including all TRL levels promotes realism about industrial valuations among academic researchers.

- **PhD+ programme**
  - PhD+ student develops product and process from ideas to transferred technology (TRL3) with consideration of commercial, manufacturing and quality aspects, whereas traditional PhD student typically does not go beyond TRL1.

- **Technology Validation in Lab**
  - **Design**
  - **Engineering**

- **Industry**
  - **Manufacturing**

- **Academic research typically ends at TRL3 but validation decreases risks (TRL4+)**

- **Technology Readiness Levels in the H2020 programme**

**InForMed Pilot Line will bridge the gap**

- New treatments
- New/improved functionality
- Heavy ⇒ Portable
- Lower cost

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**This work is part of InForMed, a project funded by ECSEL Joint Undertaking (JU), grant no: 2014-2-662155, website www.informed-project.eu**
Smart ablation catheter with optical shape sensing

Technical Solution  (Philips, Fraunhofer IZM, Osypka AG, Lust Hybrid)

A smart ablation catheter to increase the success rate of atrial fibrillation (AF) ablations

Key attributes
• Steerable RF ablation catheter
• Optical shape sensing
• cMUT based transducer
• Tip outer diameter 2.3 mm

Innovations

• Integrated flexible interconnects (F2R)
• High-frequency cMUTs (20-30 MHz)
• ASIC for U/S signal enhancement
• Tracking shape of ablation catheter with OSS demonstrated

Demonstrator

• Integration of dummy and functional catheter is in progress
• Working demonstration is planned for Feb ’2018

Catheter ablation is a growing treatment for atrial fibrillation

Market Forecast (Europe)

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>2016</th>
<th>2020</th>
<th>2024</th>
<th>CAGR (14–24)</th>
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<tbody>
<tr>
<td>Diagnostic Catheter Procedures</td>
<td>4.9%</td>
<td>4.0%</td>
<td>2.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Ablation Catheter Procedures</td>
<td>6.3%</td>
<td>4.7%</td>
<td>2.1%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>
WP4 – DEMO2: Advanced electrophysiology devices

Technical Solution: From Petri dishes to Organ On Chips

Pharmaceutical companies are heralding the development of dynamic cell culture environments to replace traditional petri dishes and reduce false positives and negatives during pre-clinical cardiotoxicity tests. Organ-on-Chips (OOC) are micro-fabricated chips that can be used to simulate in vivo human physiology by promoting cell and tissue growth in vitro by means of mechanical and perfusion input. These cell-culture environments are expected to improve the predictivity of cardiotoxicity tests. DEMO 2 aims at developing novel OOC devices to mechanically stimulate cardiac in vitro tissue and monitor them via optical and electrophysiological techniques.

MARKET FACTS:

28% drug withdrawals in USA due to cardiac toxicity;
OOC Market estimated: $ 31.5 Million, CAGR (2020): 70%;
In Vitro Cardiotoxicity Market estimated: $ 2 billion.

Innovations: From Academia to Market

Demonstrator: System

- Silicon-based microfabrication;
- Include cell culture environment;
- Equipped with MEA.
- Accommodates packaged chip;
- Provides interface to sensors and actuators in the chips;
- Contains signal conditioning.

- Conditioning Box;
- MCS read-out system.

BIOCOMPATIBILITY TESTS

Goal: Test the biocompatibility of newly developed Cytostretch packaging materials with Pluricyte® Cardiomyocytes;
Readout: Monitor cell and monolayer appearance with light microscopy and verify beating of cardiomyocytes using calcium dye.
Results: Lower cell density was observed in the cell culture on the device. While the cardiomyocytes appeared normal, no calcium transients were observed. Future tests will investigate the causes (increased maturity/decreased functionality...).
Minimally Invasive Bioelectronic Implants

Technical solution

1. Safety capacitors on SOI wafers

2. Flex-2-Rigid (F2R)

3. Flip-chip of an ASIC

4. Coating electrode with PEDOT

5. Wrapping

6. Encapsulation:
   - Ceramic layer
   - Parylene
   - Silicone

Chip-in-the-Tip

40-electrode DBS probe

Innovations

- Pt based flip-chip of daisy chains
- PEDOT deposition on Pt electrode

Implantable F2R

- Step 1. Fabrication of capacitors (IPDs) on an SOI wafer.
- Step 2. Separation of the IPDs with embedded trenches.
- Step 3. Fabrication of a foldable device with flexible interconnects and stimulation electrodes in Parylene-platinum based F2R.

- 100 μm thin ASIC

Demonstrator

- Foldable mock-up of implantable F2R

Exploitation/impact

- Platform for bioelectronics manufacturing
- Ultimate miniaturization
- High-level of integration
- Long-term stability and reliability
- Improvement of patients safety
- More precise treatment

Biocompatible and biostable coatings:
- Al₂O₃, Al₂O₃+TiO₂, TiO₂ (LT), HfO₂,
- Parylene C
- Medical silicone
Application target
Rapid detection of pneumonia most common causing agents in serum samples, such as *Streptococcus pneumoniae*.

Technical Solution – Components, subsystems, System Integration Highlights & main achievements

**System architecture**

**Microfluidic chip: mold injection fabrication**

**System integration – microfluidics – sensor - electronics - housing**

Innovations – progress beyond state of the art, Highlights & main achievements

**Microfluidics original design (Unizar) : Three microchambers for mixing**

Microarray in central microchamber – spotted by Micronit

Immuno-assay implemented in microfluidic chip

**Demonstrator – Prototypes, exploitation, expected impact**

**Prototype integration almost finalized**

**Immuno-assay and validation by University of Cordoba & Hospital Universitario Infantil Virgen del Rocio (Sevilla)**

- Meant to replace lateral flow chromatography rapid tests (qualitative + low specificity/sensitivity) in the clinic, for respiratory infectious disease diagnostics.
- Competitive advantages: The multiplexing capability (microarray) allows the screening of over 10 pathogens in less than 20 min. Allows practitioner to choose if antibiotic treatment is needed, and which one is to be used.
- The cost of the device and cartridges is compensated by reduction in false negatives/positives and savings in antibiotic treatment and the number of determinations in one single test.
ECG monitoring system

Cardiovascular disease causes 3.9 million deaths in Europe. Bodycap and ESIEE Paris aims to develop an accurate and reliable cost effective solution for ambulatory cardiac monitoring. The main challenge is to find the right compromise between the disposable and the reusable part.

Development of ECG flexible substrate and evaluation on thick film polymer and metallization (Parylene (50 μm) and Polymer biocompatible), with up to 3 level of metals

- Optimization of metal adhesion on parylene substrate
- Evaluation of conductive ink for fast prototyping on flexible substrate
- Evaluation of new photosensible polymer to achieve soft substrate for medical applications

Demonstrator

Functional ECG sub-module on standard PCB and Parylen fil sub-module m

Perspectives:
- ECG measurement could be improved through accelerometer integration
- A flash memory connected to a BLE communication protocol will allow the ambulatory monitoring
- Microcontroller and power management optimization
Technical Solution – Plantar pressure measurements

State-of-the-art solutions for motion analysis:
- Dynamic plantar pressure systems
- 3D scanners
- User-oriented software

Why in-shoe systems:
- Not limited to a laboratory, but measures a patient’s natural gait.
- Measures pressure between foot and shoe (and not between shoe and floor).
- No temporal limitation.
- No spatial limitation.

Limitations today:
- Small number of sensors
- Limited sampling rate
- Bulky system (driving and read-out electronics is connected to the lower legs) reducing user comfort and influencing natural gait
- Limited durability
- Limited usage time because of limited power supply

Innovations – Smart, reliable shoe insoles with integrated arrays of pressure sensors

Vision:
Study and develop high-end pressure sensing insoles that overcome the current issues related to durability and user-friendliness
- High sensor resolution
- High measurement frequency
- High reliability and accuracy
- User comfort
- Noiselessly reduced cabling
- No interference with motion
- Resistant to harsh environment

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Demonstrator – Prototypes, exploitation, expected impact

Envisioned requirements:
- Accurate & Reliable
- Portable
- Easy to use & comfortable
- Versatile API to allow integration with various other analysis technology

Resolution
- 4 sensors per cm²

Sampling frequency
- Up to 1000Hz

Insole size
- Up to EU 47

Maximal insole thickness
- < 2mm

Maximal insole weight
- < 300g

Pressure range
- 0-200 N/cm²

Battery life
- Minimal 2 hours recording

Real-time feedback rate
- Ethernet / Bluetooth

Electronic driving board

Ag-printed insole prototype

Cu-based insole prototype

Ag-printed prototype

Cu-based prototype

Mock-up

Ag-printed insole design

Cu-based insole design
Micro-fabricated devices increasingly find their way to the frontends of medical equipment where they form the interface between the human body and the system.

Topics
- Organ on Chip
- Electroceuticals
- Clinical Robotics
- Smart catheter for cardiovascular interventions
- Handheld diagnostics
- Smart body patches
- In-body / minimally invasive instrument tracking
- The MEMS Ultra-sound revolution
- Computer aided planning & navigation
- Bridging the “valley of Death” with open pilot lines and platforms

Chair
Prof. dr. ir. Ronald Dekker
TUDelft / Philips Research

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