1995-2025
三十周年
30 ANS

Research Activities 2024-2025

LIMMS

Laboratory for Integrated Micro-Mechatronic Systems

LIMMS/CNRS-IIS IRL 2820

Booklet outlines

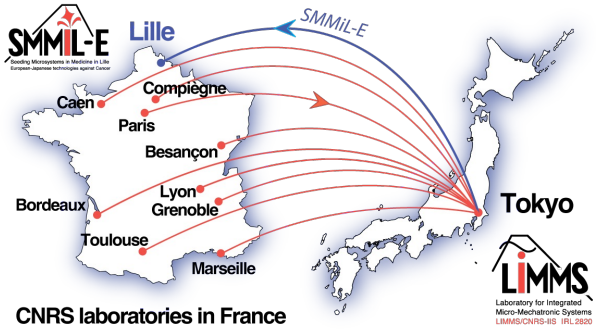
Welcome to the Laboratory for Integrated Micro-Mechatronic Systems (LIMMS/CNRS-IIS IRL 2820)

Creation and achievements

LIMMS (Laboratory for Integrated Micro Mechatronic Systems) is a joint laboratory between CNRS Engineering Institute and the University of Tokyo (IIS - Institute of Industrial Science). LIMMS researchers are hosted in 17 research groups mainly located on Komaba Research Campus of the University of Tokyo. Since its creation in 1995 the laboratory has been working in the field of micro/nanotechnologies and BioMEMS.

LIMMS was created in 1995 as a cooperation unit between CNRS (then SPI Department and now CNRS Engineering). Soon after it was established, the laboratory benefited largely from the strong support from the Japan Society for the Promotion of Science (JSPS).

In 2000, LIMMS was relocated, together with IIS, to the Komaba Research Campus (Tokyo/MeguroKu), where exceptional technological facilities are provided.



CNRS laboratories in France

SMMIL-E, Lille

LIMMS, Tokyo

1995
creation of LIMMS

3
research axis

Energy
Quantum & Molecular Tech.
Bio

4
main grants

2019-2024 JSPS C2C
2019-2025 CREST-JST
2022-2029 PEPR MoleculArchiv
2024-2030 PEPR MED-OOC

4
EPI

2024 - 2025

48 papers
25
7
16

18 conferences
10
2
6

Since 2004

547 papers

593 conferences

2024 - 2025

22 contracts

114 people
involved in LIMMS activities

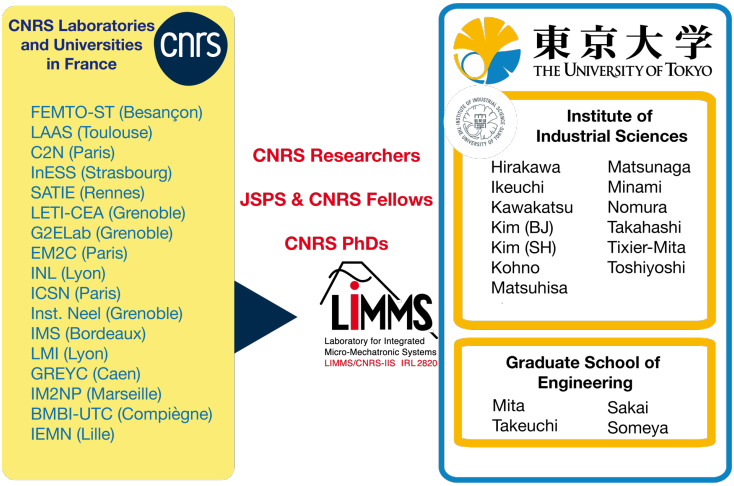
Since 1995

438 people welcome

49 CNRS researchers
27 CNRS post-doc
81 JSPS post-doc
14 IIS post doc
10 CNRS Research Eng.
35 PhD students
102 Internships
22 administrative staff
…

2023
ecoLIMMS started

16
New research teams created in France by former LIMMS members



Since the IRL 2820 foundation in 2004 (IRL= International Research Laboratory), LIMMS has been eligible to apply for French, Japanese and European research projects and grants-in-aid.

After successful review meetings, LIMMS was renewed for three terms (2010-2030). During this period, LIMMS extended its structure to European partners through EUJO-LIMMS, a project funded by the European Union (Dec. 2011 - May.2016) along with a first Core-to-Core program (April 2012 - March 2017) of the JSPS.

In 2014, LIMMS took a new step in its development by inaugurating a mirror location in Lille (France) inside a hospital. The SMMiL-E project, Seeding Microsystems in Medicine in Lille, first research location of IIS out of Japan, gathers IIS, CNRS, Centre Oscar Lambret and Lille University.

In 2017, LIMMS was involved as a partner of the iLite consortium (for innovation in Liver tissue engineering, 2017-2022), an university research hospital project, granted by the French program-investment for the future (Program Investissement d'Avenir).

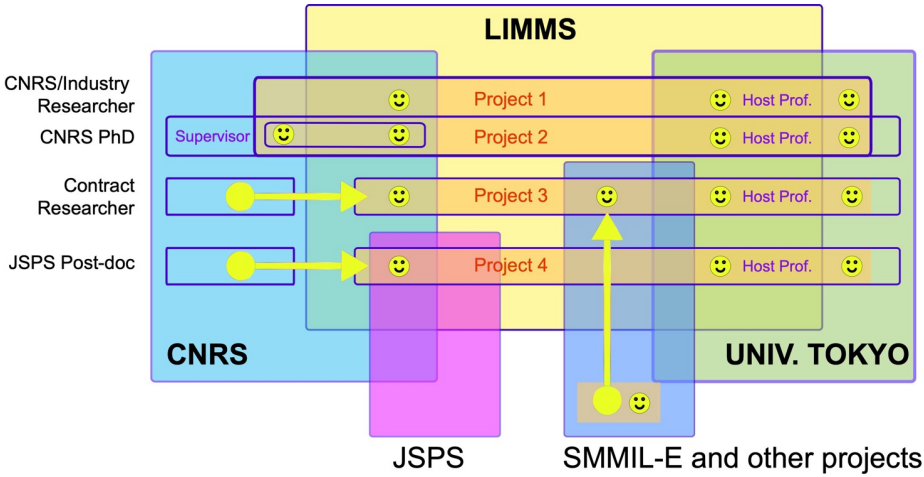
In 2019, a second JSPS Core-to-Core program (JSPS) was assigned to LIMMS (April 2019-March 2024) to promote the interactions more specifically in Bio-oriented activities with SMMiL-E and the partners of iLite.

In 2020, a CREST (JST) project targeting thermal management in silicon devices was attributed to LIMMS (October 2019-March 2025).

In 2021, an Integrate Research Network 'LIMMS Kiko' (period 2021-2031) of the University of Tokyo centered on LIMMS activities was started to extend connections with 55 Japanese professors from 8 Institutes and Schools including fields such as engineering, medicine, information science and philosophy.

In 2022, LIMMS was involved in the MoleculArxiv PEPR (Programme et Equipements Prioritaires de Recherche) as one of its key laboratories, and a CNRS $(RI)^2$ project (Recherche à Risque et à Impact) along the same topic is also led by LIMMS since 2024.

In 2024 also, the EURA-LIMMS IRN (CNRS international research network) was started.



In 2024/2025 about 110 people were involved in LIMMS activities including Host Professors (17) and their teams, CNRS researchers (10), engineers (1), JSPS post-doctoral fellows (3), contract based post-doctoral fellows (8), PhD students (5), internships (16), collaborators (47) and administration staff (5).

Organization

LIMMS combines the expertise of French and Japanese scientists in order to explore new scientific domains related to micro and nanotechnologies. Researchers who are recruited by LIMMS are hosted in the Japanese research groups affiliated to LIMMS. The scientific interaction is thus optimal.

LIMMS' structure is organized to handle challenging joint projects. These projects follow the scientific policy promoted by both Directors (CNRS and IIS), and approved by the CNRS Engineering Institute within its interdisciplinary policy with other CNRS Institutes, IIS and JSPS. Each scientific project gathers a LIMMS researcher, the Host Professor heading his/her host lab (The University of Tokyo), and associated lab members (see structure of LIMMS on the figure above).

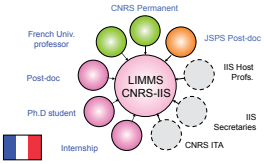
Research costs: salaries of researchers are supported by both CNRS and IIS (CNRS, IIS staff, post-doctorates, PhDs and trainees) or by JSPS, JST, ANR or EU (post-doctorates and PhDs).

The University of Tokyo covers salaries of the group of host professors and provides all technological platforms (1200 m² of cleanrooms, biological and biophysics experimental labs, AFM characterization lab, etc.), as well as its operational costs. It is also supporting dedicated administrative staff.

CNRS provides CNRS researchers salaries and the annual research budget, in the framework of a collaboration contract between CNRS and IIS, The University of Tokyo.

Laboratory for Integrated Micro-Mechatronic Systems
LIMMS/CNRS-IIS IRL 2820

LIMMS Recruiting Protocol



1. How to apply to LIMMS/CNRS-IIS (UMI 2820)

a. You have a CNRS researcher position

Step 1:	Step 2:	Step 3:	Step 4:	
(1) Visit to LIMMS for several days (2) Definition of research subject	Validation by LIMMS And by your laboratory	Applying for LIMMS position at INSIS (or institute you belong to)	Approval by National Committee Decision from INSIS	Arrival in Japan
Year N-1	Sep/Oct Year N-1	Autumn Year N-1	Autumn session Year N-1 or Spring session Year N	Sep/Oct Year N

b. You are (associate) professor in French University

Step 1:	Step 2:	Step 3:	Step 4:	
(1) Visit to LIMMS for several days (2) Definition of research subject	Validation by LIMMS And by your University	Applying for "Accueil en délégation" to move to CNRS temporary position	Transfer of the application with agreements to the Regional delegation of CNRS	Arrival in Japan
Year N-1	Sep/Oct Year N-1	Autumn Year N-1	January Year N	Sep N or Feb. N+1

c. You are Ph. D student (to apply for the JSPS Post-doc program)

Step 1:	Step 2	Step 3:		
Positions appear in LIMMS web sites and ABG	Application screening by LIMMS	Application screening by CNRS and JSPS	Expected arrival Sep. 1st – Nov. 30 for Spring Campaign	Arrival in Japan
Spring Campaign				

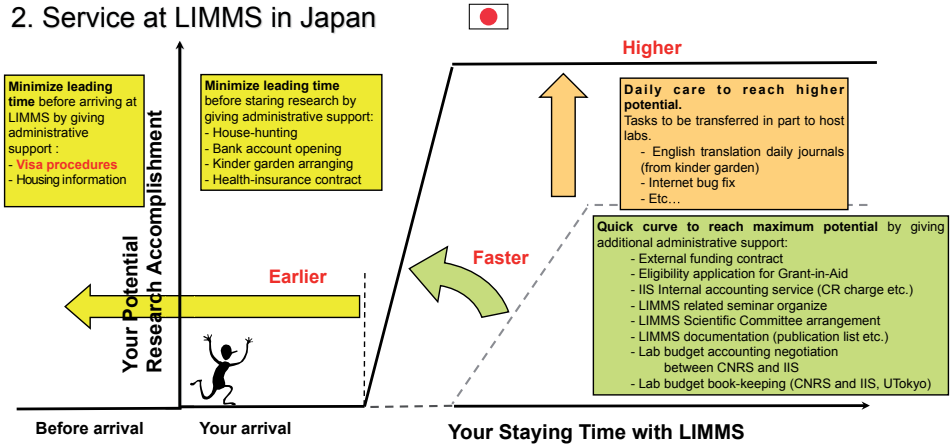
2 Campaigns / year

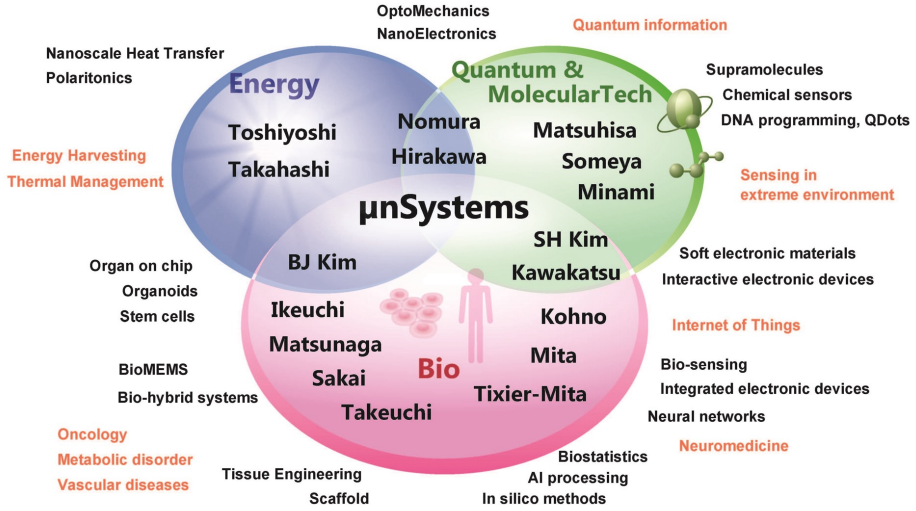
Step 1:	Step 2:	Step 3:	
Positions appear in LIMMS web sites and ABG	Application screening by LIMMS	Application screening by CNRS and JSPS	
Autumn Campaign		Expected arrival April 1 – Sep. 30 for Autumn Campaign	

d. You are student (to apply for Master internship , French doctoral program)

Step 1:	Step 2:	Step 3:	
Position available at LIMMS and Advertisement in web sites (CNRS, LIMMS …)	Application screening by LIMMS	Transfer of the application with approval to CNRS. Recruiting protocols	Arrival in Japan

2. Service at LIMMS in Japan





Scientific Policies

Since 2023, the LIMMS direction has highlighted three general fields of applications in micro and nanotechnologies by proposing three specific research axis:

Energy

Quantum and Molecular Technologies

Bio

Those three fields are illustrating recent MEMS, BioMEMS and Nanotechnology developments. They reflect the orientations of LIMMS in new technologies related to societal demands.

In Energy axis, LIMMS researchers obtained worldclass results with the development of phononic crystals for heat focusing. LIMMS technologies are at the cutting-edge regarding thermoelectric micro-devices and have confirmed new concepts in thermionic cooling. Interface research programs are also settled to find solutions to power the Internet of Thing (IoT) based on energy harvesters integrated

The Quantum and Molecular Technologies axis is a highly interdisciplinary field that combines cutting research from physics, chemistry, and biology. This axis bridges the two other axes (energy and biology), while also exploring its own unique research questions. At the heart of this axis lies the exploration and integration of quantum technology and molecular technology. Quantum technology is concerned with the use of quantum mechanics to develop new technologies as for instance manipulating the transport of heat, electron or light, while molecular technology deals with the study and manipulation of molecules and their properties. Our research ranges from fundamental endeavor such as single-electron transfer in electrochemistry to the storing of massive data in DNA, the sensing of biomolecules, or the integration of electronic devices into our everyday life with flexible electronics.

The new **Bio** axis gathers three themes. Disease treatment via prevention and detection is investigated by developing new devices for diagnosis and vaccine delivery. With a complementary approach, implantable tissues and devices are also key activities.

This branch is related to complex tissues opening to organ modelling where the cellular and even the molecular scale are investigated. Researchers seek to better understand the blood vessel formation, the neuronal communication behaviour and the interaction of the metabolic organs such as liver and pancreas. By studying different organs, LIMMS aims at understanding the role of tissues and especially cell interactions in diseased and healthy tissues.

BioMEMS such as platforms with multi-modal sensors and actuators are developed in LIMMS to help investigating organ behaviour and create biohybrid systems. Biocompatible materials and/or cells are also used to create Bio-robotic systems. A particularity of the Bio axis is the complementary contribution of an international team, SMMIL-E. Its activities are focused on research against cancer, at the interface between BioMEMS and Organ modelling.

SMMiL-E (Seeding Microsystems in Medicine in Lille)

The SMMiL-E project includes the setting-up of a new platform of the Institute of Industrial Science of the University of Tokyo (IIS) in the Lille university-hospital area, close to medical teams. First research location of IIS out of Japan, this implantation is backed by CNRS, Centre Oscar Lambret and Lille 1 University, as a IRL, International Joint Unit, mirror site of LIMMS/CNRS-IIS (IRL 2820). The new site was approved by the four partners and inaugurated on June 16th, 2014.

Goal : SMMiL-E aims at setting-up and implement a comprehensive research program on BioMEMS against Cancer in a sustainable international high-level collaboration. The project synergizes Bio-MEMS research from LIMMS/CNRS-IIS with research against Cancer performed in Lille under the labeled SIRIC ONCO - Lille program.

Research Activity in SMMiL-E

The scientific activities encompass BioMEMS research against Cancer, technology development and bio related experiments, as an original interdisciplinary approach to the SIRIC ONCO-Lille program. The projects aim at bridging fundamental and clinical research around four work packages:

WP1 Biomolecular mechanisms of the tumor resistance to treatment (DNA degradation under therapeutic irradiations, Microtubules stabilization in chemotherapy).

WP2 Cellular evaluation and diagnosis: Stem cells and circulating tumor cells detection and sorting, study of cell senescence and tumor dormancy.

WP3 Cells interaction and therapeutic targets: in vitro tumor angiogenesis, cellular mobility and metastatic processes.

WP4 Biological adhesives and neotissues: cellular fibers and postsurgery recovery.

By means of an upstream research, this program targets more effective disease detection, a strengthened efficacy of therapy and posttreatment monitoring, for a better care to patient.

CREST (JST) project

2019 - 2025

A CREST project (JST program) was awarded to LIMMS in October 2019 supporting the Energy Harvesting and Management activities. This five years project (250 Millions Yen) involves two teams, and aims at developing scientific understanding and demonstrators of phonon polariton heat transfer in silicon micro and nanodevices.
This project has been involving four LIMMS researchers (from August 2020).

PEPR MoleculArxiv

2022 - 2029

The dazzling amount of data that humanity generates requires novel solutions for long-term storage. Storing data in the form of DNA, similar to living beings, is a promising option due to its enormous density: 100 g of DNA could in principle store all the data kept in datacenters around the world.

The PEPR MoleculArXiv aims to make of France a key player in DNA storage by involving more than 20 interdisciplinary laboratories from CNRS. LIMMS plays a key role as it is in charge of coordinating and integrating experimental and theoretical progress into a demonstrator that writes information in DNA at a rate of 1 bit per second -100x faster than commercial synthesis in 5 years.

The PEPR will also foster French and European communities and aim to propose a European FET-flagship. Applications will include cold data archiving, marking, calculation, and molecular engineering.

https://pepr-moleculararxiv.fr/le-pepr/

PEPR MED-OOC

2024 - 2030

Despite the billions of dollars invested in pharmaceutical research and development, the approval process for new drugs remains lengthy and expensive. The overall success rate of clinical trials for new drugs is only about 10% because traditional cell culture models, animal models) have limited predictive value. In addition, current cell culture models do not mimic *in vivo* mechanisms and do not easily allow for inter-patient variability, an essential aspect of personalized medicine. The development of *in vitro* models that faithfully mimic *in vivo* conditions is therefore clearly one of the cornerstones of future health challenges.

The main objective of the PEPR MED-OOC will be to promote this new generation based on patient-derived cells and tissue precursors such as organoids, with the aim of recapitulating the (patho)physiological reality of the patient's organ, combined with advanced "on-chip" monitoring capabilities.

The budget will support priority flagship projects and specific calls for projects, the creation of open centers for the integration and clinical exploitation of O&OoC, industrial implementation, economic analyses in terms of public health, European synergies and investment in the training of a new generation of O&OoC specialists. **In this frame LIMMS** is involved in a demonstrator to simulate the cross talk between liver, adipocytes and blood vessel involved in the development of the **metabolic syndrome.** The project will lenght until 2030 and reinforce synergy between France and Japan

JSPS Core-to-Core program JETMeE

Core-to-Core Program
研究拠点形成事業

2019 - 2024

Since 2012, the Japan Society for the Promotion of Science (JSPS) has implemented the Core-to-Core Program, comprising two components: (A) Advanced Research Networks and (B) Asia-Africa Science Platforms.

In 2019, a second JSPS Core-to-Core program was assigned to LIMMS (April 2019-March 2024) to promote the interactions more specifically in Bio- oriented activities with SMMIL-E and the partners of iLite. JSPS granted "Core-to-Core (A) advanced research networks program" to the Institute of Industrial Science (PI: Prof. Beomjoon Kim, LIMMS director) with a 15 Million Japanese Yens / Year, for 5 years, as matching fund to SMMiL-E, iLite, and EPFL research funds.

This program aims at creating world-class research hubs and foster young researchers through networking to advance multilateral collaboration in cutting-edge fields of science. It funds matching activities to SMMiL-E and iLite by supporting UTokyoIIS to send Japanese researchers to CNRS and EPFL and to reinforce scientific collaborations. The Program name is JETMeE in frame of the Core-to-Core, meaning "Japan- Europe Research Hub for Translational Medical Engineering".

https://www.jetmee.jp/

2023 ~

"We are part of the problem, so let's be part of the solution."

EcoLIMMS is a group of researchers who share a commitment for climate change questions, and ask ourselves how we can, as researchers, have a positive impact on the planet. EcoLIMMS was formed in April 2023.

The two main missions established are: (i) act at the laboratory scale, and (ii) organize events to communicate on scientific research and climate change (beyond the lab).

At the lab scale, a monthly newsletter is sent to the lab members to share information on a selected topic, and on specific events related to climate change and environment. The work group has also started working on the greenhouse gas balance of LIMMS which is an interesting tool to evaluate and then optimize our behaviours and practices.

Regarding the events, a crosstalk event was organized in February 2024 with a researcher from Human and Social Sciences and another one from Science and Technology. Other events will be organised over the coming year. This action is in line with the commitments of the CNRS and The University of Tokyo.

LIMMS KIKO

The University of Tokyo Integrated Research Network

The LIMMS KIKO is engaged in a cross disciplinary research for the improvement of the Quality of Life including mental, physical and cultural aspects and addressing societal problems of aging and declining population which developed countries will face, by applying the results of international collaborative research in the Micro-nano interdisciplinary fields such as Nanobiology, μTAS, Silicon Neurons, IoT, and Energy Harvester, etc.

LIMMS KIKO, (LIMMS= "Laboratories for International Research on Multidisciplinary Micro Systems") was established April 1st 2021 for a period of 10 years and is based on the LIMMS/CNRS-IIS IRL 2820, which has been managed by CNRS and IIS for 25 years as a Japan-France collaborative research center, in order to transcend departmental boundaries and comprehensively bring in the intellectual creativities of the University of Tokyo.

https://kiko.limms-tokyo.org/en/

2021 - 2031

International Research Network EURA-LIMMS

The EURA-LIMMS network aims to create a Europe-Asia network for the development of innovative technologies in energy, bioengineering, and molecular sciences. The objective is to revive the success of the NAMIS network supported by the CNRS, by adapting the themes to the current research axes of LIMMS. The network will promote the education of students and the exchanges between member teams from: The University of Tokyo, Seoul National University, National Taiwan University, National University of Singapour, EPFL, Helmoltz, Imtek, University of Twente and CNRS.

Contact : N. Clément

International Project Team – Equipe Projet Internationale

International Project Teams that are joining researchers of LIMMS and of a CNRS laboratory in France on a given topic. The four following teams are presently running: BioMeg with IMS in Bordeaux on Biomorphic science, MinanoBio with LAAS in Toulouse on MIcro-&NANO-technology for BIO-engineering and bio-sensing, TEAMS with BMBI on Therapeutics and Engineering Against Metabolic Syndrome and SUNRYSE with IM2NP in Marseilles on Structured Nano-systems for energy conversion and management. The teams no only activiate student and researcher exchanges but also raise fund from CNRS and universities to promote research works.

LIMMS Key Figures and Collaborations

Since its creation, the LIMMS has welcomed in total 438 members including 49 CNRS researchers, 81 JSPS post-doctorates, 27 CNRS post-doctorates, 14 IIS post-doctorates, 35 PhD students, 10 CNRS research engineers, 63 collaborators, 2 industrial collaborators, 102 internships, 22 administration staff, etc...

Since 2004, LIMMS has published more than 547 journal papers (including publications in high impact journals such as Nature -/Chemistry, /Biotechnology, /Communications-, NanoLetters, Physical Review Letters...), and more than 593 communications to international conferences.

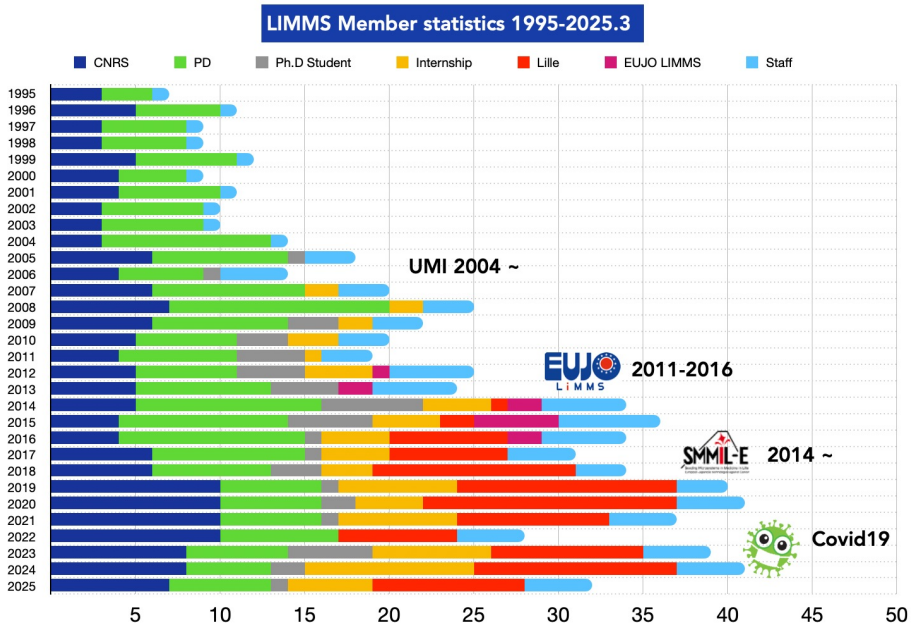
In 2024-2025, our members published 48 journal papers and 18 communications in international conferences.

In this period, LIMMS members have managed 6 grants (3 by JSPS, 1 by JST and 2 by others) and 22 contracts (EU, PEPR, ANR, Region...).

Former LIMMS members maintain collaborations with Japanese host professors and CNRS laboratories in France (SAKURA programs, PICS and JSPS Bridge).

More than 16 new research teams, often followed by technology exchanges and sharing from LIMMS, were created by former members back in France.

LIMMS has also been pivotal to launching **international research networks** such as the CIRMM/IIS « Center for International Research on Micro nano Mechatronics », the « Global Research Network » of IIS and the NAMIS « Nano Micro Systems » linking CNRS to IIS and to prestigious institutions such as EPFL, SNU, VTT, IMTEK.



Events

Kick-off of the EURA-LIMMS IRN, Tokyo, October 10th and 11th 2024

The IRN (International Research Network) EURA-LIMMS of CNRS involving both Asian and European institutions was launch in the University of Tokyo IIS October 10th and 11th 2024. The network Universities and Organizations were presented in front of 40 attendees. A rump session concluded the meeting.

LIMMS Workshop in Bordeaux, November 4th to 5th 2024

LIMMS has organized its yearly Workshop in the University of Bordeaux November 4th to 5th 2024. Japanese Host Professors have presented their activities in front of the audience of CNRS Researchers and Professors of the University of Bordeaux, especially from the IMS laboratory.

4th Aix-Marseille University/IIS UTokyo Workshop, October 14th to 15th, 2024.

The 4th CNRS-AMU-UTokyo workshop was co-organized with LIMMS and IM2NP at Marseille. Speakers from Institut Fresnel, CINAM and IM2NP in one hand, and from IIS in the other hand took part in the workshop to share their expertise on topics regarding flexible electronics, photonics, magnetism, and energy efficient semiconductor devices (Co-organizers: Kazuhiko Hirakawa and Marc Bescond).

LIMMS Evaluation, October 16th 2024.

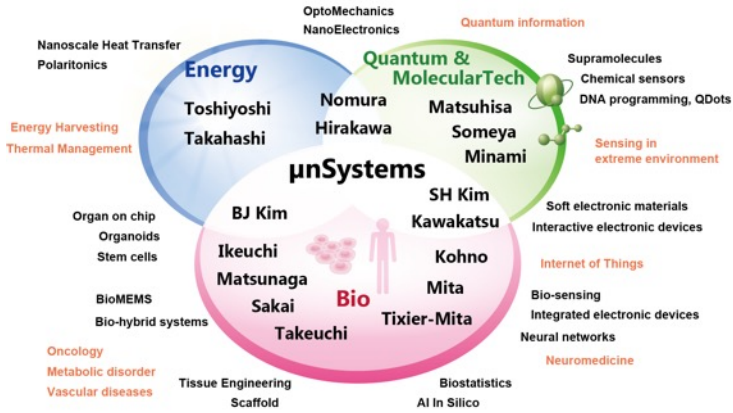
On October 16th 2024, LIMMS was evaluated over the 2021-2025 quinquennial in the CNRS headquarter of Paris. The morning was dedicated to a closed meeting between the Committee members and the LIMMS Direction. In the afternoon, Japanese Professors and French LIMMS members presented their activities. The first feedback of the committee was encouraging and positive.

SMMiL-E/UTC 2025 School on BioMEMS (5th Ed.), Feb. 2025.

SMMiL-E hosted an international school on bioMEMS in collaboration with BMBI CNRS laboratory of UTC (University of Technology of Compiègne), from February 17th to 28th, 2025. This educational event, held for the fourth time, aimed to introduce the main aspects of bioMEMS technology through a multidisciplinary team (22 lecturers in Lille and 8 lecturers in Compiègne) with backgrounds in biology, clinics and engineering.

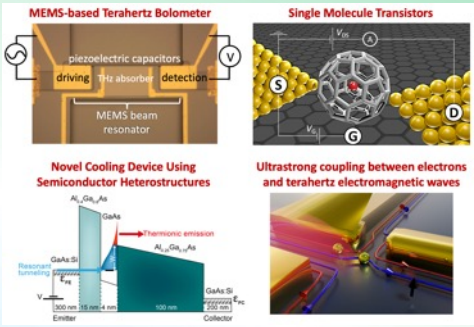
9 students from the Institute of Industrial Science, The University of Tokyo, 15 students from the University of Lille, 3 students from JUNIA, and 9 students from UTC attended this program and were highly encouraged to join projects between SMMiL-E, UTC and IIS.

Host Laboratories



Pr. Kazuhiko HIRAKAWA

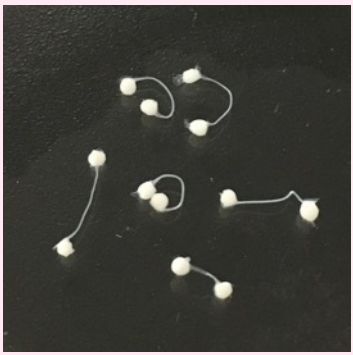
- MEMS/NEMS-based terahertz detectors
- Semiconductor heterostructure thermionic cooling devices
- Single molecule/quantum dot transistors
- Terahertz dynamics of quantum nanostructures for quantum information processing



http://thz.iis.u-tokyo.ac.jp

Pr. Yoshiho IKEUCHI

- Neural tissue engineering and brain organoids
- Neuronal morphology and development
- Protein synthesis in neurons
- Human pluropotent stem cell-derived neurons

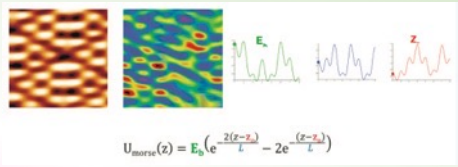


www.bmce.iis.u-tokyo.ac.jp

Host Laboratories

Pr. Hideki KAWAKATSU

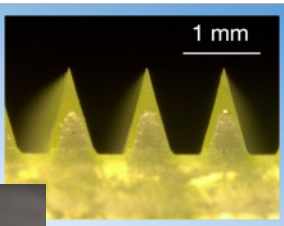
- Color AFM with chemical contrast
- Force and vibration measurement of reproductive cells
- Quantitative color AFM through Molecular functionalisation of AFM tips

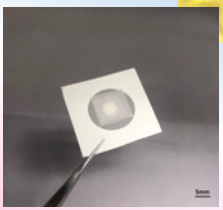


www.inventio.iis.u-tokyo.ac.jp

Pr. Beomjoon KIM

- MEMS, Bio-NEMS, Micro/nano patterning, soft lithography
- SAM patterning for cell culturing/bio sensors
- Heat transfer in nano structures, Micro/nano heaters for molecular Engineering
- Microneedle patch for new drug delivery system
- Energy harvesting, power MEMS



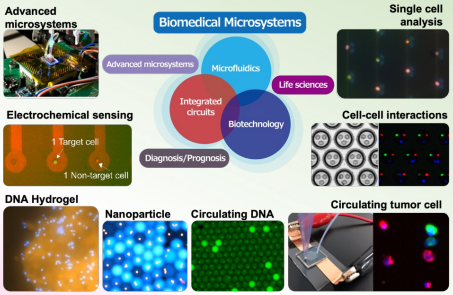


Health monitoring Microneedles patch

www.kimlab.iis.u-tokyo.ac.jp

Associate Pr. Soo Hyeon KIM

- Single cell analysis
- Single molecule detection
- Biomedical microsystems for liquid biopsy
- 2D flow cytometry
- Electrochemical sensing
- DNA computing

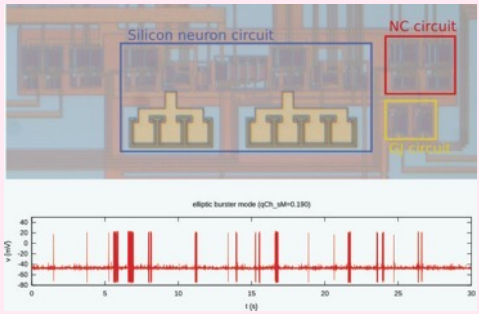


www.shkimlab.iis.u-tokyo.ac.jp

Host Laboratories

Pr. Takashi KOHNO

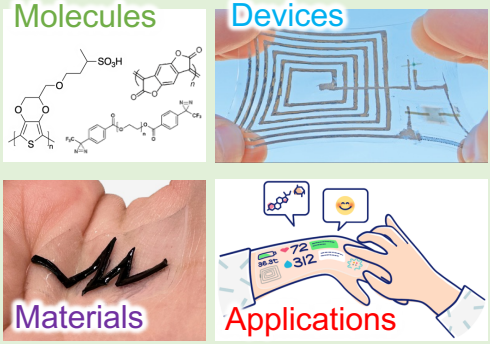
- Neuromimetic silicon neuronal network circuits and their application to neuromimetic artificial intelligence
- Architectural design of the neuromimetic computing



www.neumis.iis.u-tokyo.ac.jp

Associate Pr.
Naoji MATSUHISA

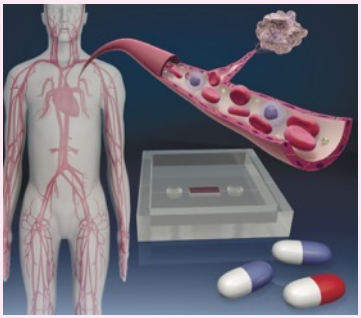
- Stretchable electronics
- Soft materials
- Conducting polymers
- Wearable devices
- Human-computer interfaces



https://www.naojimatsuhisa.com/

Pr. Yukiko MATSUNAGA

- Tissue engineering
- Biomaterials
- In-vitro microvessels model
- Vascular biology

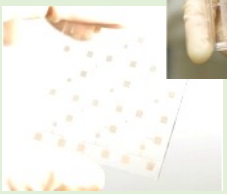


www.matlab.iis.u-tokyo.ac.jp

Host Laboratories

Associate Pr. Tsuyoshi MINAMI

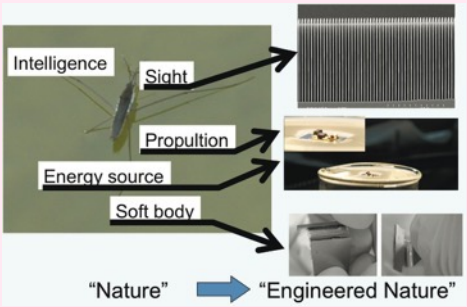
- Organic TFT-based chemical sensors
- Supramolecular sensor arrays



www.tminami.iis.u-tokyo.ac.jp

Pr. Yoshio MITA

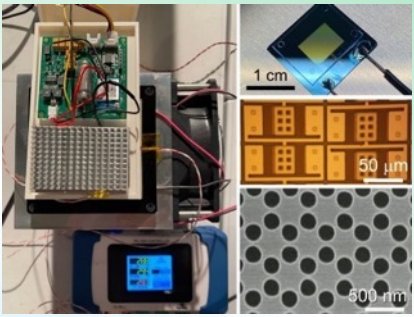
- Integrated MEMS-VLSI technology
- Nature Engineered Microdevices
- Nano deep 3D MEMS optoelectronic systems
- Autonomous microrobot
- Bio-inspired perception LSI systems



http://www.if.t.u-tokyo.ac.jp/

Pr. Masahiro NOMURA

- Physics of nanoscale phonon/heat transport
- Nano-Si thermoelectric energy harvesting
- Quantum transducer via spin-optomechanics



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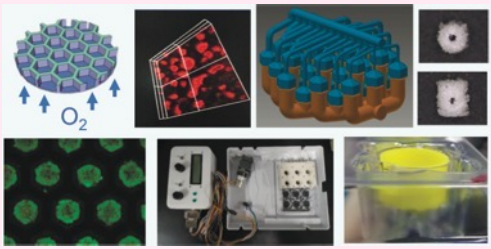
Host Laboratories

Pr. Yasuyuki SAKAI

- Physiological micro cell culture system (MPS) based on microfluidics, micropatterning and hierarchical cellular organization
- 3D microfabrication and biofabrication for engineering of implantable tissues
- High-cell density propagation and differentiation of stem/progenitor cells



http://orgbiosys.t.u-tokyo.ac.jp/sakai/

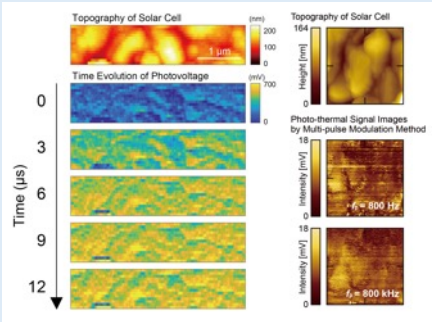
Pr. Takao SOMEYA

- Flexible electronics using organic transistors
- Large-area sensors and actuators
- Molecular/organic electronics
- Printing technologies for large-area electronics
- Printed MEMS switches for power transmission

www.ntech.t.u-tokyo.ac.jp

Pr. Takuji TAKAHASHI

- Multiple analyses of solar cell materials by photo-assisted nanoprobes
- Development of novel measuring methods to improve performance in SPMs
- Analysis of individual fine current paths in CNT-FETs by MFM

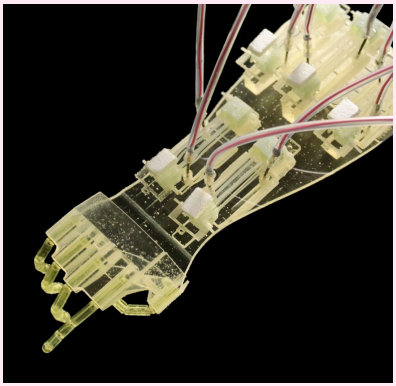


www.spm.iis.u-tokyo.ac.jp

Host Laboratories

Pr. Shoji TAKEUCHI

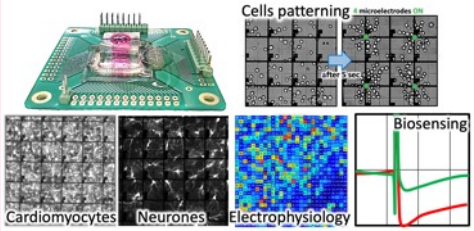
- Biohybrid Robotics
- Cultivated Meat
- Cell-based Sensors
- Organoid on a Chip
- Artificial Cells



www.hybrid.t.u-tokyo.ac.jp

Associate Pr. Agnès TIXIER-MITA

- Thin-Film-Transistor platform for multi-modal bio-sensing
- Real-time biomimetic platform for neuro-cardiac investigations
- Systems for simultaneous optical and electrical measurements on cardiomyocyte cell culture



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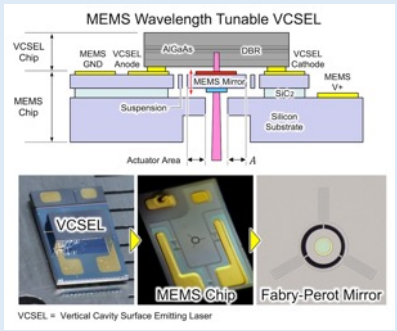
Pr. Hiroshi TOSHIYOSHI

- Optical MEMS
- RF-MEMS
- THz metamaterials
- CMOS-MEMS integration
- Energy harvesters



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Director (CNRS)

Sebastian VOLZ

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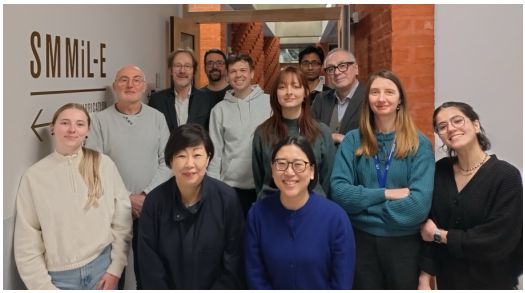
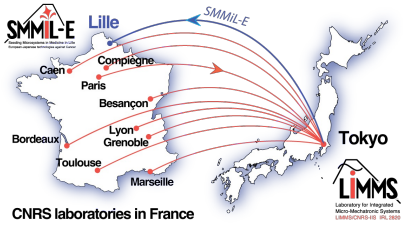
IRN Director

Nicolas CLÉMENT	(LAAS-CNRS)

SMMiL-E, Lille



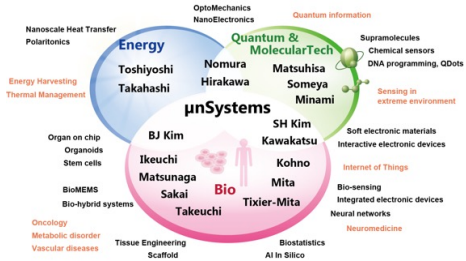


LIMMS, Tokyo

Research Projects

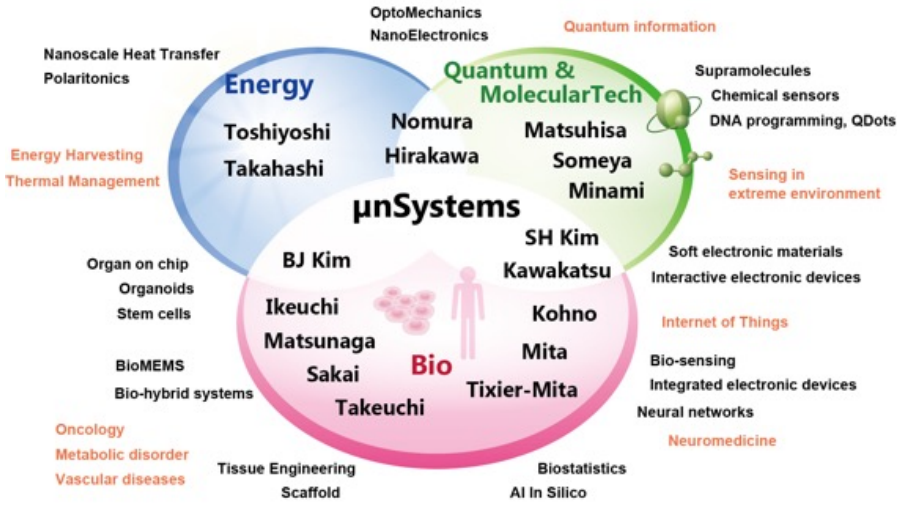
The laboratory operates in three fields:

- **Energy**
- Quantum and Molecular Technologies
- **Biology**



Details about all research projects conducted from April 1st 2024 to the March 31st 2025 will be given in the following part of the booklet.

Energy Axis


OptoMechanics
NanoElectronics
Quantum information
Nanoscale Heat Transfer
Polaritonics
Energy
Quantum &
MolecularTech
Supramolecules
Chemical sensors
DNA programming, QDots
Toshiyoshi
Takahashi
Nomura
Hirakawa
Matsuhisa
Someya
Minami
Energy Harvesting
Thermal Management
Sensing in
extreme environment
μnSystems
SH Kim
Kawakatsu
BJ Kim
Soft electronic materials
Interactive electronic devices
Organ on chip
Organoids
Stem cells
Ikeuchi
Matsunaga
Sakai
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Kohno
Mita
Tixier-Mita
Internet of Things
Bio-sensing
Integrated electronic devices
Neural networks
Neuromedicine
BioMEMS
Bio-hybrid systems
Oncology
Metabolic disorder
Vascular diseases
Tissue Engineering
Scaffold
Biostatistics
AI In Silico

Evaporative Electron Cooling in Semiconductor Heterostructures

Alec Cochard

Hosted in Hirakawa Lab

Keywords: Thermionic emission, Cooling, Nanoscale

Context and Objectives

Moore's Law tells that the number of transistors doubles every two years. However, today physical limits are reached and processors overheating due to the incapacity to evacuate the heat produced by the Joule effect.

Project idea is to take the heat from integrated circuits and evacuate it with more efficiency using the thermionic effect (Electrons transfer thermal energy by phonon interaction) in a quantum well [1]. The effect can be improved by using these quantum wells in cascade.

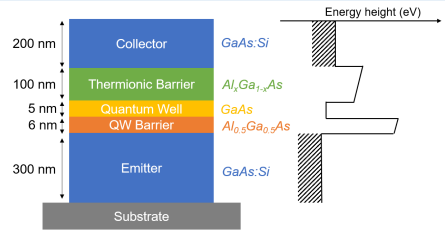

Fig.1. Layers of the thermionic device (left). Compared with induced energy height barriers (right). Heat is transferred from top to bottom.

Results & Perspectives

Good accordance between theory and data for different barrier height, showing efficiency of the photoluminescence measurement. Electron cooling up to 10K achieved

Next step of the project is to apply photoluminescence measurement to quantum cascade cooling structure. Method must be improved at high temperature.

Methods

Fabrication:

Thermionic device structure is made with layers of GaAs and $GaAl_xAs_{(1-x)}$. Barrier height is controlled by Al doping.

Characterization:

Photoluminescence of quantum well with potential difference from environment from 100K to 320K;

Modeling:

Planck's law used with reference curve to determine quantum well temperature.

Comparison to a theoretical model [2].

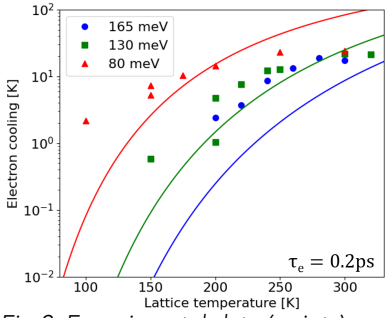

Fig.2. Experimental data (points) compared to curve of electron cooling in quantum well for different barrier heights.

References

[1] Xiangyu Zhu et al. Physical Review Applied, 2021, 16 (6)

[2] Xiangyu Zhu et al. Physical Review Applied, 2024, 22 (3)

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LIMMS Internal Project

Liquid-vapor Two-Phase Flow Boiling in Asymmetric Micro-Structured Manifold Microchannel for Electronics Cooling

Masahiro Nomura

Hosted in Nomura Lab

Fundings: LIMMS Internal Project

Keywords: Phase change, Cooling, chip thermal management

Context and Objectives

Developing embedded two-phase cooling system for electronics.

Regulating the liquid-vapor flow in microchannel using asymmetric structure.

The high diodicity of channel can refrain from vapor backflow and improve the instability.

We aim at cooling solution for the challenge of advanced thermal management in 3D heterogeneous integrated electronics.

Methods

Fabrication:
Clean-Room silicon processes;
Microfluidics.

Characterization:
Flow boiling experimental setup;
Atomic Force Microscope.

Modeling:
CFD calculation by COMSOL.

Context and Objectives

Demonstrators include:

- Proof of concept
- Design with diodicity
- Improved boiling instability

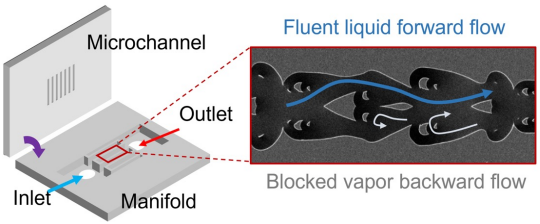

Fig.1. Channel with diode design

Perspectives

Design two-phase cooling system;
Reducing system instability;
Enhancing critical heat flux;
Solving the issue of great heat dissipation from densely packed electronic components.

References

[1] H. Shi, S. Grall, R. Yanagisawa, L. Jalabert, S. Paul, S.H. Kim, J.L. Viovy, H. Daiguji, and M. Nomura, "Chip cooling with manifold-capillary structures enables 10^5 COP in two-phase systems," Cell Rep. Phys. Sci., 102520 (2025).

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Limits of Phonon Interference in Phononic Crystals at Nanoscale

Roman Anufriev

Hosted in Nomura Lab

Keywords: Phononic crystals, nanoscale heat transport

Context and Objectives

Phononic crystals are artificial periodic structures that leverage phonon wave interference to control phonon transport. Their practical implementations span from evenly planted trees to periodic nanostructures, thus covering a vibration frequencies from seismic waves to the sound and heat. Yet, spatial and spectral limits of phonon interference are unknown. I use Brillouin light scattering to experimentally investigate phonon interference.

Methods

Fabrication:
Clean-room nanofabrication

Characterization:
Time-Domain Thermo Reflectance;
Brillouin light scattering spectroscopy
Raman spectroscopy

Modeling:
Finite element method
Monte Carlo phonon transport
Fluctuational Electrodynamics

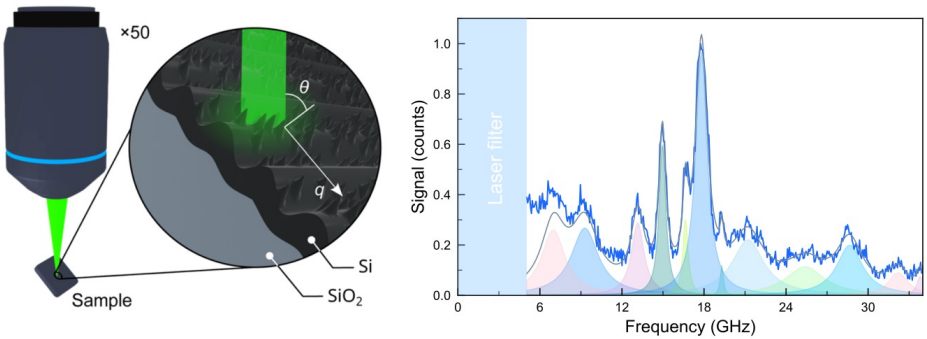

Fig.1. Brillouin light scattering spectroscopy experiments

Perspectives

Applications of nanoscale phononic crystals for quantum computing, sensing, and microelectronics.

References

[1] Diego et al., The European Physical Journal Plus Plus 139, 1032 (2024)

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Nanophononics for Future Quantum Technology

Michele Diego

Collaborators:
Roman Anufriev, Gabrielle Mazevet-Schargrod,, Jade Hardouin
Hosted in Nomura Lab

Fundings: Japan Science and Technology Agency Moonshot R&D
Keywords: Nanophononics, quantum nanophononics, optomechanics

Context and Objectives

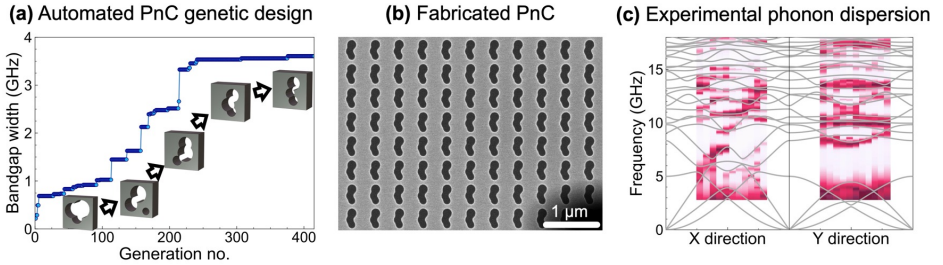
The rise of phononic devices operating in the quantum regime opens new possibilities for quantum communication and mechanical quantum computing [1]. However, optimizing device design to extend phonon lifetimes and coherence times remains a key challenge. Our research advances phononic nanodevices through inverse design optimization [2], topological interfaces, and hyperuniform waveguiding. By engineering robust, high-coherence phononic systems, we aim to establish a scalable platform for future quantum technologies [3].

Methods

Fabrication:
- Electron beam lithography
- Nanopatterning
- Reactive ion etching
- NEMS

Characterization:
- Optics (Brillouin / Raman spectroscopy)
- Electro-acoustics (interdigital transducers for generation/detection of acoustic waves)

Design:
- Finite element methods
- Genetic algorithm optimization



a. Optimization process of the phononic crystal based on inverse design method. b. Fabricated structure with optimized design c. Comparison between the designed phonon dispersion relation (gray lines) and Brillouin light scattering measurements (red color).

Perspectives

- Novel designs optimization methods for long-lived phononic devices
- Low temperature measurements for exploration of the quantum regime

References

[1] H. Qiao et al., Science (2023)
[2] M.Diego et al., ACS Nano (2024)
[3] M.Diego et al., Phys. Rev. Appl. (2024)

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CREST Project: Surface Phonon-Polariton Heat Transfer (2019-2025)

Sebastian Volz

Hosted in Nomura Lab

Fundings: JST-CREST, Kakenhi B

Keywords: Radiation, Cooling, Nanoscale

Context and Objectives

Designing nanoscale heat spreaders in silicon devices.
Investigating a new heat transfer channel based on SPhP in the in-plane direction.
In ultrathin films at high-T, SPhPs are the predominant heat carriers.
We aim at experimentally demonstrating this prediction and then manipulate SPhP by guiding, tunneling, rectifying and focusing.

Methods

Fabrication:
Clean-Room silicon processes.
Characterization:
Time-Domain Thermo Reflectance;
3 omega; IR Camera and FTIR.
Modeling:
Analytical solution of Maxwell;
Boltzmann and Heat conduction Equations;
Fluctuational Electrodynamics (SCUFF-EM open source code)

Context and Objectives

Demonstrators include:

- Proof of concept
- Focusing and tunneling
- Switching and rectifying
- Trapping

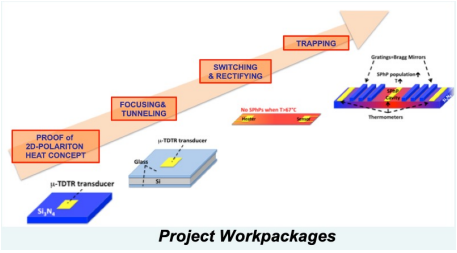

Fig.1. Stages of the CREST Project

Perspectives

Design SPhP Diodes;
Exploiting modulated regimes;
Use SPhPs to control far-field thermal radiation.

References

[1] S Tachikawa, et al.
Physical Review Letters 132 (18), 186904, (2024).

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Modeling of the Heat Transport Driven by Surface Electromagnetic Waves

Jose Ordonez-Miranda

Hosted in Nomura Lab

Fundings: JST-CREST and Kakenhi B

Keywords: Surface polaritons, Heat transport modeling, 2D heat radiation.

Context and Objectives

With the continuous miniaturization of devices with enhanced operation rates, the overheating of the used nanomaterials has become very challenging, as it limits their applications and wastes energy that is mainly released into the environment. We are addressing this scientific challenge by studying the heat transport not only inside the nanomaterials' volume but also along their interfaces via surface electromagnetic waves. These evanescent waves are powerful heat carriers that can enhance the heat transport driven by phonons, photons, and electrons [1]. Our research aims to develop analytical and numerical models for discovering new physical effects and quantifying the polariton thermal energy.

Results

We have predicted a dimensional crossover in far-field thermal radiation between the subwavelength gold membranes (Fig. 1(a)). As the membrane thickness decreases from the bulk to the nanoscale, we observe a transition from 3D to 2D heat transfer, which is characterized by a distinct minimum plateau in thermal conductance (Fig. 1(b)). This behavior, absent in polar dielectrics, stems from the coupling and decoupling of long-range surface plasmon-polariton modes [1].

Perspectives

The discovered minimum plateau falls below the blackbody limit (dashed lines in Fig. 1(b)) due to its 2D nature and, therefore, could be used for probing far-field thermal radiation in metallic nanostructures in Earth and the universe.

Methods

Maxwell's equations of electromagnetism for predicting the existence and propagation of surface polaritons.

Boltzmann transport equation for finding the temperature and heat flux profiles.

Fluctuational electrodynamics for quantifying the thermal radiation driven by polaritons.

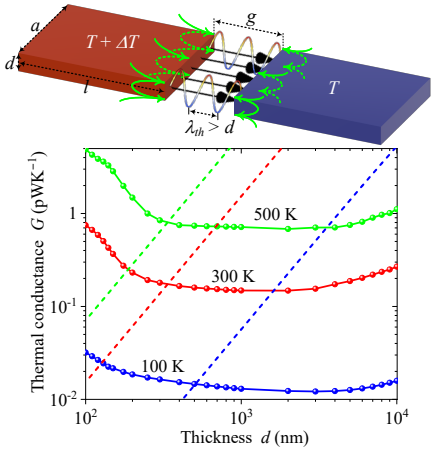

Fig. 1: (a) Scheme of two membranes exchanging thermal radiation through photons (wavy lines) and polaritons (green lines). (b) Thermal conductance as a function of the membranes' thickness.

References

[1] J. Ordonez-Miranda, et al., Phys. Rev. Applied 22, L031006 (2024).

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Ultra-High-Temperature Vacuum Prober for Electrical and Thermal Measurements

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Hosted in Nomura Lab

Fundings: JST-CREST (S. Volz)

Keywords: Extreme Instrumentation, Thermal Conductivity, Diffusivity.

Context and Objectives

Electrical measurements at ultra-high temperature (> 900 K) are crucial for evaluating the reliability of devices targeting harsh environment applications. Electrical and thermal properties of materials can be measured by the electro-thermal method called 3-omega, so far reported up to 780 K. Optical methods are standard for measuring diffusivity at extreme temperatures.
Here we developed vacuum probe station and measured the thermal properties of a bulk sapphire up to 1150 K.

Results

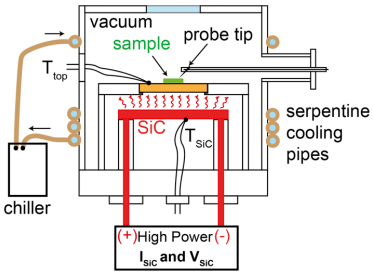
We evaluated the linear and non-linear temperature coefficients of resistance of two patterned Cr/Pt micro resistors separated by a distance of 8.83 um. We implement those TCRs in an analytical thermal model [1] for retrieving both the thermal conductivity and diffusivity of a bulk sapphire. Results are in excellent agreement with the literature data.

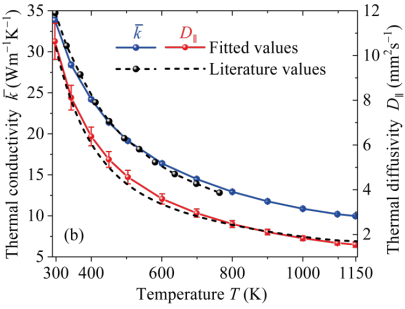
Perspectives

The setup is suitable for testing sensors, transistors and devices for operating in harsh environment, especially those made of wide bandgap semiconductor and carbon based microsystems.

Methods

A sample is heated by the radiations emitted from a SiC holder [2], in vacuum. Six probes can contact the pads of a device. We use the 3w/2w setup to evaluate the thermal conductivity and diffusivity of a bulk sapphire substrate from 300 to 1150 K.





References

[1] J. Ordonez-Miranda, et al., JAP (2023).
[2] L. Jalabert et al. (submitted)

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Enhancement of Thermal Radiation via the Hybridization of Surface Phonon-Polaritons and Guided Modes

Maëlie Coral – Tom-Eliot Jullien

Hosted in Nomura Lab

Fundings: JST-CREST, Kakenhi B

Keywords: Radiation, Cooling, Nanoscale

Context and Objectives

Surfaces phonon-polaritons (SPhPs) are electromagnetic surface waves generated by the coupling of infrared photons and optical phonons at the interface of polar materials. Even though these evanescent waves have been widely exploited to enhance the cross-plane heat transport in nanocavities (1), recent studies show that they can also enhance significantly the in-plane heat flux emitted by macroscopic cavities. For a vacuum cavity in between two parallel flat plates of SiO_2, theory predicts that the maximum enhancement of the radiative heat flux appears for a cavity gap of around 1 cm (2).

Methods

In this work, we aim to provide evidences of this enhancement driven by SPhPs. A theoretical study of the flux in silicon and silica cavities is studied using SCUFF-EM - a software based on the fluctuating surface current (FSC) method for simulating electromagnetic interactions, including thermal radiation. Unlike SiO_2, Si does not support the SPhPs propagation and therefore we compare our measurements for Si and SiO2 cavities to provide a proof of concept of the SPhPs contribution. To complete the study, FTIR measurements using an integrating sphere are performed to access the diffuse frequency response of the SPhPs contribution.

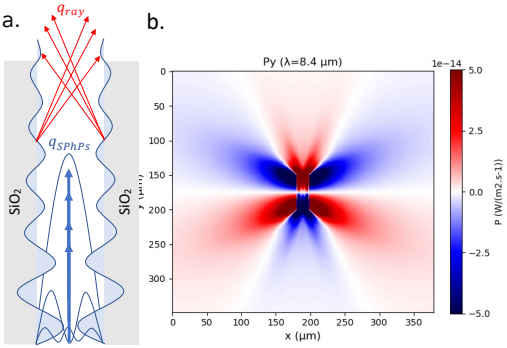

Fig.1.a. Scheme of a vacuum cavity between two identical polar materials supporting the in-plane propagation of SPhPs via cavity modes (blue lines). Classical and Planck radiation (red arrows) adds up to this latter contribution. b. Poynting vector mapping of the cavity effect for SiO_2 at 8.4 μm, maximal wavelength of SPhPs propagation. The cavity effect is isolated by dividing the impact of two independent walls.

Perspectives

Use this effect to design SPhP diodes.

Study the influence of cavity size on the field

Investigate regime changes as the distance from the cavity aperture increases

References

[1] S.-A. Biehs and al.: Rev. Mod. Phys. 93, 025009, 2021.

[2] S. Volz and al.: Phys. Rev. Applied 18, L051003, 2022.

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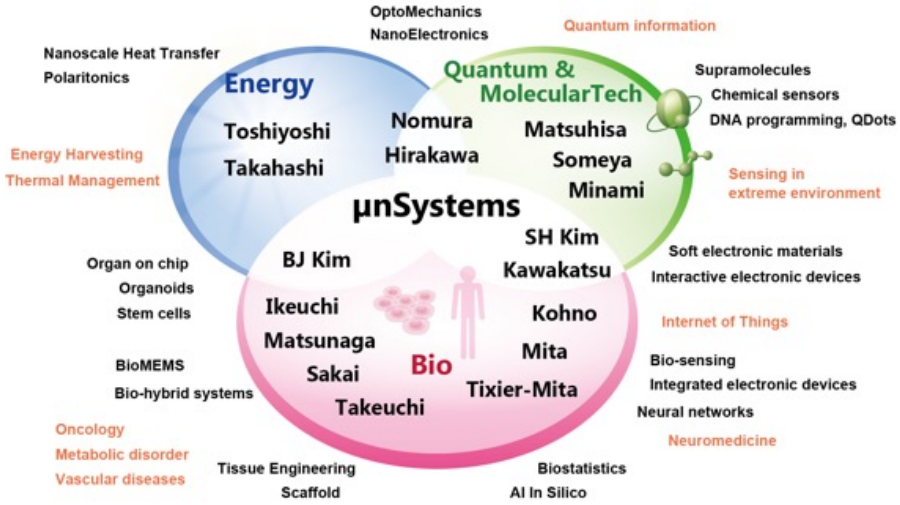
Quantum and Molecular Tech.

Axis



Massive Data Storage on DNA and Artificial Polymers

Anthony Genot, Paul Bruand, Audrey Cochard, Sona Roy, Yannick Tauran, Elias Boudjella, Adrien Rey, Robin Deteix, Gwenael Bonfante, Axel Levy

Hosted in S.H.Kim Lab

Fundings: PEPR MoleculArXiv (2022-2029)

Keywords: DNA data storage, DNA synthesis, DNA sequencing, microfluidic platform

Context

Data storage is crucial in our society: exabytes of data are generated every year in France (communication, culture, finance, politics, industries, etc.) and the "digital universe" will grow to over 175 zettabytes (10^{21}) in 2025. Current data warehouses use electronic, magnetic and optical media, which have limited durability and density. DNA on the other hand, is extremely dense and stable, but it is currently costly and slow to synthetize.

Objectives and Methods

- Write 1 unique bit per second (100x faster than currently)
- Write 10 GB of data in 24 hours with off-the-shelf parallelization

How?

Making synthesis fast and scalable (WP1&3)
Making storage efficient and secure (WP2)
Making DNA storage practical (WP4)

Objectives and Methods

ICS, IS2M	IPMC, ICR SACS, IGBMC	IRISA, I3S, LaTIM, LIP
POLYMER CHEMISTRY	SEQUENCING TECHNOLOGIES	BIOINFORMATICS
DNA&ENZYMES CHEMISTRY	MICROFLUIDIC & INTEGRATION	SIGNAL THEORY
Gulliver, UMR3523, UMR3528	LIMMS, LIP	I3S, EURECOM, IRISA Lab-STICC

- **20 M€** over **84 months**
- **LIMMS** is at the forefront of experimental implementation
- **16 French laboratories**, including **6 flagship labs**

Perspectives

- Maturation of technology
- Collaboration with French and Japanese industrials
- Application to Japanese maching funds

Publications/References

[1] Okumura et al., Nature, 2022

[2] Genot et al., Nature Chemistry, 2016

[3] Lobato et al., Nature Chem. Engineering, 2024

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Thermodynamic and Rheological Analysis of DNA Nanostar Hydrogels

Hajar Ajiyel

Hosted in S.H. Kim Lab

Fundings: JSPS 2024

Keywords: DNA, rheology, thermodynamics, nanotechnology, hydrogels

Context

The sequence of nucleic acids can be designed to program self-assembly into a multitude of forms, such as DNA hydrogels. Their study has focused on their formation and not so much on the thermodynamic and rheological properties with relation to the sequence design. Therefore, we aim to link the various characteristics of the DNA hydrogel to its design, and make a global study at different scales. Applications of DNA hydrogels are anticipated in many fields; in therapeutics, biosensing, etc [1].

Objectives

- Establish a phase diagram of DNA nanostars
- Measure the thermodynamic and mechanical properties of DNA nanostar hydrogels in the bulk gel phase
- Study the effect of the design of the nanostars on the macroscopic properties of the resulting hydrogel
- Have a global understanding of the physics of DNA nanostar hydrogels

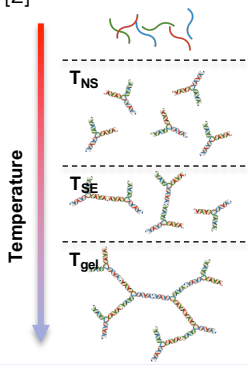
Perspectives

- Study the phase separation properties of DNA nanostar hydrogels;
- Design hydrogels with prescribed properties for biomedical applications.

Methods

- **Thermodynamics:**
  Differential scanning calorimetry; Isothermal calorimetry (in collaboration with Institut Néel, Grenoble).
- **Rheology:**
  Dynamic light scattering (SH Kim Lab); Micropipette aspiration (in collaboration with Yanagisawa Lab); Rheometry (in collaboration with ILM, Lyon).
- **Design:**
  DNA structures design (SH Kim Lab).

Fig.1. Formation of DNA nanostar hydrogels [2]



References

[1] Y. Sato et.al., Sci. Adv. 2020
[2] Biffi et. al., PNAS 2013

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Establishing a Bridge between Quantum Devices and Electrochemistry

Henri Vo Van Qui

Hosted in S.H.Kim Lab

Fundings: ANR HYPOSEL, MITI Pressure

Keywords: Electrochemistry, microfluidic, shot noise, quantum device

Context and Objectives

In many different coherent diffusive systems, a reduction of the shot noise has been predicted and observed by the mesoscopic physics community.
We developed a novel theory to describe the electrical noise in electrochemical systems, predicting the same reduction of shot noise.
We aim at experimentally demonstrating this prediction by studying the current noise associated with the oxidation and reduction of free Ferrocene molecules – which act as single electron shuttles – and their diffusion across a liquid microgap.

Results

This setup combines in a novel way microfluidics, room temperature noise measurement and electrochemistry. The obtained I-V curves fit well with our analytical model and stochastic simulations. The construction of this novel analytical model allows to bridge electrochemistry and quantum devices. This opens an avenue to apply these tools to the study of room temperature electron transfer in biological systems.

Perspectives

Noise measurements are underway to confirm the theoretical prediction.
The setup is also starting to be used for a molecular single electron pump experiment.

Methods

A micro-gaped device was fabricated in clean room.

Building and optimization of an electrical noise measurement setup associated to a microfluidics setup.

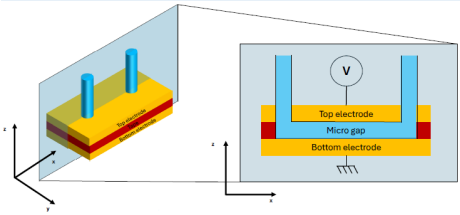

Fig.1. Schematics of the micro gap device.

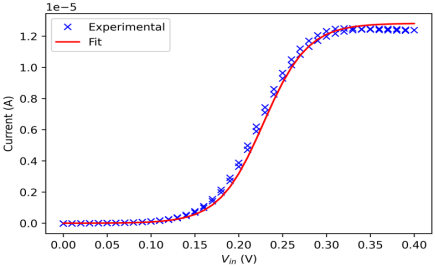

Fig.2. Experimental and theoretical current curve.

References

[1] Grall, S. *et al.* Electrochemical Shot Noise of a Redox Monolayer. *Phys. Rev. Lett.* **130**, 218001 (2023).
[2] Zevenbergen, M. A. G. *et al* Fast Electron-Transfer Kinetics Probed in Nanofluidic Channels. *J. Am. Chem. Soc.* **131**, 11471–11477 (2009).

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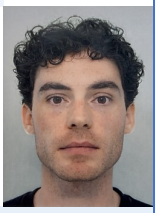
Soft Electronics: Stretchable Water-Processed Organic Photodetector

Hugo Laval

Hosted in Matsuhisa Lab



Fundings: JSPS Postdoctoral Fellowship (Standard)

Keywords: Soft electronics, Nanoparticles, Sensors, Hydrogels

Context and Objectives

Stretchable organic photodetectors enable real-time health monitoring with flexibility and near-infrared (NIR) sensitivity [1]. Our project aims to get advantage of organic semiconductor nanoparticle from water-based inks which offer an eco-friendly solution [2], and a powerful building block to achieve soft and stretchable photoactive layers.

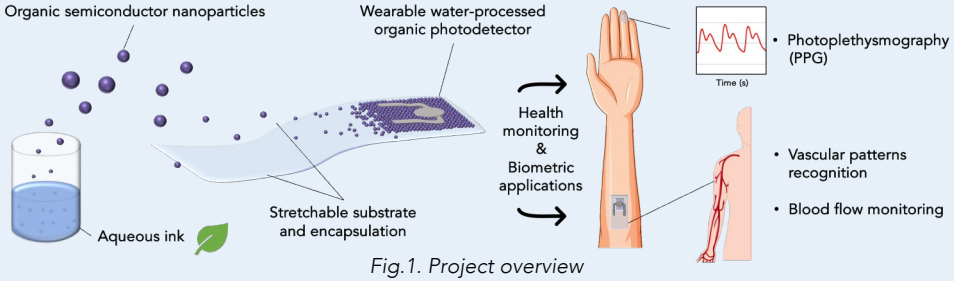


Fig.1. Project overview

Strategies

A **first strategy** to achieve our objective is to develop a novel semiconducting hydrogel [3], incorporating our waterborne nanoparticles. These nanoparticles can be formed with NIR sensitive materials able to modulate the current through the gel. A **second strategy** consists in the elaboration of composite nanoparticles made of organic semiconductors and an elastomer, which aims to unlock the stretchability of the resulting nanoparticles-based film.

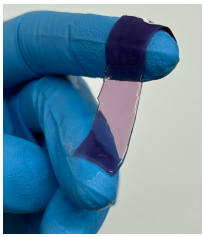


Fig.2. Ultra conformable semiconducting hydrogel

Perspectives

- Exploring ionic and electronic conductive hydrogels.
- Designing nanofibrils instead of nanoparticles to improve charge transport.

References

[1] Z. Wang *et al.*, *Wearable Electron.* 2024.

[2] A. Holmes *et al.*, *ACS Nano 2023.*

[3] P. Li *et al.*, Science 2024.

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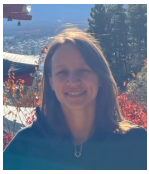
Invisible On-skin Electrochromic Displays

Séverine de Mulatier

Hosted in Matsuhisa Lab



Fundings: JSPS

Keywords: Wearable Technologies, Soft Electronics, Nanomaterials

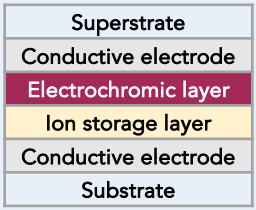
Context and Objectives

Next-generation wearables are expected to be soft, conformable and worn on-skin. They should also remain unconspicuous, visually and by touch, for better acceptance from users [1].
Electrochromic Displays (ECD) are an interesting technology for low-voltage, safe usage of screens directly attached on skin.

Fig.1. ECD based on PEDOT

Methods

We aim to fabricate a fully transparent ECD with transparent elastomers for sub- and superstrates, silver nanowires transparent electrodes, and Ru-based electrochromic polymer [2] that can switch from purple to transparent.



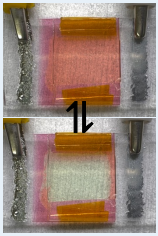
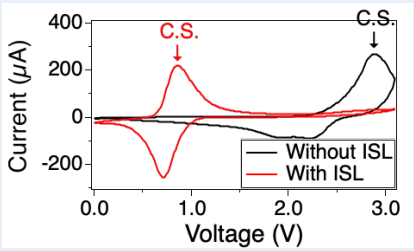


Fig.2. ECD architecture and pictures of color switching in a polyRu-based ECD

Current work

We are currently improving the stability of the stack by adding an ion storage layer (ISL) in the ECD structure. The complementary charges combination during EC reaction lowers the color switching (C.S.) voltages below the silver oxidation voltage, preventing damages in the electrodes during cycling.



Perspectives

In addition to soft and conformable mechanical properties, the future display will remain visually unperceivable. With improved cycling durability, it can be interfaced with sensors and electronics for long-term wearables.

References

[1] Shimura et al., Adv. Electron. Mater. (2023), 9, 2200512. [2] Lu et al., ACS Appl. Electron. Mater. (2023), 5, 12, 6677–6685

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Eye-Tracking by Measuring Strain of Eyelids (2024-2025)

Warda Djadda

Hosted in Matsuhisa Lab

Fundings: Tateisi Science and Technology Foundation

Keywords: Eye tracking, Circuit design, Real-time prediction

Context and Objectives

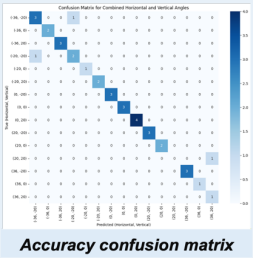
Implementing circuit including Arduino module for data collection. Initial resistance is around 600 to 800 ohm.
Designing algorithms to complete data processing, including data calibration, data normalization and data regression. The accuracy can reach up to 90%.
Applying polynomial regression and nearest point search based on the strain sensors to predict angles. The angle error is less than 3 degrees.
We aim at experimentally realizing real-time eye-tracking through strain sensors with optimization algorithms development.

Methods

- **Fabrication:**
  Au-cracked strain sensor processing.
- **Characterization:**
  Screen display system; NPS;
  Data clean and normalization; RMSE.
- **Modeling:**
  Min-Max Normalization;
  Piecewise Polynomial Regression;
  Log-likelihood optimization
  (open source code)

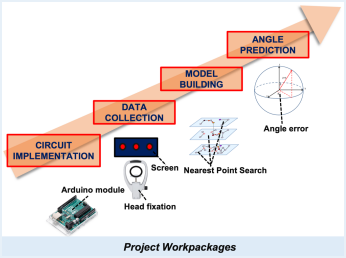
Context and Objectives

Demonstrators include:
- Circuit implementation
- Data collection
- Data clean and processing
- Angle prediction



Accuracy confusion matrix

Fig.1. Confusion matrix

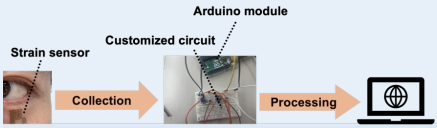


Project Workpackages

Fig.2. Project workpackages

Perspectives

Change Arduino module;
Improving circuit to avoid small resistance oscillations;
Applying machine learning and deep learning algorithms to improve accuracy.



System structure

Fig.3. System structure

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Redox Flow Battery Characterizations and Optimization by Spectroelectrochemistry

Stéphane Chevalier

Hosted in Minami Lab

Fundings: CNRS – Univ. Tokyo Joint PhD Program

Keywords: Heat and Mass Transfers, Imaging, Microfluidic, Electrochemistry

Context and Objectives

Designing optimized redox flow batteries on chip

Investigating the mass and charge transfers in laminar flow

Research hypothesis: In laminar redox flow battery, mass diffusion and charge transfers can be well controlled and measured to optimize their performances.

We aim at experimentally control the mass diffusion and real time monitoring of the electrochemical kinetics by developing new chemical sensors on chip

Context and Objectives

Demonstrators include:

- Proof of concept
- Spectroscopic imaging
- 3D optimization of the channels
- Integration of chemical sensors

Methods

Fabrication:

Clean-Room silicon processes.

Characterization:

Visible and infrared imaging spectroscopy

Electrochemical impedance spectroscopy

Modeling:

Analytical solutions of mass and charge transfers equations;

Mass diffusion, Tafel kinetics and electrostatic equations

COMSOL Multiphysics and Matlab codes

Fig.1. Working principle of redox flow battery on chip

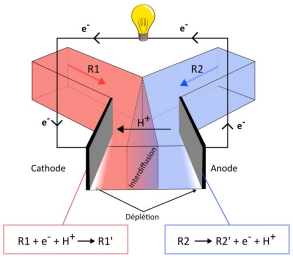

FIGURE 1.2 – Schéma d'une PCM.

Perspectives

Proof of concept with integrated sensors

Upscaling the system toward greater power (few W)

Use the characterization technique developed in this project for other electrochemical systems

References

[1] S. Chevalier, et al., Chem. Eng. J. Adv. 8 (2021) 100166.

[2] B.S. De, et al., Sustain. Energy Fuels. 4 (2020) 6234–6244.

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Biology

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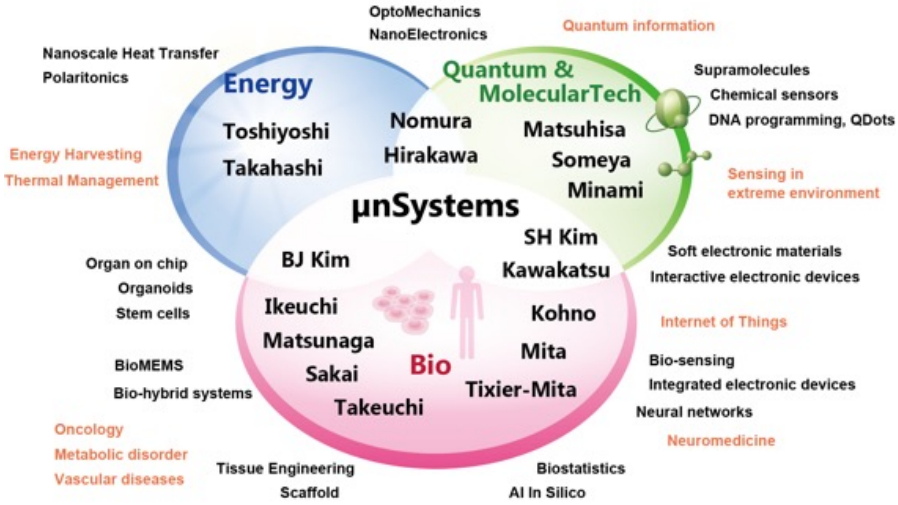

MIMIC : Microvessels – Impact of the Microenvironment's Intrinsic Characteristics

Baptiste Alric

Hosted in Matsunaga Lab

Fundings: JSPS, Kakenhi

Keywords: Organ-on-chips, Angiogenesis, Microfabrication

Context and Objectives

At the Matsunaga lab, our project focuses on enhancing our knowledge of the physical characteristics of artificial microvessels and their surrounding environment[1]. Our aim is to create more precise organ-on-a-chip models by controlling this microenvironment. To achieve this, we are collaborating with partners in Japan and France to develop various cellular models and innovative methods to evaluate these physical properties[2]. Our findings underscore the critical role these properties play in microvessels physiology, structure and function[3].

Methods

We utilize custom-made microfluidic chips to construct our microvessels (see Fig. 1). We create channels by using acupuncture needles to carve pathways within hydrogels—a protein-based gel that is approximately 90% water—allowing us to culture endothelial cells in a channel-like formation.

To characterize the microenvironment, we use a novel technique that use dynamic fluid movement to assess the material's elasticity and permeability [1]. And for the microvessels we use porosity assay, bright field microscopy and confocal microscopy (see Fig. 2).

Results

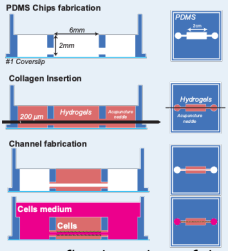

Fig.1. Microfluidics chips fabrication

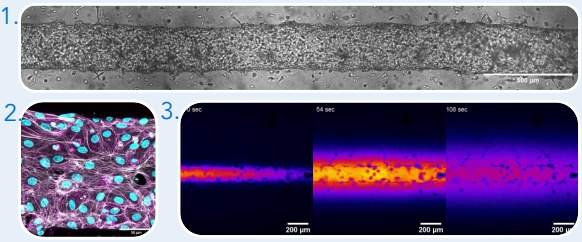

Fig.2. Microvessels Characterization (1.BF 2. Confocal microscopy 3. Porosity assay

Perspectives

These models not only deepen our insight into various biological processes but also support the development of drug screening methods to pinpoint effective treatments for specific conditions. The next step of our research is to complexify our model to be even more physiologically relevant.

References

[1] J.Cacheux, *et al.* "*Science Advances* 9.31 (2023): eadf9775.

[2] J.Cacheux *et al. STAR protocols* 5.2 (2024): 102950.

[3] D. Alcaide *et al. Biochemical and Biophysical Research Communications* 724 (2024): 150234.

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LIMMS Internal Project: Development of a New Tool to Characterize Barrier Function of Microvessels

Baptiste Alric, Jean Cacheux, Laurent Jalabert, Jose Ordonez, Aurelien Bancaud, Masahiro Nomura, Yukiko Matsunaga

Hosted in Matsunaga Lab

Fundings: Internal project LIMMS FY2024

Keywords: artificials microvessels, physical properties, instrumentation

Context and Objectives

To study **artificial microvessels** created in our lab, we need a better understanding of how the **physical properties of the surrounding gels** impact these vessels.

To achieve this, we previously developed **complementary tools** based on **pressure measurements and mathematical modeling** to extract the physical properties of these gels [1].

Now, our goal is to **increase the complexity of our system** by:

1.Modifying the gels to include additional components.

2.Incorporating endothelial cell-lined vessels to study not only the physical properties of these complex gels but also the **barrier function of the cell layer**.

Methods

We used a system based on our previous research, composed of pressure sensors placed on top of our gels [1]. With the help of our pressure controller, we create a displacement of liquid in the gels and **measure the change in pressure in the cavity on top of those gels**. The new system provides better control of these functions thanks to a newly developed informatics program. Additionally, it includes **temperature measurement, an incubation system essential for using live cells, and synchronization with a microscope**, allowing us to combine these measurements with microscopy acquisition(cf. figure 2).

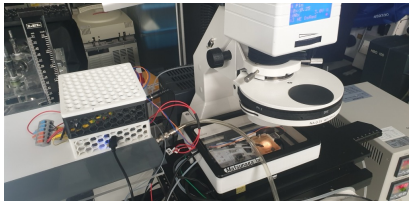

Figure 1: Our new system mounted on a microscope.

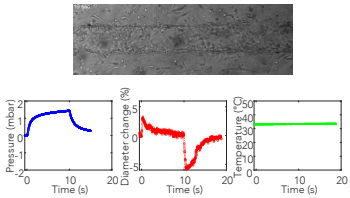

Figure 2: Image acquisition performed simultaneously with pressure, diameter, and temperature measurements.

Perspectives

This new system will allow us to better understand our microvessel system and provide a dynamic way to determine the barrier function of these vessels, opening the door to the development of new **systems for drug assay applications**.

References

[1] J. Cacheux et al., "*Science Advances* 9.31 (2023): eadf9775.

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Microvessel-on-a-chip for the Study of Parenchymal Solute Transport in the Context of Brain Clearance

Daniel Alcaide Martin

Hosted in Matsunaga Lab

Fundings: SPRING-GX Q-STEP

Keywords: Microfluidics, Vasculature, Glymphatic system

Context and Objectives

The lack of lymphatic vasculature in the brain puts to question how homeostasis is achieved in this key organ. For a while now, studies point towards an active waste removal pathway propelled by brain arteries' pulsations injecting clean cerebrospinal fluid into the brain and pushing the waste out of the brain. This process is assisted by glial cells, hence it is known as the glymphatic system.

Our *in vitro* model is the first one to allow glymphatic-like, pressure-driven transport studies based on arterial pulsations.

Methods

Our device (Fig. 1) hosts two parallel straight microvessels (MVs) and a third acellular channel in between them, all suspended in a collagen hydrogel.

Periodical pressure actuation over one of the MVs, acting as the artery, while the other MV remains passive, as the vein. The acellular channel allows us to inject fluorescent molecules to study their movement in the device.

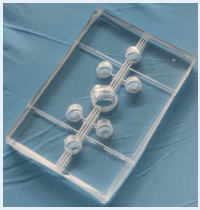

Fig. 1 – Microfluidic device

Results

Glymphatic clearance is hardly observed *in vivo*, making it difficult to probe its physical working principles. In our chip, glymphatic clearance is observed by tracer displacement and evacuation from the hydrogel.

We observe more efficient tracer displacement when applying pulsatile arterial pressure than constant, which favors the current description of the glymphatic system.

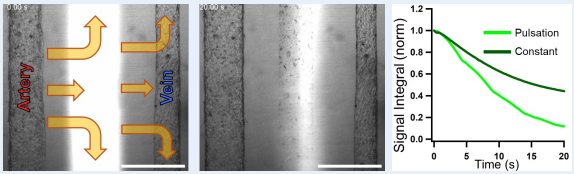

Fig. 2 – Artery pulsations eject more effectively fluorescent tracers compared to constant pressure

Perspectives

We expect this technology to cast some light upon the principal physical principles governing the glymphatic system. Pulsations seem necessary for effective interstitial flow generation, this could be supported by computational simulations of the system.

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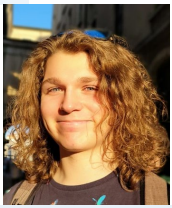
Assessing the Effects of Growth Factors in a Lymphatic Vessel-on-a-chip

Jules Edwards

Hosted in Matsunaga Lab

Fundings: CNRS International (LAAS-CNRS, Toulouse)

Keywords: Lymphatic vessel, Organ-on-chip, Growth factors, Polarization

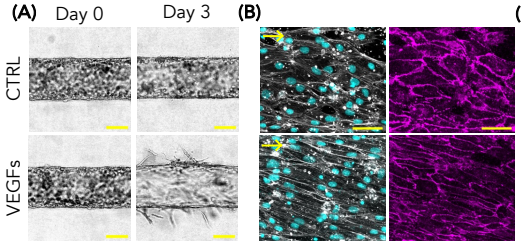


Context and Objectives

The lymphatic vessels play a key role in tissue homeostasis and drainage of interstitial fluids. Impaired lymphatic function thus plays a role in various diseases and complications, such as secondary lymphedema or cancer. [1]
Understanding the formation of new vessels from existing ones – lymphangiogenesis – is crucial to better understand these pathologies. The use of pro-lymphangiogenic factors, such as vascular endothelial growth factor (VEGF) A and C, in a controlled environment is key to better understand this mechanism.

Methods

The lymphatic vessel-on-a-chip (LVoC), embedded in type I collagen gel, allowing us to recapitulate a controlled microenvironment. We cultivate the lymphatic vessels in VEGF-supplemented media for 3 days, during which they are monitored daily, before fixation.
By using different imaging techniques, such as basic brightfield imaging coupled with machine learning driven segmentation and immunofluorescent stainings, we are able not only to assess, but also quantify the effects of VEGFs on lymphatic vessels.



While VEGF-A and -C effects are well known, their combined use displays a drastic increases in lymphatic sprouting, and cell polarisation aligned with the vessel axis. This synergitical response demonstate the importance of VEGF receptors in lymphatic vessels.

Fig.1. – Cocktail effect of VEGF A and VEGFs on the LV models. (A) Bright field microscopies. (B) Immunofluorescent stainings of F-actin and nucleus. (C) Quantification of polarity of cell nucleus. Bars: 100µm in (A) and 50µm in (B).

Perspectives

Cell polarisation has been observed in lymphatic vessels as a response to shear stress [2], but polarisation by biochemical stimuli has not been reported yet. The use of inhibitors and transcriptomic analysis will allow to better understand the underlying mechanisms behind the observed synergistical effect.

References

[1] K. Alitalo, et al., *Nature*, **438**, 946-953 (2005).
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Impedimetric Electrochemical Immunosensor for Monitoring Microvessel Stroke Models

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Fundings: Severo Ochoa PhD Fellowship (BP21-029/EB24-15)

Keywords: Electrochemistry, immunosensors, stroke.

Context and Objectives

Impedimetric immunosensors are powerful tools for monitoring proteins in a continuous and label free manner. These sensors translate the immunorecognition process into an increase in the impedance of the system when an AC is applied.

This system can be used for determination of proteins on the outlet of organ- on-a-chip models[1]. For this purpose, a microvascular stroke model comprised of human astrocytes and endothelial cells is being developed, where the release of GFAP (glial fibrillar acidic protein) can be tracked when exposed to hypoxic conditions.

Methods

An impedimetric immunosensor for GFAP was obtained by modifying a three-electrode system with a self assembled monolayer (SAM) and an anti-GFAP antibody. GFAP was chosen as it is a widely know stroke damage biomarker[2].

For the development of the stroke model, human and mouse astrocytes were evaluated, as well as different culture protocols to induce stroke-like conditions to the astrocytes in 2D and 3D.

Results

The immunosensor presents an increase in impedance when exposed to GFAP, which can be applied to the stroke microvessel model to track the release of GFAP under hypoxia. This system can be used to deepen the understanding of the processes involved in stroke, but also for screening drugs that can promote the recovery of homeostasis.

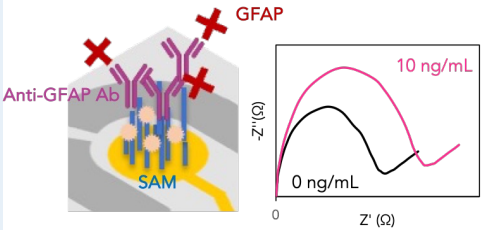

Fig.1. Sensor scheme (left) and change in EIS in the presence of GFAP (right)

Perspectives

After validating the sensor with 2D and 3D cultures, the stroke microvessel system can be coupled to a flow system and the appropriate hypoxic conditions can be applied to study the release of GFAP. This methodology can then be easily switched to any other target molecule for real-time flow measurements.

References

[1] H.M.N. Ahmad et al. Biosensors, **13**, 983 (2023).

[2] C. García-Cabo et al. Cerebrovasc. Dis., **53**(5), 515-518 (2023)

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Understanding Human Brain Mechanisms through Organoid Circuit Modeling

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Hosted in Ikeuchi Lab

Fundings: Spring GX Fellowship, ANRI Fellowship

Keywords: Neuroengineering, neural organoids, neuron, optogenetics

Context and Objectives

Limited access to a living human brain tissue has made it very difficult to study it. Recent advances in stem cell biology has led to the discovery of neural organoids, which are lab-grown miniature organ-like tissues resembling the brain. This model recapitulates key features of the brain and has opened up new possibilities to study development, function and dysfunction of human brain cells in a dish.

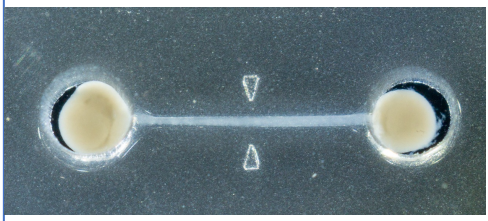

Fig.1. Image of connected neural organoid in a microfluidic device.

Methods

Microfluidic devices are used that can guide axonal growth between neural organoids, enabling precise control over neural circuit formation. This mimics macroscopic inter regional connections found in our nervous system. The connected organoids are plated on electrode arrays which enables to monitor the electrical activity of the neurons in the organoid. Furthermore, neural activity of cells can be controlled with electrical or optogenetic manipulations and evoked response can be studied

Results

We show that :

- Organoids in microfluidic devices can be connected via axon bundles.
- Connection between organoids show signal exchange and propagation.

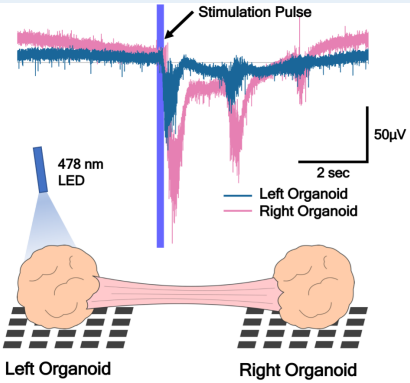

Fig.2. Optogenetic stimulation of the left organoid induces a burst that propagates to the connected organoid.

Perspectives

I connect different tissues and create circuits present in our body to build new platforms and technologies that can be used to study our nervous system.

References

[1] Osaki, Duenki, Chow et al., Nat. Commun., 2024

[2] Duenki et al., Adv. Healthcare Mater., 2025

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Development of Real-time Biomimetic Neural Network Connected with Living Neurons

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Hosted in Ikeuchi Lab

Fundings: JSPS

Keywords: Biohybrid, Real-time, Neuroprostheses, Spiking Neural Network, SoC FPGA

Context and Objectives

Characterization and modeling of biological neural networks is important field to understand the mechanisms governing the functioning of the brain and the different pathologies that can affect it. We intend to provide a tool to investigate neurological disorders through bio-realistic models working real-time.

Methods

Highly biologically coherent neuron models are implemented on SoC FPGA (programmable logic circuits and processors on a single chip) to emulate neuronal networks in real-time. Tuning the different parameters of the model or of the network allows to emulate or reproduce behaviors of the biology.

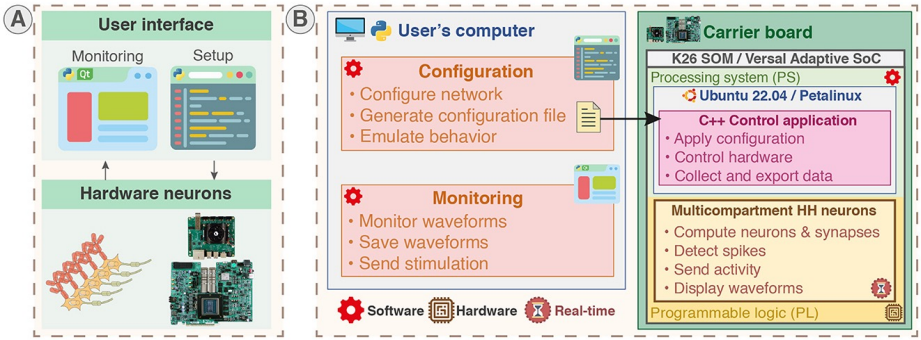

Fig.1. System overview of the real-time hardware-based emulator for multicompartment Hodgkin-Huxley neurons.

Results

Two open-source platforms (BioemuS and BioemuM) were designed for biohybrid experiments and used for:

- Closed loop experiments
- Real time emulation
- Biomimetical stimulator

Perspectives

Essential tools for the realization of electroceutic therapies and neuroprostheses for the treatment of neurodegenerative diseases were designed.

References

[1] R. Beaubois et al., Nat. Comm, (2024).

[2] R. Beaubois et al., Frontiers in Neurosciences, (2024).

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Biohybrid Neurocardiac Platform for Electroceutical Approach

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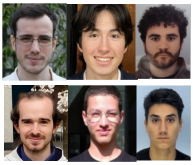
Hosted in Tixier-Mita Lab

Fundings: Murata, Senteikenkyu

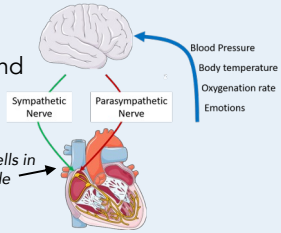
Keywords: Biohybrid, FPGA, Cardiomyocyte, Real-time stimulation



Context and Objectives

To investigate the neurocardiac axis involved in cardiovascular diseases, an electronic platform that reproduces the interaction between the brain and the heart in real-time is developed.

It has been interfaced with In-vitro neurons and cardiomyocyte cell cultures.



Description of neurocardiac axis

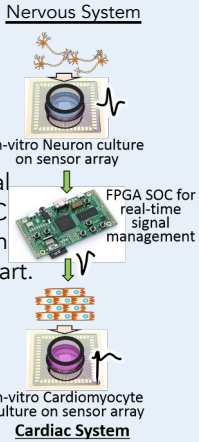
Methods

- Here, a biomimetic stimulation nervous system is realized.

⇒ Implementation of a biomimetic mathematical model in and FPGA SOC to imitate the stimulation of pacemaker cells in heart.

⇒ On one side: neuron sensing.

⇒ On the other side: cardiomyocyte real-time Stimulation.



Results

For demonstration, the FPGA system was used to stimulate cardiomyocyte cell culture.

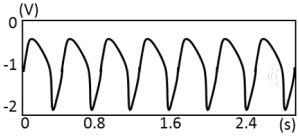


Fig.1. Output of the FPGA: biomimetic pacemaker model.

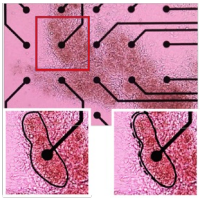


Fig.2. Carciomyocyte cell culutured on MEAs.

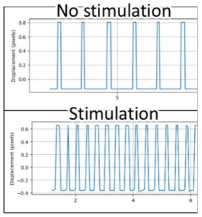


Fig. 3. Results of optical observation of contraction

Perspectives

Biomimetic stimulation on cardiomyocyte cells has been successful.

Next step: neuron activity sensing and processing for real-time cardiomyocyte cell stimulation.

In the future: realize the feed-back control from heart cells to neurons.

References

[1] Faure, PM., Tixier-Mita, A., Levi, T. "A digital hardware system for real-time biorealistic stimulation on in vitro cardiomyocytes". Artif Life Robotics **29**, 473–478 (2024).

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Spatiotemporal and Multimodal Analyses of Cardiomyocyte Cell Culture

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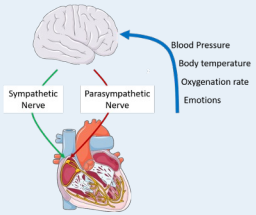
Hosted in Tixier-Mita Lab

Fundings: Murata, Senteikenkyu

Keywords: Saptiotemporal measurement, Multimodal sensing, Data processing

Context and Objectives

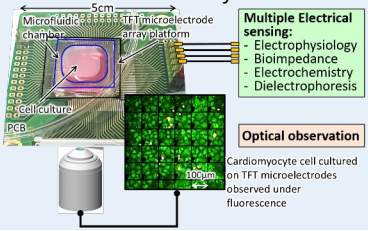
Cardiovascular disease (CVD) is the first cause of death in the world, and involves the neurocardiac axis. In-vitro investigations allow precise measurement of the different parameters involved. Here, a platform permitting spatiotemporal and multimodal investigation has been developed.



Description of neurocardiac axis

Methods

- Development of a platform managing optical data together with multiple electrical data.
- Development of a Python software to process the multiple data and associate them for analyses.



Results

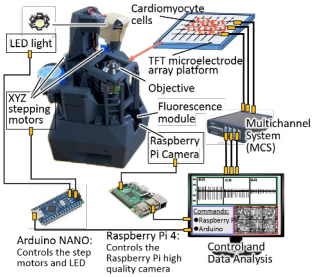


Fig.1. Mini-microscope for long-term experiments in the incubator and optical/electro-physiological measurement.

Fig.2. Software for multi-data association

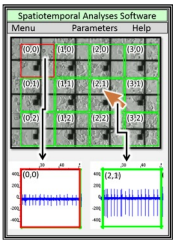
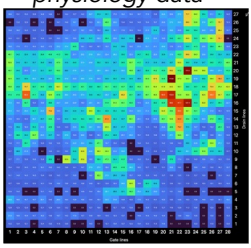


Fig. 3. Heatmap of 2D electro-physiology data



Perspectives

The optical/electrical data association software and the 2D data processing software will be combined next and improved to allow real-time investigation.

In the future, the whole platform will include other measurements (impedance etc.)

References

[1] Tchekioun R., Sureau A., Ihida S., Toshiyoshi H., Tixier-Mita A., "Data processing software for spatiotemporal and multimodal analyses of cardiomyocyte cell culture", 16th iMEMS JSAP Symposium , Sendai, Nov. 25-28 2024.

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Neuro-cardiac in-vitro System for Real-time Investigations

Juliette Flamant, Alexis Mallet, Justine Vérité, Tom Duffourg, Vladimir Blais, Salomé Vautier

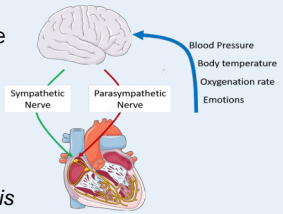
Hosted in Tixier-Mita Lab

Fundings: Murata, Senteikenkyu

Keywords: Neuro-cardiac, Nifedipine, Norepinephrine, Electrophysiology

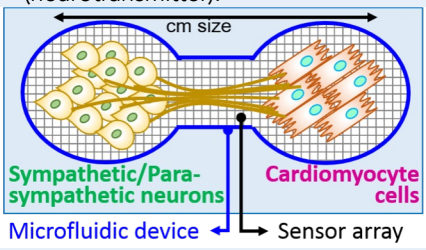
Context and Objectives

Cardiovascular disease (CVD) is the first cause of death in the world, and involves the neuro-cardiac axis. In-vitro investigations allow precise measurement of the different parameters involved. Here, a microfluidic device for in-vitro neuro-cardiac system real-time investigation is proposed.



Description of neurocardiac axis

Methods

- Development of a microfluidic device for neuro-cardiac co-culture.
- Use chemicals to imitate disease (arrhythmia) or neuron stimulation (neurotransmitter).
- 

Results

Chemical was applied on cardiomyocyte cell culture. Electrophysiology and optical data were obtained simultaneously.

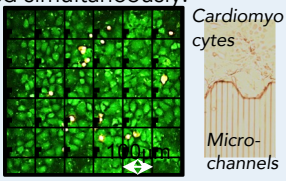


Fig.1. Cardiomyocyte cells were cultured on the sensor array.

Fig.2. Nifedipine was used to imitate arrhythmia.

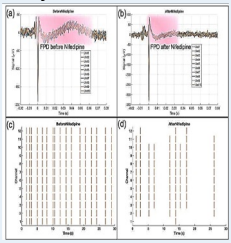
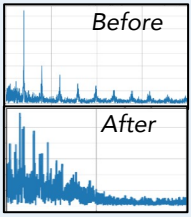


Fig. 3. Norepinephrine stimulation (Fourier transform)



Perspectives

A microfluidic neuro-cardiac platform is under development.

The combination of chemical stimulation with electrical and optical sensing makes a powerful investigation platform.

References

[1] Hu X., Flamant J., Ihida S., Sugita J., Fujiu K., Tixier-Mita A., Toshiyoshi H., "Multimodal Characterization of Cardiomyocytes Cell Culture Using a TFT-MEA", *under submission.*

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Spiking Neural Network for Unsupervised Spike Sorting in Real-time on FPGA

Jérémy Cheslet

Hosted in Ikeuchi Lab

Fundings: ANR BRAIN-Net, UBGRS 2.0, (ANR-20-SFRI-0001)

Keywords: Spike sorting, SNN, STDP, FPGA, real-time, HD-MEA

Context and Objectives

- Neural prosthetics are potential treatments for neurodegenerative diseases, but it requires deep understanding of neural populations [1].
- Spike sorting is an operation that extract important features from neural-recordings while considerably reducing the amount of data to save.
- However, low-power, accurate, real-time spike sorting is still a challenge [1].

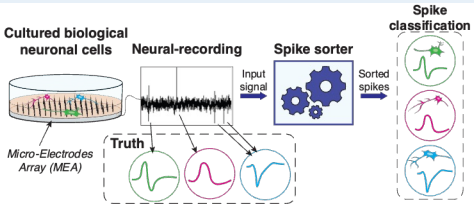


Fig.1 – Principle of spike sorting: find which neurons are spiking in the neuronal culture.

Method

Inspired from [2], we implemented a 3-layer SNN on FPGA. [3] shows a preliminary version for low-cost spikes/bursts detection.

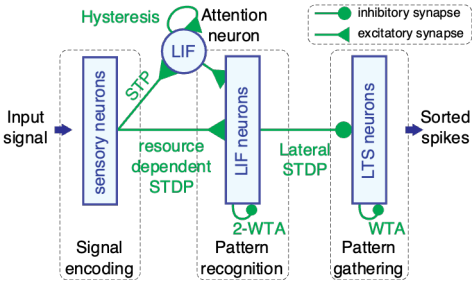
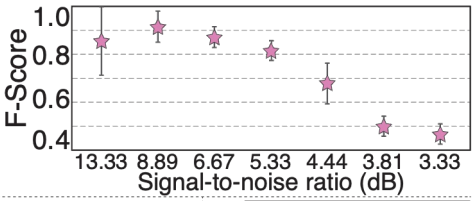


Fig.2 - Structure of the SNN

Results

- The SNN sorts with an accuracy on par with offline methods after a few minutes of unsupervised training.
- It processes in real-time at low-power due to its low hardware consumption.



AMD Kria KR260 board

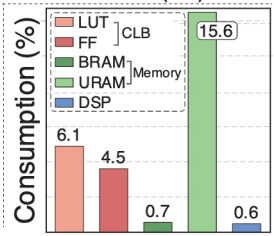


Fig.3 – Results on AMD K26 SOM

Perspectives

- Use HD-MEA data to further improve the spike sorting accuracy.
- Perform bio-hybrid experiments.

References

[1] Zhang et al, J. Neural Eng., 2023
[2] Bernert et al, Int J Neural Syst., 2018
[3] Cheslet et al, IEEE BioCAS, 2023

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Investigation of the Metabolic Syndrome Development using Organ on Chip Technologies

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Hosted in Sakai/Nishikawa Lab

Fundings: JSPS; PEPR Medoc, ANR Track NAFLD Chaire UTC/DOT

Keywords: Organ-on-a-chip, Metabolic syndrome

Context and Objectives

Metabolic Syndrome (MSy) has a prevalence ranging to 24.6–34.7% of the population in Japan in early 2000s and up to 36% in European countries. In this project, we will develop on organ-on-chip technology to address these key challenges, to move a step closer towards understanding, diagnostics and therapies of metabolic syndrome.

Methods

We propose to

- To build an innovant bio artificial organ research strategy using organ on chip
- To establish a specific metabolic syndrome model with which we will track the kinetics of the disorders
- To identify biomarkers and therapeutic solutions regarding the disease specificity using multi omic technology.

Results

Human-induced Pluripotent Stem Cells (hiPSCs)-derived liver cells were cultured and matured in a microfluidic environment. Hepatic maturation on chip was observed and subpopulation identification was performed (Fig. 1A, 1B). Then, we proposed a protocol to differentiate hiPSCs into pancreatic-like-cells.The protocol led to the development of spheroids producing C-peptide and containing cells positive to insulin and glucagon. Sequencing revealed complex heterogenous bi-hormonal profiles (Fig. 1C, 1D).

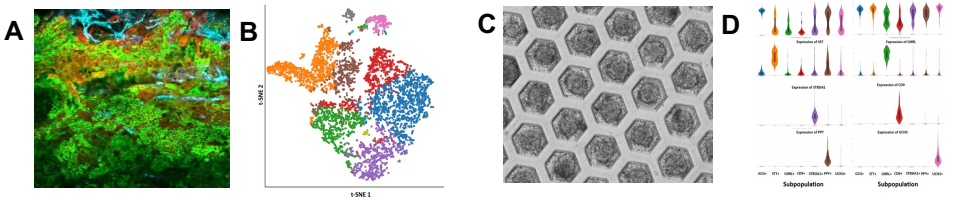

*Fig 1: **A** Liver on chip (green albumin, red CK19, blue PECAM1), **B** Liver single sequencing clustering (Scheidecker et al., 2024); **C** Beta like cells in honeycombs , **D** bihormonal patterns [2]*

Perspectives

The perspectives are the induction of the liver pathology and the integration of the liver pancreas axis

References

[1] Scheidecker et al., Biofabrication 2024

[2] Morisseau et al., Molecular omics, 2023

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LIMMS Internal Project
Investigation of Steatosis Propagation using Organ-on-a-chip

Hanyuan Wang

Hosted in Sakai/Nishikawa Lab

Fundings: CNRS/UTokyo PhD program, JSPS, LIMMS internal project

Keywords: hiPSC, organ on liver, liver, NAFLD

Context and Objectives

Non-alcoholic Fatty Liver Disease (NAFLD), a complex disorder with a high worldwide prevalence, is one of main cause of critical liver diseases. The lack of therapeutic solution of NAFLD leads to an unmet need to develop an efficient *in vitro* disease model to investigate its onset, propagation and the effects of drugs.

In our study, we used organ-on-a-chip technology to tested dietary free fatty acid (FFA) on a liver model to reproduce and investigate the disease progression.

Methods

Hepatocytes-like cells, liver endothelial-like cells and hepatic stellate-like cells were were differentiated from human induced pluropotent stem cells. After maturation in a microfluidic biochips[1,2] (Fig 1). the cells were exposed to mixture of FFA for 14 days to induce NAFLD.

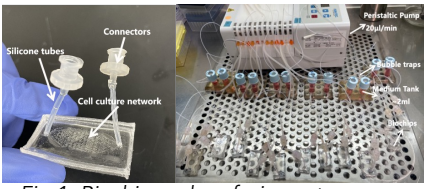

Fig 1: Biochip and perfusion set up

Results

FFA exposures modified cell morphology, increased lipid accumulation and collagen synthesis as shown in Fig. 2. FFA exposure increased fibroblasts like cell populations as shown in Fig 3.

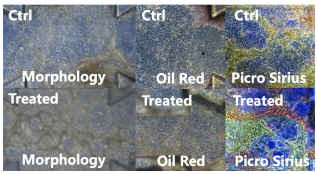

Fig.2 endpoint morphology, lipid accumulation and collagen staining

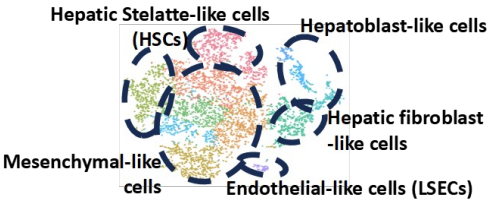

Fig.3 cell populations within treated biochip reclustering

Perspectives

1) NAFLD recovery related drug testing;
2) Introduce macrophages (Kuppfer cells) into the system;
3) NAFLD self recovery attempt on the model.

References

[1] Danoy, M. et al. Biochemical Engineering Journal. 2022
[2] Baudoin, R. et al. Biotechnology Progress. 2007

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Long Term Cultures of HepaSH cells in 3D Spheroids for Pre-clinical Applications

Carla Meschini

Hosted in Sakai-Nishikawa Lab

Fundings: Hauts de France – Université de Technologie de Compiègne, chair "Disruptive Organoid Technologies against metabolic syndrome"

Keywords: Hepatocytes, Spheroids, Honeycombs, *In Vitro model*

Context and objectives

In vitro models are essentials during preclinical studies in order to reduce animal experimentation and to explore alternative therapeutic strategies. Traditional two-dimensional (2D) cell cultures have long been used to study liver function and toxicity, but they fail to fully replicate the complex microenvironment of the liver. In contrast, three-dimensional (3D) culture systems offer improved cellular interactions and functionality [1]. Despite these advancements, there remains a critical need for novel in vitro liver models that better mimic the native hepatic functions. In this context, the HepaSH™ model has emerged as a promising approach to address these limitations [2].

Methods

1) HepaSH™ cells consist on chimeric cells made from primary human hepatocytes matured *in vivo* (mice liver).
2) PDMS Honeycombs were realized and placed into 24 well plate. Cells were culture for 20 days before performing several assays.

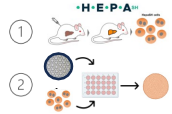

Fig.1. Schematic representation of HepaSH spheroid formation

Results

In this study, we successfully generated HepaSH™ spheroids thanks to PDMS Honeycombs. The experiments showed that cells can aggregate into a standardized and reproducible 3D structure and keep this conformation until 20 days after seeding. Mesurements also showed that these cells expressed hepatic markers (albumin and biliary salts) as well as CYP activity.

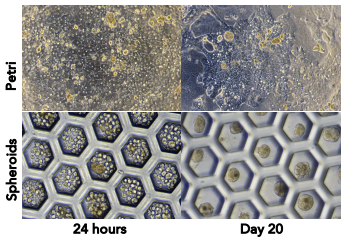

Fig.2. Microscopic observation of HepaSH™ cells in PDMS honeycombs at 24 hours and 20 days after seeding, in Petri (2D) vs. in honeycombs (3D)

Perspectives

- Transcriptomic analysis of hepatic markers and maturation markers (Albumin, Alpha-foeto protein)
- Cryopreservation assay on these spheroids and viability assay after thaw

References

[1] Pasqua M, et al. *Tissue Eng Part A*. 26(11-12):613-622 (2020)

[2] Uehara S, et al. *Biochem Biophys Res Commun*. 663:132-141. (2023)

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LIMMS Internal Project
Mathematical Modelling of Lipid Accumulation and Reactive Oxygen Species during Steatosis

Morgane Lagier

Hosted in Sakai/Nishikawa Lab

Fundings: ANR Track NAFLD, LIMMS internal project

Keywords: Liver, Simulation, computational biology

Context and Objectives

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in western countries. It can be dichotomically divided into simple steatosis, generally associated with a benign outcome, and steatohepatitis (NASH), characterized by progression to hepatic fibrosis/cirrhosis, hepatocellular carcinoma (HCC) and increased mortality. There is currently no pertinent drug therapy. We propose to use in silico numerical methods to simulate the pathology and to test therapeutical strategy.

Methods

We propose the development of a canonical digital twin of the liver. We will integrate the in vitro and in vivo data to an in silico framework of system biology models to extrapolate predictions to humans.
We build a multi cellular agent-based model including hepatocye, Kupffer, endothelial and stelatte cells. The cells are organised along a sinusoid like structures.
The code is computed in C and run an university cluster
We reproduced the accumulation of lipid in hepatocyte and the subcequent lipo toxicity

Results

Preliminary model conception:

- Source code: Prof Cleri[1] and Dr Bazir[2]
- Liver cells implementation (Fig 1)
- Species kinetics computation
- Metabolism integration (Fig 1)
- Cell death, migration, division

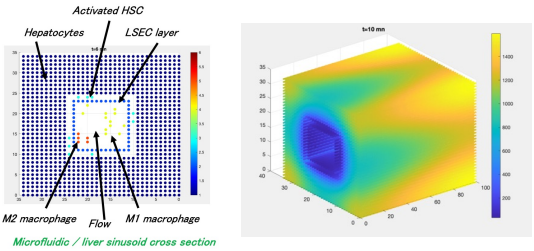

Fig.1. Example of reconstructed geometry and lipid accumulation

Perspectives

- Algorithm optimization
- Complete physiopathology
- Run disease simulations

References

[1] Cleri et al., Euro Phys J. E 2019

[2] Bazir et al., submitted

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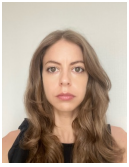
SOI-CMOS Large-scale Integrated Circuit for Particle Detection

Anne-Claire Eiler

Hosted in Mita Lab

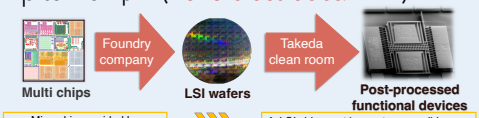


Fundings: JST-CREST, Kakenhi, JSPS Core-to-Core, MEXT X-nics, ARIM

Keywords: CMOS, silicon on insulator (SOI), large-scale integrated (LSI), coulter counter

Context and Objectives

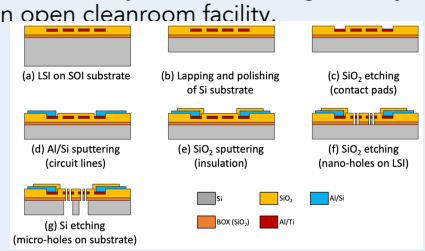
Development of a LSI microchip for coulter measurement, using the SOI technology for faster switching :
- array of 640 electrodes
- electrode size: 44.0 µm x 36.4 µm
- sensing array: ~2.03 mm x 0.80 mm
- pitch: 51 µm (~393 electrodes/mm^2)



Design, fabrication, and post-processing of microchips for desired applications

Methods

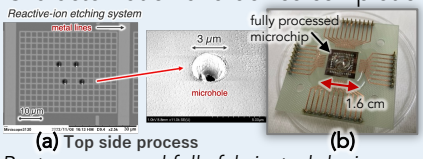
Post-processing on matrices of electrodes controlled by transistors integrated by LSI in open cleanroom facility.



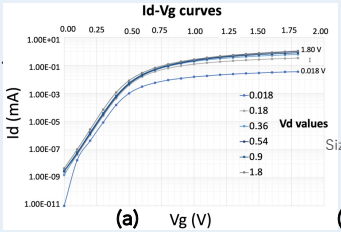
Process workflow for fabrication of a coulter counter: lapping/polishing, top side holes etching, deposition, back side holes etching

Results

Characterization and device completion.



Post-process and fully fabricated device:
a) *top side etching of 3 um holes;*
b) *fully processed microchip on PCB with PDMS chamber*



Id_{max} → 1.0 mA
Vd_{max} → 1.8 V
gm_{max} → 1.0 mS
V_{TH} → ~0.5 V

Size of transistor = 5.0 µm

→ 200 µA/µm
→ 200 µS/µm

Electrical characterization of the integrated transistors:
a) *drain current vs gate voltage with logarithmic scale;*
b) *electrical parameters of the transistors*

Perspectives

Fabrication of a fully functional LSI microchip to be used as a counter coulter. Additional post-processes include the development of an electrode array for electrophysiological measurements.

References

[1] Y. Mita et al., Japanese Journal of Applied Physics 56, 06GA03, 2017

[2] Y. Chen et al., Sensors and Actuators B: Chemical 213, 375-381, 2015

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LIMMS Internal Project
Advancing 3D and 4D Microswimmers for Robotic Biomanipulation

Gilgueng Hwang

Hosted in : Mita Lab / B.J.Kim Lab

Fundings: LIMMS internal project, JSPS , CNRS PEPS, CNRS IEA

Keywords: Bio/chemical sample analysis, soft microswimmer

Context and Objectives

I have focused on developing 3D and 4D microswimmers to push the boundaries of robotic biomanipulation. The objective has been to design and control microscale robotic agents capable of autonomous or externally guided movement, enabling precise handling of biological samples. This work contributes to the growing field of micro-robotics for biomedical applications, addressing challenges in single-cell manipulation, targeted drug delivery, and biofluid navigation.

Methods

Over the years, I have developed multiple types of microswimmers with different actuation mechanisms and fabrication techniques:

- Magnetic microswimmers: Designed for remote actuation in fluidic environments.
- 4D-printed shape-morphing microswimmers: Utilizing stimuli-responsive materials for dynamic transformation.

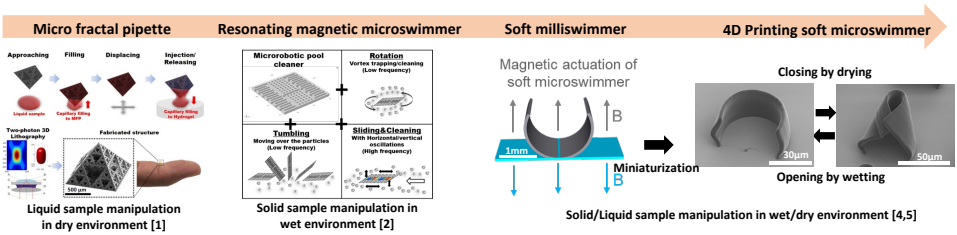
Fabrication techniques such as MEMS process, two-photon polymerization (TPP) and 4D printing were employed to create complex microstructures. Motion control was achieved using magnetic, and fluidic actuation methods, enabling precise maneuvering in confined biological environments.

Results

This research led to the successful development of microswimmers capable of navigating biological fluids, adapting their shapes dynamically, and interacting with living cells. Key findings include:

- Controlled navigation in microfluidic systems with high spatial accuracy.
- On-demand shape transformation of 4D microswimmers for adaptive transport.

The image below illustrates the progression of microswimmer designs developed at LIMMS, showing the evolution from early rigid structures to advanced 4D shape-morphing microswimmers.



Perspectives

This work provides a foundation for future advancements in microscale robotics. Future research could explore AI-driven control strategies, in vivo applications, and further integration with biological systems. These microswimmers hold great promise for next-generation medical interventions, precision diagnostics, and targeted therapeutics.

References

[1] D. Decanini, et al., Review of Scientific Instruments 91, 086104 (2020)
[2] G. Hwang, et al., Sensors and Actuators A: Physical 318, 112502 (2021).
[3] G. Hwang, et al., IEEE Transactions on Semiconductor Manufacturing 34(3), 248-255 (2021)
[4] D. Decanini, et al., IEEE MEMS 2023, Munchen, Germany, 21-24 (2023)
[5] D. Decanini, et al., IEEE MEMS 2024, Austin, Texas, USA, (2024)

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LIMMS Internal Project
Microstructuring of Resorbable Scaffolds for Vascularized in-vitro 3D Tissues

Vincent Salles

Hosted in B.J.Kim Lab

Fundings: LIMMS internal project

Keywords: Direct-write electrospinning, resorbable and functional scaffolds, tissue engineering

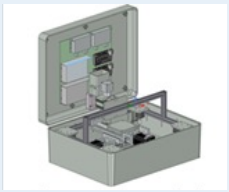
Context and Objectives

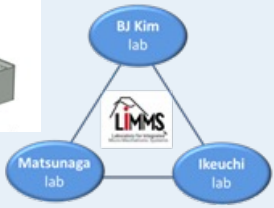
The proposed approach consists in creating in vitro, using resorbable materials, an architecture of interconnected vessels and micro-vessels connected to a microfluidic system to continuously feed the vascular system via which it will be possible to feed the cells positioned around. On a long term, complex architectures could be implanted and sutured to the patient's vascular system.

Method

The fabrication process of the scaffold is based on a combination of a 3D printer and an electric field applied between a nozzle and a printing stage. For this project, a peculiar machine was designed and supplied. This project is carried out in collaboration with 3 host-labs, as shown below.

Direct-write electrospinning





Involved collaborators

Results

Fabrication:

Scaffolds: Thin channels and grids made of PCL (Polycaprolactone)

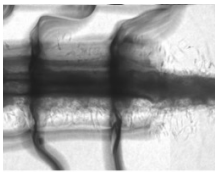
Chips: Design of PDMS chips suitable for cell seeding

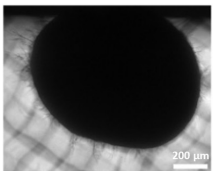
Characterization:

Microscopy (optical & SEM), 3D-tomography

Cell culture:

HUVECs (human umbilical vein endothelial cells) & neuronal cells (iPS)





Channel (PCL) + HUVECs (left) and spheroid of neuronal cells on a PCL grid (right)

Perspectives

Study the quality of the HUVEC layer in the channels

Use a natural material to replace PCL

References

[1] L. Bourdon et al.,J. Funct. Biomater. 2023, 14, 263

[2] C. Xu et al., Biomed. Microdevices 2023, 25, 32

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Advanced Porous Scaffolds for in-vitro Vascularization

Yousra Analy

Hosted in B.J.Kim Lab

Fundings: B.J.Kim lab / LIMMS

Keywords: Microvessel-on-chip, 3D printing, electrospinning

Context and Objectives

- Manufacturing of a microscale electrospun scaffold by 3D printing.
- Simulating perfusion rates through resorbable architectures.
- Adapting the optical characterization to study cell proliferation around the neo-formed vascular network.

Methods

- **Fabrication:**
3D printing of PCL electrospun fibers
- **Characterization:**
Immunofluorescence staining and confocal microscopy for cells' adhesion characterization

Results

Demonstrators include:

- Scaffold fabrication
- Scaffold functionalization
- HUVEC seeding
- Co-culture with neural spheroids

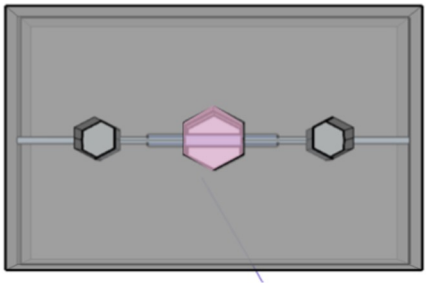

Fig.1. Porous scaffold embedded in collagen matrix in PDMS chip

Perspectives

- Design complex network of microvessels;
- Pursue co-culture tests to produce vascularized tissue;

References

[1] D. Richards, et al., Ann Biomed Eng 45(1):132–147 (2016).
[2] J. Cacheux, et al.STAR Protoc 5(2):102950 (2024).

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Development of Optical Microneedle Lens Array for Skin Cancer Photodynamic Therapy

Anthony Lefebvre

Hosted in B.J.Kim Lab

Fundings: Institute of Industrial Science (IIS)

Keywords: Microneedles device, Photodynamic therapy, Light, skin cancer

Context and Objectives

Skin cancer is one of the most common cancers worldwide with an increasing incidence every year (1). Topical treatment like photodynamic therapy (PDT) are promising new approach for local forms. However, efficiency is limited by penetration of both light and molecules deep in the skin layer (2). Microneedles (MNs) are emerging as a device that can help resolve this penetration issues.

In this study, we aim to developed a dual function optical microneedle device to ensure both delivery of light and photosensitizer molecules to tumor cells for photodynamic therapy treatment.

Methods

Fabrication:
Optical Microneedles Lens Array (OMLA) device fabrication by hot embossing

Characterization:
Resistance of OMLA to compression
Light diffusion simulations and assay on human skin

Biological assay:
Coating of MNs form the OMLA device with 2 photosensitizer molecules, Rose Bengal or 5-ALA

In vitro photodynamic therapy using coated MNs on melanoma cell line

Results

Designing dual function microneedle lens array device investigating the capacity of the device to transmit the light

Demonstration include:

- MNs insertion resistance characterization
- Light diffusion simulation
- Red light diffusion through human skin
- Coating of MNs with molecules
- *In vitro* proof of concept of PDT using OMLA *in a melanoma cell line.*

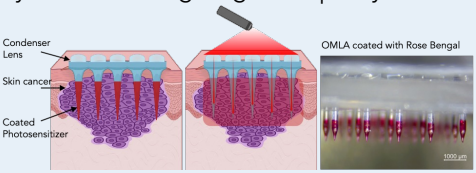

Fig.1. Schematic representation of PDT using OMLA (left) image of Rose Bengal coated OMLA (right)

Perspectives

Optimizing the coating concentration of photosensitizer molecules
Performed *in vitro* assay using 3D culture models and *in vivo* proof of concept in mouse models

References

(1) Leiter U, Keim U, Garbe C. Adv Exp Med Biol. 2020;1268:123–39.
(2) Li, Q.; Gao, T.; Jiao, B.; Photomed Laser Surg 2011, 29, 501–507.
(3) Li, D.; Hu, D.; Xu, H. Biomaterials 2021, 264, 120410.

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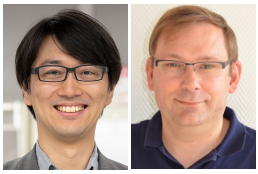
LIMMS Internal Project
Development of Cancer Nerve Interaction Device

Yoshiho Ikeuchi & Robert-Alain Toillon



Hosted in Ikeuchi lab; Univ of Lille

Fundings: LIMMS internal project
Keywords: Microfabrication, organoids, molecular biology, cellular biology, neuroscience, cancer, oncology

Context and Objectives

The interactions between nerve and cancer cells are involved in tumor proliferation, metastasis and resistance to therapies. However, this interaction is only partially described due to a lack of reproducible and robust experimental models. The aim of the work carried out as part of this project is to develop these in vitro models.

Results

- **IPS-derived sensitive neurons**

- Development of growing conditions and differentiation
- Definition of microdevice culture conditions
- Validation by differentiation markers

- **Characterization of interaction**

- Measurement of cancer cell/sensory nerve interactions
- Effects of co-culture on phenotypes
- Transcriptomic analyses

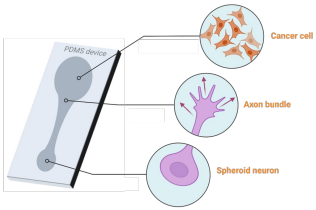


Fig.1. PDMS device design

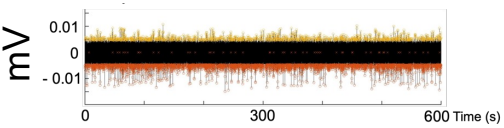


Fig.3. Recording electrical activity in nerve cells

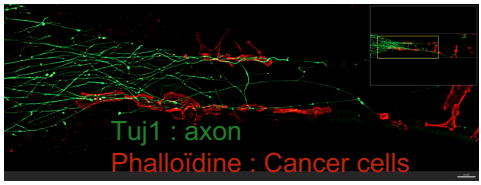


Fig.2. nerve/cancer interaction

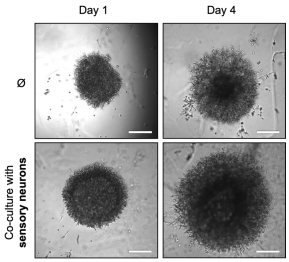


Fig.4. Cancer cell invasion

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CYTOMEMS : Instrumentation for Biophysical Cytometry with Statistical Learning

Dominique Collard

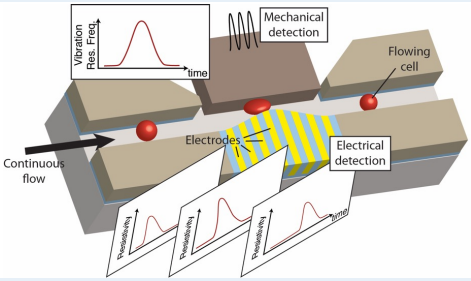
Hosted in SMMiL-E (Lille)

Fundings: ANR Project

Keywords: MEMS cytometry, biophysical cell characterization, IA

Context and Objectives

The objective of CYTOMEMS is to demonstrate the first smart MEMS equipment performing high content biophysical characterization of cells in flow for their classification by statistical learning.



Methods

Cell characterization is carried out by a BioMEMS device incorporating a microchannel for the passage of cells and equipped with fixed and mobile electrodes enabling both electrical and mechanical measurements of these cells in flux. The position of the mechanical sensor is tuned in real time to characterize the cell under controlled deformations knowing the cell size from upstream electrical measurement.

After a phase of training on different cell lines, cell identification is performed by statistical classification analyzing a comprehensive set of biophysical (electrical and mechanical) parameters.

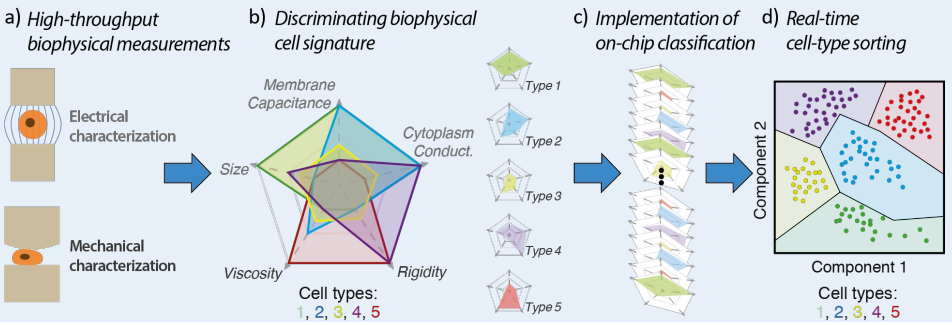


Fig.1. Graphical view of the main objectives of CYTOMEMS recapitulating the main hypothesis.

Perspectives

CYTOMEMS is a 3 years ANR projects 2022-2024 with the following 4 partners :

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Distinguishing Cancer Cells Based on their Biophysical Properties

Cagatay Tarhan

Hosted in SMMiL-E (Junia)

Fundings: ANR, Region HdF / I-Site, SATT

Keywords: Single-cell analysis, biophysical characterization

Context and Objectives

- Biological processes related to cells are influenced by changes in cell shape and structural integrity.
- Biophysical properties can potentially reflect the state of cells' health.
- Can we use biophysical parameters as metastatic biomarkers?

Methods

- Microfluidic device for cell handling
- Silicon Nano Tweezers (SNT) for biophysical measurements
- AI for distinguishing cells

(i) SNT tips for capturing single cells.
(ii) Actuators for manipulation & detect.
(iii) Capacitors as displacement sensors.

Results

- SNT, integrated with microfluidics, allows single cell characterization (Fig. 1).
- A displacement sensor allows compression assays during continuous sensing.
- AI algorithms are used to distinguish cell lines.
- Three different breast cancer cell lines were analyzed.
- The cell line with high metastatic potential (SUM159PT) showed softer mechanical properties than the cell line with low metastatic potential (MCF7), which was softer than non-malignant cell line (MCF10A).

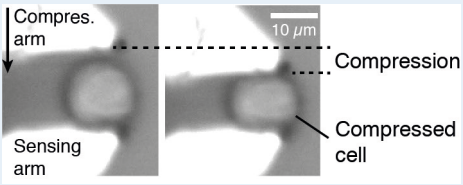

Fig.1: Compression assay with SNTs.

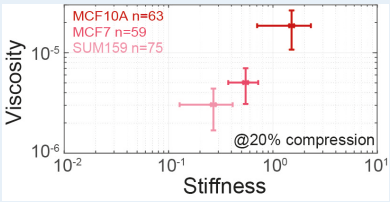

Fig.2: Comparison of different cell lines.

Perspectives

- Obtaining biophysical signature of CTCs distinguish according to metastatic potential
- Towards diagnostic products, drug testing platforms, disease monitoring and treatment prediction instruments.

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Cells Pairing in Microfluidic Devices for Biological Analysis

Faruk Shaik

Hosted in SMMiL-E (Lille)

Fundings: Fondation ARC, INCa PLBIO

Keywords: single cell interaction, cell pairing, immunological synapse

Context and Objectives

- Immunological synapse (IS) is essential for investigating efficient immunologic treatments for cancer studies.
- We aim to fabricate a MEMS device for single cell pairing of individual immune cells and leukemic cells for this purpose

Methods

A multilayer microfluidic platform with specific geometries targeting high-throughput deterministic pairing for two different cell sizes in a unidirectional flow format.

Introducing an auxiliary flow alters the effective channel height allowing efficient small-cell trapping.

In short, we perform controlled high throughput single-cell pairing for immunological synapse study.

Results

- T cells and leukaemia cells are trap in controlled manner, with high throughput.
- IS dynamics is monitored for hours.
- Cell pairing is established for monitoring Ca2+ signature of T-cells.

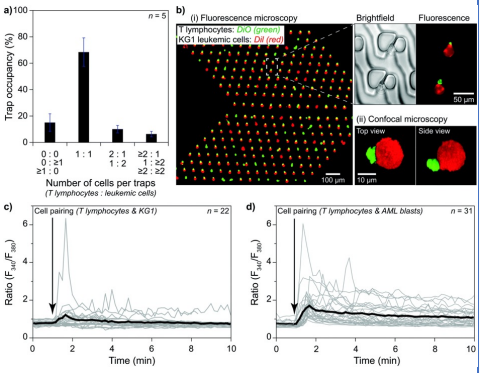

Figure 1: Cell pairing and monitoring their activities [1].

Perspectives

Fabrication of integrated device for single cell pairing.

Characterization of patients sample. Calcium signature study.

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ImmunoMEMS Project: MEMS – based Versatile Cell Assembly for Advanced Cell Interaction Assays

Dana Simiuc

Hosted in SMMiL-E (Lille)

Fundings: SATT Nord

Keywords: immunological synapse, cell pairing, Bio-MEMS

Context and Objectives

The immunological synapse is essential to study effective immunological treatments, to increase the chance of survival of patients with metastasis cancer.

Methods

- **Fabrication**:
  Clean-Room silicon processes and 2 photon polymerization printing.
- **Characterization**:
  Imaging: optic (brightfield and fluorescence) and electronic (SEM).
  Flow tests resistance.
  Flexibility: external actuators.

Context and Objectives

- Within ImmunoMEMS project we aim to create a device that can pair cancer and immune cells to recreate the immunological synapse and measure its response [2].
- Once the test has been carried out, it is possible to recover the cells of interest.

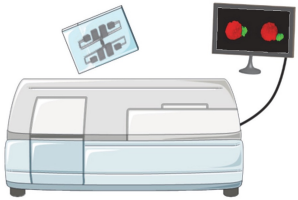

Fig.1. Bio-MEMS device

Perspectives

- Biological validation.
- Continuous device fabrication.
- Start-up creation to valorize the technology.

References

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Vascular Barrier Models in Cancer

Fabrice Soncin

Hosted in SMMiL-E (Lille)

Fundings: ANR, Ligue contre le Cancer, Fondation ARC, IRCL

Keywords: blood vessels, cancer, inflammation, immunity, microfluidics

Context and Objectives

We design blood vessels-on-chip devices to study the molecular mechanisms which regulate the vascular barrier, immune activation, and how they participate in vessel integrity, angiogenesis, and extravasation of blood-borne immune cells. We also study the effects of anti-cancer therapies used in patients on the functions of the vascular barrier.

Methods

Blood vessels-on-chip are made in PDMS-glass devices, designed and fabricated at SMMiL-E facilities. They are seeded with primary human endothelial and perivascular cells from various organs. Biological validations are made using cell and molecular biology approaches, confocal microscopy, RT-qPCR and functional assays.

Results

Alice M. Leroy (Univ. Lille Ph.D student, Y3) studies the effects of anti-cancer drugs and radiotherapy on the vascular barrier and immune activation in our blood vessels on-chip models.

Ibtihal Hezili (Univ. Lille Ph.D. student, Y2) sets up a perfused blood vessel on-chip angiogenesis model to study the effects of anti-cancer drugs and radiation therapy on this process.

Julie Vrevin (post-doc in collaboration with Dr. S. Mitra) studies the effects of modified cytokines on blood vessel permeability and inflammation.

Perspectives

Assess the role of biological signals & environment components on blood vessel functions, screen for active drugs and anti-cancer treatments on blood vessel permeability, activation, and angiogenesis.

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LIMMS Internal Project
Quantum-Electrochemistry and DNA-Protein Interactions for Cancer Screening

Fabrizio Cleri

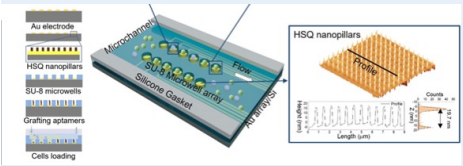
Hosted in SMMiL-E (Lille), LIMMS (Tokyo)

Fundings: LIMMS Internal Project 2024

Keywords: Microsystems, molecular biology, computer modelling

Context and Objectives

We develop a novel technology, highly-sensitive, minimally invasive, high-throughput and potentially low-cost, for cancer screening by monitoring circulating tumor cells and extracellular vesicles. The device is based on quantum electrochemistry detection via grafted DNA aptamers + redox species in a microfluidic chip.

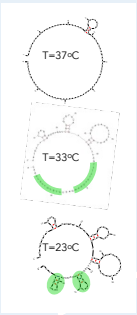


The Role of Computer Modelling

Design, analysis, and technology of the microfluidic device, is completed by two basic computer modelling actions:

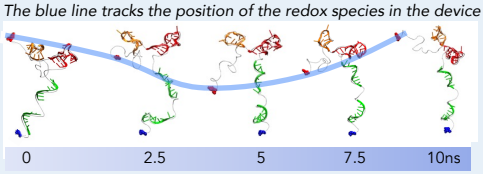
1. all-atom molecular dynamics simulations, to characterize the experimental configuration at the single-atom scale (electrode surface, DNA, redox species, target proteins);

2. quantum-mechanical electron transport simulation, using detailed information from the molecular-scale dynamics to obtain the tunneling current in the device.



Thermodynamic simulation of the denaturation of the anti-CD44 DNA aptamer with increasing temperature

Molecular simulation of a DNA aptamer targeting CD44 protein
The blue line tracks the position of the redox species in the device



Recent Results

Study of the dynamics of the molecular structure of DNA aptamers, as a function of the running temperature of the microfluidic device, and of the ionic concentration in solution. We identified a set of anti-CD44 aptamers and modelled their interaction with CD44 target.

Project Partners

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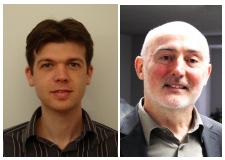
Developing the Interdisciplinary Space for SMMiL-E Projects

Jean-Claude Gerbedoen & Fabrice Soncin



Hosted in SMMiL-E (Lille)

Fundings: JUNIA (JCG salary) and CPER Cancer (Equipment)

Keywords: Microfabrication, cell culture, molecular&cellular biology

Context and Objectives

Since the SMMiL-E projects are at the intersection of biology, engineering and clinics, they require dedicated facilities within the hospital campus.

Imaging

- Field emission scanning electron microscopy (with cryo option)
- Airyscan confocal microscopy
- Inverted microscopy for BF, Fl, PC and DIC imaging
- Upright microscopy for brightfield imaging
-Nucleic acids & protein gel imaging systems

L2 cell culture room

Bio-room

Molecular Biology

-Classic & real-time PCR systems
-DNA/RNA & protein quantification and analyses equipment
-Abs/Lum/Fluo/Alphascreen plate reader

Microfabrication

-Lithography (direct writing, mask aligner)
-Deposition (sputtering, evaporator, parylene coater)
-Etching (Reactive Ion Etching, wet etching)
-Characterization (probe station, profilometer, SEM)
-Rapid prototyping (stereolithography SLA, Nanoscribe with two-photon polymerization, Computed Numerical Control)

Microfabrication equipment in the cleanroom

Cell Biology

-Cell culture hoods
-Tri-gas incubators
-Culture under perfusion system
-Dedicated inverted microscopes with BF, PC, and Fl imaging
-Bioprinter
-Cell electroporation system

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