IEE1860
LECTURE 1

Tamás Pardy
TalTech Lab-on-a-Chip

12.01.2022

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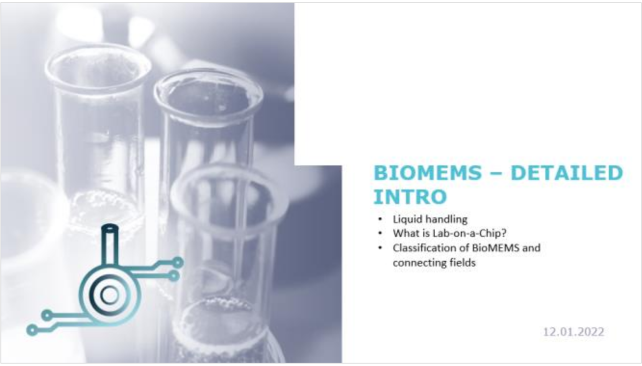
OVERVIEW



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STUDY ORGANIZATION

- Evaluation criteria
- Ways to attend
- Modules
- Learning outcomes

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STUDY ORGANIZATION

Week	Topic
1	Quick and dirty intro to the course and field
2	Fluid mechanics 1: basic theory
3	Fabrication 1: basic fabrication, rapid prototyping
4	Seminar 1
5	Fluid mechanics 2: advanced theory, FEM & CFD
6	Fabrication 2: advanced fabrication, mass production
7	Seminar 2
8	Sensors in laboratory automation
9	Actuators in laboratory automation
10	Adaptive laboratory automation
11	Seminar 3
12	Applications 1
13	Applications 2
14	Seminar 4

Module 1: basic theory & fabrication

Module 2: advanced theory & simulation, mass production

Module 3: sensors & actuators

Module 4: applications

Labs correspond to lectures

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STUDY ORGANIZATION

Track 1: fully online	Track 2: online participatory	Track 3: contact learning
• Listen to lectures online • Watch labs online • No evaluation • No registration	• Listen to lectures online • Join seminars online • Watch labs online • Perform computer exercises remotely • Registration mandatory • Evaluation on next slide	• Contact/hybrid lectures • Contact/hybrid seminars • All labs performed in contact learning • Registration mandatory • Evaluation on next slide

STUDY ORGANIZATION

Final grade:

91 – 100 % = "5" (excellent)
81 – 90 % = "4" (very good)
71 – 80 % = "3" (good)
61 – 70 % = "2" (satisfactory)
51 – 60 % = "1" (poor)
0 – 50 % = "0" (failed)

- Lectures – **Σ40 pts**
  - 4 modules, 4 seminars (max. 10 pts. each)
- Labs – **Σ60 pts**
  - Lab report at the end (max. 60 pts.)
    - Written lab report (55 pts.)
    - Results files (5 pts.)
- Participating at labs and submitting results are mandatory! Failing to do so will result in failing the course.

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PRACTICAL PART

- (computer) Rapid prototyping I.
- (computer) Finite element analysis I-III.
- (experimental) Rapid prototyping II. (max. 3 students at once)
- (computer) Droplet microfluidics (max. 3 students at once)
- Lab report on all labs done (individual, except for the parts done in teams)

LEARNING OUTCOMES

Theoretical foundation		Fluid mechanics, simulation, fabrication etc.
Sensors & actuators		Principles, working mechanism, networking
Practical knowledge		Design, fabrication, characterization of BioMEMS devices for research
Application of BioMEMS		Ability to continue independent specialization in the field
+1: improved presentation skills & experience		

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STUDY ORGANIZATION

- Evaluation criteria
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INTRODUCTION TO BIOMEMS

- Context and background
- Lab-on-a-Chip: the focus of this course
- Who we are and how to contact us

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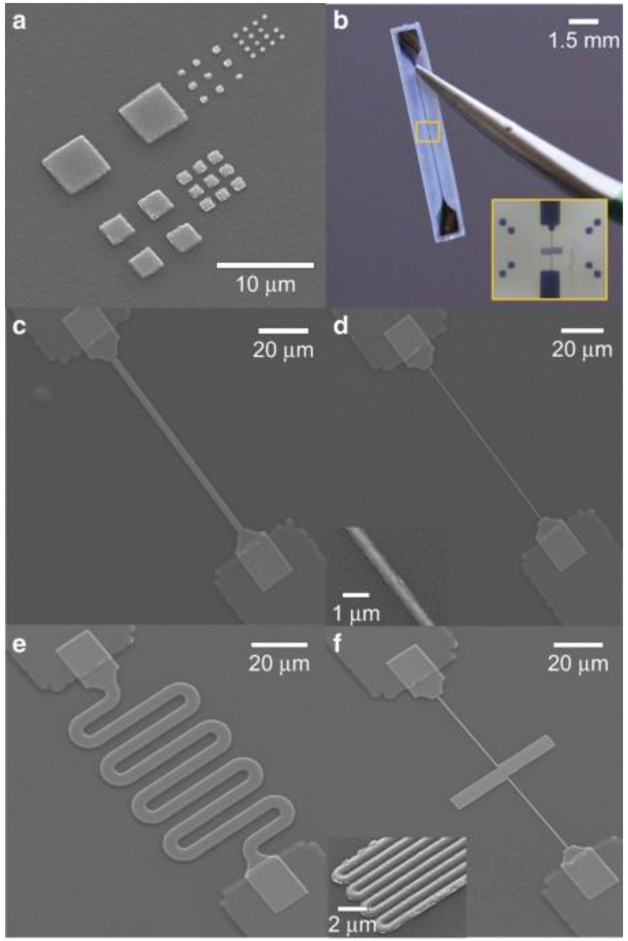
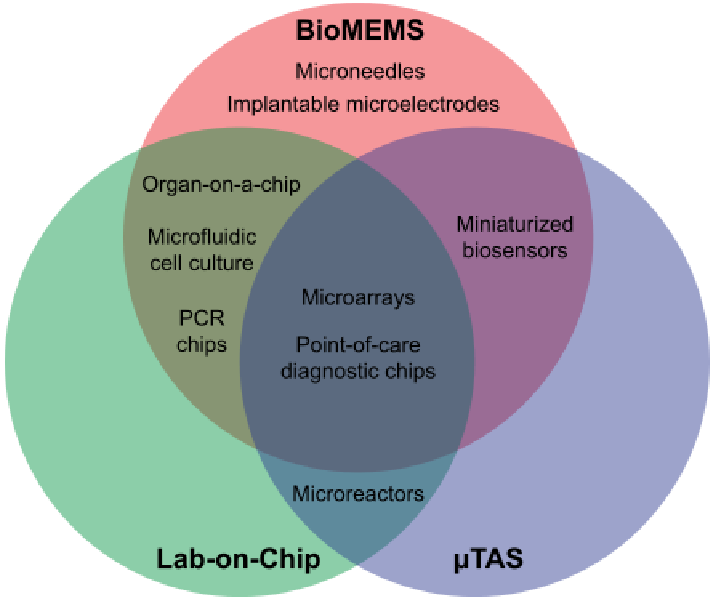
INTRODUCTION TO BIOMEMS

- Bio-MEMS = biomedical **microelectromechanical** systems
  - Focus: miniaturization of biomedical technology

- Subset: **Lab-on-a-Chip**
  - Focus: miniaturization of laboratory automation



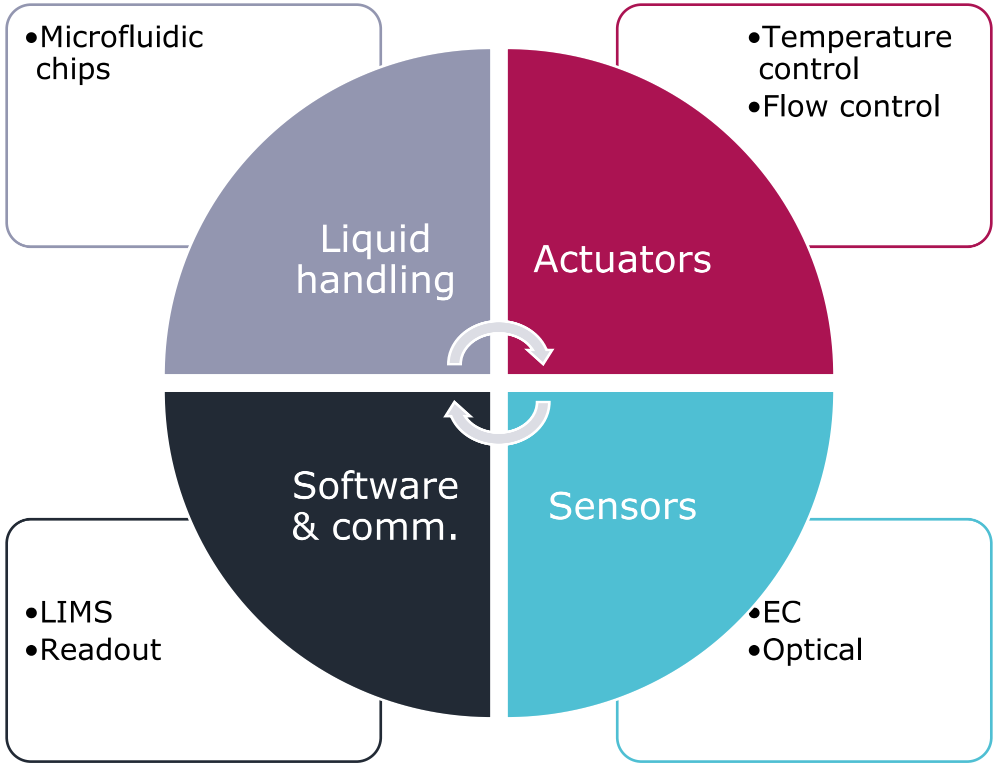


INTRODUCTION TO BIOMEMS

- **Lab-on-a-Chip**:
  a device that integrates one or several **laboratory functions** on a single integrated circuit of only **millimeters** to a few square centimeters to achieve **automation** and high-throughput screening.

- **Microfluidics:**
  liquid handling in sub-millimetre scale

- **Lab-on-a-Chip device** = microfluidic chip + supporting electronics (typically)



LoC = microscale laboratory automation

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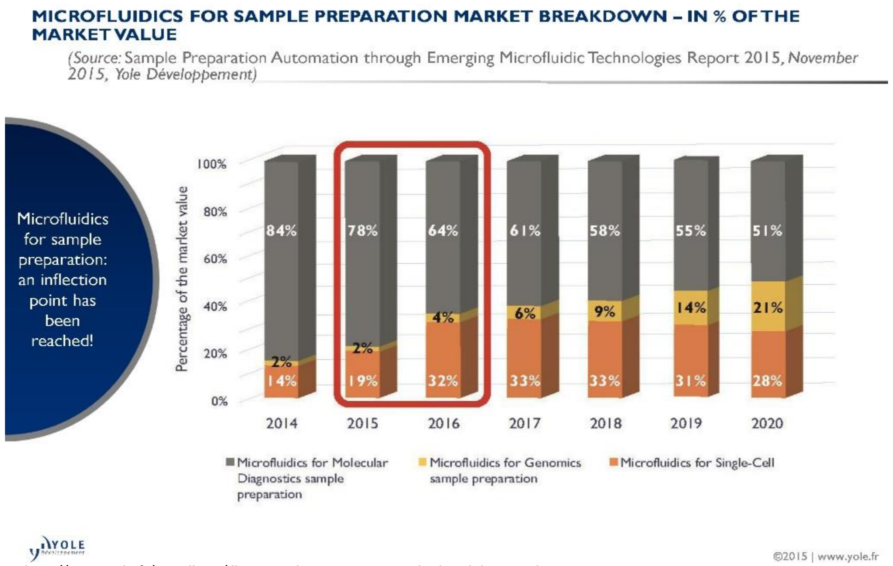
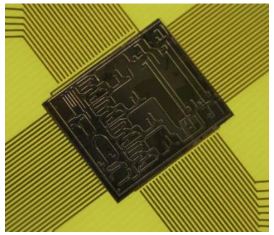
INDUSTRIAL LIQUID HANDLING AND LAB-ON-A-CHIP

- **Liquid handling**
  - Crucial to analytical chemistry – it's the mixing, shaking, storing, dispensing etc. of liquids.
  - However, it typically involves a lot of manual labour by trained personnel (>1k€/person/month)…
- **Automation:**
  - Liquid handling robots (~100k€ investment + training + infra)
  - **Microfluidics** and Lab-on-a-Chip (~10k€ investment + training + infra)
- **Advantages of microfluidics**:
  - Portability and scalability
  - Tighter volume control in μl and nl scale



http://www.yole.fr/iso_album/illus_samplepreparation_marketbreakdown_yole_nov_1.jpg

http://resources.mynewsdesk.com/image/upload/t_next_gen_article_large_480/pi1tsmtrghtsd4l0zzpn.jpg



https://en.wikipedia.org/wiki/Lab-on-a-chip#/media/File:Labonachip20017-300.jpg

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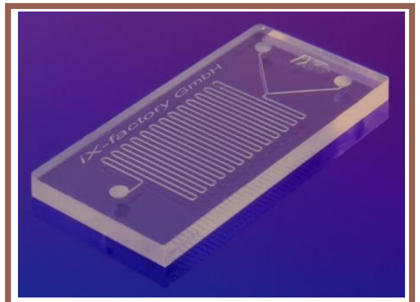
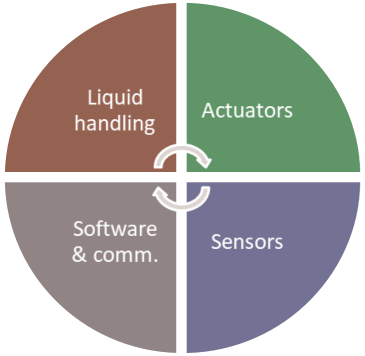
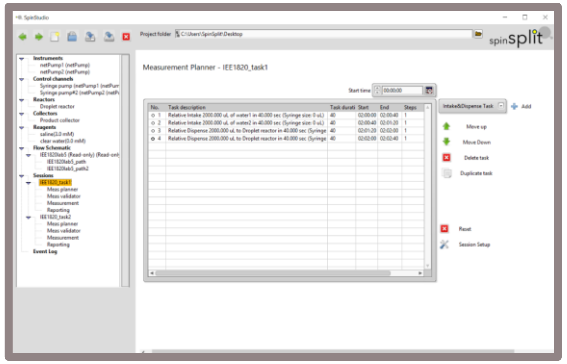
LAB-ON-A-CHIP FLOW CHEMISTRY SETUP

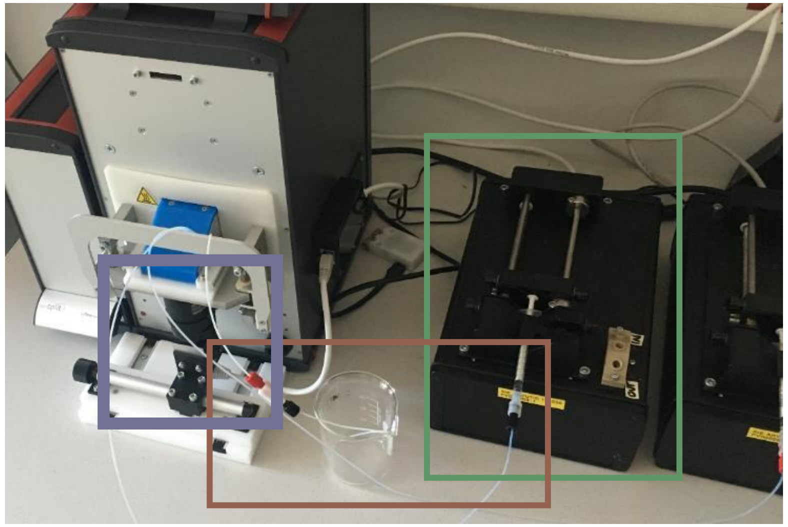
- **Liquid handling:**
  - Polymer/glass/silicon microfluidic chips connected by tubing
- **Actuators:**
  - **Pumps,** valves
  - **Temperature regulation**
- **Sensors:**
  - **Cameras**, spectrophotometers, impedimetric sensors
- **Software & communication:**
  - Connection to PC via USB/Ethernet
  - Workflow-based software control



https://www.fluigent.com/microfluidic-expertise/how-to-choose-a-microfluidic-chip/







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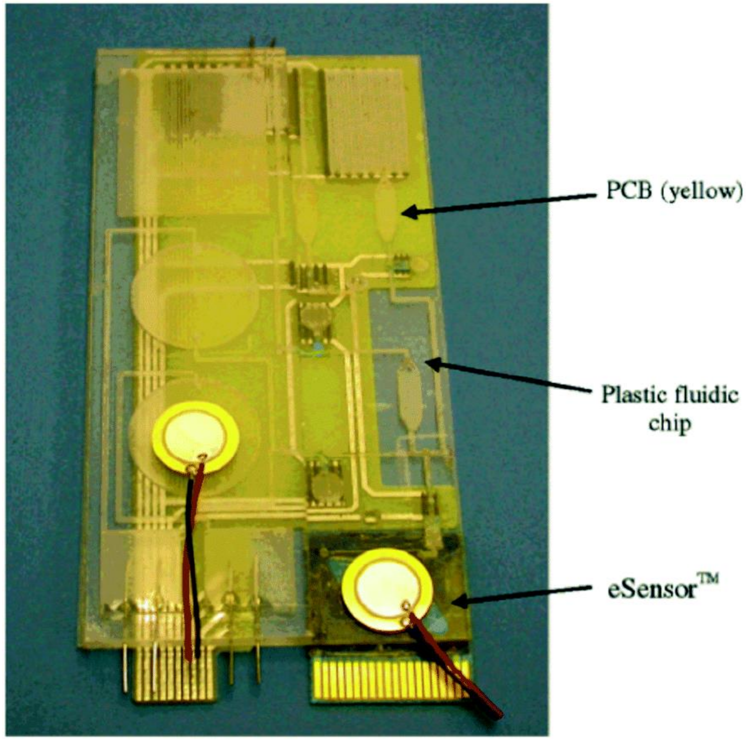
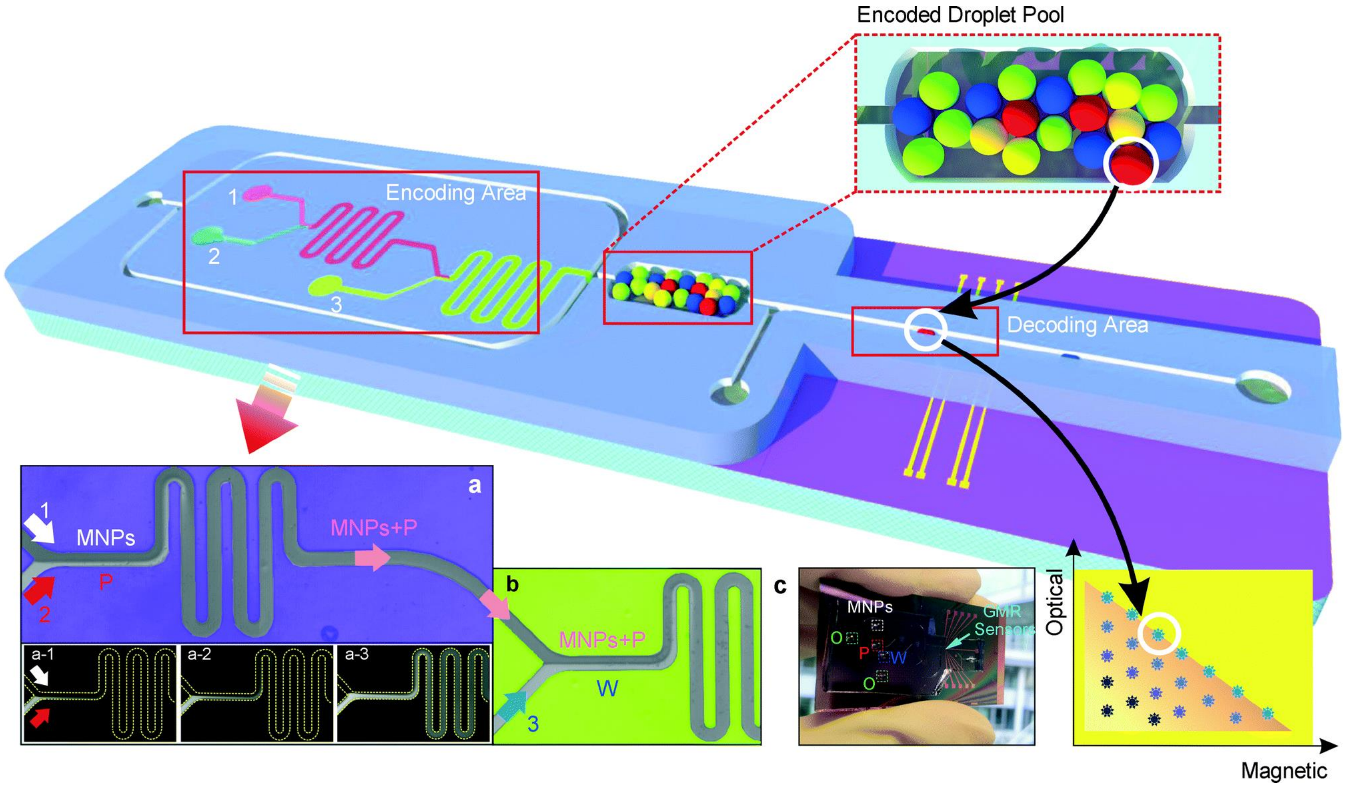
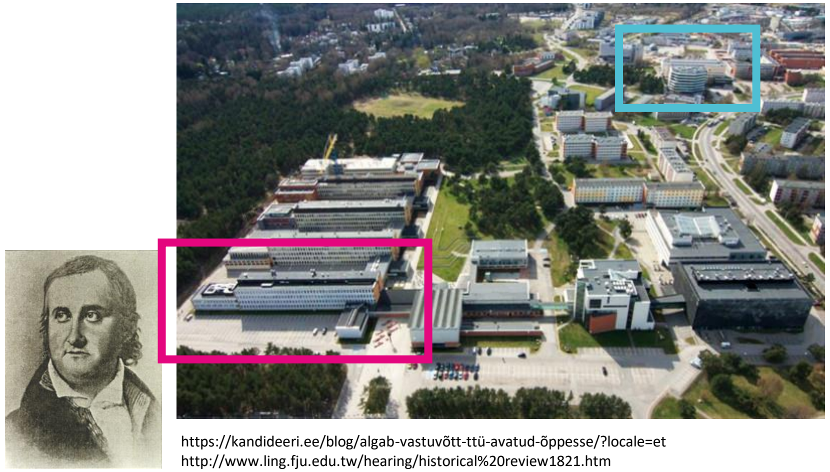
BIOMEMS & LAB-ON-A-CHIP





TALTECH LAB-ON-A-CHIP

- We work on Lab-on-a-Chip research at TalTech
- We are **electrical engineers** and **biologists/chemists**
- **Follow us on Facebook** to get the latest news!
- Check out our webpage to **contact us!**



https://kandideeri.ee/blog/algab-vastuvõtt-ttü-avatud-õppesse/?locale=et
http://www.ling.fju.edu.tw/hearing/historical%20review1821.htm

Webpage

Facebook

MŰEGYETEM 1782

self diagnostics

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connected health Estonian HealthTech Cluster

INTRODUCTION TO BIOMEMS

- Context and background
- Lab-on-a-Chip: the focus of this course
- Who we are and how to contact us

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INTRODUCTION OF LECTURERS

12.01.2022

TAMÁS PARDY

- Name: Tamás Pardy
- Origin: Hungary
- Field: biomedical engineering, Lab-on-a-Chip (5 years in industry, ~10 years in research), industrial liquid handling (1 year in industry)
- Skills: thermal engineering, LoC design and esp. rapid prototyping, programming and scripting (MATLAB, C++, C#)
- Tamas.pardy@taltech.ee

ETIS

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IMMANUEL SANKA

ETIS

- Name: Immanuel Sanka
- Origin: Indonesia
- Education:

  Master – Uppsala University, Sweden

  Bachelor – Universitas Gadjah Mada, Indonesia
- Field: microfluidics and bioinformatics, monodisperse/polydisperse droplet-based analysis, image analysis, genomics, single-cell omics analysis, and protein prediction
- Skills: Python, R, macro, CAD, and linux commands
- Immanuel.sanka@taltech.ee

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ABOUT STUDENTS

- Who are you? Where are you from? Which faculty?

- Former knowledge about
  - liquid handling?
  - CAD and rapid prototyping (e.g. 3D printing)?
  - FEM?

- Would you like to write a thesis with a BioMEMS topic?

FOLLOW US ON FACEBOOK FOR NEWS!

INTRODUCTION OF LECTURERS

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BIOMEMS – DETAILED INTRO

- Liquid handling
- What is Lab-on-a-Chip?
- Classification of BioMEMS and connecting fields

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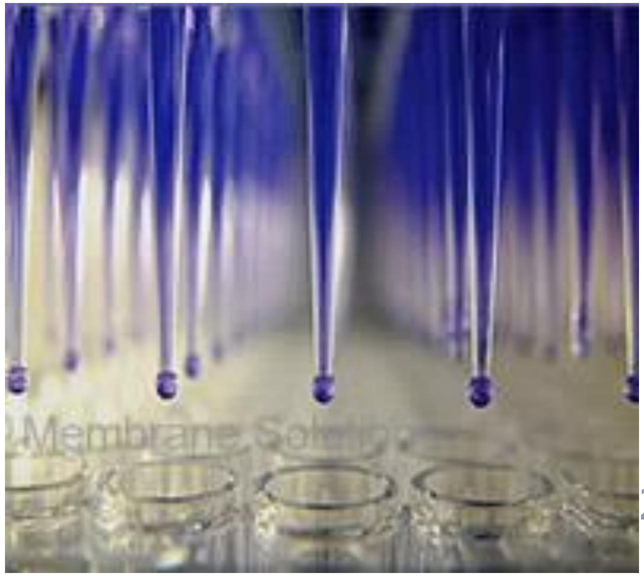
INDUSTRIAL LIQUID HANDLING: WHAT, HOW, WHY?

- **What?** Liquid handling is what you do most often in an analytical laboratory – it's the mixing, shaking, storing, dispensing etc. of liquids.
- **How?** With automated liquid handling and more recently microfluidics.
- **Why?** Because wet chemistry is usually pretty wet :D

- Pipetting stuff together is really boring… (and it costs a lot)

http://www.artel-usa.com/wp-content/uploads/2015/01/pipetting-ergonomics-300x230.jpg



https://www.membrane-solutions.com/img/product/liquid1.jpg

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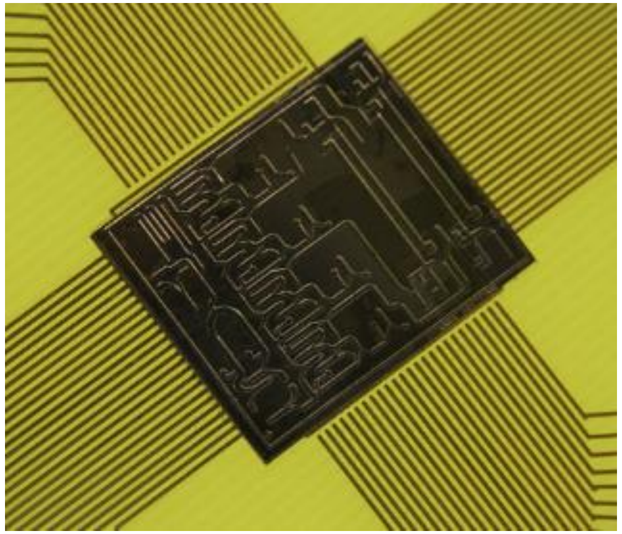
INTRODUCTION: FROM BIG TO SMALL (I.)

- **Automated liquid handling:**
  - liquid handling robots dispense and manipulate (mix, shake, heat etc.) liquids according to the desired assay workflow.
  - Pipetting robots are general-purpose modular platforms.

- **Lab-on-a-Chip**:
  - a device that integrates one or more laboratory functions on a single integrated (fluidic) circuit in the sub-centimetre size regime.
  - Lab-on-a-Chip devices are typically application-specific (like ASIC).

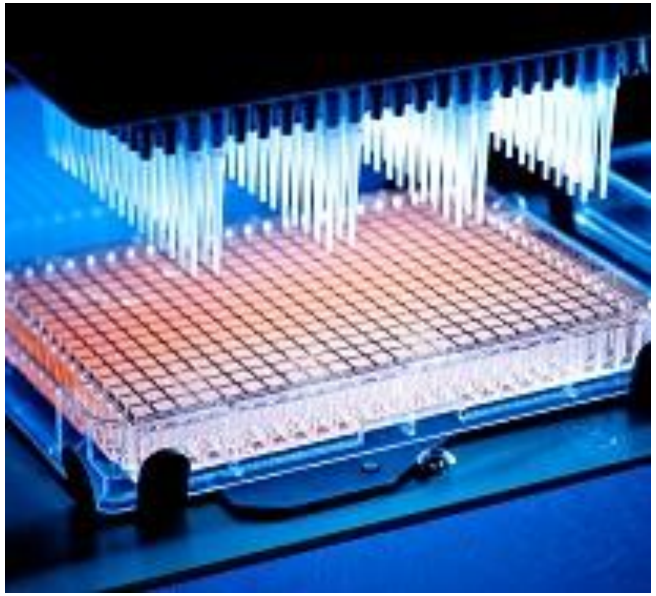
http://resources.mynewsdesk.com/image/upload/t_next_gen_article_large_480/pi1tsmtrghtsd4l0zzpn.jpg



https://en.wikipedia.org/wiki/Lab-on-a-chip#/media/File:Labonachip20017-300.jpg

INTRODUCTION: FROM BIG TO SMALL (II.)

- **High-throughput screening:**
  - Large-scale biological/chemical experimentation carried out in a specialized professional setting.
  - *Characterized by: large sample batches, high initial investment and operational costs (1M$), needs professional personnel, tied to a laboratory*
- **Point-of-Care rapid tests**:
  - Small-scale tests carried out at the point of care (e.g. bedside testing) or at home
  - *Characterized by: low cost (1$), short learning curve (untrained or minimally trained personnel), portability*



http://www.criver.com/getattachment/21a61995-93db-44a5-9c91-e9172ecb4bca/img/

http://www.acepnow.com/wp-content/uploads/2014/10/POCtesting.jpg

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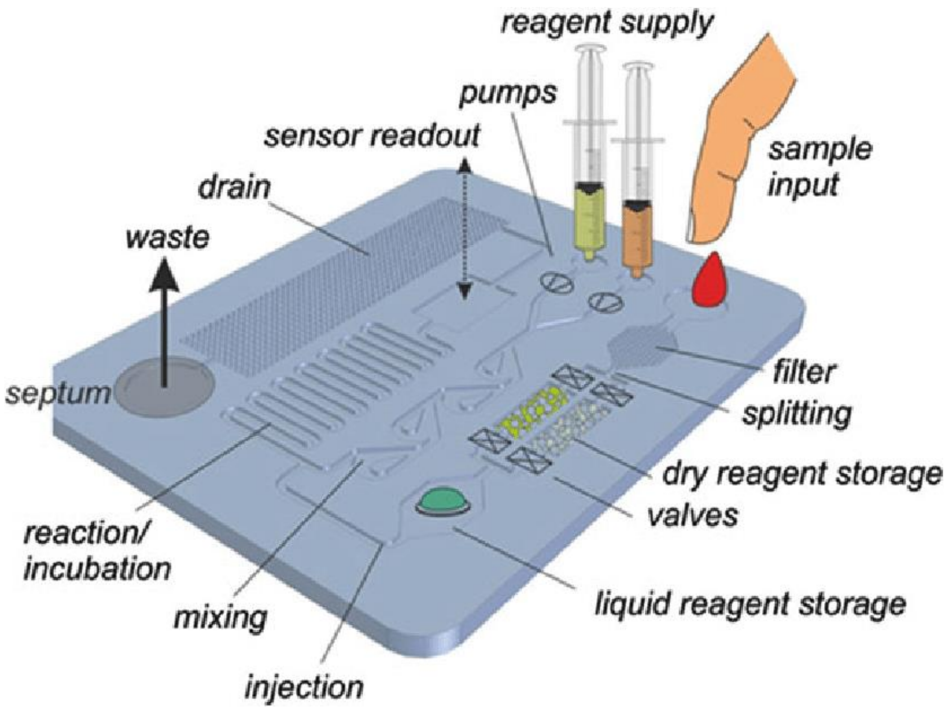
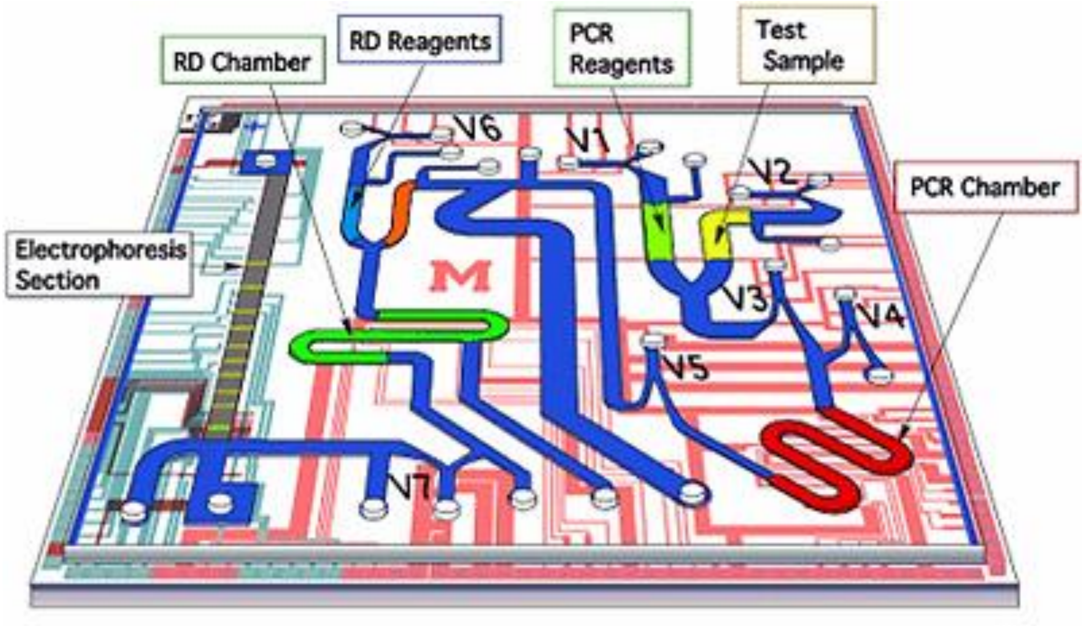
WHAT IS A LAB-ON-A-CHIP (LOC)?

*"A **lab-on-a-chip** is a miniaturized device that integrates onto a single chip one or several analyses which are usually done in a laboratory, analyses such as DNA sequencing or biochemical detection."*



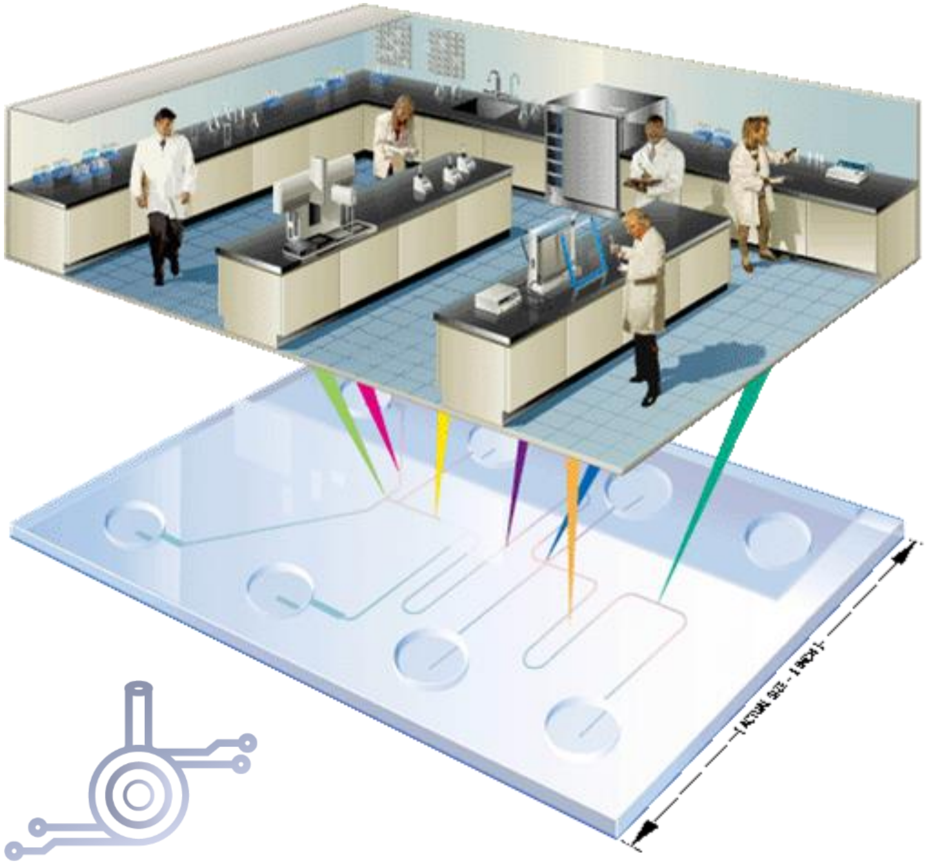


Schematic of the "Genotyper" device, developed by researchers at the Univ. of Michigan, which could identify different strains of flu. Image credit: Dr Ronald Larson, via NIAID.

https://www.researchgate.net/figure/Lab-on-a-Chip-devices-for-point-of-care-applications-usually-comprise-a-number-of-passive_fig20_281080765

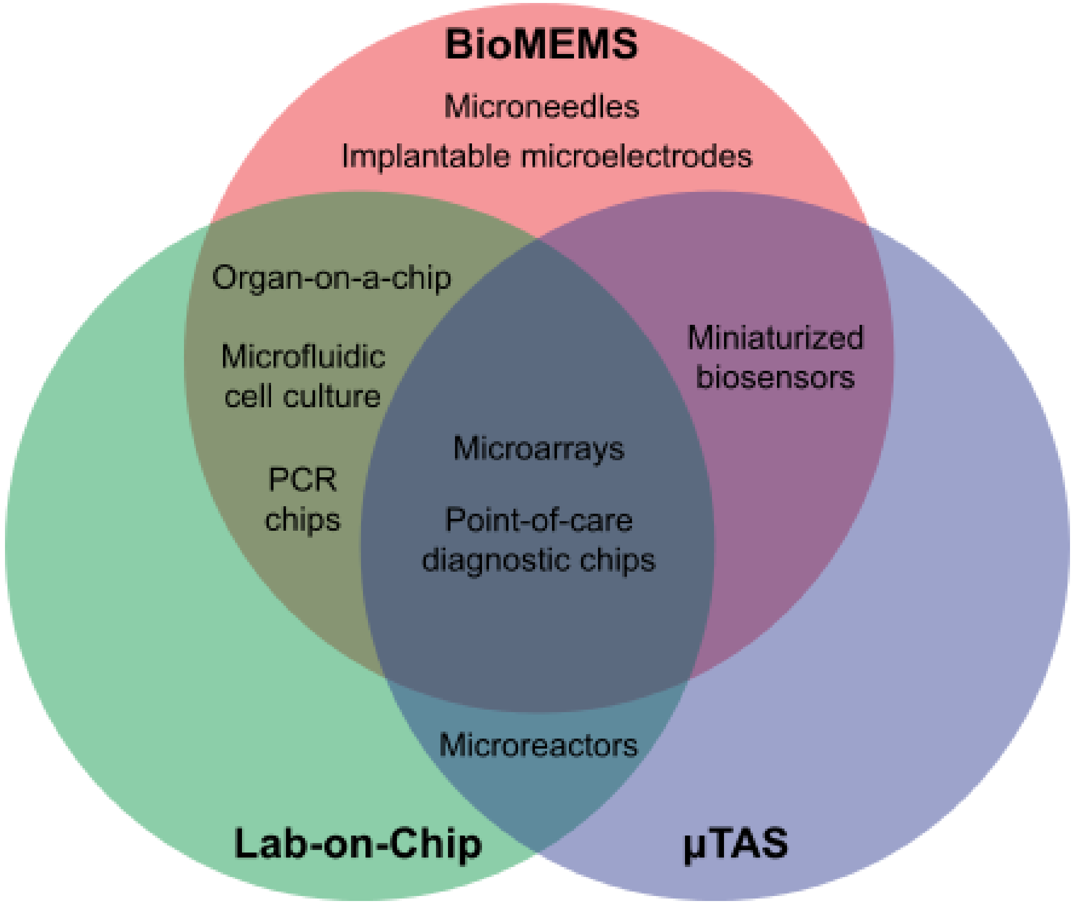
Ref: http://www.azonano.com/article.aspx?ArticleID=3081 (10/2016)

LAB-ON-A-CHIP/MICRO-TAS



"Chip-In-a-Lab"

"Lab-On-a-Chip"
"µTAS"



A Venn diagram outlining and contrasting some aspects of the fields of bio-MEMS, lab-on-a-chip, µTAS. (https://en.wikipedia.org/wiki/Microarray)

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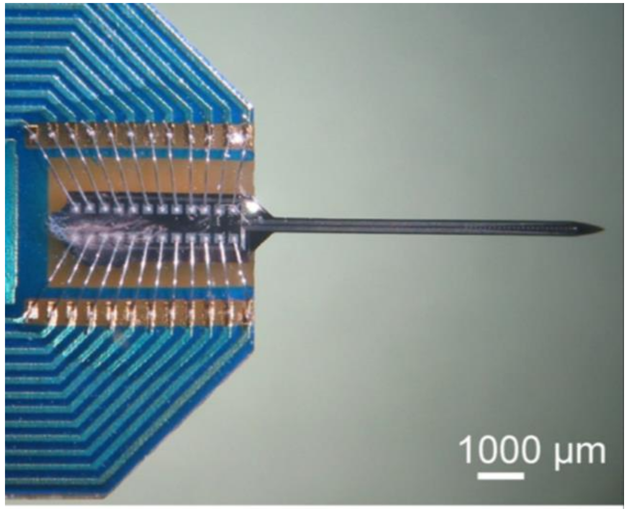
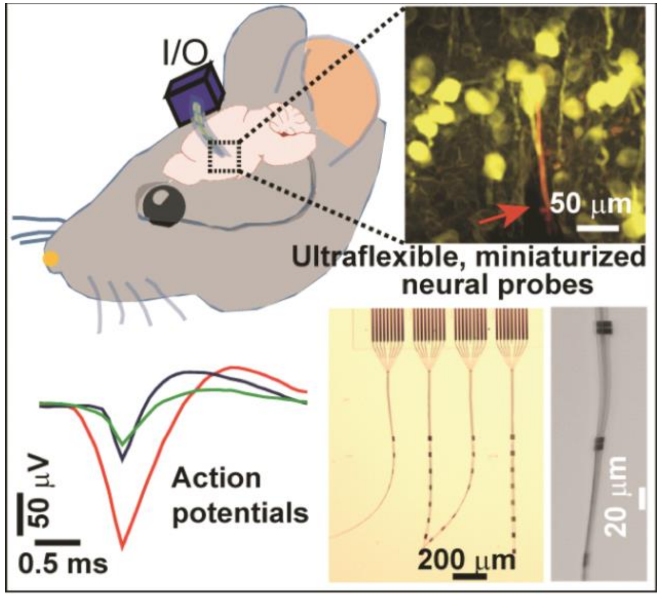
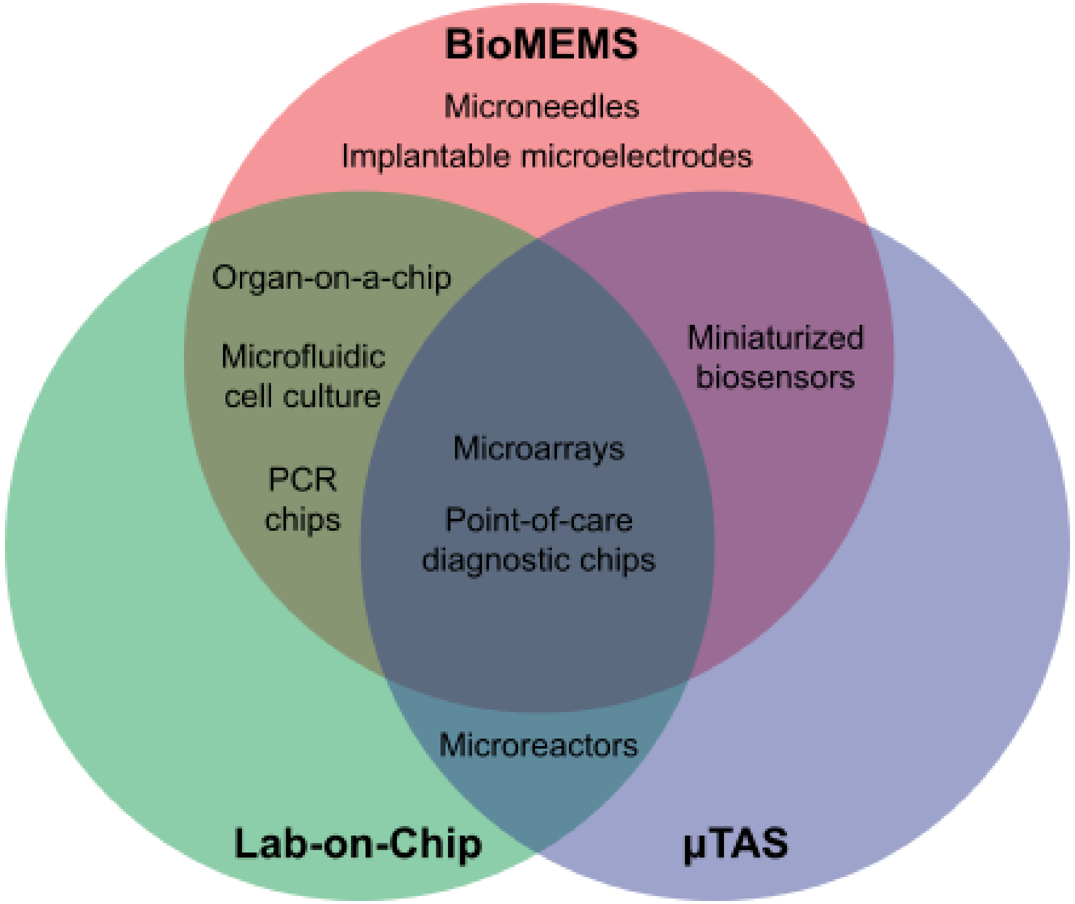
https://www.gene-quantification.de/lab-on-chip.html

BIOMEMS



Not part of the course, but mentioned in IEE1570 Cognitronics



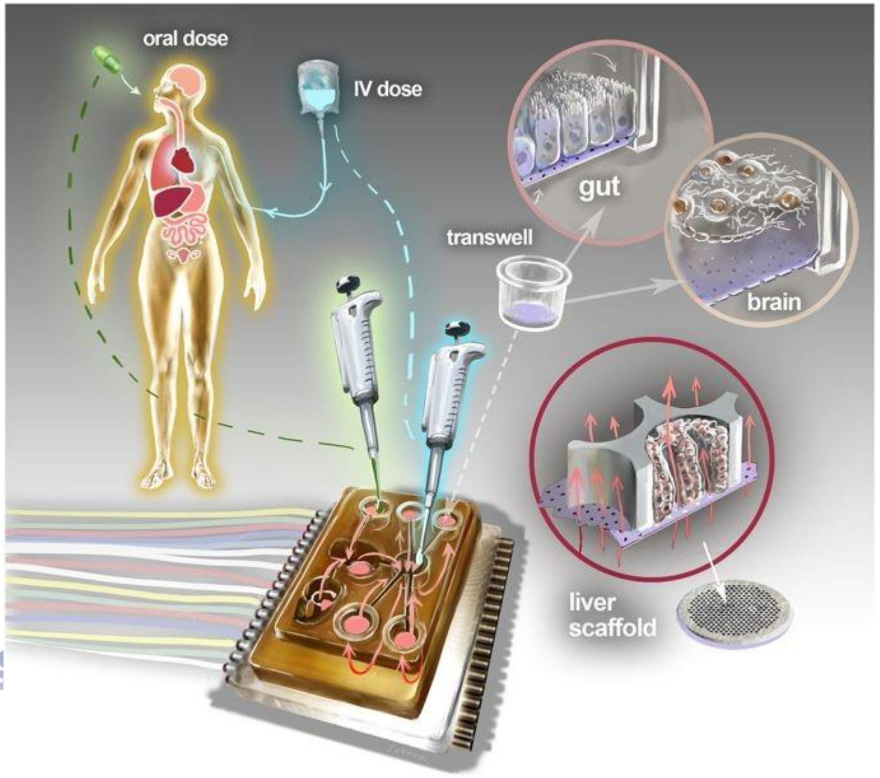


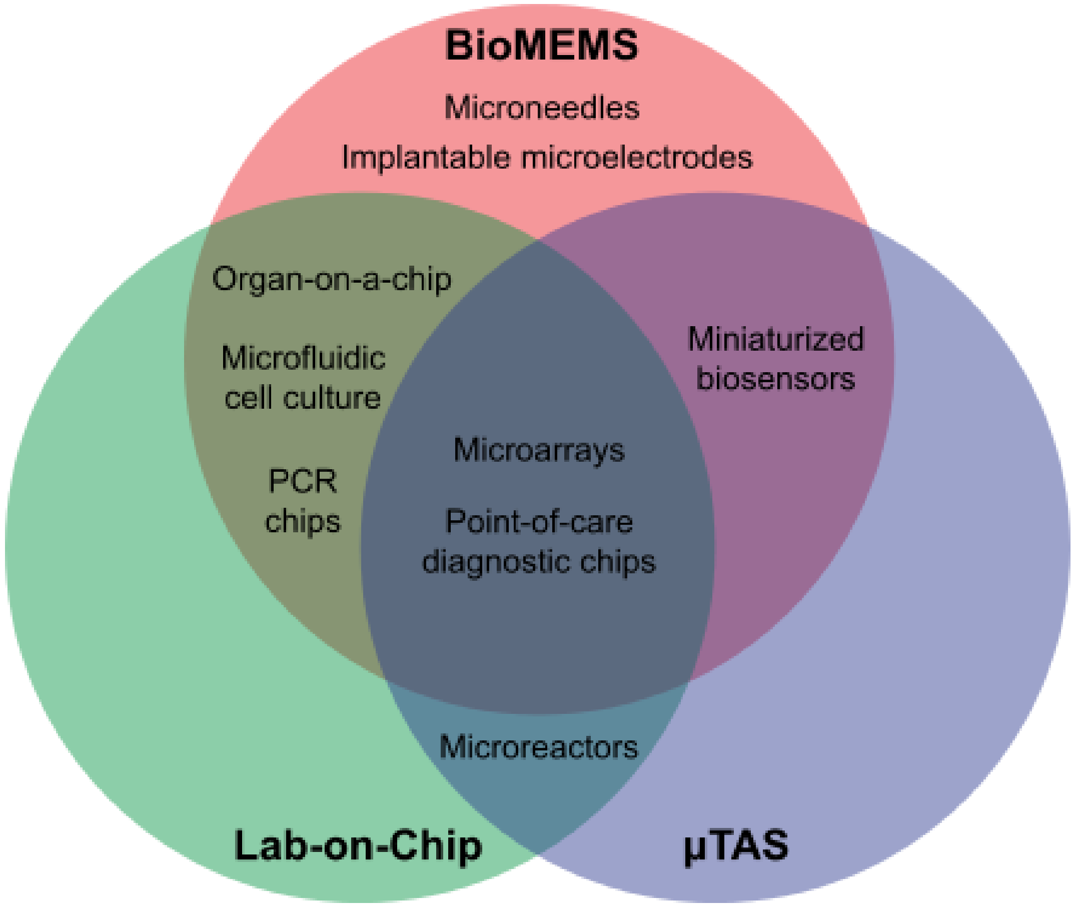
A Venn diagram outlining and contrasting some aspects of the fields of bio-MEMS, lab-on-a-chip, µTAS. (https://en.wikipedia.org/wiki/Microarray)

http://www.mems.hu/BioMEMS
https://physicsworld.com/a/tiny-intracortical-probe-monitors-neural-activity/

ORGAN-ON-CHIP (OOC)

Watch at home
https://www.youtube.com/watch?v=CpkXmtJOH84





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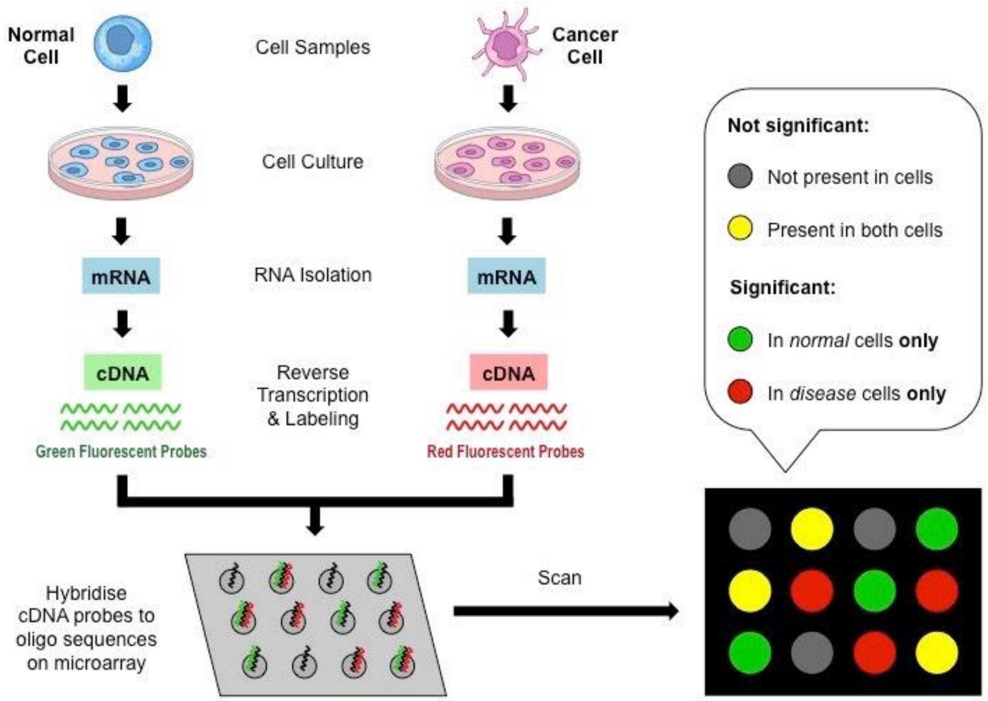
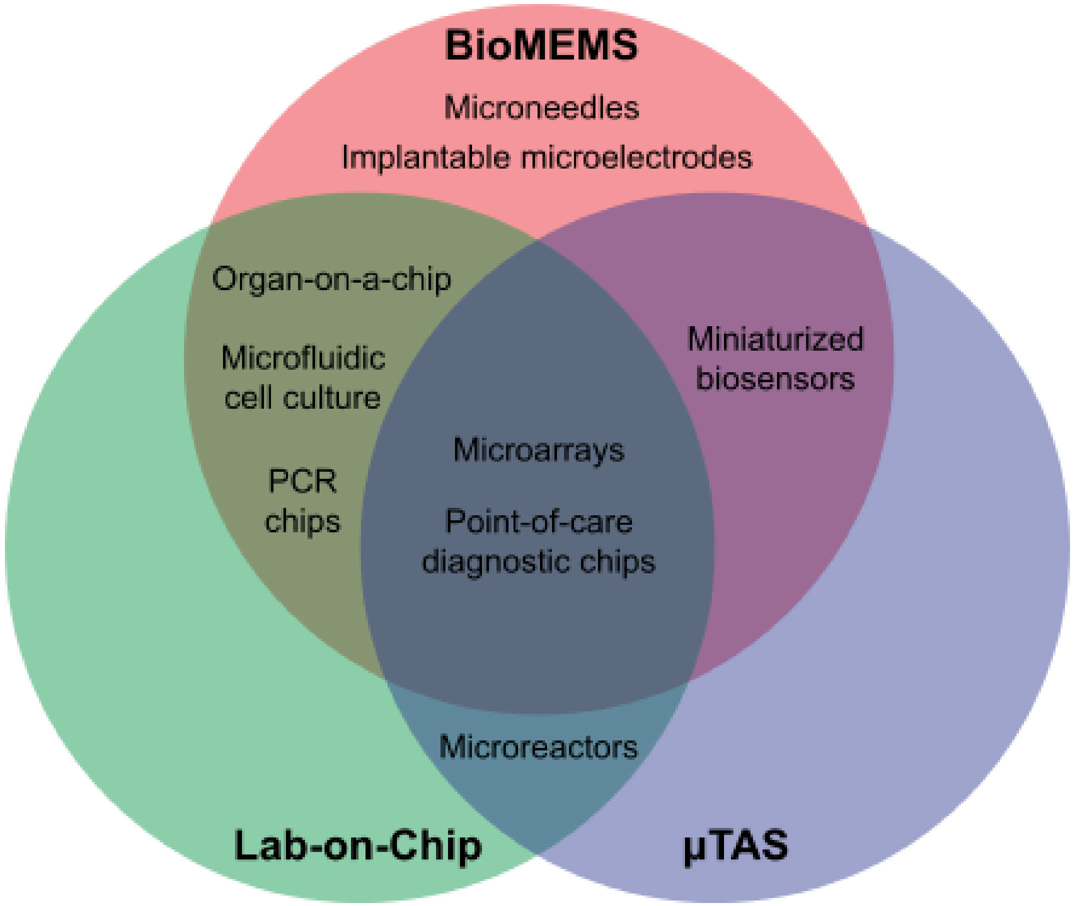
https://www.certara.com/2019/09/03/integrating-organ-on-chips-in-silico-models-for-translational-pharmacology-applications/?ap=PKPD

MICROARRAYS





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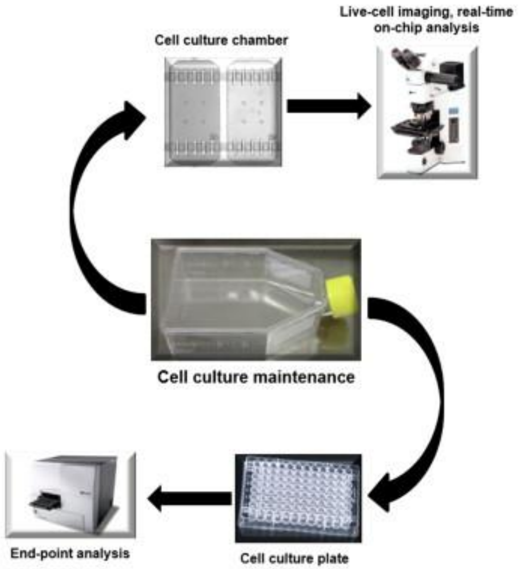
https://ib.bioninja.com.au/options/untitled/b4-medicine/dna-microarrays.html

MICROFLUIDIC CELL CULTURE

Macroscopic cell culture

Typical advantages

- Established culture material
- Standardized measurement of pH, CO_2, and O_2
- Established culture protocols
- Standardization and availability of assays
- Ability to scale up a single experiment



Typical challenges

- Rigid culture surface
- Fixed device architecture
- High reagent consumption
- Perfusions and chemical gradients are difficult to achieve
- Stagnant culture media
- Mainly end-point analysis

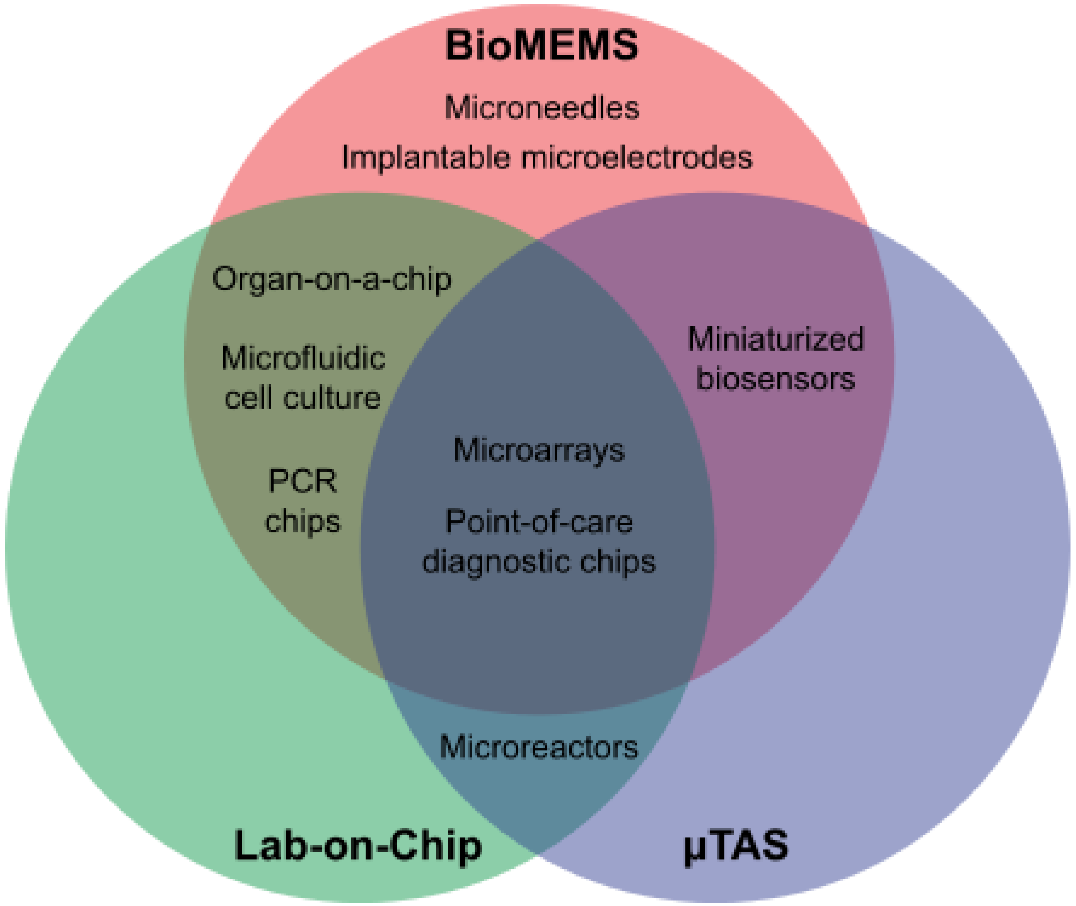
Microfluidic cell culture

Typical advantages

- Flexibility of device design
- Experimental flexibility & control
- A low number of cells is sufficient
- Single cell handling
- Real-time, on-chip analysis
- Automation
- Direct coupling to downstream analysis systems
- Ability to perform perfusion culture
- Controlled co-culture
- Reduced reagent consumption

Typical challenges

- Non-standard culture protocols
- Novel culture surface (e.g. PDMS)
- Small volumes, challenging subsequent analytical chemistry
- Complex operational control and chip design



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https://www.researchgate.net/publication/264460495_Advantages_and_challenges_of_microfluidic_cell_culture_in_polydimethylsiloxane_devices

BIOMEMS – DETAILED INTRO

- Liquid handling
- What is Lab-on-a-Chip?
- Classification of BioMEMS and connecting fields

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LAB-ON-A-CHIP AND MICROFLUIDICS

- Lab-on-a-Chip and microfluidics
- Relevance to modern industry
- Application areas
- Microfluidics and its applications
- Comparison to traditional instrumentation
- Limitations
- Future perspective

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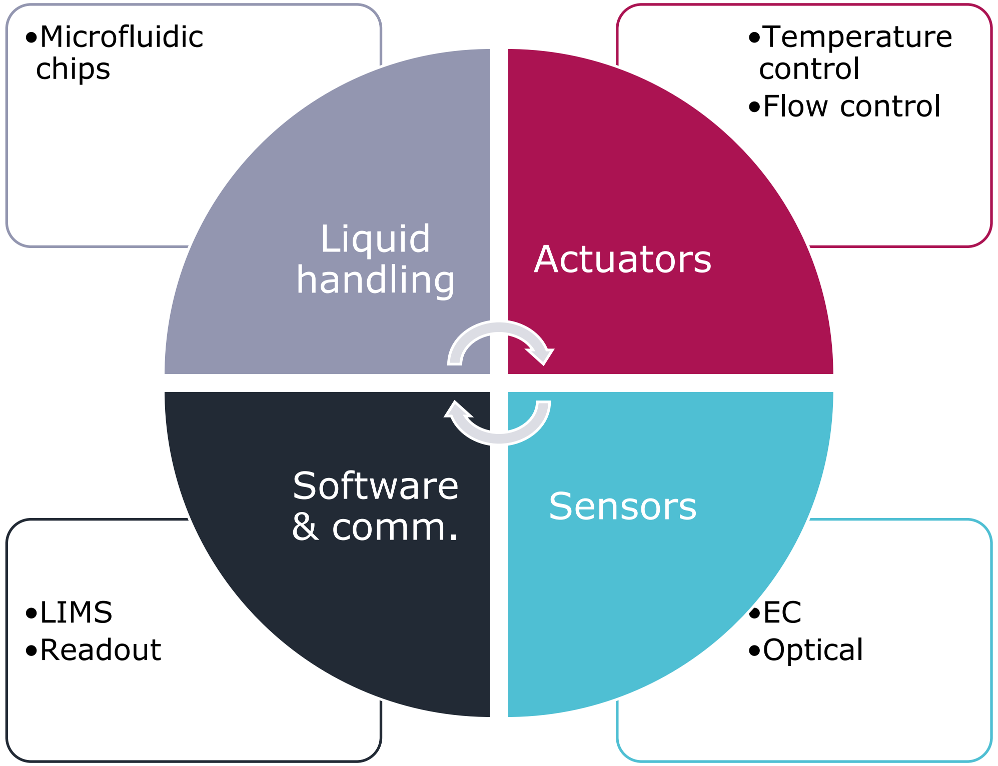
LAB-ON-A-CHIP: QUICK-AND-DIRTY INTRO

- **Lab-on-a-Chip**:
  - a device that integrates one or several **laboratory functions** on a single integrated circuit of only **millimeters** to a few square centimeters to achieve **automation** and high-throughput screening.
- In the traditional sense, a subset of **MEMS**.
- **Microfluidics:** liquid handling in sub-millimetre scale
- **Lab-on-a-Chip device** = microfluidic chip + supporting electronics (typically)

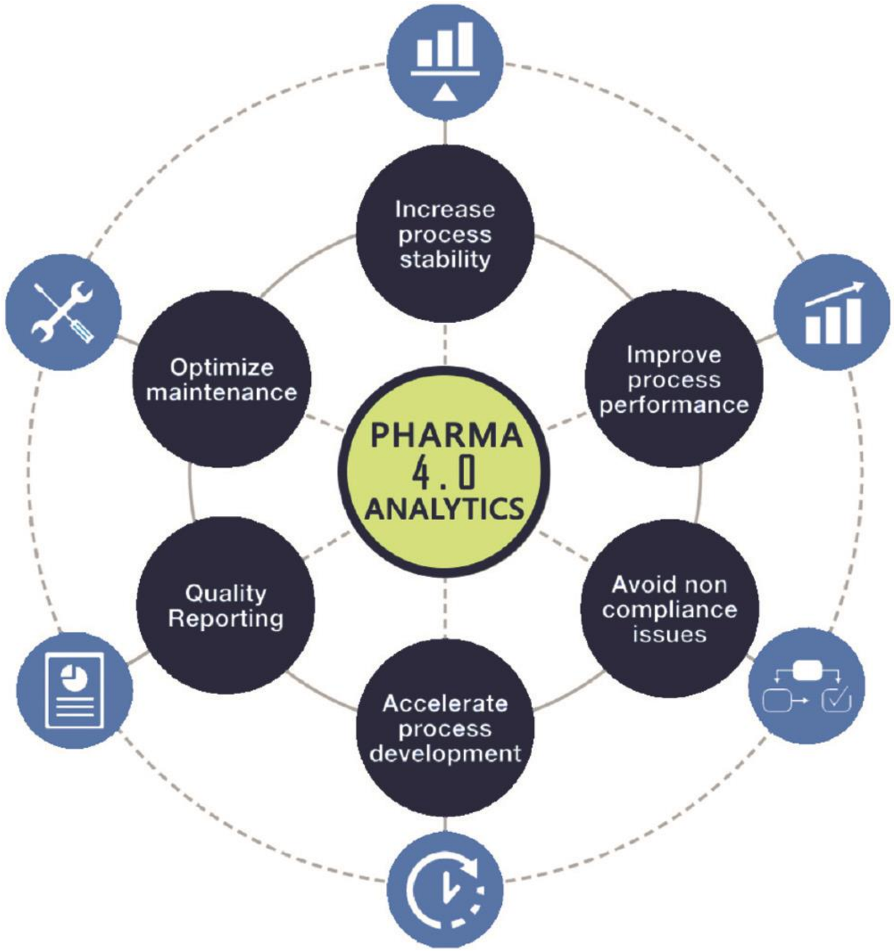
LoC = microscale laboratory automation



WHERE CAN LAB-ON-A-CHIP SHINE?

- **Pharma 4.0 (industry 4.0 in pharmaceutical industry)**
  - Status quo in pharma industry is synthesis of drugs via batch chemistry
  - Large volumes, low unit cost, but…
  - …worse process control than with LoC (monitoring and adapting parameters)
  - …in case of an error, the loss is significant

- **High-throughput drug screening**
  - Lab-on-a-Chip can also contribute greatly to high-throughput screening (discovery) and thus drug development



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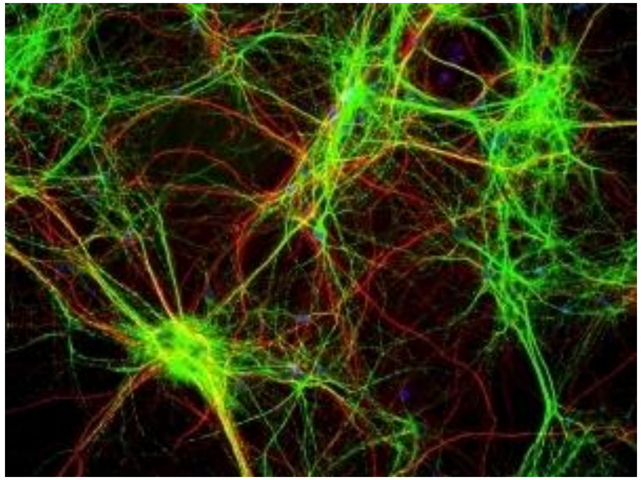
https://www.chemanager-online.com/en/topics/pharma-biotech-processing/pharma-40

APPLICATION AREAS

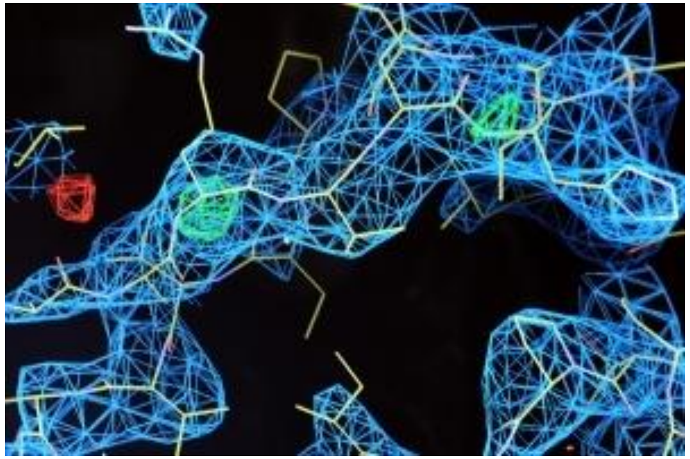
Proteomics

Chemistry

Cell biology



Molecular biology



http://www.elveflow.com/microfluidic-tutorials/microfluidic-reviews-and-tutorials/introduction-to-lab-on-a-chip-2015-review-history-and-future/

HOW DOES IT COMPARE TO TRADITIONAL INSTRUMENTATION?

Microfluidics

- **Low liquid volumes** (lower cost, less waste etc.)
- **Excellent volume control** in sub-microliter range
- **Better process control** in chemistry (faster response, e.g. in thermal control for exothermic reactions)
- **Compactness** and massive parallelization, lower unit cost
- Good for disposable applications
- Fast analyses

Liquid handling robots

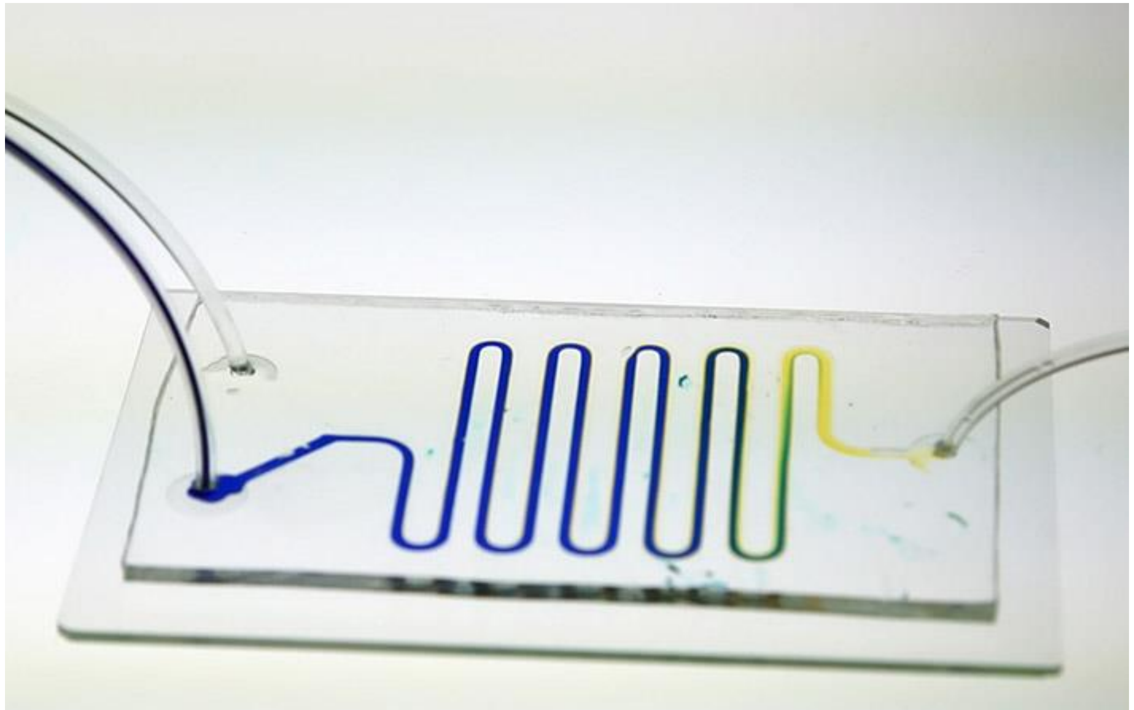
- The only fair comparison is with automated liquid handling (manual cannot compete)
- **High throughput**
- **Microliter precision** – excellent precision in the milliliter-microliter range (air displacement pipettes)
- **Modularity and customization** – e.g. integration of centrifuge, plate reader etc.
- **Significant initial cost** followed by significant savings on manual labor

LIMITATIONS OF MICROFLUIDICS

Slow commercialization	Difficult regulatory environment Technical issues Unclear financing in national healthcare
Bad SNR	Small size + high sensitivity = picking up a lot of noise
External instrumentation	By default, microfluidic chips are supported by external instrumentation pumps, temperature control, instrument control, sensors etc.
Complex manufacturing	expensive instrumentation and highly specialized personnel
Side-effects of scaling down	Unforeseen surface or chemical interactions, e.g. capillary forces, wall adhesion, bubble formation and **clogging**

MICROFLUIDICS

Close-up of a PDMS-glass snake mixer chip



FROM MICROELECTRONICS TO MICROFLUIDICS

1959
Richard Feynman – ”There’s plenty of room at the bottom”

1960s
Microelectronic IC

1970s
MEMS

1980s
Microflow sensor, microvalves, micropumps

1990s
Microfluidics

MILESTONES

1970–1990

Essentially nothing (apart from the Stanford gas chromatographer)

1990

First liquid chromatograph (Manz et al)
μTAS concept (Manz, Graber, Widmer, Sens.Actuator, 1991)

1990–1998

First elementary microfluidic systems (micromixers, microreactors, separation systems,..)

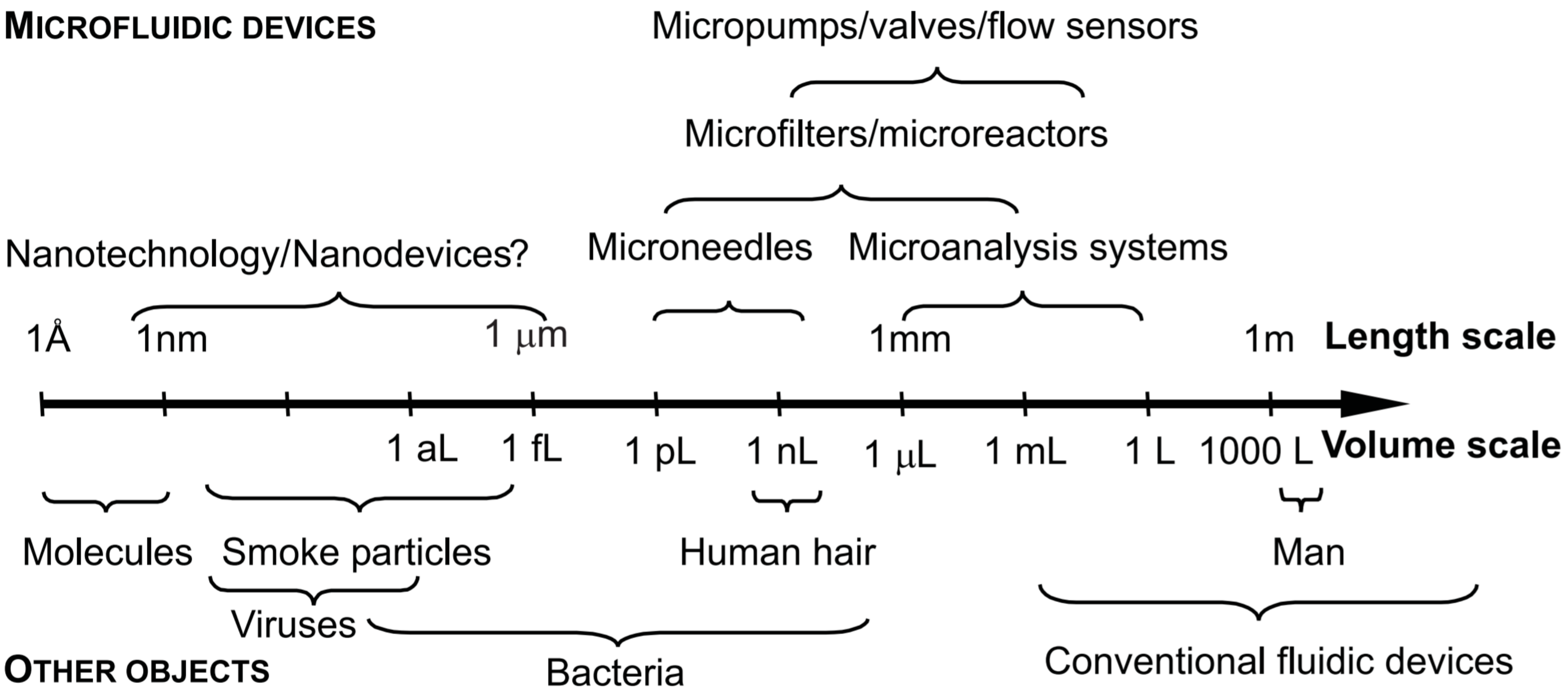
1998–2004

Appearance of soft lithography technology, which fostered the domain. All sorts of microfluidic systems with various levels of complexity are made, using different technologies

MICROFLUIDICS

„Microfluidics covers the science of fluidic behaviors on the micro/nanoscales and the engineering of design, simulation, and fabrication of the fluidic devices for the transport, delivery, and handling of fluids on the order of microliters or smaller volumes"

It is the science and technology of systems that process or manipulate small (10-9 to 10-18 liters) amounts of fluids, using channels with dimensions of tens to hundreds of micrometers.



TALTECH TALLINN UNIVERSITY OF TECHNOLOGY

Fundamentals and Applications of Microfluidics. By Nam-Trung Nguyen, Steven T. Wereley. 2002

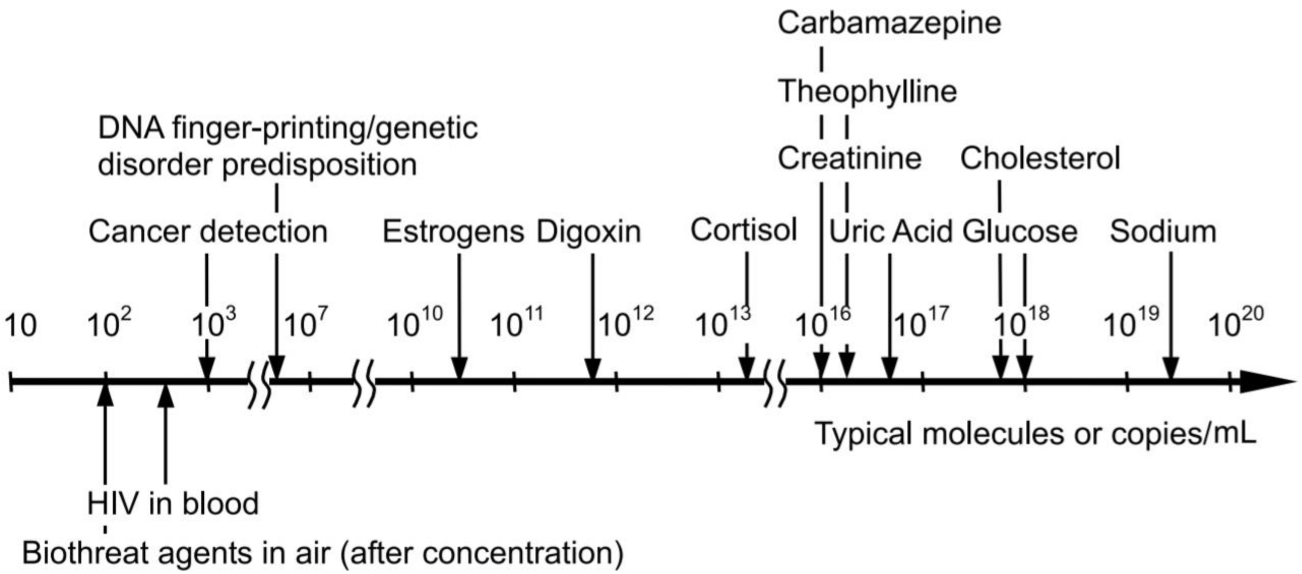
MICROFLUIDICS

Relation between sample volume and analyte (target to be detected) concentration

$$V = \frac{1}{\eta_S N_A A_i}$$

$V:$ *sample volume* (m^3)
$\eta_S:$ *sensor efficiency* $\in]0;1[$
$N_A:$ *Avogadro number* $= 6.02 \cdot 10^{23} \left[\frac{1}{mol}\right]$

$A_i:$ *analyte concentration* $\left[\frac{mol}{m^3}\right]$



Concentrations of typical diagnostic analytes in human blood or other samples. (*After*: [7].)

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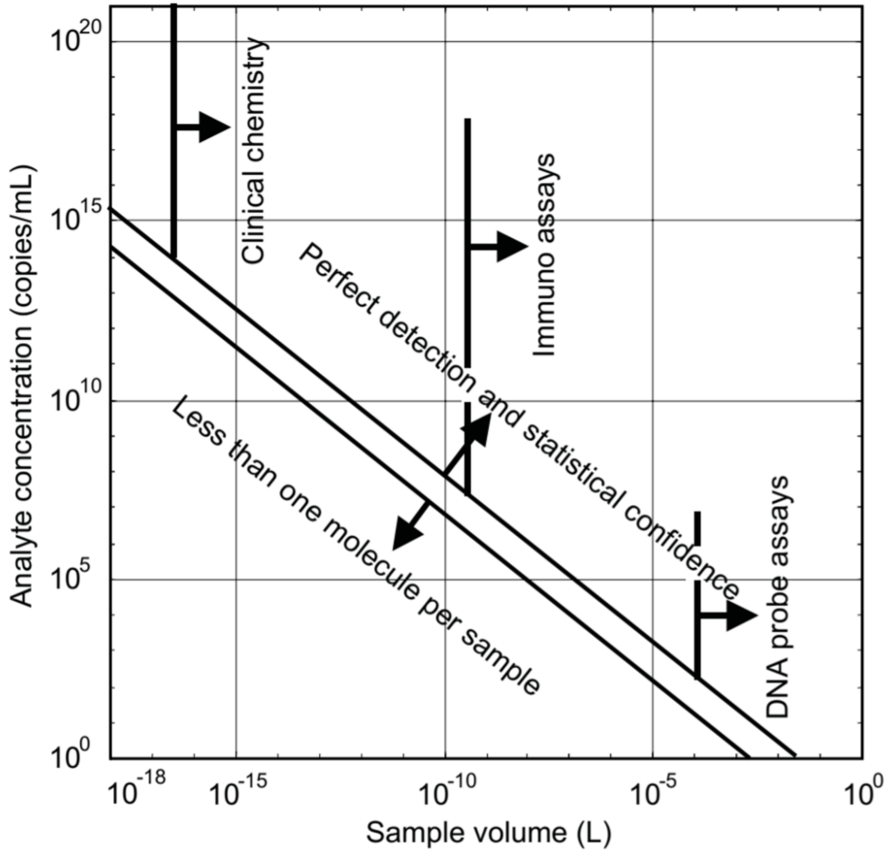


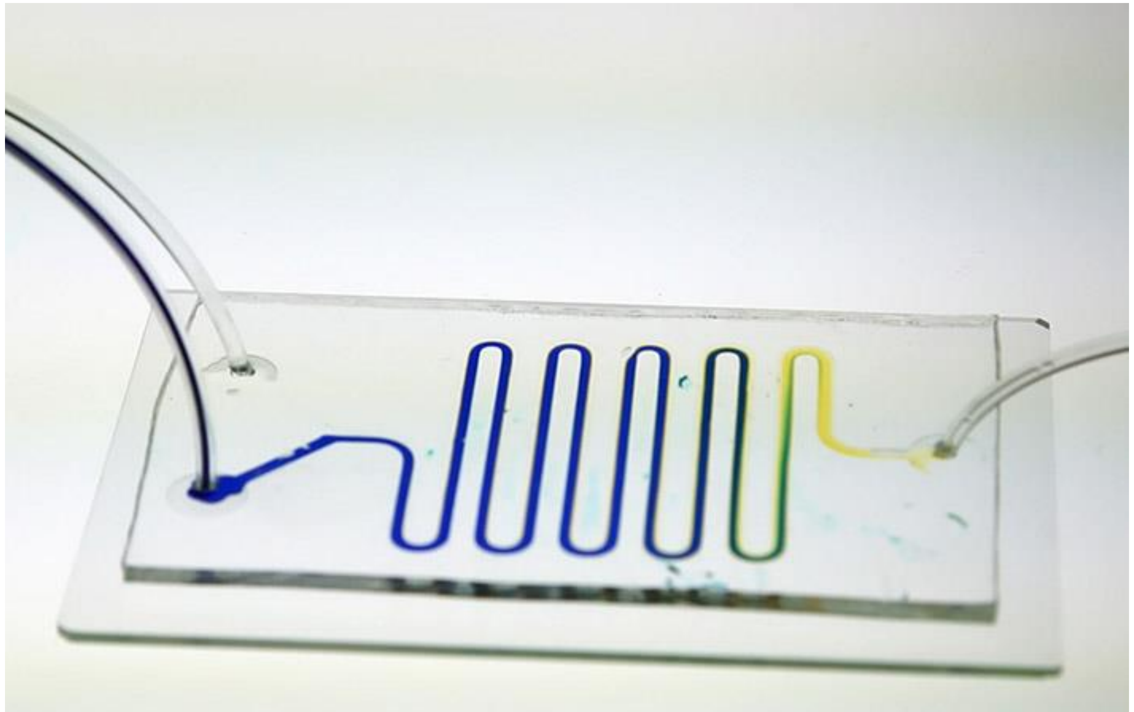
The required analyte concentration/sample volume ratio for clinical chemistry assays, immunoassays, and DNA probe assays.

Fundamentals and Applications of Microfluidics. By Nam-Trung Nguyen, Steven T. Wereley. 2002

BRANCHES OF MICROFLUIDICS

Continuous flow microfluidics

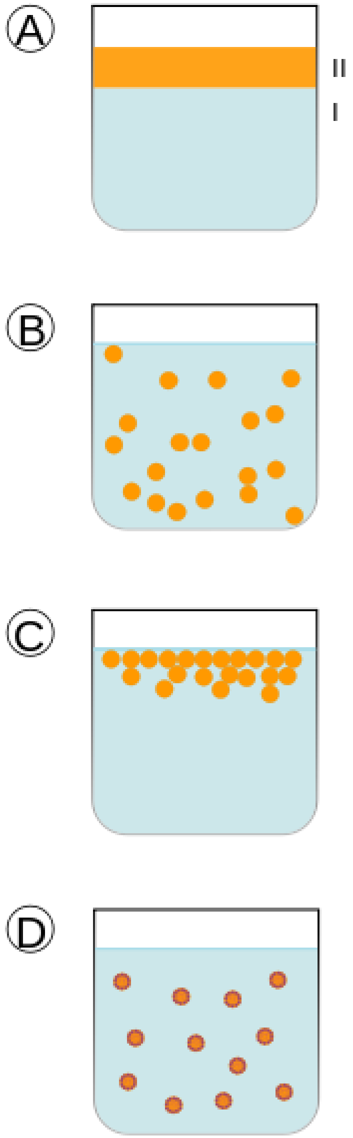
- Constant, regular, continued flow
- Enables to manipulate continuous flow of liquid through microchannels
- Pumps: external pressure pumps or integrated mechanical micropumps.
- Applications: bioanalytical, chemical, energy and environmental fields.

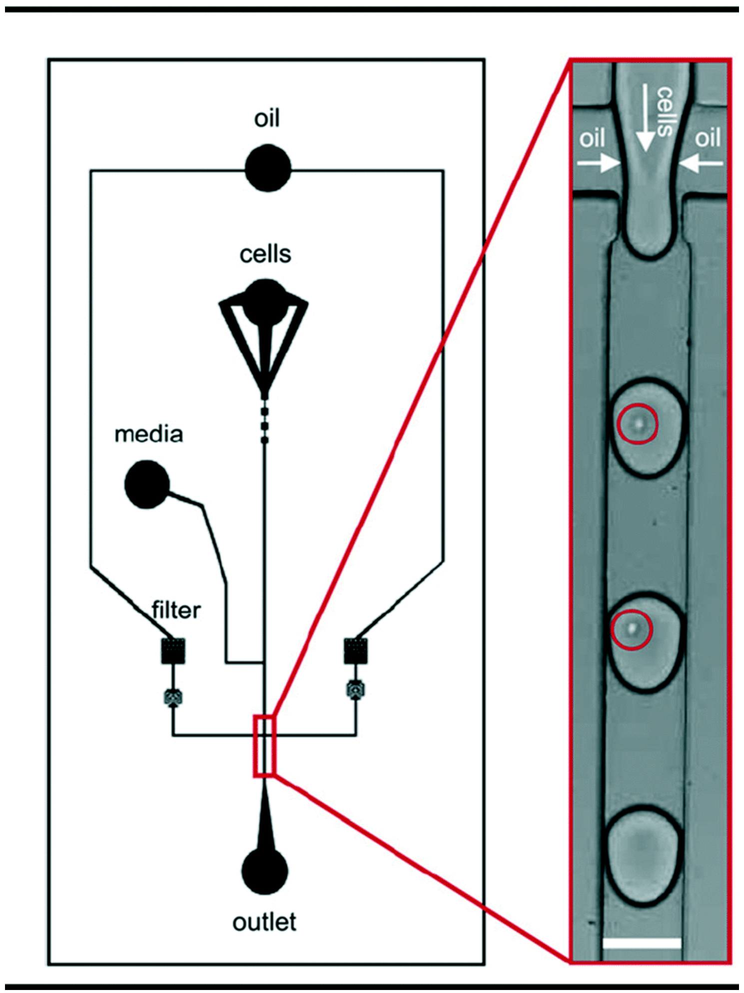


BRANCHES OF MICROFLUIDICS

Discrete/droplet microfluidics

- Aka. **emulsions: typically of immiscible liquids mixed together** (e.g. oil + water)
- Fluid is discretized into physically separate phases by hydrodynamic focusing, forming droplets in a continuous phase (two-phase flow, typically water droplets in oil)
- Applications: synthesis of nanoparticles, single cell analysis, encapsulation of biological entities
- Each droplet can have different reagents, as they are disjunct from one another

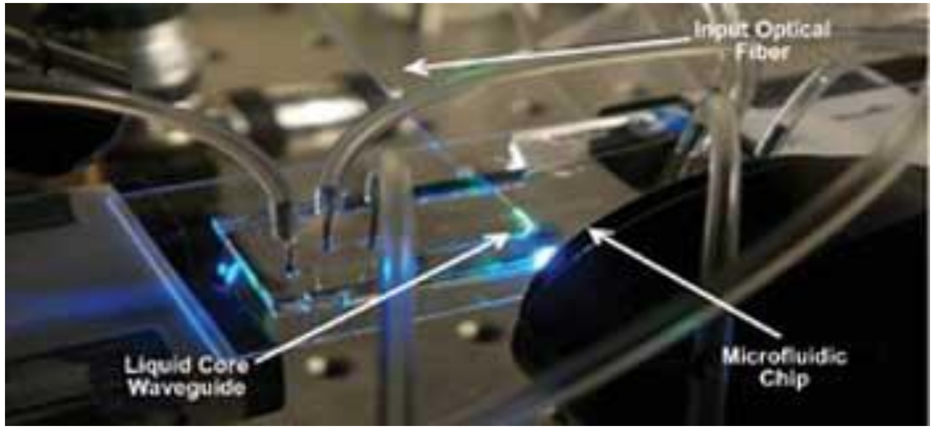


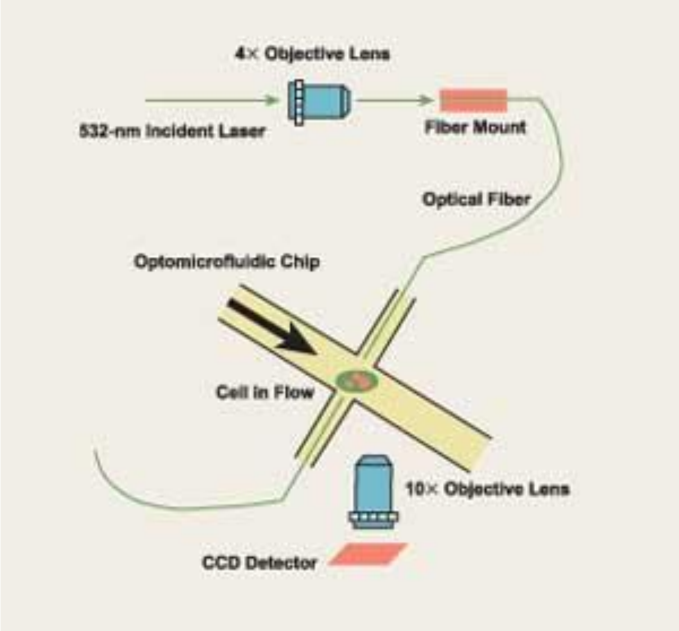


BRANCHES OF MICROFLUIDICS

Optofluidics

- Emerging fast-growing field combining microphotonics, optics and microfluidics
- **Optofluidics merges light and liquids** into miniaturized optical devices that take advantage of the properties of fluids to generate high precision and flexibility
- Optofluidic applications: lab-on-chip devices, fluid waveguides, deformable lenses, microdroplets lasers, displays, biosensors, optical switches or molecular imaging tools.



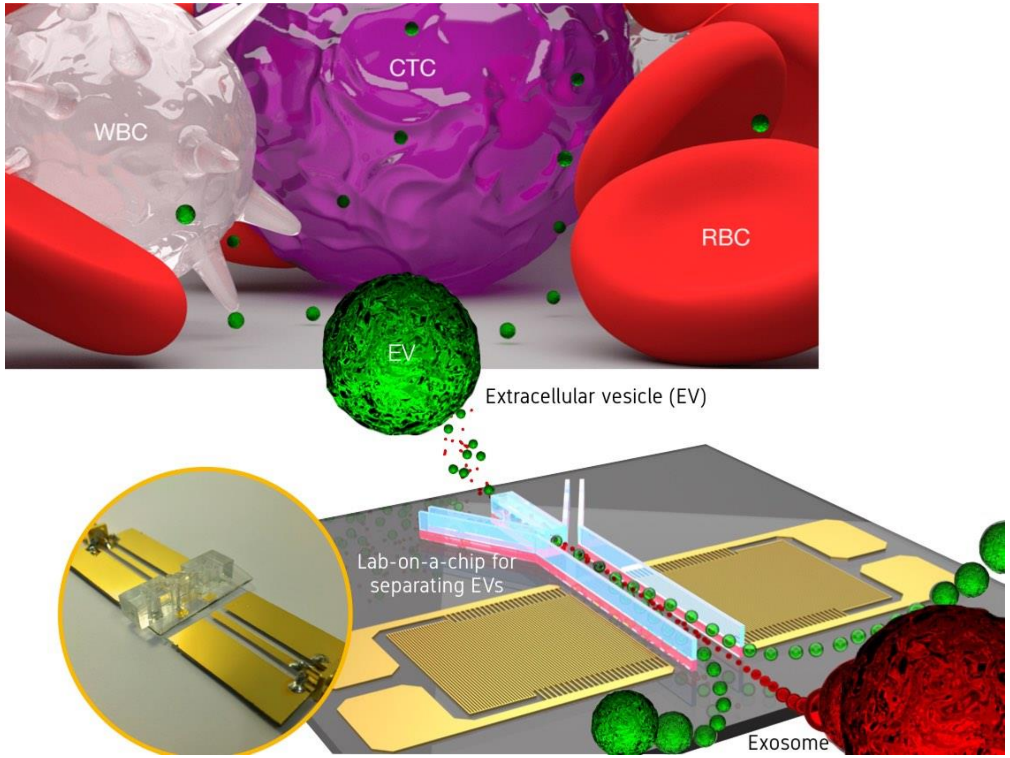


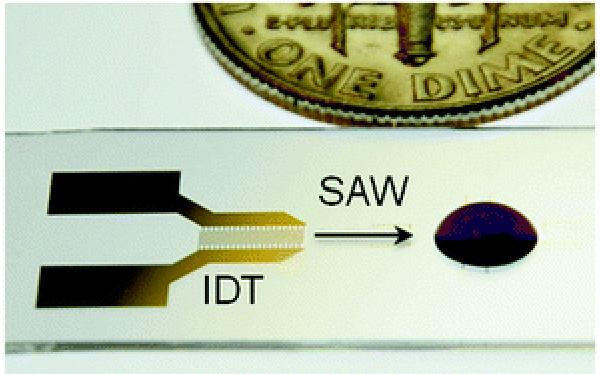
https://www.photonics.com/Articles/Optofluidics_and_the_Real_World_Technologies/a47300

BRANCHES OF MICROFLUIDICS

Acoustofluidics

- Acoustofluidics is the **integration of ultrasonic waves with microfluidic systems** to manipulate fluids and particles in microscale flows.
- Advantages: simple fabrication, high biocompatibility, versatility, compact and inexpensive devices and accessories, fast and effective fluid actuation, contact-free and non-invasive particle/cell manipulation, and compatibility with other lab-on-a-chip components





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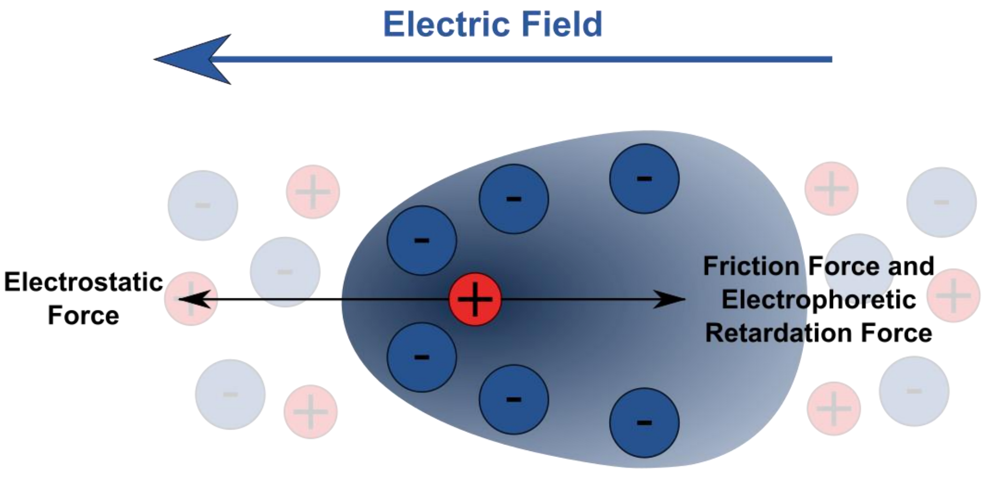
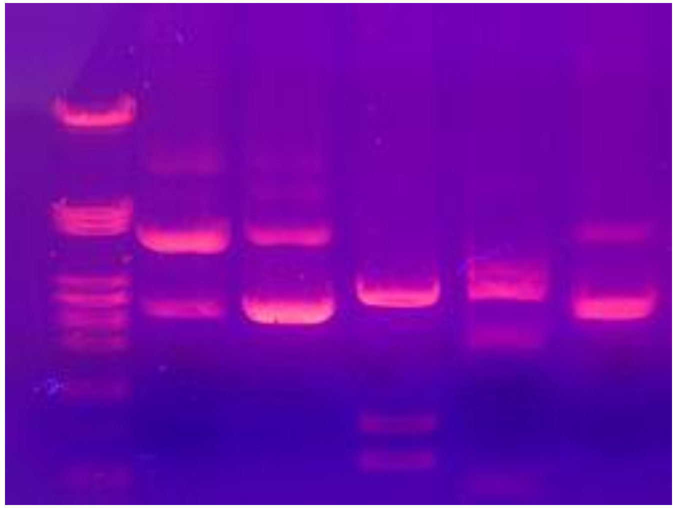
https://www.ntnu.edu/acoustofluidics
http://acoustofluidics.pratt.duke.edu/research/overview-acoustofluidics
https://pubs.rsc.org/en/content/articlelanding/2013/lc/c3lc50361e#!divAbstract

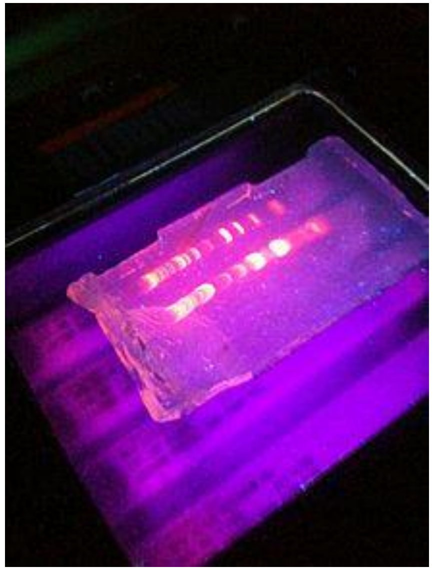
BRANCHES OF MICROFLUIDICS

Electrophoresis

- Electrophoresis is a technique used in clinical and research laboratories in order to separate molecules based on their size, electrical charge and shape.
- Electrophoresis **rests on the movement of ions in an electric field**.
- Electrophoresis of positively-charged ions is called cataphoresis, while electrophoresis of negatively-charged particles is called anaphoresis. This method is used for both DNA and RNA analysis.







FUTURE PERSPECTIVE IN HEALTHCARE AND MEDICINE

- Decentralized diagnostics
- Continuous monitoring and home diagnostics
- Integration with the medical Internet of Things
- Shorter time from test to result
- Access to state-of-the-art diagnostics in developing countries

LAB-ON-A-CHIP AND MICROFLUIDICS

- Lab-on-a-Chip and microfluidics
- Relevance to modern industry
- Application areas
- Microfluidics and its applications
- Comparison to traditional instrumentation
- Limitations
- Future perspective

12.01.2022

IEE1860 BIOMEMS

Contact: tamas.pardy@taltech.ee

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self diagnostics

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