Recent Achievements in Point-of-Care Diagnostics

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Data Science Applications in Physics
Balkan School in Tirana 2024

Contents

-Applied Nanotechnology Research Group, Saxion UAS

-Diagnostics, Nanotechnology-based sensors

-Photonic biosensors

-Examples with applications of biosensors

-Future developments for Point-of-Care testing

-Conclusions

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Saxion University of Applied Sciences

-one of the largest institutions of higher education in the Netherlands (3 locations: Enschede, Deventer & Apeldoorn)

-~27,000 students (3,500 int., 74 nationalities), 2,800 employees

-research areas:
Areas & Living, Health & Wellbeing, Smart Industry

-interdisciplinary and practice-oriented research

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NanoBio

Applied NANO TECHNOLOGY

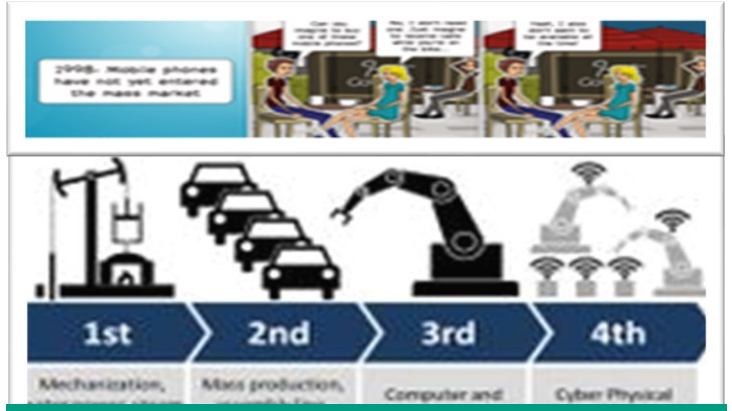
Applied Nanotechnology Research Group

-Applied research at the interface of micro- and nanotechnology and life sciences

Molecular Sensing Technologies

Lab/Organ-on-a-Chip Technologies

Nanostructured Surfaces & Nanomaterials



Societal Embedding of Nanotechnology

NanoBio

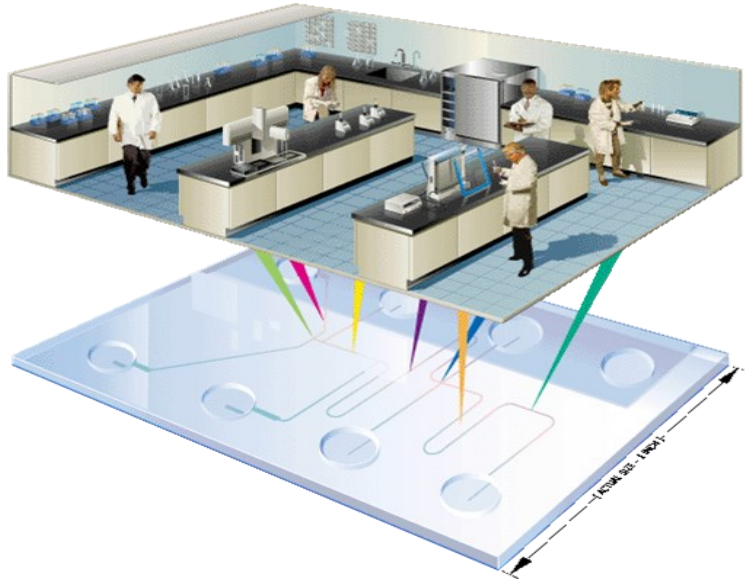
Applied NANO TECHNOLOGY

Molecular Sensing Technologies

-Sensitive and specific detection of various analytes

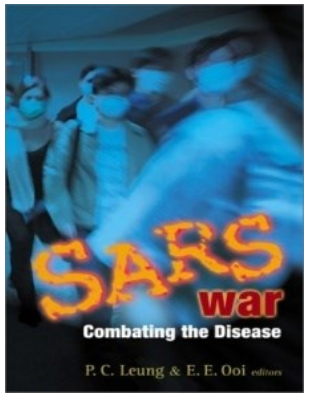
-Development of demonstrators for specific applications

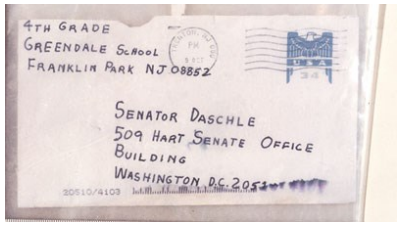
-Medical diagnostics, food safety, environmental monitoring



Introduction

- Market Pull: High need for rapid/sensitive detection methods:





=> Rapid/sensitive tests using Photonic Biosensors

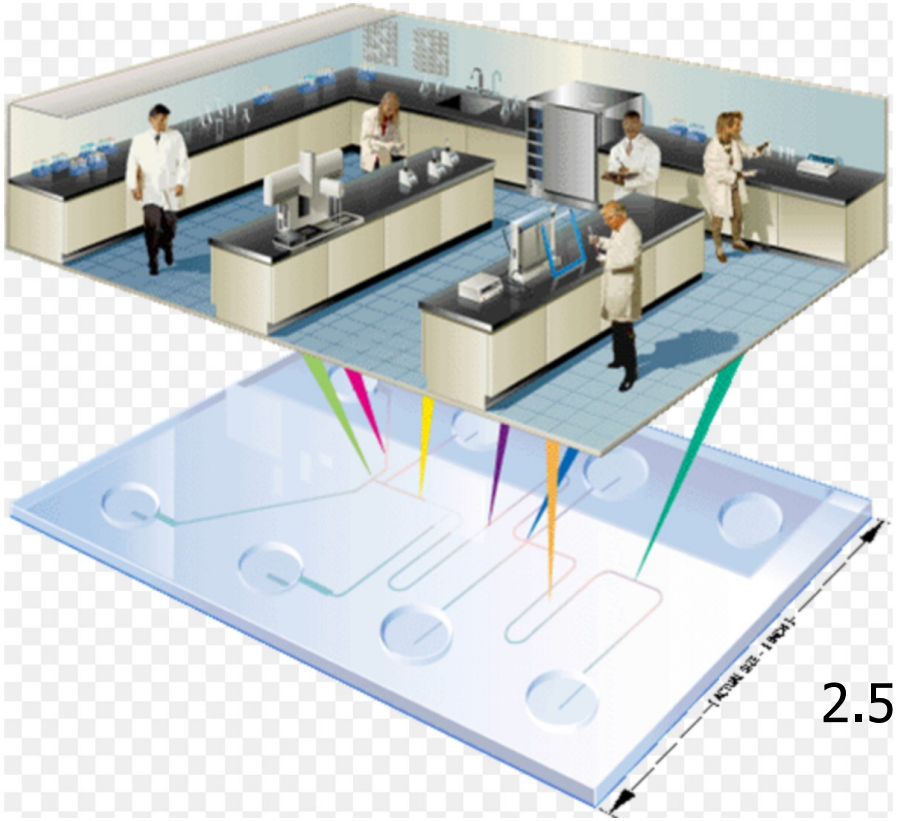
Applied NANO TECHNOLOGY

Introduction

- Technology push: Lab-on-a-Chip & Nanotechnology

Lab

Chip



2.5 cm

=> Point-of-Care testing using Handheld Devices

Applied NANO TECHNOLOGY

Introduction

Biosensors

The ultimate biosensor should be able to measure:

-specific bacteria, viruses, biomarkers (protein/DNA), etc

-in a complex medium (blood, serum, saliva, urine, milk, etc)

-at very low concentrations, yet with very high resolution

-on site and real-time: Point-of-care (POC)

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Introduction

Diagnostics Requirements

-high sensitivity: low concentration

-good specificity: analyte of interest

-rapid test: on-line (real-time) monitoring

-multiplexing capability: several analytes (panel testing)

-stand-alone operation: portable/handheld device

-at site / in-line monitoring

-low cost of production & operation: affordable

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Introduction

Diagnostics Market

Global market for diagnostic disposables amounts > $ 40 billion

- In vitro diagnosis on basis of antibodies (immuno-assays): US$ 8 billion p.a. in 2006

- In vitro (human) diagnostics DNA (PCR) market: ~ US$ 5.4 billion in 2008

- World market food safety tests ~ US$ 5 billion in 2011

- Using LOC Biosensors these billion dollar global markets are being addressed: these markets grow with at least 8% c.a.g.r.

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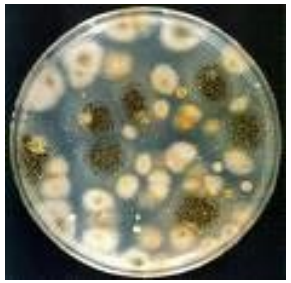
Introduction

Current Detection Methods

Plate count:

-bacteria growth in petri dish

-days to achieve results



ELISA:

-sample preparation

-hardware cost > 200k€

-hours to obtain results

PCR:

-hardware cost > 50k€

-intensive sample preparation

-hours to obtain results

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Introduction

Current Detection Methods

Disadvantages:

-labor-intensive and expensive

-time consuming (need hours to days)

-requires specialized lab & trained personnel

-not suitable for Point-of-Care testing (POCT)

New technology is needed:

-faster and affordable tests

-possibility for hand-held devices

-suitable for POCT

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Introduction

New (Nano-) Technologies

-Nanowires, Surface Acoustic Waves, Magnetic Beads, …

-Atomic Force Microscopy

-Raman Spectroscopy

-Rupture event scanning

=> Further investigation for development of
Point-of-Care (POC) / in-line systems is required

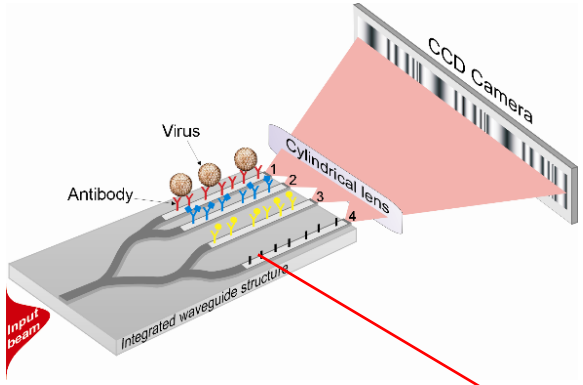
Lab-on-a-Chip Photonic Nanotechnology:

LOC Photonic (Bio)Sensors

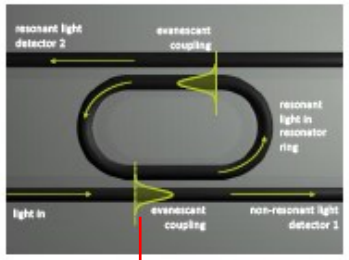
Applied NANO TECHNOLOGY

Photonic Biosensors

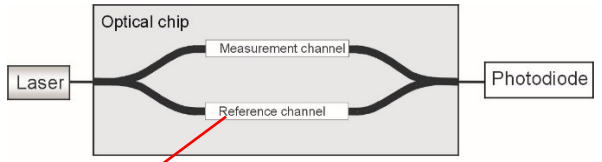
MYI

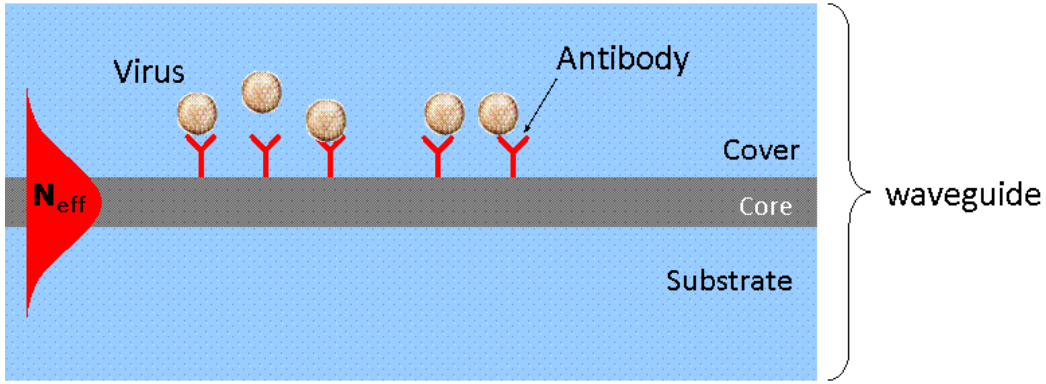


MRR



(a)MZI





Evanescent field detection principle

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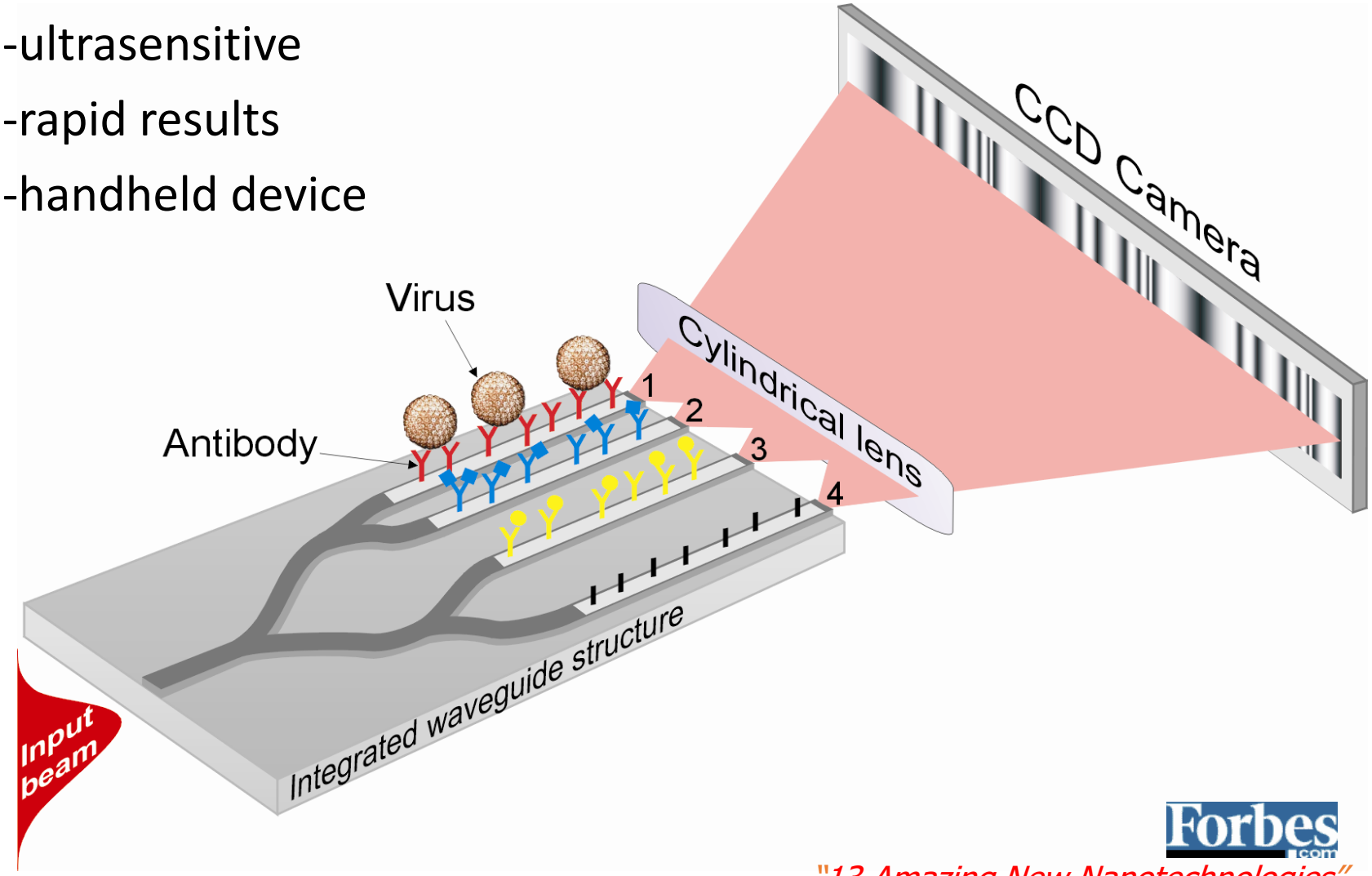
Photonic Biosensors

Multichannel Young Interferometer

-ultrasensitive

-rapid results

-handheld device

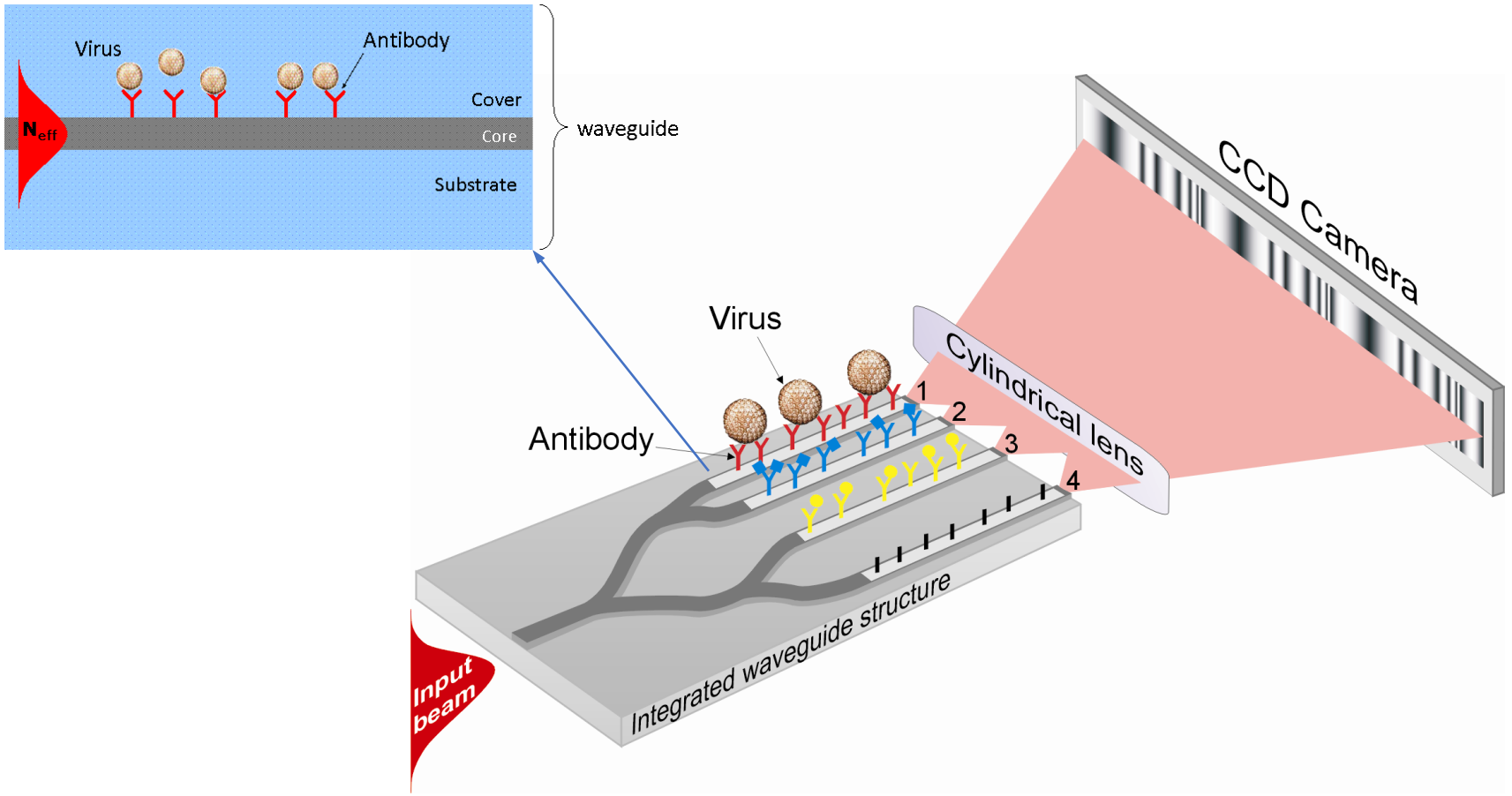


"13 Amazing New Nanotechnologies"

A. Ymeti *et al.*, *Nano Letters* 7, 394-397 (2007)

Photonic Biosensors

Evanescent field principle



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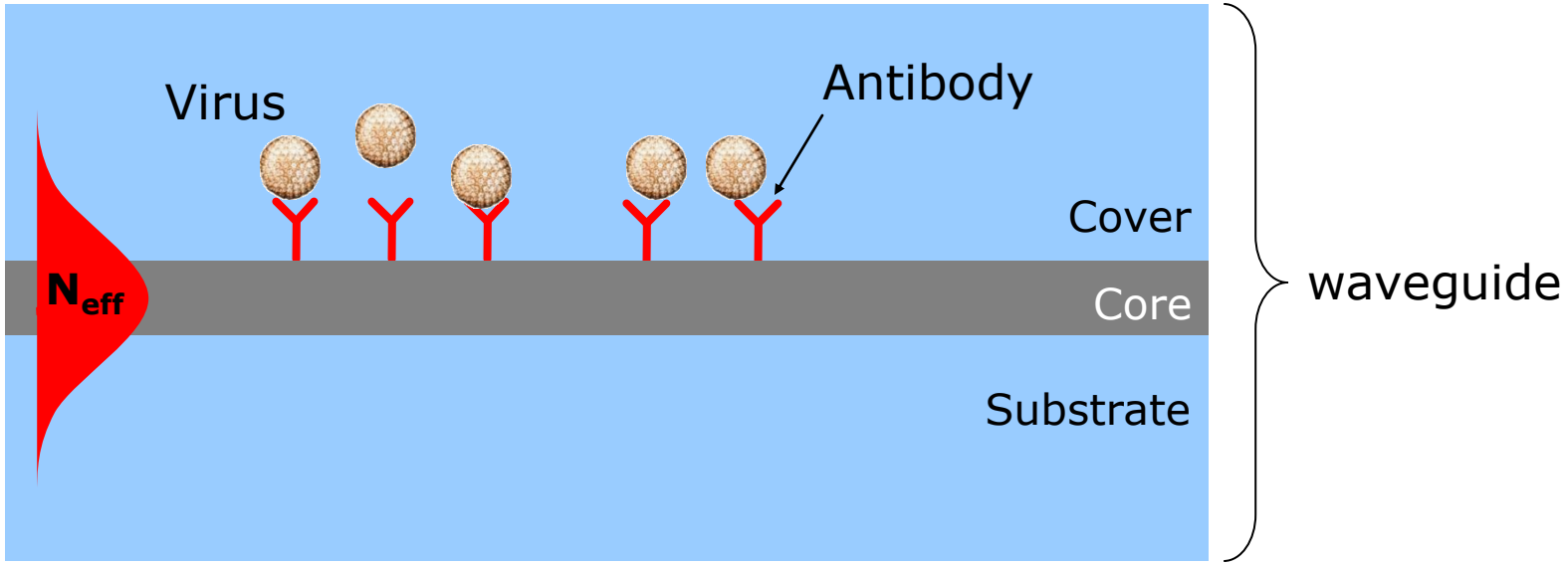
"13 Amazing New Nanotechnologies"

Photonic Biosensors

Evanescent field principle



Binding → Change of propagation speed → Δsignal

A. Ymeti *et al.*, *Sensors Act. B* 83, 1-7 (2002)

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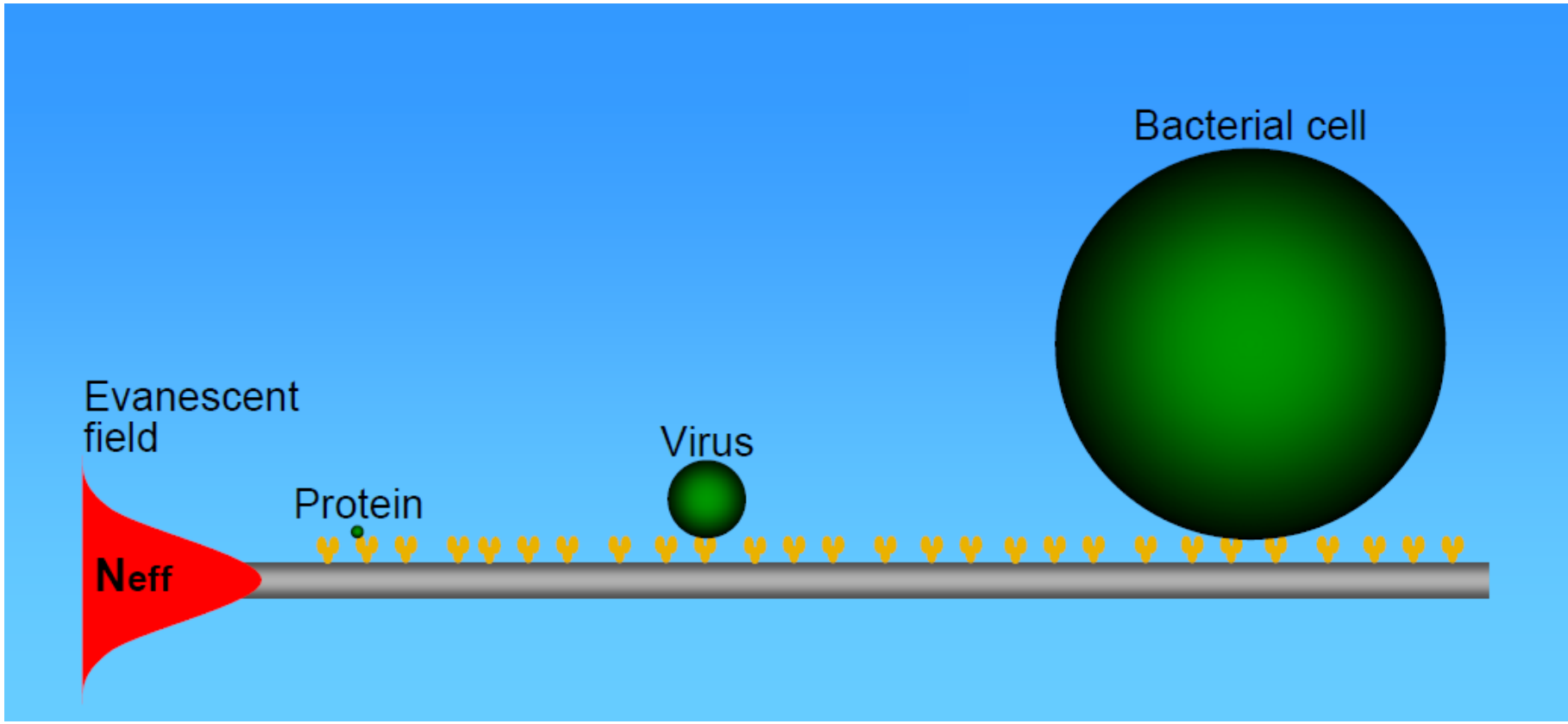
Photonic Biosensors

Analyte detection



- $S_{bact./cell} \sim 10^2 \times S_{virus} \sim 10^4 \times S_{protein}$

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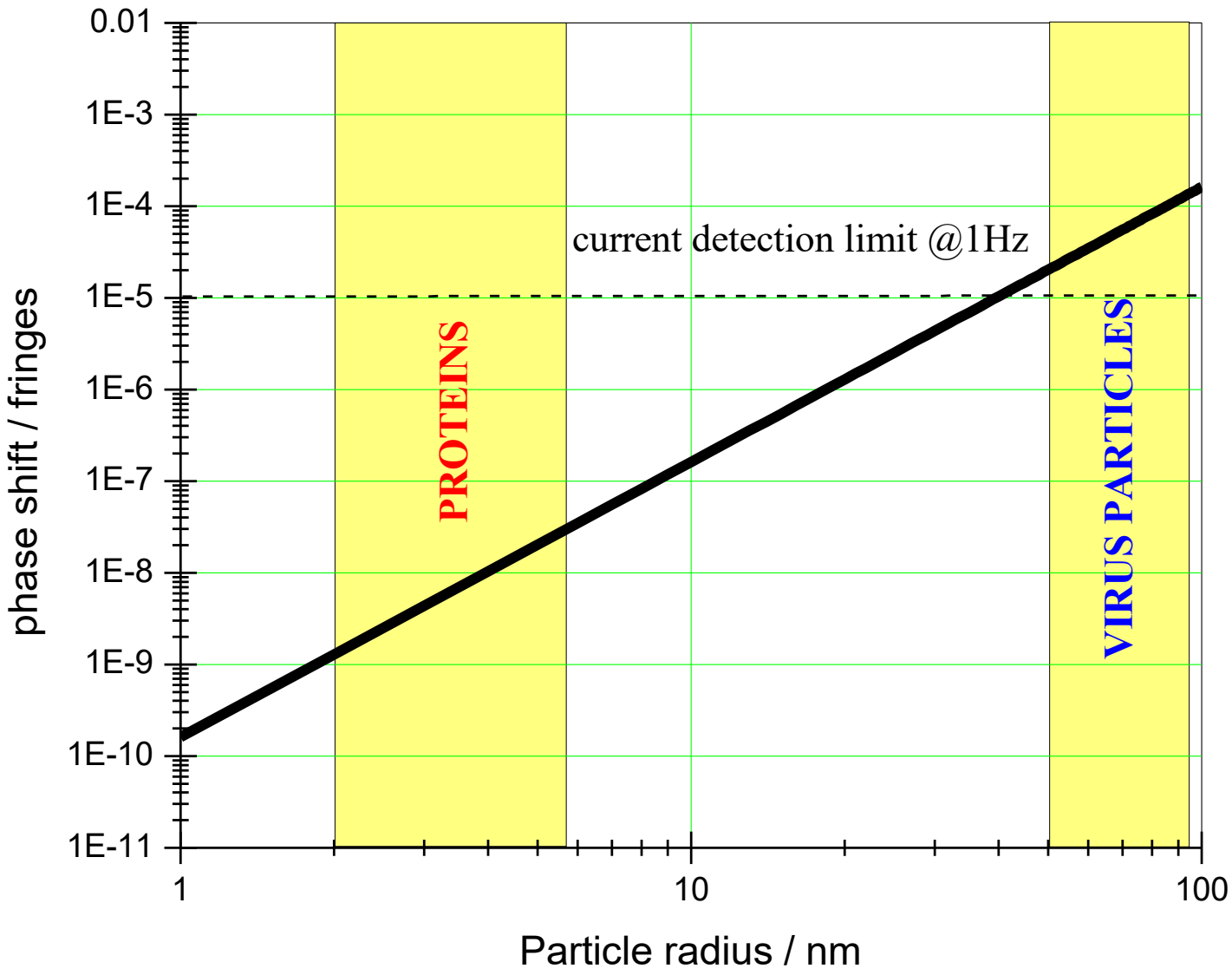
Photonic Biosensors

Analyte detection



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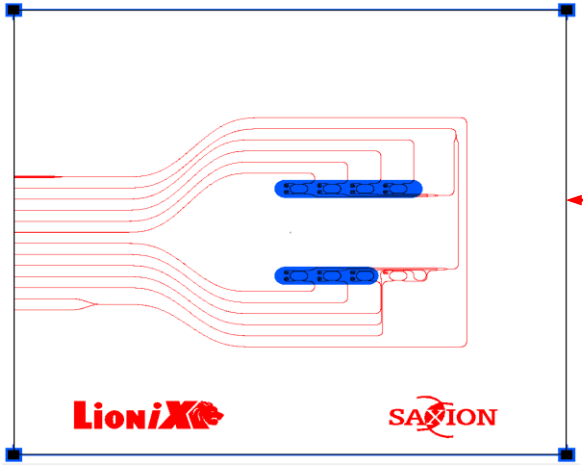
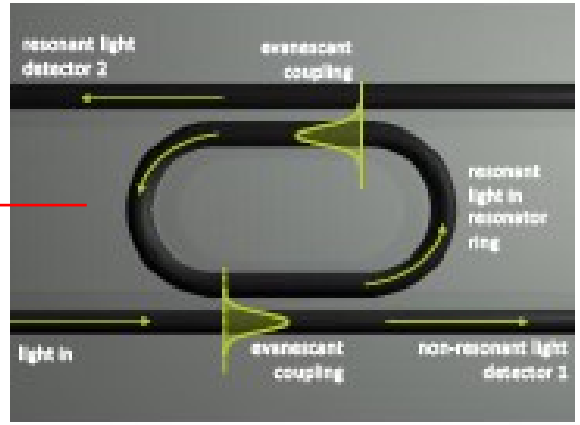
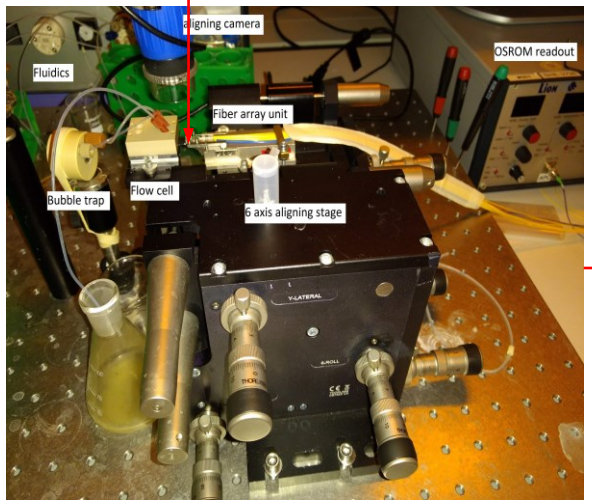
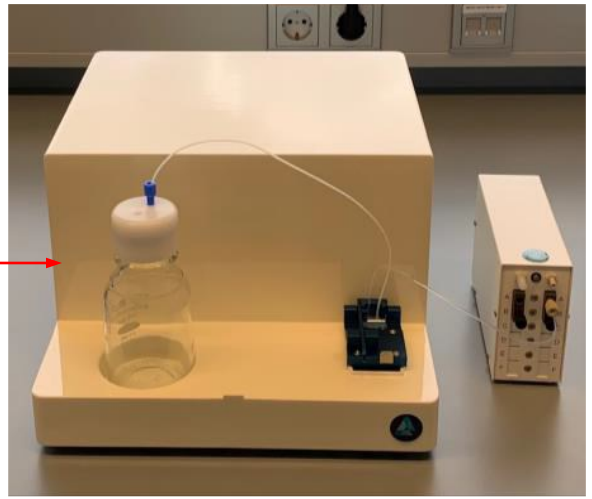
Biosensor prototypes

Microring resonator









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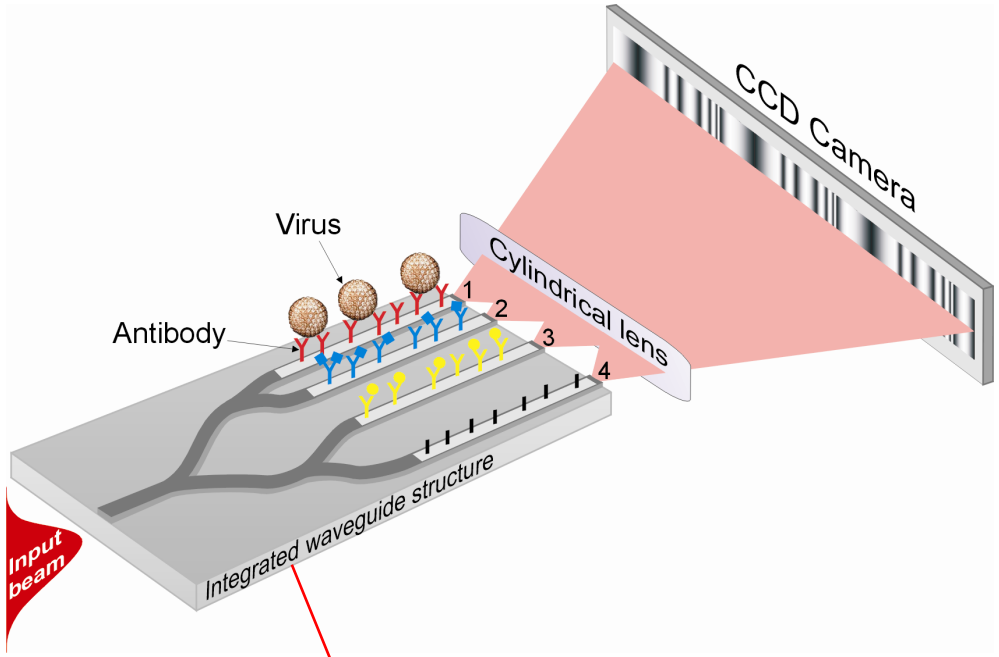
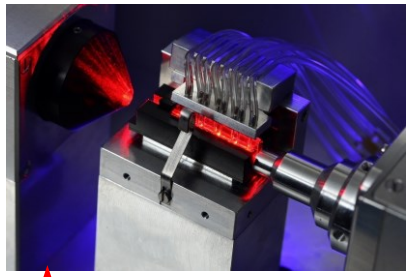
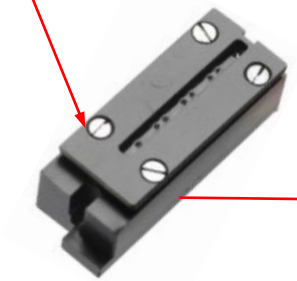
Biosensor prototypes

Multichannel interferometer



Nanotechnology at work





LOC System

Readout Detector

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Photonic Biosensors

Applications / Validations

- Early disease diagnosis: e.g. cancer biomarkers
  -high probability for disease curing
  -high-cost savings
  -improve patient life
- Rapid POC testing: LIFESAVER, e.g. TBI biomarkers
- Food safety: bacteria (Salmonella, Listeria, etc)
- National security: viruses

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Photonic Biosensors

Validation Strategy

-selection of proper receptors to achieve high specificity

-optimization of chip coating to achieve high sensitivity

-measurement of ≠ analyte conc's for sensor calibration

-benchmarking with gold standard methods: ELISA, PCR, etc.

-testing with clinically relevant (patient) samples

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Photonic chip coating

bioanalytics xantec

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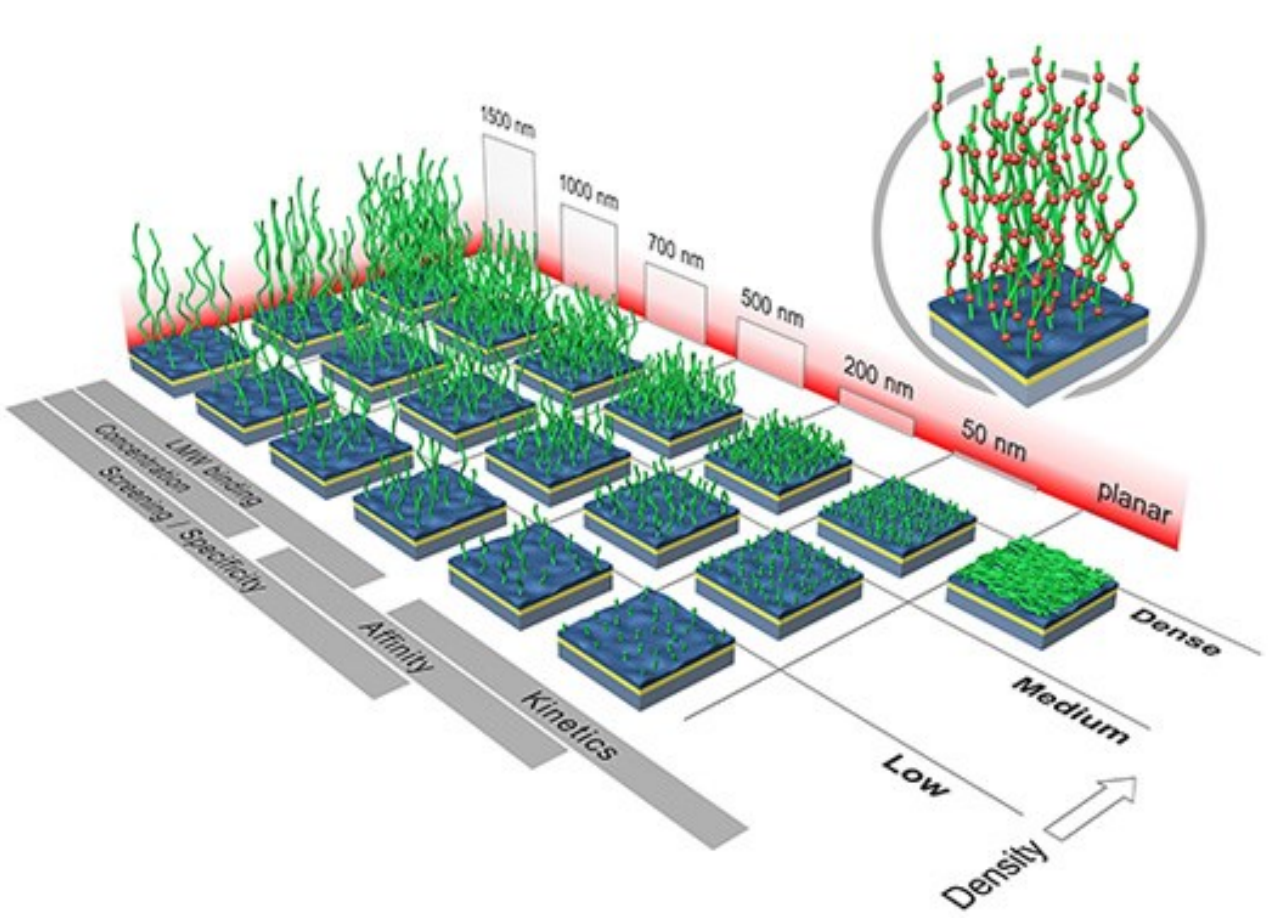
Chip surface functionalization



NanoBio Lab

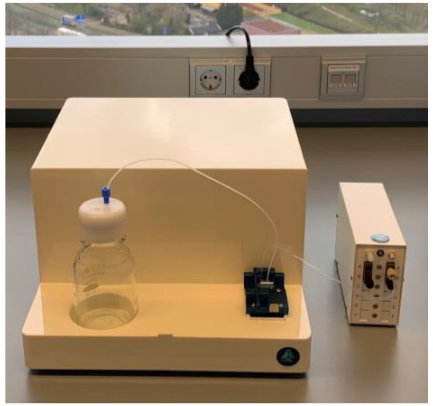
1. ELISA
2. Spotter (chip coating)
3. SPR instrument
4. Photonic biosensor prototypes: MRR, (a)MZI & MYI

1

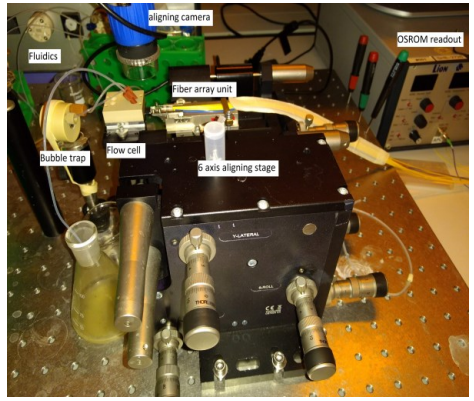
2

3

4 (MRR)



4 (MZI)



4 (MYI)

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Project examples

PHOBIOSENS:
Rapid detection of antibiotics in milk using photonic biosensors

COVISENS:
Rapid, accurate SARS-CoV-2 virus Detection at the POC settings

DIAMOND2 / DIASENS:
Sensitive detection of insulin in patient samples for early diagnosis of diabetes

BVD-SENS:
Rapid diagnosis of BVD-virus in milk using photonic biosensors

GLUCOSENS:
A new glucose sensor for artificial pancreas

PHOBIO SENS

COVISENS

DIAMOND2

BVD-SENS

GLUCOSENS

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DELTA DIAGNOSTICS

MEDLON
a Unilabs company

COVISENS

Rapid COVID-19 Detection with Photonic Biosensors

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COVISENS

COVID-19 Pandemics

Gold standard methods based on PCR:

Specific and accurate, but time- and labor intensive, expensive, require trained personnel and specialized lab: 24-48 hrs

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COVISENS

COVID-19 Pandemics

Rapid methods based on lateral flow test:

-rapid and easy-to-use
-less specific and accurate, especially at low viral loads

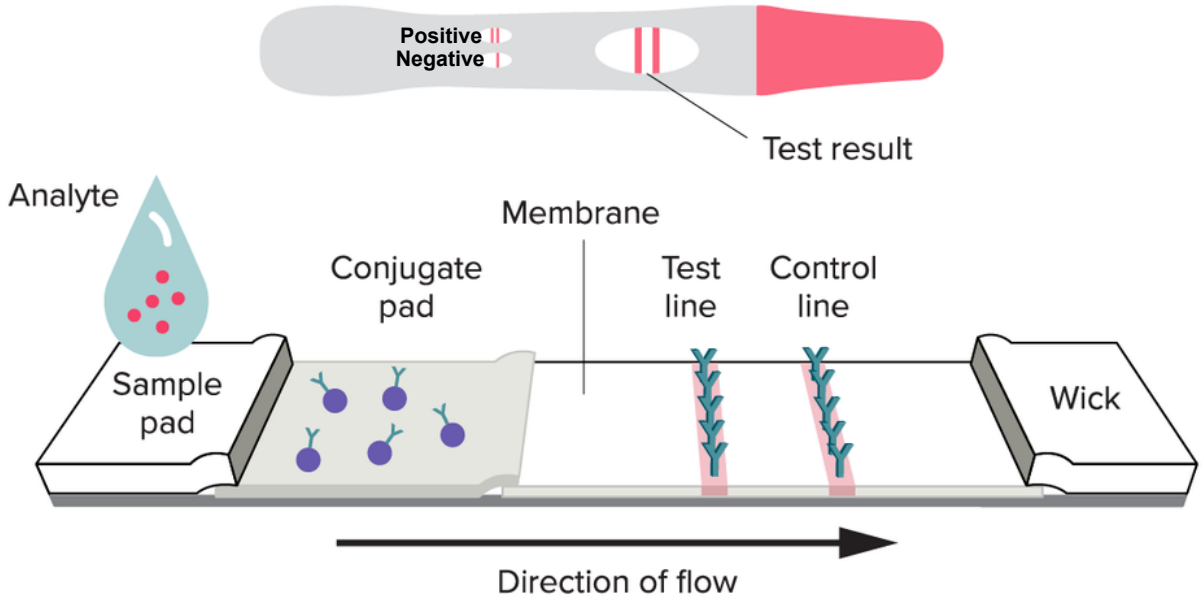

Figure 2: Schematic overview of a lateral flow test

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COVISENS

Abbott PANBIO COVID-19 AG rapid test

Claims: 98,1% sensitivity, 99,8% specificity

In reality: 71,4% sensitivity, 99,8% specificity

Journal of Infection
Volume 82, Issue 3, March 2021, Pages 391-398

Roche SARS-CoV-2 Rapid Antigen Test

Claims: 83,3% sensitivity, 99,1% specificity

In reality: Medium (Ct 25-<30), 50%-95%

Journal of Virological Methods
Volume 288, February 2021, 114024

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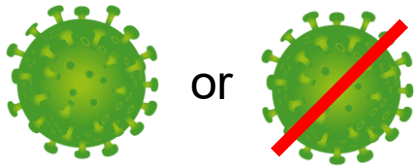
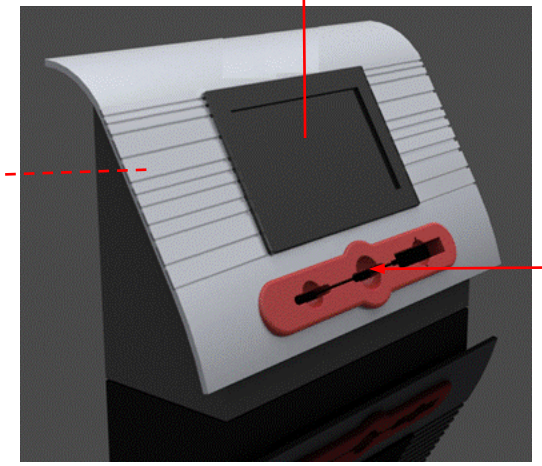
Final Goal

Portable/Handheld Device

Handheld device
(STAR TREK Tricorder)

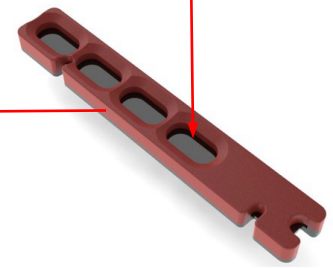
Sample analysis result





Portable Detector

Sample



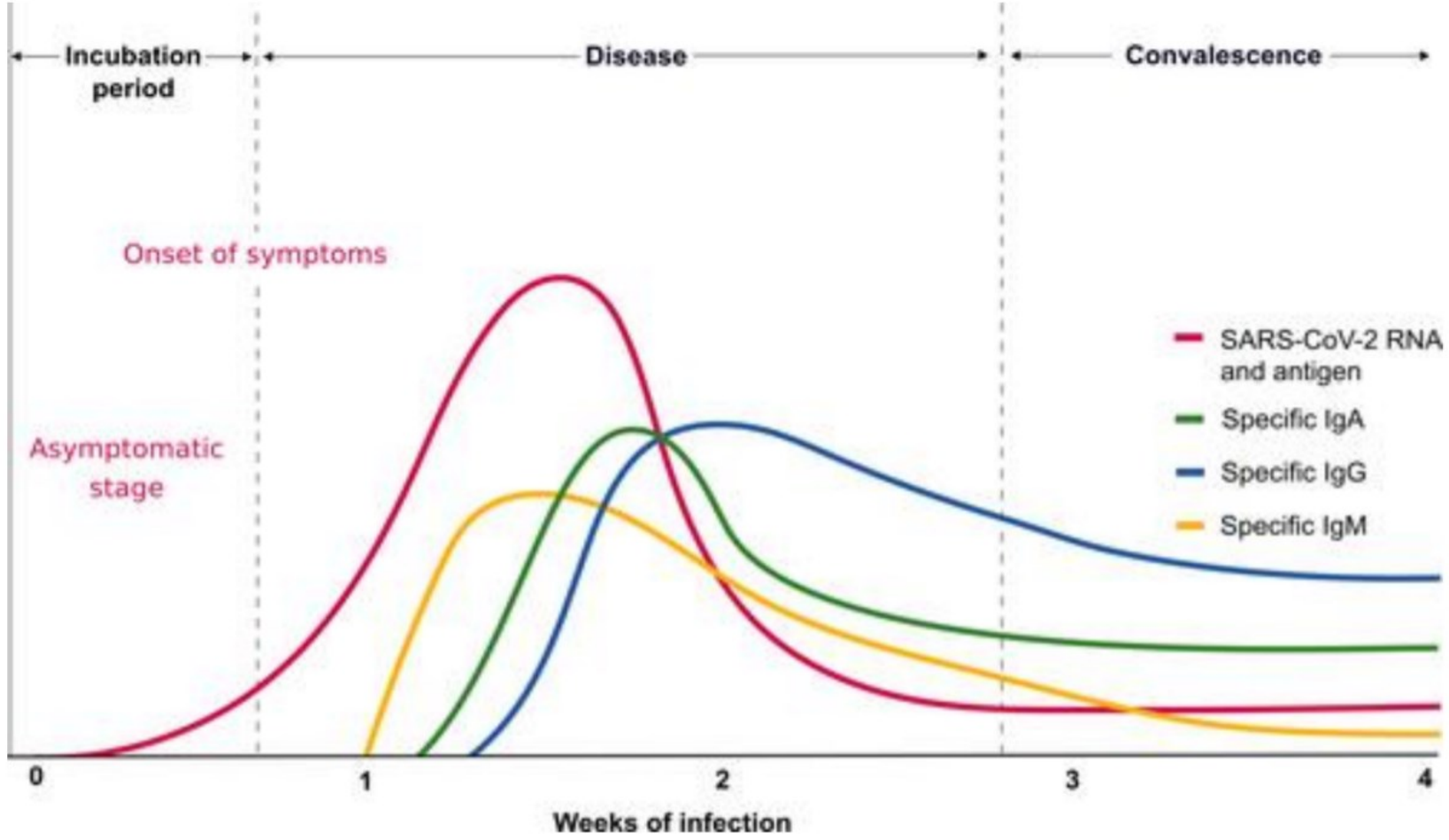
Lab-on-a-Chip system

COVISENS

Serological test

-detects Abs in (patient) serum samples

-determines previous infections, building up & immunity preservation



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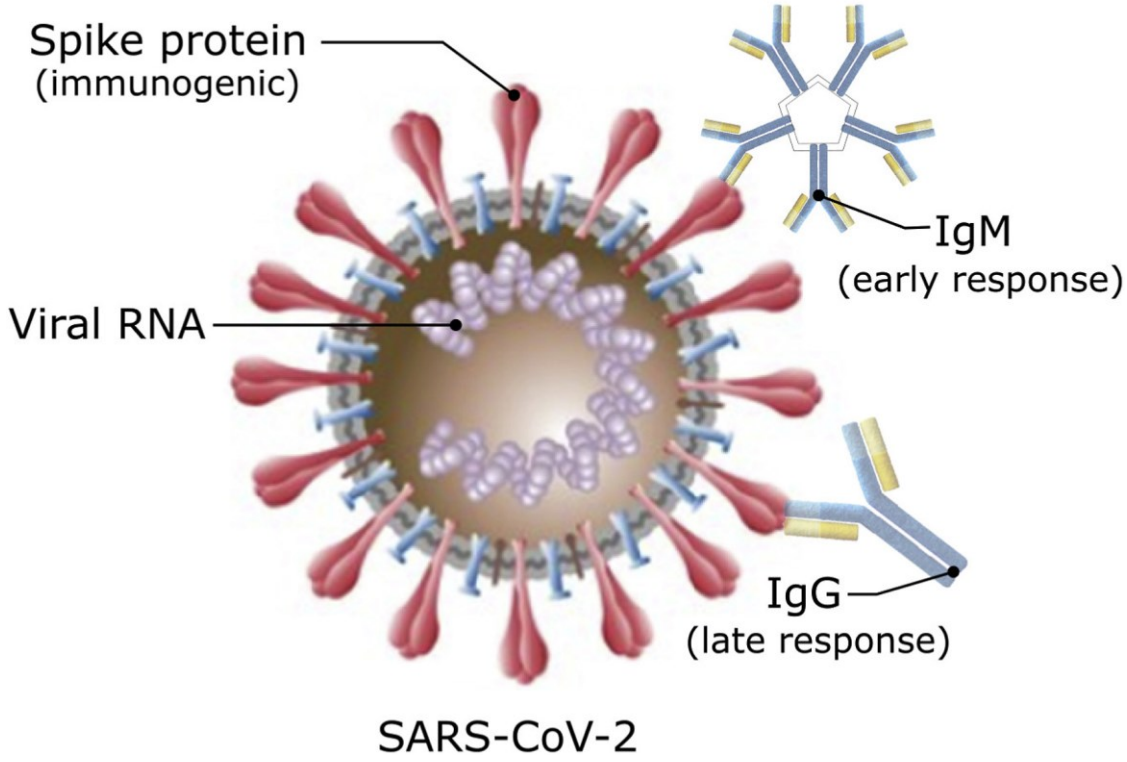
COVISENS

First Results

Detection of SARS-CoV-2 *spike protein* and/or *IgG/IgA/IgM antibodies*:



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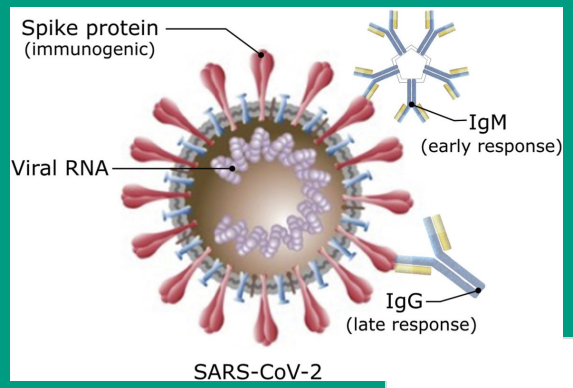
COVID-19 Antibody (IgM/IgG/IgA) test

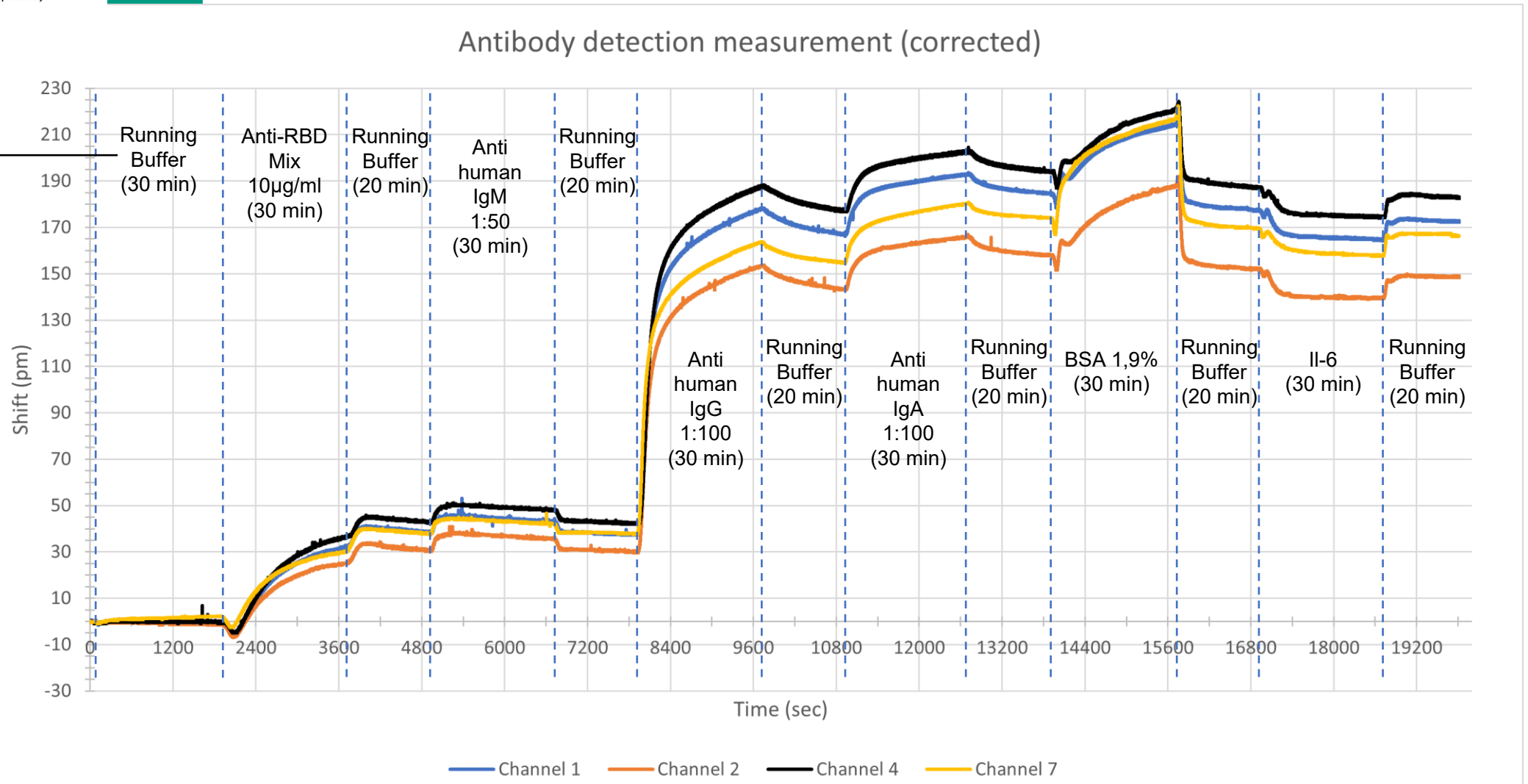


-Hydrogel (30nm) coated chip

-IgM(970kDa), IgG(150kDa), IgA(160kDa)

<u>Running Buffer:</u>
PBS:
- 137mM NaCl
- 2,7mM KCl
- 2 mM KH_2PO_4
- 8 mM Na_2HPO4

1% BSA
0,5% Casein
0,1% Tween20



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Clear.

WAGENINGEN UNIVERSITY & RESEARCH

zgt
Ziekenhuisgroep Twente

INREDA

LipoCoat

MEDLON
a Unilabs company

VIVALDI
GEZONDHEIDSCENTRUM

MIJN LEEFSTIJL OP RECEPT

micronit

MinacNed
Association for Microsystems and Nanotechnology

Diabetesvereniging Nederland

Diabetes Fonds

DIAMOND2

DIAgnosis & MONitoring of Diabetes type 2

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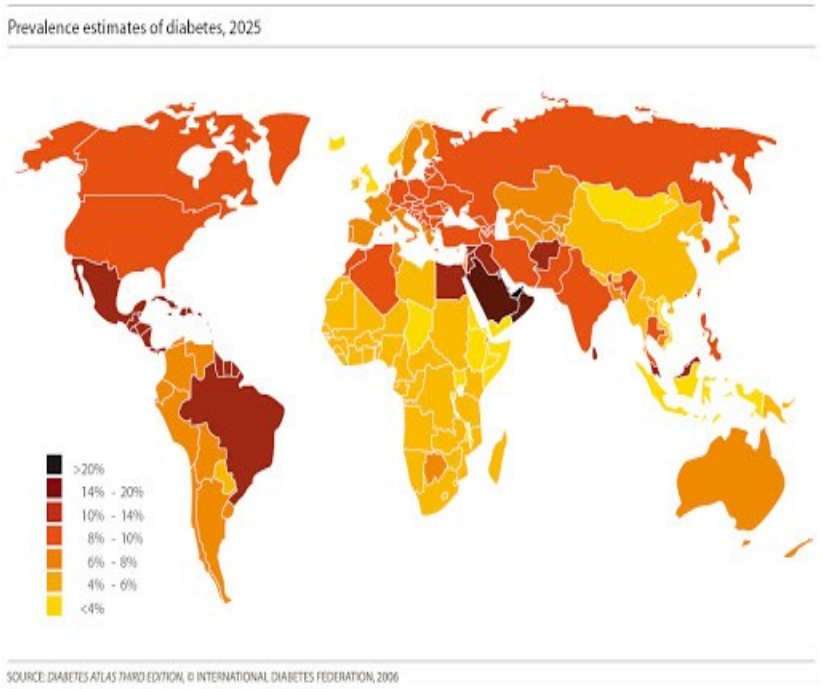
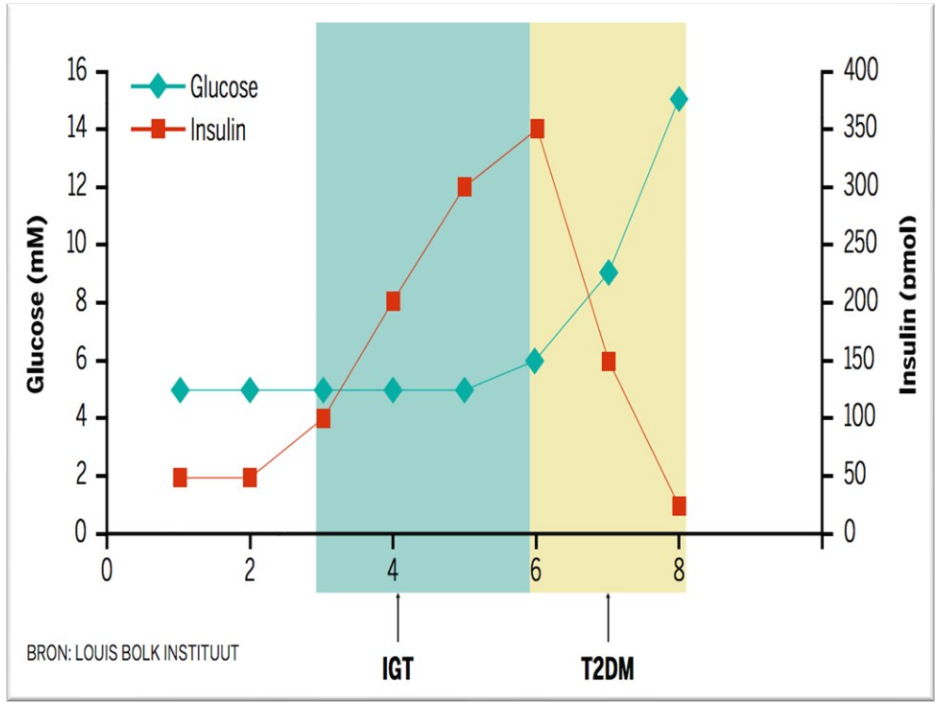
DIAMOND2

-2019, 463 M people worldwide have diabetes (17% healthcare costs!)

-prevalence rises exponentially (4x in the last 3 decades!)

-NL: half population with overweight & 1.1 M have diabetes





=> New methods for early diagnosis of diabetes are urgently required

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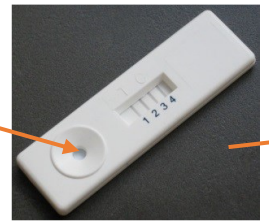
Goal

Realization of a demonstrator that can accurately and quickly determine serum/blood insulin concentrations, which can be used to warn people in risk groups for type 2 diabetes at an early stage and to encourage a healthier lifestyle (better diet, more exercise) to prevent diabetes.

End-users / patients / health professionals

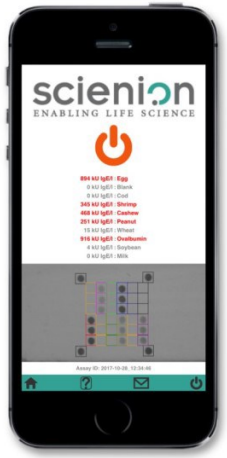
Implementation

Blood sample



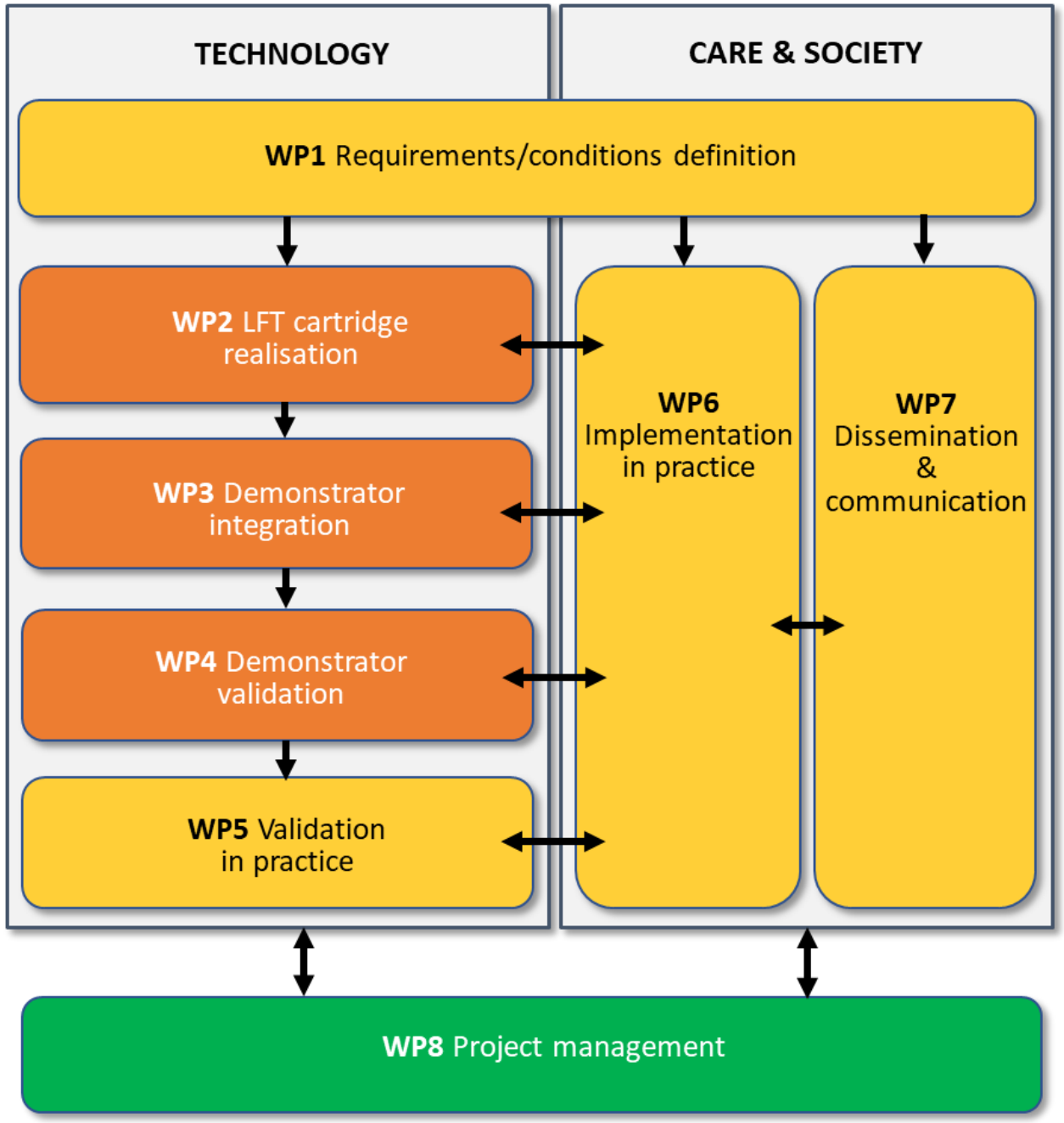
Lateral flow assay

Real-time reader



Blood analysis result

Work Packages



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Consortium Partners

Knowledge Institutions:
- Saxion, Applied Nanotechnology
- Saxion, Smart Health
- WUR, BioSensing & Diagnostics

Companies:
- Inreda Diabetic (Robin Koops)
- Micronit (Marko Blom)
- Lipocoat (Jasper de Weerd)
- Clear (Madelon Bracke)
- ZGT (Goos Laverman)
- Medlon (Hans Krabbe)

Social and other partners:
- Mijn Leefstijl op Recept (Inge Out)
- Vivaldi gezondheidscentrum (Frank Greeven)
- Diabetesfonds (Roel Nahuis)
- Diabetesvereniging Nederland (Angela de Rooij)
- MinacNed (Annerie Heesink)

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Photonic Biosensors

Conclusions

-lab is no longer needed: Point-of-Care

-much cheaper and easy-to-use

-faster: sample in/answer out, potential lifesaver

-technology for mass production: affordable chips

-biofunctionalization important for assay development

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Molecular Sensing Technologies

Conclusions

-various projects/applications defined/studied

-optical/photonic biosensor prototypes/demonstrators available

-protocols developed for chip coating & testing/validation

-biofunctionalization using hydrogels seems promissing

-POP & validation tests performed for various applications

-broad network with (inter-)national research institutions, SMEs, industry & end-users

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