Biosensing with silicon photonics

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KTH – Micro and Nanosystems

IR cameras (www.flir.com)

IR bolometer

Silicon microneedles

Transdermal drug delivery systems

Photonic ring resonator biosensors

Lab-on-a-Chip

Polymer microfluidics

RF filter

RF switch

Micro fuel cell (www.myfuelcell.se)

MEMS 3D Integration

Medical MEMS

RF/Microwave MEMS

Energy & Actuators

Micro-Optics

Microfluidics Lab-on-Chip
Outline

- Why do we need biosensors sensors?

- Biosensor definition.

- The fundamentals of photonic waveguide based biosensing

- Silicon waveguides as biosensors.

- Liquid sample handling for photonic biosensors.

- Reducing temperature sensitivity.
Why do we need biosensors?

- When intruded by a disease causing virus or bacterium, the **body releases** biomolecules called **antibodies** into the blood.
- The antibodies attach selectively to a part of the intruder called **the antigen**, to label it for attack by the immune system.

Accurate disease diagnosis requires the measurement of the concentration of these antibodies.

- The concentration is very low (ng/ml), and there are other biomolecules in blood of much higher concentration (mg/ml).

By fixing an antigen on a biosensor surface, the attachment of antibodies can be measured with high selectivity.
More applications of biosensors

• Medical diagnostics
• Drug development
• Explosives and narcotics detection
• Environmental monitoring
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• **Biosensor definition.**

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What are biosensors?

Some commercial examples:

- Attana QCM: www.attana.com
- Corning EPIC: www.corning.com
- Biacore SPR: www.biacore.com
- Roche Accu-Chek: www.accu-chek.com

- In general, biosensors are devices to characterize a chemical quantity: the analyte
- Biosensors can be used to:
  - Determine analyte concentration
  - Study the kinetics of chemical reactions of the analyte
The formal definition of a biosensor

IUPAC\(^1\) definition:

“A biosensor is a self-contained integrated device which is capable of providing \textit{selective quantitative analytical information using a biological recognition element which is in direct spatial contact with a transducer element}.”

\(^1\)IUPAC: International Union of Pure and Applied chemistry
Analytes

- Biosensors can be used to study:
  - Ions: \( K^+ \), \( Cl^- \), \( Ca^{2+} \), ...
  - Gasses: \( CO_2 \), \( NH_3 \), ...
  - Sugars
  - Alcohols
  - Oligonucleotides (short single stranded DNA chains)
  - Various proteins and peptides: Antibodies, antigens
  - Viruses
  - and more ...
The fundamental idea of biosensing is using the work done by biological evolution to create highly selective biomolecular pairings.

Using one part of the pair as a recognition element allows selective measurement of the other part.

The biological recognition system provides selectivity and translates information from the biochemical domain (often an analyte concentration $C$) into chemical or physical output.

Biological recognition elements can be:
- Oligonucleotides (short single stranded DNA chains)
- Enzymes
- Antigens/Antibodies...
Biological recognition elements

- The biological binding reactions generally work only in water.

- This is a serious limitation for biosensors that are adversely affected by the viscous damping of liquids.

- For example: Resonating micromechanical cantilevers have shown mass detection limits of:
  - zeptograms ($10^{-21}$) in vacuum [1]
  - but nanograms ($10^{-9}$) in liquid [2]

Transducer elements

• The purpose of the transducer is to transform the output from the recognition system to a form suited for data analysis and storage (usually electrical).
• Often the output of the recognition system is a mass change ($\Delta m$) or a charge change ($\Delta q$).
• Most often these quantities are eventually translated to a frequency change ($\Delta f$) or a current change ($\Delta i$) of an electrical signal.
• Complete biosensors can thus be described by their transduction chains. For example:

$$\Delta C \Rightarrow \Delta q \Rightarrow \Delta i$$

or

$$\Delta C \Rightarrow \Delta m \Rightarrow \Delta f$$
## Classification of biosensors

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Recognition</th>
<th>Transduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ions</td>
<td>Enzymes</td>
<td>Electrochemical</td>
</tr>
<tr>
<td>Dissolved gasses Vapors</td>
<td>Enzymes Antibodies Receptor proteins</td>
<td>Electrochemical Piezoelectric Optical</td>
</tr>
<tr>
<td>Substrates (molecules upon which enzymes act)</td>
<td>Enzymes Membrane receptors Whole cells Plant or animal tissue</td>
<td>Electrochemical Piezoelectric Optical Calorimetric</td>
</tr>
<tr>
<td>Antibody/Antigen Virus</td>
<td>Antigen/Antibody</td>
<td>Electrochemical Piezoelectric Optical Surface plasmon</td>
</tr>
<tr>
<td>Various proteins</td>
<td>Receptor proteins</td>
<td>Electrochemical Piezoelectric Optical Surface plasmon</td>
</tr>
</tbody>
</table>
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Interaction of light and matter:
Wavelength change (refractive index)

Speed of light in vacuum: \( c \)
Wavelength in vacuum:
\[
\lambda_0 = \frac{c}{f}
\]

In water light slows down to \( v' \)
Wavelength in water:
\[
\lambda' = \frac{v'}{f} = \frac{\lambda_0}{n_w}
\]

Wavelength in a biomolecule solution: \( \lambda'' = \frac{\lambda_0}{n_s} < \lambda' \)

\( n \) is the material's refractive index
Waveguides for light control, by microfabrication

$n_c > n_b > n_s$
Guided wave propagation

Electric field \((E_y)\) of the light wave in the A-A’ cross-section

- Liquid sample
  - \(n_s\)
- Core
  - \(n_c\)
- Bottom cladding
  - \(n_b\)

\[ \lambda = \lambda_0/n_{\text{eff}} \rightarrow \text{Effective refractive index of waveguide} \]

\[ n_{\text{eff}} = f(n_b, n_s, n_c) \]
Evanescent field based biosensing with photonic waveguides

- Cross section along guide
- Electric field of the propagating light wave
- Biomolecule binding

Increased wg. effective index:

$$\Delta \lambda / \lambda = \Delta n_e / n_e$$
Photonic waveguide circuits for $\Delta \lambda$ read out

- The transduction chain of a photonic biosensor is:

  $\Delta C \rightarrow \Delta m \rightarrow \Delta n \rightarrow \Delta \lambda$

- We need to read out $\Delta \lambda$.
- Lithography enables fabrication of functional photonic circuits.
- The **directional coupler** permits nearly lossless splitting and combining of light.
Ring resonators for $\Delta \lambda$ read out

- Off resonance $\Rightarrow$ Most of light transmitted
- On resonance $\Rightarrow$ Light coupled to ring $\Rightarrow$ Transmission minimum
- Surface binding $\Rightarrow$ $n_e$ increase $\Rightarrow$ Resonance wavelength increase: $\Delta \lambda_0$

Light in at free space wavelength $\lambda_0$

$m = 10$

Transmitted light to detector

$\lambda_0 \rightarrow \lambda'_{0}$

New transmission spectrum of ring

$\frac{m \lambda_0}{n_e} = 2 \pi R$

Surface binding

$\frac{m \lambda_0}{n_e} = 2 \pi R$ fixed

Transmitted light to detector

Directional coupler

$R=70 \ \mu m$

Light in

Light out

Ring resonator
Ring resonator sensing fundamentals

Quality factor

\[ Q = \frac{\lambda}{\Delta \lambda} \]

The Q limits the achievable sensor resolution.

Volume sensitivity

\[ S_V = \frac{\partial \lambda}{\partial n} \]

Resonance wavelength shift per refractive index unit change of top cladding.

Surface sensitivity

\[ S_S = \frac{\partial \lambda}{\partial \sigma} \]

Resonance wavelength shift for surface density change of surface coating.
An example ring resonator biosensor chip

Biosensor cartridge

Ring resonator transducer

Antigen-Antibody pair

Optical sensor array

Light in

Light out

750 µm

70 µm

1 µm

Layout of sensor array optical circuit

Grating coupling

Integrated optical components

Waveguide

Ring-resonator

Splitter

Grating coupler
Waveguide cross-section

A-A'

Strip waveguide

Slot waveguide

Evanescent wave

Increased light-analyte interaction

Time average of optical power through cross section
(TM, $\lambda$=1310 nm)

(TE, $\lambda$=1310 nm)
Volume refractive index measurement of ethanol and methanol dilutions

Limit of detection: 

\[
\text{noise level / sensitivity} = 5 \times 10^{-6} \text{ RIU}
\]

State of the art refractometers: $10^{-8}$ RIU
Selective surface bio-coating by spotting

Spotting robot

Spotting jets
Biological recognition components

Chip spotted with BSA

Not spotted
Spotted

Sensor M5
Sensor M6

Bus
Ring
Precipitated salt crystals on surface
Coupler
Biosensing

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Biosensing with silicon waveguides

The high refractive index of silicon waveguides provide two benefits for sensing:

1. Rings can be made very small without reducing Q by bending loss,
2. The evanescent electric field at the silicon surface is very high, yielding high sensitivity for surface sensing.

![Graph showing the electric field intensity (|E|) for different materials](image)
Biosensing with silicon waveguides


Label-free detection limit of a few hundred molecules.
Multiplexing

Signal enhancement

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Challenge: Cost-efficient microfluidic integration
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- Minimize wafer footprint of microfluidics
- Bonding compatible with biofunctionalization
- Extendable to wafer scale
Off-Stoichiometric Thiol-Ene (OSTE) polymer technology enables new solutions for Lab-on-a Chip

- Tailor-made mechanical properties
- Patternable wettability
- Injection molding
- Photolithography
- Bonding to Si
- Compatible with biofunctionalization
OSTE: photolithography

Photolithography enables footprint efficient vias
OSTE: bonding

Bonding compatible with biofunctionalized surfaces

C.F. Carlborg et al. MicroTAS 2011
Fabrication: concept

**TOP mold + photomask**

Glass mask fabrication

Chromium patterns

SU8 reliefs

Molding and photolithography of OSTE

OSTE microfluidic layer

PDMS mold fabrication

**BOTTOM mold**

Dry bonding

1 step Si standard CMOS process

Integrated chip ready for photonic sensing

Silicon photonic chip
Fabrication: process

BONDING
DEVELOPMENT
30 s in Butyl acetate
13 s CURING
A biophotonic sensor with microfabricated sample handling system.
A biophotonic sensor example: Refractive index sensing
Refractive index sensitivity

S = 50 nm/RIU

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Temperature sensitivity

- For practical biosensing we need to reach a detection limit of $10^{-6}$ RIU.
- Water has a thermo optic co-efficient of $\kappa_{H2O} = -1.1 \times 10^{-4}$ RIU/K.

→ Waveguide based biosensors normally need temperature control.

(SPR-BIAcore T100)
Athermal waveguides

Thermo-optic coefficients

\[ \kappa = \frac{\partial n}{\partial T} \]

\[ \kappa_{\text{H}_2\text{O}} = -1.1 \times 10^{-4} \frac{\text{RIU}}{K} \]

\[ \kappa_{\text{Si}} = 2.4 \times 10^{-4} \frac{\text{RIU}}{K} \]

\[ \kappa_{\text{SiO}_2} = 1.1 \times 10^{-5} \frac{\text{RIU}}{K} \]

Cross-section

Strip waveguide

- A-A'
- \( n = 1.3 \)
- \( \kappa < 0 \)

Slot waveguide

- \( n = 1.5 \)
- \( \kappa > 0 \)

Optical power

(TE mode, \( \lambda = 1550 \text{ nm} \))

If we can make

\[ \frac{\partial n_{\text{eff}}}{\partial T} \approx \kappa_{\text{H}_2\text{O}} P_{\text{H}_2\text{O}} + \kappa_{\text{Si}} P_{\text{Si}} + \kappa_{\text{SiO}_2} P_{\text{SiO}_2} \]

\[ P_{\text{H}_2\text{O}} \approx P_{\text{Si}} \Rightarrow \frac{\partial n_{\text{eff}}}{\partial T} \approx 0 \]

\( \Rightarrow \) Athermal waveguide

Athermal slot-waveguide design

Temperature dependence of effective index

Calculated with COMSOL Multiphysics® FEM mode solver
Evaluation circuit

Mach-Zehnder Interferometer

Slot-waveguide (Si)

Lower cladding (SiO₂)

Summary

• By fixing a receptor to a photonic sensor surface, antibodies can be measured with high selectivity.

• Biomolecules binding within the evanescent field of a sensing waveguide shorten the wavelength of light in the guide.

• Slot waveguides are good bulk sensors, marginal benefit for surface sensing.

• However, silicon slot waveguides enable athermal photonic biosensors.

• Cost-efficient microfluidic integration on silicon sensors challenging: OSTE
Outlook

• Silicon waveguide based photonic transducers already good enough for many practical applications.

• However, benefits over existing biosensors is not clear enough yet to make an impact.

• Improvements in microfluidics integration (pumping, filtering etc.) necessary to leverage the benefits of CMOS fabrication.

• Unique features for future exploration:
  - Low absolute mass detection limit.
  - Spatial resolution by sensor arrays.
Further reading


Apodized through-etched grating couplers for single lithography circuits

M. Antelius, K. B. Gylfason, and H. Sohlström,
"An apodized SOI waveguide-to-fiber surface grating coupler for single lithography silicon photonics,"
Grating design

Periodic grating optimization

Power ratio coupled into fiber

Maximum coupling at $(0.69, 0.8, 0.53)$

Power ratio reflected back into photonic circuit

$(0.69, 0.8, 0.2)$

Apodization

Power into fiber

Back reflected power

BOX thickness dependence

(b)

Design point $(2.2, 72)$

$\text{Coupling efficiency (power percentage into fibre)}$ [%] vs $\text{Buried oxide (BOX) thickness [µm]}$
Field profile in grating cross-section

**Periodic through etched**
- 21% back reflection
- 53% overlap with fiber mode

**Apodized through etched**
- 0.1% back reflection
- 72% overlap with fiber mode
Implementation and experiments