MEMS Technology
in
Biomedical Sensor Application

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MEMS Technology
in
Biomedical Sensor Application

- **Presentation Outline**
- *Biomicroelectromechanical system (BioMEMS)
- *Microfabricated Biosensor Devices
- *State-of-the-art optical biosensor: SPR sensor
- *Frontier of Nanoscale biomolecular study
- *Conclusion

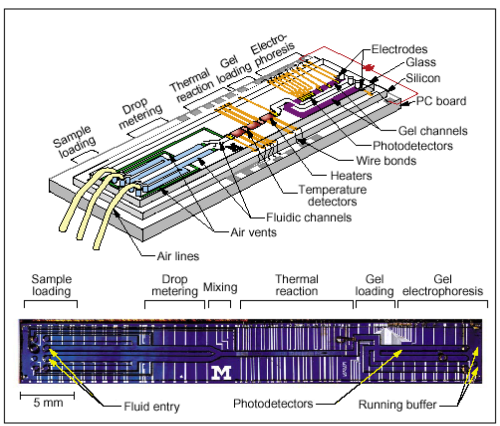
Biomicroelectromechanical systems

Biomicroelectromechanical systems

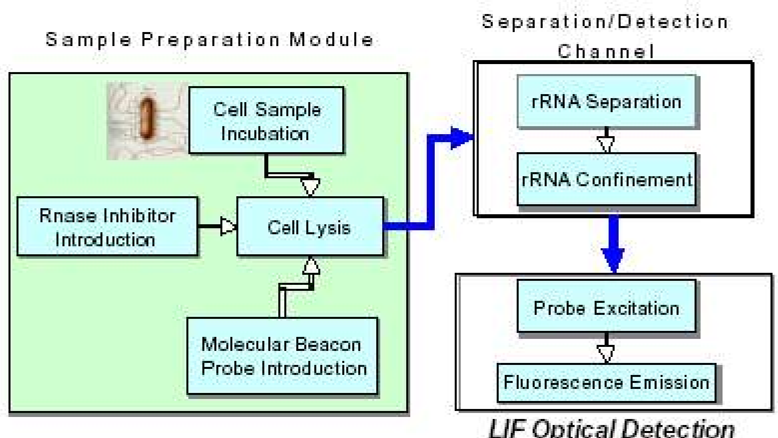
Definition of Bio-MicroelectroMechanical Systems (BioMEMS):

1. From systemic aspect-

   BioMEMS usually contains sensors, actuators, mechanical structures and electronics. Such systems are being developed as diagnostic and analytical devices at diagnostic and analytical devices. Suzanne Berry,TRENDS in Biotechnology Vol.20 No.1,pp.3, January 2002



Miniaturized PCR System
Science,1998,282:484-487



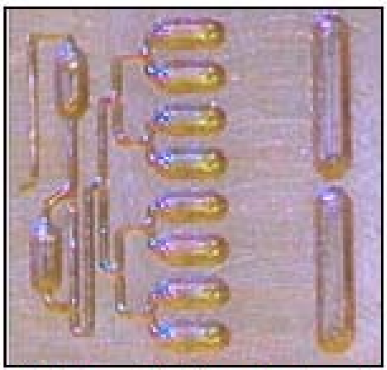
Design of Integrated DNA Detection System
http://ho.seas.ucla.eda

Biomicroelectromechanical systems

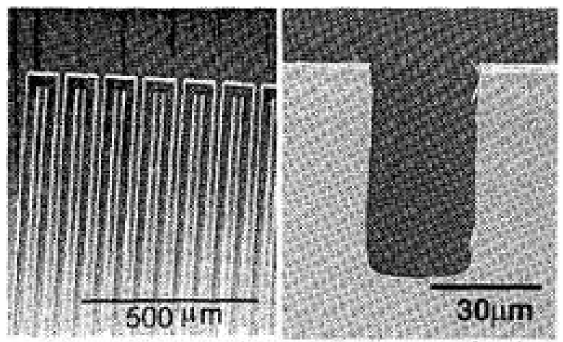
2. From component aspect

BioMEMS is the research of microfabricated devices for biological applications.

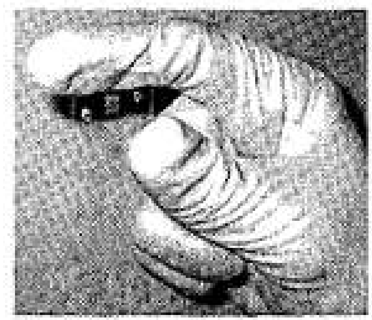
Tejal A. Desai et al, Biomolecular Engineering, 17 (2000) 23–36



PFC™ micro fluid analysis circuit in SeqPrep™ Chip



Top and Crosssectional SEM images of etched micro-capillary patterns.

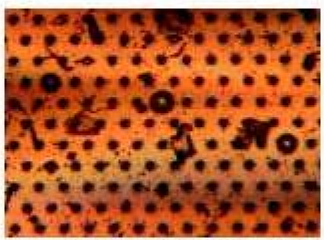


Micro-capillary electrophoresis (µ-CE) chi

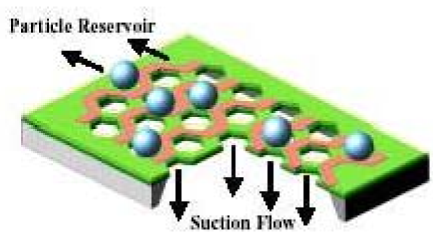
Kikuchi, T.; Ujiie, T.; Ichiki, T.; Horiike, Y. Microprocesses and Nanotechnology Conference, 1999.Digest of Papers. Microprocesses and Nanotechnology '99.
1999 International , pp178 –179,1999

Biomicroelectromechanical systems

3. MEMS technology is an engineering solution for biomedical problems



Micro-size particle capturing
(micro-filter)



Particle transport into the liquid delivery system
(electrode deposited micro-filter)

Airborne particle collection filter

http://ho.seas.ucla.eda

BioMEMS in Biomedical Field

BioMEMS encompasses all interfaces and intersections of the life sciences and clinical disciplines with microsystems and nanotechnology.

Related area:

- Micro & nanotechnology for drug delivery,
- Tissue engineering, harvesting, manipulation
- Biomolecular amplification,
- Sequencing of nucleic acids
- Proteomics
- Microfluidics and miniaturized total analysis systems (microTAS)
- Biosensors
- Molecular assembly,
- Nano-scale imaging, and integrated systems

Adapted from Cambridge Healthtech Institute
http://www.genomicglossaries.com

Bio-microelectromechanical systems (bioMEMS)

MEMS

- Silicon based Material
- Electrical & Mechanical interface integration
- Moving part in micromachining system

-active component

BioMEMS

- Biocompatible Material
- Biomolecular & physical parameter (electrical,mechanical optical) transducer integration
- Motion medium in passive substrate

-microfluidic driving force

A quite different thinking process from MEMS to BioMEMS

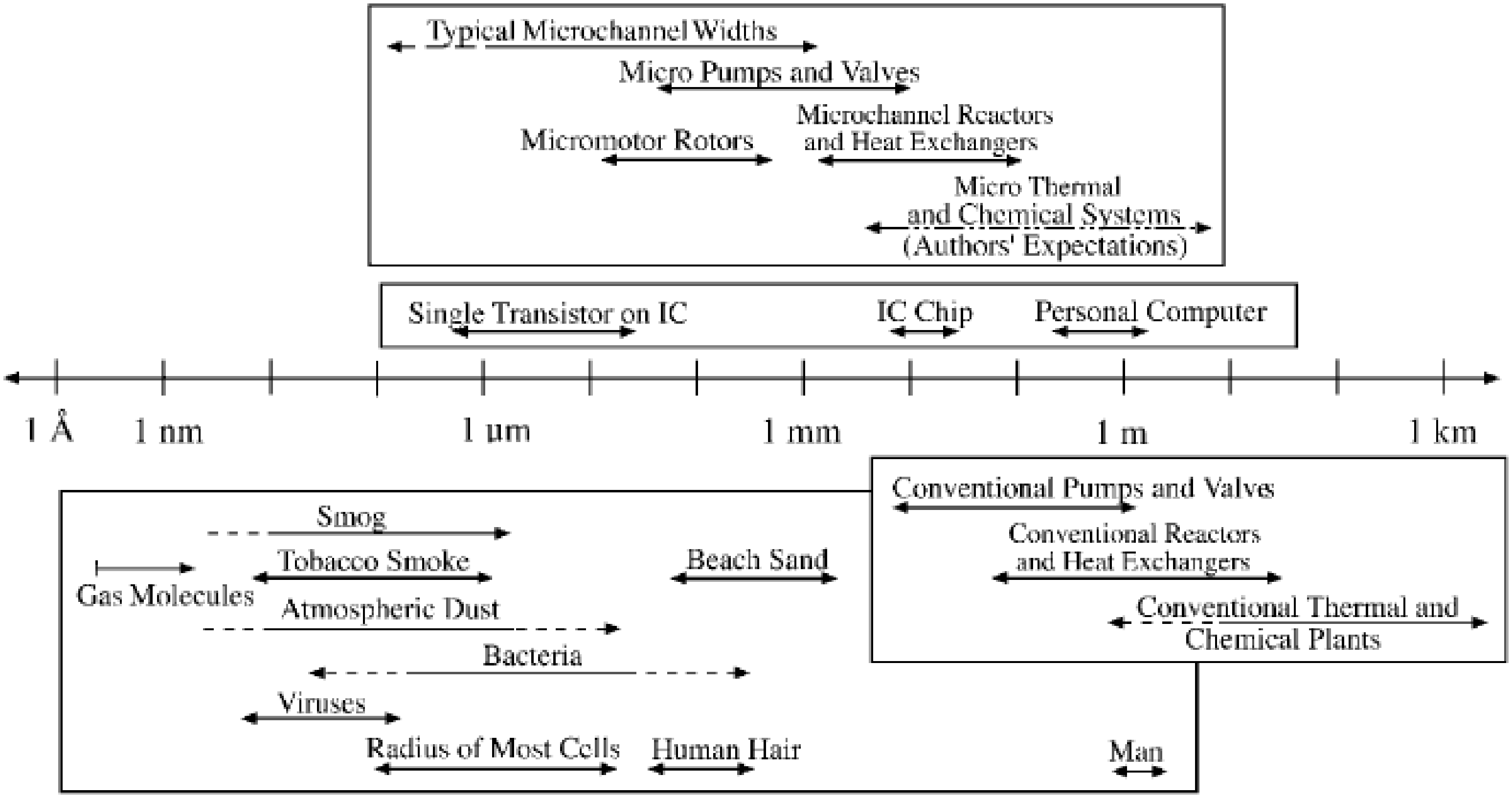
Bio-microelectromechanical systems (bioMEMS)

A BioMEMS Platform for Biomedical Device?

- IC incompatible fabrication process (glass, polymer substrate)
- Batch manufacture is not a portion for each bio-based device.
- Biomaterial sterilization consideration
- BioMEMs packaging techniques for hybrid substrate or multichip system lead the way

BioMEMS in Biosensor Development

A supporting technology for manipulating biomolecules at the micro-scale world.



Biosensor

- Classfication
- 1.Electrochemical sensor
- 2.Immunosensor

  Definition:

  a sensor based on the pairing of a molecular recognition affinity pair. For i. e. Antigen(Ag)-Antibody(Ab) binding

  *electrochemical type-by chemicalelectical signal transform

  *optical type-by optoelectrical signal transform

.

Biosensor

The affinity is a crucial concern

- Affinity is used to describe a reversible biomolecular interaction

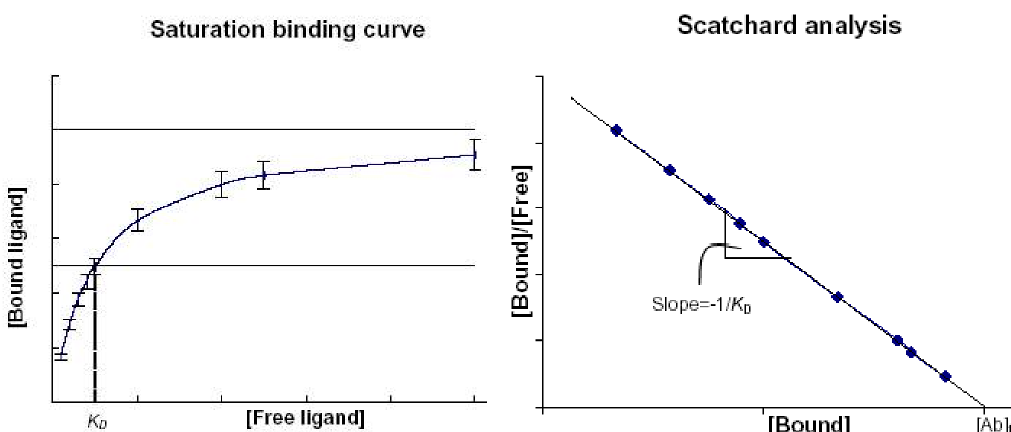
  also means the tightness of Ad-Ag binding

$$Ab + Ag \Leftrightarrow AbAg$$

Dissociation constant K_D

$$K_D = \frac{[Ab][Ag]}{[AbAg]}$$

$$K_A = \frac{1}{K_D}$$



http://www.immun.lth.se

- Affinity determines the specificity of biosensor
- The nonspecific binding is an important issue when selecting Ag-Ab pairs

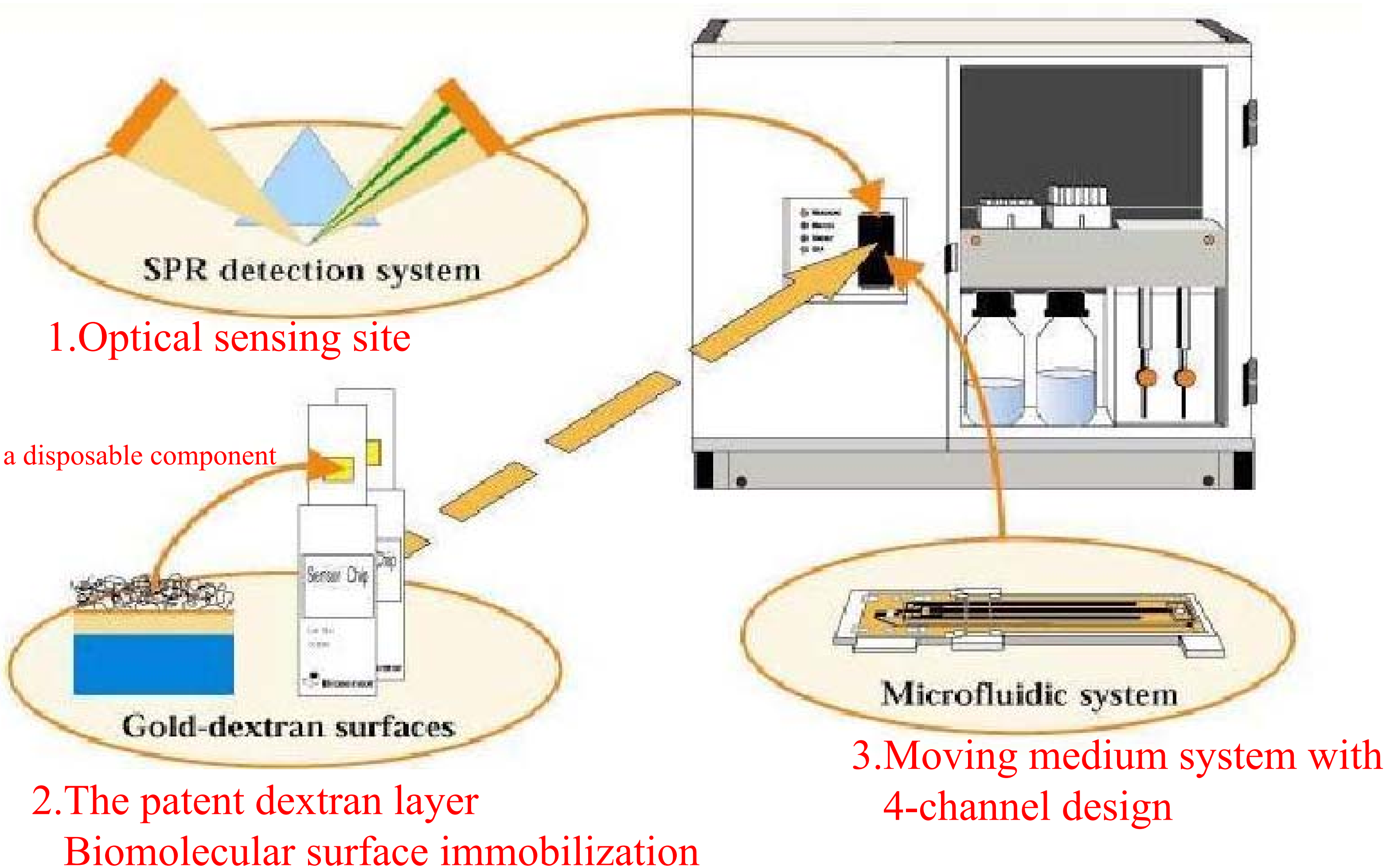
Optical Biosensor

Synonymous with optical immunosensor

1. Simutaneous response time
2. No reference electrode requirement
3. Not subject to electrical interface and high sensitivity
3. Nondestructive method
4. Multiwavelength measurement at the same reagent

State-of-the-art optical biosensor:
Surface Plasmon Resonance (SPR) Biosensor

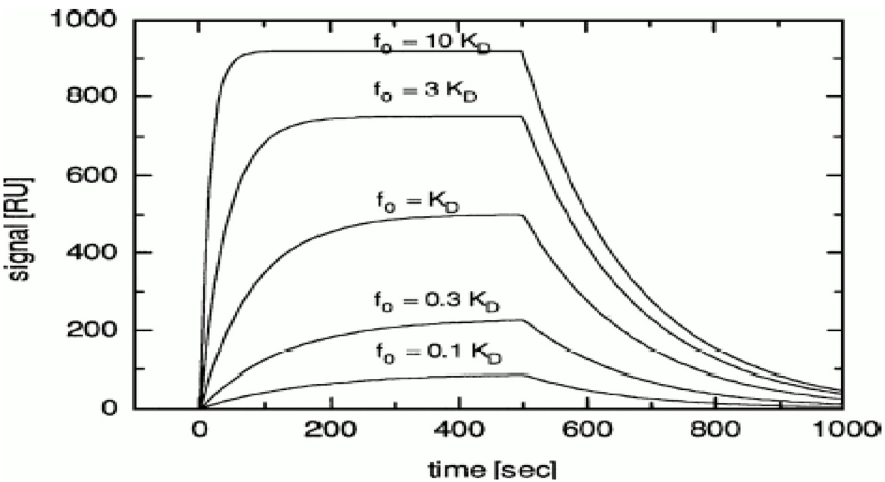
Surface Plasmon Resonance (SPR) Biosensor
-the commercial scheme of BIAcore 2000 system



Surface Plasmon Resonance (SPR) Biosensor

-Data analysis of BIAcore 2000 system

SPR typical association and dissociation curves with different ligand concentrations (f_0)



$K_D = k_{off}/k_{on}$

association

$k_{obs} = k_{on}f_0 + k_{off}$

$R(t) = R_{eq}(f_0)\,[1 - \exp(-k_{obs}t)]$

approaching equilibrium plateau signal

$R_{eq}(f_0) = R_{max}\,[1 + k_{off}/(k_{on} + f_0)]^{-1} = R_{max}\,[1 + K_D/f_0]^{-1}$

does not require modeling of binding process, independent of mass transport limitations

dissociation ($f_0 = 0$, $t>t_0$)

$R(t) = R(t_0)\exp[-k_{off}(t-t_0)]$

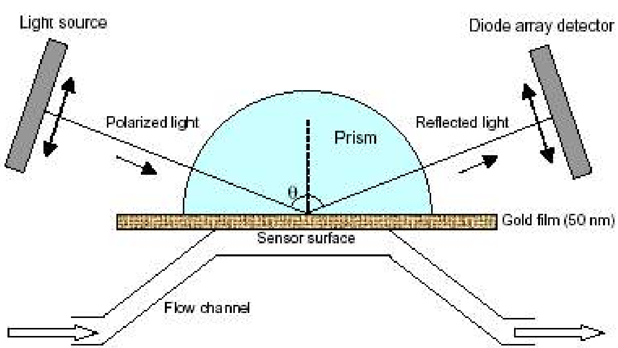
R is proportional to complex [XL], $f_0 = [L]$

The association and dissociation curve reveal the association/dissociation constant estimation

SPR biosensor can be regarded as a vital research instrument for biomolecular kinetic mechanism research

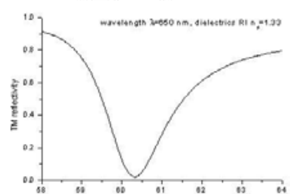
Surface Plasmon Resonance (SPR) Biosensor -Principles of SPR biosensor

- An incident plane polarized light at a specific angle can be almost totally absorbed into a thin metal film(e.g., gold or silver) deposited onto a prism.The resonant coupling of the light energy into a free-electron cloud on the metal surface is called surface plasmon resonance



SPR sensing site components

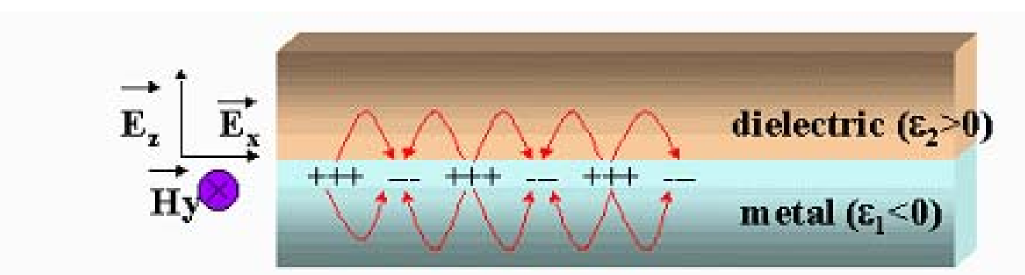
1.TM mode polarized light source
2.High refractive index coupler
3.Thin metal film(Au, Ag)
4.Flow channel(optional)

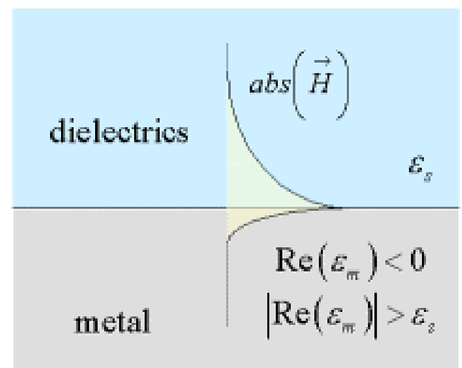


Surface Plasmon Resonance (SPR) Biosensor -Principles of SPR biosensor

- What is SPR ???

  Definition: Surface plasmon resonance is a charge-density oscillation that exist at the interface of two media with dielectric constants of opposite signs.(e.g. metal & dielectric)



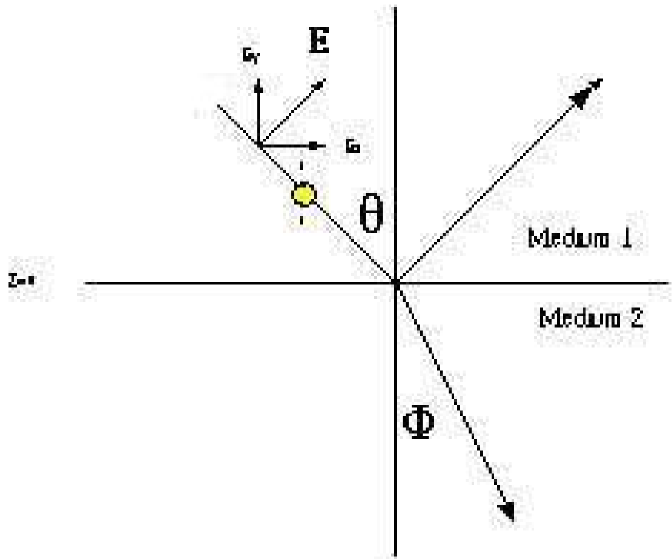


Surface plasma oscillations belongs to a transverse EM wave

Surface Plasmon Resonance (SPR) Biosensor -Principles of SPR biosensor

- Optical excitation of SPR

A p-polarized (TM mode) EM wave of incident light source



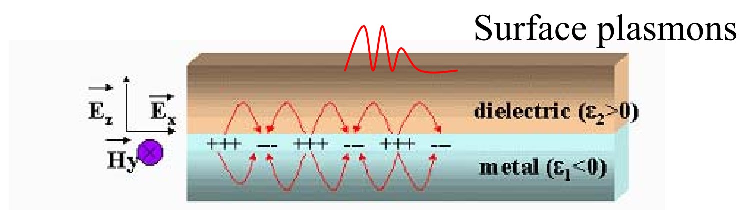
$$D_z = \varepsilon_0 \times \varepsilon_1 \times E_{z1} = \varepsilon_0 \times \varepsilon_2 \times E_{z2}$$

ε_0 permittivity of free space

ε_1 permittivity of medium1

ε_2 permittivity of medium2

The equation demonstrates a continuous electric field along interface



When surface plasmons are excited, there is a discontinuous electric field between interface due to free electron oscillation on metal layer

$$\varepsilon_{metal} = 1 - (\omega_p / \omega)^2$$

When $\omega < \omega_p$, electrons respond to the applied field and the dielectric constant of metal is negative.

Surface Plasmon Resonance (SPR) Biosensor
-Principles of SPR biosensor

- Maxwell equation of surface plasmon wave

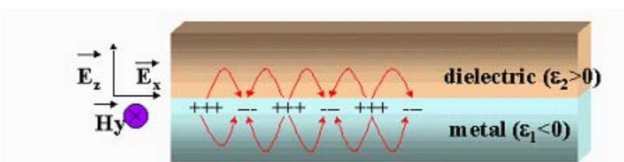
$$E_1 = \left(E_{x1}, 0, E_{Z1}\right) \times \exp\left[i(K_x.x - \omega t)\right] \exp(iK_{Z1}.Z)$$
$$E_2 = \left(E_{x2}, 0, E_{Z2}\right) \times \exp\left[i(K_x.x - \omega t)\right] \exp(iK_{Z2}.Z)$$
$$H_1 = \left(0, H_{Y1}, 0\right) \times \exp\left[i(K_x.x - \omega t)\right] \exp(iK_{Z1}.Z)$$
$$H_2 = \left(0, H_{Y2}, 0\right) \times \exp\left[i(K_x.x - \omega t)\right] \exp(iK_{Z2}.Z)$$

- Boundary condition: $E_{x1}=E_{x2}$ and $H_{y1}=H_{y2}$

$$\frac{\varepsilon_1}{K_{Z1}} = \frac{\varepsilon_2}{K_{Z2}}$$

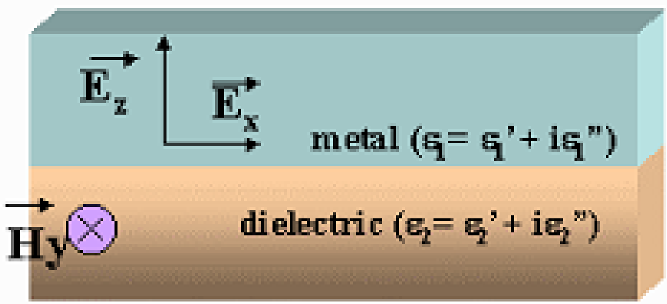
$$K_{Z1} = \left(\neg K_x^2 + \varepsilon_1.K^2\right) \quad K_{Z2} = \left(\neg K_x^2 + \varepsilon_2.K^2\right.$$

$$K_x = K\left(\left(\varepsilon_1.\varepsilon_2\right)/(\varepsilon_1 + \varepsilon_2)\right)^{1/2}$$



Surface Plasmon Resonance (SPR) Biosensor
-Principles of SPR biosensor

- Dispersion relation of surface plasmons

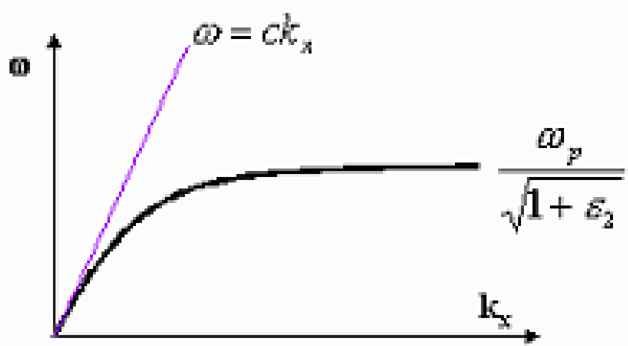


Field components:

$$F^{(l)} = F_0^{(l)} e^{i(k_x x - \omega t) - \alpha^{(l)}|z|}, \quad l = 1, 2$$

$$k_x = k_x' + ik_x'' = \sqrt{\frac{\varepsilon_1 \varepsilon_2}{\varepsilon_1 + \varepsilon_2}}\left(\frac{\omega}{c}\right)$$

Dispersion relation:



Confined propagating mode: $\varepsilon_1' < -\varepsilon_2'$

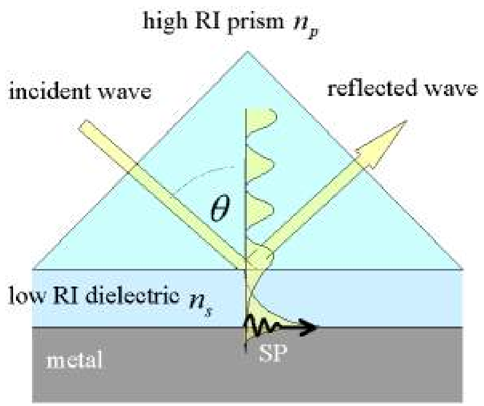
$$\varepsilon_1' = 1 - \frac{\omega_p^2}{\omega^2}$$

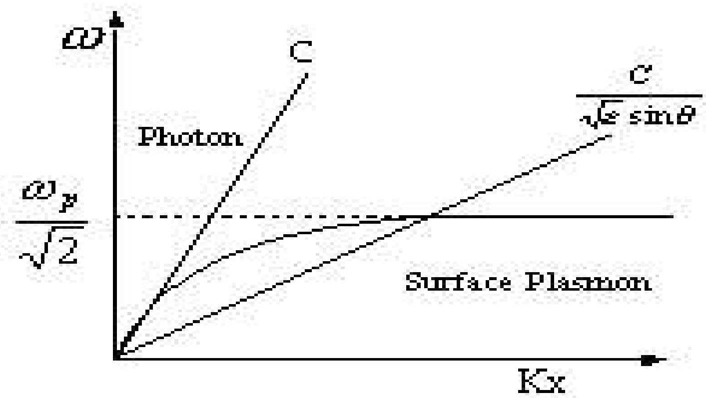
$$As \quad \omega \uparrow, \varepsilon_1' \rightarrow -\varepsilon_2' \text{ and } \omega \rightarrow \frac{\omega_p}{\sqrt{1+\varepsilon_2'}}$$

Surface plasmon can't be directly excited by an incident light

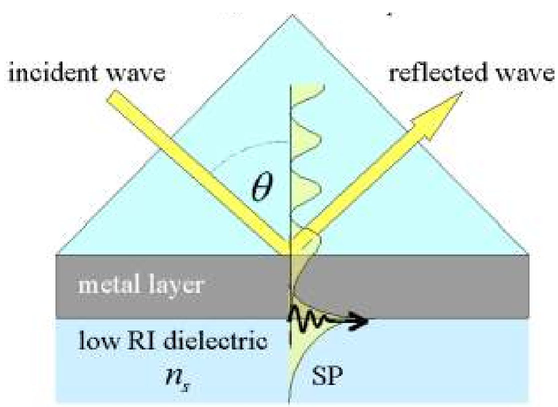
Surface Plasmon Resonance (SPR) Biosensor -Principles of SPR biosensor

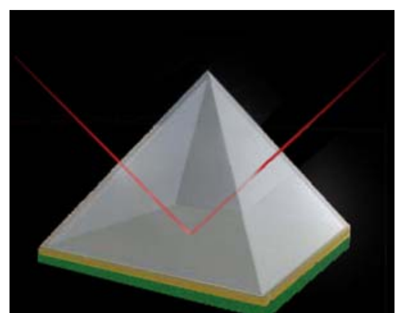
- The Otto/Kretschmann Configuration
  An evanescent field platform





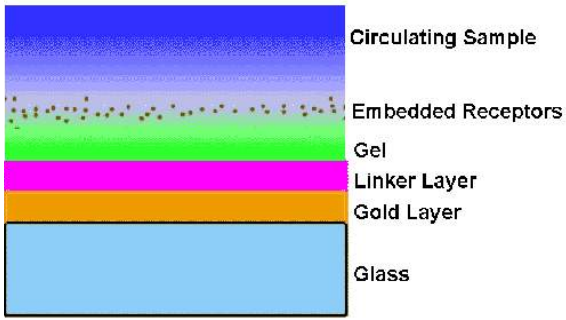
Dispersion relation of incident photon

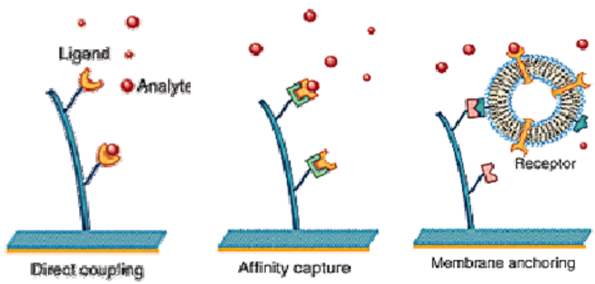




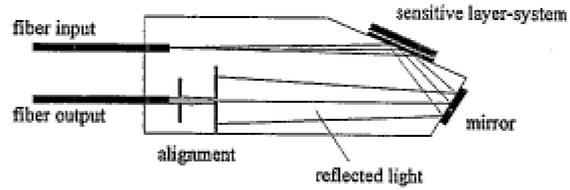
The Kretschmann /Otto Configuration the Evanescent Wave

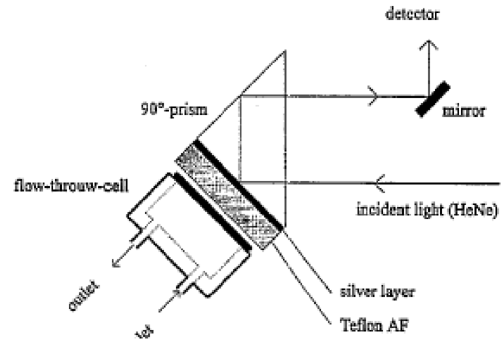
- Sensing element design

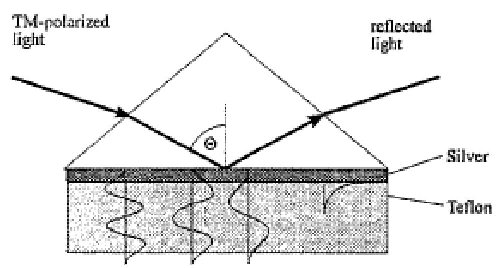




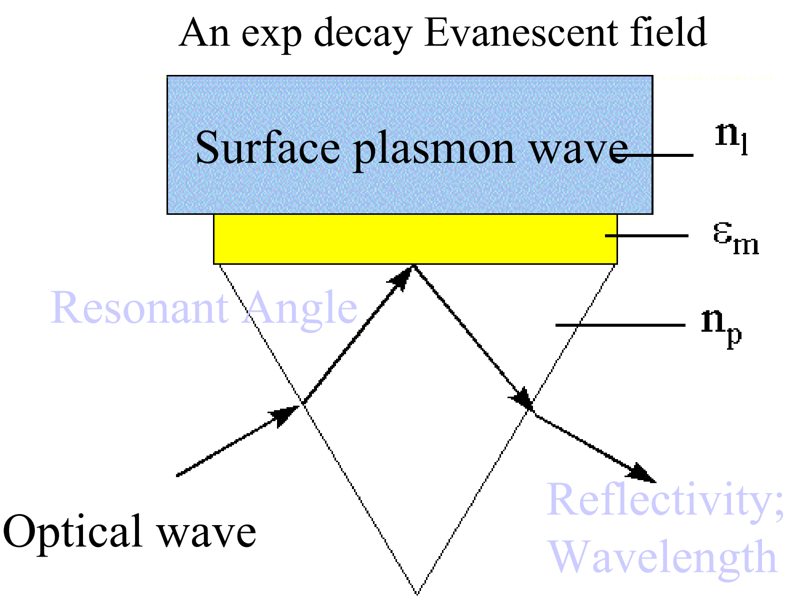
High affinity linker layer selsction

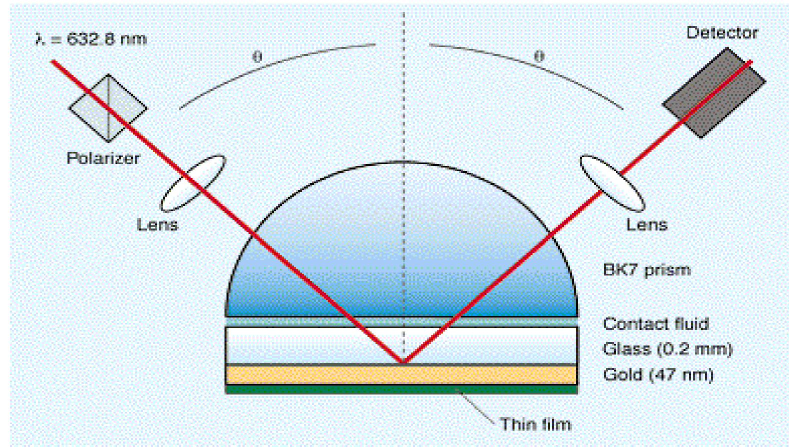




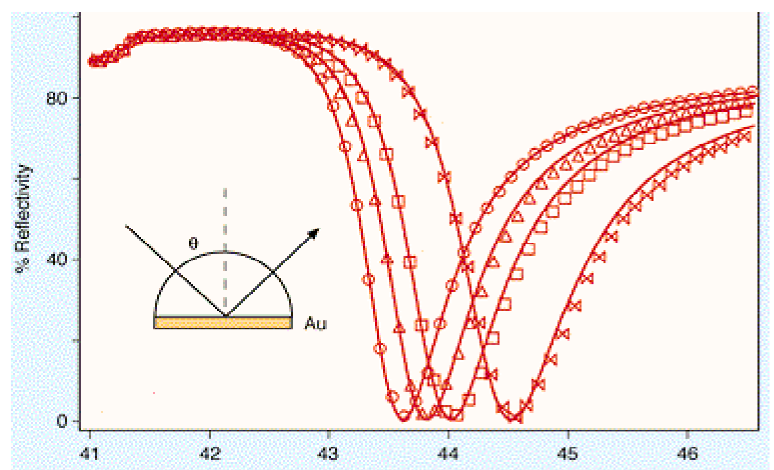


Optical System Layout for SPR Excitation





The Kretschmann configuration



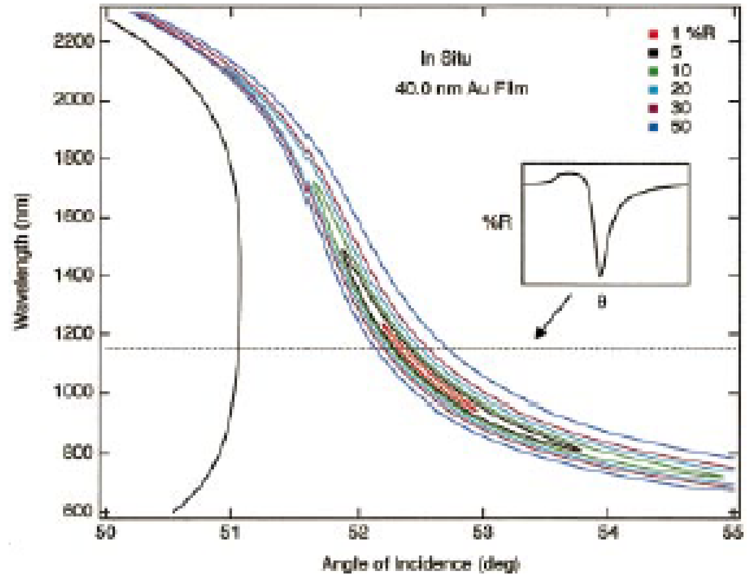
SPR Angle Shift Measurement Fresnel Calculation

- Parameters-wavelength, reflectivity
- Complex 3-phase Fresnel calculation

  prism/gold film/water
- A theoretical 2-dimension contour

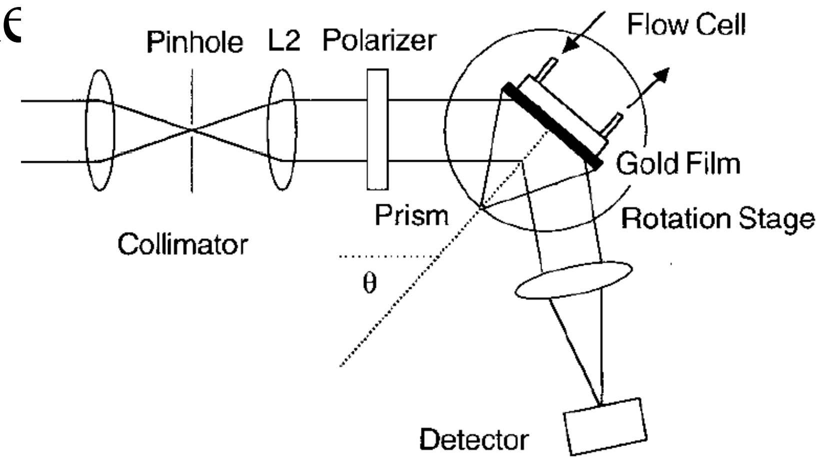
  // y-axis SPR reflectivity-wavelength

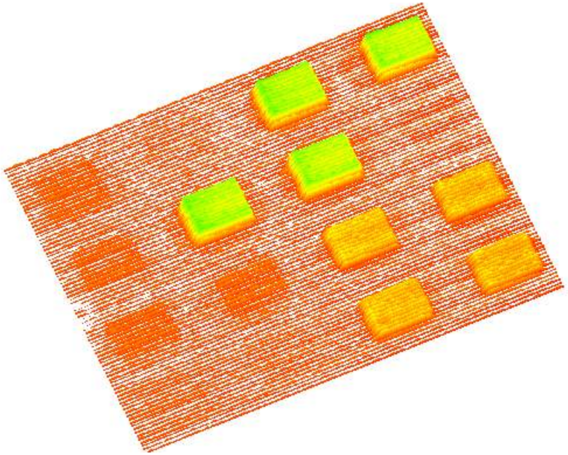
  // x-axis SPR reflectivity-angle



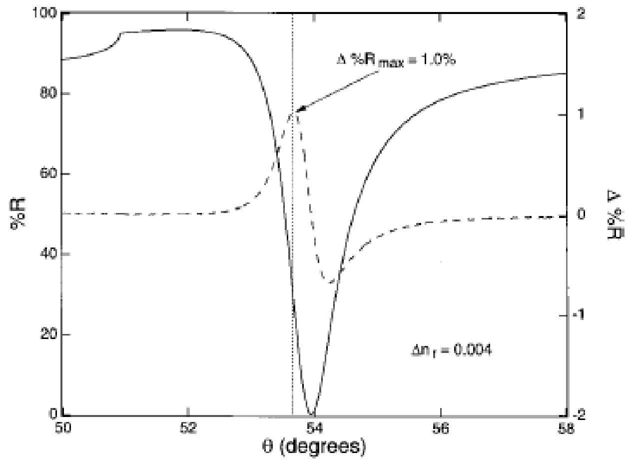
Optical System Layout for SPR Excitation

- Fixed Angle Measureme
  - SPR imaging system
  a in situ measurement



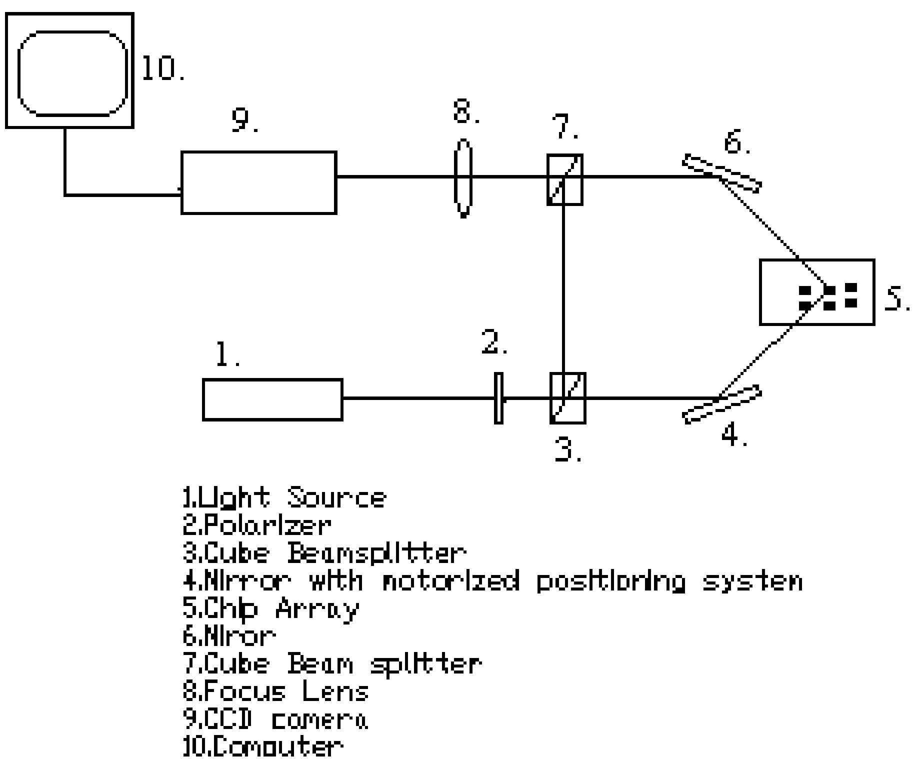


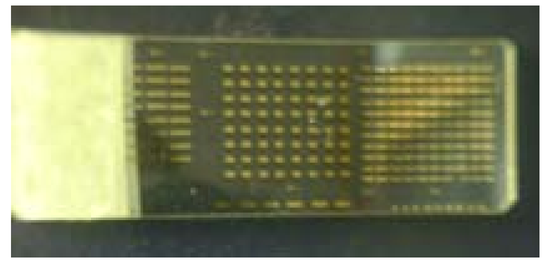
SPR imaging surface reconstruction

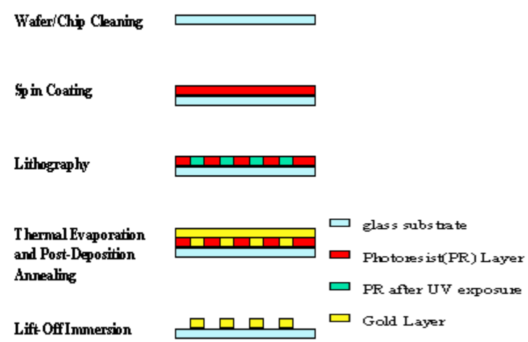


Optical System Layout for SPR Excitation

- Phase change Measurement







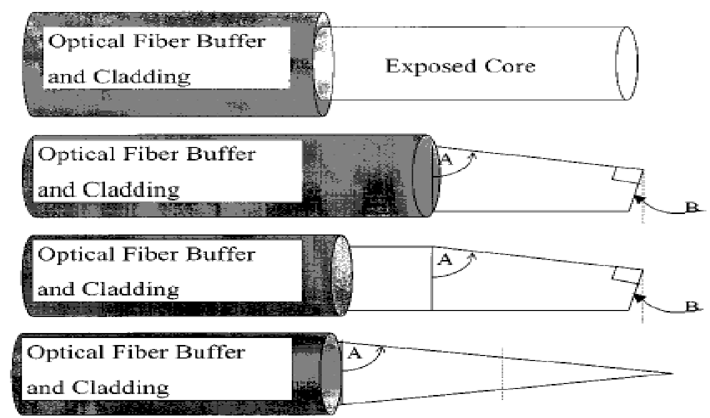
Miniaturation of SPR Optical System the optical fiber format

- Optic Fiber Consideration

  Fiber material-glass fiber , HiBi fiber

  Single mode or Multimode-
- Sensor Geometry Design
  - Residual cladding depth(d_0)-
  - Polish Side-
  - Tip angle-resonant angle?
  - Metal film thickness

    45-75nm



- Homola(1996): Amplitude SPR sensor based on side polished single mode fiber offer superior sensitivity

Conclusion:

- Miniaturization optical device
- Enhance specificity
- Disposable component for point of care
- A near field imaging for nano-scale object

Thanks for your attention