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Plasmonics, Bloch surface waves and Nano-photonic Elements for BioSensing Application

Protein aggregation and degenerative diseases

Valeria Musi

Institute of Microengineering (IMT)
Optics & Photonics Technology Laboratory

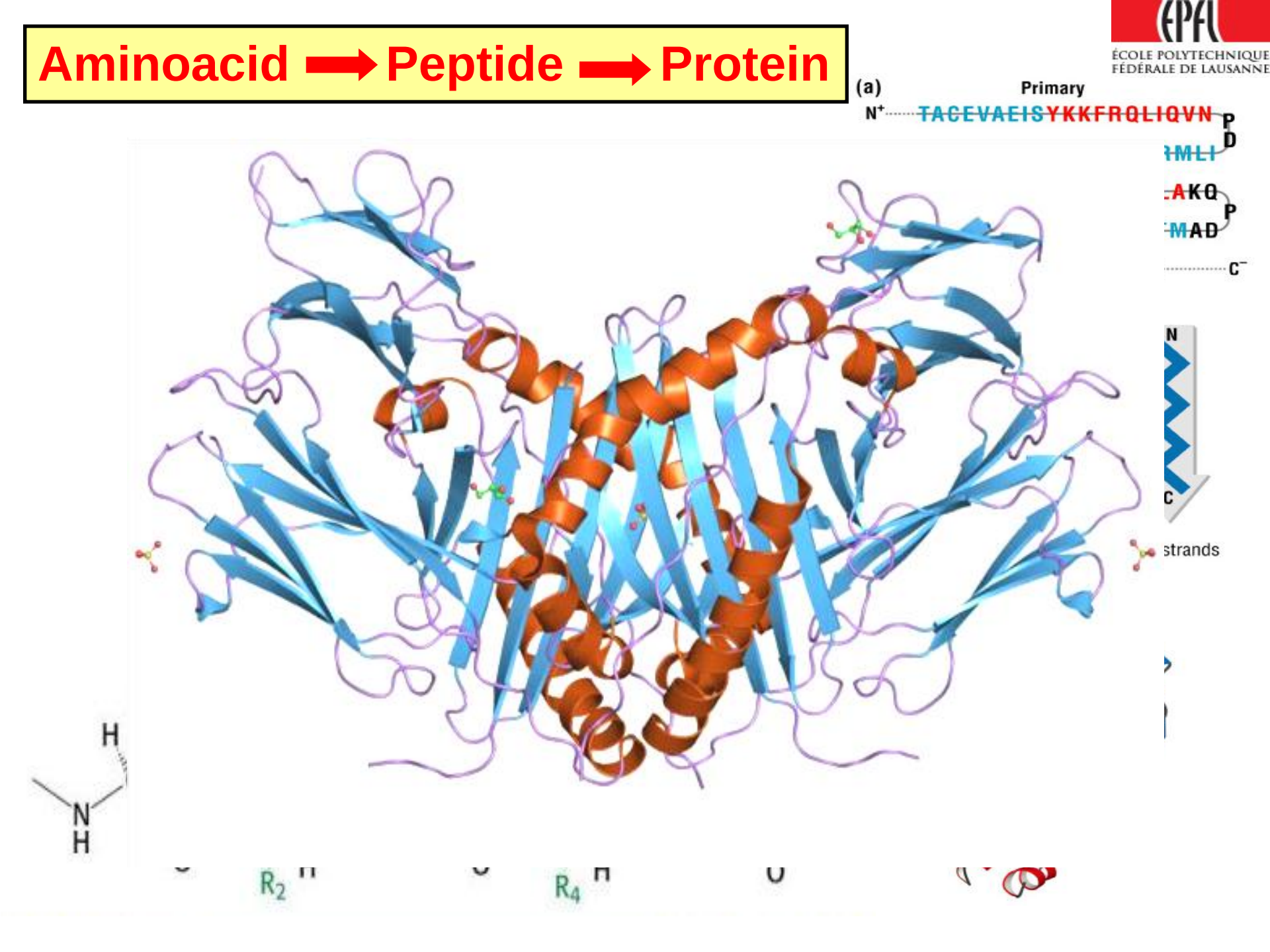
bmpn.ch

03-10-2010

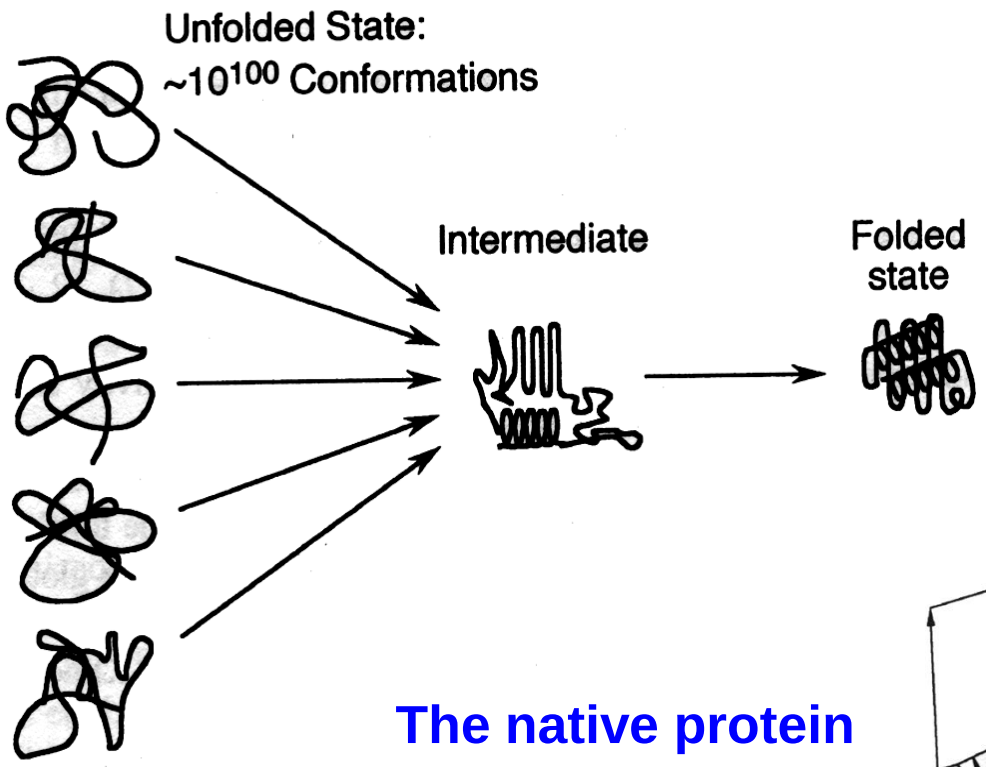
Outline

- Protein misfolding and degenerative diseases
- Sensing platforms developed in OPT lab
- Sensitivity enhancement by Bloch Surface Waves
- Conclusions

Aminoacid ➡ Peptide ➡ Protein

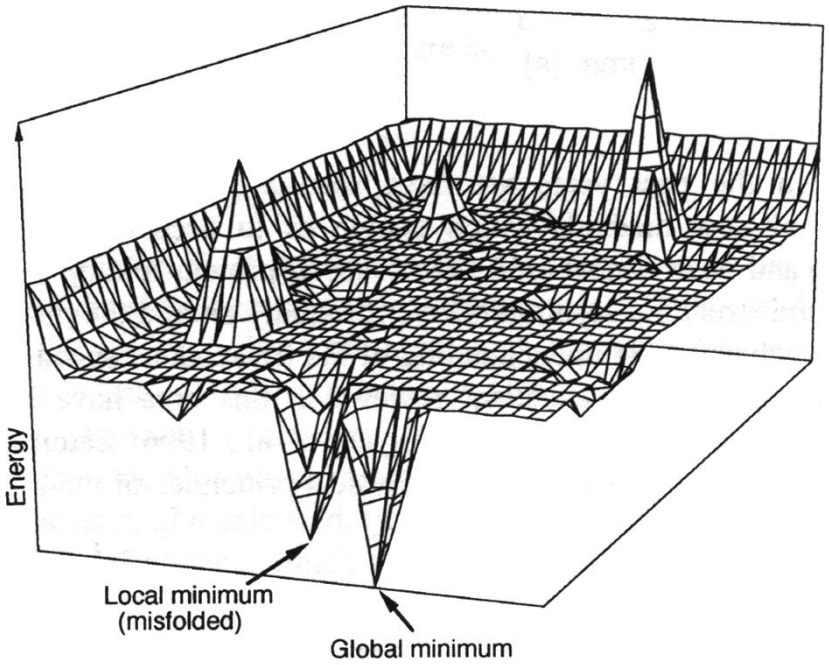


Protein folding



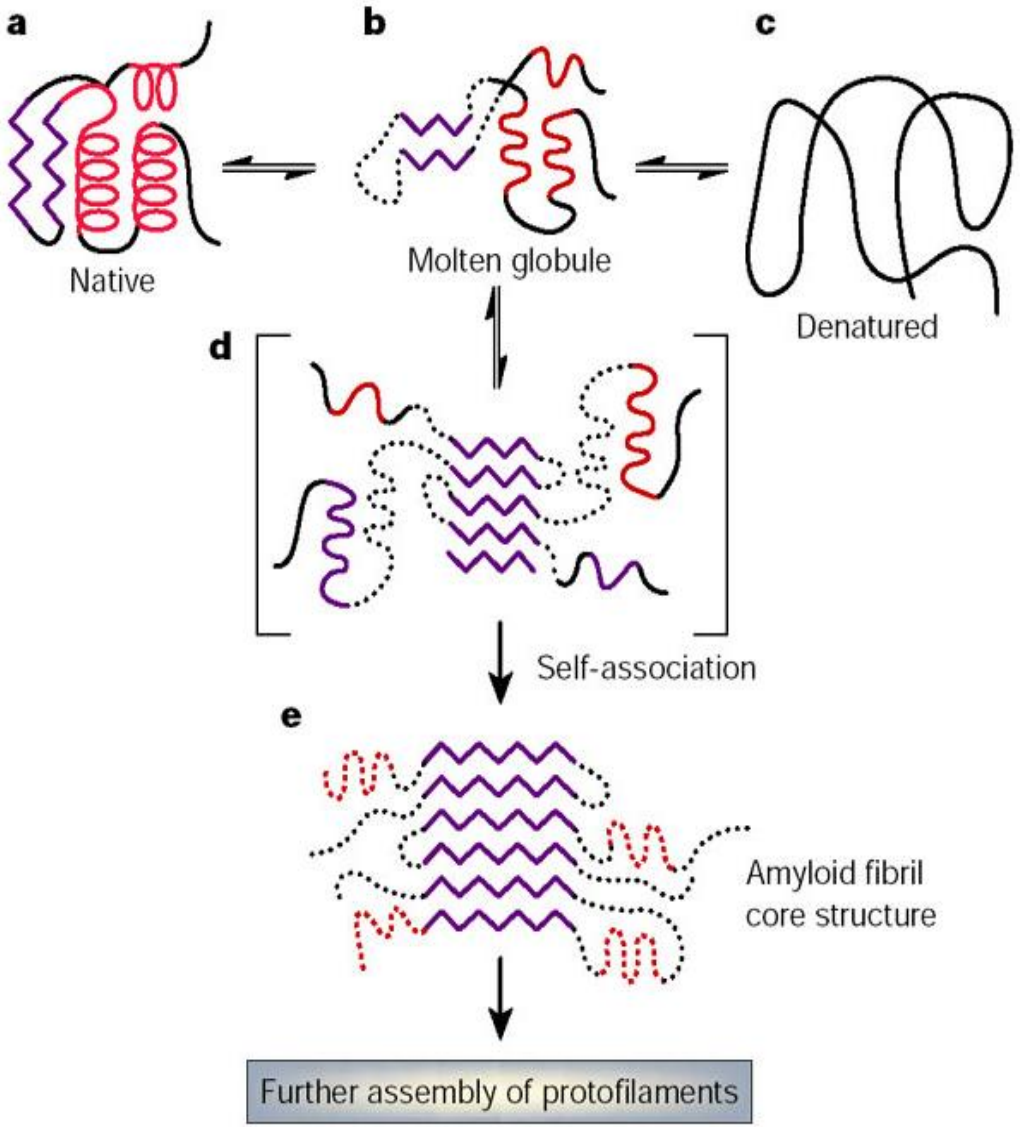
Folding must proceed through defined intermidiate pathways

The native protein structure corresponds to the minimum free energy.



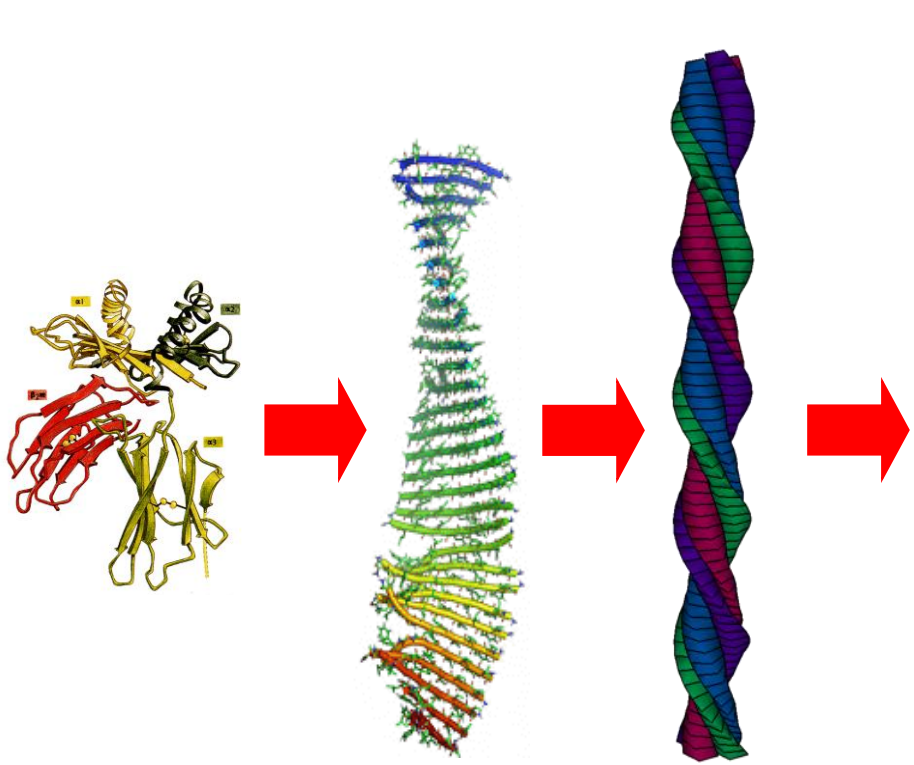
Dobson C. (2003) Protein folding and misfolding, *Nature 426*, 884-890

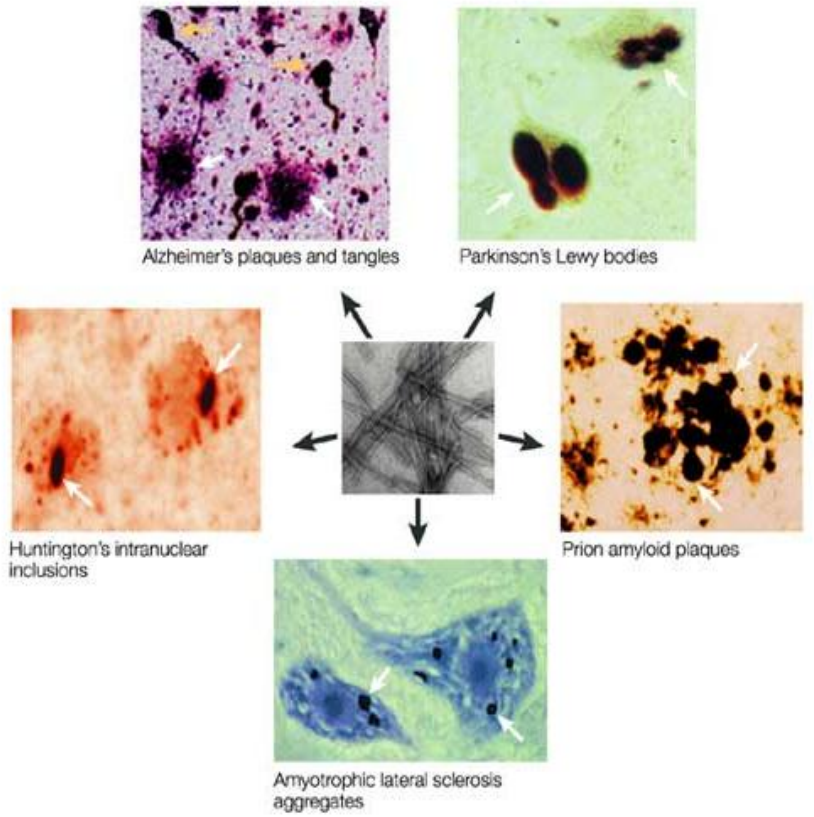
Protein misfolding



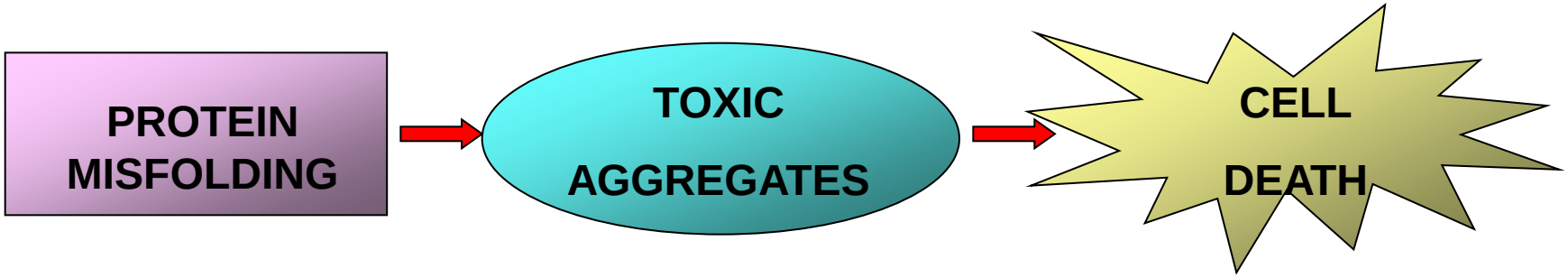
- **Conformational changes due to mutations, environmental stress, aging**
- **Normally folded protein interacts with misfolded protein (seeding)**
- **Formation of toxic aggregates. Loss of the physiological function**

Amyloidosis and Degenarative Diseases





An increasing number of pathologies are associated with the formation of large aggregates often fibrillar (amyloid) which contain misfolded proteins and which are eventually toxic for the organism



DISEASE	AGGREGATING PROTEINS
Alzheimer's disease	Amyloid β-peptide
Transmissible Spongiform Encephalopathies	Full-length prion protein or fragments
Hereditary cerebral haemorrhage with amyloidosis	Amyloid β-peptide or Cystatin C
Parkinson's disease; dementia with Lewy bodies	α-Synuclein
Frontotemporal dementia with parkinsonism	Tau
Type II diabetes	Amylin
Medullary carcinoma of the thyroid	Procalcitonin
Atrial	c factor
Amyotrophi	mutase
Polygluta	s within proteins
Primary sys	chains or fragments
Secondary systemic amyloidosis	Fragments of serum amyloid A protein
Familial amyloidotic polyneuropathy 2	Fragments of apolipoprotein A1
Senile systemic amyloidosis	Wild-type transthyretin and fragments
Familial amyloidotic polyneuropathy 1	Mutant transthyretin and fragments
Familian Mediterranean fever	Fragments of serum amyloid A protein
Haemodialysis-related amyloidosis	β_2-Microglobulin
Finnish hereditary amyloidosis	Fragments of mutant gelsolin
Lysozyme amyloidosis	Full-length mutant lysozyme
Insulin-related amyloid	Full-length insulin
Fibrinogen α-chain amyloidosis	Fibrinogen α-chain variants

Large impact into human health since the diseases are all currently incurable.

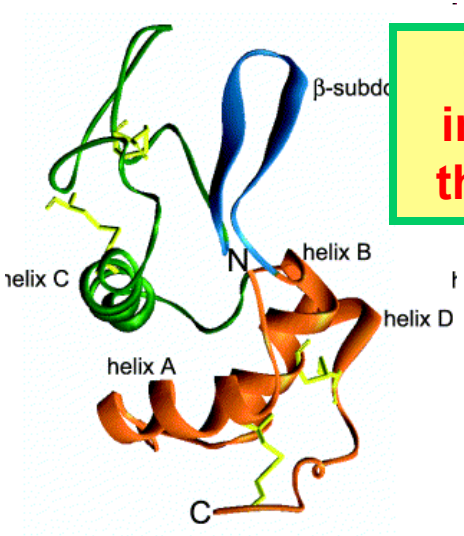
Clear understanding to design therapeutic strategies

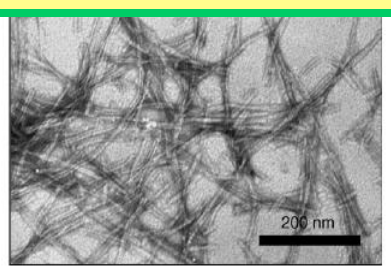
Lysozyme systemic Amyloidosis

- Lysozyme systemic amyloidosis or Familia
renal,
laryng

- Lysc
and largely used as model system for aggregation studies

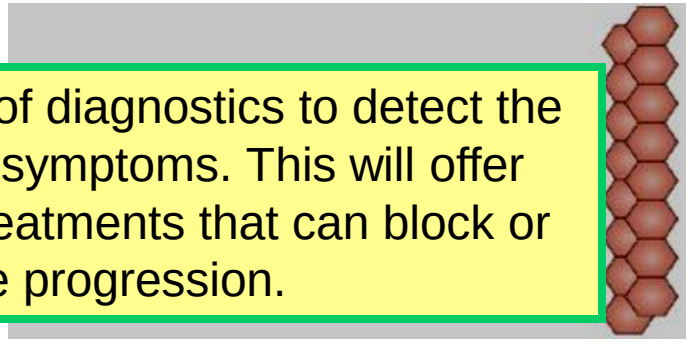
pH 5.2, T=20C





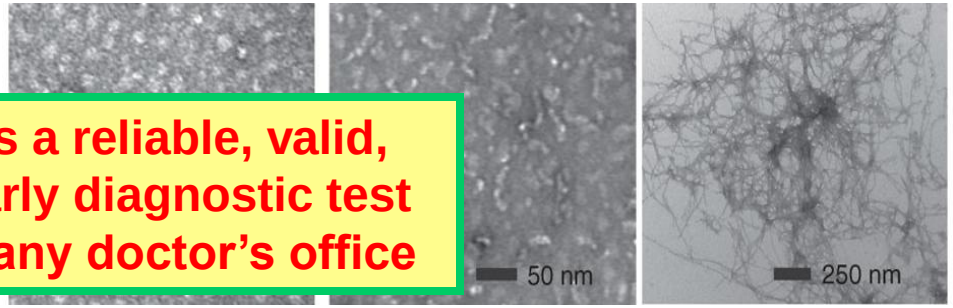
Trexler et al. (2007) The formation of amyloid fibrils from proteins in the lysozyme family. *Curr Protein Pept Sci*. 8, 537-57

Alzheimer's Disease (β-amyloids)

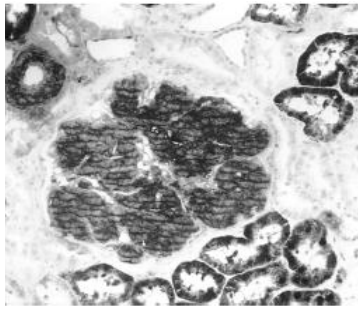


Abeta Oligomers Protofibrils Fibrils

pH 7.4, T=4C



pH 7.4, T=37C



Ahmed et al. (2010) Structural conversion of neurotoxic amyloid-beta(1-42) oligomers to fibrils. *Nat Struct Mol Biol. 17 (5),* 561-7

It is imperative to develop new forms of diagnostics to detect the disease prior to the onset of clinical symptoms. This will offer patients the prospect of preventive treatments that can block or significantly curb disease progression.

The ultimate goal is a reliable, valid, inexpensive, and early diagnostic test that can be used in any doctor's office

Micro-nano strategy for bio-sensing

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Biomedical application

Early diagnosis of aberrant degenerative pathologies that are caused by the formation of amyloid fibrils (protein aggregates).

Detect and characterize the early dynamic events of aggregation.

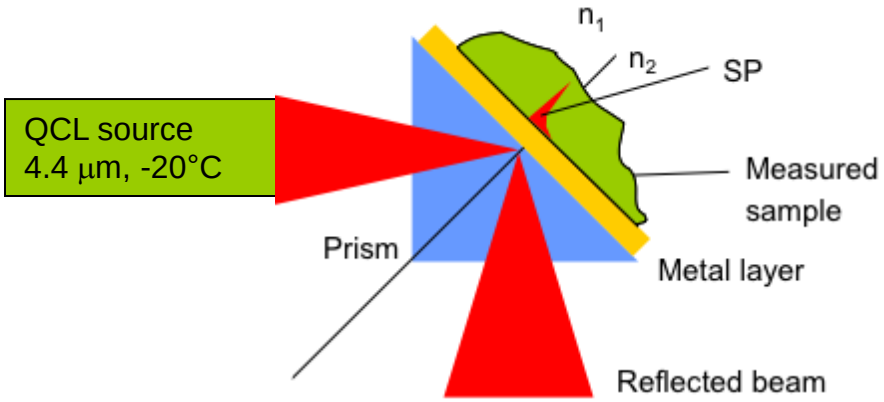
Label-free surface waves based sensors

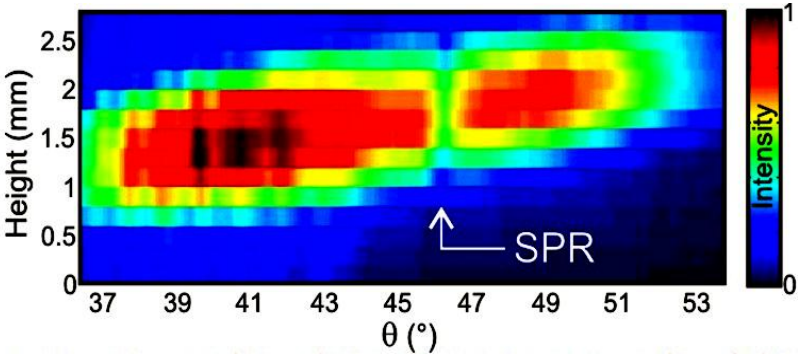
Sensing platform selective to optical variations caused by conformational changes in proteins (aggregation). Measurements of refractive index variation.

Surface Plasmon Resonance (SPR)
Nano-photonics
Bloch Surface Waves

Optical methods properties: extreme surface sensitivity, real time response, versatility, surface functionalisation compatibility, low cost and possibility of miniaturization and integration.

SPR: Mid-IR Optical Setup (4.4 μm)



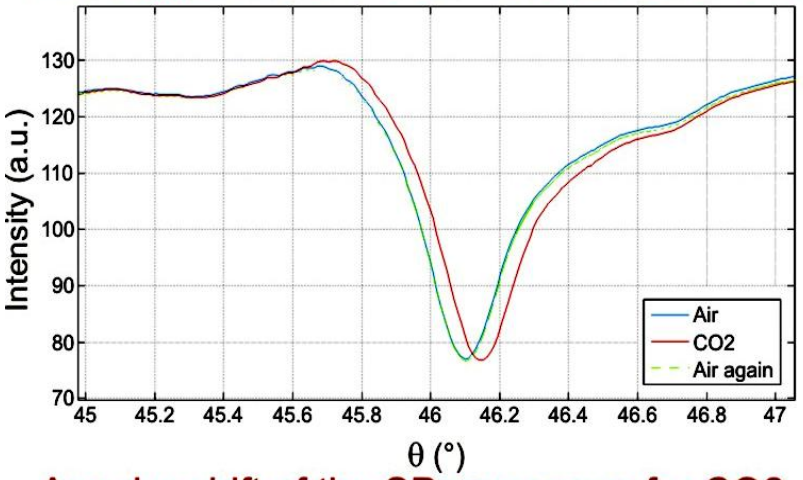


- The **mid-IR Surface Plasmon Resonance** optical sensor is operating at **4.4μm**.

- Highly sensitive measurements of the **refractive index** (n) variation of the analyte: **detection of CO_2 concentration in N_2.**

- The plasmon is excited (**Quantum Cascade Laser** source) at the surface of a thin Ti\Au layer deposited on a CaF2 prism.

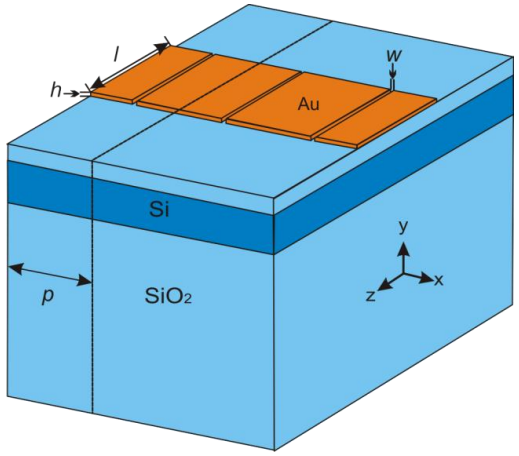
Intensity profile of the SP resonance for CO2

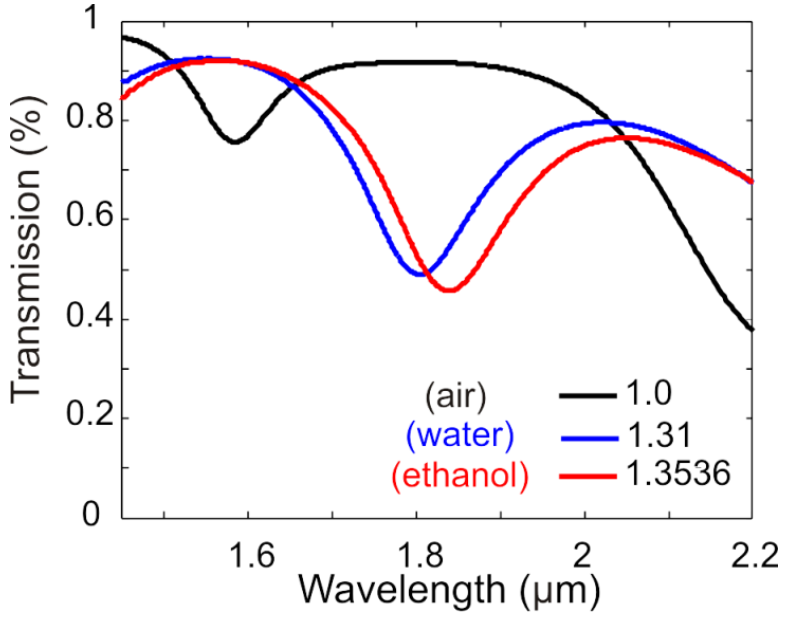


Angular shift of the SP resonance for CO2

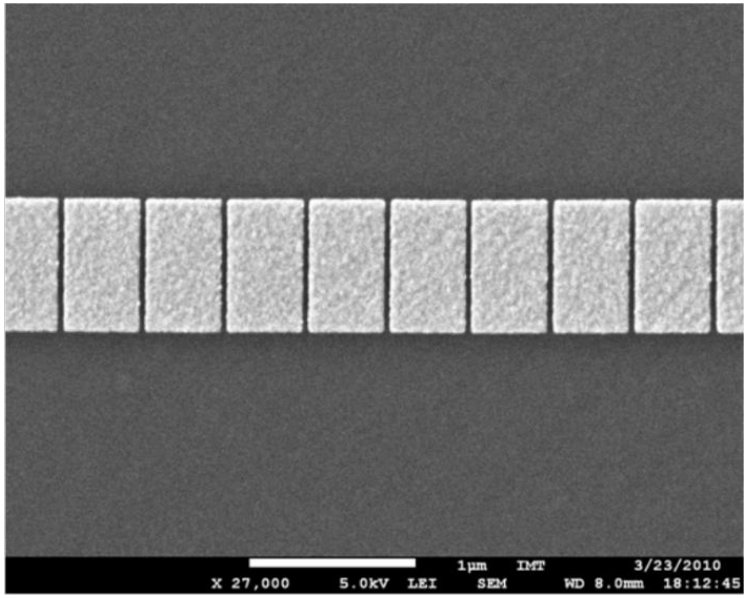
Herminjard et al. (2009) Surface Plasmon Resonance sensor showing enhanced sensitivity for CO2 detection in the mid-infrared range *Opt. Express 17*, 293-303

Nanostructure for sensing

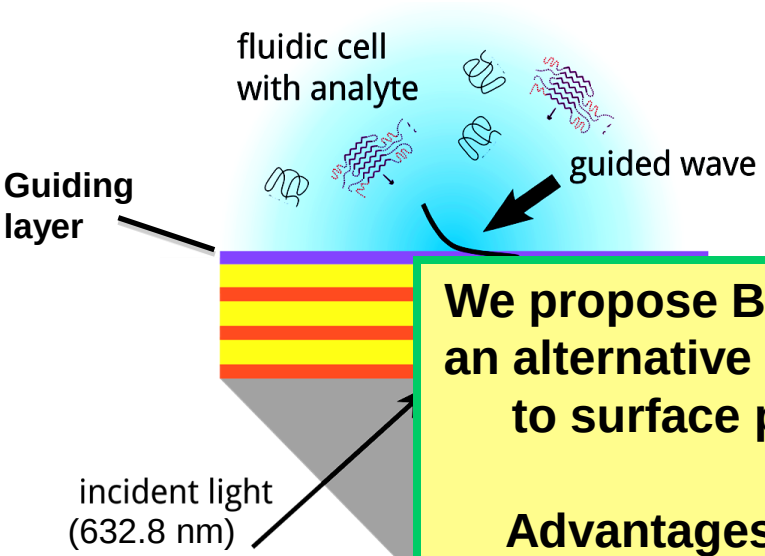


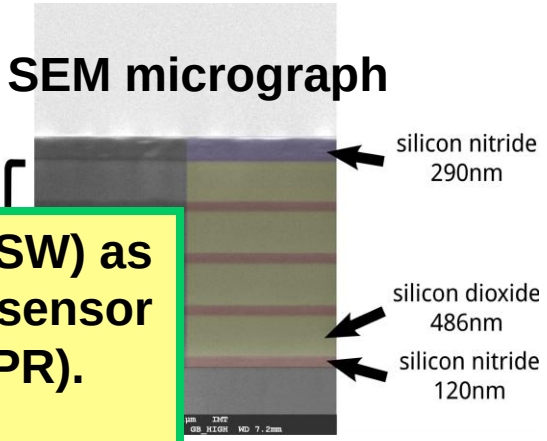


- **Metallic slot waveguide cavity** integrated to a planar dielectric silicon slab waveguide.
- The array of slits allows the confinement of the **electromagnetic field at the surface**.
- **Refractive index sensing**: the transmission spectrum is sensitive to the slot parameters (geometry) and the material filling the slot .
- **Small volumes of analyte**: the active part of the sensor is about 800nm x 15μm
- **Parallel measurements and easy integration into planar devices**



Bloch Surface Waves sensing principle



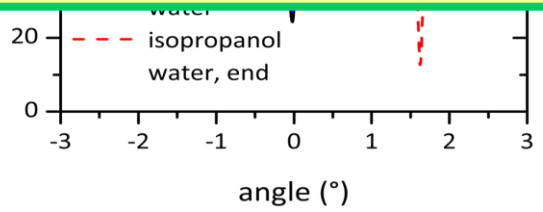


We propose Bloch surface waves (BSW) as an alternative biocompatible optical sensor to surface plasmon resonance (SPR).

Advantages: lower absorption losses, sharper resonance peaks, high propagation length, wide tunability

BSW sensors are made exclusively of dielectric materials, providing additional design freedom

- Surface electrom
surface of **periodic**
- Kretschmann configuration
- Fixed wavelength, variable angle

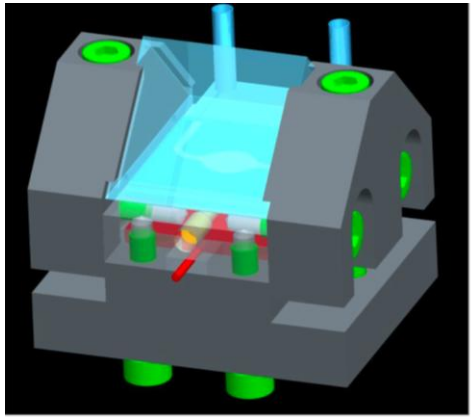


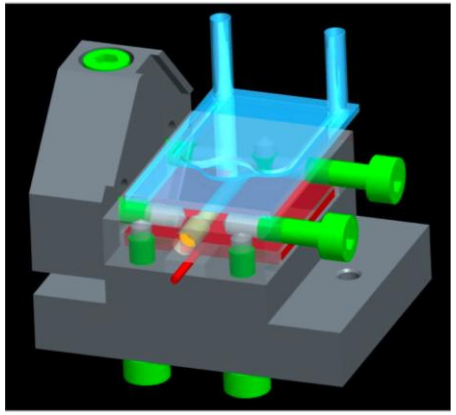
The angular shift corresponds to **refractive index variations**

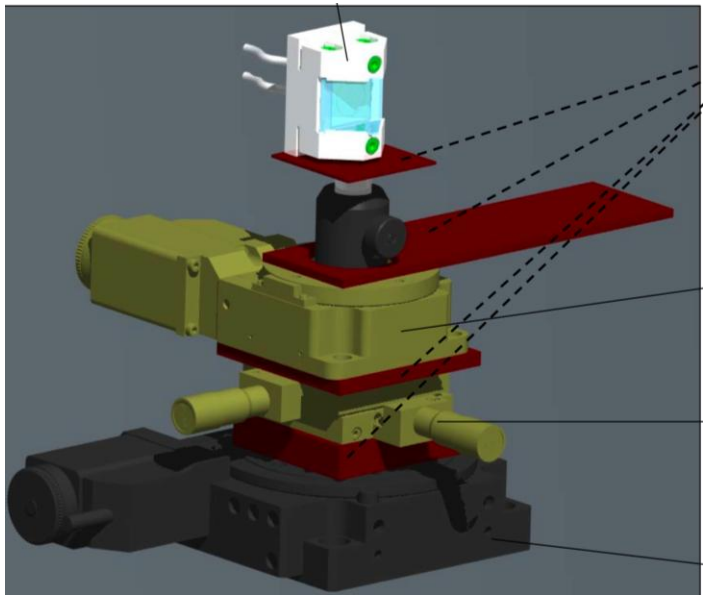
Paeder et al. (2009) Detection of protein aggregation with a Bloch surface wave based sensor. *SUBMITTED*

Descrovi et al. (2008) Near-field imaging of Bloch surface waves on silicon nitride photonic crystals. *Optics express 16* 5453-64

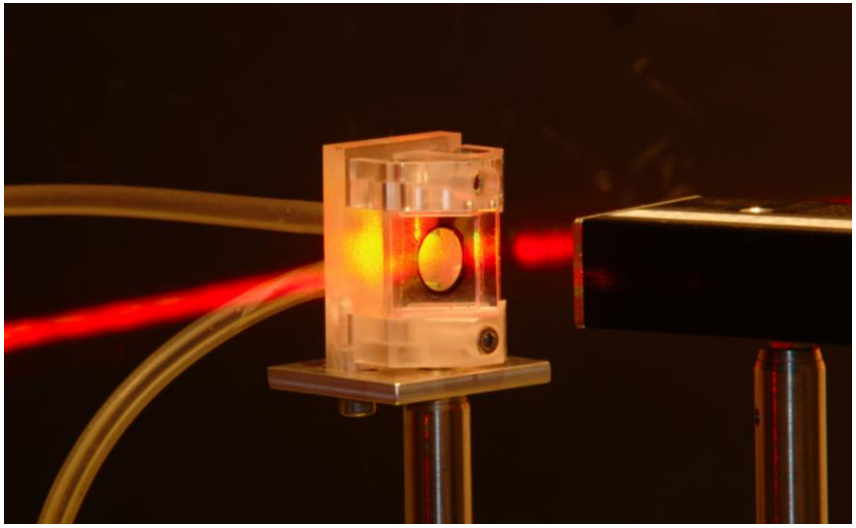
BSW: sensing setup and elements







- **Temperature control system (peltier)**
- **Polymeric-based microfluidic circuit**
- **Controlled flow and temperature in the active region of the sensor.**



Paeder et al. (2009) Detection of protein aggregation with a Bloch surface wave based sensor. *SUBMITTED*

BSW: experimental results

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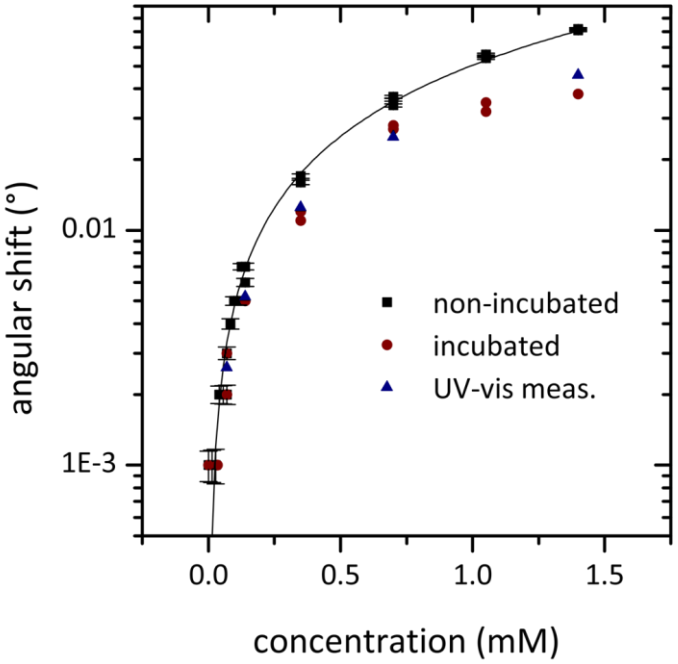
Static measurements

Lysozyme dissolved in 10^{-2}M HCl (pH 2)
- concentrations: 35µM to 1.4mM
-Incubation: 1 week at 65 °C

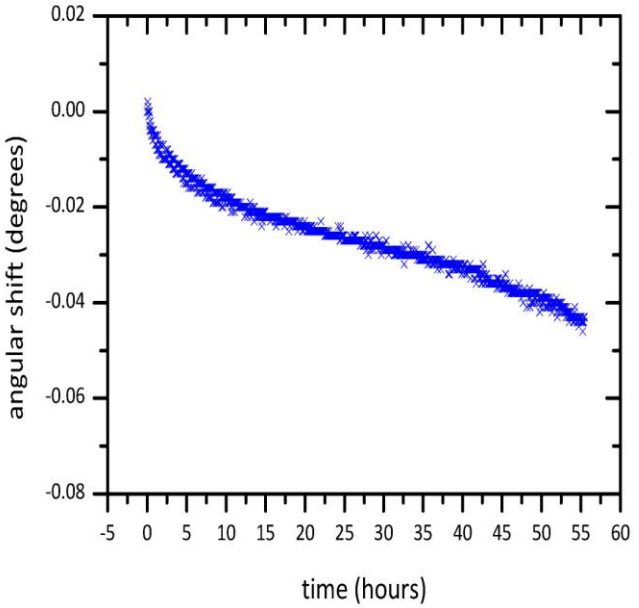
Protein aggregates are discriminated in concentrations of 140µM or higher



Time resolved measurements

- Monomeric Amyloid-beta samples are placed in a microfluidic cell with temperature control
- measurements are taken during the incubation process

40µm Amyloid-beta: 50 hours at 37°C
pH7.4



Paeder et al. (2009) Detection of protein aggregation with a Bloch surface wave based sensor. *SUBMITTED*

Conclusions and Prospective

SPR, BSW and nanostructure based sensors can be easily adapted for biological and medical applications

- High sensitivity provided by light localized at surfaces
- Detection of proteins near to physiological concentrations
- Possibility to perform chemical functionalizations for specific biosensing
- Integration of polymeric microfluidic circuits

-

SPR measurements with liquids in the mid-infrared for biology applications

Nano-structures allow parallel measurements and easy integration

BSW are supported by a wide range of dielectric materials

Acknowledgments

Prof. Hans Peter Herzig

Vincent Paeder (BSW)
Sylvain Herminjard (SPR)
Dr. Matthieu Roussey (Nanostructures)

Lubos Hvozdara
Lorenzo Sirigu
Wataru Nakagawa
Hilal Lashuel
Emiliano Descrovi
Annalisa Pastore