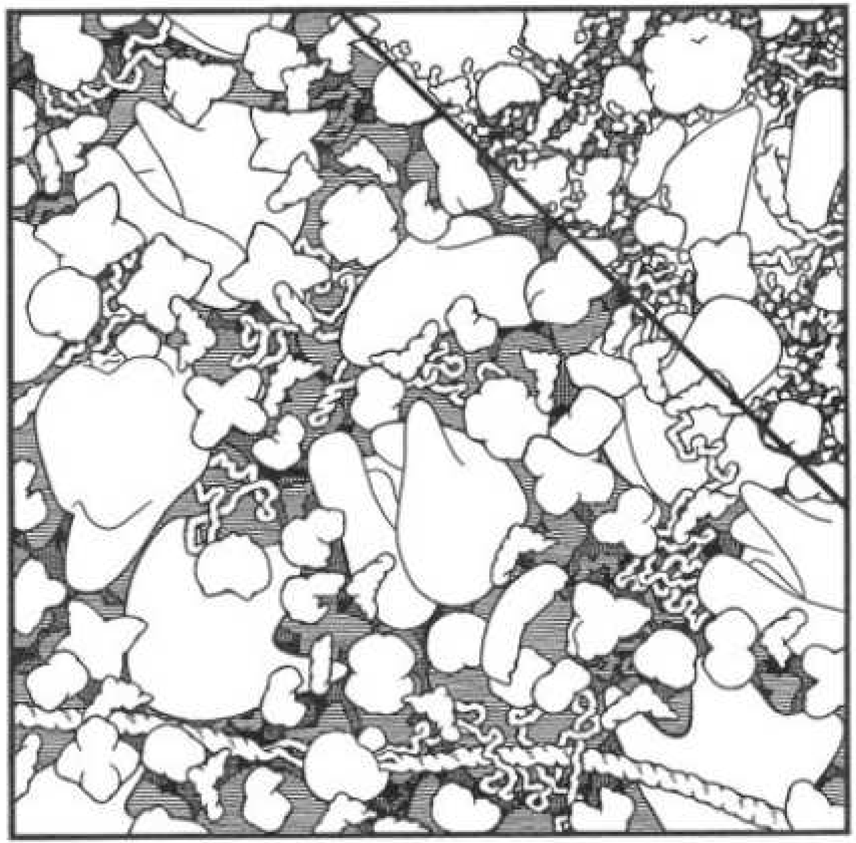
UNIVERSITY OF EXETER | LIVING SYSTEMS INSTITUTE

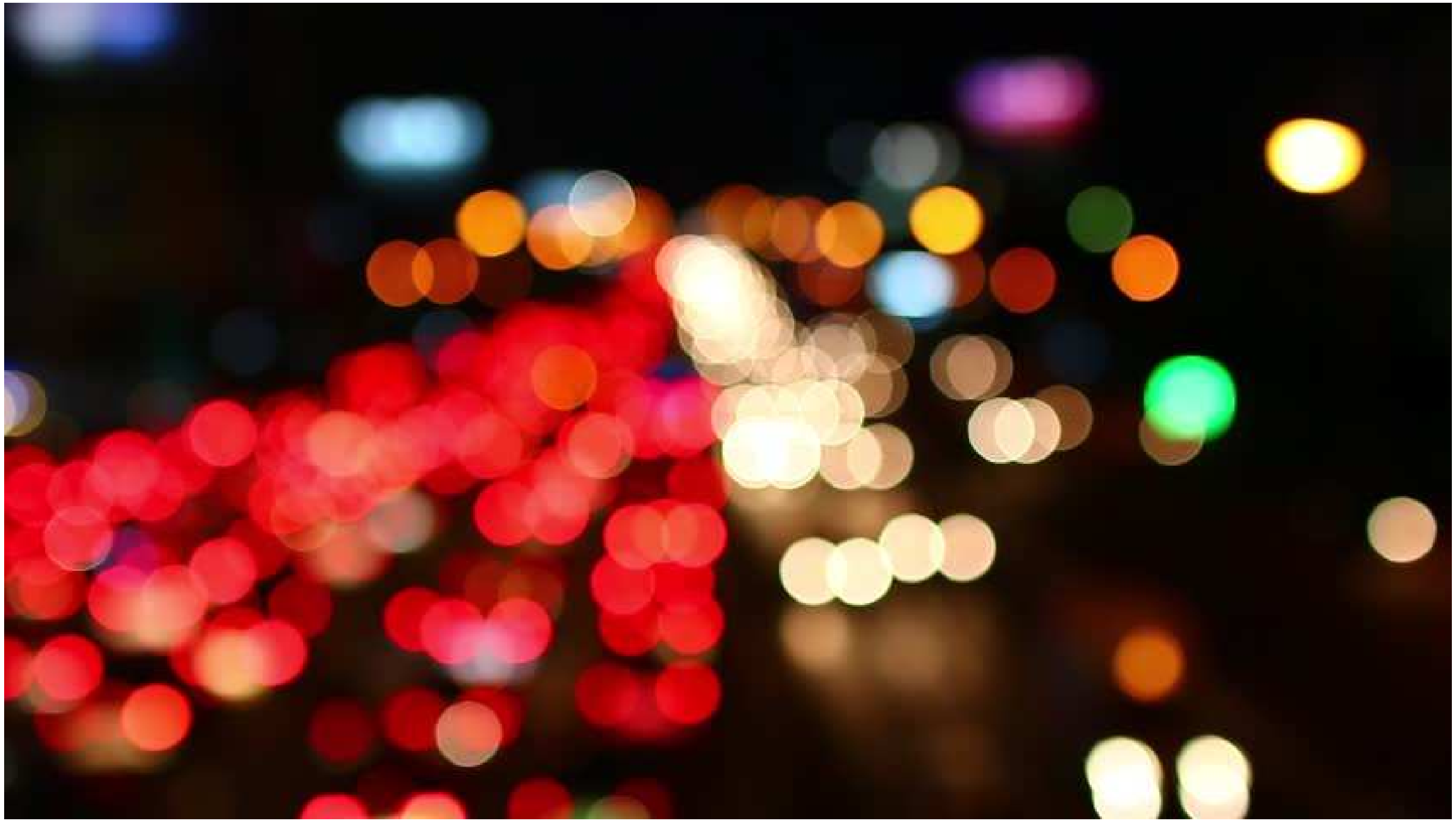

- **Frank Vollmer –**

University of Exeter, UK

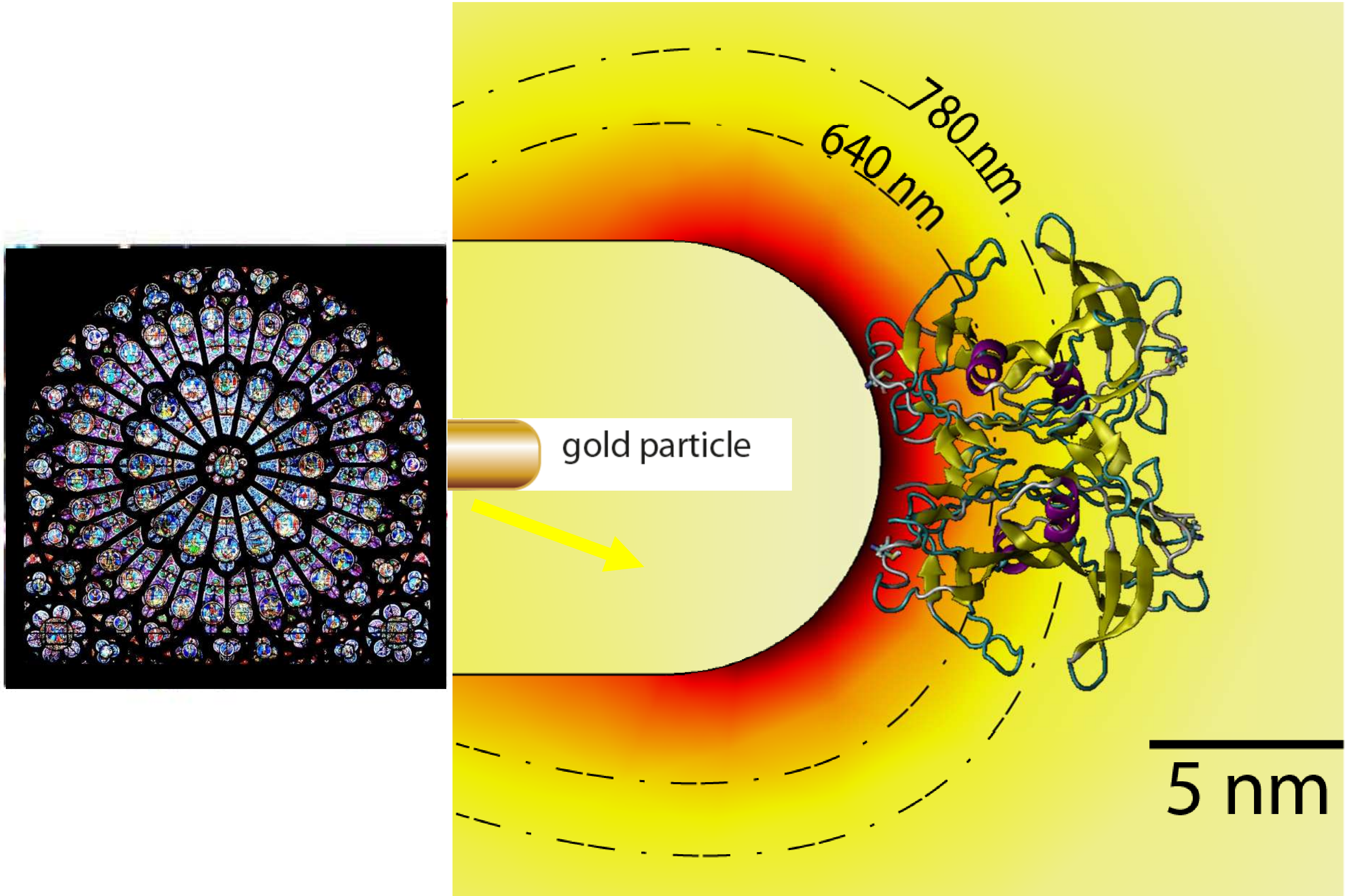

# Exploring the Nanoscale with Optoplasmonic Sensors

From David Goodsell, *The Machinery of Life* (1993)



Source: googleimages



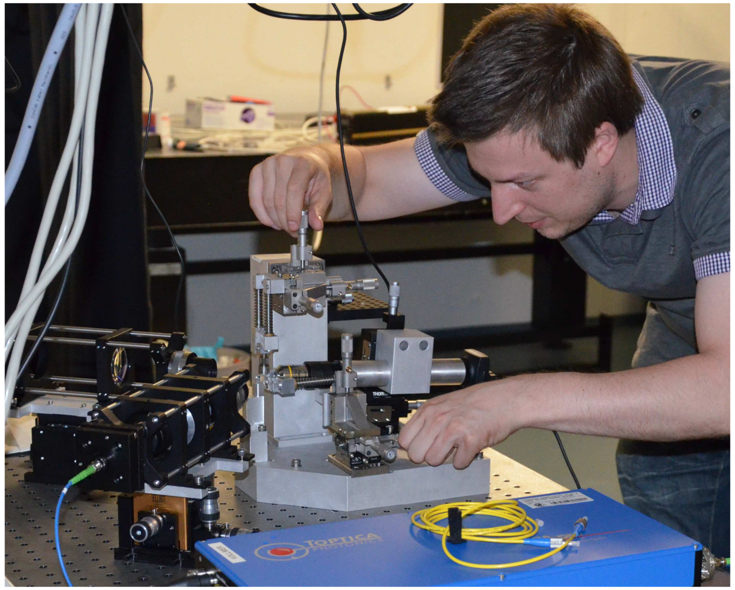
780 nm
640 nm
gold particle
5 nm

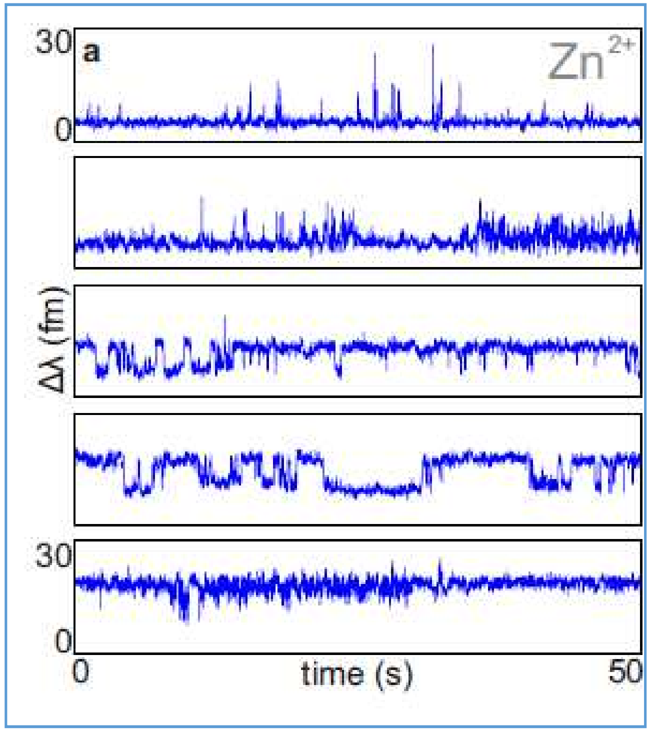
# Observing the Machinery of Life directly with Light

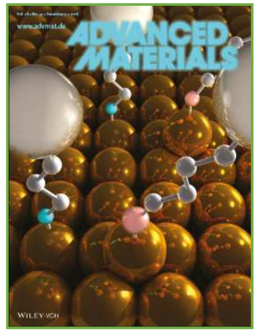
…. to understand how the machinery of life functions

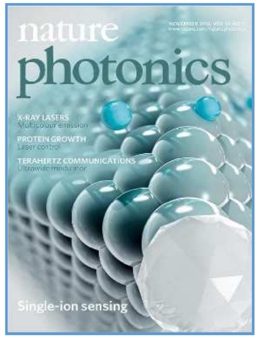
…. to detect the establishment of disease early and rapidly

…. to realise novel single-molecule biosensors, diagnostic tools, and drug screens

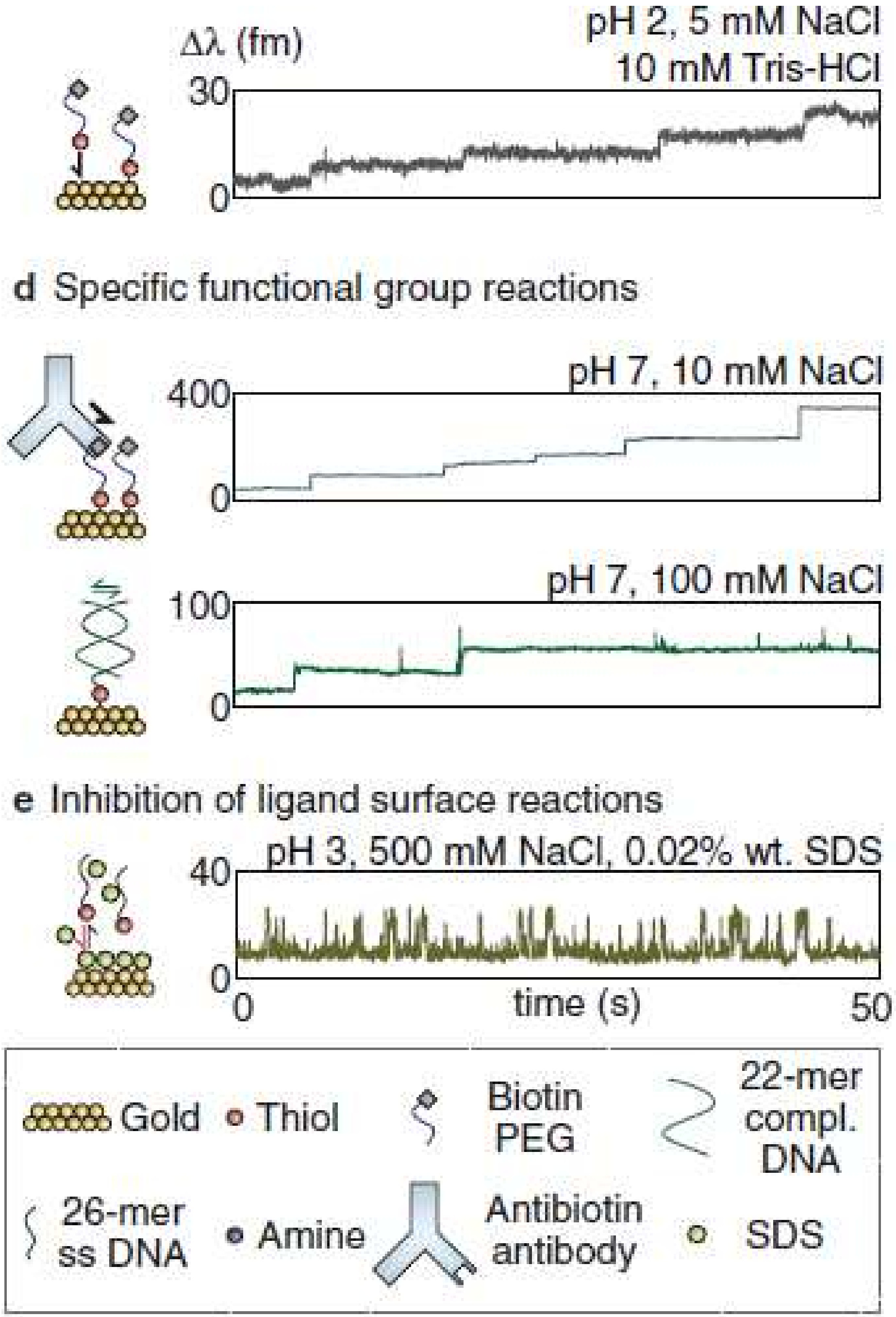




Kim E, Baaske MD, Vollmer F.
*In Situ Observation of Single-Molecule Surface Reactions from Low to High Affinities*
***Advanced Materials***, 28, **2016**



ultraprecise
lasers

micro/nano-
sensors

# Outline

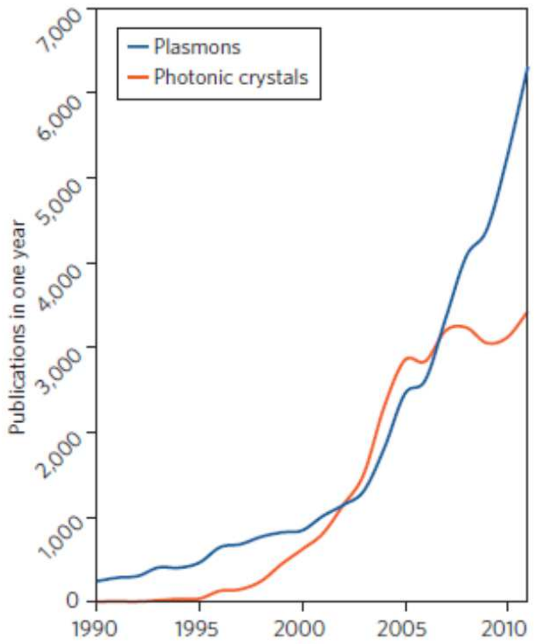
1. How can we visualise nanoscale processes with precision lasers and nanosensors?
2. How can we enhance the signal so drastically?
3. Which biomolecular processes can we study? Timescales? Nanomachines?
4. Outlook

# TUTORIAL REVIEW

## Nanoplasmonics for chemistry

Guillaume Baffou[a] and Romain Quidant*[bc]

Cite this: *Chem. Soc. Rev.*, 2014, **43**, 3898




From Nature Photonics 2012 Editorial

### Surface plasmon resurrection

The realization that coupling of photons to charges at metal interfaces allows subdiffraction-limit localization of light has revived the field of surface plasmons. How long will it last?

NANO LETTERS

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Letter

### Single Unlabeled Protein Detection on Individual Plasmonic Nanoparticles

Irene Ament†, Janak Prasad†‡, Andreas Henkel†, Sebastian Schmachtel†, and Carsten Sönnichsen*†
† Institute for Physical Chemistry, University of Mainz, D-55128 Mainz, Germany
‡ Graduate School Materials Science in Mainz, Staudingerweg 9, D-55128 Mainz, Germany

*Nano Lett.*, **2012**, *12* (2), pp 1092–1095
**DOI:** 10.1021/nl204496g

*NATURE NANOTECHNOLOGY* | LETTER

Optical detection of single non-absorbing molecules using the surface plasmon resonance of a gold nanorod

Peter Zijlstra, Pedro M. R. Paulo & Michel Orrit

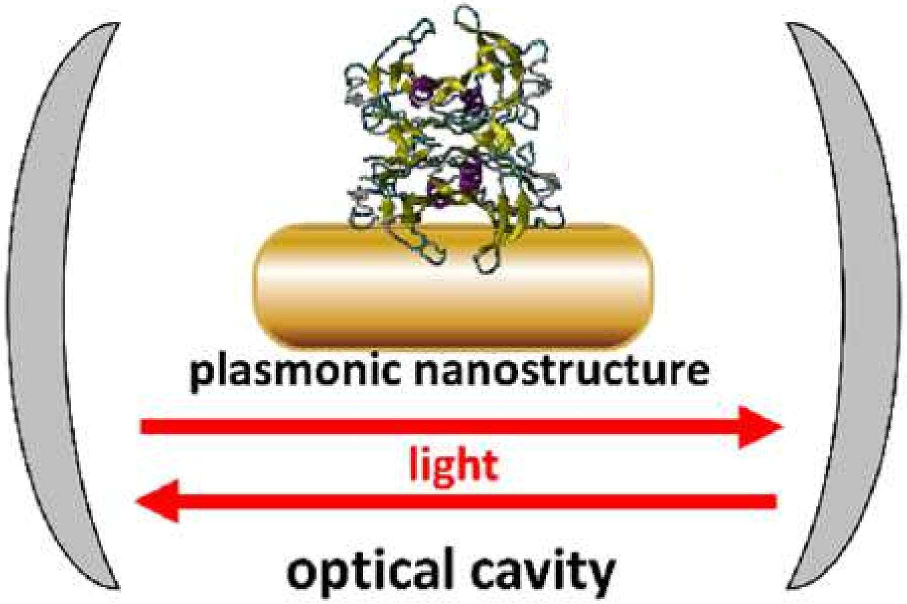
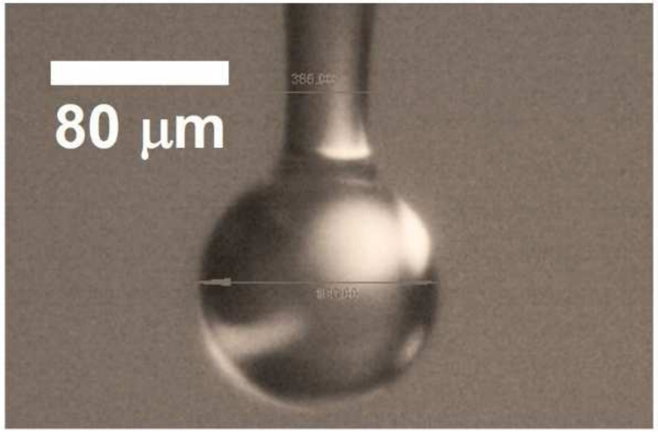
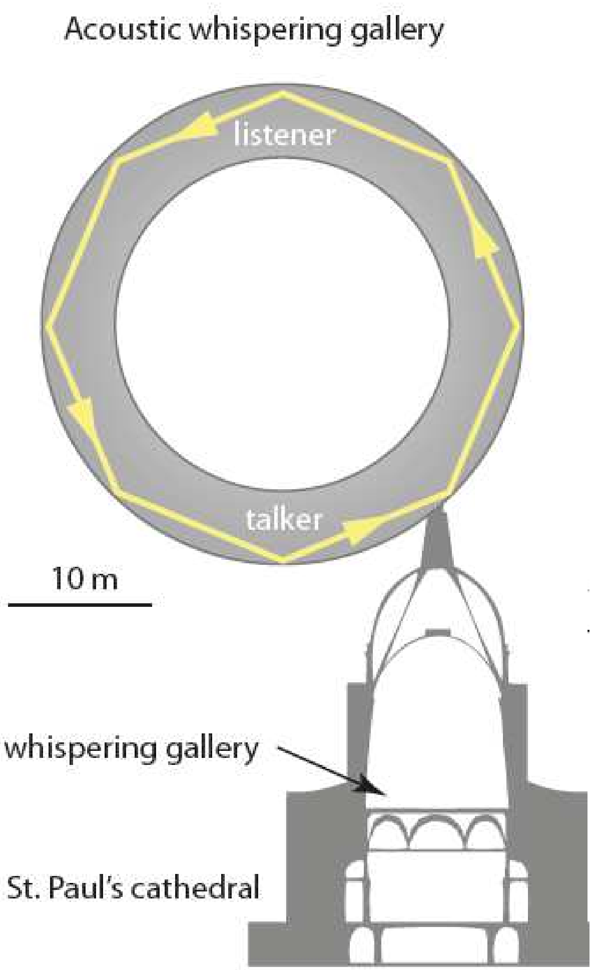
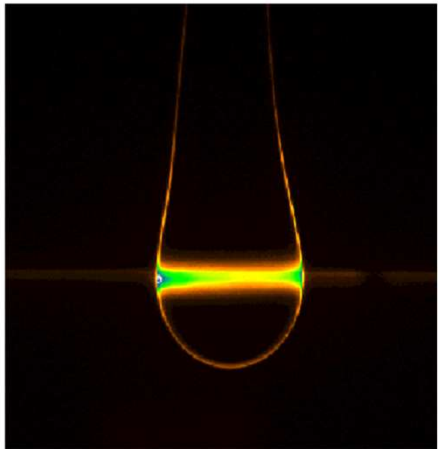

plasmonic nanostructure
light
optical cavity

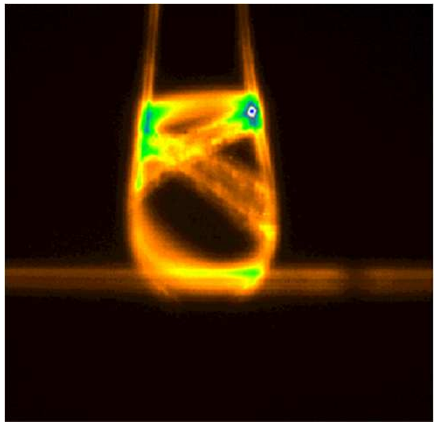

Image source: google images

# MICROCAVITY: GLASS MICROSPHERE

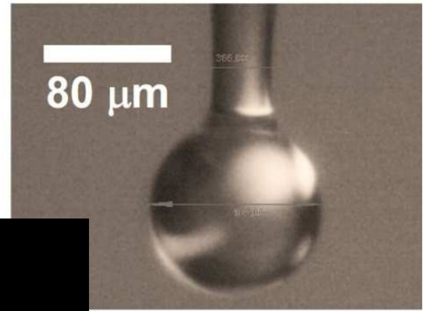


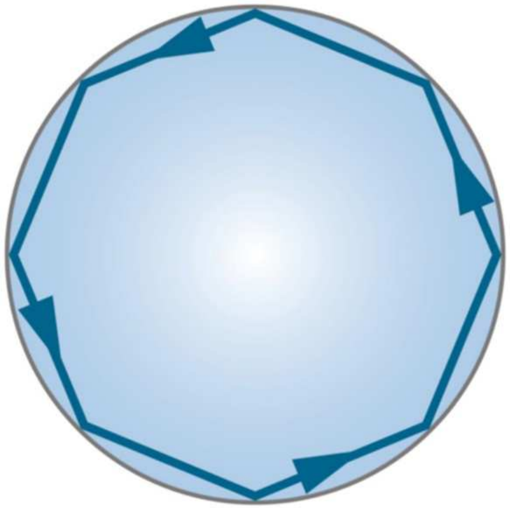



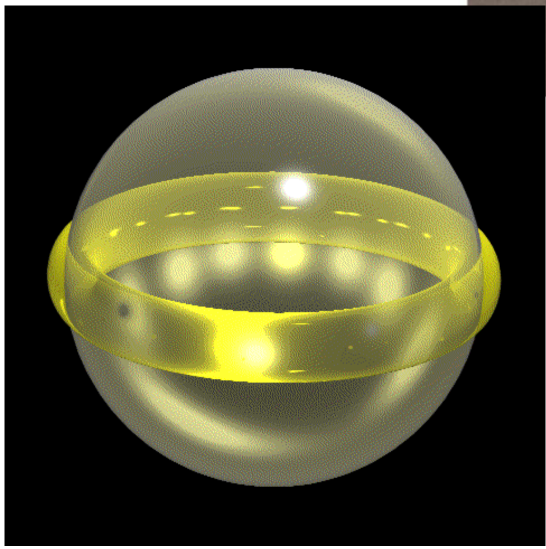


## Optical Resonance in Glass Microsphere



Geometric optics



Wave optics

**one precise wavelength / frequency!**

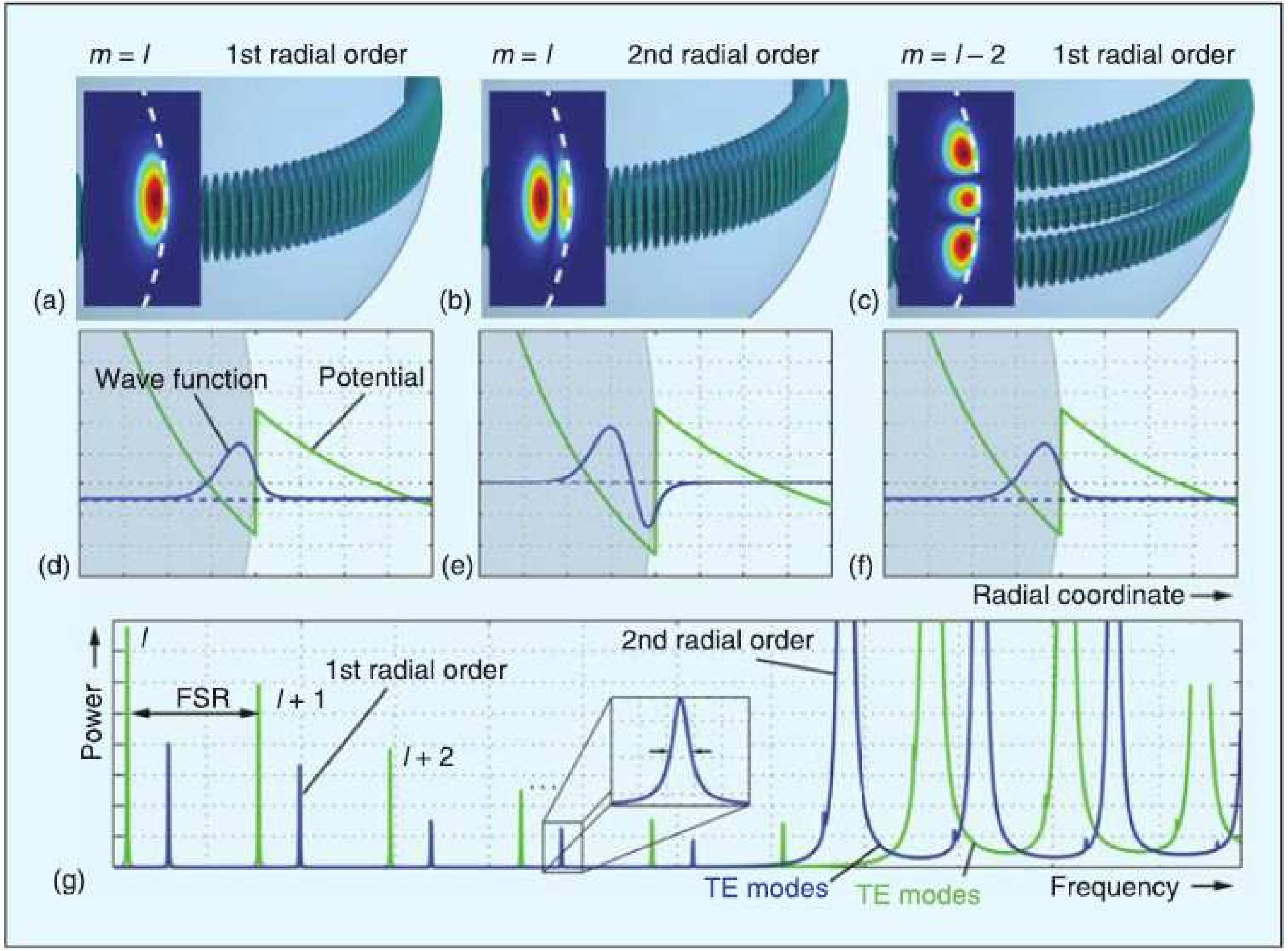
# WHISPERING GALLERY MODES IN GLASS MICROSPHERES

**Q ~ $10^{6-7}$**

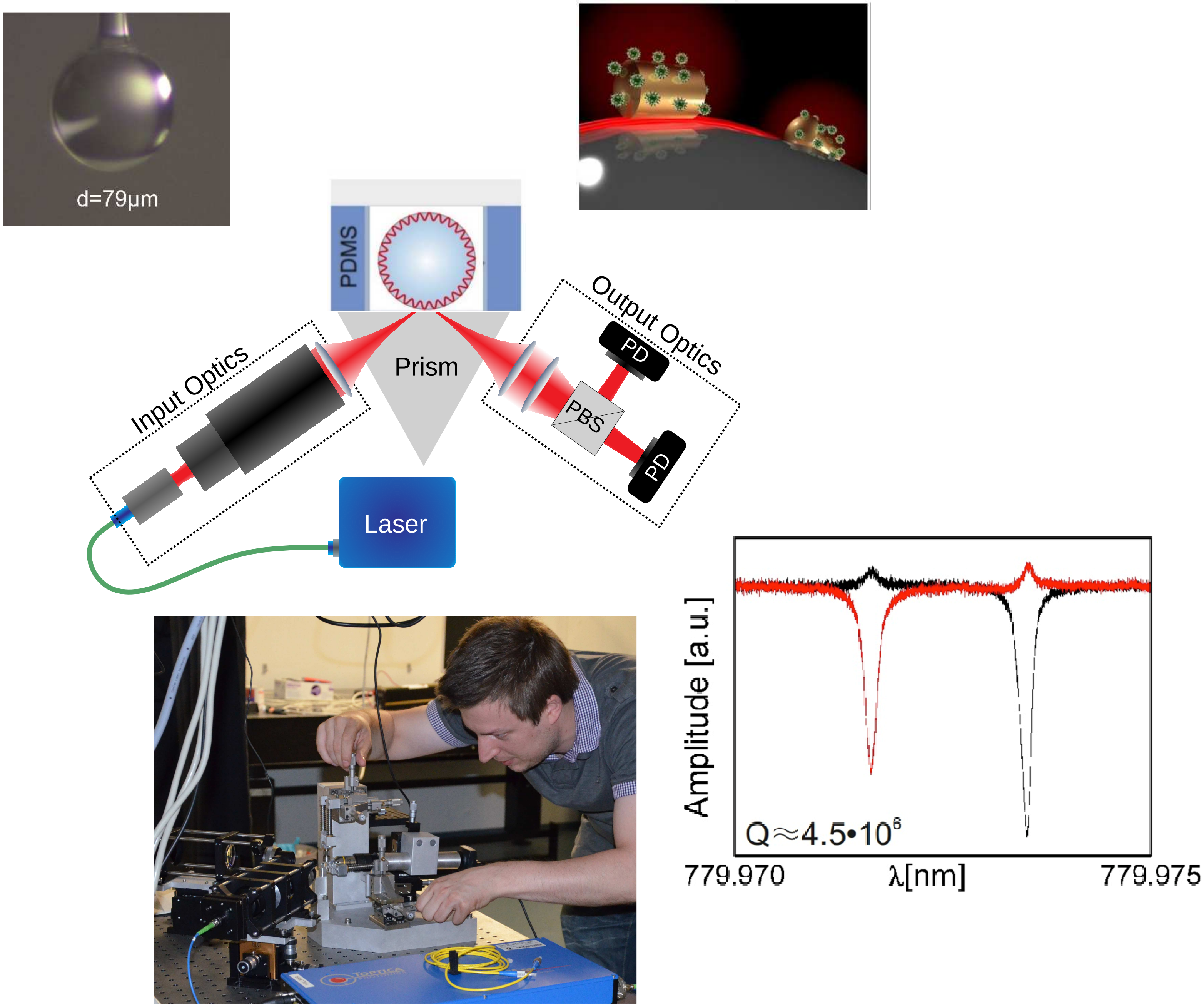
**FSR ~ 1 nm**

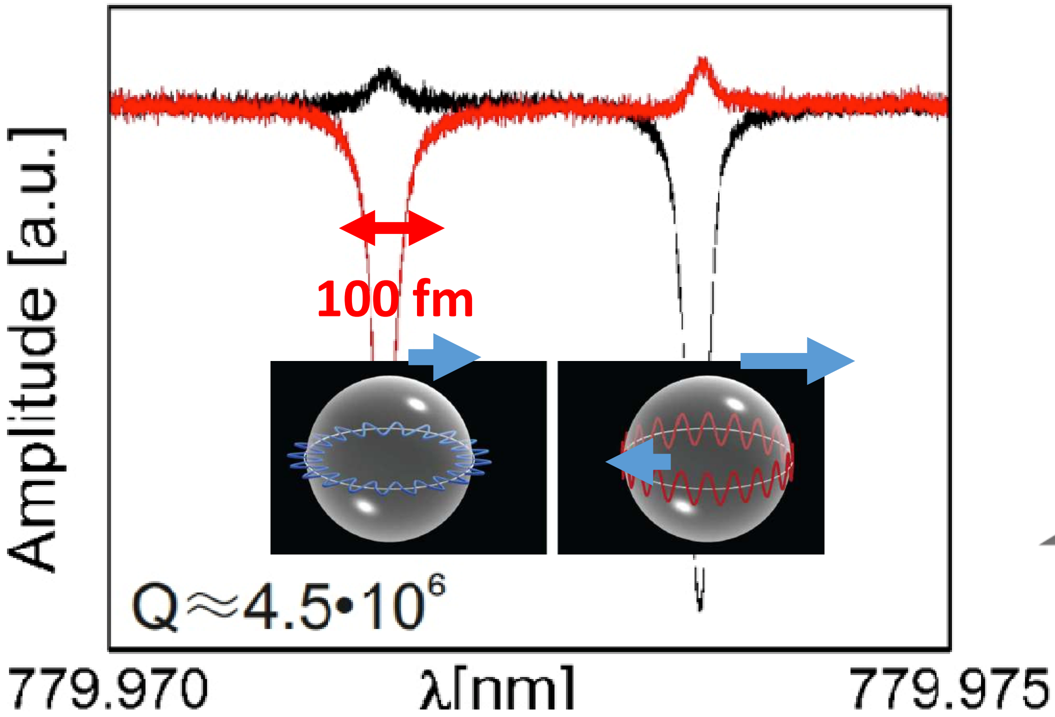
**Finesse > 1000**

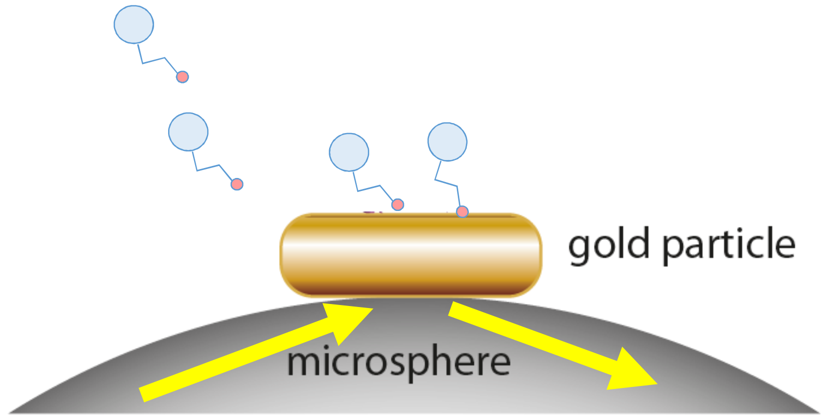
**visible to near-IR**

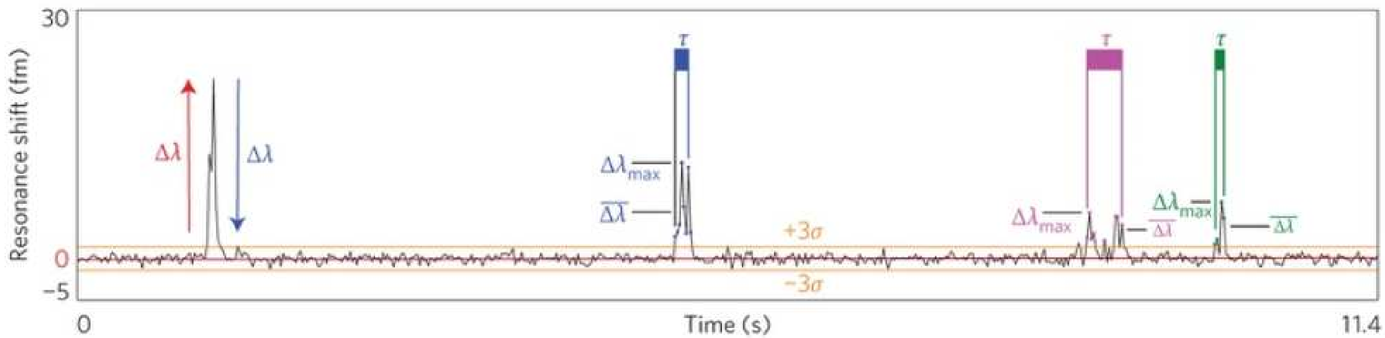



M. R. Foreman, J. Swaim and F. Vollmer, Advances in Optics and Photonics (2015).


d=79µm
PDMS
Prism
Input Optics
Output Optics
PD
PBS
PD
Laser
Amplitude [a.u.]
Q≈4.5•10⁶
779.970
λ[nm]
779.975



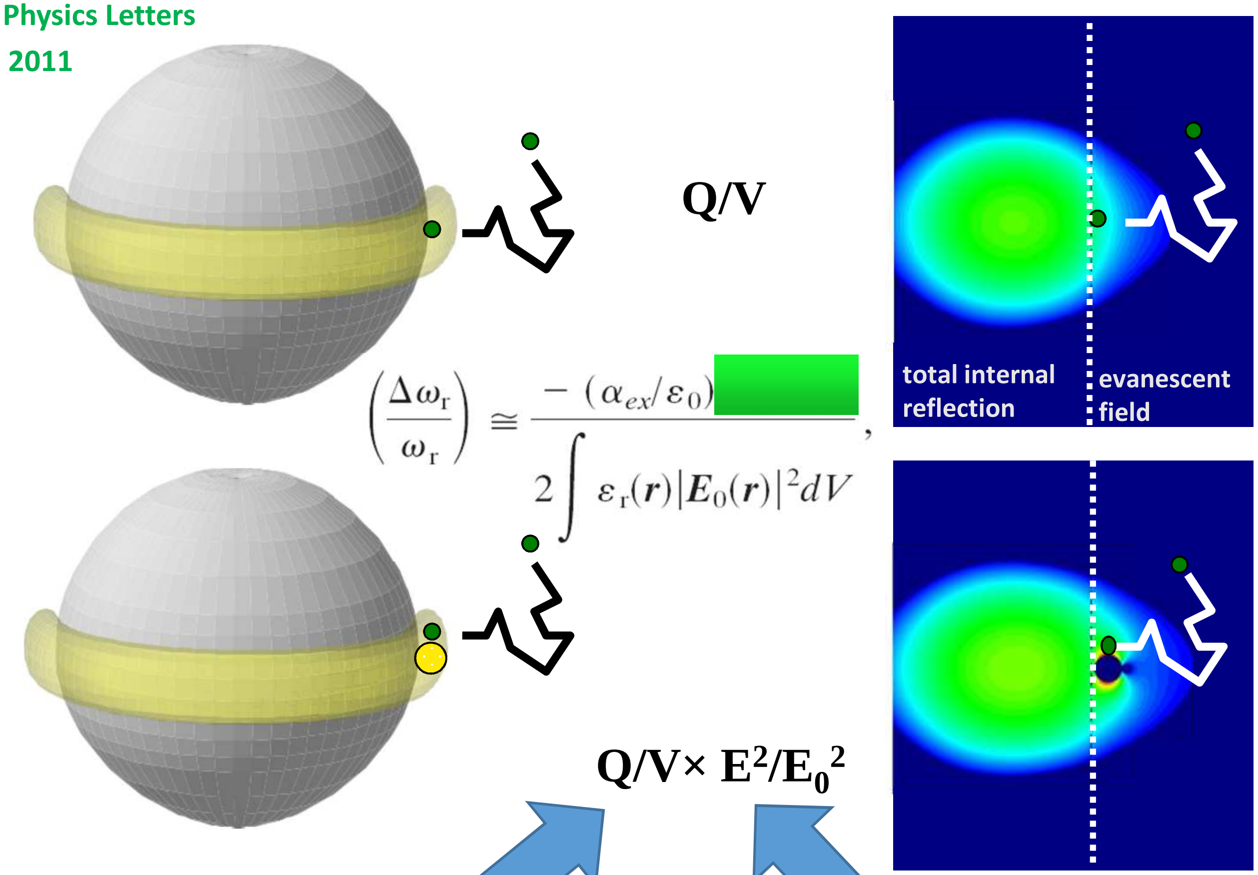




**adaptable for detecting virtually any biomolecule**

# Why so sensitive?

# Sensing Mechanism

Applied Physics Letters
May 4th, 2011




$$\left(\frac{\Delta\omega_r}{\omega_r}\right) \cong \frac{-(\alpha_{ex}/\varepsilon_0)}{2\int \varepsilon_r(\boldsymbol{r})|\boldsymbol{E}_0(\boldsymbol{r})|^2 dV},$$

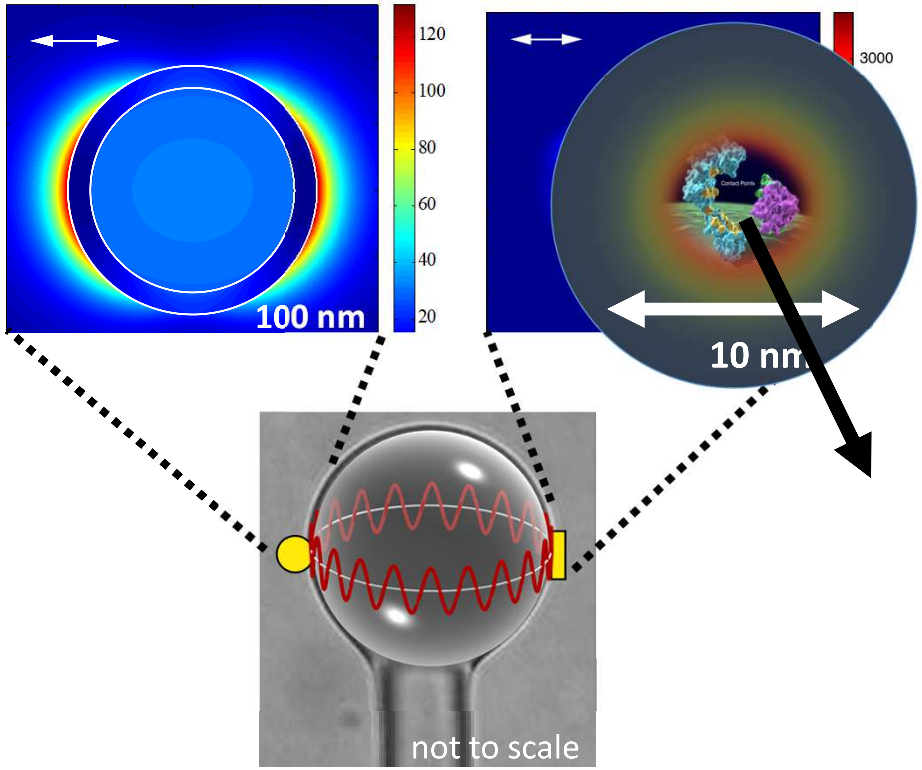
$$Q/V \times E^2/E_0^2$$

sensing with optical microavities

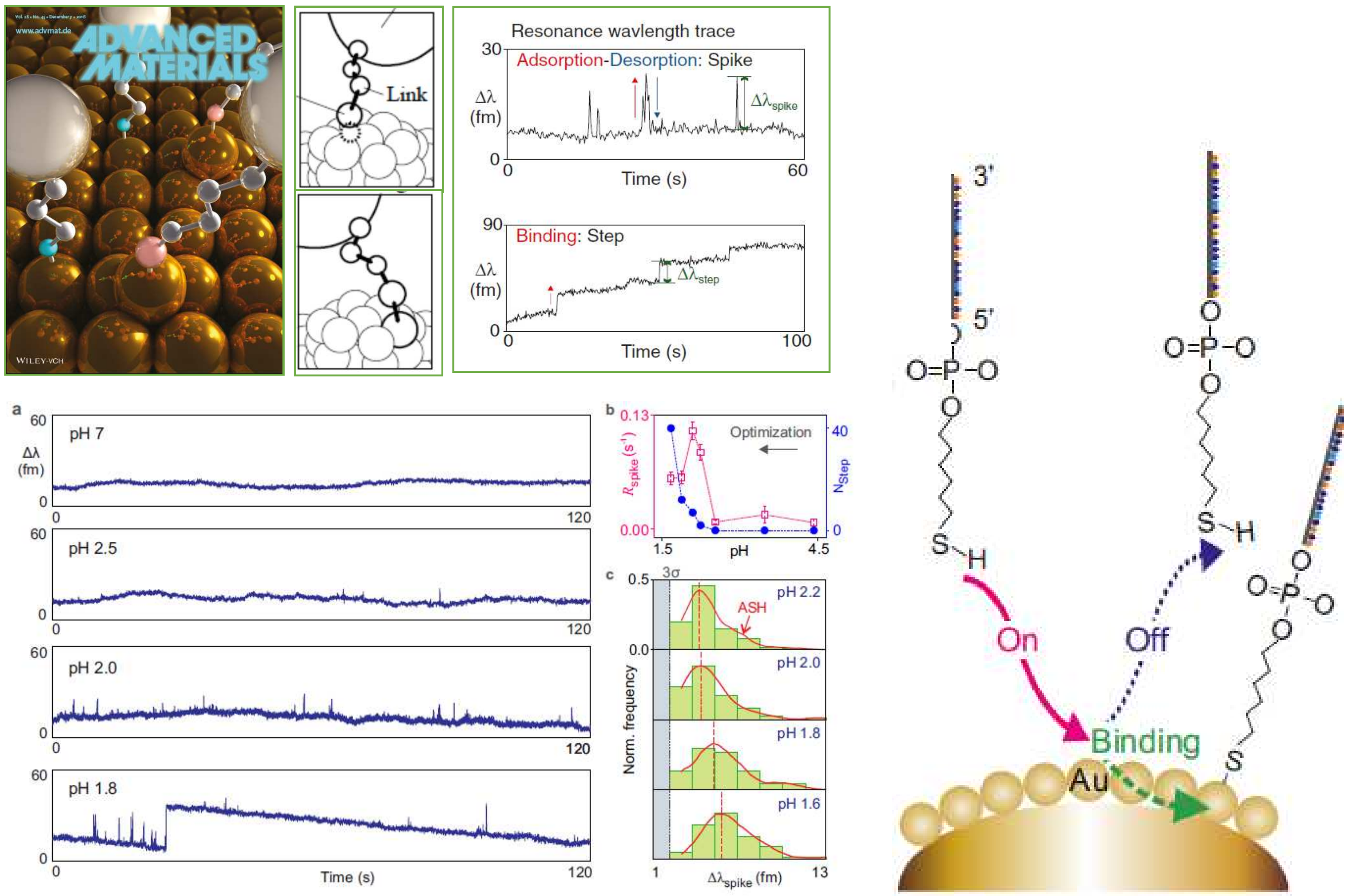
sensing with optoplasmonic microavities
**x1000**

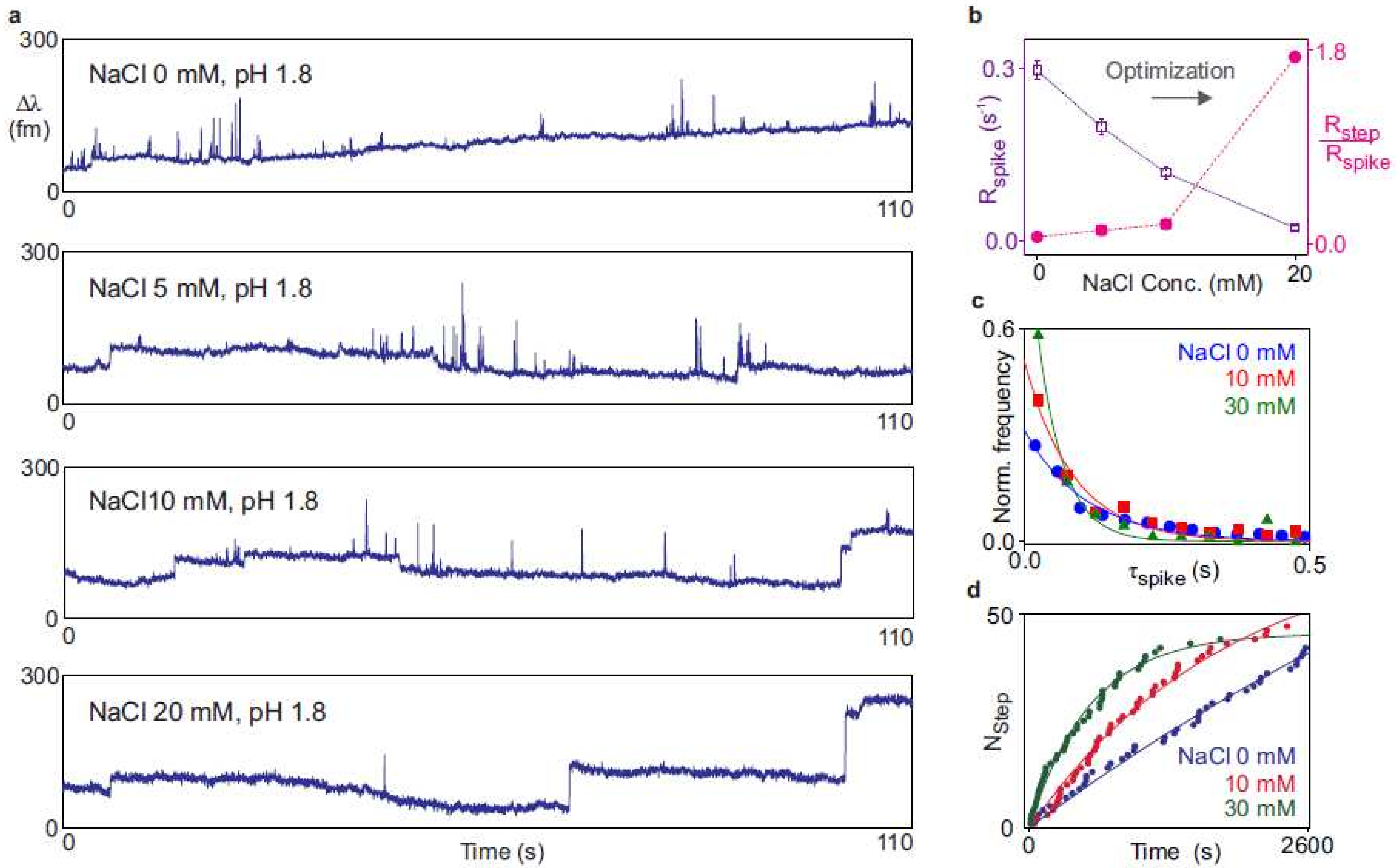
# PLASMONIC ENHANCEMENTS

100 x enhancement




1000 x enhancement

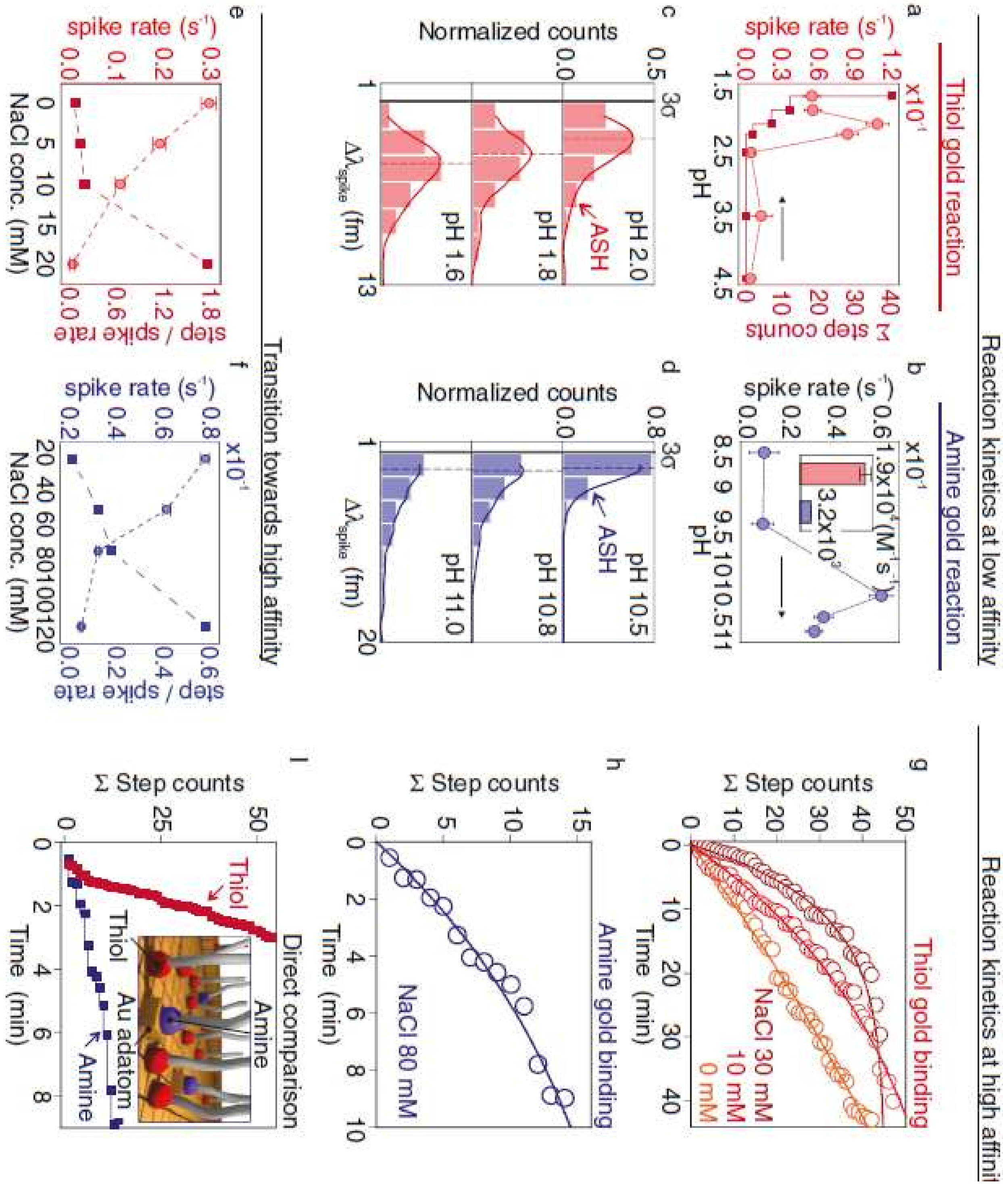

ADVANCED MATERIALS
www.advmat.de
WILEY-VCH
Link
Resonance wavlength trace
Adsorption-Desorption: Spike
Binding: Step
Δλ (fm)
Time (s)
Δλspike
Δλstep
a
pH 7
pH 2.5
pH 2.0
pH 1.8
b
Optimization
Rspike (s-1)
NStep
pH
c
3σ
ASH
pH 2.2
pH 2.0
pH 1.8
pH 1.6
Norm. frequency
Δλspike (fm)
3'
5'
O=P-O
S-H
On
Off
Binding
Au
S

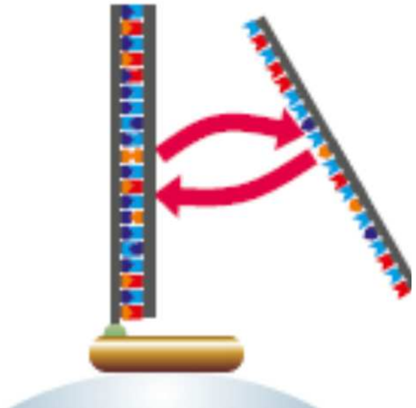


a
300
Δλ
(fm)
0
0
110
NaCl 0 mM, pH 1.8
NaCl 5 mM, pH 1.8
NaCl10 mM, pH 1.8
NaCl 20 mM, pH 1.8
Time (s)
b
0.3
0.0
1.8
0.0
R_spike (s^-1)
R_step / R_spike
Optimization
0
20
NaCl Conc. (mM)
c
0.6
0.0
Norm. frequency
0.0
0.5
τ_spike (s)
NaCl 0 mM
10 mM
30 mM
d
50
0
N_Step
0
2600
Time (s)
NaCl 0 mM
10 mM
30 mM

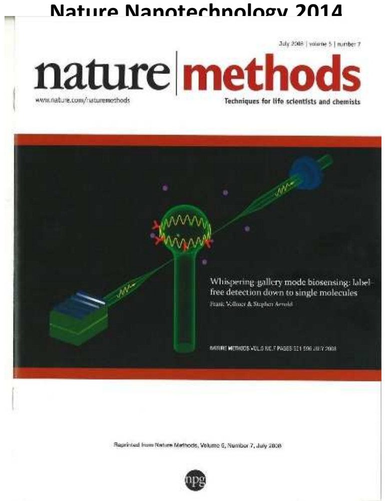
# In Situ Observation of Single-Molecule Surface Reactions from Low to High Affinities

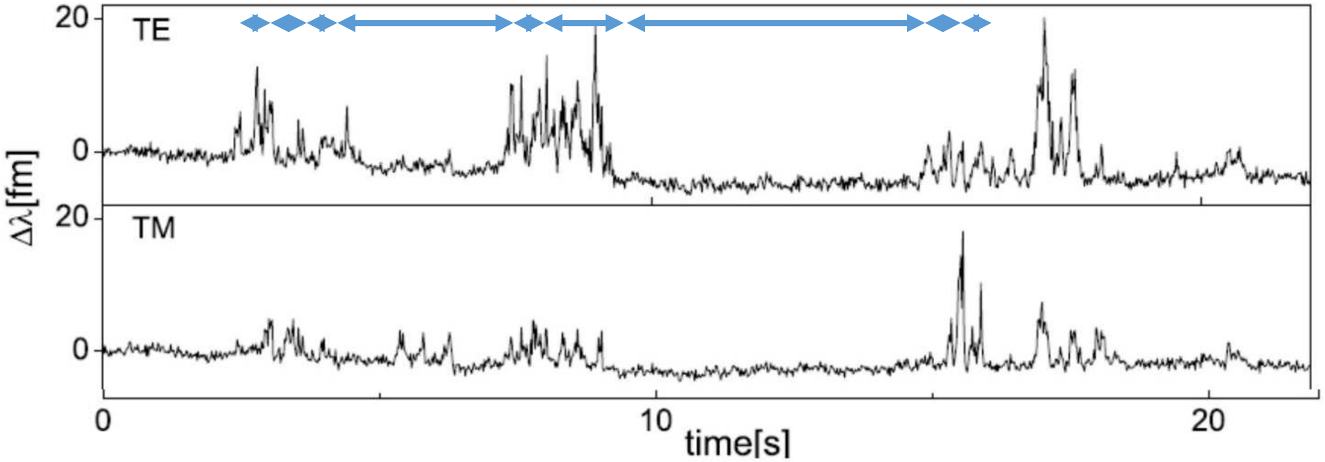
*Eugene Kim, Martin D. Baaske, and Frank Vollmer**

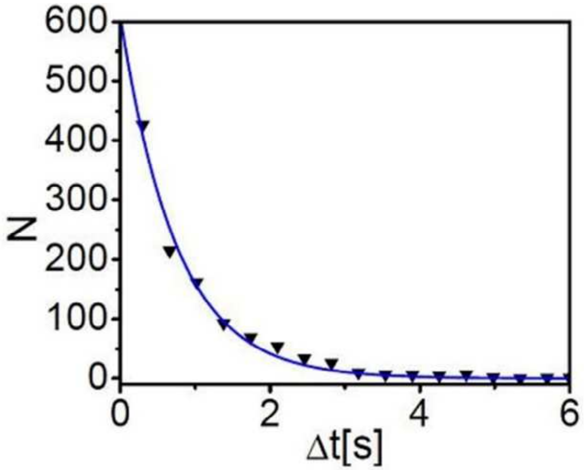


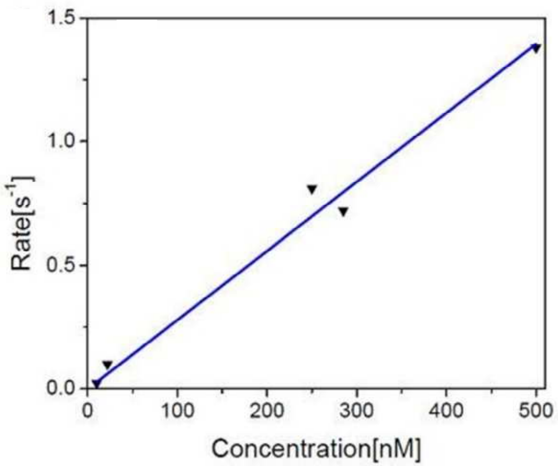


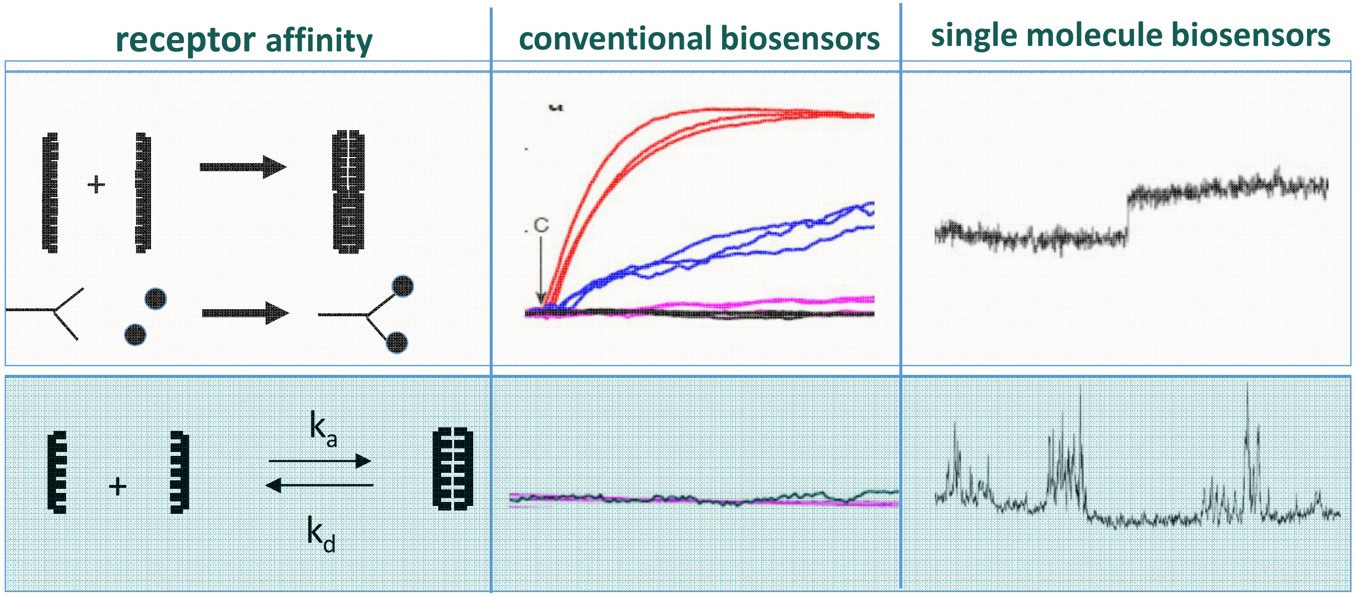
Baaske, Foreman, Vollmer
**Nature Nanotechnology 2014**




receptor affinity
conventional biosensors
single molecule biosensors
C
k_a
k_d

# Opportunities with Label-Free Single Molecule Biosensors

enzymes as „receptors“
biochemical analysis of single molecules

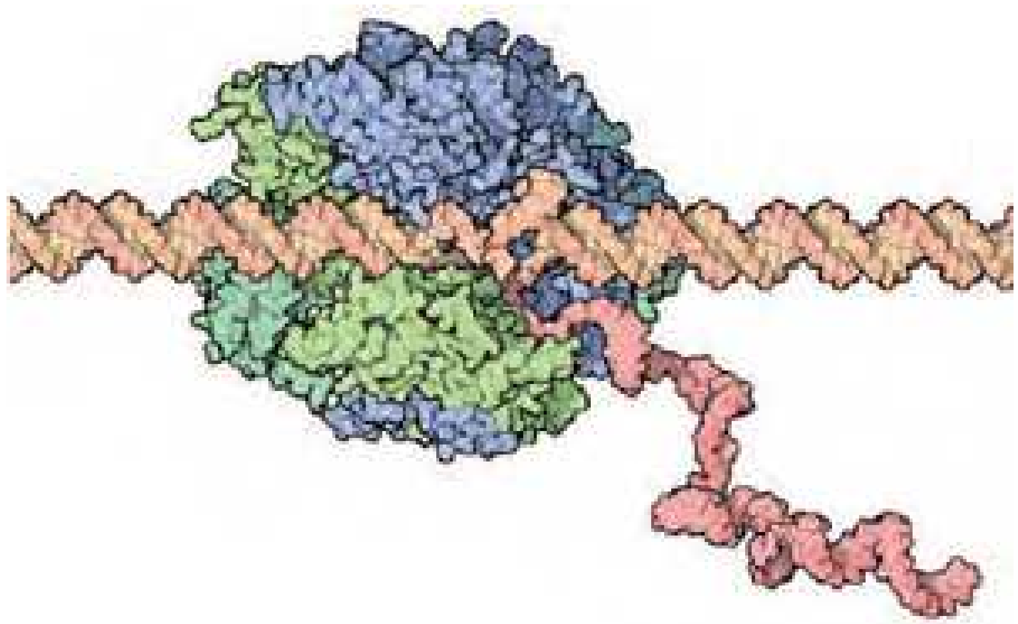
ligand fishing, drug discovery?

kinetic fingerprinting in complex environments

no sensor regeneration

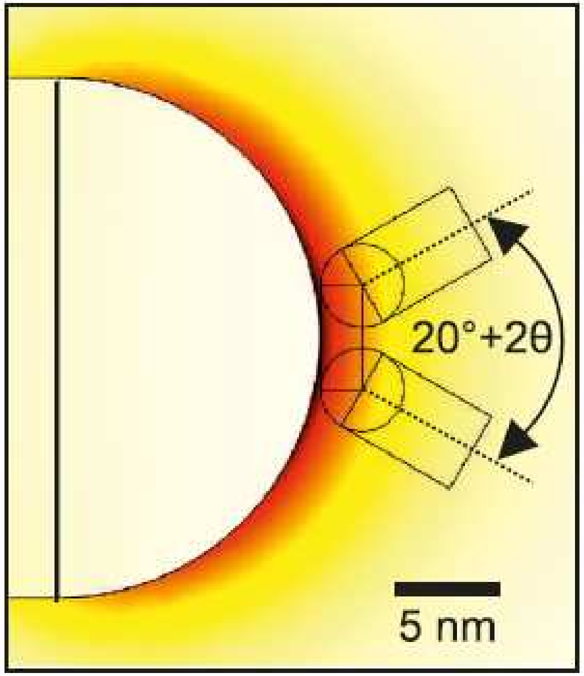
highest sensitivity in optical domain

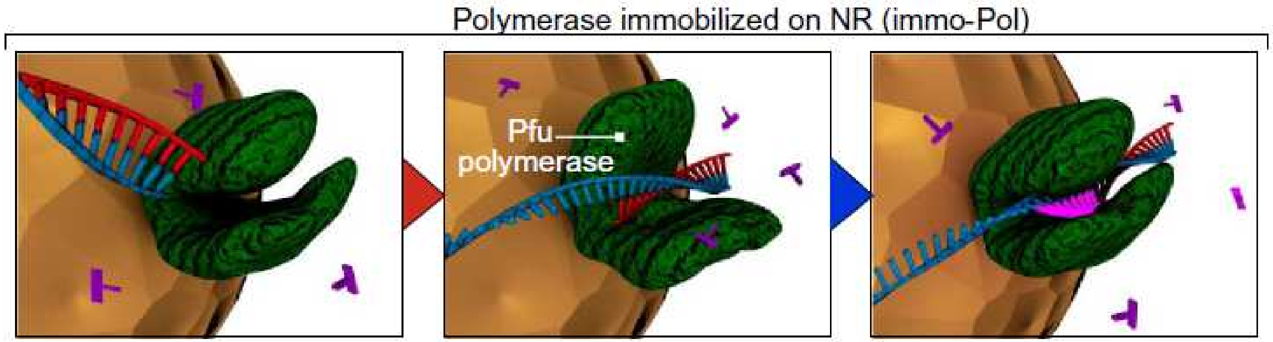
potential for very high time (ns) resolution



From David Goodsell, *The Machinery of Life* (1993)

# OBSERVING THE MOTIONS OF NANOMACHINES




SCIENCE ADVANCES | RESEARCH ARTICLE

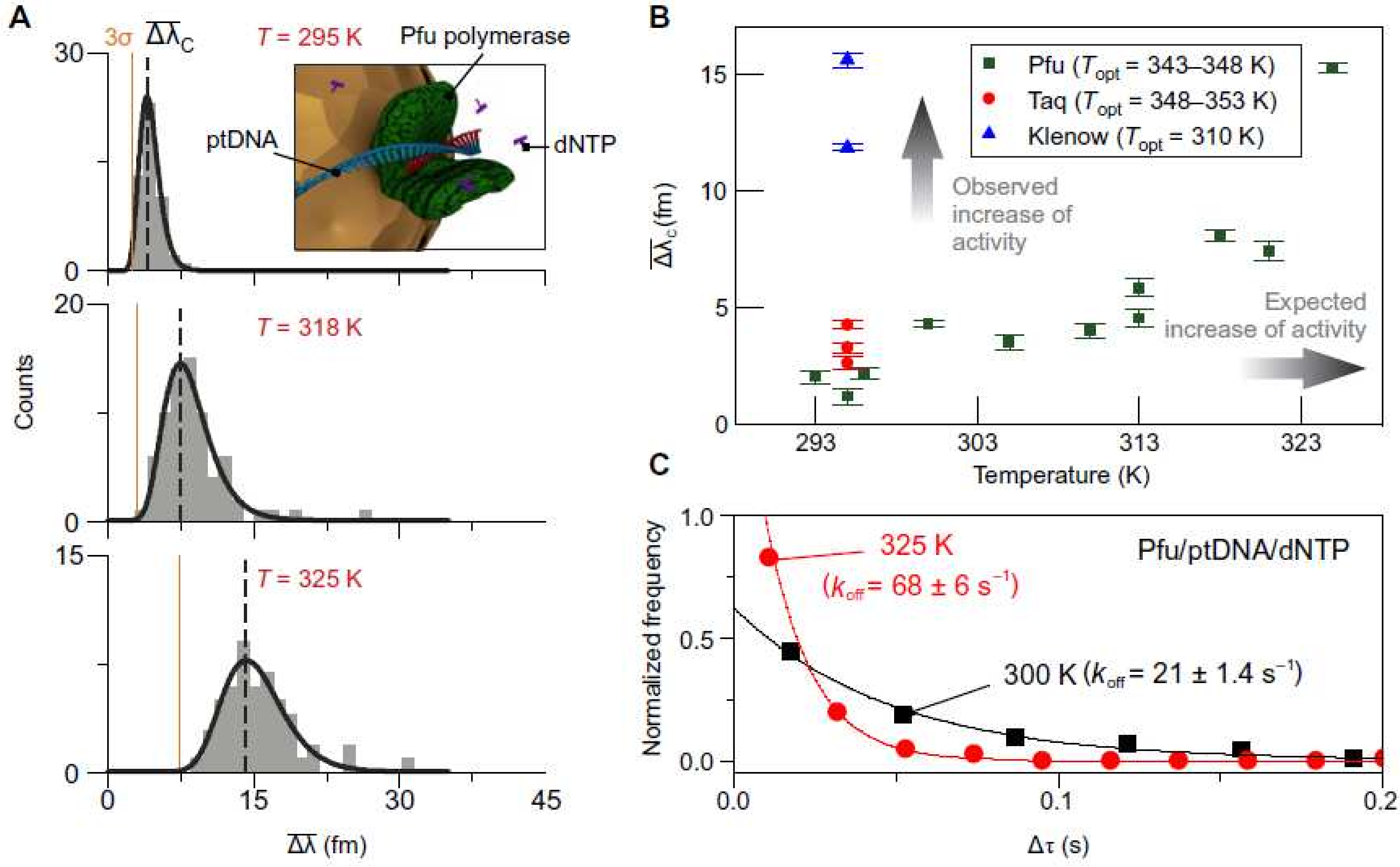
BIOPHYSICS

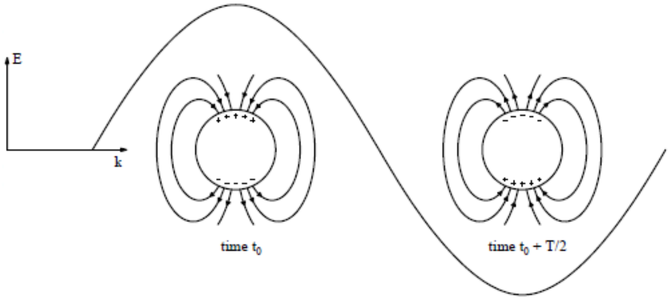
**Label-free optical detection of single enzyme-reactant reactions and associated conformational changes**

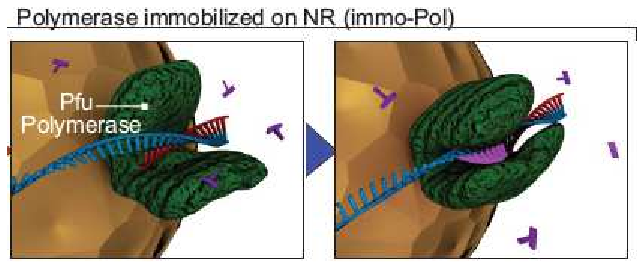

Eugene Kim,*† Martin D. Baaske,*† Isabel Schuldes,†‡ Peter S. Wilsch,† Frank Vollmer*§

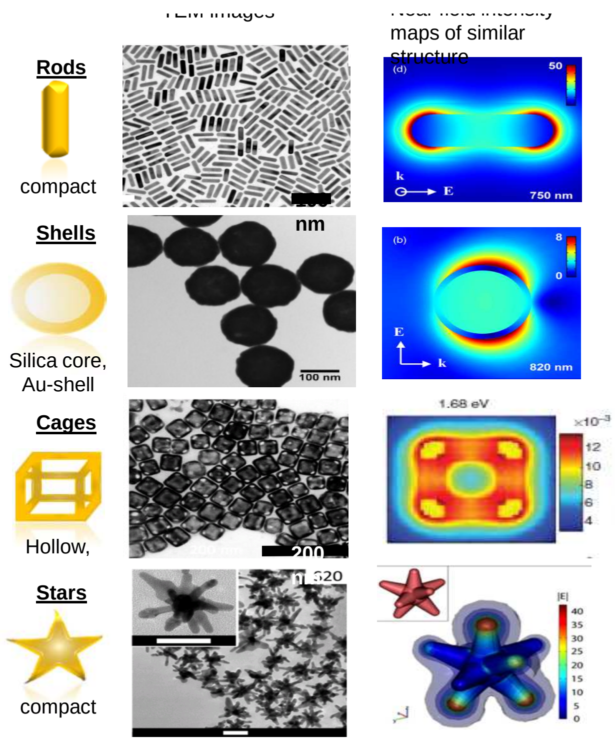

$$\Delta\lambda \propto \alpha_e\left(\int_{V_m(t_2)}|E(r)|^2 dV - \int_{V_m(t_1)}|E(r)|^2 dV\right)$$
$$= \alpha_e\Big(I(t_2) - I(t_1)\Big) = \alpha_e \Delta I$$

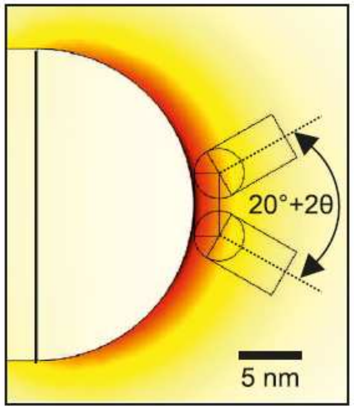
$$I_{\exp,k} = \bar{I}_k = (\tau_m)^{-1}\int_{t_0}^{t_0+\tau_m} I(t)\,dt$$

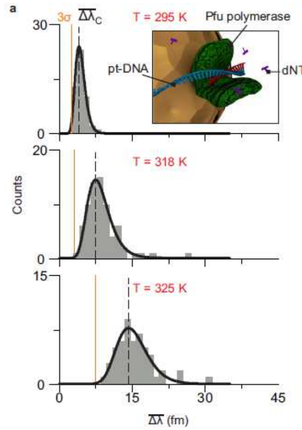

A
3σ
$\overline{\Delta\lambda}_C$
T = 295 K
Pfu polymerase
ptDNA
dNTP
T = 318 K
T = 325 K
Counts
$\overline{\Delta\lambda}$ (fm)
B
Pfu ($T_{opt}$ = 343–348 K)
Taq ($T_{opt}$ = 348–353 K)
Klenow ($T_{opt}$ = 310 K)
Observed increase of activity
Expected increase of activity
$\overline{\Delta\lambda}_c$ (fm)
Temperature (K)
C
Pfu/ptDNA/dNTP
325 K
($k_{off}$ = 68 ± 6 $s^{-1}$)
300 K ($k_{off}$ = 21 ± 1.4 $s^{-1}$)
Normalized frequency
Δτ (s)


E
k
time $t_0$
time $t_0$ + T/2

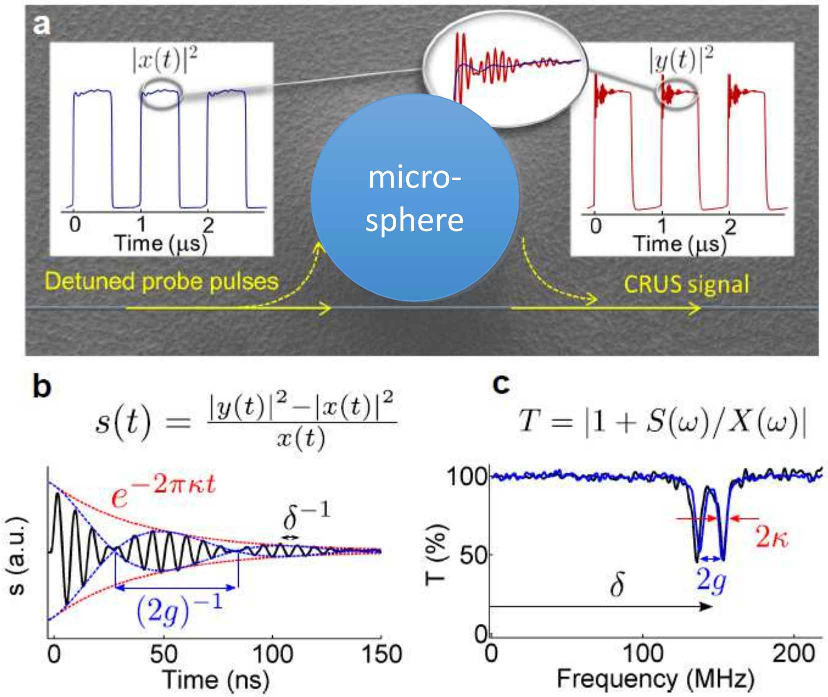

Polymerase immobilized on NR (immo-Pol)
Pfu
Polymerase


maps of similar
Rods
compact
Shells
Silica core,
Au-shell
Cages
Hollow,
Stars
compact
nm
100 nm
750 nm
820 nm
1.68 eV
|E|


20°+2θ
5 nm


T = 295 K
Pfu polymerase
pt-DNA
T = 318 K
T = 325 K
Counts
ΔΛ (fm)

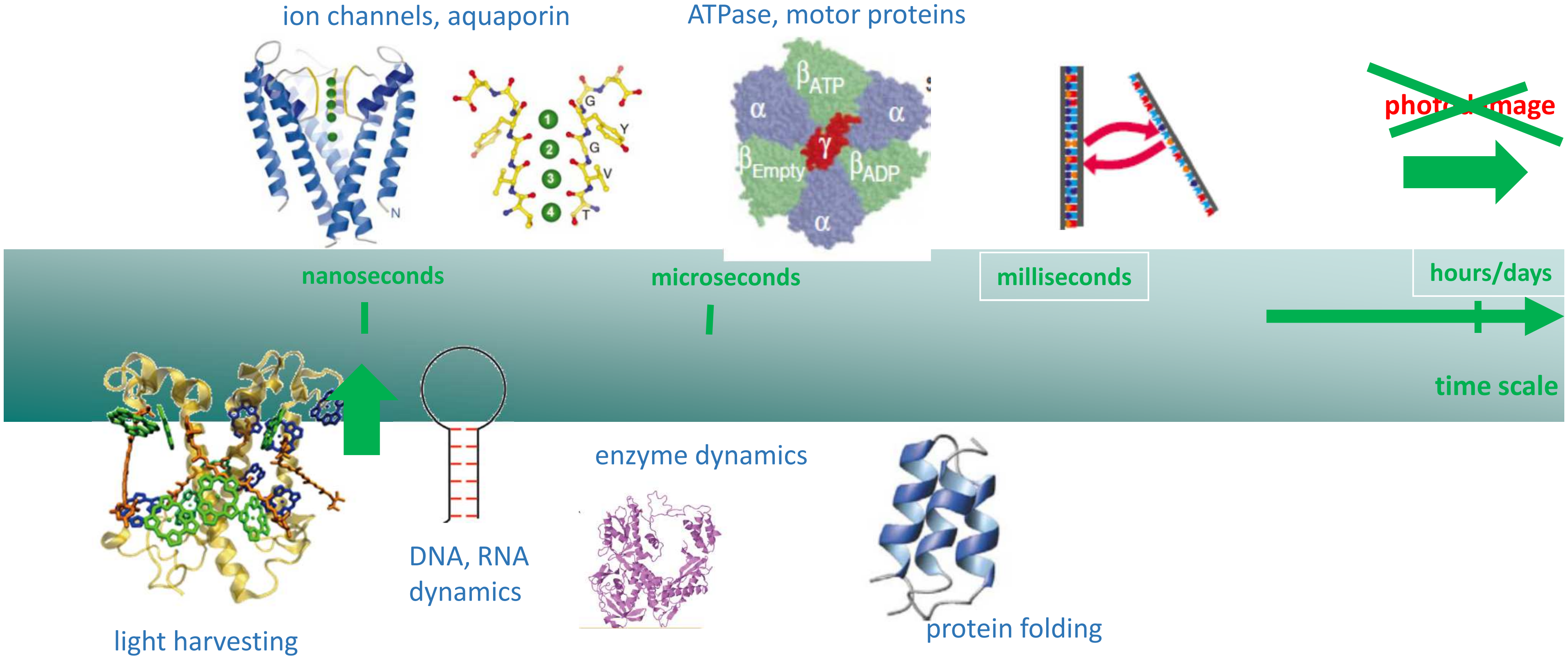
# + TIME RESOLUTION: RING-UP SPECTROSCOPY



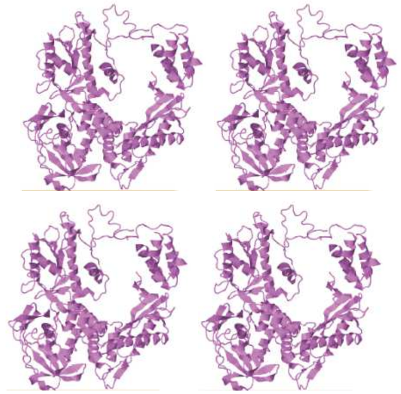

collaboration with Weizmann Institute, Vollmer *et.al.,* Nature Communications 2015

## Single molecule time resolution

$Q=\omega\tau$



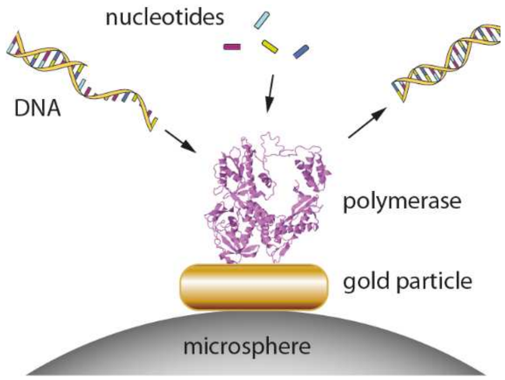
## THE RESEARCH FIELD "STRUCTURE DETERMINATION"



static structure:
crystallography

dynamic structure:
NMR, ESR, DLS, SAS, fluorescence
**ensemble** measurements
need for **synchronization**, **labels**

## OUR APPROACH: PROBE THE DYNAMICS OF STRUCTURE




# not to scale

**single molecule structural dynamics**

**label-free**, time dependent and non-destructive

highest **sensitivity** in optical domain

one of the „holy grails" of structure determination

$P(E) = \alpha * E$ → perturbation of microcavity resonances

$\Delta$ wavenlength [fm]

# RE[$\alpha$]

$$\frac{\delta\omega}{\omega_0} \approx -\frac{\int_{V_p}[\varepsilon_p(\mathbf{r}) - \varepsilon_h]\mathbf{E}^\dagger(\mathbf{r}) \cdot \mathbf{E}'(\mathbf{r})\mathrm{d}\mathbf{r}}{2\int_V \varepsilon(\mathbf{r})\mathbf{E}^\dagger(\mathbf{r}) \cdot \mathbf{E}'(\mathbf{r})\mathrm{d}\mathbf{r}} \approx -\frac{\mathrm{Re}[\alpha]}{2}\frac{f|\mathbf{E}(\mathbf{r}_p)|^2}{\int_V \varepsilon(\mathbf{r})|\mathbf{E}(\mathbf{r})|^2\mathrm{d}\mathbf{r}},$$

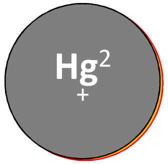
$\Delta$ linewidth [fm]

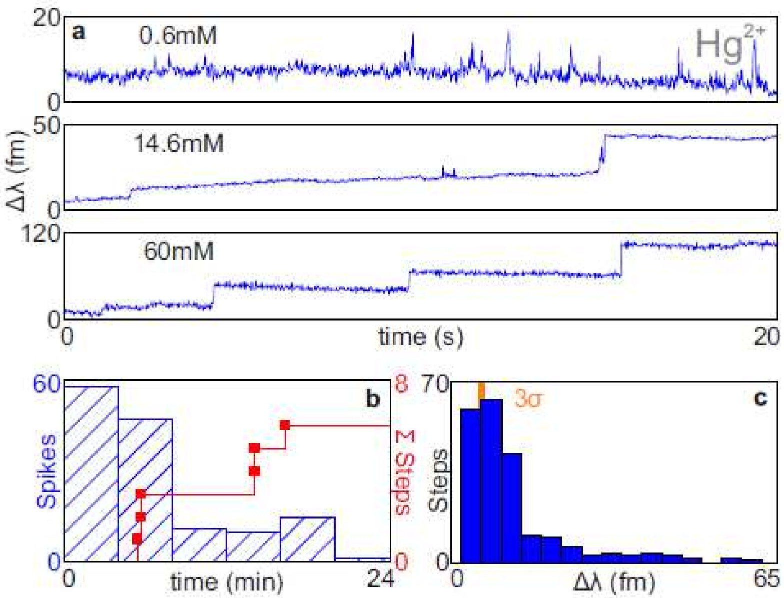
# IM[$\alpha$], $\alpha^2$

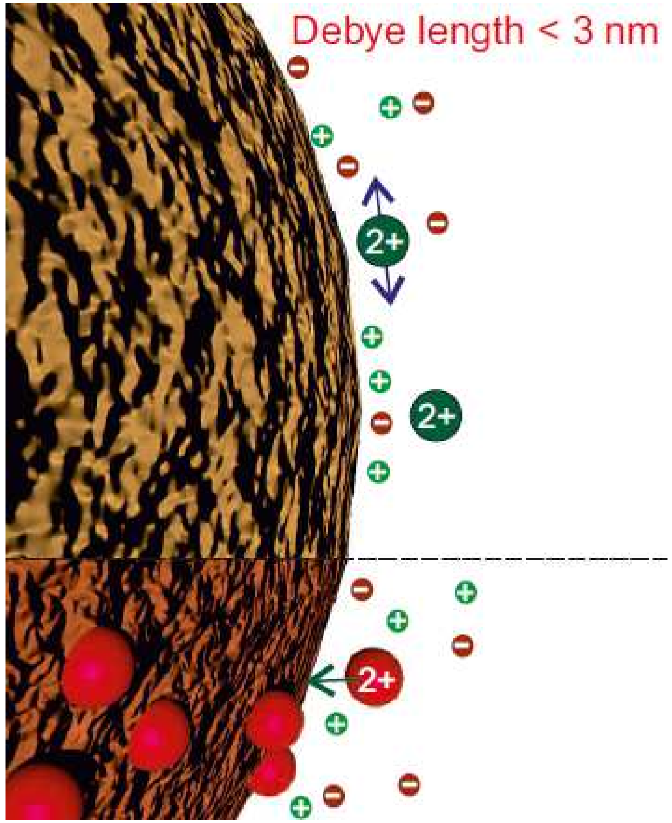
$$\frac{\delta\gamma_{\mathrm{abs}}}{\omega_0} \approx \mathrm{Im}[\alpha]\frac{|\mathbf{E}(\mathbf{r}_p)|^2}{\int_V \varepsilon(\mathbf{r})|\mathbf{E}(\mathbf{r})|^2\mathrm{d}\mathbf{r}}.$$

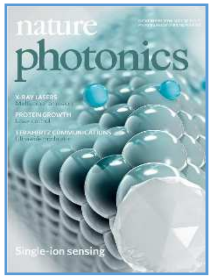
$$\delta\gamma_{\mathrm{sca}} = \frac{n_h^5\omega_0^4\varepsilon_0}{6\pi c^3}\frac{|\alpha|^2|\mathbf{E}(\mathbf{r}_p)|^2}{\int_V \varepsilon(\mathbf{r})|\mathbf{E}(\mathbf{r})|^2\mathrm{d}\mathbf{r}}.$$

# Taking Detection to the Limit: Single Atomic Ions



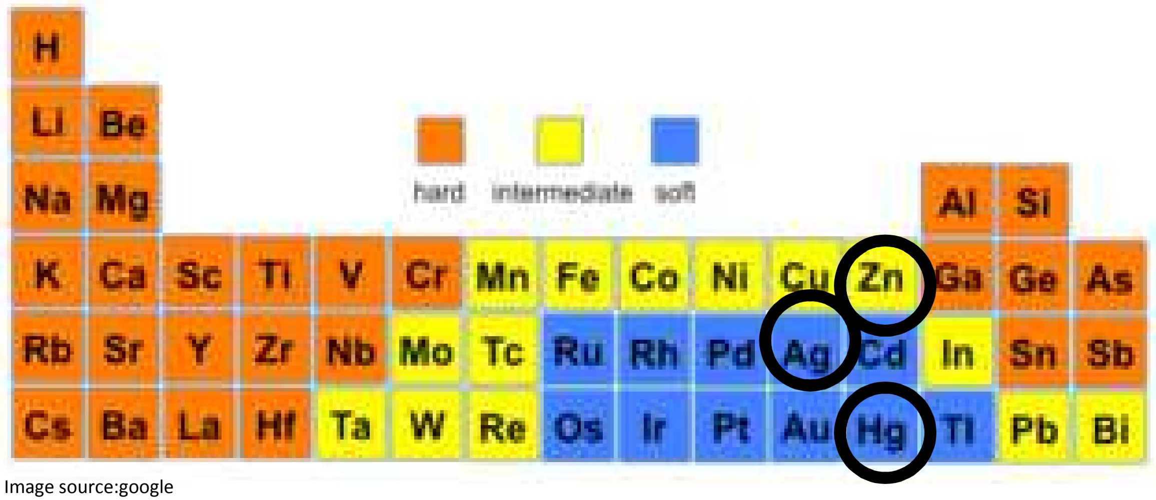
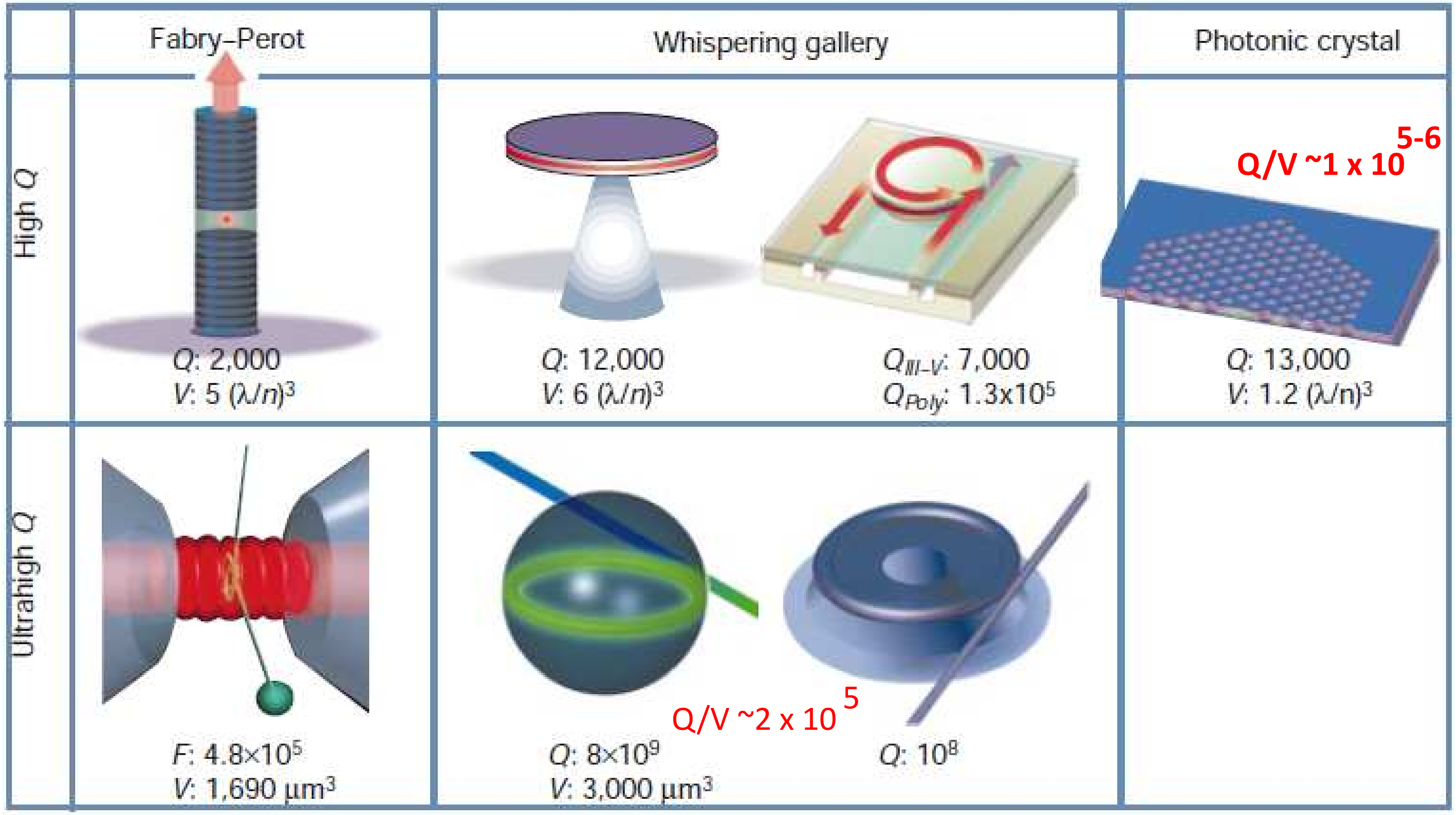


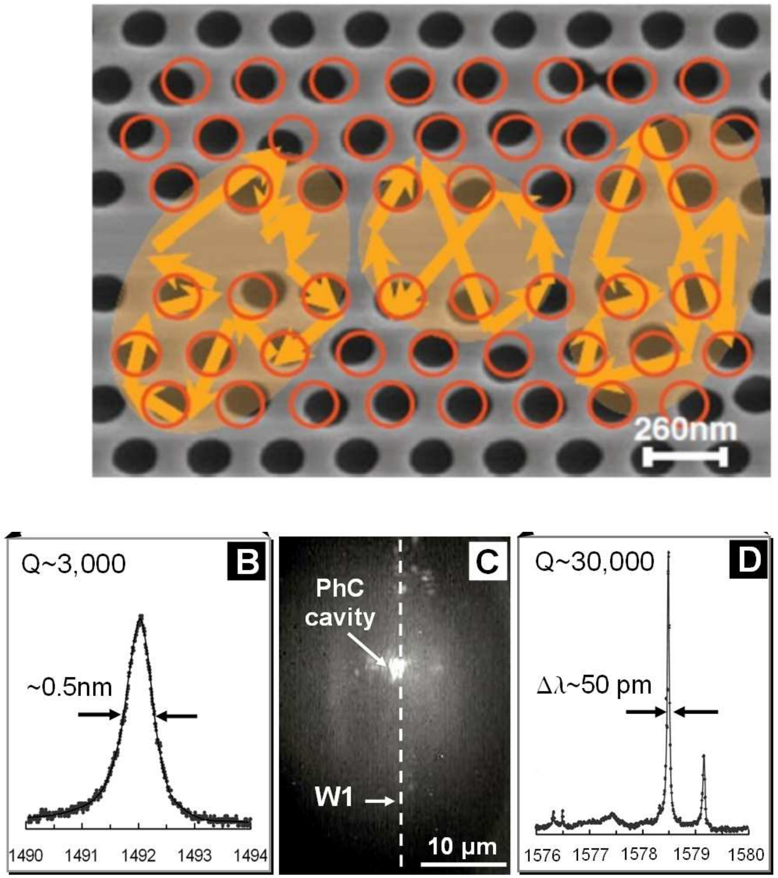

Image source:google

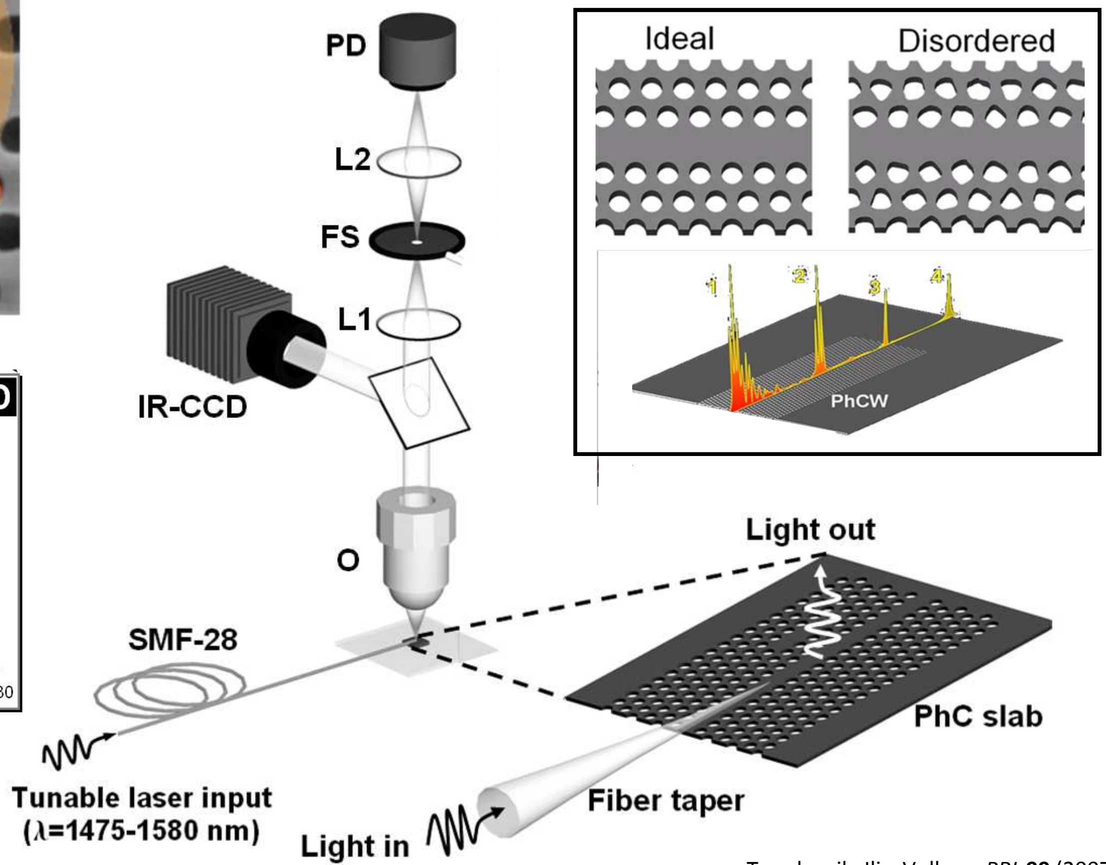




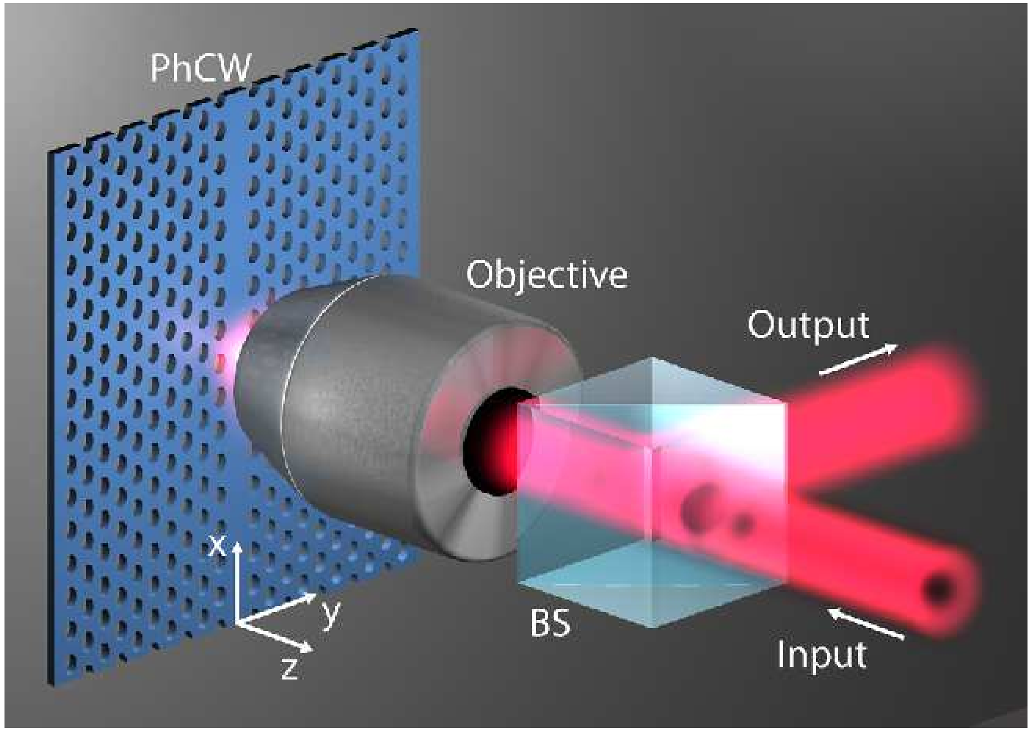
NATURE | VOL 424 | 14 AUGUST 2003 | www.nature.com/nature

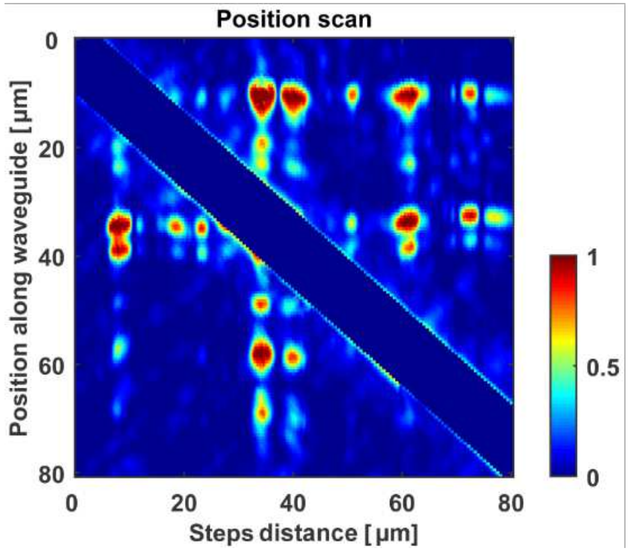
Vahala et.al.

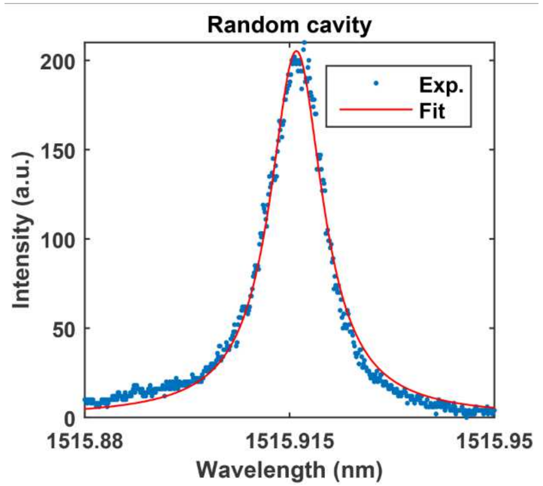



Topolancik, Ilic, Vollmer *PRL* **99** (2007)



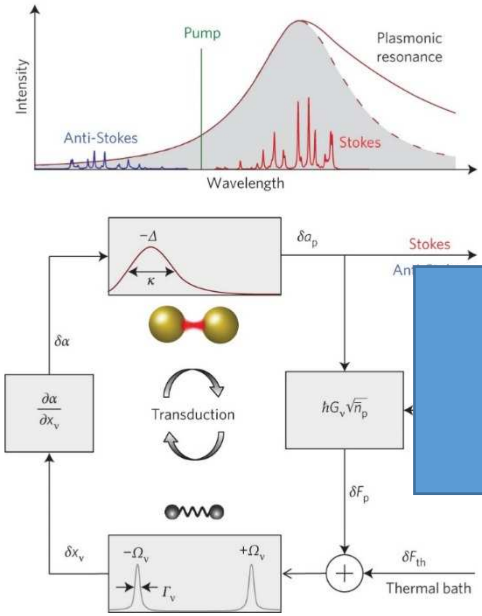




Mahdavi A, Roth P, Xavier J, Paraïso TK, Banzer P, Vollmer F. (2017)[Free space excitation of coupled Anderson-localized modes in photonic crystal waveguides with polarization tailored beam](), *Applied Physics Letters*, volume 110, pages 241101-241101, article no. 24, DOI:10.1063/1.4986187h

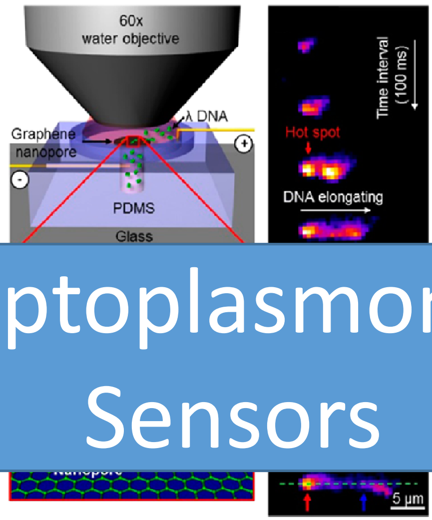
# Optoplasmonic Sensors

## Light to manipulate molecular vibrations/motions?



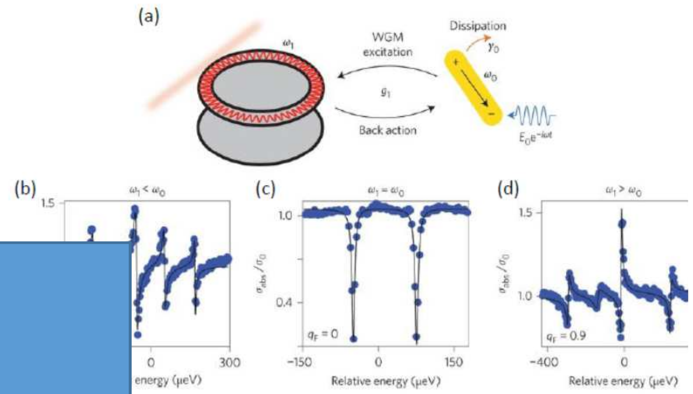

P. Roelli, C. Galland, N. Piro, T. J. Kippenberg.. *Nat. Nanotechnol.* 11(2): 164-169 (2016).

## Explore other hybrid plasmonic resonators/cavities?



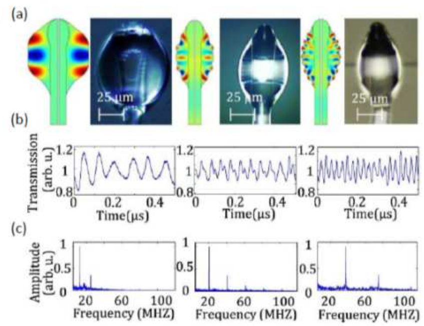

S. Nam, I. Choi, C. C. Fu, K... Zettl, and L. P. Lee. *Bioph*... A. ...4).

## Miniaturise single-molecule spectroscopy?



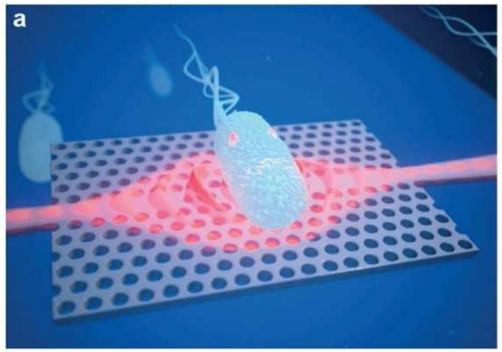

..., N. Thakkar, E. H. Horak, S. C. Quillin, C. Cherqui, K. A. Kn... ...dsmith. *Nat. Photonics* 10(12): 788-795 (2016).

## Droplet sensing?




T. Carmon. Droplet optomechanics. *Optica* 3(2): 175-178 (2016).

## Study biological systems on chip?



*Lab Chip* 13(22): 4358-4365 (2013).

## Advances in Optoplasmonic Sensors — Combining Optical Nano/Microcavities and Photonic Crystals with Plasmonic Nanostructures and Nanoparticles"

Jolly Xavier[a,b,*], Serge Vincent[a,b,*], Fabian Meder[b,c,*], and Frank Vollmer[a,b,*,†]

***Nanophotonics*** (2017), volume 1, DOI:10.1515/nanoph-2017-0064.


Lab on a Chip

ROYAL SOCIETY OF CHEMISTRY

CRITICAL REVIEW

Check for updates

Cite this: *Lab Chip*, 2017, 17, 1190

### Towards next-generation label-free biosensors: recent advances in whispering gallery mode sensors

Eugene Kim,[a] Martin D. Baaske[a] and Frank Vollmer[ab]

### Whispering gallery mode sensors

Matthew R. Foreman Jon D. Swaim and Frank Vollmer*

Max Planck Institute for the Science of Light, Laboratory of Nanophotonics and Biosensing, Günther-Scharowsky-Straße 1, 91058 Erlangen, Germany

*Corresponding author: frank.vollmer@mpl.mpg.de

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# THANK YOU!

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Martin Baaske

Frank Vollmer (Prof)
Jolly Xavier (Research Fellow)
Tom Constant (Postdoc)
Hsin-Yu Wu (Postdoc)
Siva Subramanian (PhD)
Serge Vincent (PhD)

**open PhD positions!**

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Mill Bay

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## Optoplasmonic Sensors

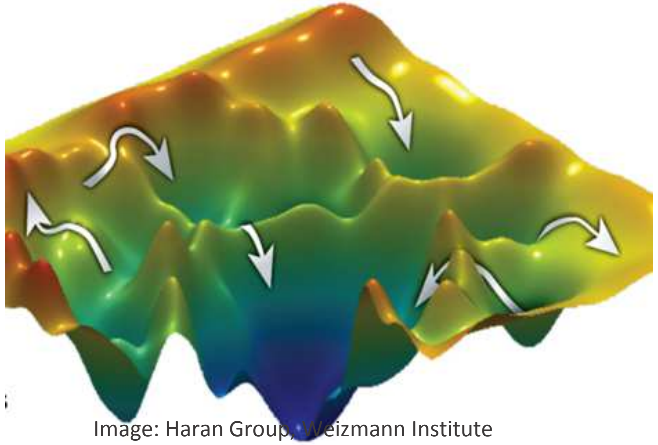
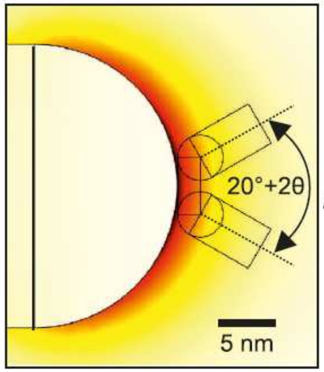
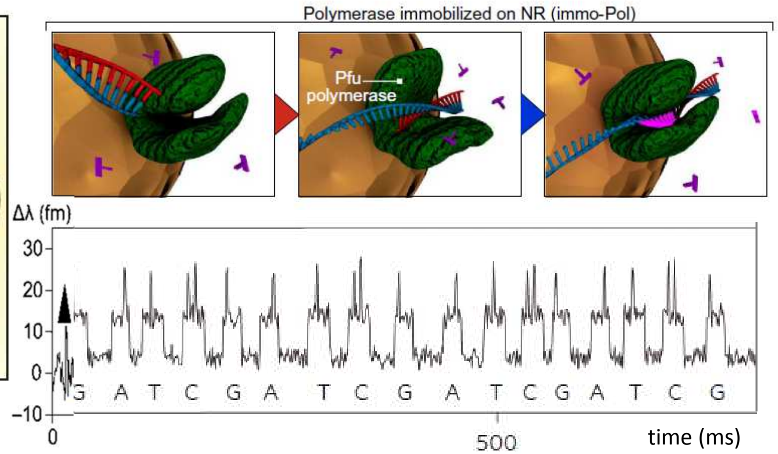


Image: Haran Group, Weizmann Institute




**Self-Assembly** → **Structure** → **Function**

**Living Systems** →

← **Synthetic Biology**

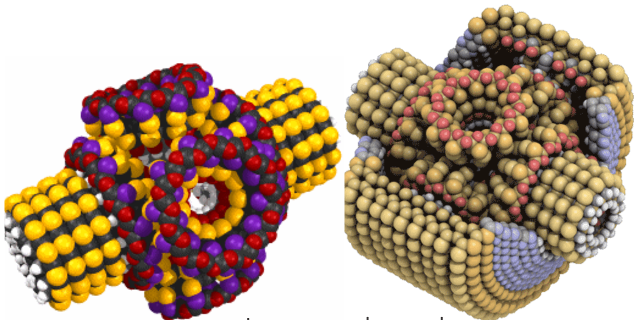
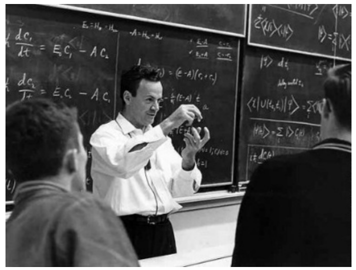
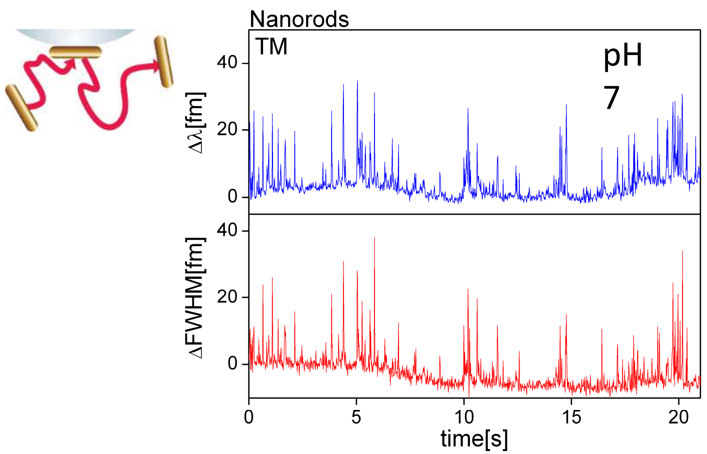


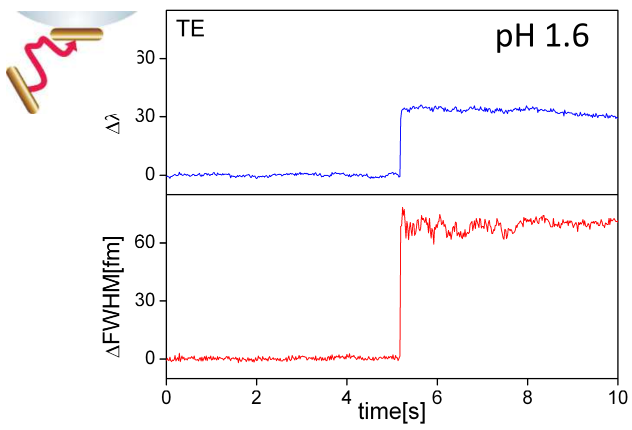
Image: google search



"The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom." (Feynman, 1961)

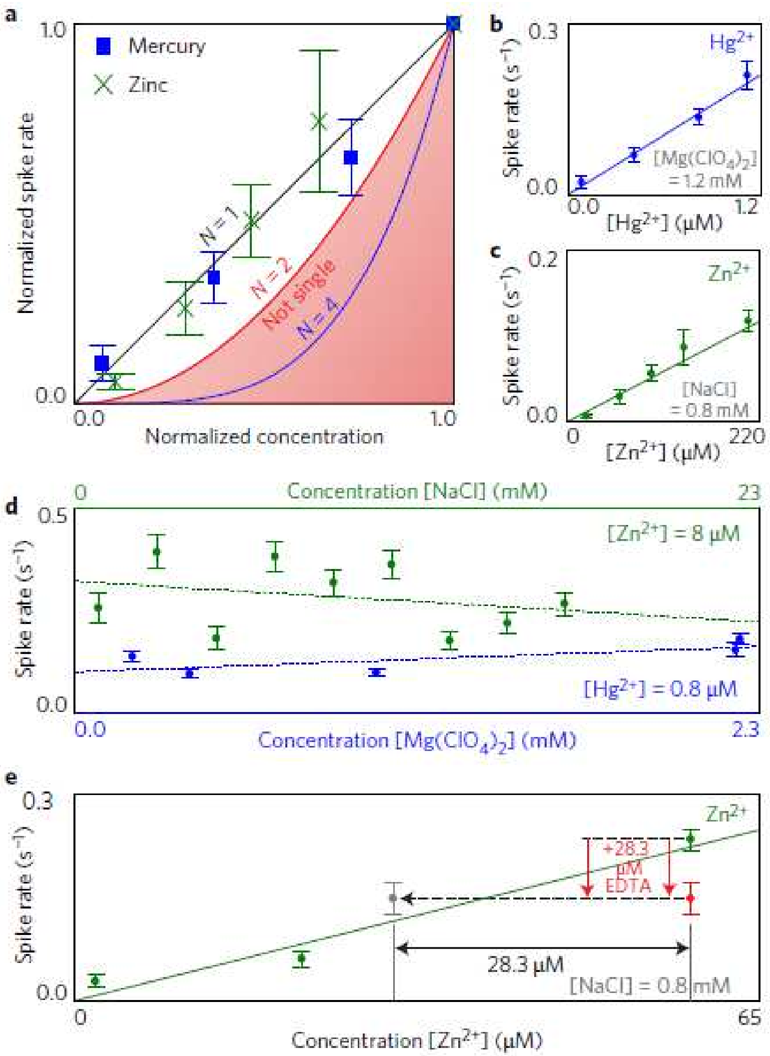
# I. Nanorod Loading from Solution



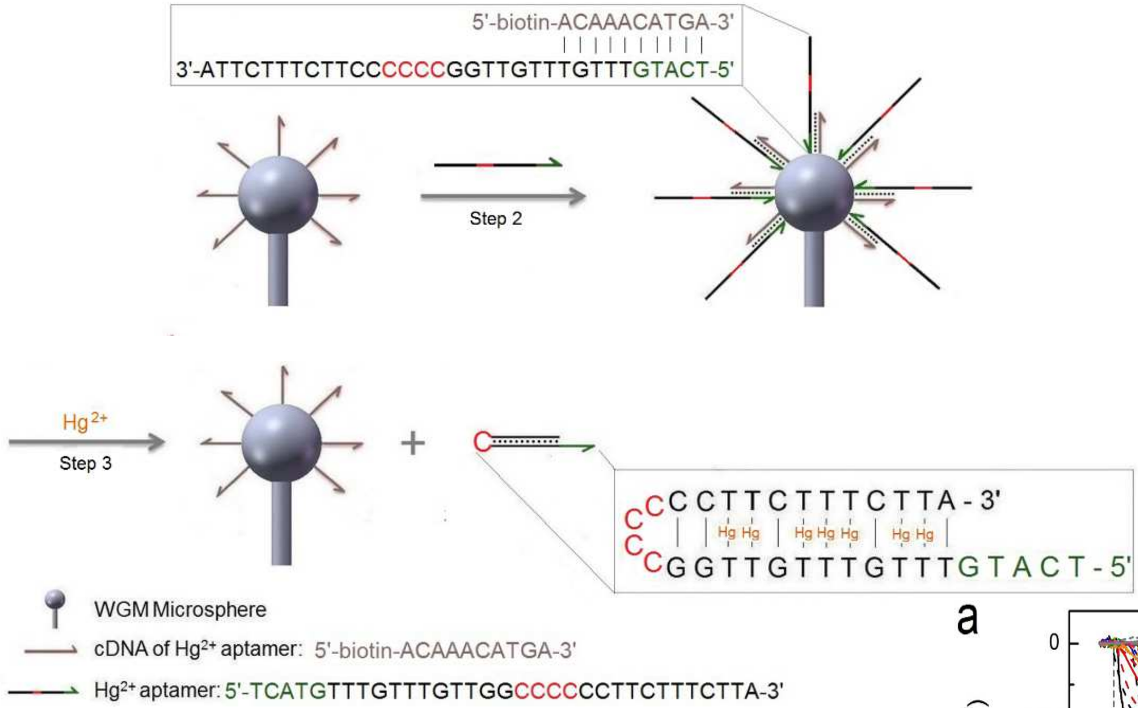


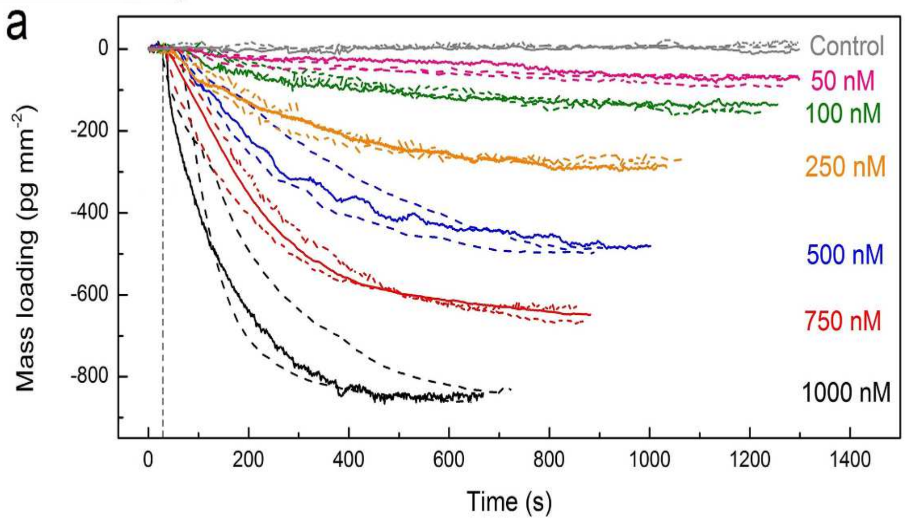

Page 42



a
1.0
0.0
Mercury
Zinc
Normalized spike rate
N = 1
N = 2
Not single
N = 4
0.0
1.0
Normalized concentration
b
0.3
0.0
Spike rate (s⁻¹)
Hg2+
[Mg(ClO4)2]
= 1.2 mM
0.0
1.2
[Hg2+] (μM)
c
0.2
0.0
Spike rate (s⁻¹)
Zn2+
[NaCl]
= 0.8 mM
0
220
[Zn2+] (μM)
d
0
Concentration [NaCl] (mM)
23
0.5
0.0
Spike rate (s⁻¹)
[Zn2+] = 8 μM
[Hg2+] = 0.8 μM
0.0
Concentration [Mg(ClO4)2] (mM)
2.3
e
0.3
0.0
Spike rate (s⁻¹)
Zn2+
+28.3
μM
EDTA
28.3 μM
[NaCl] = 0.8 mM
0
65
Concentration [Zn2+] (μM)

# Label-free Mercury (II) Ion Detection





*sensors*

*Article*

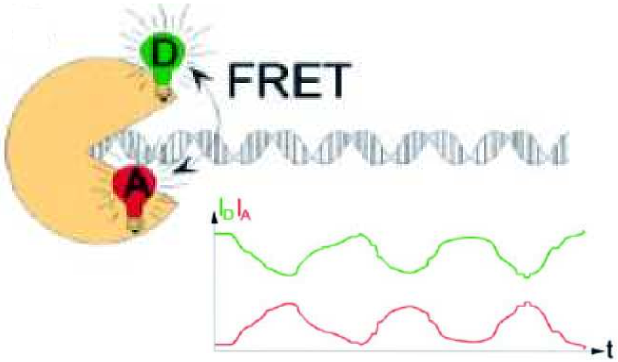

**Integrating a DNA Strand Displacement Reaction with a Whispering Gallery Mode Sensor for Label-free Mercury (II) Ion Detection (2014)**


**Fengchi Wu[a,b,c], Yuqiang Wu[c], Zhongwei Niu[a], and Frank Vollmer[c,d*]**

[a]Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China
[b]University of Chinese Academy of Sciences, Beijing 100080, China
[c]Laboratory of Nanophotonics & Biosensing, Max Planck Institute for the Science of Light, Erlangen, D-91058, Germany
[d]Division of Biomedical Engineering, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA

# FLUORESCENCE VS LABEL-FREE

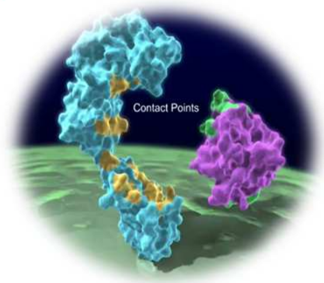
## Local Dynamics of Single Labels

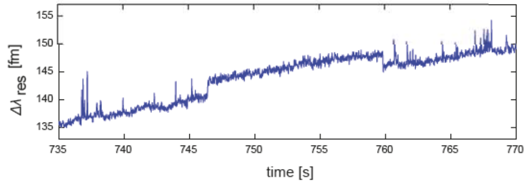



Shimon Weiss, SCIENCE, VOL 283, page 1686.

Single Molecule Fluorescence, FRET, STED, ....
NMR

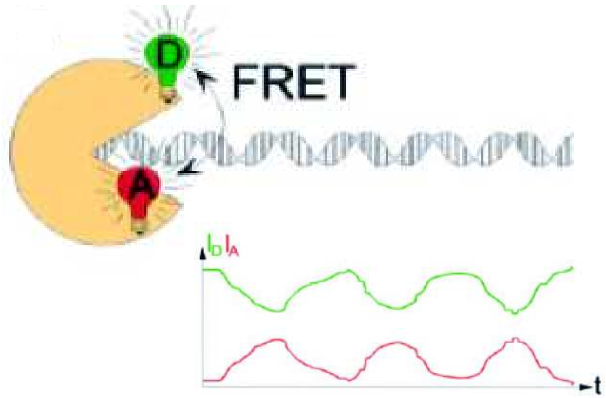
## Large- /Nanoscale Dynamics of entire, label-free Biomolecule



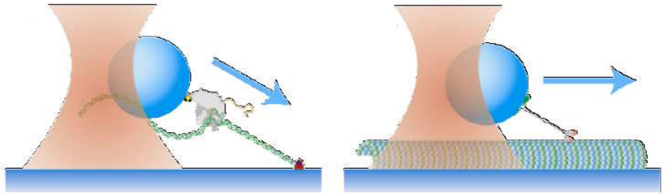

$$P(E) = P_0 + \alpha * E + \beta * E^2 + \ldots$$

# SINGLE MOLECULE TECHNIQUES

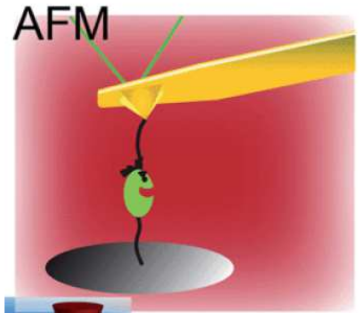



Shimon Weiss, SCIENCE, VOL 283, page 1686.

Optical Tweezer



Joshua W. Shaevitz, A Practical Guide to Optical Trapping




M.J. Jacobs, Blank Chem.Sci. (2014) vol. 5:1680-1697