Towards Quantum Biosensing and Bioimaging

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Motivation

ACS NANO

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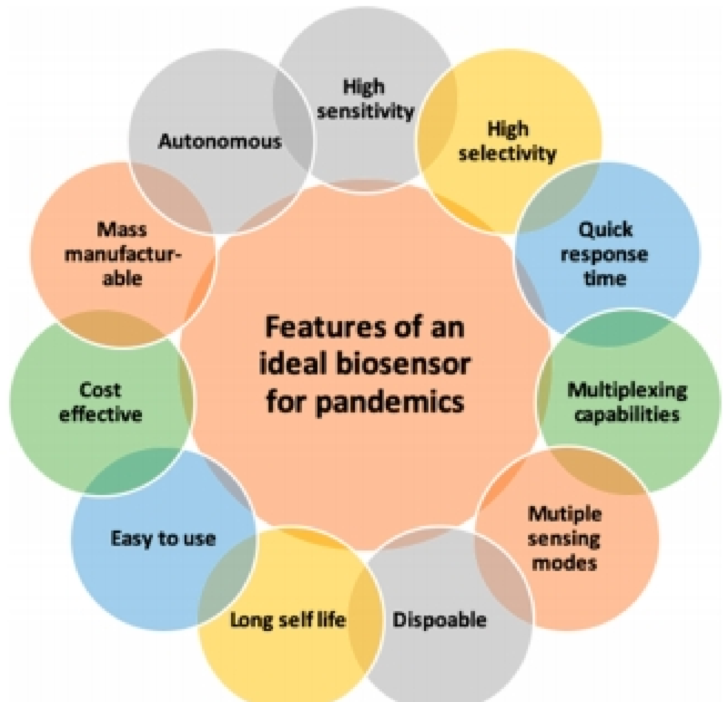
Opportunities and Challenges for Biosensors and Nanoscale Analytical Tools for Pandemics: COVID-19

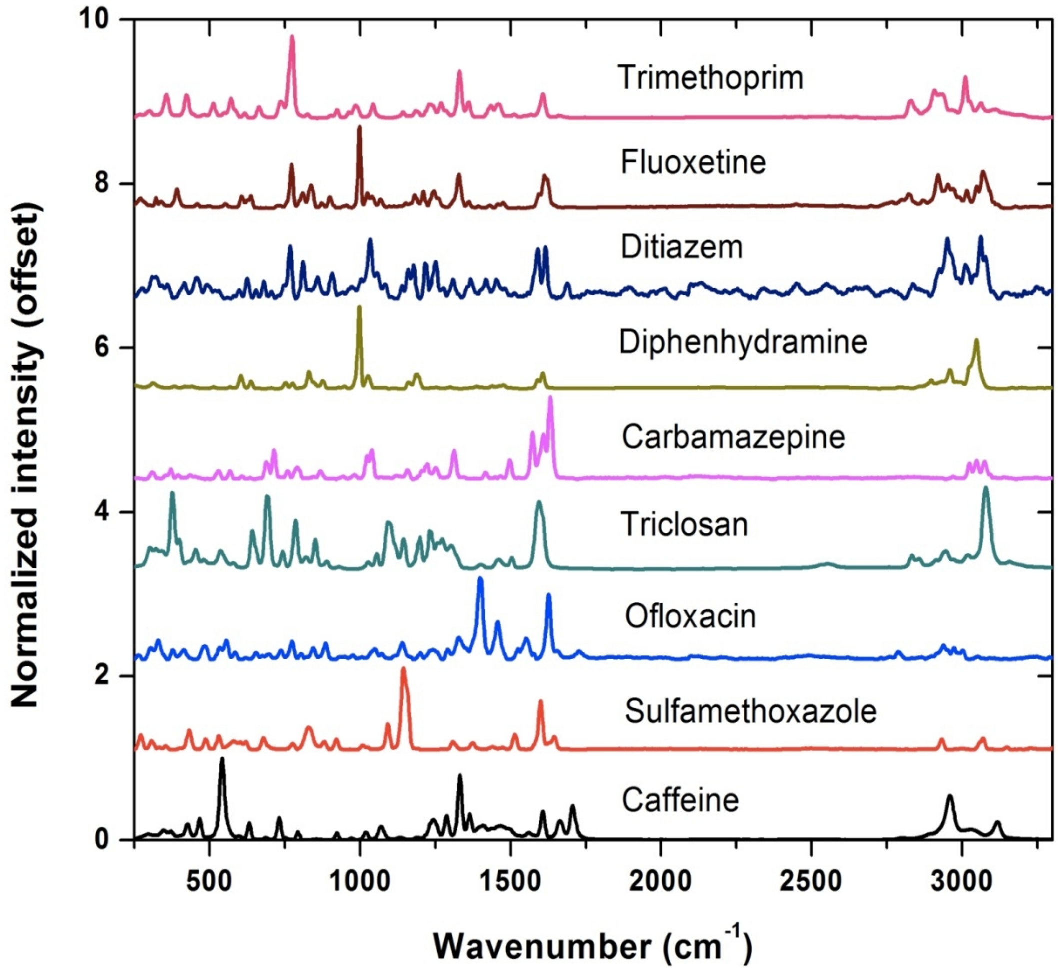
Nikhil Bhalla,* Yuwei Pan, Zhugen Yang,* and Amir Farokh Payam*

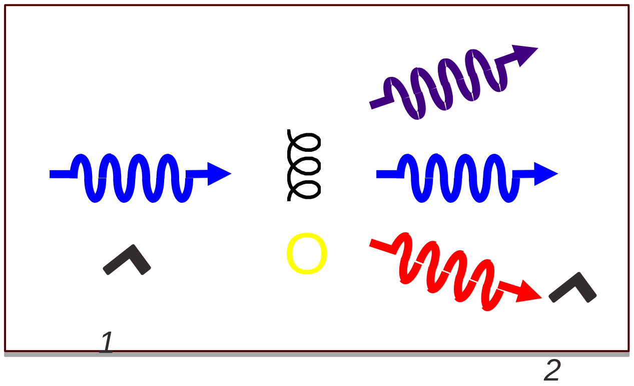
Cite This: *ACS Nano* 2020, 14, 7783–7807 Read Online

COVID-19 motivates us to develop adaptable, ultrasensitive platform for quick detection and identification of "whatever" is out there.



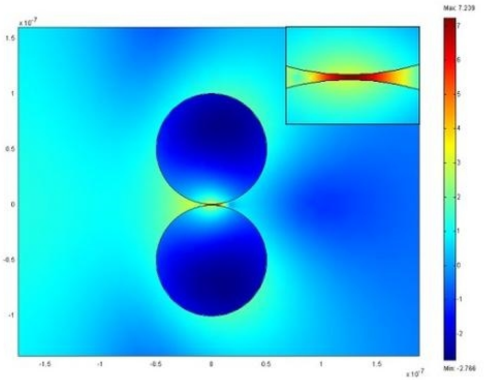
Vibrational spectroscopy





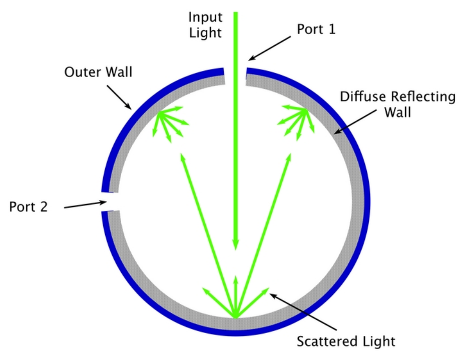
Raman spectroscopy: chemical sensing and imaging in a natural environment

Enhanced Raman spectroscopy



Plasmonic effects (Surface Enhanced Raman Scattering)

Kneipp, K., Kneipp, H., Itzkan, I., Dasari, R. R., Feld, M. S., 1999. Ultrasensitive chemical analysis by Raman spectroscopy. *Chemical Reviews* 99: 2957-2988.



<u>Disadvantages:</u>

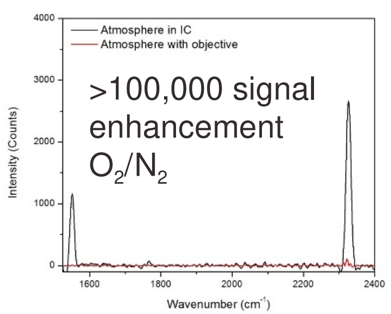
Molecules have to be at the hot spot

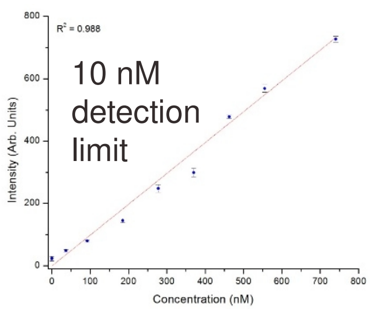
Reduced laser power to avoid local heating

Au and Ag do not last long in harsh environment

Raman spectra are affected by Stark shift

Quantifying molecules (emitters) is non-trivial





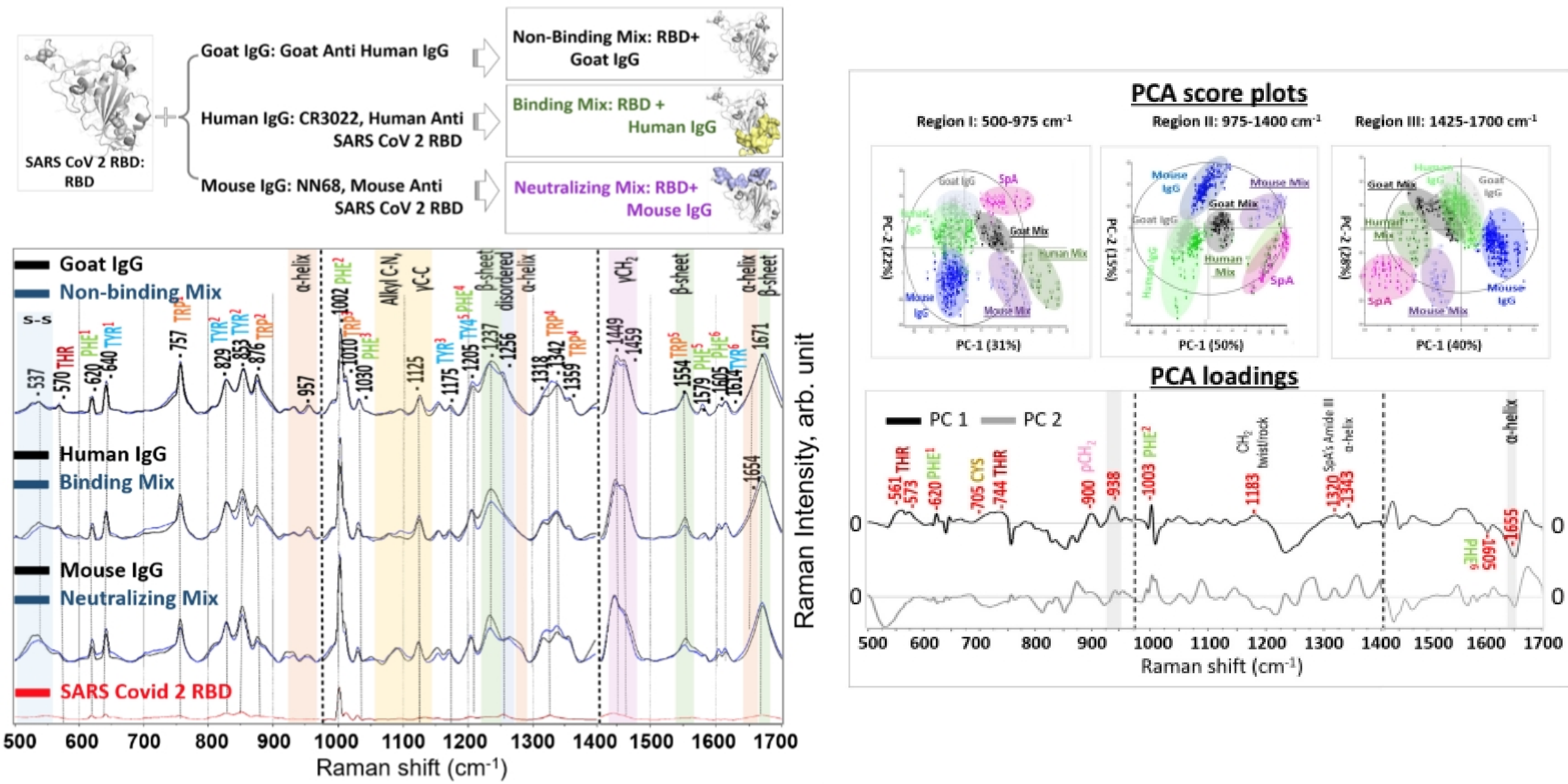
PNAS

Ultrasensitive detection of waste products in water using fluorescence emission cavity-enhanced spectroscopy

Joel N. Bixler[a], Michael T. Cone[a], Brett H. Hokr[a], John D. Mason[a], Eleonora Figueroa[a], Edward S. Fry[a], Vladislav V. Yakovlev[a], and Marlan O. Scully[a,b,c,1]

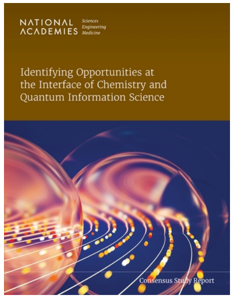
[a]Texas A&M University, College Station, TX 77843; [b]Princeton University, Princeton, NJ 08540; and [c]Baylor University, Waco, TX 76706

Label-free drug interaction screening via Raman microscopy



N. Altangerel, et al, *PNAS* **120**(30), e2218826120 (2023).

Motivation



National Academies Consensus Study: priority research directions

Develop new approaches and techniques for addressing and controlling multiple electron and nuclear spins and optical cycling centers in molecular systems.

Develop techniques to probe molecular qubits at complex interfaces to inform their systematic control.

Develop enhanced spectroscopic and microscopic techniques by creating

i. entangled photon sources with higher yield and better spectral coverage, and

ii. high-finesse cavities and nanophotonics for molecular qubit systems.

Develop and exploit alternative approaches to spin polarization and coherence control (e.g., chirality-induced spin selectivity and electric field effects).

Use molecular systems to teleport quantum information over distances greater than 1 μm with high fidelity.

Develop molecular quantum transduction schemes that take advantage of entangled photons as well as entangled electrons and nuclear spins.

Advance quantum sensing techniques to further understand biological systems.

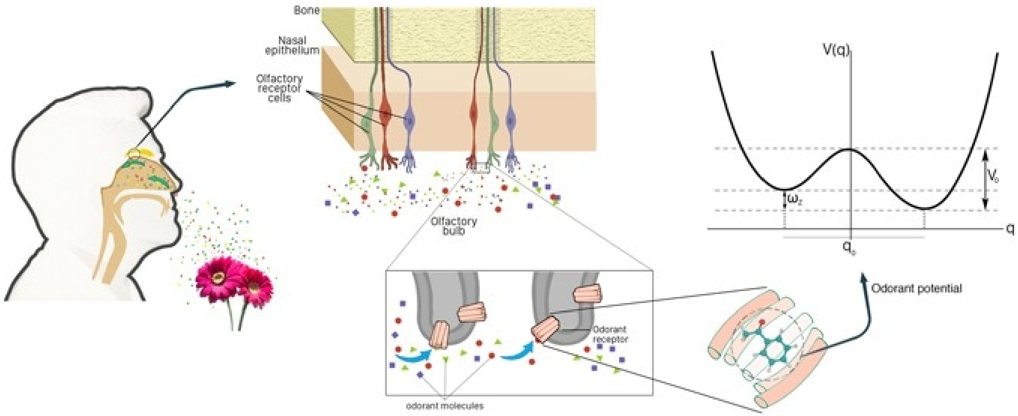
Use bio-inspired quantum processes for the development of new quantum technologies.

Provide broadly accessible state-of-the-art measurement techniques and instrumentation for the chemistry community to accomplish all of the above goals.

Quantum advantage

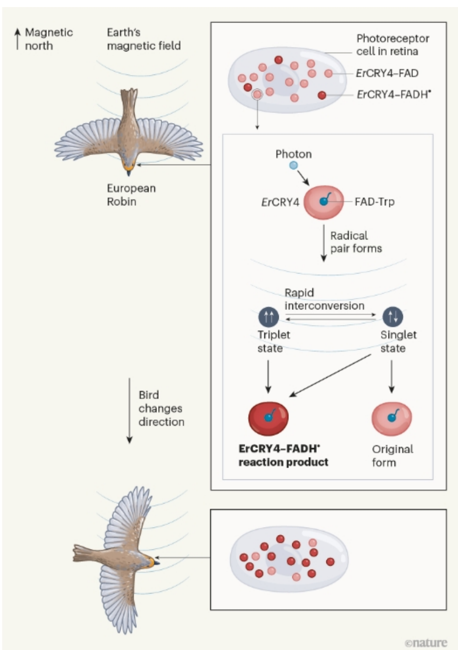
- **Ultimate sensitivity**: in any measurement classical noise is defined by the number of photons (events) measured; quantum measurements do not have this limit.
- **Enhanced specificity** through quantum spectroscopy by assessing states which are not available using classical light excitation.
- **Background noise reduction and improved spatial resolution** through quantum correlations.

Quantum-based sensing is not new



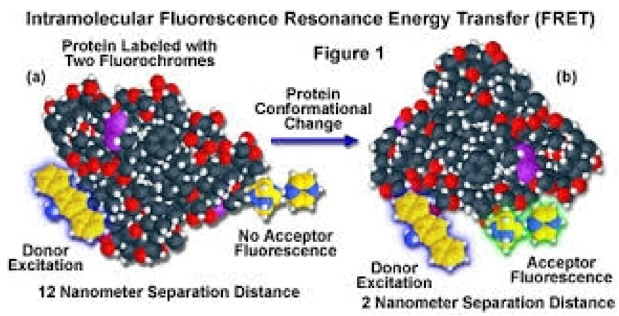
Olfaction

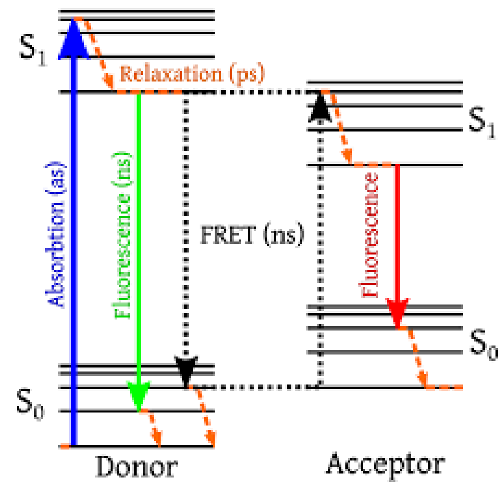
Franco, M. I., Turin, L., Mershin, A. & Skoulakis, E. M. Molecular vibration-sensing component in Drosophila melanogaster olfaction. *Proc. Natl. Acad. Sci. USA* **108**, 3797–3802 (2011).



Magnetosensing

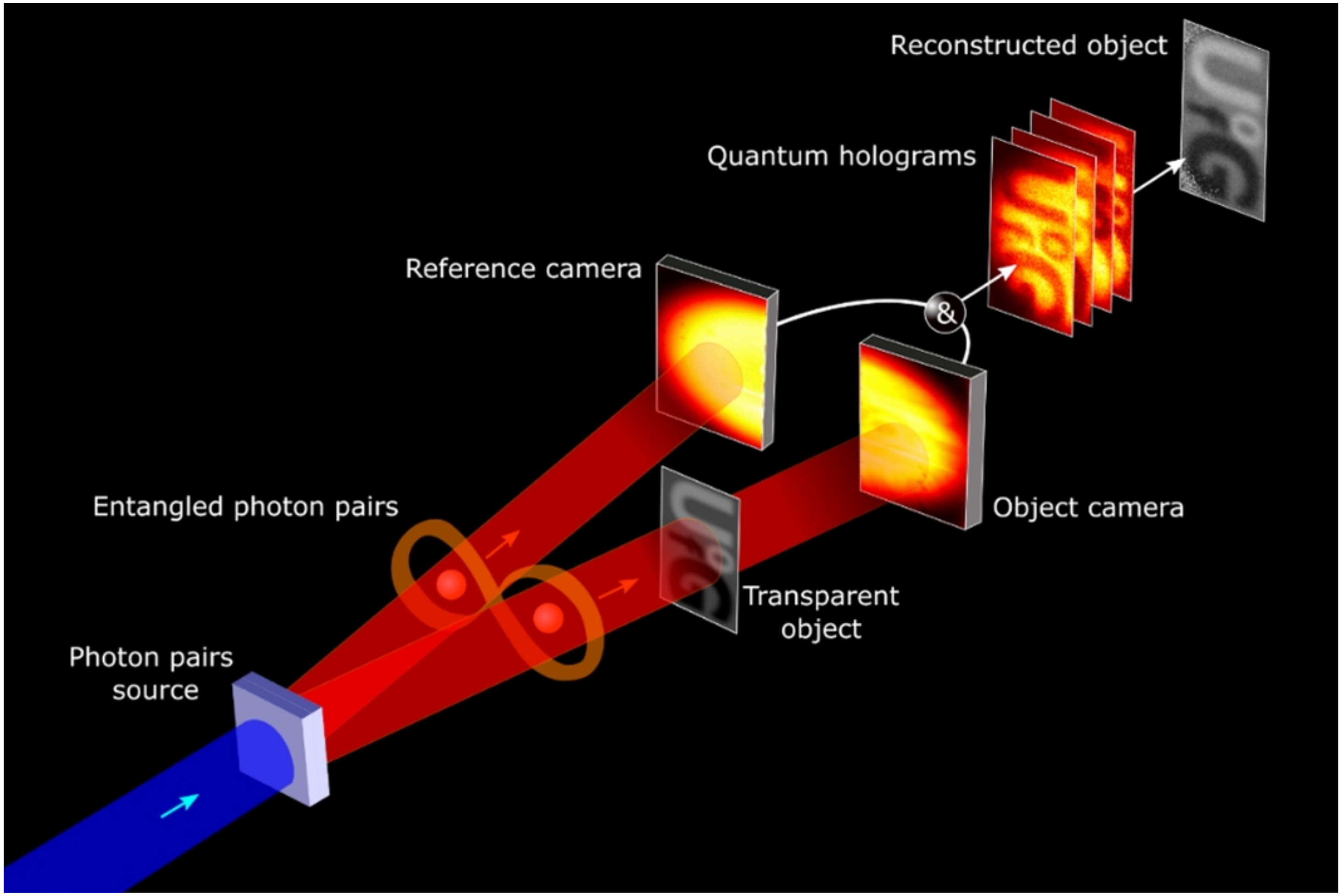
J. Xu, et al, Magnetic sensitivity of cryptochrome 4 from a migratory songbird, *Nature* **594**, 535-540 (2021).





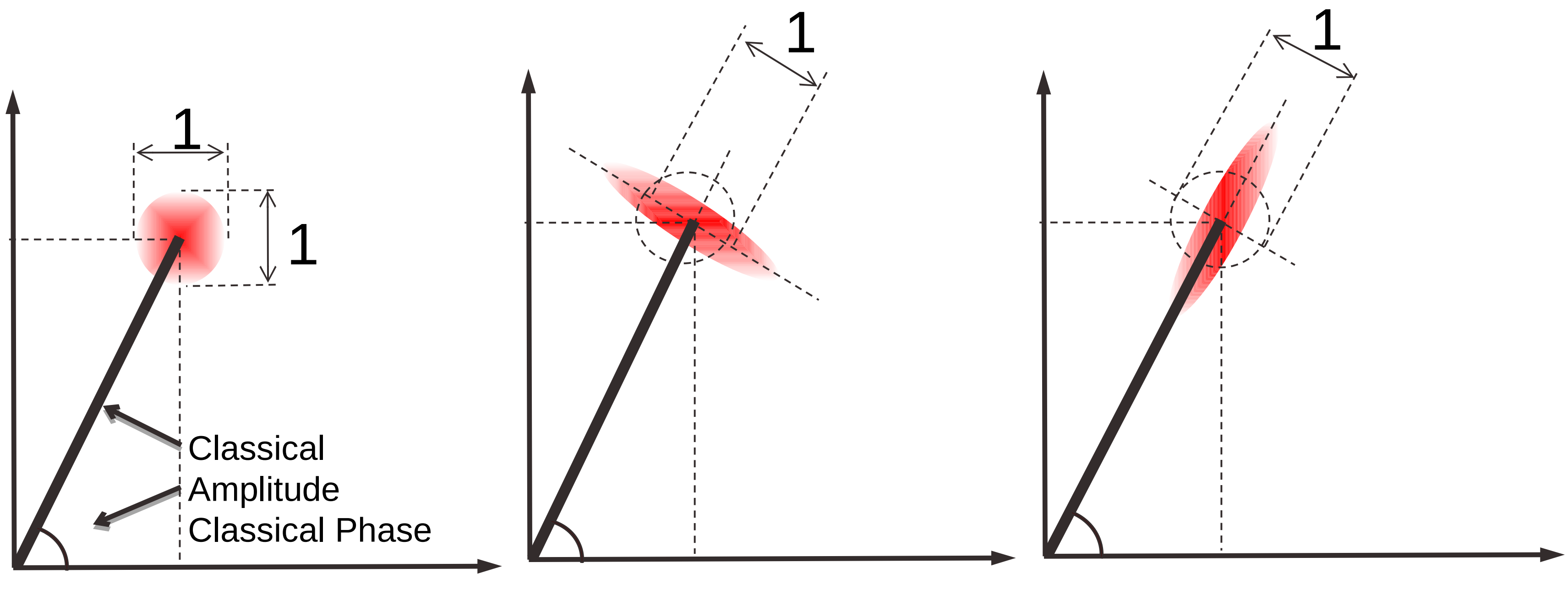
Förster resonance energy transfer

Entangled photons



https://andor.oxinst.com/

Squeezed light



Coherent state:

Amplitude quadrature squeezed:

Phase quadrature squeezed:

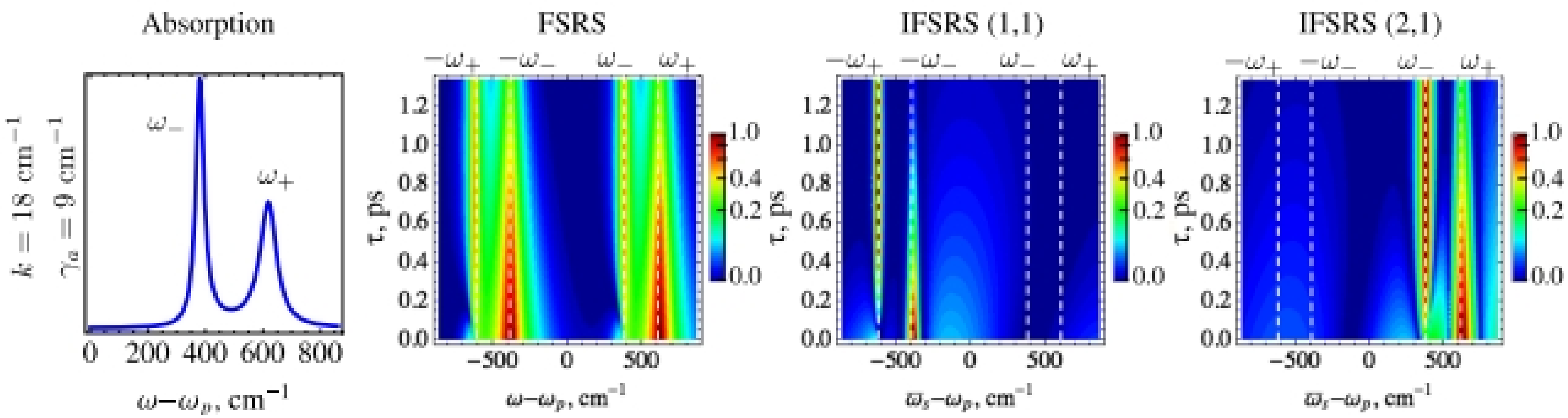
Enhanced spectroscopy

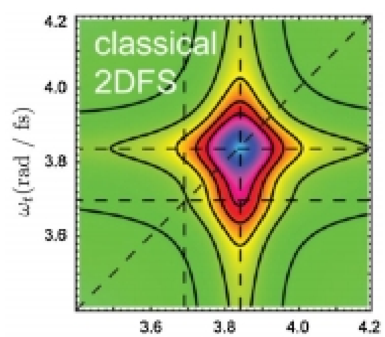
REVIEWS OF MODERN PHYSICS, VOLUME 88, OCTOBER–DECEMBER 2016

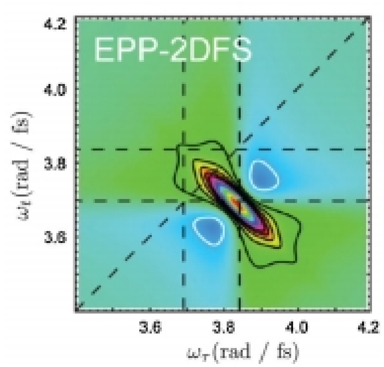
Nonlinear optical signals and spectroscopy with quantum light

Konstantin E. Dorfman,* Frank Schlawin,† and Shaul Mukamel‡

See also T. Goodson et al, *PNAS* **120**(35), e2307719120 (2023).







Quantum light more information without classical limitation of allowing to achieve both high spectral and high temporal resolution.

Dynamics of biological system becomes a sensor.

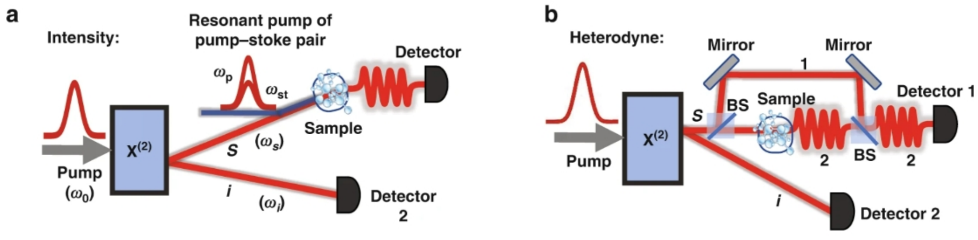
Enhanced spectroscopy

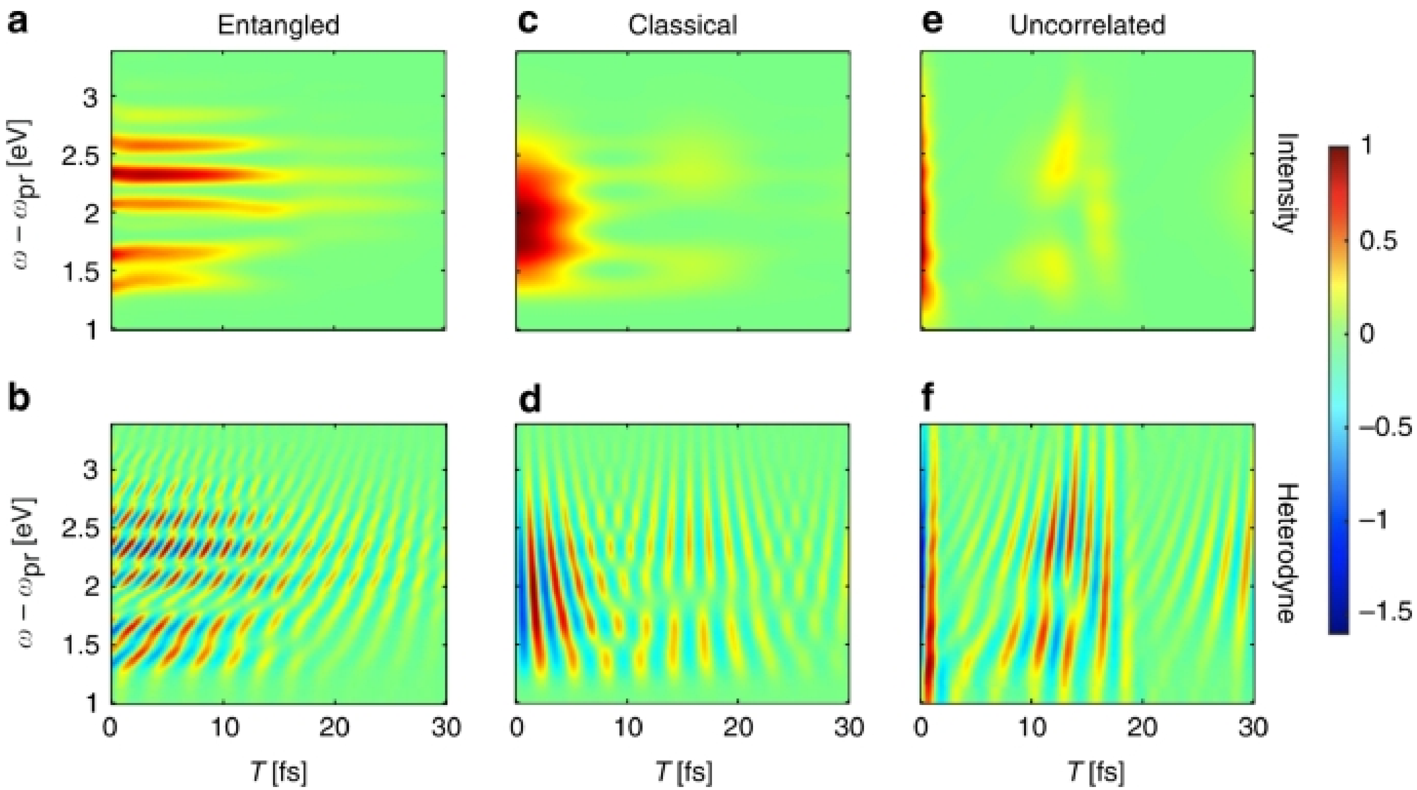
Article | Open access | Published: 14 September 2022

Entangled photons enabled time-frequency-resolved coherent Raman spectroscopy and applications to electronic coherences at femtosecond scale

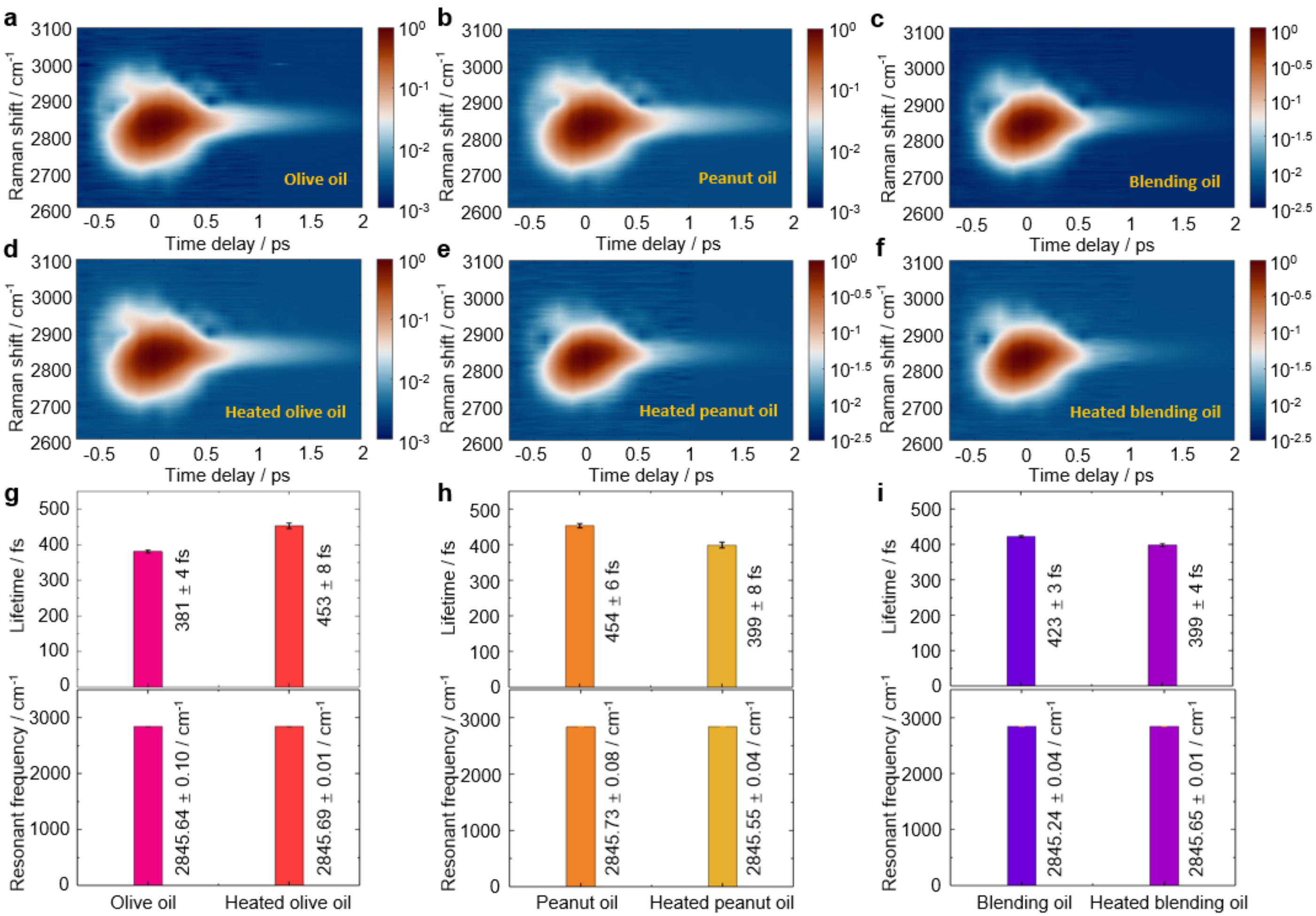
Zhedong Zhang, Tao Peng, Xiaoyu Nie, Girish S. Agarwal & Marlan O. Scully

Light: Science & Applications **11**, Article number: 274 (2022) | Cite this article





Enhanced spectroscopy



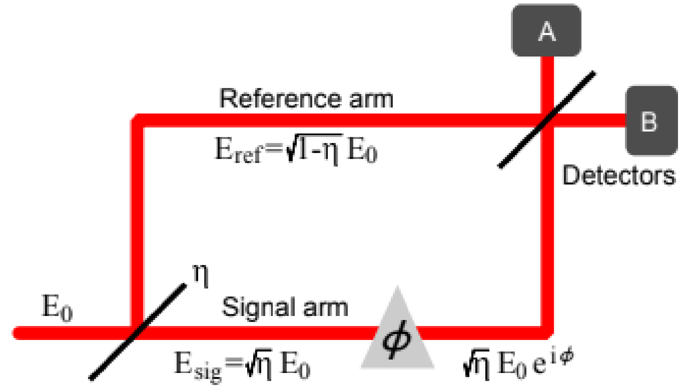
H. Zhu et al, What is cooking in your kitchen: seeing "invisible" with time-resolved coherent anti-Stokes Raman spectroscopy," *Anal Bioanal Chem* **415**(26), 6471-6480 (2023).

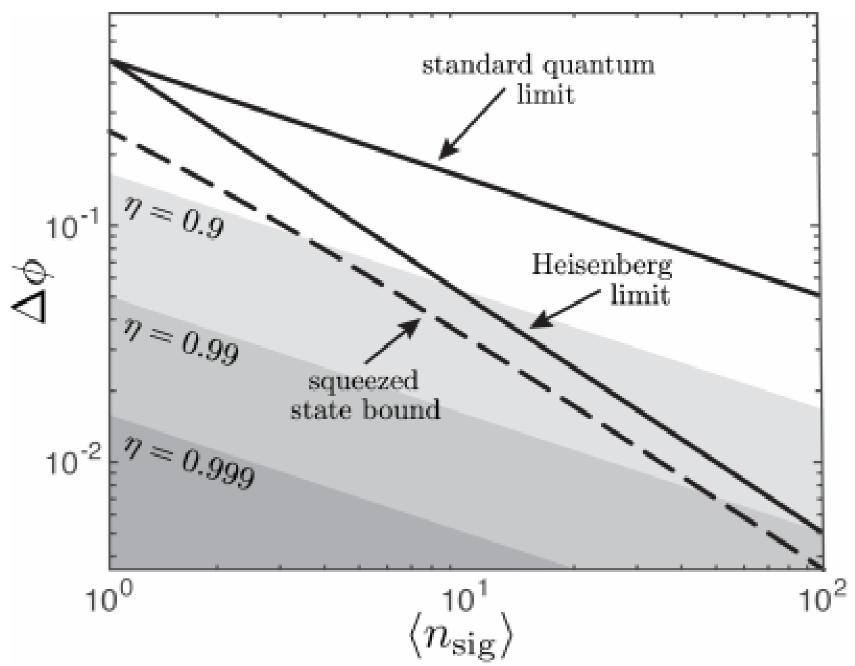
Enhanced sensitivity

ELSEVIER
Physics Reports
Volume 615, 23 February 2016, Pages 1-59

Quantum metrology and its application in biology

Michael A. Taylor [a b], Warwick P. Bowen [a]





$$\Delta\phi_{\mathrm{SQL}} = \sqrt{V(\phi)} = \frac{1}{\sqrt{\langle n_0 \rangle}}$$

$$\Delta\phi_{\mathrm{Heisenberg}} \geq \frac{1}{\langle n_0 \rangle}$$

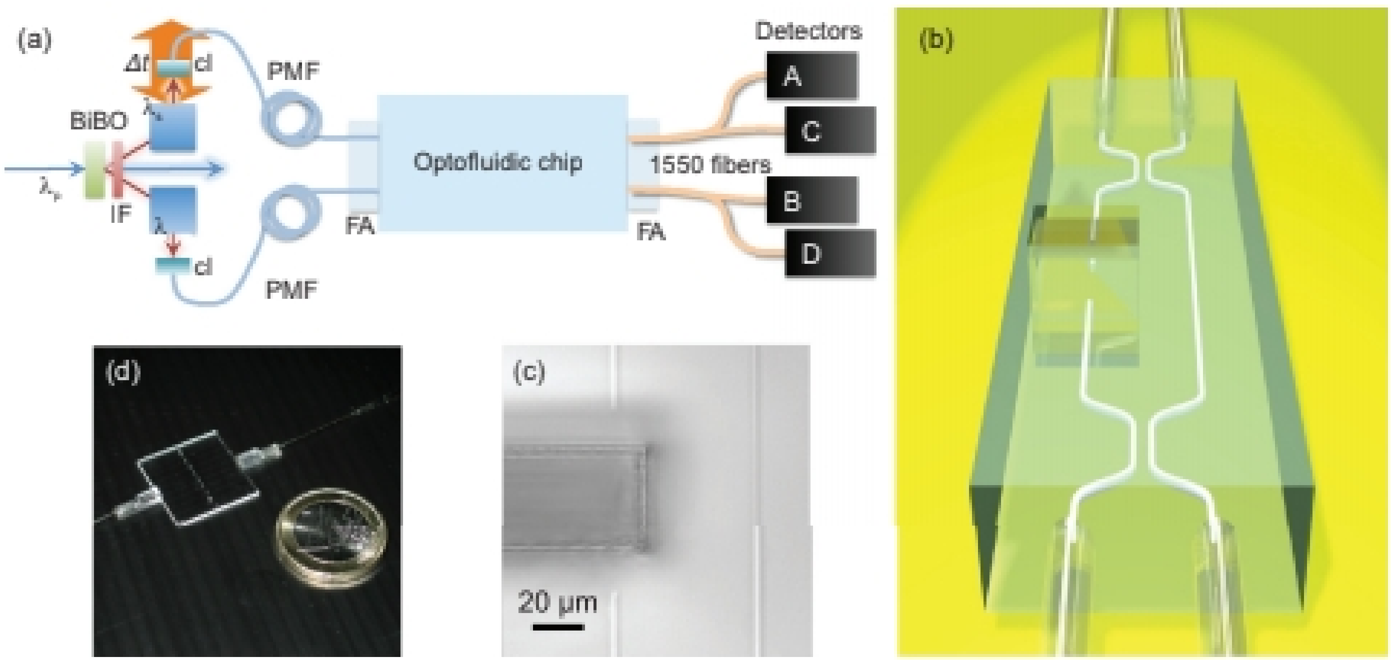
$$\Delta\phi_{\mathrm{squeezed}} \geq \frac{1}{2\sqrt{\langle \hat{n} \rangle V(\hat{X})}}$$

Enhanced sensitivity

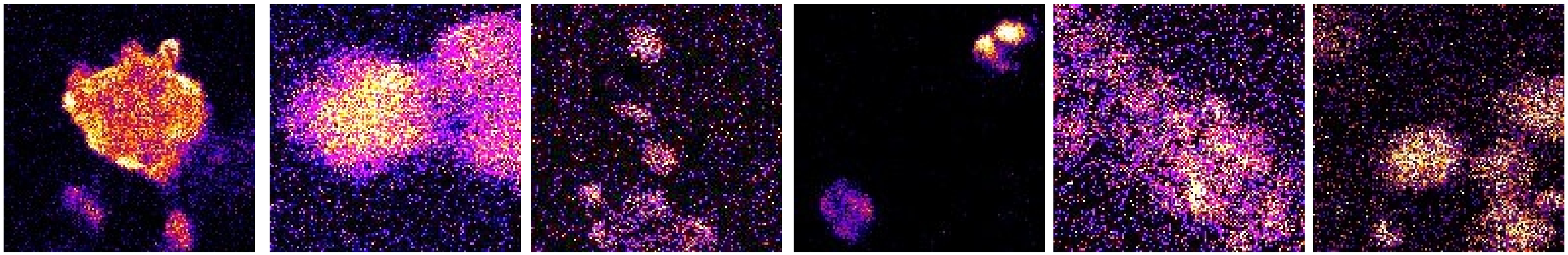
APPLIED PHYSICS LETTERS **100**, 233704 (2012)

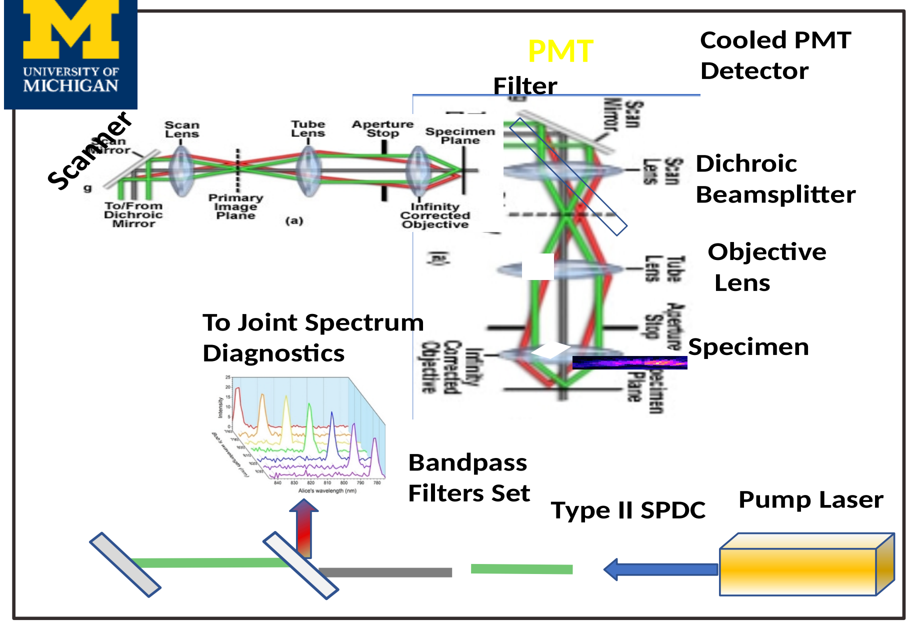
Measuring protein concentration with entangled photons

Andrea Crespi,[1,2] Mirko Lobino,[3] Jonathan C. F. Matthews,[3] Alberto Politi,[3] Chris R. Neal,[4] Roberta Ramponi,[1,2] Roberto Osellame,[1,2] and Jeremy L. O'Brien[3,a)]
[1]*Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche, Piazza L. da Vinci, 32, I-20133 Milano, Italy*
[2]*Dipartimento di Fisica, Politecnico di Milano, Piazza L. da Vinci, 32, I-20133 Milano, Italy*
[3]*Centre for Quantum Photonics, H. H. Wills Physics Laboratory and Department of Electrical and Electronic Engineering, University of Bristol, Merchant Venturers Building, Woodland Road, Bristol BS8 1UB, United Kingdom*
[4]*Microvascular Research Labs, School of Physiology and Pharmacology, Preclinical Vet Building, University of Bristol, Bristol BS2 8EJ, United Kingdom*



Ultralow flux of entangles photons preserves biological samples





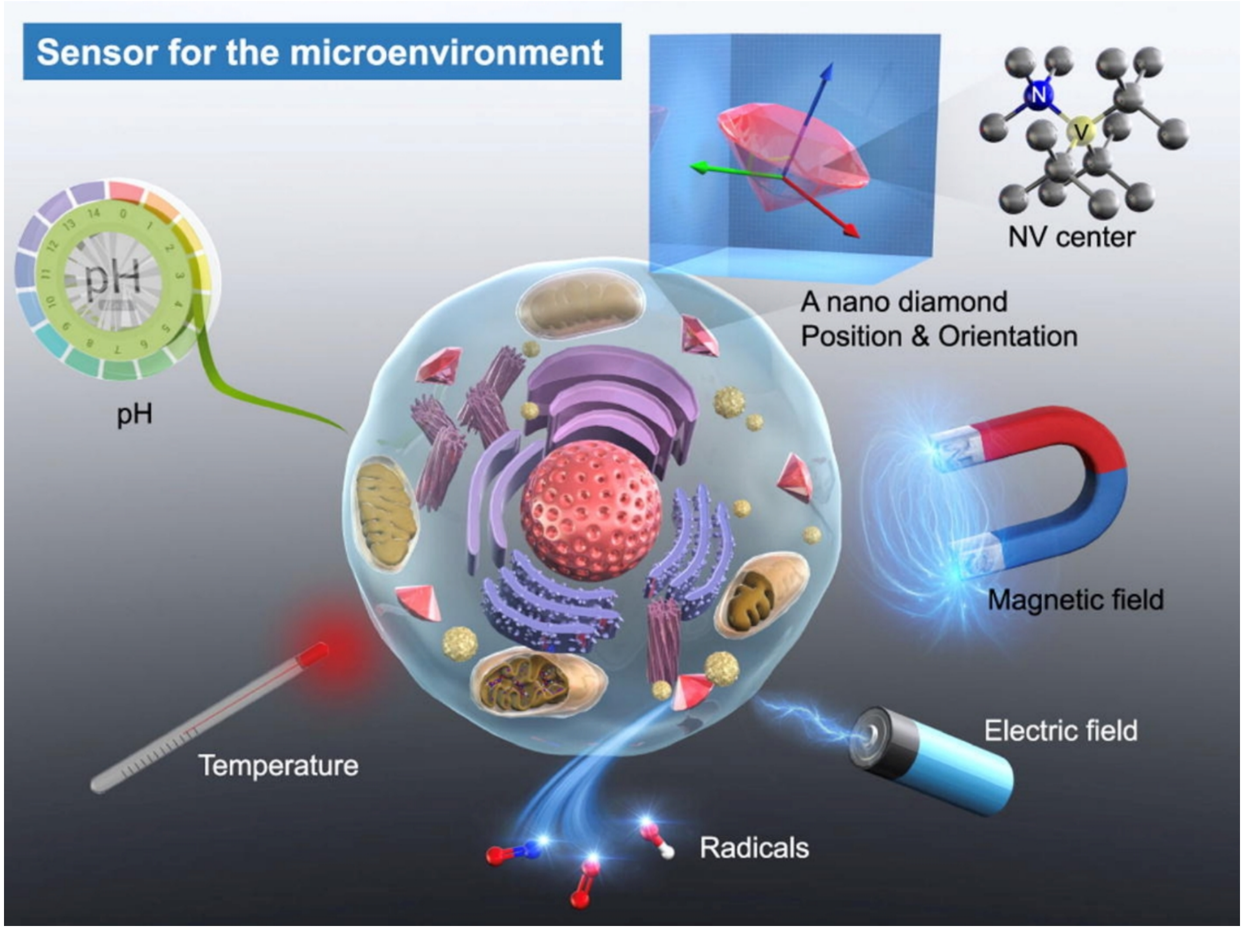
Entangled two-photon imaging can probe individual cells, large cells colonies, groups of cells, and different stages of mitosis for two different lines of cancer cells, details of plant root metabolite dynamics with very low excitation flux (~10^7 photons/s) allowing for longer non-invasive scans.

Varnavski, O. et al, *J. Phys. Chem. Lett.* **2022**, *13*, 2772–2781.

Eshun, A.; et al, *Acc. Chem. Res*. **2022,** *55,* 991–1003.

Varnavski, O.; et al, *J. Am. Chem. Soc.,* **2020**, *142*, 12966-12997.

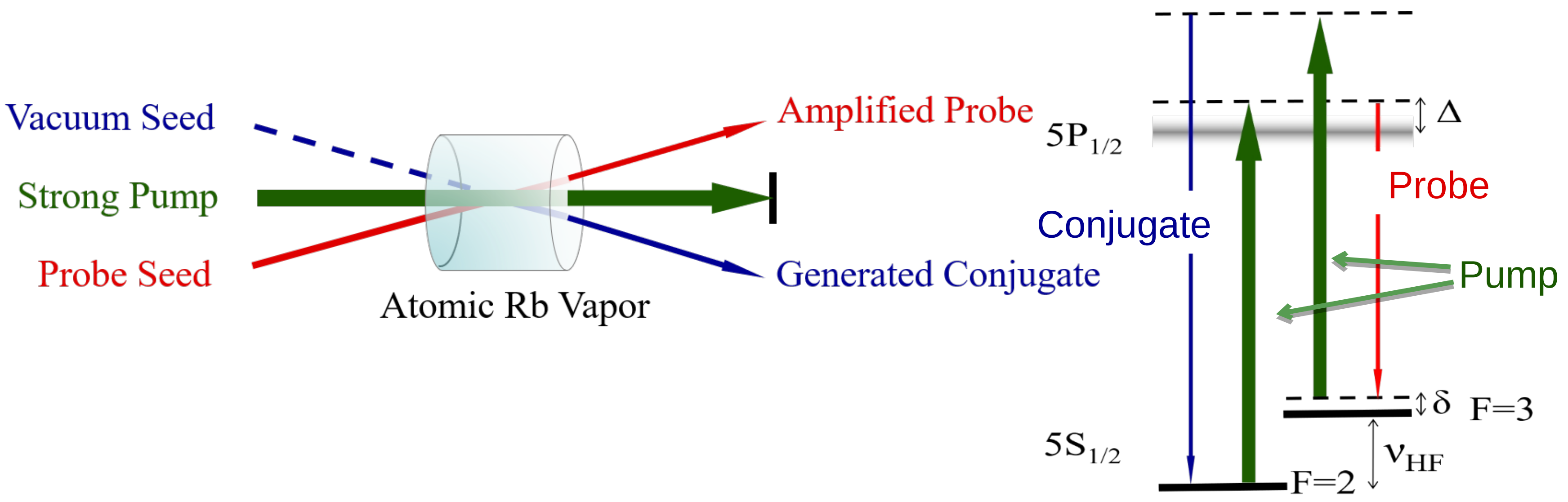
Sensing with quantum systems



Electric field: G Balasubramanian, et al, *Nature* **455**(7213), 648-651 (2008).
Thermometry: J. Choi, *PNAS*, **117**(26), 14636-14641 (2020).
Electric field: F. Dolde, et al, Nature Physics **7**, 459–463 (2011).

Squeezed light generation

Four-wave mixing (4WM) in atomic Rubidium-85 vapor

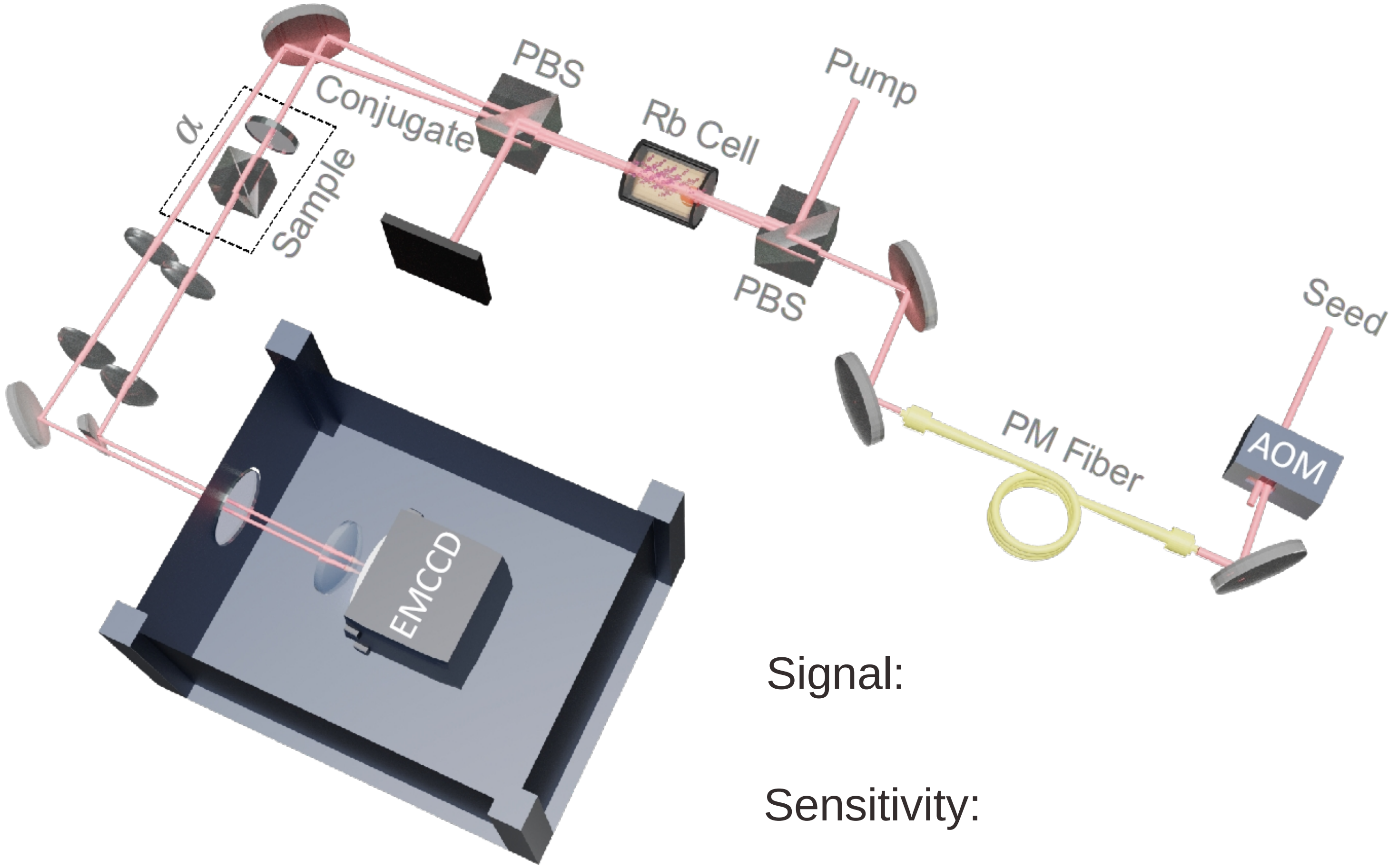


Why four-wave mixing in Rb:

Δ~1 GHz, δ=-5 MHz, ν_{HF}=3.036 GHz

- Very narrow bandwidth ~ **10 MHz**
- High photon flux ~ **10^{13} to 10^{16} photons/s**
  — much higher than most single photon down conversion sources
- High intensity squeezing ~ **7 dB**

Quantum enhanced absorption measurements



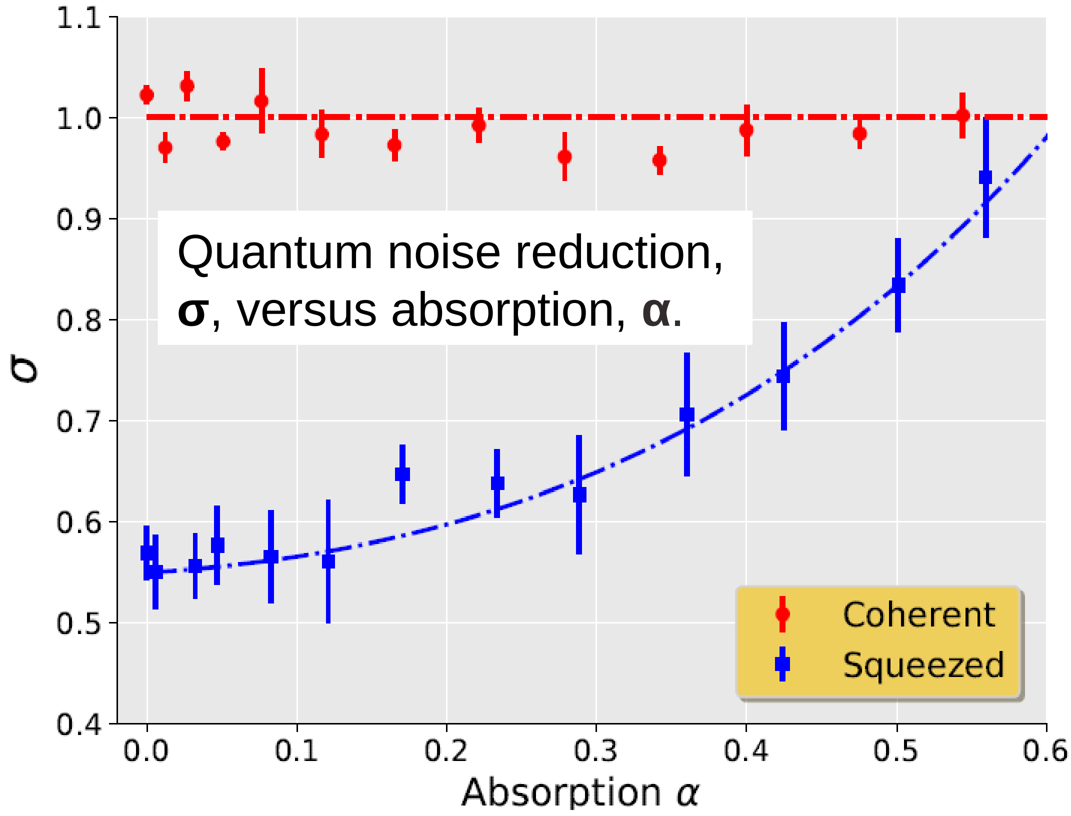
Signal:

Sensitivity:

Li et al., *Phys. Rev. Appl.* **15**, 044030 (2021).

Neither homodyne / lock-in nor logic coincidence is required.

Quantum enhanced absorption measurements



- The system is shot-noise limited when using coherent light as the probe.
- Better quantum noise reduction is achieved with faint absorption levels.
- Excellent agreement between theory and experiment.

The 10 biggest science stories of 2022

The Guardian

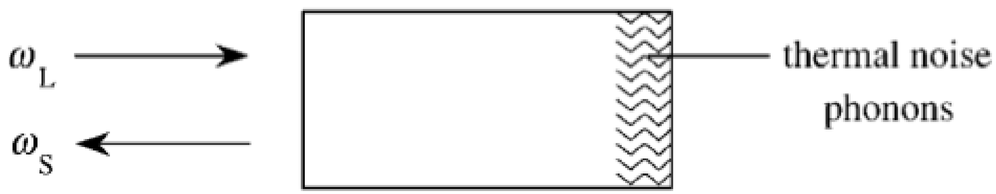
7. Soft cell, hard cell...

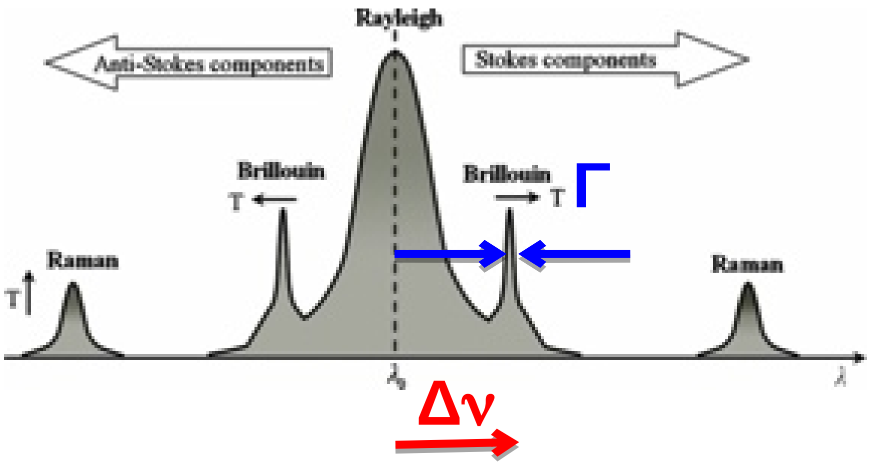
When we think about what influences how the cells inside our bodies develop, we often think of biological or chemical factors. But physical forces - what's known as the "mechanical" environment - can be just as critical to a cell's journey. The ability of cells to sense and respond to their mechanical environment has been known for several decades: for example, stem cells grown on soft jelly-like gels will become different cell types compared with stem cells grown on stiff glass-like surfaces.

> **" Brillouin microscopy is non-damaging, allowing you to 'see' the stiffness of cells without touching them**

Early signs of diseases such as cancer and Alzheimer's are often associated with changes in cell stiffness. However, it has been difficult to measure the stiffness of cells and organs inside our bodies, and how they change during development and disease. Tools to measure cell mechanical properties have relied on applying forces to the cell - essentially poking or cutting a cell and seeing how it responds. This is often invasive and damaging, and isn't easily performed on living cells or organs inside animals, let alone humans.

Brillouin microscopy: viscoelastic assessment



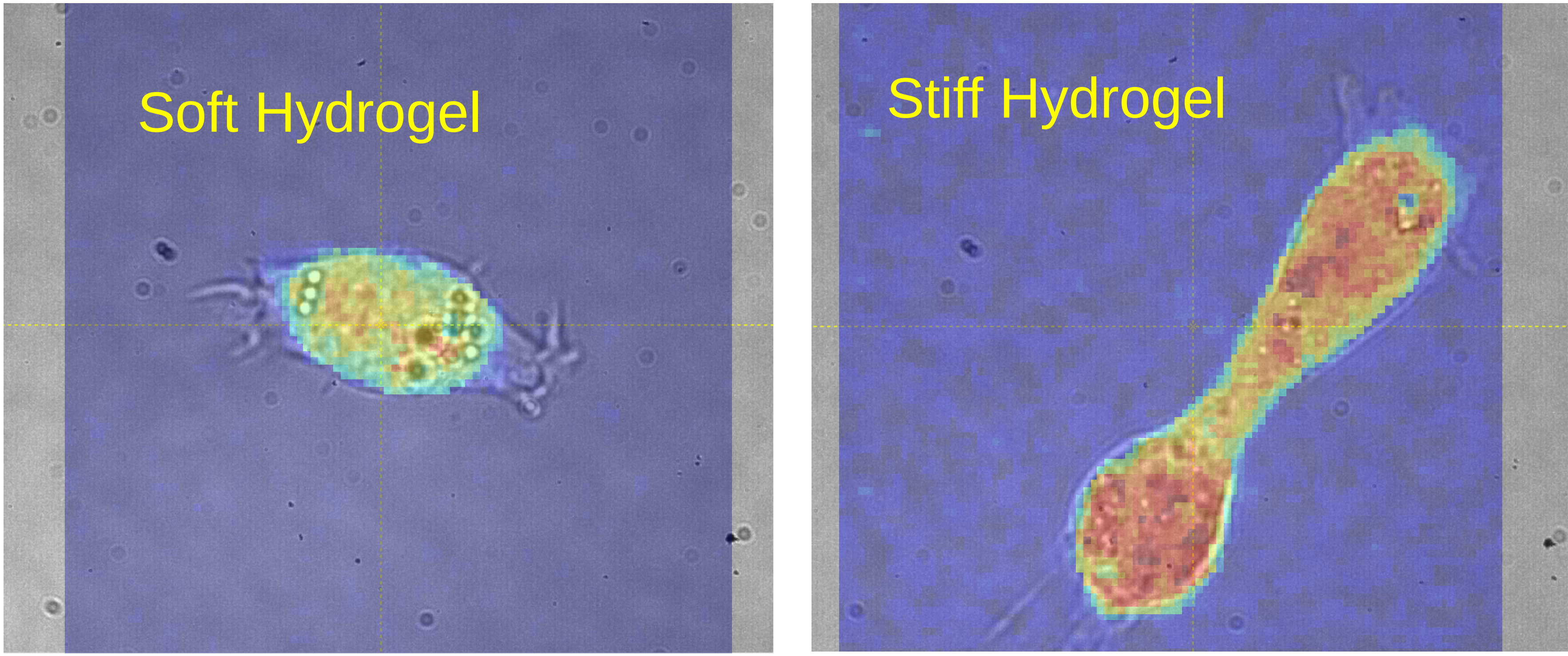


$G^{*}=G' + i\,G'' =$
$=$ ✈$v^2+i\,(2$✈v^3➔$),$

Velocity which is proportional to the **frequency shift**

Attenuation which is proportional to the **line-width**)

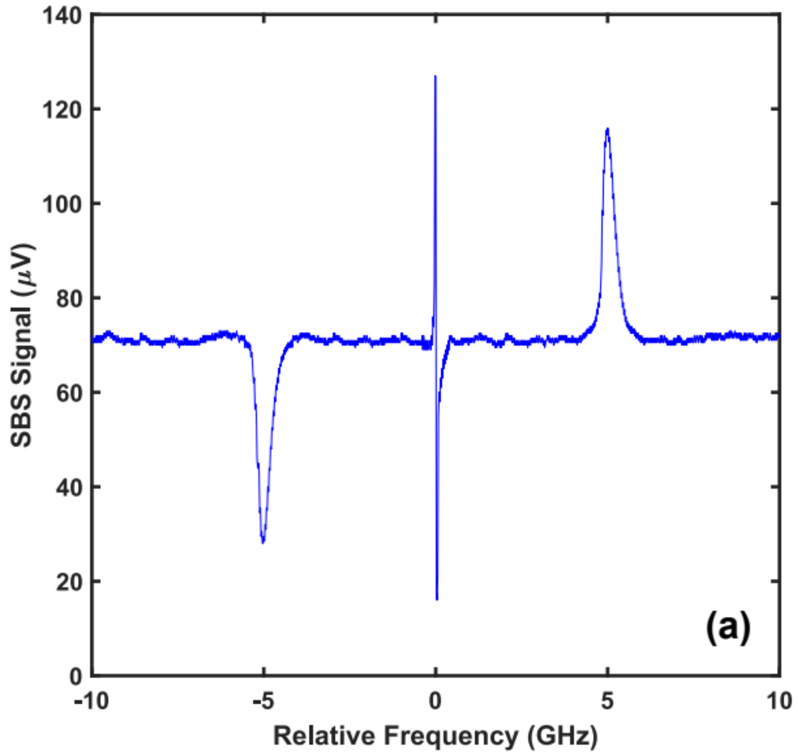
Cells are sensitive to environment

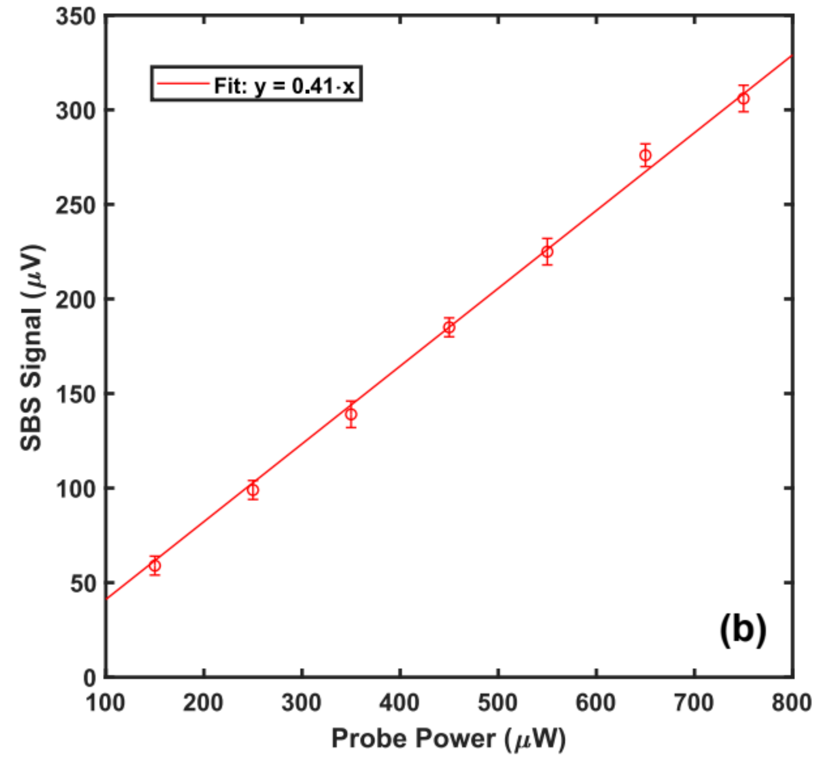


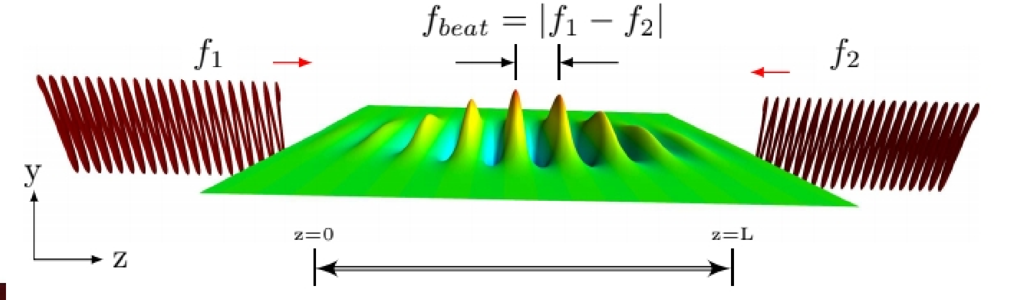
Increased ECM stiffness induces cytoskeleton stiffening. Brillouin microscopy allows imaging at high spatial resolution without cell destruction.

V. Cheburkanov et al (2023) TBP

Stimulated Brillouin spectroscopy with classical light

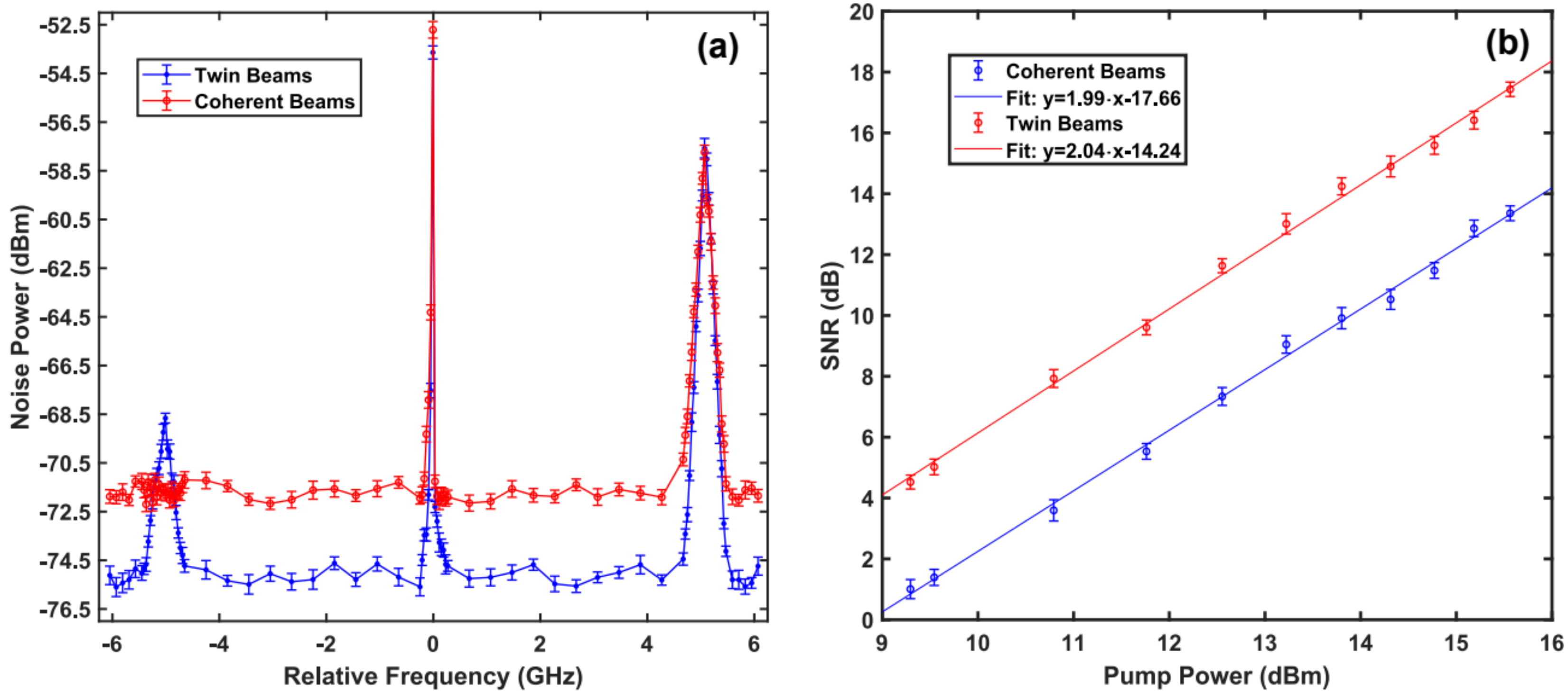




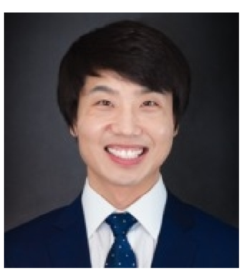


Following C. Ballmann et al *Sci Rep* 5, 18139 (2015)

Stimulated Brillouin spectroscopy with quantum light



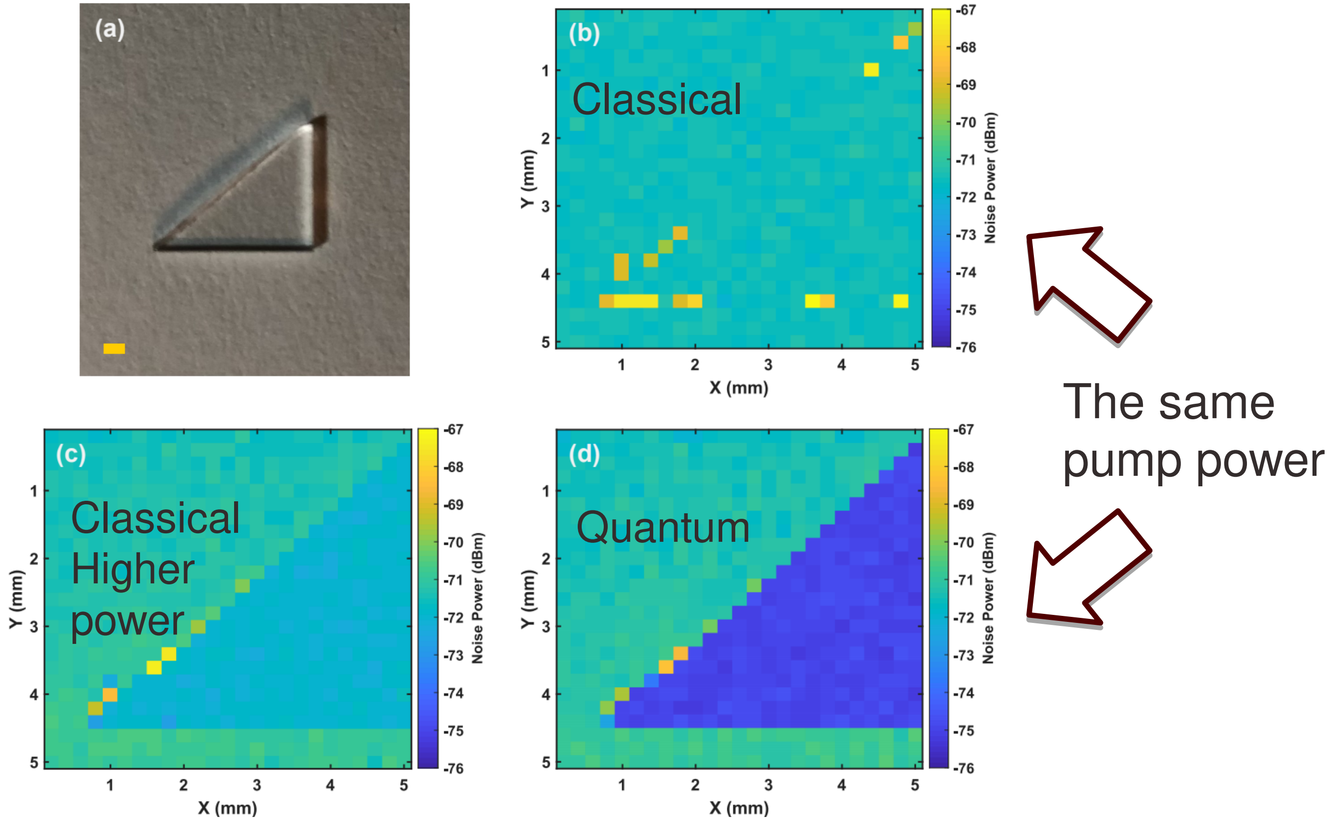
Quantum advantage is clearly seen



Tian Li
U. of Tennessee

T. Li et al, *Optica* 9(8), 959-964 (2022)

Stimulated Brillouin spectroscopy with quantum light



Quantum advantage is clearly seen

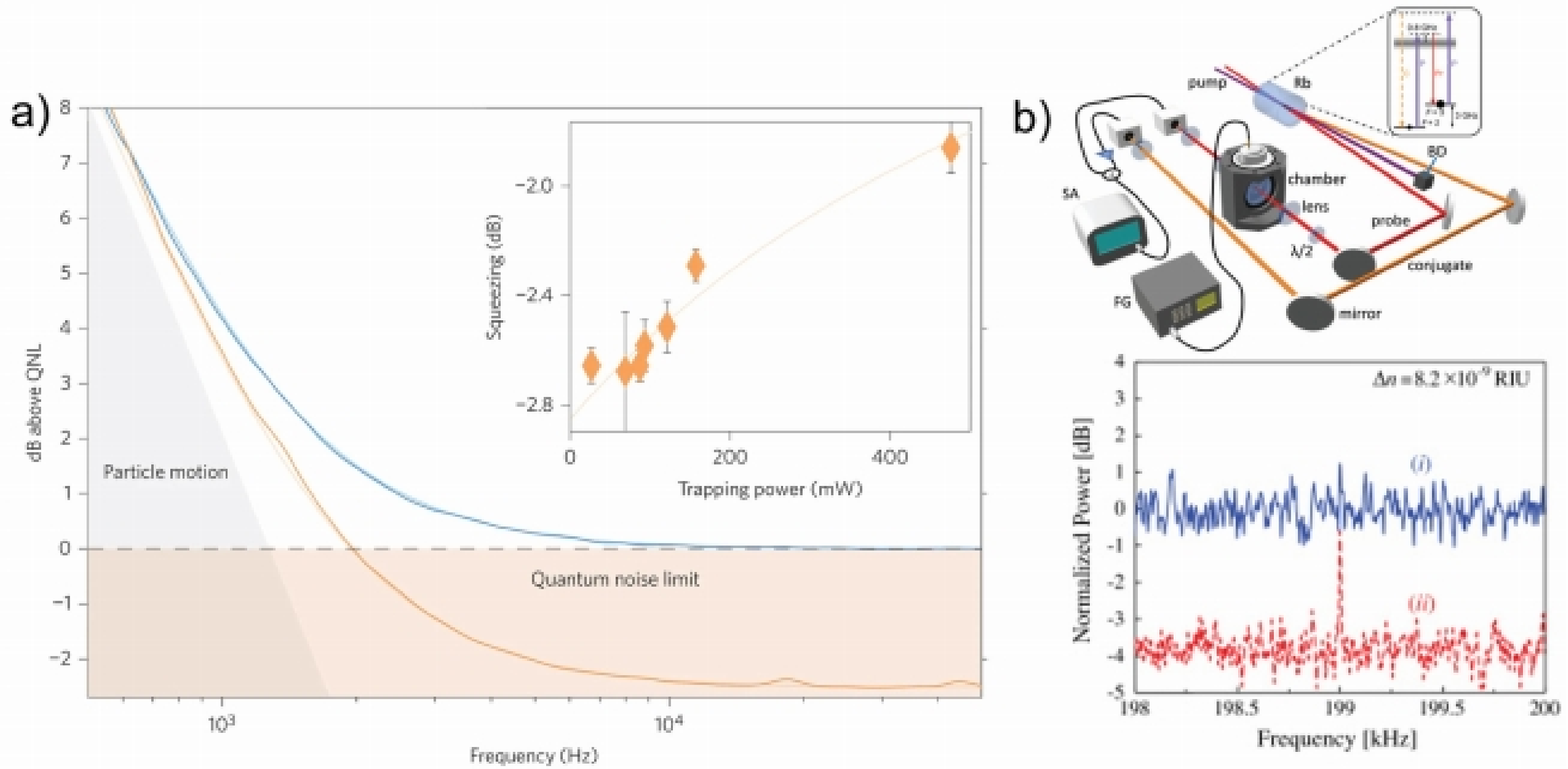
T. Li et al, *Optica* 9(8), 959-964 (2022)

Enhanced sensitivity

Quantum Biotechnology

*Nicolas P. Mauranyapin, Alex Terrasson, and Warwick P. Bowen**

Adv. Quantum Technol. **2022**, 5, 2100139

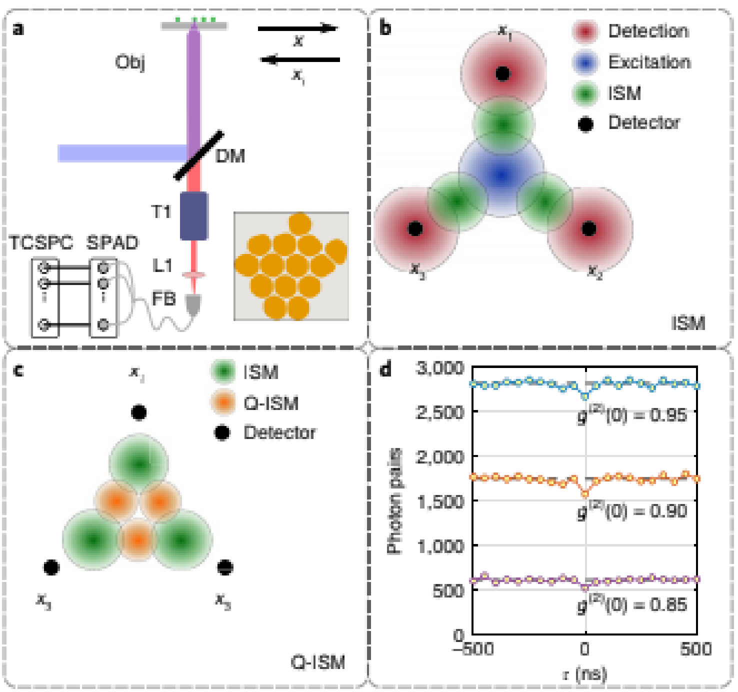


Enhanced spatial resolution

Super-resolution enhancement by quantum image scanning microscopy

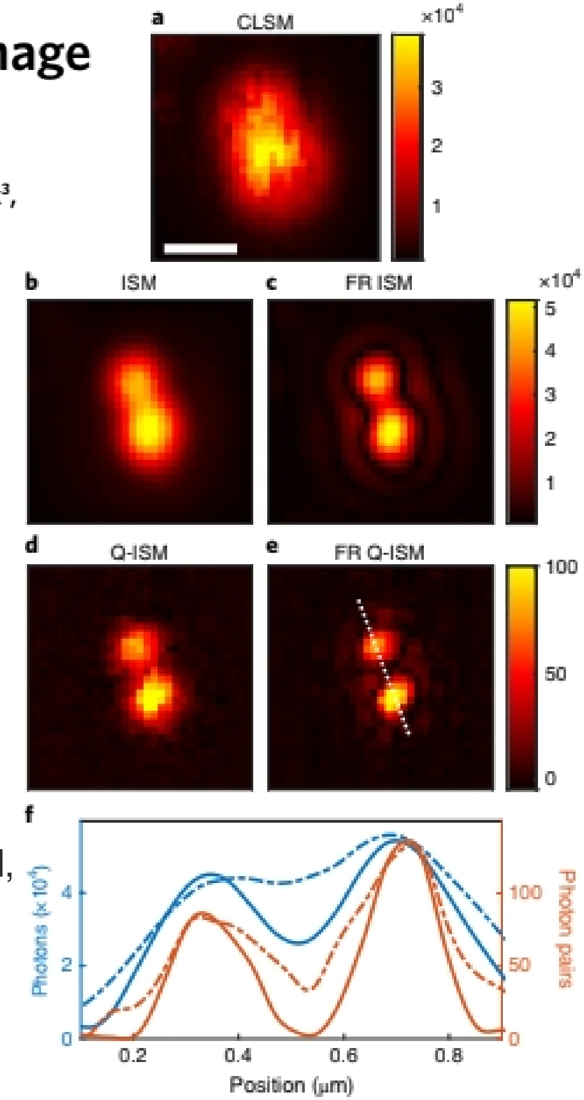
Ron Tenne[1,4], Uri Rossman[1,4], Batel Rephael[1,4], Yonatan Israel[1,2], Alexander Krupinski-Ptaszek[3], Radek Lapkiewicz[3], Yaron Silberberg[1] and Dan Oron[1*]

NATURE PHOTONICS | VOL 13 | FEBRUARY 2019 | 116–122 |



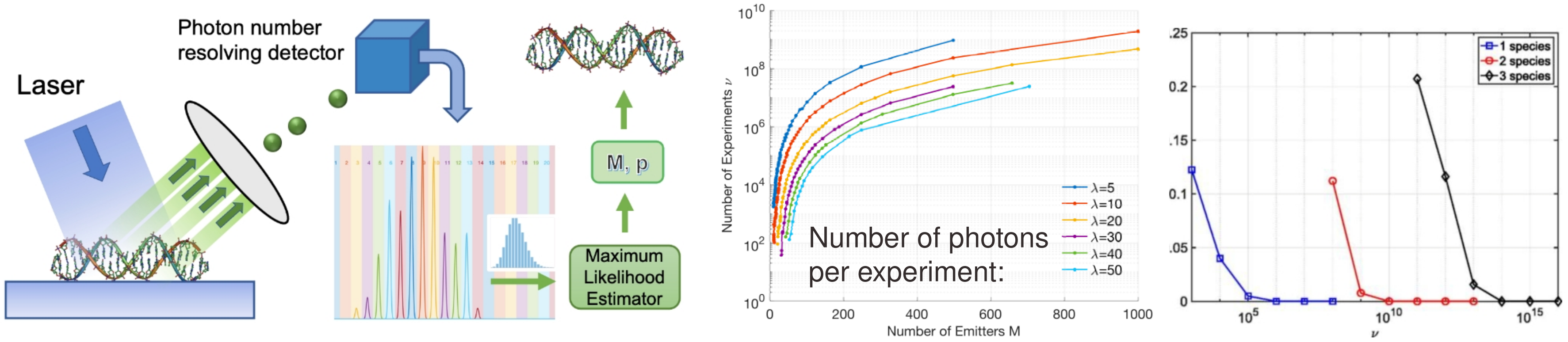
Quantum correlations (missing detection of photon pairs) improves spatial resolution by 2x.

See also
G. S. Agarwal et al, *Optica* **4**(5), 580 (2017)



Counting molecules / emitters

Motivation: no matter how tight you focus your light beam, there are more than 1 molecules in the excitation volume. **Can quantum measurements (photon correlations) help in counting those?**



Simple idea: many superresolution optical imaging modalities are relying on imaging (identifying a center of mass of) a single emitter. Most biological systems, like DNA, RNA, etc. are represented by a large number of emitters. By counting those emitters at any given spot, you can find their exact distribution.

S. Li, et al, "En route to nanoscopic quantum optical imaging: counting emitters with photon-number-resolving detectors," *Opt. Express* 30, 12495 (2022).

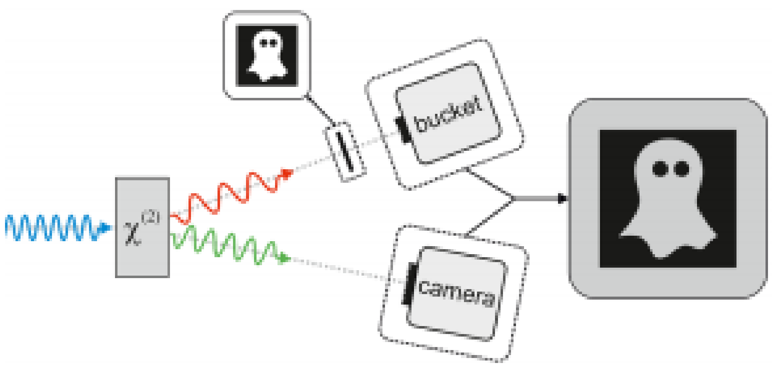
W. Li, et al, "Estimation of the number of single-photon emitters for multiple fluorophores with the same spectral signature," *AVS Quantum Sci.* **5**, 041401 (2023).

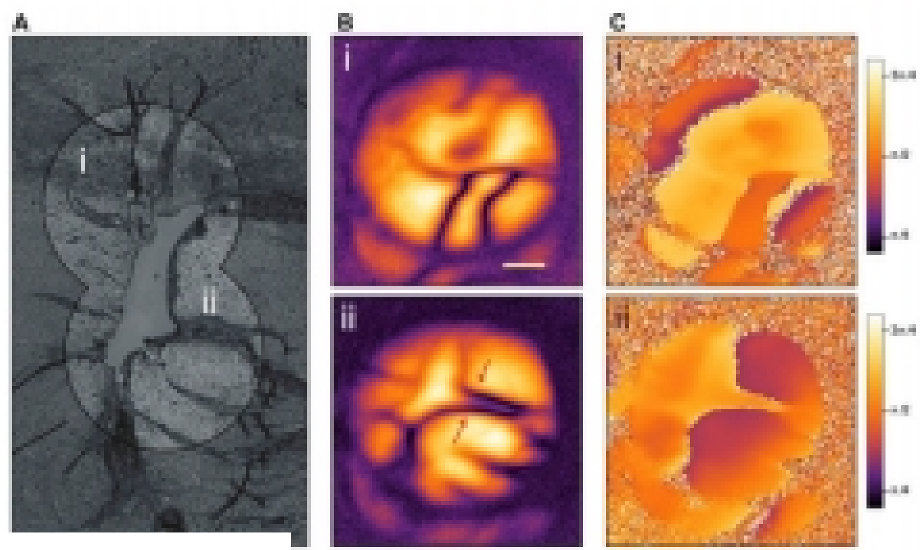
“Ghost” sensing / imaging

Quantum Sensing with Extreme Light

Mirco Kutas, Björn Erik Haase, Felix Riexinger, Joshua Hennig, Patricia Bickert, Tobias Pfeiffer, Michael Bortz, Daniel Molter, and Georg von Freymann**

Adv. Quantum Technol. **2022**, *5*, 2100164





Microscopy with undetected photons in the mid-infrared

INNA KVIATKOVSKY, HELEN M. CHRZANOWSKI, ELLEN G. AVERY, HENDRIK BARTOLOMAEUS, AND SVEN RAMELOW Authors Info & Affiliations

SCIENCE ADVANCES • 14 Oct 2020 • Vol 6, Issue 42 • DOI: 10.1126/sciadv.abd0264

Summary and Implications

- Quantum light offers several non-trivial advantages over conventional classical light sensing and imaging
- Quantum light is useful for biological applications where system can potentially suffer from excessive light exposure
- There are many fundamental questions to be explored and new technologies which need further development

What is next?

Australia invested $150+ million into Quantum Biotechnology Center focused on quantum sensing and imaging

The Australian Research Council
Centre of Excellence in
Quantum
Biotechnology

UTS UNIVERSITY OF TECHNOLOGY, SYDNEY

Flinders University

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UOW AUSTRALIA

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What is next?

Vatican Academy acknowledged quantum sensing applications as the priority direction for the World's science and technology.

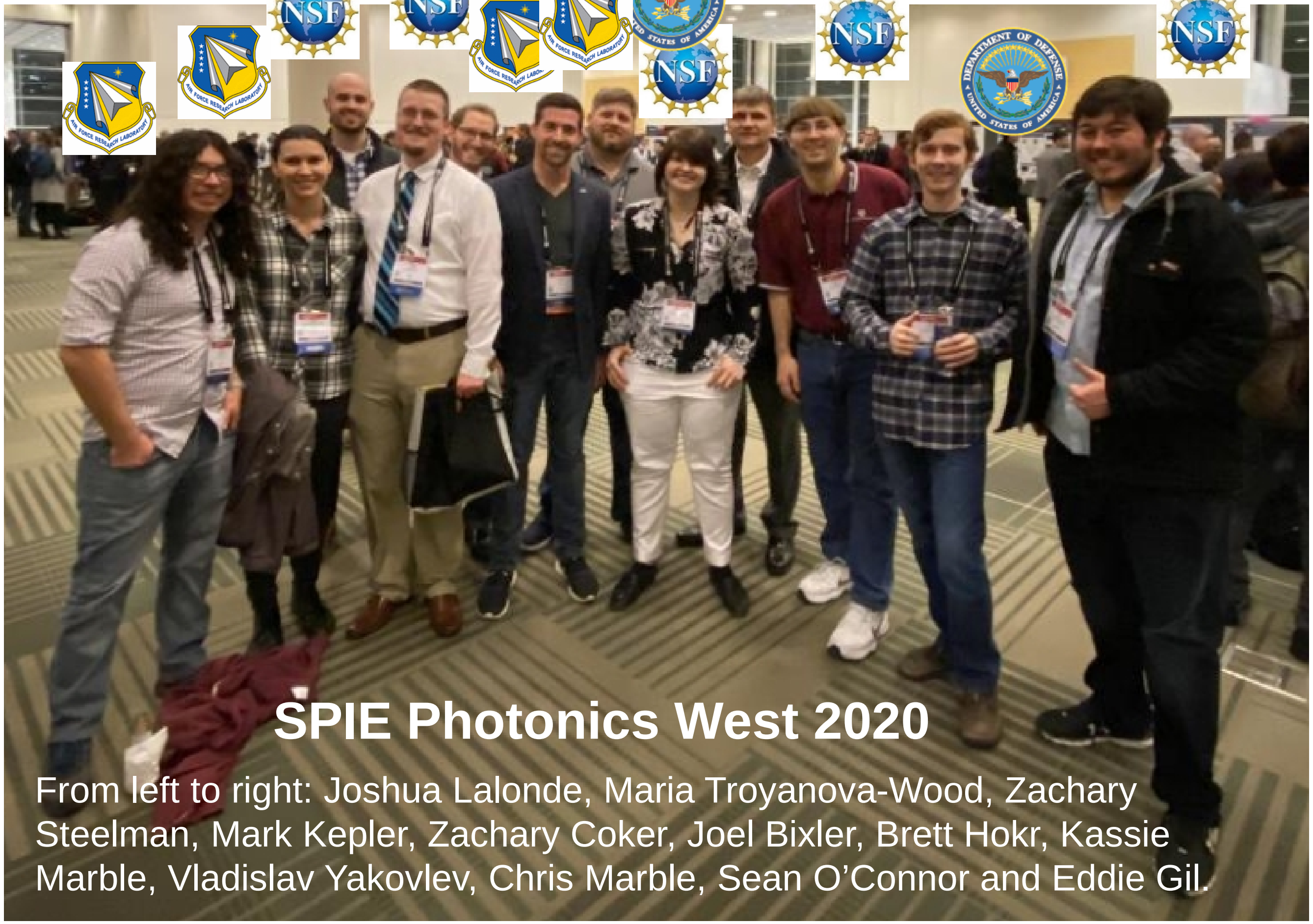
My heroes


Joseph Harrington

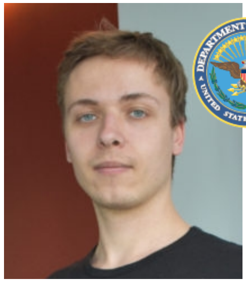

Ethan Keene


Jason Pipal


Matthew Davis


SPIE Photonics West 2020

From left to right: Joshua Lalonde, Maria Troyanova-Wood, Zachary Steelman, Mark Kepler, Zachary Coker, Joel Bixler, Brett Hokr, Kassie Marble, Vladislav Yakovlev, Chris Marble, Sean O’Connor and Eddie Gil.


Dominik Doktor

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Jace Willis


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