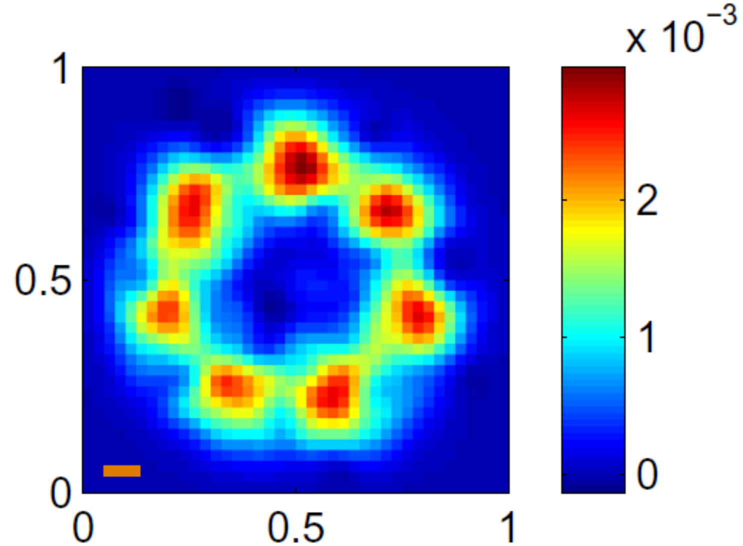
Quantum enhanced microscopy

Dan Oron

Dept. of Molecular Chemistry and Materials Science
Weizmann Institute, Rehovot, Israel.



Korea Universtity, April 2024

Outline

I. A brief history of (classical) optical microscopy

II. Quantum-inspired and quantum photon statistics based microscopy

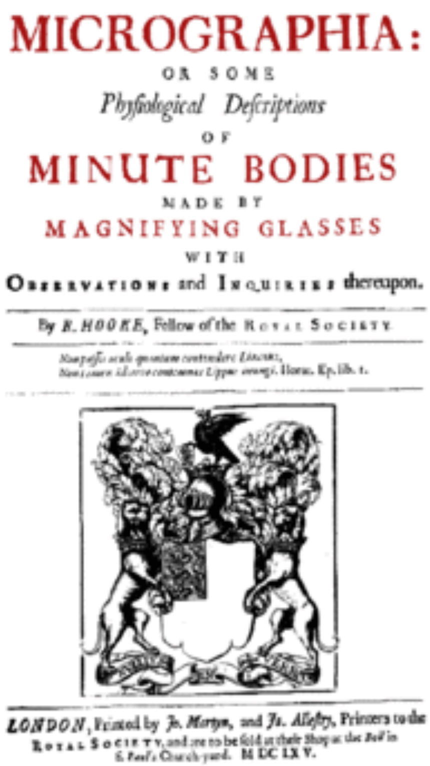
III. Quantum entanglement and squeezing based imaging

I. A brief history of optical microscopy

- The optical microscope
- Polarization microscopy
- Abbe limit of resolution
- Phase imaging
- Fluorescence microscopy and the confocal microscope
- Near-field imaging
- Multiphoton microscopy: TPEF, SHG, THG, CARS/SRS
- Superresolution imaging: STED, PALM/STORM, SOFI, SIM/ISM, MINFLUX

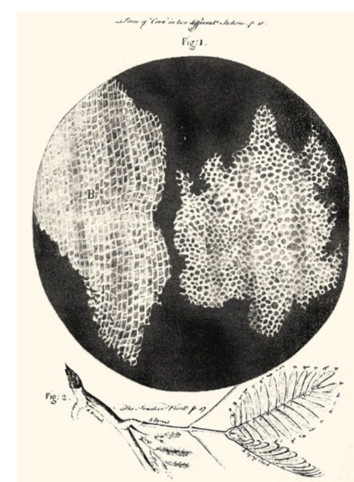
Optical microscopy

Has a long history, but more "scientific" efforts are traced back to the early-mid 17th century


MICROGRAPHIA:
OR SOME
Physiological Descriptions
OF
MINUTE BODIES
MADE BY
MAGNIFYING GLASSES
WITH
OBSERVATIONS and INQUIRIES thereupon.

By R. HOOKE, Fellow of the ROYAL SOCIETY.

LONDON, Printed by Jo. Martyn, and Ja. Allestry, Printers to the ROYAL SOCIETY, and are to be sold at their Shop at the Bell in S. Paul's Church-yard. M DC LXV.

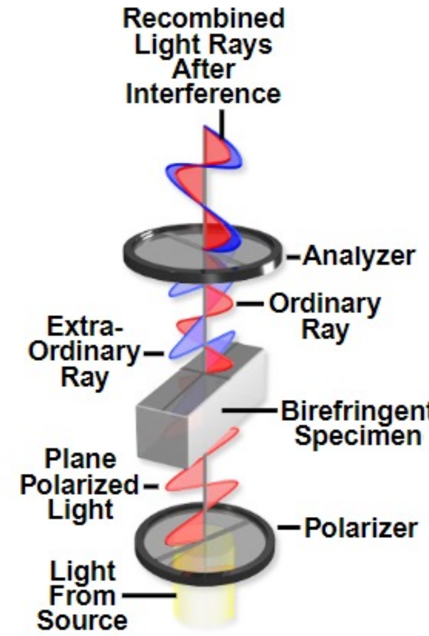


Micrographia is published: 1665

Polarization imaging

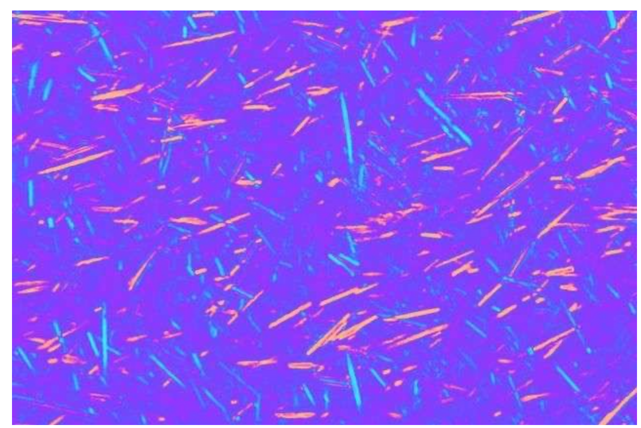
A set of interference-based techniques to study birefringence in the sample.

Still commonly used in mineralogy, some subfields in life science and materials science (polymers, organic crystals)



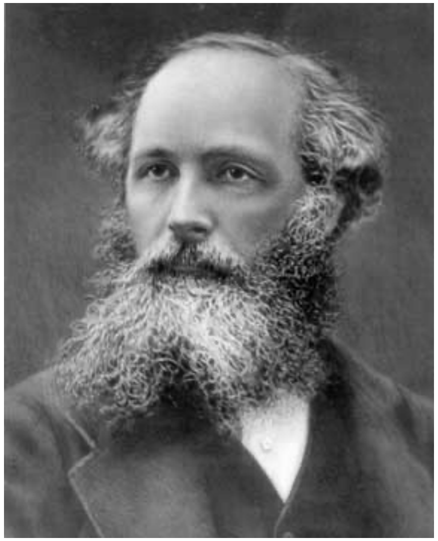
Henry Fox Talbot (1800-1877)

David Brewster (1781-1868)



Gout diagnostics (uric acid crystals)

Light is an electromagnetic wave



James Maxwell,
UK (1831-1879)

THE
LONDON, EDINBURGH AND DUBLIN
PHILOSOPHICAL MAGAZINE
AND
JOURNAL OF SCIENCE.

[FOURTH SERIES.]

MARCH 1861.

XXV. *On Physical Lines of Force.* By J. C. MAXWELL, *Professor of Natural Philosophy in King's College, London**.

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0}$$

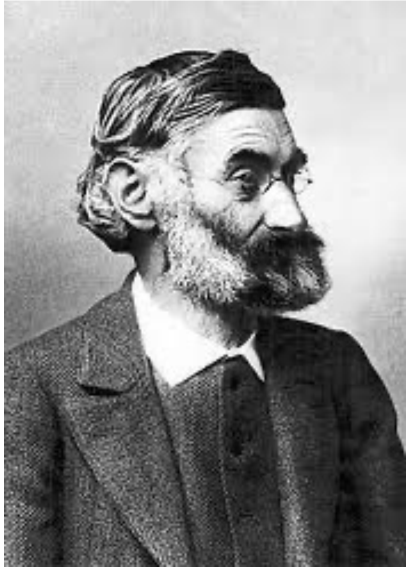
$$\nabla \cdot \mathbf{B} = 0$$

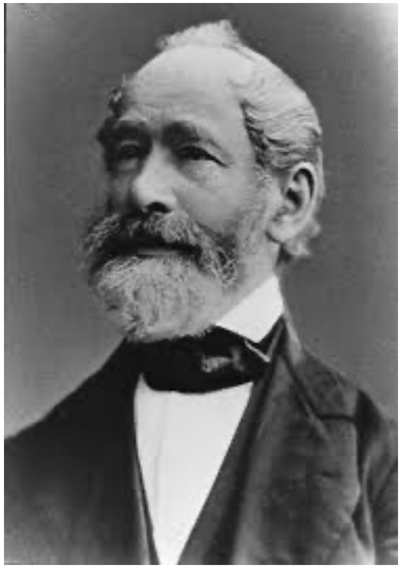
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

$$\nabla \times \mathbf{B} = \mu_0 \mathbf{J} + \mu_0 \varepsilon_0 \frac{\partial \mathbf{E}}{\partial t}$$

There exists a solution for free-space propagation of an electromagnetic waves whose speed (given by known constants of nature) equals the speed of light as known from astronomical measurements

1873: The birth of the optical microscope (as we know it …)



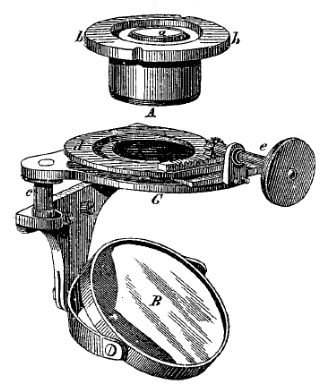


No particles can be resolved (nor the characters of any really existing structure recognised) when they are situated so closely together that not even the first of a series of diffraction pencils produced by them can enter the objective simultaneously with the undiffracted rays.

cor

By DR. E. A

the respective minimum value is found (purely central illumination being employed) by dividing the wave length by the sine of half the angle of aperture, and half that product when, other circumstances being equal, the illumination is as oblique as the objective will admit, whatever be its aperture.



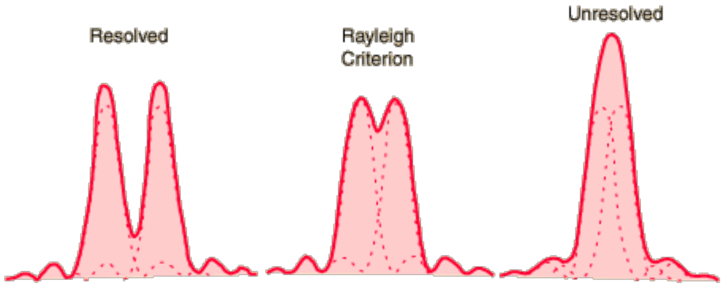
($^2/_3$ natürl. Grösse.)

Resolution

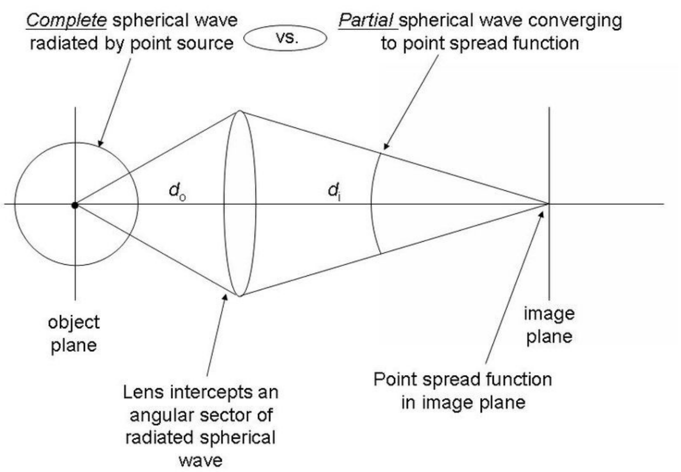
Optical resolution describes the ability of an imaging system to resolve detail in the object that is being imaged.

This is not to be confused with precision of measurement

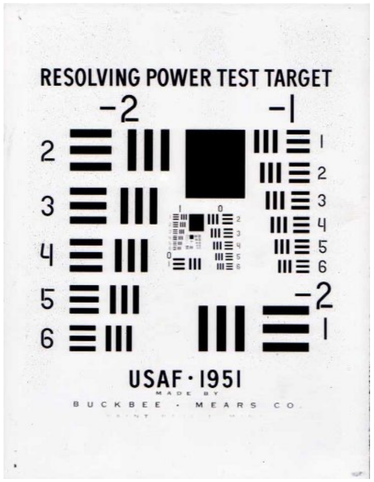
Rayleigh criterion



Imaging system



Abbe criterion



What is assumed in the Abbe derivation?

- Linear optics
- Time independent sample
- Homogeneous illumination
- No “extra information”
- Implicitly – classical physics

Each of these properties presents a ‘loophole’ through which the diffraction barrier can be broken (more about that in a bit).

Phase microscopy (Zernike)

Fritz Zernike, Netherlands (1888-1966)

Physics 1953

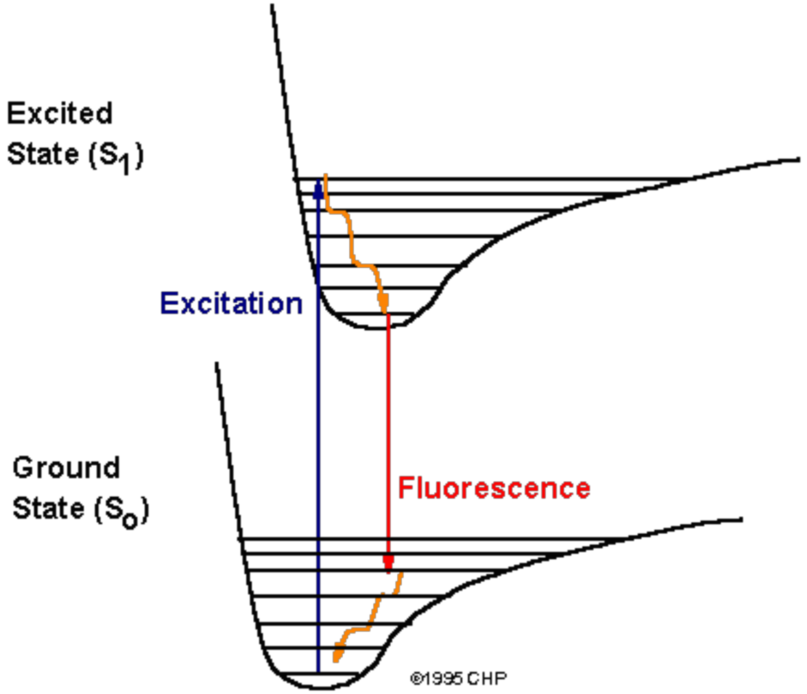
The thorough theoretical foundation that we owe to the genius of Ernst Abbe … that brought its optical and illumination system very close to perfection.

But even Abbe's theory had a gap, for it took into account only those conditions in which the microscopic objects appear against the background as a result of their contrasts in colour and intensity

It was this gap in Abbe's theory that in the 1930's led Zernike to re-investigate the … processes … that give rise to the image in a microscope. Even if the eye is not able to discern the change undergone by a beam of light when it passes through a transparent object, the change does nonetheless exist …

Fluorescence microscopy

High energy photons are absorbed in the sample and lower energy photons are emitted



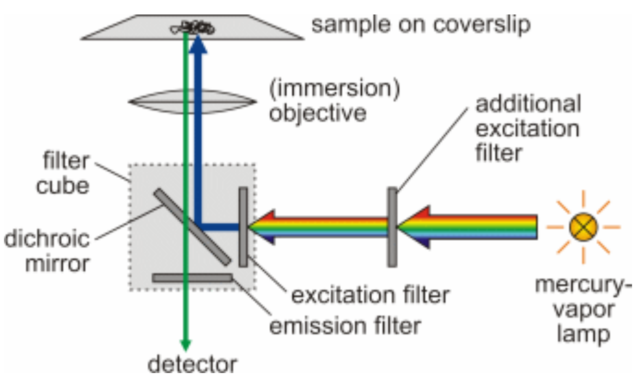
Fluorescent markers can be very bright (quantum yield ~100%) but undergo photobleaching, typically after ~10^9 emitted photons

Fluorescence microscopy

Advantages:

- Easy separation between excitation and emission light (background-free)
- Ability to specifically label organelles or molecules

The conventional (since ~1940's) fluorescence microscope



Fluorescent proteins and genetically engineered cell lines and animals now enable monitoring of intracellular chemistry

Roger Tsien | Martin Chalfie | Osamu Shimomura

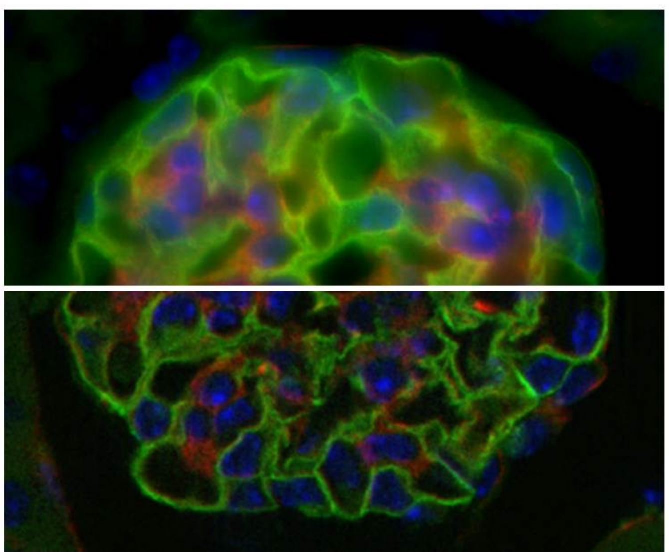
Chemistry 2008

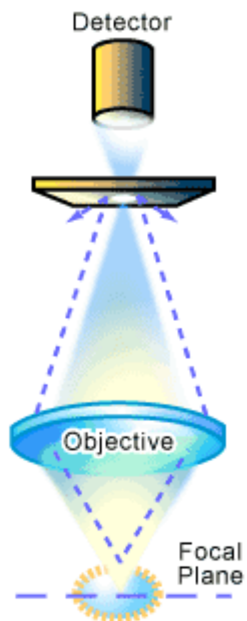
Confocal microscopy

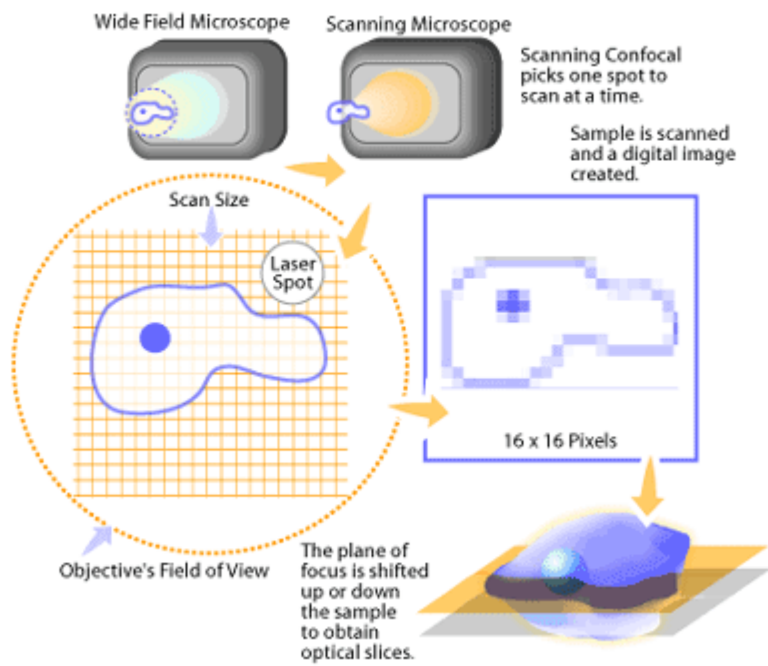
Marvin Minsky, USA (1927-2016)

Minsky overcame the problem of depth resolution in a standard microscope by transitioning to a scanning microscope.

The confocal microscope is the first to have given up on “imaging”. The image is a digital entity collected point by point.



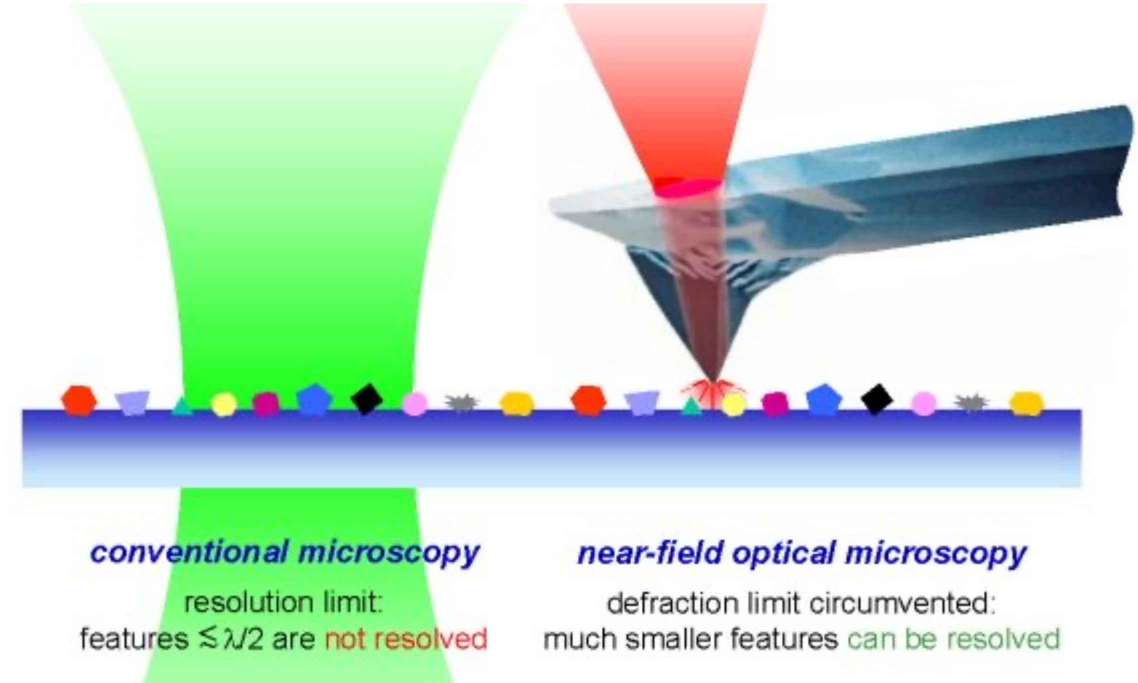




Near-field microscopy

Dieter Pohl, Switzerland (1938-)

Aaron Lewis, Israel (1946-)



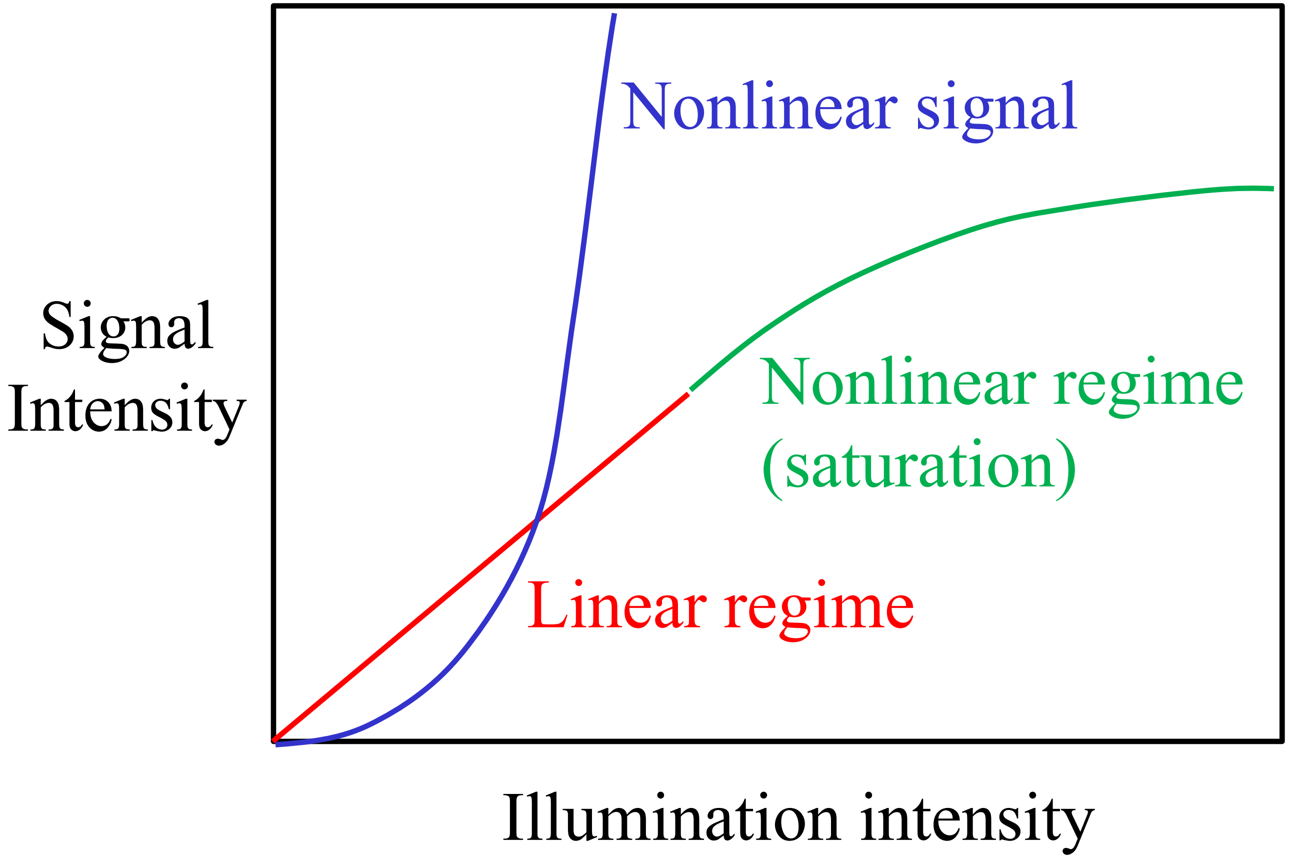
Breaking the Abbe limit but at a very hefty price: the scanning tip has to approach the sample surface

Super-resolution fluorescence near-field scanning optical microscopy

A. Harootunian, E. Betzig, M. Isaacson, and A. Lewis

School of Applied and Engineering Physics, Cornell University, Ithaca, New York 14853

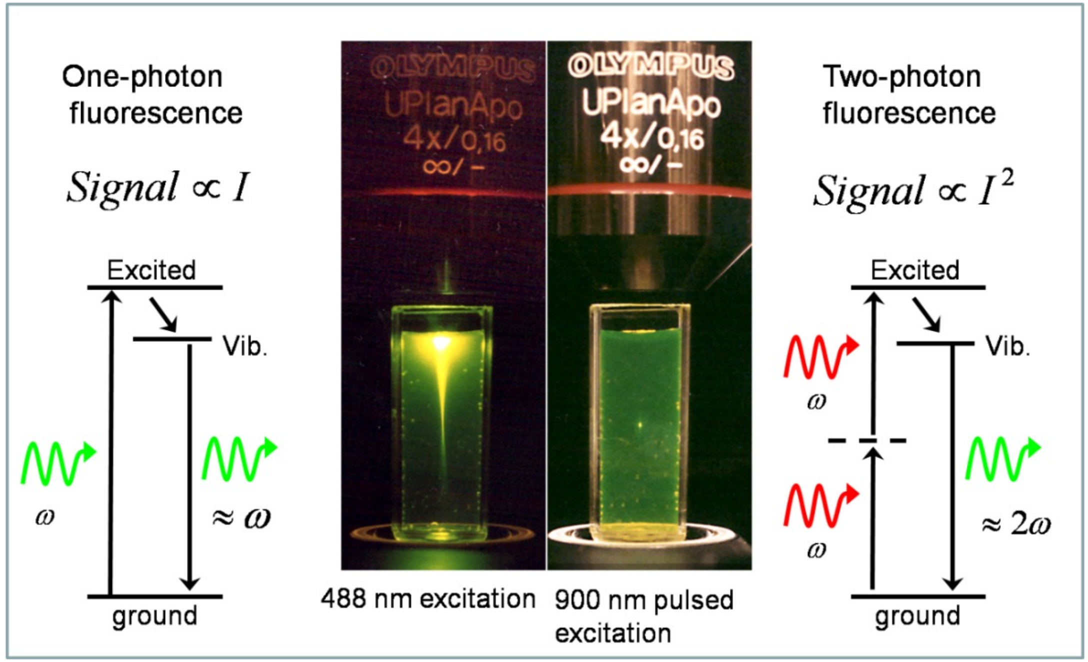
Nonlinear microscopy



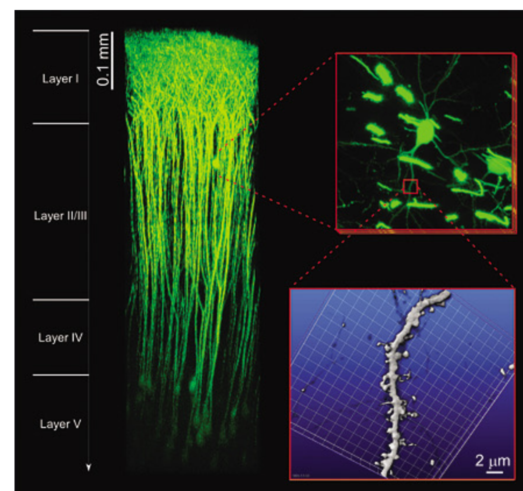
Multiphoton fluorescence microscopy

Maria Goeppert Mayer (1906-1972)

Physics 1963



The nonlinear dependence on excitation intensity provides intrinsic sectioning without a confocal pinhole and enables work in scattering media (first experiments 1990)

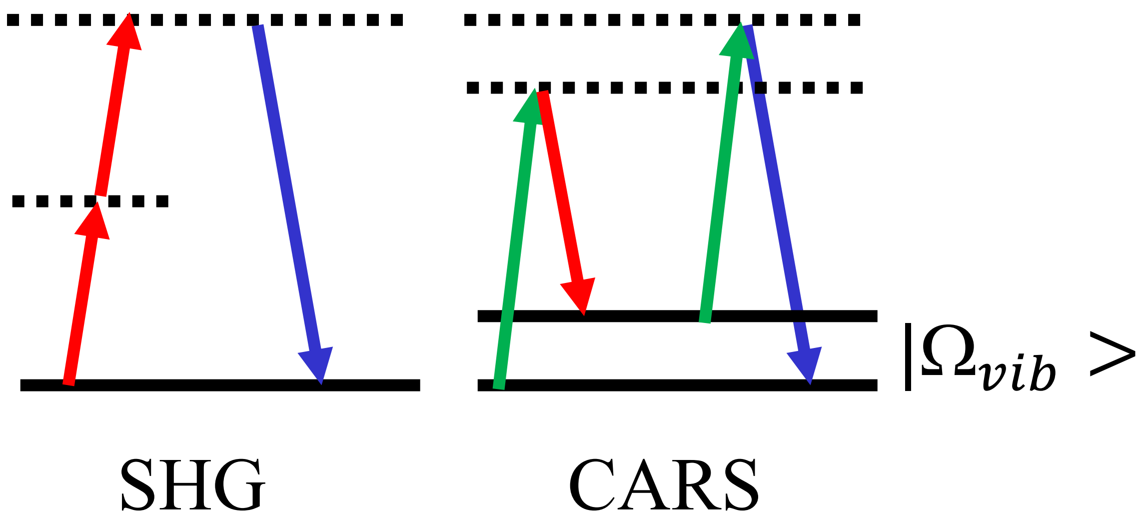


Coherent nonlinear microscopy

In a coherent process the final state of the medium is the same as the initial state, requiring both **energy** and **momentum** conservation

Harmonic generation

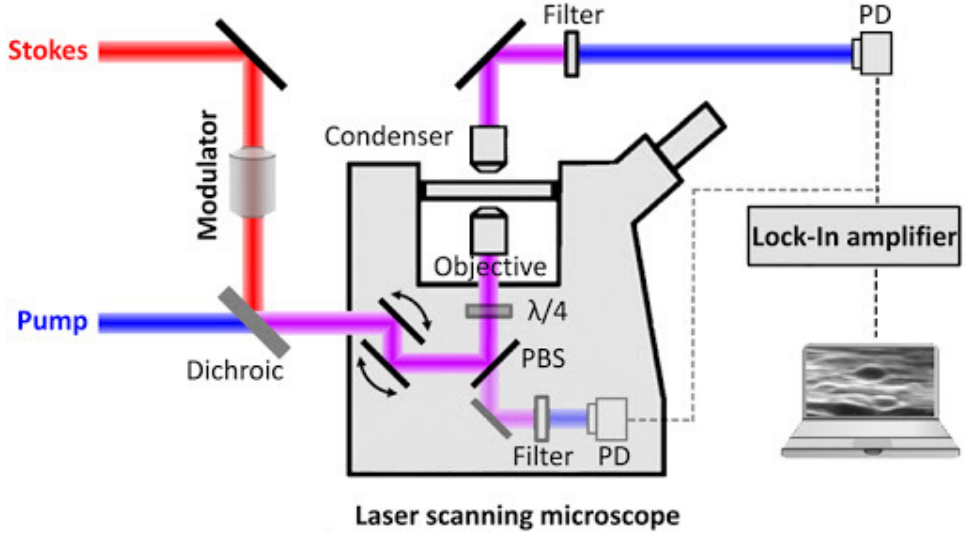
Four-wave mixing

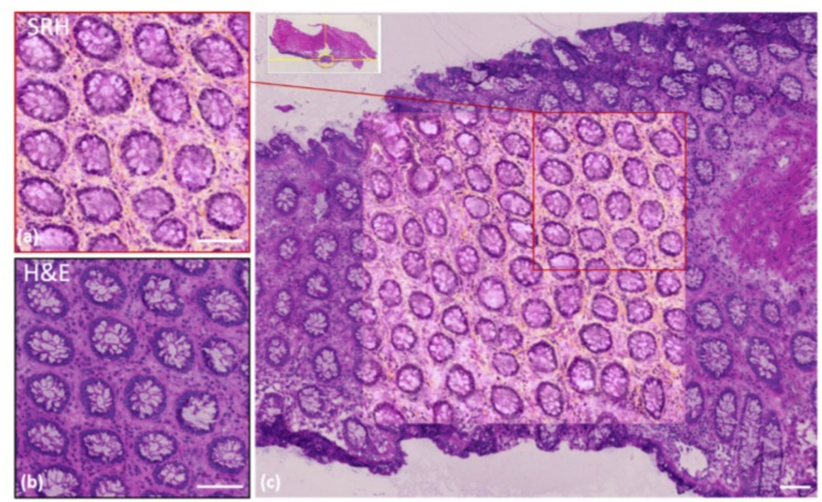


Coherent nonlinear microscopy

In a coherent process the final state of the medium is the same as the initial state, requiring both **energy** and **momentum** conservation

Example: coherent Raman imaging





Major application in recent years has been in histology using lipid lines (~3000 cm^{-1})

B. Sarri et al., Biomed. Optics Express 10, 5378 (2019)

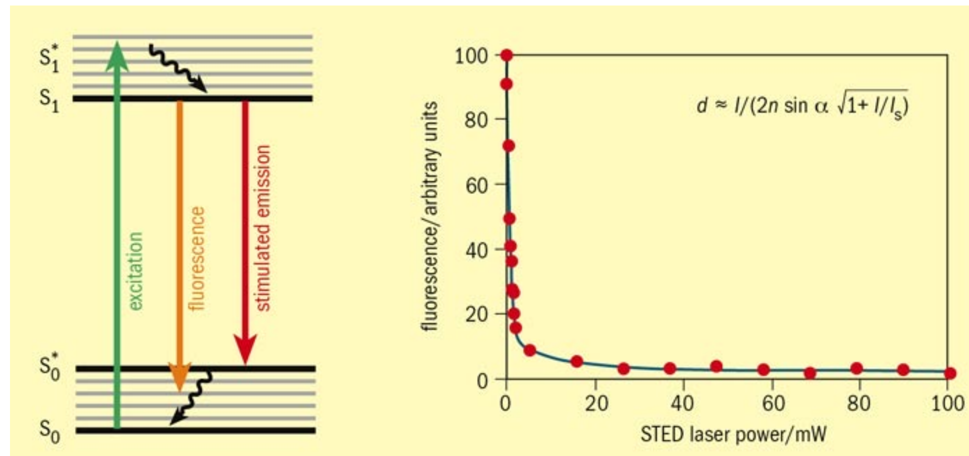
STED

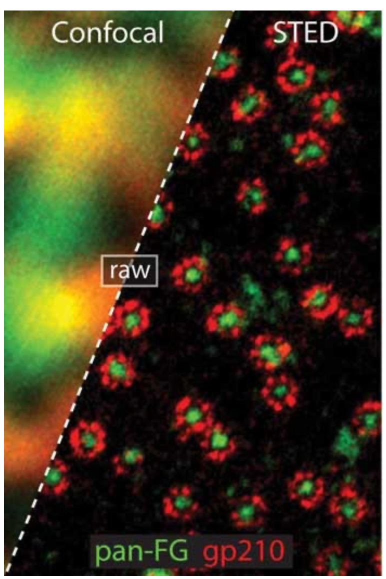
STimulated Emission Depletion imaging is based on saturated turn-off of the fluorescence by light

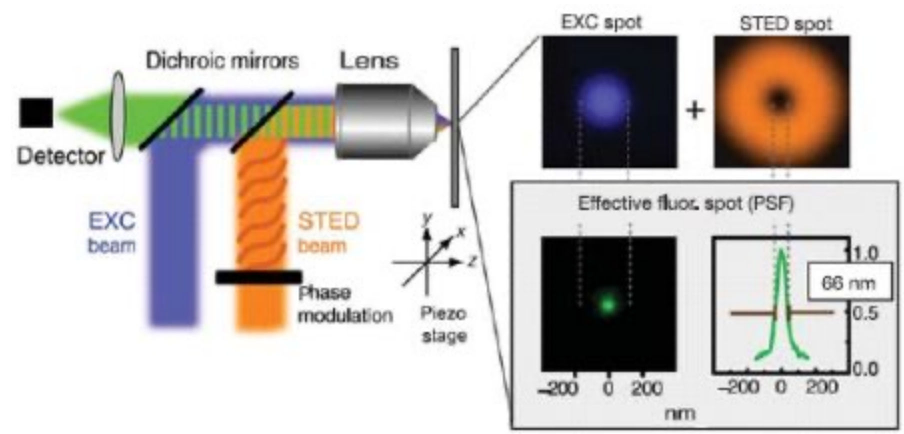
Scanning

Works with many organic dyes

Issues with photobleaching

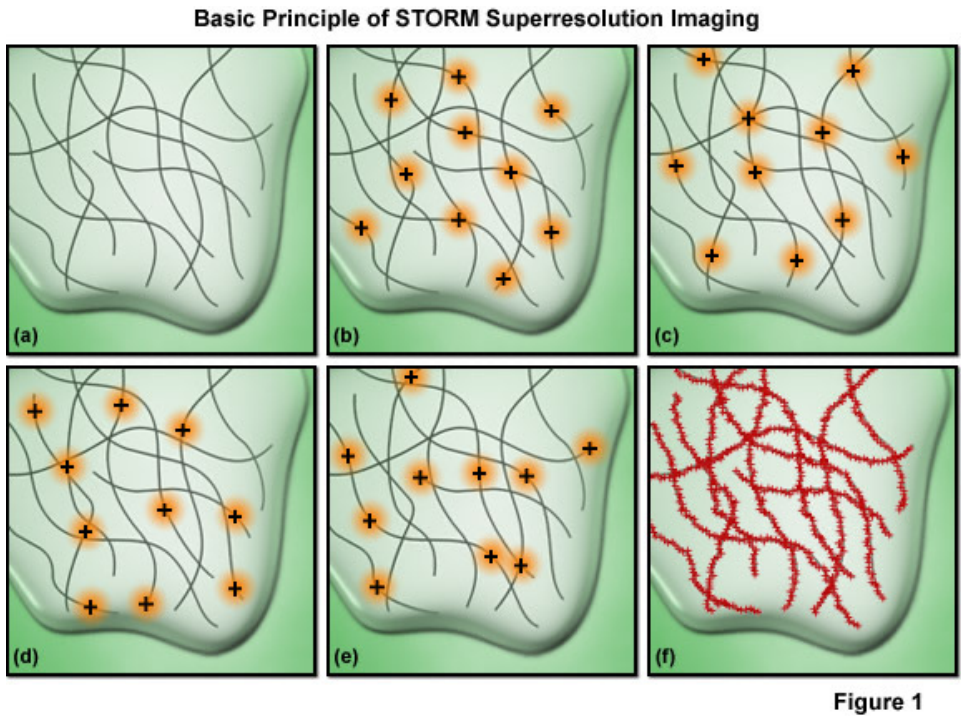


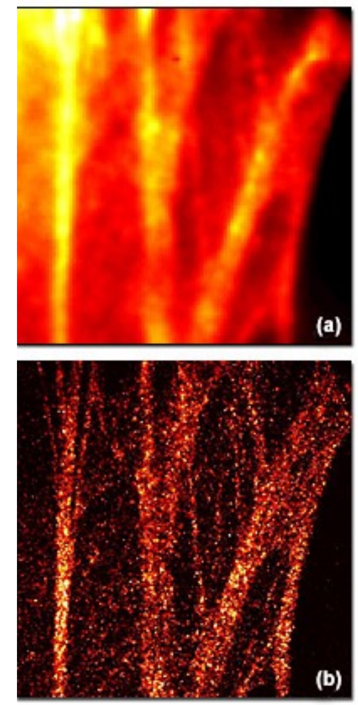




PALM/STORM

Optics is very good at measuring centroids well beyond the "transform" or "diffraction" limit (limited only by the signal-to-noise ratio)





Wide-field, but need photoactivable fluorophores and typically quite slow

Relatively small modification to microscope

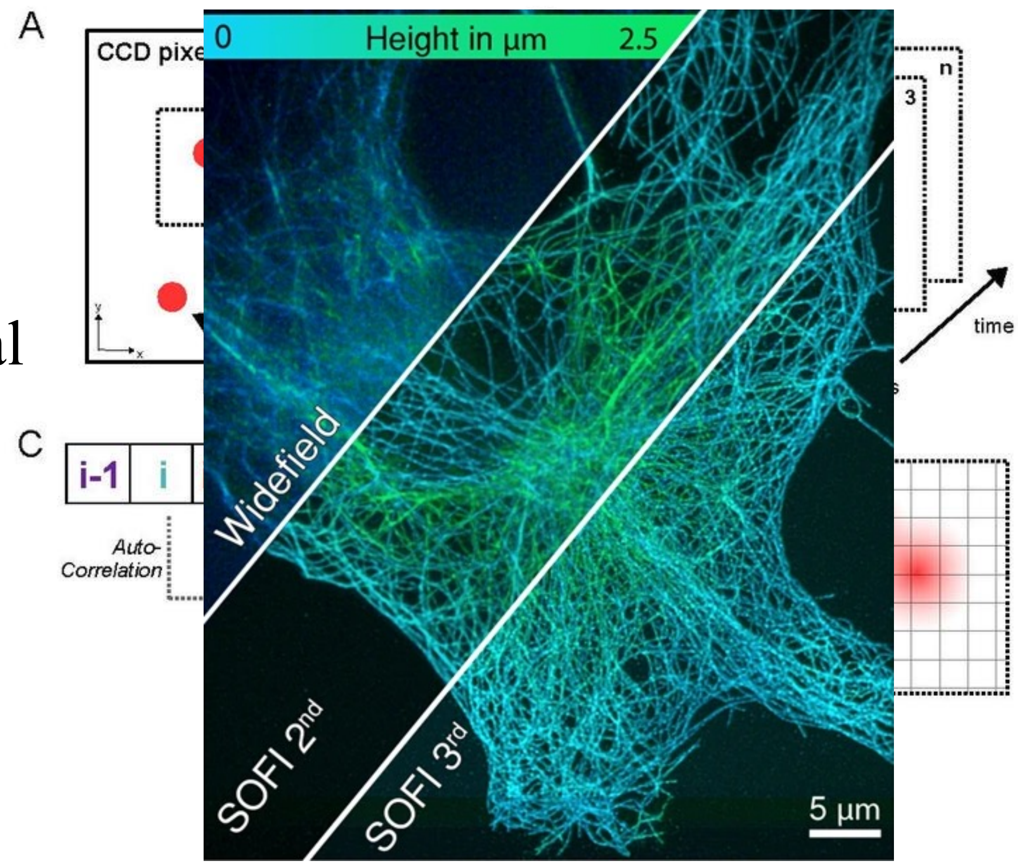
SOFI

Super-resolution optical fluctuation imaging uses uncorrelated intermittency of emitters to extract spatial information using time series of images.

Light from a single emitter is only correlated with itself.

High-order correlations reveal better resolved position.

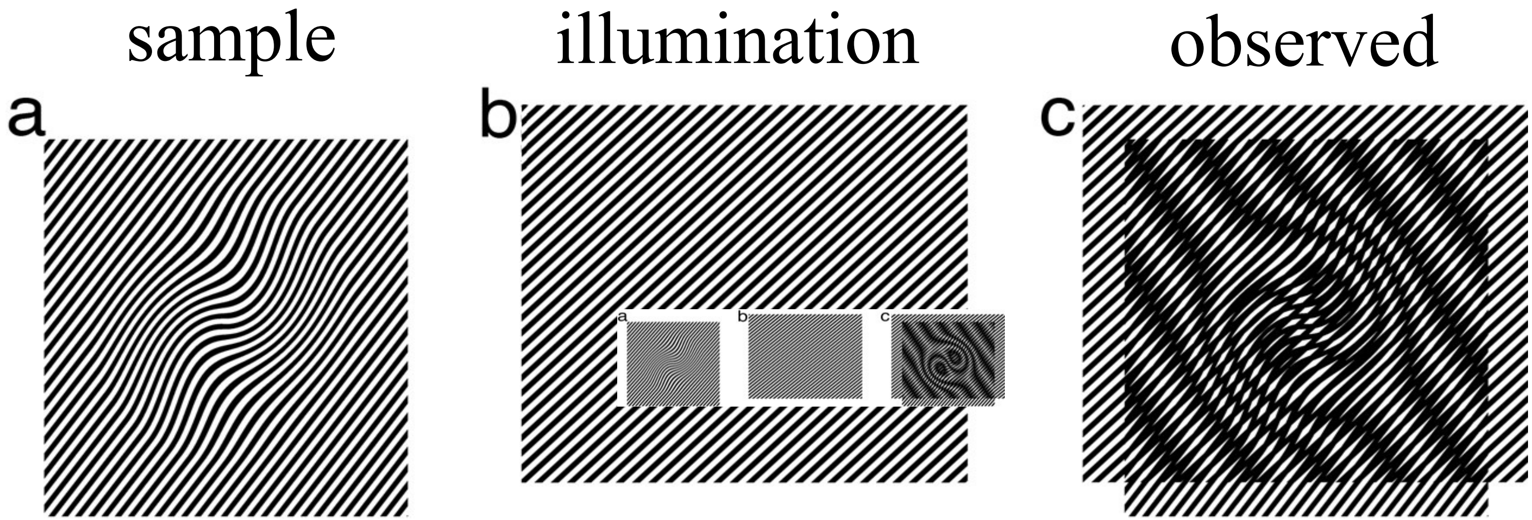
Brightness depends on fluctuation dynamics.



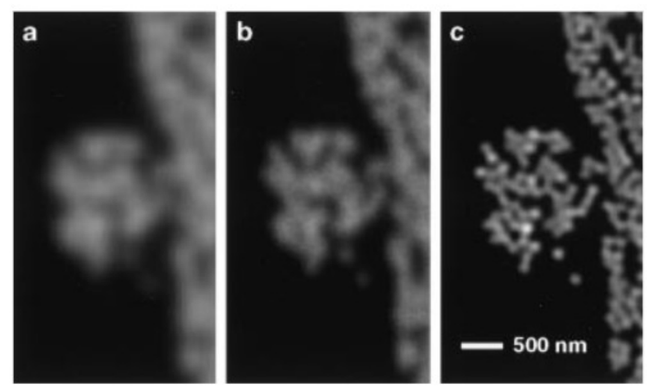
Dertinger et al., PNAS 106, 22287 (2009)

SIM

Structured illumination microscopy takes advantage of Moire patterns to 'downconvert' high frequency information to observable spatial frequencies



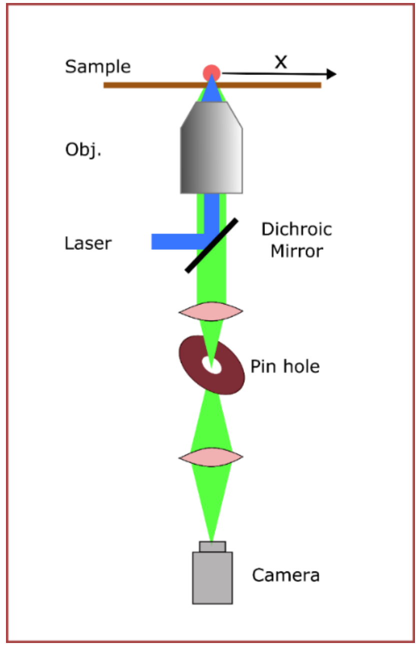
This is not an easy modality as it requires stability during multiple exposures of gratings, but is very fast and efficient.

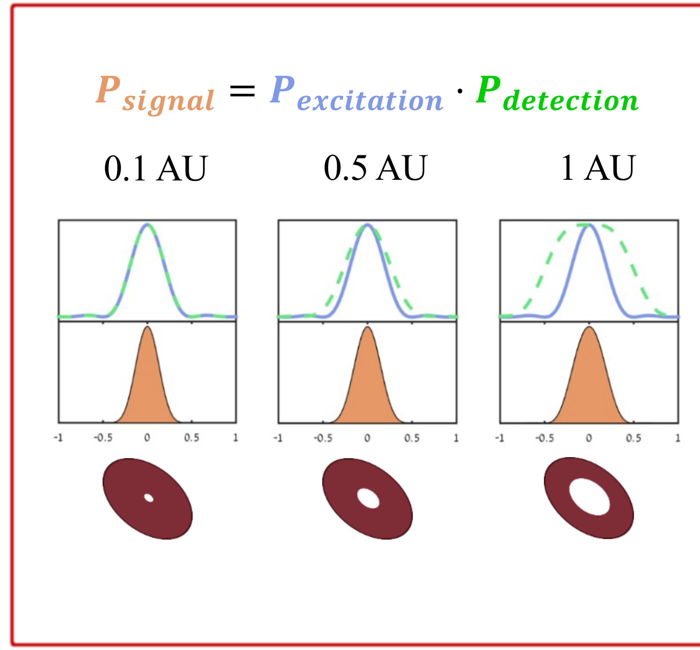


M.G.L. Gustafsson, J. Microscopy 198, 82 (2000)

ISM

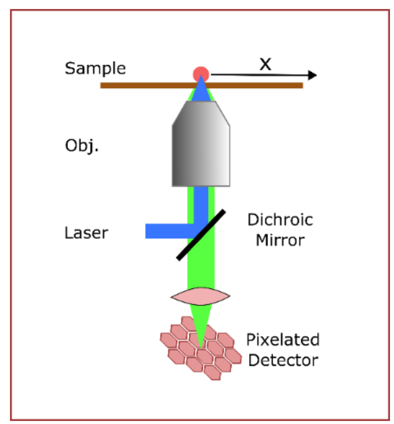
Confocal microscopy usually provides improvement in axial resolution but little improvement in transverse resolution

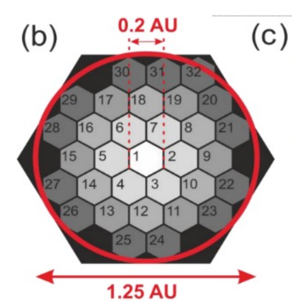




Intuitively, using a pixelated detector can recover improved transverse resolution with no penalty on signal intensity!
With proper analysis, this is called Image scanning Microscopy.

A pixelated confocal detector

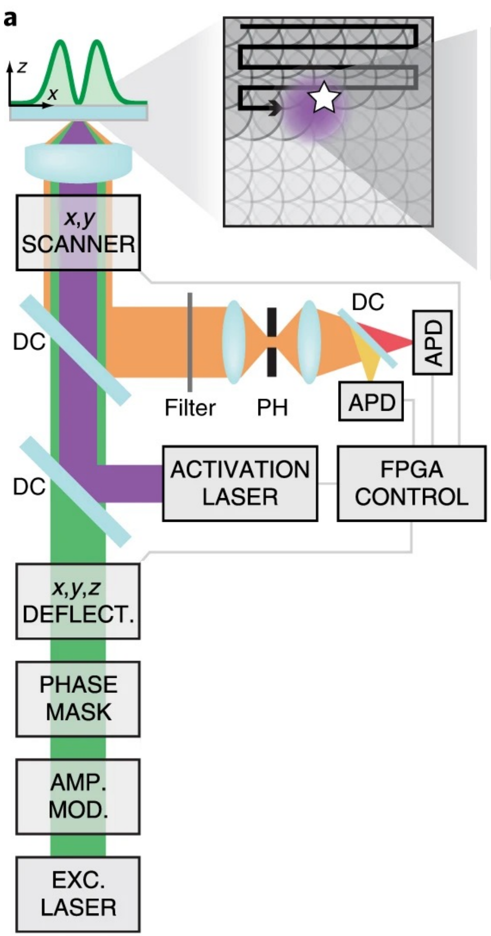


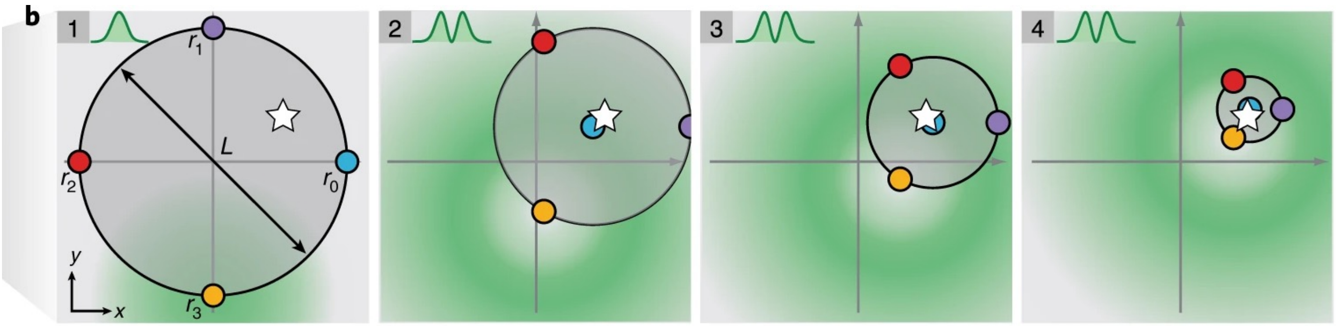


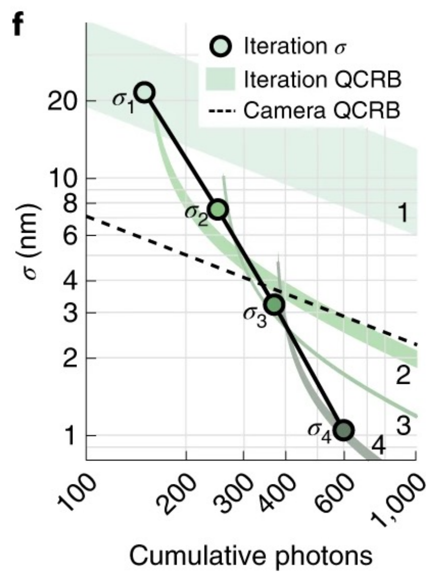
C.B. Muller, J. Enderlein, Phys. Rev. Lett. 104, 198101 (2010)

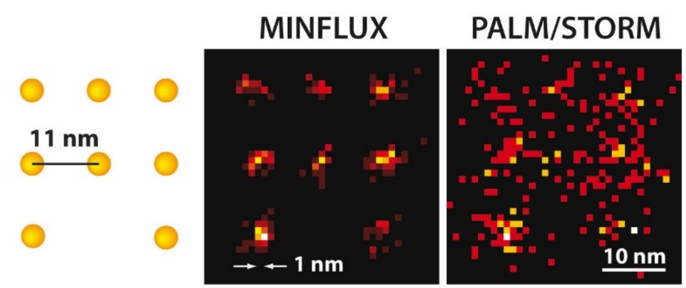
MINFLUX

A variant of localization microscopy which can use photons “more efficiently” (saturate the qCRb, more next hour…) by localizing the emitting molecule to a dark spot









There is a cost – speed…

K.C Gwosh et al., Nature Methods 17, 217 (2020)

Quantum resources

In 2003 Dowling and milburn coined a distinction between the first and second quantum revolutions

10.1098/rsta.2003.1227

THE ROYAL SOCIETY

Quantum technology: the second quantum revolution

By Jonathan P. Dowling[1] and Gerard J. Milburn[2]

[1] *Quantum Computing Technologies Group, Section 367, Jet Propulsion Laboratory, Pasadena, CA 91109, USA*

[2] *Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Wilberforce Road, Cambridge CB3 0WA, UK and Centre for Quantum Computer Technology, The University of Queensland, St Lucia, QLD 4072, Australia*

Published online 20 June 2003

We are currently in the midst of a *second quantum revolution*. The first quantum revolution gave us new rules that govern physical reality. The second quantum revolution will take these rules and use them to develop new technologies. In this review we discuss the principles upon which quantum technology is based and the tools required to develop it. We discuss a number of examples of research programs that could deliver quantum technologies in coming decades including: quantum information technology, quantum electromechanical systems, coherent quantum electronics, quantum optics and coherent matter technology.

Quantum resources

The first quantum revolution revolved around wave-particle duality and the uncertainty principle

The second quantum revolution is centered on the use of entanglement as a resource, stemming from the violation of Bell inequalities

Applications in imaging have made use of both of these principles, although the division is somewhat artificial…

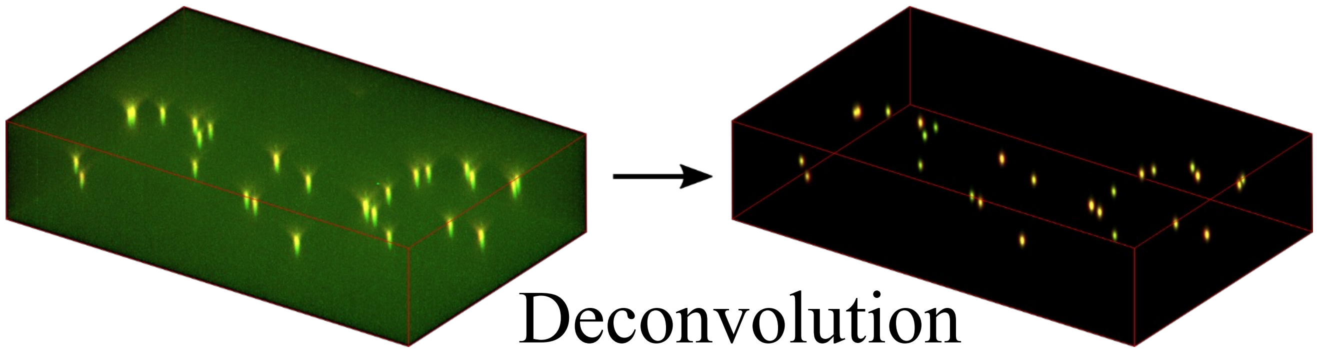
Questions before the break?

II. “Poor man’s” quantum imaging

- Computational imaging
- The Cramer-Rao bound
- The quantum Cramer-Rao bound
- Imaging by mode sorting
- Hanbury Brown and Twiss – the concept of the photon
- The meaning of photon statitistics
- Emitter counting
- Photon statistics as a resource in imaging

Computational Imaging

Historically, in microscopy an image was formed by physical means. Computational augmentation was often applied as post-processing

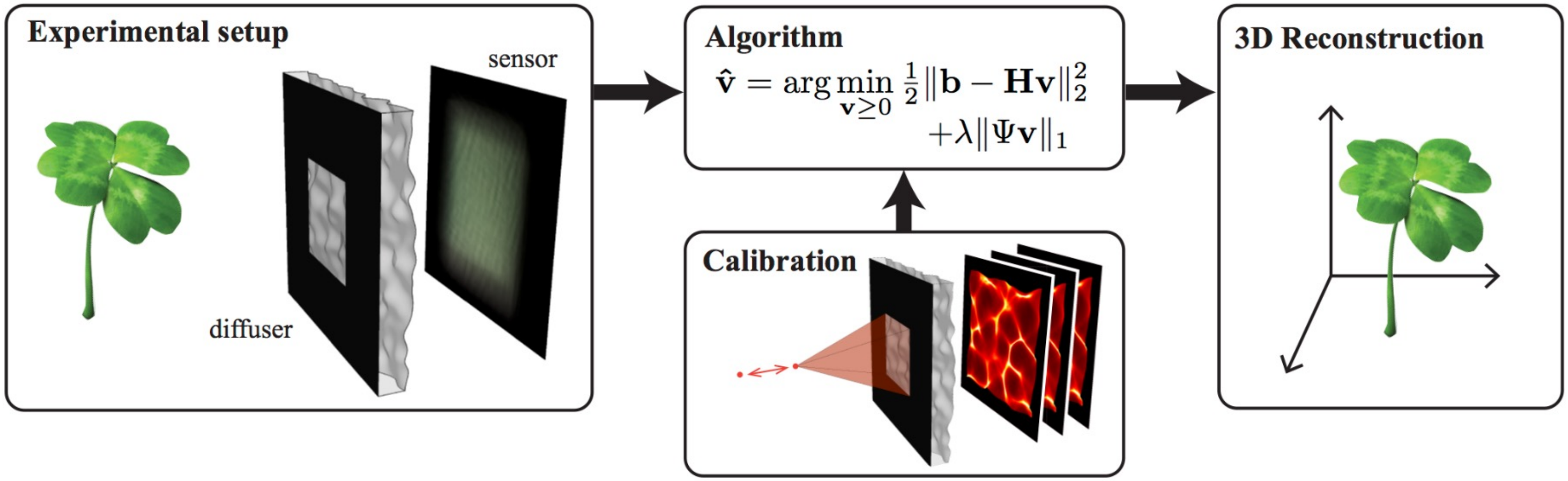


In computational imaging, the object is never imaged in full – it is retrieved computationally from other measurements (often not in the real space basis).

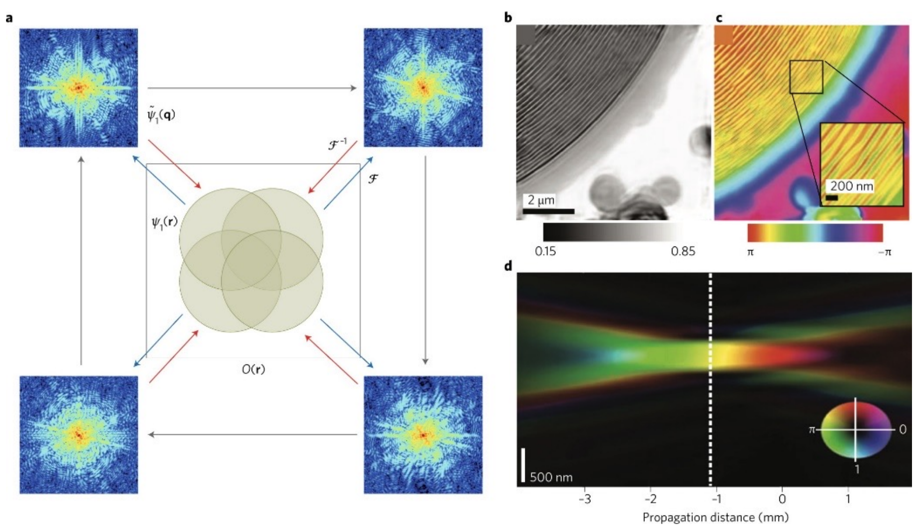
Examples: CT, Ptychography, Structured illumination

Examples

Diffusercam based lensless imaging



X-ray Ptychography



The Cramer-Rao bound

The Cramér–Rao bound (CRB) relates to estimation of a deterministic (fixed, though unknown) parameter:

The precision of any unbiased estimator is at most the Fisher information.

For n independent observations with unknown mean θ and known variance σ^2, this boils down to:

$$\mathrm{Var}(\theta) \geq \frac{\sigma^2}{n}$$

Which is the familiar Gaussian statistics result

Wikipedia: Cramer-Rao bound

The quantum Cramer-Rao bound

The quantum Cramér–Rao bound is the quantum analogue of the classical Cramér–Rao bound. It bounds the achievable precision in parameter estimation with a quantum system.

The quantum Fisher information is an upper bound on the Fisher information over all possible observables.

We can loosely translate that as “Let us look for the measurement scheme that maximizes the Fisher information”

Wikipedia: quantum Cramer-Rao bound

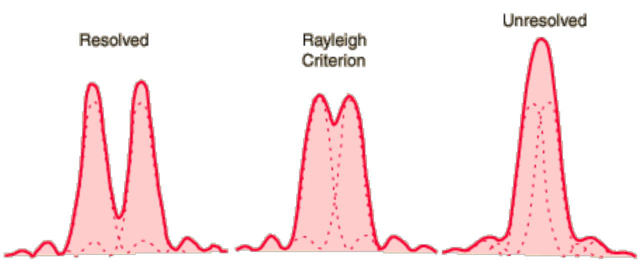
Resolving two incoherent emitters

Selected for a Viewpoint in *Physics*
PHYSICAL REVIEW X **6,** 031033 (2016)

Quantum Theory of Superresolution for Two Incoherent Optical Point Sources

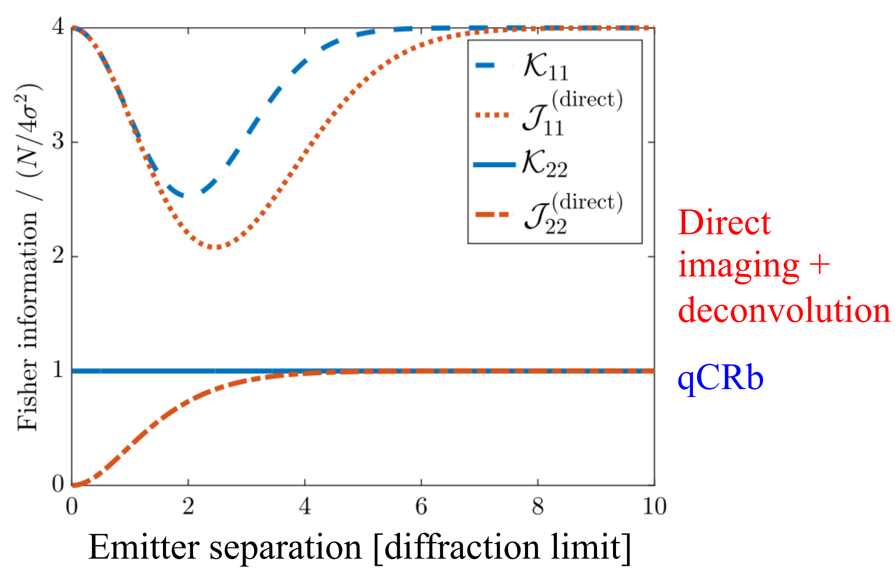
Mankei Tsang,[1,2,*] Ranjith Nair,[1] and Xiao-Ming Lu[1]
[1]*Department of Electrical and Computer Engineering, National University of Singapore, 4 Engineering Drive 3, Singapore 117583*
[2]*Department of Physics, National University of Singapore, 2 Science Drive 3, Singapore 117551*
(Received 8 November 2015; revised manuscript received 4 January 2016; published 29 August 2016)

The problem:



Two emitters which are not "resolved" by the Rayleigh criterion can still be resolved following deconvolution, but… is this the best way to go?

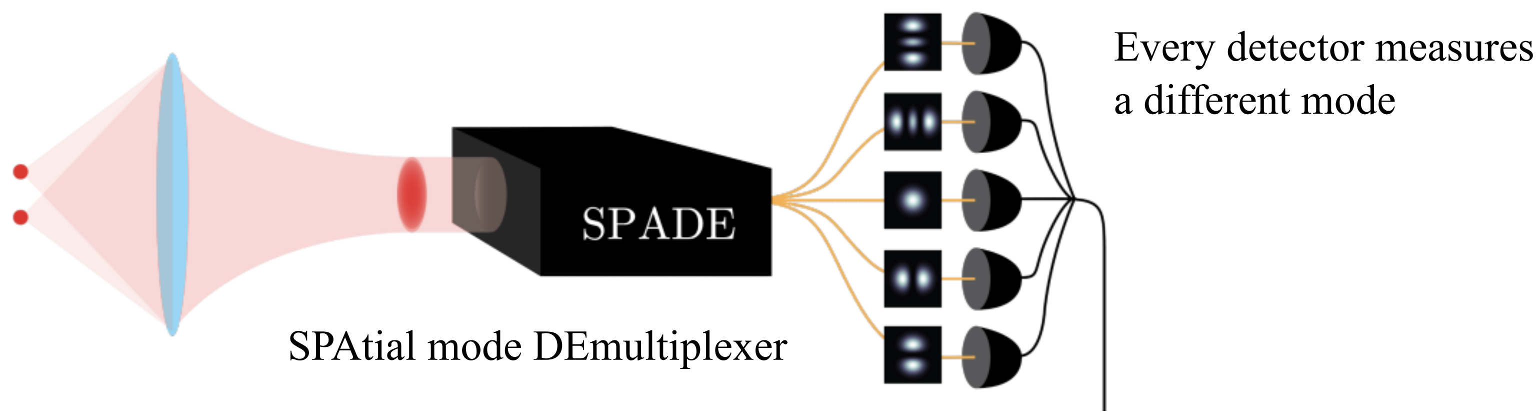
Direct imaging, though standard, is but one of the infinite measurement methods permitted by quantum mechanics.



SPADE

The qCRb calculation shows that there exists a good way to measure the separation, but does not point at which…

What if instead of measuring in the real space basis you measure in a modal basis?

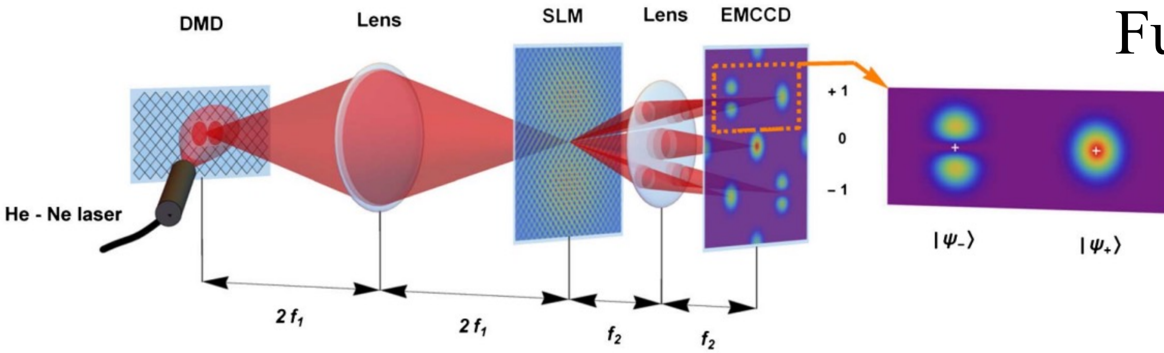


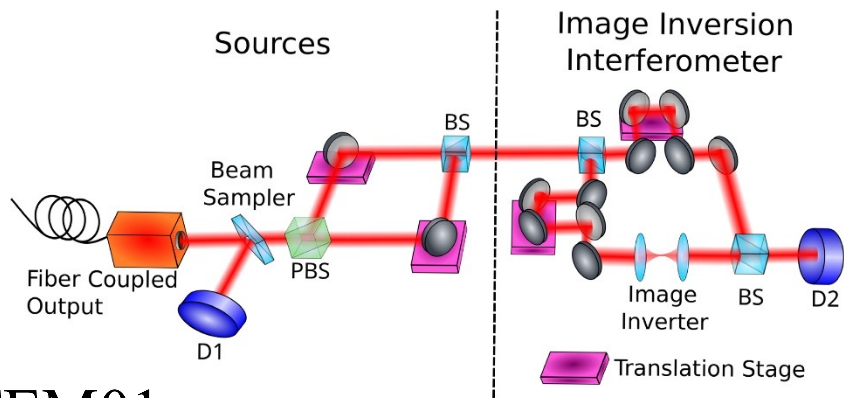
With HG modes this can saturate the qCRb (for this particular problem) and is hence optimal

Rouviere et al., Optica 11, 166 (2023)

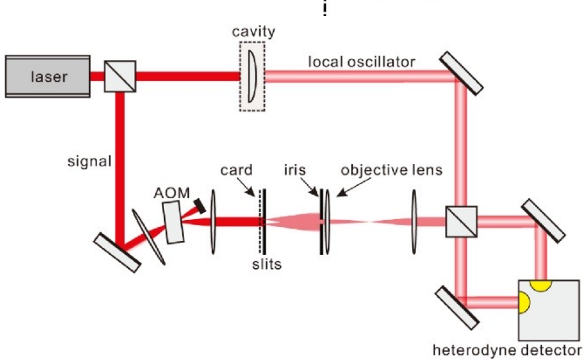
Early SPADE implementations

Full mode sorter

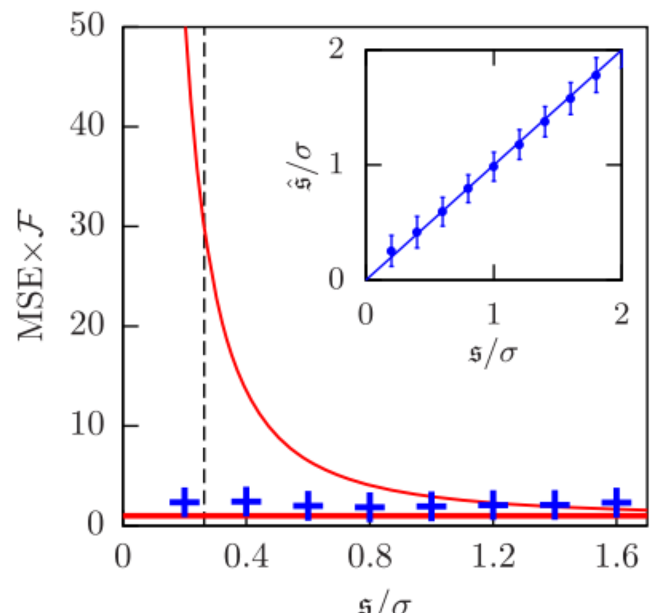




Just TEM01



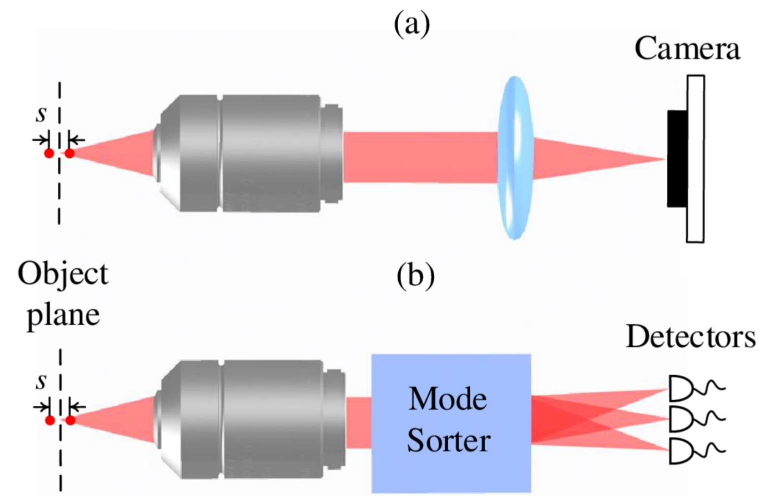
End result: it works…

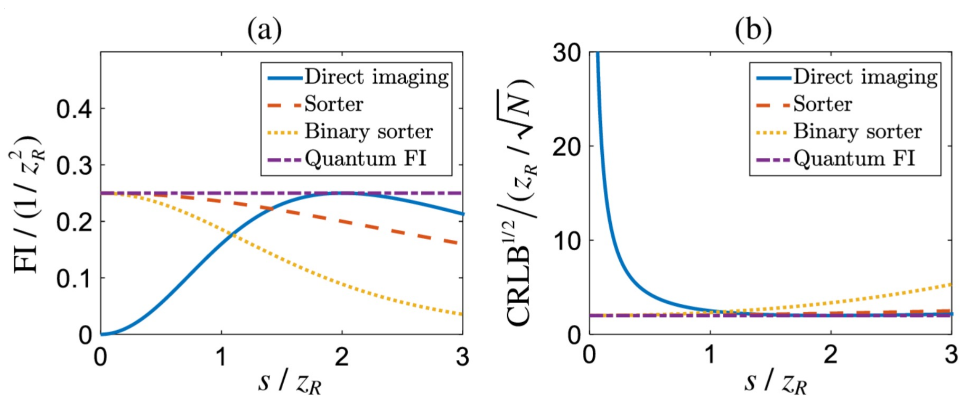


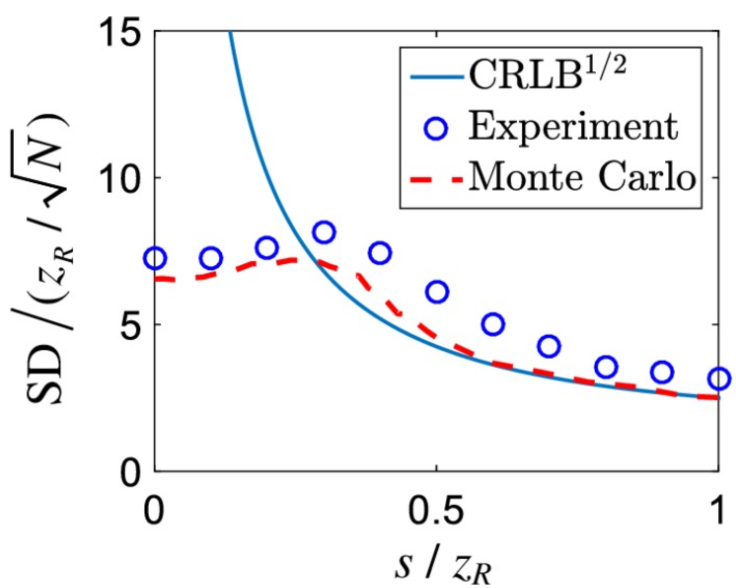
Paur et al., Optica 3, 1144 (2016) ; Tang et al., Opt. Express 24, 22004 (2016) ;
Yang et al., Optica 3, 1148 (2016).

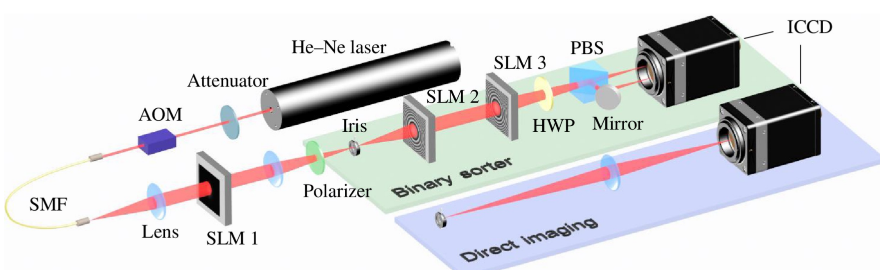
Out-of plane implementation

Can this be generalized to other cases?
Another simple case – axially separated emitters.







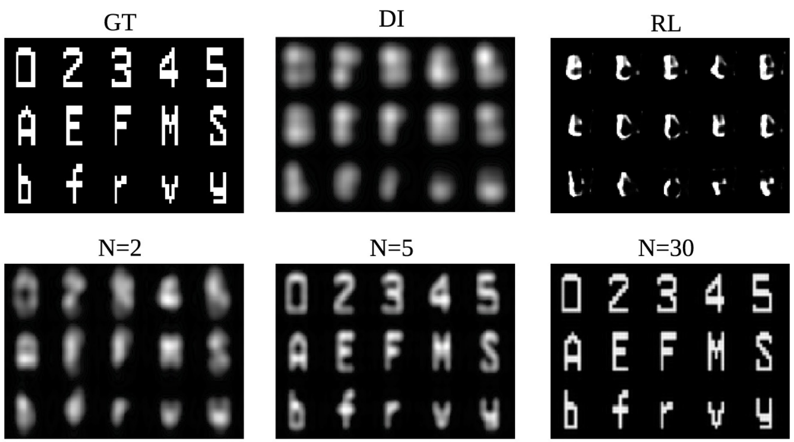


Zhou et al., Optica 6, 534 (2019)

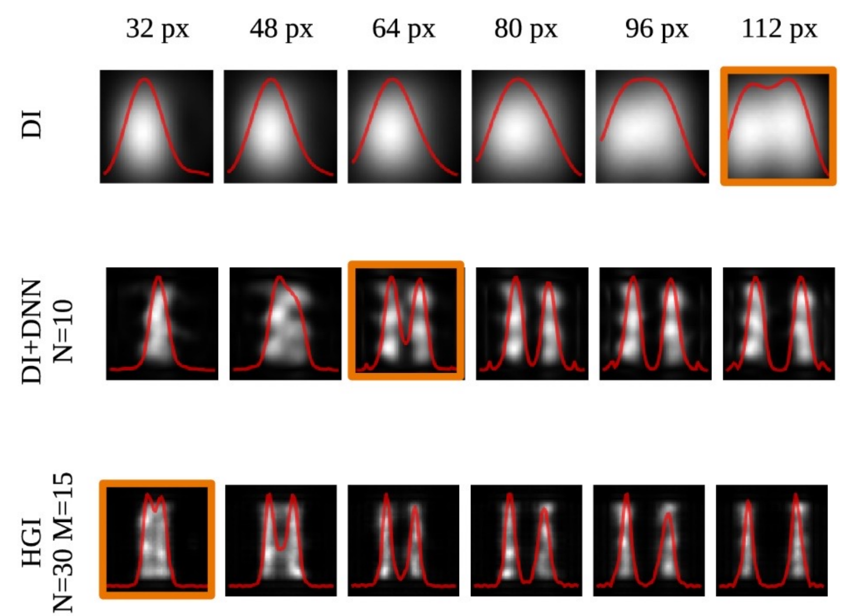
A general imaging method?

Well, that depends on the number of modes and how well you sort them…

Simulation: direct image, deconvolution and mode sorting with N^2 modes



Experiment: direct image, deconvolution (via neural network) and mode sorting with 15 modes

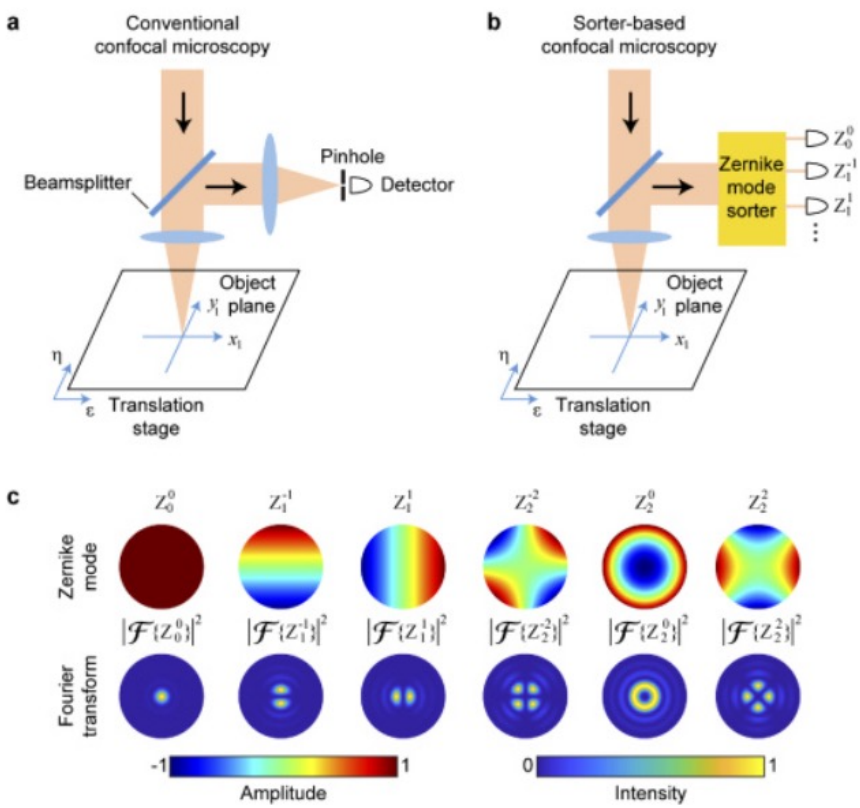


Although samples are 2D and somewhat artificial, there is promise here

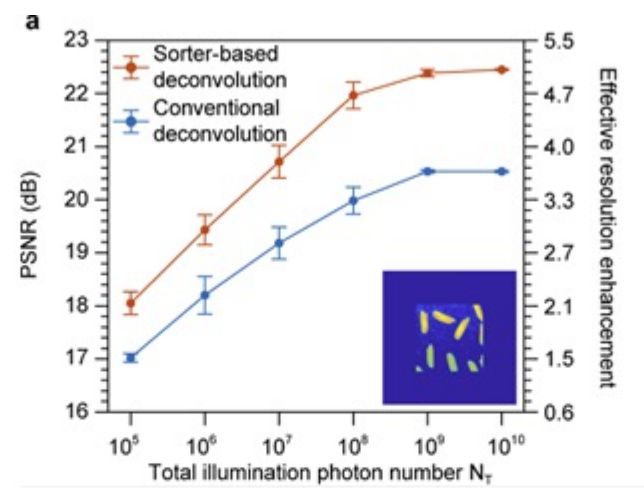
Frank et al., Optica 10, 1147 (2023)

A general imaging method?

There is perhaps a better chance of this to be useful in a confocal setup due to limited image complexity



Here too, sorter based deconvolution outperforms "conventional" deconvolution



Bearne et al., Optics Express 29, 11784 (2021)

Is any of this really “quantum”?

Short answer: No

Long answer: If classical measurements saturate the qCRb you do not need to resort to quantum measurements…

Longer answer: Classical measurements were only proven to saturate the qCRb in very simple scenarios. In others, there is likely some quantum advantage!

So lets go one more quantum step further

Photon correlations: The Hanbury Brown and Twiss stellar interferometer

HB&T proposed a new kind of telescope to measure the angle subtended by an object in the sky – which does not require a large mirror to resolve the size

1046 NATURE November 10, 1956 VOL. 178

A TEST OF A NEW TYPE OF STELLAR INTERFEROMETER ON SIRIUS

By R. HANBURY BROWN
Jodrell Bank Experimental Station, University of Manchester
AND
DR. R. Q. TWISS
Services Electronics Research Laboratory, Baldock

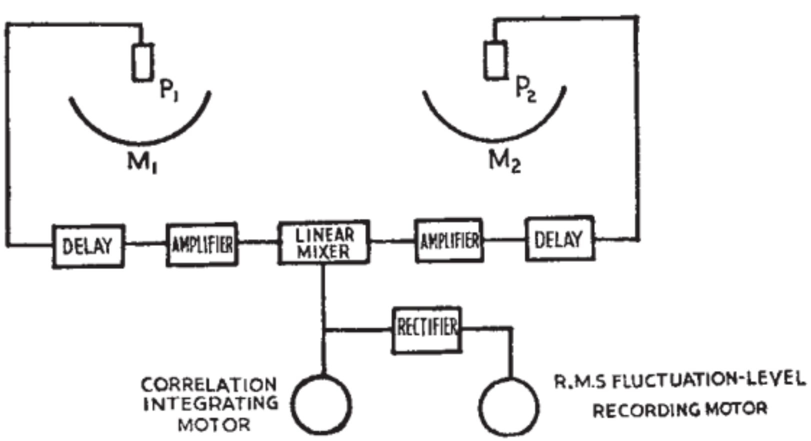


Fig. 1. Simplified diagram of the apparatus

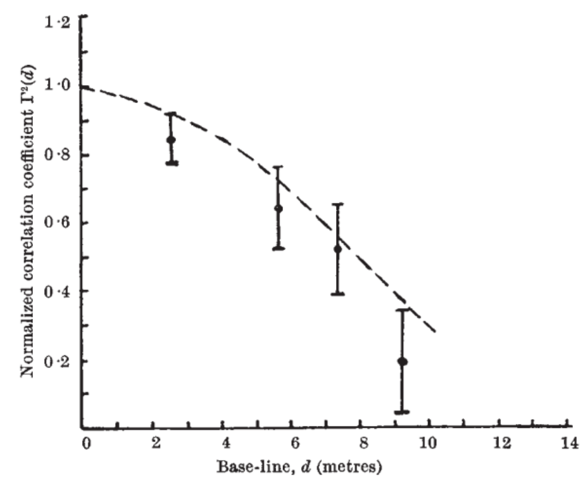
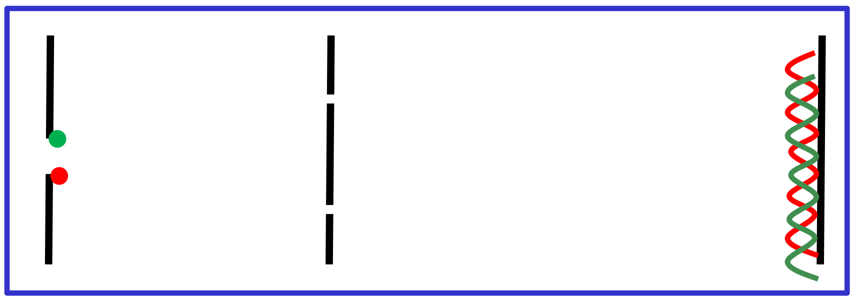


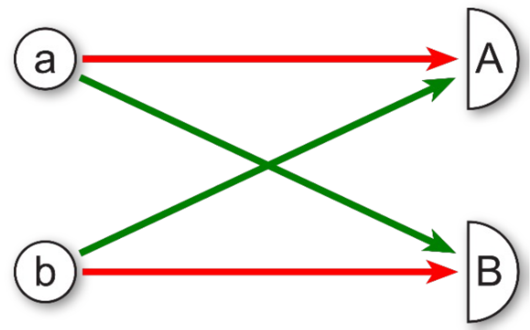
Fig. 2. Comparison between the values of the normalized correlation coefficient $\Gamma^2(d)$ observed from Sirius and the theoretical values for a star of angular diameter 0·0063″. The errors shown are the probable errors of the observations

The Hanbury Brown and Twiss stellar interferometer

- How can light from a star, which is incoherent, generate interference?
- Is HB&T interference a classical or quantum effect?



Classical explanation (due to HB & T)

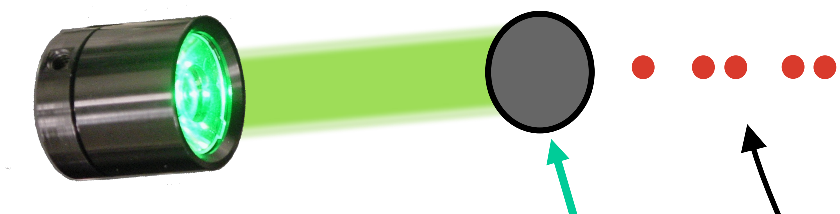


Quantum explanation (due to Fano, Glauber, Mandel)

Although the result was not easily accepted by the scientific community, it set the basis for much of today's quantum optics

Quantum emitters

Most fluorescent markers used in biology are quantum emitters. As such, they emit photons one at a time.



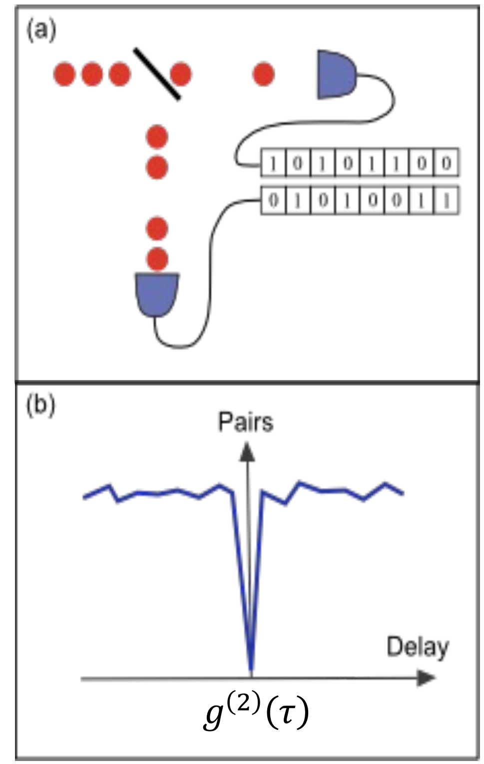
Classical light source

Quantum emitter

- Dye molecules
- Quantum dots
- Defect emission
- Atoms
- Ions

Single photon at a time

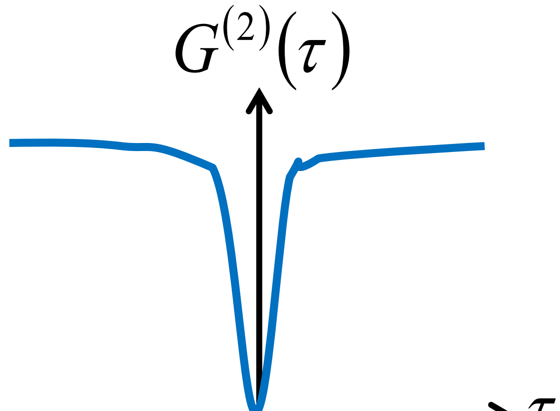
HB&T interferometer



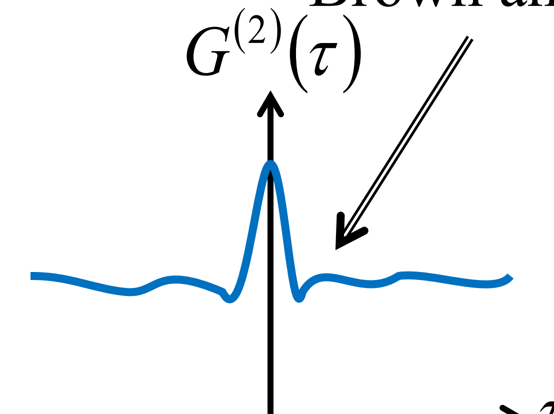
Antibunching

What do photon statistics mean?

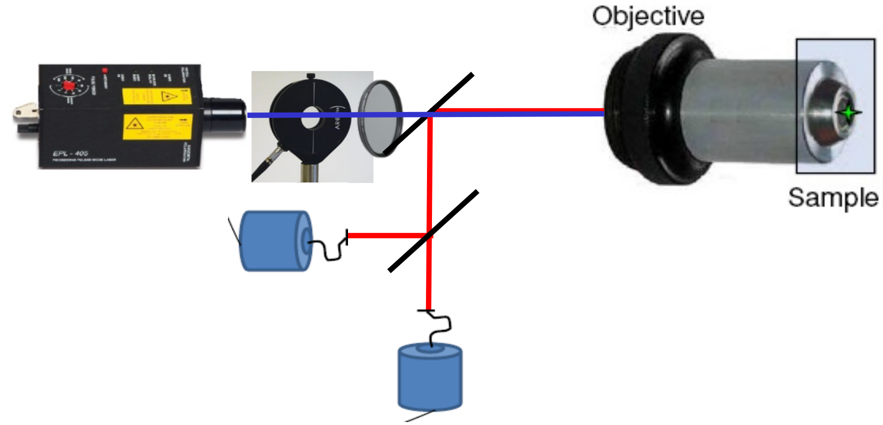
Intensity Correlation $G^{(2)}(\tau) = \langle I(t) I(t+\tau) \rangle$



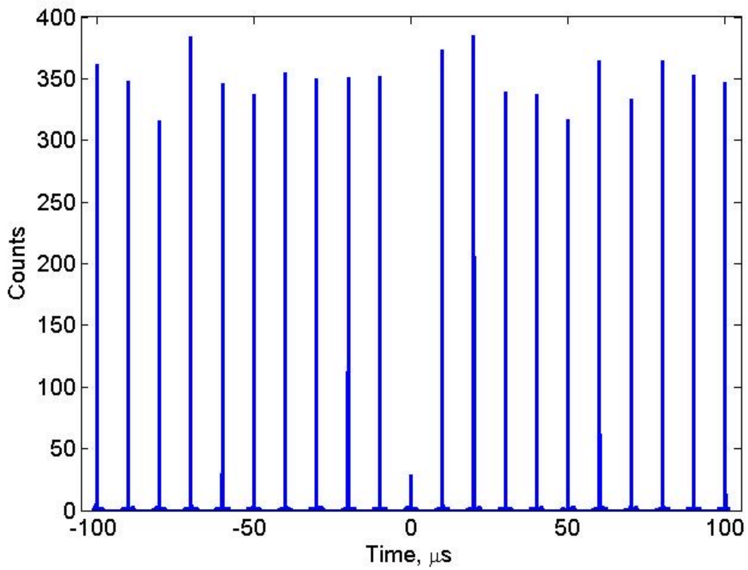
Used by Hanbury Brown and Twiss



Antibunching



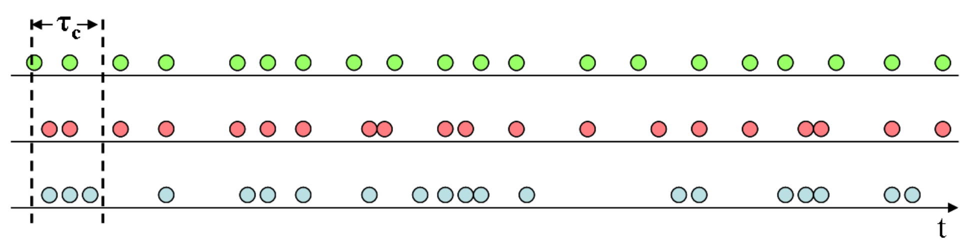
Autocorrelation of fluorescence from a quantum dot



10 μs interval between pulses

Central peak < ½ indicates a single emitter

The photon stream from a quantum emitter is more uniformly distributed in time

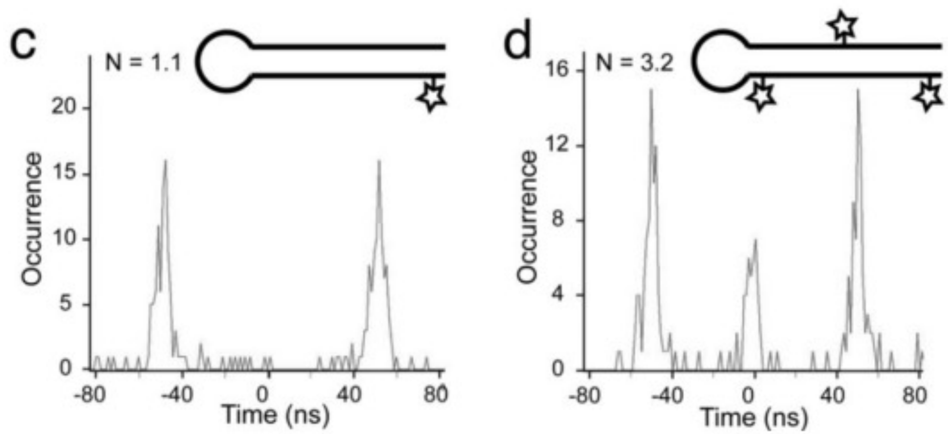


Photon statistics and emitter counting

In a system with N identical emitters, antibunching is quenched. The probability to observe photon pairs increases with the number of pairs of emitters ($\sim N^2$), while the 'missing pairs' increase as N, resulting in:

$$g^{(2)}(t) = 1 - \frac{1}{N} e^{-t/\tau}$$

This can be used as an efficient way to count (identical and uncoupled) emitters.



S. Fore et al., IEEE J. Selected Topics in Quantum Electronics 13, 996 (2007).
K. Grusmayer, D-P. Herten, Advanced Photon Counting Springer Series on Fluorescence 159 (2014)

Photon statistics and spatial resolution

Classical emitter:

Poissonian photon number distribution, variance $V = <N>$

Fluorescence:

M excitation pulses, probability to detect a photon P

Mean: $<N> = M\,P$

Variance: $V = <N^2> - <N>^2 = M\,P\,(1\text{-}P) = (1\text{-}P)\,<N>$

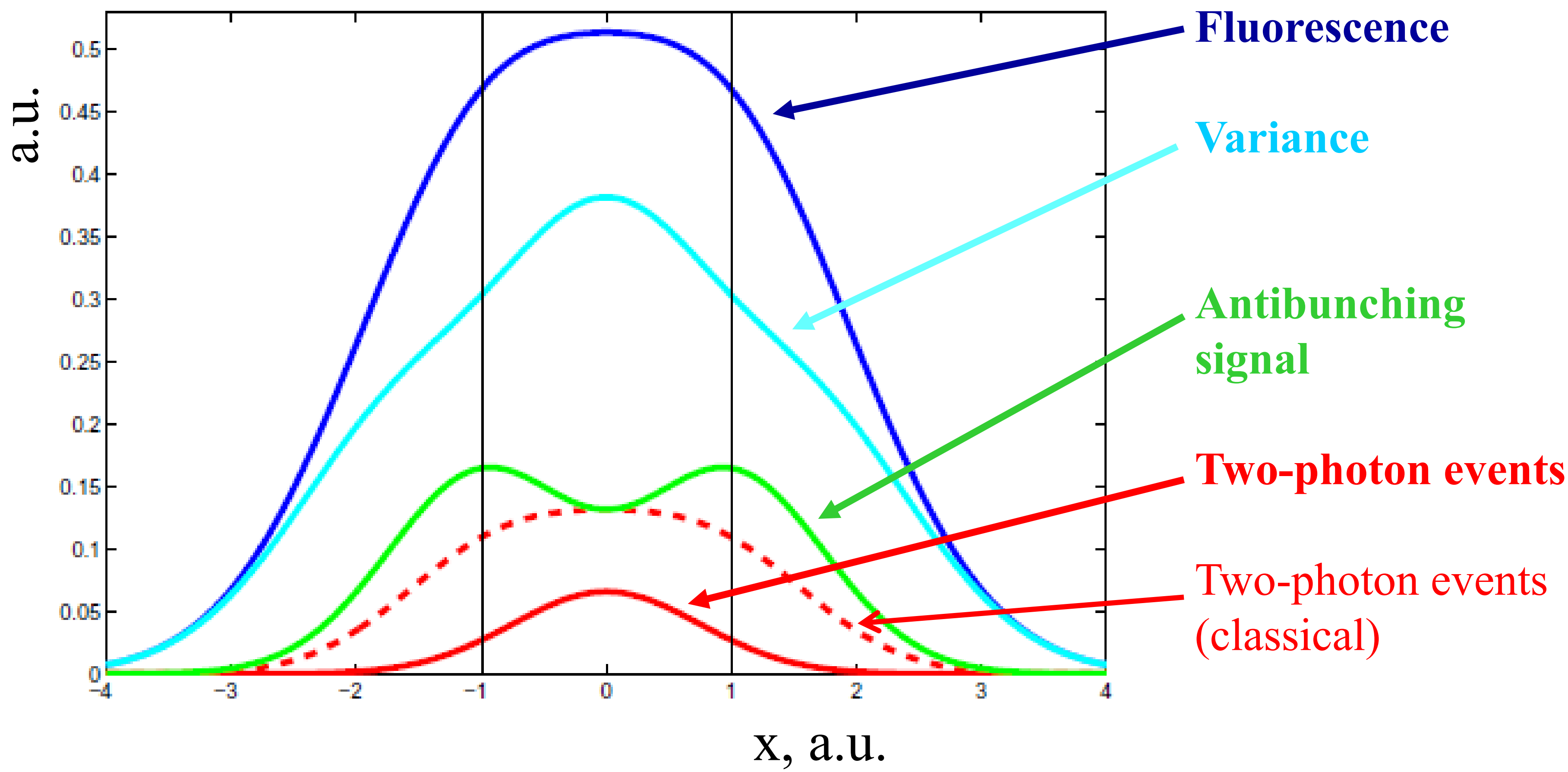
Reduced quantum fluctuations

The antibunching signal: $A = V_{\mathbf{CLASSICAL}} - V \propto P^2$

Narrower PSF!

O. Schwartz, DO, Phys. Rev. A 85, 033812 (2012).

Two fluorophores example

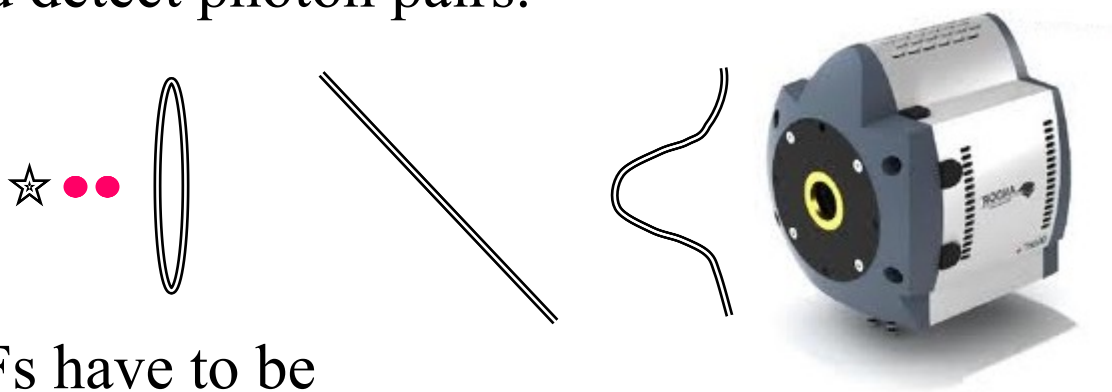


O. Schwartz, DO, Phys. Rev. A 85, 033812 (2012).

An alternative explanation

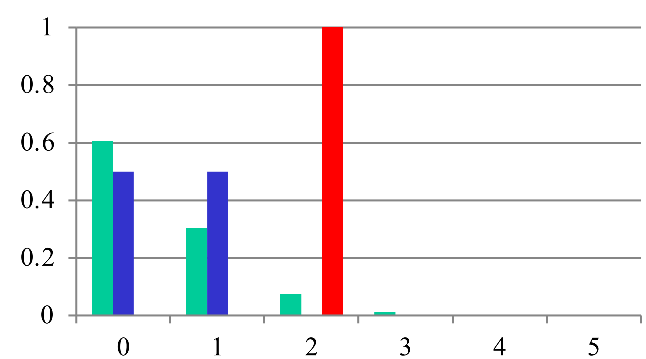
Hell's gedanken experiment

Suppose we have an emitter which always emits photons in pairs …
and detect photon pairs.



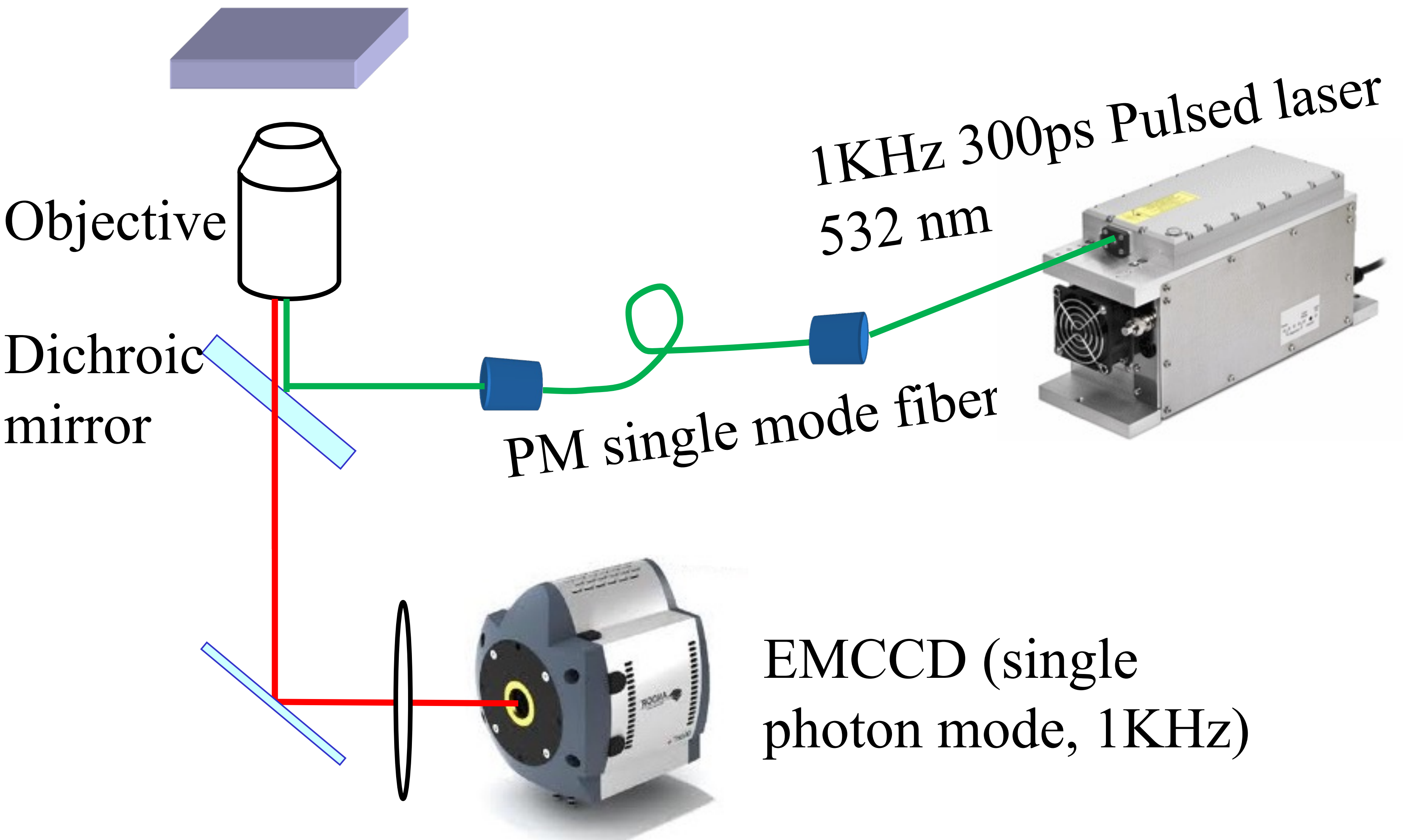
PSFs have to be multiplied by one another!

Poisson
2-photon emitter
Antibunched



S.W. Hell, J. Soukka, P.E. Hanninen, Bioimaging 3, 64 (1995).

Experimental implementation with a CCD



O. Schwartz, DO, et al., Nano Lett. 13, 5832 (2013).

Experimental implementation with EMCCD

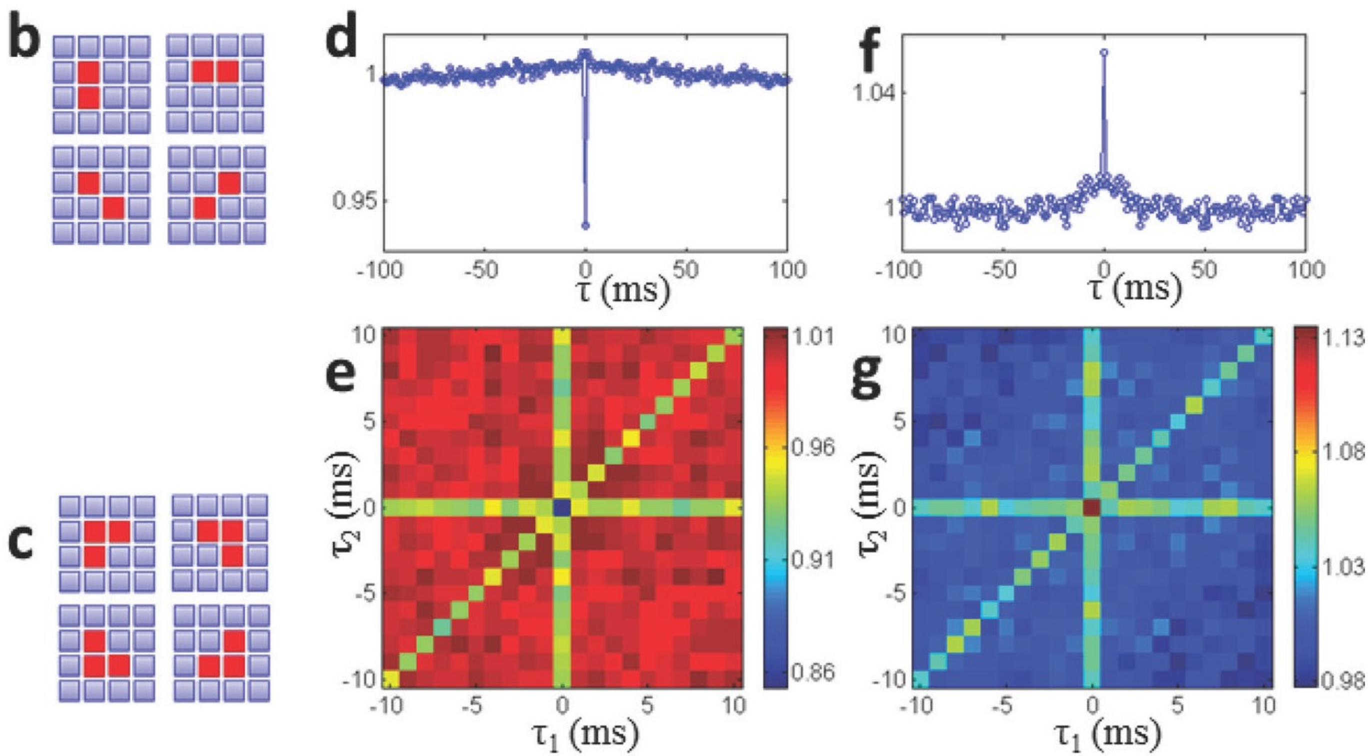
All data has to be analyzed on a single frame, so unlike SOFI, we use spatial correlations, and correct for camera artifacts

Antibunched emission

Classical emission

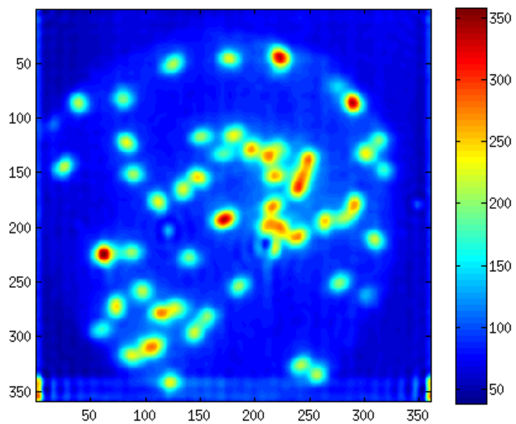
Second order correlations

Third order correlations

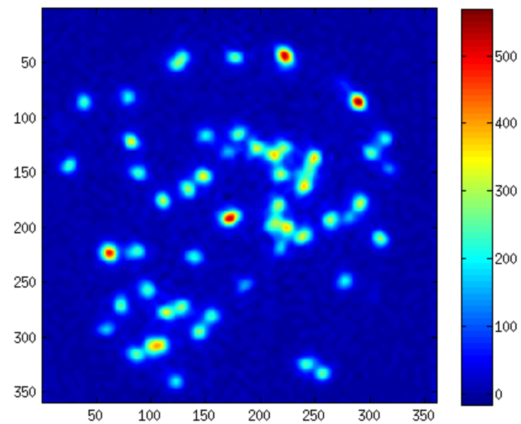


O. Schwartz, DO, et al., Nano Lett. 13, 5832 (2013).

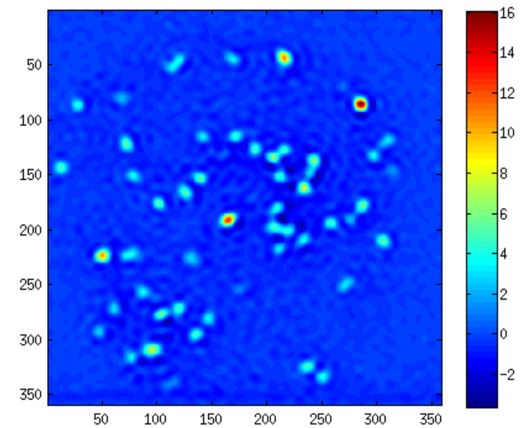
Experimental results



Integrated intensity
($3*10^6$ pulses)



Antibunching
signal



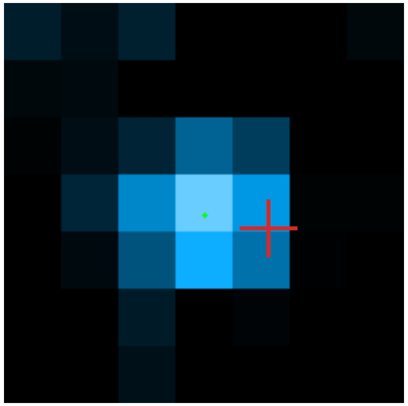
3rd order
antibunching
signal

It works, but is, however, quite impractical –
Imaging is limited by the frame rate of the camera …
Resolution increase is < x2, but orders of magnitude slower

O. Schwartz, DO, et al., Nano Lett. 13, 5832 (2013).

Back to localization based imaging

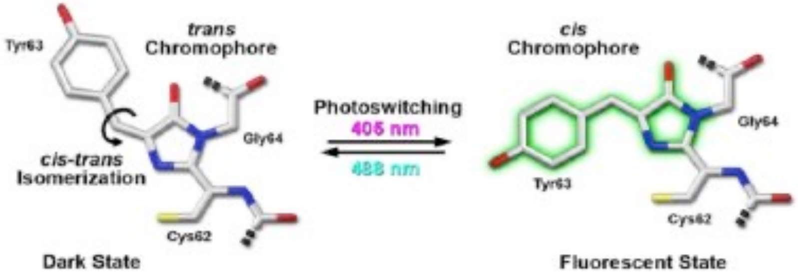
An isolated emitter can be localized well beyond the diffraction limit



$\sigma \approx \sigma_{PSF} / N^{1/2}$

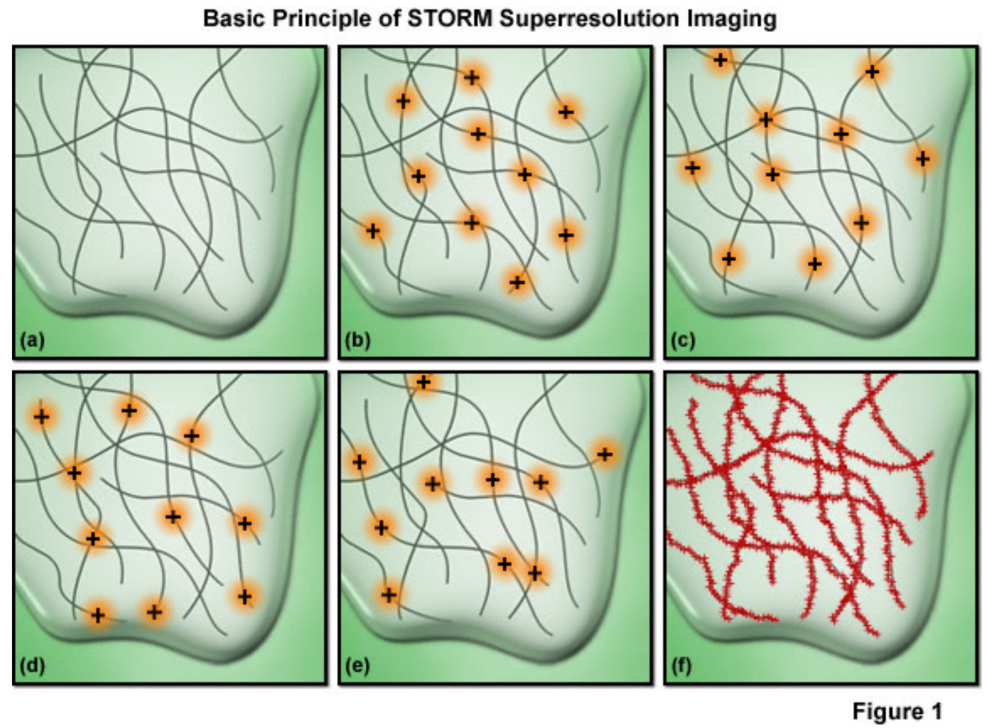
Thompson et al., *Biophys. J.*, 2002

Making a dense collection of fluorophores sparse?

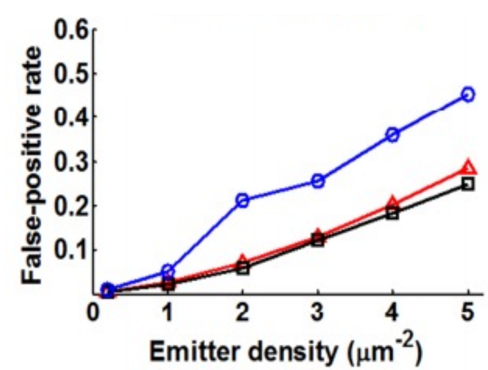


Reminder: photoactivation based imaging

- Photoactivate only a dilute sub-ensemble of emitters
- Localize these
- Deactivate all emitters



But we need <1 emitter per diffraction limited volume.
Denser labels lead to localization errors (overcome with "smart" algorithms)



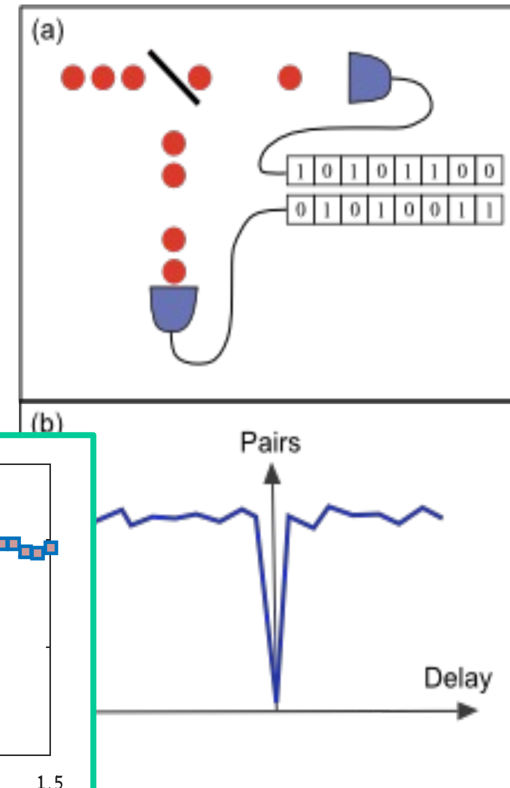
Wang et al, Opt. Express, 20, 16039 (2012)

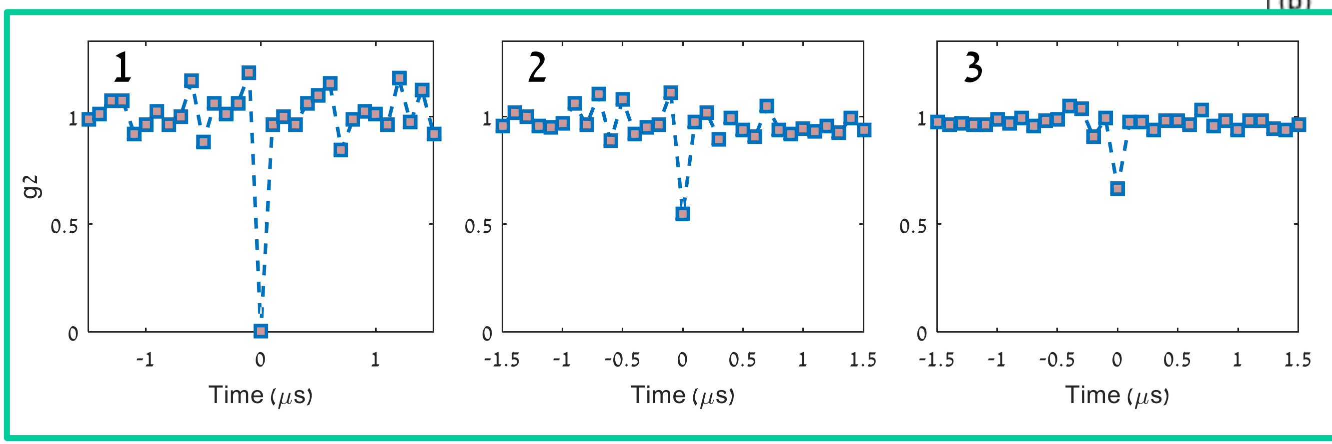
More information for localization

Most readily used labels are quantum emitters

Measurement of photon statistics can reveal the number of emitters

$$g^{(2)}(\tau = 0) = 1 - \frac{1}{\mathrm{n}}$$





Simulation. 50ms. Emission rate: 250 KHz per emitter

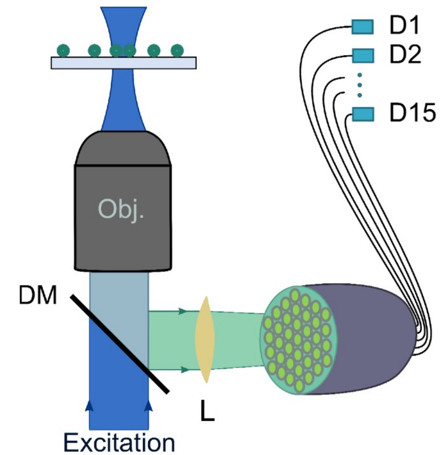
Need fast, multichannel detector for this!

Weston et al., Anal. Chem. 74, 5342 (2002)

A fiber bundle as a fast camera

An alternative detector

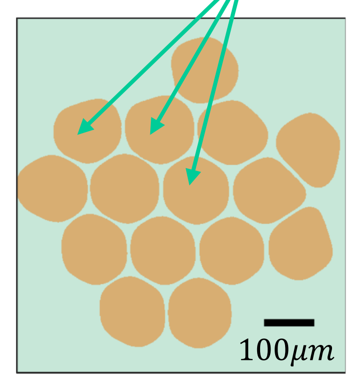
- Fiber bundle input in image plane
- Output of fibers fan-out into 15 APDs



Effective camera

- 15 pixels covering ~5 diffraction limited spots
- Nanosecond temporal resolution
- Single photon sensitivity

Single ‘pixels’

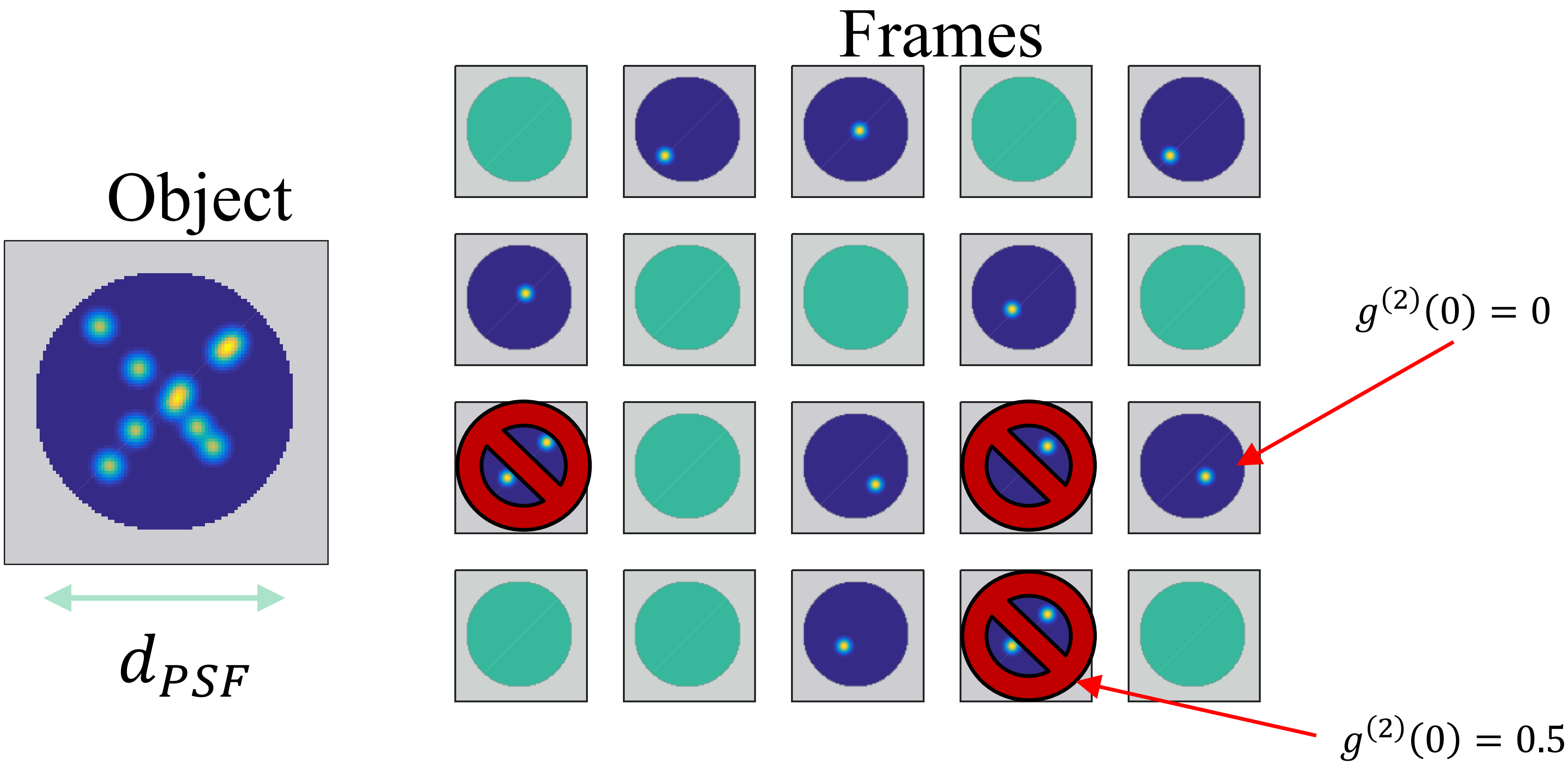


Simultaneous photon correlation measurements across the “image”

Potentially scalable

A simple example for application

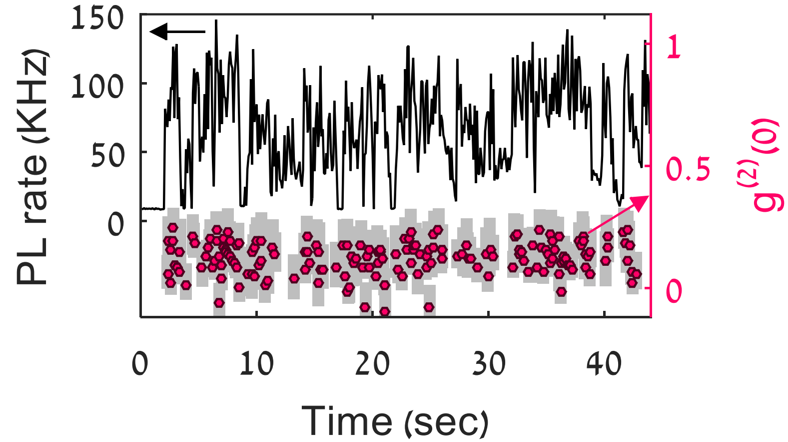
Use $g^{(2)}$ to post select image data containing only one emitter



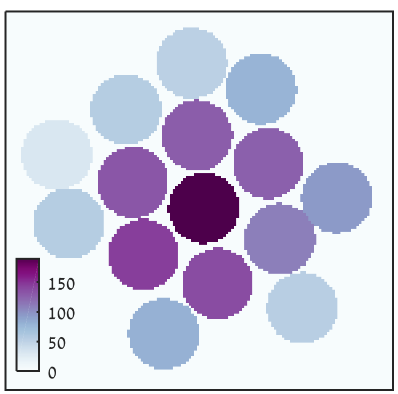
Use only frames with single emitters to localize with precision and no errors

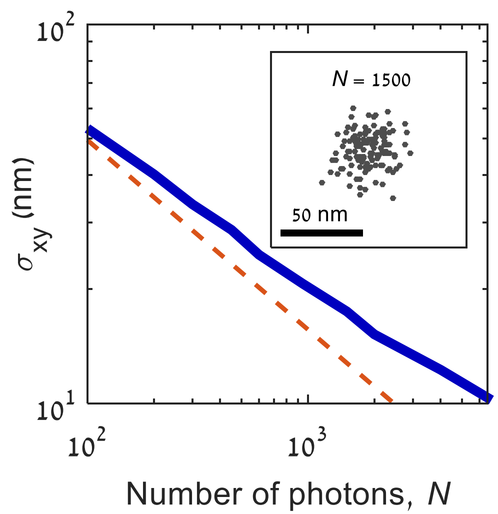
Single dot localization

Integrating over the bundle we monitor the blinking and $g^{(2)}$



Using spatial information to localize a single emitter





1500 photons

⇓

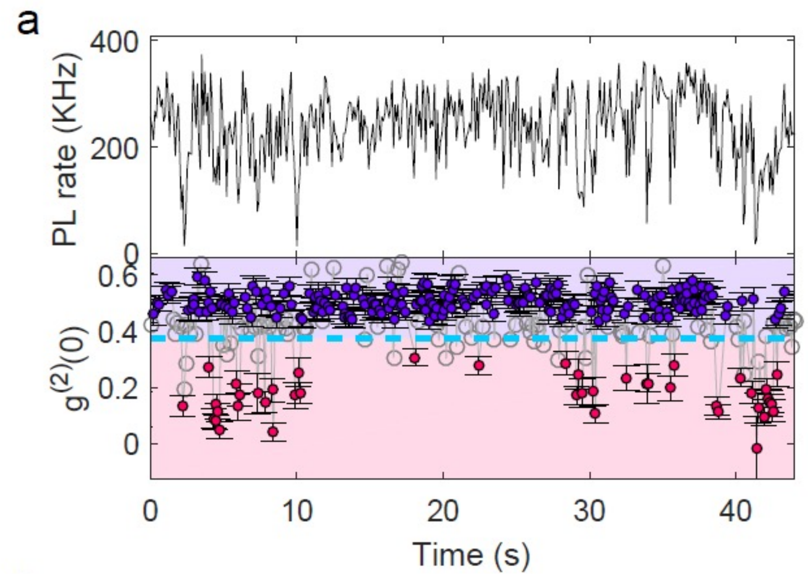
15nm resolution

(near shot noise)

Y. Israel, R. Tenne, DO, Y. Silberberg, Nature Communications 8, 14786 (2017)

Two particle discrimination

Post selecting single emitter ‘frames’



Resolve two QDs

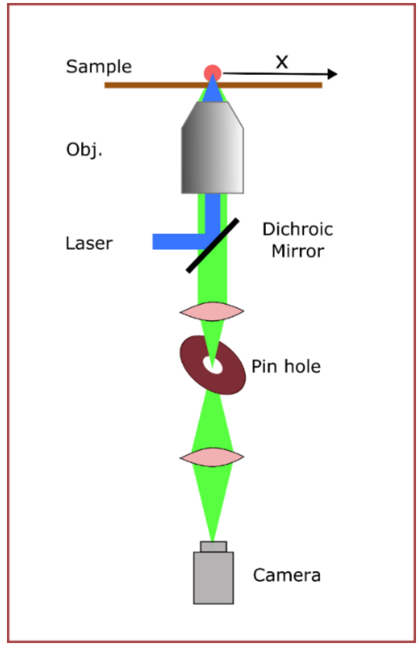
QDs separated by 100nm

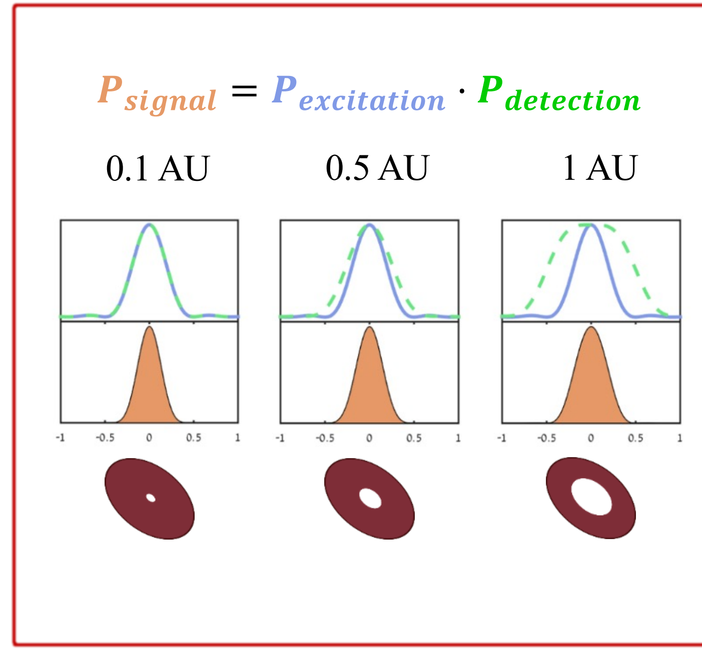
40 seconds track (color coded)

Y. Israel, R. Tenne, DO, Y. Silberberg, Nature Communications 8, 14786 (2017)

Improving confocal microscopy

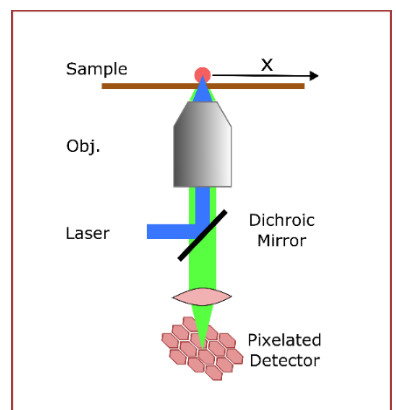
Confocal microscopy usually provides improvement in axial resolution but little improvement in transverse resolution





A pixelated confocal detector

Intuitively, using a pixelated detector can recover improved transverse resolution with no penalty on signal intensity!



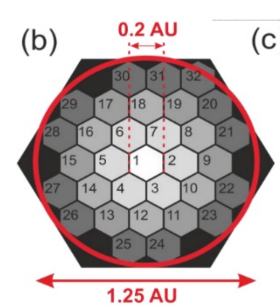


Image scanning microscopy ("Airyscan")

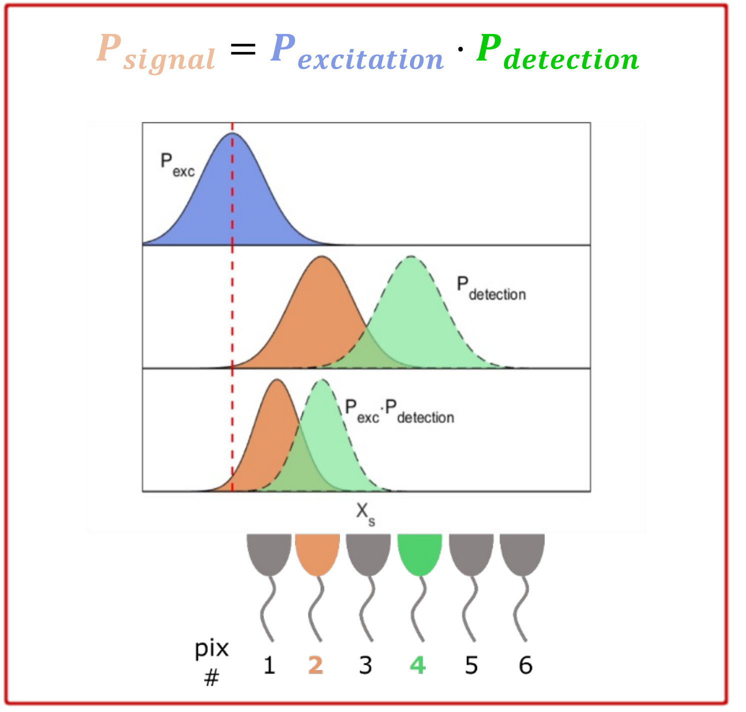
ISM relies on "pixel reassignment": The position of the emitter is expected to be half-way between the center of the excitation spot and the detection spot.

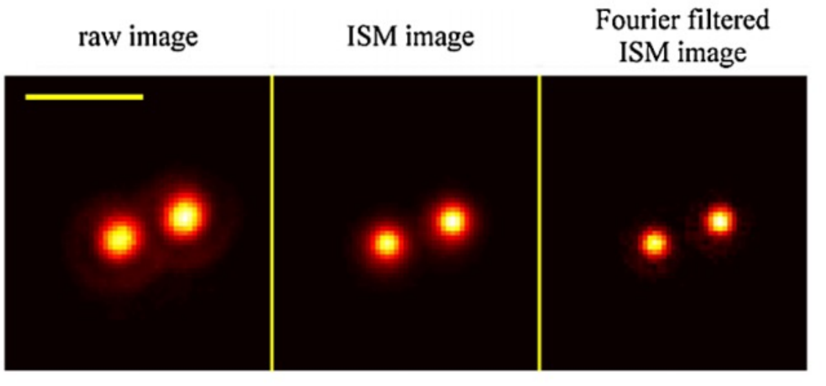
↓

PSFs multiplied by one another

↓

$\sqrt{2}$ increase in resolution, 2 with Fourier analysis

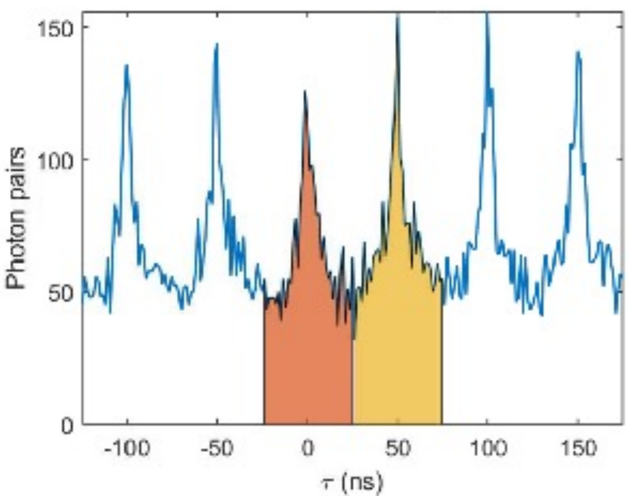




Sheppard, Optik 80, 53 (1988)
Muller and Enderlein, PRL 104, 198101 (2010)

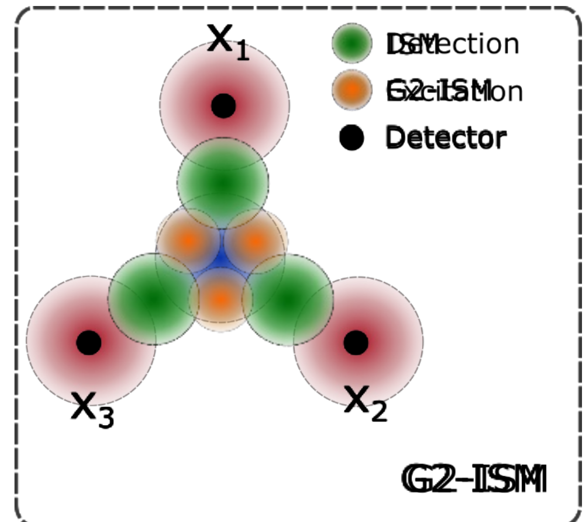
Photon correlations in ISM

Each emitter is a source of “missing pairs”, associated with two excitation and two detection events



$$P_{G2} = (P_{excitation})^2 \cdot P_{det}(x_1) \cdot P_{det}(x_2)$$

4X resolution enhancement



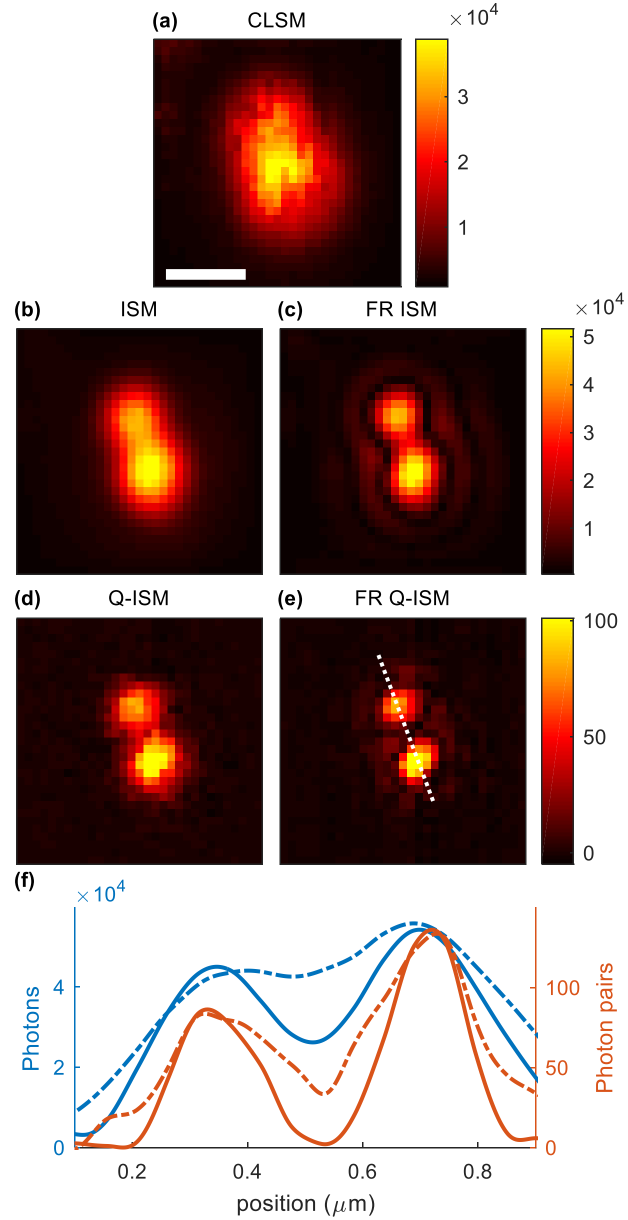
R. Tenne, DO et al., Nature Photonics, 13, 116 (2019)

Demonstration of quantum ISM

Two isolated quantum dots

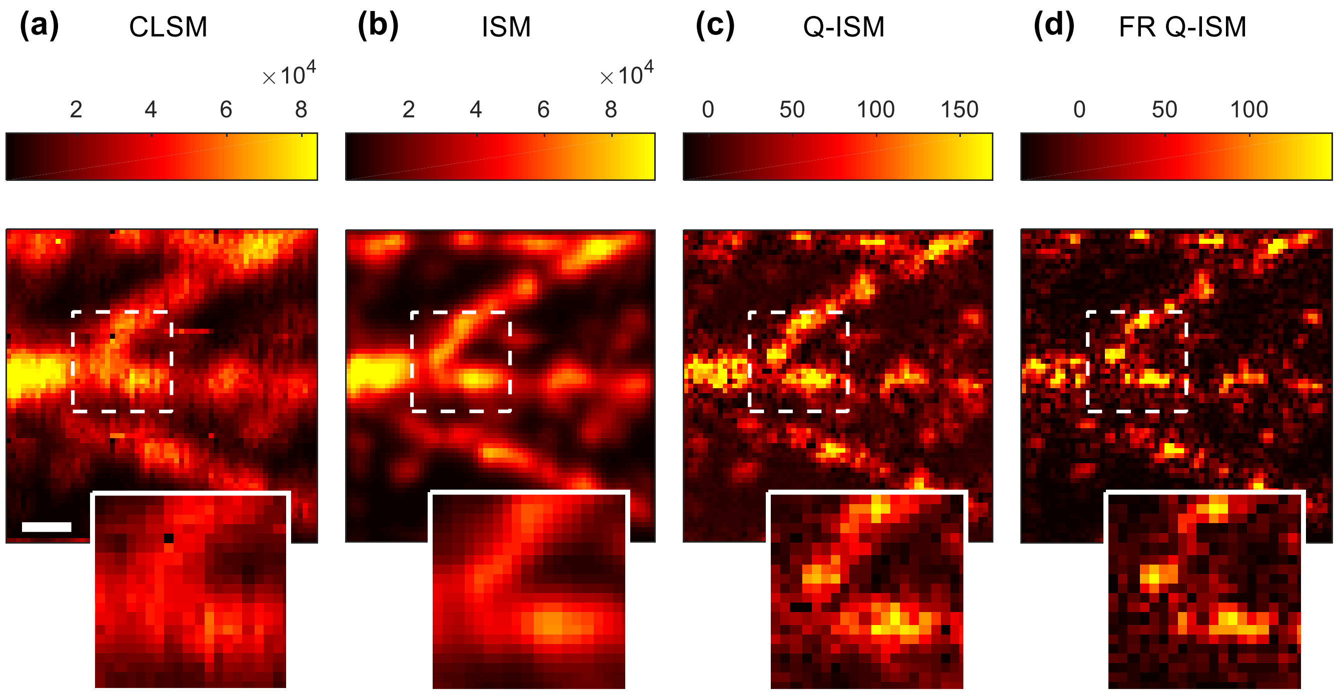
Maximal theoretical improvement is:
$\sqrt{2}$ for ISM,
2 for FR-ISM and Q-ISM
4 for FR-Q-ISM

In practice we get (Rayleigh criterion):
1.3
1.95, 1.75
2.35



R. Tenne, DO et al., Nature Photonics, 13, 116 (2019)

quantum ISM of a biological sample



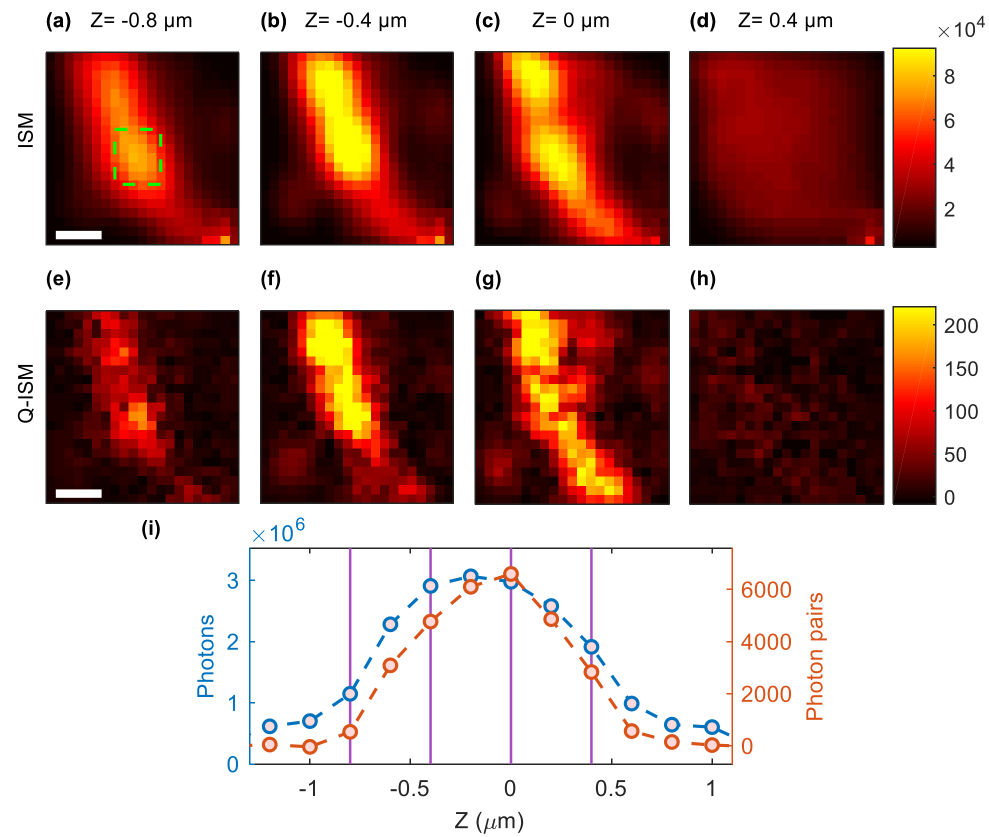
A 3 μm x 3 μm section of micro-tubules in a fixed 3T3 cell labeled with fluorescent quantum dots (QDot 625, Thermo Fisher).

R. Tenne, DO et al., Nature Photonics, 13, 116 (2019)

Axial resolution enhancement in Q-ISM

In ISM, the signal scales as z^{-2} (like a 2-photon process)

In Q-ISM the signal scales as z^{-6} (like a 4-photon process)



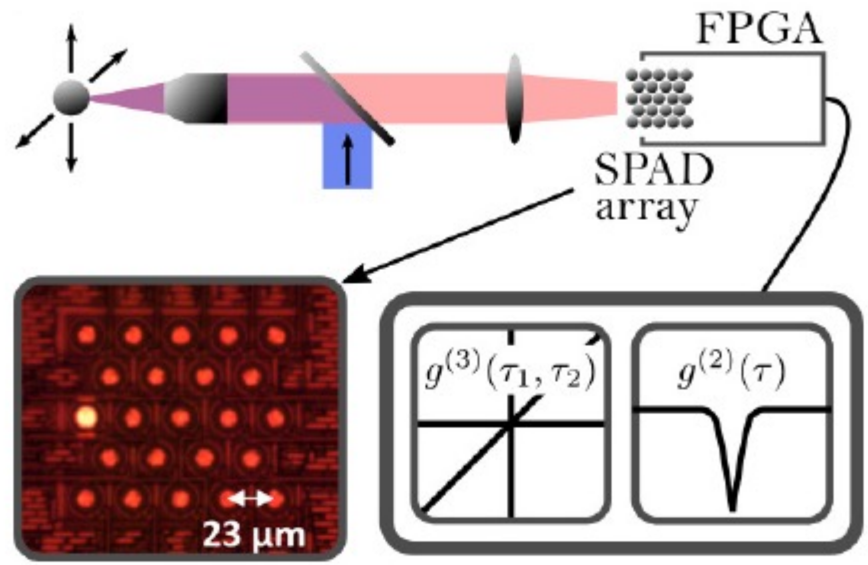
Q-ISM provides the best axial sectioning of any multiphoton technique currently in use

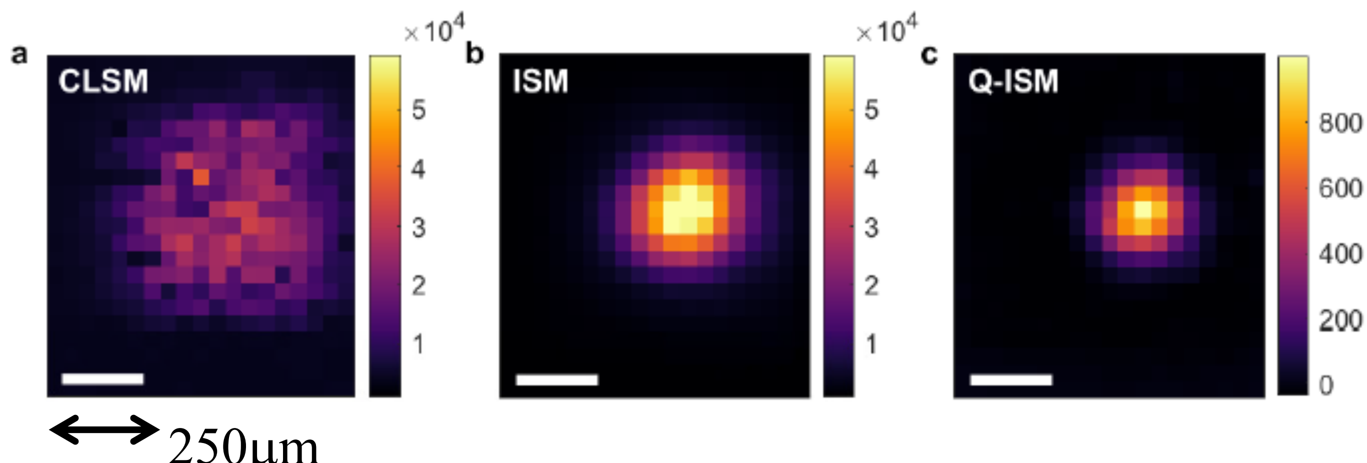
R. Tenne, DO et al., Nature Photonics, 13, 116 (2019)

Implementation with “practical” detectors

Replace the fiber bundle + 15 detectors (~100k$) with a CMOS SPAD array (<10k$)

Crosstalk is an issue but can be overcome since it is time-independent



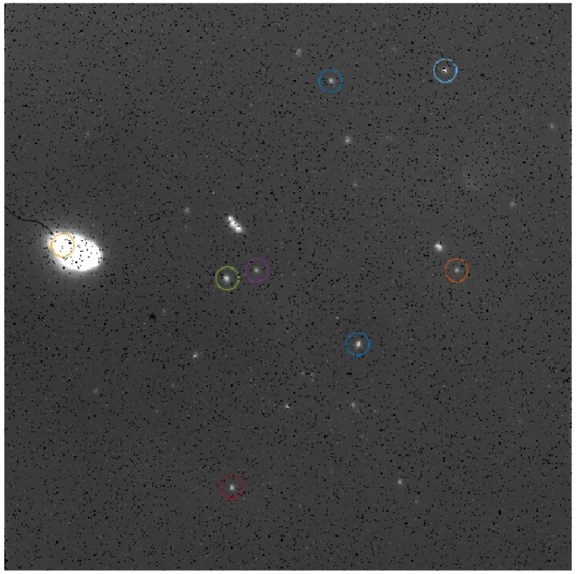


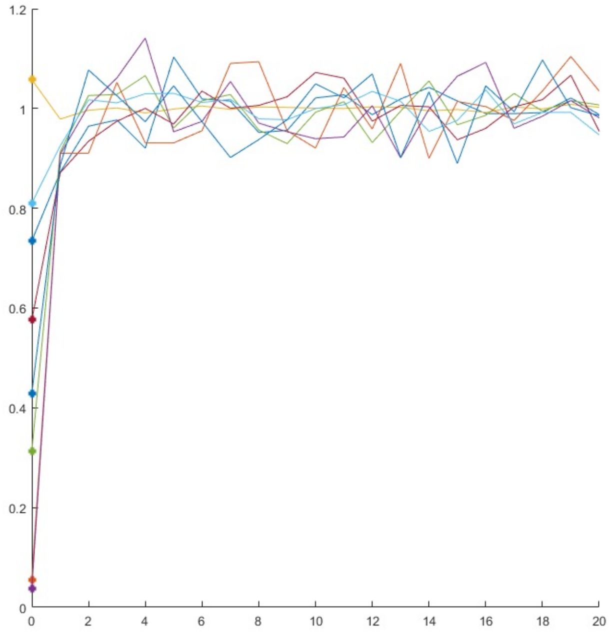
G. Lubin, DO et al., Optics Express 27, 32863 (2019)

Implementation with "practical" detectors

With large format imaging detectors we can detect photon statistics in a wide field of view.

¼ megapixel SPAD array





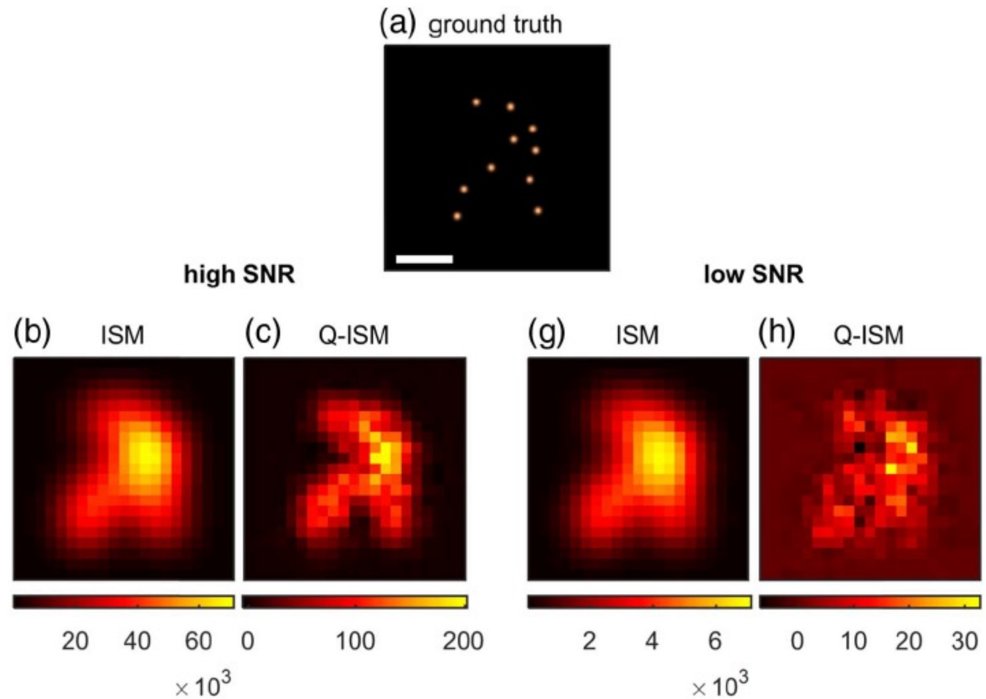
S. Elmalem, DO et al., in preparation

Can we speed statistics based imaging up?

Missing pairs arrive slowly … how many do we need to get the resolution benefit?

Naively – need to get SNR of ~10 on $g^{(2)}$ signal, so 100’s

But… we have the high SNR intensity measurement as a constraint for algorithmic reconstruction

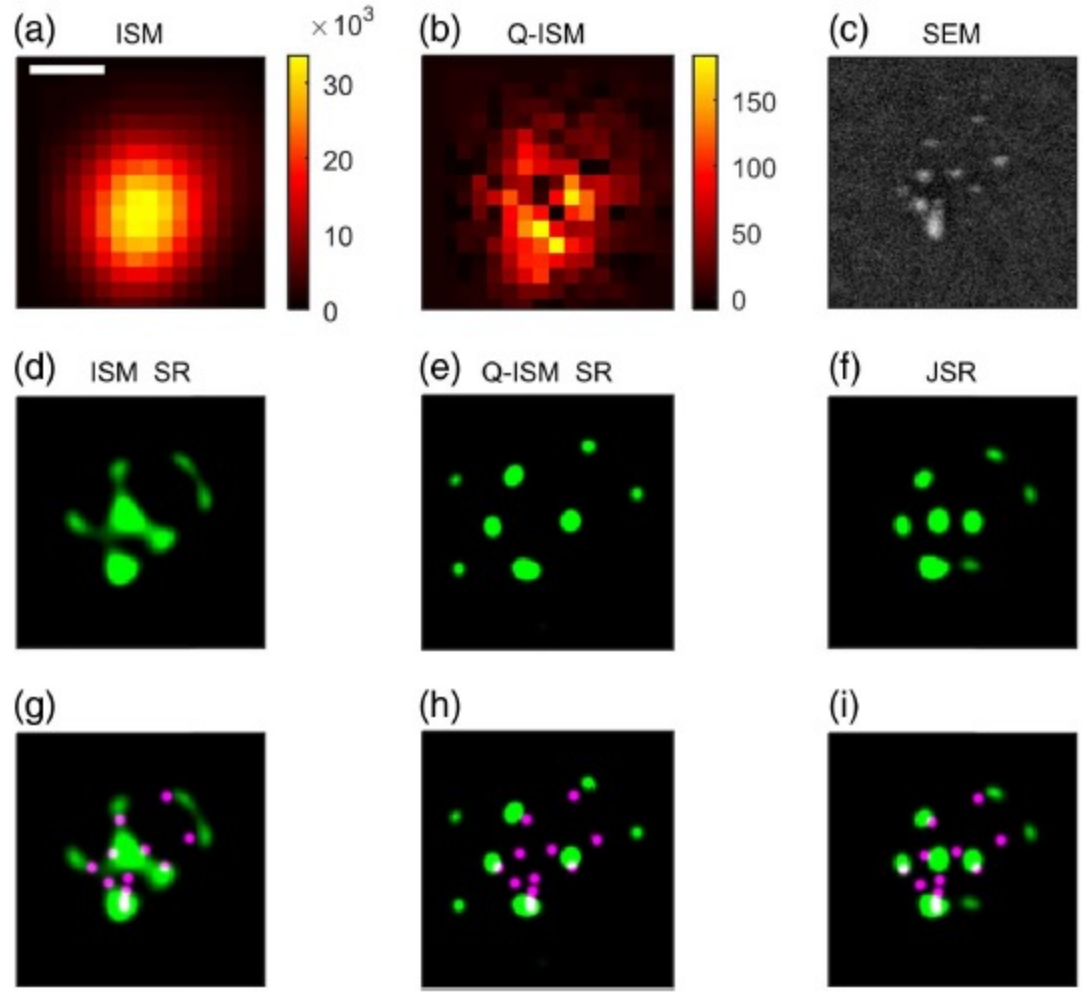


U. Rossman, DO et al., Optica 6, 1290 (2019)

Can we speed statistics based imaging up?

We use joint sparse recovery methods to harvest information from low (~3) SNR measurements

Results agree well with ground truth obtained by correlative EM



U. Rossman, DO et al., Optica 6, 1290 (2019)

Interim conclusions (from part II)

- The quantum Cramer-Rao bound presents the information limit from a measurement and can surpass alternative measurement schemes (classical or quantum)

- The fact that light is composed of indivisible packets of energy (“photons”) is by itself a resource for imaging

- Photon correlations contain extra information that assists sub-diffraction limited imaging or localization

- Measuring photon statistics is much easier with emerging single photon detector array technology

- Some types of “Quantum imaging” are already closer to implementation than commonly thought

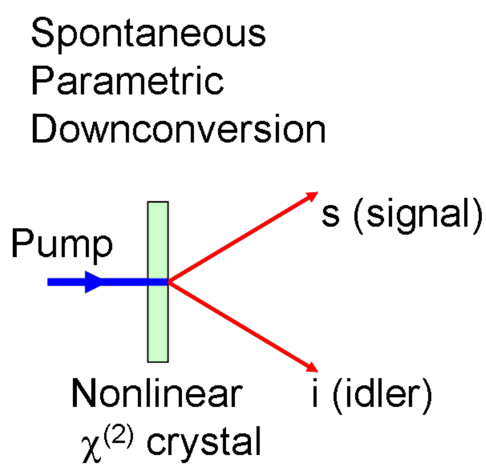
III. Entanglement-based imaging

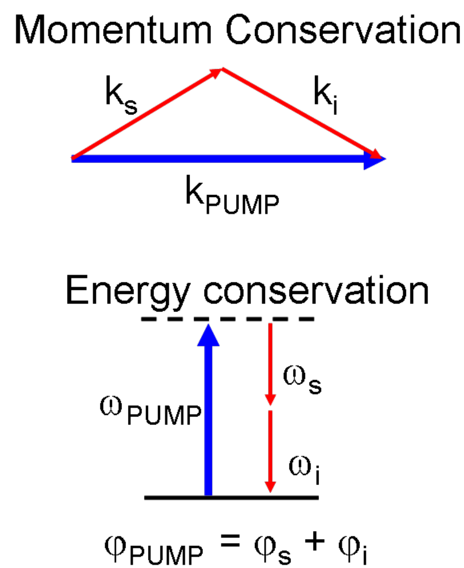
- Entanglement and squeezing
- The Heisenberg limit
- Ghost imaging
- Entangled two photon absorption
- Imaging with N00N states
- Imaging with squeezed light
- Imaging with momentum and polarization entanglement
- Detectors and practicalities

Entanglement

Consider two quantum systems, A and B in states $|\psi_A\rangle$ and $|\phi_B\rangle$
If the state of both cannot be written as a separable inner product:
$|\psi_A\rangle \otimes |\phi_B\rangle$ the two systems are entangled.

Generating entangled photon pairs is "easy" by SPDC…

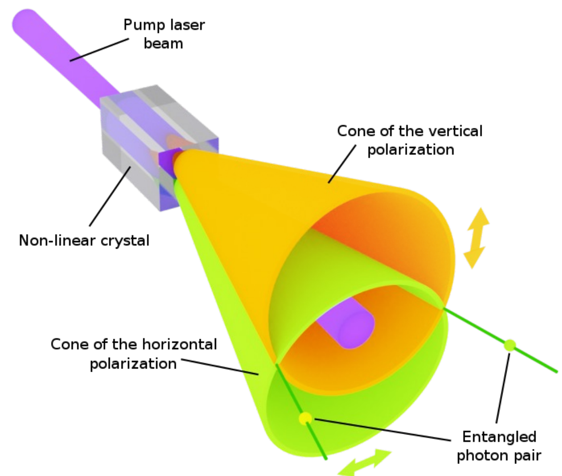




But there are also other ways.

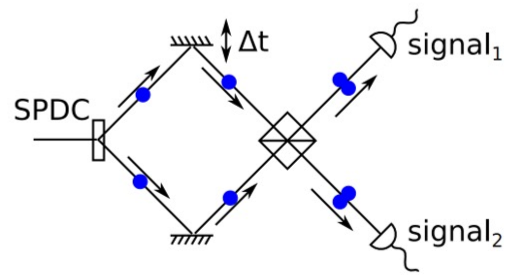
Entanglement

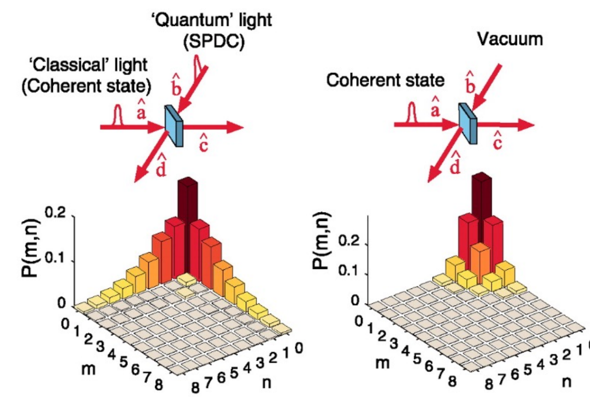
Entangled states can be qubits
$|k^{-}H\rangle\,|k^{+}V\rangle + |k^{+}H\rangle\,|k^{-}V\rangle$
(Bell state)



k-space and polarization entanglement

can be bosonic
$|N\rangle\,|0\rangle + |0\rangle\,|N\rangle$
(N00N state)

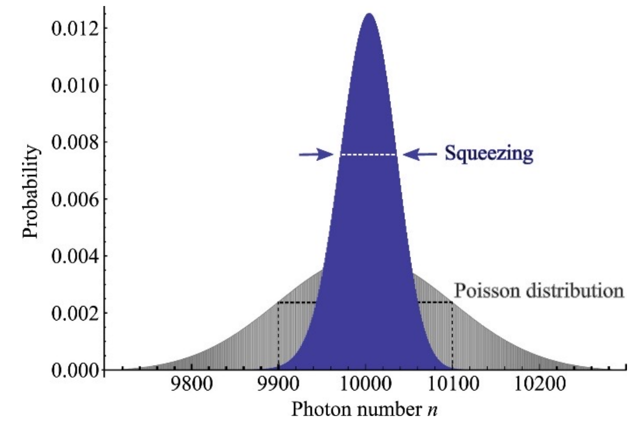




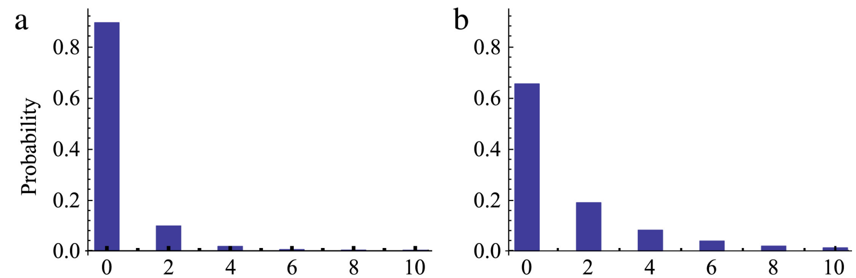
And can even be in continuous variables (like time end energy)

Squeezing

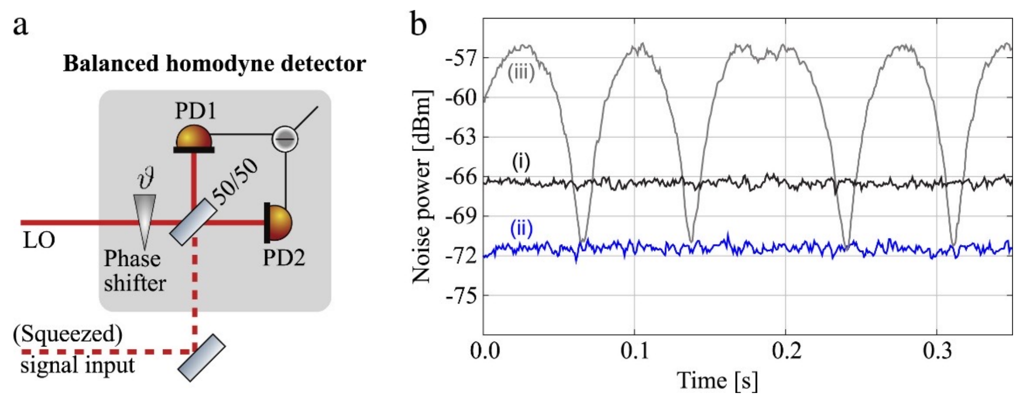
Squeezing refers to states which can have a macroscopic number of photons but whose phase/amplitude uncertainty is modified.



Squeezing is obtained via $2\omega \Rightarrow \omega$ conversion in an optical parametric amplifier



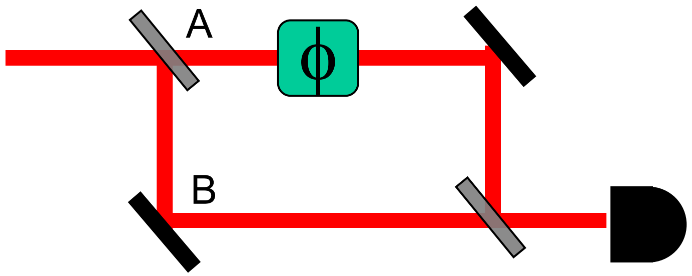
Shot noise in a homodyne detection scheme with “classical” and “squeezed” vacuum



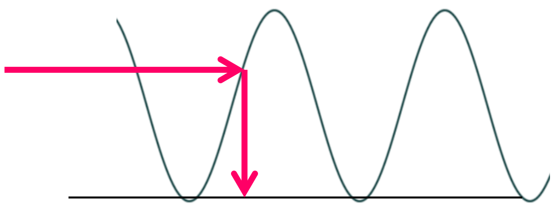
R. Scnabel, Physics Reports 684, 1 (2017)

The Heisenberg limit

Phase (or distance) Measurement:



$$I(\phi) = \cos^2(\phi/2)$$

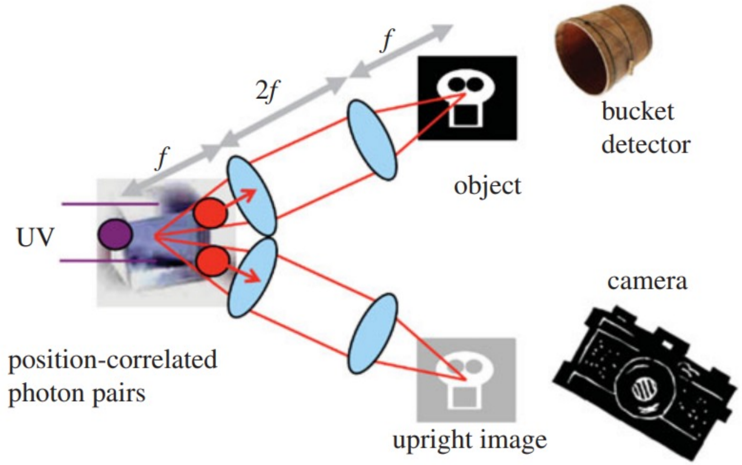


Shot Noise Limited Measurement: $\Delta\phi = 1/\sqrt{N}$

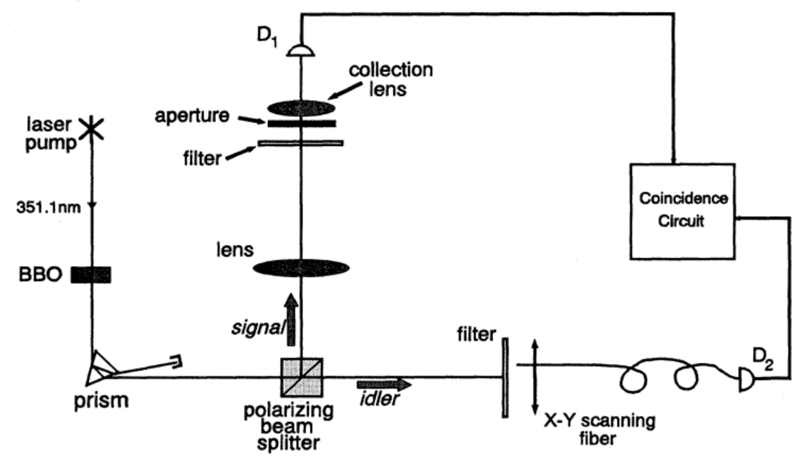
Heisenberg Uncertainly limit: $\Delta\phi = 1/N$

Ghost Imaging

In ghost imaging, light transmitted through a sample is measured by a bucket detector, while a twin beam is imaged by a camera and coincidences are recorded



Initial experiments used photon pairs from SPDC as the sources of position/momentum correlated photons

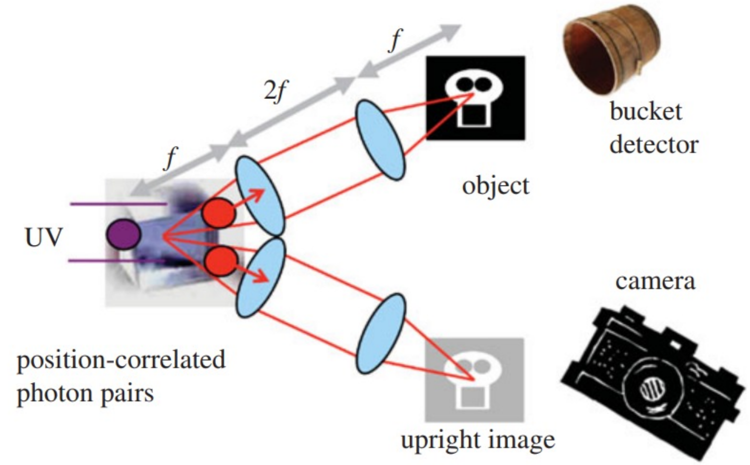


Is ghost imaging necessarily quantum?

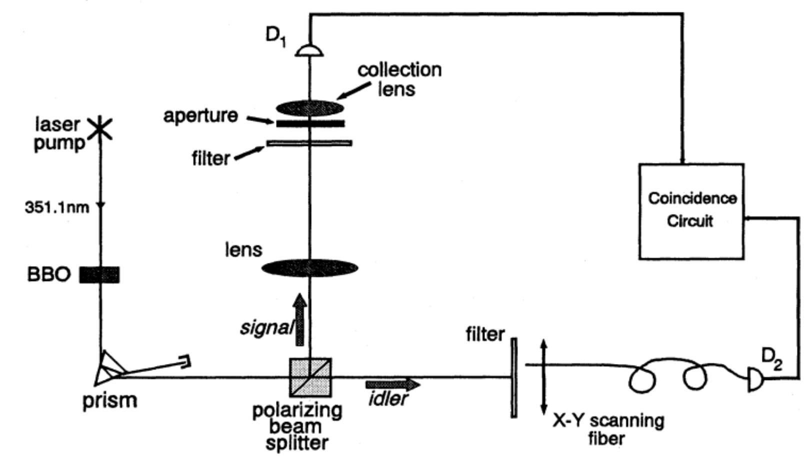
Pittman et al., Phys. Rev. A 52, R3429 (1995)

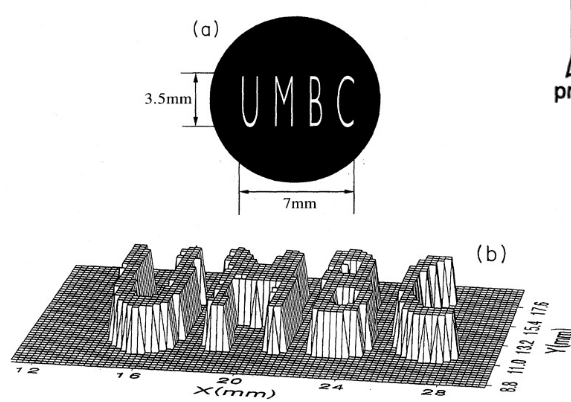
Ghost Imaging

In ghost imaging, light transmitted through a sample is measured by a bucket detector, while a twin beam is imaged by a camera and coincidences are recorded



Initial experiments used photon pairs from SPDC as the sources of position/momentum correlated photons





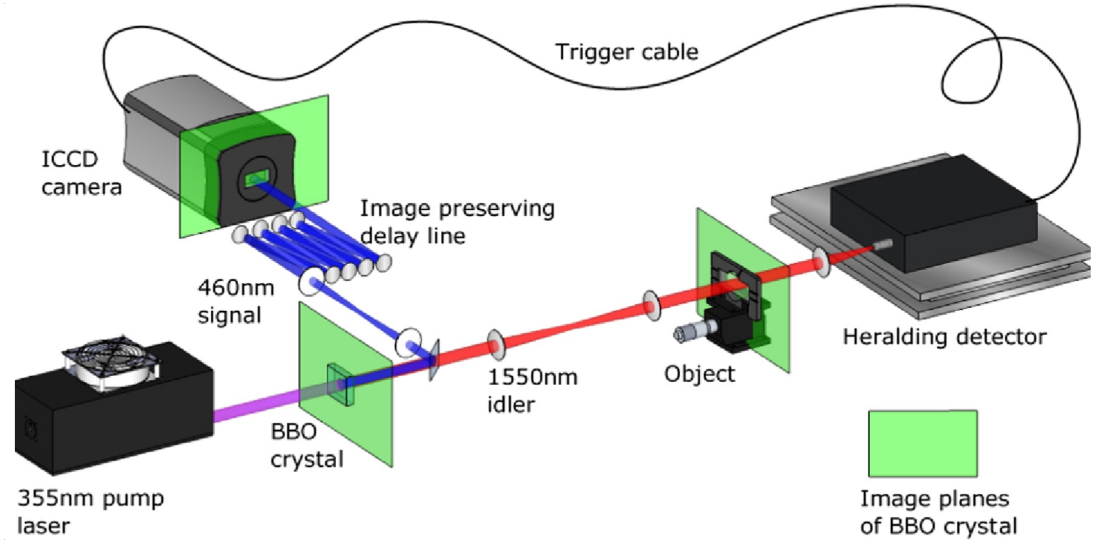
Pittman et al., Phys. Rev. A 52, R3429 (1995)

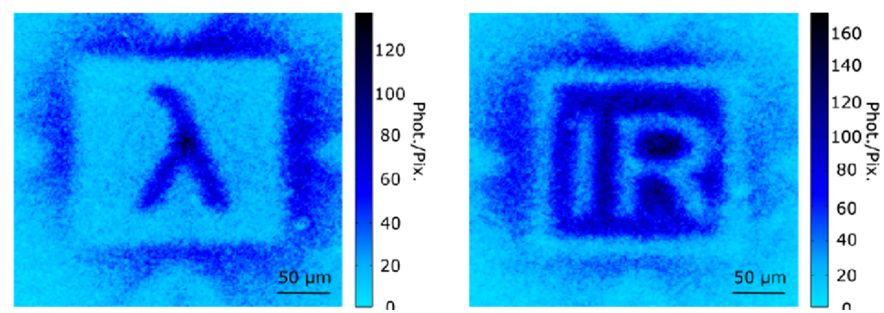
Ghost Imaging

Imaging in one spectral range while detecting photons in another

Imaging in the IR is difficult but there are good IR bucket detectors. Using non-degenerate correlated photons you can perform IR imaging with a visible imaging detector

Main issue: Throughput



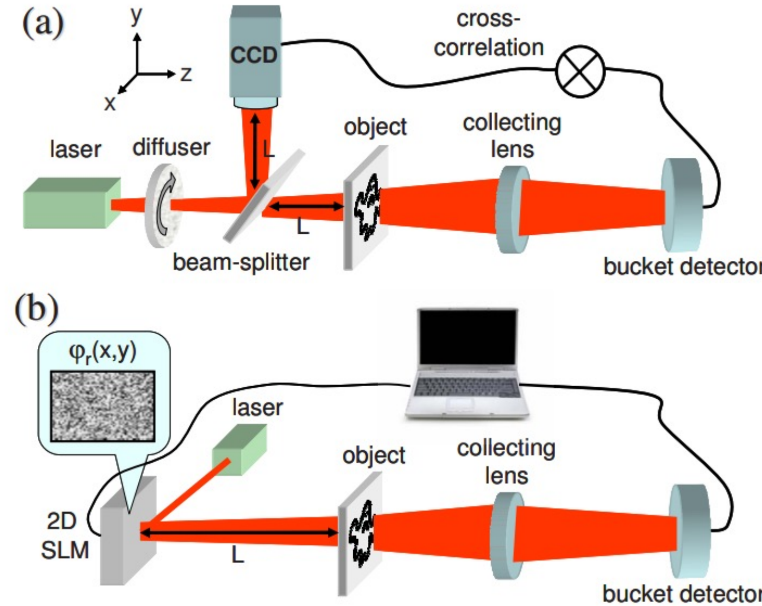


Is ghost imaging necessarily quantum?

Pittman et al., Phys. Rev. A 52, R3429 (1995)

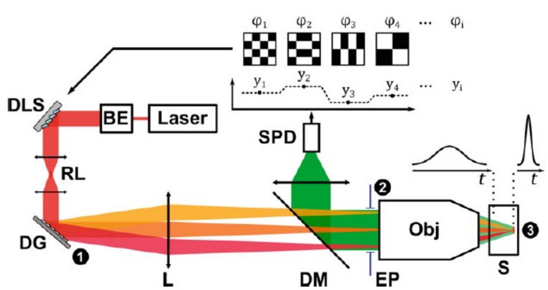
Classical analogs of ghost Imaging

Since it relies on correlations in real space or in momentum space, ghost imaging can be performed with pseudothermal light (using $g^{(2)}>1$). In fact, this can be done computationally, without an imaging detector.

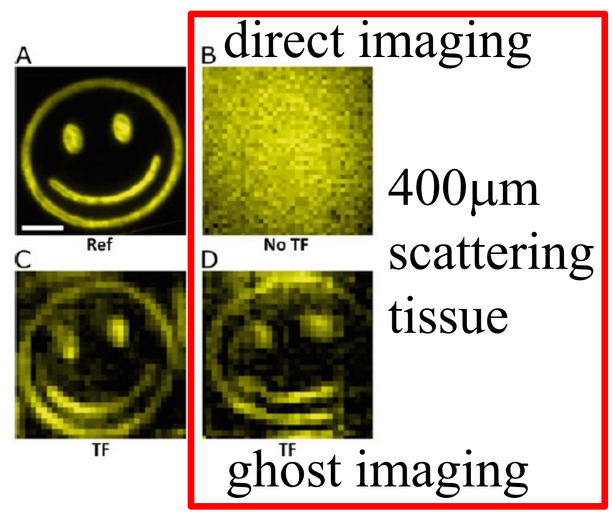


Why do this? Example from wide-field two-photon imaging

Excitation beam insensitive to scattering



Signal highly scattered

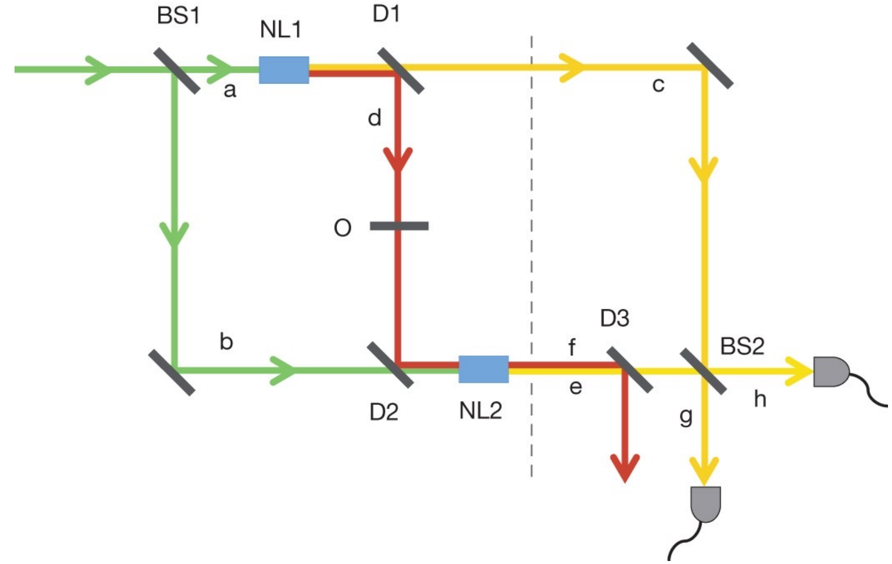


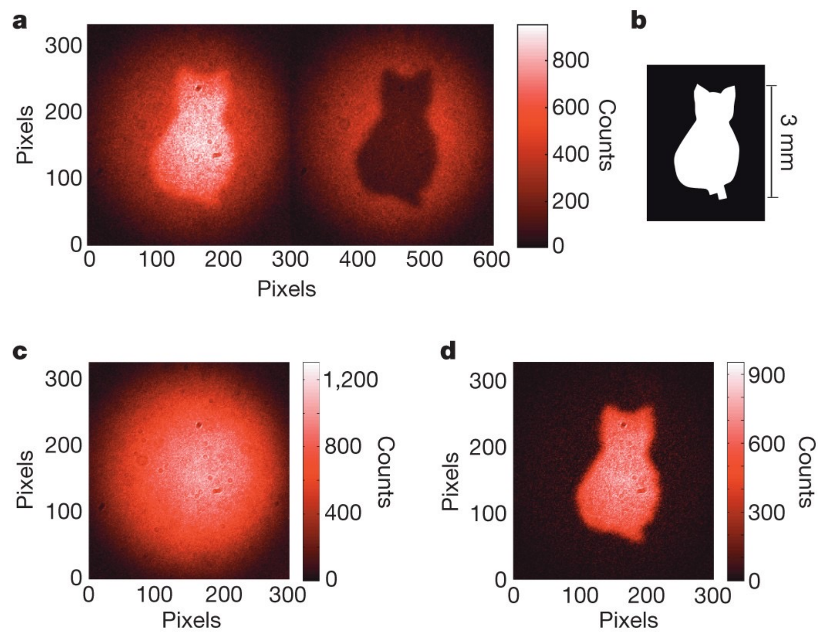
Valencia et al., Phys. Rev. Lett 94, 063601 (2005) ; Katz et al., Phys. Rev. A 79, 053840 (2008) ;
Wijesinghe et al., Opt Lett. 44, 4981 (2019).

Imaging with nondegenerate entangled photons

Since there is no "which path" information for photons generated in the first and second nonlinear crystals, information from the object is relayed onto the interference between the two idler beams

This is reflected in the output of the two beamsplitter ports





Lemos et al., Nature 512, 409 (2014)

Imaging with nondegenerate entangled photons

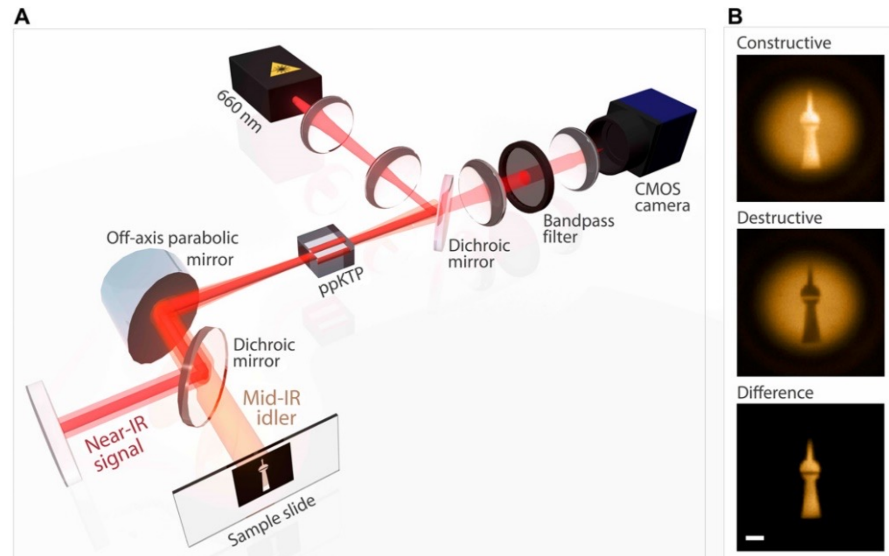
This enables to measure Mid-IR absorption with a silicon based camera.

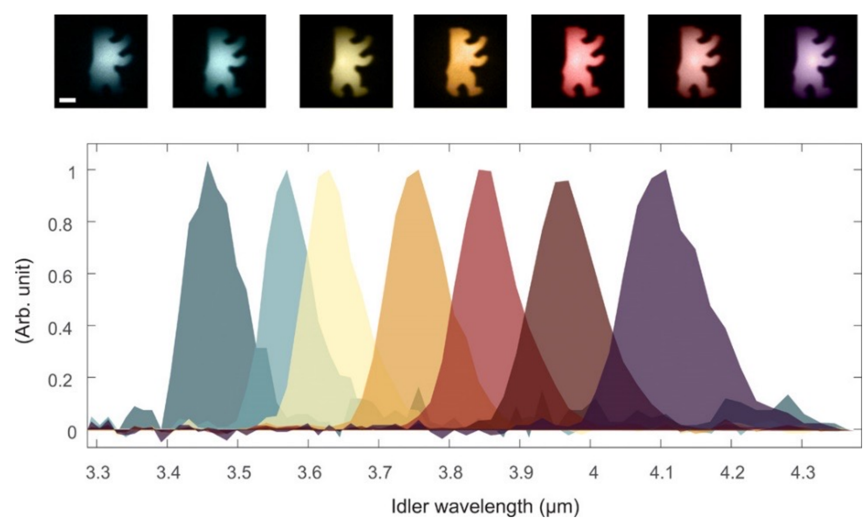
This can be performed in a frequency scanning mode (using PPKTP) to perform mid-IR hyperspectral imaging

Limitations:

- FOV vs. crystal thickness (phase matching)
- Nonlinear crystal size

Current record resolutions are inferior to direct imaging

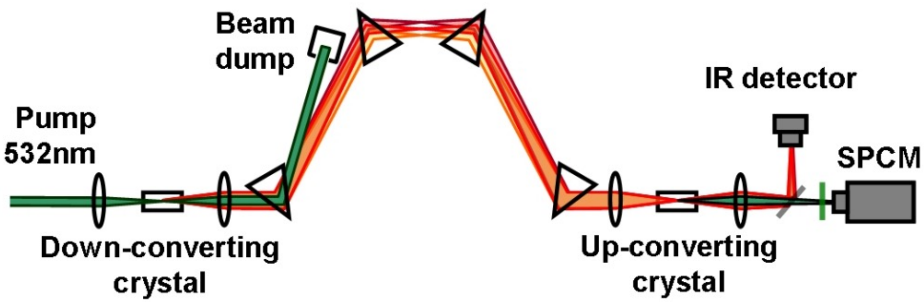


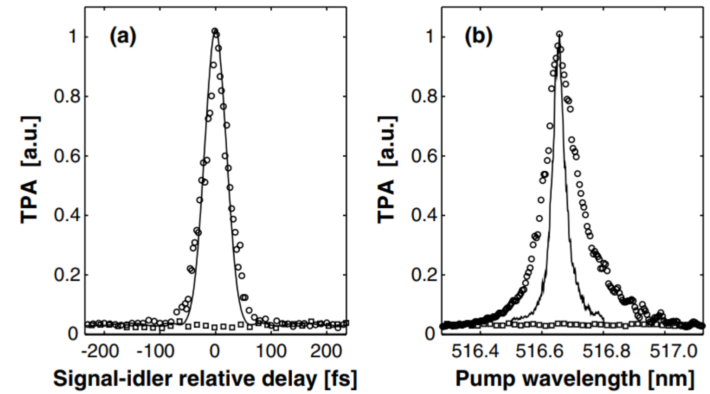


Kviatkovsky et al., Science Advances 6, eabd0264 (2020)

Entangled two-photon absorption

Broadband downconverted light is a bit like an ultrashort pulse…
when it comes to two photon absorption or SHG



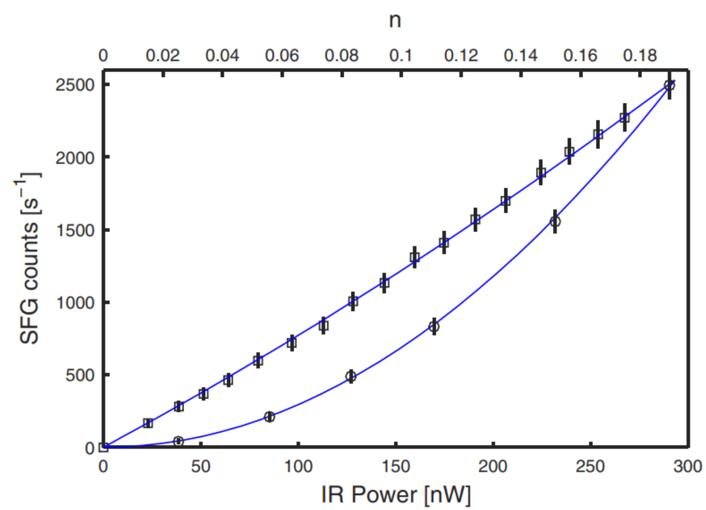


But there is one big difference:
the dependence of TPA on the
excitation power is linear in the
weak excitation regime

bandwidths

Photons/mode

$$\frac{I^c}{I^{ic}} \approx \frac{B}{(\gamma_p + \gamma_f)} \frac{n^2 + n}{n^2},$$

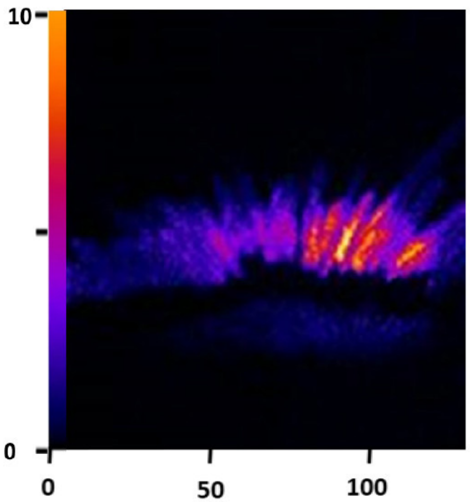


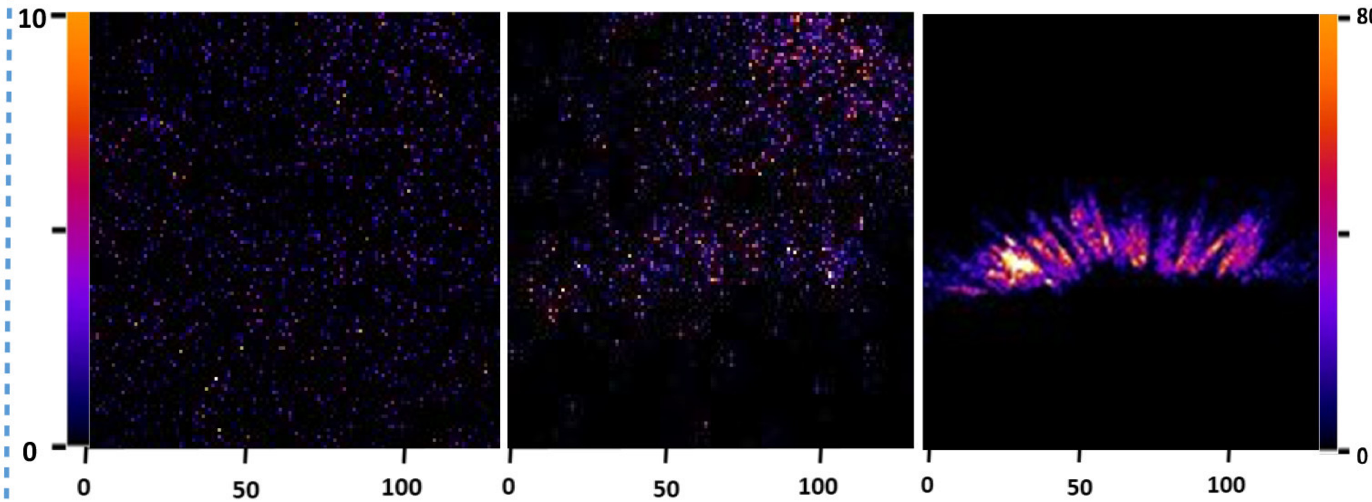
Dayan et al., Phys. Rev. Lett. 93, 023005 (2004) ; Dayan et al., Phys. Rev. Lett. 94, 043602 (2005)

Is this useful for imaging with molecular dyes?

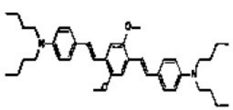
Entangled two-photon microscope image

Classical light TPA- microscope images





Excitation flux: **10^7** photons/s



Excitation flux: **$0.96*10^{12}$** photons/s

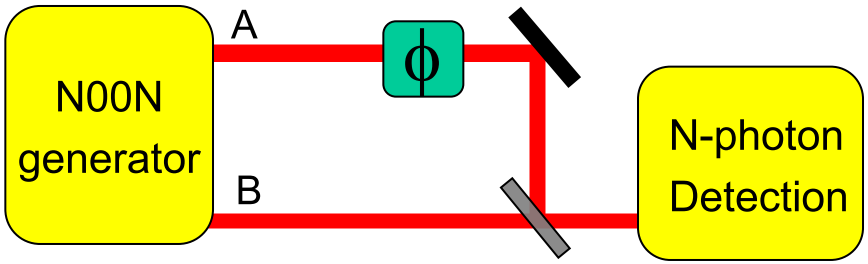
Excitation flux: **$0.96*10^{13}$** photons/s

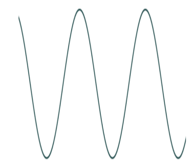
Excitation flux: **$5*10^{13}$** photons/s

E-TPA image obtained after 2 hours of integration, and not all of it is e-TPA. Utility is definitely yet to be proven

Varnavski et al., JACS 142, 12966 (2020) ; Varnavski et al., Proc. Natl. Acad. Sci. USA 120, e2307719120 (2023)

Interferometry with N00N states





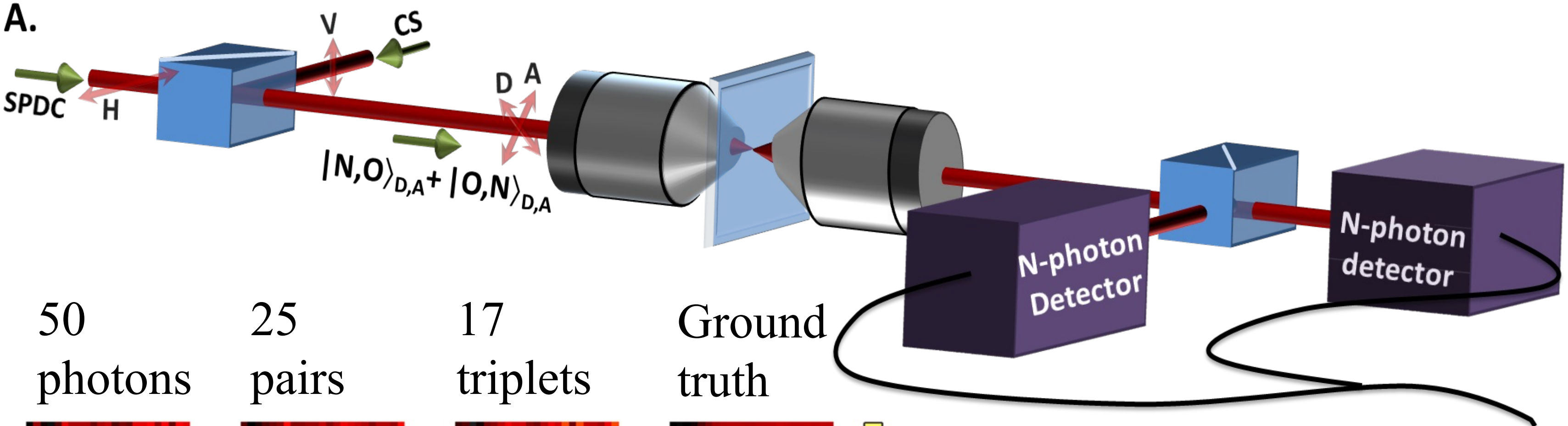
$$|N\rangle_A|0\rangle_B+|0\rangle_A|N\rangle_B \rightarrow e^{i\varphi N}|N\rangle_A|0\rangle_B+|0\rangle_A|N\rangle_B \quad \rightarrow \cos^2\left(N\varphi/2\right)$$

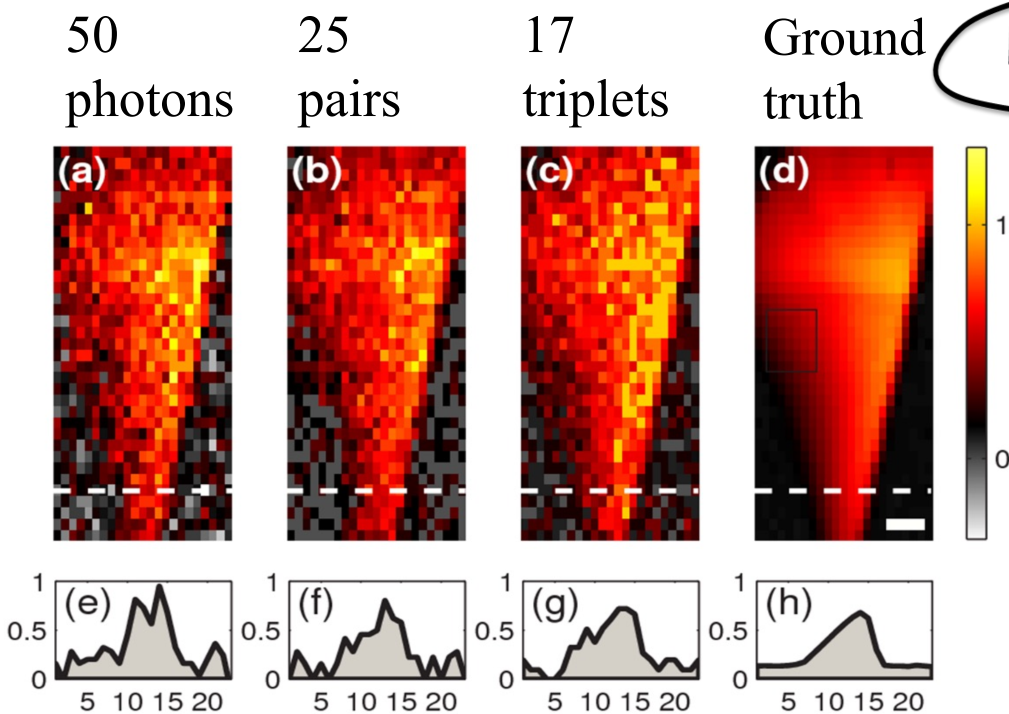
High-NOON states collect phase N times faster than coherent states – they behave as if their wavelength is N times shorter!

Can reach the Heisenberg limit

Requires quantum state generation and quantum detection

Heisenberg limited polarization imaging





But this is very fragile… and in the absence of nonlinearity can be shown not to improve spatial resolution

Y. Israel et al., Phys. Rev. Lett 112, 103604 (2014).

Imaging with squeezed light

Whenever a local oscillator is used in a homodyne measurement, the dominant noise term is shot noise of the local oscillator

Strong LO

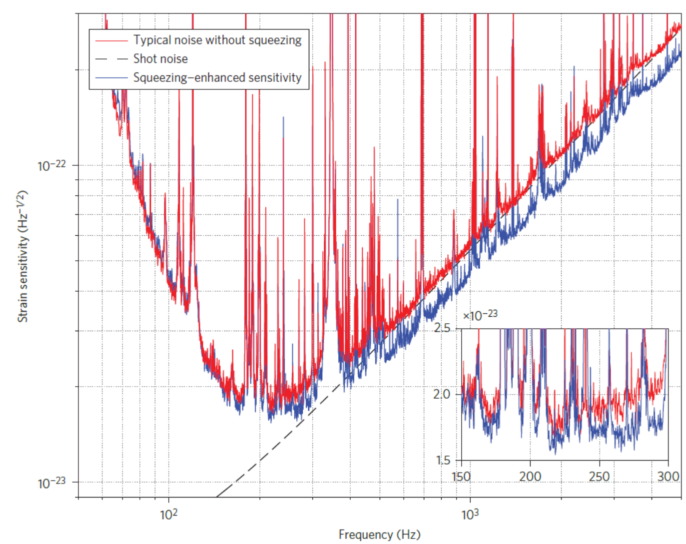
Weak signal

$$\left|E_{LO}+E_{Sig}\right|^2 \approx \underbrace{\left|E_{LO}\right|^2}_{\text{background}} + \underbrace{2E_{LO}\,E_{Sig}}_{\text{signal}} \quad \left(\gg \left|E_{sig}\right|^2\right)$$

$$\Delta\left|E_{LO}+E_{Sig}\right|^2 \approx \underbrace{2\left|E_{LO}\right|\left|\Delta E_{LO}\right|}_{\text{dominant noise}}$$

Squeezing can reduce this noise floor, improving measurement sensitivity!

This has already been applied in LIGO

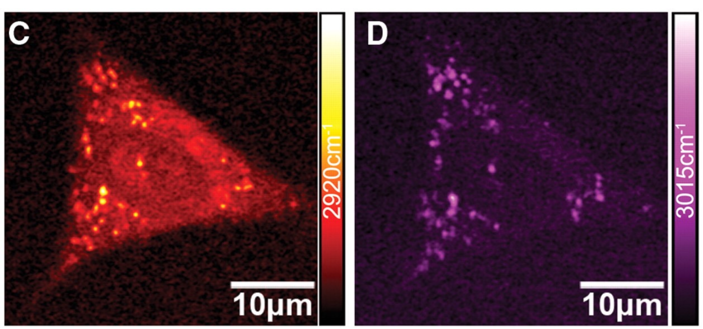


LIGO, Nature Photonics 7, 613 (2013).

Stimulated Raman Scattering microscopy

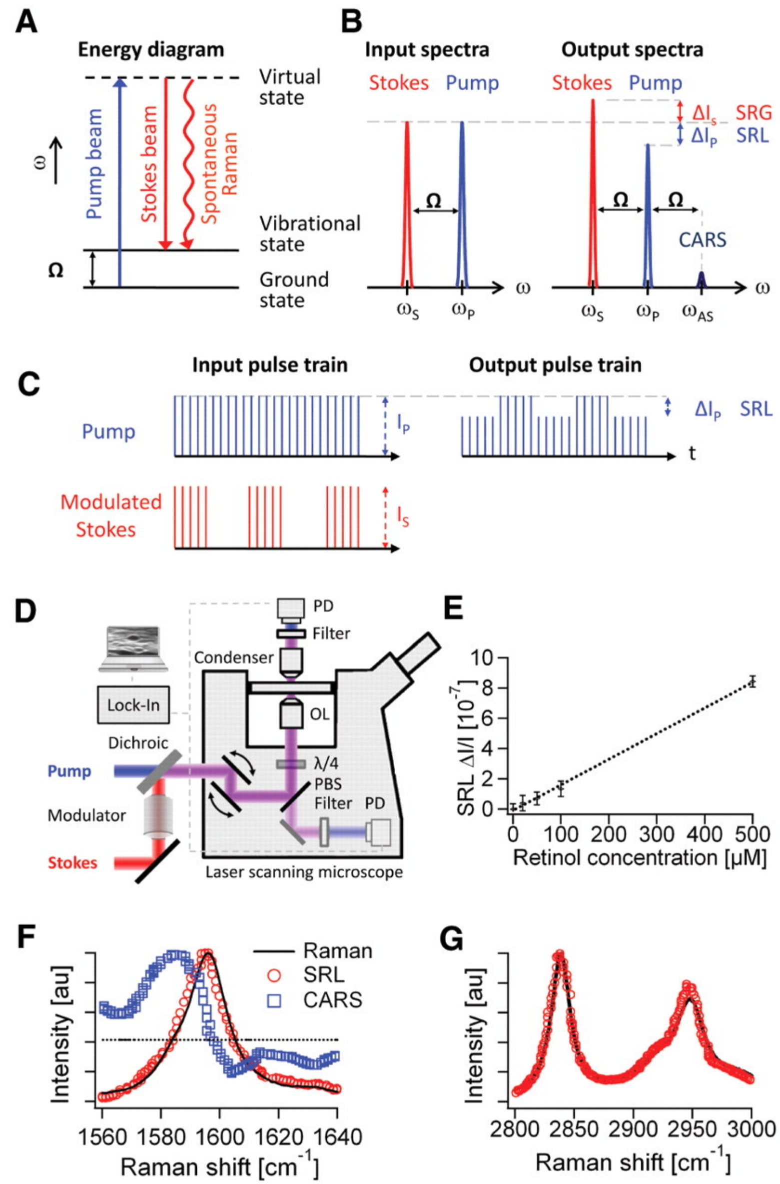
SRS microscopy is a nonlinear imaging modality which directly accesses the Raman susceptibility (as in spontaneous Raman) and is based on modulation transfer due to stimulated Raman Loss/Gain.

Its sensitivity is usually limited by shot noise of the unmodulated excitation beam.



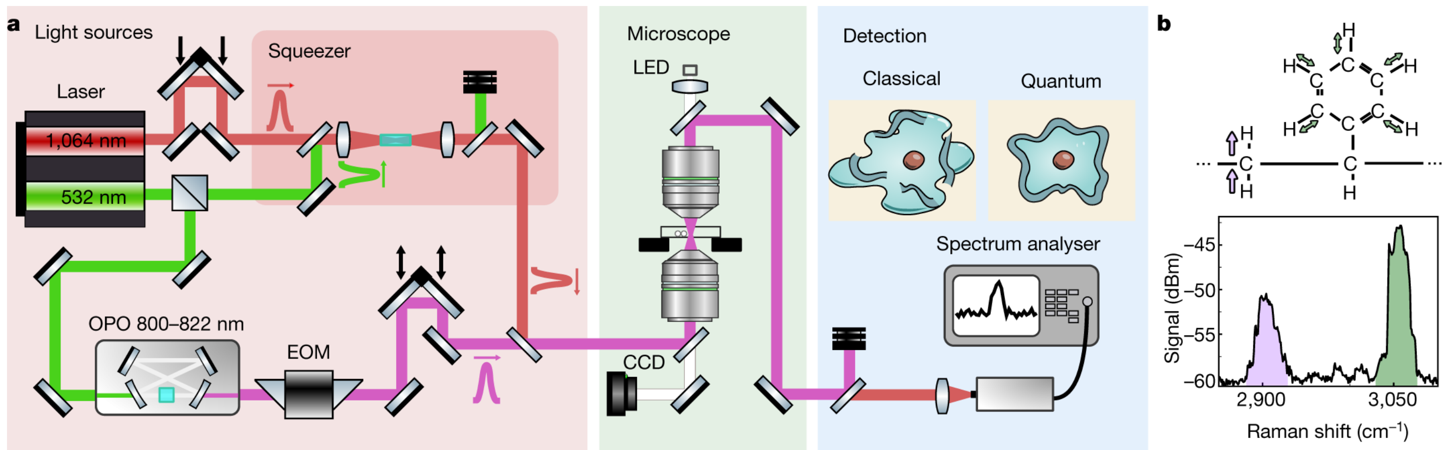
Imaging different fatty acids

Freudiger et al., Science 322, 1857 (2008).

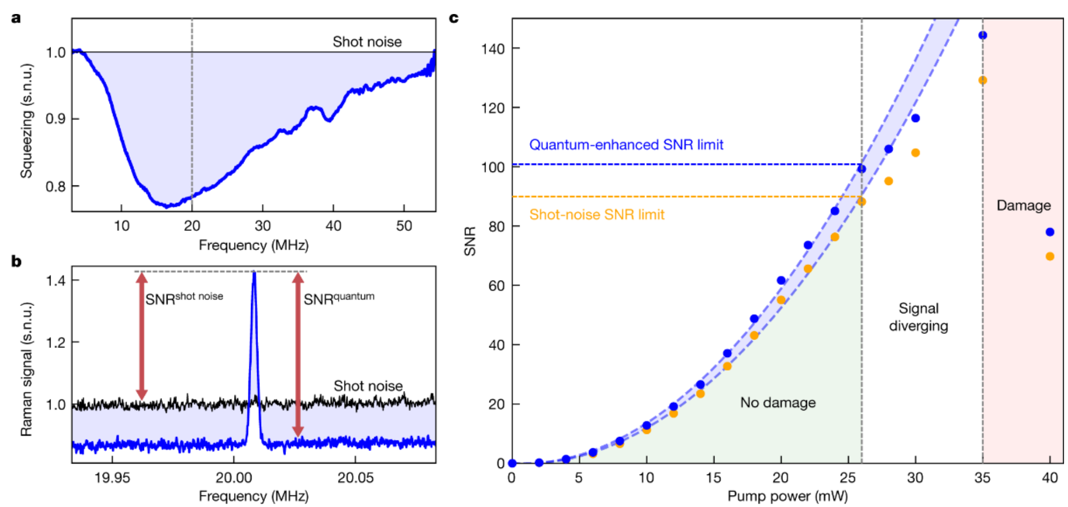


Quantum enhanced SRS microscopy

Same as in LIGO, use squeezing to reduce SRS noise floor



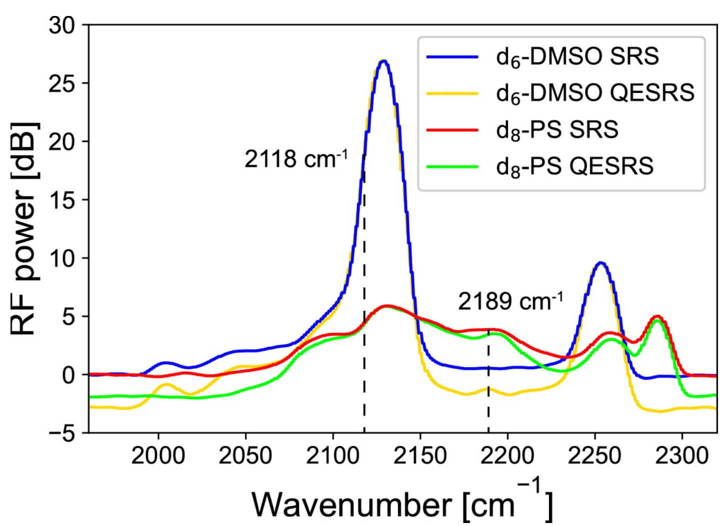
With 0.6dB squeezing, the SNR is improved 15%. More recent implementations are up to ~1.2dB squeezing

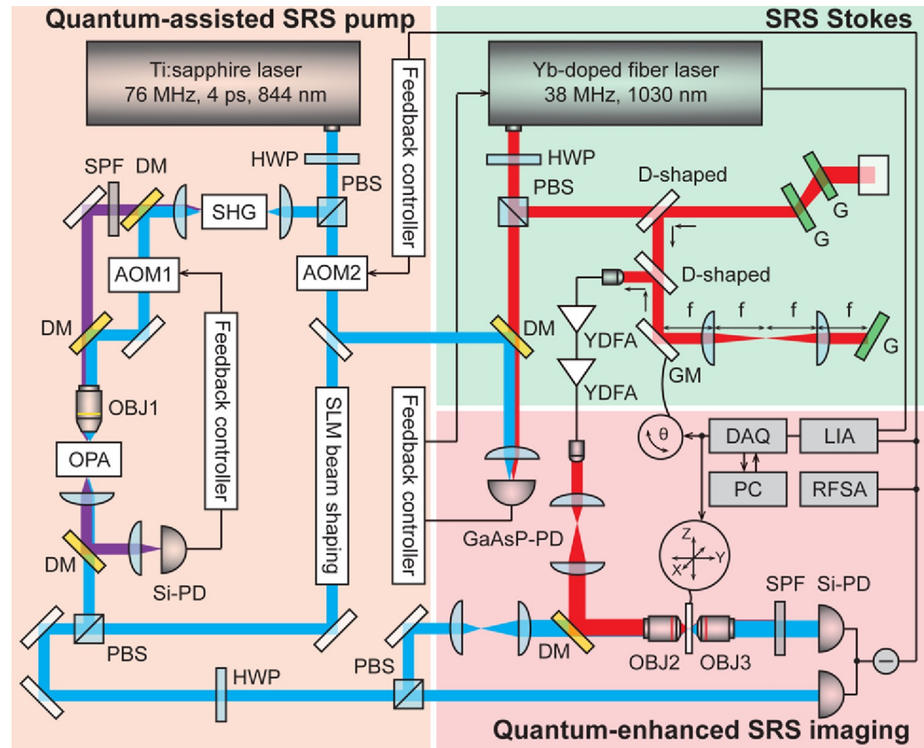


Casacio et al., Nature 594, 201 (2021).

Quantum enhanced SRS microscopy

Balanced detection enables to achieve a better advantage in squeezing (~2.9dB), but comes at a 3dB cost to the signal…





Is this a game-changer? Not yet… equivalent to ~20% improved sensitivity in concentration or enhanced speed…
but with a few more dB of squeezing it might just get to be important.

Xu et al., Opt. Lett. 47, 5829 (2022).

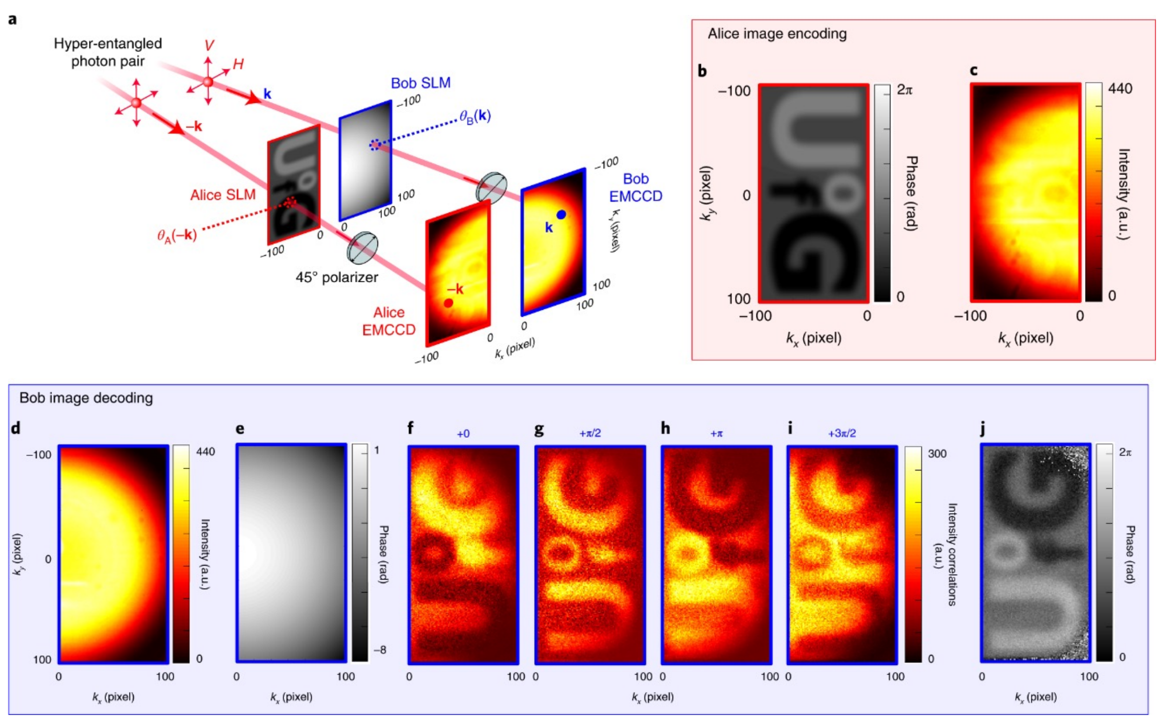
Holography with entangled photons

Using a polarization-momentum entangled state one can code spatial phase dependence in the polarization degree of freedom

$$|k^{-}V\rangle\,|k^{+}V\rangle + e^{i\varphi(k)}\,|k^{+}H\rangle\,|k^{-}H\rangle$$

Insensitivity to classical noise and insensitivity to phase noise in k and –k since it affects both states equally

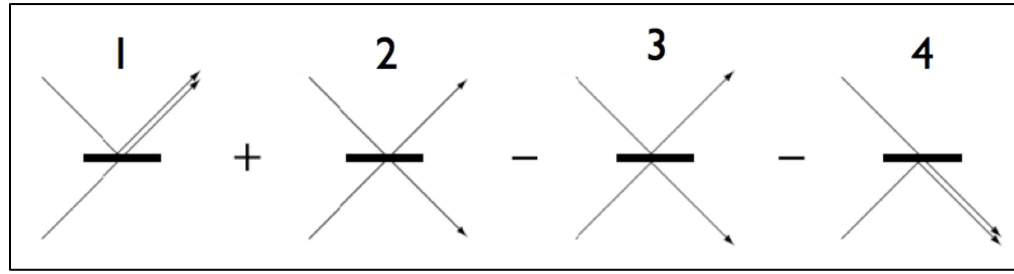
2X spatial resolution (relative to signal/idler wavelength)



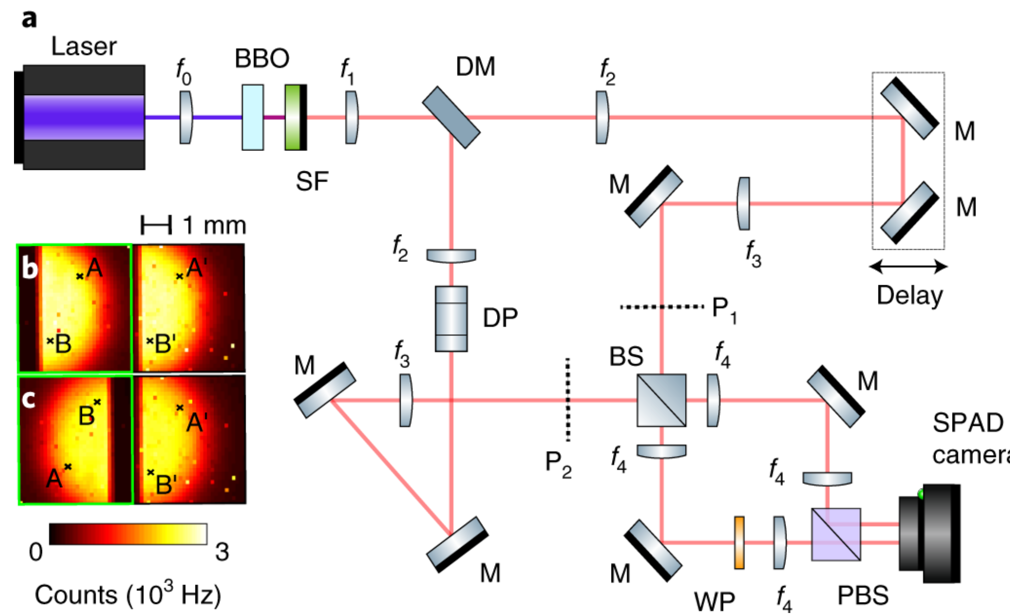
Defienne et al., Nature Physics 17, 591 (2021).

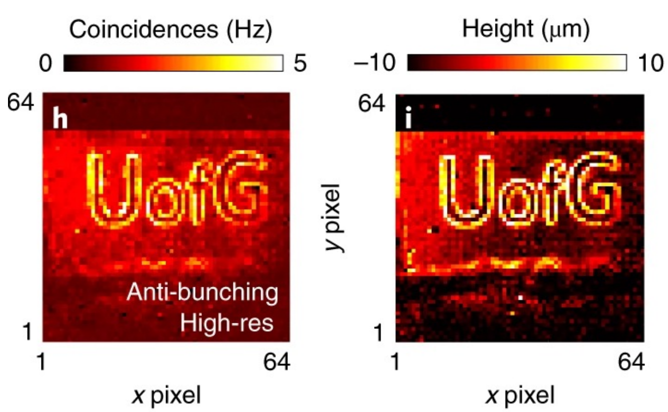
Profiling with HOM imaging

HOM: identical photons bunch at a beamsplitter



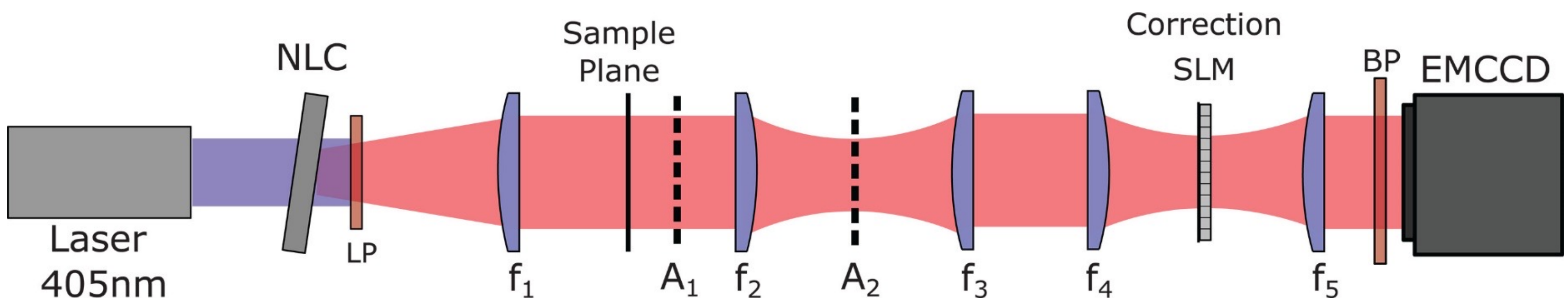
HOM imaging: Perform this across the field of view. Depth sensitivity is determined by photon bandwidth





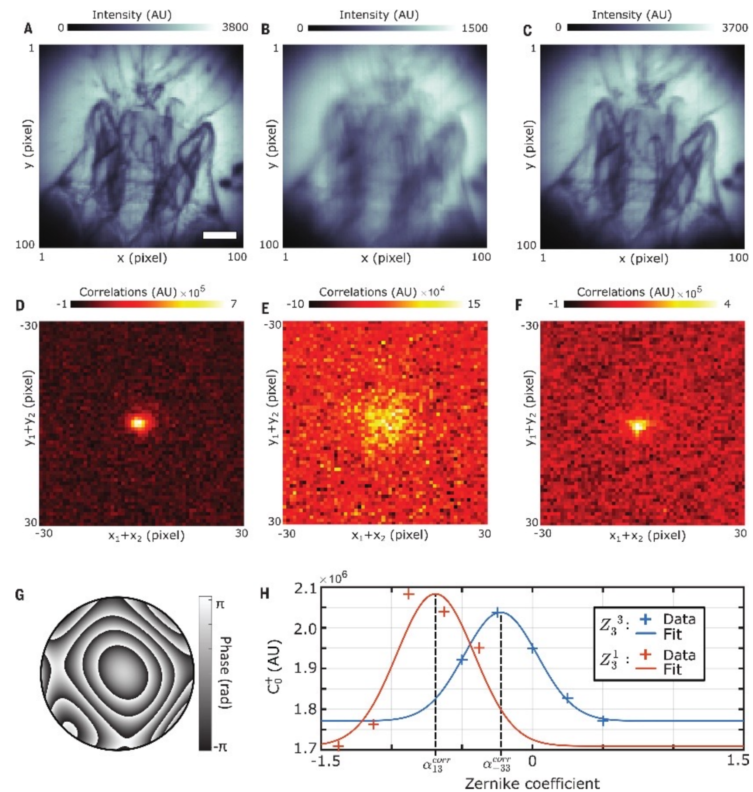
Hong, Ou, Mandel, Phys. Trev. Lett. 59, 2044 (1987) ; Ndagano et al., Nature Photonics 16, 384 (2022).

Adaptive optics with entangled photons



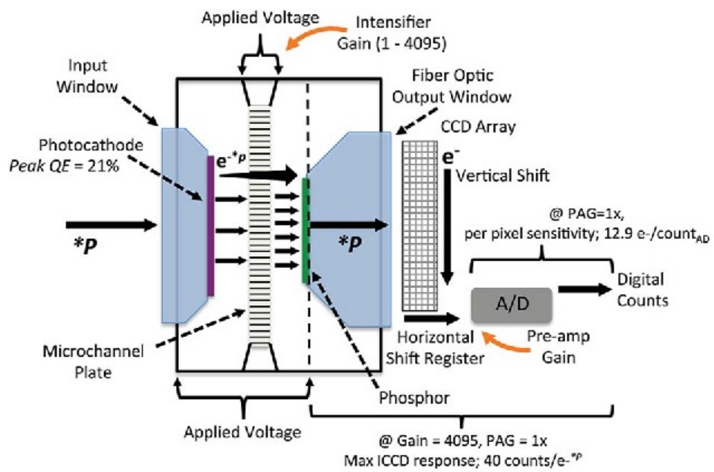
Adaptive correction of aberrations in an optical system is often based on a guide star or on the image properties.

Position entanglement deteriorates with aberrations and thus the magnitude of the correlation signal itself can serve as the feedback



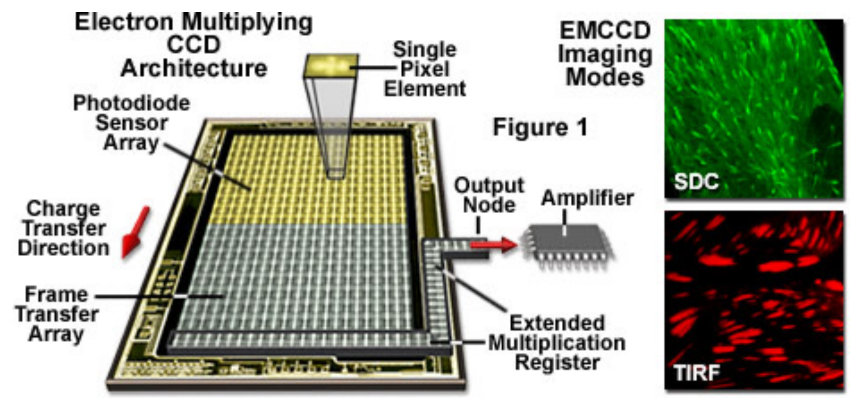
Cameron et al., Science 383, 1142 (2023).

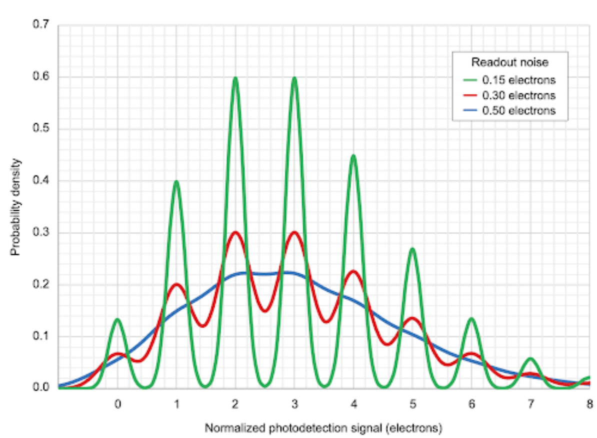
Single photon imaging detectors



Intensified CCD: low quantum yield, possible gating, amplification noise

EMCCD: High yield, amplification noise (CIC), reasonable readout (1kHz)

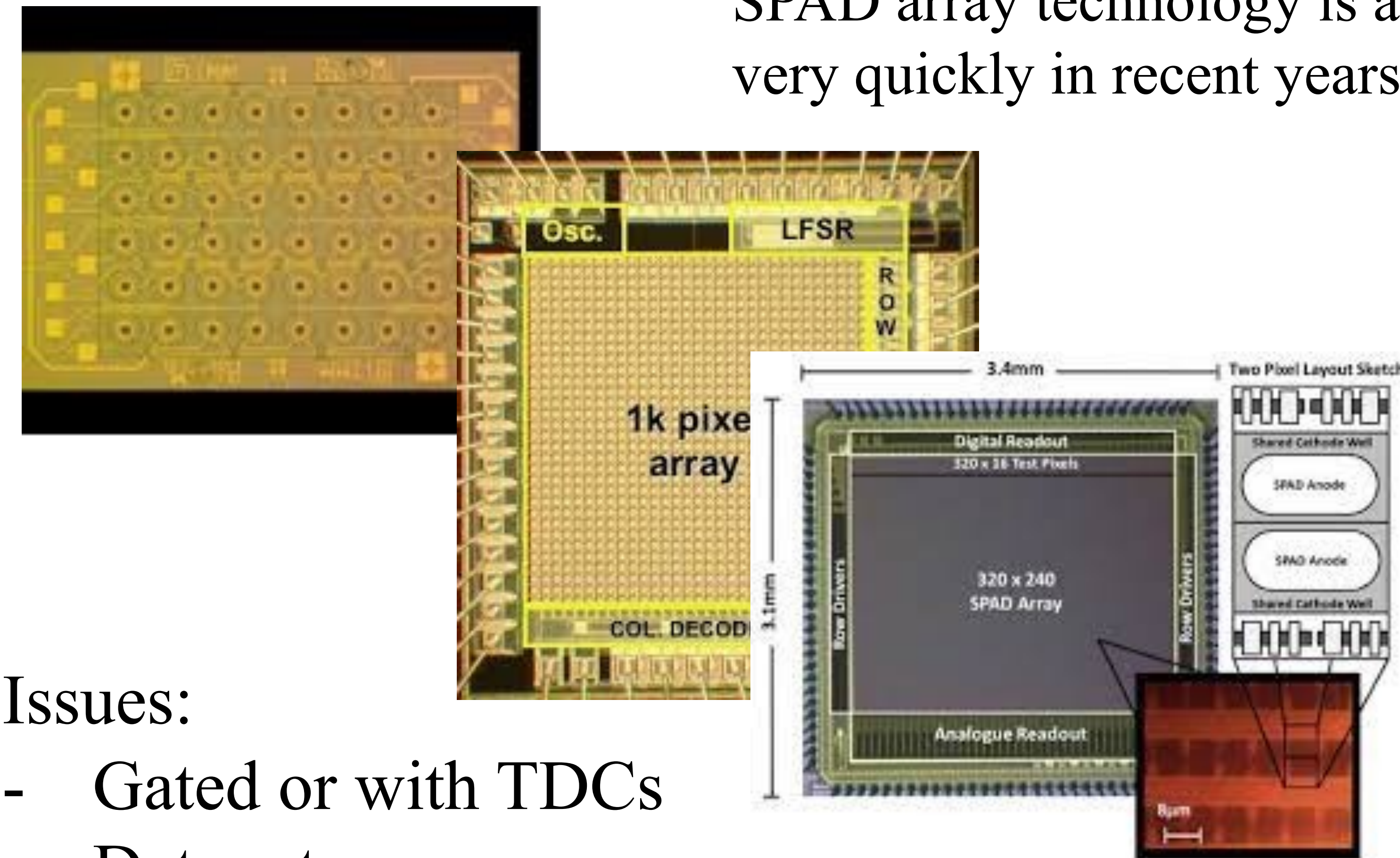




QCMOS: High yield, readout noise almost there but not quite, very low frame rate (25Hz)

Single photon imaging detectors

SPAD array technology is advancing very quickly in recent years



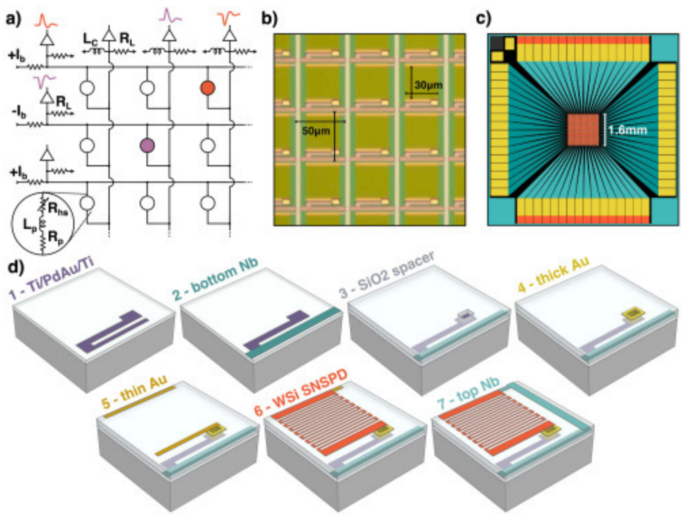
Issues:

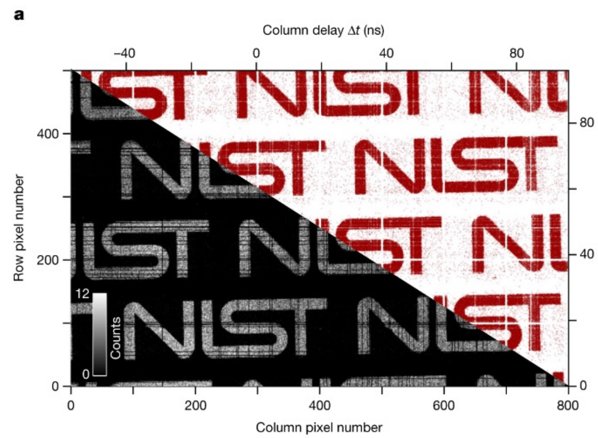
- Gated or with TDCs
- Data rates
- Crosstalk
- NIR sensitivity (InGaAs?)

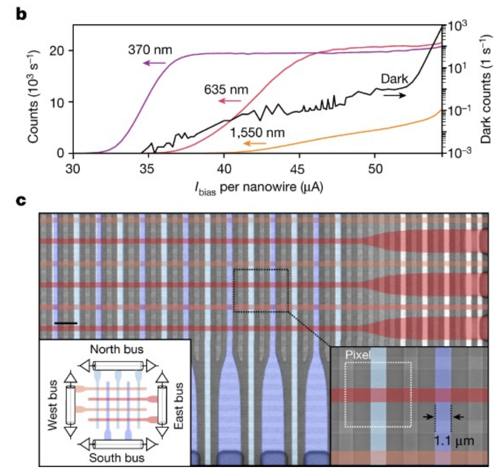
Now at 1Mpixels … and counting

Single photon imaging detectors

Superconducting nanowire arrays are also making big steps forward, reaching kPixels in 2019 and ~1MPixel in 2023.







Likely to become a leading technology but requires cryocooling and still has issues with rate and readout

Wollman et al., Optica 27, 35279 (2019) ; Oripov et al., Nature 622 730 (2023).

Interim conclusions (from part III)

- A variety of potential ways to enhance microscopy with entangled or squeezed light, but technical difficulty with both quantum state generation and quantum state detection.

- Technological development of better sources and better detectors is key to making any of this work in practice

- New ideas keep popping up… there seems to still be a lot of room for development also in methods

- There is still a long way to go for imaging with squeezed light and with entangled photons to be of real utility or advantage over "classical" microscopy

For further reading

There are two recent reviews on this topic:

- Bowen et al., “Quantum Light Microscopy”, Contemporary Physics, https://doi.org/10.1080/00107514.2023.2292380 (2023)

- Moodley and Forbes, “Advances in Quantum Imaging with Machine Intelligence”, Laser Photonics Rev. 2300939 (2024)

- Defienne et al., “Advances in Quantum Imaging”, to appear in Nature Photonics (2024).