Image scanning microscopy with quantum and classical correlations

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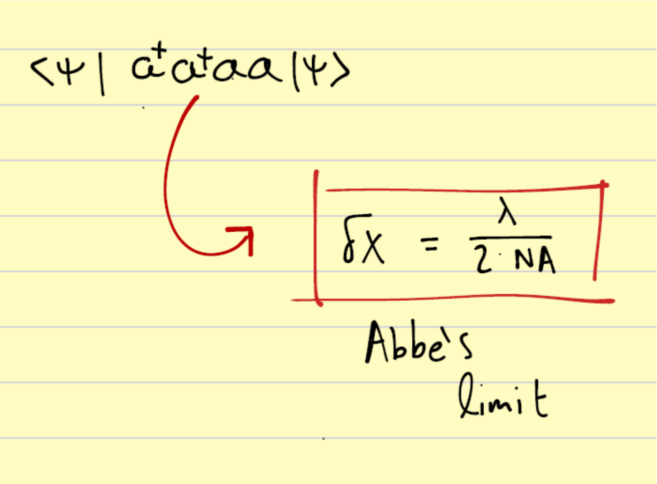

ISSW 2020

Weizmann Institute

Dan Oron

Yaron Silberberg

Bat-el Raphael

Uri Rossman

Yonatan Israel

Gur Lubin

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EPFL, AQUA lab

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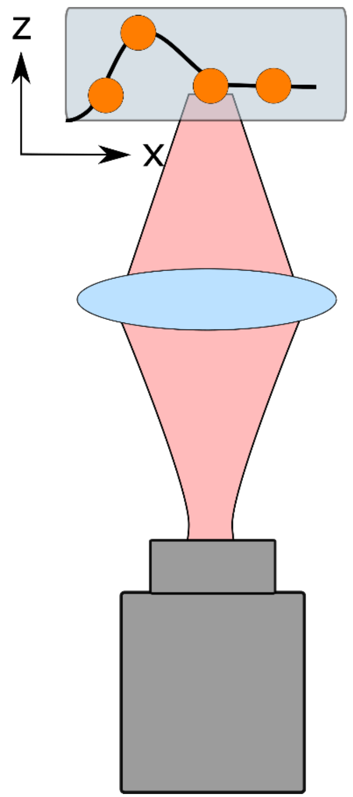
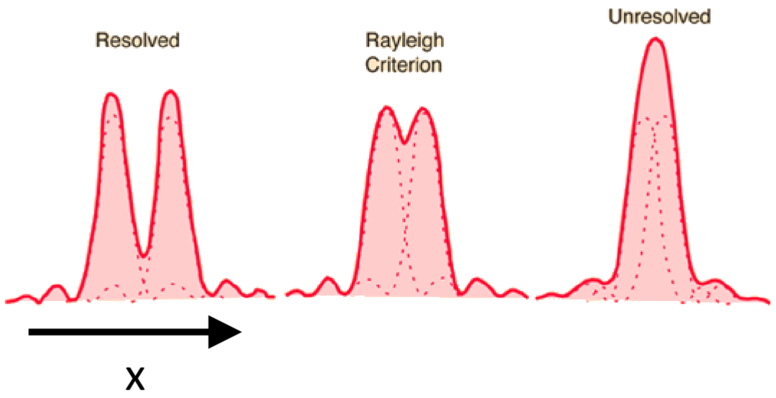
Yaron Silberberg 1951-2019

The resolution problem



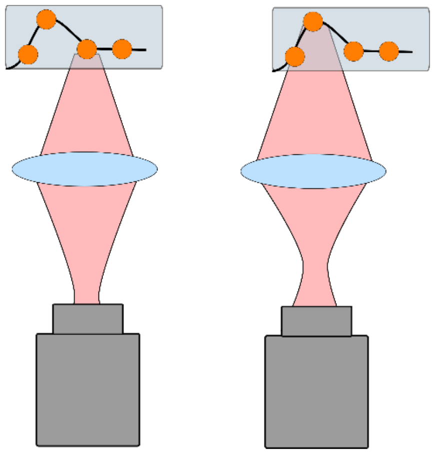
Lateral resolution
Rayleigh criterion

$$\Delta x = 1.22 \cdot \frac{\lambda}{2NA} \sim 200\ nm$$

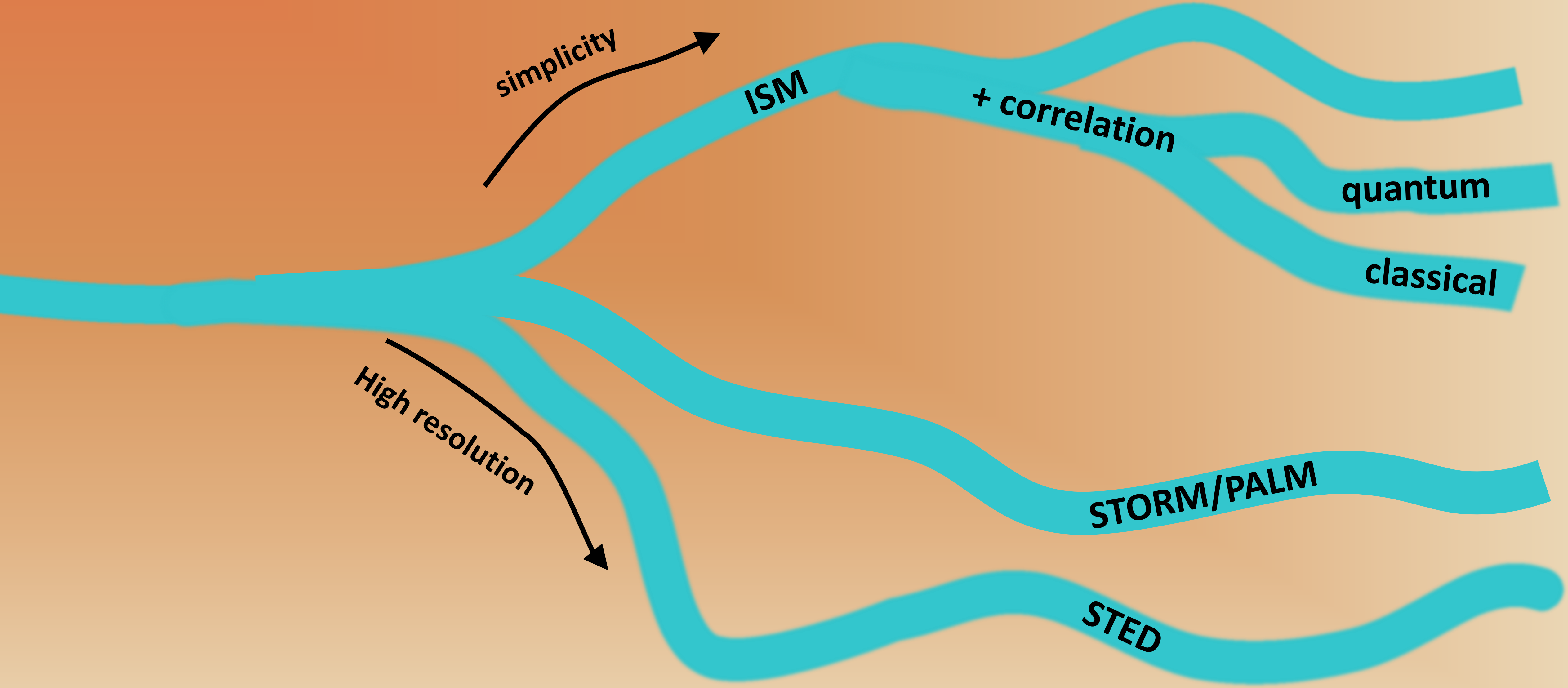


Axial sectioning
Rayleigh range

$$\Delta z \sim \frac{\lambda}{(NA)^2} \sim 1 \mu m$$



Super-resolution “flow chart”



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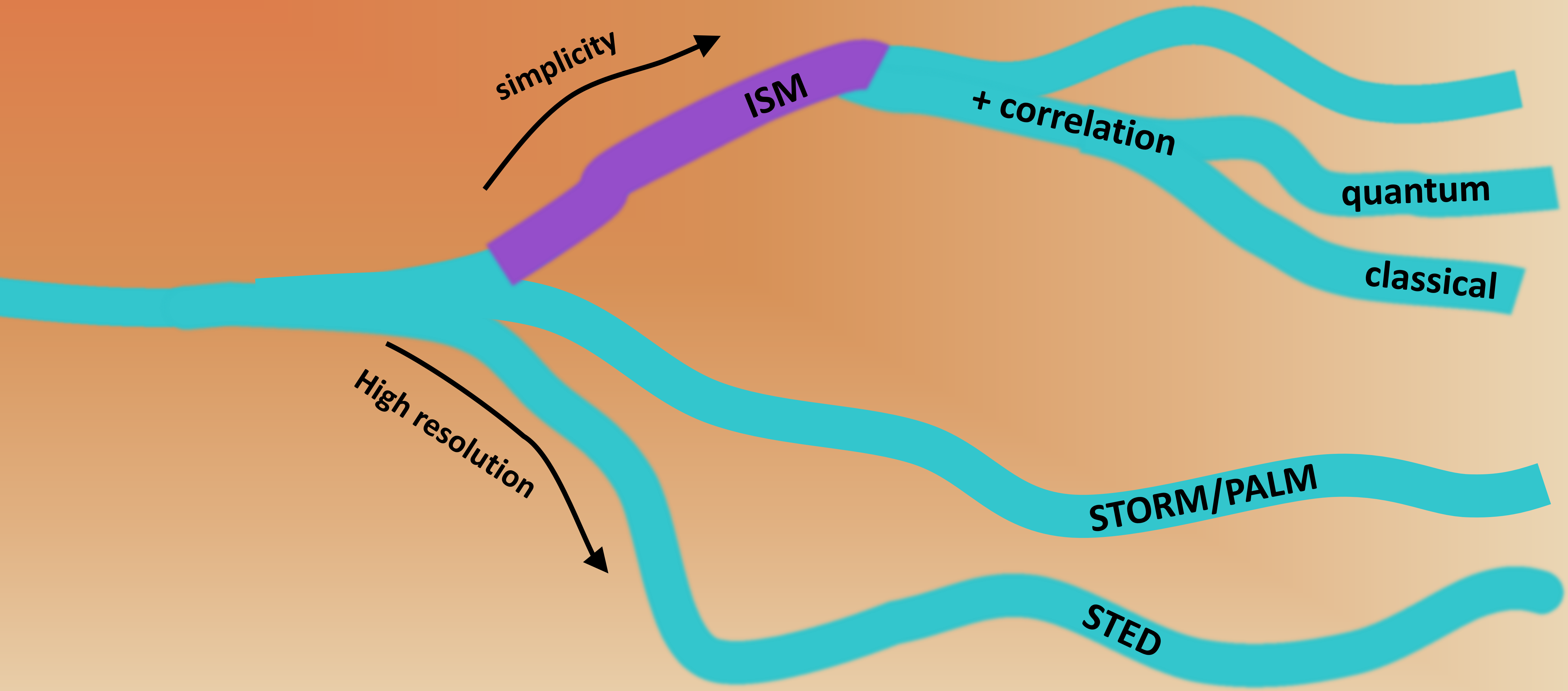
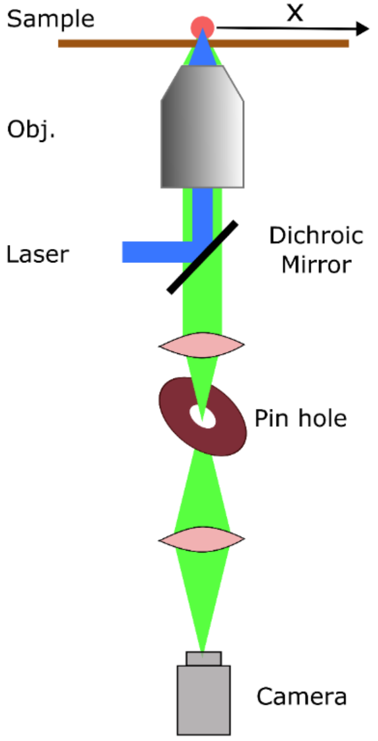
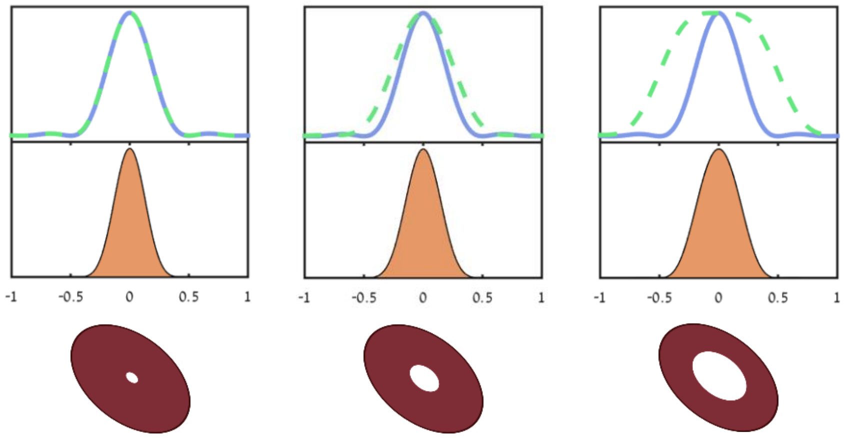


Super-resolution in a confocal microscope?



$$P_{signal} = P_{excitation} \cdot P_{detection}$$

0.1 AU   0.5 AU   1 AU



x2 resolution (--)

for the price of

x10 less signal (-)

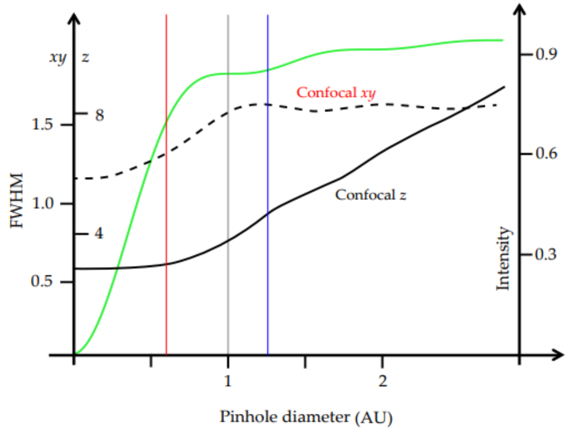
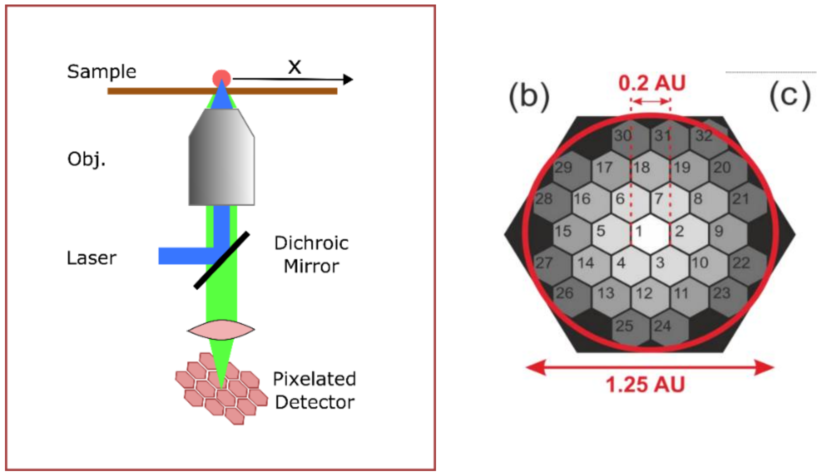


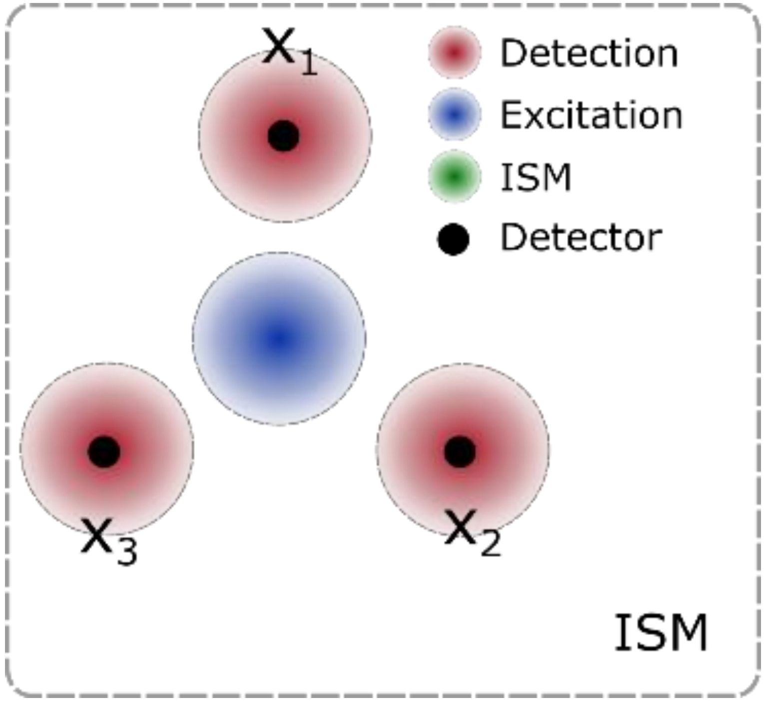
Image Scanning Microscopy \ Airy scan

- Exchange pinhole with a detector array
- Scan sample
- Shift images and sum

A pixelated confocal detector



$$P_{signal} = P_{excitation} \cdot P_{detection}$$



Sheppard, C. J. R. *Optik (Stuttg).* **80,** 53–54 (1988)
Muller and Enderline, *PRL*, 2010

Image Scanning Microscopy \ Airy scan

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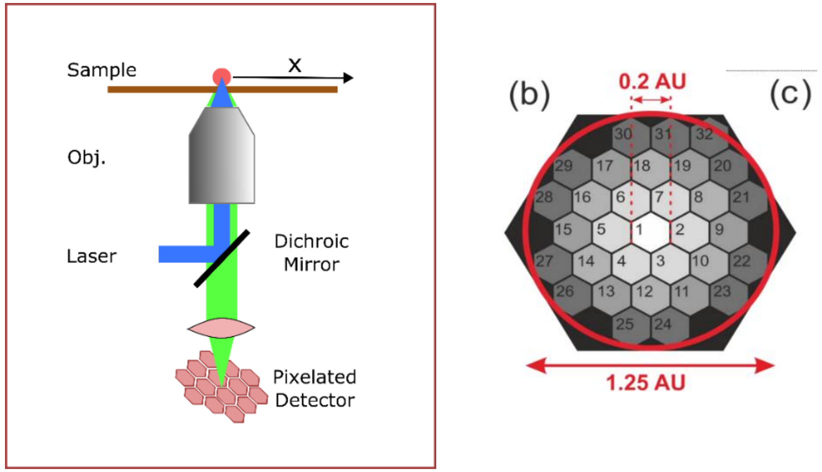
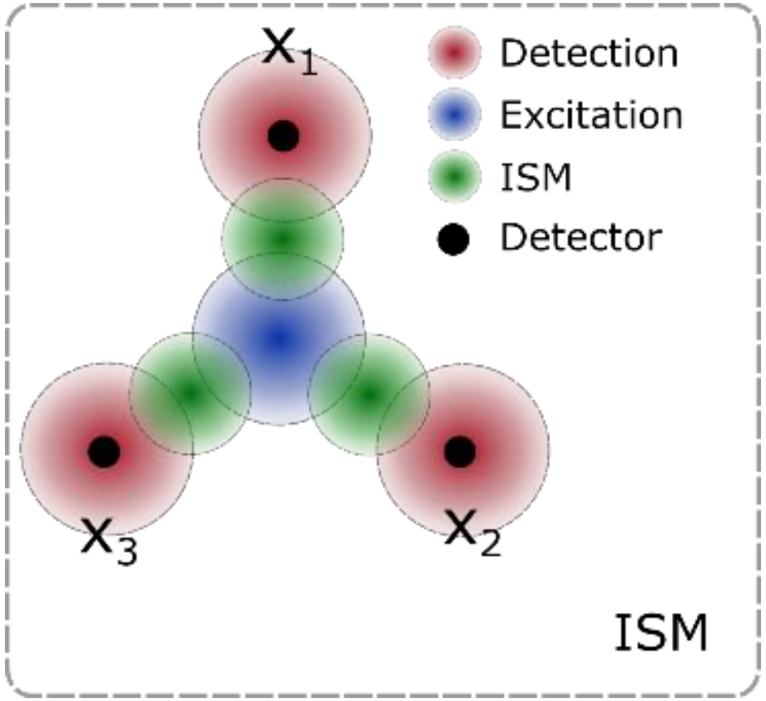
A pixelated confocal detector





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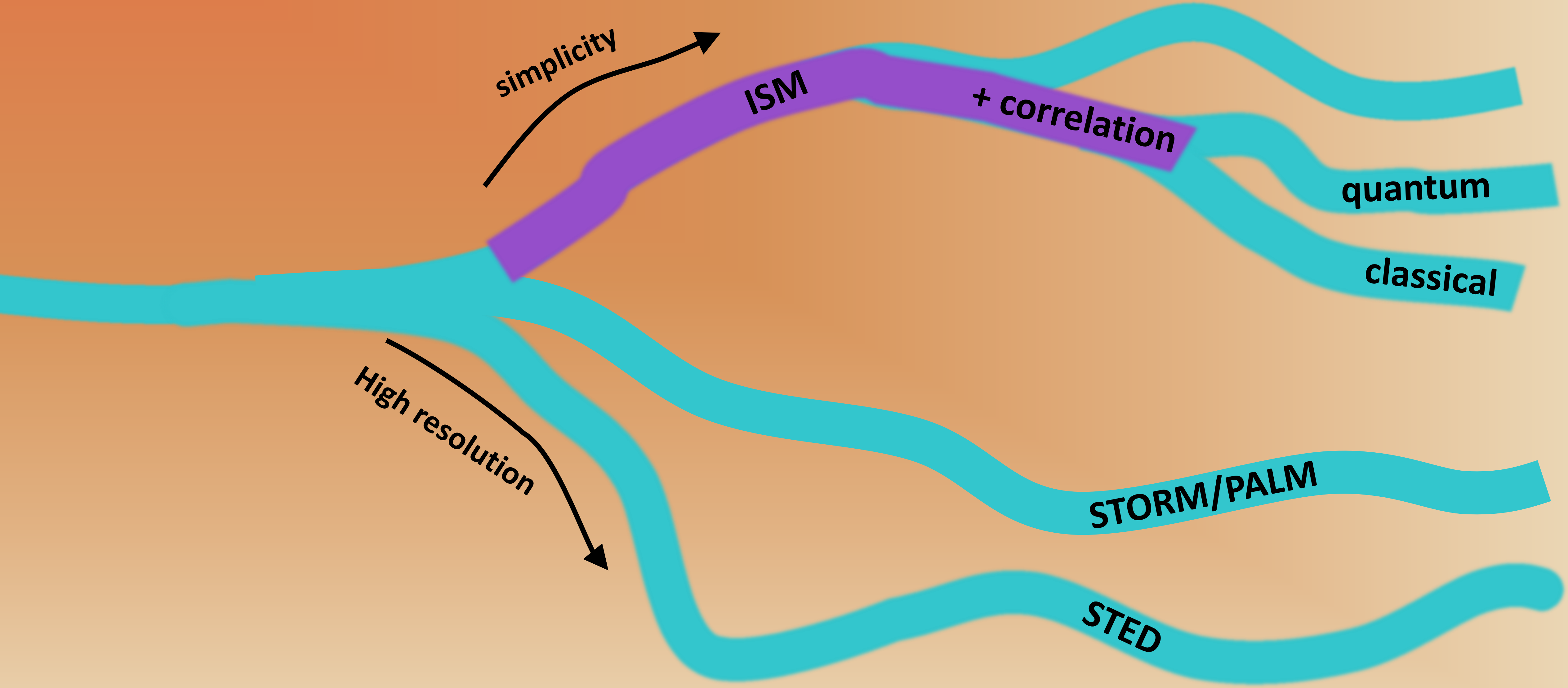
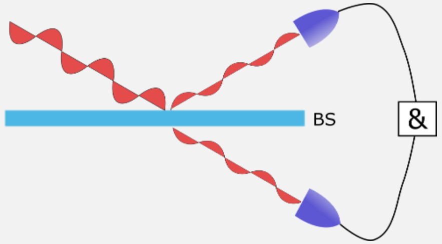
Super-resolution “flow chart”



Temporal correlation: bunching and antibunching

Hanbury-Brown and Twiss setup



$$g^{(2)}(\tau) = \frac{\langle I(t)I(t+\tau)\rangle}{\langle I(t)\rangle^2}$$

Bunching

Intensity fluctuations

$$g^{(2)}(\tau) > 1$$

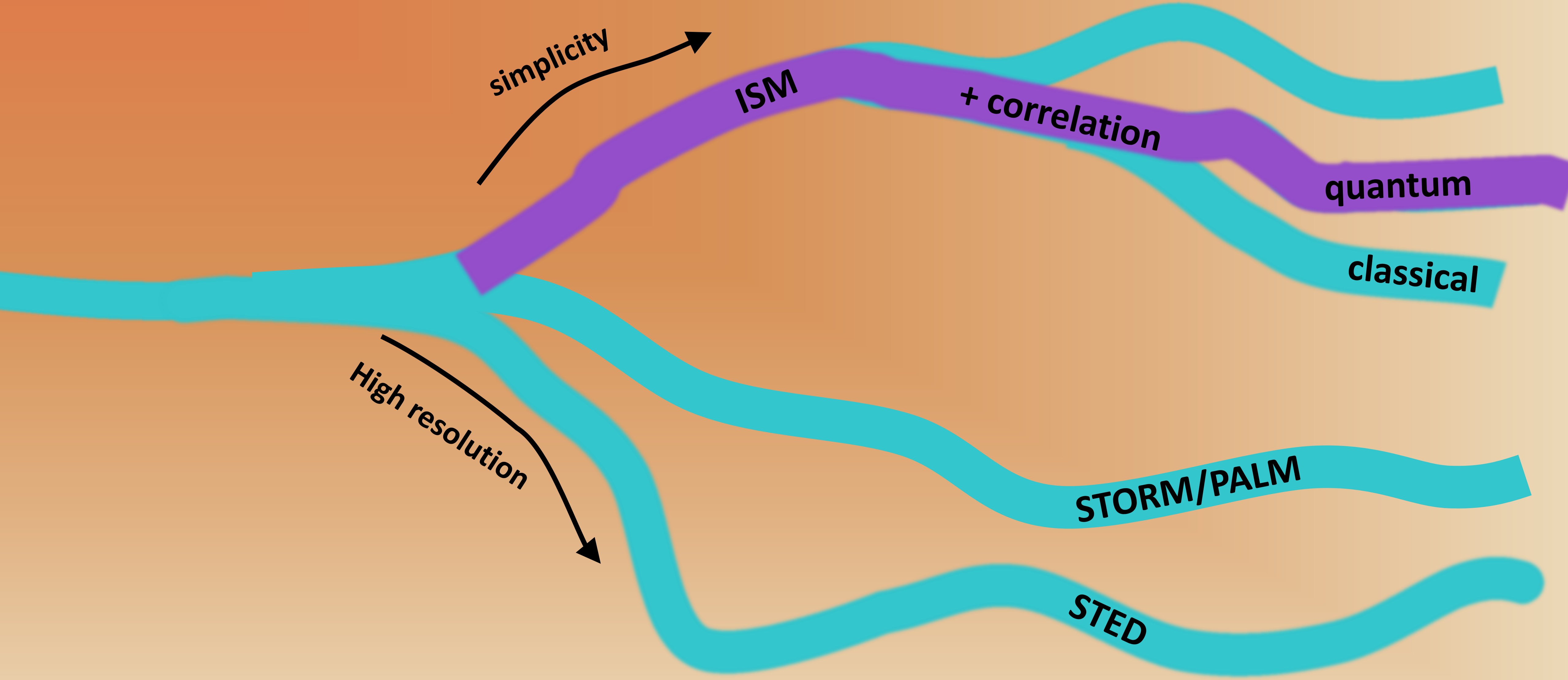
Antibunching

Single photon emitters

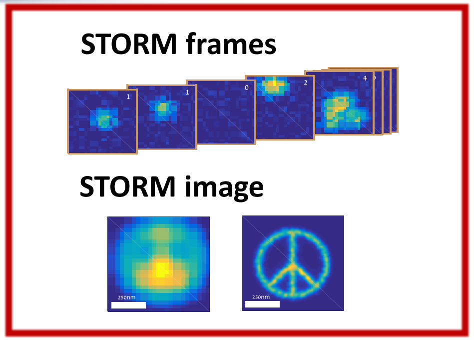
$$g^{(2)}(\tau) < 1$$

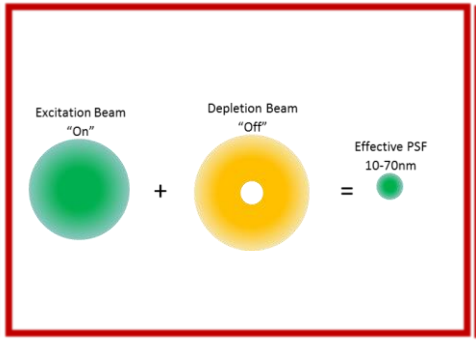
A strictly quantum phenomenon

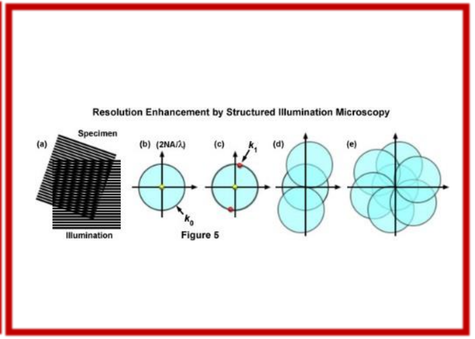
Super-resolution “flow chart”



Breaking the limit – Super-resolution at a glance





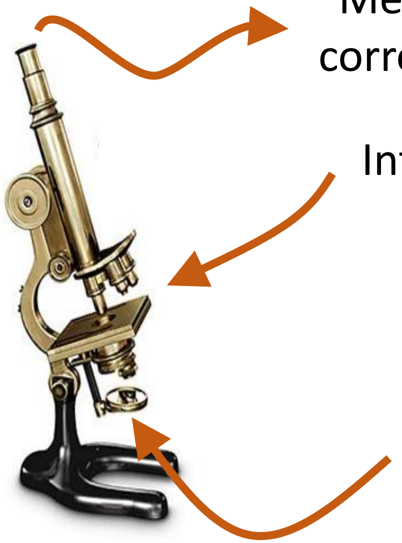


Assumptions:

	PALM\STORM	STED	SIM\ISM
• Linear response	✓ ✗	✗	✓
• Uniform illumination	✓	✗	✗
• Far-field detection	✓	✓	✓
• Time independent image	✗	✓	✓
• Classical light	✓	✓	✓

Can quantum optics contribute?

The promise of quantum optics for microscopy



Measure correlation

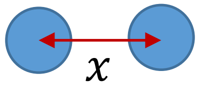
Interact with sample

Shine a quantum state of light

- Phase sensitivity
- Absorption sensitivity
- Quantum lithography

Boto,…,Dowling, *PRL* **85** (2000)
Brida,…., Berchera, *Nat. Photonics*, **4** (2010)
Ono,…,Takeuchi, *Nat. Comm.* **4** (2013)
Israel,…,Silberberg, *PRL* **112** (2014)
Toninelli,…,Padgett, *Optica* **6** (2019)

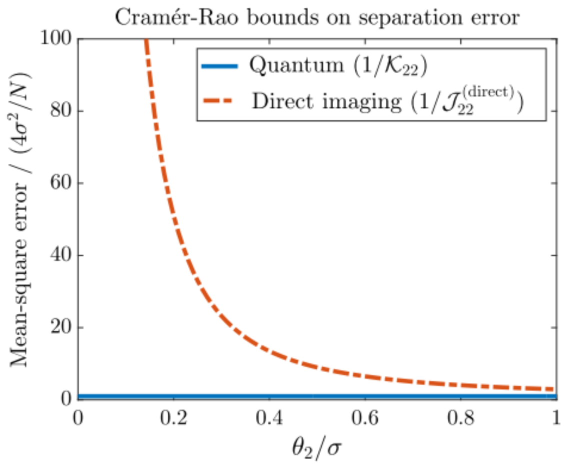
What is the minimal δx (CRLB)?



Classical: 'Explodes' for low x

Quantum: Constant shot noise

δx



x

Tsang et al, PRX 6 (2016)
Demkowicz-Dobrzański, *PRL* **121** (2018)

A ubiquitous quantum state of light

Classical light source **Quantum emitter**

Dye molecules

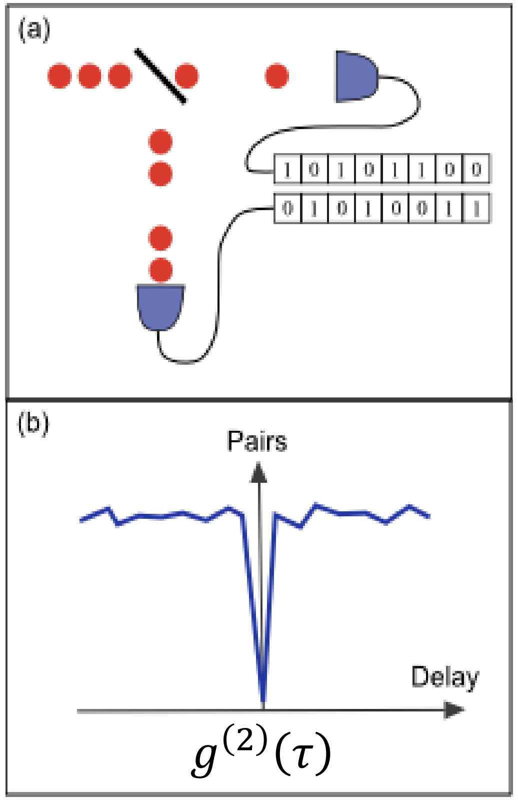
Quantum dots

Solid state defects

Atoms

Some proteins

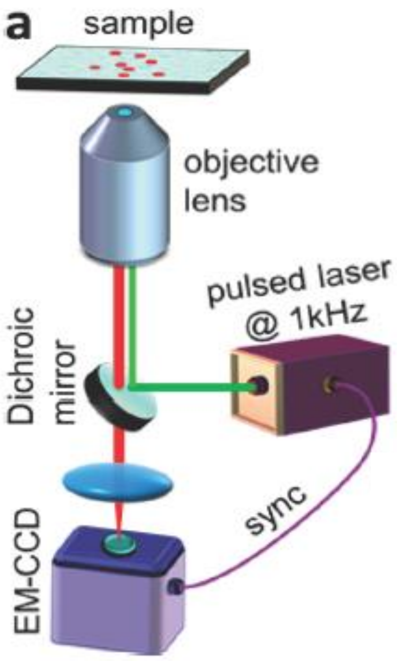
Single photon at a time



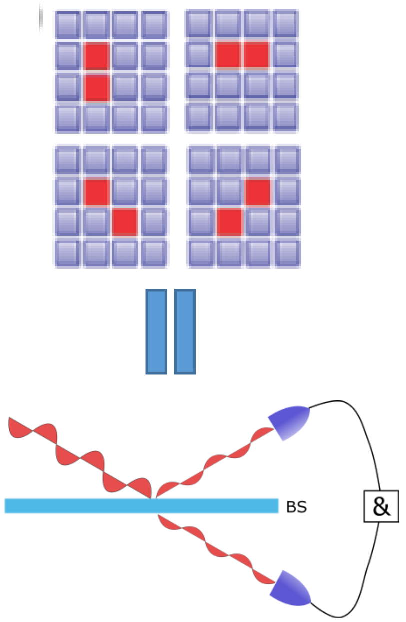
Antibunching

Quantum correlations measured with a camera

Measure single photons with a camera



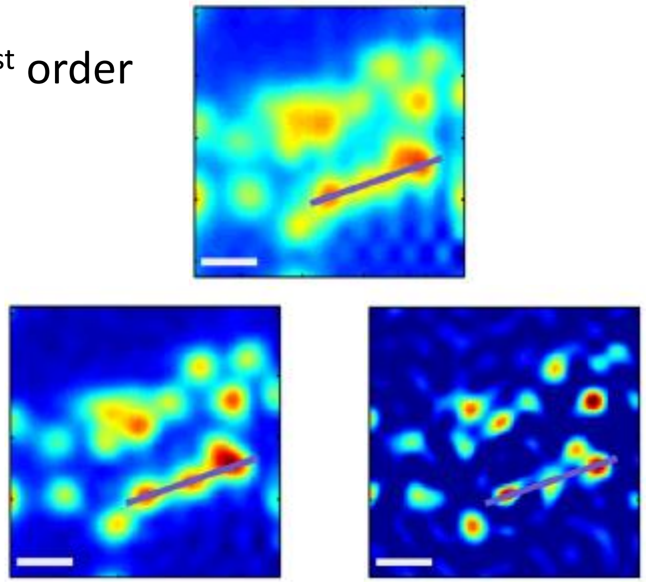
Correlate neighboring pixels

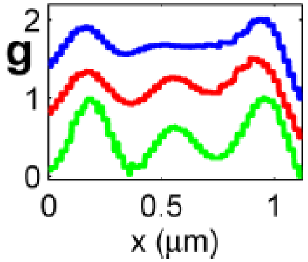


1st order

2nd order

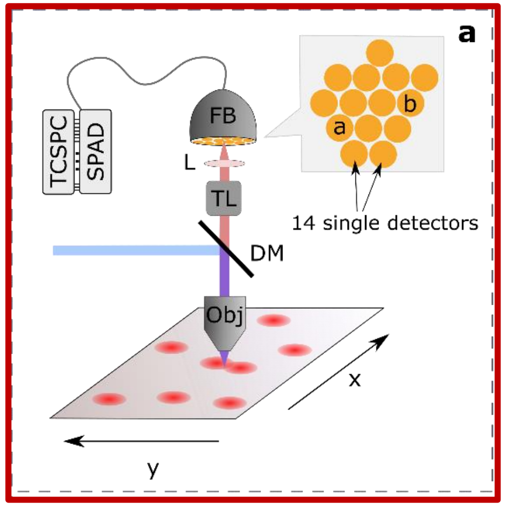
3rd order



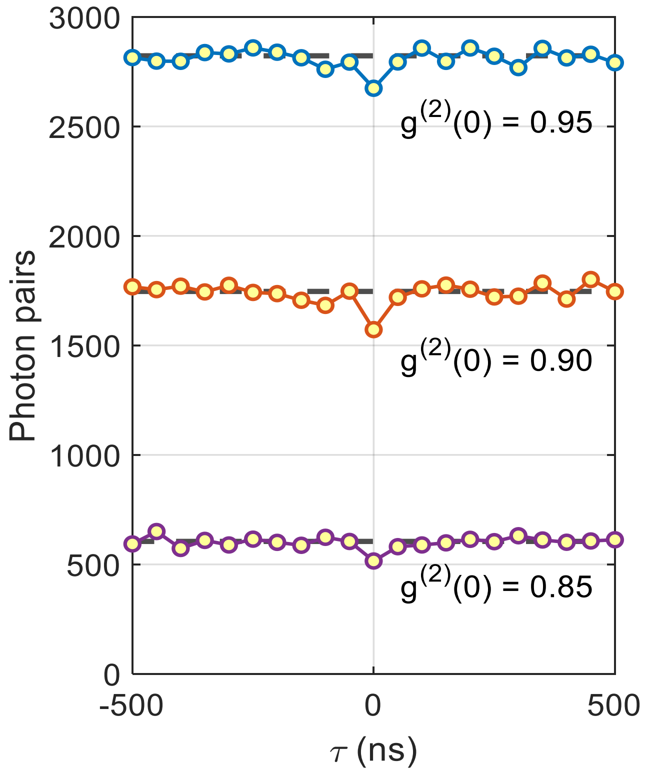


O. Schwartz, J. M. Levitt, RT, S. Itzhakov, Z. Deutsch, and D. Oron, *Nano Lett.,* 13 (2013),

Q-ISM: 4 times resolution enhancement

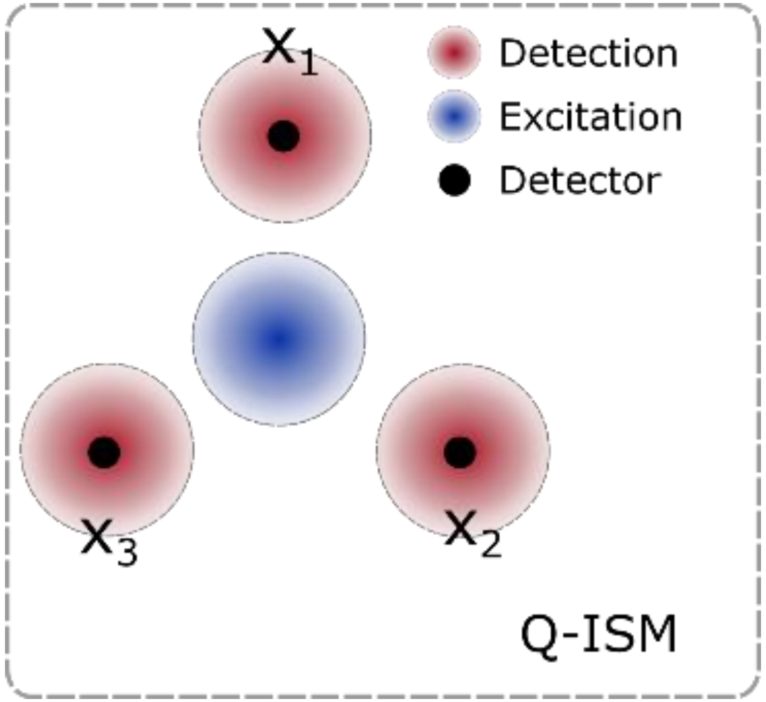


Each emitter is a source of 'missing' photon pairs



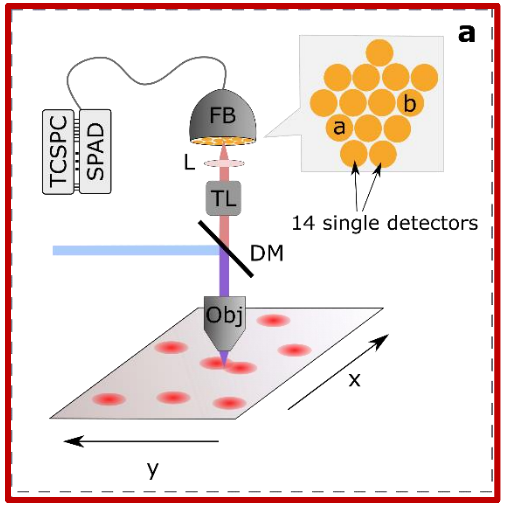
$$P_{G2} = (P_{excitation})^2 \cdot P_{det}(x_1) \cdot P_{det}(x_2)$$

4X resolution enhancement



RT*, Rossman*, Rephael* *et al*, Nature Photonics 13, 116 (2019)

Q-ISM: 4 times resolution enhancement



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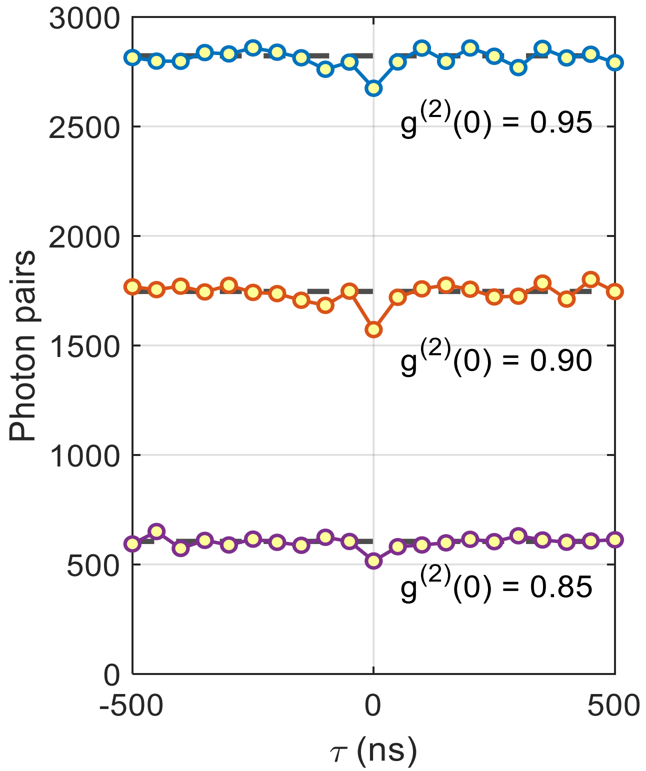

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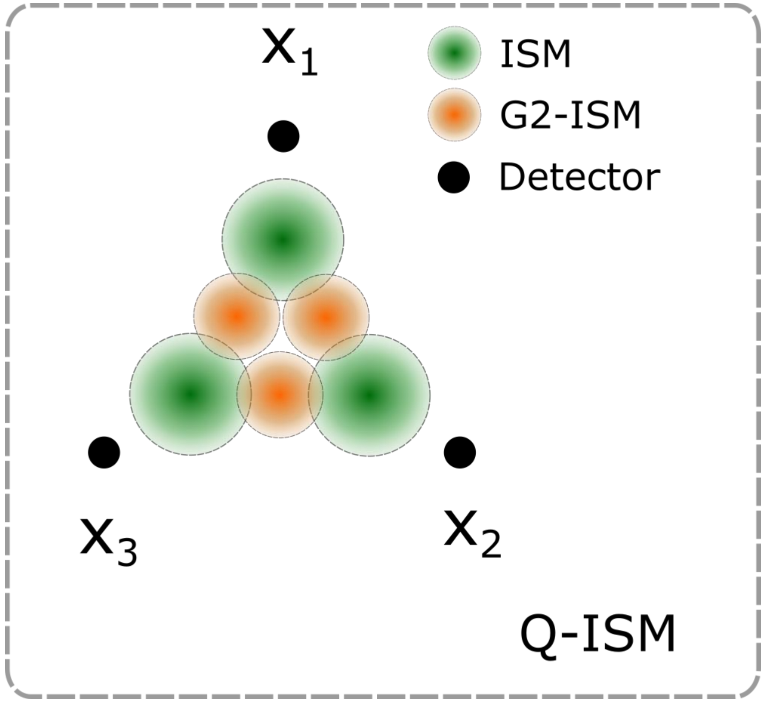
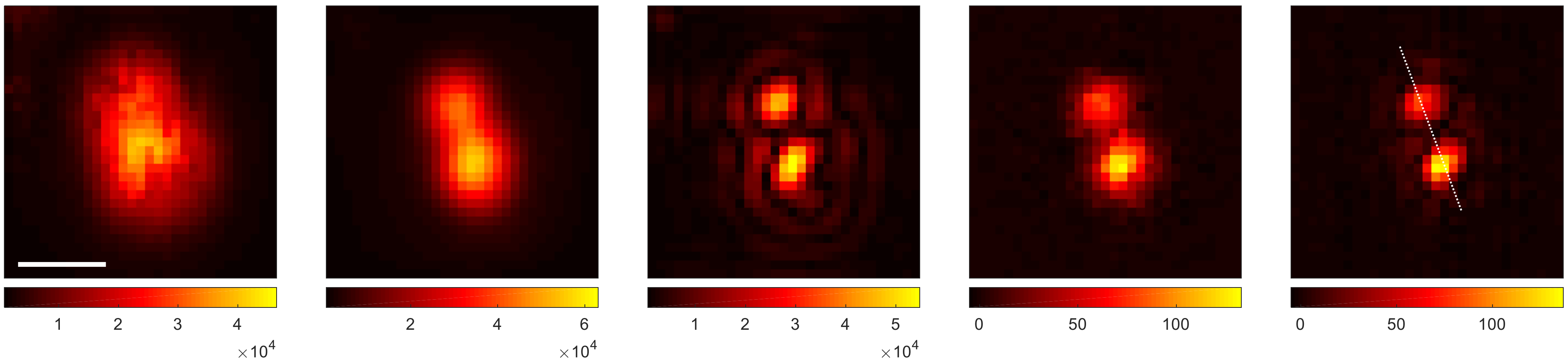
4X resolution enhancement

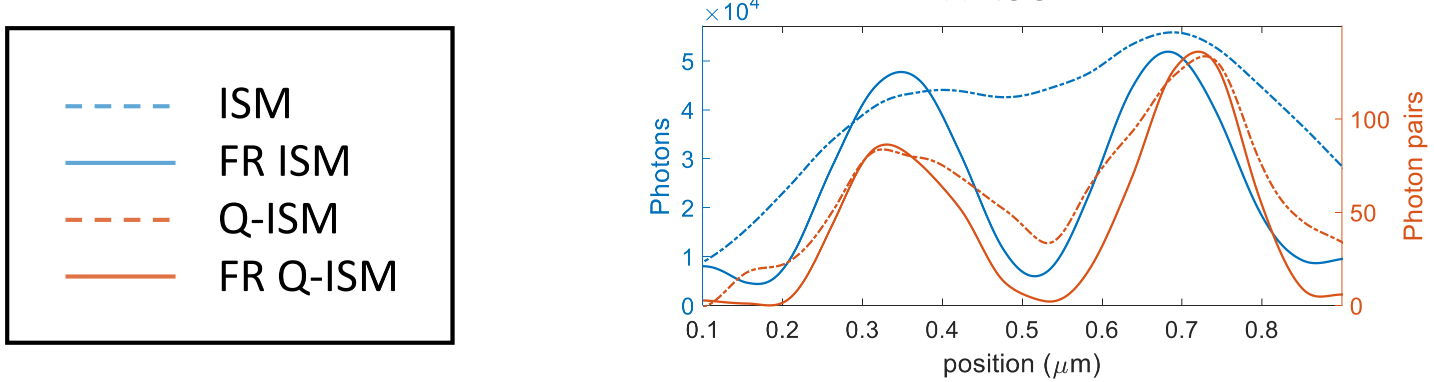


RT*, Rossman*, Rephael* *et al*, Nature Photonics 13, 116 (2019)

Q-ISM: Transverse (xy) resolution demonstration



	*Confocal	ISM	**FR ISM	Q-ISM	FR Q-ISM
Resolution	~450 nm	~350 nm	~230 nm	~260 nm	~190 nm
Enhancement	x1	X1.3	X1.95	X1.7	X2.4



* Scale bar: $0.25\mu m$

** FR = Fourier Reweighting

RT*, Rossman*, Rephael* *et al*, Nature Photonics 13, 116 (2019)

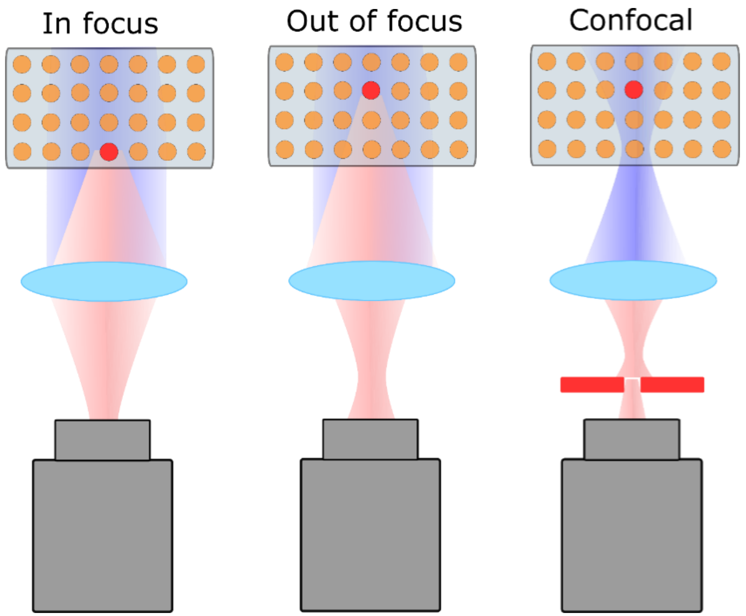
Q-ISM: Axial (z) resolution demonstration

Widefield

In focus and out of focus planes contribute equally

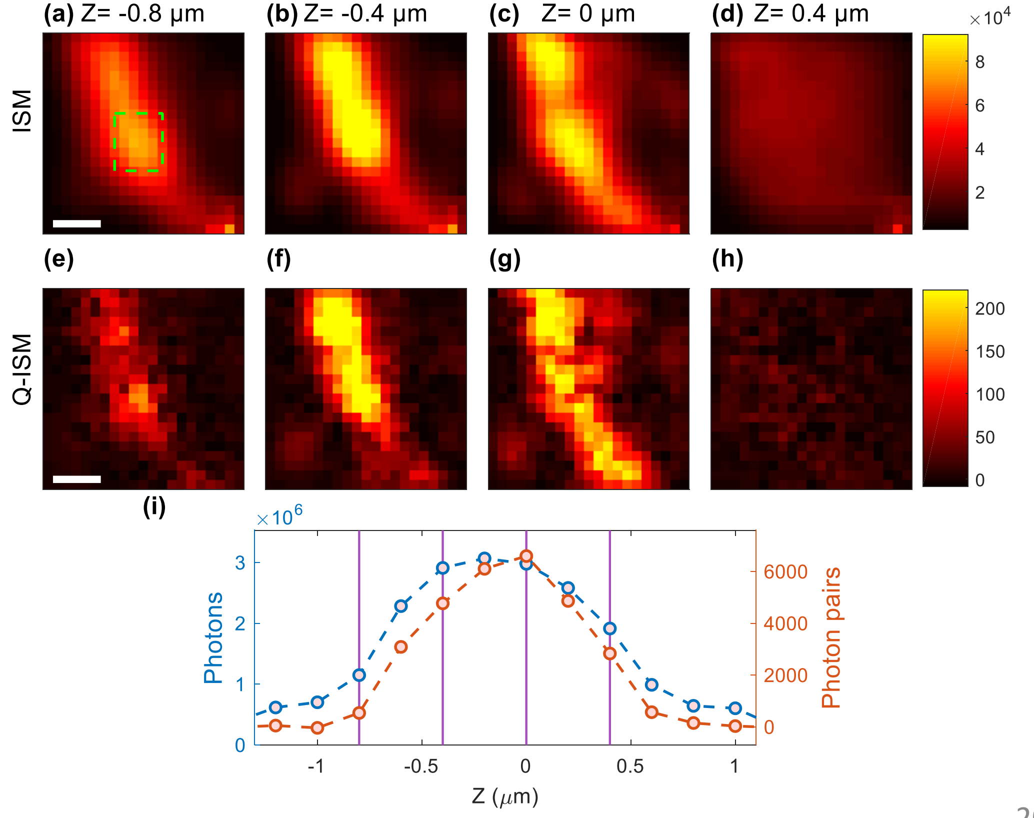
Confocal

$$P_{signal} = P_{excitation} \cdot P_{detection} \propto \frac{1}{z^2}$$

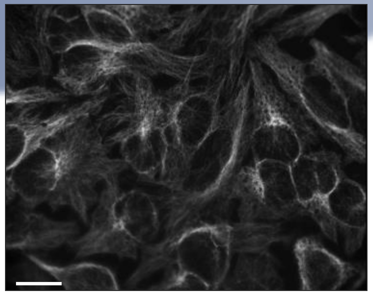


Q-ISM

$$P_{G2} = (P_{excitation})^2 \cdot P_{det}(x_1) \cdot P_{det}(x_2) \propto \frac{1}{z^6}$$

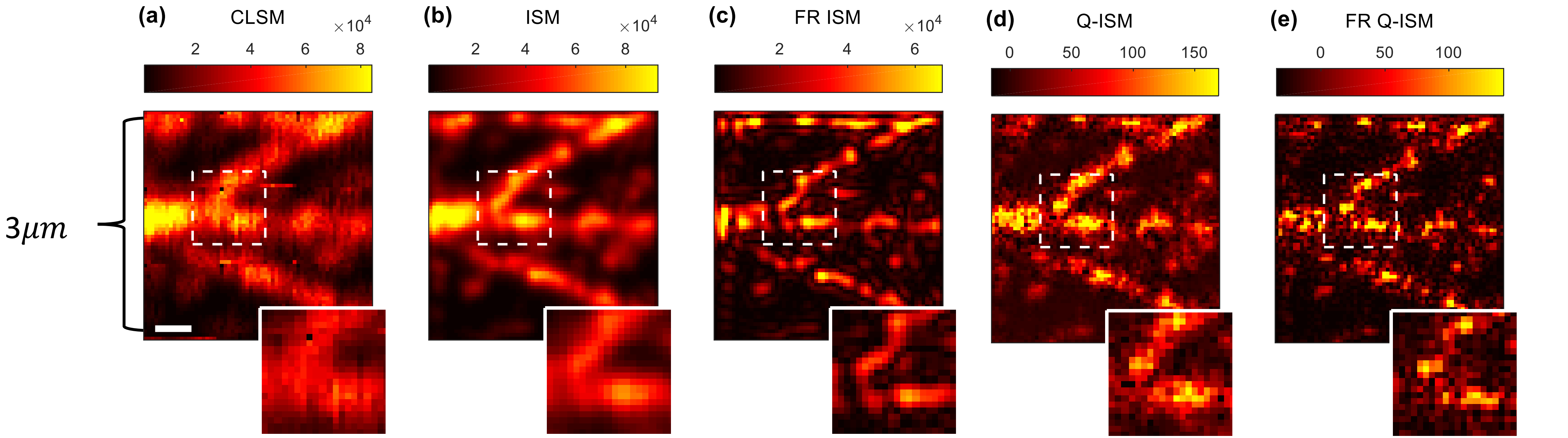


A quantum effect in a biological sample



Widefield fluorescence imaging

3T3 cells. Micro-tubules labeled with quantum dots

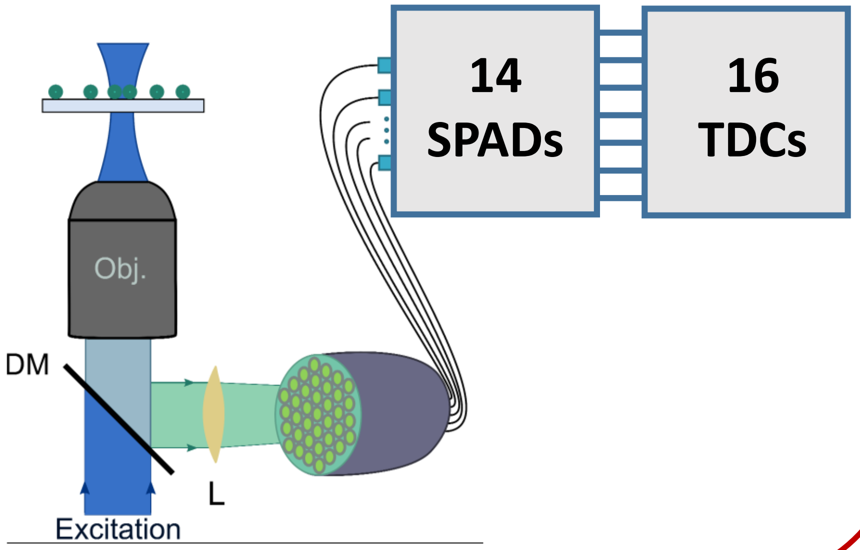


Samples courtesy of Prof. Yuval Ebenstein, TAU

RT*, Rossman*, Rephael* *et al*, Nature Photonics 13, 116 (2019)

From expensive and cumbersome to SPAD arrays

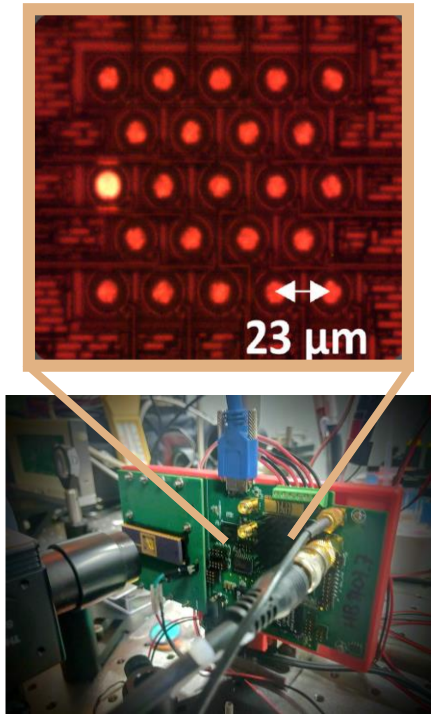
- Image on fiber bundle
- Individual SPADs
- A separate TDC card



Israel, RT *et al., Nat. Comm.*, **8**, (2017)

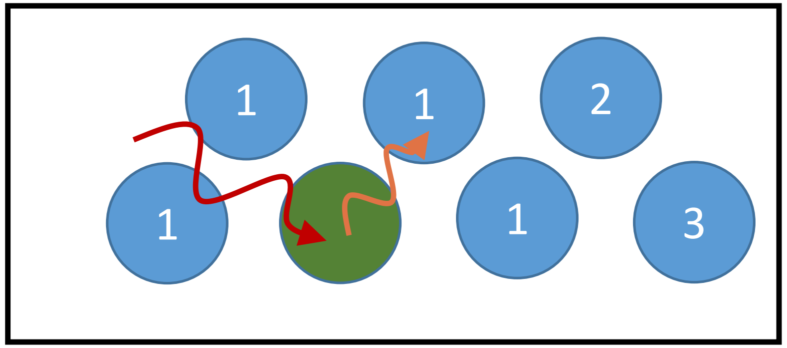
- SPAD 23
- ~50% max PDP
- FPGA time-stamping

EPFL, AQUA lab

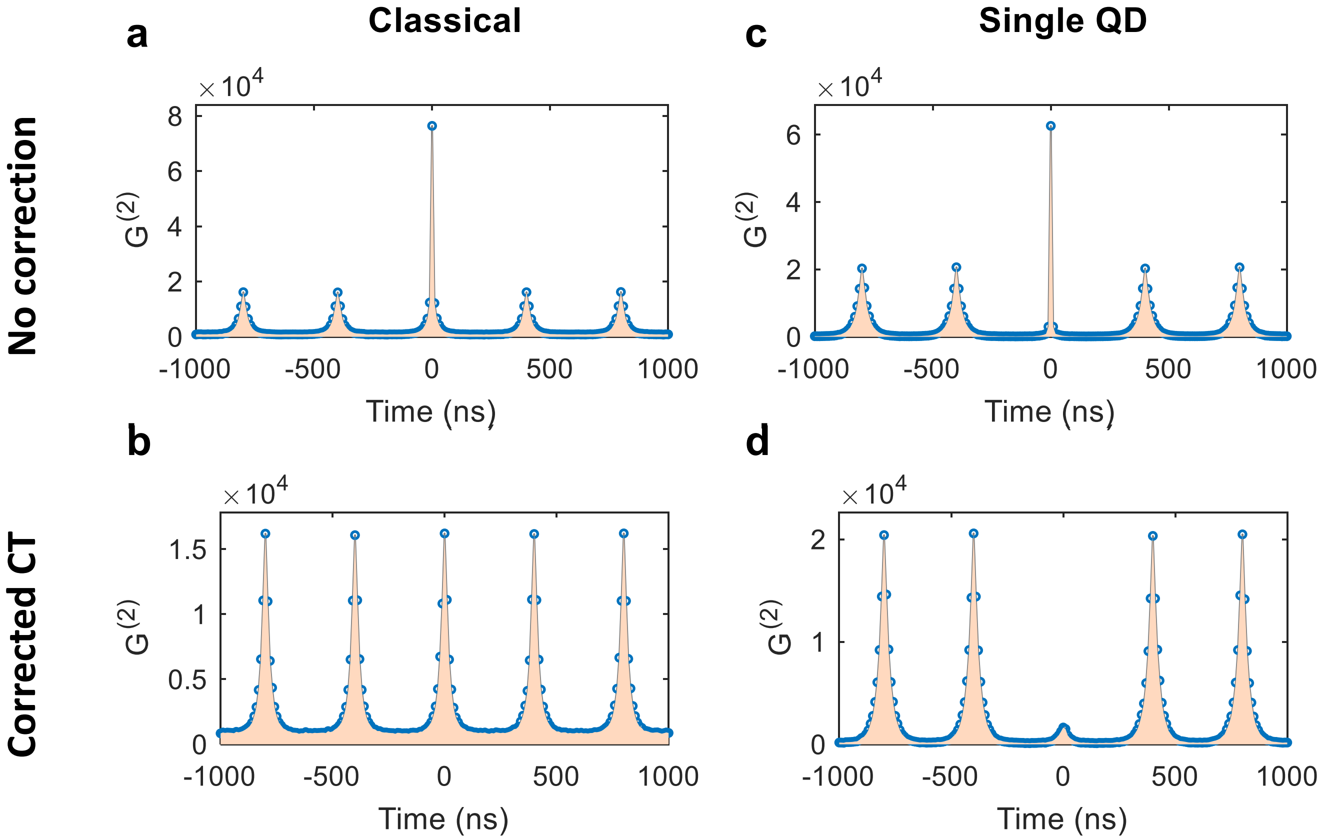


Bruschini *et al.*, *Light: Science & Applications* **8**, 87 (2019)
Antolovic *et al.*, *Opt. Exp.*, **26**, 17 (2018)

HBT with an on-chip SPAD array

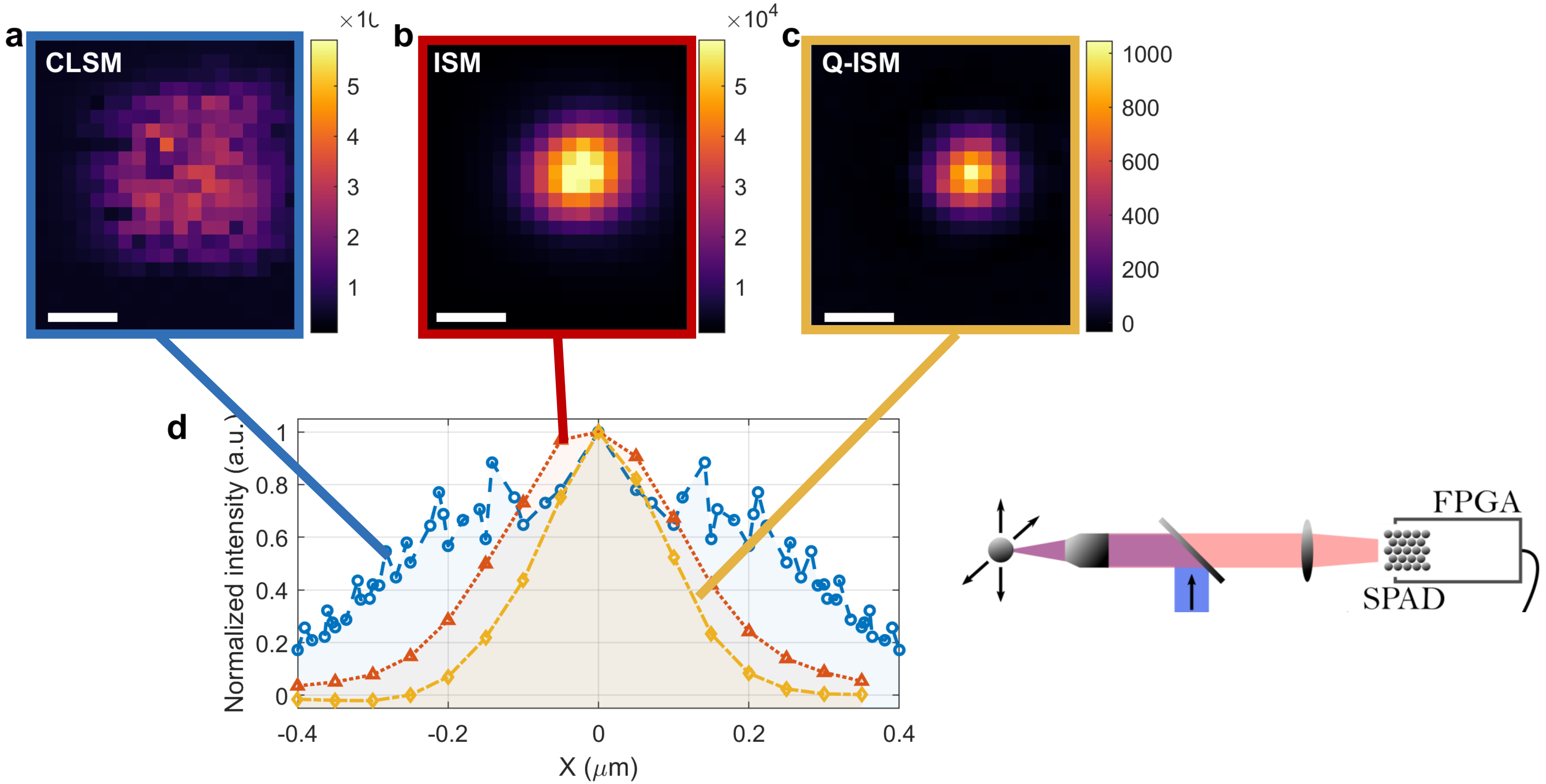


False positive
zero delay pair



Lubin*, RT*, Antolovic* *et al.,* Opt. Express 27.23 (2019)

Q-ISM with a SPAD array



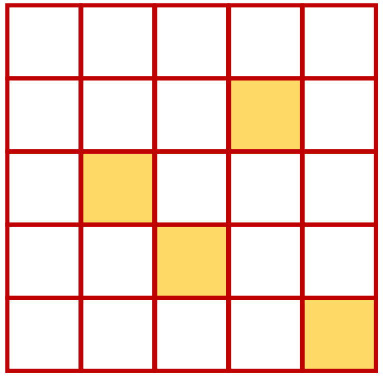
Lubin*, RT*, Antolovic* *et al.,* Opt. Express 27.23 (2019)

Can we join forces? Sparsity reconstruction

Image similarity

sparsity

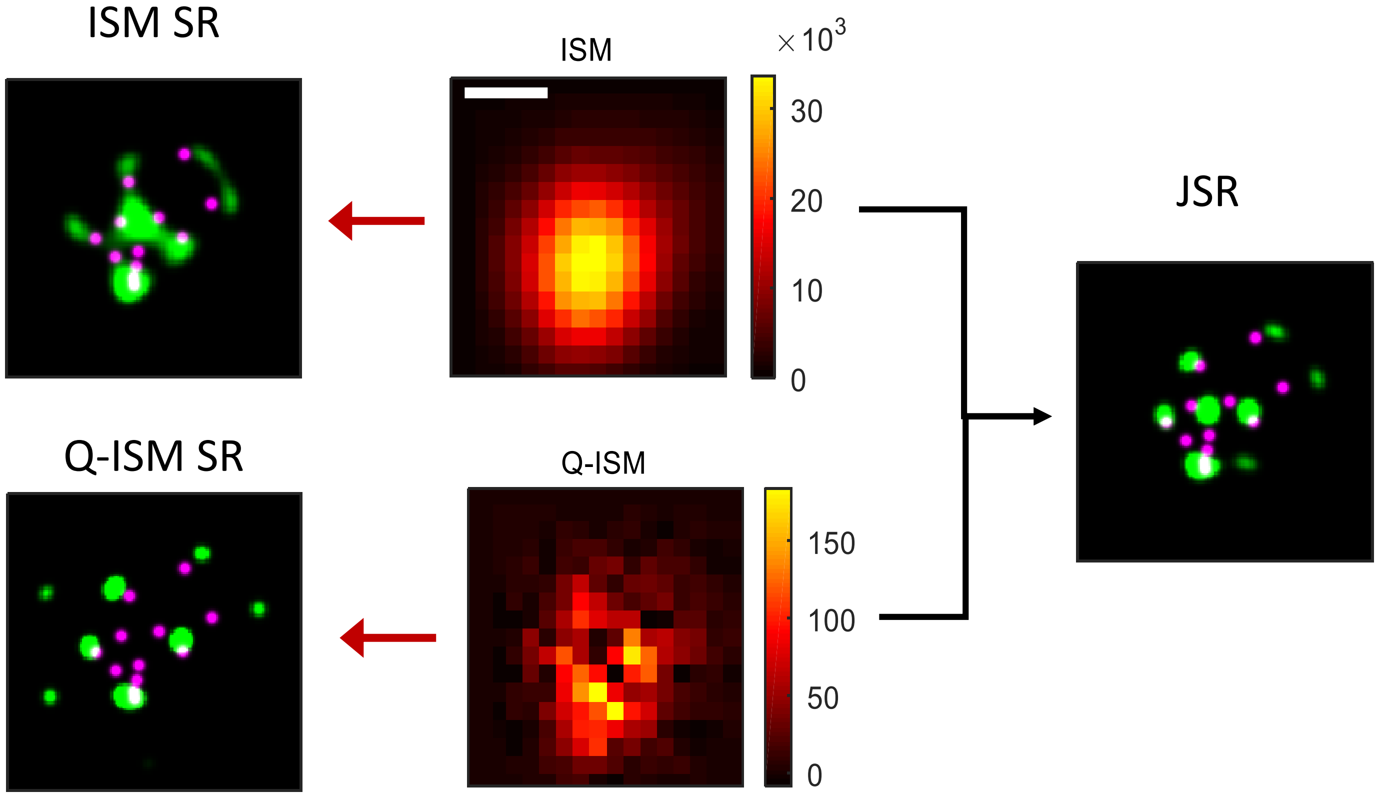
$$\min_{x}\{\|Ax - y\|_2^2 - \lambda\|x\|_1\}$$



$\boldsymbol{x}$

$\boldsymbol{A}$ – dictionary (conv with PSF)

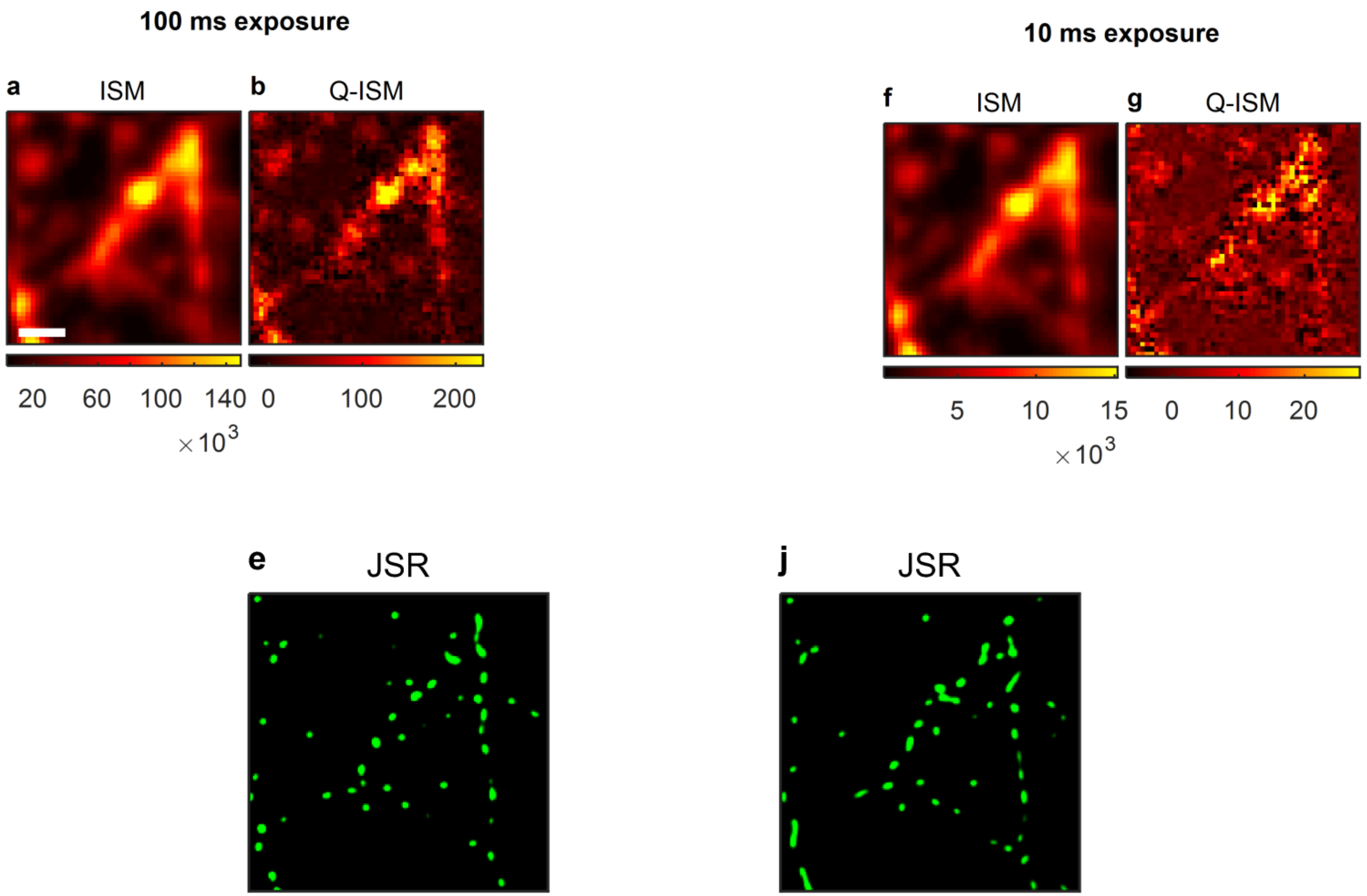
$$\min_{x_1, x_2}\{\|A_1x_1 - y_1\|_2^2 + \eta\|A_2x_2 - y_2\|_2^2 + \lambda\|X\|_{2,1}\}$$



Rossman, RT *et al*, Optica 6 (2019)

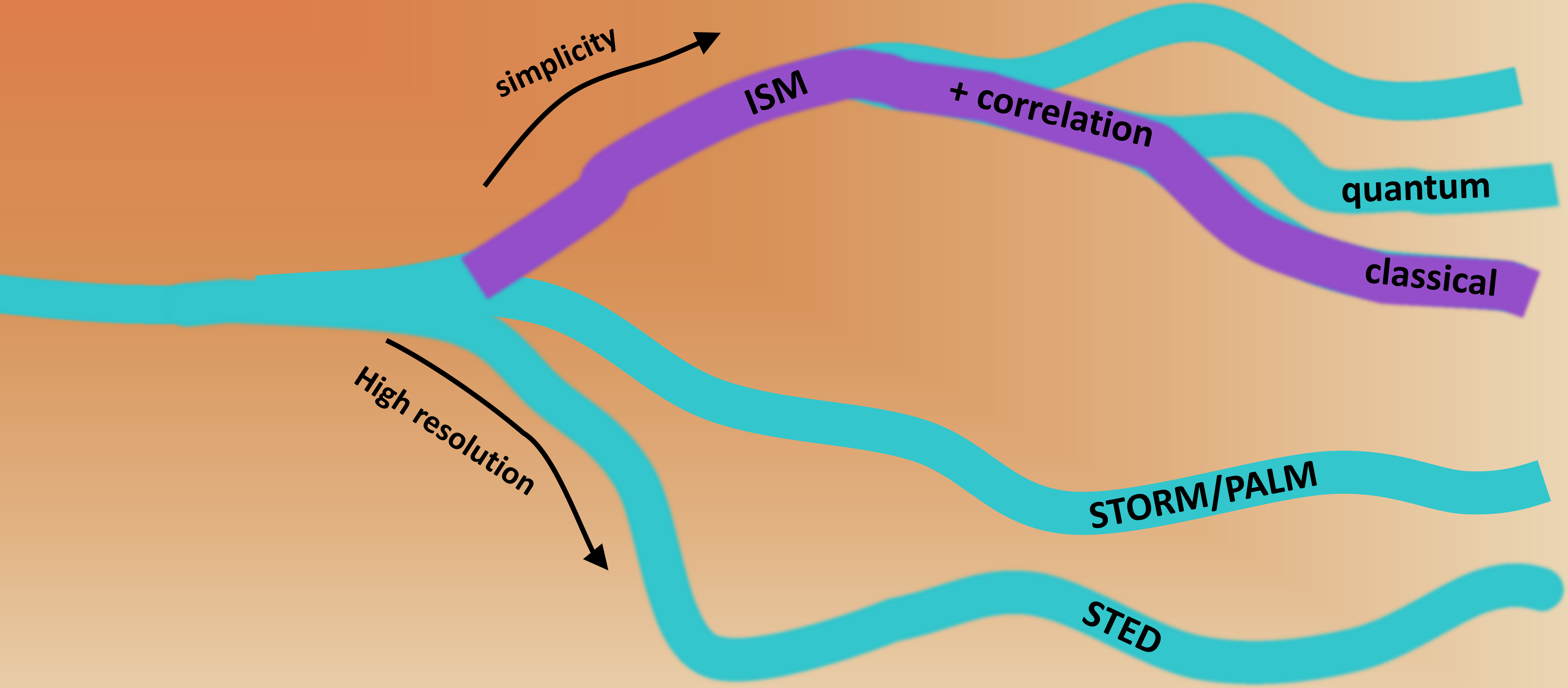
In collaboration with Yonina Elder, Weizmann

Reconstruction of a cell sample



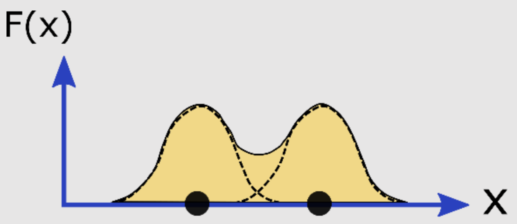
Rossman, RT *et al*, Optica 6 (2019)

Super-resolution "flow chart"



SOFI: Using emitter fluctuations

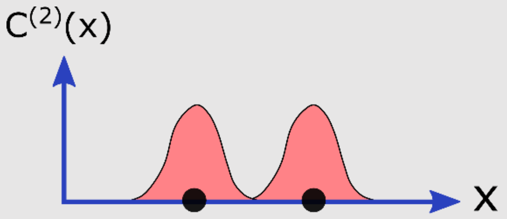
PL image



$$F(x)=F(x+x_0)+F(x-x_0)$$

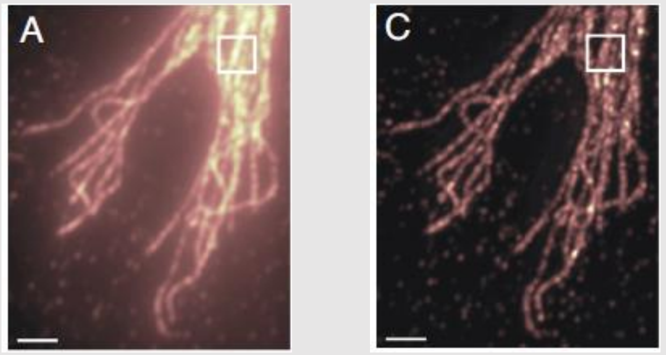
SOFI image

$$C^{(2)}(x) = \langle (F(x,t) - \langle F(x) \rangle)^2 \rangle$$



$$C^{(2)}(x)=F(x+x0)^2+F(x-x0)^2$$

Detringer, …, Weiss, Enderlein, PNAS, 106, 52 (2009)



PL image **SOFI image**

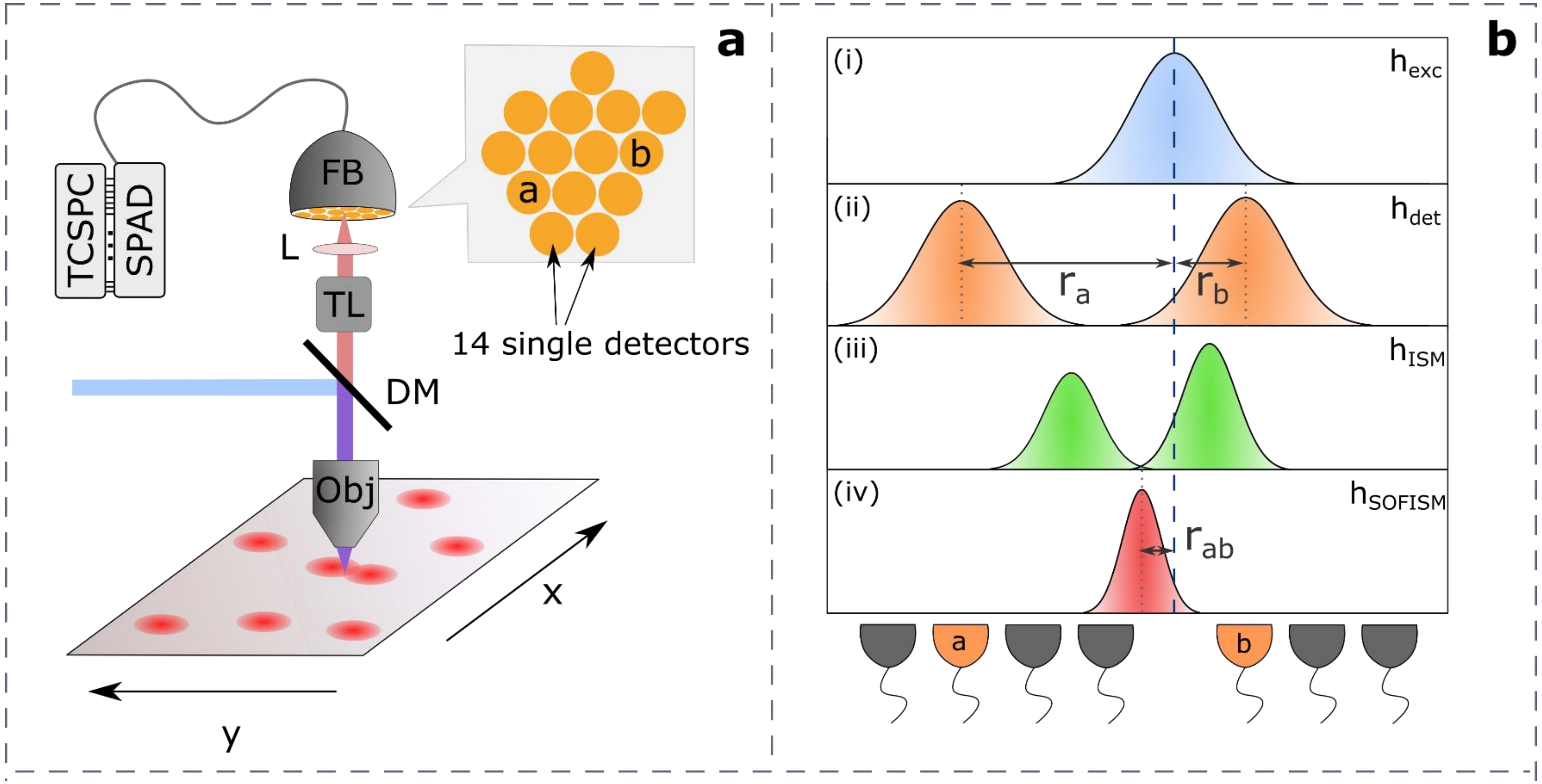
Not only with quantum dots

- **Dyes**
  (Dertinger *et al*, Ang. Chem., 49 (2010))
- **Fluorescent proteins**
  (Dedecker *et al*, PNAS, 109, (2012))

SOFI + ISM = SOFISM

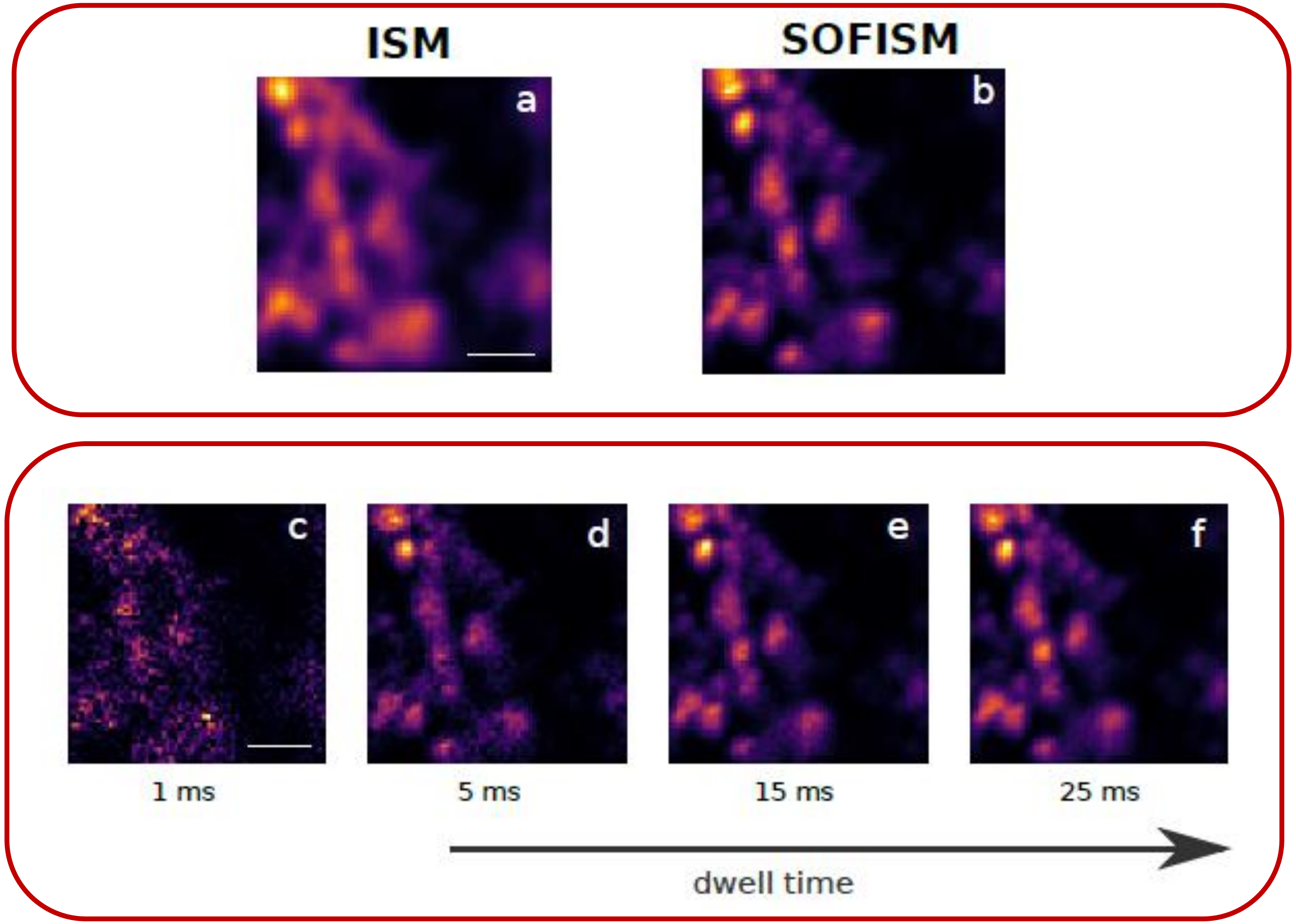
$$C^{(2)}(x) = \langle F_a(x,t) \cdot F_a(x,t) \rangle - \langle F_a(x,t) \rangle \langle F_b(x,t) \rangle$$

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



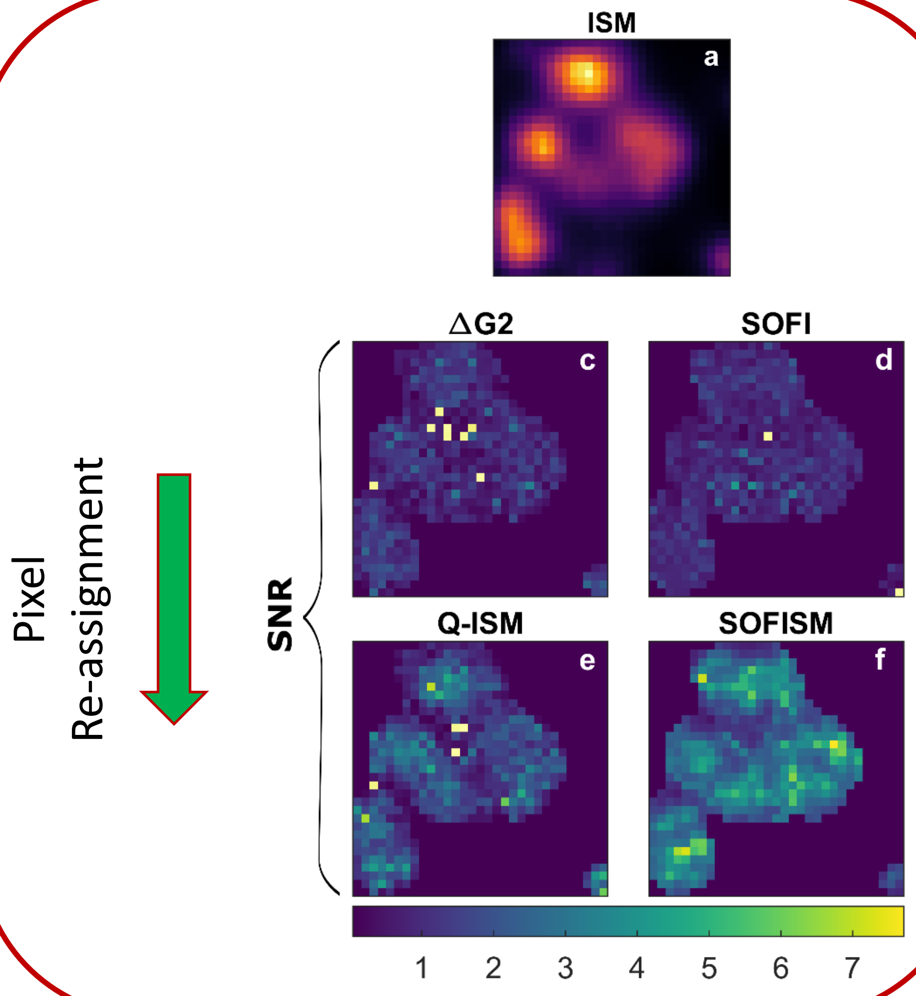
Sroda*, Makowski*, RT*,…,Lapkiewicz, arXiv, 2002.00182 (2020)

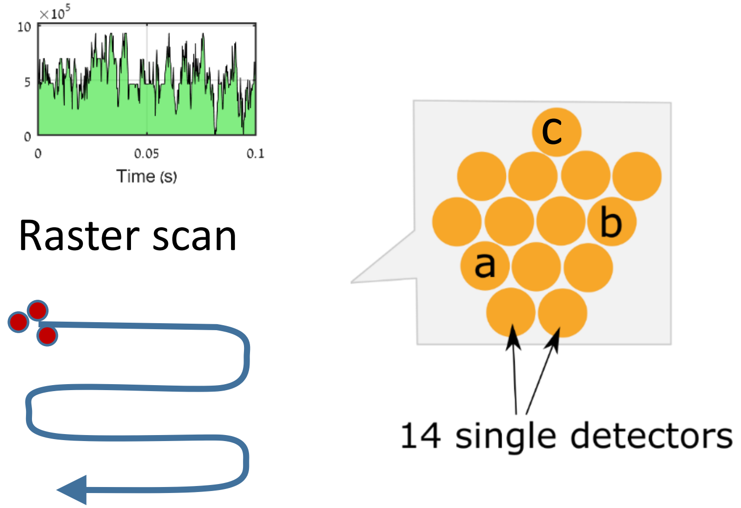
Same resolution shorter acquisition



Sroda*, Makowski*, RT*,…,Lapkiewicz, arXiv, 2002.00182 (2020)

Multiple detectors, multiple sampling periods



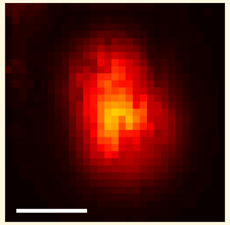


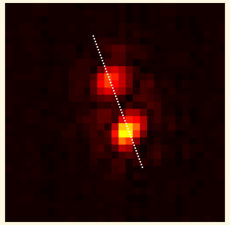
- Same scene observed by multiple detectors at different times
- Better sampling of $C^{(2)}(\tau)$
- ISM is critical for SOFI SNR

Sroda*, Makowski*, RT*,...,Lapkiewicz, arXiv, 2002.00182 (2020)

Summary

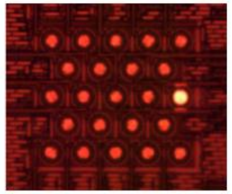
Image scanning microscopy

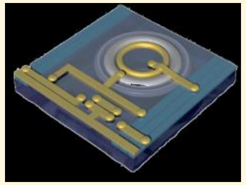




Photon correlation contrast in an image scanning microscopy scheme

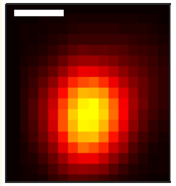
Photon correlation with a SPAD array

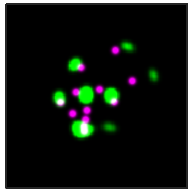




Measure photon correlation with a CMOS SPAD array

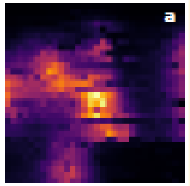
Joint sparsity reconstruction

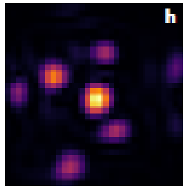




Algorithmic reconstruction from millisecond exposure, quantum and classical data

SOFI and ISM: coming together





Using classical fluctuations as the contrast of image scanning microscopy

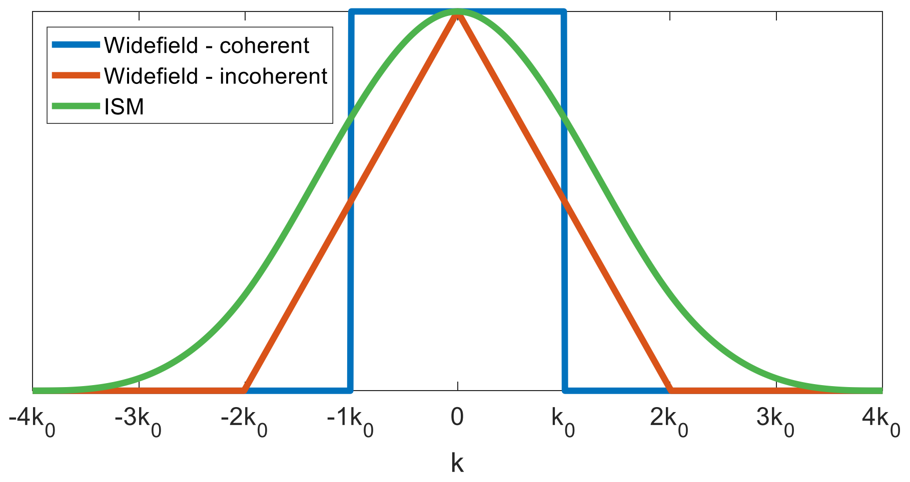
Fourier re-weighting (deconvolution)

The point spread function (PSF) of ISM

Real space $$h_{ISM}(x) = P_{excitation} \cdot P_{detection} = h_{in}(x) \cdot h_{in}(x) = h_{in}^{\mathbf{2}}(x)$$

Momentum space $$\tilde{h}_{ISM}(k) = h_{in}(k) * h_{in}(k)$$

1D PSF in momentum space

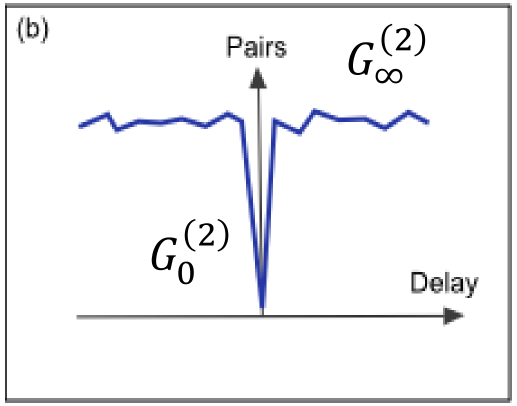


Counting the missing photon pairs

G2ISM

$$G_{AB}^{(2)}(x) = G_{\infty}^{(2)}(x) - G_{0}^{(2)}(x) =$$

$$= \sum_{i=1}^{n} [h_e(x_i - x_s)]^2 \cdot [h_{im}(x_i - x_s)]^2$$

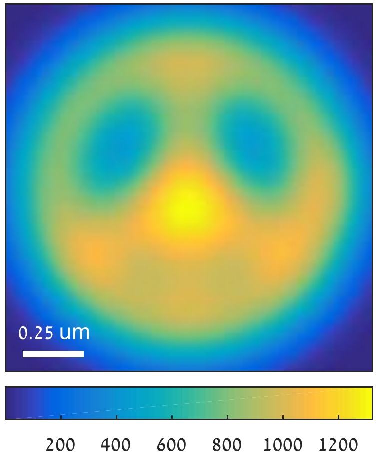


Simulated

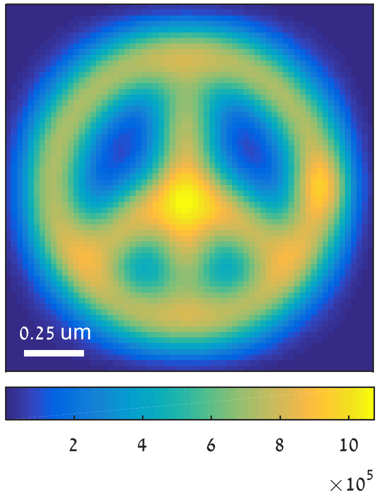
66 QDs. 25nm, 250msec steps.

Including dark current and Poissonian noise

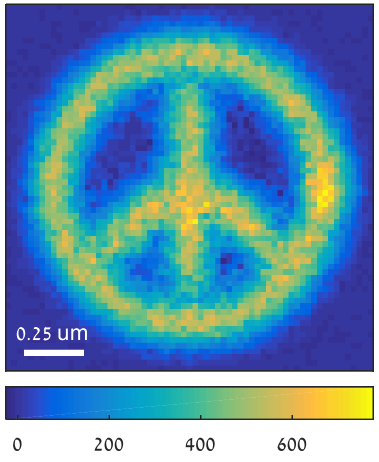
Widefield

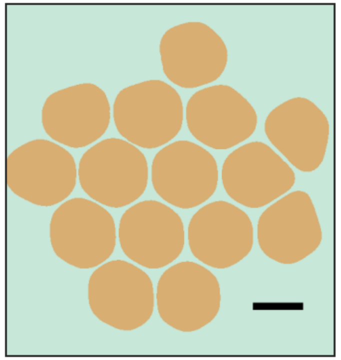


ISM



G2ISM

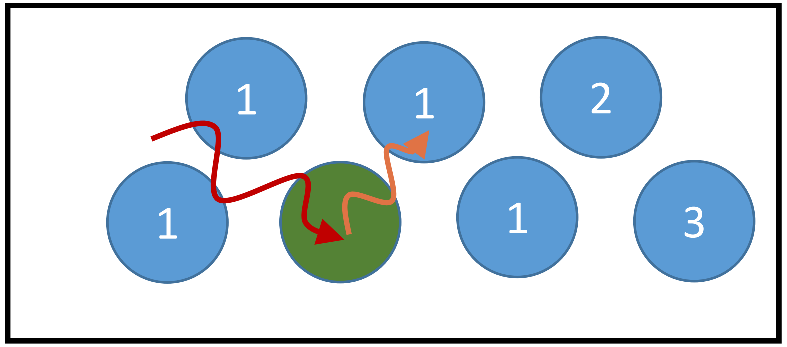




HBT with an on-chip SPAD array

Main challenge:

Optical cross-talk

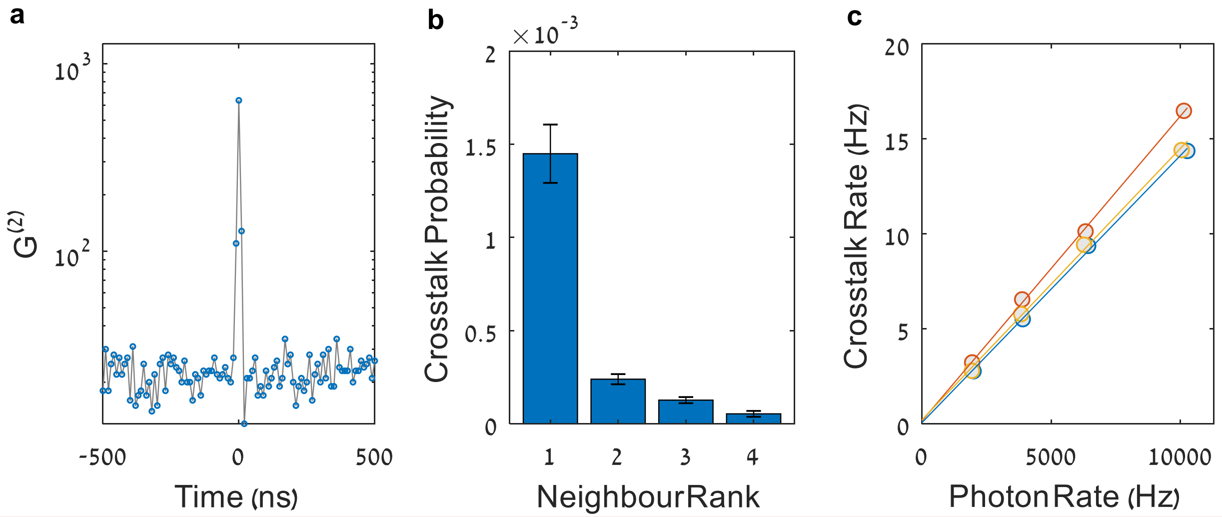


False positive zero delay pair

Hesong Xu et al. Procedia Engineering 87 (2014)

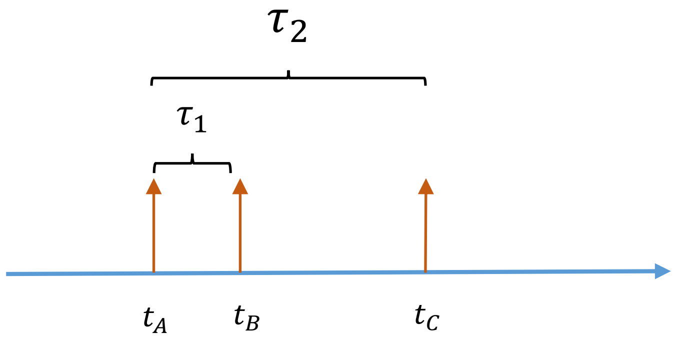
Nearest neighbor cross-talk

$\sim 1.5 \cdot 10^{-3}$



Higher order HBT with one port

Three photon events



$$\tau_1 = t_B - t_A$$

$$\tau_2 = t_C - t_A$$