

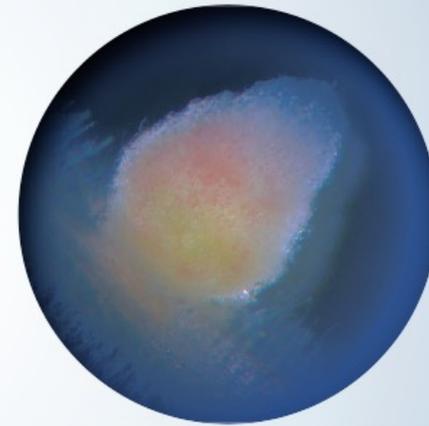
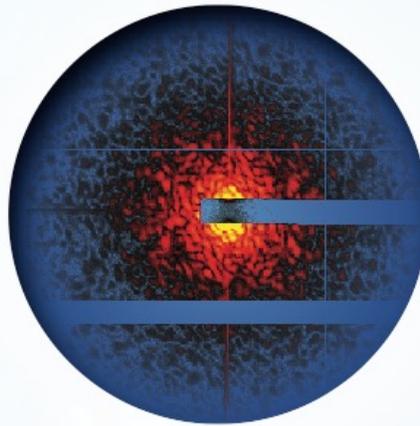
# Toward a Quantum Enhanced Microscope for Imaging Biological Systems

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Supported through DoE-BER Bioimaging Science Program  
<https://science.osti.gov/ber/Research/bssd/BCIS>

# A QUANTUM ENHANCED X-RAY MICROSCOPE



Andrei  
Flurasu  
Exptl.  
Design



Andrei  
Nomerotsk  
i,  
Detectors



Cinzia da  
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Materials



Frank  
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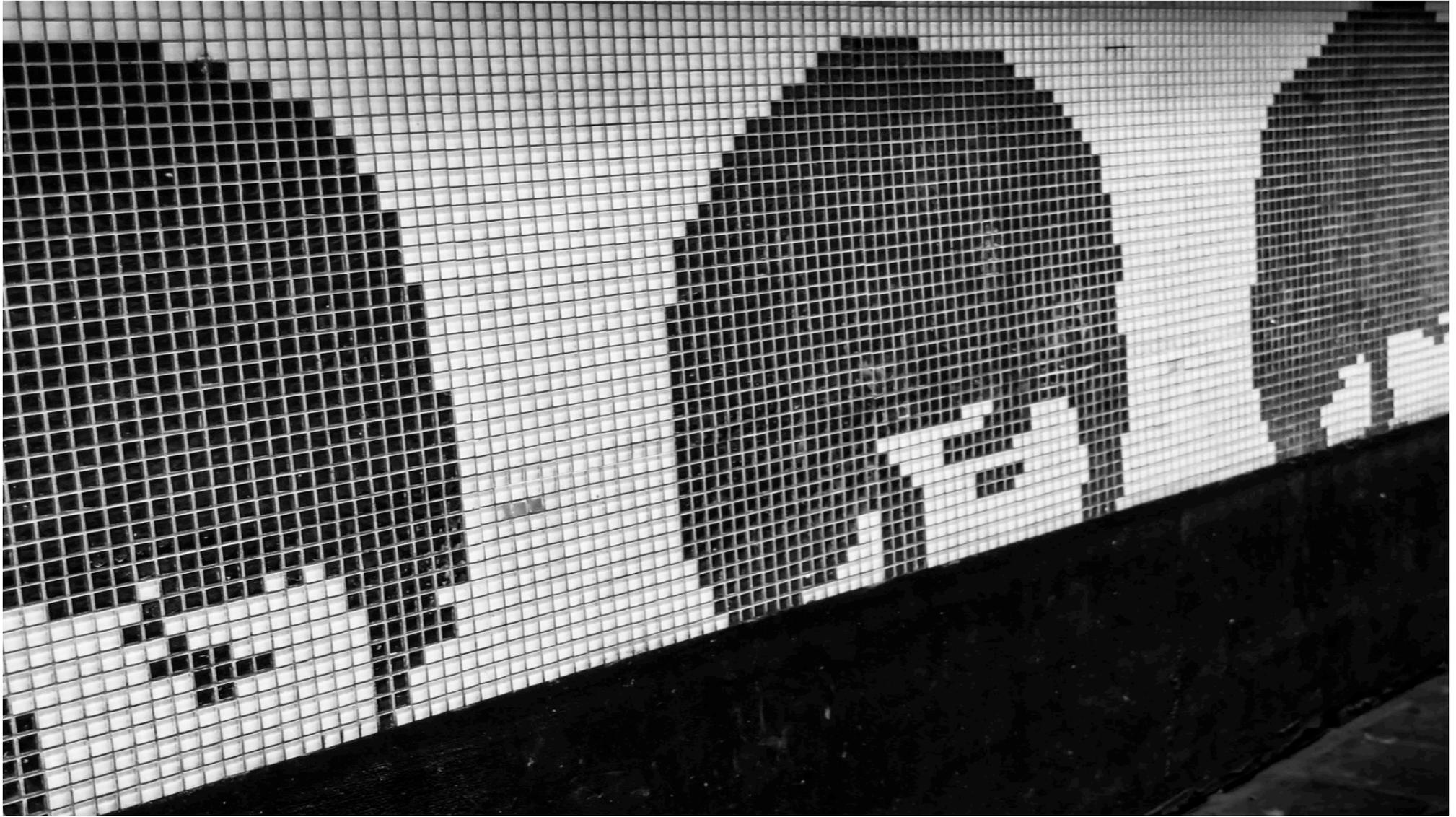


Tim Paape,  
Plant-  
Microbe  
Interactions

- The potential to provide low-dose images of unprecedented resolution and low radiation damage.

Partners: NSLS-II, Biology Dept, CSI,  
SBU, Flatiron Inst./NYU

A few words by way of  
introduction





For almost 20 years I worked in Grenoble, France  
establishing the Structural Biology program at the  
European lightsource and developing large scale  
collaborations



# The center for biomolecular science

Brings the people and technology together to deliver high impact science.



Bio Physical, Chemical, and Medical Sciences



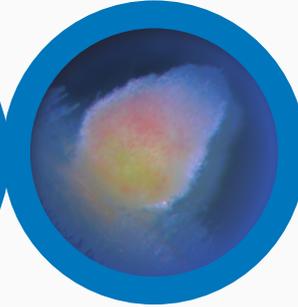
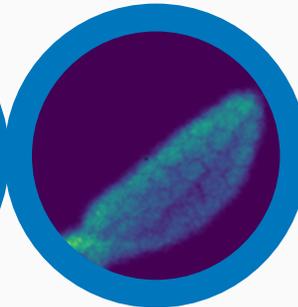
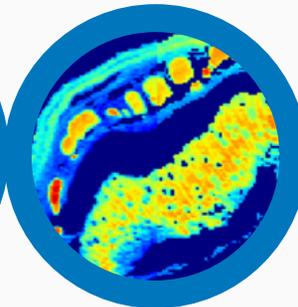
Plant Science



Cell and Tissue Analysis



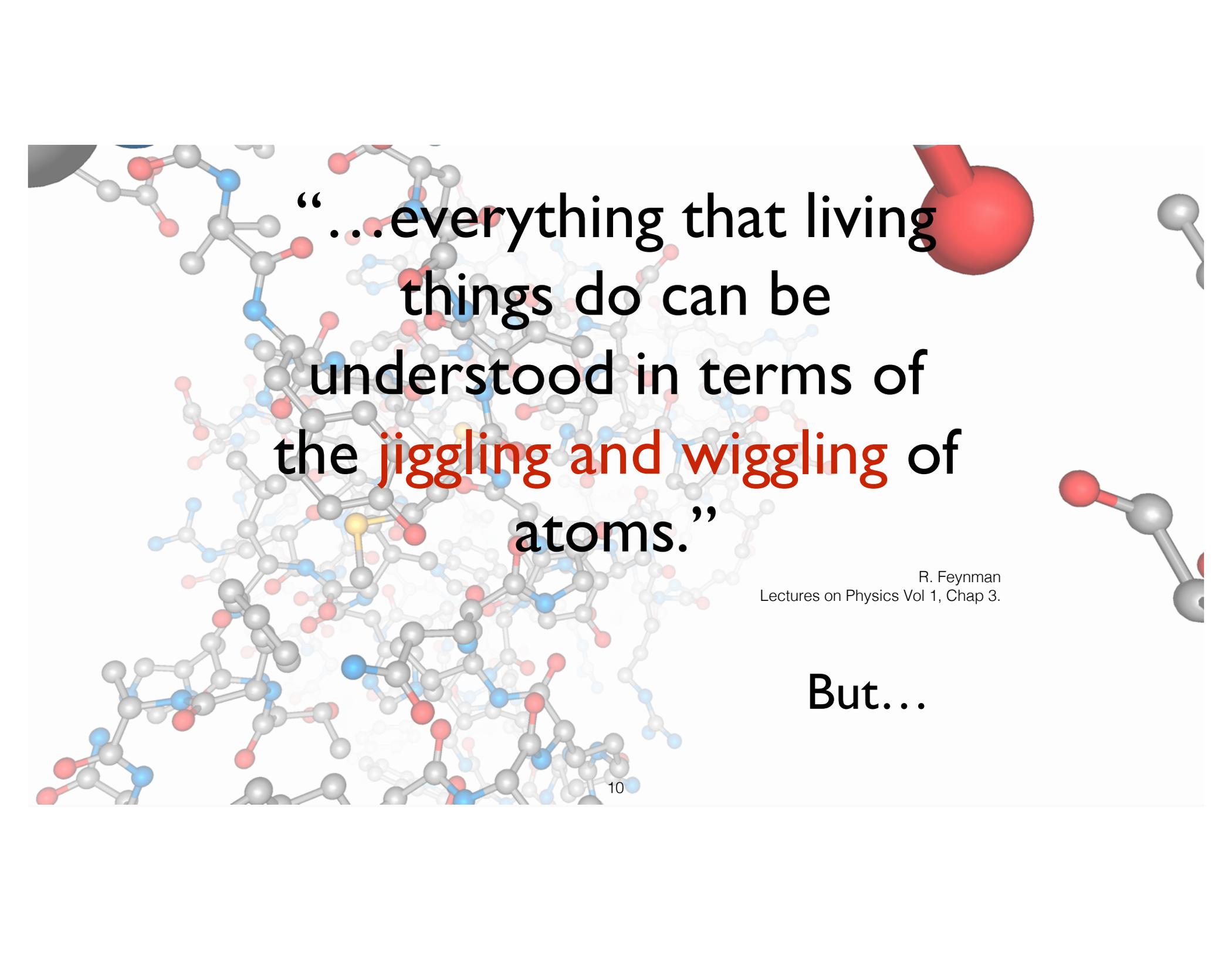
Environmental Chemistry



We have also established a cryogenic  
electron microscopy facility



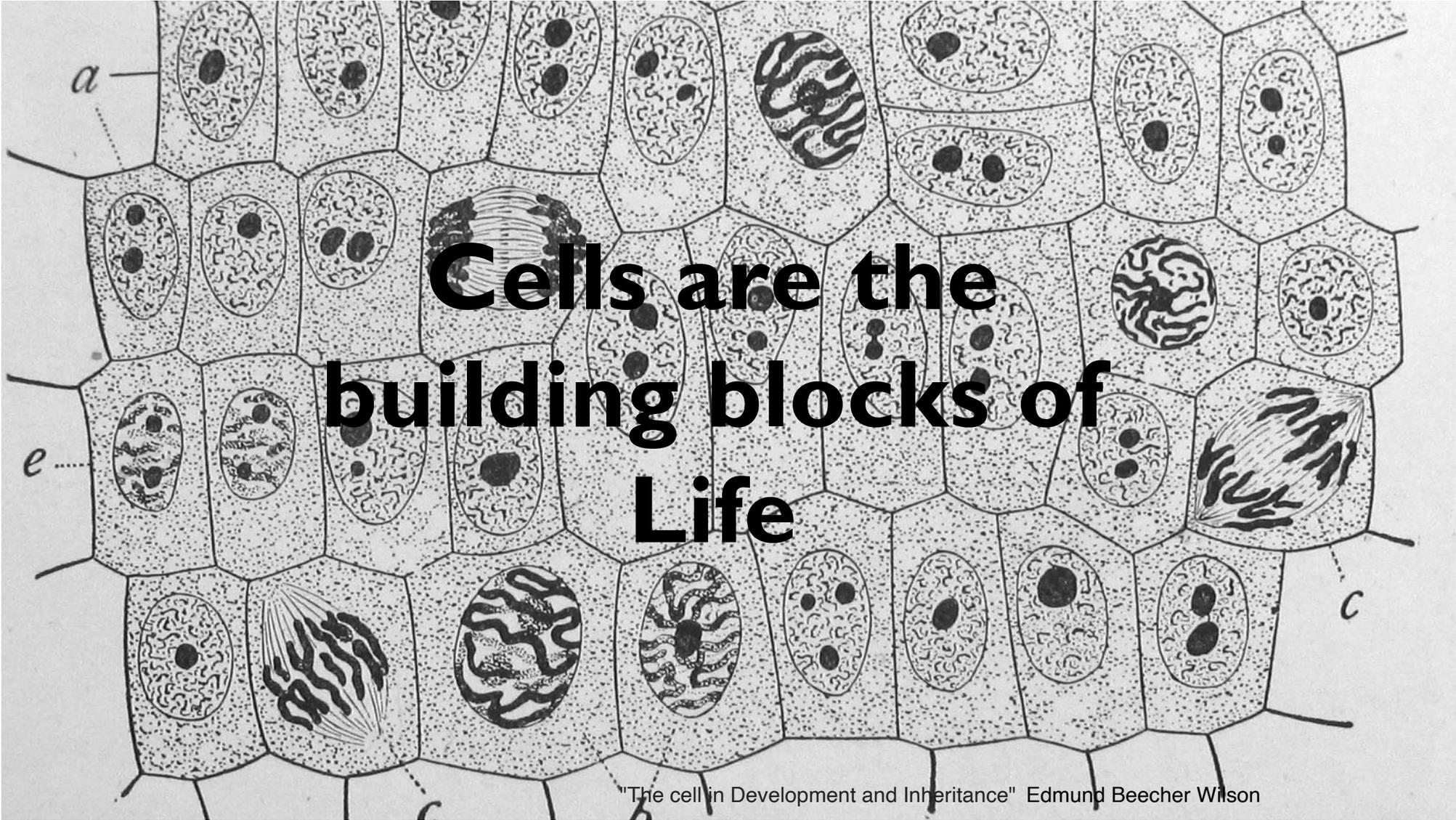
# Motivation



“...everything that living things do can be understood in terms of the **jiggling and wiggling** of atoms.”

R. Feynman  
Lectures on Physics Vol 1, Chap 3.

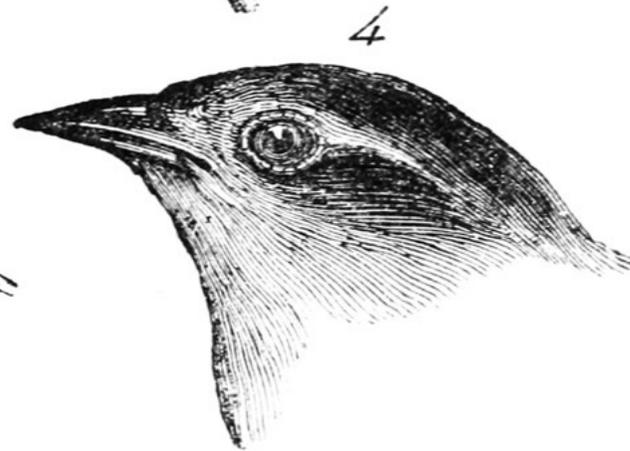
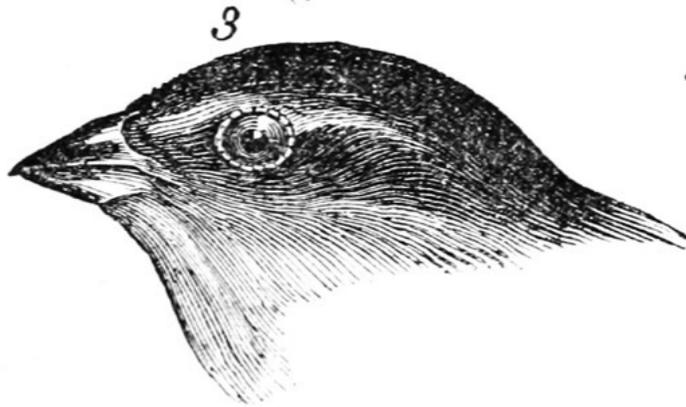
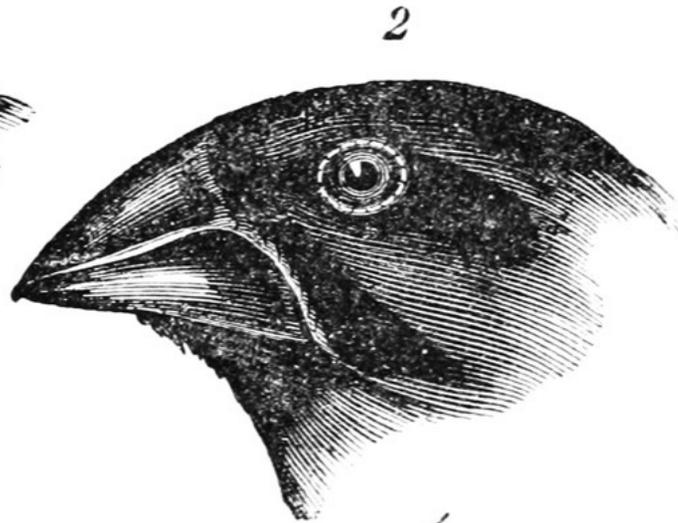
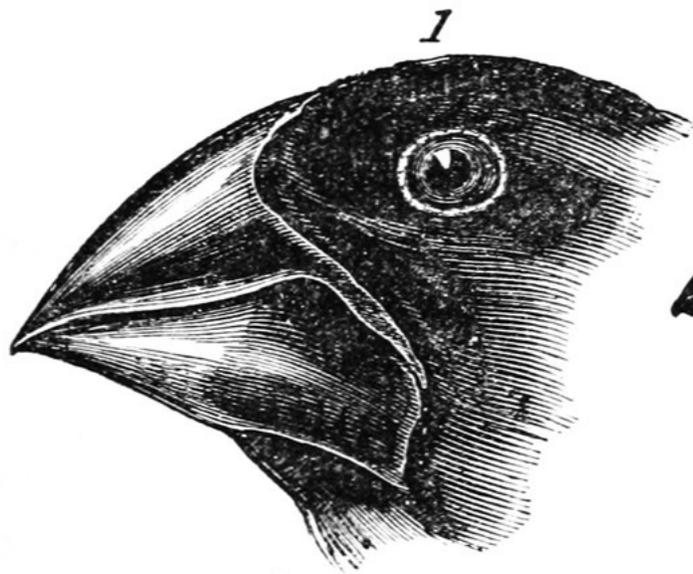
But...



**Cells are the  
building blocks of  
Life**

"The cell in Development and Inheritance" Edmund Beecher Wilson





1. *Geospiza magnirostris*.  
3. *Geospiza parvula*.

2. *Geospiza fortis*.  
4. *Certhidea olivacea*.

Our desire is to understand  
Biological function in sufficient  
detail to recognize the impact  
of the biological molecules in a  
cellular context.

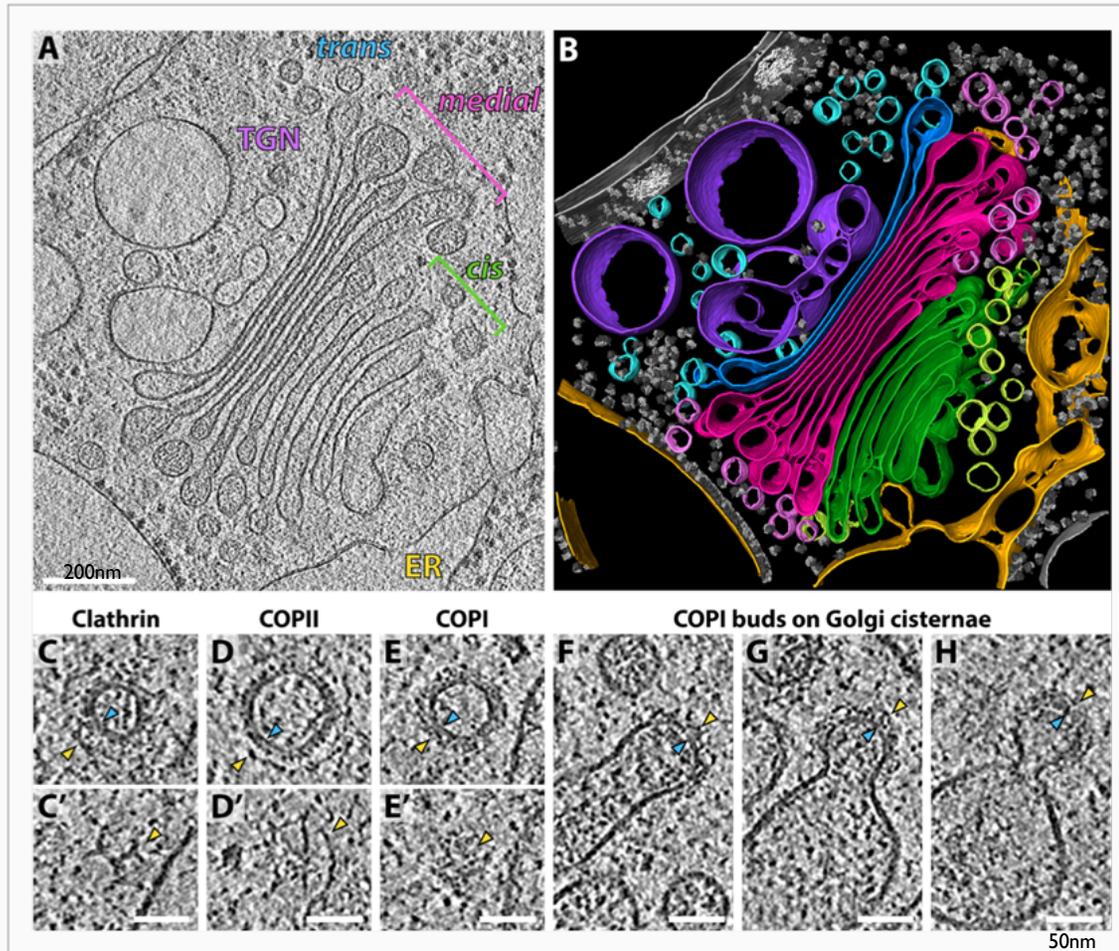
We have friends in other fields — in biology, for instance. We physicists often look at them and say, “You know the reason you fellows are making so little progress?” (Actually I don’t know any field where they are making more rapid progress than they are in biology today.) “You should do things like we do.” They could answer us — but they’re polite, so I’ll answer for them: “What *you* should do

R. Feynman  
There's Plenty of Room at the Bottom, 1959

“What *you* should do  
in order for *us* to make more rapid progress is to make  
the electron microscope 100 times better.”

R. Feynman  
There's Plenty of Room at the Bottom, 1959

Better microscopes have now been built,  
this is of some significance in what follows.



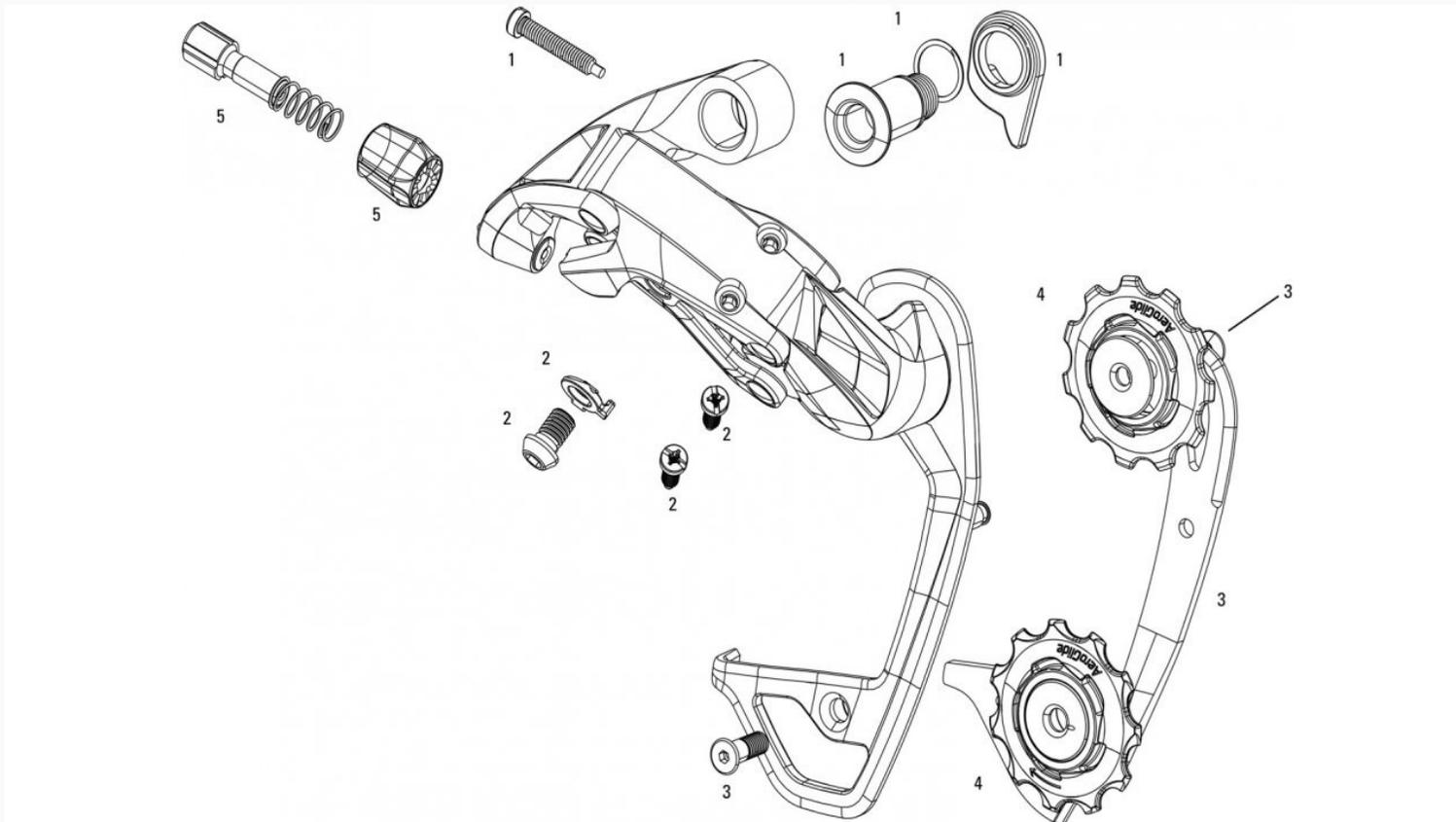
Molecular architecture of the *Chlamydomonas* Golgi apparatus and transport vesicles revealed by in situ cryo-Electron Tomography

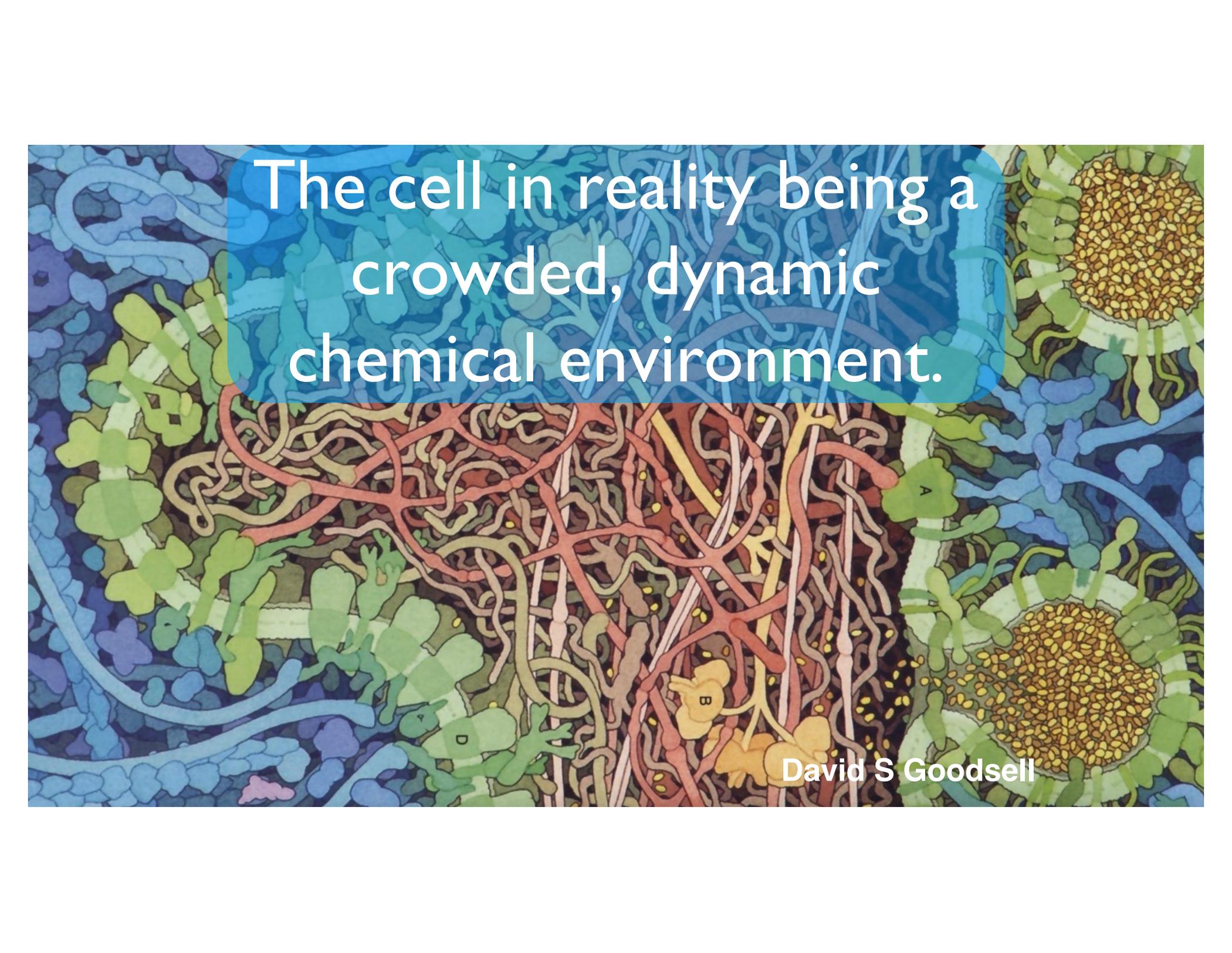
The Structural Biology of  
components offers great  
insight, but it does tend to  
be reductionist.

This structure, on its own does not  
tell you how it relates



# To more complex assemblies.

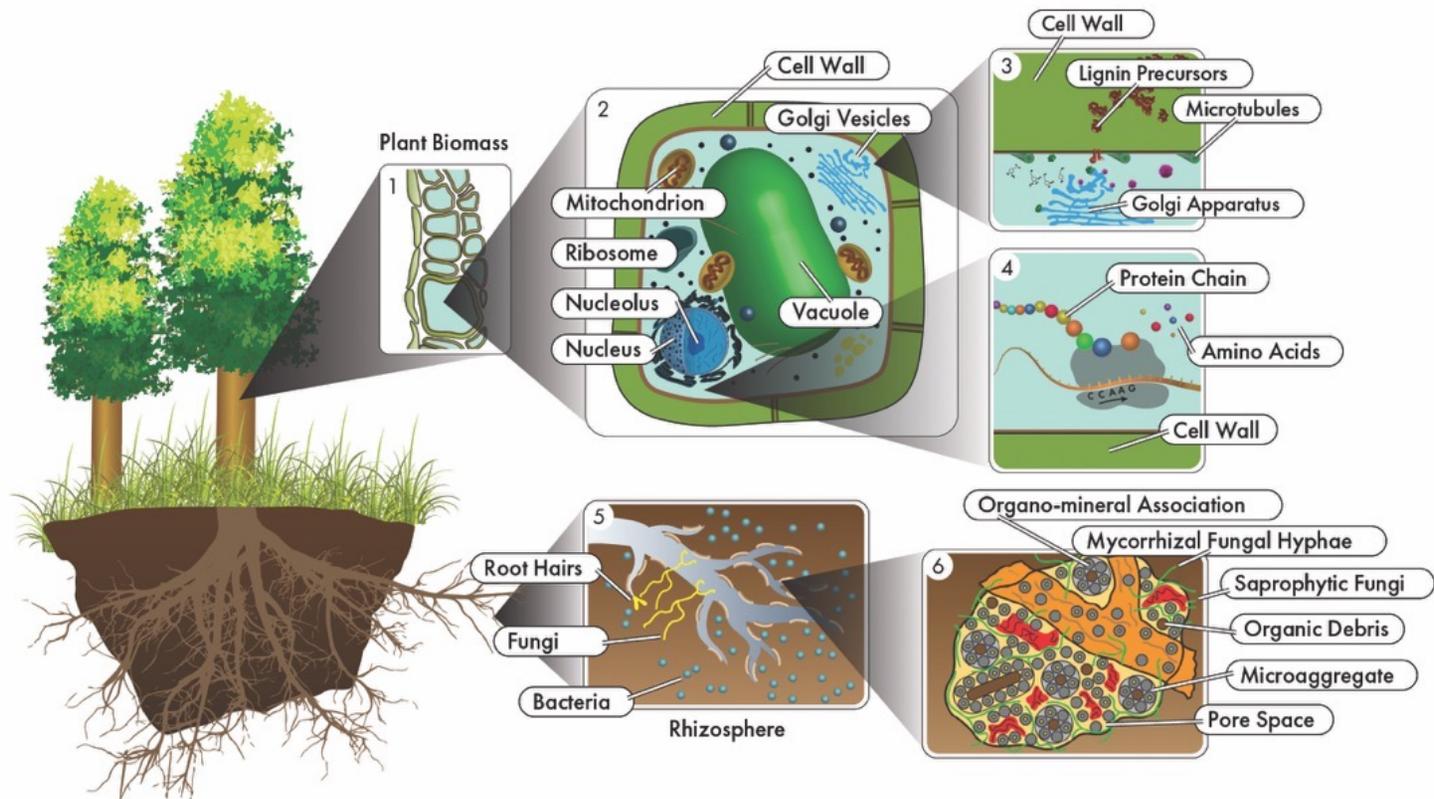




The cell in reality being a crowded, dynamic chemical environment.

David S Goodsell

# The “cell” lives in a context.



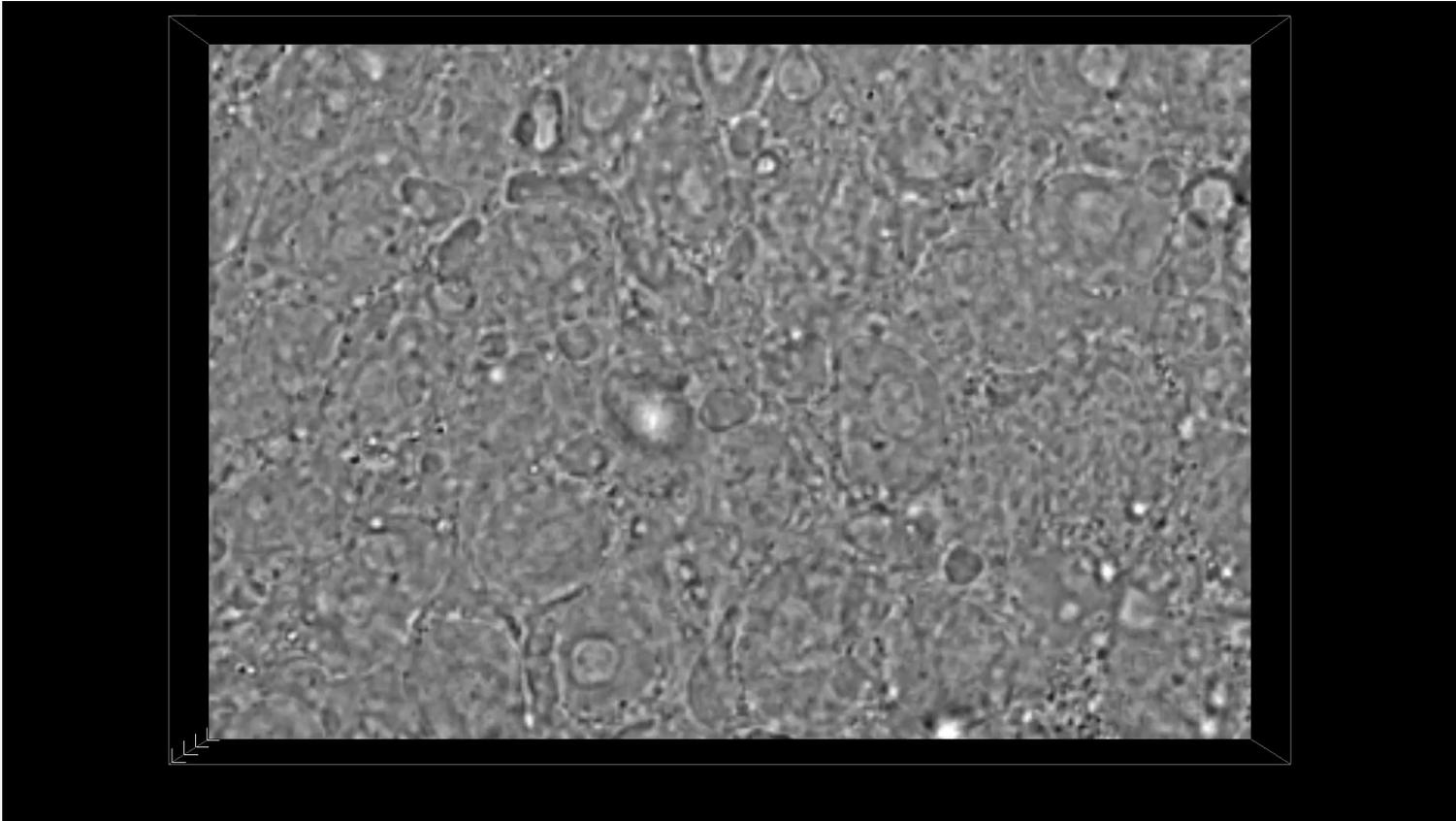
**My Assertion:** To understand cellular life and to engineer improved function, or treat diseases, we need to understand biology in a cellular context. *That is* we need to develop accurate phenotypic models of cells. These models need to include high (enough) resolution structural information.

Our quantum enhanced X-ray microscope proposal aims to (eventually) enable imaging *in-situ* to high resolution for thick biological systems.

# There are some issues...

- Spatial resolution versus sample thickness vs information content.
- Radiation damage.
- Data complexity and amount of data.
- Obtaining statistically significant numbers of samples.
- Making the whole accessible for non-experts.
- Accessing the instruments in a sensible fashion.
- Resolving these issues is going to be tough, so we need to want to optimize the Physics and apply the tools for Biology.

The time is right: Biology research  
is ready for new imaging methods



G. Johnston, Allen Institute for Cell Science

Which brings us to our  
Ghost Imaging project.

# The delivery of an x-ray quantum microscope is built upon four pillars

- Establishing the experimental methods
- Researching non-linear media for parametric down conversion
- Applying these to physical methods to biological systems:
- Creating robust mathematical models and data analysis workflows.

# What our aims are in this project?

Establish imaging of bio-samples with a new type x-ray microscope. To achieve this goal we will:

- Establish the x-ray configuration that enables the routine application of the technique.
- Develop new materials for spontaneous parametric down-conversion to create entangled x-ray photons.
- Create the data analysis and inversion codes to allow for image formation.
- Apply ghost-imaging to significant biological questions. In addition, harmonize these results with other imaging methods we are developing.

# Why will this make a difference?

- There is a trade-off when imaging with x-rays. This being the battle between spatial resolution and radiation damage to the sample.
- Even with cryogenic protection of the sample, the radiation damage issue remains, with the addition of sample preparation artifacts.
- High resolution, low dose imaging, may be possible using ghost imaging, without sample preparation artifacts.

# Ghost imaging

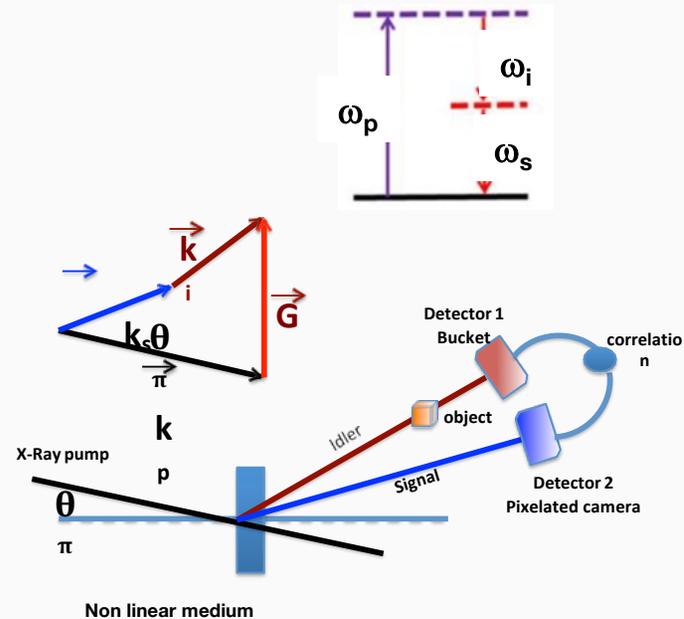
- Imaging using light that never physically interacted with the object to be imaged...
- One light field interacts with the object, and a separate light field fall on the imaging detector.
- Ghost imaging depends upon the ability to detect the coincidence and correlations between these two beams.
- While the entangled photons suggest a purely quantum process ghost imaging only uses the spatial correlation of the photon pairs, a property that could be derived from a classical source.

# We consider two forms

- T1: Photons created as a direct consequence of the process of parametric down-conversion, an incoming pump photon creates a pair of entangled photons, termed signal and idler photons, which are strongly correlated in position.
- T2: In a typical classical ghost imaging scenario, a simple beam splitter creates a copy (duplicating both intensity and phase) of a spatially structured beam where the fidelity of the copy is limited only by the Poissonian statistics of the photon numbers in the two beams.

# Ghost Imaging with entangled photons

- p=pump, s=signal, i=idler
- The effect of parametric down conversion (PDC) is the spontaneous decay of a photon of frequency  $\omega_p$  into two of frequencies  $\omega_i$  and  $\omega_s$  in an optically non-linear medium
- Due to energy conservation,  $\omega_p = \omega_i + \omega_s$
- Due to momentum conservation  $k_p = k_i + k_s$

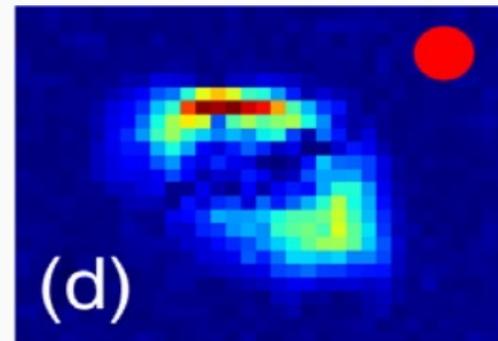
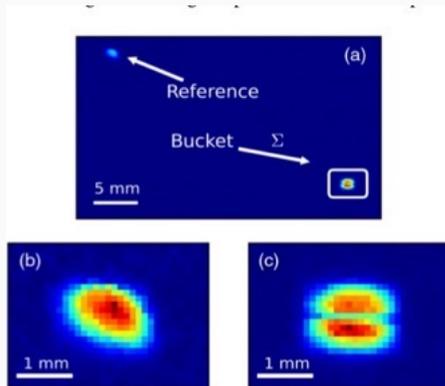
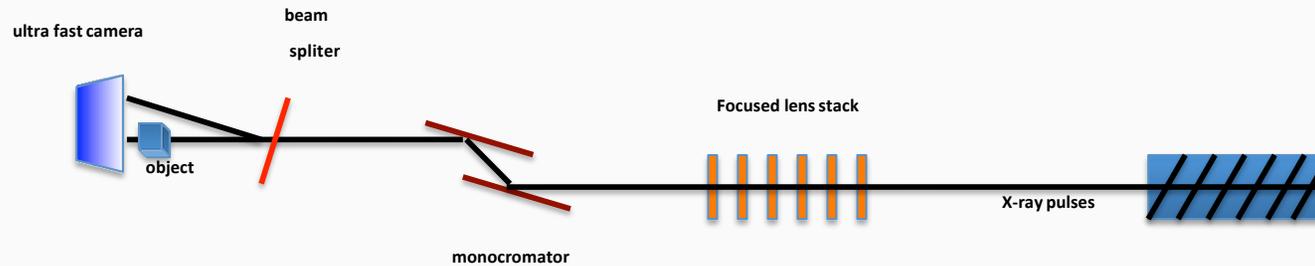


The challenge: finding a non-linear medium to produce enough entangled X-Rays

Diamond crystals often used in transmission mode where the loss is being controlled

Spontaneous Emission Controlled Materials

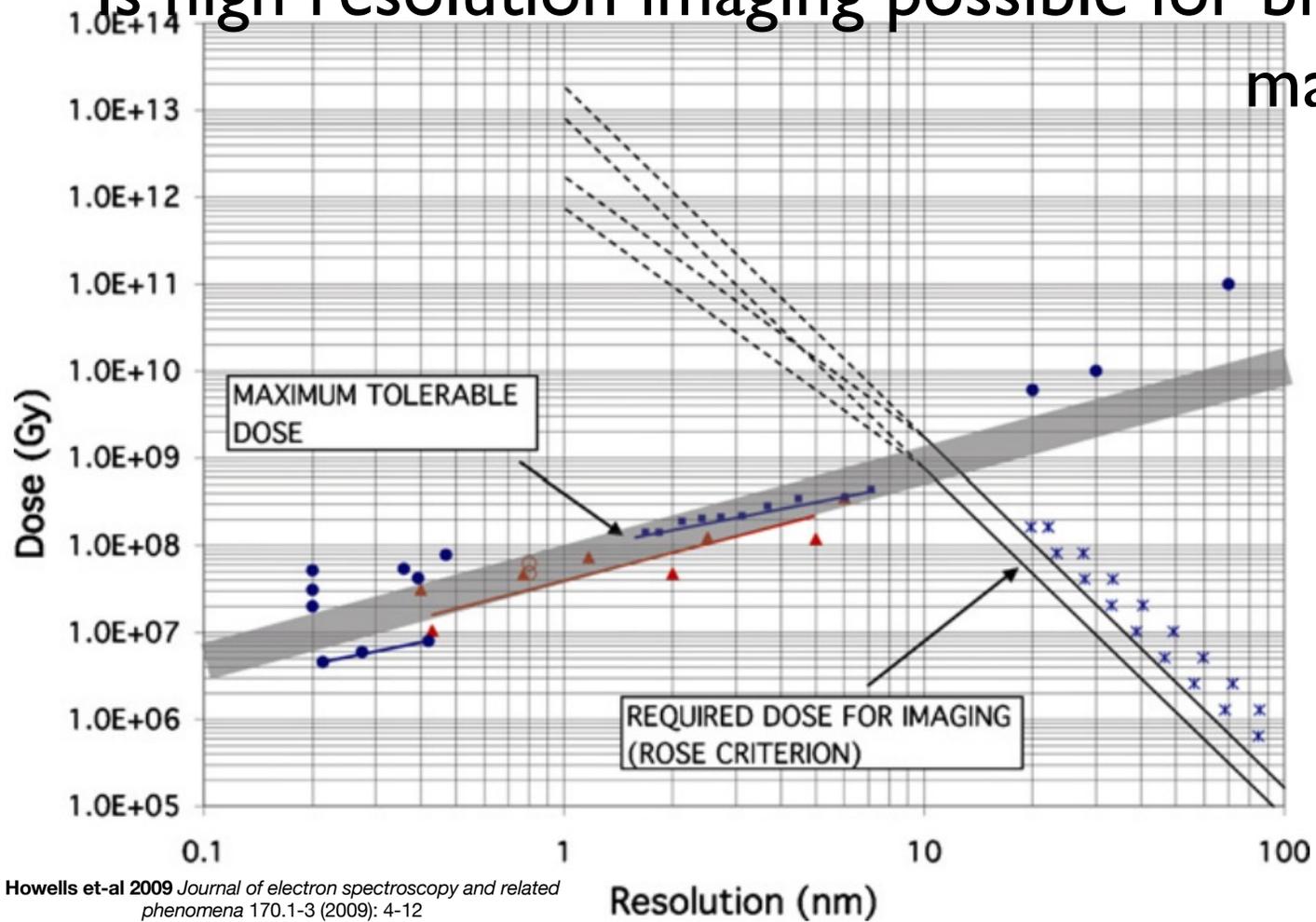
# Ghost Imaging with thermal (chaotic) light



The challenges:

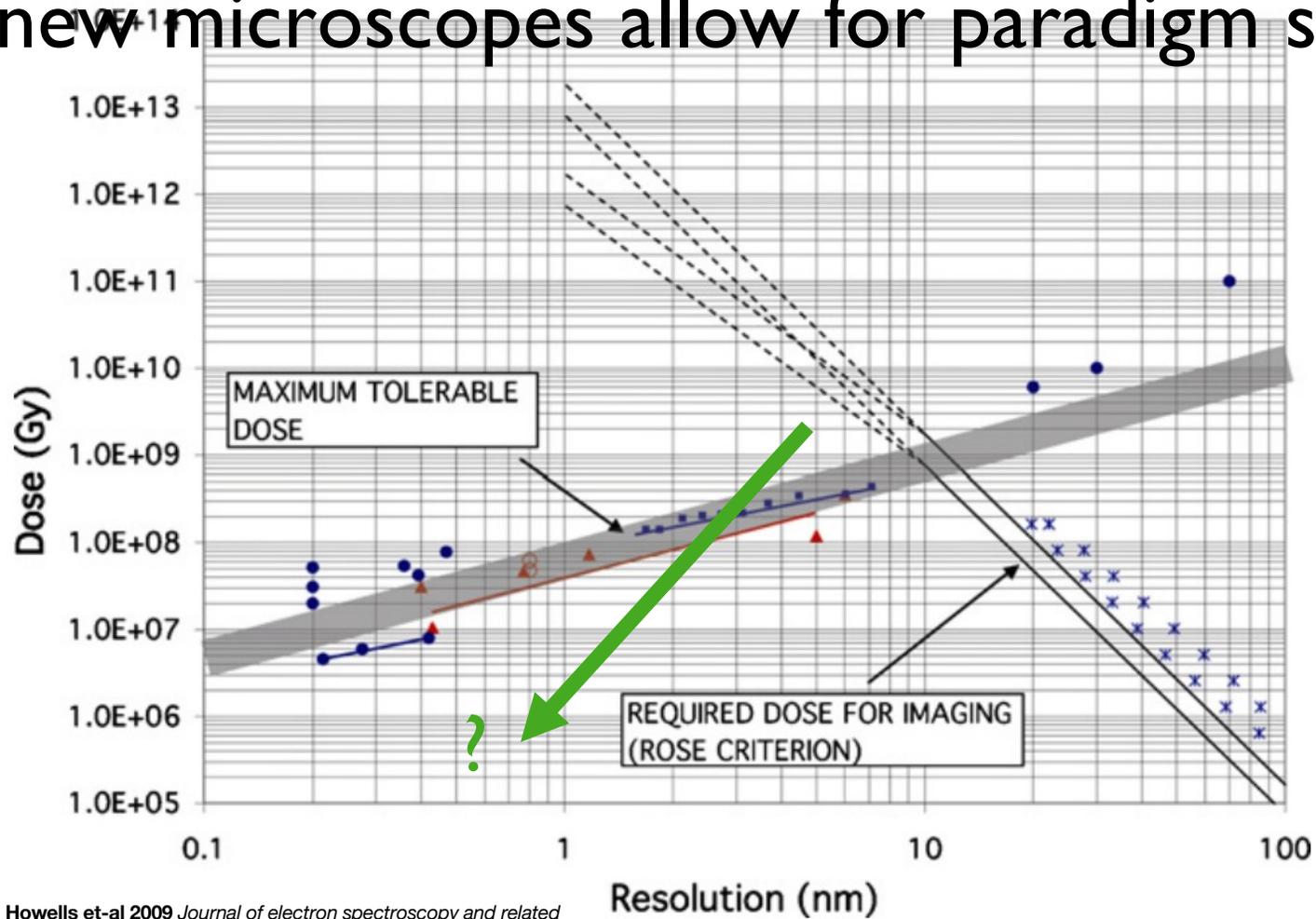
- ✓ High intensity X-ray beams.
- ✓ High speed, high resolution cameras.
- ✓ Correlation algorithms, software.

# Is high resolution imaging possible for biological materials?



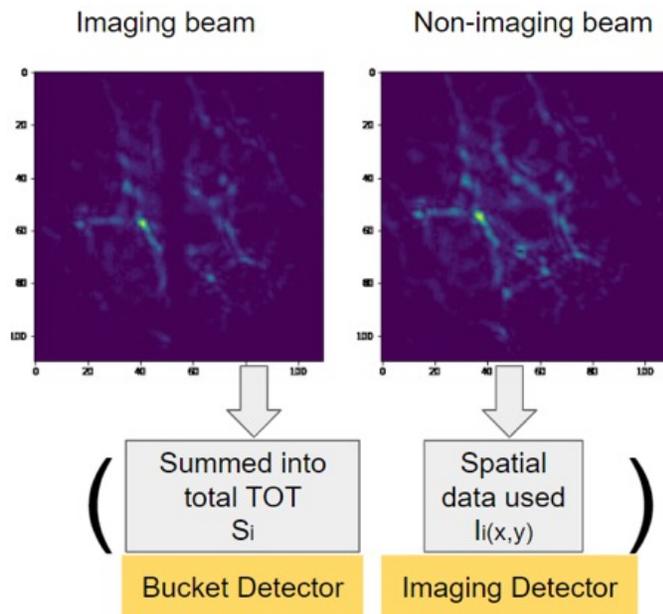
Howells et-al 2009 *Journal of electron spectroscopy and related phenomena* 170.1-3 (2009): 4-12

# Do new microscopes allow for paradigm shifts?



Howells et-al 2009 *Journal of electron spectroscopy and related phenomena* 170.1-3 (2009): 4-12

# Offline test system

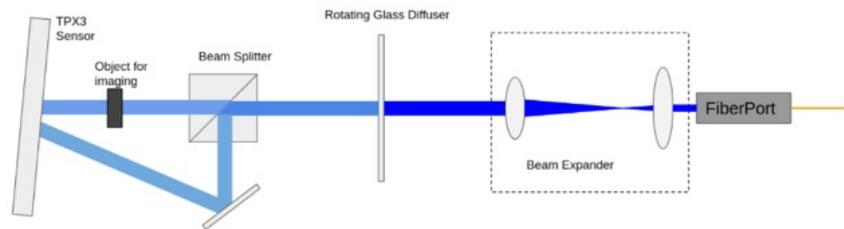


Produced by correlating bucket data from the imaging beam with spatial data from the non-imaging beam

$$N = 1000 \text{ pulses/sec} * 10 \text{ sec} = 10^4 \text{ frames}$$

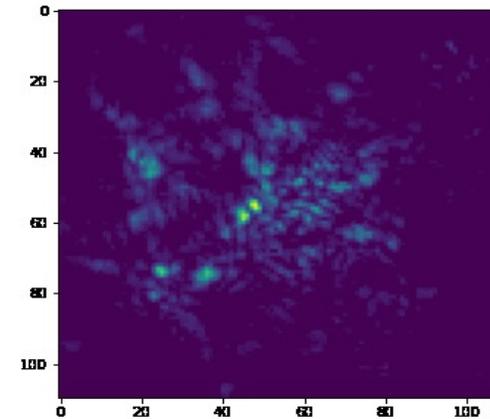
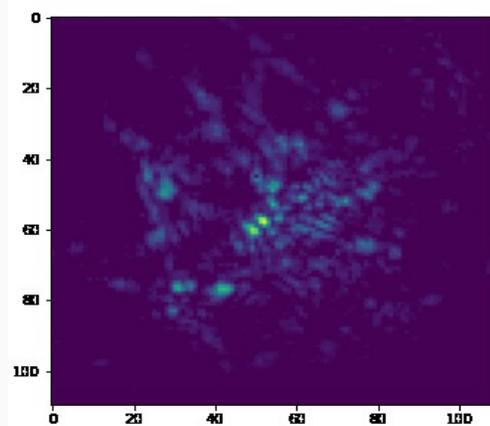
$$G(x,y) = \langle SI(x,y) \rangle - \langle S \rangle \langle I(x,y) \rangle$$
$$\approx \frac{1}{N} \sum_{i=1}^N S_i I_i(x,y) - \frac{1}{N^2} \sum_{i=1}^N S_i \sum_{i=1}^N I_i(x,y),$$

Over N frames

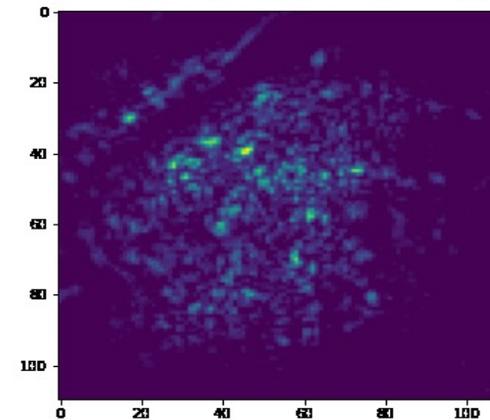
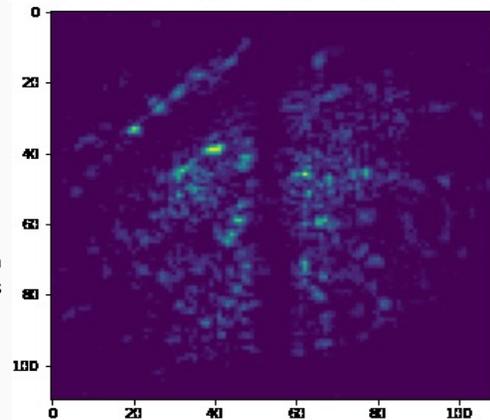


# Initial work with optical system.

Two beams with no object present



Two beams with object (wire) present in one of the beam paths

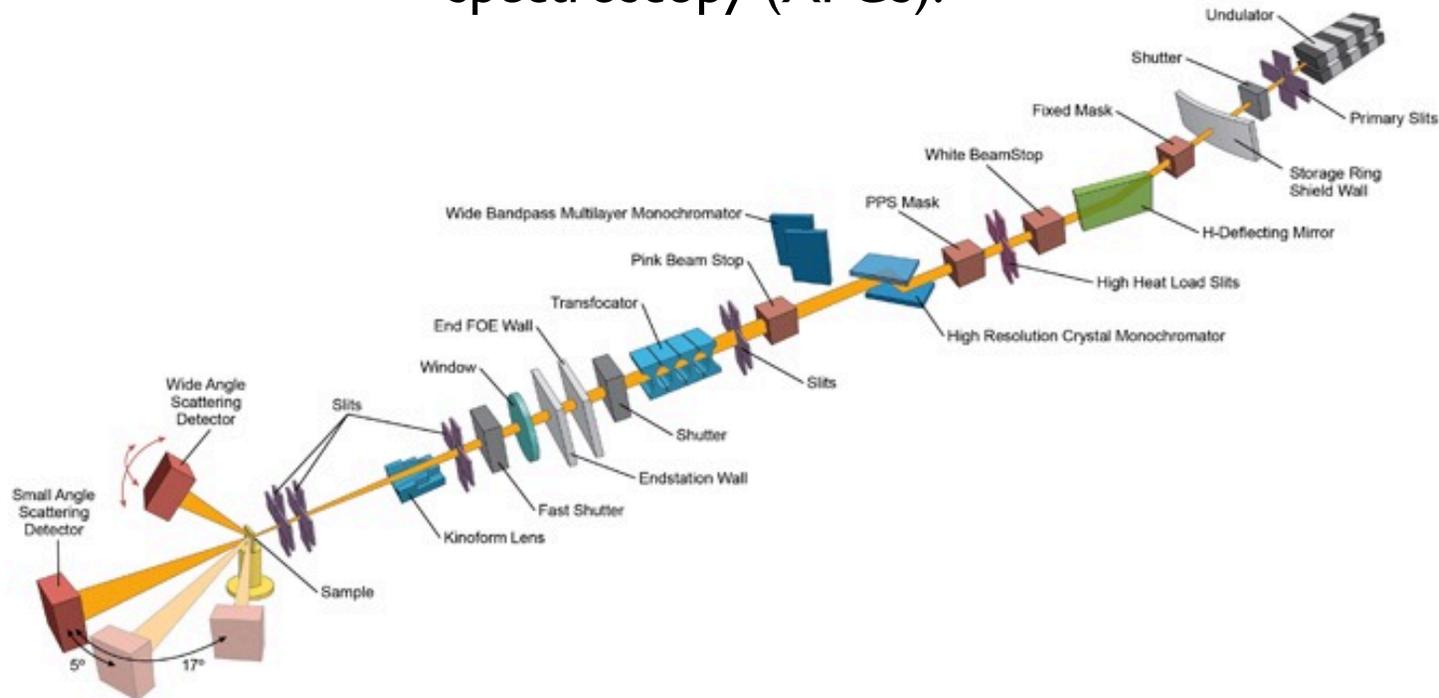


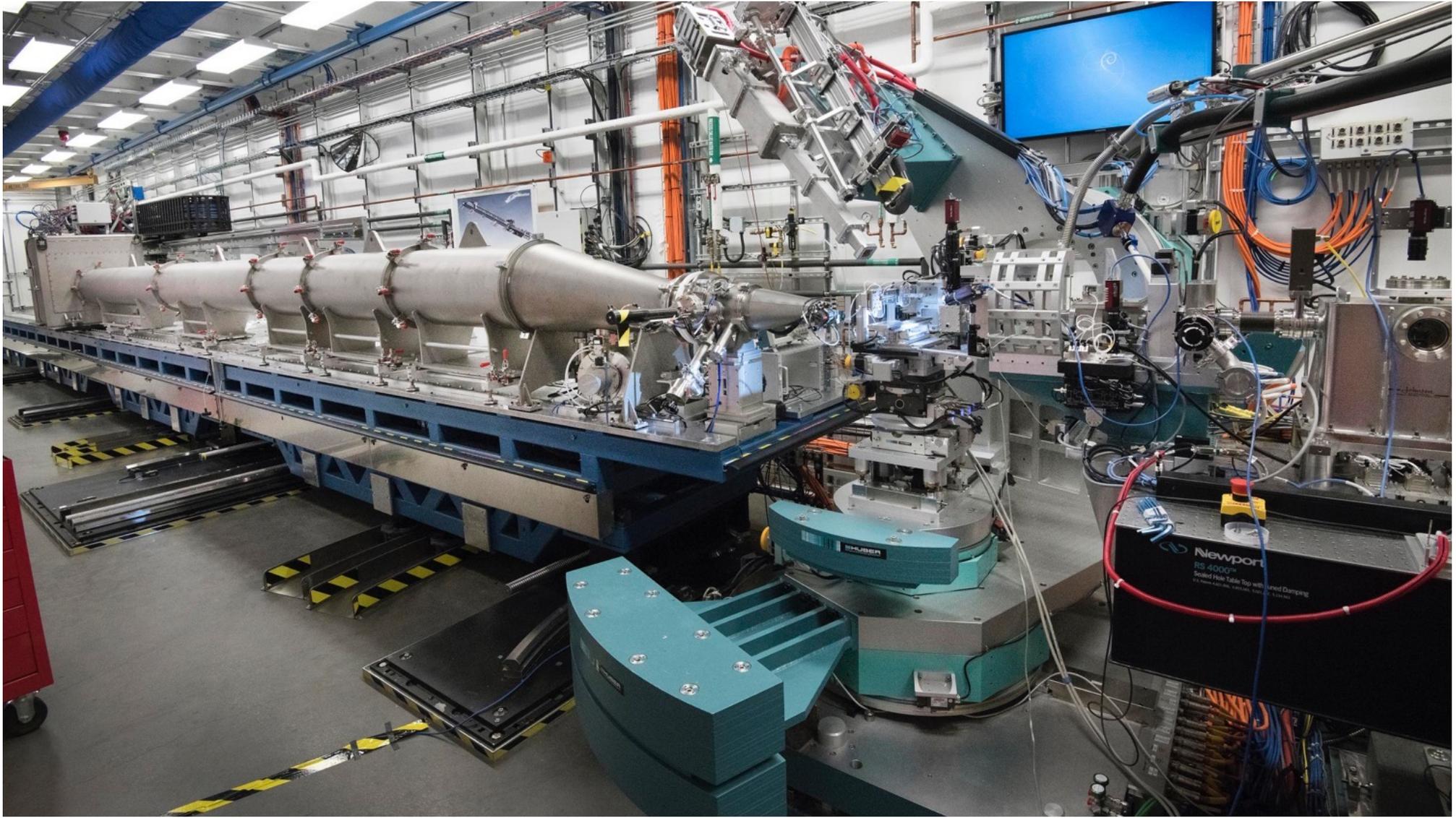
Sum this

Correlate from this

# Our “x-ray quantum microscope”:

Coherent Hard X-ray Scattering (CHX) beamline is dedicated to studies of nanometer-scale dynamics in materials using x-ray photon correlation spectroscopy (XPCS).





# CHX offers many advantages

- High flux of coherent X-ray at high energy : imaging thick samples
- Stable source of coherent over days: data acquisition and image signal.
- Configurable and adaptable sample environment: allowing exploration of X-ray preparation methods and sample environments.
- Mature instrument controls system: rapid adaptation to new protocols.

# Biological Research

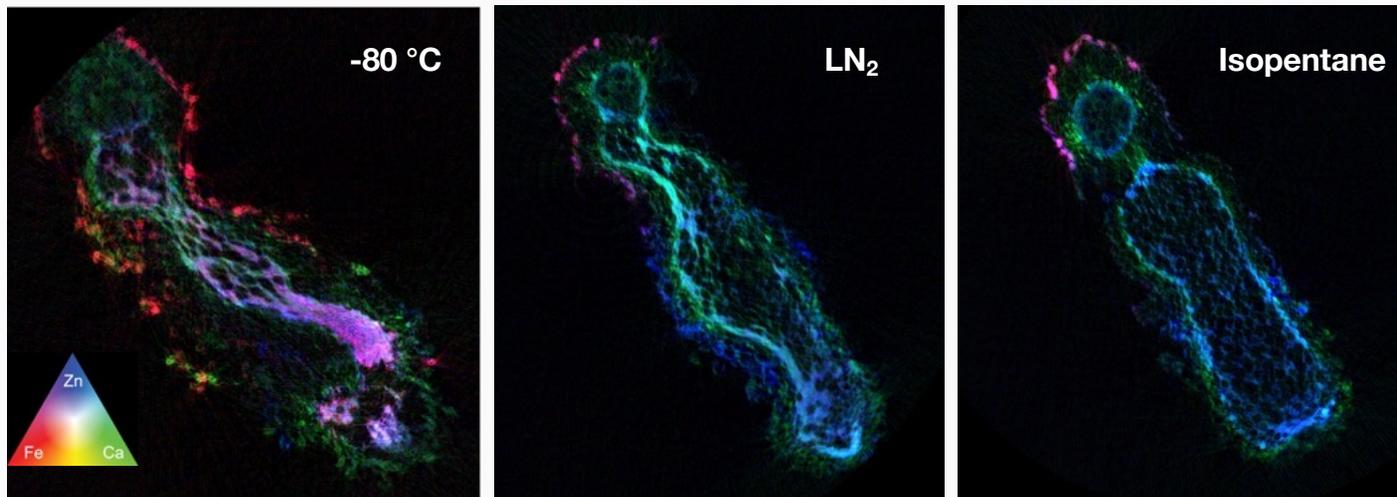
Biological systems: There is growing interest in the role that microbes play in increasing host-plant resilience to stressful or toxic conditions. *Medicago truncatula* is the model legume species that we will study in its symbiotic interactions with *Sinorhizobium medicae* and *S. meliloti*.

Together, the *Medicago-Sinorhizobium* system provides a powerful experimental biological system to study molecular and biochemical level processes.

Sample development and preparation is underway.

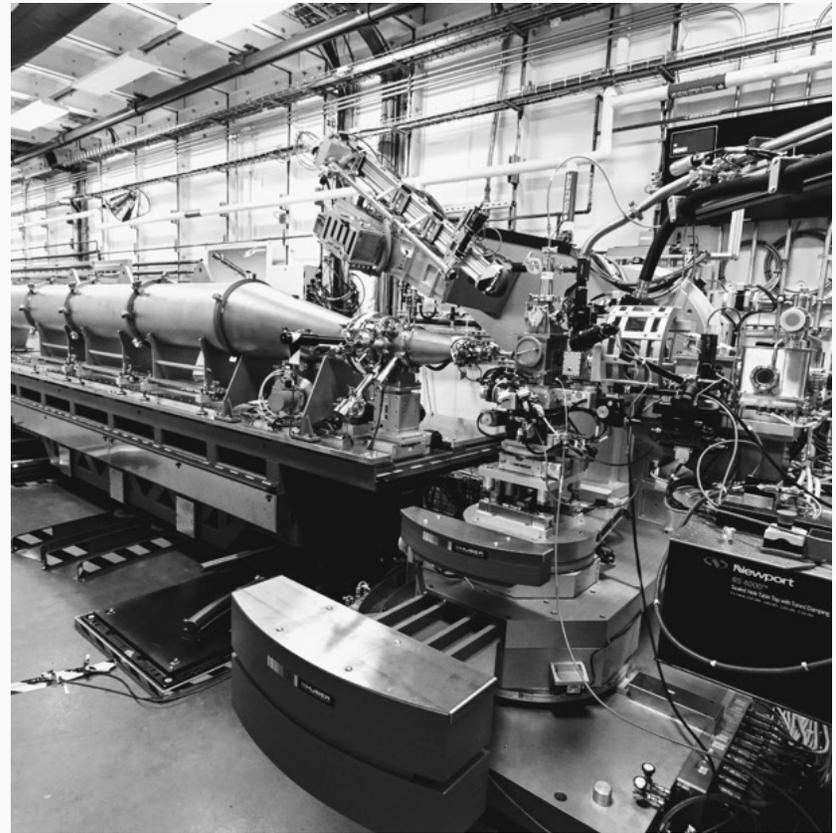
# 3-D trace element imaging

XRF microtomography of Medicago N<sub>2</sub>-fixing root nodules



- Sample preservation is key for biological and environmental specimen
- Comparison of freeze-dehydration methods: -80 °C, liquid nitrogen, and isopentane

## First type-2 ghost imaging experiments at NSLS-II



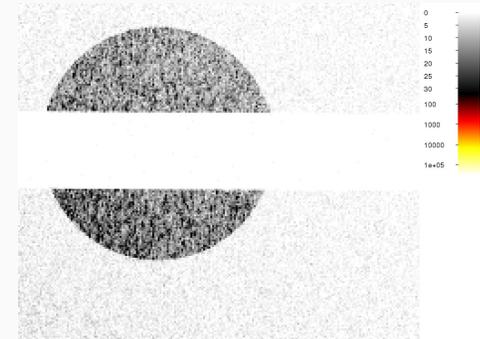
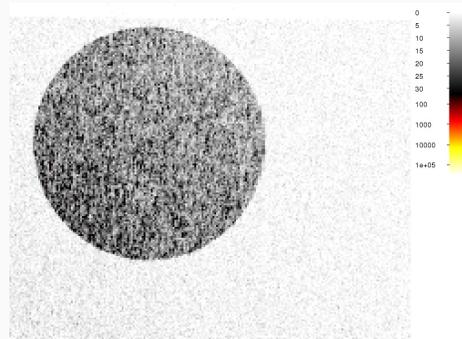
# Tools to enable the experiments

Non-Linear Media for spontaneous parametric down conversion: in the X-ray region available media have very low cross sections for the conversion. A key element of our research program is to investigate new systems capable of higher efficiency generation of entangled x-rays. The research is underway and the novel media will be tested as they are made available to us.

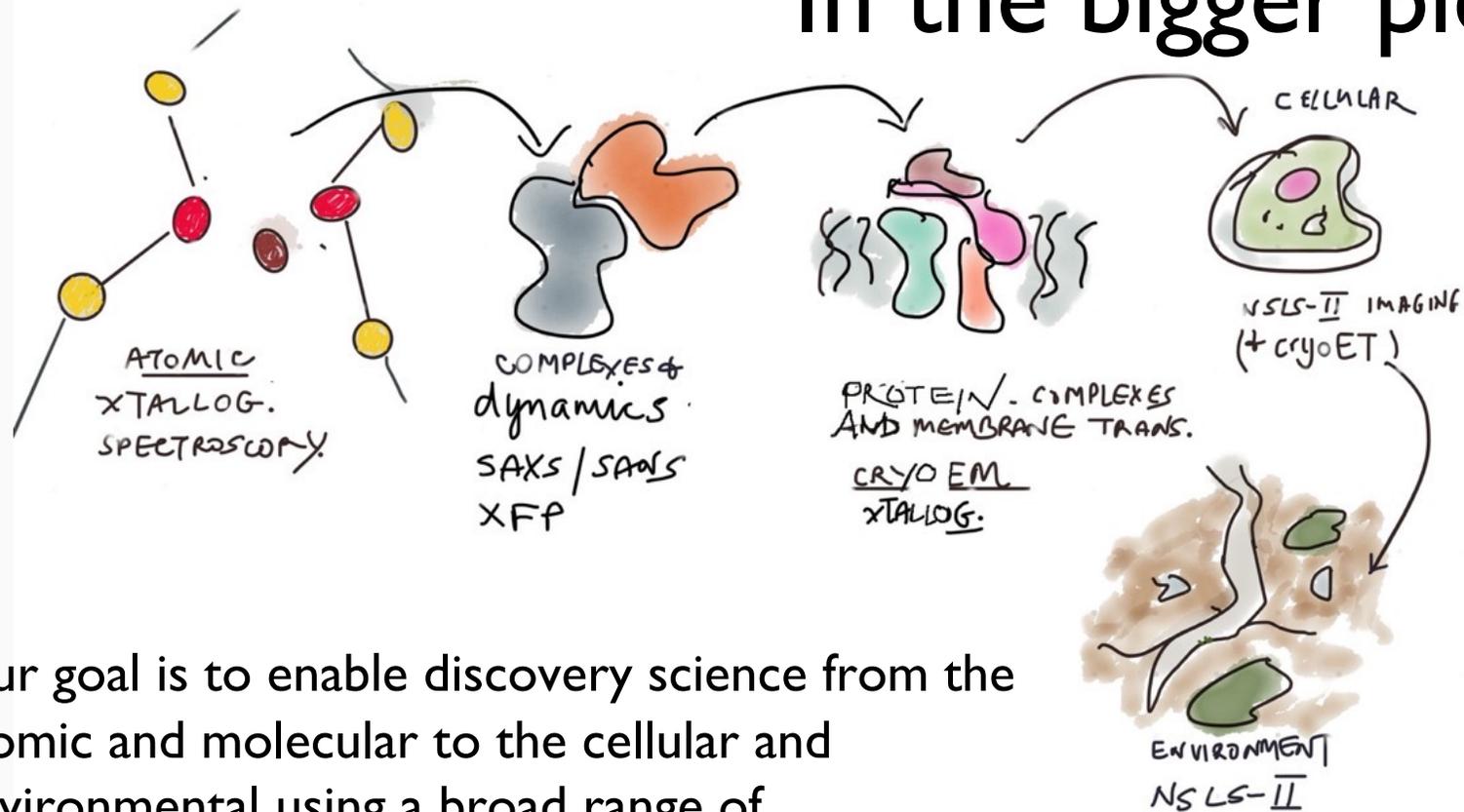
Detectors for imaging: The quantum imaging experiments with x-rays will require large area detectors with best possible timing resolution. We are acquiring large detectors capable to accommodate both x-ray beams. The nanosecond timing resolution provided will enable the time stamping of individual x-rays and, therefore, efficient coincidence analysis pair-by-pair.

# Planning for the short term

- Our approach is to build successively more sophisticated experiments building upon our increased knowledge and the input of experts.
  - We aim to demonstrate type 2 ghost imaging with x-rays.
  - Put in place the data-analysis systems for efficient data analysis.
  - Continued investigation of materials for parametric down conversion.
  - Establish the place of the program in the x-ray ghost imaging community
    - symposium series.



# In the bigger picture



Our goal is to enable discovery science from the atomic and molecular to the cellular and environmental using a broad range of measurement techniques.

# Those who are actually doing the work:

Leo Fang,  
Andrei Fluerasu,  
Andrei Nomerotski,  
Cinzia Da Via,  
Timothy Paape,  
Lonny Berman,  
Petr Ilinski,  
Francis Alexander,  
Beverly Agtuca,  
Ning Bao,  
Kwang Min Lin,  
Meifeng Lin,  
Elisha Siddiqui,

Denis Dolzhenko,  
Alex Parsells,  
Joshua Richard



Our long term aim is to be able to change this artists impression into a modellable, predictable system.