NSLS-II and research into combating COVID-19 at BNL

J.P. Hill, Director, NSLS-II

CAC May 15th 2020

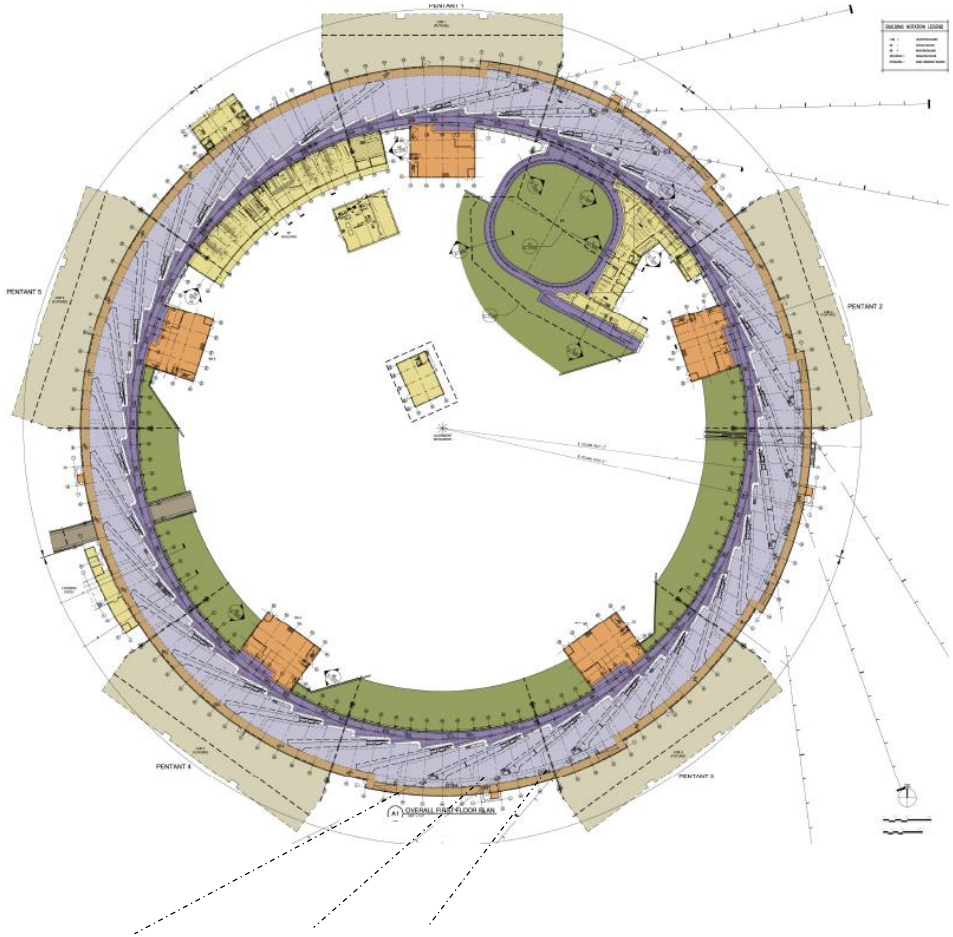
U.S. DEPARTMENT OF ENERGY | Office of Science

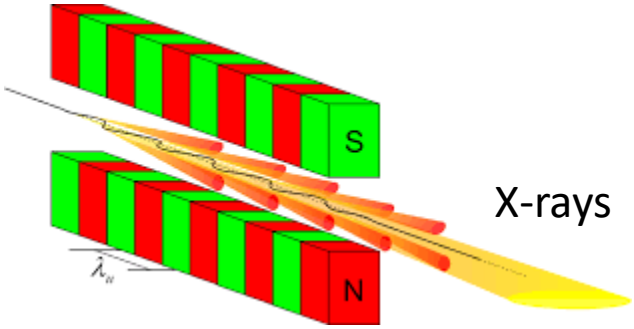
BROOKHAVEN NATIONAL LABORATORY

NSLS-II – A World-Leading Microscope

- NSLS-II is a state-of-the-art light source covering far infrared to hard X-rays
- Offers best in-the-world characterization capabilities
- Compatible with devices, real-world materials and “operando” conditions
- ~1 km around, can fit Yankee Stadium inside the ring

NSLS-II: Best in class from far-IR to hard x-ray

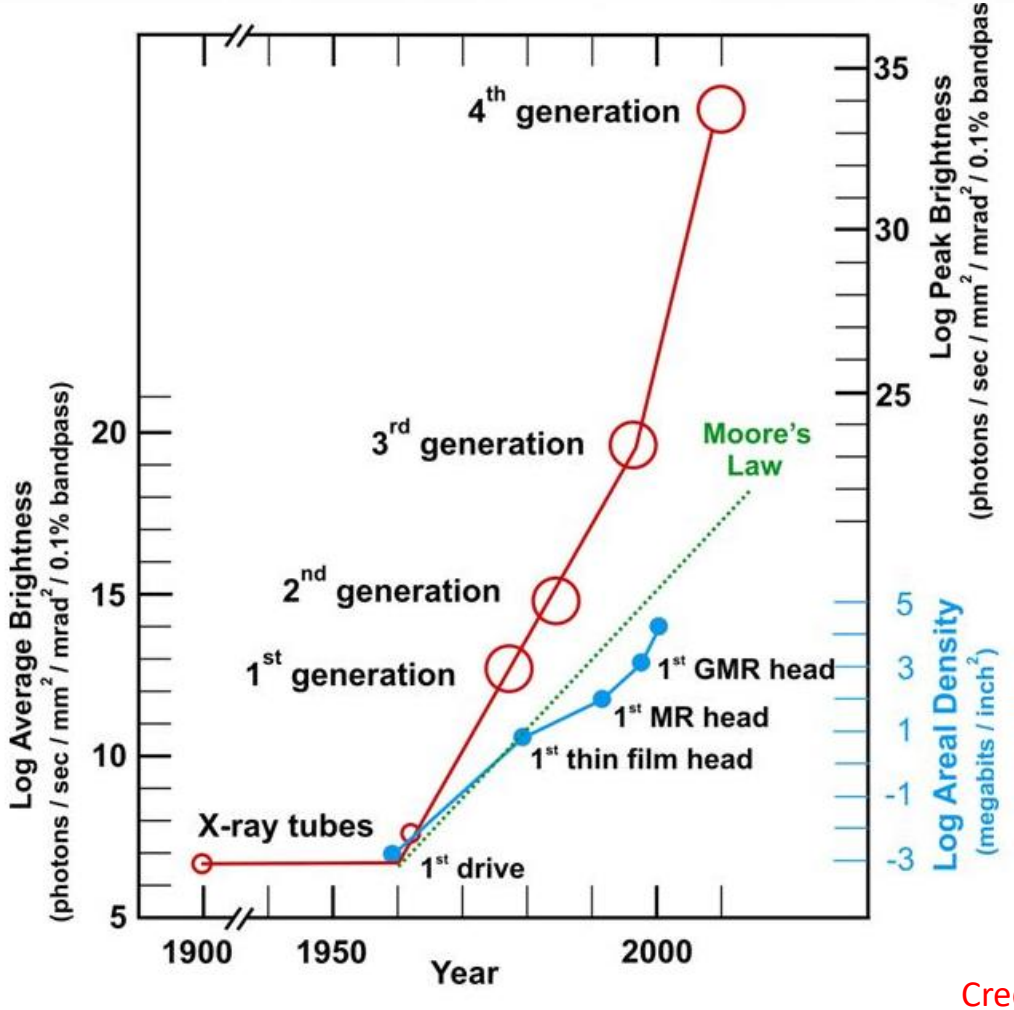




User Facility

- Capacity for ~ 60 beamlines
- 1800 Users in FY19
- Proposal access. Free if intend to publish.
- Proprietary fee ($430/hr)

X-ray sources brightness vs time and Moore's Law



Improvements in x-ray sources have outpaced even Moore's Law in microelectronics.

This has driven advances in the x-ray field that are as revolutionary as seen in the field of computing

Credit: J. Stohr

NSLS-II capabilities

Exquisite resolution and sensitivity, and the expertise to use them.

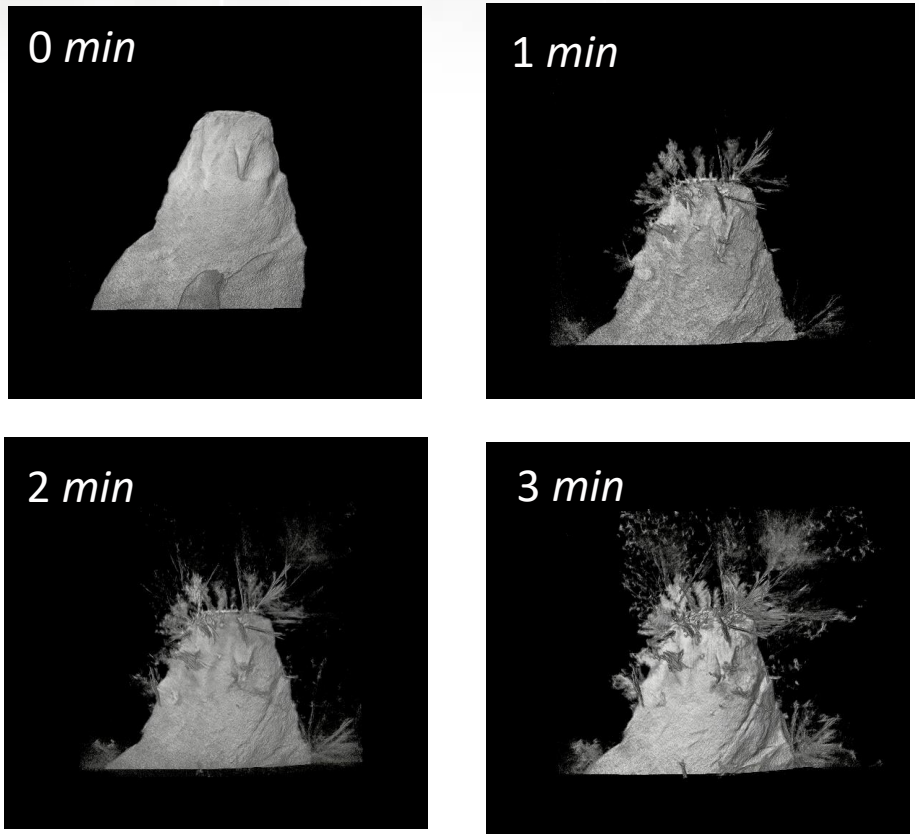
Some examples of the work we do:

1) **Energy storage**: Chemistry in real time on the nm length scale
   - Can we prevent your cell phone batteries dying?
   - Can we store wind-generated electricity?
2) **Materials synthesis**: Novel nano-functional materials
   - Can we build better solar cells?
   - Can we design new ways to deliver medicines?
3) **Environmental Science**: understanding toxins moving through plants
   - How can we protect the food web?
4) **Microelectronics**: Legacy electronics and state-of-the-art
   - Can we ensure our electronics perform as we expect?
5) **Magnetism**: Spintronics
   - What materials are beyond Moore's law?

Energy Storage

Full field imaging

- 30 nm spatial resolution over 100 micron field of view
- 3D images in seconds
- x10 faster than any similar instrument in the world
- Allows first 3D movies of dynamic processes



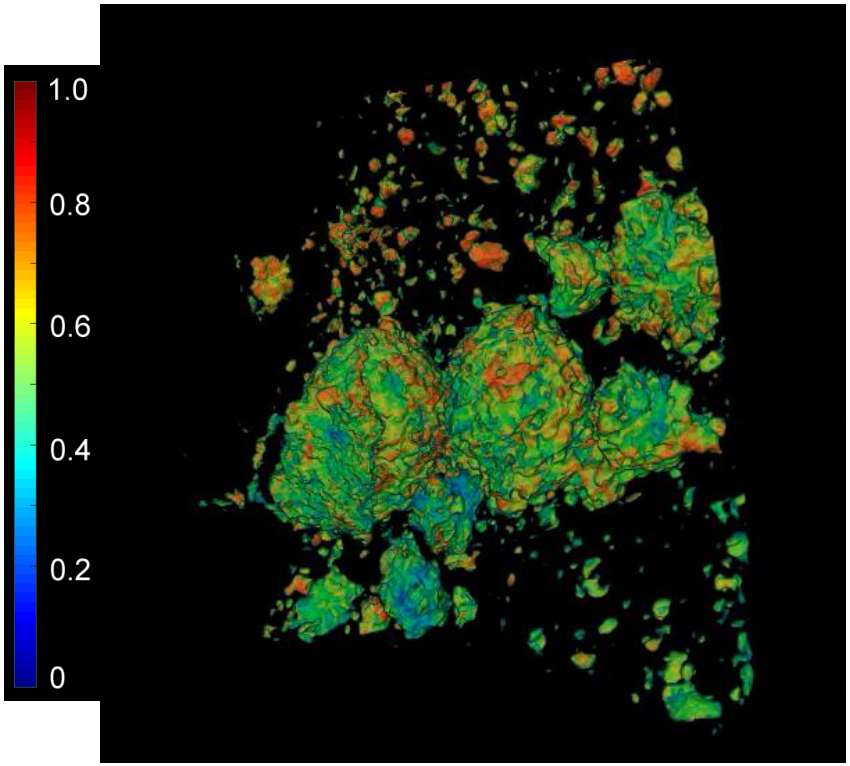
Appl. Phys. Lett (2018)

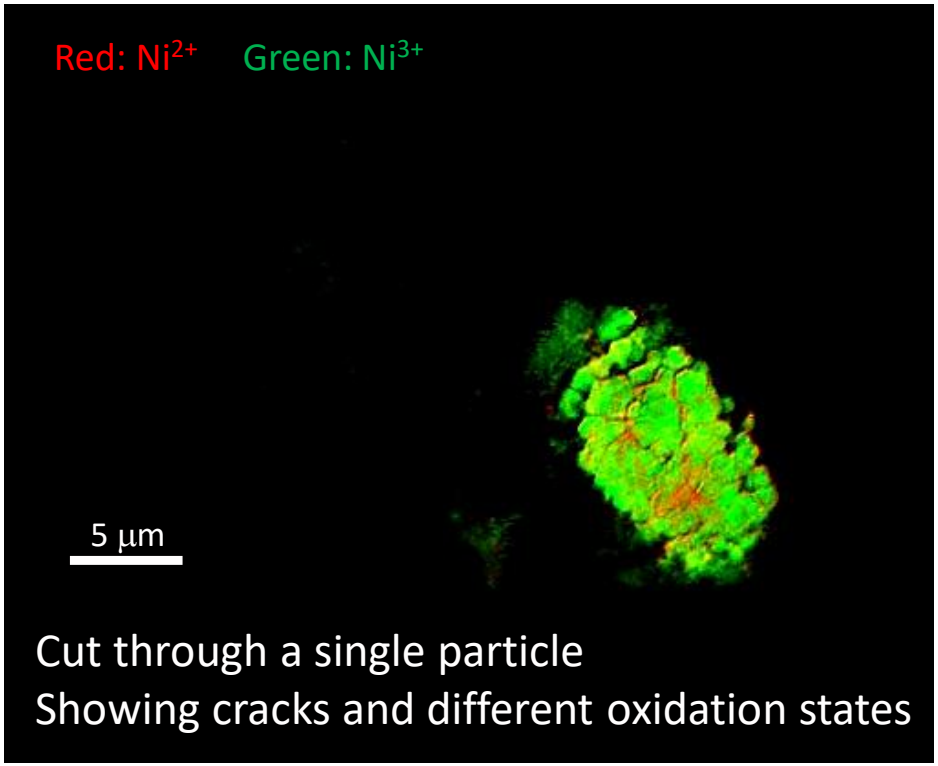
Tracking 3D silver nano-dendritic growth in real time, under *in-situ* chemical reaction conditions: $Cu + AgNO_3 \rightarrow Ag + Cu(NO_3)_2$

Energy Storage

Brightness of x-ray beam allows very fast imaging with nanoscale resolution in 3D

3D rendition of Ni^{3+} concentration

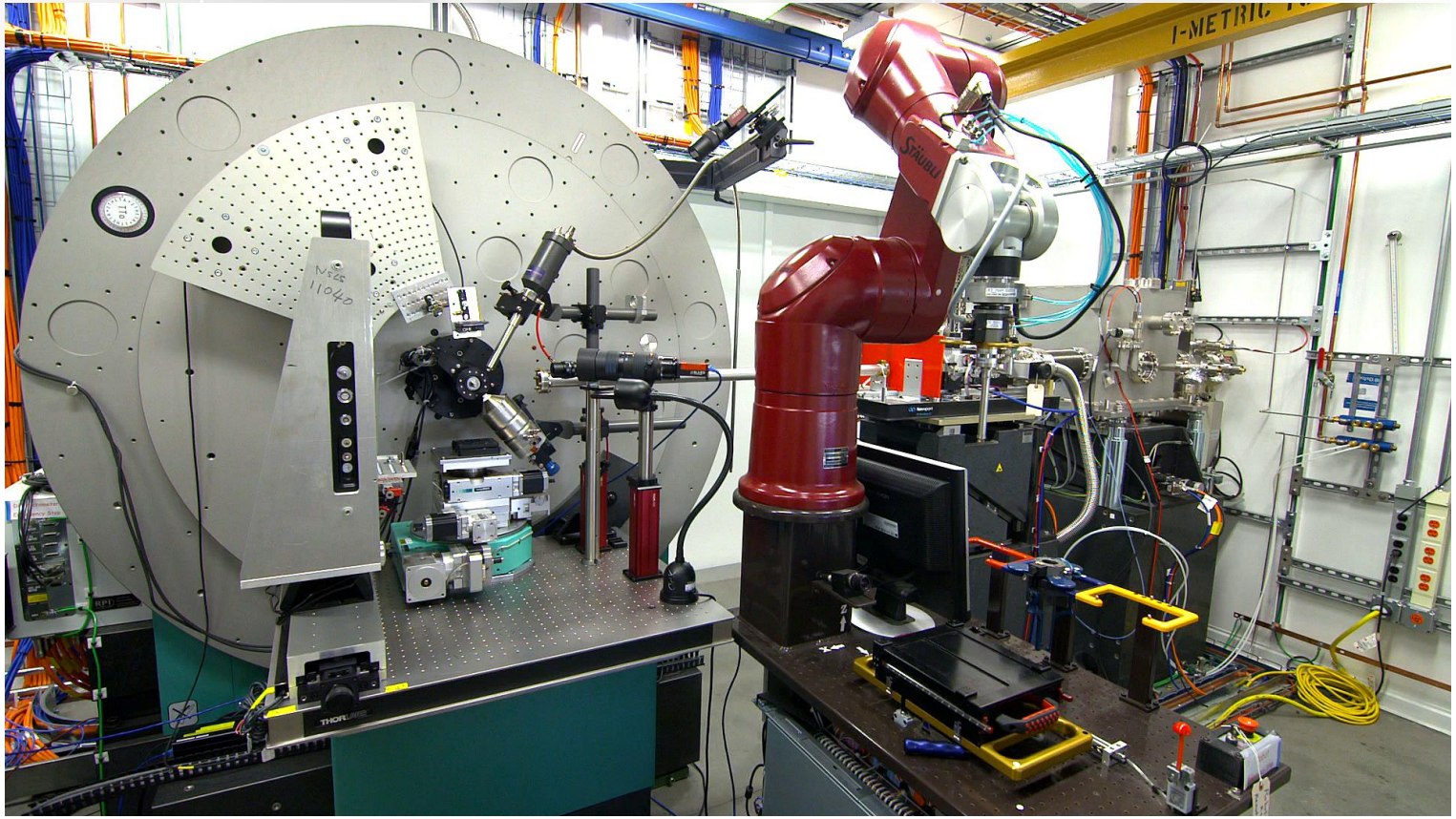




Cut through a single particle
Showing cracks and different oxidation states

Materials Synthesis

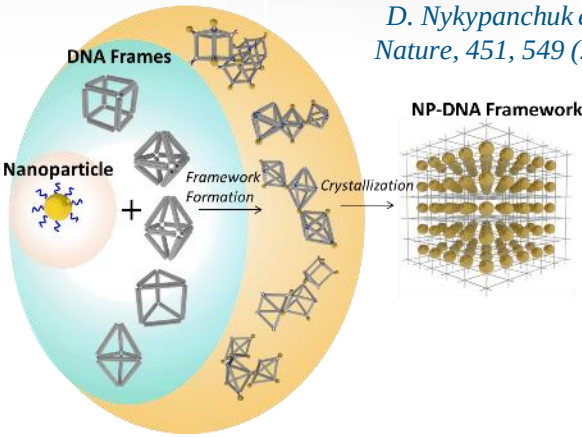
Measurements of atomic structure



- Precise measurements of atomic structure *in-situ*
- Synthesis, batteries, catalysts, nanoparticles,…..
- Robot to process large numbers of samples quickly

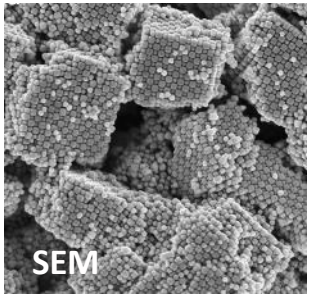
DNA guided assembly

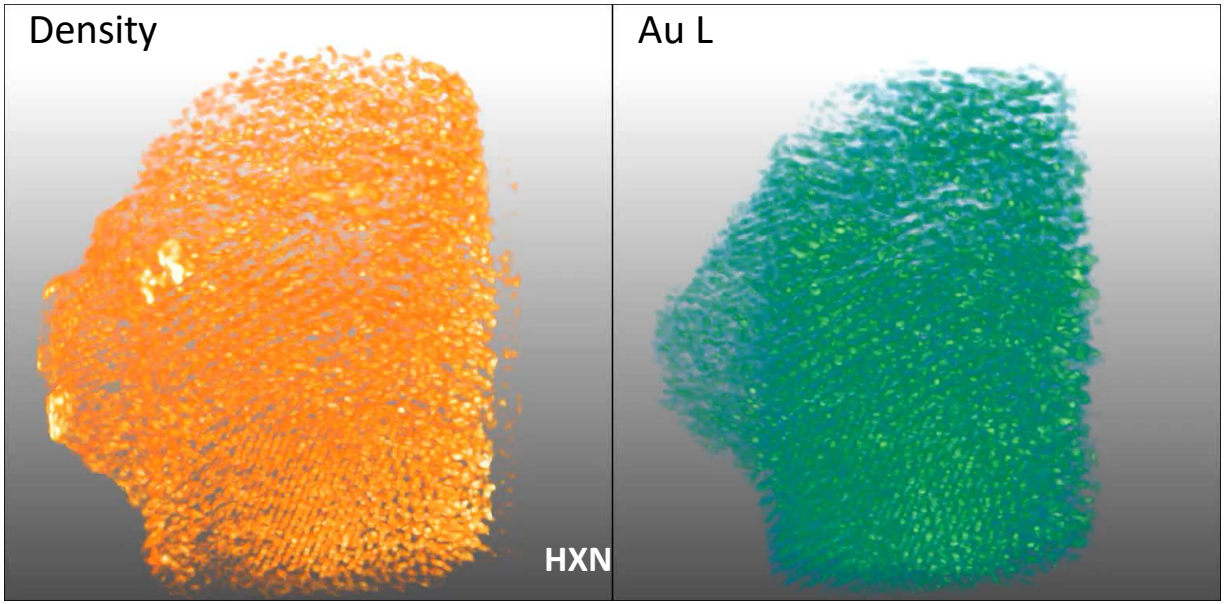
O. Gang (CFN), H. Yan (NSLS-II)



D. Nykypanchuk et al, Nature, 451, 549 (2008)

- DNA-guided 3D assembly process offers the potential to synthesize entirely new materials

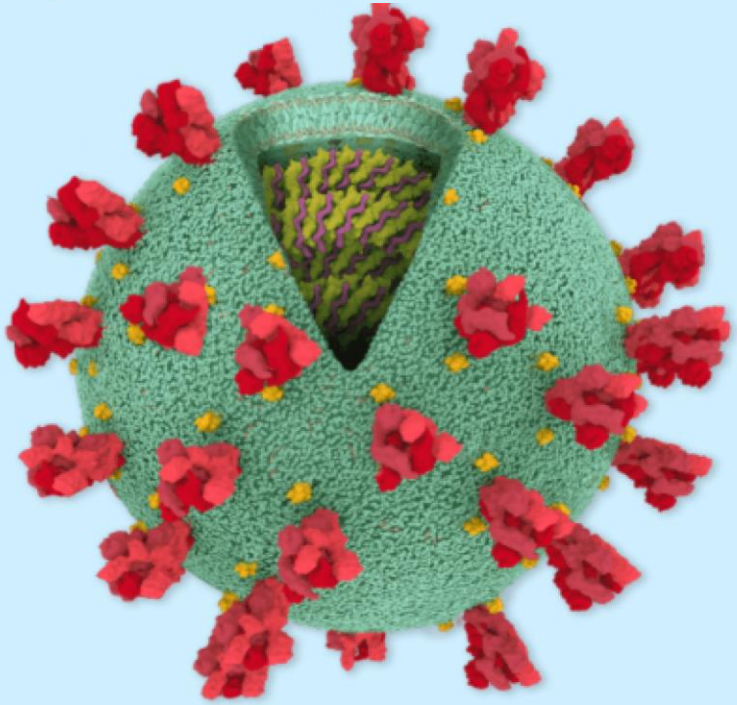




SARS-COV-2 research at NSLS-II

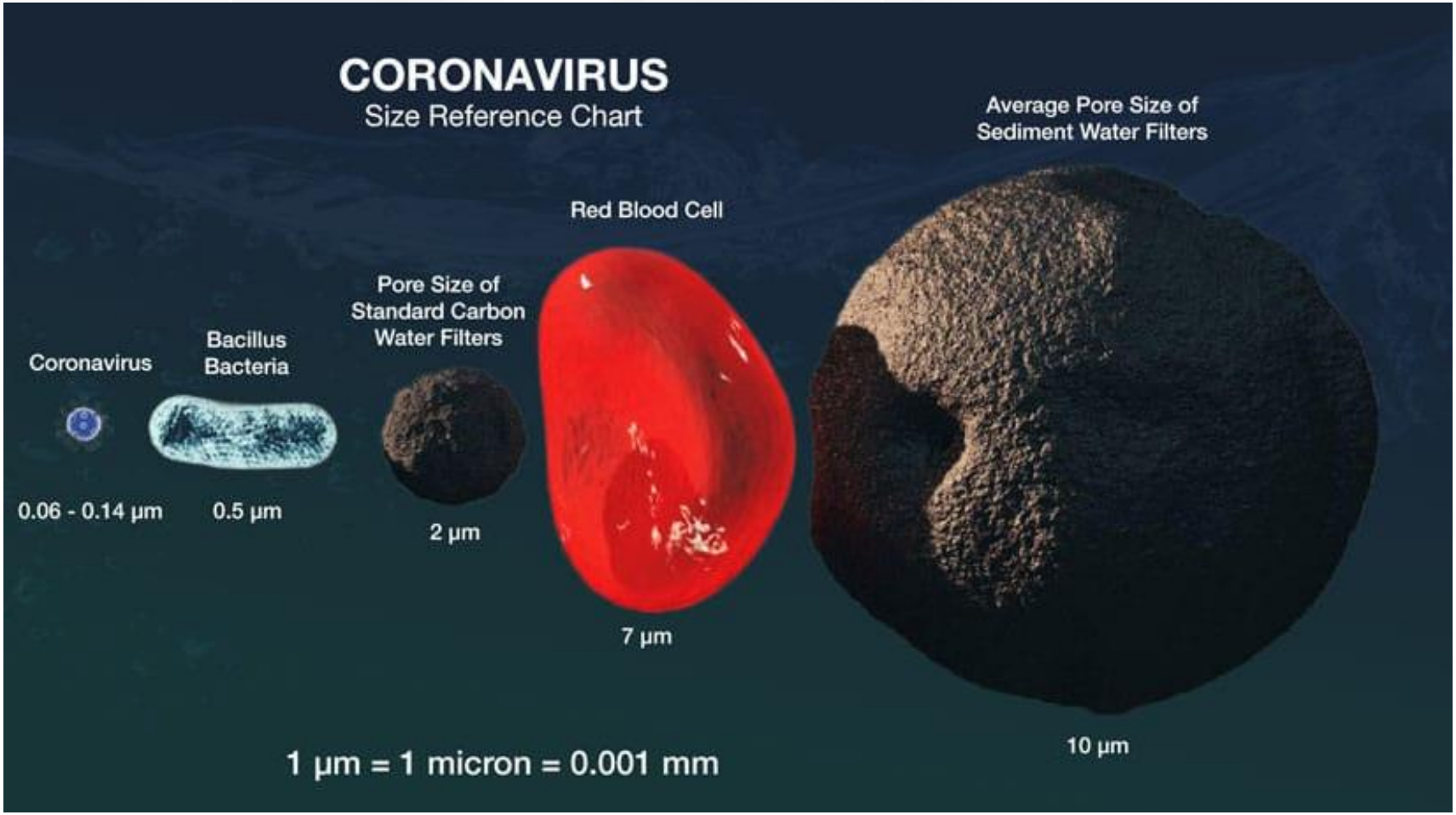
SARS-COV-2

NY Times April 3rd

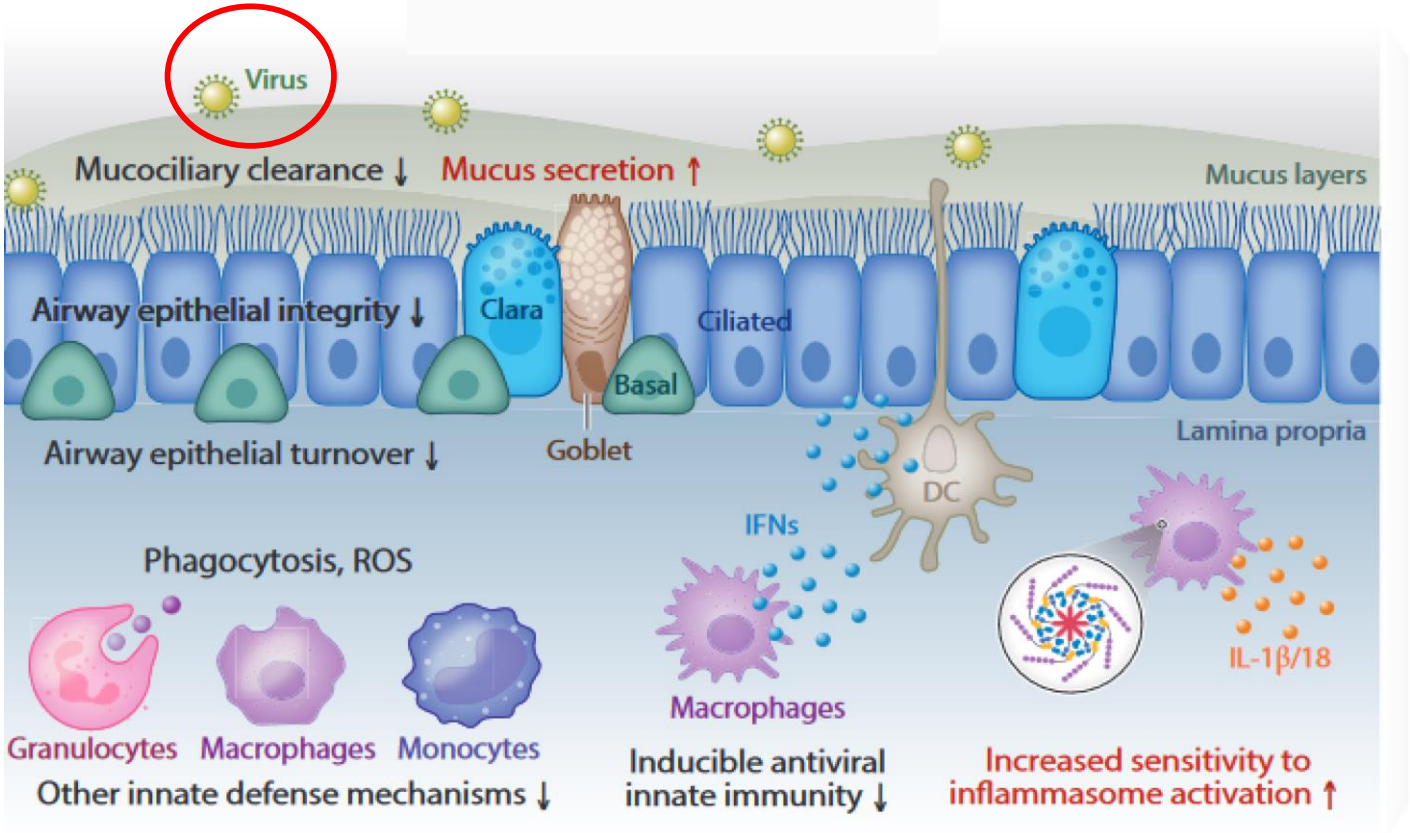


A virus is "simply a piece of bad news wrapped up in protein," the biologists Jean and Peter Medawar wrote in 1977.

Size of virus particle

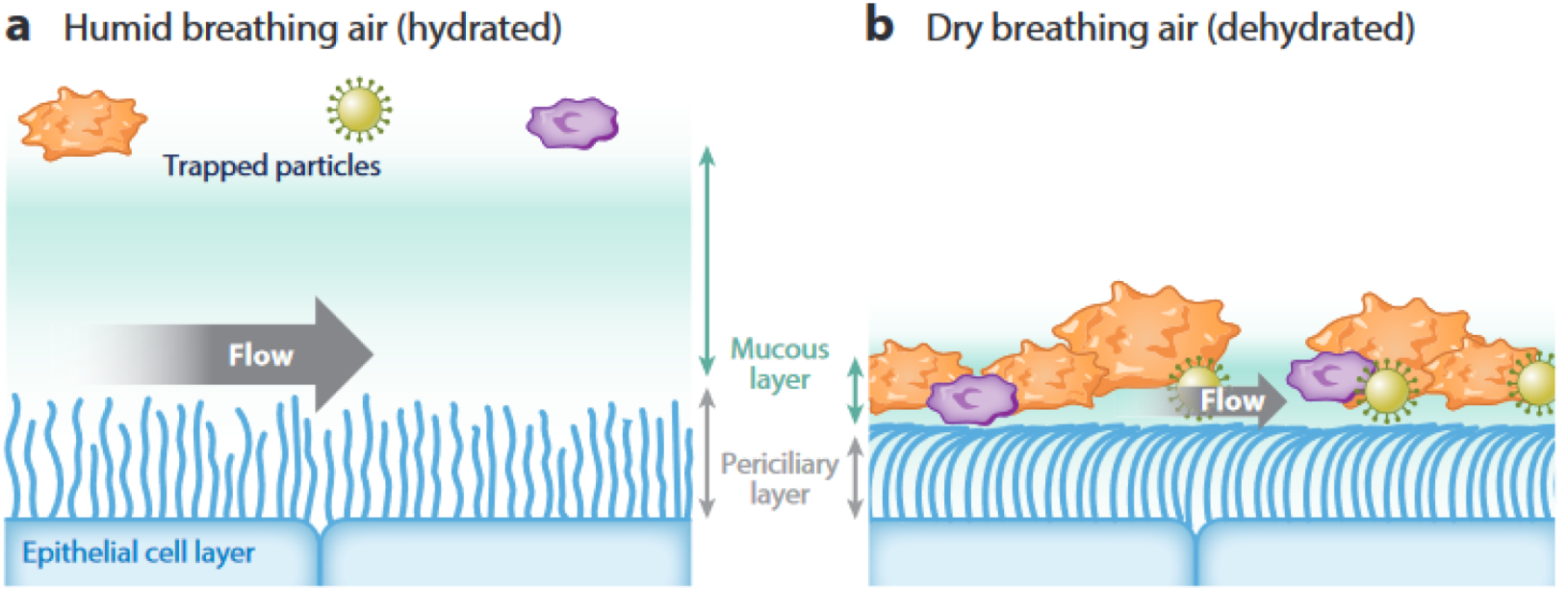


Respiratory Tract



Moriyama et al, Ann Rev Virol, 16 March 2020

Primary Defense

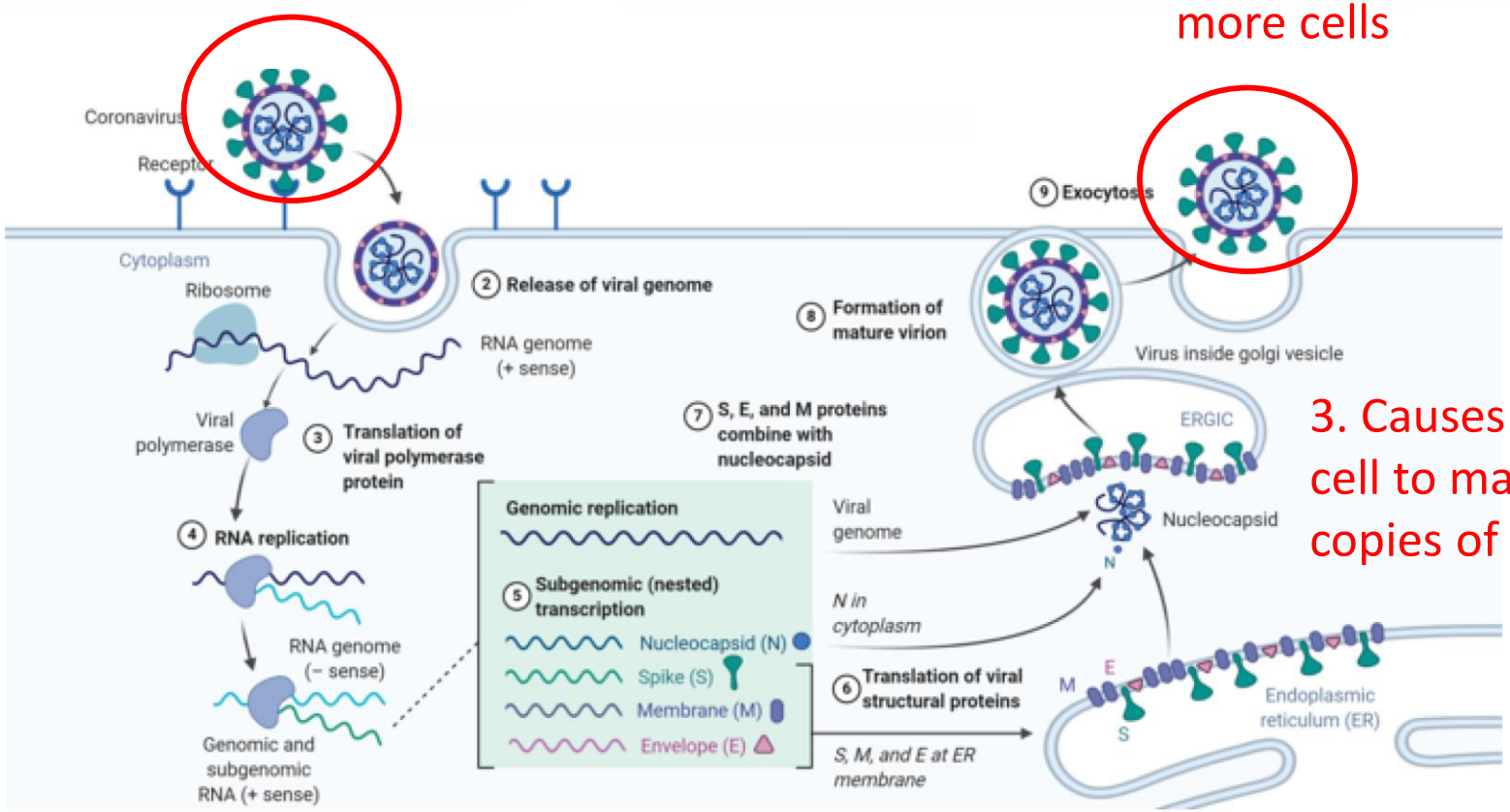


Moriyama et al, Ann Rev Virol, 16 March 2020

Keep hydrated. Use room humidifier

How the virus infects you

1. Virus binds to a “receptor” on your cell



2. Releases its genome inside your cell

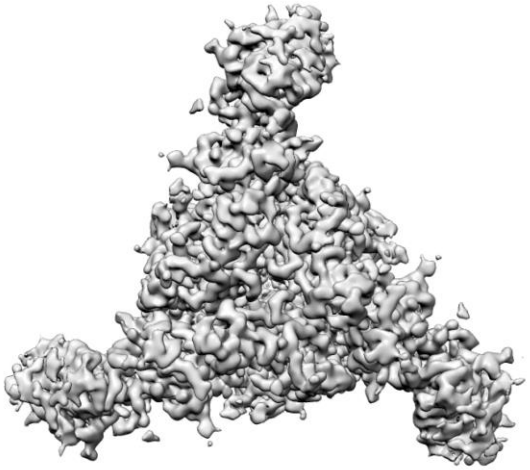
3. Causes your cell to make more copies of the virus

4. Ejects those copies into the body to infect more cells

Protein structure

We need to understand the precise shape of the key proteins involved in the replication of the virus in order to interrupt it

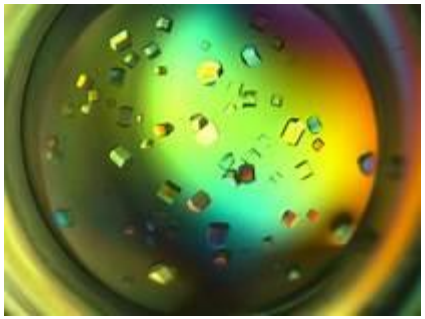
A lot has been learned since Jan 2020:



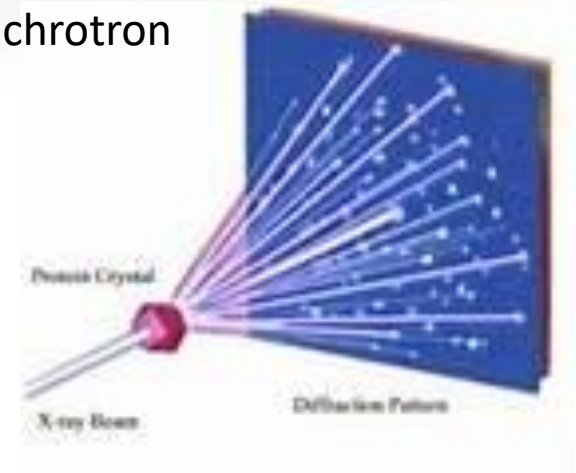
The spike protein structure

How to determine the atomic structure

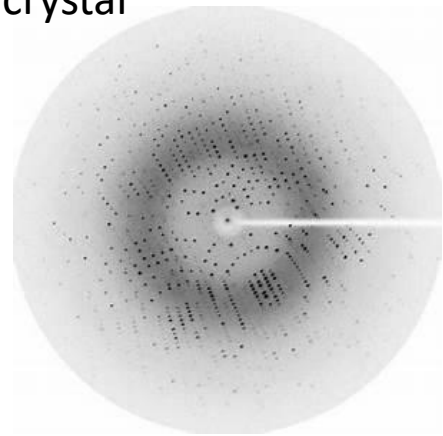
1. Protein crystals



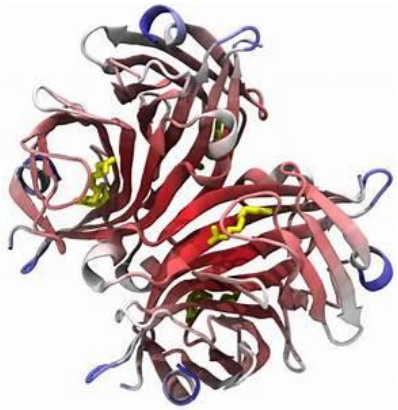
2. Synchrotron x-rays



3. X-ray diffraction pattern from crystal



4. Atomically precise protein structure

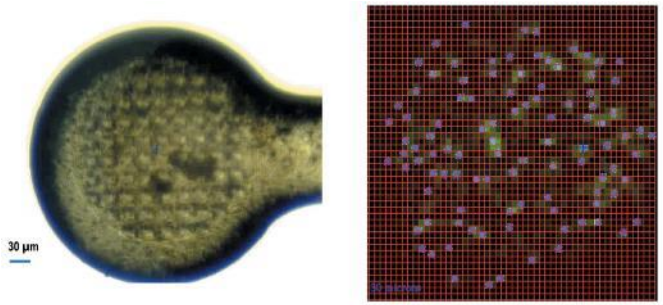


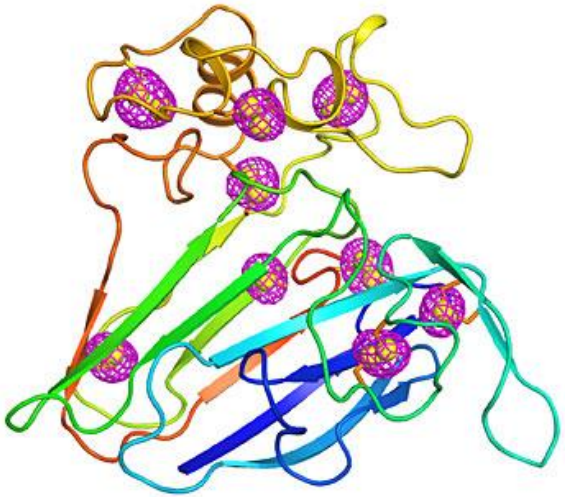
96% of all drugs approved by the FDA in the last 15 years used synchrotron x-rays.

How does NSLS-II help?

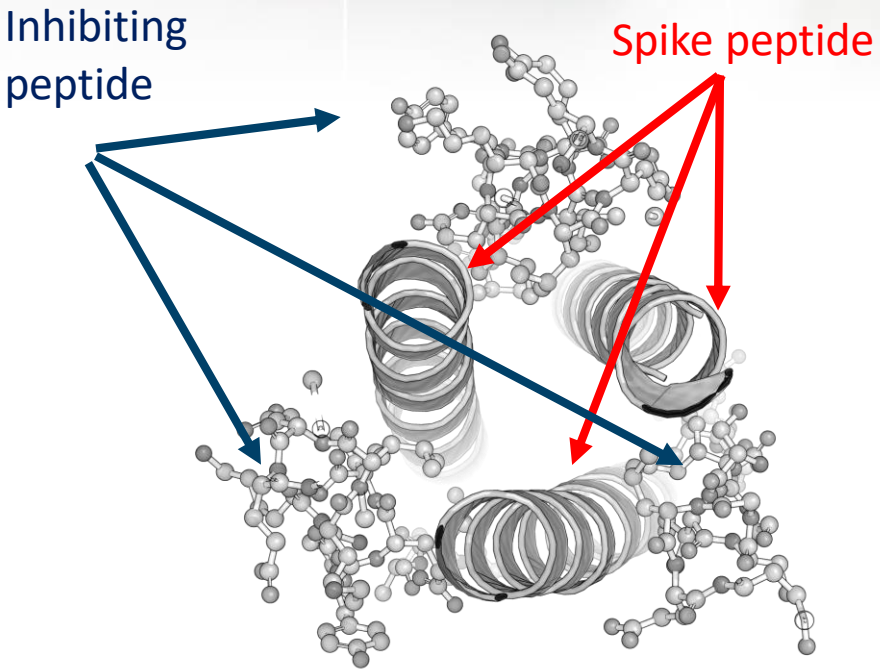
- X-ray scattering from protein crystals gives structure to atomic precision
- Growing large enough single crystals is the bottleneck in determining structure
- Automation and intense x-ray beams at NSLS-II allow the study of smallest crystals in the world
- Down to ~ 1 micron (1/100th of the width of a human hair)
- This greatly speeds up solving the structure and searching for new drugs

Guo et al. *IUCr J.* **6**, Part 4, July 2019.

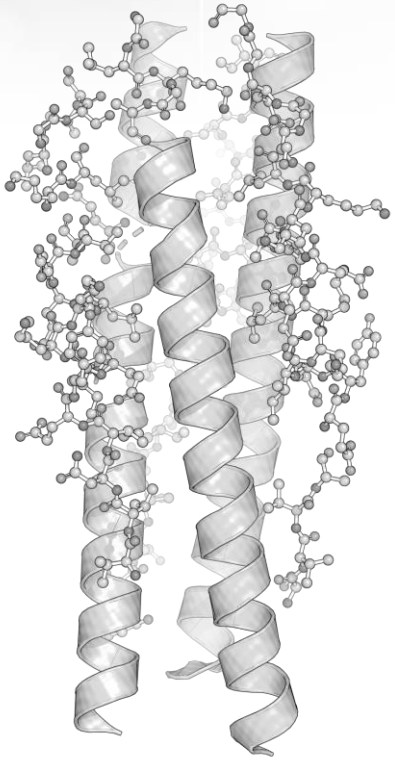




Some NSLS-II results:



Top view



Side view

Goal is to find something that binds with the spike protein and prevents it fusing with our cell membrane

Peptide = piece of a protein

Inhibiting viral proteins

Another approach at NSLS-II is to try and disrupt the viral proteins once they are inside your cell

The main protease from COVID-19, with ligand bound

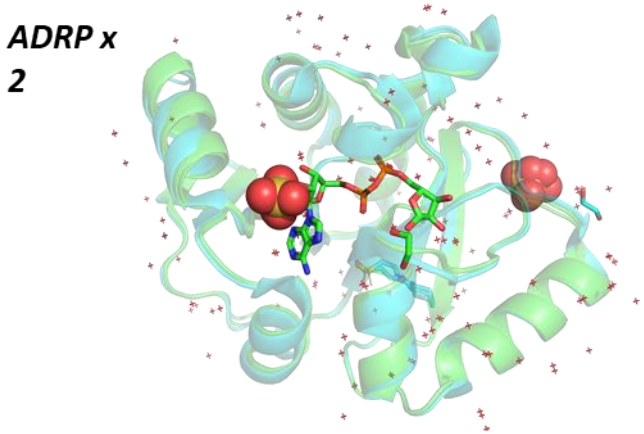
Is it possible to repurpose existing (FDA approved) drugs to inhibit this proteins activity?

We have grown crystals of this and are presently trying various drugs to see if we can determine how and where they bind

Starting materials provided by M. Walsh Diamond Lightsource UK

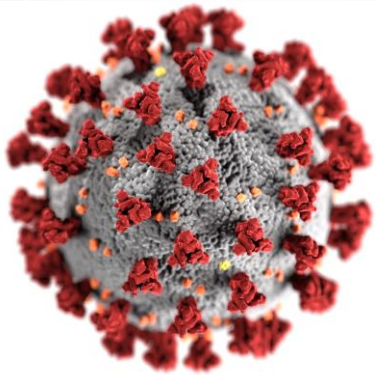
How is it safe?

1. We are NOT looking at the virus itself. We are looking at pieces of some of the proteins
2. These pieces cannot infect a cell
3. The pieces are synthesized in a lab, knowing the gene sequence of the viral protein. They do NOT come from the virus. There is no chance of a virus particle being included in the synthesis
4. Think of them like “photocopies”. They are inert
5. The crystals are kept at liquid nitrogen temperatures and tracked in and out of the lab. A robot handles them at the beamline

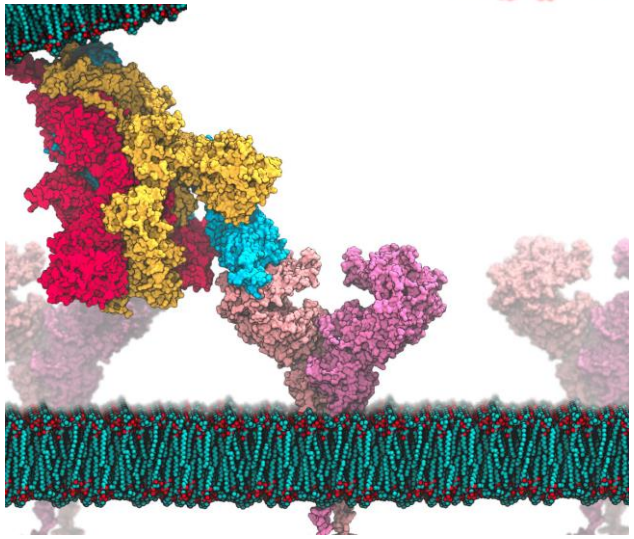


Computational Research

Computer-based Drug Discovery



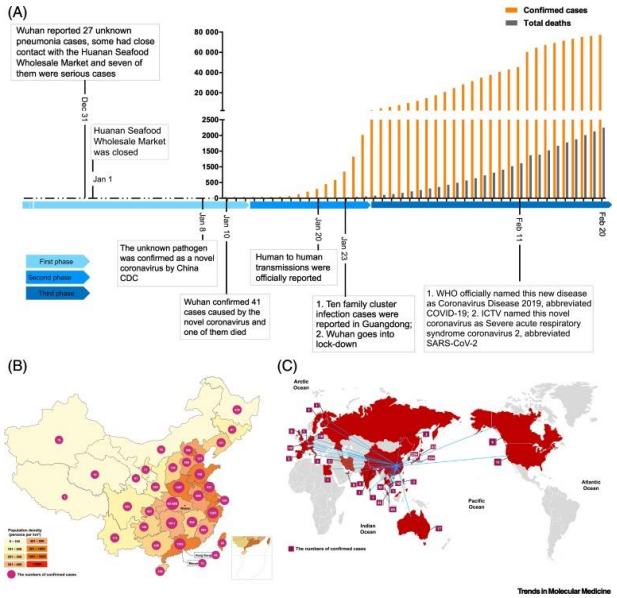
- There are 68 ‘Pockets’ on the spikes where a potential vaccine/drug could ‘bind’ to stop the virus from connecting
- 4 billion drug compounds that could potentially ‘bind’ to those pockets
- Gives **68 x 4 billion** possibilities!
- BNL and partners are using computers to test out all possible options and assess which ones are most likely to succeed.
- The most likely drug compounds can then be tested through experiments and drug trials.



Work funded by DOE’s National Virtual Biotechnology Laboratory

Epidemiology: Predicting the spread of infection

- Goal is to predict:
  - How many will get infected? How many will need hospital treatment? What measures will be effective?
- These questions need to be answered for a given region:
  - What protective measures are in place and when? Are people adhering to restrictions? How many people travel through the region? What is the general health of the population?
- Running these complex models is very time consuming and each model has to be run many, many times to account for different scenarios and changes.
- Using Artificial Intelligence, BNL and its partners are creating faster models that would allow us to study more scenarios quicker - this will help us to gain more confidence in the results

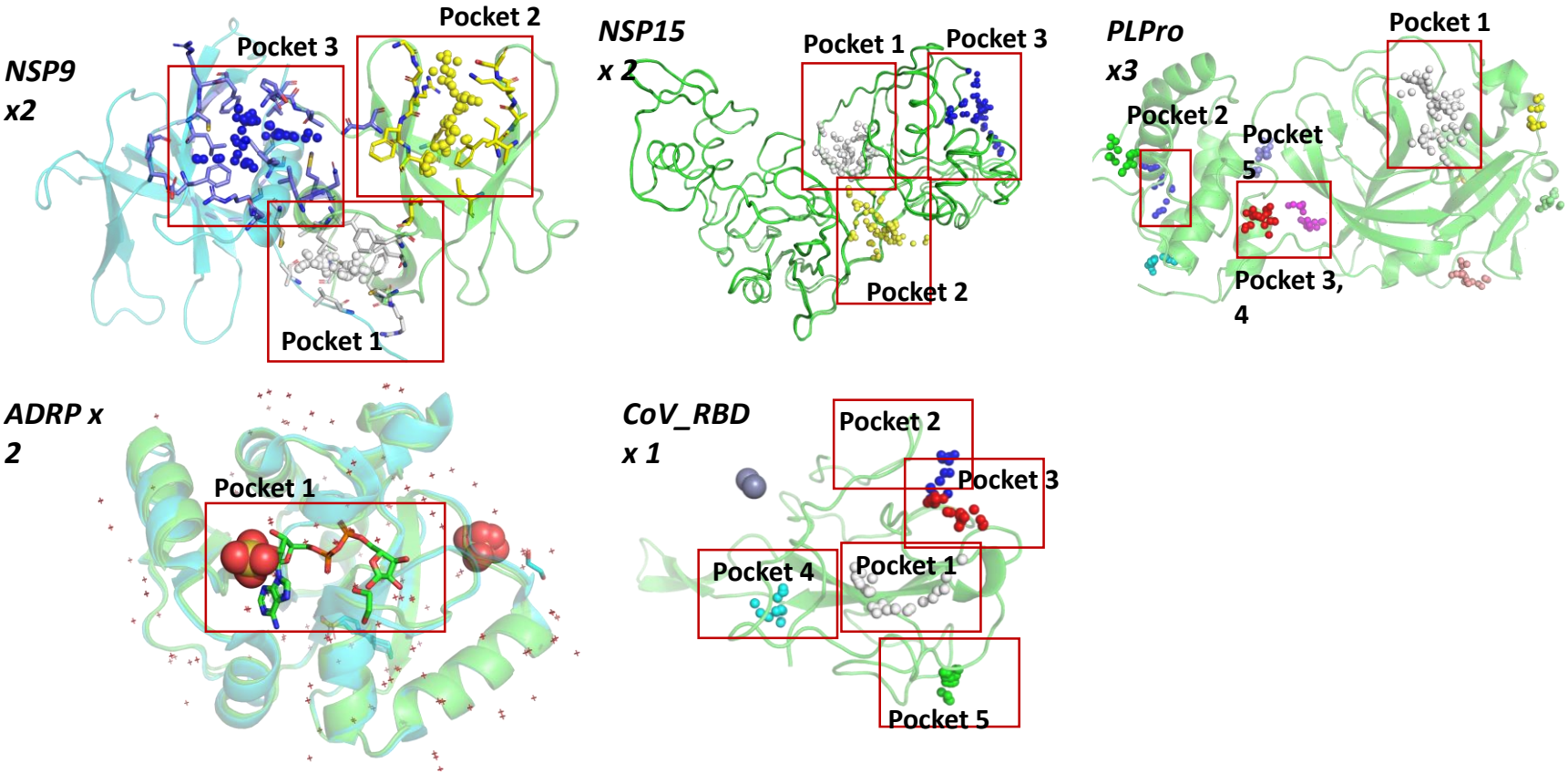


Summary: Some good news

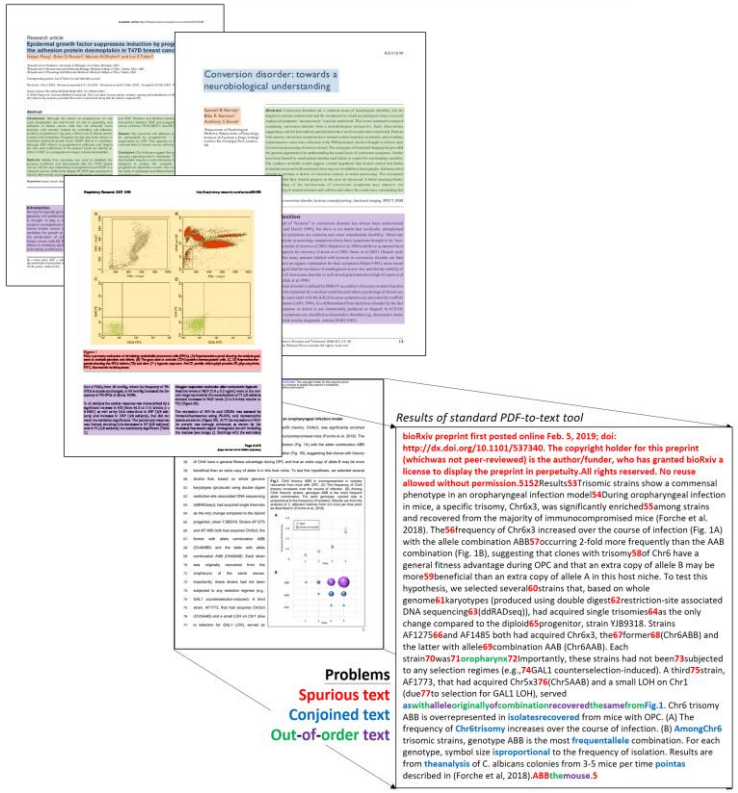
- We understand a lot about Coronaviruses
- A solution will be found. Likely first anti-virals, then vaccines
- We have many good avenues to explore, verify and move forward
- The DOE National labs are working together
- International cooperation is happening
- BNL is part of the fight
  - Drug discovery
  - Computer modeling
  - Virus transport
  - Materials manufacturing

BACKUP

Targets and binding sites



Searching the Literature for the Researchers



- Over **70,000** research papers have been published on aspects of Covid-19
- Having the latest information point to new avenues and avoid wasting time on dead ends.
- However no one can read so many papers - several 1000s a week
- BNL is using Artificial Intelligence to analyse the papers and answer simple questions - what has been written about X, has someone reported symptom Y, has anyone looked at drug compound x?
- We can find relevant text, images and tables in the publications quickly and show them to the researchers.

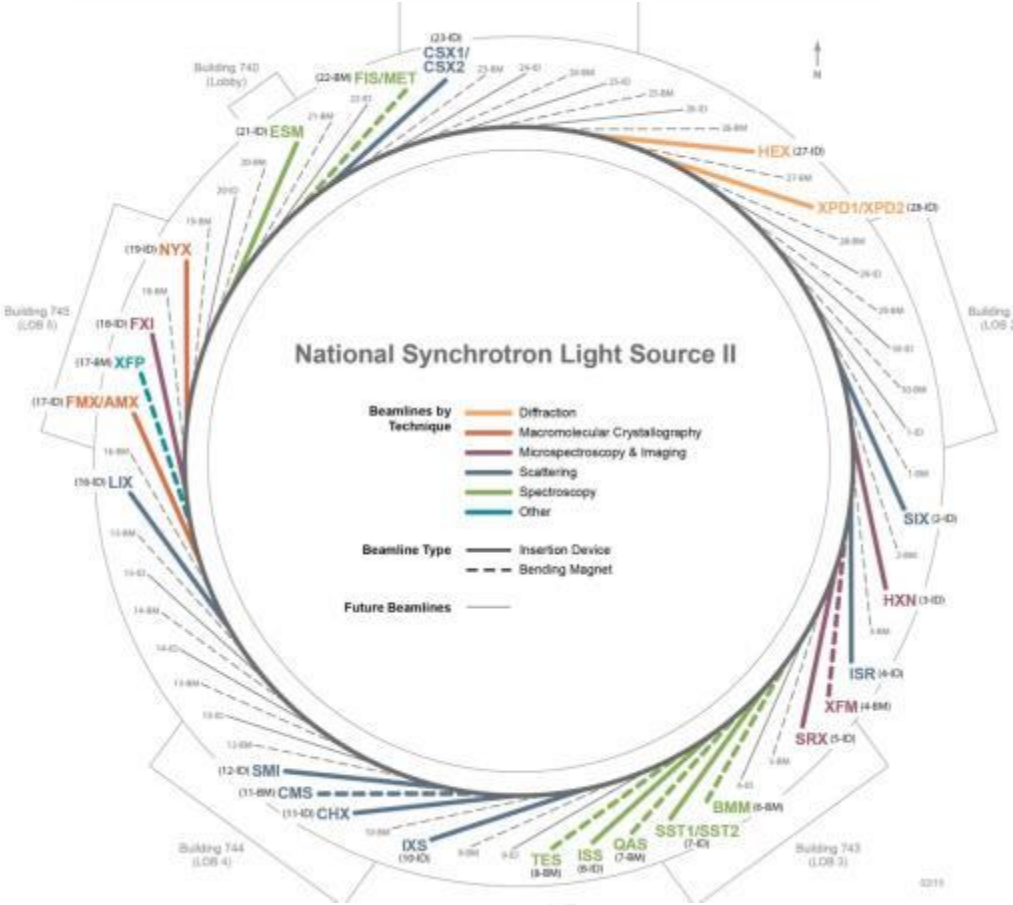
Summary

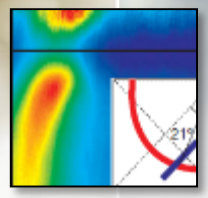
- NSLS-II provides state-of-the-art tools and the scientist experts to use them
- Having impact in wide ranging scientific areas
- User facility – free to use with intent to publish research
- A number of partnering mechanisms available to develop additional capabilties

NSLS-II Beamlines

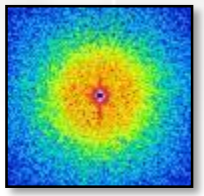
- 28 Operating/Commissioning
- 1 Under Development

http://www.bnl.gov/ps/nsls2/beamlines/map.php



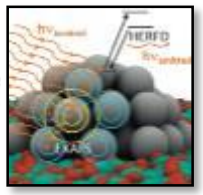


Soft X-Ray Scattering & Spectroscopy
Electronic and magnetic structures and excitations

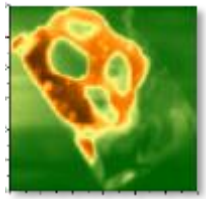


Complex Scattering
Soft materials, structures and dynamics

Diffraction & In Situ Scattering
Hard materials, *in operando* Structure



Hard X-Ray Spectroscopy
Chemical reactions *in operando*

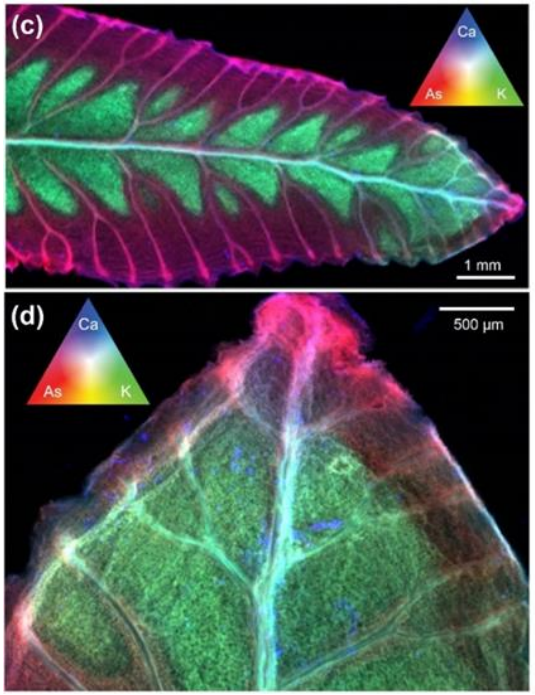


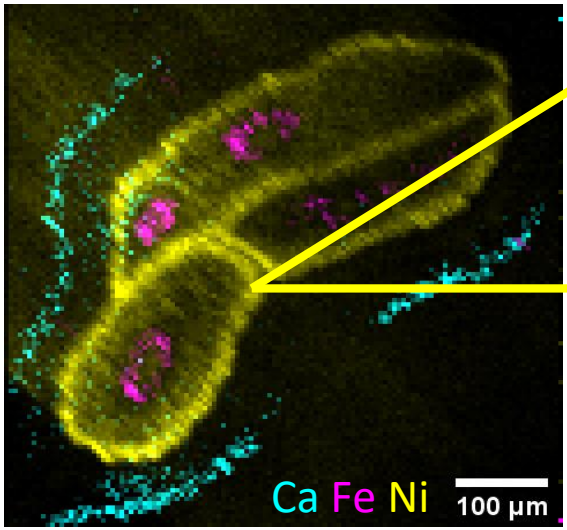
Imaging & Microscopy
Chemical, structural and morphological imaging down to 5nm

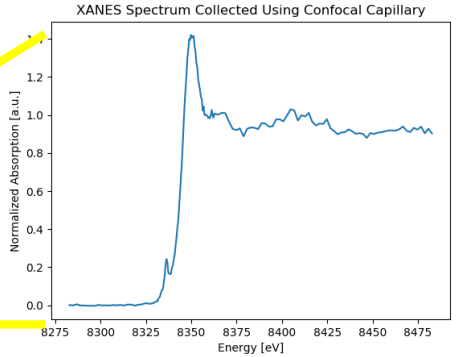
Structural Biology
Protein structures to 1 A resolution from ~1 micron crystals

Spectroscopic imaging from nm to mm

Arsenic uptake in leaves







Kopittke *et al.*, 2018. Plant Physiology (DOI: 10.1104/pp.18.00759).

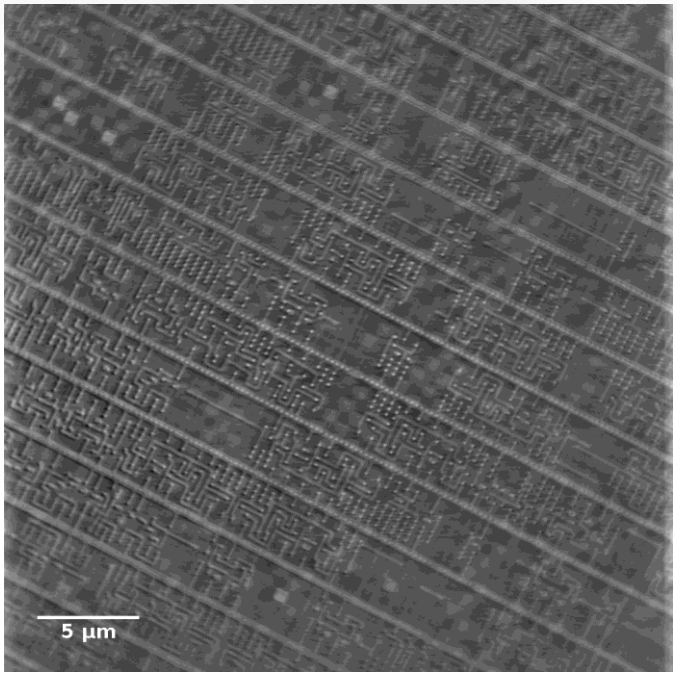
Not just elemental sensitivity, but spectroscopic (chemical) information too with unprecedented resolution and sensitivity

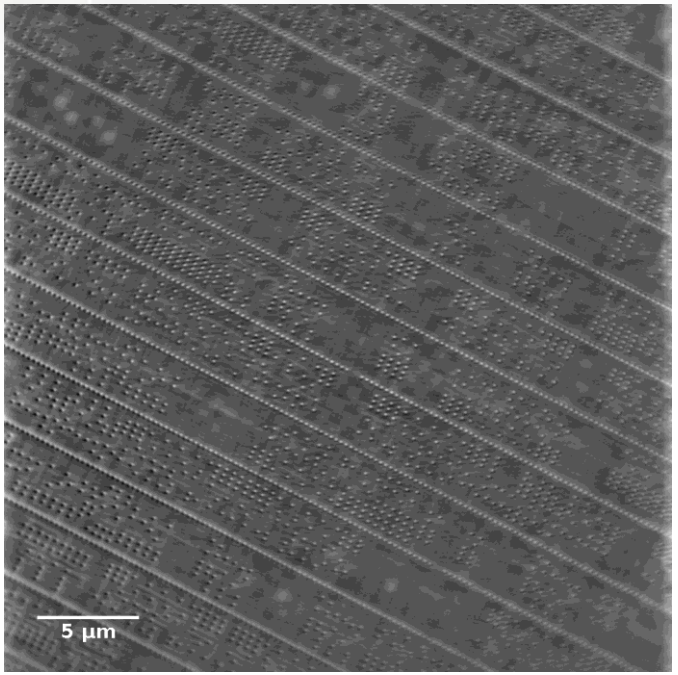
Microelectronics

NSLS-II and Microelectronics

- Legacy electronics – mapping chip architecture of existing chip sets
- State-of-the-art electronics – understanding the factors limiting the performance of current technologies
- 'Beyond-Moore's law' - carrying out the basic science behind the next generation information processing and storage, including technologies such as neuromorphics, spintronics, magnonics, …

Imaging of microelectronics

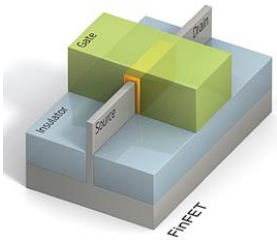




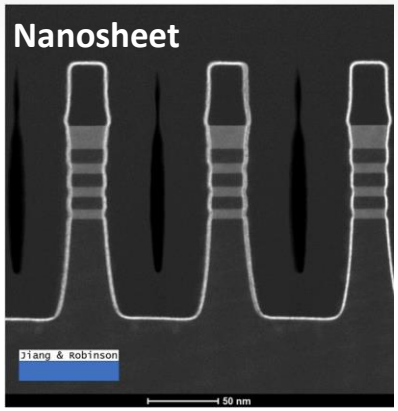
Two different layers in the integrated circuit
Smallest features are 90 nm
Complete 3D tomography data set taken in 15 seconds* (~300 projections)
~ 500-1000X faster compared with lab-based TXM
*limited by camera frame speed, not photon flux. With a faster camera, total time will be < 10 s

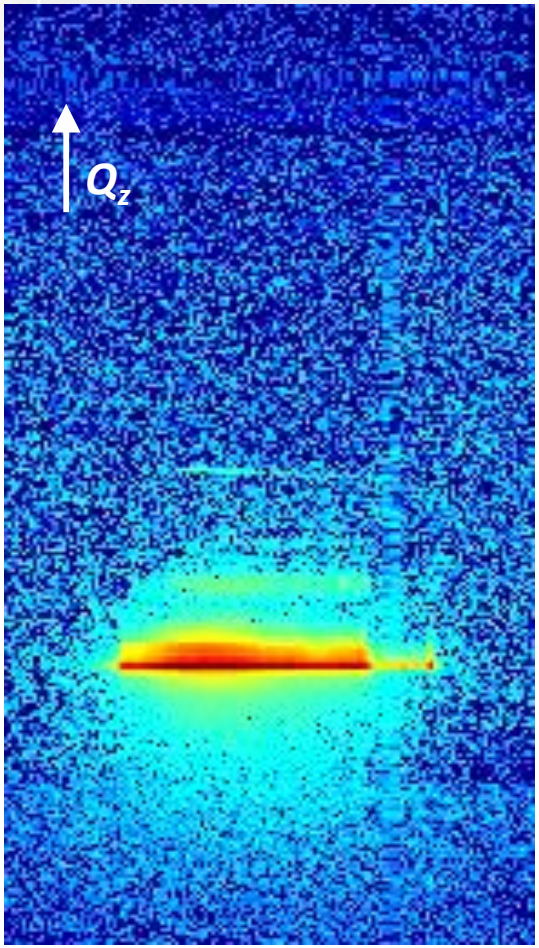
Scanning imaging: Nano Diffraction from Nanosheet

FinFET



IBM





- Strain determines performance of the next-generation microprocessors *e.g.* in IBM's new nanosheet technology
- Studied 7 nm thick and 100 nm wide nanosheet
- Can do such measurements while current is flowing - operando

C. Lavoie, C. Murray, J. Jordan-Sweet (IBM);

H. Yan, X. Huang, Y. Chu (NSLS-II)

Nano-diffraction at HXN (5 sec/frame)

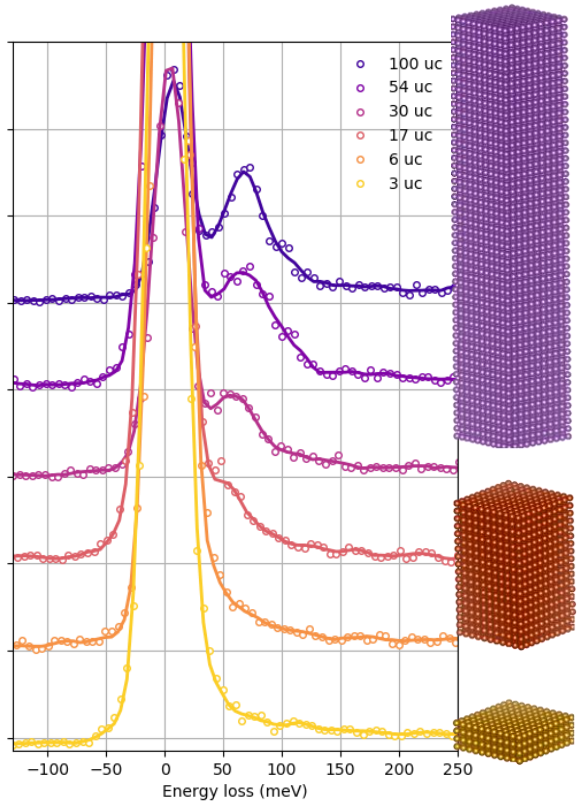
IBM Research. Samples fabricated at SUNY-Poly

Beyond Moore's law: Using spin-waves for information processing

Spin waves are potentially much more energy efficient

SIX is only beamline in the world with the resolution to carry out these measurements

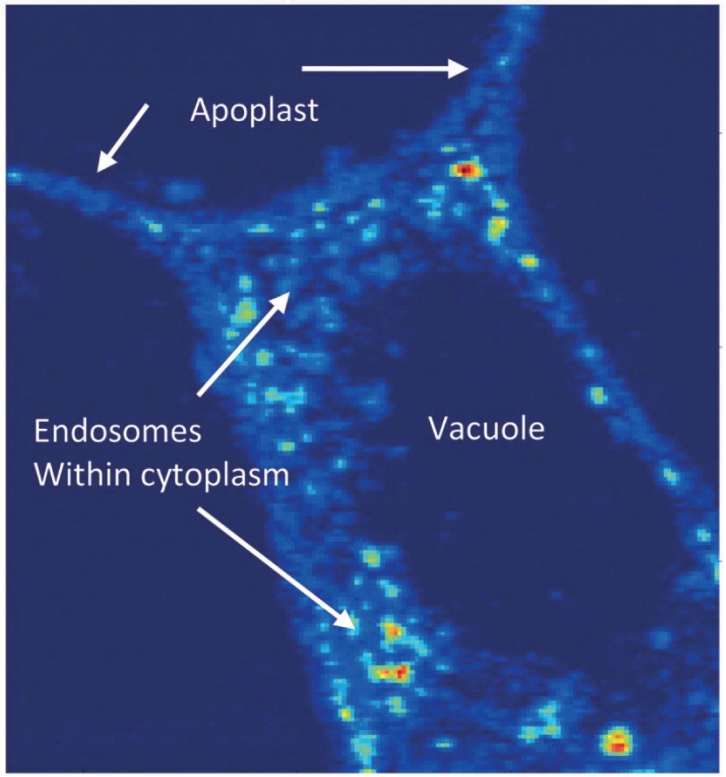
First results: Spin –waves in ultra-thin films of Iron



Valentina Bisogni

Environmental Science

A Nanomaterial's Journey through a Tomato Plant



Scientific Achievement

Revealed how a manufactured nanomaterial (MNM) based on Ce travels through a tomato plant on a subcellular level.

Significance and Impact

This study will enhance our ability to predict how properties of MNM such as CeO_2 – used in rechargeable batteries – influence the uptake, transformation, and transfer of nanomaterials in terrestrial food webs.

J. Li, R. V. Tappero, A. S. Acerbo, H. Yan, Y. Chu, G. V. Lowry, J. M. Unrine. *Environ. Sci.: Nano* **6**, 273 (2019).