Biology with X-ray Free-electron Lasers (BioXFEL)
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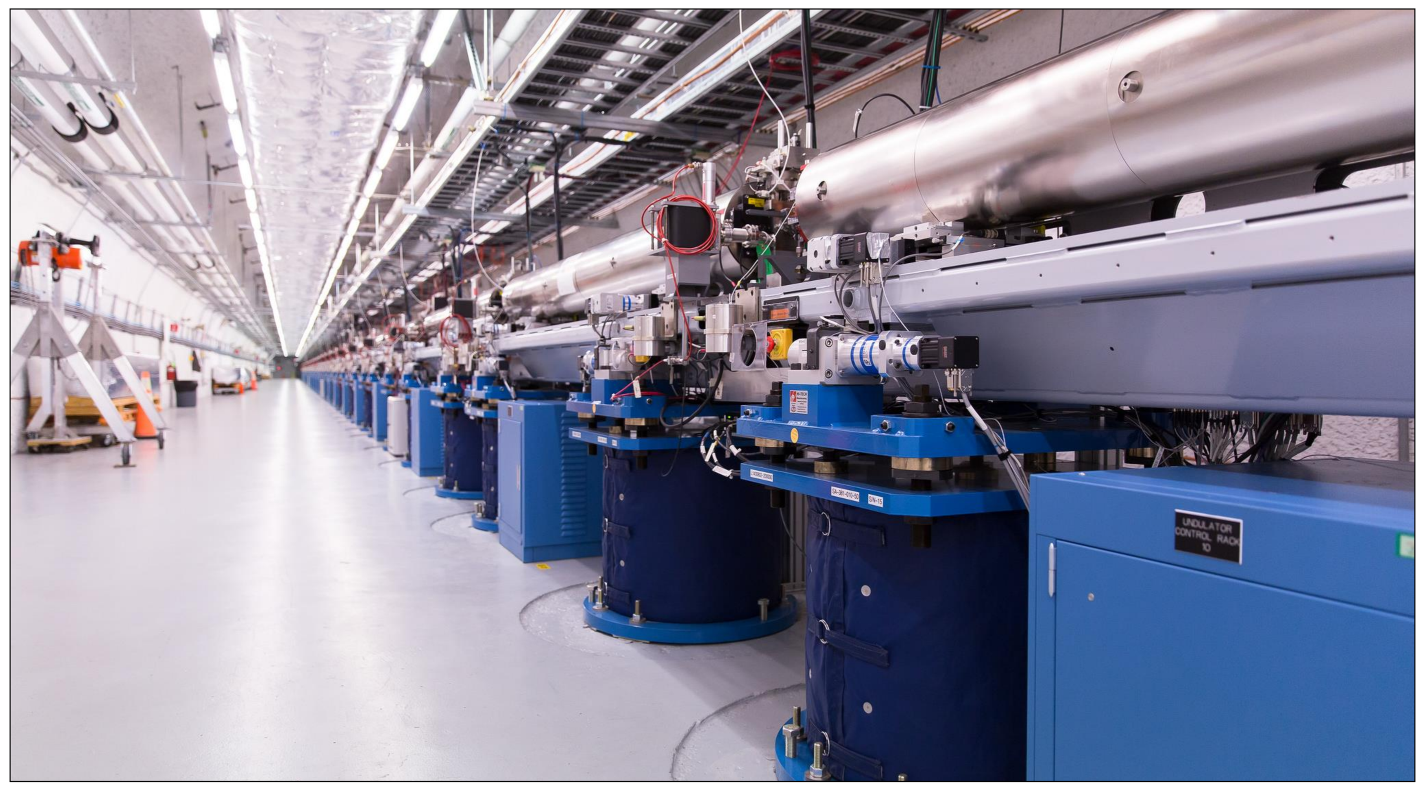
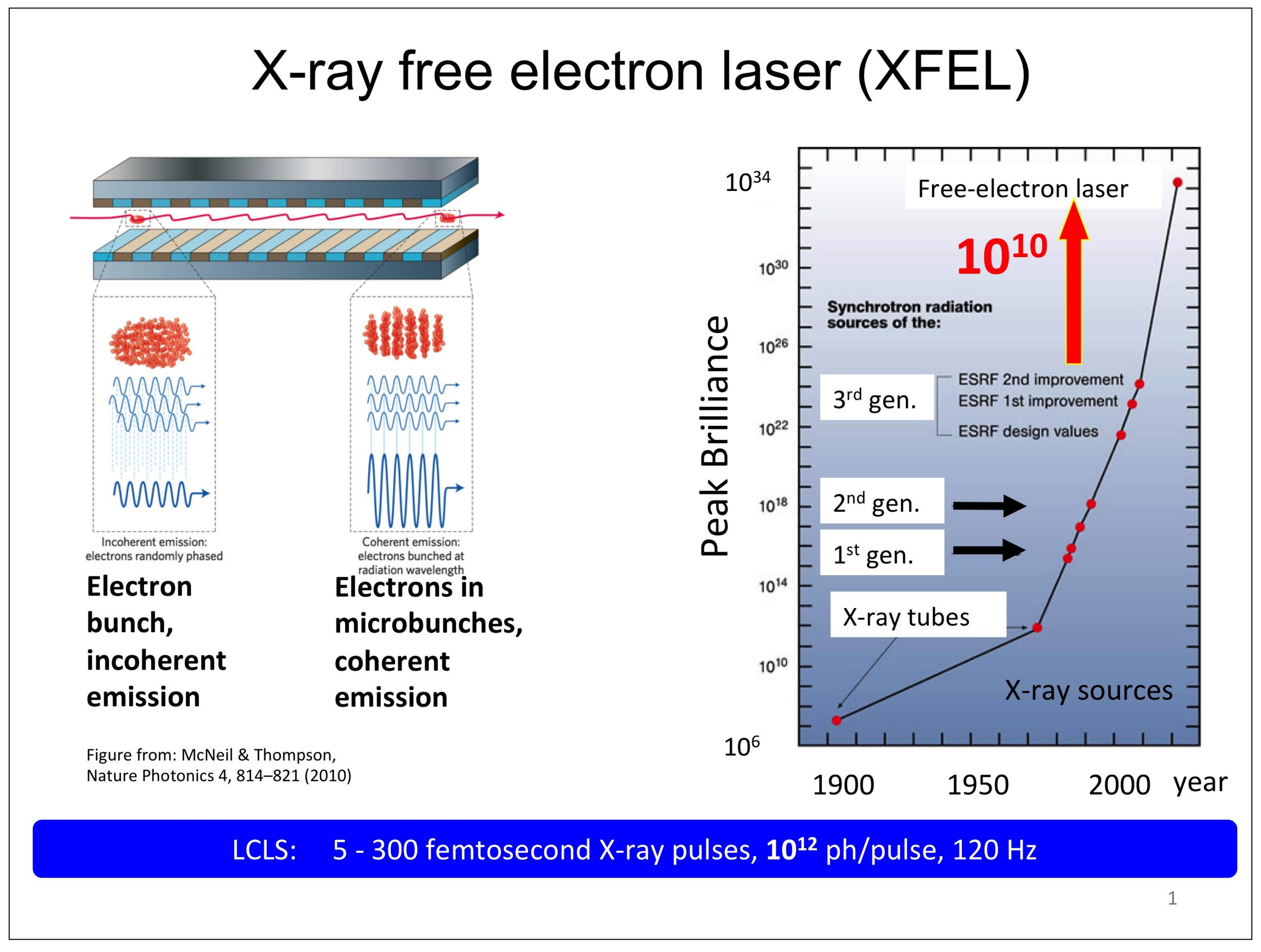
Introduction and Scientific Background

BioXFEL's mission is to develop, test, and promulgate a new paradigm for structural biology: Determining the high-resolution structure and conformational evolution of macromolecules without the need for large crystals, beyond the limit currently set by radiation damage, at room temperature and under controlled chemical conditions. This interdisciplinary effort spans engineering, physics, mathematics, computer science, biochemistry, and biology, involving ten universities, one research institute, three national laboratories, two international research institutes, and one industrial partner.

Our principal tool is the x-ray free-electron laser, as exemplified at this moment by the Linac Coherent Light Source (LCLS) sited at the SLAC National Laboratory near Stanford University. The LCLS has heralded a profound revolution in scientific knowledge. The LCLS is a technological leap over synchrotron sources producing X-ray pulses as short as 10 femtoseconds (10^{-14} seconds) containing up to 10^{13} photons. This pushes the experimental boundaries to smaller samples (such as nanocrystals only a few µm^3 in volume), weaker scatterers and finer time resolution. The XFEL beam produces coherent scattering across micrometer-sized objects, enabling whole new imaging modalities previously impossible.

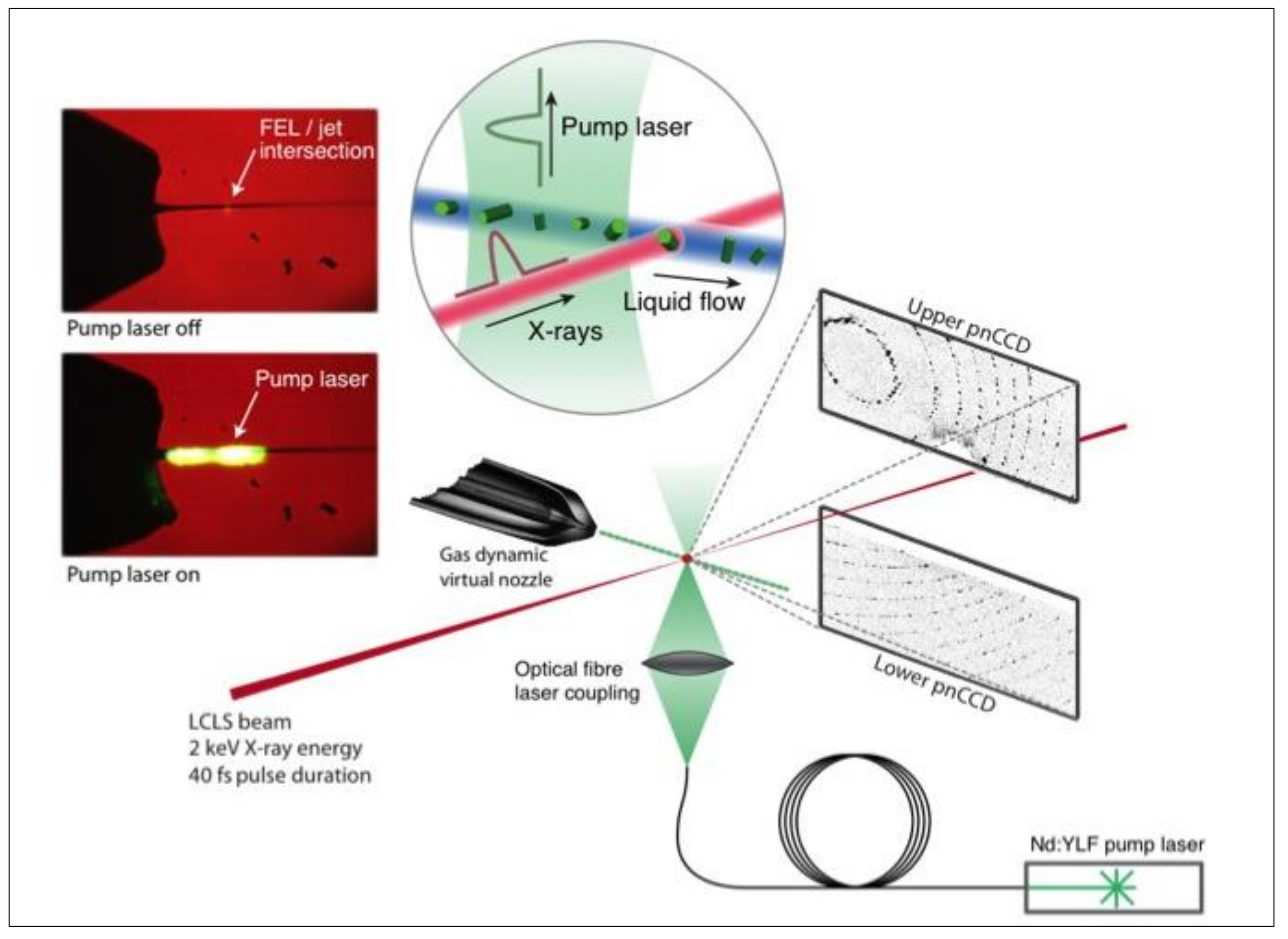


Above: view of LCLS accelerator that creates ultra-short, high energy pulses of electrons used to create x-ray laser light. **Below**: *at upper left* the electron bunches (red dots) are injected into an array of opposed magnets with alternating polarities, forcing the pulses to follow a sinusoidal path. *Lower left* shows blow-up of a pulse. Because they are accelerating, electrons in a bunch radiate x-rays. As the pulse moves through the array, interaction with the radiation field causes it to break up into microbunches spaced one wavelength apart. The waves radiated by these microbunches add in phase to make incredibly intense, coherent radiation. *Right* shows peak brilliance of various sources on a log scale



In its first three years BioXFEL has produced ~100 papers, many in the highest impact journals, spanning achievements in crystallography, algorithm development, and hardware innovation.

•Nanocrystallography has become a reality. Almost 100 structures have been determined at XFELs, including many challenging membrane proteins.
•We have made dramatic progress on the problem of the beam missing the crystal – "low hit rate".
•Time-resolved solution scattering experiments have revealed how the photosynthetic reaction center deals with the unique problems of energy management consequent to the multiphoton absorption of light by its antenna complex. Instead of unfolding the protein this energy is funneled to the lipid layer at the surface of this membrane proteins, using a process called a "protein quake."
•Using the flashbulb effect of ultra-short XFEL pulses, BioXFEL scientists led by Marius Schmidt have created a molecular movie of the light-sensitive Photoactive Yellow Protein as it moves through its functional cycle. This movie shows clearly the first molecular event in vision, the trans-to-cis bond rotation in the coumaric acid chromophore linked to this protein. See below.

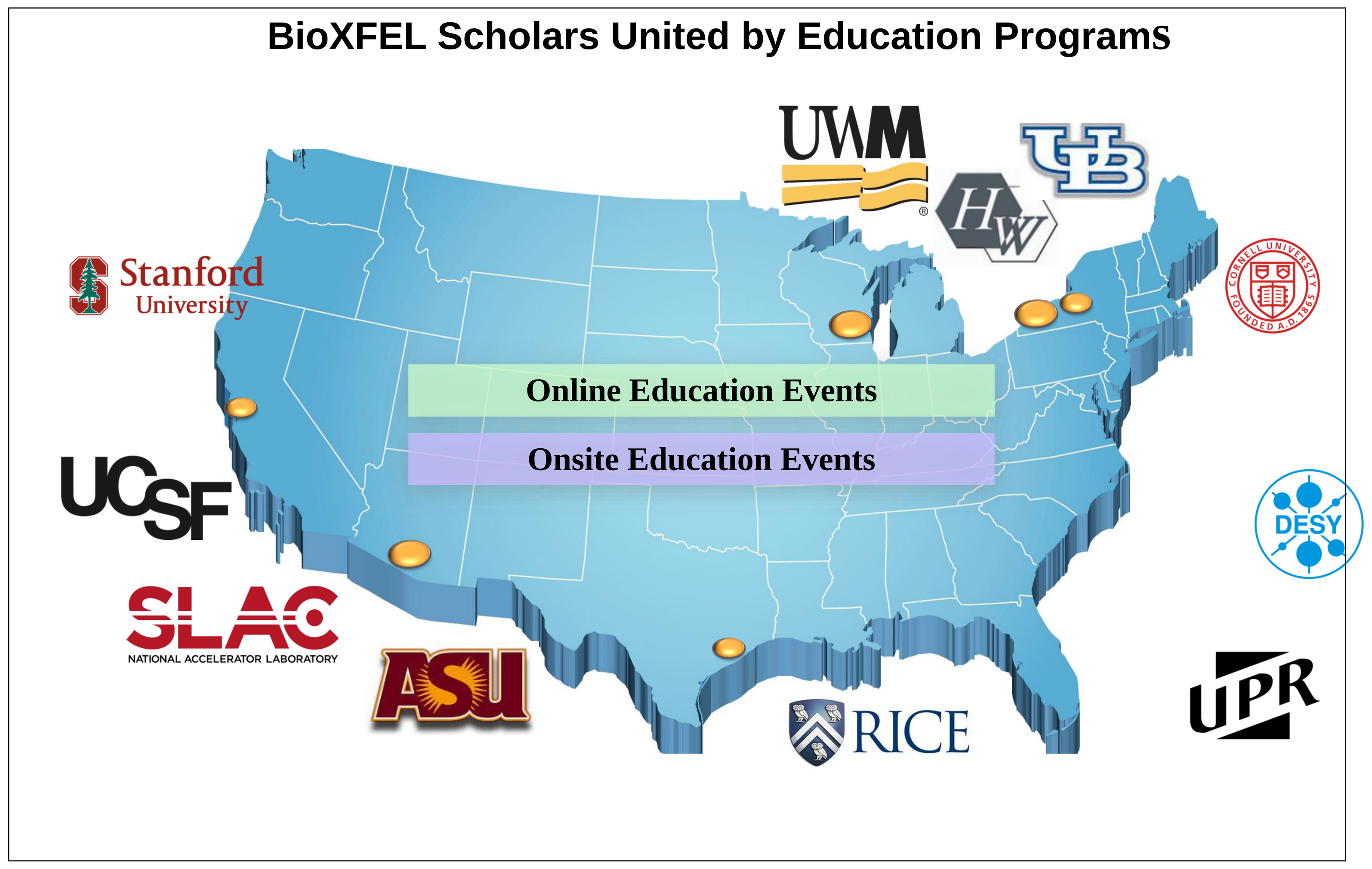


Layout of time-resolved crystallography experiment. XFEL beam (red) moves *lower left* towards *upper right*, and strikes a light-activatable protein crystal carried in a jet of liquid created by the nozzle. Scattered x-rays are captured by upper and lower panels *middle right*. Lower middle show optical laser pulse aimed at crystal to activate it. The interaction region is enlarged at upper middle, showing the optical pump laser striking the crystal jet just before the x-ray beam. The delay between the activation and the imaging steps is varied by the time it takes the liquid to flow from the pump laser beam to the x-ray beam, and each time delay represents a single frame of a molecular movie. The red panels at *upper left* show the crystal-carrying stream being illuminated by the optical laser.

BioXFEL Participants

University at Buffalo, SUNY (Lead)	Hauptman-Woodward Institute
Cornell University	University Wisconsin, Milwaukee
Rice University	Arizona State University
Stanford University	University of California, SF
University of Southern California	University of Pittsburgh
SLAC National Laboratory	Lawrence Berkeley Nat Lab
Industrial Macromolecular Crystallography Association	University of Puerto Rico
EXFEL, DESY, Hamburg Germany	Many others

Education & Diversity Programs



The BioXFEL Education and Diversity programming employs a customized trainee-centric approach. BioXFEL scholars have created a cohesive group, known as the Association of BioXFEL Young Scientists (ABYS) to direct and personalize their own educational experiences and professional development activities. ABYS informs the Education and Diversity Committee of their requests and priorities so that the Committee may develop specific programs, directly addresses the needs of the students and postdoctoral scholars. Our new diversity plan has been redesigned to focus on collaborations with minority-serving institutions by creating a customized set of programs. These programs are designed to fully integrate the members of the institutions into the scientific and educational objectives of the Center while also meeting the needs of the participants. Our collaboration with UPR will be used to develop programs and guidelines for incorporation of minorities that are underrepresented in science and can be applied to future collaborations.

Summary of Education Programs

BioXFEL workshops

1. Crystallization workshop at HWI
2. Data analysis workshop at ACA (July 2014, 2015, 2016)
3. Single Particle Imaging workshop at UWM (September 2015)
4. Protein Production and Purification Workshop (UPR Mayaguez)
5. Remote data collection workshop w/ SSRL (UPR Rio Piedras)

Professional development activities

1. Professional Development seminars at annual conferences
2. BioXFEL postdoctoral scholarship award
3. BioXFEL graduate student cross-training scholarship award
4. Beam time proposal writing exercise at crystallization workshop
5. NSF Professional Development Workshop (August Annually))
6. Professional development materials available on website

Online colloquium series

1. BioXFEL online lecture series presented by BioXFEL scientists
2. BioXFEL scholar journal club presented by BioXFEL scholars
3. Online Crystallography Courses

Internship programs

1. Undergraduate research internships at HWI/UB, ASU, UWM, and Rice Universities
2. UPR graduate student internships
3. Villages training program for high school students at ASU