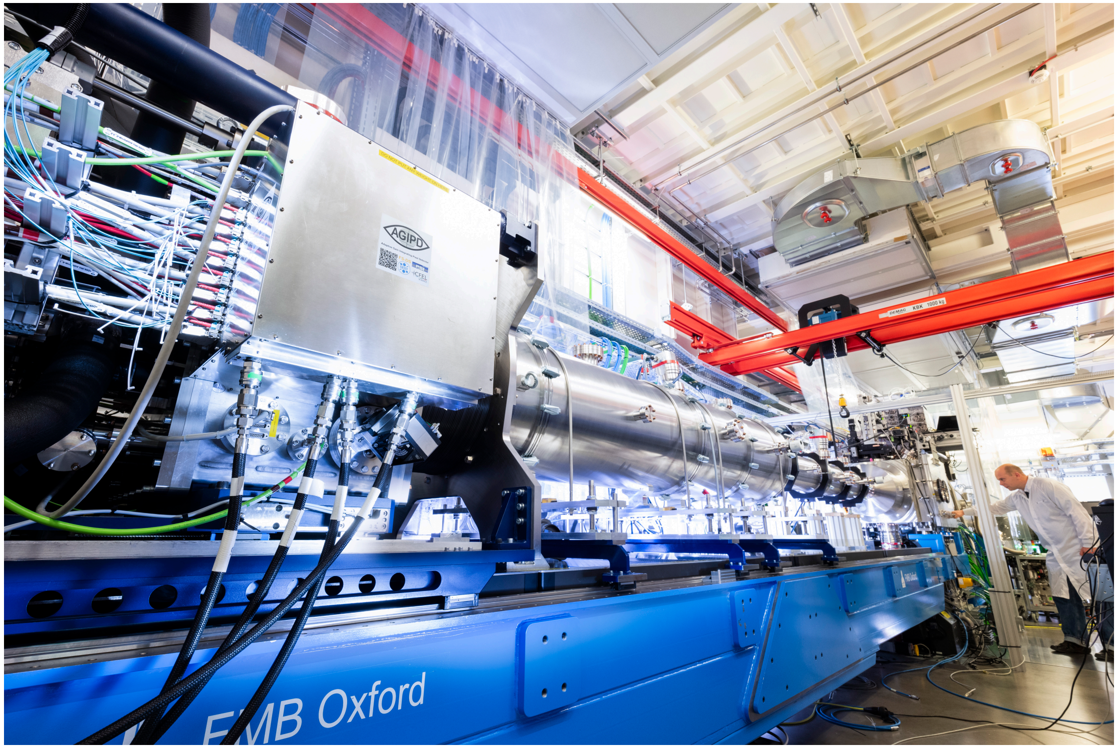
Serial crystallography with XFELs: Overview and photon beam requirements

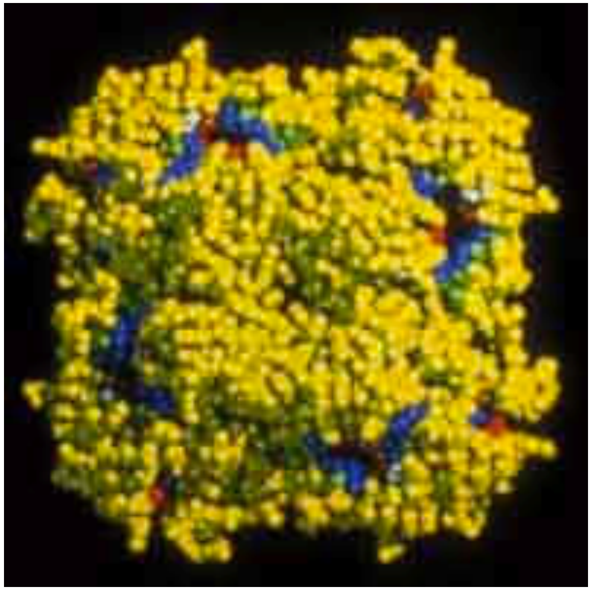
Adrian Mancuso

Leading Scientist SPB/SFX Instrument
European XFEL



Why look at the structure of biomolecules? Why do it at an XFEL?

- Structure of a molecule -> function
- Structure allows, eg, Rational Drug Design, Understanding of human biochemistry.
- Photons (X-rays) allow depth information from intact systems at atomic resolution.
- XFELs make it possible to determine the structure of molecules that are *unable to be imaged by other means*. These are structures typically of biological importance, < microns in size and include membrane proteins—the major class of proteins addressed by modern medicine.



Influenza virus structure - A protein from the influenza virus

Image: J. Varghese et al, CSIRO Health Sciences & Nutrition

Serial crystallography: Structure determination from very small crystals

Crystallography of "small", "radiation sensitive" or "dynamic" samples

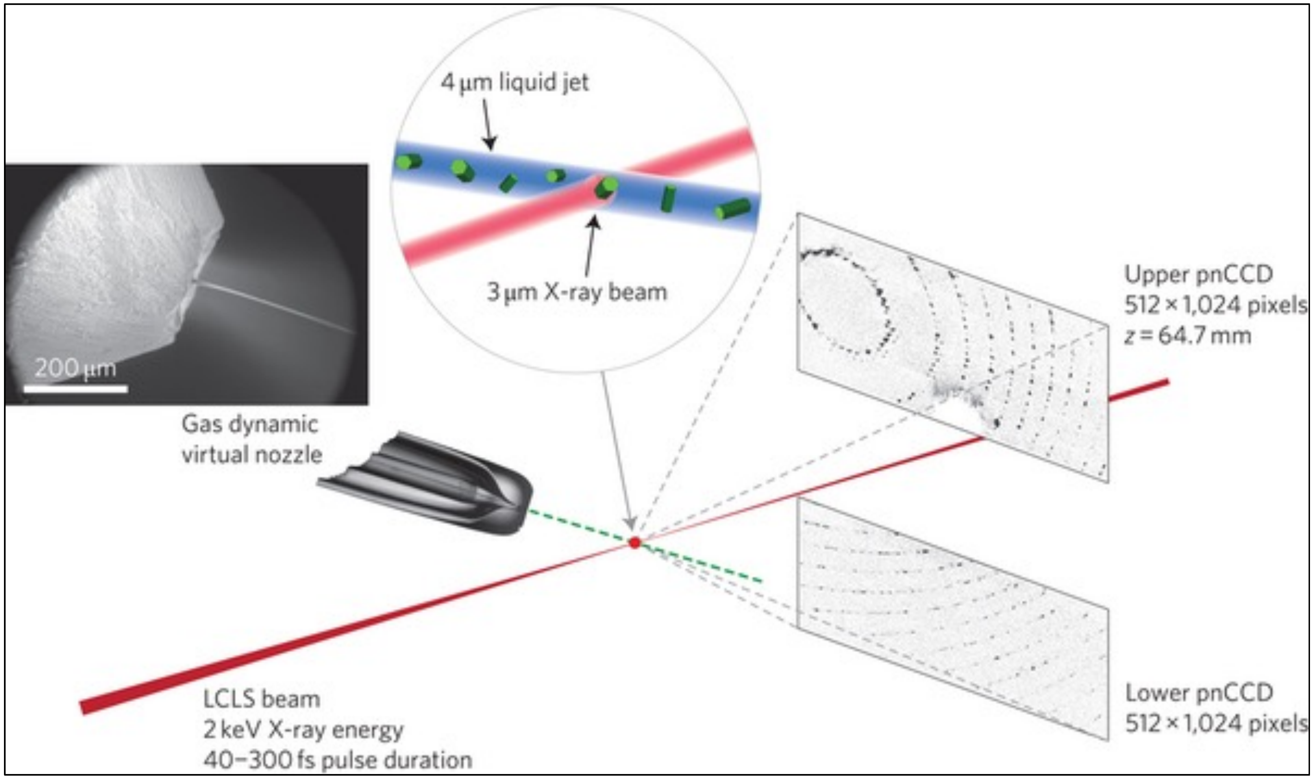


Image from: Barty, et al, Nature Photonics 6, 35–40 (2012)

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Structure determination from very small crystals

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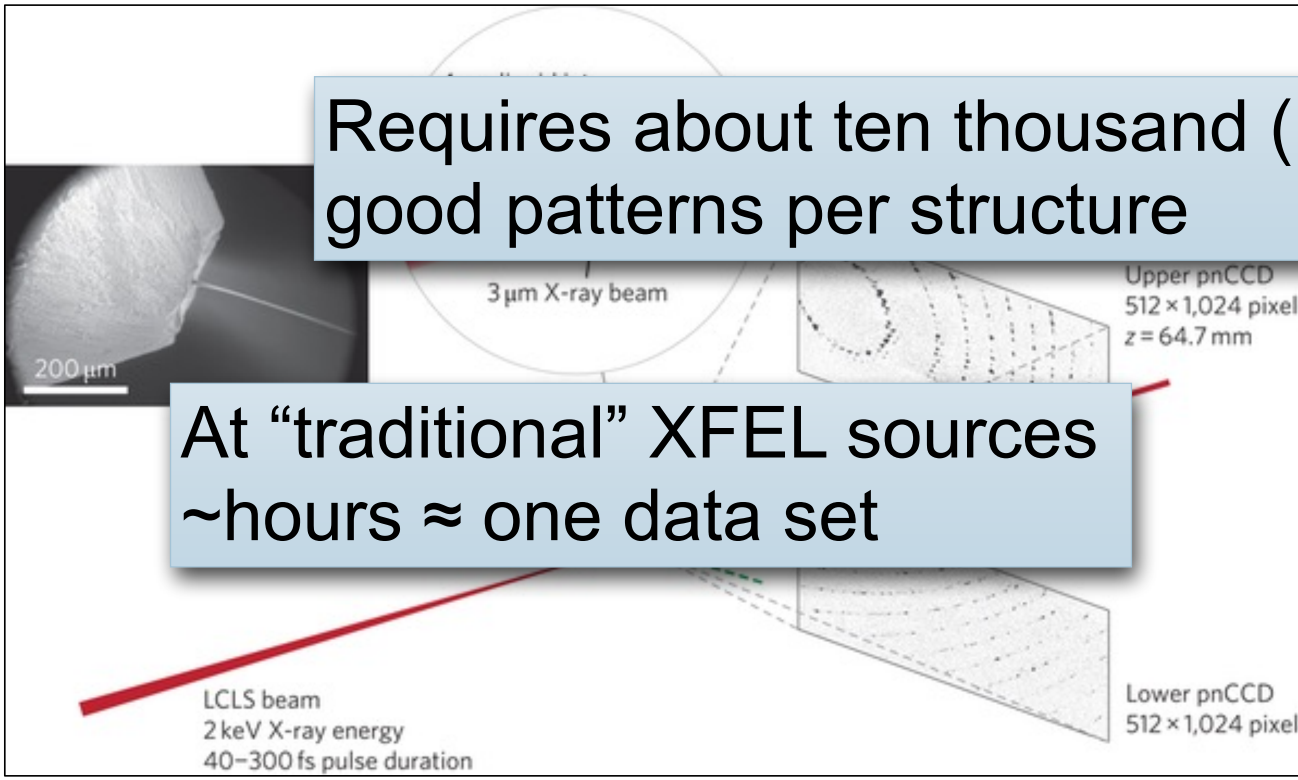

Requires about ten thousand (10 000) good patterns per structure

At "traditional" XFEL sources ~hours ≈ one data set

Image from: Barty, et al, Nature Photonics 6, 35–40 (2012)

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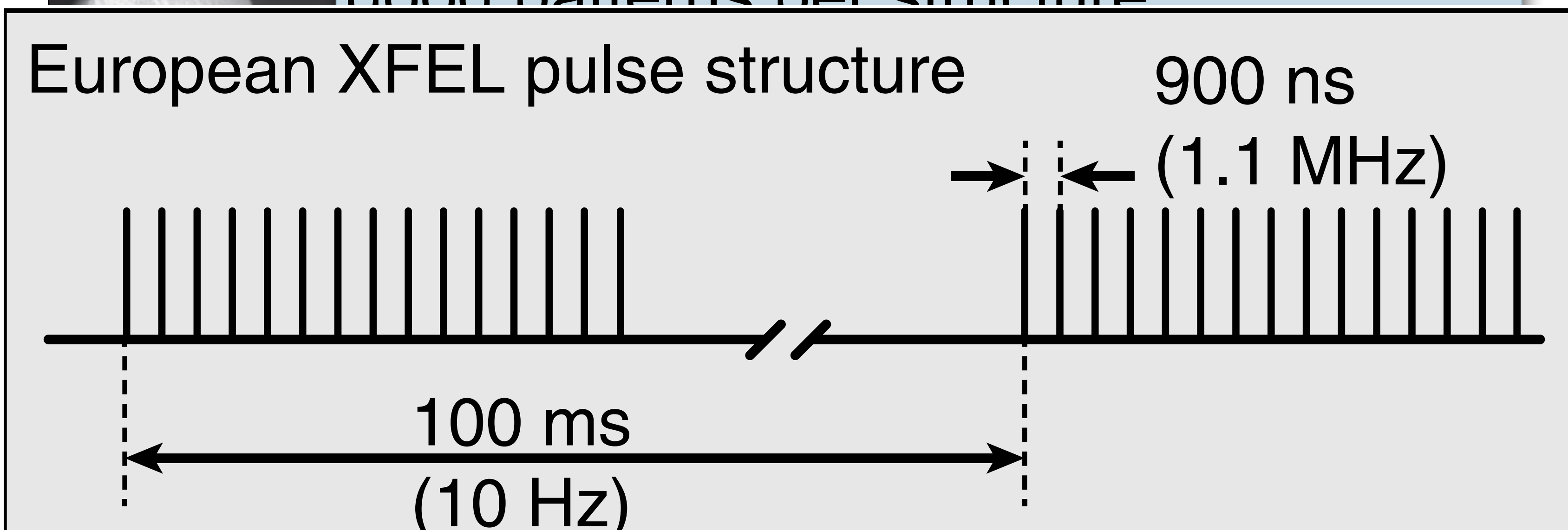

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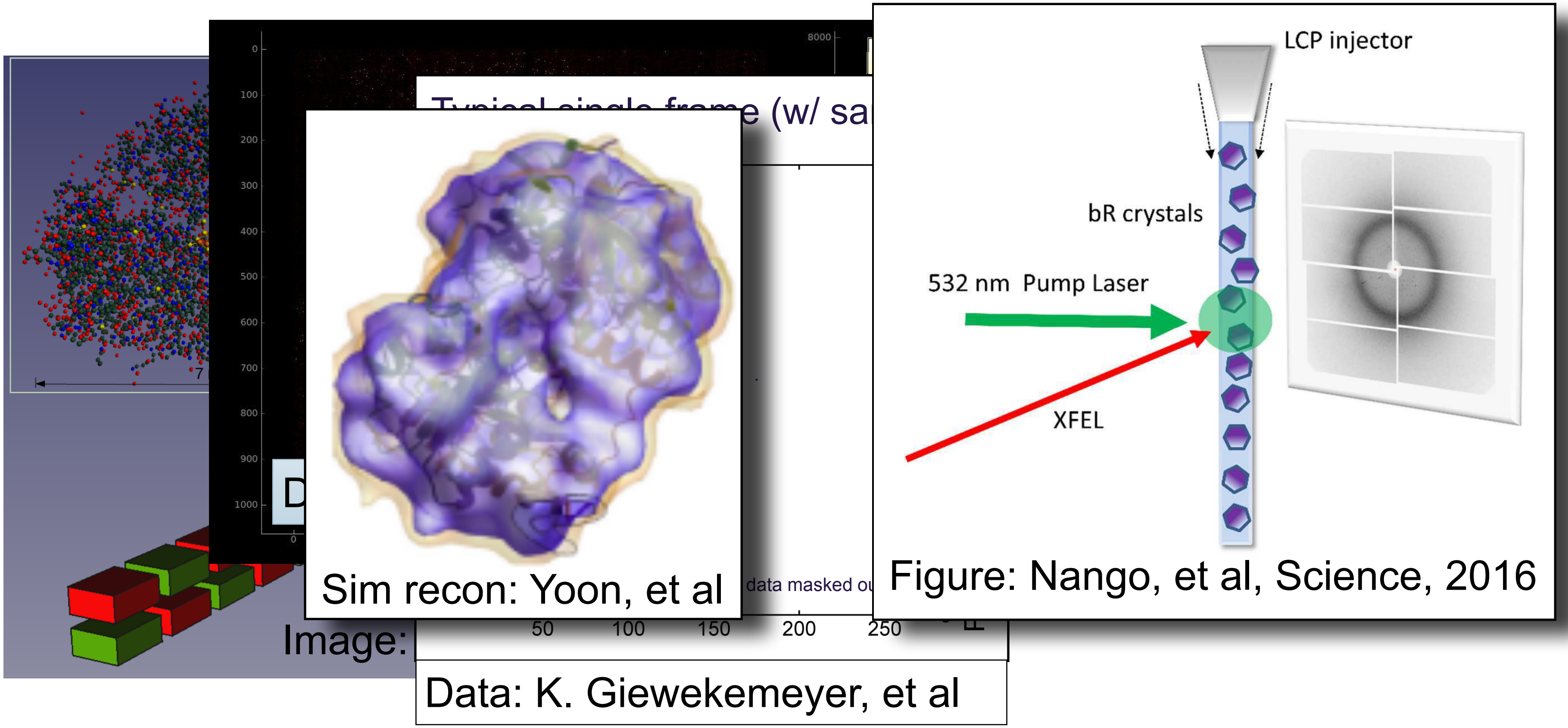
Reminder: The scope of the XFEL Structural Biology



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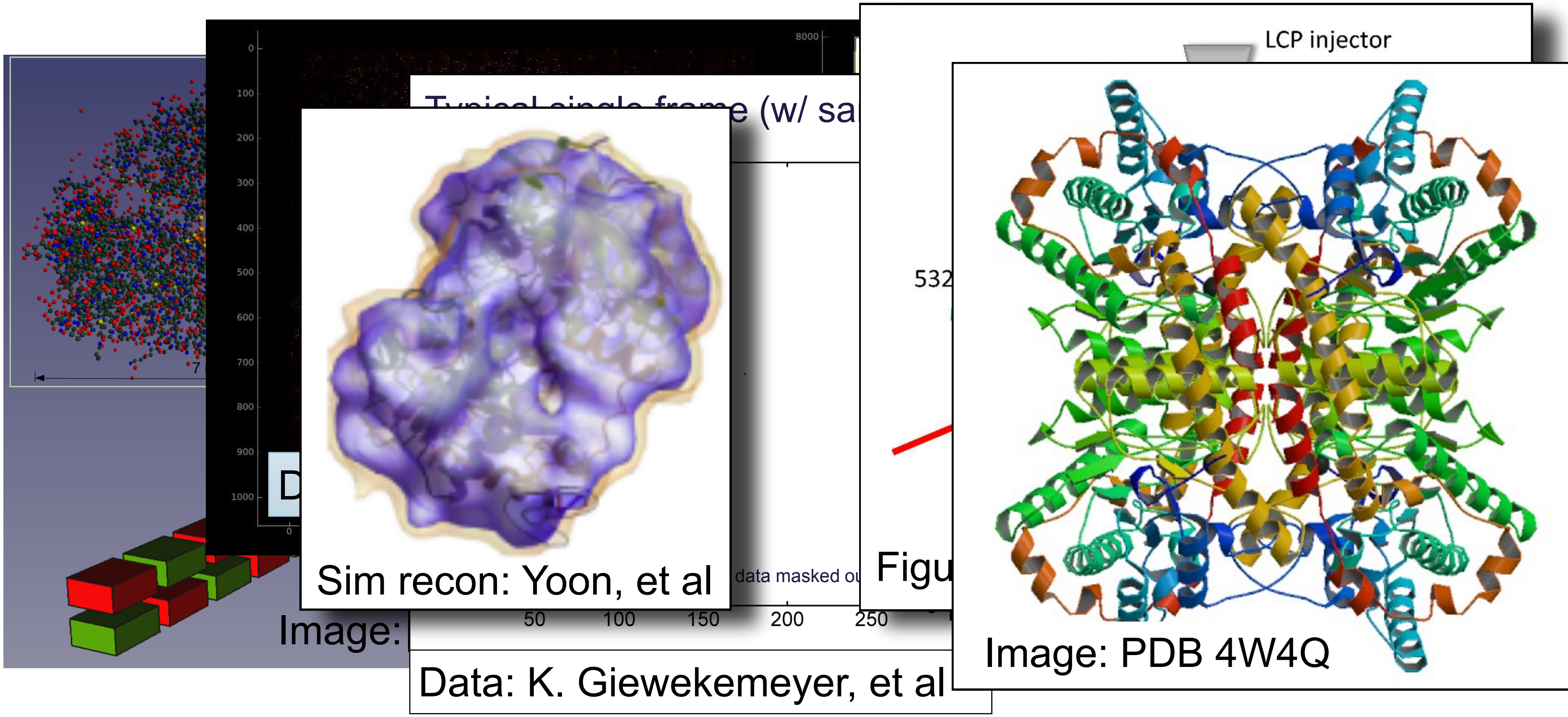
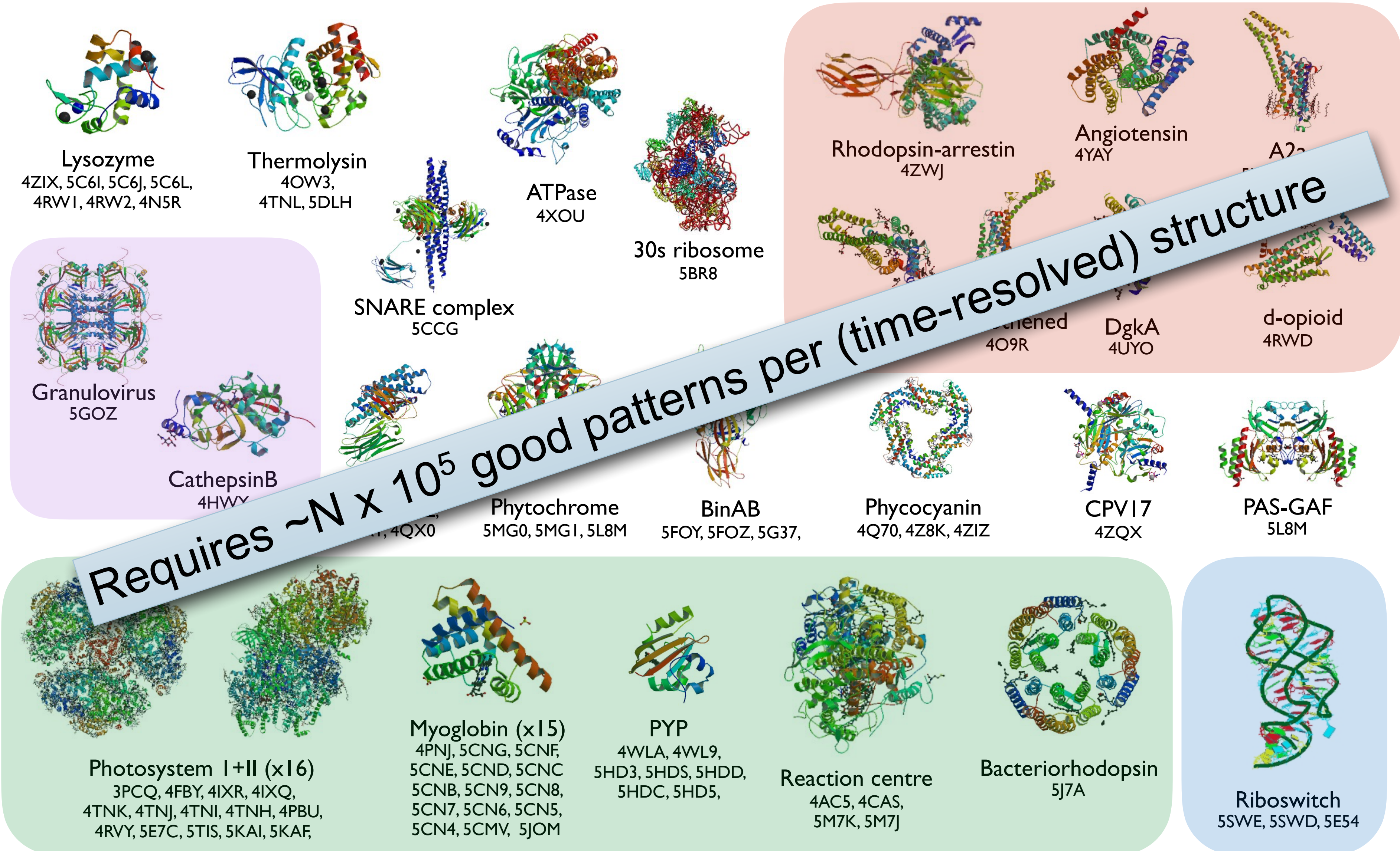


Everything forward scattering—predominantly **Serial Crystallography** and **single particle imaging** of biological samples
and including time resolved experiments (pump-probe, mixing)

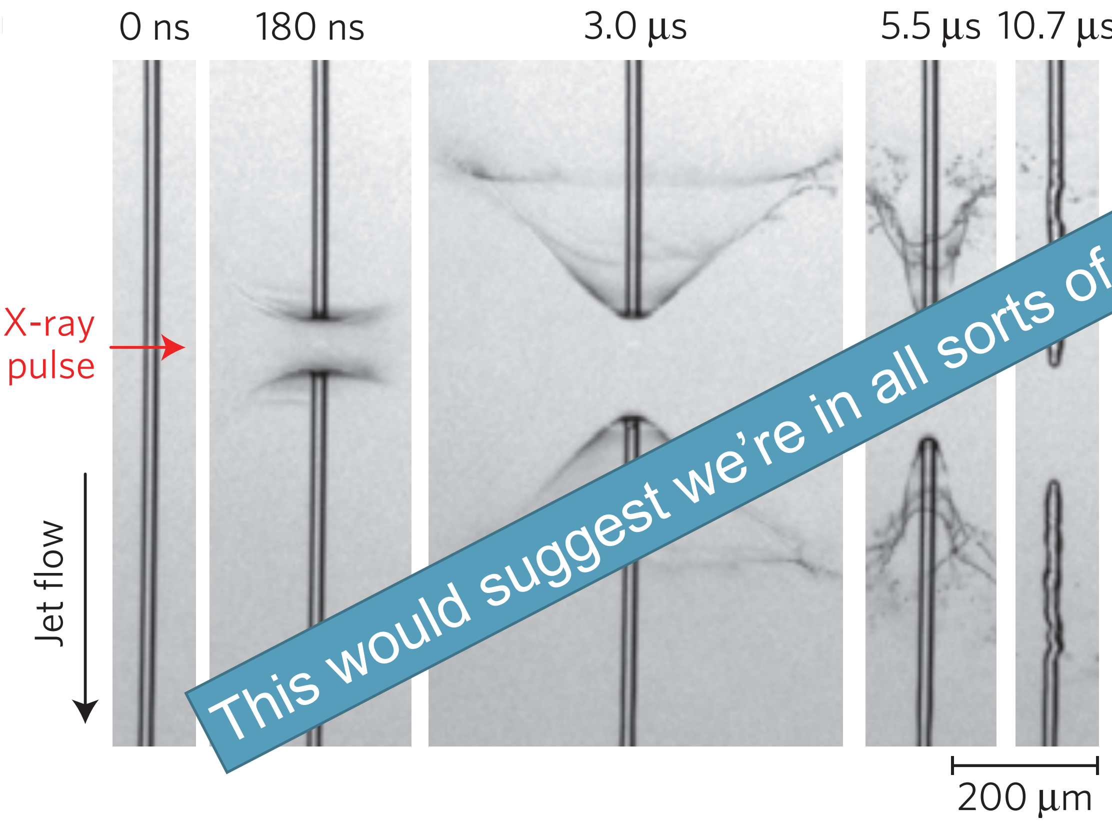
XFELs are used to solve difficult to crystallise and radiation sensitive proteins, and for time resolved structural dynamics

Slide: Anton Barty, CFEL, DESY



From LCLS: >117 From SACLA: >77 (as of March '18–more now!)

So we've got a bunch of neat tools, but can we do an experiment that exploits the repetition rate?



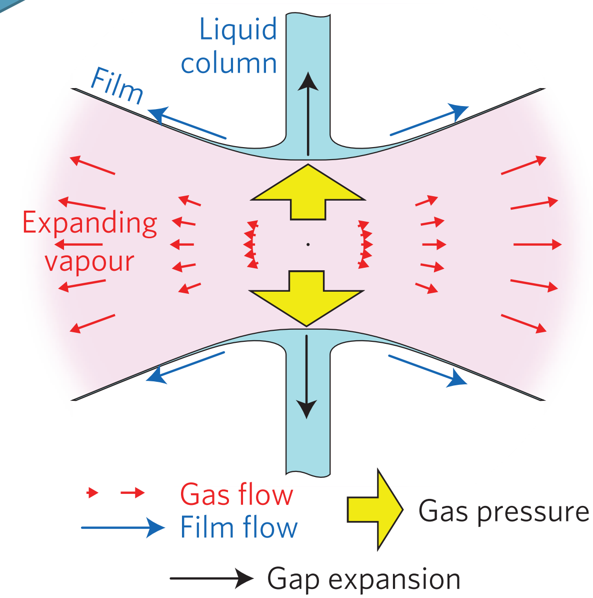
This would suggest we're in all sorts of trouble at MHz rates!

Shock waves propagate even faster

nature physics ARTICLES

Liquid explosions in ... ay laser pulses

Claudiu A. Stan[1]*, Despina ... aksmono[1], Raymond G. Sierra[1], Trevor A. McQueen[3] ... arth J. Williams[2†], Jason E. Koglin[2], Thomas J. Lane[2], Matt J. Hayes[2] ... ghing Liang[2], Andrew L. Aquila[2], Philip R. Willmott[2,4], Joseph ... ock[2], Sabine Botha[5†], Karol Nass[5], Ilme Schlichting[5], ... A. Stone[6] and Sébastien Boutet[2]



Claudiu Stan, et al @ LCLS, Nature Physics, 2016

Nevertheless, 100+ users wanted to explore this question (and others) anyway!

First user group (experiment 2012) was an open collaboration with 100+ participants
Lead investigator: Anton Barty

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SPB/SFX Instrument Scientists
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Grant Mills
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XFEL Detector
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Torsten Laurus
Davide Mezza
Jennifer Poehlsen
Ulrich Trunk

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Raimund Fromme
S. Holmes
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Mia Rudolph
Iosifina Sarrou
Marius Schmidt
Robin Schubert
Jonas Sellberg
Megan Shelby
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Yun-Xing Wang

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Jochen Küpper
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Alke Meents
Diana Monteiro
Xavier Lourdu
Tatiana Safenreiter
Ilme Schlichting
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Ray Sierra
John Spence
Claudiu Stan
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Uwe Weierstall

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Aaron Brewster
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Yaroslav Gevorkov
Helen Ginn
Rick Kirian
Filipe Maia
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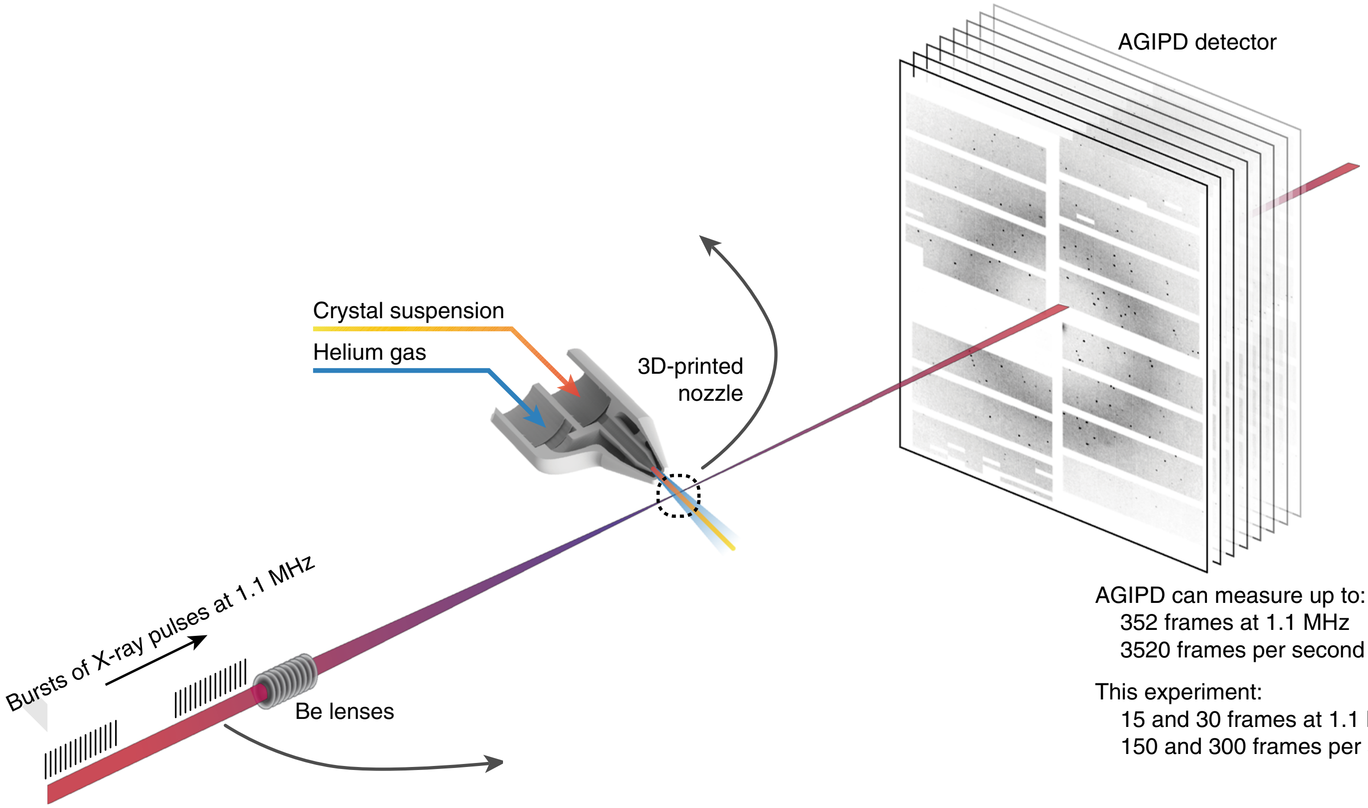
Leonce Mekinda
Thomas Michelat
Andrea Parenti
Hugo Santos
Alessandro Silenzi
Martin Teichmann
Kerstin Weger
Chen Xu
Chris Youngman
John Wiggins

First beam to first experiment ~11 weeks

Detector installed to first experiment

First user group (experiment 2012) was an open collaboration with 100+ participants
Lead investigator: Anton Barty

Schematic of first user experiment - #2012

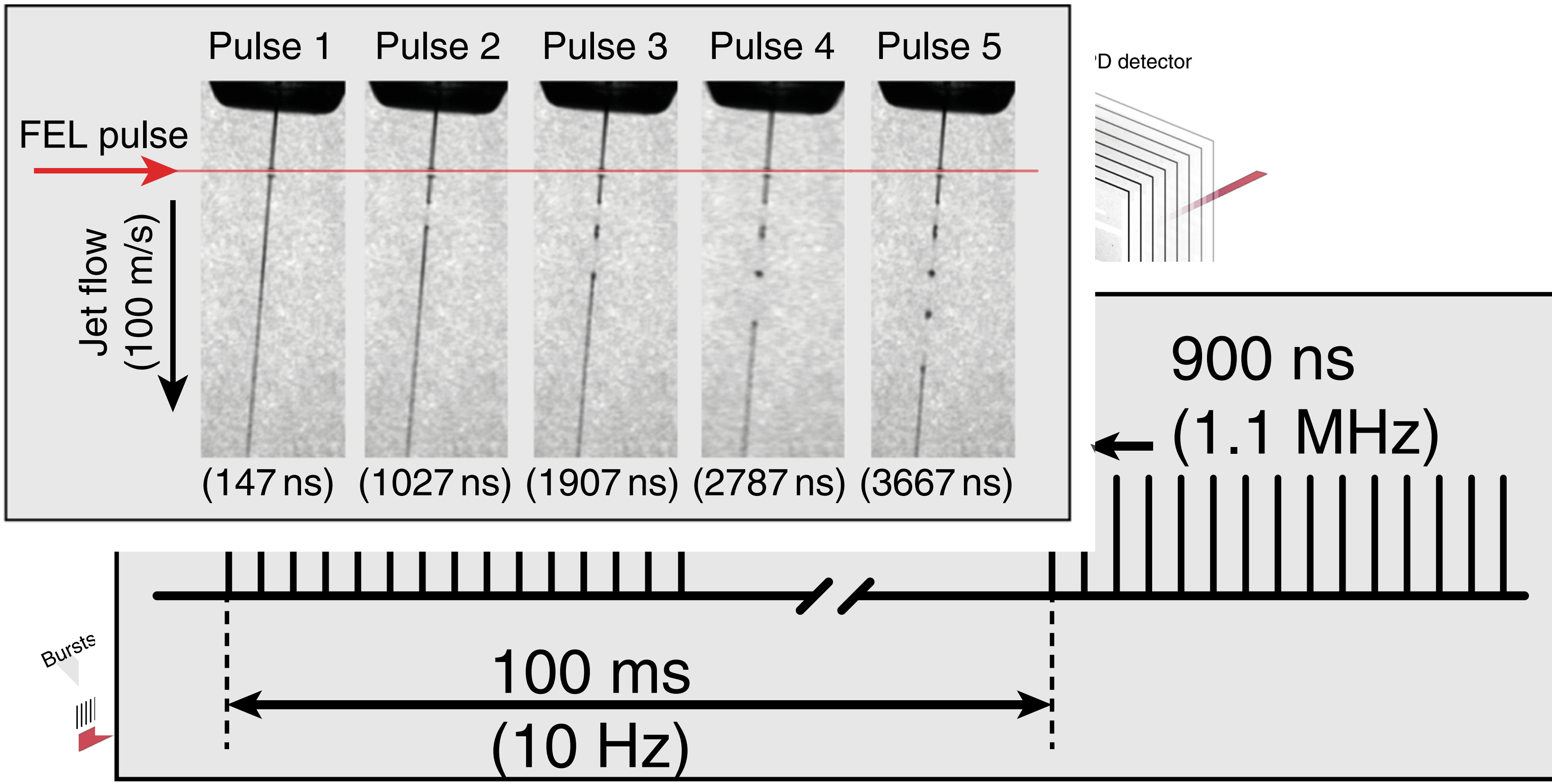


AGIPD can measure up to:
- 352 frames at 1.1 MHz
- 3520 frames per second

This experiment:
- 15 and 30 frames at 1.1 MHz
- 150 and 300 frames per second

Wiedorn, et al, Nat. Comms., 2018

Schematic of first user experiment - #2012



Wiedorn, et al, Nat. Comms., 2018

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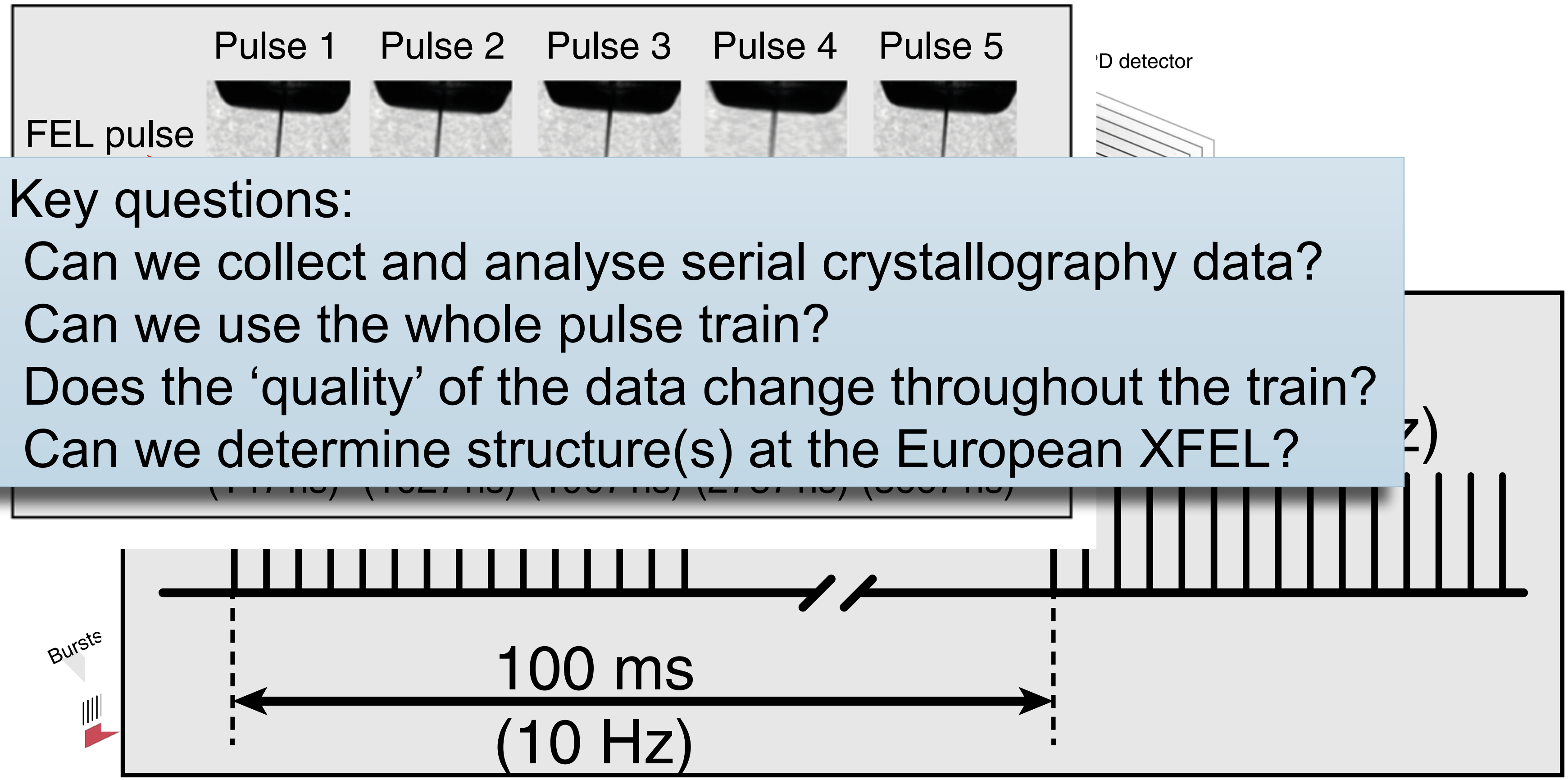
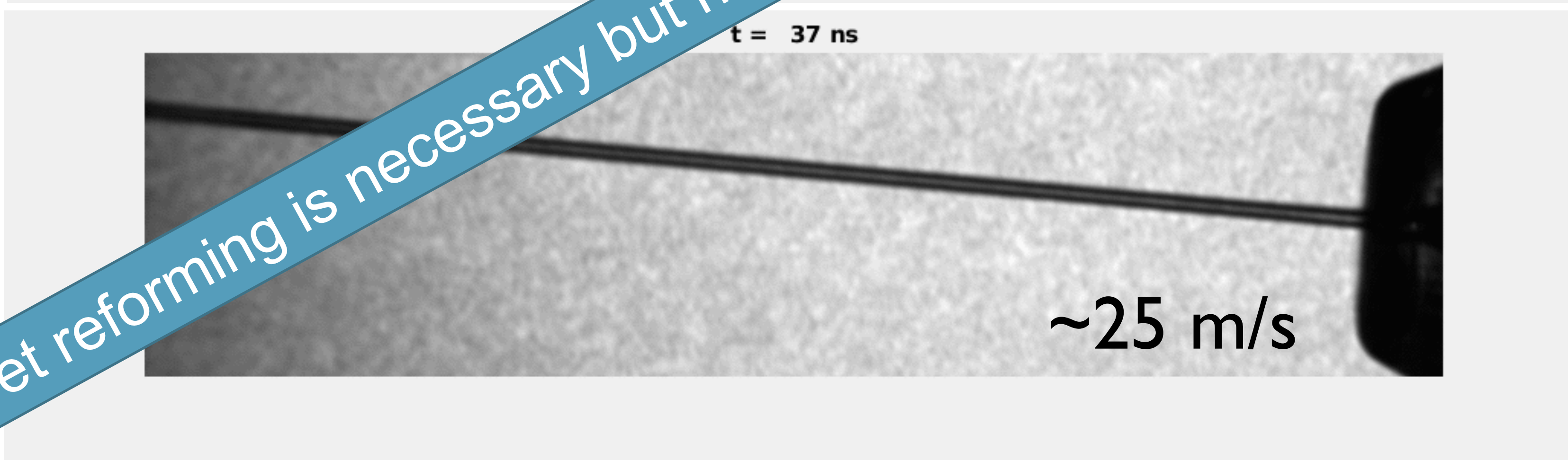


Key questions:

- Can we collect and analyse serial crystallography data?
- Can we use the whole pulse train?
- Does the 'quality' of the data change throughout the train?
- Can we determine structure(s) at the European XFEL?

Wiedorn, et al, Nat. Comms., 2018

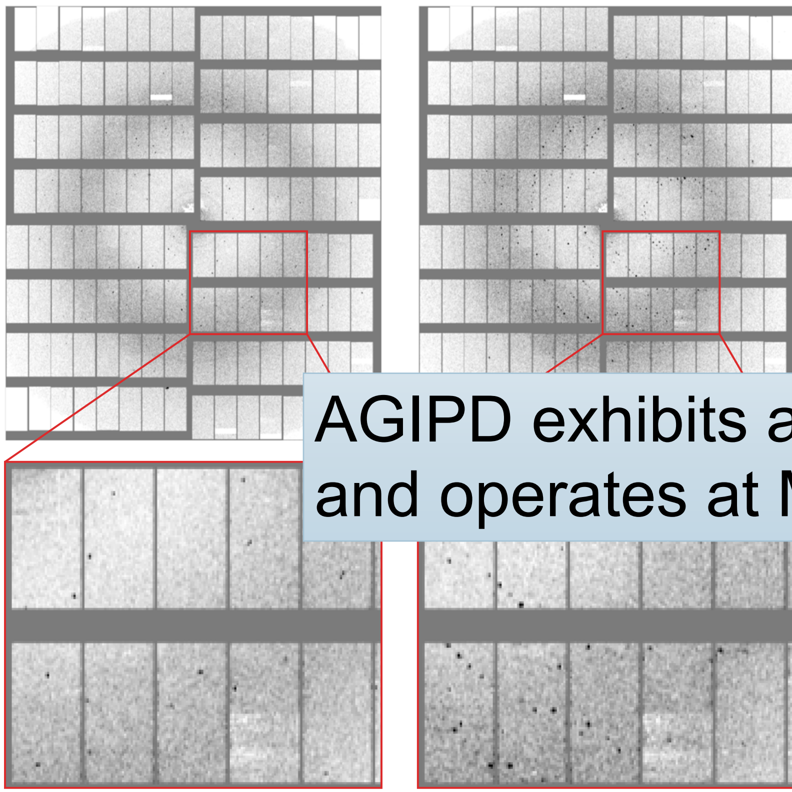
and for slower pulses it does not support the repetition rate



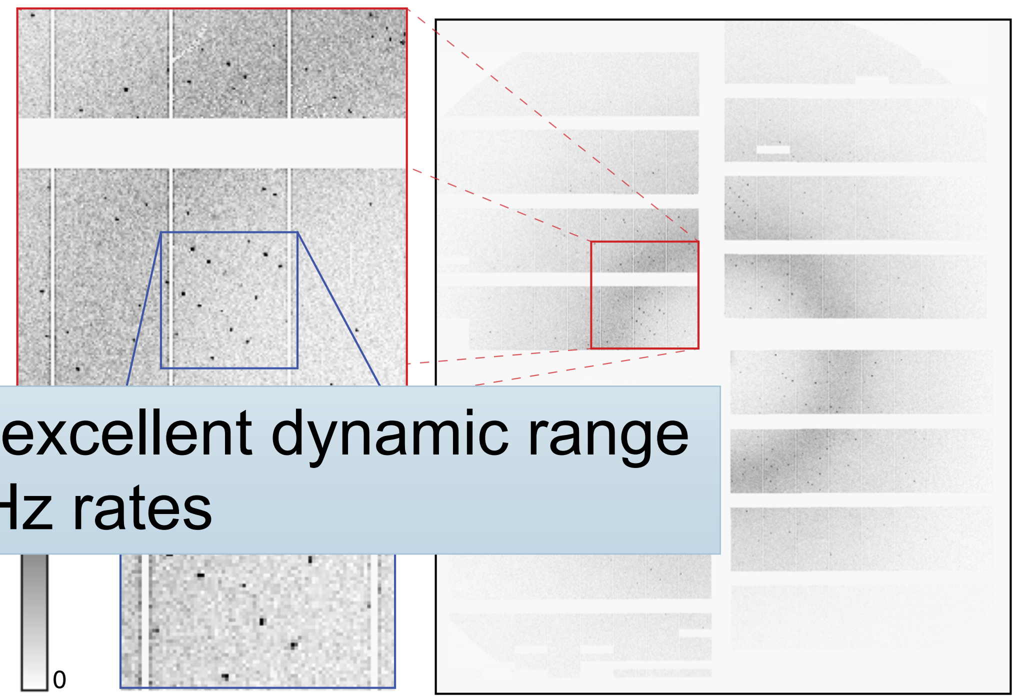
Jet reforming is necessary but not sufficient condition for MHz SFX

Max Wiedorn, Claudio Stan, Pablo Villanueva-Perez

The AGIPD (2D detector) looks great when calibrated and exhibits an excellent dynamic range



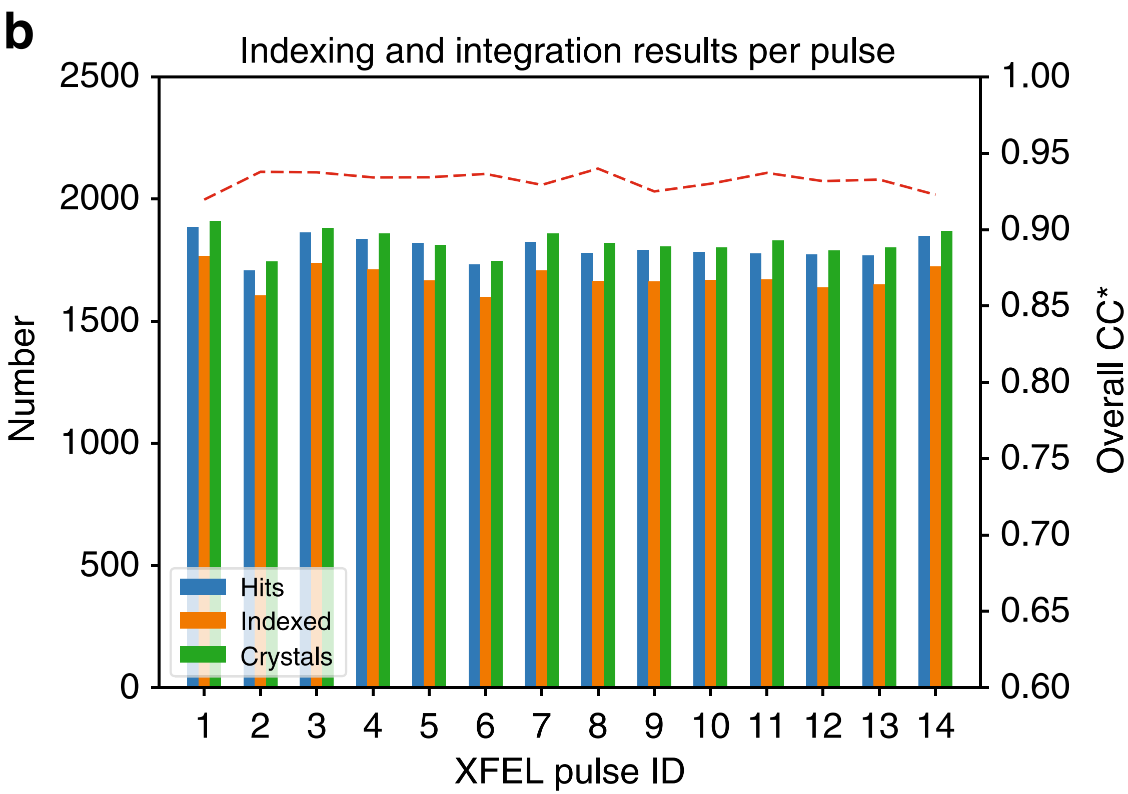
Grünbein, et al, Nat. Comms. (2018)



Wiedorn, et al, Nat. Comms., 2018.

AGIPD exhibits an excellent dynamic range and operates at MHz rates

Various metrics show data quality independent of position of pulse in train (for early experiment conditions)



Wiedorn, et al, Nat. Comms., 2018.

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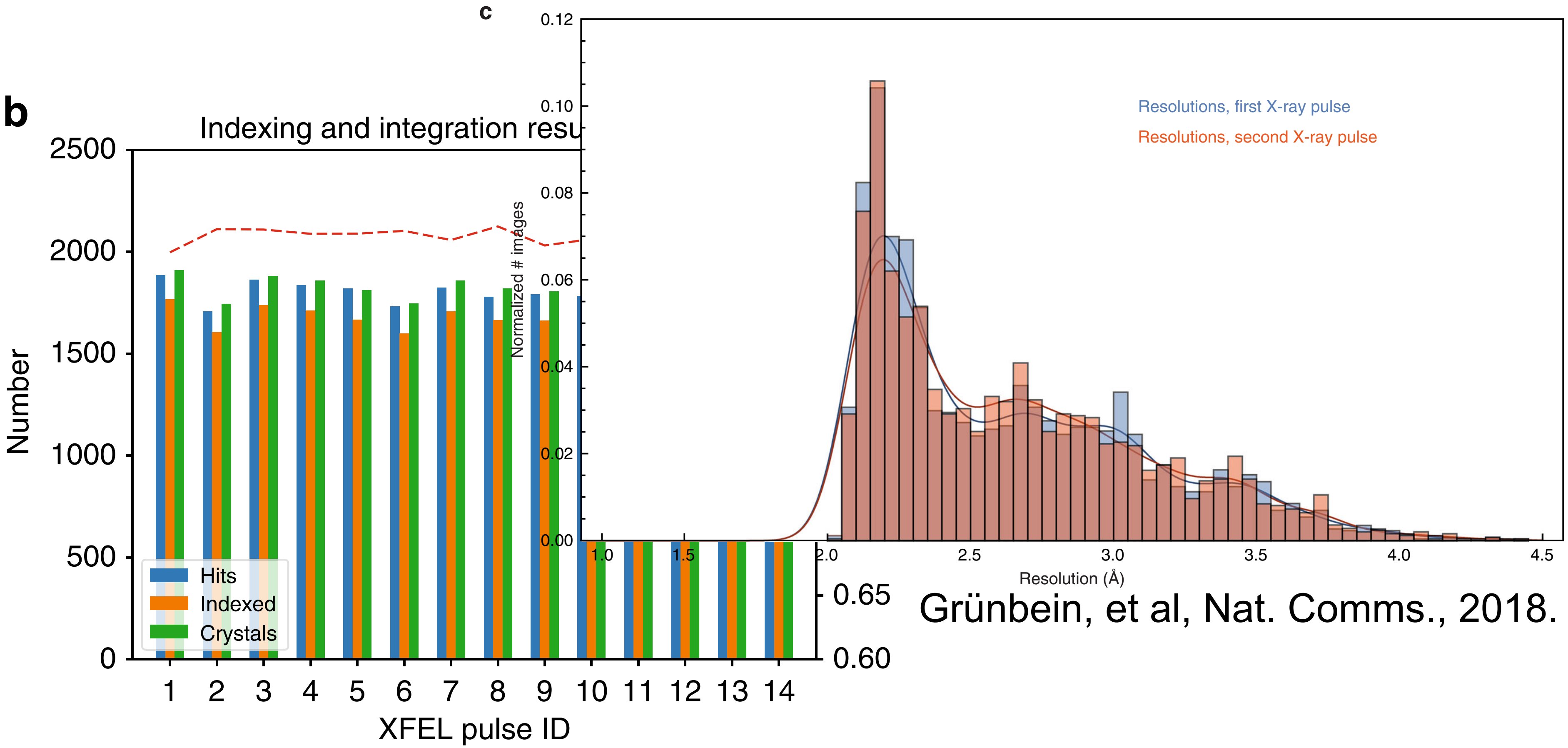


Grünbein, et al, Nat. Comms., 2018.

Wiedorn, et al, Nat. Comms., 2018.

High quality density maps produced

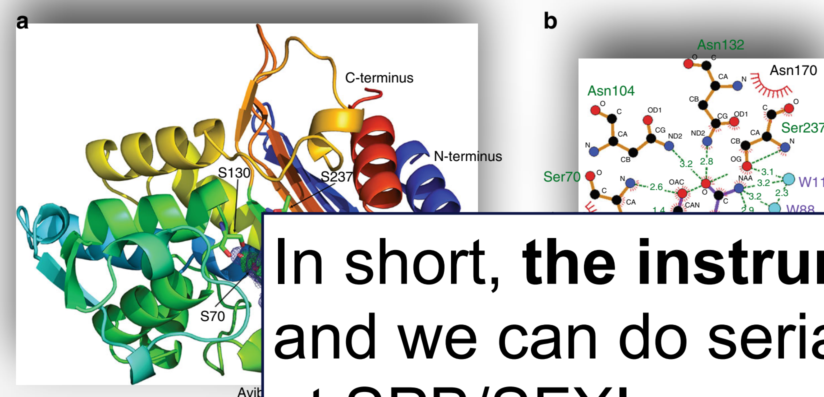
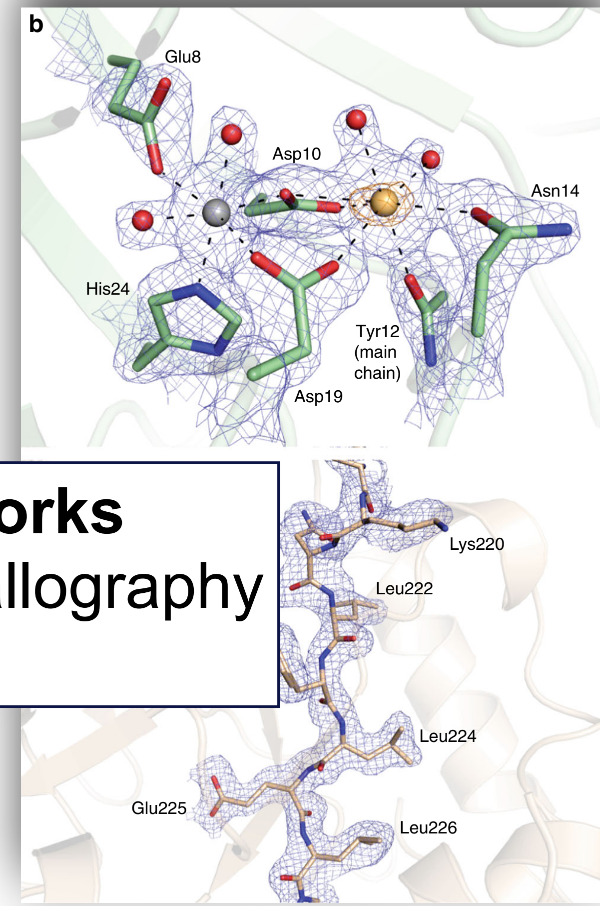


Fig. 6 Structure of CTX-M-14 β-lactamase determined
avibactam from molecular replacement using a solvent
of covalently bound avibactam to OG of Ser70, stabilized by hydrogen bonds and hydrophobic interactions with surrounding amino acids of CTX-M-14. Figure was prepared using Ligplot[49]

In short, **the instrument works** and we can do serial crystallography at SPB/SFX!



ig. 3 MHz serial femtosecond crystallography of jack bean proteins. **a** ⁄icroscope image of the microcrystalline mixture of jack bean proteins that ⁄as injected into the X-ray beam, clearly showing different types of crystal orms. The scale bar is 10 µm. **b** Map quality for the concanavalin A tructure. The metal binding site is shown, with the simulated annealing omposite omit map contoured at 1.0σ shown as a blue mesh and the nomalous difference density map (5.0σ) shown as an orange mesh. elected residues are shown as sticks, the calcium and magnesium ions as ellow and grey spheres, respectively. Water molecules are shown as red pheres. **c** Map quality for the concanavalin B structure. Part of one of the -strands of the TIM-barrel is shown as sticks, with the simulated annealing omposite omit map (1.0σ) shown as a blue mesh

↑ Wiedorn, et al, Nat. Comms., 2018

Grünbein, et al, Nat. Comms., 2018 →

Can be measured (ideally) in minutes at MHz rates!

First user papers from the European XFEL

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06156-7 OPEN

Megahertz serial crystallography

Max O. Wiedorn et al.[#]

The new European X-ray free electron laser is the first X-ray free-electron laser capable of delivering X-ray pulses with a megahertz inter-pulse spacing, more than four orders of magnitude higher than previously possible. However, to date, it has been unclear whether it would indeed be possible to measure high-quality structures at megahertz pulse repetition rates. Here, we show that high-quality structures can indeed be obtained using currently available operating conditions at the European XFEL. We present two complete data sets, one from the well-known model system lysozyme and the other from a so far unknown complex of a β-lactamase from *K. pneumoniae* involved in antibiotic resistance. This result opens up megahertz SFX as a tool for reliable structure determination, substrate screening and the efficient measurement of the evolution and dynamics of molecular structures using megahertz repetition rate pulses available at this new class of X-ray laser source.

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-05953-4 OPEN

Megahertz data collection from protein microcrystals at an X-ray free-electron laser

Marie Luise Grünbein[1], Johan Bielecki[2], Alexander Gorel[1], Miriam Stricker[1], Richard Bean[2], Marco Cammarata[3], Katerina Dörner[2], Lars Fröhlich[4], Elisabeth Hartmann[1], Steffen Hauf[2], Mario Hilpert[1], Yoonhee Kim[2], Marco Kloos[1], Romain Letrun[2], Marc Messerschmidt[2,5], Grant Mills[2,6], Gabriela Nass Kovacs[1], Marco Ramilli[2], Christopher M. Roome[1], Tokushi Sato[2,7], Matthias Scholz[4], Michel Sliwa[8], Jolanta Sztuk-Dambietz[2], Martin Weik[9], Britta Weinhausen[2], Nasser Al-Qudami[2], Djelloul Boukhelef[2], Sandor Brockhauser[2,10], Wajid Ehsan[2], Moritz Emons[2], Sergey Esenov[2], Hans Fangohr[2], Alexander Kaukher[2], Thomas Kluyver[2], Max Lederer[2], Luis Maia[2], Maurizio Manetti[2], Thomas Michelat[2], Astrid Münnich[2], Florent Pallas[2], Guido Palmer[2], Gianpietro Previtali[2], Natascha Raab[2], Alessandro Silenzi[2], Janusz Szuba[2], Sandhya Venkatesan[2], Krzysztof Wrona[2], Jun Zhu[2], R. Bruce Doak[1], Robert L. Shoeman[1], Lutz Foucar[1], Jacques-Philippe Colletier[9], Adrian P. Mancuso[2], Thomas R.M. Barends[1], Claudiu A. Stan[11] & Ilme Schlichting[1]

X-ray free-electron lasers (XFELs) enable novel experiments because of their high peak brilliance and femtosecond pulse duration. However, non-superconducting XFELs offer repetition rates of only 10–120 Hz, placing significant demands on beam time and sample consumption. We describe serial femtosecond crystallography experiments performed at the European XFEL, the first MHz repetition rate XFEL, delivering 1.128 MHz X-ray pulse trains at 10 Hz. Given the short spacing between pulses, damage caused by shock waves launched by one XFEL pulse on sample probed by subsequent pulses is a concern. To investigate this issue, we collected data from lysozyme microcrystals, exposed to a ~15 μm XFEL beam. Under these conditions, data quality is independent of whether the first or subsequent pulses of the train were used for data collection. We also analyzed a mixture of microcrystals of jack bean proteins, from which the structure of native, magnesium-containing concanavalin A was determined.

First user papers from the European XFEL

nature COMMUNICATIONS

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nature COMMUNICATIONS

…tein
…electron laser

…Miriam Stricker[1], Richard Bean[2], …ich[4], Elisabeth Hartmann[1], Steffen Hauf[2], Mario Hilpert[1], …, Marc Messerschmidt[2,5], Grant Mills[2,6], Gabriela Nass Kovacs[1], …, Tokushi Sato[2,7], Matthias Scholz[4], Michel Sliwa[8], …Weik[9], Britta Weinhausen[2], Nasser Al-Qudami[2], Djelloul Boukhelef[2], …Wajid Ehsan[2], Moritz Emons[2], Sergey Esenov[2], Hans Fangohr[2], Alexander Kaukher[2], …x Lederer[2], Luis Maia[2], Maurizio Manetti[2], Thomas Michelat[2], Astrid Münnich[2], …, Guido Palmer[2], Gianpietro Previtali[2], Natascha Raab[2], Alessandro Silenzi[2], Janusz Szuba[2], …Venkatesan[2], Krzysztof Wrona[2], Jun Zhu[2], R. Bruce Doak[1], Robert L. Shoeman[1], Lutz Foucar[1], …ques-Philippe Colletier[9], Adrian P. Mancuso[2], Thomas R.M. Barends[1], Claudiu A. Stan[11] & Ilme Schlichting[1]

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Now: 10x more data per second as other XFELs

Soon: ≳ 30 times more data per second

Great news for all high rep-rate XFELs

Alternate sample delivery method(s)

- Commissioning setup M. Sikorski, et al, SPB/SFX
- Liquid Jet, B. Doak & R. Shoeman, Max Planck institute for Medical Research (with XFEL sample environment)
- Aerosol Jet, Uppsala University with XFEL sample environment

Alternate sample delivery method(s)

Fixed target sample delivery has many advantages

- ng setup M. Sikorski, et al, SPB/SFX
- d Jet, B. Doak & R. Shoeman, Max Planck institute for Medical Research (with XFEL sample environment)
- Aerosol Jet, Uppsala University with XFEL sample environment

Photon Beam Parameters for future (TR-) SFX Experiments

	Present	Future Liquid jet experiments	Future Fixed target experiments
Repetition rate	Up to MHz rates	MHz rates possible and in many cases desirable	Presently ~120 Hz, and perhaps up to low kHz possible
Pulse energy	Few mJ	At least few mJ	At least few mJ
Photon energies	5-16 keV	5-16 keV (Some case for even higher energies, if suitable detector exists)	5-16 keV (Some case for even higher energies, if suitable detector exists)
Pulse duration	Tens of fs	Perhaps shorter than tens fs	Perhaps shorter than tens fs
Bandwidth	~0.5%	Ideally variable up to few %	Ideally variable up to few %

Headline Conclusions

- For the parameters used (1.1 MHz rep rate, 15 um spot—no **the European XFEL rep rate can be successfully exploite** for both serial crystallography (and SPI)
- **Day one instrument works—first structures determined!** Publishable results generated!
- Still plenty of work to be done at the instrument, however already we can use SPB/SFX for serial crystallographic structure determination and first single particle imaging projects!
- **High repetition rate** XFELs do indeed offer more data per unit time for both SFX and SPI
  - This should have significant benefits for the development of SPI just by generating larger data sets that can be mined and 'cut' in various ways—**more is more!**
- **Fixed target sample delivery** is limited to perhaps **low kHz rates**, however, is also a very viable way of doing structural biology at XFELs
  - Also yes much less sample (which can often be very valuable)
- Whatever rep rate is used, detectors that work at that rate are required too!

Acknowledgments: People—the most important components

Zunaira Ansari
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