Hybrid Approach for Biomolecular Structure Modeling

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Structural Biology

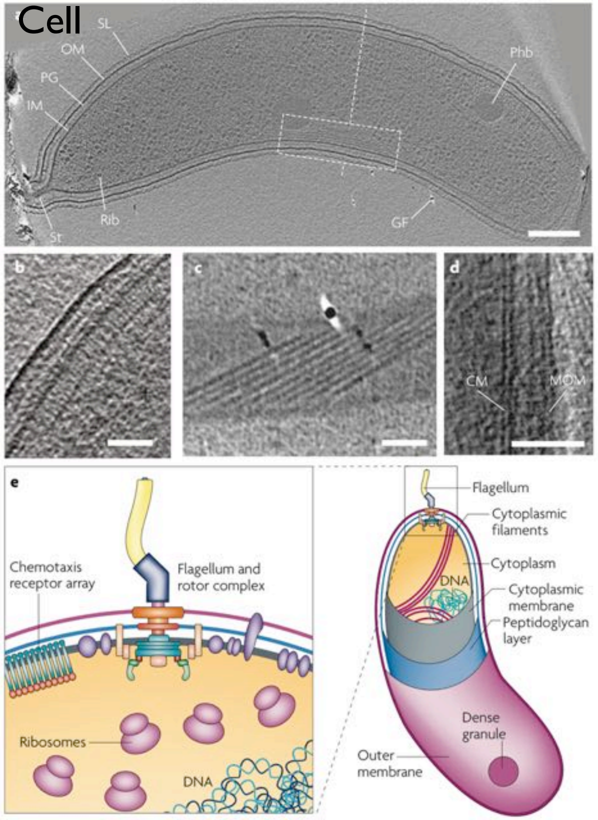
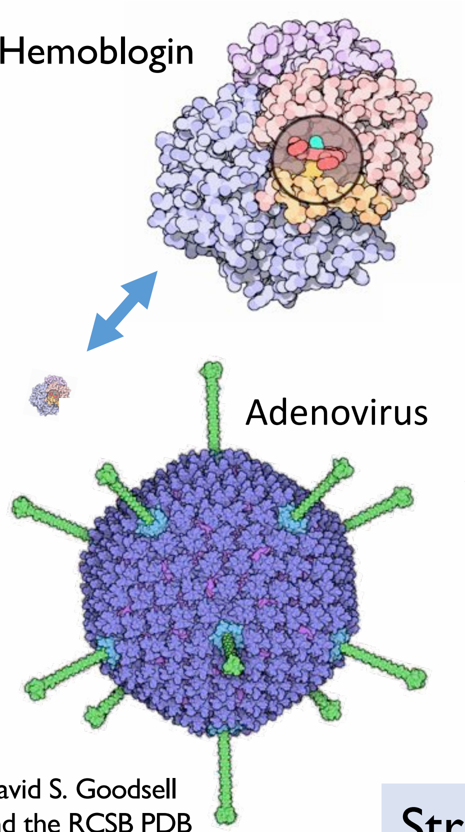


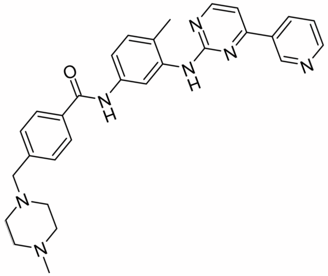
Image from: Milne & Subramaniam, Nat. Rev. Microbiol 2009



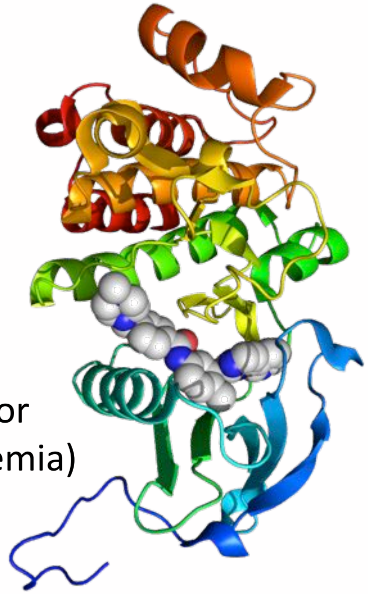
Hemoblogin

Adenovirus

David S. Goodsell and the RCSB PDB



Imatinib (Gleevec®)
Tyrosine Kinase inhibitor
Anticancer drug (Leukemia)

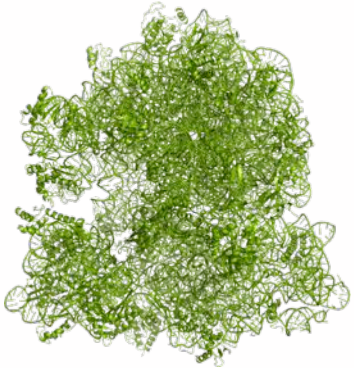


https://en.wikipedia.org/wiki/Imatinib

<u>Structures of biomolecules</u> are important to understand functions, and for drug development

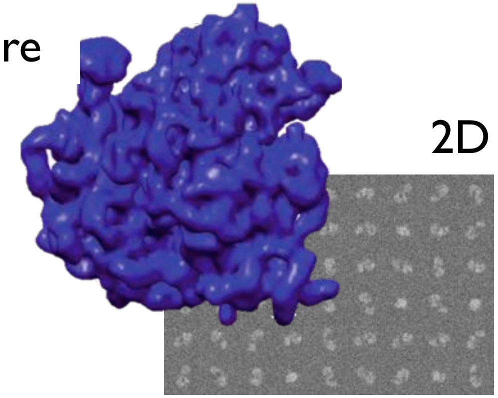
Dynamics is essential for function

Integrative/Hybrid Modeling



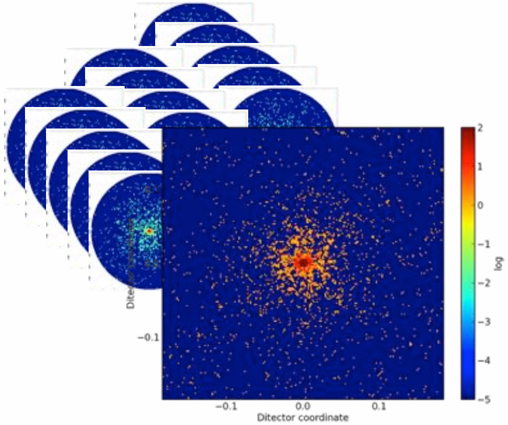
X-ray crystallography
NMR structure

3D structure



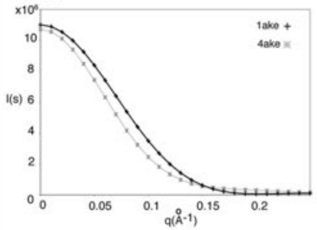
2D images

Cryo-Electron Microscopy
(volume/images)

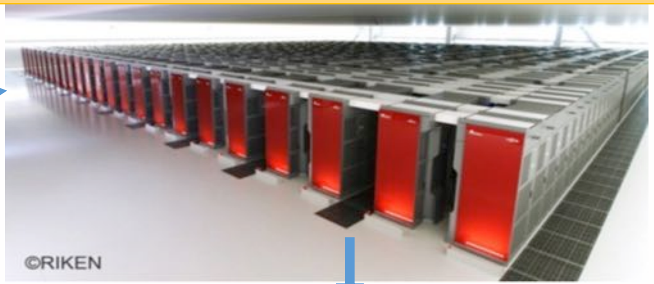


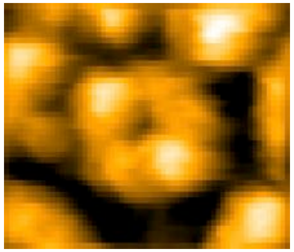
X-ray Free Electron Laser (XFEL)

Simulation & Modeling



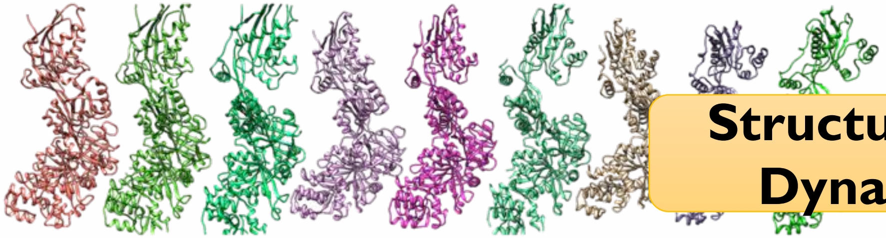
SAXS





Uchihashi (2018)

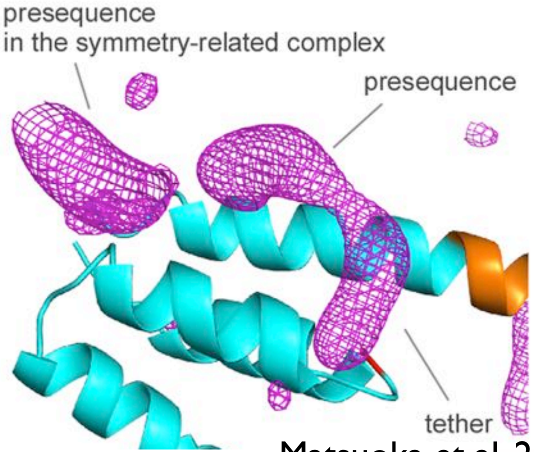
Atomic Force
Microscopy



Structure and Dynamics

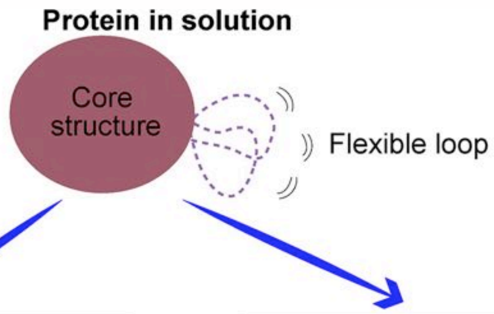
Interpretation of new X-ray crystallography data

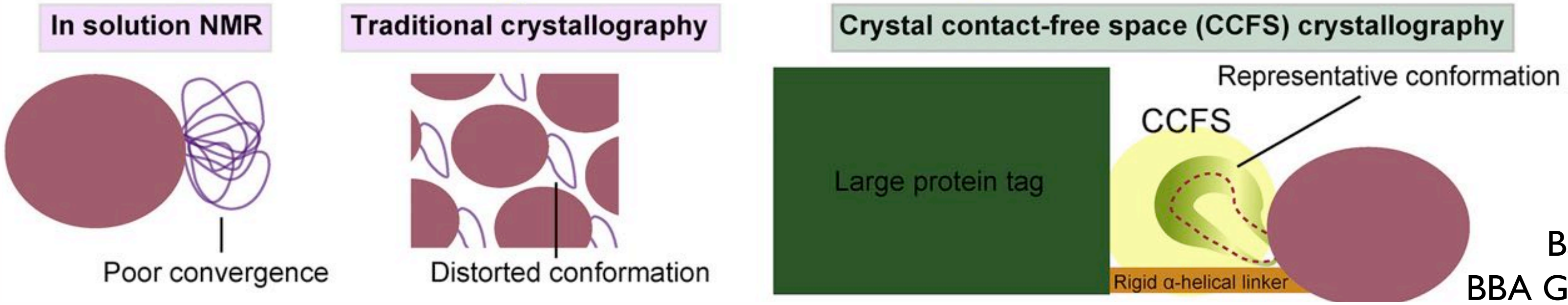
- X-ray crystallography provides structural information at high-resolution
- Cryo temperatures, crystal packing, artificially modified proteins
- Crystal contact-free space (CCFS) to reconciling X-ray structures with dynamics in solutions
- **MD simulations** to refine interpretations



Matsuoka et al, 2016

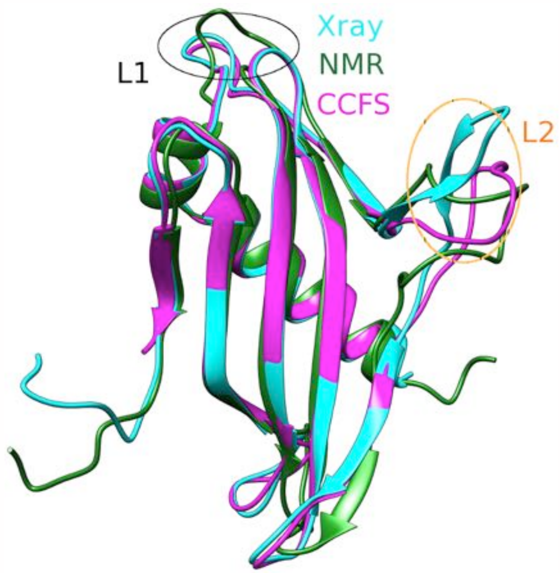
Kohda's group
Kyushu University



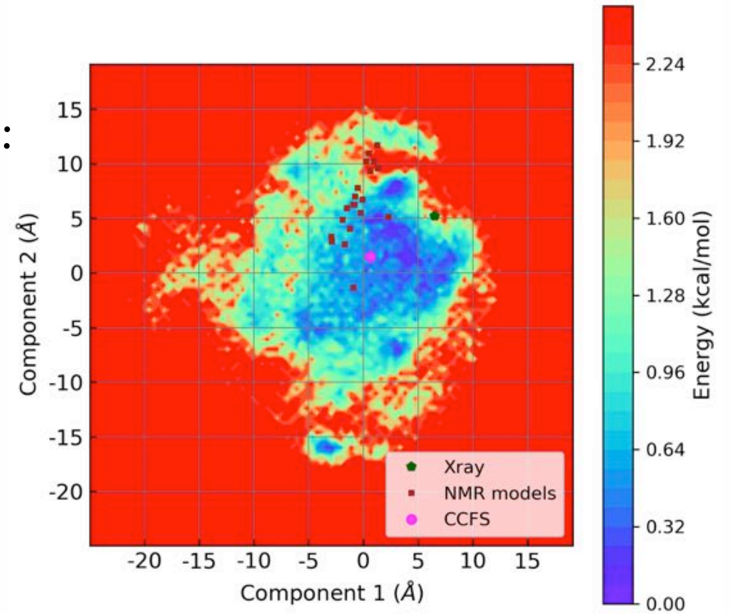


Bala et al,
BBA Gen 2020

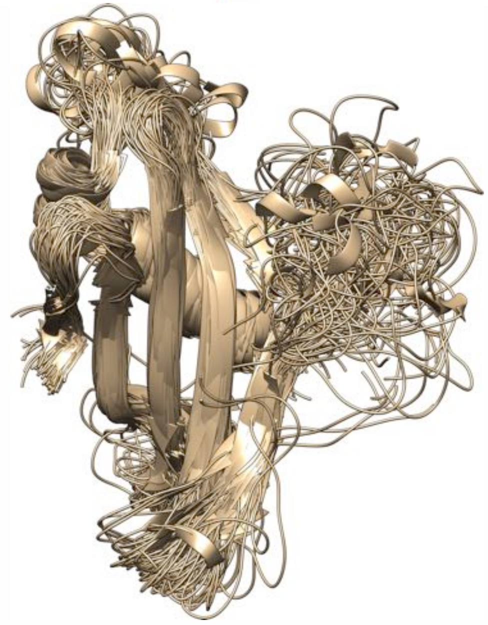
Dynamics of Flexible Loop: MD and Exp



Tim21 loop2 conformation: Experimental data are inconsistent



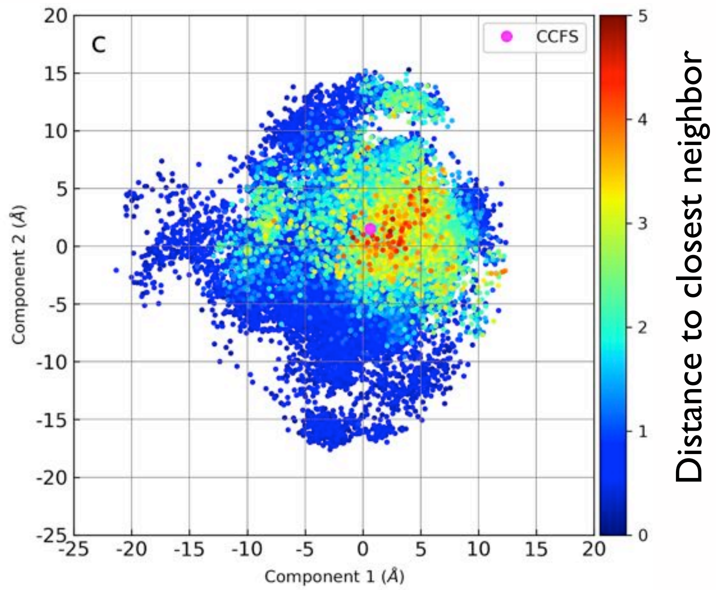
MD trajectory vs Experimental Data CCFS best agreement



Conf ensemble from modeling & MD

~40 μsec

Crystal packing can be examined by MD to improve crystal design



Bala et al *BBA General Subjects* (2020), Srivastava et al *BBA General Subjects* (2020)

Fitting X-ray into Cryo-EM Data

Implementation of biased molecular dynamics simulation with EM volume

Bias strength

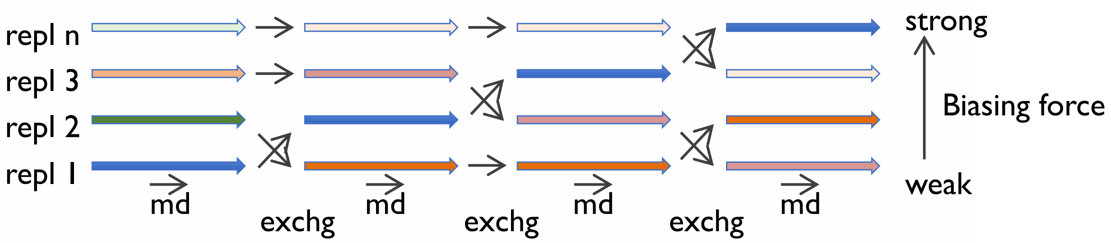
$$E = E_{\text{molecule}} + k(1 - f_{EM})$$

Molecular Mechanics
- all atom models
- coarse grained model

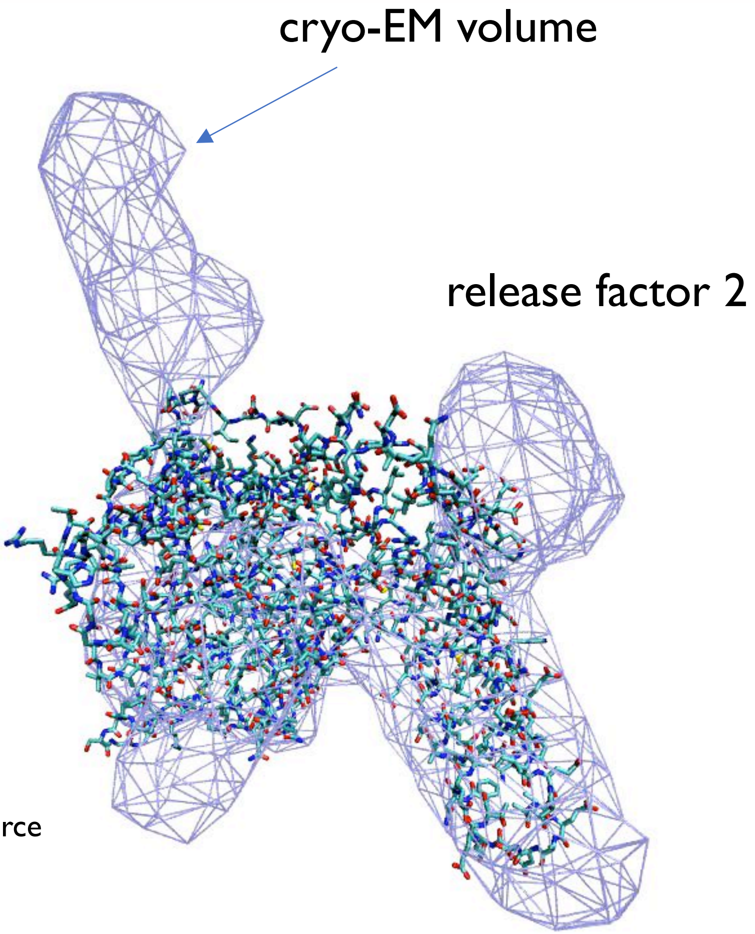
Biasing Force
- model ⇔ map agreement
  ~ low energy

GENESIS

Generalized-ensemble simulation system



Replica exchange: Different biasing force constant k_i is assigned to each replica

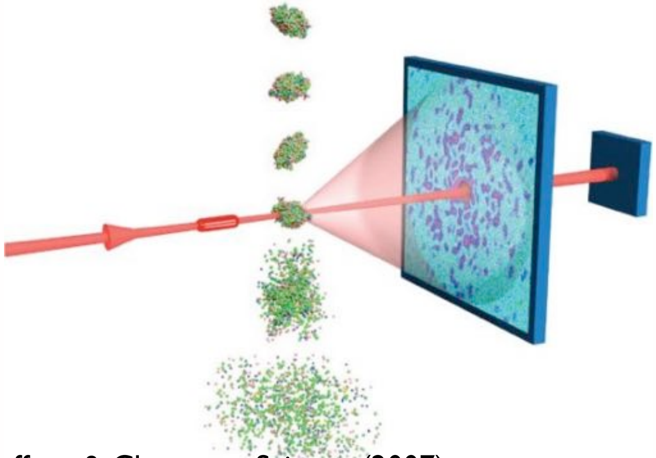


Miyashita et al (2017), Mori et al (2019)

Biomolecule Imaging by X-ray Free Electron Laser

Single-particle coherent diffraction imaging (CDI)

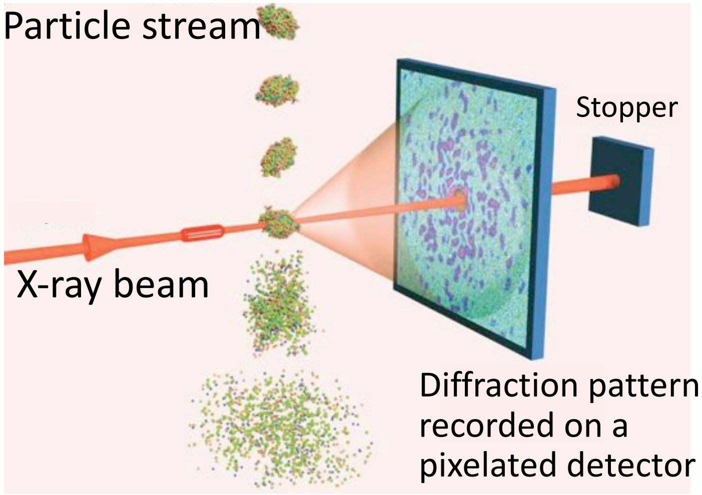
Experimental setup for single particle CDI



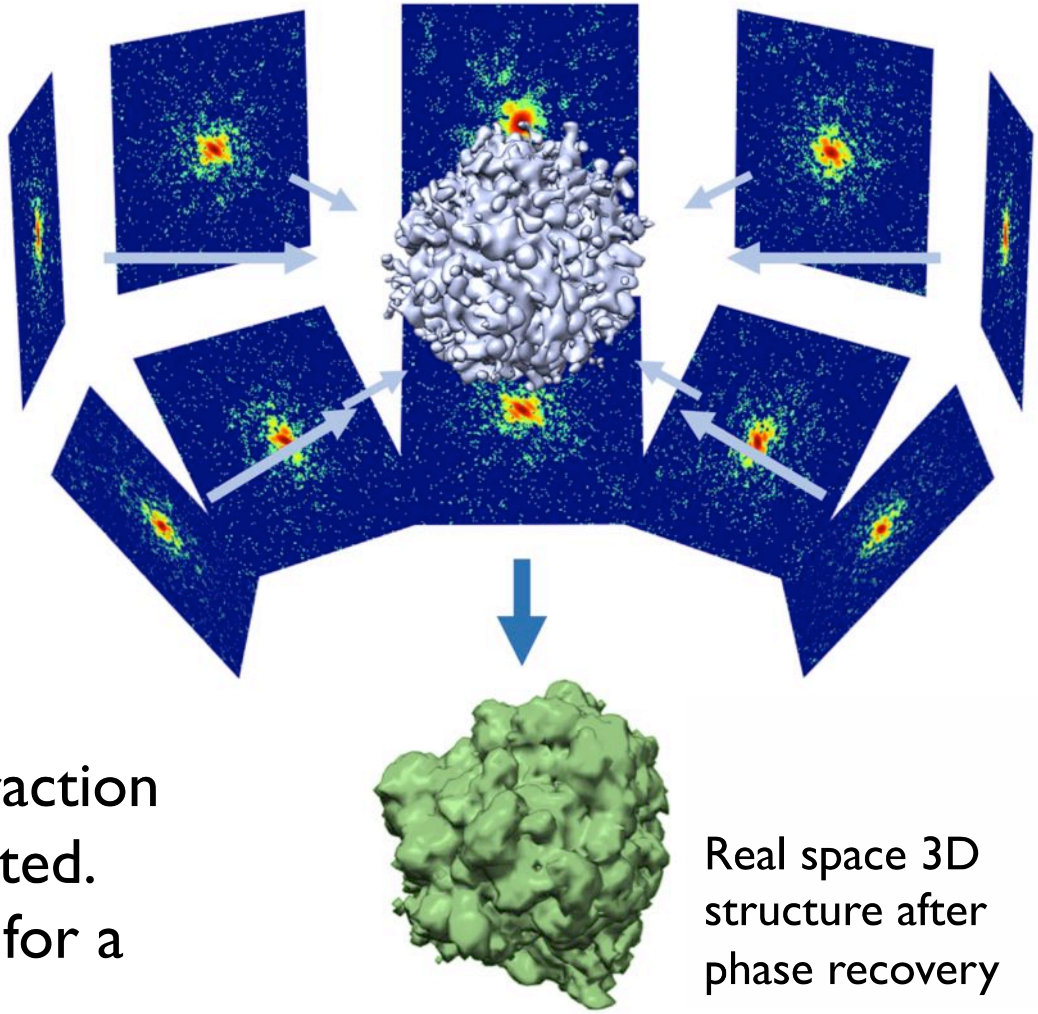
Gaffney & Chapman, Science (2007)

- Application to noncrystallizable samples
- Challenging approach with potentially very high impact
  - Single molecule in natural condition
  - Time-resolved study on Dynamics
  - Requires strong beam

3D Reconstruction from XFEL Single Particle Data



K. J. Gaffney and H. N. Chapman, *Science* (2007) 316 1444-1448

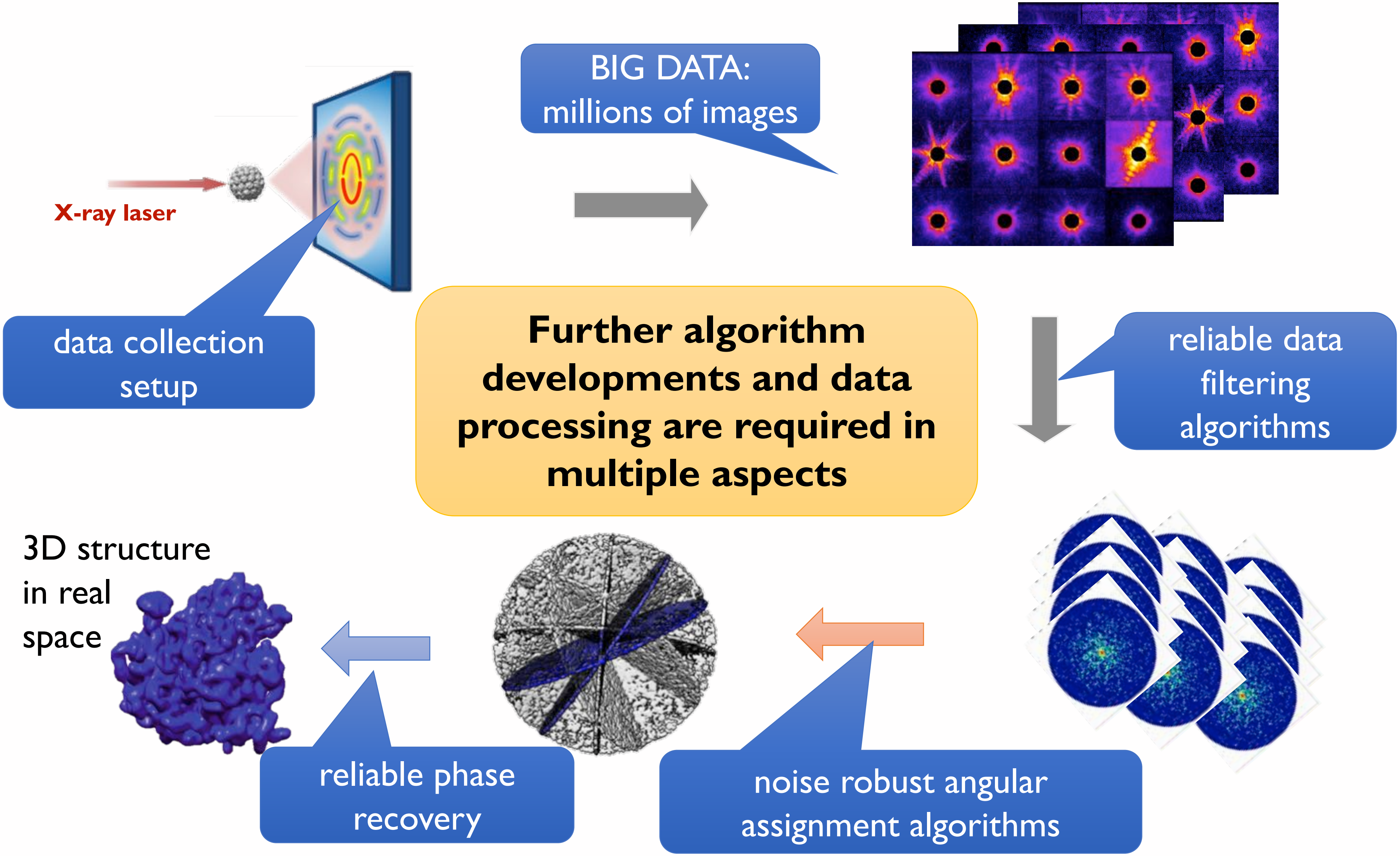


Real space 3D structure after phase recovery

- Angles are not known
- Arrangement of all 2D diffraction patterns need to be calculated.
- Computationally extensive for a large dataset
- Applications to experimental data with Nishino group @ Hokkaido U

Nakano et al, JSR 2017, 2018
Nakono et al, Biophys. Physicobiol. 2019

Challenges for Biomolecular Modeling from XFEL Data



BIG DATA:
millions of images

data collection setup

Further algorithm developments and data processing are required in multiple aspects

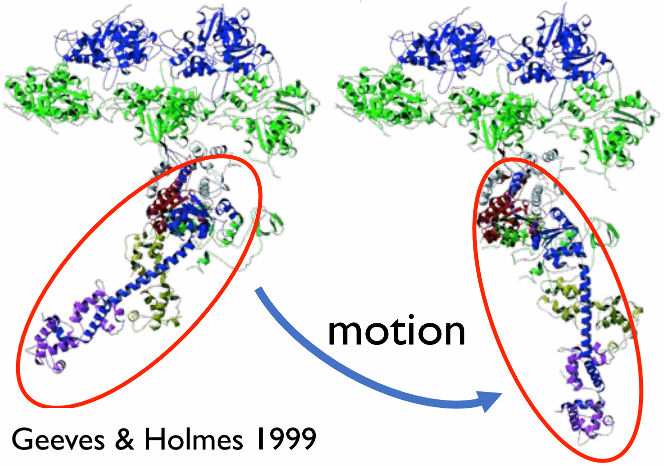
reliable data filtering algorithms

3D structure in real space

reliable phase recovery

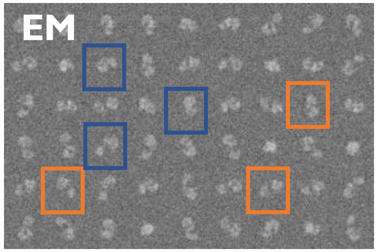
noise robust angular assignment algorithms

Challenges: going from Structure to Dynamics



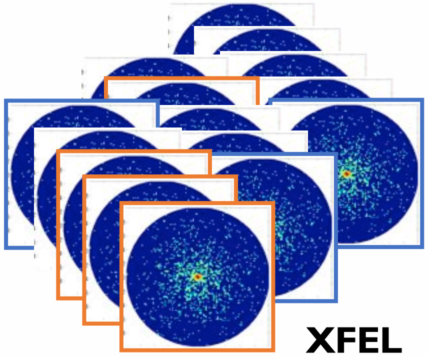
Geeves & Holmes 1999

- More experimental data are collected.
- New time resolved experimental techniques
- Modeling of conformational dynamics through analyses of large data sets

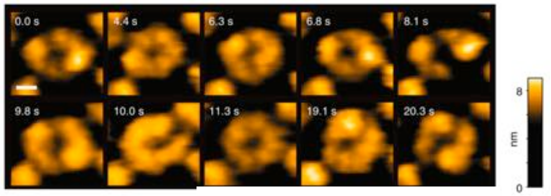


Millions of images

Multiple conformations captured

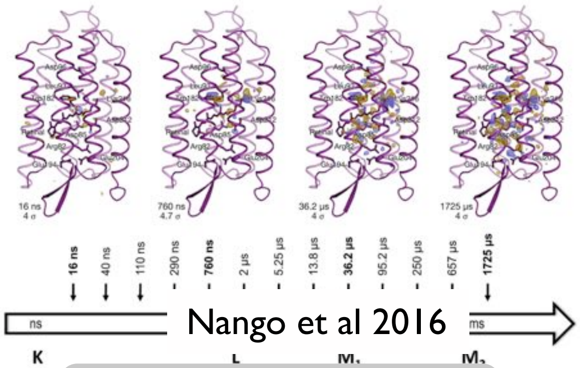


XFEL



Uchihashi et al 2018

Highspeed AFM

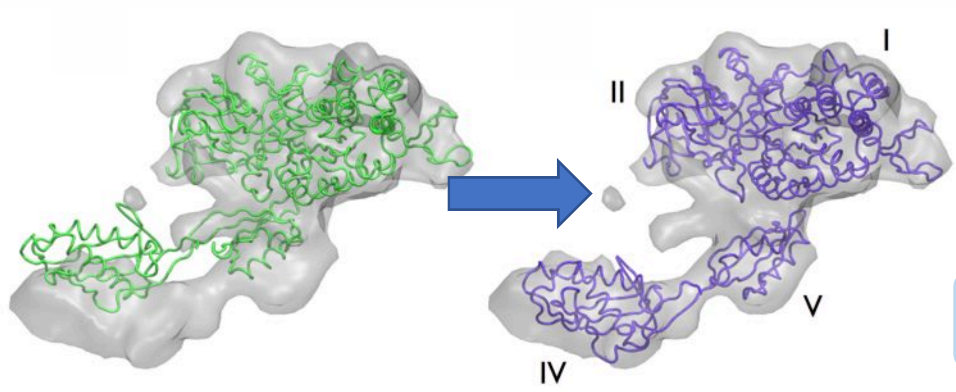


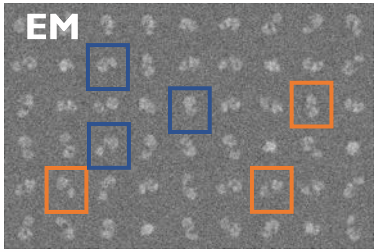
Nango et al 2016

Time-resolved SFX by XFEL

Summary

- Development of computational algorithms and tools for integrative structural biology and applications
- Obtain new structural and dynamical information combining experimental data and simulation
- More experimental data and more complex biological molecules require further computational resources and algorithms: Development of tools to utilize new data using Fugaku





Millions of images

Multiple conformations captured

Acknowledgements

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