A Bayesian approach to integrate cryo-electron microscopy data into MD simulations with PLUMED

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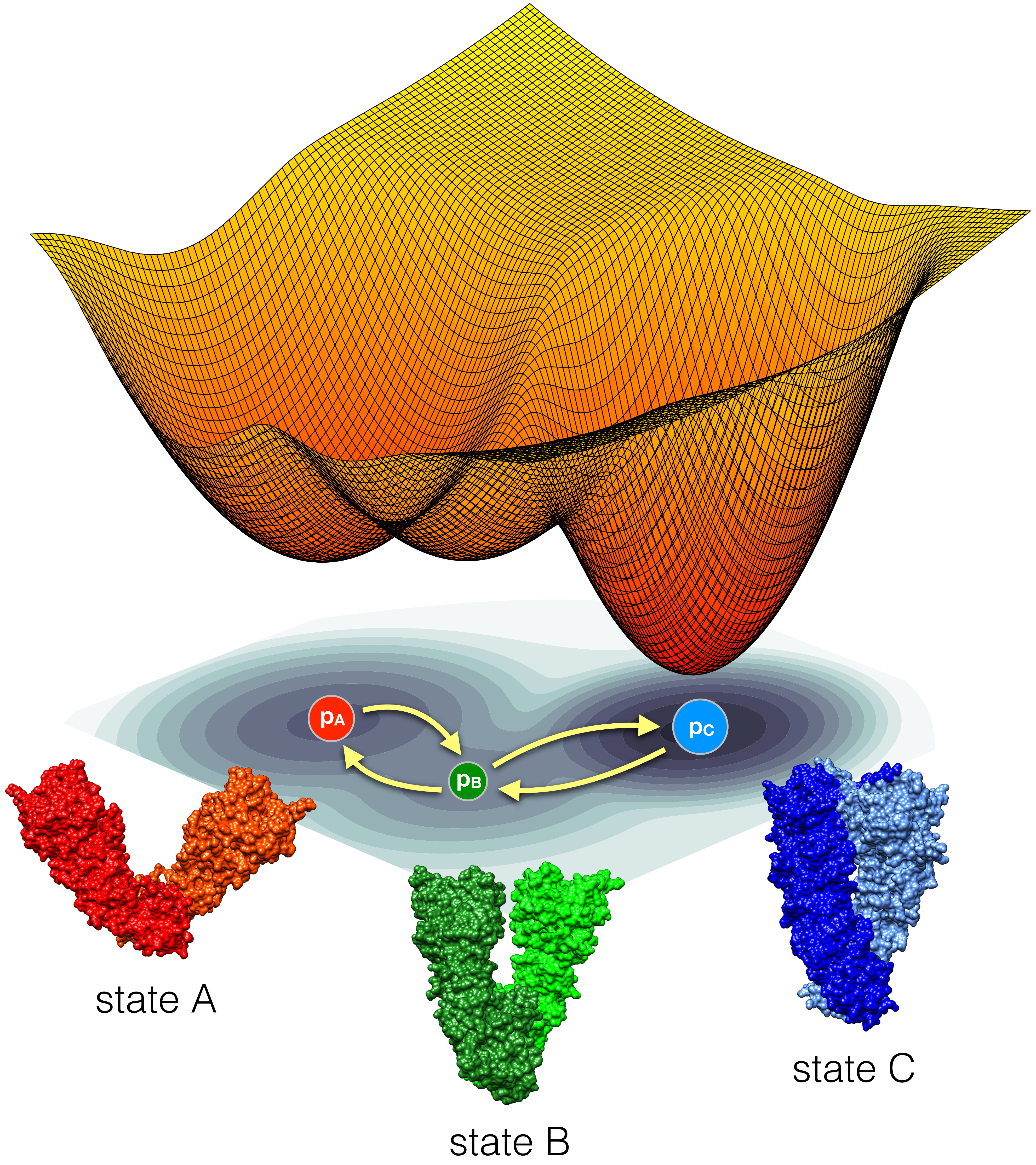
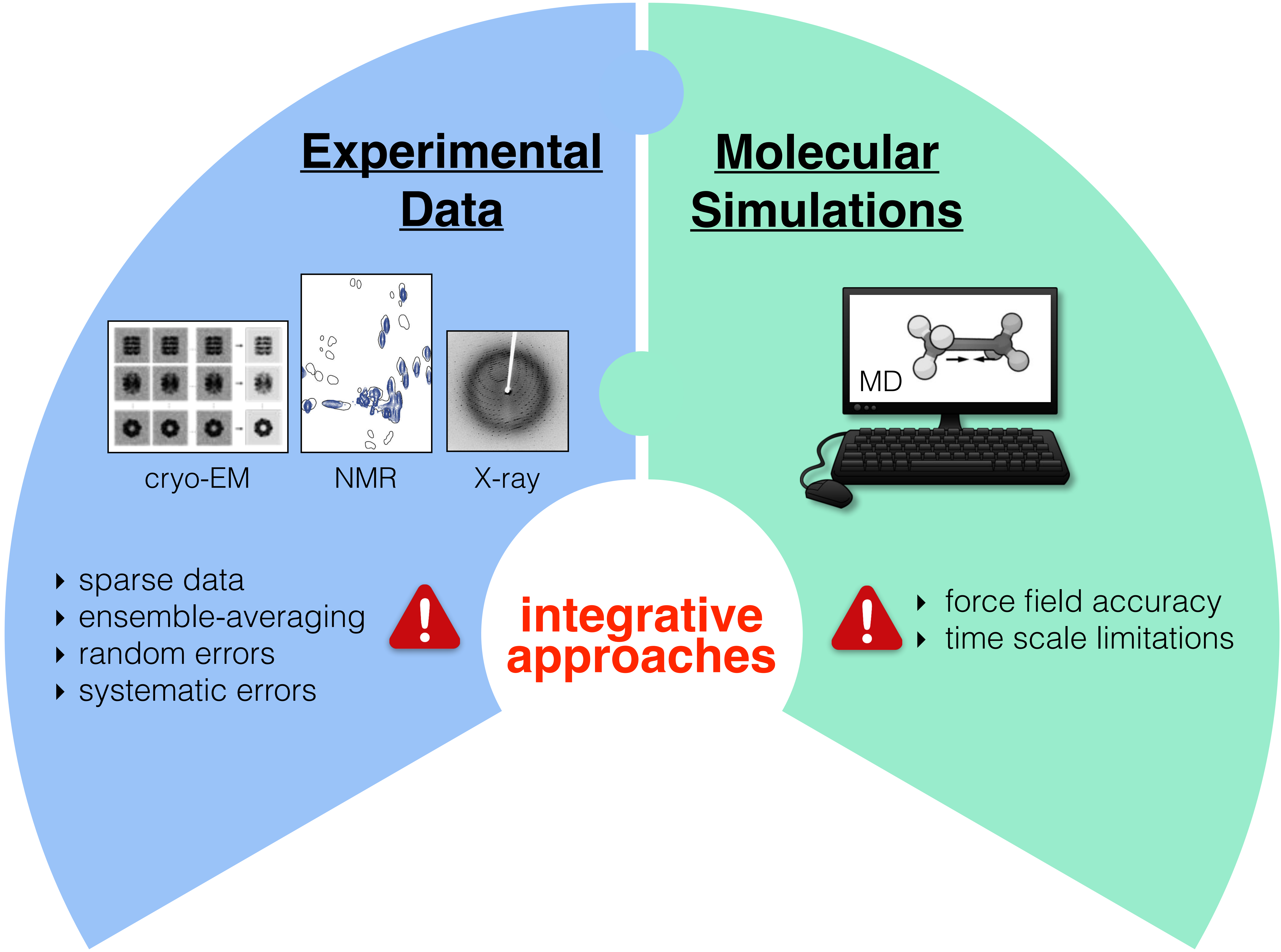
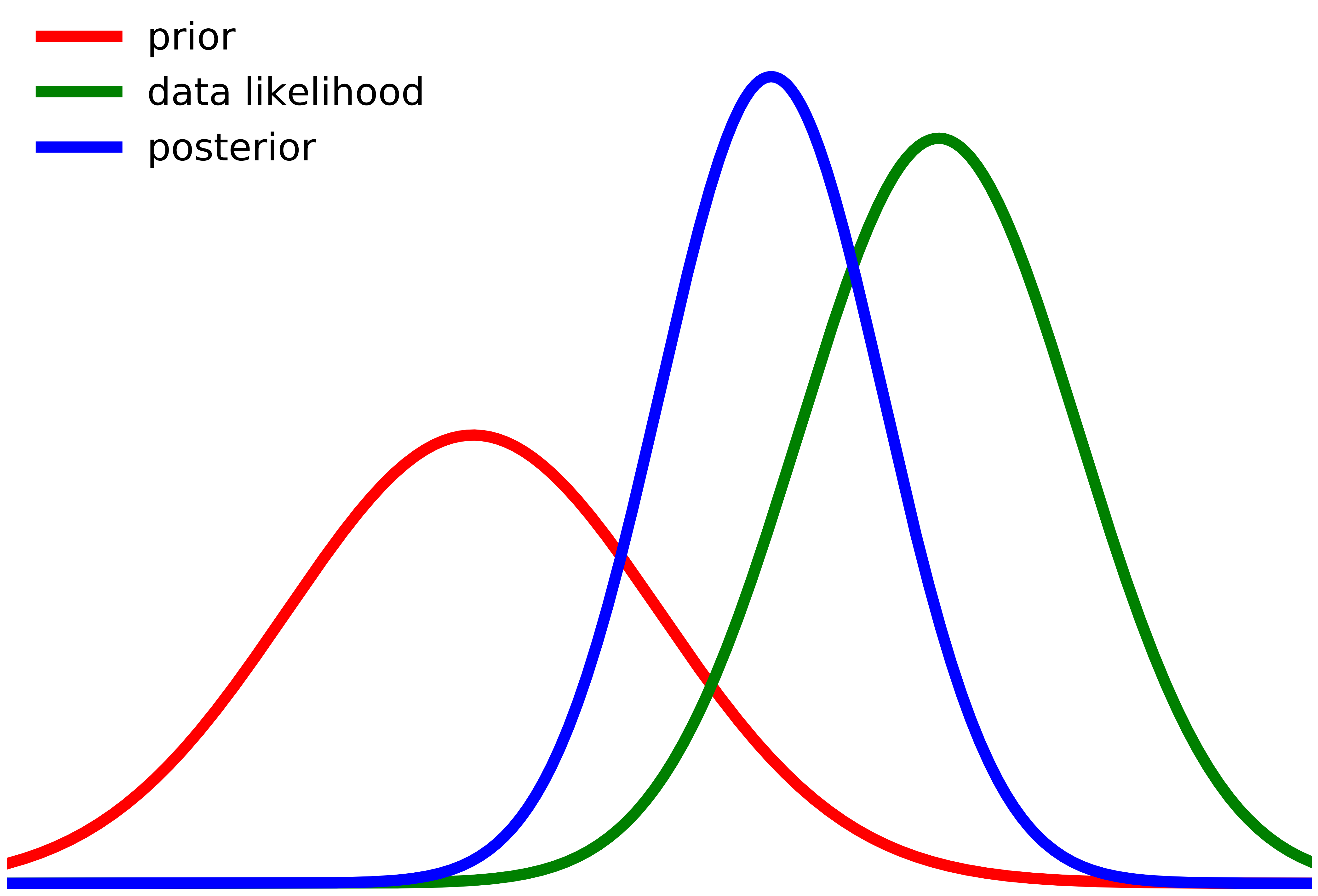
Biological functions from structure and dynamics



The best of both worlds: integrative or *hybrid* approaches



How? A little help from Bayes



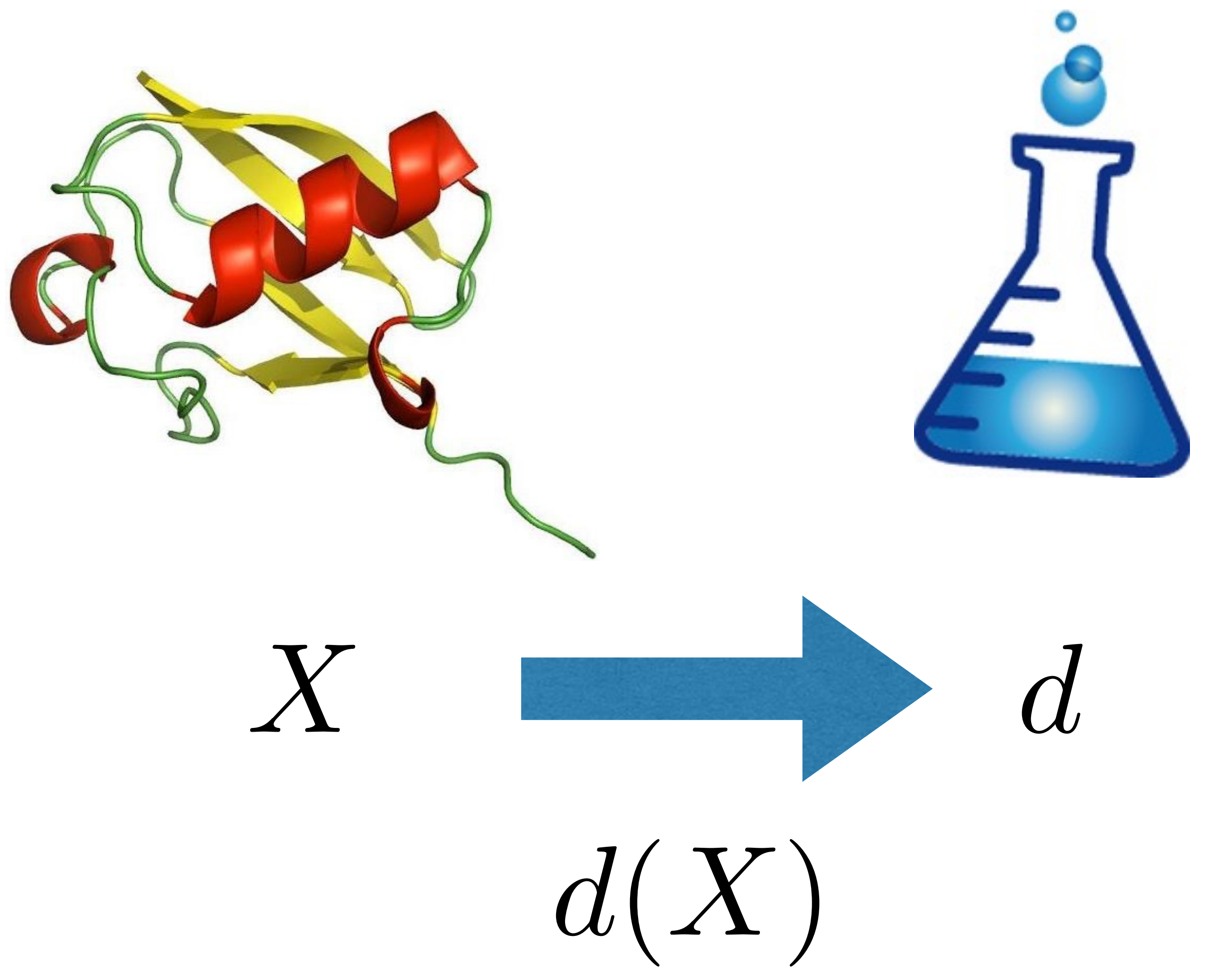
Thomas Bayes (maybe)
1702-1761

$$p(X, \sigma | d) \propto p(d | X, \sigma) \cdot p(X) \cdot p(\sigma)$$

posterior likelihood priors

The ingredients I

1) Define a *forward model*, i.e. a predictor of the experimental data from a structural model:



<u>Examples</u>

NOE: 1/distance^6
Chemical Shifts: SPARTA, SHIFTX, …
SAXS: CRYSOL, FoXS, …
Cross-links: distances, …
Cryo-EM: Gaussians centered on atoms positions

2) Define a *noise model*, i.e. a model of the deviation between predicted and measured data. Typically Gaussian or LogNormal distribution:

$$p(d|X,\sigma,I) = \frac{1}{\sqrt{2\pi\sigma}} e^{-\frac{[d-d(X)]^2}{2\sigma^2}}$$

large error = high tolerance for deviations
small error = small tolerance for deviations

errors in experimental data **and** predictors

The ingredients II

3) Choose the *priors*, i.e. your favorite MD force field

$$p(X|I) = e^{-\frac{E_{FF}(X)}{k_B T}}$$

and a prior for the uncertainty parameter(s):

$$p(\sigma|I) = \frac{1}{\sigma}$$

Jeffrey's prior

$$p(\sigma_i|\sigma_0, I) = \frac{2\sigma_0}{\sqrt{\pi\sigma_i^2}} exp\left(-\frac{\sigma_0^2}{\sigma_i^2}\right)$$

Outliers prior

4) Sample (MD, MC, or combined methods) using the following potential hybrid energy function:

large error = weak restraint

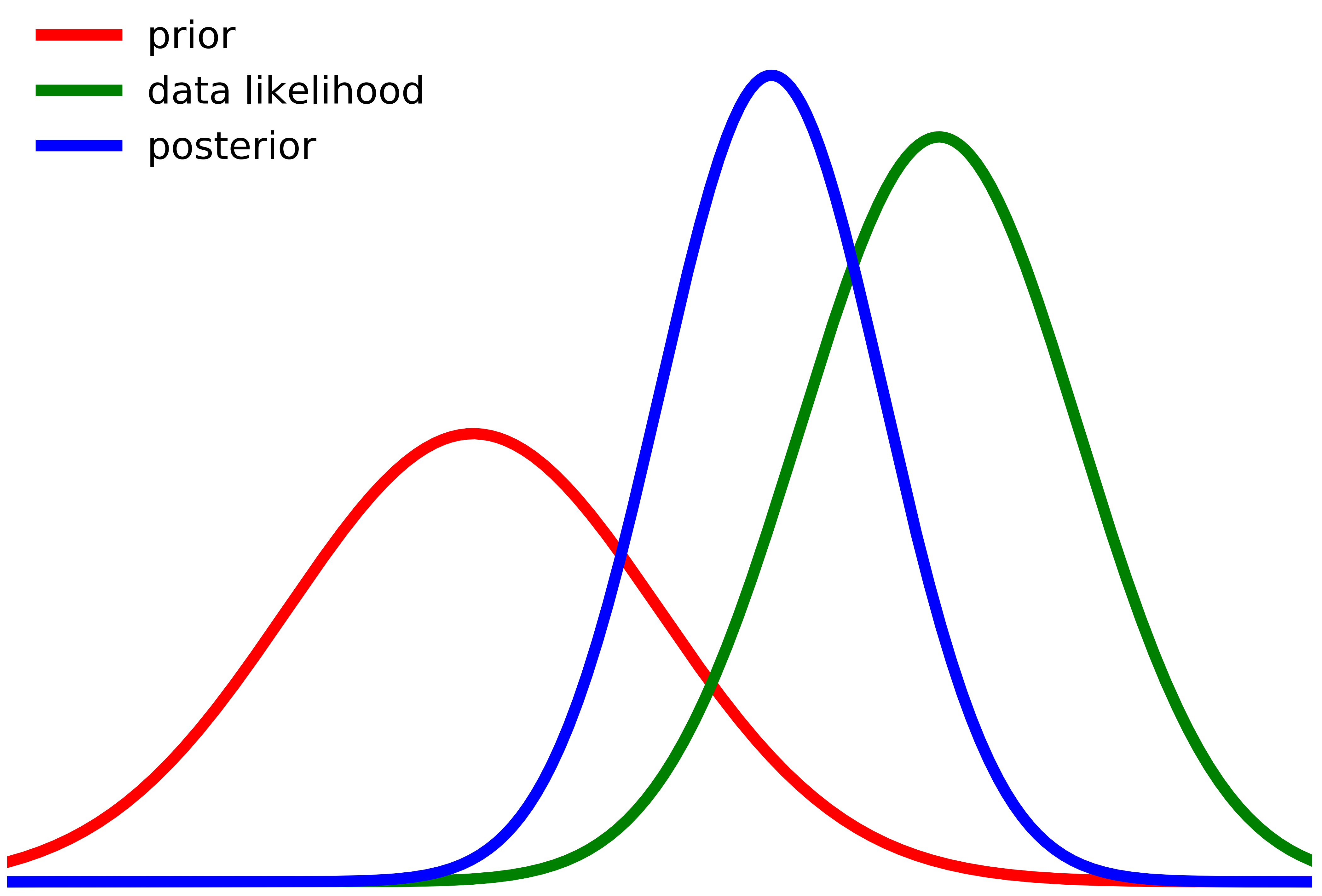
small error = strong restraint

$$E = -k_B T \log p(X, \sigma|d) = E_{FF}(X) + \frac{k_B T}{2\sigma^2}[d - d(X)]^2 + E(\sigma)$$

hybrid energy | **MD force field** | **data restraint** | **error restraint**

Inferential structure determination

Rieping *et al.* Science 2005

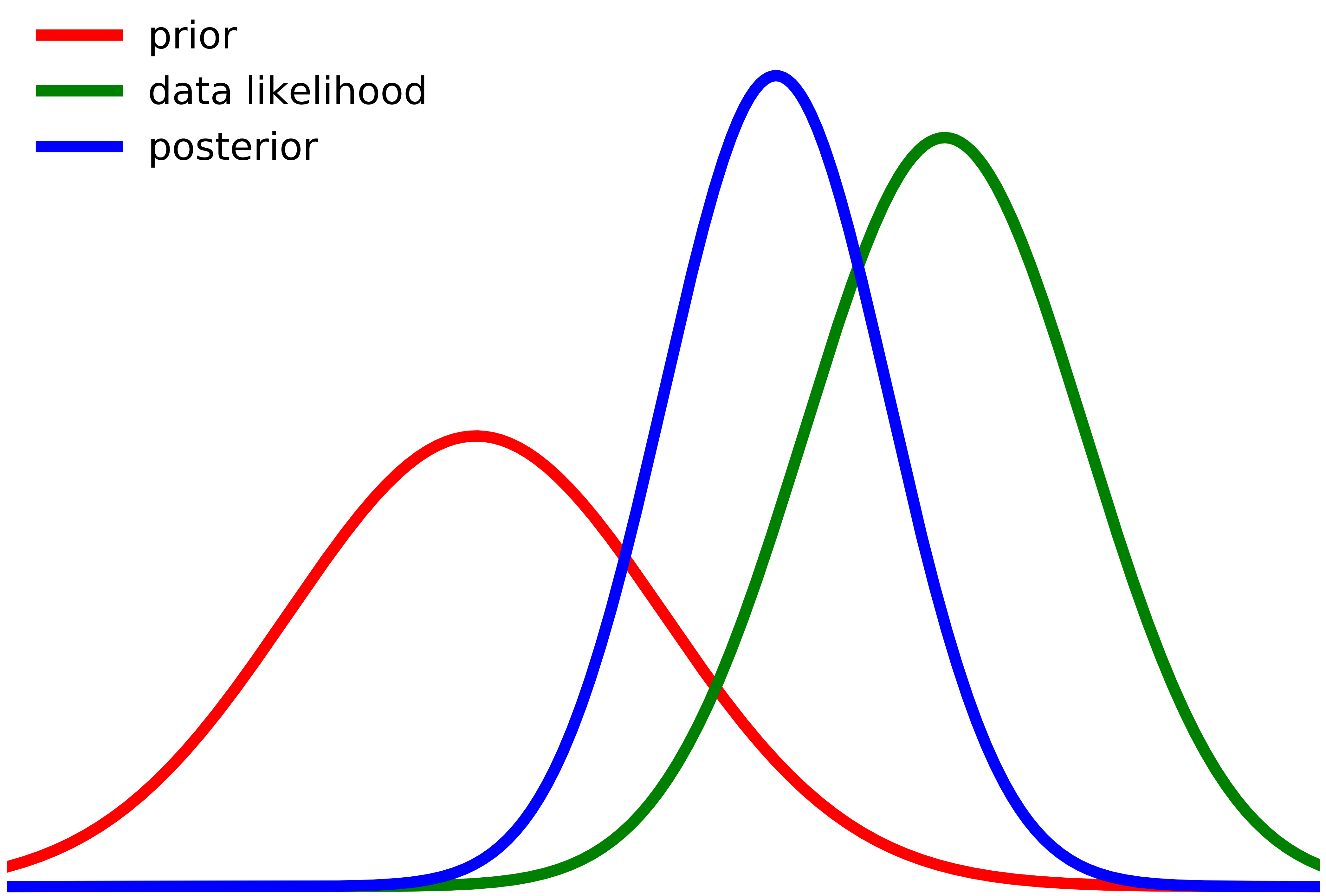


$$p(X,\sigma|d) \propto \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{[d-d(X)]^2}{2\sigma^2}} \cdot e^{-\frac{E_{FF}(X)}{k_B T}} \cdot p(\sigma)$$

posterior **likelihood** **priors**

Inferential structure determination

Rieping *et al.* Science 2005



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hybrid energy

MD force field

data restraint

error restraint

Inferential structure determination

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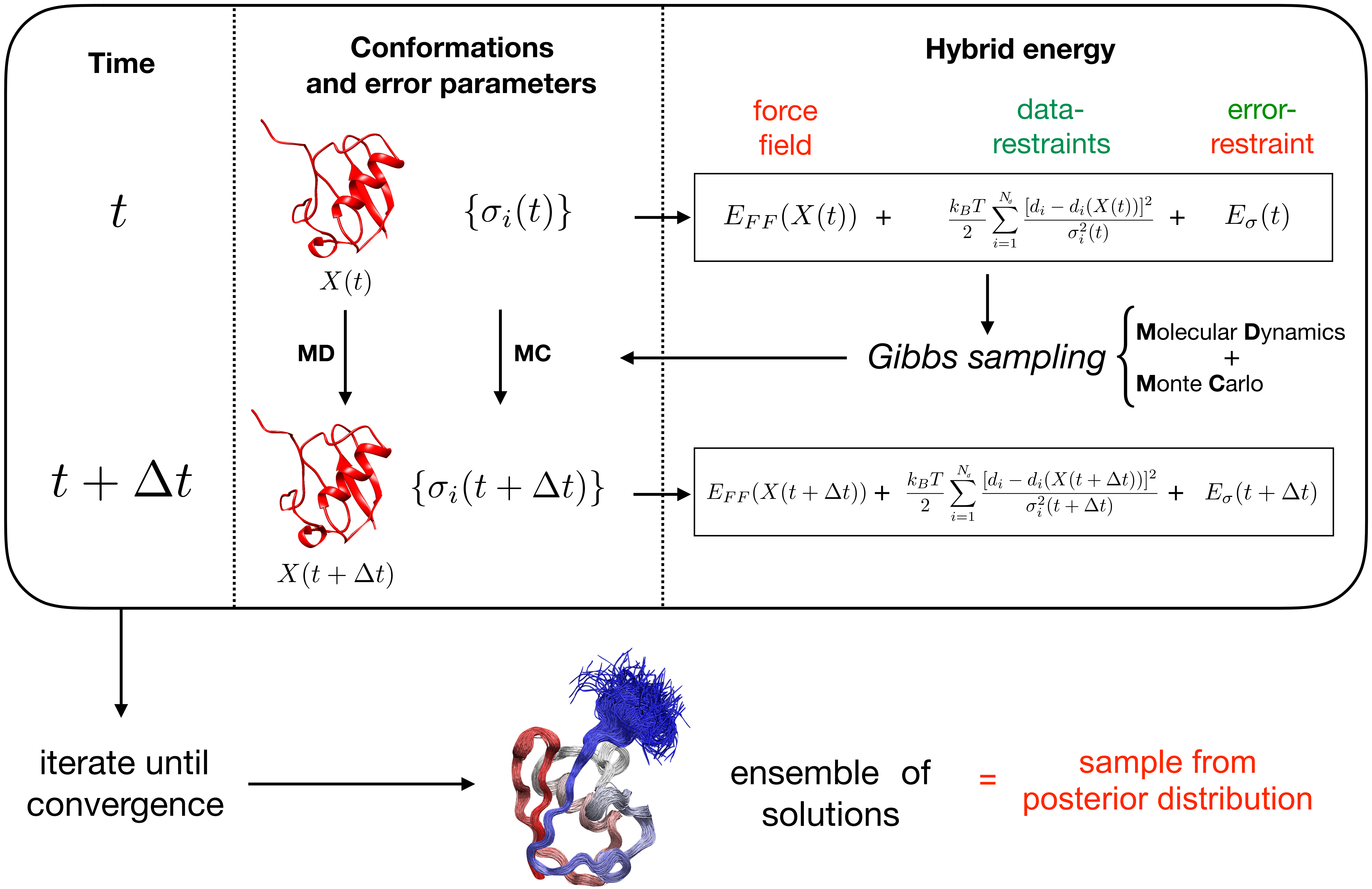


The advantages of the Bayesian approach

- Information other than experimental data can be rigorously incorporated into the modelling

- <u>Errors in the data</u> are accounted for

An *uncertainty parameter* σ is associated to the data and inferred along with the structure X

$$p(X, \sigma | D, I) \propto p(D | X, \sigma, I) \cdot p(\sigma | I) \cdot p(X | I)$$

- Data from different experiments is automatically <u>balanced</u>

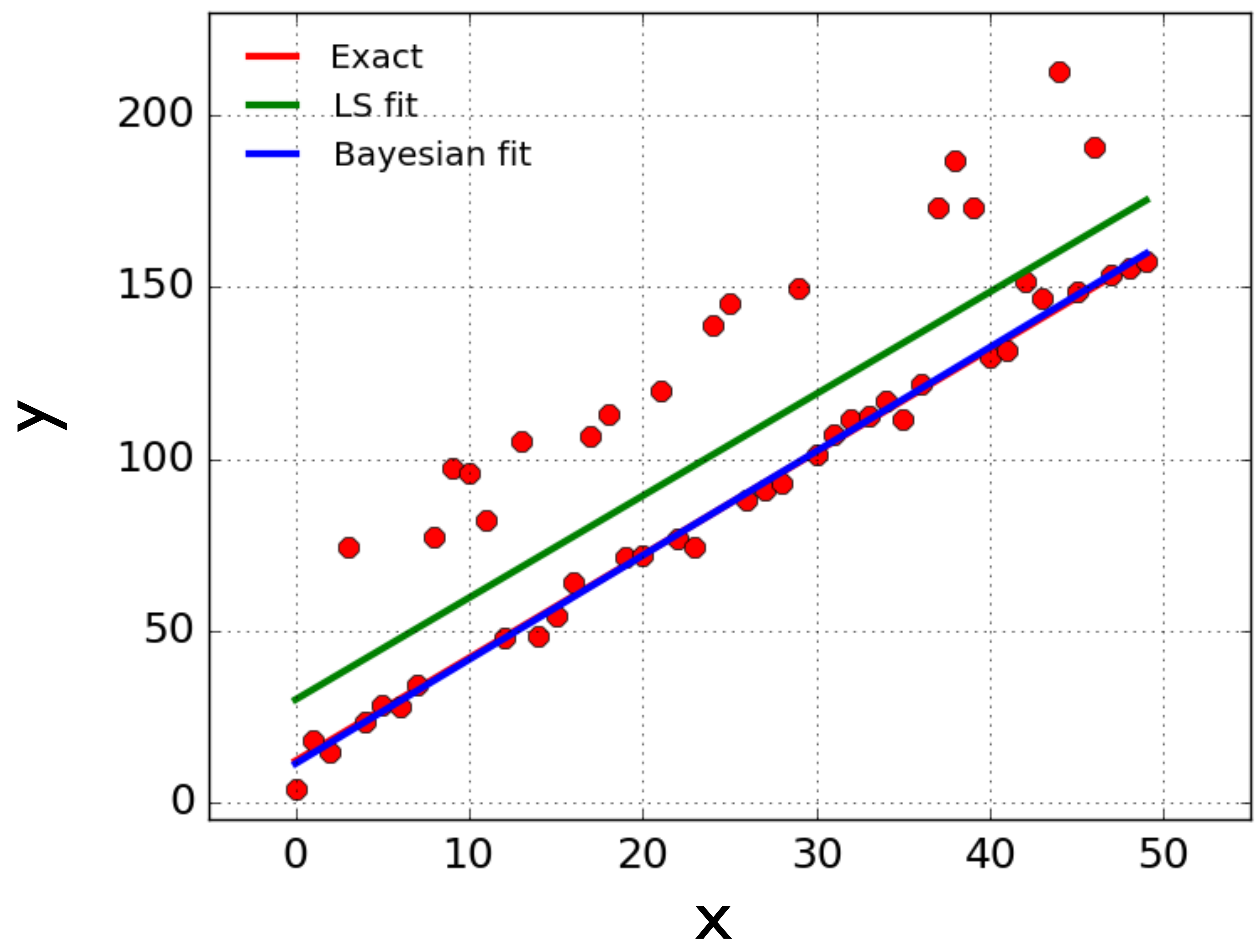
$$p(X, \{\sigma_i\} | \{d_i\}, I) \propto \left[\prod_i p(d_i | X, \sigma_i, I) \cdot p(\sigma_i | I) \right] \cdot p(X | I)$$

<u>The *weight* of each experimental data point in the construction of the structural model(s) is automatically determined based on its accuracy</u>

Example: Bayesian linear fit

Let's suppose our data can be described by a linear relation, with some error

Gaussian noise + 30% outliers



$$y=Ax+B$$

$A_0=3.0$ $B_0=12.0$

$A_{LS}=2.9$ $B_{LS}=29.8$

$A_B=3.0$ $B_B=11.3$

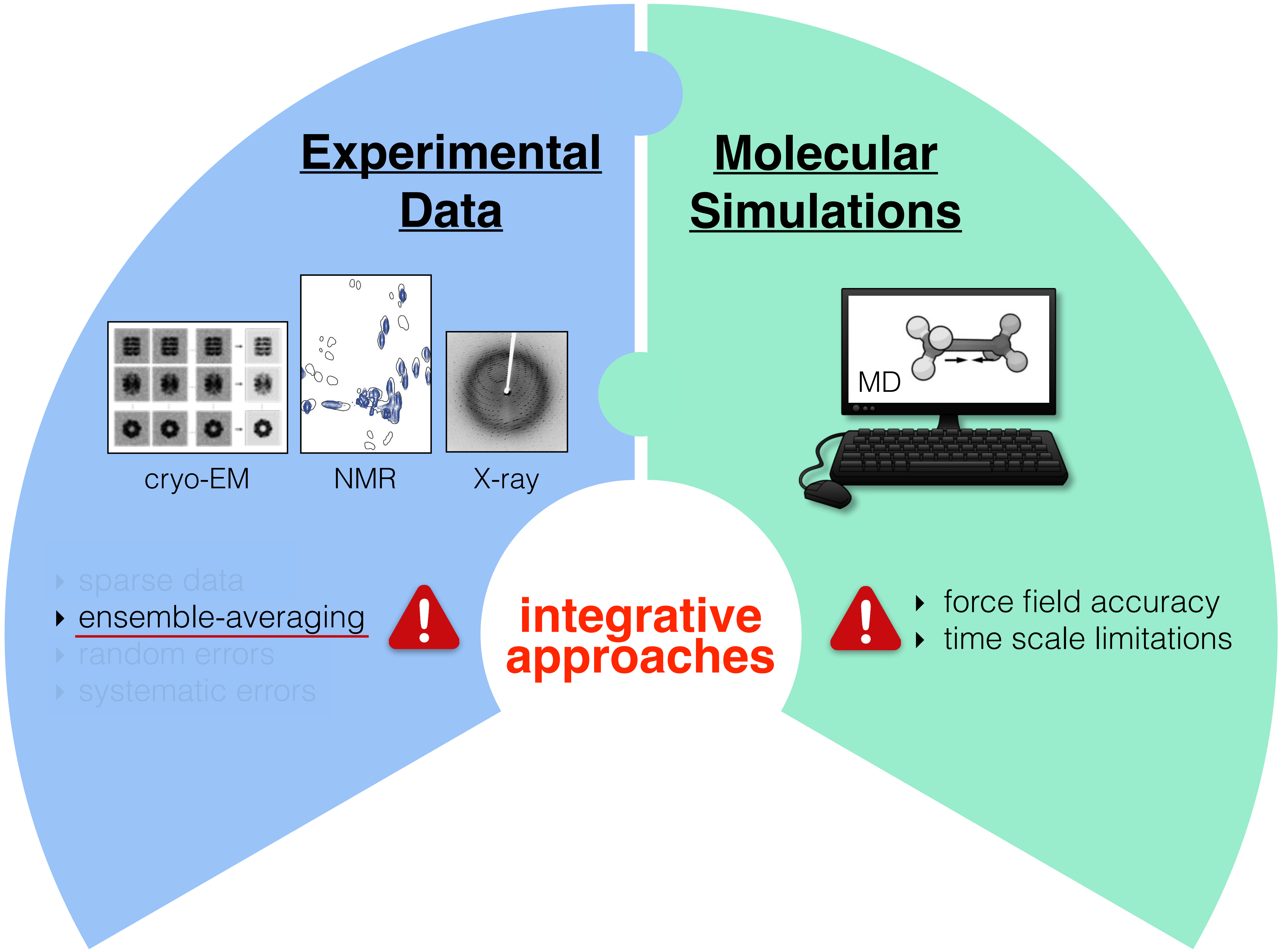
$$p(A, B, \sigma_0 | \{Y_k\}, I) \propto \prod_k \frac{1}{\sigma_k \sqrt{2\pi}} e^{-\frac{[f(x_k)-Y_k]^2}{2\sigma_k^2}} \cdot \frac{2\sigma_0}{\sqrt{\pi \sigma_k^2}} e^{-\frac{\sigma_0^2}{\sigma_k^2}}$$

Posterior probability

$$f(x_k) = Ax_k + B$$

Linear forward model

The best of both worlds: integrative or *hybrid* approaches



Inferential determination of structural ensembles with Metainference

Bonomi *et al.* Sci Adv 2016

META INFERENCE

$$E_{MI}(\mathbf{X},\sigma) = k_B T \cdot \sum_{r=1}^{N} \left\{ -\log p(X_r) + \sum_{i=1}^{N_d} (d_i - f_i(\mathbf{X}))^2 \frac{1}{2\sigma_{r,i}^2} + \log \sigma_{r,i} - \log p(\sigma_{r,i}) \right\}$$

hybrid energy

*multiple-replica sampling

MD force field

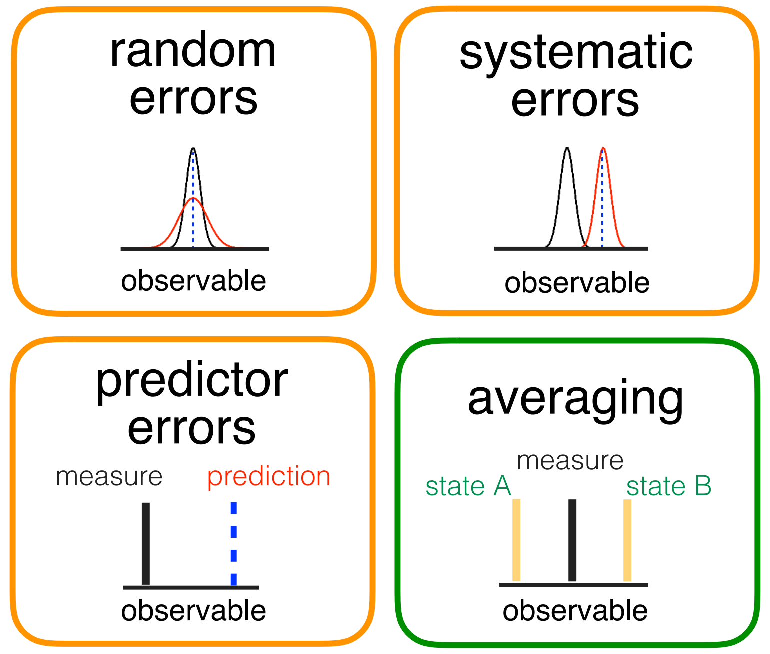
prior knowledge

data restraints

agreement with <u>experimental data</u>

error restraints

information about all the errors at play



*Lindorff-Larsen *et al.* Nature 2005
Cavalli, Camilloni, Vendruscolo. J Chem Phys 2013
Hummer, Köfinger. J Chem Phys 2015

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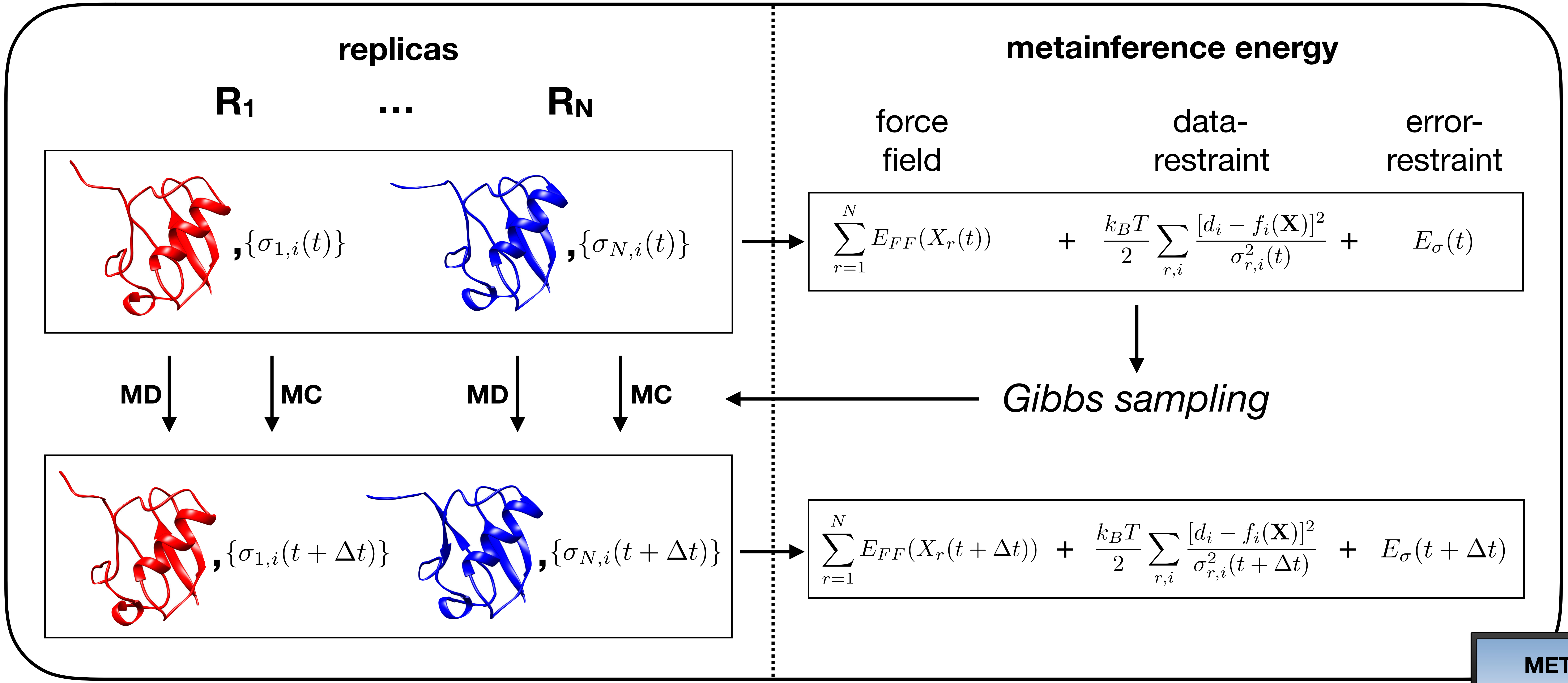
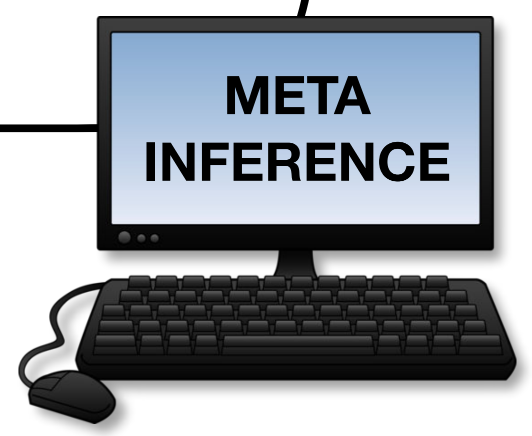
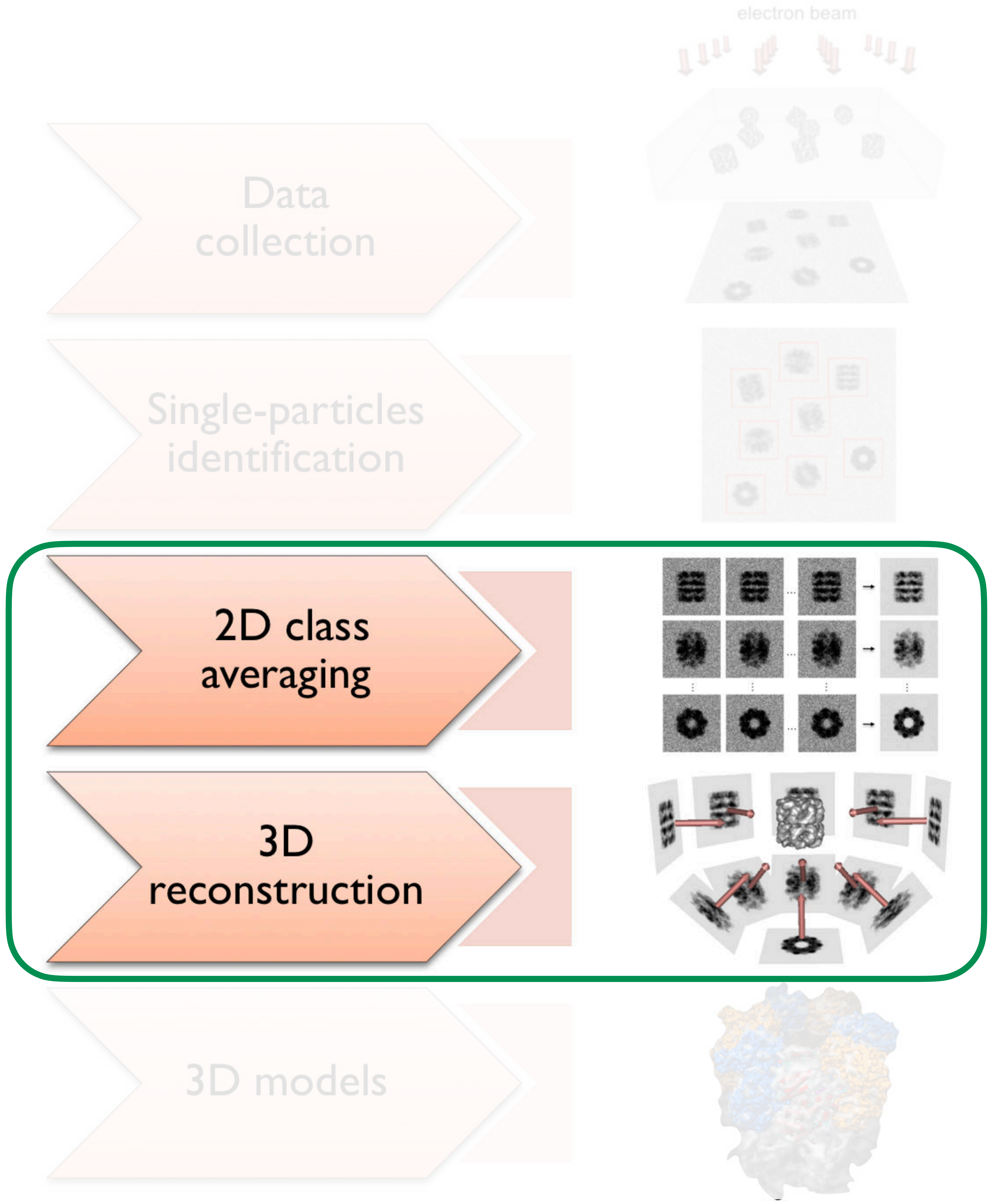


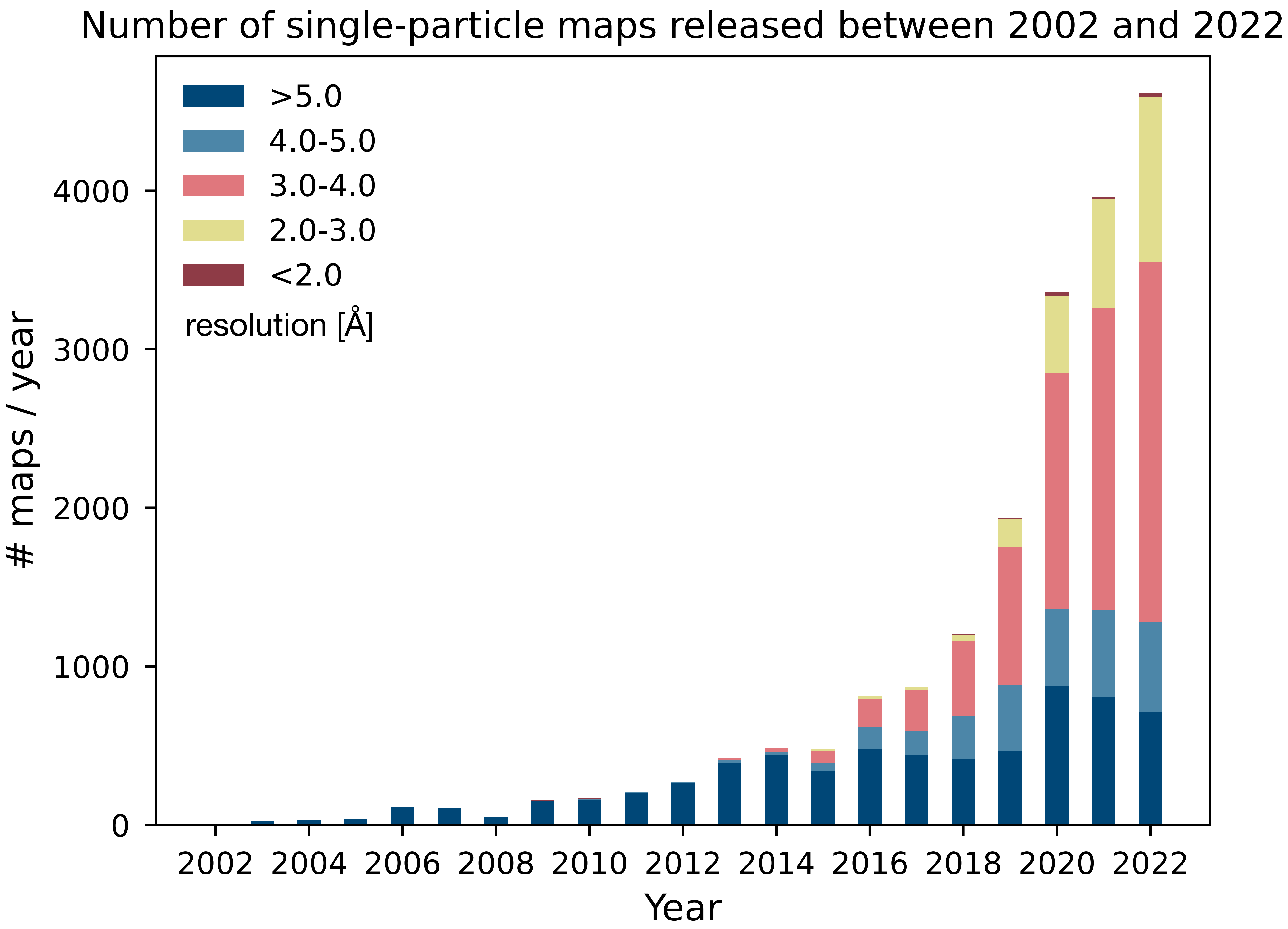


Minimal perturbation of the prior ensemble
Maximum Entropy principle*

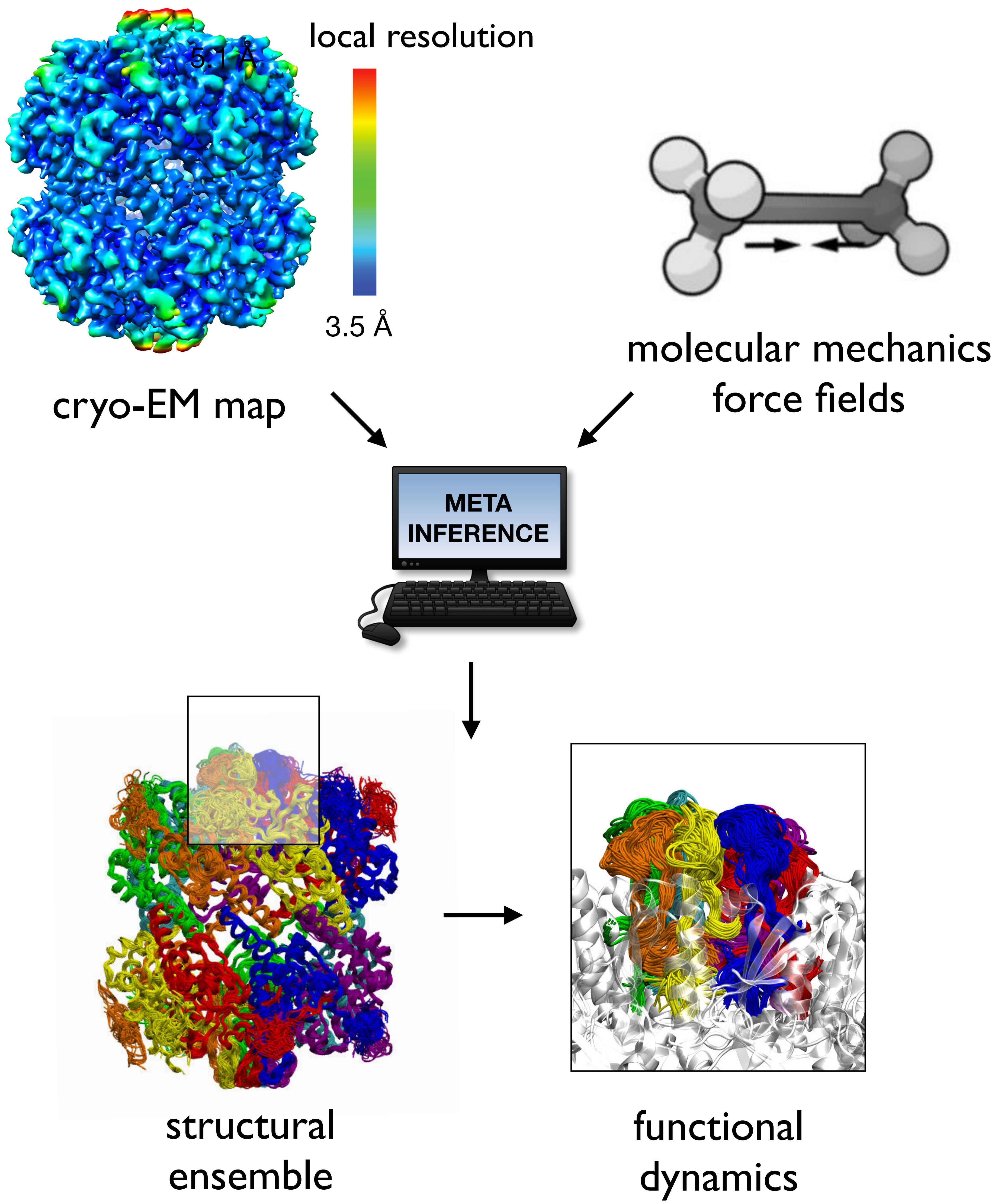
*see Hummer & Köfinger. J Chem Phys 2015

The cryo-EM resolution revolution





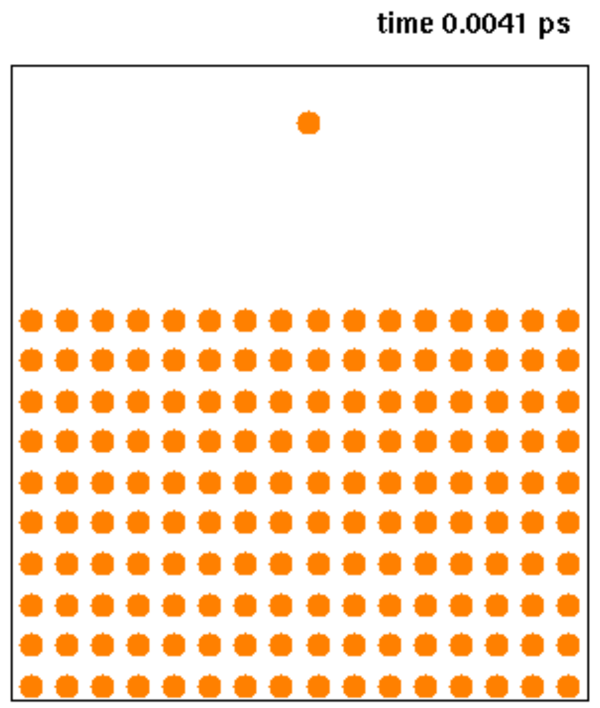
The cryo-EM resolution revolution



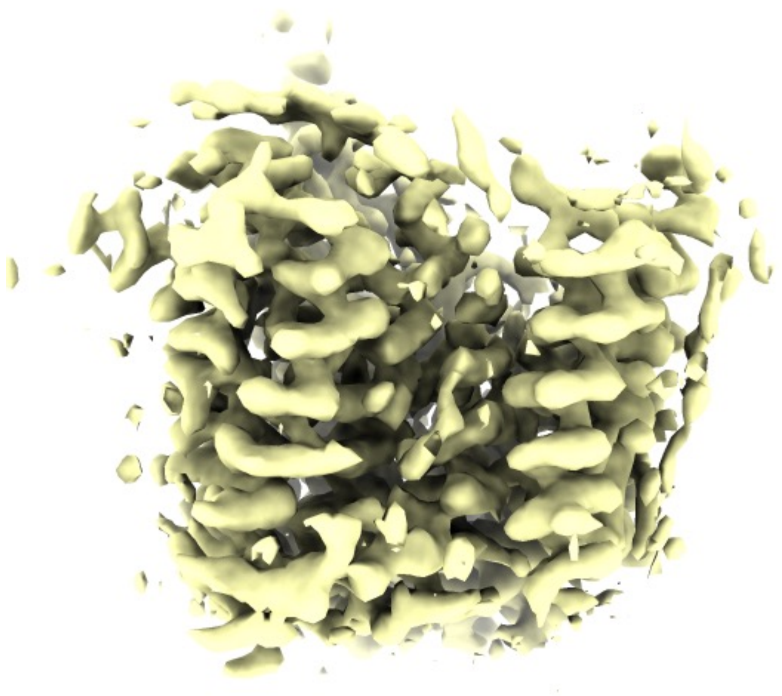
Integrate cryo-EM into MD simulations with EMMIVox

Hoff & Bonomi. In preparation; Bonomi, …,Pellarin. Structure 2019

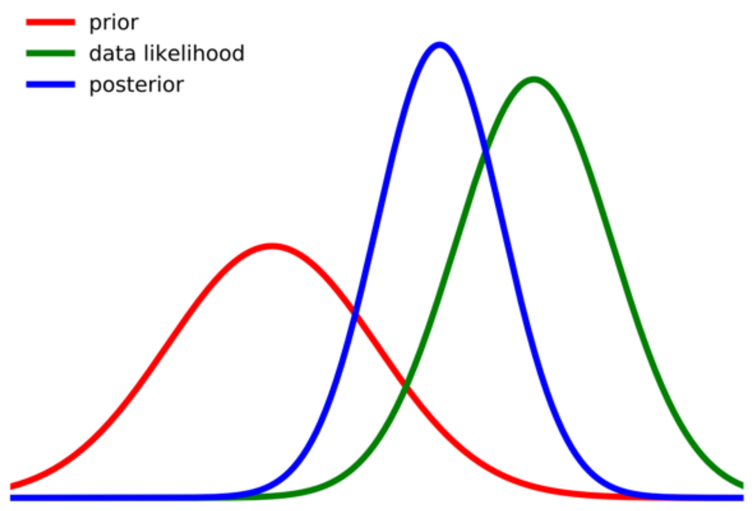
Accuracy of MD is limited!



Experimental data

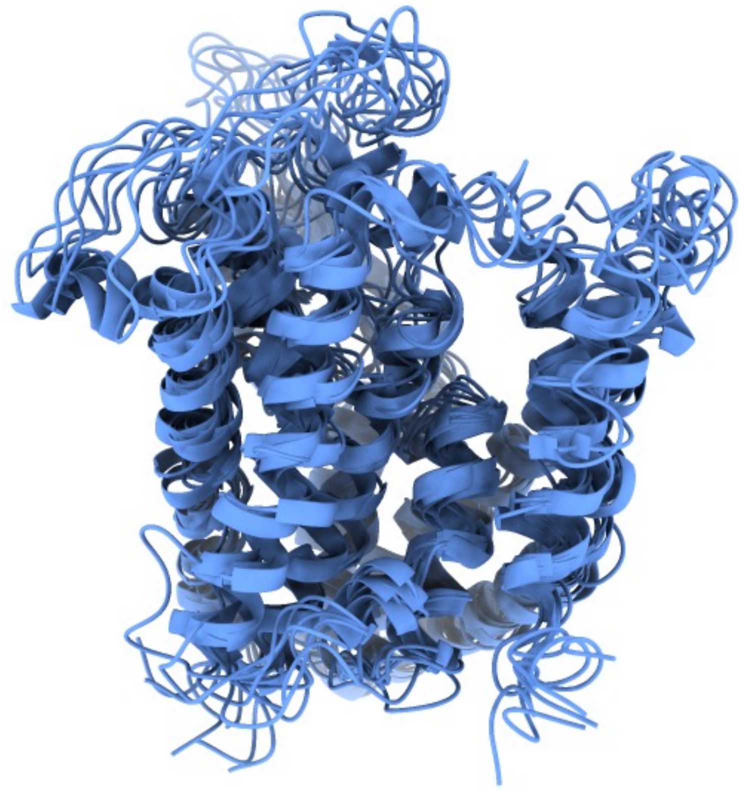


Bayesian inference



$$p(X,\sigma|d) \propto p(d|X,\sigma) \cdot p(X) \cdot p(\sigma)$$

Structural models



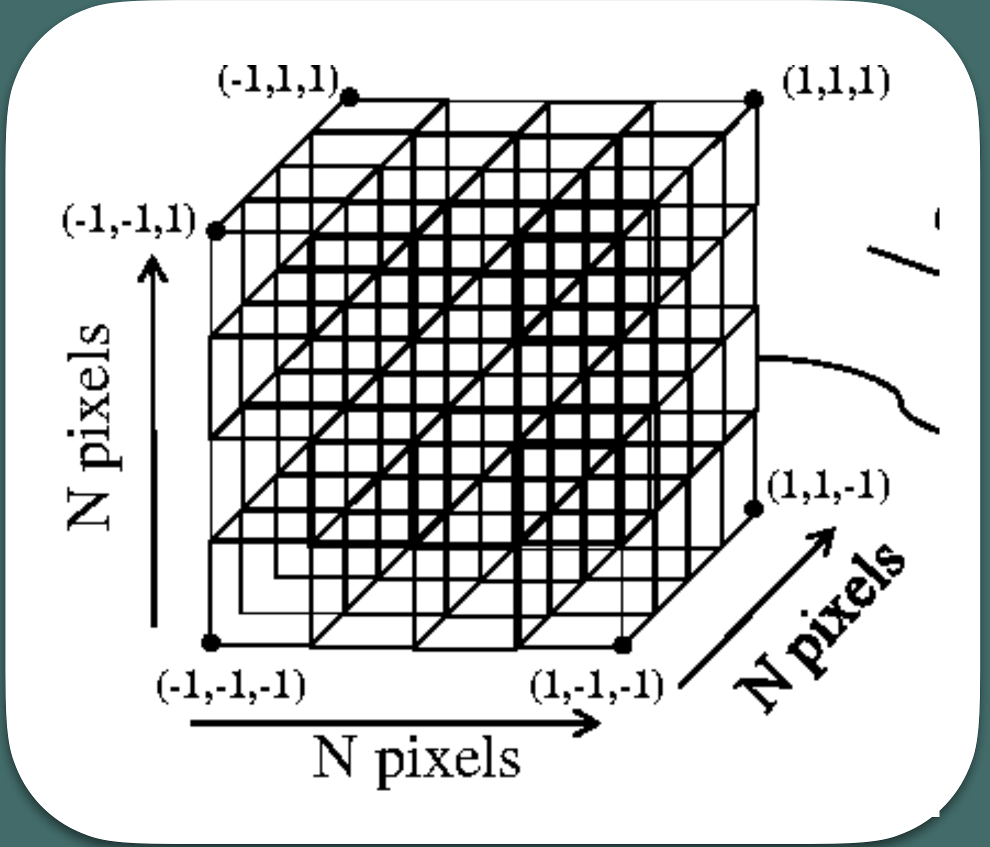
Objectives:

- Improving stereochemical quality of deposited PDBs (fewer clashes, …)
- Modelling structural ensembles with Metainference
- Integrating other experimental data (NMR, SAXS, EPR, …)

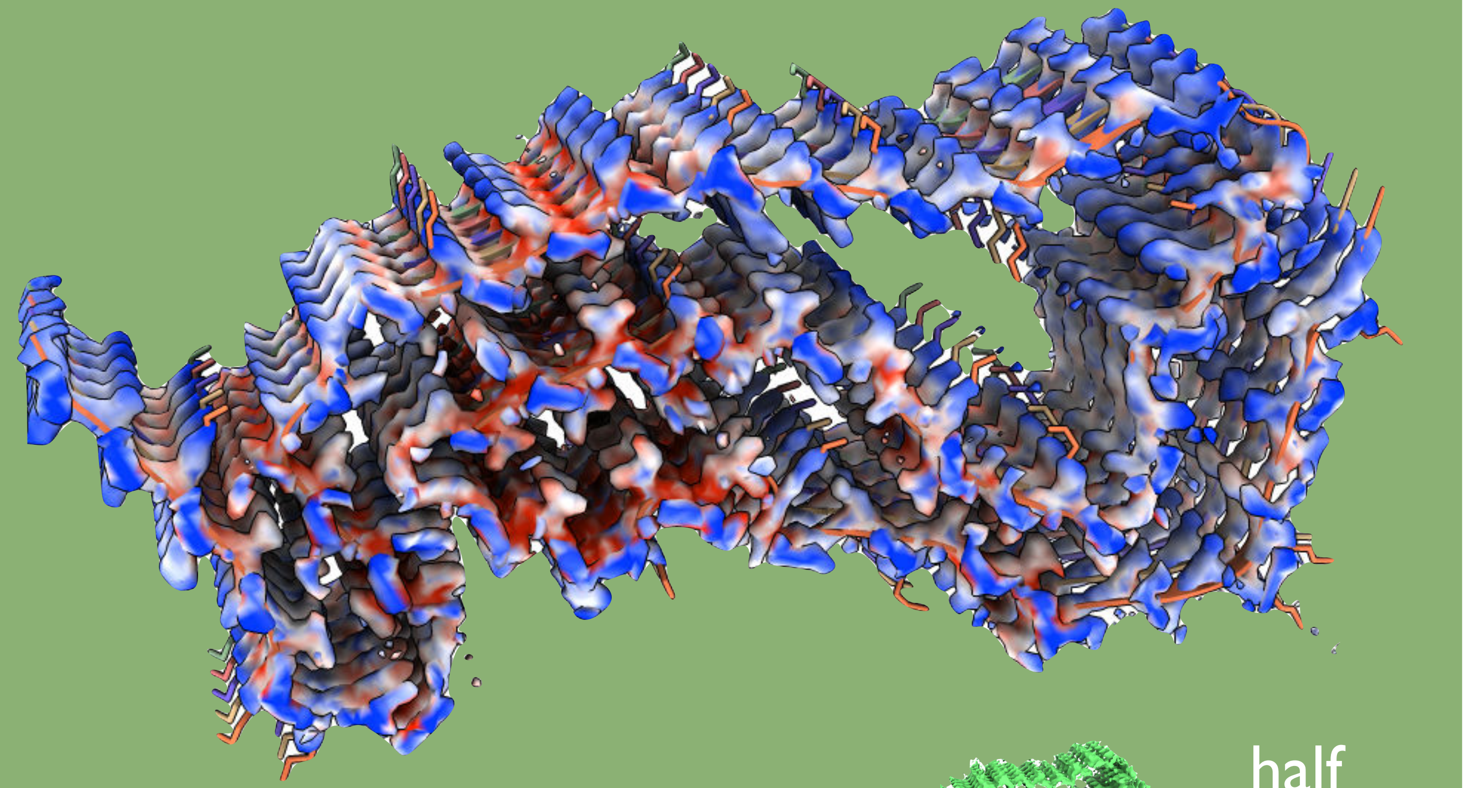
Integrate cryo-EM into MD simulations with EMMIVox

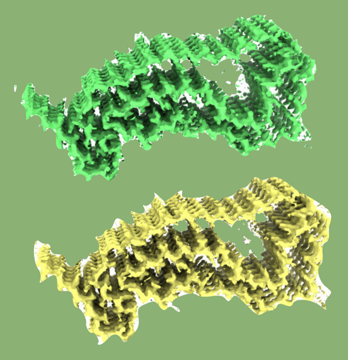
Hoff & Bonomi. In preparation; Bonomi, …,Pellarin. Structure 2019

Estimate correlation between voxels



Estimate "experimental noise" for each voxel





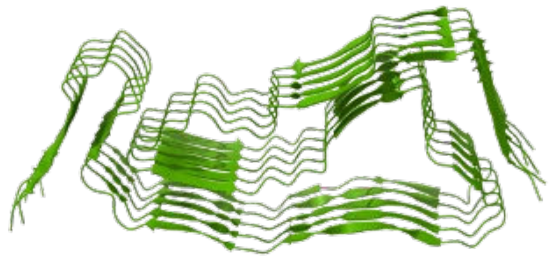
Gaussian noise model for each voxel

$$p(\phi_{D,i}|M) = \frac{1}{\sqrt{2\pi}\sigma_i} \cdot exp\left[-\frac{(\phi_{D,i} - \phi_{M,i})^2}{2\sigma_i^2}\right]$$

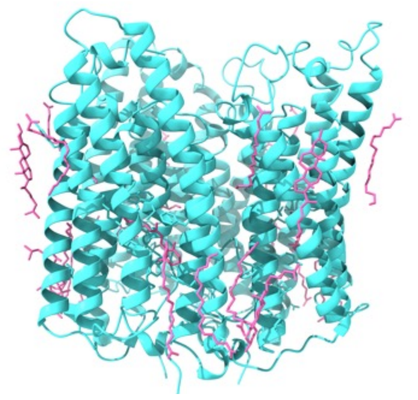
- remove correlated voxels
- one error parameter per voxel
- minimum value from error map
- error marginalization

Better balance between stereochemical quality and fit to the map

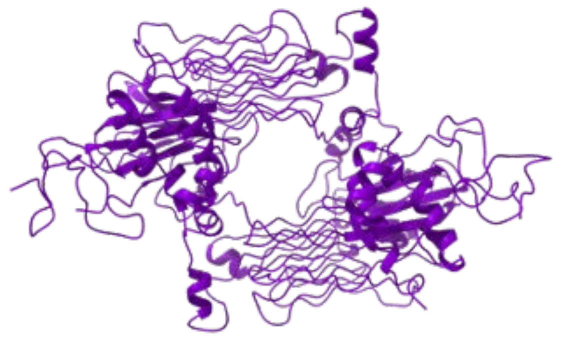
7p6a



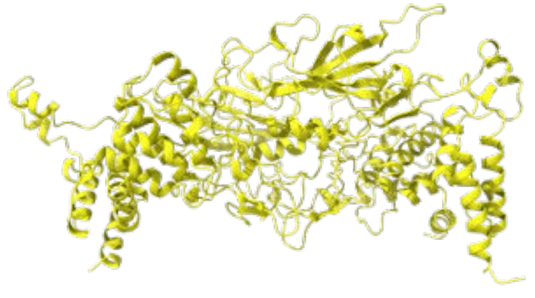
7w9w



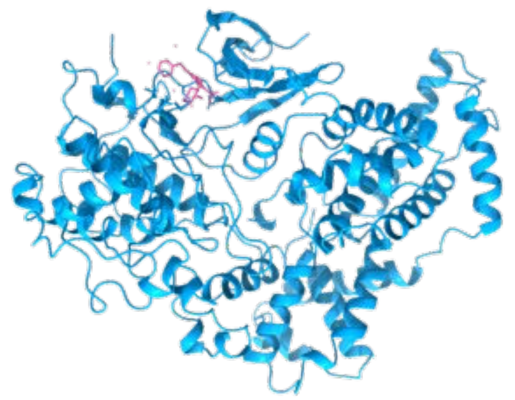
7n00



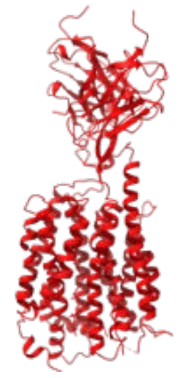
7t4n



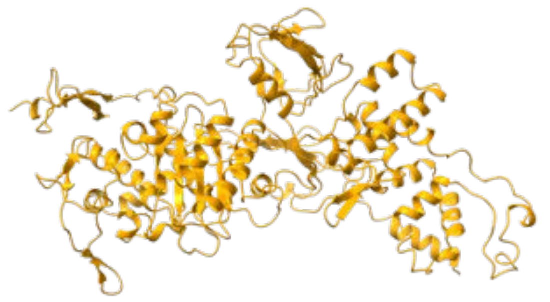
7b5o



7mjs



7lq6



7nqk

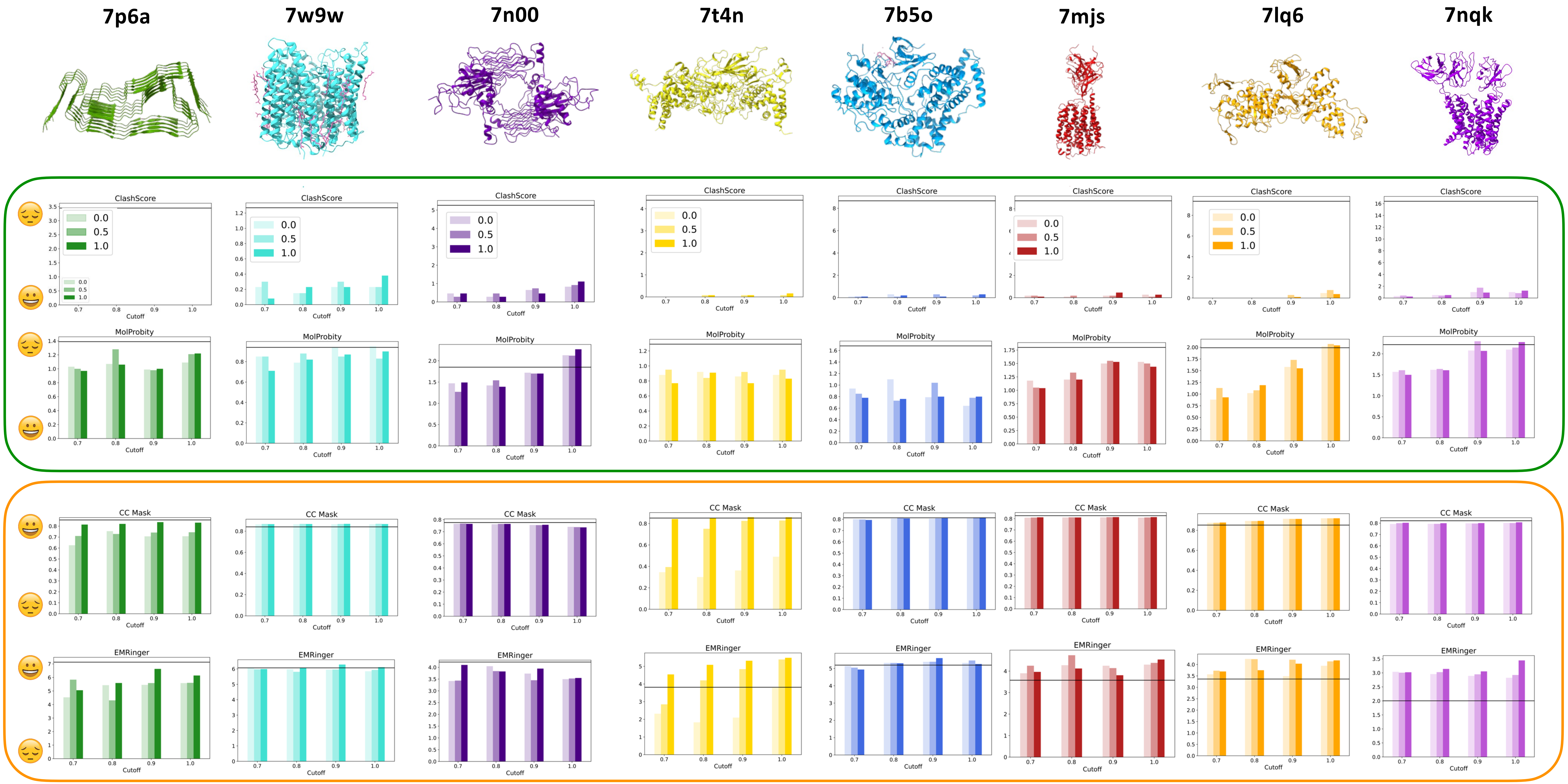
Clash between atoms: Clashscore

Overall sterochemical quality: Molprobity

Fit model/map: CC_mask

Correct positioning of sidechains: EMRinger

Better balance between stereochemical quality and fit to the map



EMMIVox is implemented in PLUMED

Bonomi *et al.* CPC 2009; Tribello *et al.* CPC 2014

PLUMED

www.plumed.org

- open-source, freely-available
- community-developed
- enhanced sampling methods for MD
- analysis tools
- algorithms for integrative biology

NAMD Scalable Molecular Dynamics

DL_POLY

OpenMM

QUANTUMESPRESSO

GROMACS FAST. FLEXIBLE. FREE.

ESPResSo

CP2K

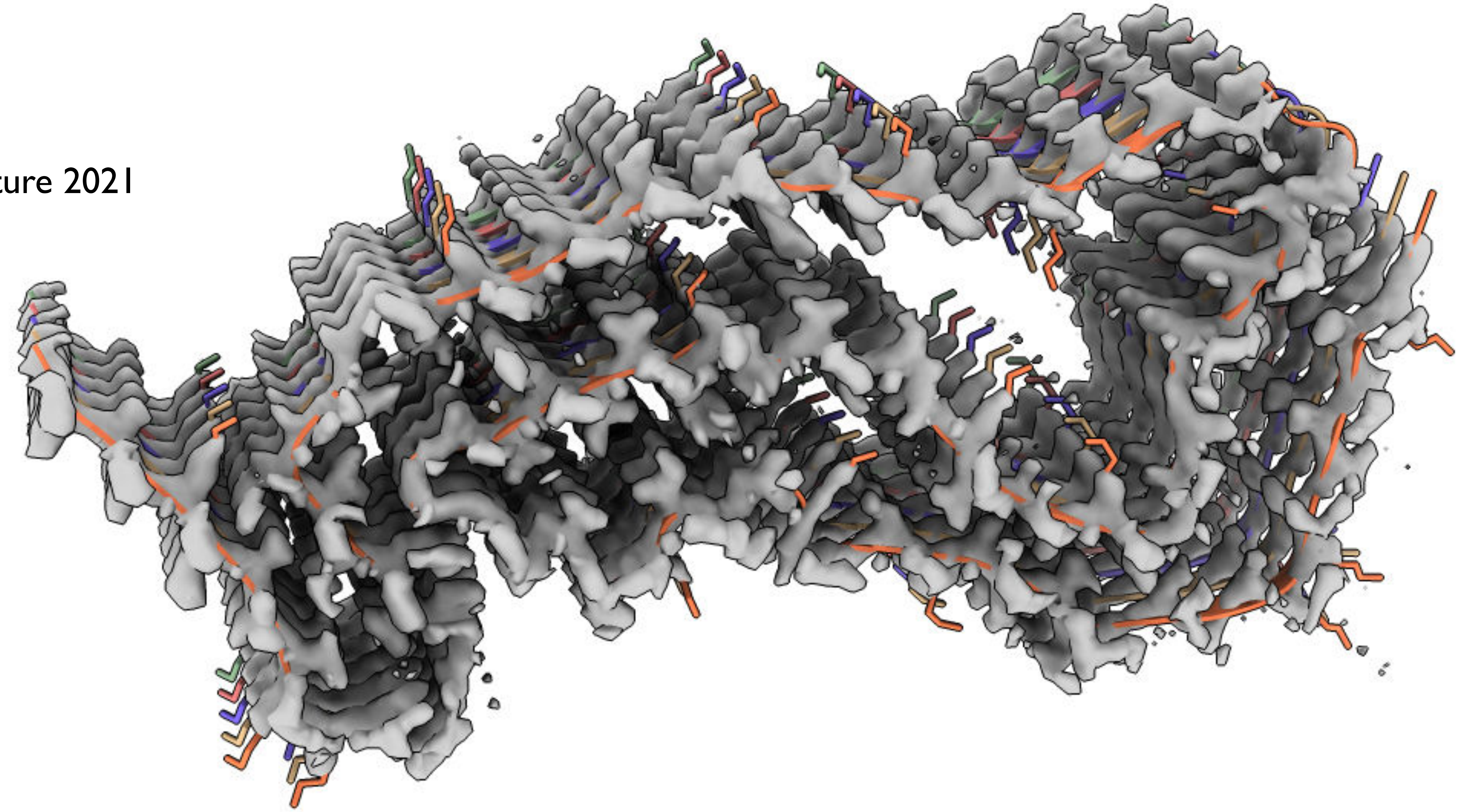
LAMMPS

OpenPathSampling

Today's system
Tau filament from the brains of individuals with PSP

*PDB 7p6a
EMDB 13223
resolution 1.9 Å

*Shi, …, Scheres. Nature 2021



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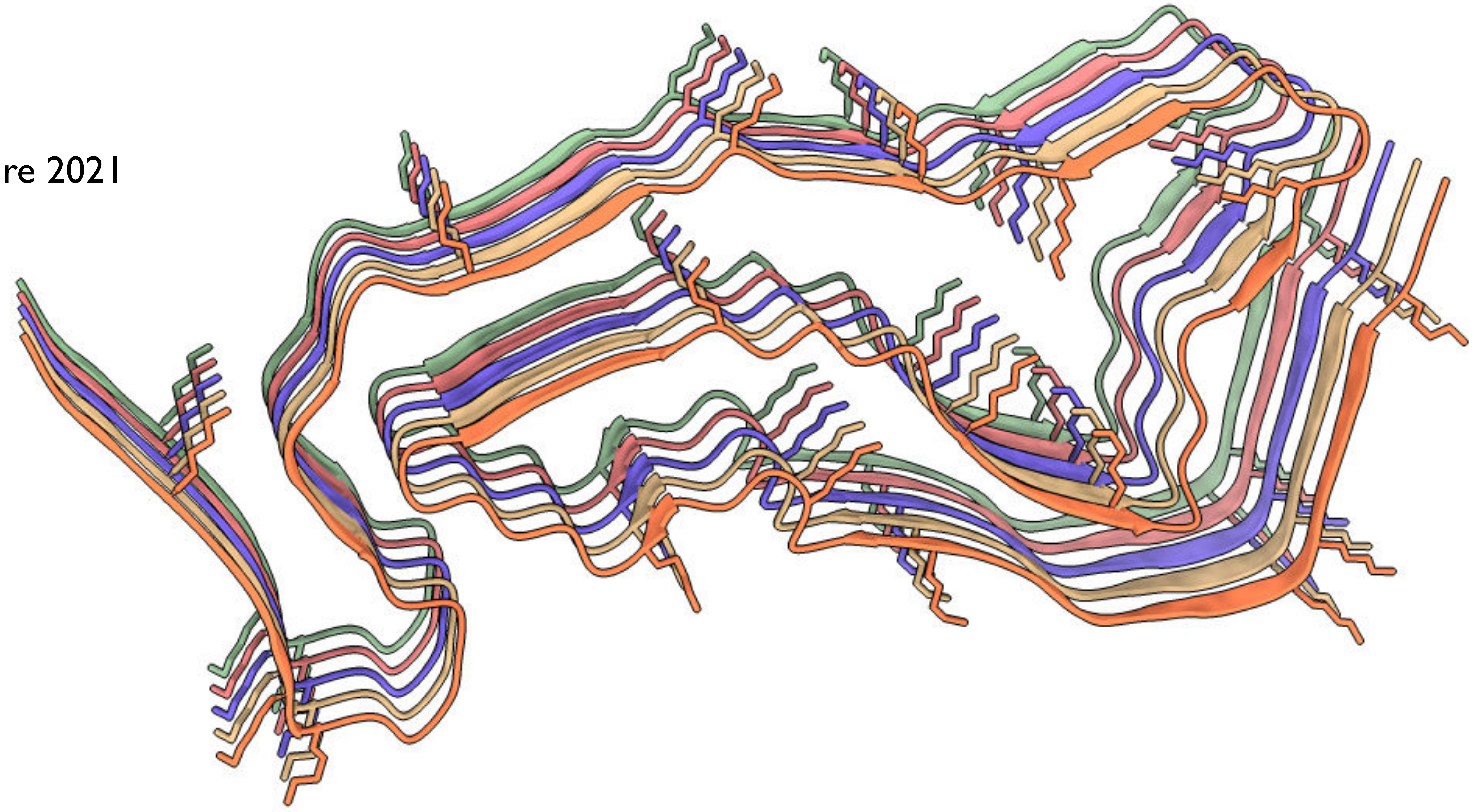
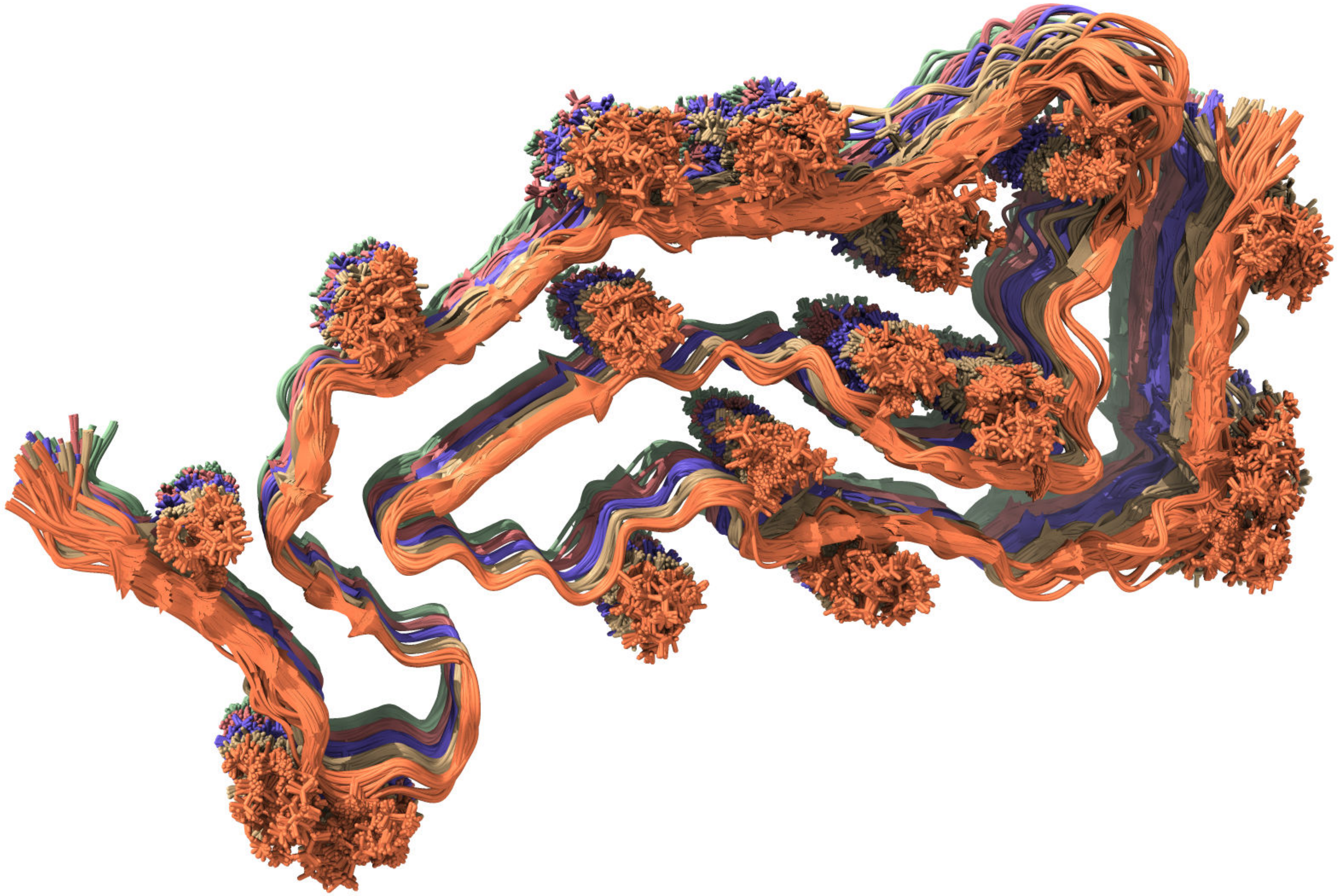


Exercise 1
Compare EMMIVox refined model and deposited PDB

	Validation metric	deposited PDB	EMMIVox model
Fit model-map	CC_Mask		
	EMRinger		
Stereochemical quality	Clashscore		
	Molprobity		

Exercise 2
Determining structural ensembles with EMMIVox and Metainference



Fit
model-map

Validation metric	deposited PDB	EMMIVox model	EMMIVox ensemble
CC_Mask			

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Le calcul intensif au service de la connaissance

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