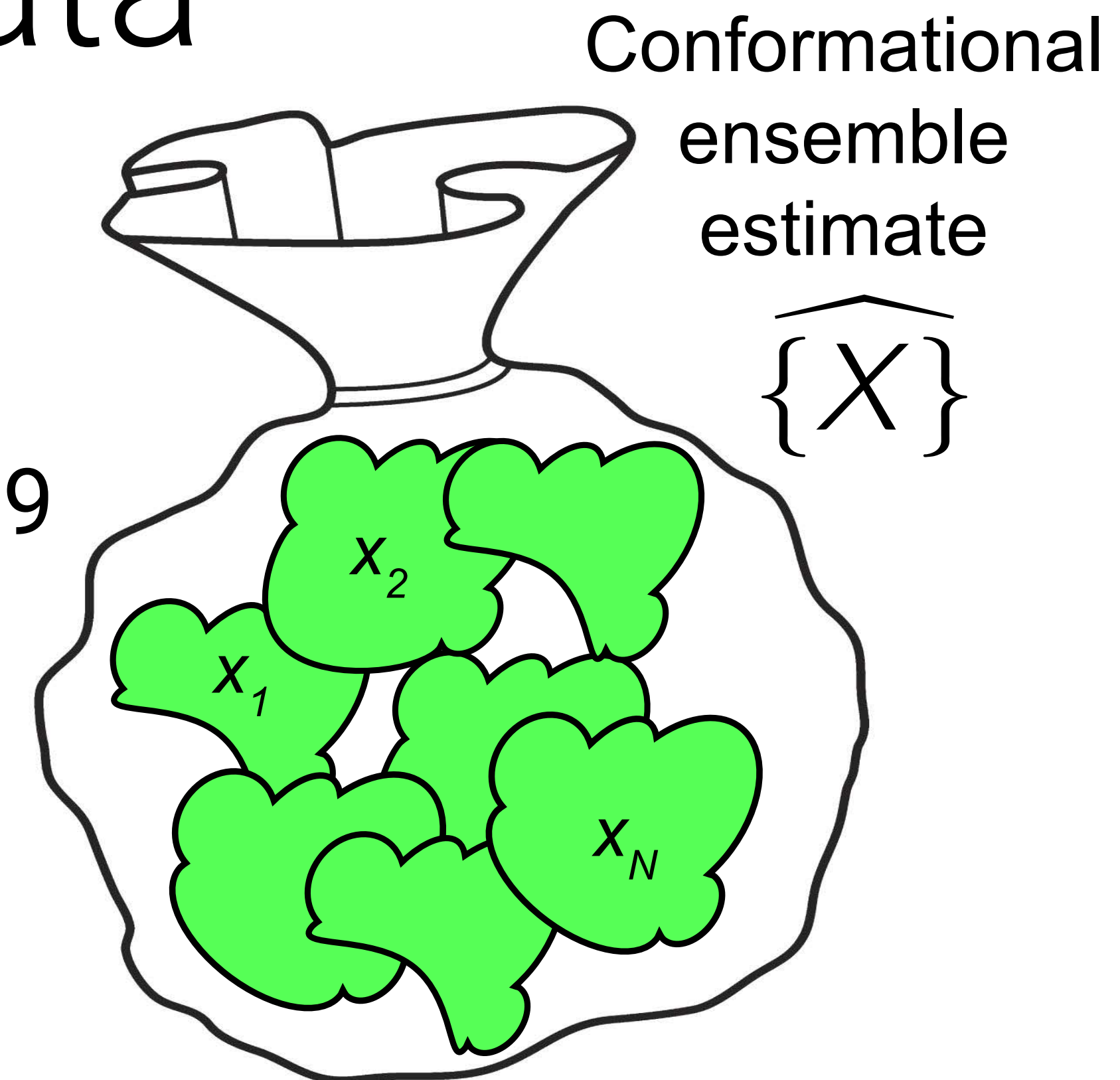
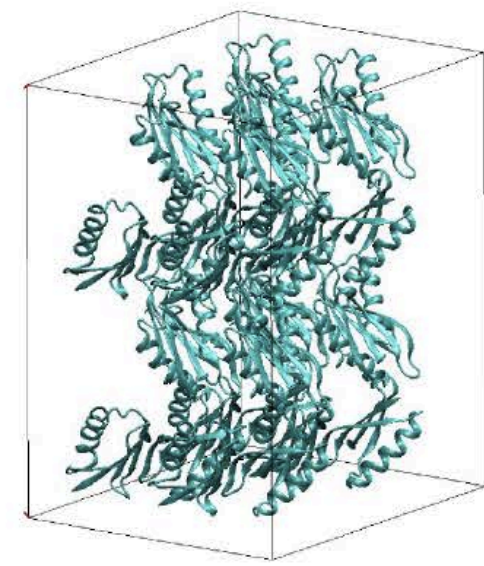


Hybrid refinement of heterogeneous conformational ensembles using spectroscopic data

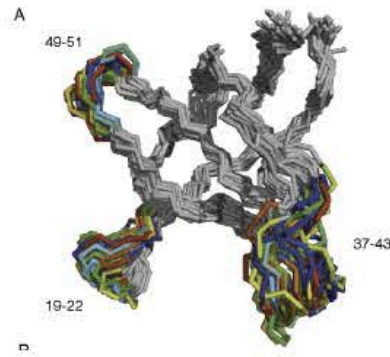
Jennifer M. Hays
University of Virginia
Blue Waters Symposium 2019



Proteins exhibit a broad range of flexibility



Dynamics in microcrystalline proteins

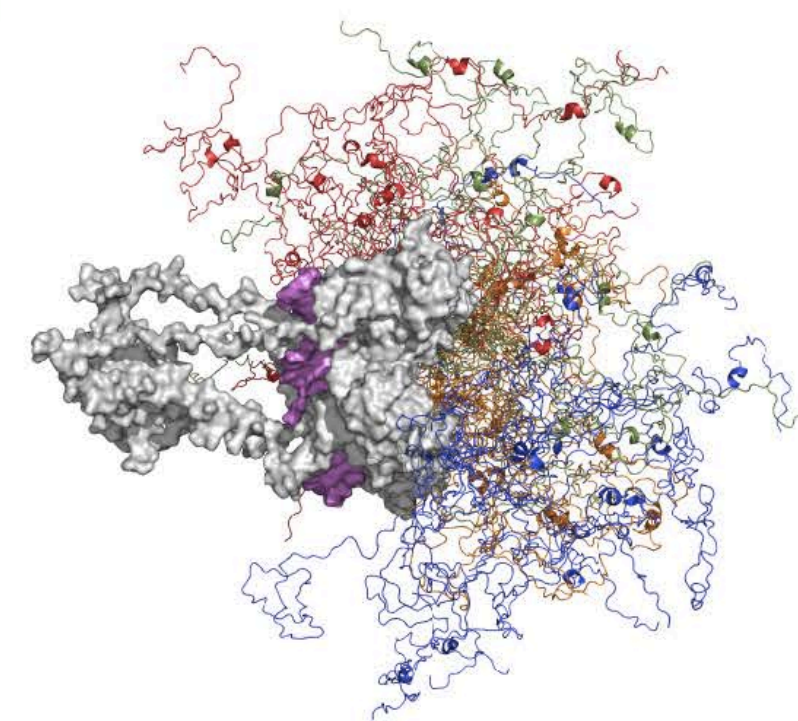


Local dynamic modes on multiple timescales....

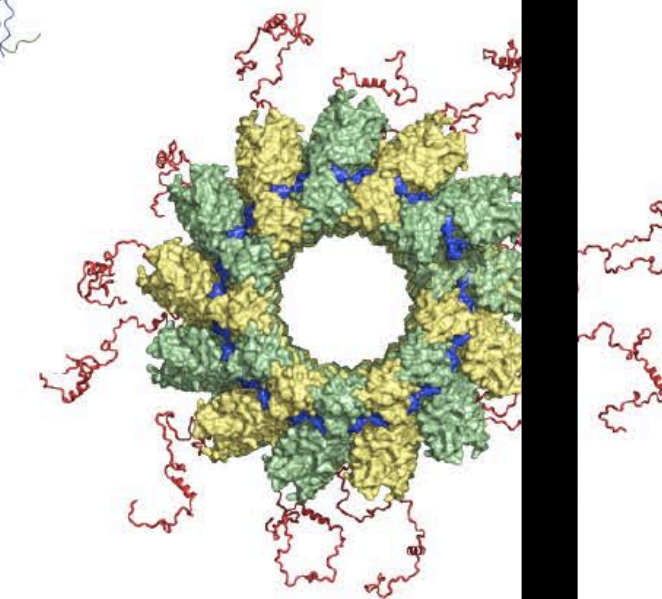


...and their role in functional complexes

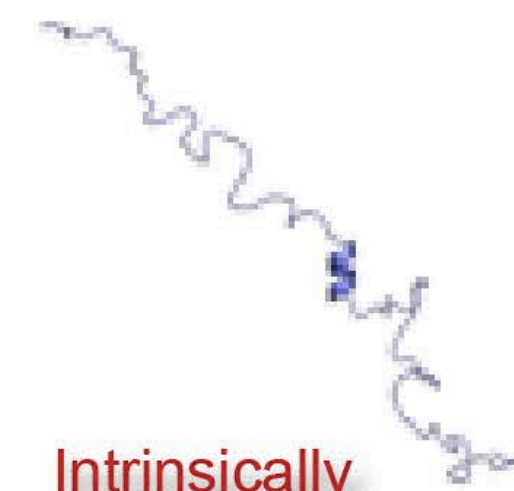
Multidomain proteins with flexible linkers



Multidomain proteins with highly disordered functional domains



Flexible domains in highly ordered assemblies



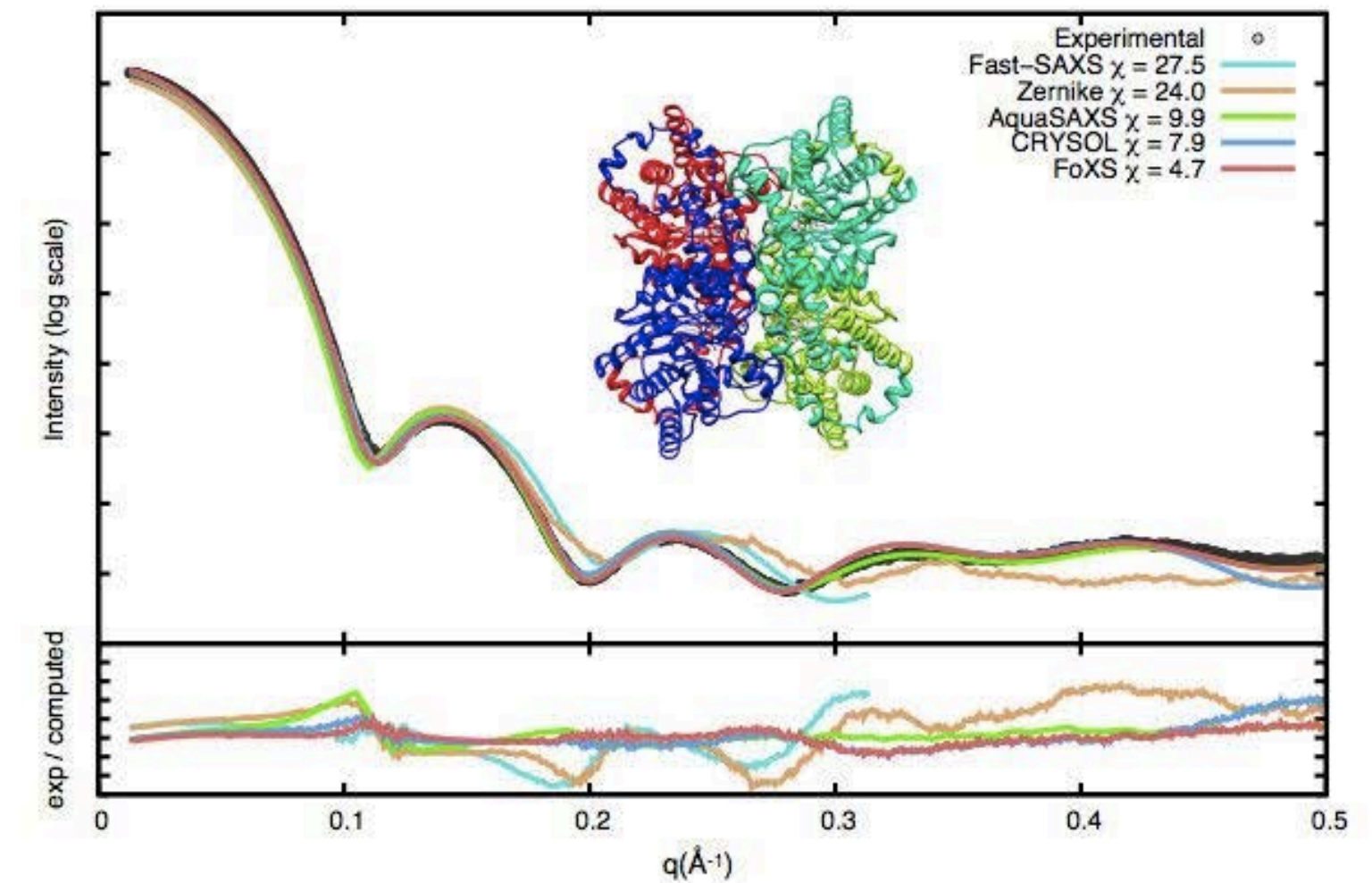
Intrinsically disordered proteins

Estimating the conformational ensembles of flexible proteins: a difficult inverse problem

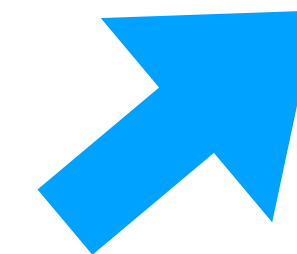
Experimental data tend to come in two varieties:

1. Ensemble average quantities (NMR, SAXS).
2. Distributional data that are sparse over the atomic coordinates (DEER, FRET).

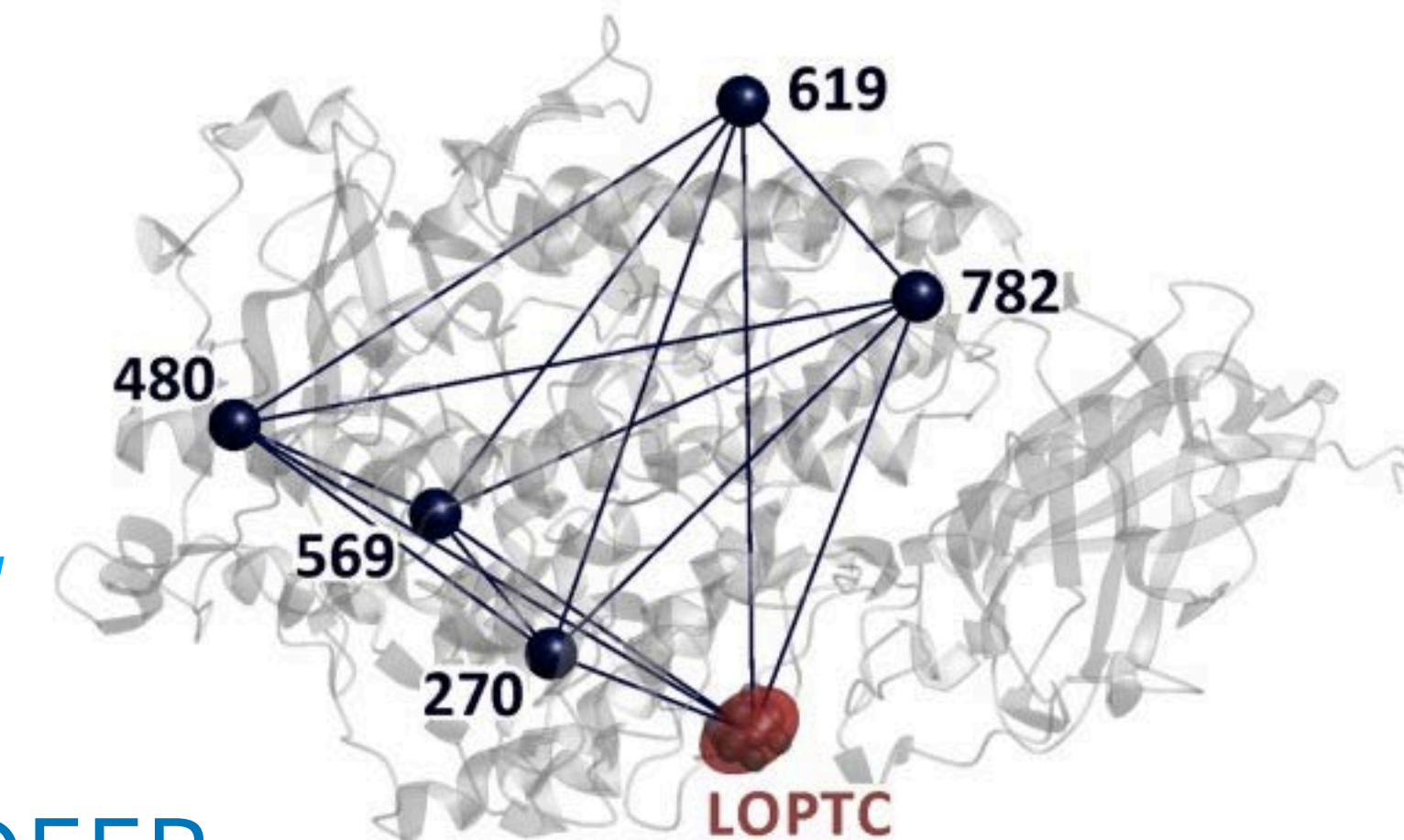
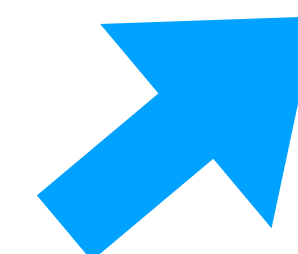
Duhovny, Kim, & Sali, *BMC Structural Biology*, 2012



Single structure prediction from SAXS



Sparse labels from DEER



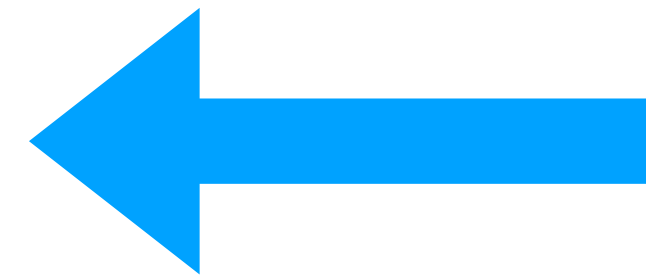
Jeschke, *Protein Science*, 2017

Estimating the conformational ensembles of flexible proteins: a difficult inverse problem

Experimental data tend to come in two varieties:

1. Ensemble average quantities (NMR, SAXS).

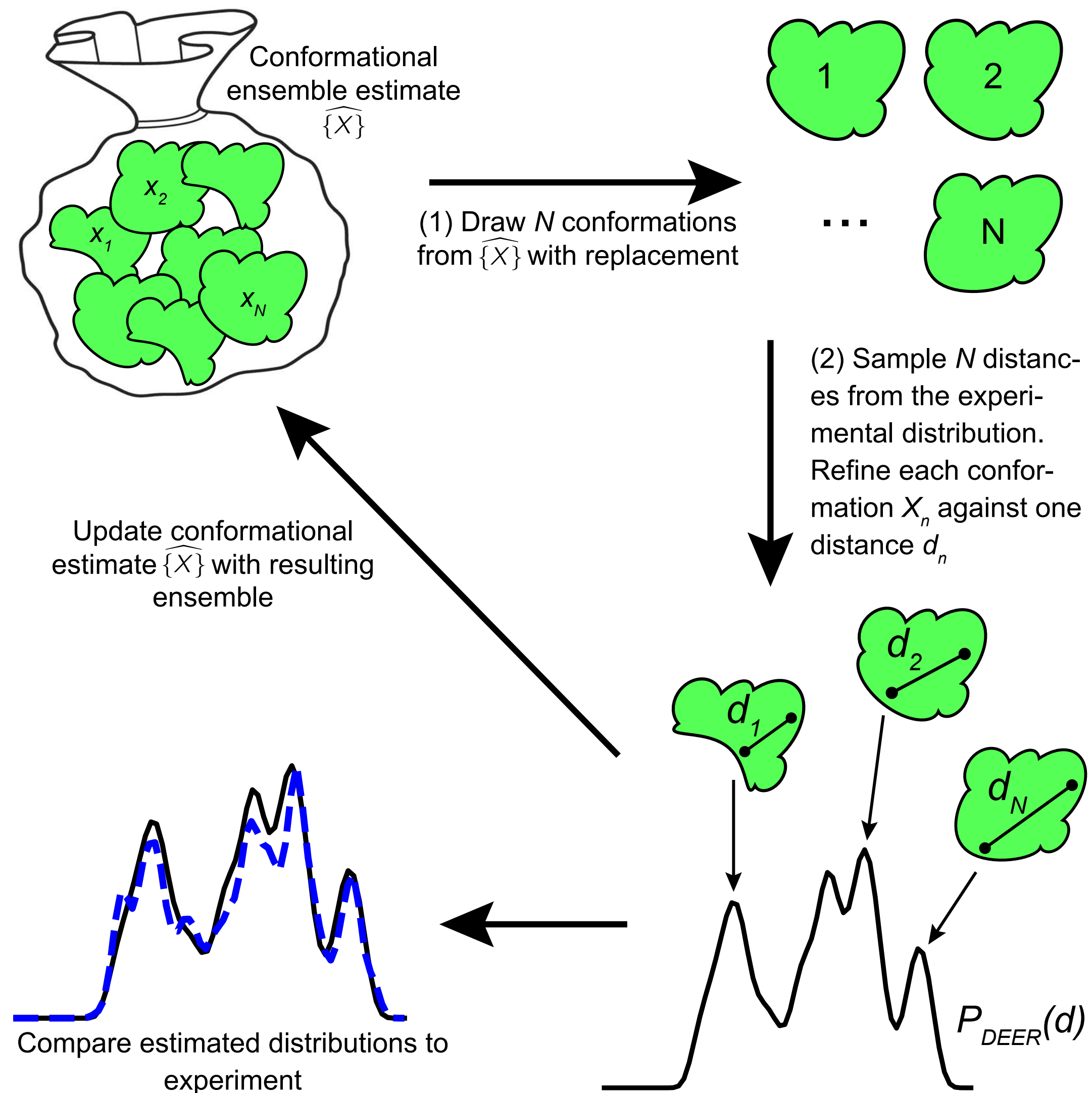
2. Distributional data that are sparse over the atomic coordinates (DEER, FRET).



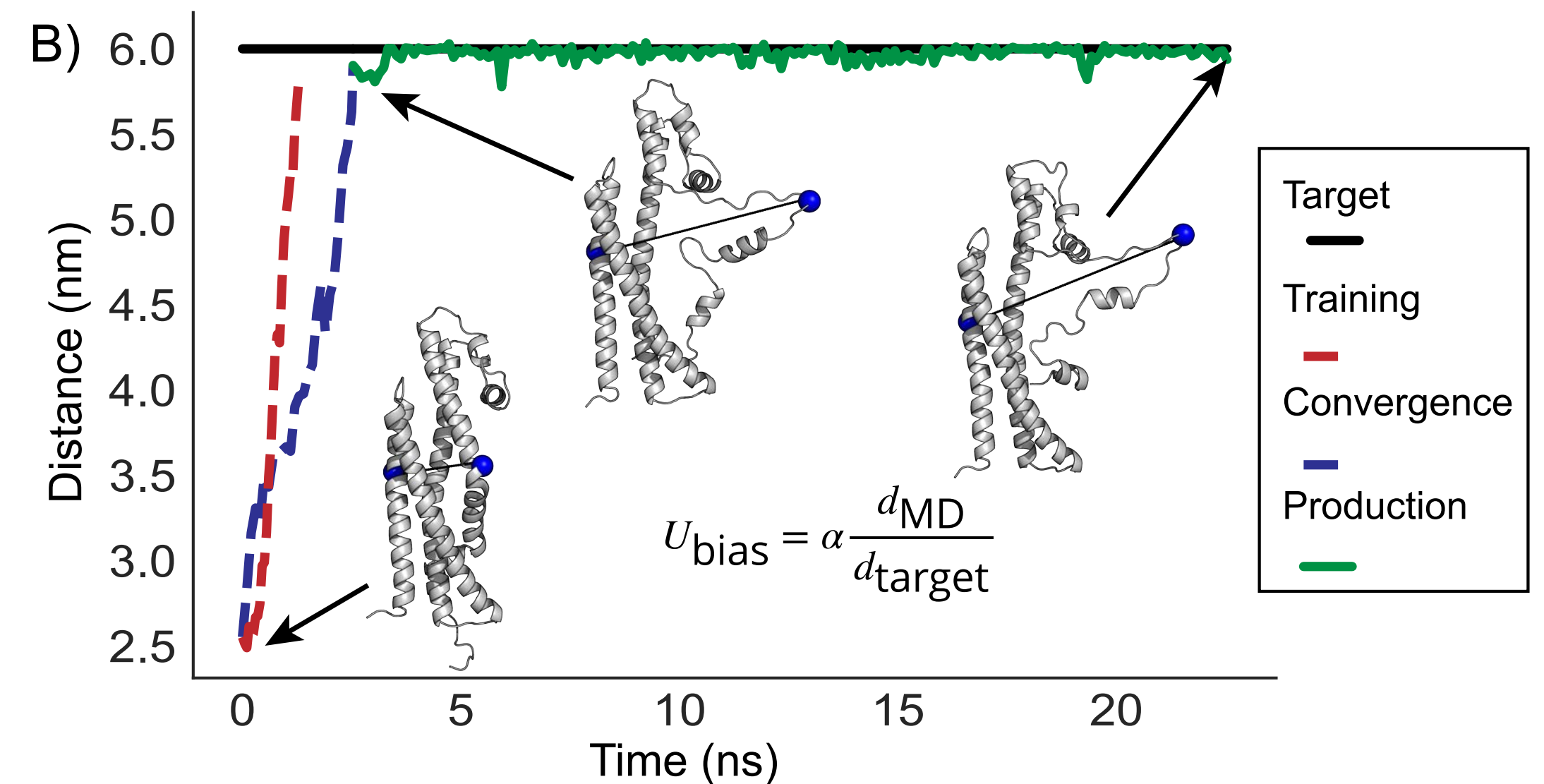
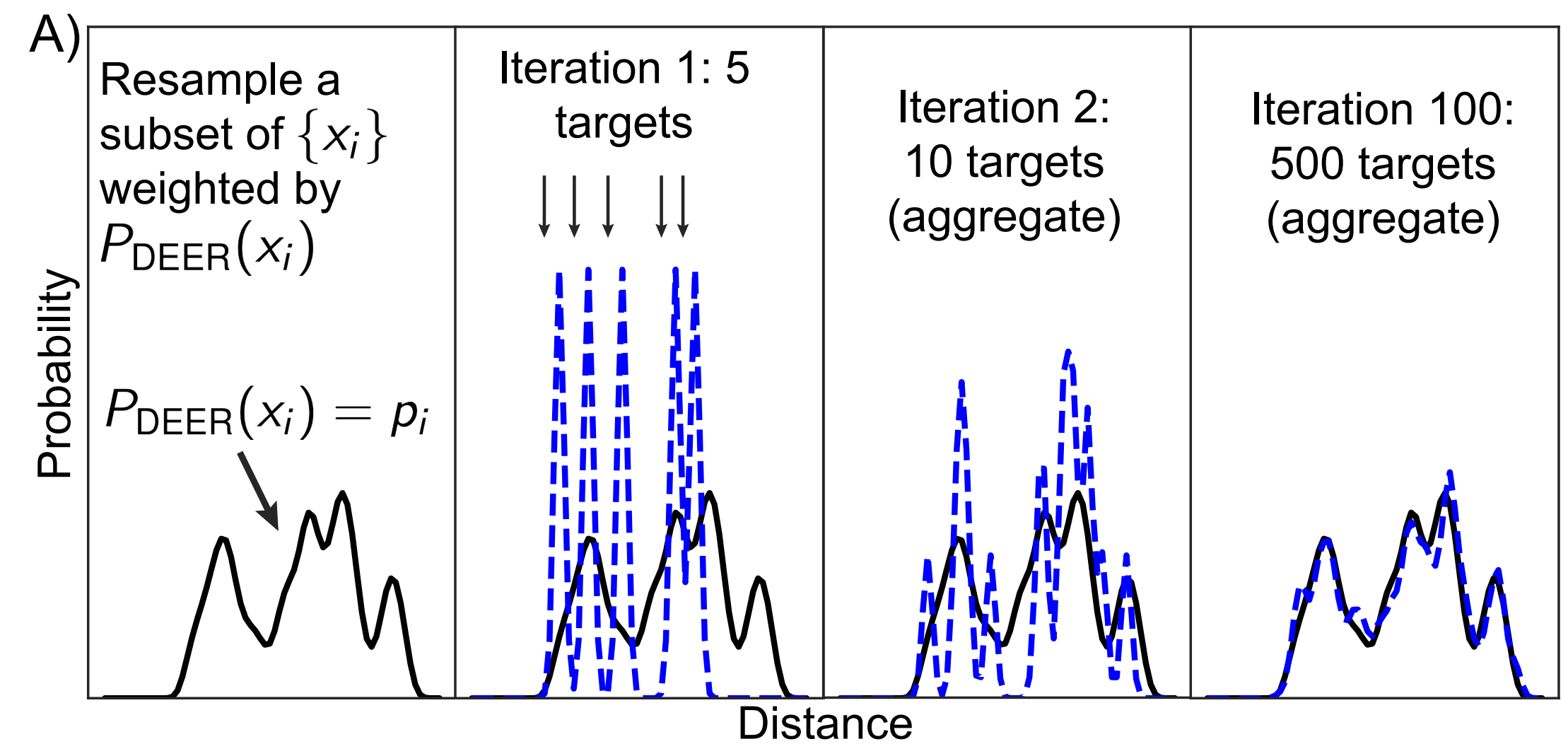
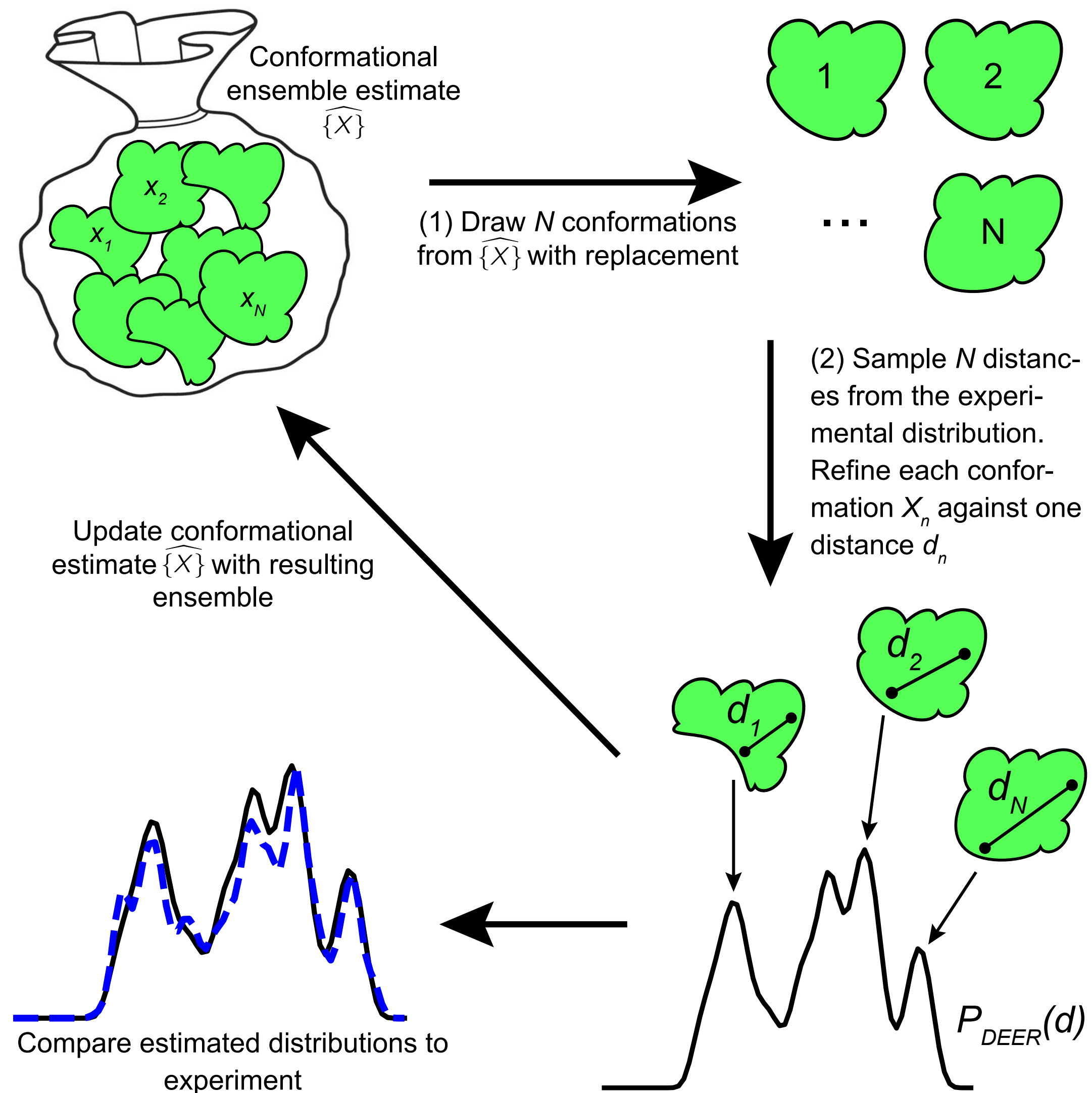
Lot's of great work has been done to leverage ensemble average quantities

These data are harder to deal with!

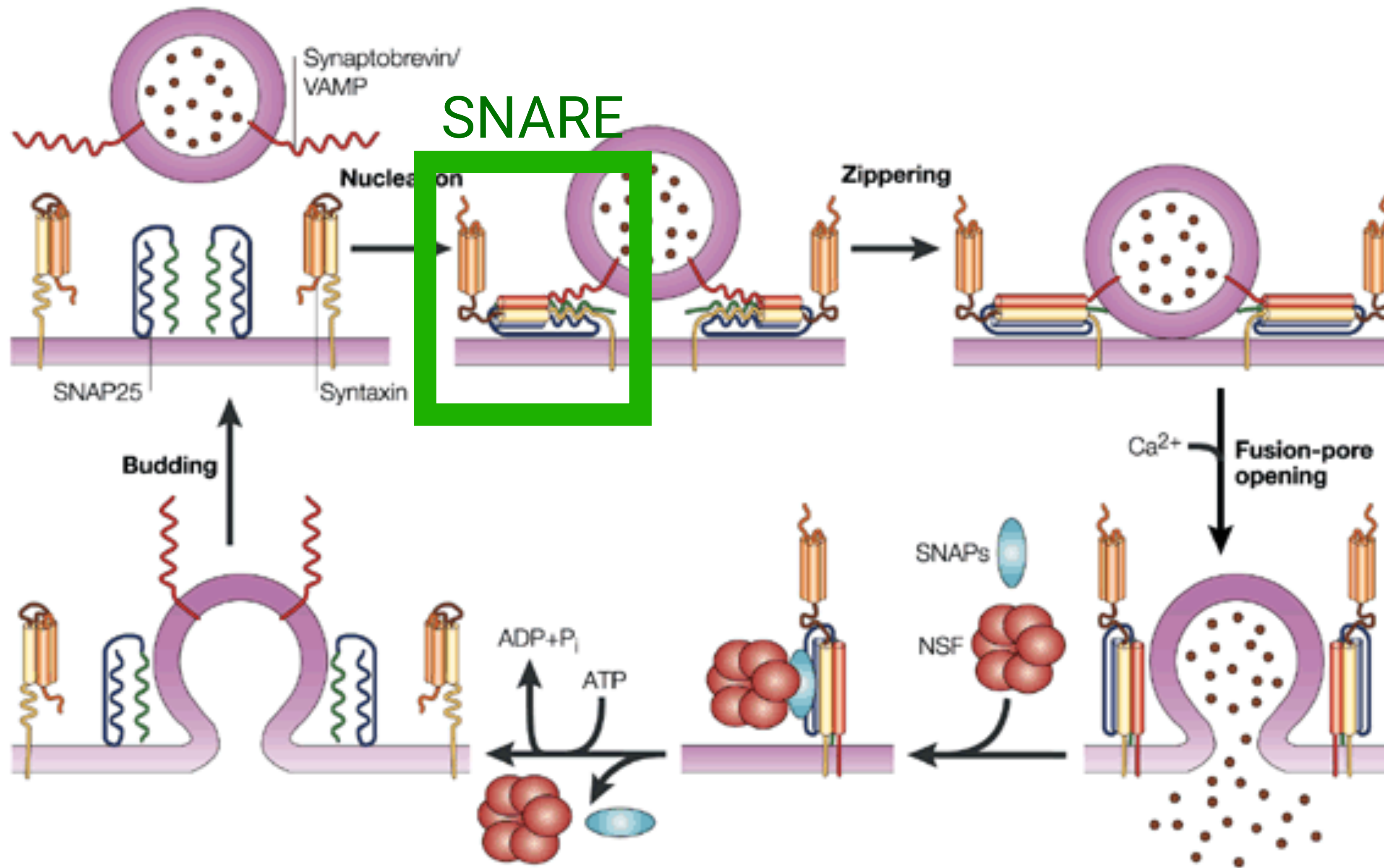
Bias-resampling ensemble refinement (BRER)



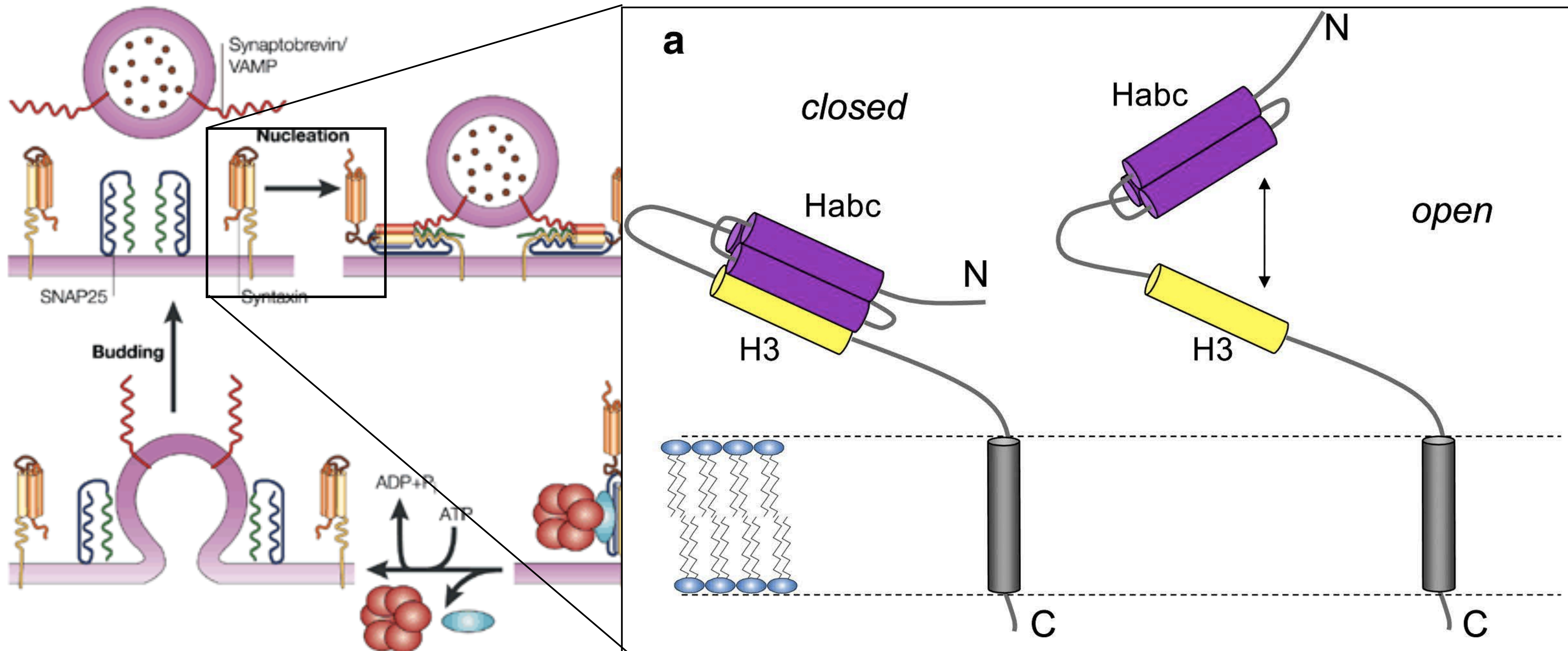
Bias-resampling ensemble refinement (BRER)



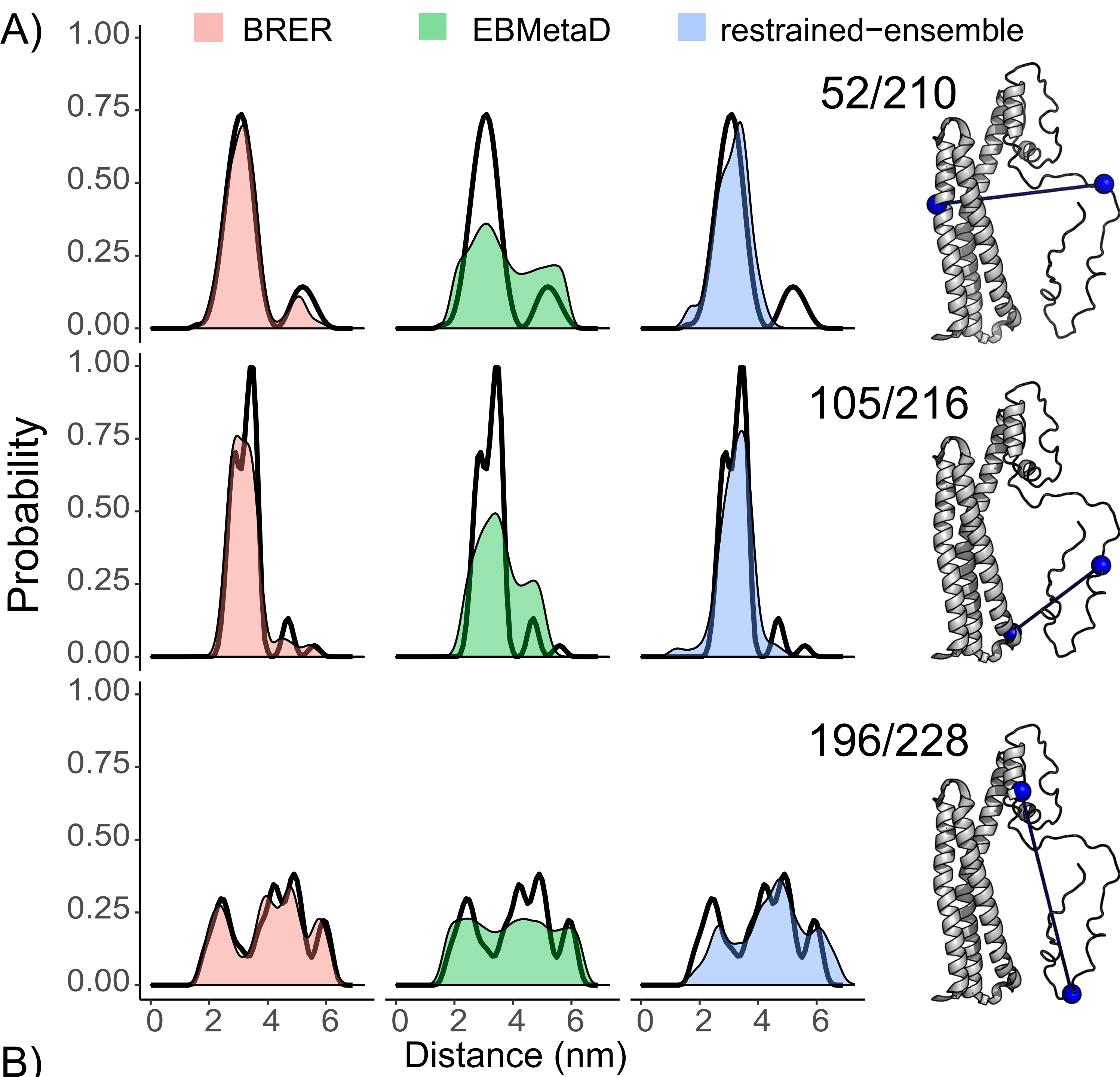
Syntaxin and SNAREs



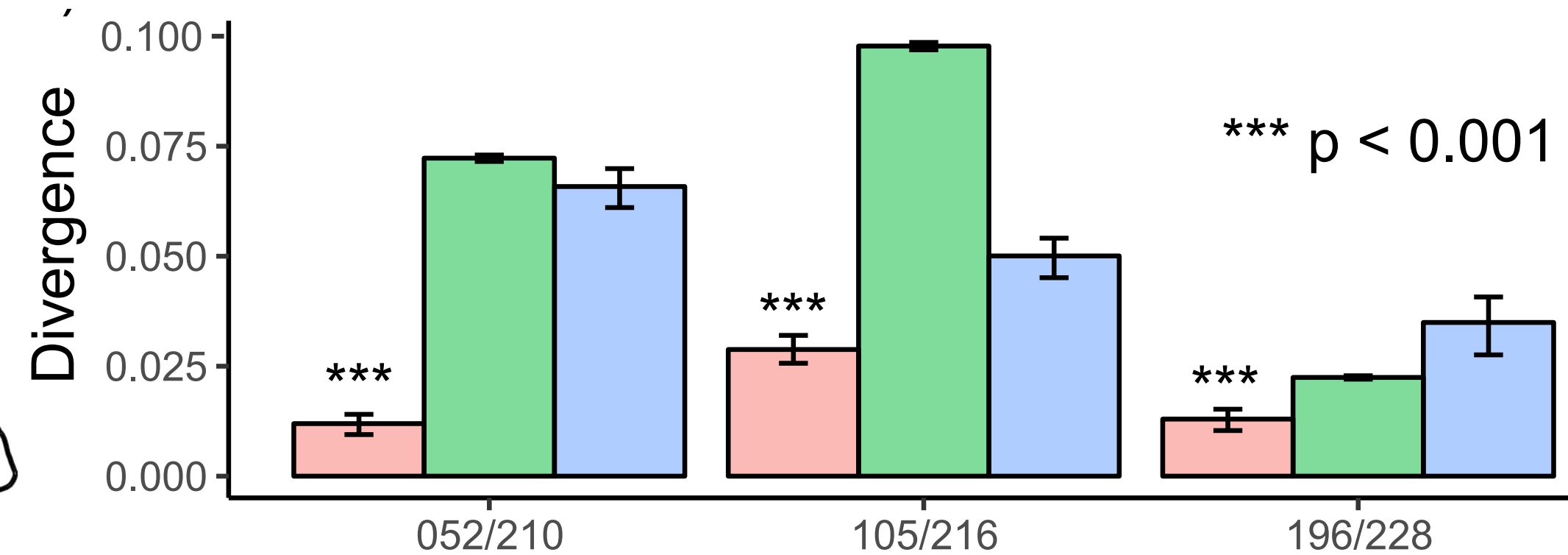
Syntaxin and SNAREs



Dawidowski and Cafiso, *Biophys J.*, 2013

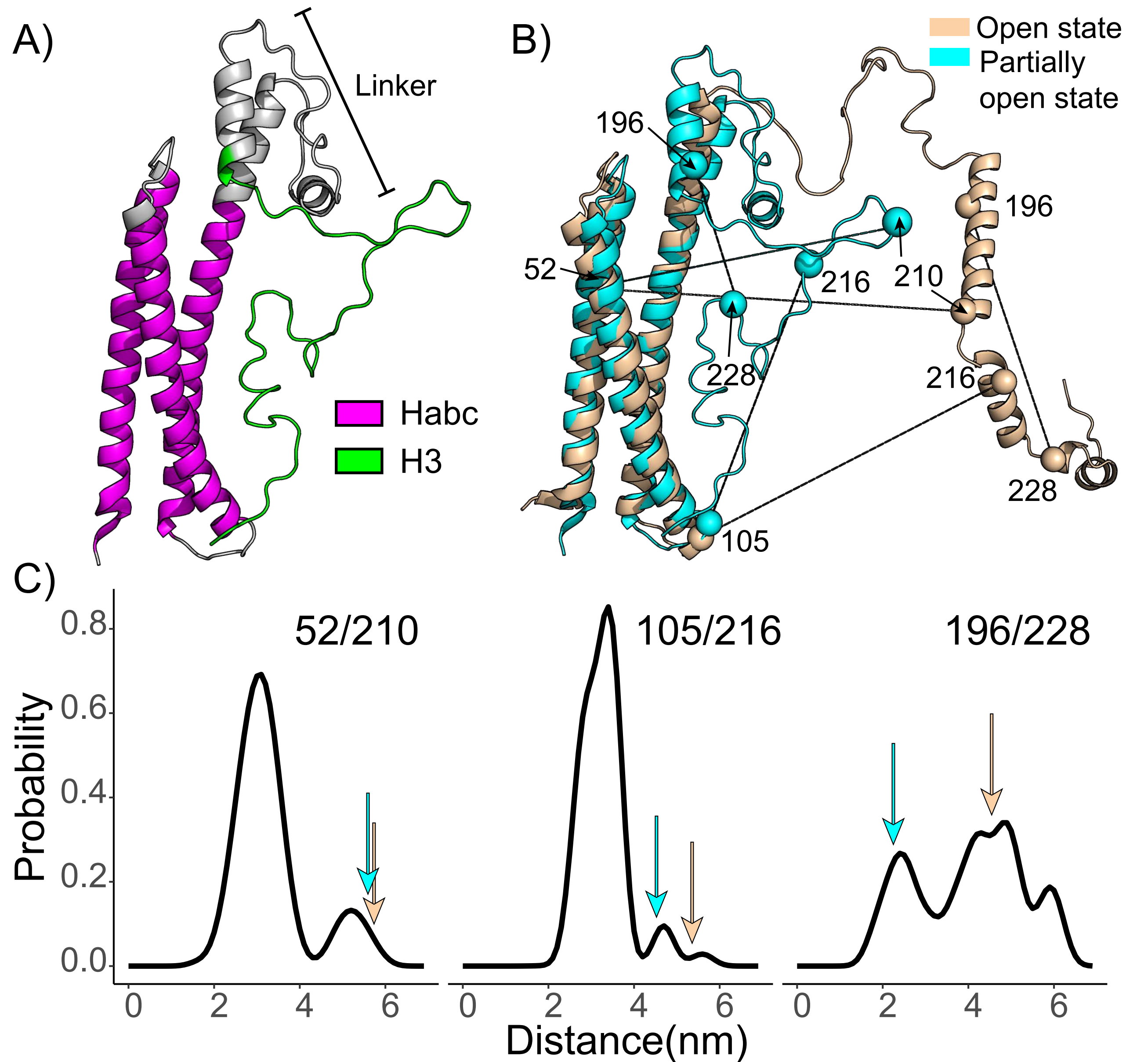


**BRER refinement of
syntaxin
conformational
ensemble reproduces
the experimental
distributions very
well**



B)

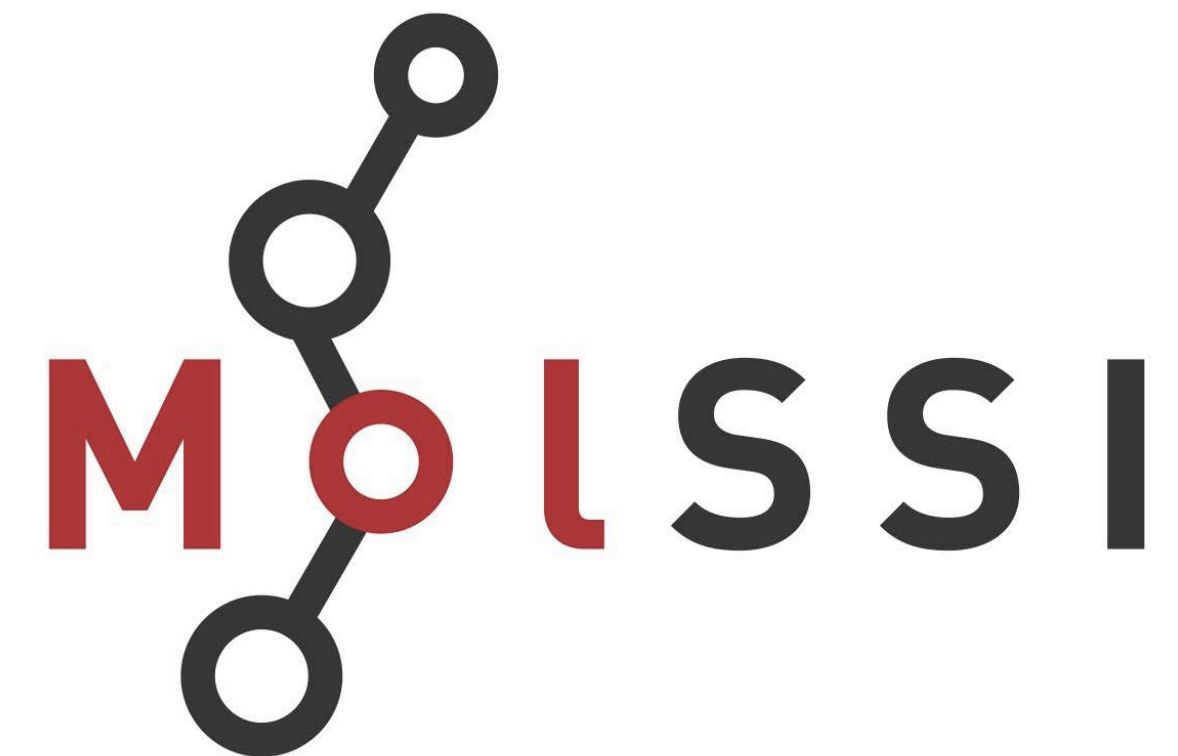
BREER refinement reveals previously unresolved partially open syntaxin states



Thank you!

- Kasson Lab
 - Peter Kasson
 - **Eric Irrgang**
 - Ania Pabis
 - Anjali Sengar
 - Ricardo Ferriera

- Cafiso Lab
 - Dave Cafiso
 - Damian Dawidowski



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Thank you!

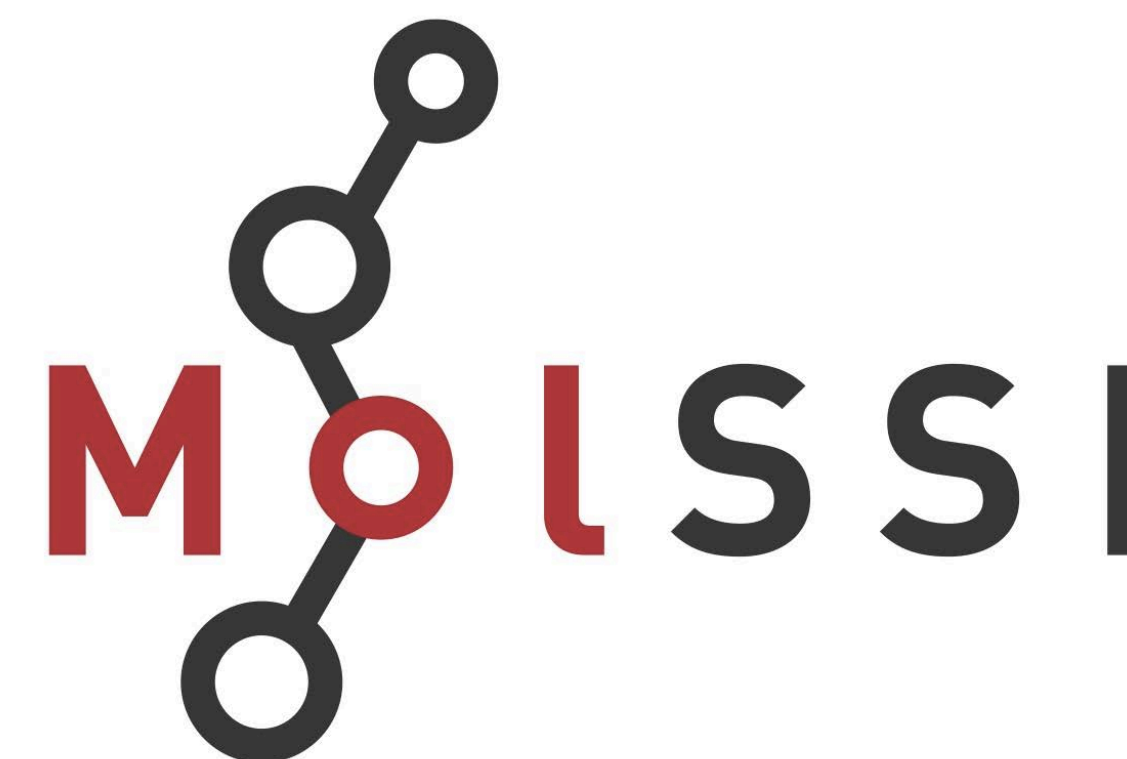
I use Blue Waters because...

- 15 μ s of all-atom simulation data for this project
- Over the course of my fellowship used over 200k node-hours
- Support team

Hays et al., *Ang. Chemie*, 2018

Hays, Cafiso, & Kasson, *JPC Letters*, 2019

D
Cafiso
Dawidowski



Anjan Senigal

- Ricardo Ferriera

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