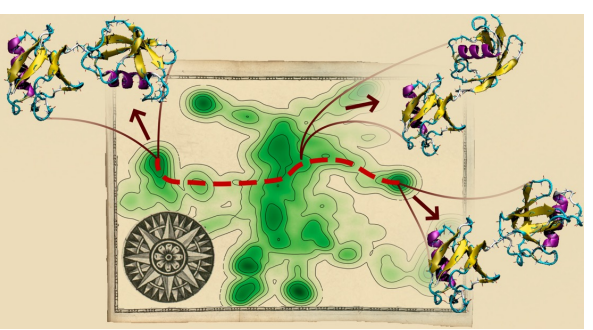
Universität Konstanz

Machine learning in biomolecular simulations: from characterizing conformational free energy landscapes to scale bridging

Christine Peter

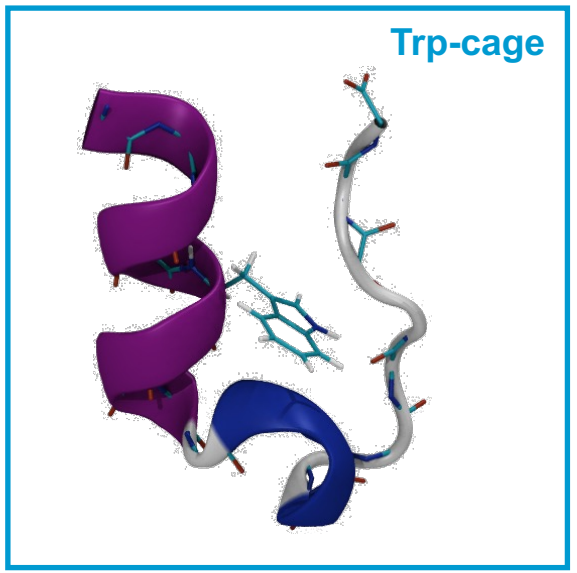
ECT* Workshop, Trento 2024

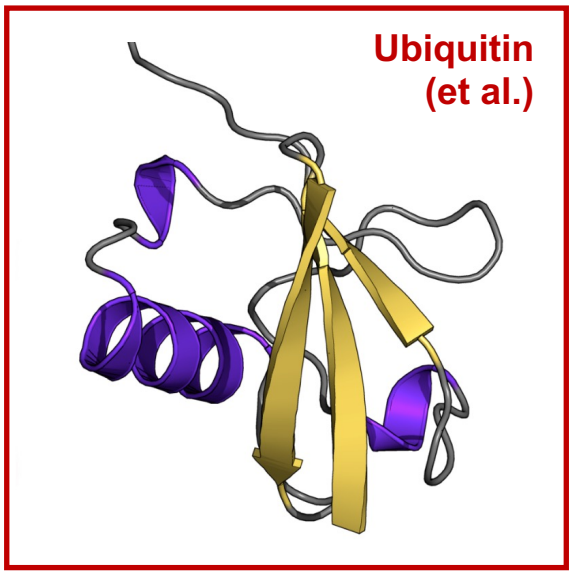


Outline

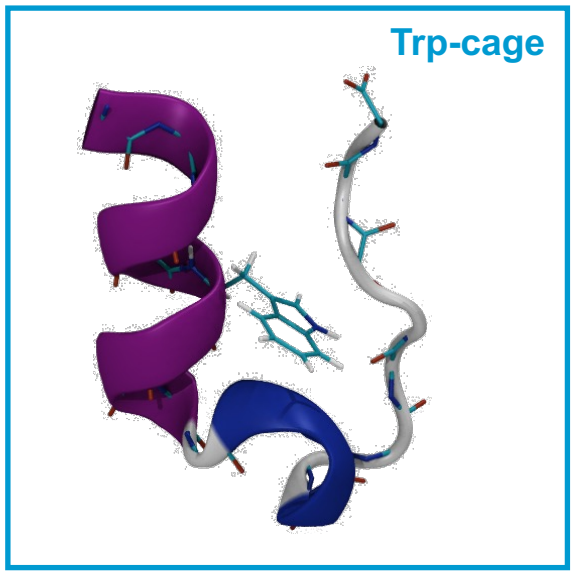
- Setting the stage
- EncoderMap
  - Learning meaningful representations of conformational phase space
  - Generating protein conformations and visualizing molecular motion
- Extracting meaningful feature sets from graph representations of proteins
  - Generating residue interaction landscapes
- Utilizing low-dimensional embeddings for clustering
  - Identifying conformational states
- Backmapping based sampling
  - Linking scales through low-dimensional representations

Two recurring systems

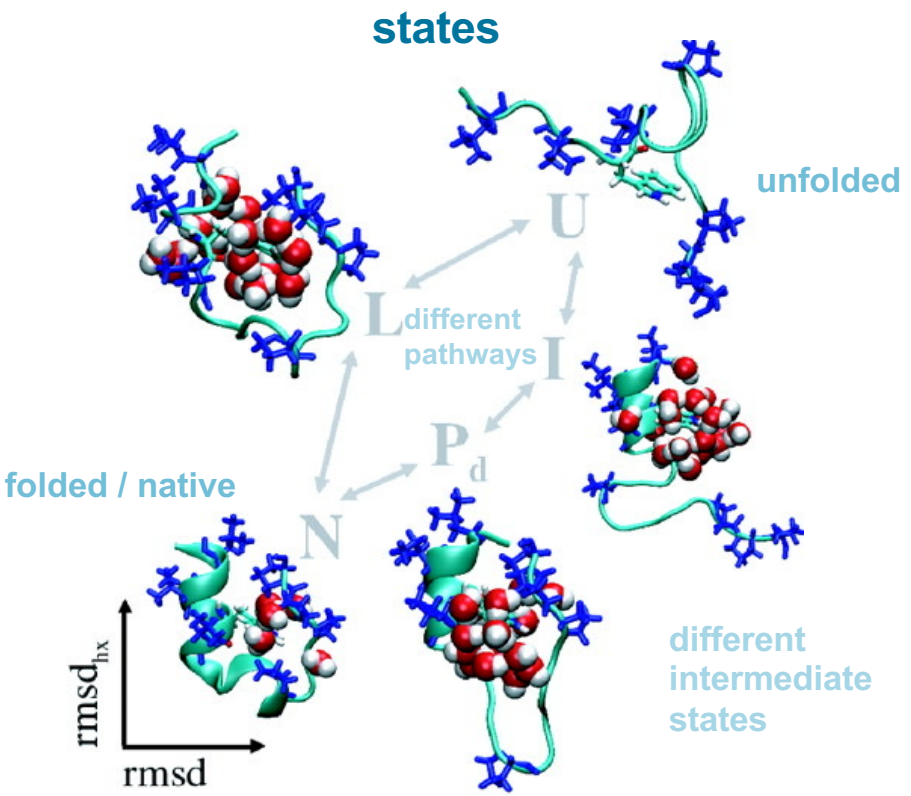




Two recurring systems

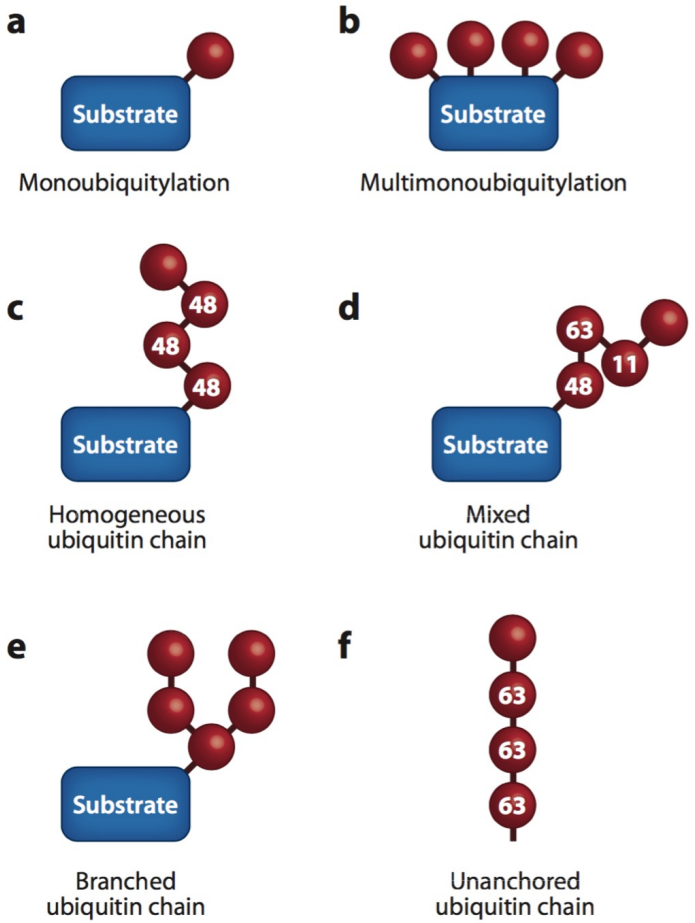


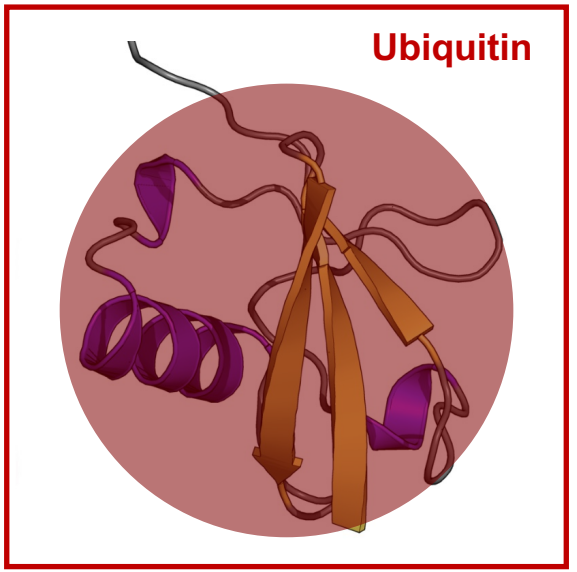
- folding
- states
- features & CVs
- low-dimensional representations



Juraszek, J. and P. G. Bolhuis.
PNAS 103.43 (2006): 15859-15864.

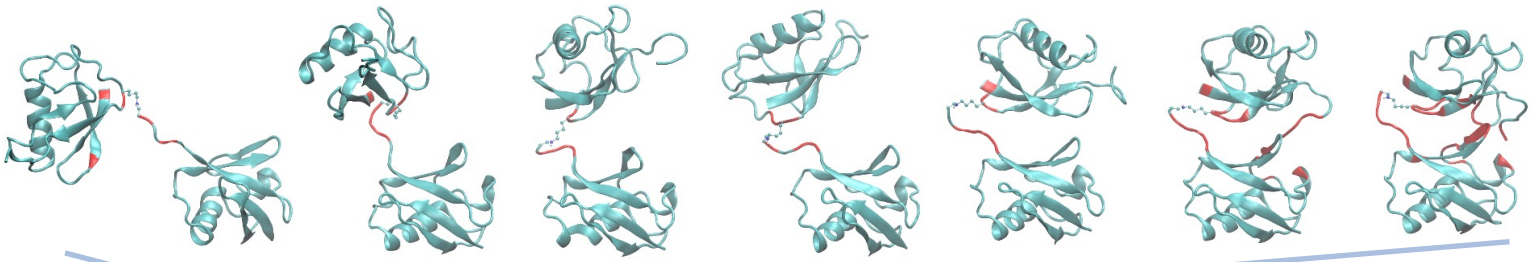
Two recurring systems: Trp-cage and Ubiquitin et al.



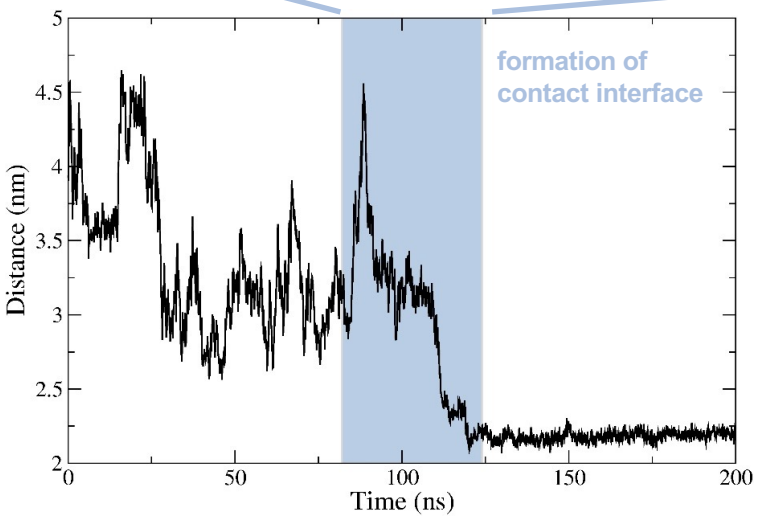


- protein-protein interactions
- protein interfaces
- sampling / scale-bridging

An atomistic simulation of K48-linked di-Ubiquitin

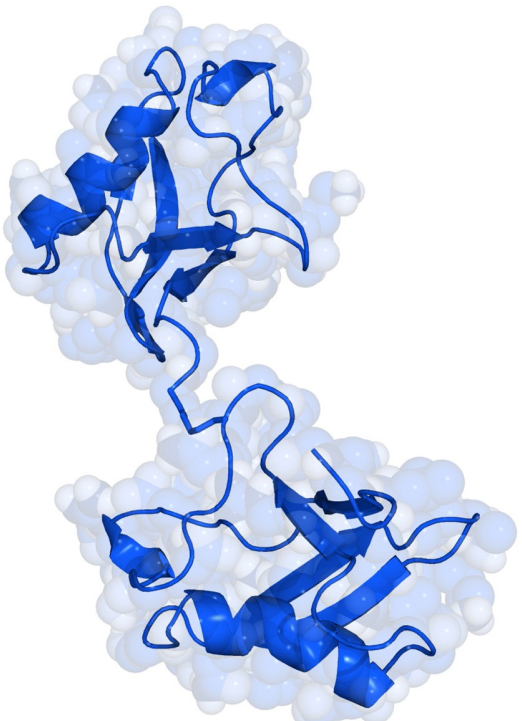


protein interfaces



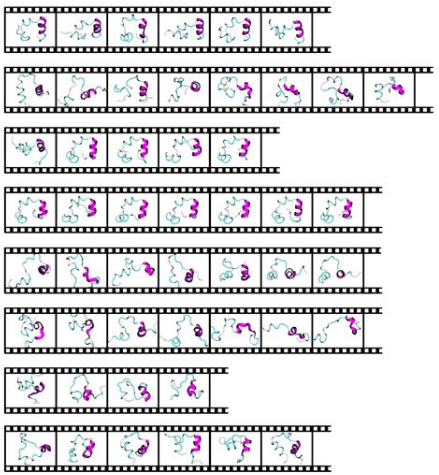
the accessible timescales are too short
➔ need for enhanced sampling

A coarse grained simulation of K48-linked di-Ubiquitin

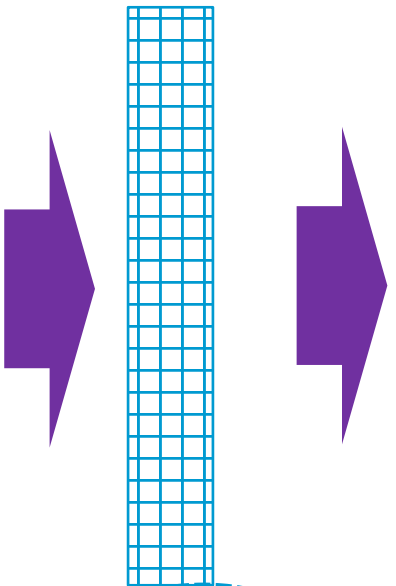


➔ Need for methods to characterize conformational phase space

Low-dimensional representations of conformational phase space



Simulation data (Cartesian coordinates)



Input data set (features)

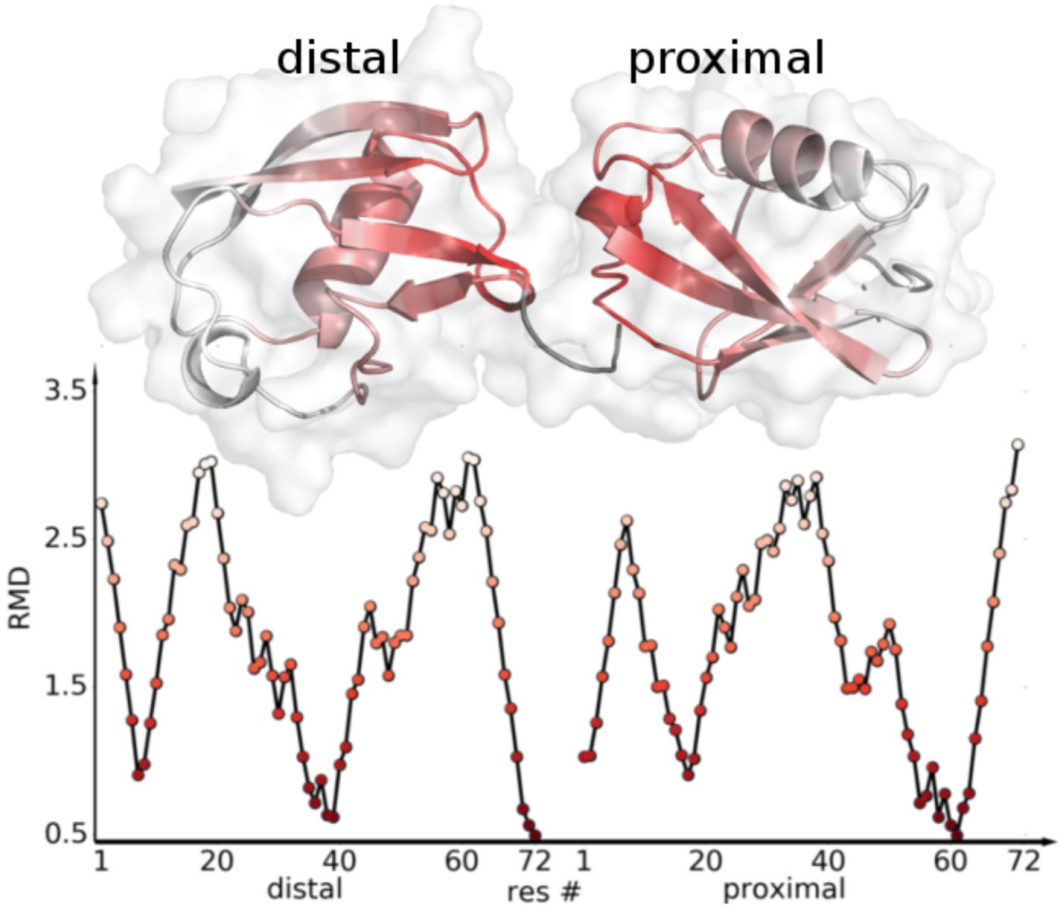
internal distances, dihedrals, ...

Dimensionality reduction
PCA, MDS, ...

Map in low-dim space

Conformational states

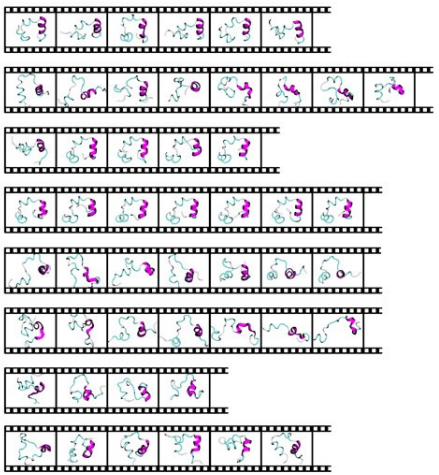
Collective variables that characterize dimer structures



➔ 144 residue-wise minimum distances (RMD)

➔ fingerprints of each structure

Low-dimensional representations of conformational phase space



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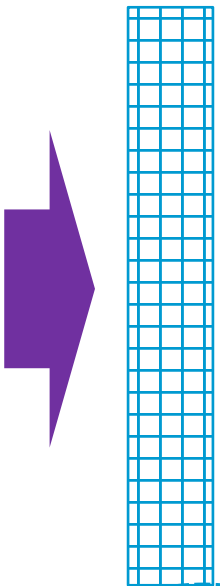


Input data set (features)

internal distances, dihedrals, ...

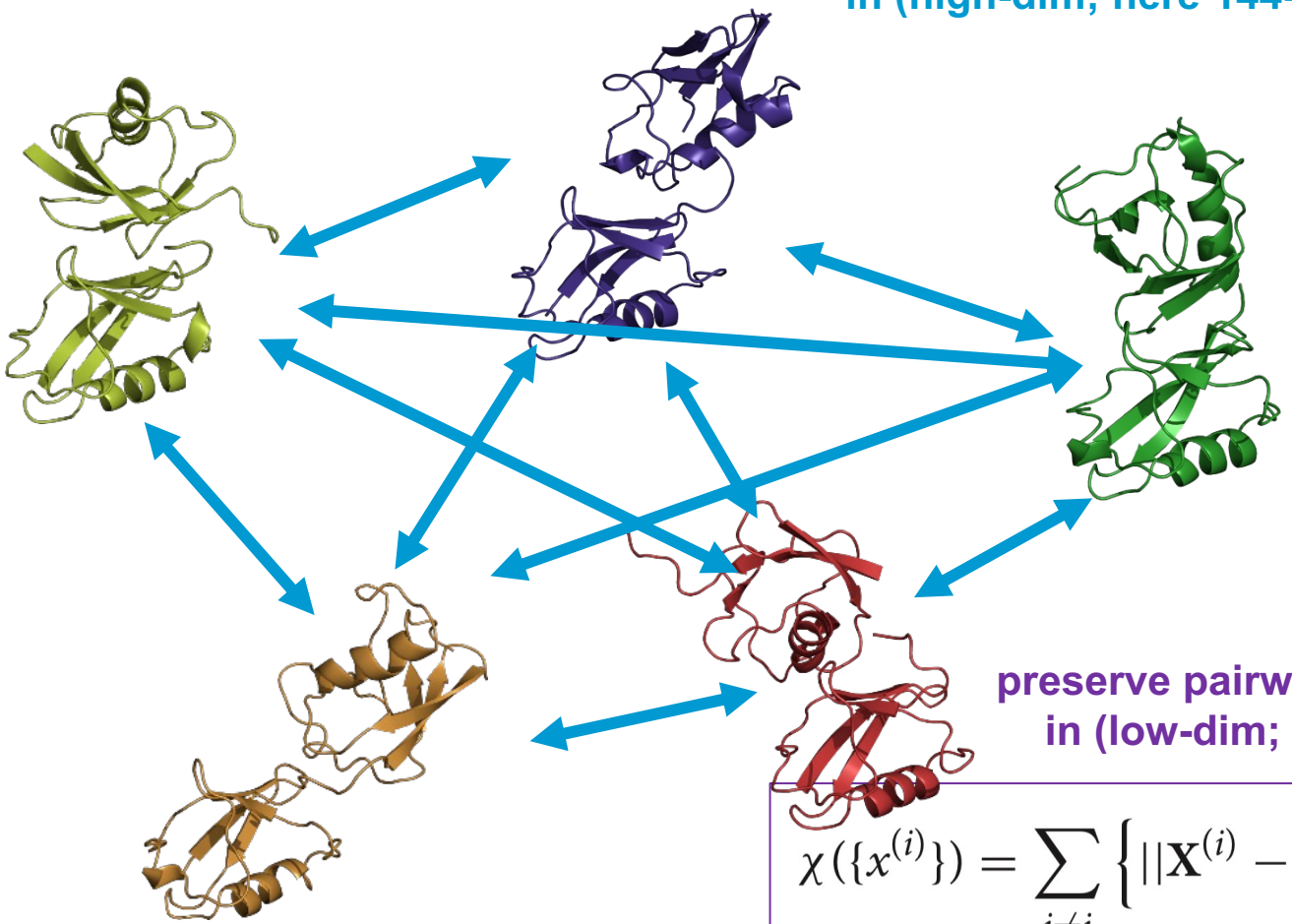
Dimensionality reduction
PCA, MDS, ...

Map in low-dim space

Conformational states

The idea behind metric multidimensional scaling

pairwise differences/distances between structures
in (high-dim; here 144-dim) feature space



preserve pairwise differences/distances
in (low-dim; here 2-dim) embedding

$$\chi(\{x^{(i)}\}) = \sum_{i \neq j} \left\{ ||\mathbf{X}^{(i)} - \mathbf{X}^{(j)}|| - ||\mathbf{x}^{(i)} - \mathbf{x}^{(j)}|| \right\}^2$$

The idea behind SketchMap (Ceriotti et al J. Chem. Theory Comput. 2013)

distances in high- and low-dimensional spaces are transformed by a **sigmoid function**

$$s(r,a,b) = 1 - (1 + (2^{a/b} - 1)(r/\sigma)^a)^{-b/a}$$

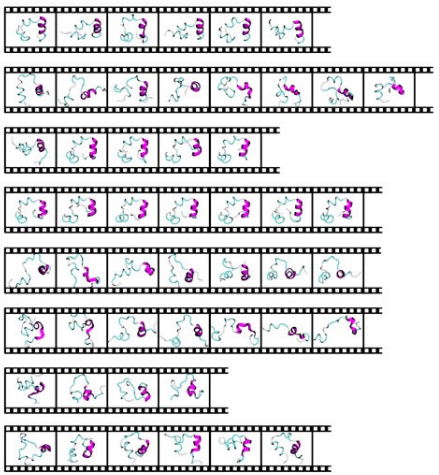
produce mapping by minimizing stress function for **landmark** structures:

$$\chi^2 = \sum_{i \neq j} \left[s(R_{ij}, A, B) - s(r_{ij}, a, b) \right]^2$$

calculate projection **x** of any high-dimensional point **X** by minimizing:

$$\sigma^2(\mathbf{x}) = \sum_{i=1}^{N} \left[s(R_i(\mathbf{X}), A, B) - s(r_i(\mathbf{x}), a, b) \right]^2$$

Low-dimensional representations of conformational phase space



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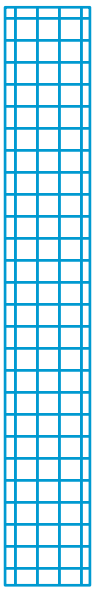


Input data set (features)

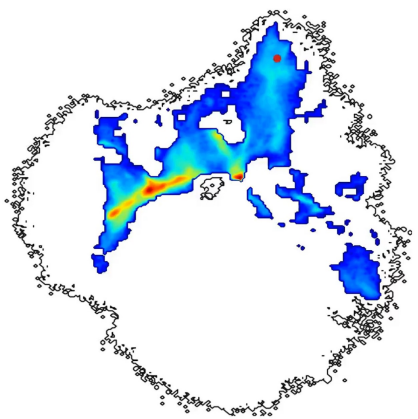
RMDs

Dimensionality reduction
here: SketchMap
- MDS-like
- sigmoid function
- uses landmark points
- projection of all data

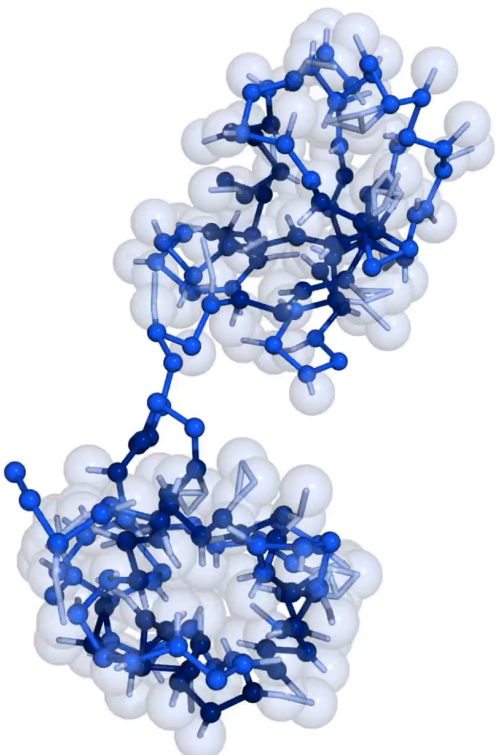
Ceriotti et al *J. Chem. Theory Comput.* **2013**

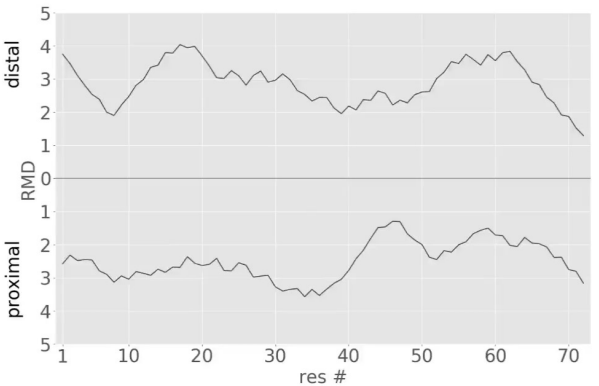
Map in low-dim space

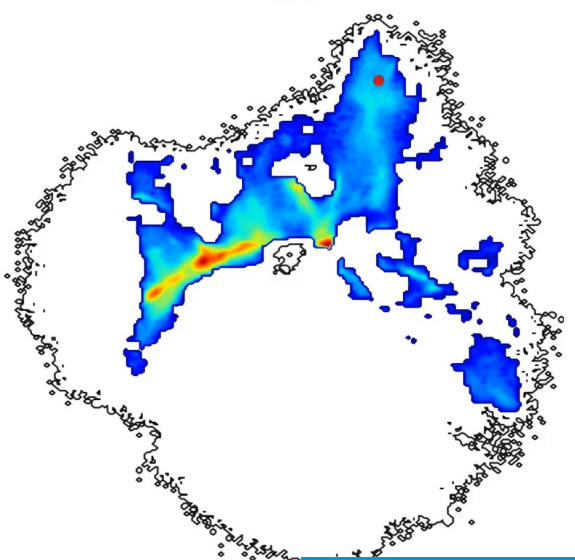
Conformational states



Residue-wise minimum distances as input features: Illustration for one simulation







➔ need for methods to process huge datasets

Berg, Kukharenko, Scheffner, & Peter, 2018, *PLOS Comp. Biol.* 14, e1006589

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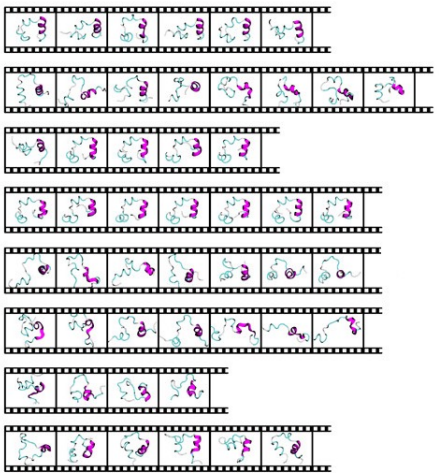
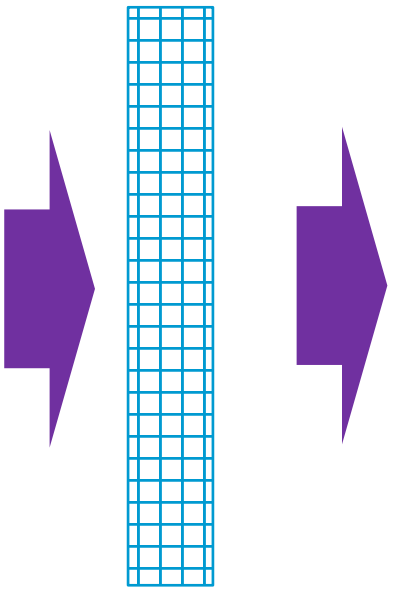
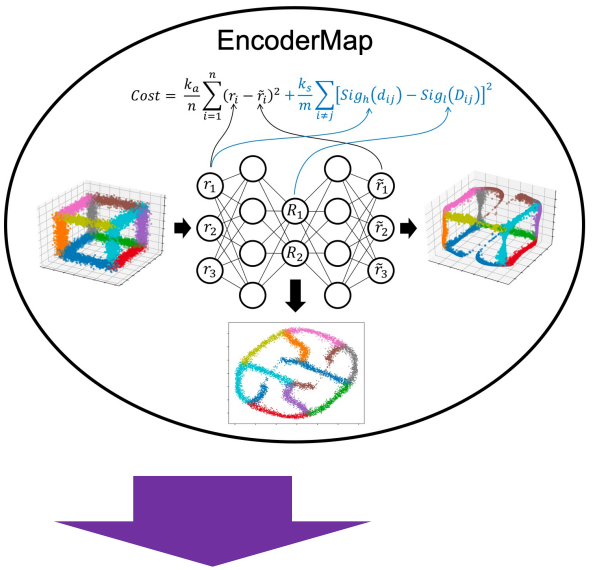






Simulation data (Cartesian coordinates)

Input data set (features)

internal distances, dihedrals, ...

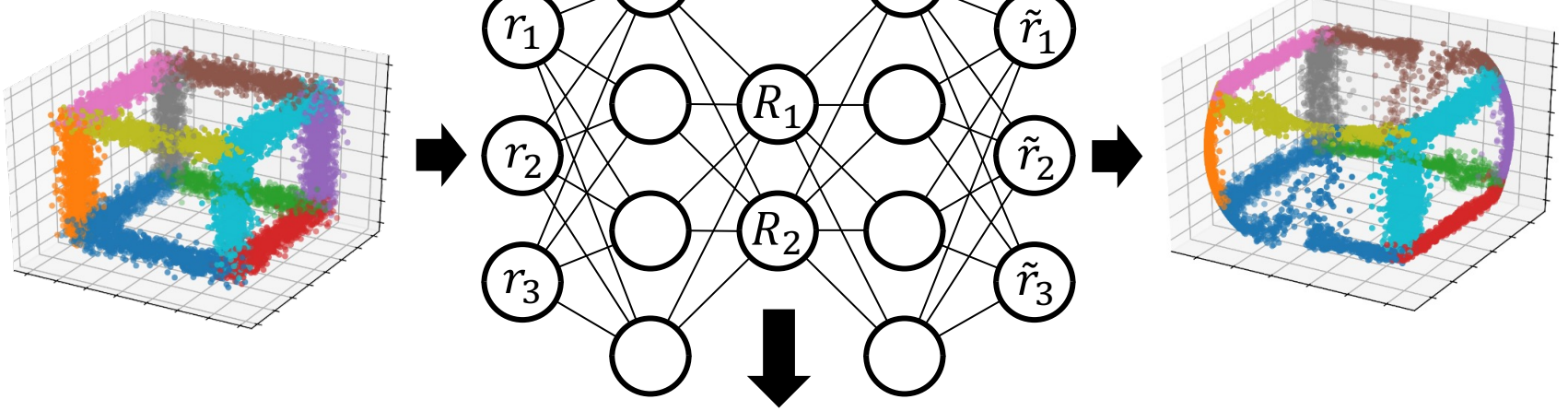
Map in low-dim space

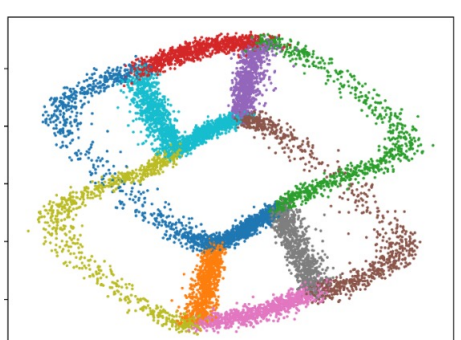
Conformational states

Lemke & Peter, 2019, JCTC, 15, 1209-1215
Lemke, Berg, Jain, Peter, 2019, *J. Chem. Inf. Model,* 59, 4550

github.com/AG-Peter/EncoderMap

$$Cost = \frac{k_a}{n}\sum_{i=1}^{n}(r_i - \tilde{r}_i)^2$$





Lemke & Peter, 2019, JCTC, 15, 1209-1215
Lemke, Berg, Jain, Peter, 2019, *J. Chem. Inf. Model,* 59, 4550

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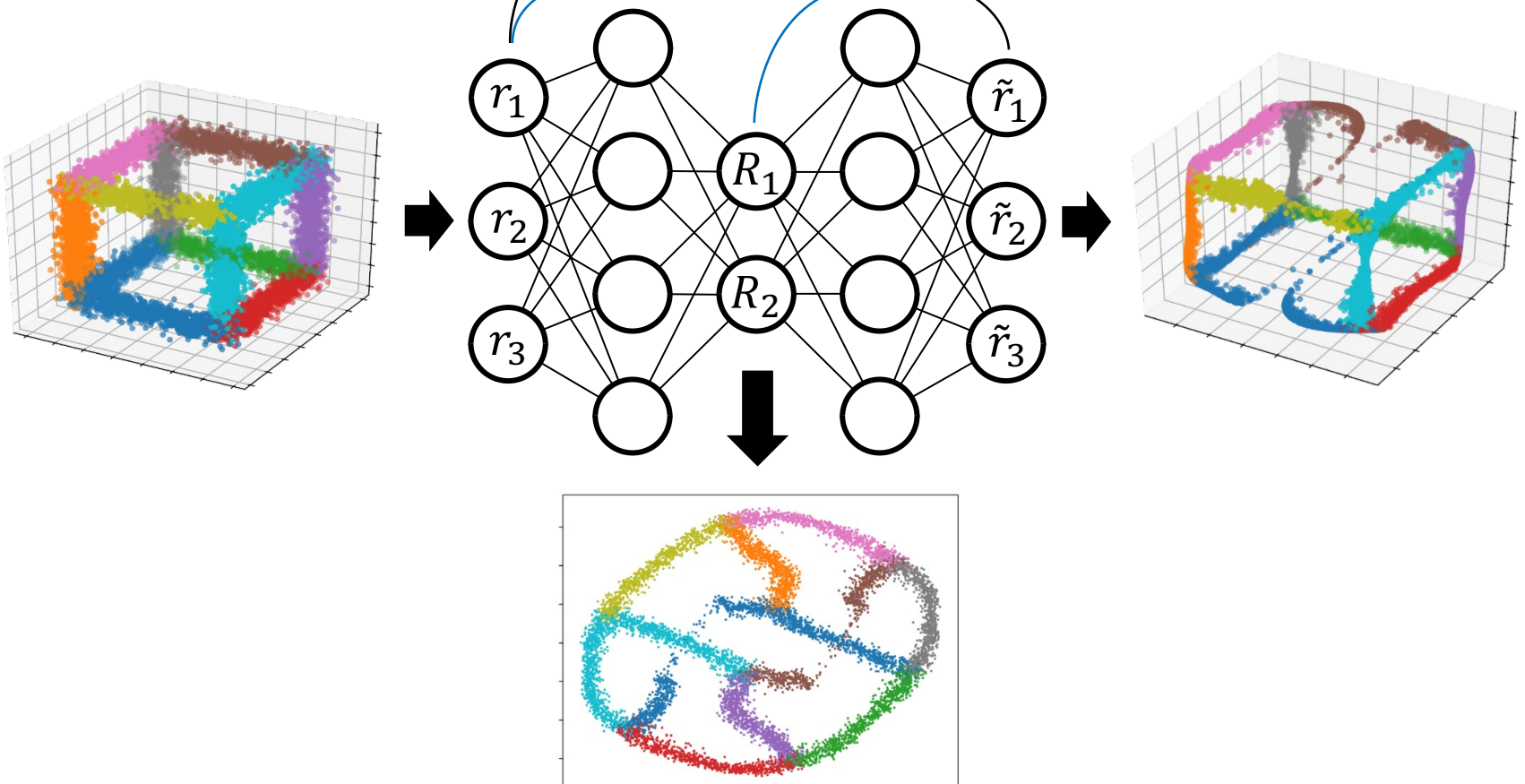
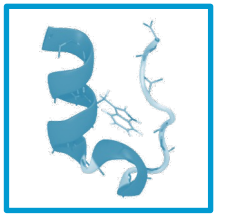
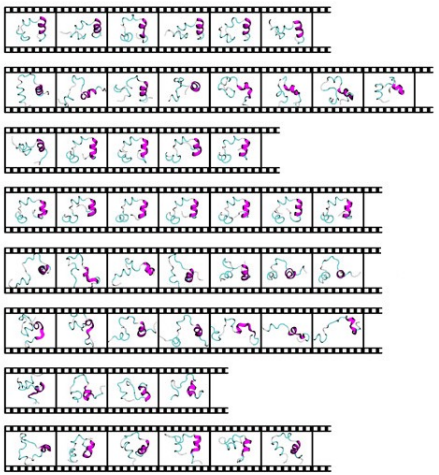
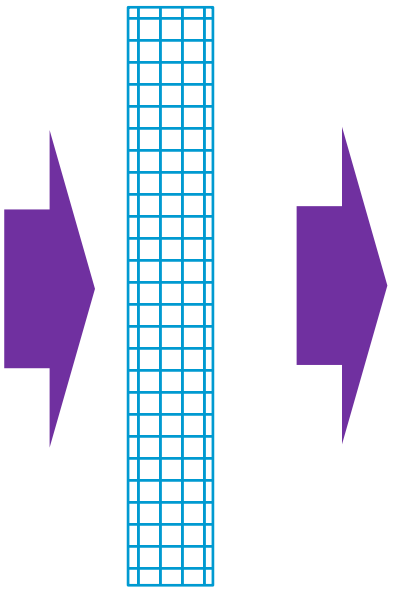
$$Cost = \frac{k_a}{n}\sum_{i=1}^{n}(r_i - \tilde{r}_i)^2 + \frac{k_s}{m}\sum_{i\neq j}\left[Sig_h(d_{ij}) - Sig_l(D_{ij})\right]^2$$

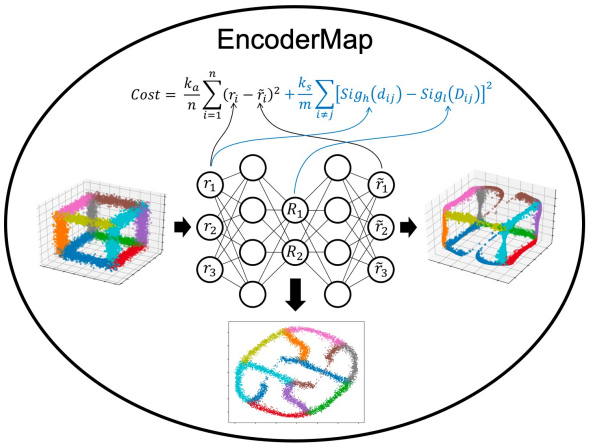


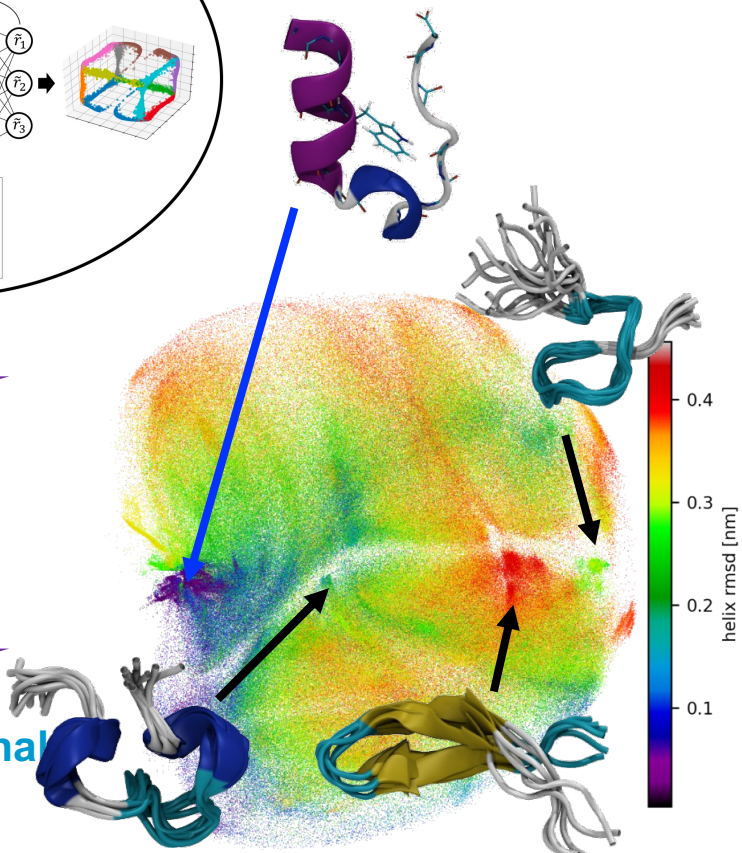
EncoderMap example 1: Trp-cage











Simulation data (Cartesian coordinates)

Input data set (features)

internal distances, dihedrals, ...

Map in low-dim space

Conformational states

Lemke & Peter, 2019, JCTC, 15, 1209-1215
Lemke, Berg, Jain, Peter, 2019, *J. Chem. Inf. Model,* 59, 4550

github.com/AG-Peter/EncoderMap

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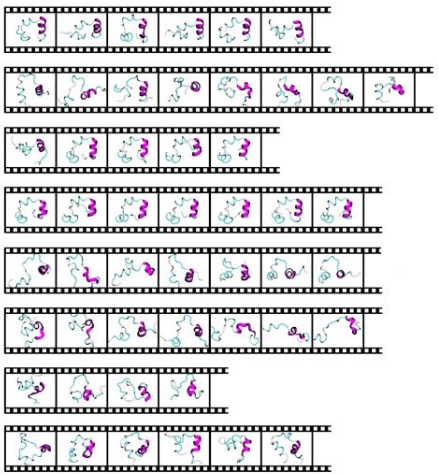
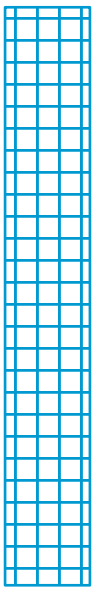
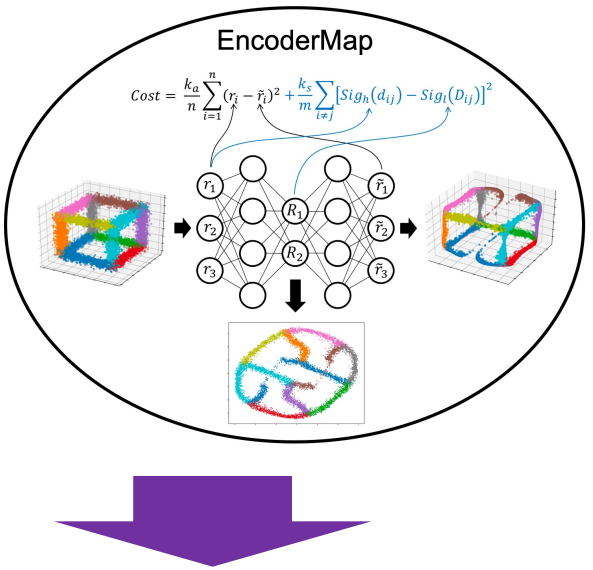
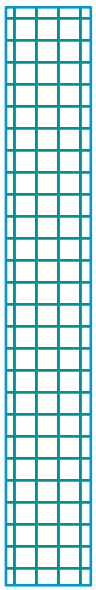
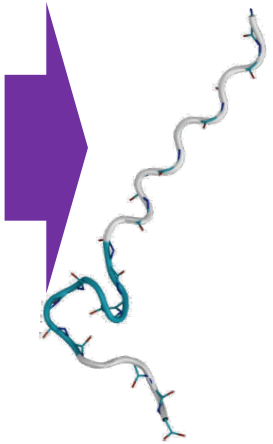










(Cartesian) Structure reconstruction

Simulation data (Cartesian coordinates)

Input data set (features)

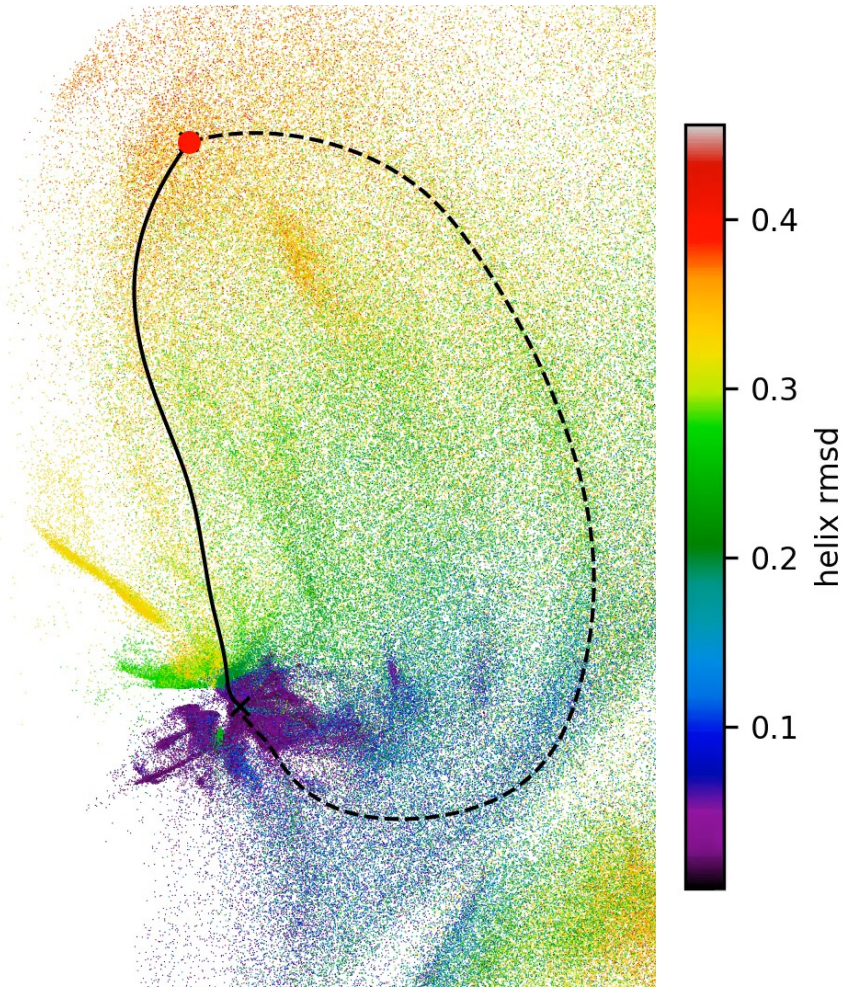
internal distances, dihedrals, ...

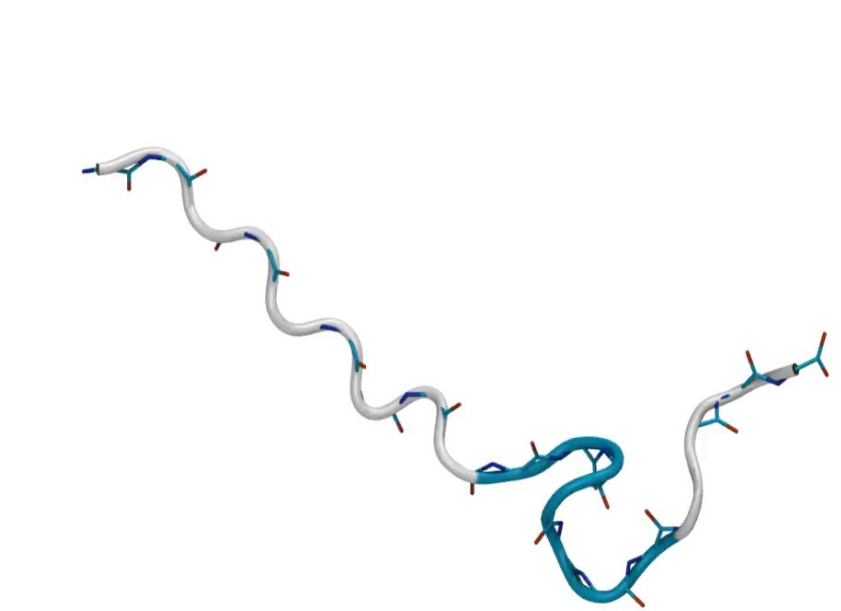
Map in low-dim space

Conformational states

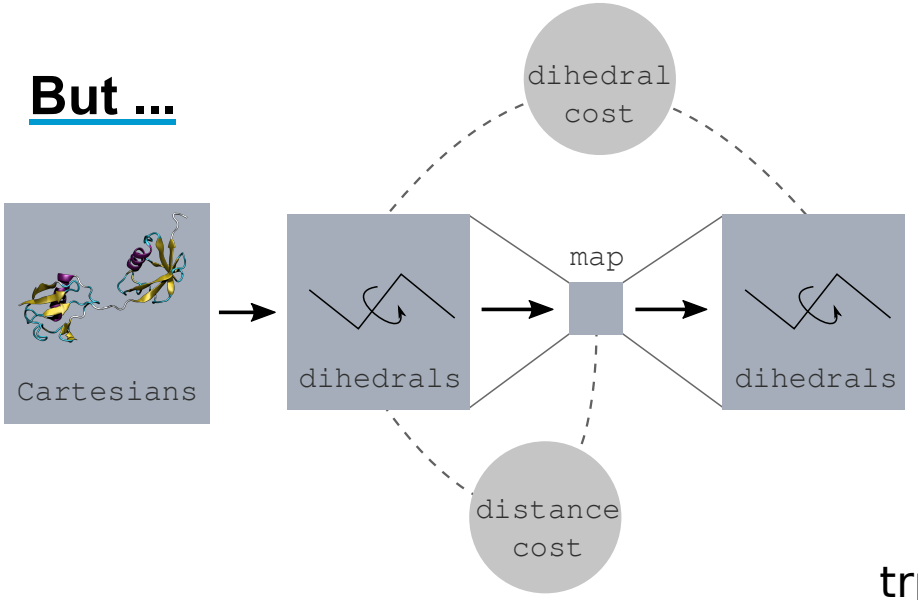
Generated data (in feature space)

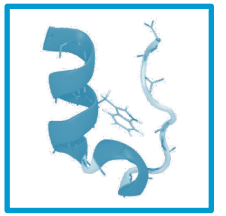
dihedrals, ...

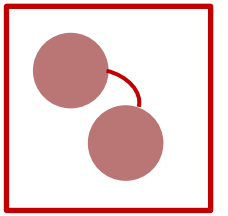




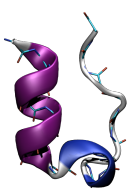
But ...



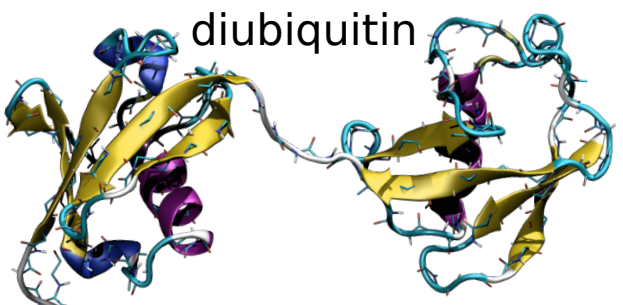




trp-cage

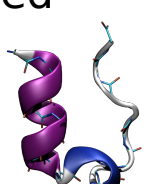


diubiquitin



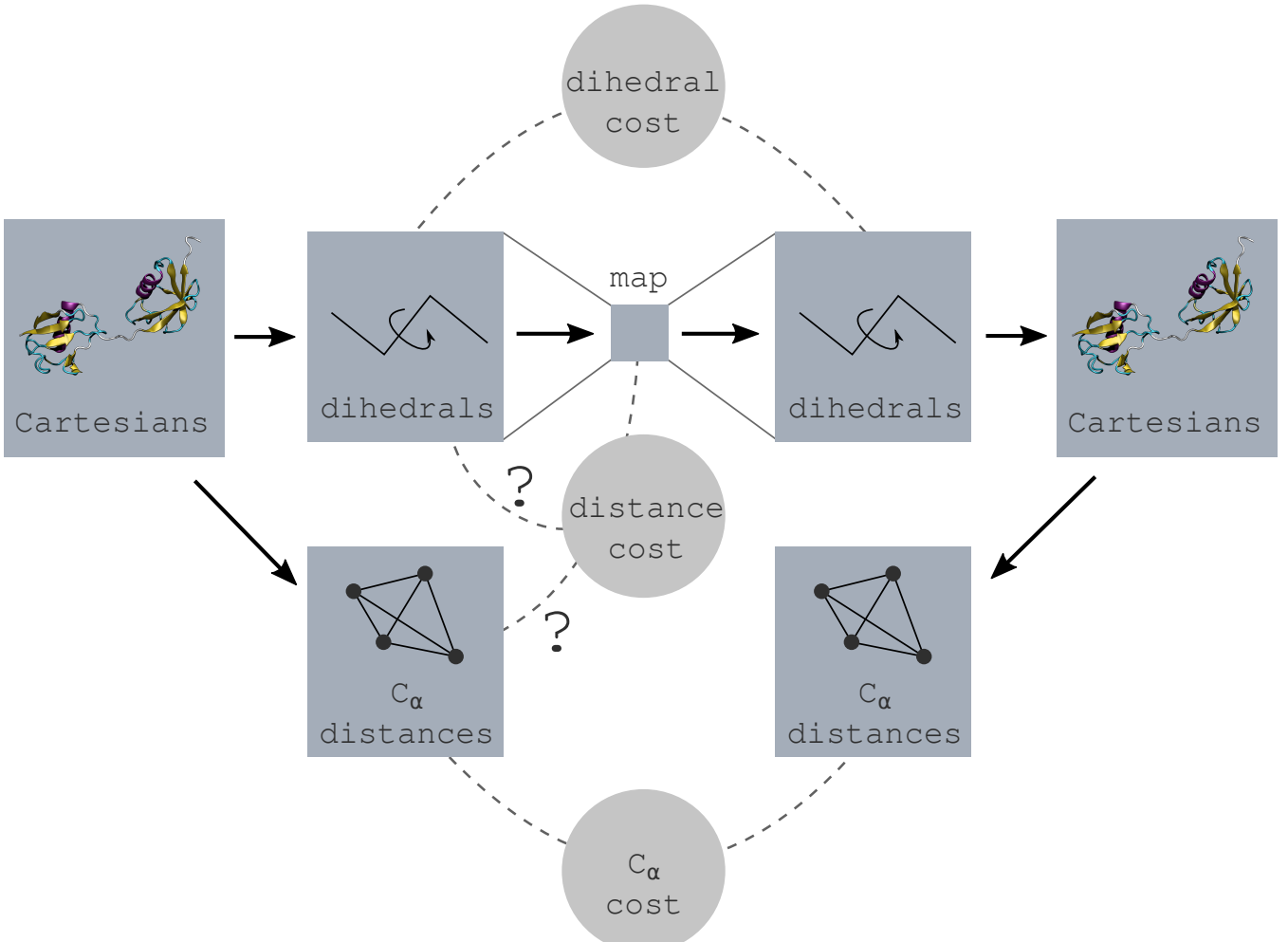
original

generated

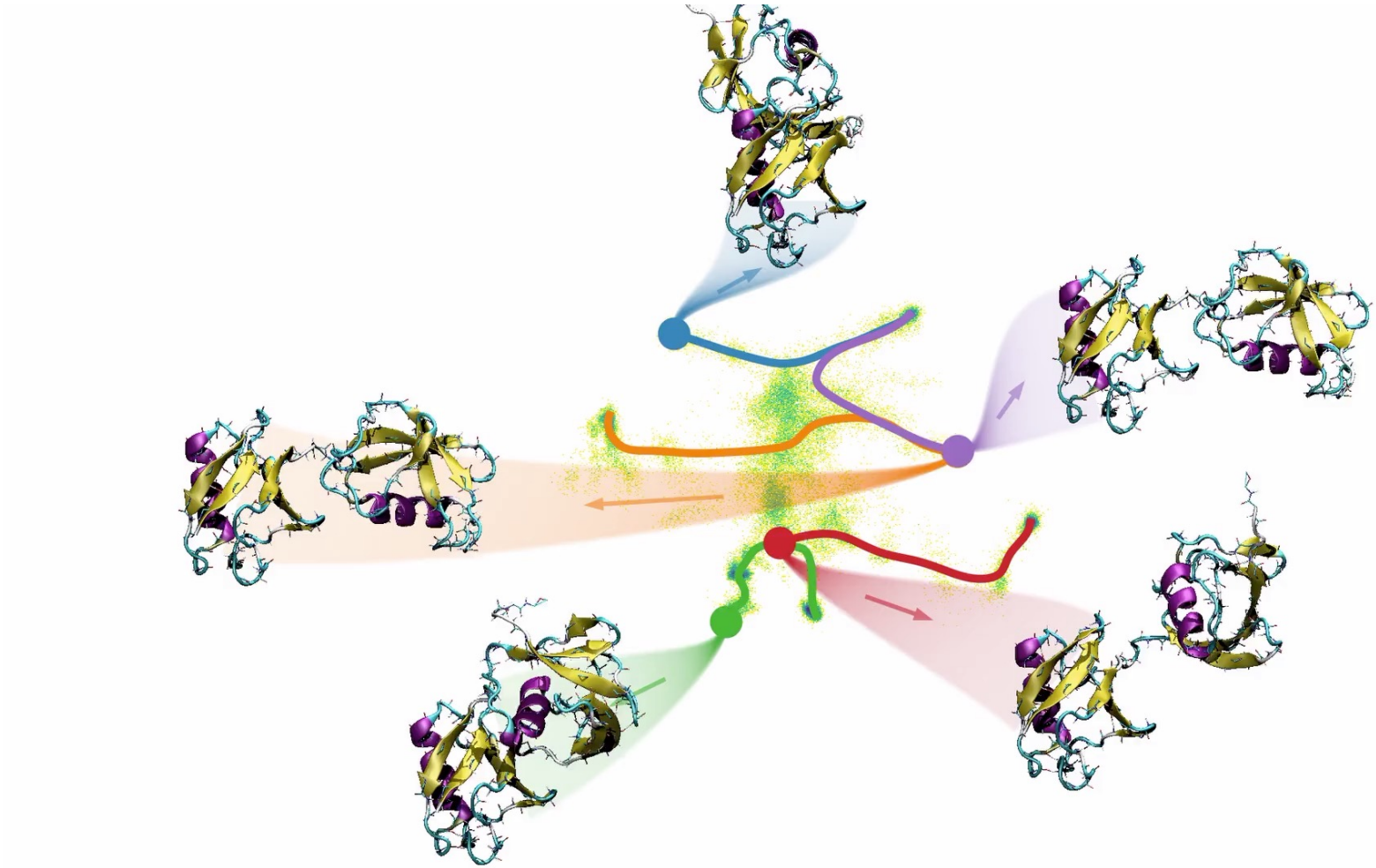


EncoderMap (II)

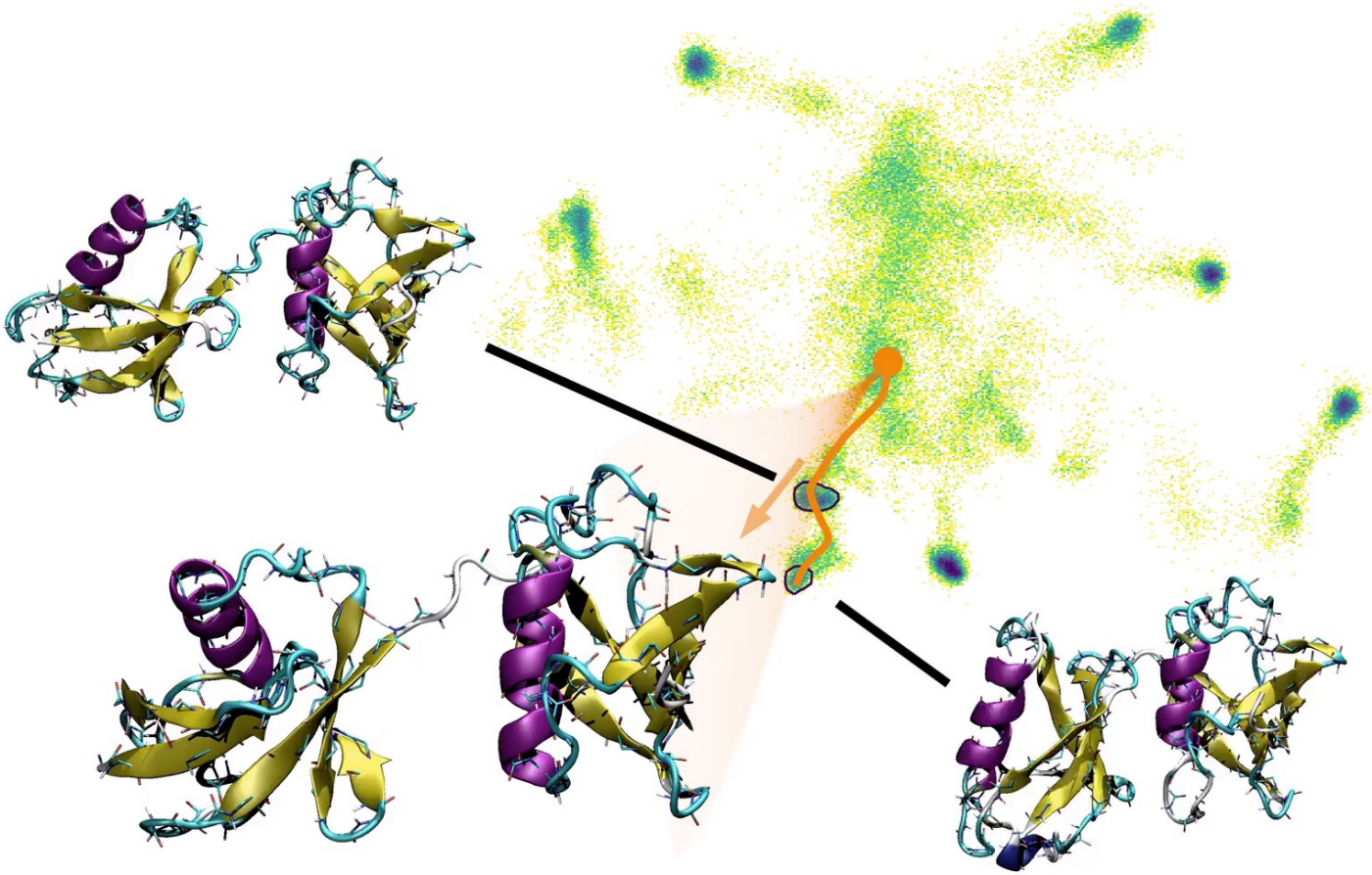
$$C = k_{\mathrm{dih.}} C_{\mathrm{dihedral}} + k_{\mathrm{C}_\alpha} C_{\mathrm{C}_\alpha} + k_{\mathrm{dist.}} C_{\mathrm{distance}}$$



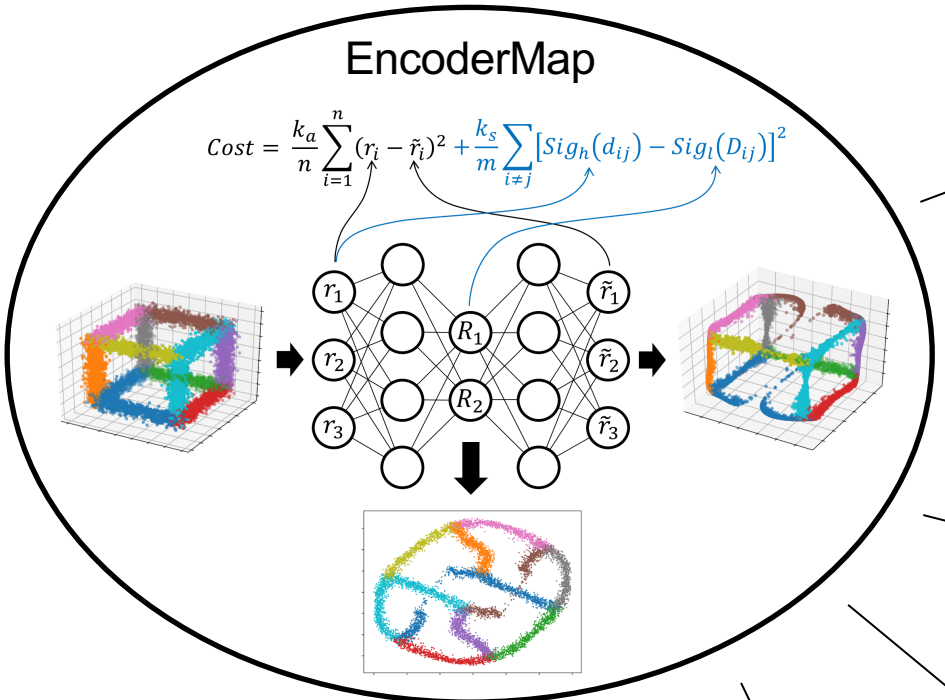
Example 2: M1-linked di-Ubiquitin – generating paths



Example 2: M1-linked di-Ubiquitin – visualizing important motions



Lemke, Berg, Jain, Peter, 2019, *J. Chem. Inf. Model,* 59, 4550



Computationally efficient

No landmarks required

Yields a function to map from high-d to low-d

Yields a function to map from low-d to high-d

Can deal with nonlinear data/structures

Preserves distances

➔ EncoderMap: combines advantages of a NN autoencoder and SketchMap/MDS

Outline

- Setting the stage
- EncoderMap
  - Learning meaningful representations of conformational phase space
  - Generating protein conformations and visualizing molecular motion
- Extracting meaningful feature sets from graph representations of proteins
  - Generating residue interaction landscapes
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- Backmapping based sampling
  - Linking scales through low-dimensional representations

➔ the input features matter

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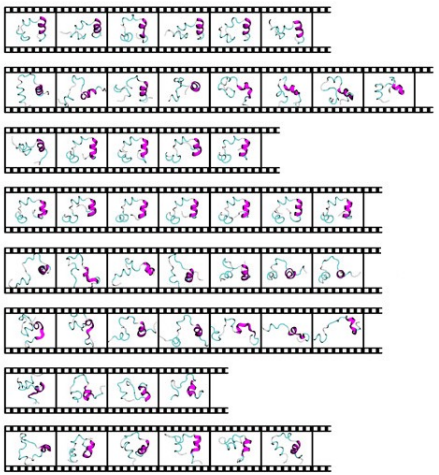
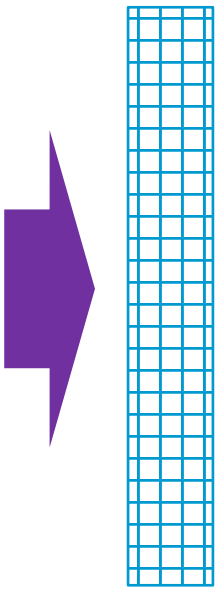
Extracting meaningful feature sets from protein graph representations



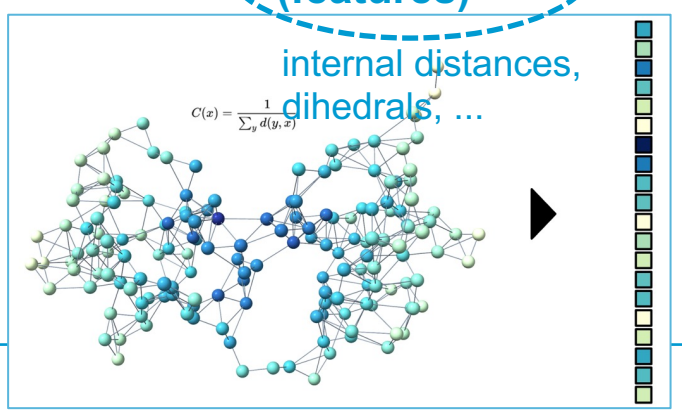


Dimensionality reduction
PCA, MDS, EncoderMap ...

Simulation data (Cartesian coordinates)

Input data set (features)

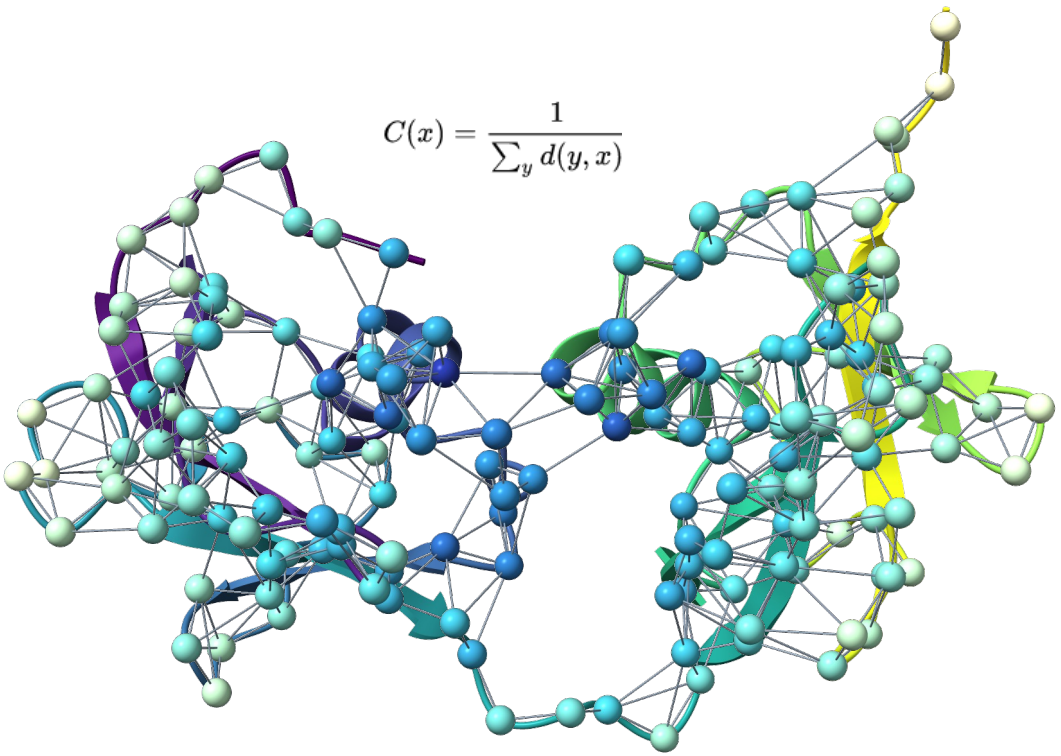
internal distances, dihedrals, ...

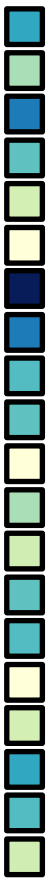


Map in low-dim space

Conformational states

Extracting meaningful feature sets from protein graph representations

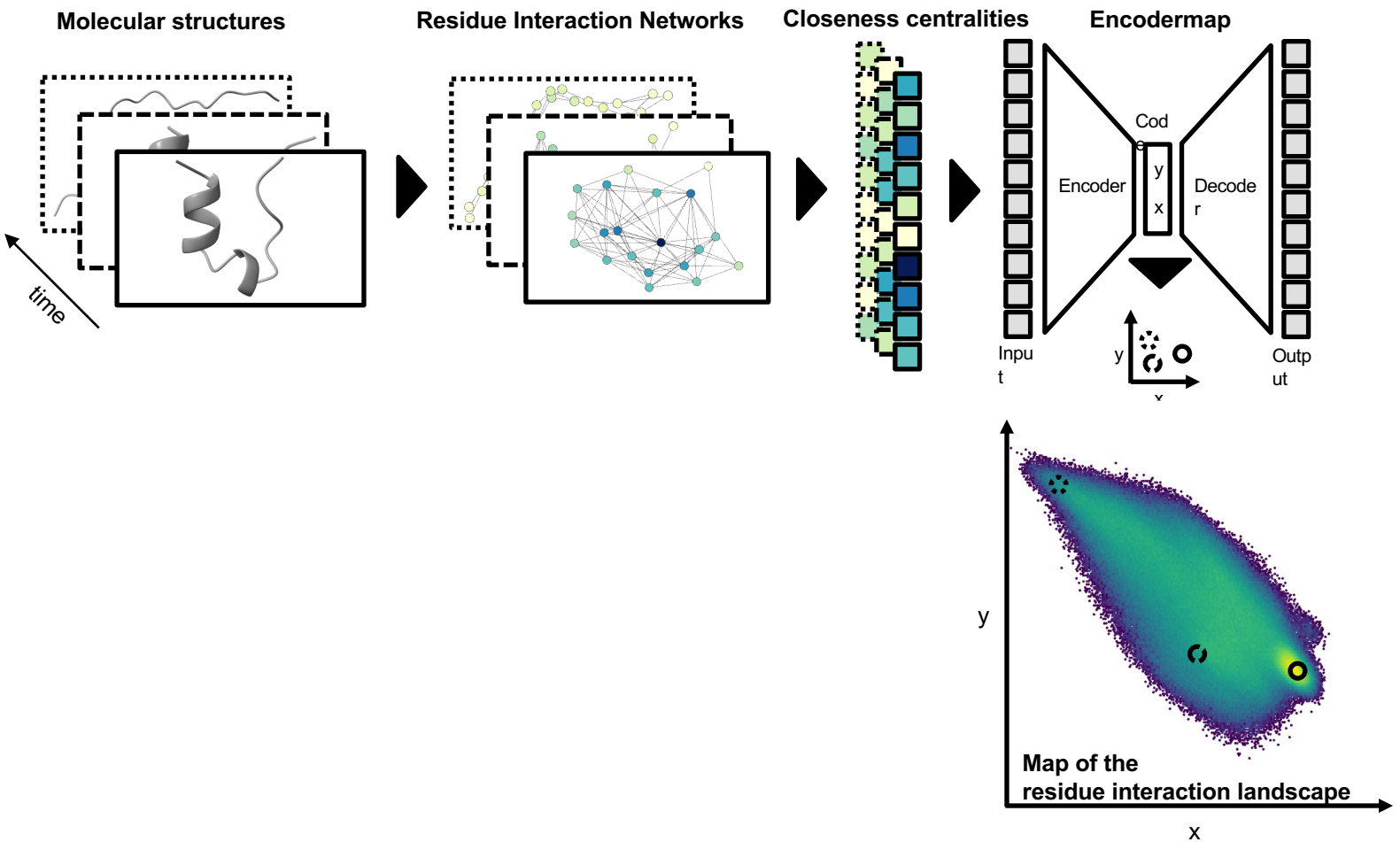




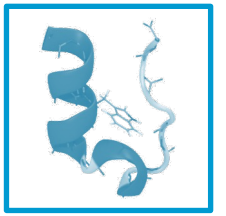
➔ Closeness centrality: „How close is a node to all other nodes in the network?“

➔ Feature set that captures role of each residue in the protein structure

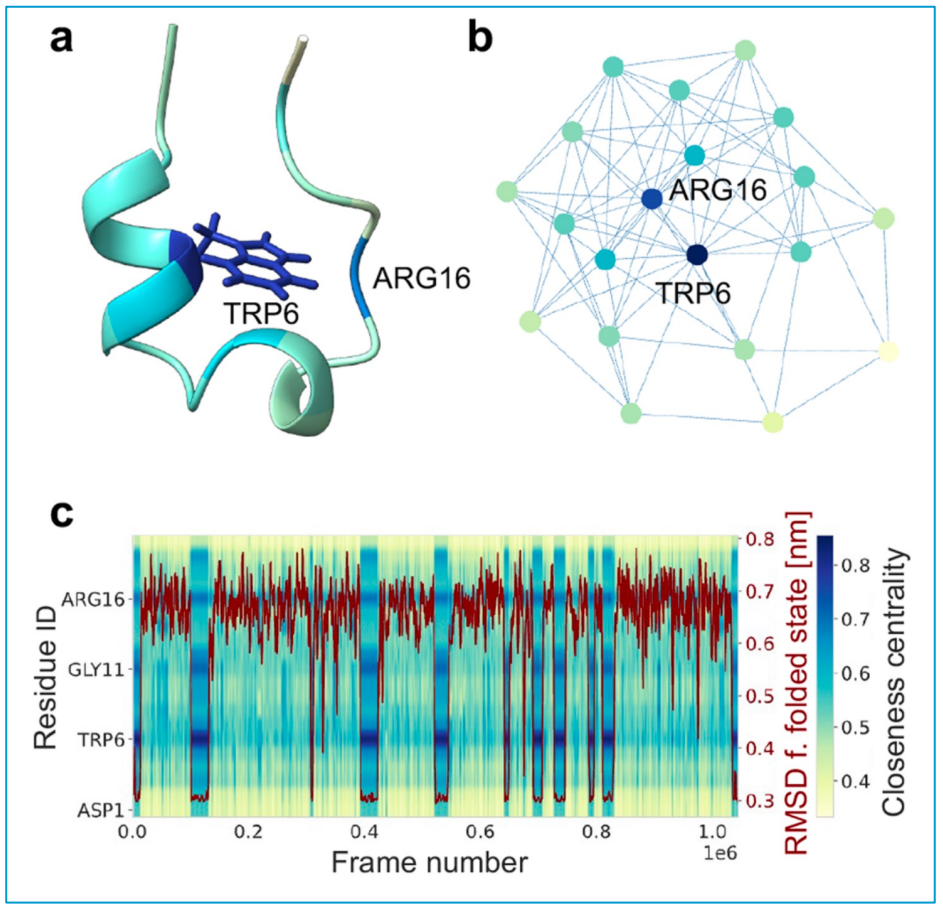
Workflow


Molecular structures
Residue Interaction Networks
Closeness centralities
Encodermap
time
Encoder
Cod
e
y
x
Decode
r
Inpu
t
Outp
ut
y
Map of the
residue interaction landscape
y
x

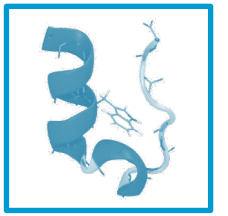
Example 1: Trp-cage

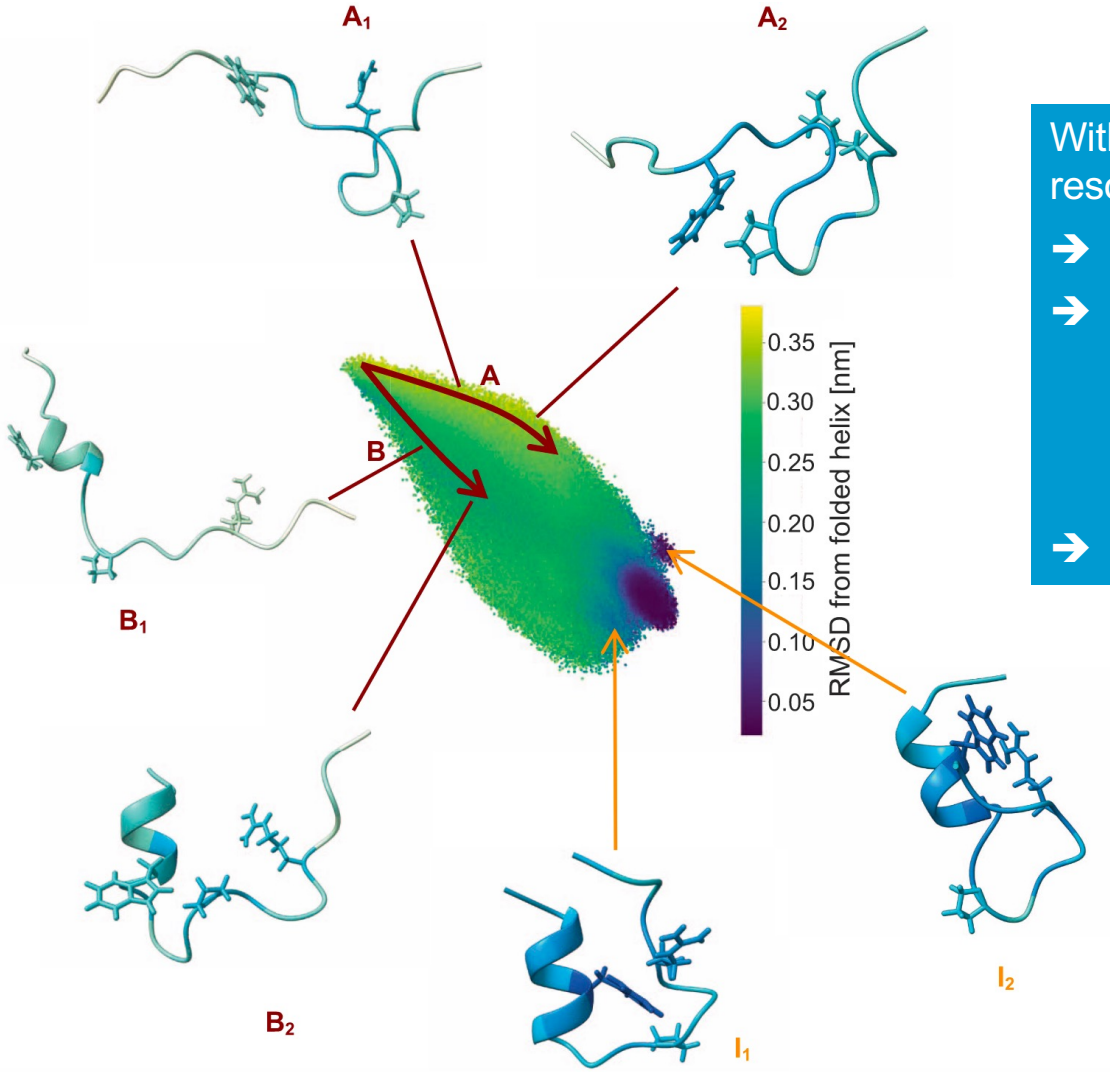


Trp-Cage



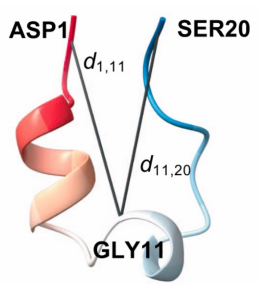
Residue interaction landscape of Trp-cage



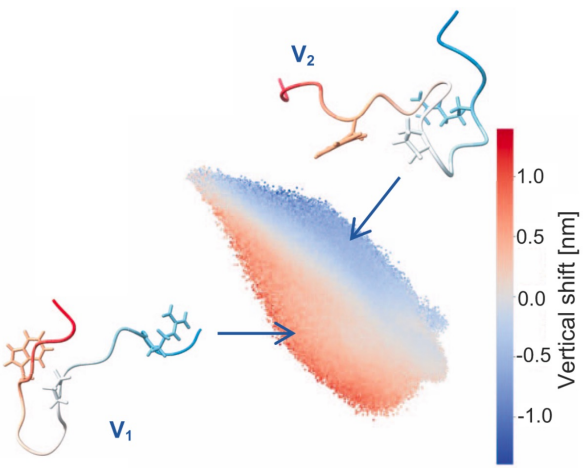


Without protein-specific prior input, the map resolves known folding behaviors

- ➔ Separation of folded and unfolded states
- ➔ Two folding pathways:
  - A: Nucleation-condensation; hydrophobic collapse first
  - B: Diffusion-collision; helix forms first
- ➔ Near-native intermediates



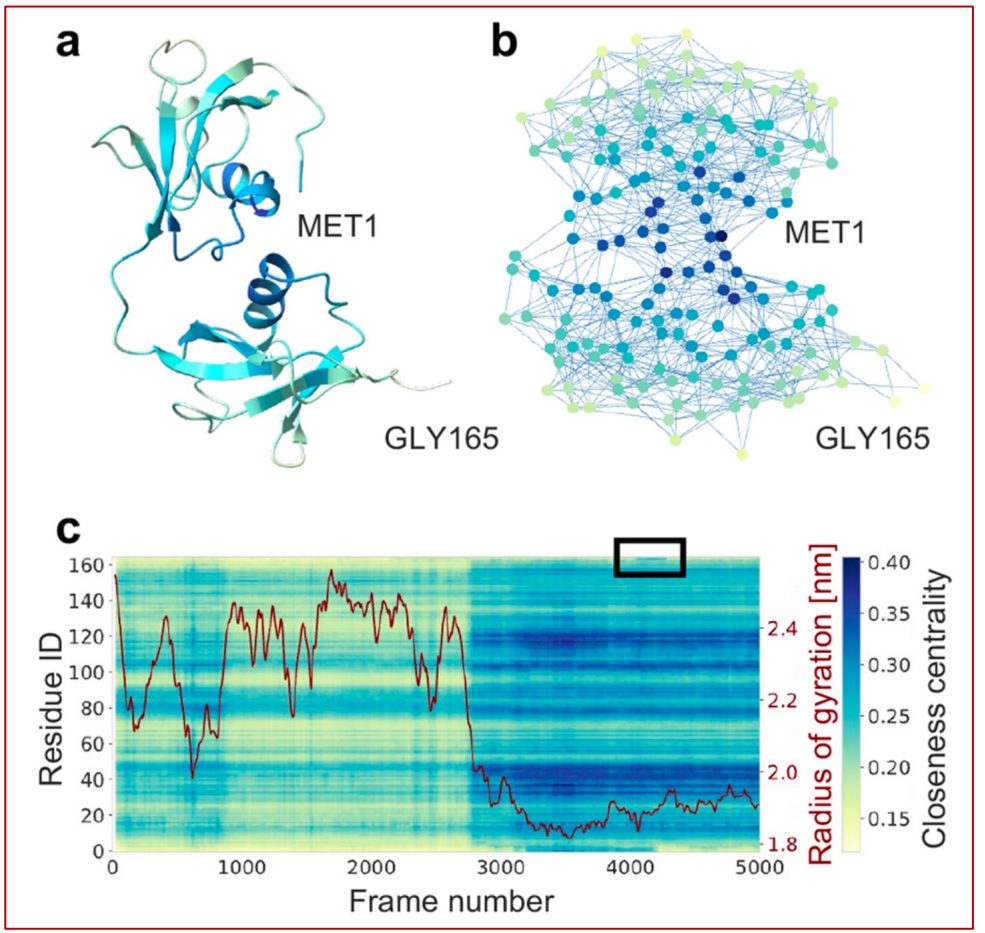
Vertical shift: $d_{11,20}$-$d_{1,10}$



Example 2: FAT10

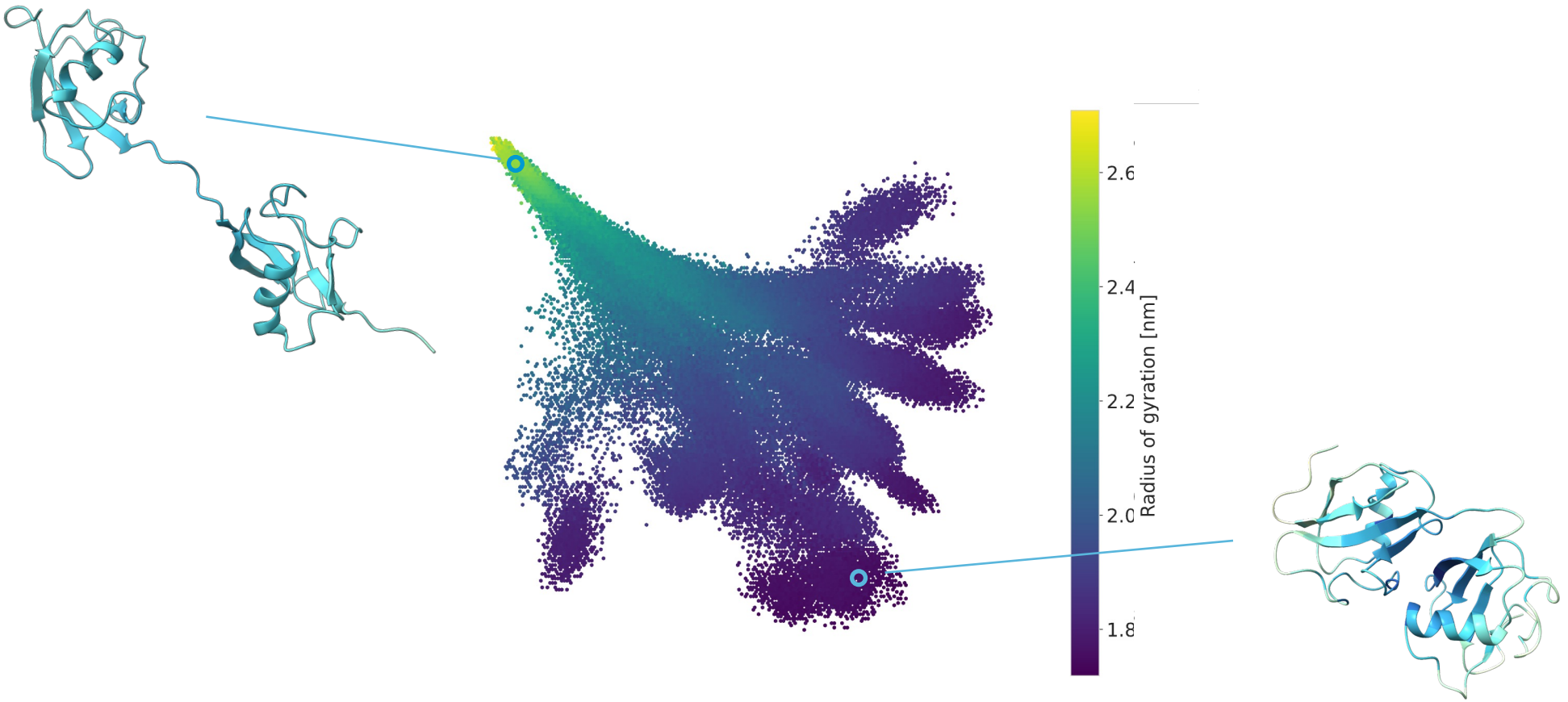
Trp-Cage

FAT10

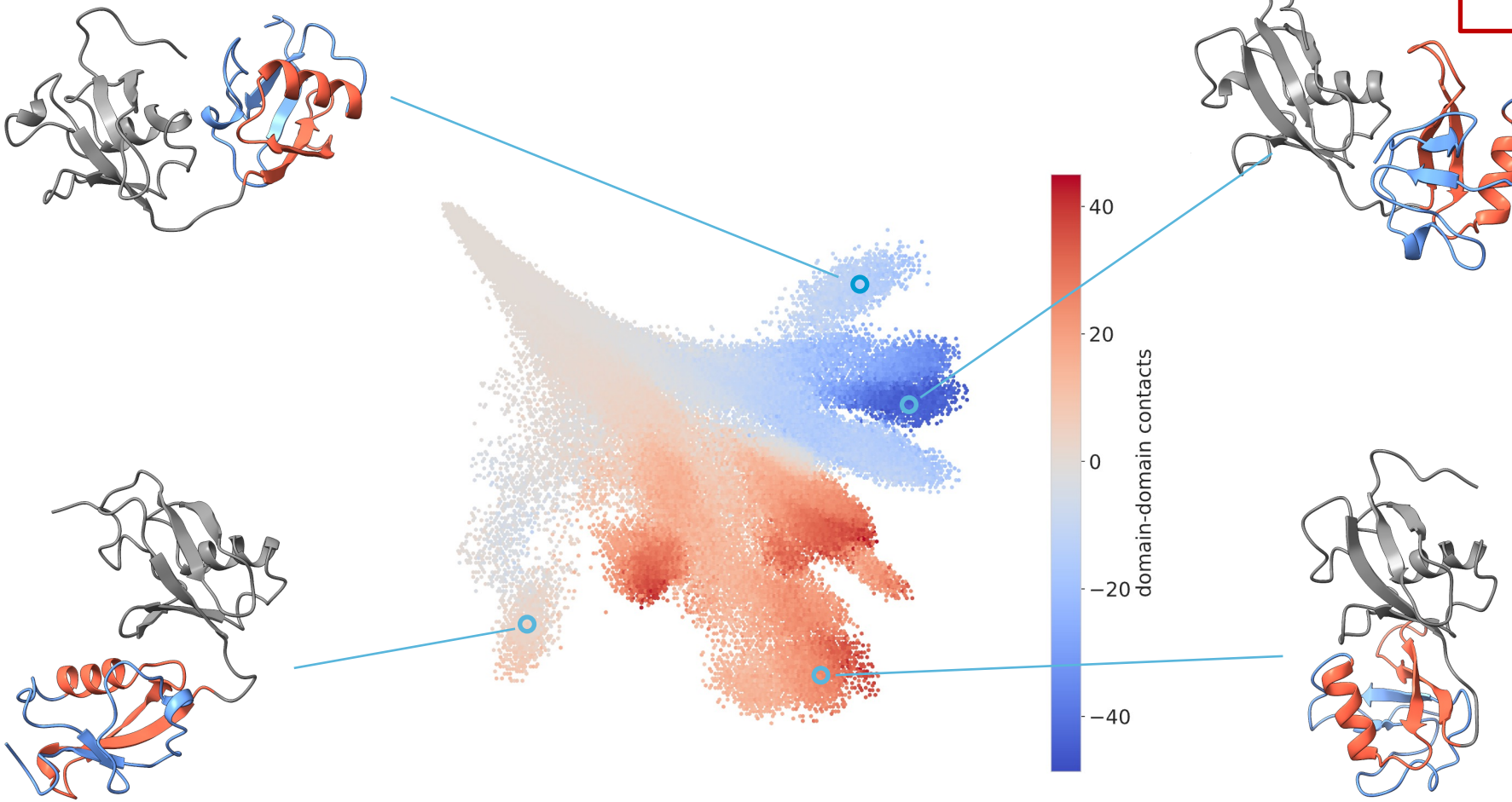


Franke & Peter, 2023, JCTC, https://doi.org/10.1021/acs.jctc.2c01228

Residue interaction landscape of FAT10

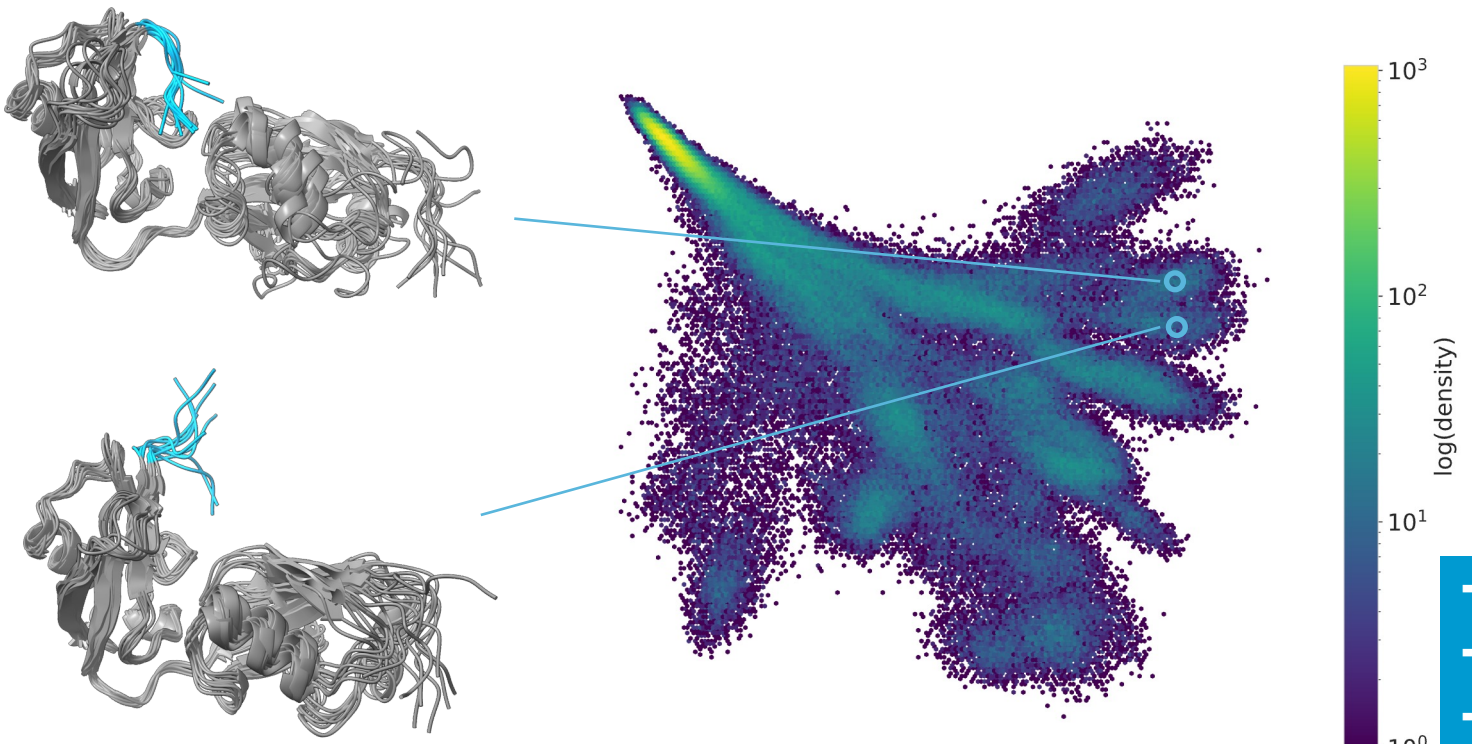


Residue interaction landscape of FAT10



Franke & Peter, 2023, JCTC, https://doi.org/10.1021/acs.jctc.2c01228

Residue interaction landscape of FAT10



- ➔ global interpretability
- ➔ resolves meaningful details
- ➔ useful for visualization and further down-stream processing

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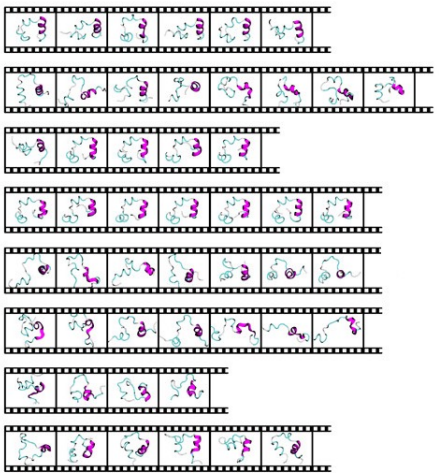
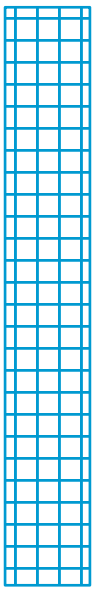
Clustering



Simulation data (Cartesian coordinates)



Input data set (features)

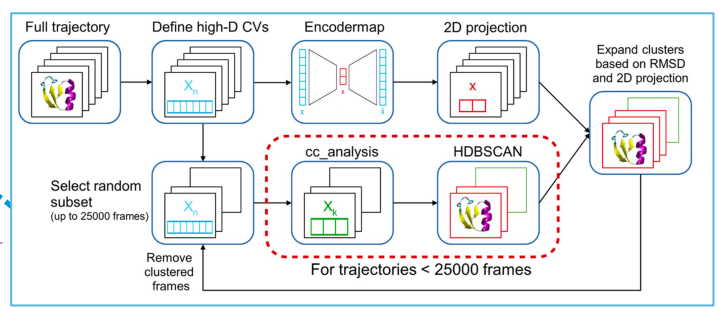
internal distances, dihedrals, ...

Dimensionality reduction
PCA, MDS, EncoderMap ...

Map in low-dim space

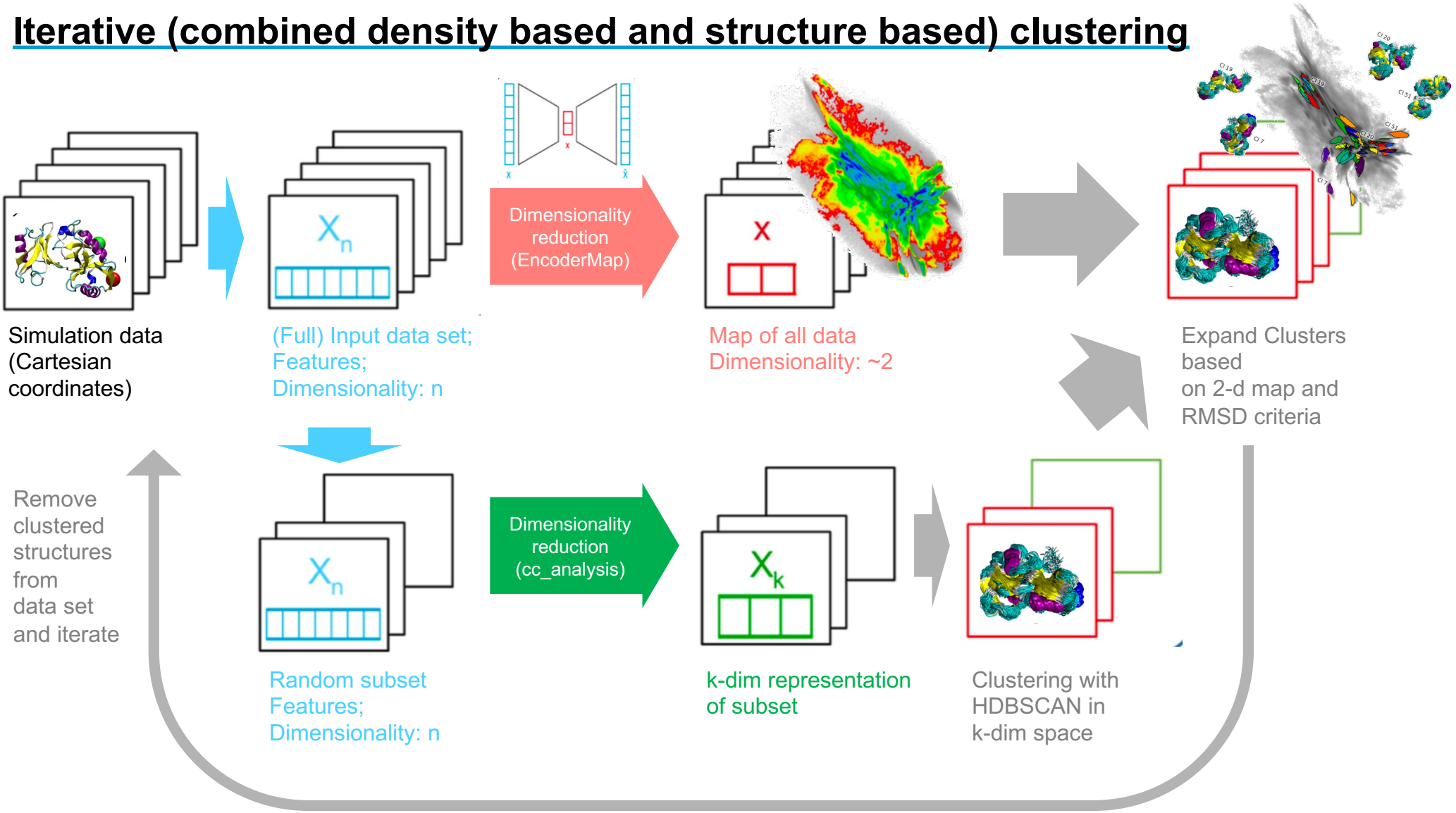
Conformational states

Efficient iterative (combined density-based and structure-based) clustering

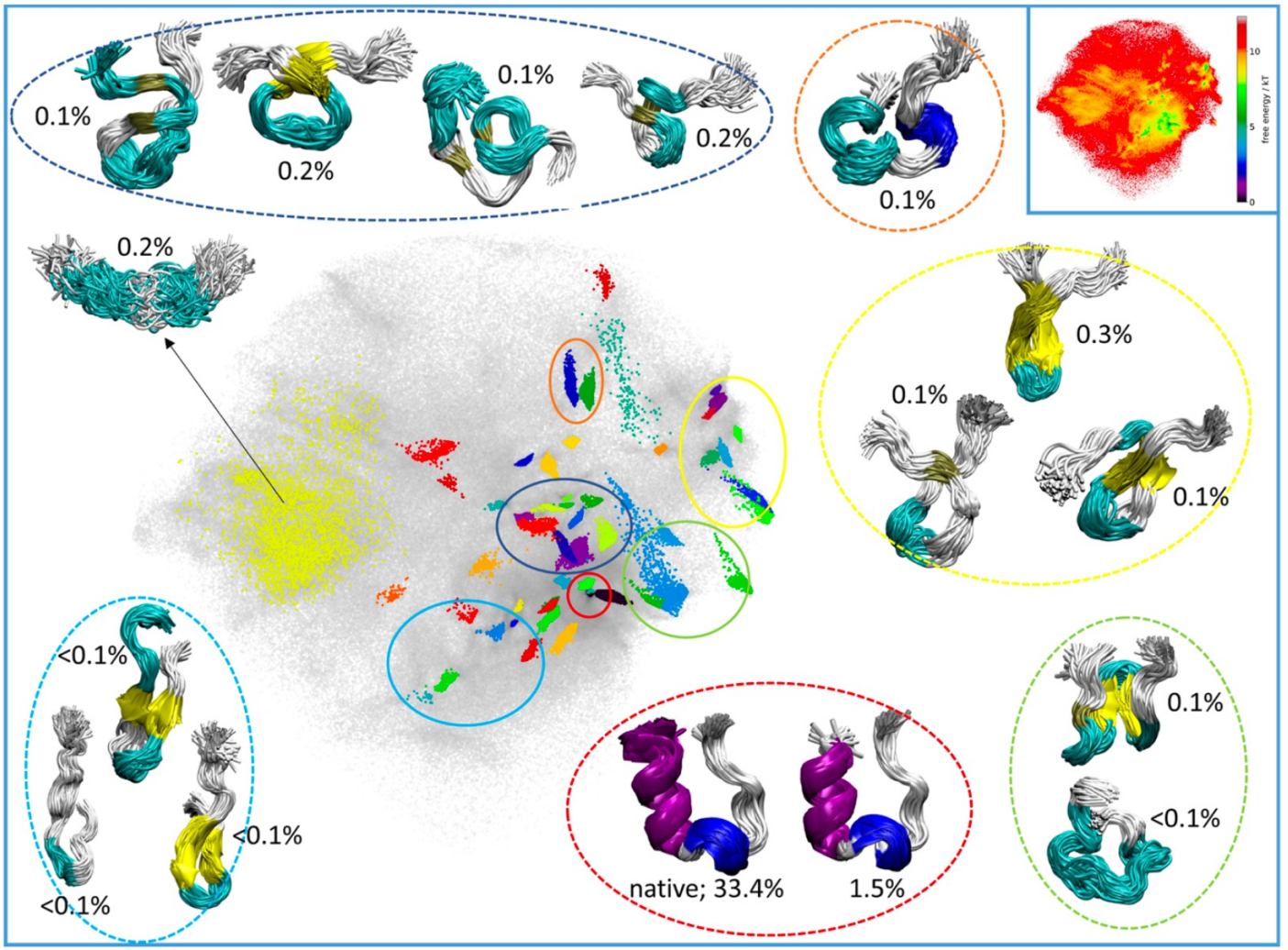


Hunkler et al
J. Chem. Phys. 158, 144109 (2023)

Iterative (combined density based and structure based) clustering

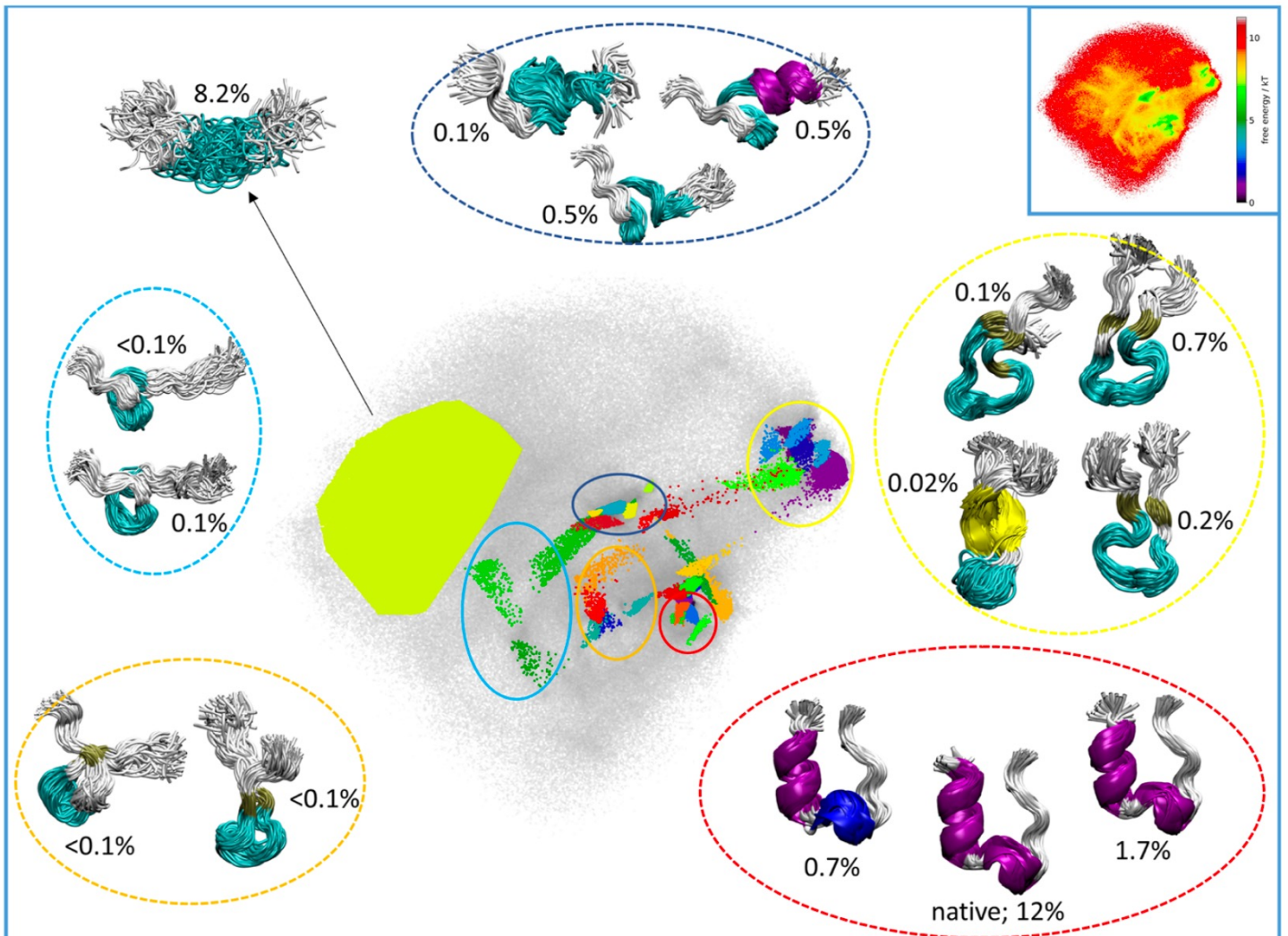


Example 1: Trp-cage



TC5b (40 temperature RE trajectories)

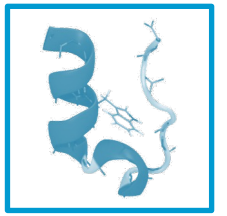
Example 1: Trp-cage



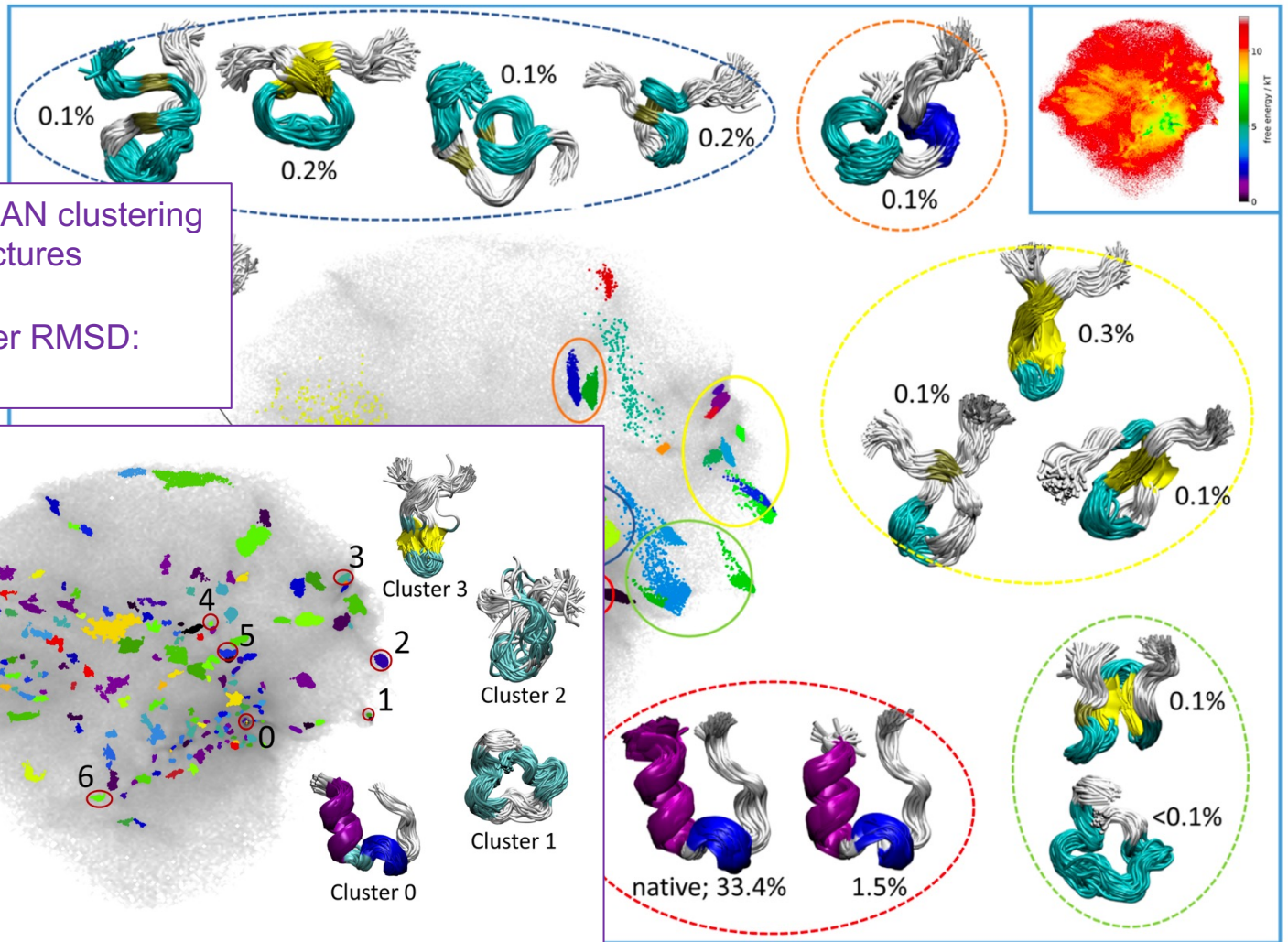
TC10b
(DE Shaw trajectories)

Hunkler et al J. Chem. Phys. 158, 144109 (2023)

Example 1: Trp-cage



direct HDBSCAN clustering
< 15% of structures assigned;
average cluster RMSD:
2.25 Å



~60% of structures assigned;
average cluster RMSD:
1.34 Å

TC5b (40 temperature RE trajectories)

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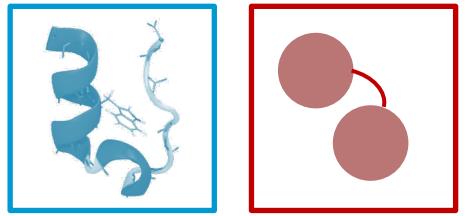

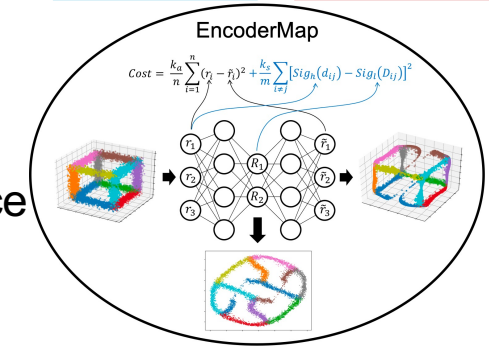

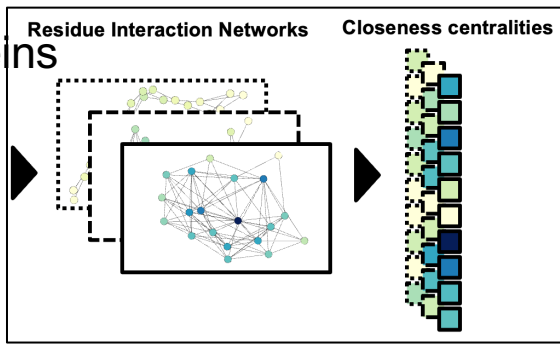

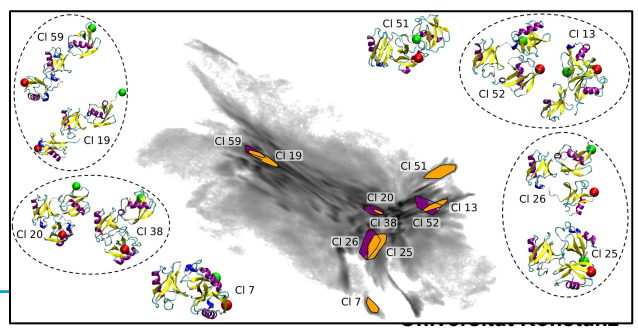

Acknowlegements