Simplify to understand: extracting insight from high-dimensional simulation datasets of biological systems via information-theoretic approaches

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ALPACA Workshop
ECT*, Trento, September 2023

Data are easier and easier to get

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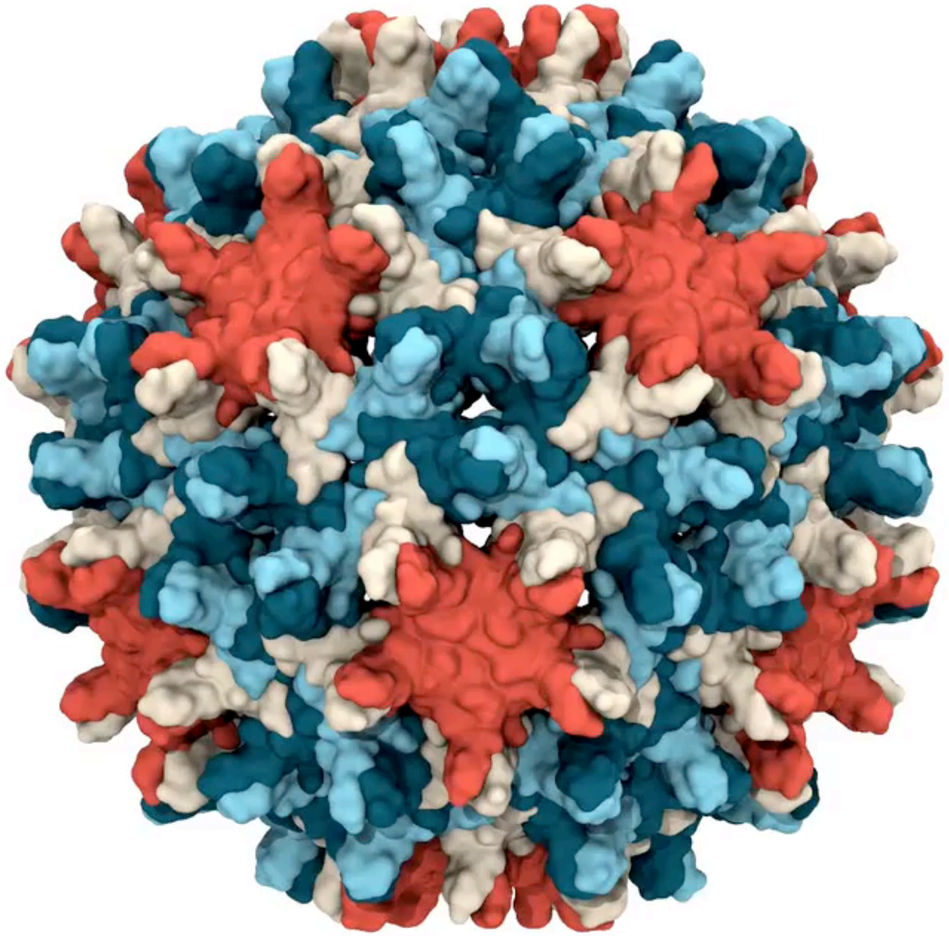
All-atom MD simulations



Hadden *et al.*, eLife 2018

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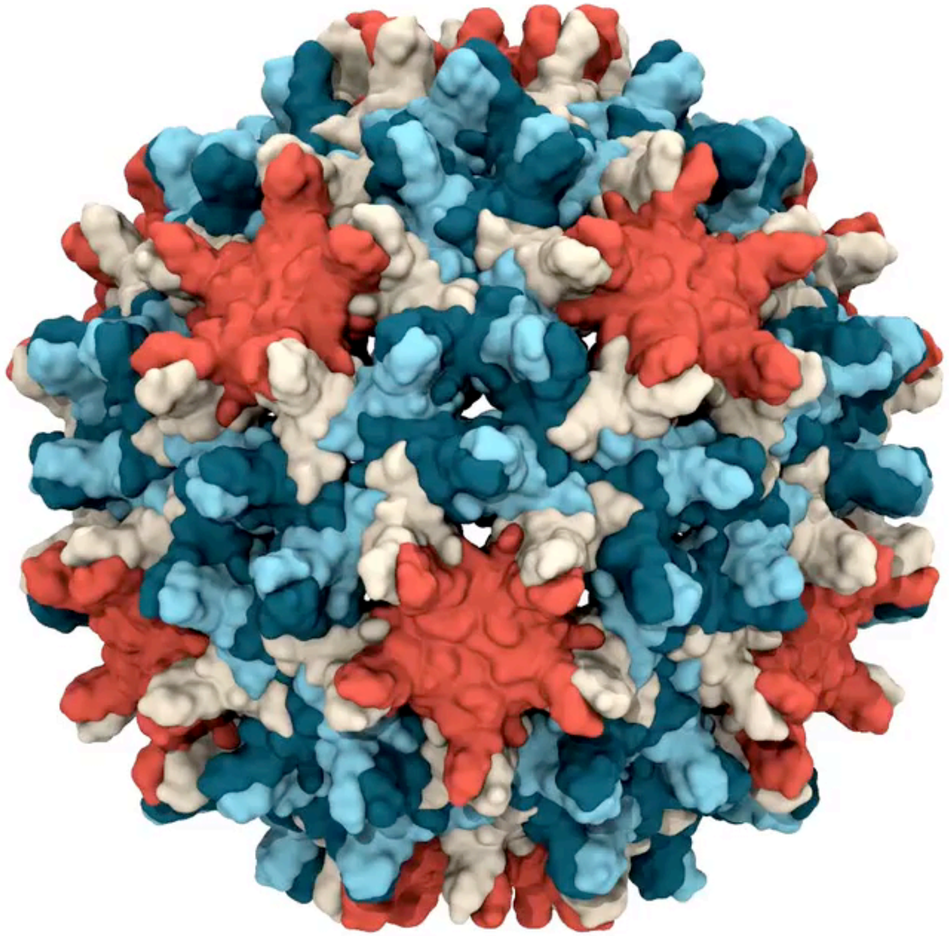
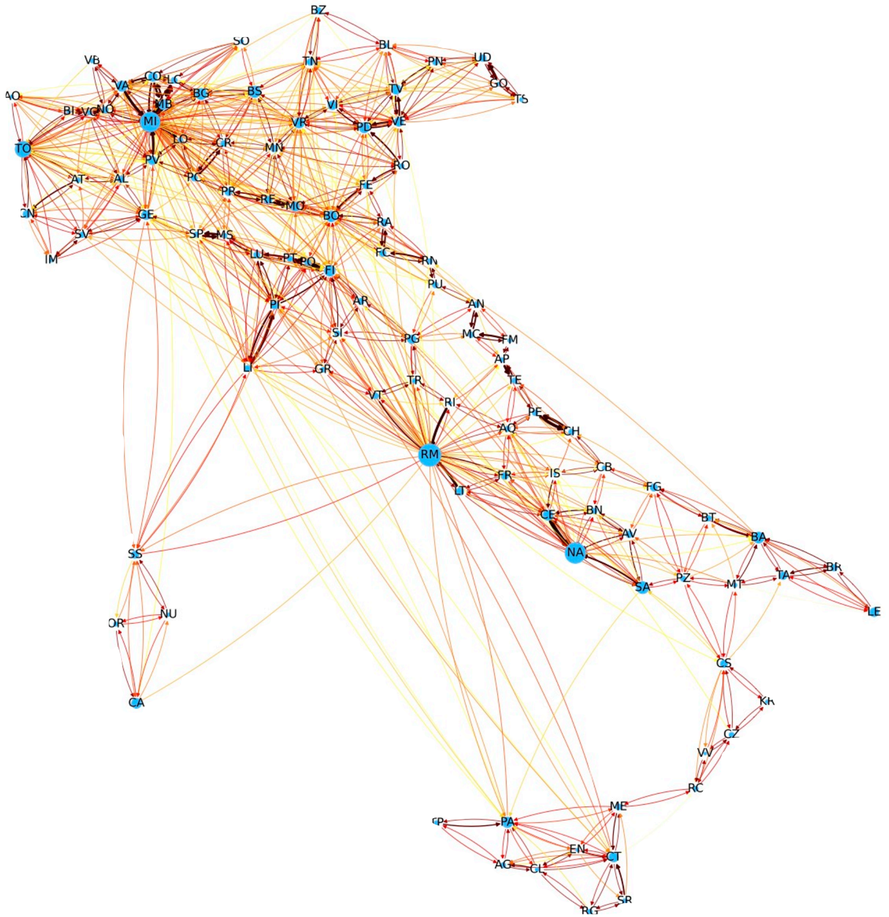


Hadden *et al.*, eLife 2018

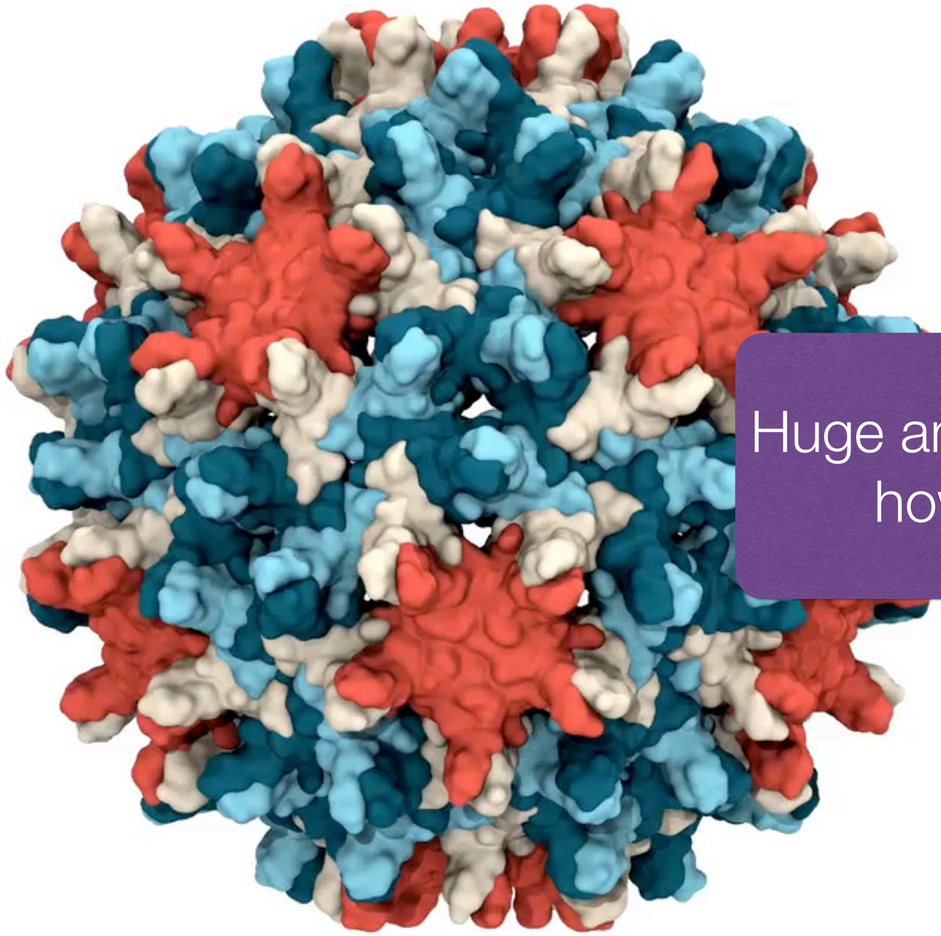
Aggregate digital databases



Morand, Yip, Velegrakis, Lattanzi, Potestio, Tubiana, *arXiv* 2023

Data are easier and easier to get

All-atom MD simulations



Hadden *et al.*, eLife 2018

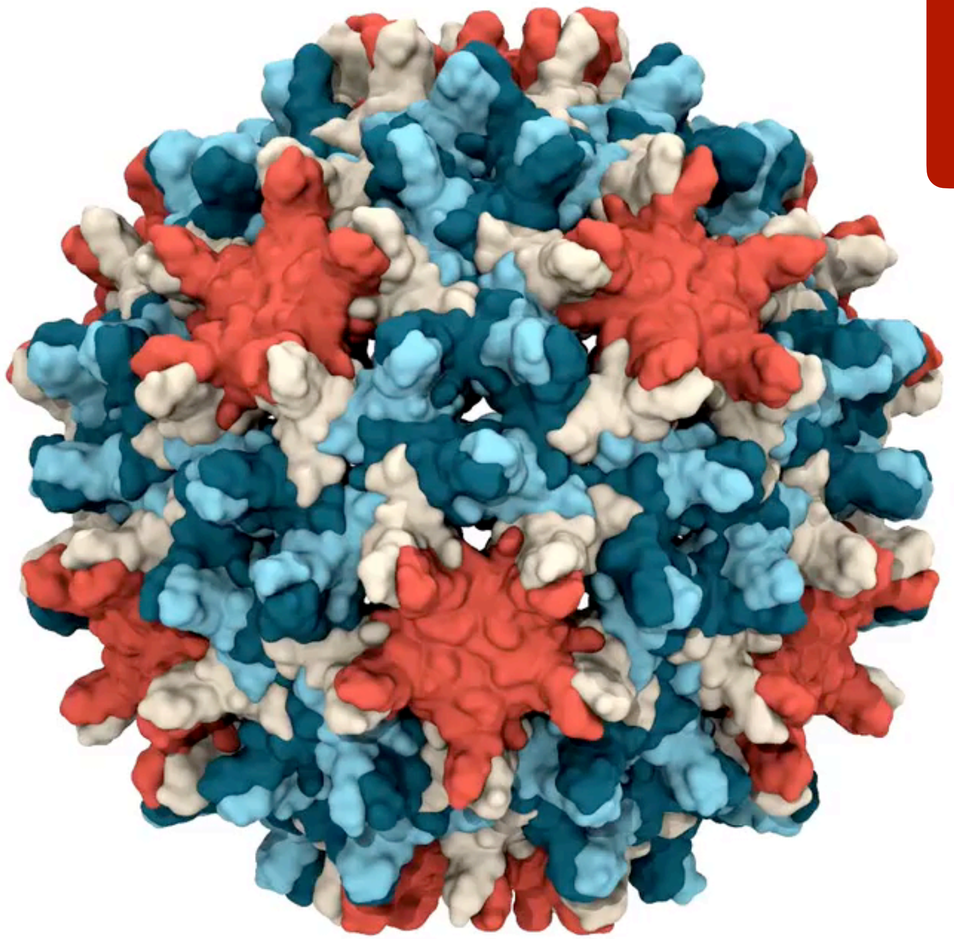
Aggregate digital databases

Morand, Yip, Velegrakis, Lattanzi, Potestio, Tubiana, *arXiv* 2023

Huge amount of generated data:
how to extract insight?

Data are easier and easier to get

All-atom MD simulations



Hadden *et al.*, eLife 2018

$$\vec{F} = m\vec{a}$$

10^6 atoms for 10^9 configurations of the system

```
ATOM   1153  CD   GLN X 408     110.020  92.423  42.297  0.00  0.00
ATOM   1154  OE1  GLN X 408     110.283  93.074  43.331  0.00  0.00
ATOM   1155  NE2  GLN X 408     108.983  91.618  42.373  0.00  0.00
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ATOM   1157 HE22  GLN X 408     108.471  91.768  43.225  0.00  0.00
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ATOM   1164  CB   GLN X 409     114.444  97.423  43.339  0.00  0.00
ATOM   1165  HB1  GLN X 409     115.314  97.840  43.844  0.00  0.00
ATOM   1166  HB2  GLN X 409     113.900  96.872  44.111  0.00  0.00
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ATOM   1174 HE22  GLN X 409     111.343 100.484  44.321  0.00  0.00
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ATOM   1179  CA   PHE X 410     116.976  93.435  43.590  0.00  0.00
ATOM   1180  HA   PHE X 410     117.124  93.938  44.557  0.00  0.00
ATOM   1181  CB   PHE X 410     116.299  92.042  43.824  0.00  0.00
ATOM   1182  HB1  PHE X 410     116.161  91.560  42.866  0.00  0.00
ATOM   1183  HB2  PHE X 410     115.259  92.135  44.154  0.00  0.00
ATOM   1184  CG   PHE X 410     117.011  91.074  44.747  0.00  0.00
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ATOM   1186  HD1  PHE X 410     116.520  92.142  46.584  0.00  0.00
ATOM   1187  CE1  PHE X 410     117.746  90.542  46.998  0.00  0.00
ATOM   1188  HE1  PHE X 410     117.720  90.932  48.007  0.00  0.00
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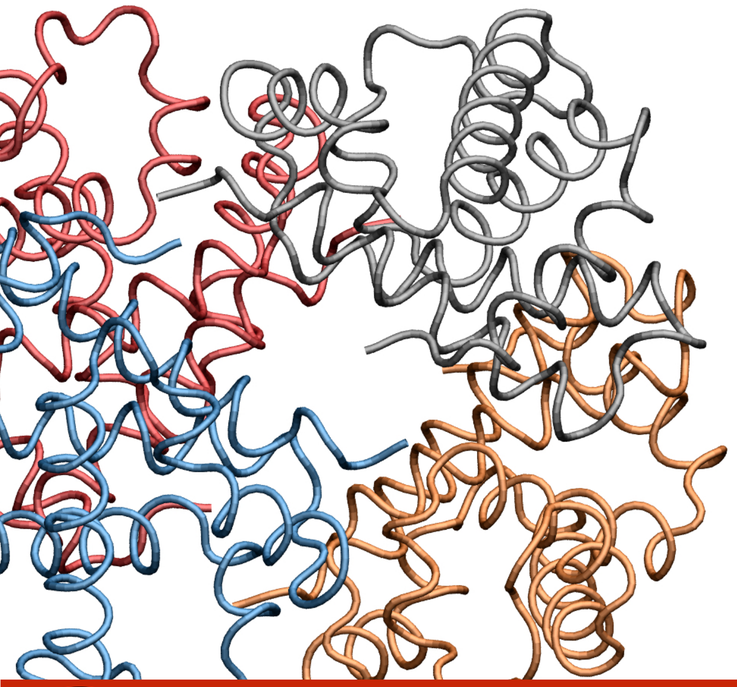
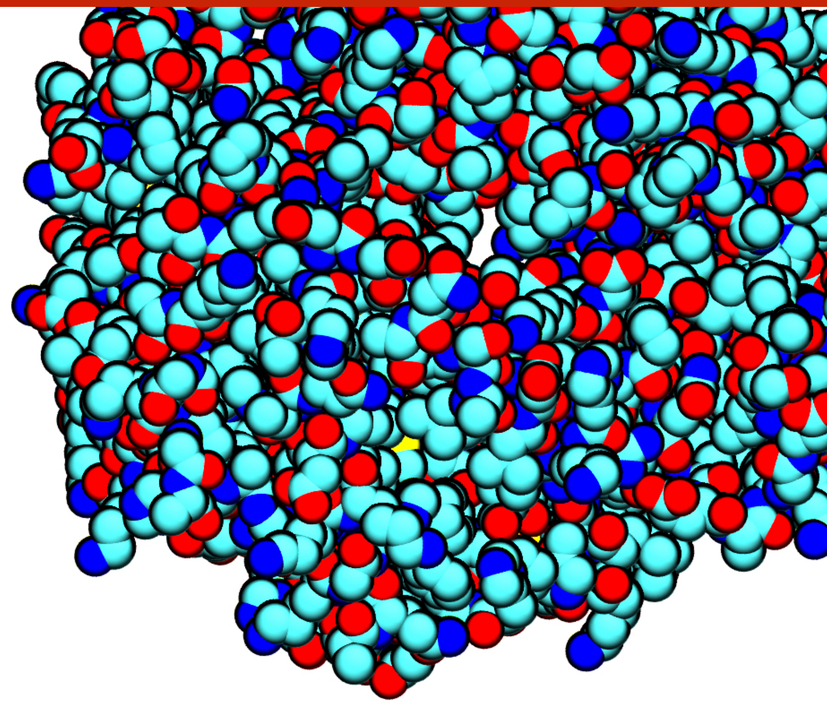
ATOM   1191  CE2  PHE X 410     118.374  89.090  45.183  0.00  0.00
ATOM   1192  HE2  PHE X 410     118.911  88.260  44.740  0.00  0.00
ATOM   1193  CD2  PHE X 410     117.779  89.966  44.293  0.00  0.00
ATOM   1194  HD2  PHE X 410     117.894  89.832  43.227  0.00  0.00
ATOM   1195  C    PHE X 410     118.379  93.352  42.972  0.00  0.00
```

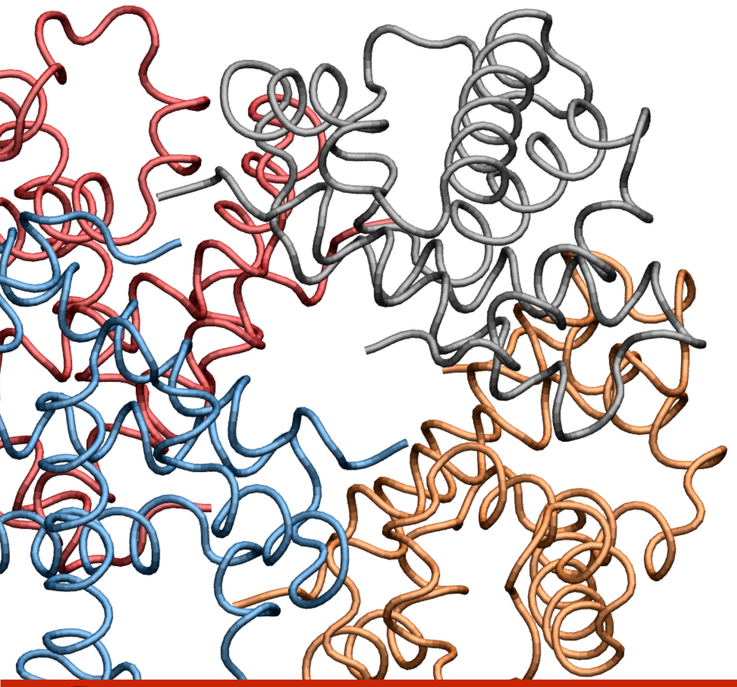
Simplify to understand

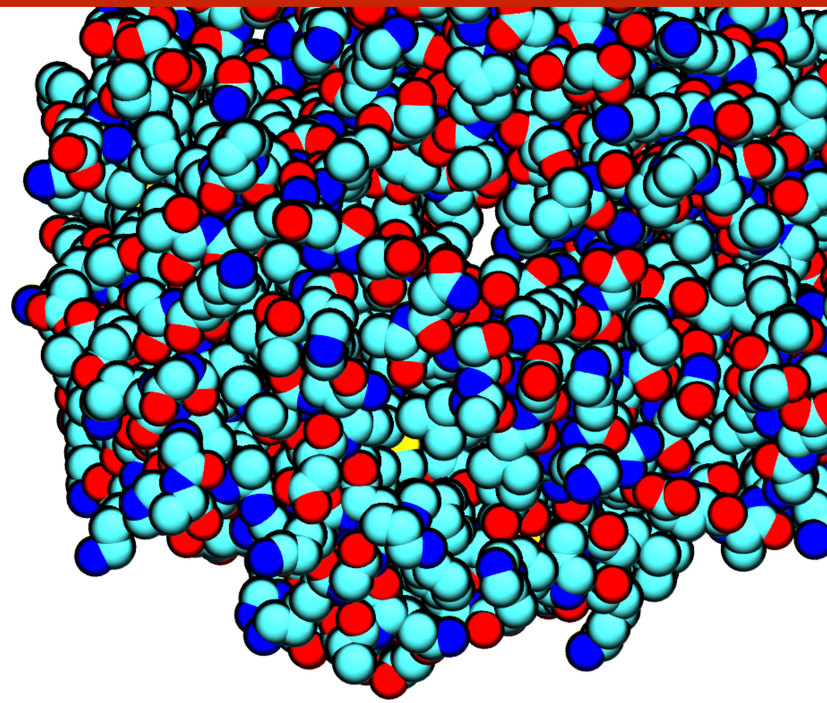




Simplify to understand

DATA != INFORMATION

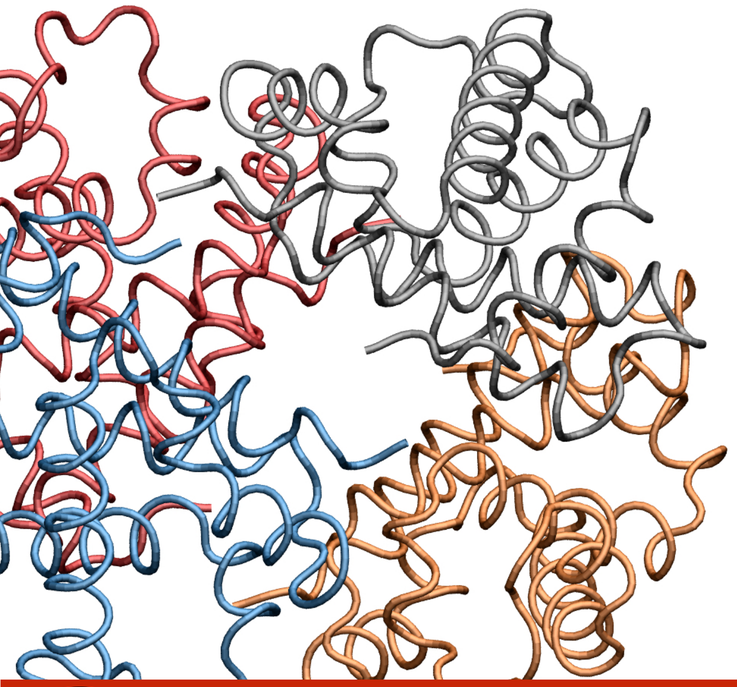


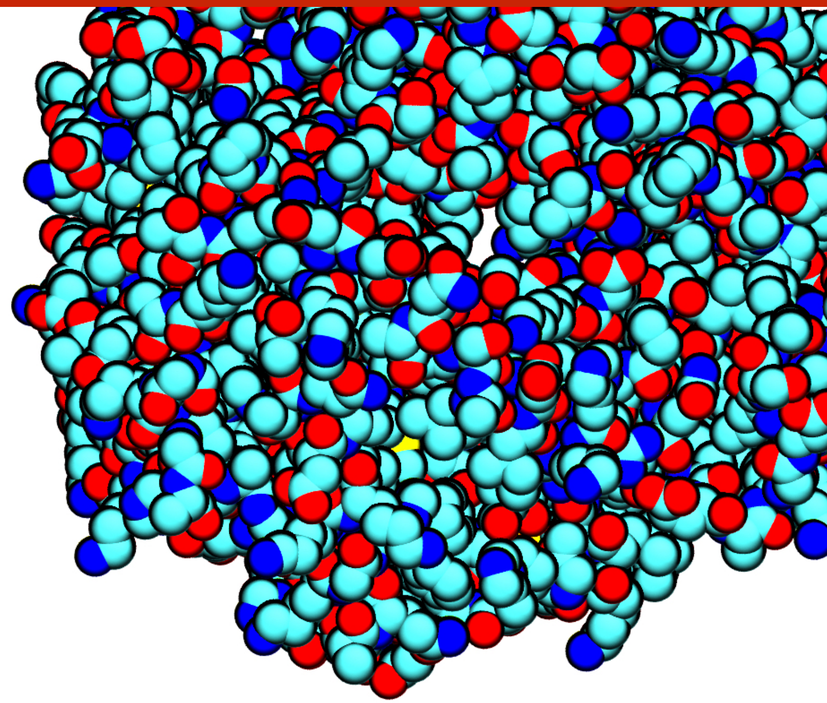


Simplify to understand

DATA != INFORMATION

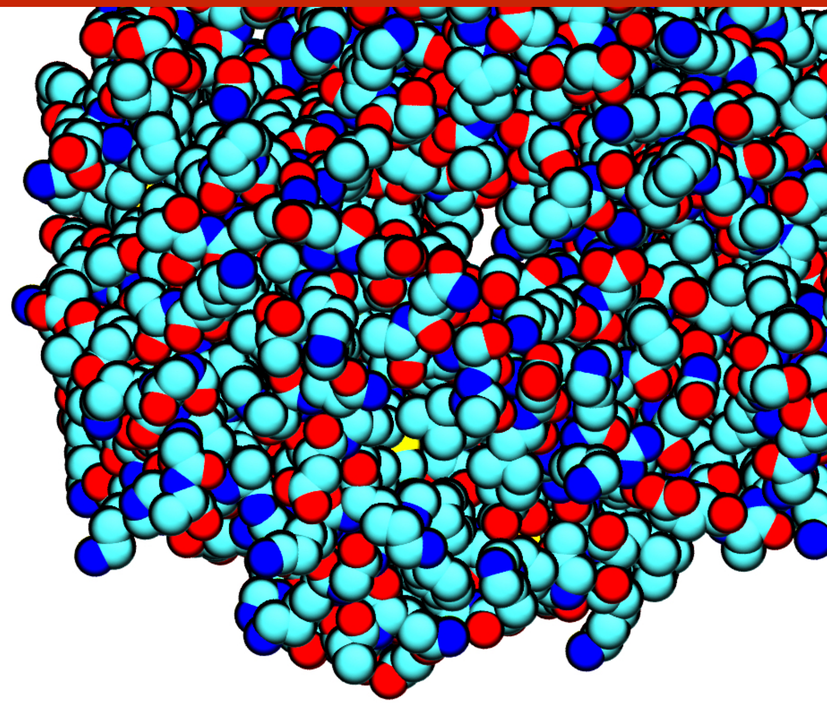
Simplify "just right"
to understand
without losing information





Simplify to understand

DATA != INFORMATION



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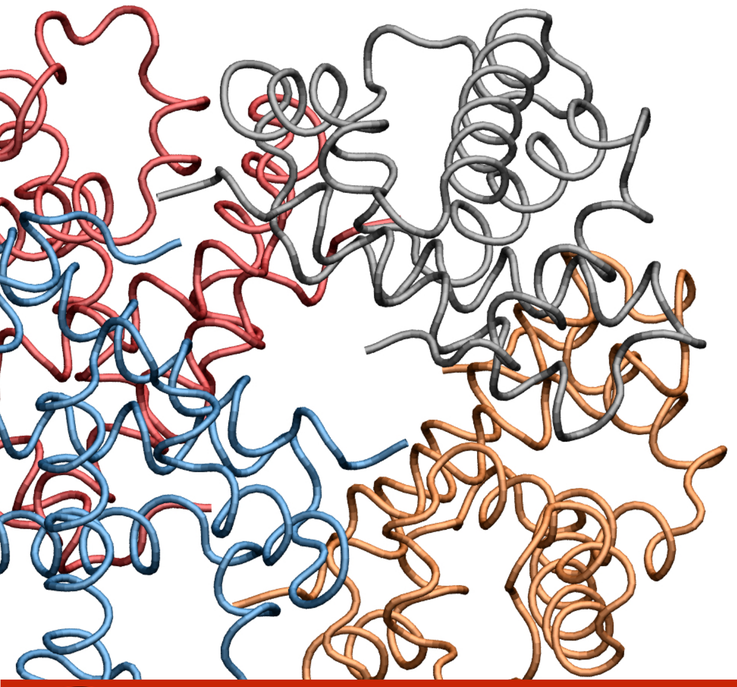

Dimensionality reduction:
in terms of what variables?

Simplify to understand

```
ATOM   1153  CD   GLN X 408     110.020  92.423  42.297  0.00  0.00
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ATOM   1163  HA   GLN X 409     115.146  96.965  41.356  0.00  0.00
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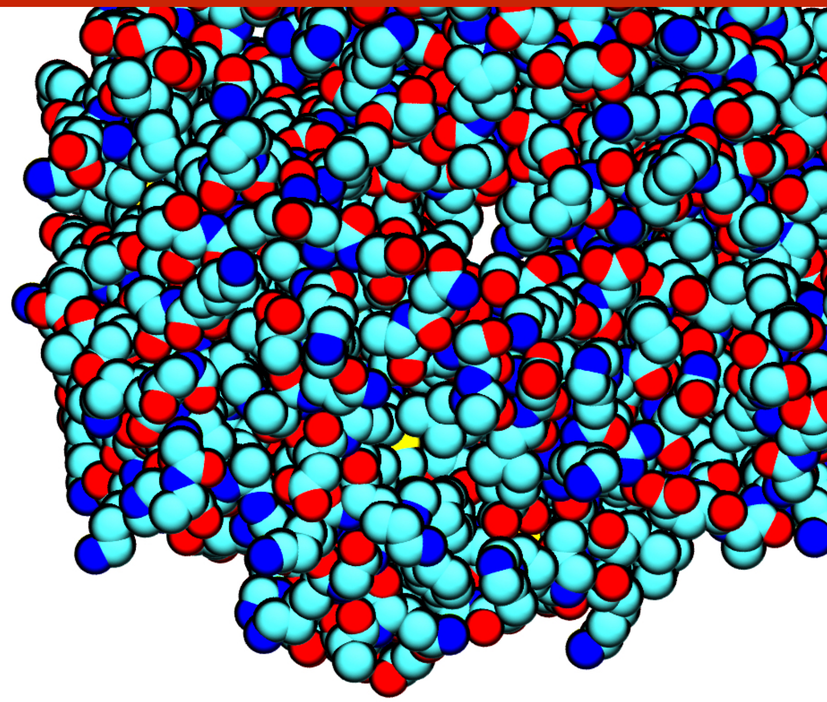
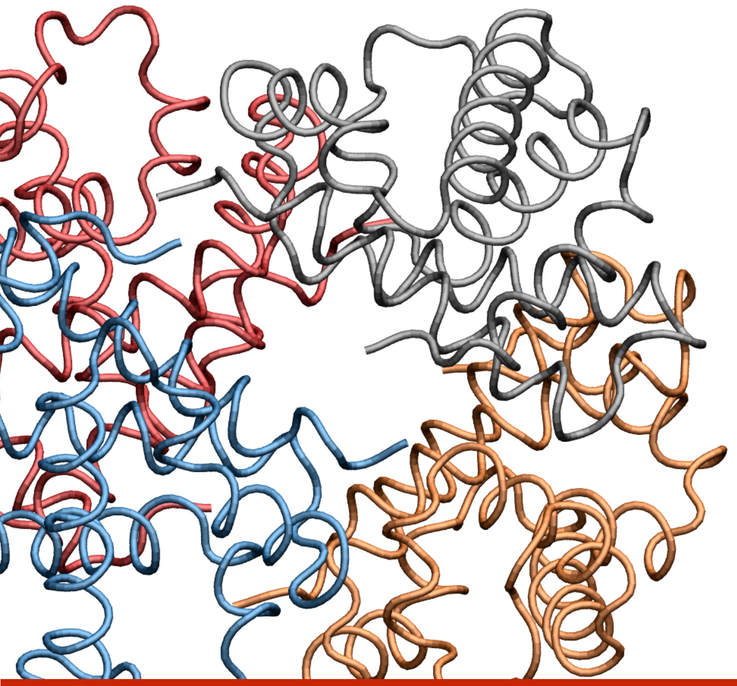
ATOM   1165  HB1  GLN X 409     115.314  97.840  43.844  0.00  0.00
ATOM   1166  HB2  GLN X 409     113.900  96.872  44.111  0.00  0.00
```





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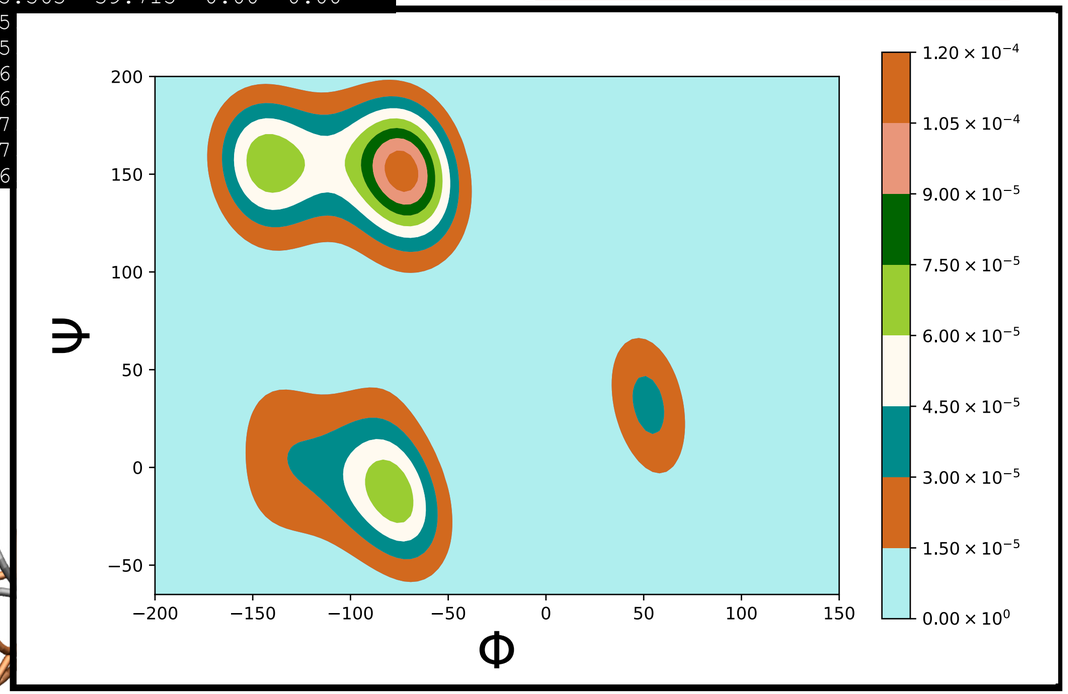
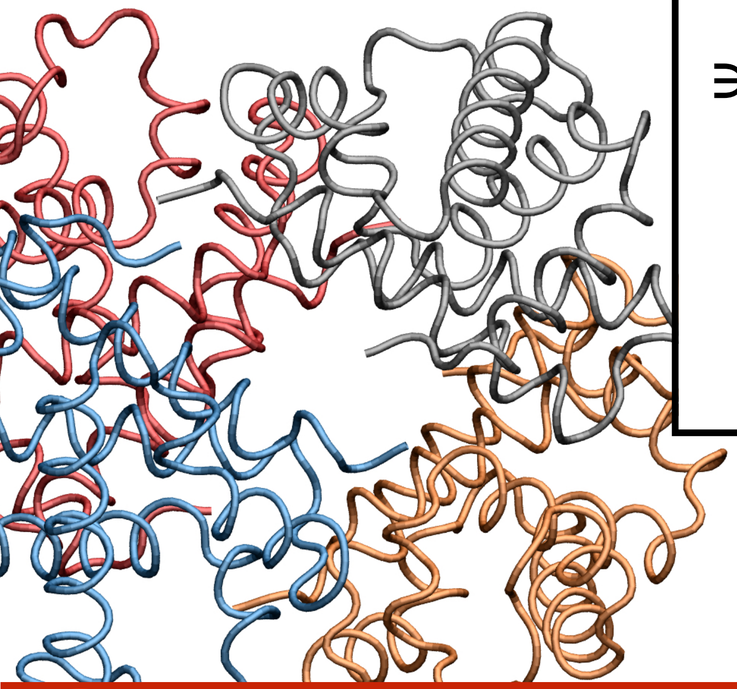
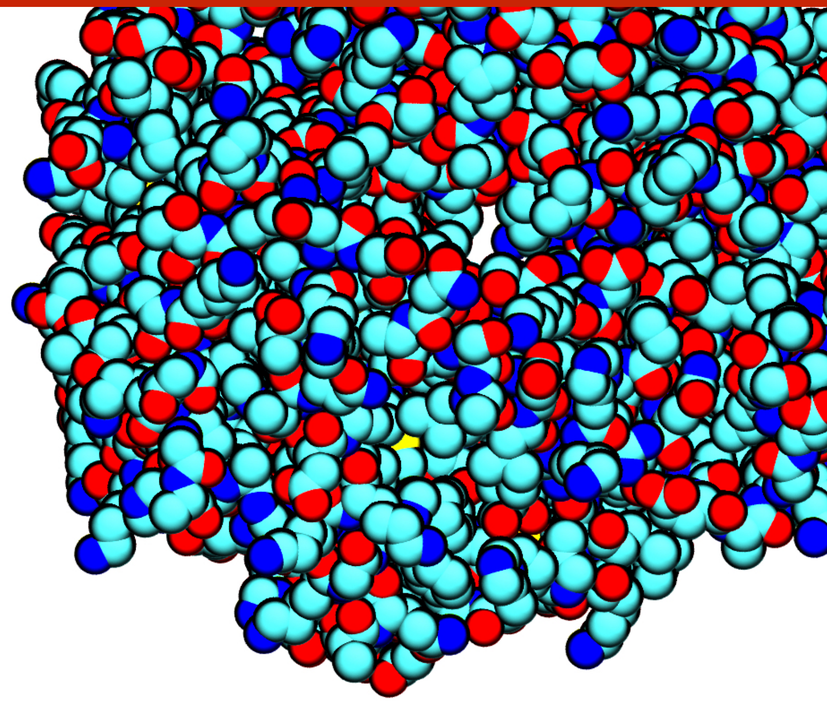
```

Collective variables







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ATOM   1165  HB1  GLN X 409     115.314  97
ATOM   1166  HB2  GLN X 409     113.900  96
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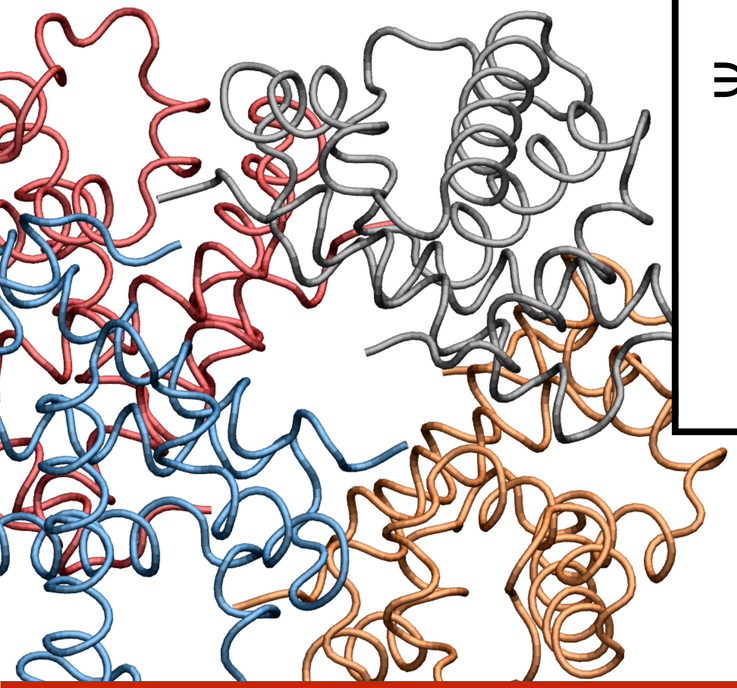
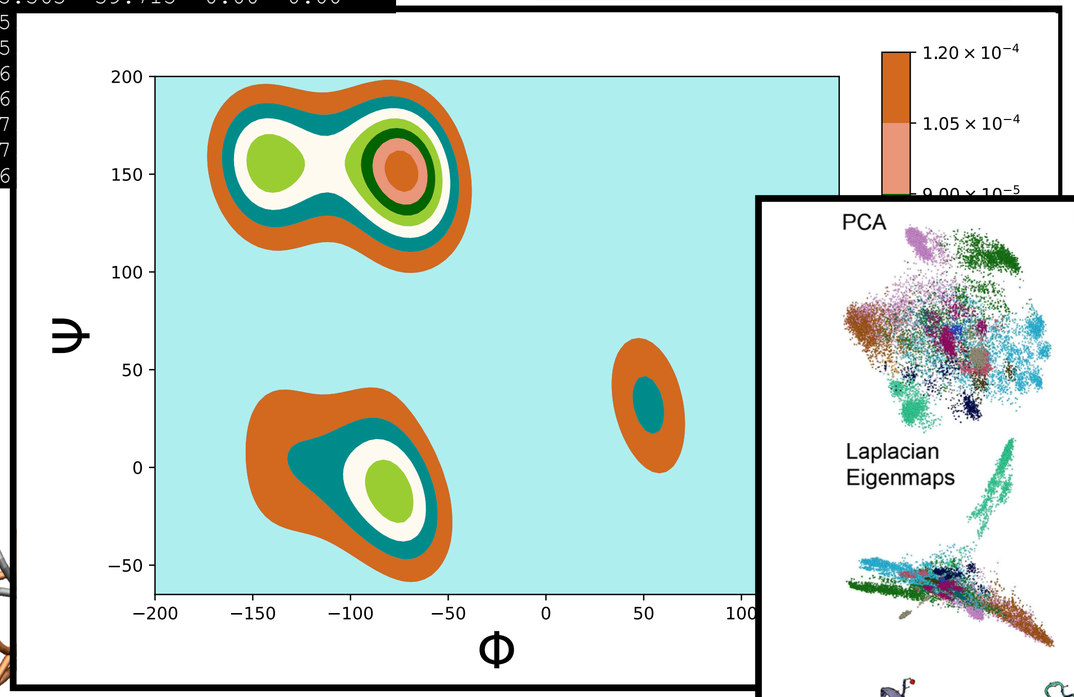
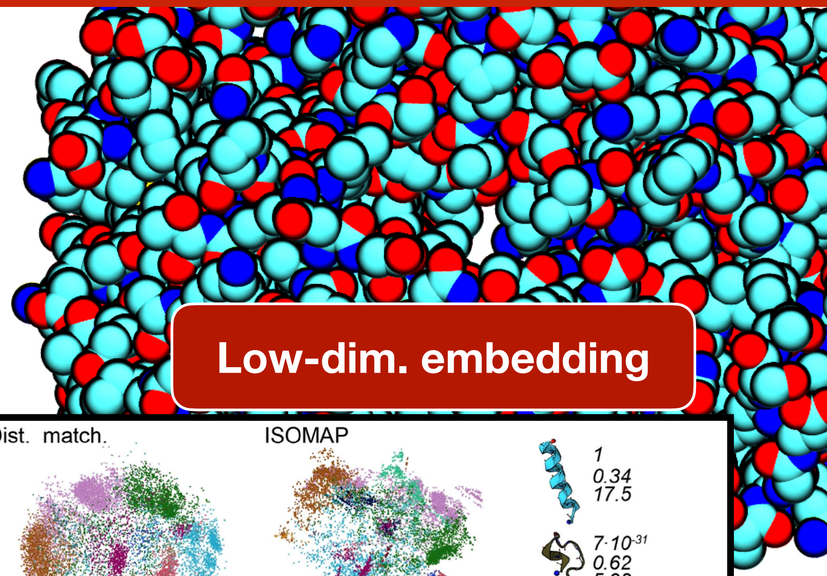
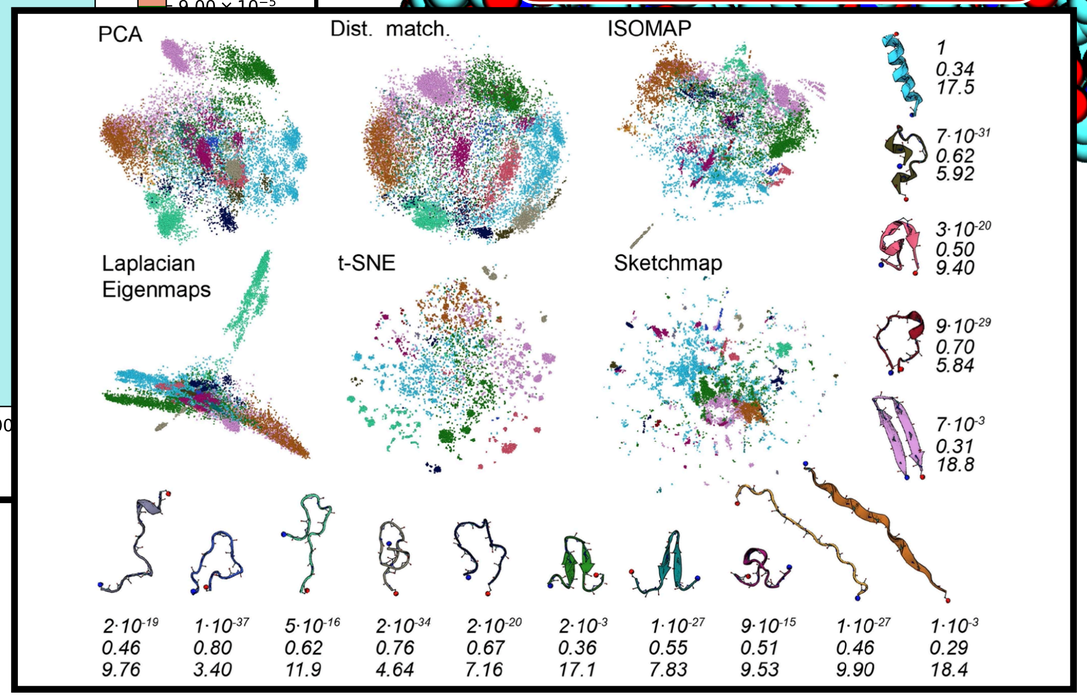
Collective variables







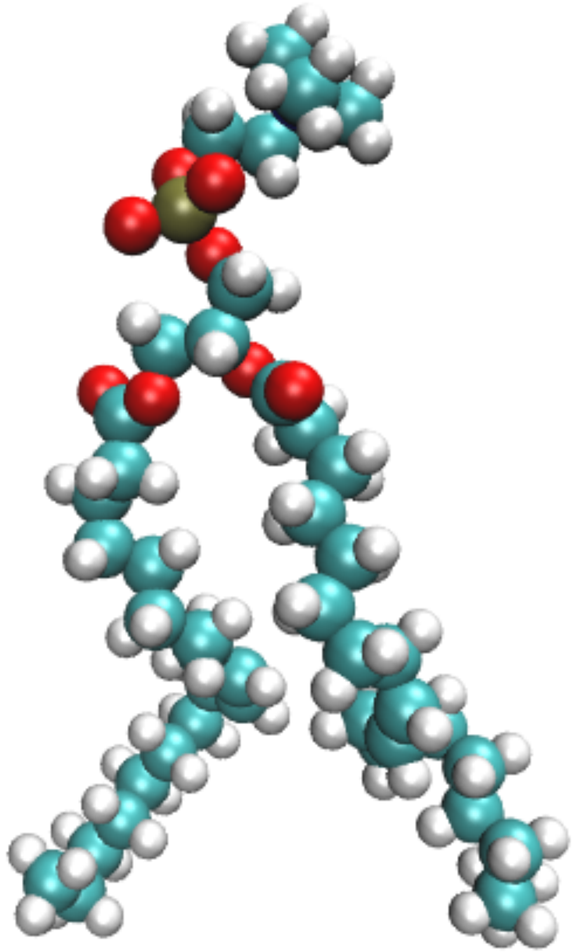
Low-dim. embedding



Tribello, Gasparotto, Front. Mol. Biosci. 2019

Coarse-graining (CG)

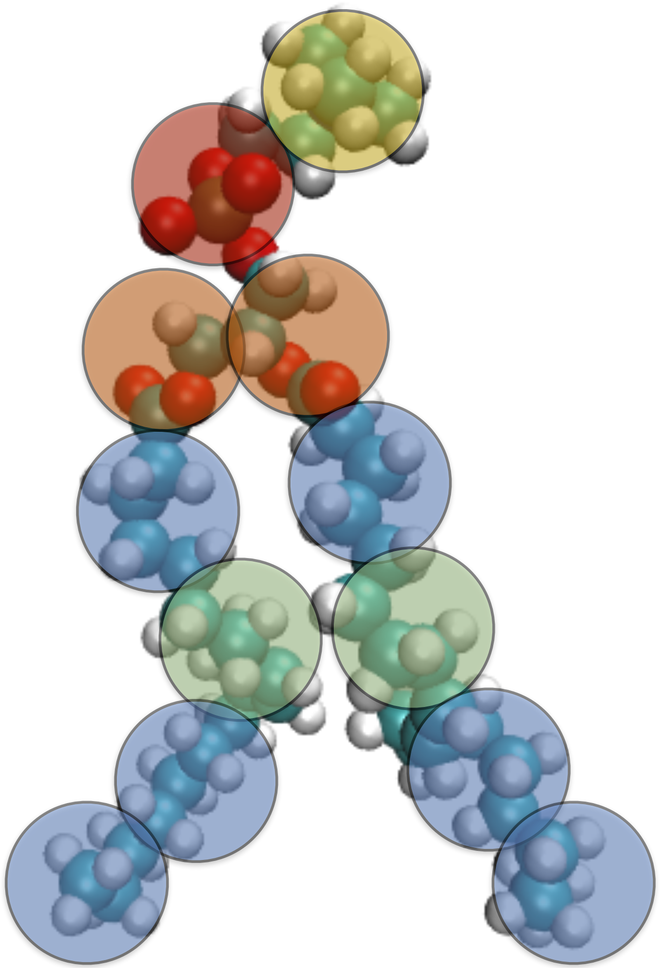
AA representation



Rudzinski, Noid, J. Chem. Phys. 2011

Coarse-graining (CG)

CG representation

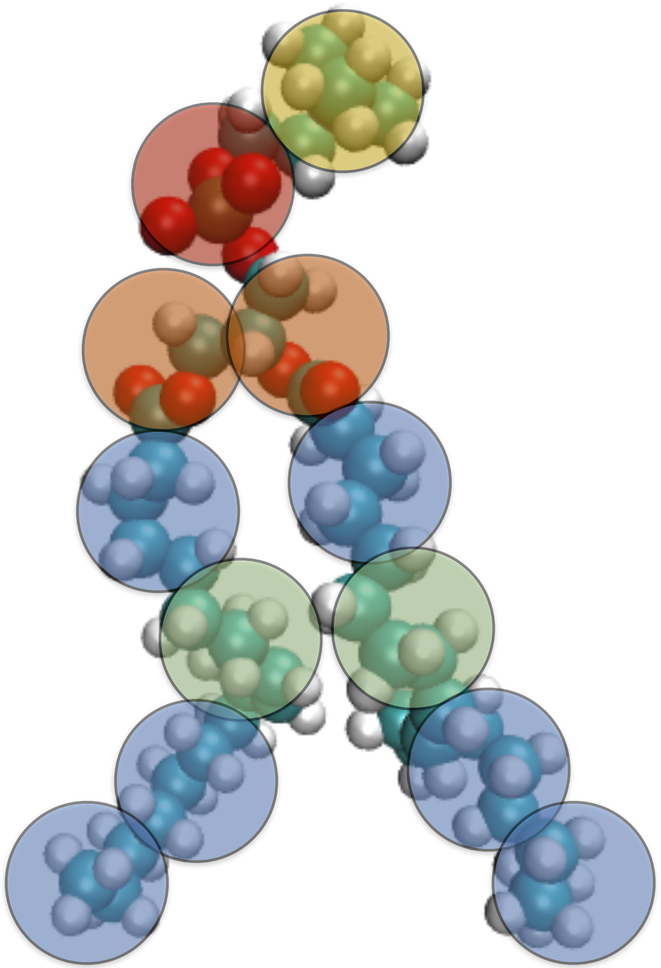


Describe the system in terms of a **reduced** number of particles: **CG filter**

Rudzinski, Noid, J. Chem. Phys. 2011

Coarse-graining (CG)

CG representation



Describe the system in terms of a **reduced** number of particles: **CG filter**

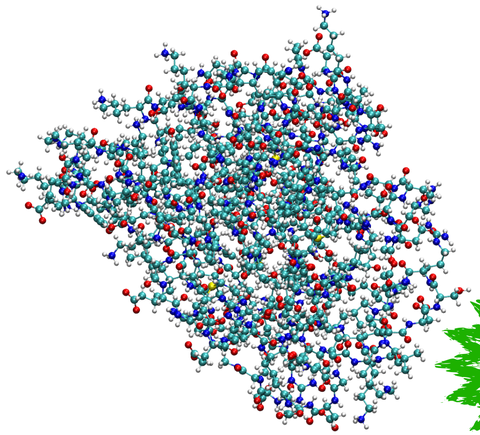
Degree of detail employed can be **modulated**

Intuitive interpretation of the outcome

Rudzinski, Noid, J. Chem. Phys. 2011

CG filters

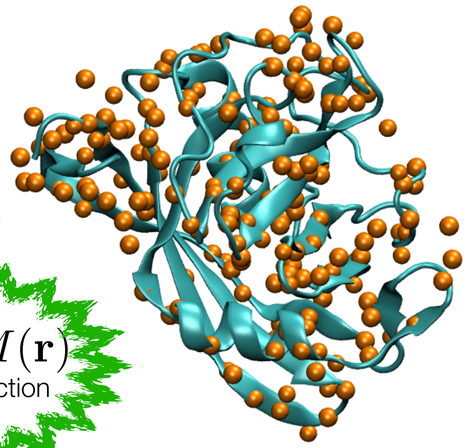
High-resolution model



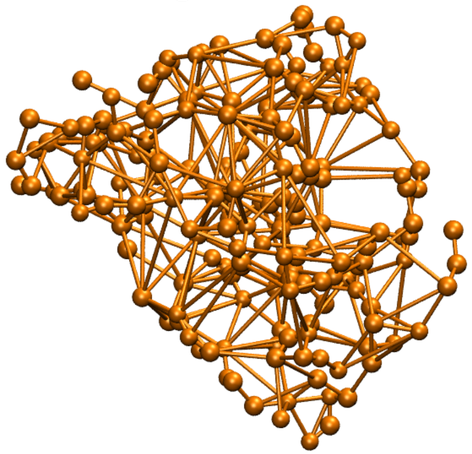
$$\mathbf{R}_I = M(\mathbf{r})$$

Mapping function

Choice of the sites

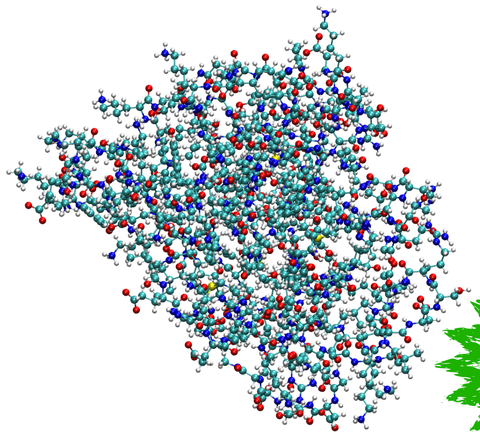


Coarse-grained model

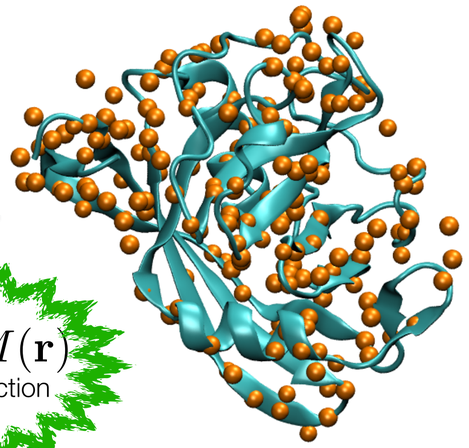


CG filters

High-resolution model



Choice of the sites



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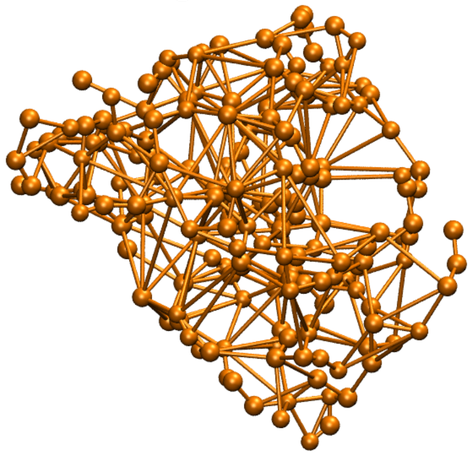
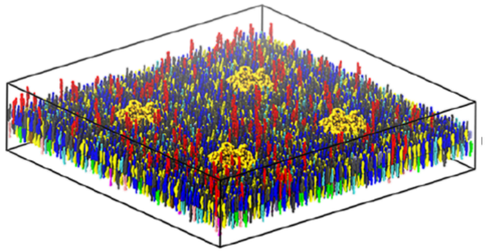
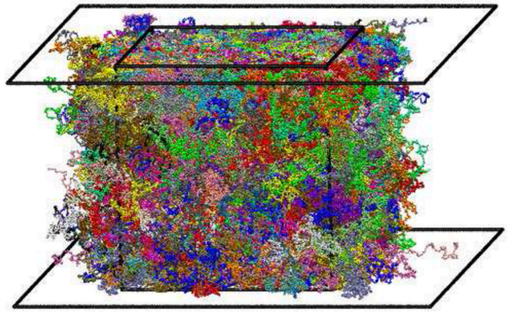
Mapping function

Coarse-grained model

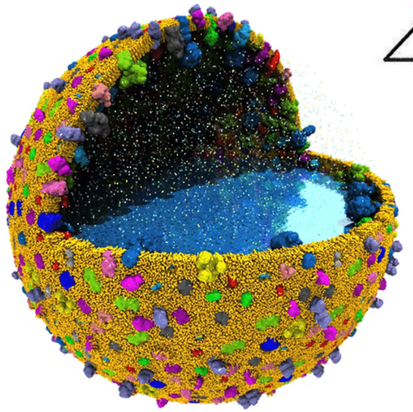




Corradi *et al*., ACS Cent. Sci. 2018

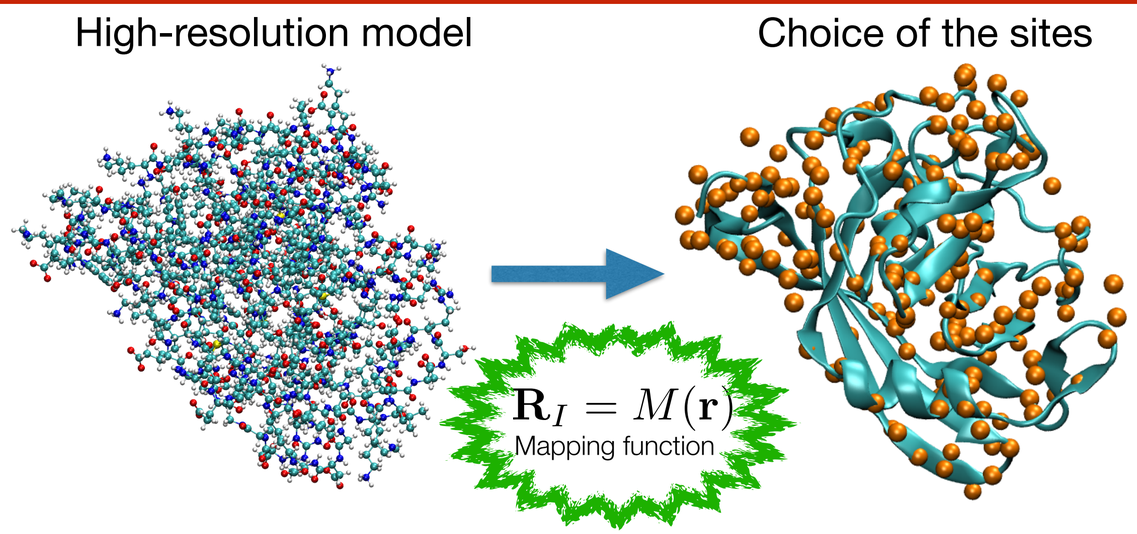


Hsu et *al.,* J. Chem. Phys. *2020*



Vermaas, *et al*., J. Chem. Inf. Model. 2022

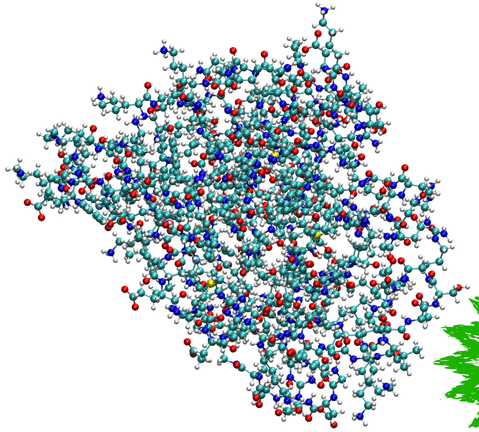
CG filters



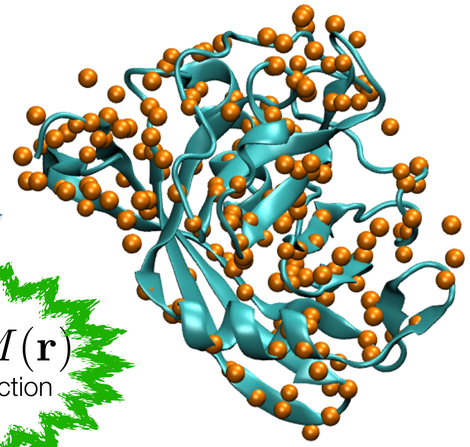
Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

CG filters

High-resolution model

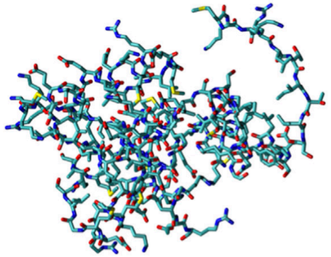


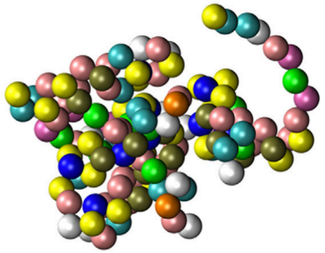
Choice of the sites



$$\mathbf{R}_I = M(\mathbf{r})$$

Mapping function



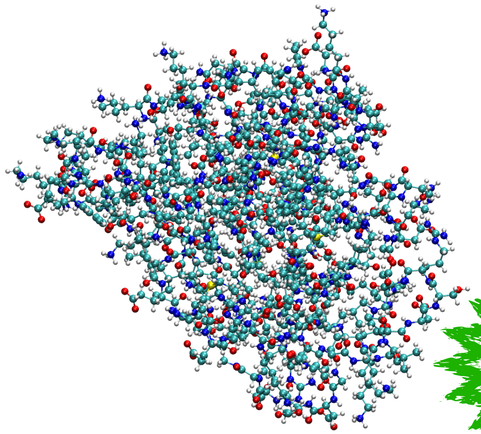


Observe the system with a pair of CG glasses: **information loss**

Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

CG filters

High-resolution model



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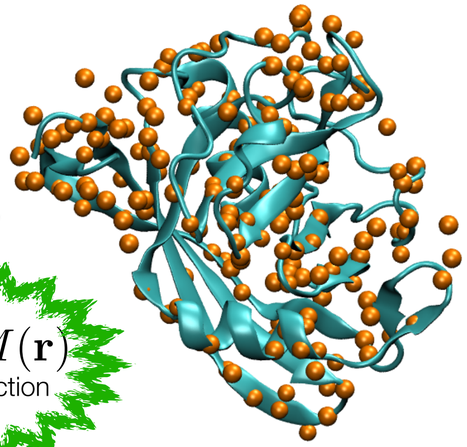

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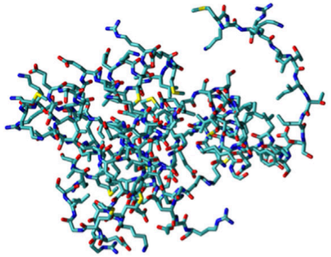
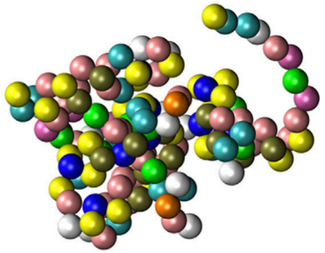




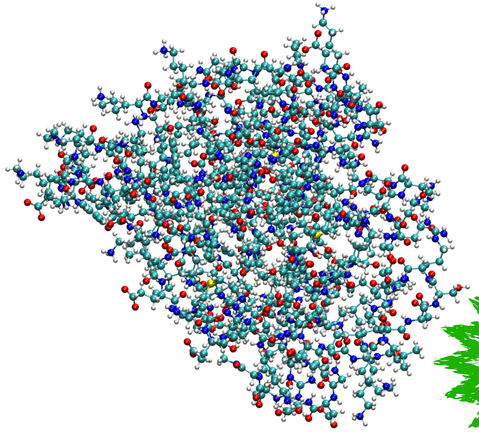
Observe the system with a pair of CG glasses: **information loss**

Optimize the glasses to extract relevant information from the data

Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

CG filters

High-resolution model



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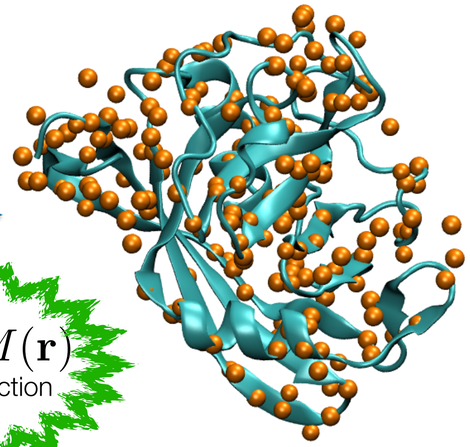

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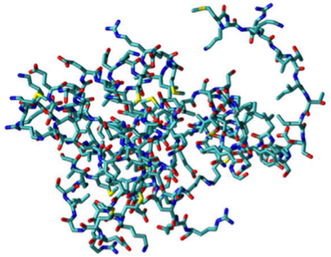
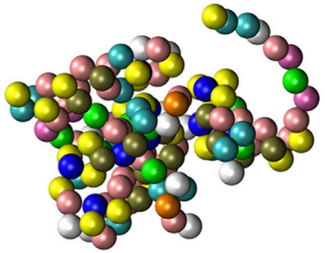
Mapping function

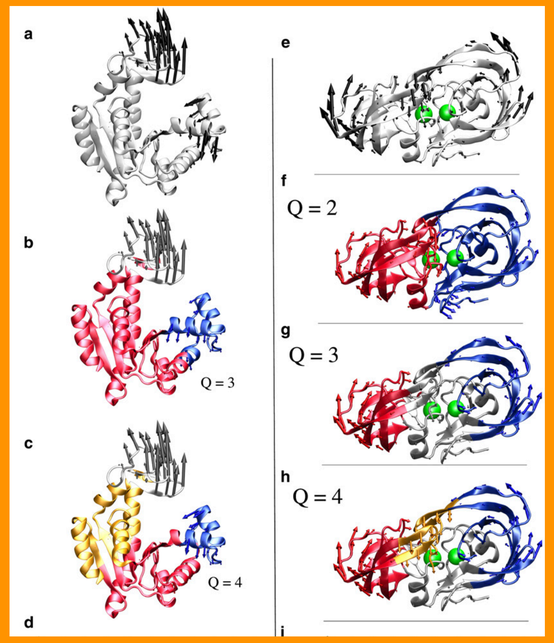




Observe the system with a pair of CG glasses: **information loss**

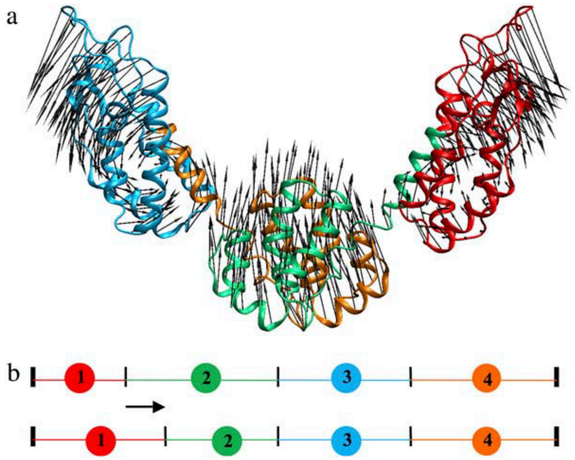
Optimize the glasses to extract relevant information from the data

Coarse-grained filters to **understand** a property or behaviour



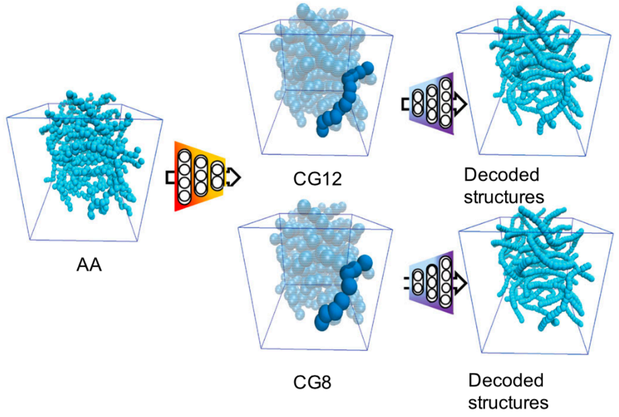
Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

CG filters

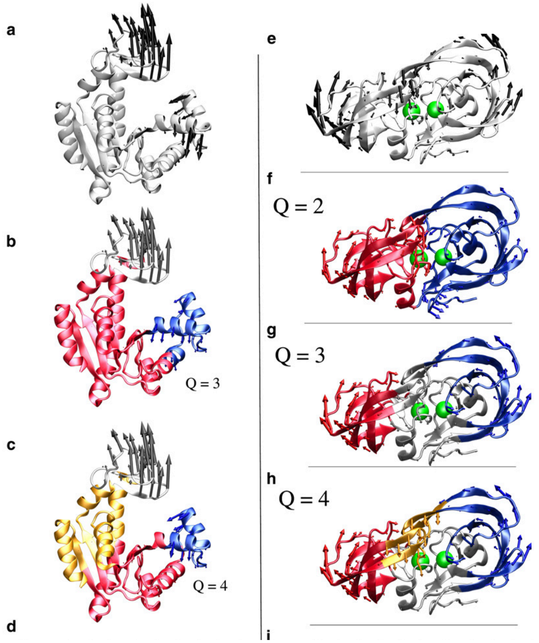


$$\chi^2 = \frac{1}{3N}\sum_{I=1}^{N}\frac{1}{n_t}\sum_{t=1}^{n_t}\left(\sum_{i\in I}\sum_{j\geq i\in I}|\Delta\mathbf{r}_i^{ED}(t)-\Delta\mathbf{r}_j^{ED}(t)|^2\right)$$

Zhang, Lu, Noid, Krishna, Pfaendtner, Voth
BJ 2008

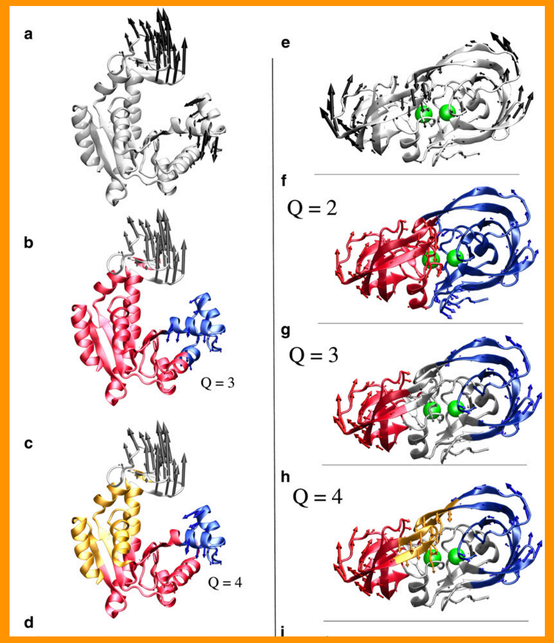


Wang, Gomez-Bombarelli
NPJ Comput. Mater. 2019



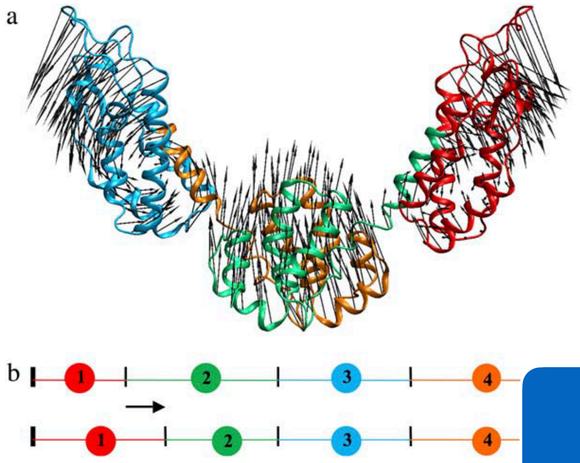
Potestio, Pontiggia, Micheletti
BJ 2009

Coarse-grained filters to
understand
a property or behaviour



Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

CG filters



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Zhang, Lu, Noid, Krishna, Pfaendtner, Vot
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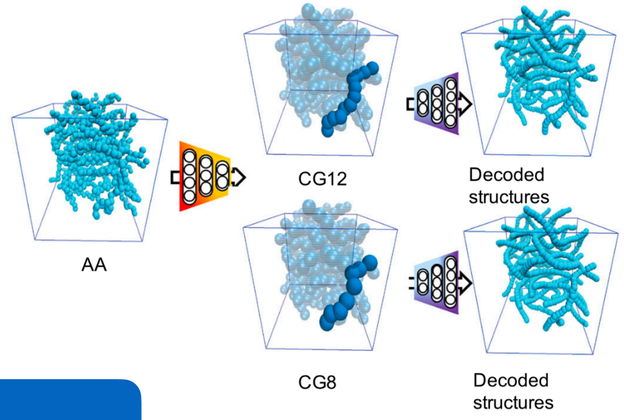
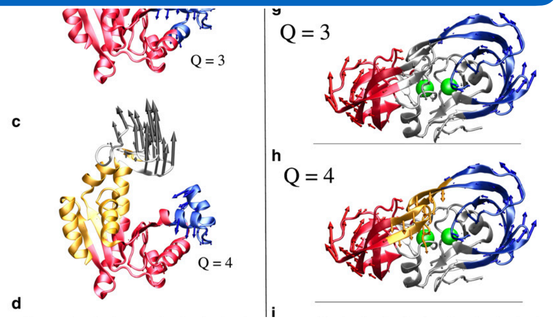


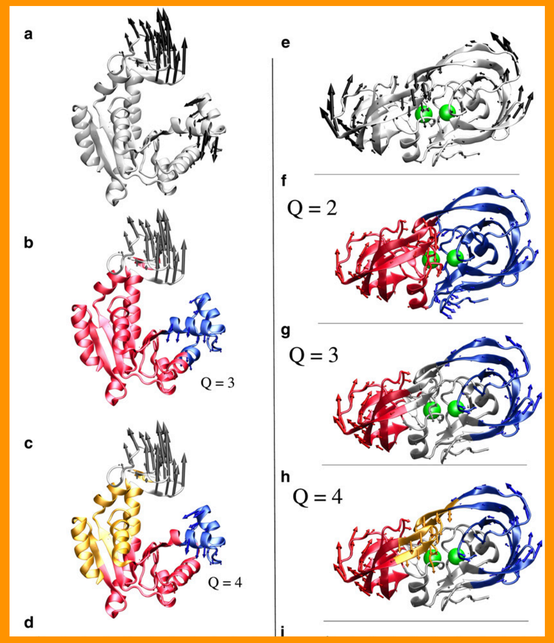
Wang, Gomez-Bombarelli
NPJ Comput. Mater. 2019

Optimize the CG filter based on quantitative criteria: In our case, **minimize the information loss arising from coarse-graining**



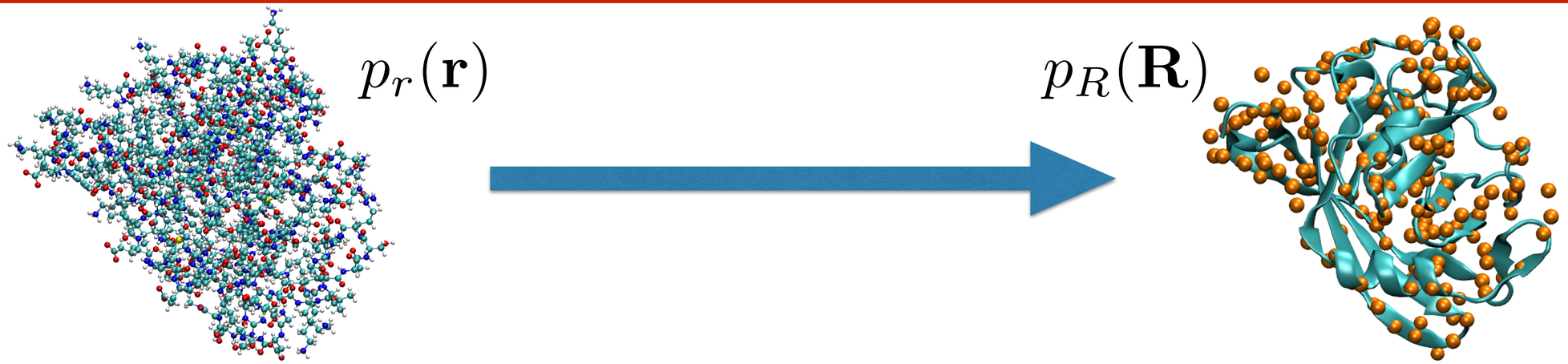
Potestio, Pontiggia, Micheletti
BJ 2009

Coarse-grained filters to **understand** a property or behaviour



Giulini, Rigoli, RM *et al.*, Front. Mol. Biosci. 2021

Information loss in coarse-graining



Rudzinski, Noid, J. Chem. Phys. 2011
Giulini, RM, Shell, Potestio, JCTC 2020

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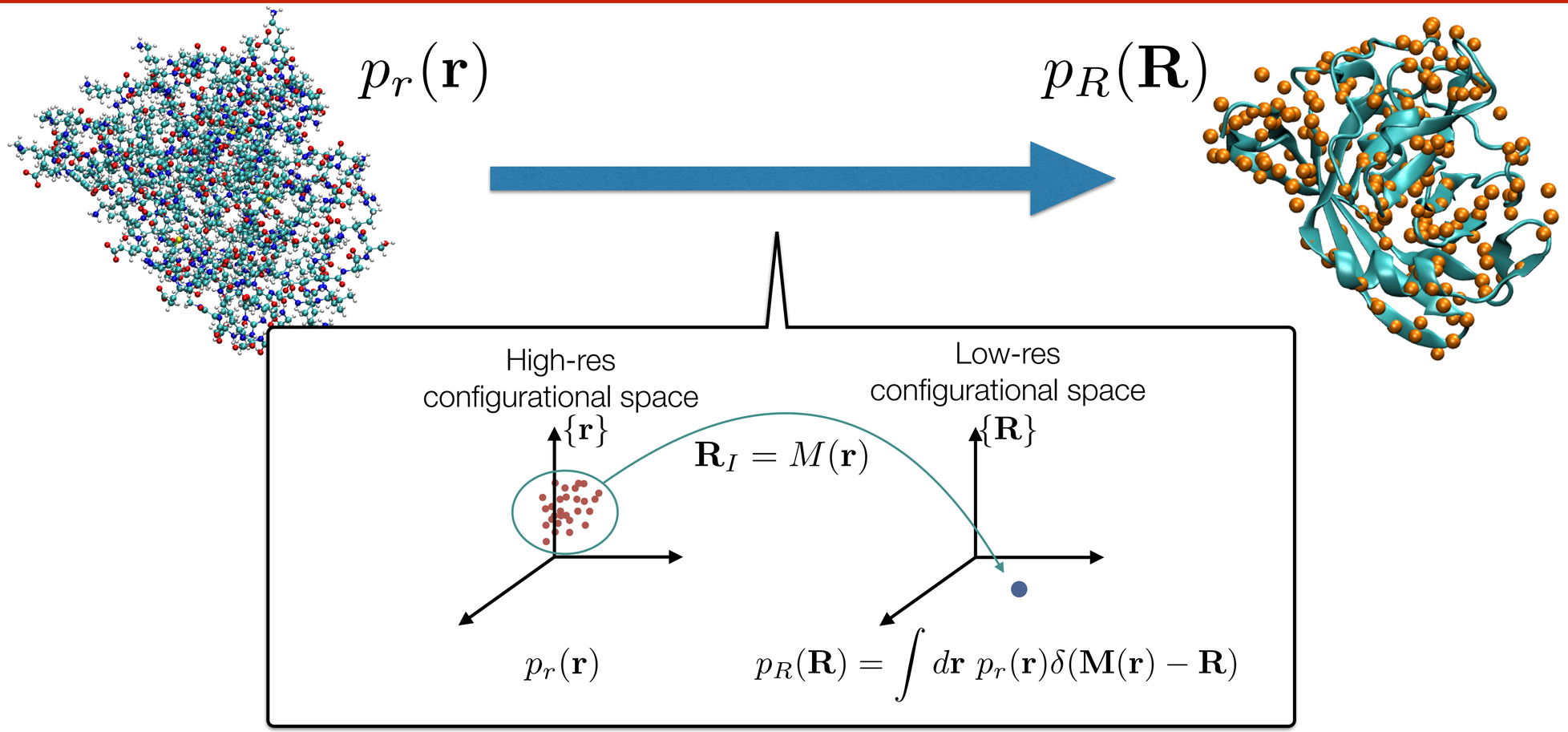

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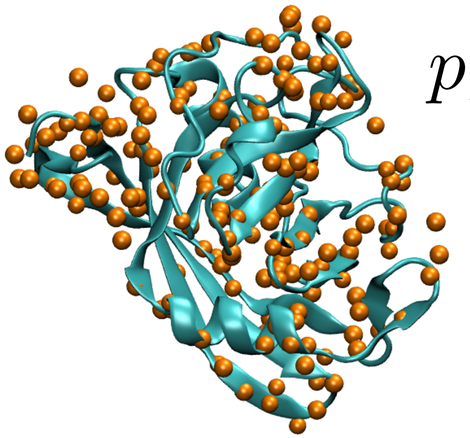
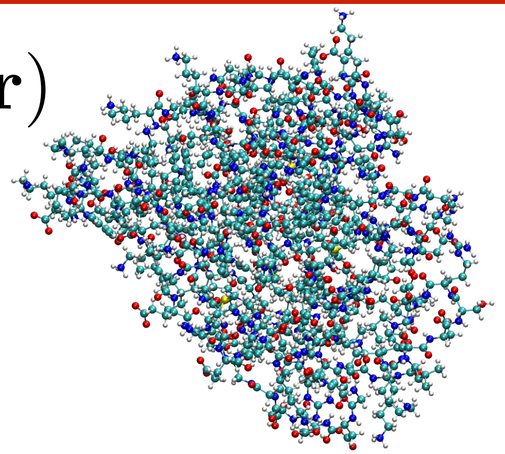


$$p_R(\mathbf{R})$$

$$\bar{p}_r(\mathbf{r}) \neq p_r(\mathbf{r})$$



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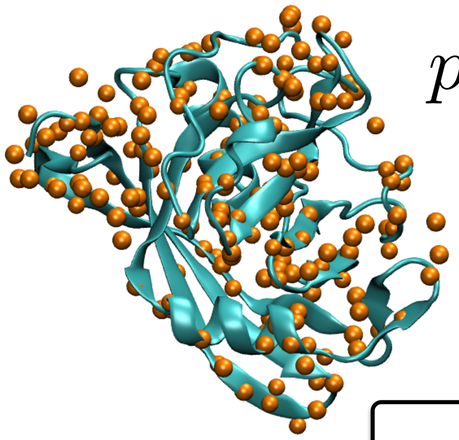

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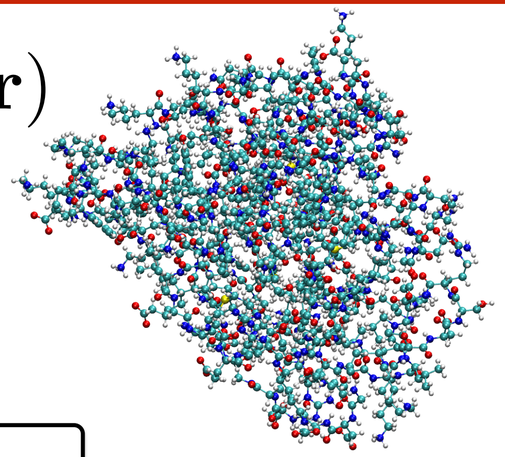

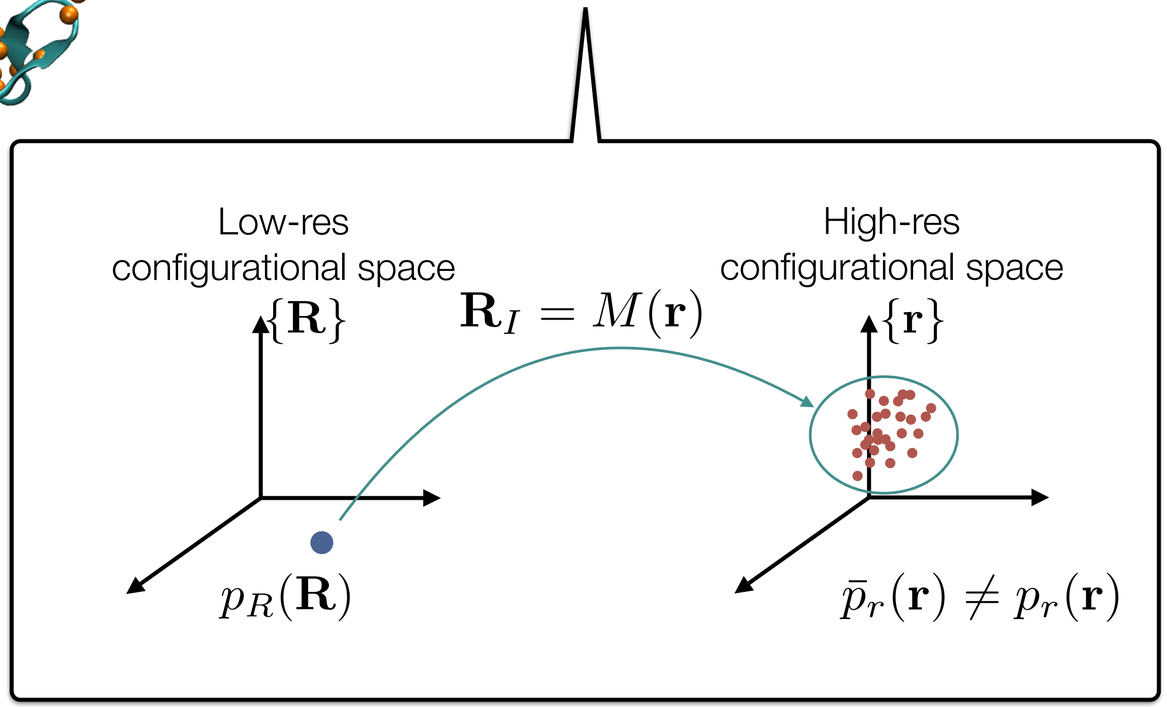

Rudzinski, Noid, J. Chem. Phys. 2011
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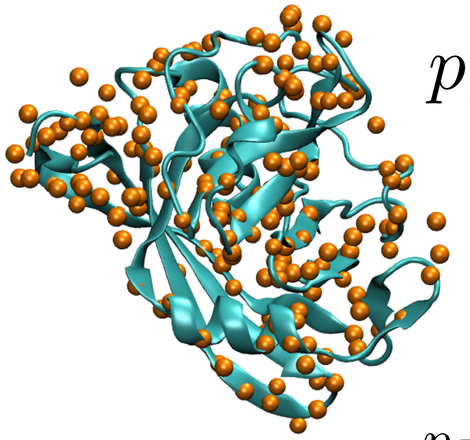

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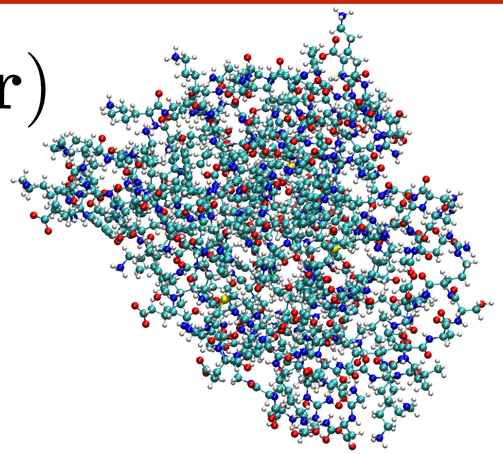
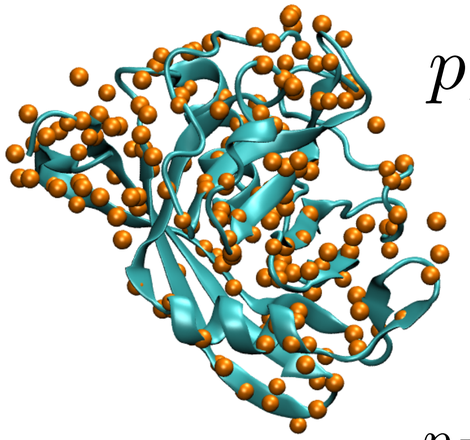


$$\bar{p}_r(\mathbf{r}) = \frac{p_R(\mathbf{M}(\mathbf{r}))}{\Sigma(\mathbf{M}(\mathbf{r}))}$$

Each microstate **r** receives the average probability of the macrostate **R** it maps onto

Rudzinski, Noid, J. Chem. Phys. 2011
Giulini, RM, Shell, Potestio, JCTC 2020

Information loss in coarse-graining



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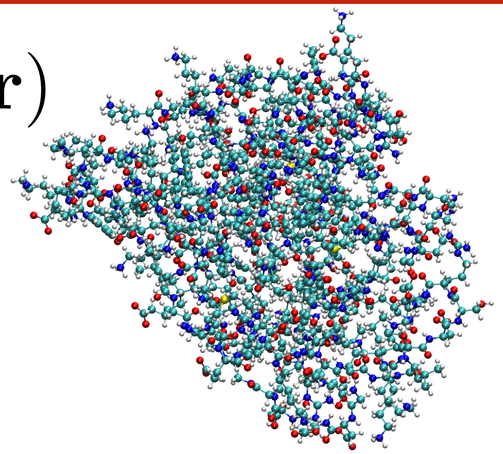

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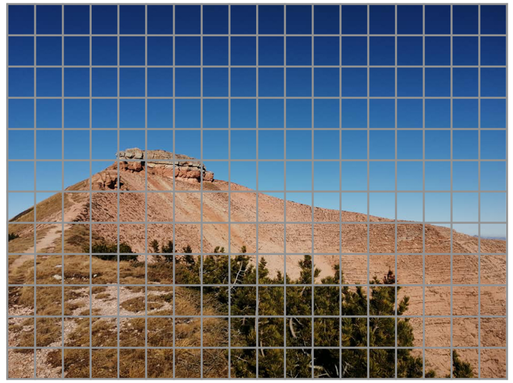
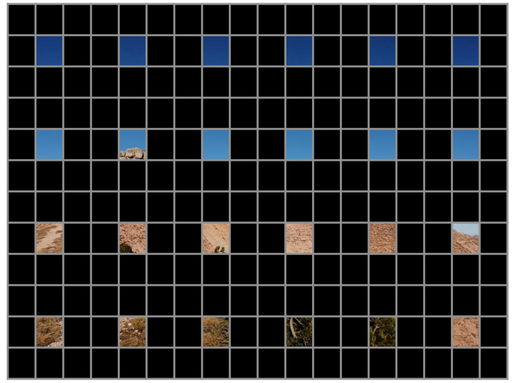
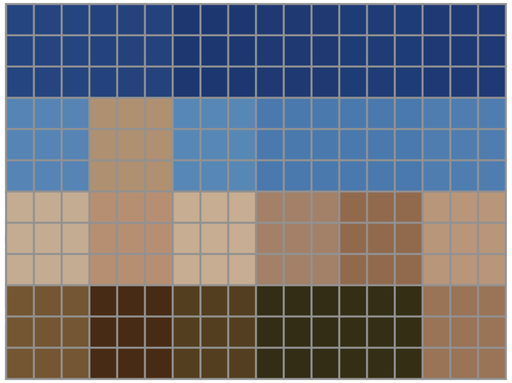


Original high resolution representation



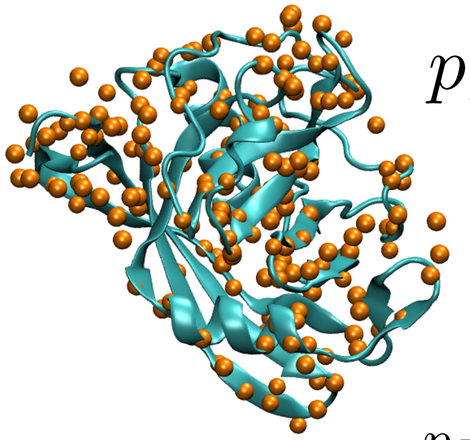
Filtering



Reconstructed high resolution representation

Rudzinski, Noid, J. Chem. Phys. 2011
Giulini, RM, Shell, Potestio, JCTC 2020

Information loss in coarse-graining



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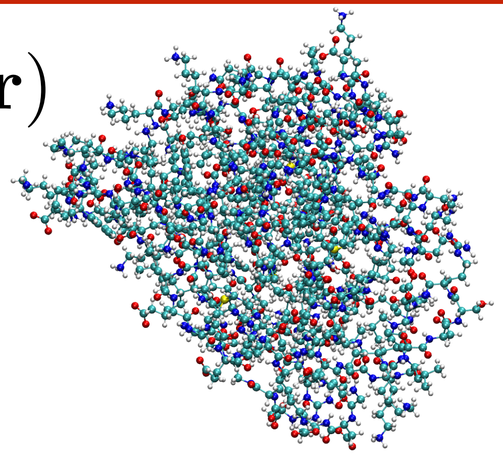

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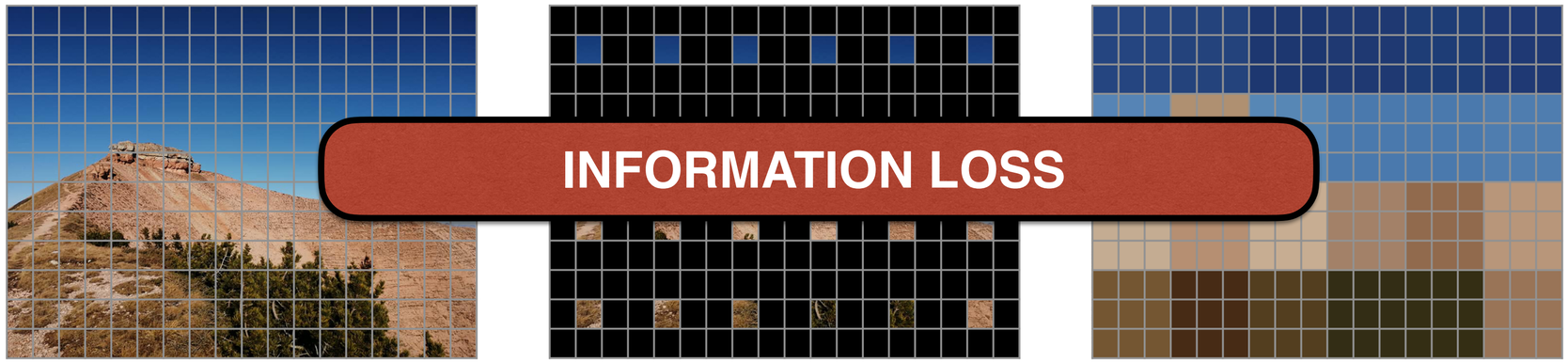

Original high resolution representation

Filtering

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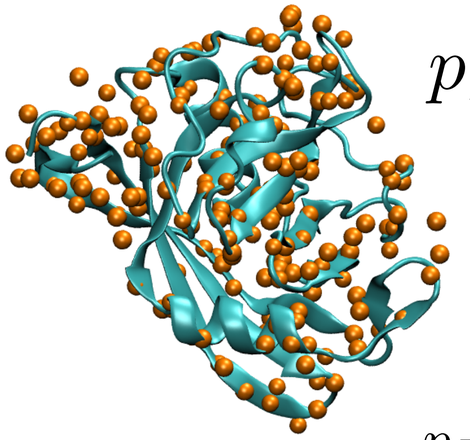
Giulini, RM, Shell, Potestio, JCTC 2020

Information loss in coarse-graining



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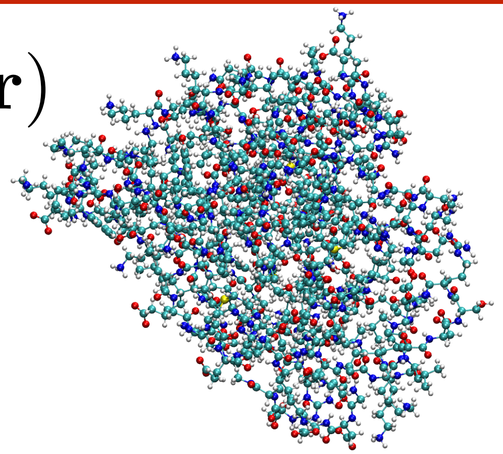

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Mapping entropy

$$S_{map} = k_B \int d\mathbf{r}\; p_r(\mathbf{r}) \ln \left[\frac{p_r(\mathbf{r})}{\bar{p}_r(\mathbf{r})} \right]$$

Quantifies the information loss arising from coarse-graining

DEPENDS ONLY ON THE CHOICE OF THE CG SITES

high resolution representation **Filtering** **high resolution representation**

Rudzinski, Noid, J. Chem. Phys. 2011
Giulini, RM, Shell, Potestio, JCTC 2020

Estimating the information loss

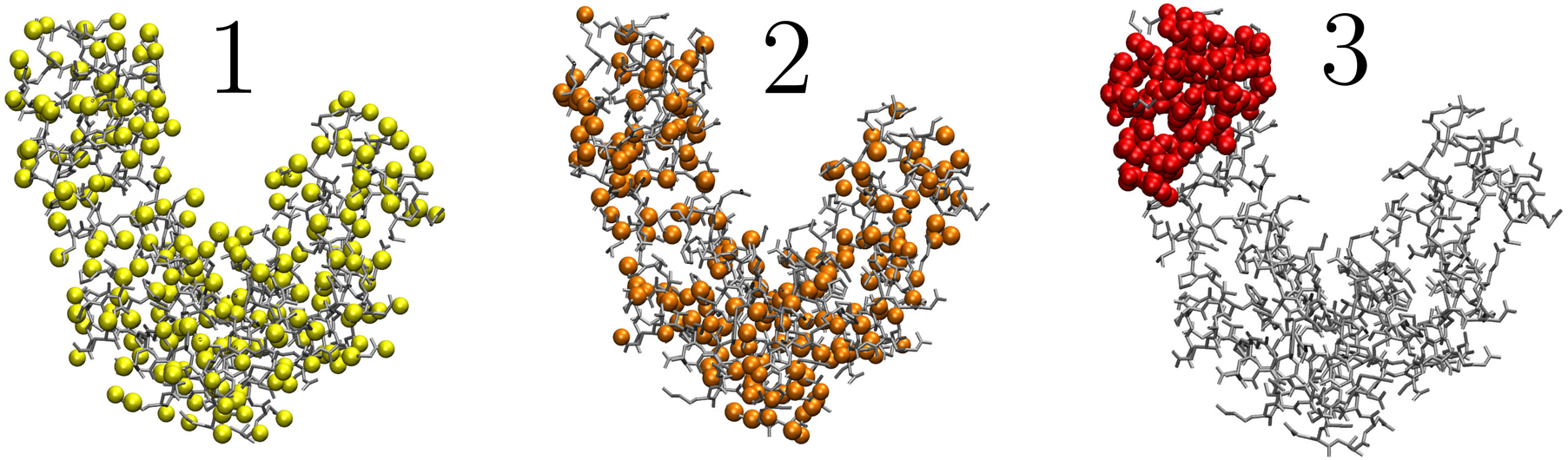
$$S_{map} \approx k_B \frac{\beta^2}{2} \int d\mathbf{R} p_R(\mathbf{R}) \langle (u - \langle u \rangle_{\beta|\mathbf{R}})^2 \rangle_{\beta|\mathbf{R}}$$

Giulini, RM, Shell, Potestio, JCTC 2020

Estimating the information loss

$$S_{map} \approx k_B \frac{\beta^2}{2} \int d\mathbf{R} p_R(\mathbf{R}) \langle (u - \langle u \rangle_{\beta|\mathbf{R}})^2 \rangle_{\beta|\mathbf{R}}$$

Calculating the mapping entropy of a CG representation



Giulini, RM, Shell, Potestio, JCTC 2020

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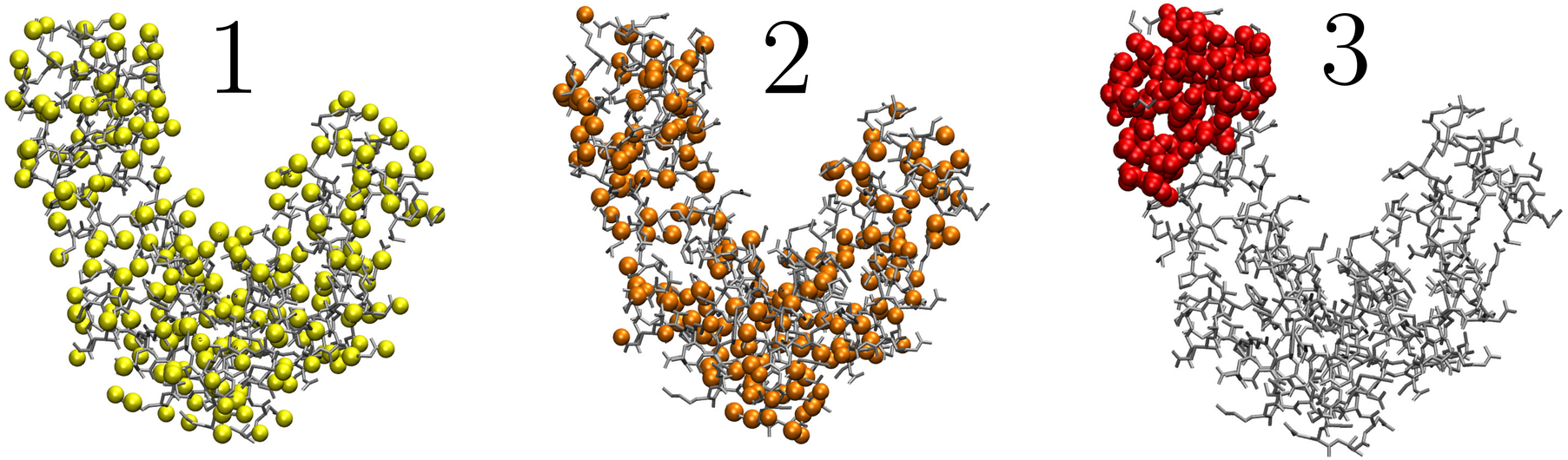


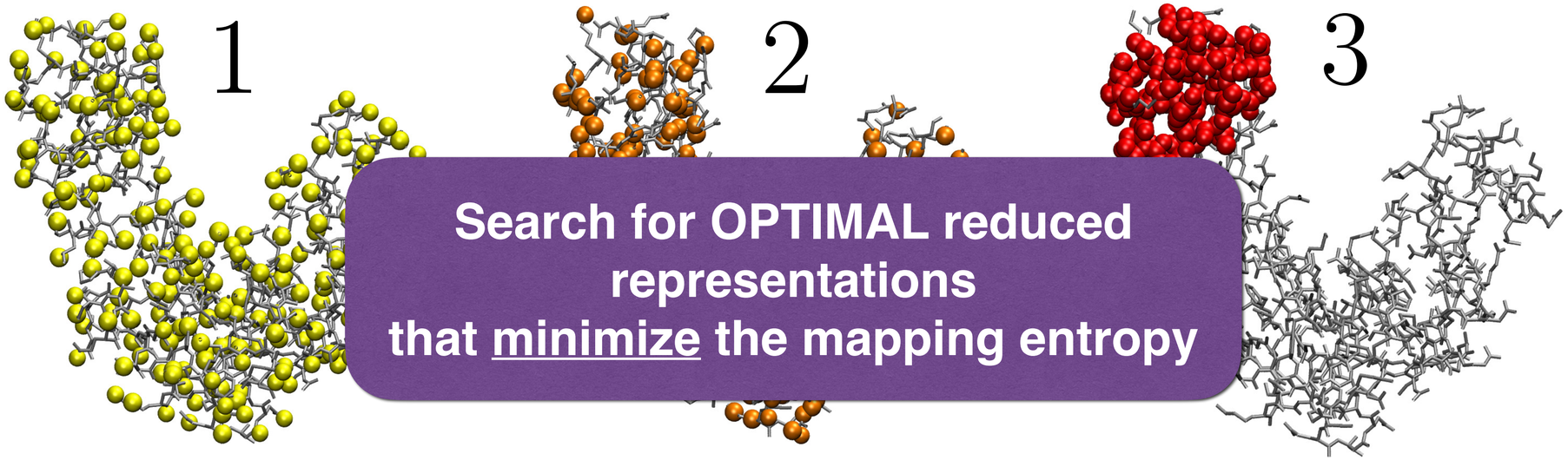
Ranking mappings according to the information they **retain: smaller S_{map}**

Giulini, RM, Shell, Potestio, JCTC 2020

Estimating the information loss

$$S_{map} \approx k_B \frac{\beta^2}{2} \int d\mathbf{R} p_R(\mathbf{R}) \langle (u - \langle u \rangle_{\beta|\mathbf{R}})^2 \rangle_{\beta|\mathbf{R}}$$

Calculating the mapping entropy of a CG representation



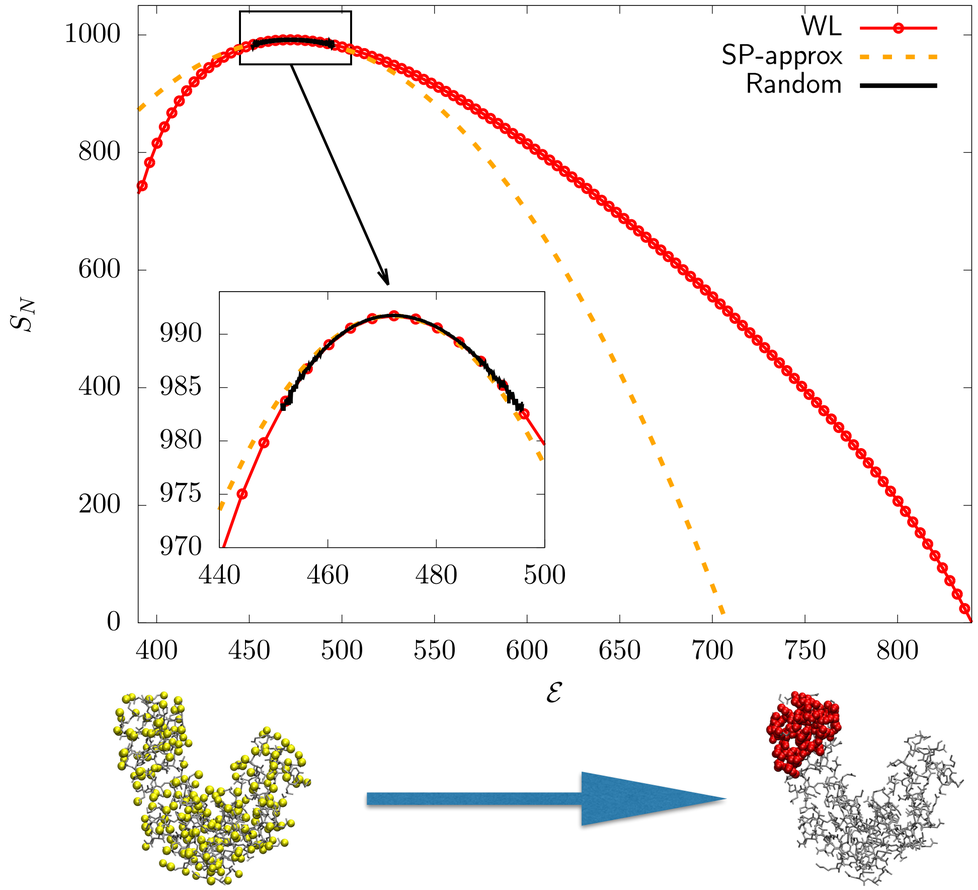
Search for OPTIMAL reduced representations that <u>minimize</u> the mapping entropy

Ranking mappings according to the information they **retain: smaller S_{map}**

Giulini, RM, Shell, Potestio, JCTC 2020

Estimating the information loss

$$\#\text{selections}(\mathcal{E}) \propto e^{S_N(\mathcal{E})}$$



RM, Giulini, Potestio, EPJB 2021

Ca

1

Ranking

ntation

3

ain: smaller S_{map}

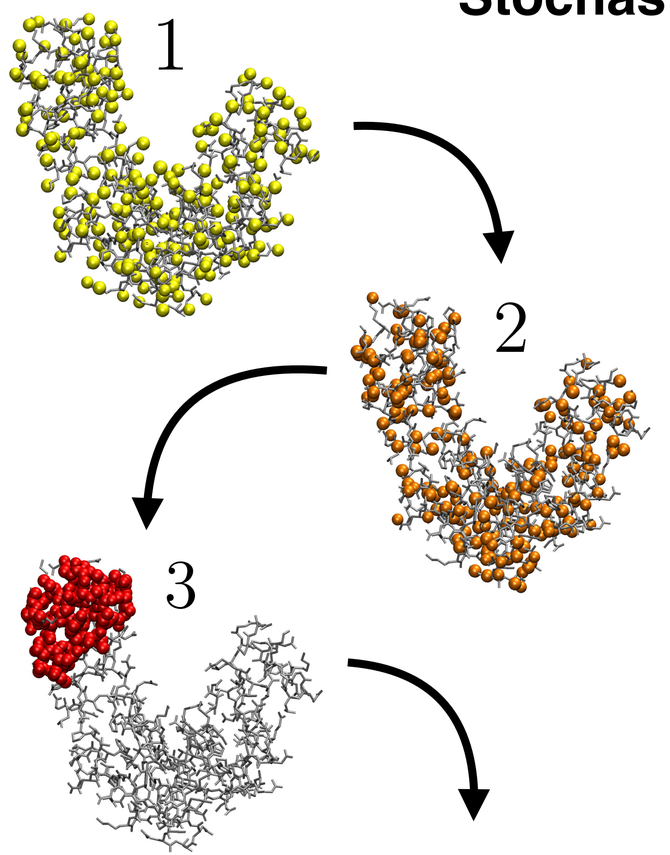
S_{map}

Giulini, RM, Shell, Potestio, JCTC 2020

Minimizing the information loss

Looking for maximally informative selections of CG sites:

Stochastic minimization of S_{map} over the mapping space



Giulini, Rigoli, RM, *et al.*, JCTC 2020
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021
RM, Giulini, Potestio, EPJB 2021

Minimizing the information loss

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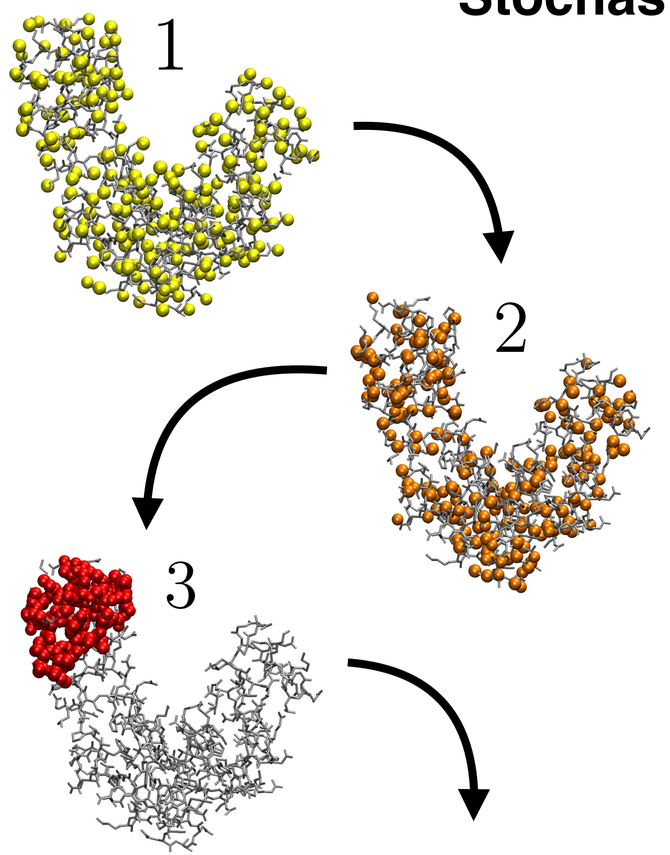
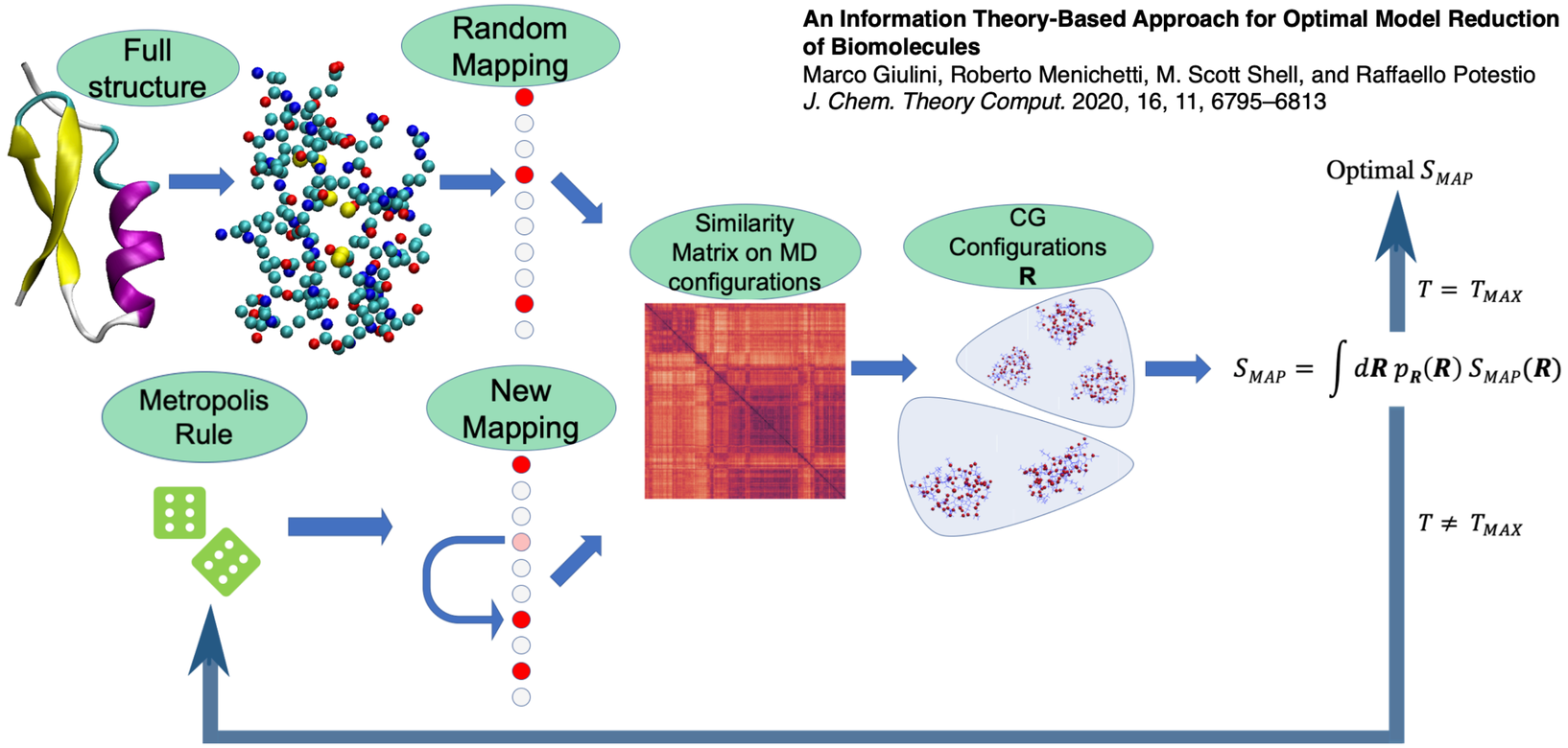
Stochastic minimization of S_{map} over the mapping space





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J. Chem. Theory Comput. 2020, 16, 11, 6795–6813

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Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021
RM, Giulini, Potestio, EPJB 2021

Minimizing the information loss

Looking for maximally informative selections of CG sites:

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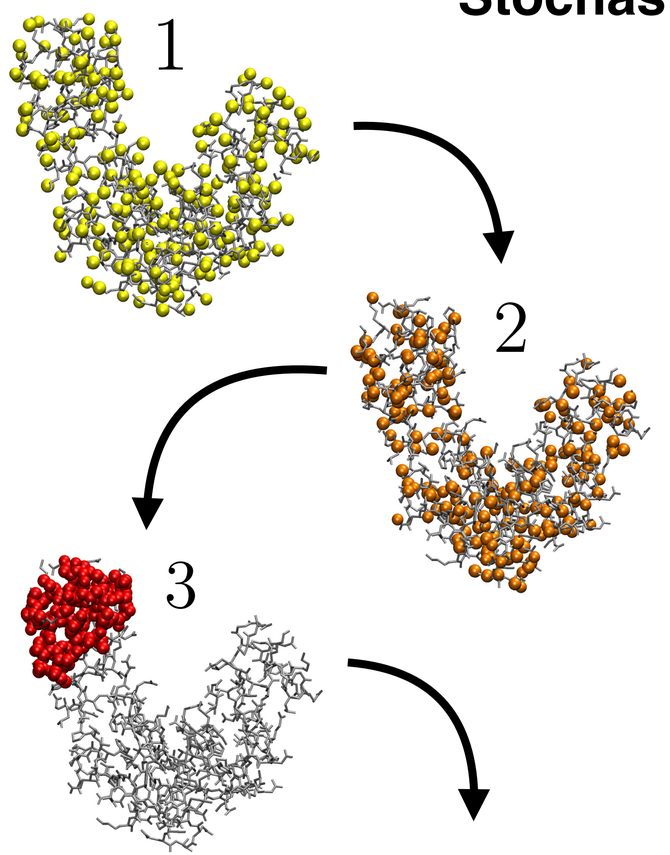

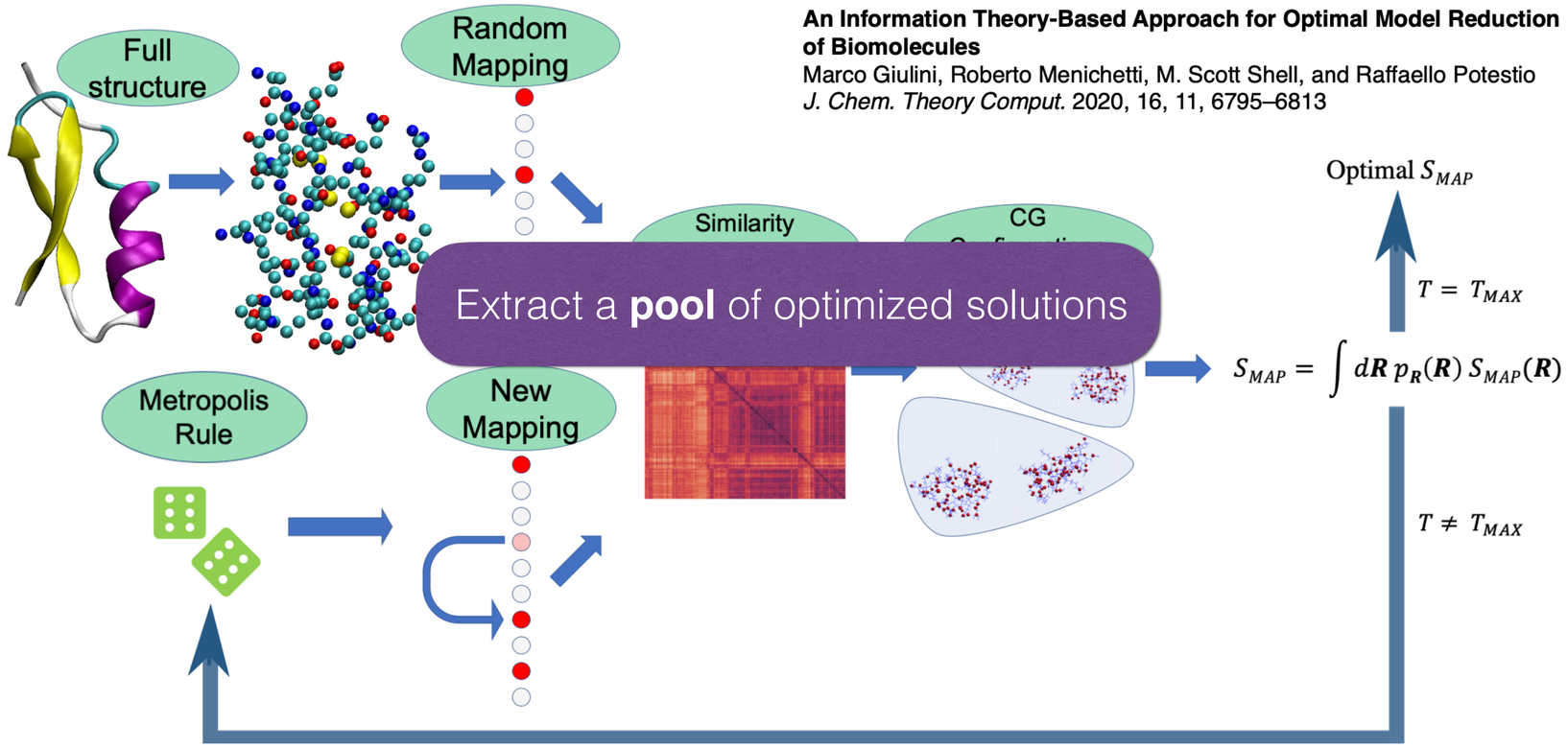

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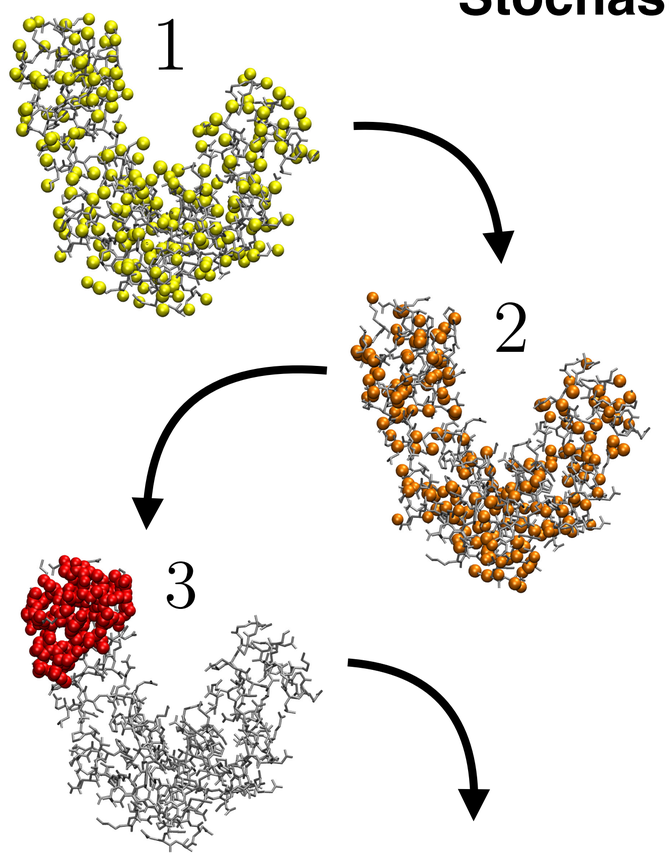

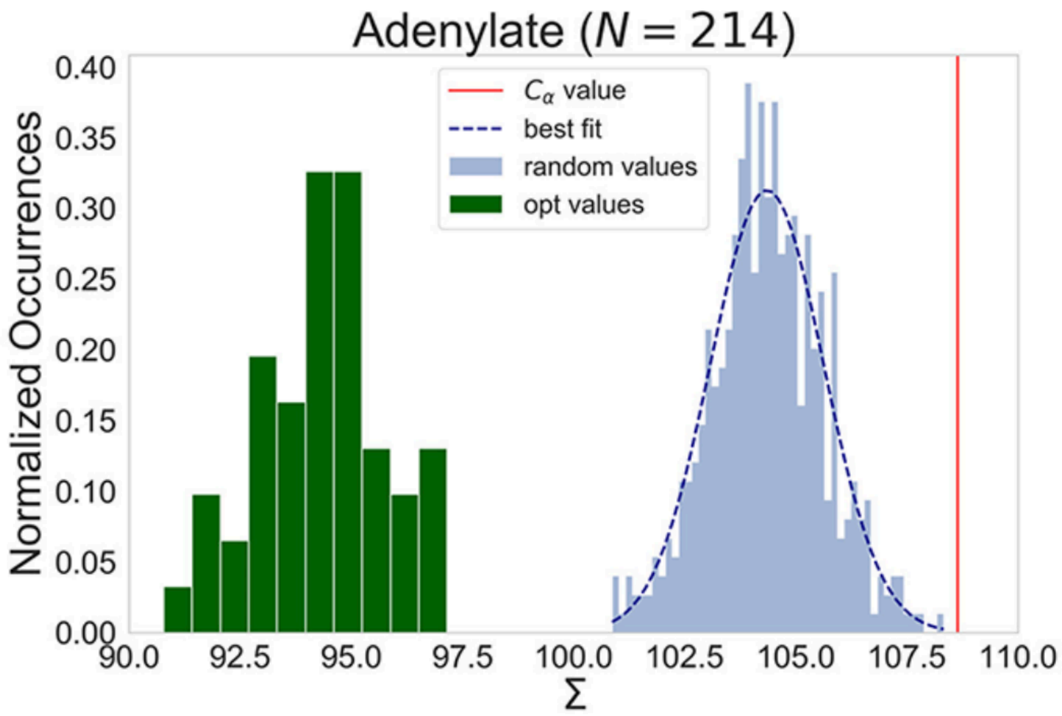

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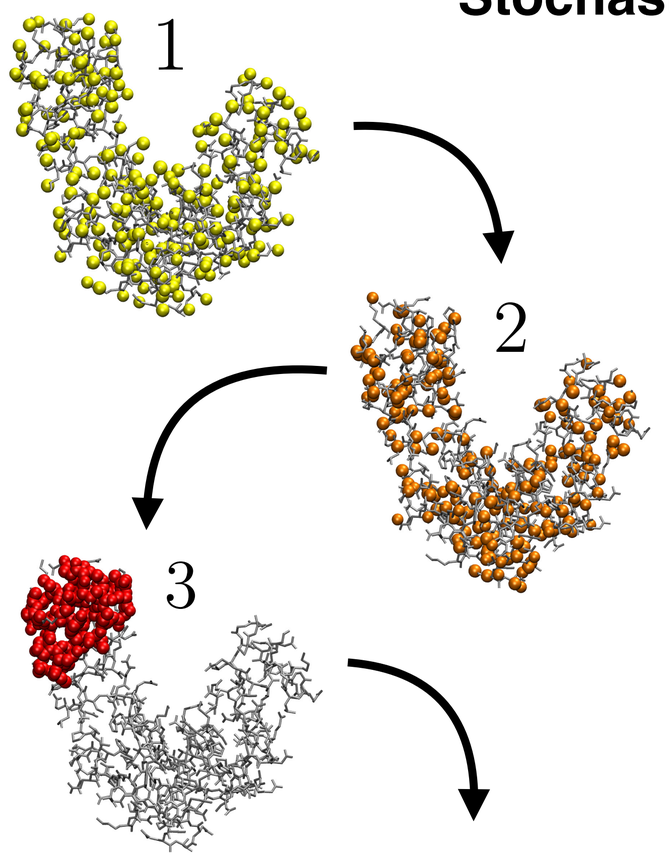

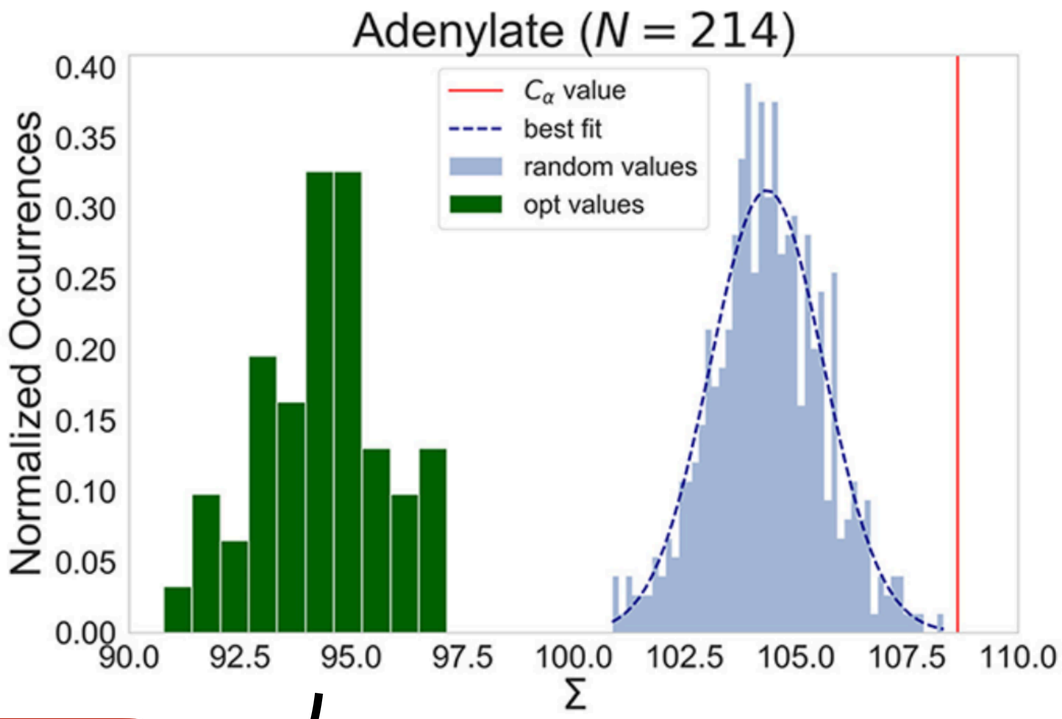

Maximally-informative CG mappings consist of a list of atoms: **statistical analysis of the pool of optimized solutions**

Giulini, Rigoli, RM, *et al.*, JCTC 2020
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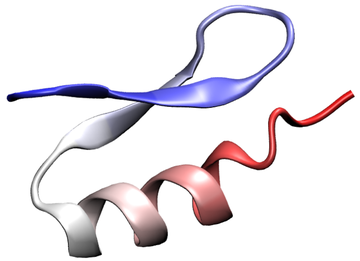
Investigating the nature of optimal mappings

Application to Tamapin



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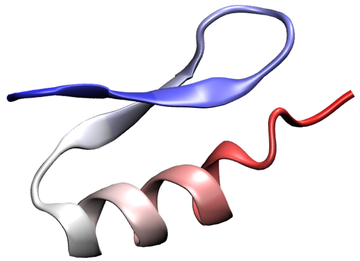

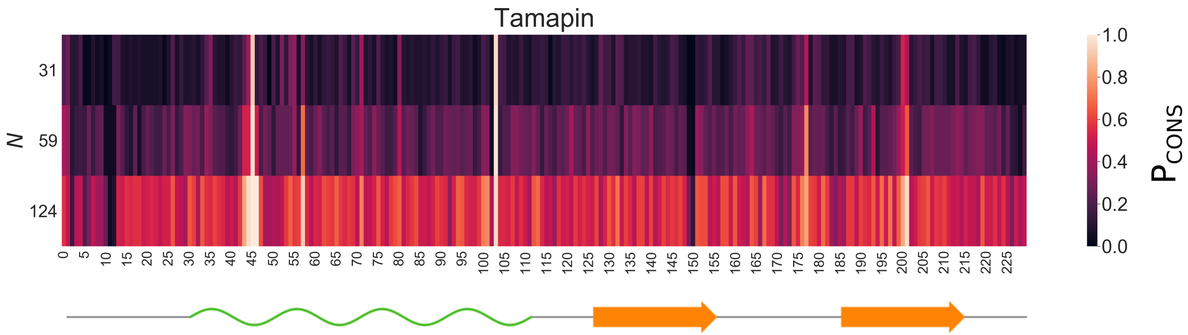

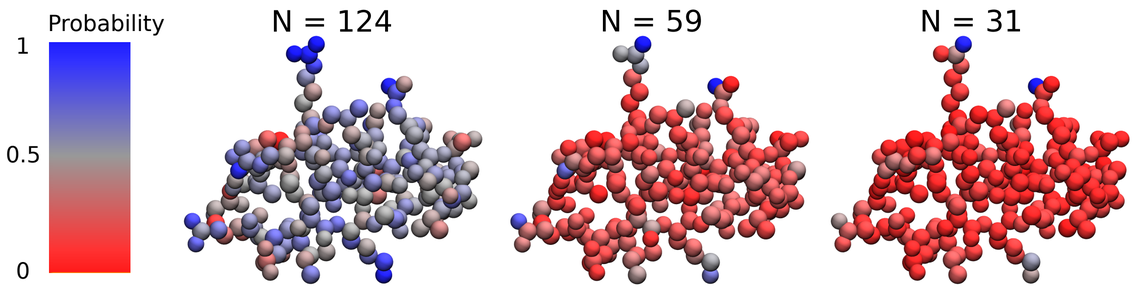

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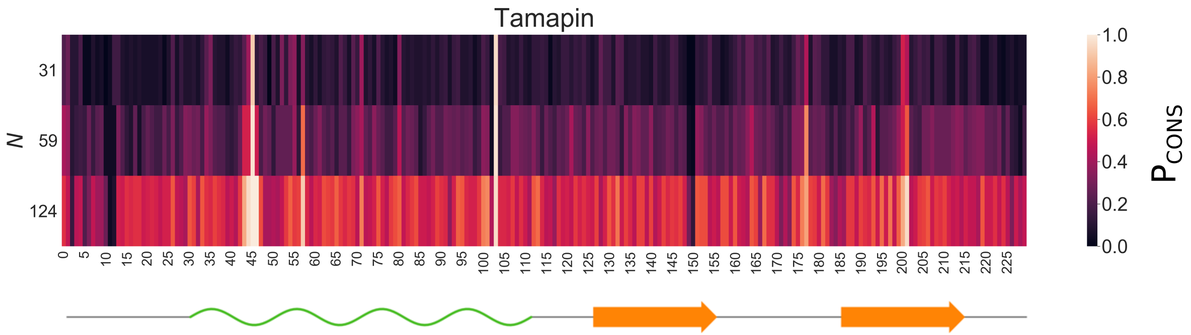
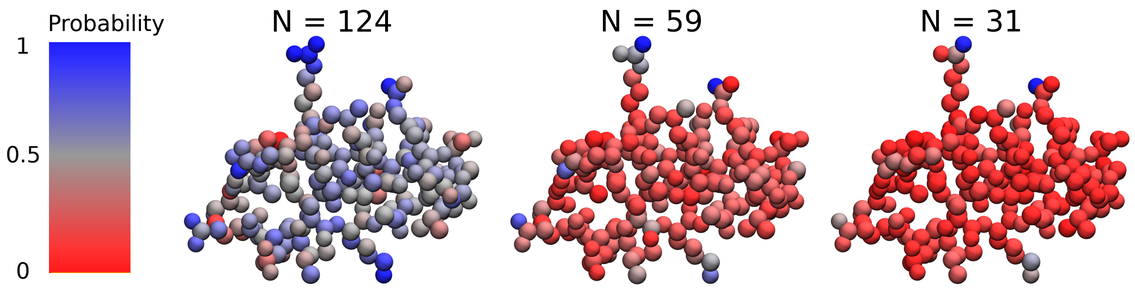
Biologically relevant residues are singled out in an unsupervised manner





Giulini, RM, Shell, Potestio, JCTC 2020

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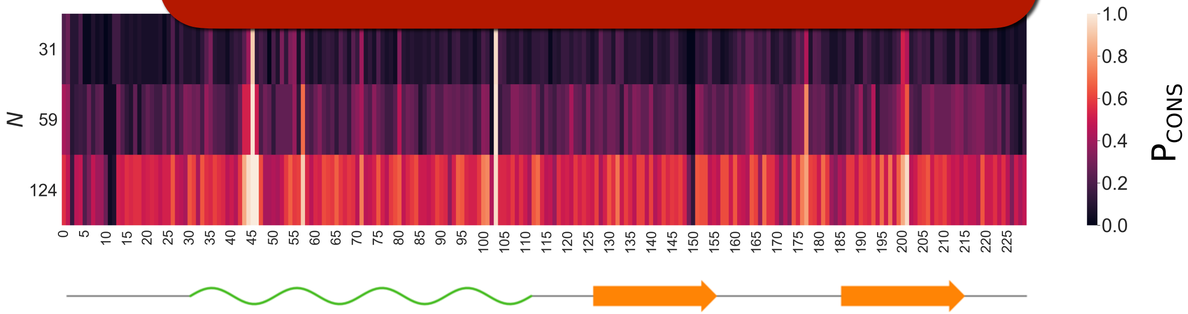

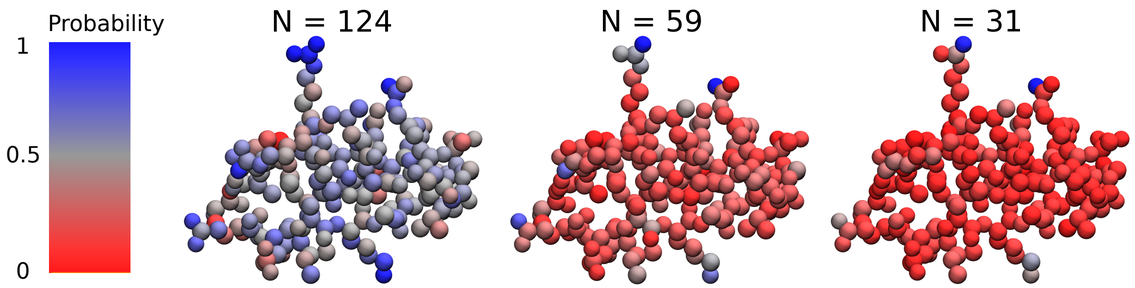

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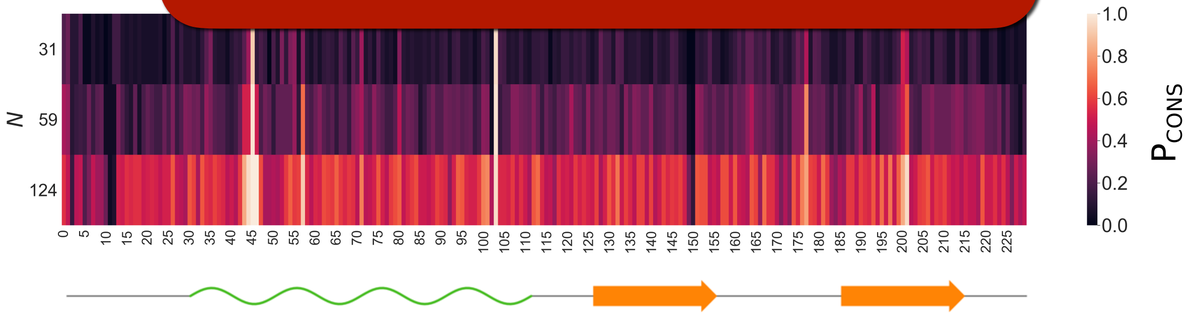
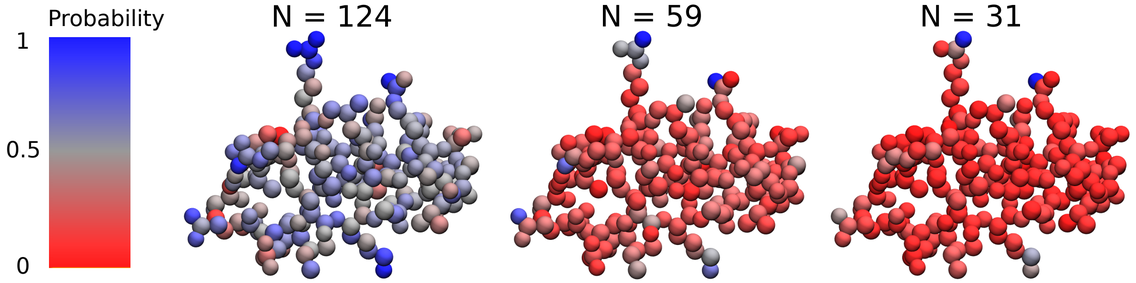
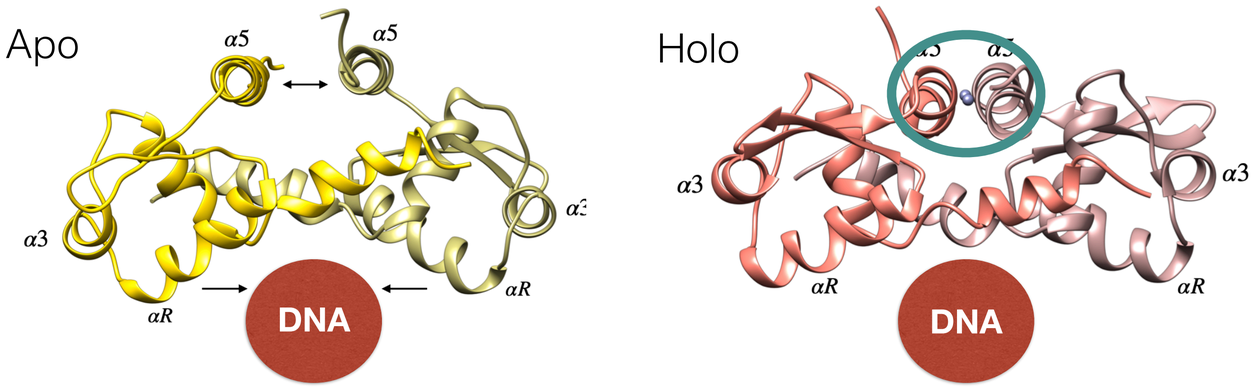




Giulini, RM, Shell, Potestio, JCTC 2020

Application to CzrA transcription repressor



Rigoli, Giulini, RM, Potestio, in preparation

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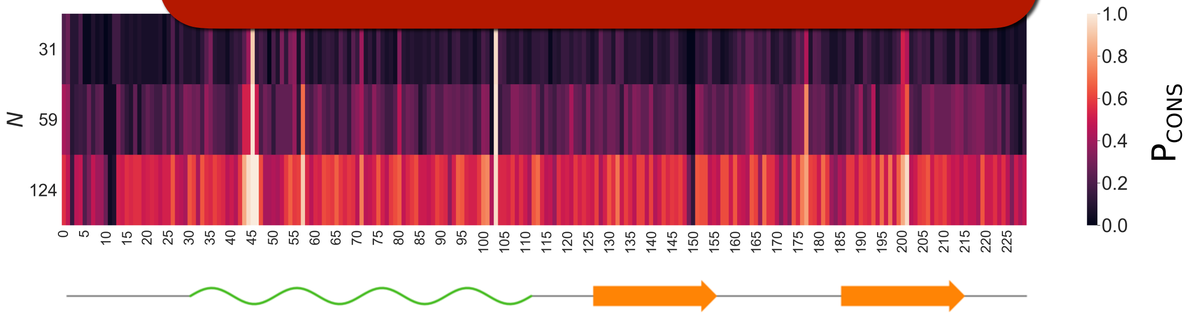
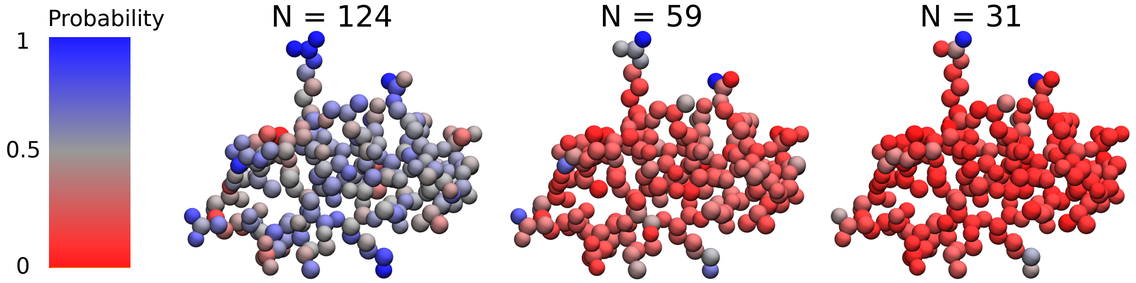
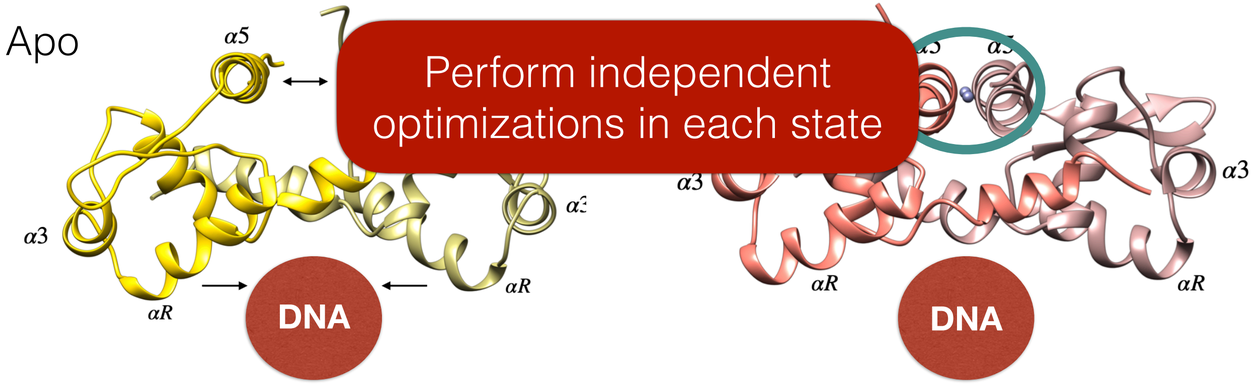




Giulini, RM, Shell, Potestio, JCTC 2020

Application to CzrA transcription repressor

Perform independent optimizations in each state



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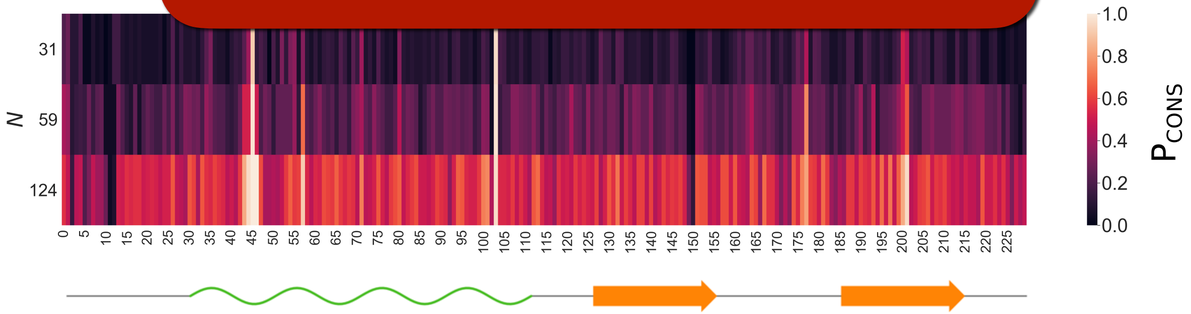

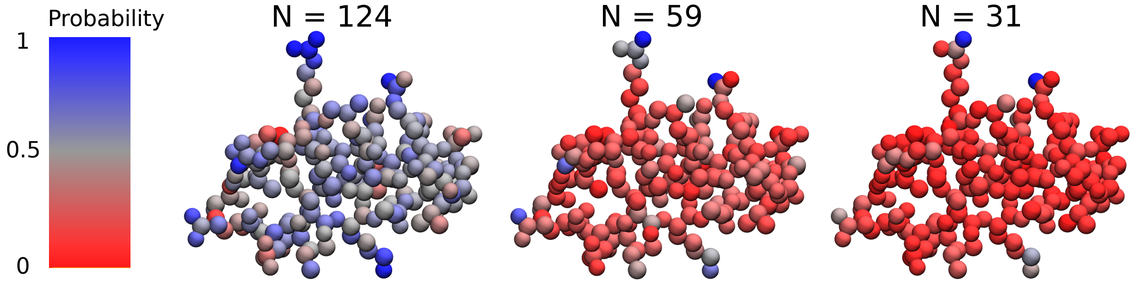

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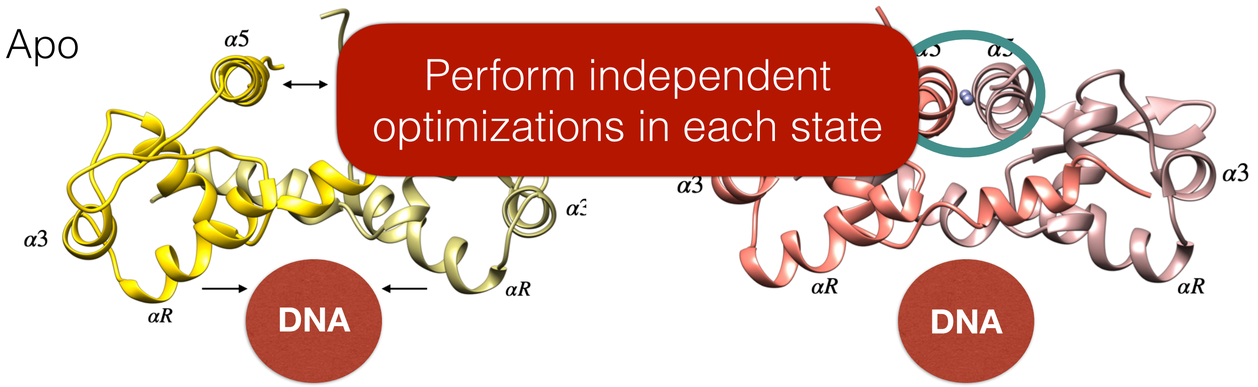

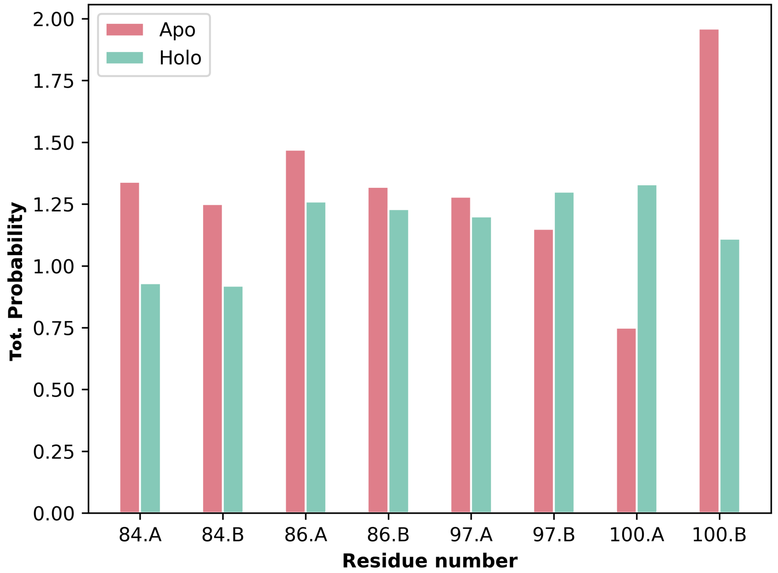

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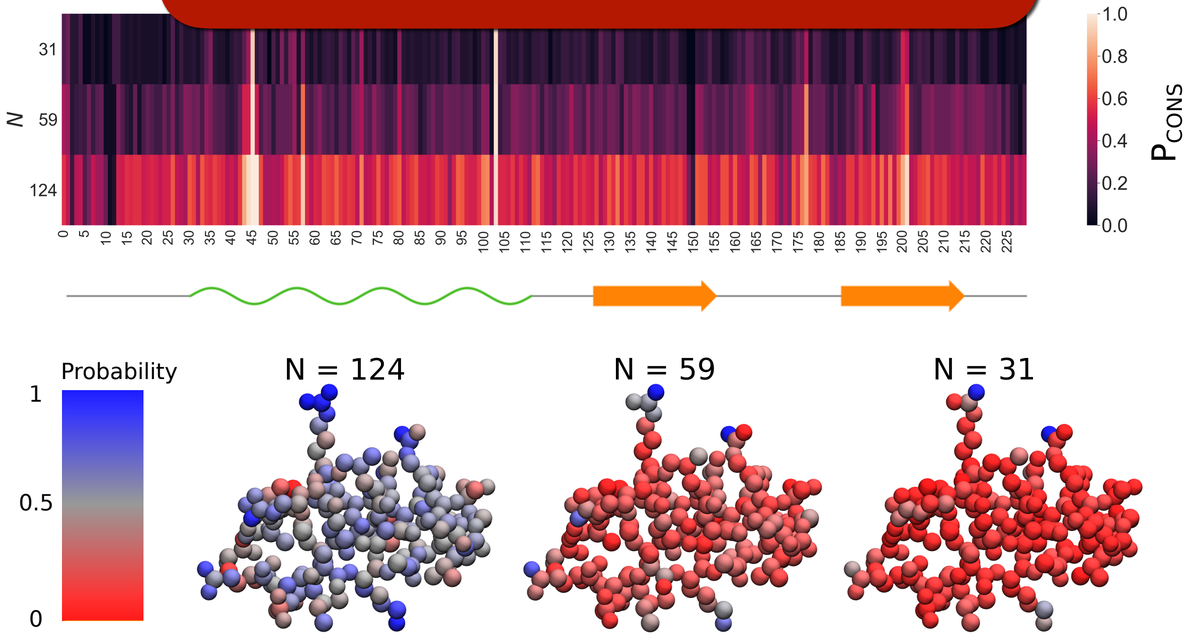
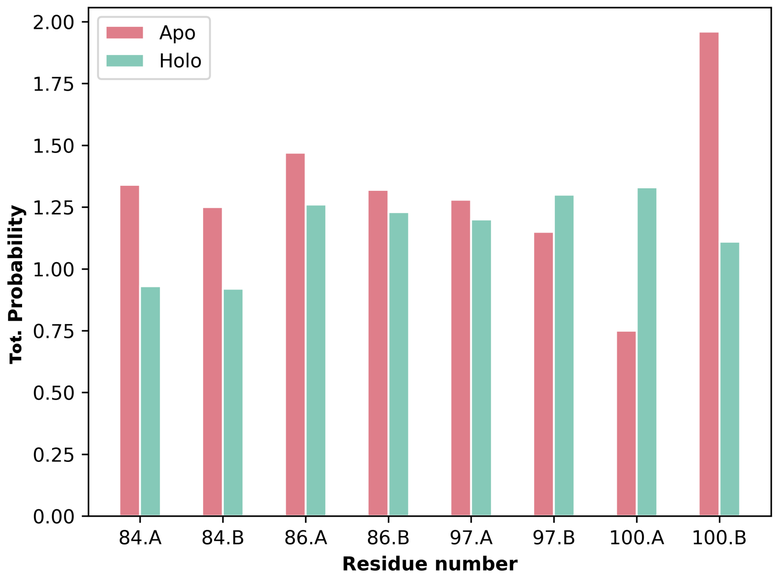


Giulini, RM, Shell, Potestio, JCTC 2020

Application to CzrA transcription repressor

Perform independent optimizations in each state

Biologically relevant residues "deactivate" in presence of the partner



Rigoli, Giulini, RM, Potestio, in preparation

S_{map} via Deep Graph Networks

Calculating the mapping entropy is a computationally expensive task

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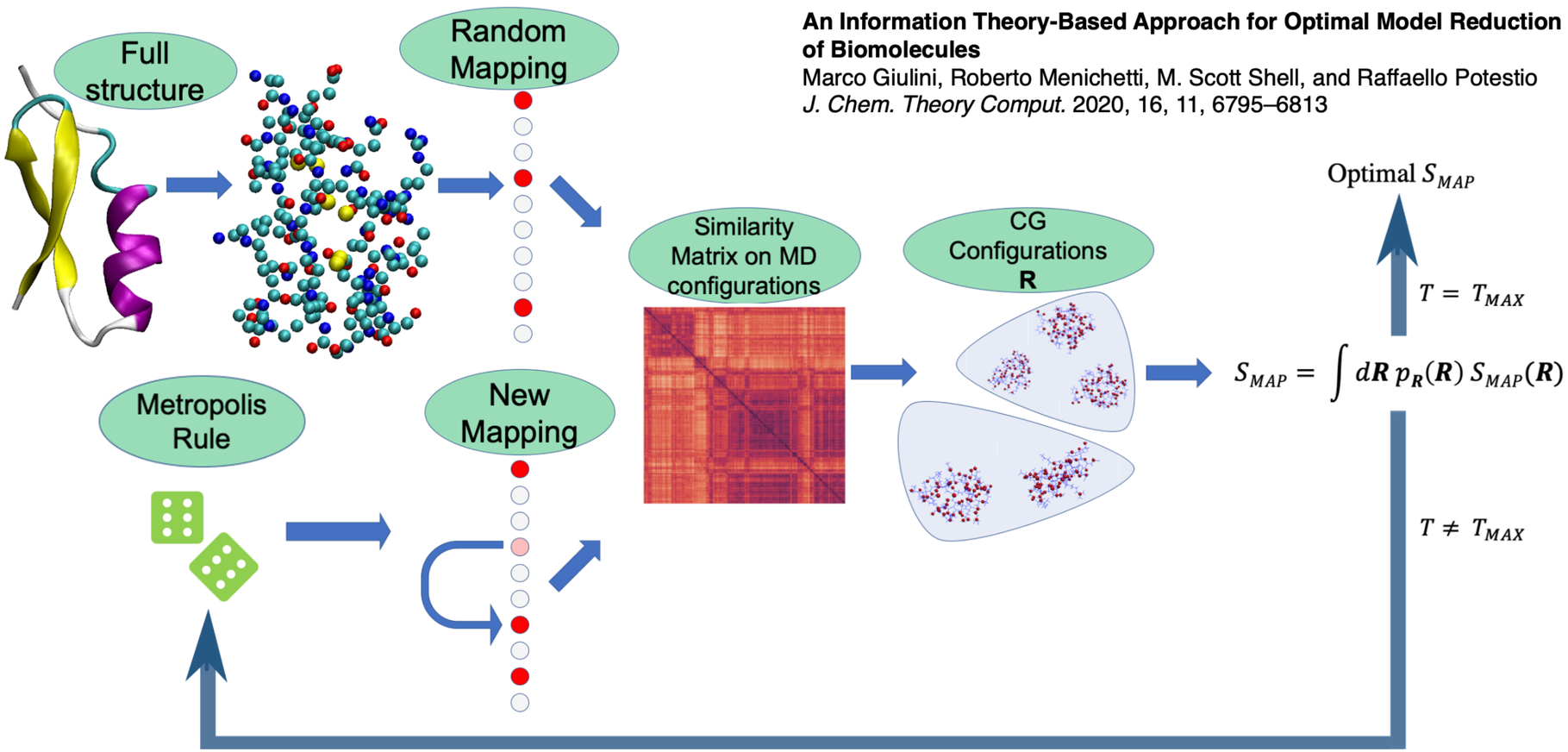

Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

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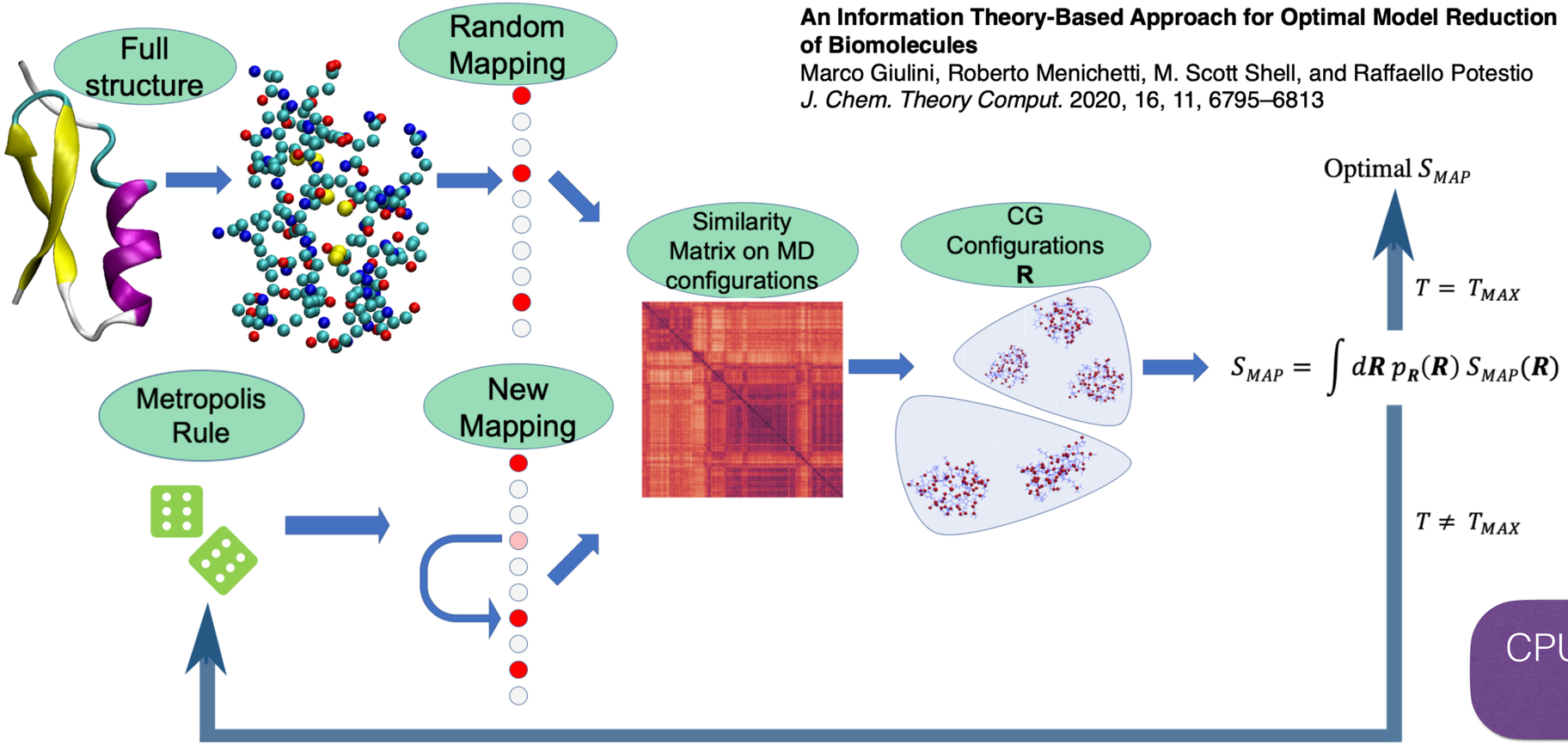

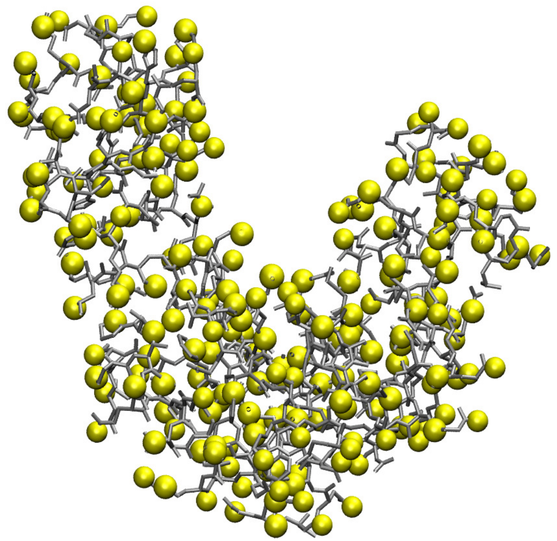

CPU time required for a **single** S_{map} calculation: **~10 minutes**

Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

S_{map} via Deep Graph Networks

Artificial Intelligence to speed up calculations: Deep Graph Networks

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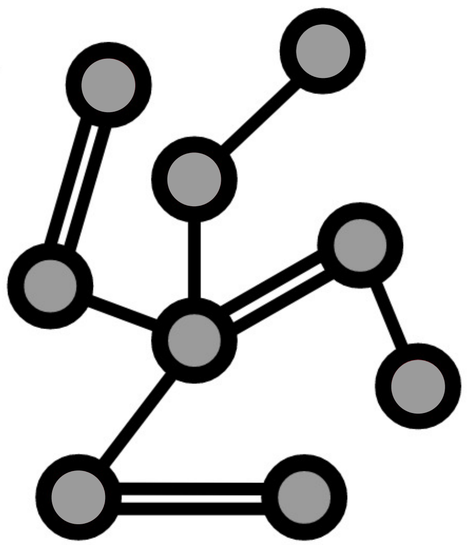
S_{map} via Deep Graph Networks

Artificial Intelligence to speed up calculations: Deep Graph Networks

Encode the (static) structure of the molecule in a graph



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S_{map} via Deep Graph Networks

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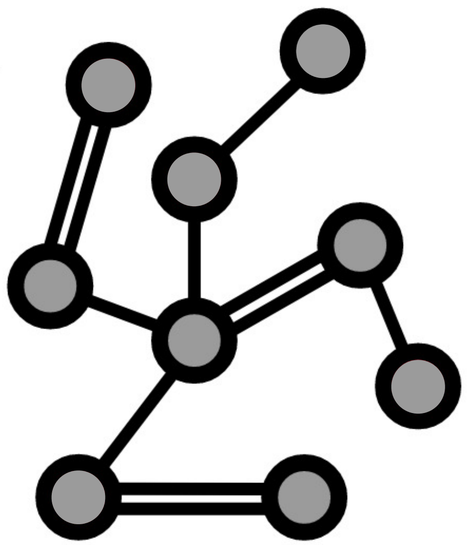
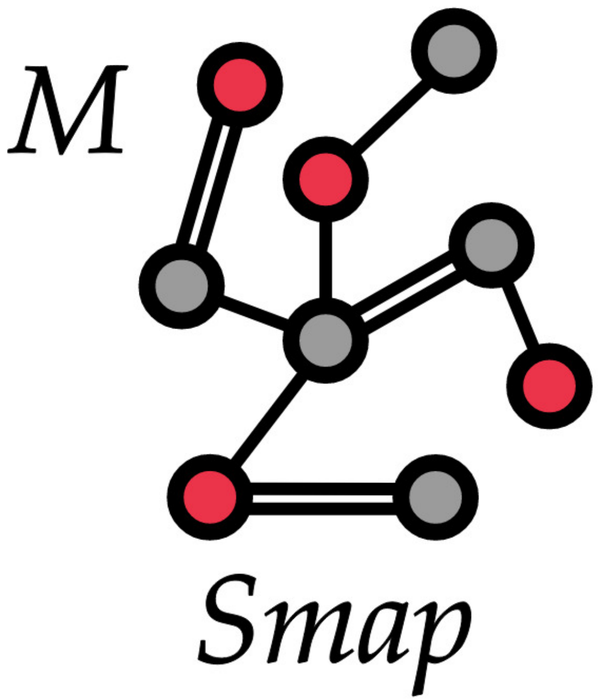
Encode the (static) structure of the molecule in a graph

Employ DGNs to predict the mapping entropy





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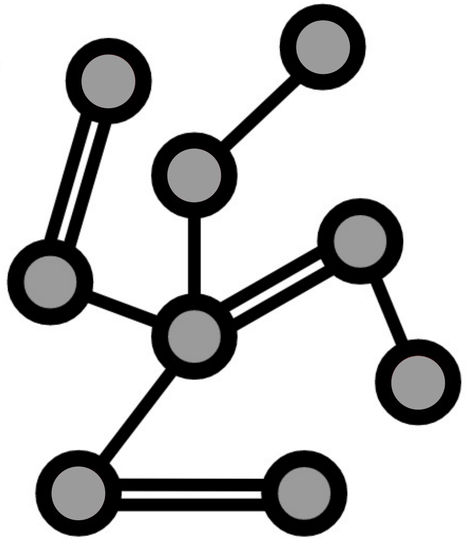
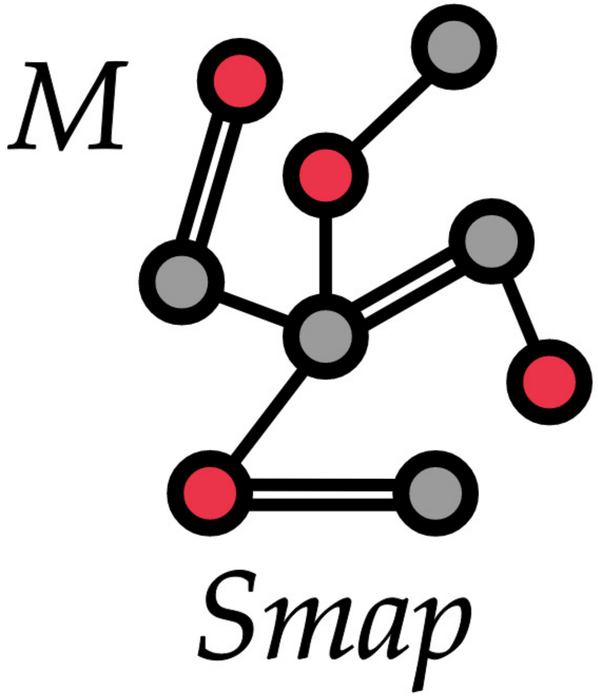
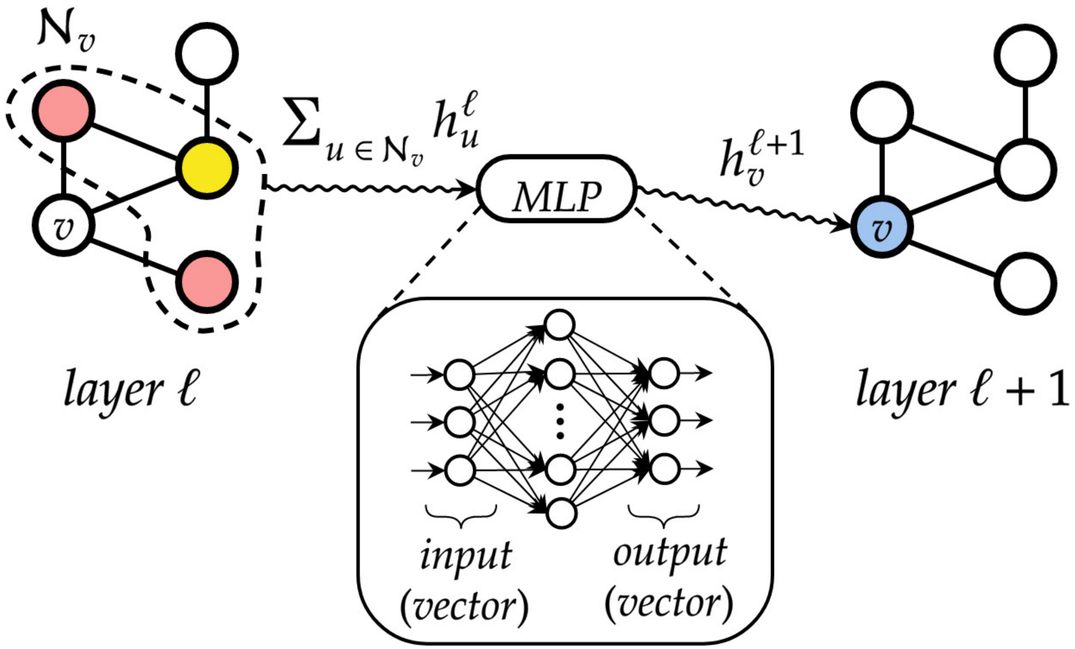
$$\mathbf{h}_v^{\ell+1} = MLP^{\ell}\left(\left(1+\epsilon^{\ell}\right) * \mathbf{h}_v^{\ell} + \sum_{u \in \mathcal{N}_v} \mathbf{h}_u^{\ell} * e_{uv},\right)$$







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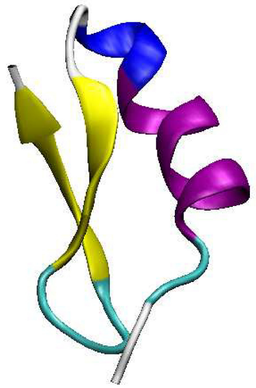
Tamapin



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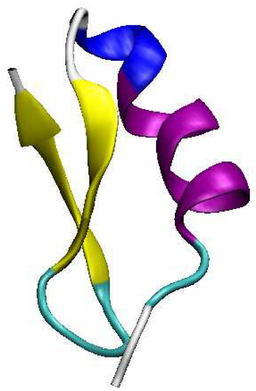
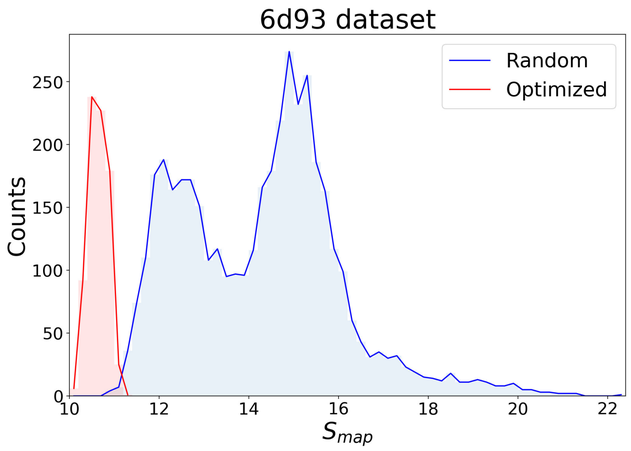
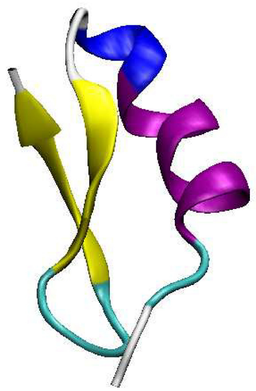


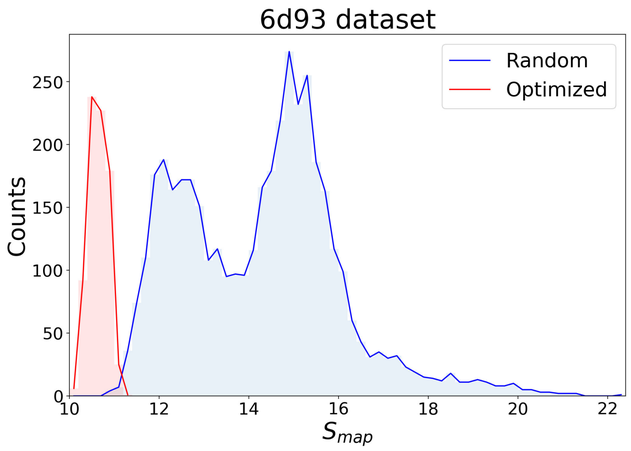


Training the DGN on the S_{map} of
- Random CG representations
- Maximally informative CG representations:
vanishing statistical weight

S_{map} via Deep Graph Networks

Tamapin





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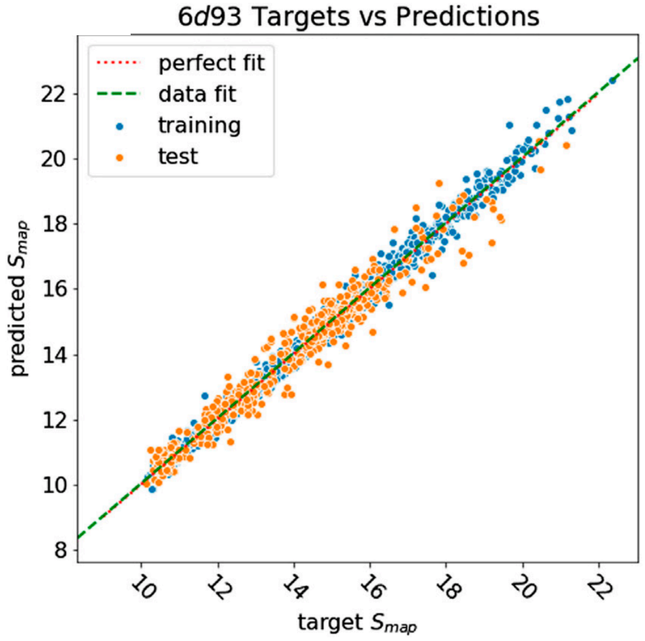
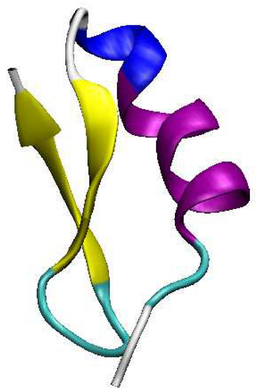
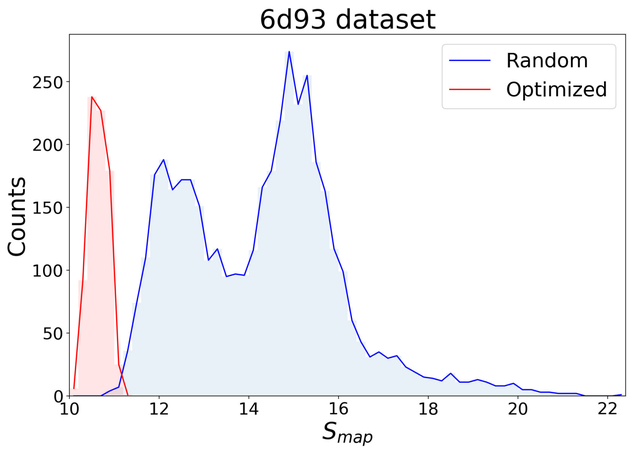


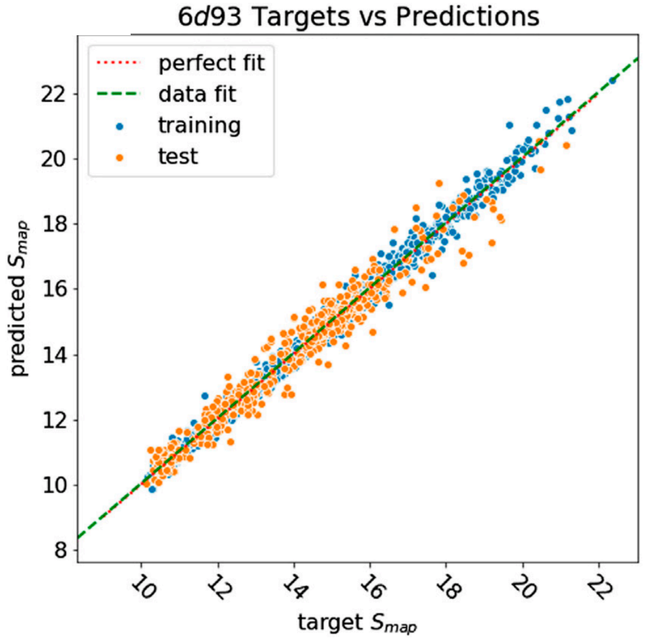
The DGN succeds in predicting
the S_{map} of both classes.
Speedup wrt standard algorithm:
10^3 (CPU) - 10^5 (GPU)

S_{map} via Deep Graph Networks

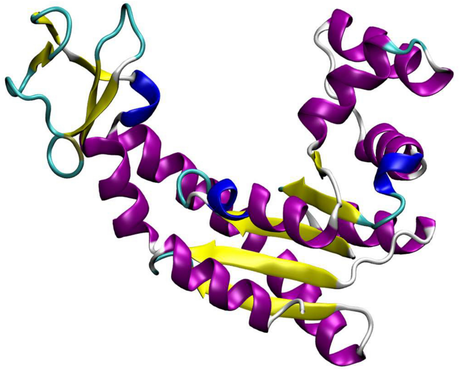
Tamapin

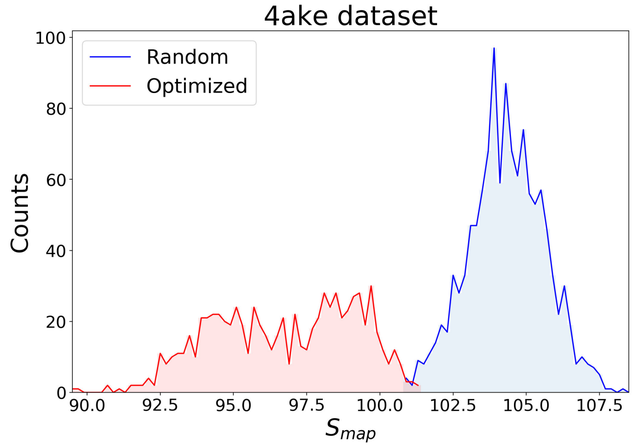


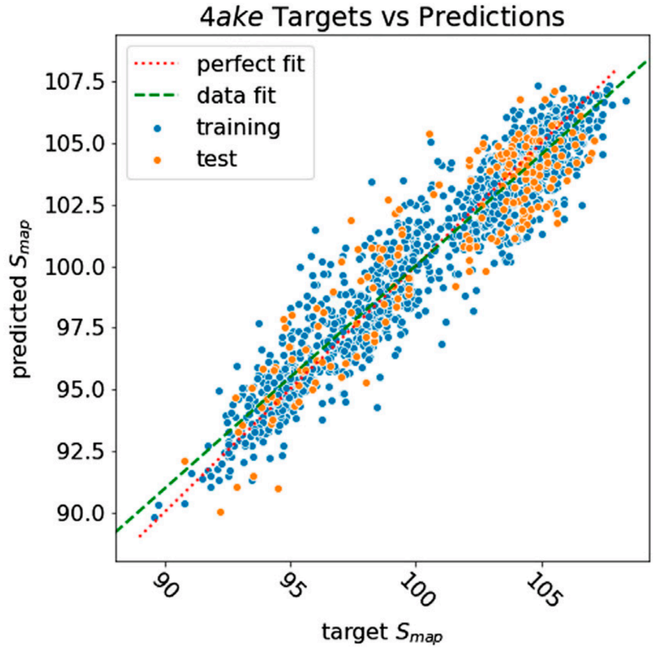




Adenylate Kinase



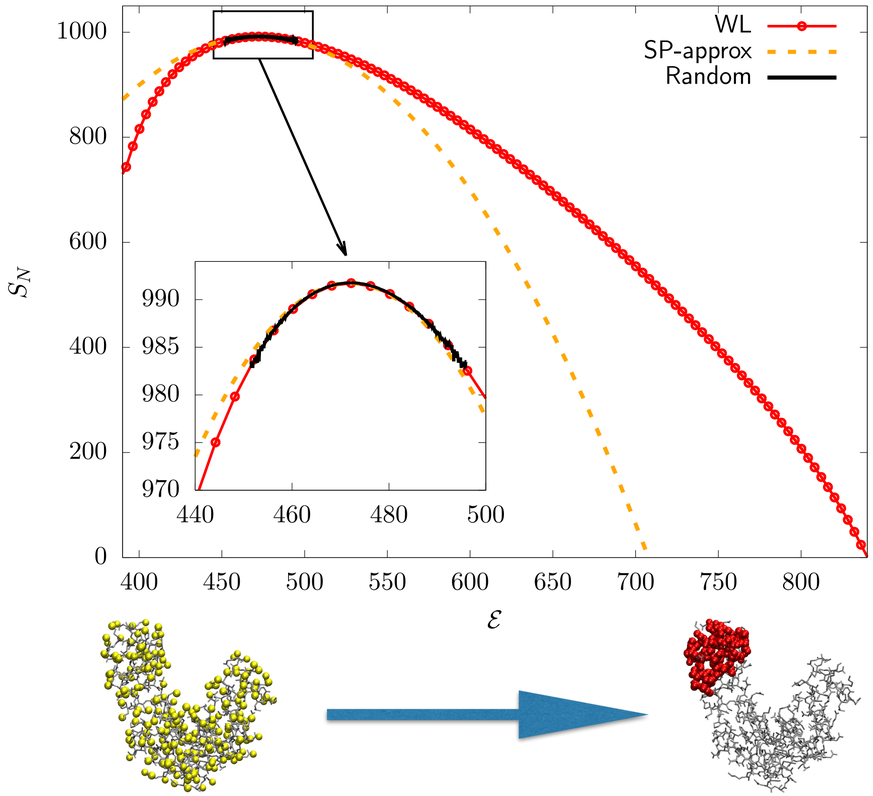




S_{map} via Deep Graph Networks

Speedup generated by DGNs: quasi-exhaustive exploration of the S_{map} landscape

$$\#\text{selections}(\mathcal{E}) \propto e^{S_N(\mathcal{E})}$$



RM, Giulini, Potestio, EPJB 2021
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

S_{map} via Deep Graph Networks

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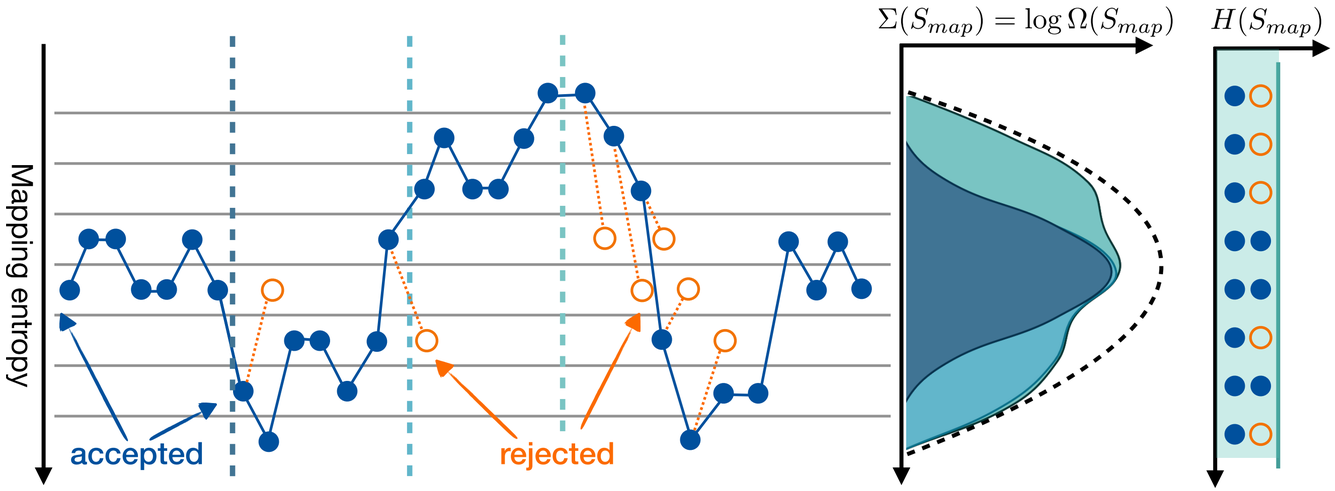
Combine the trained DGNs with the Wang-Landau sampling algorithm **to reconstruct the density of states $\Omega(S_{map})$**



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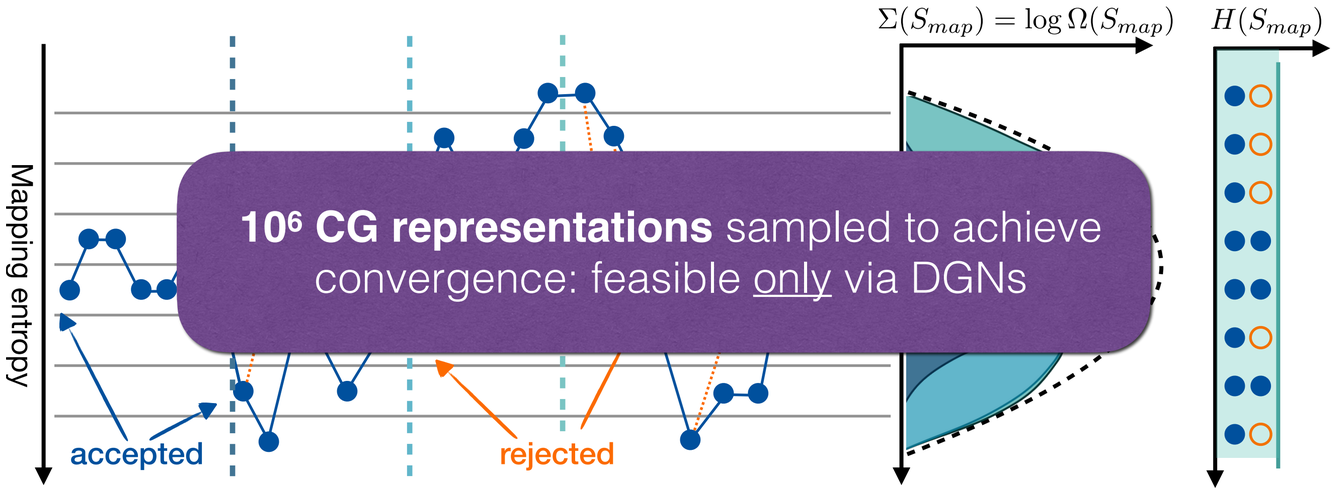

10^6 CG representations sampled to achieve convergence: feasible only via DGNs

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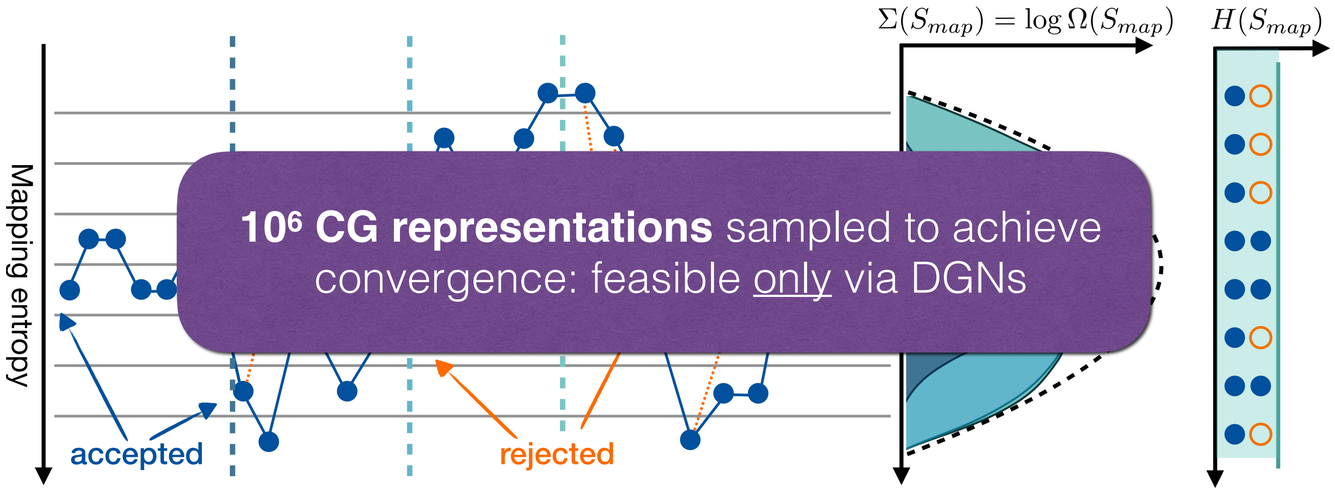

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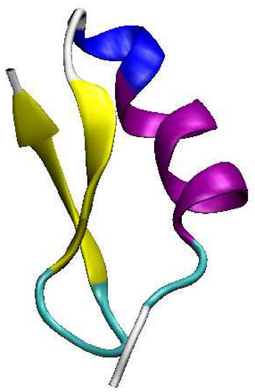
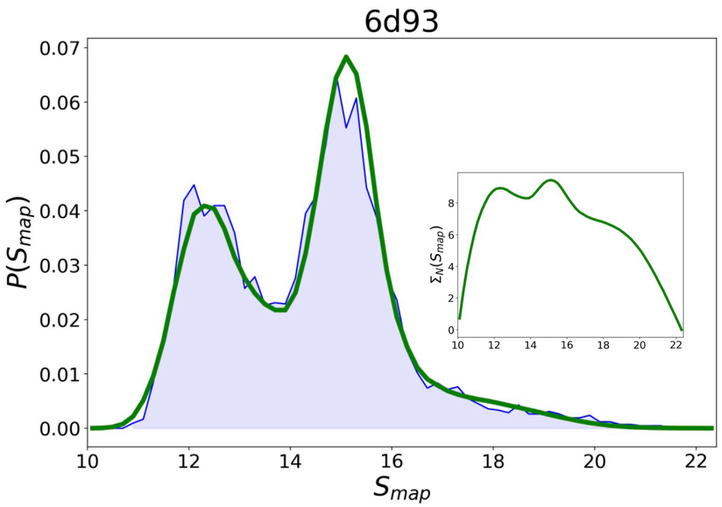
Tamapin





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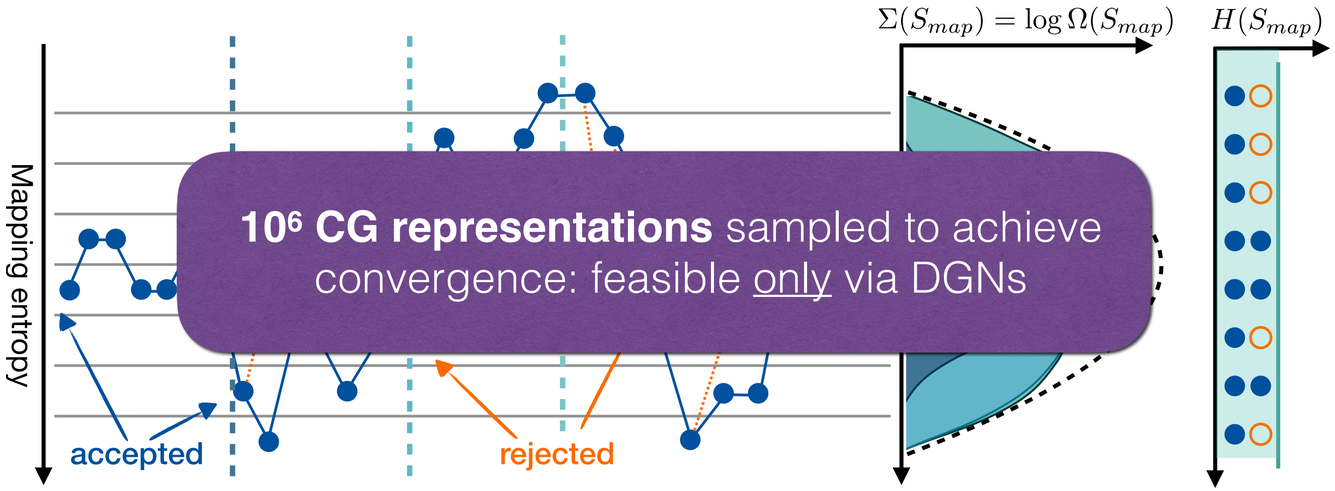

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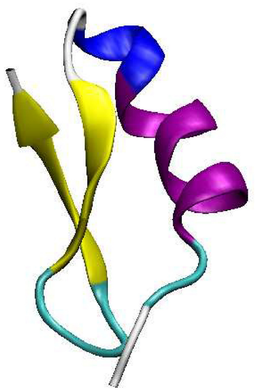

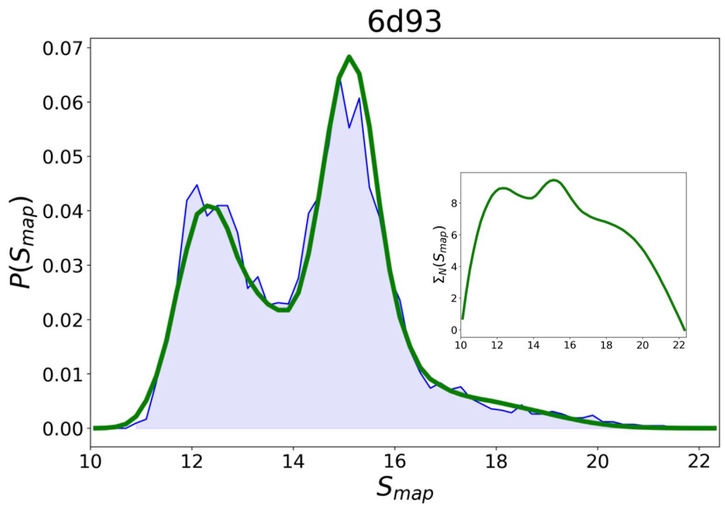

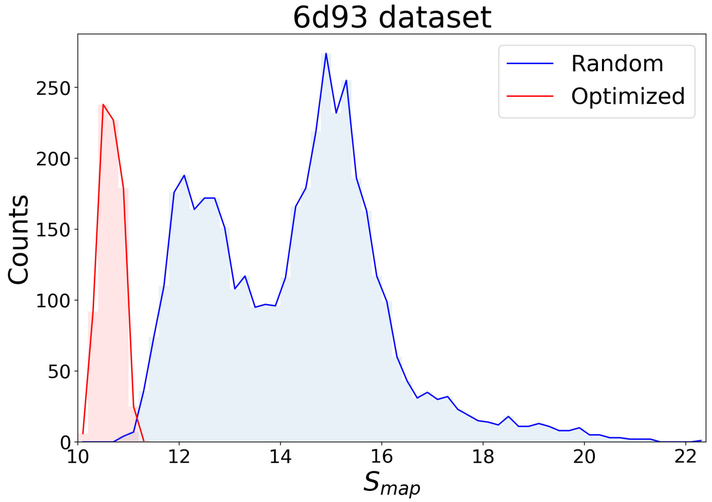

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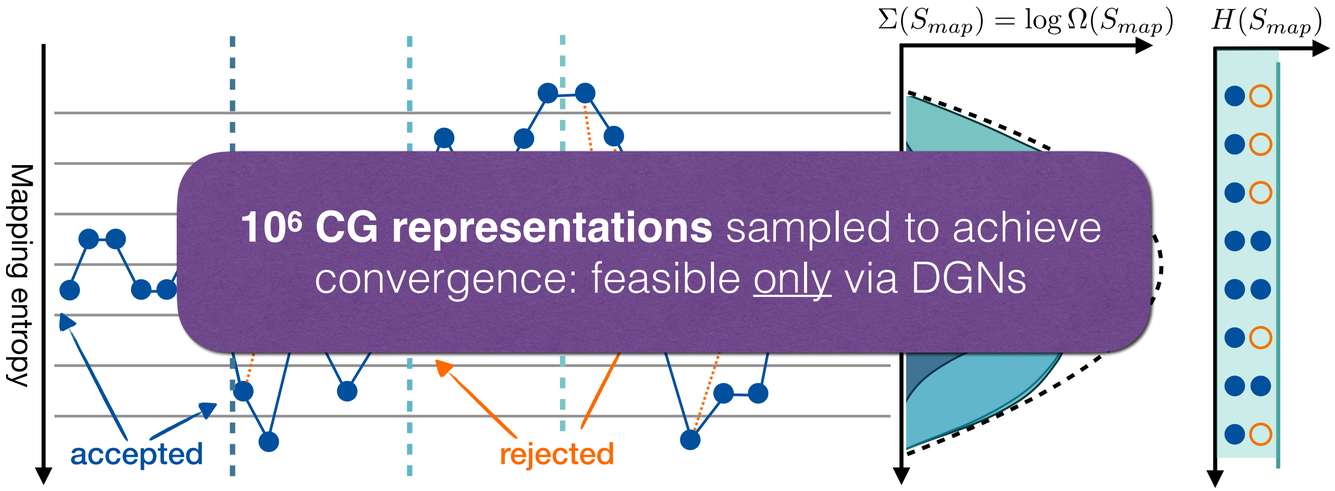

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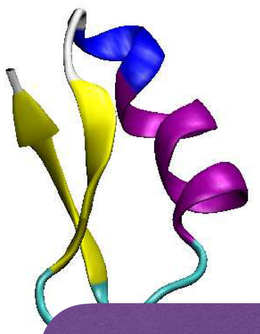

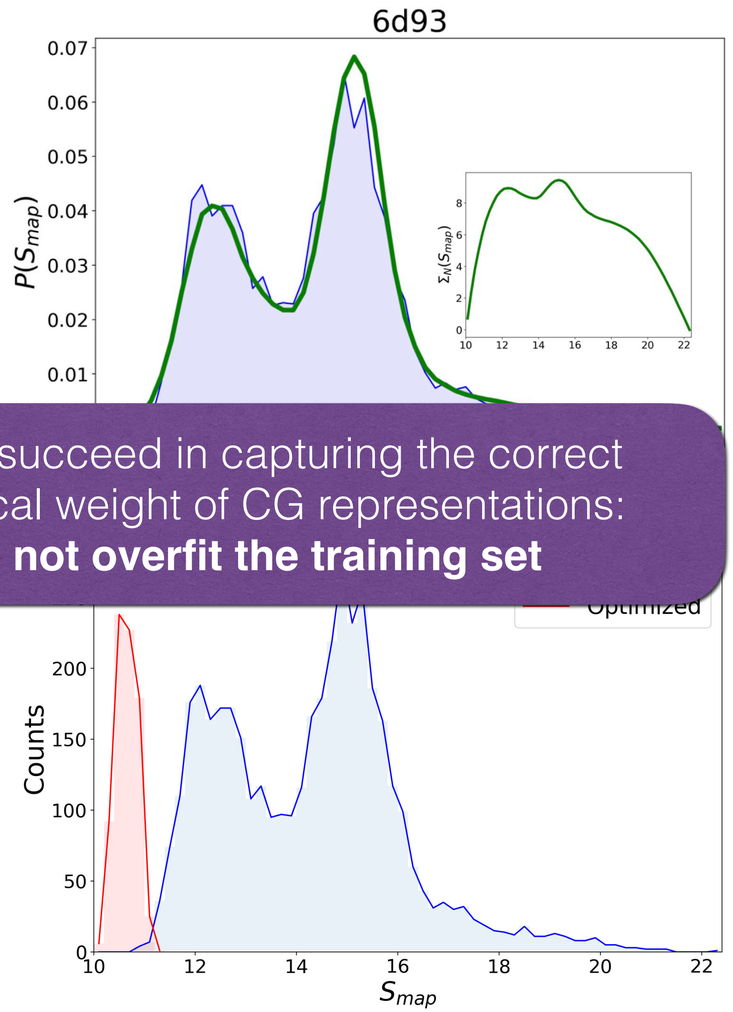

DGNs succeed in capturing the correct statistical weight of CG representations: **do not overfit the training set**

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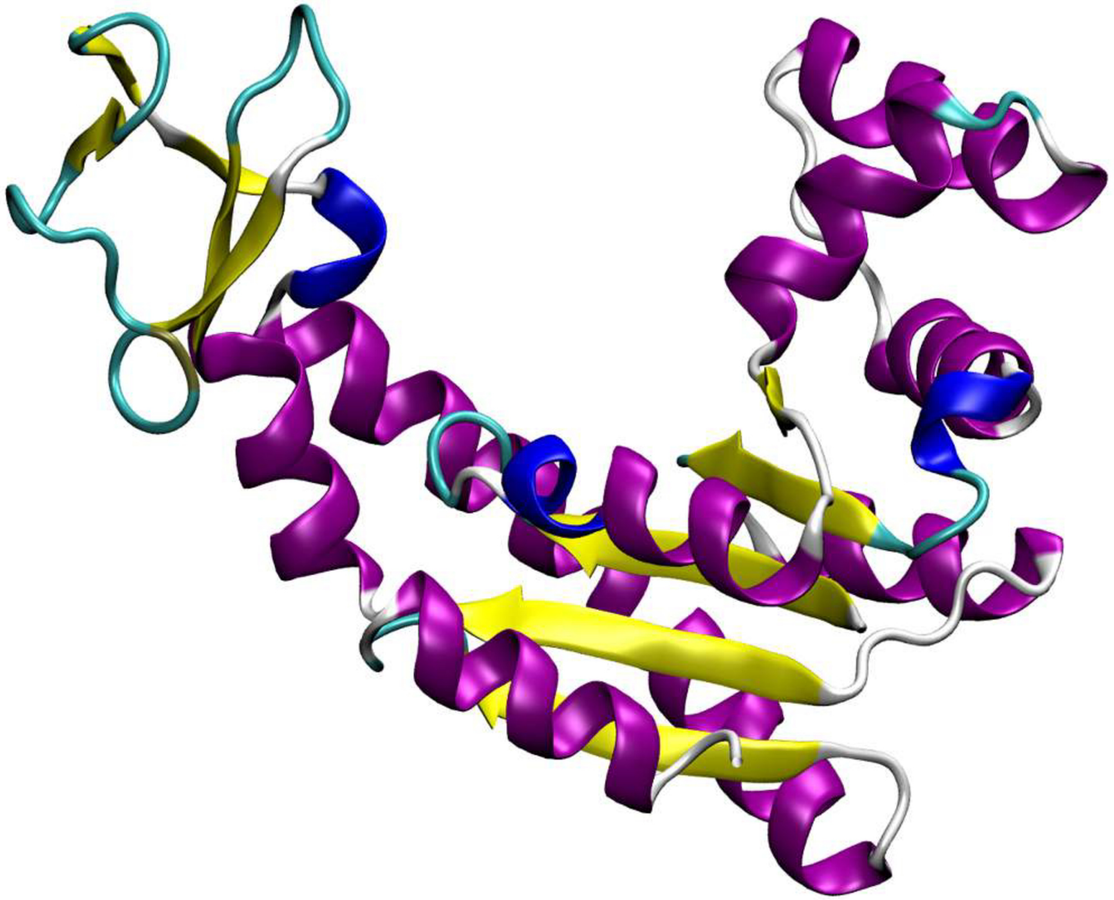
Application to neural systems

Being based on information-theoretic quantities, the mapping entropy protocol is extremely general



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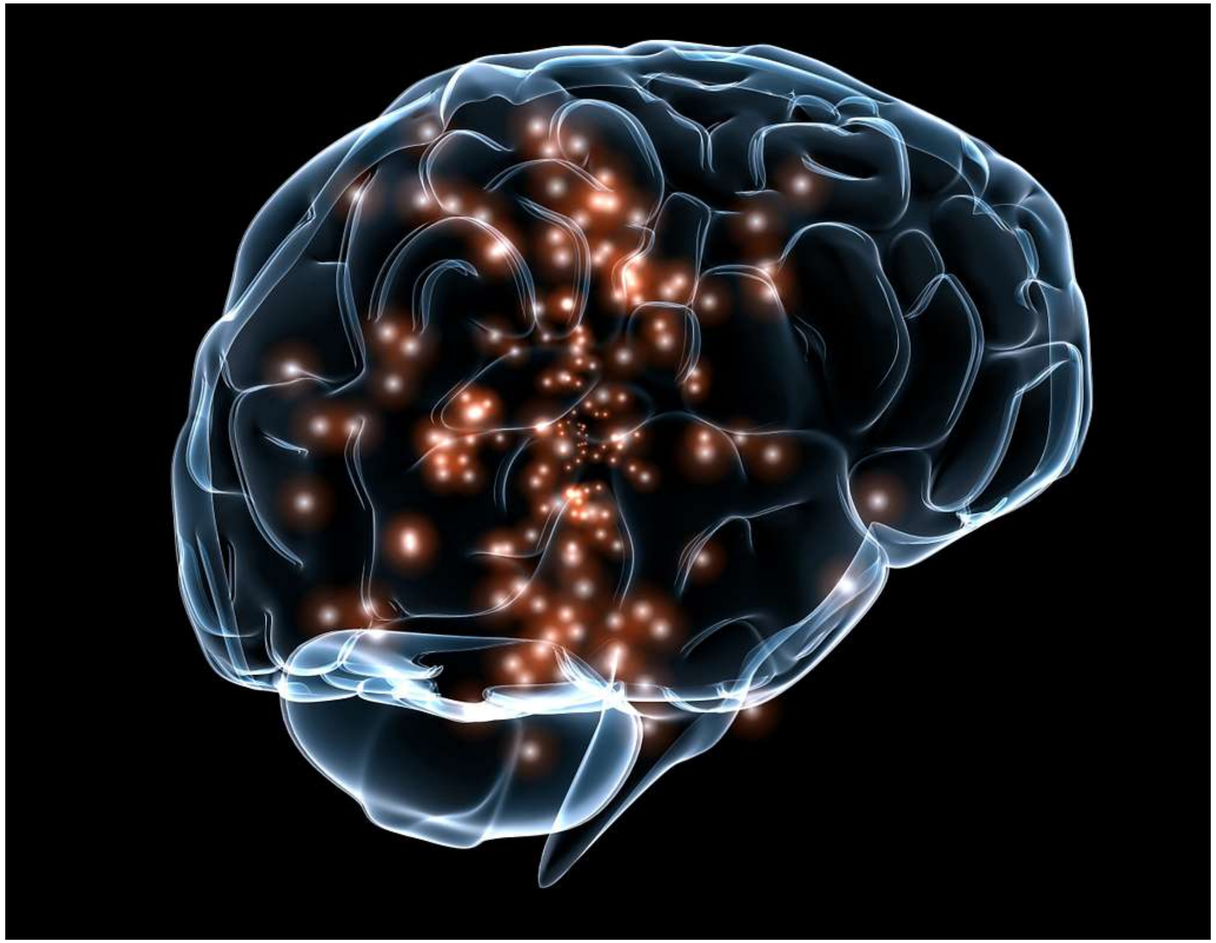
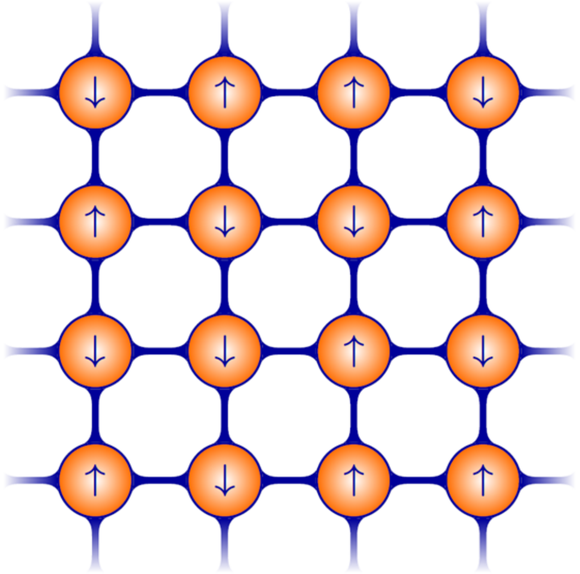


Neural system: Hopfield model



$$H(\sigma_1, ..., \sigma_N) = -\frac{1}{2}\sum_{i \neq j} J_{ij}\sigma_i\sigma_j$$

Couplings $J_{ij} = \sum_{\mu=1}^{p} \xi_i^\mu \xi_j^\mu$

Memory patterns $\xi_i^\mu, \quad \mu = 1, ..., p$

Hopfield, PNAS (1982)
Amit, *Modeling Brain Function: The World of Attractor Neural Networks* (1989)
Aldrigo, RM, Potestio (in preparation)

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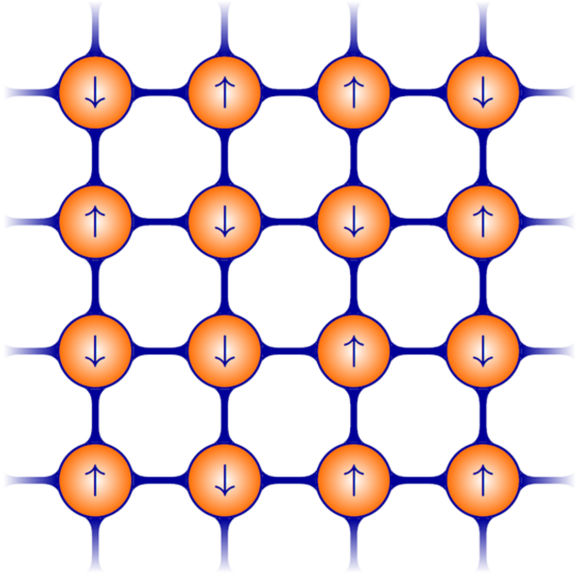

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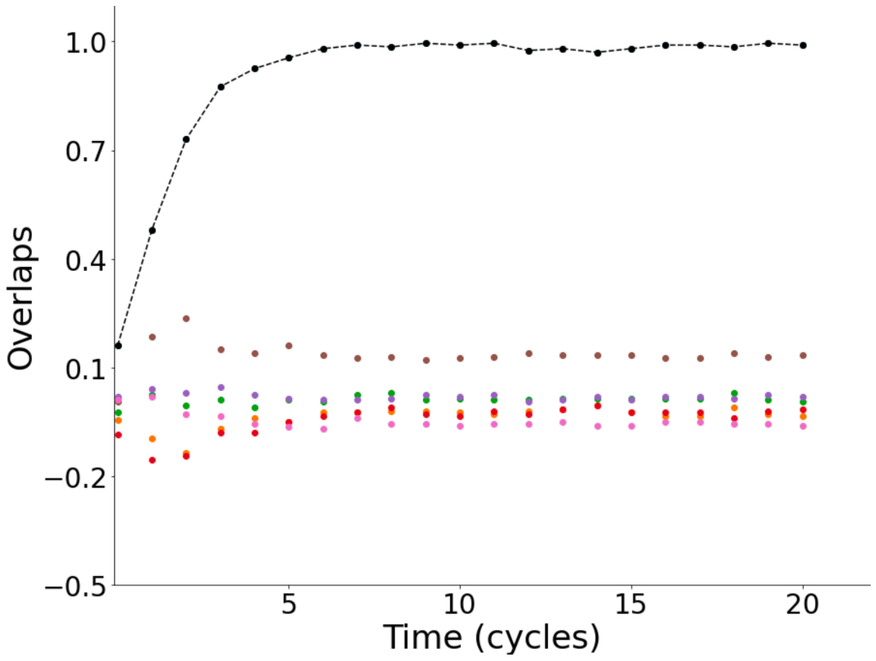
Nonlinear evolution of the configurations

Model's dynamics retrieves memory patterns

Overlaps $m^\mu = \frac{1}{N}\sum_i \xi_i^\mu \sigma_i$



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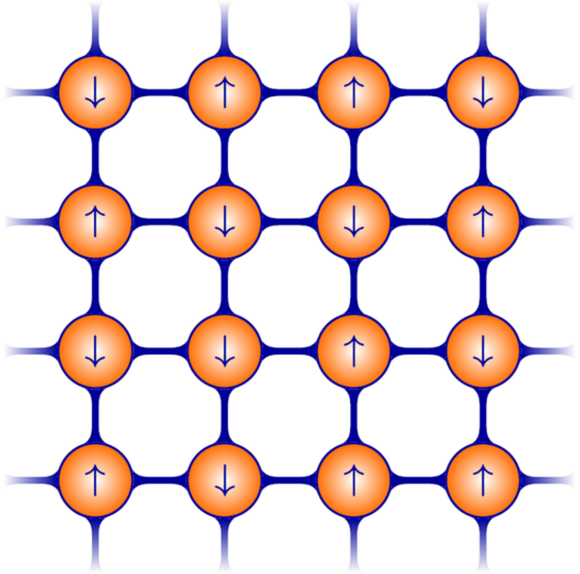

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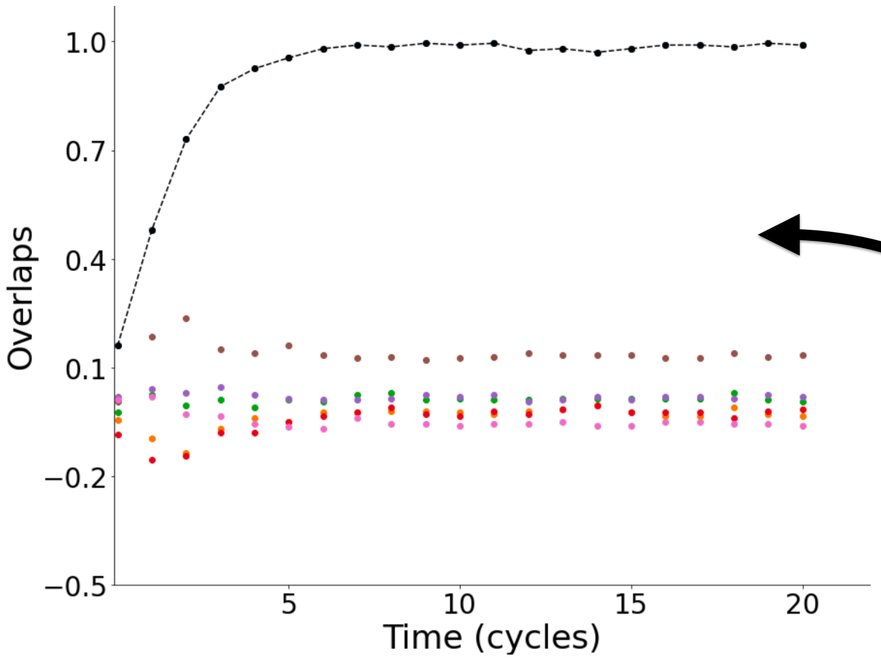

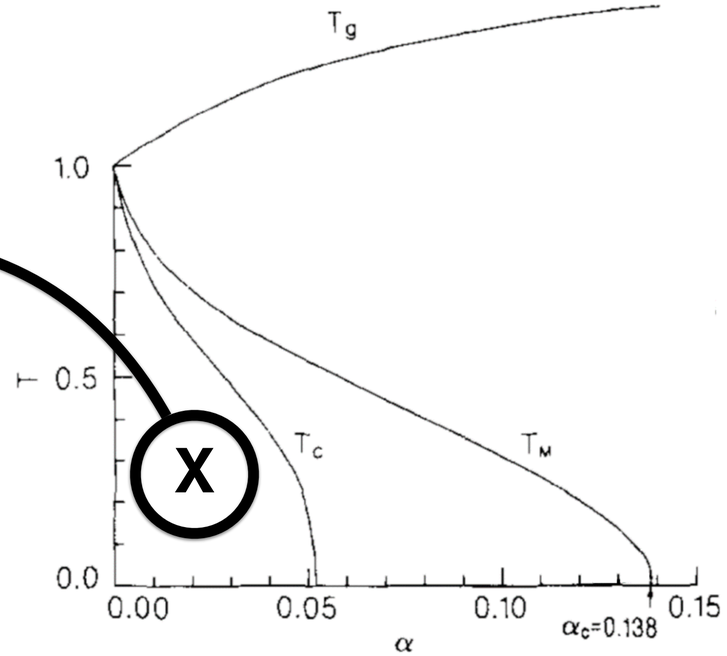

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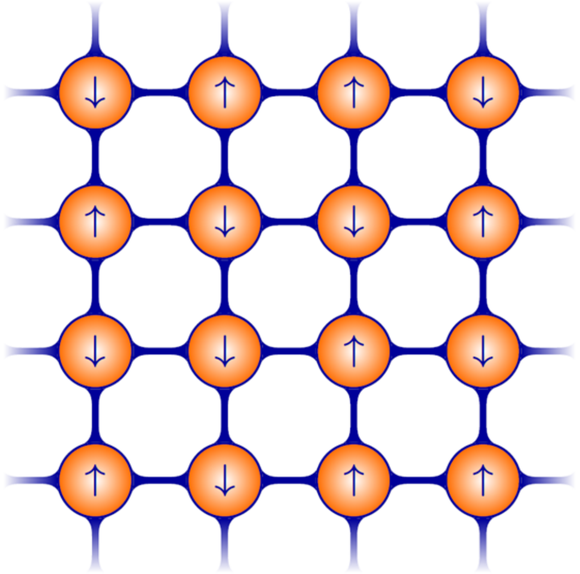

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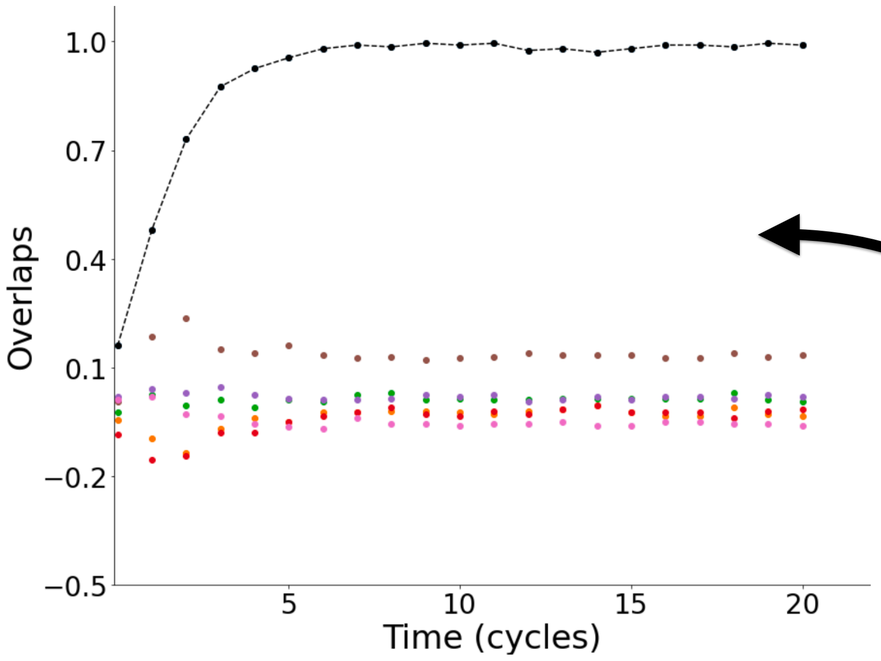

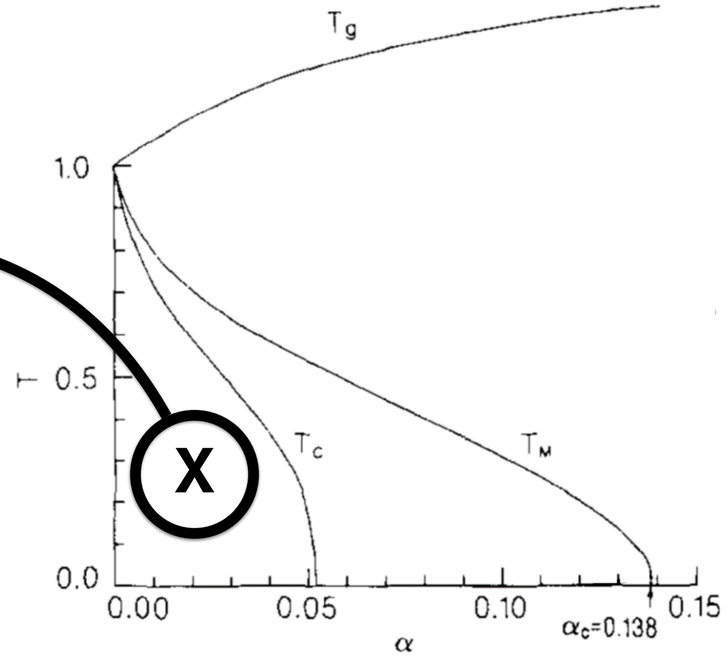

Looking for the **most informative** neurons!

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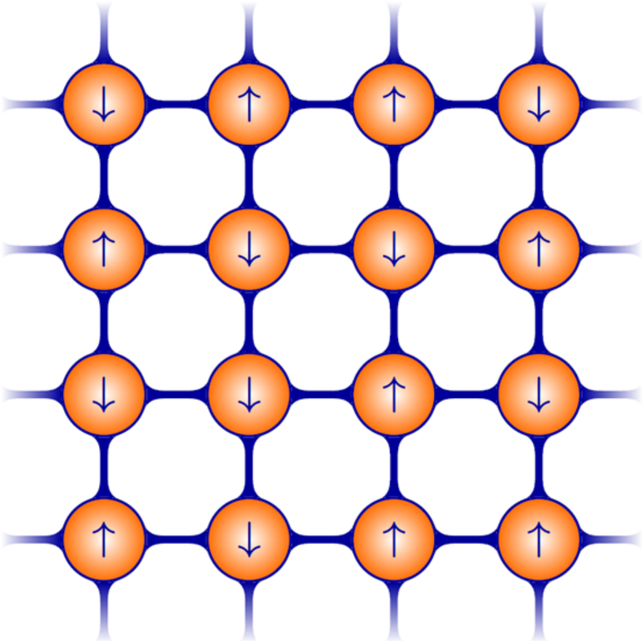
Detection of maximally-informative neurons

CG'ing the Hopfield model

1) Simulate the Hopfield model



Aldrigo, RM, Potestio (in preparation)

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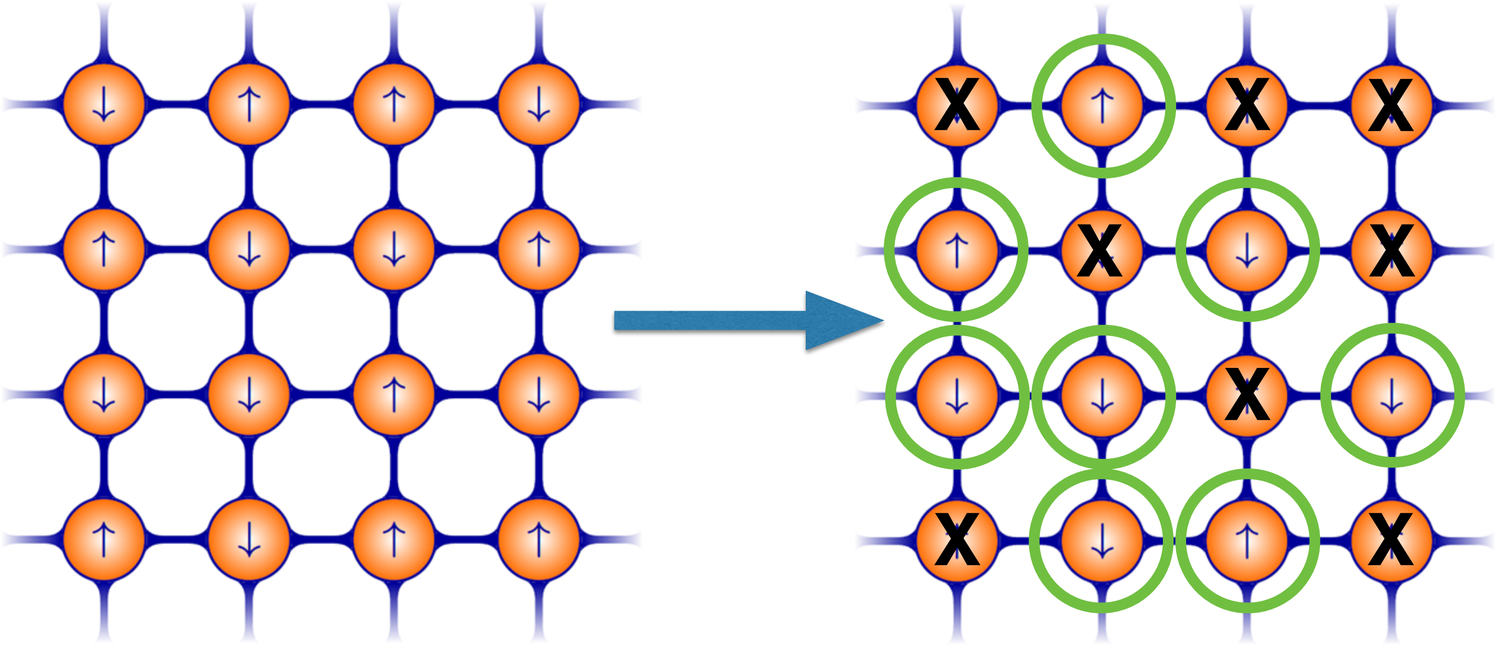
2) Select a subset of retained neurons



Aldrigo, RM, Potestio (in preparation)

Detection of maximally-informative neurons

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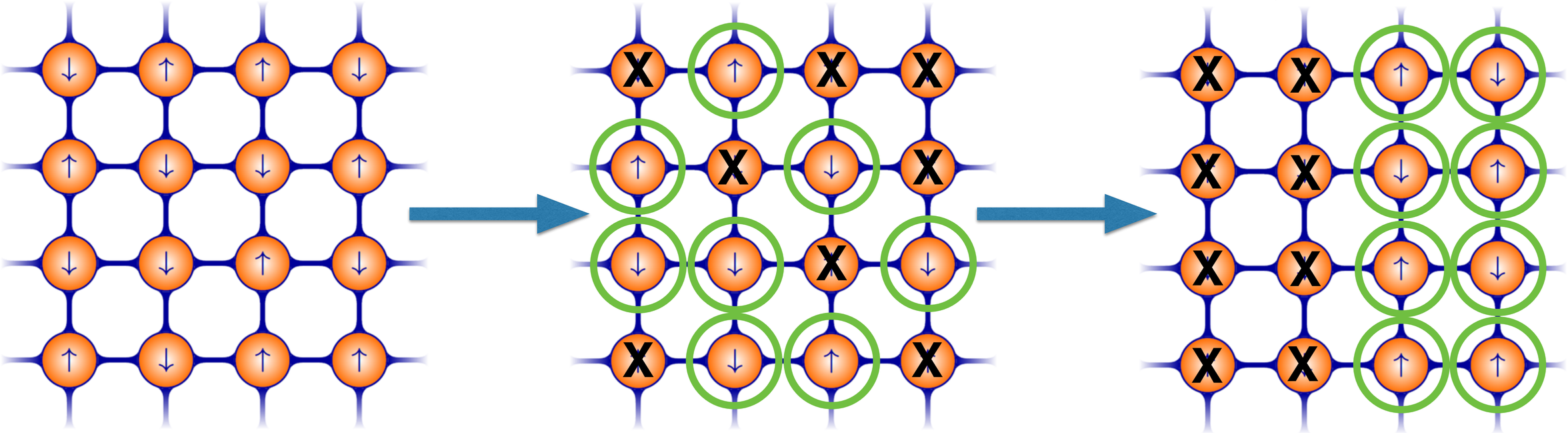
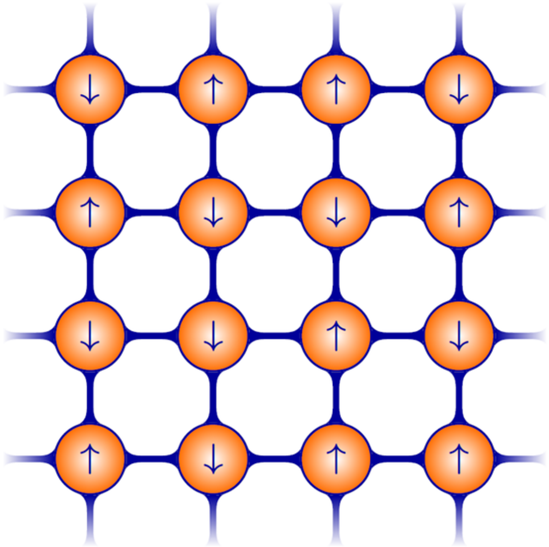
3) Optimize the selection to detect **maximally-informative** neurons



Aldrigo, RM, Potestio (in preparation)

Resolution/Mapping-Entropy analysis

- Simulate the high-resolution Hopfield model
- **Empirical** reference probability $p(\sigma_1, ..., \sigma_N)$



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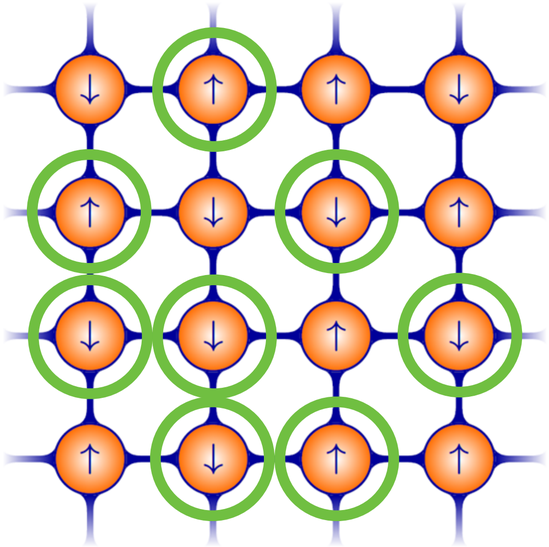

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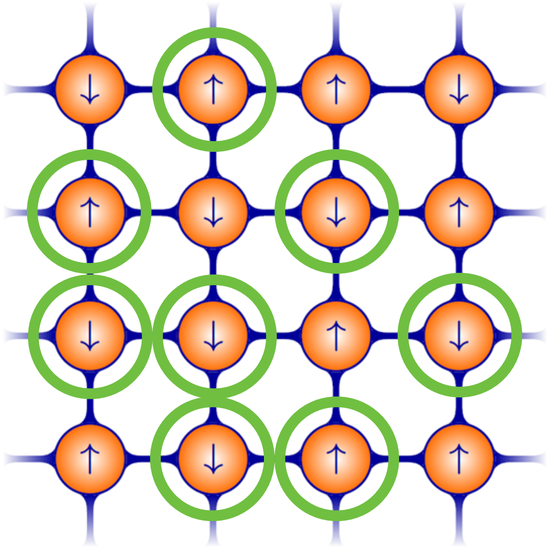

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Resolution of the neuron selection

$$\mathcal{H}_M = -\sum_{\{S_i\}} P(S_1, ..., S_n) \ln P(S_1, ..., S_n)$$

- **Depends** on the specific selection
- **Decreases** by decreasing the number of retained neurons

Aldrigo, RM, Potestio (in preparation)

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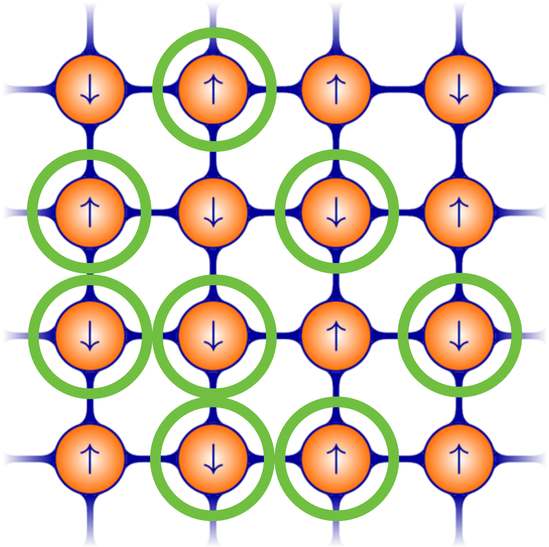

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Information loss generated by the selection: mapping entropy

$$S_M^{map} = \sum_{\{\sigma_i\}} p(\{\sigma_i\}) \ln \left(\frac{p(\{\sigma_i\})}{\bar{p}_M(\{\sigma_i\})} \right)$$

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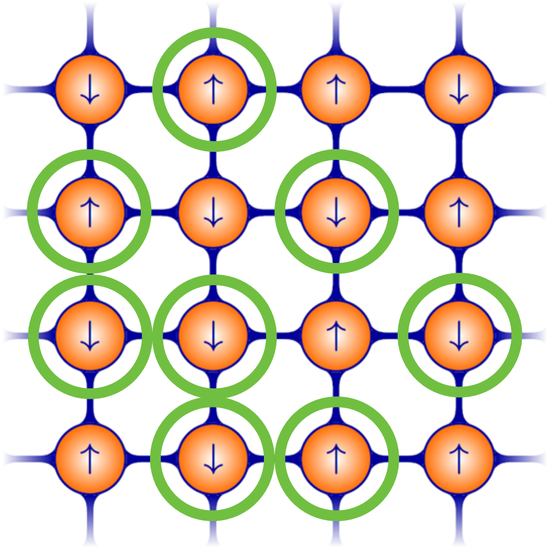

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Maximally informative neurons:
minimize the mapping entropy
in the space of possible selections!

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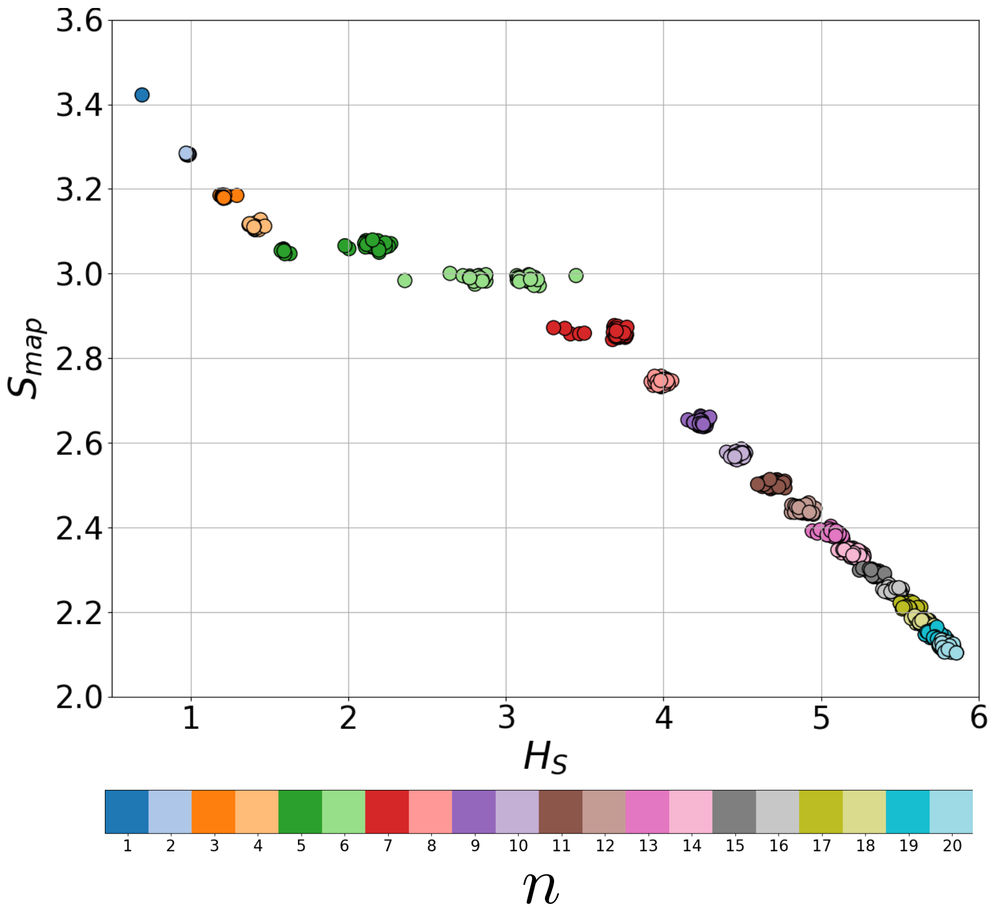
Resolution/Mapping-Entropy analysis

Maximally informative selection of neurons that **minimize the mapping entropy**

Hopfield model with N=100 neurons and 5 memory patterns



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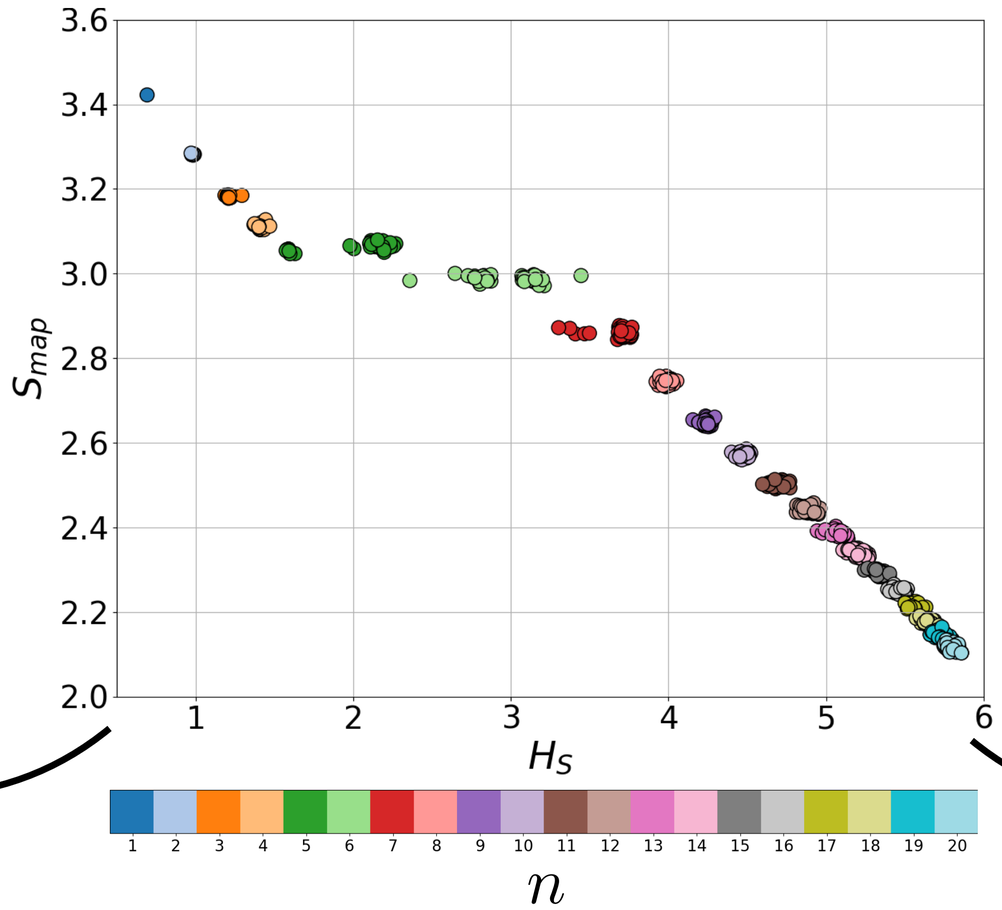
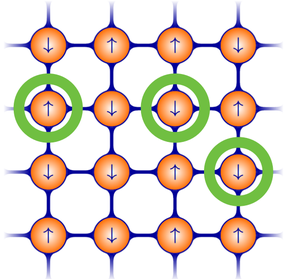
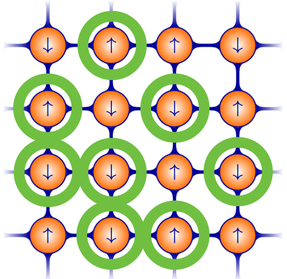


Low resolution



High resolution



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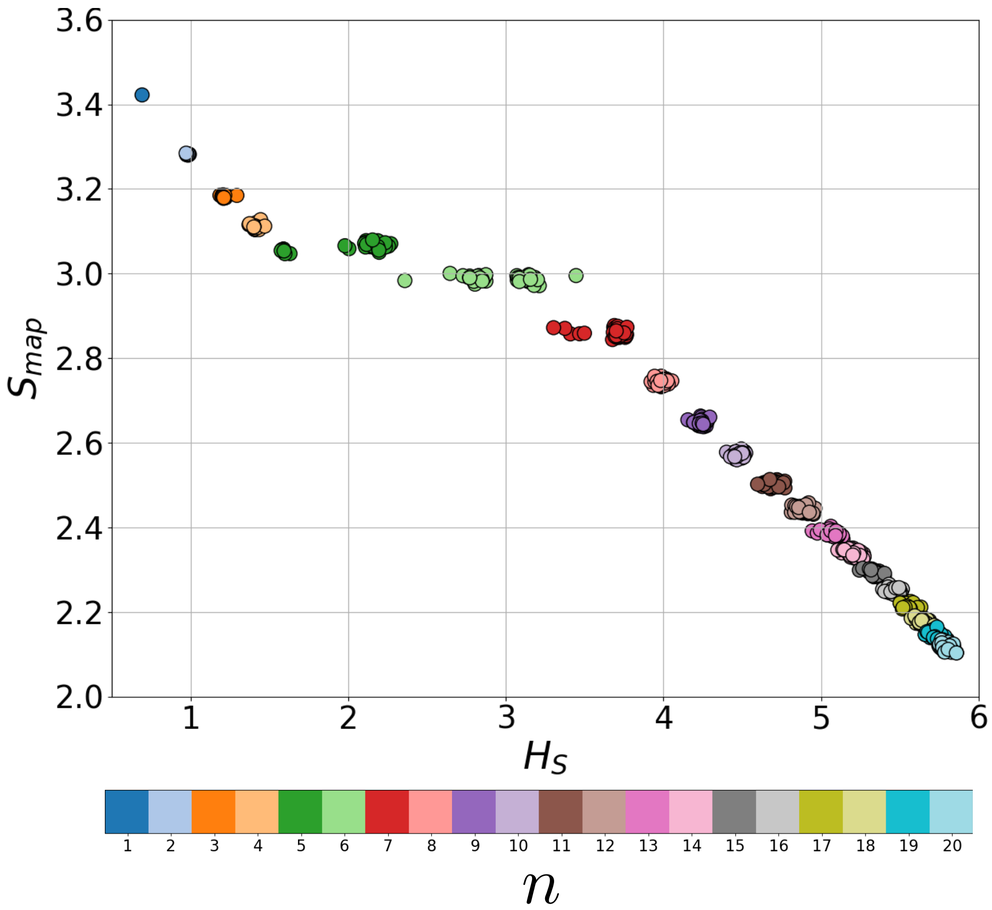

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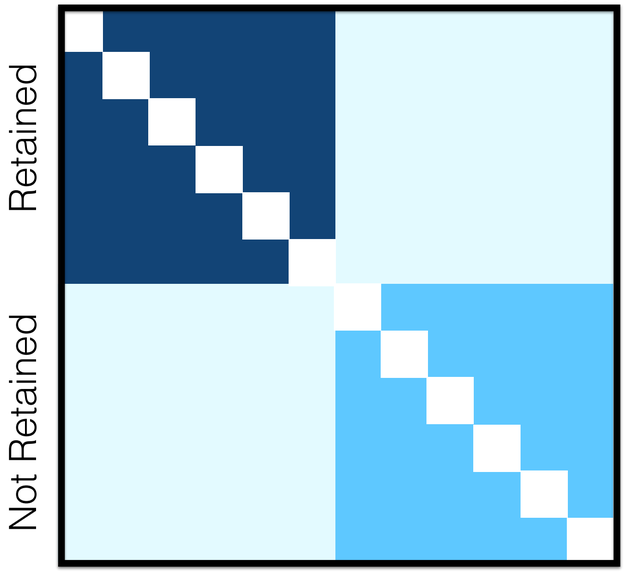
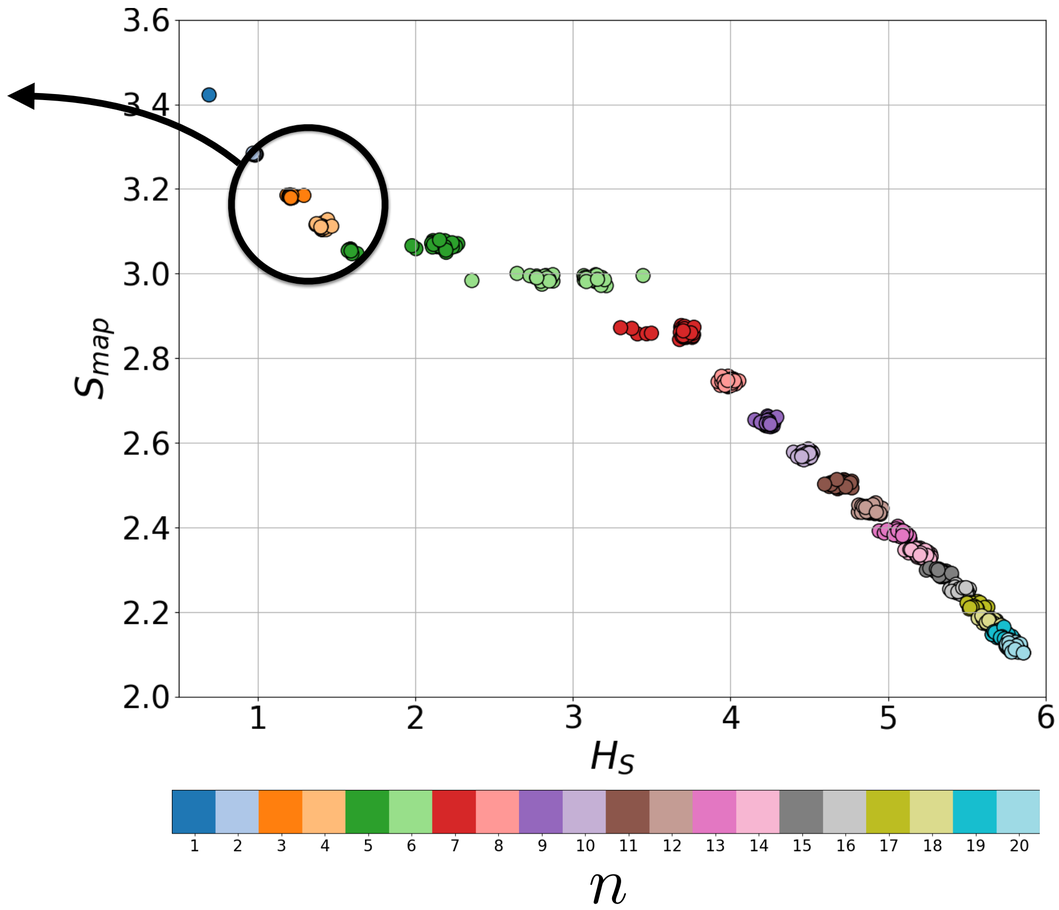
Ordered coupling matrix $|J_{ij}|$





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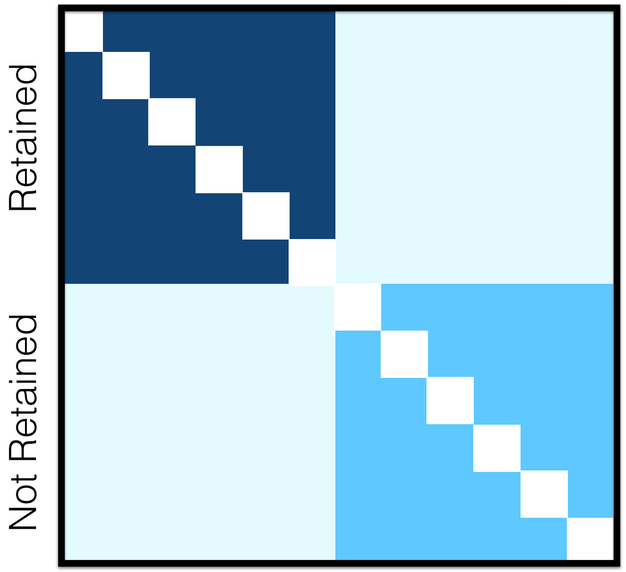

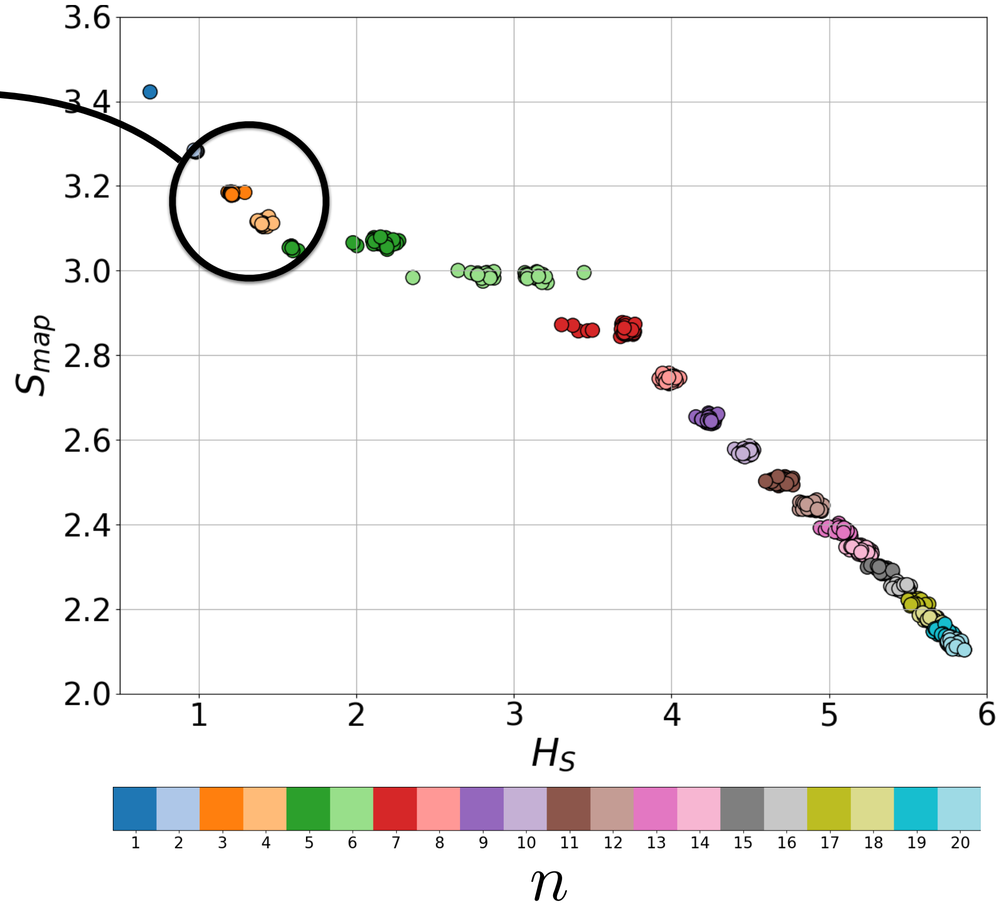

Strongly interacting retained neurons, weakly coupled with the integrated ones

Aldrigo, RM, Potestio (in preparation)

Resolution/Mapping-Entropy analysis

Maximally informative selection of neurons that **minimize the mapping entropy**

Hopfield model with N=100 neurons and 5 memory patterns

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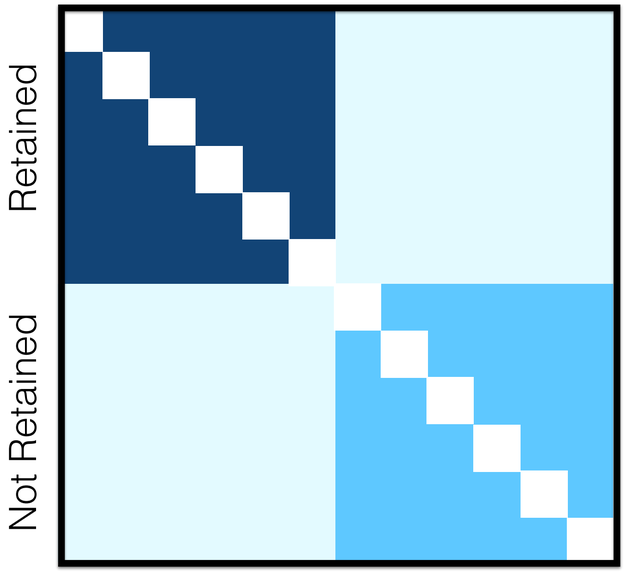

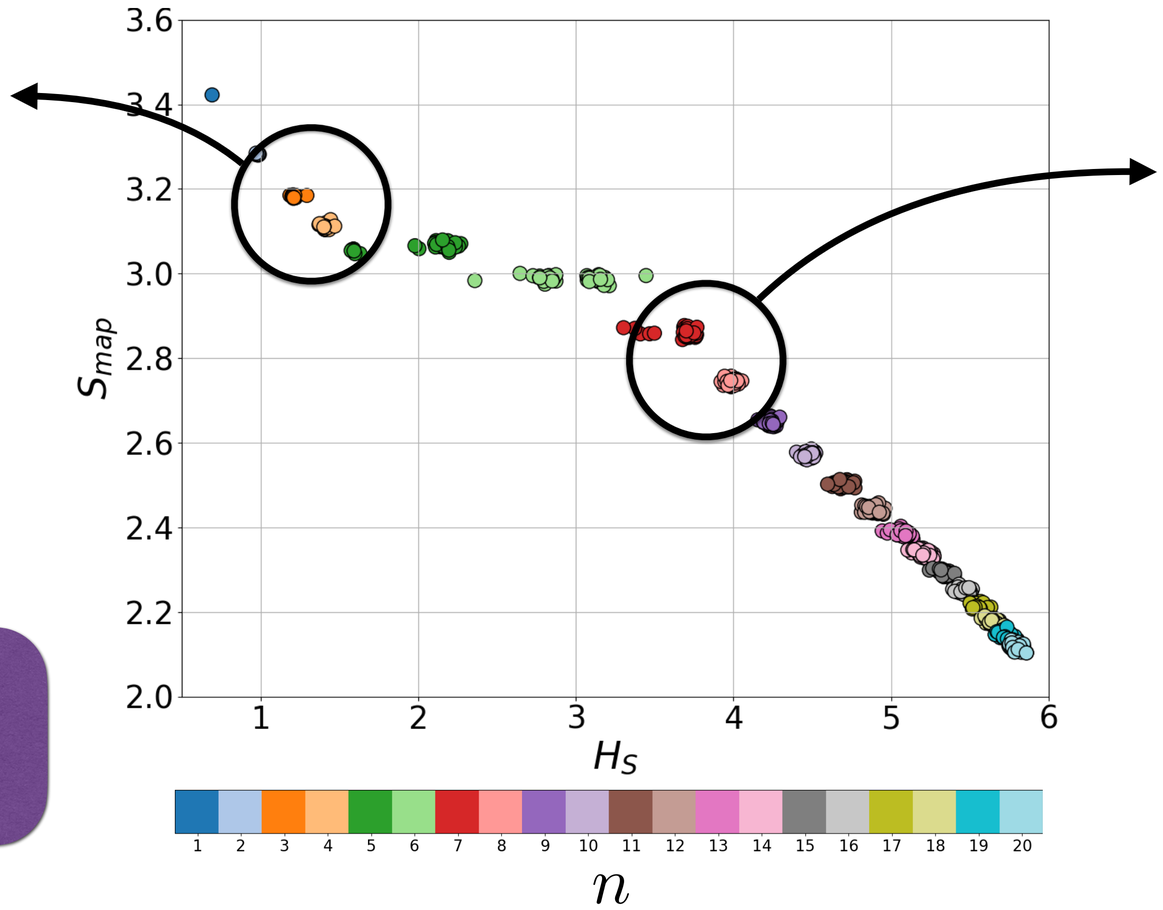

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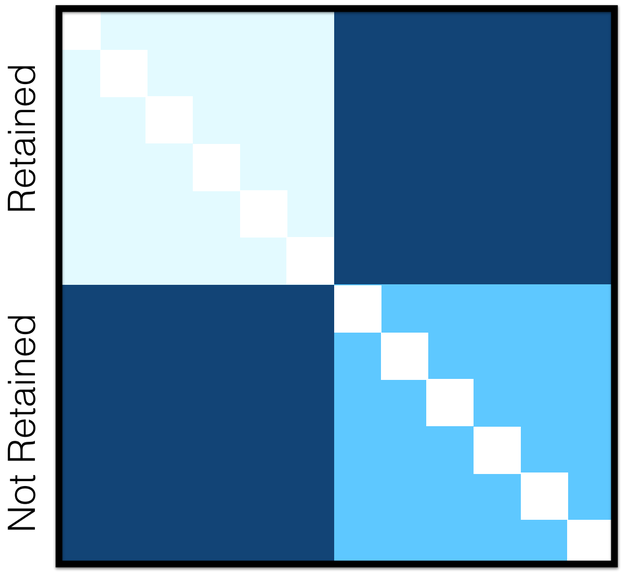

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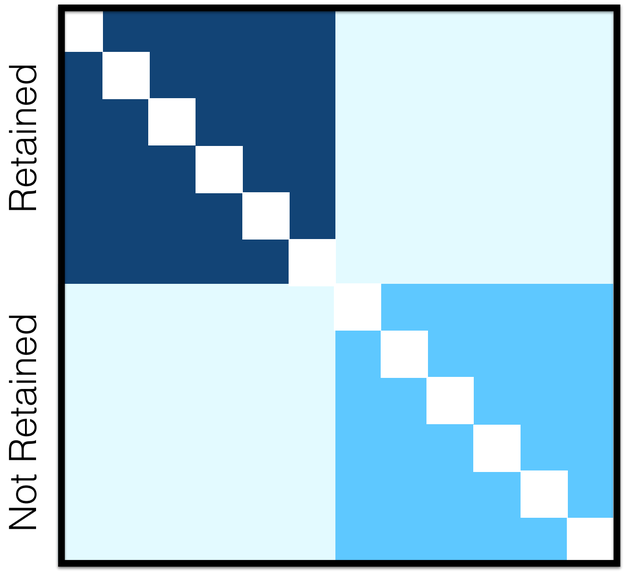

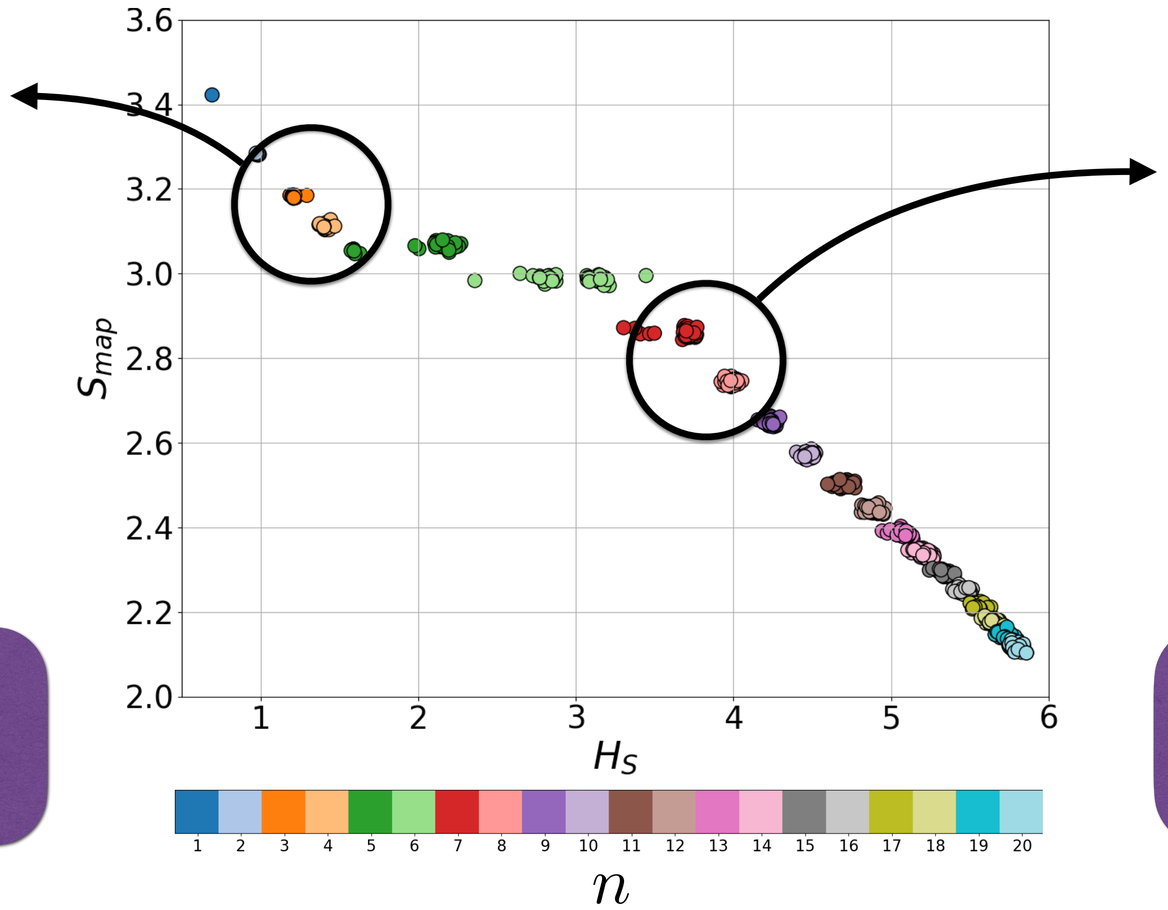

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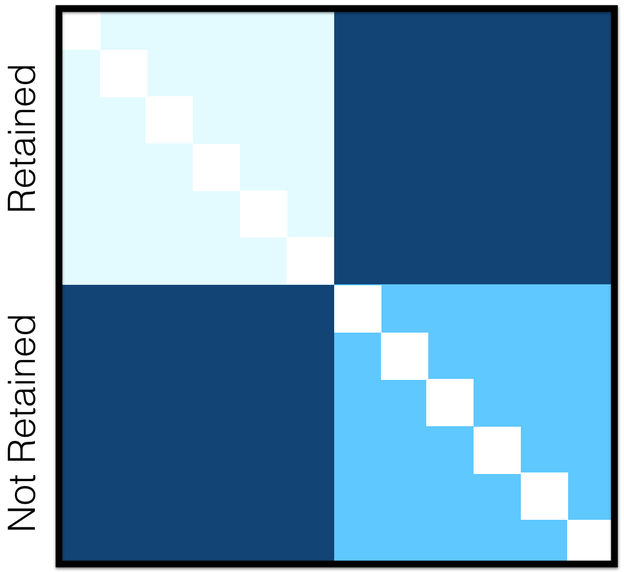

Strongly interacting retained neurons, weakly coupled with the integrated ones

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Aldrigo, RM, Potestio (in preparation)

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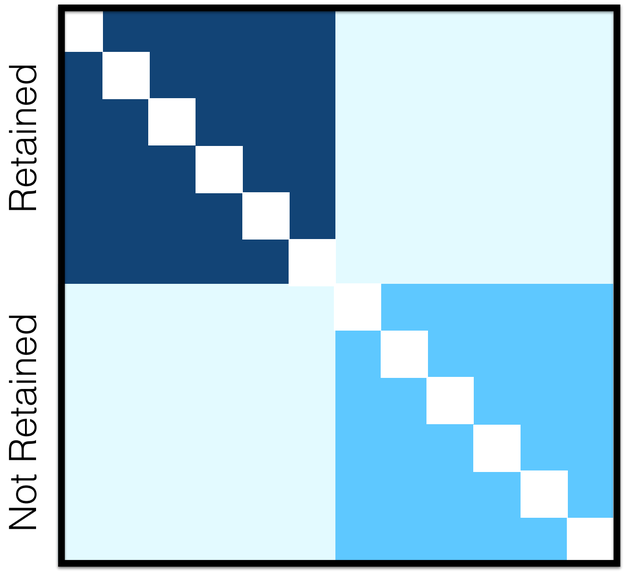

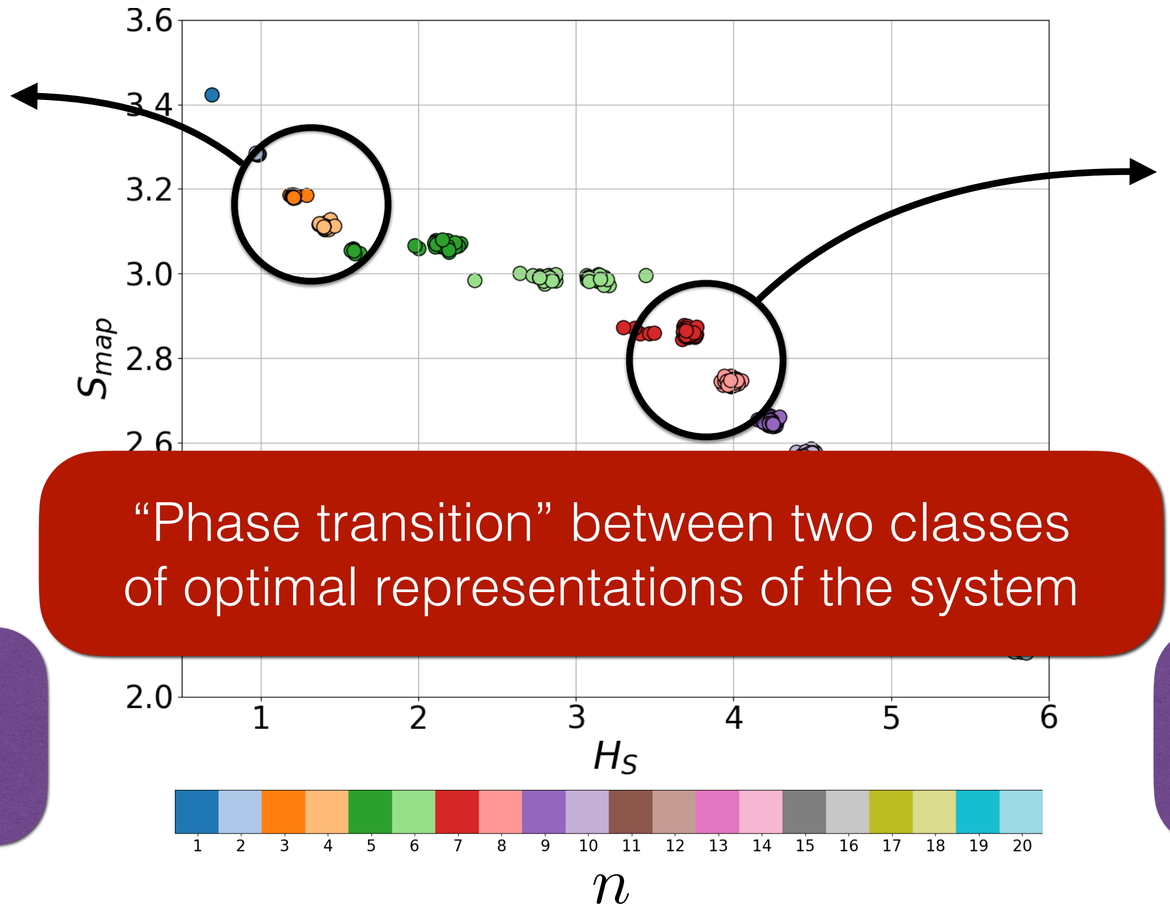

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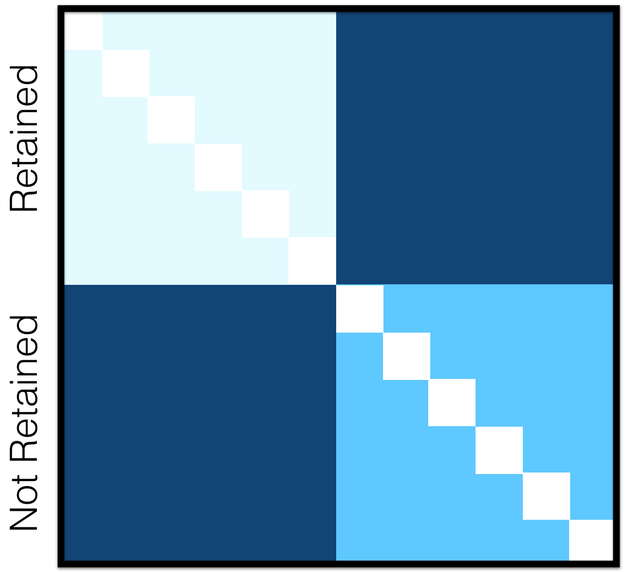


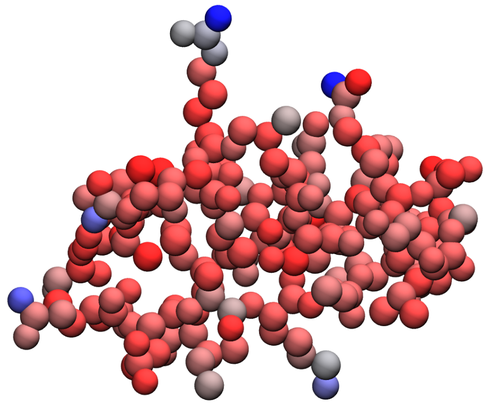
"Phase transition" between two classes of optimal representations of the system

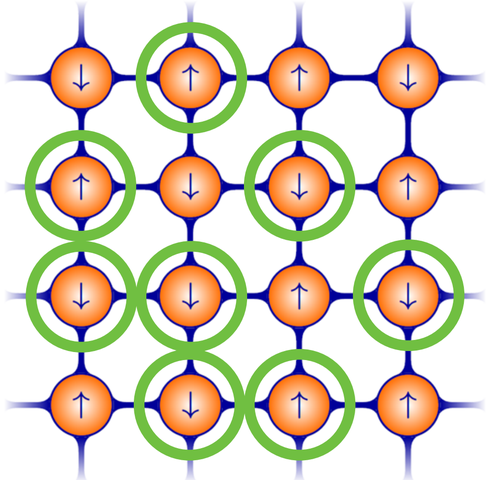
Strongly interacting retained neurons, weakly coupled with the integrated ones

Weakly interacting retained neurons, strongly coupled with the integrated ones

Aldrigo, RM, Potestio (in preparation)

Conclusions





- CG filters as a mean to gain insight on the behavior of complex systems
- CG'ing procedures result in a loss of statistical information
- Maximally-informative CG representations single out biologically relevant residues of a macromolecular system in an unsupervised manner
- Deep Graph networks can be employed to speed up information loss calculations and to achieve a quasi-exhaustive exploration of the mapping space
- Application of the mapping entropy protocol to a neural system: maximally informative neurons in a Hopfield model
- Phase separation of the maximally informative representations of the system depending on the observational level of detail

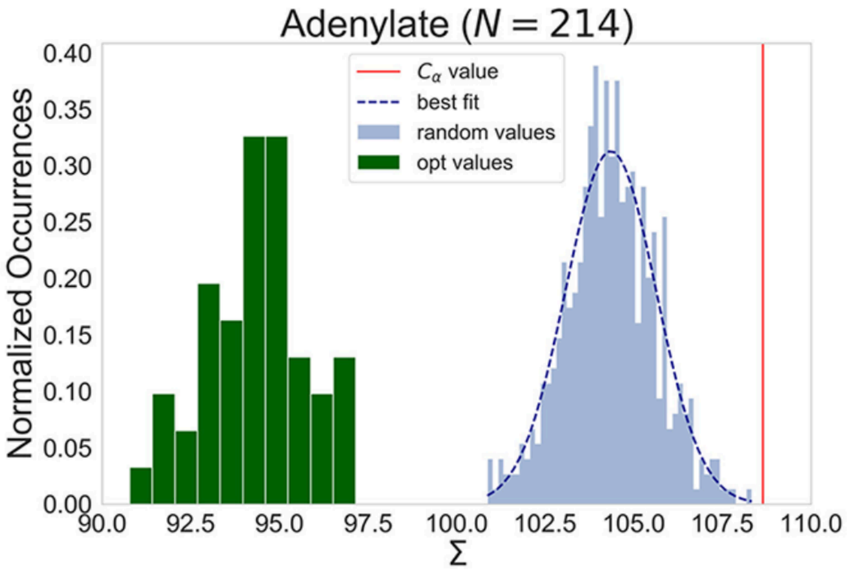
Thank you for the attention!

Acknowledgments

Potestio Lab:
(& former members)

Raffaello Potestio
Thomas Tarenzi, now at UoB (UK)
Giovanni Mattiotti
Marco Giulini, now at UU (NL)
Roberto Menichetti
Elio Fiorentini, now at AM (IT)
Marta Rigoli, now at CIBIO (IT)
Margherita Mele
Lorenzo Petrolli
Manuel Micheloni
Camilla Spreti

Characterizing the space of solutions



Giulini, RM, Shell, Potestio, JCTC 2020

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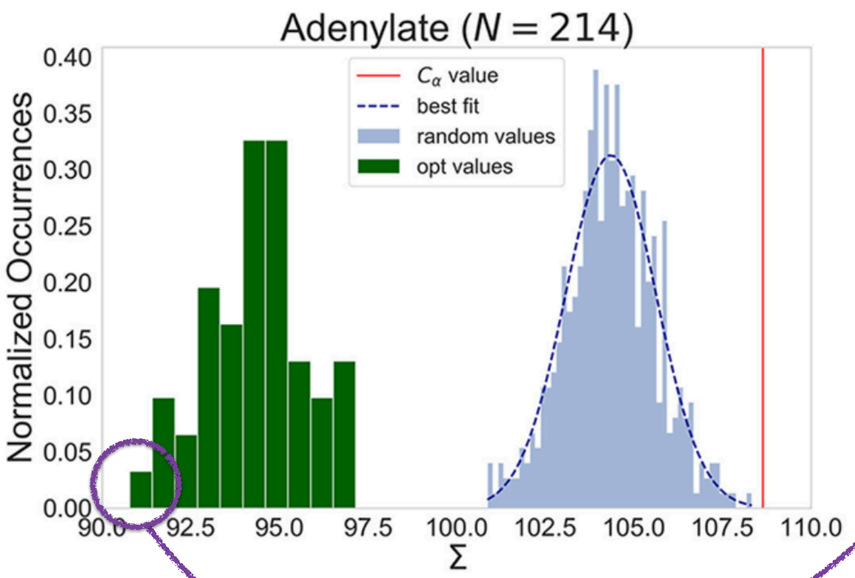
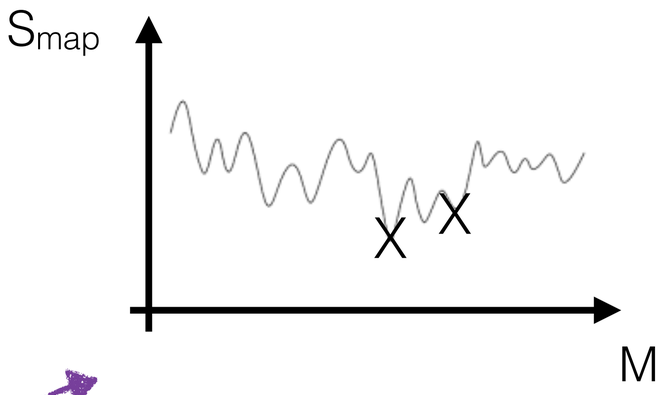
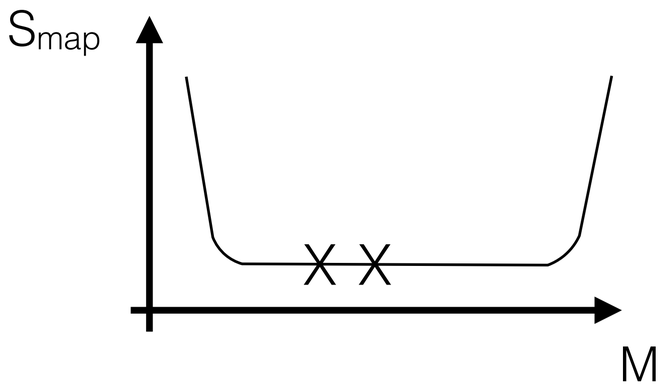




VS



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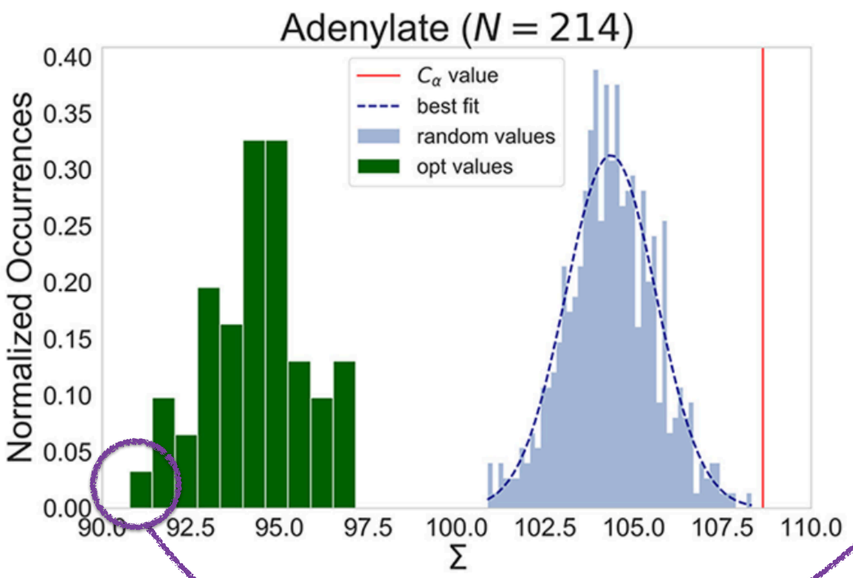

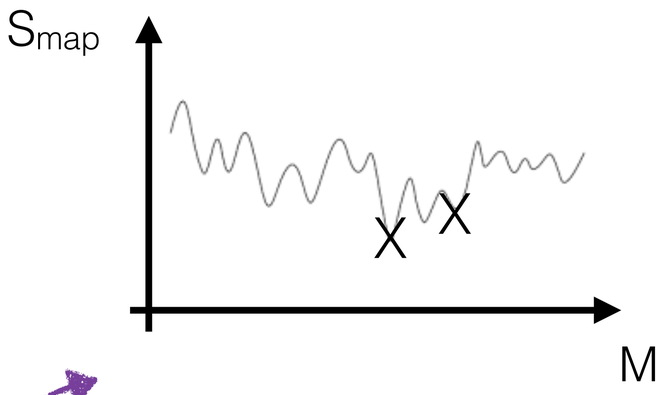

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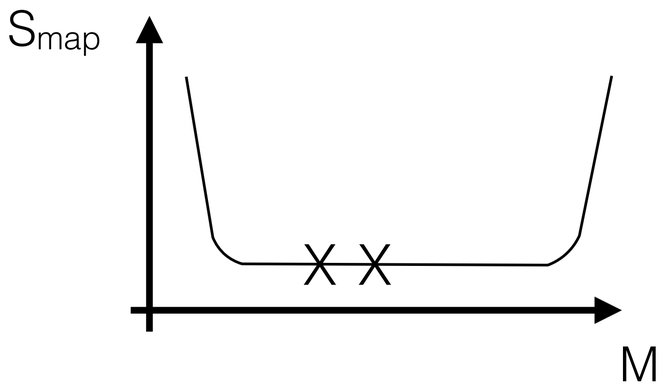

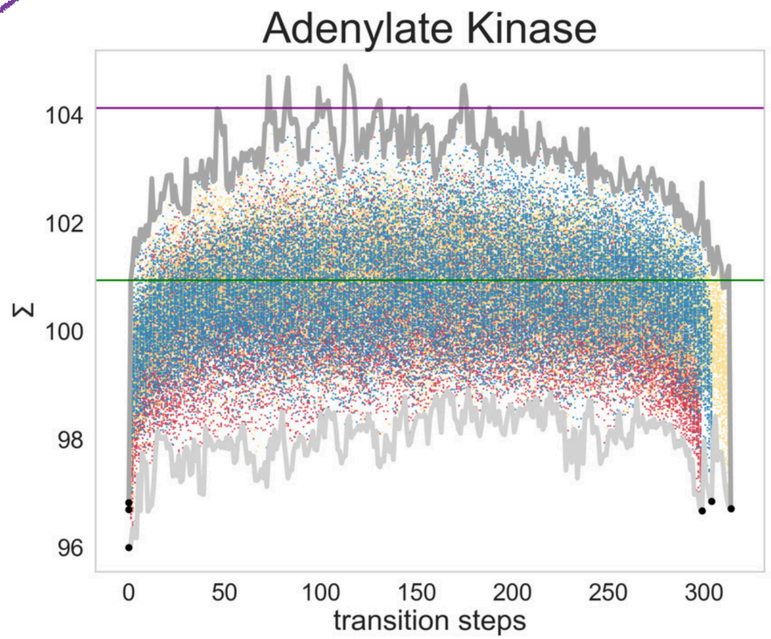

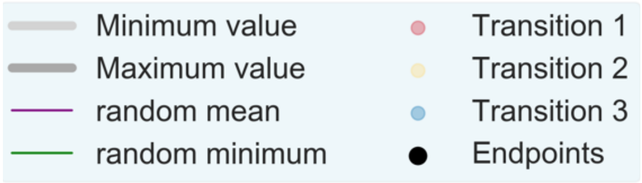

Giulini, RM, Shell, Potestio, JCTC 2020

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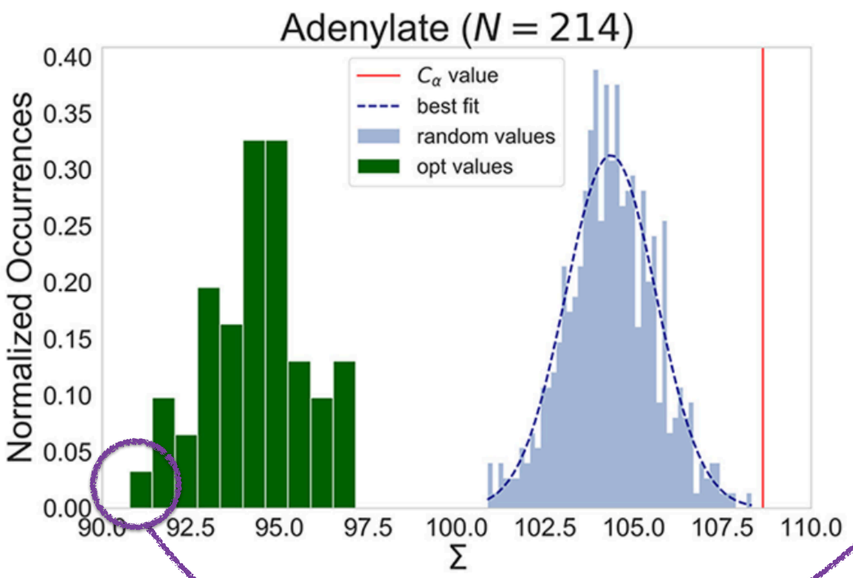
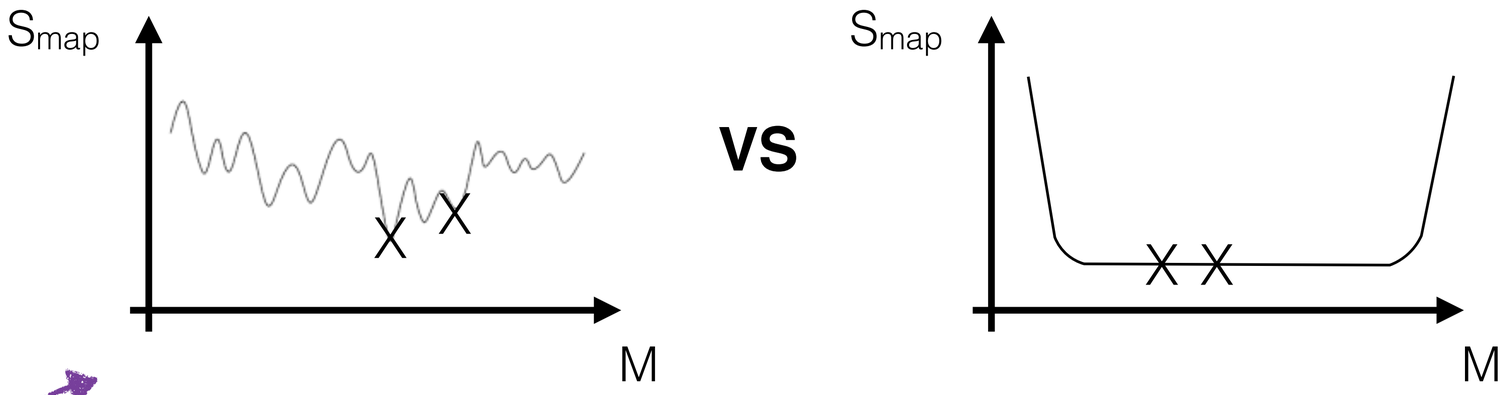
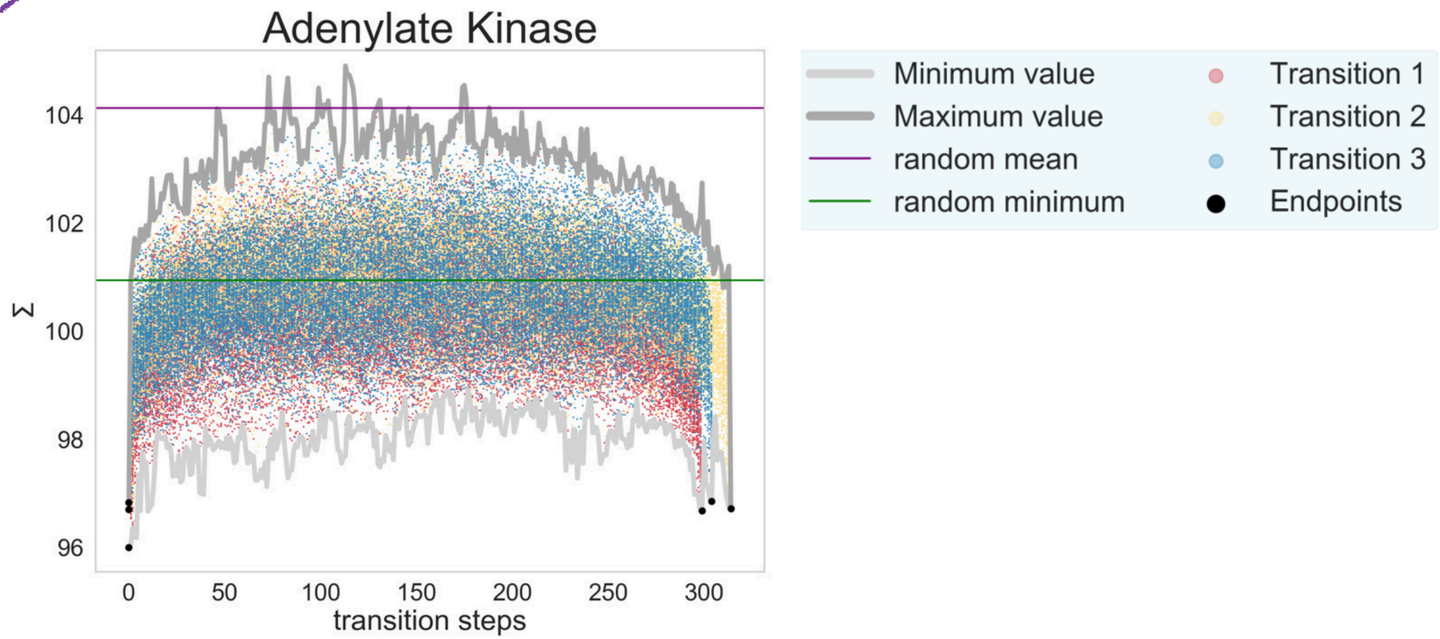




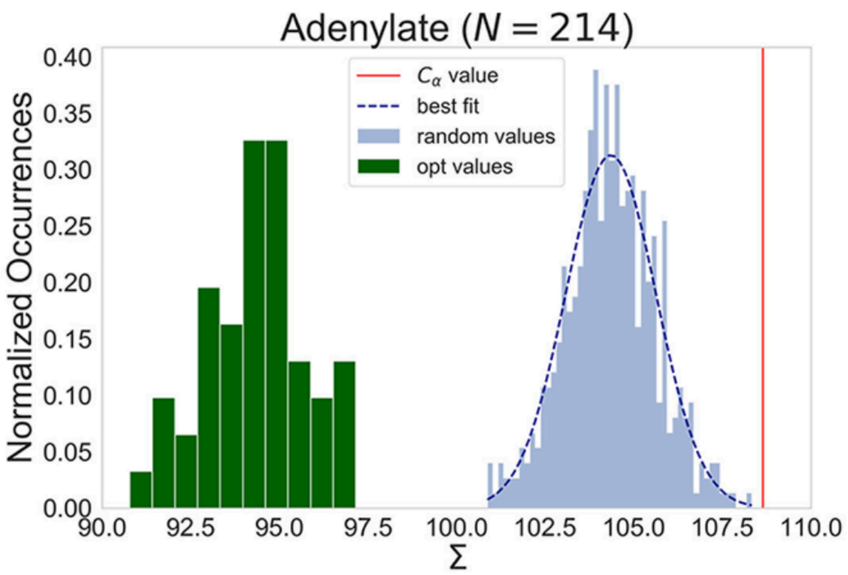


Optimized solutions are isolated points in the mapping entropy landscape

Atoms conserved with high probability are likely present in many uncorrelated solutions

Giulini, RM, Shell, Potestio, JCTC 2020

Characterizing the space of solutions



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State-dependence of optimal mappings

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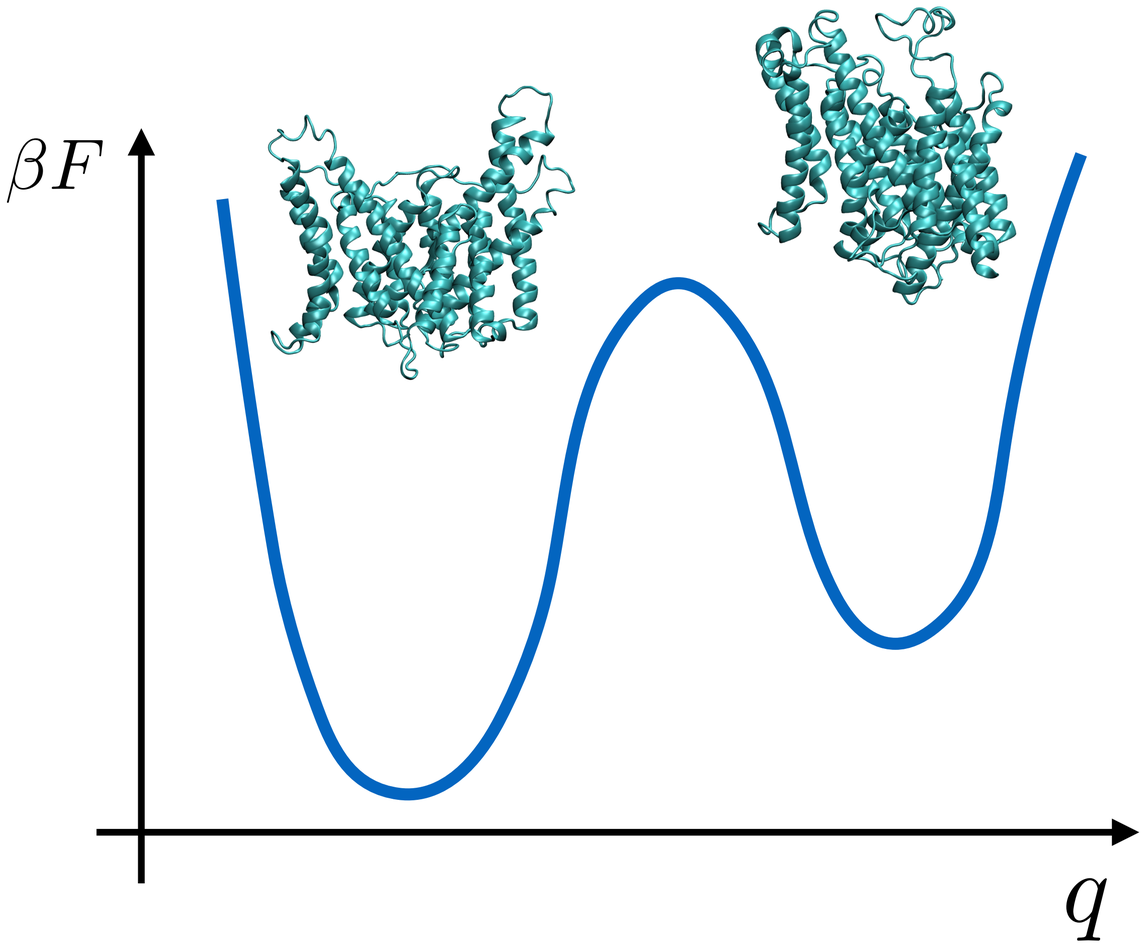
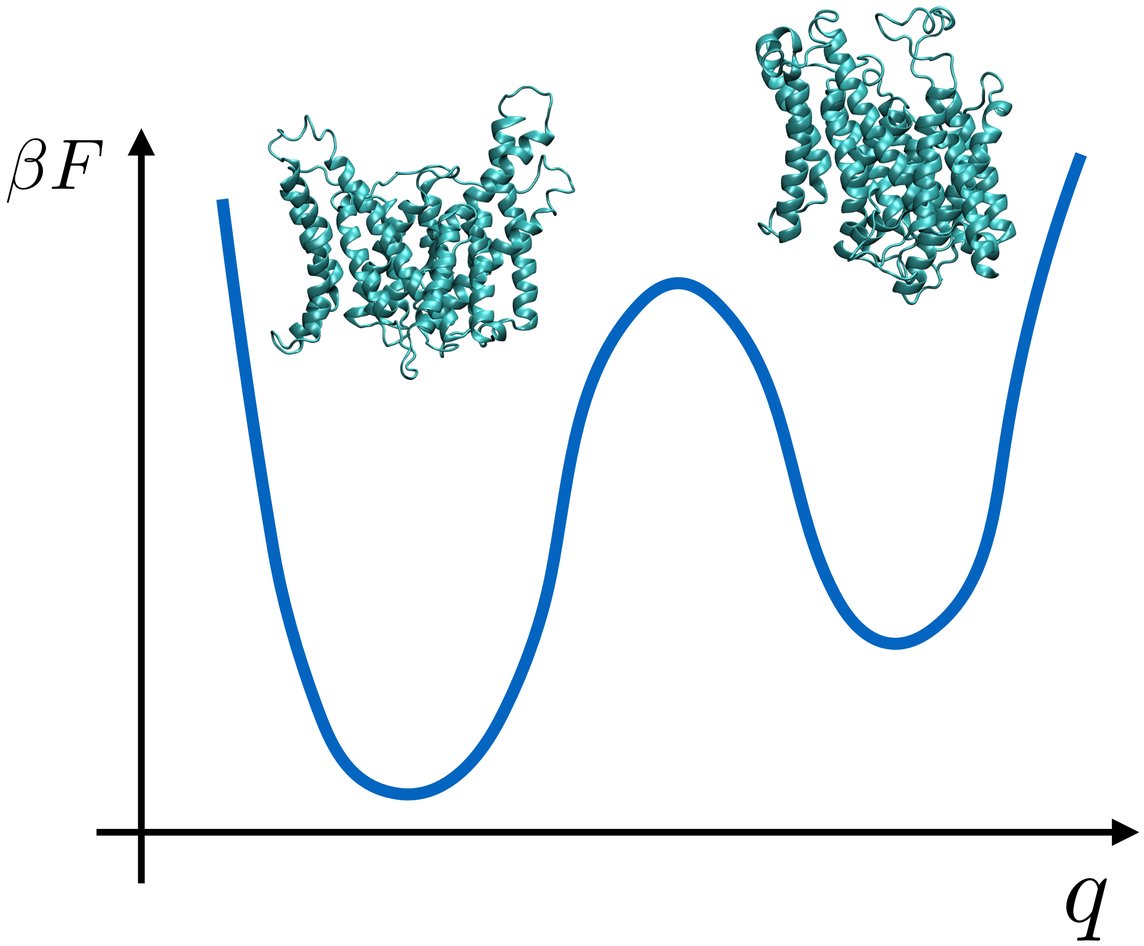
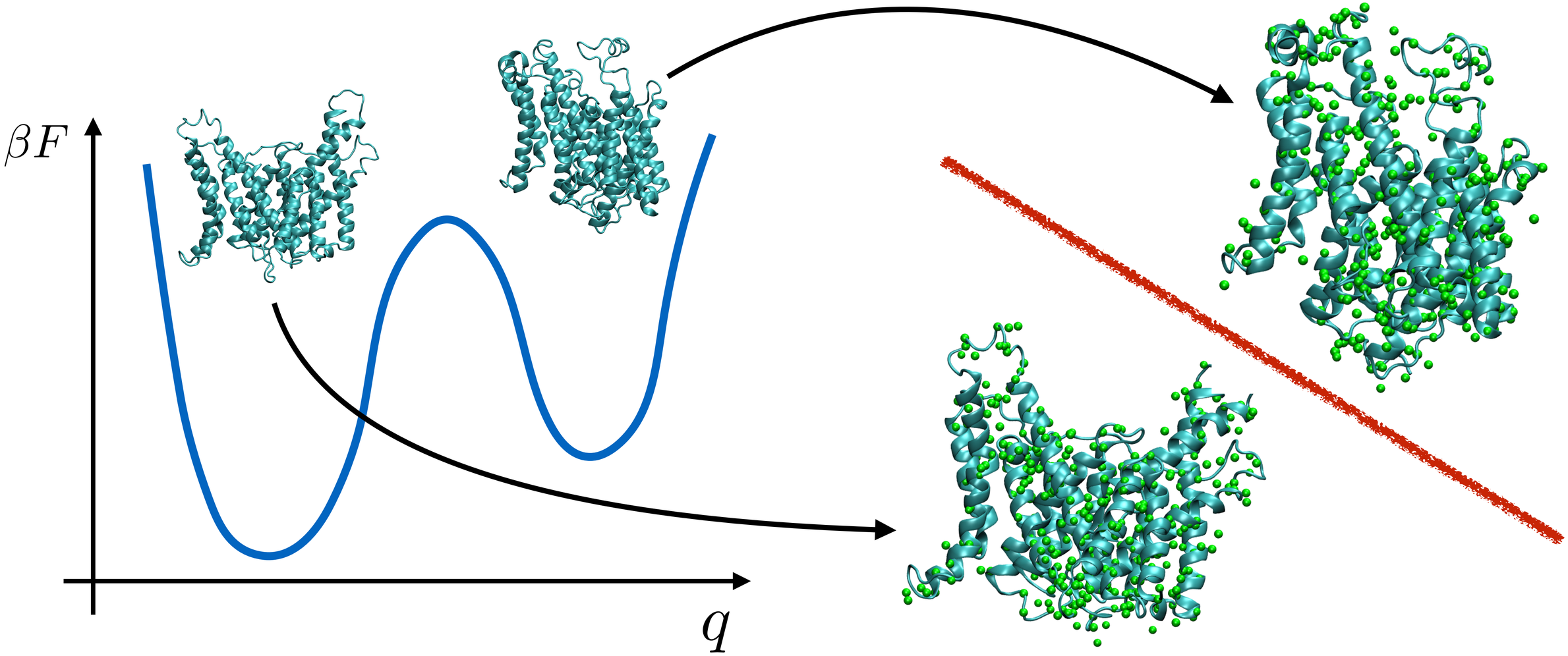


State-dependence of optimal mappings

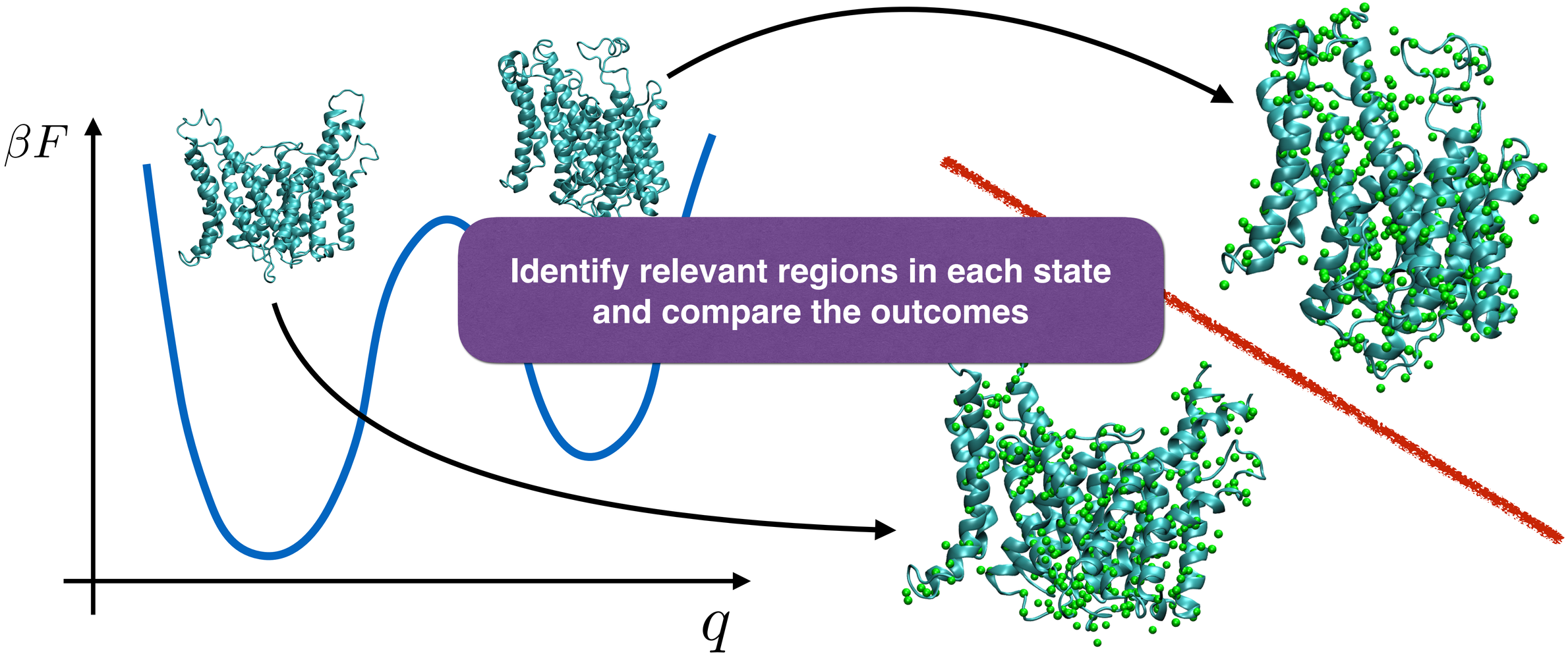


Search for mappings that minimize the information loss within each basin

State-dependence of optimal mappings



State-dependence of optimal mappings



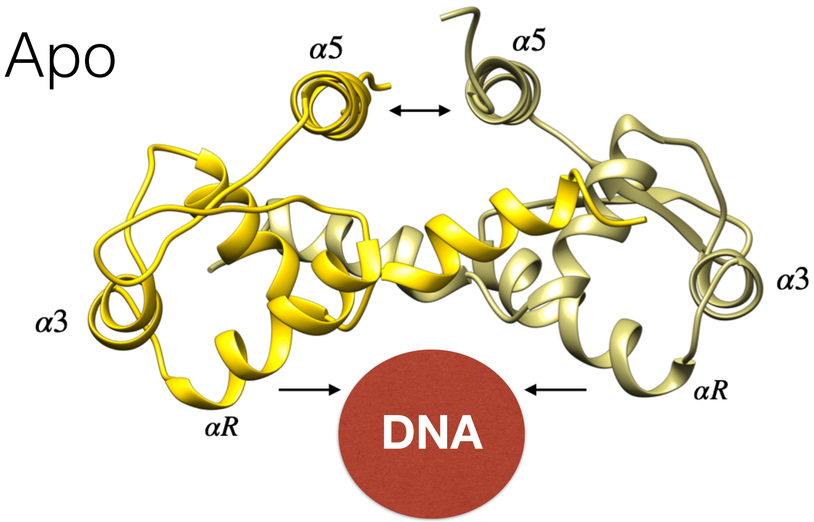
Identify relevant regions in each state and compare the outcomes

Application: CzrA transcription repressor

Rigoli, Giulini, RM, Potestio, in preparation

Application: CzrA transcription repressor

Apo



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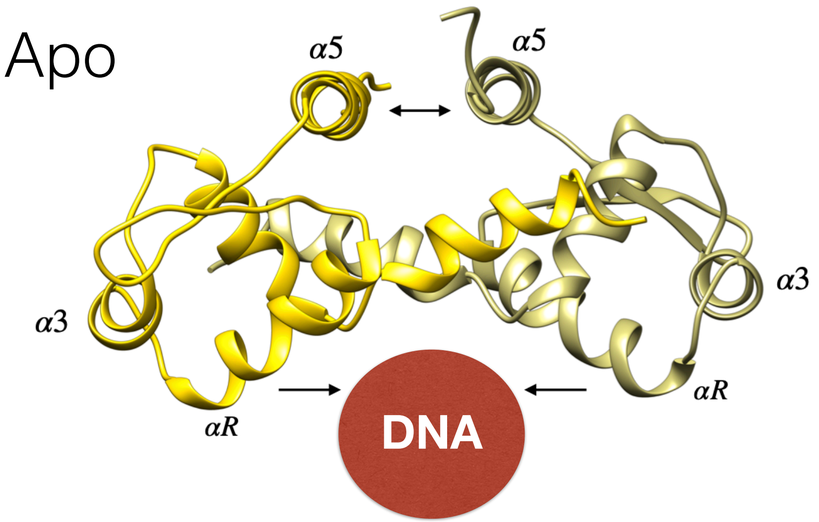
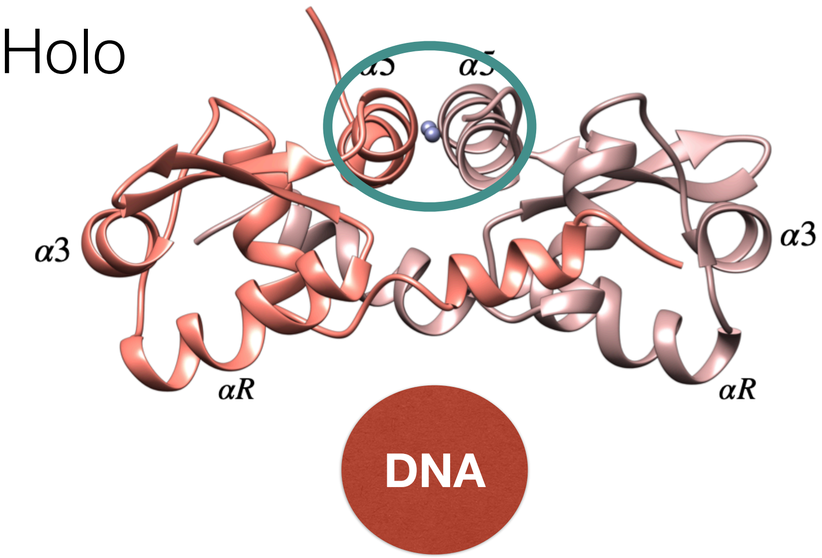


Holo



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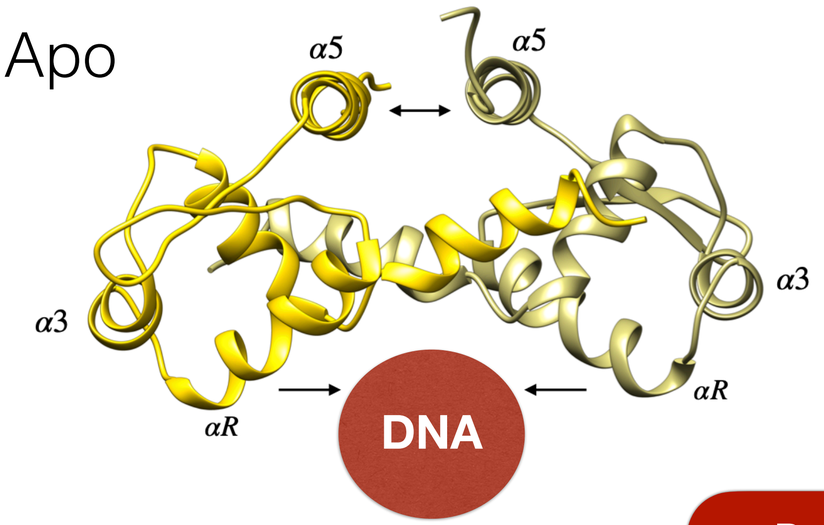
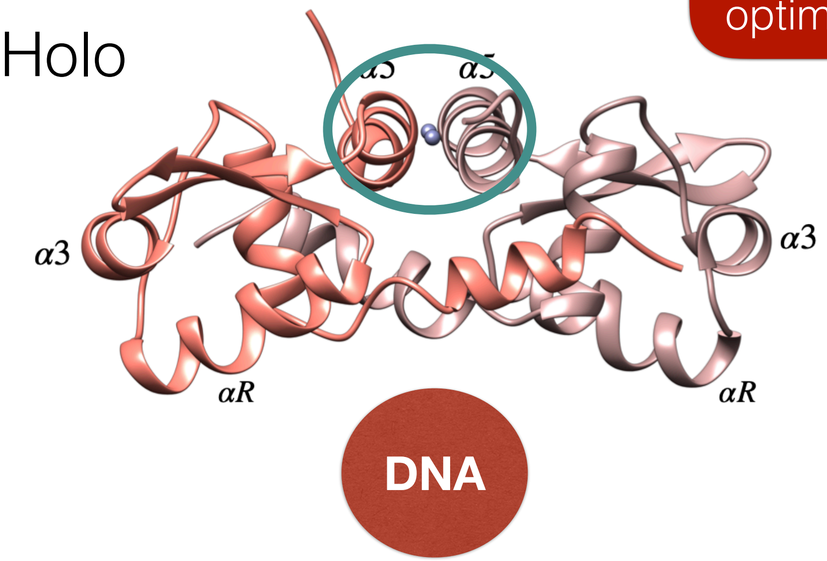


Perform independent optimizations in each state

Holo



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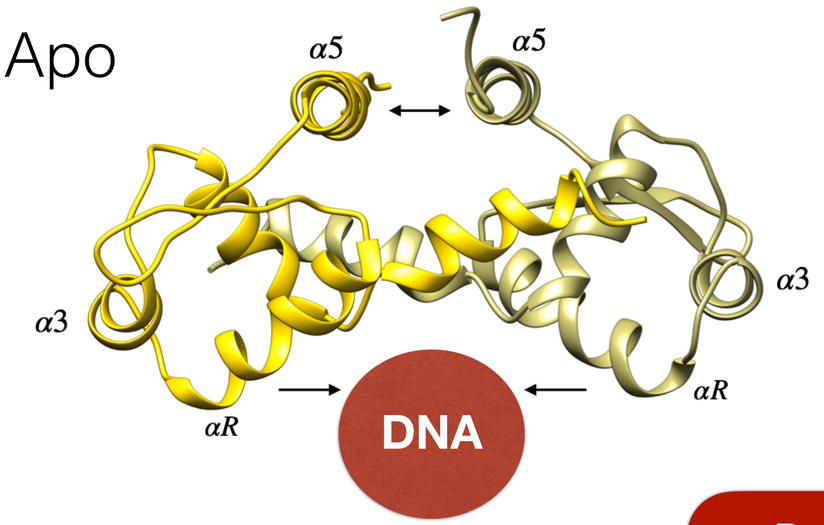

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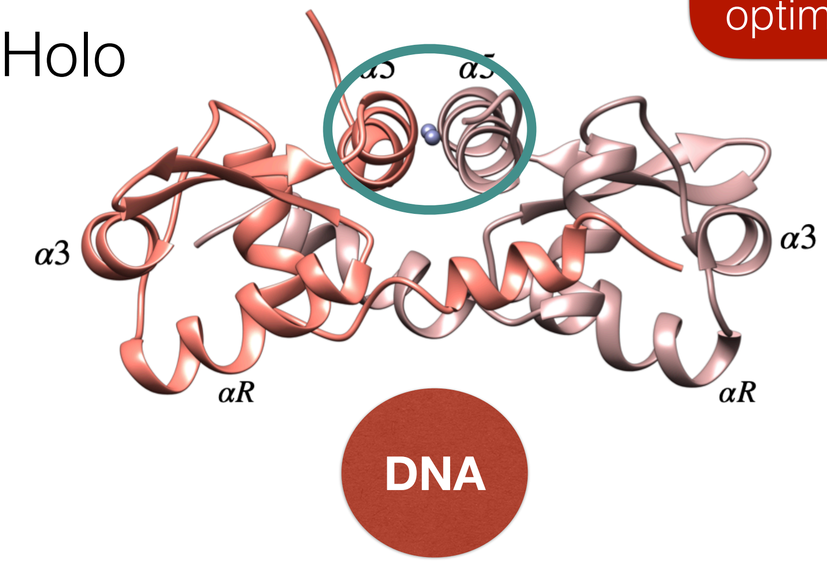

Biologically relevant residues slightly "deactivate" between Apo and Holo

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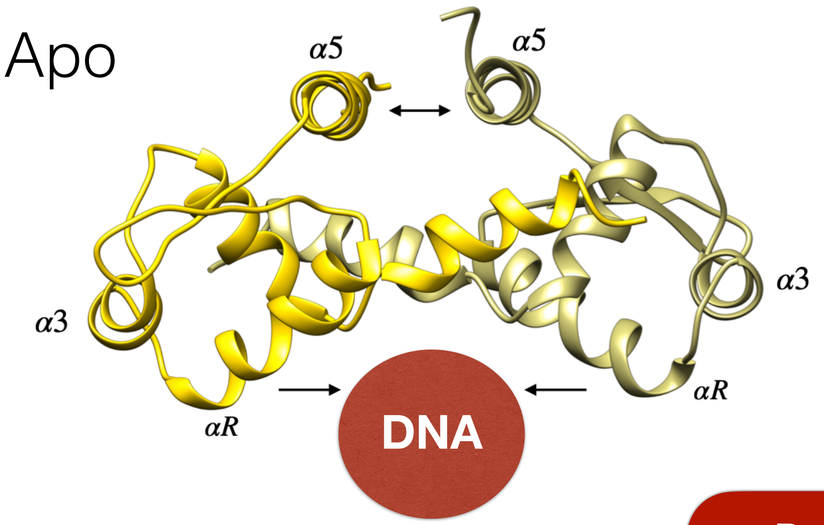

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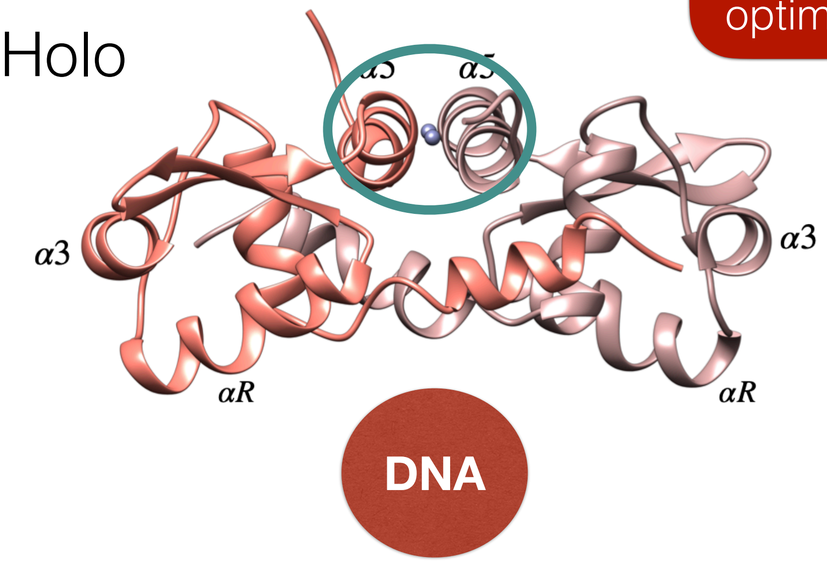

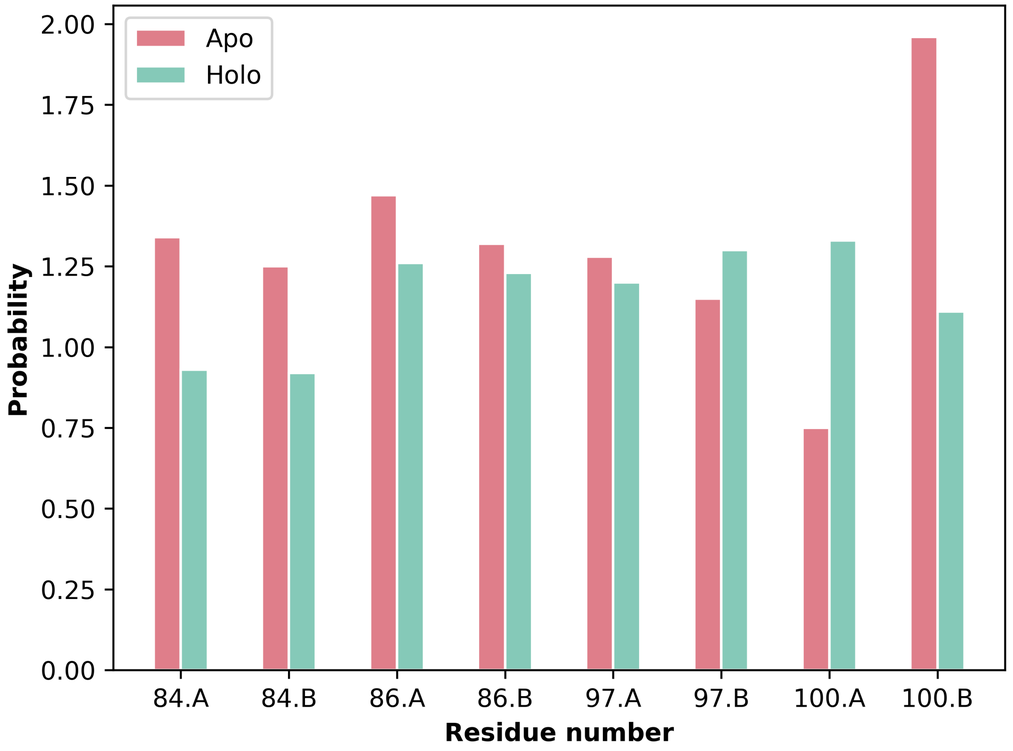

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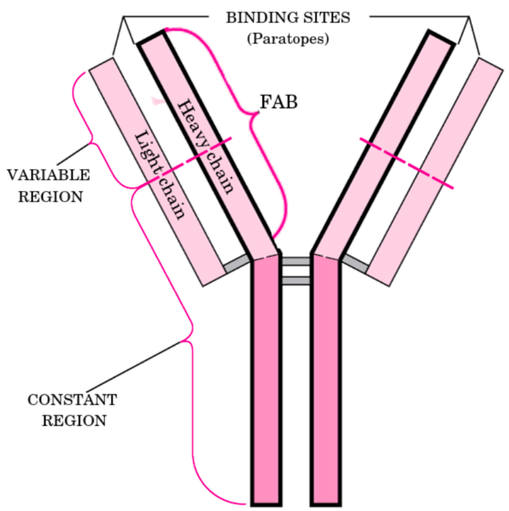
Rigoli, Giulini, RM, Potestio, in preparation

Application: G6 Antibody and VEGF-A antigen



Galante, Tarenzi, Potestio, preliminary results

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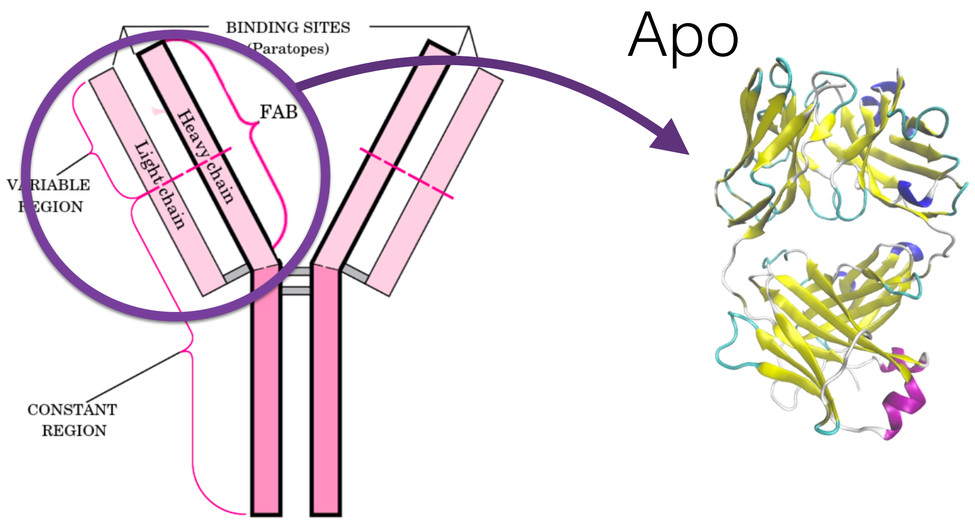

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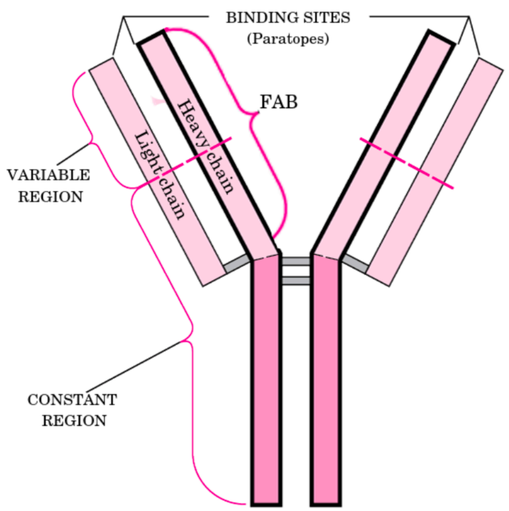

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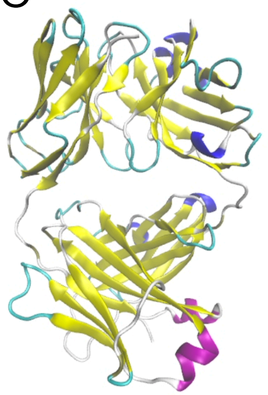

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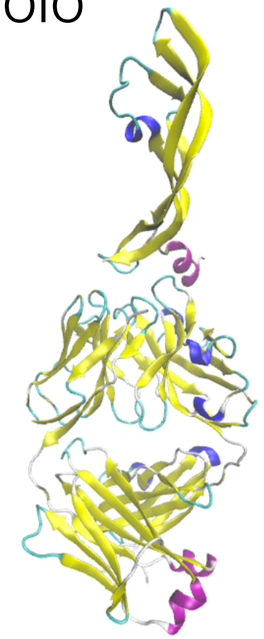

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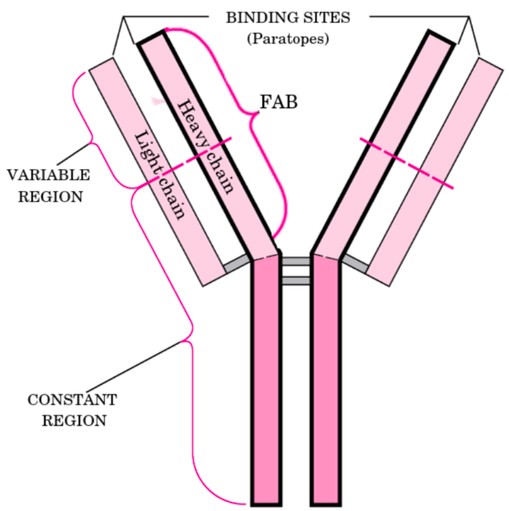

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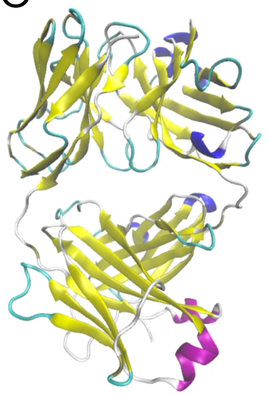

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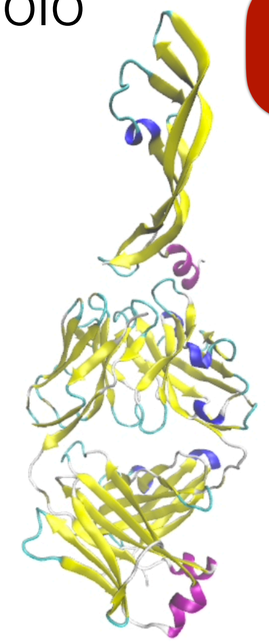

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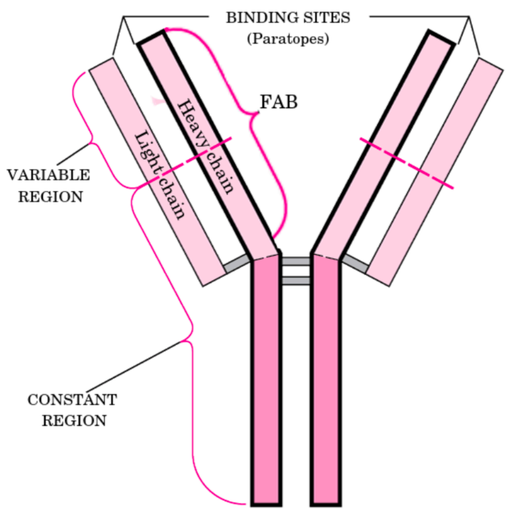

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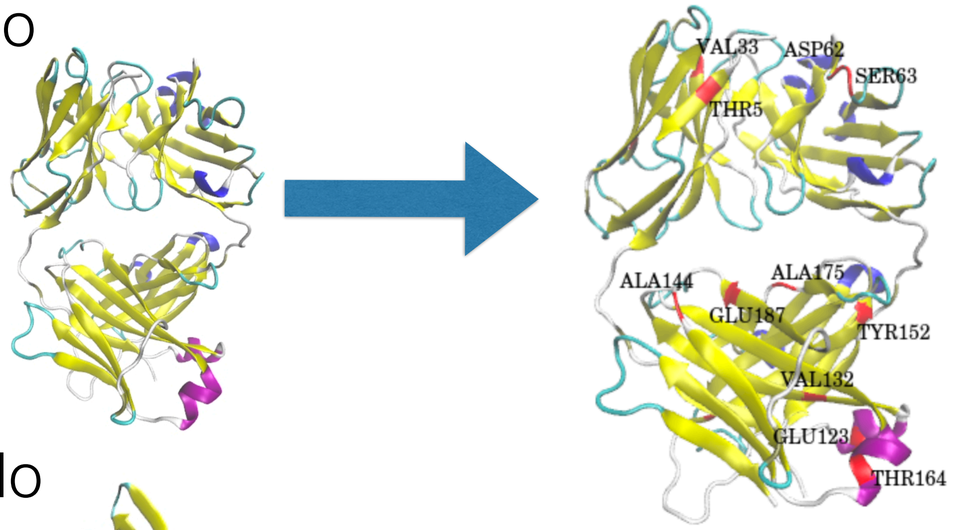

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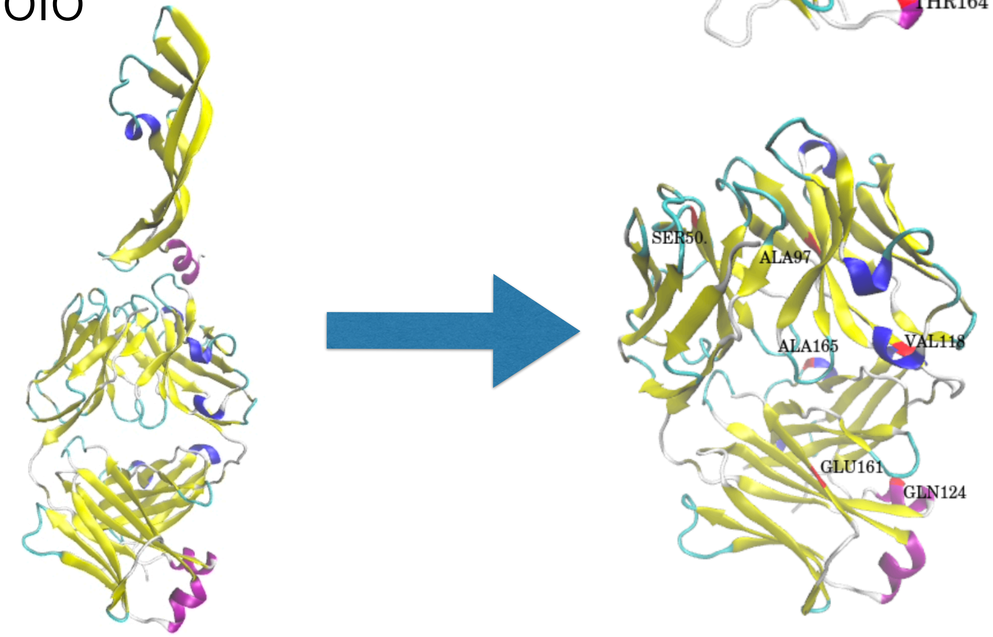

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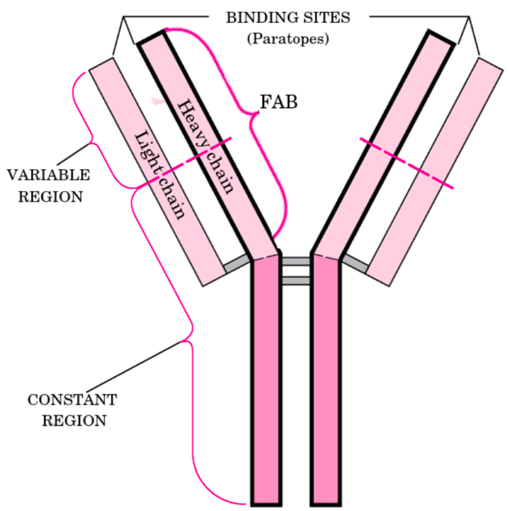

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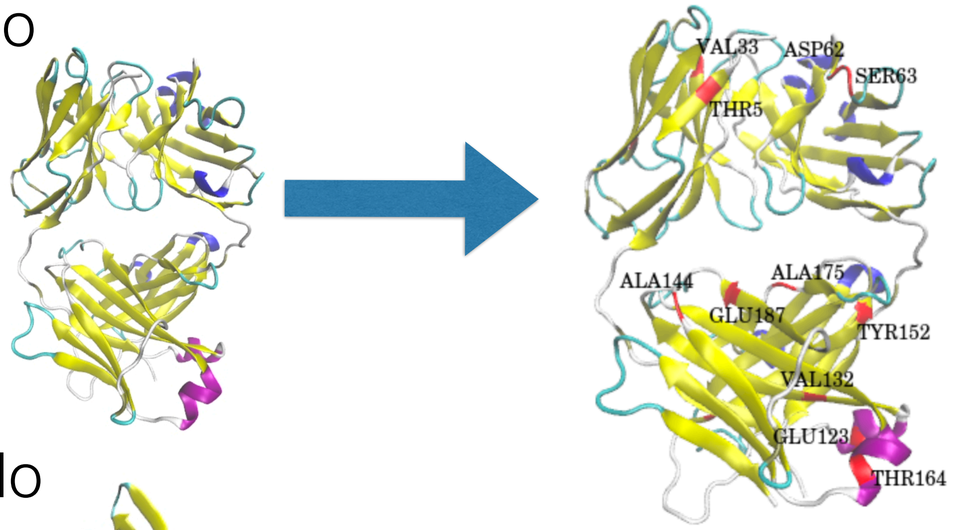
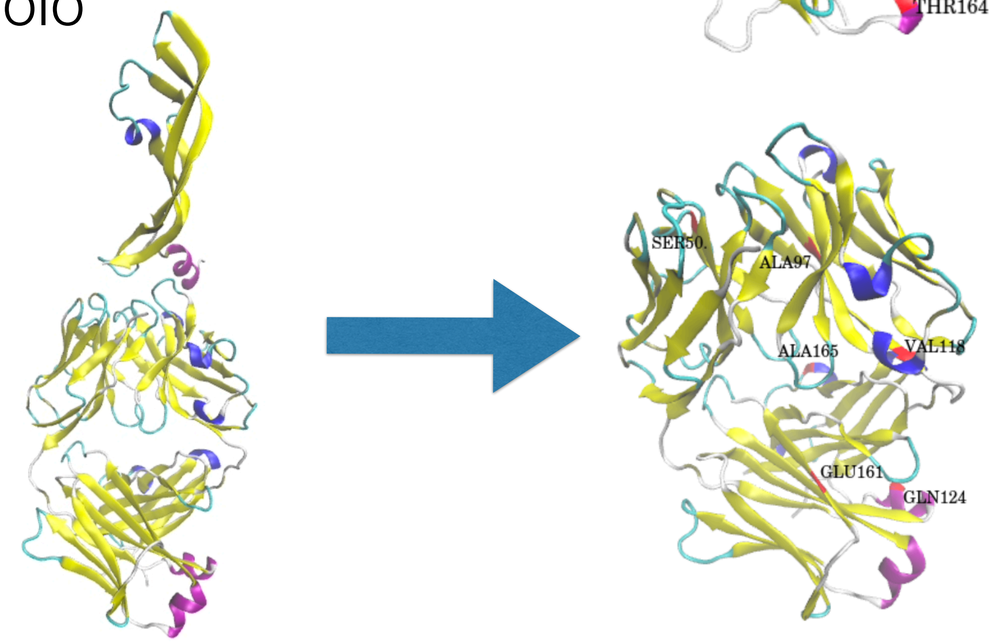
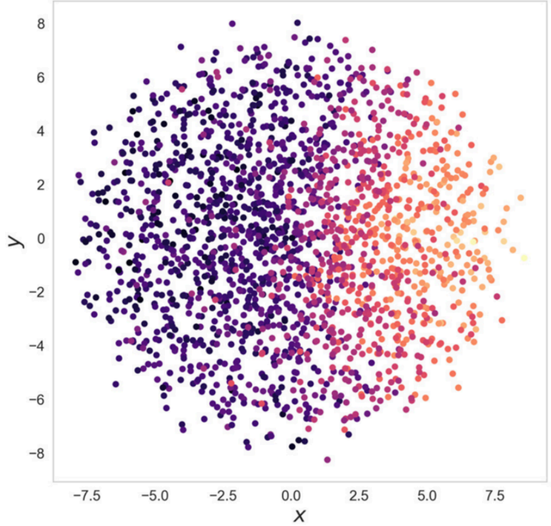


Holo



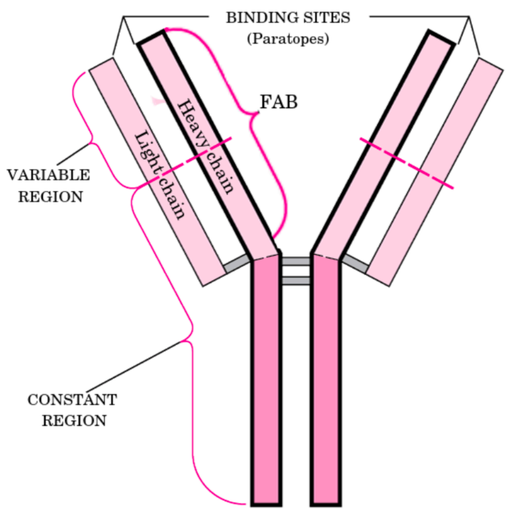
The curse of the space dimensionality

An exhaustive sampling of all mappings is unfeasible

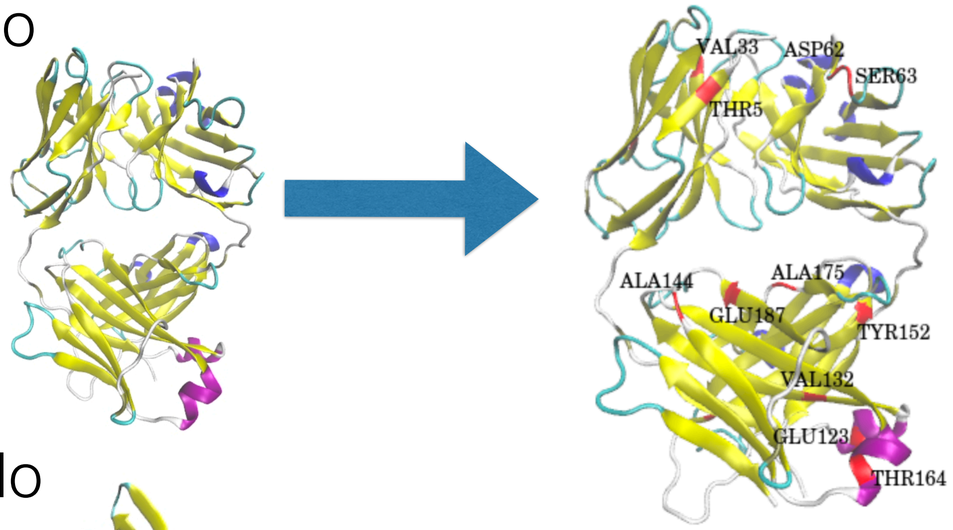


Galante, Tarenzi, Potestio, preliminary results

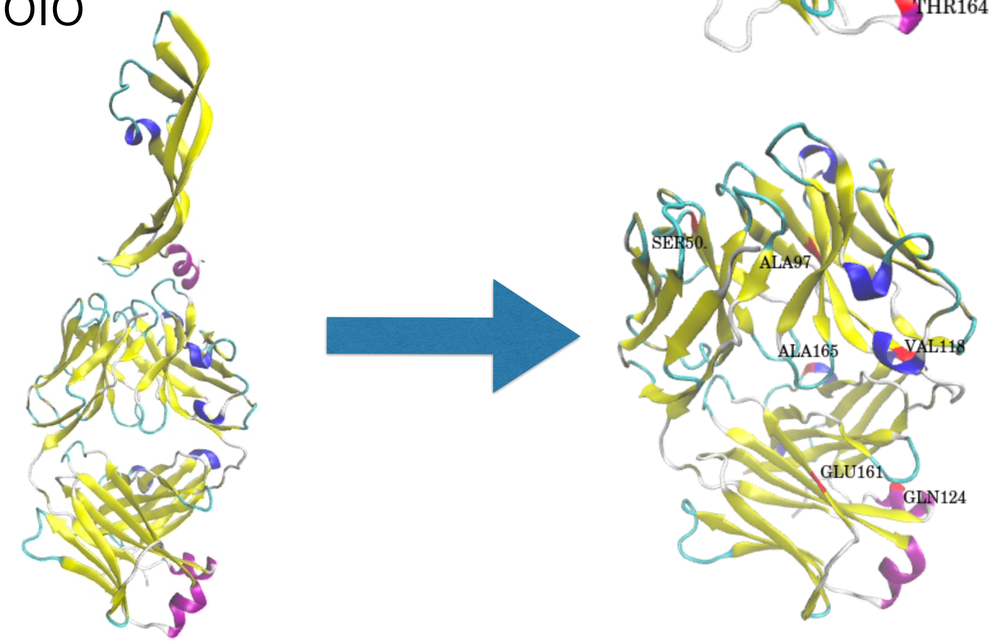
Application: G6 Antibody and VEGF-A antigen



Apo



Holo



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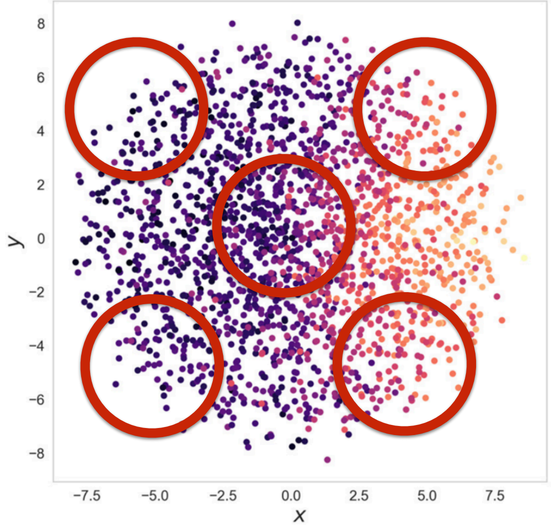

Explore according to the distance

$$\mathcal{D}(M, M')$$

Galante, Tarenzi, Potestio, preliminary results

S_{map} via deep graph networks

Speedup generated by DGNs: quasi-exhaustive exploration of the S_{map} landscape

RM, Giulini, Potestio, EPJB 2021
Errica, Giulini, RM *et al*., Front. Mol. Biosci. 2021

S_{map} via deep graph networks

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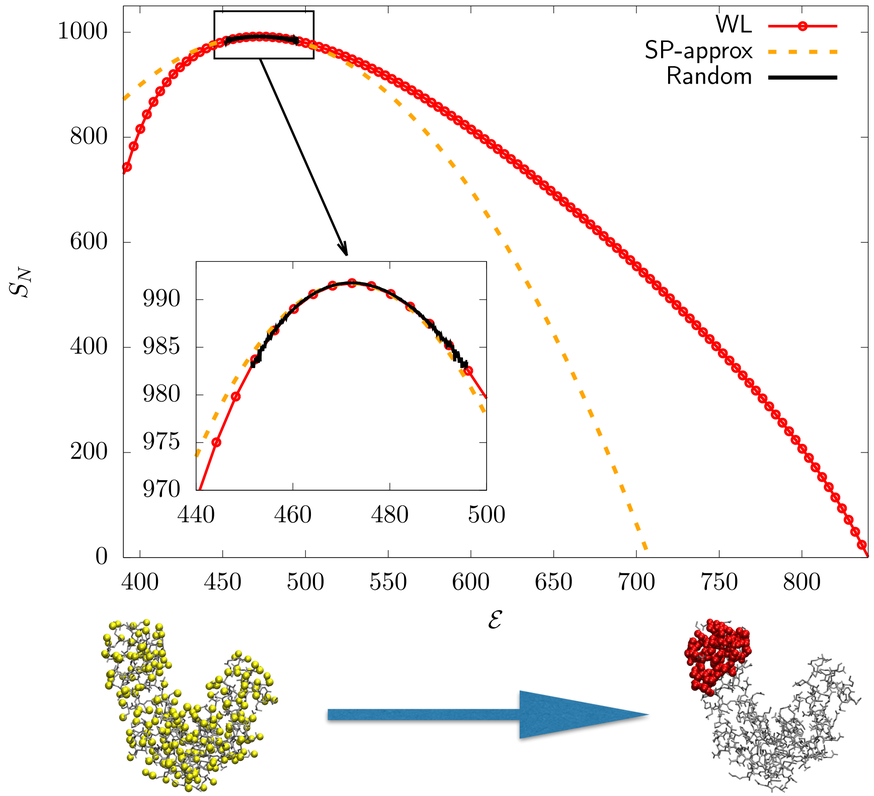
$$\#\text{selections}(\mathcal{E}) \propto e^{S_N(\mathcal{E})}$$



RM, Giulini, Potestio, EPJB 2021
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

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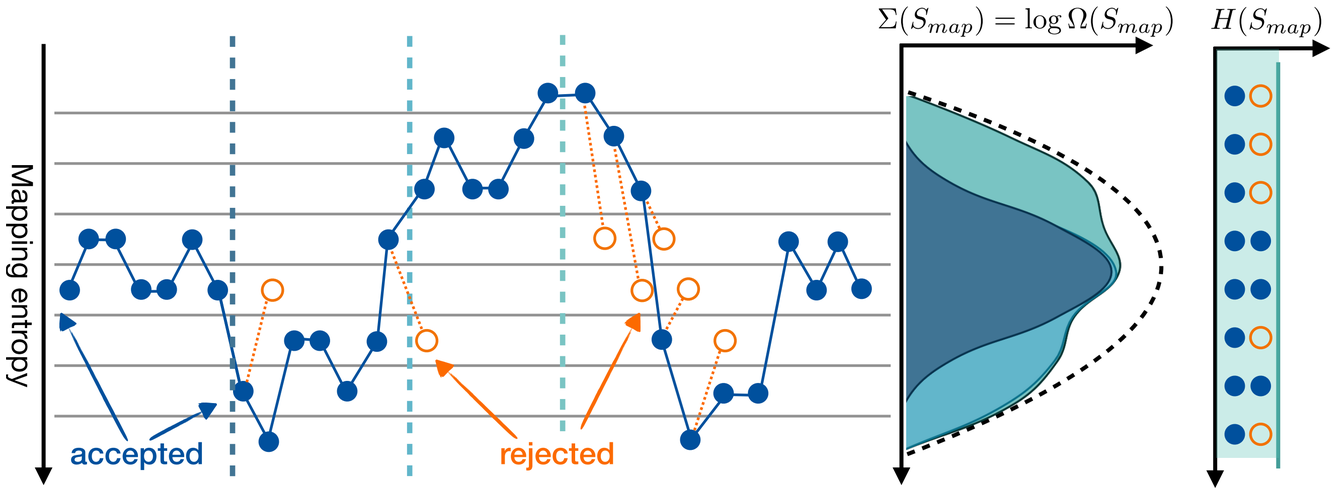
Combine the trained DGN with the Wang-Landau sampling algorithm **to reconstruct the density of states of S_{map}**



RM, Giulini, Potestio, EPJB 2021
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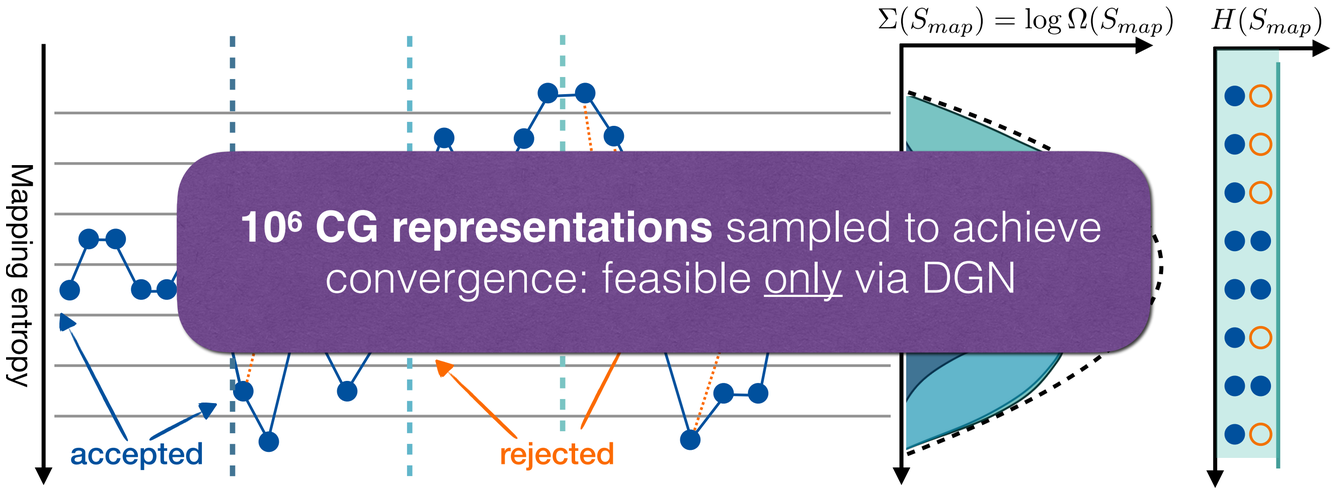

10^6 CG representations sampled to achieve convergence: feasible only via DGN

RM, Giulini, Potestio, EPJB 2021
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

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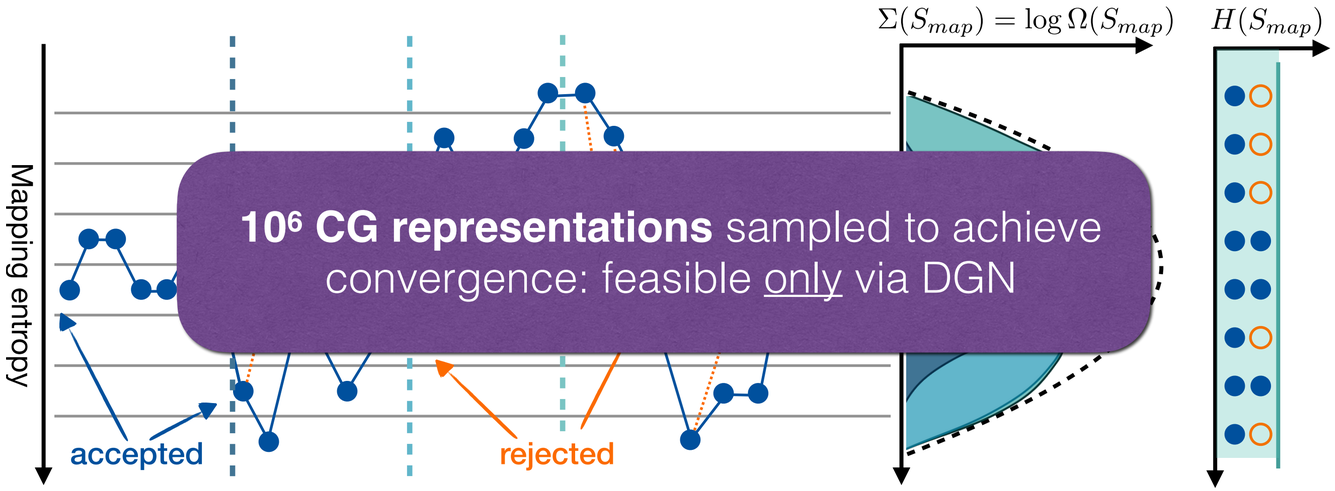

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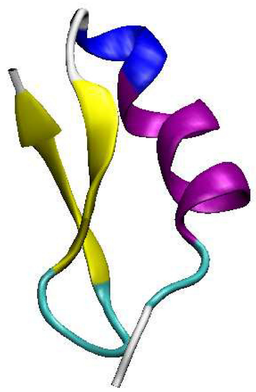
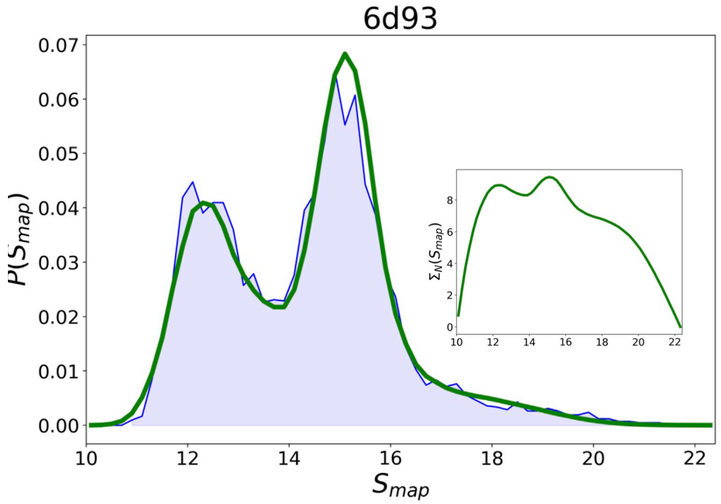
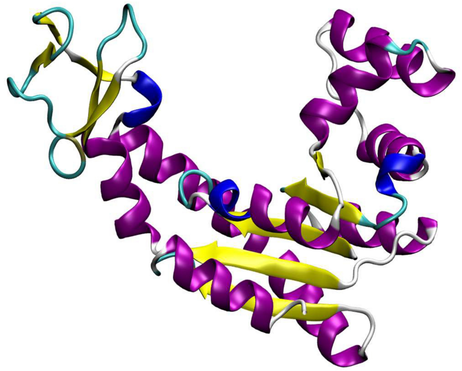
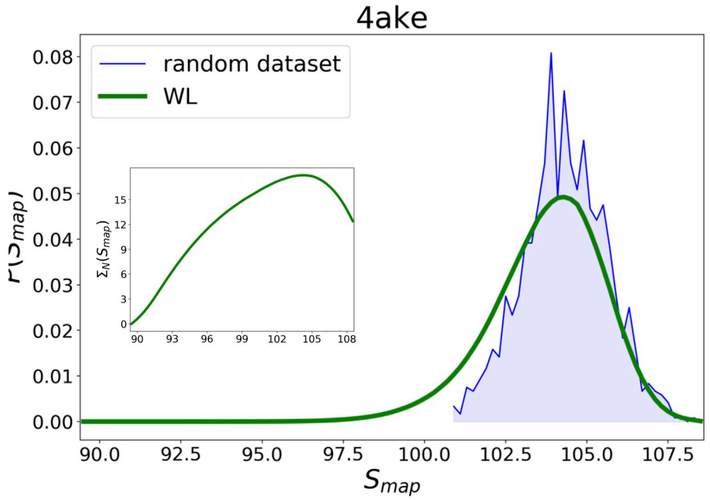
Tamapin





Adenylate Kinase





RM, Giulini, Potestio, EPJB 2021
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

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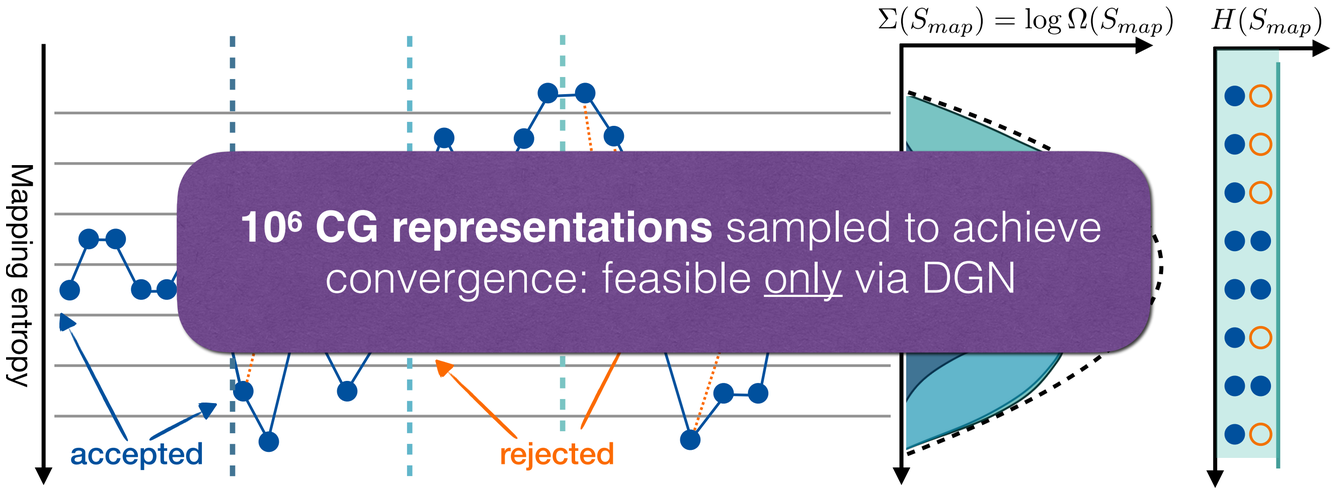

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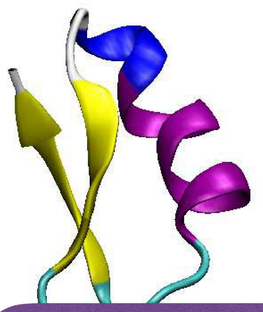
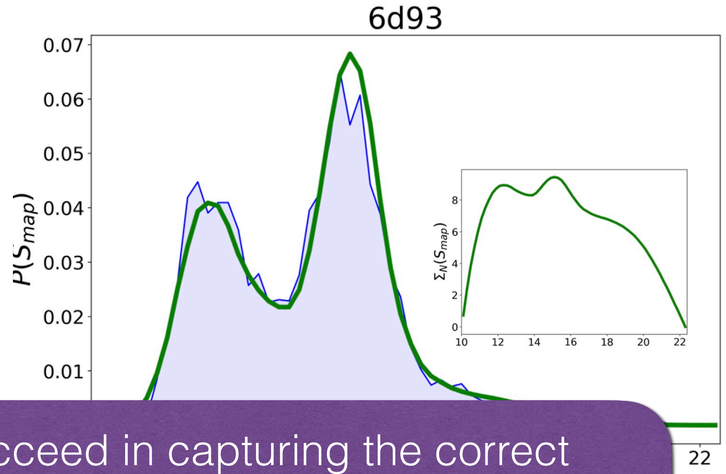
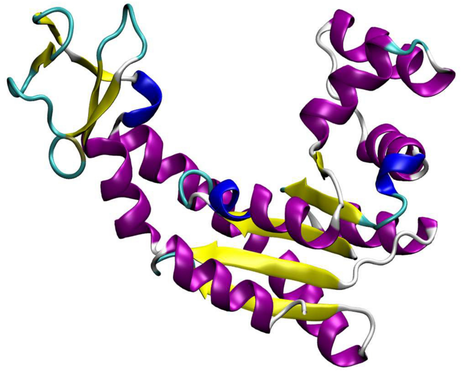
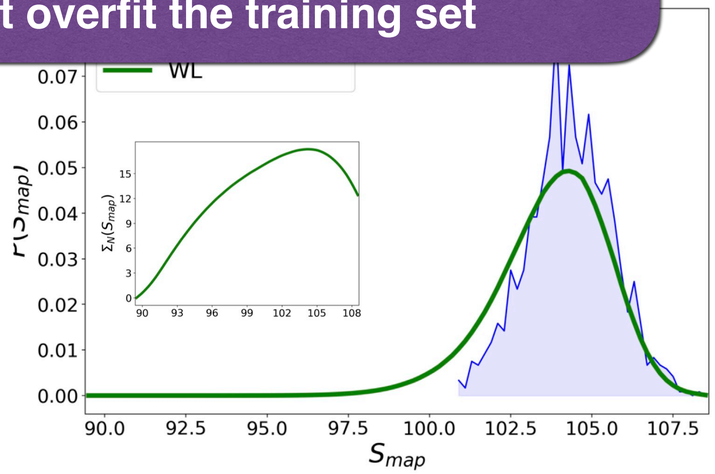




DGNs succeed in capturing the correct statistical weight of CG representations: **do not overfit the training set**

Ader



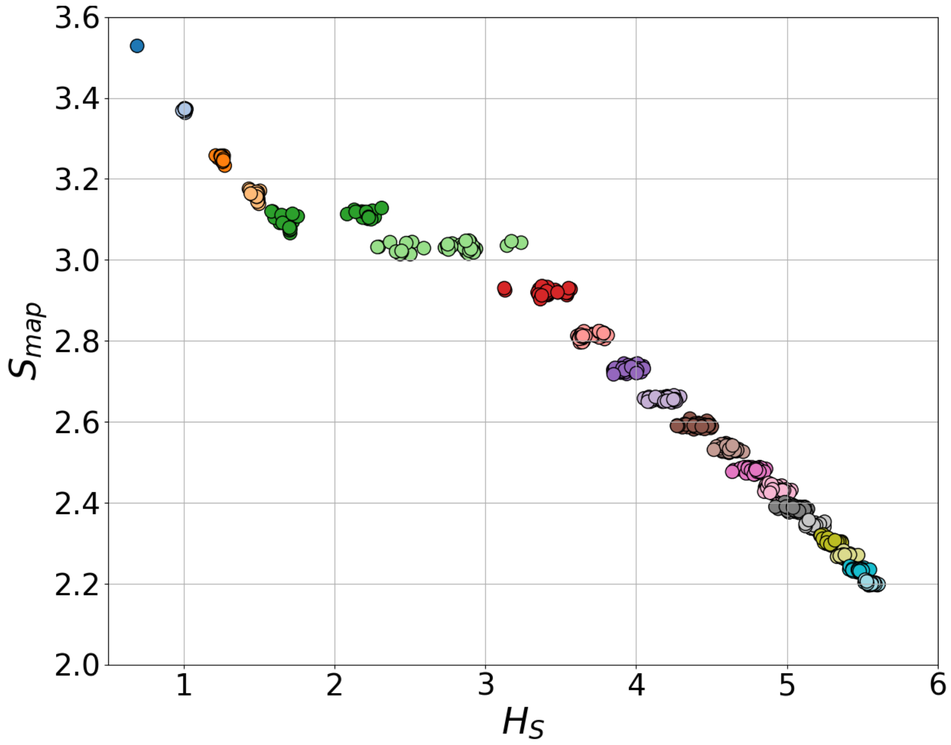


RM, Giulini, Potestio, EPJB 2021

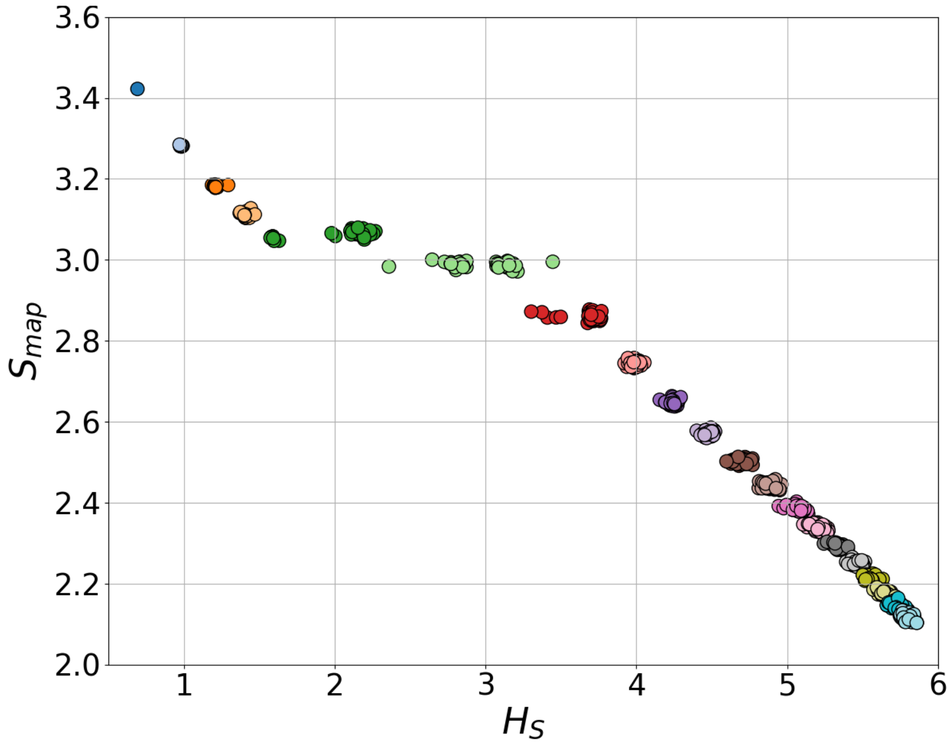
Errica, Giulini, RM *et al.*, Front. Mol. Biosci. 2021

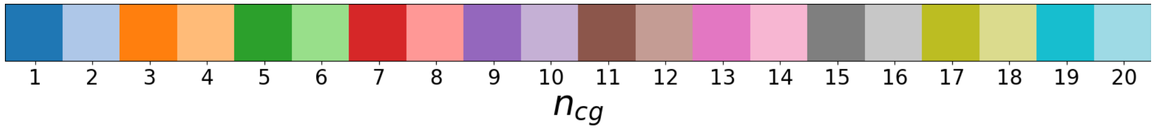
Moving towards the SG phase

N=100 neurons, p= 4 patterns

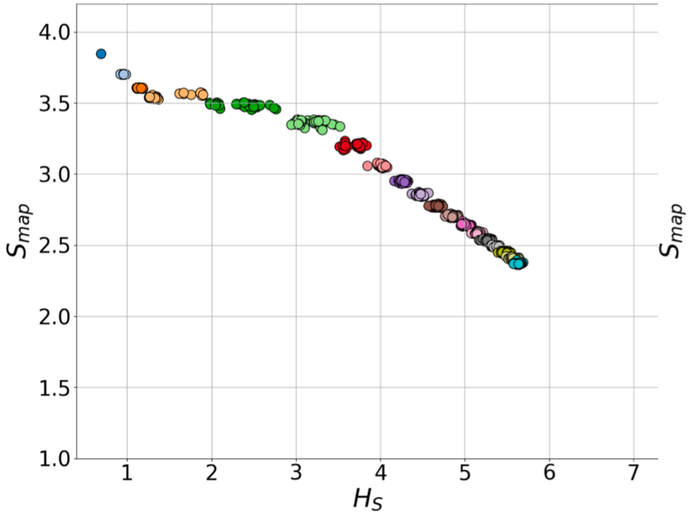


N=100 neurons, p= 5 patterns

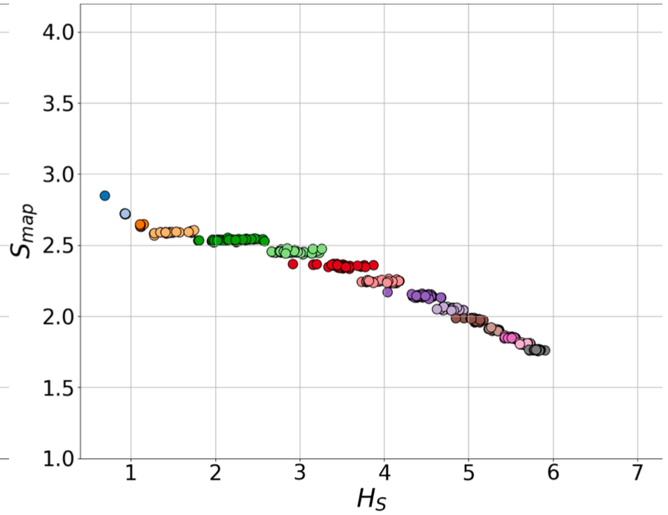




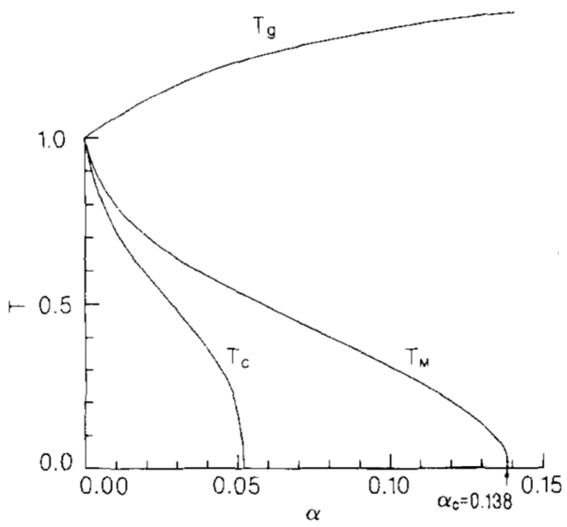
Moving towards the SG phase

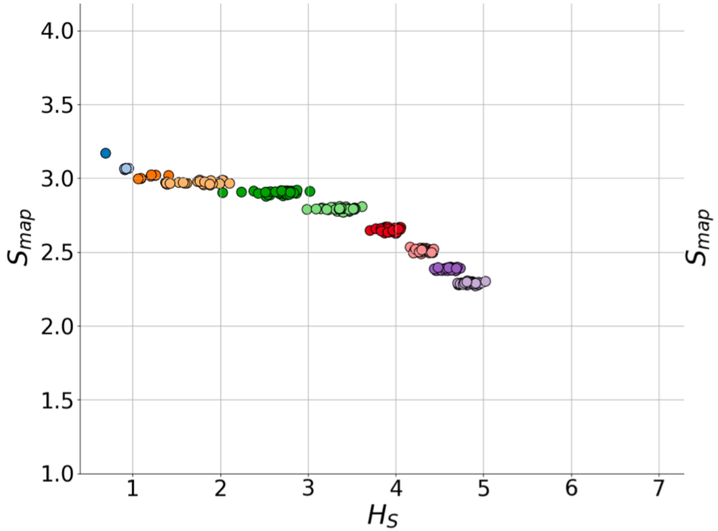


(e) $p = 6$

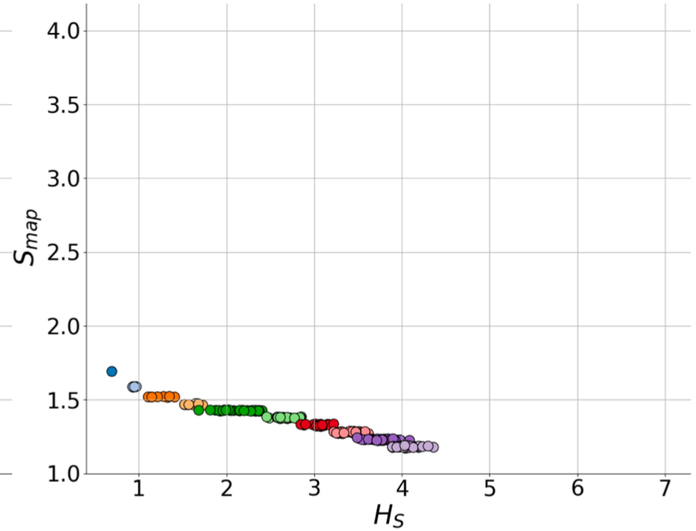


(f) $p = 7$

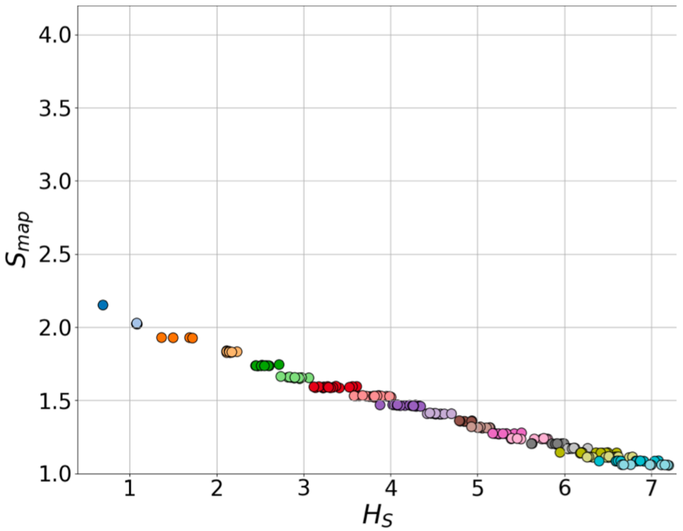




(a) $p = 8$



(b) $p = 9$

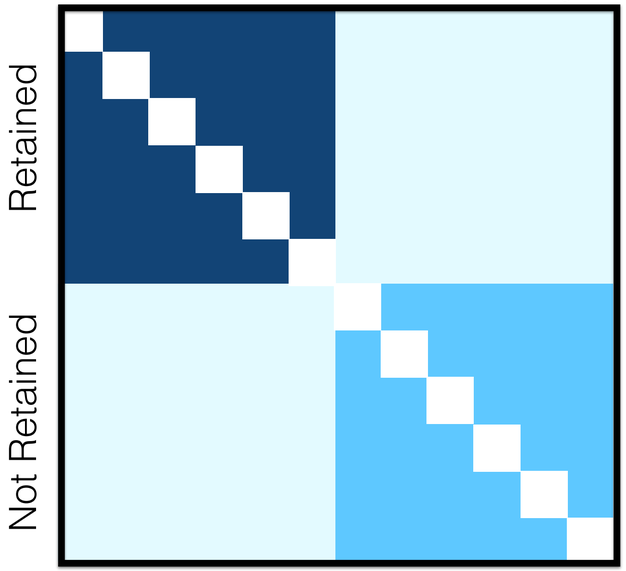


(c) $p = 10$

Semidispersion spectrum

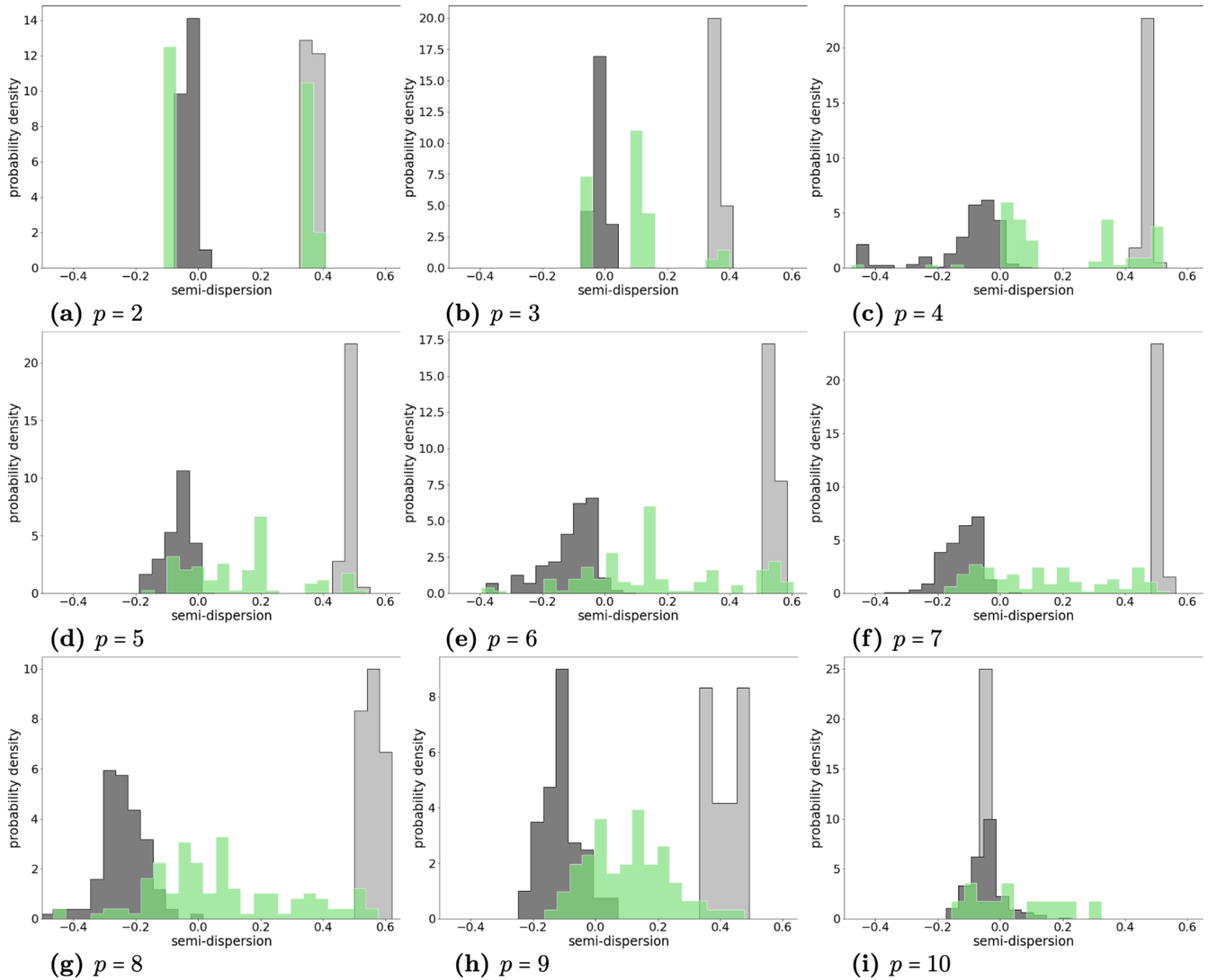
$$S = \left(\begin{array}{c|c} s^* s^* & s^* s \\ \hline s\ s^* & s\ s \end{array}\right)$$

Ordered coupling matrix $|J_{ij}|$



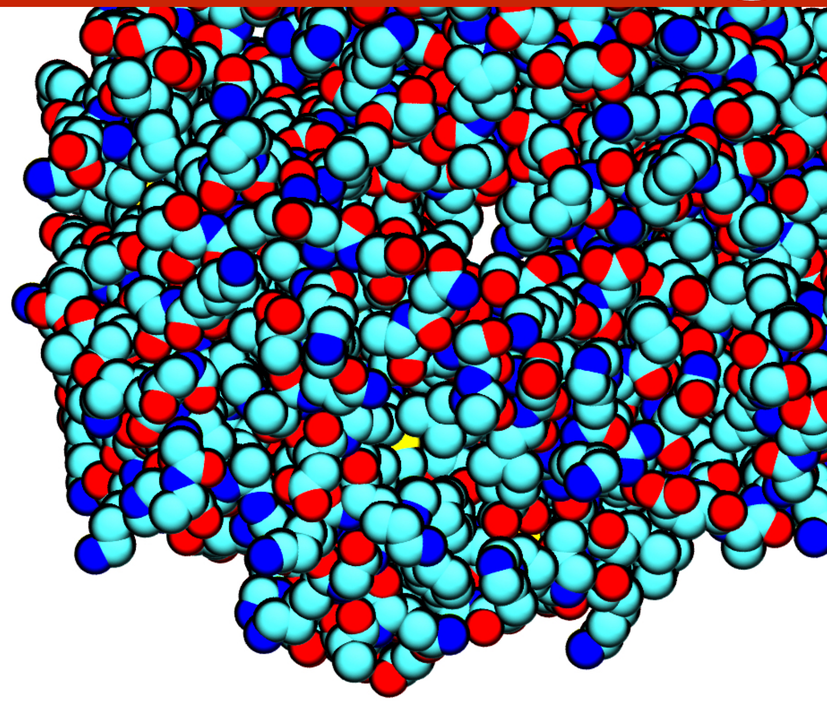
Semidispersion

$$\rho = \frac{\langle |J| \rangle_{s^* s^*} - \langle |J| \rangle_{s s^*}}{\langle |J| \rangle_{s^* s^*} + \langle |J| \rangle_{s s^*}}$$

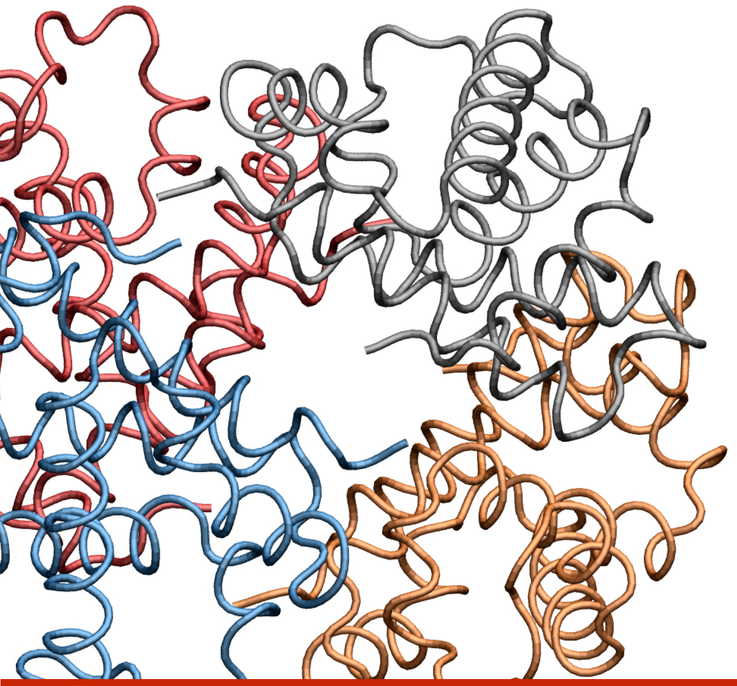


Simplify to understand

DATA != INFORMATION



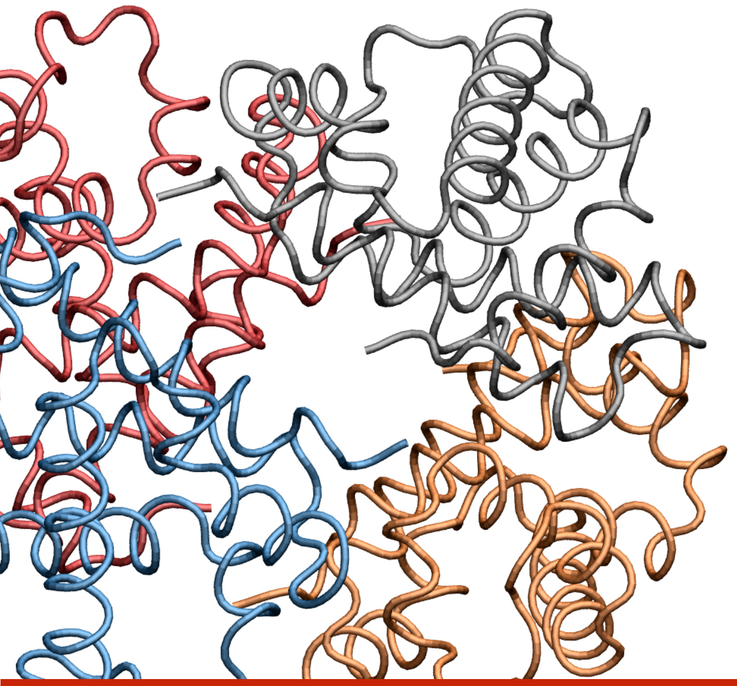
Simplify "just right"
to understand
without losing information



Dimensionality reduction:
in terms of what variables?

Simplify to understand

```
ATOM   1153  CD   GLN X 408     110.020  92.423  42.297  0.00  0.00
ATOM   1154  OE1  GLN X 408     110.283  93.074  43.331  0.00  0.00
ATOM   1155  NE2  GLN X 408     108.983  91.618  42.373  0.00  0.00
ATOM   1156 HE21  GLN X 408     108.656  91.204  41.511  0.00  0.00
ATOM   1157 HE22  GLN X 408     108.471  91.768  43.225  0.00  0.00
ATOM   1158  C    GLN X 408     113.167  95.332  40.798  0.00  0.00
ATOM   1159  O    GLN X 408     113.764  95.563  39.715  0.00  0.00
ATOM   1160  N    GLN X 409     113.578  95.654  42.042  0.00  0.00
ATOM   1161  H    GLN X 409     113.018  95.252  42.780  0.00  0.00
ATOM   1162  CA   GLN X 409     114.881  96.418  42.260  0.00  0.00
ATOM   1163  HA   GLN X 409     115.146  96.965  41.356  0.00  0.00
ATOM   1164  CB   GLN X 409     114.444  97.423  43.339  0.00  0.00
ATOM   1165  HB1  GLN X 409     115.314  97.840  43.844  0.00  0.00
ATOM   1166  HB2  GLN X 409     113.900  96.872  44.111  0.00  0.00
```



Simplify to understand

Collective variables

```
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ATOM   1161  H    GLN X 409     113.018  95.252  42.780  0.00  0.00
ATOM   1162  CA   GLN X 409     114.881  96.418  42.260  0.00  0.00
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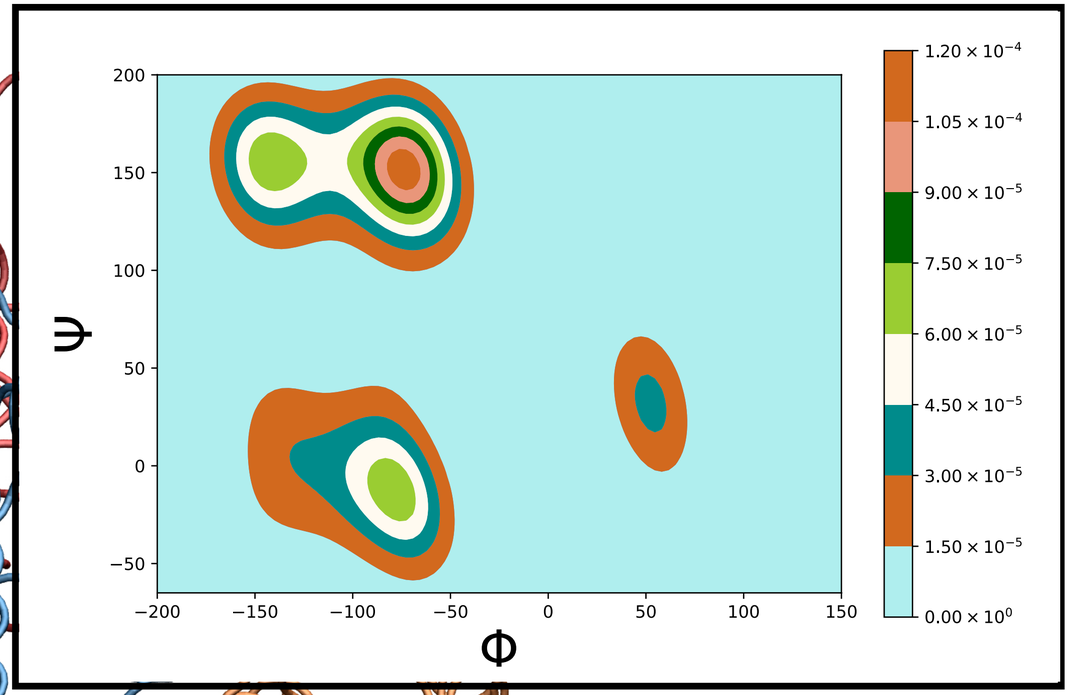
ATOM   1164  CB   GLN X 409     114.444  97.423  43.339  0.00  0.00
ATOM   1165  HB1  GLN X 409     115.314  97.840  43.844  0.00  0.00
ATOM   1166  HB2  GLN X 409     113.900  96.872  44.111  0.00  0.00
```



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```
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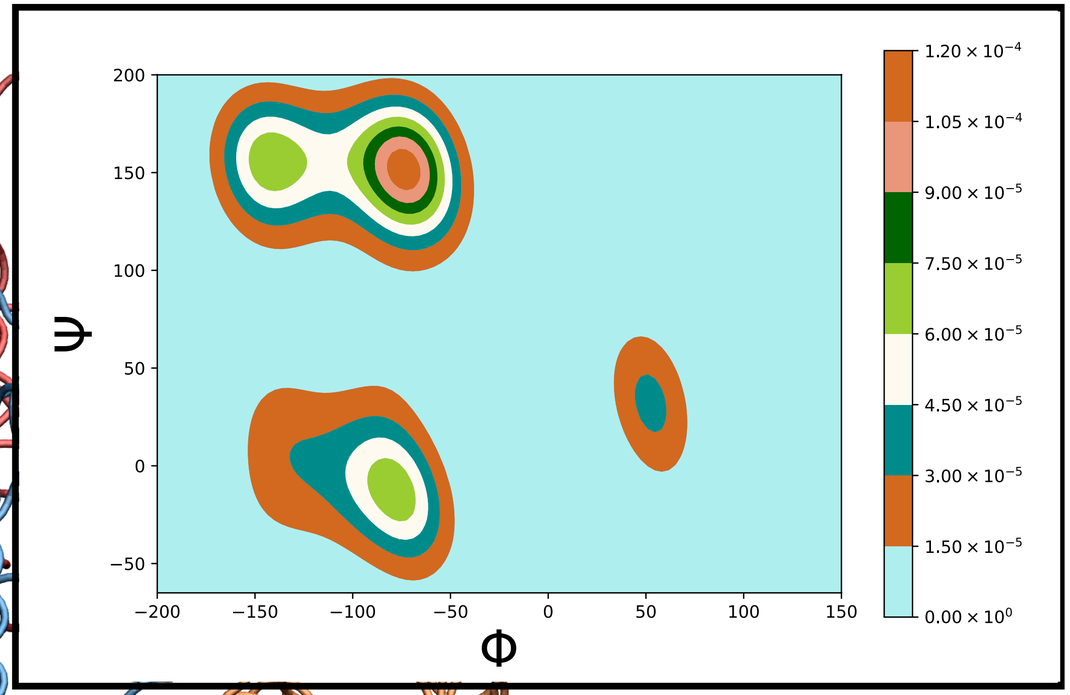
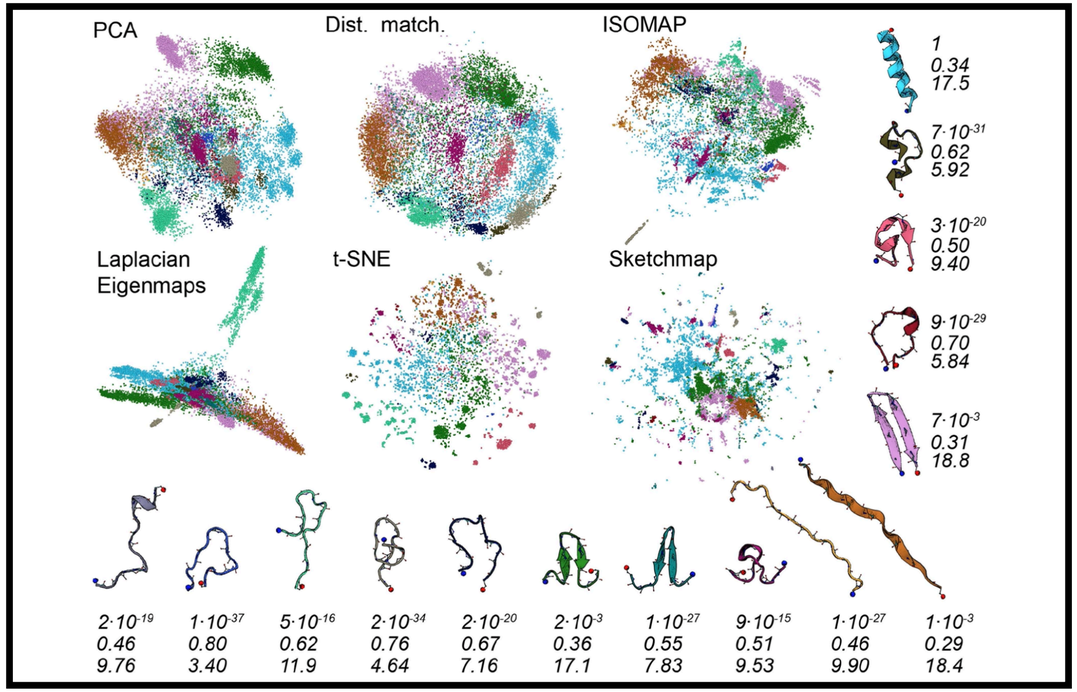
ATOM   1165  HB1  GLN X 409     115.314  97.840  43.844  0.00  0.00
ATOM   1166  HB2  GLN X 409     113.900  96.872  44.111  0.00  0.00
```

Collective variables



Low-D embedding



Tribello, Gasparotto, Front. Mol. Biosci. 2019