



HAL
open science

Exploration of conformations for an IDP

Shu-Yu Huang, Chi-Fon Chang, Jung-Hsin Lin, Thérèse Malliavin

► **To cite this version:**

Shu-Yu Huang, Chi-Fon Chang, Jung-Hsin Lin, Thérèse Malliavin. Exploration of conformations for an IDP. The 27th Biophysics Conference, May 2023, Hualien, Taiwan. hal-04545891

HAL Id: hal-04545891

<https://cnrs.hal.science/hal-04545891>

Submitted on 14 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

EXPLORATION OF CONFORMATIONS FOR AN IDP

Shu-Yu Huang(1), Chi-Fon Chang(2), Jung-Hsin Lin(1)
and Th r se E Malliavin(3)

(1) Research Center for Applied Sciences, Academia Sinica, Taipei, Taiwan, (2) Genomics Research Center, Academia Sinica, Taipei, Taiwan, (3) Laboratoire de Physique et Chimie Th oriques (LPCT), University of Lorraine, Vandoeuvre-l s-Nancy, France

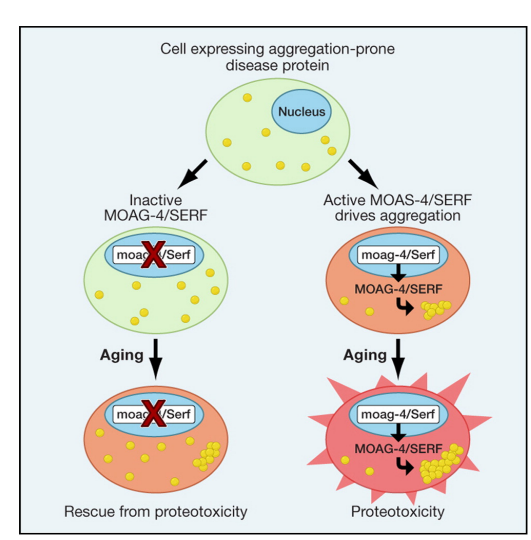
Abstract

Intrinsically disordered proteins (IDP) are at the center of numerous biological processes, and attract consequently extreme interest in structural biology. A systematic enumeration of protein conformations, based on distance geometry, was performed on SERF1a, a 62-residue IDP involved in interactions with amyloid peptides. The results obtained with the threading-adapted interval Branch-and-Prune (TAiBP) approach haven been analyzed using various input predictions for backbone torsion angles ϕ and ψ , provided by TALOS and δ 2D, as well as a NOE measurement. The fitting of SAXS data permitted to select various sets of conformations depending on the input predictions. The similarity between profiles of local gyration radii provides to a certain extent a converged view of the SERF1a. A better convergence of these profiles is observed when using the TALOS inputs than using the δ 2D inputs. All sets of conformations point to the same locations for maxima of pocketedness along protein sequences.

Experimental measurements

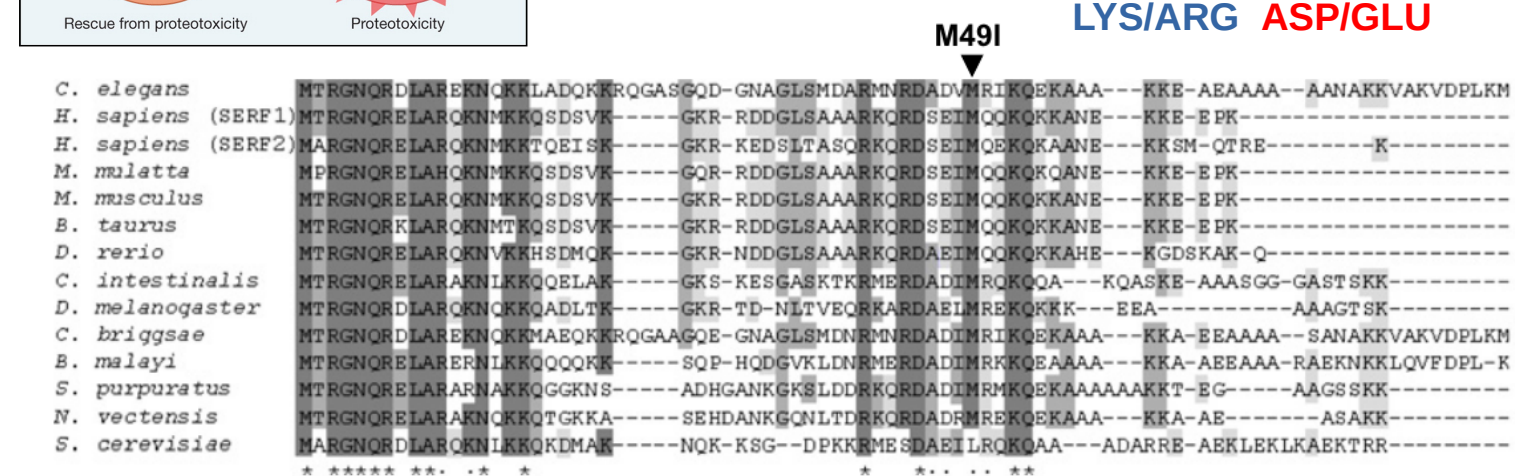
NMR spectra were recorded at 298K on Bruker Avance 800MHz equipped with cryoprobe, using samples of 0.5mM ^{13}C - ^{15}N - labeled SERF1a in 20mM NaPi, and 20mM NaCl buffers. Spectra were processed with TopSpin 3.6.5 (Bruker) and peak picked with SPARKY. SAXS data were measured at NSRRC by Dr Orion Shih and Yi-Qi Yeh.

Function of SERF1a



VanHam et al. Identification of MOAG-4/SERF as a regulator of age-related proteotoxicity. Cell 2010.

a positive regulator of aggregate formation :
- for polyglutamine diseases
- for amyloid-beta
- for alpha-synuclein

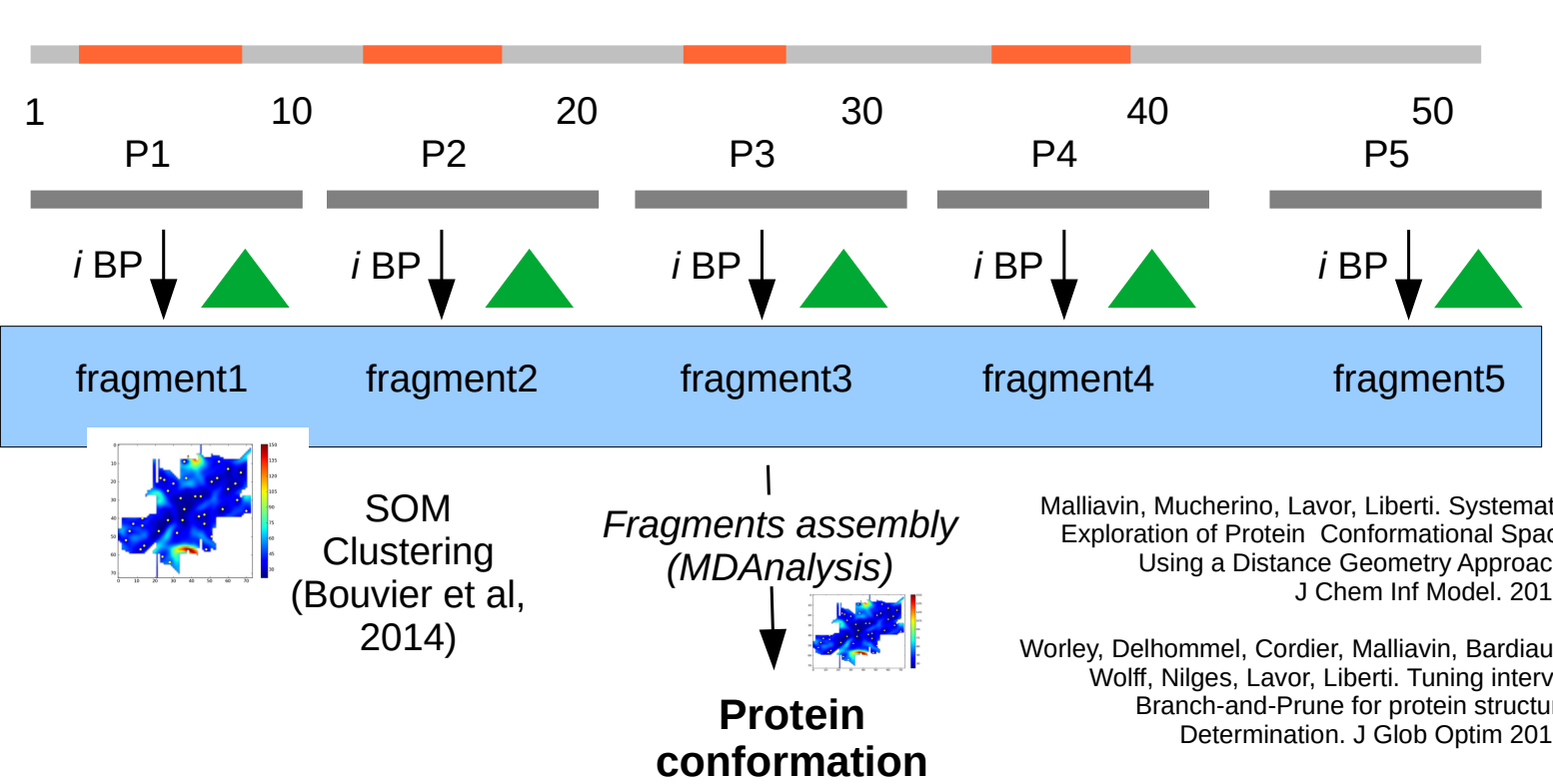


Collab. JH Lin, S Huang and C-F Chang
Academia Sinica, Taiwan

Van Ham et al, Cell 2010

TAiBP approach

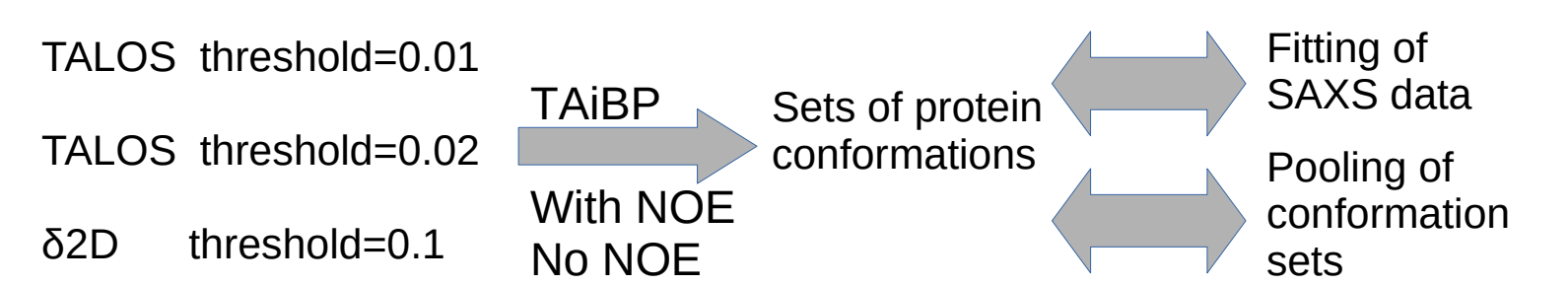
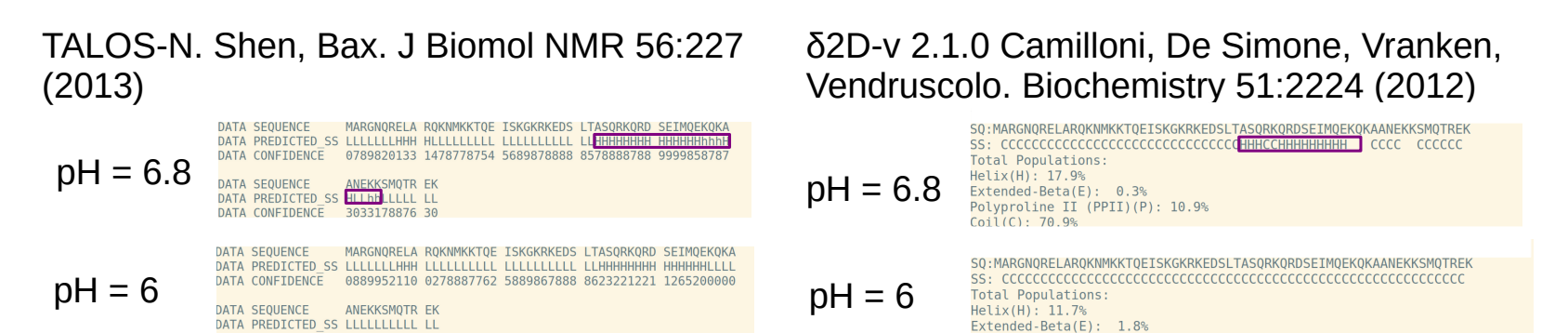
Input : regions of ϕ, ψ angles
iBP step : iBP algorithm with varying systematically the values of angles ϕ, ψ within their regions to obtain conformations of protein fragments
Assembly step : Build the protein chain by assembling the fragments



Malliavin, Mucherino, Lavor, Liberti. Systematic Exploration of Protein Conformational Space Using a Distance Geometry Approach. J Chem Inf Model. 2019;
Worley, Delhomme, Cordier, Malliavin, Barilau, Wolf, Milgus. Lavor, Liberti. Tuning Interval Branch-and-Prune for protein structure Determination. J Glob Optim 2018

Procedure of calculation

General scheme for generation of IDP conformations



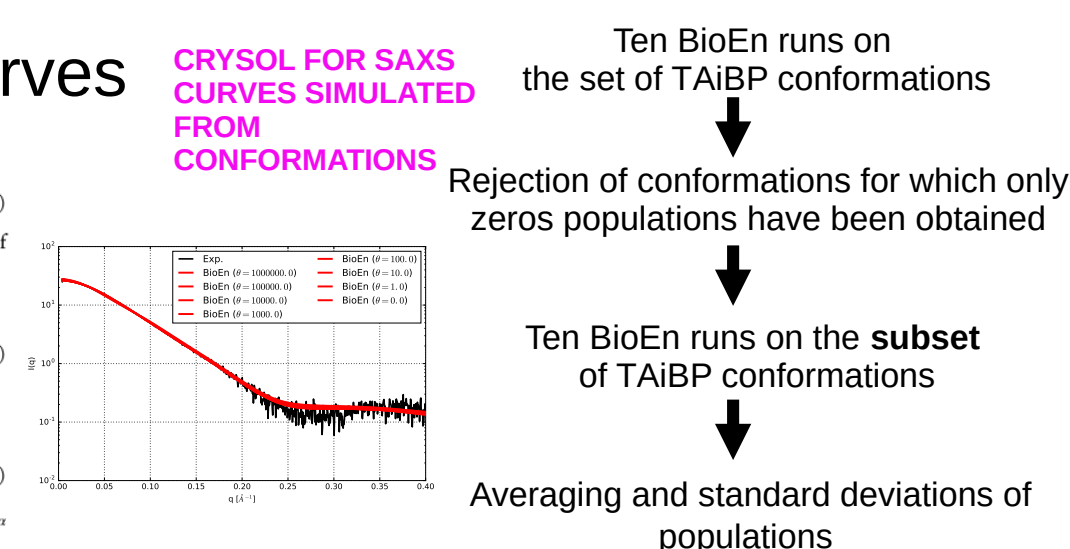
Fitting SAXS data

Fitting of SAXS curves

BioEn (Bayesian approach)

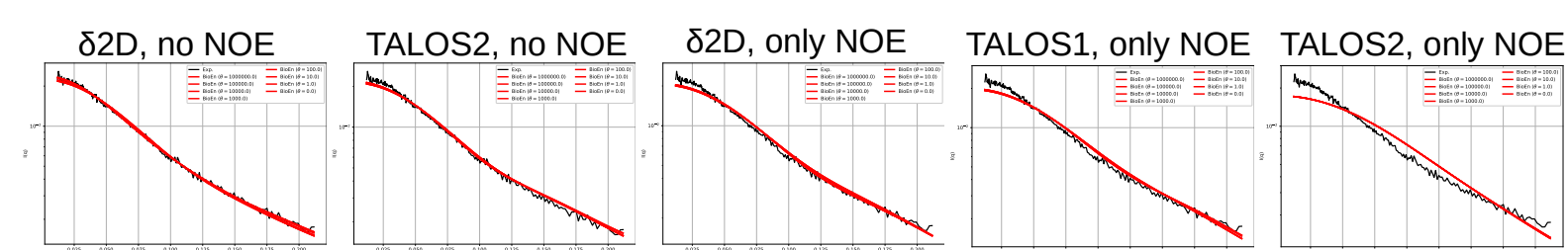
$$P(k) \propto \exp(-\chi^2) = \prod_{i=1}^N \frac{w_i}{\sum_{j=1}^N w_j}$$

where $w_i = \sum_{k=1}^N \frac{1}{w_{ik}}$ is the Kullback-Leibler divergence¹¹. Both refined weights w_i

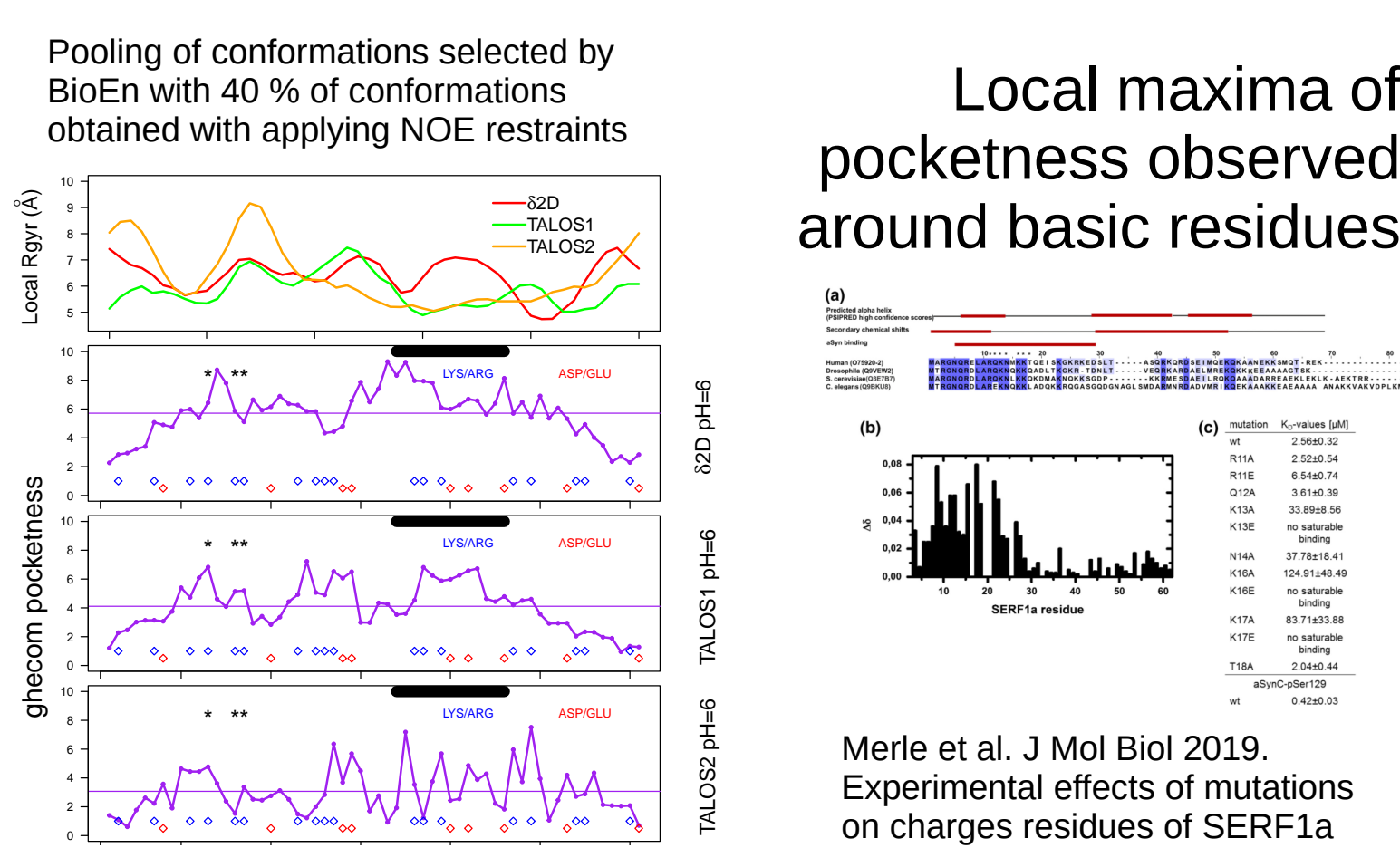


λ (nm)	Conformation numbers	Populations percentage	Conformation numbers	Populations percentage	Conformation numbers	Populations percentage
147	183 ± 0.6	117	21.2 ± 0.6	117	91.4 ± 6.6	
149	27.7 ± 0.9	119	21.1 ± 1.3	139	30.9 ± 3.6	
159	3.1 ± 0.1	159	22.5 ± 0.6	42	23.5 ± 0.6	
52	18.9 ± 0.4	42	4.4 ± 2.5	52	11.0 ± 4.3	
58	16.9 ± 0.5	52	10.9 ± 0.9	56	2.2 ± 4.3	
58	13.2 ± 0.3	58	23.0 ± 0.9	58	81.1 ± 6.1	
		98	16.2 ± 1.6	98	26.4 ± 3.4	

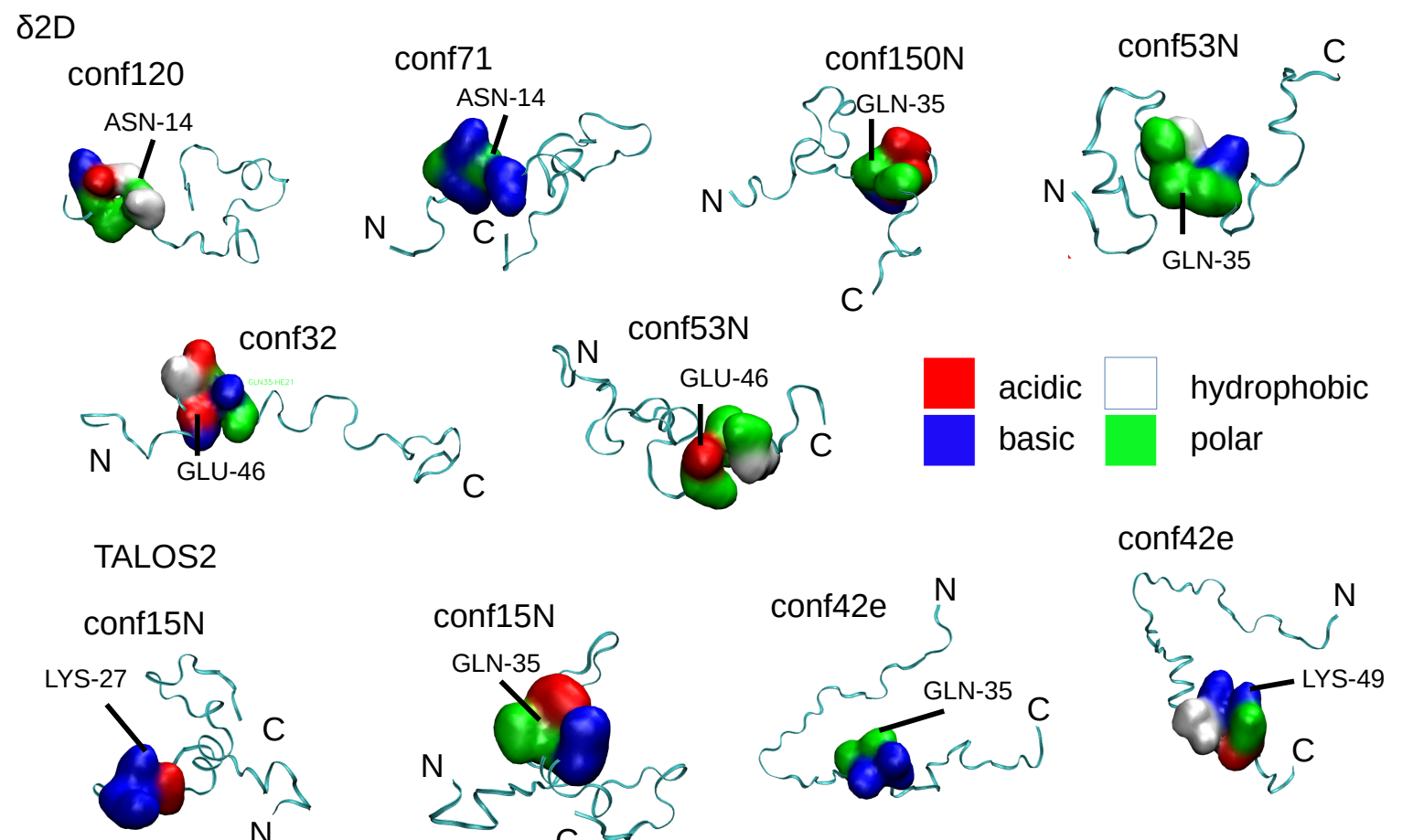
Inputs	NOE	Final χ^2	Initial # of conformations	Final # of conformations	Final radius of gyration (Å)	Populations (>10%)
delta2D	No	1.5	122	10	25.8	38, 22, 22
	TALOS1	No	1.1	191	3	24.4
TALOS1	No	1.7	93	10	26.8	43, 21, 13
TALOS2	No	1.4	73	2	22.6	60, 40
	No	1.8	51	4	23.8	70, 14, 14
delta2D	only	3.9	171	2	20.5	84, 15
	TALOS1	only	7.1	178	1	19.4
TALOS1	only	6.3	179	1	19.6	100
TALOS2	only	2.2	152	2	21.9	84, 15
	only	16.7	51	2	16.4	71, 28



Pocket detection



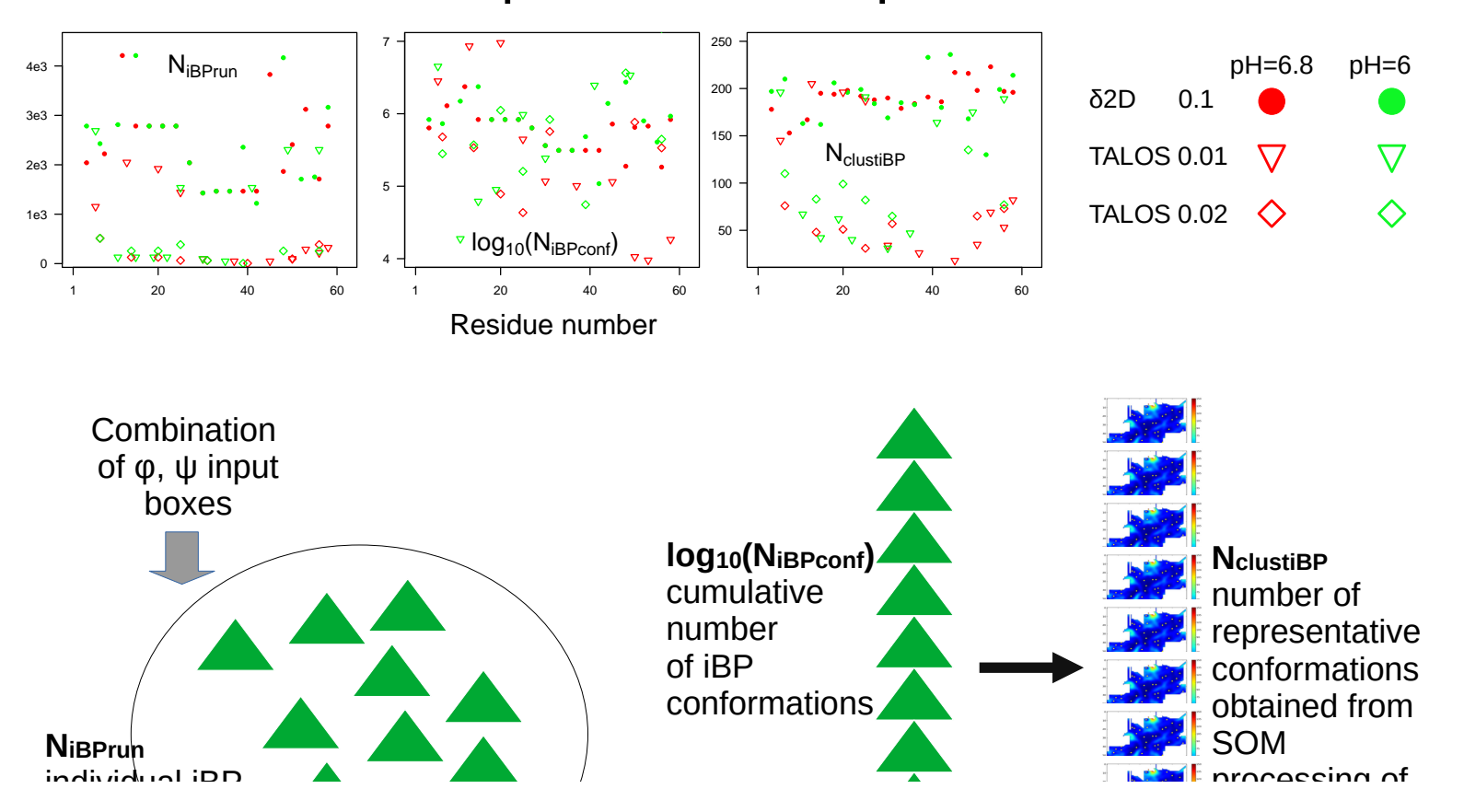
Examples of possible binding pockets sampled in conformations of SERF1a



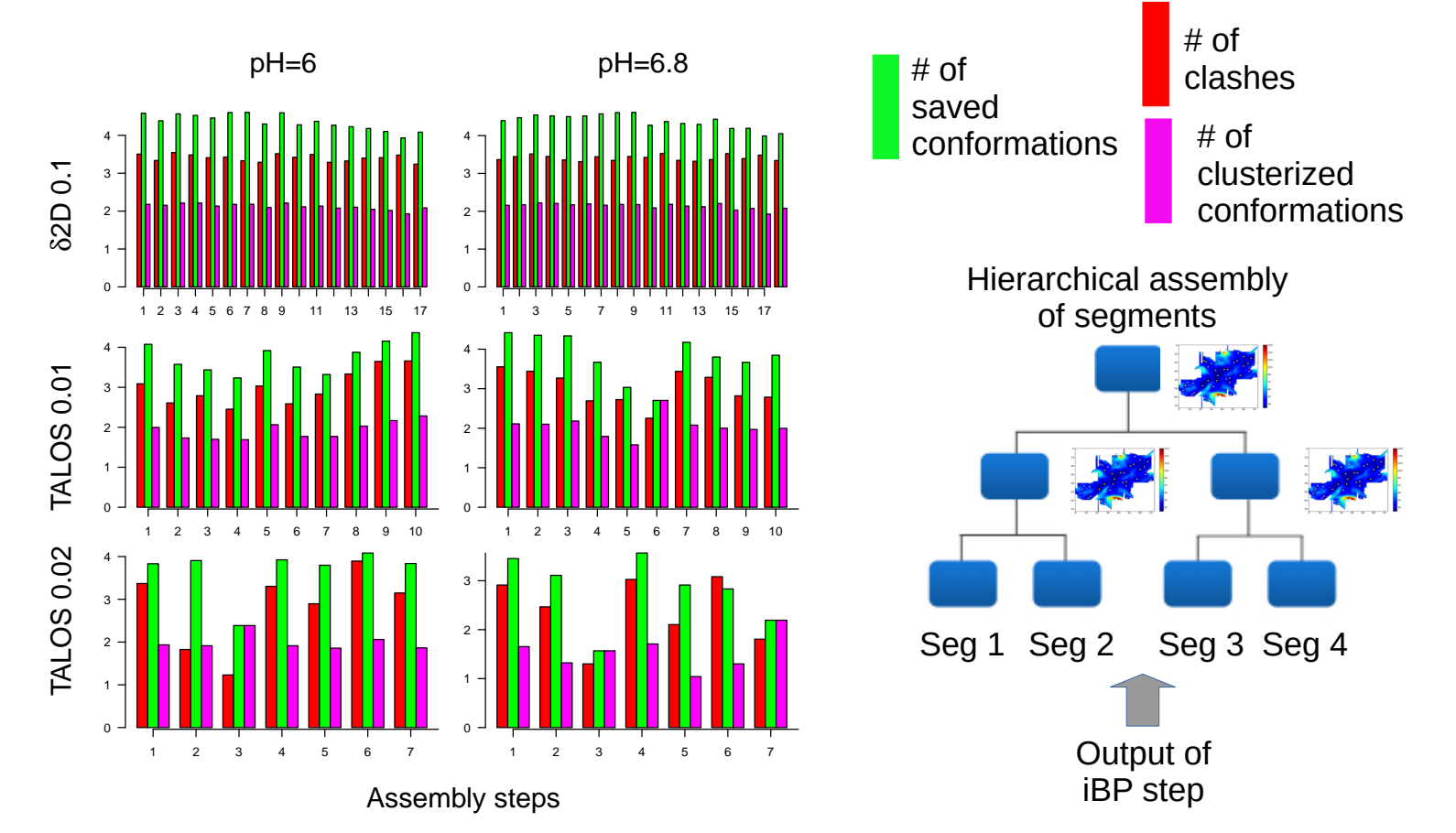
Merle et al. J Mol Biol 2019. Experimental effects of mutations on charges residues of SERF1a

Calculation examples

TAiBP run: examples of iBP steps



TAiBP run: examples of assembly steps



References

- [1] S. F. Falsone et al. "SERF protein is a direct modifier of amyloid fiber assembly". In: *Cell Rep* 2 (2012), pp. 358–371.
- [2] D. F rster et al. "Low-resolution description of the conformational space for intrinsically disordered proteins". In: *Sci Rep* 12 (2022), p. 19057.
- [3] T. E. Malliavin. "Tandem domain structure determination based on a systematic enumeration of conformations". In: *Sci Rep* 11 (2021), p. 16925.
- [4] T. E. Malliavin et al. "Systematic Exploration of Protein Conformational Space Using a Distance Geometry Approach". In: *J Chem Inf Model* 59 (2019), pp. 4486–4503.
- [5] Y. Shen and A. Bax. "Protein structural information derived from NMR chemical shift with the neural network program TALOS-N". In: *Methods Mol Biol* 1260 (2015), pp. 17–32.
- [6] C. Camilloni et al. "Determination of secondary structure populations in disordered states of proteins using nuclear magnetic resonance chemical shifts". In: *Biochemistry* 51 (2012), pp. 2224–2231.
- [7] D. I. Svergun, C. Barberato, and M.H.J. Koch. "CRYSOLE - a Program to Evaluate X-ray Solution Scattering of Biological Macromolecules from Atomic Coordinates". In: *J. Appl. Cryst.* 28 (1995), pp. 768–773.
- [8] J. K fingger et al. "Efficient Ensemble Refinement by Reweighting". In: *J Chem Theory Comput* 15 (2019), pp. 3390–3401.