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EXPLORATION OF CONFORMATIONS FOR AN IDP

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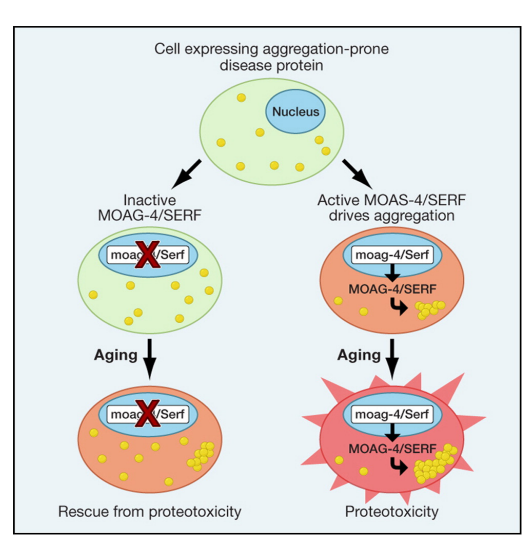
Abstract

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.

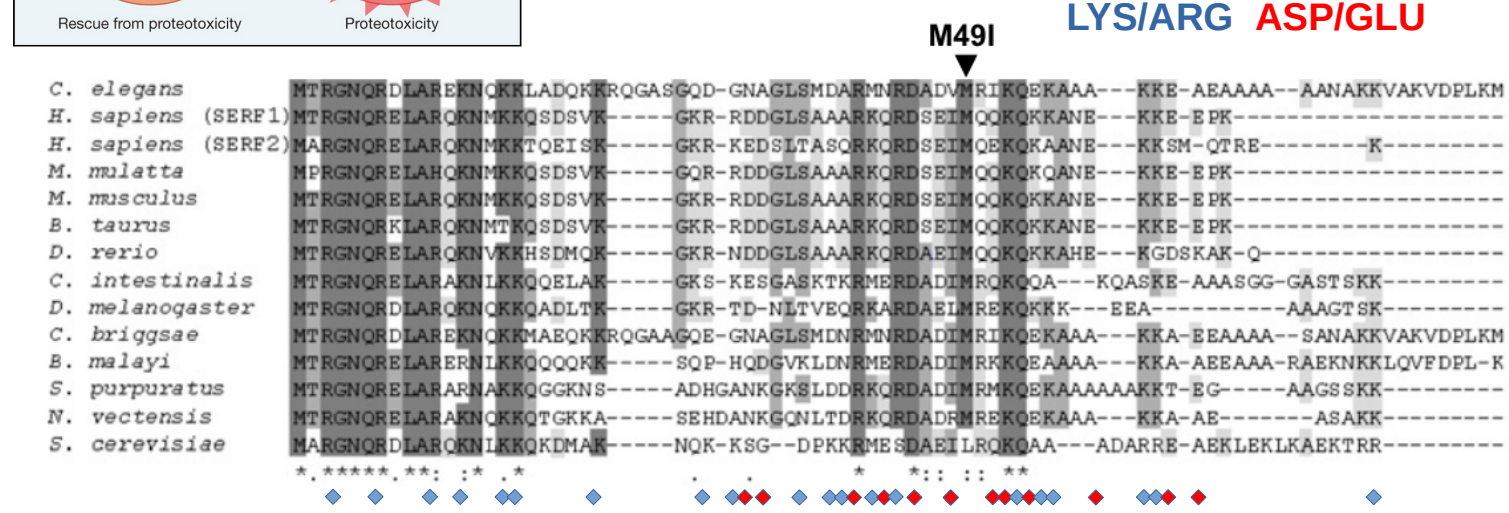
Function of SERF1a



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

a positive regulator of aggregate formation :

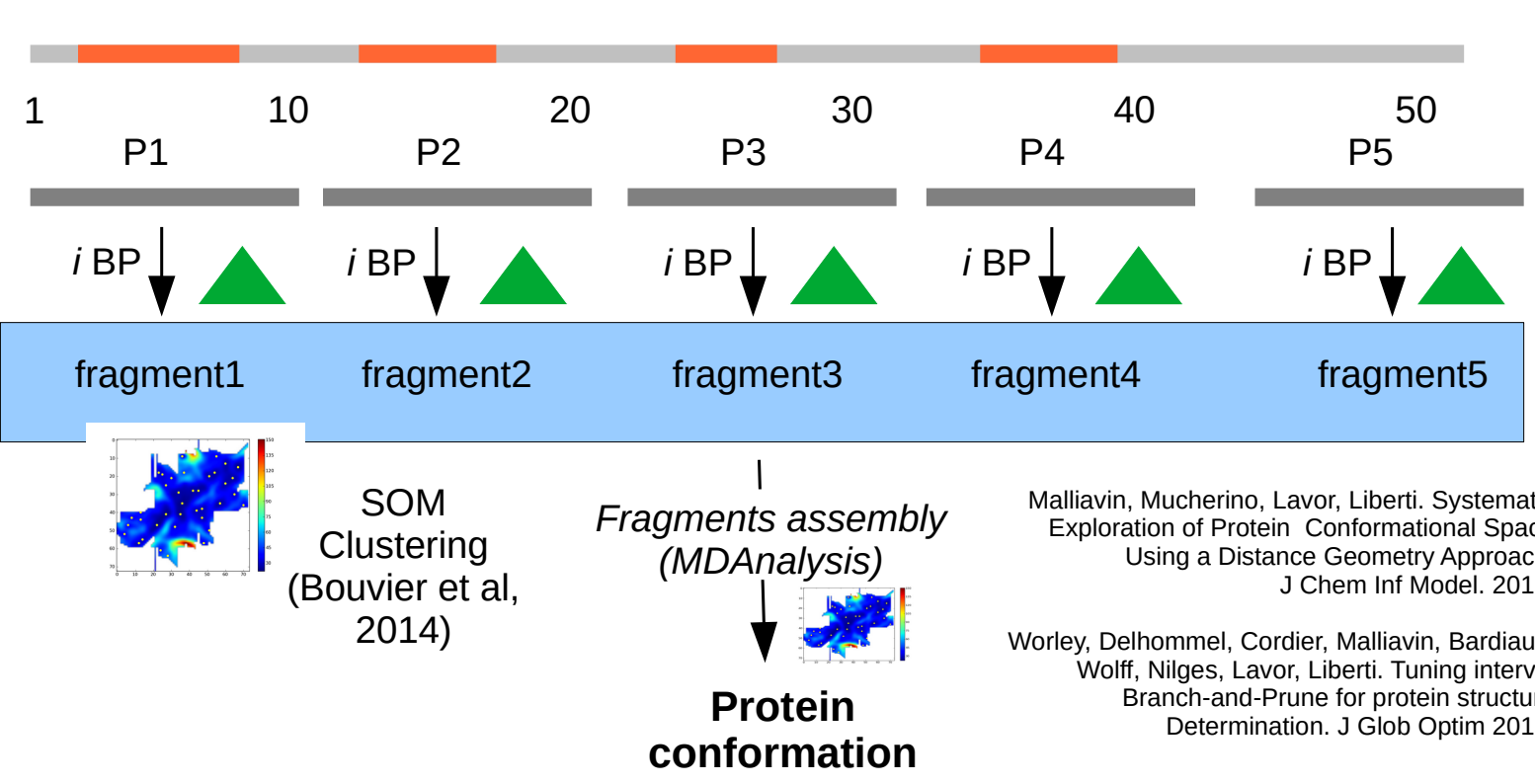
- for polyglutamine diseases
- for amyloid-beta
- for alpha-synuclein



Collab. J-H Lin, S Huang and C-F Chang Academia Sinica, Taiwan Van Ham et al, Cell 2010

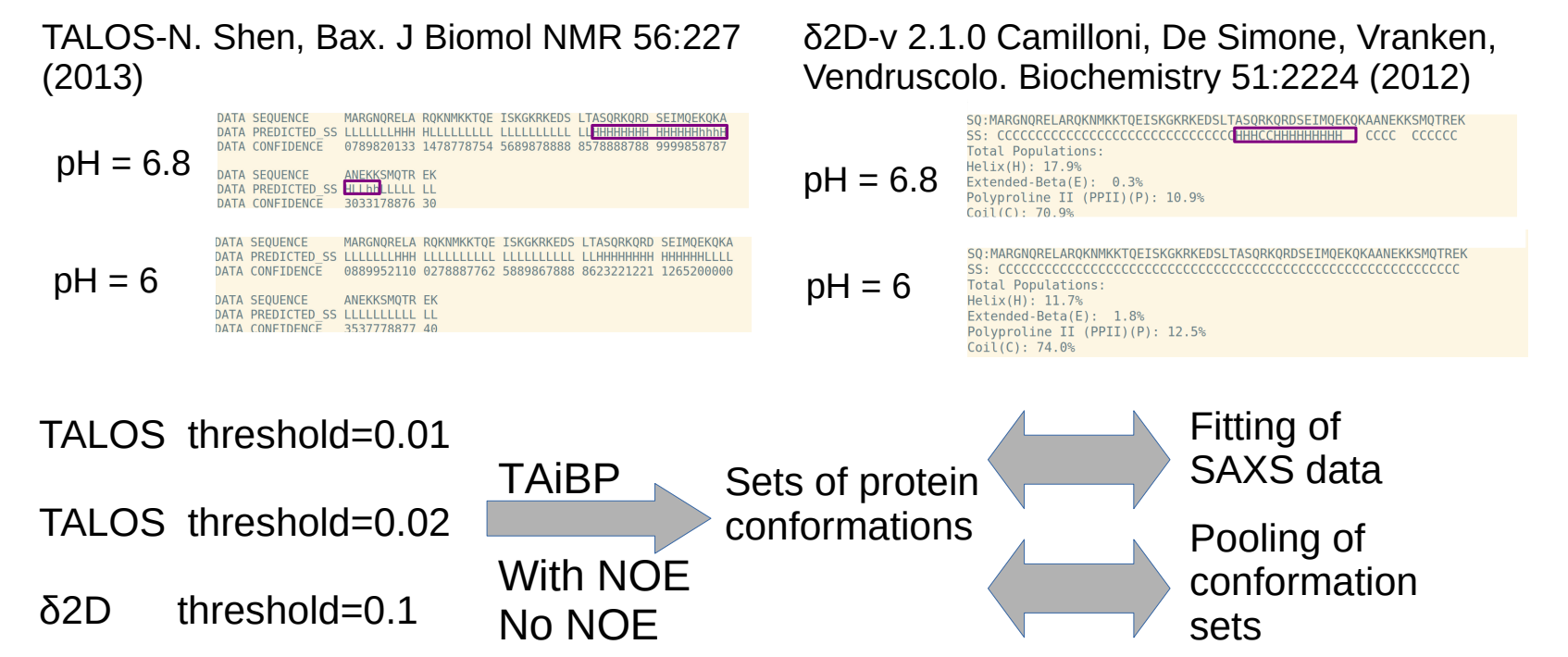
TAiBP approach

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



Procedure of calculation

General scheme for generation of IDP conformations



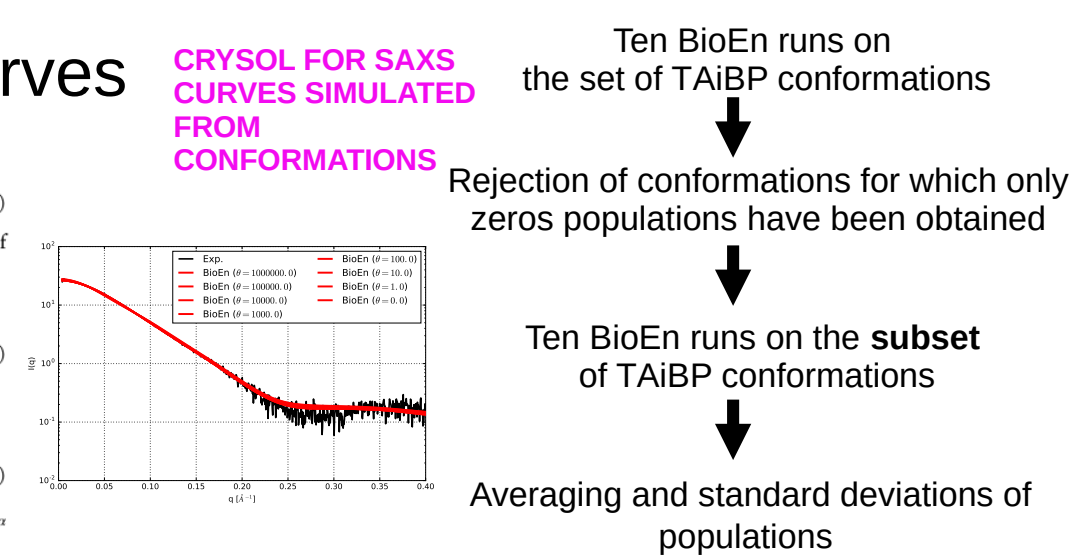
Fitting SAXS data

Fitting of SAXS curves

BioEn (Bayesian approach)

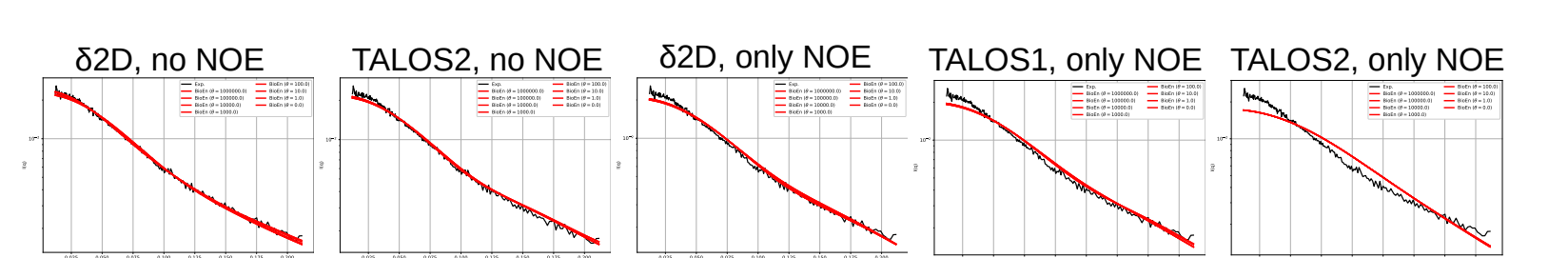
$$P(\text{data}) \propto P_w(P|\text{data})$$

$$P(\text{data}) \propto \exp(-\chi^2) = \prod_{i=1}^N \frac{1}{\sigma_i} \exp\left(-\frac{(I_i - \mu_i)^2}{\sigma_i^2}\right)$$

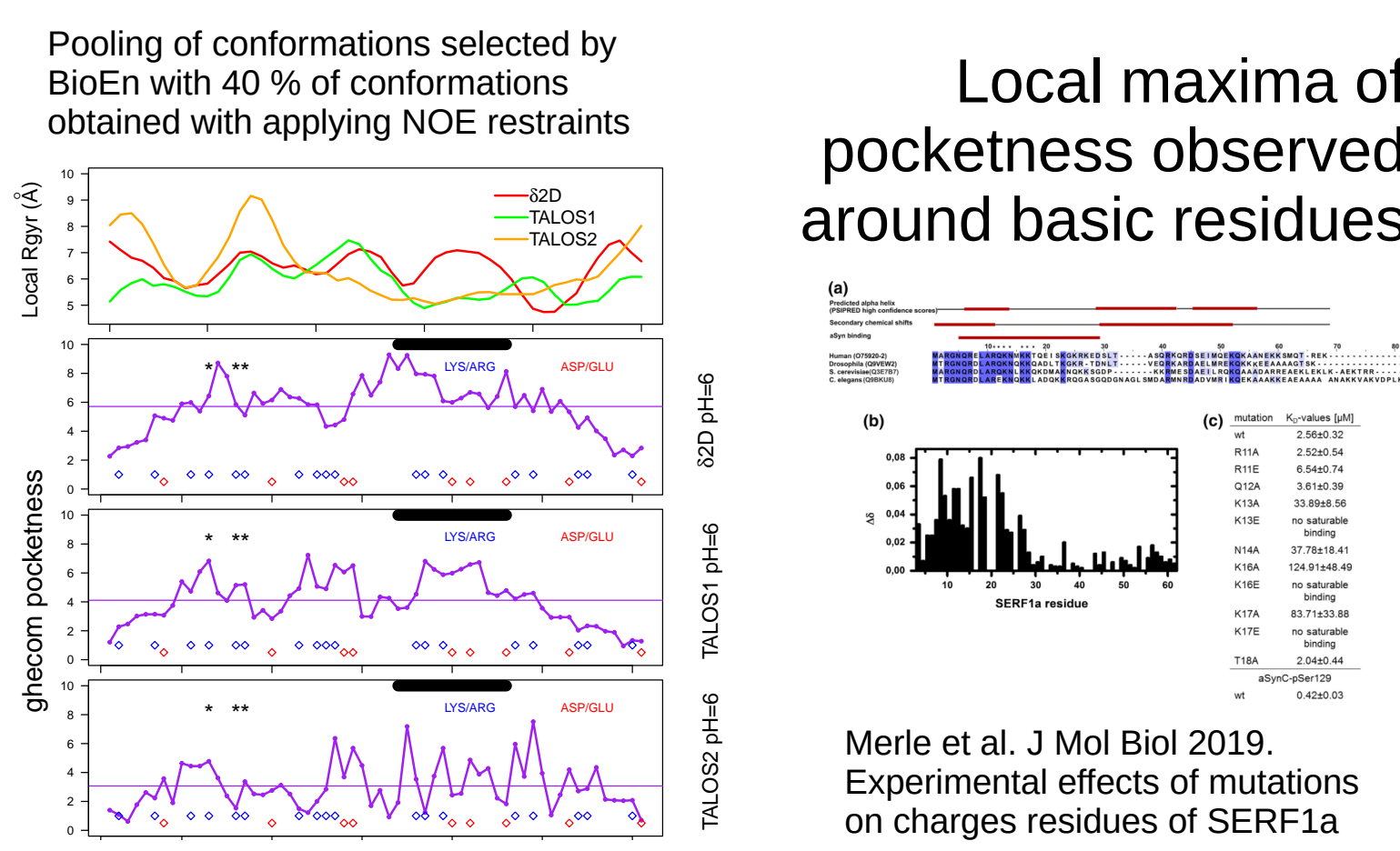


λ (nm)	Conformation numbers	Populations percentage	Conformation numbers	Populations percentage	Conformation numbers	Populations percentage
147	183 ± 0.6	117	21.2 ± 0.6	117	91.4 ± 6.6	
149	27.7 ± 0.9	119	21.1 ± 1.3	139	30.9 ± 3.6	
159	5.1 ± 0.1	159	22.5 ± 0.6	42	25.3 ± 0.6	
52	18.9 ± 0.4	42	4.4 ± 2.5	52	11.0 ± 4.3	
58	16.9 ± 0.5	52	10.9 ± 0.9	56	2.2 ± 4.3	
58	15.2 ± 0.5	56	23.0 ± 0.9	58	81.5 ± 6.1	
58	16.2 ± 1.6	98	16.2 ± 1.6	98	26.4 ± 3.4	

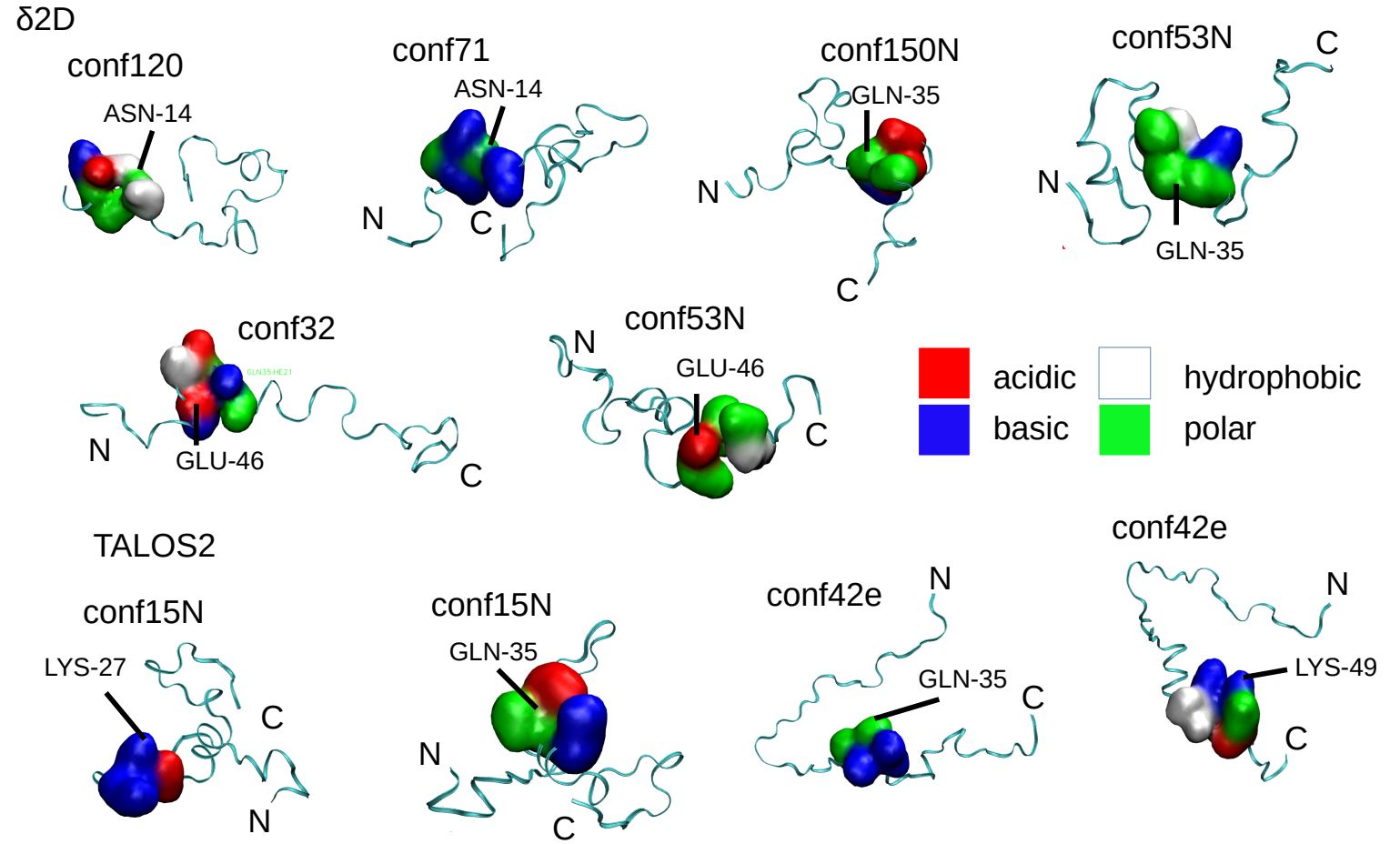
Inputs	NOE	Final χ^2	Initial # of conformations	Final # of conformations	Final radius of gyration (Å)	Populations (>10%)
δ 2D	No	1.5	122	10	25.8	38, 22, 22
TALOS1	No	1.1	191	3	24.4	63, 30
TALOS1	No	1.7	93	10	26.8	43, 21, 13
TALOS2	No	1.4	73	2	22.6	60, 40
TALOS2	No	1.8	51	4	23.8	70, 14, 14
δ 2D	only	3.9	171	2	20.5	84, 15
TALOS1	only	7.1	178	1	19.4	100
TALOS1	only	6.3	179	1	19.6	100
TALOS2	only	2.2	152	2	21.9	84, 15
TALOS2	only	16.7	51	2	16.4	71, 28



Pocket detection

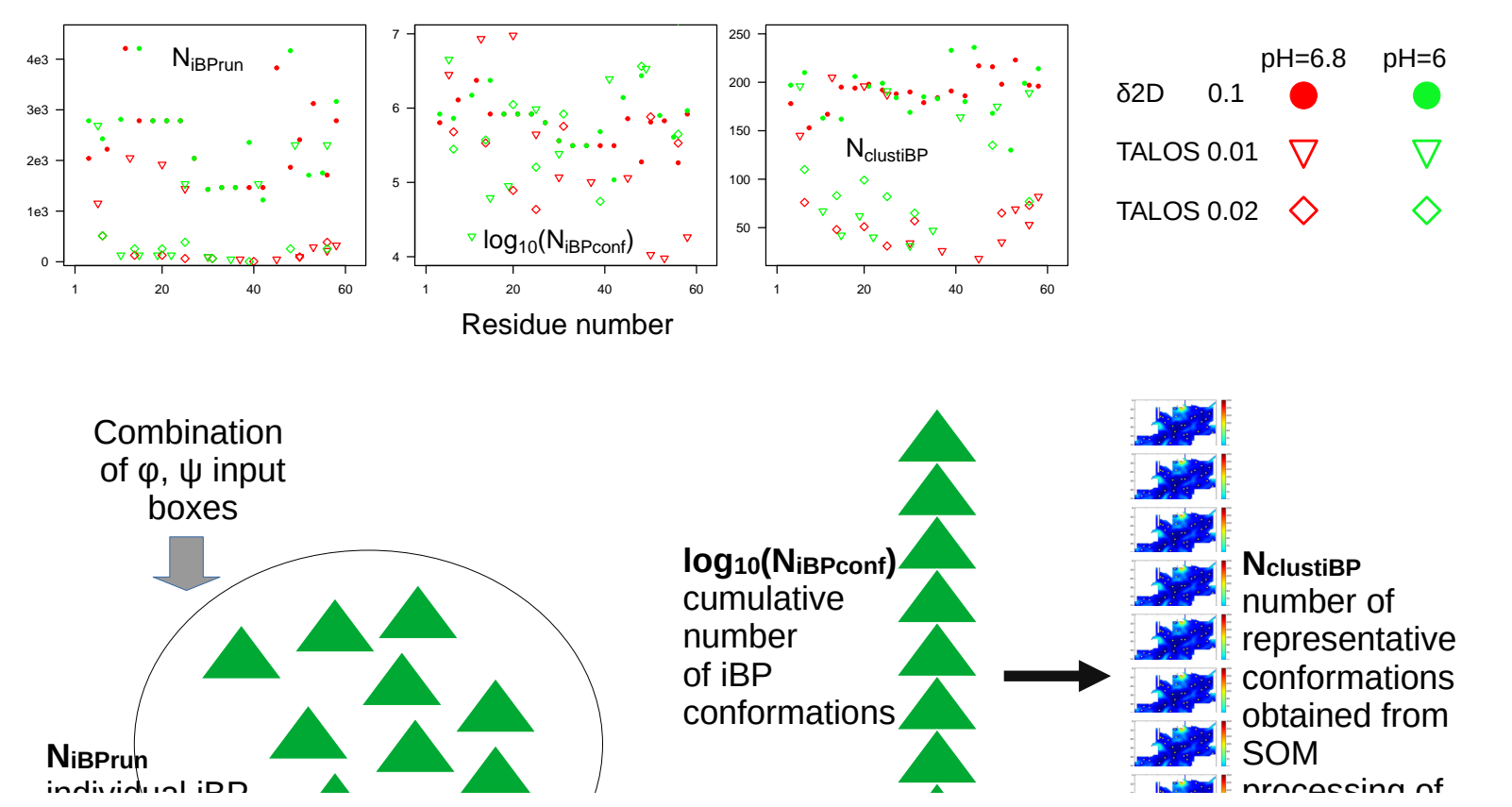


Examples of possible binding pockets sampled in conformations of SERF1a

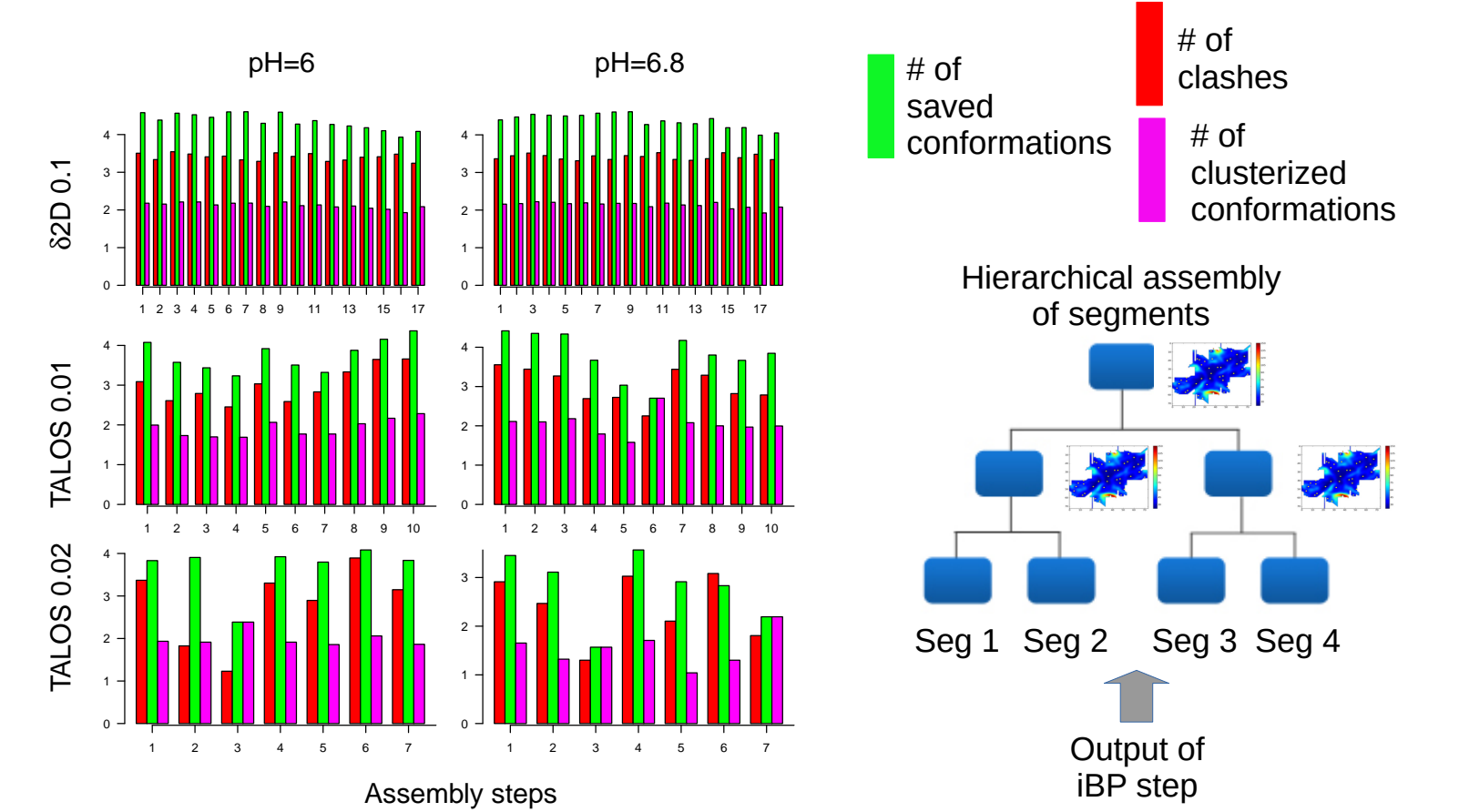


Calculation examples

TAiBP run: examples of iBP steps



TAiBP run: examples of assembly steps



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