5 Artwork

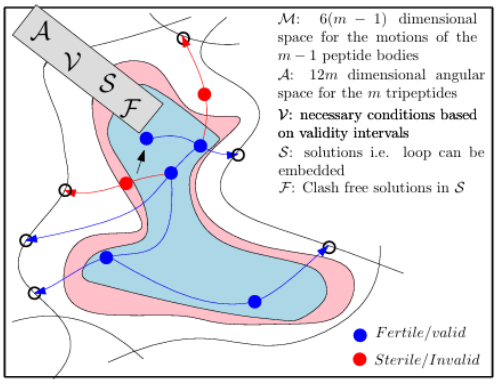

Figure 1: **Sampling a loop involving m tripeptides: spaces involved, and algorithm overview.** Spaces used: $\mathcal{A}$: a $12m$ dimensional angular space coding the internal geometry of all tripeptides; $\mathcal{V} \subset \mathcal{A}$: subspace characterized by necessary conditions for the m individual TLC problems to admit solutions; $\mathcal{S} \subset \mathcal{V}$: subspace such that the TLC associated with each individual tripeptide admits solutions; $\mathcal{F} \subset \mathcal{S}$: subspace such that the solutions to TLC do not yield any steric clash between any $\{N, C_\alpha, C, O, C_\beta\}$ atom pair. The Hit-and-Run algorithm is started at the point indicated by an arrow. It is used to find intersection (empty bullets) between 1D trajectories (blue curves) in the angular space of the tripeptides, and hyper-surfaces bounding the regions defining necessary conditions for the m individual TLC problems to admit solutions. One point is then generated on the curve segment joining the staring point and the intersection point. This point is fertile if all TLC problems admit solutions, and sterile otherwise. The number of conformations obtained is the product of the individual numbers for the m tripeptides. The process starts again from a fertile point with at least one solution without any steric clash.

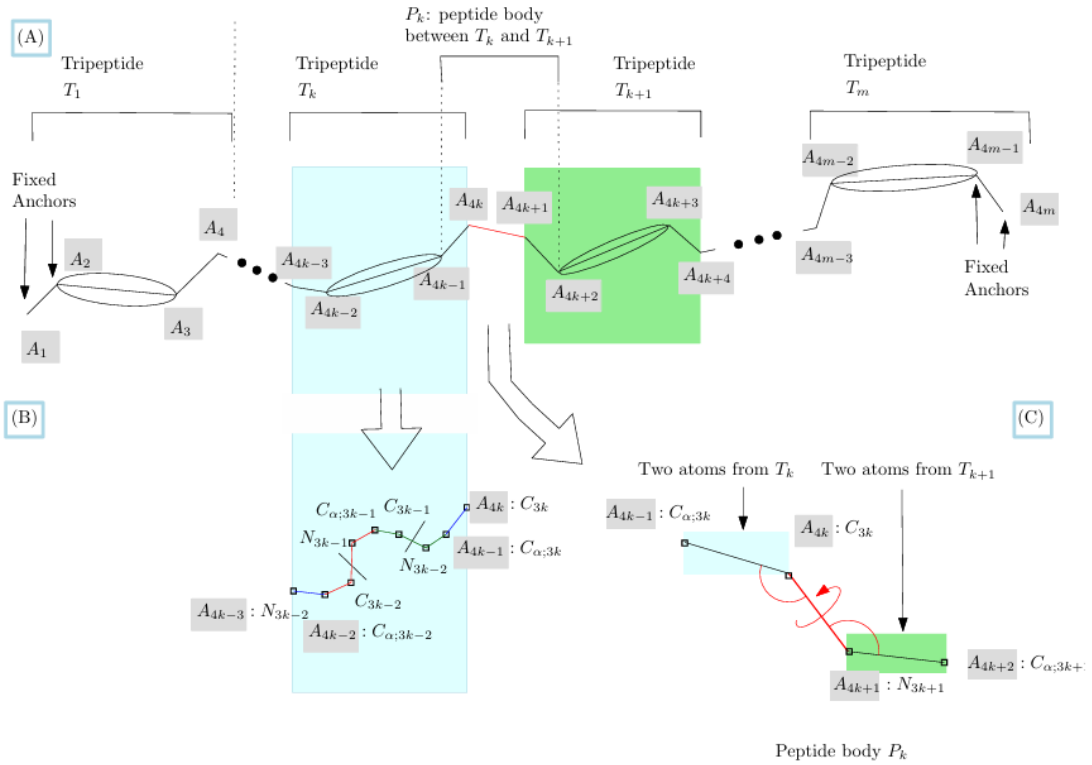

Figure 2: **Loop decomposition into tripeptides and peptide bodies, and associated geometric model. (A)** The k-th tripeptide is represented by two segments (its two legs) and an ellipsis. In red, the peptide bond between the consecutive tripeptides T_k and T_{k+1}. The peptide body encompasses the peptide bond, as well as one atom to the left and the right. **(B)** Atoms within the k-th tripeptide. **(C)** Geometry of the peptide bond linking tripeptides T_k and T_{k+1} with constrained bond lengths, valence angles, and torsion angle – in red. These four atoms form the rigid body P_k.

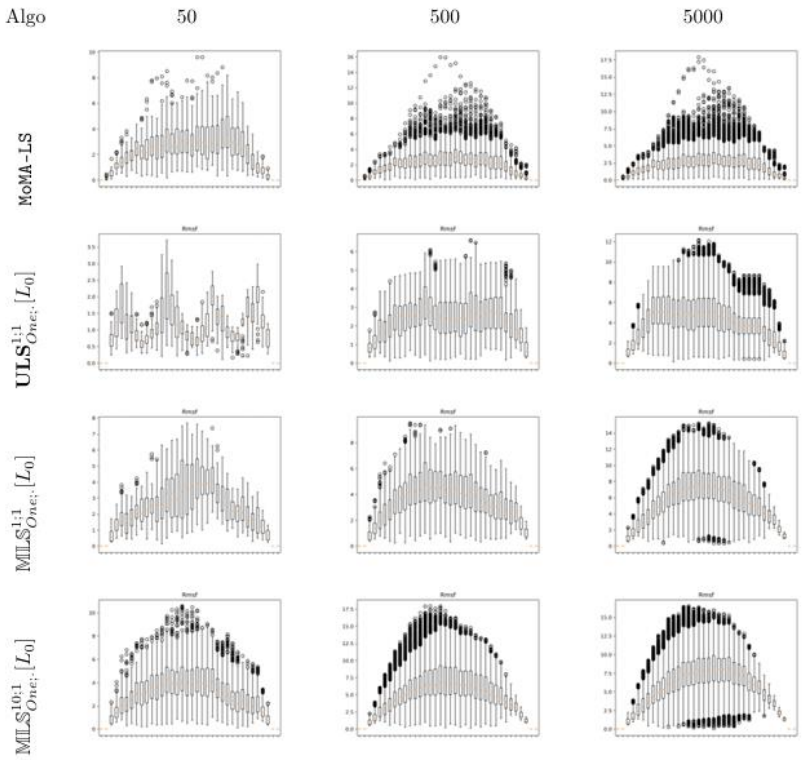

Figure 3: **Loop PTPN9-MEG2: Backbone RMSF for the 12 amino acid long loop PTPN9-MEG2.** Simulations started from the conformation/landmark L_o – see text. Each tick on the x-axis corresponds to a heavy atom of the loop – 36 in this case. For `MoMA-LS`, note that only one atom is fixed on the left hand side of the loop, since the ω angle preceding the loop is also sampled.

	L_1 min/maxlRMSD	L_2 min/maxlRMSD	L_3 min/maxlRMSD
`MoMA-LS`, 50	1.00/3.81	1.03/3.80	1.38/4.11
`MoMA-LS`, 500	0.78/4.29	0.77/4.30	1.11/4.70
`MoMA-LS`, 5000	0.74/4.92	0.73/4.94	0.99/4.97
$\mathbf{ULS}^{1;1}_{one;50}[L_0]$	0.57/2.51	0.56/2.52	1.59/2.63
$\mathbf{ULS}^{10;1}_{one;50}[L_0]$	0.40/3.50	0.40/3.50	1.44/3.84
$\mathbf{ULS}^{1;1/4}_{one;50}[L_0]$	0.89/2.82	0.88/2.83	1.76/3.36
$\mathbf{ULS}^{10;1/4}_{one;50}[L_0]$	0.52/4.49	0.51/4.50	1.45/4.99
$\mathbf{ULS}^{1;1}_{one;500}[L_0]$	0.57/4.23	0.56/4.26	1.59/4.31
$\mathbf{ULS}^{10;1}_{one;500}[L_0]$	0.40/4.66	0.40/4.68	1.44/5.09
$\mathbf{ULS}^{1;1/4}_{one;500}[L_0]$	0.89/4.92	0.88/4.95	1.76/5.10
$\mathbf{ULS}^{10;1/4}_{one;500}[L_0]$	0.52/5.23	0.51/5.27	1.45/5.52
$\mathbf{ULS}^{1;1}_{one;5000}[L_0]$	0.57/5.27	0.56/5.30	1.59/5.43
$\mathbf{ULS}^{10;1}_{one;5000}[L_0]$	0.40/5.35	0.40/5.37	1.44/5.86
$\mathbf{ULS}^{1;1/4}_{one;5000}[L_0]$	0.89/5.34	0.88/5.36	1.76/5.79
$\mathbf{ULS}^{10;1/4}_{one;5000}[L_0]$	0.52/5.35	0.51/5.39	1.45/5.80
$\mathbb{MLS}^{1;1}_{one;50}[L_0]$	0.57/3.43	0.57/3.44	1.57/3.66
$\mathbb{MLS}^{10;1}_{one;50}[L_0]$	0.52/4.81	0.51/4.83	1.03/5.23
$\mathbb{MLS}^{1;1/4}_{one;50}[L_0]$	1.78/4.59	1.77/4.60	2.02/4.88
$\mathbb{MLS}^{10;1/4}_{one;50}[L_0]$	1.32/5.22	1.33/5.23	1.38/5.87
$\mathbb{MLS}^{1;1}_{one;500}[L_0]$	0.57/4.69	0.57/4.71	1.57/4.88
$\mathbb{MLS}^{10;1}_{one;500}[L_0]$	0.52/5.77	0.51/5.79	1.03/6.28
$\mathbb{MLS}^{1;1/4}_{one;500}[L_0]$	1.78/5.53	1.77/5.56	1.90/5.84
$\mathbb{MLS}^{10;1/4}_{one;500}[L_0]$	1.32/5.75	1.33/5.78	1.38/6.29
$\mathbb{MLS}^{1;1}_{one;5000}[L_0]$	0.57/5.67	0.57/5.69	1.57/6.26
$\mathbb{MLS}^{10;1}_{one;5000}[L_0]$	0.52/5.93	0.51/5.96	1.03/6.50
$\mathbb{MLS}^{1;1/4}_{one;5000}[L_0]$	1.71/5.91	1.71/5.95	1.61/6.32
$\mathbb{MLS}^{10;1/4}_{one;5000}[L_0]$	1.32/5.93	1.33/5.96	1.38/6.50

Table 1: **Loop PTPN9-MEG2: exploration to reach landmark conformations. Using option *One* to retain a single solution per step.** Four conformations of loop PTPN9-MEG2 form two clusters: L_0, L_1, L_2 and L_3. For `MoMA-LS`, we compute min and max lRMSD distances to these landmarks. For $\mathbf{ULS}^{N_V;N_{OR}}_{\text{One|All};N_{ES}}$ and $\mathbb{MLS}^{N_V;N_{OR}}_{\text{One|All};N_{ES}}$, starting from L_0, we compute the maxlRMSD (resp. minlRMSD values) values to assess the ability to get away from the cluster (resp. approach conformation L_3).

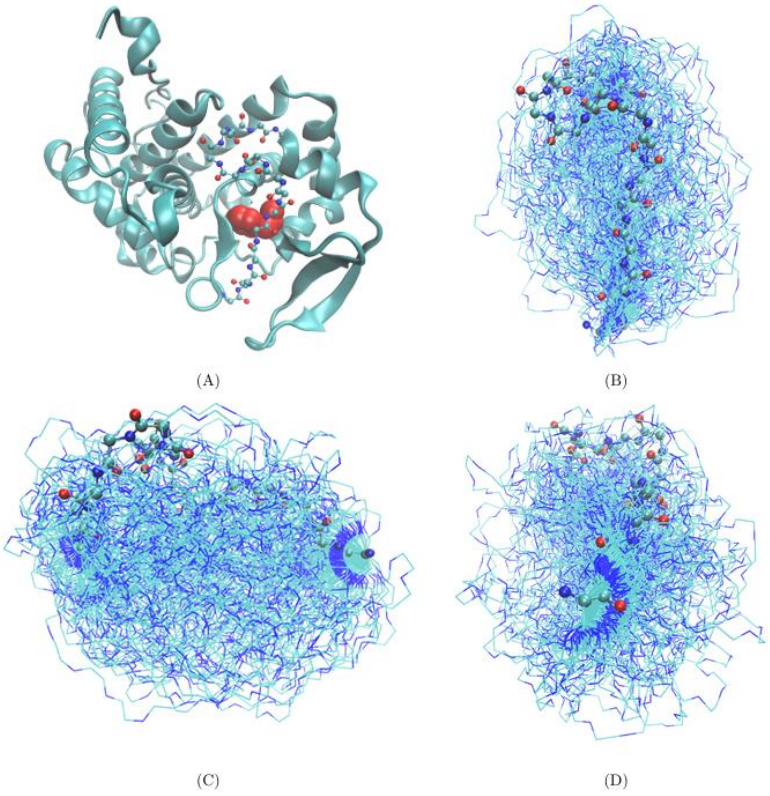

Figure 4: **Loop CCP-W191G, 15 amino acids.** Loop found in cytochrome C peroxidase (CCP). Loop specification: pdbid: 2rbt, chain X, residues 186-200. Conformations generated by algorithm $\mathrm{MLS}^{1:1}_{One;250}$. **(A)** Overview of the protein: cartoon mode: protein; CPK mode: loop; VDW representation: ligand N-Methylbenzylamine. **(B,C,D)** Top, side, front view of the loop conformations. Protein omitted for the sake of clarity.

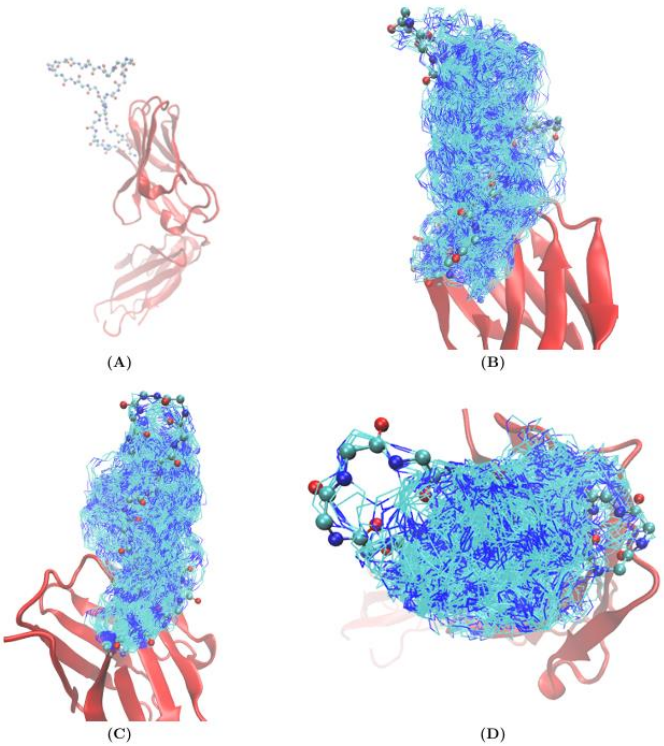

Figure 5: **CDR-H3-HIV, 30 amino acids.** The loop is a complementarity-determining region (CDR-H3) from PG16, an antibody with neutralization effect on HIV-1 [40]. Loop specification: pdbid: 3mme; chain A; residues: 93-100, 100A-100T, 101, 102. Conformations generated by algorithm $\mathrm{MLS}^{1:1}_{One;250}$. **(A)** Variable domain (red) and the 30 a.a. long CDR3. **(B,C,D)** Side/front/top view of 250 conformations .