Algorithms and Learning for Protein Science

Molecular kinematics, inverse problems, loop sampling

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Overview

- Theory/algorithms
  - Exploring high dimensional spaces: RRT and HAR
  - Loop closure
- Protein science
  - Tripeptide/Triaxial loop closure
  - Loop sampling

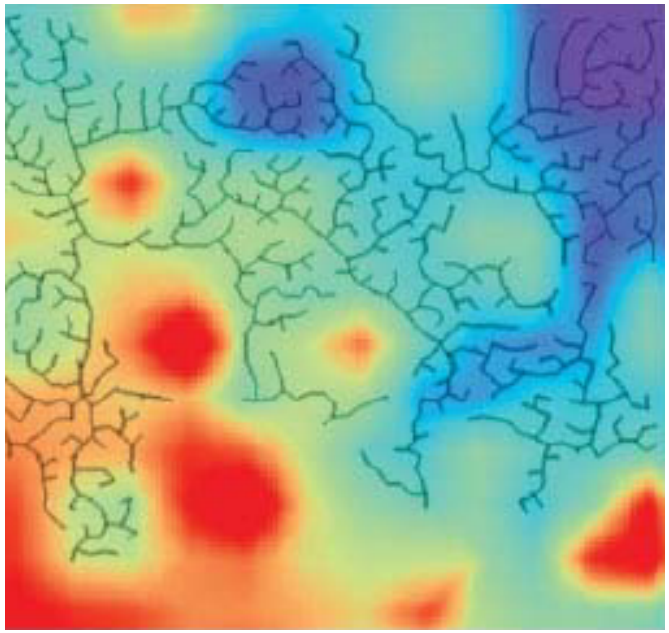
Loop sampling

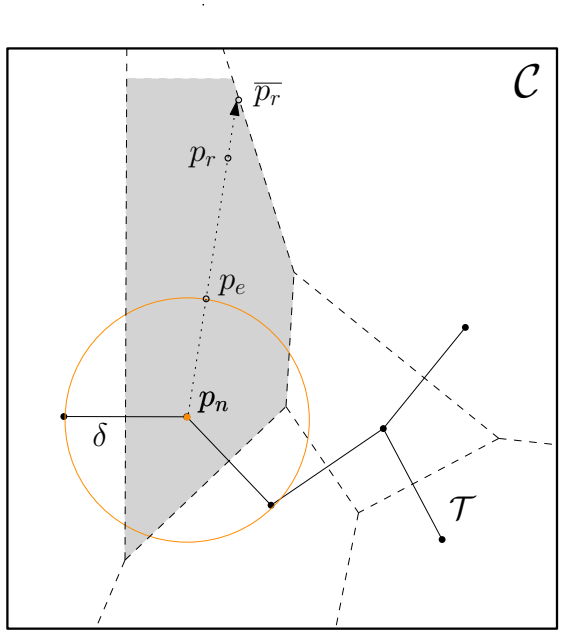
Exploring high dimensional spaces: two methods

Exploring Potential Energy Landscapes:

transition based rapidly exploring random trees (T-RRT)

- ▷ Goal: sample basins and transitions, avoiding trapping
- ▷ Algorithm growing a random tree favoring yet unexplored regions
  - node to be extended selection: *Voronoi* bias
  - node extension: interpolation + Metropolis criterion (+temperature tuning)
- ▷ Limitations: oblivious to local minima; not a Markov chain



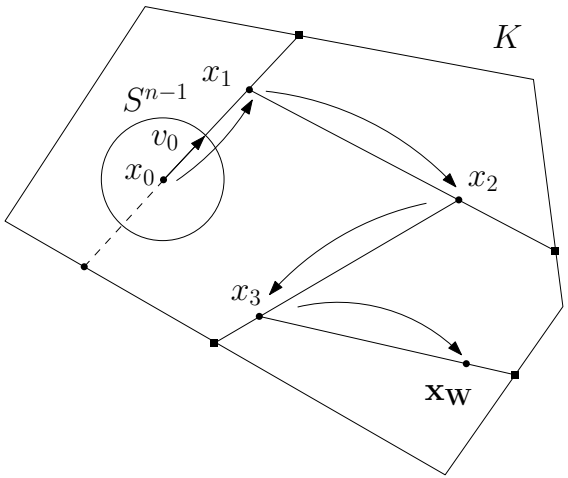


▷Ref: LaValle, Kuffner, IEEE ICRA 2000

▷Ref: Jaillet, Corcho, Pérez, Cortés, J. Comp. Chem, 2011

Random walk: hit-and-run

- ▷ Goal: sample point in K according to a prescribed density f in a polytope K
- ▷ (Random-direction) hit-and-run: random point x_W after W steps



- ▷ Iteratively:
  - pick a random vector
  - move to random point on the chord $l \cap K$, chosen from the distribution induced by f on l
- ▷ Comments:
  - risk of being trapped near a vertex
  - large W helps *forgetting* the origin x_0

▷ Thm (Berbee et al) The limit distribution induced by HR is uniform in K.

▷ Thm (Vempala et al) HR can be modified to sample an isotropic Gaussian (restricted to K).

▷ Thm (Lovász) Let r and R denote the radii of the largest inscribed and circumscribed balls for K. One sample generation: $O^\star(d^3)$.

▷Ref: Berbee et al, Math. Prog., 1987

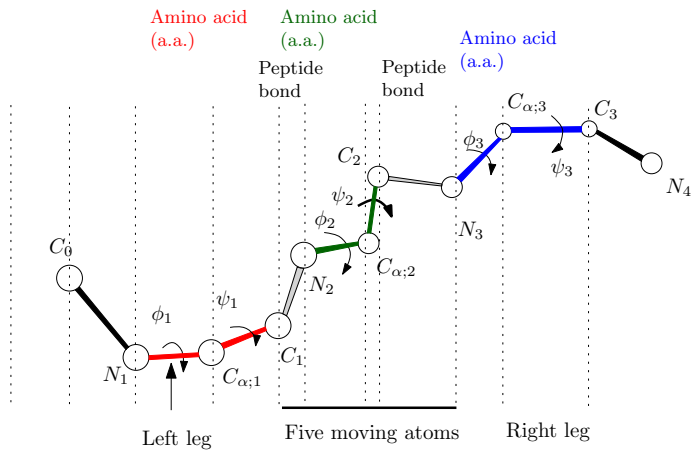
▷Ref: Lovász, Math. Prog. Ser. A, 1999

▷Ref: Lovász, Vempala, SIAM J Comp., 2006

Loop sampling

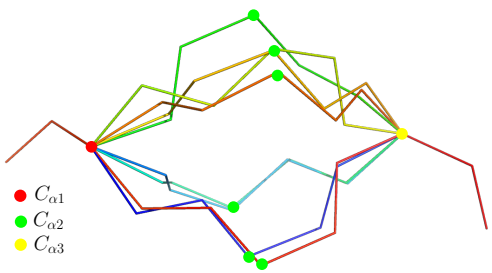
Tripeptide Loop Closure – TLC

- TLC: for 3 amino acids, fix all internal coordinates BUT the $(\phi_i, \psi_i)_{i=1,2,3}$ angles

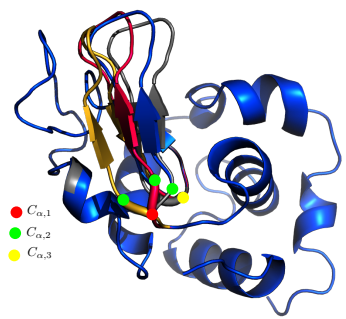


$\Rightarrow$ Find all possible values of the six angles $(\phi_i, \psi_i)_{i=1,2,3}$ compatible with the remaining fixed internal coordinates (bond lengths, valence angles, ω_i)

- Theorem: at most 16 solutions $\leftrightarrow$ real roots of a degree 16 polynomial
- The three amino acids may not be consecutive



3 consecutive a.a.

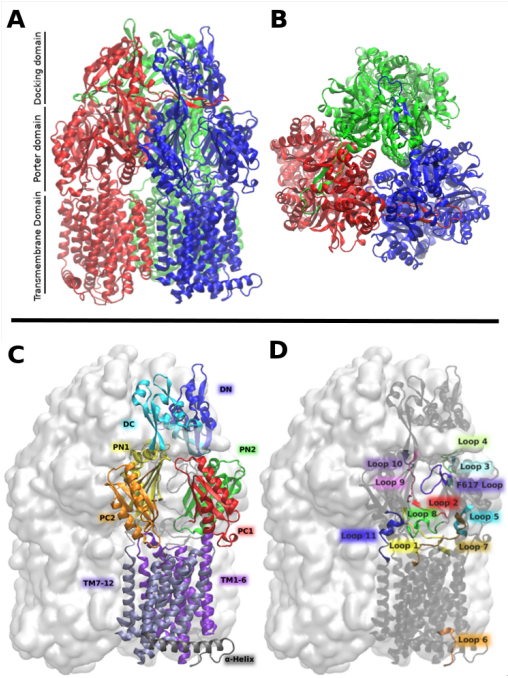


3 a.a. sandwiching SSE–CDRs

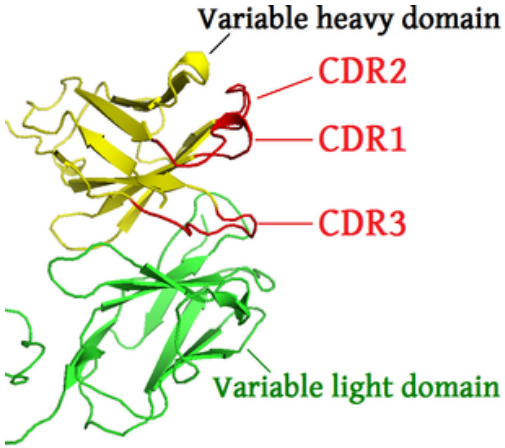
- Ref: Go and Scheraga, Macromolecules, 1970
- Ref: Coutsias et al, J. Comp. Chem., 2004

Loops: biological relevance and dynamics

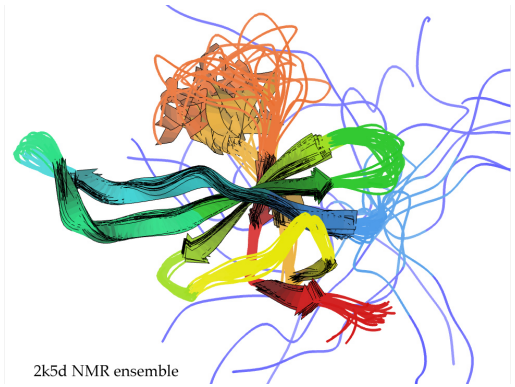
- Loops in biological processes



AcrB/RND



CDRs



IDP (2k5d/NMR)

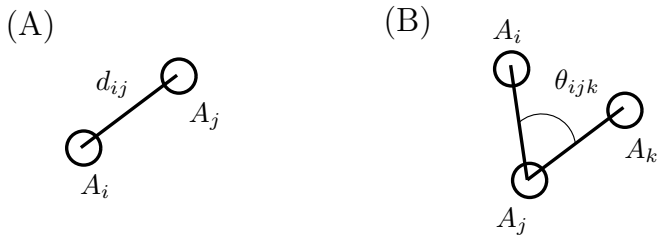
- Action modes
  - (Structure) Global dynamics: global motions of domains
  - (Thermodynamics) Localized dynamics of CDR in antibodies (binding affinity)
  - (Mix) IDP and more generally highly flexible regions

- Open problems: accurate predictions for structure / thermodynamics / kinetics

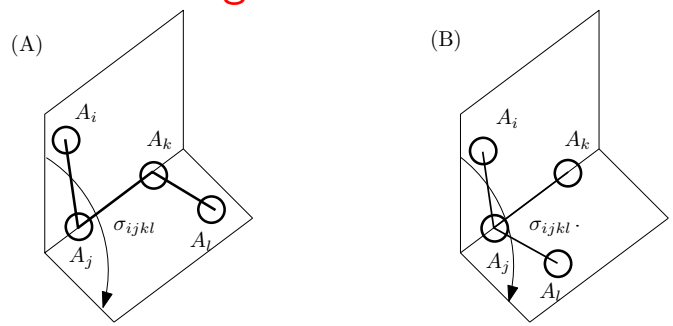
Geometric models: Cartesian and internal coordinates

▷ Cartesian versus internal coordinates: $\{x_i y_i z_i\}_i$ versus $\{d_{ij}, \theta_{ijk}, \sigma_{ijkl}\}$

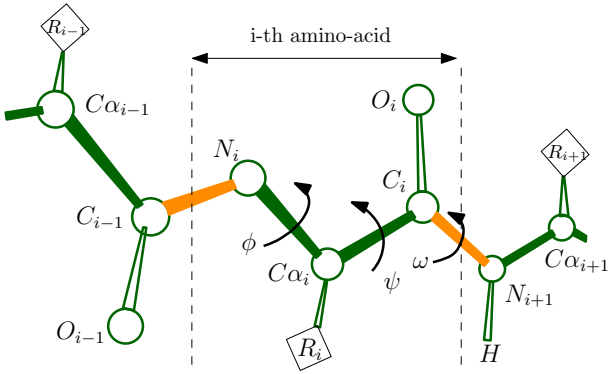
▷ Bond length and valence angle



▷ Dihedral angles



▷ Protein backbone

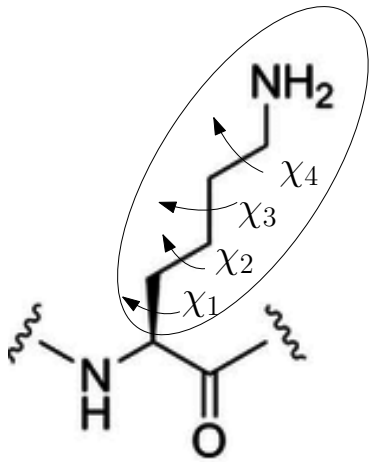


Ramachandran diagram, per a.a. type:

- bivariate distribution for (ϕ, ψ)

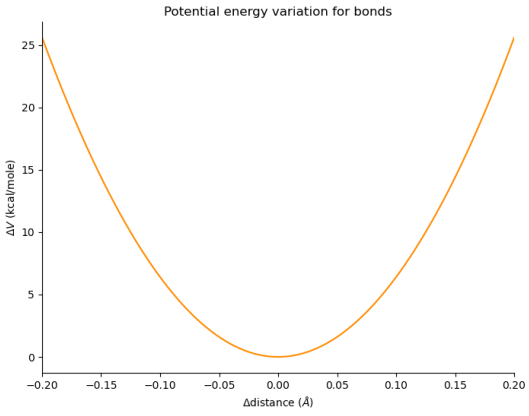
▷ Side chain: 20 natural amino acids

Exple: Lysine, 4 dihedral angles

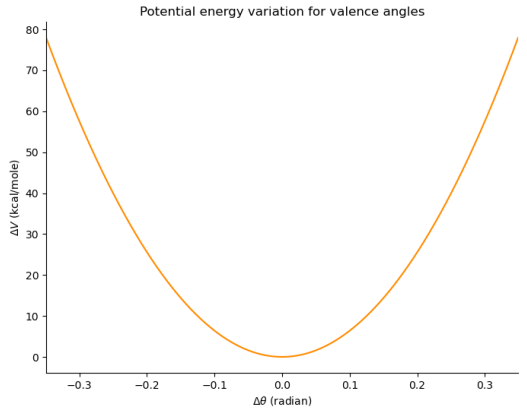


LYS

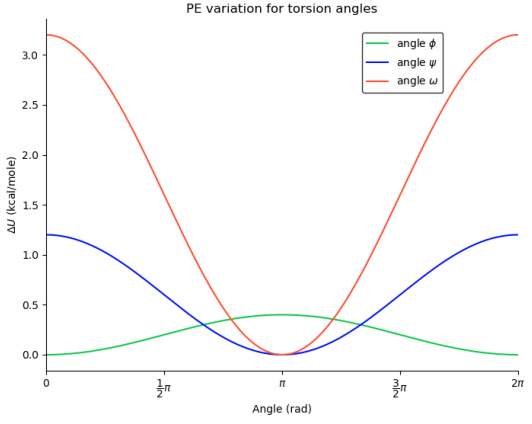
Softness of Internal coordinates –force constants from CHARMM 36



Bonds: $\delta d_{ij} \sim .2\text{Å} : \Delta V \sim 20 kcal/mol$



Valence angles: $\delta\theta_{ij} \sim 10^\circ : \Delta V \sim 20 kcal/mol$



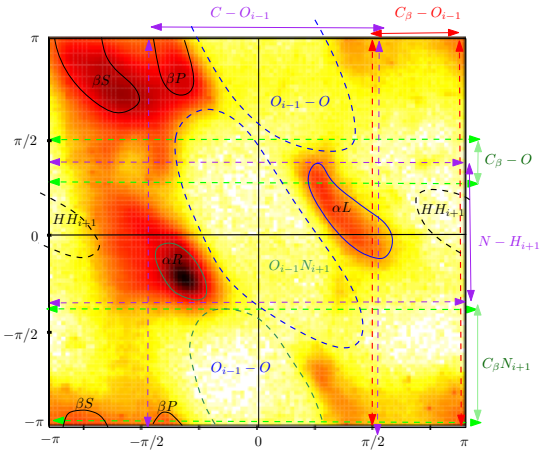
Torsion angles:$\Delta V \sim 3 - 4 kcal/mol$

Dihedral angles:

- are indeed *soft* coordinates, but. . .
- long range steric clashes,
- yield complicated inverse problems. for loop closure

The Ramachandran diagrams

▷ Ramachandran diagrams and populated regions

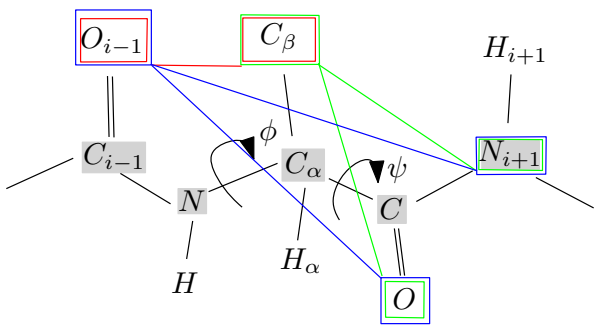


- Main regions: $\alpha L, \alpha R, \beta S, \beta P$
- Three prototypical diagrams
  - Glycine – no side chain/chiral C_α
  - Proline – side chain cycles on N
  - Others – with C_β and chiral C_α

▷ Distance constraints and the Ramachandran tetrahedron

$C1 : C_\beta - O_{i-1}$ $C2 : C_\beta - O + C_\beta N_{i+1}$

$C3 : O_{i-1} - O + O_{i-1} N_{i+1}$



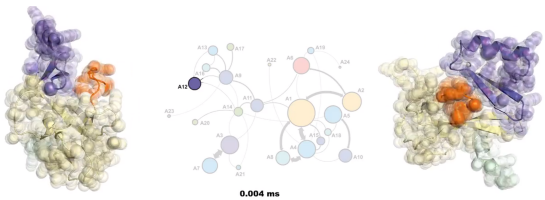
▷Ref: Stereochemistry of polypeptide chain configurations, JMB, 1963; Ramachandran et al

▷Ref: Revisiting the Ramachandran plot, Protein Science, 2003; Ho et al

Challenge *Dynamics of proteins*: specification

- Input: structure(s) of biomolecules + potential energy model
- Output
  - Thermodynamics: meta-stable states and observables
  - Kinetics: transition rates, Markov state models
- Time-scales
  - Biological time-scale $>$ millisecond
  - Integration time step in molecular dynamics: $\Delta t \sim 10^{-15} s$

- 162 amino acids, $>$ 2000 atoms
- 5.058ms of simulation time
- $\sim$ 230 GPU years on NVIDIA GeForce GTX 980 processor



Ref: Chodera et al, eLife, 2019; Youtube link

Tripeptide Loop Closure – TLC

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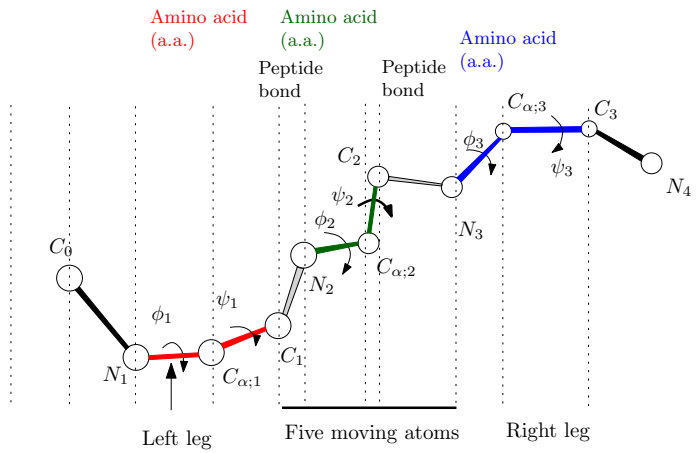

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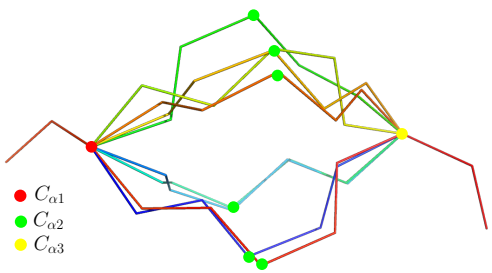

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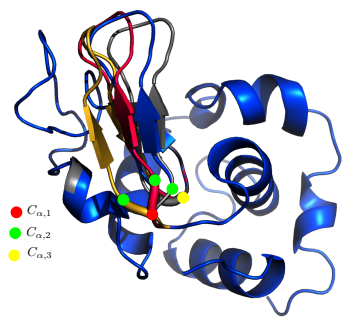

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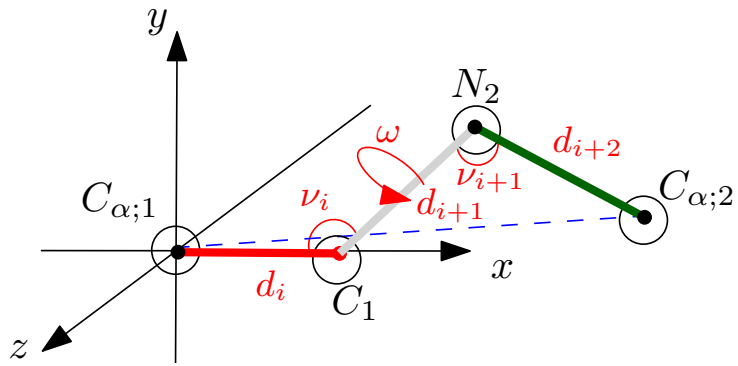
The peptide bond and peptide rigid bodies

▷ The peptide bond defines a rigid body:

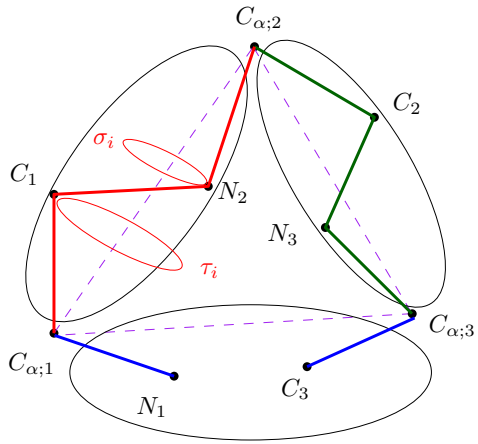


$$||C_{\alpha;2} - C_{\alpha;1}|| = Const$$

Internal coordinates fixed

- Bond lengths
- Valence angles
- ω angle

▷ The C_α triangle is rigid



- $C_{\alpha;2}$ belongs to the intersection of two spheres centered at $C_{\alpha;i}$ $C_{\alpha;i+2}$ $\Rightarrow$ C_α triangle has fixed geometry
- Legs fixed + C_α triangle rigid: rotate the three (colored) rigid bodies,

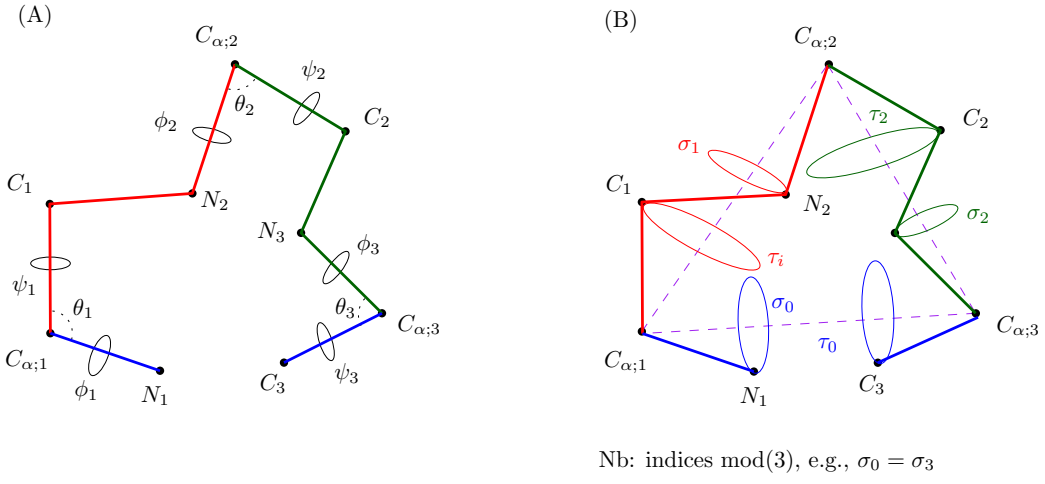
▷ Observations:
- one solves for six rotation angles $\{(\tau_i, \sigma_i)\}_{i=1,2,3}$
- **TLC parameterized in an angular space of dim. 12**

▷Ref: Coutsias et al, J. Comp. Chem., 2004

▷Ref: Cazals et al, Proteins, 2022

TLC model: from six to three angles

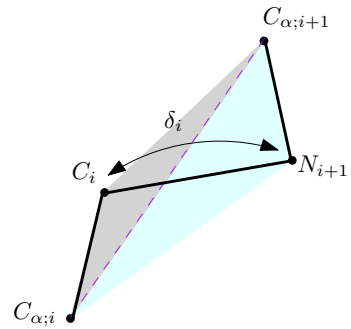
▷ Motions of the 3 rigid bodies: 6 angles



Nb: indices mod(3), e.g., $\sigma_0 = \sigma_3$

▷ . . . which are actually three

$$\sigma_i = \tau_i + \delta_i \qquad (1)$$



$\delta_i = \angle\text{Plane}(C_{\alpha;i}C_{\alpha;i+1}C_i), \text{Plane}(C_{\alpha;i}C_{\alpha;i+1}N_{i+1})$

▷ Key ingredients of TLC:

- Initially: six dihedral angles $\{(\phi, \psi)\}_{\{i=1,2,3\}}$
- Then: three pairs $\{\delta_i, \tau_i\}$
- Finally: three angles τ_i

▷ The valence angle constraints: the θ_i angles at the $C_{\alpha;i}$s must remain constant.

$\Rightarrow$ It is the coupling introduced by the θ_i angles onto the rotation angles τ_i yields a degree 16 polynomial.

▷Ref: Coutsias et al, 2004

The three local frames

▷ Local frames and individual rotations:

- Defining invidividual rotations

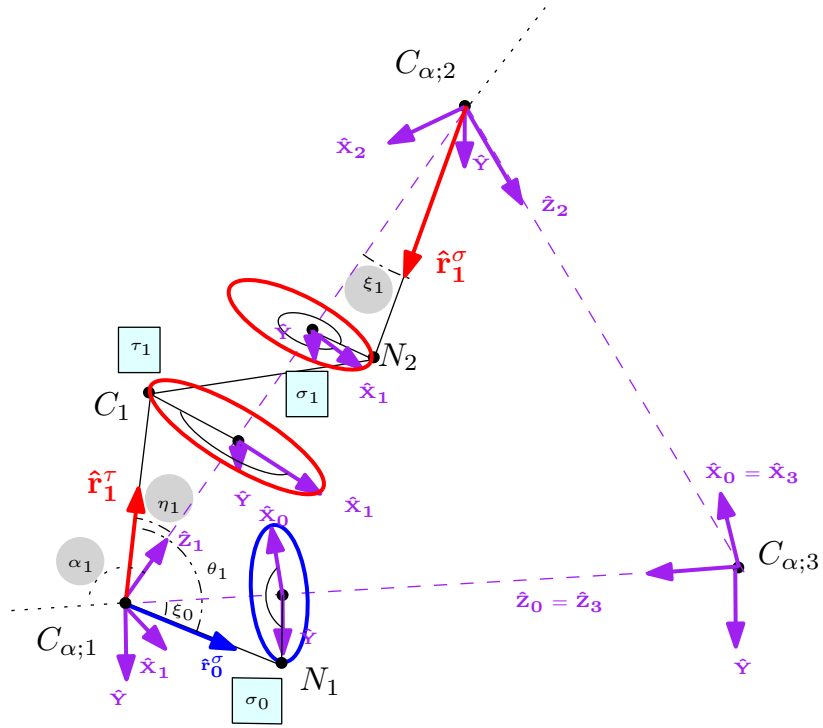
$\hat{\mathbf{r}}_\mathbf{i}^{\sigma}$; $\hat{\mathbf{r}}_\mathbf{i}^{\tau}$

- Orthonormal local frames:

Nb: $\hat{\mathbf{Z}}_\mathbf{i}$ = Unit vector along $\mathbf{C}_{\alpha;\mathbf{i}}\mathbf{C}_{\alpha;\mathbf{i+1}}$

$\hat{\mathbf{Y}}_\mathbf{i} \equiv \hat{\mathbf{Z}}_{\mathbf{i-1}} \times \hat{\mathbf{Z}}_\mathbf{i}$ Nb: $\hat{\mathbf{Y}}_\mathbf{i} = \hat{\mathbf{Y}}$

$\hat{\mathbf{X}}_\mathbf{i} = \hat{\mathbf{Y}}_\mathbf{i} \times \hat{\mathbf{Z}}_\mathbf{i} = (\hat{\mathbf{Z}}_\mathbf{i} \cdot \hat{\mathbf{Z}}_{\mathbf{i+2}})\hat{\mathbf{Z}}_\mathbf{i} - \hat{\mathbf{Z}}_{\mathbf{i+2}}$



▷ Angular description of the tripeptide: $4 \times 3 = 12$ angles

$$\begin{cases} \alpha_i & = \angle \hat{\mathbf{Z}}_\mathbf{i}\hat{\mathbf{Z}}_{\mathbf{i-1}} \\ \xi_i & = \angle - \hat{\mathbf{Z}}_\mathbf{i}\hat{\mathbf{r}}_\mathbf{i}^{\sigma} \\ \eta_i & = \angle \hat{\mathbf{Z}}_\mathbf{i}\hat{\mathbf{r}}_\mathbf{i}^{\tau} \\ \delta_i & = \angle \mathrm{Plane}(C_{\alpha;i}C_{\alpha;i+1}C_i), \mathrm{Plane}(C_{\alpha;i}C_{\alpha;i+1}N_{i+1}) \end{cases} \tag{2}$$

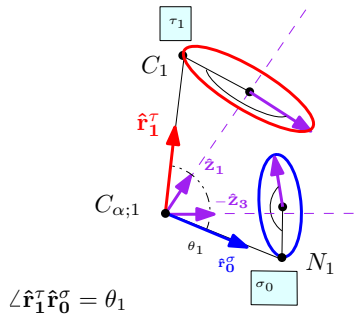
▷ Four tuple of angles for $C_{\alpha;i}$ of tripeptide T_k: $\mathsf{A}_{k,i} = \{\alpha_{k,i}, \eta_{k,i}, \xi_{k,i-1}, \delta_{k,i-1}\}$

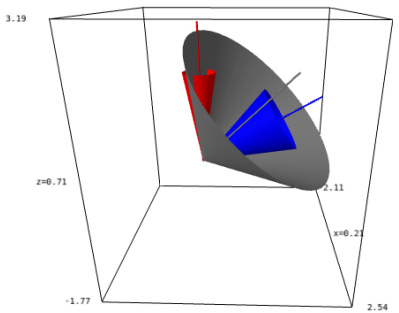
Rotations and dot product

Vectors in local frames; dot product in global frame

▷ Rotations of C_i and N_i: the two cones problem

- N_i, angle σ_i:
  vector $\hat{\mathrm{r}}^{\sigma}_{\mathrm{i}-1}$ about $\hat{\mathrm{Z}}_{\mathrm{i}-1}$
- C_i, angle τ_i:
  vector $\hat{\mathrm{r}}^{\tau}_{\mathrm{i}}$ about $\hat{\mathrm{Z}}_{\mathrm{i}}$





▷ Expressions of rotation vectors in local frames:

$$\text{In frame:}(\hat{\mathrm{X}}_{\mathrm{i}-1}, \hat{\mathrm{Y}}, \hat{\mathrm{Z}}_{\mathrm{i}-1}): \quad \hat{\mathrm{r}}^{\sigma}_{\mathrm{i}-1} = -\cos\xi_{i-1}\hat{\mathrm{Z}}_{\mathrm{i}-1} + \sin\xi_{\mathrm{i}-1}(\cos\sigma_{\mathrm{i}-1}\hat{\mathrm{X}}_{\mathrm{i}-1} + \sin\sigma_{\mathrm{i}-1}\hat{\mathrm{Y}}) \tag{3}$$

$$\text{In frame}(\hat{\mathrm{X}}_{\mathrm{i}}, \hat{\mathrm{Y}}, \hat{\mathrm{Z}}_{\mathrm{i}}): \quad \hat{\mathrm{r}}^{\tau}_{\mathrm{i}} = \cos\eta_i\hat{\mathrm{Z}}_{\mathrm{i}} + \sin\eta_{\mathrm{i}}(\cos\tau_{\mathrm{i}}\hat{\mathrm{X}}_{\mathrm{i}} + \sin\tau_{\mathrm{i}}\hat{\mathrm{Y}}) \tag{4}$$

▷ Valence angle constraint equation: θ_i kept constant

$$\begin{aligned}\langle \hat{\mathrm{r}}^{\sigma}_{\mathrm{i}-1}, \hat{\mathrm{r}}^{\tau}_{\mathrm{i}} \rangle = &-\cos\xi_{i-1}\cos\eta_i\cos\alpha_i \\ &-\cos\xi_{i-1}\sin\eta_i\cos\tau_i\sin\alpha_i \\ &-\cos\eta_i\sin\xi_{i-1}\cos\sigma_{i-1}\sin\alpha_i \\ &+\sin\xi_{i-1}\sin\eta_i(\cos\sigma_{i-1}\cos\tau_i\cos\alpha_i + \sin\sigma_{i-1}\sin\tau_i) \\ &= \cos\theta_i.\end{aligned} \tag{5, 6}$$

Algebra: the degree TLC solutions via the 16 polynomial

▷ Change of variables:

$$u_i = \tan(\tau_i/2), w_i = \tan(\sigma_i/2). \tag{7}$$

▷ Re-write the valence angle constraint – see also Eq. 21:

$$A_i w_{i-1}^2 u_i^2 + B_i w_{i-1}^2 + C_i w_{i-1} u_i + D_i u_i^2 + E_i = 0, \tag{8}$$

where the coefficients A_i, B_i, C_i, D_i, E_i depend on the angles $\theta_i, \alpha_i, \eta_i, \xi_{i-1}$.

▷ Perform another round of elimination for the w_{i-1} – coupling via δ_i: yields three three biquadratic polynomials in three variables, namely
$P_1(u_3, u_1), P_2(u_1, u_2), P_3(u_2, u_3)$

- By the Bernshtein-Kusnirenko-Khovanskii theorem, at most 16 solutions.
- The bound is tight.

▷ Using resultants: degree 16 polynomial in 1 variable

▷ Nb: the bound it tight.

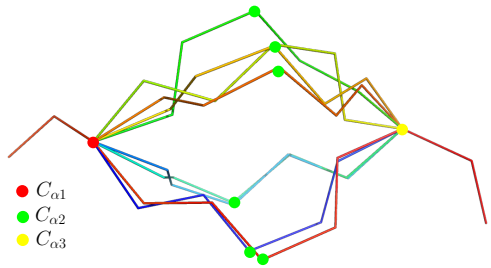
▷ Robust solutions: requires some care since π is involved

▷Ref: Cox,Little,O'Shea, Using algebraic geometry, 2005
https://en.wikipedia.org/wiki/Bernstein%E2%80%93Kushnirenko_theorem

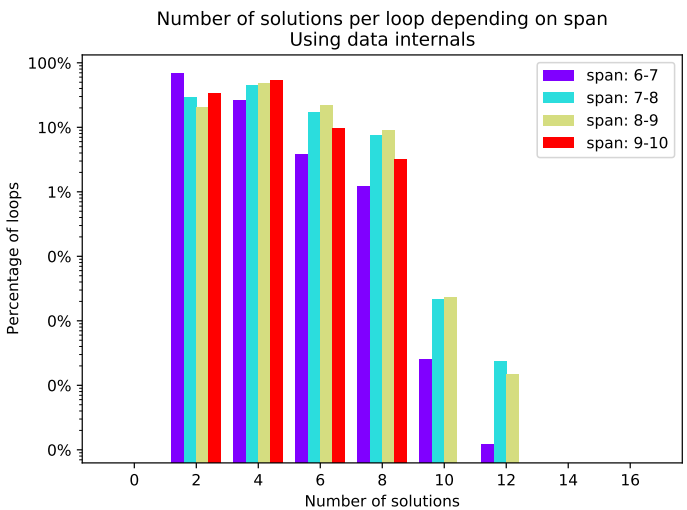
Loop sampling

TLC: number of solutions and atomic displacements

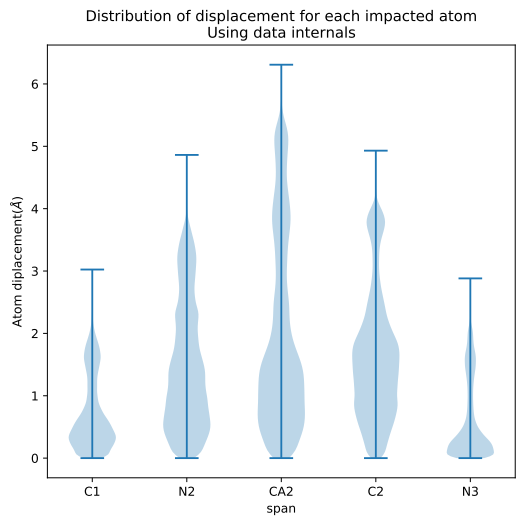
- Dataset: $\sim$ 2.6 million tripeptides in *loops* from high-resolution non redundant PDB structures



- # of solutions: function of span



- Atomic displacements

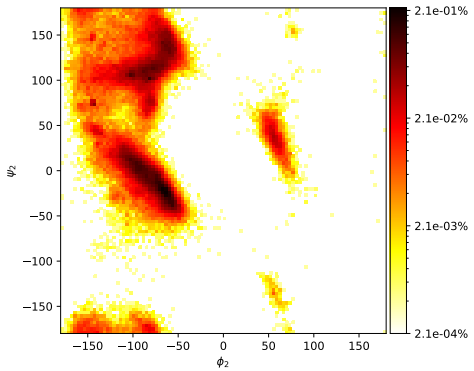


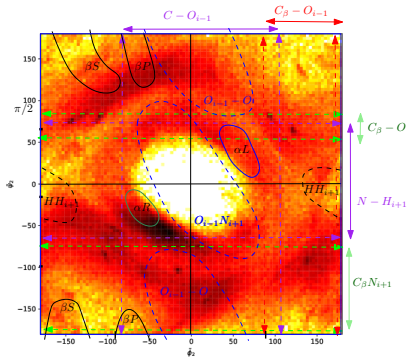
Interpolatory properties of TLC reconstructions

in the Ramachandran domains of the 3 amino acids

- Method: for the 3 Ramachandran domains (since 3 peptides):
  - compare the distribution of data versus reconstructions
  - distinguish on a per-class amino acid basis
- Ramachandran distributions

ASP





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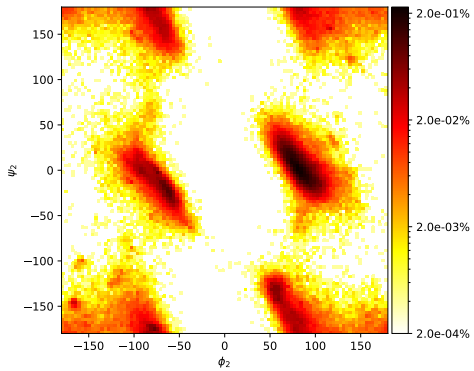
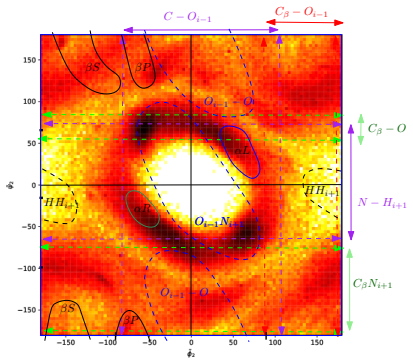




Data: $\mathcal{R}_{\mathcal{D},i}$ Reconstructions \ data: $\mathcal{R}_{\overline{\mathcal{D}},2}$

- NB: *transient* regions discovered – absent from crystals

Loop sampling

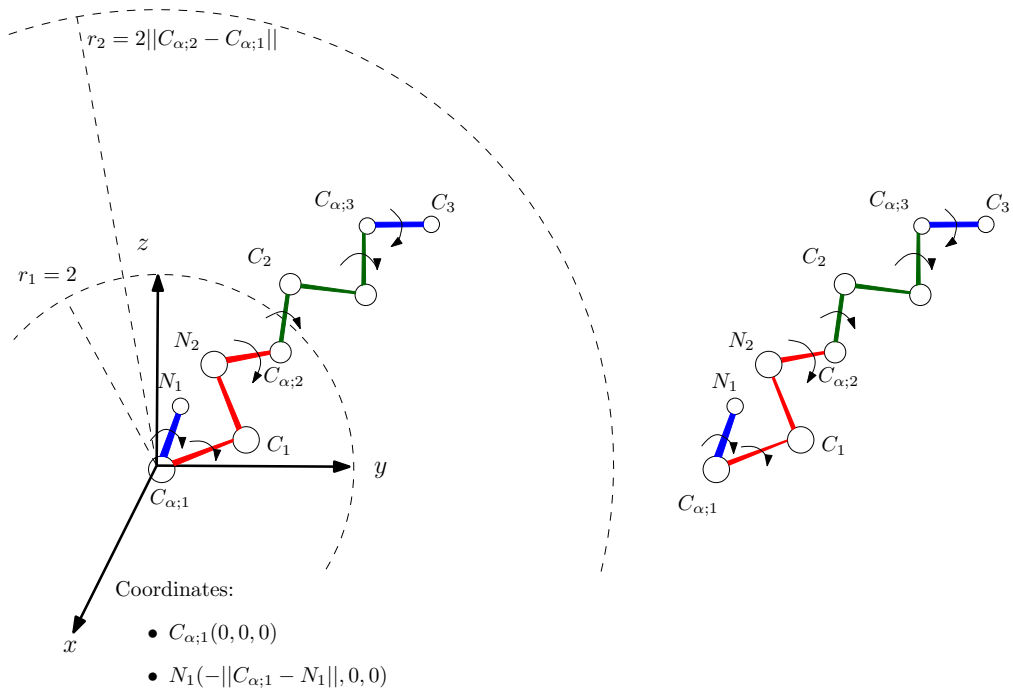
TLC with moving legs and embeddable tripeptides

▷ Geometric model:

- Tripeptide such that : left leg $N_i C_{\alpha;i}$ fixed, right leg $C_{\alpha;i+2} C_{i+2}$ free to move
- Six dihdedral angles $\{\phi_i, \psi_i\}$ free

▷ Question: provide necessary conditions on the position of the first and last segment–the **legs**, for the Tripeptide Loop Closure (TLC) algorithm to hold solutions.

▷ Nb: the relative position of legs suffices; in that case, position + orientation of $C_{\alpha;i+2} C_{i+2}$ yields a 5-dim search space.



Embedding tripeptides: recap

- Defining invidividual rotations

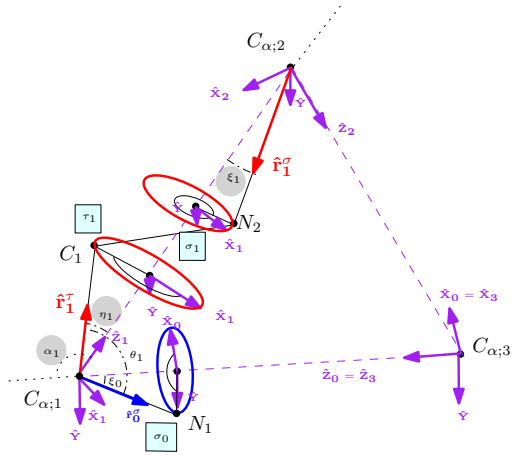
$\hat{\mathbf{r}}_{\mathbf{i}}^{\sigma}$; $\hat{\mathbf{r}}_{\mathbf{i}}^{\tau}$

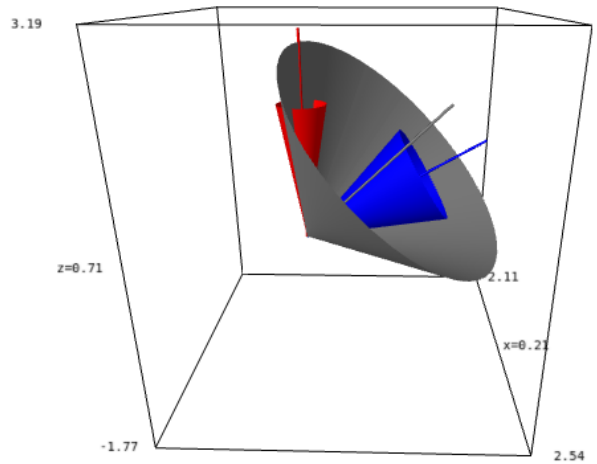
- Orthonormal local frames:

Nb: $\hat{\mathbf{Z}}_{\mathbf{i}}$ = Unit vector along $\mathbf{C}_{\alpha;\mathbf{i}}\mathbf{C}_{\alpha;\mathbf{i+1}}$

$\hat{\mathbf{Y}}_{\mathbf{i}} \equiv \hat{\mathbf{Z}}_{\mathbf{i-1}} \times \hat{\mathbf{Z}}_{\mathbf{i}}$ Nb: $\hat{\mathbf{Y}}_{\mathbf{i}} = \hat{\mathbf{Y}}$

$\hat{\mathbf{X}}_{\mathbf{i}} = \hat{\mathbf{Y}}_{\mathbf{i}} \times \hat{\mathbf{Z}}_{\mathbf{i}} = (\hat{\mathbf{Z}}_{\mathbf{i}} \cdot \hat{\mathbf{Z}}_{\mathbf{i+2}})\hat{\mathbf{Z}}_{\mathbf{i}} - \hat{\mathbf{Z}}_{\mathbf{i+2}}$





▷ 1. From the position of legs: compute $\{\alpha_{k,i}, \eta_{k,i}, \xi_{k,i-1}, \delta_{k,i-1}\}_{i\in\{1,2,3\}}$

▷ 2. TLC: find the (σ, τ) angles such that:

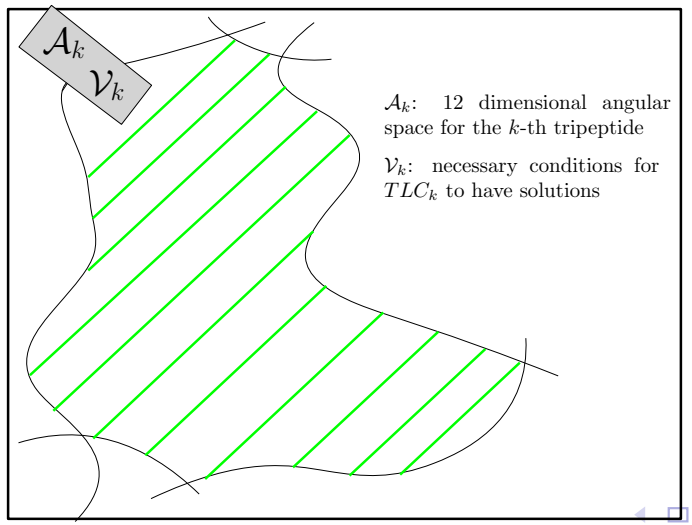
$$\langle \hat{\mathbf{r}}_{\mathbf{i-1}}^{\sigma}, \hat{\mathbf{r}}_{\mathbf{i}}^{\tau} \rangle = \cos\theta_i. \tag{9}$$

▷ Our goal:

- Conditioning of the solutions wrt the $\{\alpha, \xi, \eta, \delta\}$ via necessary conditions
- Ability to sample uniformly solutions given the necessary conditions

Sampling strategy based on validity intervals: overview

- Angular representations:
  - $C_{\alpha;i}$ from tripeptide T_k: four tuple of angles $\mathsf{A}_{k,i} = \{\alpha_{k,i}, \eta_{k,i}, \xi_{k,i-1}, \delta_{k,i-1}\}$ with $i \in \{1, 2, 3\}$
  - Tripeptide T_k, 12-dim angular space: $\mathsf{A}_k = \{\mathsf{A}_{k,1}, \mathsf{A}_{k,2}, \mathsf{A}_{k,3}\}$.
- Strategy:
  - Assume we have necessary conditions for the angles, as a finite set of **validity intervals** $I = \{[a_i, b_i]\}$
  - Assume each bound a_i or b_i is defined by an implicit equation in the 12 angular variables
  - By the implicit function theorem (assuming it applies): each equation corresponds to a hyper-surface
  - Domain enclosed by these hyper-surfaces: domain within which TLC solution lie



Validity Intervals and Depth One Validity Intervals (DOVI)

▷ Validity intervals: for each angle $\tau_{k,i}$, one can compute 2+2 intervals on S^1, representing (stringent) necessary conditions for TLC to admit solutions:

$$\text{(Initial)}\mathcal{I}_{\tau_{k,i}} = \{I_{\tau_{k,i}}\} \text{ with } I_{\tau_{k,i}} = [I_\tau^{\min}(\mathsf{A}_{k,i}), I_\tau^{\max}(\mathsf{A}_{k,i})] \tag{10}$$

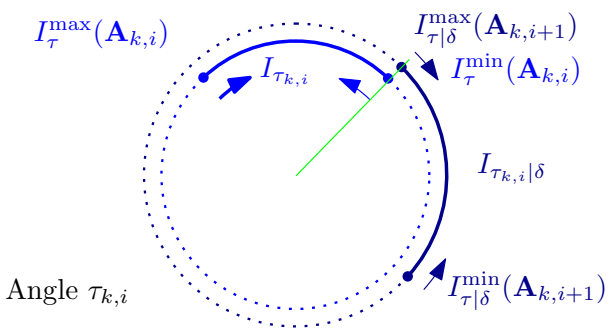
$$\text{(Rotated)}\mathcal{I}_{\tau_{k,i}|\delta} = \{I_{\tau_{k,i}|\delta}\} \text{ with } I_{\tau_{k,i}|\delta} = [I_{\tau|\delta}^{\min}(\mathsf{A}_{k,i+1}), I_{\tau|\delta}^{\max}(\mathsf{A}_{k,i+1})] \tag{11}$$

Indeed:

- $I_{\tau_{k,i}}$: obtained from the invariance of θ_i at $C_{\alpha;i}$
- $I_{\tau_{k,i}|\delta}$: obtained from $I_{\sigma_{k,i}}$ via the relation $\sigma_i = \tau_i + \delta_i$
- NB: 2 initial and 2 rotated: intervals bounds in $[0, \pi]$ + symmetry wrt C_α plane

▷ Intersection of validity intervals: necessary conditions expressed as intervals

$$I_{\tau_{k,i}} \cap I_{\tau_{k,i}|\delta}.$$



Limit case: implicit equation in the 12 dimensional space $\mathcal{A}_k$.

Limit case: $I_\tau^{\max}(\mathbf{A}_{k,i}) = I_{\tau|\delta}^{\min}(\mathbf{A}_{k,i+1})$

Validity domain for tripeptide T_k:

intersecting two initial and two rotated intervals

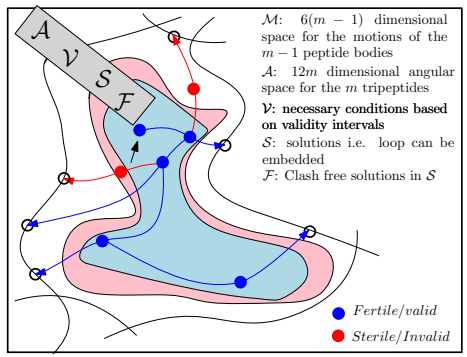
▷ Rigid body I of tripeptide T_k: angles tuples $\rightsquigarrow$ Depth One Validity Intervals

$$\mathrm{DOVI}_{\tau_{k,i}}(\cdot) : \mathcal{A}_k \mapsto \emptyset + (\mathcal{I}_{\tau_{k,i}} \cap \mathcal{I}_{\tau_{k,i}|\delta})^4. \tag{12}$$

▷ The *angular* validity domain $\mathcal{V}_k$ for T_k:

For the angle $\tau_{k,i}$: the domain $\mathcal{V}_k \subset \mathcal{A}_k$ such that

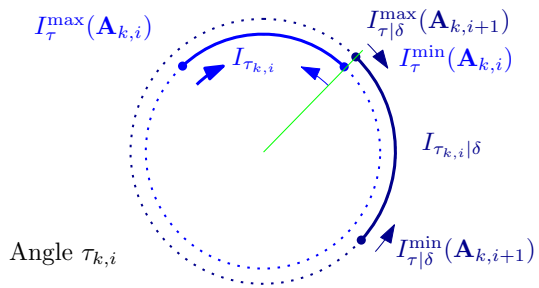
$$\forall k, \forall i, \forall a \in \mathcal{V}_k : \mathrm{DOVI}_{\tau_{k,i}}(a) \neq \emptyset.$$



▷ Non empty intersection for 2 intervals $I_{\tau_{k,i}} \in \mathcal{I}_{\tau_{k,i}}$ and $I_{\tau_{k,i}|\delta} \in \mathcal{I}_{\tau_{k,i}|\delta}$: conditions

$$\begin{cases} I_{\tau}^{\max}(\mathrm{A}_{k,i}) = I_{\tau|\delta}^{\min}(\mathrm{A}_{k,i+1}) \\ \text{or } I_{\tau}^{\min}(\mathrm{A}_{k,i}) = I_{\tau|\delta}^{\max}(\mathrm{A}_{k,i+1}) \end{cases}$$

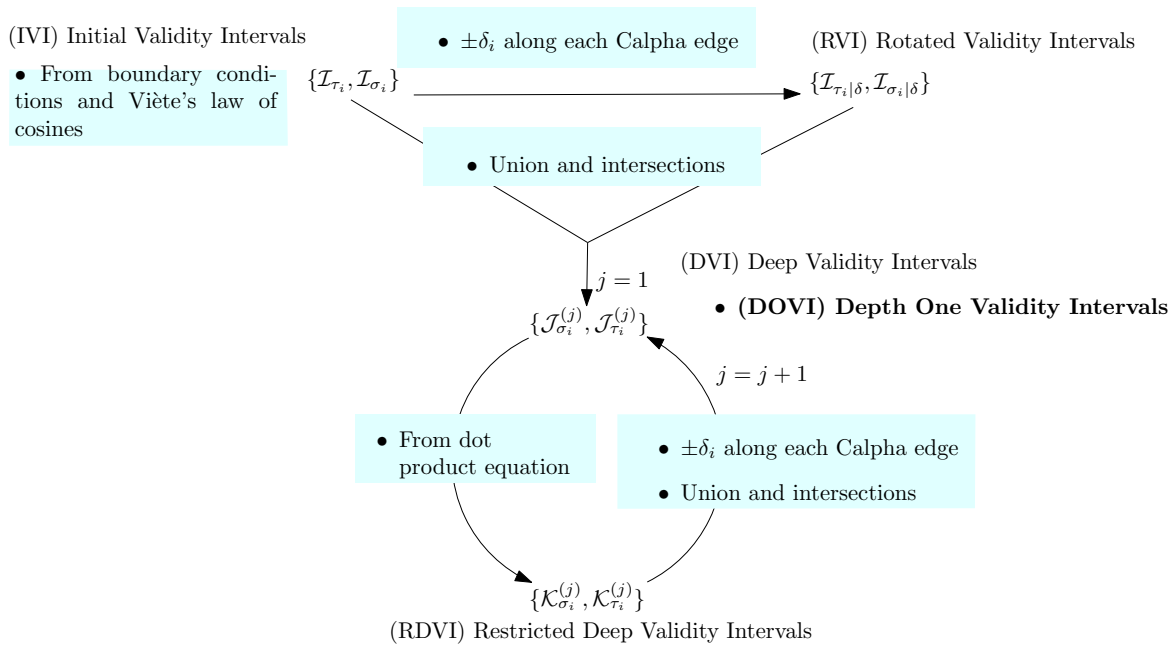
$\Rightarrow$ **two implicit equations in** $\mathcal{A}_k$: two sub-manifolds $\mathcal{V}_k$



Limit case: $I_{\tau}^{\max}(\mathbf{A}_{k,i}) = I_{\tau|\delta}^{\min}(\mathbf{A}_{k,i+1})$

Validity intervals: deep *i.e.* iterated VI

- Two types of constraints:
  - Coherence along each edge of the C_α triangle – via ω angle
  - Constraint on θ_i at each C_α
- A sequential and iterative construction: interval types used
  - Initial VI
  - Rotated VI
  - Deep VI and Restricted Deep VI



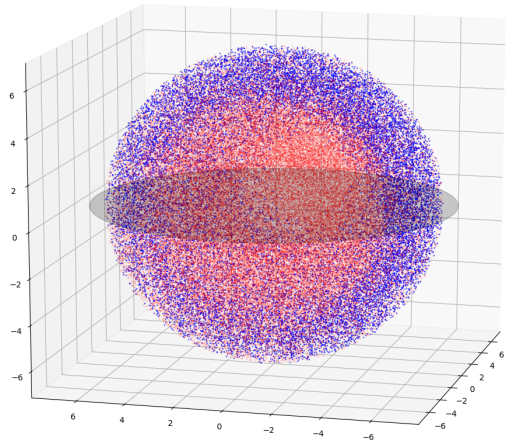
Stringency of necessary conditions: assessment

- Reminder: the search space is 5D
- Evaluation of the stringency of validity intervals:
  - Take random instances of peptides – in the 5D space
  - Identify positives (P) and negatives (N)
  - Given that N = True Negative + False Positives

$$\text{Strigency of necessary condition } c : \frac{FP(c)}{N} \tag{13}$$

- Nb: projecting the 5D points into 3D: coordinates of $C_{\alpha;i+2}$

Stringency of necessary conditions: results



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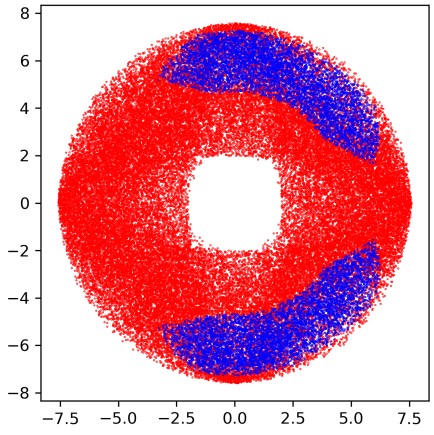

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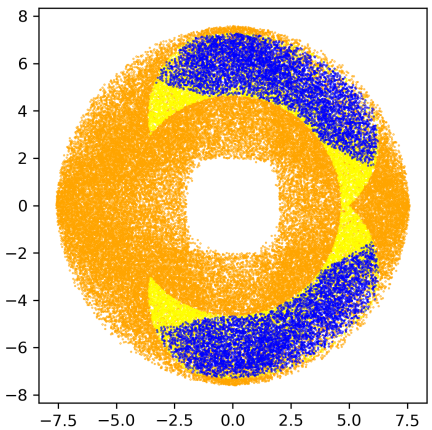

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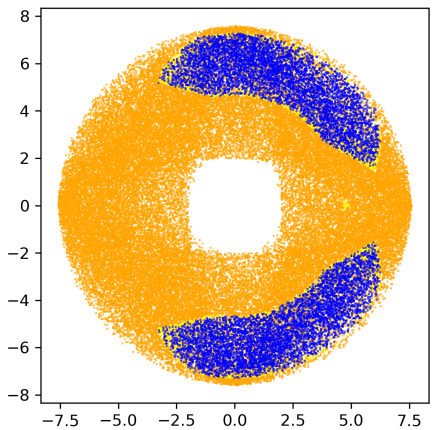


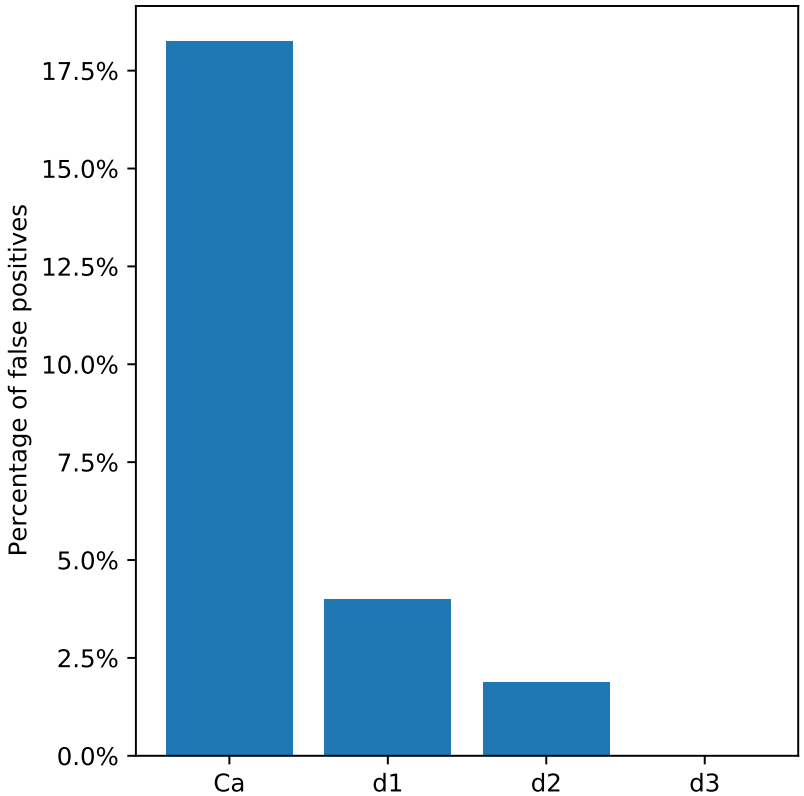
(D)

- (A,B) Random TLC instances: position of $C_{\alpha;i+2}$. Blue/red: fertile/sterile point.
- (C) C_α valence constraints: False Positives in yellow
- (D) Depth 1 validity intervals: False Positives in yellow

▷ Nb: FP reduced significantly...but beware of the bias due to the 3D projection!

Stringency of deep validity intervals

- Stringency: initial validity intervals + deep validity intervals



- Observation: the % of FP decreases
- Conjecture: the intervals converge towards the solutions of TLC

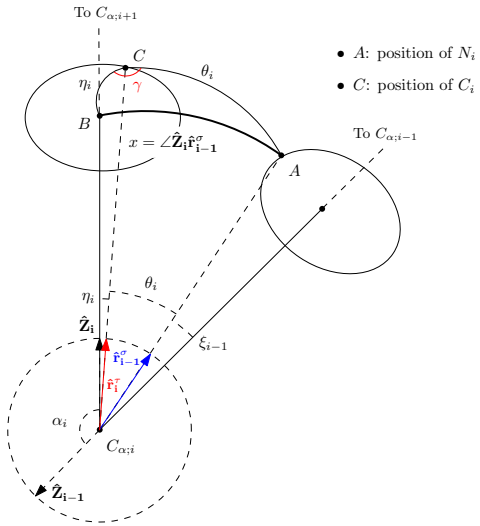
Initial Validity Intervals: bounds

▷ Obs: limit cases for the dot product $\langle \hat{\mathbf{r}}^{\sigma}_{\mathbf{i}-1}, \hat{\mathbf{Z}}_{\mathbf{i}} \rangle = \cos(\theta_{\mathbf{i}} \pm \eta_{\mathbf{i}})$.

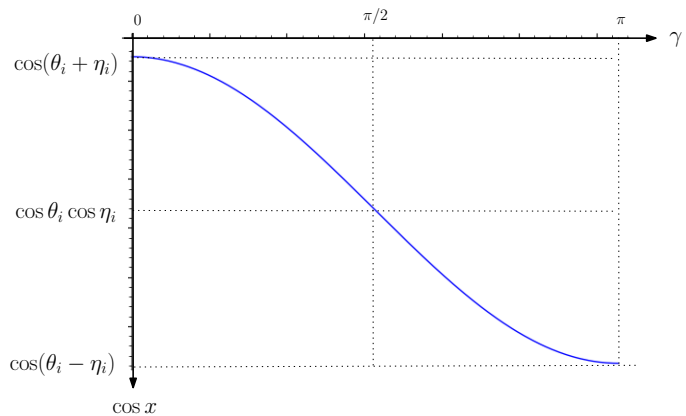
Proof: Viète's law of cosines for the spherical triangle ABC:

$$\cos x = \cos\theta_i \cos\eta_i + \sin\theta_i \sin\eta_i \cos\gamma. \tag{14}$$

Extreme values for $\gamma = 0, \pi$: $\cos(\theta_i \pm \eta_i)$



Viète formula of cosines



$\cos x$

▷ Final step:

- plug the extreme values into the dot product $\langle \hat{\mathbf{r}}^{\sigma}_{\mathbf{i}-1}, \hat{\mathbf{r}}^{\tau}_{\mathbf{i}} \rangle$
- $\Rightarrow$ polynomial in cos, sin of the 12 angles + the 3 σs

Valence angle constraint: the case of σ_{i-1} (II)

▷ $\sigma_{i-1;-}$: first limit case
start with the dot product

$$\langle \hat{\mathbf{r}}^{\sigma}_{i-1}, \hat{\mathbf{Z}}_i \rangle = -\cos\sigma_{i-1}\sin\xi_{i-1}\sin\alpha_i - \cos\xi_{i-1}\cos\alpha_i. \tag{15}$$

$$\langle \hat{\mathbf{r}}^{\sigma}_{i-1;-}, \hat{\mathbf{Z}}_i \rangle = \cos(\theta_i + \eta_i) \tag{16}$$

from which we obtain

$$\begin{cases} S^- = \frac{+\cos(\theta_i - \eta_i) + \cos\xi_{i-1}\cos\alpha_i}{\sin\xi_{i-1}\sin\alpha_i} \\ \sigma_{i-1;-} = \arccos S^- \end{cases} \tag{17}$$

When $S^- \to 1^-, \sigma_{i-1;-} \to 0^+$. Therefore,

$$S^- > 1, \tag{18}$$

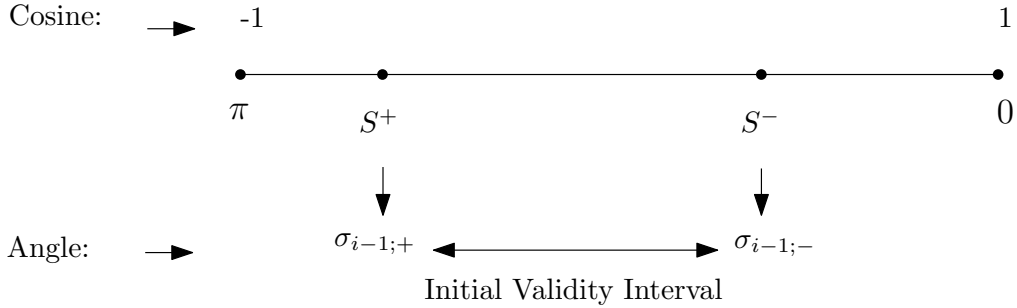
we set $\sigma_{i-1;-} = 0$, so that any value $\sigma_{i-1} \leq \sigma_{i-1;+}$ is valid.

▷ $\sigma_{i-1;+}$: mutatis mutandis

▷ Result: validity interval $I_{\sigma_{i-1}} = [\sigma_{i-1;-}, \sigma_{i-1;+}] \subset [0, \pi]$

C_α valence constraints

▷ Conditions to define the four extreme angles: the case of σ_{i-1}



Definition 1. (C_α valence constraints) The C_α *valence constraints* are the *necessary validity conditions* defined by :

- Angle $\sigma_{i-1;-}$: the condition $\sigma_{i;-} < \sigma_{i;+}$ requires $S^- \geq -1$.
- Angle $\sigma_{i-1;+}$: the condition $\sigma_{i;-} < \sigma_{i;+}$ requires $S^+ \leq 1$.
- Angle $\tau_{i;-}$: the condition $\tau_{i;-} < \tau_{i;+}$ requires $T^- \geq -1$.
- Angle $\tau_{i;+}$: the condition $\tau_{i;-} < \tau_{i;+}$ requires $T^+ \leq 1$.

For the constraint to be verified all these conditions must be valid for all three $\{(\sigma_{i-1}, \tau_i)\}$ pairs.

▷ Application: pick a tripeptide geometry $\{\alpha_i, \xi_i, \eta_i, \delta_i\}$, and check whether the four previous conditions are fulfilled.

Validity Intervals: Initial and Symmetric

Pairs of Validity Intervals

- Angle σ_{i-1}:
  - Validity interval $I_{\sigma_{i-1}} = [\sigma_{i-1;-}, \sigma_{i-1;+}] \subset [0, \pi]$
  - Symmetric interval with respect to the plane $C_{\alpha;i} C_{\alpha;i+1} C_{\alpha;i+2}$:

$$I^{'}_{\sigma_{i-1}} = [\sigma^{'}_{i-1;-}, \sigma^{'}_{i-1;+}] \stackrel{Def}{=} [2\pi - \sigma_{i-1;-}, 2\pi - \sigma_{i-1;+}].$$

    Nb: values in $(\pi, 2\pi]$.

- Angle τ_i: mutatis mutandis

Definition 2. (Initial validity intervals) The *initial validity interval* for σ_{i-1} are defined by:

$$\mathcal{I}_{\sigma_{i-1}} = I_{\sigma_{i-1}} \cup I^{'}_{\sigma_{i-1}} \tag{19}$$

Likewise, the *initial validity interval* for τ_i are defined by:

$$\mathcal{I}_{\tau_i} = I_{\tau_{i-1}} \cup I^{'}_{\tau_i}. \tag{20}$$

Extreme angles: visualization

- Dot product surface:

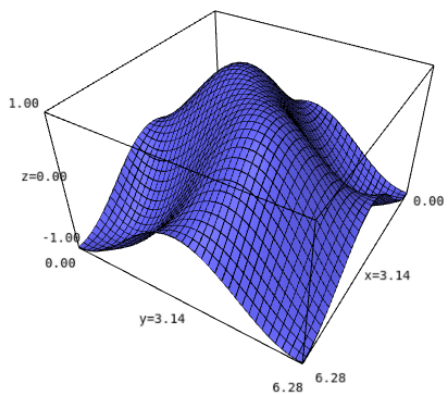
$$f(\sigma_{i-1}, \tau_i) = \langle \hat{\mathbf{r}}_{i-1}^{\sigma}, \hat{\mathbf{r}}_i^{\tau} \rangle \tag{21}$$

$$= -\cos\xi_{i-1}\cos\eta_i\cos\alpha_i \tag{22}$$
$$-\cos\xi_{i-1}\sin\eta_i\cos\tau_i\sin\alpha_i$$
$$-\cos\eta_i\sin\xi_{i-1}\cos\sigma_{i-1}\sin\alpha_i$$
$$+\sin\xi_{i-1}\sin\eta_i(\cos\sigma_{i-1}\cos\tau_i\cos\alpha_i + \sin\sigma_{i-1}\sin\tau_i)$$

$$= \cos\theta_i \tag{23}$$

  - angles $\sigma_{i-1;-}$ and $\sigma_{i-1;+}$ correspond to planes orthogonal to the σ_{i-1}; dito for $\tau_{i;-}$ and $\tau_{i;+}$

- Dot product surface and extreme angles $\sigma_{i-1;-}, \sigma_{i-1;+}, \tau_{i-1;-}, \tau_{i-1;+}$



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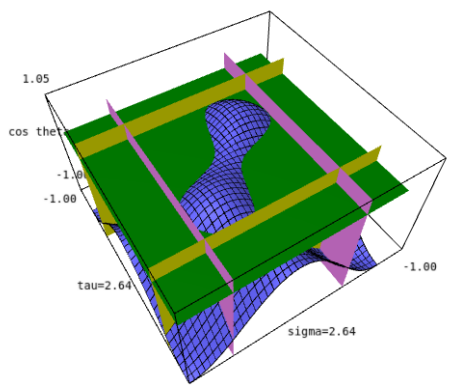

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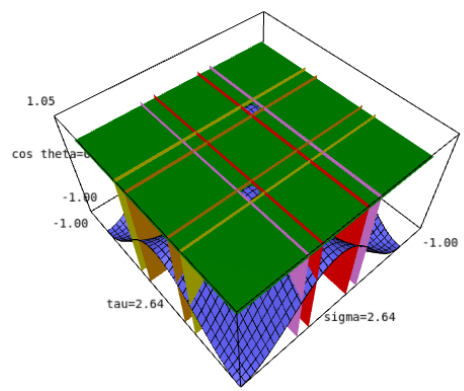


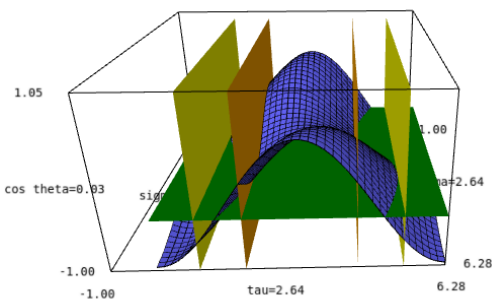
(C)

Nb: $\alpha_i = 100, \chi_{i-1} = 50, \eta_i = 50$ **(A)** Whole surface **(B)** With horizontal plane $\cos\theta_i = \cos 9°$. Intersection curve: 1 c.c. **(C)** With horizontal plane $\cos\theta_i = \cos 35°$. Intersection curve: 2 c.c.

Dot surfaces and their classification

Definition 3. (Signature at C_α) Consider the endpoints of the validity intervals, in this order $\sigma_{i-1;-}, \sigma_{i-1;+}, \tau_{i;-}, \tau_{i;+}$. The *signature* of a TLC problem is a string in $\{N, P, Z\}^4$ –one letter for each each extreme angle, with the following convention:

- letter N for $cos(endpoint) < -1$,
- letter P for $cos(endpoint) > 1$,
- letter Z for $-1 < cos(endpoint) < 1$.



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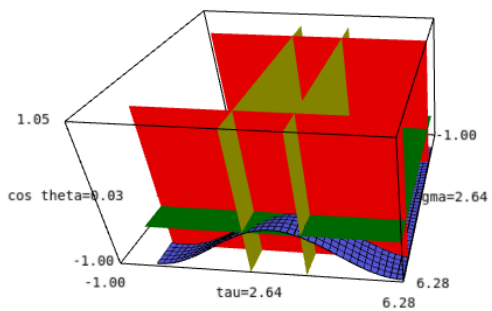
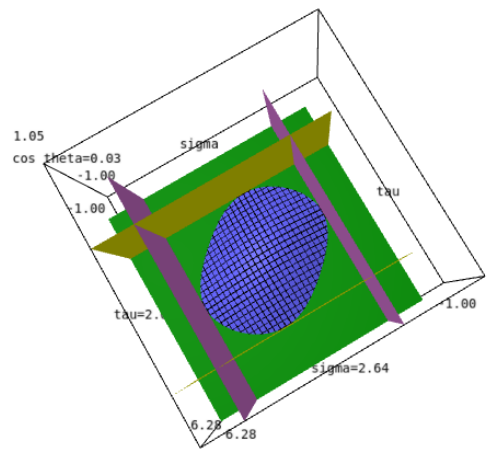


PZZN



ZNZN

Dot surfaces and validity intervals for the dataset of random TLC instances. (A) The 7 signatures (Def. 3) in terms of extreme angles for the data set of random TLC instances. In all cases, the green plane corresponds to $\cos\theta_i = \cos 111.6°$. A signature reads as follows: N:negative ie dot product < -1; Z: zero ie dot product $\in [-1, 1]$; P: positive ie dot product > 1. **(B)** Validity intervals.

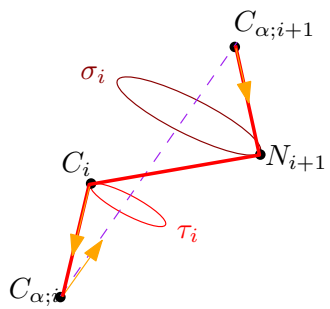
Rotated validity intervals (I)

- Along C_α edge:

$$\sigma_i = \tau_i + \delta_i. \tag{24}$$

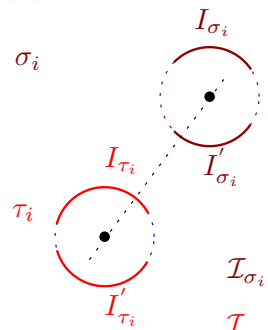
- Rotated interval for an angle: obtained from the value of its twin angle (from τ_i for σ_i, and vice-versa)

(A)



$\delta_i = \angle\text{Plane}(C_{\alpha;i}C_{\alpha;i+1}C_i), \text{Plane}(C_{\alpha;i}C_{\alpha;i+1}N_{i+1})$

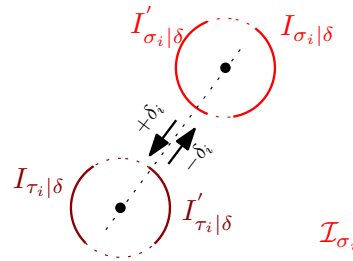
(B)



$\mathcal{I}_{\sigma_i} = \{I_{\sigma_i}, I'_{\sigma_i}\}$

$\mathcal{I}_{\tau_i} = \{I_{\tau_i}, I'_{\tau_i}\}$

(C)



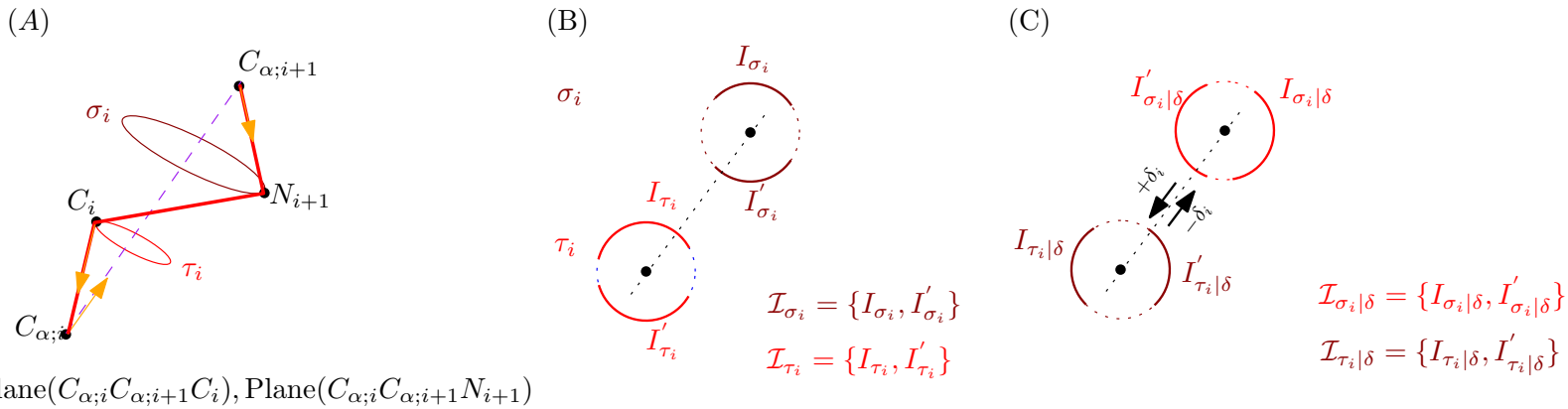
$\mathcal{I}_{\sigma_i|\delta} = \{I_{\sigma_i|\delta}, I'_{\sigma_i|\delta}\}$

$\mathcal{I}_{\tau_i|\delta} = \{I_{\tau_i|\delta}, I'_{\tau_i|\delta}\}$

Rotated validity intervals (II)

Definition 4. (Rotated validity intervals) The rotated validity intervals for the angles and τ_i are defined by:

- for σ_{i-1}: $\mathcal{I}_{\sigma_{i-1}|\delta} = I_{\sigma_{i-1}|\delta} \cup I'_{\sigma_{i-1}|\delta}$ with:
  - $I_{\sigma_{i-1}|\delta}$: interval for σ_{i-1} obtained by applying Eq. (24) to $I_{\tau_{i-1}}$. (Nb: uses the edge $C_{\alpha;i}C_{\alpha;i-1}$ of the C_α triangle.)
  - $I'_{\sigma_{i-1}|\delta}$: interval for σ_{i-1} obtained by applying Eq. (24) to $I'_{\tau_{i-1}}$. (Nb: uses the edge $C_{\alpha;i}C_{\alpha;i-1}$ of the C_α triangle.)
- for τ_i: dito



$\delta_i = \angle\text{Plane}(C_{\alpha;i}C_{\alpha;i+1}C_i), \text{Plane}(C_{\alpha;i}C_{\alpha;i+1}N_{i+1})$

Deep Validity Intervals: depth 1

- Intervals obtained so far:
  - The conditions on σ_{i-1} and τ_i inherent to the conservation of the valence angles (Eq. (26)).
  - The conditions exploiting rotated validity intervals, stemming from Eq. (24)
- Combination: intervals combined as follows $(I_{\cdot_{i-1}}, I'_{\cdot_{i-1}}) \times (I_{\cdot_{i-1}|\delta}, I'_{\cdot_{i-1}|\delta})$, which yields *depth one validity intervals*:

Definition 5. (Depth one validity intervals) The *depth 1 inter-angular interval* set $\mathcal{J}^{(1)}_{\sigma_{i-1}}$ for σ_{i-1}:

$$\mathcal{J}^{(1)}_{\sigma_{i-1}} = (I_{\sigma_{i-1}} \cap I_{\sigma_{i-1}|\delta}) \cup (I_{\sigma_{i-1}} \cap I'_{\sigma_{i-1}|\delta}) \cup (I'_{\sigma_{i-1}} \cap I_{\sigma_{i-1}|\delta}) \cup (I'_{\sigma_{i-1}} \cap I'_{\sigma_{i-1}|\delta}) \quad (25)$$

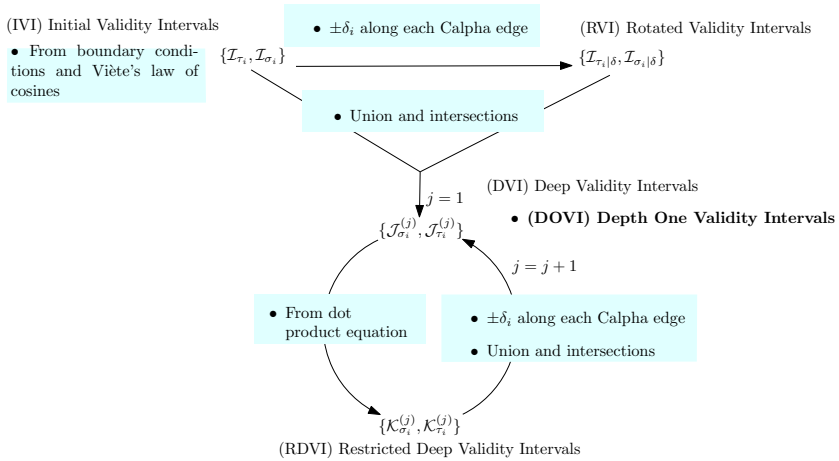
depth 1 inter-angular interval set $\mathcal{J}^{(1)}_{\tau_i}$ for τ_i: dito.

Definition 6. (Depth 1 inter-angular constraint) The *depth 1 inter-angular constraint* for σ_{i-1} is $\mathcal{J}^{(1)}_{\sigma_{i-1}} \neq \emptyset$.

The *depth 1 inter-angular constraint* for τ_i is: $\mathcal{J}^{(1)}_{\tau_i} \neq \emptyset$.

For the constraint to be verified all these conditions must be valid for all three $\{(\tau_i, \sigma_{i-1})\}$ pairs.

Depth-n validity constraints: outline



▷ Depth 1 validity intervals:

- Initialization via the limit conditions – from Viète law of cosines:

$$\begin{cases} \langle \hat{\mathbf{r}}^{\sigma}_{\mathbf{i}-\mathbf{1};-}, \hat{\mathbf{Z}}_{\mathbf{i}} \rangle = \cos(\theta_{\mathbf{i}} + \eta_{\mathbf{i}}), \\ \langle \hat{\mathbf{r}}^{\sigma}_{\mathbf{i}-\mathbf{1};+}, \hat{\mathbf{Z}}_{\mathbf{i}} \rangle = \cos(\theta_{\mathbf{i}} - \eta_{\mathbf{i}}) \end{cases}$$

- Then refinement thanks to intersections with Rotated validity intervals

▷ Depth-n validity intervals:

- Given a DVI of depth j (initially, $j = 1$), apply the valence angle constraint to obtain the twin interval on τ_i from σ_{i-1} and vice-versa, using

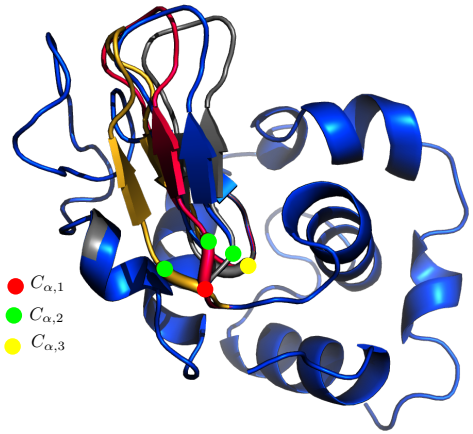
$$\langle \hat{\mathbf{r}}^{\sigma}_{\mathbf{i}-\mathbf{1}}, \hat{\mathbf{r}}^{\tau}_{\mathbf{i}} \rangle = \cos\theta_i. \tag{26}$$

- Iterate

Loop sampling

Metaphor: two problems with global+local components

Paris / San Francisco / Stanford:
30' + 30' minutes



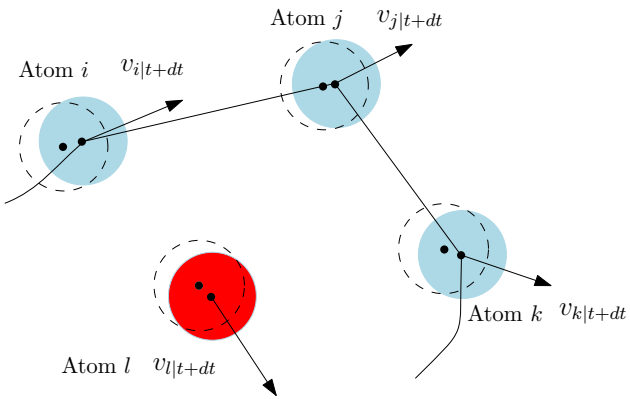
Biomolecules: identifying stable states and their probabilities

- First leg:
  - Paris to San Francisco airport (SFO): ???
  - Biomolecules, finding large amplitude conformational changes between states: my methods based on inverse problems
- Second leg:
  - SFO to Stanford: shuttle, cab
  - Biomolecules: studying equilibria with molecular dynamics

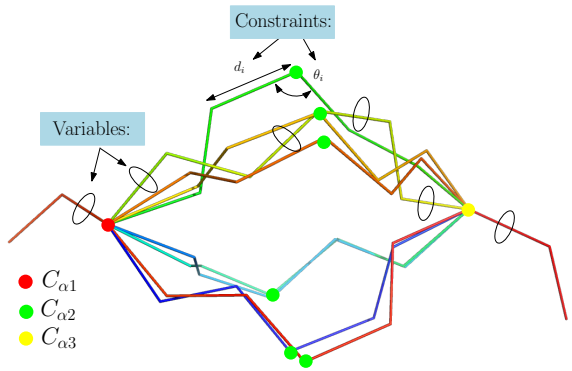
$\Rightarrow$ our methods vs classical methods: complementary

Next gen sampling: scientific punchline, originality and risks

- Three classes of techniques to study the dynamics of biomolecules:
  - Direct problems: molecular dynamics
  - Inverse problems of the loop closure type using internal coordinates
  - (Deep learning based: no massive data at hand–at this stage)



Molecular dynamics, time-steps of 10^{-15}s:
$\|\Delta x_i\| \sim 1/100$Å

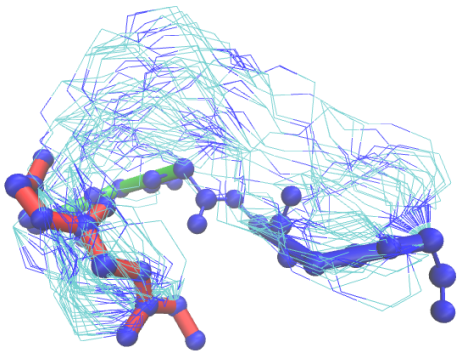


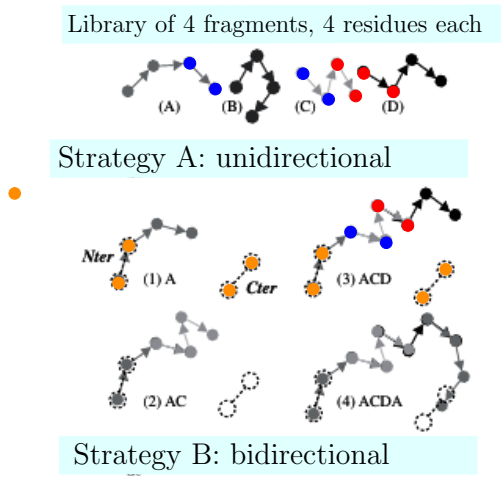
Inverse problems, typical changes:
$\|\Delta x_i\| \sim 1 - 10$Å

- Using internal coordinates: originality
  - Fast methods to predict large amplitude conformational changes
    - NB: geometric proxy/priors for classical methods such as MD
- Using internal coordinates: caveats
  - Risks: model accuracy (solvent, side chains), statistical biases
  - Gains: unmatched diversity and speed

Protein Loop Sampling: main approaches

- ▷ Classical approaches:
  - ~~Molecular dynamics~~: cost + handling loop closure
  - Non rigid geometry–but solution space is continuous (manifold)
  - Data driven/combinatorial greedy methods + inverse kinematics
  - Dihedral angles only/rigid geometry + inverse kinematics (TLC)





- ▷ Open questions:
  - Global loop parameterization amenable to sampling: all a.a. on equal footing
  - Uniform sampling in $\{(\phi, \psi)\}$ angle space,
  - Connection with thermodynamics,
  - Complexity: how hard are these problems?

▷Ref: Dod et al 1983; Cortés and Siméon, 2004; Levitt, Guibas et al, 2005; Snoeyink et al, 2005; Latombe et al, 2005; Cortés et al 2019, etc

▷Ref: Cazals et al; 2022

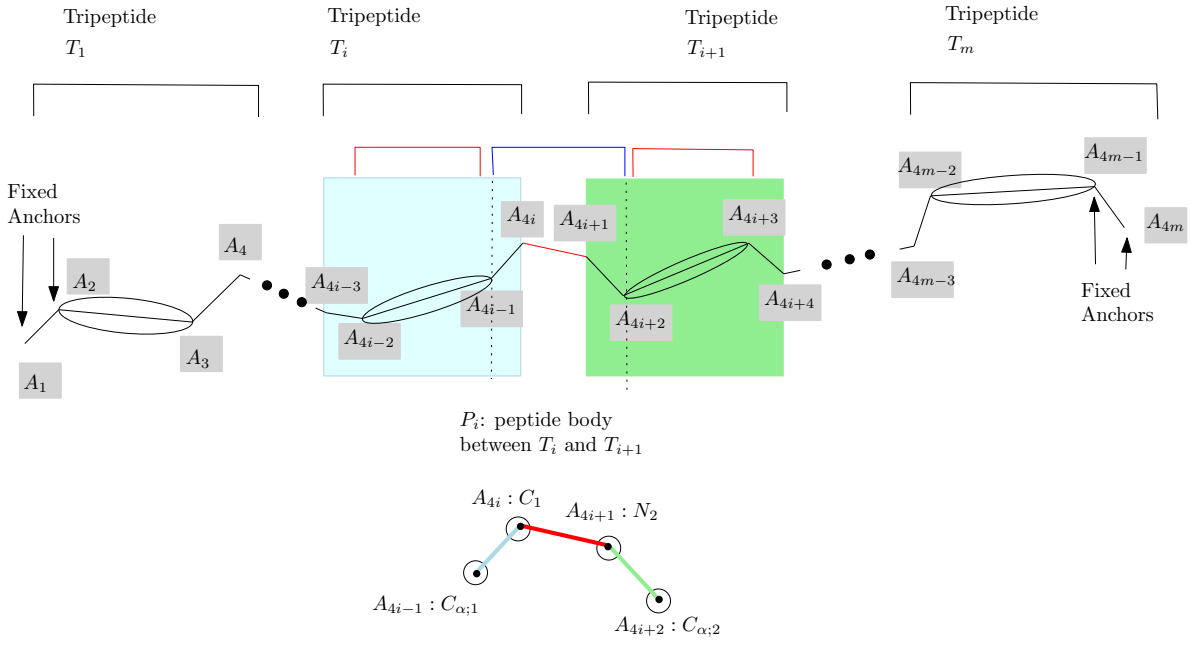
Loop sampling: difficulties and main approaches

- Main difficulties
  - Space of solutions: a continuous space – if #dihedral angles > 6
  - *Walking* on this constrained *manifold*: geometrically/numerically difficult
  - Incremental construction based on tripeptides: combinatorial explosion
- A mixed discrete - continuous approach
  - `Rosetta` KIC for a chain with n amino acids: perturb the dihedral angles of $n-3$ a.a.; then close the chain on the last 3 with TLC
  - Concatenation of solutions yielded by tripeptides: grow chains from left and right; close with TLC
- The problem remains difficult:
  - Practice: orphan loops in databases / IDPs
  - Theory: no global parametric solution

▷Ref: Kolodny, Guibas, Levitt, Koehl, 2005
▷Ref: Kortemme et al, Nat. Methods, 2009
▷Ref: Cortes et al, Bioinformatics, 2018
▷Ref: Deane et al, Bioinormatics, 2018
▷Ref: Cazals, O'Donnell; Submitted

TLC teleportation, rigid motions, and frames

▷ Loop decomposition into tripeptides and connecting peptide bodies



- Tripeptide: 9 atoms, 5 moving via *teleportation*
- Peptide body connecting two tripeptides: rigid ... whence rigid motions
- Consequence: two classes of citizens
  - peptide bodies within tripeptides
  - peptide bodies connecting tripeptides

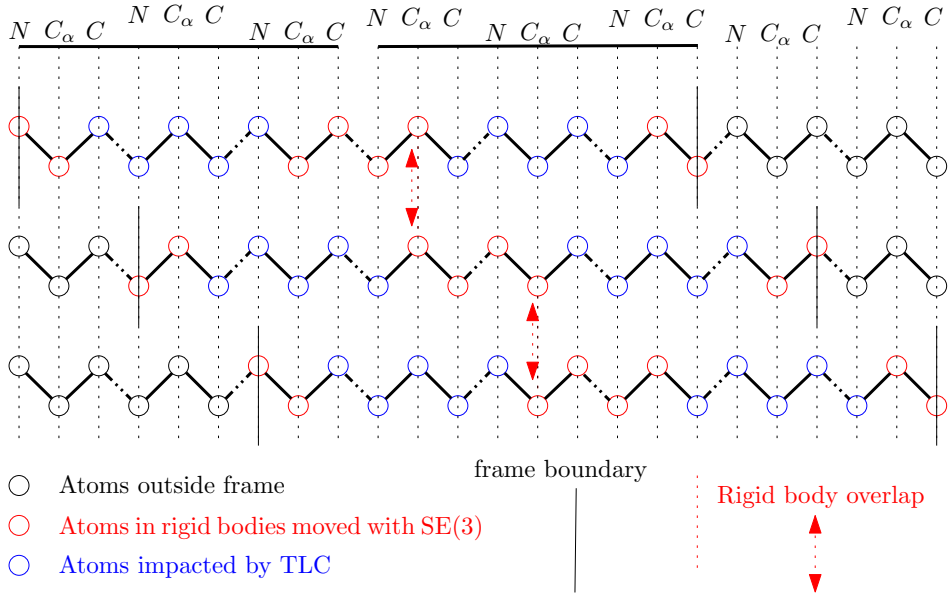
$\Rightarrow$ corrected via frame shifting

Frames involved in whole loop sampling

Definition 7. Subset of the loop to which individual TLC are applied.

- Frame shifting:
  - frame 1 starting at the first a.a. always contains n tripeptides regardless of N;
  - frame 2 at the second peptide contains $n-1$ tripeptides if $N \mod 3 = 0$ and n;
  - frame 3 at the third peptide contains n if $N \mod 3 = 2$ and $n-1$ otherwise.

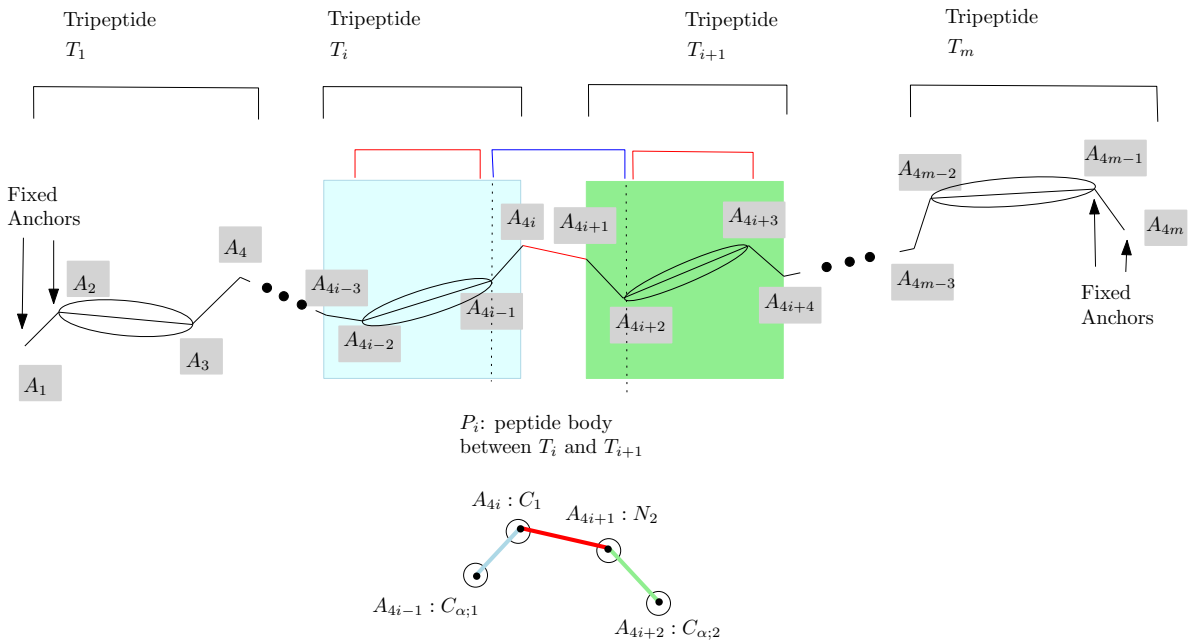
- The three frames obtained for a chain of $N = 3n+2$ a.a., with $n = 2$



Global geometric model

- Loop studied L: $M = 3 \times m$ amino, m tripeptides: $L = T_1, \ldots, T_m$
- Loop decomposition: rigid peptide bodies and their complements

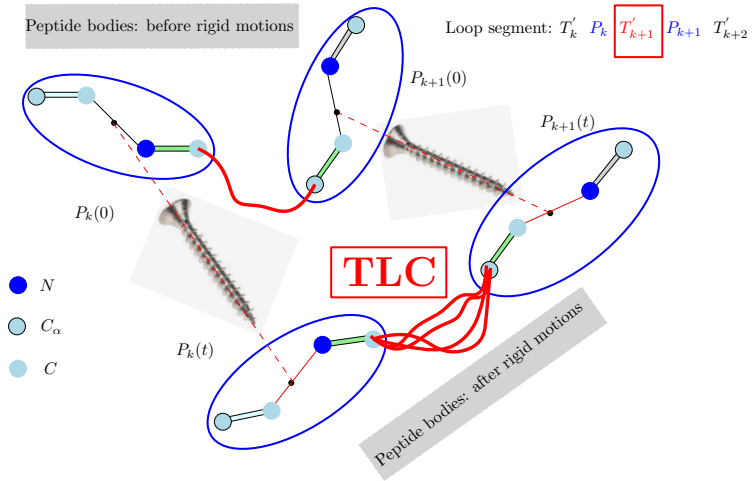
$$L = P_0 \; T_1^{'} \; P_1 \; \ldots \; P_{k-1} \; T_k^{'} \; P_k \; \ldots \; P_{m-1} T_m^{'} P_m. \tag{27}$$



- Parametric space:
  - For one peptide body: $SE(3) = SO(3) \times \mathbb{R}^3$
  - For one tripeptide: solution space of TLC. . . except that
    - The angular parameterization of TLC $\{\alpha, \xi, \eta, \delta\}$: depends on $SE(3) \times SE(3)$ since the left and right legs come from P_{i-1} and P_{i-1}

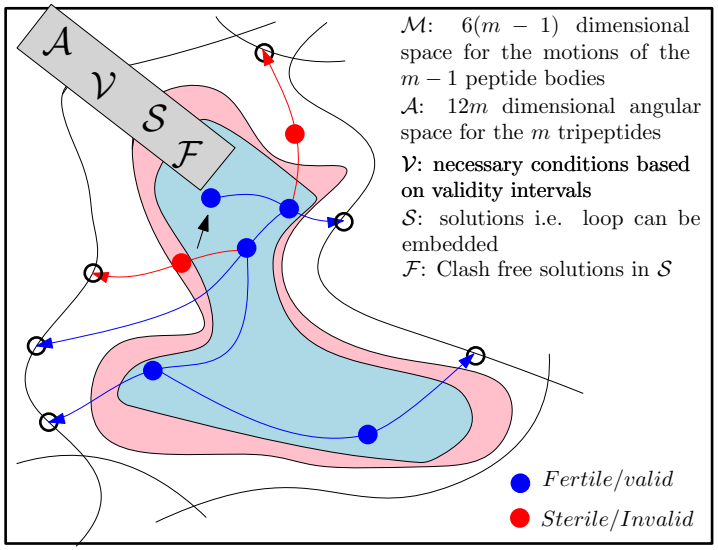
Sampling one frame: spaces involved and main idea

- Loop decomposition into: rigid peptide bodies and tripeptides cores



$$L = P_0\ T'_1\ P_1\ \ldots$$
$$P_k\ T'_{k+1}\ P_{k+1}\ \ldots$$
$$P_{m-1}\ T'_m P_m.$$

- Random sampling of loop conformations using Hit-and-Run:



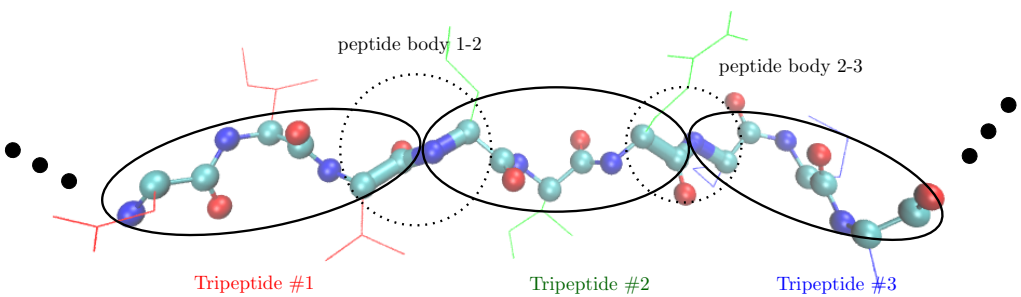
- Aim: perform rejection sampling in a region $\mathcal{V}$ containing all valid loop geometries.
- How: with Hit-and-Run in a domain characterizing necessary conditions – cf validity intervals

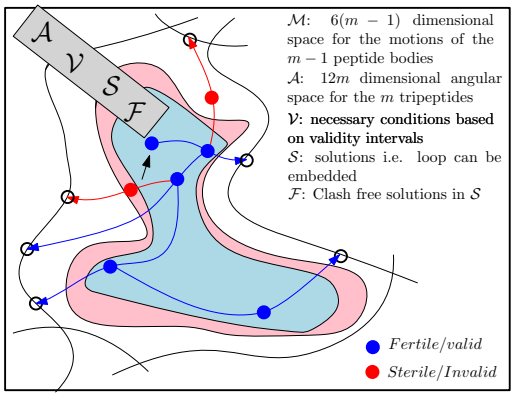
Sampling one frame: spaces involved and solution sketch

▷ Global parameterization of the conformational space of the loop: based on rigid bodies associated with peptide bonds

- $\mathcal{M}$: motion space for the $m-1$ peptide bodies, essentially $(SE(3))^{m-1}$
- $\mathcal{A}$: $12m$-dimensional angular space coding the geometry of tripeptides
- $\mathcal{V}$: domain bounded by 24 hyper-surfaces in $\mathcal{A}$, corresponding to Validity Constraints Necessary Constraints for TLC to admit solutions
- $\mathcal{S}$: the fertile space, where TLC admits one solution for each tripeptide
- $\mathcal{F}$: clash free solutions in $\mathcal{S}$ for $\{N, C_\alpha, C, O, C_\beta\}$ pairs

▷ Number of solutions: $\prod_i$(num solutions tripeptide i)





Angular representations: tripeptide and loop

- Angular representation of a tripeptide: the 2×4 angles

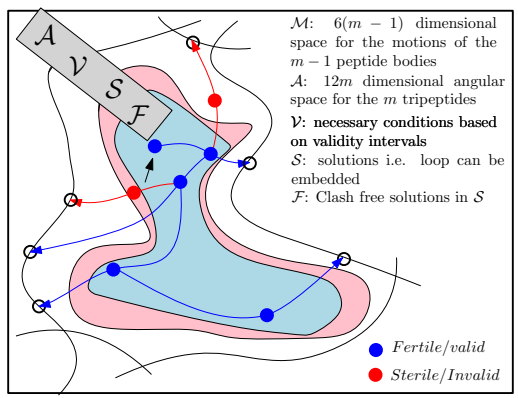
Definition 8. Let $\mathrm{A}_{k,i} = \{\alpha_{k,i}, \eta_{k,i}, \xi_{k,i-1}, \delta_{k,i-1}\}$ be the set of angles associated with $C_{\alpha;i}$ in the k-th tripeptide T_k.
The *angular representation* of a tripeptide T_k is the 12-tuple $\mathrm{A}_k = \{\mathrm{A}_{k,1}, \mathrm{A}_{k,2}, \mathrm{A}_{k,3}\}$.
The corresponding 12-dimensional space is denoted $\mathcal{A}_k$.

Definition 9. (Angular conformational space $\mathcal{A}$) The *angular conformational space* of the loop L is the $12m$ dimensional space defined by the product of the m angular space of the individual tripeptides:

$$\mathcal{A} \stackrel{Def}{=} \prod_{k=1}^{m} \mathcal{A}_k. \tag{28}$$

Validity domain for the whole chain L with m tripeptides

- Angles τ: $3m$ angles τ (3 for each tripeptide)
- Recap per angle τ:
  - For one angle: at most 4 Depth One Validity Intervals (DOVI)
  - For each DOVI: 2 sub-manifolds of $\mathcal{A}_k$ defined by limit cases; yields (at most) 8 sub-manifolds in $\mathcal{A}_k$.
- For one tripeptide: 3 τ angles $\Rightarrow$ 24 constraint surfaces in the 12 dimensional angular space $\mathcal{A}_k$.
- Enumerating constraints:
  - One tripeptide: 24
  - Whole loop: $24m$



Motion space for peptide bodies

Moving peptide bodies with rigid motions

- ▷ Configuration spaces for motions:
  - One peptide body: $\mathcal{R} : (S^2 \times [0, A)) \times (S^2 \times [0, 2\pi)) \subset SE(3)$
  - The $m-1$ peptide bodies in the loop L: $\mathcal{M} = \mathcal{R}^{m-1}$
- ▷ Peptide body motions: sample $m-1$ independent screw motions (translation+rotation)
- ▷ Overall linear interpolation $r \in \mathcal{M}$: between the identity and the rigid motion corresponding to r:

$$\text{Ray}(V) = \{\gamma(t) = Id + tV, \text{ with } \gamma(0) = Id\}. \tag{29}$$

- ▷ Restriction to each peptide body: defines a rigid transformation

$$\gamma_k : [0, 1] \mapsto SE(3), \gamma_k(0) = Id, \tag{30}$$

- ▷ Position of the k-th peptide body $P_k(t)$ at time t:

$$P_k(t) = \gamma_k(t) P_k(0). \tag{31}$$

Algorithm overview

▷ For a given angle τ:

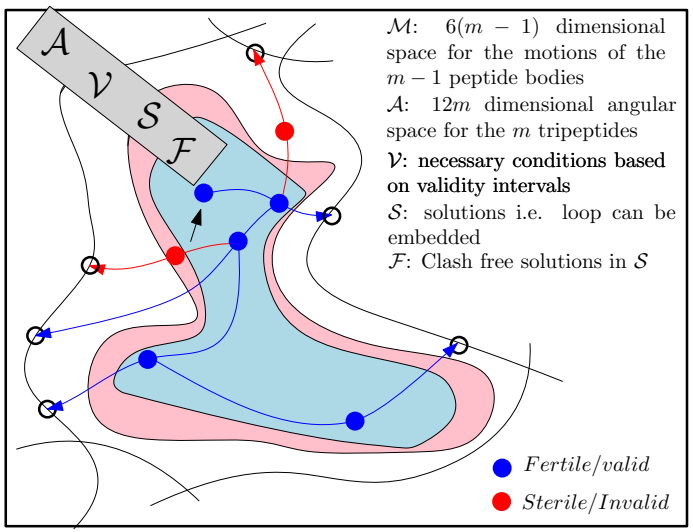
$$t \text{ determines the positions of peptide bodies whence tripeptide legs} \tag{32}$$

$$\rightsquigarrow \text{ kinetic angular representation } \mathrm{A}_i(t) \text{ of } T_k \tag{33}$$

$$\rightsquigarrow \text{ kinetic validity intervals } I_{\tau_{k,i}}(t), I_{\tau_{k,i}|\delta}(t) \tag{34}$$

▷ Example condition for kinetic depth 1 validity interval to be $\neq \emptyset$:

$$I_{\tau}^{\max}(\mathrm{A}_{k,i}(t)) = I_{\tau|\delta}^{\min}(\mathrm{A}_{k,i+1}(t)) \tag{35}$$



▷ Algorithm overview:

- For each angle $\tau_{k,i}$: find the closest intersection with the 24 hyper-surfaces, along the 1D curve defined by the rigid motion interpolation.
- Let t_{max} be the corresponding value of t: draw $t_s \leftarrow \mathrm{Uniform}(0, t_{max})$
- Apply the rigid transforms defined by t_s to the $m-1$ peptide bodies
- Solve the m individual TLC problems

Sampling algorithm for one frame: pseudo-code

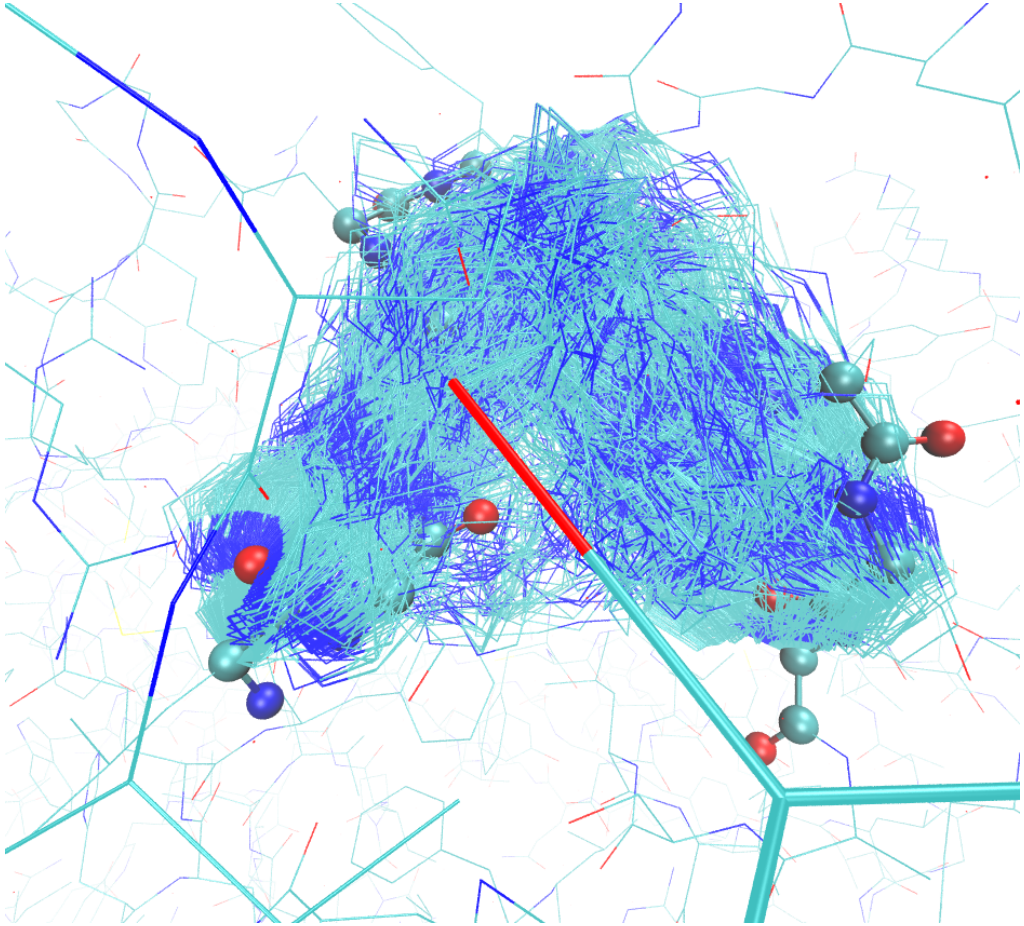
Input: p_j: point from which the move is made; corresponds to $t = 0$
Output: a point $\in \mathcal{S}$
Var t_{max}: initialized using the smallest value of $t > 0$ breaking triangular inequality in a given tripeptide
V: Random direction (Eq. 29)
for i $\in \{1, ..., m\}$ **do**
    for l $\in \{1, 2, 3\}$ **do**
        // Angle $\tau_{k,i}$: process the (at most) 24 equations
        $S = \{t_{max}\}$
        // Process all interval pairs
        for $I_{\tau_{k,i}}(t) \in \mathcal{I}_{\tau_{k,i}}(t)$ **do**
            for $I_{\tau_{k,i}|\delta}(t) \in \mathcal{I}_{\tau_{k,i}|\delta}(t)$ **do**
                $S_{tmp} \leftarrow$ numerical solutions for Eq. **??** and **??** $t \in [t_{min}, t_{max}]$
                $S = S \cup S_{tmp}$
            end for
        end for
        Sort S by ascending order
        Let t_k be the k-th element of S
        $u_k := \frac{t_k + t_{k+1}}{2}$
        $k = 1$
        // Stop when no validity interval can be defined for $\tau_{k,i}$
        while $\text{DOVI}_{\tau_{k,i}}(u_k) \neq \emptyset$ **do**
            $t_{max} = t_k$
            $k = k + 1$
        end while
    end for

Algorithms and parameters

- Unmixed loop sampler $\mathrm{ULS}^{N_V;N_{OR}}_{One|All;N_{ES}}[p_0]$:
  - $One|All$ a flag indicating how many solutions are retained at each embedding step,
  - N_{ES} the number of embedding steps,
  - N_V the number of random trajectories followed in motion space,
  - N_{OR} the output rate (the number of steps in-between the ones where conformations get harvested),
  - p_0: the starting configuration.

- Mixed loop sampler $\mathbb{MLS}^{N_V;N_{OR}}_{One|All;N_{ES}}[p_0]$: every other step, the loop is shifted by 1 or 2 units to also sample the peptide bodies.

VMD demo



Loops sampling: ϕ, ψ and ω

- Typical values of the torsion angle ω:
  - SSE?
  - loops?

Loops sampling: ϕ, ψ and ω

- Typical values of the torsion angle ω:
  - SSE? $\pi \pm 2 - 3^\circ$
  - loops? $\pi \pm 15^\circ$

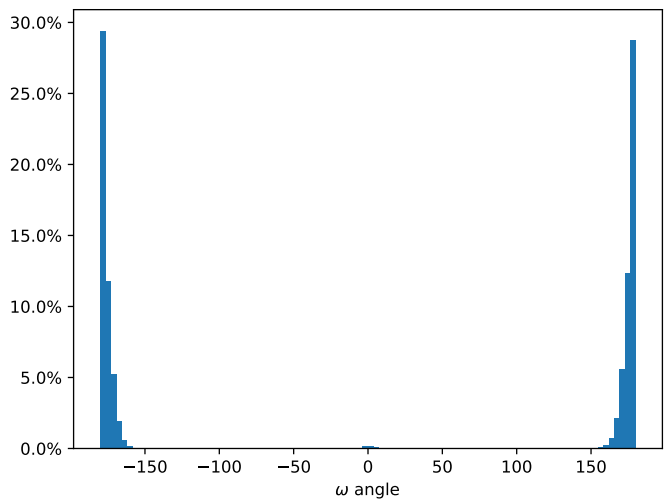
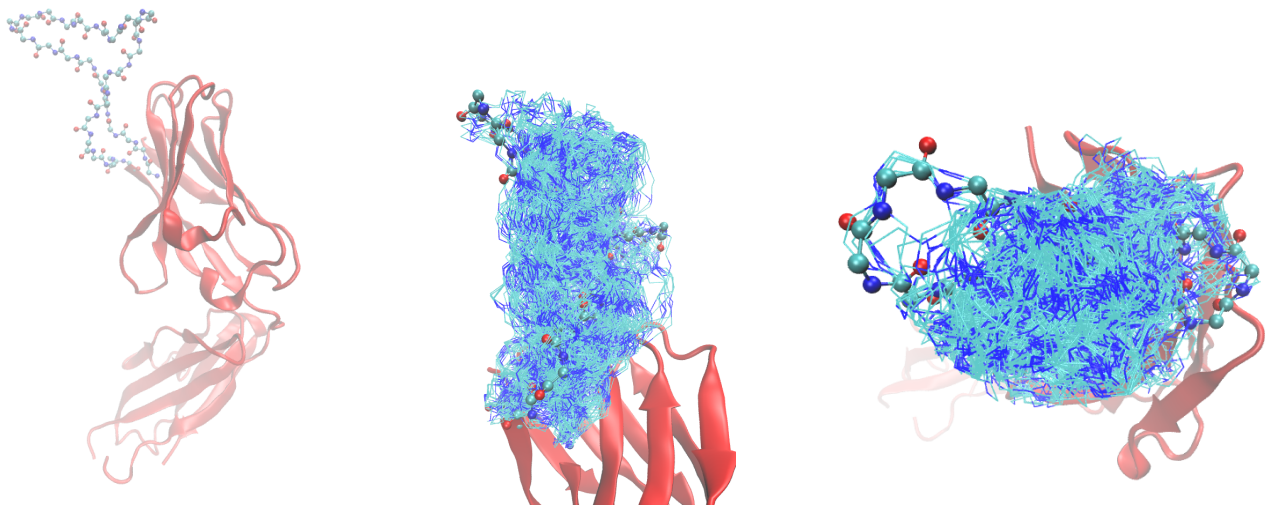


Illustration: CDR-H3-HIV, 30 amino acids

▷ System:

- The loop is a complementarity-determining region (CDR-H3) from PG16, an antibody with neutralization effect on HIV-1.
- pdbid: 3mme, chain A; residues: 93-100, 100A-100T, 101, 102.



Conformations generated by algorithm $\mathbb{MLS}^{1;1}_{One;250}$. **(A)** Variable domain (red) and the 30 a.a. long CDR3. **(B,C)** Side/top view of 250 conformations.

▷ Generation speed: $\sim$ 10 conformations per second

Results: sampling and study of fluctuations

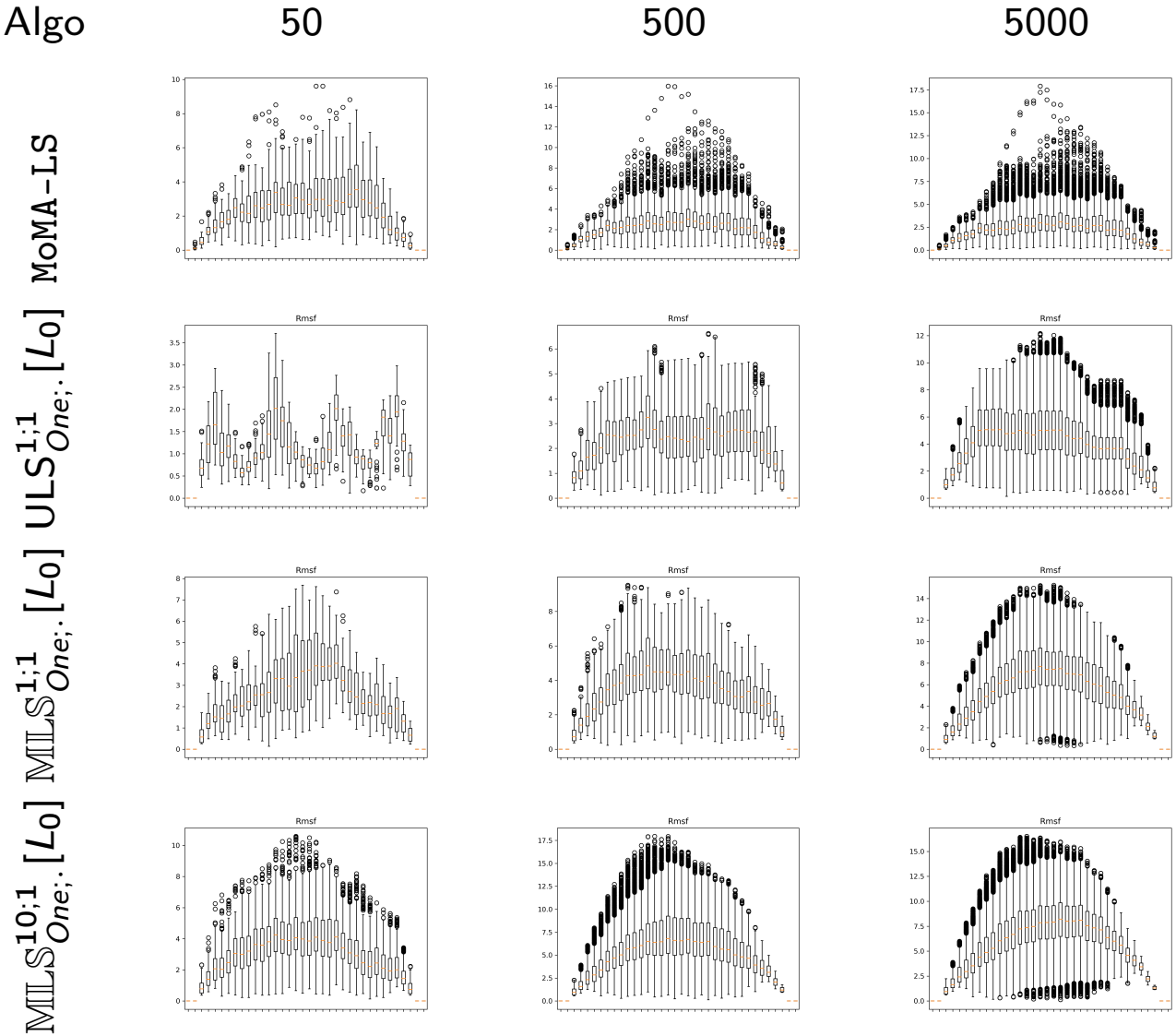
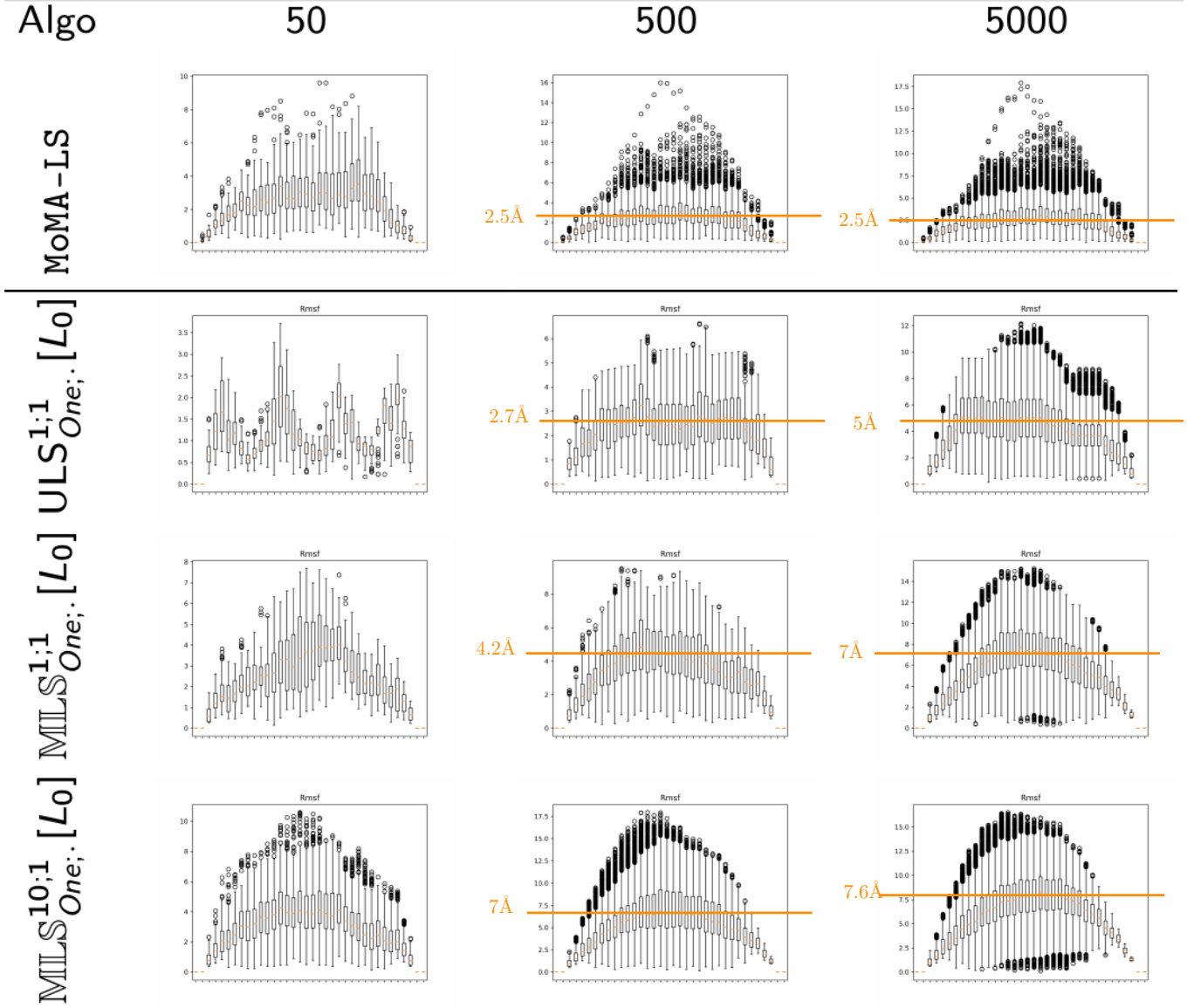


Figure: **Backbone RMSF (36 atoms) for the 12 amino acid long loop PTPN9-MEG2.**

Results: sampling and study of fluctuations



Backbone RMSF (36 atoms) for the 12 amino acid long loop PTPN9-MEG2.

Outlook

- Key features:
  - First global parametric model of protein loops amenable to effective sampling strategies a-la Hit-and-Run
  - Results: on par or better with state-of-the-art methods
    - Atomic fluctuations along the loop
    - Mutual reachability for existing conformations
  - Insights on the intrinsic difficulty of the problem–via random walks and curved polytopes
- Open problems:
  - Uniformity of sampling (Theorem)
  - Connexion to micro-canonical ensembles and densities of states
  - Sampling with side chains

Loop sampling

Open problems

- Tightness of the Depth-N Validity Constraints
- Uniformity of the sampling in solution space
- Mixing dihedral angles and the remaining internal coordinates

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