SE(3) Diffusion Model with Applications to Protein Backbone Generation

by Yim, Trippe, De Bortoli, Mathieu, et. al

M2 MVA, Algorithms for Protein Science

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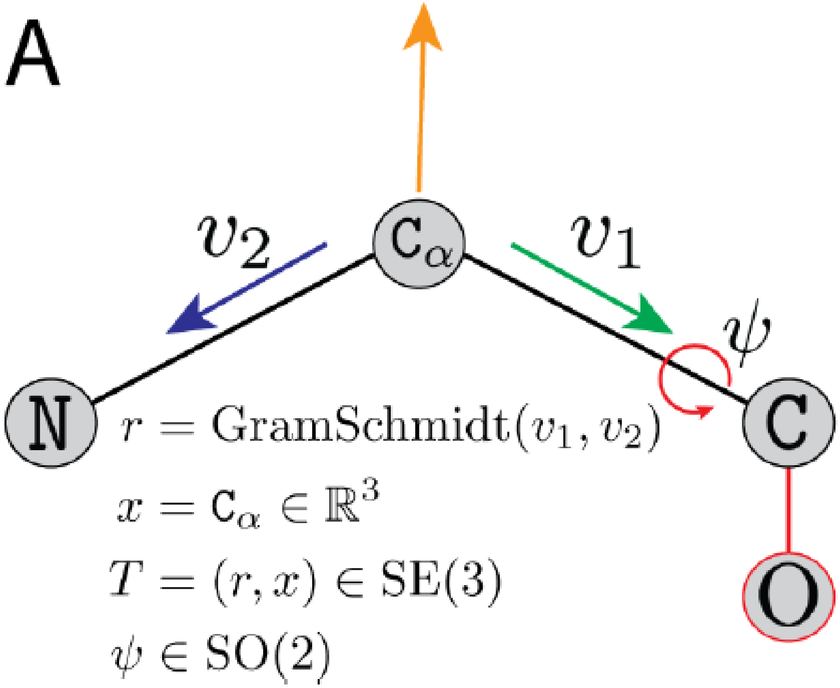
Representation of the protein backbone

A frame $X \in \mathbb{R}^3$ is positioned via a rigid transformation,

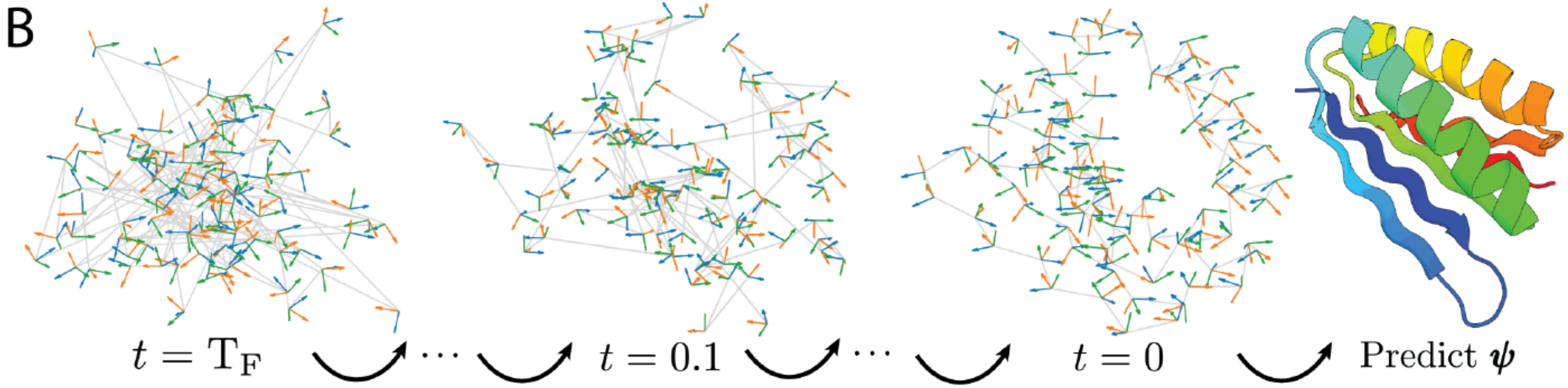
$$T \cdot X = RX + x$$

with,

$$\begin{cases} T = (R, x) \in \mathrm{SE}(3) \\ R \in \mathrm{SO}(3) \\ x \in \mathbb{R}^3 \end{cases}$$



Goal: diffusion on $\mathrm{SE}(3)^N$



Reminder on diffusion processes

Transform initial distribution p_I into data distribution p_T

Denoising equations:

$$\text{Forward equations: } \dot{X}_t = b_t(X_t) + dB_t, X_0 \sim p_T$$

$$\text{Fokker-Planck: } \dot{p}_t = \nabla^* p_t b_t + \Delta p_t$$

$$\text{Backward equations: } \dot{X}_t = -b_t(X_t) + \underbrace{\nabla_X \log p(X_t)}_{\text{score}} + dB_t, X_0 \sim p_I$$

Score approximation: $\nabla_X \log p(X_t) = \mathbb{E}_{X_0 \mid X_t}\left[\nabla_{X_t} \log p(X_t \mid X_0)\right]$

The group $\mathrm{SE}(3)$

As a group $\mathrm{SE}(3) = \mathrm{SO}(3) \ltimes \mathbb{R}^3$

$\Rightarrow (R, x) \cdot (R', x') = (RR', Rx' + x)$

As a manifold $\mathrm{SE}(3) = \mathrm{SO}(3) \times \mathbb{R}^3$

$\Rightarrow \langle (\boldsymbol{R}, \boldsymbol{x}) \mid (\boldsymbol{R}', \boldsymbol{x}') \rangle_{\mathbf{SE(3)}} = \langle \boldsymbol{R} \mid \boldsymbol{R}' \rangle_{\mathbf{SO(3)}} + \langle \boldsymbol{x} \mid \boldsymbol{x}' \rangle_{\mathbb{R}^3}$

The group $\mathrm{SO}(3)$

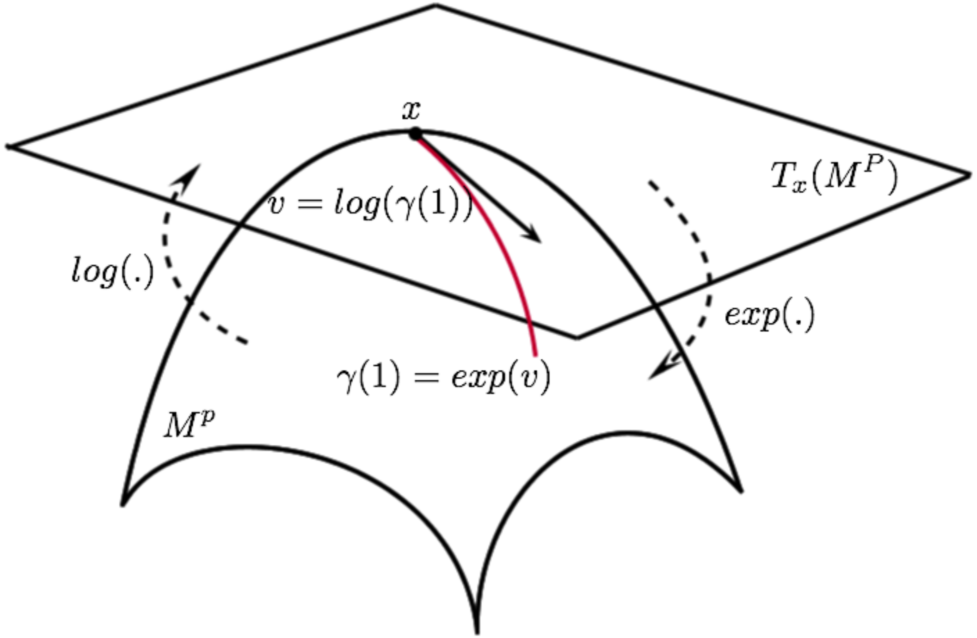
The Lie algebra $\mathfrak{so}(3)$ is the tangent space at identity.

Basis of $\mathfrak{so}(3)$:

$$\overbrace{\begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}}^{Y_1} \overbrace{\begin{pmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \\ -1 & 0 & 0 \end{pmatrix}}^{Y_2} \overbrace{\begin{pmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}}^{Y_3}$$

Exponential map $\exp : \mathfrak{so}(3) \to \mathrm{SO}(3)$:

$$\exp(R) = \sum_{k \geq 0} \frac{R^k}{k!}$$



Brownian motion on $\mathrm{SO}(3)$

Separation of metrics ⇒ brownian motion splits:

$$\boldsymbol{B^{\mathrm{SE}(3)} = \left(B^{\mathrm{SO}(3)}, B^{\mathbb{R}^3}\right)}$$

Sample $z_1, z_2, z_3 \sim \mathcal{N}(0, \Delta t)$

Brownian motion increment: $\boldsymbol{R_{t+\Delta t} = R_t \exp\left(\sum_i z_i Y_i\right)}$

⇒ Associated Fokker-Planck equation ?

Parametrization of $\mathrm{SO}(3)$

Axis-angle parametrization: $R = \exp(\theta K)$ with

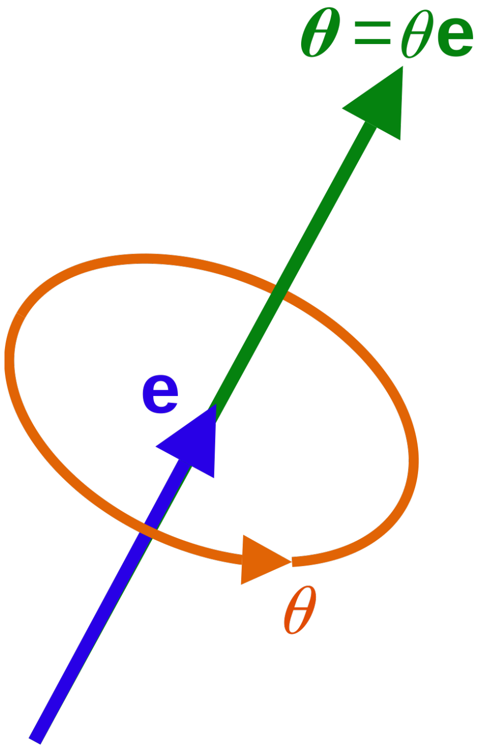
$$\begin{cases} \theta \in [0, 2\pi] \\ K = \sum_i e_i Y_i \\ e = (e_1, e_2, e_3) \in \mathbb{S}^2 \end{cases}$$

Rodrigues formula:

$$\exp(\theta K) = \mathrm{Id} + \sin(\theta) K + (1 - \cos(\theta)) K^2$$

Inverse:

$$\begin{cases} \theta(R) = \cos^{-1}\left(\frac{\mathrm{Tr}(R)-1}{2}\right) \\ K(R) = \frac{(R_{32}-R_{23})Y_1+(R_{13}-R_{31})Y_2+(R_{21}-R_{12})Y_2}{2\sin(\theta)} \end{cases}$$



Representations and characters of $\mathrm{SO}(3)$

l-dimensional representation $\rho : \mathrm{SO}(3) \to \mathrm{GL}(V)$ with $\dim(V) = l$, respecting

$$\begin{cases} \rho(RR') = \rho(R)\rho(R') \\ \rho(e) = \mathrm{Id} \end{cases}$$

l-dimensional character $\chi_l : \mathrm{SO}(3) \to \mathbb{R}$ associated with ρ:

$$\chi_l(R) = \mathrm{Tr}(\rho(R)) = \frac{\sin\left(\left(l + \frac{1}{2}\right)\theta(R)\right)}{\sin\left(\frac{1}{2}\theta(R)\right)}$$

Peter-Weyl theorem: $(\chi_l)_l$ is orthonormal basis of $L^2(\mathrm{SO}(3))$

$\Rightarrow f = \sum_l d_l \chi_l$

The Laplace-Beltrami operator

For $f \in C^\infty(\mathrm{SO}(3), \mathbb{R})$:

$$\Delta_{\mathrm{SO}(3)} f(R) = \sum_i \partial_t^2 f(R \exp(tY_i))$$

Its eigenfunctions are the characters:

$$\begin{cases} \Delta_{\mathrm{SO}(3)} \chi_l = \lambda_l \chi_l \\ \lambda_l = -l(l+1) \end{cases}$$

On $\mathrm{SE}(3)$, the operator splits:

$$\Delta_{\mathrm{SE}(3)} = \Delta_{\mathrm{SO}(3)} + \Delta_{\mathbb{R}^3}$$

Heat equation on $\mathrm{SO}(3)$

$$\begin{aligned}
\dot{p}_t = \frac{1}{2}\Delta_{\mathrm{SO}(3)} p_t &\Leftrightarrow \sum_l d_l'(t)\chi_l = \frac{1}{2}\sum_l d_l(t)\Delta_{\mathrm{SO}(3)}\chi_l \\
&\Leftrightarrow \sum_l d_l'(t)\chi_l = -\frac{1}{2}\sum_l d_l(t) l(l+1)\chi_l \\
&\Leftrightarrow d_l'(t) = -\frac{1}{2} l(l+1) d_l(t) \\
&\Leftrightarrow d_l(t) = d_l(0) e^{-\frac{1}{2}l(l+1)t}
\end{aligned}$$

Fokker-Planck in $\mathrm{SO}(3)$: $\boldsymbol{p(R_t \mid R_0) = \sum_l (2l+1) e^{-\frac{1}{2}l(l+1)t} \chi_l(R_0^T R_t)}$

Score function on $\mathrm{SO}(3)$

The gradient splits:

$$\nabla_{R,x} f(R,x) = (\nabla_R f(R,x), \nabla_x f(R,x))$$

Translation gradient is given by:

$$\nabla_{x_t} \log p(x_t \mid x_0) = \frac{e^{-\frac{1}{2}t} x_0 - x_t}{1 - e^{-t}}$$

For rotations: $\nabla_R \theta(R) = \frac{R \log(R)}{\theta(R)}$ so that:

$$\nabla_{R_t} \log p(R_t \mid R_0) = \frac{\nabla_\theta p(R_t \mid R_0)}{p(R_t \mid R_0)} \frac{R_0^T R_t \log(R_0^T R_t)}{\theta(R_0^t R_t)}$$

Diffusion equations on $\mathrm{SE}(3)$

$$\text{Forward diffusion: } \begin{cases} \dot{x}_t = -\frac{1}{2} x_t + dB_t^{\mathbb{R}^3} \\ \dot{R}_t = dB_t^{\mathrm{SO}(3)} \\ (R_0, x_0) \sim p_T \end{cases}$$

$$\text{Backward diffusion: } \begin{cases} \dot{x}_t = \frac{1}{2} x_t + \nabla_{x_t} \log p(x_t \mid x_0) + dB_t^{\mathbb{R}^3} \\ \dot{R}_t = \nabla_{R_t} \log p(R_t \mid x_0) + dB_t^{\mathrm{SO}(3)} \\ (R_0, x_0) \sim p_I \end{cases}$$

Rotation-invariant diffusion

Work on $\mathrm{SE}(3)_0^N = \left\{(R, x) \in \mathrm{SE}(3)^N \text{ such that } \frac{1}{N}\sum_i x_i = 0\right\}$

$\Rightarrow$ Centered equations for translations:

$$\text{Forward centered: } \dot{x}_t = -\frac{1}{2}Px_t + PdB_t^{\mathbb{R}^3} \underset{t\to\infty}{\longrightarrow} P_\#(\mathcal{N}(0,1)^{\otimes N} \otimes \mathcal{U}(\mathrm{SO}(3))^{\otimes N})$$

$$\text{Backward centered: } \dot{x}_t = \frac{1}{2}Px_t + \nabla_{x_t}\log p(x_t \mid x_0) + PdB_t^{\mathbb{R}^3}$$

Theorem: if p_I is $\mathrm{SO}(3)$-invariant and drift and diffusion coefficients are $\mathrm{SO}(3)$-equivariant, the backward equations remain $\mathrm{SO}(3)$-invariant and the score remains $\mathrm{SO}(3)$-equivariant.

The score network

The FramePred algorithm predicts a denoised frame:

$$\hat{T}_0^t = f_t^\theta(T_t)$$

and optimized to minimize the DSM loss:

$$\mathbb{E}\left[\lambda_t \left\| s_t^\theta(T_t) - \nabla_{T_t} \log p(T_t \mid T_0) \right\|^2\right]$$

$$\text{with } s_t^\theta(T_t) = \nabla_{T_t} \log p\left(T_t \mid \widehat{T}_0^t\right)$$

f_t^θ also outputs ψ angles for oxygen atoms.

Practice: FramePred

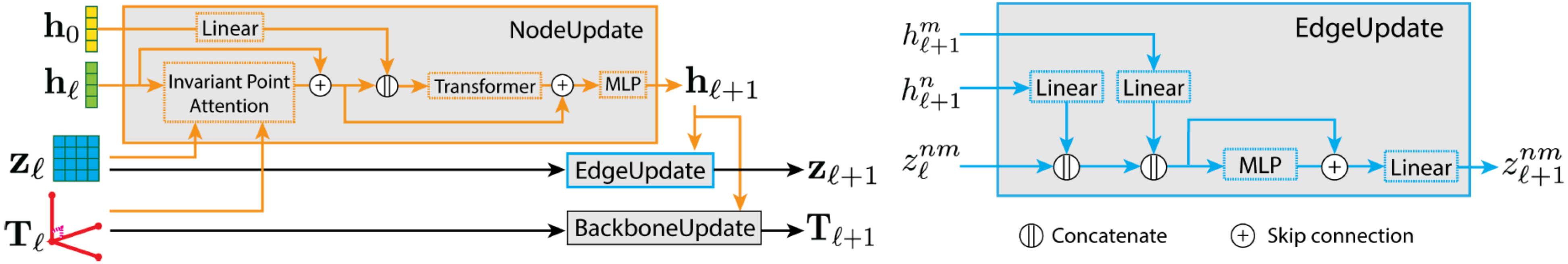


Figure 1: Backbone transformer. h_l: node embedding, z_l: edge embedding. IPA is $\mathrm{SE}(3)$-invariant.

Practice: auxiliary losses

To avoid steric clashes or chain breaks at the end of training:

$$\mathcal{L}_{\mathrm{bb}} = \frac{1}{4N} \sum_{a,n} \left\| a_n - \hat{a}_n \right\|^2$$

$$\mathcal{L}_{\mathrm{2D}} = \frac{1}{Z} \sum_{\substack{n,m \\ a,b \\ d_{\mathrm{ab}}^{\mathrm{nm}} < 0.6}} \left\| d_{\mathrm{ab}}^{\mathrm{nm}} - \hat{d}_{\mathrm{ab}}^{\mathrm{nm}} \right\|^2$$

$\Rightarrow$ Allows to train the positioning of oxygen atoms.

Results: designability

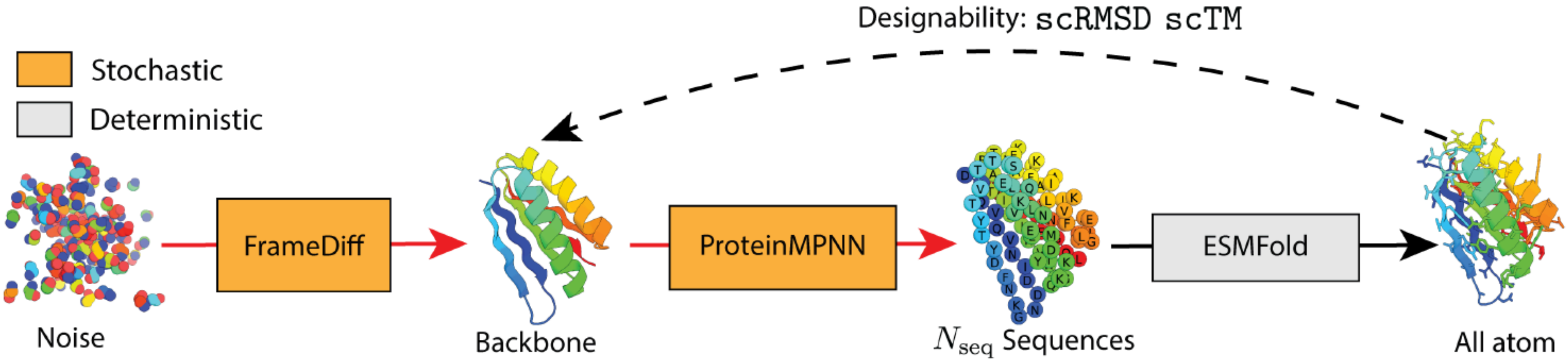


Figure 2: Protocol for computing designability of a generated backbone.

Results: plots

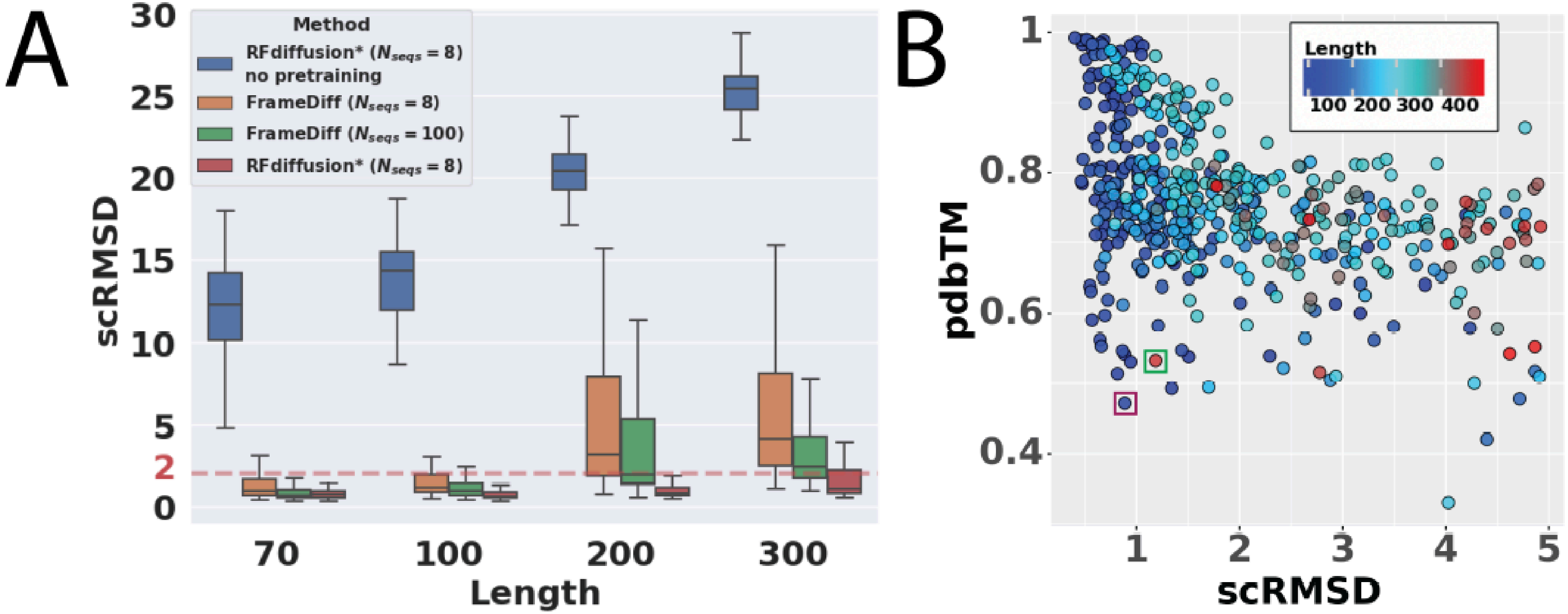


Figure 3: (A) Designability (scRMSD) against length of the generated backbone for different models. (B) Novelty (pdbTM) against designability (scRMSD) for FrameDiff.

Experiments (1/2): Noise

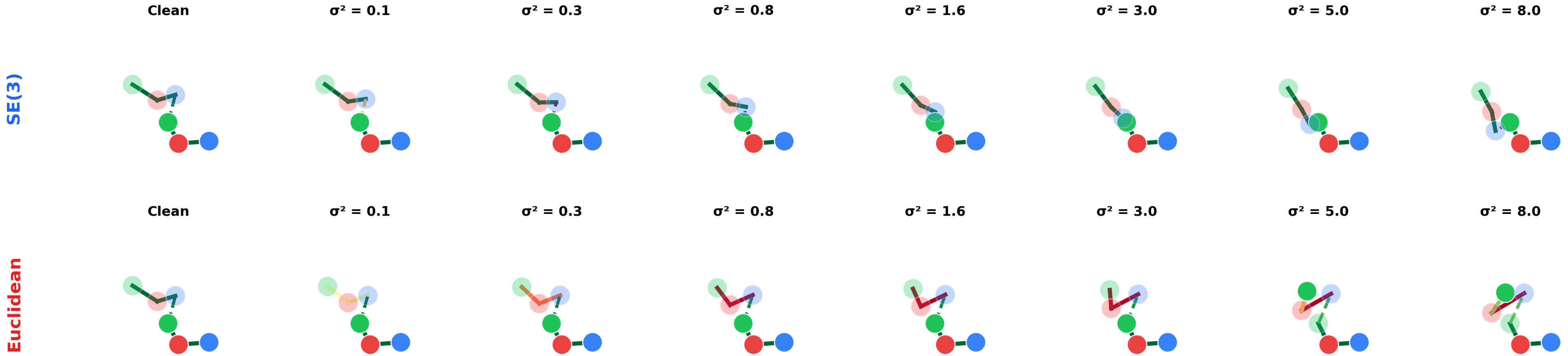


Figure 4: Noise propagation in both $SO(3)$ and $\mathbb{R}^3$. Blue: N, red: C_α, green: C, red bond: broken bond.

Experiments (2/2): Interpolation

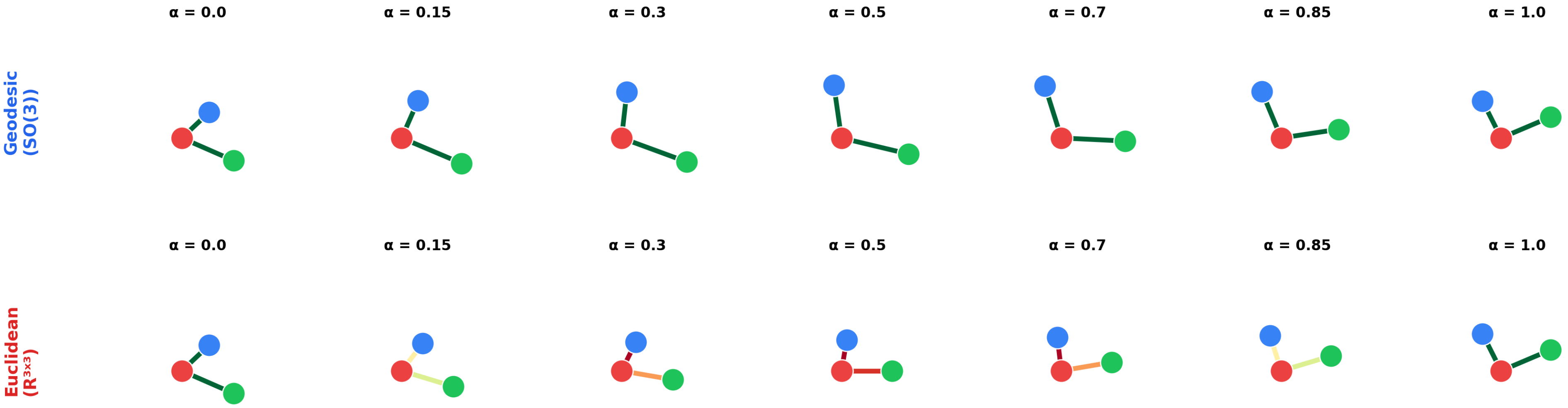


Figure 5: Interpolation in $SO(3)$ and $\mathbb{R}^3$. Blue: N, red: C_α, green: C, peptide bond: - -, red bond: broken bond.

Conclusion & future work

From diffusion to flow matching

- FrameFlow [1] → **ReQFlow** [2]
- OriginFlow [3]
- EffieDes [4] / MAProt [5]

Conclusion

- Rigorous framework
- Samples can generalize beyond the PDB
- ReQFlow $\rightarrow$ AlphaFold $\rightarrow$ Lab

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