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Flexibility-conditioned protein structure design with flow matching

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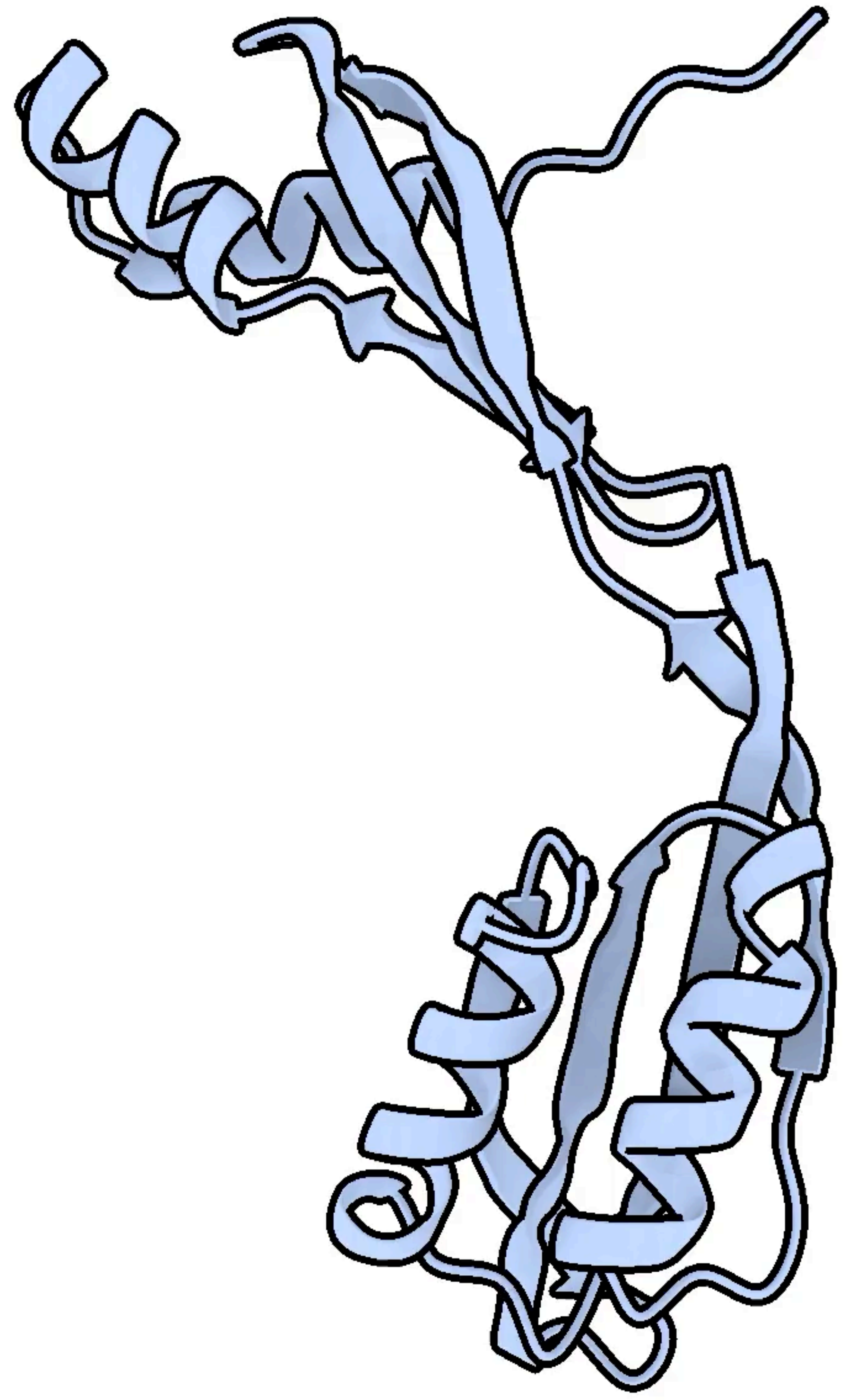
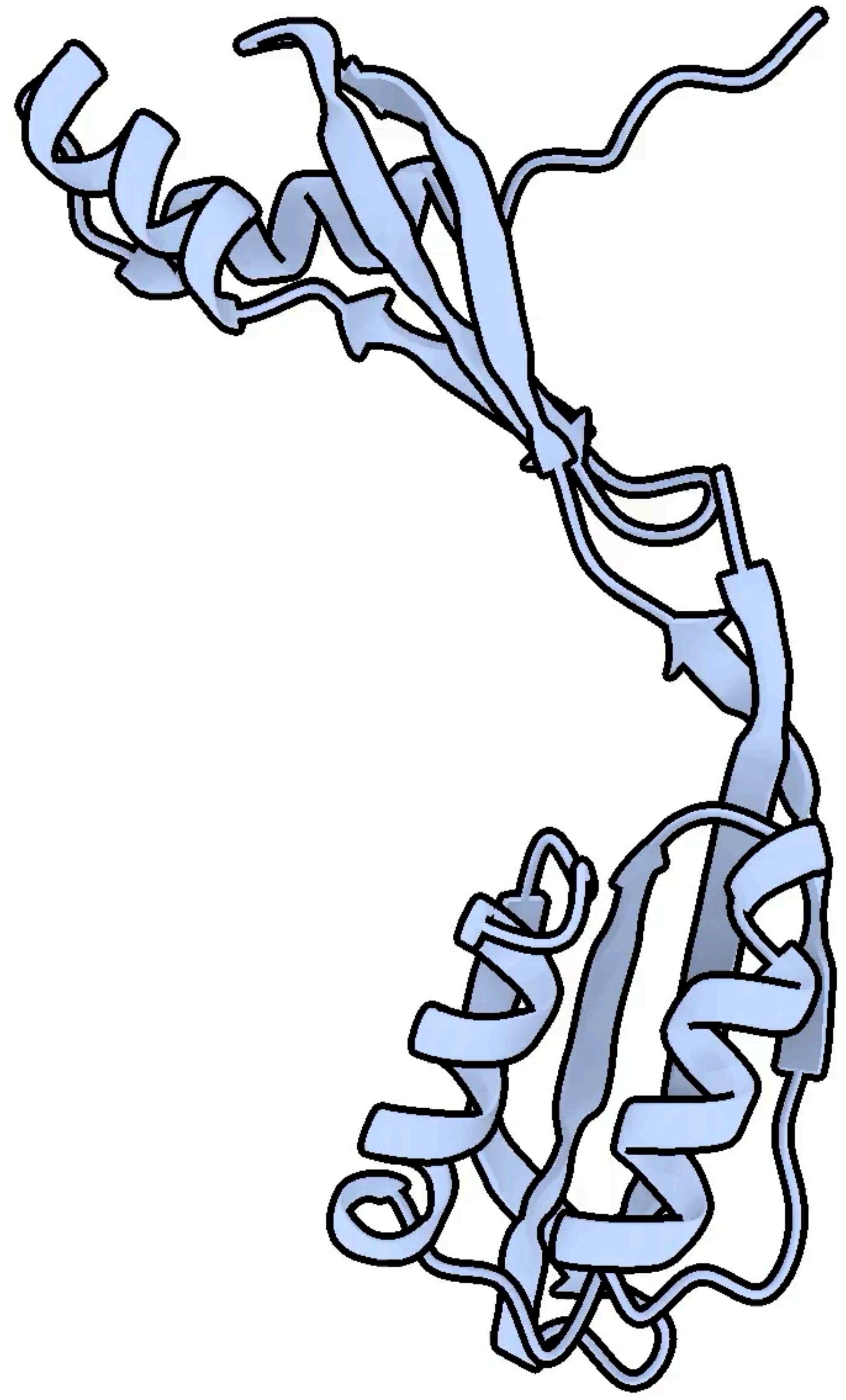
Functional protein structures are dynamic



Functional protein structures are dynamic



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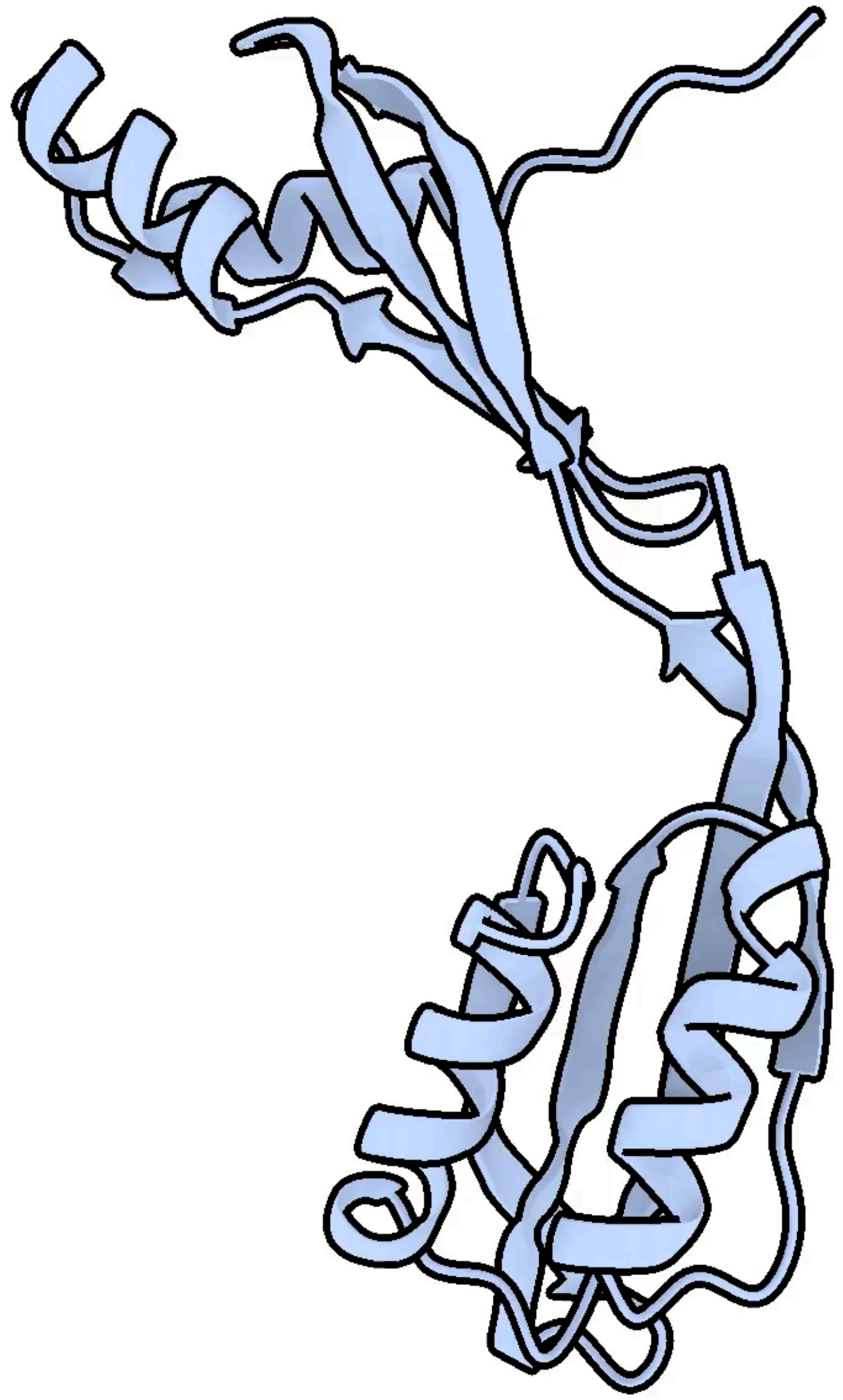

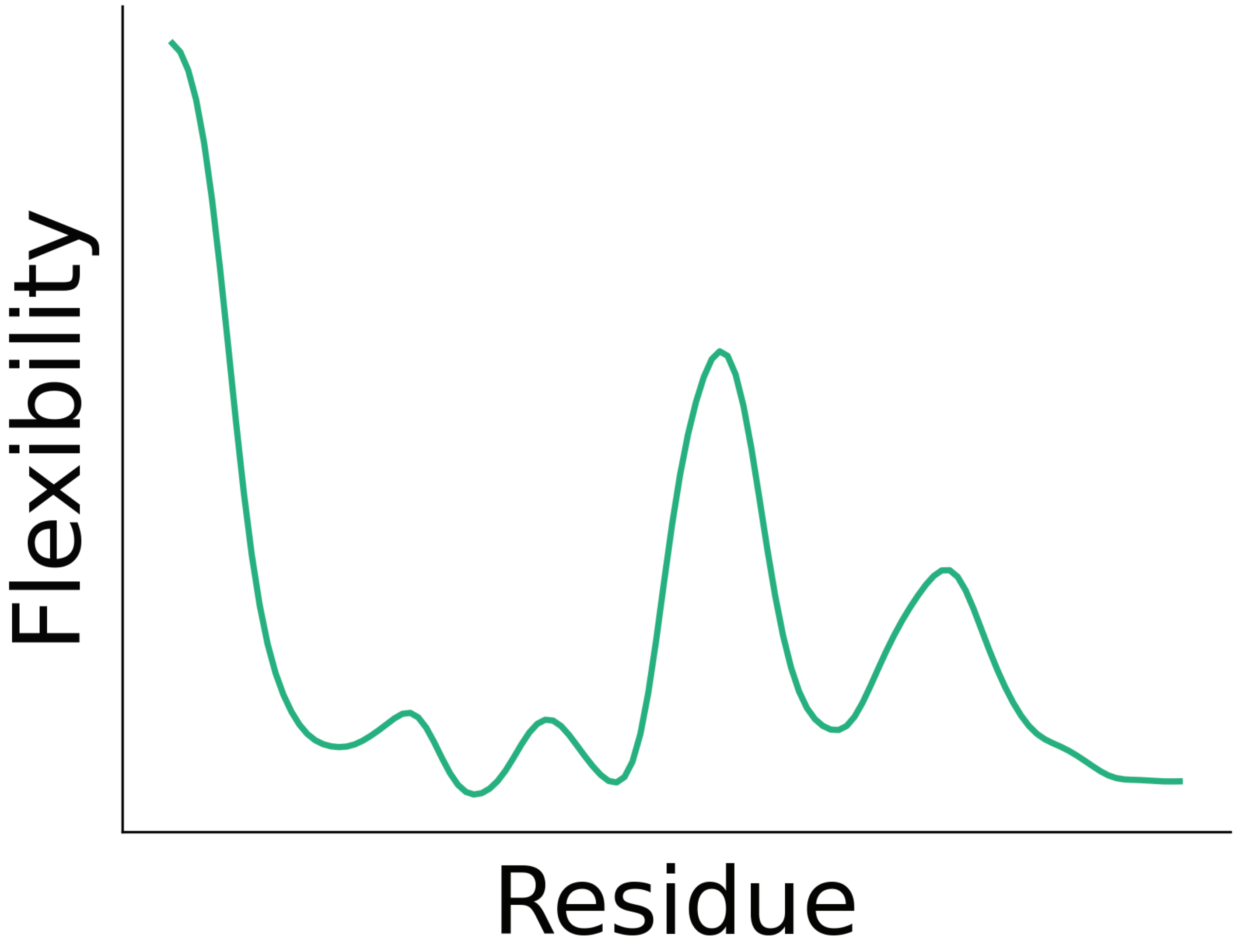

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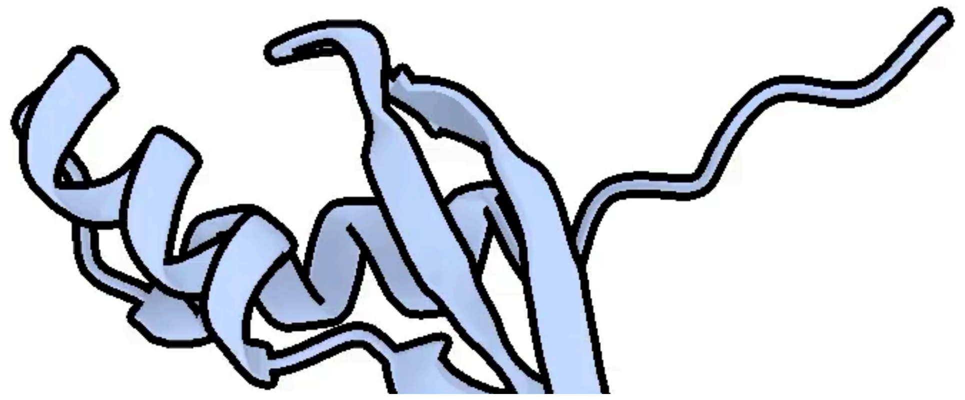
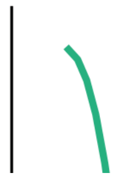
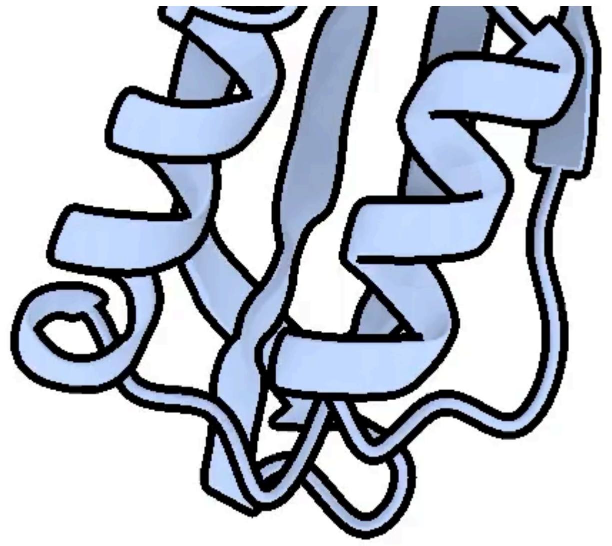


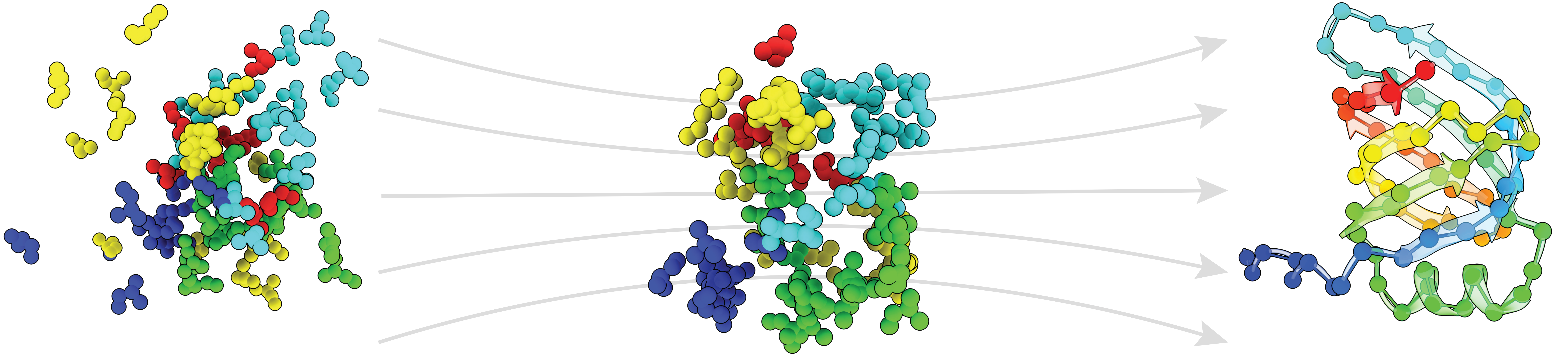


Can we condition protein structure generation on flexibility?



FliPS: Flexibility-conditioned protein structure design

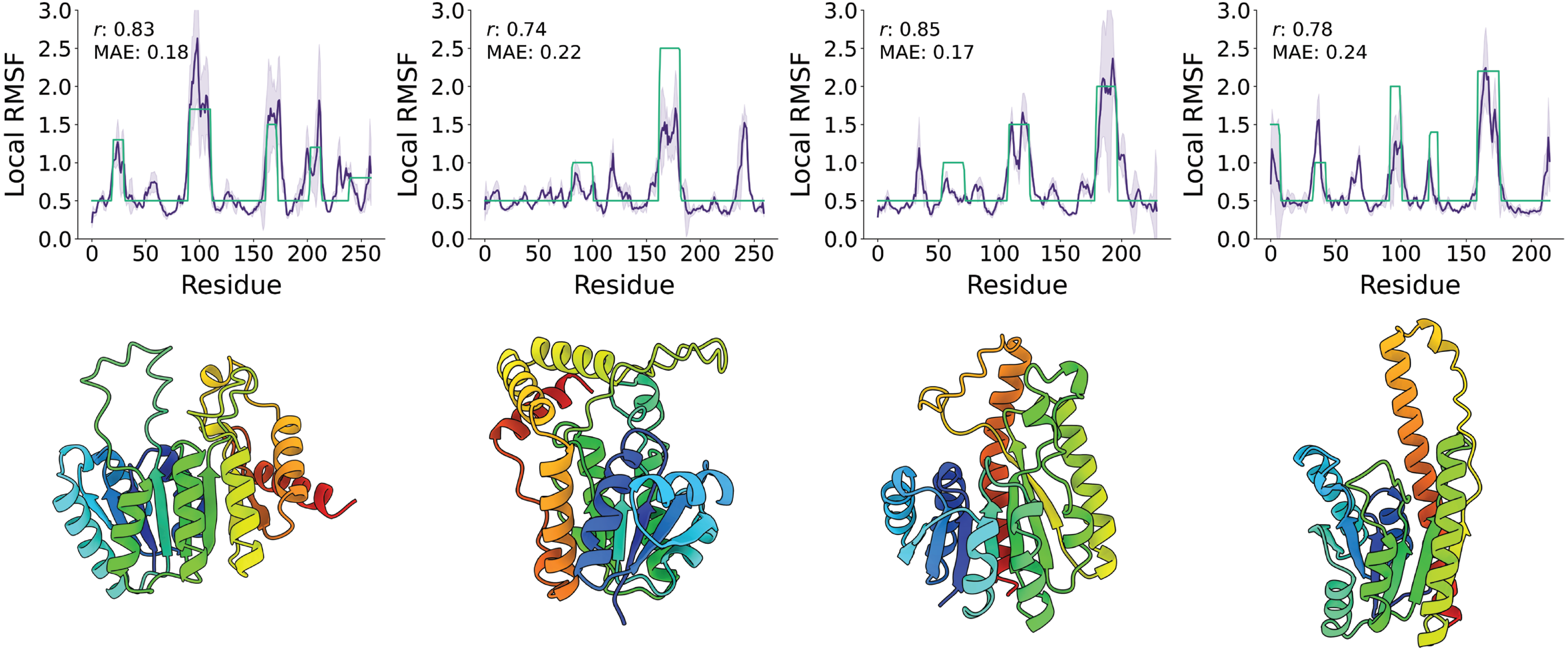
$$\mathbf{T}_{noised} \sim p_0 \qquad \phi(\mathbf{T}, t, \xi) = \mathbf{T} + \int_0^t v(\mathbf{T}, t', \xi)\, dt' \qquad \mathbf{T}_{denoised} \sim p_1$$



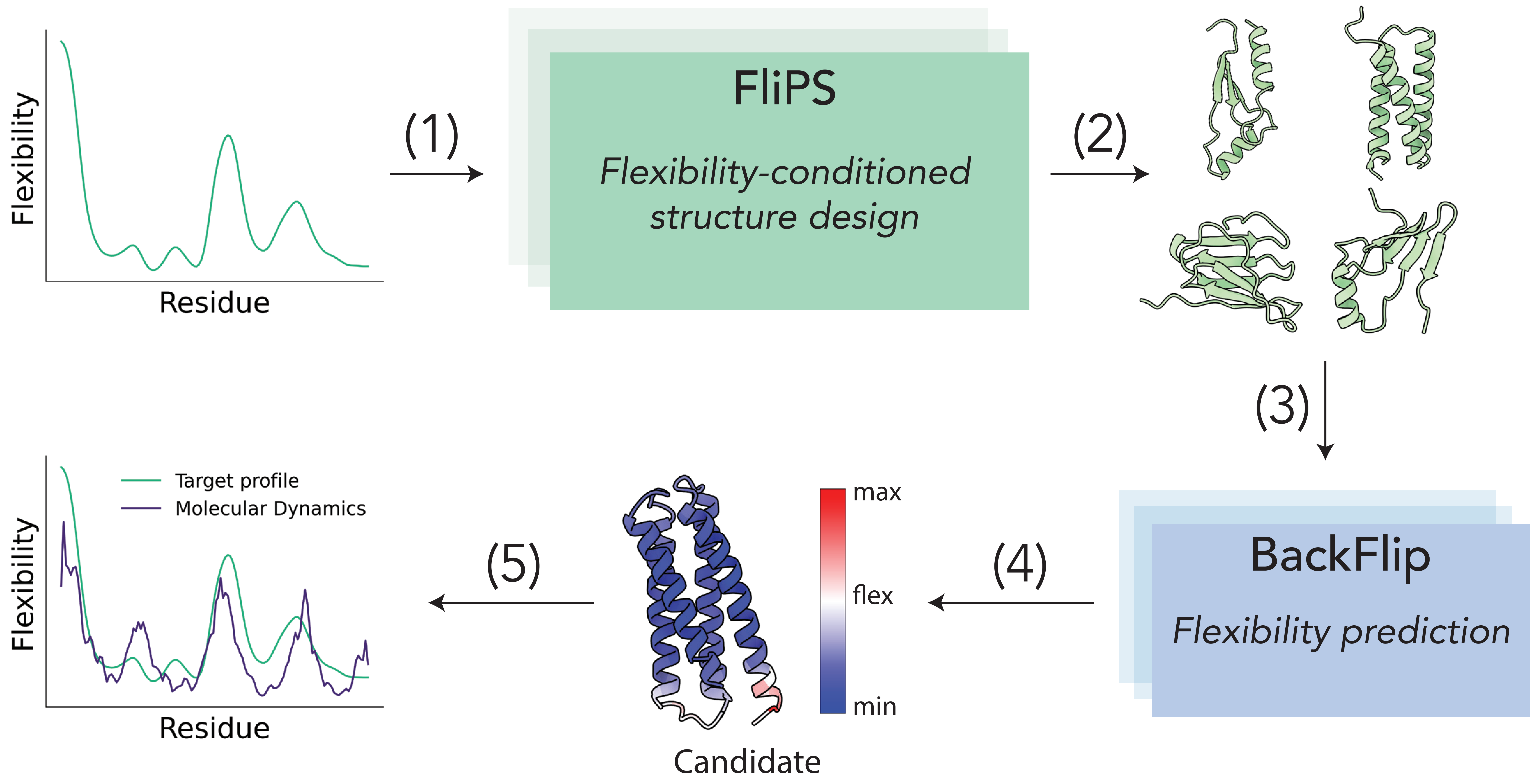
`t = 0` `t = 0.66` `t = 1`

$$\mathbf{T}_i = \{r_i, x_i\} \in \mathrm{SE}(3)$$

Structures generated by FliPS reflect target flexibility



Framework to design and screen protein structures for desired flexibility



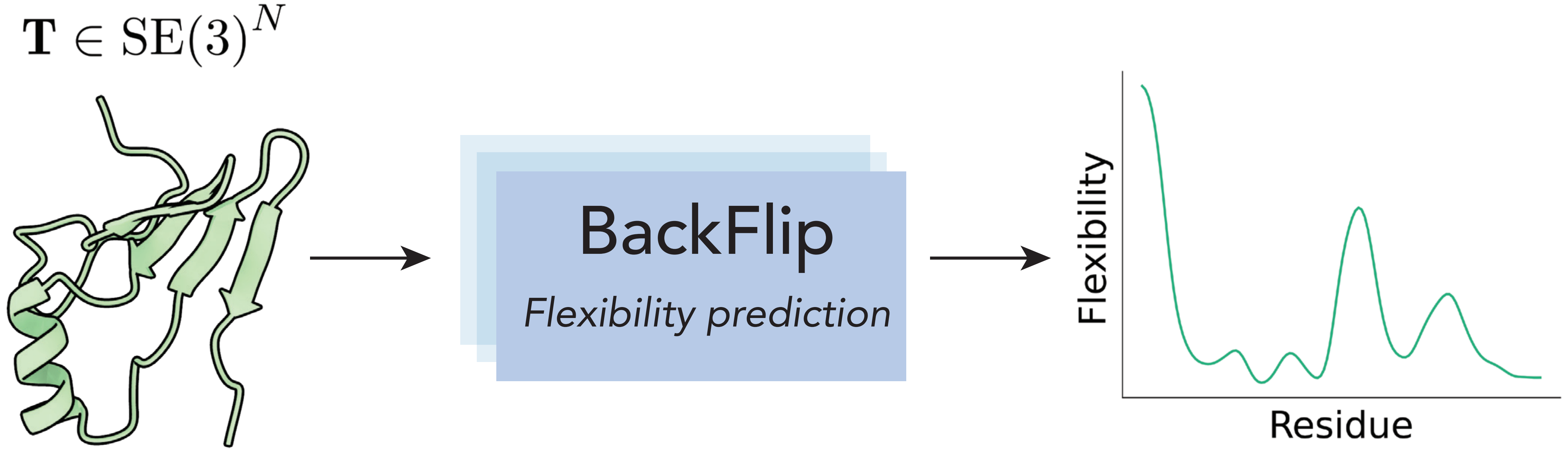
FliPS

Flexibility-conditioned structure design

BackFlip

Flexibility prediction

BackFlip: Backbone Flexibility predictor



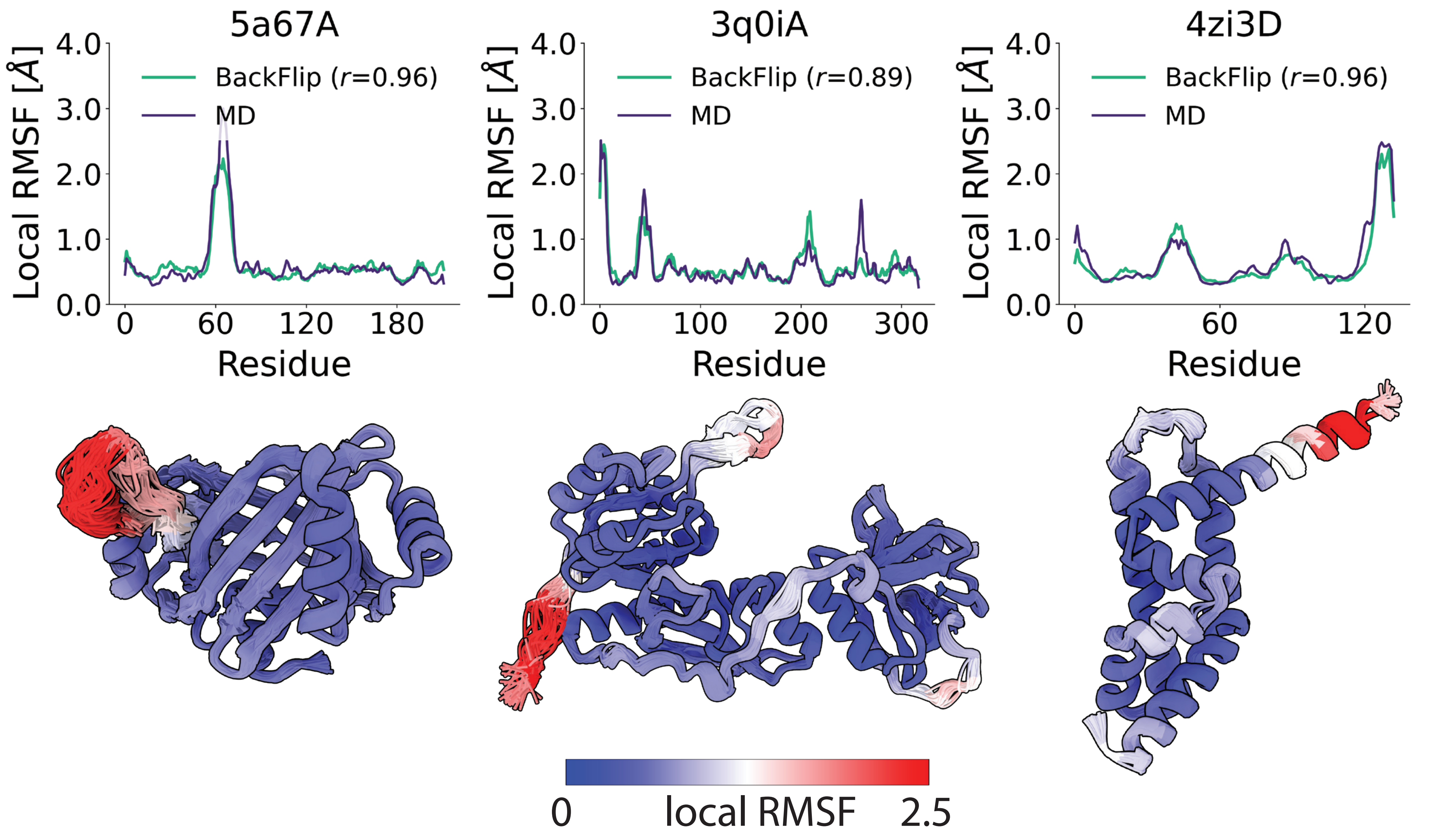
$\mathbf{T} \in \mathrm{SE}(3)^N$

BackFlip

Flexibility prediction

ATLAS Molecular Dynamics (MD) dataset of 1390 proteins

	ATLAS test set		**De novo proteins**		
	Global r (↑)	MAE [Å] (↓)	Global r (↑)	MAE [Å] (↓)	Time [s] (↓)
MD (Ground Truth)	0.84 (0.00)	0.14 (0.00)	0.80 (0.01)	0.10 (0.00)	$\mathcal{O}$(10,000)
BackFlip	0.80 (0.00)	0.17 (0.00)	0.73 (0.00)	0.11 (0.01)	0.6



BackFlip flexibility screening of RFdiffusion and FoldFlow2 yields samples with worse flexibility metrics

	MD of top samples		
	r (↑)	MAE [Å] (↓)	Novelty (↓)
4 hand-drawn profiles			
FliPS	**0.79** (0.01)	**0.21** (0.00)	0.61 (-)
RFdiffusion-BFS	0.41 (0.02)	0.31 (0.00)	0.57 (-)
FoldFlow2-BFS	0.35 (0.02)	0.34 (0.00)	**0.48** (-)

BackFlip flexibility screening (BFS)

$$s(\xi, \xi_{\text{ref}}) = w_{\text{corr}}\, r(\xi, \xi_{\text{ref}}) - w_{\text{mae}}\, \mathbf{MAE}(\xi, \xi_{\text{ref}})$$

References

[1] Joseph L. Watson et al. "De novo design of protein structure and function with RFdiffusion." Nature 620.7976 (2023): 1089-1100.
[2] Huguet, Guillaume et al. "Sequence-augmented SE(3)-flow matching for conditional protein backbone generation." arXiv preprint arXiv:2405.20313 (2024).

Summary

- We introduce a flexibility-conditioned flow matching generative model for protein structure **FliPS** and a flexibility predictor **BackFlip**
- We propose a framework to design de novo proteins with desired flexibilities
- Target flexibilities of proteins generated with FliPS are recapitulated in MD

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