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SE(3) Flow-Matching Framework for Nucleic-Acid–Conditioned Protein Binder Design

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Generative design of protein binders conditioned on target 3D structure has advanced for protein and small-molecule targets, yet explicit conditioning on nucleic acids is not widely established. We present an extension of FrameFlow, an SE(3) flow-matching backbone generator, to design protein–nucleic acid complexes with nucleic-acid context explicitly modeled throughout. We evaluate two motif-scaffolding regimes, both taking the 3D coordinates of the nucleic acid and the binding motif as input: (i) soft-conditioned co-generation, which uses the provided coordinates as conditioning features but does not hold them fixed, allowing the model to jointly resample the motif, nucleic acid, and scaffold, and (ii) hard-constrained scaffolding, which holds the provided motif and nucleic-acid coordinates fixed and samples only the surrounding scaffold. We generate protein–nucleic-acid complexes and assess structural quality. Preliminary results indicate that explicit nucleic-acid conditioning yields backbones and interfaces consistent with the specified motifs, supporting the feasibility of motif-aware design for nucleic-acid-binding proteins.