Benchmarking Flow Matching Methods for RNA Structure Modelling

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TL;DR: RNA structure modelling remains a challenging problem for deep learning. Here we review and benchmark flow matching approaches for RNA structure modeling with the hope that it will be a good summarization of related work.

1 Introduction

- Ribonucleic acid (RNA) molecules are central to cellular function, and their 3D structures are key to their diverse functions.
- However, **accurately modeling RNA 3D structures remains a significant challenge** due to limited experimental data and the molecule's inherent flexibility.
- **Flow matching**, a generative technique learning complex data distributions, **has recently been adapted for diverse RNA structure modeling tasks targeting different goals.**

A hairpin loop from a pre-mRNA. Source: wikipedia

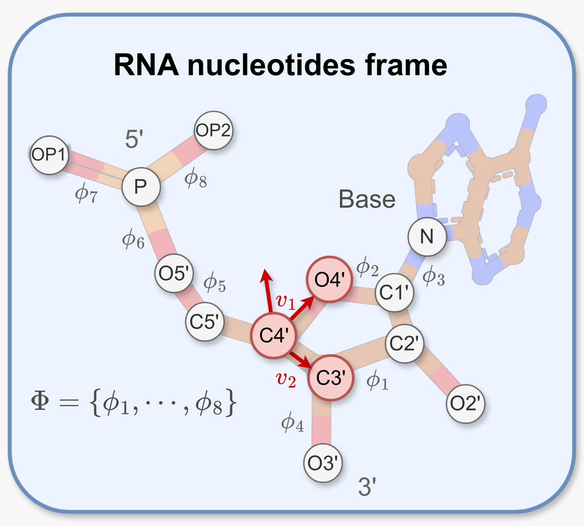


Image Credit: Anand et al. (2024)

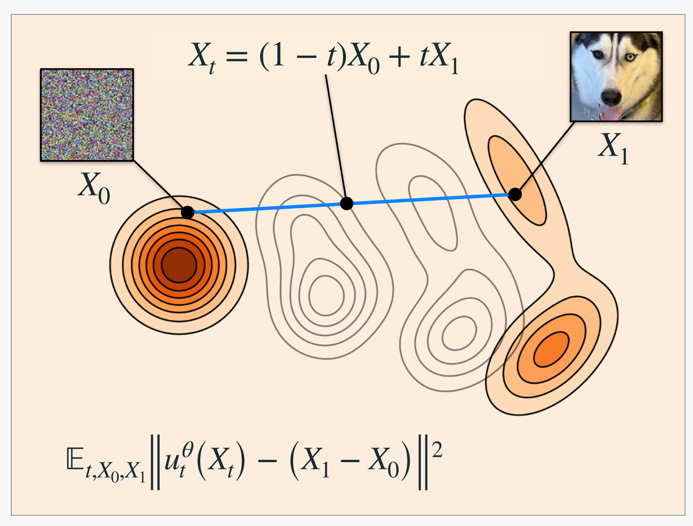


Image Credit: Hamu, Chen, Lipman (NeurIPS Tutorial)

2 Overview of Flow Matching Methods

- The **recent applications of flow matching to RNA** modeling has taken diverse strategies **targeting distinct sub problems.**

Conceptual depiction of flow matching for RNA structure modelling

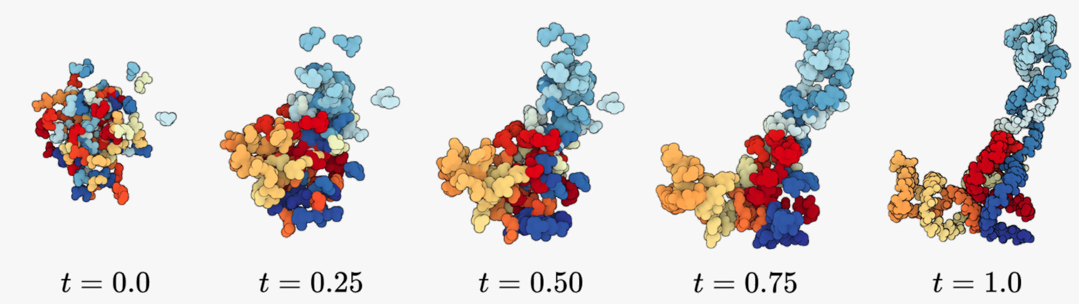


Figure adapted from Anand et al. (2024)

- Evaluating these varied approaches **requires a common baseline** focusing on fundamental geometric accuracy.

Capability	**RNA-FrameFlow** [1] Anand et al., 2024	**RNAFlow** [2] Nori & Jin, 2024	**RNAbpFlow** [3] Tarafder & Bhattacharya, 2025	**RNA-EFM** [4] Abir & Zhang, 2025
Primary Task	De Novo Backbone Design	Protein Conditioned Co-Design	Sequence and base-pair conditioned Design	Protein Conditioned Co-Design
Inputs Needed	None	Protein	Sequence & BPs	Protein, Energy
Output	Backbone	Sequence + Backbone Structure	All-atom Structure	Sequence + Backbone Structure
Protein-Aware?	×	✓	×	✓
Sequence Design?	×	✓	×	✓
All-atom?	×	×	✓	×

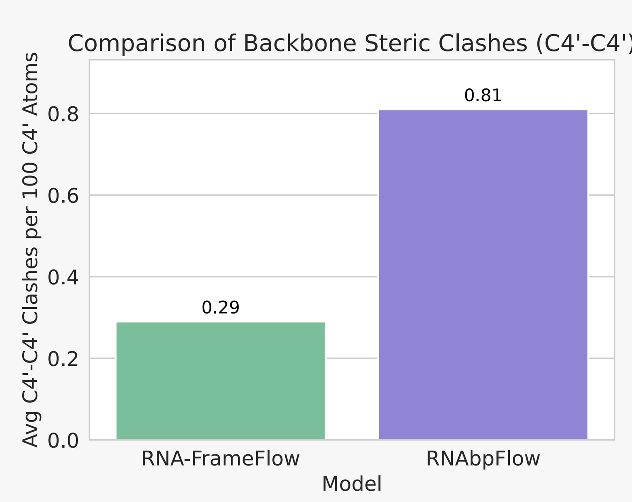
3 Benchmarking Strategy

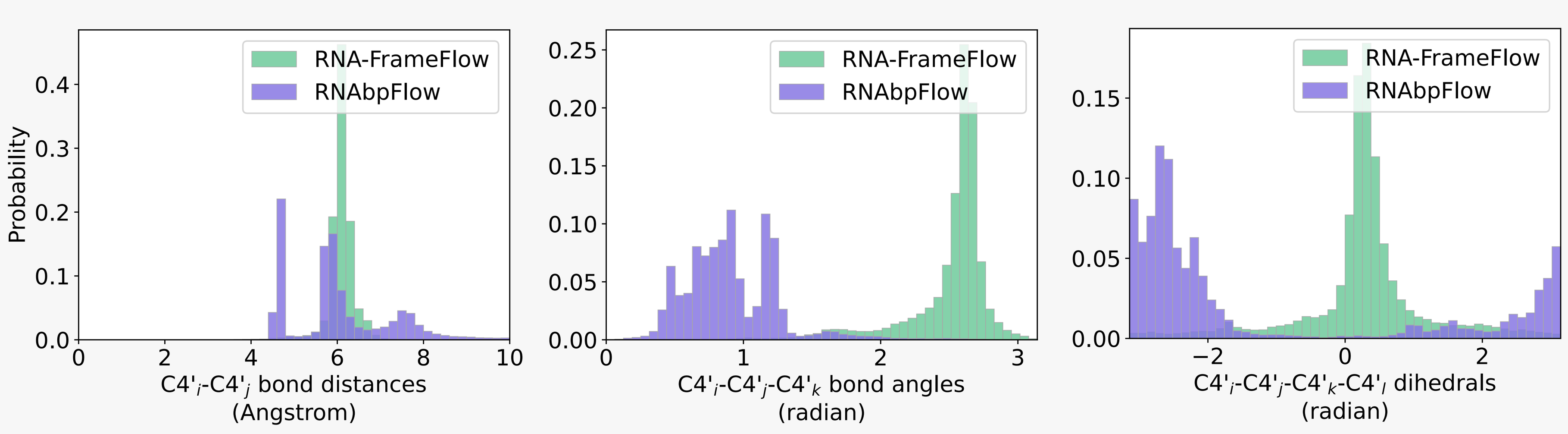
- Because the models target different outputs (backbone vs. all-atom), our strategy assesses both shared geometric quality and unique task performance
- **Goal**: Evaluate and compare RNA-FrameFlow (unconditional backbone) and RNAbpFlow (conditional all-atom) flow matching methods.
- **Approach:** Hierarchical benchmarking focusing on:
  - **1. Core Backbone Quality (Common Ground):**
    - Assess geometric realism via distributions of backbone bond lengths, angles, and dihedrals.
    - Quantify backbone steric clashes.
    - Compare generated distributions against known RNA geometry / training data.
  - **2. Task-Specific Performance:**
    - RNA-FrameFlow: Evaluate validity using self-consistency TM-score (scTM).
    - RNAbpFlow: Evaluate accuracy vs. native structures (RMSD, TM-score, lDDT) and all-atom clashes.
  - **3. Computational Efficiency:**
    - Compare sampling times.

4 Results

1.Core Backbone Quality (Common Ground):

- RNAbpFlow shows somewhat bi-modal distributions, suggesting greater structural diversity. Bond angles and dihedral distributions are interestingly different among the two methods
- Furthermore, RNAbpFlow backbones have significantly more steric clashes. Although the original RNAbpFlow paper utilized standard all-atom clash scores in its benchmarks, our C4'-focused result similarly suggests potential steric challenges in structures generated by RNAbpFlow.





*We generated 600 structures for RNA-FrameFlow and 200 structures for RNAbpFlow to obtain these results

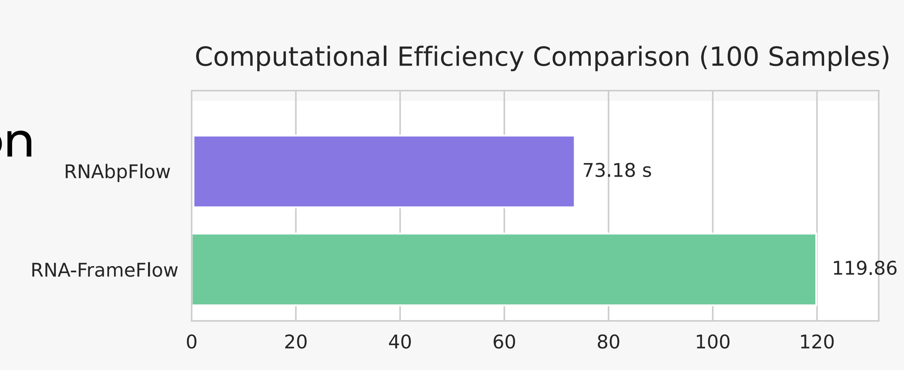
2. Task-Specific Performance

- Here we list the most relevant task specific performances as reported in the original papers [1,3].

Method	Evaluation Task	Metric	Value
RNA-FrameFlow	Self-Consistency	% Validity (scTM ≥ 0.45)	41.0%
RNAbpFlow	Accuracy vs Native (Native BPs)	Avg. TM-score	0.51
		Avg. lDDT	0.72
		Avg. RMSD (Å)	7.79
		Avg. Clash Score	46.97

3. Computational Efficiency

- Evaluated by timing the generation of 100 structures for length 96 for both methods across 3 runs on a NVIDIA RTX 4060 GPU



5 Conclusions & Future Work

- By the final report we intend to expand this benchmarking to all four methods. With the obtained insights, we will postulate how incorporating RNA sequence-derived information, could potentially enhance the performance of these flow matching models.

References

[1] Anand, Rishabh, et al. "RNA-FrameFlow: Flow Matching for De Novo 3D RNA Backbone Design." arXiv preprint arXiv:2406.13839 (2024).
[2] Nori, Divya, and Wengong Jin. "RNAFlow: RNA Structure & Sequence Design via Inverse Folding-based Flow Matching." arXiv preprint arXiv:2405.18768 (2024).
[3] Tarafder, Sumit, and Debswapna Bhattacharya. "RNAbpFlow: Base pair-augmented SE (3)-flow matching for conditional RNA 3D structure generation." bioRxiv (2025): 2025-01.
[4] Abir, Abrar Rahman, and Liqing Zhang. "RNA-EFM: Energy based Flow Matching for Protein-conditioned RNA Sequence-Structure Co-design." bioRxiv (2025): 2025-02.