ENSEMBLE-AWARE STRATEGIES FOR TARGETING HIV-1 TAR

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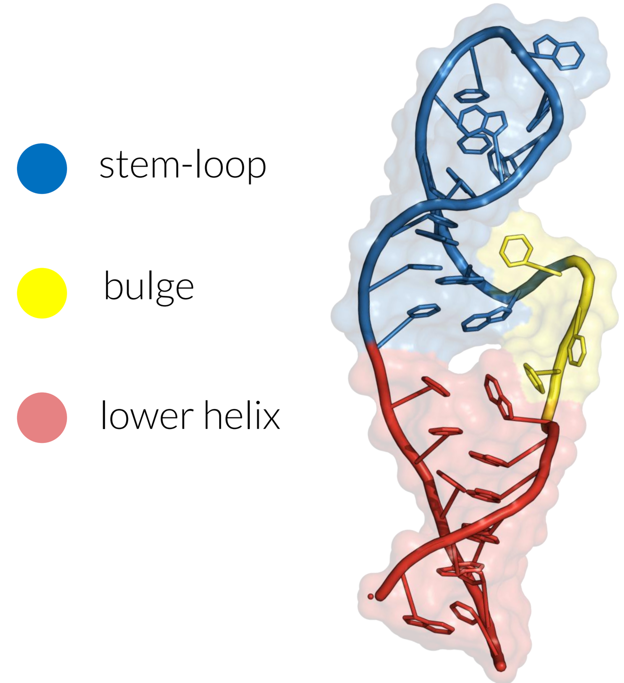
Introduction

- The trans-activation response element (TAR) is an RNA stem-loop structure located at the 5' end of the HIV-1 genome [1].
- The conformation of the stem-loop is fundamental for the interaction with Integrase (IN) and Tat protein [2].
- No experimental structure of the TAR IN complex is currently available.



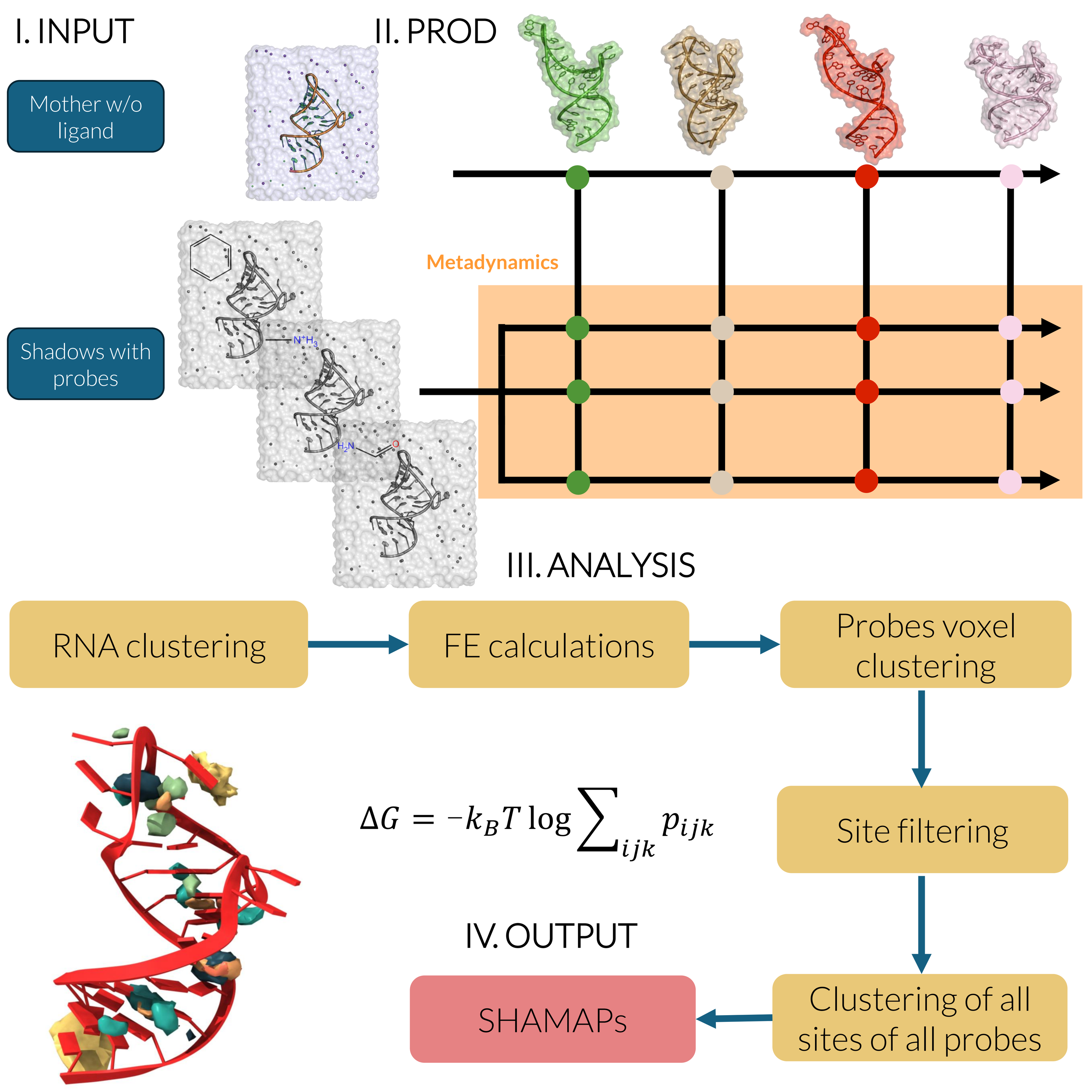
- Due to the high intrinsic flexibility of this small RNA, its conformational space is wide and complex.
- Residual dipolar couplings provide experimental information for ensemble level characterization.

1. DISCOVERY OF TAR-IN DISRUPTORS

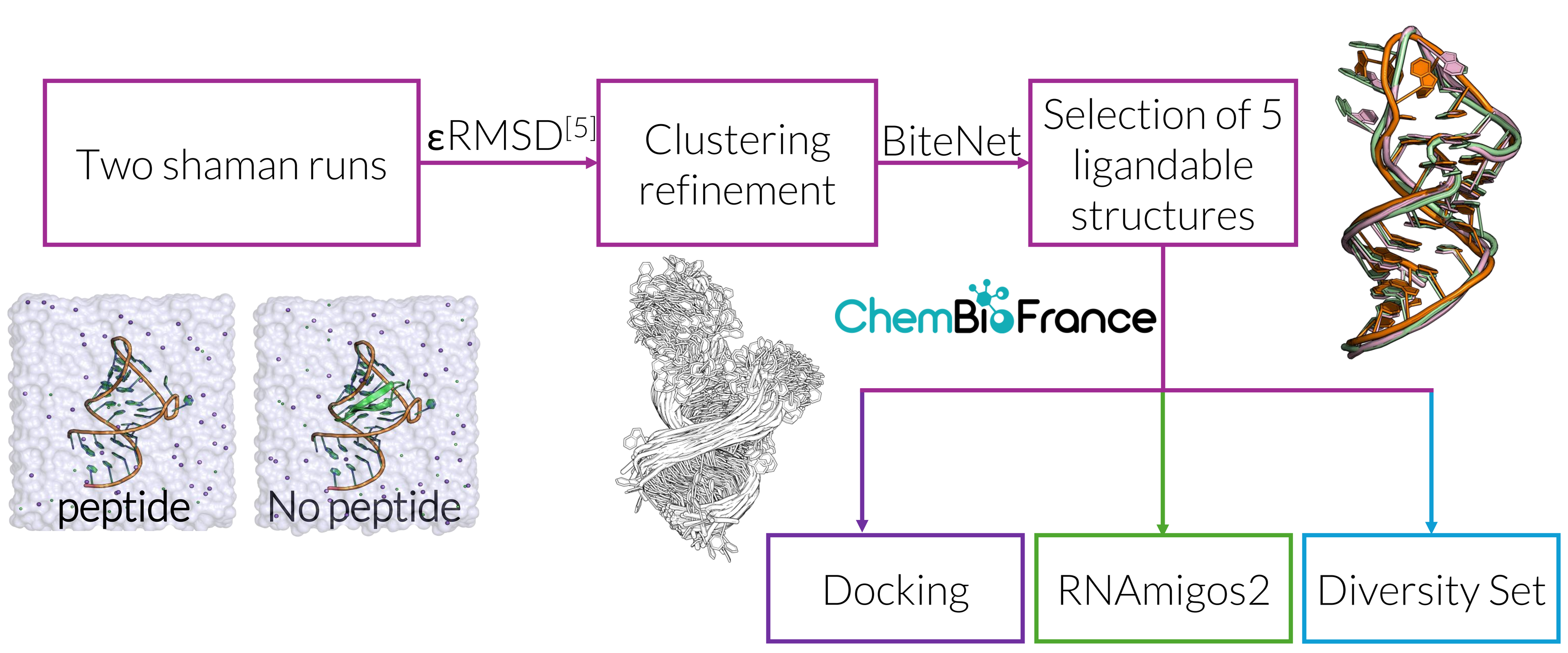
SHAMAN Protocol

SHAdow Mixed solvent metAdyNamics (SHAMAN) [3] is a computational tool for binding site identification in dynamic RNA structural ensembles.

- Exploration of **conformational landscapes** with molecular dynamics (MD) simulations.
- Identification of **small-molecule binding sites** by coupling mixed-solvent MD and metadynamics



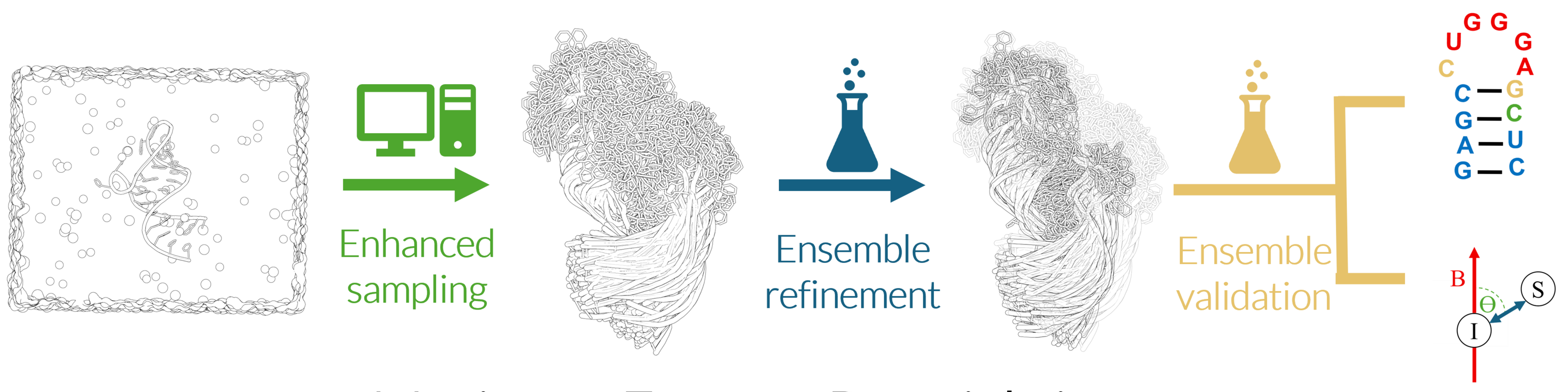
Virtual Screening Workflow



- **200 selected molecules** tested as TAR-IN interaction disruptors.
- εRSMD as a metric improved cluster analysis within the SHAMAN workflow.

2. RECONSTRUCTION OF THE TAR CONFORMATIONAL ENSEMBLE

Integration Workflow



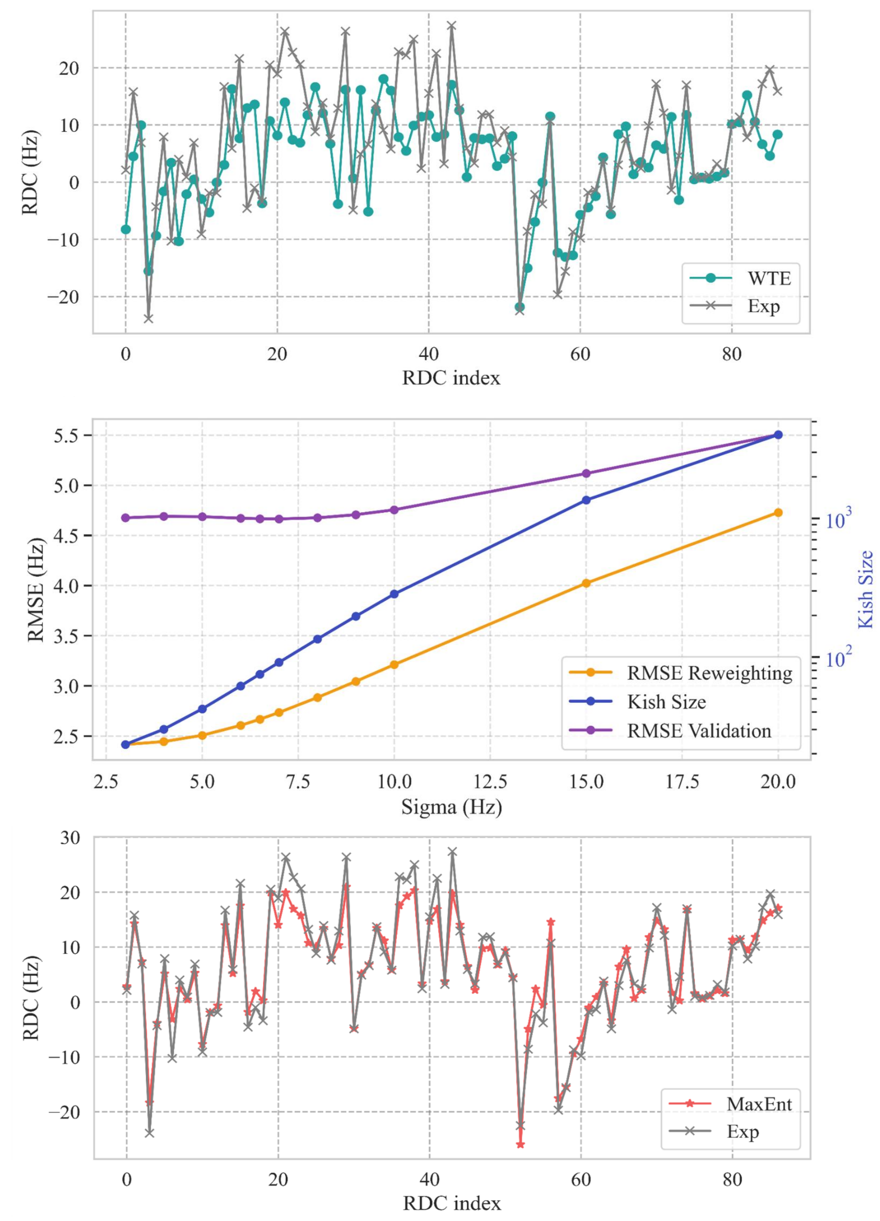
Maximum Entropy Reweighting

The Maximum Entropy reweighting [6] **minimally perturbs** the prior while correcting ensemble population weights.

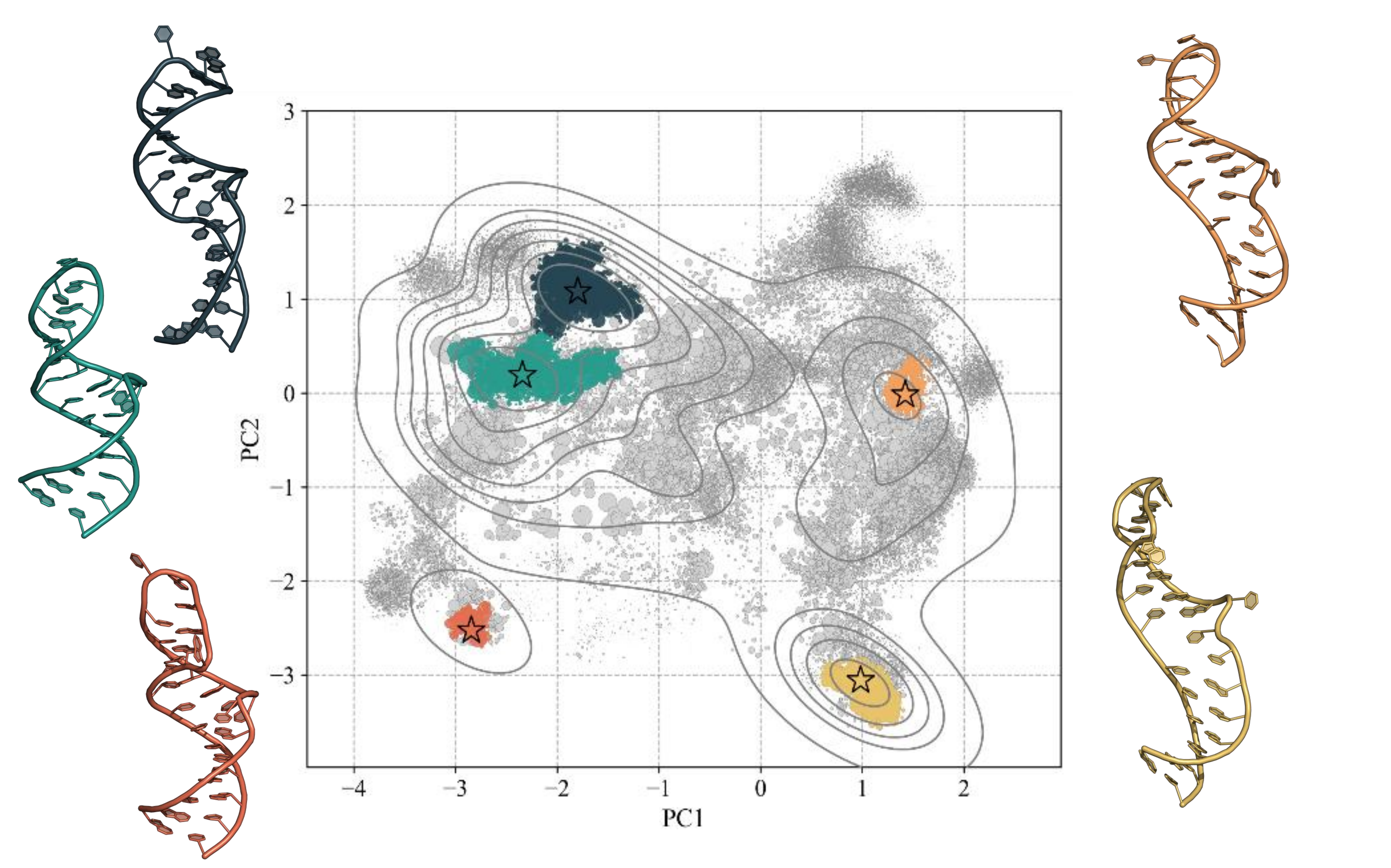
$$S[P||P_0] = -\int d\boldsymbol{q} P(\boldsymbol{q}) \ln \frac{P(\boldsymbol{q})}{P_0(\boldsymbol{q})}$$

$$\begin{cases} P_{ME}(\boldsymbol{q}) = \arg \max_{P(\boldsymbol{q})} S[P||P_0] \\ \int dq s_i(q) P(\boldsymbol{q}) = \langle s_i(\boldsymbol{q}) \rangle = s_i^{exp}, i = 1, \dots, M \\ \int d\boldsymbol{q} P(\boldsymbol{q}) = 1 \end{cases}$$

- Experimental noise modeled via a regularization term $(\boldsymbol{\sigma})$
- Improved RDC agreement RMSE 8.4 Hz⇒ 2.8 Hz



Reconstructed Conformational Ensemble



- The integration of enhanced sampling simulations and experimental data yielded an **accurate conformational ensemble** of TAR.
- Representative cluster structures can be used as starting points for **multiple SHAMAN runs** to extend the explored conformational space.

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References
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