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Advancing RNA-Ligand Binding predictions with Thermodynamic Integration and Alchemical Transfer Approaches

RNA is emerging as a promising therapeutic target due to its central role in regulating diverse cellular functions. However, accurately predicting ligand binding affinities to RNA remains a major computational challenge, largely due to RNA's intrinsic flexibility and structural heterogeneity. In this work, we benchmark two alchemical free energy methods—Thermodynamic Integration (TI)1 and the Alchemical Transfer Method (ATM)2—to estimate binding free energies for a representative set of RNA–ligand. By systematically comparing these approaches, we assess their accuracy, robustness, and sensitivity to structural fluctuations. Our findings offer practical guidelines for modelling RNA–ligand interactions and contribute to the development of more reliable tools for RNA-targeted drug design. Ultimately, this work supports the rational design of novel, high-affinity ligands for RNA, advancing the discovery of next-generation RNA-based therapeutics.

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