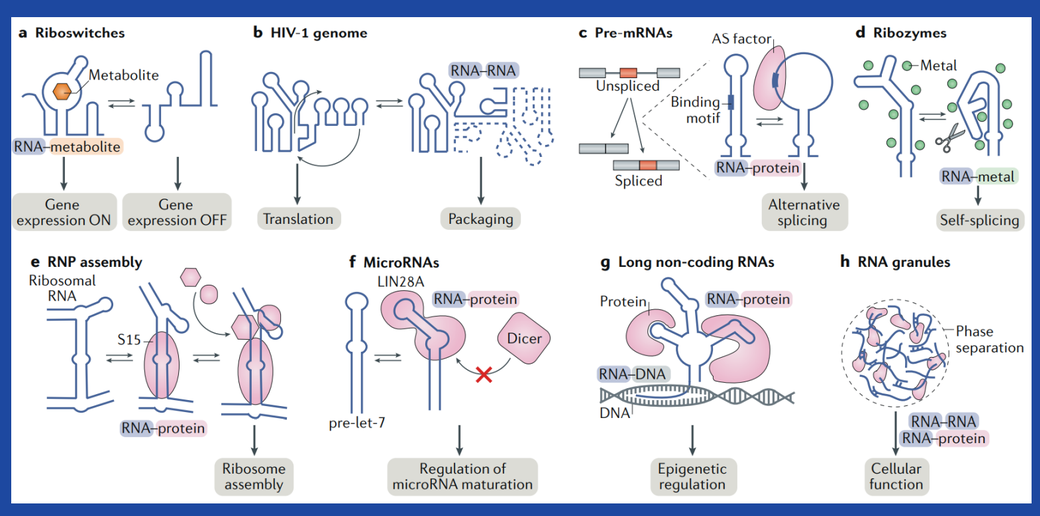
Using Unassigned NMR Chemical Shifts to Model RNA Secondary Structure

The Structure and Function of RNA

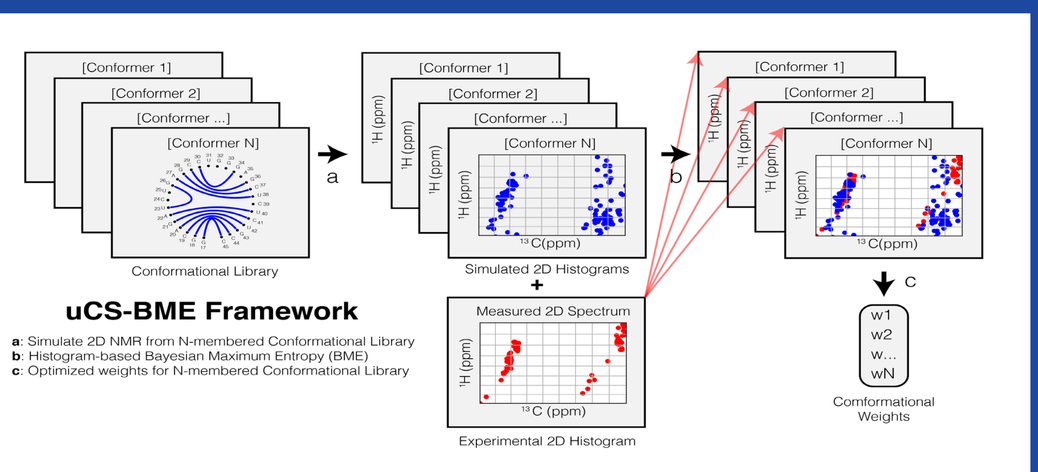
- Recent research has found that a molecule called **ribonucleic acid (RNA)** plays a number of fundamental roles within all cells.
- In order to understand how it performs these vital functions, it is important that we understand the structure of RNA.
- A variety of diseases (such as cancer, lupus, and epilepsy) have RNA involved in their pathogenesis and an understanding of RNA structure will help treat such diseases.
- Current approaches to RNA structural prediction are either strongly limited by our understanding of RNA thermodynamics or require difficult-to-collect data.
- My project focused on developing an approach to predict RNA structure using only easy-to-collect experimental data.



(Ganser et al.)

Results

- Overall, we were able to demonstrate that our model was able to predict RNA structure with high (greater than 85%) accuracy.
- Consequently, we were able to demonstrate that the uCS-BME framework is a viable method for RNA structural prediction, both in research and in industry.
- We were able to test our model by using it to predict the secondary structure of regions of the SARS-CoV-2 (the virus that causes COVID-19) viral genome.
  - Our model was able to predict the structure with accuracy on par with or better than that of the most commonly used RNA structural prediction tool.
- In addition, our model showed high accuracy for large RNA sequences as compared with conventional RNA prediction tools whose accuracy tends to greatly decrease for long RNA segments.



(Moudgal et al.)

Chemical Shifts and NMR

- **Chemical shifts** are a type of experimental data collected through a method known as NMR spectroscopy.
- Essentially, chemical shift readings help us understand the chemical environment around each atom in a molecule.
- Consequently, chemical shifts can be used to refine predictions of RNA structure.

The Bayesian/Maximum Entropy Method

- In order to predict the structure of a given RNA molecule, we used tools to generate a set of possible structures based on energy considerations (generally, the structures with the lowest energy are likely to be the natural structure).
- We then used a statistical method called the **Bayesian/Maximum Entropy (BME)** method to assign weights to each possible structure.
  - The weights represent the probability that the given structure will be experimentally sampled.
  - Essentially, structures with higher weights are more likely to be found in living cells.
- The BME method attempts to assign weights to maximize agreement with experimental data (chemical shifts).
- However, if we attempt to assign weights to perfectly match the experimental data, the model would be extremely susceptible to experimental variation.
- Thus, the BME method attempts to fit the experimental data while also preventing the model from deviating too much from the initially assumed weights.

Applications

- We believe that this tool can be used to help researchers in both academia and industry to better understand the function of RNA in a variety of diseases in order to develop novel diagnostics and therapeutics for these diseases.
- Additionally, we hope that our model can help elucidate the mechanisms through which RNA performs its various functions.
- Finally, it is our hope that models like this one can help researchers achieve one of the ultimate goals in the biosciences: to gain a predictive understanding of the function of living systems.

References

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- Bottaro, S.; Bengtsen, T.; Lindorff-Larsen, K. Structural Bioinformatics; Springer, 2020; pp 219–240.
- Ganser, L.R., Kelly, M.L., Herschlag, D. *et al.* The roles of structural dynamics in the cellular functions of RNAs. *Nat Rev Mol Cell Biol* **20**, 474–489 (2019). https://doi.org/10.1038/s41580-019-0136-0
- Zhang, K.; Frank, A. T. Probabilistic Modeling of RNA Ensembles Using NMR Chemical Shifts. J. Phys. Chem. B 2021, 125, 9970–9978.