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Computational methods for comparing and integrating multiple probing assays to predict RNA secondary structure

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1-AMIB team, Inria Saclay 2-LIX, 3-CNRS, 4-Laboratoire de cristallographie et RMN Biologiques, Paris Descartes

1-Introduction

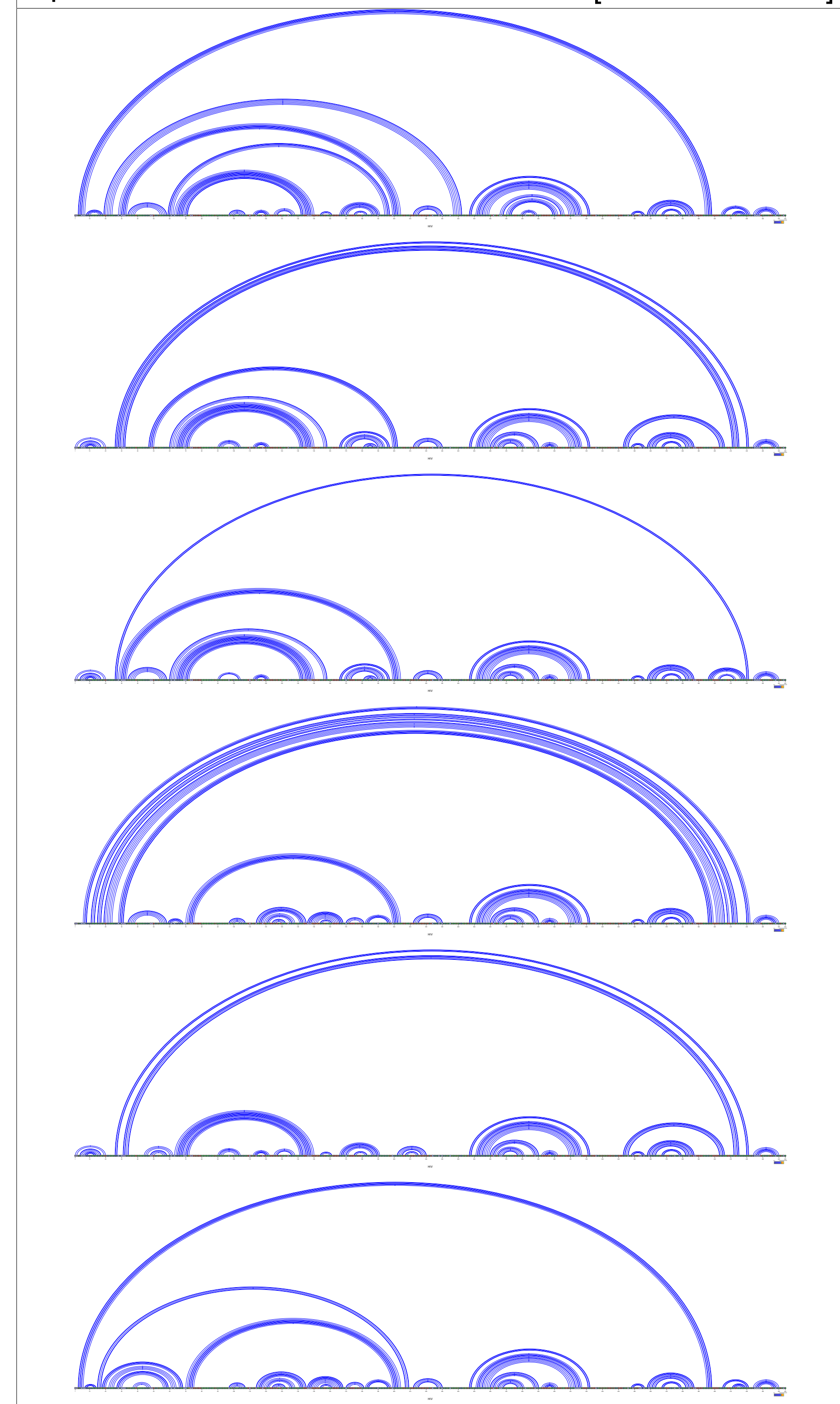
- RNA is key to understand many biological processes.
- RNA maintains a stable tertiary structure.
- The determination of the structure allows understanding its operating mechanism.
- We study the 444nt long **VIH1 Gag-IRES**.

RNA Structure determination

- 3D structure can be resolved experimentally [remains expensive and time-consuming].
- Computational methods allows to have accurate secondary structure predictions (PPV \approx 75%). Less accurate predictions for long RNA.
- + Experimental Data [Chemical(SHAPE) \ Enzymatic] improve predictions.

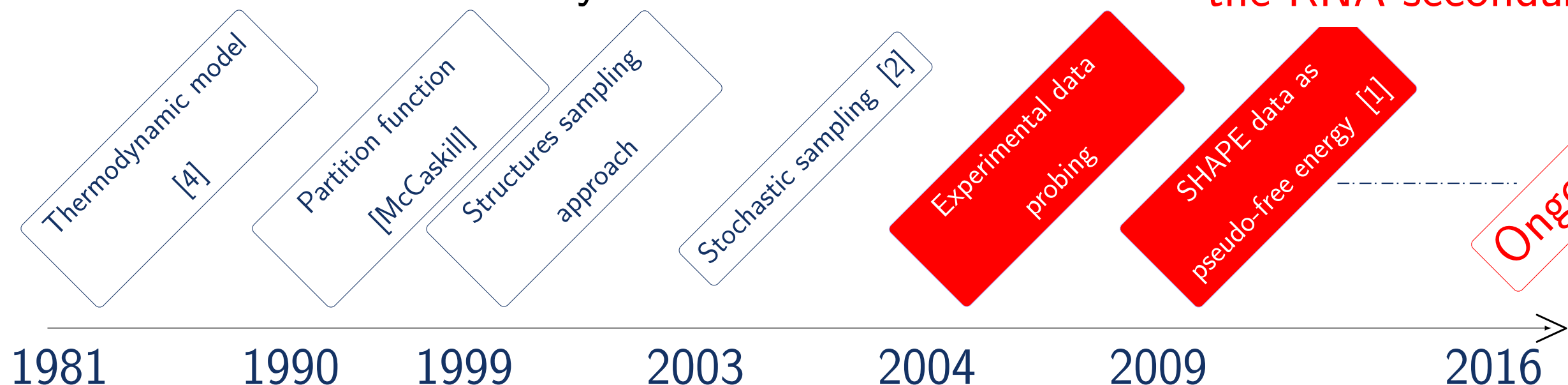
3-Results

Optimal centroid structures from 140. [8000 structures]



State of the art

Evolution of computational approaches to predict the RNA secondary structure:



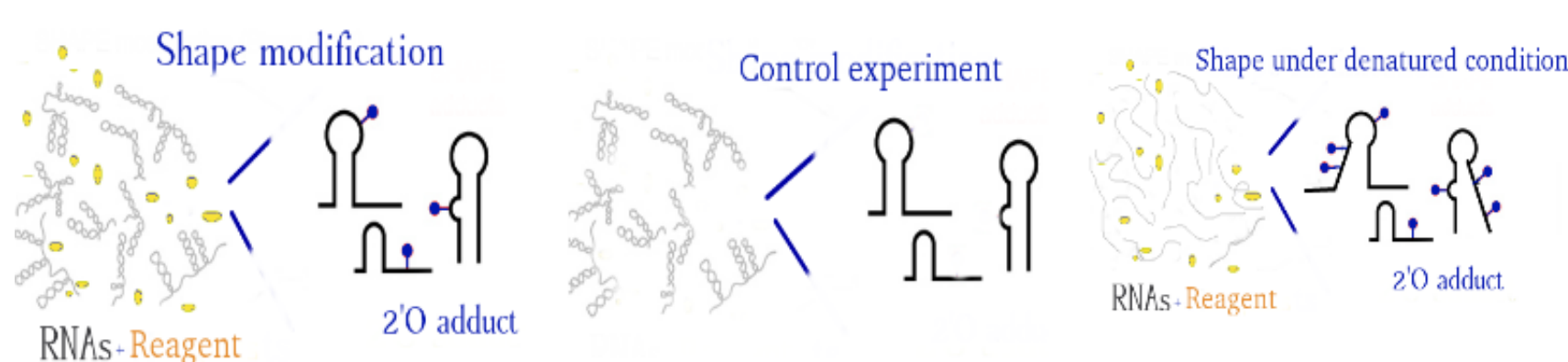
Objectives

- Apply sampling approach with SHAPE data to predict the RNA secondary structure.

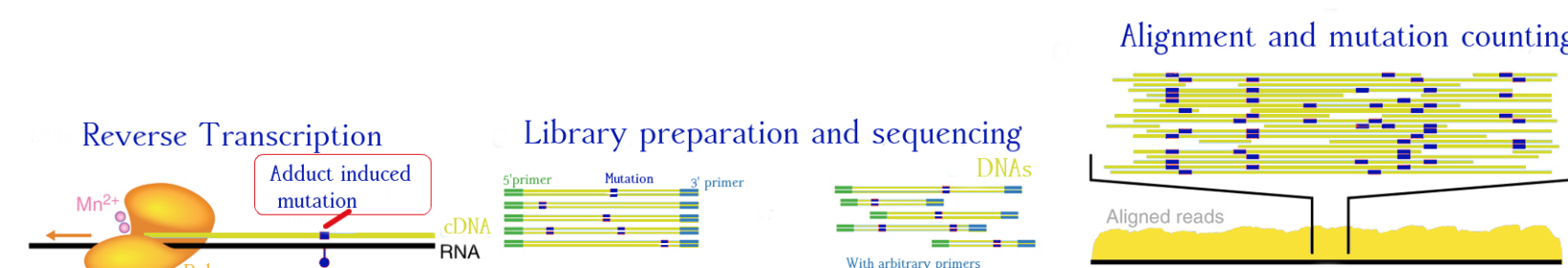
2-Material & Methods

2-1 Experimental data

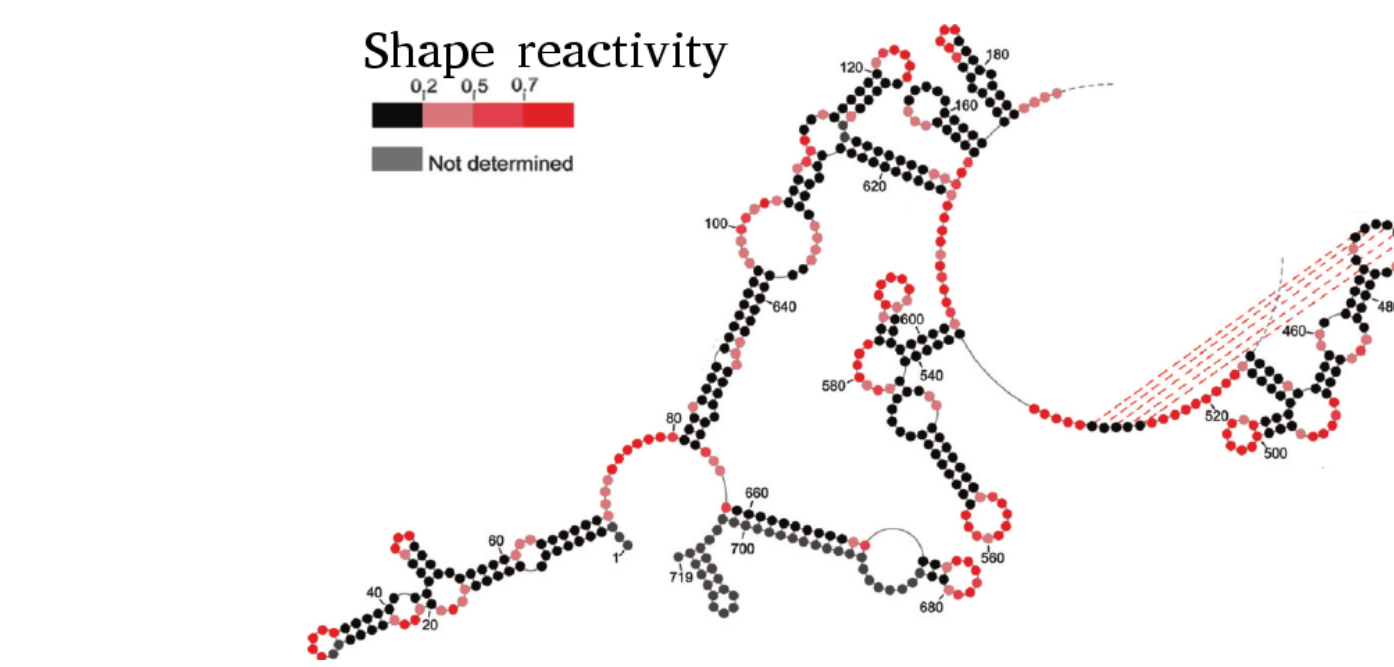
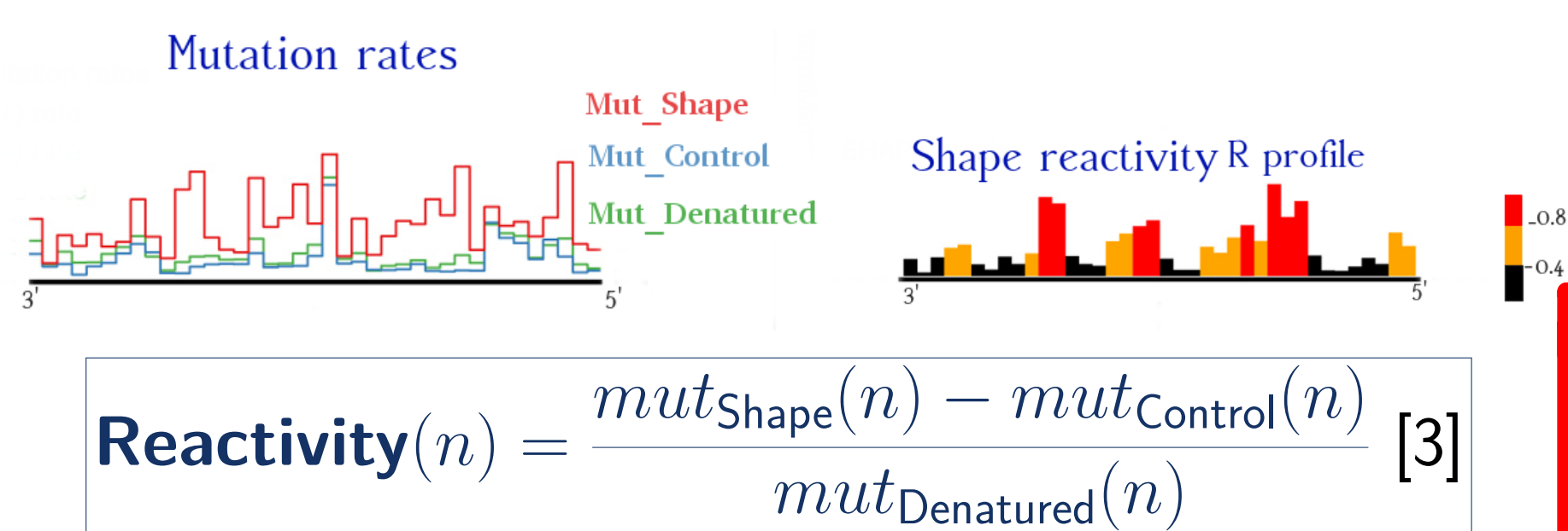
SHAPE-Map experiments



High Throughput Sequencing



SHAPE reactivity calculation



V-Enzymatic cleavage targets paired nucleotides.
T-Enzymatic cleavage reveals unpaired nucleotides.

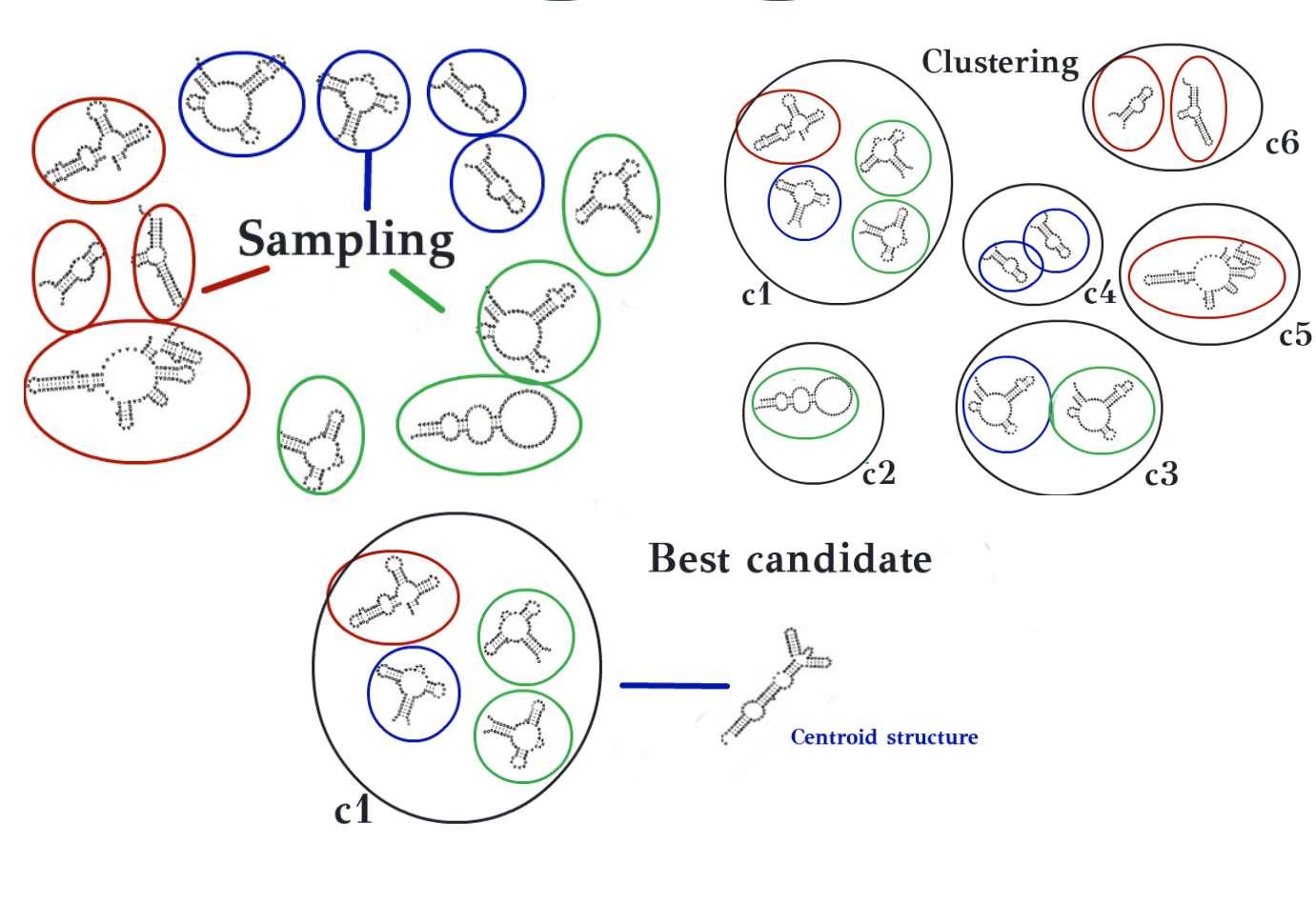
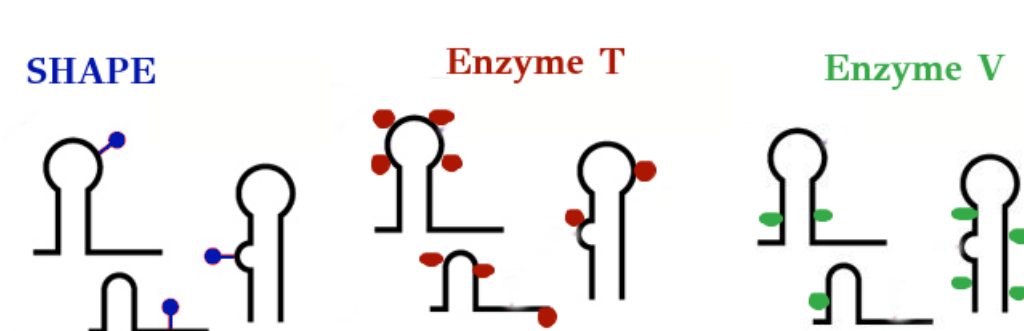
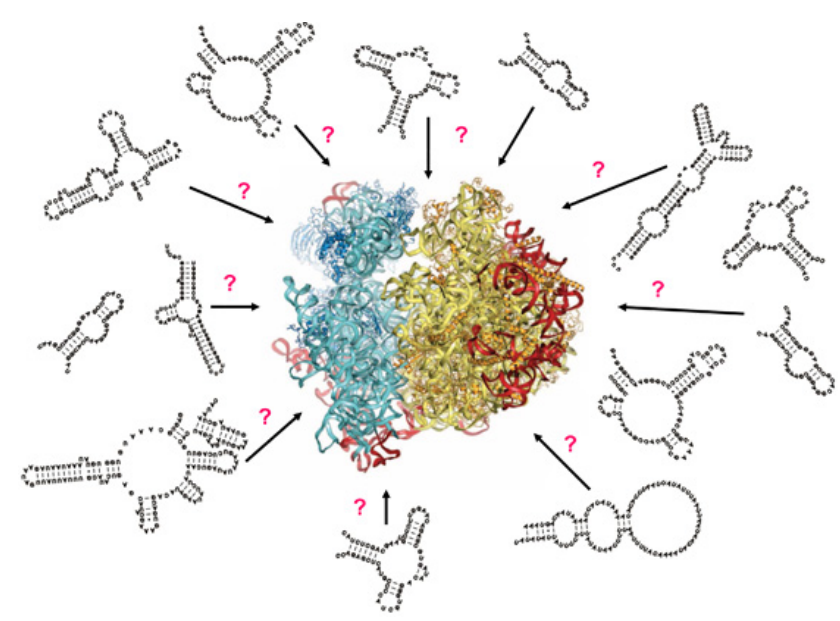
4-Conclusion & perspectives

- We have obtained a set of models supported by our integrative approach, those models are subject to validation.
- Some of centroid structures have shown high compatibility with existing proposed structural models.
- We will extend the approach to the simultaneous analysis of probing data for a set of RNA variants.

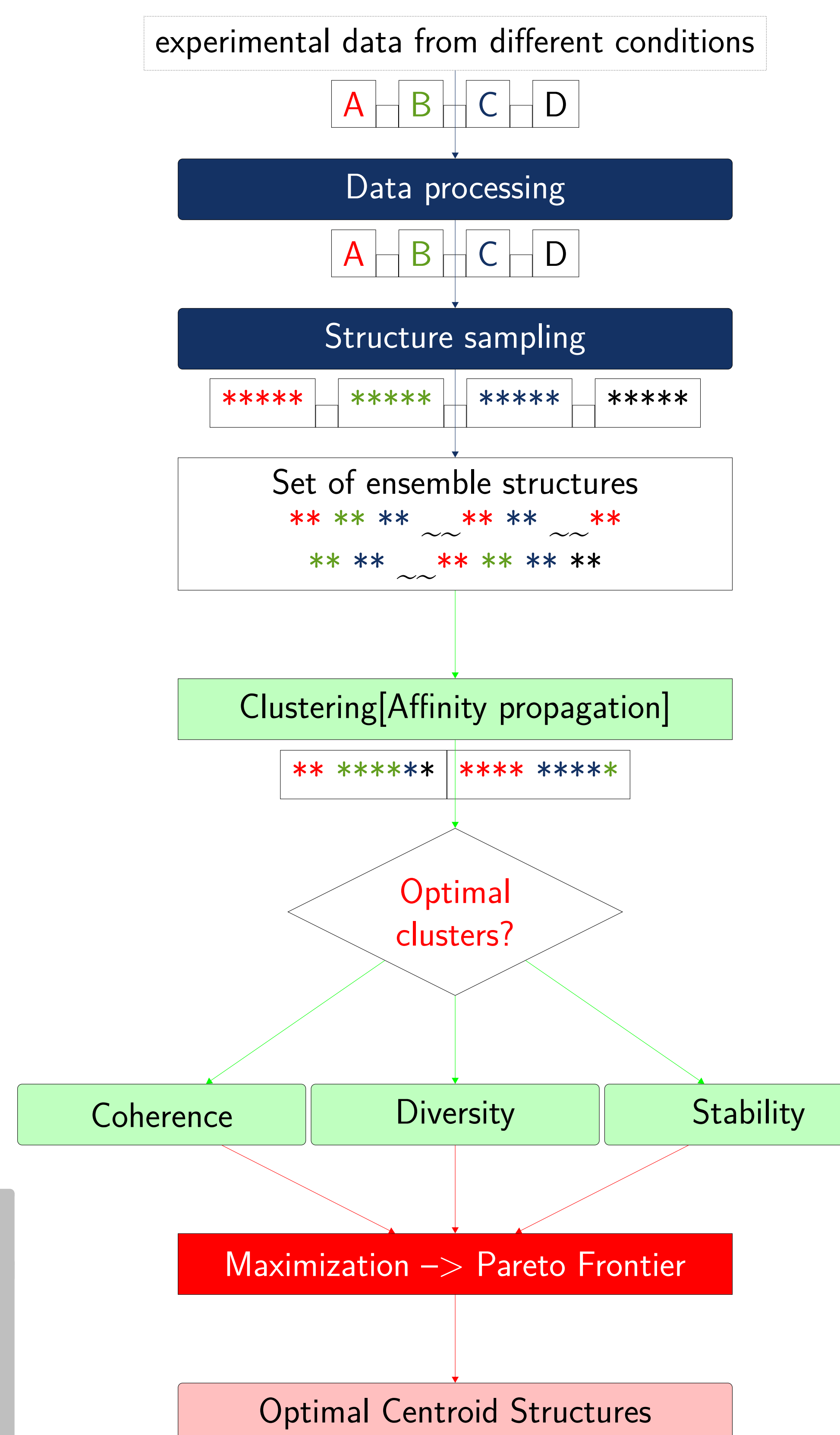
Boltzmann probability to observe a structure S :

$$P(S) = \frac{e^{-\frac{E_S}{kT}}}{Z}$$

with Z the partition function: $Z = \sum_{S \in \mathcal{S}} e^{-\frac{E_S}{kT}}$.



2-2 Sampling/Clustering workflow



References

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For a cluster \mathcal{C}

- Coherence** \equiv Base pairs **Mean Distance** in \mathcal{C} .
- Diversity** \equiv Number of **present conditions**.
- Stability** \equiv Sum of **Boltzmann probabilities**.