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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN

Bernhard Thiel, Peter Kerpedjiev,  
Ivo Hofacker

*tbi*

# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



## Overview

### ► Introduction

What is RNA-structure and how to coarse grain it?

### - Building 3D structures

How to build and sample 3D structures?

### - Integrating it with cryo EM/ AFM

How to improve our model?

How to aid interpretation of experimental data?

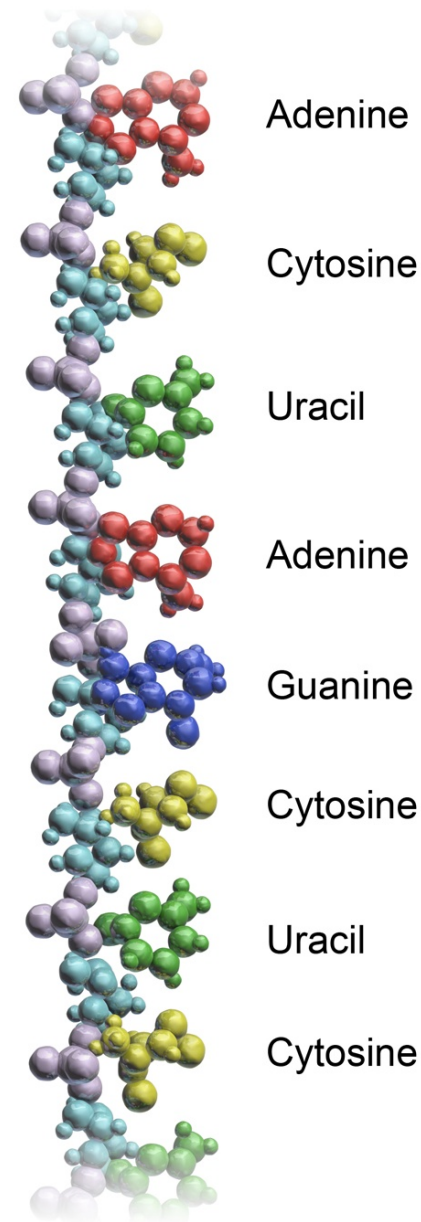
# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Introduction »

## What is RNA?

- Transcribed from DNA
- Single stranded
- Lengths up to a few thousand nucleotides



**Image:** Blausen.com staff. "Blausen gallery 2014".  
Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010.  
CC BY 3.0, <https://commons.wikimedia.org/>

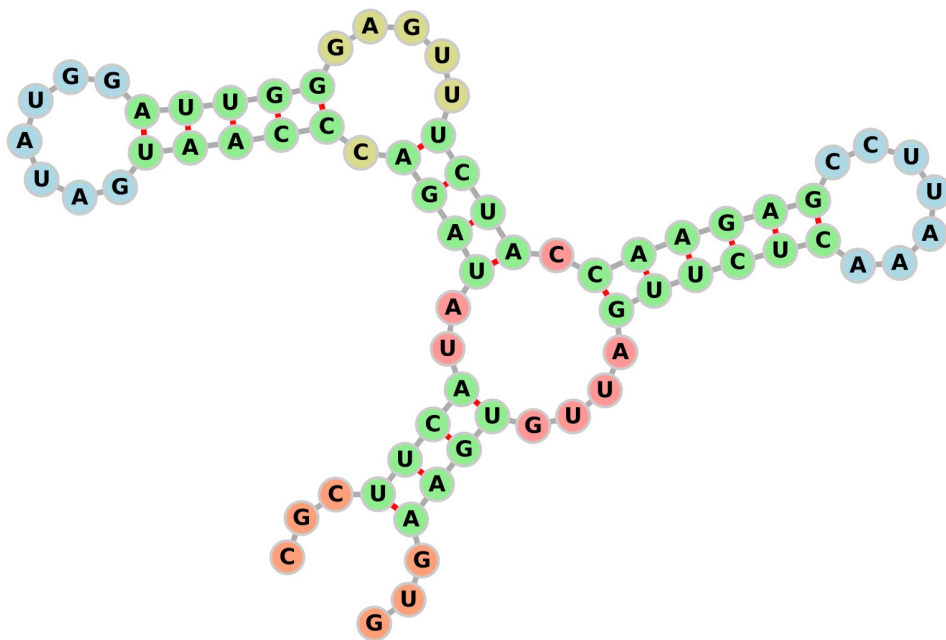
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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Introduction »

RNA secondary structure



- Intramolecular basepairs
- Structure carries function
- Good structure prediction algorithms

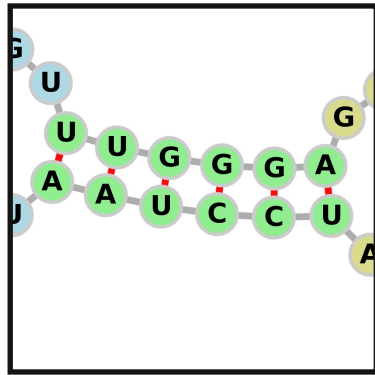
RNA secondary structure

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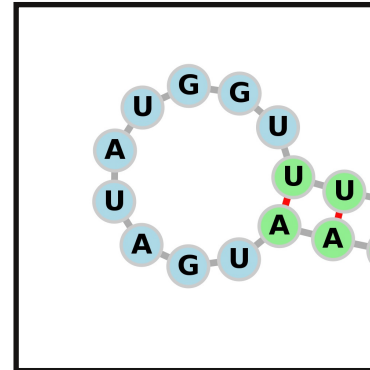


Introduction »

RNA structural elements

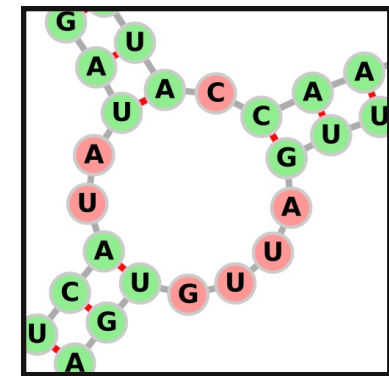
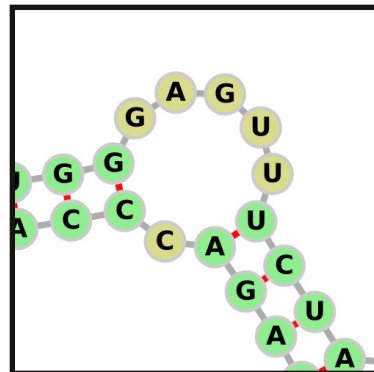


Stem



Hairpin

Interior loop



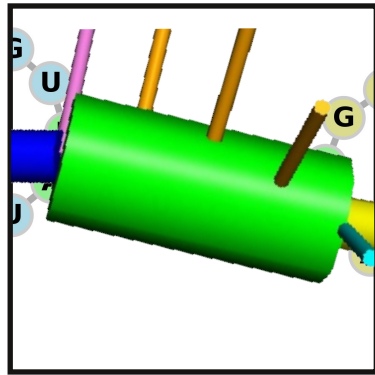
Multiloop

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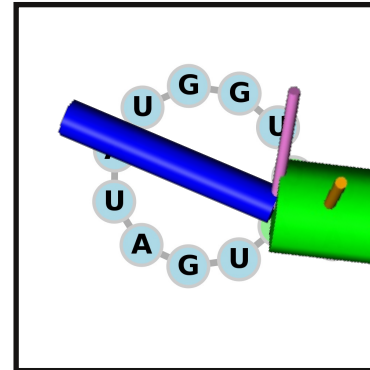


Introduction »

RNA structural elements

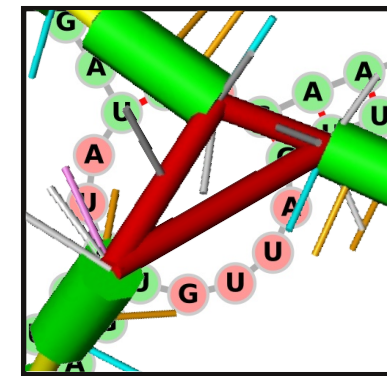
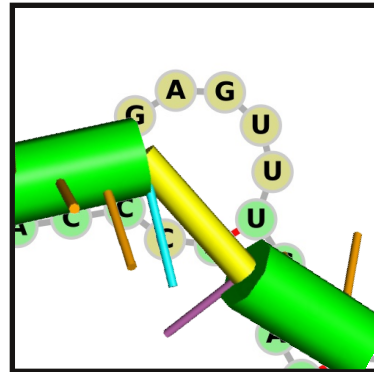


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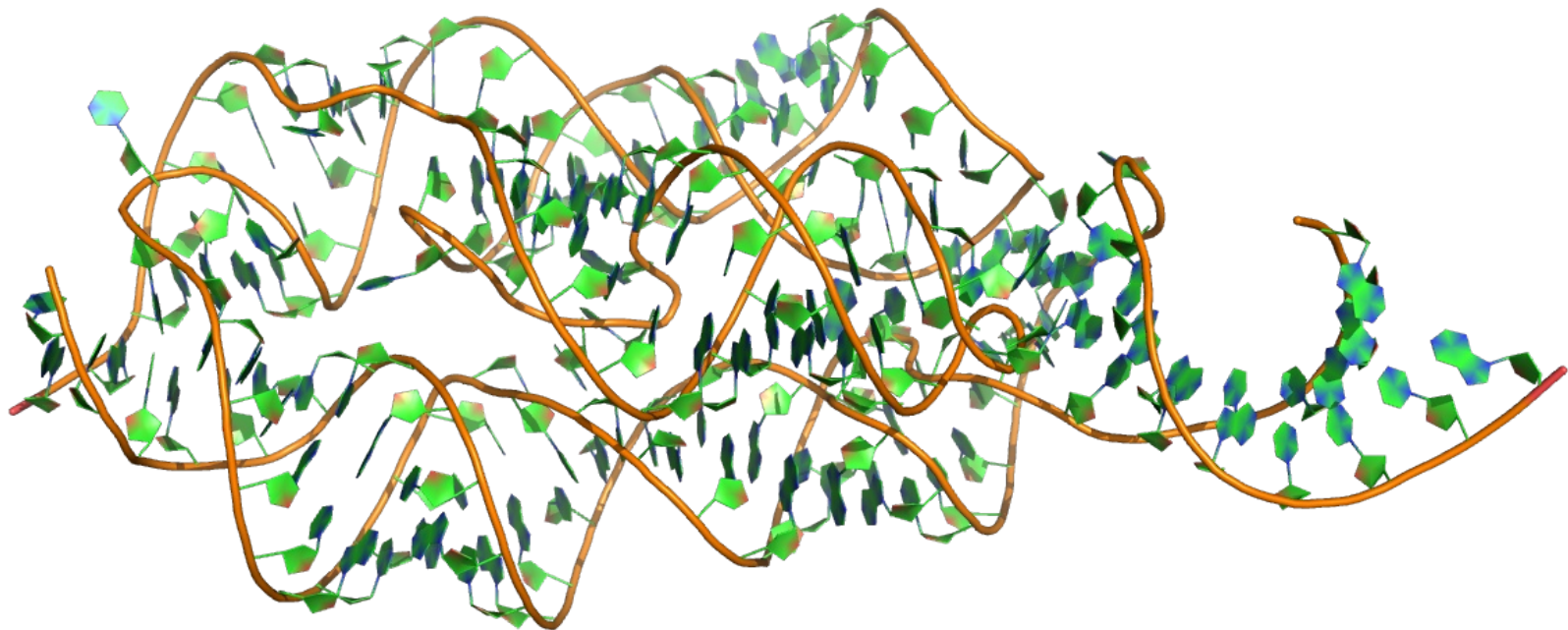
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Introduction »

3D structure

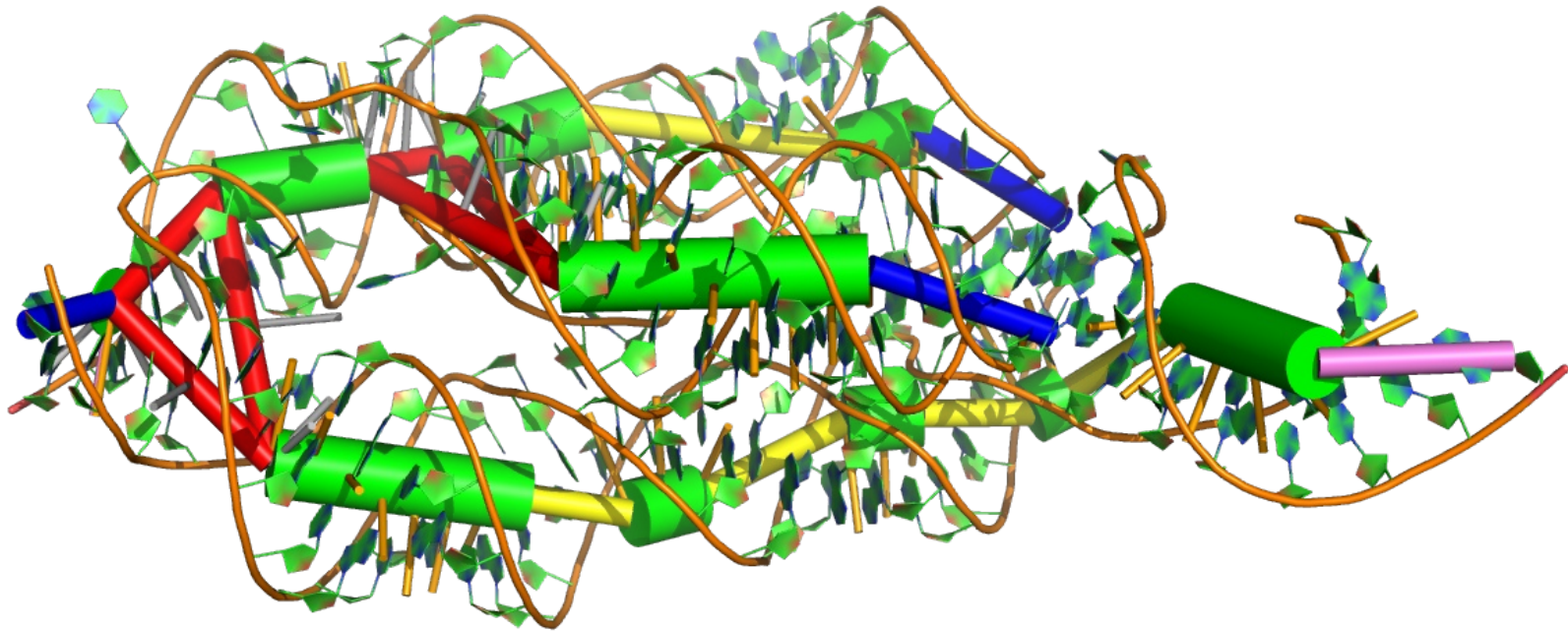


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Introduction »

Coarse grained 3D structure



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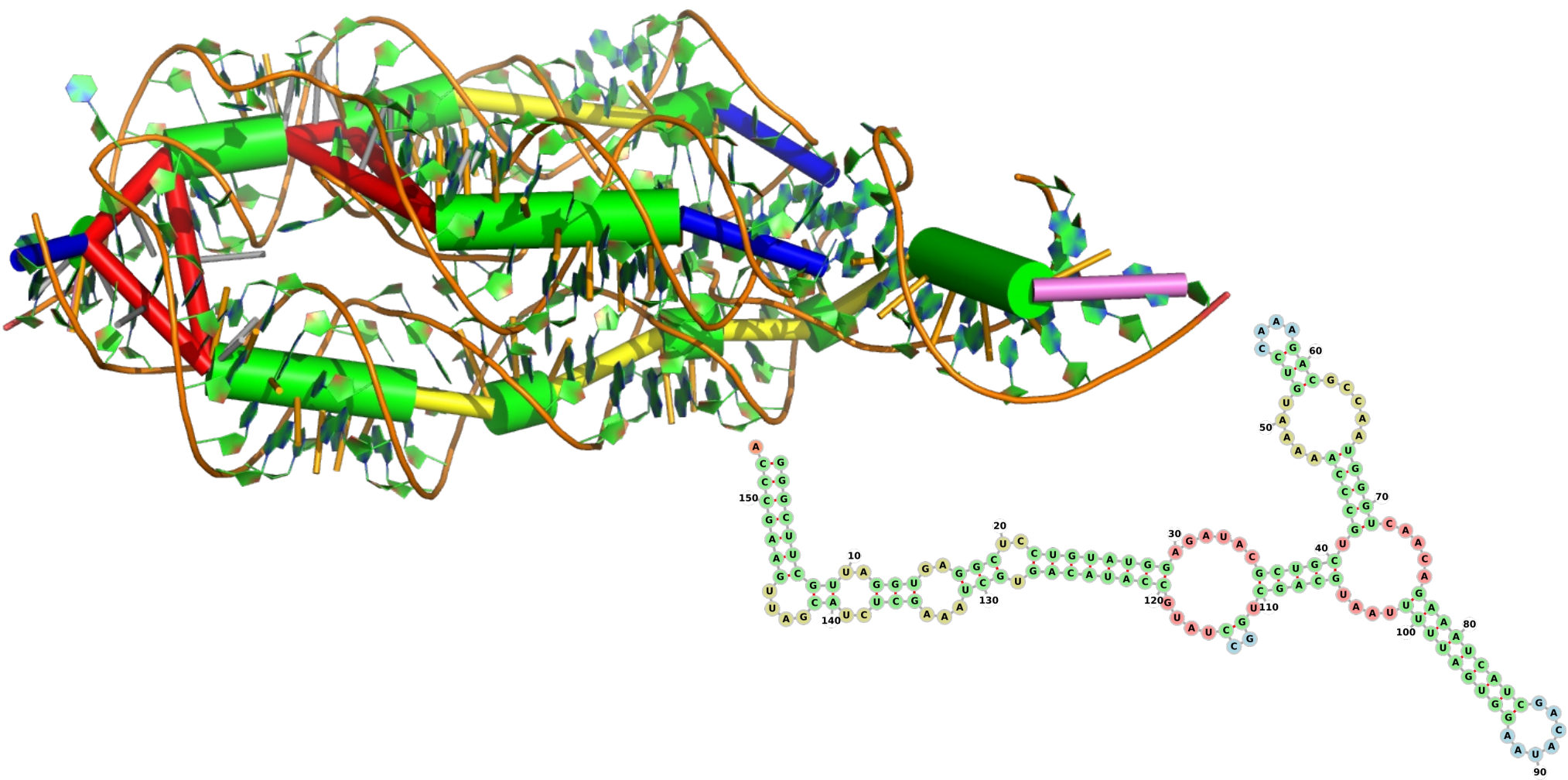


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Introduction »

Coarse grained 3D structure



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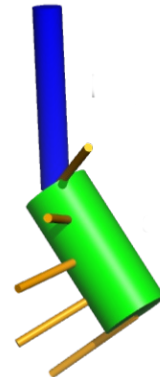
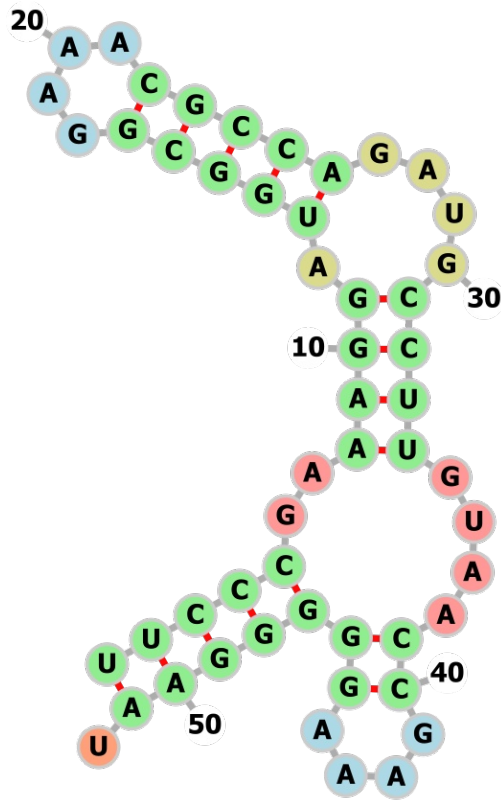
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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Ernwin »

Building a structure

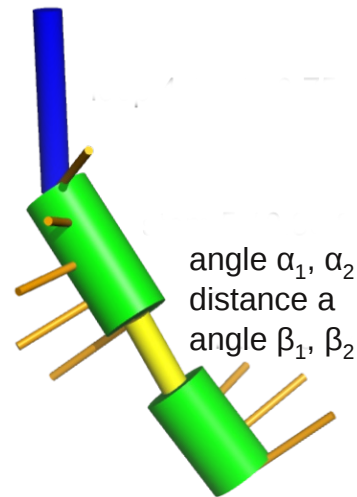
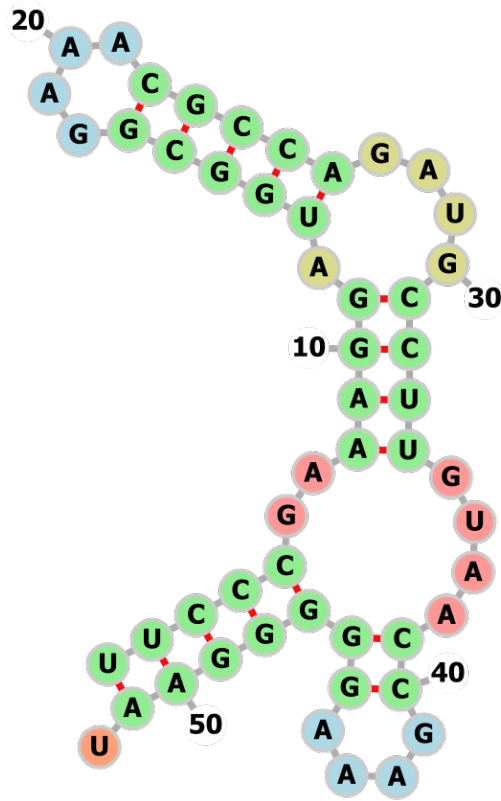


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Ernwin »

Building a structure

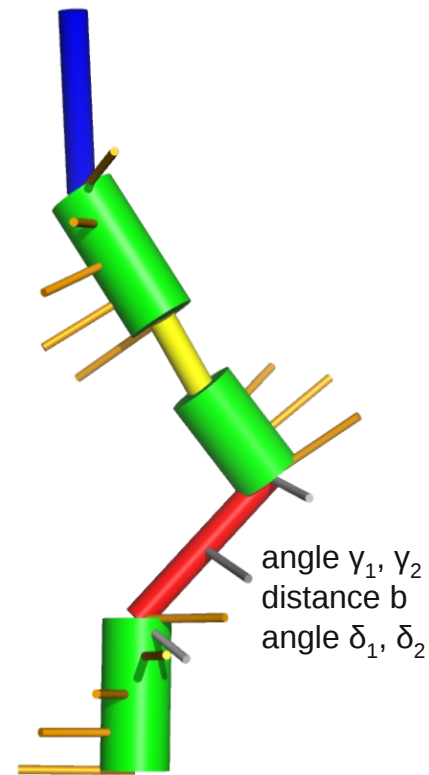
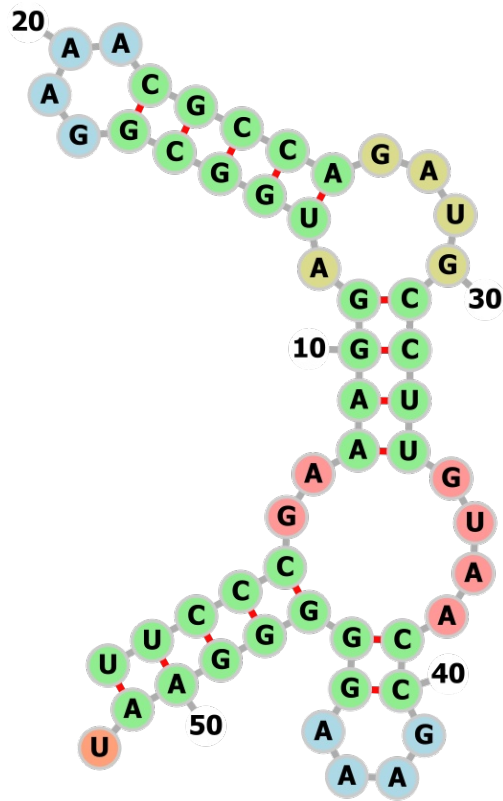


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Ernwin »

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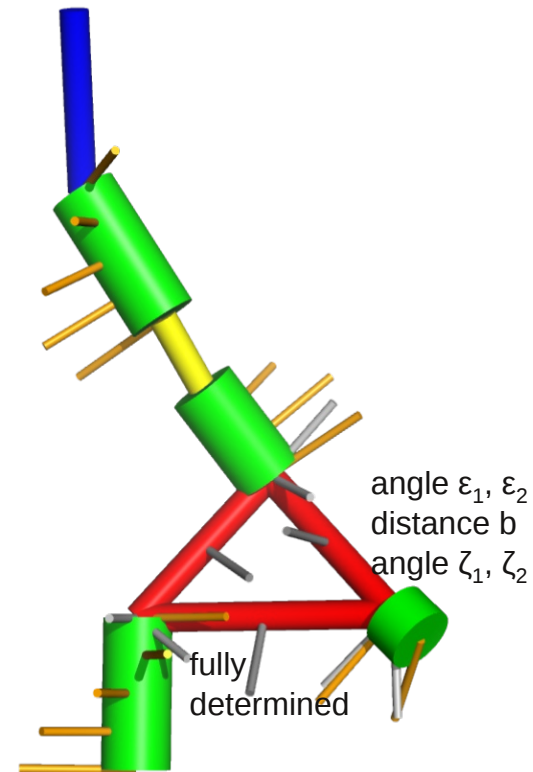
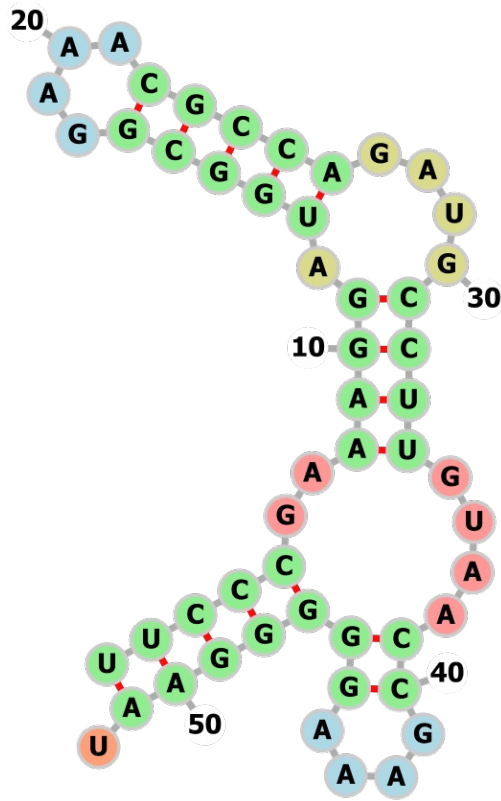


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Ernwin »

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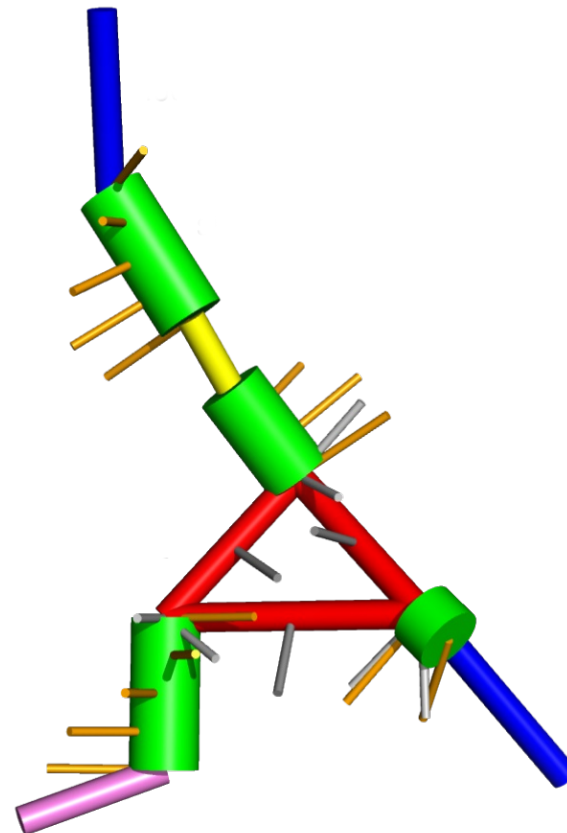
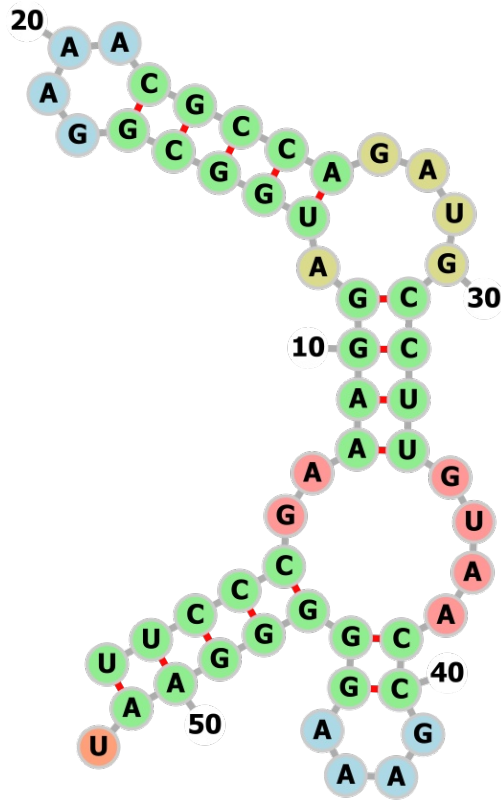


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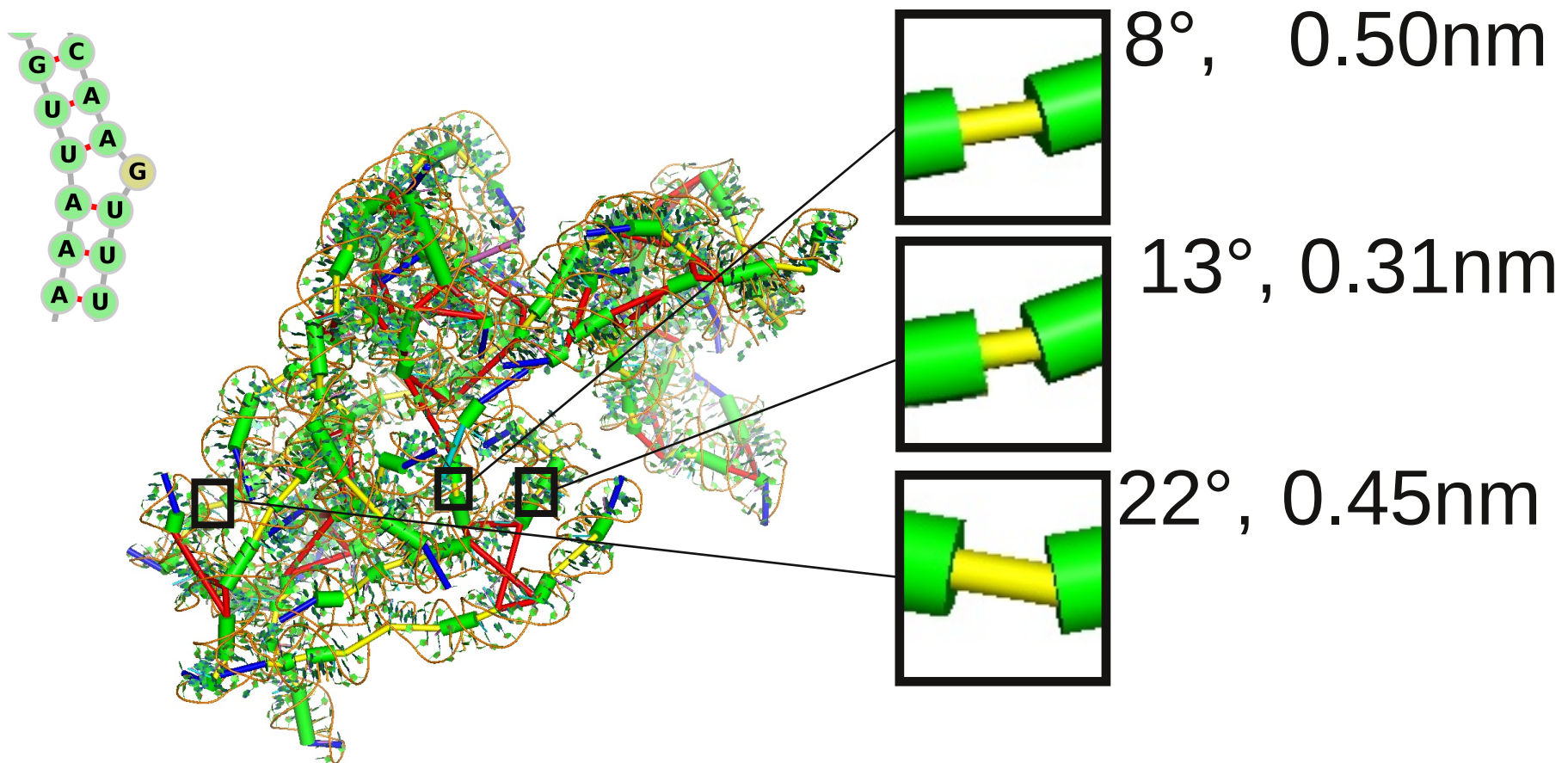
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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Ernwin »

Structure sampling



Sample length and angle from known structures

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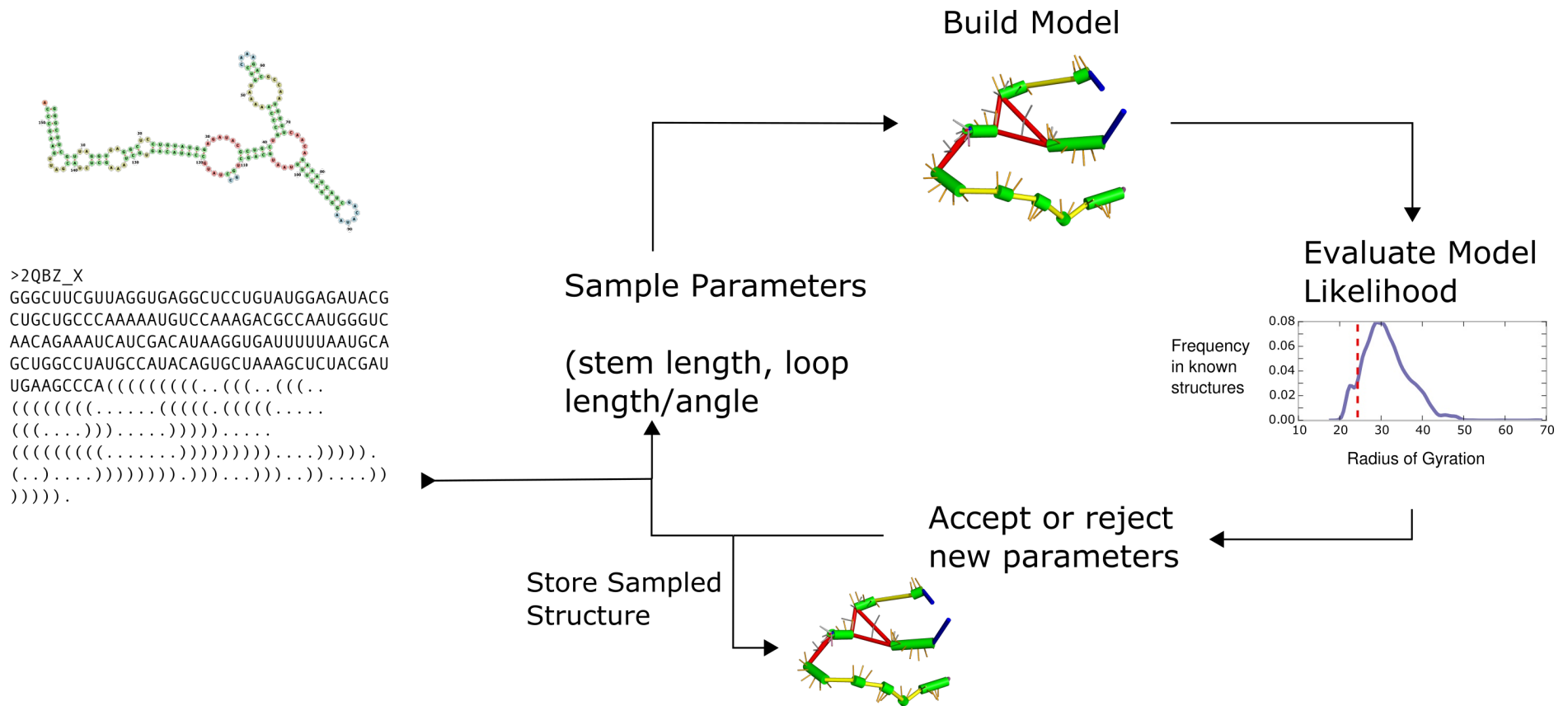


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Ernwin »

Metropolis-Rosenbluth Monte Carlo

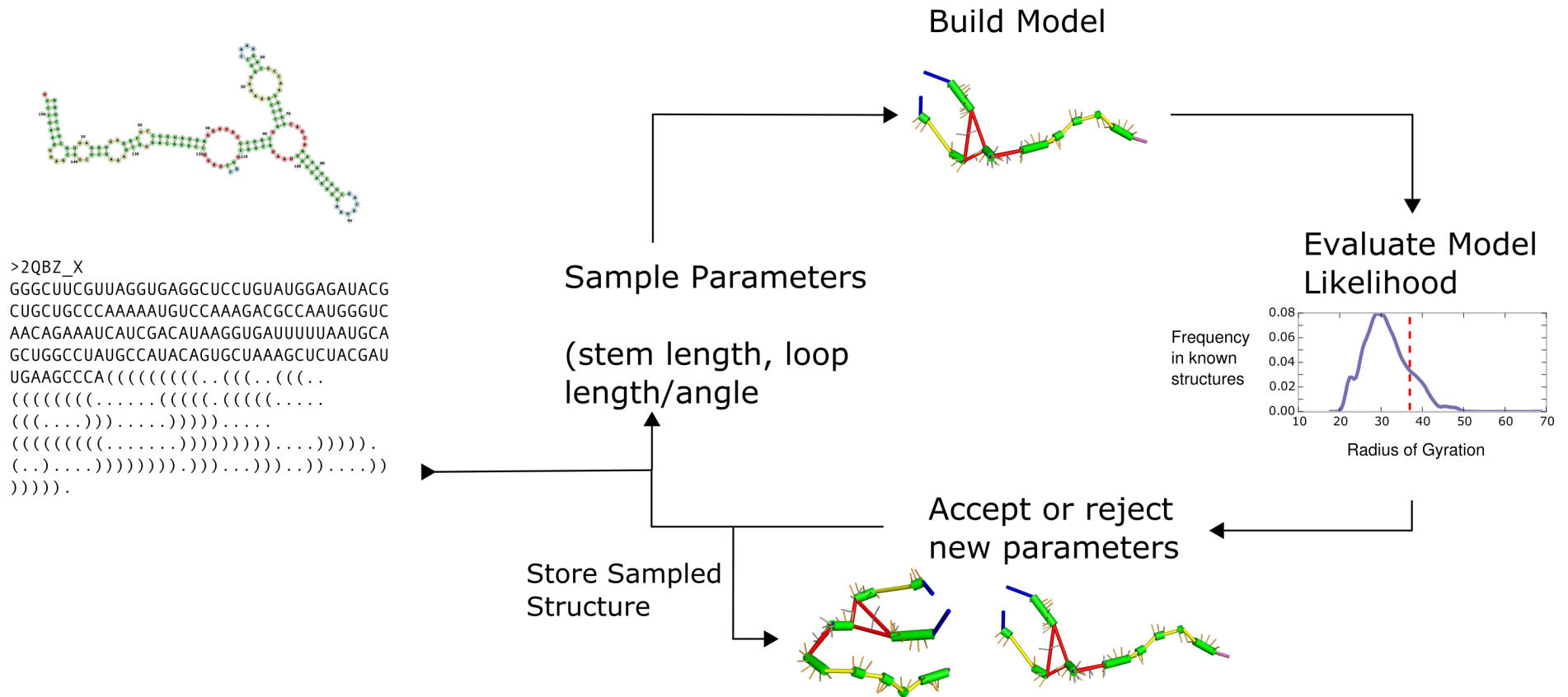


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Ernwin »

Metropolis-Rosenbluth Monte Carlo

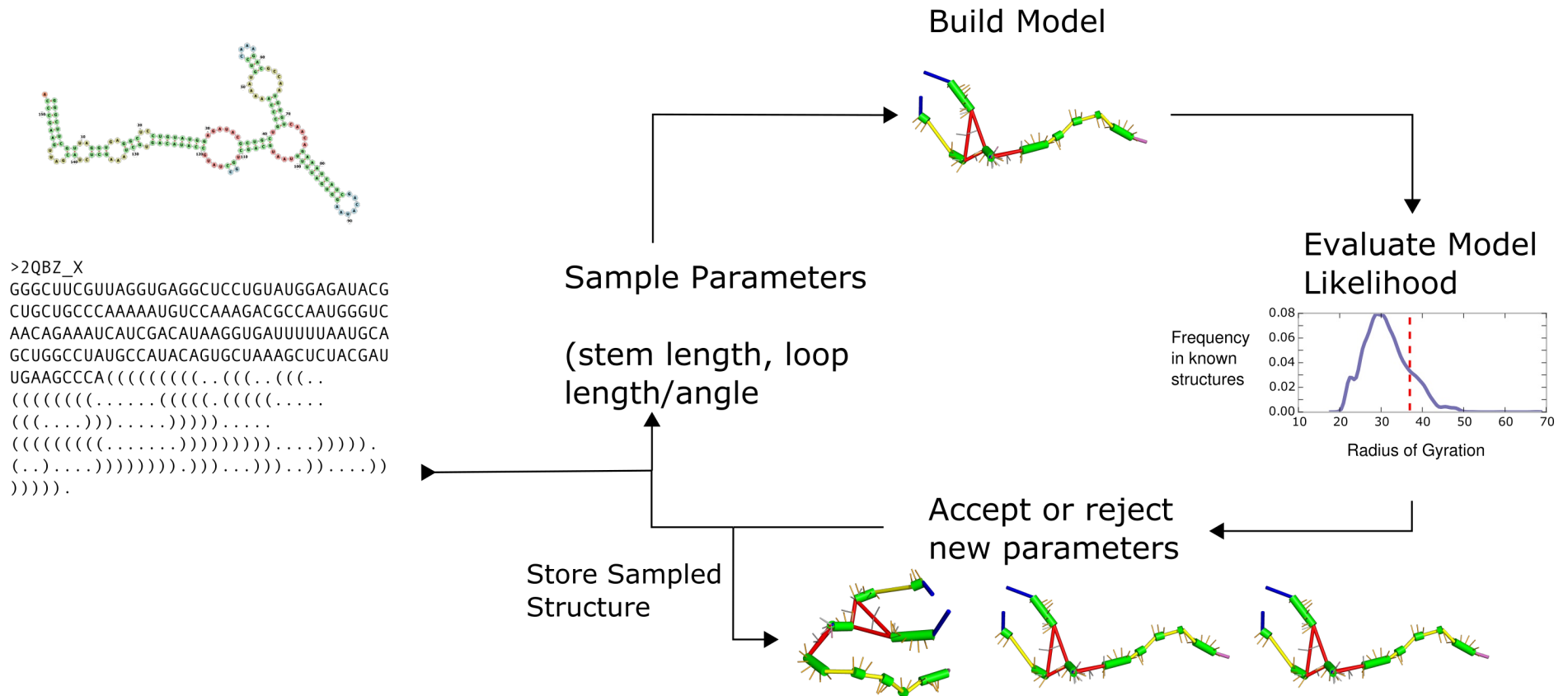


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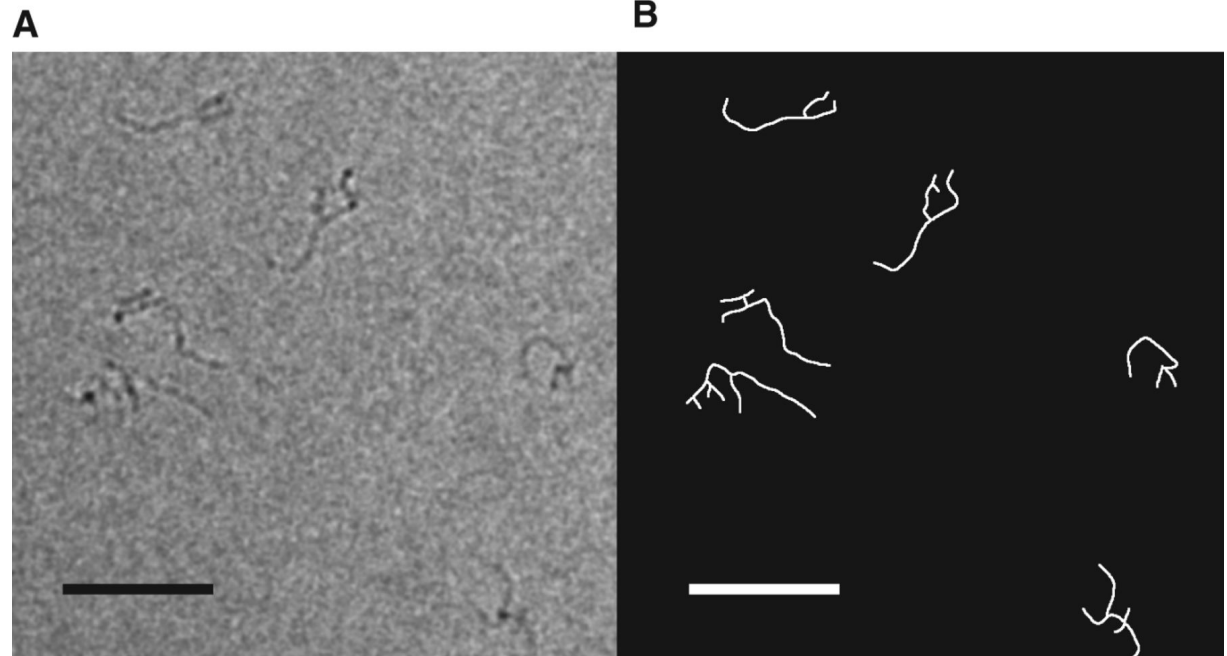
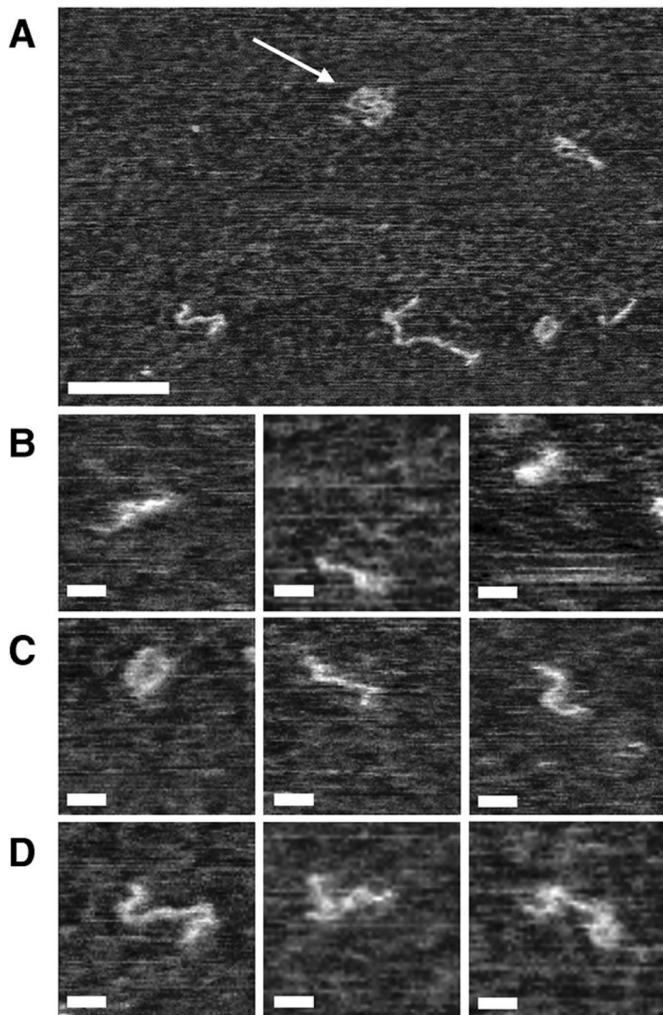
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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Projections »

AFM & Cryo-EM



Rees F. Garmann et al. RNA 2015;21:877-886

Sonja Petkovic et al.  
RNA 2015; 21: 1249-1260

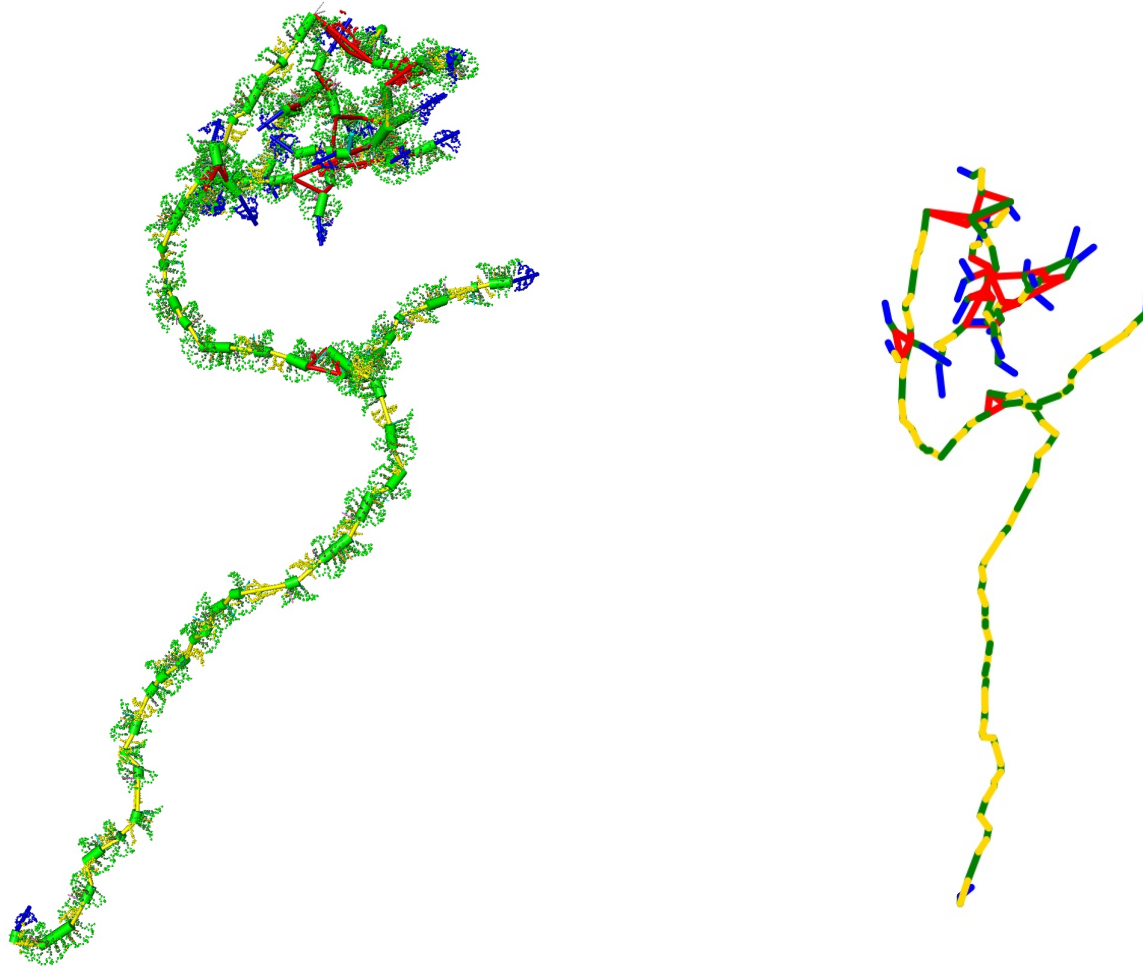
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# Integrating Cryo-EM with Coarse Grained RNA 3D Structure Prediction in ERNWIN



Projections »

Generating 2D projections

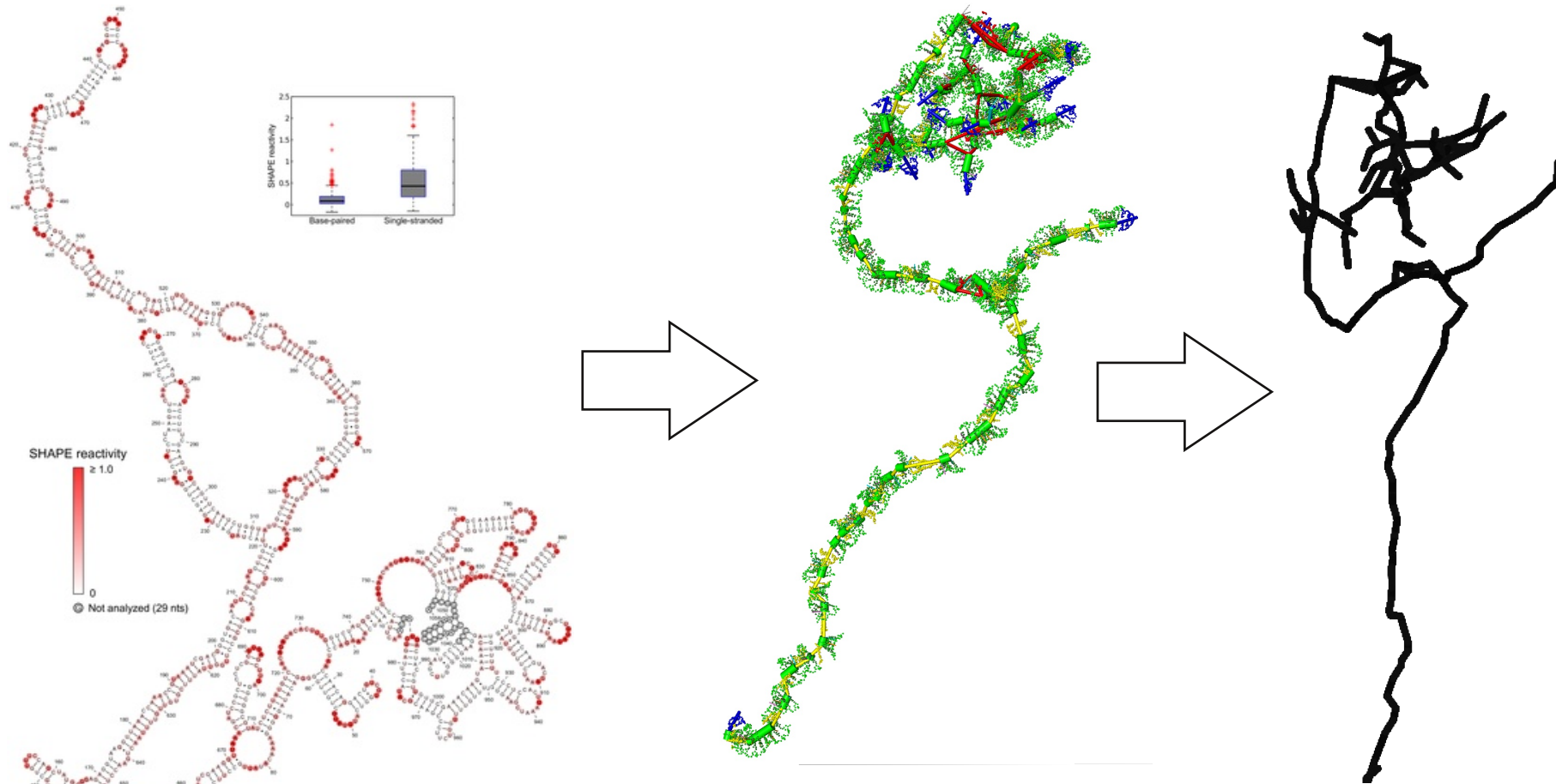


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Projections »

2D -> 3D -> 2D



## Sattelite Tobacco Mosaic Virus

Athavale SS, Gossett JJ, Bowman JC, Hud NV,  
Williams LD, et al. (2013) PLoS ONE 8(1): e54384.

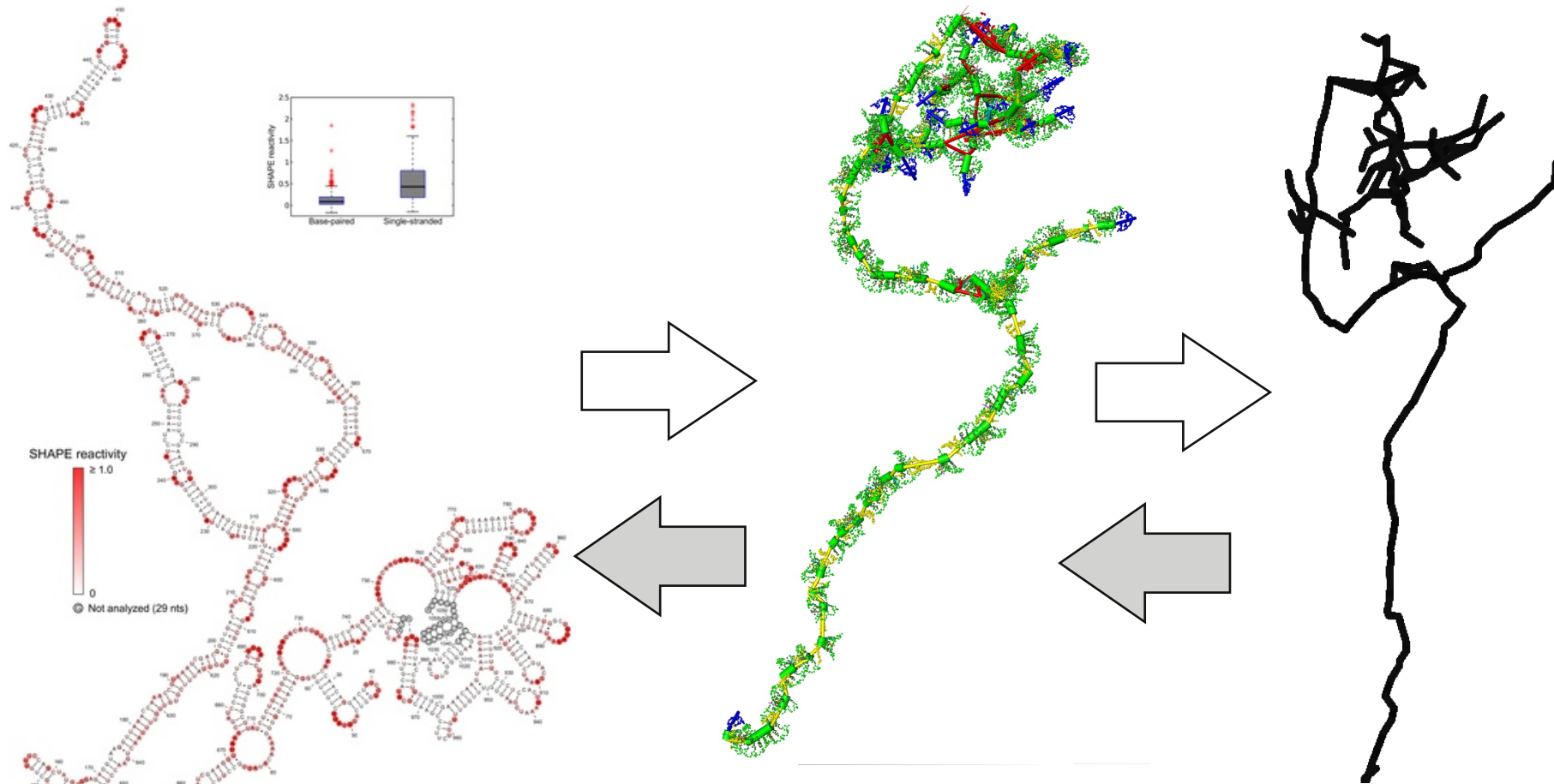
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Projections »

2D <- 3D <- 2D



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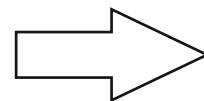
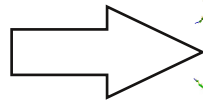
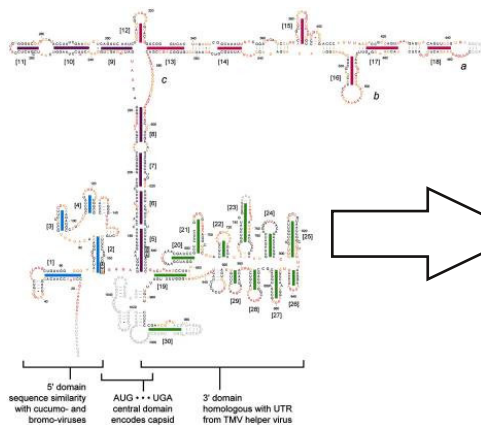
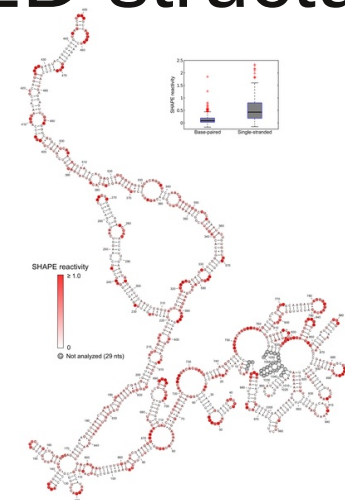
Projections »

Our Approach

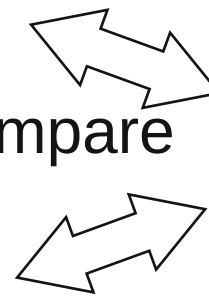
2D structure

3D model

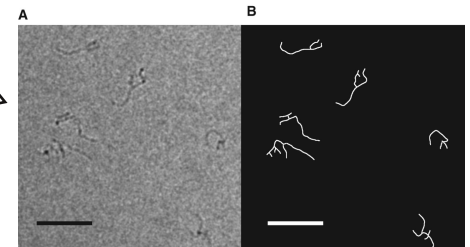
Projection



Compare



Experiment



## 2D Structures:

**Top:** Athavale SS, Gossett JJ, Bowman JC, Hud NV, Williams LD, et al. (2013) PLoS ONE 8(1): e54384.

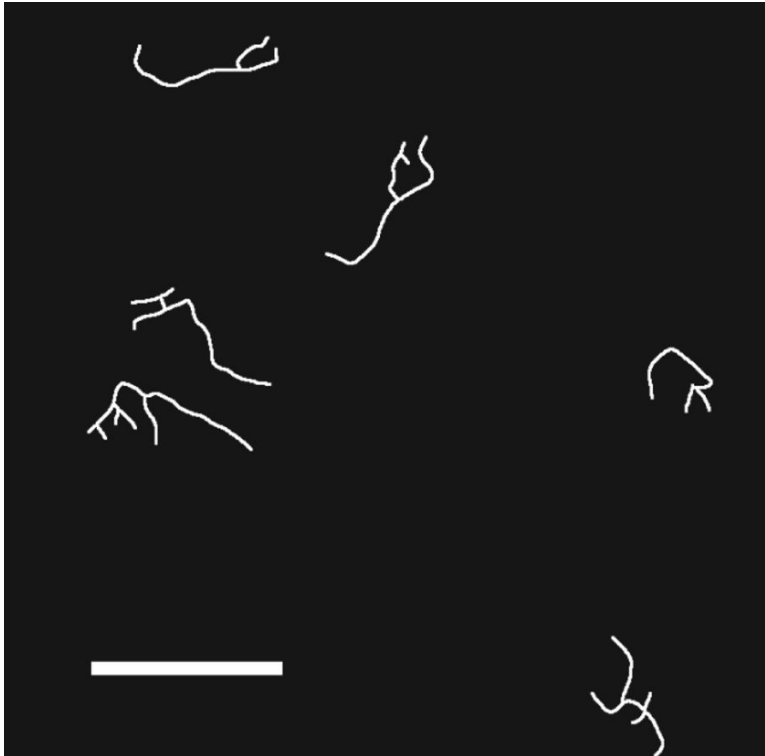
**Bottom:** Eva J. Archer; Mark A. Simpson; Nicholas J. Watts et al. Biochemistry 2013, 52, 3182-3190.

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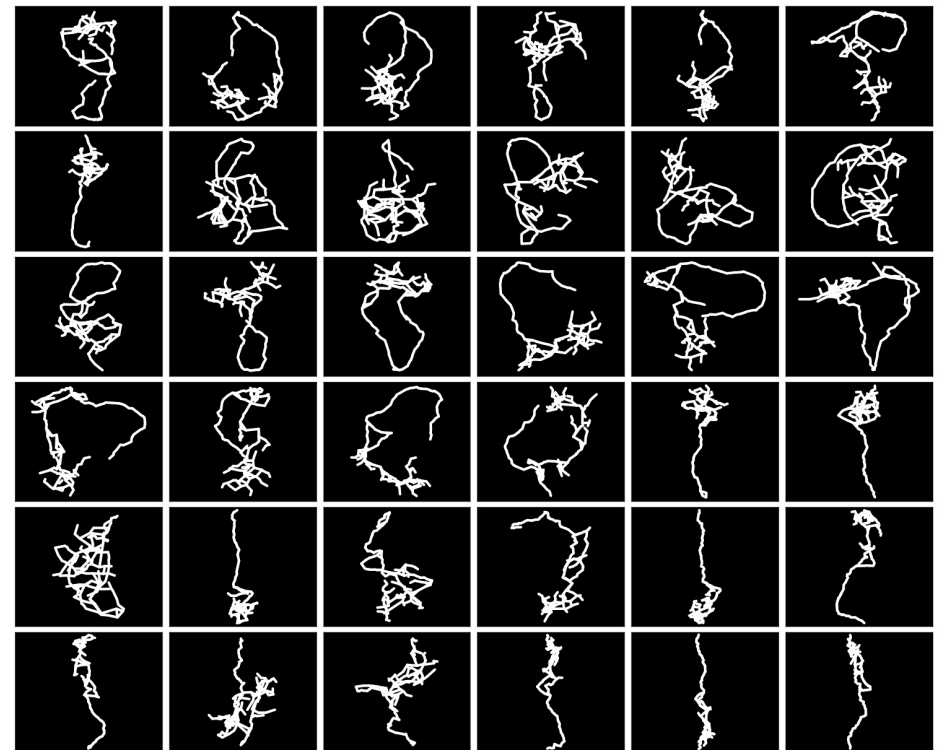


Projections »

Comparing Projections



Rees F. Garmann et al. RNA 2015;21:877-886



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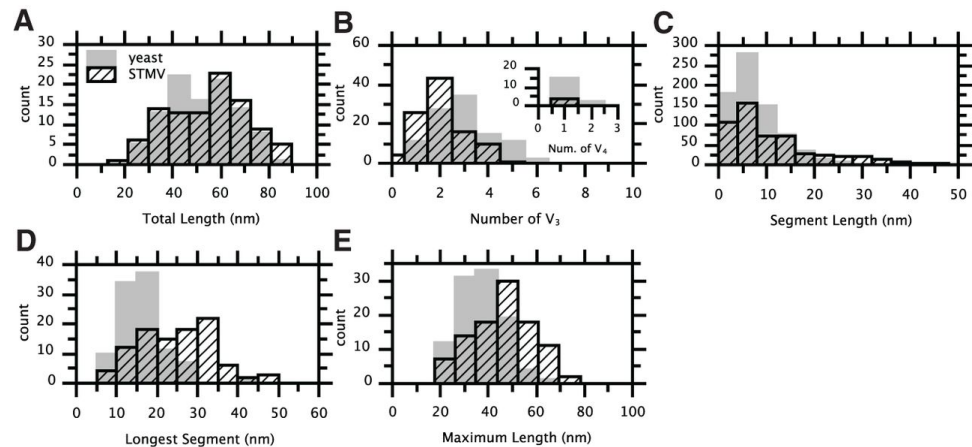
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Projections »

Comparing Projections

## Using graph-based descriptors



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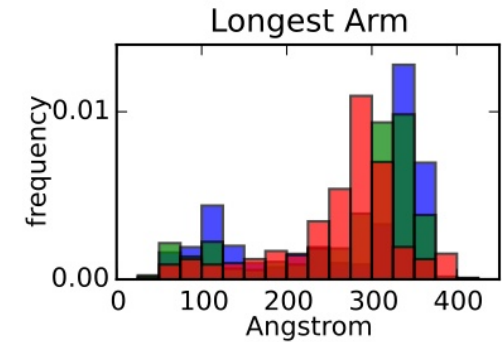
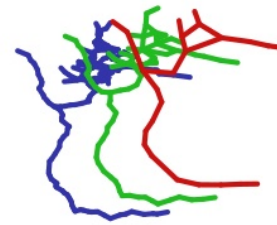
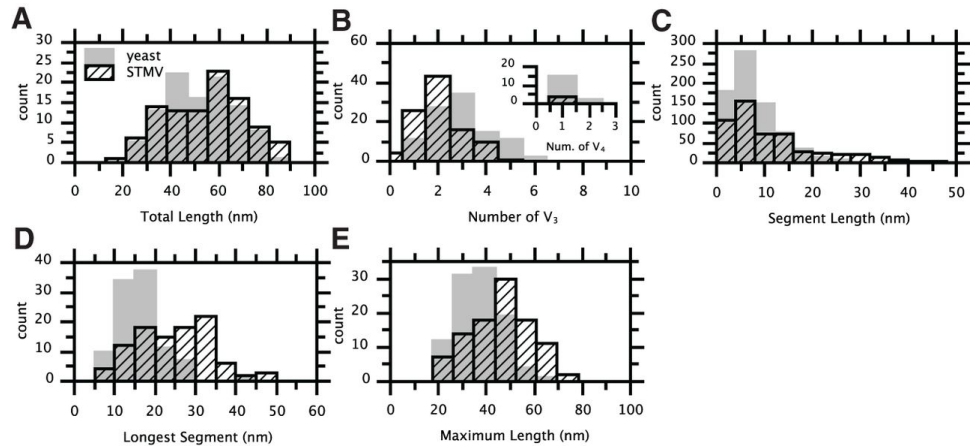
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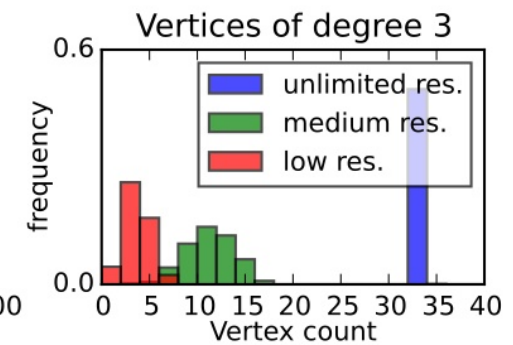
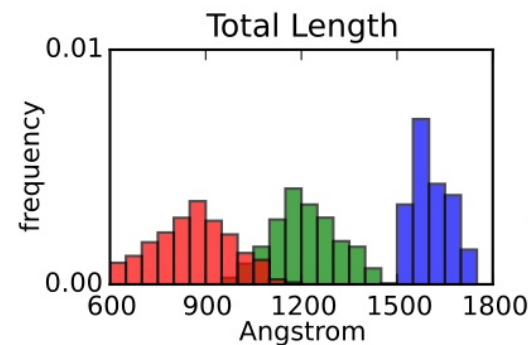
Projections »

Comparing Projections

## Using graph-based descriptors



Rees F. Garmann et al. RNA 2015; 21:877-886



Problem:

Resolution dependency

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Projections »

Comparing Projections

## Hausdorff Distance

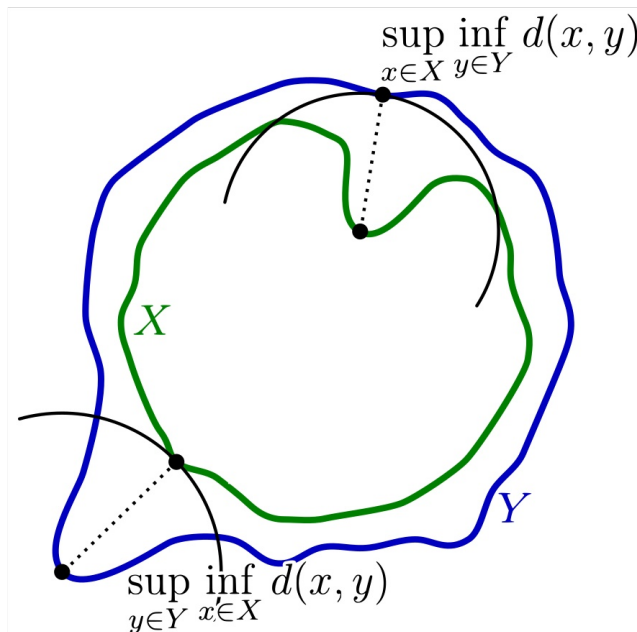


Image: Rocchini/ wikipedia (CC-BY3.0)



?

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Problem:

Rotation and translation

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Projections »

Directing our sampling

Projected Length:

$$a' = a \cdot \cos \psi$$

Angle between vectors:

$$b = \cos(\pi/2 - \psi) = \frac{\vec{a} \cdot \vec{p}}{|\vec{a}| \cdot |\vec{p}|}$$

Trigonometric formula:

$$\cos(\pi/2 - \arccos b) = \sqrt{1 - b^2}$$

Target energy:

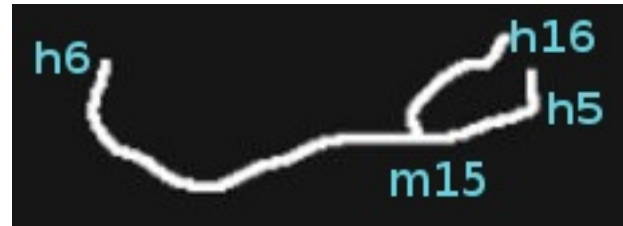
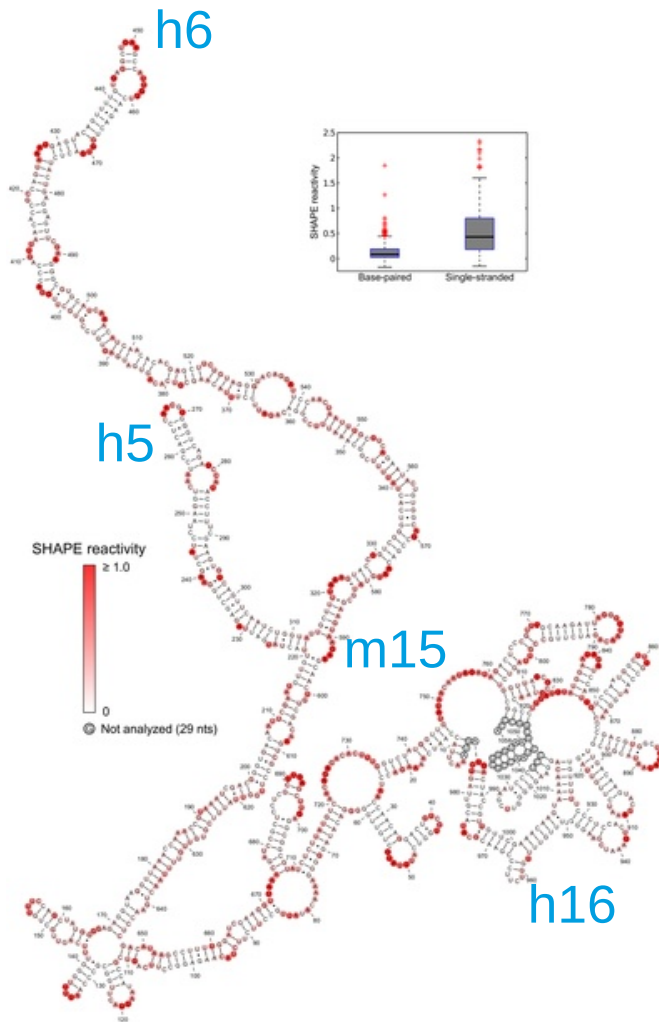
$$\min_{\vec{q} | q=1} \sum_i |(\vec{a}_i \cdot \vec{q})^2 - (a_i^2 - a_i'^2)|$$

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Projections »

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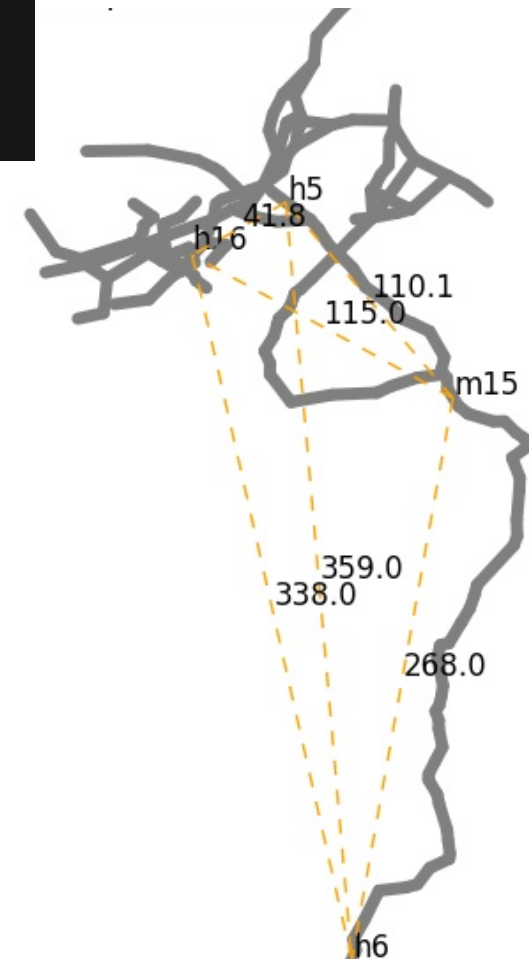
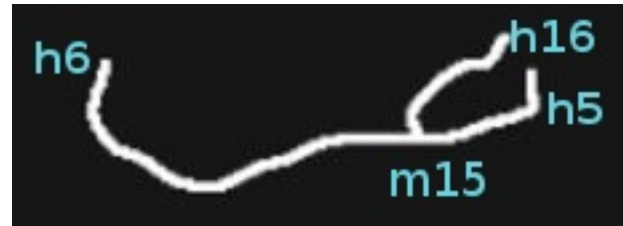
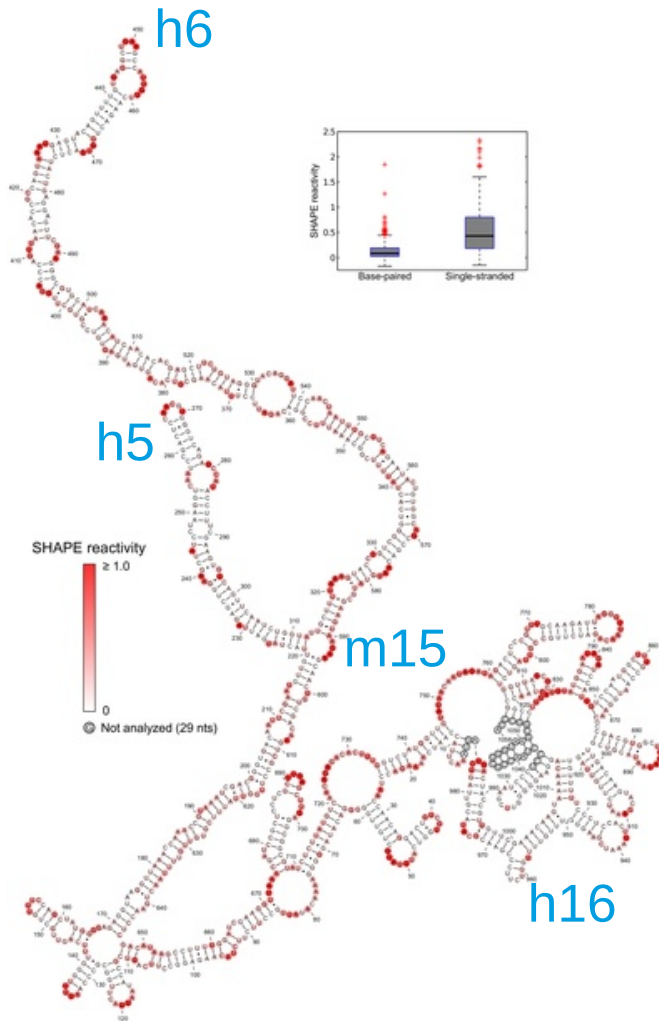


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Projections »

Directing our sampling





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## Conclusion & Outlook

- EM images help to improve  
3D structure prediction
- Coarse grained structure prediction helps  
interpret EM images
- Goal: Score match between secondary  
structure and image

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## Acknowledgement

- Peter Kerpedjiev
- Ivo Hofacker
- Colleagues at the TBI

FWF

DK  
rna  
Biology