

# Predicting a lncRNA 3D structure with the help of SAXS data

B. Thiel

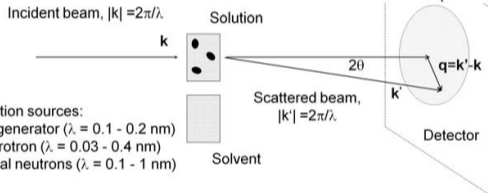
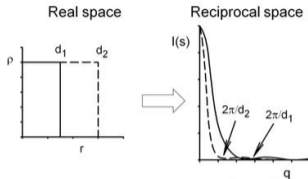
11 Feb 2019, TBI Winterseminar Bled



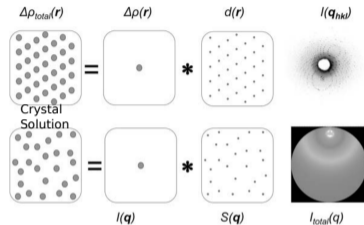




# Scattering by macromolecules



Radiation sources:  
 X-ray generator ( $\lambda = 0.1 - 0.2$  nm)  
 Synchrotron ( $\lambda = 0.03 - 0.4$  nm)  
 Thermal neutrons ( $\lambda = 0.1 - 1$  nm)



- ▶ Fixed intramolecular distances
- ▶ Variable intermolecular distances
- ▶  $|q| = q = \frac{4\pi}{\lambda} \sin \theta$

Predicting a  
 IncRNA 3D  
 structure with the  
 help of SAXS data

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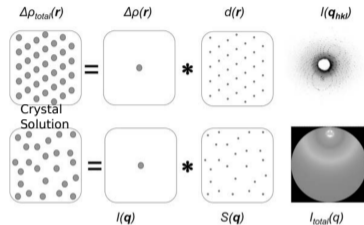
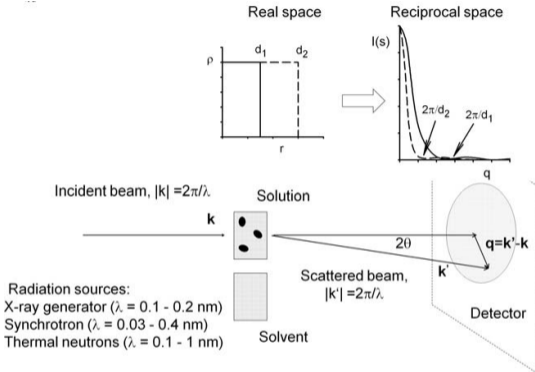
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# Scattering by macromolecules

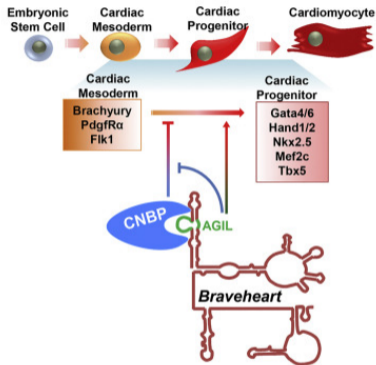


- ▶ Fixed intramolecular distances
- ▶ Variable intermolecular distances
- ▶  $|\mathbf{q}| = q = \frac{4\pi}{\lambda} \sin \theta$

# Scattering in solution

- ▶ Spherical average
- ▶ Effect of background
- ▶ Effect of hydration shell

# The RNA bvht



- ▶ found in mouse
- ▶ related to heart

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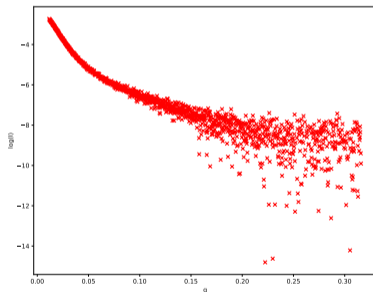
Summary

- ▶ Collaboration with  
Karissa Y.  
Sanbonmatsu,  
Doo Nam Kim  
and Patel Trushar

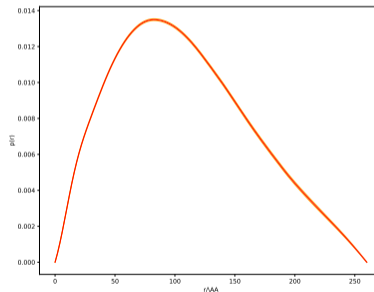


# Experimental SAXS data

- ▶  $I(q)$ : Intensity as a function of the momentum transfer (or angle)



- ▶  $p(r)$ : Distribution of electron-electron distances



# Pipeline

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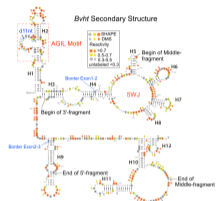
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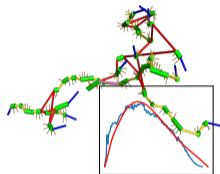
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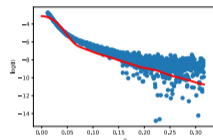
**SHAPE**  
RNAfold  
manual folding



**ERNWIN**  
match  $p(r)$   
of ensemble



**clustering**  
selection of  
structures



**CRY SOL**<sup>1,2</sup>  
validate  
 $I(q)$

<sup>1</sup>Franke et al, IUCr 2017, doi: 10.1107/s1600576717007786

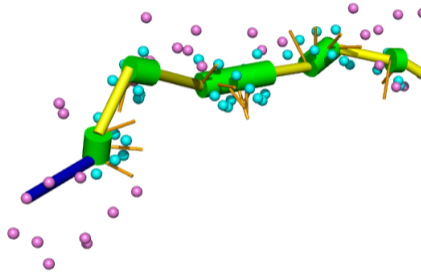
<sup>2</sup>Svergun et al, IUCr 1995, doi: 10.1107/s0021889895007047

# Ernwin sampling

- ▶ ignore hydration shell
- ▶ use 1 point per residue

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- ▶ ignore hydration shell
- ▶ use 1 point per residue



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# Ernwin sampling - matching $p(r)$ of ensemble

Predicting a  
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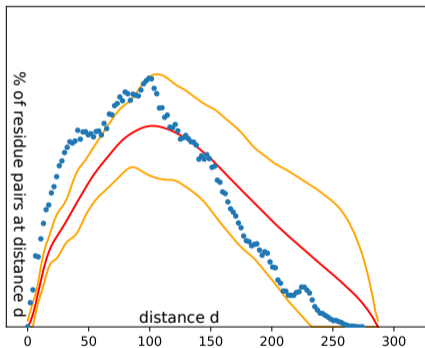
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# Ernwin sampling - matching $p(r)$ of ensemble

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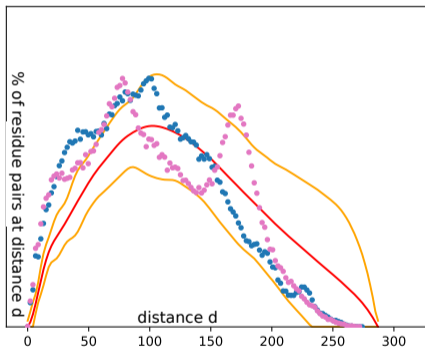
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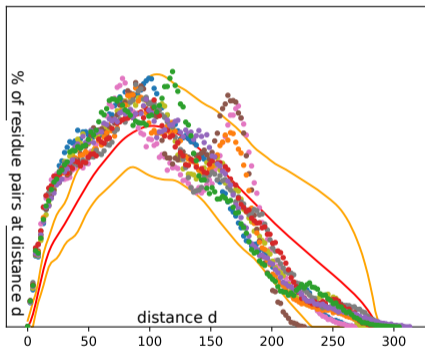
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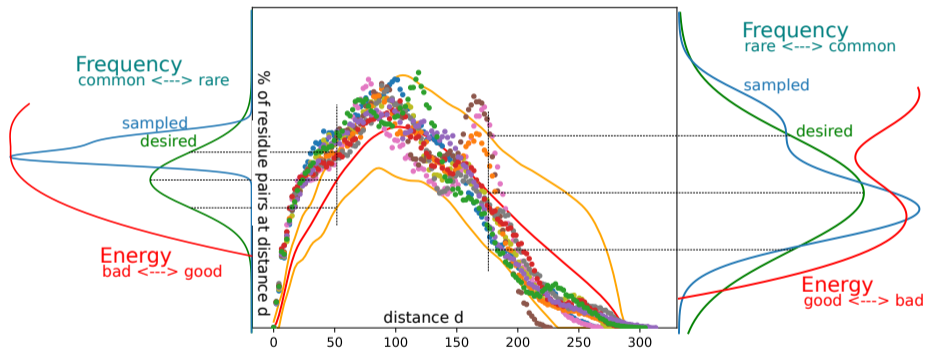
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# Ernwin sampling - matching $p(r)$ of ensemble





# Ernwin sampling - matching $p(r)$ of ensemble

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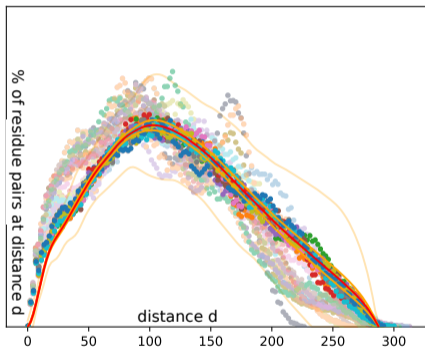
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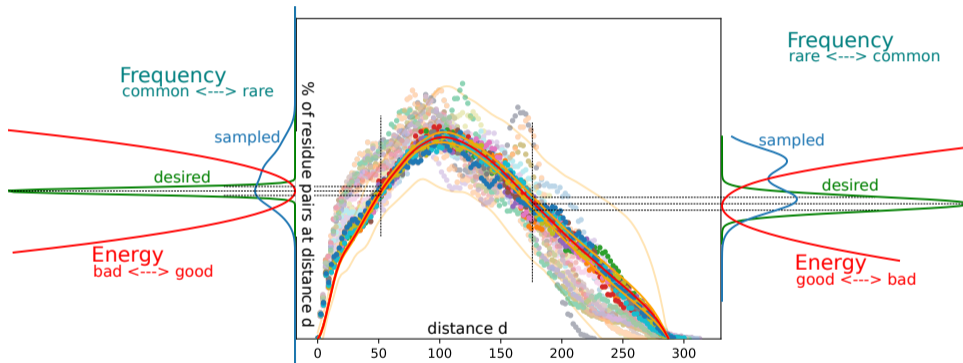
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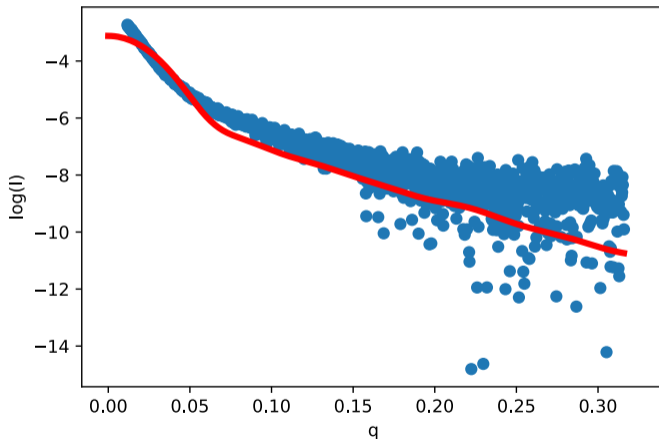
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# Evaluation with CRY SOL<sup>3,4</sup>

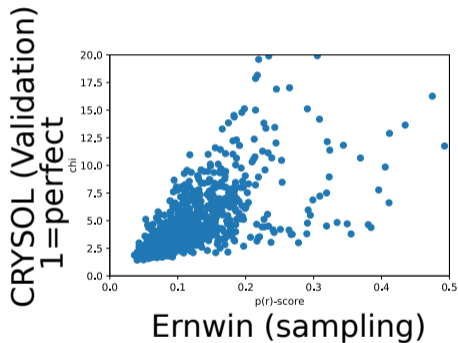
- ▶ all-atom
- ▶ fits contrast of hydration shell to experiment



<sup>3</sup>Franke et al, IUCr 2017, doi: 10.1107/s1600576717007786

<sup>4</sup>Svergun et al, IUCr 1995, doi: 10.1107/s0021889895007047

# Evaluation with CRY SOL



Predicting a  
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# Evaluation with CRY SOL

Predicting a  
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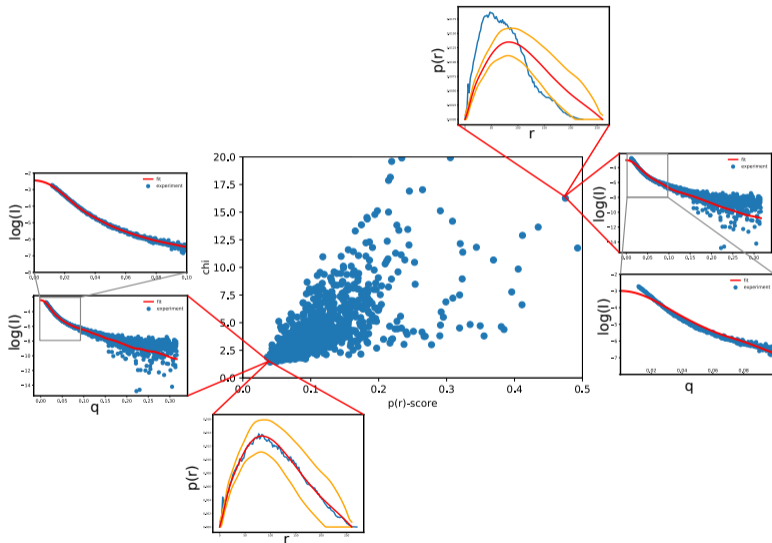
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# Evaluation with CRY SOL

Predicting a  
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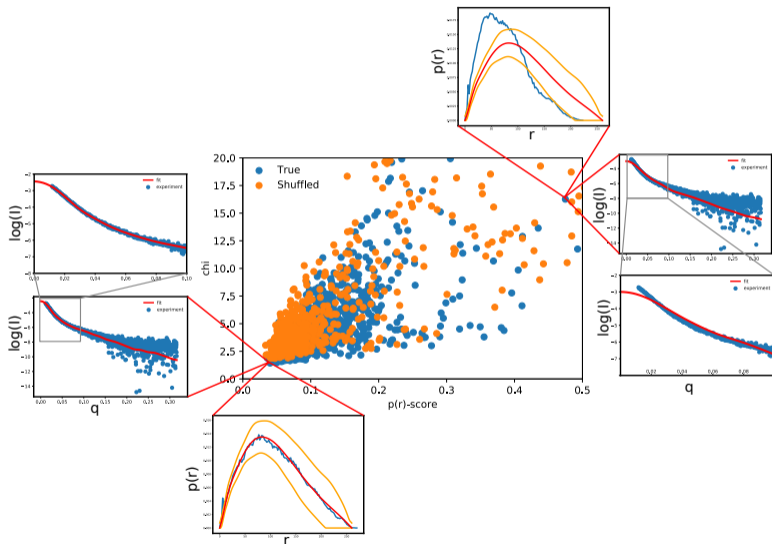
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# Are our predictions good enough?

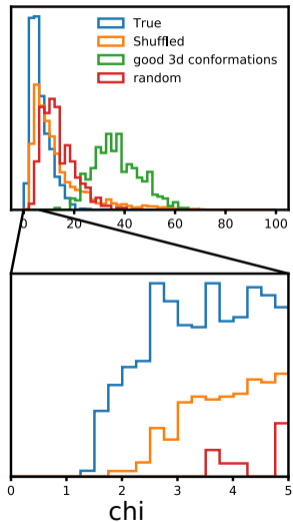
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# Braveheart is strange!

Predicting a  
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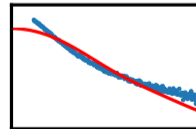
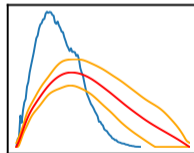
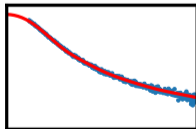
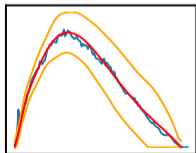
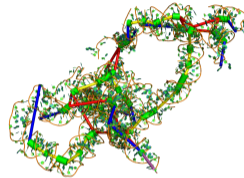
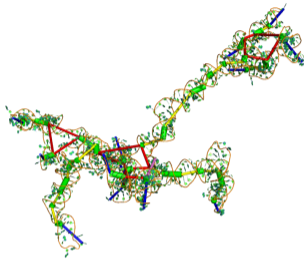
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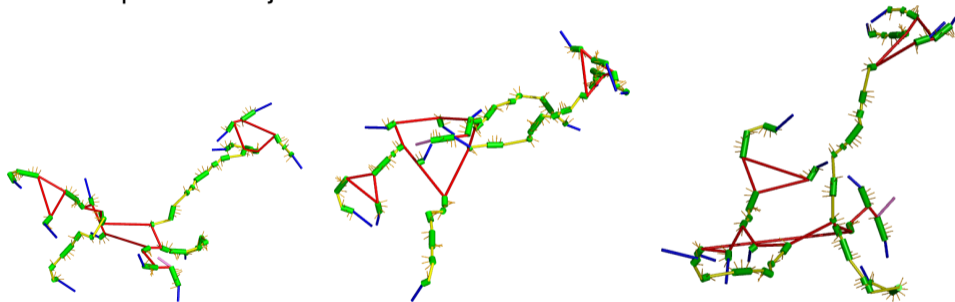
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# Best structures

From independent trajectories



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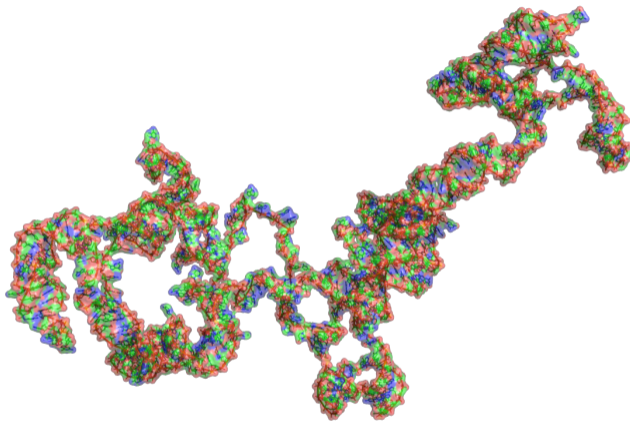
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# Best structure



► Outlook: Try CRY SOL 3.0

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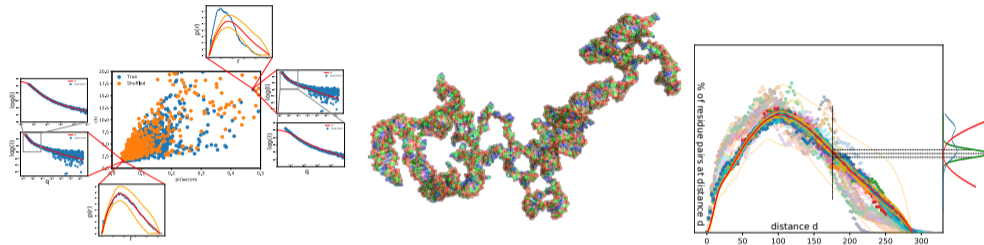
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# Summary and outlook



- ▶ Method to direct sampling towards experimental distance distribution
- ▶ Coarse-grained  $p(r)$ . Not perfect correlation with  $\chi^2$
- ▶ Can get to  $\chi^2$  below 1.5 (correct structure would be 1.1)
- ▶ Generate starting conformations for less coarse-grained approaches