The Meltable Wormlike Chain

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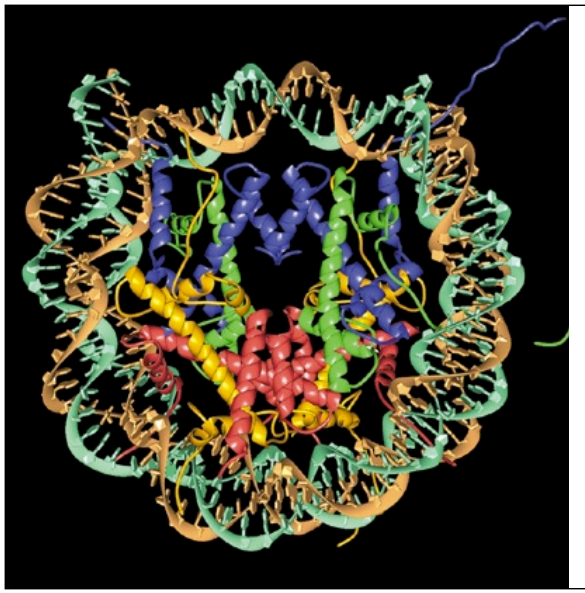
Overview

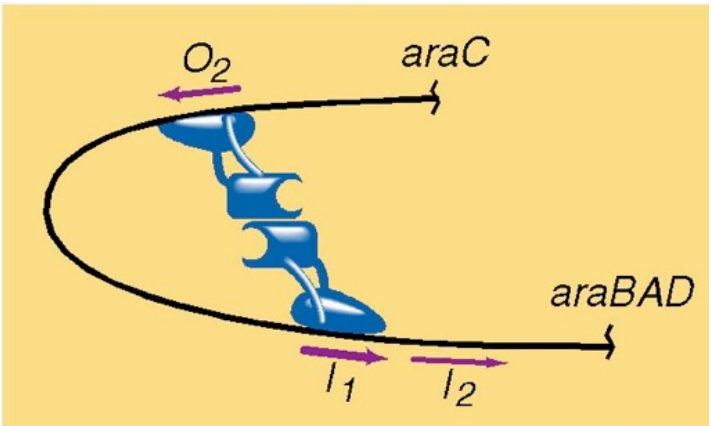
- Measuring DNA Elasticity
- Modelling DNA Elasticity
- Theoretical Advances
- Novel Experimental Methods

DNA Elasticity Matters

- DNA is often tightly bent *in vivo*
  - Eukaryotic packaging in nucleosomes

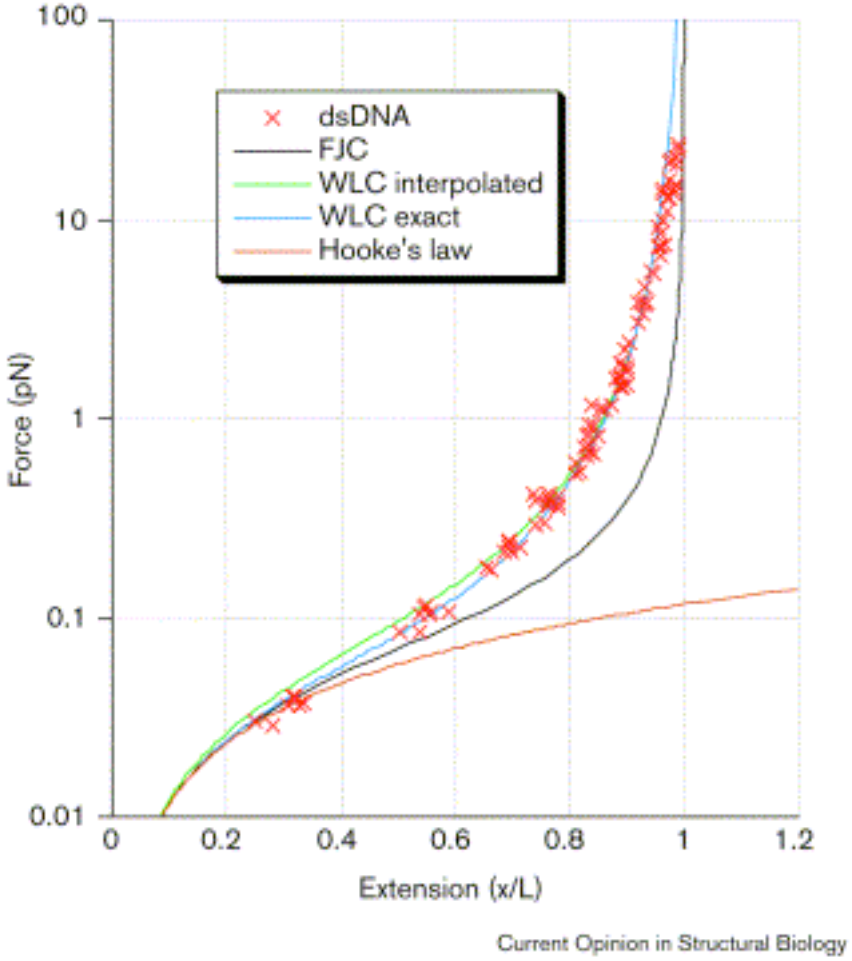


- Details of DNA flexibility influences many cellular processes
  - Transcriptional regulation



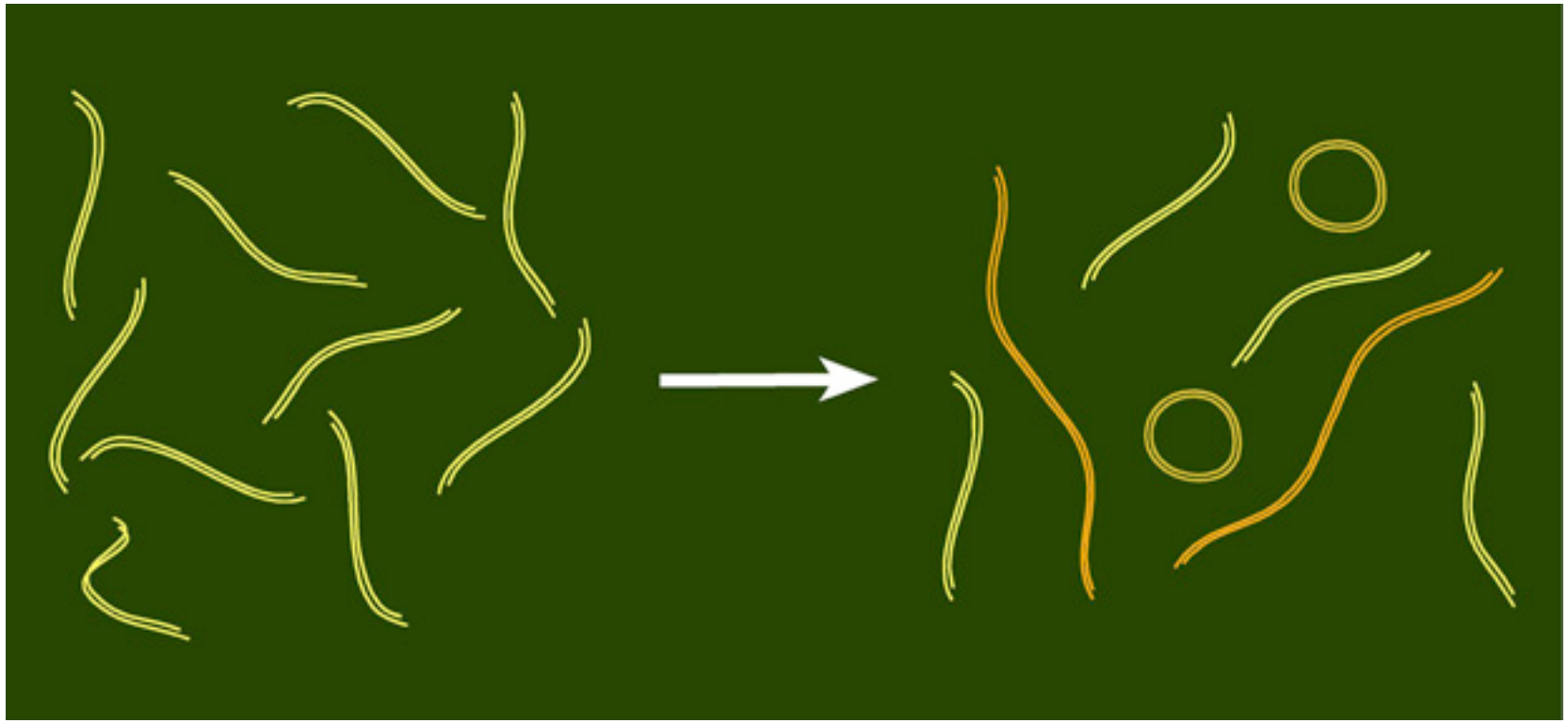
Measuring DNA Elasticity

Single Molecule Force-Extension Works Well For Studying Long DNA

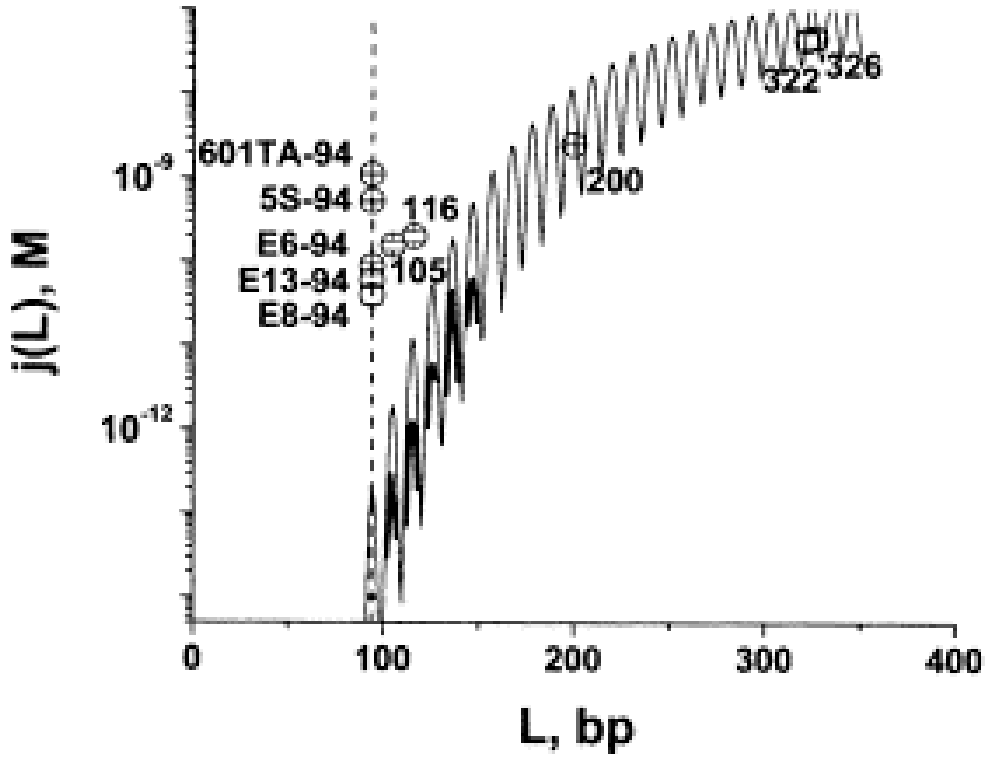


Smith, *et al*, *Science* 1992

Cyclization probes shorter DNA



WLC may break down for small DNA strands

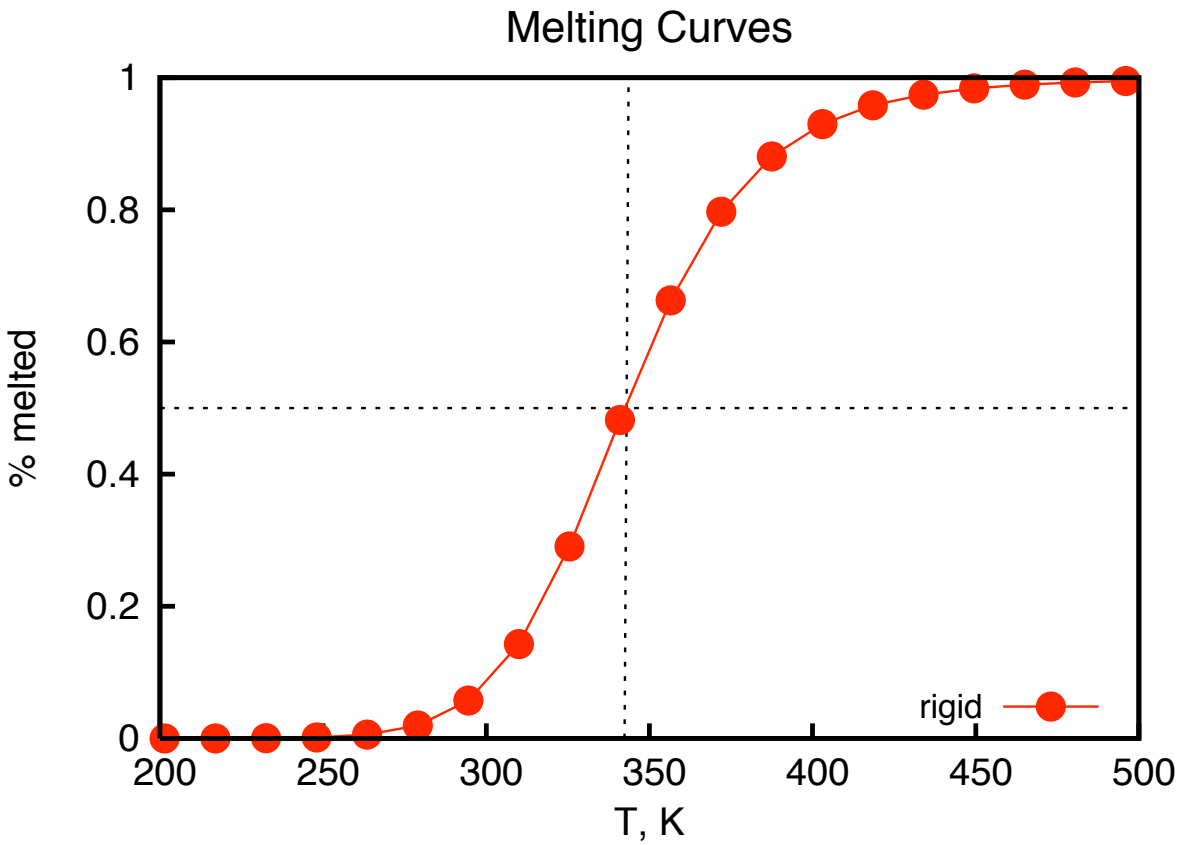


Cloutier & Widom, *Mol Cell* 2004

Modelling DNA Elasticity

Meltable Lattice Models of DNA

- No Sequence Dependence
- No Nearest Neighbor Interactions



Meltable Wormlike Chain (MWLC)

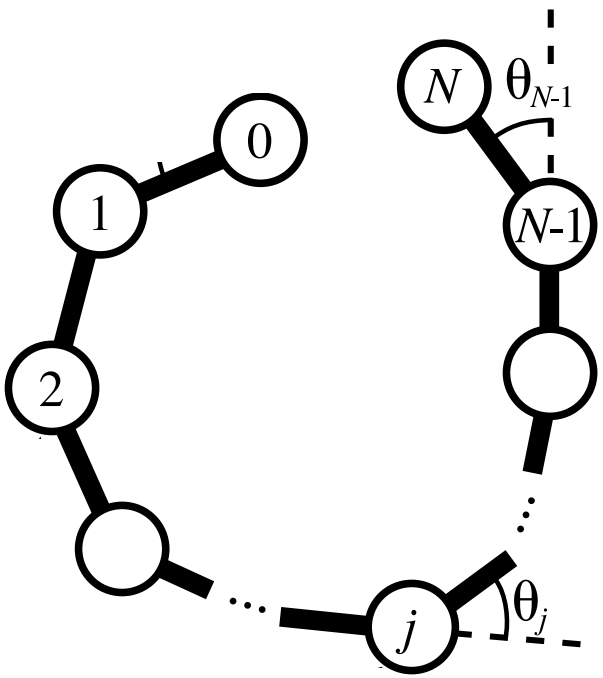
hybridized bending energy

melted bending energy

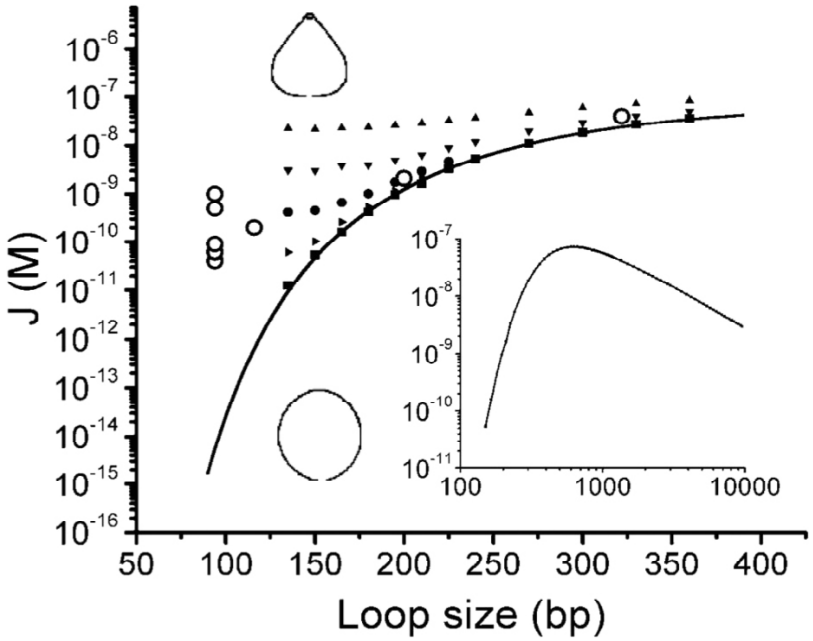
$$\mathcal{H}(n,\theta) = \delta_{n,0}\left[\frac{k_{\mathrm{B}}T\ell_{\mathrm{D}}}{d}(1-\cos\theta)\right] + \delta_{n,1}\left[\Delta\mu(T) + \frac{k_{\mathrm{B}}T\ell_{\mathrm{M}}}{d}(1-\cos\theta)\right]$$

melt energy

Melts are much more flexible: $\ell_{\mathrm{M}} << \ell_{\mathrm{D}}$

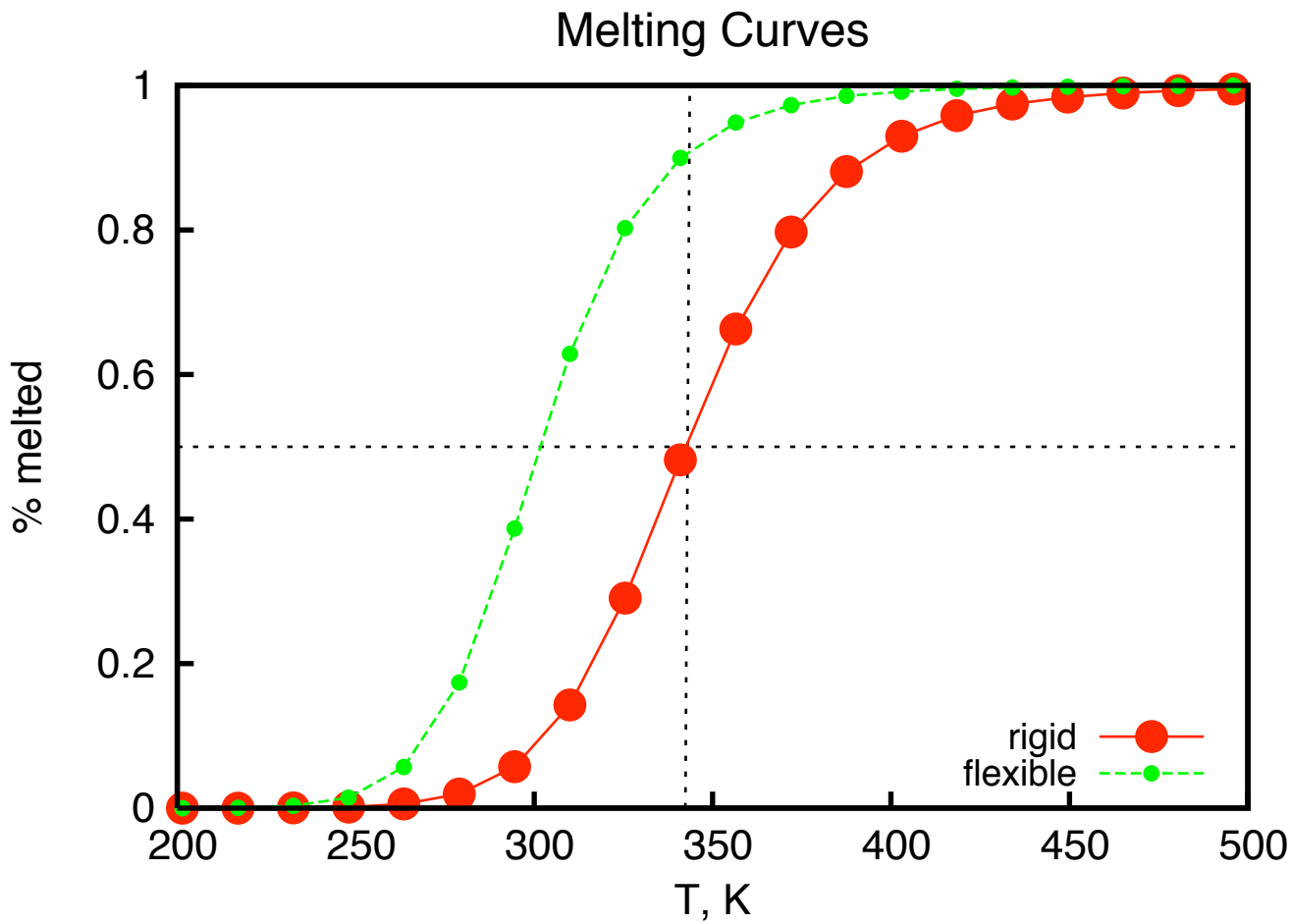


The MWLC



Yan & Marko, *PRL* 2004

Gives Wrong Melt Behaviour



Understanding Why

Integrate Out Bending Fluctuations to get Renormalized Lattice Model from MWLC

$$\exp\left(-\beta\overline{\mathcal{H}}_{\text{chain}}[\{n_i\}]\right) = \int_{-1}^{1} d(\cos\theta_1) \int_{-1}^{1} d(\cos\theta_2) \ \ldots \int_{-1}^{1} d(\cos\theta_{N-1}) \exp(-\beta\mathcal{H}_{\text{chain}}[\{n_i\},\{\theta_i\}])$$

↓

[Math]

↓

Effective 3-D model melt energy

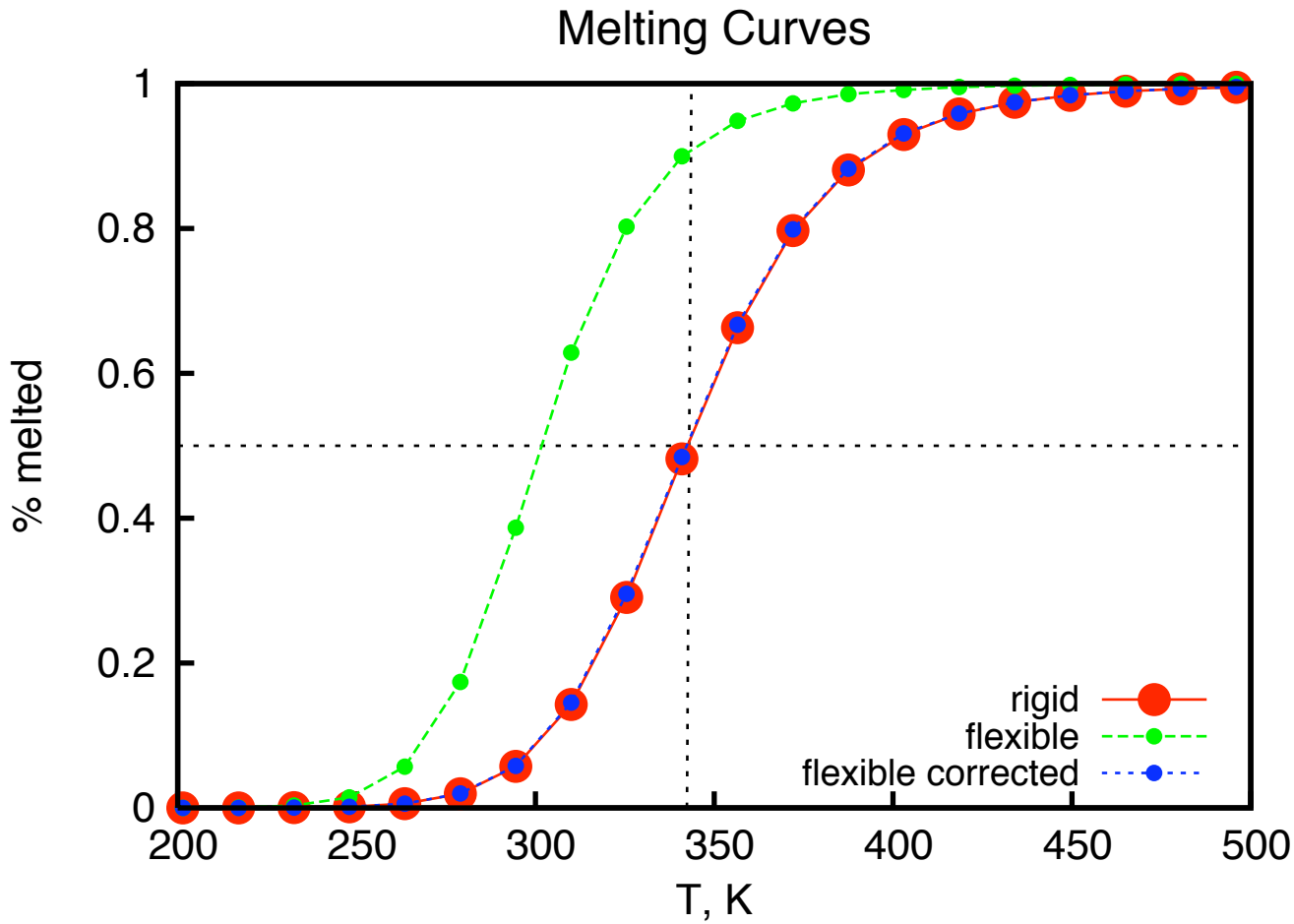
Lattice model melt energy

$$\overline{\Delta\mu} - \Delta\mu = -k_{\text{B}}T \ln\left[\frac{\ell_{\text{D}}}{\ell_{\text{M}}}\left(\frac{1-\exp(-2\ell_{\text{M}}/d)}{1-\exp(-2\ell_{\text{D}}/d)}\right)\right]$$

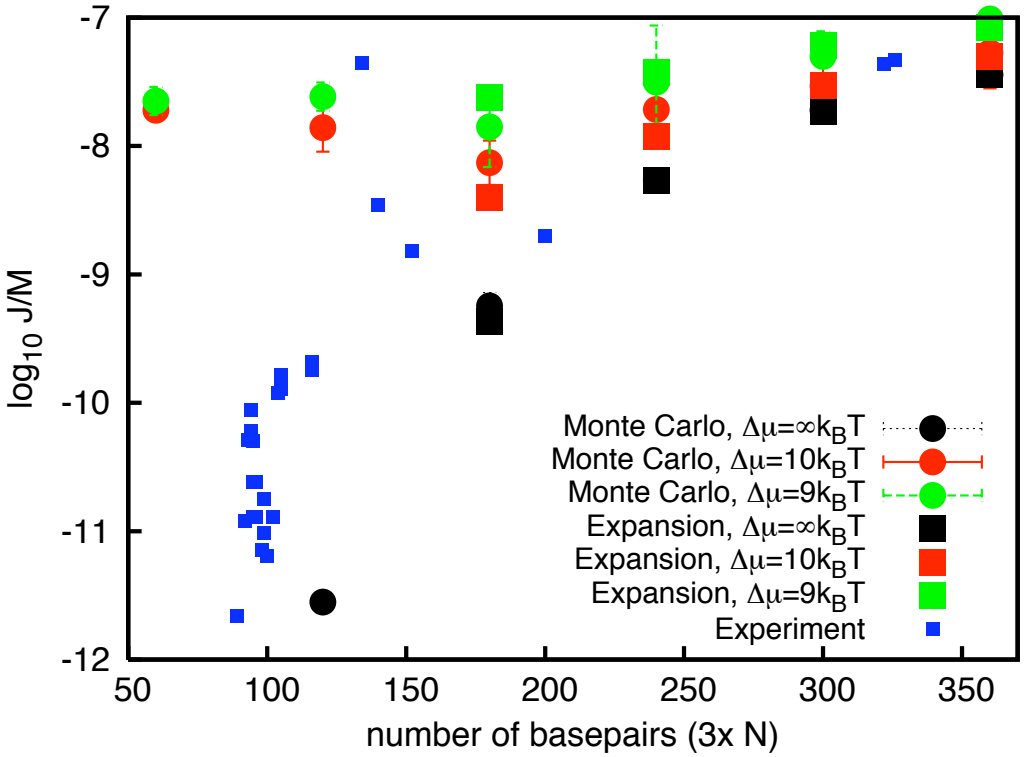
$$= -3.7k_{\text{B}}T$$

Entropic Boost

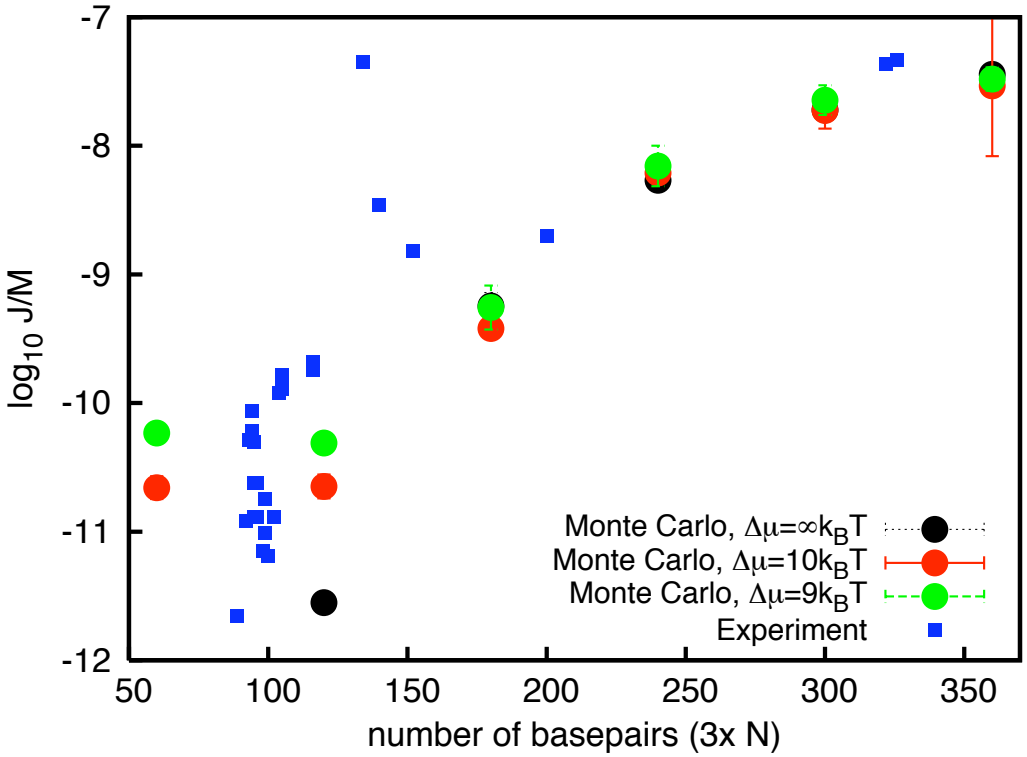
Correct Melt Behaviour



Cyclization Results Change



Uncorrected

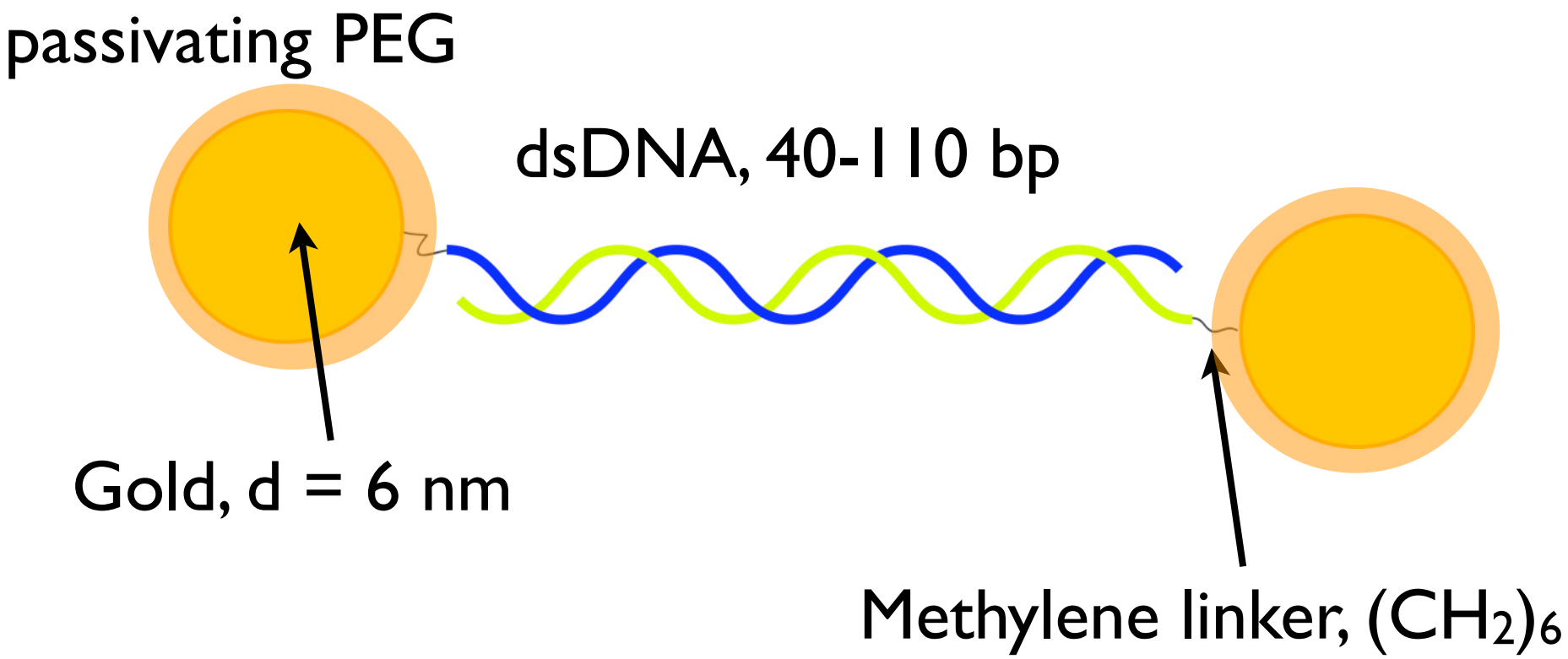


Corrected

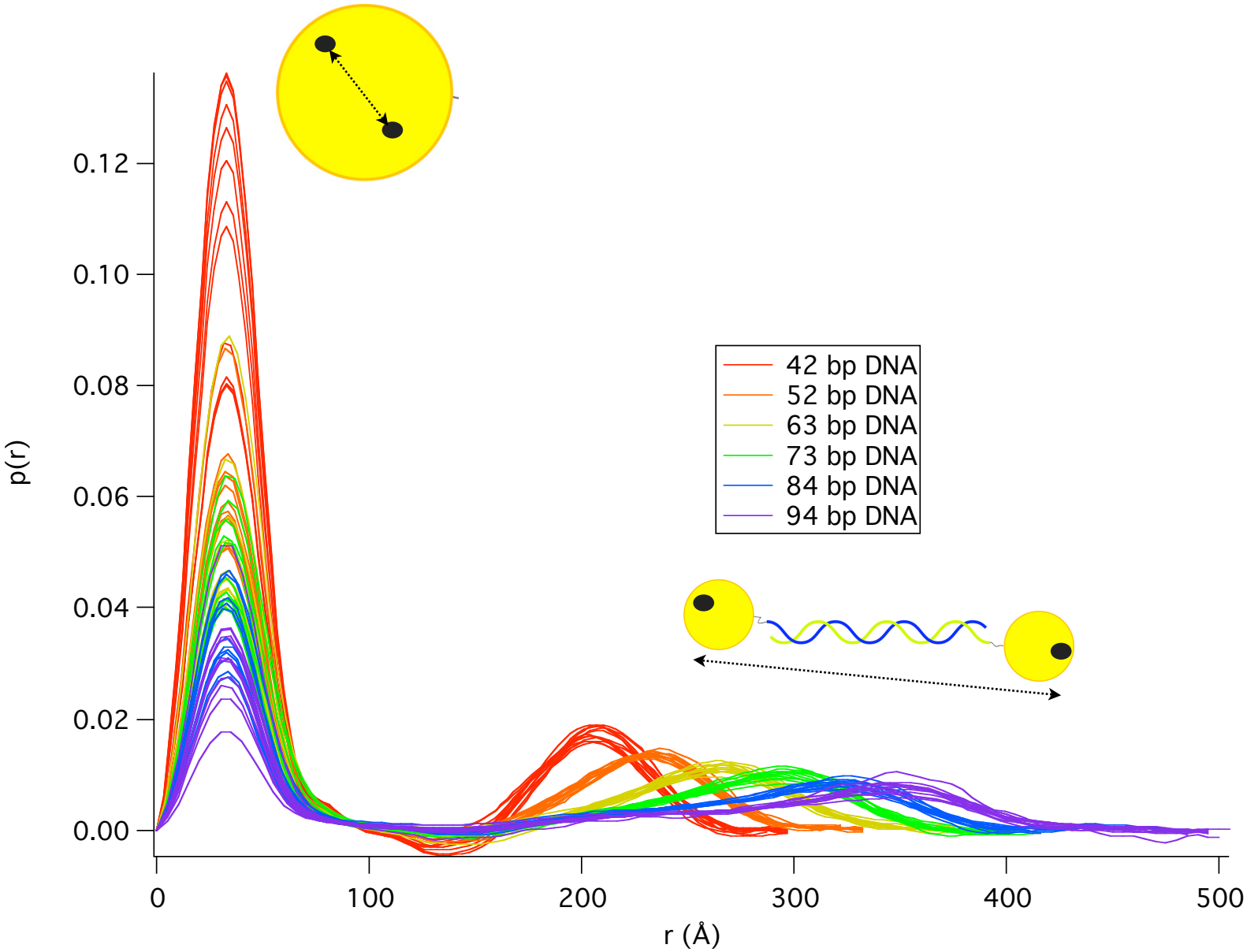
Using Wang-Landau Sampling

Applications - SAXS

Experimental Set-Up



Experimental Results

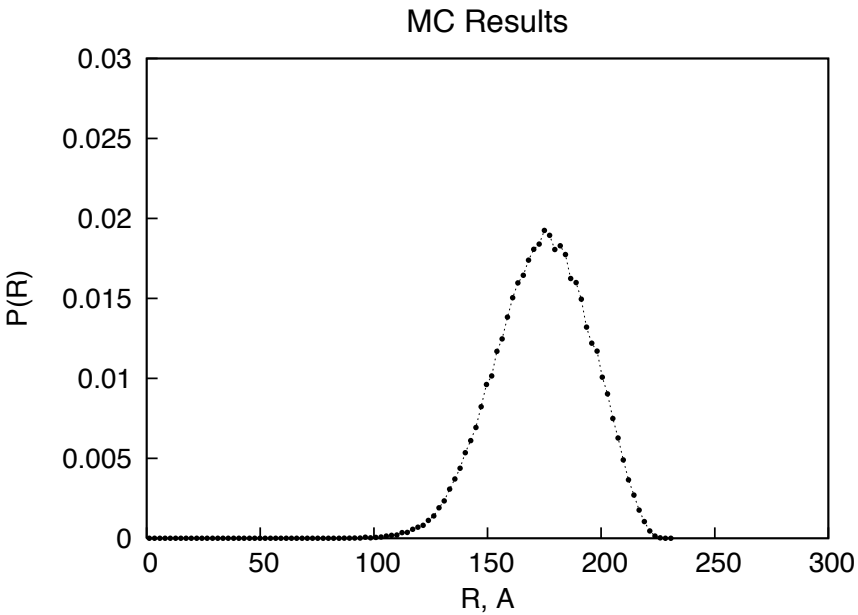


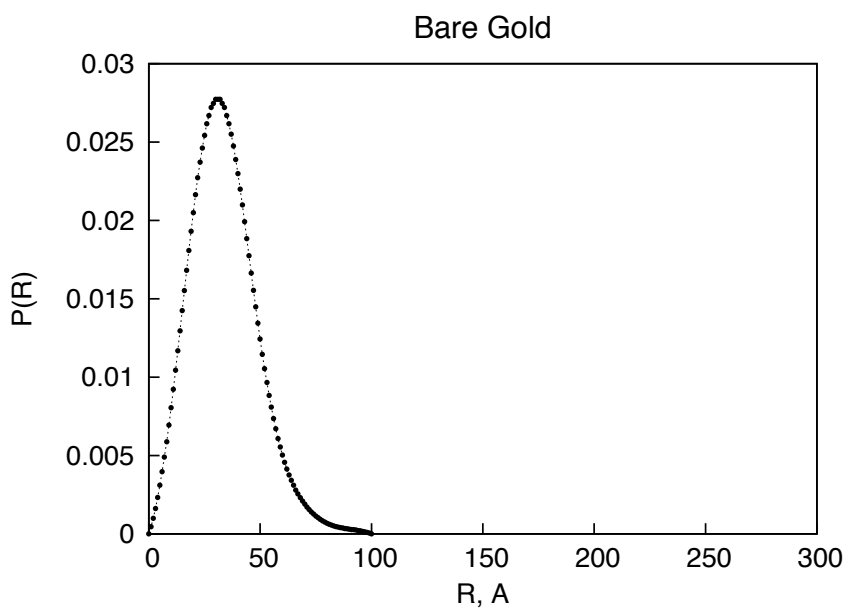
Samples *Entire* Distribution

Computational Modeling

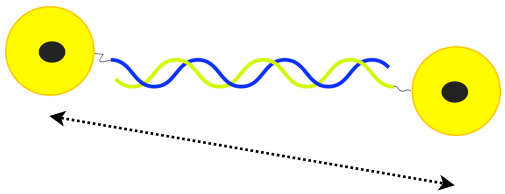
- Start with MWLC
- Add:
  - gold
  - linkers
  - excluded-volume
- Monte Carlo Importance Sampling

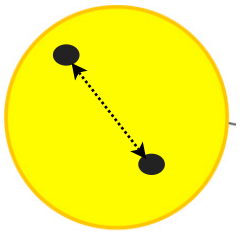
Basic Procedure

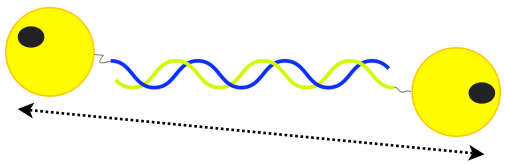


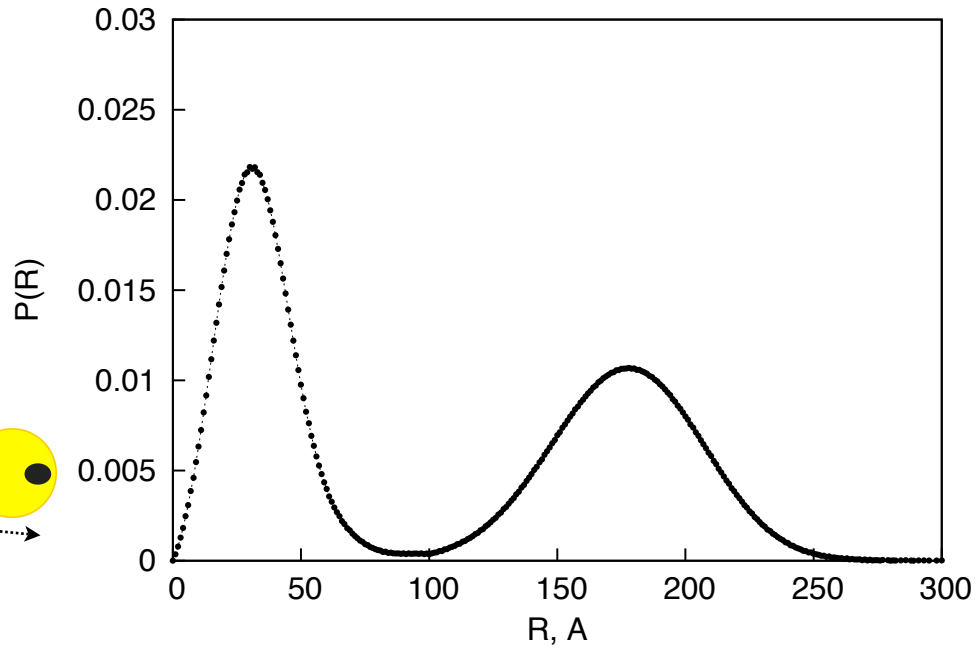


Convolve

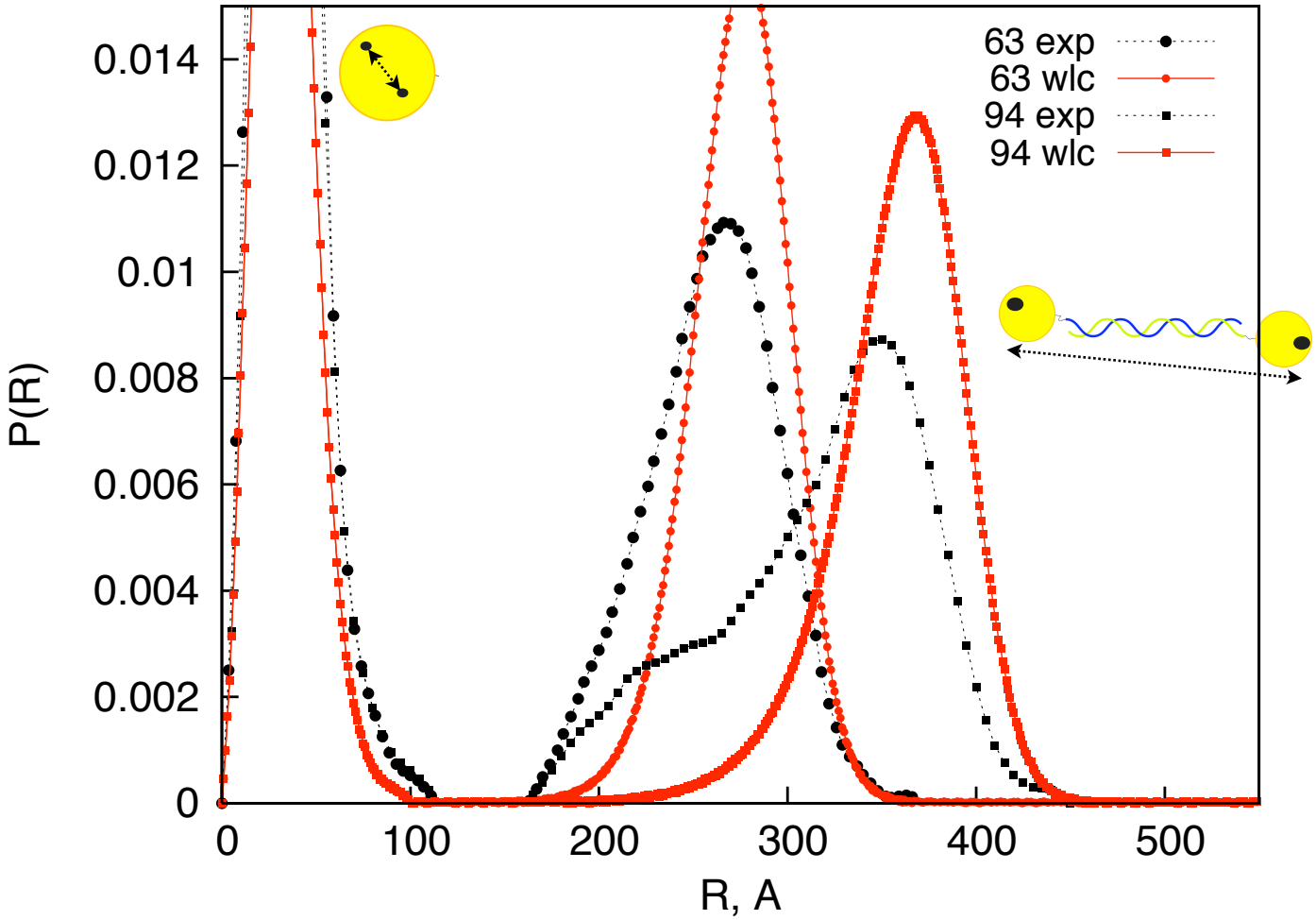




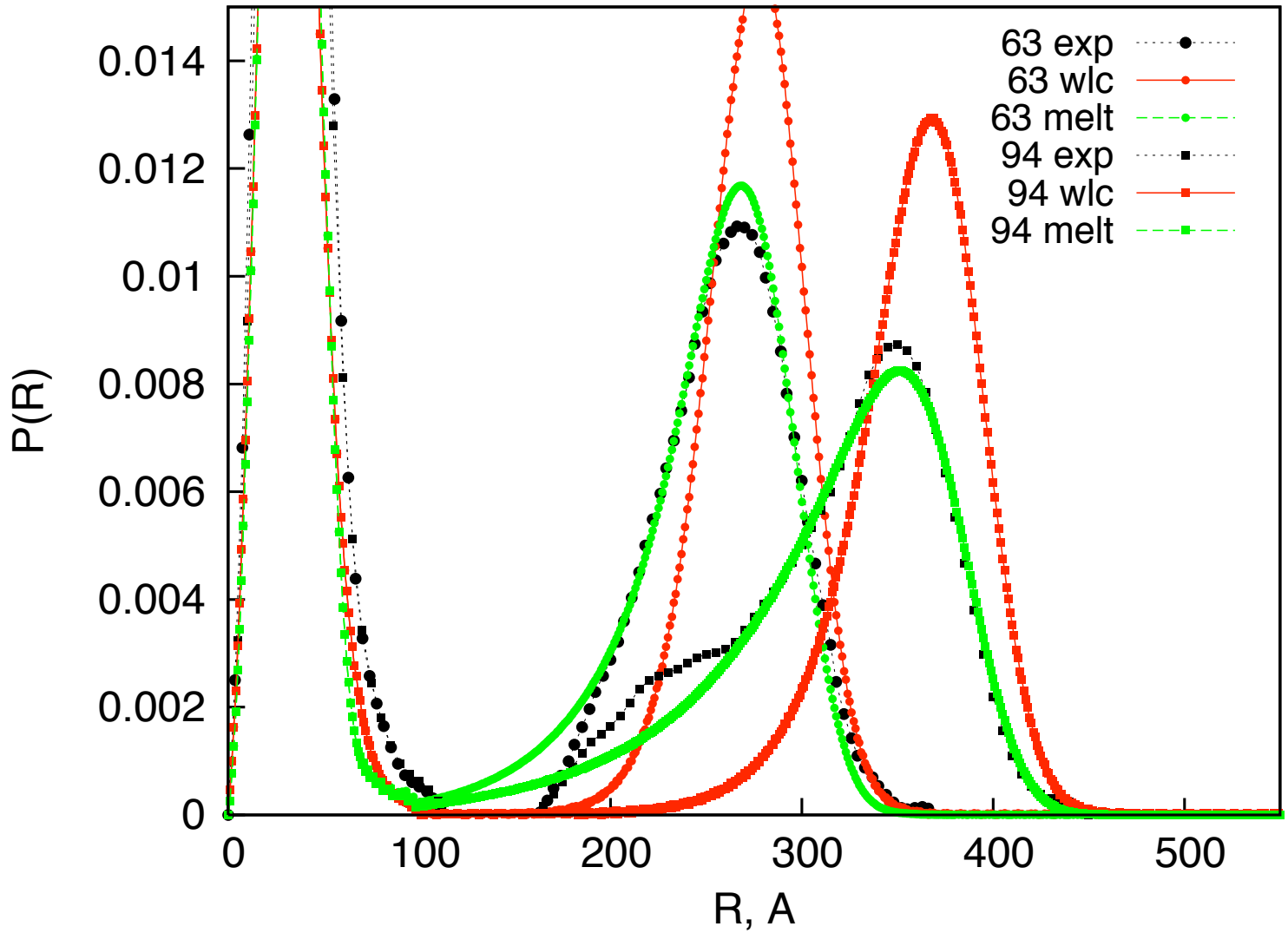




Experimental and Computational Comparison



~7kT Melts Fit Data Very Well



Further Complications

- Electrostatic interactions b/w gold and DNA
- Linker mechanics
  - esp. interactions with passivating PEG
- Gold nanoparticle size polydispersity

Conclusions

- Careful Entropic Accounting Needed to Understand Effects of Melts and Reproduce Cyclization Experiments

- Reasonable Melt Free Energies Produce Good Fits to Robust Gold-SAXS Data

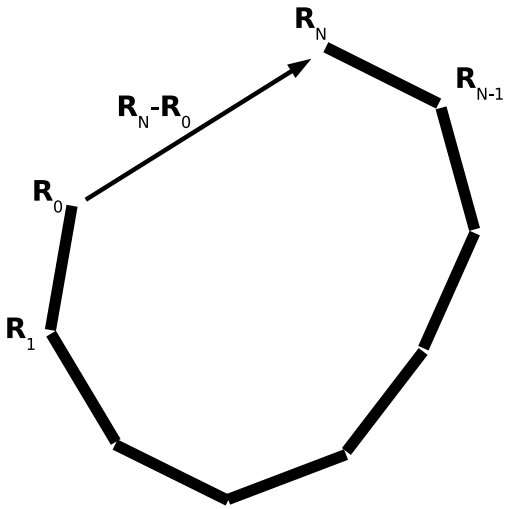
Acknowledgments

- Phillip Geissler
- Alex Mastroianni
- Geissler Lab, esp. Team Semiflex, *esp.* Steve Whitelam
- NSF

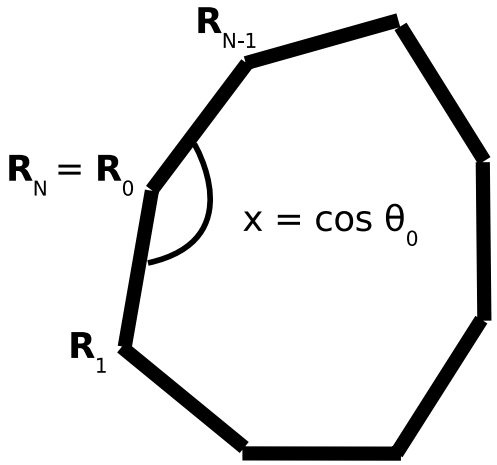
[not to scale]

Wang-Landau Sampling

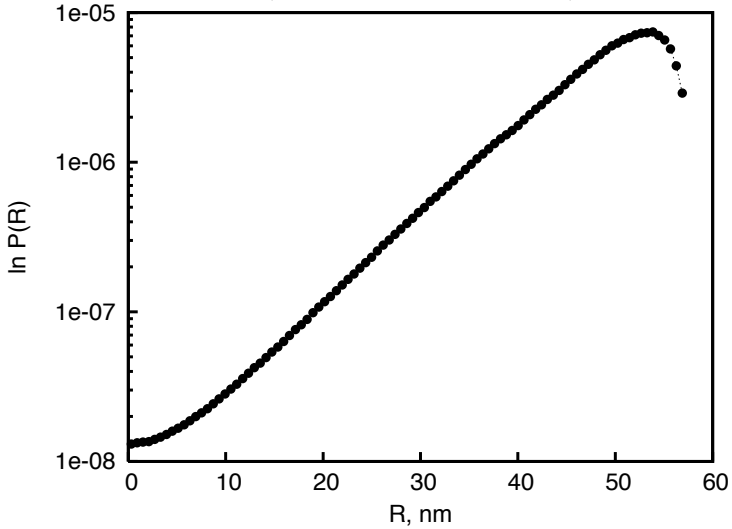
Spatial



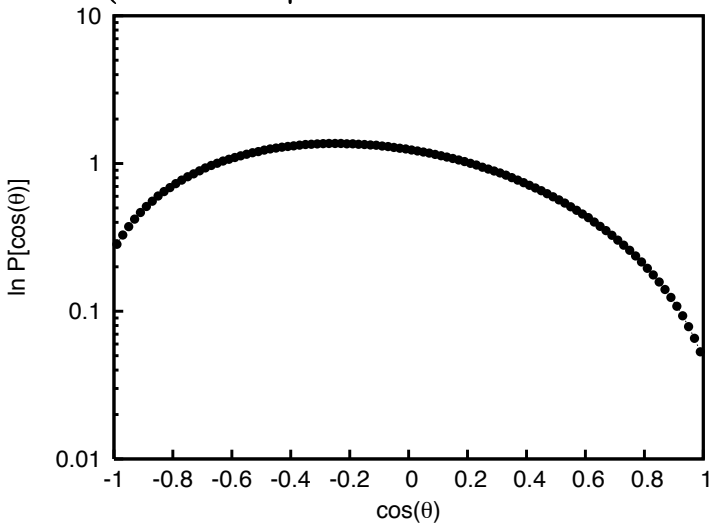
Angular



$$P(R_N - R_0)$$



$$P(\cos\theta | R_N - R_0 = 0)$$

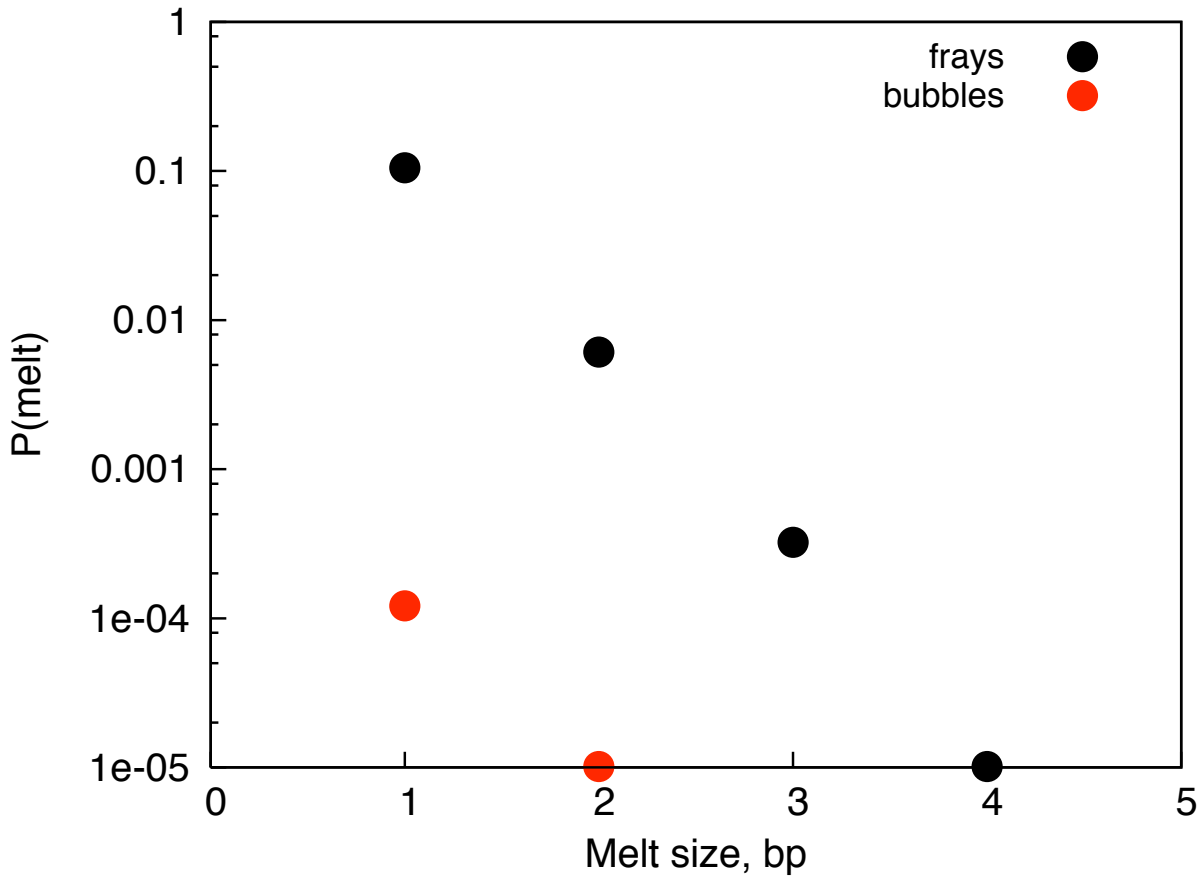


$$J \propto P(R_N - R_0 = 0) \frac{\int \mathrm{d}\cos\theta \quad P(\cos\theta | R_N - R_0 = 0) q(\cos\theta)}{\int \mathrm{d}\cos\theta \quad q(\cos\theta)}$$

$$q(\cos\theta) = e^{-\beta \mathcal{H}_{\mathrm{hyb}}(\cos\theta)} + e^{-\beta \mathcal{H}_{\mathrm{melt}}(\cos\theta)}$$

More Realistic Melts

- Sequence Dependence
- Melt Nucleation Energy
- Non-Extensive Entropy



Drastically Reduce Bubbles

More Realistic Melt Models

Sequence-dependent Enthalpy Correction

$$\mathcal{H} = [\epsilon_{\tau_i} - TS_m(T) + \Delta\Delta\mu]\delta_i^M$$ Melt Extension

$$+ \frac{1}{2}\epsilon_{BM}(\delta_i^B\delta_{i+1}^M + \delta_i^M\delta_{i+1}^B)$$ Melt Nucleation

$$- T\sum_{n=1}^{N-i}\Delta S_{loop}(n,0)\delta_{i-1}^B\delta_{i+n}^B\prod_{s=0}^{n-1}\delta_{i+s}^M$$

Non-extensive Entropy

Adapted from Whitelam, *et al*, *Biophys J* 2007

Still Same Correction Term

Uncertainty About Melting Mechanics

- What Size?

- What Energy?

Alternative Approaches

- De-convolution
- Comparison in q-space