

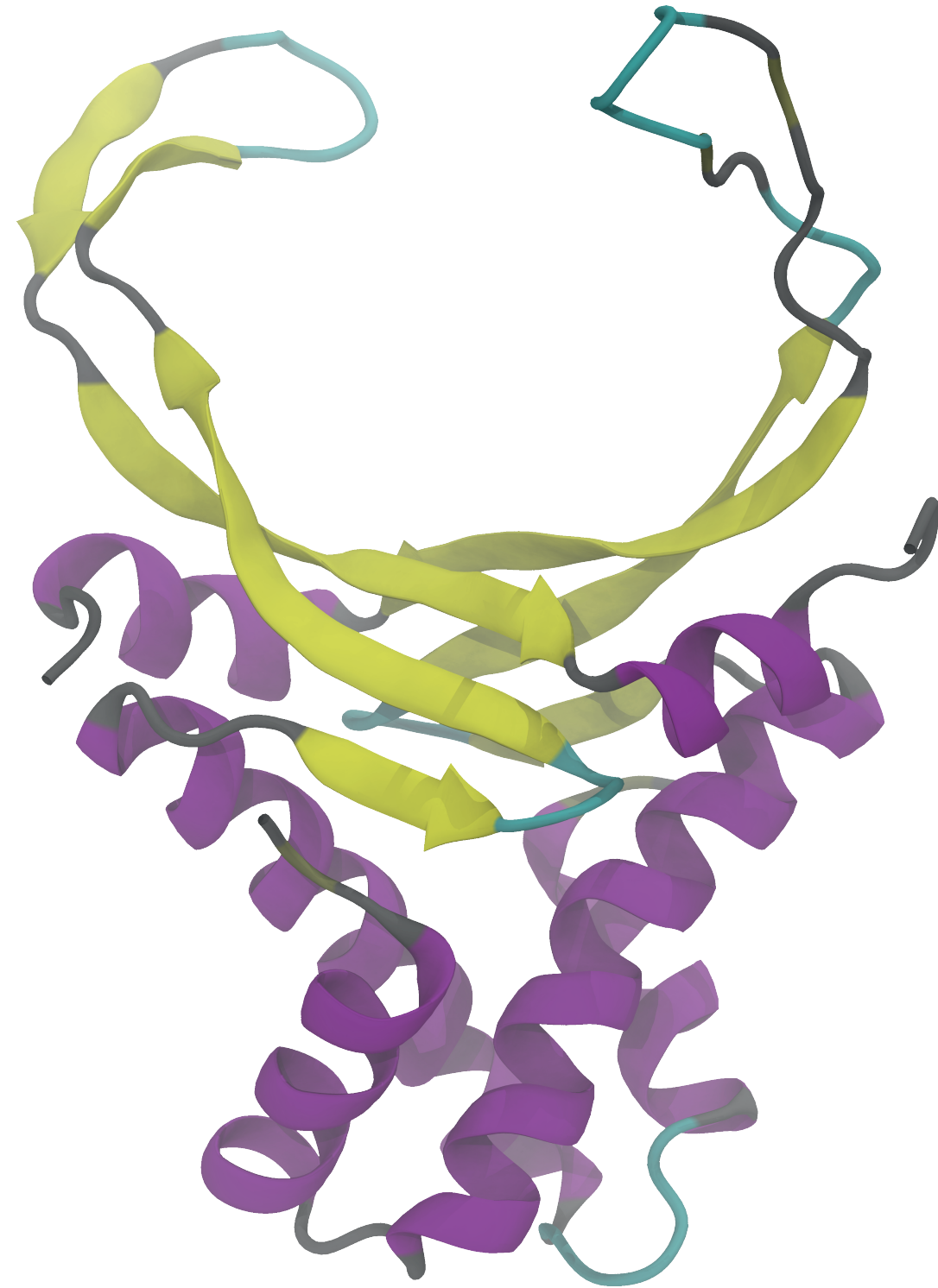
Atomistic simulations reveal modality of IHF–DNA binding

George D Watson • S Yoshua • M C Leake • A Noy

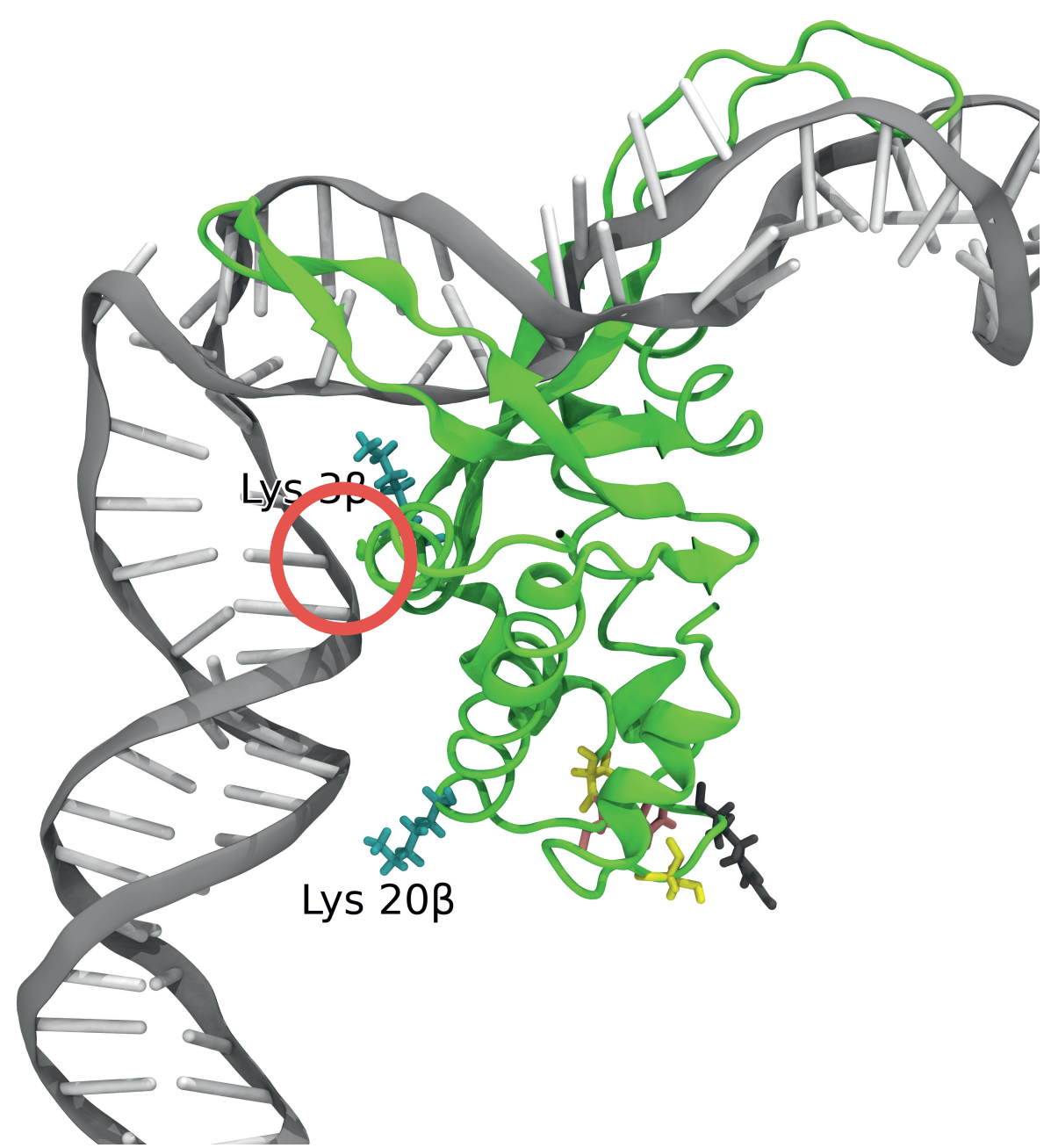
Department of Physics • University of York • YO10 5DD
george.watson@york.ac.uk • <https://georgewatson.me>

Integration host factor (IHF)

- > Prokaryotic **nucleoid-associated protein**
- > Functional analogue of histones
- > **Bends DNA** by $\sim 160^\circ$
- > Binds **specifically** by indirect readout
- > IHF & HU regulate around 120 *E. coli* genes [1]
- > Stabilises **biofilms** [2]

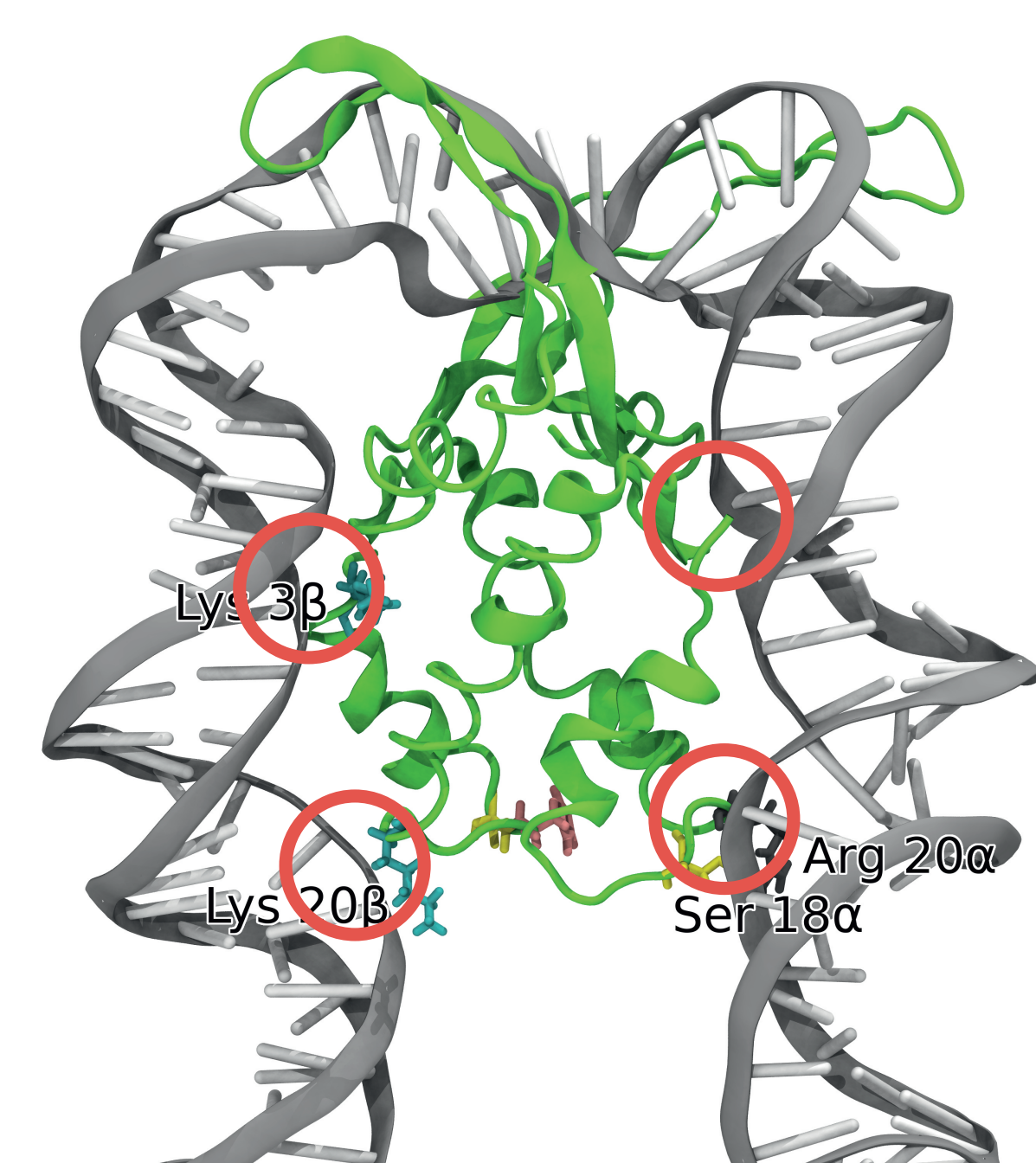
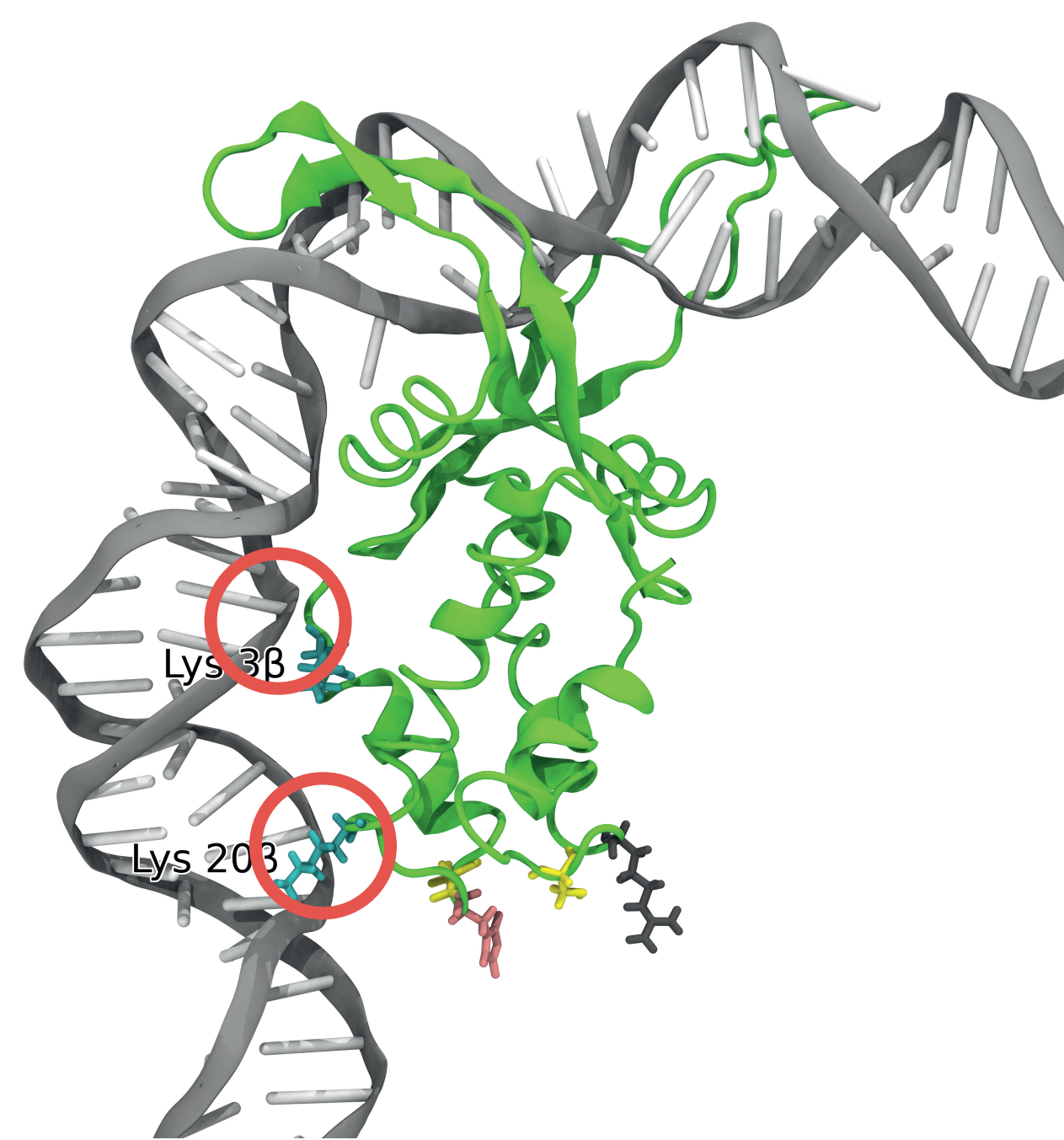


IHF binds DNA in 3 substates



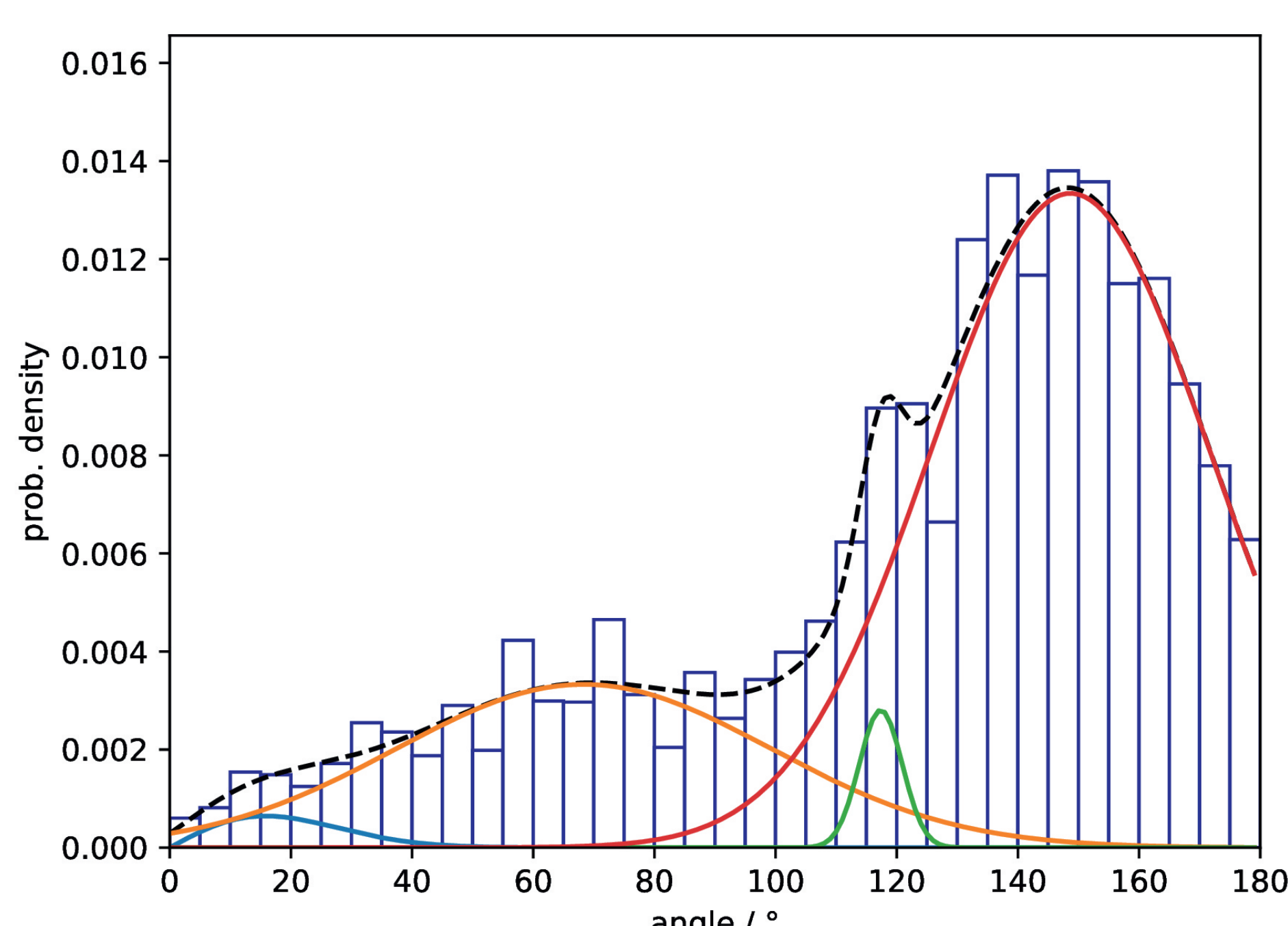
- > “**Unwrapped**” state
- > $\sim 60^\circ$ bend
- > Bending within range for naked DNA
- > The A-tract makes a **single contact** with IHF
- > **Highest free energy**

“**Half wrapped**” state <
 $\sim 120^\circ$ bend <
 Novel observation confirms existing FRET data [3] <
 IHF binds only the A-tract to **one side** of the binding site <



- > “**Fully wrapped**” state
- > $\sim 160^\circ$ bend
- > Known from crystal structure
- > DNA binds to **both sides** of the protein
- > **Lowest free energy**

- > Following binding, the DNA–IHF complex progresses downwards through these **metastable** states

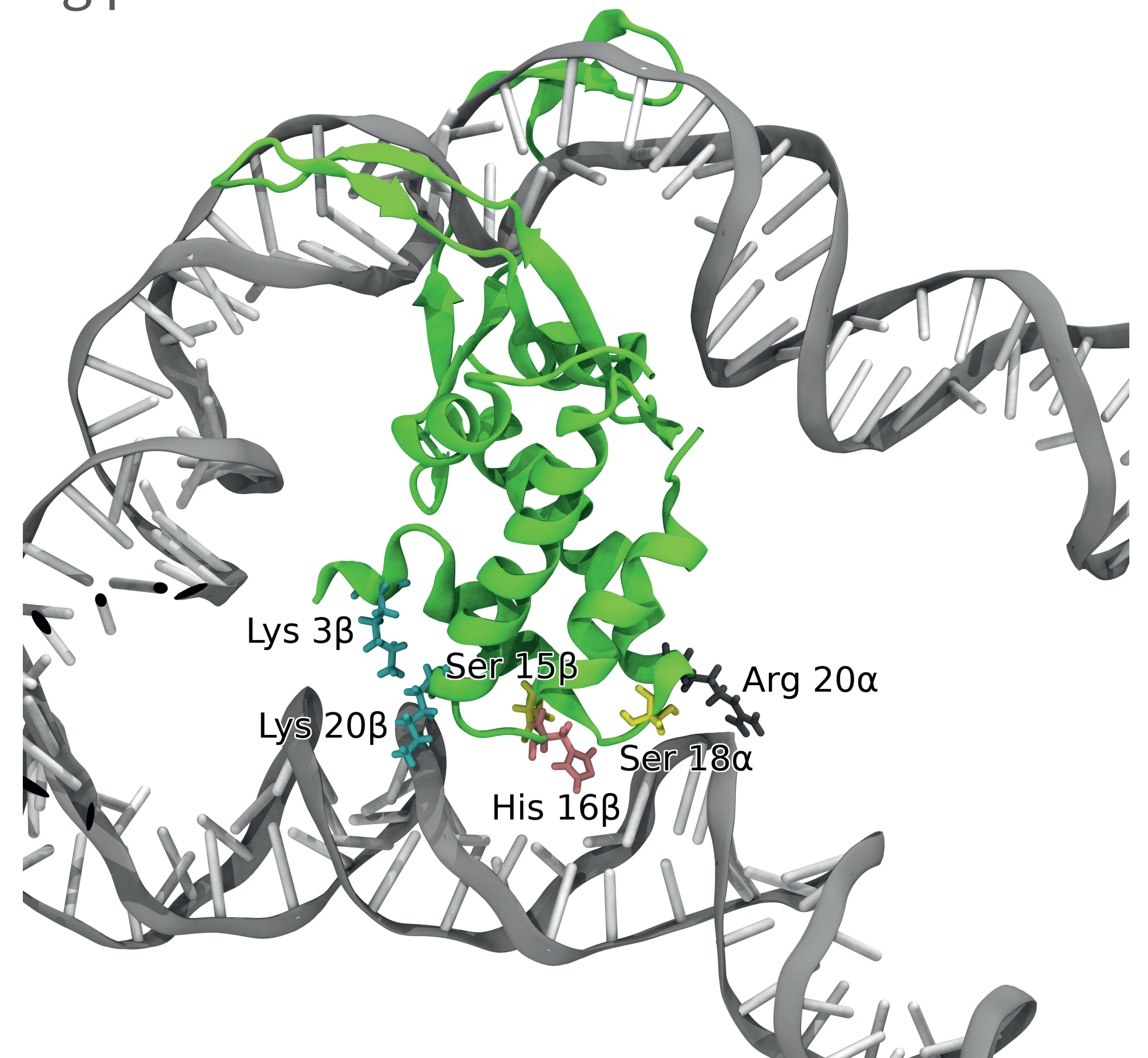


Corresponding peaks appear in the histogram of bend angles across several simulations.

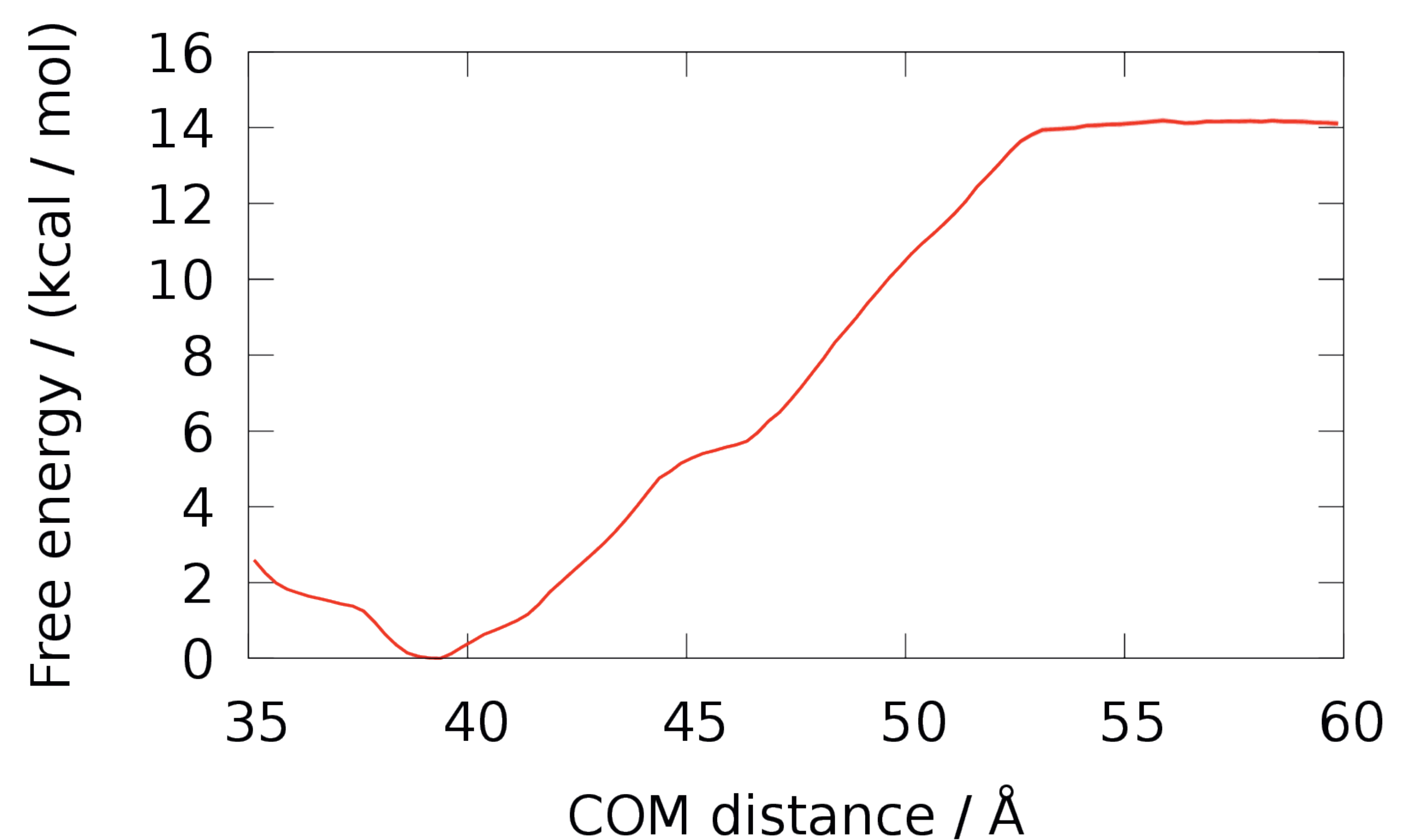
Here, a 2D projection of the trajectories was used for comparison with AFM data.

IHF can bridge DNA

- > A single IHF molecule can bind at least two pieces of DNA, forming a **bridge** between them
- > Bridges **constrain DNA structure & topology**
- > Could explain why IHF exists at extracellular DNA crossing points in biofilms



- > IHF bridges involve **nonspecific** hydrogen bonding with the DNA backbone
- > Umbrella sampling simulations demonstrate that bridging is **energetically favourable**



Methods

- > Atomistic **molecular dynamics** simulations using **AMBER**
 - \$ Explicit & implicit solvent
- > Free-energy calculations using **umbrella sampling** & weighted histogram analysis method (**WHAM**)
- > Results agree with measurements from **atomic force microscopy** (AFM) by S. Yoshua

References

1. Swinger K K, Rice P A 2004 *Curr. Opin. Struct. Biol.* **14** 28
2. Novotny L A et al. 2013 *PLoS ONE* **8** e67629
3. Connolly M et al. 2018 *J. Phys. Chem. B* **122** 11519