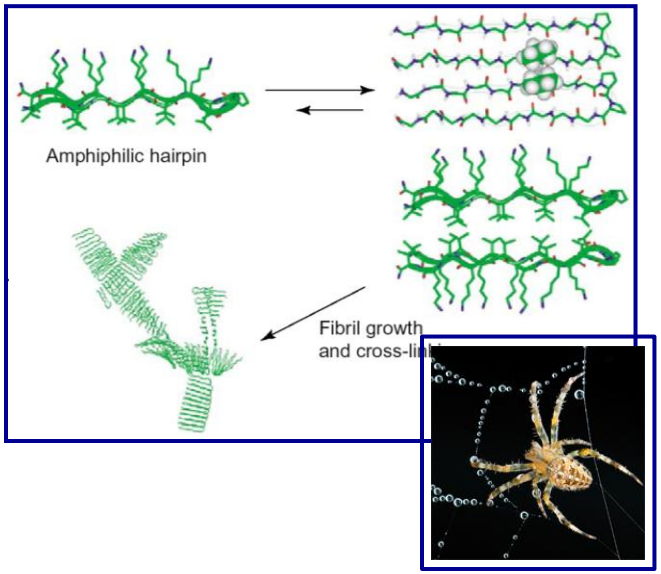
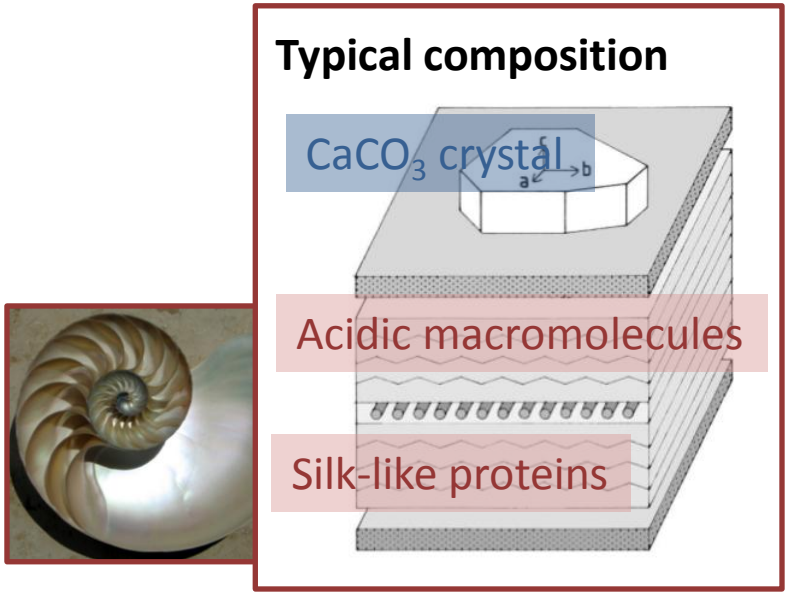
Topics biomolecular simulation group

- peptide aggregation,
  peptide- and protein-based materials
- organic/inorganic hybrid materials
- formation of large protein aggregates





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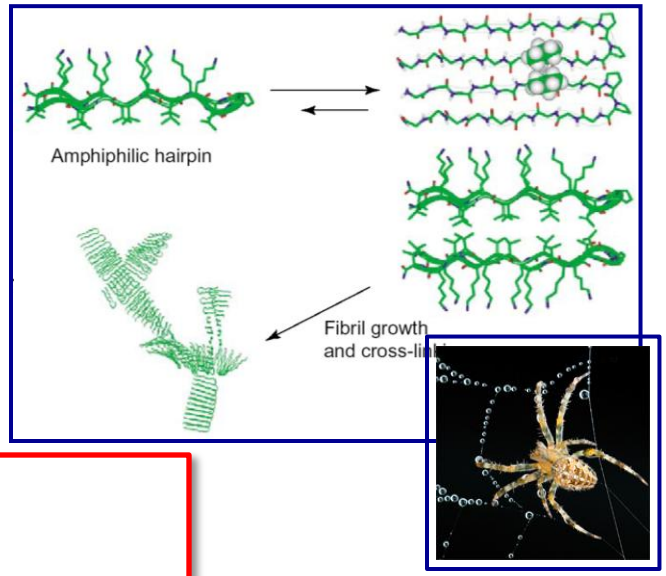
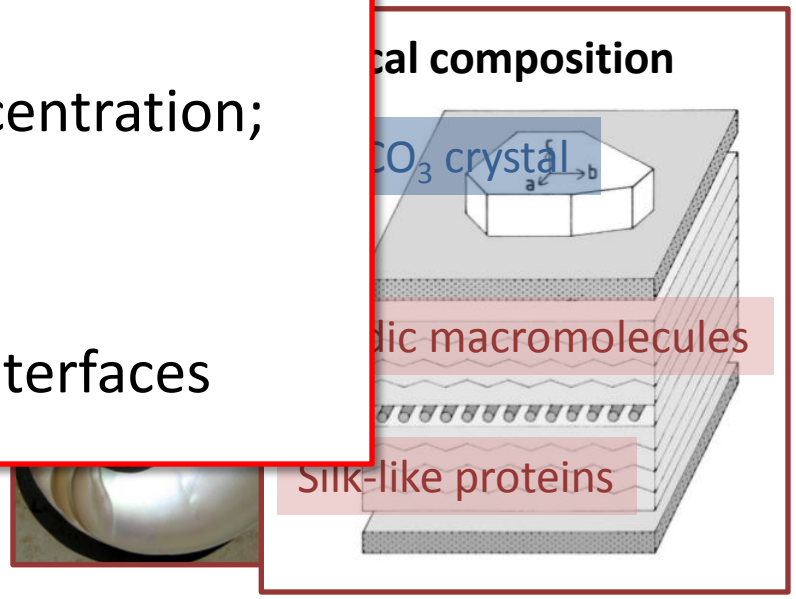


- Representability (thermodynamic & structural properties)
- Transferability (change of concentration; phase separation)
- Interactions with surfaces & interfaces



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Christoph Globisch, MPI-P

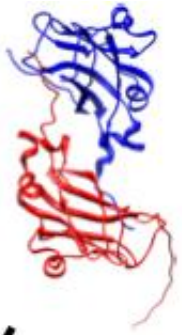
Tristan Bereau, formerly CMU

Venky Krishnamani, CMU

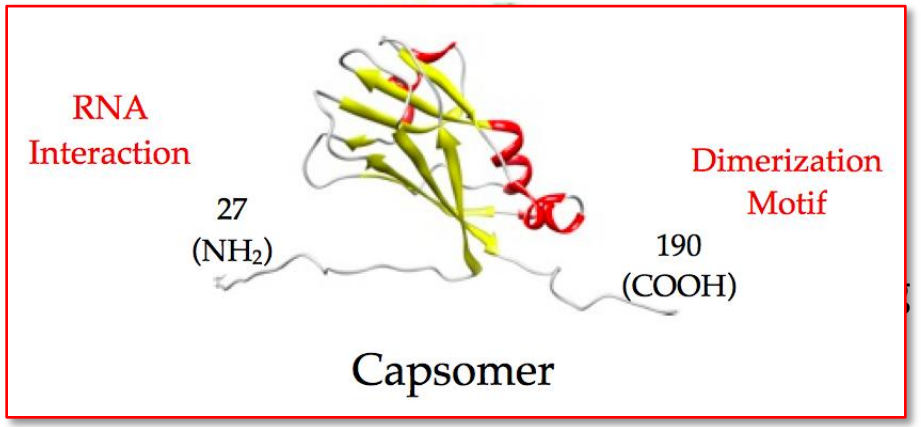
Markus Deserno, CMU

Formation of large protein aggregates:
Multiscale simulation of virus capsids

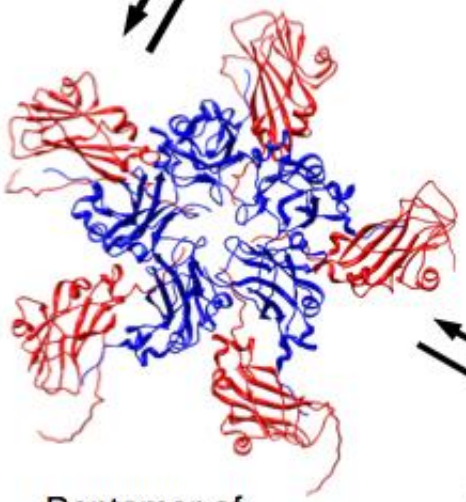
Model system CCMV
(cowpea chlorotic mottle virus)



Dimer

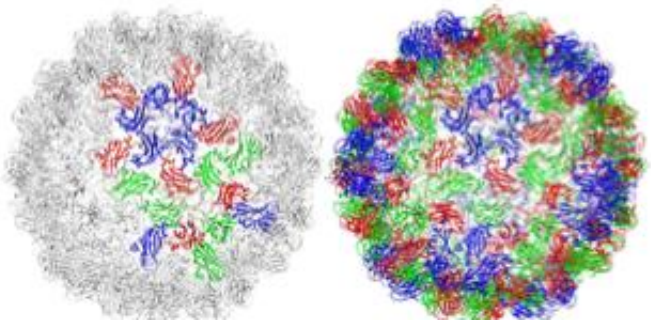


proposed
assembly
pathway



Pentamer of
Dimers (POD)

T3 capsid by cooperative
addition of dimers



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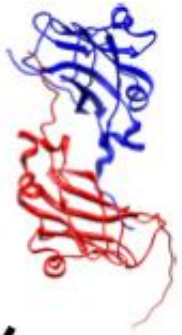
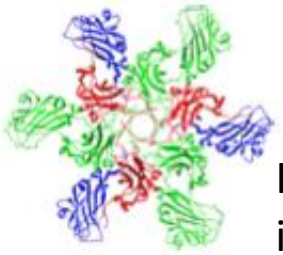
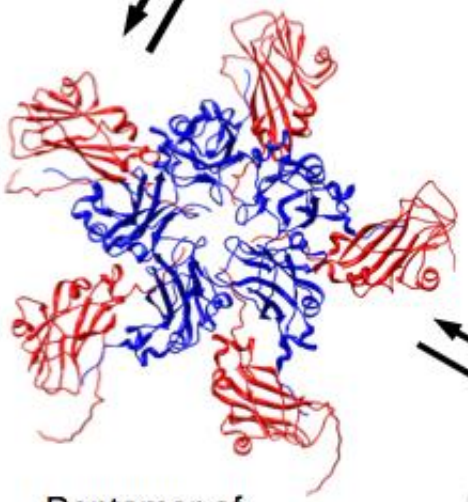


Dimer



Hexameric interface: stability, swelling

proposed assembly pathway



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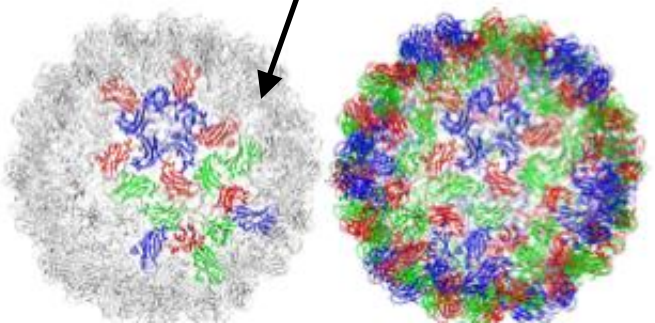

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Multiscale simulation of virus capsids

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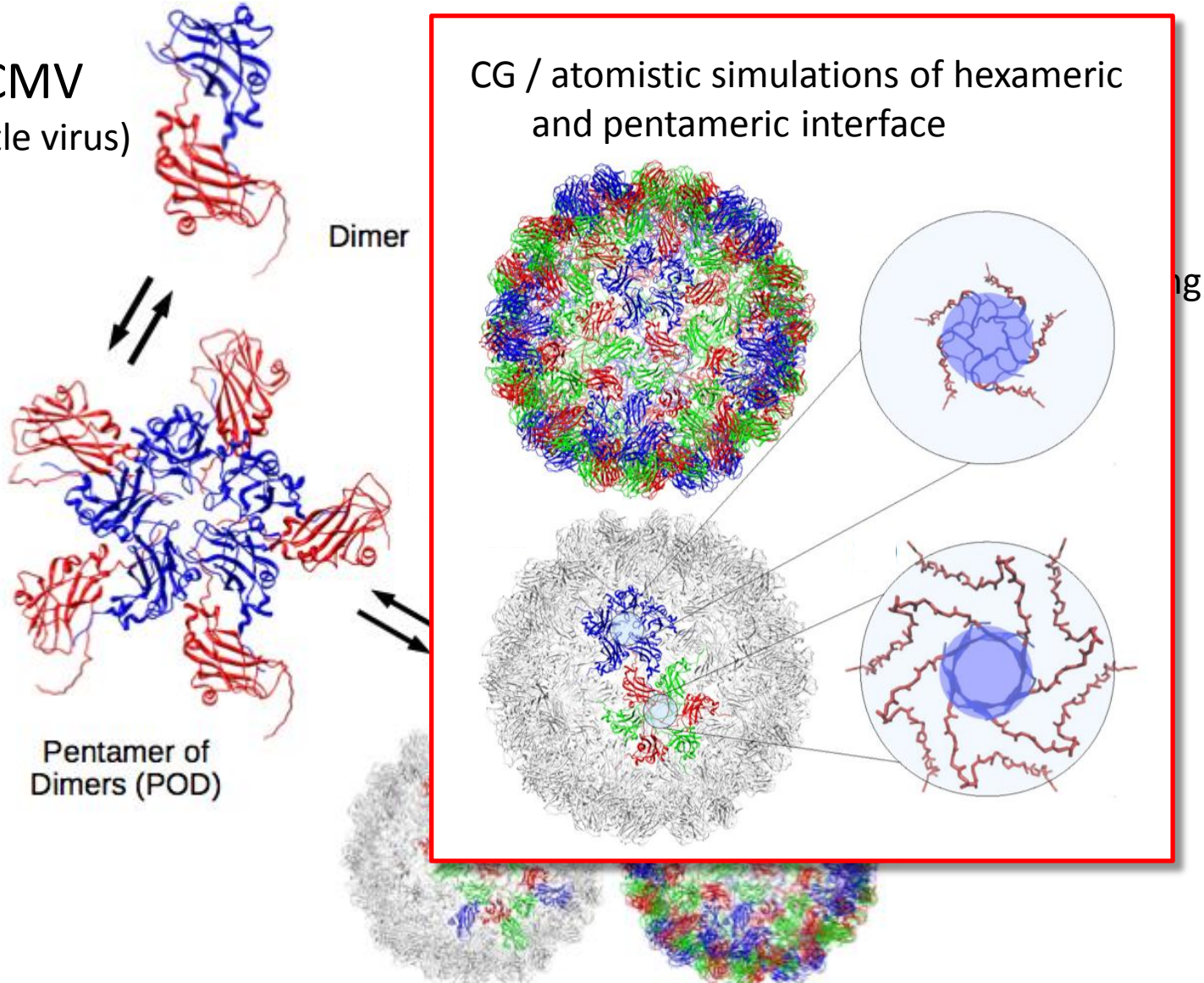
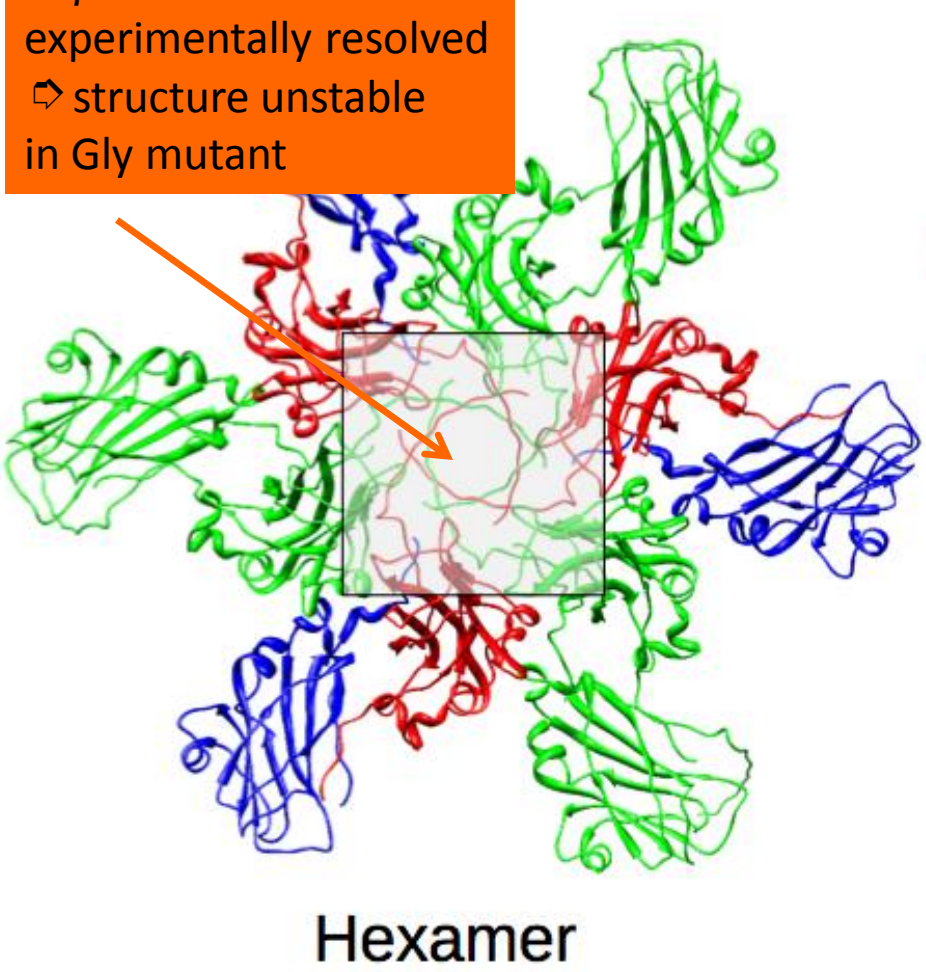


Multiscale simulation of virus capsids

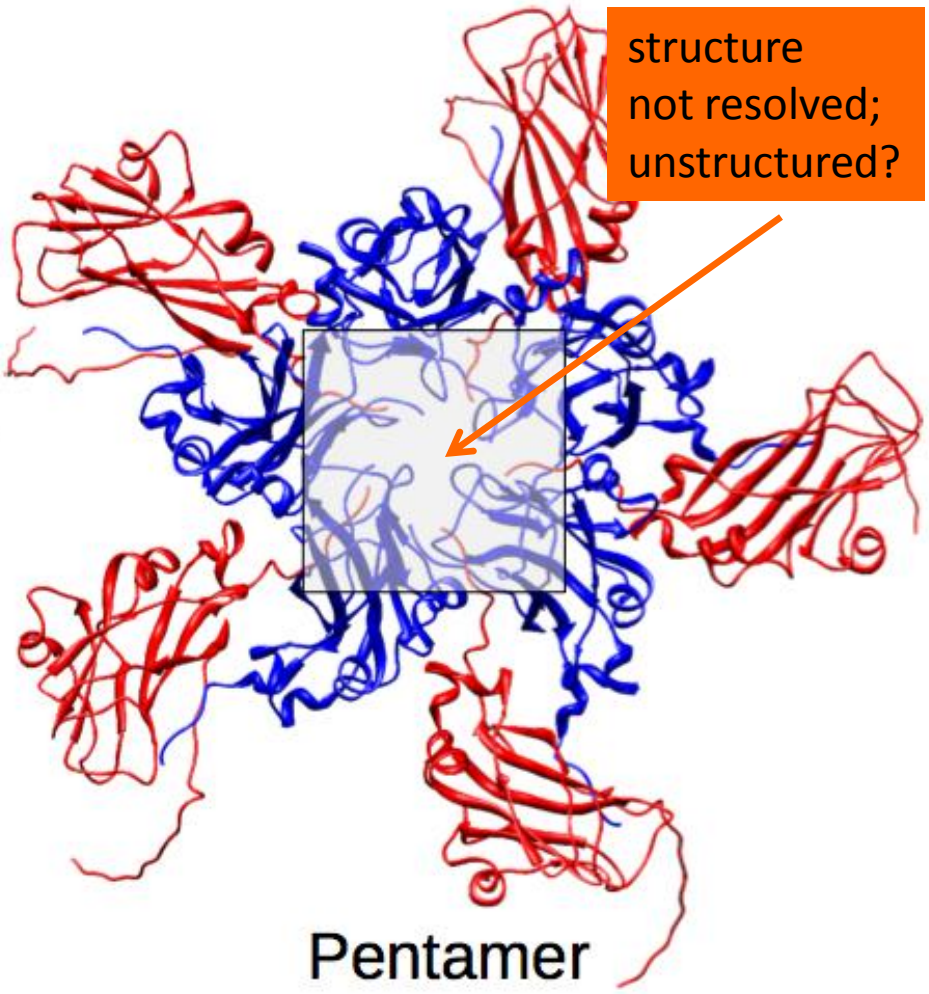
CG / atomistic simulations of hexameric and pentameric interface

→β–barrel structure experimentally resolved
➪ structure unstable in Gly mutant



Hexamer

structure not resolved; unstructured?

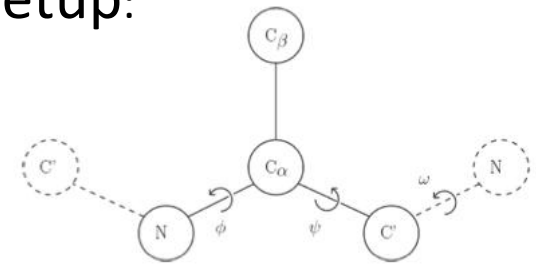


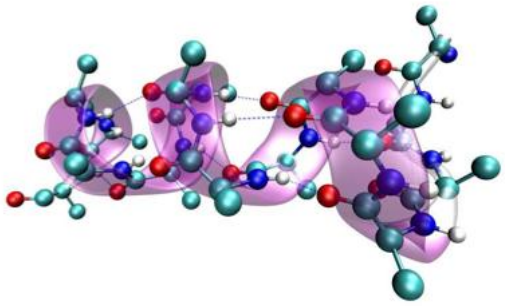
Pentamer

Multiscale simulation of virus capsids

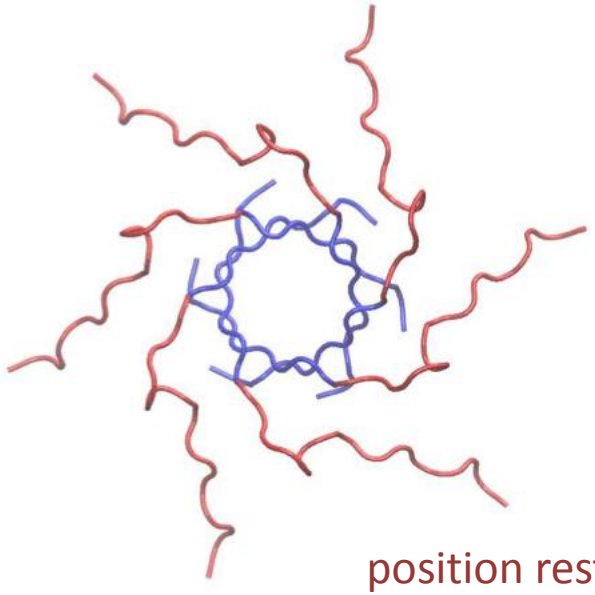
CG / atomistic simulations of hexameric and pentameric interface

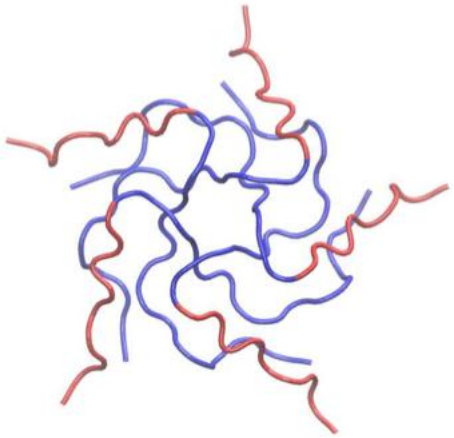
Setup:





CG model by
Bereau & Deserno, *J. Chem Phys* **2009**

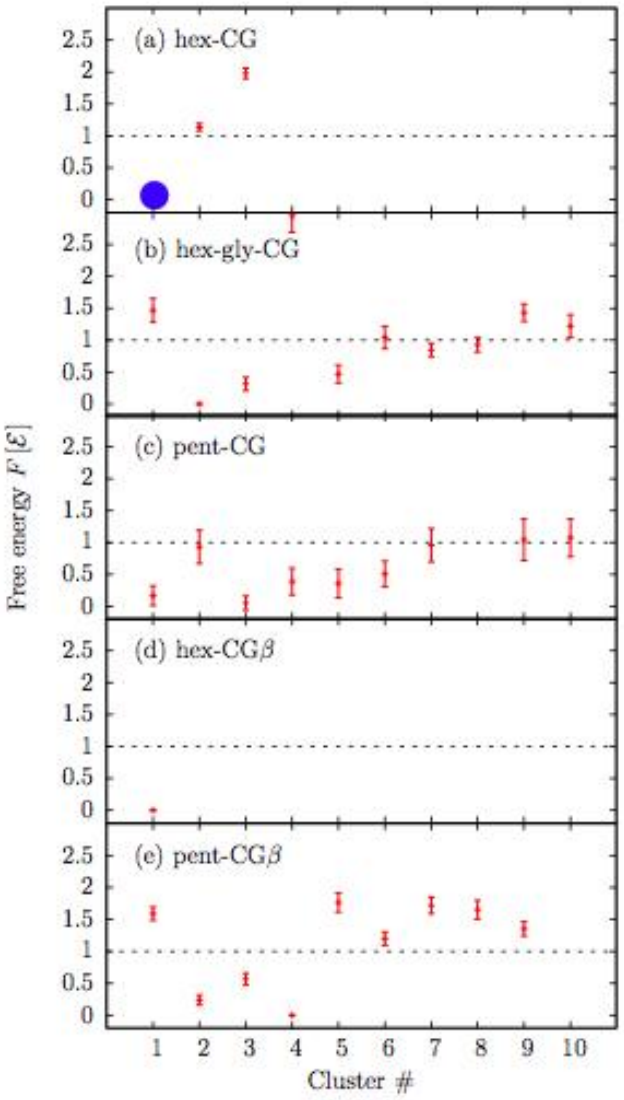




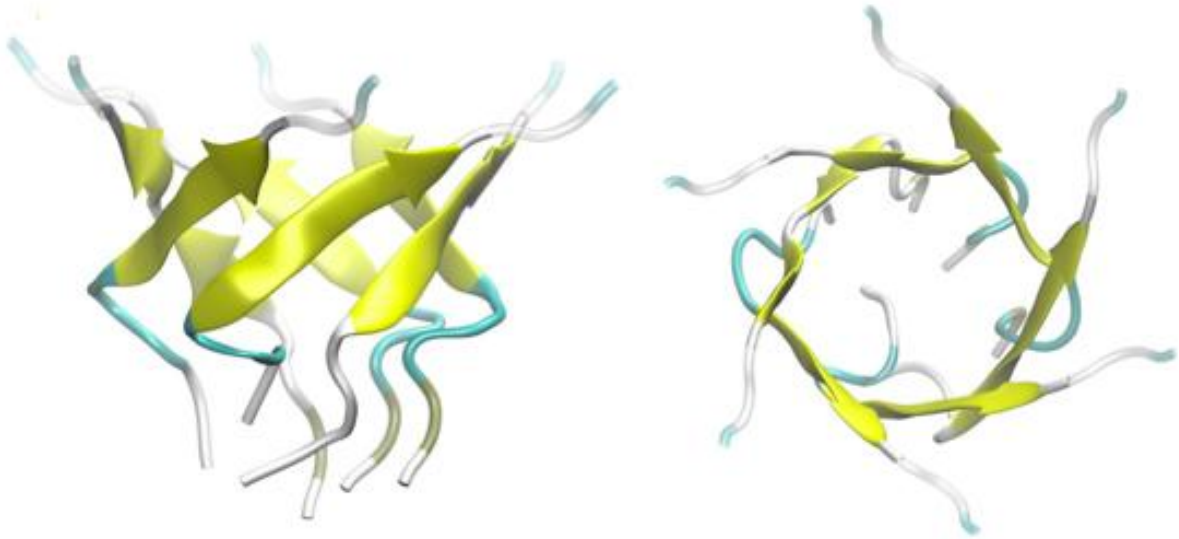
position restrained regions

- CG REMD simulations
- Clustering and free energy reweighting (WHAM)
- Atomistic simulations after backmapping

The wild-type hexamer

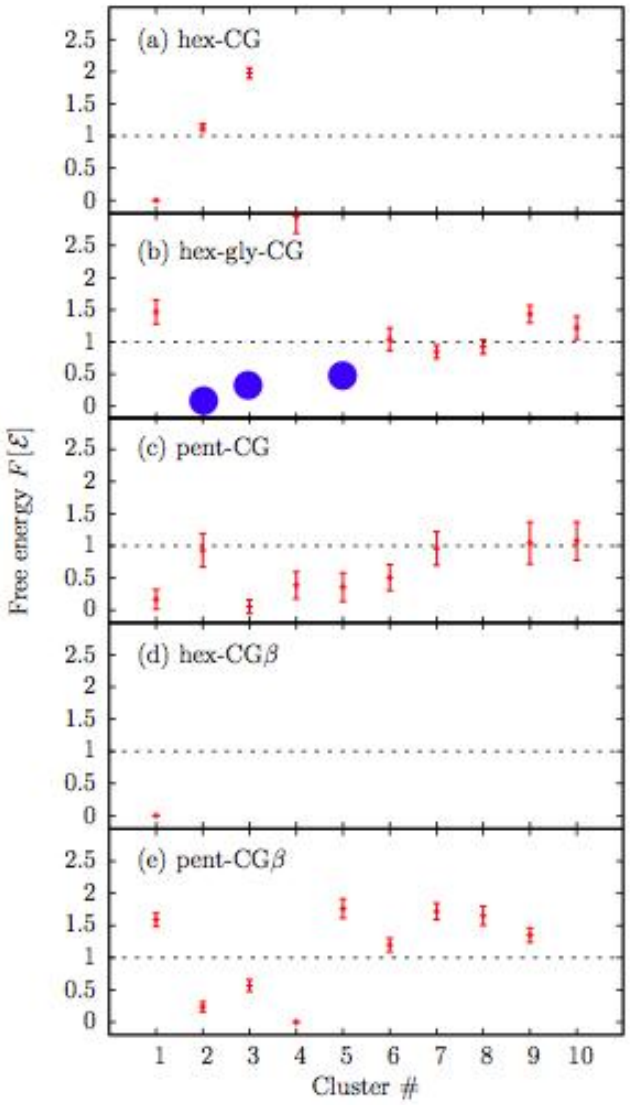


52%

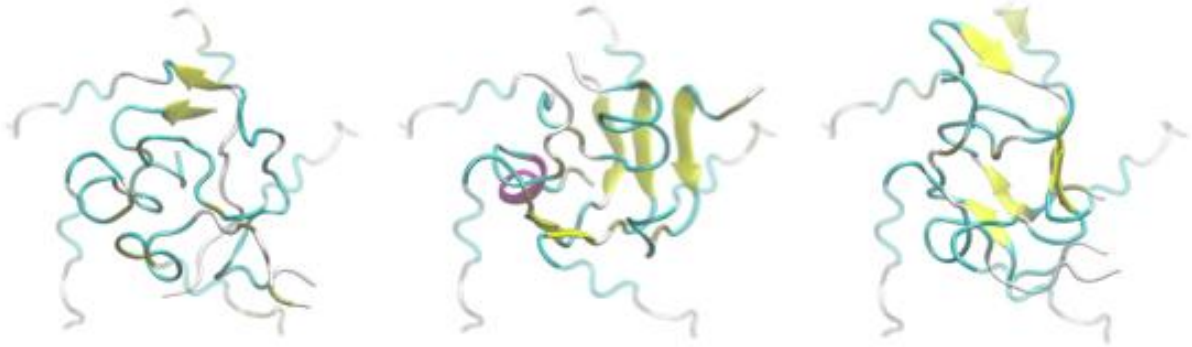


very stable beta barrel – as it should be

The Gly-mutant hexamer

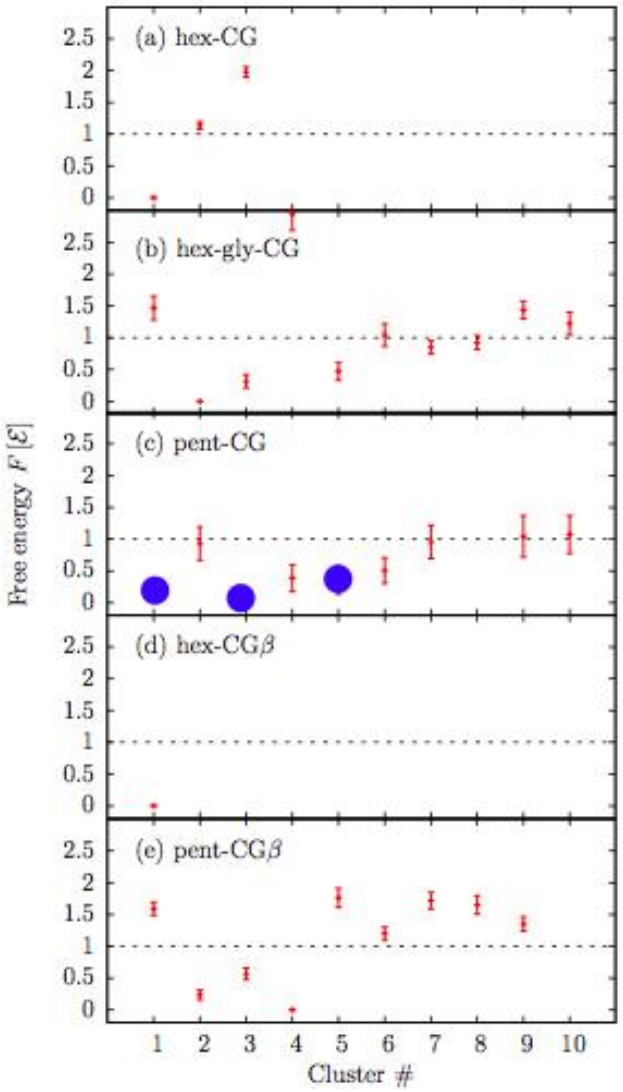


11%, 10% and 9.4%

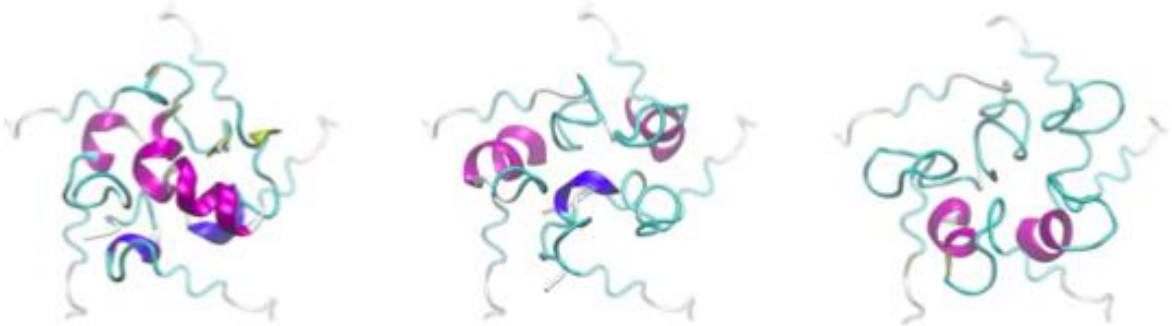


no stable beta barrel – as it should be

The pentamer – regular CG model



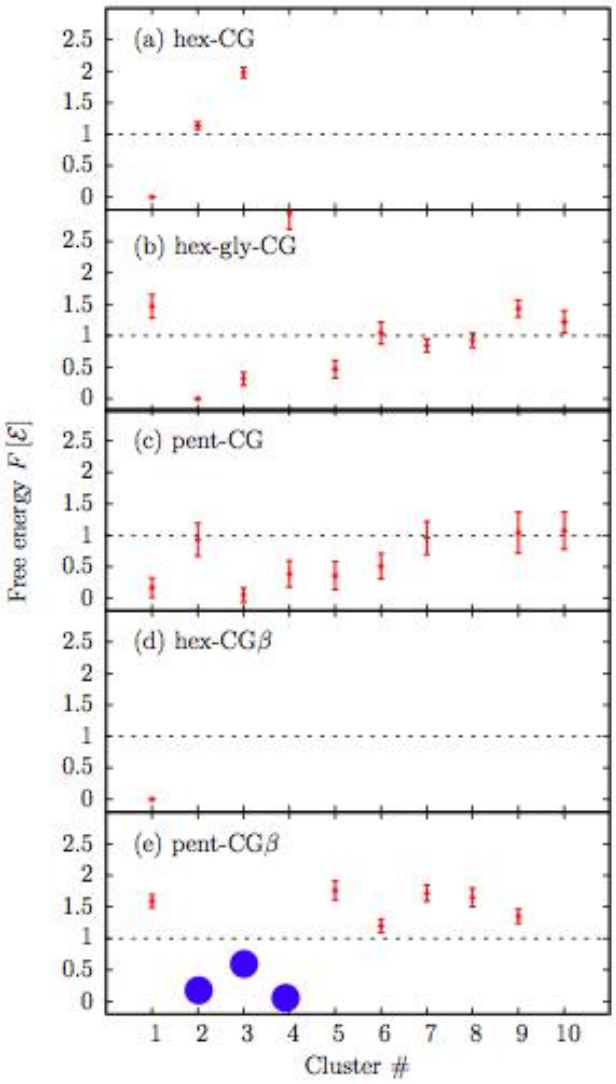
8.2%, 5.6% and 5.1%



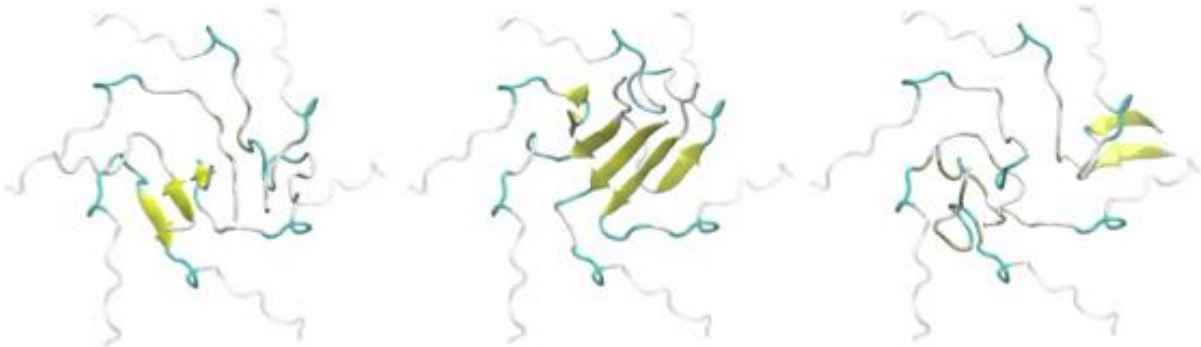
➪ no beta barrel
➪ multiple structures of similar stability

How “realistic” are these structures?
Is there no beta barrel possible in the pentameric interface?

The pentamer – beta-biased CG model

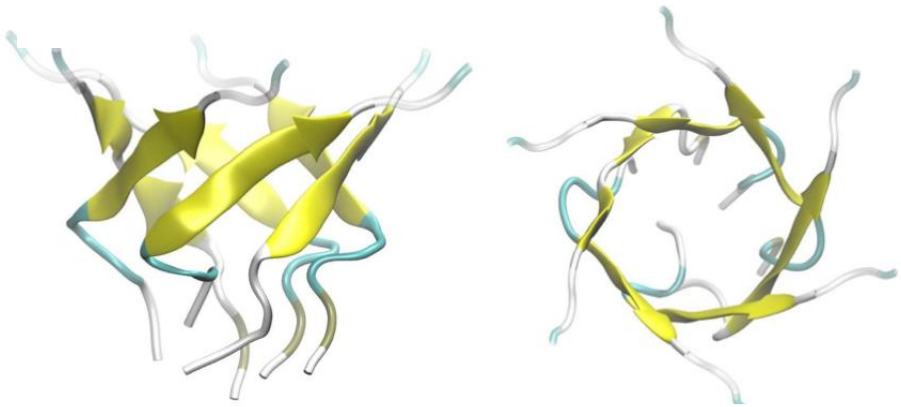


7.3%, 5.7% and 3%



Multiscale simulation of virus capsids

Structure of hexameric interface reproduced in CG model (incl. mutants)



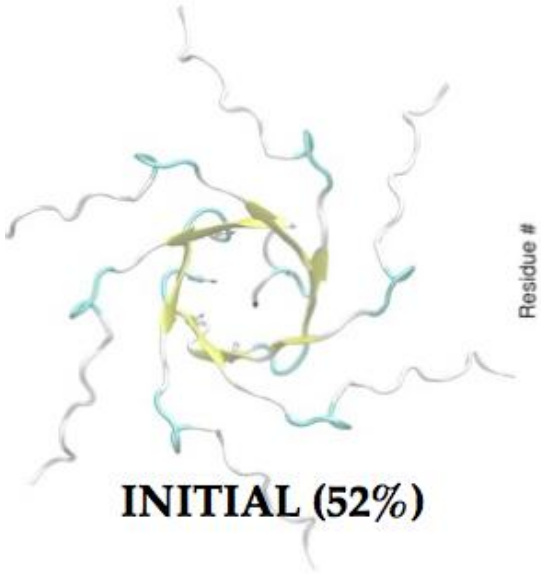
Why backmap?

- ➪ Comparison w. experiment
- ➪ Handing over to higher-resolution calculation (e.g. QM/MM)
- ➪ Assessing the CG model
  compared to a (presumably) more accurate model

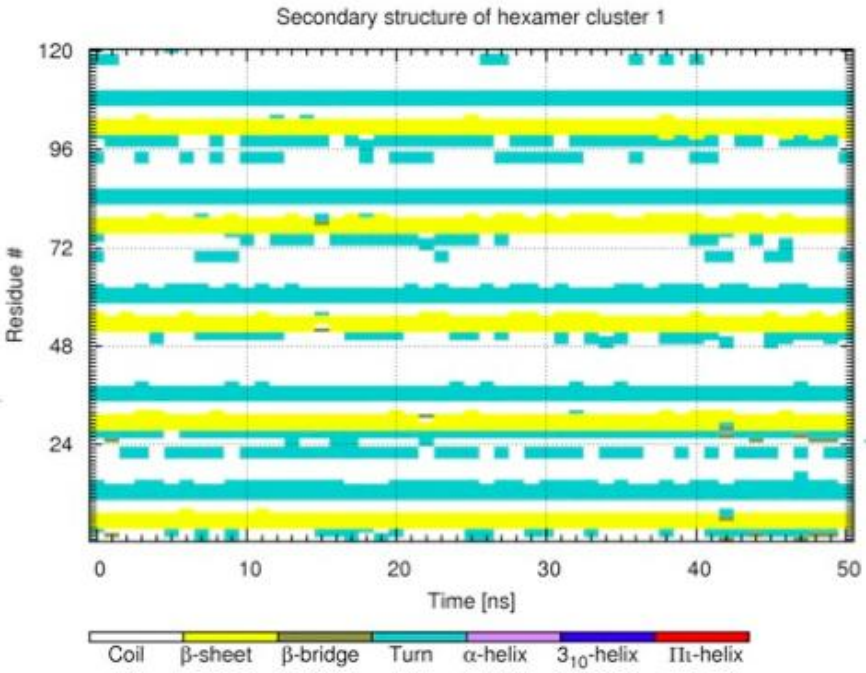
➔ CG approach opens possibility to study these unstructured regions in proteins

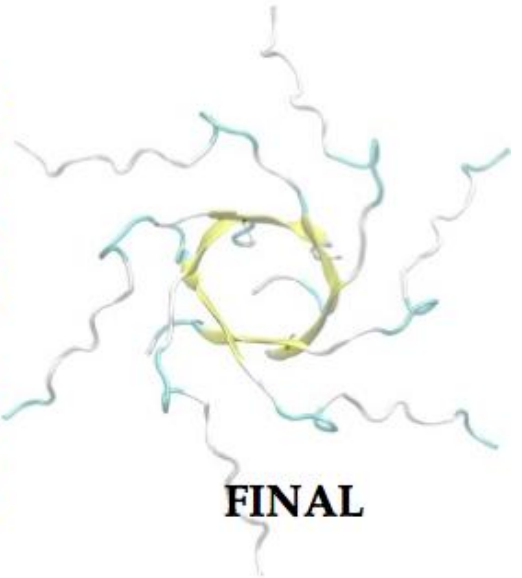
What happens after backmapping ?

… at the hexameric interface:



INITIAL (52%)

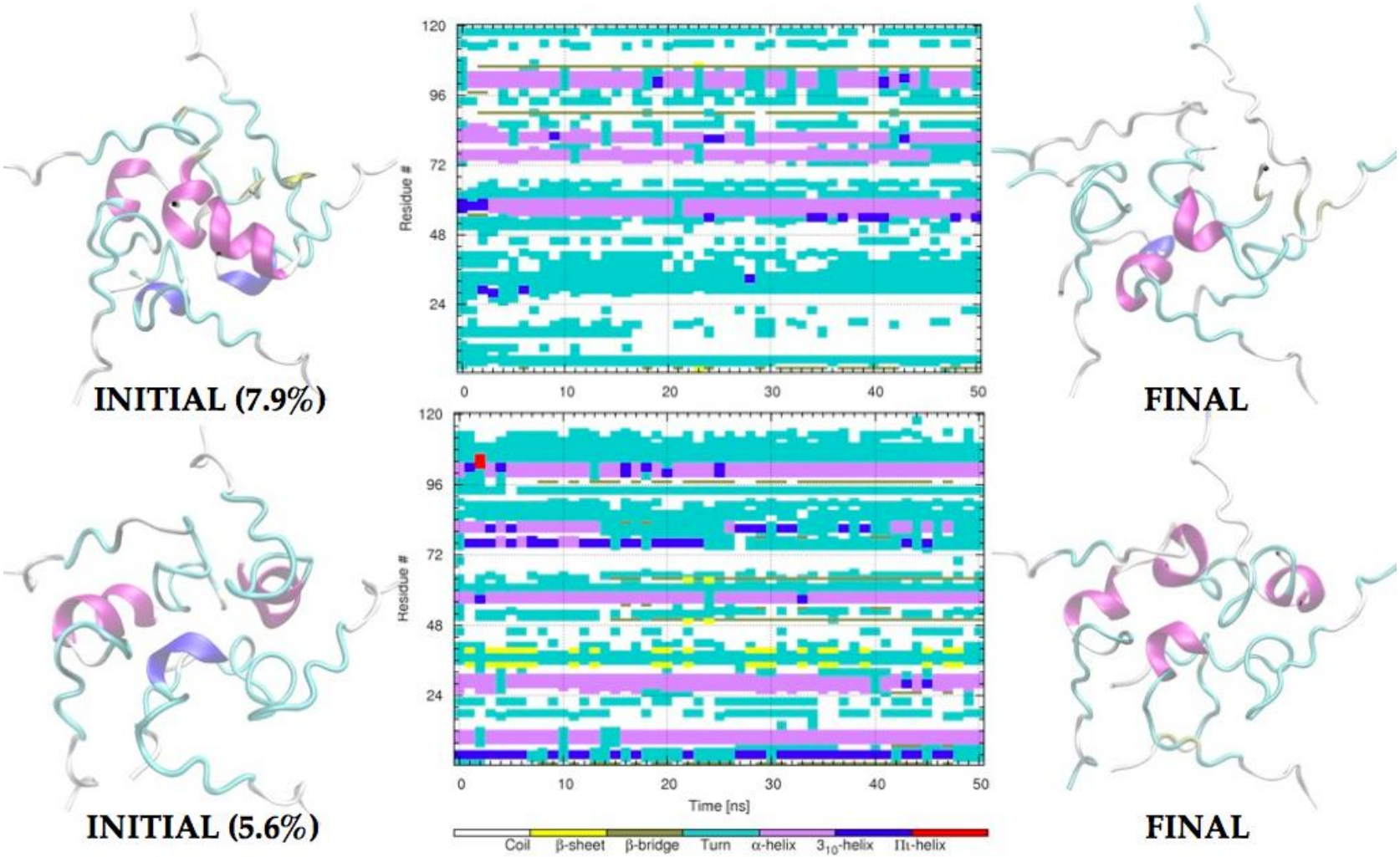




FINAL

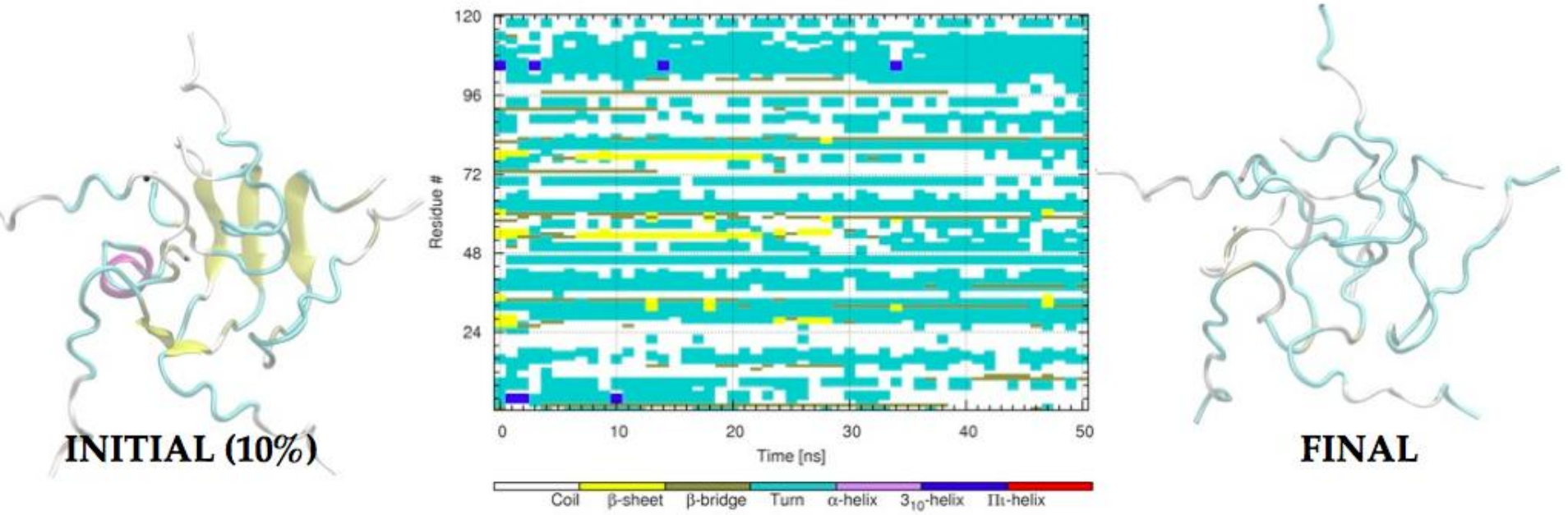
What happens after backmapping ?

… at the pentameric interface:



What happens after backmapping ?

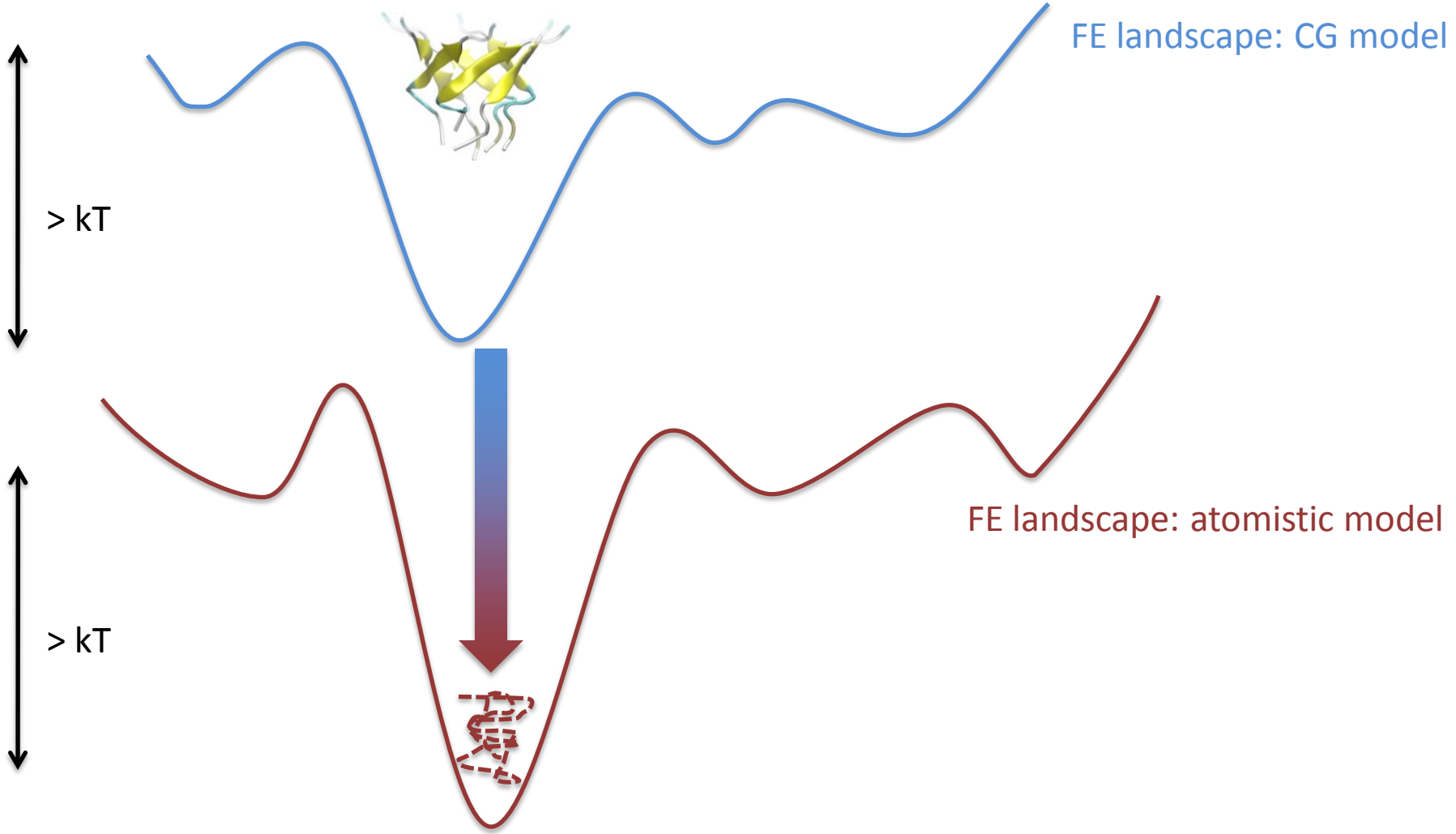
… at the pentameric interface with “CG artifacts” :



- How does one quantify this?
  (In both cases the atomistic structure “runs away” from the CG one.
  However for the “good” CG model, the ensembles still “appear to agree better)
- How does one assess the difference between CG and
  atomistic model for rather shallow FE landscapes?

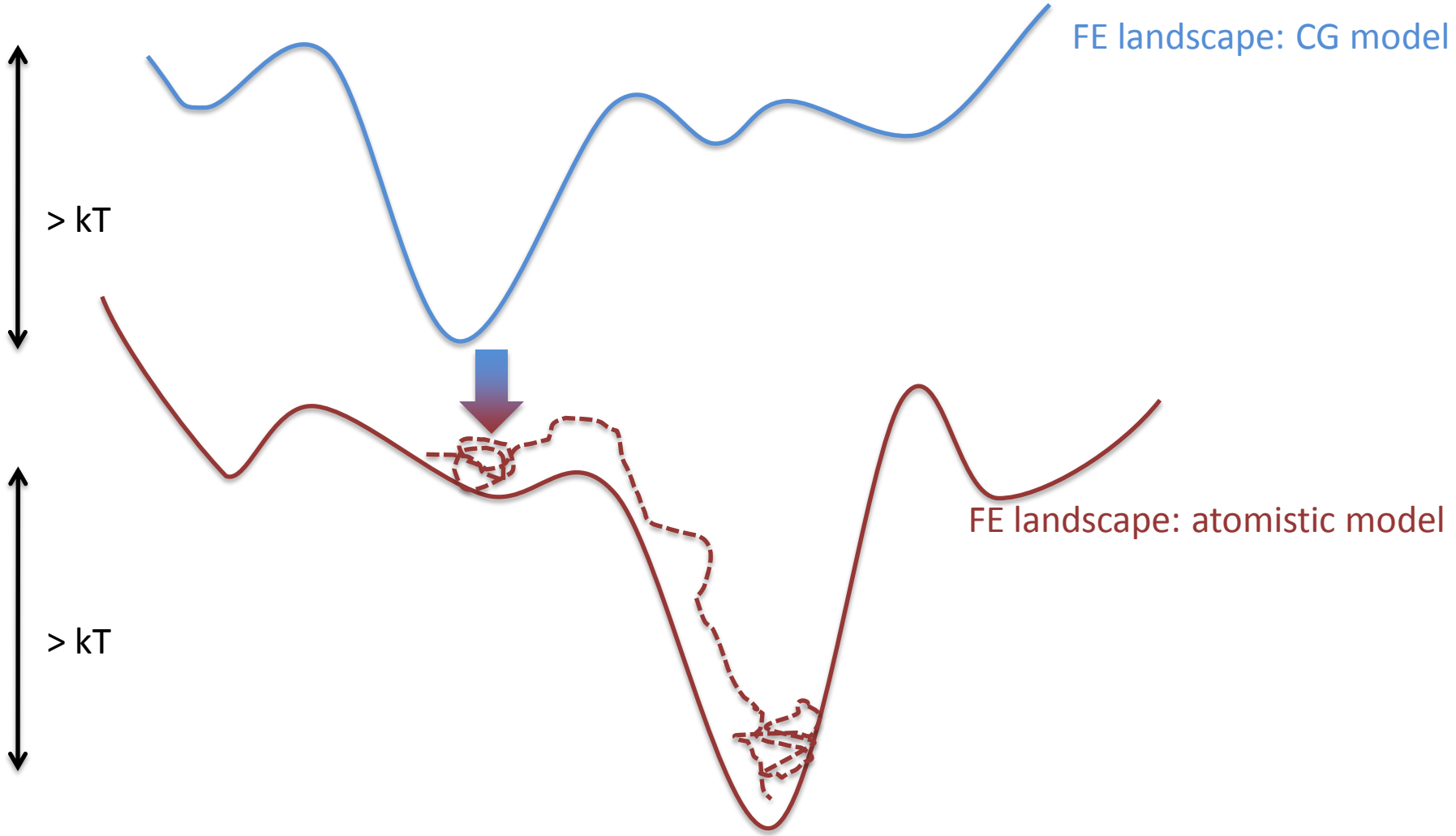
Can we do better than just backmap?

The simple case: CG and atomistic FE minima are deep and agree structurally



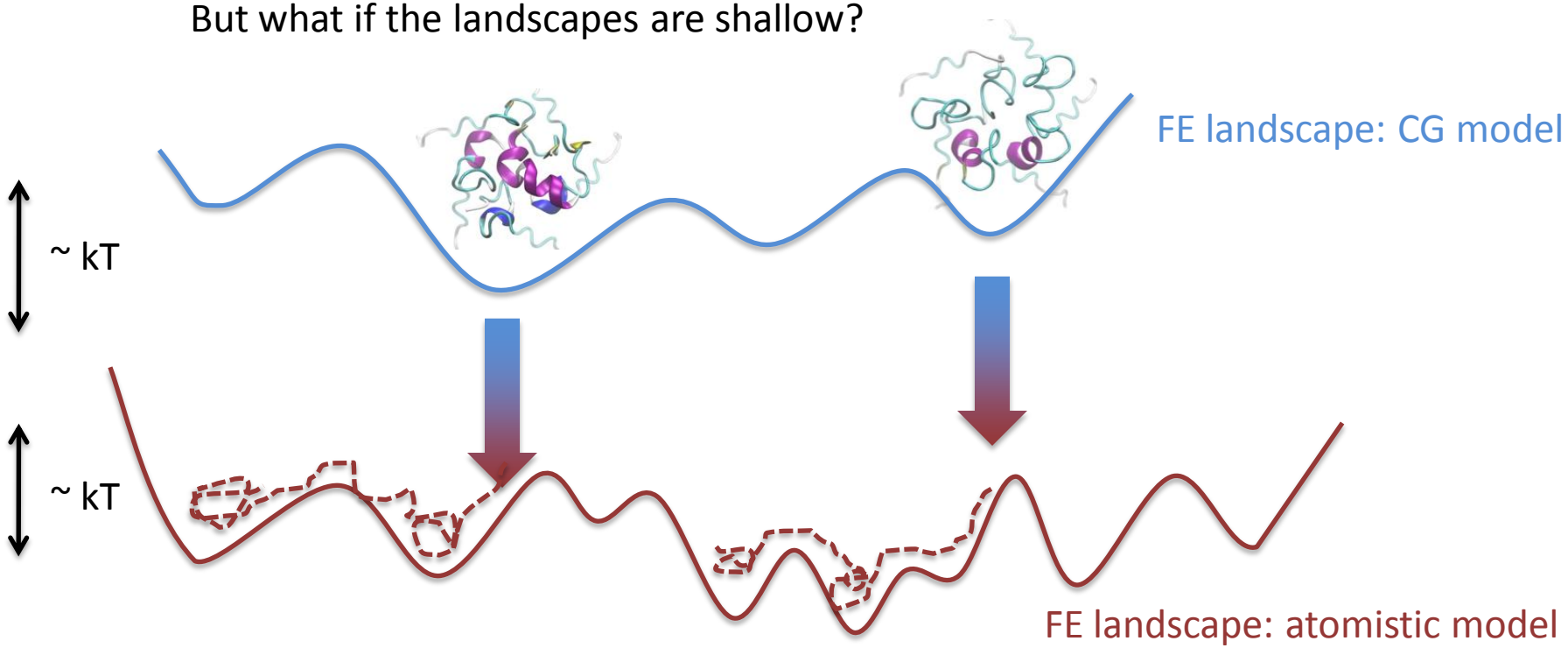
Can we do better than just backmap?

Another simple case: CG and atomistic FE minima are deep but the models “disagree”



Can we do better than just backmap?

But what if the landscapes are shallow?



- Use the CG model for sampling
- Backmap
- One option: Sample atomistically (multiple times) and recluster
- Or: “measure” the FE difference of the various basins between the models
- Note: one might want to not have to use an order parameter