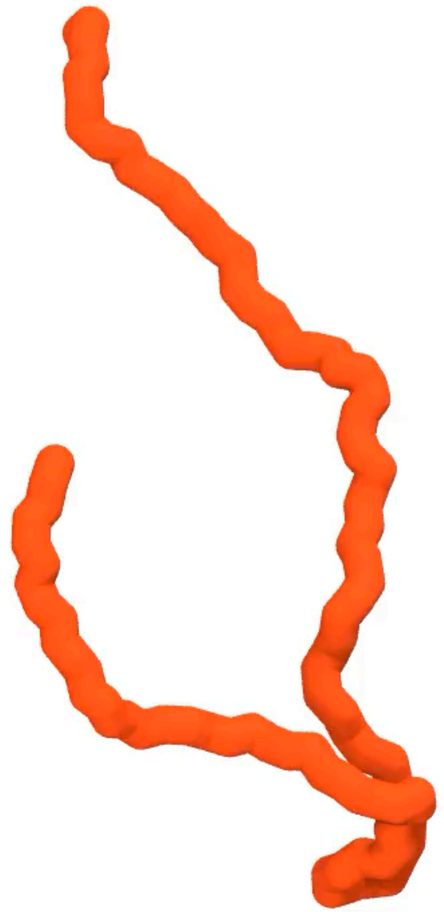
IDPs, Martinize2, Vermouth

Applications of the Martini 3 protein model



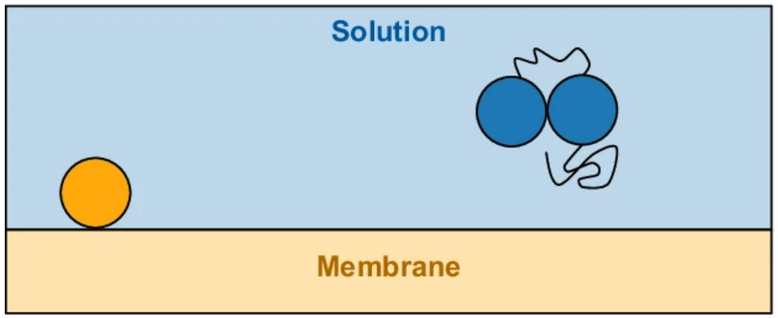
Chris Brasnett, University of Groningen, 12/08/2025

IDPs I: Motivations and challenges

- Martini 3: Wide range of parameterisation targets to improve protein behaviour over Martini 2
    - Proteins are less ‘sticky’, and pack together better
- IDPs have attracted ever-increasing attention
    - Significantly related to phase separation propensity/biomolecular condensates
- **Challenge 1**: Martini 3 protein targets mostly related to *folded* protein behaviour
- **Challenge 2**: Other force field development (e.g. ff19sb, DES-amber, charmm36m) demonstrates balancing folded/unfolded protein behaviour an *exceptionally* challenging task

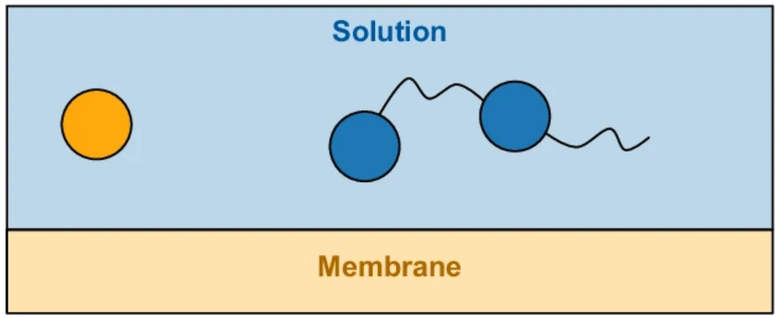
IDPs II: developing Martini models

Unmodified Martini 3



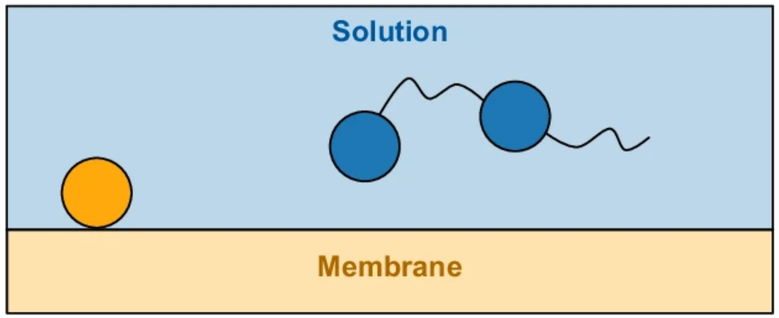
- Multidomain proteins and IDPs too compact
- Poor agreement with SAXS and PREs
- Proteins bind specifically to membrane

↑ Protein-water interactions



- Multidomain proteins and IDPs expand
- Improved agreement with SAXS and PREs
- Lowered affinity for membranes

↓ Protein-protein interactions



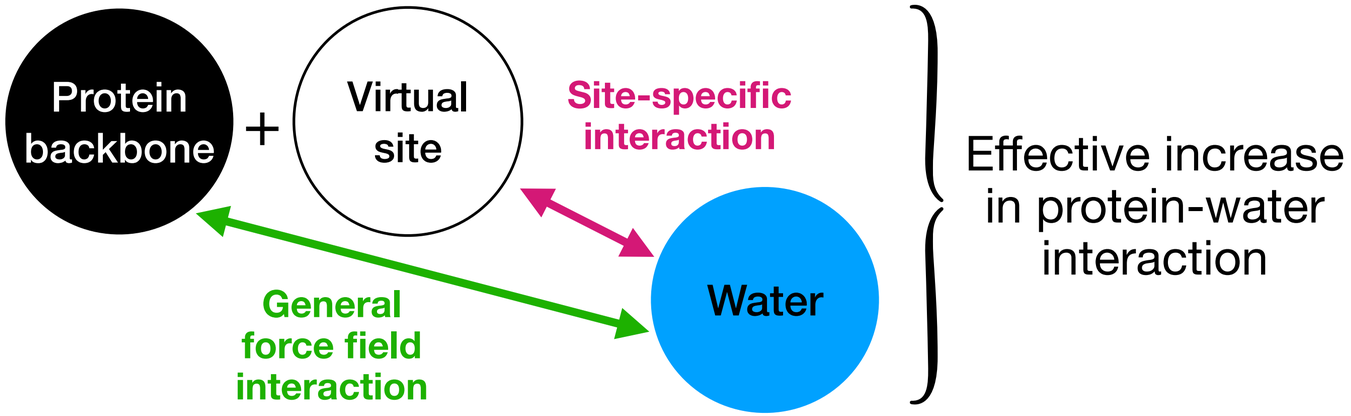
- Multidomain proteins and IDPs expand
- Improved agreement with SAXS and PREs
- Retained affinity for membranes

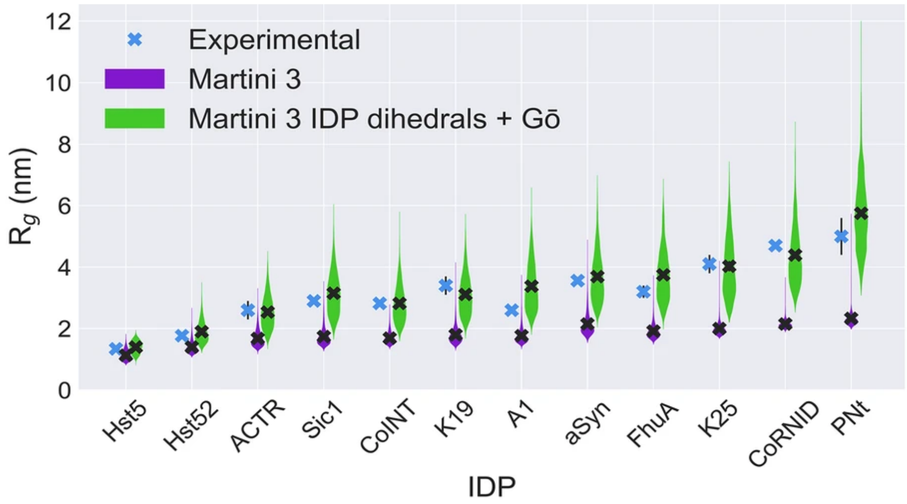
Thomasen, F.E. *et al. J. Chem. Theory Comput*. (2022)
Thomasen, F.E. *et al. Nat. Commun.* (2024)

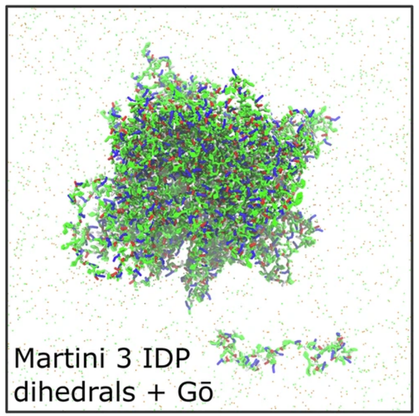
→ 'traditional' (c.f. ff99sb-ws) rescaling of protein-water interactions goes some way to recapturing IDR/MDP dimensions in Martini 3

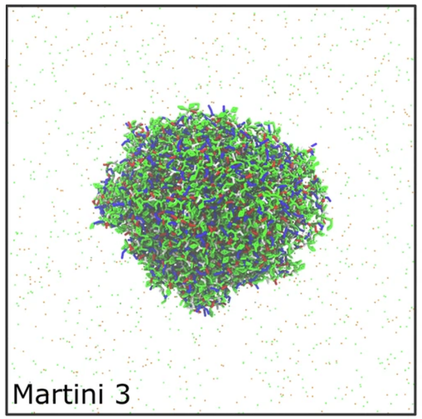
IDPs III: GōMartini + water biasing

- Building on both water biasing approach and taking advantage of GōMartini infrastructure.
- Adaptable biasing method for all kinds of secondary structures and regions.
- Some general improvements to bonded parameters for IDR conformations.





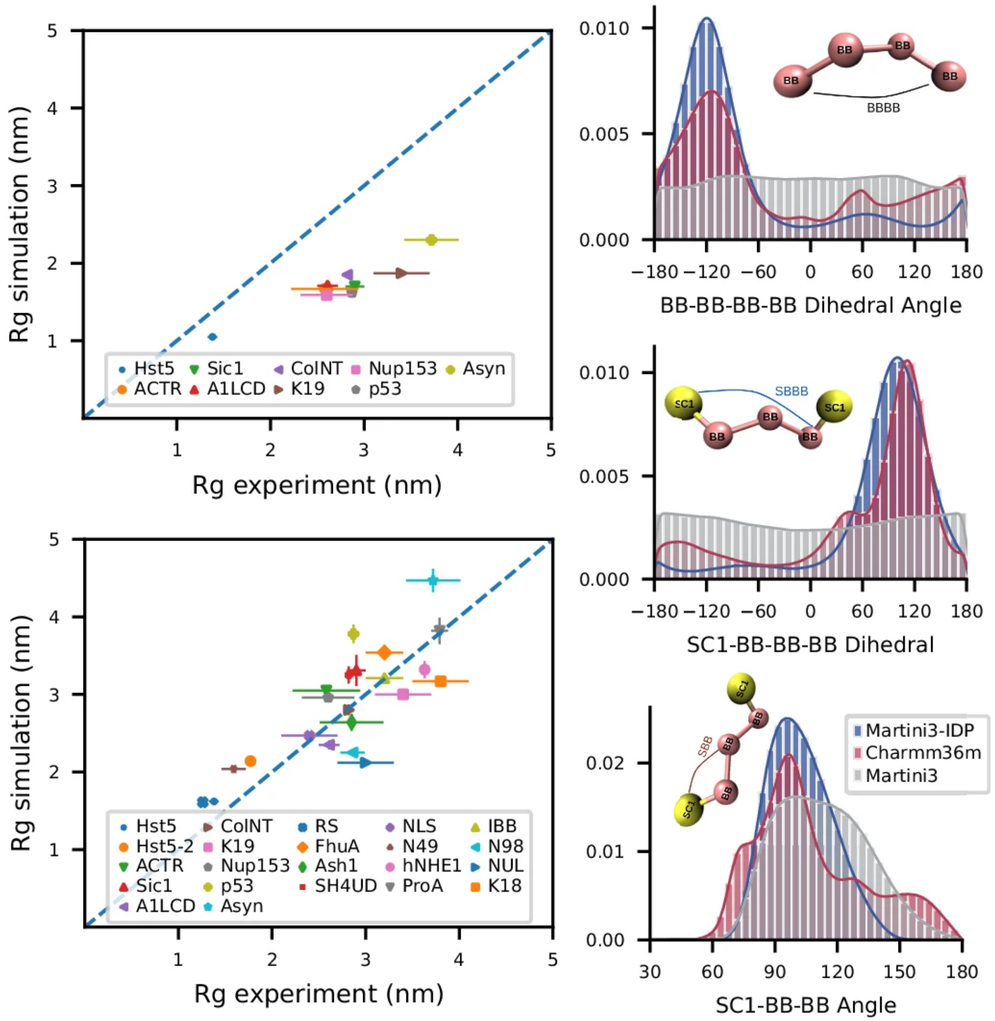




Souza, P.C.T. *et al. Nat. Commun.* (2025)

IDPs IV: Martini3-IDP

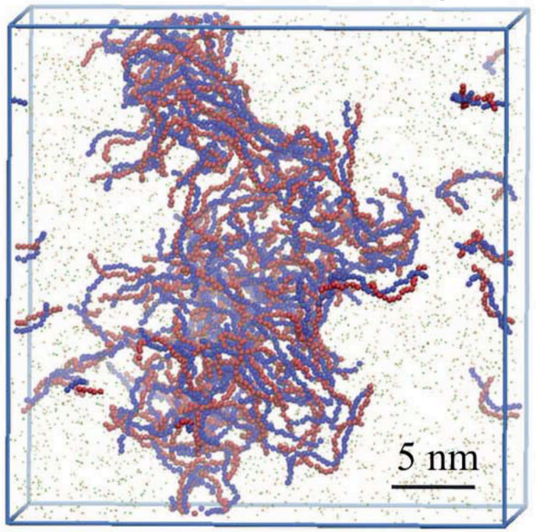
- Monumental effort from Liguo to fully develop and validate specialised parameters for IDRs in Martini proteins.
  - **Without disturbing the core interaction matrix**
- Validated for IDPs, MDPs, ligand-IDP binding, and IDP-membrane association.
- Phase separation behaviour reproduced close to quantitative agreement.



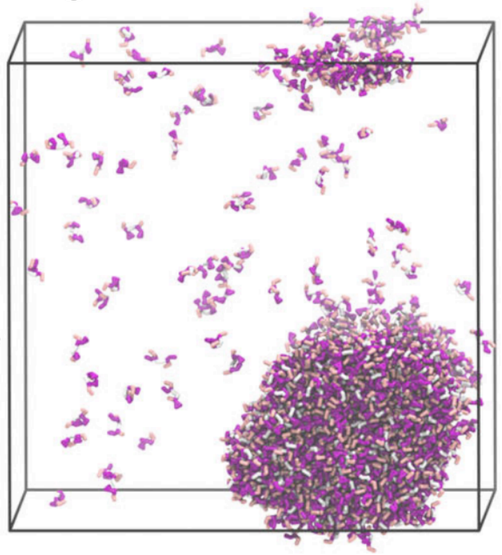
Wang, L. *et al. Nat. Commun.* (2025)

IDPs V: Biomolecular condensates

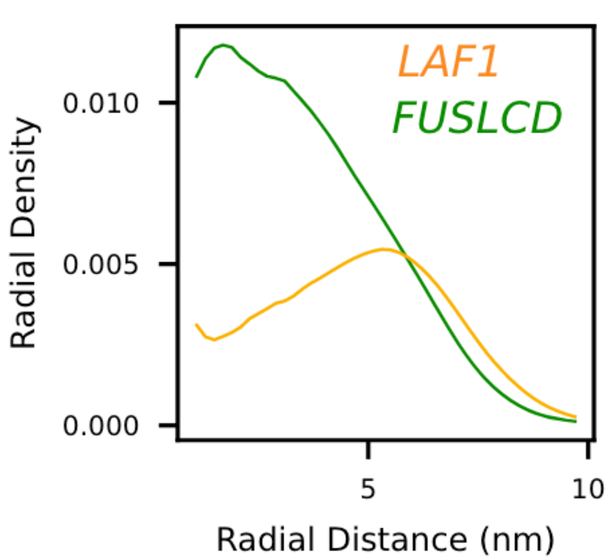
- Reproducing phase separation behaviour of IDPs a major target of (re-)parameterisation efforts.
- Wide range of phase separating systems now modelled successfully by a number of groups using Martini 3 + variants.

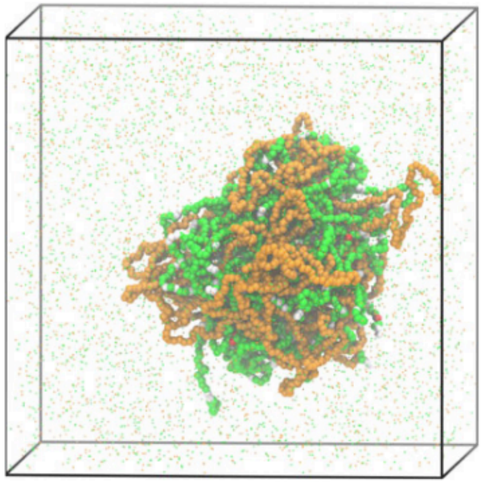


Polyelectrolytes
Tsanai, M. *et al.*
Chem. Sci. (2021)



Short synthetic peptides
Brasnett, C. *et al.*
Commun. Chem. (2021)





Multiphase, multicomponent IDP condensates
Wang, L. *et al.*
Nat. Commun. (2025)

IDPs VI: IDPs + Martini tools

- IDP functionality fully integrated into the Martini software ecosystem
    - Pure IDPs: Polyply (See Fabian's lecture later in the week) for parameter generation and coordinate setups
    - MDPs/proteins with IDRs: Martinize2
        - Annotate regions as disordered, apply IDR specific parameters for either water biasing or Martini3-IDP
        - Integrates the IDP forcefield together with other features, e.g. elastic networks, Gō models, PTMs, etc.

Martinize2 + Vermouth

- **Vermouth**:
    - Comprehensive Python library for resolution transformation and simulation parameter preparation
    - Written with only a few dependencies: lightweight to install
- **Martinize2**:
    - Program built from Vermouth functionality to convert an atomistic input structure (.pdb, .cif) into gromacs coordinate and topology files for simulations.
- **How do I use Martinize2?**
    - Let's have a live demonstration

Applications and Development of Vermouth

"A Protein is a Set Of Coo[illegible]tes"

- Gromacs quote from A.P. Heiner

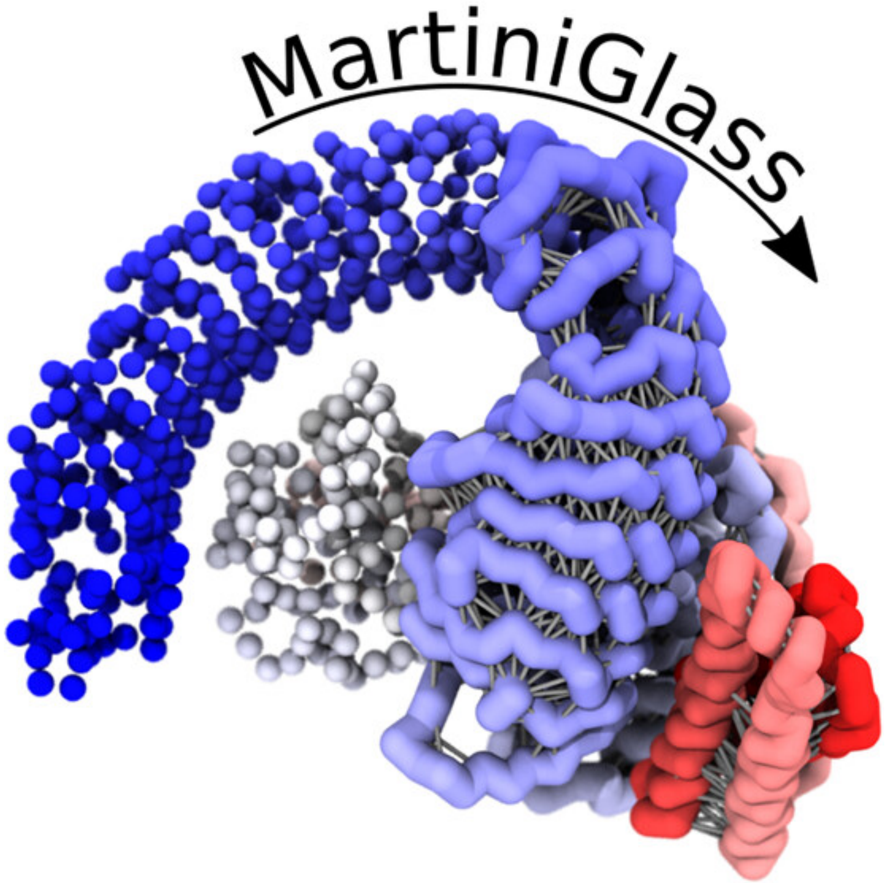
Nodes and Edges in a Graph

- Vermouth: Not just Martinize2!
  - VERsatile, MOdular, and Universal Tranformation Helper
- Powerful and extendable features for topology editing for any kind of molecule
- Let's have a look

Applications of Vermouth: MartiniGlass

We all like looking at our simulations in our favourite visualisation software…

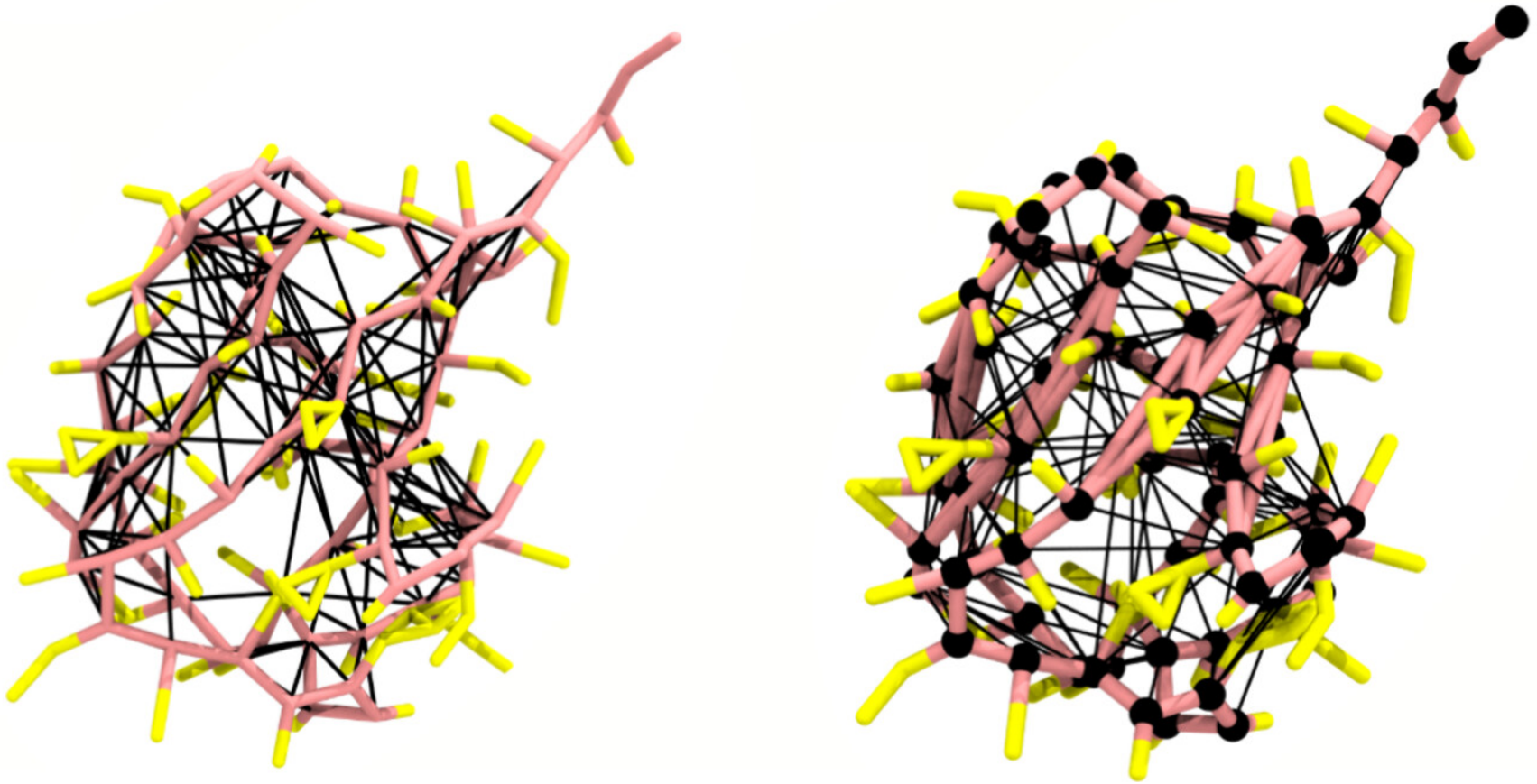
but at best we can make Martini molecules look like overlapping spheres in VMD



MartiniGlass is powered by Vermouth to manipulate molecular topologies so we can visualise continuous molecules in VMD

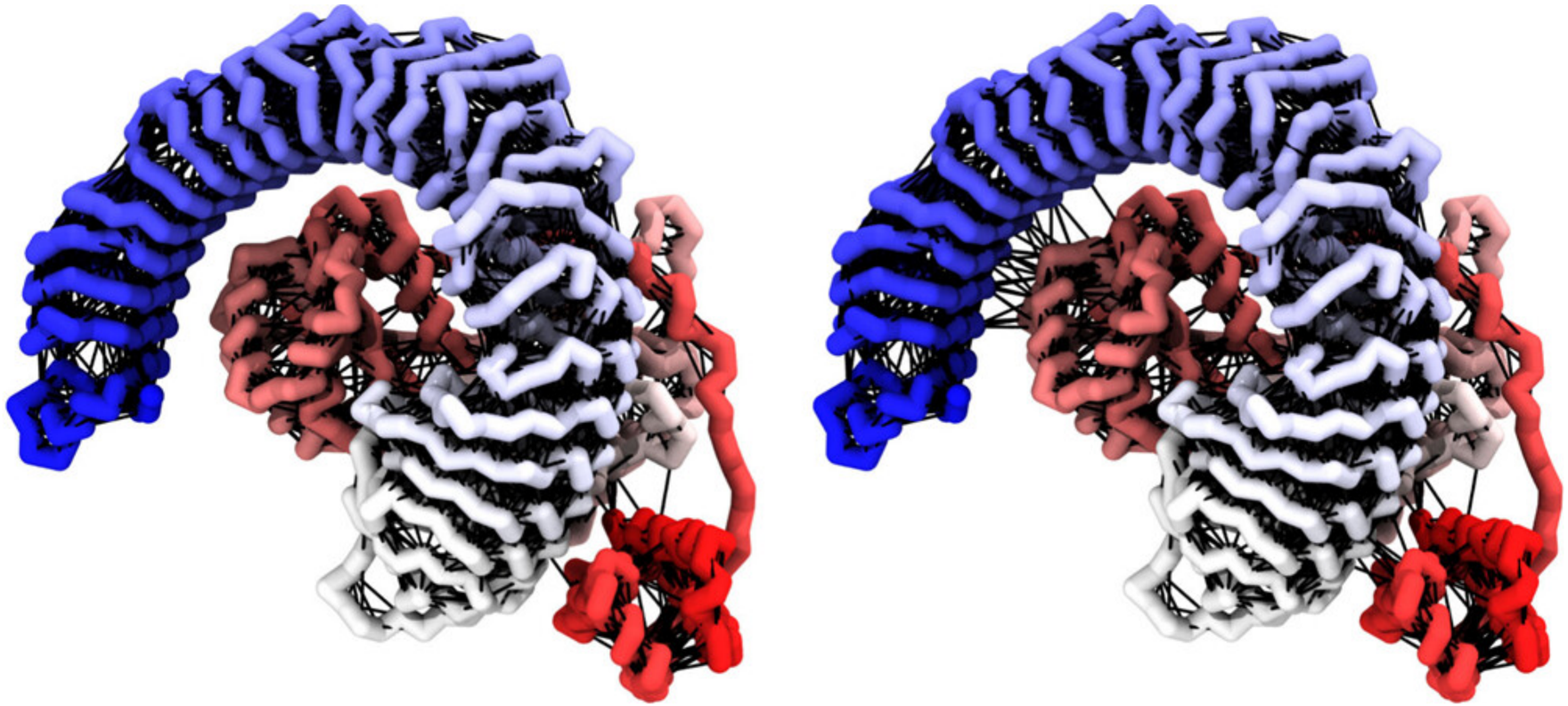
Brasnett & Marrink *JCIM* (2025)

Applications of Vermouth: MartiniGlass



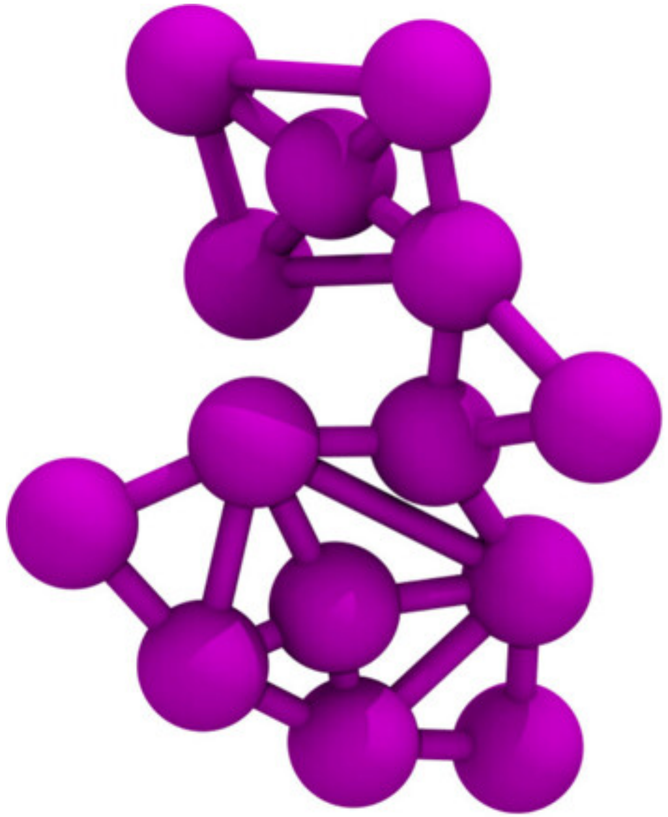
Proteins: visualise elastic (left) or Gō networks (right)

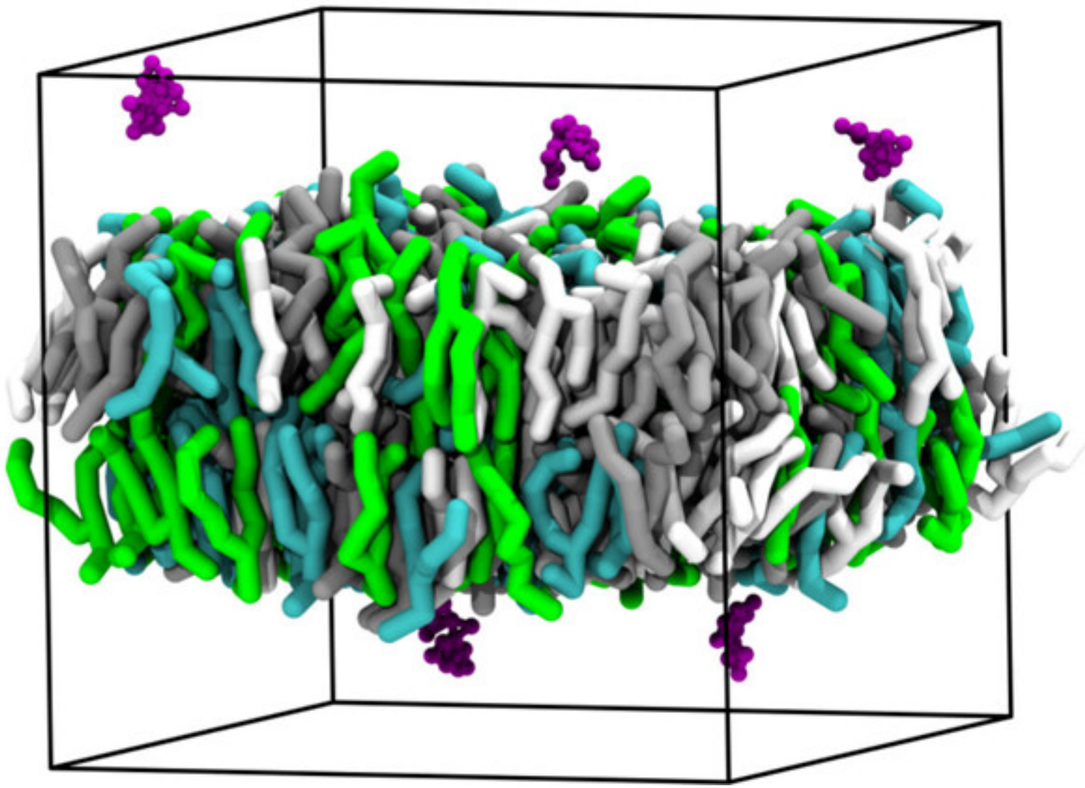
Applications of Vermouth: MartiniGlass



Elastic networks: overcome VMD limitations with custom scripts

Applications of Vermouth: MartiniGlass





Not only for proteins! MartiniGlass can help visualise **any** system!

Take homes

- **Martini3-IDP**
    - Carefully optimised IDP force field for Martini proteins
    - **Well integrated with parameters for folded proteins**
    - Captures many IDP phenomena (e.g. conformational ensembles, small molecule binding, phase separation) very well
- **Vermouth-Martinize**
    - Vermouth != Martinize2, Martinize2 != Vermouth
    - Many useful features for topology manipulation
- Interested in helping to develop Vermouth? **Please talk to us!**

Acknowledgments

- IDPs: Siewert-Jan Marrink, Paulo C. T. Souza, Liguo Wang & the protein task force

- Vermouth-Martinize: Peter Kroon & Fabian Grünewald