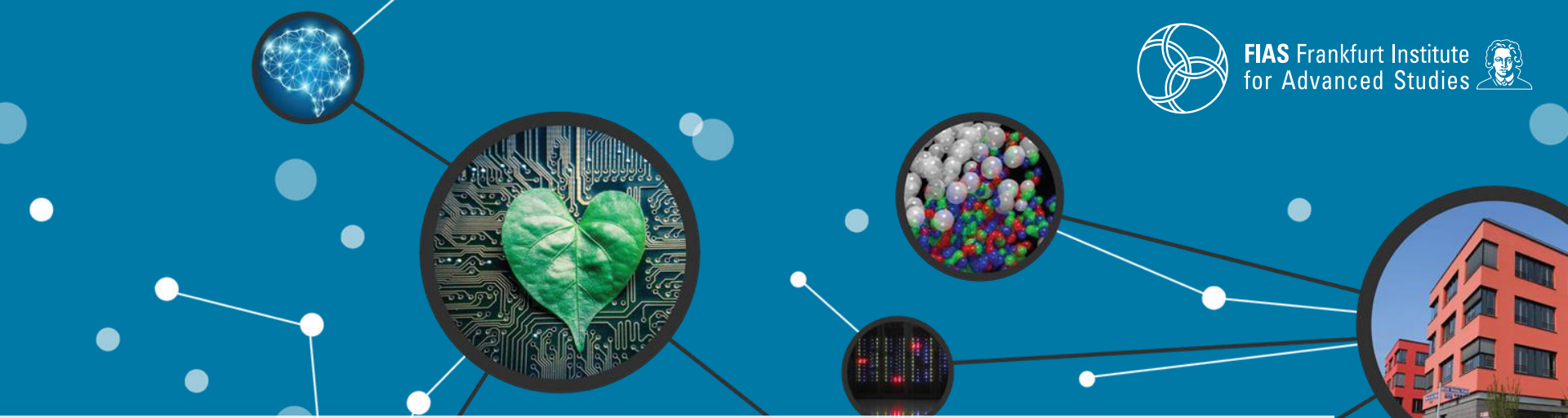


FIAS Frankfurt Institute for Advanced Studies

Introduction to the protein models in Martini 3

Sebastian Thallmair

Martini Workshop 2025, Groningen

Today's Martini menu

Tuesday, August 12 Zernike campus, Bernoulliborg, building 5161

Room 5161.0151
09:00-10:30 hours: LECTURE: Martini model for proteins
Sebastian Thallmair/Adolfo Poma
10:30-11:00 hours: Tea/Coffee break
11:00-12:30 hours: LECTURE: Martini IDPs/Highres backbone/ProLint
Chris Brasnett/Luis Borges/Daniel Ramirez

12:30-13:30 hours: LUNCH (bring your own)

Zernike campus, Linnaeusborg, building 5173
Room 5173.0169 (Tea/coffee at around 3 PM)
13:30-17:00 hours: HANDS-ON SESSION 2: MARTINI PROTEINS
Tutorials at different levels on proteins

Zernike campus, area in front of building 5161.0151
17:00-19:00 hours: POSTER SESSION with SNACKS & DRINKS

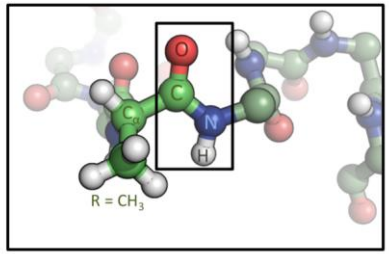
A list of titles will be provided.

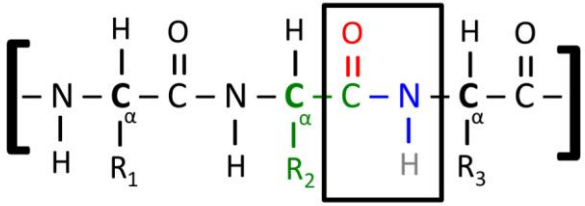
Proteins

- Essential nutrients for the human body – 17 kJ/g
  lipids 33 kJ/g

- Biopolymers and macromolecules
  consisting of 20 natural amino acids

- Large spectrum of functions
  - catalysis
  - signaling
  - providing structure
  - transport





https://en.wikipedia.org/wiki/Protein

John Kendrew, 1958

AlphaFold, 2025

CG Martini 3

750 *J. Phys. Chem. B* **2004,** *108,* 750−760

Coarse Grained Model for Semiquantitative Lipid Simulations

Siewert J. Marrink,* Alex H. de Vries, and Alan E. Mark

Department of Biophysical Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Received: August 22, 2003; In Final Form: October 29, 2003

7812 *J. Phys. Chem. B* **2007,** *111,* 7812−7824

The MARTINI Force Field: Coarse Grained Model for Biomolecular Simulations

Siewert J. Marrink,*,† H. Jelger Risselada,† Serge Yefimov,‡ D. Peter Tieleman,§ and Alex H. de Vries†

Groningen Biomolecular Sciences and Biotechnology Institute & Zernike Institute for Advanced Materials, Department of Biophysical Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands, Zernike Institute for Advanced Materials, Department of Applied Physics, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands, and Department of Biological Sciences, University of Calgary, 2500 University Drive NW, Calgary AB T2N 1N4, Canada

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Received 16 June 2020 Accepted 22 February 2021

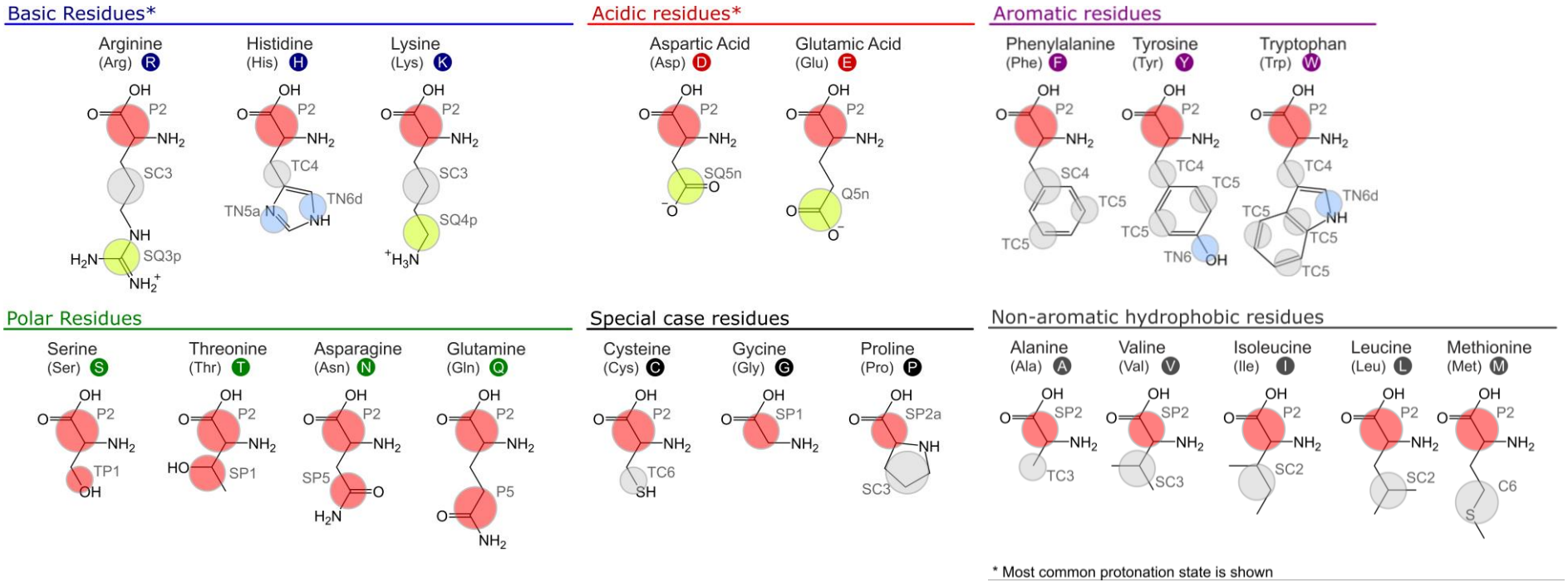
ARTICLES https://doi.org/10.1038/s41592-021-01098-3 nature methods

Check for updates

Martini 3: a general purpose force field for coarse-grained molecular dynamics

Paulo C. T. Souza[1,2], Riccardo Alessandri[1], Jonathan Barnoud[1,3], Sebastian Thallmair[1,4], Ignacio Faustino[1], Fabian Grünewald[1], Ilias Patmanidis[1], Haleh Abdizadeh[1], Bart M. H. Bruininks[1], Tsjerk A. Wassenaar[1], Peter C. Kroon[1], Josef Melcr[1], Vincent Nieto[2], Valentina Corradi[5], Hanif M. Khan[5,6], Jan Domański[7,8], Matti Javanainen[9,10], Hector Martinez-Seara[9], Nathalie Reuter[6], Robert B. Best[8], Ilpo Vattulainen[10,11], Luca Monticelli[2], Xavier Periole[12], D. Peter Tieleman[5], Alex H. de Vries[1] and Siewert J. Marrink[1]

CG Martini 3 representations of amino acids



[1] T. Duve, *et al.*, *bioRxiv* (2025).

[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).

Protein structures and their key interactions

- Different types of interactions stabilize proteins:
  - hydrophobic interactions
  - polar interactions
  - hydrogen bonds
  - charged interactions
  - disulfide bonds, etc.
- In particular the directionality of H bonds is challenging in CG models
- Additional bonded interactions are needed

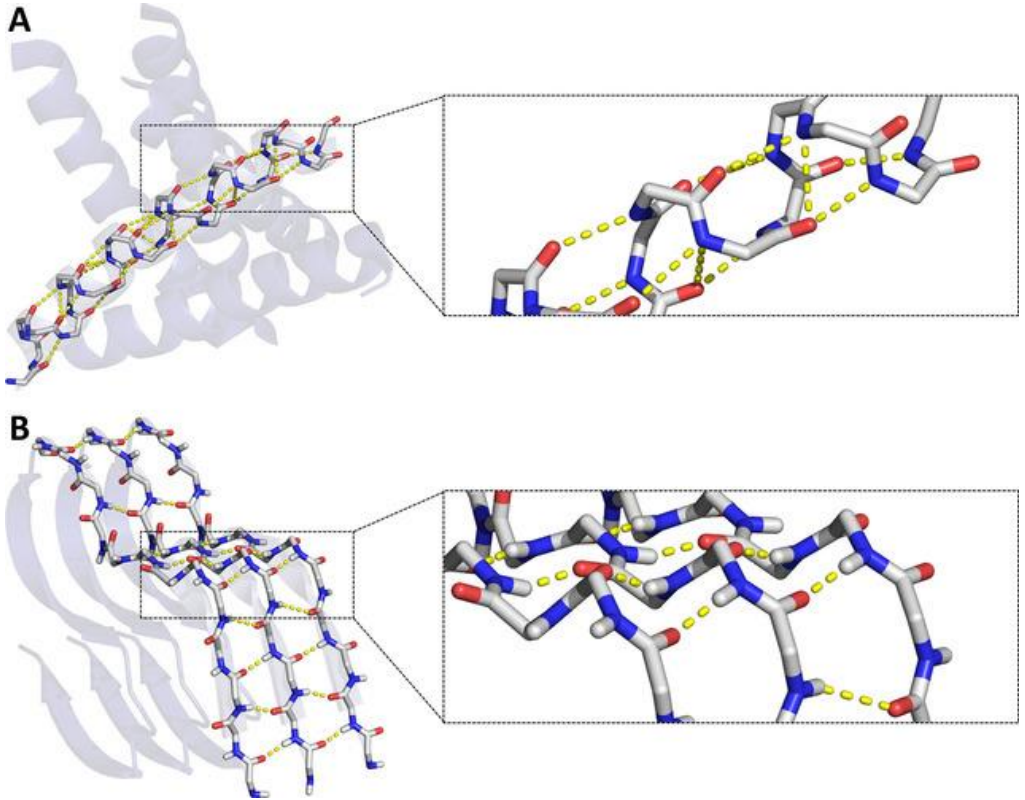
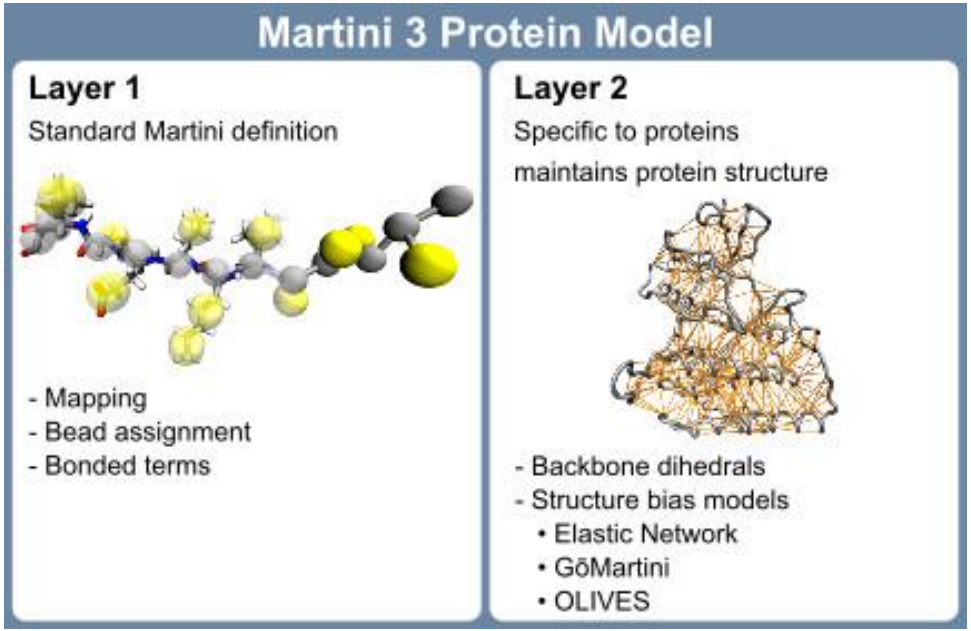


figure from V. Sereikaité, *et al.*, *ChemBioChem* **19**, 2136 (2018).

CG Martini 3 protein model has two layers

- Layer 1: standard Martini definition
- Layer 2: secondary structure-specific dihedrals and structure bias models
- Both layers are decoupled and can be developed independently

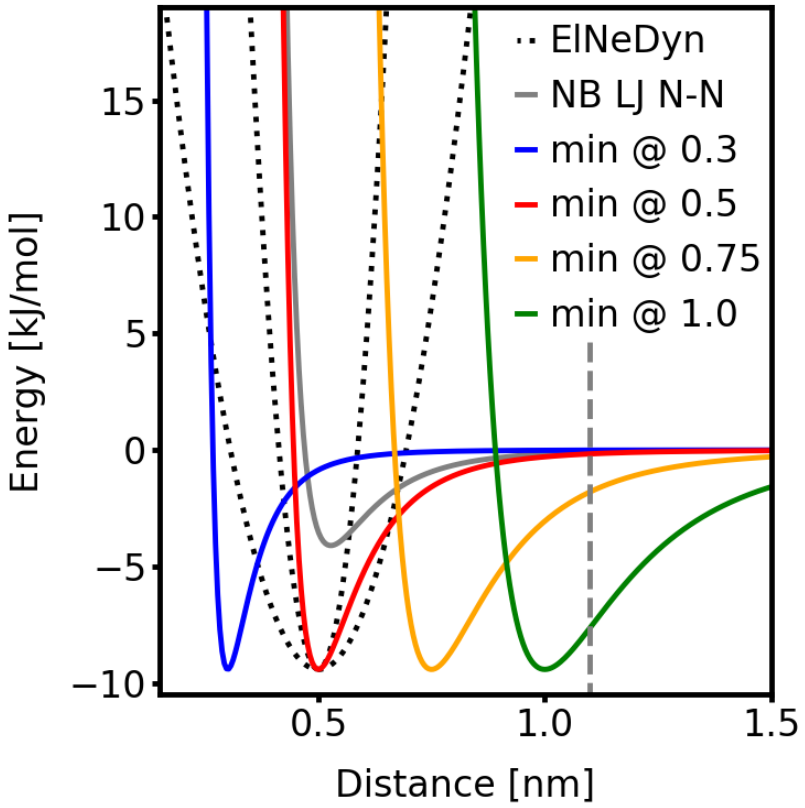


[1] T. Duve, *et al.*, *bioRxiv* (2025).
[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).

Additional stabilization required for tertiary structure

- Currently, three choices for structure bias models:
  - **Elastic Network** (EN) with harmonic potentials [3,4]
  - **GōMartini 3**: Gō-like model with Lennard-Jones (LJ) potentials [2]
  - **OLIVES**: Gō-like model with Lennard-Jones (LJ) potentials [5]

- Proteins part I(b) tutorial



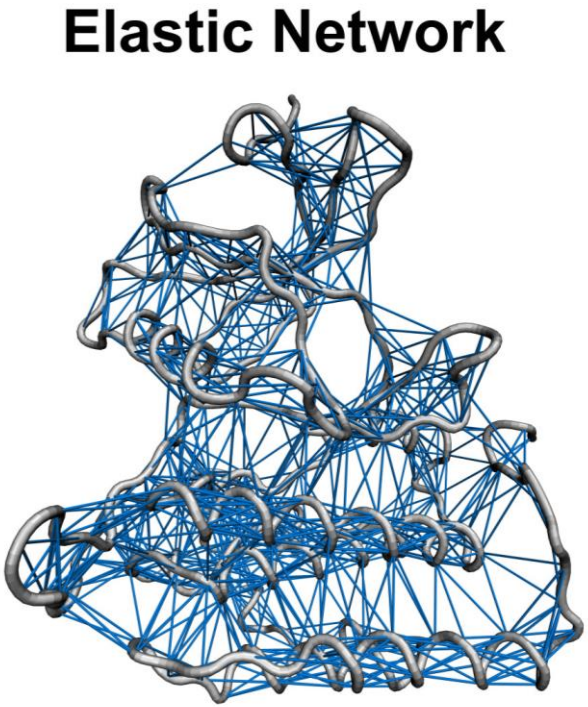
[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).
[3] P. C. T. Souza, *et al.*, *Nat. Methods* **18**, 382 (2021).
[4] P. C. Kroon, *et al.*, *eLife* **12**, PR90627 (2023).
[5] K. B. Pedersen, *et al.*, *J. Chem. Theory Comput.* **20**, 8049 (2023).

Elastic network model

- Bonded terms applied to backbone (BB) beads at the backbone center of mass
- Elastic bond introduced if:
  - residues are separated by at least 2 residues
  - BB distance d is shorter than the cutoff distance R_c
- Harmonic potential connects the BB beads

$$V(d) = 0.5\, k\, \left(d - R_{eq}\right)^2$$

- Typical setup:
  cutoff distance $R_c = 0.8 - 1.0$ nm
  force constant $k = 700 - 1000$ kJ/(mol nm^2)



Preparing and fine-tuning your elastic network model

- Martinize2 command [4]:

```
martinize2 <...> -ff martini3001 -elastic -ef 700.0 -el 0.5 -eu 0.9
```

- Optimization of cutoff distance R_c and force constant k

- Additional fine-tuning options:
  - distance-dependent force constant k options `-ea -ep`
  - Removal of EN bonds in flexible protein regions

```
[ bonds ]
...
; Rubber band
   1    7 1 0.79915 700.0
   1   11 1 0.6977 700.0
   1   13 1 0.8159 700.0
   1  364 1 0.7891 700.0
   3   11 1 0.47668 700.0
   3   13 1 0.57024 700.0
   3   15 1 0.81049 700.0
   3  212 1 0.85239 700.0
...
```

[4] P. C. Kroon, *et al.*, *eLife* **12**, PR90627 (2023).
www.github.com/marrink-lab/vermouth-martinize

GōMartini 3 model

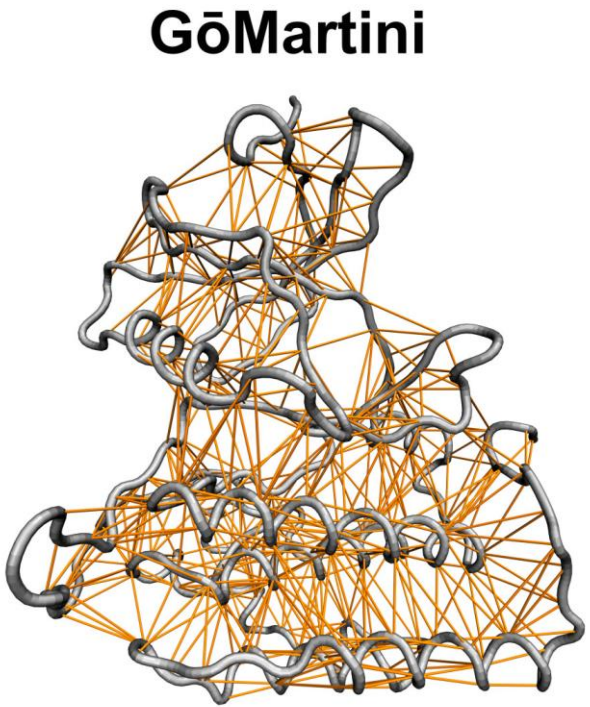
- Bonded terms applied to backbone (BB) beads at the backbone center of mass
- Native contacts define the introduced bonds
- Gō bond introduced if:
  - residues are separated by at least 3 residues
  - BB distance d is shorter than the cutoff distance R_c
- LJ potential connects the BB beads

$$V_{LJ}(d) = 4\varepsilon\left[\left(\frac{\sigma}{d}\right)^{12} - \left(\frac{\sigma}{d}\right)^{6}\right]$$

- Typical setup:

  cutoff distance $R_c = 1.0 - 1.1$ nm

  dissociation energy $\varepsilon = 9.4 - 15$ kJ/mol



Implementation of the GōMartini 3 model

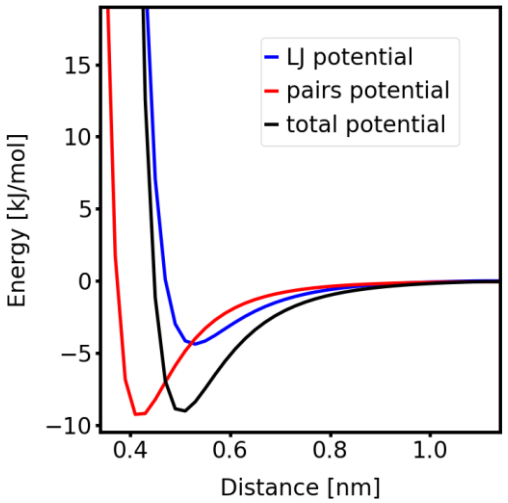
- Virtual sites are used for the Gō-like interactions [5]
  - Generation of additional bead types
  - Non-bonded cutoff is applied to Gō-like interactions

  ⟶ advantageous for domain decomposition

- Regular non-bonded terms excluded for Gō-like contacts

  ⟶ more accurate protein structures

- Contact map based on
  - Overlap criterion of all amino acid atoms
  - Additional contacts via repulsive contacts of structural units (rCSU) [6]



[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).
[6] K. Wołek, *et al.*, *J. Chem. Phys.* **143**, 243105 (2015).

Preparing and fine-tuning your Gō-like model

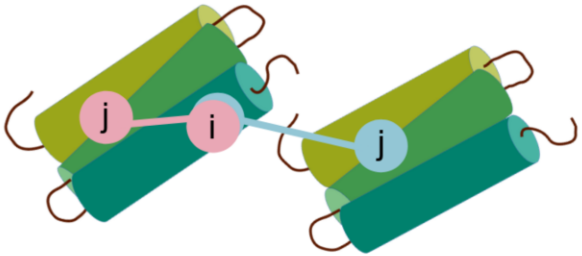
- Files generated by Martinize2 (or create_goVirt.py):
  - `go_atomtypes.itp` — virtual bead definitions
  - `go_nbparams.itp` — Gō interaction table
- Definition of `GO_VIRT` variable activates Gō-like model
- Files have to be included in the `martini.itp` file
- Pitfalls:
  - Multiple chains / protein copies
  - Atomistic .pdb file

[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).

OliGōmers: Extension of GōMartini 3

- Addresses the challenge of simulating oligomers with GōMartini 3

- Multi-layered virtual site implementation
  - intra pairs
  - inter pairs
  - regular CG-BB



		INTRA Gō i-j pair			INTER Gō i-j pair			
			intra	inter		intra	inter	
INTRA Gō		VS_{intra} (ε_{intra})	●	●	VS_{inter} (ε_{inter})	●	●	INTER Gō
		VS_{inv} ($\varepsilon_{inv} = -\varepsilon_{intra}$)	●	●	Excl. *inter*	●		
		Excl. *inv*	●		CG-BB (ε_{BB})	●	●	INTRA CG-BB
INTER CG-BB		CG-BB (ε_{BB})	●	●	$VS_{inv\text{-}BB}$ ($\varepsilon_{inv\text{-}BB} = -\varepsilon_{BB}$)	●	●	
		Excl. *CG-BB*	●		Excl. D	●		

[7] K. Korshunova, *et al.*, *J. Chem. Theory Comput.* **20**, 7635 (2024).

OLIVES model

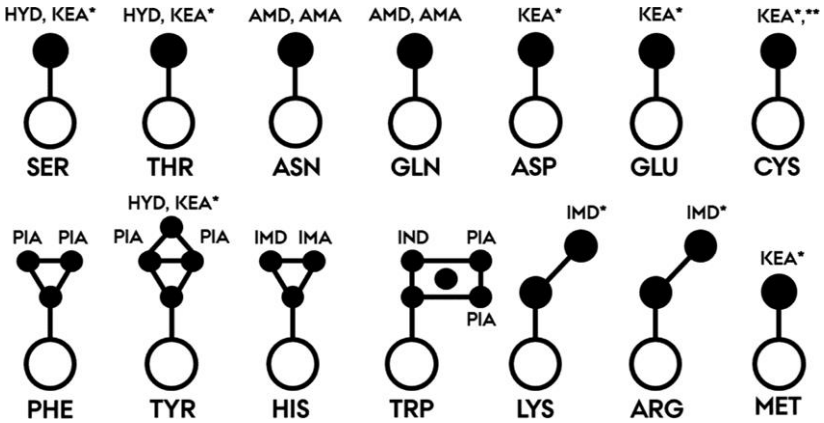
- Bonded terms applied to the beads containing the interacting atoms/fragments
- Eight classes define the introduced bonds
- LJ potential connects the BB beads

$$V_{LJ}(d) = 4\varepsilon\left[\left(\frac{\sigma}{d}\right)^{12} - \left(\frac{\sigma}{d}\right)^{6}\right]$$

- QM calculated H bond dissociation energies

  ε = 8.8 – 33.3 kJ/mol

  → scaling option is available (but not tested)



[kcal/mol]	HYD	AMD	IMD	IND
KEA	3.54	4.06	5.78	5.12
AMA	4.51	5.44	6.92	6.27
IMA	6.24	6.55	7.96	7.11
PIA*	4.97**	5.31	6.17	2.10

[a](HYD) hydroxyl donor, (AMD) amide donor, (IMD) imidazole donor, (IND) indole donor, (KEA) ketone donor, (AMA) amide acceptor, (IMA) imidazole acceptor, and (PIA) π acceptor. Note that the majority of the results were obtained by DFT calculations, which have a typical error of 2 kcal/mol.[34] *π acceptor energies are divided by 2 internally, spreading the energy across two beads, as illustrated in Figure 1. **Average of two results in the original work by Du et al.[18]

[5] K. B. Pedersen, *et al.*, *J. Chem. Theory Comput.* **20**, 8049 (2023).

OLIVES model

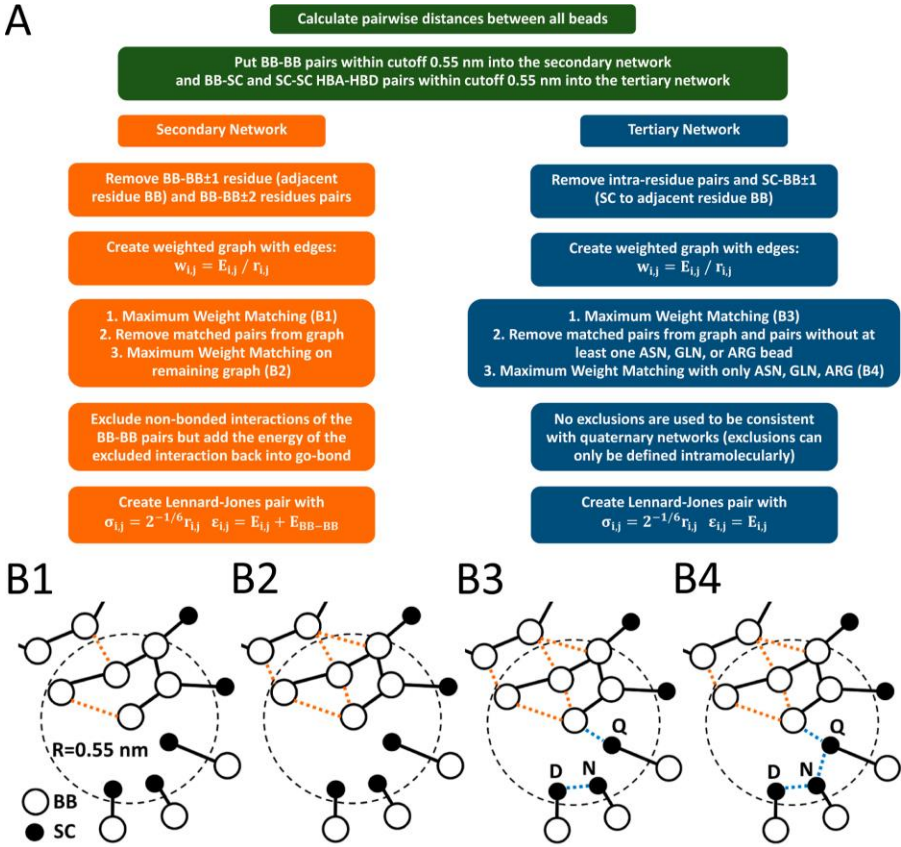
- Bonded terms applied to the beads containing the interacting atoms/fragments
- Eight classes define the introduced bonds
- LJ potential connects the BB beads

$$V_{LJ}(d) = 4\varepsilon\left[\left(\frac{\sigma}{d}\right)^{12} - \left(\frac{\sigma}{d}\right)^{6}\right]$$

- QM calculated H bond dissociation energies

  ε = 8.8 – 33.3 kJ/mol

  → scaling option is available (but not tested)
- Gō bond introduced if:
  - BB-BB: separated by at least 2 residues
  - BB-SC: separated by at least 1 residue
  - distance d is shorter than the cutoff R_c = 0.55 nm



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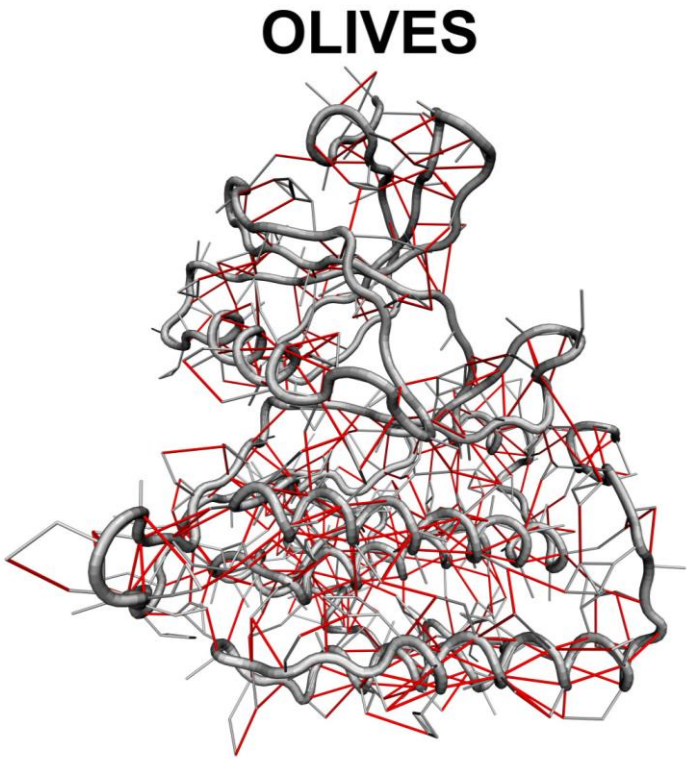


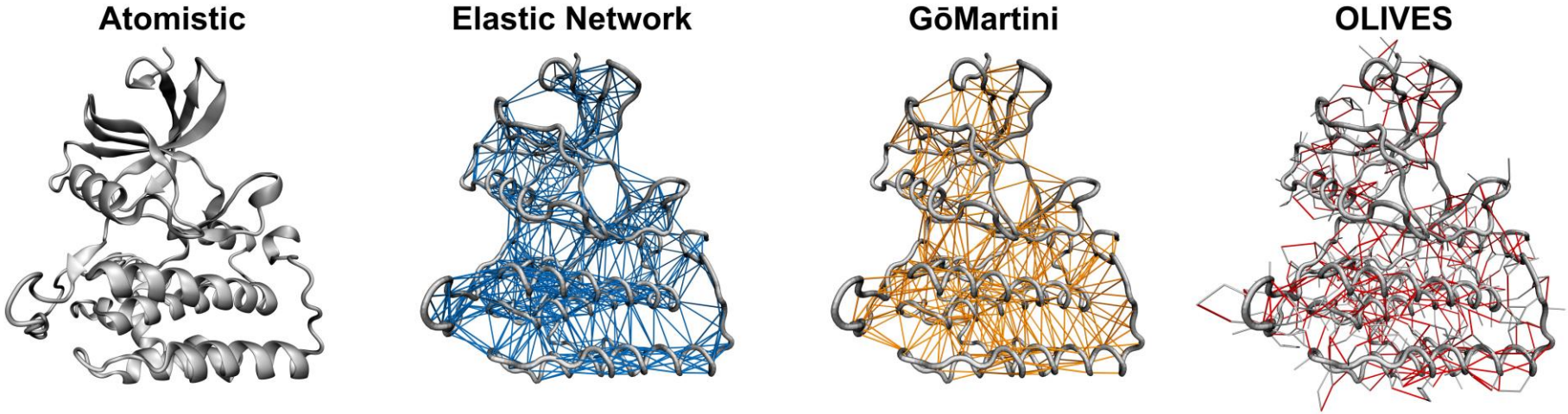
Comparison of the different protein models

Martini w/o bias
no additional bonds

Elastic Network
BB distances define contact map
harmonic potentials
1004 bonds

GōMartini 3 model
natural contacts define contact map
LJ potentials
609 bonds

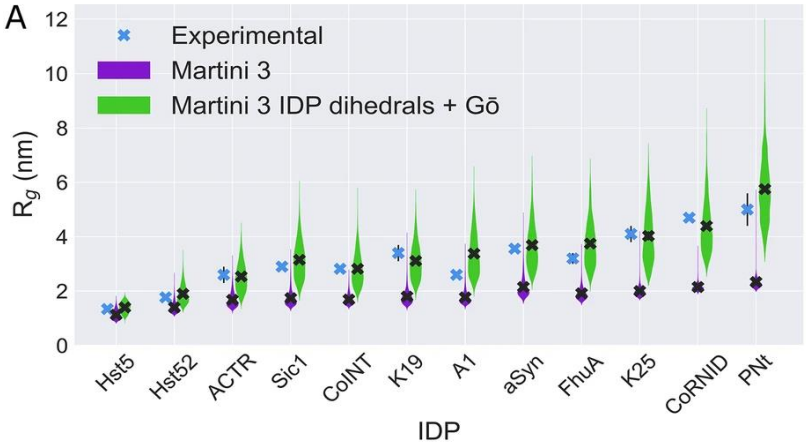
OLIVES model
chemical contacts define contact map
LJ potentials
374 bonds

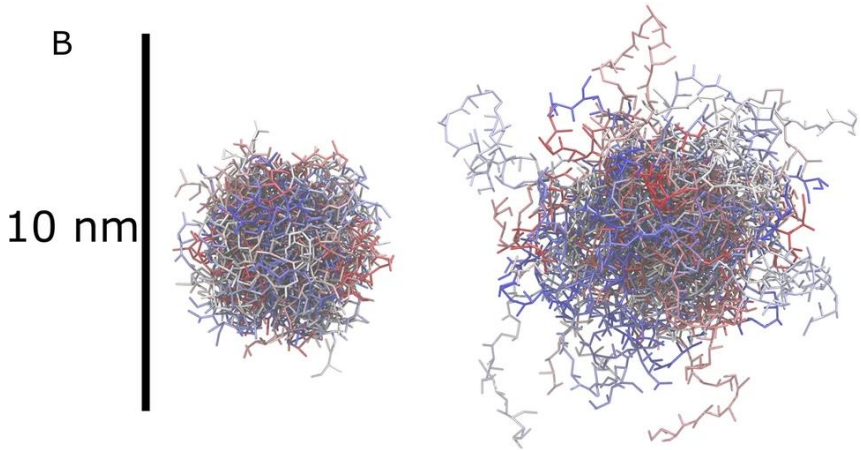


[1] T. Duve, *et al.*, *bioRxiv* (2025).

Protein models for intrinsically disordered proteins (IDPs)

- Water bias via virtual BB sites of GōMartini 3
- Flexible approach for environmental bias corrections
  - IDPs



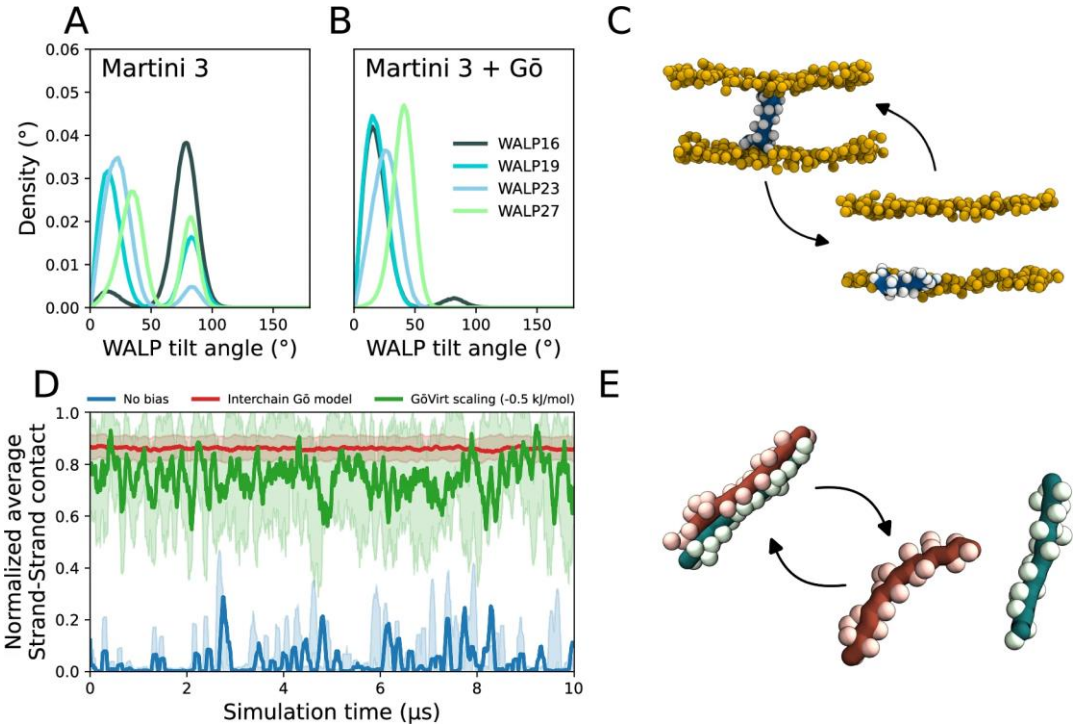


[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).

Protein models for intrinsically disordered proteins (IDPs)

- Water bias via virtual BB sites of GōMartini 3

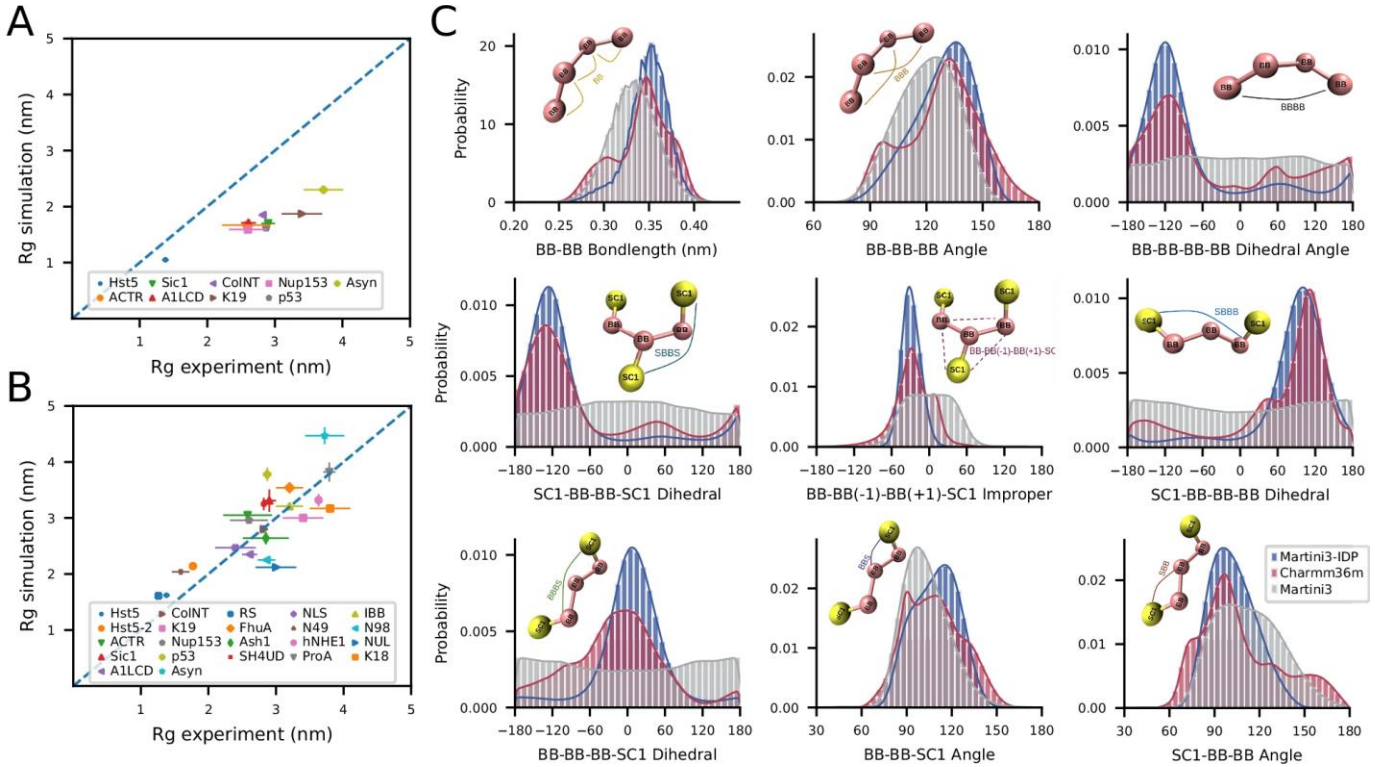
- Flexible approach for environmental bias corrections
  - IDPs
  - single-pass transmembrane helices
  - β-sheet dimers



[2] P. C. T. Souza, *et al.*, *Nat. Commun.* **16**, 4051 (2025).

Protein models for intrinsically disordered proteins (IDPs)

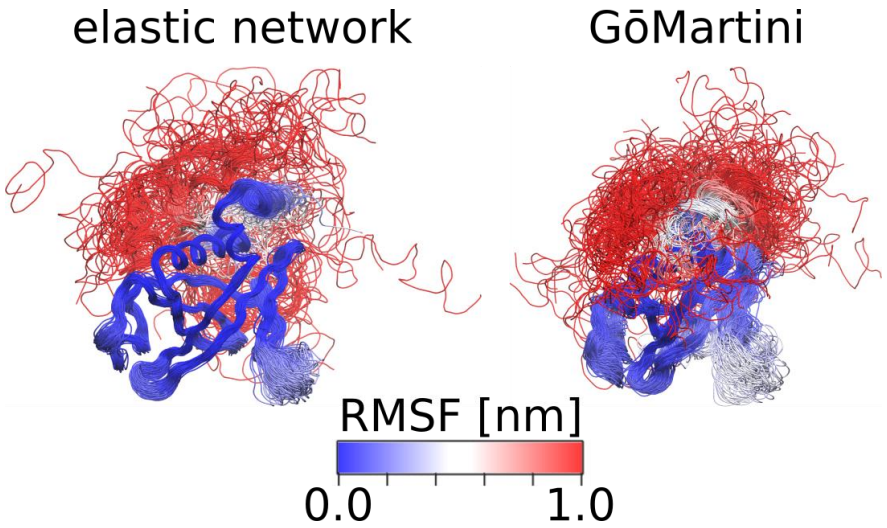
- Martini-IDP:
  a specific Martini protein model for IDPs
- Dihedral angels in the backbone added
- Improve the too high compactness of IDPs
- Proteins part I(c) tutorial

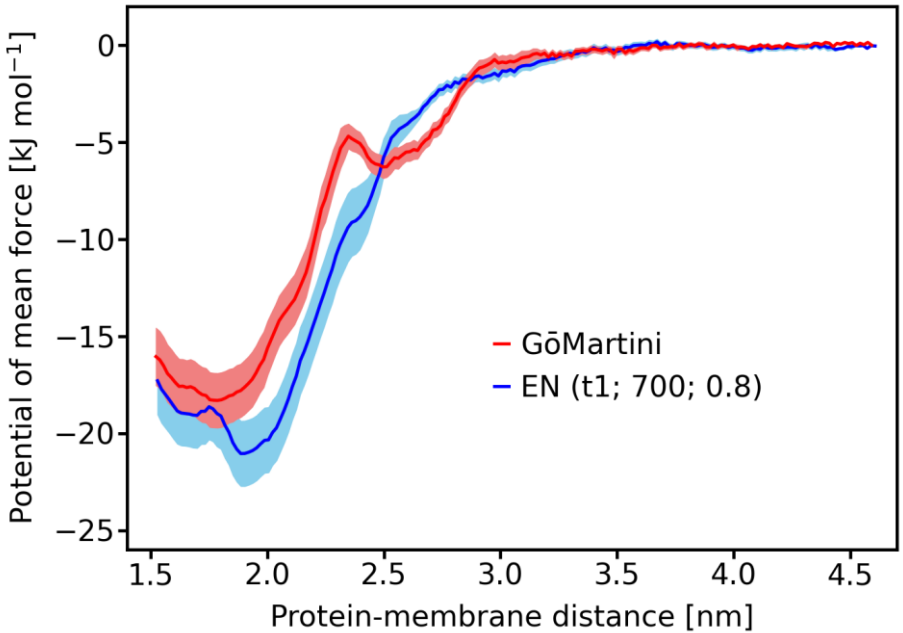


[8] L. Wang, *et al.*, *Nat. Commun.* **16**, 2874 (2025).

Show case I – PH domains

- PI(4,5)P_2 binding PH domain of phospholipase C (δ1)
- Elastic network more rigid than GōMartini
- GōMartini suggests long-distance minimum known from other PH domains [7]

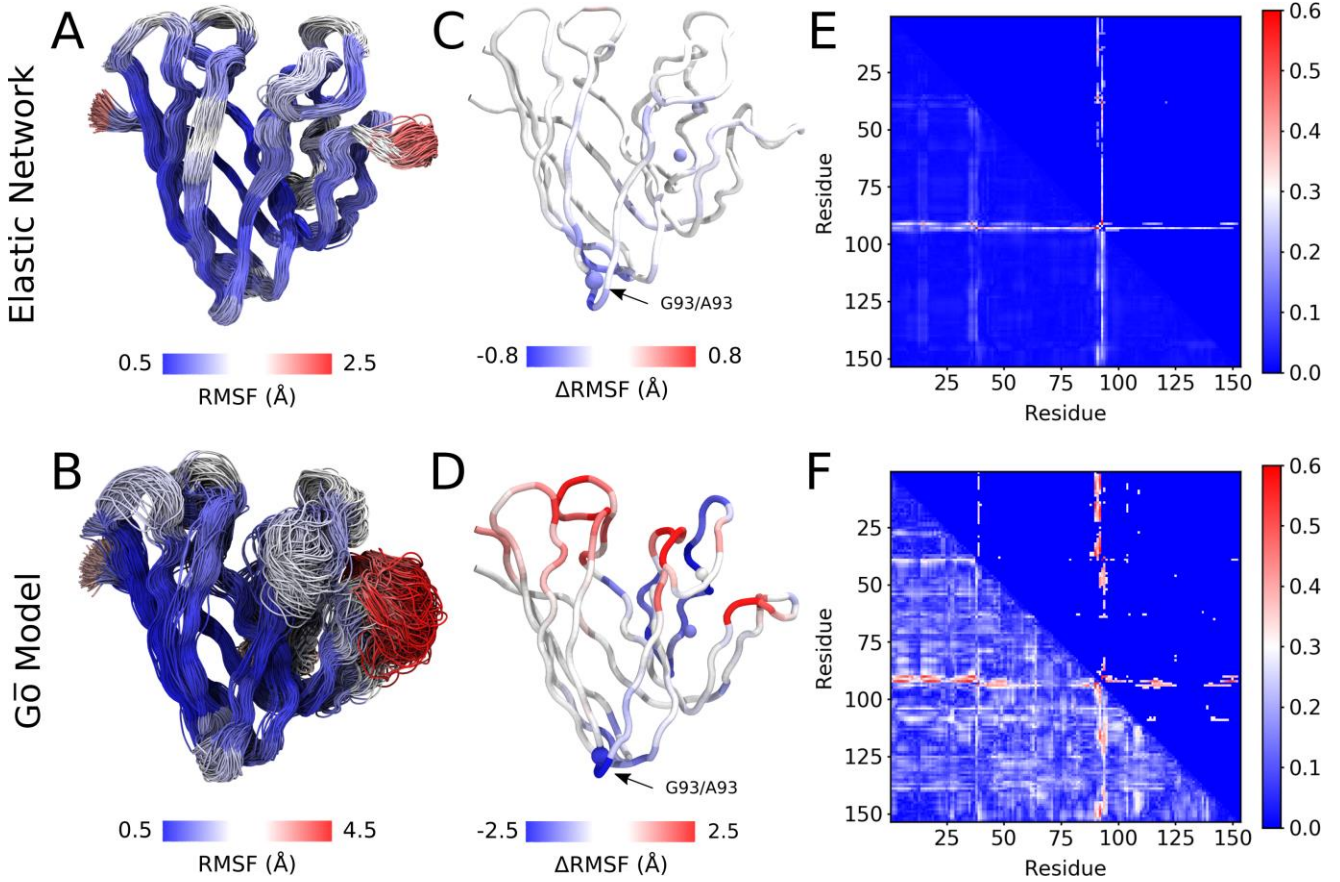




[9] F. B. Naughton, *et al.*, *J. Mol. Biol.* **430**, 372 (2018).

Show case II – allosteric pathway in SOD1 mutant

- G93A mutant destabilizes electrostatic loop
- Increased spatial demand of the mutation
- Elastic network results in highly rigid protein model
- GōMartini model enables structural response of the protein



[10] P. C. T. Souza, S. Thallmair, *et al.*, *J. Phys. Chem. Lett.* **10**, 7740 (2019).

Summary

- Directionality of **hydrogen bonds** is **important** for protein structures
- **Faithful representation** of tertiary and quaternary structure of proteins
  requires additional layer of stabilizing interactions
- **Elastic network:**
  - Harmonic potentials from distance criterion
  - Rigid protein structure
- **GōMartini:**
  - Lennard-Jones potentials from native contact map
  - More flexible protein structure
- **OLIVES:**
  - Lennard-Jones potentials from H bonding network
  - More flexible protein structure
- Intrinsically disordered proteins:
  water-bias corrections or **Martini3-IDP**

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FIAS Frankfurt Institute for Advanced Studies
SCALE
MARIE CURIE ACTIONS