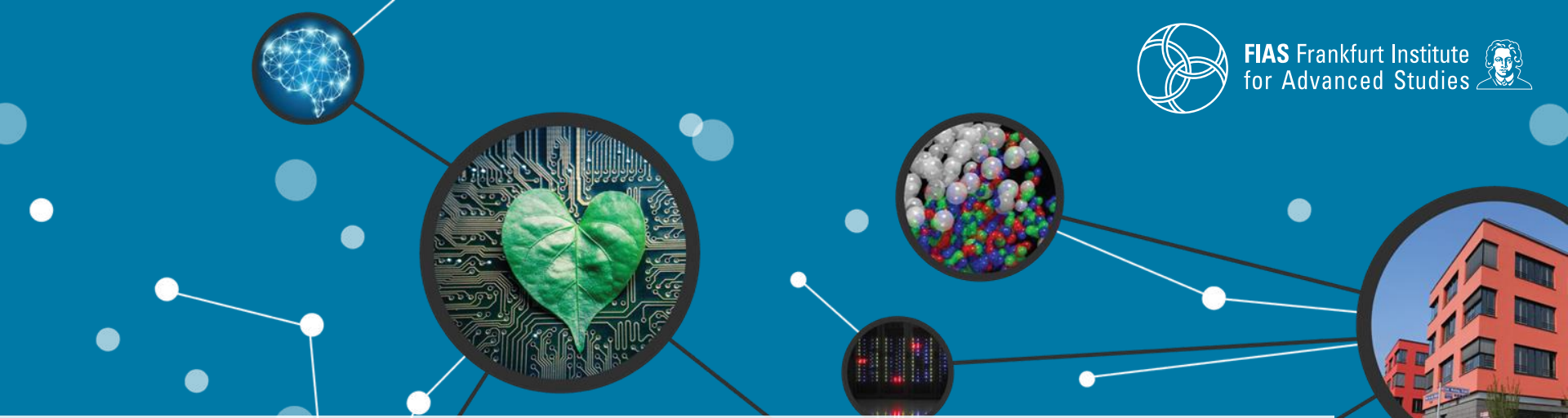

FIAS Frankfurt Institute for Advanced Studies

Protein models in Martini 3: elastic networks and Gō-like models

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online Martini workshop 2021

Outline

- Protein structures and their key interactions
- Protein models in Martini 3
  - Elastic network model
  - Gō-like model
- Show cases
  - PH domain
  - Allosteric pathway in SOD1 mutant
  - AFM profile of protein complexes
- Summary

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

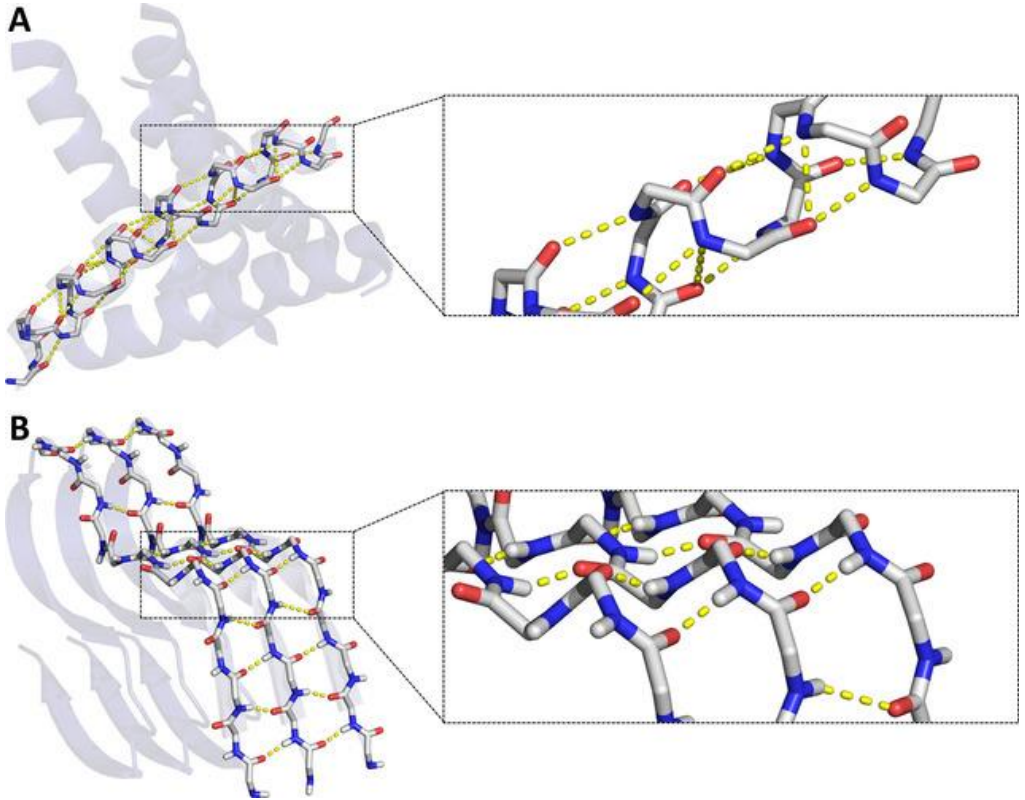
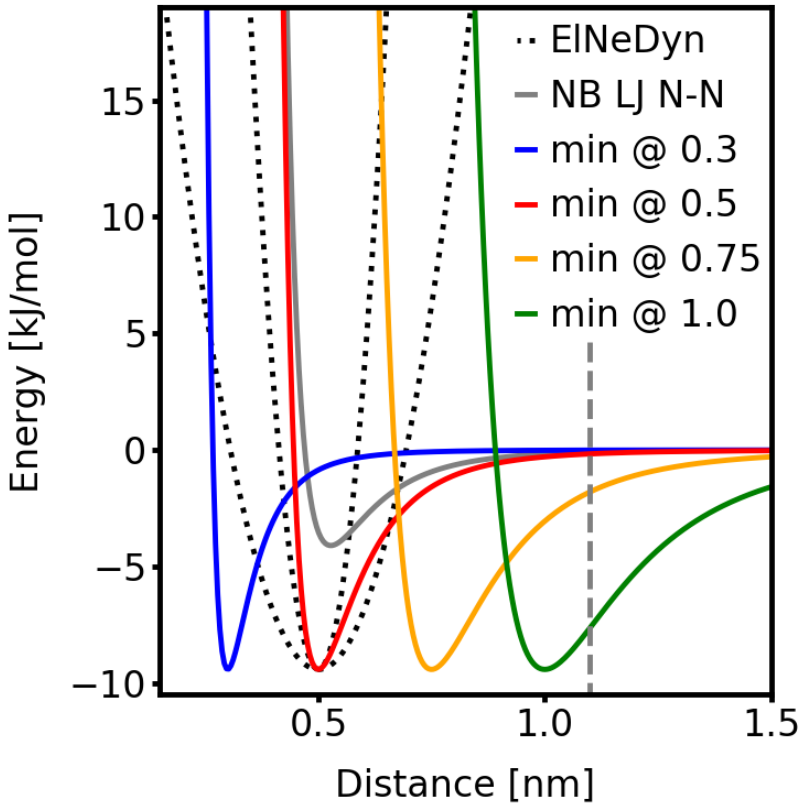


figure from V. Sereikaité, *et al.*, *ChemBioChem* **19**, 2136 (2018).

Additional stabilization required for tertiary structure

- 2-layered protein models in Martini 3:
  - bonded & non-bonded interactions [1]
  - structural models

- Two choices for dedicated structural models:
  - elastic networks (EN) with harmonic potentials [2]
  - Gō-like model with Lennard-Jones (LJ) potentials [3]



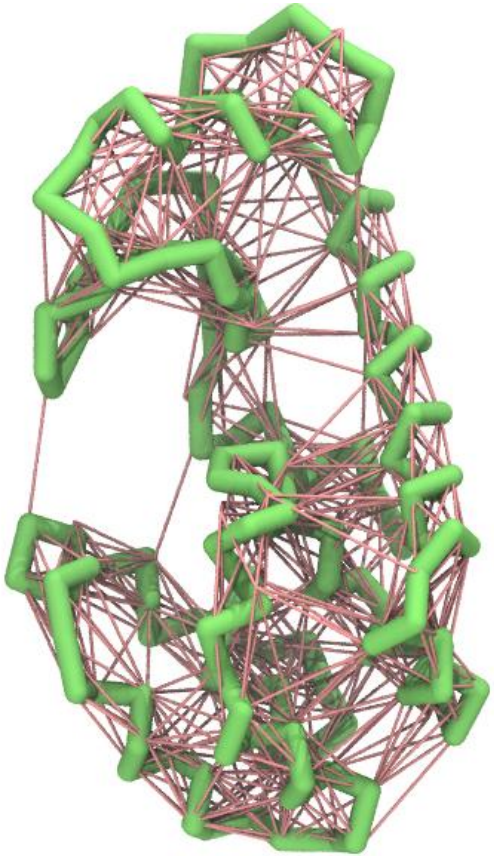
[1] P. C. T. Souza, *et al.*, *Nat. Methods* **18**, 382 (2021).
[2] D. H. de Jong, *et al.*, *J. Chem. Theory Comput.* **9**, 687 (2013).
[3] A. B. Poma, *et al.*, *J. Chem. Theory Comput.* **13**, 1366 (2017).

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.*, *in preparation* (2021). www.github.com/marrink-lab/vermouth-martinize

Gō-like model

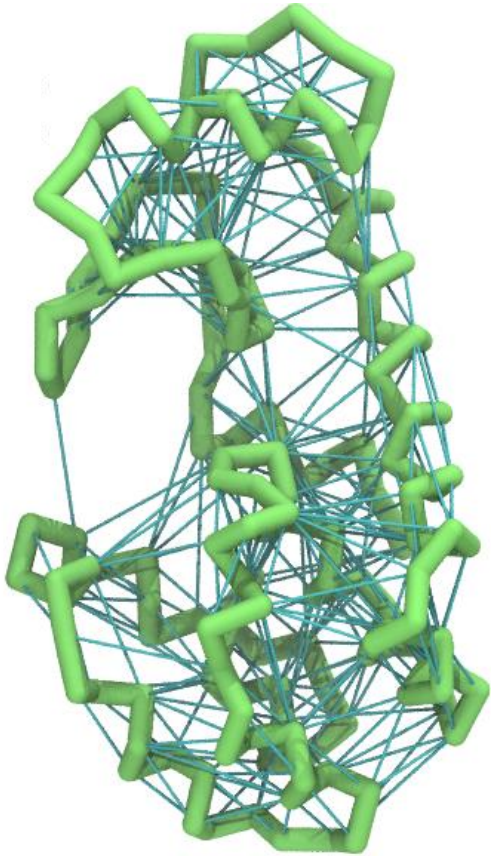
- Bonded terms applied to backbone (BB) beads at the backbone center of mass
- Native contacts define the introduced bonds
- Gō bond introduced if:
  - residues are separated by at least 3 residues
  - BB distance d is shorter than the cutoff distance R_c
- LJ potential connects the BB beads

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

- Typical setup:

  cutoff distance $R_c = 1.0 - 1.1$ nm

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



Implementation of the Gō-like model

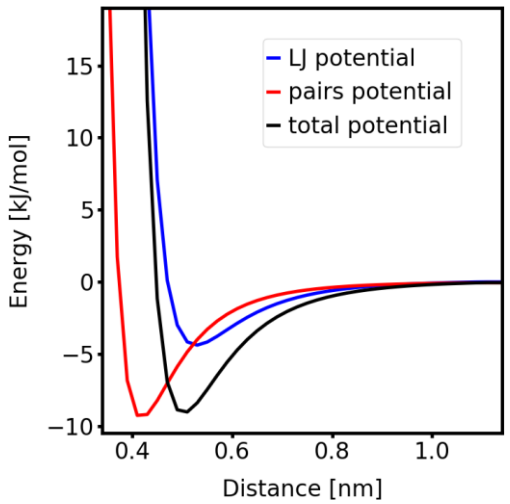
- Virtual sites are used for the Gō-like interactions [5]
  - Generation of additional bead types
  - Non-bonded cutoff is applied to Gō-like interactions

  ⟶ 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]



[5] P. C. T. Souza, R. A. Moreira, S. J. Marrink, A. B. Poma, S. Thallmair, *in preparation* (2021).
[6] K. Wołek, *et al.*, *J. Chem. Phys.* **143**, 243105 (2015).

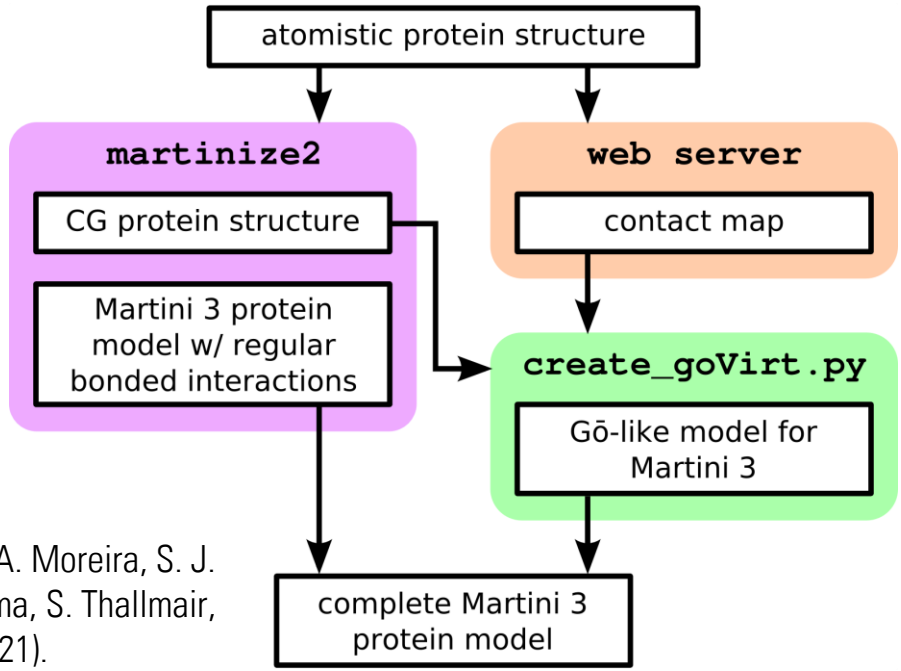
Preparing and fine-tuning your Gō-like model

- Martinize2 command [4]:
  `martinize2 <...> -ff martini3001 -govs-include -govs-moltype t4l`

- Contact map via web server
  http://info.ifpan.edu.pl/~rcsu/rcsu/index.html

- Use create_goVirt.py script [5]:
  `./create_goVirt.py -s -f --Natoms --moltype t4l --go_eps 12.0 --cutoff_short --cutoff_long`

- Optimization of dissociation energy ε and cutoff distance R_c



[5] P. C. T. Souza, R. A. Moreira, S. J. Marrink, A. B. Poma, S. Thallmair, *in preparation* (2021).

Preparing and fine-tuning your Gō-like model

- Files generated by create_goVirt.py:

`<name>_BB-part-def_VirtGoSites.itp`	virtual bead definitions
`<name>_go-table_VirtGoSites.itp`	Gō interaction table
`<name>_exclusions_VirtGoSites.itp`	Gō exclusions
`<name>_go4view_harm.itp`	visualizing Gō-like bonds

- Definition of `GO_VIRT` variable activates Gō-like model

- Files are included in the martini.itp and protein.itp file

- Pitfalls:
  - Multiple chains / protein copies
  - Atomistic .pdb file

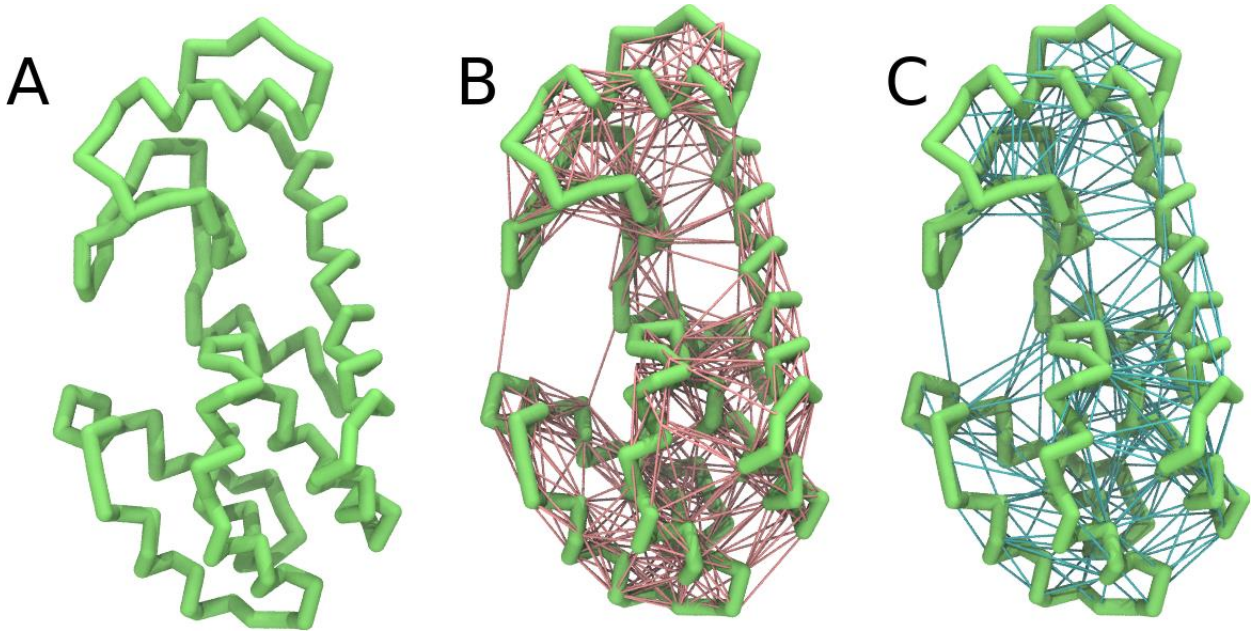
[5] P. C. T. Souza, R. A. Moreira, S. J. Marrink, A. B. Poma, S. Thallmair, *in preparation* (2021).

Comparison of the different protein models

Martini w/o bias
no additional bonds

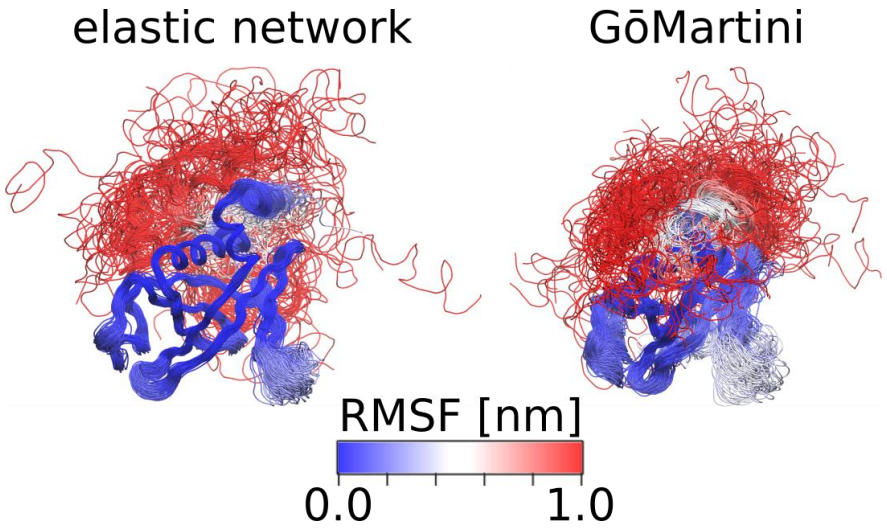
elastic networks
BB distance defines contact map
harmonic potentials
684 bonds

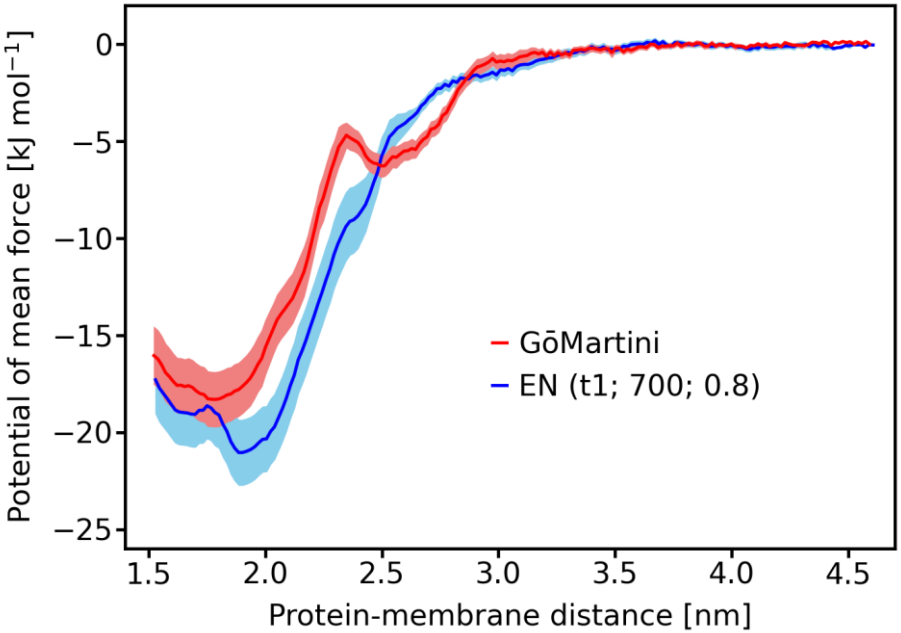
Gō-like model
natural contacts define contact map
LJ potentials
333 bonds



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]

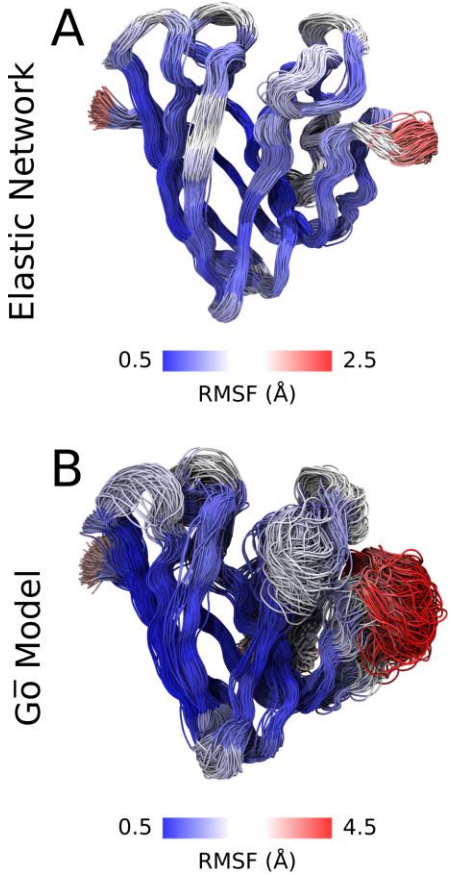




[7] F. B. Naughton, *et al.*, *J. Mol. Biol.* **430**, 372 (2018).

Show case II – allosteric pathway in SOD1 mutant

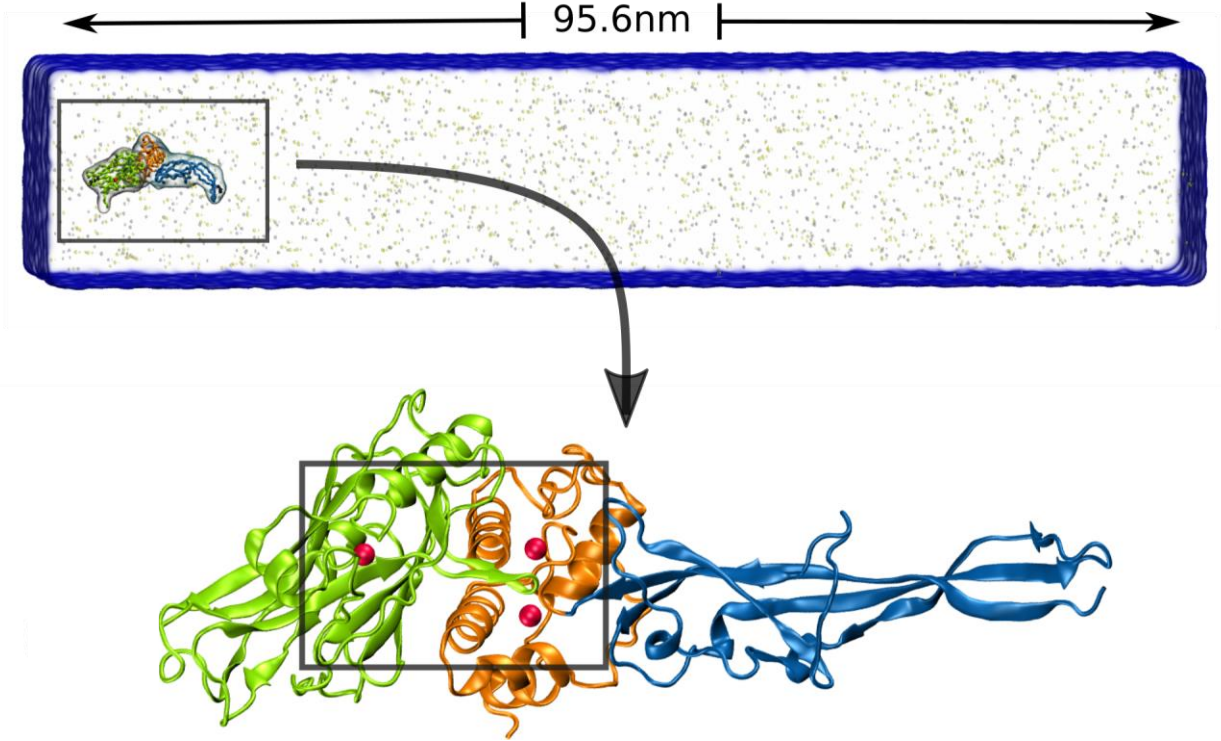
- G93A mutant destabilizes electrostatic loop
- Increased spatial demand of the mutation
- Elastic network results in highly rigid protein model
- GōMartini model enables structural response of the protein



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

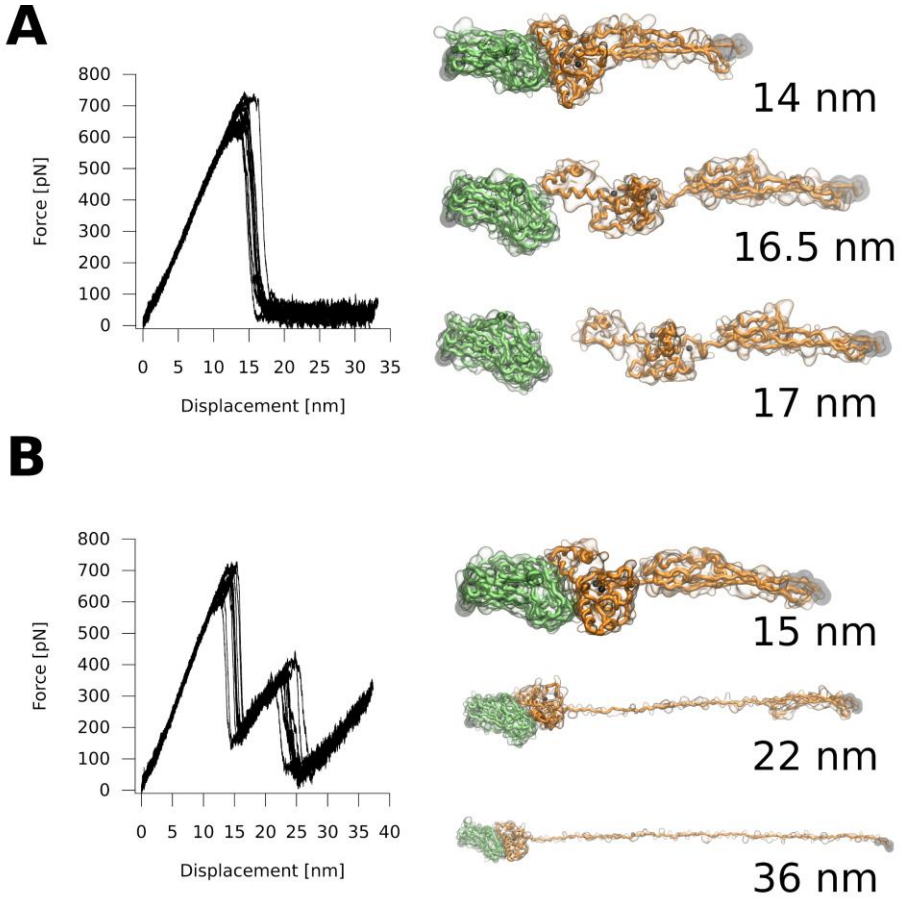
Show case III – AFM profile of protein complexes

- Cohesin-dockerin dimer stabilized by Ca^{2+} ions
- GōMartini model enables protein unfolding to model AFM force profiles



Show case III – AFM profile of protein complexes

- Cohesin-dockerin dimer stabilized by Ca^{2+} ions
- GōMartini model enables protein unfolding to model AFM force profiles
- Two main unfolding pathways compare well to experiments and atomistic simulations [9]

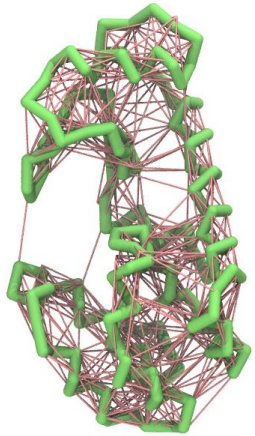


[9] R. C. Bernardi, *et al.*, *J. Am. Chem. Soc.* **141**, 14752 (2019).

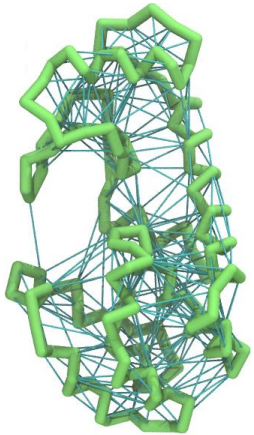
Summary

- 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
  - Distance criterion between BB beads
  - Rigid protein structure
- **GōMartini:**
  - Lennard-Jones potentials
  - Native contact map
  - More flexible protein structure
- Show cases emphasize **more dynamic and flexible**
  protein structures with **GōMartini**

Elastic network



GōMartini



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