Martini Workshop 2025

Registration details for upcoming workshop in Groningen.

Day 2: Martini Model for Proteins

Part II – The Sampling of Conformational Changes

(Tutorial Proteins - Part II(b): Protein complexes)

Adolfo Poma Bernaola

Multiscale Simulation of Complex Systems
Group IPPT-PAN

Outline

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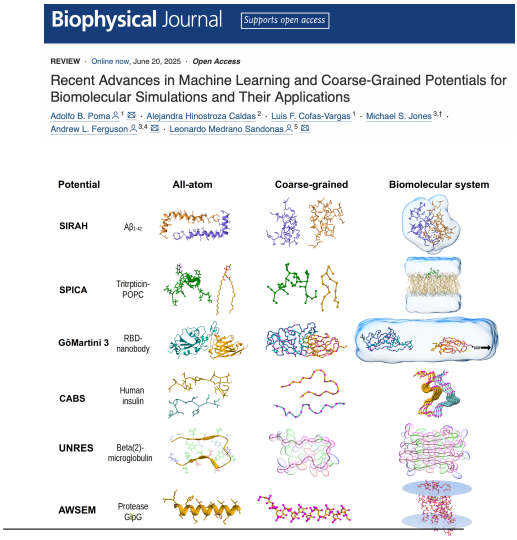
The age of biomolecular simulation



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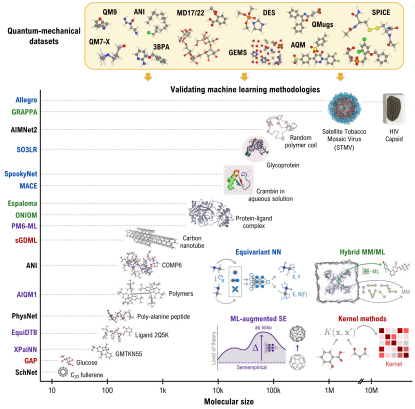
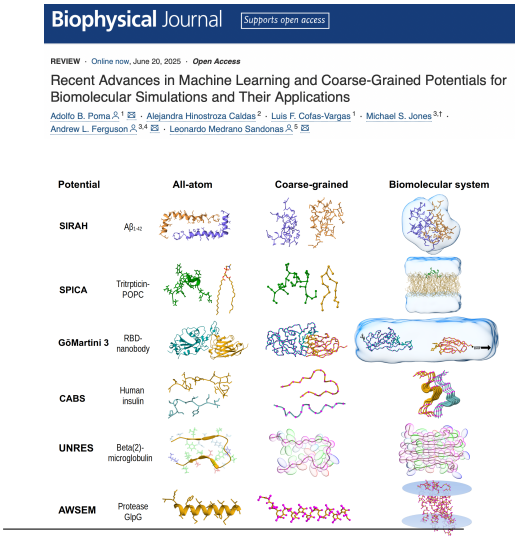


- ✓ CG and ML approaches can study complex (bio)systems in equilibrium.
- ✓ ML methods are evolving faster than traditional all-atom methods and in the race for generic force fields.
- ✗ Large conformational changes remain a challenge for ML methods.

The age of biomolecular simulation



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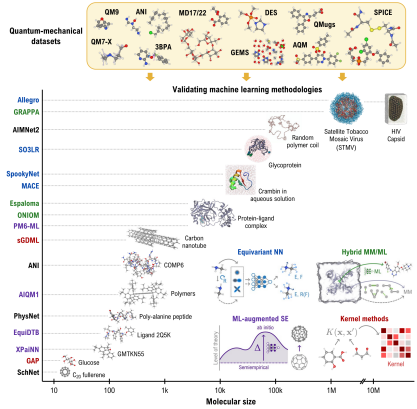

- ✓ CG and ML approaches can study complex (bio)systems in equilibrium.
- ✓ ML methods are evolving faster than traditional all-atom methods and in the race for generic force fields.
- ✗ **Large conformational changes remain a challenge for ML methods.**

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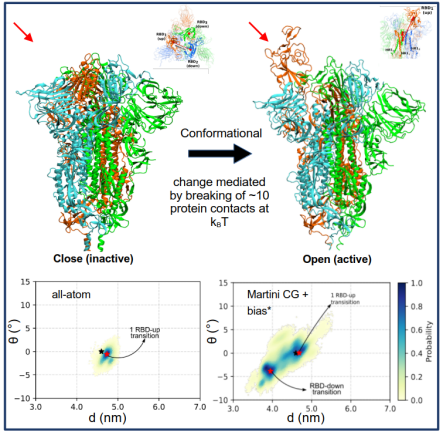
Large Conformational Changes in Proteins with Martini 3

What are conformational changes?

- Transitions between different structural states
- Often triggered by:
  - Ligand binding
  - pH, temperature shifts
  - Post-translational modifications
- Can involve domain motion, loop shifts, or allosteric transitions

Biological relevance:

- Signal transduction
- Enzyme activation/inhibition
- Molecular recognition



SARS-CoV-2 spike protein, ≈3000 residues, 10nm long, transitions by N-glycan/mechanical forces, breaking protein contacts.

Casalino, et al. *ACS Central Science*, 6(10), 1722–1734 (2020). Moreira, R.A., et al. *Materials*, 13, 5362 (2020).
Olivos-Ramirez. G., Optimizing GōMartini 3 for large protein assemblies. *Work in progress.*

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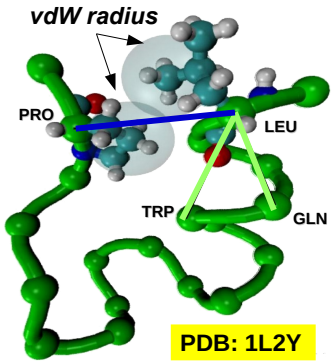
Determination of native contacts in proteins: From grapes to amino acids

Developed by Marek Cieplak at IFPAN (1950-201). It defines C_α atoms as interaction centers.



- **CM determination**: calculate atomic overlap between N,C and O atoms
- σ_{ij} is based on $r_{\min} = d(|C_i^\alpha - C_j^\alpha|)$ such $\sigma_{ij} = r_{\min}/2^{1/6}$

$$U_{\text{native}} = U_{\text{bonded}}^{NAT}(\mathrm{k_r}, k_\theta, k_\phi) + \sum_{i<j}^{NAT} 4\epsilon' \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] \text{ and } U_{\text{non-native}} = \sum_{i<j}^{NON} 4\epsilon' \left(\frac{\sigma_{\text{rep}}}{r_{ij}} \right)^{12}$$

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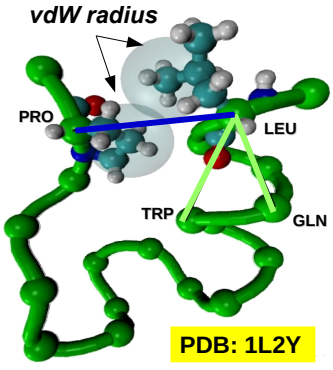

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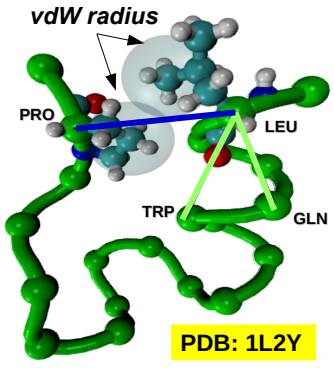

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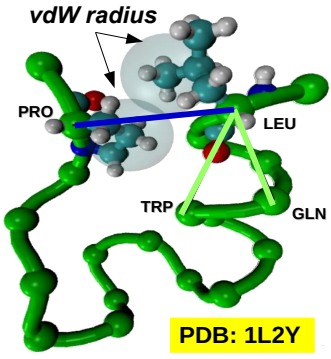

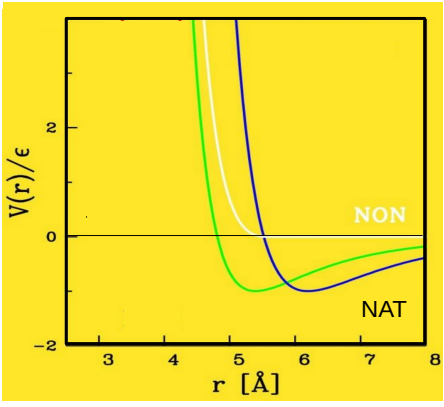

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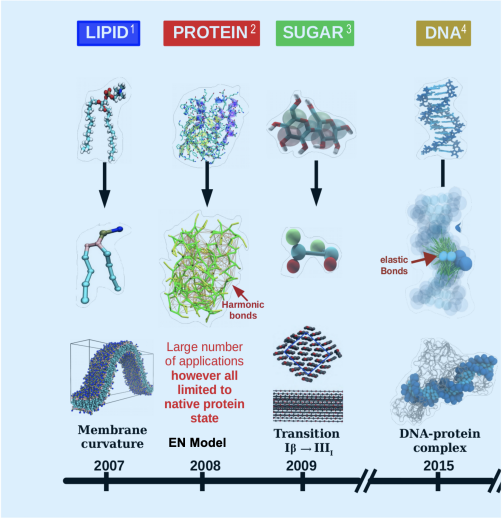
Protein model biases for conformational changes– timeline



MARTINI 1.0 MARTINI 2.0

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[2] L. Monticelli et al. JCTC 4, 819 (2008)
[3] C.A. Lopez et al. JCTC 5, 3195 (2009)
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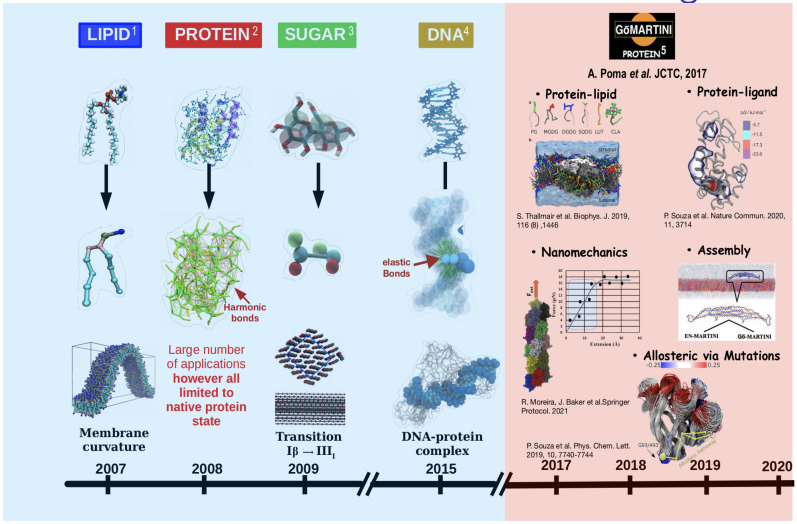

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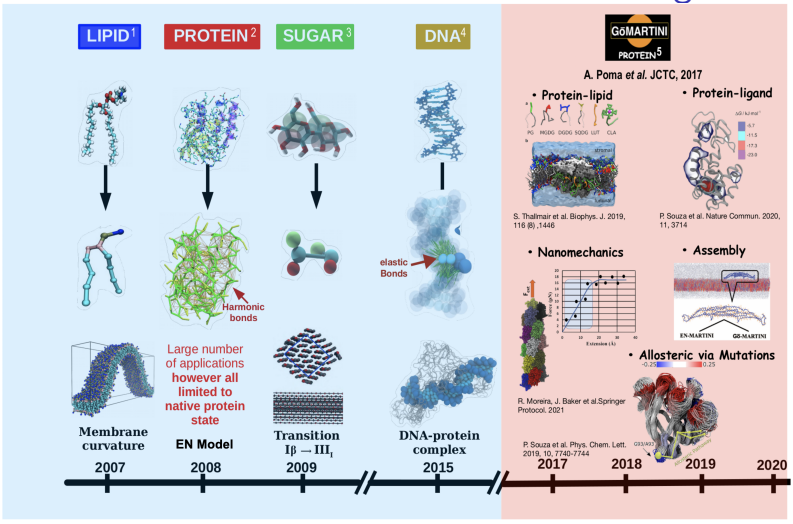

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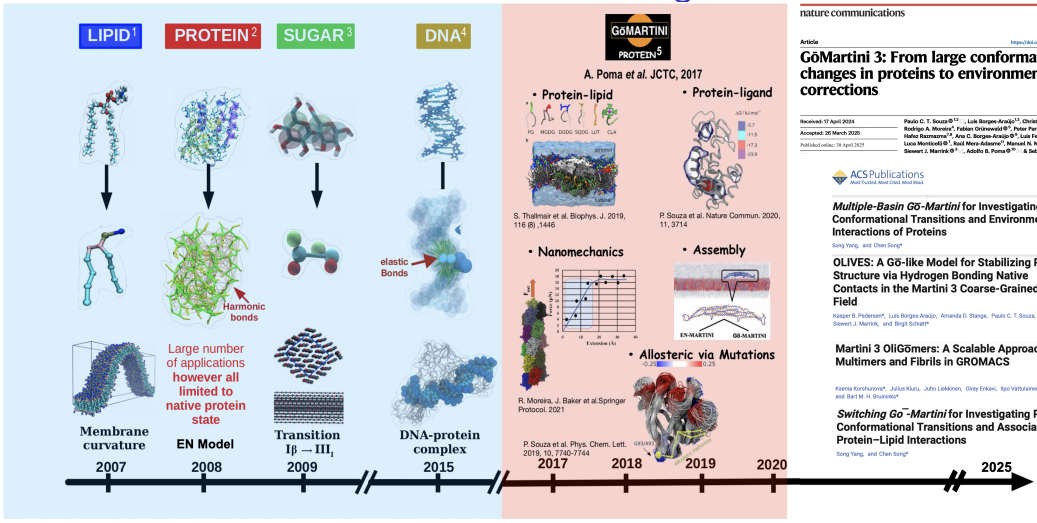

nature communications

Article

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GōMartini 3: From large conformational changes in proteins to environmental bias corrections

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Paulo C. T. Souza[1,2], Luis Borges-Araújo[2,3], Christopher Brasnett[1], Rodrigo A. Moreira[4], Fabian Grünewald[1], Peter Park[5,6], Ligun Wang[5], Heiko Razmazma[7,8], Ana C. Borges-Araújo[9], Luis Fernando Cofas-Vargas[10], Luca Monticelli[11], Raúl Mera-Adasme[12], Manuel N. Melo[13], Sangwook Wu[14], Siewert J. Marrink[1], Adolfo B. Poma[15] & Sebastian Thallmair[16]

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***Multiple-Basin Gō-Martini* for Investigating Conformational Transitions and Environmental Interactions of Proteins**

Song Yang, and Chen Song*

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Kasper B. Pedersen*, Luis Borges-Araújo, Amanda D. Stange, Paulo C. T. Souza, Siewert J. Marrink, and Birgit Schiøtt*

Martini 3 OliGōmers: A Scalable Approach for Multimers and Fibrils in GROMACS

Ksenia Konshunova*, Julius Kiuru, Juho Liekkinen, Giray Enkavi, Ilpo Vattulainen, and Bart M. H. Bruininks*

***Switching Gō~Martini* for Investigating Protein Conformational Transitions and Associated Protein–Lipid Interactions**

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[4] J.J. Uusitalo et al. JCTC 11, 3932 (2015)

MARTINI 3.0

[5] A.B Poma et al. JCTC 13, 1366 (2017)
[6] P. Souza, …, A.B. Poma, S. Thallmair. *Nat. Commun.* 16, 4051 (2025)

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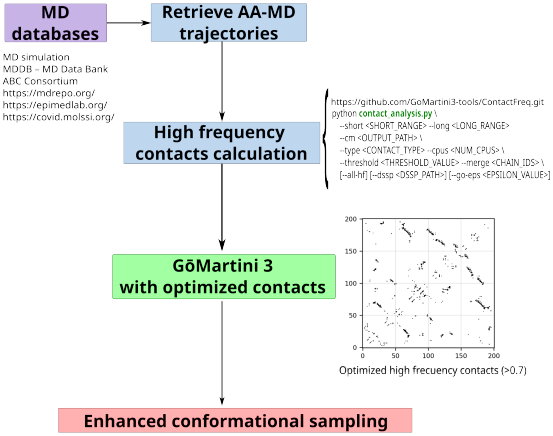
GōMartini 3: Optimization via high frequency contacts

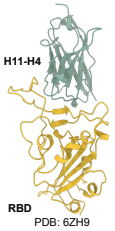
$$\mathcal{U}_{\text{GōMartini}} = U^{\text{Martini 3}}_{\text{bonded}} + \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon_{\text{rel}} r_{ij}} + \sum_{i<j} 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \overset{\text{NC optimised}}{\sum_{i<j}} 4\epsilon'\left[\left(\frac{\sigma'_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma'_{ij}}{r_{ij}}\right)^{6}\right]$$

- Electrostatics: interaction between charged (Q) particles
- Typical particle size $\sigma \sim 0.47$ nm; $\varepsilon = 2 - 5.6$ kJ/mol
- GōMartini uses virtual sites at BB (C_α); $\epsilon' = 12 - 15$ kJ/mol, contact range 0.3–1.1 nm



[7] PC. Souza et al., Martini 3: a general purpose force field for coarse-grained molecular dynamics, Nat. Methods 18, 382–388 (2021).

GōMartini 3: The pipeline for protein complexes



(a) All-atom/AlfaFold[8]

Structure preparation

Consider PDB structures with “all atoms”, otherwise model them.

[8] J. Jumper et al. Highly accurate protein structure prediction with AlphaFold. *Nature* 596, 583–589 (2021).

[9] L. Cofas-Vargas et al. The GōMartini approach: Revisiting the concept of contact maps. *Acta Phys. Pol. A*, 145(3), p. S9 (2024).

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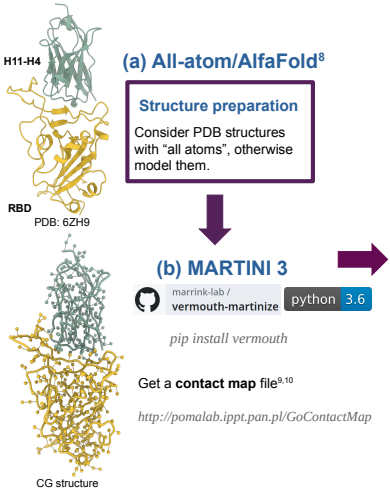

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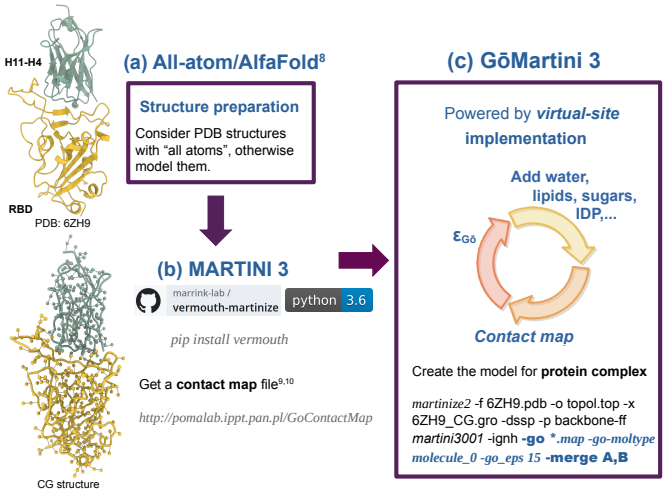

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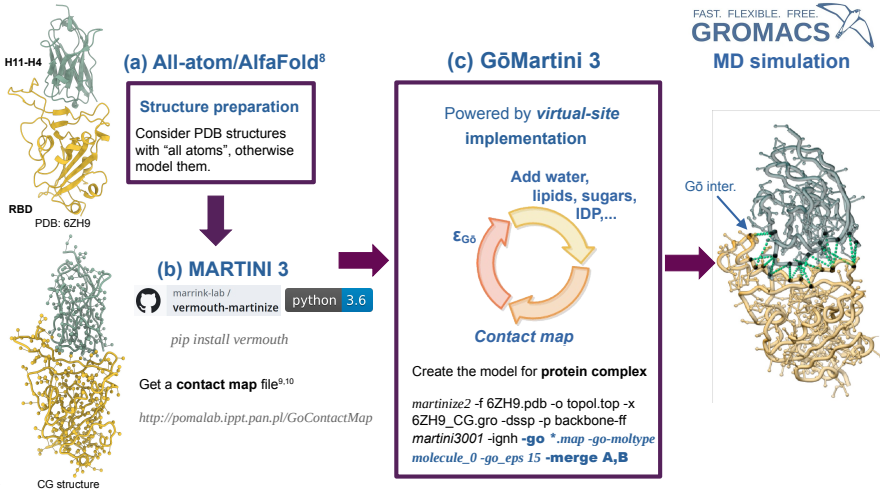

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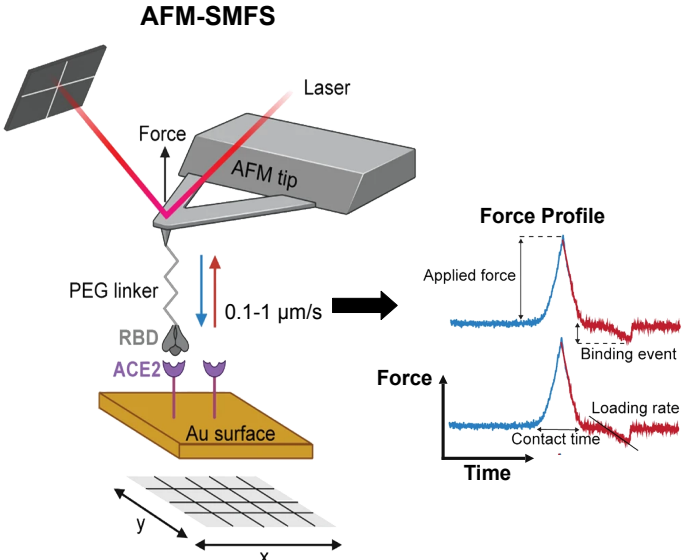

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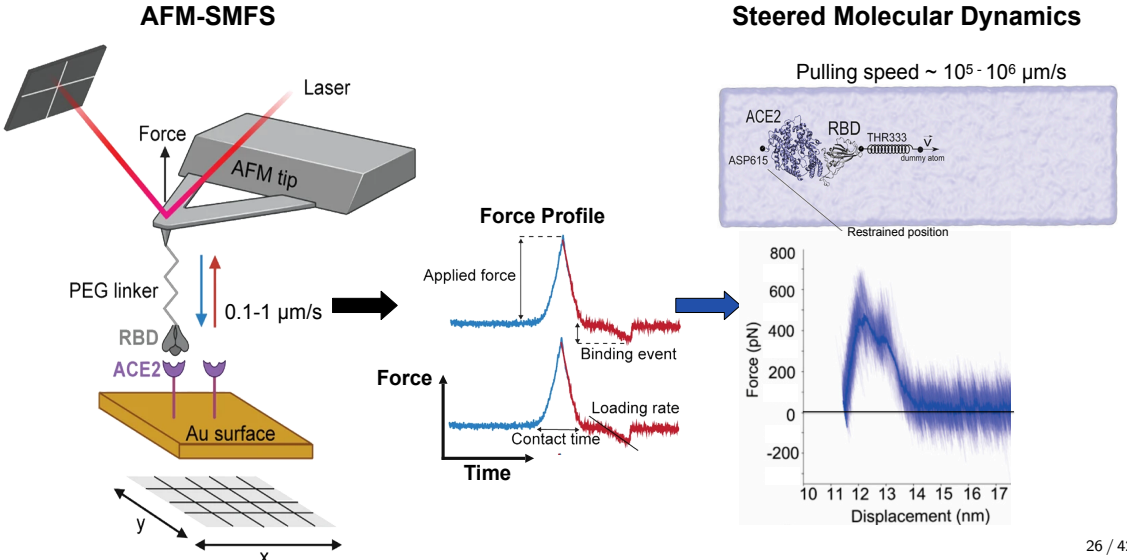

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A therapeutic complex: CTL4:anticalin

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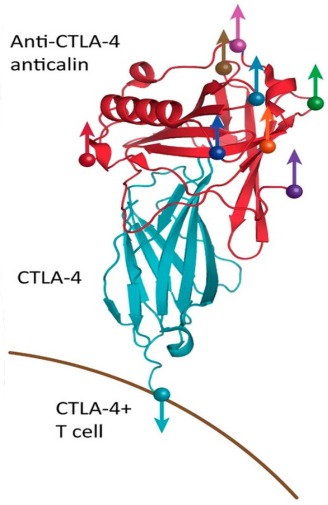

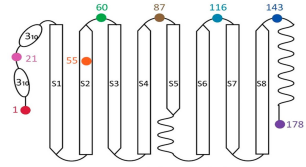

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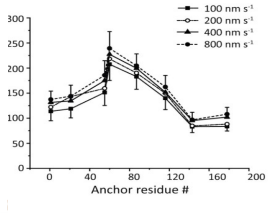
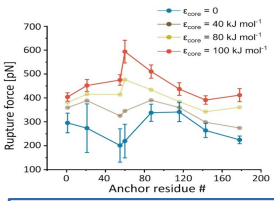


SMFS with Gō-Martini

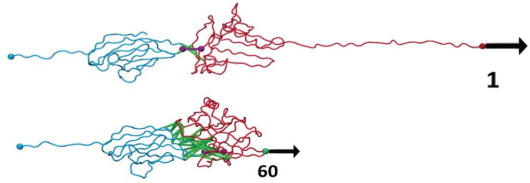


- Martini 3 FF [8]
- Virtual-site GōMartini implementation in preparation (2022) or via *http://cgmartini.nl*

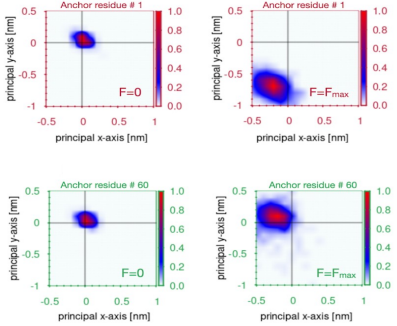
[11] Z. Liu, R. Moreira, A. Dujmović, H. Liu, B. Yang, A. B. Poma, and M. A. Nash, Nano Letters 22(1), 179 (2021).

A therapeutic complex: CTL4:anticalin

GōMartini pathways



Anticalin center-of-mass



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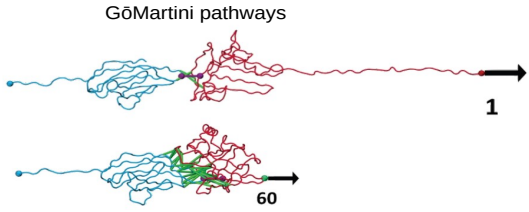

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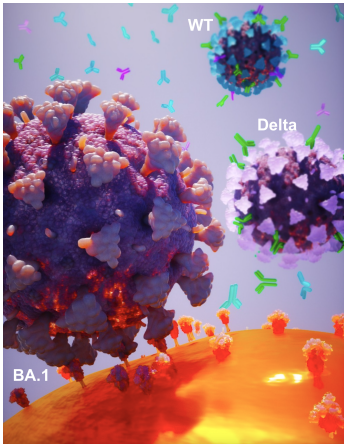
Lessons learnt from COVID-19 pandemic



- Boosted or natural immune responses were able to neutralize some of the earliest variants (WT, Delta), but the emergence of Omicron variants posed a public health concern for future outbreaks.
- The role played by mechanical forces during *viral entry* was found to be fundamental [13-15]. This property may influence the immune response and the design of antibody therapies.

”

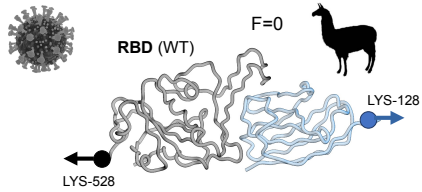
[13] M. Koehler,..., A.B. Poma and D. Alsteens, Molecular insights into receptor binding energetics and neutralization of SARS-CoV-2 variants." Nat. Commun.12.1 (2021)

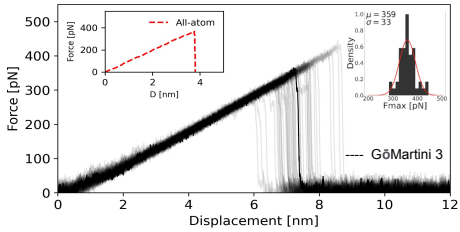
[14] A. Rai,..., A.B. Poma and D. Alsteens, Single-molecule study of the binding interface stability of SARS-CoV-2:ACE2, ACS Nanoscience Au, 4, 136-145 (2024).

[15] Bauer, M.S., Gruber, S., Hausch, A. et al. Single-molecule force stability of the SARS-CoV-2–ACE2 interface in variants-of-concern. Nat. Nanotechnol. 19, 399–405 (2024).

SARS-CoV-2:nanobody complex

All-atom SMD simulation[16] reported rupture force (F_{max}) values of the RBD (WT)/H11-H4 complex in the range of 400-500 pN. Limited sampling and far from SMFS exp. conditions (i.e. low loading rate).





[16] M. Golcuk, et al. J. Chem. Inf. Model., 62, 10, 2490–2498 (2022).

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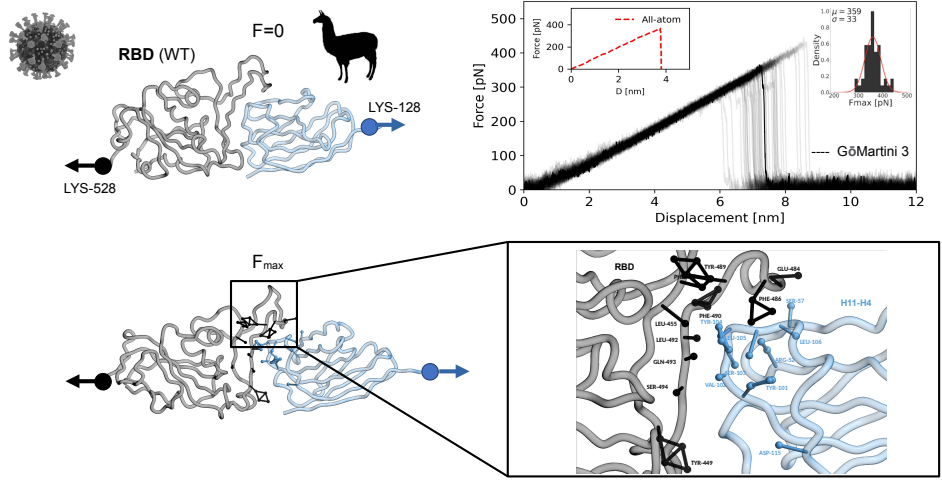

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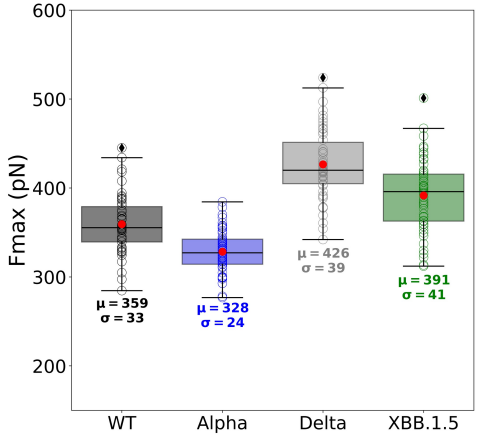
A systematic nanomechanical study of SARS-CoV-2 variants [17].



[17] Cofas-Vargas, L. F.,..., A. B. Poma. Microtubules in Martini: Parameterizing a heterogeneous elastic-network towards a mechanically accurate microtubule. PNAS nexus 16(40), 18

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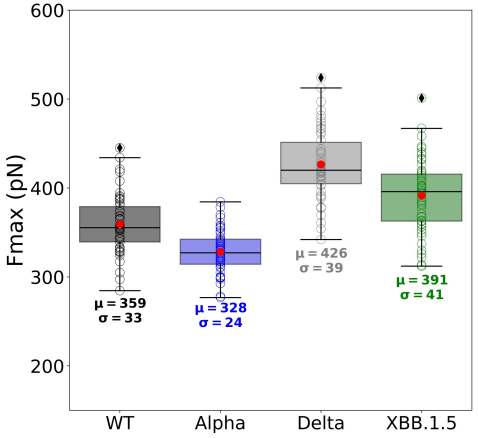
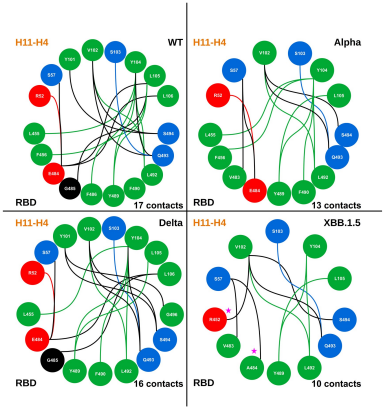


Nanomechanical fingerprint



Contacts at rupture force F_{max}

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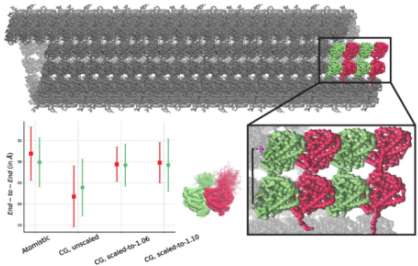
Large fluctuations in microtubules via EN model

Reparametrization of a heterogeneous elastic-network towards to capture the long-time fluctuation of microtubules [18].



Iteratively Refined Distance EN protocol

$$K_{ij,0} = K_{\text{initial}} \frac{\min_{i,j}\{\sigma_d^2(i,j)\}}{\sigma_d^2(i,j)}$$

$$K_{ij,n+1} = K_{ij,n} - \alpha \frac{k_B T}{R_C^4} [\sigma_{d,\text{atom}}^2(i,j) - \sigma_{d,\text{CG}}^2(i,j)]$$

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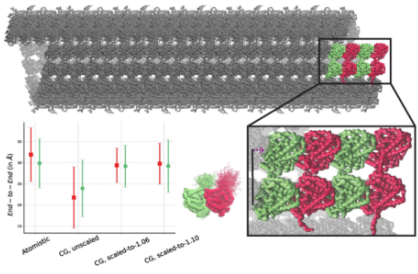

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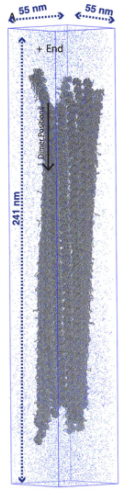

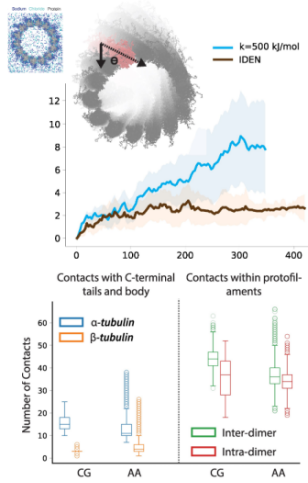

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Take away messages...

1. GōMartini 3 is computationally more efficient, implemented via virtual-sites and compatible with domain decomposition implementation in `GROMACS` (>2023.5).
2. Protein complexes undergoing non-equilibrium processes via large mechanical forces require additional Gō interactions at the interface to compensate Martini 3 FF.
3. GōMartini 3 provides molecular insight into the nanomechanics in protein complexes and supports AFM-SMFS experiments, with much less computational effort compare to AA-SMD simulations.

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- Prof. David Alsteens (The Université Catholique de Louvain, Belgium)
- Prof. Michael Nash (ETH Zurich, Switzerland)
- Prof. Marta Bally (Umeå University, Sweden)

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Dr. Rodrigo Moreira
(BCAM, Spain)

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–Thank you for your attention–

–Any questions?–