RICE | CTBP
Center for Theoretical Biological Physics

unesp

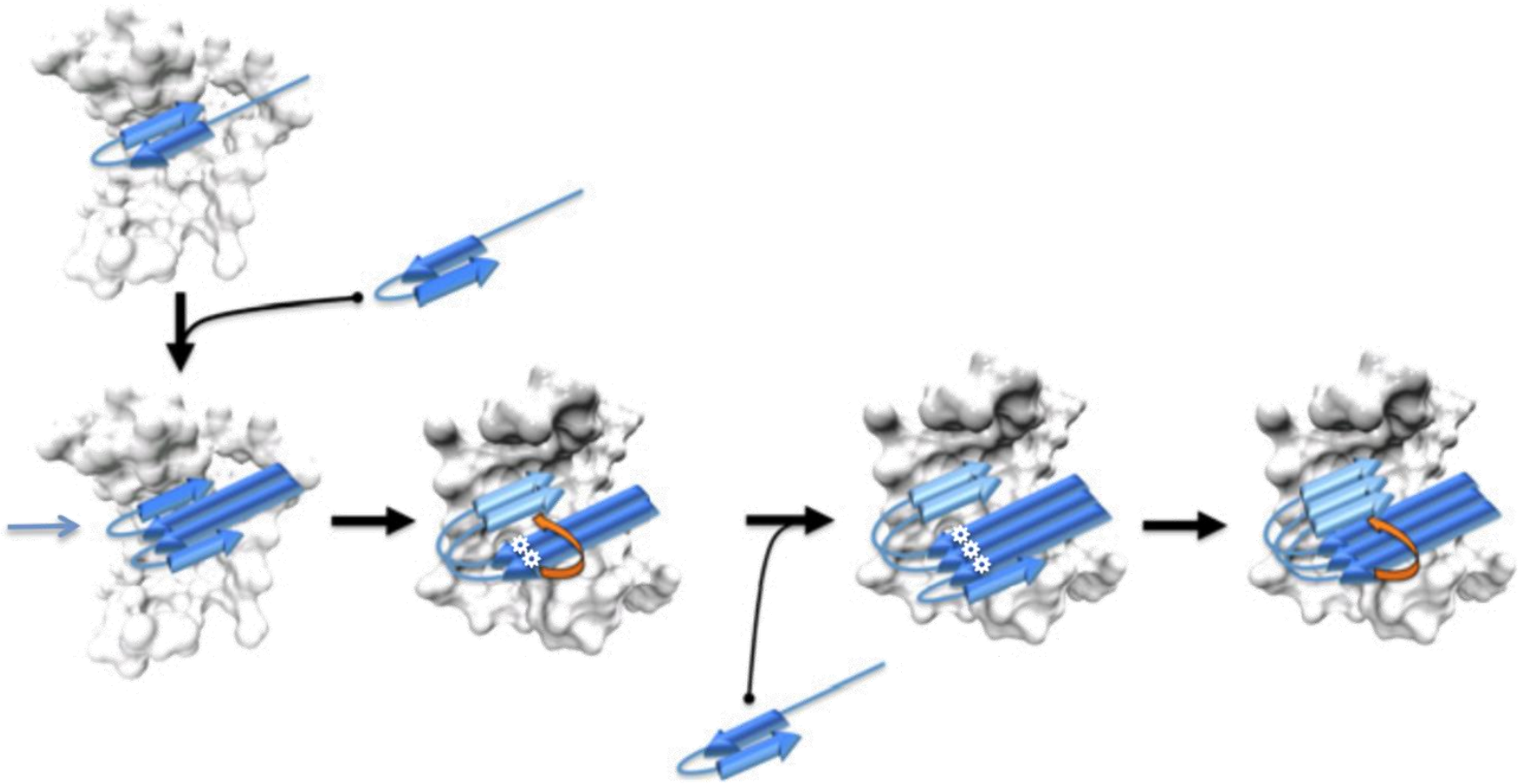
Mechanisms of Secondary Nucleation in Amyloid-beta Aggregation

Murilo Sanches

Peter Wolynes Carlos Bueno Vitor Leite

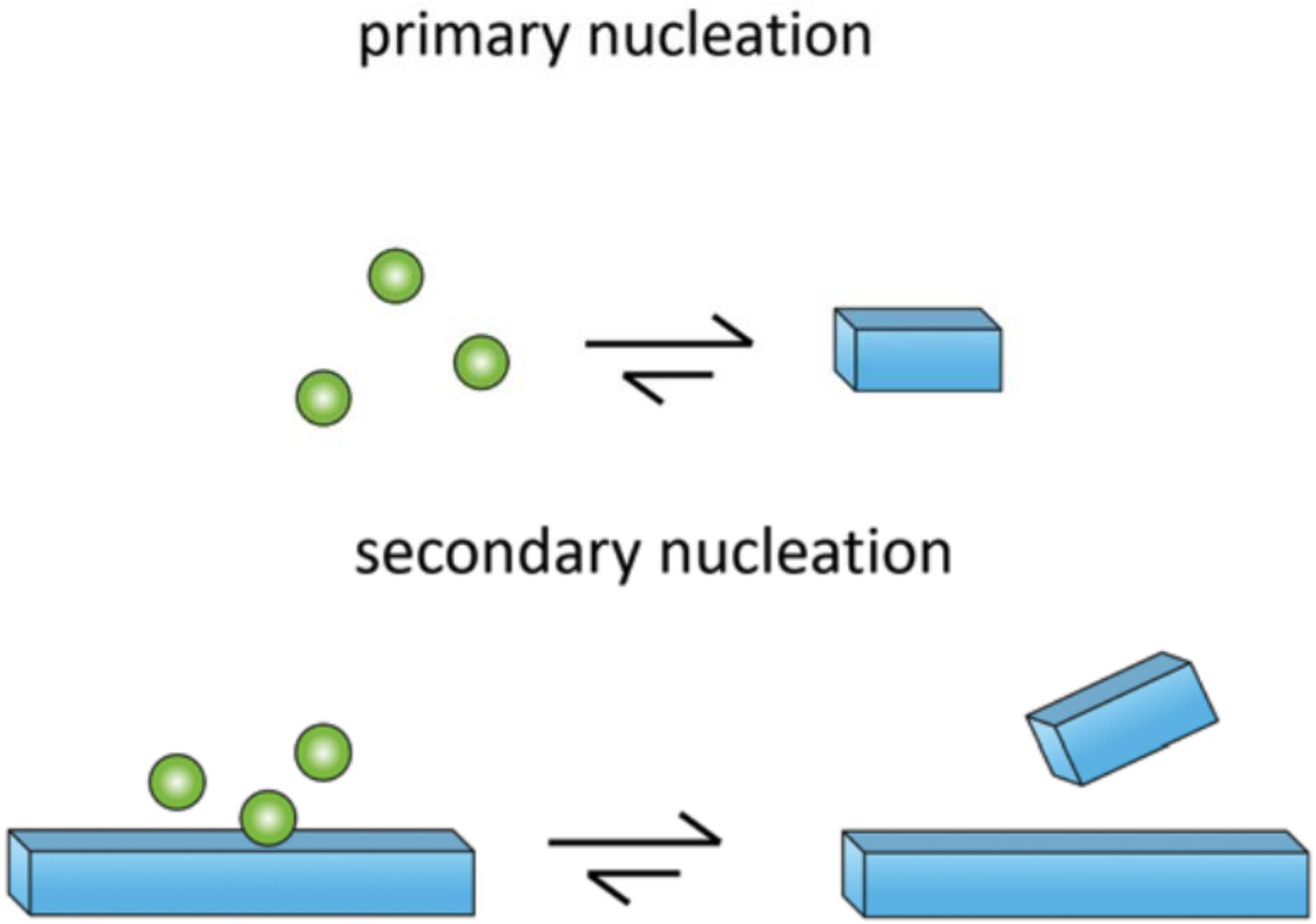
Amyloid-β Aggregation Process

- Amyloid precursor protein ➔ Aβ40 and Aβ42 ➔ Aggregation ➔ Fiber



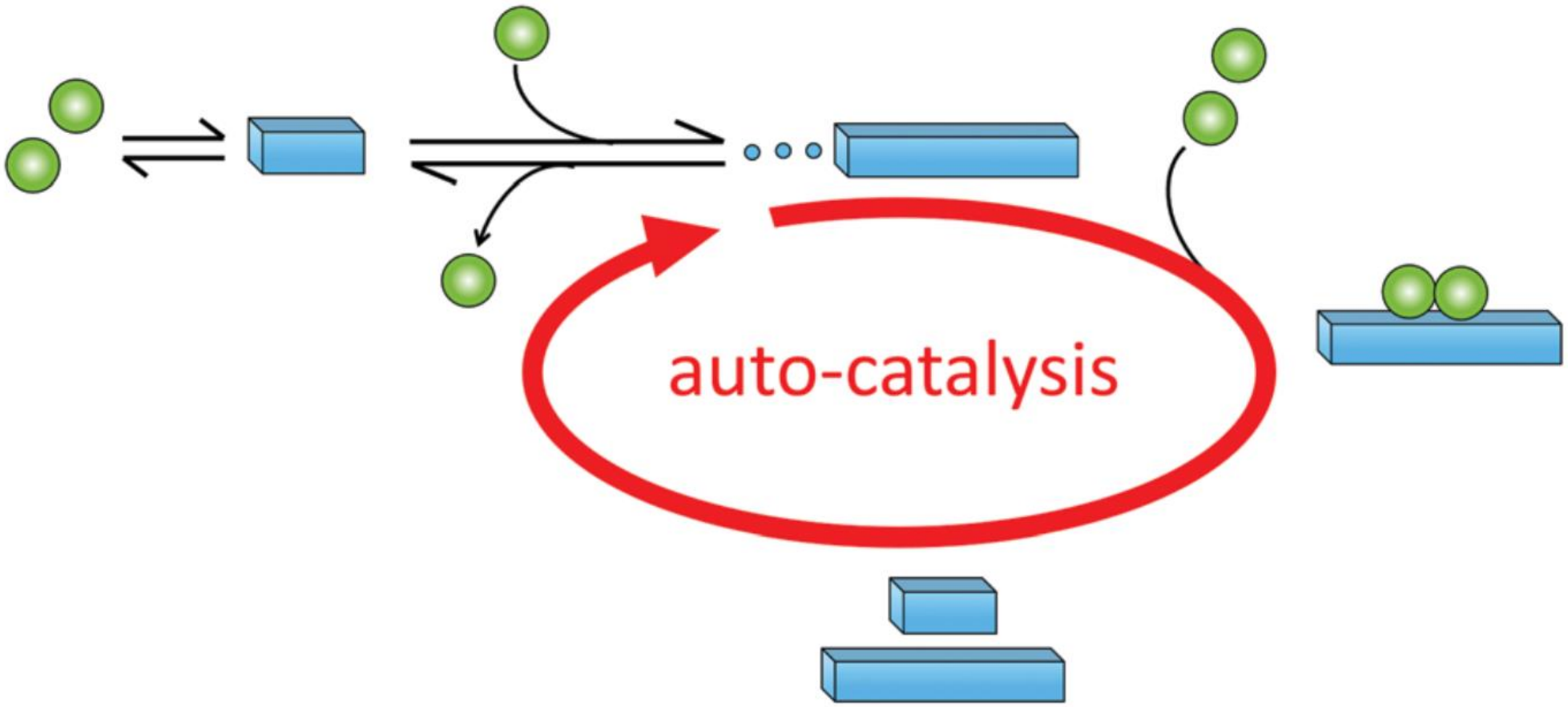
Zheng, W., Tsai, M. Y., Chen, M., & Wolynes, P. G. (2016). Exploring the aggregation free energy landscape of the amyloid-β protein (1–40). Proceedings of the National Academy of Sciences, 113(42), 11835-11840.

Secondary nucleation of Amyloid-β



Törnquist, M., Michaels, T. C., Sanagavarapu, K., Yang, X., Meisl, G., Cohen, S. I., ... & Linse, S. (2018). Secondary nucleation in amyloid formation. Chemical communications, 54(63), 8667-8684.

Secondary nucleation of Amyloid-β

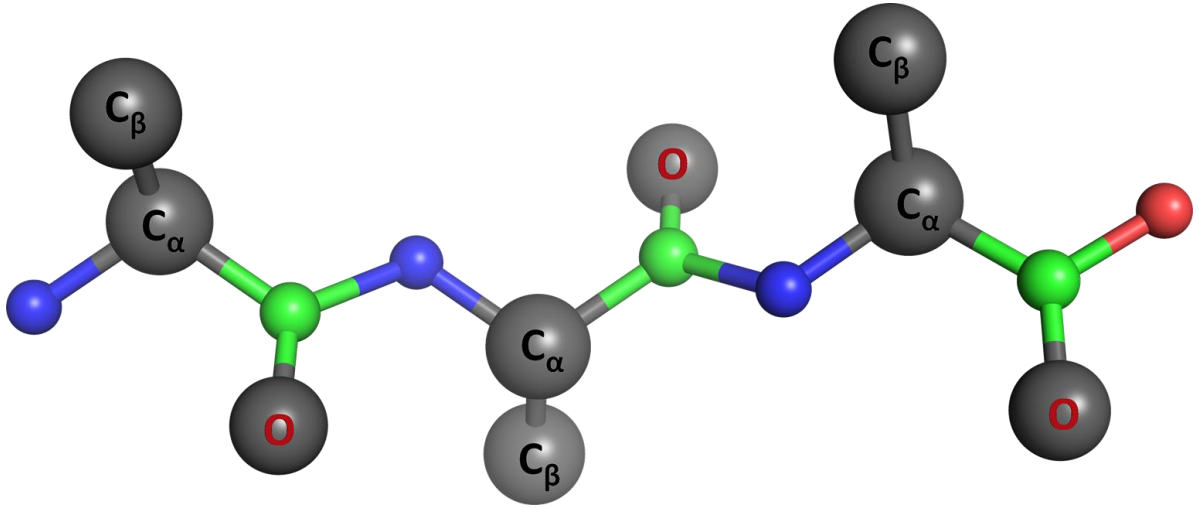


Törnquist, M., Michaels, T. C., Sanagavarapu, K., Yang, X., Meisl, G., Cohen, S. I., ... & Linse, S. (2018). Secondary nucleation in amyloid formation. Chemical communications, 54(63), 8667-8684.

AWSEM Potential

$$V_{total} = V_{backbone} + V_{contact} + V_{burial} + V_{helical} + V_{FM}$$

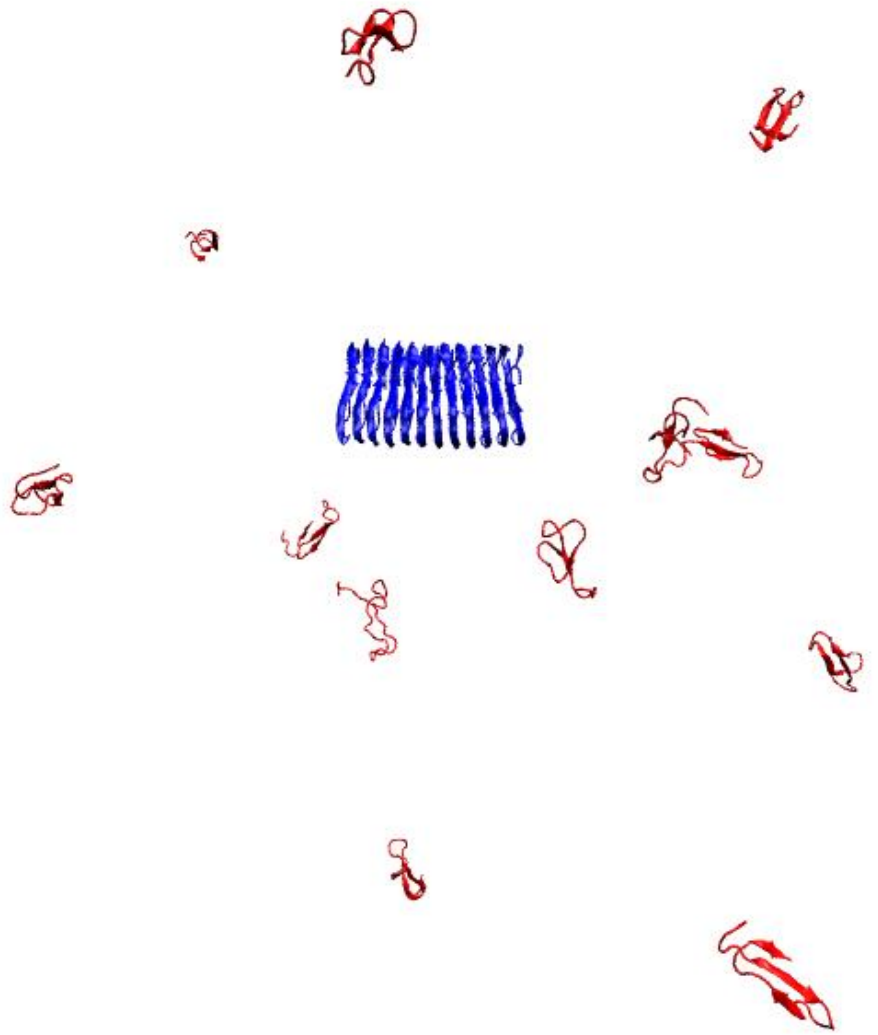
$$V_{repulsive}(r) = \epsilon \left[\left(\frac{\sigma}{r} \right)^2 - 1 \right]$$



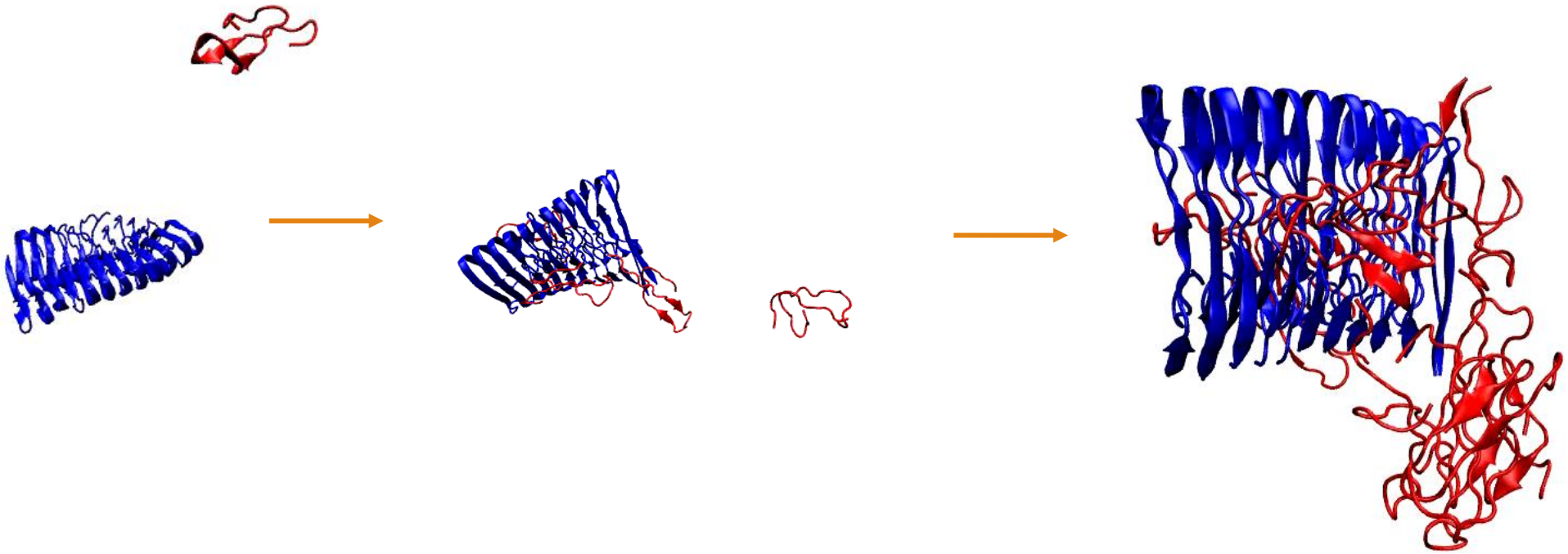
Davtyan, A., Schafer, N. P., Zheng, W., Clementi, C., Wolynes, P. G., & Papoian, G. A. (2012). AWSEM-MD: protein structure prediction using coarse-grained physical potentials and bioinformatically based local structure biasing. The Journal of Physical Chemistry B, 116(29), 8494-8503.

Secondary nucleation Aβ42

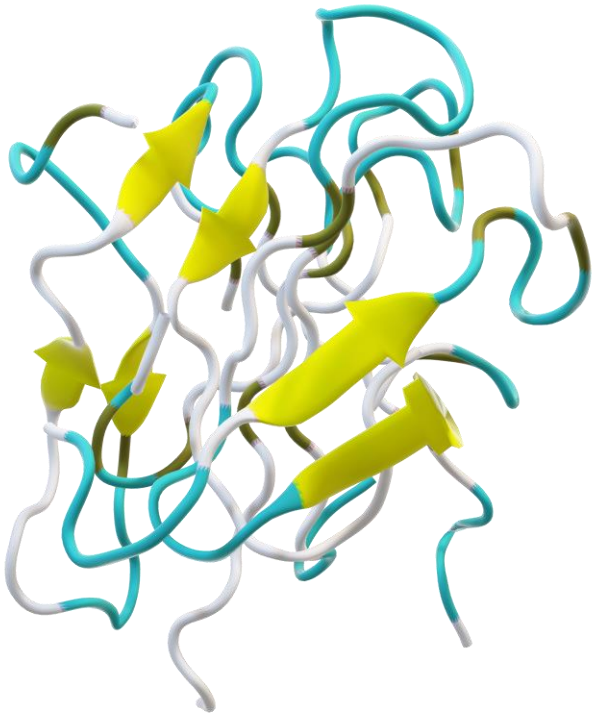
- PDB ID: 2MXU
- Fibril: 12 chains
- Solution: 12 free monomers
- Simulations box: 272 Å^3
- Concentration: 1 mM

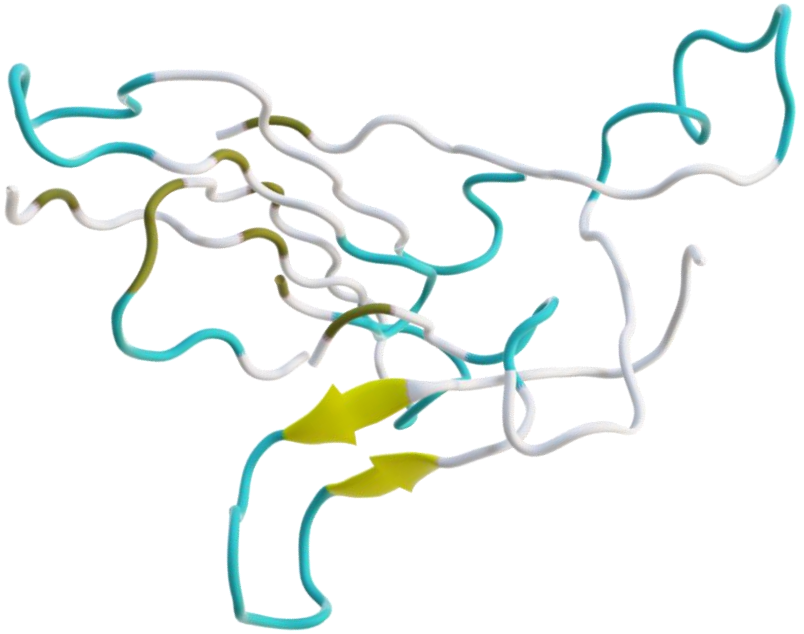


Aggregating Simulations



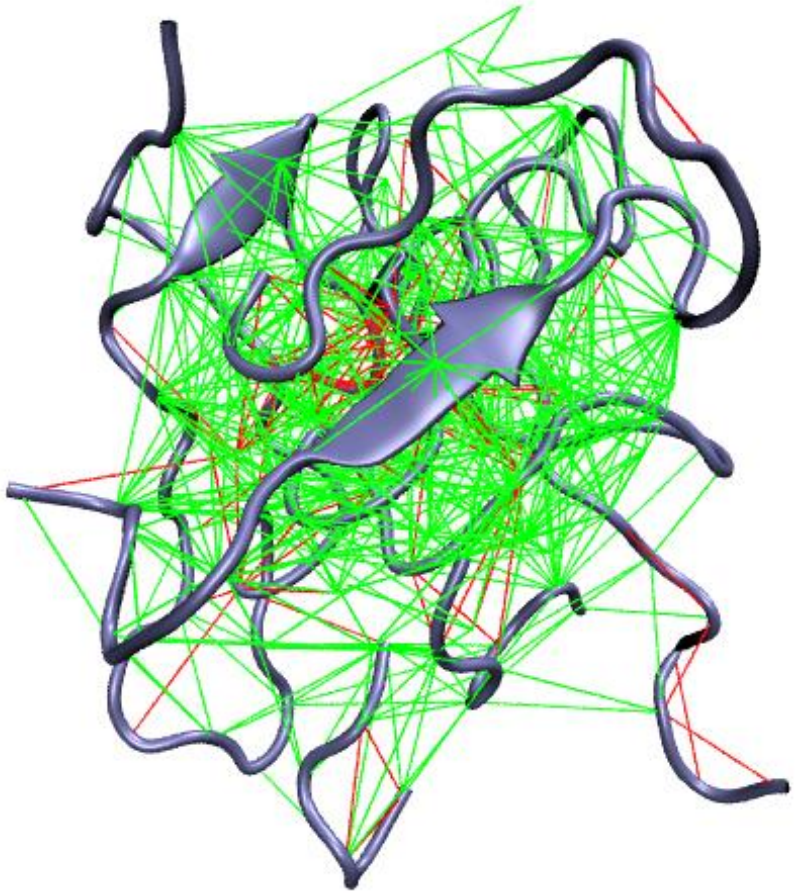
Aggregates at the final frame

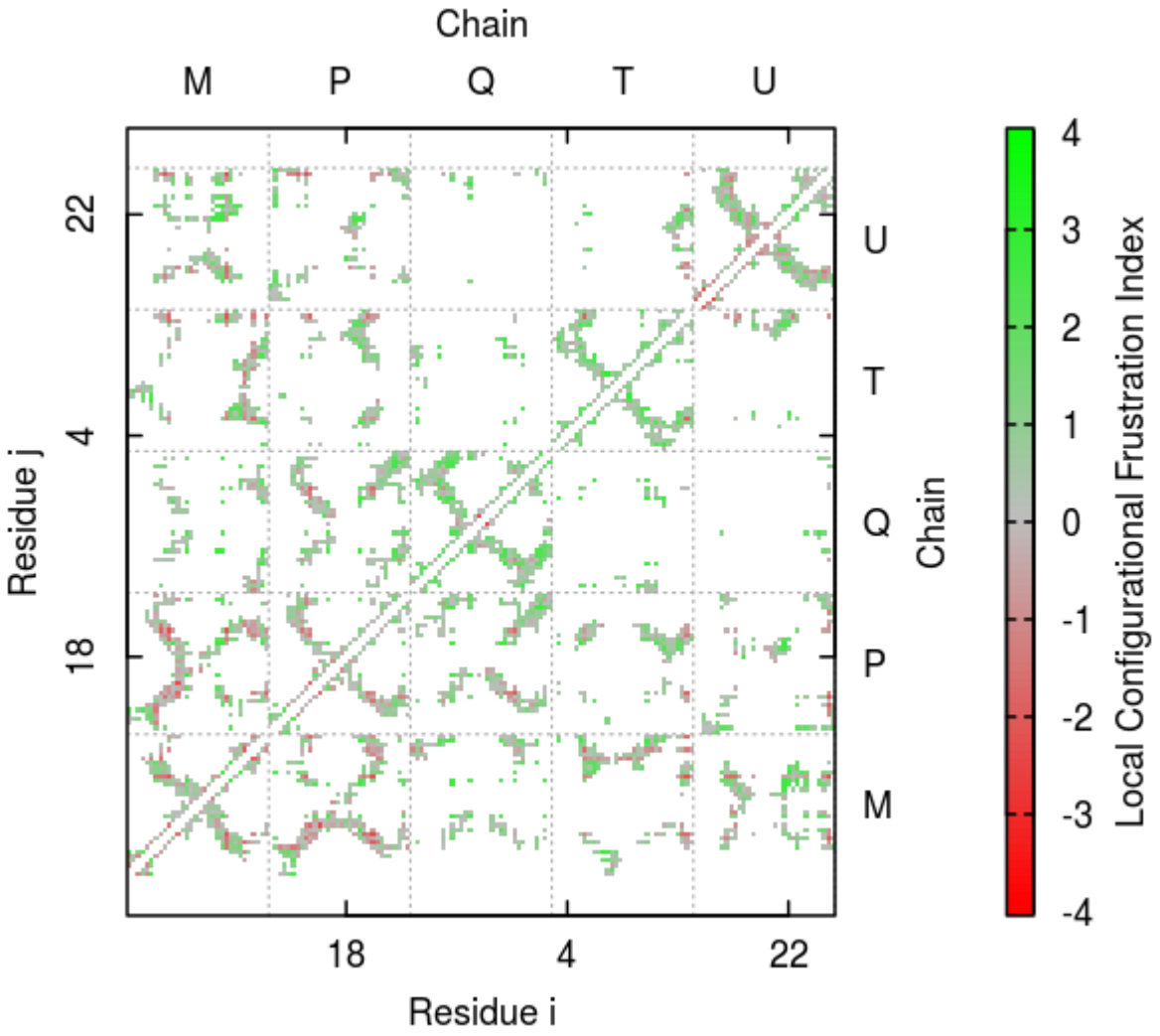




Aggregates at the final frame

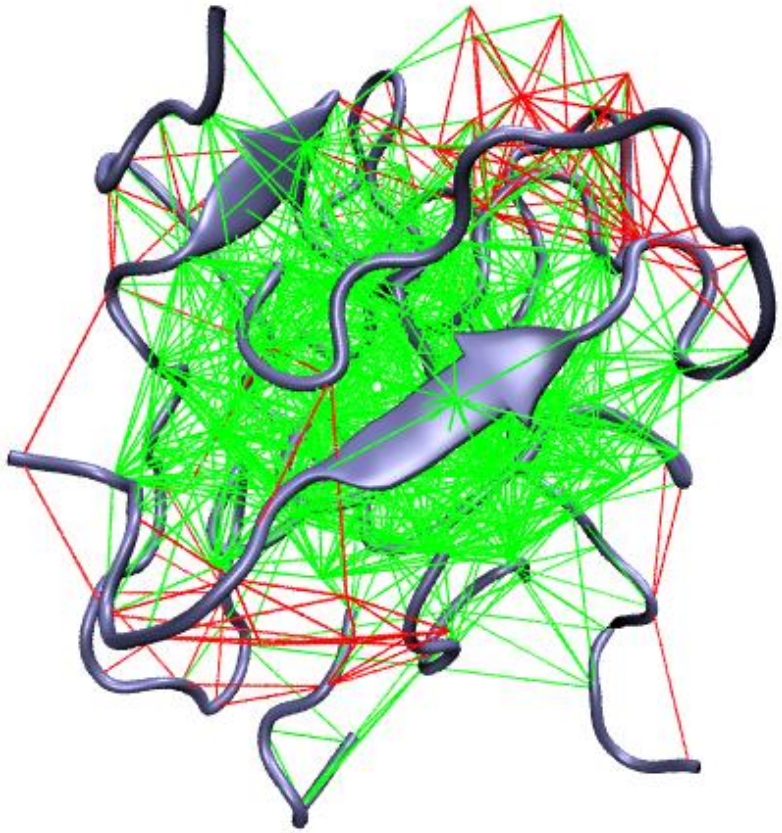
Configurational

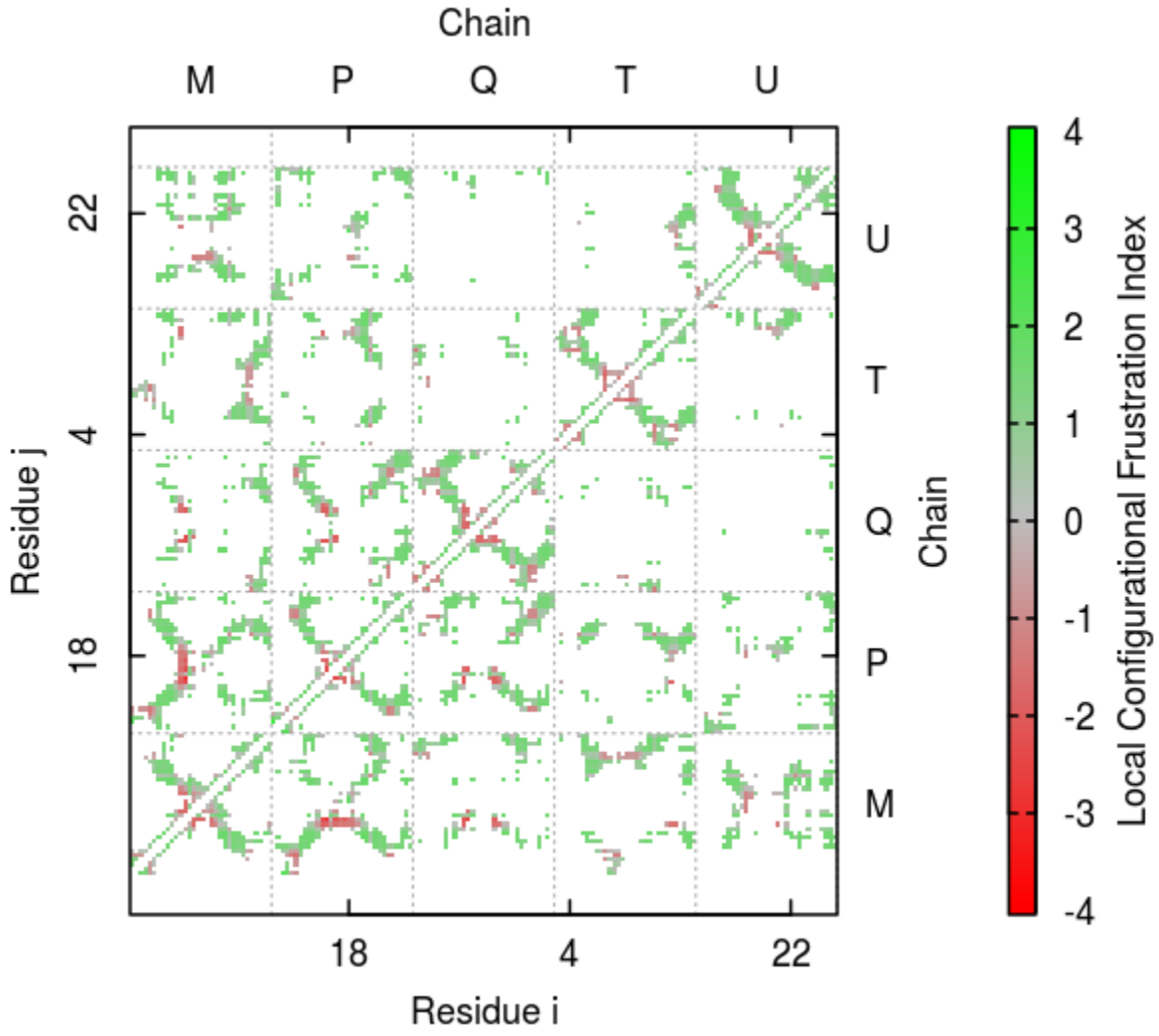




Aggregates at the final frame

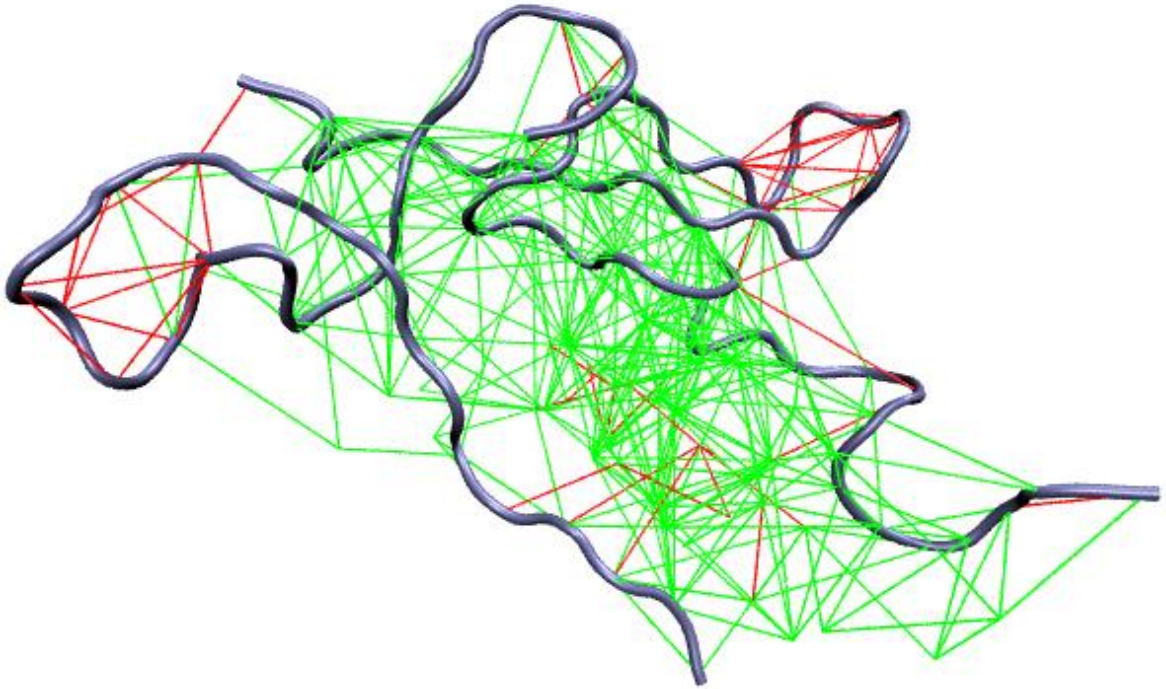
Mutational

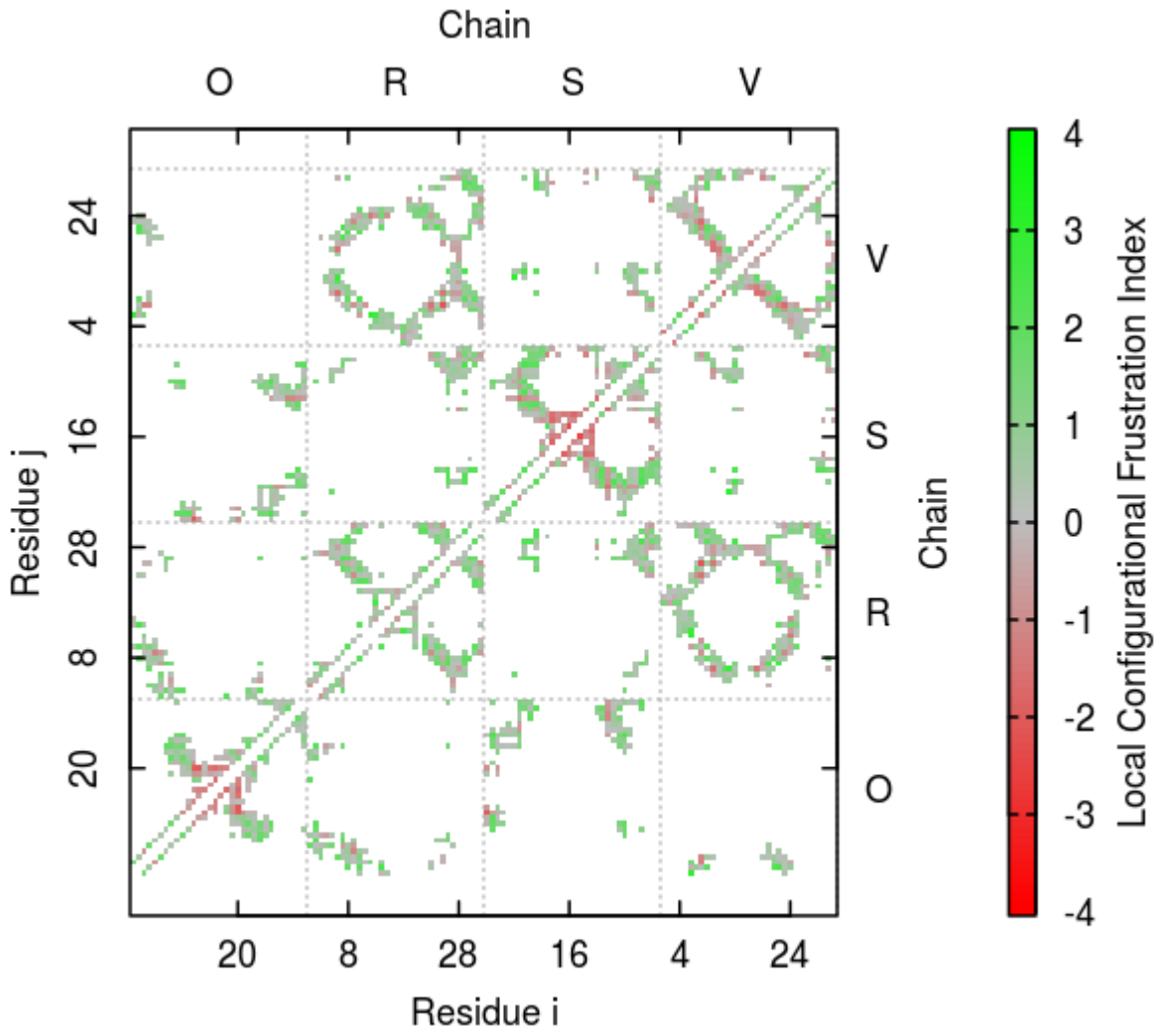




Aggregates at the final frame

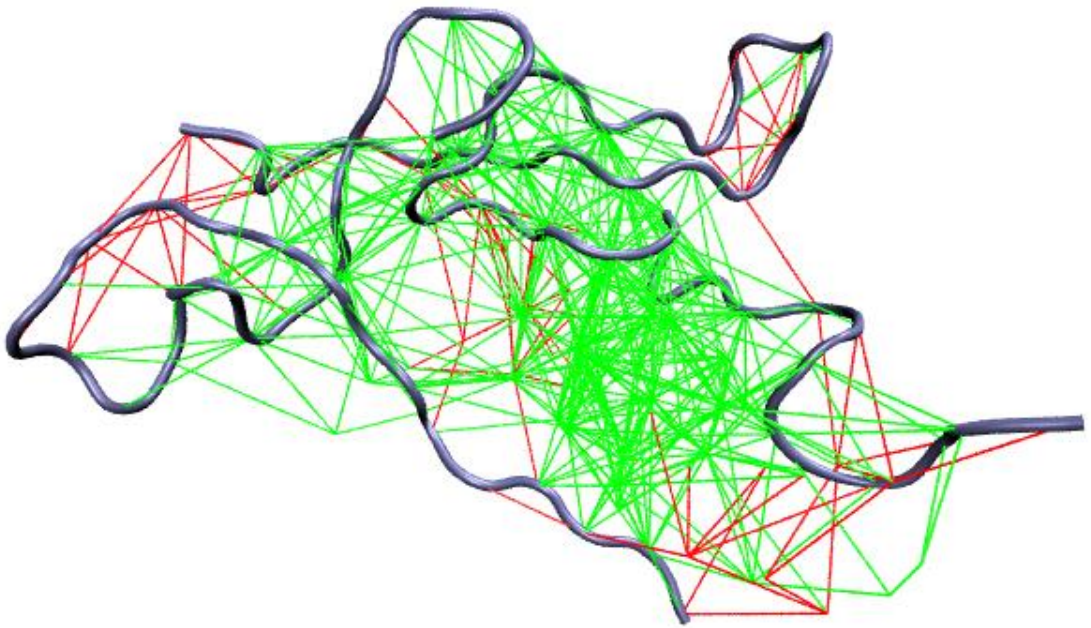
Configurational

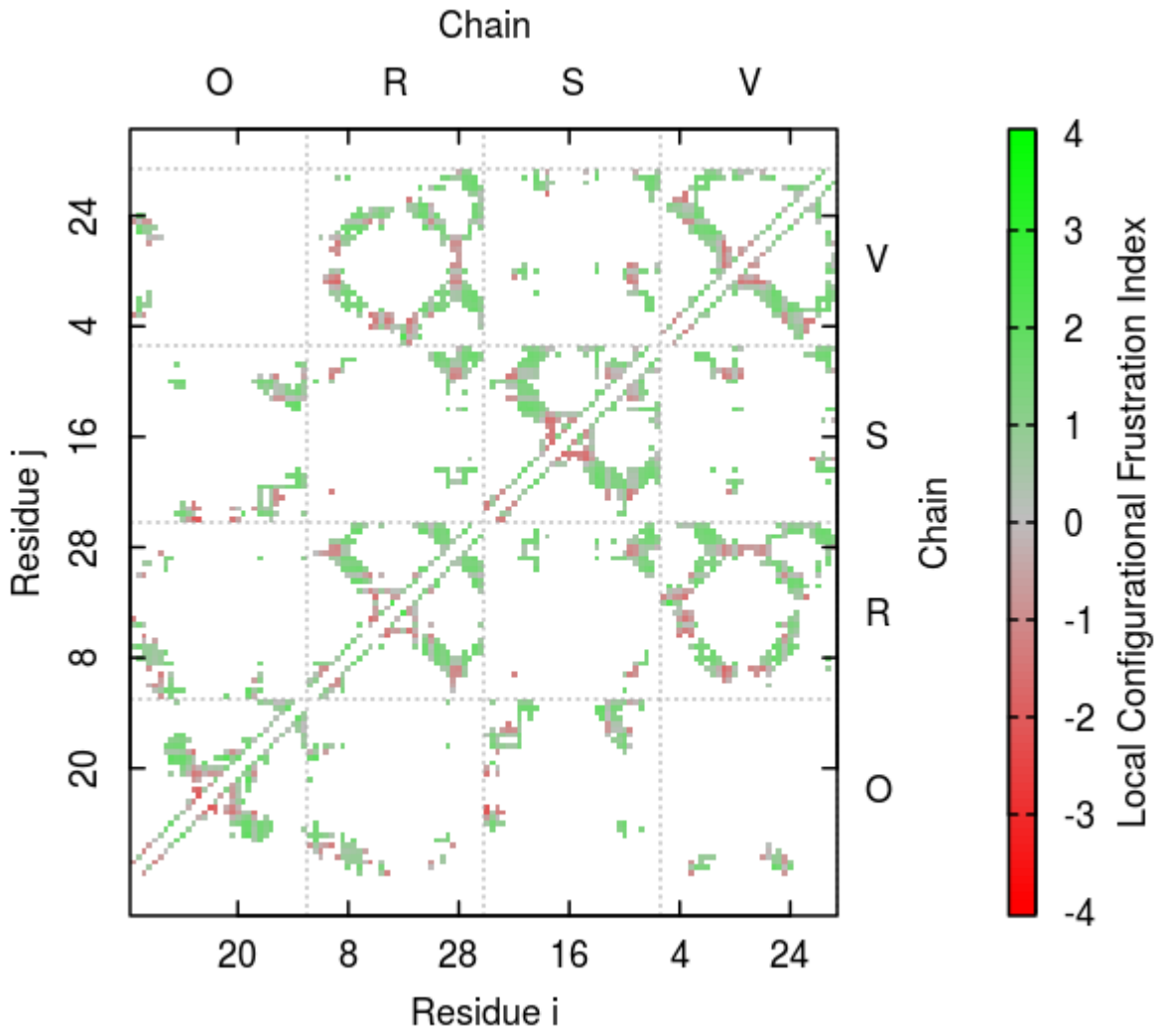




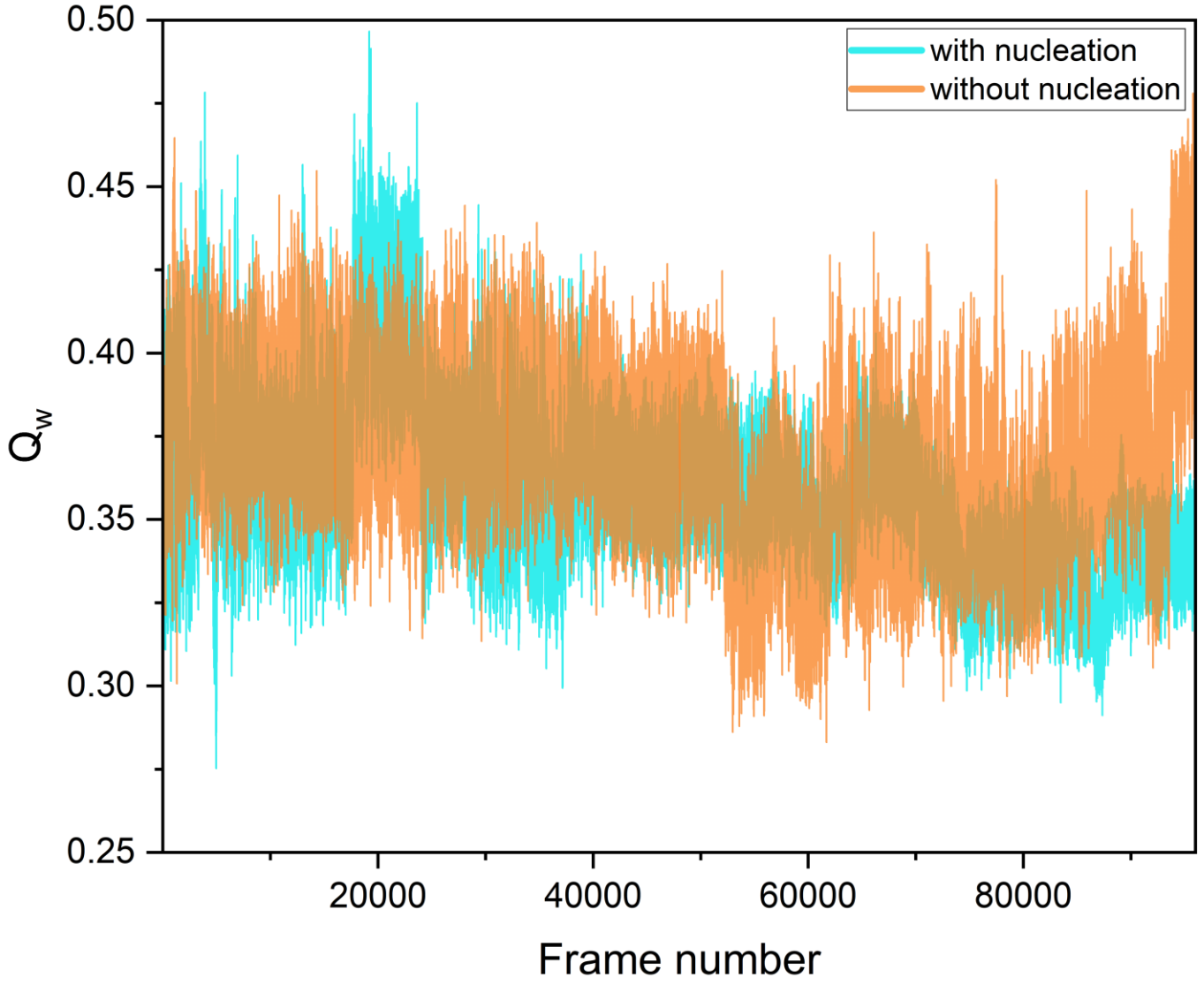
Aggregates at the final frame

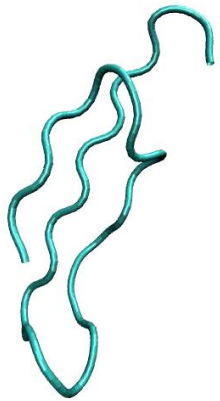
Mutational



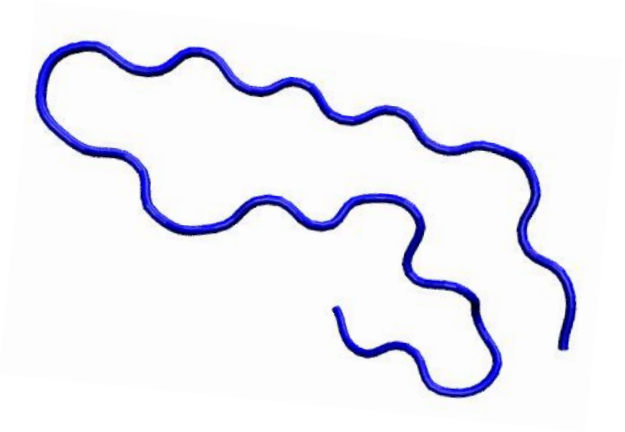


Polymorphic of the first monomer

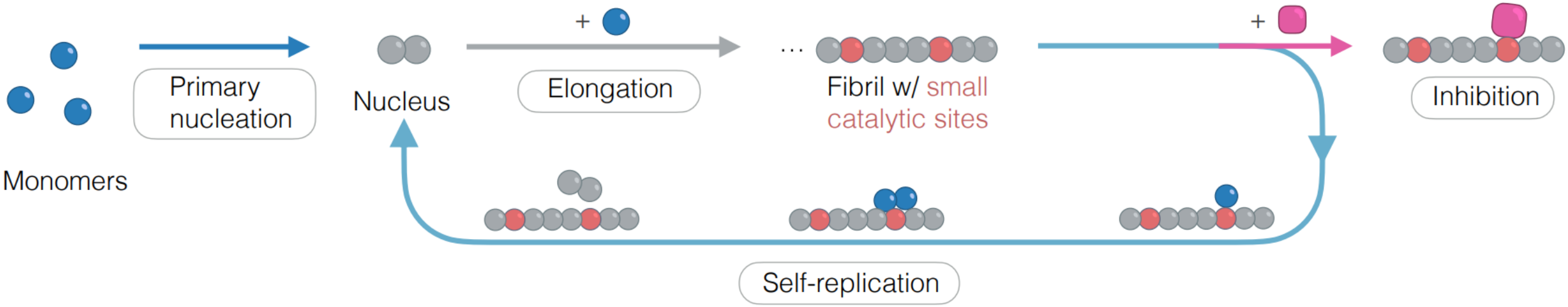




Reference:



Replication occurs on small and isolated fibril sites



Curk, S., Krausser, J., Meisl, G., Frenkel, D., Linse, S., Michaels, T. C., ... & Šarić, A. (2024). Self-replication of Aβ42 aggregates occurs on small and isolated fibril sites. Proceedings of the National Academy of Sciences, 121(7), e2220075121.

Conclusions

- Fibril formations was not observed.
- Monomers may not always find the specific sites for secondary nucleation, leading to oligomers formations.
- The oligomer formation might be related to toxicity, since it is possible to form new aggregates from it.

New questions

- How does these oligomers compare to the ones obtained from primary nucleation?
- How to locate the specific sites to observe secondary nucleation?
- How much energy is required for the secondary nucleation process to occur?

Acknowledgement

- Vitor Leite, UNESP, Brazil
- Peter Wolynes, CTBP, EUA
- José Onuchic, CTBP, EUA
- Carlos Bueno, CTBP, EUA
- Victor Tsai, Tamkang University, Taiwan
- Kaitlin Knapp, CTBP, EUA
- Mengyan Wang, CTBP, EUA
- Finley Clark, CTBP, EUA
- Larissa Adolfo, UNESP, Brazil
- Rafael Viegas, UNESP, Brazil
- Ingrid Martins, UNESP, Brazil
- Antônio Oliveira Jr, CTBP, EUA
- Maria Freiberg, UBA, Buenos Aires
- Vinicius Contessoto, CTBP, EUA
- Ronaldo Oliveira, CTBP, EUA
- Steven Luo, CTBP, EUA
- Juliana Camargo, UNESP, Brazil

RICE | CTBP
Center for Theoretical Biological Physics