

Entropy Production and Generation of Protein Aggregate Models using Fokker Planck Dynamics

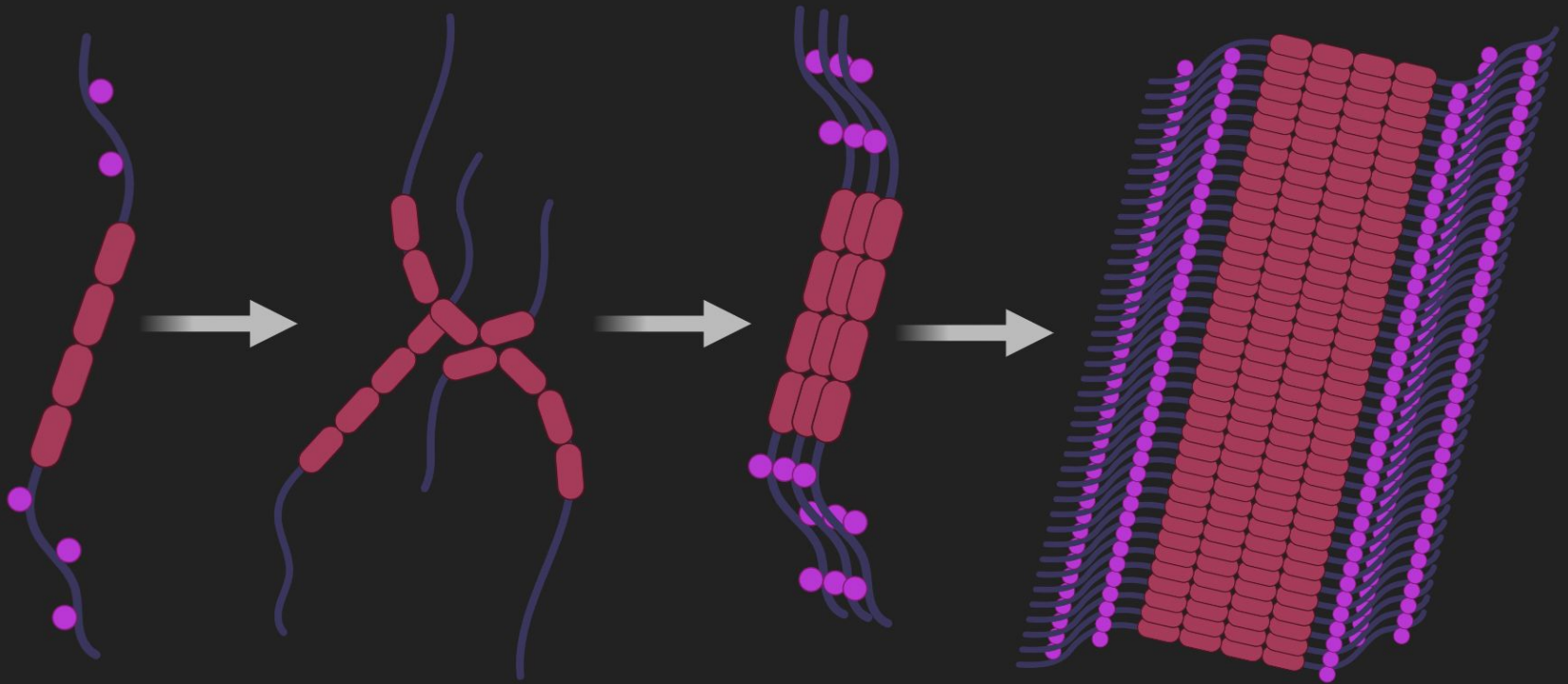
Leslie Cook, Preet Sharma

Non-Linear Science Research Group
Center for Theoretical Research



MIDWESTERN STATE UNIVERSITY

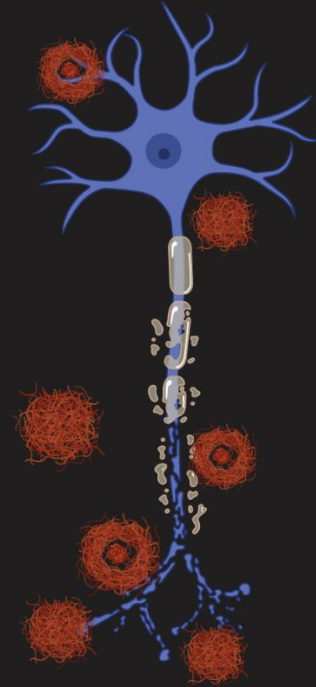
Self-Assembly of Intrinsically Disordered Proteins



Effects of Protein Aggregate Associated Disease



Healthy neuron



Diseased neuron



Attributing Factors

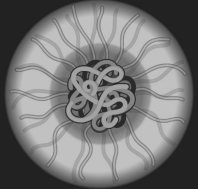
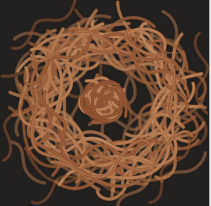
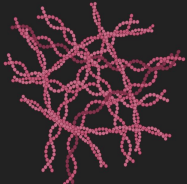
Sequence based

- Hydrophobicity
- Net charge
- Propensity for secondary structures

Environment based

- Protein concentration
- Temperature
- pH
- Salt concentration
- Shaking

Corresponding Diseases

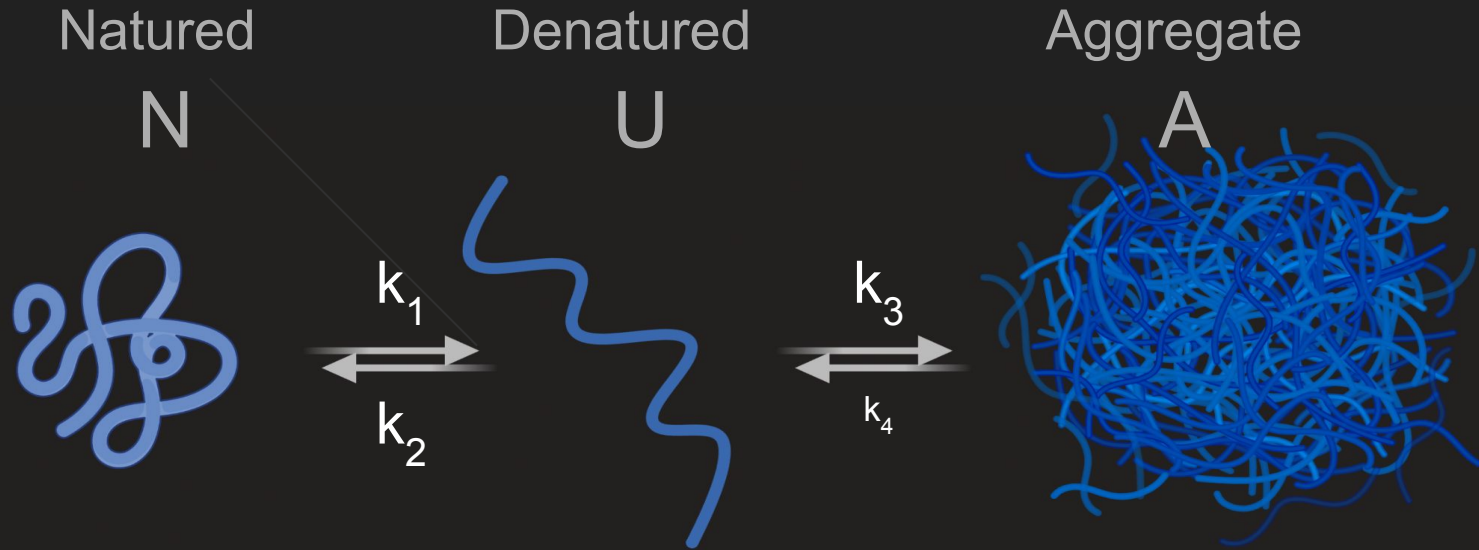
Disease	Protein of Interest	Aggregation Type
Parkinson's disease	α -Synuclein	Lewy Bodies 
Alzheimer's disease	Amyloid- β	Amyloid Fibrils 
Chronic Traumatic Encephalopathy	Tau	Fibrillary Tangles 

Complexity of Protein Aggregation

Unfortunately, it's not as simple as one protein per disease.

- Post-mortem examinations of patients with neurodegenerative disease have shown that A- β and Tau are both hallmarks of Alzheimer's and Parkinson's dementia.
- A region of the α -Synuclein protein termed NAC (non-amyloid β -component) has been found in amyloid plaques associated with AD.

Mass-Action Chemical Kinetics



$$\frac{dN}{dt} = -k_1 N + k_2 U \quad | \quad \frac{dU}{dt} = k_1 N - k_2 U - k_3 U + k_4 A \quad | \quad \frac{dA}{dt} = k_3 U - k_4 A$$

The stochastic (c) and mass-action (k) rate constants are related unit conversions and statistical factors as follows

$$c_i = V^{1-\nu_i} k_i$$

where, ν_i is the i^{th} stoichiometric parameter (a.k.a. state change).

We consider the reactions are all unimolecular such that,

$$\nu_i = 1, \text{ therefore } c_i = k_i.$$

We assume the process is Markovian, meaning that future states are independent of previous states, on the interval, $[t, t + \Delta t]$. Then applying the first order approximation from the stochastic theory of reaction kinetics, we obtain a function of molecular interactions, ω_i , in terms of displacement (x), N (natured), and A (aggregate) states. :p O.o

$$\omega_i = f_i(x, N, A)\Delta t + O(\Delta^2),$$

Fokker-Planck Dynamics

Recall that,

$$\left[\frac{dN}{dt} = -k_1N + k_2U \right] + \left[\frac{dU}{dt} = k_1N - k_2U - k_3U + k_4A \right] + \left[\frac{dA}{dt} = k_3U - k_4A \right] = 0$$

We build an equation to calculate the probability distribution of x at time, t , using Fokker-Planck dynamics.

$$\begin{aligned} \frac{\partial P(x,t)}{\partial t} = & (k_1N + k_4A)P(x-1,t) + (k_2 + k_3)(x+1)P(x+1,t) \\ & + (k_1N + k_2x + k_3x + k_4A)P(x,t) \end{aligned}$$

Conclusion



- Mathematical models of biological systems are significant for the development of bioinformatic simulations that can capture the conditions of real-life systems to bridge the gap between in vitro and in vivo research..
- Data obtained from these models will contribute to the development of new technologies to detect, treat, and hopefully cure neurodegenerative diseases caused by protein aggregation.

citations

1. @misc{winn2017youmans, title={Youmans and Winn neurological surgery. Ed}, author={Winn, HR}, year={2017}, publisher={Elsevier, Philadelphia, PA}}
2. @book{lennarz2013encyclopedia, title={Encyclopedia of biological chemistry}, author={Lennarz, William J and Lane, M Daniel}, year={2013}, publisher={Academic Press}}
3. @book{daroff2014encyclopedia, title={Encyclopedia of the neurological sciences}, author={Daroff, Robert B and Aminoff, Michael J}, year={2014}, publisher={Academic press}}
4. @incollection{youssef2018pathology, title={Pathology of Brain Aging and Animal Models of Neurodegenerative Diseases}, author={Youssef, Sameh A}, booktitle={Conn's Handbook of Models for Human Aging}, pages={899--908}, year={2018}, publisher={Elsevier}}
5. @article{doherty2020short}, title={A short motif in the N-terminal region of α -synuclein is critical for both aggregation and function}, author={Doherty, Ciaran PA and Ulamec, Sabine M and Maya-Martinez, Roberto and Good, Sarah C and Makepeace, Jemma and Khan, G Nasir and van Oosten-Hawle, Patricija and Radford, Sheena E and Brockwell, David J}, journal={Nature structural & molecular biology}, volume={27}, number={3}, pages={249--259}, year={2020}, publisher={Nature Publishing Group}}
6. @misc{centers for disease control and prevention_2022, title={FASTSTATS - leading causes of death}, url={https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm}, journal={Centers for Disease Control and Prevention}, publisher={Centers for Disease Control and Prevention}, year={2022}, month={Jan}}
7. @article{bisaglia2006structure, title={Structure and topology of the non-amyloid- β component fragment of human α -synuclein bound to micelles: Implications for the aggregation process}, author={Bisaglia, Marco and Trolino, Alessandra and Bellanda, Massimo and Bergantino, Elisabetta and Bubacco, Luigi and Mammi, Stefano}, journal={Protein science}, volume={15}, number={6}, pages={1408--1416}, year={2006}, publisher={Wiley Online Library}}
8. @misc{upadhyay2021dynamics, title={Dynamics of unfolded protein aggregation}, author={Utkarsh Upadhyay and Chandrima Barua and Shivani Devi and Jay Prakash Kumar and R. K. Brojen Singh}, year={2021}, eprint={2111.04103}, archivePrefix={arXiv}, primaryClass={q-bio.SC}}
9. @article{rousseau2022biochemical, title={Biochemical Problems, Mathematical Solutions}, author={Rousseau, Marc R and Santilli, Mois}, journal={AIMS Mathematics}, volume={7}, number={4}, pages={5662--5669}, year={2022}}
10. All images created with BioRender.com