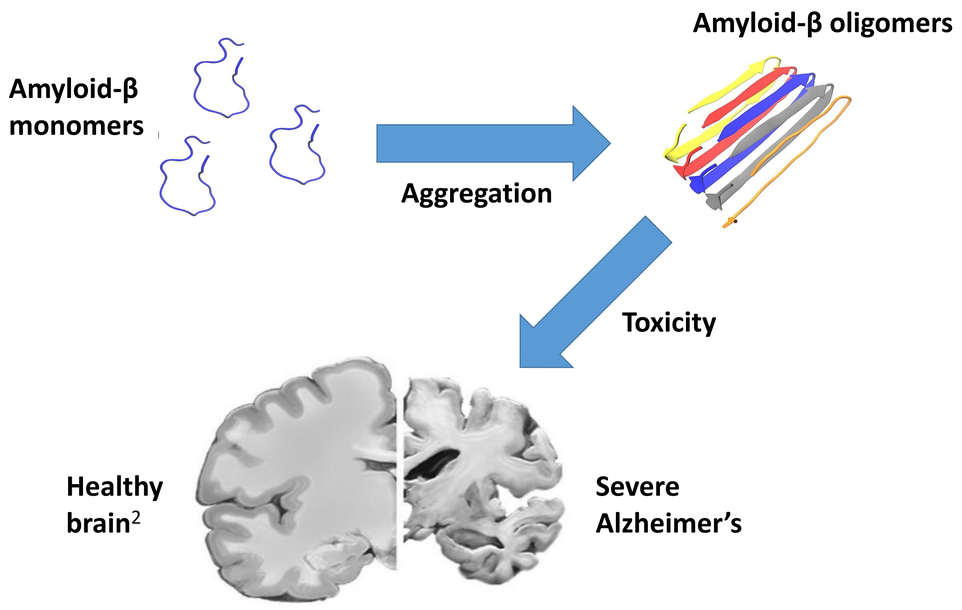
Machine Learning for Analysis of Molecular Dynamics Simulations

Petr Kouba, Stanislav Mazurenko, Jiří Sedlář, Josef Šivic

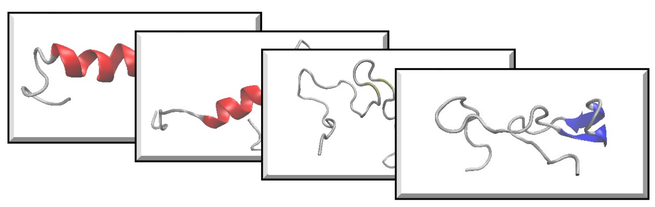
Introduction

Our project employs **Machine Learning** and **Artificial Intelligence** techniques to examine **Molecular Dynamics** simulations of the **Amyloid-β** peptide. We study the peptide under different conditions: in water (**free Amyloid-β**) and in the presence of small molecules that are suspected of altering its conformational dynamics (**Amyloid-β + small molecule**). As the peptide is believed to be the hallmark of **Alzheimer's Disease**, our objective is ultimately to contribute toward a deeper understanding of the disease and its potential treatment.

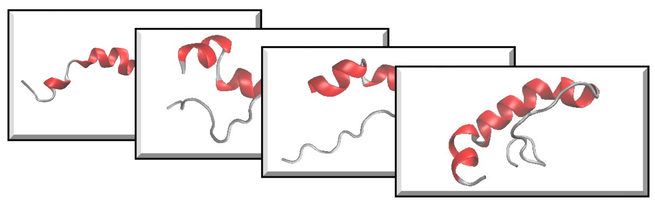
- **Alzheimer's Disease** is the 7th leading cause of death globally[1], with no efficient drugs available to date
- The aggregation of the intrinsically disordered **Amyloid-β** peptide plays a crucial role in Alzheimer's Disease onset
- Potential drugs may include small molecules preventing the **aggregation** of **Amyloid-β**
- The fact that **Amyloid-β** is **intrinsically disordered** significantly complicates its *in silico* modeling and analysis
- **Artificial Intelligence** shows excellent potential to facilitate the task of analyzing the dynamics of intrinsically disordered proteins



Data



Simulation of free Amyloid-β

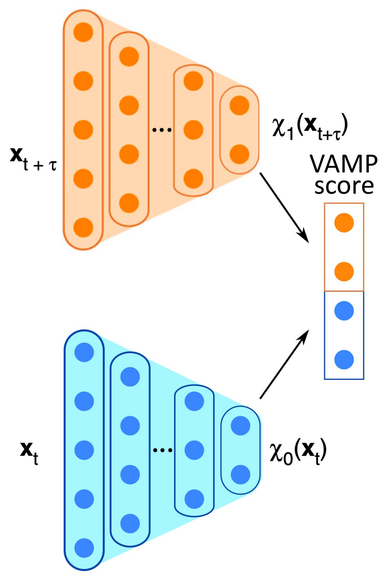


Simulation of Amyloid-β + small molecule

Molecular Dynamics Simulations

- Rich source of information regarding protein dynamics on **short timescales**
- May be **difficult to interpret**

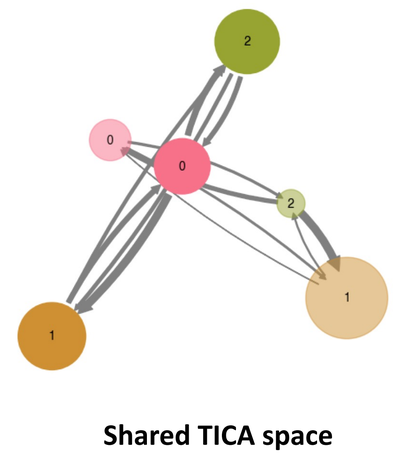
Methods



VAMPnet[3] Neural Network

- Trained end-to-end on the simulated data
- Estimates the **Markov State Model** describing the protein dynamics

Output



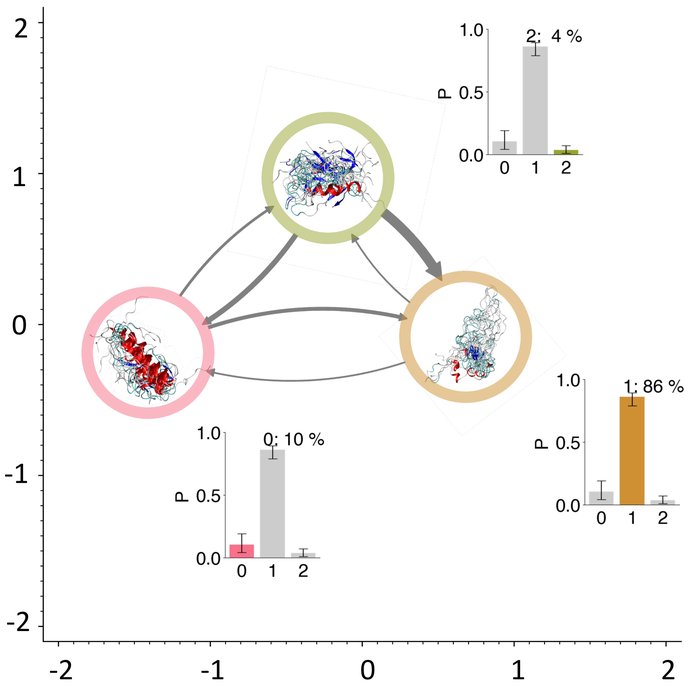
Shared TICA space

Markov State Models

- Describe dynamics on **long timescales**
- **Easier to interpret** than raw simulations
- **Allow comparison** of free Amyloid-β vs. Amyloid-β + small molecule systems

Preliminary results and future directions

TICA space of free Amyloid-β



The free Amyloid-β system is dominated by a highly populated **disordered** state.

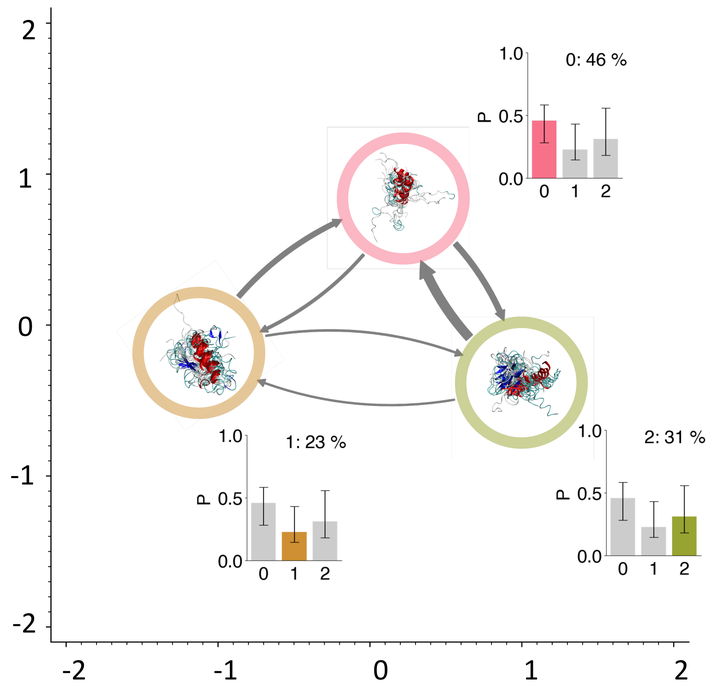
In contrast, the system with the small molecule exhibits more **order.**

The system with the small molecule tends towards conformations containing **α-helices**, which may **prevent** the **aggregation** of the peptide.

Next steps:

- Examine how Artificial Intelligence could enhance the data generation step
- Apply the analysis pipeline to other proteins related to Alzheimer's Disease

TICA space of Amyloid-β + small molecule



Acknowledgements:

Sérgio M. Marques, Lucas Disson, David Bednář, Joan Planas-Iglesias, Zainab Sanusi, Antonín Kunka, Anthony Legrand, Zbyněk Prokop, Tomáš Pajdla, and Jiří Damborský

References:

1. WHO Report (2019), The top 10 causes of death
2. Taylor K., Oxford University Press (2020), ISBN: 0191864676, (Brain Image Credit)
3. Mardt et al., Nat Commun **9**, 5 (2018), DOI: 10.1038/s41467-017-02388-1

MUNI | RECETOX · LOSCHMIDT LABORATORIES · FACULTY OF ELECTRICAL ENGINEERING CTU IN PRAGUE · CZECH INSTITUTE OF INFORMATICS ROBOTICS AND CYBERNETICS CTU IN PRAGUE · IMPACT Intelligent Machine Perception Project CZ.02.1.01/0.0/0.0/15_003/0000468 · VSB TECHNICAL UNIVERSITY OF OSTRAVA | IT4INNOVATIONS NATIONAL SUPERCOMPUTING CENTER · Brno Ph.D. Talent