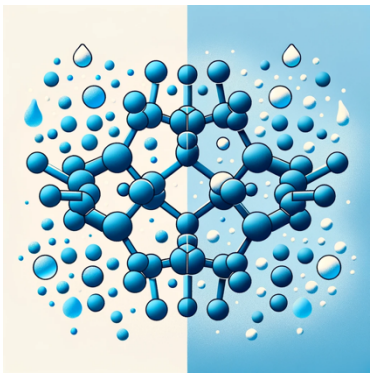
# Isotope effects on amyloid aggregation



Contact: Dr. Ioana M. ILIE
Van 't Hoff Institute for Molecular Sciences
University of Amsterdam
Email: i.m.ilie@uva.nl
Website: ioanailie.org

**Background:** Protein misfolding and aggregation are associated with some of the most intractable neurodegenerative disorders. The aggregation process is largely unknown. It is generally believed that H/D-isotope substitution has no effect on molecular structure, and only on chemical rates if proton transfer is involved. However, it was recently found that amyloid fibrilization of insulin is much slower in $D_2O$ than in normal water[1] (Fig. 1), and for some proteins, such as elastin-like polypeptides or globular proteins, even the *structure* is different in $H_2O$ and $D_2O$. The differences are believed to be due to the H/D-isotope effect on hydrogen bonds.

**Rationale:** Understanding the structural and dynamic differences of fibrillization in water and heavy water can be a useful strategy to gain a better understanding on the aggregation process and the effects of the solvent.

**Goal:**

- Understand the aggregation dynamics of VEALYL, an amyloid-forming peptide derived from human insulin, in $H_2O$ and $D_2O$

## Research questions

1. How does the solvent affect the thermodynamics and kinetics of aggregate formation & their structure?
2. What are the stabilizing interactions in aggregates in $H_2O$ and $D_2O$?

## Research approaches

1. Molecular dynamics (MD) simulations
2. Turbidity measurements
3. Fluorescence spectroscopy
4. Linear and non-linear infrared spectroscopy

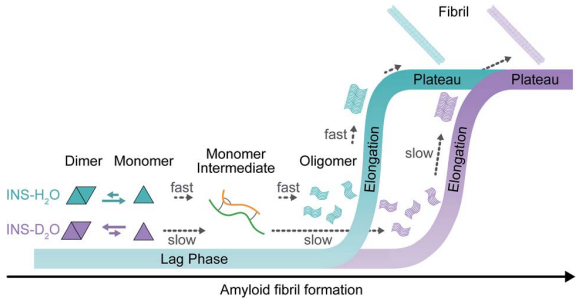



**Figure 1: Fibrillation kinetics diagram of insulin**, based on kinetic and structural analysis. insulin-H2O (blue) and insulin-D2O (purple). Figure and legend taken from ref. [1].

## Bibliography

(1) Chun, S. Y.; Son, M. K.; Park, C. R.; Lim, C.; Kim, H. I.; Kwak, K.; Cho, M. Direct Observation of Protein Structural Transitions through Entire Amyloid Aggregation Processes in Water Using 2D-IR Spectroscopy. *Chem Sci* **2022**, *13* (16), 4482–4489. https://doi.org/10.1039/D1SC06047C.