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Coach	**Supervisor(s)**	**Funding**
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Kinetic Monte Carlo modelling of amyloid beta peptide polymerization

Aim

Model development for amyloid β (Aβ) peptides ordered aggregation and formation of linearly fibrils.

Justification

Peptide polymerization is important for a number of currently incurable diseases, such as Alzheimer's disease (AD), where amyloid β (Aβ) peptides undergo ordered aggregation. Despite intensive research efforts, detailed kinetic mechanisms underlying this complex polymerization process are not well known.

The Karolinska Institute in Stockholm investigates the Aβ polymerization process, which involves two competing nucleation mechanisms (Figure 1). The fibril length distribution (FLD) was characterized using fluorescence correlation spectroscopy (FCS) and fibrillar structure by circular dichroism spectroscopy (CDS). Processing the data from both FCS and CDS leads independently to nearly identical values of the apparent rate coefficient of the overall polymerization. However, current modelling efforts are limited to (i) analytical solutions for specific cases or (ii) the method of moments, which only allows to calculate the average fibril length. Moreover, such modelling does specify competing nucleation mechanisms. The aim of this work is to use LCT expertise in the field of polymer reaction engineering to the polymerization of peptides leading to the formation of linearly growing fibrils. Kinetic Monte Carlo (*k*MC) modelling of the FLD will increase our understanding of the various competing mechanisms and may help us identify the factors accelerating the development of AD and even expedite the development of treatment for AD.

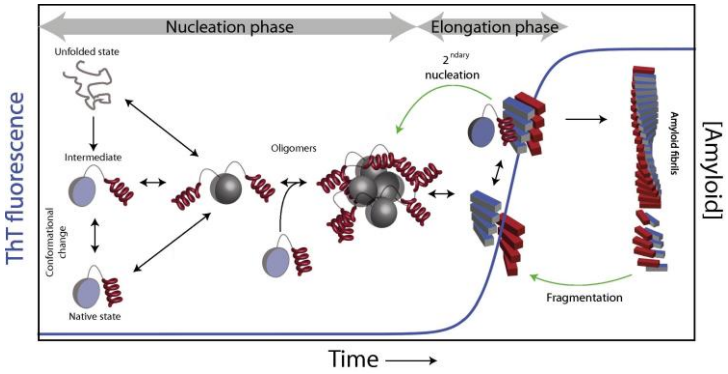

Figure 1: Polymerization of peptides toward fibrils, involving competing nucleation mechanisms. The schematic represents some of the possible routes of amyloid formation through primary (black arrows) or secondary pathways (green arrows). Assembly commences from a monomeric precursor that could be unfolded, partially folded or natively folded (left-hand side). During the nucleation phase, dynamic equilibrium between these states is responsible for generating species with increased amyloid potential, which then self-assemble. Once the critical nucleus is generated rapid formation of β-rich amyloid fibrils starts (elongation phase). Secondary mechanisms, such as secondary nucleation on the surface of preformed fibrils (or aggregates), or fibril fragmentation, are also crucial determinants of the fate of assembly. The fluorescence of thioflavin T (ThT-blue trace), a dye that binds to cross-β aggregates, is commonly used to follow the progress of the reaction.

Program

- Concise literature study of experimental and modelling techniques for Aβ peptide polymerization, exploring possible mechanisms for Aβ peptide polymerization.
- Adjusting an existing *k*MC polymerization code toward reactions of Aβ peptides and fibrils, using rate laws reported in the literature.
- Estimating elementary rate coefficients from an extensive data set provided by the Karolinska Institute.
- Identifying the factors accelerating the aggregation process by understanding the competition between primary and secondary nucleation mechanisms.

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