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## Membrane interactions in amyloid-related diseases

Amyloid-related diseases comprise a group of devastating human and animal illnesses. The most common among the human amyloid-related diseases are Alzheimer's disease, Parkinson's disease and type II diabetes mellitus. These diseases are characterised by abnormal protein aggregation into β-sheet rich molecular fibrils. Amyloid aggregation is a multi-step process. Initially, peptides that are natively or pathologically unfolded cluster together to form soluble bodies comprised of dimers, trimers or other oligomers. They then gradually form higher order oligomers, filaments and fibrils. It is widely believed today that, with few exceptions, prefibrillar aggregates lead to cellular toxicity and mature fibrils are relatively harmless [Janson et al., 1996, Lambert et al., 1998, Conway et al., 2000] (except of being a reservoir of monomers that are ready to form aggregates).

Interactions between oligomers of amyloidogenic peptides and membranes or lipids appear to be one of the main reasons for the cellular toxicity of prefibrillar intermediates. For example, it has been shown that prefibrillar structures made by islet amyloid polypeptide (IAPP) monomers, whose aggregation is leading to type 2 diabetes mellitus, insert into membranes and lead to membrane damage [Engel et al., 2008]. Interactions between amyloidogenic (poly)peptides and membranes, fatty-acids or other surfactants induce the formation of oligomers that appear to be involved in disease progression, through various mechanisms (see e.g., [Barghorn et al., 2005, Hasegawa et al., 2008, Bucciantini et al., 2012, Vestergaard et al., 2013]).

## Challenges in experimental studies of protein oligomerisation

Prefibrillar amyloidogenic structures are, by their nature, transient and dynamic, ranging in size from dimers to high order multimers and in structure from unordered, globular structures to filaments with a dense presence of β-sheet forming peptides. The monomers that aggregate typically lack ordered structures, and the native structures of disease-related amyloidogenic proteins such as amyloid-$\beta_{1-42}$ or islet amyloid polypeptide are highly unordered.

The difficulty of studying amyloid aggregation experimentally prompted the use of molecular simulations as an additional tool for biophysical studies of amyloid aggregates [Caflisch, 2006, Shea & Urbanc, 2012, Lemkul & Bevan, 2012]. Simulations can shed light on times and scales that are not covered by the experiment, provide insights on experimental findings [Engel, 2009] and lead to testable hypotheses. Simulations suggest, for example, that amyloid fibril growth may be directional (at least for the HET-s prions [Baiesi et al., 2011, Friedman & Caflisch, 2013]), but this has yet to be shown experimentally due to challenges in the planning of such experiments.

## Coarse-grained simulations of amyloid aggregation in the presence of membranes and lipids

The sizes of many molecular oligomers, and the timescale for their formation are several orders of magnitude larger than those that can be followed by atomistic simulations. As a result, coarse-grained models are very common in the field [Hung & Yarovsky, 2011, Seo et al., 2012, Derreumaux, 2013, Liguori et al., 2013]. Fairly accurate coarse-grained force fields such as MARTINI [Marrink et al., 2007] or REACH [Moritsugu & Smith, 2007] are unfortunately not suitable to follow on amyloid aggregation where the conformational changes involve secondary structure. The

approach used by Caflisch and co-workers has therefore been to develop phenomenological coarse-grained models for amyloid aggregation. In phenomenological models, a top-down approach is used to model a process. Instead of coarse-graining a collection of atoms to model membranes and peptides of different structures, lipids are represented by three beads having a single conformation [Friedman et al., 2009] and peptides by ten beads with two conformations: amyloid-prone ($\beta$) and amyloid-protected ($\pi$) [Pellarin & Caflisch, 2006]. Such models are, in principle, simple and limited. They do not enable, for example, to differentiate between peptides of different sequences. Yet despite their simplicity, the models can be tailored to study biologically-relevant amyloid aggregation. The free energy difference between the $\beta$ and $\pi$ conformers can be tuned to represent peptides that form fibrils rapidly, more slowly, or not at all. Similarly, by changing the lipid's head group size and the strength of the lipid/lipid interactions, the lipids can generate bilayered liposomes, micelles, worm-like structures and unordered aggregates, all of which are observed in experiments. The strength of the peptide-lipid interactions can be tuned, which can be used to emulate the affect of different types of biomolecular membranes (i.e., membranes whose interactions with peptides are weak, intermediate or strong).

The phenomenological coarse-grained model developed initially by Pellarin and Caflisch [Pellarin & Caflisch, 2006] and extended by Friedman *et al.* to include membranes [Friedman et al., 2009] have yield some interesting finding. Coarse-grained simulations were used to explain why growing filaments, but not mature fibrils, interfere with the membrane structure [Friedman et al., 2009]. An intriguing finding, that some membranes induce fibril degradation [Martins et al., 2008] that lead to the formation of smaller toxic aggregates (the fibrils themselves are not particularly toxic), was explained by molecular dynamics simulations [Friedman et al., 2010]. Apparently, if the peptide/lipid interactions are very strong, this may lead to the disaggregation of fibrils and formation of oligomers. Finally, the same model has been used to simulate the formation of globulomers- globular oligomers made of peptides and lipids. Their structures were shown to depend on the peptide:lipid ratio and the peptide's amyloidogenicity.

A recurrent finding coming from these studies is that the amyloidogenicity of the peptides is important for the outcome of aggregation in the presence of lipids. For example, the kinetics of fibril formation is faster in the presence of membrane when highly amyloidogenic peptides are involved but slower when the peptides are non-amyloidogenic. The explanation was that unlike highly amyloidogenic peptides, peptides of low amyloidogenicity form fibrils only in solution. This has indeed been later observed experimentally with IAPP (high amyloidogenicity) and pro-IAPP (low amyloidogenicity) [Khemtémourian et al., 2009]

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