# ULTRASOUND DRIVEN AMYLOID FIBRIL UNFOLDING INVESTIGATED BY MOLECULAR MODELLING

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## Introduction

Alzheimer's disease (AD) is the most common type of dementia. This pathology is characterized by an abnormal aggregation of misfolded proteins into plaques, causing proximal neurons death. Many pharmacological strategies have been proposed to target amyloid aggregation, but regrettably many of them have shown to be ineffective. Ultrasound based technique has shown to be a valid nonpharmacological strategy to reduce plaque size [1]. In this connection, it has been observed that stable cavitation phenomena related to ultrasound can affect protein secondary structures. Modelling techniques and in particular Molecular Dynamics (MD) can provide an adequate tool to observe biological phenomena with fine space (nanometers) and time (nanoseconds) resolution. The aim of this work is to shed light on molecular mechanisms driving the amyloid fibril unfolding during cavitation [2].

## Method

Stable cavitation phenomenon was simulated by an ad-hoc computational code, developed in this work starting from information in previous literature [3]. Models of cavitation bubbles consist in dummy beads that varies harmonically their radii, and interact with surrounding waters molecules trough a modified time-dependent Lennard-Jones potential. The stable cavitation was simulated in a molecular systems consisting of a pentameric S-shaped 1-42 Amyloid fibril (PDB:5OQV), in a box filled by explicitly modelled water (TIP3P). 3% of water molecules were replaced by bubble dummy atoms. Different replicas of non-quilibrium MD (NEMD) of bubble stable cavitation were performed in NVT (costant number of particles, temperature and volume) ensemble at 300 K. NEMD simulations were carried out until a complete fibril disaggregation was observed. Moreover, equilibrium MD (EMD) simulations, in NVT ensemble at 300K, with bubbles at fixed radius, has been carried out in order to compare results in absence of cavitation induced phenomena.

## Results

Results confirmed that ultrasound stable cavitation affects amyloid fibril stability. Indeed, while root mean squared deviation (RMSD) evaluated on the initial configuration reaches a *plateau* for the EMD simulation, for the NEMD simulation this value constantly increases (Figure 1A). Moreover, time history of contact probability on close chains residues has been studied, (Figure 1B), in order to consider residues involved in non convalent interactions. Fibril compactness is not perturbed during EMD simulation, leading to contact probability values close to 1 for all amyloid residues. On the other hand, in NEMD simulation stable cavitation phenomena results in a chain-chain contact variation, reducing the number of contacts between residues of adjacent chains. Moreover, it is possible to observe that loss of contact starts from residues involved in unstructured regions and propagates to inner residues belonging to ordered secondary structure.

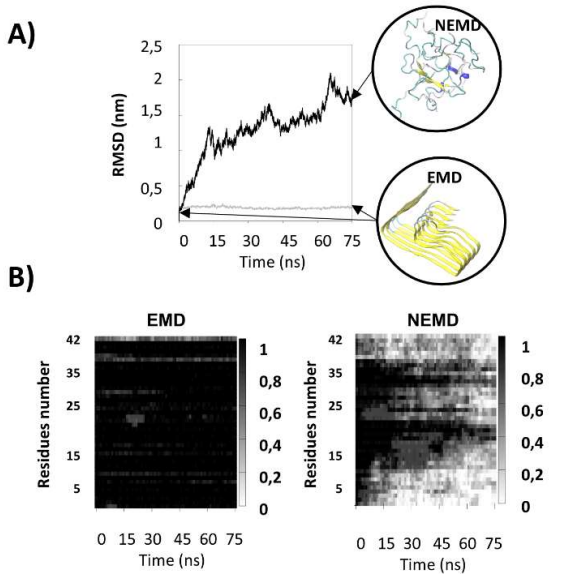


*Figure 1: A) Root mean squared deviation for NEMD (black) and EMD (light gray). B) Time history of contact probability*

## Discussion

Mechanical stimulation in the form of cycles of compression and decompression, obtained by stable cavitation, can drive amyloid fibril to destabilization and disruption. This work clearly depicts how stable cavitation acts at the molecular level. Residues belonging to unstructured regions act as seed of instability, promoting the unfolding process of close structured regions and the entire amyloid disaggregation.

## References

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3. Hoang Viet M et al,. *J. Chem. Phys.* 2016; **145**: 174113.