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Summary of PhD thesis entitled:

Molecular dynamics of intrinsically disordered proteins and their aggregates in coarse-grained models

The aim of the thesis is constructing a coarse-grained model of intrinsically disordered proteins, capable of simulating their aggregation and presenting results of those simulations for polyalanine and polyglutamine proteins of various lengths, and for gluten proteins.

Two coarse-grained models were constructed. In each of them, one amino acid residue is represented by one pseudoatom. Both models use the implicit solvent method: water molecules are represented by thermal noise and a damping term, and the molecular dynamics are described by the Langevin equation. Protein residues are connected harmonically and the backbone stiffness is described by a potential based on a random coil library. Interactions between residues (that are not neighbours in the sequence) are described by Lenard-Jones and Debye-Hückel potentials.

The first model uses the idea of a contact map, developed in the context of structured proteins. In the model constructed here, the contact map is constantly recalculated, based on various criteria stemming from the geometry of the chain. Those criteria allow a one-bead-per-residue model to recreate differences between contacts made by a sidechain and a backbone of a residue. Contacts that fulfil the geometrical criteria are switched on and off quasi-adiabatically, so the hamiltonian depends on time.

The second model uses a novel pseudo-improper-dihedral potential which also distinguishes between sidechain and backbone interactions. Both models were parameterized on a set of experimental and all-atom data. The hamiltonian of the second model does not depend on time, but the model was too slow to simulate aggregation of tens of chains. Thus, the first model was used for the simulations.

Conformational dynamics of intrinsically disordered proteins was first analyzed in the case of single chains. During simulation, conformational transitions in timescales of hundreds of microseconds were observed. A novel clustering algorithm allowed for calculating lifetimes of individual conformations. The model was also used to predict properties of homopeptides with various lengths.

Polyalanine and polyglutamine simulations made it possible to construct phase diagrams for those systems, based on clustering the chains into aggregates. A novel "amyloids glass" phase was defined, consisting of slowly diffusing anisotropic aggregates resembling amyloids fibrils. The kinetics of aggregate fusion and fission was also investigated. Lifetimes of contacts between aggregates turned out to be described by a power law.

The aggregation of gluten proteins and their fractions, gliadins and glutenins, was never simulated before. The simulations were able to recreate the increased strain resistance of gluten after mechanical deformation. A similar increase was not observed in control simulations of proteins from maize and rice seeds. The simulations confirmed existing theories that explain the extraordinary gluten viscoelasticity on a molecular level. The dynamic shear modulus was also calculated.

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