Theoretical and computational modeling of amyloid aggregation

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Principal Investigators

SCHMIT, JEREMY

Institution

KANSAS STATE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Theoretical and computational modeling of amyloid aggregation

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,285,096.33

Start date of award

15/08/2014

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Theoretical model, Amyloid, aggregation pathway, Computer Simulation, simulation

Research Abstract

DESCRIPTION (provided by applicant): Experimental studies of protein aggregation utilize protocols that accelerate aggregate formation by many orders of magnitude relative to the multi-decade timescales that characterize the onset of dis- eases like Alzheimer’s. The gap between

in vivo and in vitro aggregation timescales demands detailed theories of the aggregation process in order to extrapolate experimental observations toward physiological conditions. Current theoretical tools are not suitable for this task. Analytic theories presently lack the microscopic basis that is needed to make predictions about sequence perturbations or environmental conditions, and in silico methods struggle to reach even in vitro aggregation timescales without sacrificing necessary resolution. The applicants have developed a microscopic theory of fibril elongation that agrees with experiments with respect to the effects of temperature, denaturants, and protein concentration. This theory identifies the conformational search over H-bonding states as the slowest step in the aggregation process (an observation that is in agreement with recent simulations) and shows that this search can be efficiently modeled as a random walk in a rugged one-dimensional potential. The proposed work will expand on this model in two ways: 1) By developing new microscopic models of amyloid aggregation. These models will resolve key steps in the aggregation pathway including nucleation and the templating effect of the fibril end upon the binding of new molecules. They will also explore the kinetic competition between different modes of self-association, including oligomers and fibrils. 2) By using the insights from the preliminary model to develop a multi-scale computational algorithm to simulate fibril growth and nucleation in atomistic detail. In this algorithm, a large number of small simulations will be used to compute the system diffusion tensor in the reaction coordinate space predicted by the analytic theory. This diffusion tensor wil then be used to compute Markov state trajectories of the aggregation process. The innovation of this work is to use analytic modeling to deduce slow steps in the microscopic kinetics that are not presently resolvable by experiments or simulation, and to use these insights to develop simulation methods with greatly improved efficiency. The outcome will be the ability to resolve the effects of small sequence perturbations, such as the two amino acids differentiating the major forms of the Alzheimer’s-related peptide A, as well as a “”kinetic phase diagram”” that will allow the rational manipulation of aggregation pathways and provide a means to infer physiological consequences from in vitro experiments.

Lay Summary
PUBLIC HEALTH RELEVANCE: Aggregation diseases like Alzheimer’s are expected to place an increasing burden on public health as the population ages. The proposed research is relevant to NIH’s mission to produce fundamental knowledge about the molecular basis of these diseases to help develop effective intervention strategies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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