Robust rare event simulation for protein folding and disease-related aggregation

https://neurodegenerationresearch.eu/survey/robust-rare-event-simulation-for-protein-folding-and-disease-related-aggregation/

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Country

USA

Title of project or programme

Robust rare event simulation for protein folding and disease-related aggregation

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,596,770.64

Start date of award

01/08/2013

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Parkinson's disease & PD-related disorders

Keywords

Protein-Folding Disease, Lewy Body Dementia, Parkinson's Dementia, simulation, protein folding

Research Abstract
DESCRIPTION (provided by applicant): This proposal describes the development and application of rare event methods that will open the door to treating classes of biomolecular

problems that are challenging for existing methods owing to their multipathway character. These include problems in protein folding and aggregation that remain outstanding, despite enormous progress in those areas in recent years. The key idea is to rigorously characterize the error behavior of the methods (in particular in the low temperature limit) to derive criteria tat can be used to adaptively refocus sampling for maximal efficiency. The properties of the methods that we seek are as follows: (i) they will be capable of operating with more than a few reaction coordinates to allow treating problems without obvious choices of descriptors, (ii) they will efficiently sample reaction mechanisms that proceed via a complex network of transitions rather than a single dominant pathway, (iii) they will be fully non-equilibrium, i.e., they will generate reactive trajectories and the statistical properties of those trajectories including rates and other dynamical quantities such as time correlation functions, and (iv) the results that they provide will not depend on the particular choice of reaction coordinates (though the convergence rate typically will) or on any Markov assumptions. The proposed methods will be applied to two protein folding problems that are beyond present enhanced sampling methods. The first system is beta3s, a 20-residue designed three-stranded antiparallel beta-sheet miniprotein. We choose this system because data on its folding and unfolding exists from extensive physically weighted molecular dynamics simulations, and analyses by several groups show that it has a well-defined native state and complex dynamics that are characteristic of much larger proteins. The second system is much less well characterized, but improved means for modeling it can provide information of major biomedical significance: we will map the states and transitions accessible to monomers and oligomers of alpha-synuclein, a 140-residue intrinsically disordered protein that is linked to a number of neurodegenerative diseases, including Parkinson’s Disease and Dementia with Lewy Bodies.

Lay Summary

PUBLIC HEALTH RELEVANCE: The protein folding and aggregation processes underlying many neurodegenerative diseases are not amenable to modeling by present computational techniques. We will use rigorous mathematical error analysis to develop a new class of computational methods for molecular simulation that promises to overcome the shortcommings of existing methods. The resulting techniques will be applied to studying the dynamics of proteins linked to Parkinson’s Disease and Dementia with Lewy Bodies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Parkinson's disease & PD-related disorders

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