Computational molecular modelling as a platform for a deeper understanding of protein dynamics and rational drug design

Gianvito Grasso,[1] Lorenzo Pallante,[2] Jack A. Tuszynski,[2] Umberto Morbiducci,[2] Marco A. Deriu[2]

[1]Istituto Dalle Molle di Studi sull'Intelligenza Artificiale (IDSIA), Scuola Universitaria Professionale della Svizzera Italiana (SUPSI), Università della Svizzera Italiana (USI), Centro Galleria 2, Manno, Switzerland; [2]Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

Abstract

Elucidating structural features of protein aggregation at molecular level may provide novel opportunities for overarching therapeutic approaches such as blocking common aggregation-induced cellular toxicity pathways. In this context molecular modelling stimulates further research on amyloid aggregation modulators and modelling platforms can be used to test the efficiency of potential aggregation inhibitors aimed at destabilizing/reducing the stability of the amyloidogenic proteins.

Introduction

Several possible alternatives to the use of animal models have been suggested: *in vitro* models, cell cultures, engineered tissues, and computer models. In this context the use of sophisticated molecular and multiscale computational models may help to understand mechanisms driving physiological and pathological behavior of complex biological systems. Computational molecular modelling represents a promising prospect for advances in a number of research fields. For example, in neurodegenerative diseases, understanding molecular mechanisms driving protein function/misfunction due to misfolding may lead to rational drug design strategies based on a deeper knowledge of protein structure-function relationships. Whereas a complete replacement of animals by computer models in the field of drug design is today only a dream, the use of molecular modelling techniques have already allowed to significantly reduce the experimental efforts in terms of resources and costs of experimentation.

Materials and Methods

Molecular modelling consists of theoretical methods and computational techniques able to describe the behaviour of complex biochemical systems (*e.g.*, membranes, proteins, small molecules) and their interactions by quantum and classical physics. Whereas approaches considering the quantum level (*ab initio* approaches) provide the most detailed analysis of molecular systems, they are limited by system size and complexity and cannot yet provide enough information to investigate dynamics of proteins or protein assemblies. Molecular Mechanics and Molecular Dynamics (MD) ignore the electronic degrees of freedom and focus the modelling on nuclear positions and a classical description of atomic interactions. MD produces a molecular trajectory with atomic resolution by the iterative integration in time of Newton's equations of motion for all atomic degrees of freedom. While exploring the time evolution of the molecular system, MD is able to capture thermodynamic properties (directly comparable with experimental data) by sampling all accessible conformational microstates in a defined statistical ensemble. Due to above mentioned peculiar features, MD is becoming a relevant player in the neurodegenerative research field, being able to describe protein tendencies towards specific conformational rearrangements and protein-protein organization. Approaching this problem from an energetic point of view is of great importance especially in case of amyloidogenic proteins, given the intimate interconnection between the functional energy landscape and aggregation risk. A deeper knowledge on the above-mentioned interconnection may significantly support the design of effective pharmacological and non-pharmacological strategies capable of driving misfolded or mis-aggregated proteins toward physiological conditions and away from pathological states.

Results

Approaches such as classical and enhanced MD have already been employed to provide a quantitative estimation of the free energy landscape characterizing the early stages of protein aggregation responsible for the onset of different diseases, such as Spinocerebellar Ataxia Type-1 (SCA1)[1,2] and Alzheimer's Disease (AD).[3-5] More in detail, classical and enhanced sampling techniques have recently fully characterized the AXH aggregation pathway from monomer to tetramer, highlighting several protein mutations responsible for the destabilization of the monomer/dimer/tetramer equilibrium states. Residues identified as mainly responsible for dimer-dimer interactions may be considered as an important target space for pharmacological intervention. Computational modelling has also provided fruitful insight into the conformational dynamics and stability characterizing Aβ fibrils, represented by a polymorphic structure and responsible for the onset of Alzheimer's Disease. For example, evidence about the stability of the recently proposed S-shaped Aβ fibril model, has been provided by computational simulations.[3,5] The S-shaped architecture shows superior mechanical performance compared to the U-shaped motif due to a better distribution of the mechanical stress, indicating the importance of molecular architecture in modulating the conformational dynamics and stability of the protein assembly. This aspect must be taken into account when designing inhibitors, which should hit all achievable pathologic forms of Aβ fibrils (Figure 1).

Conclusions

Elucidating the common structural features of protein aggregation diseases at molecular level may provide novel opportu-

Correspondence: Marco A. Deriu, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy.
E-mail: marco.deriu@polito.it

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nities for overarching therapeutic approaches such as inhibiting aggregation or blocking common aggregation-induced cellular toxicity pathways. To address this issue, it is extremely important to shed light on the molecular interactions responsible for protein aggregation. Information obtained from molecular modelling stimulates further research on amyloid aggregation modulators and modelling platforms can be used to test the efficiency of potential aggregation inhibitors aimed at destabilizing/reducing the stability of the amyloidogenic proteins. A tight feedback loop between molecular modeling predictions and experimental validation will become the future backbone of successful drug discovery strategies.

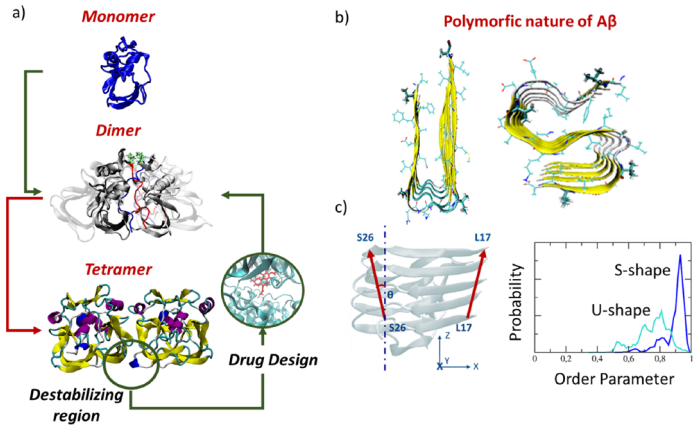

Figure 1. a) AXH monomer/dimer/tetramer. A better understanding of the protein aggregation dynamics drives the drug design; b) Polymorphic nature of Aβ amyloids; c) metrics to investigate their conformational stability. Effective compounds should be designed to destabilize all possible fibril arrangements.

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