Krajowa Konferencja Zastosowań Matematyki w Biologii i Medycynie

Sandomierz, 5th–9th September 2016

FOLDING OF KNOTTED PROTEINS UNDER NASCENT CONDITIONS AND THEIR UNFOLDING IN PROTEASOMES

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ABSTRACT

Knots in proteins have been proposed to resist proteasomal degradation. Ample evidence associates proteasomal degradation with neurodegeneration. One interesting possibility is that indeed knotted conformers stall this machinery leading to toxicity. However, although the proteasome is known to unfold mechanically its substrates, at present there are no experimental methods to emulate this particular traction geometry. Here, we consider several dynamical models of the proteasome in which the complex is represented by an effective potential with an added pulling force. This force is meant to induce translocation of a protein or a polypeptide into the catalytic chamber. The force is either constant or applied periodically. The translocated proteins are modelled in a coarse-grained fashion. We do comparative analysis of several knotted globular proteins and the transiently knotted polyglutamine tracts of length 60 alone and fused in exon 1 of the huntingtin protein. Huntingtin is associated with Huntington disease, a well-known genetically-determined neurodegenerative disease. We show that the presence of a knot hinders and sometimes even jams translocation. We demonstrate that the probability to do so depends on the protein, the model of the proteasome, the magnitude of the pulling force, and the choice of the pulled terminus. In any case, the net effect would be a hindrance in the proteasomal degradation process in the cell. This would then yield toxicity via two different mechanisms: one through toxic monomers compromising degradation and another by the formation of toxic oligomers. We also analyze folding processes in knotted proteins and demonstrate that they are facilitated by the nascent conditions at the ribosome.