Shedding light into the ribosomal exit tunnel via flexibility analysis and molecular dynamics simulation

Simone Fulle, Holger Gohlke

Computational Pharmaceutical Chemistry, Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine-University, Düsseldorf, Germany

The ribosome is a large ribonucleoprotein complex that carries out protein synthesis in all kingdoms of life by translating genetic information encoded in mRNA into the amino acid sequence of a protein. The nascent polypeptides escape the peptidyl transferase center through the ribosomal exit tunnel that spans the entire large subunit. The tunnel is involved in the control of co-translational protein folding processes, the regulation of elongation and inhibition of the protein synthesis by antibiotics [1,2]. Most of the present knowledge about the function of the ribosomal exit tunnel is derived from X-ray crystallography. This only provides us with static snapshots along conformational transitions, whereas the underlying dynamical processes remain largely unclear. E.g., there is still some disagreement over whether the ribosomal tunnel dynamically promotes the passage of the nascent peptide chain or whether the peptides pass passively through the tunnel.

First, I present global and local flexibility characteristics of the ribosomal exit tunnel revealed by constraint counting on new topological network representations of large ribosomal subunits from four different organisms [3,4]. The analyses provide critical insights into the role of the ribosomal exit tunnel during protein synthesis. The flexibility characteristics of the tunnel will be used to answer questions such as: Does the ribosomal tunnel dynamically promote the passage of the nascent peptide chain or does it act as a passive tube? To what degree can proteins fold in the tunnel? What is the origin of species-selectivity of antibiotics binding?

The above flexibility analysis says nothing about the direction and amplitude of existing motions and thus, questions related to the collective dynamics within the tunnel remain unresolved. To bridge this gap, I will present results from an all atom MD simulation of the large ribosomal subunit in explicit solvent.