Analysis of allosteric effect of pathologic variants at the light of local protein conformations

Alexandre G. de Brevern[1,2,3,*]

[1] Biologie Intégrée du Globule Rouge UMR_S1134, Inserm, Univ. Paris Diderot, Sorbonne Paris Cité, Univ. de la Réunion, Univ. des Antilles, F-75739 Paris, France
[2] Laboratoire d'Excellence GR-Ex, F-75739 Paris, France.
[3] Institut National de la Transfusion Sanguine (INTS), F-75739 Paris, France.
alexandre.debrevern@univ-paris-diderot.fr

Abstract

Proteins are highly dynamic macromolecules. To analyze their inherent flexibility, computational biologists often use molecular dynamics (MD) simulations. The quantification of protein flexibility is based on various methods such as Root Mean Square Fluctuations (RMSF) that rely on multiple MD snapshots or Normal Mode Analysis (NMA) that rely on a single structure and focus on quantifying large movements.

Alternative *in silico* approaches assess protein motions through the protein residue network or dynamical correlations from MD simulations. An alternative yet powerful approach based on small prototypes or "structural alphabets" (SAs) can be used. SAs approximate conformations of protein backbones and code the local structures of proteins as one-dimensional sequences. Protein Blocks (PBs) are one of these SAs.

Applying PB-based approaches to biological systems such as the DARC protein, the human αIIb β3 integrin and the KISSR1 protein highlighted the major interest of PBs in understanding local deformations of large protein structures. Specifically, these analyses have shown that a region considered as highly flexible through RMSF quantifications can be seen using PBs as locally highly rigid. This unexpected behavior is explained by a local rigidity surrounded by deformable regions. To go further, we used PBs to analyze long-range allosteric interactions in the Calf-1 domain of αIIb integrin and will also present new unpublished results. Our tool named PBxplore allows the analyses of MDs in terms of PBs and quantification with entropy index and also different types of visualization.

The presentation of this research will be done in 5 successive parts: (i) the presentation and interest of the PBs, (ii) the MD of the integrins, (iii) the analysis of the results using PBs with the PBxplore software, (iv) recent developments based on PBxplore to compare reference and variant proteins, i.e. providing information about potential allosteric events and (v) the extension of the analyses to the disordered protein.

Keywords: bioinformatics, computer science, protein structures, entropy, biostatistics, disorder proteins, long-range interactions.