Title: Separating the wheat from the chaff: tips on how to identify and characterize essential movements in frantically shaking proteins

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Understanding of how proteins work requires a joint description of their structural and dynamical characteristics. Both features can be studied using computational approaches, but analysing the dynamics is much more challenging than describing the structure. Molecular Dynamics (MD) simulations provide a direct way to observe molecular fluctuations with exquisite detail. But this capability represents, at the same time, a major limitation. This is because the majority of these movements are simply random thermal fluctuations. The relevant motions, those required by the protein to fulfil its biological function, appear combined with these meaningless random fluctuations.

A powerful tool to differentiate between the important and non-important motions in proteins is the Principal Component Analysis (PCA).[1] The technique is mainly used to change from a description based on local atomic coordinates to another one provided by collective coordinates, called the PC-modes. These modes describe concerted motions of different parts of the protein. It is found that a small set of them (< 1%) accounts for most of the fluctuations observed in the simulation. Thus, just a few PC-modes provide a description equivalent to hundreds or thousands of atomic coordinates. The subspace spanned by the main PC-modes is called the essential space (ES). It is assumed that it contains the motions related to the biological function of the protein. The remaining modes account for irrelevant, small-amplitude fluctuations.

In spite of the many examples in which PCA has proved useful, the PC-modes calculated by the standard procedure have a drawback that casts doubts on their actual significance and helpfulness: equivalent simulations do not afford the same modes. In this talk we will present and discuss a simple procedure that provides reproducible PC-modes for stable conformation of proteins. In so doing we will revise the fundamentals of PCA and we will introduce the formulas for the PCA of concatenated trajectories recently obtained by our group.[2] Finally we will show how the dynamics of multimeric proteins can be studied by combining PCA with a procedure that decomposes protein fluctuations into inter-chain and intra-chain movements. This procedure has provided interesting clues on the opening mechanism of the P2X4 ion channel.[3]

[1] I. Daidone and A. Amadei, "*Essential dynamics: foundation and applications*". Wiley Inter-disciplinary Reviews: Computational Molecular Science **2012**, 2, 762–770.

[2] G. Pierdominici-Sottile and J. Palma, "*New insights into the meaning and usefulness of principal component analysis of concatenated trajectories*". The Journal of Computational Chemistry **2015**, 36, 424–432.

[3] G. Pierdominici-Sottile, L. Moffatt and J. Palma, "*The dynamic behavior of the P2X4 ion channel in the closed conformation*". Biophysical Journal **2016,** 111, 2642-2650.