Modeling MS native-state amide hydrogen exchange through structural and dynamical properties

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Proteins play an important role in all biological processes. Nevertheless, to perform such functions, they depend on their structural and dynamical properties. Nowadays, to probe these properties, hydrogen/deuterium exchange (HX)-based methods are often used. Hydrogen atoms from protein surface are in continual exchange with solvent. Thus, using deuterated water, it is possible to probe selectively the deuterium incorporation for each residue/peptide, using mass spectrometry (MS). Computational methods such as normal mode analysis (NMA) are well suited to study protein dynamics since it describes protein collective motions. Last decade, several theoretical models based on protein structure were developed in order to explain HX reaction, but all fail when systematically tested. This present work aims to develop a statistical model using protein structural (e.g. number of contacts and hydrogen bonds) and dynamical properties to explain protein native state MS-HX data. We built two different linear models: *i.* structural and *ii.* structural+dynamical model, where we use the atomic fluctuations from NMA to represent protein flexibility. We next evaluate the root mean square error (RMSE), Akaike Information Criteria (AIC) and the Pearson correlation coefficient between experimental data and the fitted values. The model using only structural features was not able to efficiently explain the HX data. However, the inclusion of a dynamical variable enhanced the correlation between its fitted values and HX data. In conclusion, we showed the use of fluctuations from NMA in conjunction with structural variables from a single structure allows one to obtain the closest correlation with experimental data from MS-HX.

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