Protein design under competition for amino acids availability

Francesca Nerattini[1], Luca Tubiana[2], Chiara Cardelli[2], Valentino Bianco[2],
Christoph Dellago[2], and Ivan Coluzza[3]

[1]Faculty of Physics & VDSP member, University of Vienna, Sensengasse 8/9, 1090 Vienna, Austria
[2]Faculty of Physics, University of Vienna, Sensengasse 8/9, 1090 Vienna, Austria
[3]CIC biomaGUNE, po. Miramon 182, 20014 San Sebastian, Spain

Understanding the origin of the 20 letter alphabet of proteins is a long-lasting biophysical problem. In particular, studies focused extensively on the effect of a reduced alphabet size on the folding properties [1, 2, 3]. However, the natural alphabet is a compromise between versatility and optimisation of the available resources.

Here, for the first time, we include the additional impact of the relative availability of the amino acids. We present a computational protein design scheme that involves the competition for resources between a protein and a potential interaction partner that, additionally, gives us the chance to investigate the effect of the reduced alphabet on protein-protein interactions. We identify the optimal reduced set of letters for the design of the protein, and we observe that even alphabets reduced down to 4 letters allow for single protein folding. However, it is only with 6 letters that we achieve optimal folding, thus recovering experimental observations.

Additionally, we notice that the binding between the protein and a potential interaction partner could not be avoided with the investigated reduced alphabets. Therefore, we suggest that aggregation could have been a driving force for the evolution of the large protein alphabet.

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