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All-atom simulations reveal protein charge decoration in the folded and unfolded ensemble is key in thermophilic adaptation[1]

JONATHAN HUIHUI, LUCAS SAWLE, KINGSHUK GHOSH, University of Denver — Proteins from thermophilic organisms usually melt (unfold from folded) at a much higher temperature compared to their counterparts extracted from mesophilic organisms, despite having very similar structures and sequences. This is a long standing puzzle in protein science with the key question: Is there a general principle that evolution may have used to achieve such high thermal tolerance? However the quest for a general principle has been hampered due to the limits of experimental and computational studies that focus only on a few proteins. We tackle this by studying twelve pairs of homologous proteins from thermophilic and mesophilic pairs using detailed all-atom simulation methods. Our study reveals thermophilic proteins in the folded state have more favorable electrostatics interaction and, contrary to previous studies, we also find more favorable interaction in their unfolded state. This destabilizing effect, however, does not outweigh the favorable effect of the folded state, but highlights the importance of considering the unfolded state. Although electrostatics seems to be primary driving forces behind enhanced stability, we also notice there are secondary strategies (4 out of 12) at play where charge regulation may not be possible for functional reasons.

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