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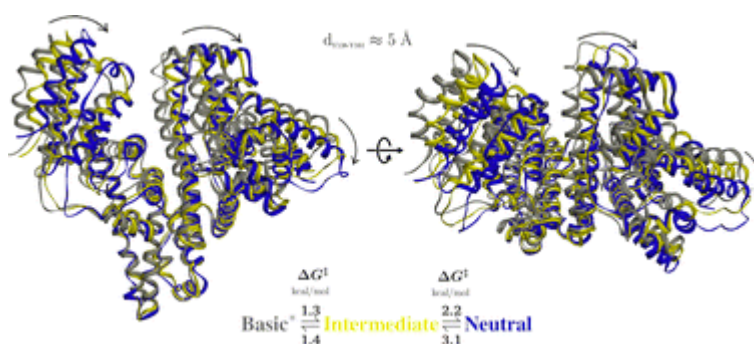
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From the journal:

Physical Chemistry Chemical Physics**Structural and thermodynamic characterization of allosteric transitions in human serum albumin with metadynamics simulations†**[Thales Souza Freire](#), ^{*a} [Julio Zukerman-Schpector](#), ^b [Ran Friedman](#) ^c and [Igneze Caracelli](#) ^d[Author affiliations](#)**Abstract**

Human serum albumin (HSA) is the most prominent protein in blood plasma, responsible for the maintenance of blood viscosity and transport of endogenous and exogenous molecules. Fatty acids (FA) are the most common ligands of HSA and their binding can modify the protein's structure. The protein can assume two well-defined conformations, referred to as 'Neutral' and 'Basic'. The Neutral (N) state occurs at pH close to 7.0 and in the absence of bound FA. The Basic (B) state occurs at pH higher than 8.0 or when the protein is bound to long-chain FA. HSA's allosteric behaviour is dependent on the number on FA bound to the structure. However, the mechanism of this allosteric regulation is not clear. To understand how albumin changes its conformation, we compared a series of HSA structures deposited in the protein data bank to identify the minimum amount of FA bound to albumin, which is enough to drive the allosteric transition. Thereafter, non-biased molecular dynamics (MD) simulations were used to track protein's dynamics. Surprisingly, running an ensemble of relatively short MD simulations, we observed rapid transition from the B to the N state. These simulations revealed differences in the mobilities of the protein's subdomains, with one domain unable to fully complete its transition. To track the transition dynamics in full, we used these results to choose good geometrical collective variables for running metadynamics simulations. The metadynamics calculations showed that there was a low energy barrier for the transition from the B to the N state, while a higher energy

barrier was observed for the N to the B transition. These calculations also offered valuable insights into the transition process.

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