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I-FSVKOR-Identification of the functional states of human vitamin K epoxide reductase from molecular dynamics simulations

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In mammalians, the enzymatic activity of vitamin K epoxide reductase (VKORC1) requires a protein conformational reorganisation that includes several transient enzymatic states involving a dynamic electron transfer. Regarding the structurally non-characterised human enzyme (hVKORC1), this process remains poorly explained and the different redox states of the enzyme generated by its biochemical transformation are unknown. We reported a 3D model of the fully reduced hVKORC1. As suggested, such model is a paradigmatic specimen used to predict the enzymatic states of a protein through exploration of its conformational space using extended molecular dynamics simulations. Distinct statistical techniques showed the great conformational variability of the protein. We searched the conformational space explored by protein using an estimation of the population of the conformations in the low dimensional space. Estimation of the energy profile by our newly developed technique, *ConfigScan*, and capture of the protein conformations at local minima provided a set of pro-models mimicking the biologically relevant states. Enzymatic functionality of each state was assigned by probing their recognition properties with respect to vitamin K. Two states were identified as contributing to two-steps vitamin K transformation. The state highly selective for native vitamin K was further validated through analyses of its free energy of binding with vitamin K agonists that showed a high correlation with the inhibiting constants, and as such, this validated our theoretical models. The generated models of the functional metastable states of hVKORC1 and their validation through in silico screening led to the concept of plausible mechanisms for enzymatic reactions.

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