

Reply to Karplus: Conformational dynamics have no role in the chemical step

We are pleased that Karplus (1) now agrees with our conclusions (2) that protein dynamics and enzyme catalysis are not coupled, despite the many assertions that they are (see relevant quotations in ref. 3). We agree (3) that rate-determining product release is not an example of chemical catalysis being coupled with dynamics but is a different phenomenon with a very minor relationship to the overall catalytic effect. We disagree with the arguments (1) that dispute our study, which quantified the coupling between conformational dynamics and chemistry (2). First, the value of k_{cat} was taken from the mesophile both because no other is available and because the precise value does not matter for any aspect of our study. Second, our paper is not about AdK but about any enzyme with a significant barrier, and the specific barriers have not been used for reaching any of our conclusions. The technical details raised (1) are misleading and obscure the fact that the popular proposition that catalysis and dynamics are coupled has never been supported by modeling the actual reaction or by direct experiments. Readers who are preoccupied with the exact source of k_{cat} are welcome to embrace the idea that enzymes work by dynamics. However, none of our conclusions are based on this rate or other specific barriers (figure 3 in ref. 2). Similarly, questioning the calibration of the model is misleading, because the finding that the conformational kinetic energy is dissipated holds for any reasonable friction.

We are told that reference 6 in ref. 1 describes equilibrium and nonequilibrium catalytic contributions, but the only catalytically significant contribution considered is associated with the electrostatic preorganization effect, which was introduced by us (4). The

crossing of the transition state has little to do with catalysis, because the transmission factor, κ , is similar in enzymes and in solution (5); additionally, we have established (2, 3) that fs and ps motions do not lead to rate enhancement, and of course, they do not facilitate millisecond processes, despite the implications that this is so (this issue is addressed in detail in ref. 3).

The assumption that short-timescale reactive trajectories can be used to explore the dynamical proposal is very problematic. Simulating such trajectories in enzymatic reactions was pioneered by us (citations in ref. 5), but they only tell us about the noncatalytic κ . The relevant possibility that the conformational energy is not dissipated on a very long timescale and drives chemistry cannot be explored by such trajectories.

Finally, trying to dismiss our coarse-grained (CG) model overlooks the fact that we also provided studies with a multi-dimensional model and obtained the same result (figure 5 in ref. 2). In any case, there is no need to compare the CG and the reactive trajectory approaches, because the second approach cannot tell us anything about the long timescale and the relevant short time features are already included in the CG model (figure S7 in ref. 2).

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The authors declare no conflict of interest.

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