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Allosteric Inhibitors Have Distinct Effects, but Also Common Modes of Action, in the HCV Polymerase

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Recently discovered information alters the interpretation of our paper published previously in *Biophysical Journal*. In the study, we used molecular dynamics (MD) simulations to understand the mechanisms that govern allosteric inhibition of the RNA polymerase from hepatitis C virus (HCV). Our findings revealed that allosteric inhibitors alter the conformations adopted by the enzyme in a manner that allows their inhibitory effects to be readily understood. Their primary modes of action were found to be: 1) restricting enzyme fluctuations to nonfunctional regions of conformational space, 2) destabilizing the enzyme to the extent that it is unable to stably adopt functional conformations, and 3) blocking RNA template access to the enzyme's active site.

One component of these studies was application of temperature accelerated molecular dynamics (TAMD) for many of the simulations. The primary goal of TAMD is to enhance conformational sampling along a specified set of coordinates known as collective variables (CVs) (1,2). These CVs can be defined as a function of two or more atomistic coordinates within a molecular system. Examples include distances, angles, or dihedral angles. The theoretical framework of TAMD rests on describing the system using a collection of Langevin equations as shown below.

$$\gamma_x \dot{x} = -\Delta E(x) + R(t) - \kappa \sum_{j=1}^{m} \left[\theta_j(x) - z_j\right] \frac{\partial \theta_j(x)}{\partial x_i} \tag{1}$$

$$\gamma_z \dot{z}_j = R'(t) + \kappa \left[\theta_j(x) - z_j\right] \tag{2}$$

$$\langle R(t) R(t') \rangle = 2\gamma k_B T \delta(t - t') \tag{3}$$

In these equations, x corresponds the coordinates of an atomistic variable, γ is a friction coefficient, κ is a force constant, k_B is Boltzmann's constant, and T is the temperature. $\theta_j(x)$ is a mapping function that extracts the value of the jth CV from the current set of atomistic coordinates, and z_j is a random variable used to propagate dynamics corresponding to the jth CV. The function $R(t)$ represents a random fluctuating force with zero mean. A key element of TAMD is the use of an elevated temperature to govern fluctuations of the variable z_j, amplifying conformational sampling along this coordinate.

We attempted to accelerate conformational sampling of the HCV polymerase by applying TAMD to a CV defined as the angle formed at the intersection of the thumb, palm, and finger subdomains in the HCV polymerase (i.e., the inter-domain angle described in the publication). In doing so, we intended to apply a modest perturbation to the system such that fluctuations in the CVs are governed by the random forces $R'(t)$ in Equation 2 rather than the deterministic forces shown in the second term of this equation. To achieve this goal, the force constants in Equations 1 and 2 were set to zero. However, we now recognize that carrying out this procedure completely decouples evolution of the variable z from propagation of the atomistic coordinates. TAMD was implemented via a Tcl interface to NAMD, which supplements the standard MD forces with those computed via TAMD. Consequently, once the atomistic coordinates are decoupled from the TAMD forces, the resulting simulations are simply conventional MD of the atomistic coordinates. The significance of this finding is that, instead of using TAMD to apply a mild perturbation to the system as originally intended, the perturbation from TAMD was completely

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removed and standard MD simulations were generated. Therefore, instead of interpreting our results based on enhanced sampling due to TAMD, these observations should be discussed in the context of standard MD simulations.

In the Materials and Methods section of the text, all references to TAMD should now be understood to refer to conventional MD. Moreover, in the paper we noted that TAMD did not significantly improve sampling. However, this observation was likely due to the removal of TAMD contributions to the system dynamics as described above. This circumstance no doubt explains the high degree of similarity between conventional MD and TAMD data in the analysis presented in the Supporting Material.

In light of this new information, we can no longer firmly assert that the inter-domain angle described in the paper is an ineffective reaction coordinate. We also cannot argue that TAMD resulted in additional sampling, since all the simulations were actually performed using conventional MD. Finally, the comparisons performed in Supporting Text S2 must be considered to highlight sampling differences between distinct sets of conventional MD data rather than between conventional MD and TAMD data. Thus, the analyses can be interpreted as a measure of the uncertainty in the results obtained from a given conventional MD trajectory. We note that there is only modest variability when physical quantities computed for the distinct sets of simulation data are compared.

The points noted above are auxiliary to the main focus of the paper. The primary goal was to understand how enzyme conformational ensembles illuminate the mechanisms of allosteric inhibition in the HCV polymerase. While the explanation of the simulation methodology now differs from what was in the original manuscript, the results and their interpretation remain unchanged. This finding does not affect the main conclusions drawn from this study.

We apologize for any confusion this error may have caused.

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