



REPLY

Reply to the Comment by T. S. van Erp et al.

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Reply

Reply to the Comment by T. S. van Erp et al.

T. DAS¹ and S. CHAKRABORTY^{2(a)}

¹ Department of Biotechnology and Biochemical Engineering, Indian Institute of Technology
Kharagpur-721302, India

² Department of Mechanical Engineering, Indian Institute of Technology - Kharagpur-721302, India

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The comment by van Erp *et al.* [1] on our recent letter [2] throws some interesting questions about the veracity of the Peyrad-Bishop-Dauxois (PBD) model [3] in explaining the melting transition of oligonucleotides in all temperature regime. Previously, the PBD model in Langevin formalism has been shown [4,5] to describe the transient openings and local melting “bubble” formation at near-ambient temperature; yet the model has not been able to reproduce the complete melting transition and strand dissociation. Moreover, the PBD model has suffered due to the definiteness of the on-site Morse potential even at infinite base pair separations. This results in non-vanishing partition functions at infinite limit and is recognized as the divergence problem. In our letter [2], we are able to eliminate the limitation by invoking a base pair separation-dependent damping coefficient (Γ). It is presumed that beyond a critical distance, the nature of molecular collisions changes due to the inevitable change in the type of interaction with surroundings and this change is reflected on the magnitude of Γ . According to van Erp *et al.* [1], any change in the damping coefficient, even if it imparts discontinuity in space, should not alter the equilibrium results. Though the remark is generally true, it is not, however, universally precise. As pointed out in several fundamental texts [6] describing the Langevin thermostat, the equilibrium value is independent for “a carefully chosen range of gamma values”, implying that beyond this range, any change in gamma value may influence the equilibrium behavior. In order to probe the pertinent consequences in the context of our study, we plot fig. 1, in which we depict the dependence of the equilibrium results on Γ . It is revealed that for a wide range of Γ (ranging from 0.001–0.05 ps⁻¹), equilibrium

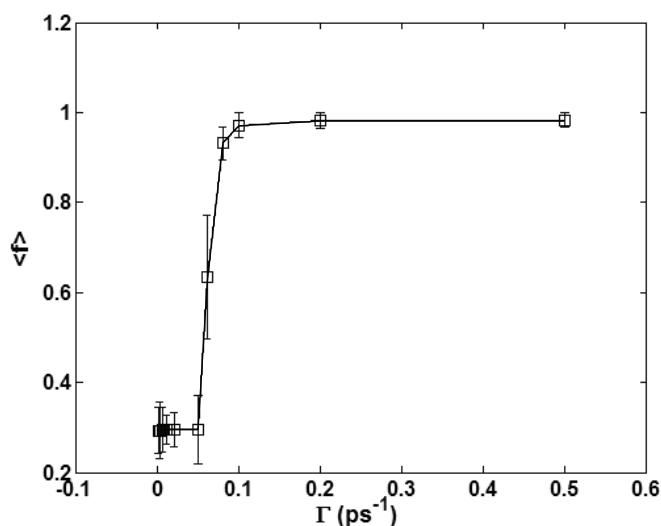


Fig. 1: Variation of equilibrium f with altering Γ (at $T = 336$ K; sequence: L42B18). Γ values at diffusion-dominated regime are always 100 times greater in magnitude. Equilibrium values have been computed in the temporal range of 200 ps to 200 ns (*i.e.* approximately 1.98×10^6 time steps).

values of f , p are independent of Γ . However, beyond these limits, the values of f and p may sensitively depend on the choice of Γ . In order to justify the need of taking such high value of Γ as considered in our study, one may argue from the point of view of the solvent effects which naturally implicate Γ values of such high orders beyond a critical limit of y . The spatial regime beyond y^{cr} being essentially diffusion dominated, one may expect the Γ value to reach the limit such as to satisfy the intrinsic relations of pure diffusion. In other words, one may expect $\Gamma \rightarrow \Gamma_{\text{diffuse}} = \frac{6\pi\mu R_b}{m}$ in the limit of the diffusion-dominated regime; where μ and R_b are the viscosity of the solution and

(a) E-mail: suman@mech.iitkgp.ernet.in

the radius of the bead, respectively. Assuming realistic values of all the relevant parameters ($\mu = 8.9 \times 10^{-4} \text{ Pa} \cdot \text{s}$, $R_b = 2 \times 10^{-10} \text{ m}$), we have determined Γ_{diffuse} to be of the order of 0.5 ps^{-1} , which is exactly the value of Γ taken beyond $y \geq y^{\text{cr}}$ in order to approximate diffusion-dominated dynamics. As evident from the parametric study (fig. 1), this value of Γ , though physically consistent, affects the equilibrium value and hence, justifies the reported results in our preceding letter [2].

Evidently, van Erp *et al.* [1] accept the view that the aforementioned proposition indeed sorts out the divergence problem within the simulation time scale of few nanoseconds. Yet they suggest that it should fail in the experimental time scale which is of the order of minutes. According to them [1], the experimental invisibility of spontaneous dissociation at any temperature is due to the persistent assembly-disassembly of DNA strands in an aqueous solution containing a large number of participating molecules. In contrast, PBD-based Langevin simulations are applicable for a molecule in absolute solitude and thus, continuous assembly-disassembly becomes inaccessible within the model framework. In this regard, we would like to illuminate on the recent single-molecule experiments based on sophisticated biophysical tools such as atomic force microscope, total internal reflection fluorescence microscope and optical tweezers (ref. [7] and references therein). These studies are conducted on the molecules in isolation and therefore, the assembly-disassembly argument does not fit well into such circumstances. Here, what van Erp *et al.* [1] undermine is the multiplicative nature of the probability distribution function $P(y, t; y_0)$ for coupled Morse oscillators. In our letter [2], we have earlier endeavored to solve the divergence problem for a single oscillator. Consequently, using our expression of $P(y, t; y_0)$, van Erp *et al.* [1] demonstrates that the probability of reaching out a reasonable separation becomes substantial if the time scale of the simulation is of the order of minutes. However, for an oligonucleotide molecule, consisting of a large number of such oscillators connected in a chain-like topology, the probability of attaining $y \rightarrow \infty$ simultaneously for all of those is several orders of magnitude less than the value estimated by van Erp *et al.* [1]. Though the net probability is difficult to calculate analytically due to their non-linear inter-dependence, one may expect it to be of the order of $P(y, t; y_0)^N$ where N is the number of base pairs. In a chain-bonded molecule like DNA, the holistic molecular stability is intrinsically embedded in the co-operative existence of neighboring base-pairs and the PBD model definitely possesses this vital ingredient through the term $W(y_n, y_m)$, which effectively includes both stacking and coupling interactions. Moreover, incorporated with Langevin thermostats, this model is extremely successful in the quantitative theoretical vindication of some experimental results involving local DNA melting or bubble formation at ambient temperature [2,4,5,8]. In this respect, we notice an

undesirable self-contradiction in the comments of van Erp *et al.* Initially, they deprecate the premelting or bubble formation as the numerical artifact (paragraph No. 3 in ref. [1]), yet later they recognize the efficacy of the PBD model at low temperature (paragraph No. 7 in ref. [1]).

In their comment, van Erp *et al.* [1] have also illustrated some basic deficiencies of the PBD model in terms of their apparent inability in accurately capturing some of the dynamic structural aspects of DNA. For example, they highlight mismatch pairing which is never accounted in the model due to the on-site nature of the Morse potential. Here, one should appreciate that the model is fundamentally one-dimensional in space and its inherent diminutive computation expenditure comes at the cost of few molecular details, namely, bending, hairpin formation, self-pairing and mismatch pairing. The under-prediction of order parameters (f , p and l), as pointed out by van Erp *et al.* [1] in their comment, arises because of these limitations. However, the aforementioned difference vanishes at elevated temperature ($T > 340 \text{ K}$) and the PBD model is nevertheless recognized as the most imperative meso-scale model [8] which computes DNA molecules much larger in size than those which are typically considered by molecular dynamics (MD) based simulations, yet it is proficient enough to reproduce both transient and equilibrium local and global melting events [3,4]. Pertinently, it must be mentioned that the mismatch pairing is a very transient event and the probability of attaining a stable mismatch pair is enormously small to consider.

To summarize, we state that the physically consistent proposition of variable Γ values over the kinetics-limited and diffusion-limited regimes essentially resolves the divergence problem of the corresponding mathematical model. With this modification, the Langevin version of the PBD model can efficiently reproduce experimental results in all temperature ranges. Further augmentations of the model may be directed towards the inclusion of appropriate phenomenological terms describing hairpin formation, mismatch pairing and other relevant events.

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