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Journal Name:	American Chemical Science Journal
Manuscript Number:	2015_ACSj_17117
Title of the Manuscript:	Kinetics and entropy production of force-induced oligomeric enzyme catalysis in a single trajectory: effect of multiple substrates
Type of the Article	Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	On the basis of previous works [42] and [43], the authors of the present manuscript deal with entropy production rate by mean of master equation approach for the oligomeric enzyme kinetics and extend their to describe the kinetics of the oligomeric enzyme to the case where different types of substrate molecules are attached with the enzyme. This entropy production was calculated along a single stochastic trajectory by using the Gillespie stochastic simulation approach of each reaction channel or sub-reaction to the medium entropy production by the formalism of forward and reverse trajectory approach. The authors construct a heuristic formula for individual reaction contribution to the medium entropy which gives a microscopic description of the medium entropy production at the level of individual sub-reactions from the knowledge of the individual sub-reaction probabilities and the initial and final populations of the species concerned over the trajectory. At the end, they generalize the single oligomeric enzyme reaction system for one specific substrate to multiple substrates. This generalization allow them to project, from the consequence of the fluctuation theorem about the individual contribution of each reaction channel to the overall medium entropy production, an insight about the mechanism of a multi-step reaction which could be a step towards the nonequilibrium thermochemistry.	In the first version we had already added the following reference[43] as suggested by the referee. Please note the printing mistake of the volume and page in the report. B. Das, K. Banerjee and G. Gangopadhyay, "Entropy production of a mechanically driven single oligomeric enzyme: a consequence of fluctuation theorem", J. Math Chem, 51, 588-602 (2013) We have also added added more reference of us. 3) As the figures have close connection with the earlier paper in by B Das K Banerjee and G Gangopadhyay, we have omitted the discussion and three figures in earlier version. In this revised version there are total seven figures. The legends in two figures are corrected which should be alright for readability.



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	Some comments are addressed below. 1) The manuscript shows a good knowledge of the previous bibliography in this topic, which is mentioned in the long bibliographic list and summarized and commented along the paper. However, it would be interesting to introduce the following paper in the reference list and to comment the link with this present manuscript. B. Das, K. Banerjee and G. Gangopadhyay, "Entropy production of a mechanically driven single oligomeric enzyme: a consequence of fluctuation theorem", J. Math Chem, 5, 1588–602 (2013) All figure legends should be improved. Sometimes they are on the curves, specifically Figure 3, 4, 8, and 9.	
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		