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Reply to "Comment on 'Validity of path thermodynamic description of reactive systems: Microscopic simulations' "

F. Baras,[1] A. L. Garcia,[2] and M. Malek Mansour[3]

[1] *Laboratoire Interdisciplinaire Carnot de Bourgogne, UMR 6303 CNRS-Université Bourgogne Franche-Comté,*
9 Avenue A. Savary, BP 47 870, F-21078 Dijon Cedex, France
[2] *Department of Physics and Astronomy, San Jose State University, San Jose, California 95192, USA*
[3] *Université Libre de Bruxelles CP 231, Campus Plaine, B-1050 Brussels, Belgium*

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The Comment's author argues that a correct description of reactive systems should incorporate an explicit interaction with reservoirs, leading to a unified system-reservoir entity. However, this proposition has two major flaws. First, as we will emphasize, this entity inherently follows a thermodynamic equilibrium distribution. In the Comment, no indication is provided on how to maintain such a system-reservoir entity in a nonequilibrium state. Second, contrary to the author's claim, the inclusion of a system-reservoir interaction in the traditional stochastic modeling of reactive systems does not automatically alter the limited applicability of path thermodynamics to problematic reactive systems. We will provide a simple demonstration to illustrate that certain elementary reactions may not involve any changes in reservoir components, which seem to have been overlooked by the author.

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The argument presented in the Comment is based on two separate assertions. First, the Comment's author states: "Let us further remark that several Markov jump processes may be considered for a given reaction network. This key point is well known." To the best of our knowledge, this statement is likely known only by the author himself, as he introduced it recently in his previous Comment article [1]. Furthermore, it contradicts a fundamental principle of probability theory, that is, "the probability associated with a random event is unique" (see, for example, Refs. [3] or [4]). We rigorously proved this result in the Introduction of our paper [2]. Recall that the proof relies on the choice of $\mathbb{Z}^n$ as the state space for a homogeneous, isothermal reactive system with n components ($\mathbb{Z}$ represents the set of non-negative integers). This choice aligns precisely with that of all authors dealing with the stochastic modeling of reactive systems because of its unique correspondence with experimentally measurable quantities [3,4].

Recently, we demonstrated that the validity of path thermodynamics is limited to reactive systems that involve only one elementary reaction leading to each type of observed composition change [5,6]. This proof relies on the traditional stochastic modeling of reactive systems established over half a century ago [3,4]. In order to restore the validity of path thermodynamics in problematic reactive systems, the Comment's author recommended the use of an "expanded state space" by incorporating a set of new variables [1]. These variables were intended to differentiate the elementary reactions that lead to the same change in composition.

However, as highlighted in our work [2], these newly introduced variables do not correspond to any observable quantities in real-life systems. This observation served as the primary motivation behind our decision to perform microscopic simulations of reactive systems. The results of these simulations unequivocally contradict the author's assertion, thereby validating the theoretical predictions based on the traditional modeling of reactive systems [2]. Now it appears that the author has revised his opinion, as there is no mention of the concept of "expanded state space" in the present Comment. Instead, he presents a different approach that we will now address.

In his Comment the author acknowledges the validity of our microscopic simulation results but argues that they fail to account for potential variations in other chemical components that act as control parameters (reservoir quantities). In other words, he contends that the investigation of the statistical properties of reactive systems must explicitly incorporate the interaction between the system and its reservoirs. In order to illustrate his arguments, the Comment's author considered the same reactive system that we used in our microscopic simulation, that is,

$$A + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2X, \qquad B + C \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B + X, \tag{1}$$

where we utilized a well-established procedure to maintain a physicochemical system out of equilibrium. This procedure involves the system interacting with external reservoirs assumed to be infinitely large, thereby ensuring that their state remains rigorously constant over time. The author claims in his Comment that, instead of solely considering the variable $X(t)$, while keeping A, B, and C constant, we should have analyzed the joint statistical trajectories of $\{X(t), A(t), B(t), C(t)\}$ which takes into account the simultaneous variations of all variables over time (cf. the last sentence of the fourth paragraph of the Comment).

However, as highlighted in the Appendix of our paper [2], the total number of particles in the system-reservoir entity remains constant, indicating that the state of such an entity is not affected by any external constraint. Specifically, we wrote,

> Finally, note that for both reaction models (2) and (4) the number of A, B, and C particles and the sum of X and solvent particles $X(t) + S(t)$ remain constant. As such, knowledge of $X(t)$ determines entirely the state of the system at each instant of time.

Consequently, it can be easily demonstrated that the resulting stationary probability distribution follows a multinomial distribution, which corresponds to a thermodynamic equilibrium distribution. No indication is provided in the Comment on how to proceed to maintain the system-reservoir entity in a nonequilibrium state. Not addressing this fundamental issue undermines the arguments criticizing our work.

But there exists a more fundamental objection against the Comment author's proposition of the new type of modeling for reactive systems. Contrary to his claim, the incorporation of a system-reservoir interaction in the traditional stochastic modeling of reactive systems does not necessarily alter the limited applicability of path thermodynamics to reactive systems with only one elementary reaction leading to observable compositional changes [2,5,6]. In fact, certain elementary reactions may simply not involve any changes in reservoir components, a possibility that the author seems to have overlooked. Consider, for example, the following set of elementary reactions,

$$S + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S + Y, \quad Y + X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2Y, \tag{2}$$

both leading either to the change of composition $X, Y \to X - 1, Y + 1$ (forward) or $X, Y \to X + 1, Y - 1$ (backward). Regardless of how we treat the reservoirs, the state trajectory of a reactive system involving the set of reactions (2) does not incorporate any information that allows us to differentiate them from each other. However, we know from the basic principles of irreversible thermodynamics that the entropy production of a reactive system is the sum of the entropy production associated with each individual reaction [7]. Consequently, properties of such a reactive system as given by path thermodynamics will inevitably contradict the actual thermodynamic properties of the system.

In conclusion, we would like to make one final remark. It is interesting to note that the author previously employed the same methodology on multiple occasions, which he now rejects in his Comment. This includes his seminal 2004 paper, where he developed the path thermodynamic theory of reactive systems [8]. Interestingly, in that paper, the author specifically considered the Schlögl model (Sec. IV in Ref. [8]) as an illustrative example of the theory. It is worth mentioning that the Schlögl model is the same type of model we used for microscopic simulation in our article, for which the author now questions the validity. In the Comment the author appears to contradict statements made in his previous work [8]. In a way, this newest Comment underscores the strength of our earlier works.

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