de la Cruz *et al.* Reply In our recent Letter [1], we study the transitions out of an oscillatory state for stochastic systems that can be described with a chemical Langevin equation (CLE). As Meerson and Smith point out in the preceding Comment [2], Langevin equations are sometimes derived using the van Kampen expansion to the leading order in the inverse of the population size in the master equation (ME) [3]. We rather derive the CLE using results dating back to early work by Kurtz regarding the Central Limit Theorem for Markov chains [4–6] and later by Gillespie [7]. The resulting CLE we use has multiplicative noise and is not recovered, even using the generalized van Kampen expansion [8]. The validity of this derivation does not rely on large system-size asymptotics, and its higher accuracy was analyzed by Grima *et al.* [8] for the first two moments of the distribution. It requires the existence of a timescale on which each reaction channel is triggered multiple times and the propensity of each reaction stays approximately constant [7]. To verify that such a condition is met in the cases discussed in our Letter, we have run exact stochastic simulation algorithm (SSA) simulations of the ME. The results are shown in Fig. 1, where, on the timescale of $\tau = 10^{-5}$, each reaction channel is triggered at least 100 times, and the maximal relative change in a reaction rate is less than 10%.

To show the accuracy of the CLE to describe the transition between a stable oscillation and a fixed point, we compare the first passage time distributions from direct Gillespie SSA simulations of the ME and numerical solutions of our CLE. The results are shown in Fig. 1. Applying the Kolmogorov-Smirnov test to the resulting empirical cumulative distribution functions, the test cannot reject the null hypothesis that the distributions are equal at a significance level $\alpha = 0.05$. Additionally, in the Letter we predicted the minimal action path using three different methods (minimizing the action, simulating the master equation, and solving the CLE). We think it is extremely unlikely that these three completely different methods will yield matching numerical artefacts, as Smith and Meerson imply.

Smith and Meerson point to references on the topic [9–13]. While relevant, none of these references deal with a comparable dynamical landscape to the one in our Letter (in which there is a stable and an unstable limit cycle). In these Letters, the dynamics are affected by a saddle point or a focus, while our Letter deals with the transition from a limit cycle crossing an unstable limit cycle without saddles. Additionally, all of these references make use of additive noise, while one of the essential aspects of the CLE is the multiplicative noise. Finally, we regret that we did not cite Smith and Meerson [14]. Since they look at extinctions, the CLE approach will not be accurate in their case, since death or degradation propensities will become negligible close to the extinction point. They suggest the use of the WKB method in this case [15], which is very accurate in predicting the quasistable distribution. The CLE, while more accurate than the van Kampen Fokker Plank equation, was inaccurate in the tails of the distributions, where all of the probabilities are vanishingly small.

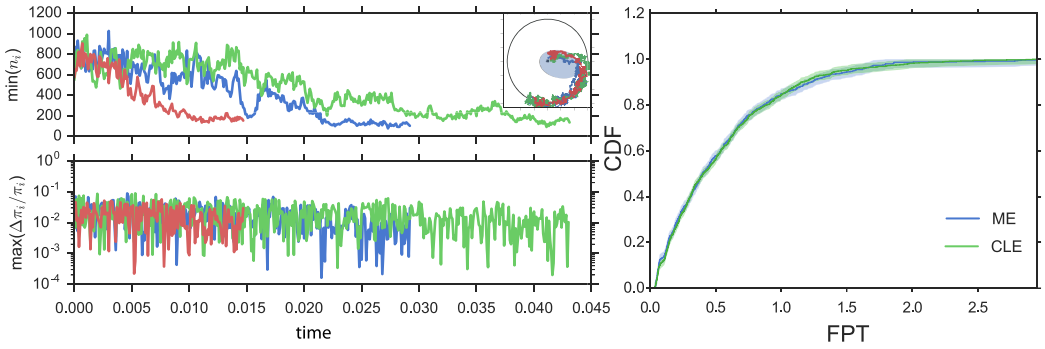

FIG. 1. (Left) Escape trajectories for three different realizations of the ME. (Top left) Minimum number of times that one of the four reactions occurs (n_i) in windows of time $\tau = 10^{-5}$ along the escape trajectory. (Inset) Trajectories for the three different realizations. (Bottom left) Maximum relative change of the propensity (π_i) among all the possible reactions in windows of time $\tau = 10^{-5}$. (Right) cumulative distribution functions of the First Passage Time for different sets of 600 jumps of the ME and the CLE. Confidence bands are created using the Dvoretzky-Kiefer-Wolfowitz inequality (confidence of 99%).

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