

Response to “Comment on ‘Nested stochastic simulation algorithm for chemical kinetic systems with disparate rates’ [J. Chem. Phys. 123, 194107 (2005)]”

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The preceding Comment¹ on our recent paper² is concerned with efficient stochastic simulation algorithms for chemical kinetic systems with disparate rates. Let us first introduce the setup. Consider a chemical kinetic system whose reactions can be divided into two groups, one containing the slow reactions specified by

$$(a_j^s(x), \nu_j^s), \quad j = 1, \dots, N_R^s, \quad (1)$$

where $x = (x_1, \dots, x_N)$ and x_k is the number of molecules of the k th species, $a_j^s(x)$ is the rate of the j th slow reaction, and ν_j^s is the stoichiometric vector of this reaction (i.e., right after reaction j , the state of the system is $x + \nu_j^s$ if it was x before the reaction), and the other group containing the fast reactions specified by

$$(\varepsilon^{-1} a_j^f(x), \nu_j^f), \quad j = 1, \dots, N_R^f, \quad (2)$$

where $\varepsilon \ll 1$ is a small parameter measuring the separation of time scale between slow and fast reactions. Then, according to results proven in the mathematics literature, the evolution of this system can be approximated by that of a limiting system containing only slow reactions given by

$$\left(\bar{a}_j^s(x) = \sum_{x'} \mu_x^f(x') a_j^s(x'), \nu_j^s \right), \quad j = 1, \dots, N_R^s. \quad (3)$$

Here $\mu_x^f(x')$ is the equilibrium probability distribution of the “virtual fast process,” i.e., the probability of finding the system in state x' after a long time if it is initiated at the state x and if only the fast reactions are allowed to occur and the slow ones are artificially turned off. This limit theorem was proven first in Ref. 8 in a slightly different setting, then further extended, e.g., in Refs. 9–11. Reference 12 presents the version in the context of Markov chains with slow and fast rates which include the case of stiff chemical systems discussed here. In Ref. 12, the notion of virtual fast process was used implicitly without using this terminology—that terminology only came later in Ref. 3. Some of these references were given in Ref. 2 and a more thorough discussion with references was given in Ref. 5. The authors of Refs. 1, 3, and 4 were apparently unaware of these results and proceeded to

rederive these statements in Ref. 3 and again in the Comment under discussion. Since Ref. 12 may not be readily accessible to the reader, as evidenced by the Comment under discussion of Ref. 1, for his/her convenience we summarize the arguments in the Addendum at the end of this Response.

In rare situations such as the simple example discussed in Refs. 1 and 2, the effective slow rates $\bar{a}^s(x)$ in Eq. (3) can be obtained in closed form formulas. In this case, one can simply use Gillespie’s original stochastic simulation algorithm^{6,7} (SSA) to simulate the limiting system instead of the original one, and neither slow scale SSA (ssSSA) nor nested SSA (nSSA) is needed. In general, however, approximations have to be made because the calculation of the rates $\bar{a}^s(x)$ is very difficult since it requires knowing explicitly the equilibrium probability distribution $\mu_x^f(x') \equiv \mu_y^f(x')$ of the virtual fast process and computing the sum in Eq. (3). While both ssSSA and nSSA rely on the existence of the limiting system, the two methods are very different in the way they use this result. ssSSA tries to approximate the effective slow rates $\bar{a}^s(x)$ in Eq. (3) analytically beforehand by introducing closure approximations: assumption of statistical independence of the various species at the level of the virtual fast process, replacement of expectations of products by products of expectations, etc. These approximations may be adequate in specific situations, but in general they are uncontrolled, and their validity is very difficult to establish and often doubtful. The results of such simulations may still be useful in some cases, but one has to understand these caveats, particularly in light of the fact that one main objective of multiscale modeling is to eliminate such *ad hoc*, uncontrolled modeling approximations.

nSSA proceeds differently. Instead of trying to approximate the effective rates $\bar{a}^s(x)$ in Eq. (3) analytically, it computes them numerically on the fly when needed. Suppose that the current state of the system is x and denoted by $x^f(t)$, a trajectory of the virtual fast process with $x^f(t=0) = x$, this trajectory can be easily generated by a SSA using only the fast reactions specified by Eq. (2). Then

$$\bar{a}^s(x) = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T a^s(x^f(t)) dt \quad (4)$$

follows from ergodicity, which guarantees that the ensemble average in Eq. (3) can be replaced by a time average.

Why is Eq. (4) useful? First, note that the evaluation of Eq. (4) has become completely seamless, as it only requires knowing the fast rates, not the slow variables nor their equilibrium distribution $\mu_x^f(x')$. Secondly, an *accurate approximation* of this limit can be obtained by taking T as a large multiple of ε . This is because the virtual fast process evolves, and equilibrates, on the fast time scale. In fact, in Ref. 5 precise estimates were given for the error made by approximating the limit in Eq. (4) using finite $T=O(\varepsilon)$. They demonstrate that nSSA is more efficient, by a factor of the order of $\varepsilon^{-1} \gg 1$, than the direct SSA for the original stiff system. nSSA is in general more costly than ssSSA. But unlike ssSSA, nSSA does not make any closure approximations and hence remains accurate for all stiff chemical systems with disparate rates. This is also typical in multiscale modeling. First-principles-based techniques are often more costly but they are also more accurate. In practice, one has to weigh accuracy versus cost in order to select the most appropriate strategy.

We also note that the strategy behind nSSA has been used before for stochastic differential equations with separated time scales, as was proposed first in Ref. 15, and it fits the general framework of the heterogeneous multiscale method.¹⁶

In Ref. 2, we asserted that ssSSA does not make any improvement over the classical SSA if there are no slow species in the system. This statement is incorrect, as was pointed out in the Comment under discussion.¹ In retrospect, the origin of this mistake is to some extent related to the notion of slow and fast species used in Ref. 3, which has been *incorrectly* advocated as the relevant slow and fast variables. This seems to have been inherited from earlier works on this subject,^{13,14} and most subsequent works on this subject seem to have followed this practice.^{17,18} This misconception is clearly exhibited in the last part of the Comment under discussion. The correct notion of slow variables in this context was explained in Ref. 2, and they are the variables which are invariant in the virtual fast process. As noted in Ref. 2, the distribution $\mu_x^f(x')$ depends only on some special linear combination $y_k = \sum_{j=1}^{N_s} b_j^k x_j$ for some appropriate weights $(b_1^k, \dots, b_{N_s}^k)$, $k=1, \dots, K$, not the full vector $x = (x_1, x_2, \dots, x_{N_s})$. The y 's are the slow variables, and thus $\mu_x^f(x') \equiv \mu_y^f(x')$. While the explicit knowledge of these variables is not essential in the implementation of the algorithms discussed here, it matters for the error analysis of these algorithms to understand the precise statement of the limit theorem, as was shown in Refs. 2 and 5.

Addendum: Khasminskii's limit theorem. Here we summarize the argument given in Ref. 12 following the ideas by the same author in Ref. 8.

Let $p(x, t)$ be the instantaneous probability distribution function in the chemical kinetics system, i.e., $p(x, t)$ gives the probability that there be $x=(x_1, \dots, x_{N_s})$ molecules of each species at time t . $p(x, t)$ satisfies the following master equation

(referred to as the forward Kolomogorov equation):

$$\dot{p}(x, t) = \sum_{j=1}^{N_R^s} (a_j^s(x - \nu_j^s) p(x - \nu_j^s, t) - a_j^s(x) p(x, t)) + \frac{1}{\varepsilon} \sum_{j=1}^{N_R^f} (a_j^f(x - \nu_j^f) p(x - \nu_j^f, t) - a_j^f(x) p(x, t)). \quad (5)$$

Using the same shorthand notation as in Ref. 12, this equation can be written as

$$\dot{p}(t) = \varepsilon^{-1} p(t)A + p(t)B, \quad (6)$$

where $p(t)A$ stands for $\sum_{x'} p(x', t)A(x', x)$, $A(x, x') = a_j^f(x) \delta_{x'=x+\nu_j^f}$, and similarly for $p(t)B$ and B . In the spirit of singular perturbation theory, look for a solution of this equation in the form of

$$p(t) = p^{(0)}(t) + \varepsilon p^{(1)}(t) + O(\varepsilon^2). \quad (7)$$

Insert this expansion into Eq. (6) and equate equal powers in ε to get the following hierarchy of equations:

$$\begin{aligned} O(\varepsilon^{-1}), \quad p^{(0)}(t)A &= 0, \\ O(\varepsilon^0), \quad p^{(1)}(t)A &= \dot{p}^{(0)}(t) - p^{(0)}(t)B, \\ \dots \end{aligned} \quad (8)$$

The first equation [which is Eq. (12) in Ref. 12] says that, to leading order in ε , the system is always at adiabatic equilibrium with respect to the fast reactions in the system. In full, this equation can be written as

$$0 = \sum_{j=1}^{N_R^f} (a_j^f(x - \nu_j^f) p^{(0)}(x - \nu_j^f, t) - a_j^f(x) p^{(0)}(x, t)), \quad (9)$$

which is precisely the equation for the equilibrium distribution of the virtual fast process used in the slow scale lemma in Ref. 13. The solutions to this equation are not unique—they are parametrized by the slow variables for the system. Assuming that the fast reactions leave invariant certain linear combinations of the species, $y_k = \sum_{j=1}^{N_s} b_j^k x_j$, $k=1, \dots, M$, where the b^k 's are such that $\sum_{j=1}^{N_s} b_j^k \nu_j^f = 0$, Eq. (9) has many solutions indexed by the *slow variables* y : these are the equilibrium distributions of the fast virtual process. If we denote by $\mu_y(x)$ these distributions, then Eq. (9) says that

$$p^{(0)}(x, t) = \sum_y q(y, t) \mu_y(x), \quad (10)$$

where $q(y, t)$ is the instantaneous probability distribution of the slow variables. Equation (9) does not specify the evolution of $q(y, t)$; an equation for the latter is provided by the solvability condition for the second equation in Eq. (8), which is obtained by multiplying this equation by $\mathbf{1}_y(x)$ [$\mathbf{1}_y(x)=1$ if $y_k = \sum_{j=1}^{N_s} b_j^k x_j$ and $\mathbf{1}_y(x)=0$ otherwise], summing over x and noting that

$$\sum_x \mathbf{1}_y(x) p^{\{1\}}(t) A = \sum_{j=1}^{N_R^f} \sum_x \mathbf{1}_y(x) (a_j^f(x - \nu_j^f) p^{\{1\}}(x - \nu_j^f, t) - a_j^f(x) p^{\{1\}}(x, t)) = 0 \quad (11)$$

by reorganizing the first sum over x and using the fact that $\mathbf{1}_y(x) = \mathbf{1}_y(x - \nu_j^f)$ by the definition of y . Thus, this operation leaves us with the following equation for $q(y, t)$:

$$\dot{q}(t) = q(t) \bar{B}, \quad (12)$$

where \bar{B} is

$$\bar{B}(y, y') = \sum_{x, x'} \mathbf{1}_{y'}(x') \mu_y(x) a_j^s(x) \delta_{x' = x + \nu_j^s}. \quad (13)$$

Equation (12) together with Eq. (10) summarizes (using different notations for the sake of clarity) the content of Proposition 3.2 in Ref. 12. It is now a simple matter to show that the system with the effective reactions in Eq. (3) satisfies $\sum_x \mathbf{1}_y(x) \bar{p}(x, t) = q(y, t)$, where $q(y, t)$ is the solution of Eq. (12).

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