Analysis and Remedy of Negativity Problem in Hybrid Stochastic Simulation Algorithm and its Application

Extended Abstract

Minghan Chen
Virginia Tech
Blacksburg, Virginia
cmhshirl@vt.edu

Yang Cao
Virginia Tech
Blacksburg, Virginia
ycao@cs.vt.edu

ABSTRACT

The hybrid stochastic simulation algorithm, proposed by Haseltine and Rawlings, can significantly improve the simulation efficiency for multiscale biochemical networks. However, the population of some species might be driven negative under certain situations. This paper investigates the negativity problem of the hybrid method based on the second slow reaction firing time. Our analysis and tests on several models demonstrate that usually the error caused by negative populations is negligible compared with approximation errors of the method itself. But for systems involving nonlinear reactions or highly sensitive species, the system stability will be influenced and may lead to system failure. The proposed Zero-Reaction rule is recommended considering its efficiency and simplicity.

CCS CONCEPTS

• **Theory of computation** → **Stochastic approximation**; • **Computing methodologies** → *Simulation evaluation*; • **Applied computing** → *Biological networks*;

KEYWORDS

Hybrid stochastic algorithm; negative population; second slow reaction firing time

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1 INTRODUCTION

The stochastic simulation algorithm (SSA) [3], widely used in simulating stochastic effects in biochemical networks, is computationally intensive and inefficient for systems with fast reactions or large populations. As biological networks at single cell levels usually have large scale discrepancies in populations of species as well as

rate constants among different reactions, research is increasingly focused on hybrid methods targeting multiscale systems [1, 4]. Haseltine and Rawlings [4] proposed a hybrid method for general cases (hereafter referred to as the HR hybrid method), which modeled part of the system by continuous dynamics (ordinary differential equations (ODEs) or Langevin equations), while keeping the rest discrete. The idea of the HR hybrid method was further improved and extended to several hybrid methods and simulation tools [5, 6].

However, in the HR hybrid method framework, populations of some reactant species may become negative if they are involved in both deterministic and stochastic systems. Take system (1) as an example. If reaction rate constants satisfy $f_1 \gg k_c$ and $b_1 \gg k_c$, the system can be divided into a fast reaction group and a slow reaction group, containing the reversible and irreversible reactions, respectively.

Assume that this system has two S_1 molecules at the beginning, and the system parameters are $f_1 = 1$, $b_1 = 9$, $k_c = 0.01$. Then, compared with the slow system, the fast ODE system can be considered at equilibrium, which gives $x_1 = 1.8$ and $x_2 = 0.2$, where x_i denotes the mean population of species S_i . Thus, when a slow reaction fires, x_2 is reduced to -0.8 . Negative populations may also appear in stochastic simulations of reaction-diffusion systems, especially when low-density species are distributed in a well-meshed space.

2 SECOND SLOW REACTION FIRING TIME

Our prior work [2] analyzed the accuracy of the HR hybrid method by studying the next slow reaction firing time (NSRFT). Since the negative population problem mostly emerges after a slow reaction, it is not enough to just study the first exit time. So, we further extend that work and study the second slow reaction firing time (SSRFT), which reflects the influence of a (possible) negative population on the firing of slow reactions. We use the same linear chain reaction network in Ref. [2] as a study example, shown below.

A particle can exit the reversible chain system through S_n with reaction rate k_c . In many applications, the reversible chain reactions can be considered as a fast subsystem and the irreversible reaction (exit to S_{n+1}) as a slow subsystem. With this partitioning strategy, if $x_n < 1$, then S_n will become negative when a slow reaction fires.

We proposed the following three strategies to handle the negativity problem.

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- **Zero-Population:** set all negative species' populations as zero whenever detected in the simulation.
- **Zero-Reaction:** set all reaction terms or propensities involving negative species as zero in corresponding subsystems until they become nonnegative.
- **Zero-Time:** when a species' population becomes negative, pause the system and run a separate virtual ODE system G'_f that only contains reactions related to the negative species. When it becomes nonnegative, restart the original system with the new system state from G'_f .

We derived the formulas of SSRFT under the chemical master equation (CME), the HR hybrid method, and the three remedies (derivations omitted). For comparison, relative error is defined as

$$e_r = \frac{|T_c - T_h|}{T_c}, \quad (3)$$

where T_c and T_h are the mean second slow reaction firing times of the CME and the HR hybrid method, respectively.

Fig. 1 illustrates the acceptable system parameter region ($e_r < 0.01$) for system sizes $n = 2$ and $n = 10$. In both cases, the SSRFT keeps the same pattern but with improved accuracy horizontally resulting from the negativity phenomenon and decreased accuracy vertically due to the accumulative method error. As the acceptable parameter region for larger linear chain systems gets smaller, the negativity problem becomes insignificant for the HR hybrid method. Since nonnegative situations occur much more frequently than negative situations, the three proposed remedies do not make a difference in the acceptable region of the HR hybrid method.

Figure 1: Contour plot of the average relative error $e_r = 0.01$ with different (k_c, m) pairs. All system parameters are set to one. Acceptable parameter pairs for the HR hybrid method can be chosen from the bottom (small k_c values) and right (large m values) regions.

3 NUMERICAL RESULTS ON A NONLINEAR SYSTEM

The previous section have shown that the HR hybrid method works fine for linear systems. Here we examine the effect of negative values on a nonlinear system, shown below.

Similarly, we partitioned the system into groups: the fast group containing the reversible reactions and the slow group containing

the remaining reactions. For the bimolecular reaction $S_2 + S_2 \xrightarrow{k_c} S_3$, when $x_2 < 0$, the propensity $a_{bi} = k_c x_2(x_2 - 1)$ is positive which can potentially cause the reaction to fire and further decrease the value of x_2 . Thus, the SSA system becomes unstable when $x_2 < 0$. Meanwhile, the ODE system becomes unstable when S_2 gets smaller than $-\frac{f_1}{4b_1}$ (one eigenvalue of the ODE system becomes positive).

In Fig. 2, our simulation results also proved that even if x_2 has less than a 1% probability to be negative, the system suffers significant error and breaks down after a certain amount of simulation time when using the HR hybrid method. Only the Zero-Reaction rule still works and generates similar results to the SSA. The Zero-Time rule failed because the separate G'_f system is unstable.

Figure 2: Final distributions of species S_2 and S_3 from the SSA, the Zero-Reaction remedy based on 10k simulations. The parameters for the nonlinear system are $f_1 = b_1 = k_c = k_s = 1$. The initial condition is $m_1 = 3, m_2 = 0$.

4 SUMMARY AND CONCLUSIONS

This paper studies the negativity problem of the HR hybrid stochastic simulation algorithm based on the second slow reaction firing time. We conclude that the negativity phenomenon does not influence the biochemical network unless the negative species are involved in nonlinear reactions that generate positive reacting terms or propensities. The proposed Zero-Reaction strategy can handle nonlinear systems with minimal computational cost.

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