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Boosted Hybrid Method for Solving Chemical Reaction Systems with Multiple Scales in Time and Population Size

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Abstract. A new algorithm, called boosted hybrid method, is proposed for the simulation of chemical reaction systems with scale-separation in time and disparity in species population. For such stiff systems, the algorithm can automatically identify scale-separation in time and slow down the fast reactions while maintaining a good approximation to the original effective dynamics. This technique is called boosting. As disparity in species population may still exist in the boosted system, we propose a hybrid strategy based on coarse-graining methods, such as the tau-leaping method, to accelerate the reactions among large population species. The combination of the boosting strategy and the hybrid method allow for an efficient and adaptive simulation of complex chemical reactions. The new method does not need *a priori* knowledge of the system and can also be used for systems with hierarchical multiple time scales. Numerical experiments illustrate the versatility and efficiency of the method.

AMS subject classifications: 65C05, 65C20

Key words: Chemical reaction, multiscale, boosting, hybrid method.

1 Introduction

Advances in experimental and computational methods over the last decades have made a quantitative, systematic understanding of cellular processes in molecular level possible [1–6]. For micro-scale biochemical systems, such as one single living cell, consider-

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able evidence indicates that stochasticity plays an important role, especially when low-molecular-number reactant species are being considered [2,3]. The usefulness of the traditional deterministic approach, based on reaction rate equations, is limited in such situation. In turn, many stochastic biochemical reaction networks have been built to take into account the randomness in biological processes. Because of the disparity of time scales and species population, the simulation of such systems is often challenging and the development of new numerical techniques for multiscale chemical reactions has become an active research field [4,7,8].

One fundamental method in simulating chemical reaction systems is Gillespie's Stochastic Simulating Algorithm (SSA) [9,10]. It can generate statistically exact trajectories of the system state by randomly sampling each reaction event. In principle, SSA applies to any chemical reaction system, but the method become computationally costly when reaction events occur very frequently in the system. This often happens because of the co-existence of fast and slow dynamics in a system, or reactions involving species with very large populations, or both.

On one hand, the co-existence of fast and slow dynamics in a system leads often to severe step-size restriction for standard methods. Such systems are called stiff and need a special numerical treatments. For stiff ordinary or stochastic differential equations, implicit methods or stabilized explicit methods (called Chebyshev methods) can be efficient [11–13]. But fast variables in chemical reaction system often fluctuate quickly around a "slow manifold", and implicit or stabilized method usually fail to capture the right stationary distribution of the fast variables [12, 14, 15]. Rao and Arkin [16] first formalized the quasi-equilibrium approximation in chemical reaction system and implemented it in SSA. Their idea was further extended by Cao et al. in developing the slow-scale SSA [17]. Both methods require explicit form of the stationary distribution for the fast variables which in general is difficult to get. To remove this restriction, E et al. developed the nested-SSA [18]. In this method, the averaged rates of the slow reactions are sampled by inner SSA, as the micro-solver acting on fast reactions only, during a period of time that is much larger than the fast time scale and at the same time much smaller than the slow time scale. Then the average rates of the slow reactions will be used by the outer SSA, as the macro-solver acting on slow reactions only, to march the system forward.

On the other hand, reactions involving species with large population size fire very frequently which also make the SSA computationally inefficient. To overcome this difficulty, Haseltine and Rawlings proposed a hybrid method for solving chemical reaction systems with disparity in species population [8]. The main idea is to apply a coarse-graining approximation (based on stochastic or ordinary differential equations) for species with large population size and SSA for species with small population size. Many variants of hybrid method have been proposed [6, 19–25]. Based on the system size, the τ-leaping method [7], chemical Langevin equations or reaction rate equations [26] are often used as the coarse solver.

Numerical algorithm that can handle both the multiple time scales and the disparity