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EDITORIAL

Stochastic Simulation of Biochemical Systems: In Memory of Dan T. Gillespie's contributions

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On April 19, 2017, sad news hit all of us in the research communities of computational biology, stochastic simulation and applied physics. Our beloved friend, Dan T. Gillespie, a research physicist best known for the stochastic simulation algorithm (SSA, also known as the Gillespie Algorithm), passed away at his home in Castaic California at the age of 78.

The impact of Dan Gillespie's work on the field of stochastic physics, computational biology and other related areas has been huge. When he first presented his original work in Gillespie (1976), it was called "completely wrong" by some prominent researchers in the field of chemistry. Certainly, it was far ahead of its time. In the late 1990s, it came to light that intrinsic stochasticity, arising from extremely small populations of key molecular species, was playing an important role in cell biology. The Gillespie algorithm was perfectly suited for simulating these systems. Since that time, it has been widely used in cell biology. Dan Gillespie's foundational publications would eventually receive over ten thousand citations, and he was well recognized as one of the founders of the field of stochastic physics in biology. His research contributions spanned a wide range of fields, including cloud physics, random variable theory, Brownian motion, Markov process theory, electrical noise, light scattering in aerosols, and quantum mechanics.

The contributions in this special issue come from researchers working in many different disciplines that have benefitted from Dan Gillespie's pioneering work. The Gillespie algorithm (Gillespie 1976, 1977) is an important modeling and simulation method, but it also suffers from inefficiency when applied to large scale systems. He and his collaborators developed different methods to improve the algorithm, such as the tau-leaping method (Gillespie 2001; Rathinam et al. 2003; Cao et al. 2005b), and the

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slow-scale SSA method (Cao et al. 2005a, c). This special issue includes a review article on rejection-based exact methods (Thanh 2018), improvements to the tau-leaping method (Beentjes and Baker 2018) and the S-leaping method (Lipková et al. 2018), and numerical analysis of the hybrid ODE/SSA method (Chen et al. 2018). In addition to the development of simulation algorithms, there have been efforts to improve the efficiency of the many simulations that are required to obtain accurate approximations to the probability density functions of the chemical species. Simulation strategies and numerical algorithms have been proposed to enable the use of fewer simulations while still maintaining high accuracy. This special issue includes work on the multilevel approach (Engblom 2018), the variance-reduced simulation method (Maginnis et al. 2019) for general Markov chains, and the low variance coupling method (Anderson and Yuan 2018).

The original Gillespie algorithm is physically accurate only for systems that are both dilute and well-mixed in the reactant (solute) molecules. An extension of the SSA for systems that are not well-mixed is the reaction–diffusion SSA (RD-SSA). It divides the system volume into subvolumes or "voxels" , which are small enough that each can be considered to be well-mixed. Chemical reactions are then considered to occur inside individual voxels and are modeled using the SSA, while diffusion is modeled via jumps from a subvolume to one of its neighbors. In this way, the Gillespie algorithm has been extended to the challenging field of spatial stochastic modeling. This special issue features several contributions in this area: Grima gives a review for spatial stochastic modeling (Smith and Grima 2018), Kang and Erban (2019) present an analysis for multiscale reaction–diffusion system and Markov Chain, and Lötstedt (2018) presents a linear noise approximation for spatially dependent biochemical networks.

To highlight Dan Gillespie's impact on related fields, this special issue also features contributions that are related to his work from other areas, such as the network-free simulation method (Suderman et al. 2018), rare event analysis (Roh 2018), sensitivity analysis for multiscale stochastic systems (Gupta and Khammash 2018), and an application of stochastic dynamics to simulation of eukaryotic flagellar growth (Rathinam and Sverchkov 2018).

These articles are by no means, or even close to a full list of work that benefited from Dan Gillespie's great scientific career. We hope that they serve as milestones in memory of a brave pioneer, a close friend, a devoted mentor, and a great physicist.

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