Stochastic 3-D Simulations for Diffusion-Controlled Reactions with Concentration-Dependent Kinetic Rates in Crowded Environments

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Short Abstract — **Models based on mass action kinetics are widely used but, in a strict sense, limited to biochemical reactions in dilute solution, where reactants freely diffuse and react in an unobstructed space. Modeling diffusion-reaction kinetics in a crowded environment, such as the cytoplasm, requires fractal-like ordinary differential equation (ODE) models. In particular, generalized mass action systems have been proposed and successfully validated for this purpose. In this paper, we establish two novel, particle-based methods to simulate biochemical diffusion-reaction systems within crowded environments. We distinguish two conceptually different situations. In the first, the ODEs capture a microscopic "reaction-only" mechanism, while diffusion is modeled separately. In the second case, the ODEs model the combined effects of both reaction and diffusion. This distinction consequently leads to two simulation methods that both effectively simulate and quantify crowding effects, including reduced reaction volumes, reduced diffusion rates, and reduced accessibility between potentially reacting particles. The proposed methods account for fractal-like kinetics, where the reaction rate depends on the local concentrations of the molecules undergoing the reaction. Rooted in an agent based modeling framework, this aspect of the methods offers the capacity to address sophisticated intracellular spatial effects, such as macromolecular crowding.**

Keywords —**generalized mass action system, diffusion-reaction, crowding**

In this paper we develop two novel, microscopic particle-based methods to simulate a biochemical diffusion-reaction system within a crowded environment, which typically is the cytoplasm. The novel contributions of these methods are the following. First, by its nature, an ODE is deterministic and continuous and does not account for spatial features. However, after embedding the ODE into a method accounting for spatial effects, their combination is applicable in discrete, stochastic, and spatial simulations. This embedding can be implemented in two distinct ways, in which phenomenological ODEs play different roles; we will discuss these later. Second, the two proposed methods effectively simulate and quantify crowding effects, including reduced reaction volumes, reduced diffusion rates, and reduced accessibility between potentially reacting particles. Third, the proposed methods account for fractal-like kinetics, where the kinetic reaction rate depends on the local concentrations of the molecules undergoing the reaction; this aspect is, to the best of our knowledge, novel in the field of stochastic simulations. Rooted in an agent based modeling framework, this aspect of the methods offers the capacity to address sophisticated intracellular spatial effects, such as macromolecular crowding, active transport along cytoskeleton structures, and reactions on heterogeneous surfaces as well as in porous media.

We first demonstrate the validity of the proposed methods with representative elementary types of biochemical processes in non-crowded spaces: an association reaction, a dissociation reaction, and their combination—the reversible reaction. These reactions will be modeled with power-law functions, according to the tenets of Biochemical Systems Theory. After this initial validation, we quantify macromolecular crowding effects theoretically and numerically through examples of enzymatic reactions. Finally, we investigate an actual experimental system representative for molecular crowding, namely the binding of dansylamide and carbonic anhydrase in artificial media, and discover some surprising results.

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References

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