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MesoRD 1.0: Stochastic reaction-diffusion simulations in the microscopic limit

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ABSTRACT

Summary: MesoRD is a tool for simulating stochastic reaction-diffusion systems as modeled by the reaction diffusion master equation. The simulated systems are defined in the Systems Biology Markup Language with additions to define compartment geometries. MesoRD 1.0 supports scale-dependent reaction rate constants and reactions between reactants in neighbouring subvolumes. These new features make it possible to construct physically consistent models of diffusion-controlled reactions also at fine spatial discretization.

Availability: MesoRD is written in C++ and licensed under the GNU general public license (GPL). MesoRD can be downloaded at http://mesord.sourceforge.net. The MesoRD homepage, http://mesord.sourceforge.net, contains detailed documentation and news about recently implemented features.

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1 INTRODUCTION

Physical modelling is increasingly important to gain insights about how biochemical processes work in living cells. Different processes do, however, need to be modeled at different levels of detail. It may, for example, be important to consider that chemical reactions are stochastic, spatially dependent or both. The combined spatial stochastic models are, for example, needed when there are slow local fluctuations that influences the rates of chemical reactions in a non-linear way or when association–dissociation events are interrupted by additional reaction before the reactants have reached uncorrelated positions (Mahmutovic *et al.*, submitted for publication). In these cases, it is desirable to have a tool that can evolve a biochemical process at different levels of detail in a physically consistent manner.

At the finest level of detail, stochastic reaction diffusion kinetics can be consistently modeled using the spatially and temporally continuous framework developed by Smoluchowski (von Smoluchowski, 1917) for reactive spheres and later extended to finite association rates (Collins and Kimball, 1949) and dissociation (Berg, 1978). It is, however, often neither necessary nor practical to model reactions at this level of detail. By discretizing space into subvolumes and keeping track of the number of molecules of each species in each subvolume and when they react, the process is described as a continuous-time discrete-state Markov process. The master equation that governs this process is known as the Reaction Diffusion Master Equation (RDME) (Gardiner, 2004; Kampen, 2007). The RDME has recently been shown to diverge and give unphysical solutions at high spatial resolution (Erban and Chapman, 2009; Isaacson, 2008). The divergence problem was solved by introducing scale-dependent bi-molecular reaction rate constants where the new mesoscopic rate constants are calculated from the microscopic framework (Fange *et al.*, 2010).

Here we describe recent developments of MesoRD (Hattne *et al.*, 2005), a tool for stochastic reaction-diffusion simulations or more specifically a tool for simulating trajectories corresponding to the RDME. How different tools (Ander *et al.*, 2004; Boulianne *et al.*, 2008; Drawert *et al.*, 2012; Kerr *et al.*, 2008; Plimpton and Slepoy, 2005; Sanford *et al.*, 2006; van Zon and ten Wolde, 2005; Wils and De Schutter, 2009) for stochastic reaction diffusion modeling compares with each other in terms of capabilities has been discussed elsewhere (Burrage *et al.*, 2011). The main enhancement compared with previous MesoRD versions and other RDME-based simulators is the use of scale-dependent mesoscopic reaction rate constants (Fange *et al.*, 2010), which allows for microscopically consistent simulations at fine spatial discretization. Scale-dependent rate constants also make it possible to simulate RDME models on planar 2D surfaces (membranes), where the problems of diffusion-controlled reactions are much more severe than in 3D because reactants do not lose spatial correlations even at large distances (Berg, 1978). Since our previous applications note (Hattne *et al.*, 2005) we have also added functionalities for defining cellular compartment geometries using triangle meshes in addition to the previously available method based on constructive solid geometries (CSG) and also included the possibility of running mean-field simulations within MesoRD.

2 IMPLEMENTATION

The core features of MesoRD are described in Hattne *et al.* (2005). In essence, MesoRD implements the Next Subvolume Method (Elf and Ehrenberg, 2004), an efficient algorithm for simulating the RDME. MesoRD reads model definitions in the Systems Biology Markup Language (SBML) (Finney and Hucka, 2003), which has earlier been extended to adhere to the MesoRD-specific requirement of spatial geometries (Hattne *et al.*, 2005) and is now also extended to the requirement of microscopic parameters.

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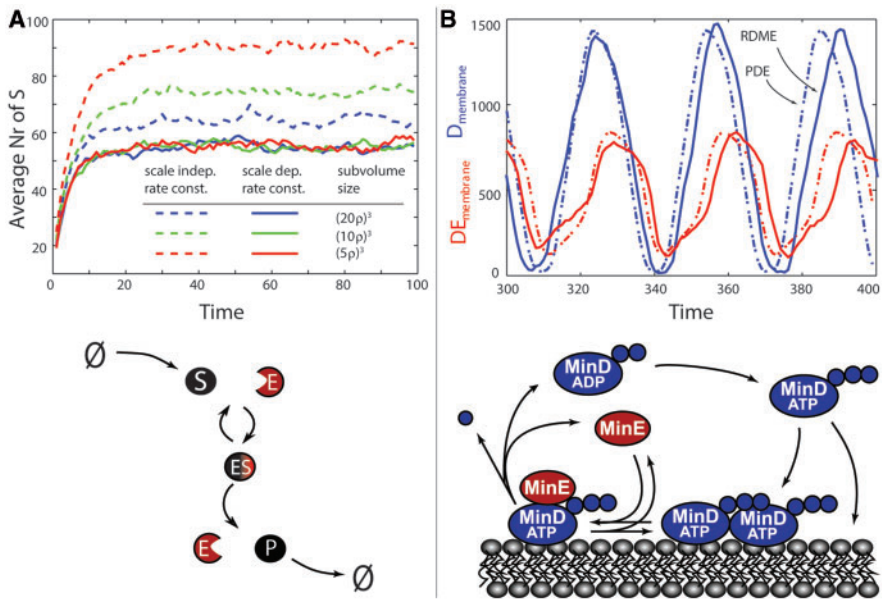

Fig. 1. (**A**) MesoRD simulations of the Michaelis–Menten reaction scheme with diffusion-controlled association of substrate and enzyme. At spatially fine-grained simulations, using small subvolumes, simulations without scale-dependent reaction rate constants diverge. This is primarily due to the fact that the diffusion part of the rate constant is modeled explicitly and should not be accounted for also in the rate constant. (Fange *et al.*, 2010). (**B**) Comparison of stochastic and mean-field MesoRD simulations of the Min-system. When there is a high local reactant density, the single RDME trajectory is expected to show high resemblance to the corresponding mean-field PDE. The PDE can be simulated in MesoRD using the same input file as for the stochastic simulation

To use scale-dependent reaction rates, the user must supply microscopic parameters, i.e. a reaction radii and a microscopic association rate constant (Berg, 1978; van Zon and ten Wolde, 2005). These are readily added as an annotation to the bi-molecular association reaction in the SBML file. MesoRD automatically scales the association and dissociation rates according to the subvolume size, as described in (Fange *et al.*, 2010). As the actual position of a molecule is not known with better accuracy than half the spatial resolution (Shannon, 1948), there is also a significant probability that bi-molecular reactions occur over subvolume boundaries. As described in Fange *et al.* (2010), this is accounted for in MesoRD by allowing for bi-molecular reactions also between reactants in neighbouring subvolumes.

In addition to the previously available CSG primitives used to construct compartment geometries, we have also included two 2D objects, rectangles and circles. These can be transformed and combined by operations already supported by MesoRD, such as rotations and unions. When using 2D geometries microscopic parameters should always be used, as association and dissociation rates will be scale dependent at all discretizations.

MesoRD can also run simulations of 3D mean-field models using the same SBML input file of the corresponding stochastic model. In the mean-field description, the average change per subvolume, as defined by RDME, is applied in each time-step. This is equivalent to a numerical solution of the corresponding partial differential equation (PDE) using a finite difference scheme based on a 7-point stencil (Fange and Elf, 2006).

3 EXAMPLES

3.1 Michaelis-Menten reaction

The RDME divergence problem at fine spatial dicretisation is illustrated using a Michaelis–Menten reaction scheme kept out of equilibrium by constantly supplying substrates and removing products. In Figure 1A, we show the misleading results one would get without using the microscopic corrections now implemented in MesoRD.

3.2 The Min system

Spatio-temporal oscillations of the MinCDE proteins are essential for localizing the *E. coli* cell-division apparatus at mid-cell. In Figure 1B, we show that the Min-model in Fange and Elf (2006) exhibits stable spatio-temporal oscillations also with a microscopically consistent treatment of the strongly diffusion-controlled binding of MinE to MinD. Furthermore, we also use MesoRD to compare the stochastic simulation results to the corresponding mean-field description.

4 CONCLUSIONS

The new capabilities in MesoRD 1.0, including the possibility to handle diffusion-controlled reactions, 2D geometries and mean-field (PDE) simulations, make it possible to make stochastic simulations at high spatial resolution, which can be directly compared with the corresponding mean-field description. This makes MesoRD not only a readily available and user friendly, but also

a versatile and physically consistent, tool for stochastic and mean-field simulations of reaction-diffusion processes.

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