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Probability distributed time delays: integrating spatial effects into temporal models

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Abstract: Cell signaling dynamics are driven by complicated processes in time and space. One classical example is the multitude of biochemical processes taking place on the plasma membrane. The highly compartmentalized structure of the membrane creates heterogeneity that is reflected in spatial phenomena such as molecular crowding, spatial segregation, cytoskeletal-induced membrane corralling, and anomalous diffusion, to name a few. With recent technological progress it is possible, though within limits, to reveal those spatial effects experimentally. A system's behavior can vary considerably as compared to its well-mixed representation, a fact that is revealed when a model is spatially-resolved (Andrews and Bray, 2004; Hattne et al., 2005; Marquez-Lago and Burrage, 2007). Hence, it has become evident that we must consider spatial aspects in our modeling approaches in order to achieve two main purposes: First, to improve our understanding of the actual cellular processes and their inherent functions, second, to make accurate representations of such processes. In the case of heterogeneous environments, purely temporal models will rarely capture the observed dynamics accurately. On the other hand, spatially explicit methods such as single particle tracking are more realistic but can be prohibitively expensive, especially for long simulation time spans. A good compromise between these approaches may be a temporal model that indirectly incorporates spatial features and effects, thus balancing accuracy and computational costs (Marquez-Lago et al., in preparation for submission). Our methodology is then composed of two steps: distribution fitting and stochastic simulation. The first step will be discussed in detail and is the main focus of our talk. The second step is achieved by using a generalization of the SSA for chemical kinetics with delays (DSSA) (see for example Barrio et al., 2006). We applied our method to a variety of scenarios of molecular translocation processes. Our simulations, as compared to those yielded by CHEMCELL (a single-particle tracking algorithm), showed high accuracy while being computed several orders of magnitude faster. We present an effective way of introducing spatial aspects into temporal models. Our research suggests that certain spatial heterogeneities can be well captured and modeled by means of time delayed processes with specific delay distributions. In some cases, this may provide new insights into complicated cellular processes and in a significantly shorter time frame than highly resolved spatial models.

Keywords: *Stochastic simulations, delays, spatiotemporal modeling.*

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CHEMCELL. Sandia National Laboratories http://www.cs.sandia.gov/~sjplimp/chemcell.html

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