

Probability distributed time delays: integrating spatial effects into temporal models

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Short Abstract — In order to provide insights into the complex biochemical processes inside a cell, modeling approaches must find a balance between their accurate representation and acceptable computational costs. This issue is particularly stressed when spatial inhomogeneities have a significant effect on system's behavior. In such cases, spatial resolution is many times introduced for accurate modeling, but these computer simulations can in turn be prohibitively expensive. In this talk we present a method incorporating probability distributed time-delays, aiming for a good compromise between computational costs and accurate representation of certain spatial processes, such as molecular diffusion and translocation between cell compartments.

Keywords — Stochastic simulations, delays, spatiotemporal modeling.

I. BACKGROUND

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 corraling, 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 [1–4]. 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 [5].

II. MATHEMATICAL AND COMPUTATIONAL METHODS

Our methodology is then composed of two steps: distribution fitting and stochastic simulation [5]. 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) [6–8]). 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 [4]), showed high accuracy while being computed several orders of magnitude faster.

III. CONCLUSION

We present an effective way of introducing spatial aspects into temporal models. Our research suggests that 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.

REFERENCES

- [1] Marquez Lago T.T., Burrage K. (2007). Binomial tau-leap spatial stochastic simulation algorithm for applications in chemical kinetics. *J Chem Phys* **127**, 104101.
- [2] Hattne J., Fange D., Elf J. (2005). Stochastic reaction-diffusion simulation with MesoRD. *Bioinformatics* **21** (12), 2923-4.
- [3] Andrews S.S., Bray D. (2004). Stochastic simulation of chemical reactions with spatial resolution and single molecule detail. *Phys Biol* **1** (3), 137-51.
- [4] CHEMCELL. Sandia National Laboratories <http://www.cs.sandia.gov/~sjplimp/chemcell.html>
- [5] Marquez Lago T.T., Leier A., Burrage K. A method for incorporating spatial processes into temporal models with delay distributions. In preparation for submission.
- [6] Barrio M., Burrage K., Leier A. et al. (2006). Oscillatory regulation of Hes1: discrete stochastic delay modelling and simulation. *PLoS Comp Bio* **2** (9), e117.
- [7] Cai X. (2007). Exact stochastic simulation of coupled chemical reactions with delays. *J Chem Phys* **126**, 124108.
- [8] Anderson D.F. (2007). A modified next reaction method for simulating chemical systems with time dependent propensities and delays. *J Chem Phys* **127**, 214107.

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