Particle-Based Stochastic Reaction-Diffusion Models in Biology
November 9-14 2014

MEALS

*Breakfast (Buffet): 7:00–9:30 am, Sally Borden Building, Monday–Friday
*Lunch (Buffet): 11:30 am–1:30 pm, Sally Borden Building, Monday–Friday
*Dinner (Buffet): 5:30–7:30 pm, Sally Borden Building, Sunday–Thursday
Coffee Breaks: As per daily schedule, in the foyer of the TransCanada Pipeline Pavilion (TCPL)
***Please remember to scan your meal card at the host/hostess station in the dining room for each meal.**

MEETING ROOMS

All lectures will be held in the lecture theater in the TransCanada Pipelines Pavilion (TCPL). An LCD projector, a laptop, a document camera, and blackboards are available for presentations.

All lectures are 30 minutes, with an additional 10 minutes for discussion.

Sunday

16:00	Check-in begins (Front Desk - Professional Development Centre - open 24 hours)
17:30–19:30	Buffet Dinner, Sally Borden Building
20:00	Informal gathering in 2nd floor lounge, Corbett Hall Beverages and a small assortment of snacks are available on a cash honor system.

Monday

7:00–8:45	Breakfast
8:45–9:00	Introduction and Welcome by BIRS Station Manager, TCPL
	Session: Biological Models and Analytical Approximations I
9:00–9:30	Attila Becskei, *Diffusion and noise in bistable systems*
9:40–10:10	Jun Allard, *Mechanics of diffusing surface molecules modulates T cell receptor sensitivity*
10:20–10:40	Coffee Break
10:40–11:10	Shev MacNamara, *Diffusion in crowded environments*
11:20–11:50	Kim "Avrama" Blackwell, *Dynamical spatial models of signaling pathways underlying synaptic plasticity*
12:00–13:00	Lunch
13:00–14:00	Guided Tour of The Banff Centre; meet in the 2nd floor lounge, Corbett Hall
14:00–14:10	Group Photo; meet in foyer of TCPL (photograph will be taken outdoors so a jacket might be required).
	Session: Mesoscopic Methods and Modeling I
14:20–14:50	Stefan Engblom, *Mesoscopic Stochastic Modeling: Diffusion Operators, Multiphysics Couplings, and Convergence*
15:00–15:30	Yang Cao, *Multigrid Discretization Strategy on Discrete Stochastic Simulation of Reaction-Difusion Systems*
15:40–16:00	Break (No coffee as too late...)
16:00–16:30	Erik De Schutter, *Parallelization of the spatial SSA on unstructured meshes*
16:40–17:10	Kevin Sanft, *Scaling properties of exact simulation algorithms for spatially discretized stochastic reaction-diffusion processes*
17:30–19:30	Dinner

Tuesday

7:00–9:00 Breakfast

Session: Biological Models and Analytical Approximations II

9:00–9:30 Carlos F. Lopez, *Use of biological model-programs in PySB to explore and calibrate cell-death decisions.*

9:40–10:10 Andreas Hellander, *Accuracy of the Michaelis-Menten approximation when analyzing effects of molecular noise*

10:20–10:40 Coffee Break

10:40–11:10 Jay Newby, *Asymptotic and numerical methods for metastable events in stochastic gene networks.*

11:20–11:50 Daniel Coombs, *Random violence: A stochastic approach to cell cytotoxicity*

12:00–13:30 Lunch

Session: Mesoscopic Methods and Modeling II

13:30– 14:00 Dan Gillespie, *The Small-Voxel Tracking Algorithm*

14:10– 14:40 Stefan Hellander, *Reaction rates for mesoscopic reaction-diffusion kinetics*

14:50–15:20 Coffee Break

15:20–15:50 Mauricio J. Del Razo, *A discrete stochastic model for reversible diffusion-controlled reactions*

16:00– 16:30 Anastasios Matzavinos, *Dissipative particle dynamics simulations of polymer networks*

17:30–19:30 Dinner

Wednesday

7:00–9:00 Breakfast

Session: Particle-Based Methods and Modeling I

9:00–9:30 Vahid Shahrezaei, *When we need particle-based reaction-diffusion simulations and when we don't*

9:40–10:10 Steven Andrews, *The Smoldyn simulator: overview, applications, and hybrid simulation*

10:20–10:40 Coffee Break

10:40–11:10 Thomas R. Sokolowski, *eGFRD in all dimensions*

11:20–11:50 Kazunari Kaizu, *E-Cell System version 4.0: an integrated platform for single-particle-level*

12:00–13:30 Lunch

13:30-17:30 Free Afternoon

17:30–19:30 Dinner

Session: Wednesday Evening Topical Talks

20:00–20:15 Leonard Harris, *Using stochastic simulations to differentiate the effects of clonal heterogeneity (extrinsic noise) from cell fate decisions (intrinsic noise) in cancer response to targeted drugs*

20:20–20:35 Ava Mauro, *A dynamic lattice version of the First-Passage Kinetic Monte Carlo method*

20:40–20:55 Peter Thomas, *Stochastic Shielding: a Novel Approach to Simplifying Random Processes on Graphs*

Thursday

7:00–9:00	Breakfast
	Session: Particle-Based Methods and Modeling II
9:00–9:30	Frank Noe, *interacting-Particle Reaction-Diffusion (iPRD) dynamics*
9:40–10:10	Thorsten Prüstel, *Novel analytical results for diffusion-influenced receptor-ligand reactions in two dimensions*
10:20–10:40	Coffee Break
10:40–11:10	Margaret E Johnson, *Free-Propagator Reweighting Integrator for Single-Particle Reaction Diffusion Dynamics in Solution and on the Membrane*
11:20–11:50	Samuel Isaacson, *Lattice Approximation of Spatially-Continuous Particle-Based Stochastic Reaction-Diffusion Models*
12:00–13:30	Lunch
	Session: Multiscale Methods and Modeling
13:30– 14:00	Ruth Baker, *Adaptive multi-level Monte Carlo methods*
14:10– 14:40	Radek Erban, *From Molecular Dynamics to Particle-based Stochastic Reaction-Diffusion Models*
14:50–15:20	Coffee Break
15:20–15:50	Hye-Won Kang, *Multiscale stochastic reaction-diffusion algorithms combining Markov chain models with SPDEs*
16:00–16:30	Christian Yates, *A PDE/compartment-based hybrid method for simulating stochastic reaction-diffusion systems*
17:30–19:30	Dinner

Friday

7:00–9:00	Breakfast
9:00-10:00	Panel on Computational Software: Linda Petzold (discussion leader, StochSS), Steven Andrews (Smoldyn), Erik De Schutter (STEPS), Andreas Hellander (PyURDME, StochSS), Kazunari Kaizu (Ecell), Frank Noe (ReaDDy).
10:00–10:30	Coffee Break
10:30-11:30	Open discussion and/or continuation of pre-break discussion.
11:30–13:30	Lunch
Checkout by 12 noon.	

** 5-day workshop participants are welcome to use BIRS facilities (BIRS Coffee Lounge, TCPL and Reading Room) until 3 pm on Friday, although participants are still required to checkout of the guest rooms by 12 noon. **

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ABSTRACTS

Speaker: **Jun Allard** (University of California Irvine)
Title: *Mechanics of diffusing surface molecules modulates T cell receptor sensitivity*
Abstract: Receptors on the surface of cells control many cellular processes. An important class of receptors, e.g., T-cell receptors, attach to molecules that are anchored to other cells or surfaces, and remain poorly understood. The T-cell receptor complex spans 15 nanometers, while other nearby molecules spans ~ 40 nanometers. Since all these molecules are mobile on the two-dimensional cell surface, the size differential has been proposed to lead to spatial segregation (mediated by the mechanical properties of the cell membranes) that triggers immune signaling. I will present a nanometer-scale mathematical model that couples membrane elasticity with compressional resistance and lateral mobility of molecules. We find robust supradiffusive segregation. The model predicts a time-dependent tension on the receptor leading to a nonlinearity which could enhance the receptors ability to make precise immune decisions. Understanding the full life-cycle of receptor dynamics raises questions involving surface diffusion of a population of molecules, and I will present open problems along with computational estimates and their biological importance.

Speaker: **Steven Andrews** (Fred Hutchinson Cancer Research Center)
Title: *The Smoldyn simulator: overview, applications, and hybrid simulation*
Abstract: Smoldyn is a particle-based cell biology simulator which represents proteins or other molecules of interest as individual spheres. These particles diffuse, undergo chemical reactions with each other, and interact with membranes and other surfaces in ways that closely mimic reality. In particular, all interaction rates are quite accurate. Smoldyn is easy to use and supports a wide variety of features. Several colleagues and I recently used Smoldyn to investigate transcription factor dynamics in cell nuclei to determine what processes enable transcription factors to locate their target genes quickly. In agreement with prior results, we found that non-specific binding and then diffusion along DNA accelerates target gene finding through a process called the antenna effect. Additionally, we found that intersegmental transfer also accelerates target gene finding; here, a transcription factor transfers directly from being non-specifically bound on one DNA segment to being non-specifically bound on an adjacent DNA segment. In separate work, Martin Robinson and I recently added adjacent-volume hybrid simulation capability to Smoldyn. Here, space is partitioned into adjacent continuum and lattice regions, which are simulated with particle-based and spatial Gillespie type methods, respectively. These enable simulations to represent high levels of detail where required but lower detail (and faster computation) elsewhere.

Speaker: **Ruth Baker** (Oxford University)
Title: *Adaptive multi-level Monte Carlo methods*
Abstract: Discrete-state, continuous-time Markov models are widely used in the modelling of biochemical reaction networks. Their complexity generally precludes analytic solution, and so we rely on Monte Carlo simulation to estimate system statistics of interest. Perhaps the most widely used method is the Gillespie algorithm. This algorithm is exact but computationally complex. As such, approximate stochastic simulation algorithms such as the tau-leap algorithm are often used. Sample paths are generated by taking leaps of length tau through time and using an approximate method to generate reactions within leaps. However, tau must be held relatively small to avoid significant estimator bias and this significantly impacts on potential computational advantages of the method.

The multi-level method of Anderson and Higham tackles this problem by cleverly generating a suite of sample paths with different accuracy in order to estimate statistics. A base estimator is computed using

many (cheap) paths at low accuracy. The bias inherent in this estimator is then reduced using a number of correction estimators. Each correction term is estimated using a collection of (increasingly expensive) paired sample paths where one path of each pair is generated at a higher accuracy compared to the other. By sharing randomness between these paired sample paths only a relatively small number of pairs are required to calculate each correction term.

In the original multi-level method, paths are simulated using the tau-leap technique with a fixed value of tau. This approach can result in poor performance where the reaction activity of a system changes substantially over the timescale of interest. By introducing a novel, adaptive time-stepping approach we extend the applicability of the multi-level method to such cases. In our algorithm, tau is chosen according to the stochastic behaviour of each sample path. We present an implementation of our adaptive time-stepping multi-level method that, despite its simplicity, performs well across a wide range of sample problems.

Speaker: **Attila Becskei** (Biozentrum, University of Basel, Switzerland)
Title: *Diffusion and noise in bistable systems*
Abstract: Bistable systems support cellular memory and differentiation and they also provide means to study noise induced transition between the two stable states. We have examined the behavior of two systems with positive feedback loops that generate bistability with and without diffusion. In the system without diffusion we measured protein and RNA concentrations. Despite having molecule numbers less than one, continuous models (stochastic differential equation and Fokker-Planck equation) provide a good approximation to the model with discrete steps to analyze noise induced transitions by comparing mean first passage times. In chromosomal epigenetic systems the range of bistability is reduced by diffusion, which is further compromised by discrete stochastic effects. These results reveal that in systems where diffusion is associated with low molecule numbers, such as chromosomal epigenetic modifications, particle-based stochastic simulations are essential to adequately describe the system behavior.

Speaker: **Kim "Avrama" Blackwell** (George Mason University, Krasnow Institute of Advanced Study)
Title: *Dynamical spatial models of signaling pathways underlying synaptic plasticity*
Abstract: The mechanisms underlying spatial specificity and discrimination of temporal pattern are some of the least understood aspects of synaptic plasticity, memory storage and information processing in neurons. The ability of neurons to increase or decrease synaptic strength depending on temporal pattern is well known, but the critical signaling pathways are still not delineated. New imaging techniques have revealed that spatial specificity varies, with some molecules (e.g. calcium) being limited to single spines and other molecules (e.g. Ras) diffusing several microns. Stimulation patterns for induction of synaptic plasticity often span minutes and the time course of activation of critical kinases range from seconds to 10s of minutes. In order to understand how interaction of these spatial aspects with various temporal patterns produces synaptic plasticity, we created NeuroRD, software that extends the Gillespie tau-leap algorithm for stochastic reactions into the diffusion domain. We use NeuroRD to efficiently simulate stochastic interactions both within spines and between spines arranged along a dendrite. We investigate the mechanisms controlling spatial specificity and temporal pattern discrimination in cortico-striatal synaptic plasticity.

Speaker: **Yang Cao** (Computer Science Department, Virginia Tech)
Title: *Multigrid Discretization Strategy on Discrete Stochastic Simulation of Reaction-Difusion Systems*
Abstract: Discrete stochastic simulation for reaction-diffusion systems is a time-consuming task. A key factor in the simulation is the discretization size in space. Recently we developed a simple formula of the optimal discretization size for reaction-diffusion systems. Based on our formula, we proposed a multigrid discretization method for stochastic simulation of multiscale reaction-diffusion systems, which applies an optimal discretization size for each species. With multiple discretization sizes for species in different reaction and diffusion scales, we greatly reduce the size of the system and achieve high efficiency. On the other hand, our study on a compartment-based model of Turing patterns using this multi grid discretization strategy has shown a different spatial pattern than classical deterministic PDE-based models as well as the stochastic reaction-diffusion models using a uniform discretization size for all chemical species.

Speaker: **Daniel Coombs** (University of British Columbia)
Title: *Random violence: A stochastic approach to cell cytotoxicity*
Abstract: This talk is about our recent work on the delivery of effector molecules from immune cells such as T and Natural Killer cells. These cells release fairly small numbers of molecules that induce cell death, into the tightly defined region of contact with a target cell (the "immunological synapse"). I will explain the background biology and the leading hypothesis of how this process works. I will then show how we used a spatial stochastic algorithm to analyze whether the hypothesis is correct and outline future experimental work. This research was done jointly with Daniel Woodsworth (BC Cancer Research Centre).

Speaker: **Stefan Engblom** (Uppsala university)
Title: *Mesoscopic Stochastic Modeling: Diffusion Operators, Multiphysics Couplings, and Convergence*
Abstract:

In this talk I will discuss stochastic modeling in the reaction-transport framework from various viewpoints. I shall initially be concerned with diffusion-controlled reactions targeting applications mainly in molecular cell biology. I will briefly review the basic setup and conditions for the validity of this type of modeling. In particular I will discuss the properties of the diffusion transport operator.

I will next discuss an application example from outside the diffusion-controlled domain, namely an approach towards multiphysics modeling of neuronal spiking activity affected by stochastic channel fluctuations. This example serves as a reminding illustration that questions of convergence are not that straightforward to answer.

Speaker: **Radek Erban** (University of Oxford)
Title: *From Molecular Dynamics to Particle-based Stochastic Reaction-Diffusion Models*
Abstract: I will discuss all-atom and coarse-grained molecular dynamics (MD) models with the aim of developing and analysing multiscale methods which use MD simulations in parts of the computational domain and (less detailed) particle-based stochastic reaction-diffusion models in the remainder of the domain. Applications using all-atom MD include intracellular dynamics of ions and ion channels. Applications using coarse-grained MD include protein binding to receptors on the cellular membrane, where modern stochastic reaction-diffusion simulators of intracellular processes can be used in the bulk and accurately coupled with a (more detailed) MD model of protein binding which is used close to the membrane.

Speaker: **Dan Gillespie** (Dan T Gillespie Consulting)
Title: *The Small-Voxel Tracking Algorithm*
Abstract: Simulating the evolution of a chemically reacting system using the bimolecular propensity function, as is done by the stochastic simulation algorithm and its reaction-diffusion extension, entails making statistically inspired guesses as to where the reactant molecules are at any given time. Those guesses will usually be physically justified if the system is dilute in the reactant molecules, but not otherwise. For non-dilute systems, an accurate simulation requires the extra effort and expense of keeping track of the positions of the reactant molecules as the system evolves. One molecule-tracking algorithm that pays careful attention to the physics of molecular diffusion is the enhanced Green's function reaction dynamics (eGFRD) of Takahashi, Tănase-Nicola and ten Wolde. This talk introduces a molecule-tracking algorithm that has the same theoretical underpinnings and strategic aims as eGFRD, but a very different implementation procedure. Called the small-voxel tracking algorithm (SVTA), it combines the well known voxel-hopping method for simulating molecular diffusion with a novel procedure for rectifying the unphysical predictions of the diffusion equation on the small spatiotemporal scale of molecular collisions. Indications are that the SVTA should be more computationally efficient than eGFRD for the problematic class of non-dilute systems.

Speaker: **Leonard Harris** (Vanderbilt University School of Medicine)
Title: *Using stochastic simulations to differentiate the effects of clonal heterogeneity (extrinsic noise) from cell fate decisions (intrinsic noise) in cancer response to targeted drugs*

Abstract: Leonard A. Harris1,2, Darren R. Tyson1,2, Vito Quaranta1,2 and Carlos F. Lopez1 Department of Cancer Biology1 and Center for Cancer Systems Biology2 Vanderbilt University School of Medicine Nashville, TN, USA

Cancer is thought to be a complex adaptive disease, whereby genetically and epigenetically distinct cell subpopulations, or clones, compete for resources within the ecosystem of the host tissue. The highly probabilistic nature of gene expression and intracellular molecular interactions confers a significant amount of randomness, or stochasticity, to cell fate decisions, e.g., division and death. Tumors are thus highly heterogeneous masses in terms of clonal composition as well as in their responses to drug treatments. This heterogeneity is believed to underlie cases of cancer recurrence and acquired drug resistance as well as the infrequent, dramatic positive responses to treatment of so-called exceptional responders. From a population dynamics perspective, clonal heterogeneity and cell fate stochasticity are distinct sources of noise, the former arising from genetic mutations and/or epigenetic transitions that are extrinsic to the fate decision signaling pathways and the latter being intrinsic to these pathways. Here, we present results of a kinetic modeling study based on experimental time course data of epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer cells, in response to erlotinib, an EGFR inhibitor. Deterministic (ODE) simulations capture the effects of clonal heterogeneity and describe the overall trends of experimentally treated tumor cell populations. However, they are not capable of explaining the observed variability of drug-response trajectories (depth of the response and time to rebound). Stochastic simulations, instead, capture the effects of intrinsically noisy cell fate decisions that cause significant variability in the trajectories. These findings indicate that stochastic simulations are necessary to distinguish the contribution of extrinsic (clonal heterogeneity) and intrinsic (cell fate decisions) noise to the variability of cancer treatment. Furthermore, they suggest that, whereas tumors with distinct clonal structures are expected to behave differently in response to drug, two clonally identical tumors may also experience vastly different outcomes, such as exceptional response vs. rapid relapse, due to the intrinsic noise of cell fate decisions. The results of this study provide a foundation for future modeling studies aimed at improving targeted cancer therapies, focused on understanding the intracellular signaling networks that govern division vs. death decisions in cancer cells.

Speaker: **Andreas Hellander** (Department of Information Technology, Uppsala University)
Title: *Accuracy of the Michaelis-Menten approximation when analyzing effects of molecular noise*
Quantitative biology relies on the construction of accurate mathematical models, yet the effectiveness of these models is often predicated on making simplifying approximations that allow for direct comparisons with available experimental data. The Michaelis-Menten approximation is widely used in both deterministic and discrete stochastic models of intracellular reaction networks, due to the ubiquity of enzymatic activity in cellular processes and the clear biochemical interpretation of its parameters. However, it is not well understood how the approximation applies to the discrete stochastic case or how it extends to spatially inhomogeneous systems. We study the behavior of the discrete stochastic Michaelis-Menten approximation as a function of system size and show that significant errors can occur for small volumes, in comparison with a corresponding mass action system. We then explore some consequences of these results for quantitative modeling. One consequence is that fluctuation-induced sensitivity, or stochastic focusing, can become highly exaggerated in models that make use of Michaelis-Menten kinetics even if the approximations are excellent in a deterministic model.Another consequence is that spatial stochastic simulations based on the reaction-diffusion master equation can become highly inaccurate if the model contains Michaelis-Menten terms.

Speaker: **Stefan Hellander** (University of California, Santa Barbara)
Title: *Reaction rates for mesoscopic reaction-diffusion kinetics*
Abstract: We derive reaction rates for simulation of general reversible reactions on Cartesian meshes at the mesoscopic scale. We show that there is a mesh size, independent of parameters, for which we can match the mean association time, the mean dissociation time, and the mean rebinding time at the mesoscopic scale with the corresponding microscopic quantities. In a numerical example we show convergence also of

the transient as we approach this mesh size, and demonstrate that fine-grained, microscopic, dynamics of the system are captured accurately.

Speaker: **Samuel Isaacson** (Boston University)
Title: *Lattice Approximation of Spatially-Continuous Particle-Based Stochastic Reaction-Diffusion Models*
Abstract: We derive a lattice, continuous-time jump process approximation of a spatially-continuous, interaction-function based stochastic reaction-diffusion model. The new model has the benefit of treating diffusion and linear reactions in exactly the same manner as the reaction-diffusion master equation (RDME). Moreover, in the limit of coarse meshes it can be shown that the RDME approximates this model. Unlike the RDME, this new, convergent reaction-diffusion master equation model (CRDME) retains bimolecular reactions in the limit that the mesh spacing approaches zero, converging to the underlying interaction-function model. The CRDME therefore offers alternatives to both Brownian Dynamics (BD) methods for solving the interaction-function model, and coupled RDME-BD methods that attempt to overcome the loss of bimolecular reactions in the RDME for small mesh sizes.

Speaker: **Margaret E Johnson** (Johns Hopkins University)
Title: *Free-Propagator Reweighting Integrator for Single-Particle Reaction Diffusion Dynamics in Solution and on the Membrane*
Abstract: We present a new algorithm for simulating reaction-diffusion equations at single-particle resolution. Our algorithm is designed to be both accurate and simple to implement, and to be applicable to large and heterogeneous systems, including those arising in systems biology applications. We combine the use of the exact Greens function for a pair of reacting particles with the approximate free-diffusion propagator for position updates to particles. By employing a trajectory-reweighing scheme in our free-propagator reweighting (FPR) method, we recover the exact association rates for a pair of interacting particles at all times. FPR simulations of many-body systems accurately reproduce the theoretically known dynamic behavior for a variety of different reaction types. FPR does not suffer from the loss of efficiency common to other path-reweighting schemes, first, because corrections apply only in the immediate vicinity of the reacting particles, and second, because by construction the average weight factor equals one upon leaving this reaction zone. Importantly, the FPR approach represents a general framework for single-particle dynamics that can be extended to physical descriptions of protein interactions with long-range forces, as we demonstrate here for Coulombic interactions. We have recently applied FPR to model protein recruitment and binding interactions on the membrane, where the transition from 3D to 2D dynamics can have a significant impact on the time-scales and equilibrium of protein interactions. Our approach can quite generally be applied to particles that react under orientational constraints or additional forces, and thus provides a foundation for building microscopic detail into meso- to macroscale simulations of reacting particle systems, including those of proteins in living cells.

Speaker: **Kazunari Kaizu** (RIKEN Quantitative Biology Center, Japan)
Title: *E-Cell System version 4.0: an integrated platform for single-particle-level simulations*
Abstract: Recently, various types of network-free techniques for a reaction-diffusion system at the molecular resolution have been proposed in contrast to conventional concentration- and network-based approaches. Meanwhile, demand for the integrated environment including modeling, simulation, visualization and analysis increases.
Here, we present a novel simulation software, E-Cell System version 4, which provides an integrated platform with a fully scriptable, network-free, rule-based modeling environment, spatio-temporal data visualizations and a variety of simulation algorithms: an exact and highly-sophisticated event-driven particle method (the enhanced Green's Function Reaction Dynamics method), Reaction Brownian Dynamics, a high-performance microscopic lattice method with a flexible representation of cellular structures (Spatiocyte), the mesoscopic spatial Gillespie method, and non-spatial methods such as the Gillespie algorithm and an Ordinary Differential Equation solver.
E-Cell rule-based modeling environment is purely implemented on the Python programming language, and

allows seamless bindings between rule-based modeling, network-free simulations, and analyses including third-party Python libraries. Users can easily switch between particle-based and network-based algorithms with almost no change in the script. Moreover, for the whole-cell-scale simulation and high performance computers, the parallelization of these particle methods is under development.
The software is available on GNU/Linux, Mac OSX and Windows 7/8 platforms, and will be distributed under the GNU General Public License (version 3).

Speaker: **Hye-Won Kang** (University of Maryland, Baltimore County, Department of Mathematics and Statistics)
Title: *Multiscale stochastic reaction-diffusion algorithms combining Markov chain models with SPDEs*
Abstract: In this talk, I will introduce a multiscale algorithm for stochastic simulation of reaction-diffusion processes. The algorithm is applicable to systems which include regions with a few molecules and regions with a large number of molecules. A domain of interest is divided into two subsets where continuous-time Markov chain models and stochastic partial differential equations (SPDEs) can be respectively used. Several examples with simulation results will be shown. This is a joint work with Radek Erban at the University of Oxford.

Speaker: **Carlos F. Lopez** (Vanderbilt University School of Medicine, Dept. of Cancer Biolory)
Title: *Use of biological model-programs in PySB to explore and calibrate cell-death decisions.*
Abstract: Programmed necrosis (a.k.a. necroptosis) has recently been discovered as a programmed cell-death alternative to apoptosis. Death receptor mediated signaling can induce either apoptotic or necroptotic cell death, through a complex biochemical network machinery, and thus represents an ideal system to understand molecular mechanisms associated with cell-decision processes. In this work we show how novel mathematical modeling approaches using our PySB language can be used to instantiate multiple mechanistic hypotheses. These can then be calibrated to experimental data, using a Bayesian-inference approach, to explore multiple mechanistic hypotheses about apoptosis or necroptosis outcomes. We test multiple model execution hypotheses and find viable mechanisms that are then validated through experiments. In particular our simulations and analysis suggest that the core decision-making machinery for apoptosis or necroptosis seems to depend on the relative concentrations and interactions among the Rip1, Caspase 8, and Bid proteins rather than a single protein. Our findings underscore the need for systems-level evaluation of multiple mechanisms in molecule-driven cell-decision processes.

Speaker: **Shev MacNamara** (UNSW)
Title: *Diffusion in crowded environments*
Abstract: We study two models of diffusion in crowded environments. Particles follow random walks on a lattice but they cannot move to a place that is already occupied. In both models, mean squared displacement does not scale linearly with time. At the boundary, correlations persist on significant length scales and fluctuations do not follow a simple Gaussian scaling.

Speaker: **Anastasios Matzavinos** (Brown University)
Title: *Dissipative particle dynamics simulations of polymer networks*
Abstract: Networks of entangled or cross-linked polymers, such as the actin cytoskeleton, are ubiquitous in phenomena pertaining to cellular and molecular biology. In many cases, the structure of these networks is dynamically altered by the mechanical feedback of biological lipid membranes and cytoplasmic flows. However, current modeling and computational approaches neglect such mechanical feedbacks for the sake of computational tractability.

In this talk, we present a *dissipative particle dynamics* approach to simulating the meso-scale dynamics of polymer networks. Our simulations explicitly include mechanical interactions with other meso-scale structures (e.g., lipid membranes) and cytoplasmic flows. We compare the results of our approach to those of Brownian dynamics simulations. We also discuss ongoing work on stochastic homogenization, bridging the gap between the meso-scale description and macroscopic models of bulk mechanical properties.

Speaker: **Ava Mauro** (University of Notre Dame)
Title: *A dynamic lattice version of the First-Passage Kinetic Monte Carlo method*
Abstract: In this talk, I will describe a method that we have developed for simulating stochastic reaction-drift-diffusion systems, in which the drift arises from spatially varying potential fields. The method combines elements of the First-Passage Kinetic Monte Carlo (FPKMC) method for simulating stochastic reaction-diffusion systems and the Wang-Peskin-Elston lattice discretization of drift-diffusion. In this combined method, which we call Dynamic Lattice FPKMC, each molecule undergoes a continuous-time random walk on its own lattice, and the lattices change adaptively over time. We have numerically demonstrated the convergence and accuracy of the method, and implemented applications motivated by cell biology.

Speaker: **Jay Newby** (Ohio State University)
Title: *Asymptotic and numerical methods for metastable events in stochastic gene networks.*
Abstract: Stochasticity in gene regulation circuits is known to cause rare extreme shifts in the expression of a gene, which can have a profound effect on the behavior of a cell. This leads to the question of how cells coordinate and regulate different sources of biochemical fluctuations, or noise, to function within a genetic circuit. Rare, noise-induced dynamical shifts in a stochastic process are known as metastable events. For example, Brownian motion in a double well potential, where the fluctuations are weak compared to the force of the potential, displays bistable switching. In general, metastable events occur when fluctuations are weak compared to deterministic forces, and the stochastic process is said to be under weak noise conditions. The challenge for stochastic modeling is to predict and explain the possible metastable behaviors and offer a testable hypothesis by quantifying the timescale on which those events are likely to occur.

Speaker: **Frank Noe** (Free University of Berlin)
Title: *interacting-Particle Reaction-Diffusion (iPRD) dynamics*
Abstract: In cellular signal transduction, what happens where and when? Addressing this question requires to deal with protein interactions that involve low copy numbers, precise stoichiometry, the spatiotemporal arrangement within molecular machines. While modern experimental techniques such as super-resolution microscopy are taking giant leaps towards watching cells in action with molecular resolution, computer simulation is still facing the challenge of combining physical detail with computational efficiency. Here we propose the interacting-Particle Reaction-Diffusion (iPRD) approach. iPRD is a fusion of particle-based reaction-kinetics and molecular dynamics including particle-interactions aiming at simulating cellular signal transduction with rigorous physical approach. I will present the theory and methodology, briefly sketch our ReaDDy implementation of iPRD and hint to some biological applications.

Speaker: **Thorsten Prüstel** (Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health)
Title: *Novel analytical results for diffusion-influenced receptor-ligand reactions in two dimensions*
Abstract: To provide the mathematical basis for a better understanding of the influence of stochastic fluctuations and spatial heterogeneities on cell membrane processes such as receptor clustering, we study Green's function (GF) solutions of the Smoluchowski equation in two space dimensions (2D). However, the corresponding expressions typically take a mathematically more complicated form than in 3D. As a consequence, their potential advantage in accelerating spatially resolved stochastic simulation algorithms may be more than offset by the cost to evaluate them numerically. To address this problem, we calculate approximate expansions for the key expressions, thereby circumventing the need for an inefficient numerical integration. The obtained expressions should prove useful for any simulation algorithm employing 2D GF. Building on our work on the 2D GFs, we also explored the general theory of the area reactivity model that describes the diffusion-influenced reaction of a receptor-ligand pair in terms of a generalized Feynman-Kac equation and that provides an alternative to the classical (Smoluchowski) contact reactivity model. Our work leads us to suggest that the usual definition of the time-dependent rate coefficient as the reactive flux at the encounter distance is deficient in the area reactivity model and we provide an alternative definition

that behaves significantly different from its classical counterpart. The resulting characterization of area reactivity parameters not only has a straightforward intuitive physical interpretation but is, moreover, excellently confirmed by numerical tests through Brownian Dynamics simulations.

Speaker: **Mauricio J. Del Razo** (Department of Applied Mathematics, University of Washington)
Title: *A discrete stochastic model for reversible diffusion-controlled reactions*
Abstract: The classical models for irreversible diffusion-controlled reactions can be derived by introducing absorbing boundary conditions to over-damped continuous standard Brownian Motion (BM) theory. As there is a clear corresponding stochastic process, we can describe them by the duality between the Kolmogorov forward equation for the dynamics of the probability distribution function and the specific stochastic trajectory of one particle. This duality is a fundamental characteristic of stochastic processes and allows simple particle based simulations to accurately match the expected statistical behavior. However, when introducing complicated boundary conditions to model reversible reactions with geminate recombinations several subtleties arise: it is unclear what the underlying stochastic process is, it becomes complicated to produce accurate simulations and it is not trivial how to perform an appropriate discretization. In this work, we derive a discrete stochastic model for reversible reactions that recovers the classical models and their boundary conditions in the continuous limit. Furthermore, all the complications encountered in the continuous models become trivial, raising the question: what model should be considered more fundamental?

Speaker: **Kevin Sanft** (University of Minnesota)
Title: *Scaling properties of exact simulation algorithms for spatially discretized stochastic reaction-diffusion processes*
Abstract: Stochastic reaction-diffusion processes are widely used to model biochemical systems. Discretizing the spatial domain leads to a discrete state, continuous time Markov jump process that can be described by the reaction-diffusion master equation. Solutions to the master equation are approximated by generating exact trajectories using variants of the Gillespie algorithm. The choice of simulation formulation and underlying data structures has a dramatic effect on computational efficiency. In this talk, I will show how the optimal algorithm choice depends on the number and relative timescales of the transition channels. For very large problems, memory hierarchy effects lead to scaling properties that differ from the asymptotic analysis, which influences the optimal simulation algorithm parameters.

Speaker: **Erik De Schutter** (Okinawa Institute of Science and Technology, Japan)
Title: *Parallelization of the spatial SSA on unstructured meshes*
Abstract: A lot of progress has been made in recent years in the field of parellelization of RDME-based methods, yet there are some unique challenges for simulators based on unstructured meshes such as STEPS [1] and URDME [2], and finding the best solution for different biological systems is an on going area of exploration.

Parallelization of exact solutions suffer from a large number of conflicts between nodes, causing many costly rollbacks and limiting the performance gain to typically less than one order of magnitude, which peaks with only a small number of cores. This has been demonstrated in previous work such as [3] and [4] and confirmed in our own tests. Further, we find that the amount of rollbacks highly depends on the loading balance of the system and therefore this approach performs badly when significant concentration gradients exist.

This has called for operator-split methods with an approximation to diffusion that involves global execution of diffusion events at predetermined times, and was first applied for regular grids such as by the Gillespie-Multi-Particle method (GMP) [5]. Even serial implementations of GMP show a performance gain compared to exact solutions, and 2 orders of magnitude gain has been demonstrated in a GPU implementation in a simple test system [6]. Therefore, operator-splitting methods are expected to provide the best parallel solution for a wide range of simulation conditions.

Multinomial direction selection, an idea first introduced by Lampoudi et al [7], shows some performance gain in our implementation compared to uniform random distribution, but depends strongly on the number of diffusing molecules. This suggest the best approach will be to introduce an adaptive algorithm that can switch between solutions depending on simulation conditions.

Our proposed solution draws on many of these ideas, making several adaptations to simulation conditions, and is uniquely tailored for tetrahedral meshes where probability of leap varies locally. As such, our solution has similarities to the MPD-RDME method discussed in [8], but with time-steps adaptive to the upper-limit in the most spatially-resolved region.

I will show our initial error analysis with application to our typical reaction-diffusion validation tests. In the literature, many interesting test systems with different dimensionalities (commonly 1D or 2D) are studied and errors sometimes quantified, yet the field would benefit from a standardization of this process especially for 3D.

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Speaker: **Vahid Shahrezaei** (Imperial College London)
Title: *When we need particle-based reaction-diffusion simulations and when we don't*
Abstract: In this talk, I first give some less known examples of where a particle-based simulation can be useful. Then, I introduce a two-step ODE model that can reproduce some non-trivial results that rely on spatio-temporal correlations that can be simulated using particle-based simulation approaches. These include examples from kinetics of proteins with multiple phosphorylation sites.

Speaker: **Thomas R. Sokolowski** (IST Austria, Klosterneuburg, Austria)
Title: *eGFRD in all dimensions*
Abstract: eGFRD (enhanced Green's Function Reaction Dynamics) is an event-driven, particle-based biochemical simulation scheme that draws its power from using analytical solutions (Green's functions) to predict next-event times and future particle positions. Thanks to its analytical foundation, it is both exact and orders of magnitude more efficient than regular Brownian Dynamics schemes. So far, eGFRD has been limited to simulations of particle diffusion and reactions in unbounded (periodic) 3D space. Here we present our recent work that extends eGFRD to comprise transport and particle reactions on and between finite surfaces in 1D and 2D. Specifically, we implement binding of particles to planar and cylindrical surfaces, diffusion and 1D active transport on these surfaces, and transfers between surfaces of equal and different type. To retain the efficiency and exactness of the scheme, we provide the required analytical solutions for the Green's functions describing these scenarios. The extended functionality is assembled into a versatile and user-friendly simulation framework, which we use to study several example systems featuring transport on lower dimension manifolds and particle interactions across different dimensions.

Speaker: **Peter Thomas** (Case Western University)

Title: *Stochastic Shielding: a Novel Approach to Simplifying Random Processes on Graphs*
Abstract: Mathematical models of cellular physiological mechanisms often involve random walks on graphs representing transitions within networks of functional states. Schmandt and Galn [1] recently introduced a novel stochastic shielding approximation as a fast, accurate method for generating approximate sample paths from a finite state Markov process in which only a subset of states are observable. For example, in ion channel models, such as the Hodgkin-Huxley or other conductance based neural models, a nerve cell has a population of ion channels whose states comprise the nodes of a graph, only some of which allow a transmembrane current to pass. The stochastic shielding approximation consists of neglecting fluctuations in the dynamics associated with edges in the graph not directly affecting the observable states. In [2], we considered the problem of finding the optimal complexity reducing mapping from a stochastic process on a graph to an approximate process on a smaller sample space, as determined by the choice of a particular linear measurement functional on the graph. The partitioning of ion channel states into conducting versus nonconducting states provides a case in point. In addition to establishing that Schmandt and Galn's approximation is in fact optimal in a specific sense, we use recent results from random matrix theory to provide heuristic error estimates for the accuracy of the stochastic shielding approximation for an ensemble of random graphs. Moreover, we provide a novel quantitative measure of the contribution of individual transitions within the reaction graph to the accuracy of the approximate process. (Joint work with Deena Schmidt, Case Western Reserve University.)

References:

[1] N. Schmandt and R. Galn, Phys. Rev. Letters. (2012), [2] D. Schmidt and P. Thomas, J. Math. Neurosci. (2014)

Speaker: **Christian Yates** (University of Bath)
Title: *A PDE/compartment-based hybrid method for simulating stochastic reaction-diffusion systems*
Abstract: Spatial reaction-diffusion models have been employed to describe many emergent phenomena in biological systems. The modelling technique for reaction-diffusion systems that has predominated due to its analytical tractability and ease of simulation has been the use of partial differential equations (PDEs). However, due to recent advances in computational power, the simulation, and therefore postulation, of computationally intensive individual-based models has become a popular way to investigate the effects of noise in reaction-diffusion systems.

The specific stochastic model with which we shall concern ourselves are known as 'compartment-based'. These models are characterised by a discretisation of the computational domain into a grid/lattice of discrete voxels between which molecules can jump. Molecules are considered to be well-mixed in each one of these voxels and can react stochastically with other molecules in their voxel with prescribed rates.

In a wide variety of biological situations, stochasticity due to low copy numbers is relevant only in particular regions of the domain. In other regions, copy numbers are sufficiently high that mean field models suffice to capture the important dynamics. Such conditions necessitate the development of hybrid models in which some areas of the domain are modelled using a continuum representation and others using an individual-based representation.

In this talk we develop hybrid algorithms which couple a PDE in one region of the domain to a compartment-based model in the other. Rather than balancing flux at the interface, we use a method which is similar to the ghost-cell method. Characteristic of this method is the individual treatment of particles as they cross the interface. A small region of the PDE domain adjacent to the compartment-based region is allowed to contribute particles to the compartment-based regime. When particles cross over the interface into this pseudo-compartment from the compartment-based regime a step-function with the mass of a single particle is added. We test our hybrid method in a variety of different scenarios and analyse the error introduced in each case.