MULTISCALE SIMULATION ALGORITHMS FOR BIOCHEMICAL SYSTEMS

FINAL PROGRESS REPORT

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1 Statement of the problem studied

Biochemical systems are inherently multiscale and stochastic. In microscopic systems formed by living cells, the small numbers of reactant molecules can result in dynamical behavior that is discrete and stochastic rather than continuous and deterministic. An analysis tool that respects these dynamical characteristics is the stochastic simulation algorithm (SSA, Gillespie, 1976), a numerical simulation procedure that is essentially exact for chemical systems that are spatially homogeneous or well stirred. Despite recent improvements, as a procedure that simulates *every* reaction event, the SSA is necessarily inefficient for most realistic problems. There are two main reasons for this, both arising from the multiscale nature of the underlying problem: (1) *stiffness*, i.e. the presence of multiple timescales, the fastest of which are stable; and (2) the need to include in the simulation both species that are present in relatively small quantities and should be modeled by a discrete stochastic process, and species that are present in larger quantities and are more efficiently modeled by a deterministic differential equation (or at some scale in between).

This project has focused on the development of fast and adaptive algorithms, and the fundamental theory upon which they must be based, for the multiscale simulation of biochemical systems. Areas addressed by this project include: (1) Theoretical and practical foundations for accelerated discrete stochastic simulation (tau-leaping); (2) Dealing with stiffness (fast reactions) in an efficient and well-justified manner in discrete stochastic simulation; (3) Development of adaptive multiscale algorithms for spatially homogeneous discrete stochastic simulation; (4) Development of high-performance SSA algorithms.

2 Summary of results

This project produced 29 papers [7, 12, 18, 11, 17, 16, 14, 15, 5, 28, 2, 1, 8, 10, 3, 24, 27, 26, 13, 22, 19, 21, 4, 20, 6, 23, 25, 9], more than 80 invited presentations, and contributed to the support of 2 postdocs and 5 Ph.D. students. Four Ph.D. students completed their degrees, and the fifth is expected to finish this academic year. The PI was elected to the National Academy of Engineering, and to Fellow of: AAAS, SIAM, ASME and ACM.

New, faster formulations of the SSA were introduced, including formulations specifically adapted to the NVIVIA general-purpose graphics processing unit (GPGPU) which achieved very substantial speedups. A theoretical foundation was developed for tau-leaping methods, along with algorithms for selecting the stepsize, maintaining non-negativity, and automatically selecting between explicit tau-leaping, implicit tau-leaping and SSA during the course of a simulation. Multiscale algorithms including slow-scale SSA and slow-scale tau-leaping were introduced, that are highly effective in dealing with stiffness. Software packages StochKit and StochKit 2 were developed and released to the community. Since releasing the Beta version of StochKit2 in March 2010, it has been downloaded more than 1770 times, and cited at least 70 times.

New algorithms were developed for spatial stochastic simulation of reaction-diffusion problems, and for efficient computation of the properties of rare events. Preliminary results in these areas have been very promising.

3 Description of Results

SSA is the workhorse algorithm for stochastic simulation in systems biology, and it will be the core of any multiscale approach. Thus it is important that it is as fast as possible. Petzold, Cao and Li [7] developed a formulation of SSA which is both faster and simpler than the previous version. Li

and Petzold [23] demonstrated that SSA is well-suited to the architecture of the NVIDIA GPGPU (general-purpose graphics processing unit), obtaining speedups of up to 150 times over the host workstation. Li, Kolpas, Petzold and Moehlis [22] showed how to make efficient use of the NVIDIA GPGPU for the simulation of fish school models.

To speed up the SSA by orders of magnitude, one must give up on the exactness. One possibility for this is tau-leaping, originally developed by Gillespie. Rather than stepping to the next reaction as in SSA, tau-leaping can skip over potentially many reactions at a time. As originally proposed, however, it had no theoretical justification, and many critical practical details remained to be addressed. Petzold, Rathinam, Cao and Gillespie [10, 24] developed the underlying theory for tau-leaping, and led the way to adaptive stepsize selection [5, 2, 6], implicit tau-leaping methods for dealing with stiffness, [25] and a fully-adaptive tau-leaping method which selects between explicit tau-leaping, implicit tau-leaping and SSA during the course of the problem [6].

Petzold, Cao and Gillespie developed a method called slow-scale SSA (ssSSA) [4, 3], for simulation of multiscale discrete stochastic systems, particularly in the situation where there are fast reactions with one or more constituent species that are present in very small population, where tau-leaping is not appropriate. The ssSSA method can be orders of magnitude faster than SSA for many biochemical simulations. In [1] they showed how and when the theory behind ssSSA can be used to justify a Michaelis-Menton type approximation for enzyme substrate reactions in the context of discrete stochastic simulation. Cao and Petzold [9] developed a slow-scale tau-leaping method that uses SSA to advance the slow reactions while taking the fast reactions to a stochastic partial equilibrium. This algorithm also introduces an adaptive algorithm for identifying fast reactions that are in stochastic partial equilibrium. Gillespie, Cao, Sanft and Petzold [29, 13] developed a novel criterion for deciding whether a Michaelis-Menten-type model reduction can be accurately accomplished in the context of stochastic simulation.

A software package called StochKit has been developed for multiscale discrete stochastic simulation of biochemical systems. StochKit is available at http://www.cs.ucsb.edu/~cse, and features state of the art software for multiscale discrete stochastic simulation, along with some analysis tools [8] for biochemical simulation. During the grant period, the Petzold research group did a complete rewrite of StochKit, enabling much greater extensibility for new algorithms, the incorporation of discrete events, and more efficient use of high performance computing. StochKit 2 is available via SourceForge.net.

Modeling of some biochemical systems requires a capability for spatial stochastic simulation. Diffusive transport presents the biggest challenge; at the length scale of a cell, diffusion is a very fast process, with communication among computer processors a bottleneck in the simulation. In [20], Lampoudi, Gillespie and Petzold introduced the multinomial simulation algorithm (MSA) to overcome this problem. The MSA uses appropriately conditioned binomial random variables for representing the net flux of molecules diffusing from any given subvolume to a neighbor. Drawert, Lawson, Petzold and Khammash proposed a different and even more efficient method, Diffusive Finite State Projection (DFSP) [12], which combines SSA for reactions with a local Finite State Projection to approximate the net diffusive transfers. DFSP has been quite effective, and is now providing the computational backbone for several modeling projects in the Petzold research group.

The complications of spatial stochastic simulation extend beyond computational complexity, to fundamental physical, biological and mathematical processes. A cell is a crowded molecular environment, whereas the SSA was derived under the assumption of an uncrowded environment. In [14], Petzold, Lampoudi and Gillespie showed, in one dimension, via theory and numerical experiments, how the propensity functions (rates) of biomolecular chemical reactions change when the volume occupied by the reactant molecules is not negligible compared to the volume of the system. Petzold, Lampoudi and Gillespie showed [19], via numerical experiments in two dimensions,

how the propensity functions and rates of biomolecular chemical reactions change when the volume occupied by the reactant molecules is not negligible compared to the volume of the system.

SSA is not effective for finding the probabilities of rare events. Because the events are rare, a great many SSA simulations must be done just to get them to occur. The estimation of their probability requires many such simulations where the rare events occur. Gillespie, Roh and Petzold [27] developed a refinement of a new algorithm called the weighted SSA (wSSA) which uses importance sampling to bias the simulation, to assess the accuracy of the estimated probability.

4 List of Invited Presentations

1. January 2012 Algorithms and Software for Discrete Stochastic Simulation of Biochemical Systems Southern California Systems Biology Conference, UC Irvine

2. June 2012 Spatial Stochastic Amplification in Cell Polarization Workshop on Scale Transitions in Chemistry and Biology, International Centre for Mathematical Sciences, Edinburgh

3. June 2012 Spatial Stochastic Amplification in Cell Polarization Eighth Conference of East Asia Section of SIAM (Keynote), Taipei

4. July 2012 Spatial Stochastic Amplification in Cell Polarization Workshop on Stochastic Modeling of Reaction-Diffusion Processes in Biology, Oxford

5. March 2011 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems SIMUtools 2011, Barcelona, Spain (plenary lecture)

6. April 2011 Spatial Stochastic Simulation of Polarization in Yeast Mating University of Illinois, Department of Computer Science, Distinguished Lecturer Series

7. April 2011 Spatial Stochastic Simulation of Polarization in Yeast Mating Georgia Institute of Technology, College of Computing, Distinguished Lecturer Series

8. May 2011 Spatial Stochastic Simulation of Polarization in Yeast Mating Massachusetts Institute of Technology, Applied Mathematics Seminar

9. June 2011 Spatial Stochastic Simulation of Polarization in Yeast Mating University of California Irvine, Center for Complex Biological Systems Seminar

10. July 2011 Spatial Stochastic Simulation of Polarization in Yeast Mating SciCADE 2011, Scientific Computing and Differential Equations, Toronto

11. July 2011 Spatial Stochastic Amplification in Cell Polarization Conference on Stochastic Systems Biology, Monte Verita, Switzerland

12. September 2011 Spatial Stochastic Amplification in Cell Polarization 9th International Conference of Numerical Analysis and Applied Mathematics, Greece

13. October 2011 Multiscale Simulation Algorithms for Biochemical Systems DOE ASCR Applied Mathematics PI meeting, Washington DC

14. October 2011 Stochasticity in Circadian Clocks Workshop on Stochastic Processes in Cell and Population Biology, Mathematical Biosciences Institute, Ohio State Univ.

15. November 2011 Stochasticity in Circadian Clocks Pomona College, Dept. of Mathematics Colloquium

16. December 2011 Computational Simulation of Multiscale Systems Council of Scientific Societies Presidents Lecture, Washington DC

17. July 2010 Model Reduction for Chemical Reaction Networks: It's a Subtle Business! SIAM Conf. on Life Sciences, Minisymposium on Computational Methods for Biochemical Systems, Pittsburgh

18. July 2010 Computational Tools and Training for Quantitative Biology Panelist, Lee Segel Forum, SIAM Conf. on Life Sciences, Pittsburgh

19. November 2010 Spatial Stochastic Simulation of Polarization in Yeast Mating Pacific Institute of Mathematical Sciences (PIMS), Univ. of British Columbia, Vancouver

20. January 2009 Multiscale Simulation of Biochemical Systems Louisiana State University, Center for Computation and Technology, IT Eminent Lecture Series

21. February 2009 Multiscale Simulation of Biochemical Systems Florida A&M University, Tallahasee, Florida

22. March 2009 Multiscale Simulation of Biochemical Systems PIMS/CSC Distinguished Lecture Series, Simon Fraser University, Vancouver, Canada

23. May 2009 Multiscale Simulation of Biochemical Systems Laurier Seminar Series in Computational Science and Applied & Statistical Modelling, Wilfrid Laurier University, Waterloo, Canada

24. July 2009 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems PRIMA (Pacific Rim Mathematical Association) Congress, Sydney, Australia

25. August 2009 Model Reduction for Chemical Reaction Networks: It's a Subtle Business! Q-Bio Conference on Cellular Information Process, Santa Fe, New Mexico

26. September 2009 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems Mathematical Biosciences Institute seminar, Ohio State University, Columbus, Ohio

27. September 2009 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems International Conference on Numerical Analysis and Applied Mathematics (ICNAAM 2009), Crete, Greece

28. October 2009 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems University of Toronto, Department of Computer Science Distinguished Lecturer Series

29. November 2009 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems Oak Ridge National Laboratory, Center for Nanophase Materials Sciences, Discovery Lecture

30. January 2010 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems UCSB Probability and Statistics Department Seminar

31. March 2010 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems Los Alamos National Laboratory, New Mexico

32. March 2010 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems New Mexico Center for the Spatiotemporal Modeling of Cell Signalling, University of New Mexico

33. April 2010 Multiscale Simulation of Biochemical Systems UCSB Department of Mathematics Hypatian Seminar,

34. May 2010 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems Caltech, Applied and Computational Mathematics Colloquium, Pasadena

35. June 2010 Discrete Stochastic Simulation of Spatially Inhomogeneous Biochemical Systems NASA JPL Seminar, Pasadena

36. Logarithmic Direct Method for Discrete Stochastic Simulation of Chemically Reacting Systems, H. Li and L. Petzold, submitted to J. Chem. Phys., 2006.

37. July 2007 Multiscale Simulation of Biochemical Systems SCICADE07, Scientific Computing and Differential Equations, St. Malo, France

38. July 2007 Multiscale Simulation of Biochemical Systems Applied Mathematical Sciences Summer Institute, Loyola Marymount University, Los Angeles

39. September 2007 Multiscale Simulation of Biochemical Systems University of Illinois (UIUC) Dept. of Chemical and Biochemical Engineering Colloquium

40. October 2007 Discrete Stochastic Simulation for Biochemical Systems State of the Art International Conference on Systems Biology (ICSB), Long Beach

41. December 2007 Multiscale Discrete Stochastic Simulation of Biochemical Systems University of Tokyo, Workshop on Research and Development in Simulation-Based Engineering and Science

42. January 2008 Multiscale Simulation of Biochemical Systems Jackson State University February 2008 Multiscale Simulation of Biochemical Systems ANZIAM 2008 Applied Mathematics Conference (AMSI lecturer), Katoomba, Australia

43. April 2008 Multiscale Simulation of Biochemical Systems University of Minnesota, Science and Technology Innovators Lecture

44. April 2008 Multiscale Simulation of Biochemical Systems University of Illinois UIUC, Computational Science and Engineering Annual Research Symposium

45. April 2008 Multiscale Simulation of Biochemical Systems Rensselaer Polytechnic Institute, Department of Mathematics Richard C. DiPrima Lecture

46. May 2008 Stiffness in the Discrete Stochastic Simulation of Biochemical Systems Helsinki University of Technology, Perspectives on Numerical Analysis Conference, Finland

47. May 2008 Multiscale Simulation of Biochemical Systems Uppsala University, Sweden

48. July 2008 Multiscale Simulation Methods for BioChemical Networks Gordon Research Conference, Theoretical Biology and Biomathematics, Il Ciocco, Italy

49. July 2008 Multiscale Simulation of Biochemical Systems CSIRO Workshop, Canberra, Australia

50. July 2008 Multiscale Simulation of Biochemical Systems Mathematics Dept. Colloquium, LaTrobe University, Melbourne, Australia

51. July 2008 Multiscale Simulation of Biochemical Systems Mathematics Dept. Colloquium, Charles Sturt University, Wagga Wagga, Australia

52. October 2008 Multiscale Simulation of Biochemical Systems Lawrence Livermore National Laboratory, Institute for Terascale Simulation Lecture Series

53. Computational Tools for Systems Biology, Arizona State University, Department of Computer Science and Engineering, Distinguished Lecture, May 2006

54. Computational Tools for Systems Biology, Cornell Workshop Stochastic Models in Cell Biology, April 2006

55. Computational Tools for Systems Biology, Caltech Beckman Institute Biological Network Modeling Center, March 2006

56. Simulation and Sensitivity Analysis for Time Dependent Systems, UCSB Mathematical Ecology Seminar, March 2006

57. Multiscale Simulation of Biochemical Systems, University of Pennsylvania, Applied Mathematics Colloquium, February 2006

58. Multiscale Simulation of Biochemical Systems, Cornell University, Dept. of Computer Science, January 2006

59. Bridging the Scales in Biochemical Simulation, Amgen, Thousand Oaks, December 2005.

60. Bridging the Scales in Biochemical Simulation, Caltech, Dept. of Mechanical Engineering, November 2005.

61. Bridging the Scales in Biochemical Simulation, Pomona College/Claremont Graduate University, Department of Mathematics, November 2005.

62. Bridging the Scales in Biochemical Simulation, Cal Poly San Luis Obispo, November 2005.

63. Bridging the Scales in Biochemical Simulation, Oak Ridge National Laboratory, Distinguished Lecture Series, Oak Ridge, November 2005.

64. Bridging the Scales in Biochemical Simulation, University of Tennessee, Distinguished Lecture Series, Knoxville, November 2005.

65. Bridging the Scales in Biochemical Simulation, Harvey Mudd College Mathematics Conference, Claremont, November 2005.

66. Bridging the Scales in Biochemical Simulation, Norwegian University of Science and Technology, Trondheim, October 2005.

67. Bridging the Scales in Biochemical Simulation, 4th Workshop on Computation of Biochemical Pathways and Genetic Networks, EML Research GMBH, Heidelberg, September 2005.

68. Bridging the Scales in Biochemical Simulation, Indian Institute of Technology Bombay, Institute Colloquium, July 2005.

69. Bridging the Scales in Biochemical Simulation, Indian Institute of Science, Bangalore, Mathematics Conference, July 2005.

70. Bridging the Scales in Biochemical Simulation, Workshop on Stochastic Models in Molecular and Systems Biology, UCSB, June 26, 2005.

71. Multiscale Stochastic Simulation Algorithm with Stochastic Partial Equilibrium Assumption for Chemically Reacting Systems, SciCADE05, International Conference on Scientific Computation and Differential Equations, Minisymposium on Stochastic Systems, Nagoya, May 24, 2005.

72. Bridging the Scales in Biochemical Simulation, Workshop on Integrative Multiscale Modeling and Simulation in Materials Science, Fluids and Environmental Science, CRM, University of Montreal, May 12, 2005.

73. Bridging the Scales in Biochemical Simulation, Virginia Tech, Interdisciplinary Center for Applied Mathematics, April 11, 2005.

74. Bridging the Scales in Biochemical Simulation, SIAM Computational Science and Engineering Meeting, plenary lecture, Feb. 12, 2005

75. Multiscale Simulation of Biochemical Networks, Stanford National Center for Biological Computing, Feb. 3, 2005

76. Multiscale Stochastic Simulation Algorithm with Stochastic Partial Equilibrium Assumption for Chemically Reacting Systems, IMA Workshop Future Challenges in Multiscale Modeling and Simulation, University of Minnesota, Minneapolis, Nov. 20, 2004.

77. Multiscale Simulation of Biochemical Networks, Department of Mechanical and Environmental Engineering Seminar, UCSB, October 25, 2004.

78. Multiscale Stochastic Simulation Algorithm with Stochastic Partial Equilibrium Assumption for Chemically Reacting Systems, Joining Forces Workshop: Intersections between Biology, Chemistry, Engineering, Informatics and Physics, ETH Zurich, Switzerland, October 14, 2004.

79. Multiscale Simulation of Biochemical Networks, Tutorial Lecture, International Conference on Systems Biology, Heidelberg, Germany, October 9, 2004.

80. Poster, International Conference on Systems Biology, Heidelberg, Germany: Stochastic Sensitivity Analysis of a Circadian Gene Network, Rudiyanto Gunawan, Yang Cao, Sotiria Lampoudi, Linda Petzold, Frank Doyle

81. Poster, International Conference on Systems Biology, Heidelberg, Germany: Efficient Formulation of the Stochastic Simulation Algorithm for Chemically Reacting Systems, Yang Cao, Hong Li, Linda Petzold

82. Poster, International Conference on Systems Biology, Heidelberg, Germany: The Heat Shock Response: Optimization Solved by Evolution? Hana El-Samad, Chris Homescu, Mustafa Khammash, Linda Petzold

83. Multiscale Simulation of Biochemical Networks, International Workshop on Complex Stochastic Systems in Biology and Medicine, LMU, Munich, Germany, October 8, 2004.

5 List of all participating scientific personnel

The personnel participating in this project were: PI: Linda Petzold, Consultant: Daniel Gillespie, Postdoctoral Research Associates: Yang Cao, Kathleen Puskar; Graduate Research Assistants: Hong Li, Marc Griesemer, Min Roh, Sotiria Lampoudi, Kevin Sanft

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