Stochastic Simulation of Reaction-Diffusion Systems: A Fluctuating-Hydrodynamics Approach

Andy Nonaka – Lawrence Berkeley National Laboratory

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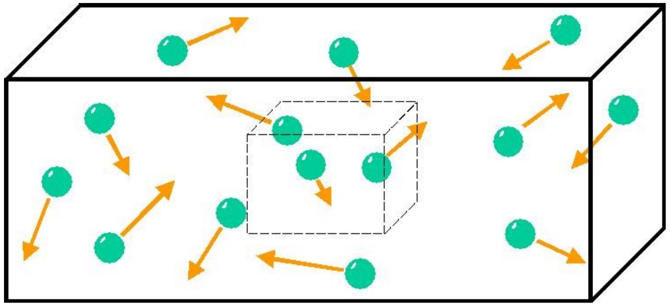
Collaborators

- Lawrence Berkeley National Laboratory
  - **Changho Kim**
  - John Bell
- San Jose State University
  - Alejandro Garcia
- Courant Institute
  - Aleksandar Donev

Introduction

- We are interested in numerical simulation of stochastic reaction-diffusion systems
- Thermal fluctuations drive movement and collision of individual molecules



- Applications include:
  - Front propagation acceleration and/or directional changes
  - Pattern formation – transient and steady state
  - Fluctuation-induced instabilities
  - Cell biology / cellular function

Introduction

- We seek a seamless approach that is efficient and accurate:
  - Our primary interest is for weak fluctuations (macroscopic scales and/or large particle count).
  - Also of concern are strong fluctuations (mesoscopic scales and/or small particle count)

- Particularly useful when populations of chemical species have different orders of magnitude, including dilute solvent-solute models.

- We use techniques developed independently for stochastic reactions and stochastic diffusion, and create new temporal integrators that combine these techniques

Reactions

- Three classes of algorithms developed for single-cell stochastic chemistry for solving the Chemical Master Equation (CME).
  - Stochastic Simulation Algorithm (SSA): track each individual reaction event sequentially by repeatedly drawing from exponential random variables.
    - Exact sampling of CME, but prohibitively expensive for many zones and large particle counts
  - Chemical Langevin Equation (CLE): augment the reaction rates with Gaussian random noise.
    - Very efficient, but fails to produces results predicted by statistical mechanics.
  - Tau Leaping: track the total number of events over a time step by drawing from a Poisson random variable
    - Efficient and accurate, as long as the chemistry is not too stiff

Diffusion

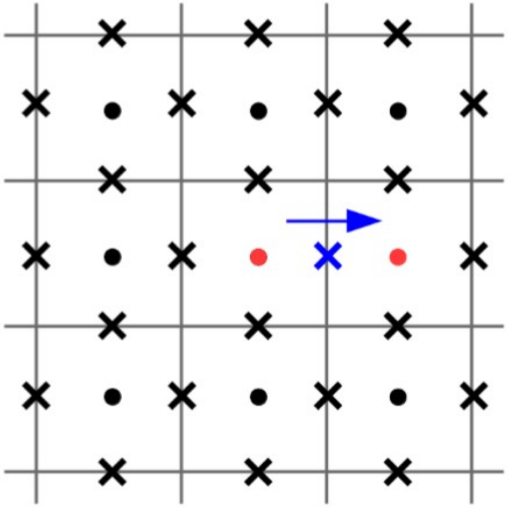
- Three classes of algorithms developed for stochastic diffusion:
  - SSA: track each individual intercell "hop" sequentially by repeatedly drawing from exponential random variables.
    - Exact sampling, but prohibitively expensive for many zones and large particle counts
  - Multinomial: track the total number of hops over a time step by drawing from a Poisson random variable
    - Efficient, accurate, but limited by explicit diffusion time step
  - Fluctuating Hydrodynamics (FHD): augment diffusive fluxes with Gaussian noise using the Landau/Lifshitz formalism
    - Efficient, accurate, and allows for both explicit and implicit temporal discretization for very large time steps

“Best of Both Worlds” Approach

- Finite volume formulation.
  - Number densities expressed as averages over Cartesian grid cells
- Fluctuating Hydrodynamics diffusion approach.
  - Diffusive fluxes augmented by Gaussian White Noise, using the Landau/Lifshitz formalism
  - Implicit diffusion treatment that can greatly exceed time step for hopping and other explicit treatments
- Reactions treated as a Poisson process, 2 choices:
  - Tau-leaping (primary option)
  - SSA also an option if chemistry is stiff.
- We develop unsplit temporal integrators that are second-order in the deterministic limit, and capture the correct spectrum of equilibrium fluctuations

Spatial Discretization

- Finite volume approach
- Number densities, n_s (for species “s”) are cell-averaged.



- Diffusive and stochastic fluxes are face-averaged.

Diffusion Model

- We can express the stochastic diffusion-only system as a system of stochastic ODEs for the number density in each cell:

diffusion coefficients

Spatio-temporal Gaussian white noise

$$\frac{\partial n_s}{\partial t} = \nabla \cdot \left(D_s \nabla n_s + \sqrt{2 D_s n_s}\, \boldsymbol{\mathcal{Z}}_s^{(\mathrm{D})} \right)$$

- When discretized in space and time one possible scheme (forward Euler) is

face-averaged Gaussian white noise

$$n_s^{k+1} - n_s^k = \Delta t D_s \nabla_{\mathrm{d}}^2 n_s^k + \sqrt{\frac{2 D_s \Delta t}{\Delta V}}\, \nabla_{\mathrm{d}} \cdot \left(\sqrt{\tilde{n}_s^k}\, \boldsymbol{W}_s^k \right)$$

discrete Laplacian (and divergence)

cell volume

face-averaged number densities

Reaction Model

- Chemical Langevin equation (CLE) for stochastic reactions:

$$\frac{dn_s}{dt} = \sum_{r=1}^{N_r} \nu_{sr} \left(a_r(\boldsymbol{n}) + \sqrt{a_r(\boldsymbol{n})}\,\mathcal{Z}_r^{(\mathrm{R})} \right)$$

stoichiometric coefficient

propensity function (reaction rate)

Gaussian white noise

- We have previously shown that describing reactions as a Markov jump process (Poisson noise) is consistent with equilibrium statistical mechanics.

(tau leaping)

$$\frac{dn_s}{dt} = \sum_{r=1}^{N_r} \frac{\nu_{sr}\mathcal{P}(a_r(\boldsymbol{n})\Delta V\,dt)}{\Delta V\,dt}$$

Poisson random variable

- We also have an option to use SSA: $\frac{dn_s}{dt} = \frac{\mathfrak{R}_s(\boldsymbol{n}, dt)}{dt}$

Temporal Discretization

- Putting diffusion and reactions together, we have developed a 2-stage, implicit, tau-leaping scheme that is second-order deterministically, and produces third-order structure factors. (ImMidTau)

$$
\begin{aligned}
n_s^\star &= n_s^k + \frac{D_s \Delta t}{2} \nabla_{\mathrm{d}}^2 n_s^\star + \sqrt{\frac{D_s \Delta t}{\Delta V}} \nabla_{\mathrm{d}} \cdot \left(\sqrt{\tilde{n}_s^k} \boldsymbol{W}_s^{(1)} \right) + \sum_{r=1}^{N_{\mathrm{r}}} \frac{\nu_{sr} \mathcal{P}^{(1)}(a_r^k \Delta V \Delta t/2)}{\Delta V}, \\
n_s^{k+1} &= n_s^k + D_s \Delta t \nabla_{\mathrm{d}}^2 \left(\frac{n_s^k + n_s^{k+1}}{2} \right) \\
&\quad + \sqrt{\frac{D_s \Delta t}{\Delta V}} \nabla_{\mathrm{d}} \cdot \left(\sqrt{\tilde{n}_s^k} \boldsymbol{W}_s^{(1)} \right) + \sqrt{\frac{D_s \Delta t}{\Delta V}} \nabla_{\mathrm{d}} \cdot \left(\sqrt{\tilde{n}((2n_s^\star - n_s^k)^+)} \boldsymbol{W}_s^{(2)} \right) \\
&\quad + \sum_{r=1}^{N_{\mathrm{r}}} \frac{\nu_{sr} \mathcal{P}^{(1)}(a_r^k \Delta V \Delta t/2)}{\Delta V} + \sum_{r=1}^{N_{\mathrm{r}}} \frac{\nu_{sr} \mathcal{P}^{(2)}((2a_r^\star - a_r^k)^+ \Delta V \Delta t/2)}{\Delta V}
\end{aligned}
$$

- We also have a stiff chemistry integrator that uses SSA (ImMidSSA)

Structure Factor for Model Equations

- The static structure factor quantifies the spectrum of fluctuations at equilibrium. For a single-species model:

$$S(\boldsymbol{k}) = \langle (\delta\hat{n}_{\boldsymbol{k}})(\delta\hat{n}^*_{\boldsymbol{k}}) \rangle \,, \quad \delta\hat{n}_{\boldsymbol{k}} = \mathcal{F}(n - \bar{n})$$

- We take the Fourier transform of the linearized reaction-diffusion equations:

$$\frac{d}{dt}\delta\hat{n}_{\boldsymbol{k}} = -Dk^2\delta\hat{n}_{\boldsymbol{k}} + \sqrt{2D\bar{n}}\, i\boldsymbol{k}\cdot\hat{\boldsymbol{\mathcal{Z}}}^{(\mathrm{D})}_{\boldsymbol{k}} - r\delta\hat{n}_{\boldsymbol{k}} + \sqrt{2\bar{\Gamma}}\,\hat{\mathcal{Z}}^{(\mathrm{R})}_{\boldsymbol{k}}$$

$$r = -a'(\bar{n}), \quad \bar{\Gamma} = \frac{1}{2}\sum_{r=1}^{N_r} \nu_r^2 a_r(n)$$

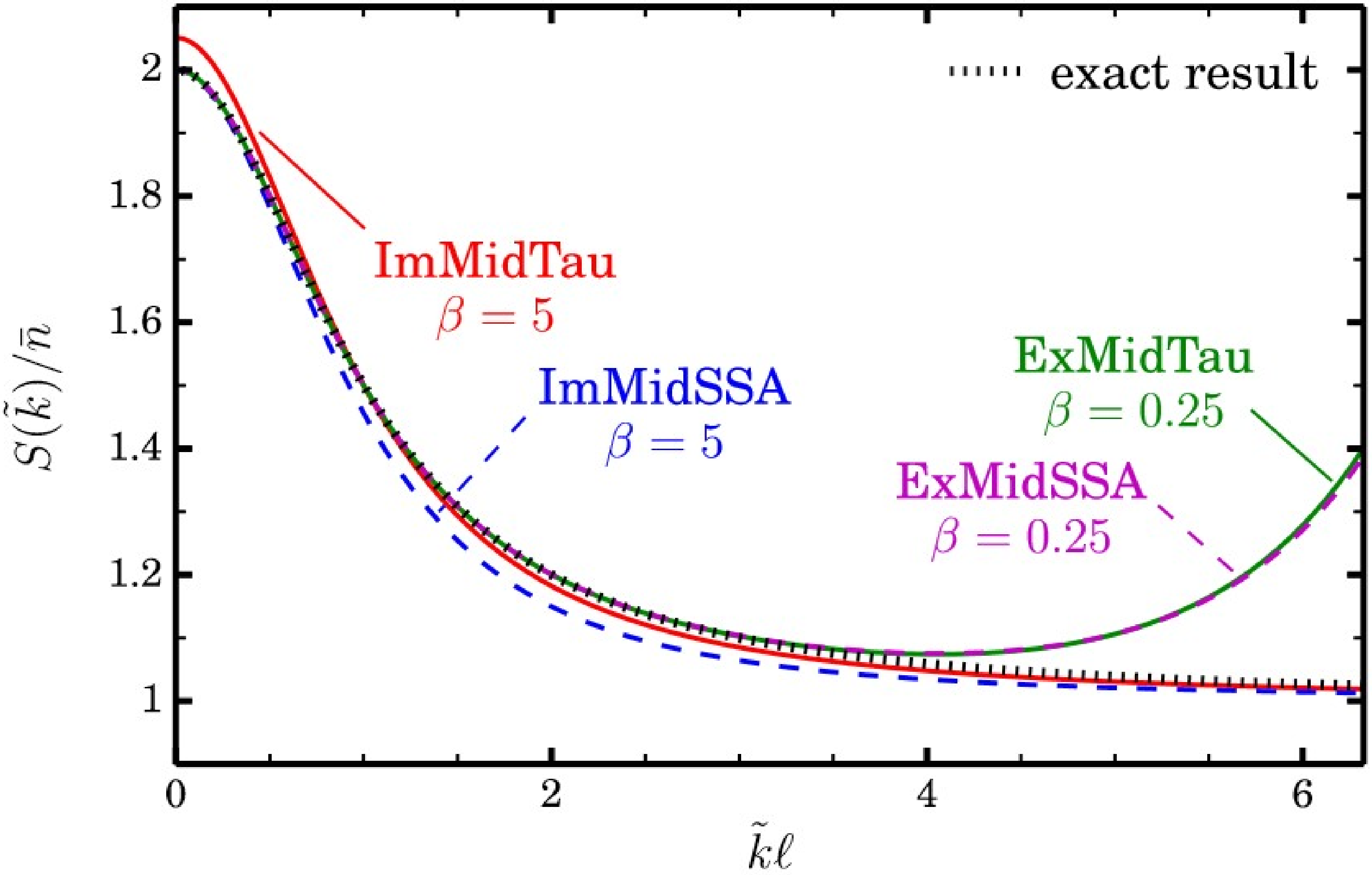
- Use the Ornstein-Uhlenbeck equation to obtain

$$S(\boldsymbol{k}) = \frac{D\bar{n}k^2 + \bar{\Gamma}}{Dk^2 + r}$$

Schlögl Model

- Single-species Schlögl model $2\mathrm{X} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3\mathrm{X} \quad \varnothing \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \mathrm{X}$
- Consider an out-of-equilibrium monostable case.
- We have analyzed the discrete structure factors for our 2-stage implicit diffusion schemes (and other 2-stage explicit-diffusion schemes) and compared to the continuum result:

Schlögl Model - Structure Factor



$\ell \sim \sqrt{D/r}$ (penetration depth)

$\beta = D\Delta t/\Delta x^2$ (explicit diffusion Courant number)

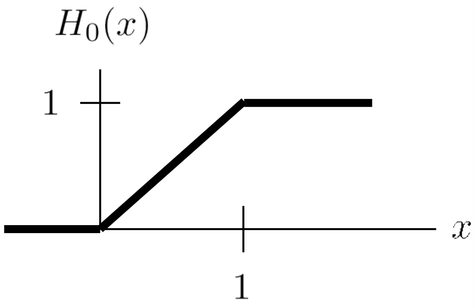
Small Number of Molecules

- Diffusion – pure arithmetic averaging of number densities to faces used to multiply stochastic fluxes is problematic.

$$\frac{dn_s}{dt} = D_s \nabla_{\mathrm{d}}^2 n_s + \sqrt{\frac{2D_s}{\Delta V}} \nabla_{\mathrm{d}} \cdot \left(\boxed{\sqrt{\tilde{n}_s}} \boldsymbol{\mathcal{W}}_s \right)$$

  - We need stochastic fluxes to “shut off” as the number density in either face approaches zero (in order to avoid driving the number densities negative)

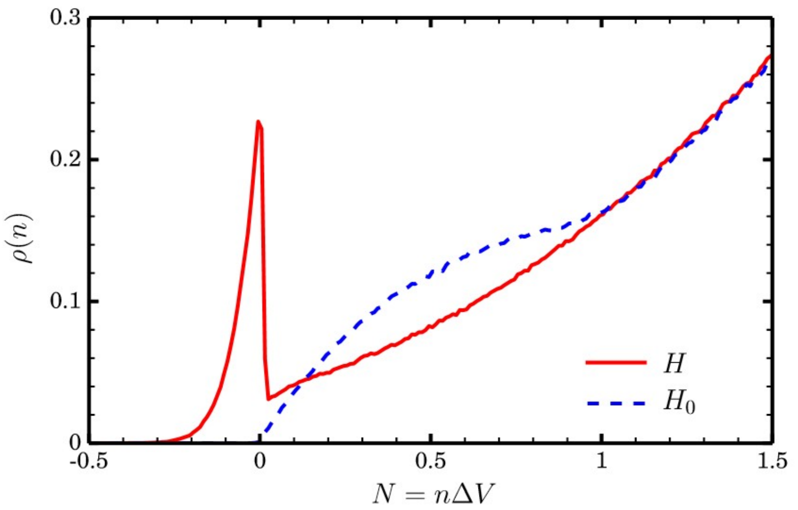
$$\tilde{n}(n_1, n_2) = \left(\frac{n_1 + n_2}{2} \right) H_0(n_1 \Delta V) H_0(n_2 \Delta V)$$



  - Smoothed Heaviside function allows for more gradual transition to zero number densities on face

Small Number of Molecules

- Using H_0, vs. H (discontinuous Heaviside), here is the distribution of number densities in a diffusion-only test with an average N = 5.



- Reactions – use continuous-range number densities with law of mass action correction, ensuring each rate is non-negative; e.g.,

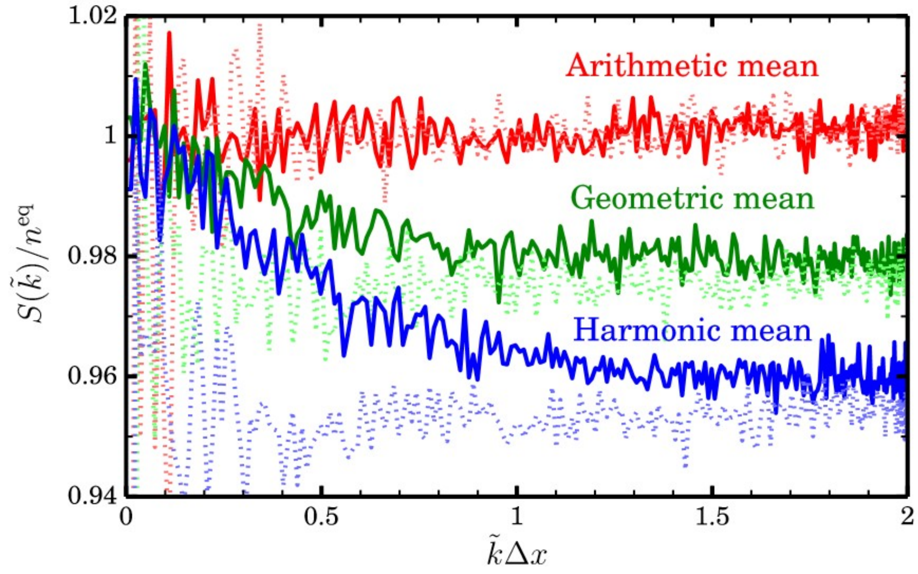
$$2\mathrm{X} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3\mathrm{X}$$

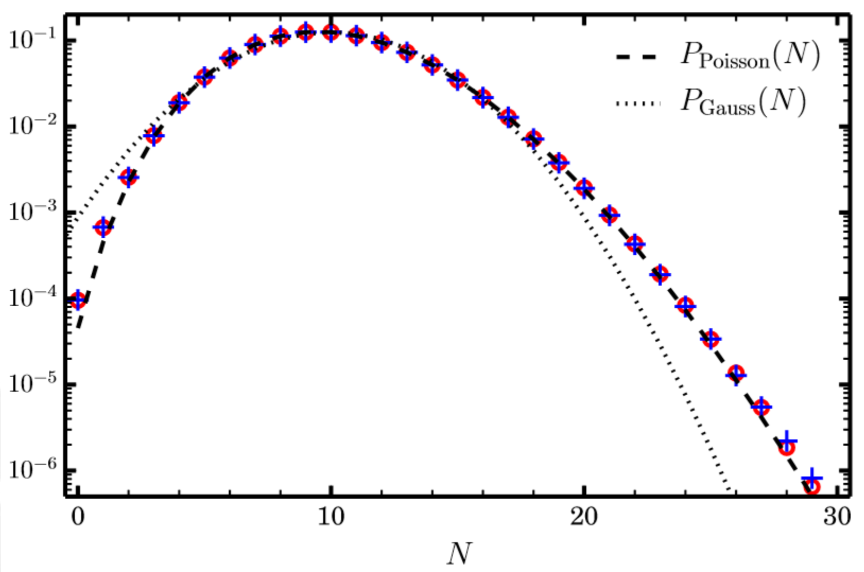
$$a(n) = k_1 n^+ (n - \frac{1}{\Delta V})^+ - k_2 n^+ (n - \frac{1}{\Delta V})^+ (n - \frac{2}{\Delta V})^+$$

$$n^+ = \max(n, 0)$$

Schlögl Model – Thermodynamic Equilibrium

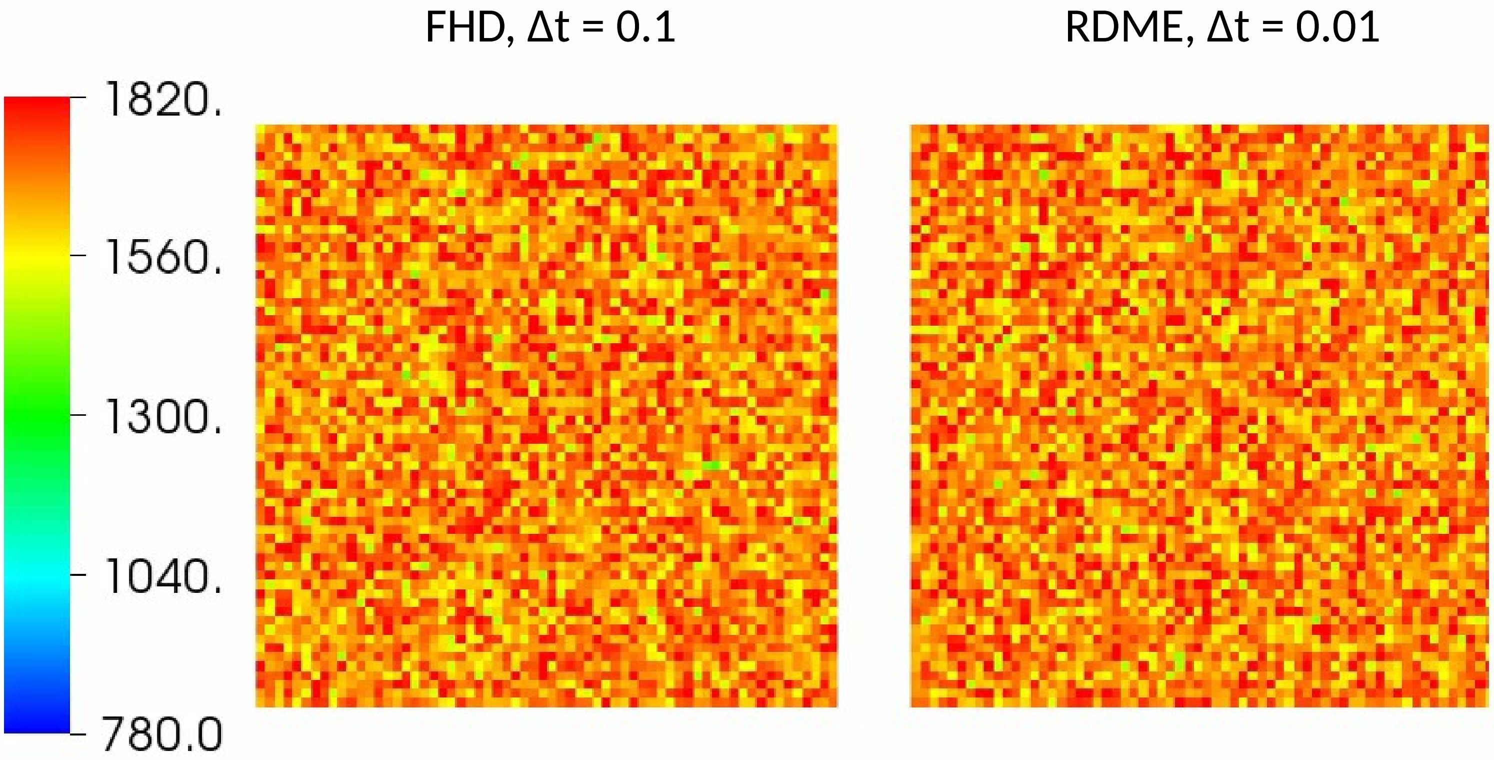
- Single-species Schlögl model $2\mathrm{X} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3\mathrm{X} \quad \varnothing \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \mathrm{X}$
- We have performed detailed analysis demonstrating we match the structure factor and equilibrium distribution for ~10 molecules per cell.





Turing-like Pattern Formation

- We compare our new approach with an RDME Scheme (Strang splitting; multinomial diffusion + SSA)
  - The movie shows the time evolution of n_U



Turing-like Pattern Formation

- Baras-Pearson-Mansour (BPM) Model
  - 3 Species, 7 Reactions
  - Diffusion coefficient and reaction rates correspond to a limit cycle

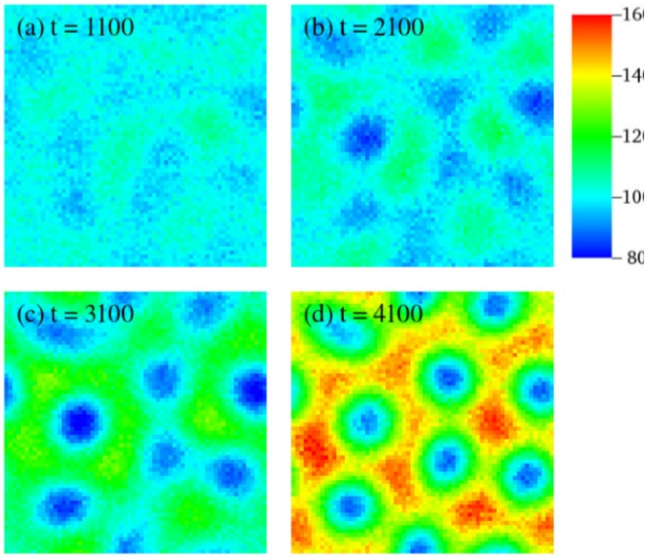
$$\mathrm{U} + \mathrm{W} \overset{k_1}{\to} \mathrm{V} + \mathrm{W}, \qquad 2\mathrm{V} \underset{k_3}{\overset{k_2}{\rightleftharpoons}} \mathrm{W},$$

$$\mathrm{U} \underset{k5}{\overset{k_4}{\rightleftharpoons}} \varnothing, \qquad \mathrm{V} \underset{k7}{\overset{k_6}{\rightleftharpoons}} \varnothing.$$

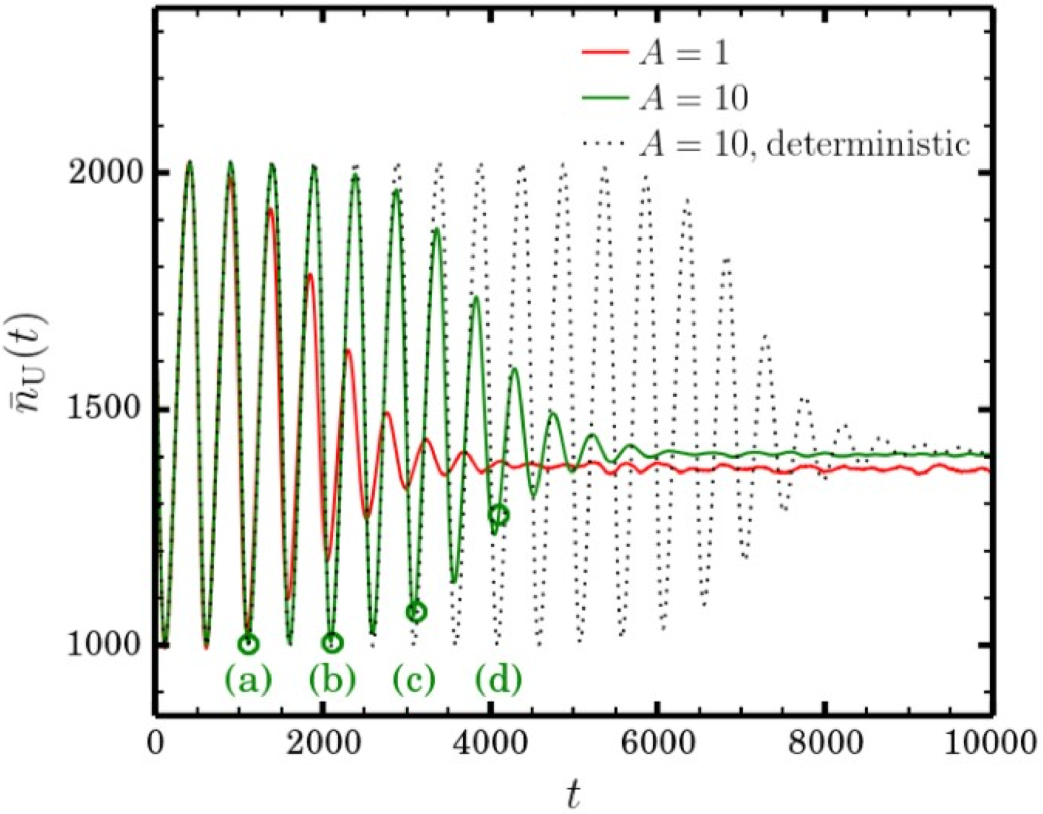
- We initialize the system by choosing a point on the limit cycle and perturbing the data with a Poisson distribution

Turing-like Pattern Formation

- Analysis of pattern formation time scales, comparing strong fluctuations (A=1), weak fluctuations (A=10), and deterministic
  - All simulations use the same random initial perturbation



RDME



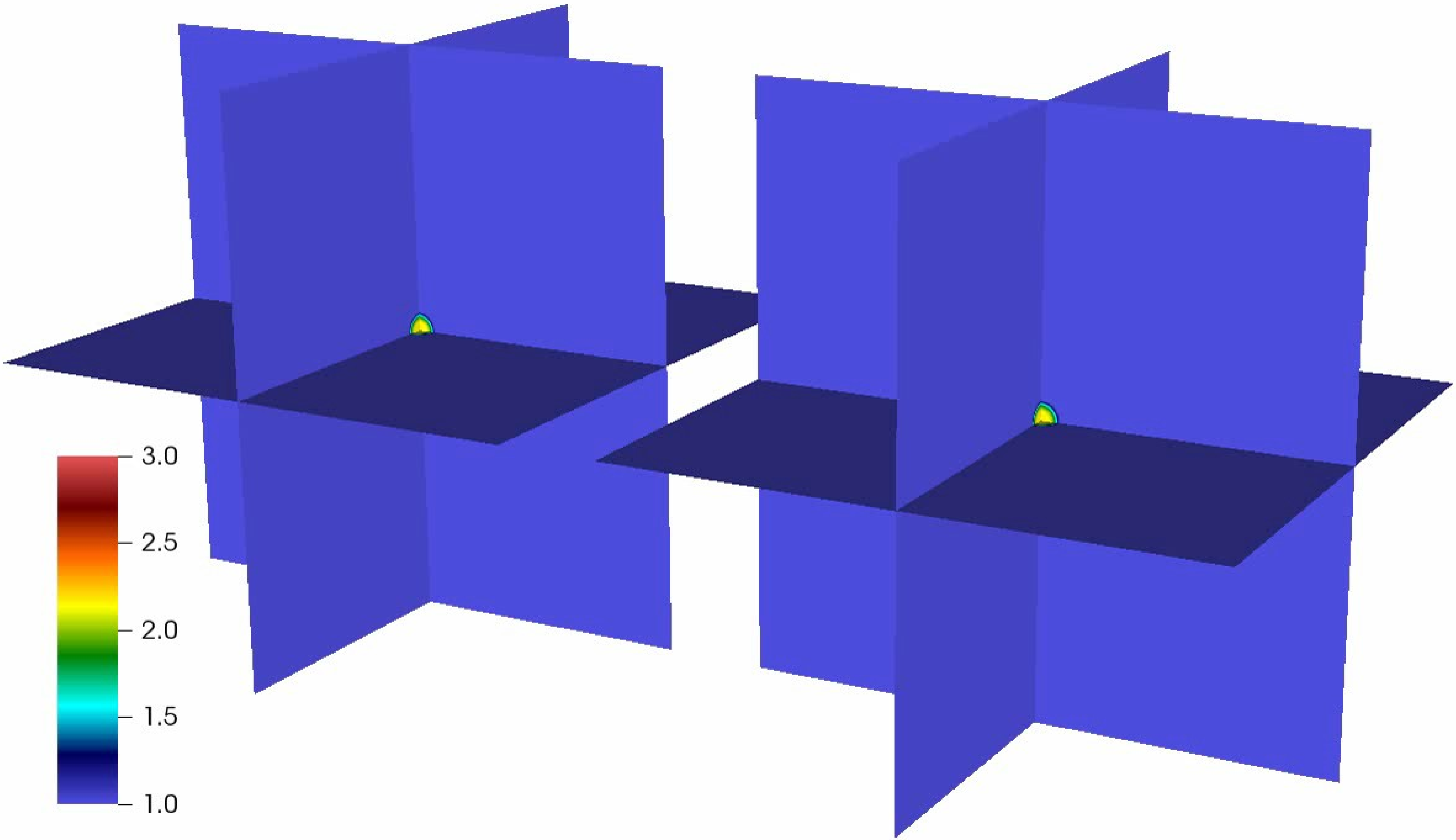
Front Propagation

- 2 species, 4 reaction model (Lemarchand)

$$\mathrm{A} \overset{k_1}{\to} \varnothing, \quad 2\mathrm{A} + \mathrm{B} \overset{k_2}{\to} 3\mathrm{A}, \quad \mathrm{B} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \varnothing.$$

- 3D simulation comparing deterministic vs. stochastic evolution
  - Parallel implementation using BoxLib allows for scalability on leadership class computing facilities.
- We initialize a spherical bubble with interior/exterior equilibrium states and perturb with Poisson noise.

Front Propagation


Deterministic

Stochastic

Conclusions / Future Work

- Our implicit diffusion, two-stage, tau-leaping scheme compares favorable to RDME for large fluctuations, and can seamlessly handle the deterministic limit.
  - SSA can be used for rapid reactions
- Implementation of reactions into existing FHD models containing more physics (advection, multicomponent diffusion, thermal gradients, barodiffusion, charged particles).
  - See the next talk by J. Peraud, **Low Mach Number Fluctuating Hydrodynamics for Electrolytes**
- Reference: C. Kim et. al, **Stochastic Simulation of Reaction-Diffusion Systems: A Fluctuating-Hydrodynamics Approach**, accepted, *J. Chem. Phys.* (on arXiv, or ccse.lbl.gov)