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Hybrid Discrete/Continuum Algor... istic Reaction Networks

Cosmin Safta[1] Khachik Sargsyan[1] Bert Debusschere[1]
Habib Najm[1]

[1]Sandia National Laboratories
Livermore, CA, USA
{csafta,ksargsy,bjdebus,hnnajm}@sandia.gov

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Outline

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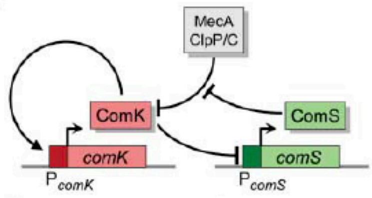
1. Stochastic Reaction Networks

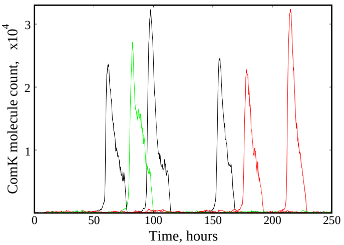
2. Discrete and Continuum Solution Approaches

3. Hybrid Solution Approach

Stochastic Reaction Networks (SRNs)



Süel et al., Science, 2007



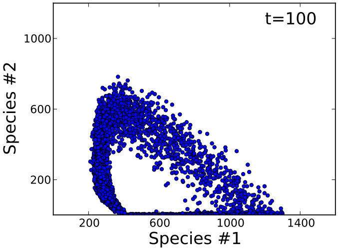
- Chemical Reactions between a small number of molecules exhibit inherent noise
  - Biochemical reaction networks (cellular signaling, gene regulatory networks)
  - Surface reaction processes (catalytic interfacial electrochemistry)
- Molecular phenomena can affect macroscale behavior
  - E.g. transition to competence in soil bacterium B. subtilis
- Discreteness makes simulation and analysis challenging

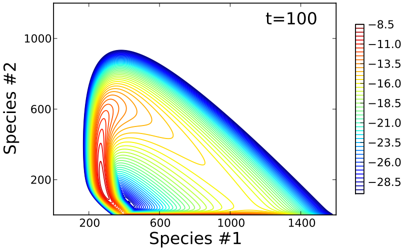
SRNs are modeled as continuous time, discrete state Markov processes

$$\frac{\partial P(\mathbf{x},t)}{\partial t} = \sum_{j=1}^{M} \alpha_j(\mathbf{x}-\boldsymbol{\nu}_j)P(\mathbf{x}-\boldsymbol{\nu}_j,t) - P(\mathbf{x},t)\sum_{j=1}^{M}\alpha_j(\mathbf{x})$$

- Governed by the Chemical Master Equation
  - Enumerated into large system of linear ODEs (one for probability at each system state)
  - Solved e.g. with exponentiation or time integration
  - Expensive due to large number of states
- Trajectories can be simulated using the Stochastic Simulation Algorithm (SSA) (Gillespie, 1977)
  - Move forward one reaction event at a time
  - Next reaction and its time are sampled from probability density function
  - Jump Markov process

CME solution versus simulation with SSA

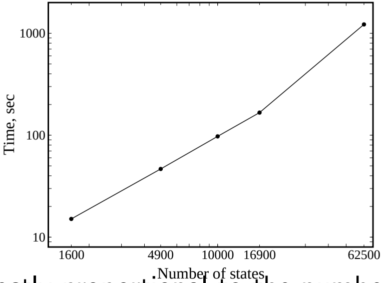




- Circadian rhythm [Ferm *et al.*, 2006]
- SSA sampled solution equivalent to CME
  - Fast (minutes), but hard to sample space exhaustively
- CME gives joint distribution of system state directly
  - Full solution, but expensive (days)

$$\emptyset \xrightarrow{w_1(Y)} Y$$
$$Y \xrightarrow{w_2(Y)} \emptyset$$
$$Y \xrightarrow{w_3(Y)} X$$
$$X \xrightarrow{w_4(X)} Y$$

Direct CME solution is prohibitively expensive except for small systems



- Solution cost directly proportional to the number of system states
- Equations tend to be stiff
- Recent developments have made the CME solution more tractable
  - Finite State Projection approach reduces effective state space [Munsky *et al.*, 2007]
  - Matrix reduction based on time-scale separation (stiffness reduction)
- Continuum approximation (in the state space) is sometimes a viable alternative

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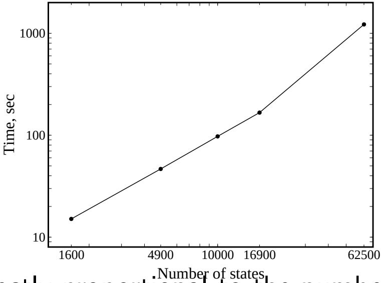

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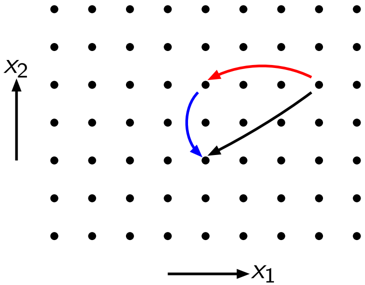
Discrete Chemical Master Equation (CME) formulation

$$\frac{\partial P(\mathbf{x},t)}{\partial t} = \sum_{j=1}^{M} \alpha_j(\mathbf{x}-\boldsymbol{\nu}_j)P(\mathbf{x}-\boldsymbol{\nu}_j,t) - P(\mathbf{x},t)\sum_{j=1}^{M}\alpha_j(\mathbf{x})$$

- Unroll $P(\mathbf{x},t)$ into a state vector

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{A}\mathbf{p}(t)$$
$$\mathbf{p}(t) = \exp(t\mathbf{A})\mathbf{p}(0)$$



- System of linear equations in $p_i(t)$
- Solve with time integration or matrix-exponentiation methods

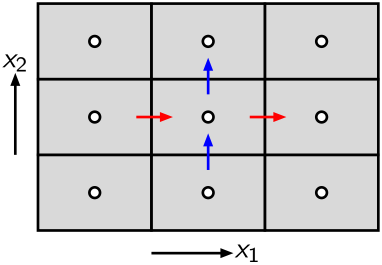
Continuum Fokker-Planck (FP) formulation

$$\frac{\partial P(\mathbf{x},t)}{\partial t} = -\sum_{i=1}^{N} \frac{\partial}{\partial x_i}\{\mathbf{f}_i(\mathbf{x})P(\mathbf{x},t)\} + \frac{1}{2}\sum_{i=1}^{N}\sum_{j=1}^{N} \frac{\partial^2}{\partial x_i \partial x_j}\{G_{ij}(\mathbf{x})P(\mathbf{x},t)\}$$

$$\mathbf{f}(\mathbf{x}) = \sum_{m=1}^{M} \alpha_m(\mathbf{x})\boldsymbol{\nu}_m$$

$$G(\mathbf{x}) = \sum_{m=1}^{M} \alpha_m(\mathbf{x})\boldsymbol{\nu}_m\boldsymbol{\nu}_m^T$$

- Discretize with grid size K
- Similar system of ODEs as CME, but much smaller set of equations

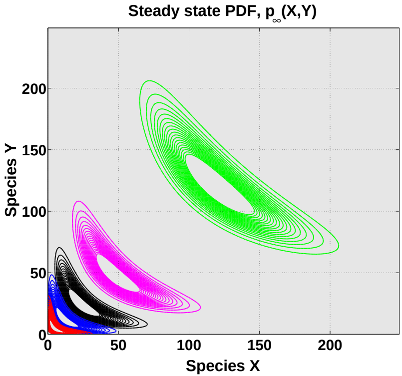


Finite Volume scheme:

- *Convection:* conservative 2^{nd} order ENO scheme local Lax-Friedriechs flux splitting/limiter. *Diffusion:* 2^{nd}-order.

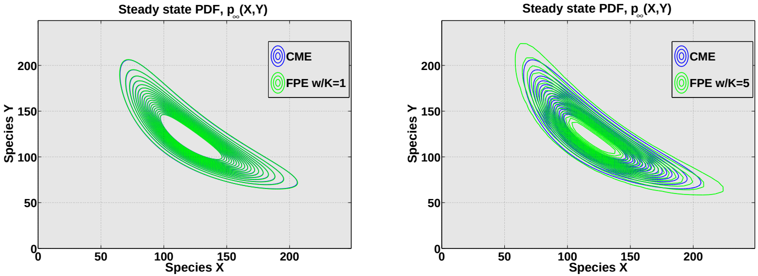
Metabolite test case

$$\emptyset \xrightarrow{k_X} X$$
$$\emptyset \xrightarrow{k_Y} Y$$
$$X + Y \xrightarrow{k_2[X][Y]} \emptyset$$
$$X \xrightarrow{\mu[X]} \emptyset$$
$$Y \xrightarrow{\mu[Y]} \emptyset$$



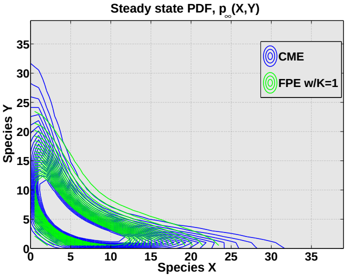
- Creation, reaction, destruction of two metabolites X and Y [Ferm *et al.*, 2006]
- Rate constants rescaled to simulate systems at 0.2, 0.5, 1, 2, 5 times the nominal volume

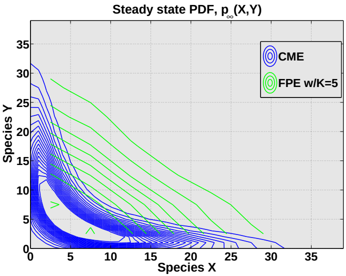
CME and FP compare well for large volume system



- FP gives good solution even on coarse mesh

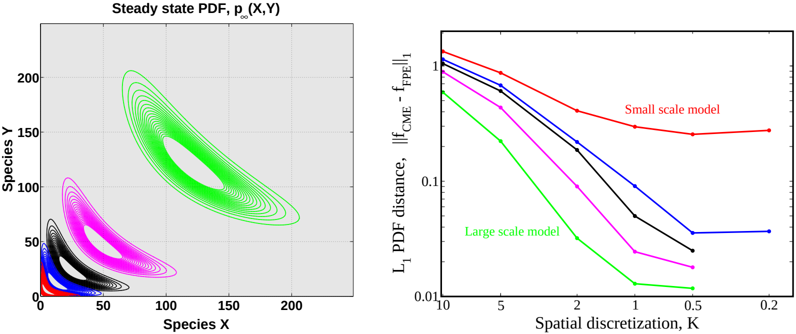
FP performs worse for small volume system





- FP misses key discrete behavior which is more important in systems with small volume (*i.e.* small number of molecules)
- FP behavior deteriorates quickly for coarser grid size

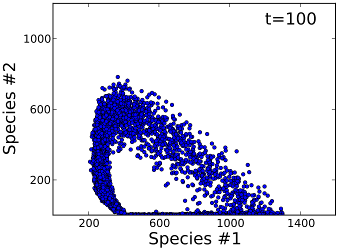
Convergence of FP with grid size

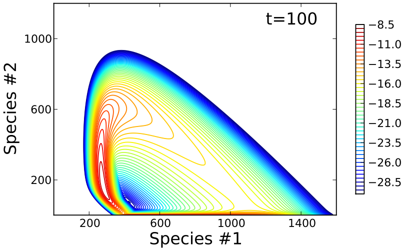


- L_1 error measure of probability over state space
- Good convergence for large volume systems
- For small systems, error unacceptable even for grids with $K < 1$

Outline

In many systems, same species can be present in both small and large number





- Both discrete and continuum formulations needed for some species
  $\longrightarrow$ looking for a more fine grained coupling approach
- Use CME where discreteness needed and FPE elsewhere
  - Discrete CME needed when low number of molecules
  - Cost savings when continuum approximation can be solved on coarse grid

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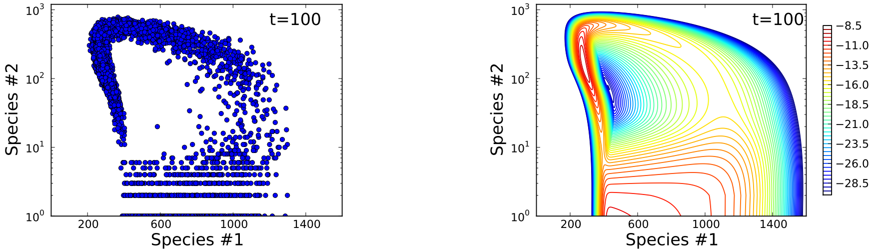

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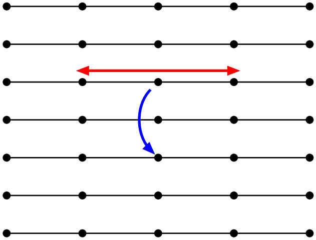
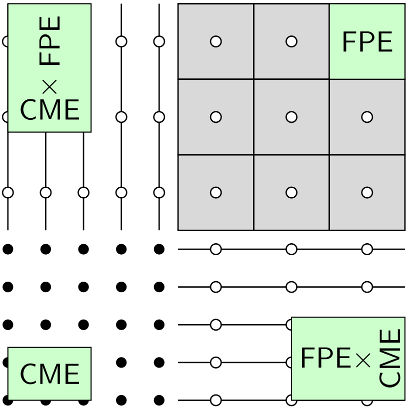
Species-Specific Formulation



- Hybrid formulation by Sjöberg, 2007
  - Species present in small number: discrete CME
  - Species present in larger number: continuum FPE
- Allows great cost savings in many systems where some species present in small numbers but most are present in large numbers

Fully hybrid, coupled CME-FPE can capture species in both small and large number

- Representation varies depending on state space
    - Use full CME where all species are in small number
    - Use Sjöberg's CME-FPE approach when some species in large number
    - Use full FPE when all species in large number
- Transition from CME to FPE in each direction when species number larger than some threshold



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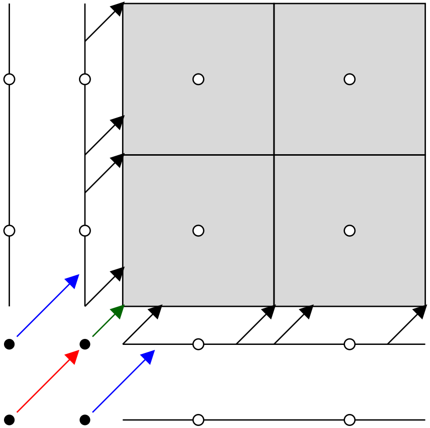
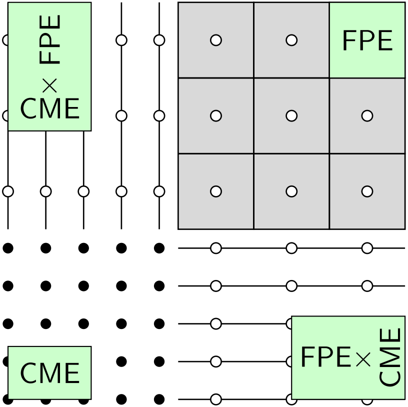
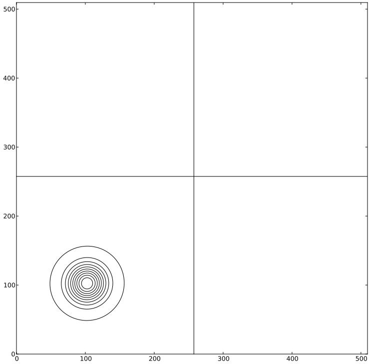
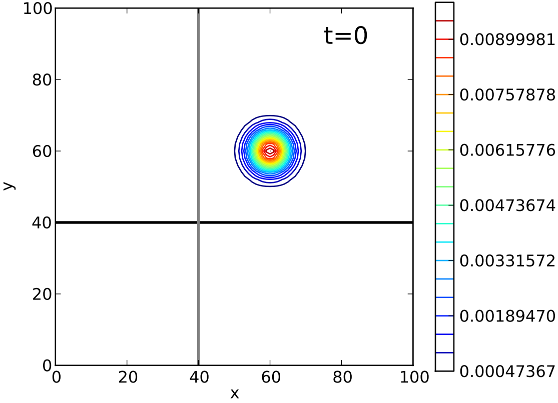


Hybrid regime tests





Metabolite test case in two-regime mode



- Grid size: $\Delta_{\mathrm{CME}} = 1$, $\Delta_{\mathrm{FPE}} = 2$
- Good agreement across interface, solution remains symmetric

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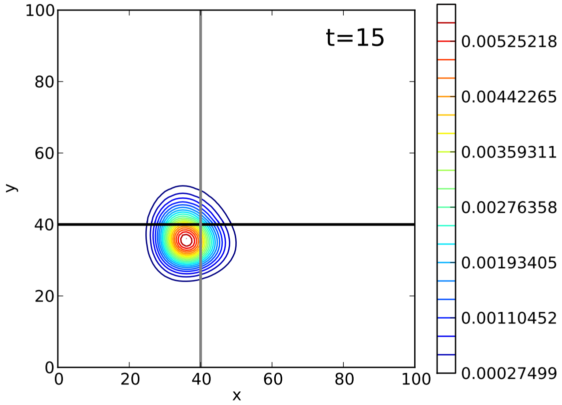

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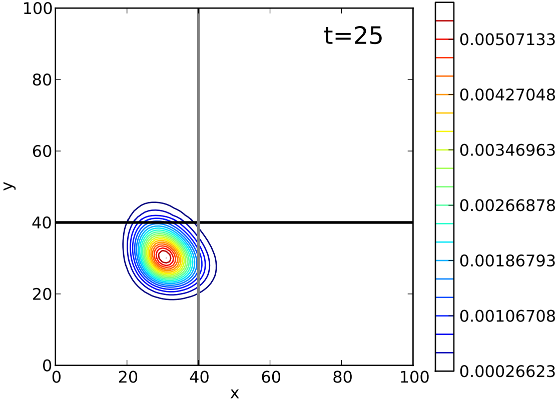

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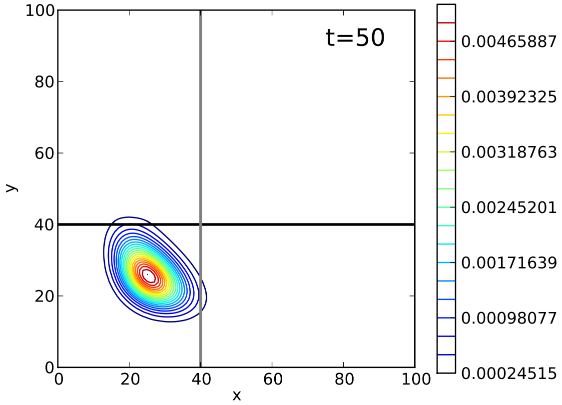

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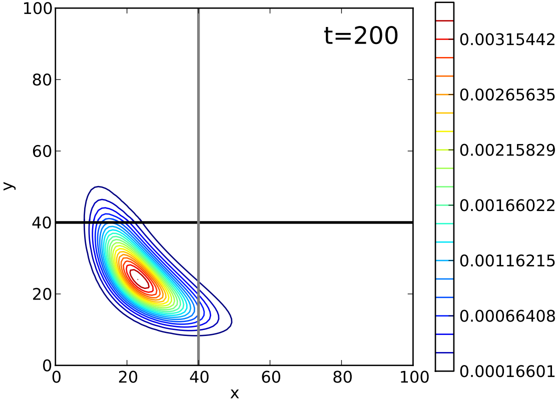

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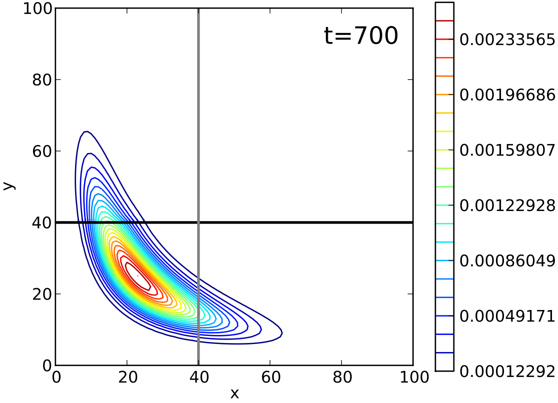

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Conclusions and ongoing work

- Direct solution of the CME is challenging
  - Cost increases exponentially with number of species
- Hybrid formulations use the proper representation where needed
  - Discrete CME when stochasticity important
  - More efficient continuum FPE approximation when discrete behavior less important
  - Choose interface location and grid coarseness to minimize size of discretized state space while maintaining sufficient accuracy
- Hybrid approach can be used in conjunction with other methods for accelerating CME solution
  - Finite State Projection algorithm
  - Stiffness reduction methods based on time scale separations
- Test results on hybrid CME-FPE coupling are promising
- Testing of hybrid scheme is ongoing for more SRN models