

Toward the Multiscale Numerical Solution of Chemically Reacting Systems

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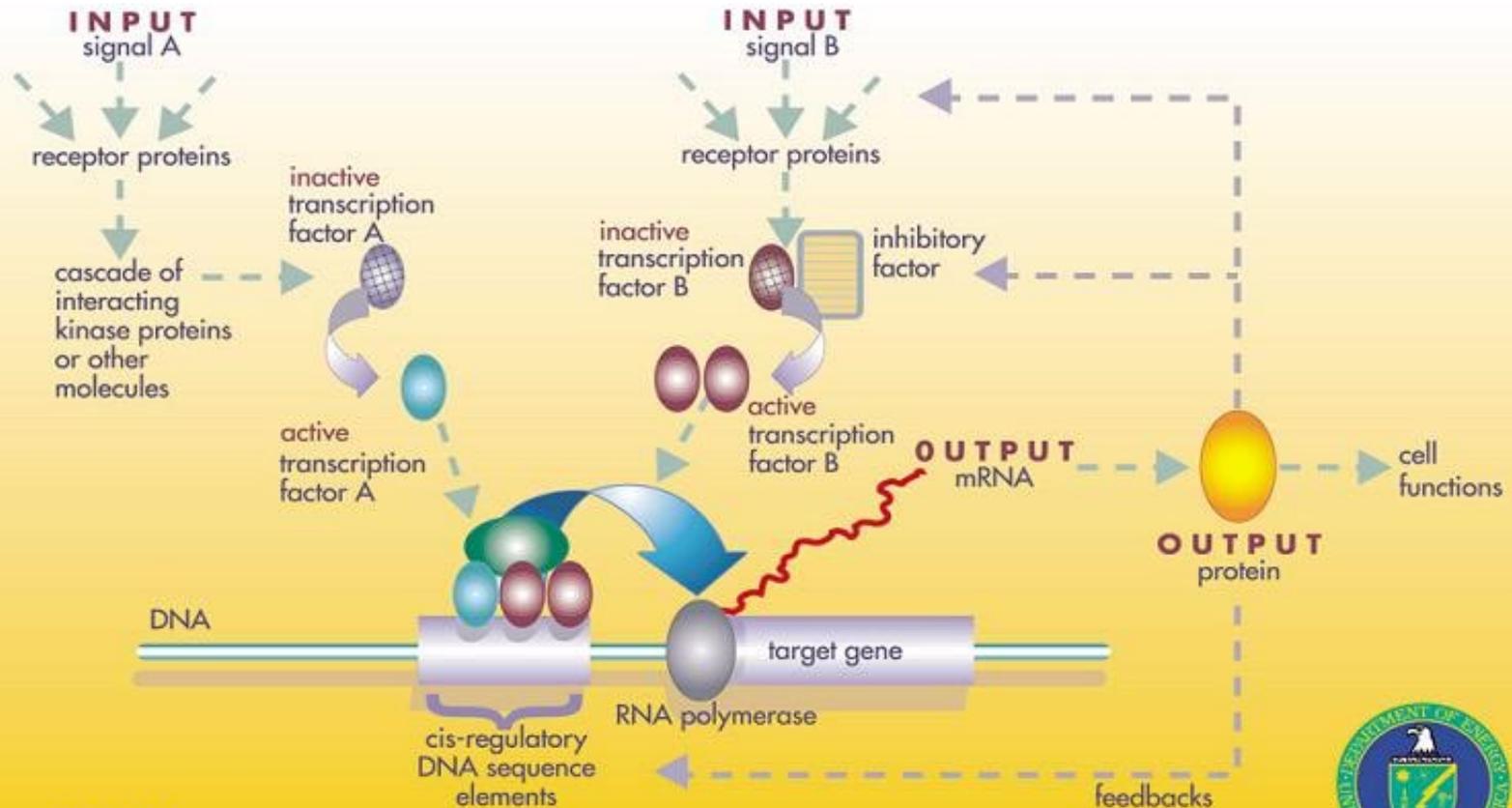
Daniel Gillespie
Caltech

with special thanks to John Doyle

Multiscale Chemically Reacting System

GENOMES to LIFE

A GENE REGULATORY NETWORK



YGG 01-0083



Multiscale Numerical Methods are Needed

- Some important chemical species may be present in very small quantities. Key chemical reactions involving these species should be modeled at a stochastic or intermediate level
- It is much too expensive to treat all of the reactions at this level

Computational models of chemical reaction systems

- **Discrete and stochastic** - Finest scale of representation for well stirred molecules. Exact description via Stochastic Simulation Algorithm (SSA) due to *Gillespie*.
- **Continuous and stochastic** - The Langevin regime. Valid under certain conditions. Described by Stochastic Differential Equations (SDE).
- **Continuous and deterministic** - The rate equations. Described by ordinary differential equations (ODE). Valid under further assumptions.

Stochastic Simulation Algorithm

- Well-stirred mixture
- N molecular species S_1, \dots, S_N
- Constant temperature, fixed volume Ω
- M reaction channels R_1, \dots, R_N
- Dynamical state $X(t) = (X_1(t), \dots, X_N(t))$

where $X_i(t)$ is the number of S_i molecules in the system

Stochastic Simulation Algorithm

- Propensity function $a_j(x)dt$ = the probability, given $X(t) = X$, that one R_j reaction will occur somewhere inside Ω in the next infinitesimal time interval $[t, t + dt]$
- When that reaction occurs, it changes the state. The amount by which X_i changes is given by ν_{ji} = the change in the number of S_i molecules produced by one R_j reaction
- $X(t)$ is a jump Markov process

Stochastic Simulation Algorithm

First reaction method:

- Generate a tentative reaction time for each reaction channel R_l according to

$$\tau_l = \frac{1}{a_l(X)} \ln \left(\frac{1}{r_l} \right)$$

where r_1, \dots, r_M are M statistically independent samplings of $U(0,1)$

- Take

$$\tau = \tau_j = \min \{ \tau_1, \dots, \tau_M \}$$

- Update

$$X \leftarrow X + \nu_j$$

Chemical Langevin Equation

If the system possesses a macroscopically infinitesimal time scale, in the sense that during any dt on that scale all of the reaction channels fire many more times than once yet none of the propensity functions change appreciably, we can approximate the jump Markov process by a continuous Markov process defined by the Chemical Langevin Equation

$$X_i(t+dt) = X_i(t) + \sum_{j=1}^M \nu_{ji} a_j(X(t)) dt + \sum_{j=1}^M \nu_{ji} a_j^{\frac{1}{2}}(X(t)) N_j(t) (dt)^{\frac{1}{2}}$$

where N_1, \dots, N_M are M temporally uncorrelated, statistically independent normal variables with mean 0 and variance 1

Reaction Rate Equation

In the limit of infinitely large molecular populations of all reactant species, the second term becomes vanishingly small in comparison to the first, yielding the deterministic reaction rate equation

$$\frac{dX_i(t)}{dt} = \sum_{j=1}^M \nu_{ji} a_j(X(t))$$

Tau-leaping method

- Given a subinterval of length τ , if we could determine how many times each reaction channel fired in each subinterval, we could forego knowing the precise instants at which the firings took place. Thus we could leap from one subinterval to the next.
- How long can that subinterval be? Tau-leaping is exact for constant propensity functions, thus τ is selected so that no propensity function changes 'appreciably'

Tau leaping : A multi-scale method of numerical simulation

- Developed by *Gillespie*
- Based on a local Poisson assumption
- Agrees with SSA in the small step size limit
- Equivalent to Forward Euler in the SDE and ODE regimes
- The explicit nature of the scheme makes it inefficient for stiff problems.

Update formula

$$\Delta X = \nu P(a(x), \tau)$$

where

ΔX Change of state

x Current state

τ Time step

$P(a, \tau)$ Poisson variable with parameters a and τ

$a_j(x)$ Propensity functions

ν_{ij} Change in species i due to reaction j

Our goals for tau-leaping

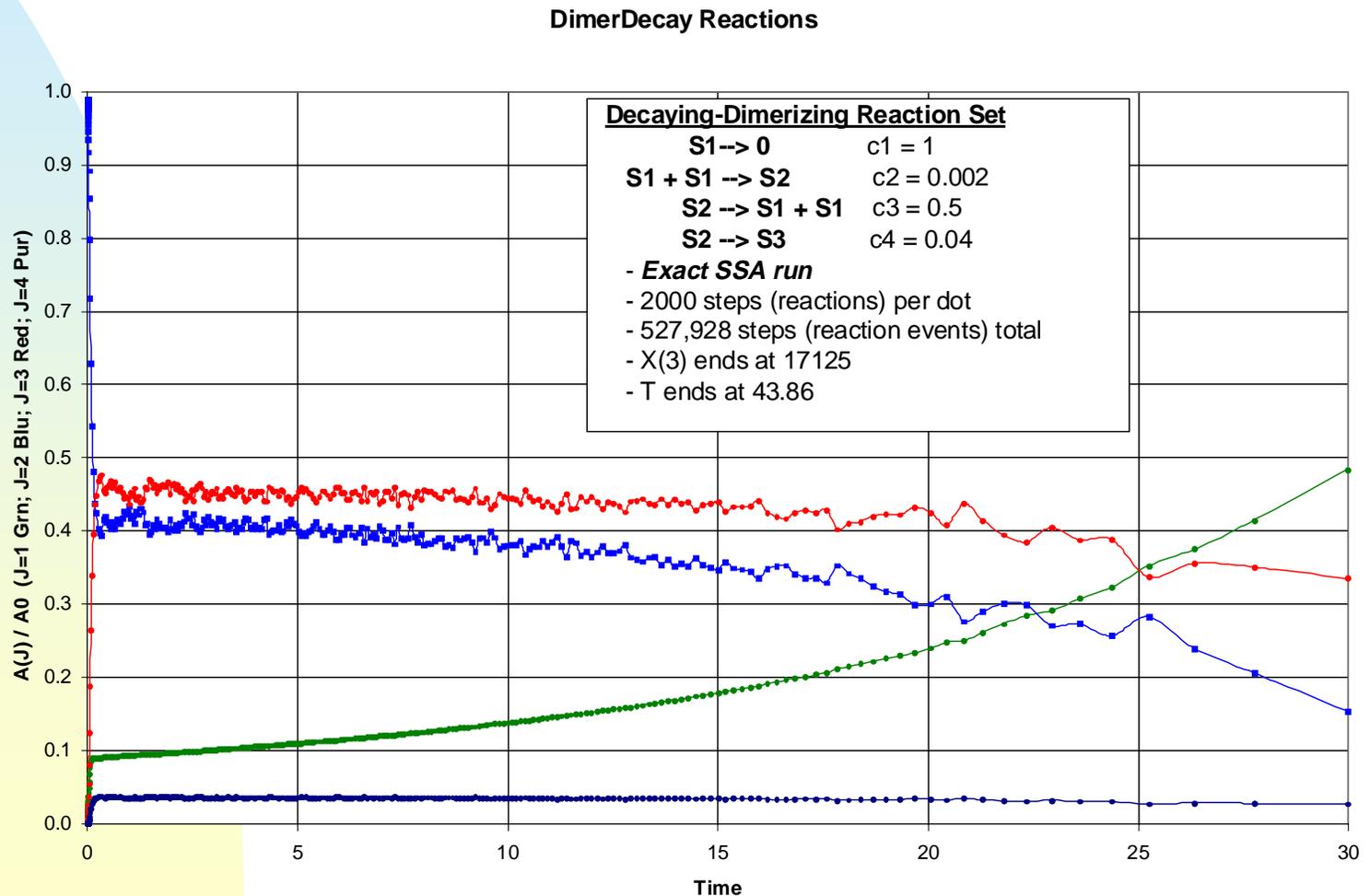
- Stiffness – how does it present itself and what can we do about it?
- Stepsize control – current algorithms don't work well, particularly for stiff systems
- Higher order methods
- Firmer theoretical basis
- Incorporation with Stochastic Simulation Algorithm, Chemical Langevin Equation and Reaction Rate Equation for a fully multiscale simulation of chemical kinetics

Stiff systems

- Exhibit **slow** and **fast** time scales.
- **Fast** reactions almost **cancel each other** while **slow** reactions **determine the trend**.
- **Explicit methods** such as Tau leaping require unreasonably **small time steps** in order to maintain stability.
- Implicit methods in general do not have step size limitations due to stability. Accuracy concerns alone determine the step size.
- **Need an implicit** version of tau leaping for stiff systems.

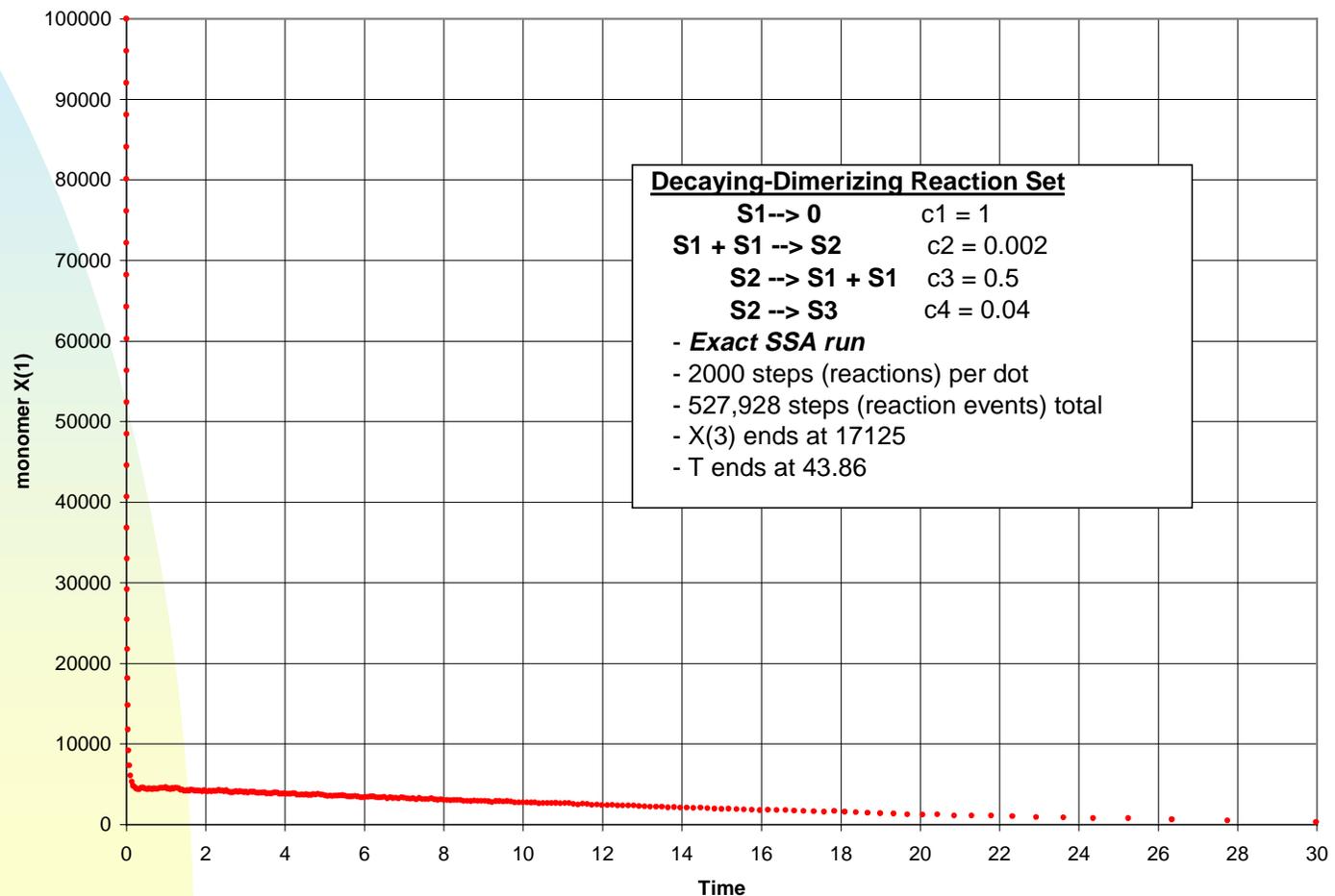
Stiff example : Decaying-dimerizing reaction set

- ◆ Plot of reaction propensities against time using SSA.
- ◆ The fast red and blue reactions almost cancel each other.



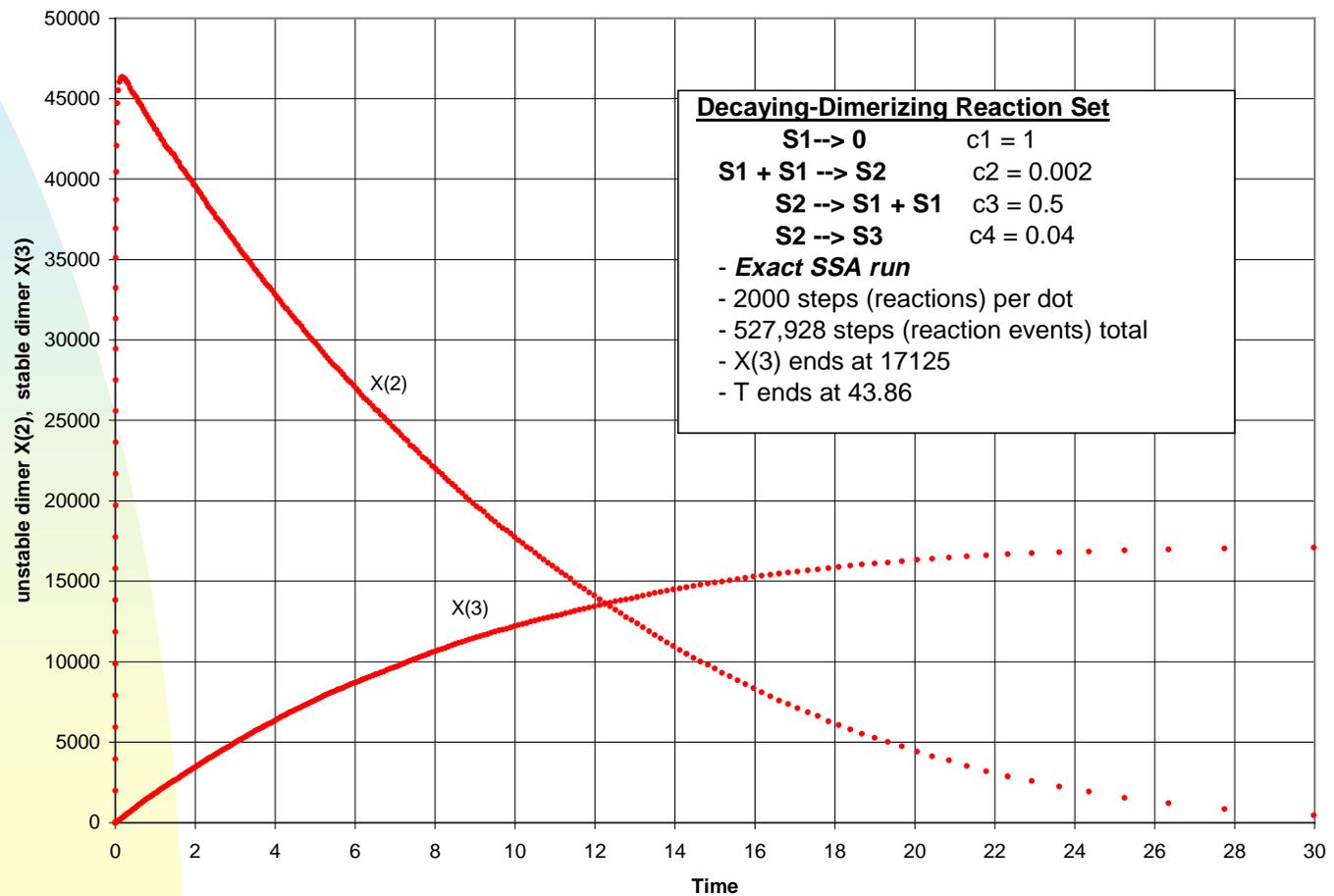
Stiff example : Decaying-dimerizing reaction set

Plot of number of species S1 against time using SSA.



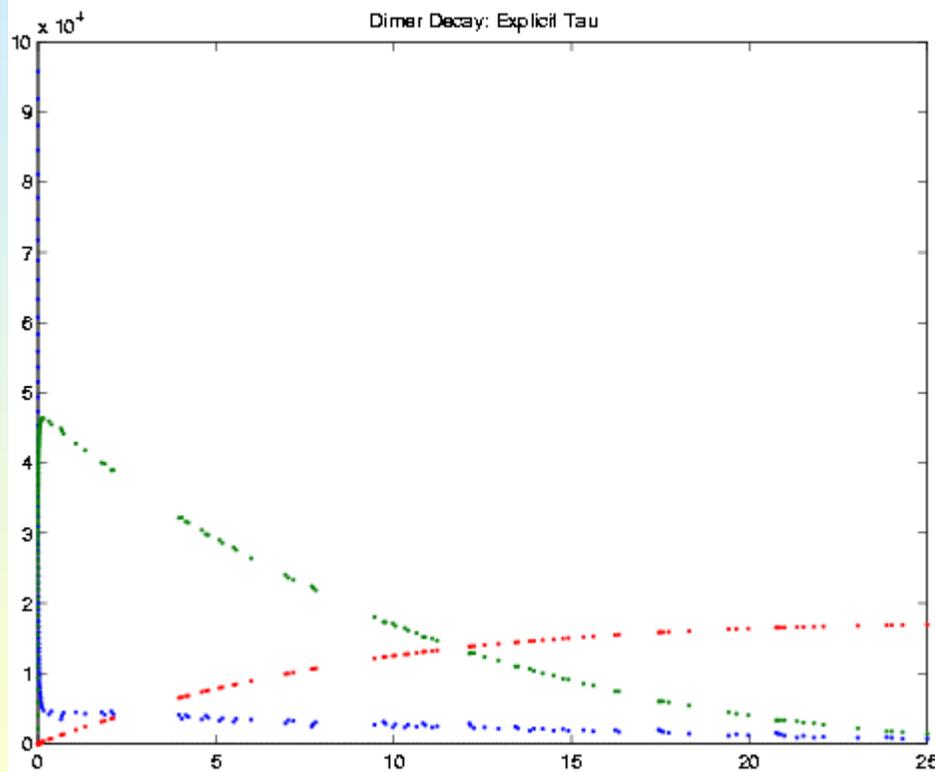
Stiff example : Decaying-dimerizing reaction set

Plot of number of species S2 and S3 against time using SSA.



Explicit tau applied to stiff problem

Decaying-Dimerizing Example



Sample trajectory

- More noise than predicted by SSA
- Instability of explicit method amplifies the noise
- Step size selection was based on rate of change of propensities (original *Gillespie* criterion)
- Step sizes are uneven due to sensitive dependence of propensities on states

Implicit Tau

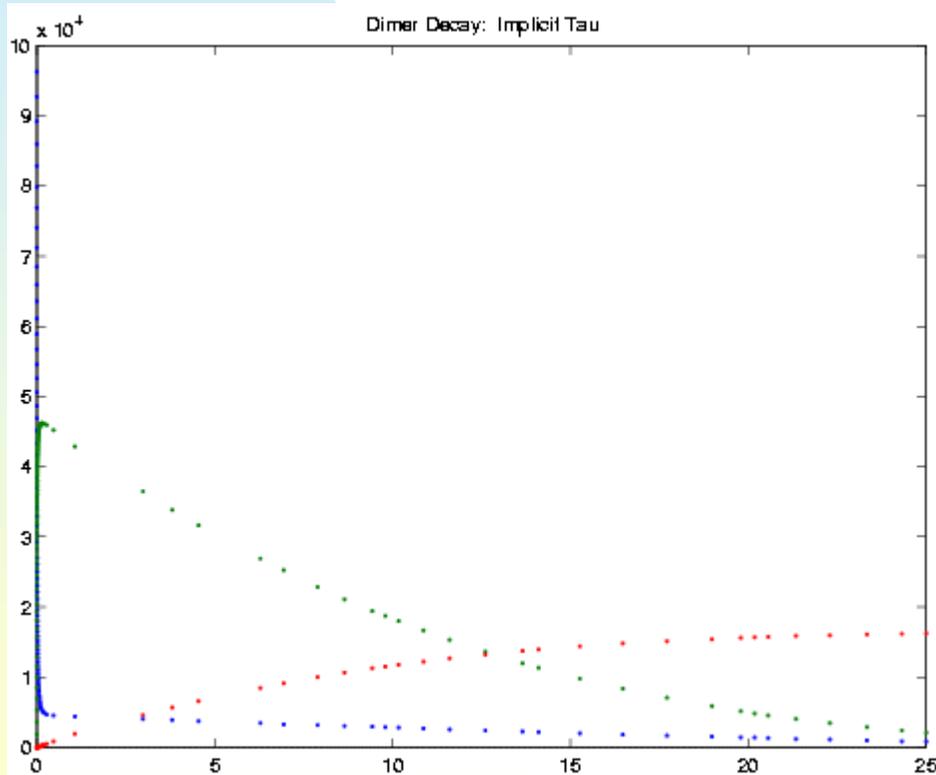
The update formula

$$\Delta X = \nu \tau a(x + \Delta X) + \nu P(a(x), \tau) - \nu \tau a(x)$$

- **Based on** the (explicit) **tau** method
- Only the **mean** part is **implicit**
- Reduces to the **Backward Euler** scheme in the SDE and ODE regimes
- **Agrees with SSA** in the small step size limit
- **Better suited for stiff** problems.

Implicit tau applied to stiff problem

Decaying-Dimerizing Example



Sample trajectory

- No extra noise due to instability as in the explicit method
- Step size selection was based on rate of change of propensities (original *Gillespie* criterion)
- Step sizes are still uneven due to sensitive dependence of propensities on states

Adaptive step size selection

Two approaches for the implicit tau

Propensity based

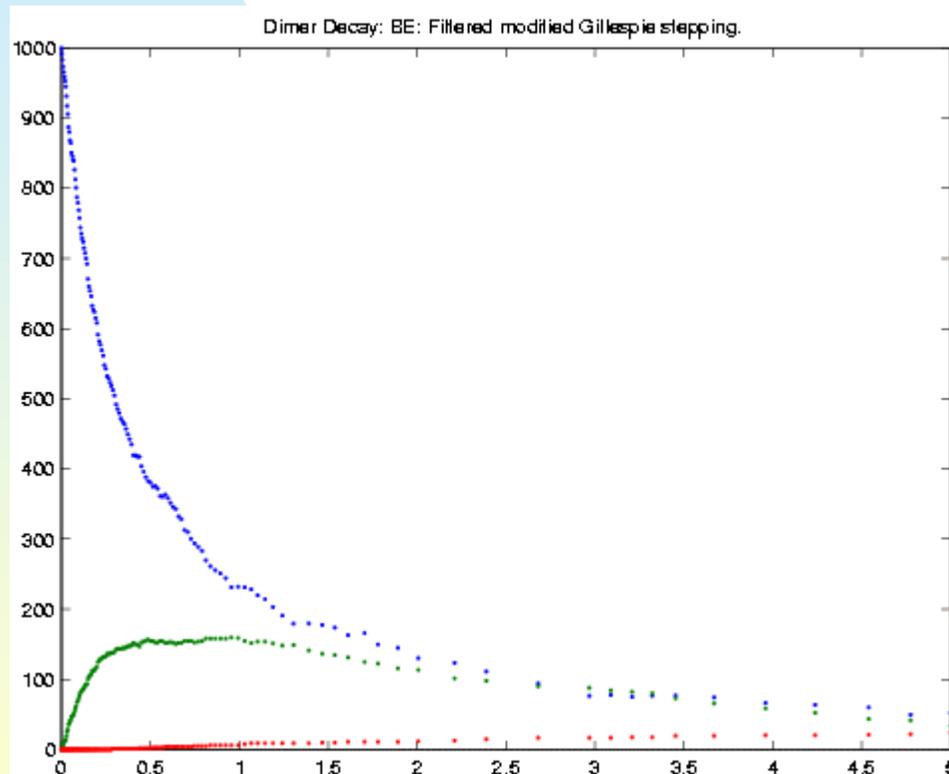
- Original criterion used by *Gillespie* requires small **relative change** in the **propensities**.
- Modified criterion adds a “**filter**” to the above which **allows** for **larger steps** for **stiff problems** and is appropriate for implicit schemes.

Estimated mean state based

- Exploits the fact that the **true mean trajectory** of an SDE **satisfies an ODE**.
- By **simulating an ensemble** of trajectories together **tracks** an approximate **solution of this ODE**.
- Uses **standard ODE local error criterion** for backward Euler to **determine step size**.

Step size selection based on filtered rate of change of propensities

Decaying-Dimerizing Example

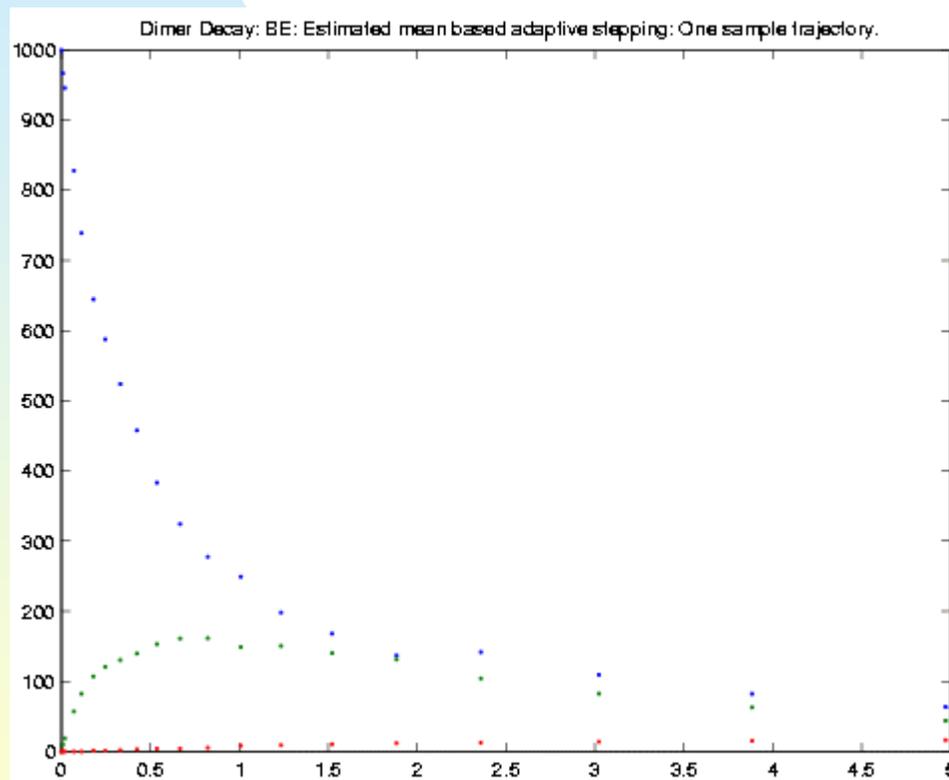


Sample trajectory

- About 130 steps - Much less than SSA
- SSA takes about 1300 reaction steps
- Implicit tau

Step size selection based on local error of estimated mean trajectory

Decaying-Dimerizing Example



Sample trajectory

- Only 20 steps - Fewer than propensity based method
- Implicit tau
- Ensemble of size 100 was used to estimate the mean trajectory

Higher order multi-scale methods

Two approaches

Heuristic approach

- Take valid higher order numerical schemes for SDEs and/or ODEs and modify in order to fit the Poisson regime
- Some success with **Trapezoidal implicit** scheme

$$\Delta X = \frac{1}{2} \nu \tau a(x + \Delta X) + \nu P(a(x), \tau) - \frac{1}{2} \nu \tau a(x)$$

Rigorous approach *(Work in progress..)*

Starting from a rigorous fine scale representation such as SSA develop equivalent of Taylor expansions.

Estimation of final state probability density functions

Methods compared against SSA

- Explicit tau
- Implicit tau
- Estimated midpoint (a method developed earlier by *Gillespie*)
- Trapezoidal implicit

Considered reaction



State x is number of $S1$

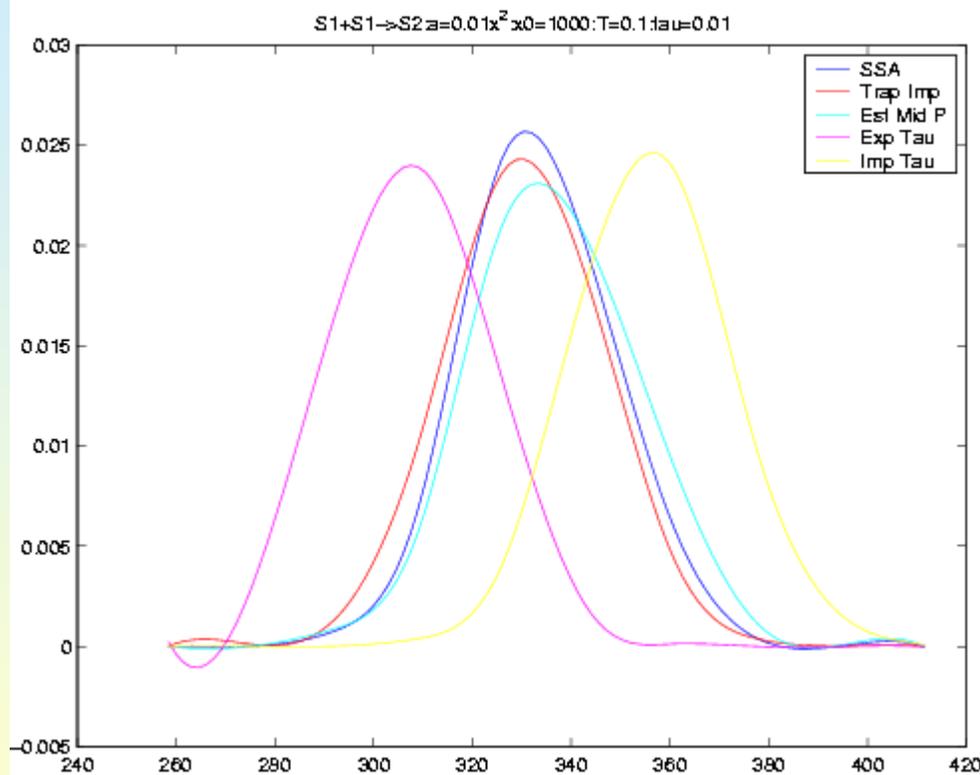
$$a(x) = 0.01x^2$$

$$\nu = -2$$

Initial state $x_0 = 1000$

Time interval = $[0, 0.1]$

Estimated final state probability density functions



Sample size

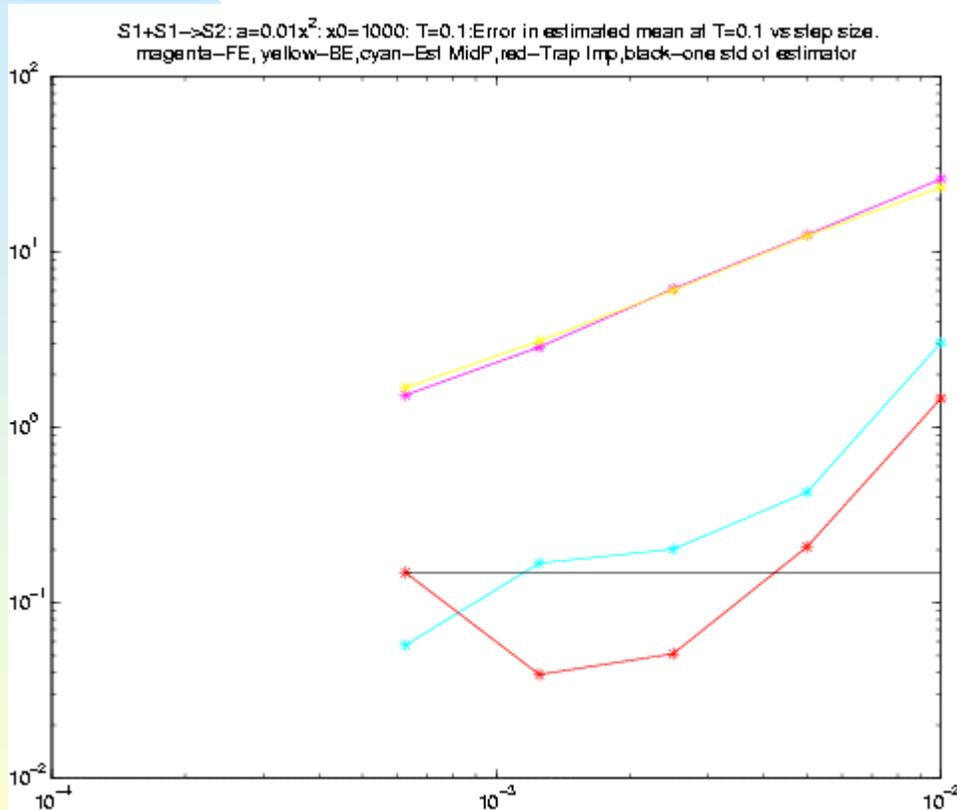
- 100,000 runs of SSA.
- 10,000 runs of all other methods.

Constant step size of 0.01 was used.

Color scheme

- Blue - SSA
- Magenta - Exp Tau
- Yellow - Imp Tau
- Red - Trap Imp
- Cyan - Est Midpoint

Error in estimated final state mean



Error in estimated mean versus step size

Sample size

- 100,000 runs of SSA.
- 10,000 runs of all other methods.

Constant step sizes of 0.01, 0.005, 0.0025, 0.00125, and 0.000625 were used

Color scheme

- Magenta - Exp Tau
- Yellow - Imp Tau
- Red - Trap Imp
- Cyan - Est Midpoint
- Black - Accuracy of estimator - *Ignore points below this!*