Using ideas from the numerical solution of ODEs to construct efficient methods for discrete stochastic chemical kinetics problems

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An overview

•Noise is important – how do we model it?

•Multiscale stochastic models and simulations for Systems Biology

•Taking ideas from the solution of ODEs : extrapolation, Runge-Kutta and linear multistep methods.

•Simulation results and conclusions.

Noise is important.
How do we model it?

Motivation: Biological evidence of noise

- “Stochasticity is evident in all biological processes … the proliferation of both noise and noise reduction systems is a hallmark of organismal evolution” – Federoff et al.(2002).
- “Transcription in higher eukaryotes occurs with a relatively low frequency in biologic time and is regulated in a probabilistic manner” – Hume (2000).
- “Gene regulation is a noisy business” – Mcadams et al. (1999).
- “Initiation of gene transcription is a discrete process in which individual protein-coding genes in an off state can be stochastically switched on, resulting in sporadic pulses of mRNA production” – Sano 2001.
- It is essential to study individual cells and to measure the cell to cell variations in biological response, rather than averaging over cell populations” – Zatorsky et al. 2006.
- **Intrinsic noise** due to small numbers of molecules and uncertainty of knowing when a reaction occurs and which it is. Relative uncertainty is inversely proportional to square root of number of molecules.

Michaelis – Menten Reaction

$$S_1 + S_2 \xrightarrow{k_1} S_3 \qquad a_1(X) = k_1 S_1 S_2$$

$$S_3 \xrightarrow{k_2} S_1 + S_2 \qquad a_2(X) = k_2 S_3$$

$$S_3 \xrightarrow{k_3} P + S_1 \qquad a_3(X) = k_3 S_3$$

The stoichiometric vectors and the Law of Mass Action gives

$$\nu_1 = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}, \quad \nu_2 = \begin{bmatrix} 1 \\ 1 \\ -1 \end{bmatrix}, \quad \nu_3 = \begin{bmatrix} 1 \\ 0 \\ -1 \end{bmatrix}$$

$$X'(t) = \sum_{j=1}^{m} \upsilon_j a_j(X(t))$$

Modelling Regimes

- **Discrete and stochastic** – Small numbers of molecules. Exact description via Stochastic Simulation Algorithm (SSA) - *Gillespie*. Large computational time.

$$X \leftarrow X + \upsilon_j$$

- **Continuous and stochastic** - A bridge connecting discrete and continuous models.

  Described by SDEs – Chemical Langevin Equation.

- **Continuous and deterministic** – Law of Mass Action. The Reaction Rate equations. Described by ordinary differential equations. Not valid if molecular populations of some critical reactant species are small.

D. Gillespie (1977) Exact stochastic simulation of coupled chemical reactions, J. Phys. Chem. 81, 2340.

Towards multiscale methods in Systems Biology

Efficient Discrete algorithms - Leap methods

Poisson (Gillespie, JCP, 115(2001),1716)

Binomial (Tian and Burrage, JCP, 2004)

Assumption: In the time period $(t, t+\tau)$, the number of reactions for reaction channel R_j is Poisson (Binomial). Larger τ

For the given criterion ε , choose a stepsize τ to satisfy the leap condition $\left|a_j(X+\lambda)-a_j(X)\right| \le \varepsilon\, a_0(X), \qquad \lambda = \nu a(X)\tau$

Generate Poisson (Binomial) numbers

Update the system

$$t \leftarrow t+\tau, \qquad X(t+\tau) \leftarrow X(t)+\sum_{j=1}^{M} \nu_j P(a_j(X(t)),\tau)$$

$$t \leftarrow t+\tau, \qquad X(t+\tau) \leftarrow X(t)+\sum_{j=1}^{M} \nu_j B(N_j, b_j(X(t))\tau)$$

Multiscale Discrete methods

- The SSA can be expensive –compute m reaction times and τ can be small
- Given a subinterval of length τ , if we can determine how many times each reaction channel fires in each subinterval, we can forego knowing the precise instants at which the firings took place. Thus we could leap from one subinterval to the next, rather than one reaction to the next.
- How long can that subinterval be? Tau-leaping is exact for constant propensity functions, thus LEAP CONDITION: is selected so that no propensity function changes “appreciably”.
- If the reactant population is large it can be moderate sized and the tau leap method gives the Explicit Euler method in SDE and ODE regimes.
- It can also be viewed as the Euler method for solving an SDE driven by jump processes.
- This is the key to looking at other methods based on ODE techniques: extrapolation, Runge-Kutta and linear multistep methods.

Extrapolation

I. T. Szekely, K. Burrage, R. Erban, K. C. Zygalakis (2012): A higher-order numerical framework for stochastic simulation of chemical reaction systems, BMC Systems Biology.2012, 6:85, DOI: 10.1186/1752-0509-6-85.

By obtaining a global error expansion for a general weak first-order method, we prove that extrapolation can increase the weak order of convergence for the moments of the Euler and the midpoint *theta and tau leap methods, from 1 to 2.*

We use a discrete stochastic global expansion via

$$\partial_t u + \mathcal{L}u = 0$$

$$u(\mathbf{x}, t) = f(\mathbf{x})$$

$$\mathcal{L}u \equiv \sum_{j=1}^{M} a_j(\mathbf{x}) \left(u(\mathbf{x} + \nu_j) - u(\mathbf{x})\right)$$

$$u(\mathbf{x}, t) = \mathbb{E}\left(f(\mathbf{X}_T) | \mathbf{X}_t = \mathbf{x}\right),$$

Problem $X \xrightarrow{k} \emptyset, \quad k = 0.1.$

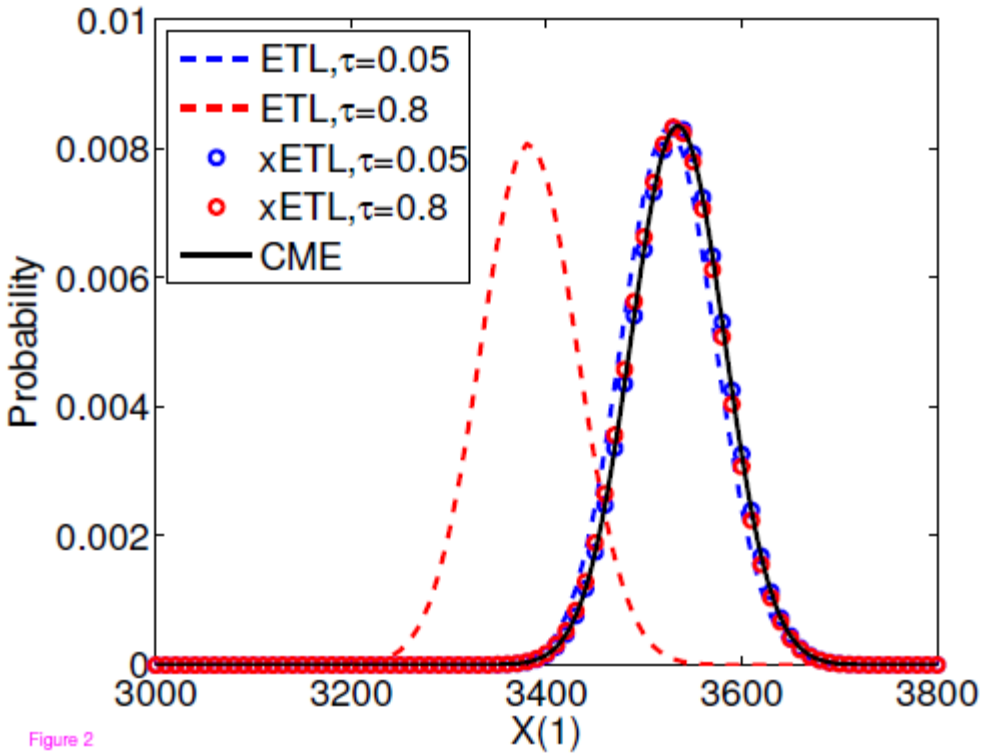
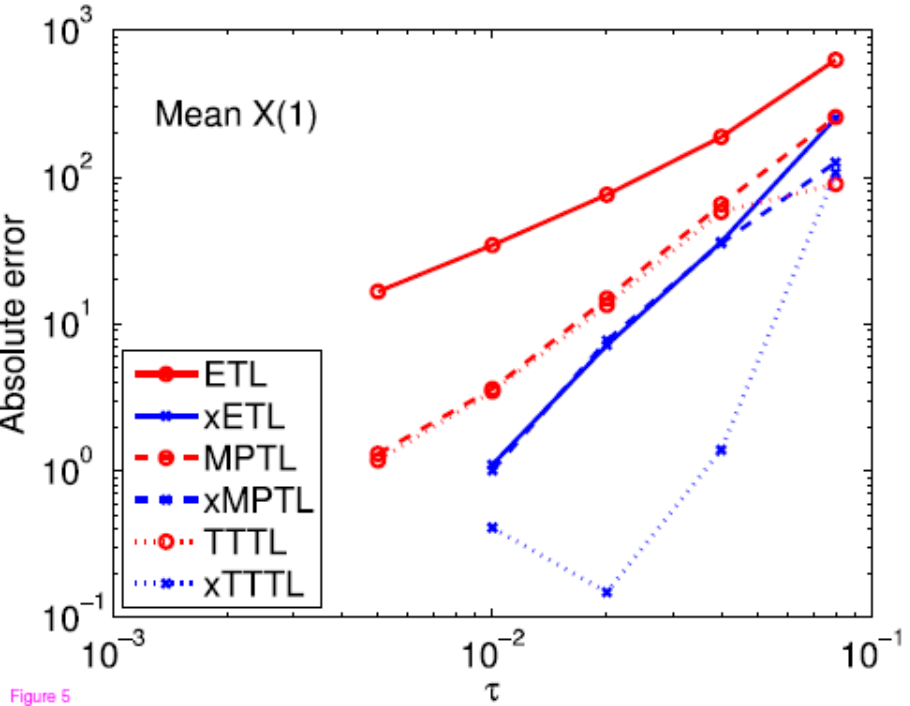


Figure 2

$$
\begin{aligned}
E_A &\xrightarrow{k_1} E_A + A, && k_1 = 15,\\
E_B &\xrightarrow{k_2} E_B + B, && k_2 = 15,\\
E_A + B &\underset{k_4}{\overset{k_3}{\rightleftharpoons}} E_A B, && k_3 = 5\times 10^{-4}, k_4 = 2,\\
E_A B + B &\underset{k_6}{\overset{k_5}{\rightleftharpoons}} E_A B_2, && k_5 = 10^{-3}, k_6 = 6,\\
A &\xrightarrow{k_7} \emptyset, && k_7 = 5,\\
E_B + A &\underset{k_9}{\overset{k_8}{\rightleftharpoons}} E_B A, && k_8 = 5\times 10^{-4}, k_9 = 2,\\
E_B A + A &\underset{k_{11}}{\overset{k_{10}}{\rightleftharpoons}} E_B A_2, && k_{10} = 10^{-3}, k_{11} = 6,\\
B &\xrightarrow{k_{12}} \emptyset, && k_{12} = 5.
\end{aligned}
$$

$$
\mathbf{X}(0) = (2\times 10^4, 1.5\times 10^4, 9500, 9500, 2000, 500, 2000, 500)^T,
$$



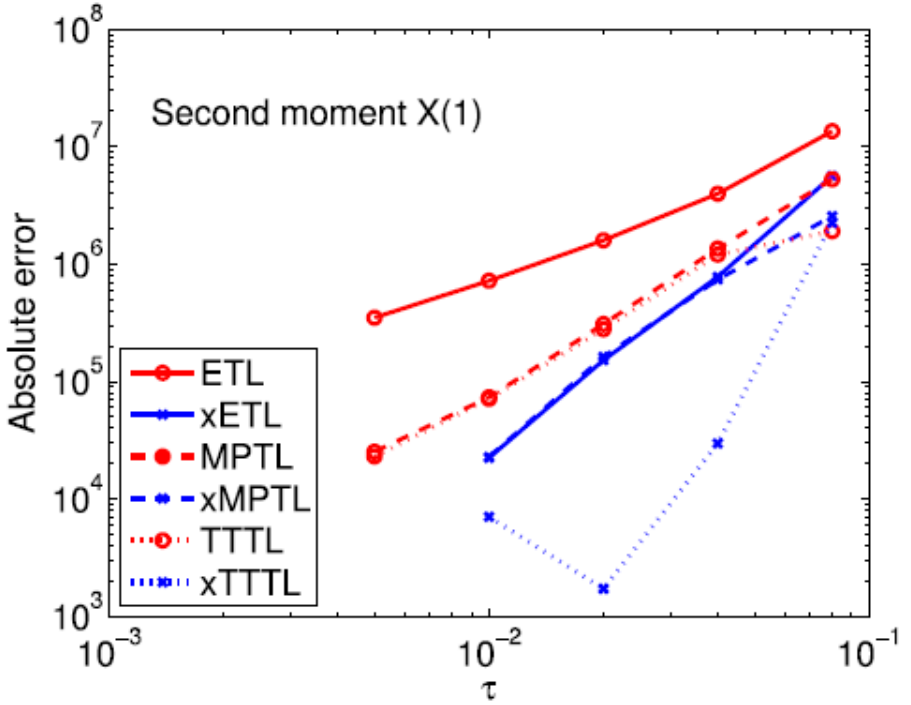


Figure 5

II. T. Székely, K. Burrage, K. C. Zygalakis and M. Barrio (2014): Efficient simulation of stochastic chemical kinetics with the Stochastic Bulirsch-Stoer extrapolation method, BMC Systems Biology, 2014, 8:71 DOI: 10.1186/1752-0509-8-71.

The Bulirsch-Stoer method is an accurate ODE solver based on Richardson extrapolation [25, 26]. A Neville table is built by repeated extrapolation of a set of initial approximations with stepsizes that are different subintervals of a larger overall step τ, and is then used to find a very accurate solution. This happens *inside each timestep*, allowing τ to be varied between steps.

Results

$X \to 2X$, with $c = 0.2$, $X(0) = 1000$

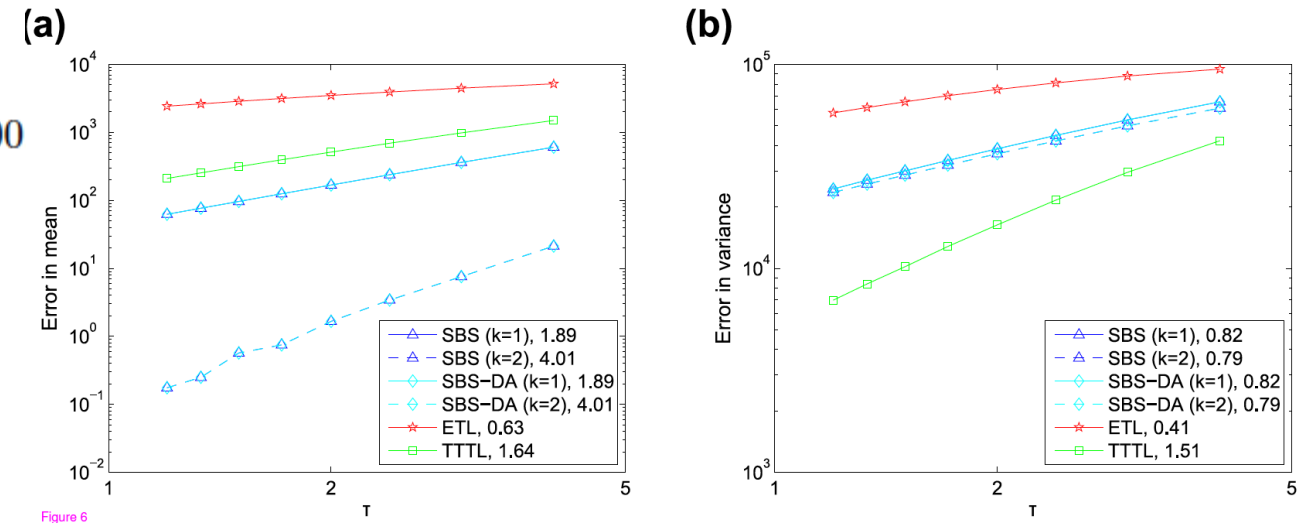


Figure 6

θ-trapezoidal τ-leap (TTTL) has weak order two in mean and variance

Hu Y, Li T, Min B: **A weak second order tau-leaping method for chemical kinetic systems.** *Journal of Chemical Physics* 2011, **135**:024113.

Mutually inhibiting enzyme system

$$
\begin{aligned}
E_A &\xrightarrow{k_1} E_A + A, && k_1 = 15,\\
E_B &\xrightarrow{k_2} E_B + B, && k_2 = 15,\\
E_A + B &\underset{k_4}{\overset{k_3}{\rightleftharpoons}} E_A B, && k_3 = 5 \times 10^{-4}, k_4 = 2,\\
E_A B + B &\underset{k_6}{\overset{k_5}{\rightleftharpoons}} E_A B_2, && k_5 = 10^{-3}, k_6 = 6,\\
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B &\xrightarrow{k_{12}} \emptyset, && k_{12} = 5.
\end{aligned}
$$

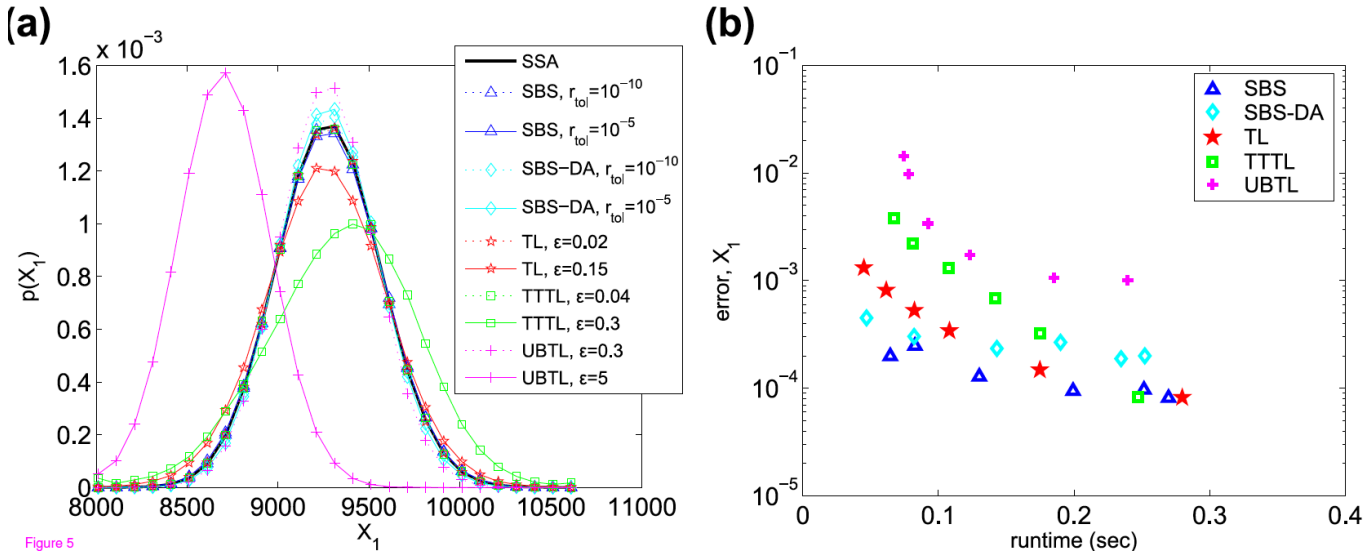


Figure 5

Why do the methods behave this way? Small noise SDEs

$$d\mathbf{X}(t) = f(t, \mathbf{X}(t))dt + \varepsilon g(t, \mathbf{X}(t))dW(t) \qquad \mathcal{O}(\tau^p + \tau^q \epsilon^r), \text{ where } q < p.$$

Runge-Kutta and linear multistep methods

III. Poisson Runge-Kutta methods

$$Y_i = X_n + \sum \upsilon_k P\left(\sum_{j=1}^{s} w_{ij} a_k(Y_j), \tau \right)$$

$$X_{n+1} = X_n + \sum \upsilon_k P\left(\sum_{j=1}^{s} \beta_j a_k(Y_j), \tau \right)$$

- Example: $s = 2$, explicit

$$Y = X_n + \sum \upsilon_k P\left(\theta\, a_k(X_n), \tau \right)$$

$$X_{n+1} = X_n + \sum \upsilon_k P\left(\left(1 - \tfrac{1}{2\theta}\right) a_k(X_n) + \tfrac{1}{2\theta}\, a_k(Y), \tau \right)$$

- Note

$$a_j(x)\,\tau >> 0$$

$$P(a_j(x), \tau) \approx N(a_j(x)\,\tau, a_j(x)\,\tau) = a_j(x)\,\tau + \sqrt{a_j(x)\,\tau}\; N(0,1)$$

$$= a_j(x)\,\tau + \sqrt{a_j(x)}\; \Delta W_j(\tau).$$

- But not truly high weak order as we not capturing higher order moments.

IV. P.Rue, J.Villa Freixa and K. Burrage (2010): Simulation methods with extended stability regions for stiff biochemical kinetics, *BMC Systems Biology*, **4:**110doi:10.1186/1752-0509-4-110.

Stochastic Runge-Kutta method

$$\mathbf{d}_n = \sum_{j=1}^{m} \nu_j L\left(\tau, a_j(\mathbf{X}_n)\right)$$

$$L(\tau, x) = \mathcal{P}(\tau x) - \tau x,$$

$$\mathbf{Y}_i = \mathbf{X}_n + \tau \sum_{j=1}^{i-1} \alpha_{ij} \mathbf{f}(\mathbf{Y}_j) + \omega_i \mathbf{d}_n, \quad i = 1, \ldots, s$$

$$\mathbf{f}(\mathbf{x}) = \sum_{j=1}^{m} \nu_j a_j(\mathbf{x})$$

$$\mathbf{X}_{n+1} = \mathbf{X}_n + \tau \sum_{j=1}^{s} \beta_j \mathbf{f}(\mathbf{Y}_j) + \mathbf{d}_n$$

Test problem

$$S_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} S_2 \qquad z = -\tau(k_1 + k_2) \qquad \mathbb{E}\left[\mathbf{X}_{n+1}\right] = R(\tau \mathbf{W}) \mathbb{E}\left[\mathbf{X}_n\right]$$

$$\mathrm{Var}\left[\mathbf{X}_\infty\right] = \psi(z) \mathrm{Var}\left[\mathbf{X}^*\right] \qquad \psi(z) = \frac{2}{z}\left(\frac{R(z) - 1}{R(z) + 1}\right)$$

Trapezoidal method

$$R(z) = \frac{1 + \frac{1}{2}z}{1 - \frac{1}{2}z} \quad \text{and} \quad \psi(z) = 1, \ \forall z.$$

For an explicit method we want ψ as close to one for as large a range of z as possible. This leads to

$$\mathbf{Y}_1 = \mathbf{y}_n$$

$$\mathbf{Y}_i = \mathbf{y}_n + \alpha_{i,i-1}\left(\tau \mathbf{f}(\mathbf{Y}_{i-1}) + \mathbf{d}_n\right), \quad i = 2, \ldots, s$$

$$\mathbf{y}_{n+1} = \mathbf{y}_n + \tau \mathbf{f}(\mathbf{Y}_s) + \mathbf{d}_n.$$

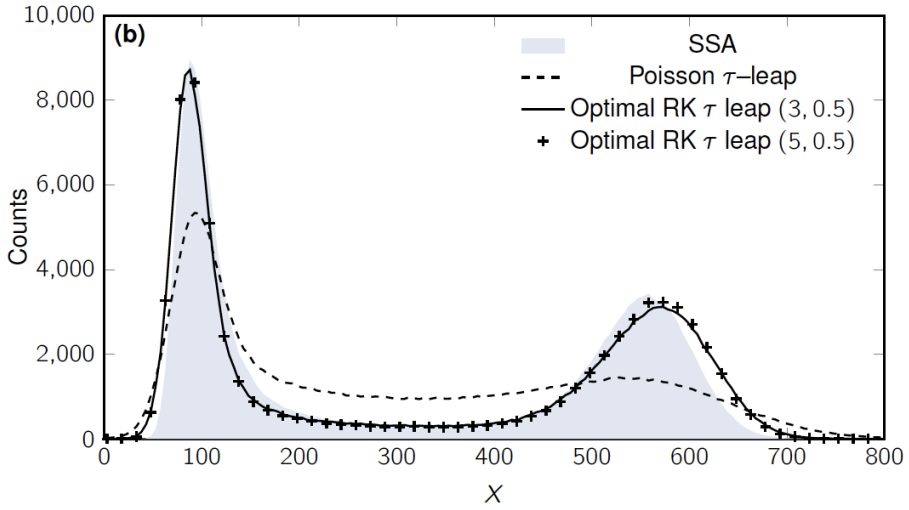
Select ϵ $|\psi(z) - 1| < \epsilon$

Bound ϵ	Stages s	Stability $l_{s,\epsilon}$	Factor vs. τ–leap	Norm. factor vs. τ–leap
0.10	3	3.94566	19.73	6.58
	5	10.1813	50.9	10.18
0.25	3	5.89563	14.74	4.91
	5	11.0001	27.5	5.5
0.50	3	8.12004	12.18	4.06
	5	15.5997	23.4	4.68

Schlogl test problem

$$
\begin{aligned}
A + 2X &\xrightarrow{k_1} 3X & k_1 &= 3 \cdot 10^{-7} \\
3X &\xrightarrow{k_2} A + 2X & k_2 &= 10^{-4} \\
X &\xrightarrow{k_3} B & k_3 &= 3.5 \\
B &\xrightarrow{k_4} X & k_4 &= 10^{-3}
\end{aligned}
$$

Results:



V. Stochastic Linear Multistep Methods for the Simulation of Chemical Kinetics, JCP 15, M. Barrio, K. Burrage, P.Burrage

ODE: Linear multistep method

$$y_{n+1} = \sum_{j=1}^{\kappa} \alpha_j y_{n+1-j} + h \sum_{j=0}^{\kappa} \beta_j f_{n+1-j}$$

Weak order 2 method

David F Anderson and Jonathan C Mattingly. A weak trapezoidal method for a class of stochastic differential equations. *Communications in Mathematical Sciences*, 9(1), 2011.

$$X^P = X_n + \sum_{j=1}^{M} \nu_j \mathcal{P}(\frac{1}{2}\tau a_j(X_n))$$

$$l_j = max\{2a_j(X^P) - a_j(X_n), 0\}, \quad j = 1, \ldots, M$$

$$X_{n+1} = X^P + \sum_{j=1}^{M} \nu_j \mathcal{P}(\frac{1}{2}\tau l_j).$$

This suggests that in order to construct methods of weak order two there must be samples of the form $\mathcal{P}(\tau a_j(\mathcal{P}(c\tau a_i(X_n))))$. These samples are akin to the double integrals of Wiener processes that are needed to construct higher order methods for SDEs [3].

Linear test problem $X \xrightarrow{c} \varnothing$

Stochastic Adams Bashforth $X_{n+1} = X_n - \mathcal{P}(z \sum_{j=1}^{k} B_j X_{n+1-j}), \quad z = \tau c$

Stochastic Adams Moulton :PC $\hat{X}_{n+1} = X_n - z \sum_{j=1}^{\infty} \beta_j X_{n+1-j}$

$$X_{n+1} = X_n - \mathcal{P}(z \sum_{j=1}^{k} \hat{\beta}_j X_{n+1-j} + z\hat{\beta}_0 \hat{X}_{n+1})$$

Theorem 3.1. *If the underlying AM has order p and the order of the starting procedure in the mean is p or $p-1$ then the mean order of the SAM will also be p.*

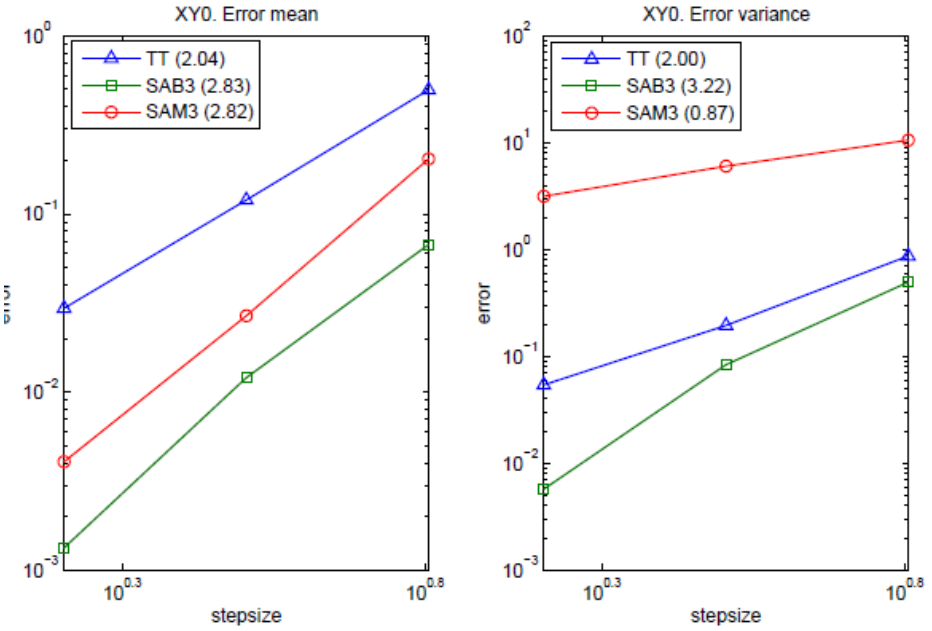
Corollary 3.1. *The mean order of the SABMs ($k \geq 3$) and SAMMs ($k \geq 2$) will be three if the Θ-trapezoidal τ-leap method is used as a starting procedure.*

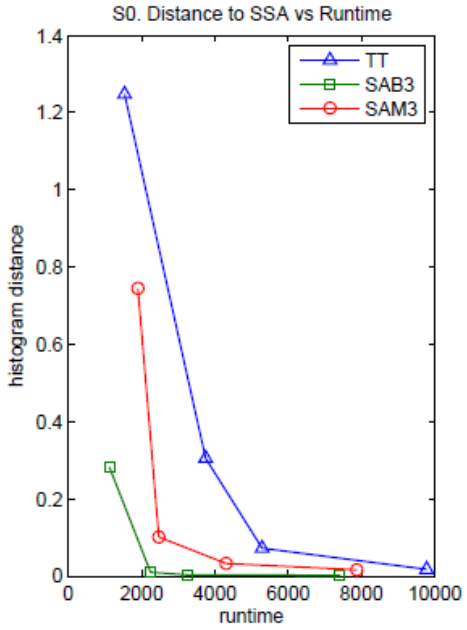
Theorem 3.2. *The correlation order of the SABMs ($k \geq 3$) is three if the Θ-trapezoidal τ-leap method is used as a starting procedure. However, the correlation order of the predictor-corrector SAMM is only one.*

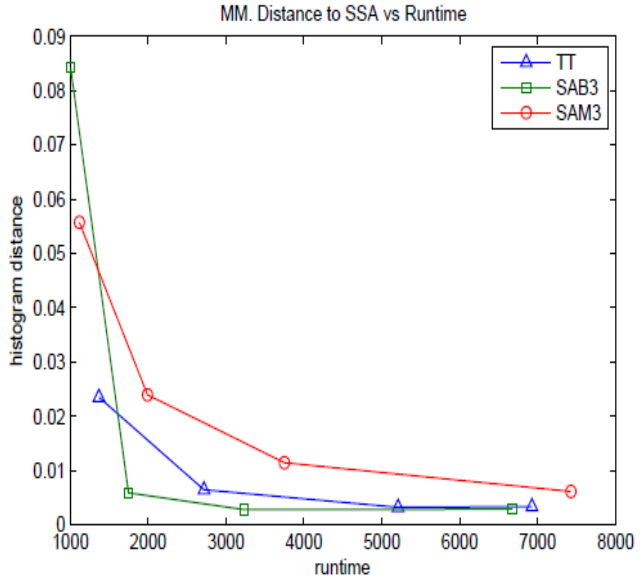
Weak order in mean and variance
X+Y -> 0

Kullback Leibler distance for

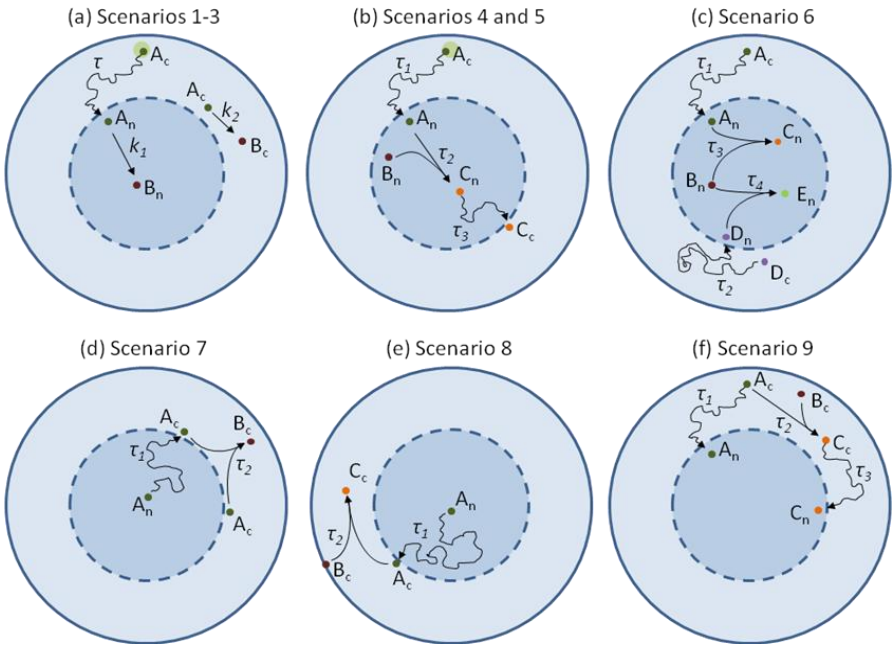
(i) Linear problem
(ii) Michaelis Menten problem







VI. T Marquez-Lago**,** A. Leier **and** K. Burrage (2010): Probability distributed time delays: integrating spatial effects into temporal models, BMC Systems Biology, **4:**19doi:10.1186/1752-0509-4-19.



incorporate spatial information by means of tailored, probability distributed time-delays.

(a) nuclear translocation of particles *Ac* followed by a unary reaction *An* → *Bn* and the translocation reaction competing with the unary reaction *Ac* → *Bc*.

(b) nuclear translocation of *Ac* followed by a nuclear binary reaction *An* + *Bn* → *Cn* followed by the cytoplasmic translocation of the product *Cn*.

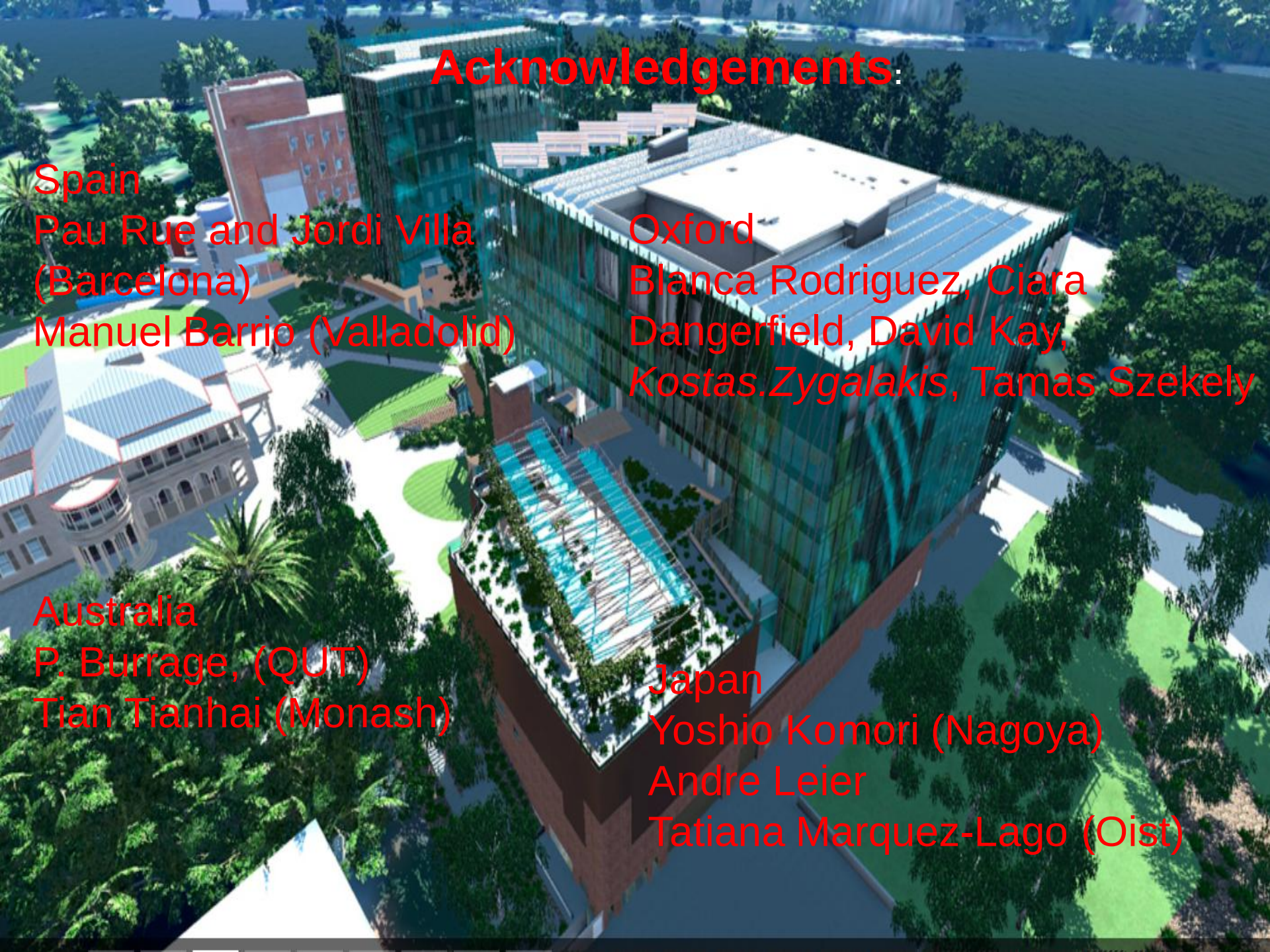
(c) upon translocation molecules *An* and *Dn* compete for the same binding partner *Bn* (*An* + *Bn* → *Cn* and *Dn* + *Bn* → *En*)

(d-e) upon translocation molecules *Ac* are able to dimerize or bind to a species initially localized in the cell membrane.

(f) upon translocation molecules *Ac* dimerize with molecules *Bc* and their product *Cc* is able to translocate back to the nucleus.

Conclusions

- Need for new stochastic methods (with good order and stability properties) in the discrete setting for Intrinsic noise modelling in Systems Biology.
- Need for multiscale approaches.
- We can use ideas from the deterministic setting to construct effective methods.
- But it is not easy to construct methods with truly high order in both mean and variance
- Issues of the sampling error and multi level (Giles) approaches to improve efficiency – applied to discrete case by Andersen and Higham.
- What can be done spatially?



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