Construction of Random Low-dimensional Manifolds for Stochastic Chemical Reaction Systems with Stiffness

Xiaoying Han*    Habib Najm**

*Department of Mathematics and Statistics, Auburn University, Auburn, AL

**Sandia National Laboratories, Livermore, CA

5th International Workshop on Model Reduction in Reacting Flows
June 28 – July 1, 2015
Lübbenau, Germany
Chemical Reaction Networks

A collection of chemical reactions that involves

- a set of $N$ “species”:
  
  $$S_i, \quad i \in \{1, \ldots, N\}$$

- a set of $M$ chemical reactions $\mathcal{R}_j, \quad j \in \{1, \ldots, M\}$:

  $$\mathcal{R}_j : \sum_{i=1}^{N} \alpha_{ij} S_i \rightarrow \sum_{i=1}^{N} \beta_{ij} S_i$$

For $i = 1, \ldots, N, \quad j = 1, \ldots, M$

- $\alpha_{ij}, \beta_{ij} \in \mathbb{Z}^+$ - stoichiometry coefficients
- $v_{ij} = \beta_{ij} - \alpha_{ij}, \quad \mathbf{v}_j := (v_{1j}, \cdots, v_{Nj})$ - change in molecular population caused by one $\mathcal{R}_j$ reaction
- $\mathbf{V} = (v_{ij})_{N \times M}$ - stoichiometry matrix.
Model Set-up

Assumption: the system is well-stirred:

- constant volume $\Omega$
- in thermal equilibrium at some constant temperature
- positions and velocities of the individual molecules ignored

$X_i(t)$ - the number of the species $S_i$ in the system at time $t$.

**Goal** estimate the state vector

$$\mathbf{X}(t) := (X_1(t), \cdots, X_N(t))$$

given that the system was in state $\mathbf{X}(t_0) = \mathbf{x}_0$ at initial time $t_0$. 
Reaction Rate Equation (RRE) - an ODE Model

- $k_j$: reaction constant for reaction $R_j$
- $R_j(X)$: algebraic form of the $j$th reaction ($j = 1, \ldots, M$)
  
  e.g., mass-action kinetics assumption: $R_j(X) = k_j \prod_{i=1}^{N} X_i^{\alpha_{ij}}$
  
  $$X(t) = \begin{pmatrix} X_1(t) \\ X_2(t) \\ \vdots \\ X_N(t) \end{pmatrix}, \quad R(X) = \begin{pmatrix} R_1(t) \\ R_2(t) \\ \vdots \\ R_M(t) \end{pmatrix}$$

The system of ordinary differential equations (ODEs) governed by the chemical reaction network is:

$$\frac{dX(t)}{dt} = V \cdot R(X).$$

* Deterministic and continuous model - aggregate behavior of the system (works well for systems of test-tube size or larger).
Stochastic Chemical Kinetics

Chemical systems - inherently stochastic, as reactions depend on random (thermal) motion.

Stochastic chemical kinetics - *describes time evolution of a well-stirred chemically reacting system, taking honest account of the system’s discreteness and stochasticity.*

- Stochastic effects become important for small system size (e.g., modeling of surface kinetics for nano-structure materials in catalysis and gene regulation of cells in biology)
- Stoichiometry information is not sufficient to completely characterize the behavior of the system.
- Need to specify the *rates* at which the various reactions take place, by specifying “propensity” (or “intensity”) functions.
Stochastic Models of Chemical Reactions

- $X_i(t)$: number of species $S_i$ at time $t$ ($i = 1, \ldots, N$).
- $\mathbf{X}(t) = (X_1(t), \ldots, X_N(t))^T$ - column-vector Markov stochastic process.
- $\mathbf{x} = (x_1, \ldots, x_N)^T \in \mathbb{Z}_+^N$ - state of the process.
- $p_x(t) = \mathbb{P}[\mathbf{X}(t) = \mathbf{x}, \text{given } \mathbf{X}(t_0) = \mathbf{x}_0]$ - the probability that, at time $t$, there are $x_1$ units of species $S_1$, $x_2$ units of species $S_2$, ..., given $\mathbf{X}(t_0) = \mathbf{x}_0$.
- $\rho_j : \mathbb{Z}_+^N \rightarrow \mathbb{R}_+$ - propensity function for the respective reaction $\mathcal{R}_j$.
- $\rho_j(\mathbf{x}) \, dt$ - given $\mathbf{X}(t) = \mathbf{x}$, the probability that reaction $\mathcal{R}_j$ takes place in the next infinitesimal time interval $[t, t + dt)$.
- $v_j$ - the $j$th column of stoichiometry matrix $V$. 
The Chemical Master Equation (CME)

Goal: infer the probability

\[ p_x(t) = p(x, t|x_0, t_0) \]

Time evolution of \( p_x(t) \):

\[
\frac{\partial p(x, t|x_0, t_0)}{\partial t} = \sum_{j=1}^{M} \rho_j(x - v_j)p(x - v_j, t|x_0, t_0) - \sum_{j=1}^{M} \rho_j(x)p(x, t|x_0, t_0).
\]

or

\[
\frac{dp_x(t)}{dt} = \sum_{j=1}^{M} \rho_j(x - v_j)p_{x-v_j} - \sum_{j=1}^{M} \rho_j(x)p_x, \quad x \in \mathbb{Z}_+^N
\]

- The CME completely determines the function \( p(x, t|x_0, t_0) \).
- The CME can be solved analytically for only a few simple cases.
- Even numerical solutions are prohibitively difficult in most cases.
Stochastic Simulation Algorithm (SSA)

SSA (Gillespie Algorithm) - Construct simulated trajectories of $X(t)$ versus $t$ by using Monte Carlo methods.

Key of construction: at time $t$

1. When will the next reaction occur - random variable $\tau$
2. Which reaction it will be - random variable $j$

Seek $p(\tau, j|\mathbf{x}, t)$ - the probability, given $X(t) = \mathbf{x}$, that the next reaction will happen in the infinitesimal interval $[t + \tau, t + \tau + d\tau)$ and will be an $\mathcal{R}_j$ reaction.

$$p(\tau, j|\mathbf{x}, t) = \rho_j(\mathbf{x}) \exp\{\rho^*(\mathbf{x})\tau\}, \quad \rho^*(\mathbf{x}) := \sum_{j=1}^{M} \rho_j(\mathbf{x})$$
SSA (Cont.)

- $\tau$ - exponential random variable with mean and standard deviation $1/\rho^*(\mathbf{x})$
- $j$ - statistically independent integer random variable with point probabilities $\rho_j(\mathbf{x})/\rho^*(\mathbf{x})$

SSA is exact, but SLOW - computationally more efficient approximate sampling algorithms are desired.

- Tau-leaping method
- Implicit tau-leaping method
- Trapezoidal method
- Hybrid methods
- Slow-scale SSA
- ...
Tau-leaping Method

Simulates multiple reactions that appear during one next time interval of length $\tau$. 

Diagram: Exact SSA vs. Tau-leaping method

- **SSA Method**
  - $R_1$, $R_3$, $R_2$, $\ldots$
  - $t_0$, $t_1$, $t_2$, $t_3$, $t_n$

- **Tau-Leaping Method**
  - $R_1$ fires $K_1$ times
  - $R_2$ fires $K_2$ times
  - $R_M$ fires $K_M$ times
  - $t_0$, $t_0 + \tau$, $t_n$
Tau-leaping: The Bridge to RRE

* Leap condition (on $\tau$): no propensity function will change significantly, i.e. $\rho_j(x)$ remains essentially constant.

* The number of times that each reaction $R_j$ fires in $[t, t + \tau)$ is a Poisson random variable ($P_j$) with mean and variance $\rho_j(x)\tau$

Leap the system approximately ahead by

$$\mathbf{X}(t + \tau) = \mathbf{X}(t) + \sum_{j=1}^{M} P_j(\rho_j(x)\tau)\mathbf{v}_j$$
Further Approximation

Assume that the leap $\tau$ is

- small enough to satisfy the leap condition
- large enough that the expected firing times of each reaction $\mathcal{R}_j$ during $\tau$ is large, i.e., $\rho_j(x)\tau \gg 1$.

Notice

* a Poisson random variable with a mean and variance $\gg 1$ can be approximated by a normal random variable with the same mean and variance.

Then

$$X(t + \tau) = X(t) + \sum_{j=1}^{M} \mathcal{N}_j(\rho_j(x)\tau, \rho_j(x)\tau)v_j$$
Chemical Langevin Equation (CLE)

Using $\mathcal{N}(\mu, \sigma^2) = \mu + \sigma \mathcal{N}(0, 1)$ to get

$$X(t + \tau) = X(t) + \sum_{j=1}^{M} \left\{ \rho_j(x) \tau + \sqrt{\rho_j(x)} \tau \mathcal{N}_j(0, 1) \right\} v_j$$

$$= X(t) + \sum_{j=1}^{M} v_j \rho_j(x) \tau + \sum_{j=1}^{M} v_j \sqrt{\rho_j(x)} \mathcal{N}_j(0, 1) \sqrt{\tau}$$

By theory of continuous Markov processes

$$dX(t) = \sum_{j=1}^{M} v_j \rho_j(X(t)) dt + \sum_{j=1}^{M} v_j \sqrt{\rho_j(X(t))} dW_j(t)$$

$W_j(t)$ - independent Gaussian white noise processes.
Stiff Chemical Reaction Systems

- Deterministic and continuous - modeled by a system of coupled ODEs, associated with stiffness in the governing equations.
- Stochastic and continuous - perturb both the fast and slow variables in its deterministic counterpart by noise to obtain singularly perturbed SDE system.

First characterization:
- deals with systems with clear separation of time-scales \( t \) and \( \tau = \varepsilon t \), with \( 0 < \varepsilon \ll 1 \).
- uses invariant manifolds to approximate the full system.
- combination of analysis and numerics.
General Singular Perturbation

\[
\frac{dx(t)}{dt} = f(x, y; \varepsilon); \quad \varepsilon \frac{dy(t)}{dt} = g(x, y; \varepsilon)
\]

- \(\varepsilon\) - small parameter.
- \(x(t) \in \mathbb{R}_+^m\) - slow variable; \(y(t) \in \mathbb{R}_+^n\) - fast variable.

Two ways to perform the limit \(\varepsilon \to 0\):

1. \(\varepsilon = 0\): reduced equation:

\[
\frac{dx(t)}{dt} = f(x, y^*(x); 0)
\]

Slow manifold: \(y = y^*(x)\). (differentiable manifold)

2. \(\tau = t/\varepsilon\): associated system:

\[
\frac{dx}{d\tau} = 0, \quad \frac{dy}{d\tau} = g(x, y; 0)
\]
Perturb both fast and slow variables by noise with different intensities according to timescales (the diffusive nature to the Brownian motion causes paths to spread like $\sigma \sqrt{t}$):

\[
\begin{align*}
    dX(t) &= f(X(t), Y(t), \varepsilon)dt + \sigma_X F(X(t), Y(t), \varepsilon)dW(t) \\
    \varepsilon dY(t) &= g(X(t), Y(t), \varepsilon)dt + \sqrt{\varepsilon} \sigma_Y F(X(t), Y(t), \varepsilon)dW(t)
\end{align*}
\]

- $\sigma_X^2, \sigma_Y^2$ - (rate of diffusion)$^2$/the speed of drift.
- $W(t)$ - standard Brownian motion.
• General stochastic fast-slow reaction mechanism

\[
\begin{align*}
    dX(t) &= V_X R(X(t), Y(t), \varepsilon) + \sigma_X F_X(X(t), Y(t), \varepsilon) dW(t) \\
    \varepsilon dY(t) &= V_Y R(X(t), Y(t), \varepsilon) + \sqrt{\varepsilon} \sigma_Y F_Y(X(t), Y(t), \varepsilon) dW(t)
\end{align*}
\]

• Fast-slow CLE

\[
\begin{align*}
    dX(t) &= V_X R(X(t), Y(t), \varepsilon) + V_X \sqrt{R(X(t), Y(t), \varepsilon)} dW(t) \\
    \varepsilon dY(t) &= V_Y R(X(t), Y(t), \varepsilon) + \sqrt{\varepsilon} V_Y \sqrt{R(X(t), Y(t), \varepsilon)} dW(t)
\end{align*}
\]

• Stochastic fast-slow system with multiplicative noise

\[
\begin{align*}
    dX(t) &= V_X R(X(t), Y(t), \varepsilon) + \sigma_X X(t) dW(t) \\
    \varepsilon dY(t) &= V_Y R(X(t), Y(t), \varepsilon) + \sqrt{\varepsilon} \sigma_Y Y(t) dW(t)
\end{align*}
\]
Noise Effect on Invariant Manifold

1. Find stationary solutions to the Fokker-Planck equation.
   - boundedness of domain for chemical reaction systems
   - separation of time scales
   - numerical simulation by integrating the system forward in time and performing ensemble to obtain PDF.
   - provide purely statistical information

2. Random dynamical system approach
   - based on path-wise analysis rather than simple ensemble of realizations
   - random invariant measures as its fundamental objects
   - a pullback approach where system runs from a time in the past until the present time
   - geometric structures emerge naturally
Random Dynamical System (RDS)

- One prototype - product of random mappings

- Two basic ingredients
  1. a model of the noise
  2. a model of the system which is perturbed by the noise
A RDS as an action on a bundle

\[
\begin{align*}
\{\omega\} \times X & \quad \{\theta(s)\omega\} \times X \\
\varphi(t, \theta(s)\omega) & = \varphi(t + s, \omega) \\
\varphi(s, \omega)x & = \varphi(t, \theta(s)\omega)\varphi(s, \omega)x \\
\varphi(t + s, \omega)x & = \varphi(t, \theta(s)\omega)\varphi(s, \omega)x \\
\theta(t)\theta(s)\omega & = \theta(t + s)\omega
\end{align*}
\]
Random Invariant Manifold

\{S(t, \omega)\}_{t \in \mathbb{R}, \omega \in \Omega} - \text{RDS over } (\Omega, \mathcal{F}, \mathbb{P}, \theta) \text{ with state space } X.

- A multifunction \{M(\omega)\}_{\omega \in \Omega} \text{ of nonempty closed sets } \{M(\omega)\}(\omega \in \Omega) \text{ contained in } X \text{ is called a random set if } 
\omega \mapsto \inf_{y \in M(\omega)} \|x - y\| \text{ is a random variable for any } x \in X.

- A random set \(M(\omega)\) is said to be random invariant for a RDS \(S(t, \omega)\) if

\[ S(t, \omega, M(\omega)) = M(\theta_t \omega), \quad \forall t \in \mathbb{R}, \ \omega \in \Omega. \]

- If a random invariant set \(M(\omega)\) can be represented as a graph of a mapping \(f(t, \omega) : X_1 \to X_2, \ X = X_1 \times X_2, \ \text{i.e.} \ M(\omega) = \{x_1, f(x_1, \omega) \}: x_1 \in X_1\}, \text{ then } M(\omega) \text{ is called a random invariant manifold (RIM).}
The Davis-Skodje Model

\begin{align*}
\dot{x}(t) &= -x(t), \\
\dot{y}(t) &= -\gamma y(t) + \gamma \frac{x(t)}{1 + x(t)} - \frac{x(t)}{(1 + x(t))^2}.
\end{align*}

\begin{align*}
\frac{dX(t)}{dt} &= -X(t)dt + \mu X(t)dW(t) \\
\frac{dY(t)}{dt} &= \left(-\gamma Y(t) + \gamma \frac{X(t)}{1 + X(t)} - \frac{X(t)}{(1 + X(t))^2}\right)dt + \sigma \sqrt{\gamma} Y(t)dW(t)
\end{align*}
Introduce the Ornstein-Uhlenbeck (O-U) processes satisfy

\[
\begin{align*}
    d\delta &= -\delta dt + \mu dW(t) \\
    d\eta &= -\gamma \eta dt + \sigma \sqrt{\gamma} dW(t)
\end{align*}
\]

- the only nontrivial process which is stationary, Gaussian and Markovian, up to allowing linear transformation of the space and time variables

Change of variables \(u(t, \omega) = X(t)e^{-\delta(\theta t \omega)}\) and \(v(t, \omega) = Y(t)e^{-\eta(\theta t \omega)}\):

\[
\begin{align*}
    \dot{u} &= -u + \delta(\theta t \omega)u \\
    \dot{v} &= -\gamma v + \gamma \eta(\theta t \omega)v + \gamma \frac{e^{\delta-\eta}u}{1 + ue^\delta} - \frac{e^{\delta-\eta}u}{(1 + ue^\delta)^2}
\end{align*}
\]
For any fixed initial data \((u_0, v_0)\) and for every \(\omega \in \Omega\), the \(u-v\) system admits a unique non-negative solution \((u(t, \omega, u_0, v_0), v(t, \omega, u_0, v_0))\) that depends continuously on the initial data.

The solution operator

\[
\varphi(t, \omega, u_0, v_0) = (u(t, \omega, u_0, v_0), v(t, \omega, u_0, v_0))
\]

defines a random dynamical system in \(\mathbb{R}^2\)

\[
\Phi(t, \omega) := \varphi(t, \omega) \cdot \begin{pmatrix}
e^{\delta(\theta_t \omega)} & 0 \\
0 & e^{\eta(\theta_t \omega)}
\end{pmatrix}
\]

is the random dynamical system generated by the original \(X - Y\) system.
Rescaling $\varepsilon = 1/\gamma$, $t \rightarrow \varepsilon t$

Introduce another O-U process $\xi$ satisfying

$$d\xi(t) = -\xi(t)\,dt + \sigma dW(t)$$

By the scale property of Wiener processes $\eta(\theta t^{-1} \omega) \overset{d}{=} \xi(t)$.

$$\frac{du}{dt} = -\varepsilon u + \varepsilon \delta(\theta t \omega) u$$  \hspace{1cm} (1)$$

$$\frac{dv}{dt} = -v + \xi(\theta t \omega) v + g(u, \theta t \omega; \varepsilon)$$  \hspace{1cm} (2)$$

$$g(u(t), \theta t \omega; \varepsilon) = \frac{u(t)e^{\delta(\theta t \omega)-\xi(\theta t \omega)}}{1 + u(t)e^{\delta(\theta t \omega)}} - \varepsilon \frac{u(t)e^{\delta(\theta t \omega)-\xi(\theta t \omega)}}{(1 + u(t)e^{\delta(\theta t \omega)})^2}$$
Existence of Invariant Manifold

Assume that $\varepsilon > 0$ is sufficiently small. Then the above random dynamical system generated by (1)-(2) has a random invariant manifold $\mathcal{M}(\omega; \varepsilon)$ which can be represented as a graph

$$\mathcal{M}(\omega; \varepsilon) = \{(u, f(u, \omega; \varepsilon)) : u \in \mathbb{R}_+\},$$

where

$$f(u, \omega; \varepsilon) = \int_0^\infty g(u, \theta \tau \omega; \varepsilon) e^{-\int_\tau^\infty (1-\xi(\theta_s \omega)) ds} d\tau.$$

Moreover, the invariant manifold $\mathcal{M}(\omega; \varepsilon)$ is exponentially tracking, i.e. $\mathcal{M}(\omega; \varepsilon)$ attracts exponentially all the solution orbits of (1)-(2).
Random Slow Manifold

Change back of variables

\[ X(t) = u(t, \omega) e^{\delta(\theta t \omega)} \]
\[ Y(t) = v(t, \omega) e^{\eta(\theta t \omega)} \]

Taking the limit of \( \varepsilon \to 0 \), using stationarity of \( \delta, \eta, \xi \) to obtain the random slow manifold of Stochastic Davis-Skodjes system:

\[ S(\omega) = \left\{ (X(\omega), Y(\omega)) : Y(\omega) = c(\omega) \frac{X(\omega)}{1 + X(\omega)}, \quad X(\omega) \geq 0 \right\} \]

where

\[ c(\omega) = \int_{0}^{\infty} e^{-\xi(\theta \tau \omega)} - \int_{\tau}^{\infty} (1 - \xi(\theta s \omega)) ds d\tau. \]

\[ \text{Probability Density} \]
The two random processes \((\delta, \eta)\) defined by

\[
d\delta = -\delta dt + \mu dW \\
d\eta = -\gamma \eta dt + \sigma \sqrt{\gamma} dW.
\]

have the following properties

\[
E(\delta_t) = 0 \\
E(\eta_t) = 0 \\
\text{Cov}(\delta_s, \delta_t) = \frac{\mu^2}{2} e^{-|s-t|} \\
\text{Cov}(\eta_s, \eta_t) = \frac{\sigma^2}{2} e^{-\gamma|s-t|}.
\]
PCE for RDE Solutions

Gaussian germ $\xi = (\xi_1, \ldots, \xi_n)$

- Defining the PCEs for $(u, v)$ via the PCEs for $(\delta, \eta)$:

\[
\begin{align*}
  u &= \sum_{k=0}^{P} u_k(t) \psi_k(\xi) \\
  v &= \sum_{k=0}^{P} v_k(t) \psi_k(\xi), 
\end{align*}
\]

- Projection integrals for their mode coefficients evaluated via quadrature using the RDE solutions evaluated at the quadrature points in $\xi$-space

\[
\begin{align*}
  u_k(t) &= \frac{1}{\langle \psi_k^2 \rangle} \int u(t, \xi) \psi_k(\xi) p_\xi d\xi \\
  v_k(t) &= \frac{1}{\langle \psi_k^2 \rangle} \int v(t, \xi) \psi_k(\xi) p_\xi d\xi.
\end{align*}
\]
Active Project II: Stochastic Computational Singular Perturbation

\[
\frac{dy}{dt} = F(y) + G(y) \frac{dW(t)}{dt}
\]  
(3)

Alternative representations of \(F\) and \(G\)

\[
F = \sum_{i=1}^{N} a_i f_i, \quad G = \sum_{i=1}^{N} \alpha_i g_i,
\]  
(4)

Evolution of \(f_i\) and \(g_i\):

\[
\frac{df_i}{dt} = \sum_{j=1}^{N} \left\{ \frac{db_i}{dt} \cdot a_j f_j + b_i \cdot J_F \cdot \left( a_j f_j + \alpha_j g_j \frac{dW(t)}{dt} \right) \right\}
\]

\[
\frac{dg_i}{dt} = \sum_{j=1}^{N} \left( \frac{db_i}{dt} \cdot \alpha_j g_j + \beta_i \cdot J_G \cdot a_j f_j \right) + \sum_{j=1}^{N} \beta_i \cdot J_G \cdot \alpha_j g_j \frac{dW(t)}{dt}
\]

\[b_i \cdot a_j = \beta_i \cdot \alpha_j = \delta^i_j, \quad i, j = 1, \cdots, N.\]
Choice of Ideal Basis

Choose $a_j$ and $\alpha_j$ such that

1. the inverse row vectors $b_i$ and $\beta_i$ can be computed accurately.
2. the matrix $\Lambda^i_j = \left( \frac{d b_i}{d t} + b_i \cdot J_F \right) \cdot a_j$ is diagonal and the diagonal elements are ordered in descending magnitudes.
3. the matrix $\Gamma^i_j = \frac{d \beta_i}{d t} \cdot \alpha_j + \beta_i \cdot J_G \cdot a_j$ is diagonalized.
4. Refinements (to be developed).
Start from CME:

\[
\frac{\partial p(x, t)}{\partial t} = \sum_{j=1}^{M} \rho_j(x - v_j)p(x - v_j, t) - \sum_{j=1}^{M} \rho_j(x)p(x; t)
\]

- \( x := (y, z) \)
- \( p(y, z; t) = p(z|y; t)p(y; t) \)
- \( \frac{dp(z|y;t)}{dt} \approx 0 \) (by QSSA)
Consistency of Different Pathways to Slow CLE

Approximated slow CME:

\[
\frac{dp(y; t)}{dt} = \sum_{j=1}^{M} \gamma_j(y - v_j^y)p(y - v_j^y, t) - \sum_{j=1}^{M} \gamma_j(x)p(y; t),
\]

where \( \gamma_j := \sum_z \rho_j(y, z)p(z|y) \) is the conditional expectation of the functional \( \rho_j(\cdot) \).

Two pathways to get the slow CLE:

1. Stiff CME → slow CME → slow CLE
2. Stiff CLE → slow CLE

This work was supported by:


Sandia National Laboratories is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy under contract DE-AC04-94-AL85000.

Thanks for your attention