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

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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 $\mathcal{R}_j, \quad j \in \{1, \ldots, M\}$:

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

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

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

Model Set-up

Assumption: the system is well-stirred:

- constant volume Ω
- 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 $\mathcal{R}_j$
- $R_j(\mathbf{X})$: algebraic form of the jth reaction ($j = 1, \ldots, M$)
  e.g., mass-action kinetics assumption: $R_j(\mathbf{X}) = k_j \prod_{i=1}^{N} X_i^{\alpha_{ij}}$

$$\mathbf{X}(t) = \begin{pmatrix} X_1(t) \\ X_2(t) \\ \vdots \\ X_N(t) \end{pmatrix} \qquad R(\mathbf{X}) = \begin{pmatrix} R_1(t) \\ R_2(t) \\ \vdots \\ R_M(t) \end{pmatrix}$$

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

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

* 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.
- $p_{\mathrm{x}}(t) = \mathbb{P}[\mathbf{X}(t) = \mathbf{x}$, given $X(t_0) = \mathbf{x}_0]$ - the probability that, at time t, there are x_1 units of species S_1, x_2 units of species S_2, ..., given $\mathbf{X}(t_0) = \mathbf{x}_0$.
- $\rho_j : \mathbb{Z}_+^N \to \mathbb{R}_+$ - 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 $[t, t + dt)$.
- $\mathbf{v}_j$ - the jth column of stoichiometry matrix V.

The Chemical Master Equation (CME)

Goal: infer the probability

$$p_{\mathrm{x}}(t) = p(\mathbf{x}, t|\mathbf{x}_0, t_0)$$

Time evolution of $p_{\mathrm{x}}(t)$:

$$\frac{\partial p(\mathbf{x}, t|\mathbf{x}_0, t_0)}{\partial t} = \sum_{j=1}^{M} \rho_j(\mathbf{x} - \mathbf{v}_j) p(\mathbf{x} - \mathbf{v}_j, t|\mathbf{x}_0, t_0) - \sum_{j=1}^{M} \rho_j(\mathbf{x}) p(\mathbf{x}, t|\mathbf{x}_0, t_0).$$

or

$$\frac{dp_{\mathrm{x}}(t)}{dt} = \sum_{j=1}^{M} \rho_j(\mathbf{x} - \mathbf{v}_j) p_{\mathrm{x}-\mathrm{v}_j} - \sum_{j=1}^{M} \rho_j(\mathbf{x}) p_{\mathrm{x}}, \quad \mathbf{x} \in \mathbb{Z}_+^N$$

- The CME completely determines the function $p(\mathbf{x}, t|\mathbf{x}_0, t_0)$.
- 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 $\mathbf{X}(t)$ versus t by using Monte Carlo methods.

Key of construction: at time t

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

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

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

SSA (Cont.)

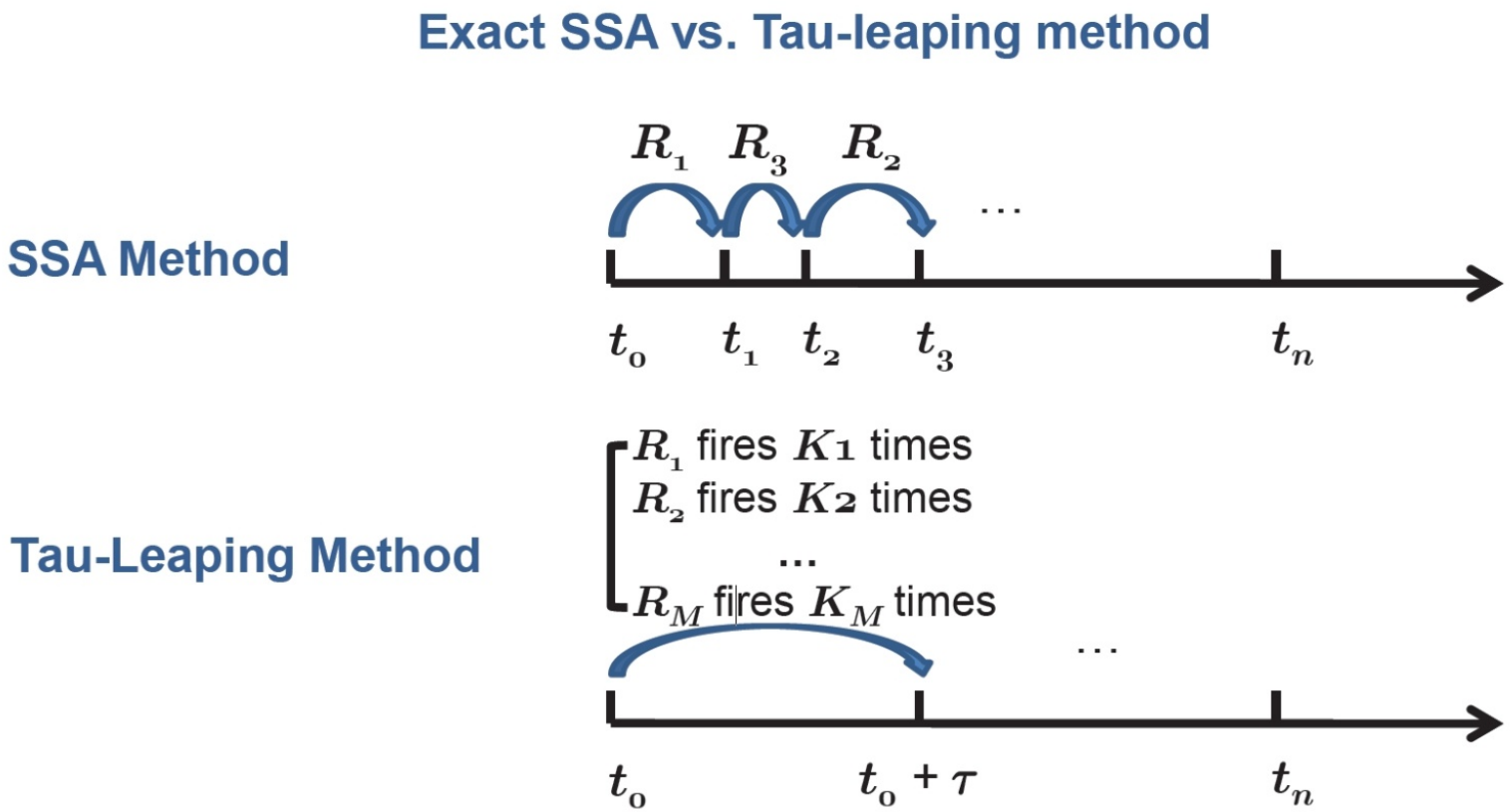
- τ - exponential random variable with mean and standard deviation $1/\rho^*(\mathbf{x})$
- j - statistically independent integer random variable with point probabilities $\rho_j(\mathbf{x})/\rho^*(\mathbf{x})$

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 τ.



Tau-leaping: The Bridge to RRE

* Leap condition (on τ): no propensity function will change significantly, i.e. $\rho_j(\mathbf{x})$ remains essentially constant.
* The number of times that each reaction $\mathcal{R}_j$ fires in $[t, t+\tau)$ is a Poisson random variable ($\mathcal{P}_j$) with mean and variance $\rho_j(\mathbf{x})\tau$

Leap the system approximately ahead by

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

Further Approximation

Assume that the leap τ is

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

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

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

Chemical Langevin Equation (CLE)

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

$$\begin{aligned}\mathbf{X}(t+\tau) &= \mathbf{X}(t) + \sum_{j=1}^{M} \left\{ \rho_j(\mathbf{x})\tau + \sqrt{\rho_j(\mathbf{x})\tau}\mathcal{N}_j(0,1) \right\} \mathbf{v}_j \\ &= \mathbf{X}(t) + \sum_{j=1}^{M} \mathbf{v}_j \rho_j(\mathbf{x})\tau + \sum_{j=1}^{M} \mathbf{v}_j \sqrt{\rho_j(\mathbf{x})}\mathcal{N}_j(0,1)\sqrt{\tau}\end{aligned}$$

By theory of continuous Markov processes

$$d\mathbf{X}(t) = \sum_{j=1}^{M} \mathbf{v}_j \rho_j(\mathbf{X}(t))dt + \sum_{j=1}^{M} \mathbf{v}_j \sqrt{\rho_j(\mathbf{X}(t))}dW_j(t)$$

$W_j(t)$ - 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

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

- ε - 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:

$$\frac{dx}{d\tau} = 0, \quad \frac{dy}{d\tau} = g(x, y; 0)$$

Stochastic singular perturbation

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 $\sigma\sqrt{t}$):

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

- σ_X^2, σ_Y^2 - (rate of diffusion)^2/the speed of drift.
- $W(t)$ - standard Brownian motion.

Singular Perturbation to Chemical Reaction Systems

- General stochastic fast-slow reaction mechanism

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

- Fast-slow CLE

$$\begin{aligned} dX(t) &= V_X R(X(t), Y(t), \varepsilon) + V_X \sqrt{R(X(t), Y(t), \varepsilon)} dW(t) \\ \varepsilon dY(t) &= V_Y R(X(t), Y(t), \varepsilon) + \sqrt{\varepsilon} V_Y \sqrt{R(X(t), Y(t), \varepsilon)} dW(t) \end{aligned}$$

- Stochastic fast-slow system with multiplicative noise

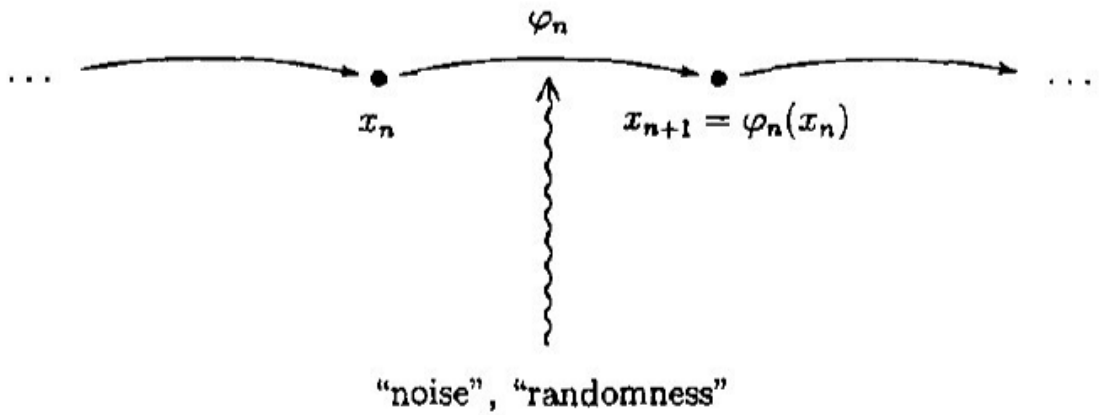
$$\begin{aligned} dX(t) &= V_X R(X(t), Y(t), \varepsilon) + \sigma_X X(t) dW(t) \\ \varepsilon dY(t) &= V_Y R(X(t), Y(t), \varepsilon) + \sqrt{\varepsilon}\sigma_Y Y(t) dW(t) \end{aligned}$$

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 perfoming 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

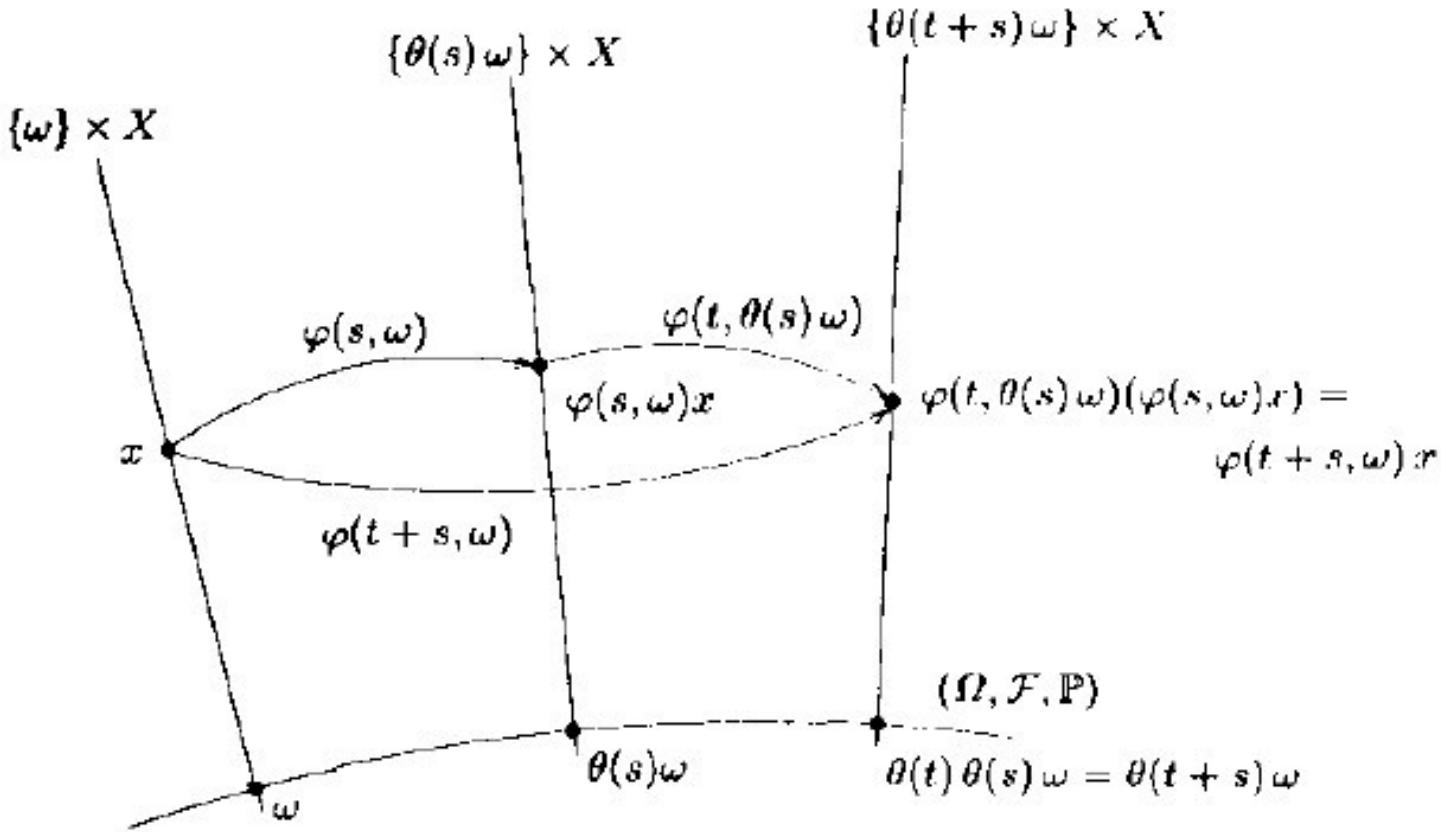
Random Dynamical System (RDS)

- 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



Random Invariant Manifold

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

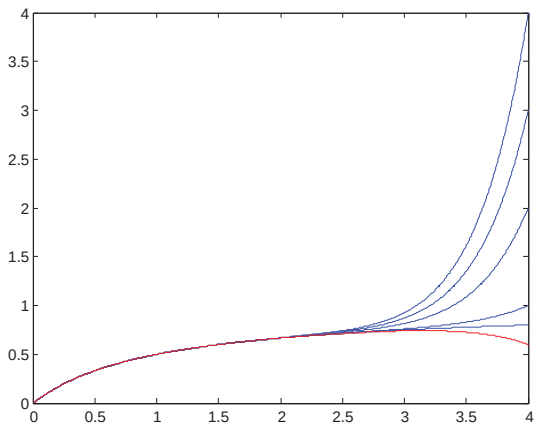
- A multifunction $\{\mathcal{M}(\omega)\}_{\omega\in\Omega}$ of nonempty closed sets $\{\mathcal{M}(\omega)\}(\omega\in\Omega)$ contained in X is called a **random set** if $\omega\mapsto\inf_{y\in\mathcal{M}(\omega)}\|x-y\|$ is a random variable for any $x\in X$.
- A random set $\mathcal{M}(\omega)$ is said to be random invariant for a RDS $\mathcal{S}(t,\omega)$ if

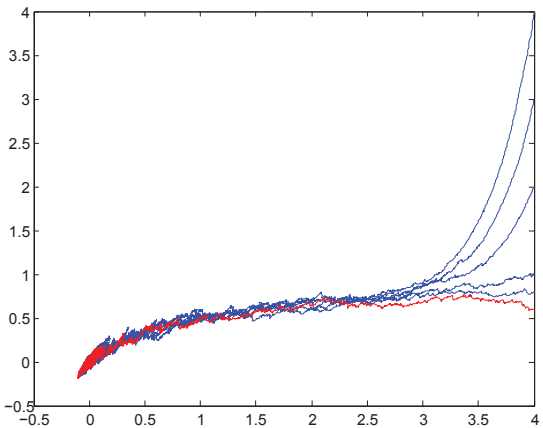
$$\mathcal{S}(t,\omega,\mathcal{M}(\omega))=\mathcal{M}(\theta_t\omega),\quad \forall t\in\mathbb{R},\ \omega\in\Omega.$$

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

The Davis-Skodje Model

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





$$\begin{aligned}dX(t) &= -X(t)dt + \mu X(t)dW(t) \\ dY(t) &= \left(-\gamma Y(t) + \gamma \frac{X(t)}{1+X(t)} - \frac{X(t)}{(1+X(t))^2}\right) dt + \sigma\sqrt{\gamma} Y(t) dW(t)\end{aligned}$$

Stochastic to Random Davis-Skodje System

1. Introduce the Ornstein-Uhlenbeck (O-U) processes satisfy

$$\begin{aligned} d\delta &= -\delta dt + \mu dW(t) \\ d\eta &= -\gamma\eta dt + \sigma\sqrt{\gamma} dW(t) \end{aligned}$$

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

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

$$\begin{aligned} \dot{u} &= -u + \delta(\theta_t\omega)u \\ \dot{v} &= -\gamma v + \gamma\eta(\theta_t\omega)v + \gamma\frac{e^{\delta-\eta}u}{1+ue^{\delta}} - \frac{e^{\delta-\eta}u}{(1+ue^{\delta})^2} \end{aligned}$$

Generation of RDS

1. 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.
2. 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 $\mathbb{R}^2$

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

is the random dynamical system generated by the original $X - Y$ system .

Rescaling $\varepsilon = 1/\gamma$, $t \to \varepsilon t$

Introduce another O-U process ξ satisfying

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

By the scale property of Wiener processes $\eta(\theta_{\frac{1}{t}}\omega) \stackrel{d}{=} \xi(t)$.

$$\frac{du}{dt} = -\varepsilon u + \varepsilon\delta(\theta_t\omega)u \quad (1)$$

$$\frac{dv}{dt} = -v + \xi(\theta_t\omega)v + g(u, \theta_t\omega; \varepsilon) \quad (2)$$

$$g(u(t), \theta_t\omega; \varepsilon) = \frac{u(t)e^{\delta(\theta_t\omega)-\xi(\theta_t\omega)}}{1 + u(t)e^{\delta(\theta_t\omega)}} - \varepsilon\frac{u(t)e^{\delta(\theta_t\omega)-\xi(\theta_t\omega)}}{\left(1 + u(t)e^{\delta(\theta_t\omega)}\right)^2}$$

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

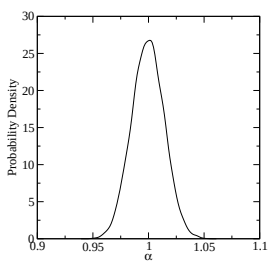
$$\begin{aligned} X(t) &= u(t,\omega)e^{\delta(\theta_t\omega)} \\ Y(t) &= v(t,\omega)e^{\eta(\theta_t\omega)} \end{aligned}$$

Taking the limit of $\varepsilon \to 0$, using stationarity of δ, η, ξ to obtain the random slow manifold of Stochastic Davis-Skodjes system:

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

where

$$c(\omega) = \int_0^\infty e^{-\xi(\theta_\tau\omega) - \int_\tau^\infty (1-\xi(\theta_s\omega))ds} d\tau.$$



Active Project I: Polynomial Chaos Application for RDS

The two random processes (δ, η) defined by

$$\begin{aligned} \mathrm{d}\delta &= -\delta \mathrm{d}t + \mu \mathrm{d}W \\ \mathrm{d}\eta &= -\gamma\eta \mathrm{d}t + \sigma\sqrt{\gamma}\,\mathrm{d}W. \end{aligned}$$

have the following properties

$$\begin{aligned} \mathrm{E}(\delta_t) &= 0 \\ \mathrm{E}(\eta_t) &= 0 \\ \mathrm{Cov}(\delta_s, \delta_t) &= \frac{\mu^2}{2} e^{-|s-t|} \\ \mathrm{Cov}(\eta_s, \eta_t) &= \frac{\sigma^2}{2} e^{-\gamma|s-t|}. \end{aligned}$$

PCE for RDE Solutions

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

- Defining the PCEs for (u, v) via the PCEs for (δ, η):

$$\begin{aligned} u &= \sum_{k=0}^{P} u_k(t)\Psi_k(\xi) \\ v &= \sum_{k=0}^{P} v_k(t)\Psi_k(\xi), \end{aligned}$$

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

$$\begin{aligned} u_k(t) &= \frac{1}{\langle \Psi_k^2 \rangle} \int u(t,\xi)\, \Psi_k(\xi) p_\xi \mathrm{d}\xi \\ v_k(t) &= \frac{1}{\langle \Psi_k^2 \rangle} \int v(t,\xi)\, \Psi_k(\xi) p_\xi \mathrm{d}\xi. \end{aligned}$$

Active Project II: Stochastic Computational Singular Perturbation

$$\frac{\mathrm{d}\mathbf{y}}{\mathrm{d}t} = F(\mathbf{y}) + G(\mathbf{y})\frac{\mathrm{d}W(t)}{\mathrm{d}t} \tag{3}$$

Alternative representations of F and G

$$F = \sum_{i=1}^{N} \mathbf{a}_i f_i, \quad G = \sum_{i=1}^{N} \boldsymbol{\alpha}_i g_i, \tag{4}$$

Evolution of f_i and g_i:

$$\begin{aligned}
\frac{\mathrm{d}f_i}{\mathrm{d}t} &= \sum_{j=1}^{N} \left\{ \frac{\mathrm{d}\mathbf{b}_i}{\mathrm{d}t} \cdot \mathbf{a}_j f_j + \mathbf{b}_i \cdot J_F \cdot \left(\mathbf{a}_j f_j + \boldsymbol{\alpha}_j g_j \frac{\mathrm{d}W(t)}{\mathrm{d}t} \right) \right\} \\
\frac{\mathrm{d}g_i}{\mathrm{d}t} &= \sum_{j=1}^{N} \left(\frac{\mathrm{d}\boldsymbol{\beta}_i}{\mathrm{d}t} \cdot \boldsymbol{\alpha}_j g_j + \boldsymbol{\beta}_i \cdot J_G \cdot \mathbf{a}_j f_j \right) + \sum_{j=1}^{N} \boldsymbol{\beta}_i \cdot J_G \cdot \boldsymbol{\alpha}_j g_j \frac{\mathrm{d}W(t)}{\mathrm{d}t}
\end{aligned}$$

$$\mathbf{b}_i \cdot \mathbf{a}_j = \boldsymbol{\beta}_i \cdot \boldsymbol{\alpha}_j = \delta_j^i, \quad i, j = 1, \cdots, N.$$

Choice of Ideal Basis

Choose a_j and $\boldsymbol{\alpha}_j$ such that

1. the inverse row vectors b_i and $\boldsymbol{\beta}_i$ can be computed accurately.
2. the matrix $\Lambda_j^i = \left(\frac{\mathrm{d}\mathrm{b}_i}{\mathrm{d}t} + \mathbf{b}_i \cdot J_F \right) \cdot \mathbf{a}_j$ is diagonal and the diagonal elements are ordered in descending magnitudes.
3. the matrix $\Gamma_j^i = \frac{\mathrm{d}\boldsymbol{\beta}_i}{\mathrm{d}t} \cdot \boldsymbol{\alpha}_j + \boldsymbol{\beta}_i \cdot J_G \cdot \mathbf{a}_j$ is diagonalized.
4. Refinements (to be developed).

Active Project III: Stochastic Quasi-Steady State Analysis [Rao (2003)]

Start from CME:

$$\frac{\partial p(\mathbf{x};t)}{\partial t} = \sum_{j=1}^{M} \rho_j(\mathbf{x}-\mathbf{v}_j)p(\mathbf{x}-\mathbf{v}_j,t) - \sum_{j=1}^{M} \rho_j(\mathbf{x})p(\mathbf{x};t)$$

- $\mathbf{x} := (y,z)$
- $p(y,z;t) = p(z|y;t)p(y;t)$
- $\frac{\mathrm{d}p(z|y;t)}{\mathrm{d}t} \approx 0$ (by QSSA)

Consistency of Different Pathways to Slow CLE

Approximated slow CME:

$$\frac{\mathrm{d}p(y;t)}{\mathrm{d}t} = \sum_{j=1}^{M} \gamma_j(y - \mathbf{v}_j^y)p(y - \mathbf{v}_j^y, t) - \sum_{j=1}^{M} \gamma_j(\mathbf{x})p(\mathbf{y};t),$$

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 $\rightarrow$ slow CME $\rightarrow$ slow CLE
2. Stiff CLE $\rightarrow$ slow CLE

Reference& Acknowledgment

- X. Han, H. Najm, *Dynamical structures in stochastic chemical reaction systems*, SIAM Journal on Applied Dynamical Systems **13** 1033 – 1051 (2014) .

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