Model reduction of partially-observed stochastic differential equations

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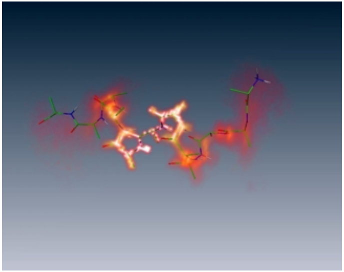
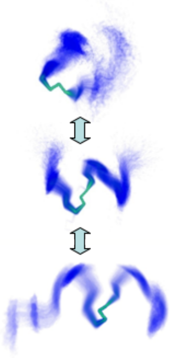
Outline

Motivation

Biological function depends on conformation's flexibility.



$1.3\mu s$ simulation of dodeca-alanine at $T = 300K$
(implicit solvent, GROMOS96 force field)



Conformational flexibility

- The microscopic dynamics (molecule & solvent) is generated by the nonlinear Hamiltonian

$$H : T^*Q \to \mathbb{R},\ Q \subseteq \mathbb{R}^{3n},\ H = p^T M^{-1} p + V(q)\,,$$

with initial conditions distributed according to $\exp(-\beta H)$.

- We suppose that the **dynamics within a conformation** can be approximated by the linear Langevin equation

$$\dot{x}(t) = (J - D)\,\nabla H_{\mathrm{lin}}(x(t)) + S\dot{W}(t)$$

where $H_{\mathrm{lin}} = \frac{1}{2}x_2^T \bar{M}^{-1} x_2 + \frac{1}{2}x_1^T \bar{L} x_1$ and

$$J = \begin{pmatrix} \mathbf{0} & \mathbf{1} \\ -\mathbf{1} & \mathbf{0} \end{pmatrix},\ D = \begin{pmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \gamma \end{pmatrix},\ S = \begin{pmatrix} \mathbf{0} \\ \sigma \end{pmatrix}$$

Conformational flexibility, cont'd

- For γ s.p.d, the system is **stable**, i.e., all eigenvalues of $A = (J - D)\nabla^2 H_{\mathrm{lin}}$ have strictly negative real part.
- The system satisfies **Hörmander's condition**. If further $2\gamma = \beta\sigma\sigma^T$, this entails ergodicity with respect to

$$d\mu(x) \propto \exp(-\beta H_{\mathrm{lin}}(x))dx\,.$$

- The Gaussian distribution $\exp(-\beta H_{\mathrm{lin}})$ indicates that **all** modes are flexible. Which are the most flexible ones?
- Often the most flexible modes are thought of as having the largest variance. **But:** variance is not always most important to the dynamics.

Conformational flexibility as a control problem

Key observations

1. Not all modes are equally stiff; moreover noise and friction may not be spatially isotropic.
2. Not all modes are observed (e.g., generalized momenta).

- We may consider flexibility as the property of being sensitive to excitations due to the noise (controllability).
- A sensible notion of flexibility should take into account what can be measured experimentally (observability).
- Determining the flexibility of a conformation therefore amounts to identifying a low-dimensional subspace of **easily controllable and highly observable modes**

Linear control systems

- For the moment let us replace the white noise by a smooth control function $u \in L^2([0,T])$, i.e.,

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Su(t)\,, \quad x(0) = 0 \\ y(t) &= Cx(t)\,, \end{aligned}$$

where $A = (J - D)\nabla^2 H_{\mathrm{lin}} \in \mathbb{R}^{2d\times 2d}$ and $y \in \mathbb{R}^k$ is a linear observable (e.g., all configurations $y = x_1$).

- VoP yields the transfer function (input-output relation),

$$G\colon L^2([0,T]) \to \mathbb{R}^k,\ y(t) = C\int_0^t e^{A(t-s)} Su(s)ds\,.$$

Model reduction by balanced truncation

- For the stable linear system $\dot{x} = Ax + Su$, $y = Cx$ compute **controllability and observability Gramians**

$$Q = \int_0^\infty \exp(At) S S^T \exp(A^T t) dt$$

$$P = \int_0^\infty \exp(A^T t) C^T C \exp(At) dt\,.$$

- **Balancing:** find a transformation $x \mapsto Tx$, such that

$$T^{-1} Q T^{-T} = T^T P T = \mathrm{diag}(\sigma_1, \ldots, \sigma_{2d})\,.$$

- **Truncation:** Project onto the first m columns of T.

Moore 1981

Properties of balanced truncation

- Interpretation of the **controllability Gramian** Q: $x \in \mathbb{R}^{2d}$ is "more controllable" than $x' \in \mathbb{R}^{2d}$ if

$$x^T Q x > x'^T Q x' \quad (|x| = |x'| = 1).$$

- Interpretation of the **observability Gramian** P: given an initial state $x(0) = x$ and zero input, $u = 0$, we have

$$\|y\|_{L^2}^2 = x^T P x.$$

- **Approximation error** (H^∞ error bound):

$$\sigma_{m+1} < \max_u \frac{\|(G - G_{\mathrm{trc}})u\|_{L^2}}{\|u\|_{L^2}} < 2(\sigma_{m+1} + \ldots + \sigma_{2d}).$$

Glover 1984, Rowley 2005

Port-controlled Hamiltonian systems

- Let's go back to our **second-order Langevin** problem and consider the stable system

$$\begin{aligned} \dot{x}(t) &= (J-D)\,\nabla H_{\mathrm{lin}}(x(t)) + Su(t) \\ y(t) &= Cx(t)\,. \end{aligned}$$

- Balancing mixes configurations and momenta. Truncation (e.g., by projection) does **not preserve structure**.
- Preserving structure requires to **impose constraints** on the Hamiltonian part (energy & structure matrix). Then

$$\begin{aligned} \dot{\xi}(t) &= (J_{\mathrm{trc}}-D_{\mathrm{trc}})\,\nabla H_{\mathrm{trc}}(\xi(t)) + S_{\mathrm{trc}}\,u(t) \\ y(t) &= C_{\mathrm{trc}}\xi(t) \end{aligned}$$

is stable with $\xi \in \mathbb{R}^m$ (odd or even dim.) and $J_{\mathrm{trc}} = -J_{\mathrm{trc}}^T$.

Hartmann et al. 2007

Partially-observed Langevin equation

- Consider the family of Langevin equations for $\epsilon > 0$

$$\begin{aligned} \dot{x}^\epsilon(t) &= (J - D)\,\nabla H_{\mathrm{lin}}(x^\epsilon(t)) + \sqrt{\epsilon} S \dot{W}(t) \\ y^\epsilon(t) &= C x^\epsilon(t)\,. \end{aligned}$$

- Using again the shorthand $A = (J - D)\nabla^2 H_{\mathrm{lin}}$, we have $Y_t^\epsilon = C X_t^\epsilon$, where X_t^ϵ, $X_0^\epsilon = 0$ is the family of solutions

$$X_t^\epsilon = \sqrt{\epsilon} \int_0^t e^{A(t-s)}\, S\, dW(s)\,.$$

- The system is **stable for all** $\epsilon > 0$. If $2D = SS^T$ it admits an ergodic invariant measure $d\mu^\epsilon \propto \exp(-H_{\mathrm{lin}}/\epsilon)$.

Controllability of the Langevin equation

- Consider the map $F : H^1([0,T]) \to C([0,T])$ and $f = F(u),\ u(0) = 0$ that is defined point-wise by

$$(Fu)(t) = \int_0^t e^{A(t-s)} S\dot{u}(s)ds\,.$$

- We introduce the **controllability function** (rate function)

$$I_x(f) = \inf_{u \in H^1, f(T)=x} \int_0^T |\dot{u}(t)|^2 dt$$

measuring the **minimum "energy"** that is needed to steer the system from $f(0) = 0$ to $f(T) = x$ within time T.

- We declare $I_x(f) = \infty$ if no such $u \in H^1$ exists.

cf. Dembo & Zeitsouni 1998

Controllability of the Langevin equation, cont'd

Theorem (Hartmann,Schütte 2008)

The controllability function $L_{\rm con}(x) = I_x(f)$ is given by

$$L_{\rm con}(x) = x^T Q(T)^{-1} x$$

with $Q(T) = \mathrm{cov}(X^\epsilon(T))$ for $\epsilon = 1$.

- Proof: Minimize $\|u\|^2_{H^1}$ subject to $(Fu)(T) = x$.
- The idea of replacing the Brownian motion $W(t)$ by its polygonal approximation $u \in H^1$ is to make sense of $I_x(f)$. If ϵ is small, LDT guarantees that $f(t)$ is "close" to $X^\epsilon(t)$.
- For $T \to \infty$, the **controllability Gramian** Q is the unique s.p.d solution of the Lyapunov equation

$$AQ + QA^T = -SS^T\,.$$

Observability of the Langevin equation

- The **observability function**

$$L_{\mathrm{obs}}(x) = \int_0^T |Y_t^0|^2 dt\,, \quad X_0^0 = x$$

measures the **output energy** up to time T in the absence of noise (i.e., $\epsilon = 0$), if $X_0^0 = x$ at time $t = 0$.

- For $T \to \infty$, it follows immediately that

$$L_{\mathrm{obs}}(x) = x^T P x\,,$$

where the **observability Gramian** P is the unique s.p.d solution of the Lyapunov equation

$$A^T P + PA = -C^T C\,.$$

Hartmann & Schütte 2008, cf. Moore 1981

Model reduction by balancing

- **Compute the Gramians** Q, P of the stable Langevin system $\dot{x} = (J - D)\nabla H(x) + SW$, $y = Cx$.
- Find the balancing transformation $x \mapsto Tx$, such that

$$T^{-1}QT^{-T} = T^{T}PT = \mathrm{diag}(\sigma_1, \ldots, \sigma_{2d})\,.$$

Notice: $T^{-1}QPT = \mathrm{diag}(\sigma_1^2, \ldots, \sigma_{2d}^2)$.

- **Constrain the system** to the subspace of the largest singular values $\sigma_1, \ldots, \sigma_m$ or, alternatively, **scale the smallest Hankel singular values** according to

$$(\sigma_{m+1}, \ldots, \sigma_{2d}) \mapsto \delta(\sigma_{m+1}, \ldots, \sigma_{2d})\,, \quad \delta > 0\,.$$

and balance the Langevin equation by $x \mapsto T_\delta x$. In the resulting perturbed system, let δ go to zero.

Properties of the balanced Langevin equation

- **Restriction** to the best controllable and observable subspace yields the constrained Langevin equation

$$\begin{aligned}\dot{\xi}(t) &= (J_{\mathrm{trc}} - D_{\mathrm{trc}})\,\nabla H_{\mathrm{trc}}(\xi(t)) + S_{\mathrm{trc}}\,\dot{W}(t)\\ y(t) &= C_{\mathrm{trc}}\xi(t)\end{aligned}$$

  with $J_{\mathrm{trc}} = -J_{\mathrm{trc}}^T$ and H_{trc} as before.
- By $2D_{\mathrm{trc}} = \beta S_{\mathrm{trc}} S_{\mathrm{trc}}^T$ and **asymptotic stability** it follows that the dynamics has the ergodic invariant measure

$$d\rho \propto \exp(-\beta H_{\mathrm{trc}})\,.$$

- Convergence of the scaled system for $\delta \to 0$ is due to **singular perturbation arguments**. In this case the effective Hamiltonian equals the free energy

$$H_{\mathrm{free}} = -\beta^{-1} \ln \rho(\xi)\,.$$

Hartmann et al. 2007, cf. Berglund & Gentz 2006, Kifer 2001

Unobservable modes

- Consider the **second-order** high-friction Langevin equation

$$\begin{aligned} \ddot{x}_1 &= -\epsilon x_1 - \dot{x}_1 + \sqrt{2\epsilon}\dot{W} \\ y &= x_1 \,. \end{aligned}$$

- Computing controllability and observability Gramian

$$Q = \begin{pmatrix} 1 & 0 \\ 0 & \epsilon \end{pmatrix}, \quad P = \frac{1}{2\epsilon}\begin{pmatrix} 1+\epsilon & 1 \\ 1 & 1 \end{pmatrix}$$

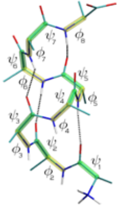
yields the joint HSV $\sigma_1 \sim 1/\sqrt{\epsilon}$ and $\sigma_2 \sim \sqrt{\epsilon}$.

- To lowest order in ϵ, the constrained equation for $\xi = x_1$ turns out to be the **first-order diffusion**

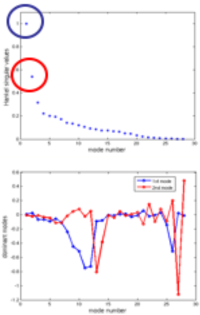
$$\dot{x}_1 = -\epsilon x_1 + \sqrt{2\epsilon}\dot{W} \,.$$

Influence of unobservable modes

Flexibility may come from unobservable modes: here, central dihedral angles and unobserved angular momenta of the freely rotating end-group are most important.



Helical conformation of octa-alanine, 14 dihedral angles plus conjugate momenta



Parametrization by HMMSDE: see Horenko & Hartmann 2007, Horenko & Schütte 2008

Take-home messages

- **Mode balancing** is a sensible approach towards molecular flexibility and model reduction that takes into account which variables can be observed.
- **Efficient numerical tools** for the computation of (exact or empirical) Gramians have recently become available.
- **Structure-preservation** for the reduced model is a subtle issue (e.g., singular structure matrix).
- **Error bounds** à la standard balanced truncation are still missing. Using averaging techniques may be a good idea.

Thanks for your attention.

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