On different notions of timescales in molecular dynamics

Origin of Scaling Cascades in Protein Dynamics

Lara Neureither

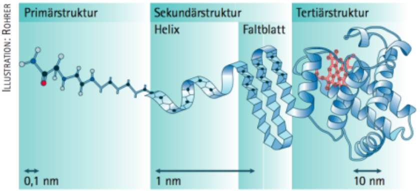
June 8, 2017

IHP Trimester "Stochastic Dynamics out of Equilibrium"

Overview

1. Motivation
2. Definition of the timescales of interest: convergence rates and mean first exit times
3. Review of results for overdamped Langevin equation
4. Approach for linear but irreversible systems: entropy production

Origin of the scaling cascades in protein dynamics



Proteinstructure (Source: MaxPlanckForschung 4/2003)

Observation:

- single point mutations $\rightarrow$ large non-local effects

Trying to understand the observations:

- study parameter sensitivies of timescales
- study relations between timescales

A model to simulate molecular dynamics

Overdamped Langevin equation

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dB_t$$

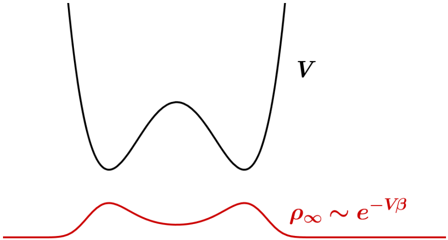
where

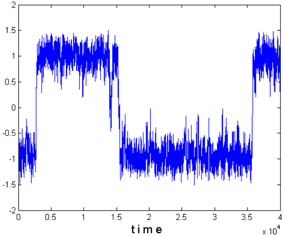
- $X \in \mathbb{R}^{3N}$: *positions* of the atoms
- $V : \mathbb{R}^{3N} \to \mathbb{R}$ is the *interaction potential*
- B_t is standard $N-$dimensional *Brownian motion*
- $\beta^{-1} \in \mathbb{R}^+$ is the *temperature*.

Illustration of the model

Overdamped Langevin equation

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dB_t$$



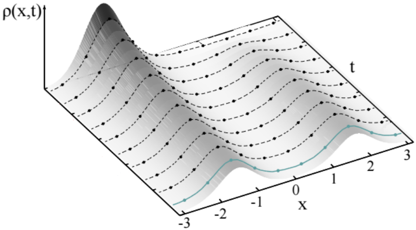


Associated probability density ρ_t and equilibrium distribution $\rho_\infty \sim e^{-V\beta}$

Quantities of interest

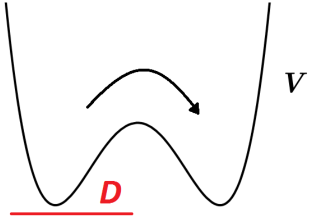
Convergence to equilibrium:

$$\|\rho_t - \rho_\infty\| \leq c\ \gamma(t)$$



Mean first exit times (MFET):

$$\mathbb{E}(\tau_x(\partial D)) = \mathbb{E}(\inf\{t > 0 : X_t \notin D\})$$



Decay towards equilibrium in $L^2_{\mu_\infty^{-1}}$

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dB_t$$

Generator: $\mathcal{L} = \beta^{-1}\nabla^2 - \nabla V \cdot \nabla$

- describes evolution of expectation values and probability densities
- is self-adjoint wrt $d\mu_\infty = \frac{1}{Z}e^{-\beta V(x)}dx$, i.e. $\langle \mathcal{L}f, g\rangle_{\mu_\infty} = \langle f, \mathcal{L}g\rangle_{\mu_\infty}$
- $spec(-\mathcal{L}) \subset \{0\} \cup [\lambda, \infty)$
- this implies convergence towards equilibrium in $L^2_{\mu_\infty^{-1}}$, i.e.

$$\|\rho_t - \rho_\infty\|^2_{L^2_{\mu_\infty^{-1}}} = \int |\rho_t(x) - \rho_\infty(x)|^2 \rho_\infty^{-1}(x)dx \leq e^{-2\lambda t}\|\rho_0 - \rho_\infty\|^2_{L^2_{\mu_\infty^{-1}}}$$

Problems:

- λ is not known
- $\rho_0 \in L^2_{\mu_\infty^{-1}} \Leftrightarrow \int \rho_0(x)^2 e^{\beta V(x)}dx < \infty$

Mean first exit times and eigenvalues of $\mathcal{L}$

Theorem [Bovier et al. 2004]: Assumptions

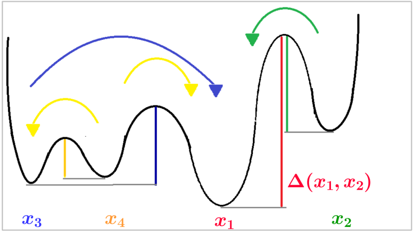
- V has n minima $x_1, \dots, x_n$
- ordering of minima according to energy barrier height possible

Define $\tau_{x_k}(S_{k-1}) = \inf\{t \geq 0 : X_t \in S_{k-1}, X_0 = x_k\}, S_{k-1} = \bigcup_{j=1}^{k-1} B_{\frac{1}{\beta}}(x_j)$.

Then $\mathcal{L}$ has n eigenvalues $0 = \Lambda_1 > \Lambda_2 > \dots > \Lambda_n$ and $\exists\ \delta > 0$ such that

$$\Lambda_k = -\frac{1}{\mathbb{E}(\tau_{x_k}(S_{k-1}))}\left(1 + \mathcal{O}(1 + e^{-\beta\delta})\right)$$

$$= -c\ exp\left(-\beta\Delta(x_k, \{x_1, \dots, x_{k-1}\})\right)\left(1 + \mathcal{O}(1 + \sqrt{\beta^{-1}}\left|\log\beta^{-1}\right|)\right),\ c > 0.$$



What we would like to do

Convergence in terms of relative entropy instead of $L^2_{\mu_\infty^{-1}}$:

$$\textit{Relative entropy} \quad H(\rho_t|\rho_\infty) = \int \rho_t(x) \log\left(\frac{\rho_t(x)}{\rho_\infty(x)}\right) dx$$

- Relation to L^1norm via *Csizsàr-Kullback/Pinsker* inequality:

$$\|\rho_t - \rho_\infty\|_{L^1} \leq \sqrt{2H(\rho_t|\rho_\infty)}$$

- L^1 is the natural norm for probability densities
- relation to measurable quantities
- applicable for any process that admits a pdf, not only reversible processes
- H is computable from simulation data

Linear but possibly irreversible processes

$$dX_t = AX_t dt + \sigma\sqrt{2\beta^{-1}} dB_t, \quad X \in \mathbb{R}^n,\ A \in \mathbb{R}^{n\times n},$$
$$\sigma \in \mathbb{R}^{n\times m}, B_t \in \mathbb{R}^m,\ m \leq n.$$

Conditions

(i) $spec(A) \subset \mathbb{C}^- = \{\lambda \in \mathbb{C} : \Re(\lambda) < 0\}$

(ii) A and σ fulfill the *Kalman rank condition*
rank$\left(\left[\sigma, A\sigma, \dots, A^{n-1}\sigma\right]\right) = n$

$\implies$ existence of unique positive invariant measure $\rho_\infty = \mathcal{N}(0, \Sigma)$.

Theorem[Arnold, Erb 2014]

$$H(\rho_t|\rho_\infty) \leq c \cdot H(\rho_0|\rho_\infty)e^{-2\lambda_A^* t},$$
$$\lambda_A^* = \min\left\{|\Re(\lambda)\| : \lambda \in spec(A)\right\},\ c \geq 1.$$

Mean first exit times and eigenvalues of the covariance

$$dX_t = AX_t dt + \sigma\sqrt{2\beta^{-1}}dB_t$$

Interested in: $\tau_x(\partial D) = \inf\{t > 0 : X_t \notin D\}, \ D = \{x : |x| < 1\}.$

Theorem [Zabczyk '85]
Assume that conditions (i) and (ii) are fulfilled s. th. $\rho_\infty = \mathcal{N}(0, \Sigma)$ exists. Let $\lambda_\Sigma^* = \max\{\lambda : \lambda \in spec(\Sigma)\} > 0, \ E = \{v : \Sigma v = \lambda_\Sigma^* v\}$.
Then for large β, i.e. small temperature

$$\lim_{\beta\to\infty} \beta^{-1} \log \mathbb{E}(\tau_x(\partial D)) = \frac{1}{2\lambda_\Sigma^*} \ \longrightarrow \text{exit time}$$

and for any $\eta > 0$ $\lim_{\beta\to\infty} \mathbb{P}(dist(X_{\tau_x(\partial D)}, E) \leq \eta) = 1 \ \longrightarrow$ exit path

We can show that

$$\lambda_A^* \geq (2\lambda_\Sigma^*)^{-1} \ \lambda_\sigma^+, \quad \lambda_\sigma^+ = \min\{\lambda > 0 : \lambda \in spec(\sigma\sigma^T)\}.$$

Analysis of relaxation behaviour

Splitting up:

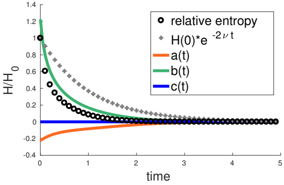
$$
\begin{aligned}
H(\rho_t|\rho_\infty) &= \int \log\left(\frac{\rho_t(x)}{\rho_\infty(x)}\right)\rho_t(x)\;dx \\
&= \frac{1}{2}\underbrace{\Big[\underbrace{Tr(\Sigma_t\Sigma_\infty^{-1}) - n}_{=a(t)}\underbrace{-Tr(\log(\Sigma_t\Sigma_\infty^{-1}))}_{=b(t)}}_{\text{Covariance}} + \underbrace{\underbrace{\mu_t^T\Sigma_\infty^{-1}\mu_t}_{=c(t)}\Big]}_{\text{Mean}}.
\end{aligned}
$$

Same structure in all terms: $z^T e^{A^T t}\Sigma_\infty^{-1}e^{At}z$.

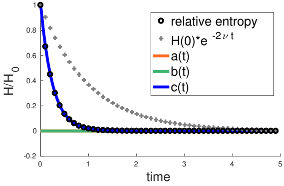
For $a(t)$ and $b(t)$: $z = (\Sigma_0 - \Sigma_\infty)^{\frac{1}{2}}$,
for $c(t)$: $z = x_0$.

Some examples for different relaxation behaviour

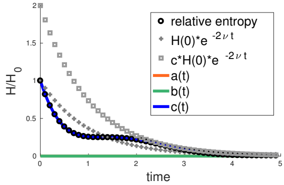
high temperature



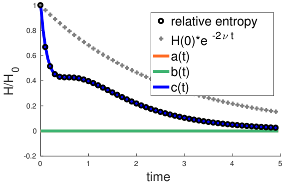
low temperature, $x_0 = EVec(A)$



low temperature, $x_0 \neq EVec(A)$



low temperature, $A = A^T$



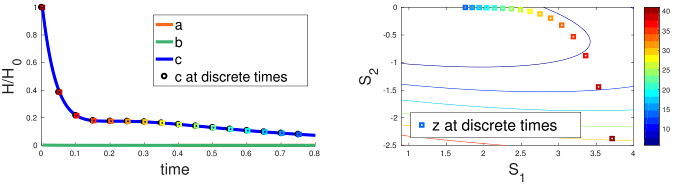
Understanding plateaus in the entropy decay

Necessary and sufficient condition for the existence of a plateau:
$\rightarrow$ degeneracy of the noise, i.e. $\det \sigma\sigma^T = 0$.

For $c(t)$ this translates to:
$\dot{c}(t) = 0 \Leftrightarrow \dot{z} \cdot \nabla p = 0 \Leftrightarrow z$ moves along contour lines of the potential p

Here $z_i(t) = e^{-\lambda_i t}(Sx_0)_i$, $p(z) = z^T S^{-T} \Sigma_\infty^{-1} S^{-1} z$ with S such that $SAS^{-1} = diag(\lambda_1, \ldots, \lambda_n)$.

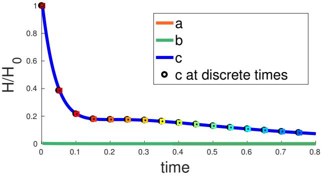
$$\det(\sigma\sigma^T) = 0$$

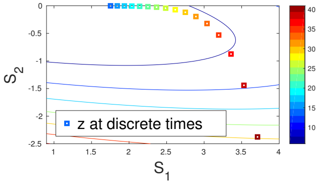


From degenerate to isotropic noise

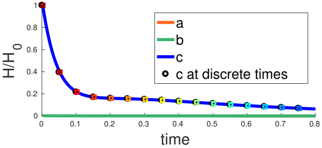
$$c(t) = z^T S^{-T} \Sigma_\infty^{-1} S^{-1} z, \;\; z_i = e^{-\lambda_i t} z_i(0), \;\; \lambda_1 = 1, \lambda_2 = 10.$$

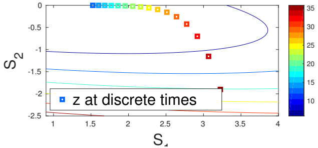
$$\det(\sigma\sigma^T) = 0$$



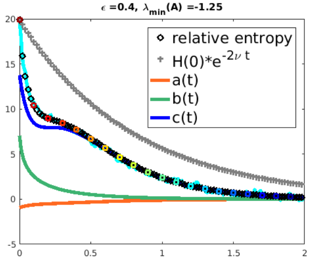


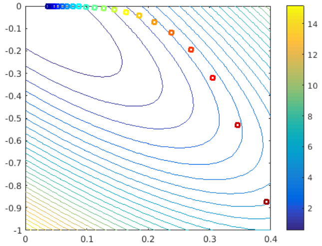
$$\det(\sigma\sigma^T) = 1$$





Identification of slow and fast?





- Can we identify slow and fast dof?
- Can we get estimates on the marginals?
- Can we get hierarchichal order of timescales?