# Macroscopic Dynamics for Nonequilibrium Chemical Reactions from a Hamiltonian Perspective

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# Outline

1. (I) Stochastic model for chemical reactions
   - WKB reformulation and Hamilton–Jacobi equation
2. (II) Large deviation principle at finite time $t$
   - Convergence from Varadhan's nonlinear semigroup to Lax-Oleinik's semigroup
3. (III) Reaction rate ODE implied by LDP
   - Law of large number path $\dot{x} = \partial_p H(0,x)$
   - Dissipative-conservative decomposition via stationary solution to $H(\nabla\psi(x),x) = 0$
4. (IV) Energy landscape: a selected stationary solution to $H(\nabla\psi(x),x) = 0$
   - LDP for invariant measures selects the unique weak KAM solution
5. (V) Importance sampling of transition paths

# General chemical reaction equations

Reaction equation : $$\boxed{\sum_{\ell=1}^{n} \nu_{j\ell}^{+} X_\ell \quad \underset{k_j^{-}}{\overset{k_j^{+}}{\rightleftharpoons}} \quad \sum_{\ell=1}^{n} \nu_{j\ell}^{-} X_\ell, \qquad j = 1, \cdots, M}$$

- Molecular species $\vec{X} = (X_\ell)_{\ell=1,\cdots n}$,
- Forward/backward reaction coefficients $\vec{\nu}_j^{\pm} = (\nu_{j\ell}^{\pm}) \in \mathbb{N}^n$,
- Reaction rates $k_j^{\pm} \geq 0$

Example:

$$2H_2 + O_2 \quad \underset{k^{-}}{\overset{k^{+}}{\rightleftharpoons}} \quad 2H_2O$$

In above notations: $n = 3, M = 1$,

$$2X_1 + X_2 \quad \underset{k_1^{-}}{\overset{k_1^{+}}{\rightleftharpoons}} \quad 2X_3; \qquad \vec{\nu}_1^{+} = (2,1,0),\ \vec{\nu}_1^{-} = (0,0,2).$$

# Macroscopic reaction rate equation(RRE)

Reaction rate equation(RRE):
Guldberg-Waage '1864

$$\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\vec{x} = \sum_{j=1}^{M} \vec{\nu}_j \left(\Phi_j^+(\vec{x}) - \Phi_j^-(\vec{x})\right)}$$

- Concentration $\vec{x} = (x_\ell)_{\ell=1:n}$,
- Reaction vector $\vec{\nu}_j = \vec{\nu}_j^- - \vec{\nu}_j^+ \in \mathbb{Z}^n$
- Law of mass action (LMA): $\Phi_j^\pm(\vec{x}) = k_j^\pm \prod_{\ell=1}^n x_\ell^{\nu_{j\ell}^\pm}$

Example:

$$2\mathrm{H}_2 + \mathrm{O}_2 \underset{\mathrm{k}^-}{\overset{\mathrm{k}^+}{\rightleftharpoons}} 2\mathrm{H}_2\mathrm{O}$$

$$2X_1 + X_2 \underset{\mathrm{k}_1{}^-}{\overset{\mathrm{k}_1{}^+}{\rightleftharpoons}} 2X_3; \qquad \vec{\nu}_1^+ = (2,1,0),\ \vec{\nu}_1^- = (0,0,2)$$

$$\vec{\nu}_1 = (-2,-1,2), \quad \Phi_1^+ = k_1^+ x_1^2 x_2,\ \Phi_1^- = k_1^- x_3^2$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\vec{x} = \vec{\nu}_1 \left(k_1^+ x_1^2 x_2 - k_1^- x_3^2\right)$$

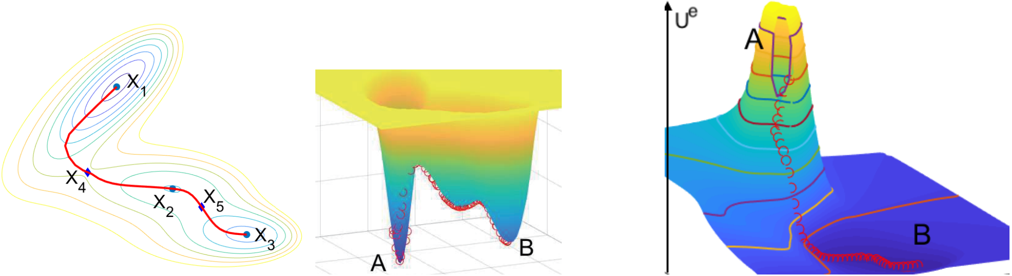
# Illustration via a gradient system with diffusion noise

- Reversible Langevin dynamics: $\mathrm{d}X_t = -\nabla U(X_t)\,\mathrm{d}t + \sqrt{2\varepsilon}\,\mathrm{d}B_t$
  - Local minima of energy landscape $U$ are local attractors, $\pi \propto e^{-\frac{U}{\varepsilon}}$.
  - Typical trajectories stay mostly within stable basin of attractors
  - [GLLL23] singular optimal control problem

$$\mathrm{d}X_t = -\nabla U(X_t) + v(X_t)\,\mathrm{d}t + \sqrt{2\varepsilon}\,\mathrm{d}B_t, \qquad v = 2\varepsilon \nabla \log h$$

committor function $h$ solves $\varepsilon \Delta h - \nabla U \cdot \nabla h = 0$ with $h = 0$ in $\bar{A}$, $h = 1$ in $\bar{B}$

  - Realizes the transition paths almost surely(effective MC), without altering the bridges



# Chemical kinematics in fixed volume $V = \frac{1}{h}$: mesoscopic random time-changed Poisson process

Recall Reaction equation : $\displaystyle\sum_{\ell=1}^{n} \nu_{j\ell}^{+} X_\ell \underset{\mathrm{k}_j^{-}}{\overset{\mathrm{k}_j^{+}}{\rightleftharpoons}} \sum_{\ell=1}^{n} \nu_{j\ell}^{-} X_i, \quad j = 1, \cdots, M$

- Counting process $\vec{X}(t) \in \mathbb{N}^n$, rescaled $X^{\mathrm{h}}(t) = h\vec{X}(t) \in \Omega_{\mathrm{h}}^{+} := \{\vec{x}_i = \vec{i}h; \vec{i} \in \mathbb{N}^n\}$ [Marcus '68], [Gillespie '72], [Lushnikov '78], [Kurtz '80],

$$\boxed{X^{\mathrm{h}}(t) = X^{\mathrm{h}}(0) + \sum_{j=1}^{M} \vec{\nu}_j h \left[ N_j^{+}\left(\frac{1}{h}\int_0^t \tilde{\Phi}_j^{+}(X^{\mathrm{h}}(s))\,\mathrm{d}s\right) - N_j^{-}\left(\frac{1}{h}\int_0^t \tilde{\Phi}_j^{-}(X^{\mathrm{h}}(s))\,\mathrm{d}s\right)\right]}$$

- i.i.d. unit rate Poisson processes $N_j^{\pm}(t)$
- Intensity in Poisson process: $\frac{1}{h}\tilde{\Phi}_j^{\pm}(X^{\mathrm{h}}) \approx \frac{1}{h}\Phi_j^{\pm}(X^{\mathrm{h}})$ LMA
- Change in counting for f/b reaction by $\pm\vec{\nu}_j$

# WKB and Hamiltonian: Diffusion v.s. Chemical reaction

| | Drift-Diffusion | Chemical Reaction |
|---|---|---|
| Process | $\mathrm{d}x_t = b(x_t)\,\mathrm{d}t + \sqrt{2\varepsilon}\,\mathrm{d}B_t$ | $X^{\mathrm{h}} \sim$ time changed Poisson process |
| Forward eq | $\partial_t \rho + \nabla \cdot (\rho b) = \varepsilon \Delta \rho$ | $\frac{\mathrm{d}}{\mathrm{d}t}\rho_i^{\mathrm{h}} = \sum_k \left( Q^h_{ki}\rho^{\mathrm{h}}_k - Q^h_{ik}\rho^{\mathrm{h}}_i \right)$ |
| $\rho_i^{\mathrm{h}} = e^{-\frac{\psi_{\mathrm{h}}(\vec{x}_i,t)}{h}}$ | $\partial_t \psi = -H(\nabla \psi, x) + \varepsilon(\nabla \cdot b + \Delta \psi)$ | $\partial_t \psi_{\mathrm{h}}(\vec{x}_i) = -h e^{\frac{\psi_{\mathrm{h}}(\vec{x}_i,t)}{h}} Q^*_{\mathrm{h}} e^{-\frac{\psi_{\mathrm{h}}(\vec{x}_i,t)}{h}} =: -H^*_{\mathrm{h}}(\psi_{\mathrm{h}}$ |
| limiting HJE | $\partial_t \psi = -H(\nabla \psi, x)$ | $\partial_t \psi(\vec{x},t) = -H(\nabla \psi(\vec{x}), \vec{x})$ |
| limiting $H$ | $H(p,x) = p \cdot (b+p)$ | $H(\vec{p},\vec{x}) := \sum_{j=1}^M \Phi_j(\vec{x}) \left( e^{\vec{\nu}_j \cdot \vec{p}} - 1 \right)$ |
| Backward eq | $\partial_t f - b \cdot \nabla f = \varepsilon \Delta f$ | $\frac{\mathrm{d}}{\mathrm{d}t} f_i^{\mathrm{h}} = \sum_k Q^h_{ik}(f^{\mathrm{h}}_k - f^{\mathrm{h}}_i)$ |
| $f_i^{\mathrm{h}} = e^{\frac{u_{\mathrm{h}}(\vec{x}_i,t)}{h}}$ | $\partial_t u = H(\nabla u, x) + \varepsilon \Delta u$ | $\partial_t u_{\mathrm{h}}(\vec{x}_i,t) = h e^{-\frac{u_{\mathrm{h}}(\vec{x}_i,t)}{h}} Q_{\mathrm{h}} e^{\frac{u_{\mathrm{h}}(\vec{x}_i,t)}{h}} =: H_h(u_{\mathrm{h}})$ |
| limiting HJE | $\partial_t u = H(\nabla u, x)$ | $\partial_t u(\vec{x},t) = H(\nabla u(\vec{x}), \vec{x})$ |

$H^*_{\mathrm{h}}(\psi_{\mathrm{h}}) := \sum_j \Phi_j(\vec{x}_i - \vec{\nu}_j h) e^{\frac{\psi_{\mathrm{h}}(\vec{x}_i) - \psi_{\mathrm{h}}(\vec{x}_i - \vec{\nu}_j h)}{h}} - \Phi_j(\vec{x}_i)$; $\qquad H_{\mathrm{h}}(\vec{x}_i) := \sum_j \Phi_j(\vec{x}_i) \left( e^{\frac{u_{\mathrm{h}}(\vec{x}_i + \vec{\nu}_j h) - u_{\mathrm{h}}(\vec{x}_i)}{h}} - 1 \right)$

# WKB reformulation $w_{\mathsf{h}} = e^{\frac{u_{\mathsf{h}}(\vec{x}_i,t)}{h}}$ for backward equation = Varadhan's nonlinear semigroup = Monotone scheme

- Varadhan's nonlinear semigroup:

$$u_{\mathsf{h}}(\vec{x}_i,t) = h\log w_{\mathsf{h}}(\vec{x}_i,t) = h\log \mathbb{E}^{\vec{x}_i}\left(w_0(X_t^{\mathsf{h}})\right) = h\log \mathbb{E}^{\vec{x}_i}\left(e^{\frac{u_0(X_t^{\mathsf{h}})}{h}}\right) =: (S_t u_0)(\vec{x}_i)$$

$$\boxed{\partial_t u_{\mathsf{h}}(\vec{x}_i,t) = he^{-\frac{u_{\mathsf{h}}(\vec{x}_i,t)}{h}} Q_{\mathsf{h}} e^{\frac{u_{\mathsf{h}}(\vec{x}_i,t)}{h}} =: H_h(u_{\mathsf{h}})}$$

- Discrete Hamiltonian:

$$H_{\mathsf{h}}(\vec{x}_i, u_{\mathsf{h}}(\vec{x}_i), u_{\mathsf{h}})$$
$$:= \sum_{j=1,\vec{x}_i+\vec{v}_jh\geq 0}^{M} \Phi_j^+(\vec{x}_i)\left(e^{\frac{u_{\mathsf{h}}(\vec{x}_i+\vec{v}_jh)-u_{\mathsf{h}}(\vec{x}_i)}{h}} - 1\right) + \sum_{j=1,\vec{x}_i-\vec{v}_jh\geq 0}^{M} \Phi_j^-(\vec{x}_i)\left(e^{\frac{u_{\mathsf{h}}(\vec{x}_i-\vec{v}_jh)-u_{\mathsf{h}}(\vec{x}_i)}{h}} - 1\right)$$

# Monotone scheme and constant solution

- Monotone preserving: Assume $(u_\mathsf{h} - v_\mathsf{h})(\vec{x}_i, t)$ achieves maximum at $(\vec{x}_i^*, t)$,

$$
\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}(u_\mathsf{h} - v_\mathsf{h})(\vec{x}_i^*) \\
\le &\frac{1}{h}\sum_{j=1, \vec{x}_i + \vec{v}_j h \ge 0}^{M} \Phi_j^+(\vec{x}_i^*) e^{\xi_i}[(u_\mathsf{h} - v_\mathsf{h})(\vec{x}_i^* + \vec{v}_j h) - (u_\mathsf{h} - v_\mathsf{h})(\vec{x}_i^*)] + \cdots \le 0
\end{aligned}
$$

- If $u_\mathsf{h}(\vec{x}_i + \vec{v}_j h) = u_\mathsf{h}(\vec{x}_i), \forall i, j,$ then $H_\mathsf{h}(\vec{x}_i, u_\mathsf{h}(\vec{x}_i), u_\mathsf{h}) = 0$
  - Constant is a stationary solution
  - Construct barriers to control polynomial growth of $\Phi_j^{\pm}(\vec{x})$

# Convergence from Varadhan's nonlinear semigroup to Lax-Oleinik's semigroup

- Variational formula for viscosity solution to HJE (Lax-Oleinik representation)

$$u(\vec{x},t) = \sup_{\vec{y}} \left(u_0(\vec{y}) - v_t(\vec{y};\vec{x})\right), \quad v_t(\vec{y};\vec{x}) := \inf_{\gamma(0)=\vec{x},\gamma(t)=\vec{y}} \int_0^t L(\dot{\gamma}(s),\gamma(s))\,\mathrm{d}s$$

- Need to prove: convergence from Varadhan's to Lax-Oleinik's semigroup)

$$\lim_{h\to 0} h \log \mathbb{E}^{\vec{x}_i}\left(e^{\frac{u_0(X_t^{\mathsf{h}})}{h}}\right) = \boxed{\lim_{h\to 0} u_{\mathsf{h}}(\vec{x}_i,t) = u(\vec{x},t)} = \sup_{\vec{y}} \left(u_0(\vec{y}) - v_t(\vec{y};\vec{x})\right)$$

Consequence: LDP at finite time $t$

- [Inverse Varadhan's lemma [Bryc, '90]]

$\lim_{h\to 0} h \log \mathbb{E}^{\vec{x}_i}\left(e^{\frac{u_0(X_t^{\mathsf{h}})}{h}}\right) = \sup_{\vec{y}} \left(u_0(\vec{y}) - v_t(\vec{y};\vec{x})\right)$ + exponential tightness $\Longrightarrow$

$X^{\mathsf{h}}$ satisfies the large deviation principle with rate $I$

# Ingredients of proof

- Perron method for the existence and uniqueness + Accretivity $\Longrightarrow$
  $-H_{\mathsf{h}}$ is m-accretive operator on $\ell^\infty$, generates $C_0$-semigroup $u_{\mathsf{h}}(\vec{x}_i,t) = S_t u_0$
- Construct barriers to control the polynomial growth of intensity $\Longrightarrow$
  Obtain discrete solution in one-point compactification space

$$\ell^\infty(\Omega_{\mathsf{h}}^*) := \{(u_{\mathsf{h}}(\vec{x}_i)) \in \ell^\infty(\Omega_{\mathsf{h}});\ u_{\mathsf{h}}(\vec{x}_i) \to \text{ const as } |\vec{x}_i| \to +\infty\}$$

- Viscosity solution via Barles-Perthame's USC/LSC envelope + Comparison principle $\Longrightarrow$
  $-H$ is an m-accretive operator on $C(\mathbb{R}^{N*})$

**Theorem (Varadhan's semigroup to Lax-Oleinik's $u_{\mathsf{h}}(\vec{x}_i,t) \to u(\vec{x},t)$)**

*Assume $\Phi_j^\pm(\vec{x}), \vec{x} \in \mathbb{R}^n$, is local Lipschitz continuous and $u^0 \in C_c(\mathbb{R}^{N*})$.*

$$u(\vec{x},t) = \lim_{\Delta t \to 0} \left( (I - \Delta t H)^{-[t/\Delta t]} u^0 \right) = \lim_{\Delta t \to 0} \left( \lim_{h \to 0} (I - \Delta t H_h)^{-[t/\Delta t]} u_h^0 \right) \in C(\mathbb{R}^{N*})$$

*is the unique viscosity solution to HJE.*

# Large deviation principle at single times

We assume

- $\Phi_j^{\pm}(\vec{x}), \vec{x} \in \mathbb{R}^n$, after zero extension, is local Lipschitz continuous
- there exists positive mass vector $\vec{m} \in \mathbb{R}_+^n$ ($m_i$ is molecular weight for $i$-th species)

$$\vec{v}_j \cdot \vec{m} = 0, \quad j = 1, \cdots, M \quad \text{(conservation of mass for j reaction)}$$

## Theorem

*Let $X^h(0) = \vec{x}_0^h \to \vec{x}_0$ in $\mathbb{R}_+^n$. Then the chemical reaction process $X^h(t)$ at each time $t$ satisfies the large deviation principle with a good rate function*

$$I(y;x,t) = \inf_{\gamma(0)=\vec{x},\gamma(t)=\vec{y}} \int_0^t L(\dot{\gamma}(s), \gamma(s))\,\mathrm{d}s$$

* A. Agazzi, A. Dembo, and J.-P. Eckmann, 2018.

# Zero cost least action = macroscopic RRE

$$H(\vec{p},\vec{x}) = \sum_{j=1}^{M} \Phi_j^+(\vec{x})\left(e^{\vec{v}_j\cdot\vec{p}}-1\right) + \Phi_j^-(\vec{x})\left(e^{-\vec{v}_j\cdot\vec{p}}-1\right), \quad L(\vec{s},\vec{x}) = \sup_{\vec{p}}(\vec{s}\cdot\vec{p} - H(\vec{p},\vec{x})) \geq 0$$

- $L \geq 0$, $L = 0 \iff \vec{s} = \partial_p H(0,\vec{x})$
- Zero cost least action = macroscopic RRE:

$$\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\vec{x} = \sum_{j=1}^{M} \vec{v}_j\left(\Phi_j^+(\vec{x}) - \Phi_j^-(\vec{x})\right) = \nabla_p H(\vec{p},\vec{x})\Big|_{\vec{p}=\vec{0}}}$$

- Consequence of LDP $\implies$ exponential rate of convergence to ODE: Fix any $t > 0$, for any $\varepsilon > 0$, there exists $h_0 > 0$ such that if $h \leq h_0$ then

$$\boxed{\mathbb{P}\{|X^{\mathrm{h}}(t) - \vec{x}(t)| \geq \varepsilon\} \leq e^{-\frac{\alpha(\varepsilon)}{2h}}}$$

where $\alpha(\varepsilon) = \inf_{|\vec{y}-\vec{x}(t)|\geq\varepsilon} I(\vec{y};\vec{x},t) > 0$.

# RRE = Hamiltonian flow + Gradient flow

Motivated by $H(\nabla\psi^{ss}(\vec{x}),\vec{x}) = 0$ (assume exists)

## Proposition

$$\boxed{\dot{\vec{x}} = \nabla_p H(0,\vec{x}) \equiv W - K(\vec{x})\nabla\psi^{ss}(\vec{x})}$$

$$W := \int_0^1 \nabla_p H(\theta\nabla\psi^{ss}(\vec{x}),\vec{x})\,\mathrm{d}\theta, \quad K(\vec{x}) := \int_0^1 (1-\theta)\nabla^2_{pp} H(\theta\nabla\psi^{ss}(\vec{x}),\vec{x})\,\mathrm{d}\theta$$

- Conservation $\langle W, \nabla\psi^{ss}(\vec{x})\rangle = H(\nabla\psi^{ss}(\vec{x}),\vec{x}) - H(0,\vec{x}) = 0$
- Onsager's response operator

$$\frac{\mathrm{d}}{\mathrm{d}t}\psi^{ss}(\vec{x}) = \langle \dot{\vec{x}}, \nabla\psi^{ss}\rangle = -\langle K(\vec{x})\nabla\psi^{ss}(\vec{x}), \nabla\psi^{ss}(\vec{x})\rangle \le 0$$

- If Hamiltonian is symmetric $H(\vec{p},\vec{x}) = H(\nabla\psi^{ss}(\vec{x}) - \vec{p},\vec{x})$ then $W = 0$, gradient flow structure for RRE

$$\frac{\mathrm{d}}{\mathrm{d}t}\vec{x} = -K(\vec{x})\nabla\psi^{ss}(\vec{x})$$

# Energy dissipation and passage from mesoscopic to macroscopic

Assume there exists a positive invariant measure $\pi(\vec{x}_i)$ and the limit exists

$$\psi^{ss}(\vec{x}) := \lim_{V\to+\infty} -\frac{\log \pi(\vec{x}_i)}{V}$$

- for any convex function $\phi$, we have the mesoscopic energy dissipation relation

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{\vec{x}_i}\phi\left(\frac{\rho(\vec{x}_i)}{\pi(\vec{x}_i)}\right)\pi(\vec{x}_i) = -\sum_{\vec{x}_i,\vec{y}_i} Q(\vec{y}_i,\vec{x}_i)\pi(\vec{y}_i)D_\phi\left(\frac{\rho(\vec{y}_i)}{\pi(\vec{y}_i)},\frac{\rho(\vec{x}_i)}{\pi(\vec{x}_i)}\right) \le 0,$$

  where $D_\phi(y,x) := (y-x)^2\int_0^1 (1-\theta)\phi''(x+\theta(y-x))\,\mathrm{d}\theta \ge 0.$
- as $V\to 0$, the mesoscopic dissipation law converges to the macroscopic dissipation law

$$\frac{1}{V}\sum_{\vec{x}_i}\rho(\vec{x}_i)\log\frac{\rho(\vec{x}_i)}{\pi(\vec{x}_i)} \to \psi^{ss}(\vec{x}^*),$$

$$\frac{1}{V}\sum_{\vec{x}_i,\vec{y}_i} Q(\vec{y}_i,\vec{x}_i)\rho(\vec{y}_i)\log\frac{\rho(\vec{y}_i)\pi(\vec{x}_i)}{\pi(\vec{y}_i)\rho(\vec{x}_i)} \to \langle K(\vec{x}^*)\nabla\psi^{ss}(\vec{x}^*),\nabla\psi^{ss}(\vec{x}^*)\rangle,$$

# Energetic: chemical thermodynamics

- Thermodynamics and entropy production rate (adiabatic + nonadibatic)

$$\boxed{\dot{S}_{\text{tot}} = \dot{S}_{\text{a}} + \dot{S}_{\text{na}}}$$

$$\frac{1}{k_{\text{B}}}\dot{S}_{\text{tot}} := \sum_j \left(\Phi_j^+(\vec{x}) - \Phi_j^-(\vec{x})\right) \log \frac{\Phi_j^+(\vec{x})}{\Phi_j^-(\vec{x})}$$

$$\frac{1}{k_{\text{B}}}\dot{S}_{\text{na}} := = \langle K(\vec{x})\nabla\psi^{ss}(\vec{x}), \nabla\psi^{ss}(\vec{x})\rangle$$

$$\frac{1}{k_{\text{B}}}\dot{S}_{\text{a}} := \sum_j \mathrm{KL}(\Phi_j^+(\vec{x})||\Phi_j^-(\vec{x})e^{-\vec{\nu}_j\cdot\nabla\psi^{ss}}) + \mathrm{KL}(\Phi_j^-(\vec{x})||\Phi_j^+(\vec{x}(t))e^{\vec{\nu}_j\cdot\nabla\psi^{ss}})$$

$$\dot{S}_{\text{a}}\Big|_{t\to+\infty} = \dot{S}_{\text{tot}}(\vec{x}^{\text{s}}) > 0 \quad \text{for NESS } \vec{x}^{\text{s}}$$

- Formally: large volume limit $\rho(\vec{x}_i, t) \to \delta_{\vec{x}^*(t)}$, all the thermodynamic quantities:

$$\boxed{\left(\mathrm{KL}(\rho||\pi), \dot{S}_{\text{tot}}, \dot{S}_{\text{a}}, \dot{S}_{\text{na}}\right)_t^{\text{mic}} \longrightarrow \left(\psi^{ss}, \dot{S}_{\text{tot}}, \dot{S}_{\text{a}}, \dot{S}_{\text{na}}\right)^{\text{mac}}\Big|_{\vec{x}^*(t)}}$$

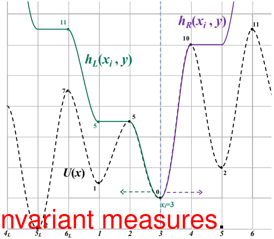
# Stationary solution $\psi^{ss}$: Maupertuis's principle and nonuniqueness

- Consider the least action problem in an undefined time horizon (Maupertuis's principle)

$$\psi^{ss}(x;\vec{x}^{\mathsf{A}}) = \inf_{T>0,\ \gamma(0)=\vec{x}^{\mathsf{A}},\, \gamma(T)=x} \int_0^T L(\dot{\gamma}(t),\gamma(t))\,\mathrm{d}t$$

- $\psi^{ss}$ is a viscosity solution to stationary HJE (zero at critical point $\vec{x}^{\mathsf{A}}$)

$$H(\nabla\psi^{ss}(\vec{x}),\vec{x}) = 0, \quad \psi^{ss}(\vec{x}^{\mathsf{A}}) = 0.$$




- $\psi^{ss}$ is a only a Peierls barrier. Global energy landscape need LDP for invariant measures. The stationary HJE has many visocosity solutions!

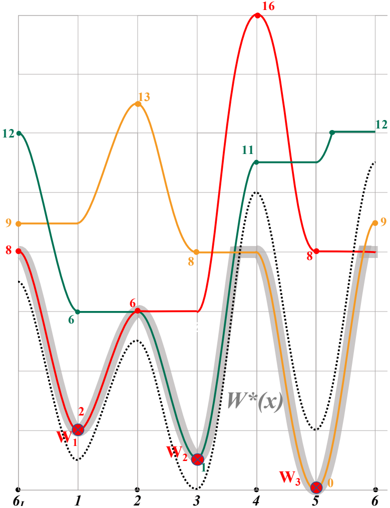
# Construct a global energy landscape (selected weak KAM solution)

- weak KAM solution to stationary HJE has variational representation

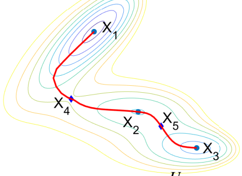
$$W(y) = \inf_{x\in\mathbb{S}^1} W(x) + v_t(x,y) = \inf_{x\in\mathbb{S}^1} W(x) + v(x,y)$$
$$= \inf_{x_i\in\mathscr{A}} W(x_i) + \psi^{ss}(x_i,y)$$

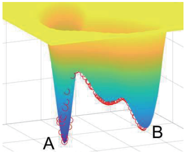
It's stationary version of Lax-Oleinik's semigroup $(S_{T+t}W)(y)$

- Selection principle for weak KAM solution: choose boundary values $W(x_i)$ such that the asymptotic behaviors at $x_i$ is captured
- $\{W_i\}$ solves the discrete weak KAM problem $W_i = \min_{j=1,\cdots,k}\{W_j + h(x_j,x_i)\}, \quad \forall i = 1,\cdots,k.$ Freidlin-Wentzell's variational formula 1969.



# Transition path between local attractors




- Langevin dynamics: $\mathrm{d}X_t = -\nabla U(X_t)\,\mathrm{d}t + \sqrt{2\varepsilon}\,\mathrm{d}B_t$
  - Local minima of energy landscape $U$ are local attractors, $\pi \propto e^{-\frac{U}{\varepsilon}}$.
  - [GLLL] singular optimal control problem

$$\mathrm{d}X_t = -\nabla U(X_t) + v(X_t)\,\mathrm{d}t + \sqrt{2\varepsilon}\,\mathrm{d}B_t, \quad v = 2\varepsilon\nabla\log h \text{ committor function}$$

    optimally controlled process realize transitions almost surely $\to$ effective MC
  - Realizes the transition paths almost surely, without altering the bridges

- Jump process on discrete state space $\Gamma$ (biochemical reactions):
  - Irreducibility and recurrence lead to a *unique* invariant measure $\pi \in \mathscr{P}(\Gamma)$.
  - A site $x \in \Gamma$ is a *local attractor* if $\pi(x) > \pi(y)$ for adjacent $y$.
  - No separation of noise and drift; no energy landscape; how to control?

- Transition path problem: study transitions between attractors, often seen as rare events.

# Transition path problem

- Denote $A, B$ as two disjoint closed set (represents metastability)
- $\tau_{AB}$ denote the first hitting time of the set $A \cup B$, i.e. $\tau_{AB} := \inf\{t \geq 0 : X_t \in A \cup B\}$.
- Set a singular terminal cost

$$f_{AB}(X_\tau) := \begin{cases} +\infty & \text{for } X_\tau \in A, \\ 0 & \text{for } X_\tau \in B. \end{cases}$$

- Difficulties: not PDE constraint deterministic optimization;
- Difficulties: singular terminal cost leads to singular control/drift in SDE
- Difficulties: do not alter the bridges of the reference/original process
- Weak formulation: martingale problem for path measure.

# Optimal change path measures s-OC$_\tau$

If the initial data $\mu$ satisfies $\mathsf{Ent}(\mu \,|\, \mathsf{R}_0) < +\infty$, then

Stochastic optimal control with a stopping time can be formulated as

$$\boxed{\gamma_{\mathrm{sto}}(\mu) := \inf \left\{ \mathsf{E}_{\mathsf{Q}} \left[ f(X_\tau) + \log \frac{\mathrm{d}\mathsf{Q}}{\mathrm{d}\mathsf{R}_{[0,\tau]}} \right] : \mathsf{Q} \in \mathscr{P}(\Omega),\ \mathsf{Q}_0 = \mu \right\}} \tag{s-OC$_\tau$}$$

This is a convex optimization for path measure $\mathsf{Q}$

# Disintegration and additive property of relative entropy

- For any measure $\mathsf{P} \in \mathscr{P}(\Omega)$, any measurable map $\phi : \Omega \to \Omega_\phi$, set $\mathsf{P}_\phi := \phi_\# \mathsf{P} \in \mathscr{P}(Y)$
- Define $\mathsf{P}^\phi$ as the conditional measure obtained via the disintegration theorem

$$\mathsf{P}(A) = \int_{\Omega_\phi} \mathsf{P}^{\phi=\eta}(A)\, \mathsf{P}_\phi(\mathrm{d}\eta) \qquad \forall \text{ measurable set } A \subset \Omega\,.$$

  shorthand notation: $\mathsf{P} = \mathsf{P}^\phi \otimes \mathsf{P}_\phi$

- If $\mathsf{P}, \mathsf{R} \in \mathscr{P}(\Omega)$ with $\mathsf{P} \ll \mathsf{R}$, then

$$\frac{\mathrm{d}\mathsf{P}}{\mathrm{d}\mathsf{R}}(\omega) = \frac{\mathrm{d}\mathsf{P}_\phi}{\mathrm{d}\mathsf{R}_\phi}(\phi(\omega))\, \frac{\mathrm{d}\mathsf{P}^\phi}{\mathrm{d}\mathsf{R}^\phi}(\omega) \qquad \text{for } \mathsf{P}\text{-almost every } \omega \in \Omega\,.$$

- Additive property of the relative entropy under disintegration

$$\boxed{\mathrm{Ent}(\mathsf{P}\,|\,\mathsf{R}) = \mathrm{Ent}(\mathsf{P}_\phi\,|\,\mathsf{R}_\phi) + \int_{\Omega_\phi} \mathrm{Ent}(\mathsf{P}^{\phi=\eta}\,|\,\mathsf{R}^{\phi=\eta})\, \mathsf{P}_\phi(\mathrm{d}\eta).}$$

# Application to transition path problem

- On closed sets $A, B \subset \Gamma$, the terminal cost $f = f_{AB} : \Gamma \to [0, +\infty]$ is

$$f_{AB}(x) := \begin{cases} +\infty & \text{for } x \in A, \\ 0 & \text{for } x \in B. \end{cases}$$

- Stopping time $\tau = \tau_{AB} := \inf\{t \geq 0 : X_t \in A \cup B\}$.
- Disintegration with $\phi = X_\tau : \Omega \to \Gamma$, the cost function can be expressed as

$$\mathrm{E}_{\mathrm{P}}\left[f(X_\tau) + \log \frac{\mathrm{dP}}{\mathrm{dR}_{[0,\tau]}}\right] = \mathrm{E}_{\mathrm{P}}\left[f(X_\tau) + \log \frac{\mathrm{dP}_\tau}{\mathrm{dR}_\tau}(X_\tau)\right] + \int_\Gamma \mathrm{Ent}(\mathrm{P}^{X_\tau = \eta} \,|\, \mathrm{R}_{[0,\tau]}^{X_\tau = \eta})\, \mathrm{P}_\tau(\mathrm{d}\eta),$$

- Set latter term to be zero by simply choosing (original bridges)

$$\boxed{\mathrm{P}^{X_\tau = \eta} = \mathrm{R}_{[0,\tau]}^{X_\tau = \eta} \qquad \text{for } \mathrm{P}_\tau\text{-almost every } \eta \in \Gamma.}$$

- One candidate: path measure $\mathrm{P}_{AB} := \mathrm{P}^*{}_\tau \otimes \mathrm{R}_{[0,\tau]}^{X_\tau}$ with

$$\frac{\mathrm{dP}^*{}_\tau}{\mathrm{dR}_\tau}(X_\tau(\omega)) = \frac{\exp(-f(X_\tau(\omega)))}{\mathrm{E}_{\mathrm{R}_{[0,\tau]}}[\exp(-f(X_\tau))]} \qquad \text{for P-almost every } \omega \in \Omega,$$

# Committor function for processes on discrete state spaces

- Committor function $h_{AB}$: unique solution of the boundary value problem:

$$\boxed{\begin{array}{ll} \int_\Gamma \overline{\nabla} h(x,y)\, L(x,\mathrm{d}y) = 0, & x \notin (A \cup B), \\ h(x) = \mathbb{1}_B(x), & x \in A \cup B. \end{array}}$$

- Probabilistic interpretation:
  - Dynkin's formula:

$$\mathsf{E}^x_{\mathsf{R}}[h_{AB}(X_{\tau_{AB}})] = h_{AB}(x), \qquad \mathsf{E}_{\mathsf{R}_{[0,\tau]}}[h_{AB}(X_\tau)] = \int h_{AB}\,\mathrm{d}\mu$$

  - $h_{AB}(x)$ provides the probability of hitting $B$ before $A$:
- In terms of $h_{AB}$, take $f(x) = -\log h_{AB}(x) = -\log \mathbb{1}_B(x)$, $x \in (A \cup B)^c$

$$\boxed{\frac{\mathrm{d}\mathsf{P}^{*}{}_\tau}{\mathrm{d}\mathsf{R}_\tau}(X_\tau(\omega)) = \frac{\exp(-f(X_\tau(\omega)))}{\mathsf{E}_{\mathsf{R}_{[0,\tau]}}[\exp(-f(X_\tau))]} = \frac{h_{AB}(X_\tau(\omega))}{\int h_{AB}\,\mathrm{d}\mu} = \frac{\mathbb{1}_B(X_\tau(\omega))}{\int h_{AB}\,\mathrm{d}\mu}}$$

[Bolhuis, Chandler, Dellago, Geissler 02], [Weinan E, Vanden-Eijnden 06], [Lu, Nolen 15], [G.LiuLiLi 23]...

# Optimal path measure and optimal control for transition path problem

**Theorem**

*Let initial law* $\mathsf{R}_0 = \mu$ *satisfy* $\operatorname{supp}\mu \subset (A \cup B)^c$ *and* $h_{AB} \in L^1(\Gamma, \mu)$. *Then,*

- (i) s-OC$_\tau$ *admits a unique minimizer given by*

$$\mathsf{P}_{AB} := \mathsf{P}_\tau \otimes \mathsf{R}^{X_\tau}_{[0,\tau]}, \qquad \mathsf{P}_\tau := \frac{h_{AB}(X_\tau)}{\mathsf{E}_{\mathsf{R}_{[0,\tau]}}[h_{AB}(X_\tau)]} \mathsf{R}_\tau;$$

- (ii) *the associated value function is* $\gamma_{\text{sto}}(\mu) = -\log \int_\Gamma h_{AB}\, \mathrm{d}\mu$.
- (iii) $\mathsf{P}_{AB} \in \mathscr{P}(\Omega)$ *solves the martingale problem MP*$(\overline{L}^v, \mu)$ *with transition kernel*

$$\overline{L}_{AB}(\omega, \mathrm{d}t\, \mathrm{d}y) := \mathbb{1}_{[0,\tau_{AB})}(t) \frac{h_{AB}(y)}{h_{AB}(X_{t^-}(\omega))} L(X_{t^-}(\omega), \mathrm{d}y)\, \mathrm{d}t, \qquad \omega \in \Omega,$$

# Conclusion

- WKB reformulation for backward equation:

  $=$ Varadhan's nonlinear semigroup

  $=$ Monotone scheme to Hamilton–Jacobi eq $\partial_t u(\vec{x},t) = H(\nabla u(\vec{x}),\vec{x})$

  $\Longrightarrow$ Lax-Oleinik's semigroup $\boxed{\lim_{h\to 0} u_{\mathrm{h}}(\vec{x}_i,t) = u(\vec{x},t)} = \sup_{\vec{y}}\left(u_0(\vec{y}) - I(\vec{y};\vec{x},t)\right)$

  a good rate function: $I(y;x,t) = \inf_{\gamma(0)=\vec{x},\gamma(t)=\vec{y}} \int_0^t L(\dot{\gamma}(s),\gamma(s))\,\mathrm{d}s$

- Importance sampling of transition paths that connect metastable states in chemical reactions.
- Zero cost action $I=0 \Longrightarrow$ mean field reaction rate eq (with concentration rate)

$$\frac{\mathrm{d}}{\mathrm{d}t}\vec{x} = \sum_{j=1}^{M} \vec{v}_j\left(\Phi_j^+(\vec{x}) - \Phi_j^-(\vec{x})\right) = \nabla_p H(\vec{p},\vec{x})\big|_{\vec{p}=\vec{0}} \equiv \mathscr{C} - K(\vec{x})\nabla\psi^{ss}(\vec{x})$$

- Energy landscape: a **selected** stationary solution to $H(\nabla\psi^{ss}(x),x) = 0$
  - LDP for invariant measures selects the unique weak KAM solution
  - Dissipative-conservative decomposition via energy landscape

**Thank you!**