The Geometric Minimum Action Method

A Least Action Principle on the Space of Curves

Thesis Defense

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Outline

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Introduction to Large Deviations Theory

Consider an SDE with drift $b(x)$ and small noise:

SDE

$$dX_t = b(X_t)\,dt + \sqrt{\epsilon}\,dW_t, \qquad X_0 = x_0.$$

- Suppose x_1, x_2 are the only stable points of the system.
- Without noise, the system would be attracted to either x_1 or x_2, depending on x_0.
- With noise, the system may leave the domain of attraction.

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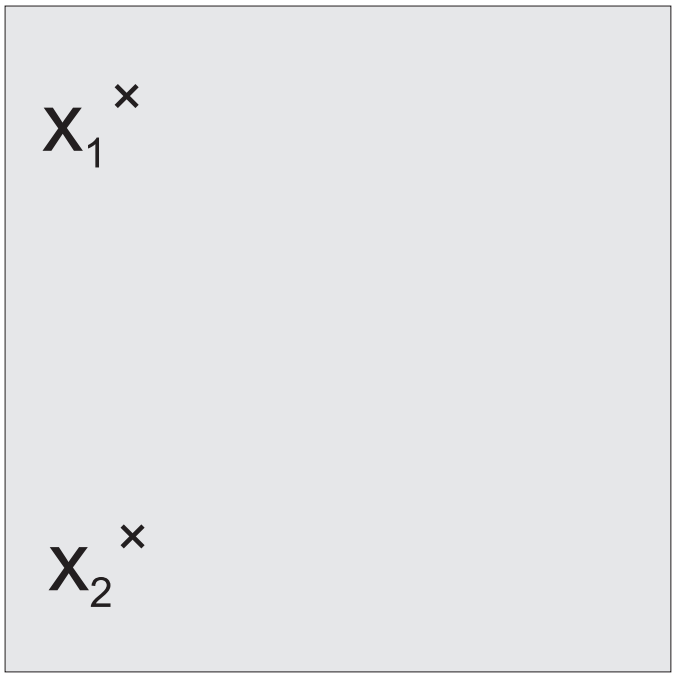

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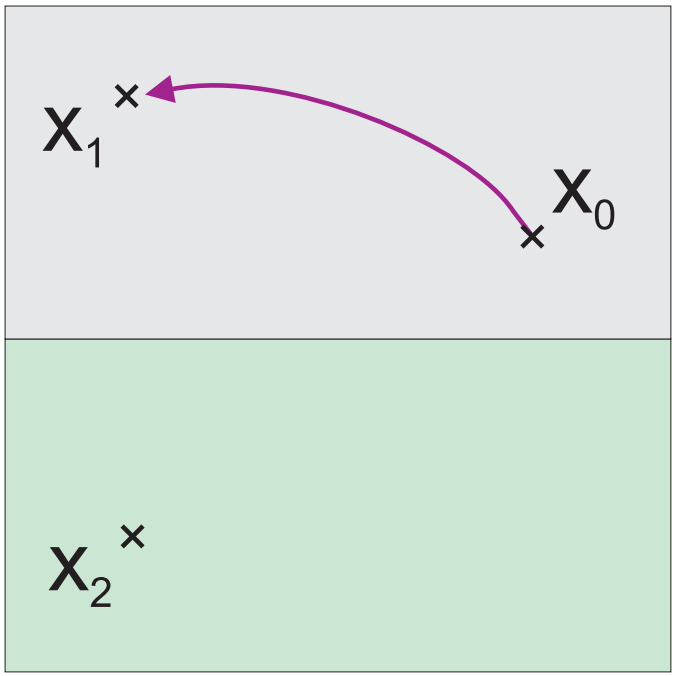

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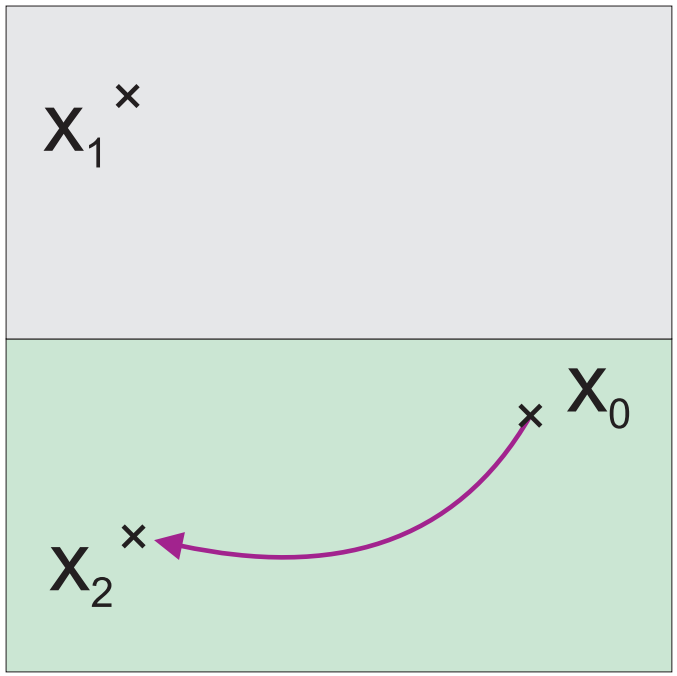

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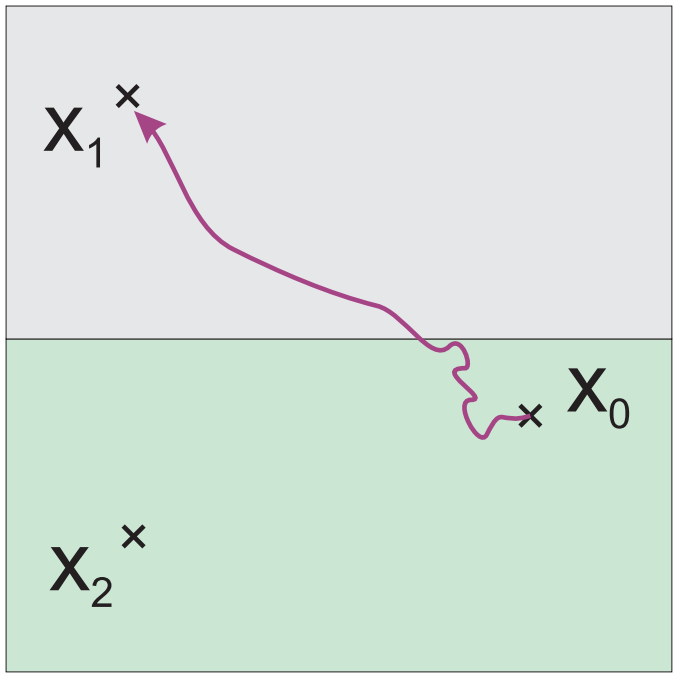

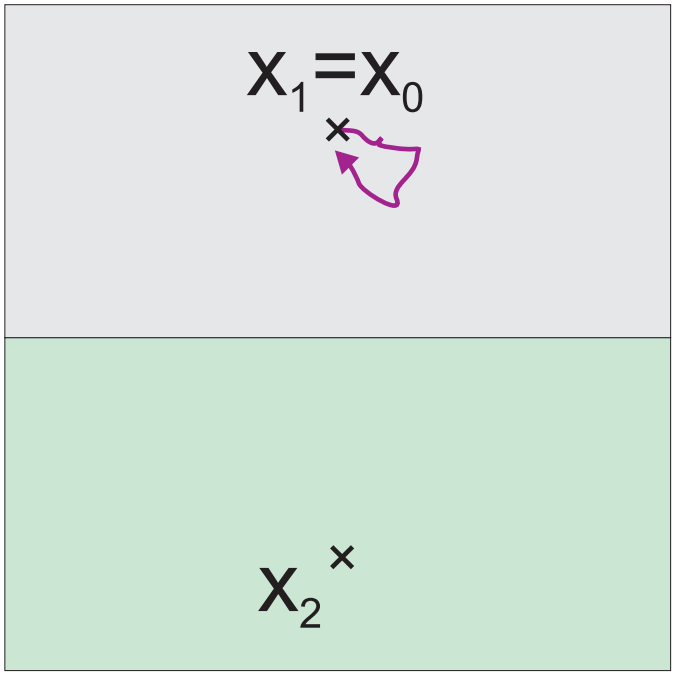

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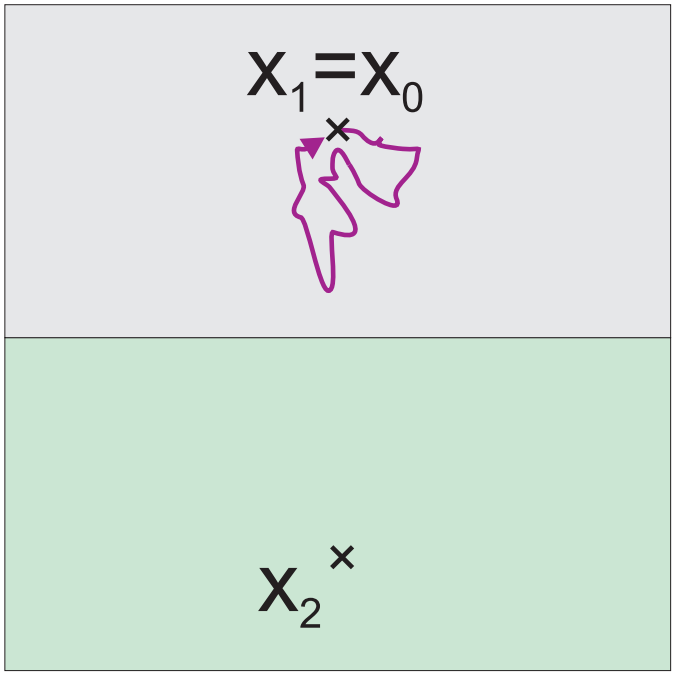
- But eventually the system will manage to fall into the other state.

Questions:

- How frequent are those rare transitions?
- What is the most likely way in which they occur?



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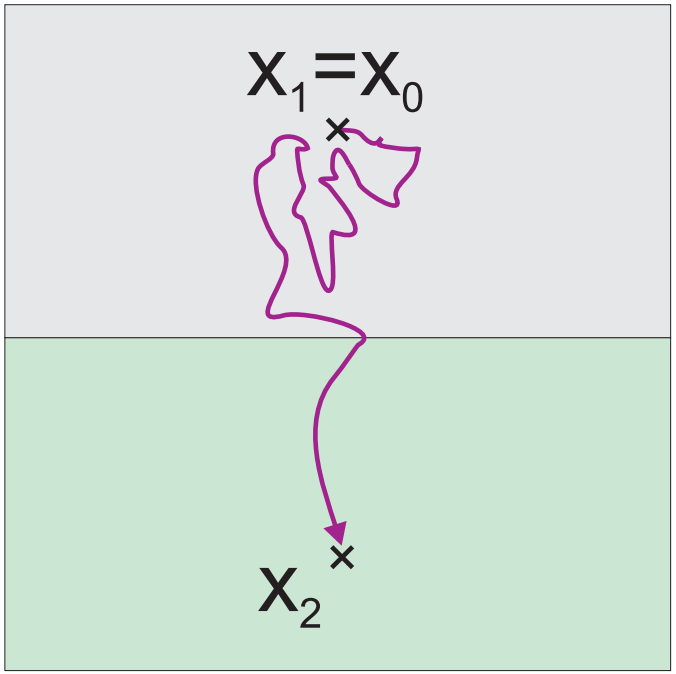

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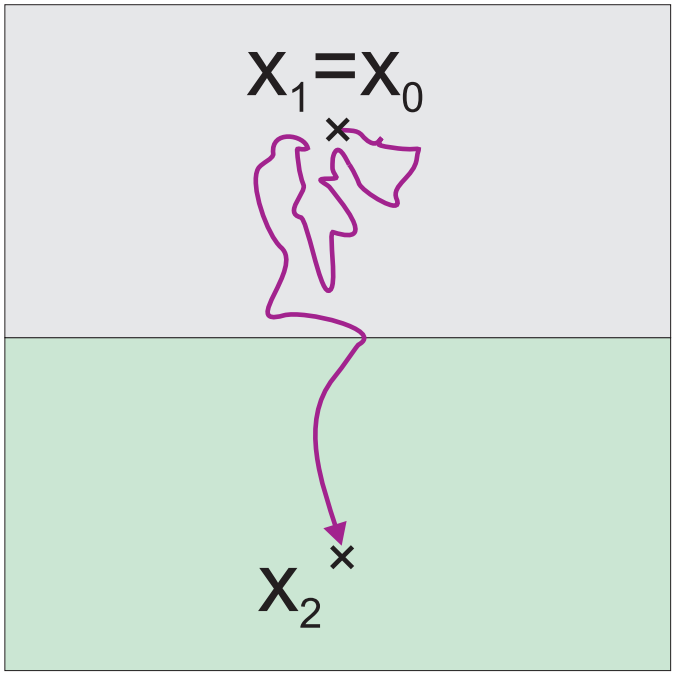

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Answer 1: Frequency of transitions

The frequency of those rare transitions is $\approx e^{-V(x_1,x_2)/\epsilon}$, where $V(x_1,x_2)$ is the quasipotential.

Definition (Quasipotential)

$$V(x_1,x_2) := \inf_{T>0} \inf_{\psi \in \bar{C}^{x_2}_{x_1}(0,T)} S_T(\psi), \quad \text{where}$$

$$S_T(\psi) := \int_0^T L(\psi,\dot{\psi})\,dt \quad \text{and}$$

$$\bar{C}^{x_2}_{x_1}(0,T) := \left\{\psi : [0,T] \to \mathbb{R}^n \mid \psi(0) = x_1,\ \psi(T) = x_2,\ \psi \text{ a.c.}\right\}.$$

Answer 2: Most likely transition path

The most likely way in which a transition occurs is to follow the minimizing path $\psi^* : [0,T^*] \to \mathbb{R}^n$ in the definition of $V(x_1,x_2)$.

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Compute the Euler-Lagrange equation and solve the boundary value ODE problem.

Problems:

- hard to do in higher dimensions
- may be ill-posed

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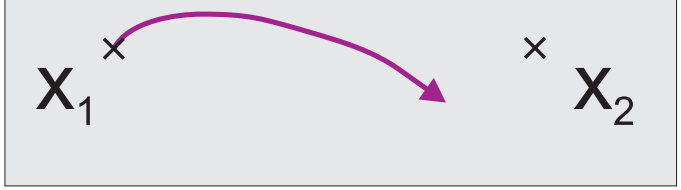

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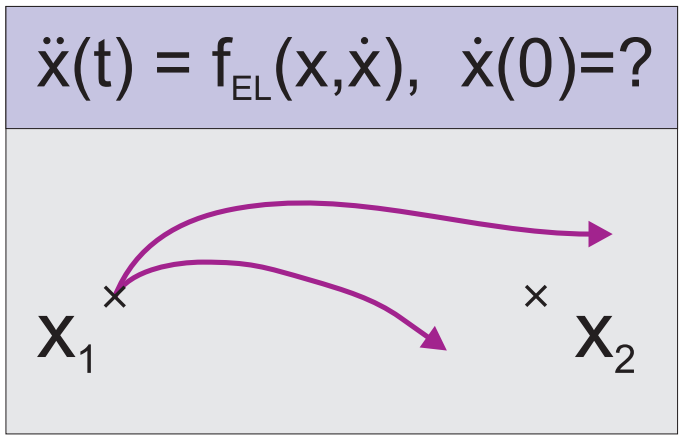

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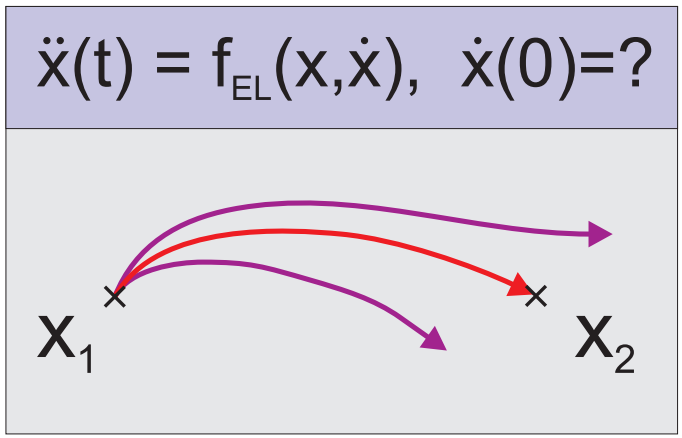

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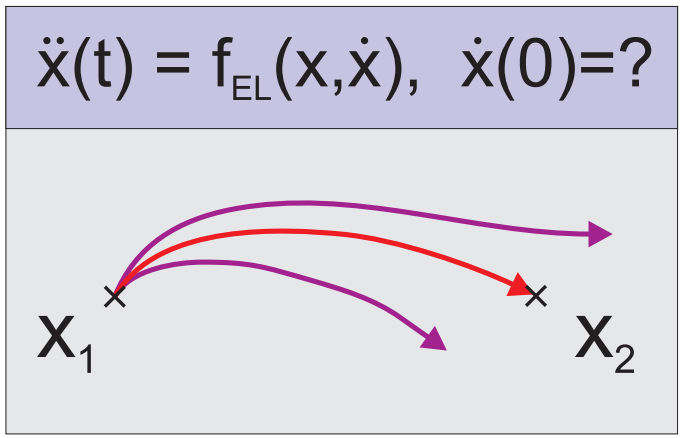

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Approach 2: The String Method

If $b(x)$ is of the form $b = -\nabla U$ then $\psi^\star \parallel b$.

$\Rightarrow$ Use 2-step-procedure: (i) follow the flow,
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Problem:

- does not apply to general SDEs, or to other types of dynamics

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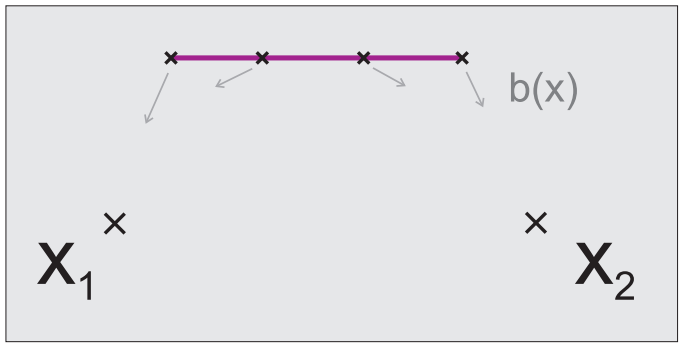

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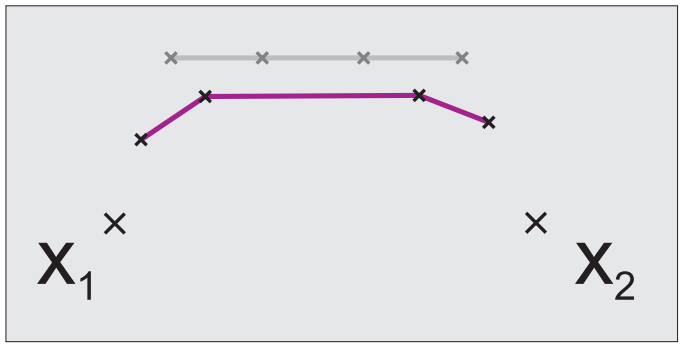

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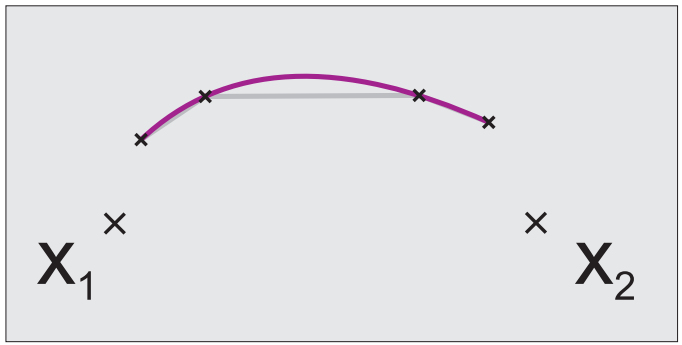

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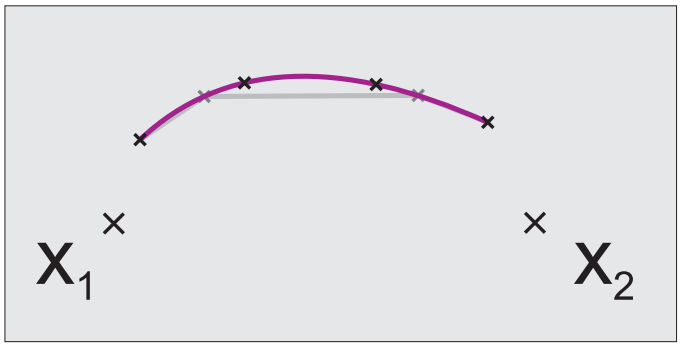

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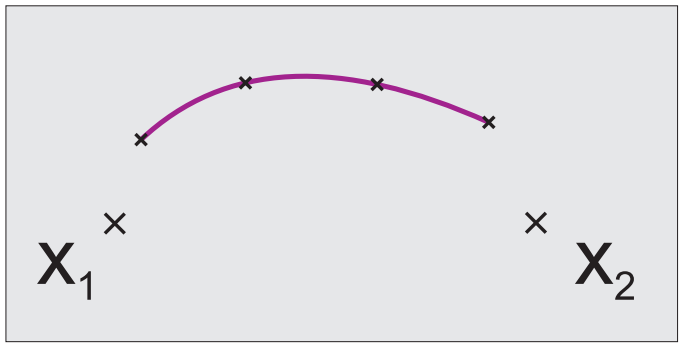

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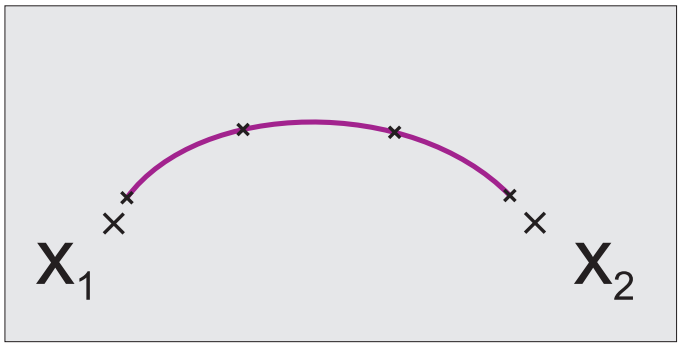

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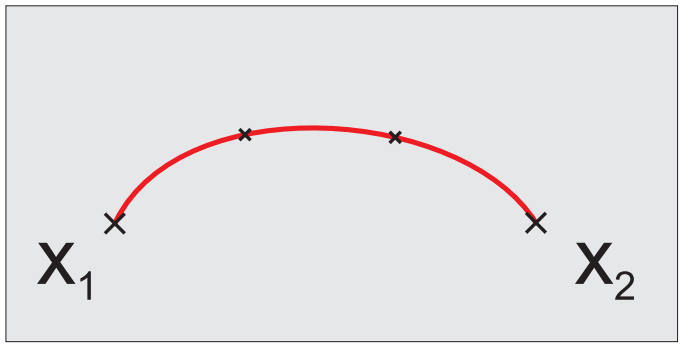

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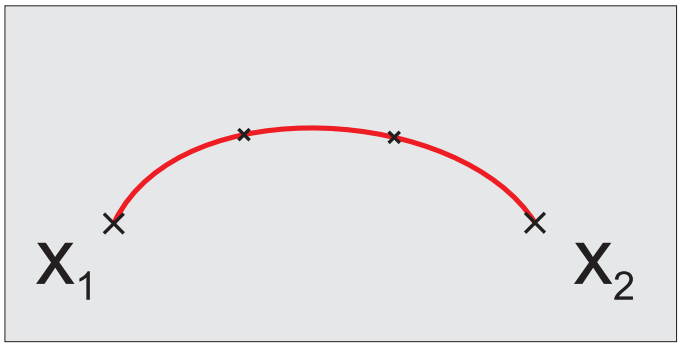

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Approach 3: The Minimum Action Method (MAM)

For fixed T, discretize the integral and use a steepest-descent method.

If x_1, x_2 are stable points then $T = \infty$, so just pick T large.

Problems:

- Grid points accumulate at x_1, x_2.
- especially if T large.
- No minimizer $(T^\star, \psi^\star)$ exists!

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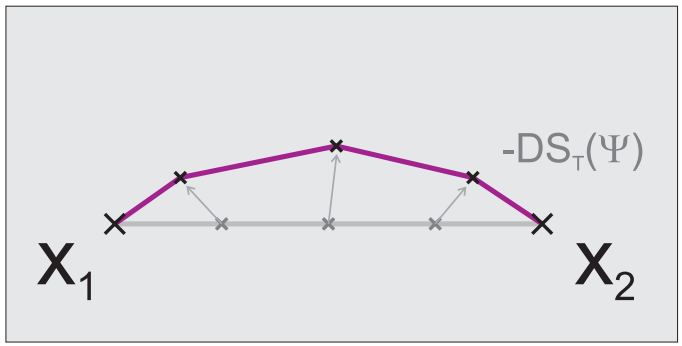

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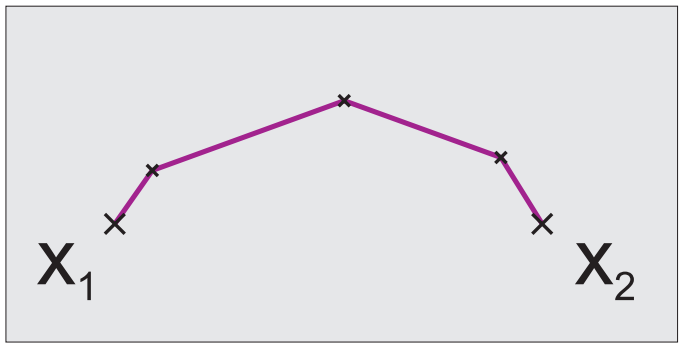

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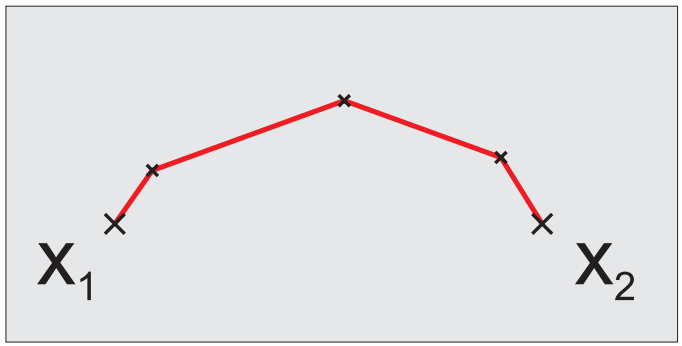

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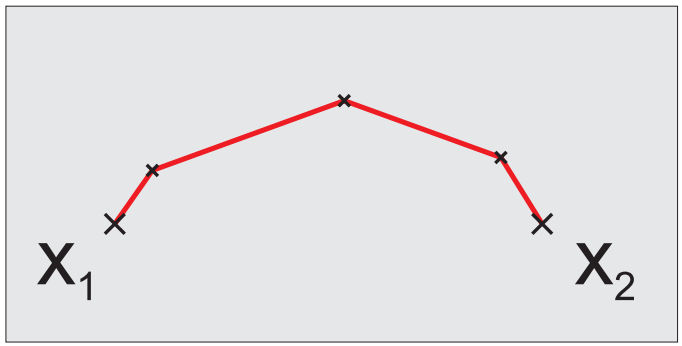

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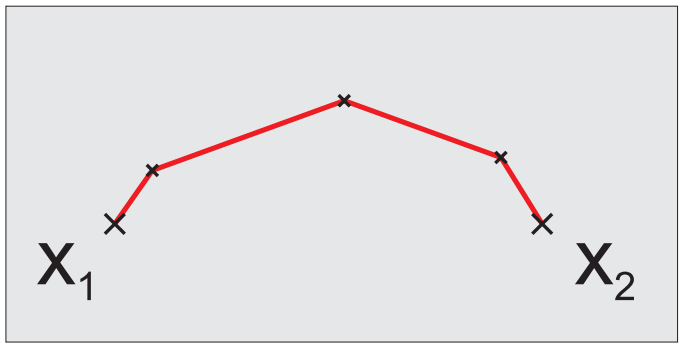

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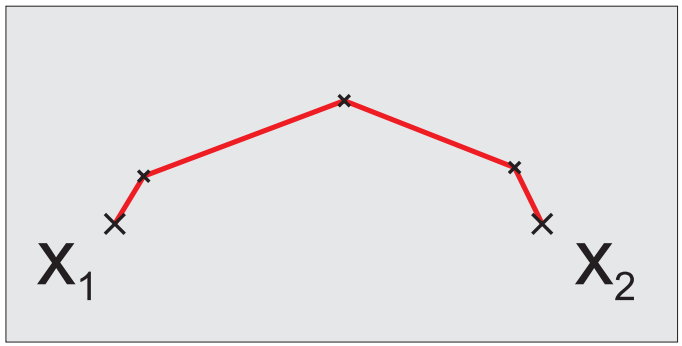

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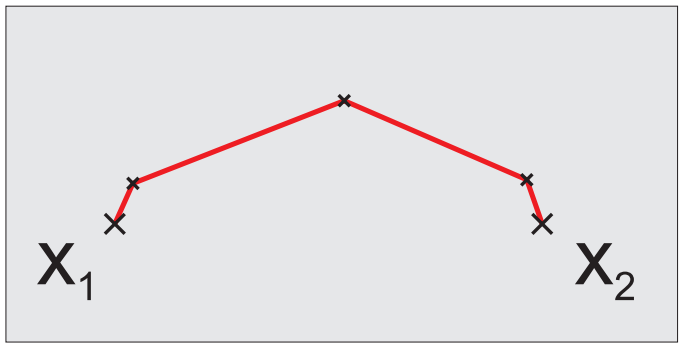

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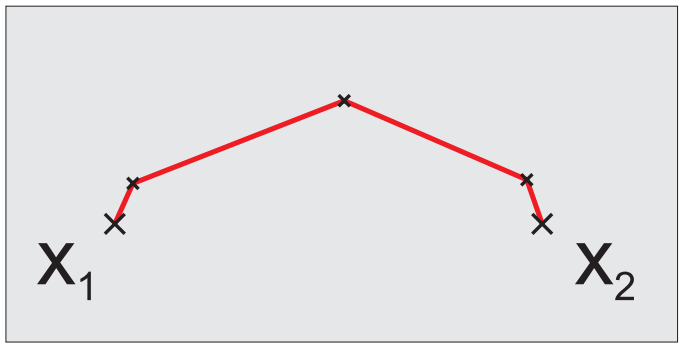

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"geometric" approach

$\Longrightarrow$ stability

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"Geometric Minimum Action Method" (gMAM)

Outline

Main Results:

- Reformulation of the quasipotential:

$$V(x_1, x_2) = \inf_{\varphi \in \bar{C}^{x_2}_{x_1}(0,1)} \hat{S}(\varphi),$$

  where $\hat{S}(\varphi)$ only depends on the curve $\gamma(\varphi)$ of φ.

- The geometric minimum action method (gMAM): an algorithm to find the *most likely transition curve*
- Applications to e.g. synthetic biology: A tool to detect sources of instability in genetic networks.

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Theorem (reformulation of the quasipotential)

$$V(x_1,x_2) := \inf_{T>0} \inf_{\psi \in \bar{C}^{x_2}_{x_1}(0,T)} S_T(\psi) = \inf_{\varphi \in \bar{C}^{x_2}_{x_1}(0,1)} \hat{S}(\varphi), \quad \text{where}$$

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The action on the space of curves $\hat{S}(\varphi)$ has the following two representations:

$$\hat{S}(\varphi) = \int_0^1 \langle \varphi', \hat{\vartheta}(\varphi, \varphi') \rangle \, d\alpha = \int_0^1 \sup_{\substack{\vartheta \in \mathbb{R}^n \\ H(\varphi,\vartheta)=0}} \langle \varphi', \vartheta \rangle \, d\alpha,$$

where the function $\hat{\vartheta}(x, y)$ is implicitly defined by

$$H(x, \hat{\vartheta}) = 0, \qquad H_\theta(x, \hat{\vartheta}) = \lambda y, \qquad \lambda \geq 0,$$

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Advantages of the new formulation:

- existence of a minimizing curve
- $\hat{S}(\varphi)$ only depends on the curve $\gamma(\varphi)$ of φ. Thus
  - we may reparametrize φ at will;
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Other important properties of $\hat{S}$ and $\varphi^\star$:

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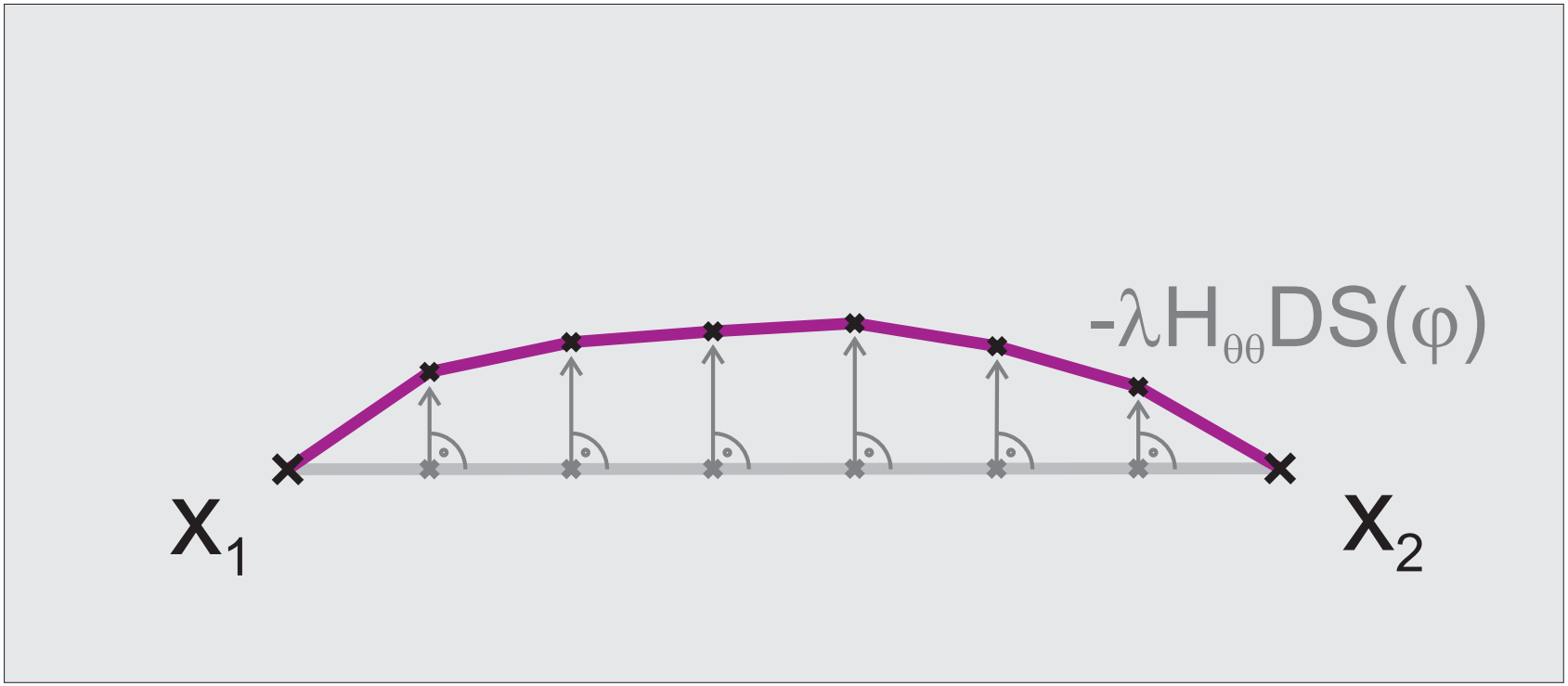

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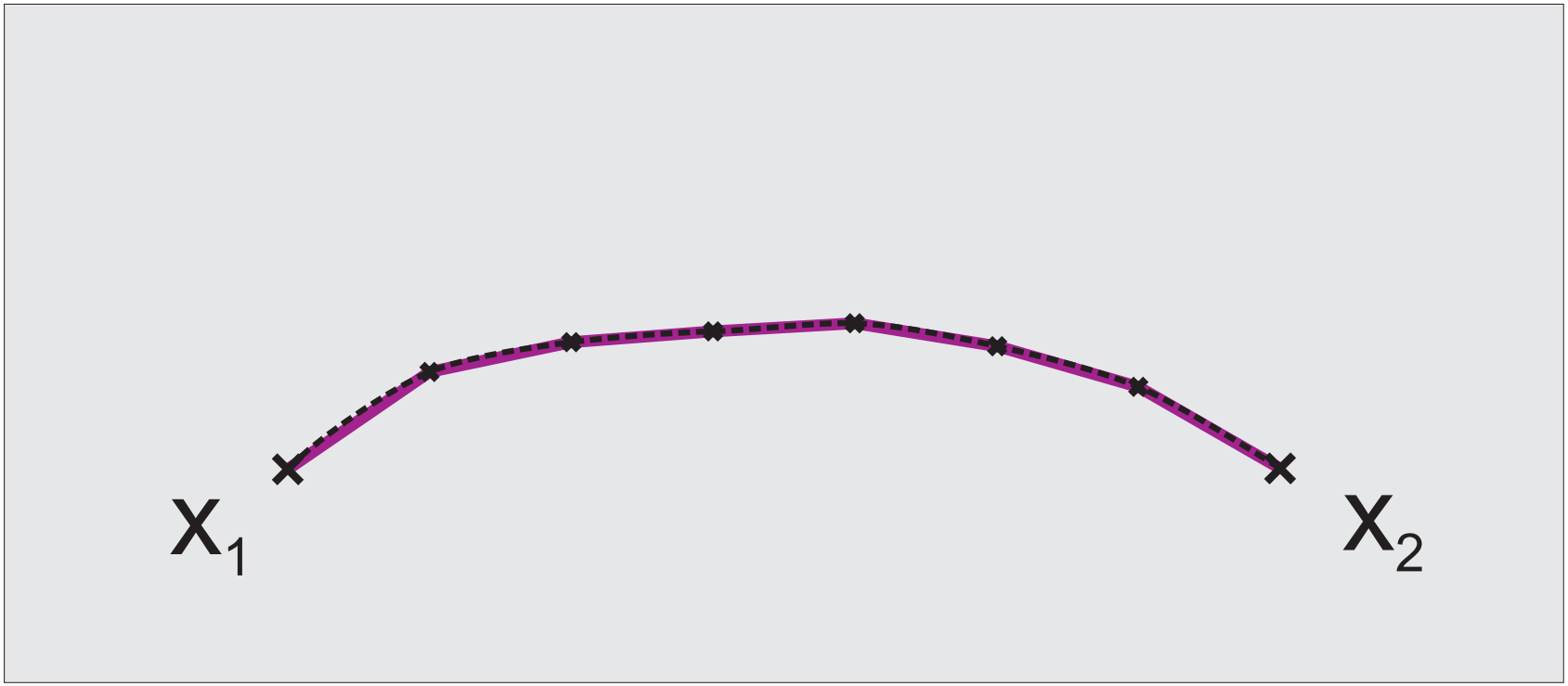

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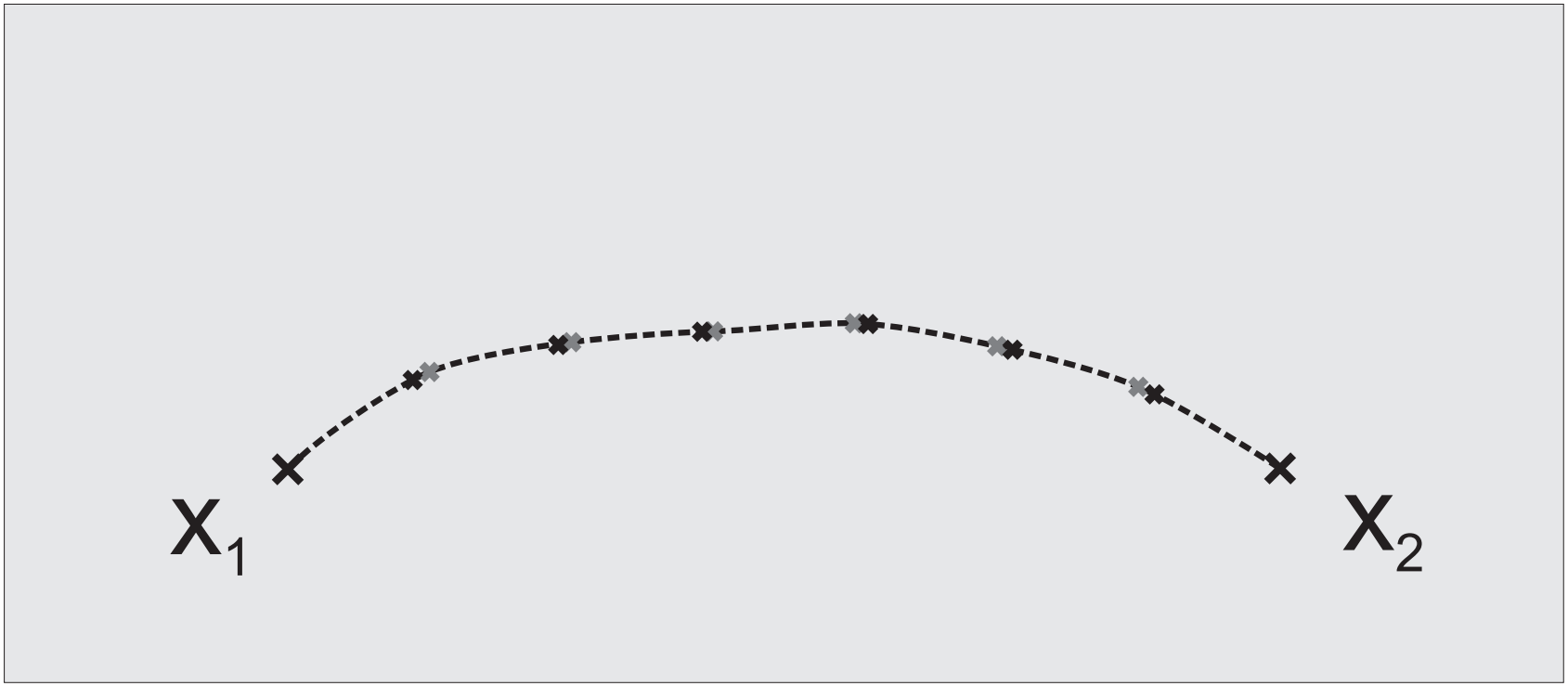

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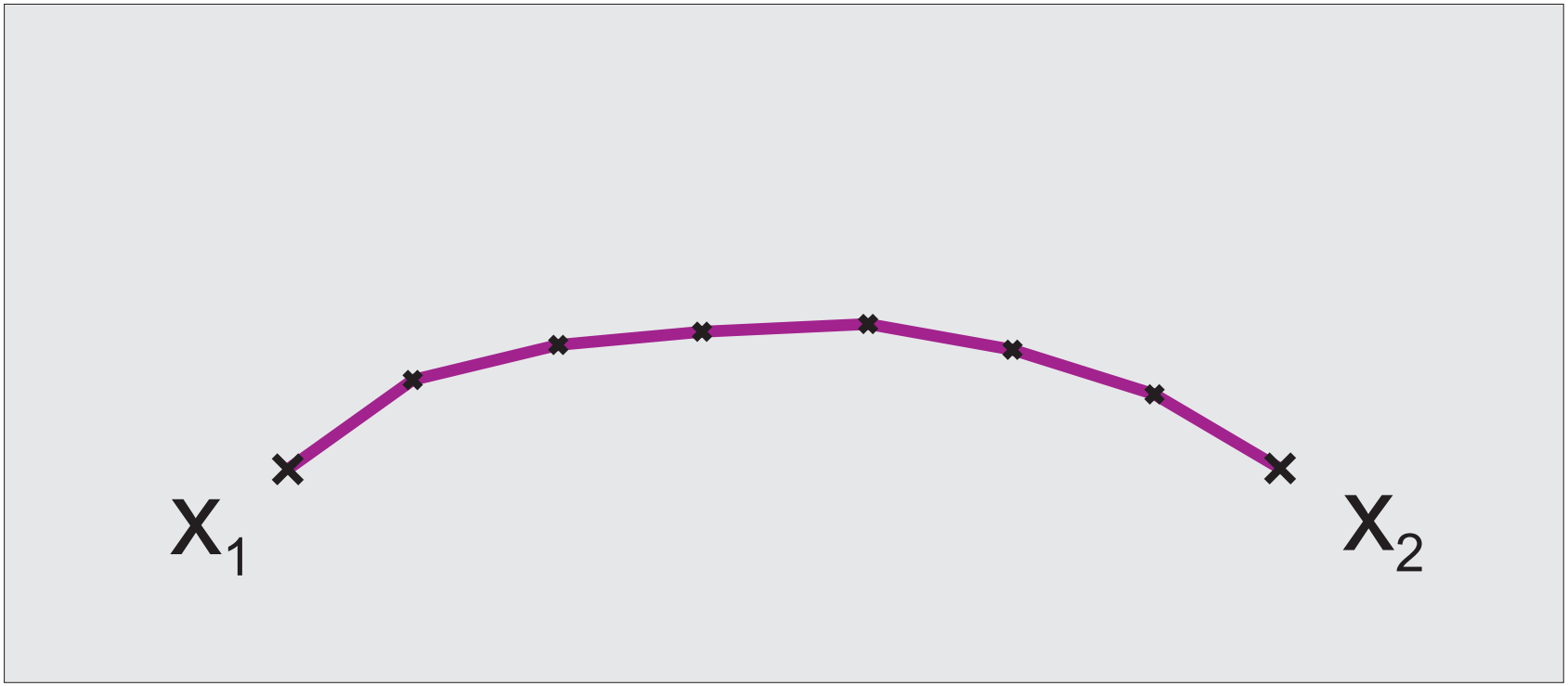

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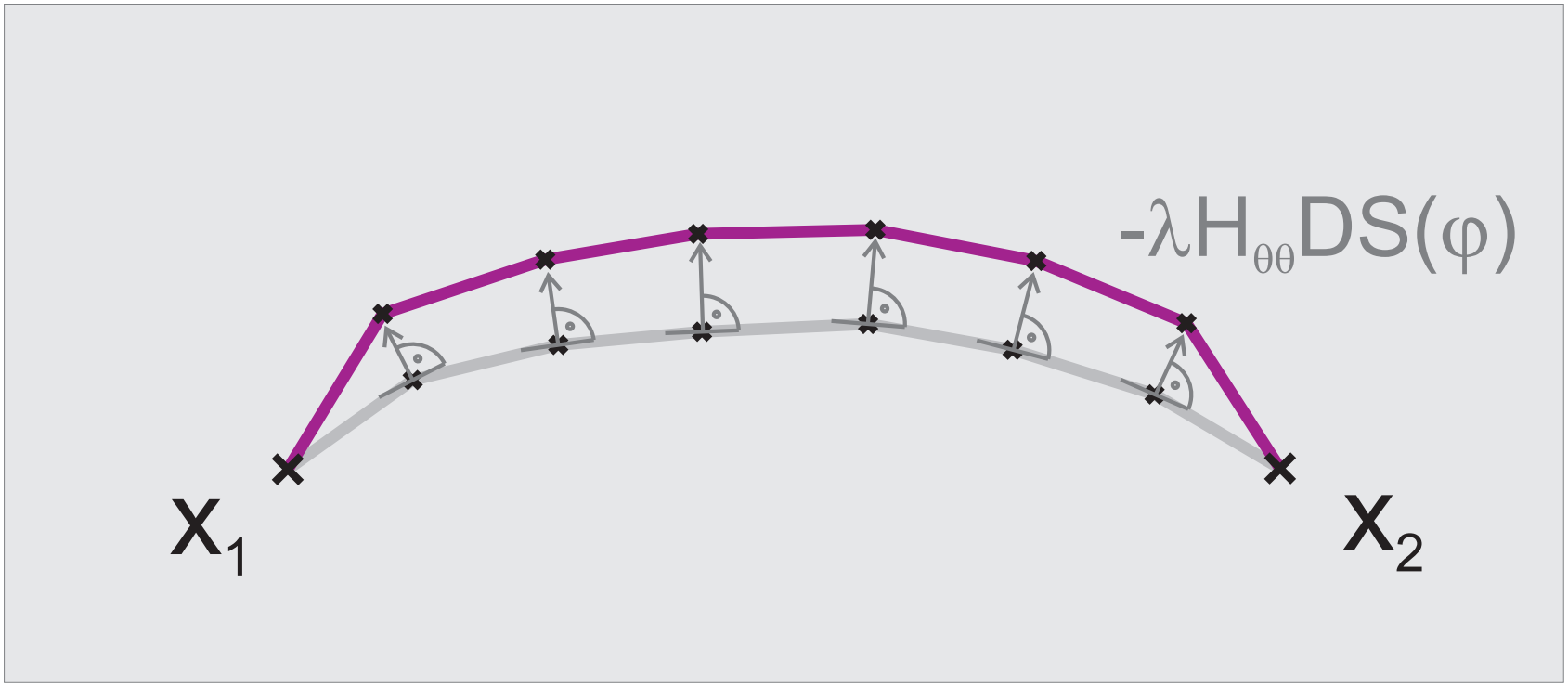

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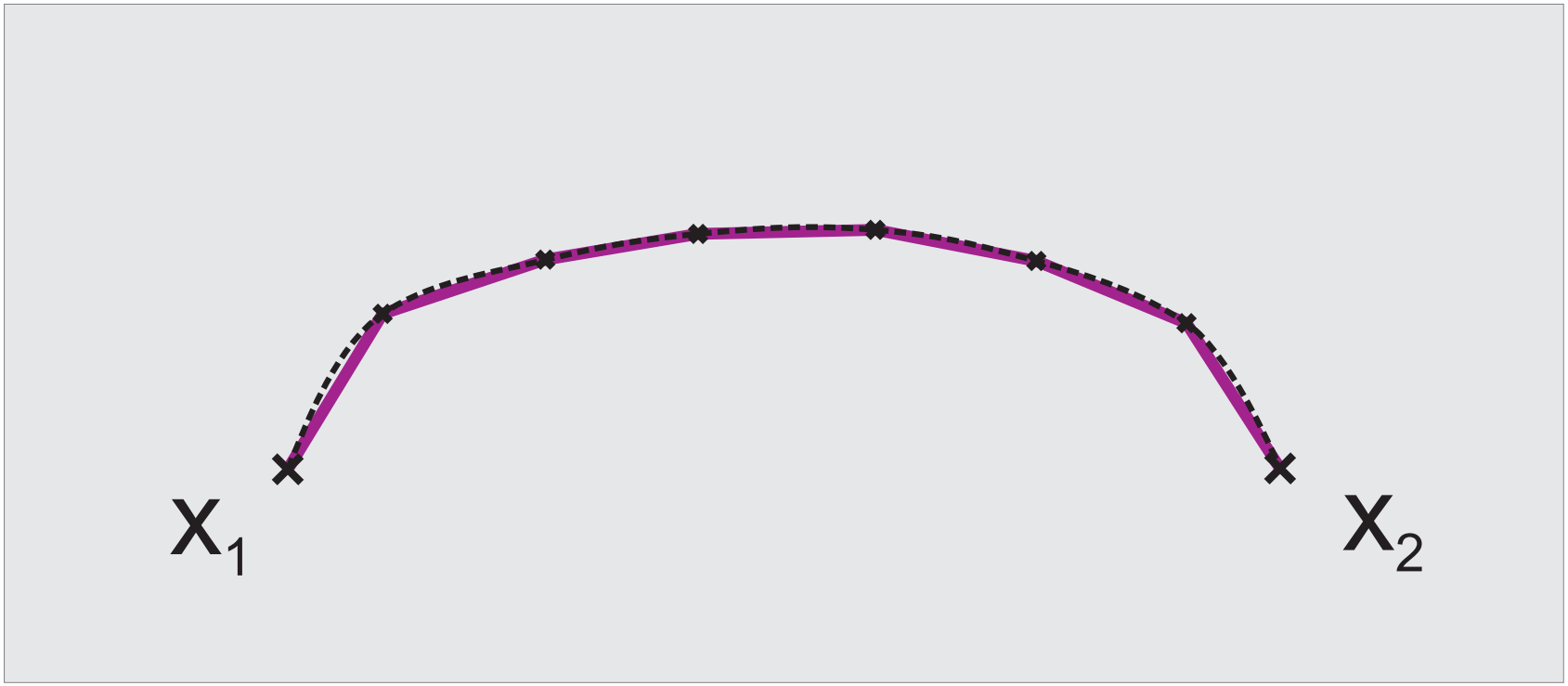

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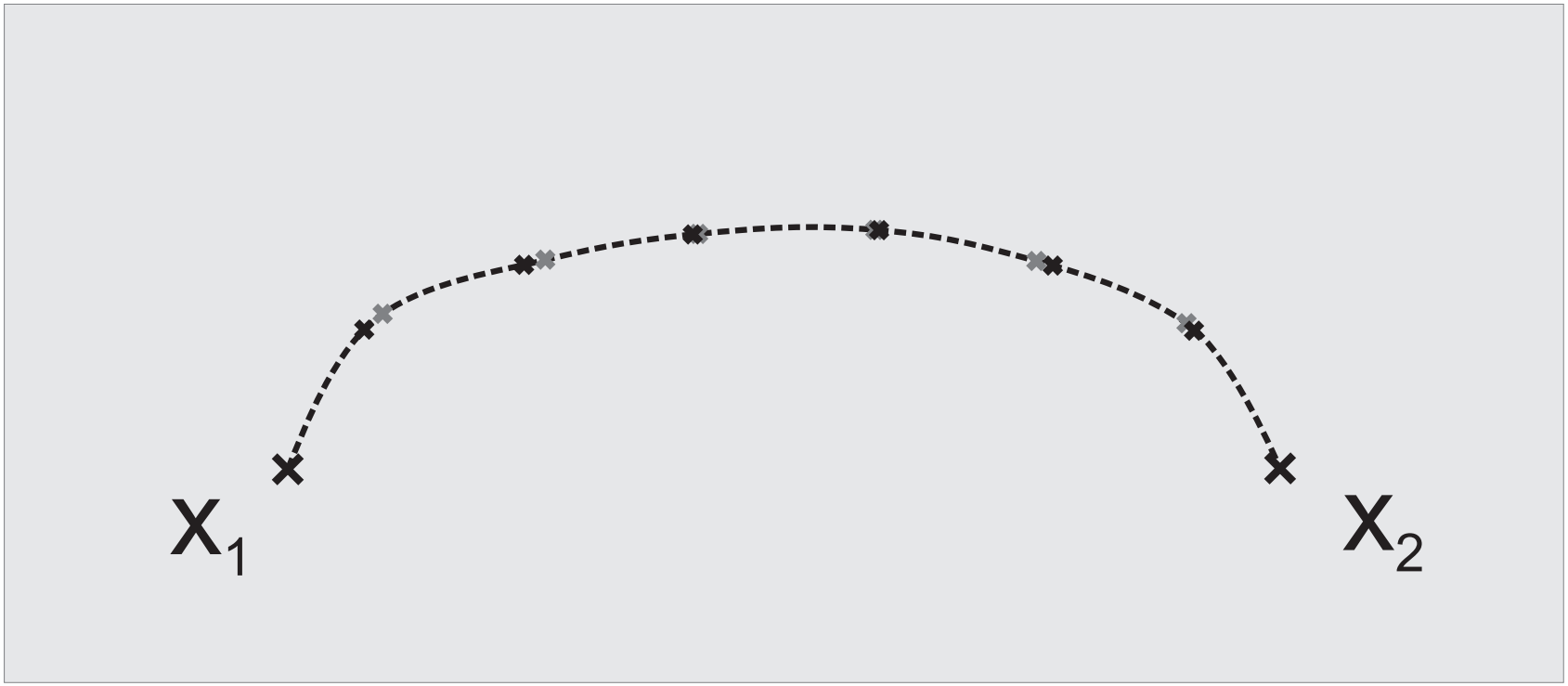

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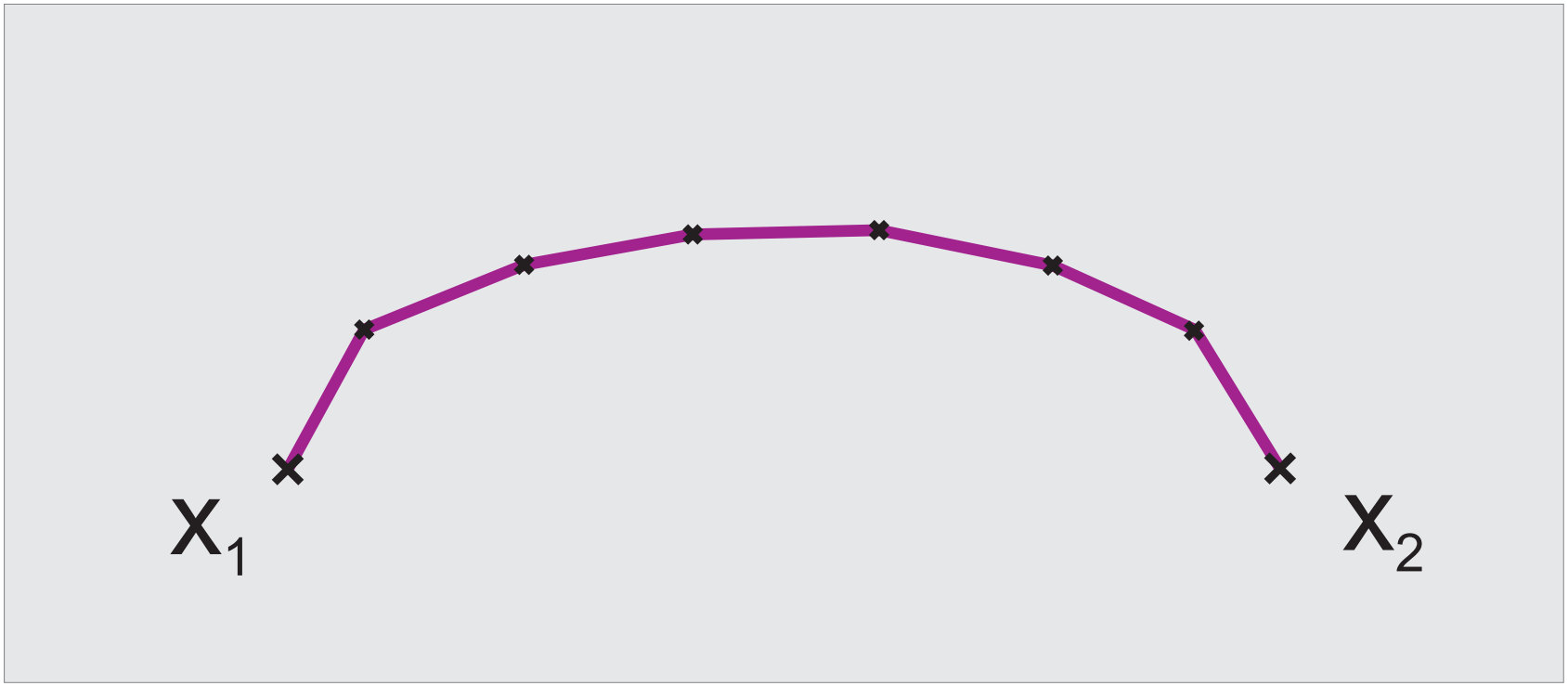

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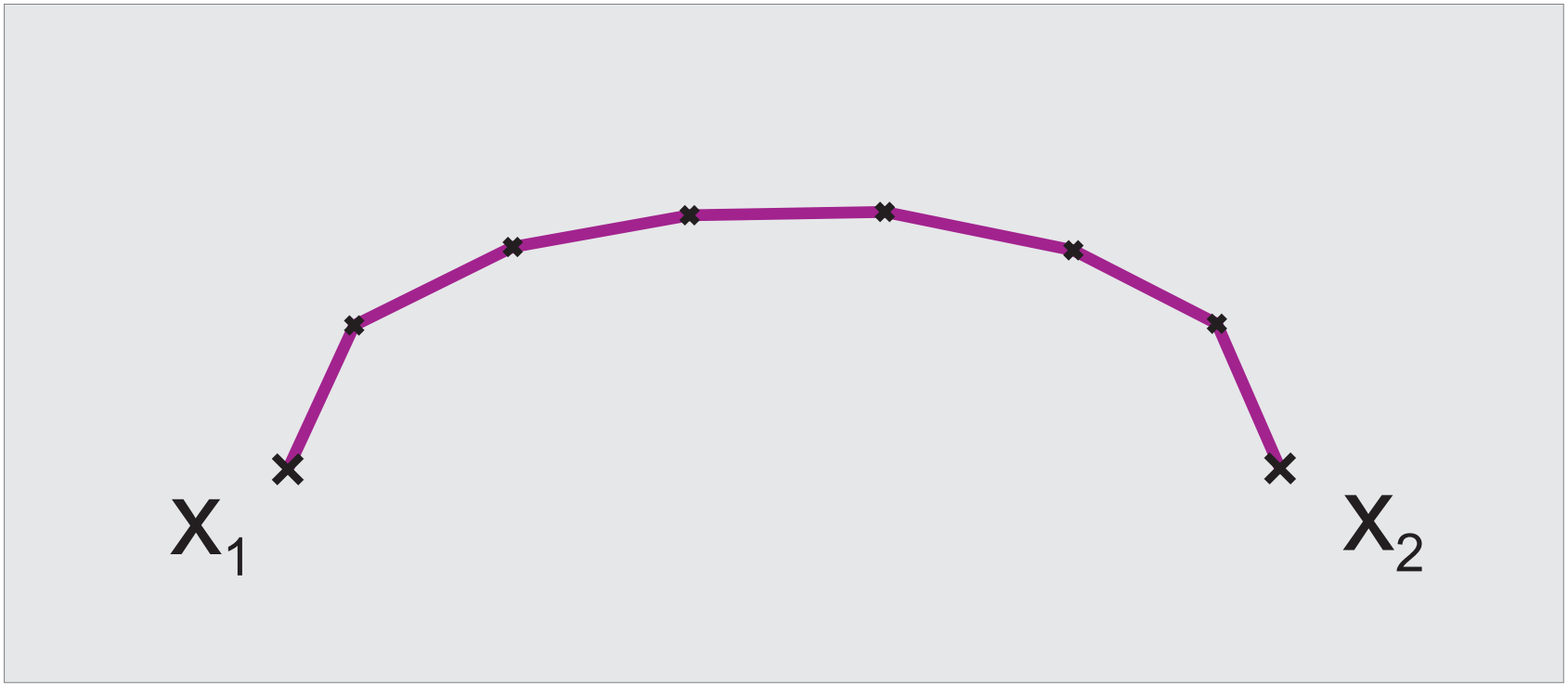

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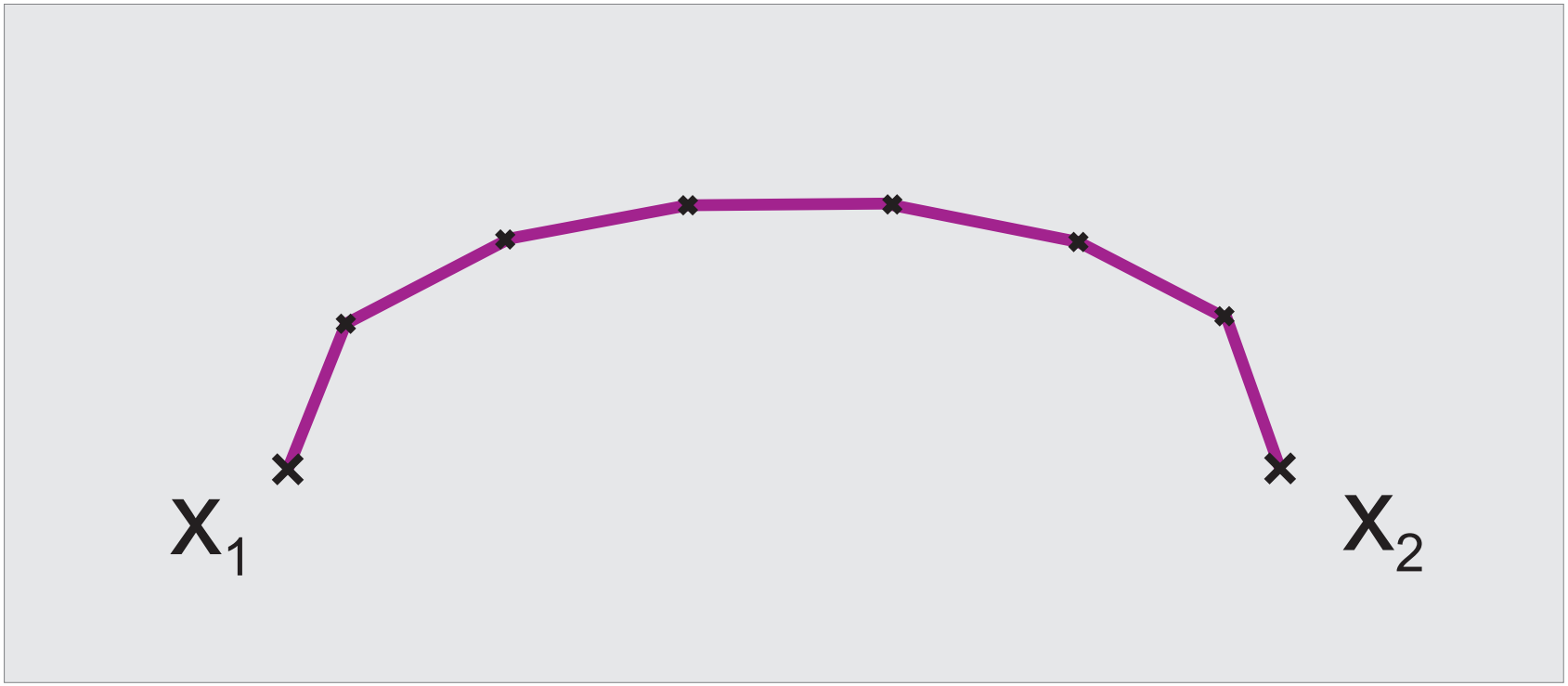

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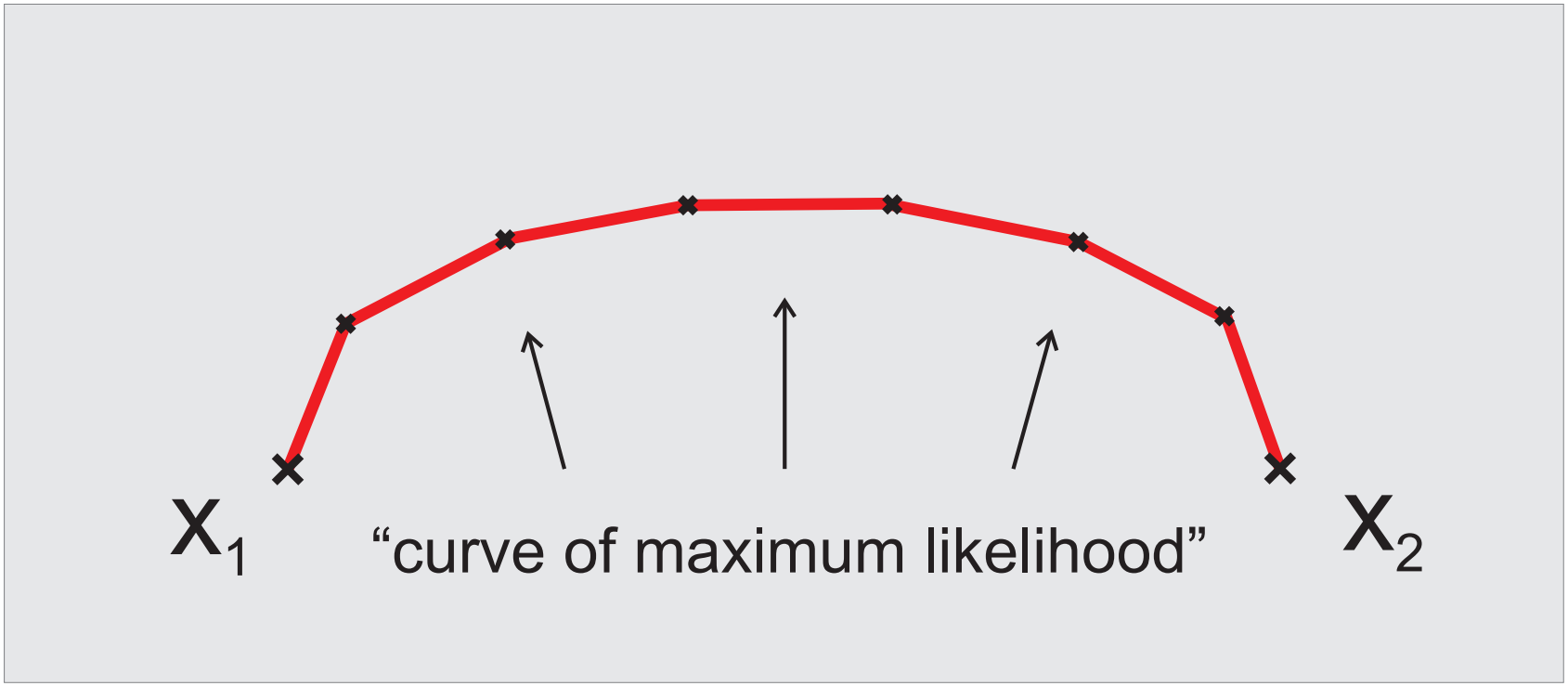
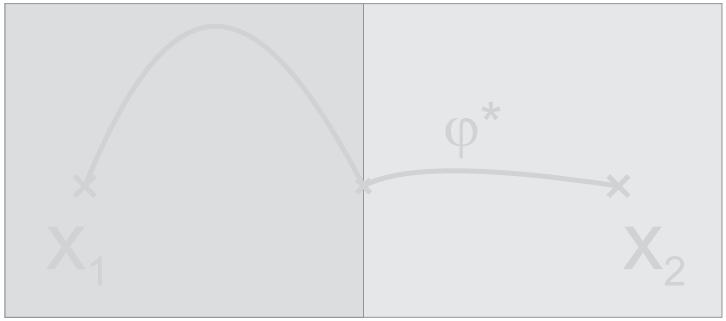


Features of the gMAM:

- runtime linear in the number of gridpoints N
- maximal stepsize $\Delta\tau$ independent of N, due to choice of metric and semi-implicit scheme
- stable even if minimizer $\varphi^\star$ has corners when passing critical points



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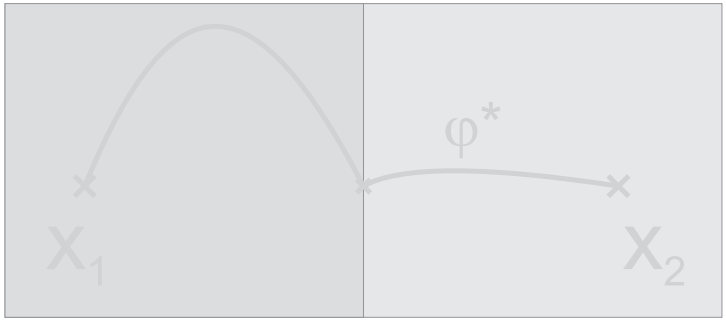

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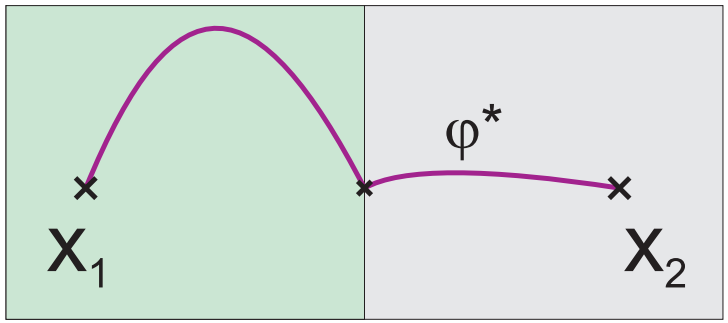

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Algorithm (gMAM):

- Choose an initial curve $\varphi^0 \in \bar{C}^{x_2}_{x_1}(0,1)$.
- Iterate:
  - At every point on the curve, compute $(\lambda, \hat{\vartheta})$.
  - Move the curve into the direction of steepest descent,

$$\begin{aligned} \partial_\tau \varphi(\tau, \alpha) &= -\lambda H_{\theta\theta} D\hat{S}(\varphi) \\ &= \lambda^2 \varphi'' - \lambda H_{\theta x} \varphi' + H_{\theta\theta} H_x + \lambda \lambda' \varphi', \end{aligned}$$

    where H_x, $H_{\theta x}$ and $H_{\theta\theta}$ are evaluated at $(\varphi, \hat{\vartheta})$.
  - Reparametrize the curve so that $|\varphi'| = const$.

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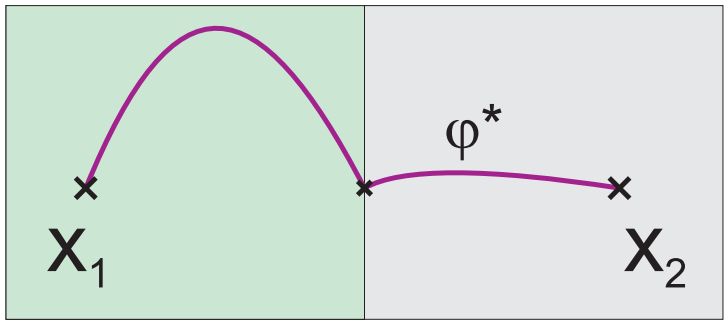

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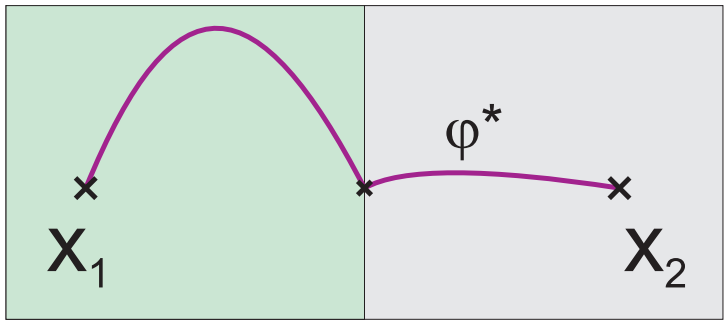

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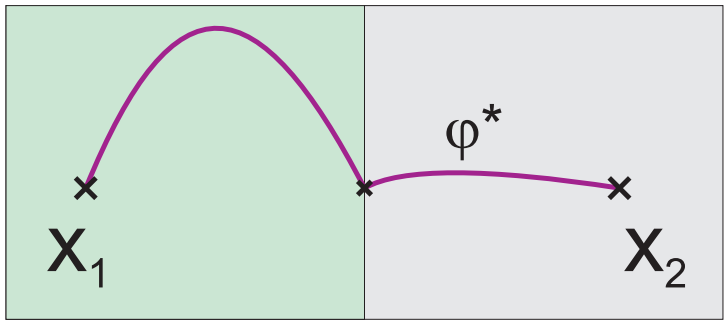

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Outline

Example 1: Maier-Stein model (SDE)

$$du(t) = (u - u^3 - \beta u v^2)\, dt + \sqrt{\epsilon}\, dW_1(t),$$
$$dv(t) = -(1 + u^2) v\, dt + \sqrt{\epsilon}\, dW_2(t).$$
$$S_T(u, v) = \frac{1}{2} \int_0^T \left((u - u^3 - \beta u v^2 - \dot{u})^2 + (-(1 + u^2) v - \dot{v})^2 \right) dt$$

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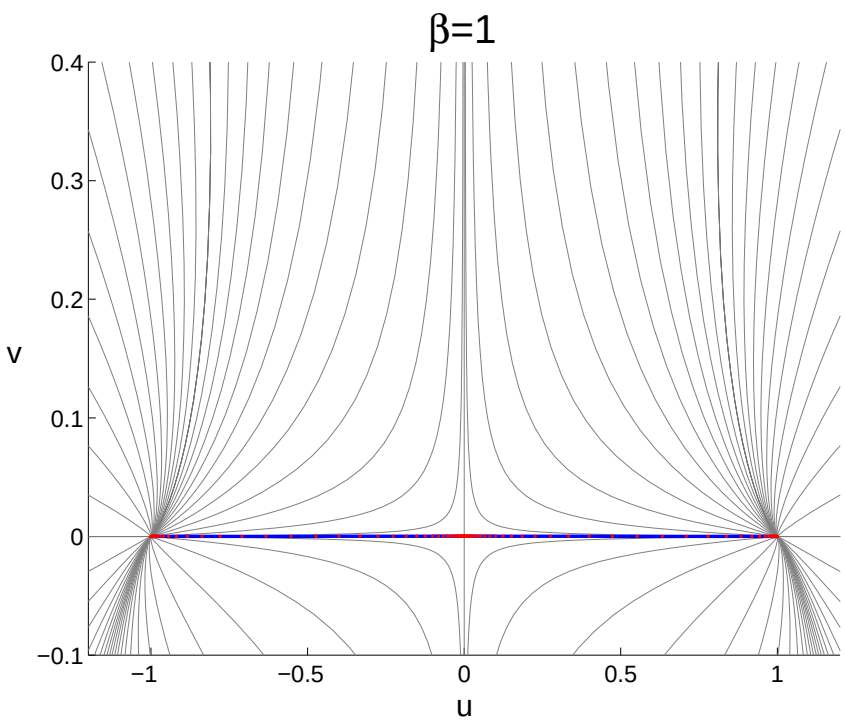

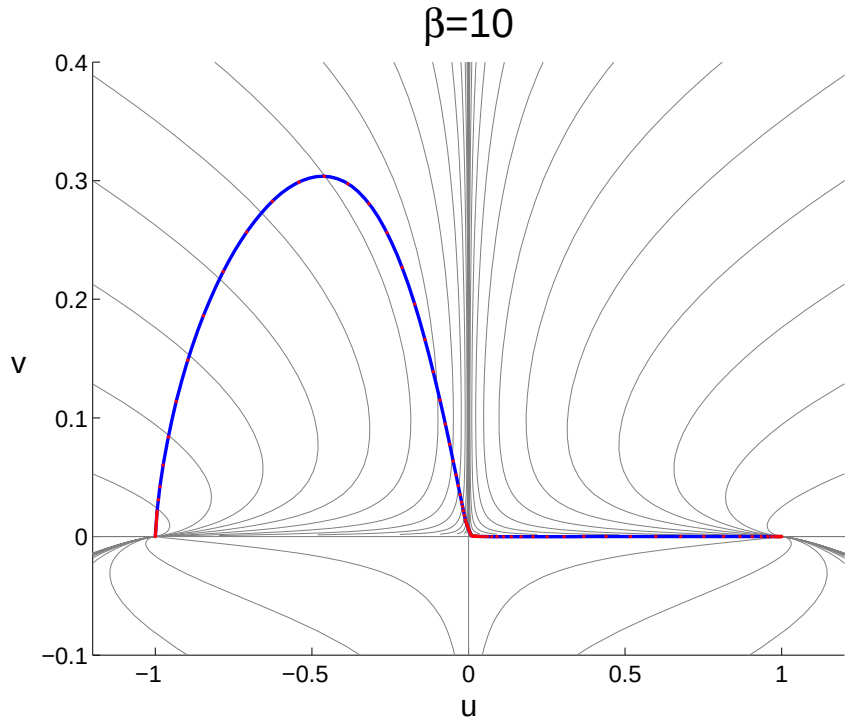

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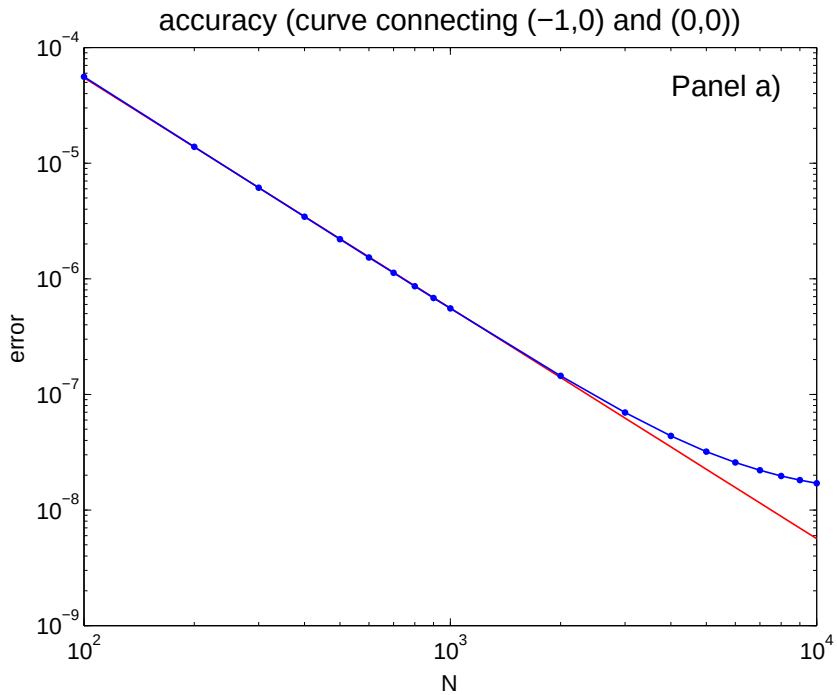

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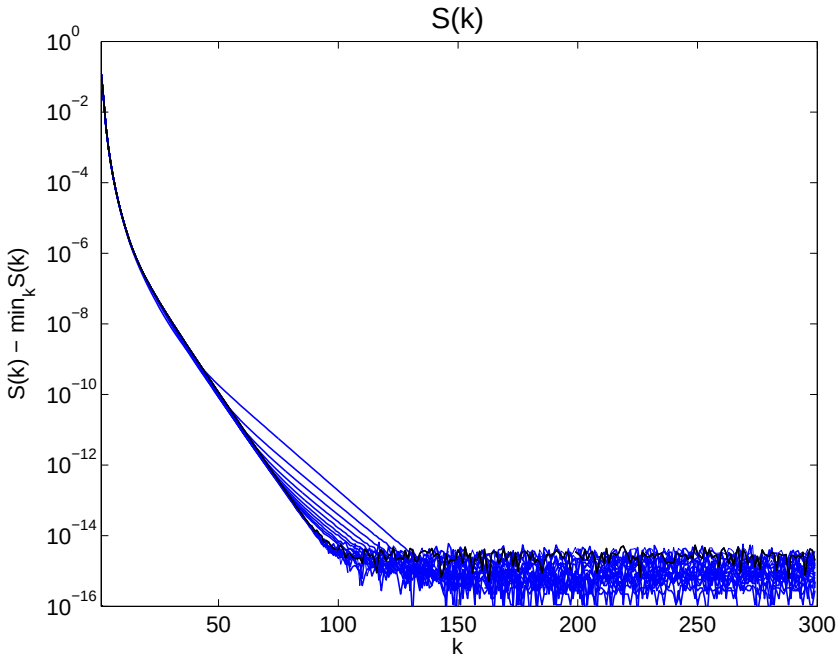

Example 2: Maier-Stein model (SPDE, 1D)

$$u_t(x,t) = \kappa u_{xx} + u - u^3 - \beta u v^2 + \sqrt{\epsilon}\,\eta_1(x,t),$$
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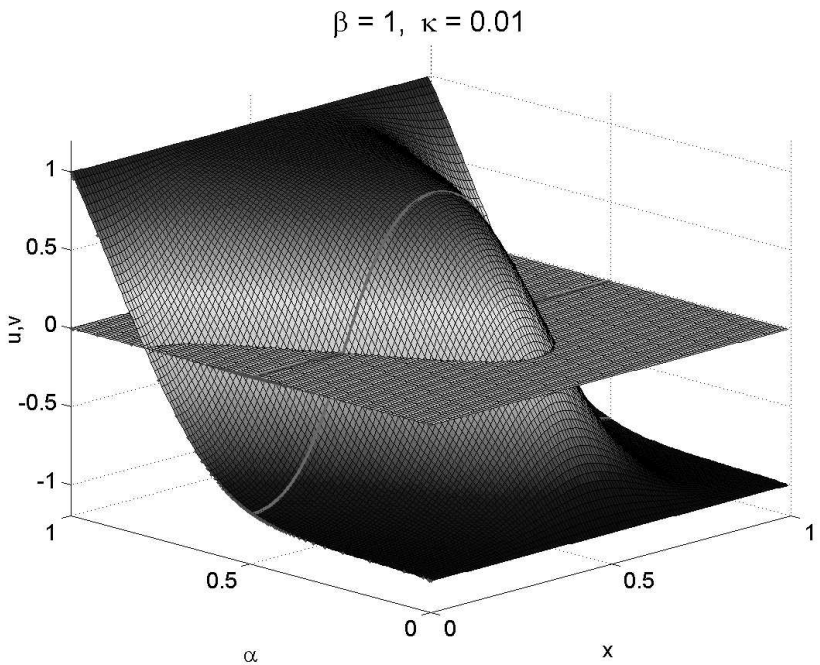

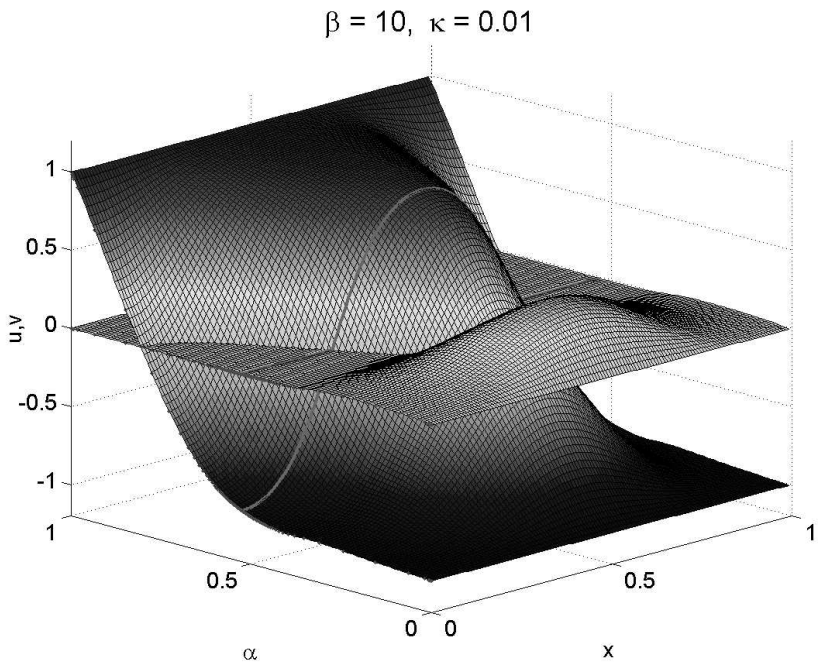

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Outline

Introduction to synthetic biology

- Synthetic biology is a newly emerging subfield of biology.
- DNA sequences are
  - designed in the computer,
  - “printed” as a DNA molecule,
  - inserted into living bacteria.
- These bacteria can fulfill certain tasks such as
  - producing vaccines in amounts not possible otherwise,
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- “Biological engineers” are thus in need of predesigned small genetic networks fulfilling basic tasks reliably.

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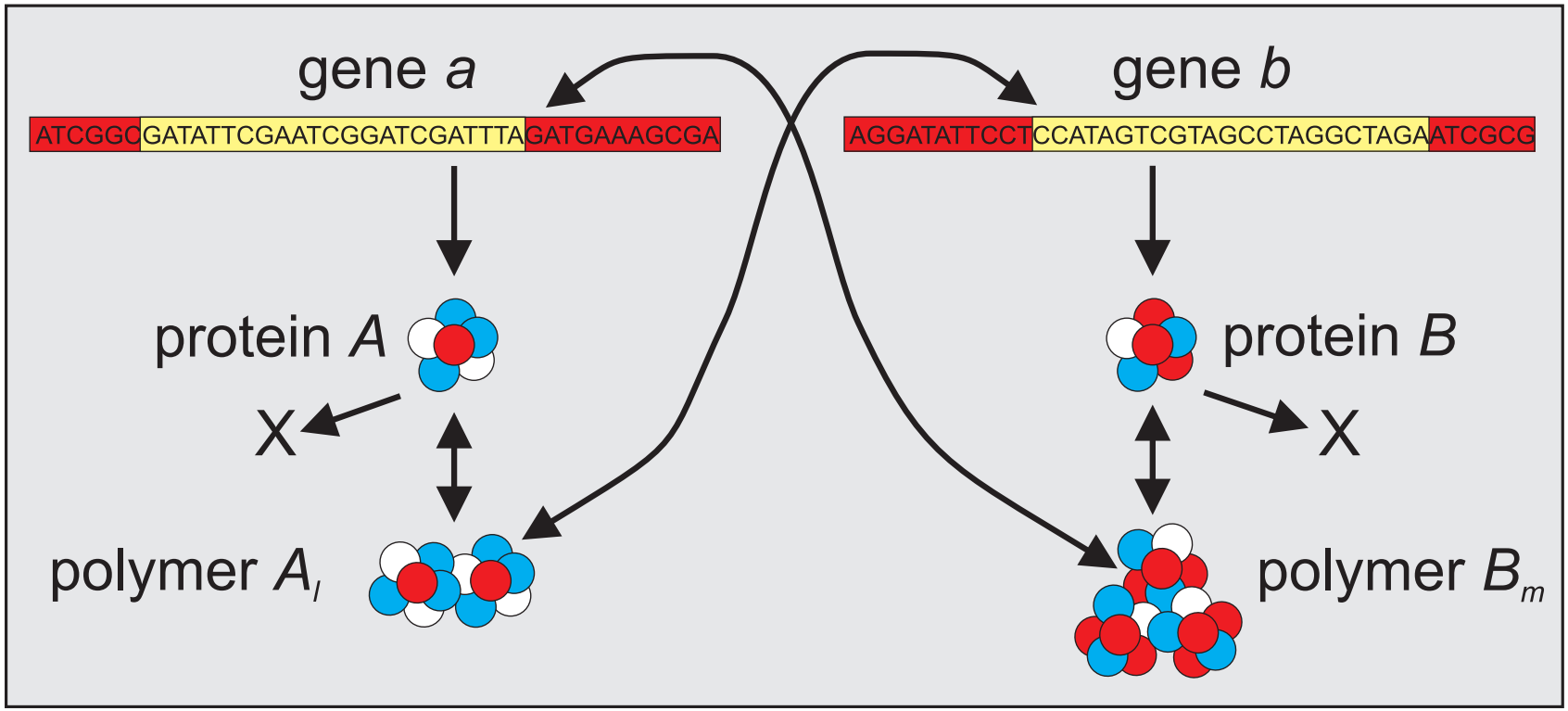
Example: The genetic switch



- The state space is $\mathbb{R}^6$:
  - $X_{1/2}$ = number of proteins A/B,
  - $X_{3/4}$ = number of polymers A_l/B_m,
  - $X_{5/6}$ = number of plasmids whose gene sides a/b are blocked.
- The protein densities are $(x_1, \ldots, x_6) = (\epsilon X_1, \ldots, \epsilon X_6)$, where ϵ^{-1} is the system size parameter (e.g. the total number of plasmids).
- The system is modelled as a continuous-time Markov chain with reactions $R_j = (\epsilon^{-1}\nu_j(x), \epsilon e_j)$, i.e.

$$\mathbb{P}\Big(X(t+dt) = x + \epsilon e_j \,\Big|\, X(t) = x\Big) \approx \epsilon^{-1}\nu_j(x)\,dt.$$

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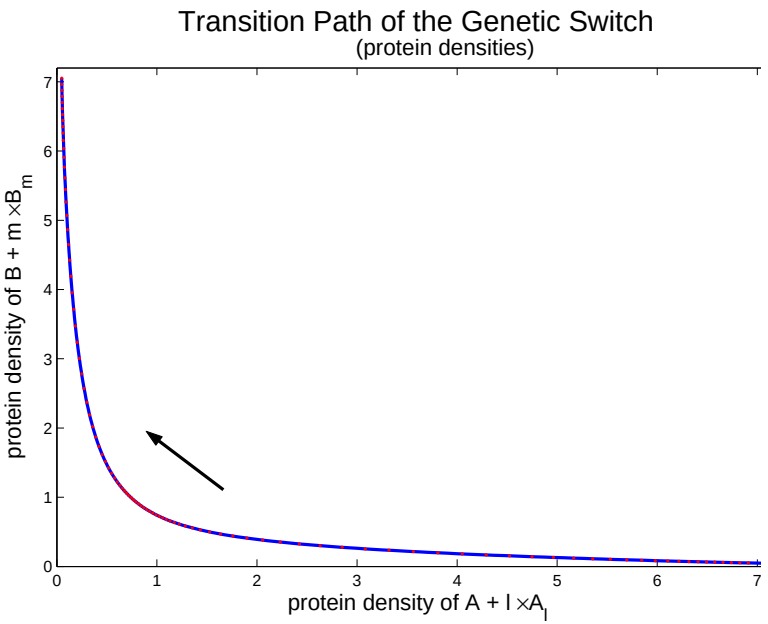
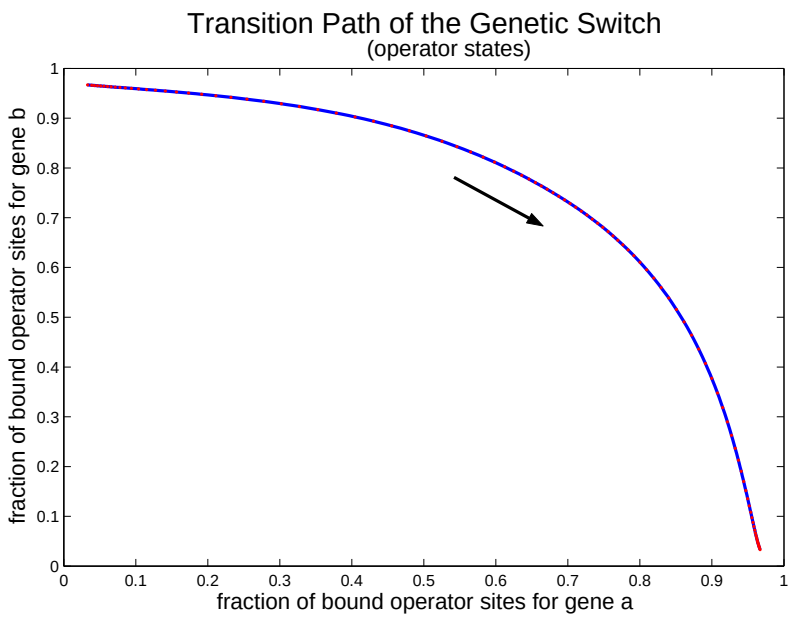
reaction type	rate	state change
protein production	$\nu_1(x) = k_1^A(1-x_6)$ $\nu_2(x) = k_1^B(1-x_5)$	$e_1 = (1,0,0,0,0,0)$ $e_2 = (0,1,0,0,0,0)$
protein degradation	$\nu_3(x) = k_2^A x_1$ $\nu_4(x) = k_2^B x_2$	$e_3 = (-1,0,0,0,0,0)$ $e_4 = (0,-1,0,0,0,0)$
polymer formation	$\nu_5(x) = k_3^A x_1^I$ $\nu_6(x) = k_3^B x_2^m$	$e_3 = (-I,0,1,0,0,0)$ $e_4 = (0,-m,0,1,0,0)$
polymer degradation	$\nu_7(x) = k_4^A x_3$ $\nu_8(x) = k_4^B x_4$	$e_3 = (I,0,-1,0,0,0)$ $e_4 = (0,m,0,-1,0,0)$
protein binding	$\nu_9(x) = k_5^A x_3(1-x_6)$ $\nu_{10}(x) = k_5^B x_4(1-x_5)$	$e_3 = (0,0,-1,0,0,1)$ $e_4 = (0,0,0,-1,1,0)$
protein unbinding	$\nu_{11}(x) = k_6^A x_6$ $\nu_{12}(x) = k_6^B x_5$	$e_3 = (0,0,1,0,0,-1)$ $e_4 = (0,0,0,1,-1,0)$

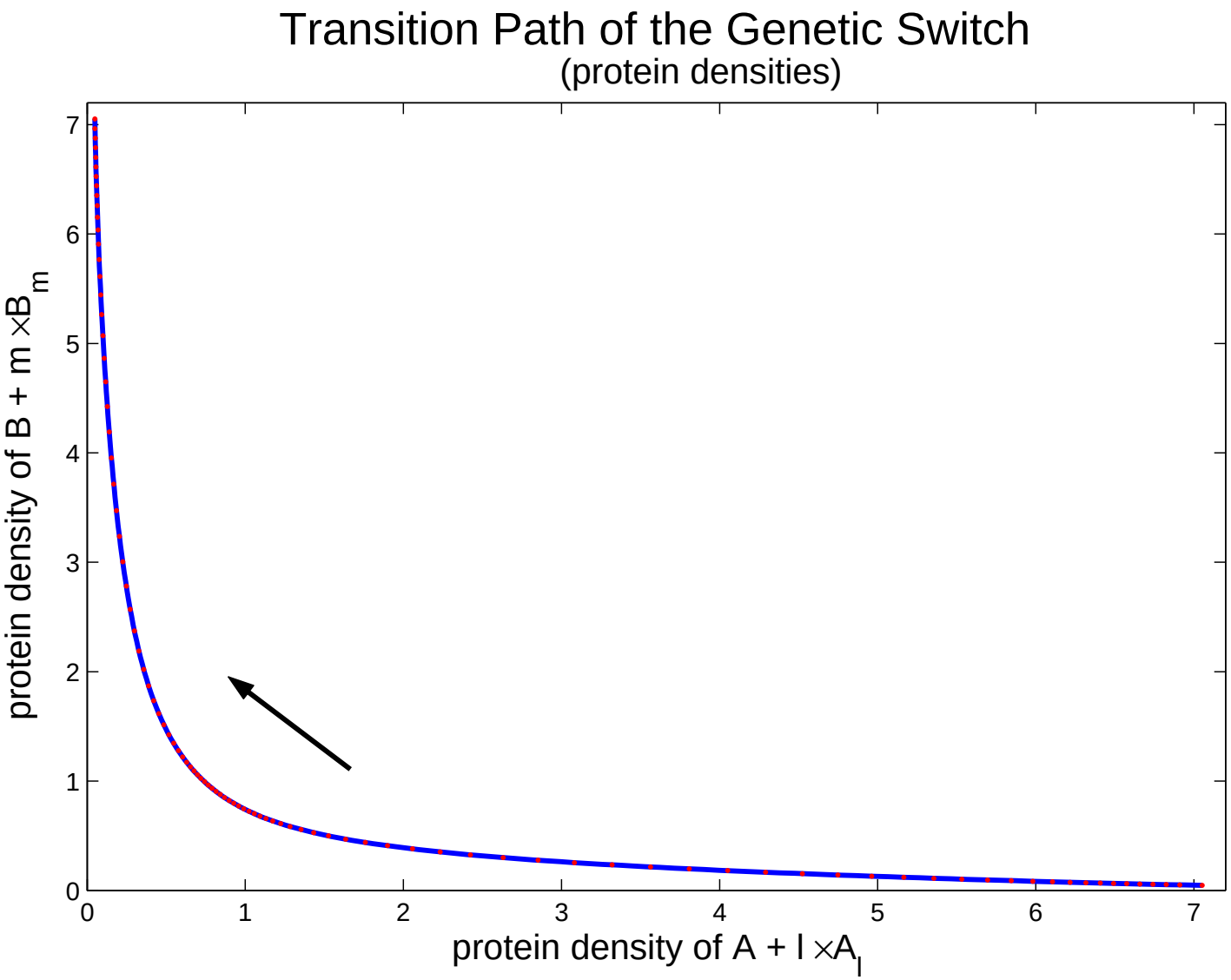
- Then the system satisfies a large deviations principle, with

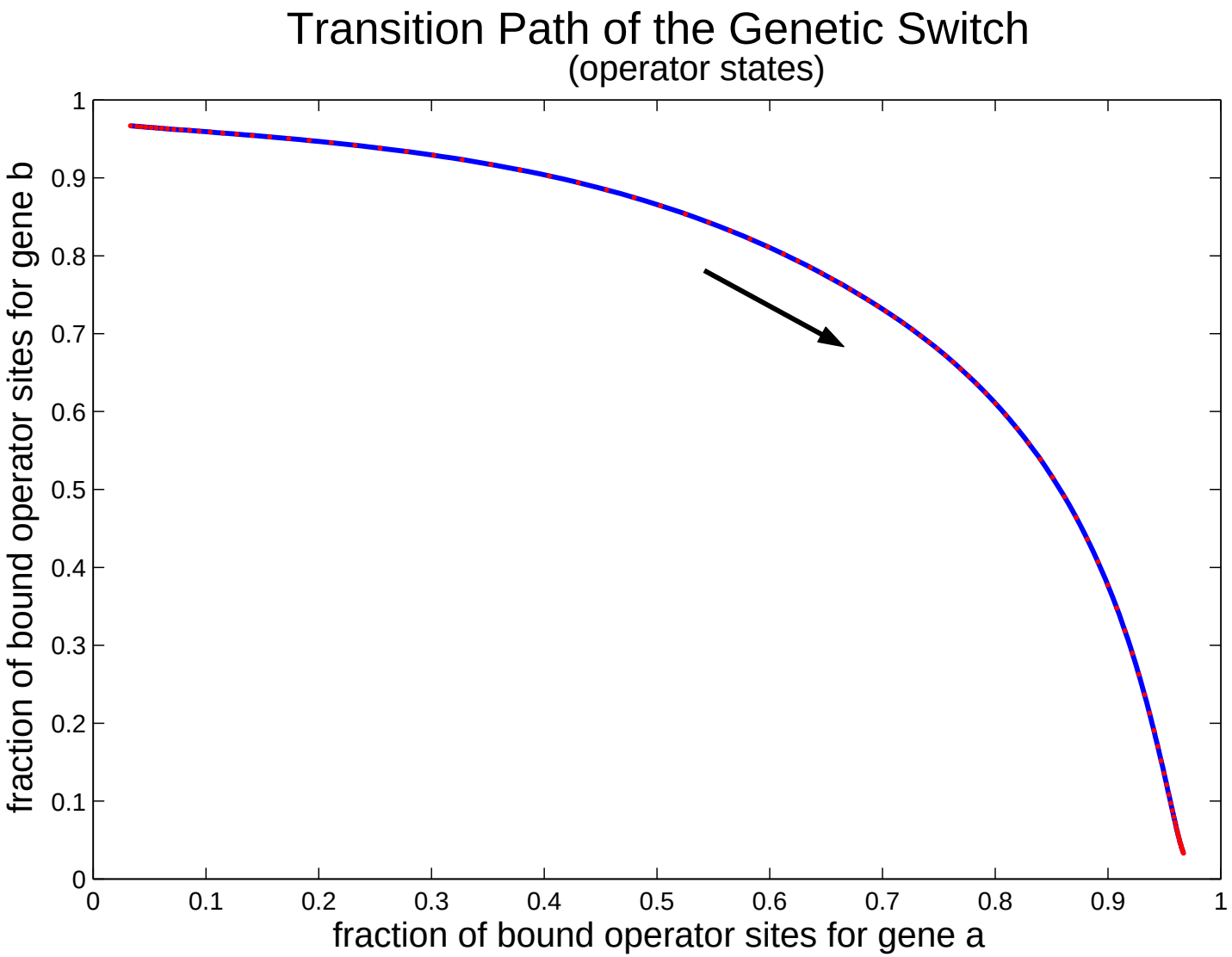
$$H(x,\theta) = \sum_{j=1}^{12} \nu_j(x)\left(e^{\langle \theta, e_j \rangle} - 1\right).$$

- The gMAM finds the following transition path:






Transition Path of the Genetic Switch
(protein densities)
protein density of B + m ×B_m
protein density of A + l ×A_l
0
1
2
3
4
5
6
7


Transition Path of the Genetic Switch
(operator states)
fraction of bound operator sites for gene b
fraction of bound operator sites for gene a
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Problems:

- The path is hard to visualize in higher dimensions.
- What are the *reasons* for the transition, i.e. which reactions R_j behave most atypically?

Solution: Maximum likelihood reaction rates $\mu_j(t)$

- Let $\mu_j(t)$ be the maximum likelihood reaction frequencies at which reaction R_j happens *during a transition*, i.e.
- if $N_j^\epsilon(t) := \{\#\text{ of reactions } R_j \text{ until time } t\}$ then $\forall \eta > 0$:

$$\lim_{\epsilon \longrightarrow 0} \mathbb{P}\Big(\sup_{t\in[0,T]} \Big|\epsilon N_j^\epsilon(t) - \int_0^t \mu_j(\tau)\, d\tau\Big| < \eta \,\Big|\, \text{transition}\Big) = 1.$$

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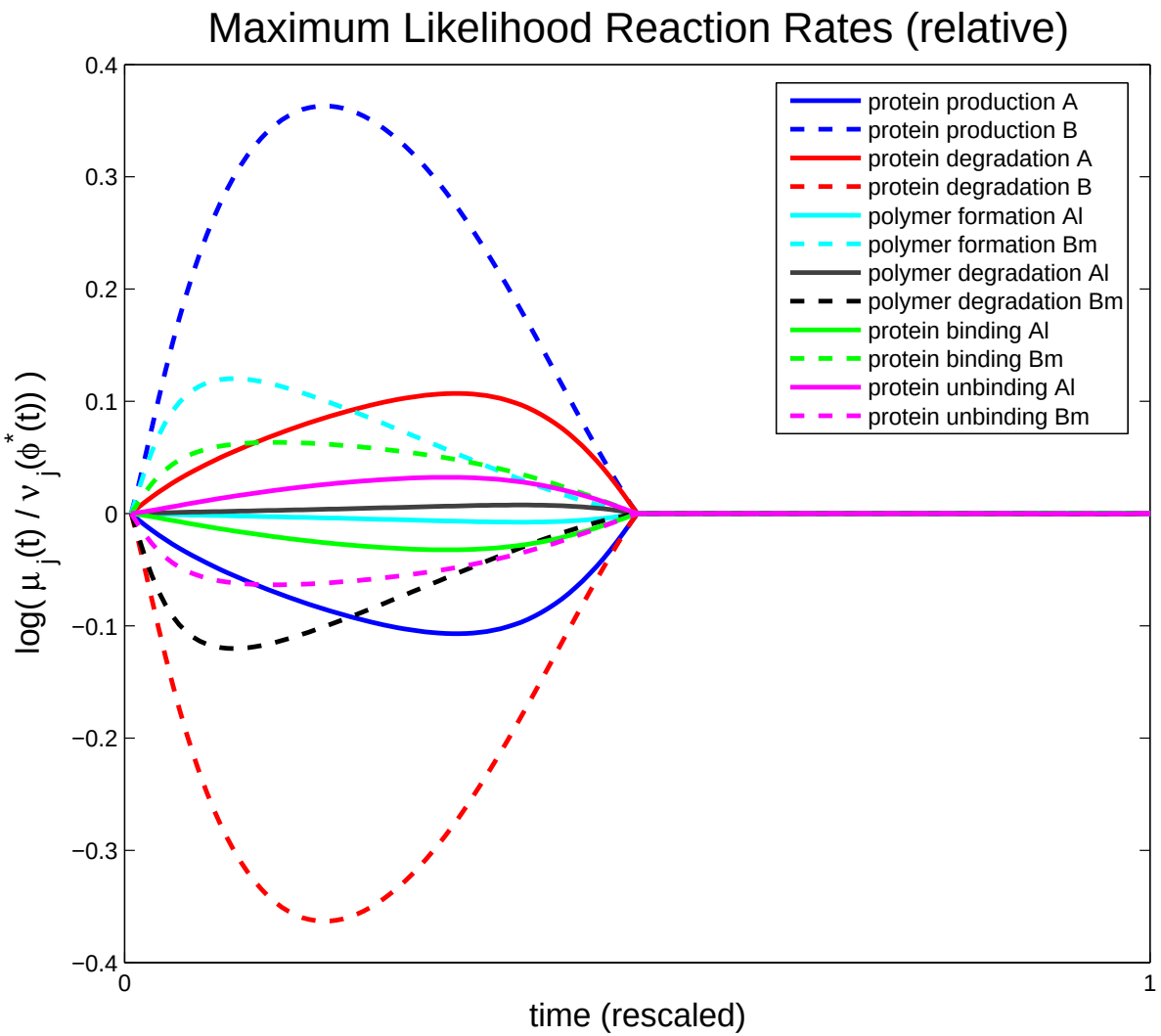
Maximum Likelihood Reaction Rates (relative)
protein production A
protein production B
protein degradation A
protein degradation B
polymer formation Al
polymer formation Bm
polymer degradation Al
polymer degradation Bm
protein binding Al
protein binding Bm
protein unbinding Al
protein unbinding Bm
0.4
0.3
0.2
0.1
0
−0.1
−0.2
−0.3
−0.4
0
1
time (rescaled)
log(μ j (t) / ν j (φ* (t)))

Outline

Summary:

- We showed the reformulation of the quasipotential:

$$V(x_1, x_2) = \inf_{\varphi \in \bar{C}^{x_2}_{x_1}(0,1)} \hat{S}(\varphi),$$

  where $\hat{S}(\varphi)$ only depends on the curve $\gamma(\varphi)$ of φ.

- Based on this, we designed the geometric minimum action method (gMAM), an algorithm to find the *most likely transition curve*.
- We demonstrated its performance on SDEs, SPDEs, Markov chains.
- On top of the gMAM we built a tool to detect sources of instability in (genetic) networks.

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Further Results:

- clean proofs of the results mentioned in this talk
- properties of $\lambda(x, y)$
- minimization with endpoint constraints / penalty terms:

$$\lim_{\epsilon \to 0} \epsilon \log \mu_\epsilon(B) = - \inf_{k=1,\dots,K} \inf_{T>0} \inf_{\psi \in \bar{C}^B_{x_k}(0,T)} S_T(\psi)$$

$$\lim_{\epsilon \to 0} \epsilon \log \mathbb{E}_{\mu_\epsilon} e^{-f(X_t)/\epsilon} = - \inf_{k=1,\dots,K} \inf_{T>0} \inf_{\psi \in \bar{C}_{x_k}(0,T)} \left(S_T(\psi) + f(\psi(T)) \right)$$

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Future Work:

- improve the gMAM to better handle stiff PDEs
- apply the gMAM to real-world biological data, collaborate with biological engineers
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