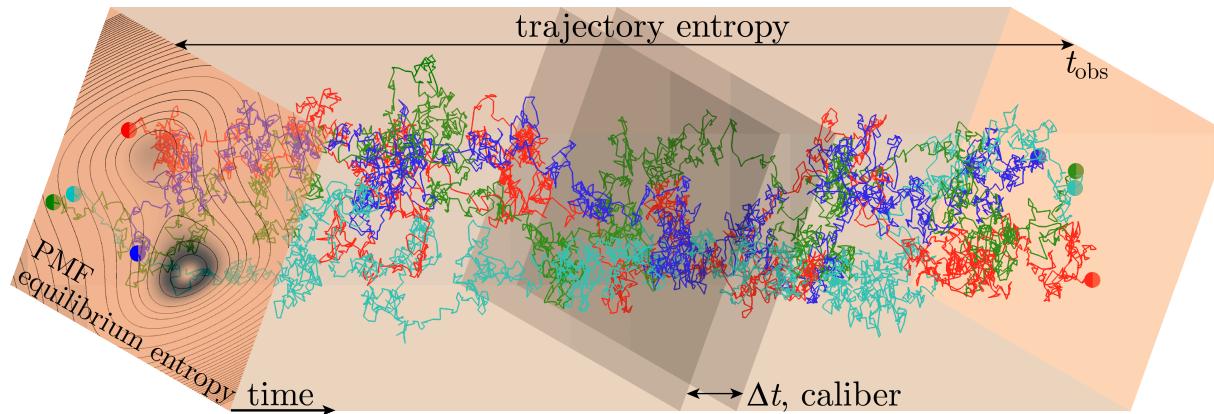


Information Thermodynamics and Bayesian Optimization: Applications to Single Molecule Experiments



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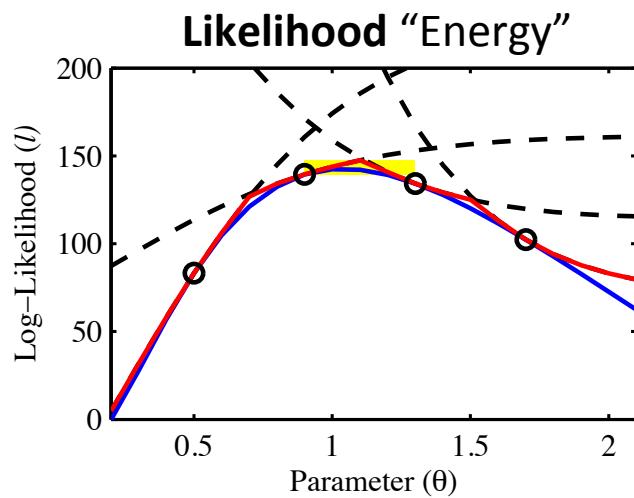
³Princeton (Chemistry)

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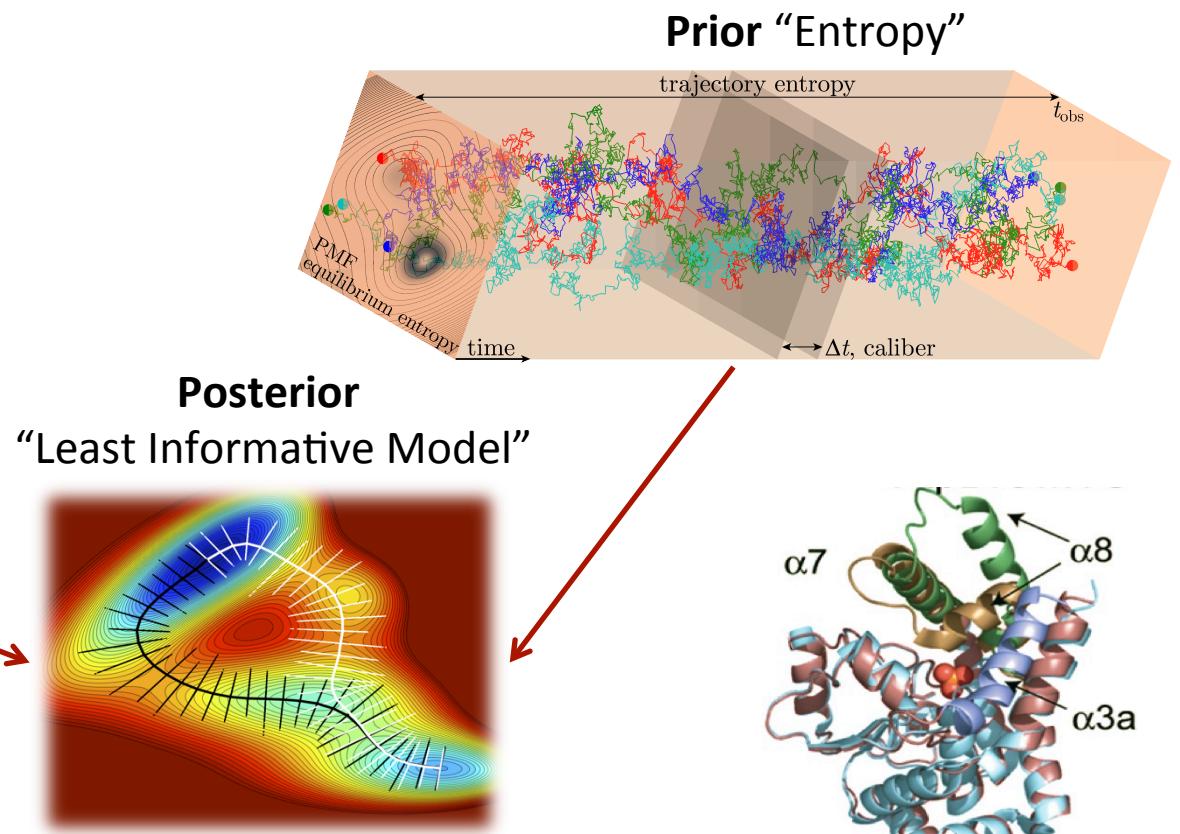


Trajectory Entropy and Information Thermodynamics for Analyzing Complex Systems

2



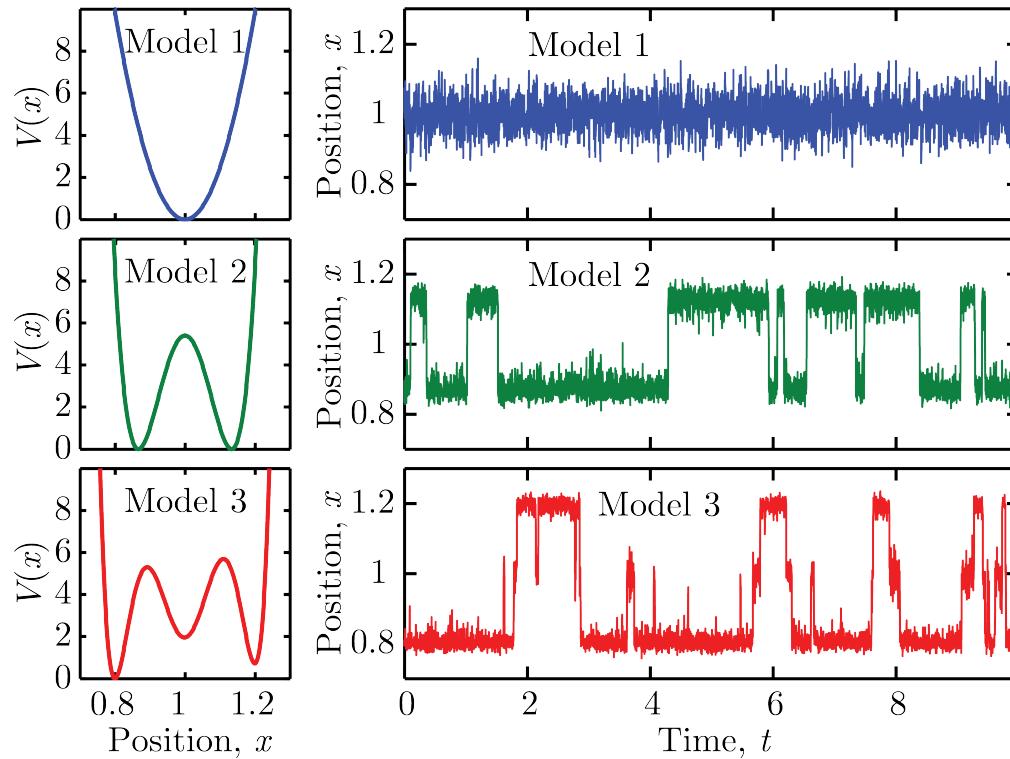
- ↗ Experiment
- ↗ Simulation



$$\mathcal{P}(\text{Model}|\text{Data}) = \frac{\overbrace{P(\text{Data}|\text{Model})}^{\text{Likelihood}} \overbrace{P(\text{Model})}^{\text{Prior}}}{P(\text{Data})}$$

Information Content of Langevin Dynamics as coarse-grained model of system dynamics

3



$$\dot{x} = \beta DF(x) + \sqrt{2D}dW_t$$

- ↗ Balance between
 - ↗ Random fluctuations
 - ↗ Deterministic forcing

- ↗ Information content
 \propto
 ↗ -(Entropy)

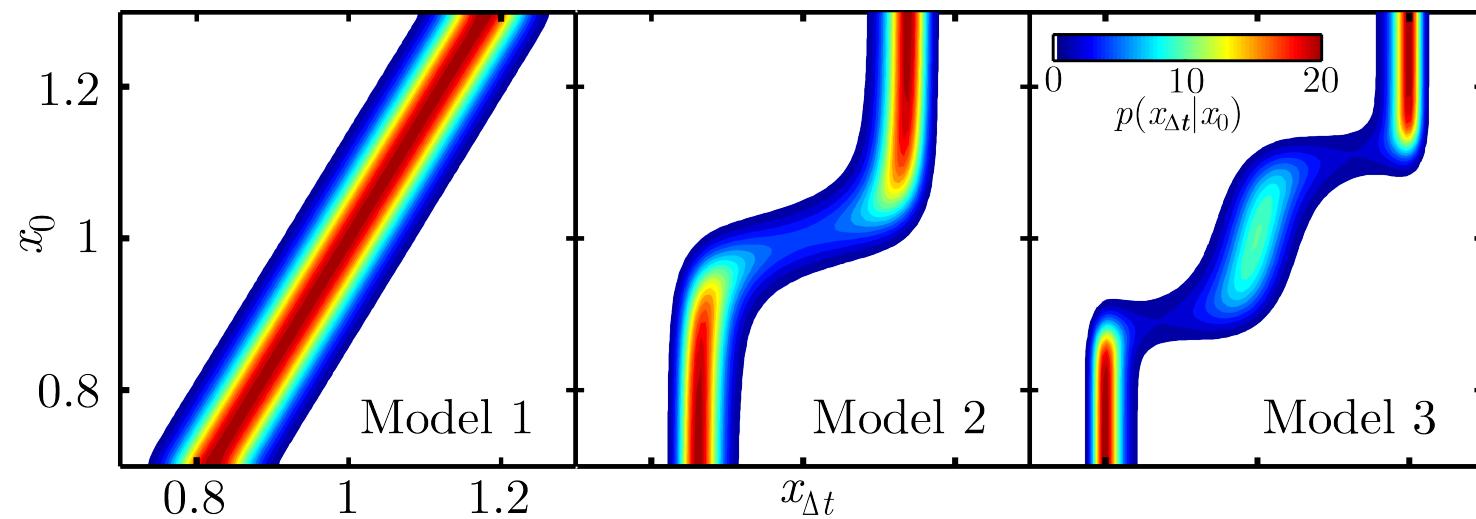
Entropy	1-well	2-well	3-well
$\int dx p_{eq}(x) \ln p_{eq}(x)$	1.683	1.683	1.683

Dynamic Correlations Measured by Jaynes Caliber at finite time step

4

↗ Jaynes Caliber

$$S(\Delta t) = - \int dx_0 dx_{\Delta t} p(x_{\Delta t}, x_0) \ln p(x_{\Delta t} | x_0)$$



↗ Information of:

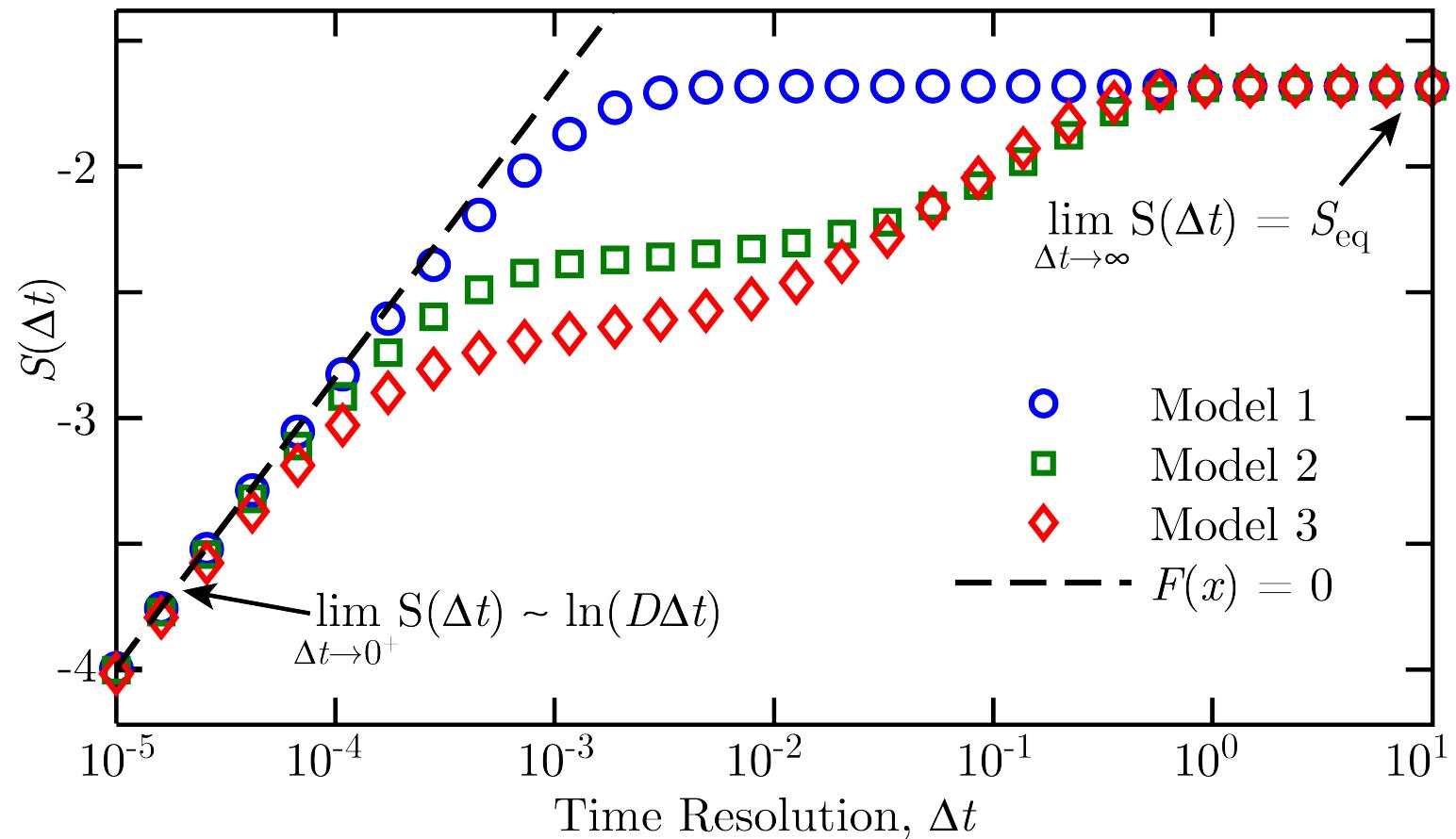
- ↗ Conditional propagator (from Fokker-Planck)
- ↗ Dynamic correlations

$$\frac{\partial p(x_t | x_0)}{\partial t} = D \frac{\partial^2 p}{\partial x_t^2} - \frac{\partial}{\partial x_t} \left(\frac{DF(x_t)}{k_B T} p \right)$$

Captures Dynamic Complexity, but, Divergence in Continuum limit due to Weiner Process

5

$$S(\Delta t) = - \int dx_0 dx_{\Delta t} p(x_{\Delta t}, x_0) \ln p(x_{\Delta t} | x_0)$$



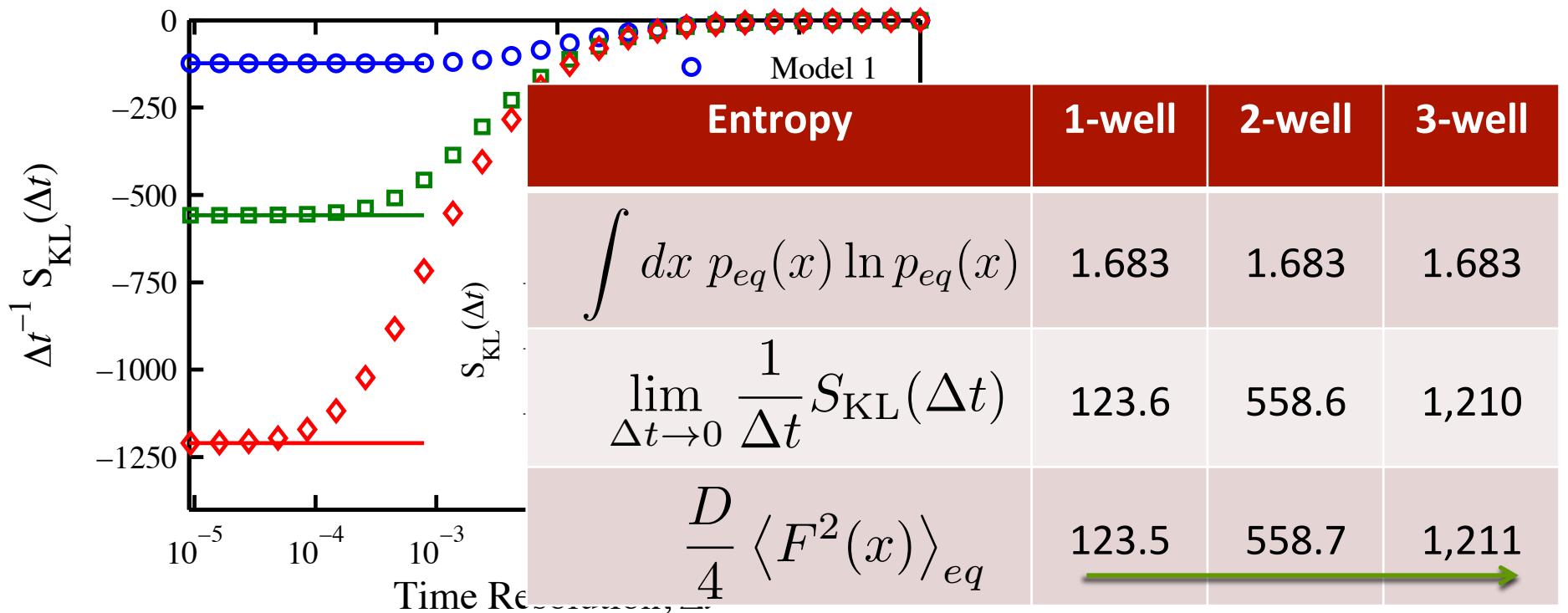
Dynamic Information as KL-Divergence w.r.t reference diffusion process

6

$$S_{\text{KL}}(\Delta t) = - \int dx_0 dx_{\Delta t} p(x_{\Delta t}, x_0) \ln \frac{p(x_{\Delta t}|x_0)}{q(x_{\Delta t}|x_0)}$$

↗ Balance into continuum limit

$$p(x_{\Delta t}|x_0) \propto q(x_{\Delta t}|x_0) \rightarrow \delta(x_{\Delta t} - x_0)$$



Entropy Measure as Path Integral over Trajectory Ensemble w.r.t reference pure diffusion process

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$$\mathcal{S} \equiv - \int_0^{t_{\text{obs}}} \mathcal{D}X(t) \mathcal{P}[X(t)] \ln \frac{\mathcal{P}[X(t)]}{\mathcal{Q}[X(t)]}$$

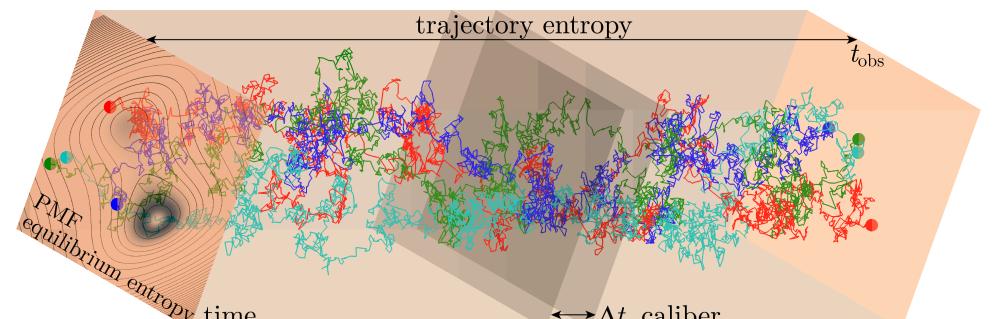
↗ Path probability from Onsager Machlup action

$$\mathcal{P}[X(t)] = e^{-E^{\text{OM}}[X(t)]}/\mathcal{Z}$$

$$E^{\text{OM}}[X(t)] = \frac{1}{4} \int_0^{t_{\text{obs}}} dt \frac{\dot{x}_t^2}{D} + DF^2(x_t) + 2DF'(x_t)$$

↗ Expectation of OM Action

$$\mathcal{S} = \langle E^{\text{OM}}[X(t)] \rangle_{X(t)} + \ln \frac{\mathcal{Z}}{\mathcal{Z}_{\text{ref}}}.$$



Analytic Entropy Functional for Continuous Stochastic Dynamics

8

$$\mathcal{S} = -t_{\text{obs}} \frac{D}{4} \langle F^2(x) \rangle_{\text{eq}} + \frac{1}{4} \left\langle \int_0^{t_{\text{obs}}} dt \frac{\dot{x}_t^2}{D} - \frac{\dot{x}_t^2}{D_{\text{ref}}} \right\rangle_{X(t)} + \ln \frac{\mathcal{Z}}{\mathcal{Z}_{\text{ref}}}$$

1. Exchange space/time integrals. 2. Derivatives of partition function

- ↗ Deterministic Force reduces entropy
- ↗ Stochastic Diffusion increases entropy

$$\mathcal{S}[F(x), D] = S_{\text{eq}} - \frac{t_{\text{obs}} D}{4} \langle F^2(x) \rangle_{\text{eq}} + \lim_{\Delta t \rightarrow 0^+} \frac{t_{\text{obs}}}{2\Delta t} \ln D$$

$$\rho_{\text{eq}}(x) = \sqrt{p_{\text{eq}}}(x); \quad \langle F^2(x) \rangle_{\text{eq}} \Leftrightarrow \int dx (\nabla \rho_{\text{eq}}(x))^2$$

Understanding Dynamics through Maximum Entropy Optimization - Mean First Passage Time Constraint

9

↗ Maximum Entropy Optimization

$$\max_{\rho(x)} \left(\underbrace{-t_{\text{obs}} D \langle \rho_{\text{eq}} | \nabla \cdot \nabla | \rho_{\text{eq}} \rangle}_{\text{Entropy}} + \sum_i \underbrace{\omega_i (\langle \rho_{\text{eq}} | C_i | \rho_{\text{eq}} \rangle - C_i)}_{\text{Constraint}} \right)$$

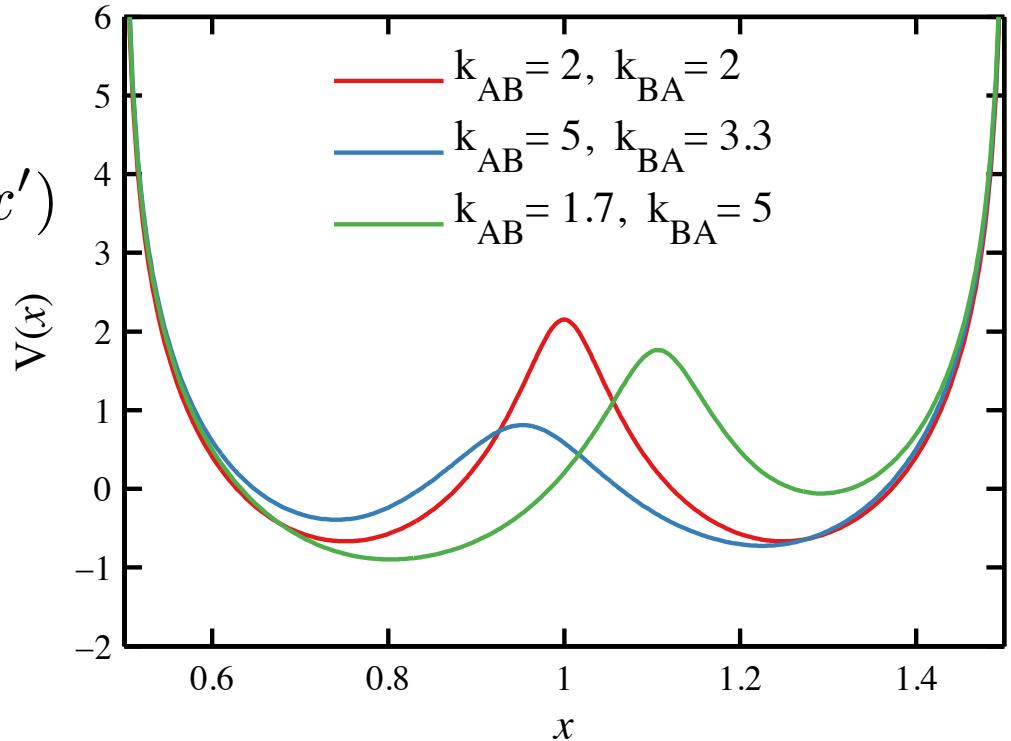
↗ Mean First-Passage Time

$$\frac{1}{D} \int_{x_A}^{x_B} dx \rho^{-2}(x) \int_{x_L}^x dx' \rho^2(x')$$

↗ Set functional derivative = 0

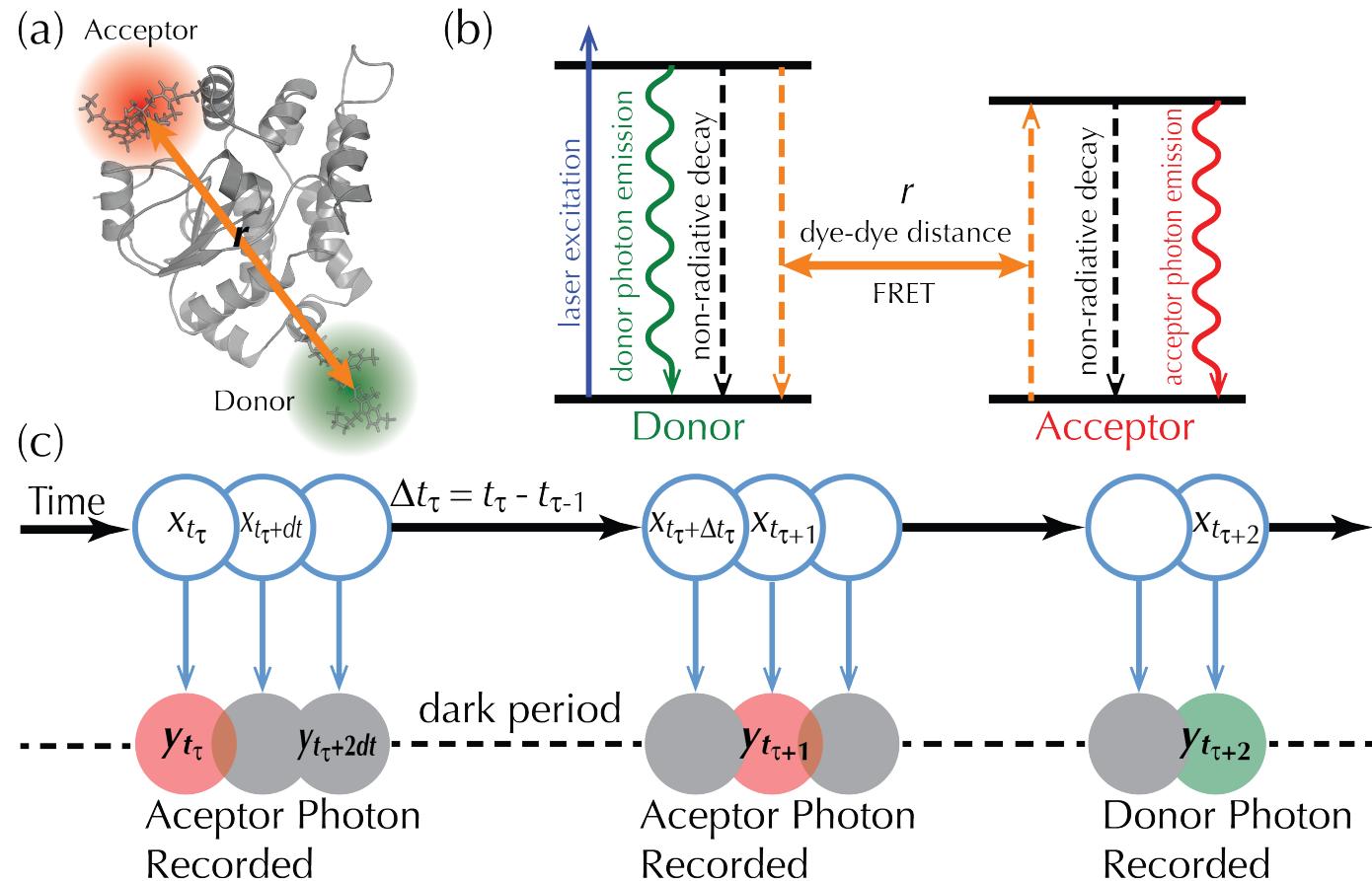
↗ Hammond-Leffler postulate

- ↗ Transition state for endothermic near products



Likelihood of Force Profile, Diffusion from single-molecule FRET

10

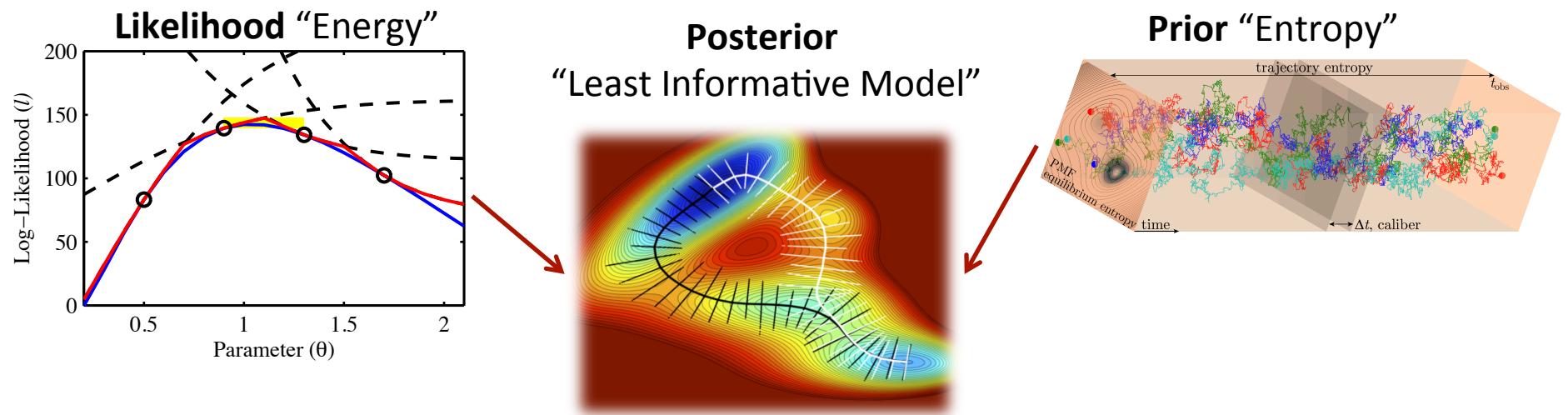


$$\mathcal{P}[Y(t)|\rho(x), D] = \langle \alpha_{t_0} | e^{-\mathbf{H}\Delta t_1} \mathbf{y}_1 e^{-\mathbf{H}\Delta t_2} \mathbf{y}_2 \dots e^{-\mathbf{H}\Delta t_{N_P}} \mathbf{y}_{N_P} | \beta_{t_{\text{exp}}} \rangle$$

Haas, Yang, Chu **JPCB** (2013)

Bayesian Posterior with Entropy Prior Gives Optimal model and is Equivalent to Free Energy

11



$$\mathcal{P}[\rho(x), \eta_F, \eta_D | Y(t)] \propto \underbrace{\mathcal{P}[\rho(x) | Y(t)]}_{\text{Likelihood}} \underbrace{e^{\eta_F D \langle \rho | \nabla^2 | \rho \rangle}}_{\text{Force}} \underbrace{e^{\eta_D \ln(D)}}_{\text{Diffusion}}$$

OPTIMAL MODEL

$$\rho(x)^* = \arg \max_{\rho(x)} \mathcal{P}[\rho(x), \eta_F, \eta_D | Y(t)]$$

HYPER-PARAMETERS

$$P(\eta_F, \eta_D | Y(t)) = \int D\rho(x) \mathcal{P}[\rho(x), \eta_F, \eta_D | Y(t)]$$

Thermodynamics of simulation, experiment combined with entropy to make inference about dynamics ¹²

$$-\ln P(\eta_F, \eta_D | Data) = \langle U \rangle - \eta_F \langle S \rangle - \eta_D \langle \ln(D) \rangle$$

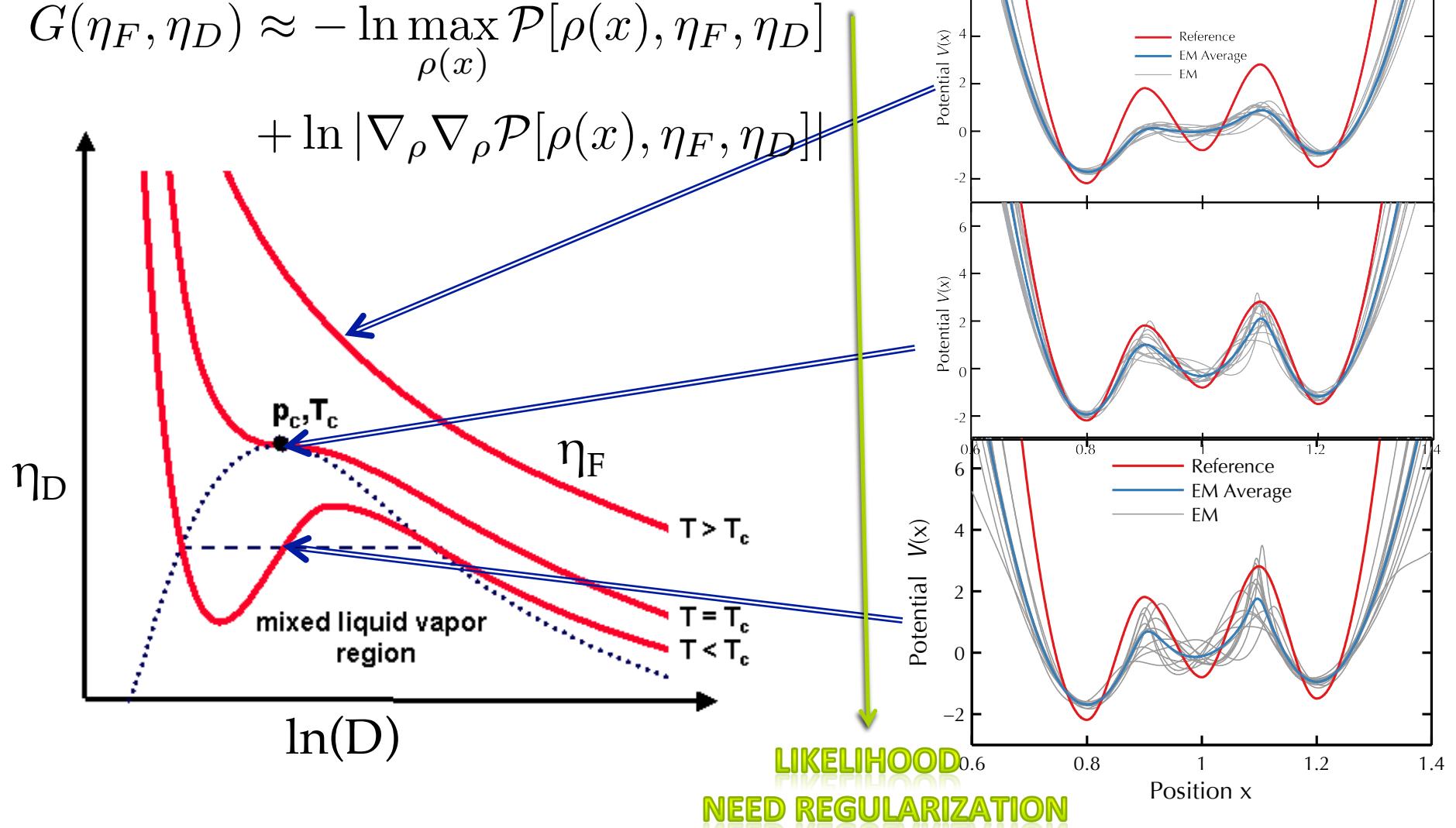
$$G(\eta_F, \eta_D) = -\ln P(\eta_F, \eta_D | Data)$$

	Static	Dynamic
Microstate	x	$X(t)$
Sufficient Statistic	$g(r)$	$Q_{eq}(x)$
Internal Energy	$U[g(r)]$	$-\ln P(Q_{eq}(x) data)$
Entropy	$p_{eq} \ln p_{eq}$	$(dQ_{eq}(x)/dx)^2$
Work	$-PdV$	$\eta_D d \ln(D)$
Temperature	T	η_F
Canonical Ensemble	NVT	$t_{obs} \ln(D) \eta_F$
Isothermal-isobaric	NPT	$t_{obs} \eta_D \eta_F$

Phase Transitions and Critical Point in Bayesian Optimization. Optimal complexity from smFRET!

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$$G(\eta_F, \eta_D) \approx -\ln \max_{\rho(x)} \mathcal{P}[\rho(x), \eta_F, \eta_D]$$



Conclusion

- ↗ Trajectory Entropy:

$$D\langle F^2(x) \rangle_{\text{eq}}$$



- ↗ github.com/krhaas/AIChE2013
- ↗ Thank you

