Predicting transition times in systems with both stochastically-switching forces and thermal noise

Katie Newhall

Feb 28, 2023

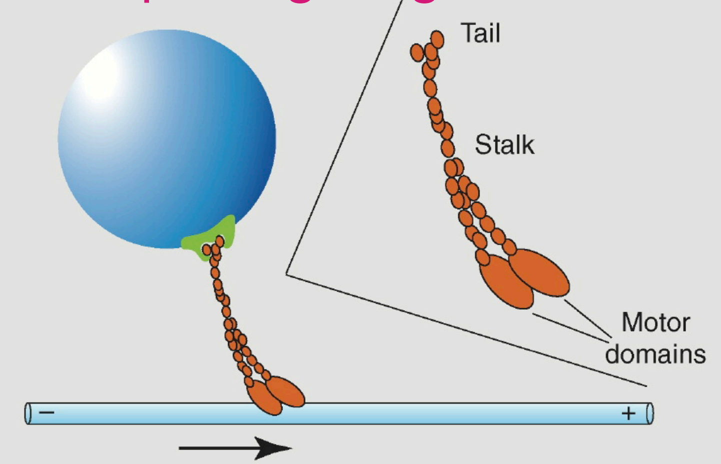
University of North Carolina at Chapel Hill

Department of Mathematics

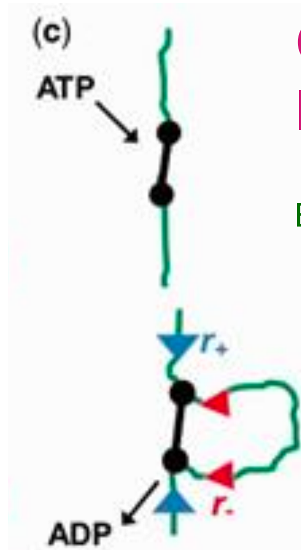
Switching Forces and Thermal Noise

Biological systems under the influence of microscale active agents such as proteins can lead to models with switching forces as agents shift between different states

Molecular Motors transporting cargo



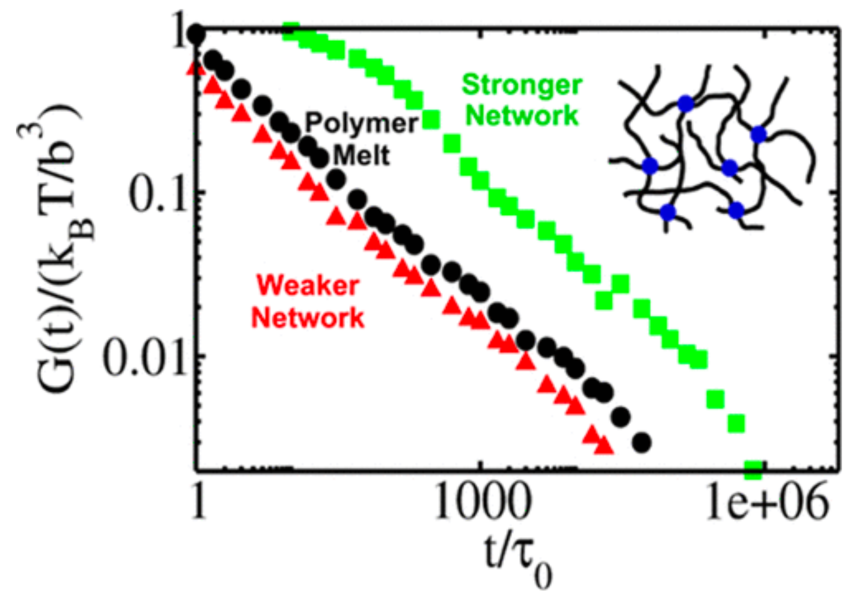
M. A. Welte (2004) Curr. Biol. 14, R525



Condensin protein loop extrusion

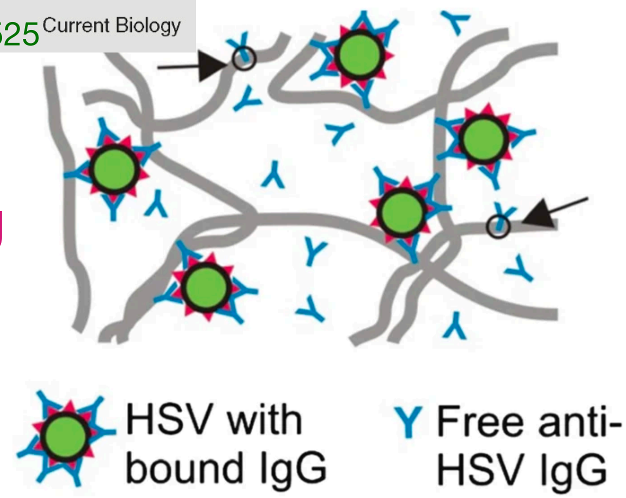
E. Alipour and J. F. Marko (2012) Nucleic Acids Res. 40, 11202

Polymer network cross-links



X.-Z. Cao and M. G. Forest (2019) J. Phys. Chem. B 123, 974

Antibodies immobilizing virus

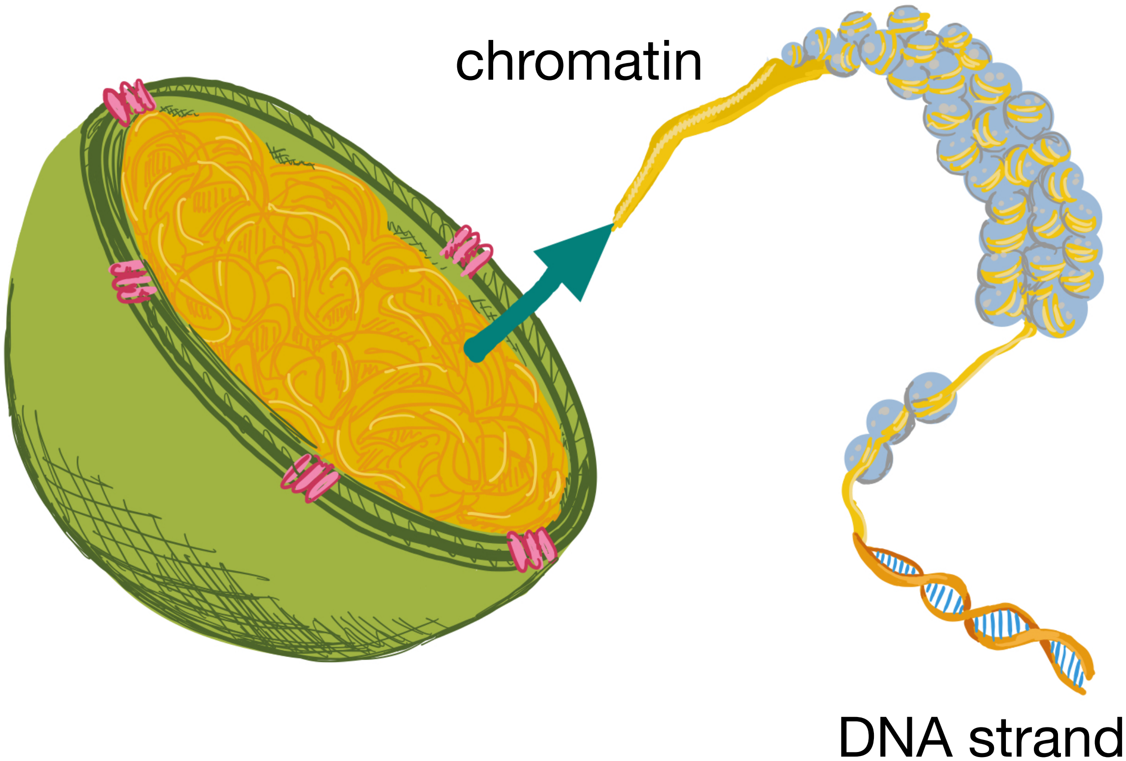


M. A. Jensen et al (2019) Bull. Math. Biol. 81, 4069

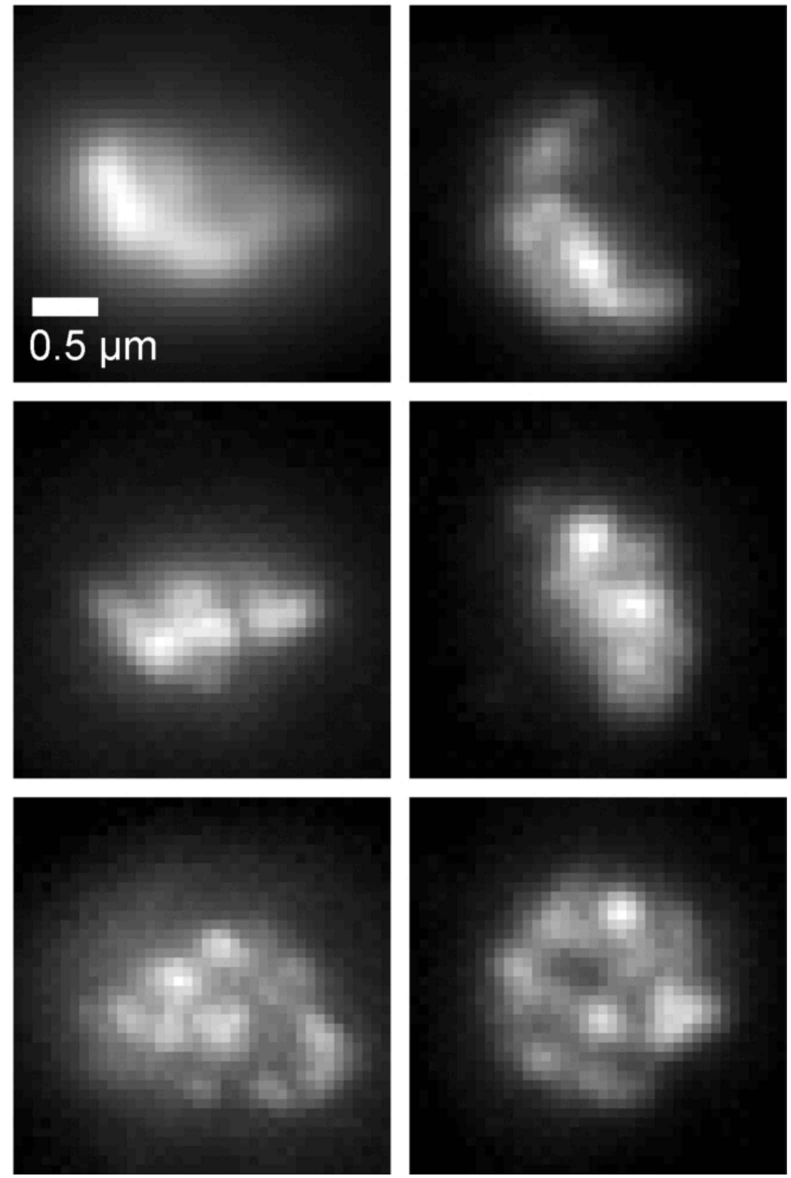
Spatiotemporal organization of genes

Condensin protein also plays role in chromatin arrangement in cell nucleus

Mechanism causing structure within the “bowl of wet noodles”



nucleolus of budding yeast spatial segregation (clusters)



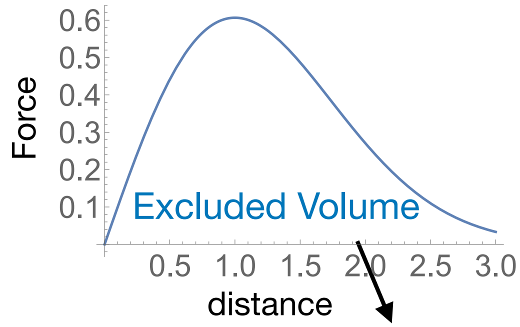
Hult et al. (2017) Nucleic Acids Research 45(19): 11159-11173

Polymer Chromosome Model

Chromatin motion obeys the dynamics of a polymer bead-spring chain

bead = 5 kilo base pairs of DNA

32 tethered chains



$$\sqrt{2\gamma k_B T}\xi(t) \qquad \langle \xi(t)\xi(s)\rangle = \delta(t-s)$$

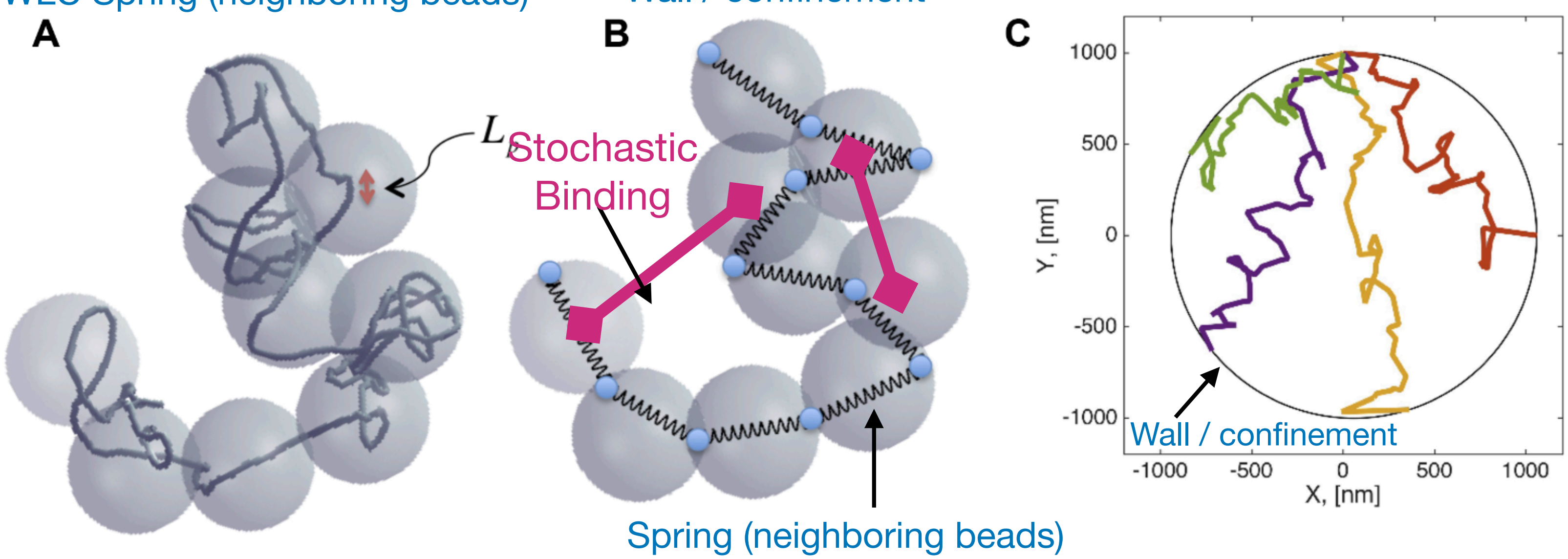
Brownian / Thermal noise

$$\gamma \frac{dX}{dt} = F^S + F^{EV} + F^W + F^B$$

WLC Spring (neighboring beads)

Wall / confinement

Additional Stochastic binding (strong spring) between nearby bead-pairs



Vasquez et al. (2016) Nucleic Acids Research 44(12): 5540-5549

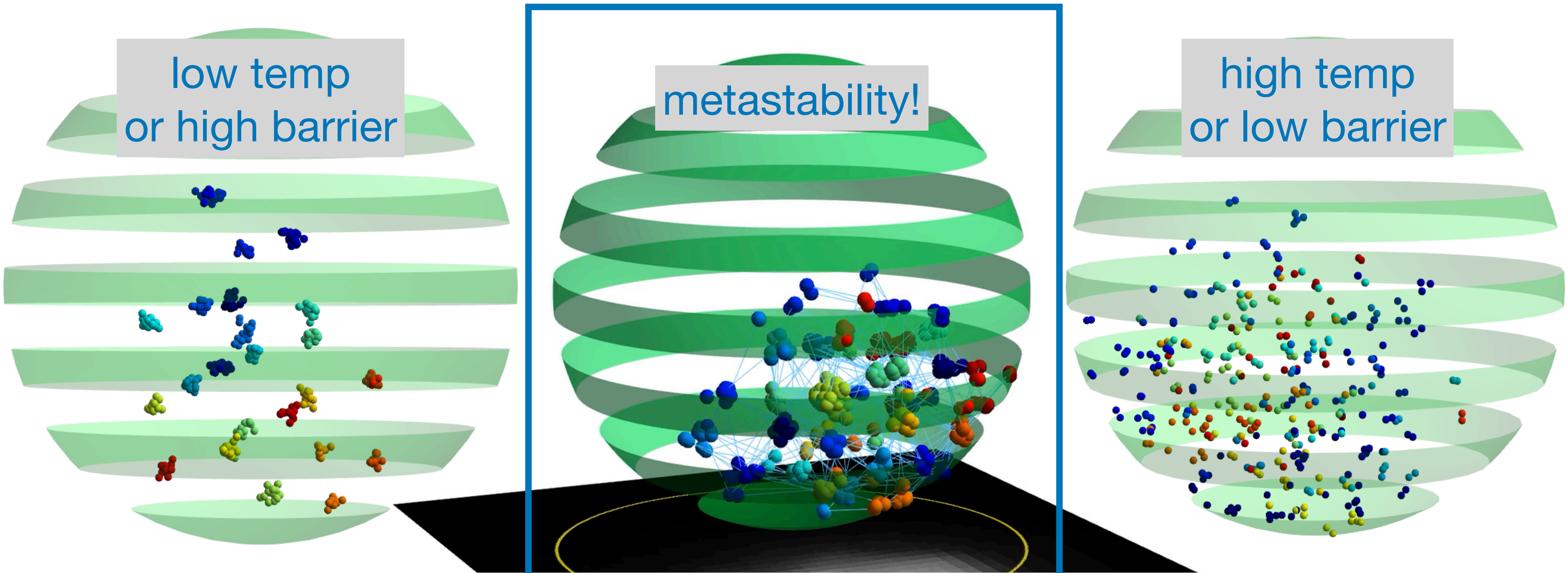
Hult et al. (2017) Nucleic Acids Research 45(19): 11159-11173

Effective Temperature and Landscape

just viewing the one chain that has the added stochastic binding

fast binding/unbinding

slow binding/unbinding



clusters
no mixing

clusters
mixing

no clusters
mixing

Behaves as if there is an energy landscape with thermal noise

stochastic binding -> effective landscape

Walker B, et al. (2019) PLoS Comput Biol 15(8): e1007124

Metastability

Thermal Equilibrium

$$\mu(X) = Z^{-1} e^{-U(X)/\epsilon}$$

overdamped Langevin Equation

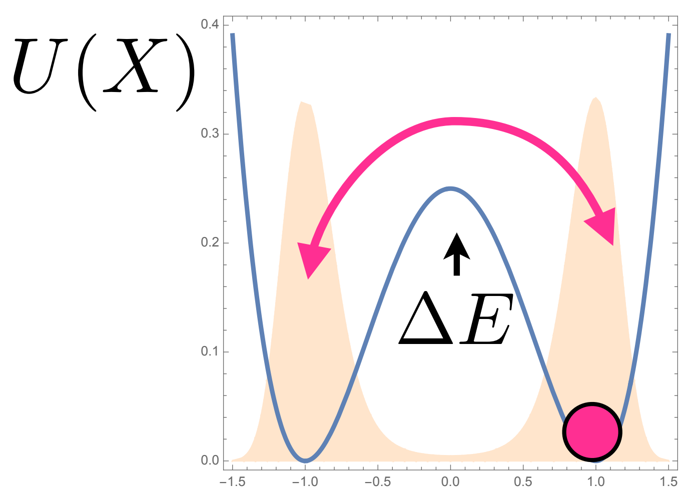
$$dX = -\nabla U(X)dt + \sqrt{2\epsilon}dW$$

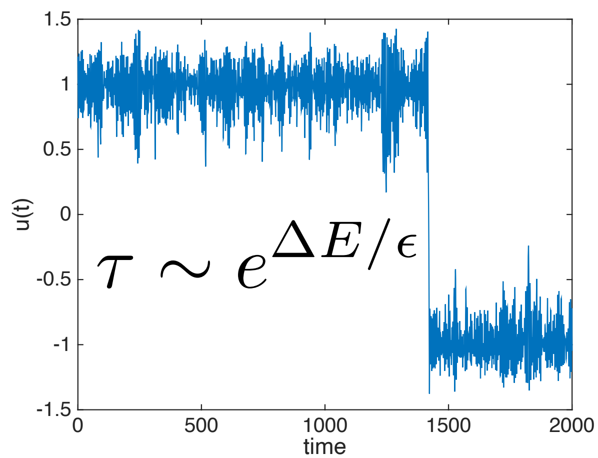
$$\epsilon = k_B T$$

potential function $U(X)$ with energy barrier ΔE

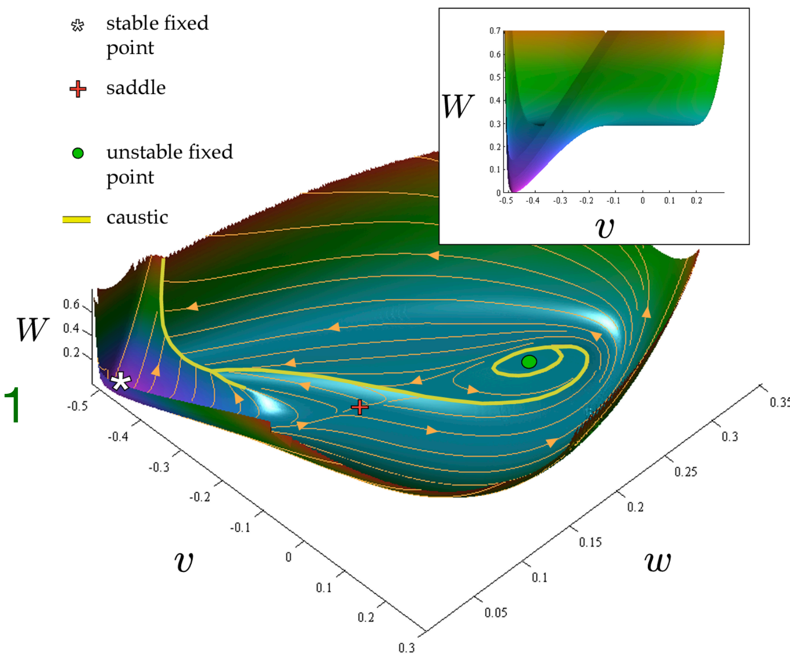
$\epsilon \ll \Delta E$

Metastability: long-lived trajectories in localized regions (near energy minimizing states) with rare transitions between these states



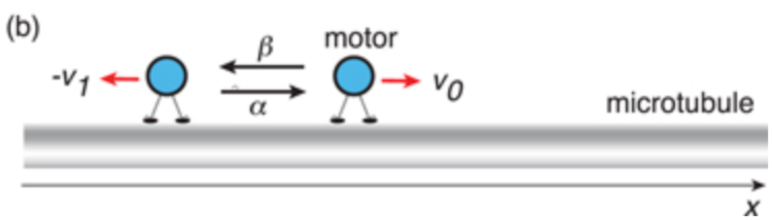


The non stochastic forces are gradient, but the presence of stochastically-switching binding forces suggests looking for a quasipotential



Account for ion channel noise in spiking neuron model

Newby (2014) SIAM J Appl Dyn Syst, 13, 4, 1756-1791



Other piecewise deterministic Markov processes like molecular motors

Bressloff (2021) J Stat Mech: Thry Exp, 043207

Review of methods for non-gradient forces

Zhou, Aliya, Aurell, Huang (2012) J R Soc Interface, 9, 77, 3539-53

Minimal 3-bead model, no chain

SDE for bead position

excluded volume as before

$$dX_i = \left(f_c^i + f_{\text{EV}}^i + f_{\text{bond}}^i\right) dt + \sqrt{2\epsilon} dW = v_i^s(X)dt + \sqrt{2\epsilon} dW$$

quadratic potential confinement

stochastically-switching Hookean spring **(CTMC)**

Markov Chain for binding state

rate matrix

$$\frac{\alpha}{\epsilon^\beta} S = \frac{\alpha}{\epsilon^\beta} \begin{pmatrix} b & c & c & c \\ a(x_1 - x_2) & -c & 0 & 0 \\ a(x_1 - x_3) & 0 & -c & 0 \\ a(x_2 - x_3) & 0 & 0 & -c \end{pmatrix}$$

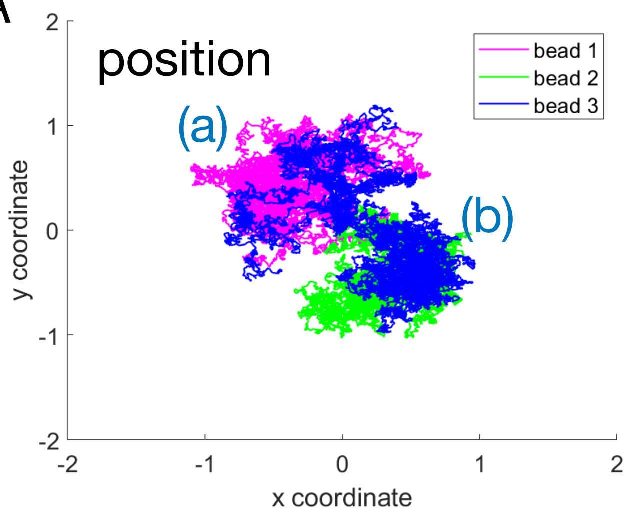
s=1: all three unbound
s=2: bead 1 bound to 2
s=3: bead 1 bound to 3
s=4: bead 2 bound to 3

affinity function

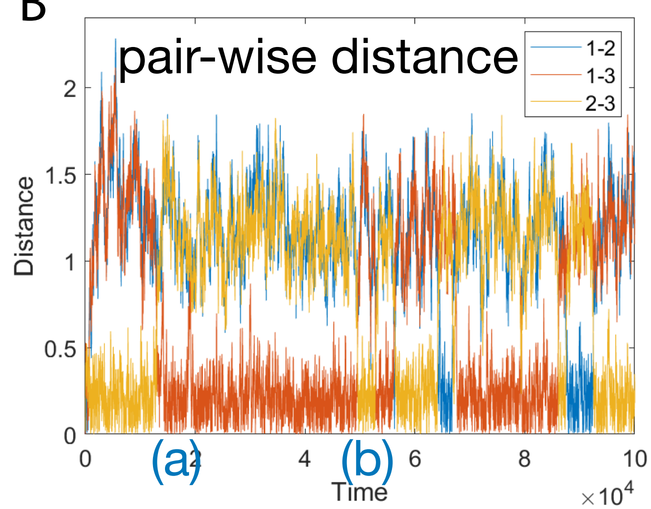
$$a(x) = \frac{2}{1 + e^{20(|x| - 0.75)}}$$

closer beads more likely to bind

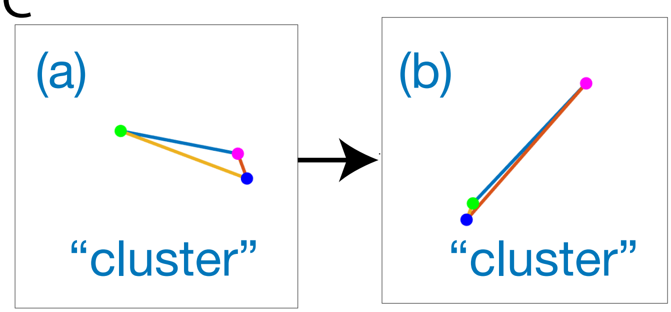
A



B



C



Metastable!!

Mathematical Framework

joint probability function for continuous variable x and discrete variable s

$$p_s(x,t) = \rho(x,t|s_t = s)\mathrm{P}(s_t = s) \quad \text{for } s = 1,2,\ldots n$$

coupled Fokker-Planck equations for steady state

$$0 = \boxed{-\sum_{i=1}^{m} \frac{\partial}{\partial x_i}\left[v_i^s p_s\right] + \boxed{\epsilon}\sum_{i=1}^{m} \frac{\partial^2}{\partial x_i^2}\left[p_s\right]} + \boxed{\boxed{\frac{\alpha}{\epsilon^\beta}}\sum_{k=1}^{n} S_{sk} p_k}$$

Fokker-Planck for each state **coupling between the states**

WKB-like ansatz for the effective thermal equilibrium

$$p_s(x) = r_s(x)\exp\left(-\frac{1}{\epsilon}W(x)\right)$$

$$s = 1\ldots n$$

$W(x)$ "**quasi-potential**" takes the role of V(x) in thermal equilibrium independent of the state s

$r_s(x)$ **superimposes the different states** (normally no pre-exponential term at lowest order in WKB)

Mathematical Framework

$$0 = \boxed{\frac{1}{\epsilon} r_s \sum_i v_i^s \frac{\partial W}{\partial x_i} + \frac{1}{\epsilon} r_s \sum_i \left(\frac{\partial W}{\partial x_i} \right)^2} + \boxed{\frac{\alpha}{\epsilon^\beta} [Sr]_s} + O(1)$$

$\beta > 1$ $\quad O\left(\frac{1}{\epsilon^\beta}\right) : S\vec{r} = 0$ Eliminate Markov Chain noise

$$O\left(\frac{1}{\epsilon}\right) : (\nabla W)_i = \sum_s v_i^s r_s$$

standard time-averaged force

$\beta = 1$ $\quad O\left(\frac{1}{\epsilon}\right) : M(x, \nabla W)\vec{r}(x) = 0$ Both noise sources combine

M matrix combines drift, diffusion, and switching matrix S

$\beta < 1$ The system equilibrates within each state s

Effective equilibrium across the states on much longer time-scale

Quasipotential

$$\beta = 1 \qquad M(x, \nabla W) = D(\nabla W) + A(x, \nabla W) + \alpha S(x) = 0$$

$$D_{ss} = \sum_{i=1}^{m} \left(\frac{\partial W}{\partial x_i} \right)^2$$ Diagonal diffusion matrix

$$A_{ss} = \sum_{i=1}^{m} v_i^s \frac{\partial W}{\partial x_i}$$ Diagonal advection matrix

Largest eigenvalue of matrix M is zero

Define largest eigenvalue to be the Hamiltonian, leads to Hamilton-Jacobi equation

$$\mathcal{H}(x, \nabla W(x)) = 0 \qquad (p = \nabla W)$$

=> most probable path ϕ parallel to gradient of quasipotential
=> log mean transition time proportional to quasipotential barrier height

$$\nabla_p \mathcal{H}(x,p)\big|_{p=\nabla W(x)} \parallel \frac{d\phi}{ds}$$ additional constraint to uniquely define W, written in terms of the most probable path

Predicting Probable States

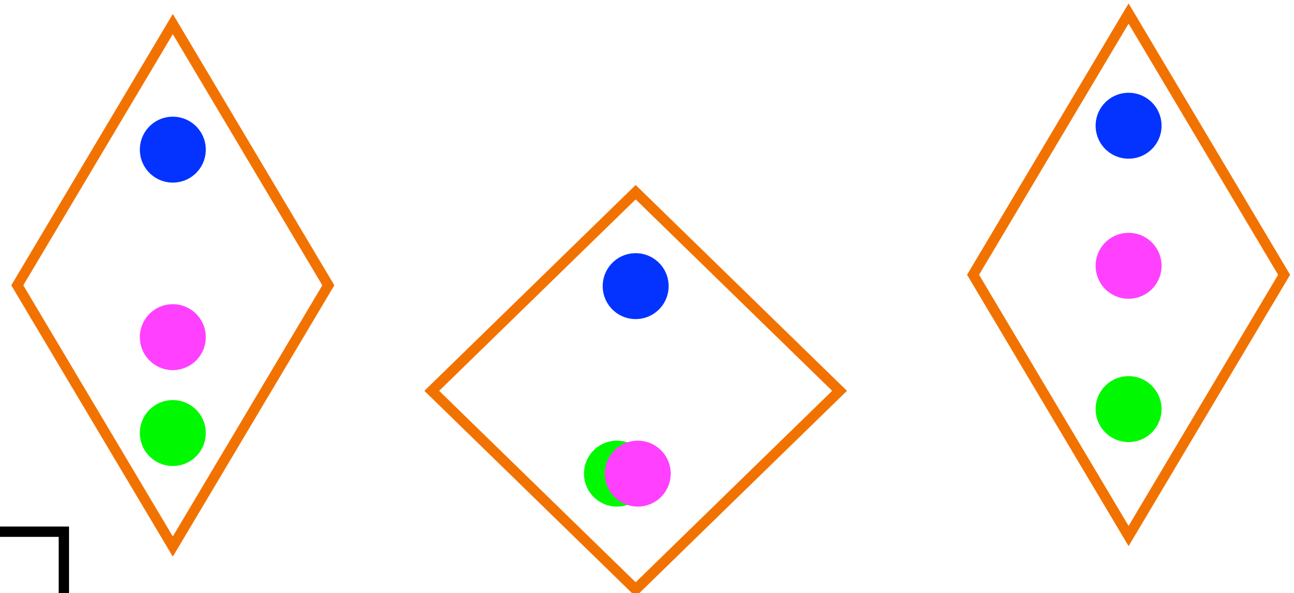
Fixed points of the deterministic dynamics (taking $\epsilon \to 0$)

$$\frac{dx_i}{dt} = \sum_{k=1}^{n} v_i^k r_k \text{ for } i = 1 \ldots m$$

are solutions to $\mathcal{H}(x, 0) = 0$

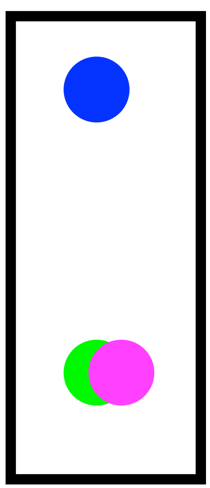
$$r = \text{null } S \qquad \sum_{k=1}^{n} r_k = 1$$

Quasi-potential Saddle Points

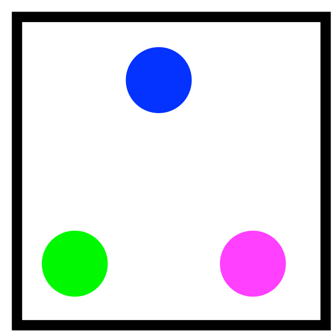


(and 2 other permutations)

Quasi-potential Minimizers



2-bead cluster



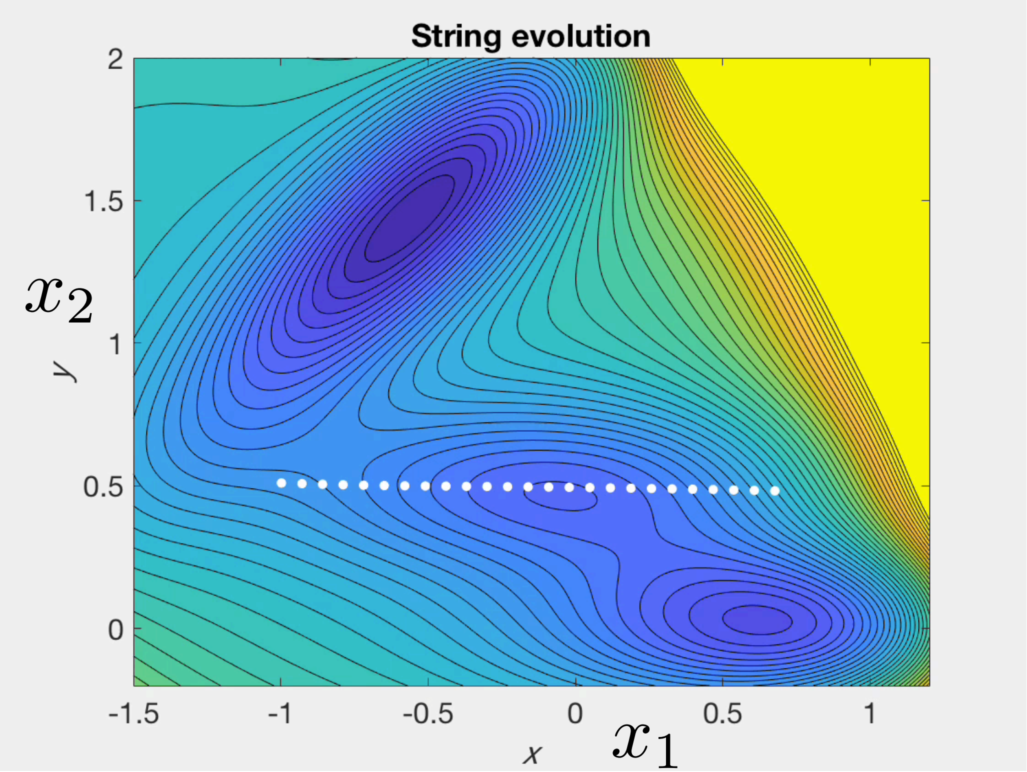
3-bead cluster

String Method (Most Probable Path)

Gradient system

$$dX = -\nabla U(X)dt + \sqrt{2\epsilon}dW$$

The energy-minimizing path is the MPP and is everywhere parallel to the gradient. To find, evolve



$$\partial_t \phi(\alpha, t) = -\nabla U(\phi(\alpha, t))$$

ϕ the path

α arc length

Numerically integrate

$$\phi_j^{k+1} = \phi_j^k - h\nabla U(\phi_j^k)$$

h time step size

$j = 1 \ldots N$ number of images along the string

After each step, interpolate the images along the string

W. E, W. Ren, and E. Vanden-Eijnden, (2007) "Simplified and improved string method for computing the minimum energy paths in barrier-crossing events," J Chem Phys, 126, p. 164103

Numerical Challenges

$\phi(s)$ Most probable path (climbing string method) $\quad \frac{d\phi}{ds} || \nabla W$

$$\mathcal{H}(x, \nabla W(x)) = 0$$

$$\nabla_p \mathcal{H}(x,p)|_{p=\nabla W(x)} \ || \ \frac{d\phi}{ds}$$

1) Solve for ∇W along path by solving above two equation 2) Update path based on ∇W

In practice, Newton's method for 1) often fails to converge due to initial guess

Fallback method: decouple the two equations

Move initial guess to try and maximize dot product of tangent to path with gradient
Then just solve $\mathcal{H}(x, \nabla W(x)) = 0$

Also noticed need for smaller time step h when using more images along the string

Schematic of Transitions

Quasipotential theory valid for transitions from the minimum

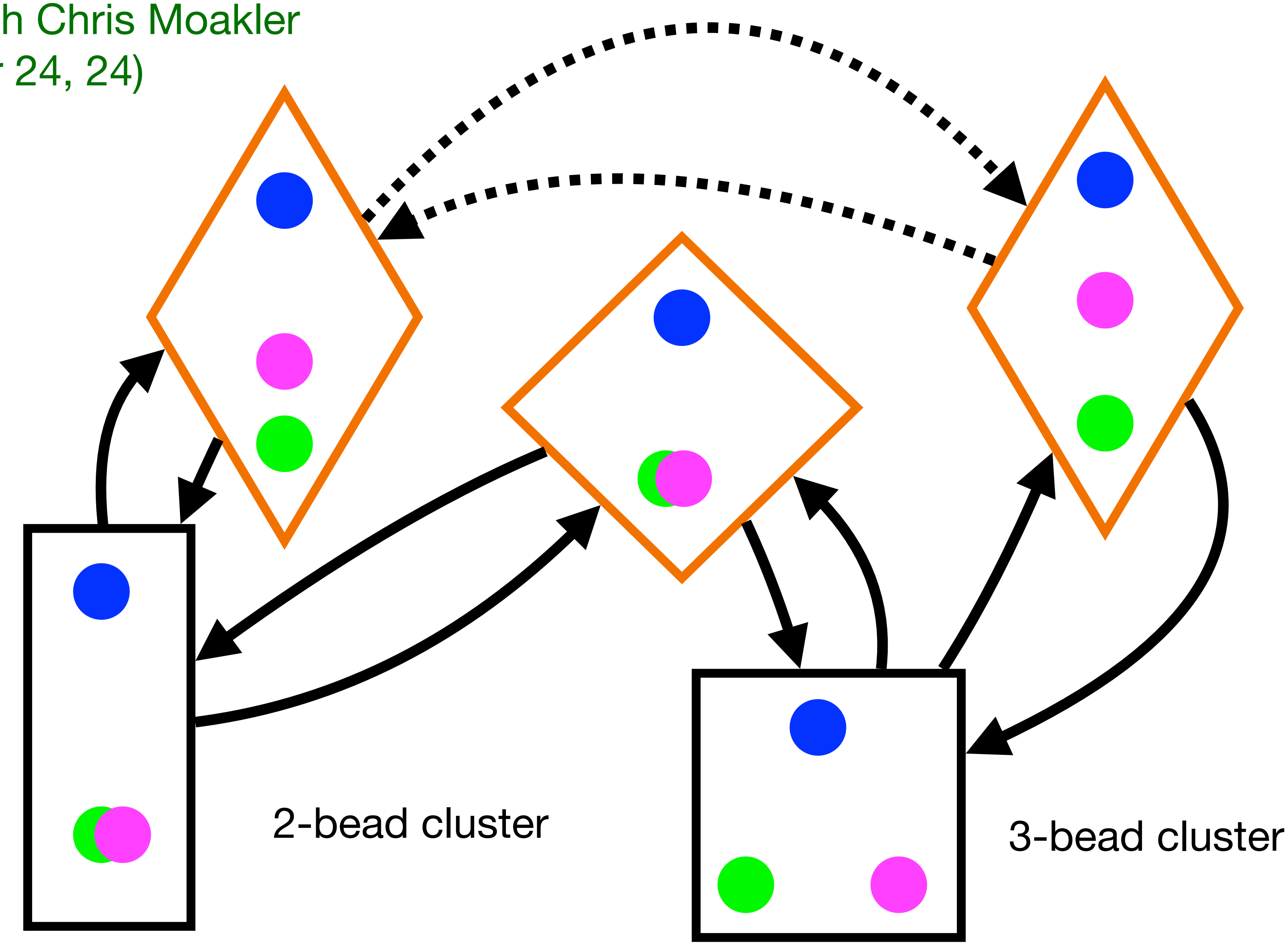
Potential transitions between saddle points shown as dashed lines

(Simple application of Hydra String Method developed with Chris Moakler (2022) Granular Matter 24, 24)

Quasi-potential Saddle Points

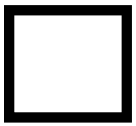
(and 2 other permutations)

Quasi-potential Minimizers

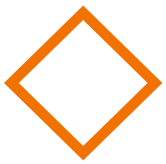


Example Transitions

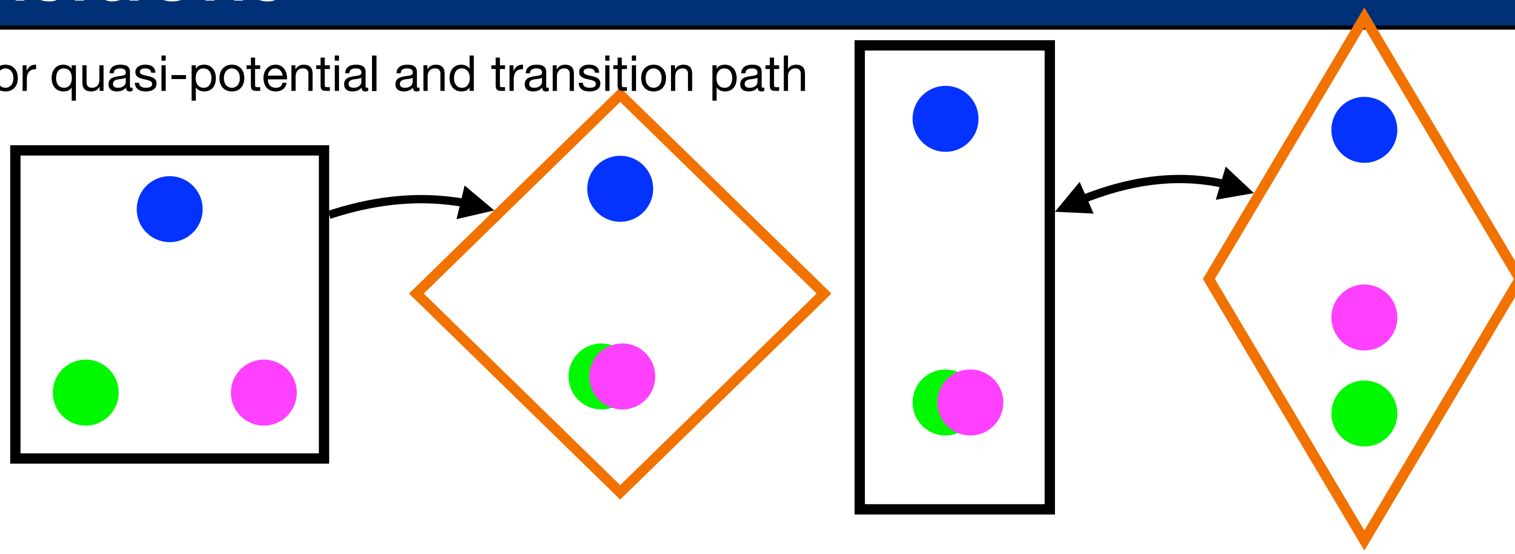
Simultaneously solve for quasi-potential and transition path



quasi-potential minimum



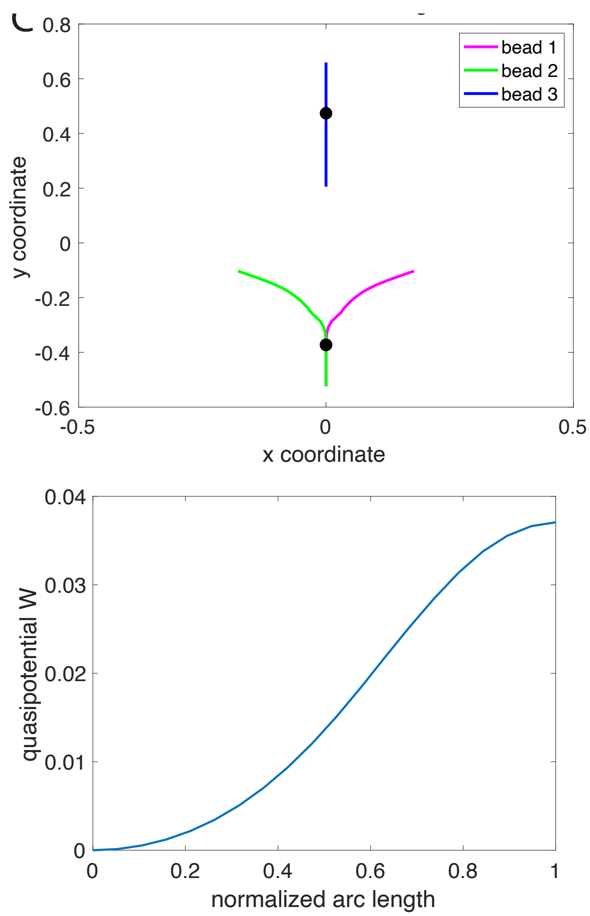
transition state

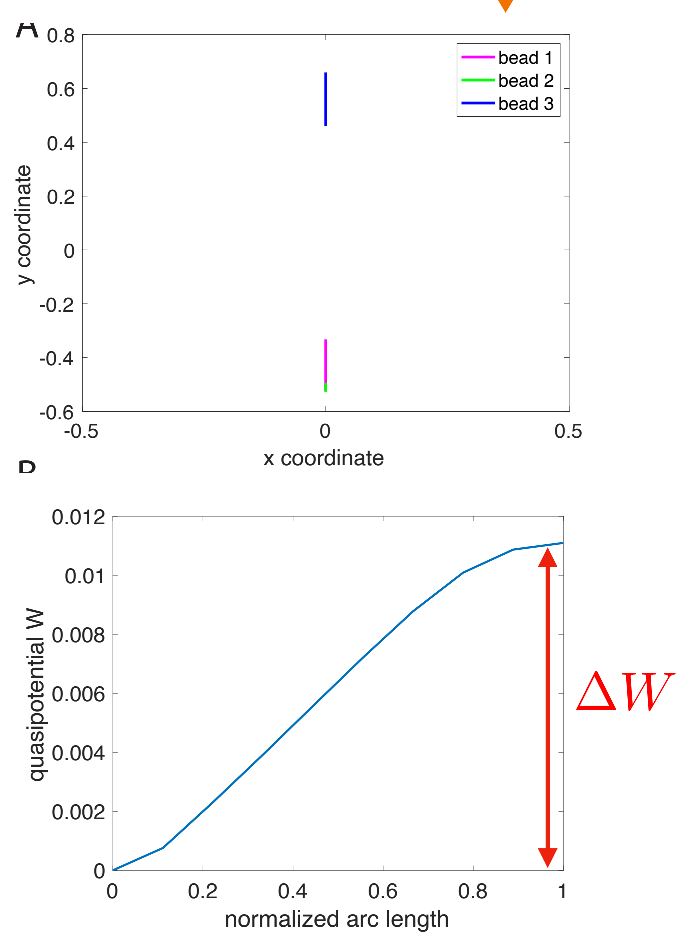


Predict the existence of 3-bead and 2-bead stable clusters

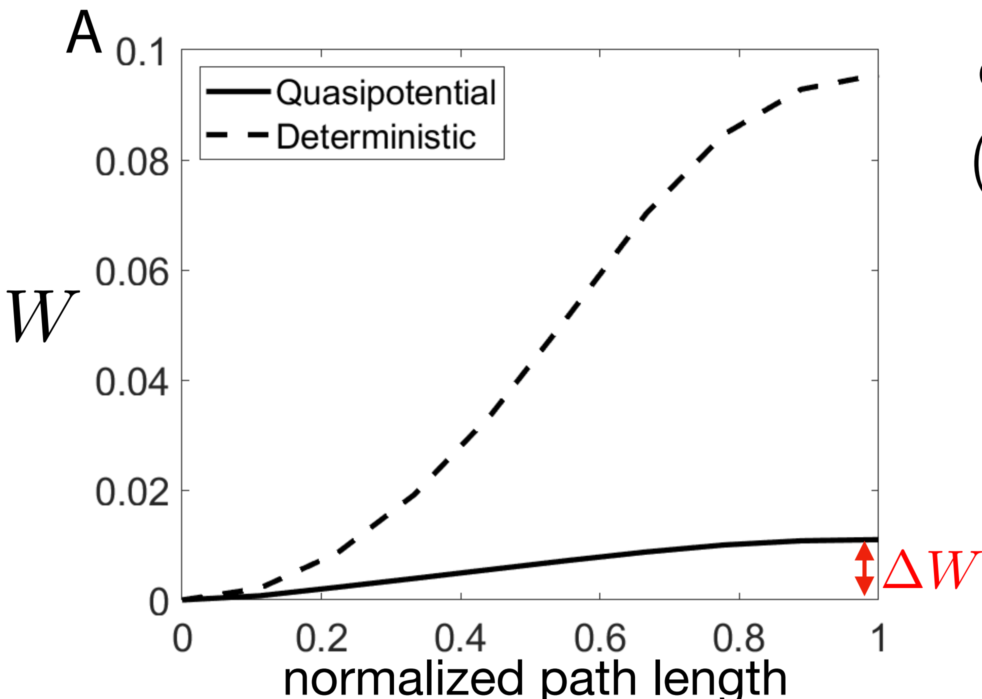
Lifetime given by

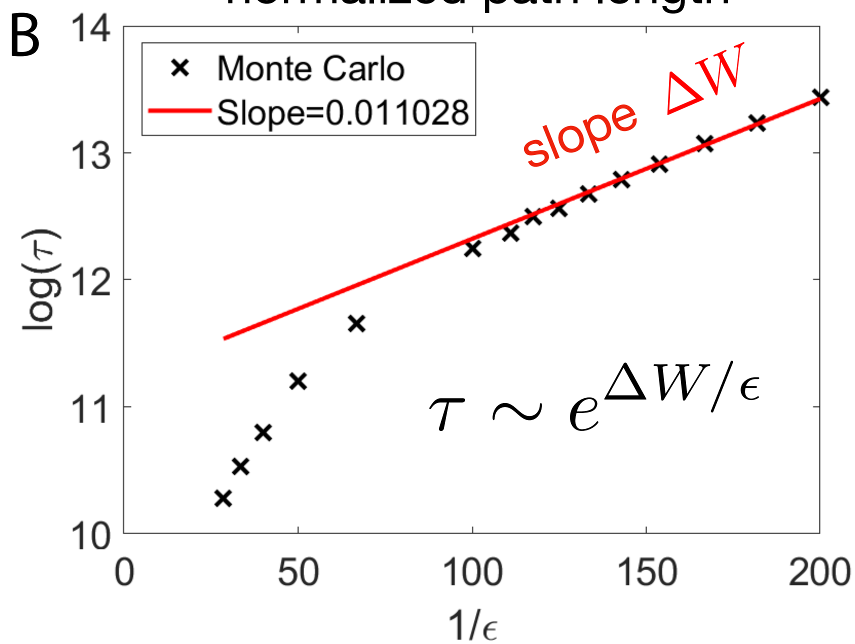
$$\tau \sim e^{\Delta W/\epsilon}$$





Monte Carlo Simulations





"Deterministic" average: found by eliminating switching noise

$$(\beta > 1) \qquad S\vec{r} = 0$$

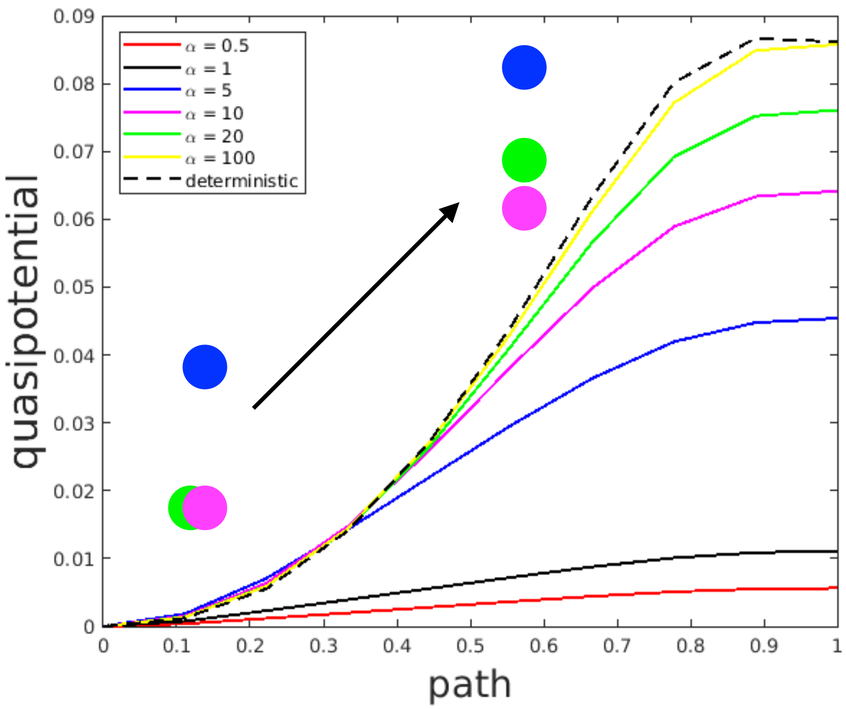
$$dX_i = \bar{v}_i(\vec{X})dt + \sqrt{2\epsilon}dW_i$$

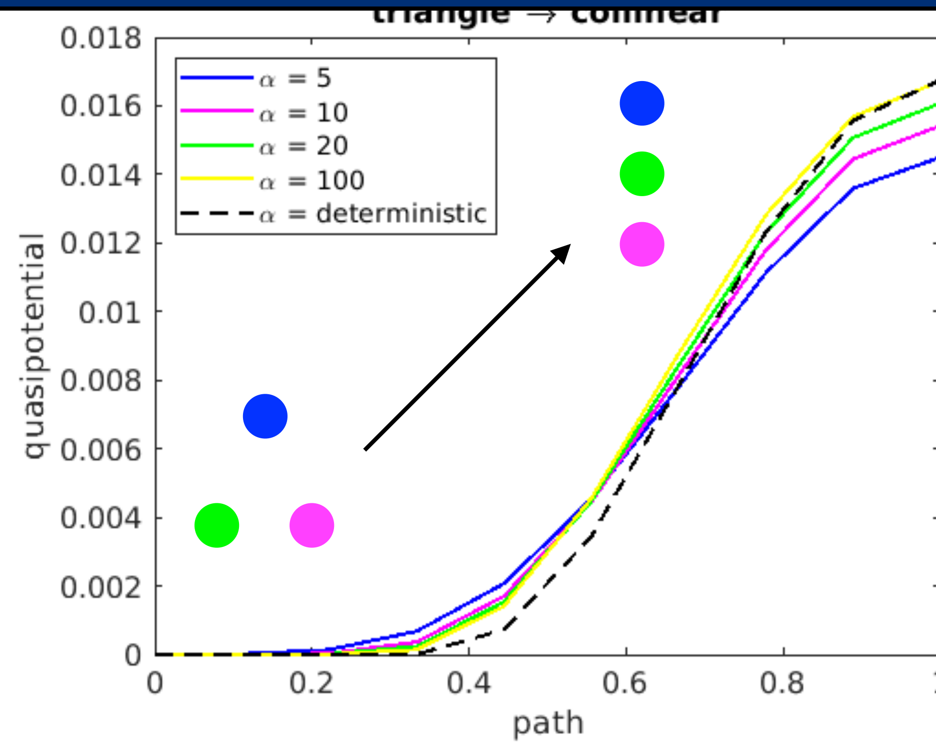
$$\bar{v}_i = \sum_s v_i^s r_s$$

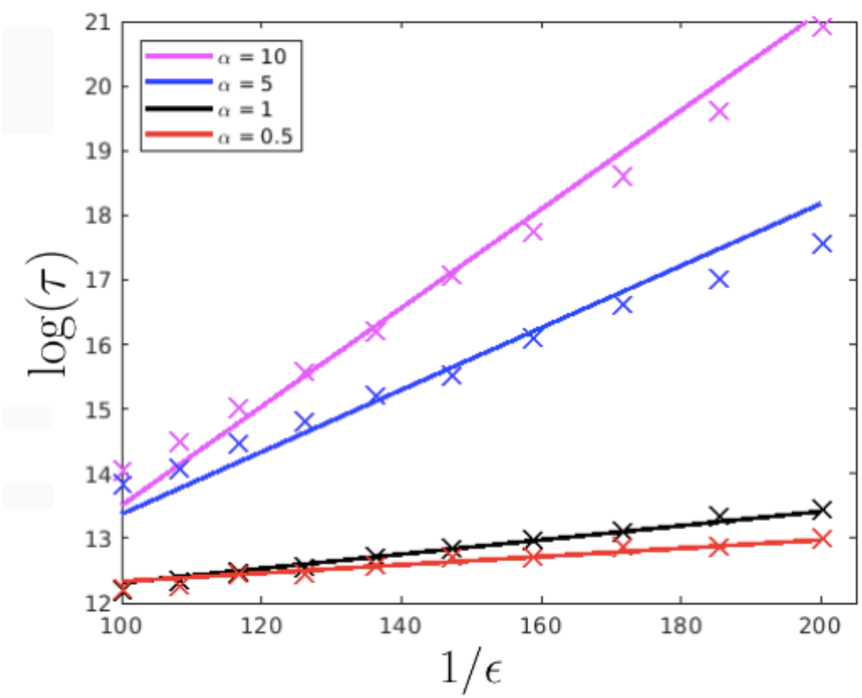
The deterministic or naive time-averaging significantly overestimates the stability of the system

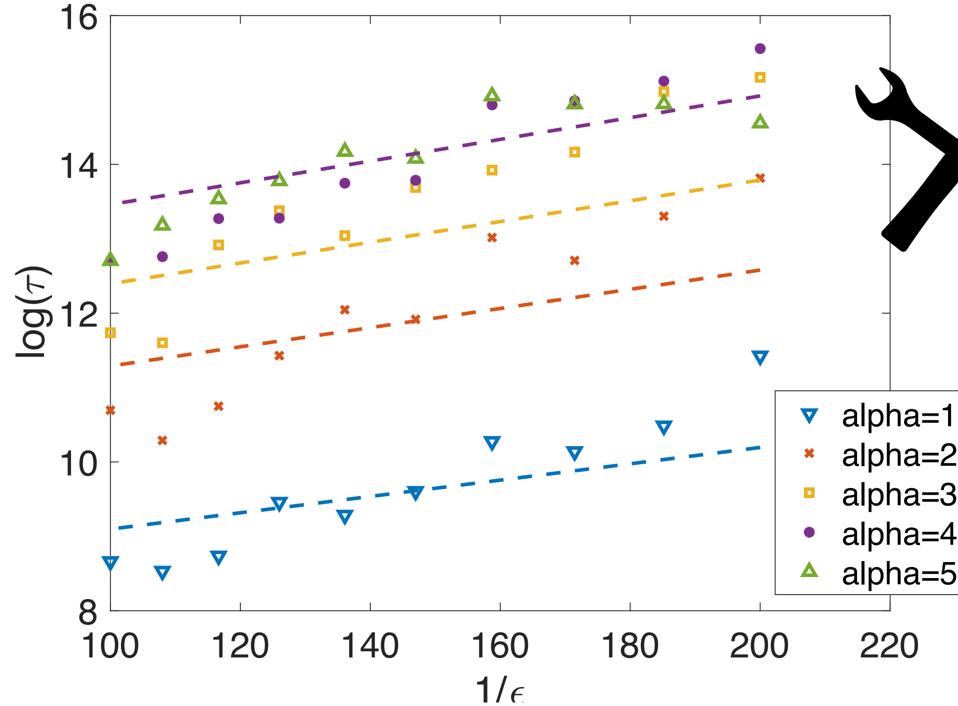
It is the interaction of the two sources of noise that allows the system to more easily overcome the "barrier" between clusters

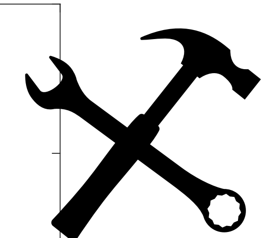
Monte Carlo Simulations







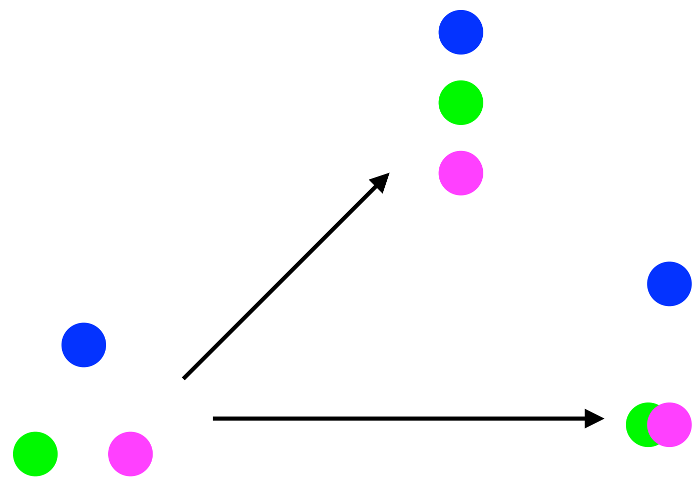




Multiple Paths

Recall there are two pathways out of the 3-bead cluster state.

While the lower energy barrier is preferred, we have not weighted both pathways to predict the MFPT



Furthermore, we have not guaranteed construction of a global equilibrium-like distribution, just a local distribution around a minimum.

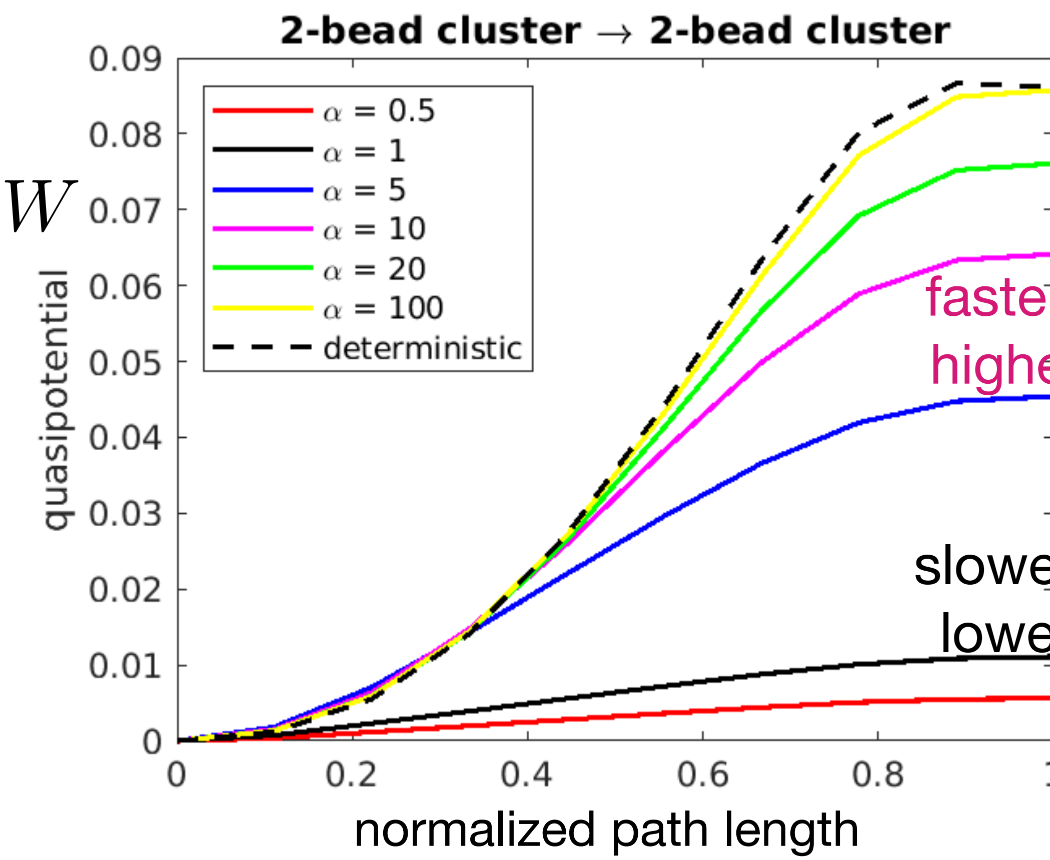
Further investigation needed to compute likelihood to find system in a given cluster state.

Effective Barrier Explains Metastability

relative strength of
binding noise vs. thermal noise:

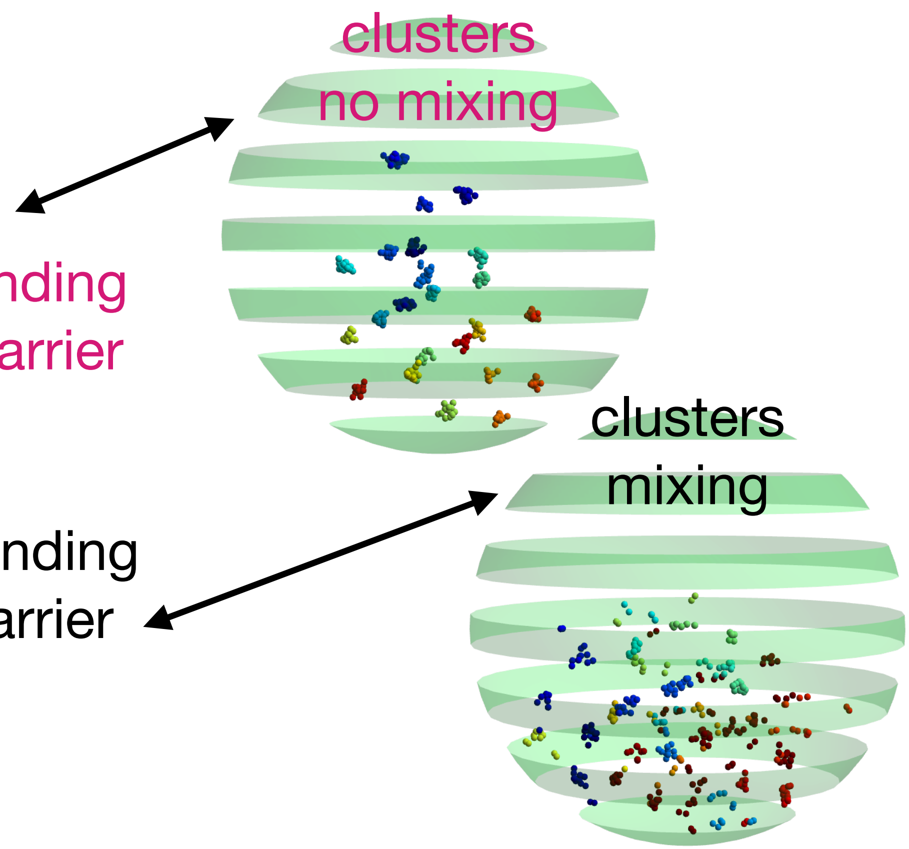
$$\frac{\alpha}{\epsilon} S \quad \text{vs.} \quad \sqrt{2\epsilon} dW$$

Change in effective energy barrier as change binding timescale, mechanism for metastability!



faster binding
higher barrier

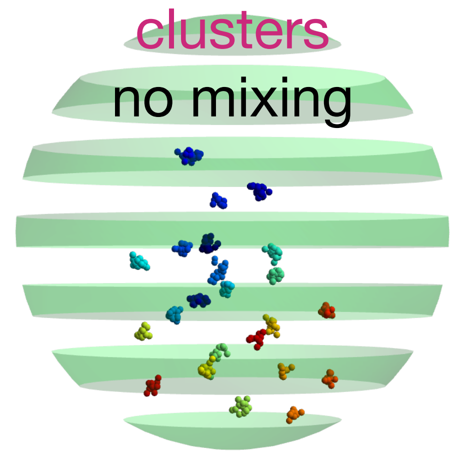
slower binding
lower barrier



Competing Timescales

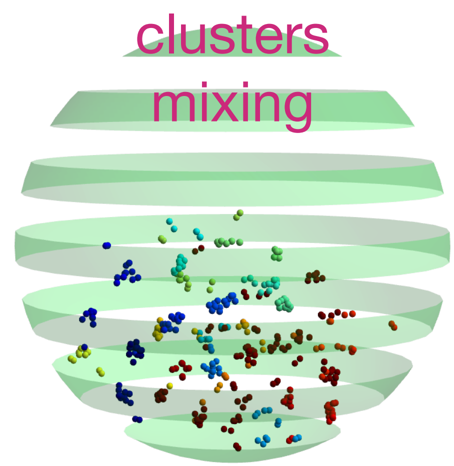
Quasi-potential framework explains metastable clusters

$\alpha \gg 1$ — switching noise to zero first, naive time-averaged force controls energy barrier

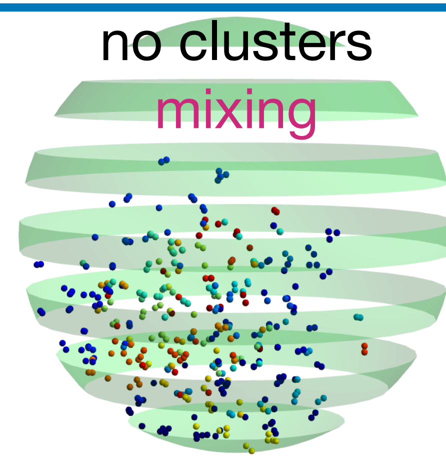


$\alpha \approx 1$ — cooperation between switching noise and thermal noise

- switching fast enough that its hard to diffuse away while force off, creating clusters
- switching not so fast that there is a chance to diffuse away while force is off, lowering effective energy barrier



$\alpha \ll 1$ — thermal noise to zero first, pair-wise bonding controlled solely by CTMC



Summary

Addition of fast transient crosslinking push the polymer model of chromosome dynamics out of equilibrium, yet at the right timescale produced metastable structure

Metastable clusters shown to emerge from a quasi-potential capturing the interplay of stochastically-switching forces and thermal noise

Walker B, KAN (2022) Numerical computation of effective thermal equilibrium in Stochastically Switching Langevin Systems
Phys. Rev. E 105:064113

Ben Walker - former graduate student, now postdoc at UC Irvine

Anna Coletti - current graduate student

Jay Newby - Dept. of Math at U Alberta

Kerry Bloom - Biology Dept. at UNC

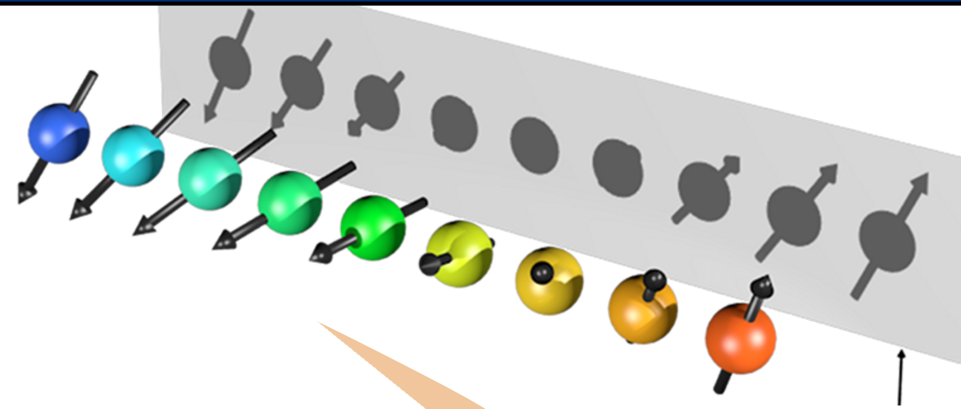
Thanks!!!

partially supported by NSF DMS 1816394

Add Geometry + Correlations

Set of N spins, $\sigma_i \in \mathbb{R}^3 \quad ||\sigma_i|| = 1$

$$H = J \sum_{<i,j>} \|\sigma_i - \sigma_j\|^2$$



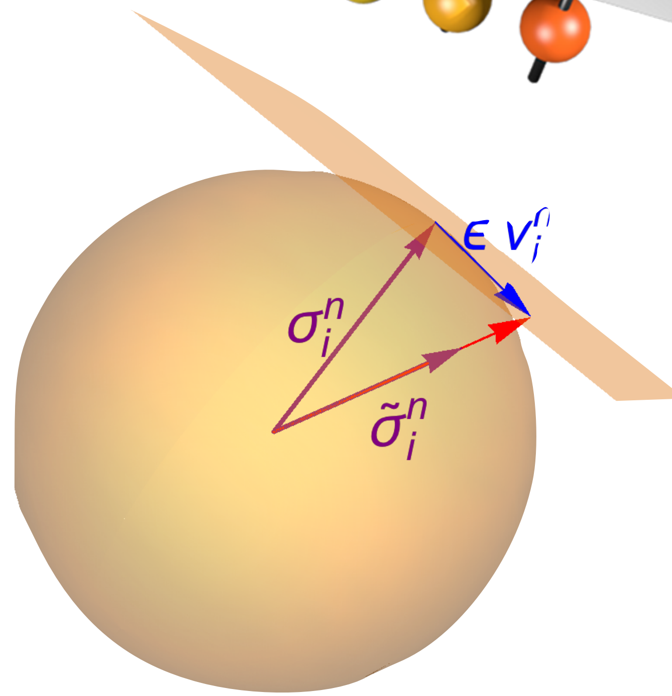
Proposal with geometry:

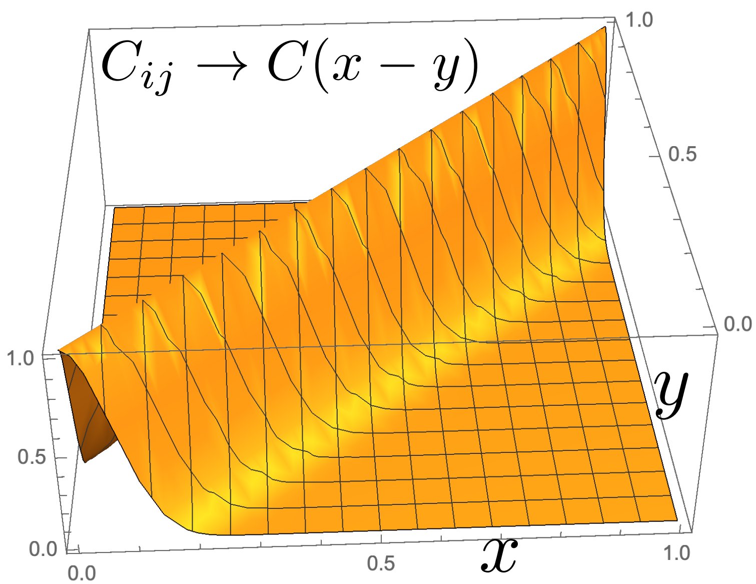
$$\nu_i^n = \mathrm{P}^{\perp}_{\sigma_i^n}(w_i^n)$$

Project noise into tangent plane for each spin

$$\tilde{\sigma}_i^n = \frac{\sigma_i + \varepsilon \nu_i}{\|\sigma_i + \varepsilon \nu_i\|}$$

Proposed spins projected back onto sphere





Correlations between noise vectors:

$$\mathbb{E}[w_i^n w_j^n] = C_{ij}$$

Covariance Matrix Eigenvalues $\quad C\phi_k = \lambda_k \phi_k$

$$\lambda_k \propto k^{-\kappa}$$

$\kappa = 0$ white noise

$\kappa > 0$ colored noise

Continuous Time Limit

cross-product

$$\boldsymbol{\sigma}_i \times \mathrm{d}\boldsymbol{W}_i \qquad P_1 = \begin{pmatrix} 0 & -Z & Y \\ Z & 0 & -X \\ -Y & X & 0 \end{pmatrix}$$

$$Q = \begin{pmatrix} \sigma_{1,q} & 0 & \dots & 0 \\ 0 & \sigma_{2,q} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \sigma_{N,q} \end{pmatrix}$$

cross-cross product

$$-\boldsymbol{\sigma}_i \times (\boldsymbol{\sigma}_i \times \mathrm{d}\boldsymbol{W}_i) \qquad P_2 = \begin{pmatrix} I - X^2 & -XY & -XZ \\ -XY & I - Y^2 & -YZ \\ -XZ & -YZ & I - Z^2 \end{pmatrix}$$

white noise: either projection results in sampling the Gibbs distribution

$$\mathrm{d}\vec{s} = PP^T \Delta_N \vec{s}\, \mathrm{d}t - \frac{2N}{\beta} \vec{s}\, \mathrm{d}t + \sqrt{2\beta^{-1} N} P \mathrm{d}\vec{W}$$

colored noise: only cross-projection results in sampling the Gibbs distribution

$$\mathrm{d}\vec{s} = P \frac{C_N}{N} P^T \Delta_N \vec{s}\, \mathrm{d}t - 2\beta^{-1} \frac{\mathrm{Tr}(\bar{C}_N)}{N} \vec{s}\, \mathrm{d}t + \sqrt{2\beta^{-1}} P C_N^{1/2} \mathrm{d}\vec{W}$$

Warning!

Wrong accept/reject probability to guarantee sampling the Gibbs distribution because the proposal is no longer symmetric: coloring projected noise is not equivalent to projecting colored noise

Continuous Time Limit

cross-product

$$\boldsymbol{\sigma}_i \times \mathrm{d}\boldsymbol{W}_i \qquad P_1 = \begin{pmatrix} 0 & -Z & Y \\ Z & 0 & -X \\ -Y & X & 0 \end{pmatrix} \checkmark \qquad Q = \begin{pmatrix} \sigma_{1,q} & 0 & \dots & 0 \\ 0 & \sigma_{2,q} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \sigma_{N,q} \end{pmatrix}$$

cross-cross product

$$-\boldsymbol{\sigma}_i \times (\boldsymbol{\sigma}_i \times \mathrm{d}\boldsymbol{W}_i) \qquad P_2 = \begin{pmatrix} I - X^2 & -XY & -XZ \\ -XY & I - Y^2 & -YZ \\ -XZ & -YZ & I - Z^2 \end{pmatrix} \times$$

white noise: either projection results in sampling the Gibbs distribution

$$\mathrm{d}\vec{s} = PP^T \Delta_N \vec{s}\,\mathrm{d}t - \frac{2N}{\beta}\vec{s}\,\mathrm{d}t + \sqrt{2\beta^{-1}N}\,P\mathrm{d}\vec{W}$$

colored noise: only cross-projection results in sampling the Gibbs distribution

$$\mathrm{d}\vec{s} = P\frac{C_N}{N}P^T \Delta_N \vec{s}\,\mathrm{d}t - 2\beta^{-1}\frac{\mathrm{Tr}(\bar{C}_N)}{N}\vec{s}\,\mathrm{d}t + \sqrt{2\beta^{-1}}\,PC_N^{1/2}\mathrm{d}\vec{W}$$

$$N \to \infty \qquad P = P_1$$

$$\partial_t \sigma(x,t) = -\sigma(x,t) \times \int_{\mathbb{T}^d} C(x-y)(\sigma \times \Delta\sigma)(y,t)dy + \sqrt{2\beta^{-1}}\sigma(x,t) \times \eta^C(x,t)$$