Update

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Goals

- ☐ Recapitulate, from the last presentation,
  - variability in exit time distribution from additional simulations after MM,
  - first order integral equation obtained from optimization of the energy barrier height,
  - automating computations of exit time fluctuations from barrier heights at fixed T.
- ☐ Simulate dependence of barrier height parameters on ambient T, and corresponding fluctuations.
  - Obtain exit time fluctuations on the Boltzmann scale
- ☐ Discuss how new simulations impact parameter choice for inspection transitions to secondary barriers in the landscape, in addition to relations between the exit time fluctuation and the temperature, and barrier height.
  - Reflect on height parameters and temperature in $\Delta_{n,n-1}\tau$.

Our equation of interest is,

$$\frac{\mathrm{d}^2\tau}{\mathrm{d}x^2} - \frac{\mathcal{U}'(x)}{k_b T}\frac{\mathrm{d}\tau}{\mathrm{d}x} = -\frac{1}{k_b T} \ ,$$

where the exit time takes the form,

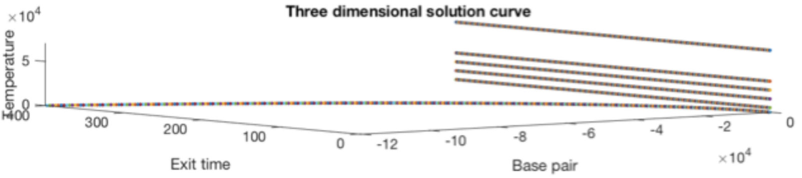
$$\tau(x) = \frac{1}{k_b T}\Bigg(\underbrace{n^2}_{=\int_0^n \int_0^n f(u) f(-v) \mathrm{d}u \ \mathrm{d}v} - \underbrace{x^2}_{=\int_0^x \int_0^x f(u) \ f(-v) \ \mathrm{d}u \ \mathrm{d}v} - \underbrace{\int_x^n f(v) \int_0^v f(u) \ \mathrm{d}u \ \mathrm{d}v}_{\approx \int_0^x f(v) \int_0^v f(u) \ \mathrm{d}u \ \mathrm{d}v - \int_0^n f(v) \int_0^v f(u) \ \mathrm{d}u \ \mathrm{d}v} \Bigg) \ ,$$

and,

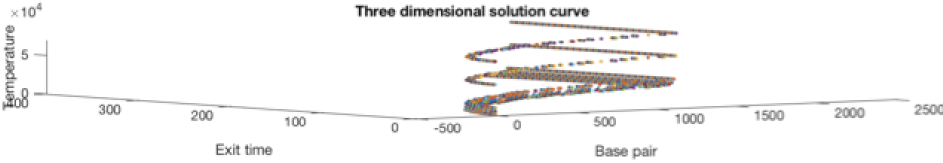
$$f(u) = \exp\left(\frac{\sqrt{\pi\sigma^2}}{2k_b T} \left(\frac{2}{\sqrt{\pi}} \int_0^{\frac{\mu-u}{\sigma}} \exp(-t^2) \ \mathrm{d}t \right)\right) \ .$$

Temperature dependent plots from the first and second additional simulations

☑ Variability in exit time distributions, post MM.

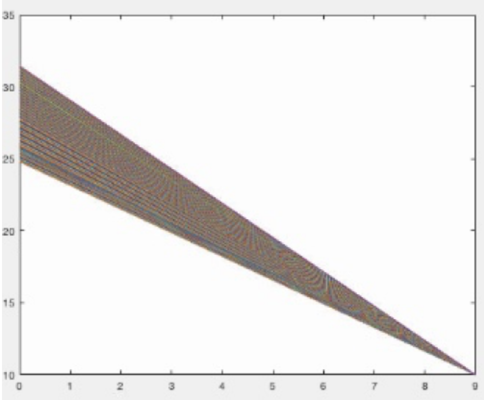


(binding in ambient unit temperature diverges)



(level sets of constant temperature yield monotonically increasing solutions in exit time)

Linear dependence of exit time fluctuation on barrier height



Linearized fluctuations about $h = 2$ (replace h with $h - 2$, sorry!)

⇳ Consolidating exponentials under the last integral

$$\boxed{\Delta_{n,n-1}\tau(T,h)} = 2n+1+\Big(\int_0^n f_h(u)\mathrm{d}u - \int_0^{n-1} f_{h-1}(u)\mathrm{d}u\Big)\Big(\int_0^v \exp\Big(\frac{0.4}{T}\{\tfrac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t\}\cdots$$

$$\Big)\cdots+\exp\Big(\frac{0.4}{T}(\tfrac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t\Big)\mathrm{d}u\Big)+\int_0^n h\Big(\Big(\exp\Big(\frac{0.4}{T}(\tfrac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\Big)-1\Big)$$

$$f_h(u)+\Big(\exp\Big(\frac{0.4}{T}(\tfrac{1}{2}\int_{\frac{\mu_2}{\sigma_2}}^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \int_{\frac{\mu_1}{\sigma_1}}^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\Big)-1\Big)f_{h-1}(u)\Big)\mathrm{d}u$$

Simulating dependence of barrier heights and T

Partition test cases within low and high temperature regimes, by

- introducing exponentials for the exit time fluctation and its first derivative,
- approximate the rate of change of the fluctuation within a sequence of neighboring isotherms with Newton's method,
- characterizations of the correlations between low and high temperature phases, reflecting considerations that,
  - in the low temperature regime, exit time fluctuations never exceed the millisecond barrier - a sequence of approximated exit times for which no exit time of more than one second,
  - in the high temperature regime, exit time fluctuations increase, over subsequent base pairs, on the order of seconds.
- a cooling down of the dynamics, in which the variance of the fluctuations vanishes after complex formation

☑ Simulate dependence of barrier height parameters on ambient T, and corresponding fluctuations.

- Determine exit time fluctuations from the constrained optimization by numerically solving the first order integral equation from the last presentation for fixed T, of the form,

$$\frac{1.6}{\sqrt{\pi}hk_bT}\ \exp\left(-\ \left\{\frac{1}{k_bT}\right\}(\mu_1 - v)^2\ \right) - \frac{0.8}{h^2k_bT}\left(\cdots\right.$$
$$\left.\frac{2}{\sqrt{\pi}}\int_0^{\frac{h}{0.4}(\mu_1 - u)} e^{-t^2}\mathrm{d}t\ \right)$$
$$= 0$$

- The fluctuation expression is,

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) = n^2 - (n-1)^2 + \int_0^n \int_0^v f_{h_i}(u)\mathrm{d}u \; f_{h_i}(v)\mathrm{d}v$$
$$\cdots - \int_0^{n-1} \int_0^v f_{h_{i-1}}(u)\mathrm{d}u \; f_{h_{i-1}}(v)\mathrm{d}v \; .$$

- After identifying the high temperature regime, analytically obtain the second barrier height depending on the fluctuation with (terms in green), for the orange term in $\Delta_{n,n-1}\tau$,

$$f_h(v) \approx \frac{v}{2}\Bigg\{\exp\left(\frac{0.4}{h_{i-1}k_b T}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{h_{i-1}}{0.4}\mu_1} \exp(-t^2)\mathrm{d}t\right)\right) + \cdots$$
$$\exp\left(\frac{0.4}{h_{i-1}k_b T}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\mathrm{d}t\right)\right) + \cdots$$
$$\exp\left(\frac{0.4}{h_{i-1}k_b T}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{h}{0.4}(\mu_1 - v)} \exp(-t^2)\mathrm{d}t\right)\right)\Bigg\} \; .$$

Obtaining the second landscape barrier height

For arbitrary fixed $\Delta_{n,n-1}\tau \in \mathbf{R}$,

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) = n^2 - (n-1)^2 + \int_0^n \int_0^v f_{h_i}(u)\mathrm{d}u \; f_{h_i}(v)\mathrm{d}v$$

$$\cdots - \int_0^{n-1} \int_0^v f_{h_{i-1}}(u)\mathrm{d}u \; f_{h_{i-1}}(v)\mathrm{d}v$$

$$\Updownarrow$$

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) - n^2 + (n-1)^2 \; + \cdots$$

$$\int_0^{n-1} \int_0^v f_{h_{i-1}}(u) \; \mathrm{d}u \; f_{h_{i-1}}(v) \; \mathrm{d}v = \int_0^n \int_0^v \Bigg\{ \; f_h(u) \; \frac{v}{2} \; \cdots$$

$$\exp\Bigg(\; \cdots \; \Bigg) + f_h(u)\frac{v}{2}\exp\Bigg(\; \cdots \; \Bigg) + \cdots$$

$$f_h(u)\frac{v}{2}\exp\Bigg(\; \cdots \; \Bigg) \; \mathrm{d}u \; \Bigg\}$$

Substituting for exponentials given from the solution $\Updownarrow$

$$f_h(u)\frac{v}{2}\exp\left(\frac{0.4}{h_{i-1}T}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{h_{i-1}}{0.4}\mu_1}\exp(-t^2)\,\mathrm{d}t\right)\right) = \cdots$$

$$\frac{v}{2}\exp\left(\frac{0.4}{h_{i-1}T}\underbrace{\left(\int_0^{\frac{h_{i-1}}{0.4}\mu_1}\exp(-t^2)\,\mathrm{d}t+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-u)}\exp(-t^2)\mathrm{d}t\right)}_{\text{Summation of error terms}}\right),$$

Remaining powers take the form $\Updownarrow$

$$\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\exp(-t^2)\,\mathrm{d}t+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-u)}\exp(-t^2)\,\mathrm{d}t\ ,$$

$$\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-v)}\exp(-t^2)\,\mathrm{d}t+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-u)}\exp(-t^2)\,\mathrm{d}t\ .$$

Obtain a variant of fluctuations predicted from $\Delta_{n,n-1}\tau \Updownarrow$

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) - n^2 + (n-1)^2 \; + \cdots$$

$$\int_0^{n-1}\int_0^{v} f_{h_{i-1}}(u)\mathrm{d}u \; f_{h_{i-1}}(v)\mathrm{d}v \; = \cdots$$

$$\int_0^n \underbrace{\frac{u^2}{4}\exp\left(\frac{0.4}{h_{i-1}k_b T}\left(\int_0^{\frac{h_{i-1}}{0.4}\mu_1}\exp(-t^2)\,\mathrm{d}t + \cdots\right.\right.}_{\text{First term}}$$

$$\underbrace{\left.\left.\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - v)}\exp(-t^2)\mathrm{d}t\right)\right)}_{\text{First term}} \; + \; \cdots$$

$$\underbrace{\mathcal{I}_2 + \mathcal{I}_3}_{\text{On the next slide....}} \qquad \mathrm{d}u \;,$$

Integrating by parts to determine $\mathcal{I}_2$ & $\mathcal{I}_3$

$$
\mathcal{I}_2 = \int_0^n \int_0^v \frac{v}{2} \exp\left(\frac{0.4}{h_{i-1} k_b T} \left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\, \mathrm{d}t + \cdots \right.\right.
$$

$$
\left.\left. \int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - u)} \exp(-t^2)\, \mathrm{d}t \right)\right) \mathrm{d}u\, \mathrm{d}v \; = \cdots
$$

$$
\int_0^n \exp\left(\frac{0.4}{h_{i-1} k_b T} \left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - u)} \exp(-t^2)\, \mathrm{d}t \right)\right) \times \cdots
$$

$$
\underbrace{\left\{ \frac{v}{2} \; \frac{\exp\left(\frac{0.4}{h_{i-1} k_b T} \left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\, \mathrm{d}t \right)\right)}{\frac{0.4}{h_{i-1} k_b T} \int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\, \mathrm{d}t} - \cdots \right.}_{\text{IBP}}
$$

$$
\underbrace{\left. \int_0^v \frac{1}{2} \exp\left(\frac{0.4}{h_{i-1} k_b T} \left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\, \mathrm{d}t \right)\right) \right\}}_{\text{IBP}} \mathrm{d}u \; .
$$

Similar u, v dependence in the last integral term

Similarly,

$$\mathcal{I}_3 = \int_0^n \int_0^v \frac{u}{2} \exp\Bigg(\frac{0.4}{h_{i-1} k_b T} \Bigg(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - u)} \exp(-t^2)\, \mathrm{d}t \quad + \cdots$$

$$\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - v)} \exp(-t^2)\, \mathrm{d}t \Bigg)\Bigg) = \cdots$$

$$\vdots$$

(Replace the upper limit of integrals associated with the error function with v instead of u in the upper limit) .

IBP equality for evaluating $\mathcal{I}_2$, $\mathcal{I}_3$ cross terms

$$\boxed{\int_0^n \frac{v}{2}\ \frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-v)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\exp(-t^2)\mathrm{d}t}\,\mathrm{d}u} \equiv \cdots$$

$$\frac{1}{2}\left\{\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-v)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\cdots\times\cdots}\right.$$

$$\left.\frac{1}{\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-v)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{v}{2})}\cdots\right)}\right\}\Bigg|_0^n-\cdots$$

$$\frac{1}{2}\ \frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-v)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_2-\frac{v}{2})}\cdots\right)\right)\Bigg|_0^n}{\frac{0.4}{h_{i-1}k_bT}\left(\int\cdots+\int\cdots\right)},$$

Simplification to the identity for computing $\mathcal{I}_2$

$$\boxed{\int_0^n \frac{1}{2} \; \frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - v)} \cdots + \int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \cdots \right)\right)}{\frac{0.4}{h_{i-1}k_bT} \int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2)\mathrm{d}t} \; \mathrm{d}u} \equiv \cdots$$

$$\frac{1}{2} \; \frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - v)} \cdots + \int_0^{\frac{h_{i-1}}{0.4}(\mu_2 - \frac{v}{2})} \cdots \right)\right)\Big|_0^n}{\frac{0.4}{h_{i-1}k_bT} \int_0^{\frac{h_{i-1}}{0.4}(\mu_1 - \frac{v}{2})} \exp(-t^2) \; \mathrm{d}t \; \frac{0.4}{h_{i-1}k_bT}\left(\int \cdots + \int \cdots \right)} \; ,$$

First order height-temperature locus from $\mathcal{I}_2$ & $\mathcal{I}_3$

The expression reads (blue terms are unchanged),

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) - n^2 + (n-1)^2 + \cdots$$

$$\int_0^{n-1}\int_0^{v} f_{h_{i-1}}(u)\,\mathrm{d}u\; f_{h_{i-1}}(v)\,\mathrm{d}v \;= \cdots$$

$$\frac{1}{2}\left\{\underbrace{\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_2-\frac{n}{2})}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots\frac{0.4}{h_{i-1}k_bT}\left(\int\cdots+\int\cdots\right)} - \cdots}_{\text{First term}}\right.$$

$$\left.\underbrace{\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_2)}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots\frac{0.4}{h_{i-1}k_bT}\left(\int\cdots+\int\cdots\right)}}_{\text{Second term}}\right\} + \left\{\cdots\right.$$

$$
\underbrace{\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\right)\right)}{\left(\frac{0.4}{h_{i-1}k_bT}\right)^2\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\times\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\right)}}_{\text{Third term}}-\cdots
$$

$$
\underbrace{\frac{\exp\left(\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\times\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)}}_{\text{Fourth term}}-\cdots
$$

$$
\left.\underbrace{\frac{1}{2}\left\{\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_2-\frac{n}{2})}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\left(\int\cdots+\int\cdots\right)}\right\}}_{\text{Fifth, sixth terms}}-\cdots\right\}.
$$

- ONLY third and fourth terms survive after cancellation

$$\Delta_{n,n-1}\tau(T, h_i, h_{i-1}) - n^2 + (n-1)^2 + \cdots$$

$$\int_0^{n-1}\int_0^{v} f_{h_{i-1}}(u)\,\mathrm{d}u\; f_{h_{i-1}}(v)\,\mathrm{d}v \;= \cdots$$

$$\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots + \int_0^{\frac{h_{i-1}}{0.4}(\;\mu_1-\frac{n}{2}\;)}\cdots\right)\right)}{\left(\frac{0.4}{h_{i-1}k_bT}\right)^2\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2}\;)}\cdots\times\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots\;+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\right)} - \cdots$$

$$\frac{\exp\left(\;\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots + \int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1\;)}\cdots\times\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\;+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)}$$

Simulation preparation

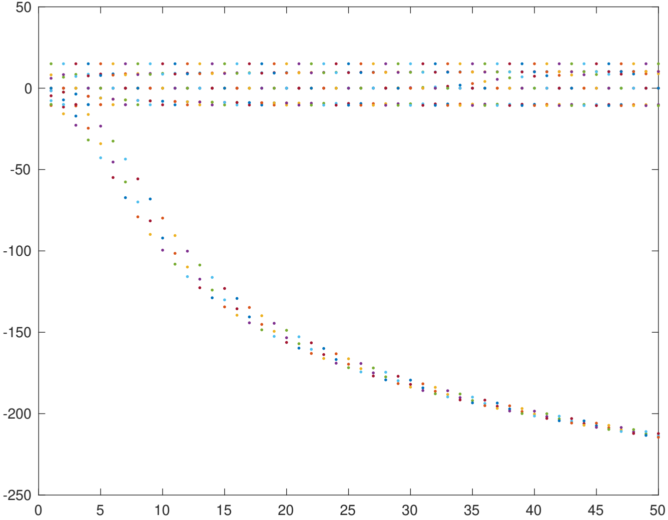
- To interpret low and high temperature parameter regimes associated with the locus formula, we approximate the roots of the function from the first order integral relation,

$$\frac{1.6}{\sqrt{\pi}hk_bT}\exp\left(-\left\{\frac{1}{k_bT}\right\}(\mu_1-v)^2\right)-\frac{0.8}{h^2k_bT}\left(\cdots\right.$$
$$\left.\frac{2}{\sqrt{\pi}}\int_0^{\frac{h}{0.4}(\mu_1-u)}e^{-t^2}\,\mathrm{d}t\right)$$
$$=0\ ,$$

with Newton's method for growing displacement from the base pair of inspection.

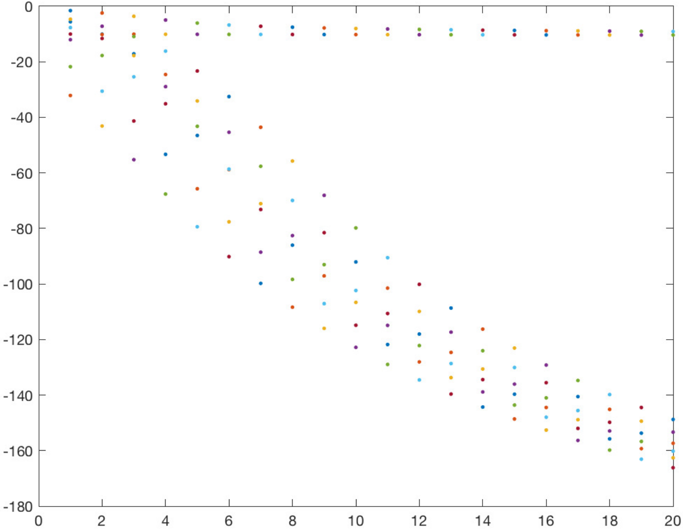
Low temperature $\Delta_{n,n-1}\tau$ optimization

Negligible fluctuations on the millisecond order aggregated before larger fluctuations for lower level sets.



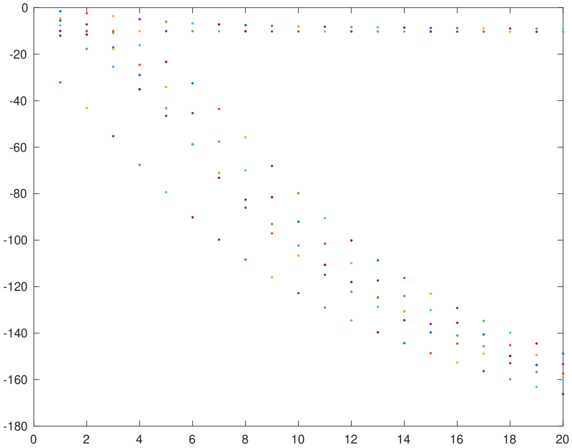
High temperature $\Delta_{n,n-1}\tau$ optimization

Exponential growth of exit time fluctuations with respect to base pair of inspection.

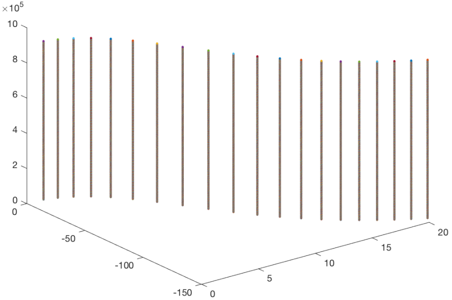


Increasing the number of trajectories in high temperature

1500 trajectories, with same axis conventions as in MM plots (increasing T on z)



Plot without any rotation in the base pair- exit time plane

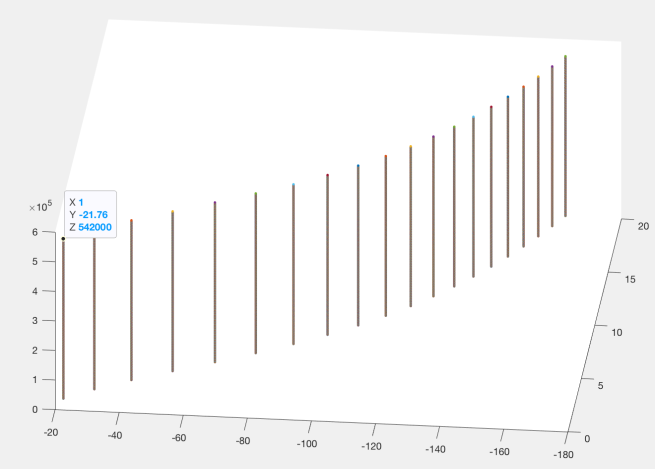


Impressions

- Negligible exit time fluctuations across different temperature level sets
- Topmost points on each temperature level set are labeled with different colors corresponding to the iteration
- *Goal*: Construct landscape trajectories from possible temperature colors from the level sets above.

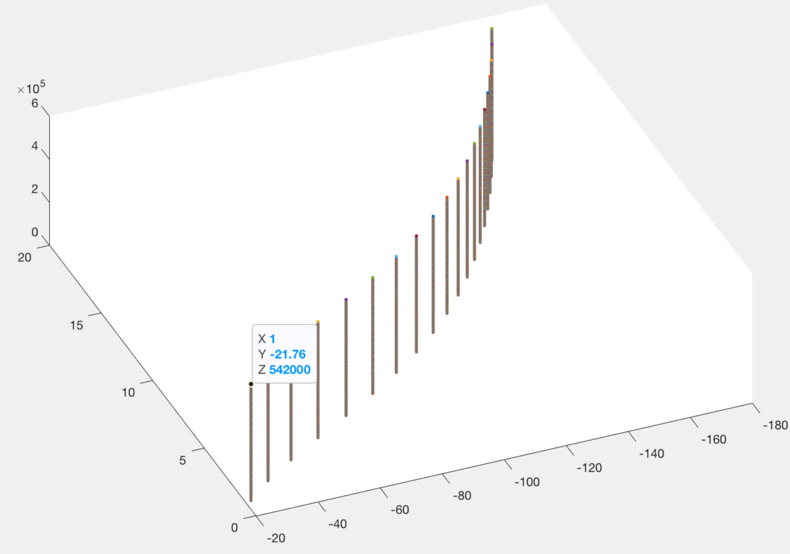
$\frac{\pi}{2}$ rotation about the base pair, exit time plane

(level set exhibiting monotonicity of first passage time with respect to temperature)

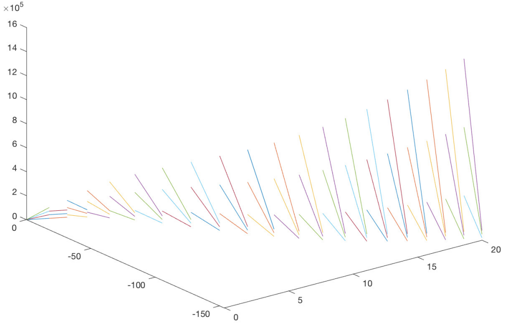


$\approx \frac{3\pi}{2}$ rotation about the same plane

(additional view of the rate of change for the exit time dampens out beyond some ambient critical T)

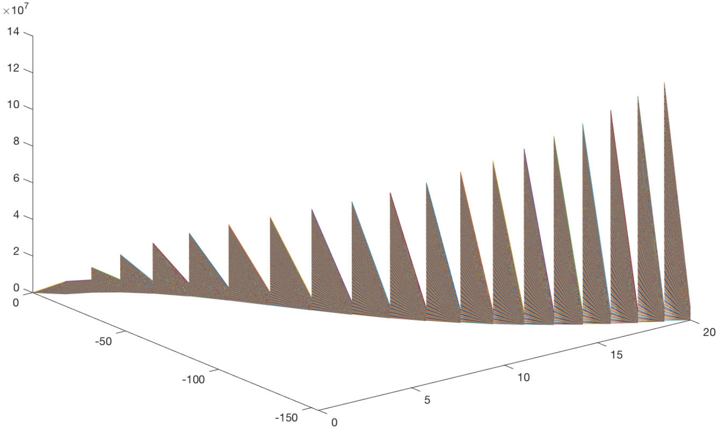


Temperature dependent simulations for (n, h, T), send $\frac{1}{k_b T} \to 0$ instead of sending $\frac{1}{T} \to 0$ in previous simulations (simulate higher temperature ensembles)



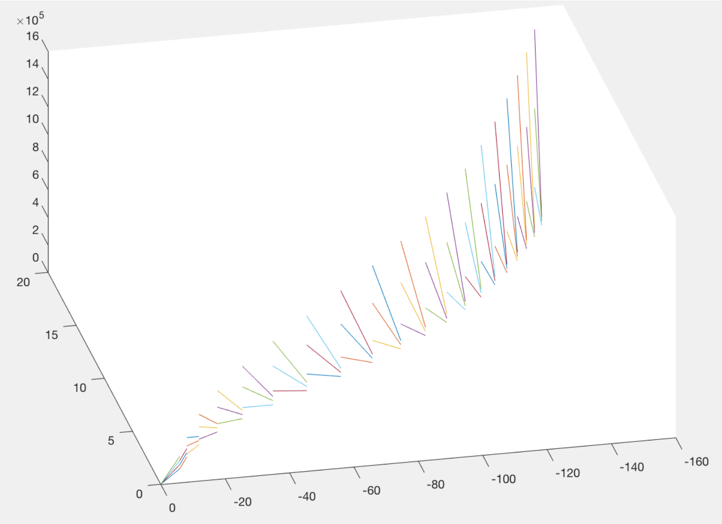
☑ Obtain exit time fluctuations on the Boltzmann scale (T ranges from 20000 to 60000 in increments of 30 for the first plot, while the range is fro 2000 to 85000, also in increments of 30, for the second plot).

Limiting shape in asymptotic temperature

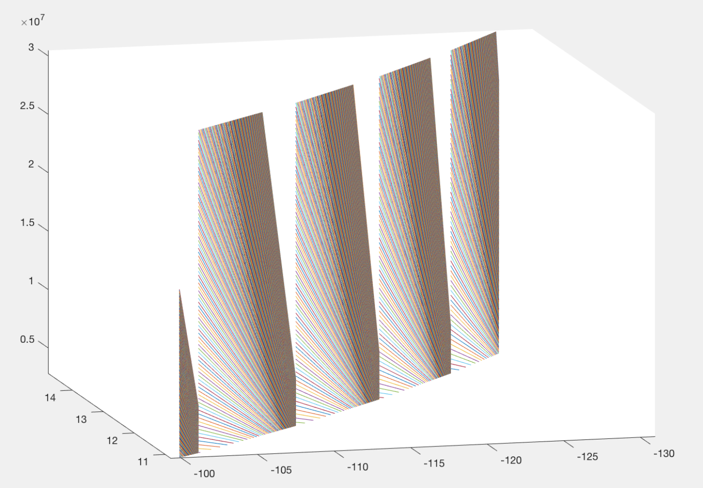


Temperature level set rotation about the base pair exit time plane

(similar rotation as shown previously)



Variability in exit time from the second barrier height



Transition to the low temperature fluctuations after high temperature dynamics & rapid mixing

- We observe the same partition of phase space, with the magnitude of the fluctuations increasing in the high temperature phase. For which height parameters will the fluctuations emerge, in addition to the corresponding exit time?
- Simulations suggest:
  - σ are responsible for broadly targeting the exit time parameter space,
  - T are responsible for targeting smaller perturbations of the exit time parameter space.

Running the procedure for other proteins

In more generality, we adjust the parameters related to,

- the length of the target sequence,
- the temperature dependent conditions for the protein complex formation fro the target sequence,
- the location of base pairs over which rapid mixing and complex formation occurs.

Overview of analytical techniques

- Analytical solution

$$\frac{\mathrm{d}^2\tau}{\mathrm{d}x^2} - \frac{\mathcal{U}'(x)}{k_b T}\frac{\mathrm{d}\tau}{\mathrm{d}x} = -\frac{1}{k_b T}\,,$$

where the exit time takes the form,

$$\tau(x) = \frac{1}{k_b T}\Bigg(\underbrace{n^2}_{=\int_0^n\int_0^n f(u)f(-v)\mathrm{d}u\,\mathrm{d}v} - \underbrace{x^2}_{=\int_0^x\int_0^x f(u)\,f(-v)\,\mathrm{d}u\,\mathrm{d}v} - \underbrace{\int_x^n f(v)\int_0^v f(u)\,\mathrm{d}u\,\mathrm{d}v}_{=\int_0^n f(v)\int_0^v f(u)\,\mathrm{d}u\,\mathrm{d}v - \int_0^x f(v)\int_0^v f(u)\,\mathrm{d}u\,\mathrm{d}v} \Bigg)\,,$$

and,

$$f(u) = \exp\left(\frac{\sqrt{\pi\sigma^2}}{2k_b T}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{\mu-u}{\sigma}} \exp(-t^2)\,\mathrm{d}t\right)\right)\,.$$

- Exit time fluctuations $\Delta_{n,n-1}\tau$

$$\Delta_{n,n-1}\tau(T,h,h-1) = n^2 - (n-1)^2 + \int_0^n\int_0^v f_h(u)\mathrm{d}u\, f_h(v)\mathrm{d}v \; - \int_0^{n-1}\int_0^v f_{h-1}(u)\mathrm{d}u\, f_{h-1}(v)\mathrm{d}v\,,$$

- Linearized fluctuations of $\Delta_{n,n-1}\tau$

⇕ Consolidating exponentials under the last integral

$$\boxed{\Delta_{n,n-1}\tau(T,h)} = 2n+1+\left(\int_0^n f_h(u)\mathrm{d}u - \int_0^{n-1} f_{h-1}(u)\mathrm{d}u\right)\Bigg(\int_0^v \exp\Bigg(\frac{0.4}{T}\{\frac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}}\exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}}\exp(-t^2)\mathrm{d}t\}\cdots$$
$$\Bigg)\cdots+\exp\left(\frac{0.4}{T}(\frac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}}\exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}}\exp(-t^2)\mathrm{d}t\right)\mathrm{d}u\Bigg)+\int_0^n h\Bigg(\left(\exp\left(\frac{0.4}{T}(\frac{1}{2}\int_0^{\frac{\mu_2-v}{\sigma_2}}\exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-v}{\sigma_1}}\exp(-t^2)\mathrm{d}t)\right)-1\right)$$
$$f_h(u)+\left(\exp\left(\frac{0.4}{T}(\frac{1}{2}\int_{\frac{\mu_2}{\sigma_2}}^{\frac{\mu_2-v}{\sigma_2}}\exp(-t^2)\mathrm{d}t - \int_{\frac{\mu_1}{\sigma_1}}^{\frac{\mu_1-v}{\sigma_1}}\exp(-t^2)\mathrm{d}t)\right)-1\right)f_{h-1}(u)\Bigg)\mathrm{d}u$$

- $\Delta_{n,n-1}\tau$ optimization in h_i

$$\frac{1.6}{\sqrt{\pi}hT}\exp\left(-\left\{\frac{1}{T}\right\}(\mu_1-v)^2\right)-\frac{0.8}{h^2T}\left(\cdots\frac{2}{\sqrt{\pi}}\int_0^{\frac{h}{0.4}(\mu_1-u)}e^{-t^2}\mathrm{d}t\right)=0$$

- Determination of second barrier height

$$\Delta_{n,n-1}\tau(T,h_i,h_{i-1})-n^2+(n-1)^2+\cdots\int_0^{n-1}\int_0^{v}f_{h_{i-1}}(u)\,\mathrm{d}u\,f_{h_{i-1}}(v)\,\mathrm{d}v=\cdots$$

$$\frac{\exp\left(\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\right)\right)}{\left(\frac{0.4}{h_{i-1}k_bT}\right)^2\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\times\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-n)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1-\frac{n}{2})}\cdots\right)}-\cdots\frac{\exp\left(\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)\right)}{\frac{0.4}{h_{i-1}k_bT}\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\times\frac{0.4}{h_{i-1}k_bT}\left(\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots+\int_0^{\frac{h_{i-1}}{0.4}(\mu_1)}\cdots\right)}$$

☑ Discuss parameter choices for the height barrier, etc.

☑ Demonstrate relations between exit time fluctuation, temperature and height from simulations.

Future plans for the next presentation

- Run simulations of the locus