Post MM update

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Goals

- ☐ Briefly summarize MM findings,
- ☐ Provide additional simulations of the binding landscape for alternate height fluctuation arrangments,
- ☐ Motivate "good" choices of the height parameter for the barrier height fluctuation in the landscape,
- ☐ Reformulate exit time fluctuation expression, for nonconstant height between neighboring base pairs of inspection, for future work in optimally determining height parameters.

Our equation of interest is,

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

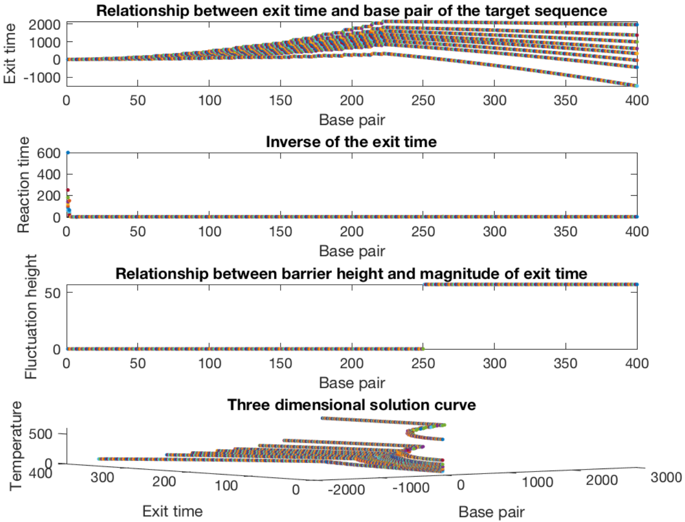
where the exit time takes the form,

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

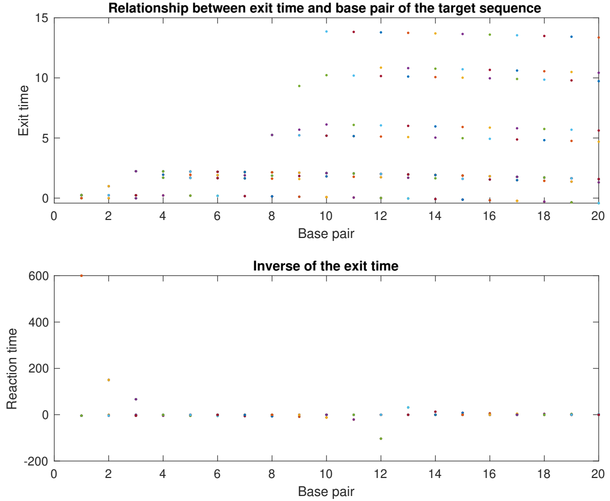
and,

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

$\approx$ 400 bp target sequences (8 temperature level sets) simulation



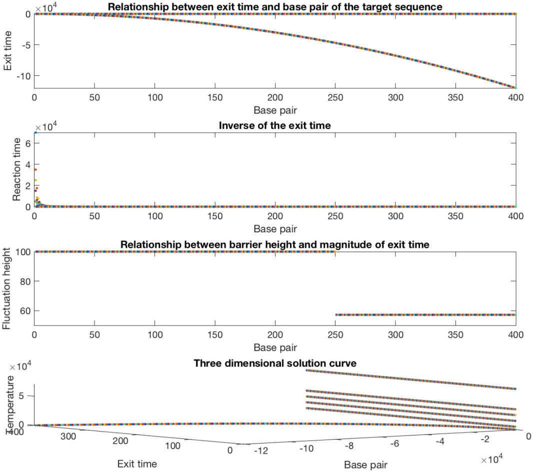
Passing to a height subsequence of the landscape for Fn Cas12a specific predictions



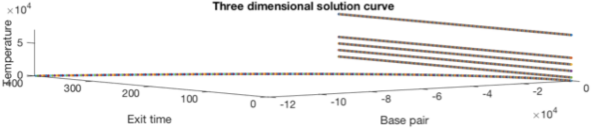
☑ Briefly summarize MM findings.

First additional simulations of the landscape for varying temperature and height arrangements

☑ Provide additional simulations of the binding landscape.



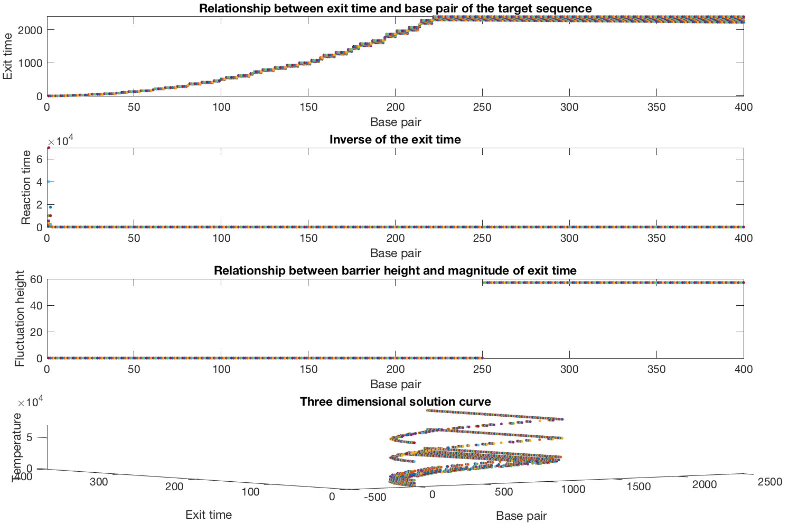
First simulation remarks



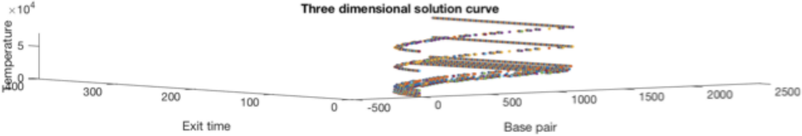
When plotted against the base pair and temperature, the approximated exit time,

- demonstrates expected numerical behavior for temperature level sets that are close to one another, in the sense that,
  - exit times from one temperature level set monotonically increase with respect to the ambient temperature of binding,
  - agrees with thermodynamic "intuition" that increasing the ambient temperature increases the exit time approximations for the target sequence,
- approaches a limiting shape in the high temperature binding phase (ie sending $T \longrightarrow \infty$),
- diverges to $-\infty$, for unit temperature of binding T otherwise.

Second additional simulation of the landscape



Second simulation remarks



In the second case, the corresponding temperature level sets for the exit times,

- exhibit more intricate behavior in the subsequences of base pairs for which the exit time monotonically vanishes and subsequently becomes negative (physically, we can interpret this as a solution to the IVP for which the barrier landscape height is not conducive for any particle flux),
- contain fewer intractable approximations for the exit time as T increases,
- demonstrate predictable qualitative behavior for increasing T.

  ☑ Motivate "good" choices of the height parameter for the barrier height fluctuation in the landscape.

Modifying the exit time fluctuation expression from the conference presentation

- Solution decomposition

$$\tau(0) \equiv \tau(n-1) + \sum_{j<n-1} \tau(j)$$

(!!!!!)

- Exit time fluctuation

$$\Delta_{n,n-1}\tau \equiv \frac{1}{k_b T}\left(n^2 - (n-1)^2 - \int_{n-1}^{n} f(v) \int_0^v f(u)\,\mathrm{d}u\,\mathrm{d}v\right).$$

☑ Reformulate exit time fluctuation expression.

With $h \equiv h_n$, $h-1 \equiv h_{n-1}$, $\mathcal{U}_1' \sim \mathcal{N}(\mu_1, \sigma_1)$, $\mathcal{U}_2' \sim \mathcal{N}(\mu_2, \sigma_2)$, $n \in \mathbf{Z}$, the expression is,

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

where,

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

$$f_{h_i}(u) = \exp\left(\frac{0.4}{k_b h_i T}\left(\frac{2}{\sqrt{\pi}} \int_0^{\frac{h_i}{0.4}(\mu_2 - u)} e^{-t^2}\mathrm{d}t\right)\right) \; ,$$

having expressed the variance in terms of the barrier height.

Reformulation steps: Obtaining boundary dependent scaling in exit time fluctuations

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

$$\cdots \int_0^v \exp\left(\frac{0.4}{T}\{\frac{1}{h}\int_0^{\frac{\mu_1-u}{\sigma_1}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_2-u}{\sigma_2}} \exp(-t^2)\mathrm{d}t\}\right) f_{h-1}(u)\mathrm{d}u - \left(\int_0^n f_h(u)\mathrm{d}u - \int_0^{n-1} f_{h-1}(u)\mathrm{d}u\right)\int_0^v \mathrm{d}v$$

$\Updownarrow$Expand the blue integral term about $h=2$

$$\Delta_{n,n-1}\tau(T,h) = n^2 - (n-1)^2 + \int_0^n \left(\int_0^v \exp\left(\frac{0.4}{T}(\frac{1}{2}\int_0^{\frac{\mu_2-u}{\sigma}} \exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_2-u}{\sigma}} \exp(-t^2)\mathrm{d}t)\right)\cdots\right.$$

$$\left. +\{\int_0^v \frac{\partial}{\partial h}\exp\left(\frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_1-u}{\sigma}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1-u}{\sigma}} \exp(-t^2)\mathrm{d}t)\right)\right)\mathrm{d}u\} h f_h(u)\mathrm{d}u - \int_0^{n-1}\cdots$$

$$\left(\int_0^v \exp\left(\frac{0.4}{T}(\frac{1}{2}\int_0^{\frac{\mu_2-u}{\sigma}} \exp(-t^2)\mathrm{d}t - \int_0^{\frac{\mu_1-u}{\sigma}} \exp(-t^2)\mathrm{d}t)\right) + \{\int_0^v \frac{\partial}{\partial h}\exp\left(\frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_2-u}{\sigma_1}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1-u}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right)\right\} h$$

$$\cdots f_{h-1}(u)\mathrm{d}u$$

$\vdots$

$\Updownarrow$

$\vdots$

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

$$= \exp\left(\frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right) - \exp\left(\frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_2}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right)$$

$$= \frac{\exp\left(\frac{0.4}{T}\left(\frac{1}{h}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t\right)\right)}{\exp\left(\frac{0.4}{T}\left(\frac{1}{h}\int_0^{\frac{\mu_2}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1}{\sigma_1}} \exp(-t^2)\mathrm{d}t\right)\right)} - 1$$

$$= \exp\left(\frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t) - \frac{0.4}{T}(\frac{1}{h}\int_0^{\frac{\mu_2}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \frac{1}{h-1}\int_0^{\frac{\mu_1}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right) - 1$$

$$= \exp\left(\frac{0.4}{T}\left(\frac{1}{h}(\int_0^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t + \int_0^{\frac{\mu_2}{\sigma_2}} \exp(-t^2)\mathrm{d}t) - \frac{1}{h-1}(\int_0^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t + \int_0^{\frac{\mu_1}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right)\right) - 1$$

$$= \exp\left(\frac{0.4}{T}\left(\frac{1}{h}(\int_{\frac{\mu_2}{\sigma_2}}^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t) - \frac{1}{h-1}(\int_{\frac{\mu_1}{\sigma_1}}^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t)\right)\right) - 1$$

Resulting formula (small typo $h-2$ instead of h)

⇕ Consolidating exponentials under the last integral

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

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

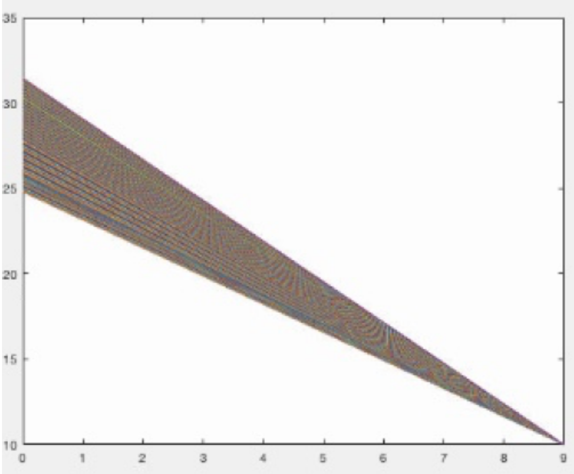
$$\left. f_h(u) + \left(\exp\left(\frac{0.4}{T}\left(\frac{1}{2}\int_{\frac{\mu_2}{\sigma_2}}^{\frac{\mu_2-v}{\sigma_2}} \exp(-t^2)\mathrm{d}t - \int_{\frac{\mu_1}{\sigma_1}}^{\frac{\mu_1-v}{\sigma_1}} \exp(-t^2)\mathrm{d}t\right)\right)-1\right)f_{h-1}(u)\right)\mathrm{d}u$$

- manageable to code from existent components - implement Trapezoidal approximation and function handle for two terms in the expansion

```
syms x
x_1 = @(x) (mu_2-x)./sigma_2;
x_2 = @(x) (mu_1-x)./sigma_1;
temp_fac = 0.4./T;
fluctuation_exp_1 = @(x) exp( temp_fac .* ((0.5.* erf(x_1(x)))-erf(x_2(x))));
syms u
val_exp_1_0 = sym(fluctuation_exp_1(0));
val_exp_1_1 = sym(fluctuation_exp_1(x./2));
val_exp_2 = sym(fluctuation_exp_1(x));

trap_exp_1 = (x./2) .* symsum(val_exp_1_0 , val_exp_1_1, val_exp_2) .* (exp((0.4./(height_2.* T)).* erf(x_1(x))));
trap_exp_2 = (x./2) .* symsum(val_exp_1_0 , val_exp_1_1 , val_exp_2) .* exp((0.4./(height_1*T)).*erf(x_2(x)));
final_handle_1 = convertCharsToStrings(trap_exp_1);
final_handle_1 =  matlabFunction(final_handle_1);
final_handle_2 = convertCharsToStrings(trap_exp_2);
final_handle_2 = matlabFunction(final_handle_2);
approx_val_1= integral(final_handle_1,0,n);
approx_val_2 = integral(final_handle_2,0,n-1);
final_res_1 = approx_val_1-approx_val_2;

syms x
syms h
second_handle_1 = @(x,h) (exp(temp_fac .*((0.5 .* (erf(x_1(x))- erf(x_1(0))) -(erf(x_2(x))- erf(x_2(0))))))-1).*(h-2) .* exp((0.4./(height
result_second_handle_1 = convertCharsToStrings(second_handle_1(x, height_2));
result_2_1= vpaintegral(result_second_handle_1,0,(n-1)+ delta);

syms x
second_handle_2 = @(x,h) (exp(temp_fac .* ((0.5 .* (erf(x_1(x)) - erf(x_1(0))) - (erf(x_2(x))-erf(x_2(0)))))) -1) .*(h-2) .* exp((0.4./(he
result_second_handle_2 = convertCharsToStrings(second_handle_2(x, height_1));
result_2_2 = vpaintegral(result_second_handle_2,0,n-1);

final_res_2 = result_2_1 + result_2_2;
```

Initial height parameter simulation: Plotting linear fluctuations of the exit time magnitude between neighboring base pairs

- Ensemble of exit time rays between subsequent base pairs



Critical point test

First order partials

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

$$= \int_0^n\int_0^v \Big\{\,\frac{\partial}{\partial h}\{f_h(u)\,\mathrm{d}u\}f_h(v)\,\mathrm{d}v\, + f_h(u)\,\mathrm{d}u\,\frac{\partial}{\partial h}\{\, f_h(v)\,\mathrm{d}v\,\}\,\Big\} - \int_0^{n-1}\int_0^v \Big\{\frac{\partial}{\partial h}\{f_{h-1}(u)\,\mathrm{d}u\,\}f_{h-1}(v)\,\mathrm{d}v + f_{h-1}(u)\,\mathrm{d}u\frac{\partial}{\partial h}\{\, f_{h-1}(v)\,\mathrm{d}v\,\}\Big\}$$

$$
= \int_0^n \int_0^v \Bigg\{ \exp\left(\frac{0.4}{hT}\left(\frac{2}{\sqrt{\pi}} \int_0^{\frac{h}{0.4}(\mu_1-u)} e^{-t^2}\,\mathrm{d}t\right)\right) \times \cdots
$$

$$
\left[-\frac{0.4}{h^2 T}\left(\frac{2}{\sqrt{\pi}} \int_0^{\frac{h}{0.4}(\mu_1-u)} e^{-t^2}\,\mathrm{d}t\right) + \cdots \right.
$$

$$
\left. \frac{0.4}{\sqrt{\pi}hT} \exp\left(- \left\{\frac{1}{T}\right\} (\mu_1 - u)^2 \right) \right] \times \cdots
$$

$$
f_h(v)\,\mathrm{d}v + f_h(u)\,\mathrm{d}u \times \exp\left(\frac{0.4}{hT}\left(\frac{2}{\sqrt{\pi}} \int_0^{\frac{h}{0.4}(\mu_1-v)} e^{-t^2}\,\mathrm{d}t \right)\right) \times \cdots
$$

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

To set $\frac{\partial}{\partial h} \equiv 0$,

- Differentiability of solutions τ in v & n,
- Similarity of the $\frac{\partial}{\partial T}$ computation with the $\frac{\partial}{\partial\ h}$ and $\frac{\partial}{\partial\ h{-}1}$ ones.

- $\Rightarrow$ The exponential is smooth in powers of u and v, and do not appear in the denominator of any expression in the solution
- $\Rightarrow$ Similarity arises from the fact that from $\frac{\partial}{\partial h}$ condition, the critical point equation is satisfied when dividing by

$$\exp\left(\frac{0.4}{hT}\left(\frac{2}{\sqrt{\pi}}\int_0^{\frac{h}{0.4}(\mu_1-u)} e^{-t^2}\,\mathrm{d}t\right)\right) f_h(n)\ ,$$

giving,

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

Future plans

- Plot relationship obtained from critical point equations to determine the magnitude of fluctuations between two subsequent base pairs,
- Obtain critical point equations for linear approximation of $\Delta_{n,n-1}\tau$,
- Solve integral equation in Matlab,
- Plot results.