Slow Dynamics in Sequence Alignment and DNA Unzipping

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1. Sequence Alignment (SA).
2. $T = 0$ and transfer matrix algorithms.
3. Finite T.
4. Dynamics and Aging.
5. Aging in the dynamics of DNA unzipping experiments.

This work: SA: E.M.; DNA: T. Hwa and E.M..

SA: T. Smith, M. Waterman, S. Karlin, S. Altschul;

SA and St. Mech.: T. Hwa, R. Bundschuh, M. Lässig, M. Muñoz.

DNA: see for example S. Cocco and R. Monasson.

Ciocco and Aachen, September 2001

Sequence Alignment

Simple model system for pattern matching ⟶ one of the most commonly used computational tools in molecular biology.

- Identification of the function of newly sequenced genes;
- Construction of phylogenic trees.

Computational biology:

compare sequences via a transfer matrix algorithm to find an optimal alignment.

"Evaluate similarity between long strings of the alphabet"

(see also: compare copies of a message sequence ruined by imperfect transmission).

Simplest problem: (local) gapless alignment.

(BLAST has a very effective code for that)

We consider an alphabet of size Λ, and 2 sequences

$$\begin{aligned}\vec{a} &= \{a_1, a_2, \cdots, a_M\} \\ \vec{b} &= \{b_1, b_2, \cdots, b_N\} \ ,\end{aligned}$$

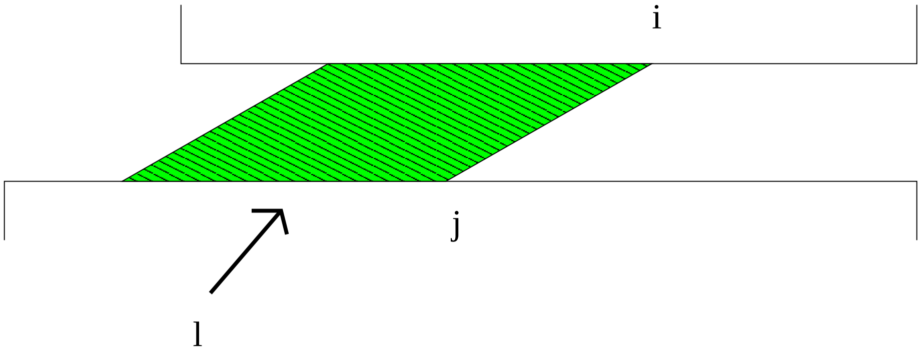
respectively of length M and N.

For example for DNA $\Lambda = 4$, alphabet $= \{A, C, G, T\}$. For proteins: twenty letters. Frequency of the letters: natural frequency of amino-acids.

A local gapless alignment of two sequences is done of two substrings of length l

$$\begin{array}{cccc} a_{i-l+1}, & \cdots, & a_{i-1}, & a_i \\ b_{j-l+i}, & \cdots, & b_{j-1}, & b_j \end{array}$$

The (gapless) alignment can be characterized by the three variables i, j and l.



In this way each alignment gets a score

$$S(i,j,l) \equiv \sum_{k=0}^{l-1} s_{a_{i-k},b_{j-k}}$$

$s_{a_{i-k},b_{j-k}}$: scoring matrix.

The typical example is the match-mismatch matrix that we have already described, with $s_{a,b}$ equal to 1 for $a=b$ and to $-\mu$ for $a \neq b$ (here the gapless case, no δ).

$$\begin{pmatrix} 1 & -\mu & -\mu & \cdots \\ -\mu & 1 & -\mu & \cdots \\ -\mu & -\mu & 1 & \cdots \\ \cdots & & & \end{pmatrix}$$

This scheme is used for DNA. Most complex schemes (Pam 20 x 20 or BLOSUM are used for proteins, accounting for many issues like for example hydrophobicity).

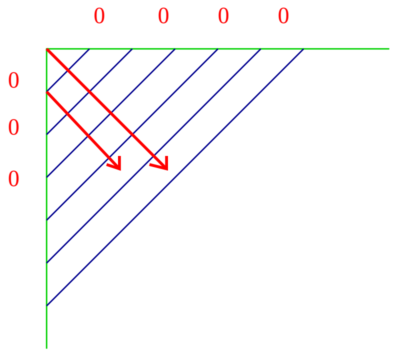
Our goal is: for a given scoring matrix we want to find the highest total score

$$\Sigma \equiv \max_{i,j,l} S(i,j,l) \; .$$

Transfer matrix algorithm: allows to compute Σ in $O(N^2)$ instead than in $O(N^3)$ steps.

$$\sigma_{i,j} = \max\left\{\sigma_{i-1,j-1} + s_{a_i,b_j}\ ,\ 0\right\}\ ,$$

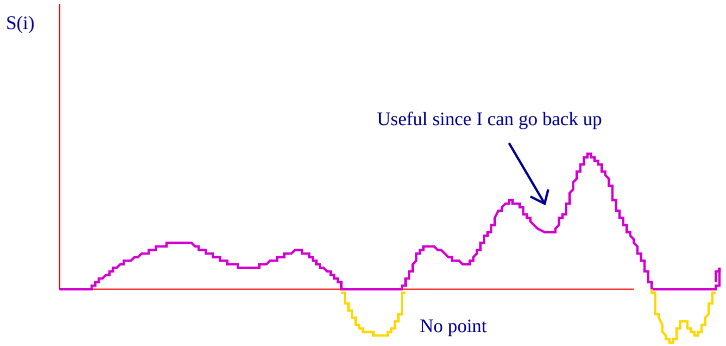
with "initial conditions" $\sigma_{0,k} = \sigma_{k,0} = 0$.



If in a given matrix site I reach a score ≤ 0 I can get a better score starting the matching from this point (i.e. matching a shorter string).

In a given site:

- optimal score zero $\Longrightarrow$ optimal l equal to zero;
- optimal score larger than zero $\Longrightarrow$ optimal l larger than zero.



Traveling on diagonal islands.

Basically: random walk with increments $s_{a,b}$, with cutoff in zero.

Optimal score:

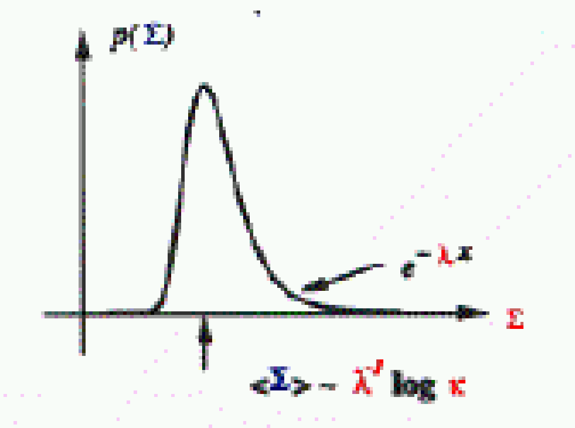
$$\boxed{\Sigma = \max_{i,j} \sigma_{i,j}}$$

To judge about the significance of a match we need to know Σ for two random sequences: we do that with same scores $s_{a,b}$ and using the observed frequencies p_a.

It has been derived rigorously (Karlin-Dembo, Karlin-Altschul) that for suitable scoring parameters

$$\boxed{P\left\{\Sigma < S\right\} = e^{-K e^{-\lambda S}}}$$

Gumbel extreme value distribution.



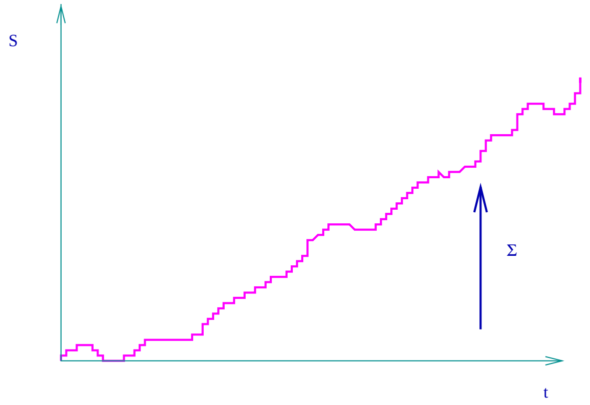
Parameters λ and K. λ: tail. K: $\langle\Sigma\rangle = \frac{1}{\lambda} \log K$.

A simple starting point and approximation: random sequences. Take $i = j$ without loss of generality (all diagonals are born equal...):
$S_{i,j} \to S_{i,i} \to S(t)$; $s(a,b) \to s(t)$; ($s(t) = 1$ with probability p and $-\mu$).

$$\begin{aligned} \sigma(t) &= \max\{S(t) + s(t), 0\} \\ \Sigma &= \max_t \sigma(t) \end{aligned}$$

This is a random walk with lower boundary. There are two phases.

$\langle s \rangle > 0 \Longrightarrow S(t)$ will increase in average (after a while the zero option becomes immaterial).

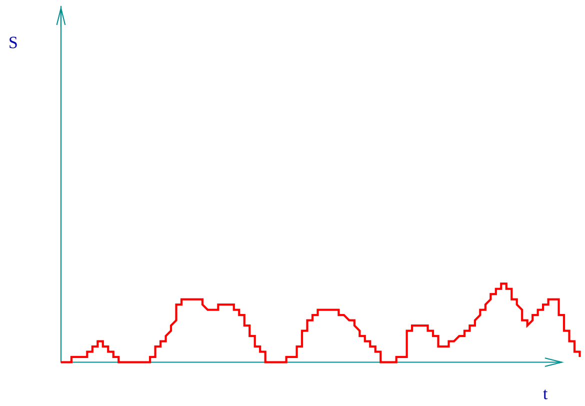


$$\langle \Sigma \rangle \simeq N \langle s \rangle$$

linear phase of local alignment.

- No match of subsequences (always match it all).
- Σ is distributed as a Gaussian random variable (central limit): not extreme valued distribution.

If $\langle s \rangle < 0$ it is all different. Now the cutoff at zero is crucial: it always comes back to play a role, even for very large sequences.



When $S(t) > 0$: random walk with independent increments. Typically it comes back to zero, since $\langle s \rangle < 0$ means a negative drift.

Large number of islands, statistically independent. Sea: part with $S(t) = 0$.

Distribution of island peak scores σ_k for continuous time and Gaussian $s(t)$ is asymptotically Poisson:
$P(\sigma_k > \sigma) \simeq Ae^{-\lambda\sigma}$

λ: typical scale of the maximal island score.

The global optimal score Σ. Take $K = \frac{N}{\langle l \rangle}$ islands.
$\Sigma = \max_k \{\sigma_k\}$ (that will turn out to be extreme valued).

$P(\Sigma < S) =\simeq e^{-\mathcal{K}e^{-\lambda S}}$

Gumbel distribution: theory of extremal statistics.
Bouchaud and Mézard work about connection of RSB in Derrida REM model and Gumbel.

Now we know a lot about the best alignment.

But what about good alignments?

Excited states ⟶ finite T problem.

Basically: count score of all islands, and weight

$$\sum_k e^{-\beta E_k}$$

For example (Y-K Yu) T=0 Needleman-Wunsch transfer matrix algorithm:

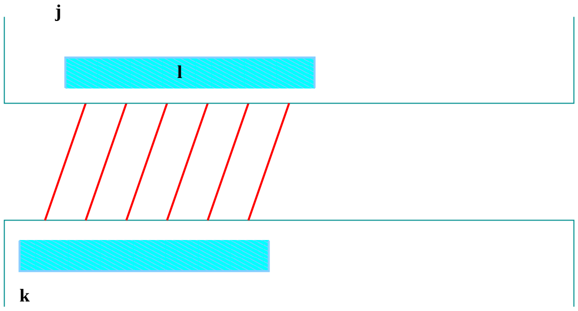
$$h(r,t+1) = \max \begin{cases} h(r,t-1) & + \quad s(r,t) \\ h(r+1,t) & - \quad \delta \\ h(r-1,t) & - \quad \delta \end{cases}$$

becomes at $T \neq 0$

$$W(r,t+1) = e^{-\beta\delta}\left(W(r+1,t) + W(r-1,t)\right) \\ + e^{-\beta s(r,t)} W(r,t)$$

finite T generalization of NW-TM.

We introduce a local dynamics. Situation is very simple for the local gapless case. We can describe the configuration with three variables: j, k, l.



Now we propose the basic moves:

$$j \to \left\{ \begin{array}{c} j+1 \\ j-1 \end{array} \right. \; ; \; k \to \left\{ \begin{array}{c} k+1 \\ k-1 \end{array} \right. \; ; \; l \to \left\{ \begin{array}{c} l+1 \\ l-1 \end{array} \right.$$

it the matching does not pass the boundary and if the length does not become smaller than zero. Energy is defined as $E = -\sum_{a=j,j+l} \sum_{b=k,k+l} s_{a,b}$

Boltzmann: $P(C) \simeq e^{-\beta E(C)}$, $\beta = \frac{1}{T}$. Use simple Metropolis algorithm. Thermal histories and annealing.

Annealing: start from high T; reduce T; compute observables for different T values: for example average score and best score found (typical of annealing optimization).

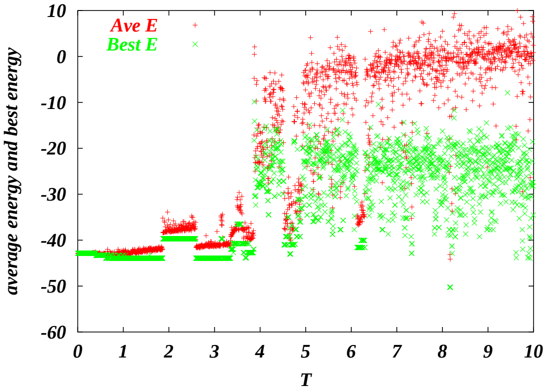
High complexity. Traps. Hints for slow dynamics.

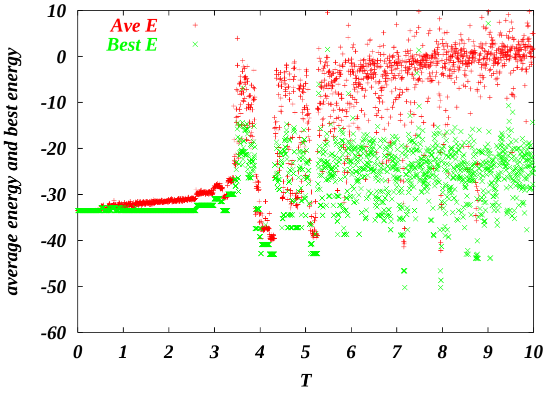
For the gaped case introduce “gap” variables, $\Gamma_i = 0$ if site i is gaped, 0 if it is connected. Same kind of results.

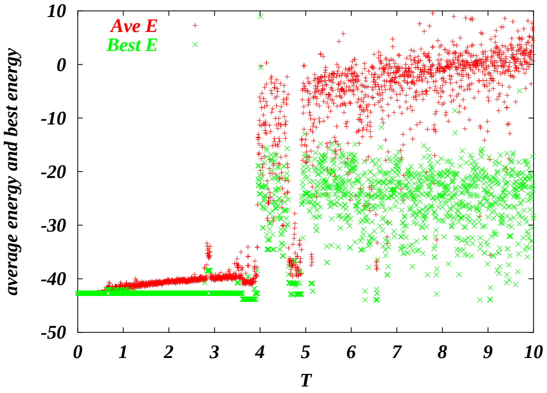
Gapless local alignment.

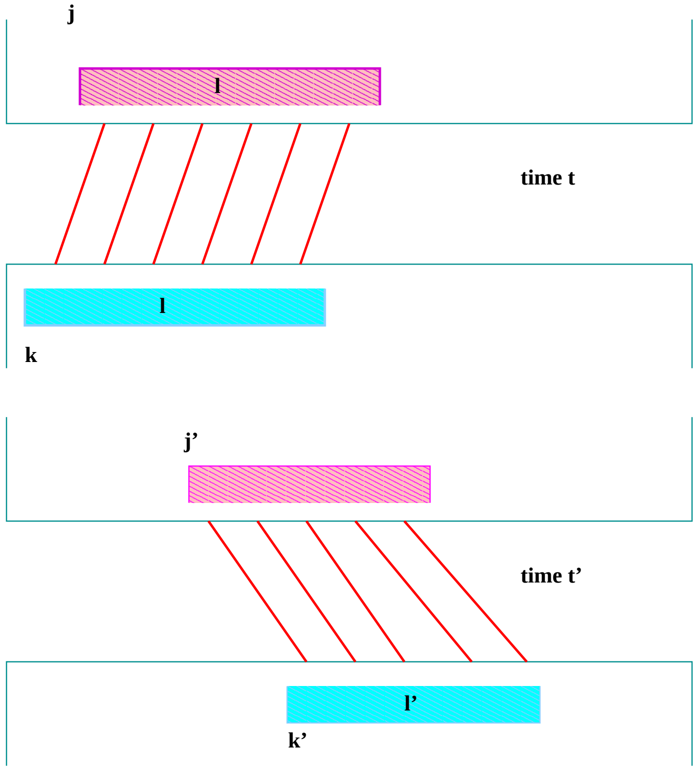
Here random quenched score matrix. 4 letter alphabet. -51 is the true ground state energy (computed via the transfer matrix method).

Note traps. In the last run the GS is not found.









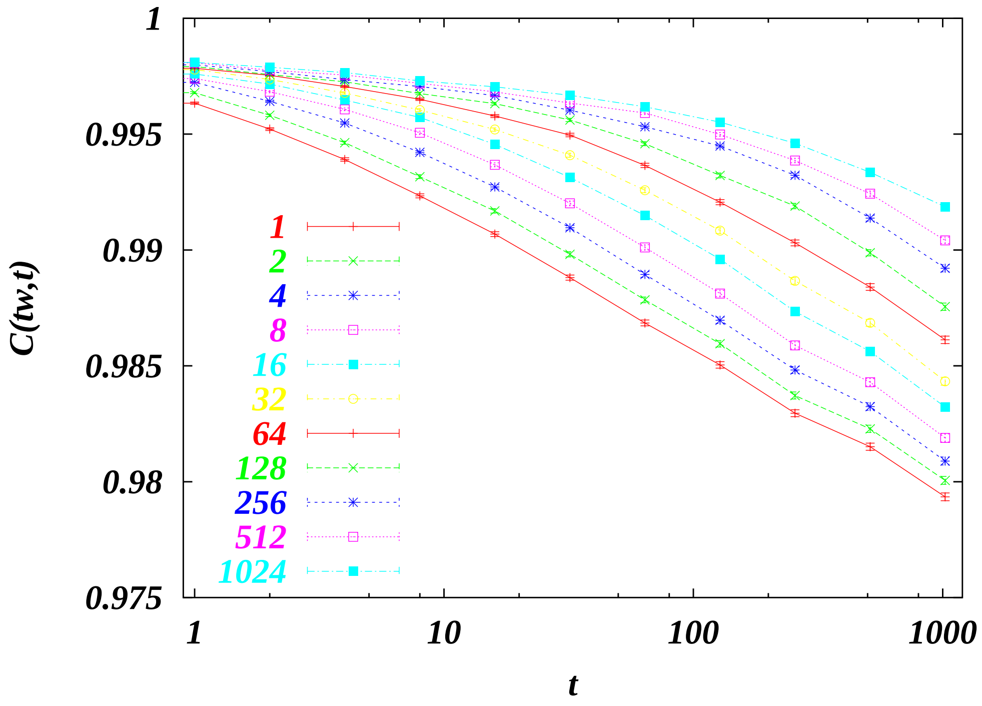
Compare the matched part of the sequence $a(t)$ at time t with the matched part of $a(t')$ at time t' and $b(t)$ at time t with the matched part of $b(t')$ at time t' (two separate correlation functions).

$\eta_i^{(a)}(t) = 0, 1$, $i = 1, \cdots N$, 0 if not matched, 1 if matched.

$\sigma_i \equiv 1 - 2\ \eta_i = \pm 1$, and

$$\sum\nolimits_i \sigma_i(t)\sigma_i(t')$$
$$= \sum\nolimits_i \left(1 - 2\ \eta_i(t) - 2\ \eta_i(t') + 4\ \eta_i(t)\eta_i(t')\right)$$
$$= N - 2\ l(t) - 2\ l(t') + 4\ \sum\nolimits_i \eta_i(t)\eta_i(t')$$

Very clear aging. No time translation invariance.



Two regimes. First decay for local wandering (stay inside a valley). Second decay region determined by length change.

A second issue, with in mind DNA unzipping experiments.

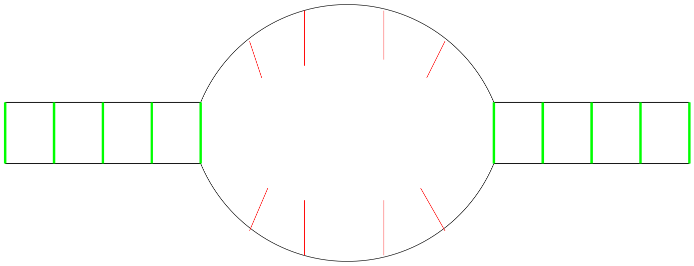
Piece of double stranded DNA: N base pairs.

A denaturation bubble is forced into the double strand

due to, say,

an applied external torque.

Single bubble approximation.



Bubble from i to j has energy:

$$E(i,j) = \sum_{k=1}^{j} \epsilon_k$$

$$Z = \sum_{1<i<j\leq N} e^{-E(i,j)/(RT)}$$

Again, finite T, Smith-Waterman: $\zeta_k \equiv \exp(-\epsilon_k)/(RT)$, $Z(j) = \zeta_j\,[1 + Z(j-1)]$, initial condition $Z(2) = \zeta_2$.

$$Z = \sum Z(j)$$

$E(i,j)$ is the energy of a bubble starting at base i and ending at base j.

Fictious point particle in $2d$:

$\hat{x}$: final site of the bubble.

$\hat{y}$: initial site of the bubble.

Valleys: energy landscape.

Distribution of valleys if depth $\mathcal{E}$:

$$\mathrm{Prob}\,(\mathcal{E} > x) \simeq K e^{-\lambda x} \text{ for large x} \; .$$

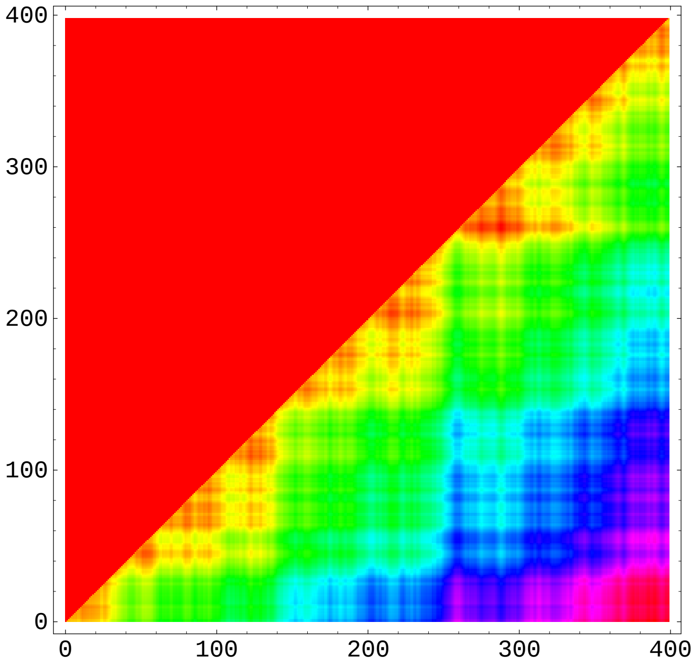
$$\left(\lambda | \sum e^{\lambda \epsilon_{a,b}} p_a p_b = 1 \text{ etcetera} \right)$$

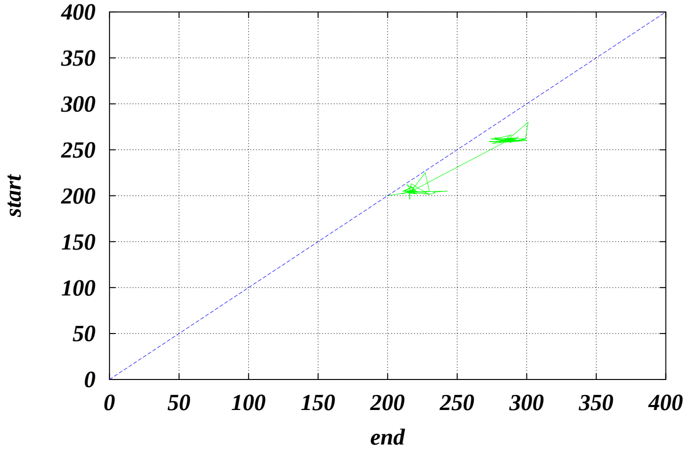
Use experimental cost parameters.

$T \simeq T_{AT}$ (energy valleys are small and shallow).

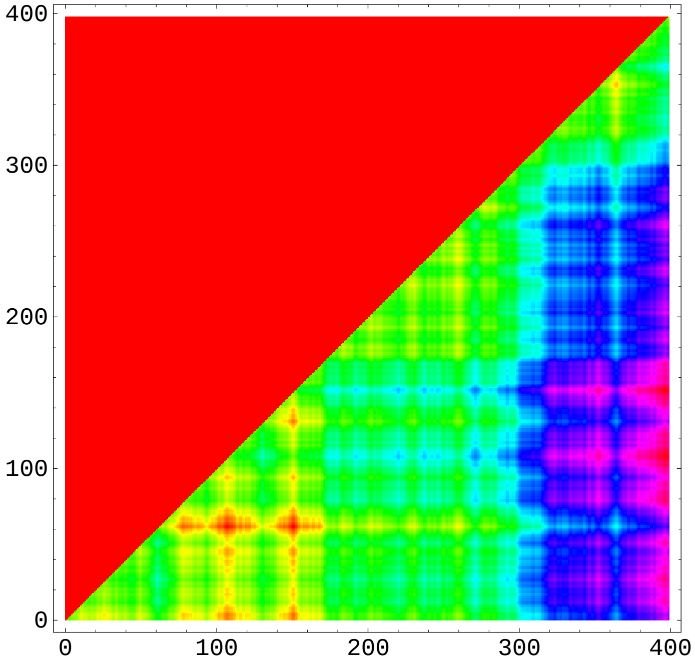
$T \to T_{GC}$ (valleys become broad and eventually extend through all system).

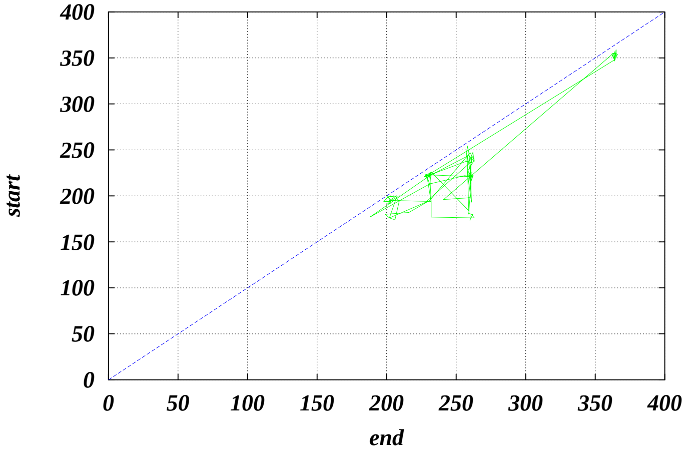
A first sample. Hue coloring. Finds two valleys, among many.





A second sample. Completely mislead...





Stacking energy

$$\epsilon(b,b') = \Delta H(b,b') - T\Delta S(b,b')$$

enthalpic contribution and entropic contribution.

Effective melting temperature

$$T(b,b') \equiv \frac{\Delta H(b,b')}{\Delta S(b,b')}$$

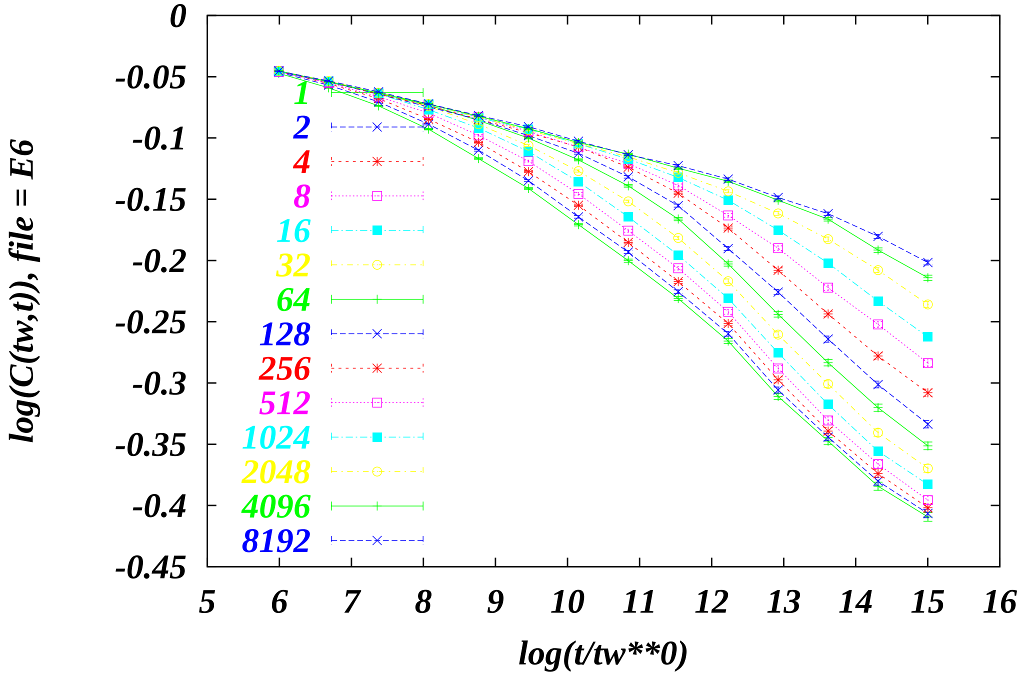
ranges from $80^o C$ for AT pairs to $125^o C$ in 1 M Na^+ concentration. $37^o C$: ϵ goes from $1 kcal/mole$ for AT pairs to $2 kcal/mole$ for GC pairs.

In the energy there is also a loop entropy term:

$$\sigma(l) \simeq s_0 T + 1.8 RT \log(l)$$

The logarithmic term is negligible for loops under 50 base pairs, so we neglect it here. The constant term implies bubble is at least 10 basis. Insert this constraint in the numerical simulation: things do not change. Single bubble picture looks reasonable and interesting.

Again, very clear aging. No time translation invariance.



Again two clear regimes.