The Role of Convex Optimization in Optimal Alignments of Random Sequences

Convex Optimization and Beyond

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Why Study Sequence Alignments?

- Where does a finite sequence fit best in a larger finite sequence?

$$gattggatcctagccctgagagatttccccccctaggaaaatttcat\ldots$$
$$\leftarrow actg \rightarrow$$

- What finite sequence among a finite choice of candidates is a best fit for a given new sequence?

$$0100011 \stackrel{?}{\rightarrow} \begin{cases} 0100001110101 \\ 11010110 \\ 111111011111 \end{cases}$$

How to Align Sequences?

$$\begin{array}{cccccccc} b & g & \star & h & o & u & s & e \\ b & i & g & \star & h & o & s & e \end{array}$$

$$\begin{array}{cccccccc} b & \sqcup & g & \star & h & o & u & s & e \\ b & i & g & \star & h & o & \sqcup & s & e \end{array}$$

- Allow the introduction of gaps subject to a penalty.
- Assign a similarity score to each pair of aligned letters.
- Maximise total score over the set of possible alignments.

To align $x_1x_2x_3 \in \mathcal{A}^3$ with $y_1y_2y_3y_4 \in \mathcal{A}^4$:

- Fix a scoring function $s : \mathcal{A}^* \times \mathcal{A}^* \to \mathbb{R}$.

- E.g., for the alignment

$$\pi : \begin{matrix} \mathfrak{G} & x_1 & x_2 & x_3 & \mathfrak{G} \\ y_1 & y_2 & \mathfrak{G} & y_3 & y_4 \end{matrix}$$

  with gaps $\mathfrak{G}$, define the total alignment score by

$$S_\pi(x, y) = s(\mathfrak{G}, y_1) + s(x_1, y_2) + s(x_2, \mathfrak{G}) + s(x_3, y_3) + s(\mathfrak{G}, y_4).$$

- To find an optimal alignment, solve

$$L_s(x, y) = \max_\pi S_\pi(x, y),$$
$$\pi^* = \arg\max_\pi S_\pi(x, y)$$

Example 1. LCS scoring function

$$
\begin{aligned}
s(\mathfrak{a}, \mathfrak{b}) &= -1 \quad \text{if } \mathfrak{a} \neq \mathfrak{b}, \\
s(\mathfrak{a}, \mathfrak{a}) &= 1 \quad \forall\, \mathfrak{a} \in \mathcal{A}, \\
s(\mathfrak{G}, \mathfrak{a}) &= s(\mathfrak{a}, \mathfrak{G}) = 0 \quad \forall\, \mathfrak{a} \in \mathcal{A}.
\end{aligned}
$$

- $L_s(x, y)$ is the length of a longest common subsequence of x and y.

- π^* identifies a longest common subsequence by dropping letters aligned with a gap in both sequences.

Example 2. BLASTZ scoring function for $\mathcal{A} = \{A, T, C, G\}$:

	A	T	C	G	$\mathfrak{G}$
A	91	-31	-114	-123	-400
T	-31	100	-125	-114	-400
C	-114	-125	100	-31	-400
G	-123	-114	-31	91	-400
$\mathfrak{G}$	-400	-400	-400	-400	$-\infty$

- $s(\mathfrak{a}, \mathfrak{b})$ represents log-likelihood that $\mathfrak{a}$ evolved into $\mathfrak{b}$ under a stochastic evolutionary model.

- $L_s(x, y)$ yields the maximum log-likelihood that x and y arose from a common ancestor via mutation, and the most likely microstructure of the mutations is exhibited by π^*.

- In reality, the log-likelihood depends on the time since evolutionary divergence.

Algorithm 1 (Dynamic Programming)**.**

1. $L_s(\emptyset, \emptyset) = 0$

   for $i, j \geq 1$

   $L_s(x_{[1,i]}, \emptyset) = \sum_{\ell=1}^{i} s(x_\ell, \mathfrak{G})$

   $L_s(\emptyset, y_{[1,j]}) = \sum_{\ell=1}^{j} s(\mathfrak{G}, y_\ell)$

   end

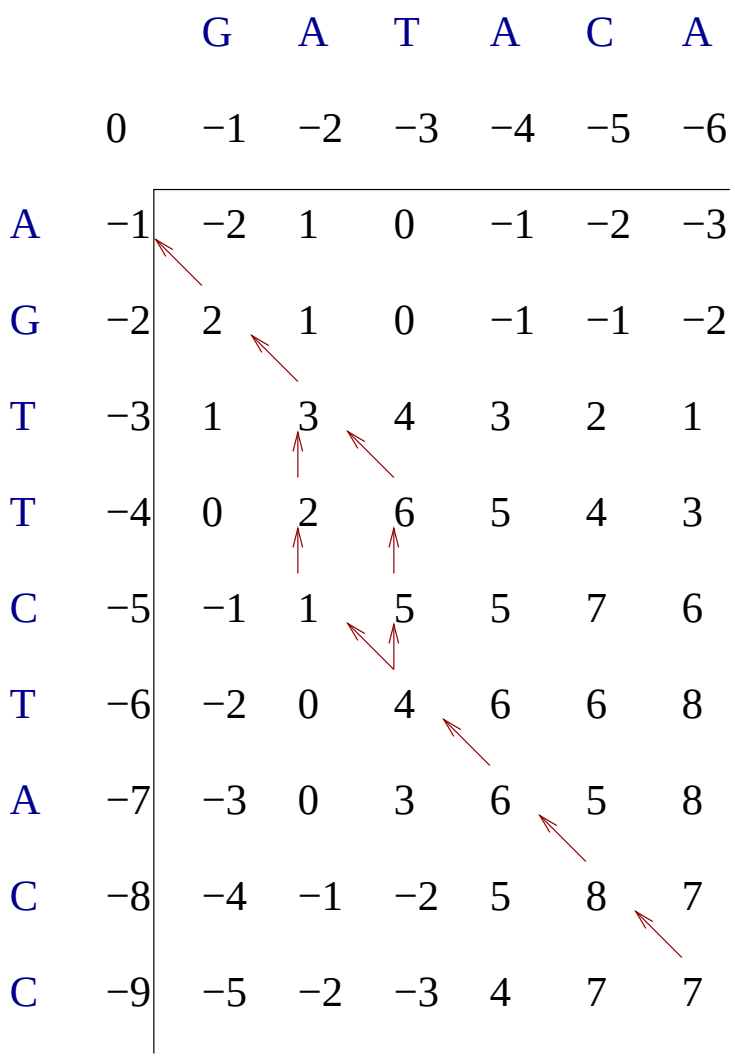
2. for $i = 1, \ldots \text{length}(x)$

   for $j = 1, \ldots \text{length}(y)$

   $$L_s(x_{[1,i]}, y_{[1,j]}) = \max\big(s(x_i, y_j) + L_s(x_{[1,i-1]}, y_{[1,j-1]}),$$
   $$s(x_i, \mathfrak{G}) + L_s(x_{[1,i-1]}, y_{[1,j]}), s(\mathfrak{G}, y_j) + L_s(x_{[1,i]}, y_{[1,j-1]})\big)$$

   end

   end


G A T A C A
0 −1 −2 −3 −4 −5 −6
A −1 −2 1 0 −1 −2 −3
G −2 2 1 0 −1 −1 −2
T −3 1 3 4 3 2 1
T −4 0 2 6 5 4 3
C −5 −1 1 5 5 7 6
T −6 −2 0 4 6 6 8
A −7 −3 0 3 6 5 8
C −8 −4 −1 −2 5 8 7
C −9 −5 −2 −3 4 7 7

Understanding the Null-Model

To decide on the significance of high scores, compare with scores achieved by random sequences

$$L_{m,n}(s) = L_s(X_{[1,m]}, Y_{[1,n]}) = L_s(X_1 X_2 \dots X_m\,,\, Y_1 \dots Y_n).$$

with i.i.d. letters $X_i, Y_j : \Omega \to \mathcal{A}$.

When $m = n$ we write $L_n(s) = L_{m,n}(s)$.

Our understanding of this null-model is still incomplete.

Three broad themes with analogue questions in percolation theory:

- Determine the Chvàtal-Sankoff constant

$$\lambda(s,\xi) = \lim_{n\to\infty} \lambda_n(s,\xi)$$

  where $\xi \in [0,1]$ is fixed and

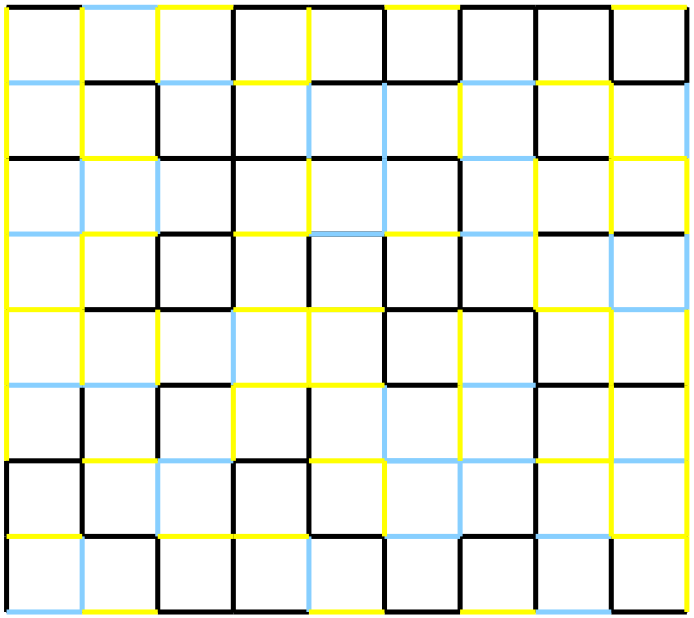
$$\lambda_n(s,\xi) = \frac{1}{n}\,\mathsf{E}\left[L_{\lfloor 2n\xi\rfloor,\lfloor 2n(1-\xi)\rfloor}(s)\right].$$

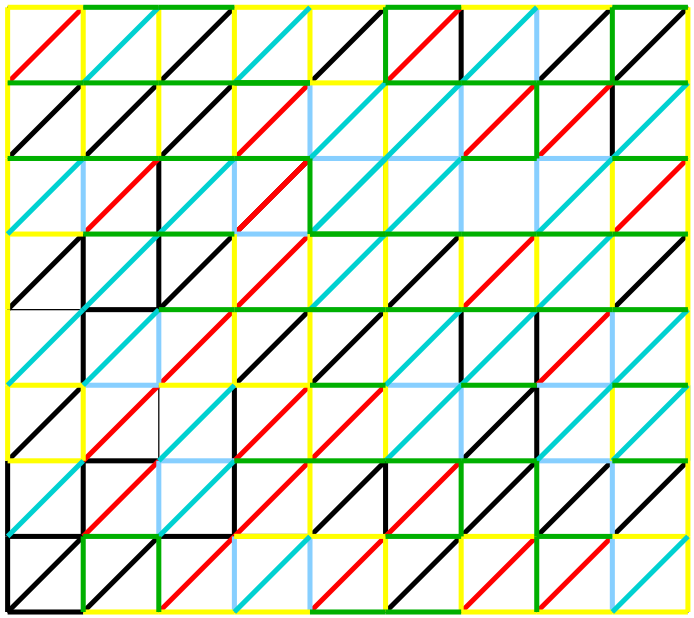
  We write $\lambda(s) = \lambda(s,1/2)$, $\lambda_n(s) = \lambda_n(s,1/2)$, and $(\xi_1,\xi_2) = (\xi, 1-\xi)$.

- Determine the fluctuation order

$$\mathsf{STD}\left(L_{\lfloor 2n\xi_1\rfloor,\lfloor 2n\xi_2\rfloor}(s)\right).$$

- Understand the microstructure of optimal alignments.





The Chvàtal-Sankoff Constant

- Subadditivity yields $\lambda_n(s) \nearrow \lambda(s)$ and in fact, $L_n(s)/n \to \lambda(s)$ almost surely.

- However, the convergence is very slow

$$\sqrt{2}\|s\|_\delta \frac{\sqrt{\ln n}}{\sqrt{n}} + \frac{2\|s\|_\infty}{n} \leq \lambda(s) - \lambda_n(s) \leq C\frac{\sqrt{\ln n}}{\sqrt{n}},$$

  where

$$\|s\|_\delta = \max_{\mathfrak{c},\mathfrak{d},\mathfrak{e}\in\mathcal{A}^*} |s(\mathfrak{c},\mathfrak{d}) - s(\mathfrak{c},\mathfrak{e})|\,,$$
$$\|s\|_\infty = \max_{\mathfrak{c},\mathfrak{d}\in\mathcal{A}^*} |s(\mathfrak{c},\mathfrak{d})|\,.$$

- Upper bound due to K. Alexander ["The rate of convergence of the mean length of the longest common subsequence." Ann. Appl. Prob. 4(4):1074–1082, 1994].

Example 3. For the LCS-scoring function, we have

$$\|s\|_\infty = 1,$$
$$\|s\|_\delta = 2.$$

- To obtain $|\lambda(s) - \lambda_n(s)| \leq 1\,\mathrm{e}\,{-2}$, we would need

$$n \approx 1.8\,\mathrm{e}\,6.$$

- To obtain $|\lambda(s) - \lambda_n(s)| \leq 1e - 3$, we would need

$$n \approx 2.4\,\mathrm{e}\,8$$

- The computational cost is $\mathrm{O}(n^2)$.

Accelerated Montecarlo Simulation for LCS

Parse sequences into pieces with known LCS,

$$\star\star\star\star\star\circ\circ\circ\star\star\star\star\circ\circ\circ\circ\circ\circ\circ\circ\circ\circ\circ\ldots$$
$$\star\star\star\star\circ\circ\circ\circ\circ\star\star\star\star\star\star\star\circ\circ\ldots$$

Two sequences $x^1 = x^1_1 \ldots x^1_{n_1}$, $x^2 = x^2_1 \ldots x^2_{n_2}$ are an m-match if

$$\begin{aligned} &L_s(x^1, x^2) = m, \\ &L_s(x^1_{[1,n_1-1]}, x^2) = m-1, \\ &L_s(x^1, x^2_{[1,n_2-1]}) = m-1, \end{aligned}$$

that is, removing the last character of any of the sequences reduces the LCS-score.

Lemma 2. *$L_n(\xi) \geq qn$ can only occur if*

$$\begin{bmatrix} x_1^1 \dots x_{\lfloor 2n\xi_1 \rfloor}^1 \\ x_1^r \dots x_{\lfloor 2n\xi_2 \rfloor}^2 \end{bmatrix} = \begin{bmatrix} x_1^1 \dots x_{\varsigma^1(m)}^1 \\ x_1^2 \dots x_{\varsigma^2(m)}^2 \end{bmatrix} \circ \dots \circ \begin{bmatrix} x_{\varsigma^1((k-1)m)+1}^1 \cdots x_{\varsigma^1(km)}^1 \\ x_{\varsigma^2((k-1)m)+1}^2 \cdots x_{\varsigma^2(km)}^2 \end{bmatrix} \circ \begin{bmatrix} \dots \\ \vdots \\ \dots \end{bmatrix}$$

is a concatenation of $k := \lfloor qn/m \rfloor$ m-matches and a remainder.

Corollary 3.

$$\mathsf{P}[L_n(\xi) \geq nq] \leq \left(\nu^{m,2}\right)^{*k} ([nq, \lfloor 2n\xi_1 \rfloor] \times [nq, \lfloor 2n\xi_2 \rfloor]) \,,$$

where $\left(\nu^{m,2}\right)^{*k}$ *is the* k*-fold convolution of the measure* $\nu^{m,2}$ *defined on* $\mathbb{N}^2$ *by*

$$\nu^{m,2}(i_1, i_2) := \mathsf{P}\left[(X_1^1 \ldots X_{i_1}^1 \,,\, X_1^2 \ldots X_{i_2}^2) \;\; \textit{is a } m\textit{-match}\right].$$

Let $B := \left[m \,,\, 2m\xi_1/q\right] \times \left[m \,,\, 2m\xi_2/q\right]$, so that

$$kB \approx [nq, \lfloor 2n\xi_1 \rfloor] \times [nq, \lfloor 2n\xi_2 \rfloor].$$

Theorem 4. *The following are equivalent,*

i) $\lambda(s,\xi) \le q$,

ii) $\limsup_{k\to\infty}\Big((\nu^{m,2})^{*k}(kB)\Big)^{1/k} < 1$,

iii) $\inf\Big\{\Lambda^{m,2}(x) - \frac{2m}{q}\langle\xi,x\rangle : \ x\in\mathbb{R}^2_-\Big\} \ < \ 0$, *where*

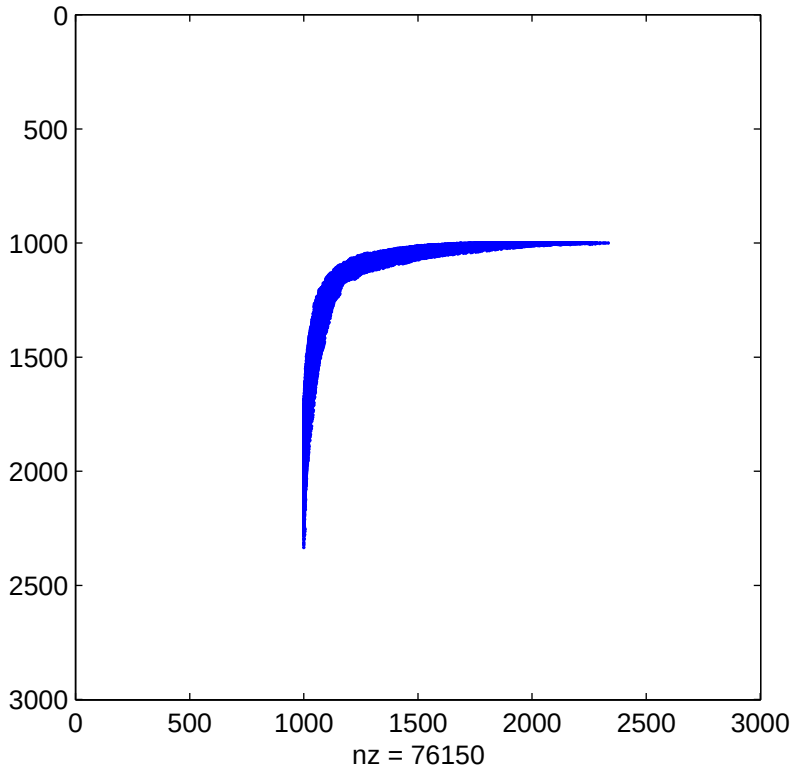
$$\Lambda^{m,2}(x) := \log\int_{\mathbb{R}^2}\nu^{m,2}(y)\,\mathrm{e}^{\langle y,x\rangle}\,dy$$

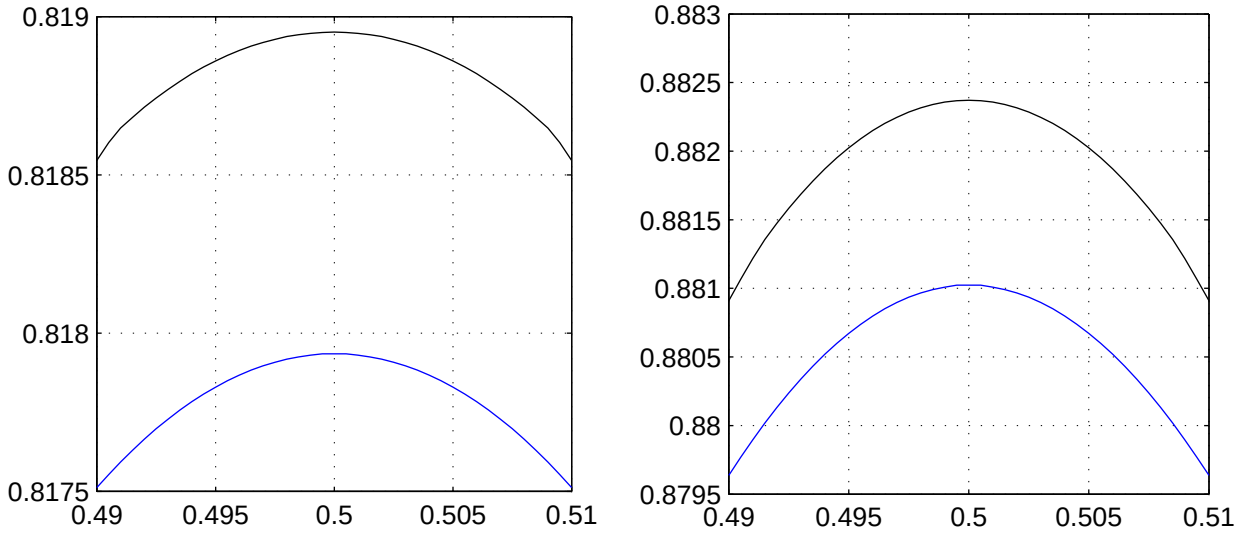
is the log-Laplace transform of $\nu^{m,2}$.

Example 4 (Durringer-H.-Matzinger, 2008)**.**

- Experiment 1: $\mathcal{A} = \{0, 1\}$, $P[X_i = 0] = 1/2$, $m = 1,000$.
- Experiment 2: $\mathcal{A} = \{0, 1\}$, $P[X_i = 0] = 0.2$, $m = 1,000$.
- Confidence level 95%.
- m and the confidence level were chosen such that computational cost equals a single simulation of $L_n(s)$ with $n = 1\,\mathrm{e}\,5$.

Experiment 2: Sparsity pattern of $\widehat{\nu}$ after $10,000$ simulations.





Estimated confidence intervals for $\lambda(s, \xi)$ show that the achieved accuracy is approximately $2\,\mathrm{e}\,{-3}$.

This corresponds to a 300'000-fold (!!) reduction in flops in comparison to brute-force simulation, which would require $n \approx 5.4\,\mathrm{e}\,7$ to achieve the same accuracy.

Steele conjecture [M.J. Steele. "An Effron-Stein inequality for non-symmetric statistics." Ann. Stat., 14: 753-758, 1958]: For LCS with i.i.d. U($\mathcal{A}$)-distributed variables X_i, Y_j,

$$\lambda(s, 0.5) = \frac{2}{1 + \sqrt{|\mathcal{A}|}}.$$

But e.g. for $|\mathcal{A}| = 2$,

$$\frac{2}{1 + \sqrt{|\mathcal{A}|}} = 0.8284 > 0.8182,$$

so with high confidence the Steele conjecture is wrong [H.-Martinez-Matzinger, 2006].

The Order of Fluctuations

Let $X = X_1 \dots X_n$, $Y = Y_1 \dots Y_n$ with i.i.d. Ber(p) letters.

- Chvàtal-Sankoff ["Longest common subsequence of two random sequences", J. Appl. Prob., 12:306–315, 1975] conjectured that in the case $p = 1/2$,

$$\mathrm{VAR}(L_n(s)) = \mathrm{o}\left(n^{2/3}\right).$$

- Steele ["An Effron-Stein inequality for non-symmetric statistics", Ann. Stat. 14:753–758, 1986] proved

$$\mathrm{VAR}(L_n(s)) \leq 2p(1-p)n.$$

- Waterman ["Estimating statistical significance in sequence alignment", Phil. Trans. R. Soc. Lond. B, 344:383-390, 1994] reports simulations that suggest that for $p < 0.5$,

$$\mathrm{VAR}(L_n(s)) = \Theta(n).$$

- Boutet de Monvel ["Extensive simulations for longest common subsequences." Eur. Phys. J. B, 7:293–308, 1999] reports simulations that suggest taht for $p = 0.5$,

$$\mathrm{VAR}(L_n(s)) = \Theta(n).$$

More recently, H.-Matzinger [2005], Lember-Matzinger [2009], Amsalu-H.-Matzinger [2012] showed that if

$$\mathsf{E}\left[L_s(\tilde{X}_{[1,n]}, \tilde{Y}_{[1,n]}) - L_s(X_{[1,n]}, Y_{[1,n]}) \,\|\, X, Y\right] \geq c$$

holds with probability $1 - \mathsf{O}(n^{-\alpha n})$, then $\mathsf{VAR}(L_n(s)) = \Theta(n)$.

- True for arbitrary scoring function s, alphabet $\mathcal{A}$, and distribution of X_i, Y_i.

- $\tilde{X}, \tilde{Y}$ obtained by selecting one letter of a specified type $\mathfrak{a}$ uniformly at random from the realised letters $X(\omega), Y(\omega)$ and changing it into a specified other type $\mathfrak{b}$.

- Bias analytically provable only in highly assymetric cases.

- Deeply connected with the problem of understanding the microstructure of optimal alignments.

- Basic tool used is Azuma-Hoeffding Inequality in the form given by McDiarmid ["On the method of bounded differences." Surveys in Combinatorics, 141:148–188, 1989]:

Theorem 5. *Let $Z_1, Z_1, \ldots, Z_m$ be i.i.d. random variables that take values in a set D, and let $g : D^m \to \mathbb{R}$ be a function of m variables with the property that*

$$\max_{i=1,\ldots,m} \sup_{z \in D^m, \widehat{z}_i \in D} |g(z_1, \ldots, z_m) - g(z_1, \ldots, \widehat{z}_i, \ldots, z_m)| \leq C.$$

Thus, changing a single argument of g changes its image by less than a constant C. Then the following bounds hold,

$$\mathsf{P}\left[g(Z_1, \ldots, Z_m) - \mathsf{E}[g(Z_1, \ldots, Z_m)] \geq \epsilon \times m\right] \leq \exp\left\{-\frac{2\epsilon^2 m}{C^2}\right\},$$

$$\mathsf{P}\left[\mathsf{E}\left[g(Z_1, \ldots, Z_m)\right] - g(Z_1, \ldots, Z_m) \geq \epsilon \times m\right] \leq \exp\left\{-\frac{2\epsilon^2 m}{C^2}\right\}.$$

Alignment Microstructure

Let π be an alignment with gaps of two sequences x, y of equal length n, and let

$$p_{\mathfrak{c},\mathfrak{d}} = \frac{\sharp \text{ pairs } (\mathfrak{c},\mathfrak{d}) \text{ aligned under } \pi}{n}.$$

Collecting these ratios in a vector $\vec{p}_\pi(x, y)$ for all pairs $(\mathfrak{c}, \mathfrak{d})$ we obtain the *empirical distribution of aligned letter pairs*.

The alignment score is a collapsed version of the information contained in the vector $\vec{p}_\pi$,

$$S(x, y) = n \sum_{(\mathfrak{a},\mathfrak{b})\in(\mathcal{A}^*)^2} p_{\mathfrak{a},\mathfrak{b}}\, s(\mathfrak{a}, \mathfrak{b}) = n\langle s, \vec{p}_\pi\rangle.$$

Example 5. For π given by

x	$\mathfrak{a}$	$\mathfrak{a}$	$\mathfrak{b}$		$\mathfrak{b}$
y	$\mathfrak{a}$		$\mathfrak{b}$	$\mathfrak{a}$	$\mathfrak{b}$,

we find

$$\begin{aligned}\vec{p}_\pi(x,y) &= (p_{\mathfrak{aa}}, p_{\mathfrak{ab}}, p_{\mathfrak{a}\mathfrak{G}}, p_{\mathfrak{ba}}, p_{\mathfrak{bb}}, p_{\mathfrak{b}\mathfrak{G}}, p_{\mathfrak{G}\mathfrak{a}}, p_{\mathfrak{G}\mathfrak{b}}) \\ &= (0.25, 0, 0.25, 0, 0.5, 0, 0.25, 0).\end{aligned}$$

Now let $X_1 X_2 \ldots$ and $Y_1 Y_2 \ldots$ be random sequences with i.i.d. random letters

$$X_i, Y_i : \Omega \to \mathcal{A}$$

with some given distribution, and let $\Pi_n^*(s)$ be an optimal alignment of $X_{[1,n]}$ and $Y_{[1,n]}$ under the scoring function s,

$$\Pi_n^*(s) = \arg\max_{\pi} S_\pi(X_{[1,n]}, Y_{[1,n]}).$$

Note that since the sequences $X_1 \ldots X_n$ and $Y_1 \ldots Y_n$ are random, $\Pi_n^*(s)$ is random, and furthermore, its choice is generally nonunique.

The associated empirical distribution $\vec{p}_{\Pi_n^*(s)}$ is thus a random vector

$$\vec{p}_{\Pi_n^*(s)} : \Omega \to \mathbb{R}_+^{|(\mathcal{A}^*)^2|}.$$

Theorem 6. *For almost all scoring functions s, the empirical distribution $\vec{p}_{\Pi_n^*(s)}$ converges almost surely to a unique point*

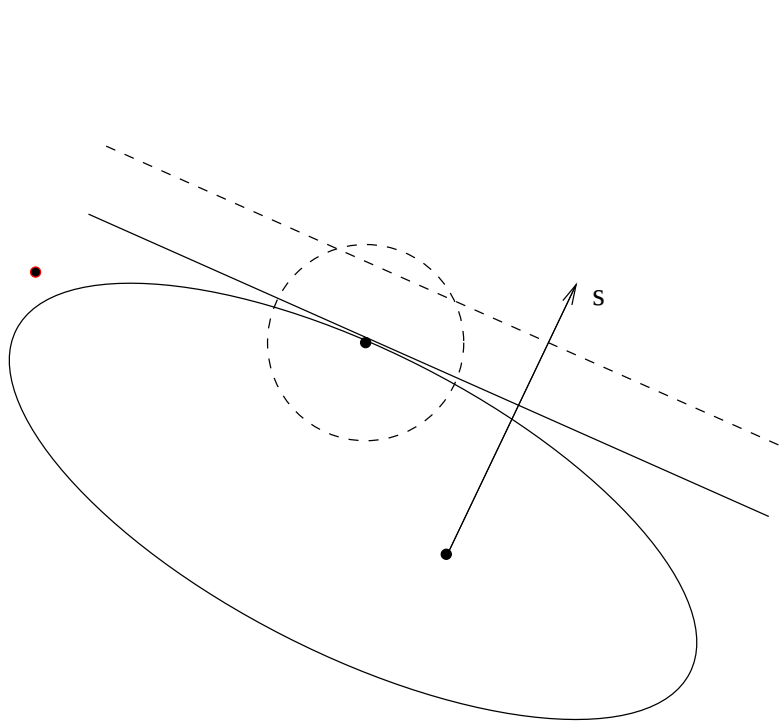
$$\vec{p}_s \in \mathbb{R}_+^{|(\mathcal{A}^*)^2|}.$$

- In fact,

$$\mathsf{P}\left[\|\vec{p}_{\Pi_n^*(s)} - \vec{p}_s\| \leq \varepsilon \text{ for all choices of } \Pi_n^*(s)\right] \geq 1 - \mathrm{e}^{-K_\varepsilon n}.$$

- The asymptotic frequencies of the alignment microstructure are thus well defined.

- This allows for the design of more powerful statistical tests on the relatedness of sequences.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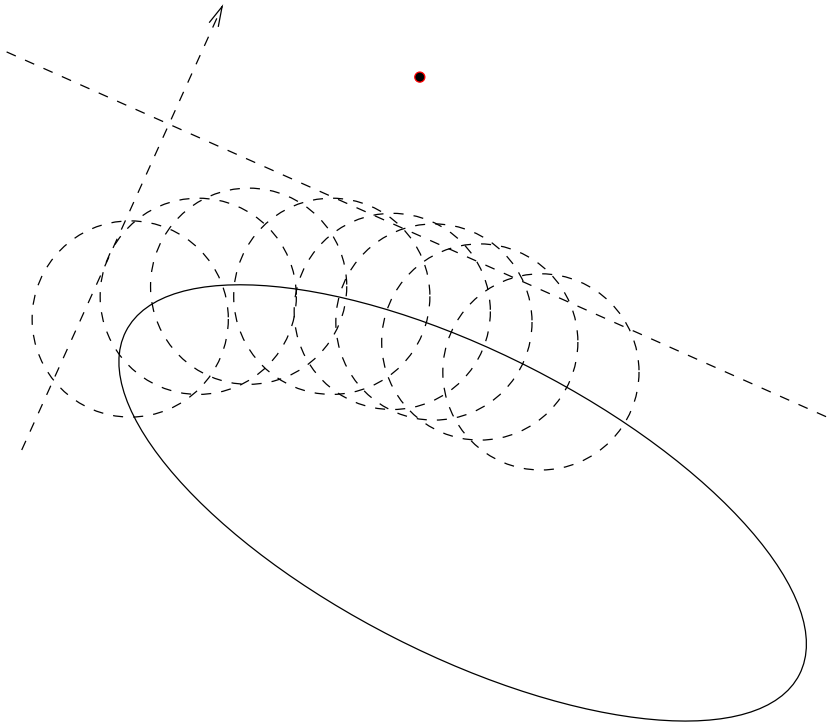


The empirical distribution may not converge when s is not chosen randomly!

- Take $\mathcal{A} = \{0, 1\}$, X_i, Y_j i.i.d. Ber(1/2) variables, and LCS scoring function.
- Subdivide the optimally aligned sequences into sections of length 3, e.g.,

$$\begin{array}{c|c|c|c|c|c} 1\ 0\ 0 & 0\ 1\ \text{G} & \text{G}\ 0\ 0 & 1\ 1\ 0 & 0\ 0\ 0 & \cdots \\ 1\ \text{G}\ \text{G} & 0\ 1\ 1 & 1\ \text{G}\ 0 & \text{G}\ \text{G}\ \text{G} & 0\ 0\ 0 & \end{array}$$

- One observes empirically that a positive proportion of triplets is of the form

$$\begin{array}{c} 0\ 1\ \text{G} \\ \text{G}\ 1\ 0 \end{array}, \begin{array}{c} \text{G}\ 0\ 1 \\ 1\ 0\ \text{G} \end{array}, \begin{array}{c} \text{G}\ 1\ 0 \\ 0\ 1\ \text{G} \end{array} \text{ or } \begin{array}{c} 1\ 0\ \text{G} \\ \text{G}\ 0\ 1 \end{array}.$$

- The first two correspond to the pattern $\begin{smallmatrix} 0 & 1 \end{smallmatrix}$ in X being aligned with the pattern $\begin{smallmatrix} 1 & 0 \end{smallmatrix}$ in Y, and the last two to the inverted situation.
- The first triplet can be exchanged for the second, and the third for the fourth without affecting $L_n(s)$.
- Interchange shifts weight from the pairing $(1, 1)$ to the pairing $(0, 0)$ in the empirical distribution.

Notes on the proof:

- Azuma-Hoeffding Inequality not applicable to empirical distribution $\vec{p}_{\Pi_n^*(s)}$, as changing a single letter in $X_1 \dots X_n$ or $Y_1 \dots Y_n$ may change the optimal alignment in a nonlocal fashion!

- However, Azuma-Hoeffiding is applicable to the function

$$(X_1 \dots X_n, Y_1 \dots Y_n) \mapsto \langle s, \vec{p}_{\Pi_n^*(s)} \rangle.$$

- The following is a compact convex set,

$$SET = \bigcap_s \left\{ x \in \mathbb{R}^{|\mathcal{A}^*|^2} : \langle s, x \rangle \leq \lambda(s) \right\}$$

- For almost all s (under the Lebesgue measure on $\mathsf{S}^{|\mathcal{A}^*|^2-1}$),

$$x^* = \arg\max_x \{\langle s, x\rangle : x \in SET\}$$

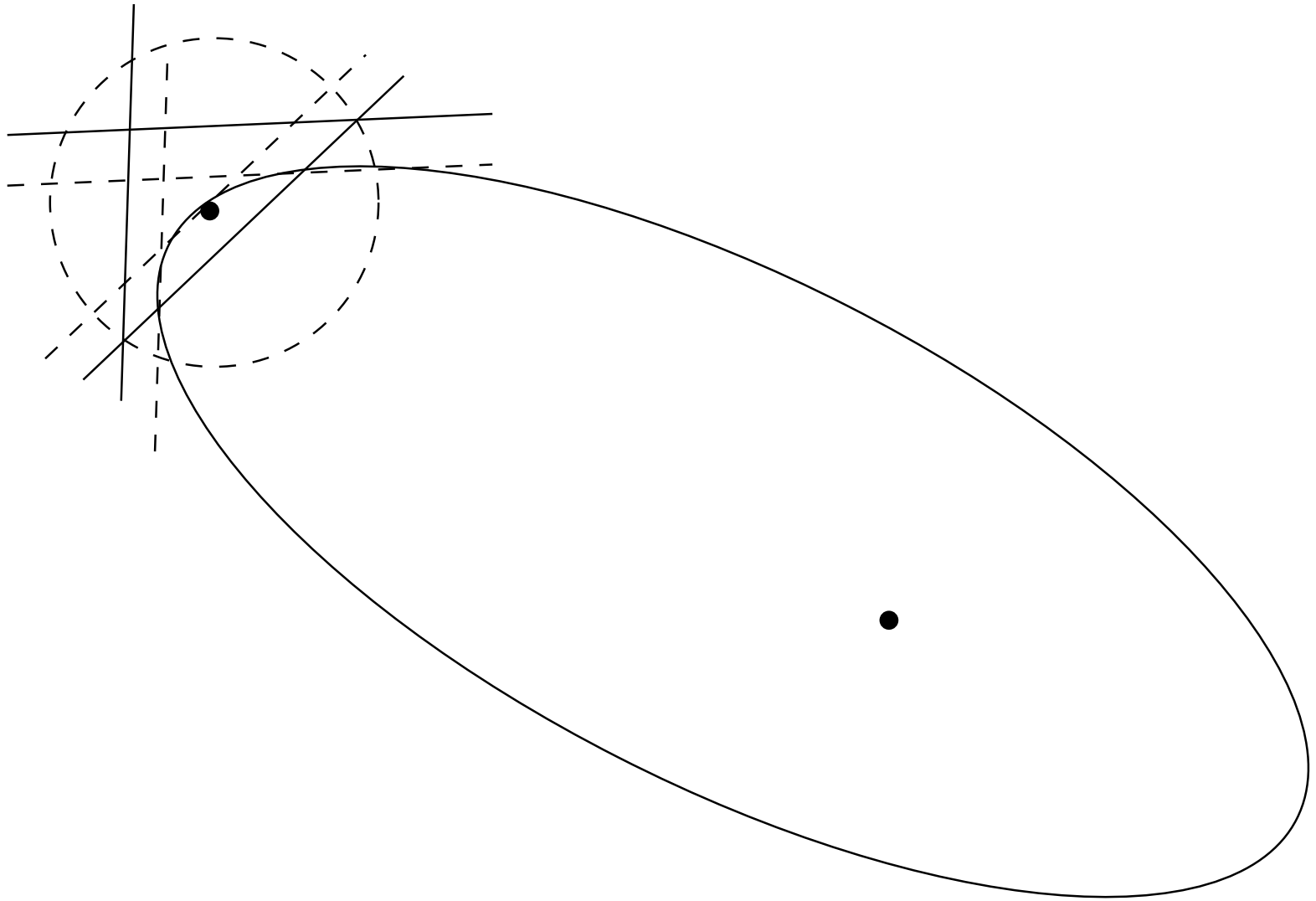
is unique.

- $\exists\ \eta < 0$, points $x_i \in \partial SET$, unit normal vectors $s_i \in \mathsf{N}_{x_i} SET$, and real numbers $\xi_i > 0$, $(i = 1, \ldots, k)$, such that

$$\{x : \langle s, x - x^*\rangle \geq \eta\} \cap \bigcap_{i=1}^{k} \{x : \langle s_i, x - x_i\rangle \leq \xi_i\} \subset B_\varepsilon(x^*).$$

- By Azuma-Hoeffing, all inequalities are satisfied with high probability.

- By Borel-Cantelli, almost sure convergence occurs.



Theorem 7. *Let s be such that $\vec{p}_s$ is unique (e.g., choose s randomly). If there exist $\mathfrak{a}, \mathfrak{b} \in \mathcal{A}$ such that*

$$\sum_{\mathfrak{c} \in \mathcal{A}^*} p_{\mathfrak{a},\mathfrak{c}} \left(s_{\mathfrak{b},\mathfrak{c}} - s_{\mathfrak{a},\mathfrak{c}} \right) > 0,$$

then

$$\mathrm{VAR}(L_n(s)) = \Theta(n).$$

- Close to proving order $\Theta(n)$ analytically in the generic case.

- Offers mechanism to verify the order $\Theta(n)$ by (non-brute-force) simulation.

More practical, weaker criterion

- Fix $\varepsilon > 0$, $\mathfrak{a}, \mathfrak{b} \in \mathcal{A}$.

- Given a scoring function $s : \mathcal{A}^* \times \mathcal{A}^* \to \mathbb{R}$, define symmetric difference

$$\begin{aligned} t_{\mathfrak{a},\mathfrak{c}} &= s_{\mathfrak{b},\mathfrak{c}} - s_{\mathfrak{a},\mathfrak{c}}, \quad \text{if } \mathfrak{c} \neq \mathfrak{a}, \\ t_{\mathfrak{c},\mathfrak{a}} &= s_{\mathfrak{b},\mathfrak{c}} - s_{\mathfrak{a},\mathfrak{c}}, \quad \text{if } \mathfrak{c} \neq \mathfrak{a}, \\ t_{\mathfrak{d},\mathfrak{c}} &= 0, \quad \text{if } \mathfrak{c}, \mathfrak{d} \neq \mathfrak{a}, \\ t_{\mathfrak{a},\mathfrak{a}} &= 2s_{\mathfrak{b},\mathfrak{a}} - 2s_{\mathfrak{a},\mathfrak{a}}. \end{aligned}$$

Theorem 8. *If* $\lambda(s) - \lambda(s - \varepsilon t) > 0$, *then* $\mathrm{VAR}(L_n(s)) = \Theta(n)$.

Simulation results:

$\mathcal{A}$	$\{0,1\}$	$\{A,T,C,G\}$
P[·]	$p_0 = 0.2, p_1 = 0.8$	$p_A = 0.4, p_T = 0.4, p_C = 0.1, p_G = 0.1$
s	LCS	BLASTZ
n	10^5	2×10^5
ε	0.5	0.9
$\frac{L_n(s) - L_n(s - \varepsilon t)}{n}$	0.0634	15.197
p-value	0.0102	2.4×10^{-4}

References

- R.A. Hauser and H. Matzinger. "Distribution of Aligned Letter Pairs in Optimal Alignments of Random Sequences". arXiv: 1211.5491.

- S. Amsalu, R. Hauser and H. Matzinger. "A Monte Carlo Approach to the Fluctuation Problem in Optimal Alignments of Random Strings. arXiv:1211.5489.

Thanks for listening!