Local Maximal Stack Scores with General Loop Penalty Function

EVA 2005, Gothenburg

Niels Richard Hansen
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This talk is based on two papers:

- Asymptotics for Local Maximal Stack Scores with General Loop Penalty Function. *To be submitted shortly.*

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- An RNA-molecule is represented as a sequence, $X_1 \ldots X_n$, of letters from the alphabet \{A, C, G, U\}.
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- Its (secondary) structure is a graph with vertex set $\{1, \ldots, n\}$.
- The graph is a partial matching: A vertex can enter in at most one edge and no loops.
- Typically edges between near neighbours (sharp turns) are not allowed.
- Typically pseudo-knots are not allowed: Pairs of edges of the form $\{i_1, j_1\}$ and $\{i_2, j_2\}$ with $i_1 < i_2 < j_1 < j_2$ are not allowed.
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- Typically pseudo-knots are not allowed: Pairs of edges of the form $\{i_1, j_1\}$ and $\{i_2, j_2\}$ with $i_1 < i_2 < j_1 < j_2$ are not allowed.
- An edge represents a hydrogen bond between nucleotides.
An example RNA-molecule from the nematode *C. elegans*. 
RNA-structures

An example RNA-molecule from the nematode *C. elegans*.

Xiong and Waterman (1997) show strong limit results for the maximum of (minus) the free energy score of RNA-structures. The free energy score being

- an additive score of the hydrogen bonded nucleotides (edges) plus
- linear penalties on the length of the loops (unpaired vertices).

The score depends on a parameter vector $\alpha$. 
Strong Limits

Let $X_1, \ldots, X_n$ be an iid RNA-sequence. Let $T_{i,j}$ denote the maximal structure score for $X_i, \ldots, X_j$ for $i < j$ and

$$M_n = \max\{ \max_{1 \leq i < j \leq n} T_{i,j}, 0 \}.$$
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If $a(\alpha) > 0$,  

$$\lim_{n \to \infty} \frac{1}{n} M_n = a(\alpha) \quad a.s.$$  

and if $a(\alpha) < 0$

$$\lim_{n \to \infty} \frac{1}{\log n} M_n = b(\alpha) \quad a.s.$$
In the logarithmic phase, \( a(\alpha) < 0 \), Xiong and Waterman conjecture that

\[
P(M_n > t) \approx 1 - \exp(-K(\alpha)n \exp(-t/b(\alpha)))
\]

for suitable large \( n \) and \( t \).
A Conjecture

In the logarithmic phase, \( a(\alpha) < 0 \), Xiong and Waterman conjecture that

\[
P(M_n > t) \simeq 1 - \exp(-K(\alpha)n \exp(-t/b(\alpha)))
\]

(1)

for suitable large \( n \) and \( t \).

For a (quite restrictive) class of stack/hairpin-loop structures we show such a result. Our result contains situations corresponding to \( a(\alpha) = 0 \) but where (1) holds.
Local scores

We proceed as follows:

Choose functions $f : \{A, C, G, U\}^2 \rightarrow \mathbb{R}$ (non-lattice) and $g : \mathbb{N}_0 \rightarrow (-\infty, 0]$. 
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- For $1 \leq i < j \leq n$ define

$$T_{i,j} = \max_{-2 \leq 2\delta < j-i} \left\{ \sum_{k=0}^{\delta} f(X_{i+k}, X_{j-k}) + g(j - i - 2\delta - 1) \right\}.$$
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  \]

- Let \( M_n = \max_{1 \leq i < j \leq n} T_{i,j} \).

\[
\begin{array}{ccc}
X_1 \ldots X_{i-1} & X_i \ldots X_{i+\delta} & X_{i+\delta+1} \ldots X_{j-\delta-1} \\
\text{stack} & \text{hairpin-loop} & \text{stack} \\
\delta+1 & j-i-2\delta-1 & \delta+1
\end{array}
\]
The scores $T_{i,j}$ fulfill the recursion

$$T_{i,j} = \max\{T_{i+1,j-1} + f(X_i, X_j), g(j - i + 1)\}.$$ 

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The Diagonals

Suppose \((X_k)_{k \in \mathbb{Z}}\) is a doubly infinite sequence of iid variables. Define recursively

\[ T_k^0 = \max \{ T_{k-1}^1 + f(X_{-k}, X_k), g(2k) \}, \quad T_0^0 = 0 \]

and

\[ T_k^1 = \max \{ T_{k-1}^2 + f(X_{-k}, X_k), g(2k + 1) \}, \quad T_0^1 = g(1). \]
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\]

\[
T_{i,j} \overset{D}{=} \begin{cases} 
T_0^{(j-i+1)/2} & \text{if } j - i \text{ is odd} \\
T_1^{(j-i)/2} & \text{if } j - i \text{ is even}
\end{cases}
\]
Reflected Random Walks

The processes $(T^i_k)_{k \geq 0}, i = 0, 1$ are random walks reflected at $g$. 

\begin{itemize}
  \item $g(n) = 0$
  \item $g(n) = -15 \log(n)$
  \item $g(n) = -n$
\end{itemize}
Reflected Random Walks

If \( M^i := \sup_{k \geq 0} T^i_k < \infty \) a.s. and \( \theta^* > 0 \) solves

\[
\mathbb{E} \exp(\theta f(X_{-1}, X_1)) = 1.
\]

then

\[
P(M^i > x) \sim K^*_i \exp(-\theta^* x)
\]

for \( x \to \infty \).
Reflected Random Walks

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then

$$\mathbb{P}(M^i > x) \sim K^*_i \exp(-\theta^* x)$$  

for $x \to \infty$.

Its necessary that

$$\mu := \mathbb{E} f(X_{-1}, X_1) < 0$$

in which case

$$\sum_{k=1}^{\infty} \exp(\theta^* g(k)) < \infty$$

is sufficient for $M^i < \infty$ a.s.
The Main Result

Define

\[ C(t) = \sum_{i=1}^{n} 1(\exists \delta : T_{i-\delta, i+\delta} > t) + 1(\exists \delta : T_{i-\delta, i+1+\delta} > t). \]

**Theorem:** With

\[ t_n = \frac{\log(K_0^* + K_1^*) + \log n + x}{\theta^*}, \]

for \( x \in \mathbb{R} \) then

\[ ||D(C(t_n)) - \text{Poi}(\exp(-x))||_{tv} \rightarrow 0 \quad (1) \]

for \( n \rightarrow \infty \). In particular

\[ \mathbb{P}(M_n \leq t_n) \rightarrow \exp(-\exp(-x)) \quad (1) \]

for \( n \rightarrow \infty \).
A consequence of the theorem is that

\[ \frac{1}{\log n} M_n \xrightarrow{\mathbb{P}} \frac{1}{\theta^*}. \]

The “parameters” involved are the functions \( f \) and \( g \) and

\[ b(f, g) = \frac{1}{\theta^*} \]

where \( \theta^* > 0 \), solving \( \mathbb{E} \exp(\theta f(X_{-1}, X_1)) = 1 \), does not depend upon \( g \).
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Moreover, for suitable \( n \) and \( t \)

\[ \mathbb{P}(M_n > t) \simeq 1 - \exp(-(K_0^* + K_1^*)n \exp(-\theta^* t)) \]
Apply Arratia et al. (1989) “Two moments suffice for Poisson approximations: the Chen-Stein method”. It involves:

- Localisation of dependencies by band-limitation: Consider only \( T_{i,j} \) with \( j - i \leq h(n) \) where

\[
\lim_{n \to \infty} h(n)^{-1} \log n = \lim_{n \to \infty} n^{-\epsilon} h(n) = 0.
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- Handling of the tail-behavior of partial maxima of reflected random walks due to band-limitation.

- Bounding probabilities of the form

$$\mathbb{P}(T_{i,j} > t, T_{i',j'} > t)$$

by the Azuma-Hoeffding inequality and exponential change of measure.
The variables $T_{1,n}$ do not form a subadditive sequence.

By other means one can sometimes establish that

$$\lim_{n \to \infty} \frac{1}{n} T_{1,n} = a(f, g).$$
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Using that $g \leq 0$ and $\mu < 0$

$$\limsup_{n \to \infty} \frac{1}{n} T_{1,n} \leq 0.$$

If $g$ is sublinear, $g(n)/n \to 0$,

$$\frac{1}{n} T_{1,n} \geq \frac{g(n)}{n} \to 0,$$

hence $a(f, g) = 0$. 
Let $g(n) = \rho n$ for $\rho < 0$. Then

$$\sum_{k=1}^{\infty} \exp(\theta^* \rho k) < \infty.$$ 

and $M^i < \infty$ a.s.
Example I

Let $g(n) = \rho n$ for $\rho < 0$. Then

$$\sum_{k=1}^{\infty} \exp(\theta^* \rho k) < \infty.$$ 

and $M^i < \infty$ a.s. If $\rho < \mu$

$$a(f, g) = \mu$$

and if $\rho > \mu$

$$a(f, g) = \rho.$$
Let $g(n) = \rho \log n$ for $\rho < 0$. Then

$$\sum_{k=1}^{\infty} \exp(\theta^* \rho \log k) = \sum_{k=1}^{\infty} k^{\theta^* \rho} < \infty$$

iff $\rho < -1/\theta^*$ and $a(f, g) = 0$. 
Example II

Let $g(n) = \rho \log n$ for $\rho < 0$. Then

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It is possible to show that for $\rho > -1/\theta^*$ then $M^i = \infty$ a.s. for $i = 0, 1$. What happens here is an open question.
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It is possible to show that for \( \rho > -1/\theta^* \) then \( M^i = \infty \) a.s. for \( i = 0, 1 \). What happens here is an open question.

When \( g \equiv 0 \) (the limiting case \( \rho \to 0 \)) is understood and

\[
\frac{1}{\log n} M_n = \frac{2}{\theta^*} \text{ a.s.}
\]

with a corresponding asymptotic extreme value distribution of \( M_n \).
Concluding Remarks

The use of extreme value distributions in local sequence alignment for significance evaluation of the alignment score is much used (BLAST) with a theoretical justification for special cases.
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- We have provided a result for sequence structure where one finds that the structure score follows asymptotically an extreme value distribution.

- Our result is particular useful when searching large sequences for local parts containing “a lot of structure”.
Concluding Remarks

- The use of extreme value distributions in *local sequence alignment* for significance evaluation of the alignment score is much used (BLAST) with a theoretical justification for special cases.

- We have provided a result for *sequence structure* where one finds that the structure score follows asymptotically an extreme value distribution.

- Our result is particularly useful when searching large sequences for local parts containing “a lot of structure”.

- The result confirms to some extent the conjecture by Xiong and Waterman – and extends the conjecture in one direction.