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*.
- The Maximum of a Random Walk Reflected at a General Barrier. *To appear in Ann. Appl. Probab.*

RNA-structures

RNA molecules are sequences of nucleotides – some forming functionally important structures.

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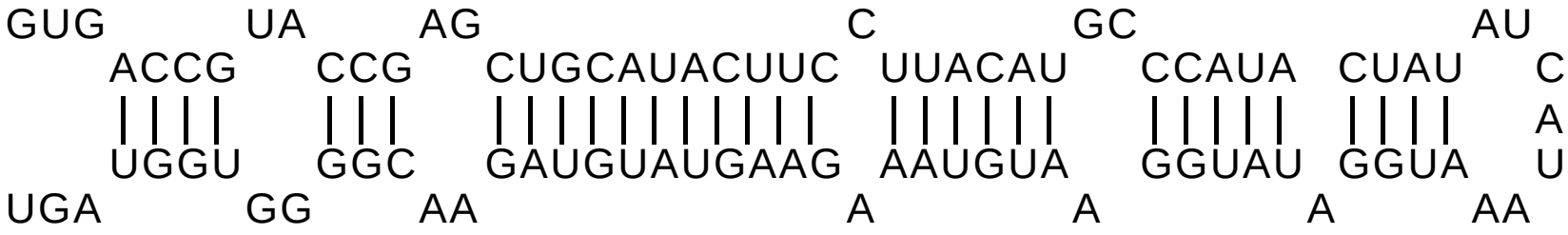
- An edge represents a hydrogen bond between nucleotides.

RNA-structures



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

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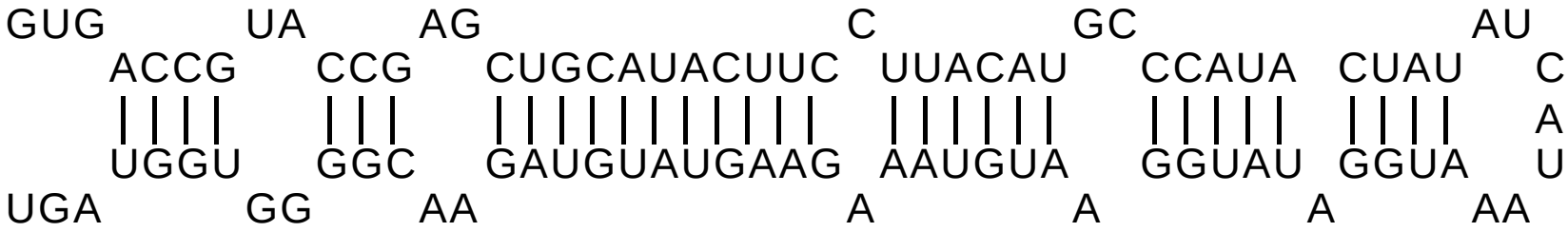

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Xiong and Waterman (1997) show strong limit results for the maximum of (minus) the free energy score of RNA-structures. The free energy score being

- 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 α.

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

If $a(\alpha) > 0$,

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

and if $a(\alpha) < 0$

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

A Conjecture

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

$$\mathbb{P}(M_n > t) \simeq 1 - \exp(-K(\alpha) n \exp(-t/b(\alpha))) \tag{1}$$

for suitable large n and t.

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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 $f : \{\mathsf{A}, \mathsf{C}, \mathsf{G}, \mathsf{U}\}^2 \to \mathbb{R}$ (non-lattice) and $g : \mathbb{N}_0 \to (-\infty, 0]$.

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- For $1 \leq i < j \leq n$ define

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

$$X_1 \dots X_{i-1} \quad \underbrace{X_i \dots X_{i+\delta}}_{\delta+1} \quad \underbrace{X_{i+\delta+1} \dots X_{j-\delta-1}}_{j-i-2\delta-1} \quad \underbrace{X_{j-\delta} \dots X_j}_{\delta+1} \quad X_{j+1} \dots X_n.$$

stack hairpin-loop stack

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

The Recursion

The scores $T_{i,j}$ fulfill the recursion

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

	X_1	X_2	X_3	X_4	X_5
X_1	$g(1)$				
X_2	0	$g(1)$			
X_3		0	$g(1)$		
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X_4			0	$g(1)$	$T_{4,5}$
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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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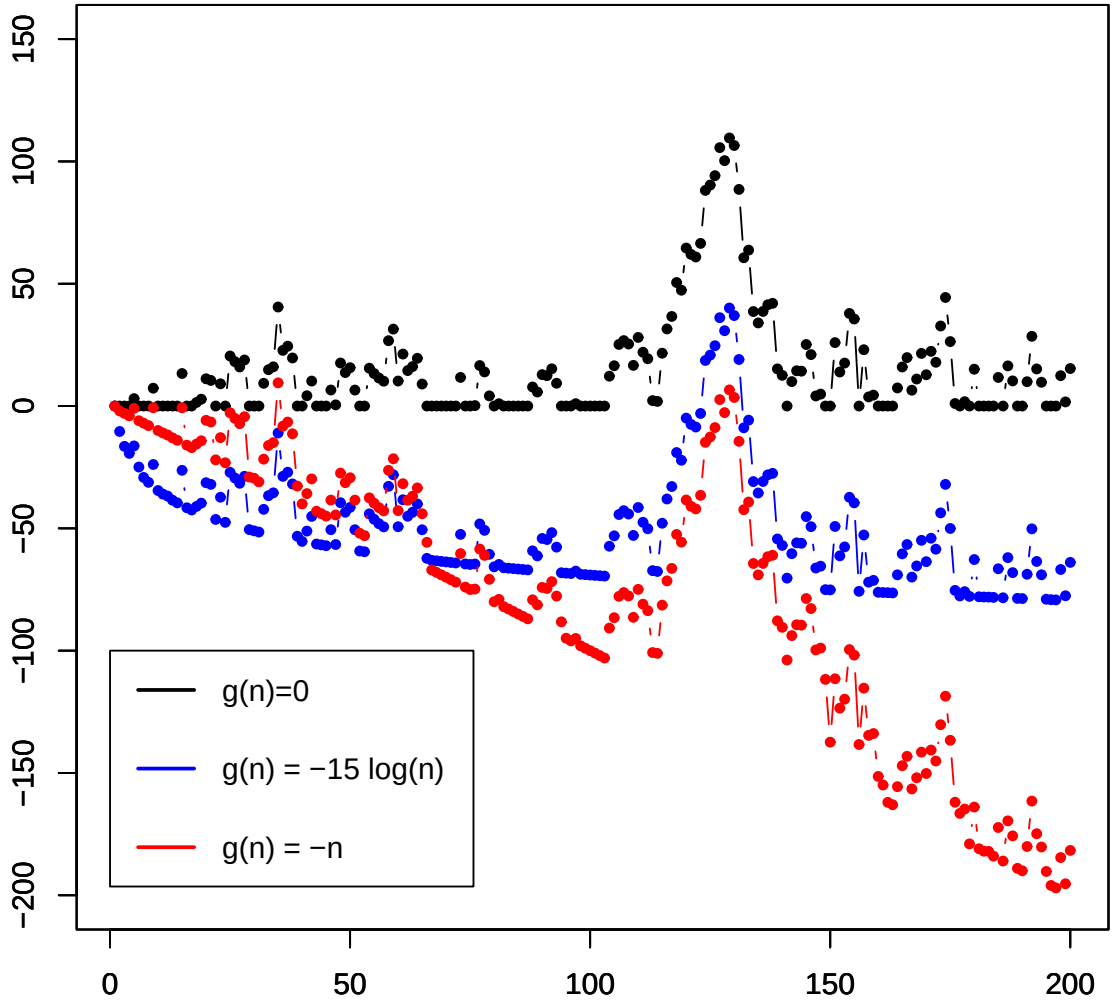
$$T_{i,j} \stackrel{\mathcal{D}}{=} \begin{cases} T^0_{(j-i+1)/2} & \text{if } j-i \text{ is odd} \\ T^1_{(j-i)/2} & \text{if } j-i \text{ is even} \end{cases}$$

Reflected Random Walks

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



Reflected Random Walks

If $M^i := \sup_{k \geq 0} T_k^i < \infty$ a.s. and $\theta^* > 0$ solves

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

then

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

for $x \to \infty$.

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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*

$$t_n = \frac{\log(K_0^* + K_1^*) + \log n + x}{\theta^*}, \tag{1}$$

for $x \in \mathbb{R}$ *then*

$$||\mathcal{D}(C(t_n)) - \mathrm{Poi}(\exp(-x))||_{tv} \to 0 \tag{1}$$

for $n \to \infty$. *In particular*

$$\mathbb{P}(M_n \leq t_n) \to \exp(-\exp(-x)) \tag{1}$$

for $n \to \infty$.

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

$$\mathbb{P}(M_n > t) \simeq 1 - \exp(-(K_0^* + K_1^*) n \exp(-\theta^* t))$$

The Proof

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

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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.

Back to Xiong and Waterman

The variables $T_{1,n}$ do not form a subadditive sequence.

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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 $a(f,g) = 0$.

Example I

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Example II

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 $a(f, g) = 0$.

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

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

with a corresponding asymptotic extreme value distribution of M_n.

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

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