Subsequence Combinatorics and Applications

Sven Rahmann

Algorithms and Statistics for Systems Biology Group
Genome Informatics, Department of Technology, Bielefeld University, Germany

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Subsequences

Fundamentals

- Σ: finite alphabet
- $s = (s_1, \ldots, s_n) \in \Sigma^n$: a string (sequence) of length n

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  $I = \{i_1, \ldots, i_k\}$ with $i_1 < \cdots < i_k \implies s_I := s_{i_1} s_{i_2} \ldots s_{i_k}$.
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First Question

How many distinct subsequences of length k exist in s?

Aside: Number of distinct substrings

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Easy, given the lcp table of the suffix array of s:
Number is $n - k + 1 - |\{i : lcp[i] \geq k\}|$.

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Number of distinct (contiguous) length-k substrings of s?

Easy, given the lcp table of the suffix array of s:
Number is $n - k + 1 - |\{i : lcp[i] \geq k\}|$.

Can be computed in $O(n)$ operations.

Counting Distinct Subsequences Efficiently

General Notational Conventions

- S: a set of sequences
- C: cardinality of S
- W: weight of S,
  e.g., $W = C/|\Sigma|^m$ if all sequences in S have length m

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Goal

Compute $C_k(s) = C_{k,n} = \sum_{a \in \Sigma} C_{k,n}[a]$.

A Recurrence on Sets

- $S_{0,j} = \{\epsilon\}$ for all j.
- $S_{0,j}[a] = \{\}$ for all j and all $a \in \Sigma$.
- For $1 \leq m \leq j$,

$$S_{m,j}[a] = \begin{cases} S_{m,j-1}[a] & \text{if } s_j \neq a, \\ S_{m-1,j-1} \circ \{a\} & \text{if } s_j = a. \end{cases}$$

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Proof

Case $s_j \neq a$: $S_{m,j-1}[a] \subset S_{m,j}[a]$ is trivial; thus prove $S_{m,j}[a] \subset S_{m,j-1}[a]$: Take $t \in S_{m,j}[a]$. Since $s_j \neq a$, already $t \in S_{m,j-1}[a]$.

s_1	$\cdots$	s_{j-1}	s_j
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Proof

Case $s_j = a$: Appending a to each $t \in S_{m-1,j-1}$ yields a distinct string $ta \in S_{m,j}[a]$, thus $S_{m-1,j-1} \circ \{a\} \subset S_{m,j}[a]$. Conversely, every $s \in S_{m,j}[a]$ can be written as $s = ta$ with $t \in S_{m-1,j-1}$.

s_1	$\cdots$	s_{j-1}	s_j
	t		a

A Recurrence on Cardinalities

- $C_{0,0} = 1$ and $C_{0,0}[a] = 0$ for all $a \in \Sigma$.
- $C_{m,j} = 0$ if $m > j$.
- For $1 \leq m \leq j$,

$$C_{m,j}[a] = \begin{cases} C_{m,j-1}[a] & \text{if } s_j \neq a, \\ C_{m-1,j-1} & \text{if } s_j = a. \end{cases}$$

Bernoulli (i.i.d.) String Model

Consider an i.i.d. model:

- $\pi := (\pi_a)_{a \in \Sigma}$: given probability distribution on Σ
- $\mathbb{P}_k(t_1 \dots t_k) := \prod_{j=1}^{k} \pi_{t_j}$
- Then $\mathbb{P}_{k+1}(ta) = \mathbb{P}_k(t) \cdot \pi_a$ for $t \in \Sigma^k$ and $a \in \Sigma$.

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Define

- $W_k(s) := \mathbb{P}_k(S_k(s))$, covered fraction of Σ^k
- $W_{m,j} := \mathbb{P}_m(S_{m,j}) = \sum_{t\in S_{m,j}[a]} \mathbb{P}_m(t)$ $(m \le k,\, j \le |s| = n)$
- $W_{m,j}[a] := \mathbb{P}_m(S_{m,j}[a])$

Recurrence on Weights

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Straightforward implementation: $O(kn|\Sigma|)$ operations.
Can be reduced to $O(k(n + |\Sigma|))$ operations.

Application: DNA Microarray Production

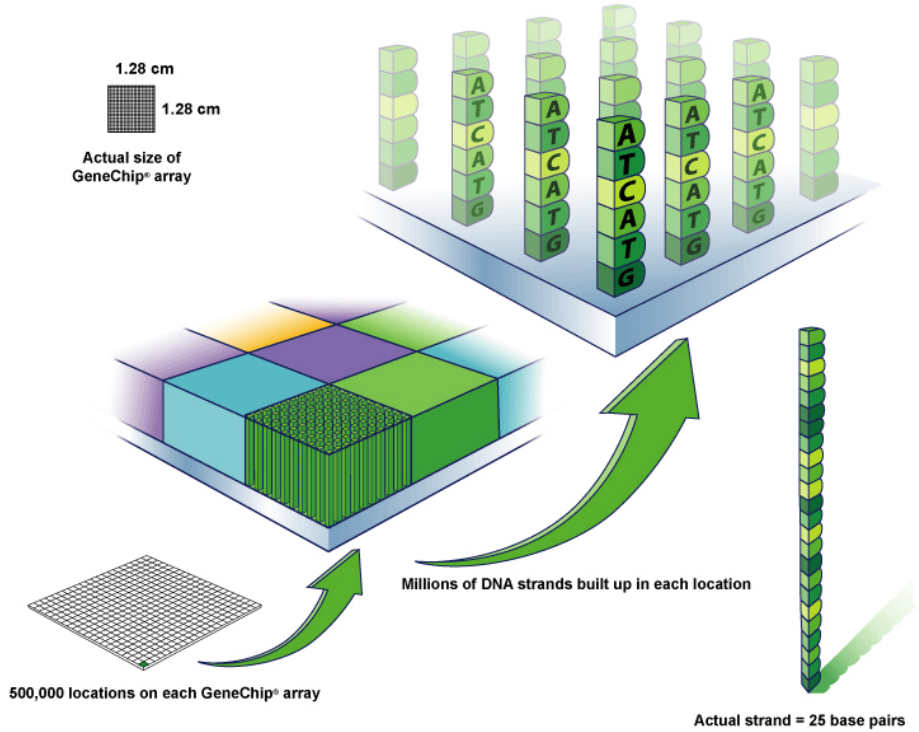
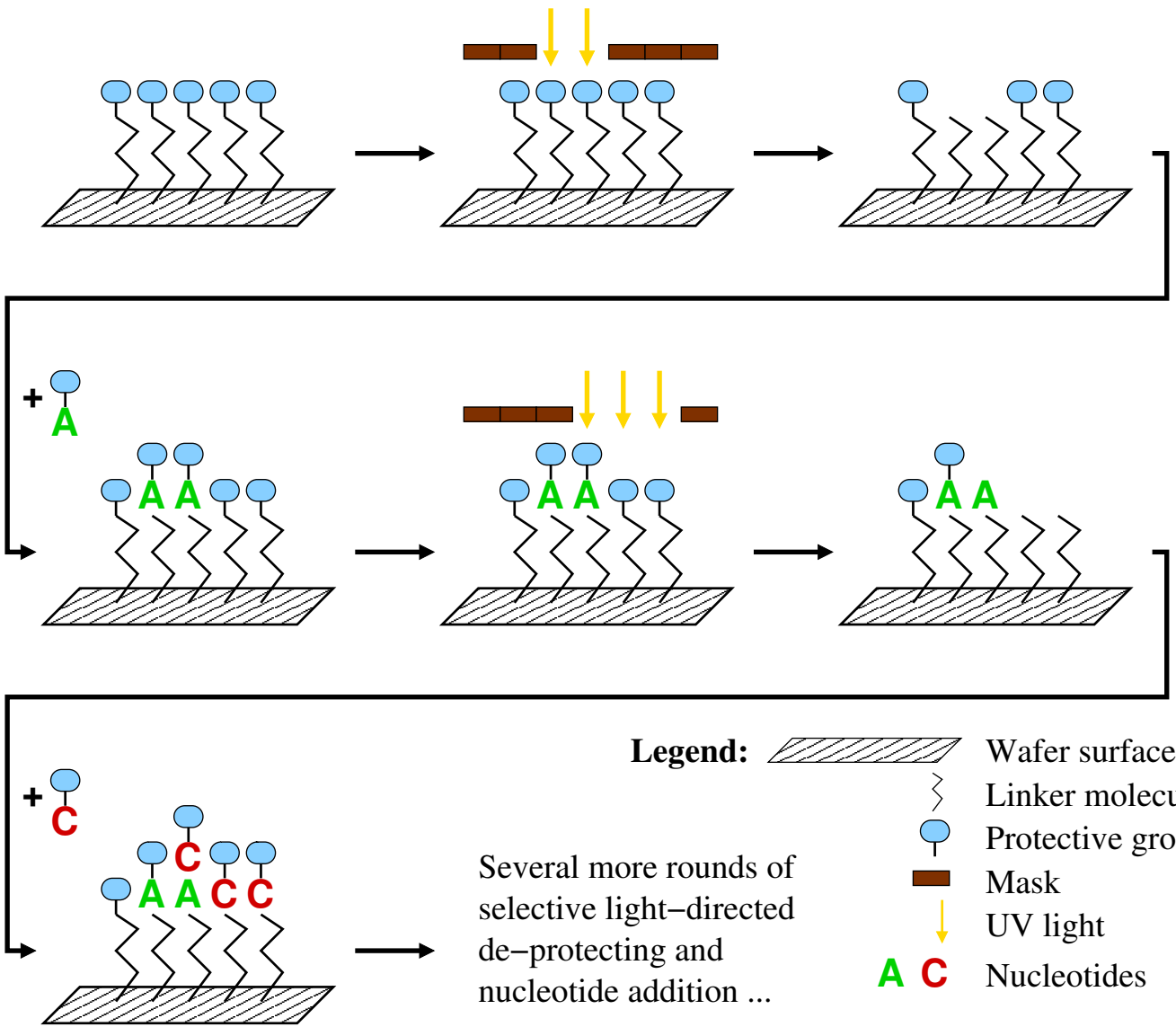


Image: Affymetrix, Inc.

- Each spot contains many copies of a probe
- 10 K to 1 M spots
- Probes are oligonucleotides (e.g. DNA 25-mers)
- One probe type, like `ACGTTAG...`, per spot

Chip Production: Probe Synthesis



Two Optimization Problems

Situation

- We know the probe sequences.
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Problem 2

Most universal deposition sequence of given length? I.e., find

$$C_k^*(n, |\Sigma|) = \max_{s \in \Sigma^n} C_k(s),$$

$$Best_k^*(n, |\Sigma|) = \{s \in \Sigma^n : C_k(s) = C_k^*(n, \Sigma)\}.$$

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Theorem (Chase, 1976)

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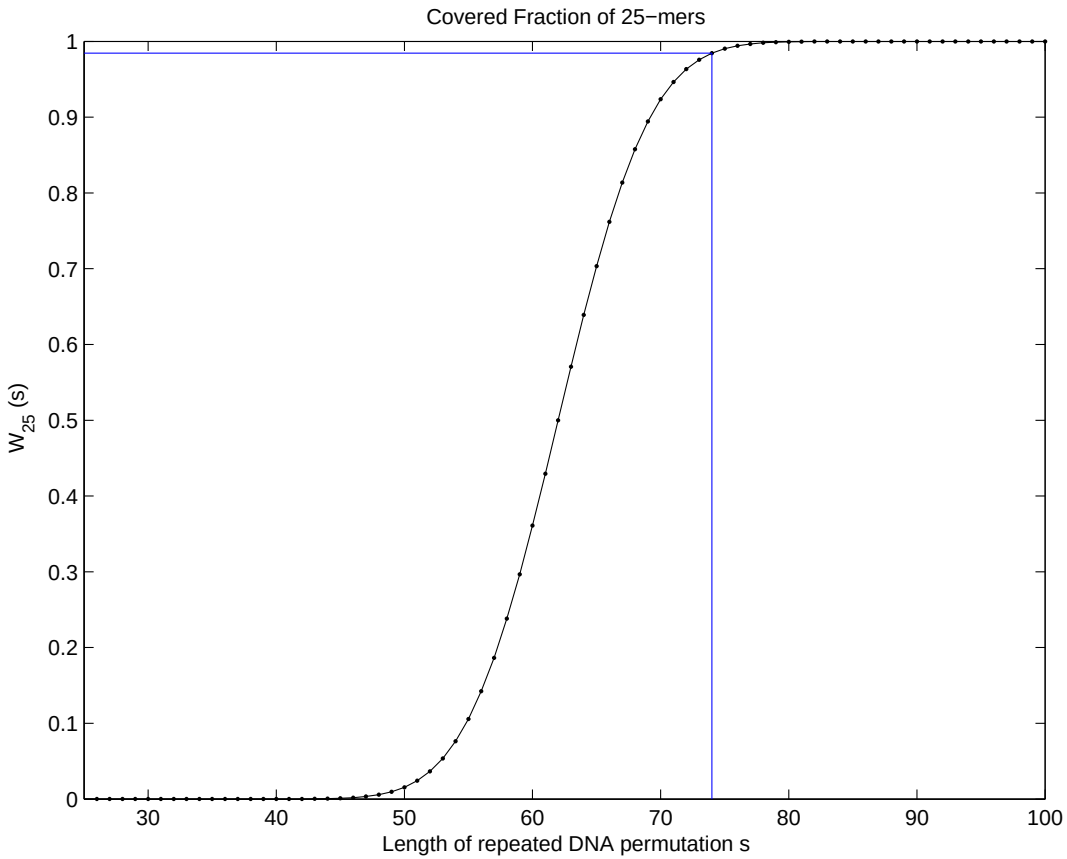
In practice:

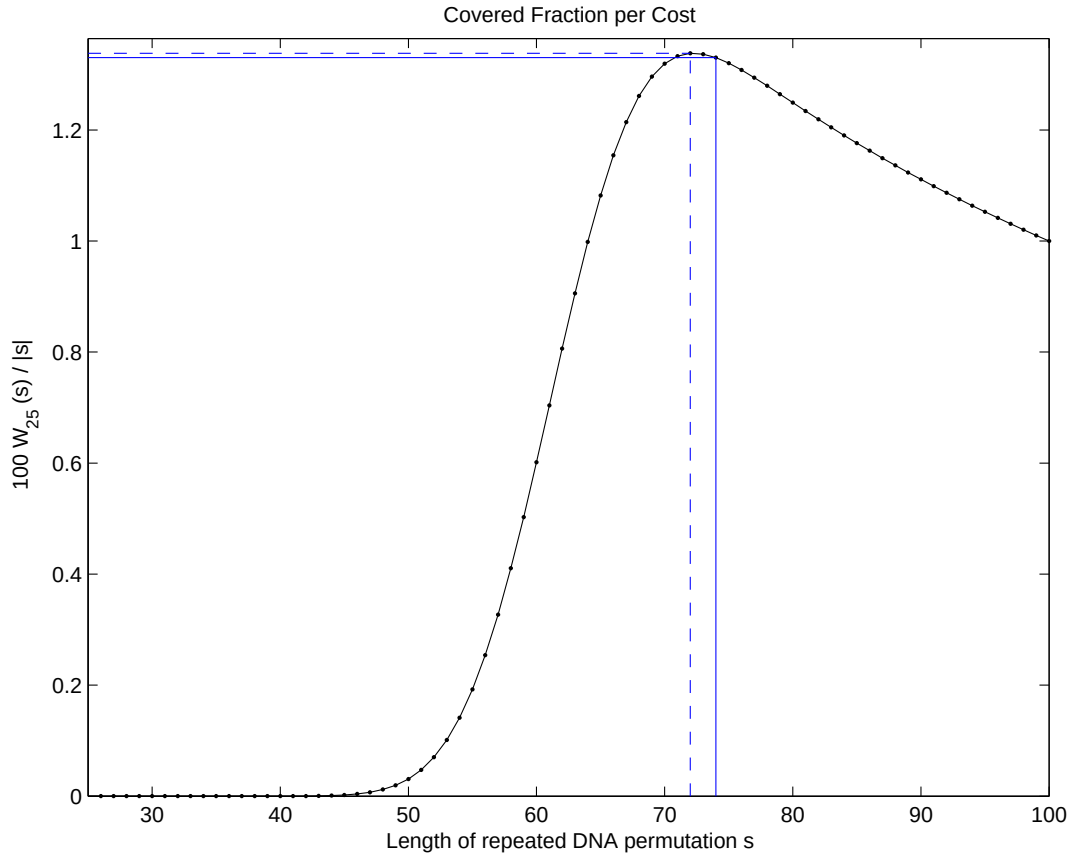
Deposition sequence $\mathrm{ACGT}^{18.5}$ (length 74) for 25-mers.

Covered Fraction of Probes



Fraction of 25-mers covered by a repeated permutation of varying length. Highlighted: s^* (length 74), 98.45% of 25-mers covered.

Value-based View



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$s^{\$}$, 72 steps, $W_{25}(s^{\$}) = 96.34\%$, $100\, W_{25}(s^{\$})/72 = 1.338$.

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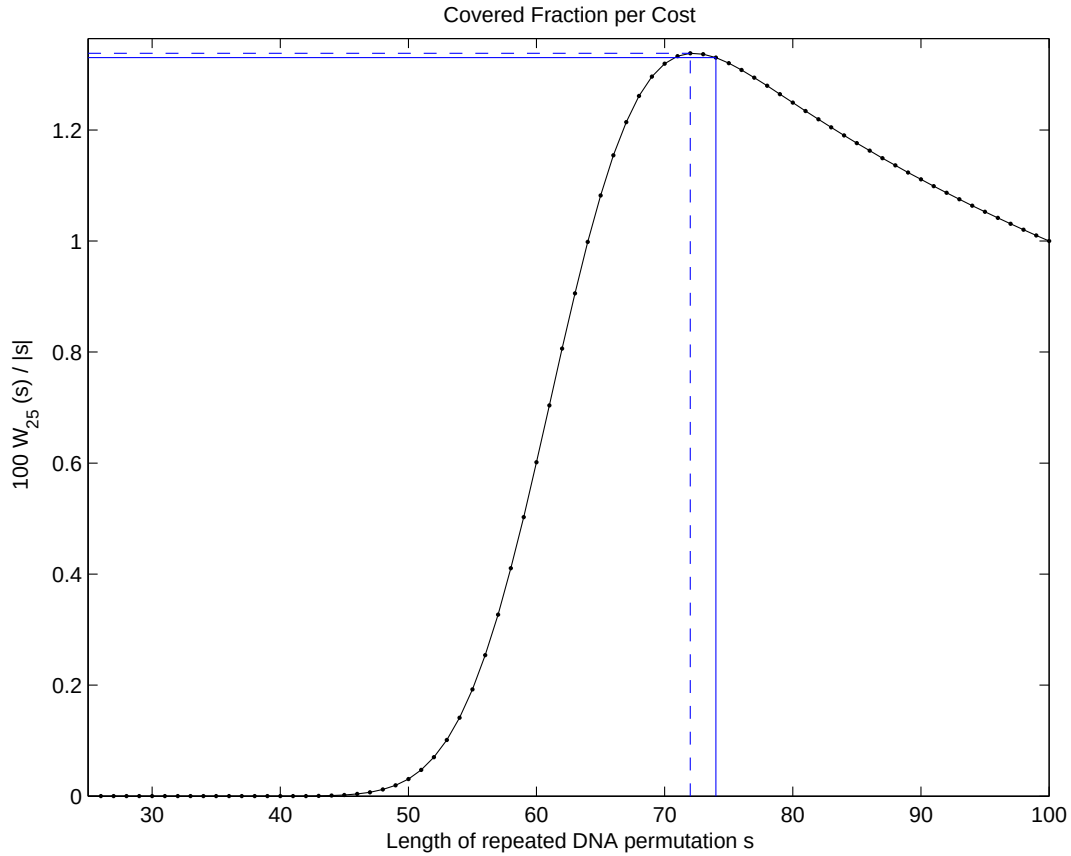

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Additional Restriction:

- t may not contain runs longer than ρ.
- Example ($\rho = 2$): Forbidden to generate AAA from BABA.
- Define Σ_ρ^k as ρ-restricted strings of length k.

Combinatorial Problems

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From now on, assume s and ρ as fixed.

Auxiliary Quantities

- $S_{m,j}[a] := \{t \in \Sigma_\rho^m : t \lhd_\rho s_1 \dots s_j \text{ and } t_m = a\}$
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Obviously,

- $S_{0,j}[a] = \{\}$
- $S_{0,j}[\overline{a}] = \{\epsilon\}$

Recurrences

Lemma (Structure)

$$\text{For } 1 \leq m \leq j, \quad S_{m,j}[a] = \begin{cases} S_{m,j-1}[a] & \text{if } s_j \neq a, \\ \bigcup_{r=1}^{\min\{\rho,m\}} (S_{m-r,j-1}[\bar{a}] \circ \{a^r\}) & \text{if } s_j = a, \end{cases}$$

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Lemma (Weights)

$W_{0,j}[\overline{a}] = 1$, $W_{0,j}[a] = 0$ *for all* $a \in \Sigma$, $j \ge 0$. *For* $m \ge 1$, $j \ge 1$,

$$W_{m,j}[a] = \begin{cases} W_{m,j-1}[a] & \text{if } s_j \neq a, \\ \sum_{r=1}^{\min\{m,\rho\}} W_{m-r,j-1}[\overline{a}] \cdot \pi_a^r & \text{if } s_j = a. \end{cases}$$

Result is $W_k(s) = W_{k,n}[\overline{a}] + W_{k,n}[a]$ *for any* $a \in \Sigma$.

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Remarks

1. W-recurrence can be implemented in $O(k(n + |\Sigma|))$ operations.
2. $\rho = \infty$: How many Σ^k-strings match $s_1 * s_2 * \ldots s_n *$?
3. Conjecture:
   Repeated permutations maximize $C_k(s; \rho)$ over $s \in \Sigma^n$ for all k

454 Sequencing

- Large-scale sequencing technology by synthesis & light emission.
- Up to 200K (short) fragments in parallel.
- Each nucleotide run is determined in one step
- Works only reliably up to run length $\rho = 8$ in practice.

Example ($\rho = 4$): Try to sequence

1. ACCTG
2. CTTTT
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by using the probing sequence

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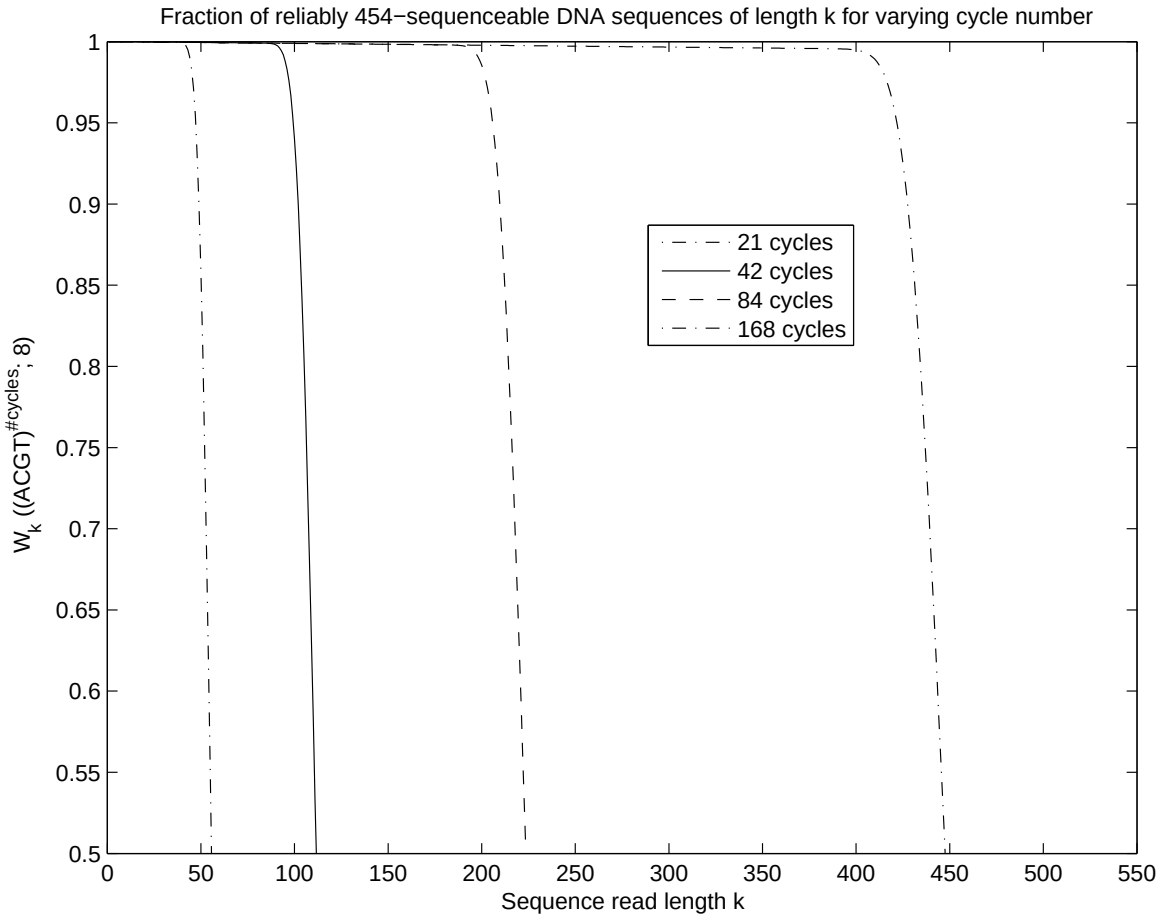
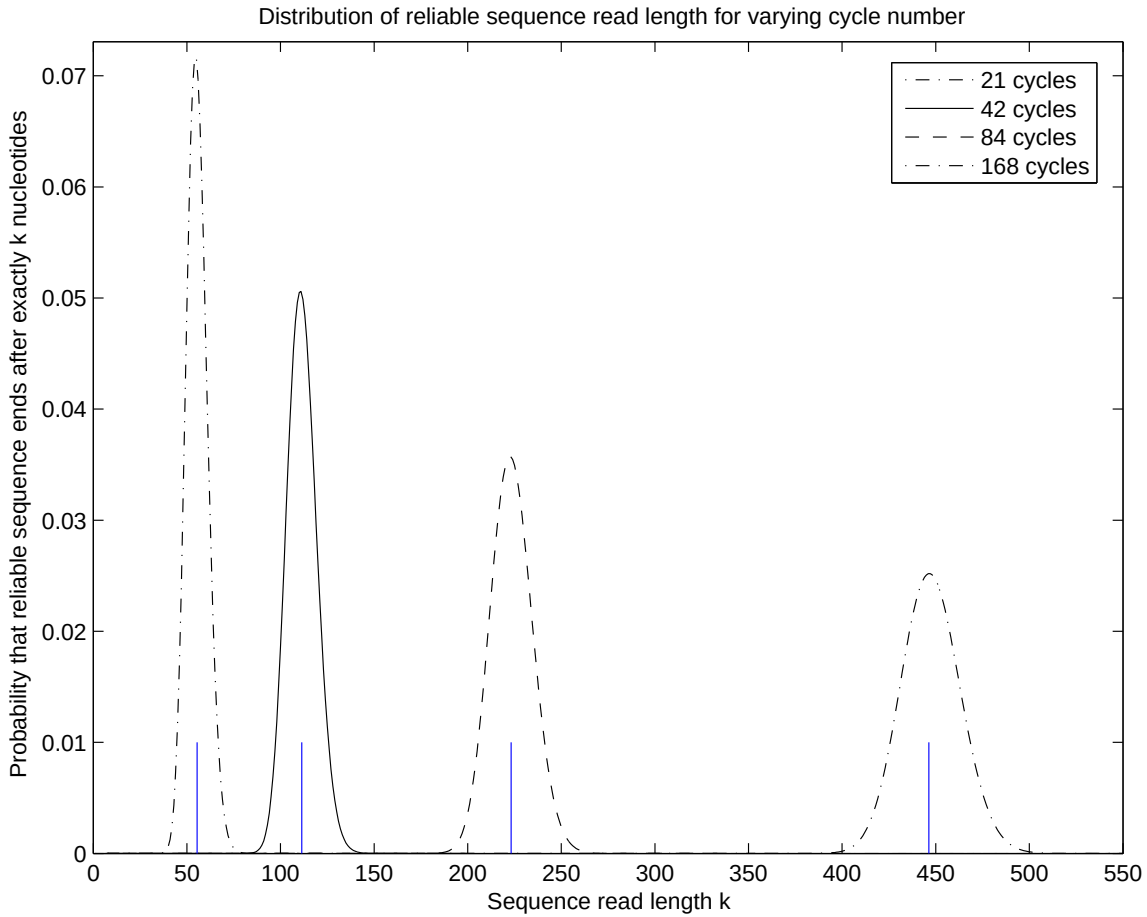
Fraction of 454-sequenceable Sequences



Fraction W_k of 454-sequenceable length-k DNA sequences by using a repeated permutation for $c \in \{21, 42, 84, 168\}$ cycles, $\rho = 8$.

Distribution of Read Lengths



Length distribution of sequenceable initial fragment of a random DNA sequence, $c \in \{21, 42, 84, 168\}$, $\rho = 8$. Vertical lines: Expectations.

Longest Increasing Subsequences

- $\Sigma := \{1, \ldots, K\} =: [K]$
- S: random sequence from Σ^K (Bernoulli model)
- $L_n := LIS(S) :=$ length of longest increasing subsequence of S

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Problem

Determine exact distribution of random variable L_n.
(How many sequences s exist with $LIS(s) = k$?)

Patience Sorting

Algorithm for computing $LIS(s)$ for given s:

- Scan s from left to right
- Track $\kappa \subset [K]$ with $|\kappa| = LIS(s_1 \dots s_j)$ after step j
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  $u : 2^{[K]} \times [K] \to 2^{[K]}; (\kappa, c) \mapsto \kappa^+$:
  - If $c \in \kappa$, do nothing, i.e., set $\kappa^+ := \kappa$.
  - If $c \notin \kappa$ and κ contains no element $> c$, add c, i.e., set $\kappa^+ := \kappa \cup \{c\}$.
  - If $c \notin \kappa$ and there exists $k \in \kappa$ with $k > c$, find the smallest such k and decrease it to c, i.e., set $\kappa^+ := \kappa \setminus \{k\} \cup \{c\}$.

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- Intuition:
  - s: sequence of cards
  - place card s_j on top of leftmost stack with higher/equal value
  - κ: set of cards on top
  - $|\kappa|$: number of stacks $= LIS$

Efficent Counting by Conditioning on κ

Avoid running patience sorting for all K^n sequences separately: Let

- $S_j(\kappa) := \{t \in \Sigma^j : \kappa_j(t) = \kappa\}$,
- $C_j(\kappa) := |S_j(\kappa)|$,
- $W_j(\kappa) := \mathbb{P}_j(S_j(\kappa))$.

Then

- $S_n(k) := \bigcup_{\substack{\kappa \subset [K], \\ |\kappa|=k}} S_j(\kappa)$,
- $C_n(k) := \sum_{\substack{\kappa \subset [K], \\ |\kappa|=k}} C_j(\kappa)$,
- $W_j(k) := \sum_{\substack{\kappa \subset [K], \\ |\kappa|=k}} W_j(\kappa)$

are set, number, weight of length-n sequences with $LIS = k$, respectively.

Efficent Counting by Conditioning on κ

- For $j = 0$:
  - $\kappa = \{\}$: $S_0(\kappa) = \{\epsilon\}$, $C_0(\kappa) = 1$, $W_0(\kappa) = 1$.
  - $\kappa \neq \{\}$: $S_0(\kappa) = \{\}$, $C_0(\kappa) = 0$, $W_0(\kappa) = 0$.
- For $1 \leq j \leq n$ and $\kappa \in 2^{[K]}$,

$$S_j(\kappa) = \bigcup_{(\kappa',c)\in u^{-1}(\kappa)} S_{j-1}(\kappa') \circ \{c\},$$

$$C_j(\kappa) = \sum_{(\kappa',c)\in u^{-1}(\kappa)} C_{j-1}(\kappa'),$$

$$W_j(\kappa) = \sum_{(\kappa',c)\in u^{-1}(\kappa)} W_{j-1}(\kappa') \cdot \pi_c.$$

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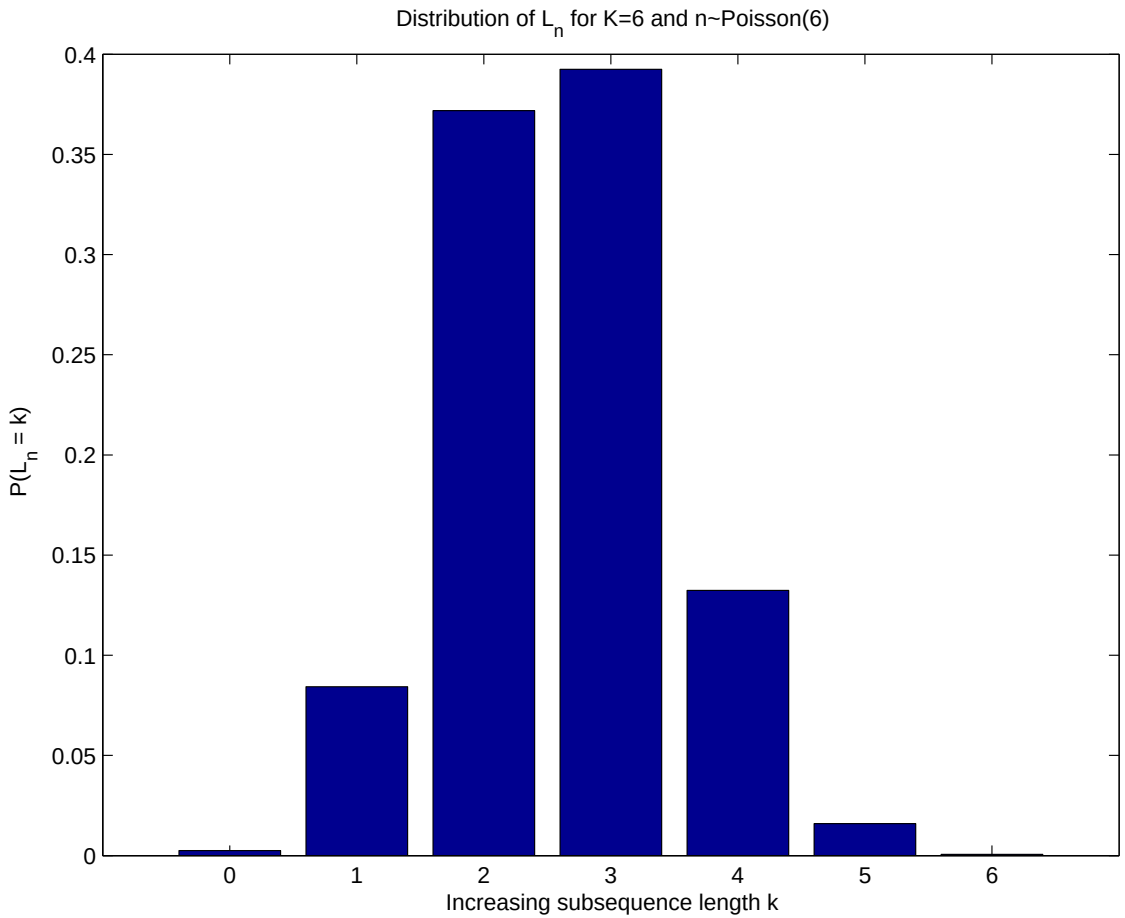
- Pull-type recurrence.
- Easier to implement: Push-type algorithm
- Number of operations: $O(nK2^K)$, FPT in K.

Application: Significance of long chains of rare motifs



LIS-length distribution, $K = 6$.
Random sequence length $N \sim \text{Poisson}(6)$.

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Properties of subsequences not widely analyzed yet.
Many more questions to ask and problems to solve!

Acknowledgments

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Thank you for listening

Questions?