Correcting a Single Deletion in Reads from a Nanopore Sequencer

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Joint work with
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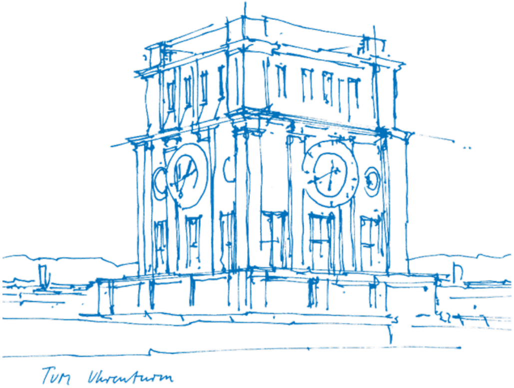
[2]Technion – Israel Institute of Technology
Department of Computer Science

July 8, 2024



Outline

Motivation

- Need for dense, reliable, robust storage media
  - Molecular storage paradigms *e.g., DNA storage.*[1]

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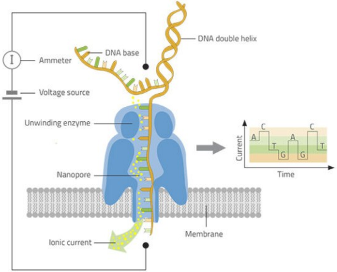
  - \+ More portable
  - — High error rates



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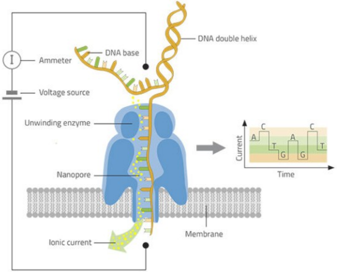
- *Aim:* Design coding techniques tailored for nanopore sequencing!



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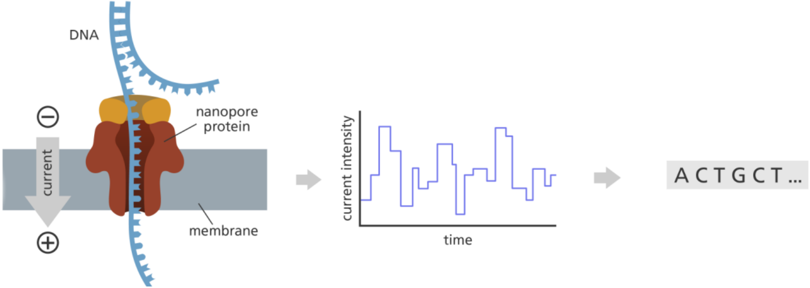
Nanopore Sequencing



Source: *"What is Oxford Nanopore Technology (ONT) sequencing?,"* https://www.yourgenome.org/facts/what-is-oxford-nanopore-technology-ont-sequencing/

- Sources of noise [MDK18] :
  - Nanopore holds $\ell > 1$ nucleotides at a time $\rightarrow$ Intersymbol interference (ISI)!
  - Strand moves irregularly $\rightarrow$ backtracking & skipping.
  - Noisy measurements

[MDK18] W. Mao *et al.*, "Models and information-theoretic bounds for nanopore sequencing," *TIT*, 2018

Prior Work

- [MDK18] $\rightarrow$ Mathematical model, capacity bounds.
- [HCW21] $\rightarrow$ Algorithm to compute capacity of an abstracted, deterministic channel model.
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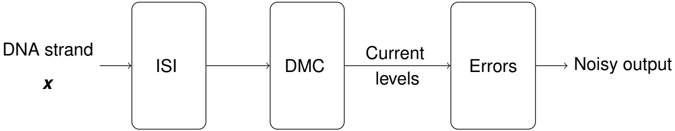

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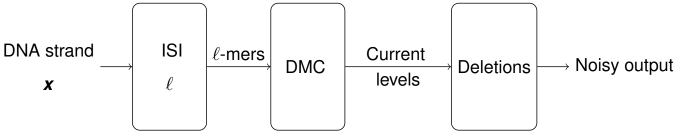

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- ISI as length-ℓ-sliding window
- Skipping effects as deletions

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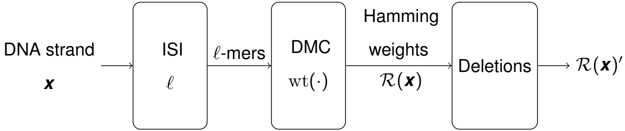

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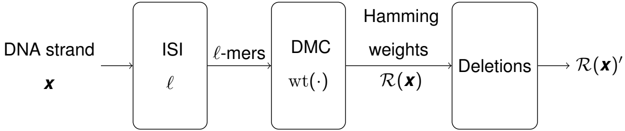

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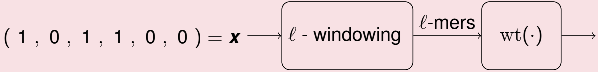

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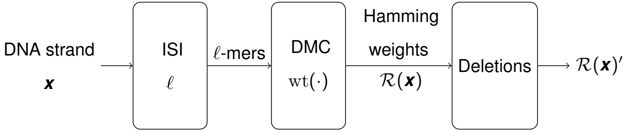

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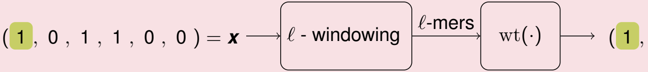

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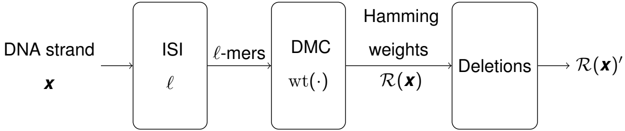

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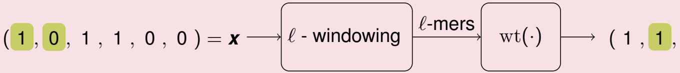

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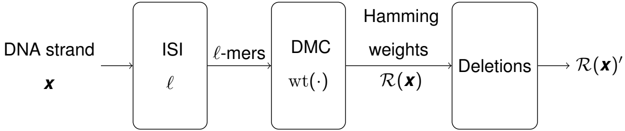

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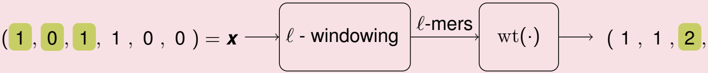

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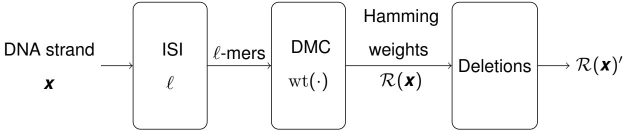

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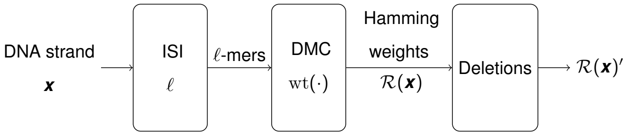

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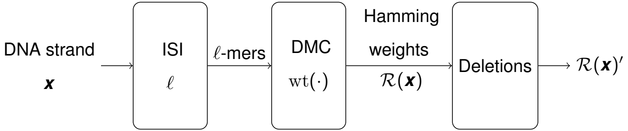

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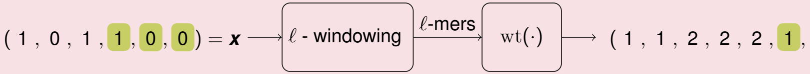

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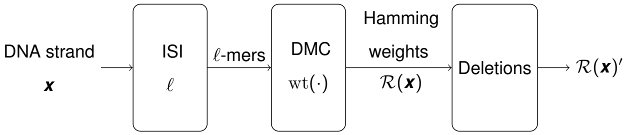

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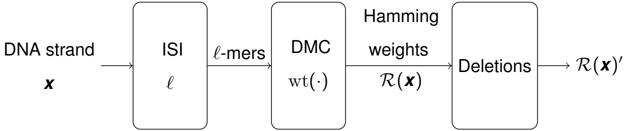

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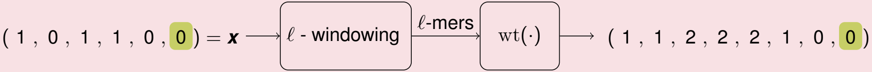

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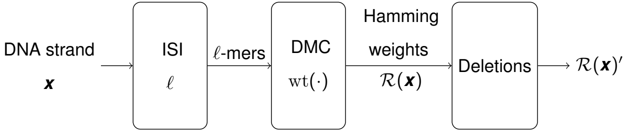

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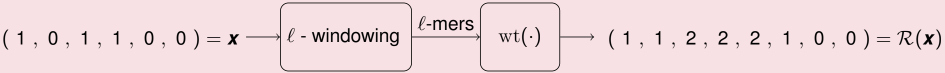

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The ℓ-***read vector*** of any $\boldsymbol{x} \in \Sigma_2^n$ is

$$\mathcal{R}(\boldsymbol{x}) = (\mathrm{wt}(x_1), \mathrm{wt}(\boldsymbol{x}_1^2), \ldots, \mathrm{wt}(\boldsymbol{x}_{n-1}^n), \mathrm{wt}(x_n))$$

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- $\geq \log n - \ell - o(1)$ min redundancy to correct 1 deletion.

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- No redundancy to reconstruct from two noisy ℓ-read vectors.

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Error-correcting Code

Definition

$\mathcal{C}$ is a t- **deletion ℓ-read code** if for all $\boldsymbol{x}, \boldsymbol{y} \in \mathcal{C}$,

$$D_t(\mathcal{R}(\boldsymbol{x})) \cap D_t(\mathcal{R}(\boldsymbol{y})) = \emptyset,$$

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- *Aim:* Find an optimal 1-deletion ℓ-read code.

Naive Deletion Correction

Definition (Read vector)

The ℓ-*read vector* of any $\boldsymbol{x} \in \Sigma_2^n$ is of length $n + \ell - 1$ and denoted by

$$\mathcal{R}(\boldsymbol{x}) = (\mathrm{wt}(x_1), \mathrm{wt}(\boldsymbol{x}_1^2), \ldots, \mathrm{wt}(\boldsymbol{x}_{n-1}^n), \mathrm{wt}(x_n)).$$

Here $\mathcal{R}(\boldsymbol{x})_i = \mathrm{wt}(\boldsymbol{x}_{i-\ell+1}^i)$ where for $j \notin [n]$, let $x_j = 0$.

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- $\mathcal{R}(\boldsymbol{x})_i - \mathcal{R}(\boldsymbol{x})_{i-1} = x_i - x_{i-\ell}$.
- $\boldsymbol{x}$ uniquely determined from the n-prefix of $\mathcal{R}(\boldsymbol{x})$.

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Naive Deletion Correction

Definition (Read vector)

The ℓ-*read vector* of any $\boldsymbol{x} \in \Sigma_2^n$ is of length $n + \ell - 1$ and denoted by

$$\mathcal{R}(\boldsymbol{x}) = (\mathrm{wt}(x_1), \mathrm{wt}(\boldsymbol{x}_1^2), \ldots, \mathrm{wt}(\boldsymbol{x}_{n-1}^n), \mathrm{wt}(x_n)).$$

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Construction

$$\mathcal{C}(n,\ell,a) = \{\boldsymbol{x} \in \Sigma_2^n : \sum_{i=1}^n i(\mathcal{R}(\boldsymbol{x})_i \bmod 2) = a \pmod{n+1}\},$$

where $a \in \{0, \ldots, n\}$.

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$\rightarrow$ Requires $\log_2(n+1)$ redundant bits.

Connection to Sticky Deletion

- **ℓ-sticky deletion** $\rightarrow$ delete in a run with $\geq \ell$ bits.

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Example ($\ell = 3$)

$$\boldsymbol{x} = (1, 0, \underline{1, 1, 1, 1}, 0, 0, 0)$$

$$\mathcal{R}(\boldsymbol{x}) = (1, 1, 2, 2, \boxed{3, 3}, 2, 1, 0, 0, 0)$$

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$$\mathcal{R}(\boldsymbol{x}) = (1, 1, 2, 2, \boxed{3, 3}, 2, 1, 0, 0, 0) \xrightarrow{\ell\text{-deletion}} \mathcal{R}(\boldsymbol{x})' = (1, 1, 2, 2, \boxed{3}, 2, 1, 0, 0, 0)$$

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- ℓ-Sticky deletion in $\boldsymbol{x} \rightarrow 0/\ell$-deletion in $\mathcal{R}(\boldsymbol{x})$!
  - A 1-deletion ℓ-read code also corrects an ℓ-sticky deletion in message.

Minimum Redundancy

Lemma

Any single-deletion ℓ-read code is also a single-ℓ-sticky-deletion-correcting code.

[FVY15] A. Fazeli *et al.*, “Generalized sphere packing bound,” *TIT*, 2015

Minimum Redundancy

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From [FVY15] and concentration arguments,

Theorem

The redundancy of any single-ℓ-sticky-deletion-correcting code is bounded from below by

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$\rightarrow$ Naive VT-like construction optimal up to additive constant!

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Comparison with Classical Channel

- ‘Classical’ $\rightarrow \ell = 1$.
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	Classical	**Nanopore**
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Correction with Two Reads

Lemma

When $\ell \geq 2$, for any two distinct $\boldsymbol{x}, \boldsymbol{y} \in \Sigma_2^n$,

$$|D_1(\mathcal{R}(\boldsymbol{x})) \cap D_1(\mathcal{R}(\boldsymbol{y}))| \leq 1.$$

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$$\begin{aligned} \mathcal{R}(\boldsymbol{x}) &= (\quad \boldsymbol{a} \quad \alpha\beta\alpha\beta\ldots\alpha\beta \quad \boldsymbol{b} \quad) \\ \mathcal{R}(\boldsymbol{y}) &= (\quad \boldsymbol{a} \quad \beta\alpha\beta\alpha\ldots\beta\alpha \quad \boldsymbol{b} \quad) \end{aligned}$$

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$\rightarrow$ Never occurs!

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Reconstruction from Two Reads

- Can reconstruct from two noisy reads with no additional redundancy!

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Algorithm: Reconstruct

Input: n, ℓ, set $\{\mathcal{R}', \mathfrak{R}'\} \subseteq D_1(\mathcal{R}(\boldsymbol{x}))$ for some $\boldsymbol{x} \in \Sigma_2^n$
Output: $\mathcal{R}(\boldsymbol{x})$

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init

    Let i and j be the first and last indices at which $\mathcal{R}'$ and $\mathfrak{R}'$ disagree.
    $\widehat{\mathcal{R}}(\boldsymbol{x}) \leftarrow (\mathcal{R}'_1, \ldots, \mathcal{R}'_{i-1}, \mathfrak{R}'_i, \mathcal{R}'_i, \ldots, \mathcal{R}'_{n+\ell-2})$;
    $\widetilde{\mathcal{R}}(\boldsymbol{x}) \leftarrow (\mathcal{R}'_1, \ldots, \mathcal{R}'_j, \mathfrak{R}'_j, \mathcal{R}'_{j+1}, \ldots, \mathcal{R}'_{n+\ell-2})$.

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if $\widehat{\mathcal{R}}(\boldsymbol{x})$ *is the ℓ-read vector of any vector in* Σ_2^n **then**

$\mathcal{R}(\boldsymbol{x}) \leftarrow \widehat{\mathcal{R}}(\boldsymbol{x})$.

- Efficient verification process [BYWY23] .

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```
init
    Let i and j be the first and last indices at which R' and ℜ' disagree.
    R̂(x) ← (R'_1, ..., R'_{i−1}, ℜ'_i, R'_i, ..., R'_{n+ℓ−2});
    R̃(x) ← (R'_1, ..., R'_j, ℜ'_j, R'_{j+1}, ..., R'_{n+ℓ−2}).
if R̂(x) is the ℓ-read vector of any vector in Σ_2^n then
    R(x) ← R̂(x).
else
    R(x) ← R̃(x).
```

Where: line 2: Let i and j be the first and last indices at which $\mathcal{R}'$ and $\mathfrak{R}'$ disagree; line 3: $\widehat{\mathcal{R}}(\boldsymbol{x}) \leftarrow (\mathcal{R}'_1, \ldots, \mathcal{R}'_{i-1}, \mathfrak{R}'_i, \mathcal{R}'_i, \ldots, \mathcal{R}'_{n+\ell-2})$; line 4: $\widetilde{\mathcal{R}}(\boldsymbol{x}) \leftarrow (\mathcal{R}'_1, \ldots, \mathcal{R}'_j, \mathfrak{R}'_j, \mathcal{R}'_{j+1}, \ldots, \mathcal{R}'_{n+\ell-2})$; line 5: **if** $\widehat{\mathcal{R}}(\boldsymbol{x})$ *is the ℓ-read vector of any vector in* Σ_2^n **then** $\mathcal{R}(\boldsymbol{x}) \leftarrow \widehat{\mathcal{R}}(\boldsymbol{x})$ **else** $\mathcal{R}(\boldsymbol{x}) \leftarrow \widetilde{\mathcal{R}}(\boldsymbol{x})$.

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Introduction

Channel Model

Minimum Redundancy

Multiple Reads

Conclusion

Summary

Results

For a simplified model of nanopore sequencing, we show

- $\log n - \ell - o(1)$ min redundancy needed to correct 1 deletion.
- Explicit construction, optimal up to additive constant.
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Thank you!

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