Correcting Multiple Substitutions in Nanopore-Sequencing Reads

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Department of Computer Science

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Biotechnology and Biological Sciences Research Council

Outline

Motivation

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

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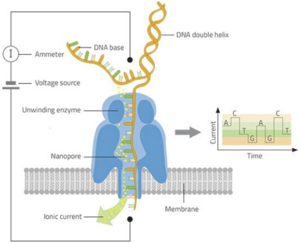
  - \+ Can read longer DNA strands
  - \+ More portable
  - – High error rates



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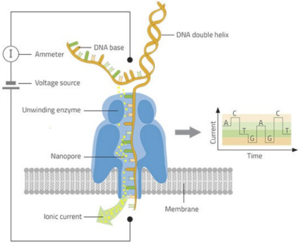
  - − High error rates
- *Aim:* Design coding techniques tailored for nanopore sequencing!



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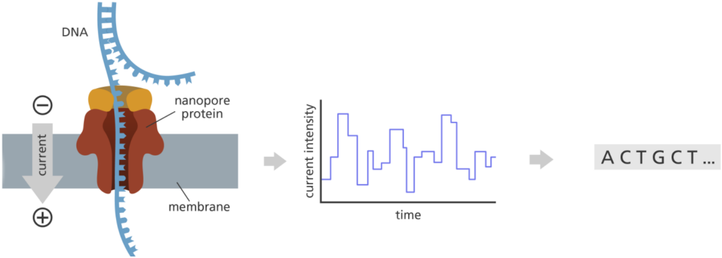
Nanopore Sequencing



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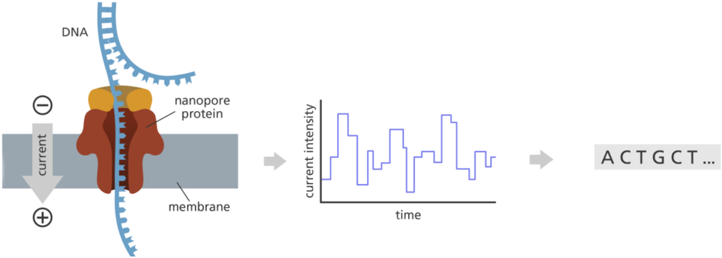

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- Sources of noise [MDK18] :
  - Nanopore holds $\ell > 1$ nucleotides at a time $\rightarrow$ Intersymbol interference (ISI)!
  - Strand moves irregularly $\rightarrow$ backtracking & skipping.
  - Noisy measurements

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

Prior Work

- Channel model & understanding capacity: [MDK18] , [HCW21] , [MVS22] , [RW25]

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- Channel model & understanding capacity: [MDK18] , [HCW21] , [MVS22] , [RW25]
- Similar channel model for racetrack memories: [CVVY21]
- [MDK18] & [CVVY21] inspired a **simplified model** of nanopore sequencing.

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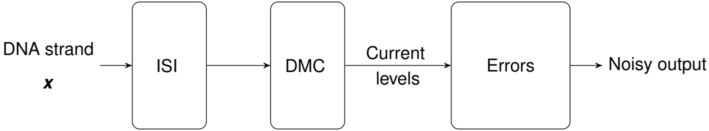

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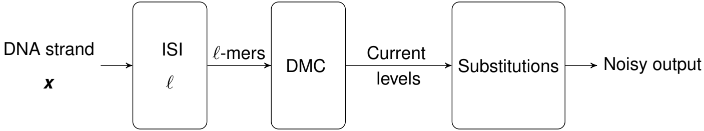

We model

- ISI as length-ℓ-sliding window
- Measurement noise as substitutions

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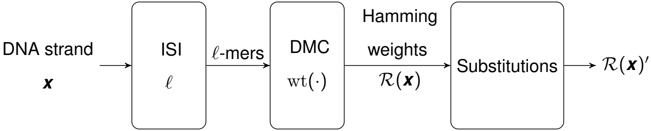

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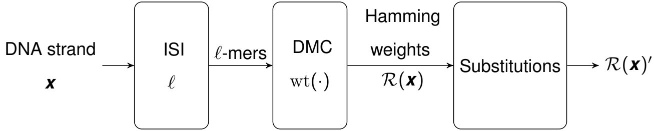

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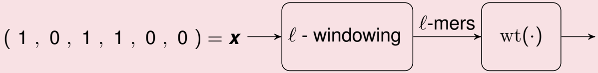

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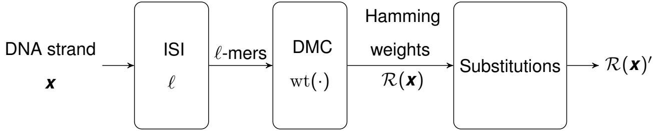

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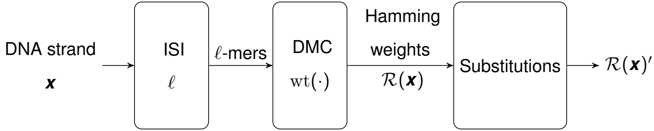

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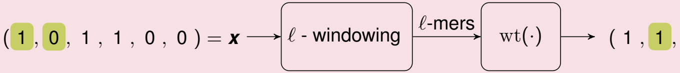

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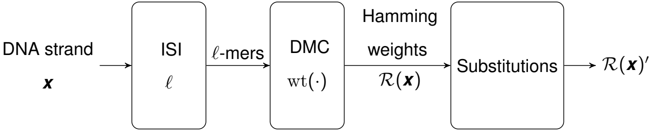

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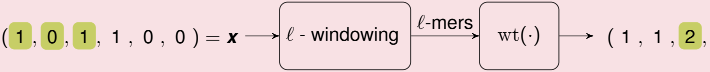

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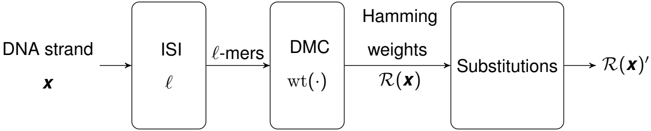

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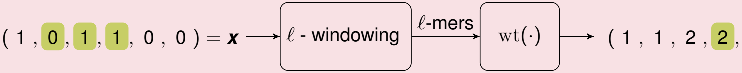

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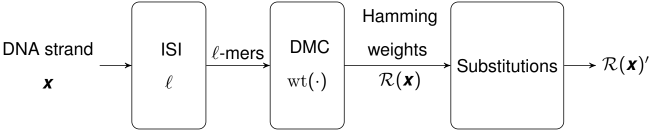

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Example ($\ell = 3$)

$$(1, 0, 1, 1, 0, 0) = \boldsymbol{x} \longrightarrow \boxed{\ell\text{ - windowing}} \xrightarrow{\ell\text{-mers}} \boxed{\mathrm{wt}(\cdot)} \longrightarrow (1, 1, 2, 2, 2,$$

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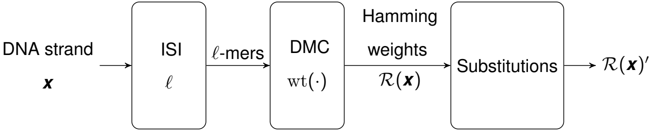

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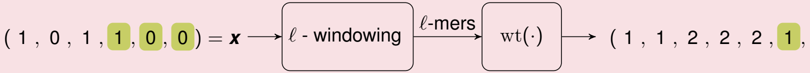

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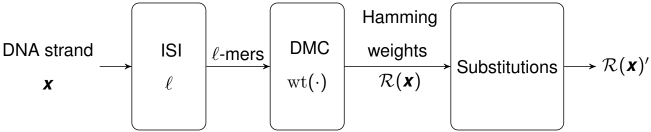

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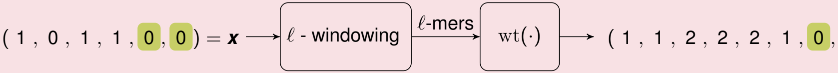

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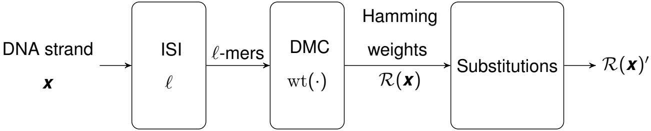

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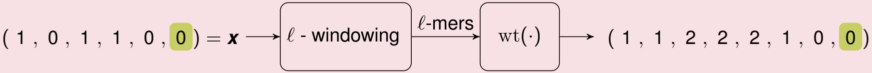

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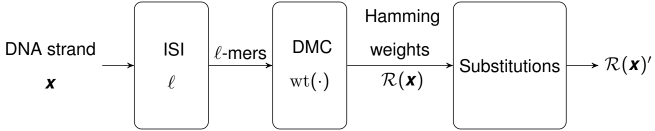

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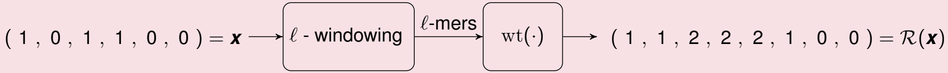

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Simplified Model

Definition

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

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

where $\mathrm{wt}(\cdot)$ denotes Hamming weight.

Y. M. Chee *et al.*, "Coding for transverse-reads in domain wall memories," in *ISIT*, 2021

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- Read vectors have special properties.
  - $|\mathcal{R}(\boldsymbol{x})_i - \mathcal{R}(\boldsymbol{x})_{i-1}| \leq 1 \impliedby \mathcal{R}(\boldsymbol{x})_i - \mathcal{R}(\boldsymbol{x})_{i-1} = x_i - x_{i-\ell}$

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  - $\sum_i \mathcal{R}(\boldsymbol{x})_i \bmod \ell = 0 \Longleftarrow \sum_i \mathcal{R}(\boldsymbol{x})_i = \ell \cdot \mathrm{wt}(\boldsymbol{x})$

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  - $\sum_i \mathcal{R}(\boldsymbol{x})_i \bmod \ell = 0$, etc.
- Can correct substitution errors of abs. value ≥ 2.

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Prior Work

- Error correction for the *read vector* channel
  - [BYWY24] , [BYWY25] , [CIV24] , [SG25] , [YYS25] ....
- *Weighted Read Vector channel* [YEY24]

[BYWY24] A. Banerjee *et al.*, "Error-correcting codes for nanopore sequencing," *TIT*, 2024

[BYWY25] A. Banerjee *et al.*, "Correcting a single deletion in reads from a nanopore sequencer," in *ISIT*, 2024

[CIV24] Y. M. Chee *et al.*, "Coding scheme for noisy nanopore sequencing with backtracking and skipping errors," in *ISIT*, 2024

[SG25] Y. Sun and G. Ge, "Bounds and constructions of ℓ-read codes under the hamming metric," *TIT*, 2025

[YYS25] W. Yu *et al.*, "On the asymptotic rate of optimal codes that correct tandem duplications for nanopore sequencing," *TIT*, 2025

[YEY24] O. Yerushalmi *et al.*, "The capacity of the weighted read channel," in *ISIT*, 2024

ℓ-Read Codes

- Read vectors possess inherent redundancy.
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Definition [Error-correcting Code]

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

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

where $E(\cdot)$ is the error ball.

Comparison with the Classical Channel

- Do ℓ-**read codes** require lesser redundancy?

[15] A. Banerjee *et al.*, "Error-correcting codes for nanopore sequencing," *TIT*, 2024
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Comparison with the Classical Channel

- Do ℓ-**read codes** require lesser redundancy?
  - ‘Classical’ $\rightarrow \ell = 1$.
  - ‘Nanopore’ $\rightarrow \ell \geq 2$.

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	Classical	Nanopore
1 substitution[15]	$\log n$	$\log \log n$
1 deletion[16]	$\log n$	$\log n - \ell$
1 deletion, 2 reads[16]	$\log \log n$	0

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Minimum Redundancy

Theorem

The redundancy of any t**-substitution** ℓ**-read code**, for $t, \ell \geq 2$, is bounded from below by

$$t \log n - O(1).$$

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The redundancy of any ***t*-substitution ℓ-read code**, for $t, \ell \geq 2$, is bounded from below by

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- But for $t = 1$, we need $\log \log n - o(1)$ redundant bits.

Minimum Redundancy

Theorem

The redundancy of any t**-substitution** ℓ**-read code**, for $t, \ell \geq 2$, is bounded from below by

$$t \log n - O(1).$$

- But for $t = 1$, we need $\log \log n - o(1)$ redundant bits.

Why? 🥲

Reconstruction from Noisy Read Vector

- Recall that for any $\boldsymbol{x} \in \Sigma_2^n$,
  - $\mathcal{R}(\boldsymbol{x})_i = \mathrm{wt}(\boldsymbol{x}_{i-\ell+1}^{i})$ and $x_i = 0$ for $i \notin [1, n]$.

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Example ($\ell = 3$)

$$\mathcal{R}(\boldsymbol{x}) \xrightarrow{\text{1substitution}} \mathcal{R}(\boldsymbol{x})' = (\ 1\ ,\ 1\ ,\ 2\ ,\ 3\ ,\ 2\ ,\ 1\ ,\ 0\ ,\ 0\ )$$

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Left to right reconstruction:

- $x_1' = 1$,

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

Left to right reconstruction:

- $x'_1 = 1$, $x'_2 = 0$, $x'_3 = 1$, $x'_4 = 2$ ✗

Reconstruction from Noisy Read Vector

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Example ($\ell = 3$)

$$\mathcal{R}(\boldsymbol{x}) \xrightarrow{\text{1substitution}} \mathcal{R}(\boldsymbol{x})' = (\ 1\ ,\ 1\ ,\ 2\ ,\ 3\ ,\ 2\ ,\ 1\ ,\ 0\ ,\ 0\ )$$

Left to right reconstruction:

- $x'_1 = 1$, $x'_2 = 0$, $x'_3 = 1$, $x'_4 = 2$ ✗
- Error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_4)$.

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

Left to right reconstruction:

- $x_1' = 1$, $x_2' = 0$, $x_3' = 1$, $x_4' = 2$ ✗
- Error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_4)$.

Right to left reconstruction:

$x_6' = 0$

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

Left to right reconstruction:

- $x_1' = 1$, $x_2' = 0$, $x_3' = 1$, $x_4' = 2$ ✗
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Right to left reconstruction:

$x_5' = 0$, $x_6' = 0$

Reconstruction from Noisy Read Vector

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

Left to right reconstruction:

- $x'_1 = 1$, $x'_2 = 0$, $x'_3 = 1$, $x'_4 = 2$ ✗
- Error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_4)$.

Right to left reconstruction:

$x'_4 = 1$, $x'_5 = 0$, $x'_6 = 0$

Reconstruction from Noisy Read Vector

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Left to right reconstruction:

- $x'_1 = 1$, $x'_2 = 0$, $x'_3 = 1$, $x'_4 = 2$ ✗
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- $x_1' = 1$, $x_2' = 0$, $x_3' = 1$, $x_4' = 2$ ✗
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- $x_1' = 0$, $x_2' = 1$, $x_3' = 1$, $x_4' = 1$, $x_5' = 0$, $x_6' = 0$
- No inconsistency, error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_8)$.

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Example ($\ell = 3$)

$$\mathcal{R}(\boldsymbol{x}) \xrightarrow{1\text{substitution}} \mathcal{R}(\boldsymbol{x})' = (\ 1\ ,\ 1\ ,\ 2\ ,\ 3\ ,\ 2\ ,\ 1\ ,\ 0\ ,\ 0\ )$$

Left to right reconstruction:

- $x_1' = 1$, $x_2' = 0$, $x_3' = 1$, $x_4' = 2$ ✗
- Error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_4)$.

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Error in $(\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_4)$.

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Example ($\ell = 3$)

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

$$\boldsymbol{y} = (\,0\,,\,1\,,\,1\,,\,0\,,\,1\,,\,0\,),\;\; \mathcal{R}(\boldsymbol{y}) = (\,0\,,\,1\,,\,2\,,\,2\,,\,2\,,\,1\,,\,1\,,\,0\,)$$

$$d_H(\mathcal{R}(\boldsymbol{x}), \mathcal{R}(\boldsymbol{y})) = 2$$

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- 2 substitutions can lead to a valid ℓ-read vector

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- 2 substitutions can lead to a valid ℓ-read vector $\implies$ can't localize!

Naive Construction

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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- $\boldsymbol{x}$ uniquely determined from n-prefix of $\mathcal{R}(\boldsymbol{x})$.

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Construction (t-substitution-ℓ-read code)

$$\{\boldsymbol{x} \in \Sigma_2^n : (\mathcal{R}(\boldsymbol{x})_1, \ldots, \mathcal{R}(\boldsymbol{x})_n) \bmod 2 \in \mathcal{C}(n,t)\},$$

where $\mathcal{C}(n,t) \subset \Sigma_2^n$ is a t-substitution-correcting code.

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$\rightarrow$ Optimal up to additive constant.

Summary

Results

For a simplified model of nanopore sequencing, we show

- $t \log n - O(1)$ min redundancy needed to correct $t \geq 2$ substitutions.
- Naive construction, optimal up to additive constant.

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Future work

- Multiple deletions & combination with substitutions.
- Weighted read vectors

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For a simplified model of nanopore sequencing, we show

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Thank you!

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