Capacity-Approaching Constrained Codes with Error Correction for DNA-Based Data Storage

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Abstract

We propose coding techniques that limit the length of homopolymers runs, ensure the GC-content constraint, and are capable of correcting a single edit error in strands of nucleotides in DNA-based data storage systems. In particular, for given $\ell, \epsilon > 0$, we propose simple and efficient encoders/decoders that transform binary sequences into DNA base sequences (codewords), namely sequences of the symbols A, T, C and G, that satisfy the following properties:

- Runlength constraint: the maximum homopolymer run in each codeword is at most $\ell$,
- GC-content constraint: the GC-content of each codeword is within $[0.5 - \epsilon, 0.5 + \epsilon]$,
- Error-correction: each codeword is capable of correcting a single deletion, or single insertion, or single substitution error.

For practical values of $\ell$ and $\epsilon$, we show that our encoders achieve much higher rates than existing results in the literature and approach the capacity. Our methods have low encoding/decoding complexity and limited error propagation.

I. INTRODUCTION

In a DNA-based storage system, the input user data is translated into a large number of DNA strands (also known as DNA sequences or oligos), which are synthesized and stored in a DNA pool. To retrieve the original data, the stored DNA strands are sequenced and translated inversely back to the binary data. Several experiments have been conducted since 2012 (see [1]–[7]), and it has been found that substitutions, deletions, and insertions are common errors occurring at the stages of synthesis and sequencing. To improve the reliability of DNA storage, several channel coding techniques, including constrained coding and error correction coding, have been introduced [8]–[12].

In a DNA strand, two properties that significantly increase the chance of errors for most synthesis and sequencing technologies are long homopolymer run [6], [7] and high (or low) GC-content. A homopolymer run refers to the repetition of the same nucleotide. Ross et al. [6] reported that a homopolymer run of length more than six would result in a significant increase of substitution and deletion errors (see [6] Fig. 5), and therefore, such long runs should be avoided. On the other hand, the GC-content of a DNA strand refers to the percentage of nucleotides that are either G or C, and DNA strands with GC-content that are too high or too low are more prone to both synthesis and sequencing errors (see for example, [6], [13]). Therefore, most experiments used DNA strands whose GC-content is close to 50% (for example, between 40% to 60% [7], or 45% to 55% [4]).

Designing efficient constrained codes to translate binary data into DNA strands that satisfy the homopolymer runlength (also known as runlength limited constraint, or RLL constraint in short) and the GC-content constraints has been a challenge. In the literature, several prior art coding techniques have been introduced, mostly focusing on one specific value of maximum runlength or requiring GC-content to be exactly 50%, also known as GC-balanced constraint [8], [9], [11], [12]. To encode GC-balanced codewords, most works used a modification of the Knuth’s balancing method for binary sequences [14]. Since the constraint is strong, the coding redundancy is large (approximately $\log n$, where $n$ is the length of each codeword). In this work, we investigate the problem of translating binary data to DNA strands whose GC-content is close to 50%, and we refer this as almost-balanced. Via a simple modification of Knuth’s method, we show that the number of redundant bits can be gracefully reduced from $\log n$ to $O(1)$.

Constrained codes can reduce the occurrence of substitution, deletion, and insertion errors in the DNA storage system. However, the constrained code itself cannot correct errors. There are recent works that characterize the error probabilities by analyzing data from experiments and then demonstrate the need for error-correction codes. For example, Organick et al. recently stored 200MB of data in 13 million DNA strands and reported substitution, deletion, and insertion rates to be $4.5 \times 10^{-3}$, $1.5 \times 10^{-3}$ and $5.4 \times 10^{-4}$, respectively [5]. Since current technologies can only synthesize strands of DNA of one-two hundred nucleotides, it is most likely that there is at most one error of each type. Motivated by this error behavior, several works focused on the construction of error-correction codes that are capable of correcting the single edit (i.e. a single substitution, or a single deletion, or a single insertion) and its variants [9], [10]. However, a problem of combining constrained codes with both the homopolymer runlength and GC-content constraints with the single-edit-correction codes has not been addressed.

In this work, we propose novel channel coding techniques for DNA storage, where the codebooks satisfy the RLL constraint, the GC-content constraint, and can also correct a single edit and its variants. During the decoding of the proposed constrained
Table I: Notation and Results Summary. The redundancy is computed for DNA codewords of length $n$, given $\ell, \epsilon > 0$.

| Encoder / Decoder | Description | Redundancy | Remark |
|-------------------|-------------|------------|--------|
| $\text{Enc}_{RLL}^A, \text{Dec}_{RLL}^A$ | encoder and decoder for $\ell$-runlength limited codes using enumeration technique | $r_A = n - \lceil \log_4 |\mathcal{C}(n, \ell, q)| \rceil$ (symbols) | Section III-A |
| $\text{Enc}_{RLL}^B, \text{Dec}_{RLL}^B$ | encoder and decoder for $\ell$-runlength limited codes using sequence replacement technique | $r_B = 1(\text{symbol})$ if $n \leq (q - 1)\ell q^{-1} + \ell - 1$ or $\lceil n/(q - 2)\ell q^{-1} + \ell \rceil$ symbols, otherwise | Section III-B |
| $\text{Enc}_{\text{GC}}^2, \text{Dec}_{\text{GC}}^2$ | encoder and decoder for $\epsilon$-balanced quaternary codes using binary template | $r_C = \lceil \log_2 ((1/2\epsilon) + 1) \rceil$ (bits) | Section IV-C |
| $\text{Enc}_{\text{GC}}^D, \text{Dec}_{\text{GC}}^D$ | encoder and decoder for $\epsilon$-balanced quaternary codes using Knuth's technique | $r_D = 2\lceil \log_4 ((1/2\epsilon) + 1) \rceil$ (symbols) | Section IV-D |
| $\text{Enc}_{(\ell, \epsilon)}, \text{Dec}_{(\ell, \epsilon)}$ | constrained encoder/decoder for $\epsilon$-balanced and $\ell$-runlength limited codes | $r_A + r_D + 4$ (symbols) or $r_B + r_D + 4$ (symbols) | Section V |
| $\text{Enc}_{(\ell, \epsilon; \text{indel})}, \text{Dec}_{(\ell, \epsilon; \text{indel})}$ | error-control encoder/decoder for $\epsilon$-balanced and $\ell$-runlength limited codes that can correct an indel | $r_A + r_D + \log_2 n + \Theta(1)$ (symbols) or $r_B + r_D + \log_2 n + \Theta(1)$ (symbols) | Section VI-B |
| $\text{Enc}_{(\ell, \epsilon; \text{edit})}, \text{Dec}_{(\ell, \epsilon; \text{edit})}$ | error-control encoder/decoder for $\epsilon$-balanced and $\ell$-runlength limited codes that can correct an edit | $r_A + r_D + 2\log_2 n + \Theta(1)$ (symbols) or $r_B + r_D + 2\log_2 n + \Theta(1)$ (symbols) | Section VI-C |

II. Notation

Let $\Sigma_q = \{0, 1, 2, \ldots, q - 1\}$ denote an alphabet of size $q \geq 2$. Particularly, when $q = 4$, we use the following relation $\Phi$ between the decimal alphabet $\Sigma_4 = \{0, 1, 2, 3\}$ and the nucleotides $\mathcal{D} = \{A, T, C, G\}$, $\Phi: A \rightarrow A, 1 \rightarrow T, 2 \rightarrow C, 3 \rightarrow G$.

Given two sequences $x$ and $y$, we let $xy$ denote the concatenation of the two sequences. In the special case where $x, y \in \Sigma_q^n$, we use $x|y$ to denote their interleaved sequence $x_1y_1x_2y_2 \ldots x_ny_n$.

Let $\sigma = \sigma_1\sigma_2 \ldots \sigma_n \in \Sigma_q^n$, denote a $q$-ary strand of $n$ nucleotides. The GC-content or weight of strand $\sigma$, denoted by $\omega(\sigma)$, is defined by $\omega(\sigma) = (1/n)\sum_{i=1}^n \varphi(\sigma_i)$ where $\varphi(\sigma_i) = 0$ if $\sigma_i \in \{0, 1\}$ and $\varphi(\sigma_i) = 1$ if $\sigma_i \in \{2, 3\}$. Given $\epsilon > 0$, we say that $\sigma$ is $\epsilon$-balanced if $|\omega(\sigma) - 0.5| \leq \epsilon$, in other words, $\omega(\sigma) \in (0.5 - \epsilon, 0.5 + \epsilon)$. In particular, when $n$ is even and $\epsilon = 0$, we say $\sigma$ is GC-balanced. Over binary alphabet, a vector $x \in \{0, 1\}^n$ is called balanced if the number of ones in $x$, or the weight $\text{wt}(x)$, is $n/2$.

On the other hand, given $\ell > 0$, we say that $\sigma$ is $\ell$-run length limited if any run of the same nucleotide is at most $\ell$. For DNA-based storage, we are interested in codewords that are $\epsilon$-balanced and $\ell$-runlength limited for sufficient small $\epsilon = o(1)$, $\ell = o(n)$.

Definition 1. A nucleotide encoder $\text{ENC} : \{0, 1\}^m \rightarrow \Sigma_q^n$ is a $(\epsilon, \ell)$-constrained encoder if $\text{ENC}(x)$ is $\epsilon$-balanced and $\ell$-runlength limited for all $x \in \{0, 1\}^m$. codes, a small number of corrupted bits at the channel output might lead to massive error propagation of the decoded bits. Our proposed combination of constrained codes with error-correction codes also helps to minimize the error prorogation during decoding.

The paper is organized as follows. We first go through certain notations in Section II. In Section III, we present two efficient RLL coding methods that limit the maximum homopolymer run in each codeword to be at most $\ell$ for arbitrary $\ell > 0$. Our methods are based on enumeration coding and sequence replacement technique, respectively. In Section IV, via a simple modification of Knuth's balancing method, we describe linear-time encoders/decoders that translate binary data to DNA strands whose GC-content is within $[0.5 - \epsilon, 0.5 + \epsilon]$ for arbitrary $\epsilon > 0$. This method yields a significant improvement in coding redundancy with respect to prior works. Then, in Section V, we present an efficient $(\ell, \epsilon)$-constrained coding method where codewords obey both RLL constraint and GC-content constraint. In Section VI, we modify the $(\ell, \epsilon)$-constrained coding so that the codewords can correct a single deletion, or single insertion, or single substitution error.

For the convenience of the reader, relevant notation and terminology referred to throughout the paper is summarized in Table I.
Motivated by the error behavior in DNA storage, we investigate constrained codes that also have error-correction capability. Such codes are referred as error-control-codes. We use $B$ to denote the error ball function. For a sequence $x \in \Sigma_q^*$, let $B^D(x)$, $B^I(x)$, and $B^S(x)$ denote the set of all words obtained from $x$ via a single deletion, single insertion, or at most one substitution, respectively, and set
\[
\begin{align*}
B^{\text{indel}}(x) & \triangleq B^I(x) \cup B^D(x), \quad B^{\text{edit}}(x) \triangleq B^S(x) \cup B^I(x) \cup B^D(x).
\end{align*}
\]

Observe that when $\sigma \in \Sigma_q^*$, both $B^{\text{indel}}(\sigma)$ and $B^{\text{edit}}(\sigma)$ are subsets of $\Sigma_q^{n-1} \cup \Sigma_q^n \cup \Sigma_q^{n+1}$. Hence, for convenience, we use $\Sigma_q^n$ to denote the set $\Sigma_q^{n-1} \cup \Sigma_q^n \cup \Sigma_q^{n+1}$.

\textbf{Definition 2.} Let $C \subseteq \Sigma_q^n$. Given $\epsilon, \ell > 0$ and the error ball function $B$, we say that $C$ is an $(\epsilon, \ell; B)$-error control codes if
(i) For all $c \in C$, $c$ is $\epsilon$-balanced,
(ii) For all $c \in C$, $c$ is $\ell$-runlength limited, and
(iii) $B(c) \cap B(c') = \emptyset$ for all distinct $c, c' \in C$.

For a code $C \subseteq \Sigma_q^n$, the rate, denoted by $\text{rate}_C$, is defined by $\text{rate}_C \triangleq (1/n) \log_q |C|$. The asymptotic rate of the family of codes $\{C(n, N; q)\}_{n=1}^{\infty}$ is defined by $\lim_{n \to \infty} (1/n) \log_q |C|$, if the limit exists.

\textbf{Definition 3.} A nucleotide encoder $\text{ENC} : \{0, 1\}^m \mapsto \Sigma_q^*$ is an $(\epsilon, \ell; B)$-error-control-encoder if $\text{ENC}(x)$ is $\epsilon$-balanced and $\ell$-runlength limited for all $x \in \{0, 1\}^m$, furthermore there exists a decoder map $\text{DEC} : \Sigma_q^* \mapsto \{0, 1\}^m$ such that the following hold.
(i) For all $x \in \{0, 1\}^n$, we have $\text{DEC} \circ \text{ENC}(x) = x$.
(ii) If $c = \text{ENC}(x)$ and $c' \in B(c)$, then $\text{DEC}(c') = x$.

Hence, we have that the code $C = \{ c : c = \text{ENC}(x), x \in \{0, 1\}^m \}$ and hence, $|C| = 2^m$. The redundancy of the encoder is measured by the value $2n - m$ (in bits) or $n - m/2$ (nucleotide symbols).

\section{Efficient Homopolymer Runlength Limited Codes}

We present two methods of constructing maximum runlength limited $q$-ary constrained codes. Method A uses enumerative coding technique to rank/unrank all codewords. While the technique is standard in constrained coding and combinatorics literature, our contribution is a detailed analysis of the space and time complexities of the respective algorithm. The encoder achieves maximum code rate, for example, when $\ell = 3, n = 200, q = 4$, the rate of the encoder is 1.98 bits/nt. However, the time and space complexity is $O(n^2)$, which makes it less attractive than the sequence replacement technique in Method B.

\subsection{Method A Based on Enumeration Coding}

Let $C(n, \ell, q)$ denote the set of all $q$-ary $\ell$-runlength limited sequences of length $n$. We first obtain a recursive formula for the size of $C(n, \ell, q)$. This recursive formula is useful in the development of the ranking/unranking methods. To this end, we partition $C(n, \ell, q)$ into $\ell$ classes and provide bijections from $q$-ary $\ell$-runlength limited sequences of shorter lengths into them. For $1 \leq i \leq \ell$, let $C_i(n, \ell, q)$ denote the set of all $q$-ary $\ell$-runlength limited sequences of length $n$ whose suffix is the repetition of a symbol in $\Sigma_q$ for exactly $i$ times. Clearly, we have $C_i(n, \ell, q) \cap C_j(n, \ell, q) = \emptyset$ for $i \neq j$ and
\[
C(n, \ell, q) = \bigcup_{i=1}^{\ell} C_i(n, \ell, q).
\]

Let $[n]$ denote the set $\{1, 2, \ldots, n\}$. Consider $\ell$ maps $\phi_1, \phi_2, \ldots, \phi_{\ell}$ where
\[
\phi_i : C(n - i, \ell, q) \times [q - 1] \mapsto C_i(n, \ell, q), \quad \text{for } 1 \leq i \leq \ell.
\]

If $x = x_1x_2 \ldots x_{n-i} \in C(n - i, \ell, q)$ and $j \in [q - 1]$, set $a$ to be the $j$th element in $\Sigma_q \setminus \{x_{n-i}\}$. Then set $\phi_i(x, j) = x_1x_2 \ldots x_{n-i}a^j$. Here, $a^j$ denotes the repetition of symbol $a$ for $i$ times.

\textbf{Theorem 4.} For $1 \leq i \leq \ell$, the map $\phi_i$ is a bijection. We then have the following recursion. For $1 \leq n \leq \ell$, $|C(n, \ell, q)| = q^\ell$, and for $n > \ell$
\[
|C(n, \ell, q)| = \sum_{i=1}^{\ell} (q - 1)|C(n - i, \ell, q)|.
\]

Therefore, $\text{rate}_{C(n, \ell, q)} = \log_q \lambda$, where $\lambda$ is the largest real root of equation $x^\ell - \sum_{i=0}^{\ell-1}(q - 1)x^i = 0$.

\textbf{Proof.} We can prove that $\phi_i$ is bijection for $1 \leq i \leq \ell$ by constructing the inverse map $\phi_i^{-1}$. Specifically, we set $\phi_i^{-1} : C_i(n, \ell, q) \mapsto C(n - i, \ell, q) \times [q - 1]$ such that for $x = x_1x_2 \ldots x_n \in C_i(n, \ell, q)$, $\phi_i^{-1}(x) = (x_1 \ldots x_{n-i}, j)$ where $j$ is the
index of $x_n$ in $\Sigma_q \setminus \{x_{n-i}\}$. It can be verified that $\phi_i \circ \phi_i^{-1}$ and $\phi_i^{-1} \circ \phi_i$ are identity maps on their respective domains. Since $\mathcal{C}(n, \ell, q) = \bigcup_{i=1}^{\ell} \mathcal{C}_i(n, \ell, q)$, we then have for $n > \ell$

$$|\mathcal{C}(n, \ell, q)| = \sum_{i=1}^{\ell} (q - 1)|\mathcal{C}(n - i, \ell, q)|.$$

We now construct the RLL-Encoder $A$ by providing a method of ranking/unranking all codewords in $\mathcal{C}(n, \ell, q)$. A ranking function for a finite set $S$ of cardinality $N$ is a bijection $\phi : S \rightarrow [N]$. Associated with the function rank is a unique unranking function $\text{unrank} : [N] \rightarrow S$, such that $\text{rank}(s) = j$ if and only if $\text{unrank}(j) = s$ for all $s \in S$ and $j \in [N]$.

The basis of our ranking and unranking algorithms is the bijections $\{\phi_i\}_{i=1}^{\ell}$ defined earlier. As implied by the codomains of these maps, for $n > \ell$, we order the words in $\mathcal{C}(n, \ell, q)$ such that words in $\mathcal{C}_i(n, \ell, q)$ are ordered before words in $\mathcal{C}_j(n, \ell, q)$ for $i < j$. For words in $\mathcal{C}(n, \ell, q)$ where $n \leq \ell$, we simply order them lexicographically. We illustrate the idea behind the unranking algorithm through an example.

Example 5. Let $n = 5, q = 4, \ell = 3$. We then have $|\mathcal{C}(n, 3, 4)| = 3|\mathcal{C}(n - 1, 3, 4)| + 3|\mathcal{C}(n - 2, 3, 4)| + 3|\mathcal{C}(n - 3, 3, 4)|$ and the values of $\mathcal{C}(m, 3, 4)$ are as follow.

| $m$ | $\ell \leq 2(m, q)$ |
|-----|-------------------|
| 4   | 1                 |
| 16  | 2                 |
| 64  | 3                 |
| 252 | 4                 |
| 996 | 5                 |

Suppose we want to compute the 900th codeword $c \in \mathcal{C}(5, 3, 4)$, in other words, $\text{unrank}(900)$. We have

$$\mathcal{C}(5, 3, 4) = \mathcal{C}_1(5, 3, 4) \cup \mathcal{C}_2(5, 3, 4) \cup \mathcal{C}_3(5, 3, 4) = \phi_1(\mathcal{C}(4, 3, 4) \times [3]) \cup \phi_2(\mathcal{C}(3, 3, 4) \times [3]) \cup \phi_3(\mathcal{C}(2, 3, 4) \times [3]),$$

Since $900 > 3|\mathcal{C}(4, 3, 4)| = 756$ and $900 < 3|\mathcal{C}(3, 3, 4)| + 3|\mathcal{C}(3, 3, 4)| = 948$, the 900th codeword of $\mathcal{C}(5, 3, 4)$, which is the $900 - 756 = 144$th codeword in $\mathcal{C}_2(5, 3, 4)$, is the image of map $\phi_2$. Since $144 = 3 \times 48 + 0$, the construction of $\phi_2$ tells us that the 144th codeword in $\mathcal{C}_2(5, 3, 4)$ is the image of the 48th codeword, $x \in \mathcal{C}(3, 3, 4)$ under $\phi_2$. The 48th word of $\mathcal{C}(3, 3, 4)$ is 344. Hence, $c = \phi_2(x, 3)$ This gives

$$\text{unrank}(900) = \phi_2(344, 3) = 34433$$

The formal unranking/ranking algorithms are described in Algorithm 1 and Algorithm 2.

**Algorithm 1** unrank($n, \ell, q, M$)

**Input:** Integers $n \geq 1, \ell \geq 1, q \geq 2, 1 \leq M \leq |\mathcal{C}(n, \ell, q)|$
**Output:** $c$, where $c$ is the codeword of rank $M$ in $\mathcal{C}(n, \ell, q)$

if $n \leq \ell$
return $M$th codeword in $\mathcal{C}(n, \ell, q)$

**Search the first index** $1 \leq j \leq \ell$ such that

$$M \leq \sum_{i=1}^{j} (q - 1)|\mathcal{C}(n - i, \ell, q)|$$

$$M' \leftarrow \sum_{i=1}^{j} (q - 1)|\mathcal{C}(n - i, \ell, q)| - M$$

$$M'' \leftarrow \lceil M'/\ (q - 1) \rceil$$

$k \leftarrow M' \ (\mod q - 1)$
return $\phi_j(\text{unrank}(n - j, \ell, q, M''), k)$

**Algorithm 2** rank($n, \ell, q, c$)

**Input:** $n \geq 1, \ell \geq 1, q \geq 2$ and codeword $c = c_1c_2 \ldots c_n$
**Output:** $M$, where $1 \leq M \leq |\mathcal{C}(n, \ell, q)|$, the rank of $c$ in $\mathcal{C}(n, \ell, q)$

if $n \leq \ell$
return rank($c$) in $\mathcal{C}(n, \ell, q)$

if the suffix of $c$ is the repetition of symbol $a$ for $i$ times then

$c' \leftarrow c_1c_2 \ldots c_{n-i}$

$i \leftarrow$ the index of $a$ in $\Sigma_q \setminus \{c_{n-i}\}$

return $(\text{rank}(n - i, \ell, q, c') - 1)(q - 1) + i + \sum_{j=1}^{i-1} (q - 1)|\mathcal{C}(n - j, \ell, q)|$
Example 6. Let \( n = 5, \ell = 3 \) and \( q = 4 \) as before. Suppose we want to compute \( \text{rank}(34433) \). Since 34433 \( \in \mathbb{C}_2(5, 3, 4) \), we have that 34433 is obtained from applying \( \phi_2 \) to 344 \( \in \mathbb{C}(3, 3, 4) \). The adding symbol is 3, which is the third element in \( \Sigma_4 \setminus \{4\} \). Therefore,
\[
\text{rank}(34433) = 3|\mathbb{C}(4, 3, 4)| + 3(\text{rank}(344) - 1) + 3 \\
= 3 \times 252 + 3 \times 47 + 3 \\
= 900.
\]
The set of values of \{\( |\mathbb{C}(m, \ell, q)| : m \leq n \)\} required in Algorithms 1 and 2 can be precomputed based on the recurrence in Theorem 4. Since the size of \( \mathbb{C}(n, \ell, q) \) grow exponentially, these \( n \) stored values require \( O(n^2) \) space.

Next, Algorithms 1 and 2 involve \( O(n) \) iterations and each iteration involves a constant number of arithmetic operations. Therefore, Algorithms 1 and 2 involve \( O(n) \) arithmetic operations and have time complexity \( O(n^2) \). For completeness, we summarize the RLL-Encoder A and RLL-Decoder A as follows.

**RLL-Encoder A.** Set \( m = \lceil \log_2 |\mathbb{C}(n, \ell, q)| \rceil \).

**INPUT:** \( x \in \{0, 1\}^m \)

**OUTPUT:** \( c \triangleq \text{ENC}^A_{RLL}(x) \in \mathbb{C}(n, \ell, q) \)

(I) Let \( M \) be the positive integer whose binary representation of length \( m \) is \( x \).

(II) Use Algorithm 1 set \( c = \text{unrank}(n, \ell, q, M) \).

(III) Output \( c \).

**RLL-Decoder A.** Set \( m = \lceil \log_2 |\mathbb{C}(n, \ell, q)| \rceil \).

**INPUT:** \( c \in \mathbb{C}(n, \ell, q) \)

**OUTPUT:** \( x \triangleq \text{DEC}^A_{RLL}(c) \in \{0, 1\}^m \)

(I) Use Algorithm 2 set \( M = \text{rank}(n, \ell, q, c) \).

(II) Let \( x \) be the binary representation of length \( m \) of \( M \).

(III) Output \( x \).

**B. Method B Based on Sequence Replacement Technique**

The sequence replacement technique has been widely used in the literature [8], [15]–[17]. This is an efficient method for removing forbidden substrings from a source word. In general, the encoder removes the forbidden strings and subsequently inserts its representation (which also includes the position of the substring) at predefined positions in the sequence. For example, Schoeny et al. [17] used only one redundant bit to encode RLL binary sequences with \( \ell \geq \lceil \log n \rceil + 3 \). However, for DNA data storage, with \( n \in [100, 200] \), it is normally required that \( \ell \leq 6 \). Recently, Immink et al. [8] described a simple method for constructing \( \ell \)-runlength limited \( q \)-ary codes. However, the required codeword length \( n \) is bounded by a function of \( \ell \) and \( q \). For example, when \( \ell = 3 \), the method is only applicable for \( n \leq 39 \) (refer to [8, Table II]). In this work, we show that such bound can be improved, and hence, the redundancy can be further reduced. For DNA storage channel, when \( n \leq 200 \), \( \ell \in \{5, 6\} \), our encoder incurs only one redundant symbol.

**Definition 7.** For a sequence \( x = x_1x_2 \ldots x_n \in \Sigma_q^n \), the differential of \( x \), denoted by \( \text{Diff}(x) \), is a sequence \( y = y_1y_2 \ldots y_n \in \Sigma_q^n \), where \( y_1 = x_1 \) and \( y_i = x_i - x_{i-1} \) (mod \( q \)) for \( 2 \leq i \leq n \).

It is easy to see that from \( y = y_1y_2 \ldots y_n = \text{Diff}(x) \), we can determine \( x \) uniquely as \( x_i = \sum_{j=1}^i y_j \) (mod \( q \)) for \( 1 \leq i \leq n \). For convenience, we write \( x = \text{Diff}^{-1}(y) \).

**Lemma 8.** Let \( x \in \Sigma_q^N \). If the longest run of zero in \( \text{Diff}(x) \) is at most \( \ell - 1 \) then \( x \) is \( \ell \)-runlength limited.

We now present an efficient encoder for \( \ell \)-runlength limited \( q \)-ary codes, and refer this as RLL Encoder B or \( \text{ENC}^B_{RLL} \). For a source data \( x \in \Sigma_q^{N-1} \), we encode \( y = \text{ENC}(x) \in \Sigma_q^N \) such that \( y \) contains no \( 0^\ell \) as a substring, and then output \( c = \text{Diff}^{-1}(y) \).

**Initial Step.** The encoder simply appends a ‘0’ to the end of \( x \), yielding the \( N \)-symbols word, \( x0 \). The encoder then checks the word \( x0 \), and if there is no substring \( 0^\ell \), the output is simply \( c = x0 \). Otherwise, it proceeds to the replacement step.

**Replacement Procedure.** Let the current word \( c = y0^pz \), where, by assumption, the prefix \( y \) has no forbidden \( 0^\ell \) and the run \( 0^\ell \) starts at position \( p \), where \( 1 \leq p \leq N - \ell \). The encoder removes \( 0^\ell \) and updates the current word to be \( c = yzRe \), where the pointer \( Re \) is used to represent the position \( p \), and

(i) \( R \in \Sigma_q^{p-1} \),
(ii) \( e \in \Sigma_q \setminus \{0\} \).

Note that the number of unique combinations of the pointer \( Re \) equals \( (q-1)q^{\ell-1} \). Note that the current word \( c = yzRe \) is of length \( N \). If, after the replacement, \( c \) contains no substring \( 0^\ell \) then the encoder returns \( c \) as the codeword. Otherwise, the
Theorem 12. Let the word \( y \) be balanced. If the word \( x \) is \( \epsilon \)-balanced, it is \( \epsilon \)-balanced.

Decoding Procedure. The decoder checks from the right to the left. If the last symbol is '0', the decoder simply removes the symbol '0' and identifies the first \( N - 1 \) symbols are source data. On the other hand, if the last symbol is not '0', the decoder takes the suffix of length \( \ell \), identifies it is the pointer, and then adds back the substring \( 0^\ell \) accordingly. It terminates when the first symbol '0' is found.

Remark 9. The bound in (1) implies that for \( q = 4, \ell \in \{4, 5, 6\} \), our encoder uses only one redundant symbol for all \( n \leq 196 \). Table 27 shows the improvement with respect to the result provided in [8]. In addition, this algorithm can be easily extended for the case of arbitrary length \( n \gg N \). The main idea is that we divide the source data into subwords of length \( N - 1 \), encode separately each subword and concatenate them. The representation pointer needs to be modified so that the concatenation between any two encoded subwords does not contain a substring \( 0^\ell \). To do so, we simply append '1' to the end of the source data instead, and require the pointers of the form \( R_e \) where \( R \in \Sigma_q^{\ell-1} \) and \( e \notin \{0, 1\} \). The replacement procedure and decoding procedure can be proceeded similarly.

| \( \ell \setminus n_{\text{max}} \) | Bound in [1] | Previous work [8] |
|---|---|---|
| 2 | 13 | 11 |
| 3 | 50 | 39 |
| 4 | 195 | 148 |
| 5 | 772 | 581 |

TABLE II: Maximum length \( n \) that an encoder can achieve the rate \((n - 1)/n\) for \( \ell \)-runlength limited quaternary codes.

IV. EFFICIENT GC-CONTENT CONSTRAINED CODES

In this section, we propose linear-time encoders/decoders that translate binary input data to DNA strands whose GC-content is within \([0.5 - \epsilon, 0.5 + \epsilon]\) for arbitrary \( \epsilon > 0 \), with fixed number of redundant bits. This method yields a significant improvement in coding redundancy with respect to the prior works. We first review the Knuth's balancing technique.

A. Knuth's Balancing Technique

Knuth's balancing technique is a linear-time algorithm that maps a binary message \( x \) to a balanced word \( y \) of the same length by flipping the first \( t \) bits of \( x \). The crucial observation demonstrated by Knuth is that such an index \( t \) always exists and \( t \) is commonly referred to as the balancing index. To represent the balancing index, Knuth appends \( y \) with a short balanced suffix of length \( \log n \) and so, a lookup table of size \( \log n \) is required.

Several works in the literature used this technique to encode DNA strands whose GC-content is exactly balanced (for example, [9], [12]), and the coding redundancy is approximately \( \log n \). We generalize this technique for binary codes first.

B. Generalization of Knuth’s Balancing Technique

Definition 10. Let \( n \) be even. For arbitrary \( \epsilon > 0 \), a binary word \( x \in \{0, 1\}^n \) is \( \epsilon \)-balanced if the weight of \( x \), \( \text{wt}(x) \), satisfies

\[
\left| \frac{\text{wt}(x)}{n} - 0.5 \right| \leq \epsilon.
\]

In other words, we have \( 0.5n - \epsilon n \leq \text{wt}(x) \leq 0.5n + \epsilon n \).

Definition 11. Let \( n \) be even. For arbitrary \( \epsilon > 0 \), the index \( t \), where \( 1 \leq t \leq n \), is called the \( \epsilon \)-balanced index of \( x \in \{0, 1\}^n \) if the word \( y \) obtained by flipping the first \( t \) bits in \( x \) is \( \epsilon \)-balanced.

We now show that such an index \( t \) always exists and there is an efficient method to find \( t \). For \( n \) even, let the \( \epsilon \)-balanced set \( S_{\epsilon,n} \subset \{0, 1, 2, \ldots, n\} \) be the set of the following indices.

\[
S_{\epsilon,n} = \{0, n\} \cup \{2\lfloor\epsilon n\rfloor, 4\lfloor\epsilon n\rfloor, 6\lfloor\epsilon n\rfloor, \ldots\}.
\]

The size of \( S_{\epsilon,n} \) is at most \( \lfloor 1/2\epsilon \rfloor + 1 \).

Theorem 12. Let \( n \) be even, \( \epsilon > 0 \). For arbitrary binary sequence \( x \in \{0, 1\}^n \), there exists an index \( t \) in the set \( S_{\epsilon,n} \), such that \( t \) is the \( \epsilon \)-balanced index of \( x \).
The trivial case, when \( x \) is \( \epsilon \)-balanced, the index \( t = 0 \), which is in the set \( S_{\epsilon,n} \). Assume that \( x \) is not \( \epsilon \)-balanced, and without loss of generality, assume that \( \wt(x) < 0.5n - \epsilon n \). Let \( \text{Flip}_k(x) \) be the word obtained by flipping the first \( k \) bits in \( x \). Since \( \wt(x) < 0.5n - \epsilon n \), we have \( \wt(\text{Flip}_k(x)) > 0.5n + \epsilon n \). Now consider the list of indices that we try to obtain an \( \epsilon \)-balanced word, \( t_1 = 2\lceil \epsilon n \rceil, t_2 = 4\lceil \epsilon n \rceil \), and so on. Since \( \text{Flip}_{t_1}(x) \) and \( \text{Flip}_{t_1}(x) \) differ at most \( 2\epsilon n \) positions, and \( \wt(x) < 0.5n - \epsilon n \), \( \wt(\text{Flip}_k(x)) > 0.5n + \epsilon n \), there must be an index \( t \) such that \( 0.5n - \epsilon n \leq \wt(\text{Flip}_k(x)) \leq 0.5n + \epsilon n \). □

We provide two methods to construct GC-Content constrained codes. The first method uses \( \epsilon \)-balanced binary codes as a template to construct \( \epsilon \)-balanced quaternary codes with at most \( \log \left( \lceil 1/\epsilon \rceil + 1 \right) \) bits of redundancy. On the other hand, the second method proceeds directly over quaternary alphabet and appends a short balanced suffix to the end of each codeword to indicate the \( \epsilon \)-balanced index.

C. Binary Construction of GC-Content Constrained Codes

When \( q = 4 \), we consider the following one-to-one correspondence between quaternary alphabet and two-bit sequences:

\[
0 \leftrightarrow 00, \quad 1 \leftrightarrow 01, \quad 2 \leftrightarrow 10, \quad 3 \leftrightarrow 11.
\]

Therefore, given a DNA sequence \( \sigma \) of length \( n \), we have a corresponding binary sequence \( x \in \{0, 1\}^{2n} \) and we write \( x = \Psi(\sigma) \) or \( \sigma = \Psi^{-1}(x) \). Let \( x = \Psi(\sigma) \in \{0, 1\}^{2n} \) and we set \( U_\sigma = x_1 x_3 \cdots x_{2n-1} \) and \( L_\sigma = x_2 x_4 \cdots x_{2n} \). In other words, \( \sigma = \Psi^{-1}(U_\sigma|L_\sigma) \). We refer to \( U_\sigma \) and \( L_\sigma \) as the upper sequence and lower sequence of \( \sigma \), respectively. The following result is immediate.

Lemma 13. Let \( \sigma \in \Sigma_4^n \). We have \( \sigma \) is \( \epsilon \)-balanced if and only if \( U_\sigma \) is \( \epsilon \)-balanced.

\( \epsilon \)-GC-Encoder C. Given \( n, \epsilon > 0 \), set \( k = \lceil \log \left( \lceil 1/\epsilon \rceil + 1 \right) \rceil \) and \( m = 2n - k \). Set \( S_{\epsilon,n} \) be the set of indices as constructed in (2.1) and we construct a one-to-one correspondence between the indices in \( S_{\epsilon,n} \) and \( k \) bits sequences.

INPUT: \( x \in \{0, 1\}^n, y \in \{0, 1\}^{n-k} \) and so \( xy \in \{0, 1\}^m \)

OUTPUT: \( \sigma = \text{ENC}_{\text{GC}}(xy) \)

(I) Search for the first \( t \) in \( S_{\epsilon,n} \), such that \( \text{Flip}_t(x) \) is \( \epsilon \)-balanced.

(II) Set \( x' = \text{Flip}_t(x) \).

(III) Let \( z \) be the \( k \) bits sequence representing index \( t \).

(IV) Set \( y' = yz \) of length \( n \).

(V) Finally, we set \( \sigma = \Psi^{-1}(x'|y') \).

Example 14. Let \( n = 10, \epsilon = 0.1, k = \lceil \log \left( \lceil 1/\epsilon \rceil + 1 \right) \rceil = 3 \), i.e. we want the GC-content of each codeword is within \([0.4, 0.6]\). The set \( S_{\epsilon,n} = \{0, 2, 4, 6, 8, 10\} \) is of size six. We construct the one-to-one correspondence between the indices and 3 bits sequences: \( 0 \to 000, 2 \to 001, 4 \to 010, 6 \to 100, 8 \to 011 \) and \( 10 \to 111 \). Suppose the input sequence is \( c = 0^{17} \), i.e \( x = 0^{10} \) and \( y = 0^{7} \). We find the index \( t = 4 \). Follow the encoder, we get \( x' = 1111000000 \) and \( y' = 0000000010 \). We then obtain \( \sigma = \Psi^{-1}(x'|y') = 2222000010 \).

\( \epsilon \)-GC-Decoder C. Given \( n, \epsilon > 0 \), set \( k = \lceil \log \left( \lceil 1/\epsilon \rceil + 1 \right) \rceil \) and \( m = 2n - k \).

INPUT: \( \sigma \in \Sigma_4^n, \sigma \) is \( \epsilon \)-balanced

OUTPUT: \( xy \in \{0, 1\}^m \)

(I) Set \( x' = U_\sigma \in \{0, 1\}^n \) and \( y' = L_\sigma \in \{0, 1\}^n \).

(II) Set \( z \) be the suffix of length \( k \) in \( y' \) and let \( t \) be the index in \( S_{\epsilon,n} \) corresponding to \( z \).

(III) Set \( x = \text{Flip}_t(x') \).

(IV) Set \( y = y' \) removes \( z \)

(V) Finally, we output \( xy \).

Remark 15. For constant \( \epsilon > 0 \), the complexity of an \( \epsilon \)-GC-Encoder C is linear and the redundancy is constant. For example, when \( n = 200, \epsilon = 0.1 \), i.e. the GC-content is within \([0.4, 0.6]\), the set \( S_{\epsilon,n} = \{0, 40, 80, 120, 160, 200\} \) is of size six. The \( \epsilon \)-GC-Encoder C uses only \( \lceil \log 6 \rceil = 3 \) bits of redundancy to indicate the \( \epsilon \)-balanced index in the lower sequence and the rate of the encoder is 1.985 bits/nt. Similarly, when \( \epsilon = 0.05 \), i.e. the GC-content is within \([0.45, 0.55]\), the \( \epsilon \)-GC-Encoder C uses only \( \lceil \log 11 \rceil = 4 \) bits of redundancy and the rate is 1.98 bits/nt.

D. Knuth-like Construction of GC-Content Constrained Codes

Consider the quaternary alphabet \( \Sigma_4 = \{0, 1, 2, 3\} \). To apply Knuth’s method, we define the flipping rule \( f : \Sigma_4 \to \Sigma_4 \), where \( f(0) = 2, f(2) = 0, f(1) = 3 \) and \( f(3) = 1 \). For a sequence \( \sigma \in \Sigma_4^n \) and index \( i \) with \( 0 \leq i \leq n \), \( f_i(\sigma) \) denotes the sequence obtained by flipping the first \( i \) symbols of \( \sigma \) under \( f \).
**Lemma 19.** Let \( \epsilon > 0 \), the index \( t \), where \( 1 \leq t \leq n \), is called the \( \epsilon \)-balanced index of \( \sigma \in \Sigma_4^n \) if the sequence \( \sigma' = f_t(\sigma) \) is \( \epsilon \)-balanced.

**Example 20.** Consider \( n = 10, \epsilon = 0.1 \). Let \( \sigma = 0000000000 \). Observe that \( f_4(\sigma) = 22222000000 \), \( f_5(\sigma) = 22222000000 \) and \( f_6(\sigma) = 22222200000 \) are \( \epsilon \)-balanced. Hence, \( t = 4, 5, 6 \) are \( \epsilon \)-balanced indices of \( \sigma \). In general, there might be more than one \( \epsilon \)-balanced index.

The following result follows from Theorem 12.

**Corollary 18.** Let \( n \) be even, \( \epsilon > 0 \). The set \( S_{\epsilon,n} \) is defined as in (2). For any sequence \( \sigma \in \Sigma_4^n \), there exists an index \( t \) in the set \( S_{\epsilon,n} \), such that it is the \( \epsilon \)-balanced index of \( \sigma \).

To encode a \( \epsilon \)-balanced sequence \( \sigma \), we first find the smallest \( \epsilon \)-balanced index \( t \) of \( \sigma \), and then flip the first \( t \) symbols of \( \sigma \) according to the rule \( f \). To represent the index, we also append a short balanced suffix to the end of codeword, and so, a lookup table of size \( |S_{\epsilon,n}| \) is required and the redundancy is \( \lceil \log \left( \frac{1}{2} + 1 \right) \rceil \). The following result is trivial.

**Lemma 19.** Let \( n, m \) be even. Assume that \( \sigma \in \Sigma_4^n \) is \( \epsilon \)-balanced and \( z \in \Sigma_4^m \) is balanced. The concatenation sequence \( \sigma z \) is also \( \epsilon \)-balanced.

**Example 20.** Let \( n = 200, \epsilon = 0.1 \), i.e. we want the GC-content is within \([0.4, 0.6]\), and the set \( S_{\epsilon,n} = \{0, 40, 80, 120, 160, 200\} \) is of size six. We construct the one-to-one correspondence between the index and a short balanced suffix of length 2 as follows: \( 0 \rightarrow 02, 40 \rightarrow 03, 80 \rightarrow 12, 120 \rightarrow 13, 160 \rightarrow 20, 200 \rightarrow 30 \). Assume that \( \sigma \in \Sigma_4^{200} \) and the \( \epsilon \)-balanced index \( t \) of \( \sigma \) is \( t = 40 \). The encoder flips the first 40 symbols in \( \sigma \) to obtain \( \sigma' \) that is \( \epsilon \)-balanced, and then append 03 to the end of \( \sigma' \). The encoder uses only two redundant symbols for \( \epsilon = 0.1 \).

We now show that the suffix can be encoded and decoded in linear time without the use of a lookup table. In addition, in order to construct an \( (\epsilon, \ell) \)-constrained code, we encode the suffix in such a way that it is also \( \ell \)-runlength limited. The details are as follows.

**Index Encoder.** Let \( n \) be even, \( \epsilon, \ell > 0 \). The set \( S_{\epsilon,n} \) is defined as in (2). Set \( k = \lceil \log_4 \left( \frac{1}{2} + 1 \right) \rceil \).

**Output:** \( p \triangleq \text{INDEX_ENC}(t) \)

(I) Let \( \tau_1 \tau_2 \cdots \tau_k \) be the quaternary representation of \( t \) in \( S_{\epsilon,n} \).

(II) Interleave the representation with the alternating length-\( k \) sequence \( f(\tau_1) f(\tau_2) \cdots f(\tau_k) \) to obtain \( p \) of length \( 2k \). In other words, set \( p = (f(\tau_1) f(\tau_2) \cdots f(\tau_k)) \).

The corresponding GC-content Encoder and Decoder are described as follows.

**\( \epsilon \)GC-Encoder D**. Given \( n, \epsilon > 0 \), set \( k = \lceil \log_4 \left( \frac{1}{2} + 1 \right) \rceil \) and \( m = 2n - 4k \). Set \( S_{\epsilon,n-2k} \) be the set of indices as constructed in (2) and we construct a one-to-one correspondence between the indices in \( S_{\epsilon,n-2k} \) and \( k \) bits sequences.

**Input:** \( x \in \{0, 1\}^m \)

**Output:** \( \sigma = \text{ENC}_{\text{GC}}^D(x) \)

(I) Set \( \sigma' = \Psi^{-1}(x) \in \Sigma_4^{n-2k} \).

(II) Search for the first \( t \) in \( S_{\epsilon,n-2k} \), such that \( t \) is the \( \epsilon \)-balanced index of \( \sigma' \).

(III) Obtain \( \sigma'' \) by flipping the first \( t \) symbols in \( \sigma' \).

(IV) Use Index Encoder to obtain \( p \) representing index \( t \) of length \( 2k \).

(V) Finally, we set \( \sigma \triangleq \sigma'' p \).

**\( \epsilon \)GC-Decoder D**.

**Input:** \( \sigma \in \Sigma_4^n \), \( \sigma \) is \( \epsilon \)-balanced

**Output:** \( x = \text{DEC}_{\text{GC}}^D(\sigma) \in \{0, 1\}^m \)

(I) Set \( p \) be the suffix of length \( 2k \) in \( \sigma \), and \( \sigma' \) be the prefix of length \( n - 2k \).

(II) Let \( z \) be the sequence of odd indices in \( p \), which is the \( k \) bits sequence representing index \( t \) in the set \( S_{\epsilon,n-2k} \).

(III) Flip the first \( t \) symbols in \( \sigma' \) according to the flipping rule \( f \) to obtain \( \sigma'' \).

(IV) Finally, output \( x = \Psi(\sigma'') \).

**Remark 21.** The advantage of Encoder C is low redundancy, however, it is hard to combine with an RLL Encoder to construct an \((\epsilon, \ell)\)-constrained encoder. In the next section, we present an efficient \((\epsilon, \ell)\)-constrained encoder using the construction of Encoder D and the two RLL Encoders presented in Section III.

V. Efficient \((\epsilon, \ell)\)-Constrained Codes

In this section, we present an \((\epsilon, \ell)\)-constrained encoder that translates binary data to DNA strands that are \( \ell \)-runlength limited and \( \epsilon \)-balanced for arbitrary \( \epsilon, \ell > 0 \). Prior to this work, literature results mostly focused on specific values of \( \epsilon \) and \( \ell \).
Example 22. Consider \( n = 10, \epsilon = 0.1, \ell = 3 \). Let \( \sigma = 0002111011 \). Observe that even though \( \sigma \) is \( \ell \)-runlength limited, it is not \( \epsilon \)-balanced. We then get \( f_3(\sigma) = 2222111011 \), is \( \epsilon \)-balanced. However, \( f_3(\sigma) \) is not \( \ell \)-runlength limited.

The above example also illustrates that the sequence \( f_i(\sigma) \) may not be \( \ell \)-runlength limited given that \( \sigma \) is \( \ell \)-runlength limited. Nevertheless, we observe that the prefix and suffix of \( f_i(\sigma) \) remain \( \ell \)-runlength limited. For brevity, given a sequence \( \sigma \in \Sigma_4^n \), we use \( P_i(\sigma) \) and \( S_n(\sigma) \) to denote the prefix and suffix of \( \sigma \) of length \( i \), respectively.

**Lemma 23.** Let \( 0 \leq t \leq n \). If a sequence \( \sigma \) is \( \ell \)-runlength limited and \( \sigma' = f_t(\sigma) \), then \( P_t(\sigma') \) and \( S_{n-t}(\sigma') \) are both \( \ell \)-runlength limited.

To ensure that the obtained sequence remains \( \ell \)-runlength limited, we simply add one redundant symbol before concatenating \( P_t(\sigma') \) and \( S_{n-t}(\sigma') \).

**Corollary 24** (Concatenate two \( \ell \)-runlength limited sequences). Let \( \sigma, \sigma' \) be \( \ell \)-runlength limited. Suppose that the last symbol of \( \sigma \) is \( \alpha \) and the first symbol of \( \sigma' \) is \( \beta \). Let \( \gamma \in \Sigma_4 \setminus \{\alpha, \beta\} \), then \( \sigma'' = \sigma \gamma \sigma' \) is \( \ell \)-runlength limited.

We illustrate the construction of \((\epsilon, \ell)\)-constrained encoder through the following example.

**Example 25** (Example 20 continued). Suppose \( n = 200, \epsilon = 0.1, \) and \( \ell = 3 \). We show that there exists an efficient \((\epsilon, \ell)\)-constrained encoder with at most 8 redundant symbols. From the data sequence \( \sigma \in \Sigma_4^{200} \), we use RLL Encoder A to obtain \( \sigma_1 = ENC_{RLL}^A(\sigma) \). This step requires two redundant symbols and hence, \( \sigma_1 \in \Sigma_4^{194} \) is \( \ell \)-runlength limited. We now search for the \( \epsilon \)-balanced index \( t \) of \( \sigma_1 \) in the set \( S_{1.194} \) of size six, i.e. \( \sigma_2 = f_t(\sigma_1) \) is \( \epsilon \)-balanced. Such index can be represented by a pointer \( p \) of size two (similar to Example 20). We follow Corollary 24 to find \( \gamma, \gamma' \) such that \( \sigma_2 = P_t(\sigma_1) \gamma S_{n-t}(\sigma_1) \gamma'/p \in \Sigma_4^{200} \) be \( \ell \)-runlength limited. To ensure that the final output is \( \epsilon \)-balanced, recall that, \( P_t(\sigma_1) S_{n-t}(\sigma_1) p \) is \( \epsilon \)-balanced, we then output \( \sigma_3 = \sigma_2 f(\gamma') f(\gamma) \). It is easy to verify that \( \sigma_3 \) is \( \ell \)-runlength limited and \( \epsilon \)-balanced. Thus, the encoder uses 8 redundant symbols to encode codewords of length 200, and hence, the rate is 1.92 (bits/nt).

We now show that the representation \( p \) of the \( \epsilon \)-balanced index can be encoded/decoded in linear time without using a lookup table. Suppose we want to encode codewords in \( \Sigma_4^n \) where \( n \) is even. Set \( k = \lceil \log_4 (|1/2\epsilon| + 1) \rceil \), and \( N = n - 2k - 4 \). Let \( r_{RLL} \) denote the maximum number of redundant symbols used by the RLL Encoder (\( ENC_{RLL}^A \) or \( ENC_{RLL}^B \)) to encode the \( \ell \)-runlength limited codewords in \( \Sigma_4^N \). We summarize our proposed \((\epsilon, \ell)\)-constrained encoder as follows.

**\((\epsilon, \ell)\)-Constrained Encoder.** Given \( n, \epsilon, \ell, n \) even and \( \ell \geq 3 \). Set \( m = 2n - 2(r_{RLL} + 2k + 4) \). Set \( S_{\epsilon,N} \) be the set of indices as defined by (2) and we construct a one-to-one correspondence between the indices in \( S_N \) and \( k \) bits sequences.

**Input:** \( x \in \{0,1\}^m \)

**Output:** \( \sigma \triangleq ENC_{\epsilon,\ell}(x) \in \Sigma_4^n \)

(I) Set \( \sigma_1 = \Psi^{-1}(x) \in \Sigma_4^n \setminus R_{RLL} - 2k - 4 \)

(II) Use RLL Encoder to obtain \( \sigma_2 = ENC_{RLL}(\sigma_1) \), where \( \sigma_2 \in \Sigma_4^n \) is \( \ell \)-runlength limited

(III) Search for the first \( \epsilon \)-balanced index \( t \) of \( \sigma_2 \) in \( S_{\epsilon,N} \)

(IV) Flip the first \( t \) symbols in \( \sigma_2 \) to obtain \( \sigma_3 = f_t(\sigma_2) \)

(V) Let \( \tau_1 \tau_2 \cdots \tau_k \) be the quaternary representation of \( t \) in \( S_{\epsilon,N} \). Set \( p = \tau_1 f(\tau_1) \tau_2 f(\tau_2) \cdots \tau_k f(\tau_k) \)

(VI) Use Corollary 24 to find \( \gamma \) and \( \gamma' \) such that \( \sigma_4 = P_t(\sigma_3) \gamma S_{n-t}(\sigma_3) \gamma'/p \) is \( \ell \)-runlength limited

(VII) Output \( \sigma = \sigma_4 f(\gamma) f(\gamma') \). Note that \( \sigma \in \Sigma_4^n \)

**Theorem 26.** The \((\epsilon, \ell)\)-Constrained Encoder is correct. In other words, \( ENC_{\epsilon,\ell}(x) \) is \( \epsilon \)-balanced and \( \ell \)-runlength limited for all \( x \in \{0,1\}^m \). The redundancy of the encoder is \( r_{RLL} + 2k + 4 \).

**Proof.** Let \( \sigma = ENC_{\epsilon,\ell}(x) \). We first show that \( \sigma \) is \( \ell \)-runlength limited. According to Corollary 24, \( \sigma_4 \) is \( \ell \)-runlength limited. Since two consecutive symbols in \( p \) are distinct, the concatenation \( pf(\gamma) f(\gamma') \) is \( \ell \)-runlength limited for all \( \ell \geq 3 \). Therefore, \( \sigma \) is \( \ell \)-runlength limited.

We now show that \( \sigma \) is \( \epsilon \)-balanced. Since \( \sigma_3 \) is \( \epsilon \)-balanced, \( p \) balanced, \( \gamma f(\gamma), \gamma' f(\gamma') \) is balanced, we have \( \sigma \) is \( \epsilon \)-balanced (according to Lemma 19).

**Remark 27.** The construction can be easily extended for \( \ell \in \{1, 2\} \). For arbitrary \( \epsilon > 0 \), \( k = \lceil \log_4 (|1/2\epsilon| + 1) \rceil = O(1) \), is a constant. Therefore, the rate of this encoder approaches the rate of the RLL Encoder. If we use the RLL Encoder based on enumeration (\( ENC_{RLL}^A \)) then the rate of the \((\epsilon, \ell)\)-constrained encoder approaches the capacity for sufficient large \( n \). However, this encoder A runs in \( \Theta(n^2) \). For DNA storage with \( \ell \in \{4, 5, 6\} \), we can use the linear time \( ENC_{RLL}^A \) to achieve as good rate as \( ENC_{RLL}^A \) (refer to Remark 9).
For completeness, we describe the corresponding \((\epsilon, \ell)\)-constrained decoder as follows.

\((\epsilon, \ell)\)-Constrained Decoder:

- **INPUT**: \(\sigma \in \Sigma_d^q\), \(\sigma\) is \(\epsilon\)-balanced and \(\ell\)-runlength limited
- **OUTPUT**: \(x \triangleq \text{DEC}_{(\epsilon, \ell)}(\sigma) \in \{0, 1\}^n\)

1. Set \(p\) be the suffix of length \(2k + 2\) and \(\sigma_1\) be the prefix of length \(n - 2k - 3\).
2. Remove the the last two symbols in \(p\).
3. Let \(z\) be the sequence of odd indices in \(p\), which is the \(k\) bits sequence representing index \(t\) in \(S_{\epsilon, N}\).
4. Flip the first \(t\) symbols in \(\sigma_1\) according to the flipping rule \(f\) to obtain \(\sigma_2\).
5. Remove the \((t + 1)\)th symbol in \(\sigma_2\).
6. Use RLL Decoder to obtain \(\sigma_3 = \text{DEC}_{\text{RLL}}(\sigma_2)\).
7. Output \(x = \Psi(\sigma_3)\).

The efficiency of our designed \((\epsilon, \ell)\)-constrained encoder are summarized in Table III. As can be seen, when the codeword length increases, the rate of our proposed encoder is only a few percent below capacity.

| Codeword length \(n\) | Capacity \(C\) | Rate of encoder \(r\) | \(\eta = r/C\) \(\%\) |
|------------------------|---------------|------------------------|---------------------|
| 100                    | 1.99542       | 1.81000                | 90.707%             |
| 200                    | 1.99578       | 1.92000                | 96.203%             |
| 300                    | 1.99577       | 1.94000                | 97.206%             |

**TABLE III**: Rate of the designed constrained encoder for \(\epsilon = 0.1\) and \(\ell = 4\).

VI. EFFICIENT \((\epsilon, \ell; B)\)-ERROR-CONTROL CODES

We now construct \((\epsilon, \ell; B)\)-error-control codes to correct the most common error in DNA data storage such as a single deletion, insertion, or substitution error. This also helps to reduce the error propagation of the constrained decoders proposed earlier. Crucial to our construction is the binary Varshamov-Tenengolts (VT) codes defined by Levenshtein [22] and the \(q\)-ary VT codes defined by Tenengolts [23].

A. Codes Correcting a Single Indel/Edit

**Definition 28.** The binary VT syndrome of a binary sequence \(x \in \{0, 1\}^n\) is defined to be \(\text{Syn}(x) = \sum_{i=1}^n i x_i\).

For \(a \in \mathbb{Z}_{n+1}\), the Varshamov-Tenengolts code \(\text{VT}_a(n)\) is defined as follows.

\[
\text{VT}_a(n) = \{ x \in \{0, 1\}^n : \text{Syn}(x) = a \pmod{n+1} \}. \tag{3}
\]

For \(a \in \mathbb{Z}_{n+1}\), the code \(\text{VT}_a(n)\) can correct a single indel and Levenshtein later provided a linear-time decoding algorithm [22]. To also correct a substitution, Levenshtein [22] constructed the following code

\[
\text{LT}_a(n) = \{ x \in \{0, 1\}^n : \text{Syn}(x) = a \pmod{2n} \}, \tag{4}
\]

and provided a decoder that corrects a single edit.

**Theorem 29** (Levenshtein [22]). Let \(\text{LT}_a(n)\) be as defined in \(\text{(4)}\). There exists a linear-time decoding algorithm \(\text{DEC}_a^L : \{0, 1\}^n \rightarrow \text{LT}_a(n)\) such that the following holds. If \(c \in \text{LT}_a(n)\) and \(y \in B^{\text{edit}}(c)\), then \(\text{DEC}_a^L(y) = c\).

In 1984, Tenengolts [23] generalized the binary VT codes to nonbinary ones. Tenengolts defined the signature of a \(q\)-ary vector \(x\) of length \(n\) to be the binary vector \(\pi(x)\) of length \(n - 1\), where \(\pi(x)_i = 1\) if \(x_{i+1} \geq x_i\), and \(0\) otherwise, for \(i \in [n-1]\).

For \(a \in \mathbb{Z}_n\) and \(b \in \mathbb{Z}_q\), set

\[
\text{T}_{a,b}(n; q) \triangleq \left\{ x \in \mathbb{Z}_q^n : \pi(x) \in \text{VT}_a(n - 1) \text{ and } \sum_{i=1}^n x_i = b \pmod{q} \right\}.
\]

Then Tenengolts showed that \(\text{T}_{a,b}(n; q)\) corrects a single indel and there exists \(a\) and \(b\) such that the size of \(\text{T}_{a,b}(n; q)\) is at least \(q^n/(qn)\). These codes are known to be asymptotically optimal. In the same paper, Tenengolts also provided a systematic \(q\)-ary single-indel-encoder with redundancy log \(n + C_q\), where \(n\) is the length of a codeword and \(C_q\) is independent of \(n\).

**Theorem 30** (Tenengolts [23]). There exists a linear-time decoding algorithm \(\text{DEC}_a^T : \{0, 1\}^n \rightarrow \text{T}_{a,b}(n; q)\) such that the following holds. If \(c \in \text{T}_{a,b}(n; q)\) and \(y \in B^{\text{indel}}(c)\), then \(\text{DEC}_a^T(y) = c\).

Recently, Chee et al. [9] presented linear-time encoders for GC-balanced codewords that are capable of correcting single edit with \(3 \log n + 2\) bits of redundancy. In the following, we use the idea of VT codes to modify the \((\epsilon, \ell)\)-constrained code so that the codebook is capable of correcting either a single indel or a single edit.
In conclusion, E

NC

Let \( \sigma \), localizing the deletion. Let \( \sigma' \) be the sequence obtained by removing the suffix \( p' \) from \( \sigma' \). Note that \( \text{Syn}(\sigma') \) and the sum of symbols in \( \sigma'' \) are known from \( p \). We then set \( y = \text{Dec}_{(a,b)}(\sigma'') \), and use the \( (\epsilon, \ell) \)-constrained encoder to obtain \( x = \text{Dec}_{(\epsilon, \ell)}(y) \).

If there is a deletion in \( p \), we do not need to do error correction here, and remove the suffix of length \( k' \) from \( \sigma' \). We then use the \( (\epsilon, \ell) \)-constrained encoder to obtain \( x = \text{Dec}_{(\epsilon, \ell)}(\sigma') \).

In conclusion, \( \text{Enc}_{(\epsilon, \ell); \text{indel}}(x) \) is \( \epsilon \)-balanced, \( \ell \)-runlength limited, and can correct a single indel for all \( x \in \{0, 1\}^m \).

**Corollary 35.** Let \( M = n + \log n + 4 \). There exists a linear-time decoding algorithm \( \text{Dec}_{\text{indel}} : \Sigma_4^M \rightarrow \mathcal{C}(\epsilon, \ell; \text{indel}) \) such that the following holds. If \( \sigma = \text{Enc}_{(\epsilon, \ell); \text{indel}}(x) \) and \( \sigma' \in \mathcal{B}_{\text{indel}}(\sigma) \), then \( \text{Dec}_{\text{indel}}(\sigma') = \sigma \).

For completeness, we describe the corresponding \( (\epsilon, \ell; \text{indel}) \)-error-control decoder as follows.

\( (\epsilon, \ell; \text{indel}) \)-Error-Control Decoder:

**Input:** \( \sigma' \in \Sigma_4^{n+k'+4} \)

**Output:** \( x \in \{0, 1\}^m \)

(I) Let \( \sigma = \text{Dec}_{\text{indel}}(\sigma') \in \Sigma_4^{n+k'+4} \)

(II) Use \( (\epsilon, \ell) \)-constrained decoder to obtain \( x = \text{Dec}_{(\epsilon, \ell)}(\sigma) \in \{0, 1\}^m \)

(III) Output \( x \)
C. Construction of \((\epsilon, \ell; B^{edit})\)-Error-Control Codes

We follow the construction in Corollary 33 to encode DNA sequences that are capable of correcting a single edit. We simply append the information of the syndrome of \(U_\sigma\) and \(L_\sigma\) to the end of each codeword. In addition, we also use the idea of the Index Encoder (refer to Section IV-D) to ensure the redundant part is balanced and \(\ell\)-runlength limited. The extra redundancy is \(2\log n + 4\). For simplicity, assume that \(k' = \log n\) is integer and \(k'\) is even.

\((\epsilon, \ell; B^{edit})\)-Error-Control Encoder. Let \(n\) be even, \(\epsilon, \ell > 0\). Set \(k = \lceil \log_4 ((1/2\epsilon) + 1) \rceil\). Set \(m = 2n - 2(r_{RLL} + 2k + 4)\), and \(N = n - 2k - 4\). Set \(S_{\epsilon, n-2k-4}\) be the set of indices as defined by (2) and we construct a one-to-one correspondence between the indices in \(S_{\epsilon, n-2k-4}\) and \(k\) bits sequences. Set \(k' = \log n\).

**INPUT:** \(x \in \{0, 1\}^m\)

**OUTPUT:** \(\sigma \triangleq ENC(\epsilon, \ell; B^{edit})(x) \in \mathcal{E}(\epsilon, \ell; B^{edit}) \cap \Sigma_4^{n+2\log n+4}\)

(I) Use the \((\epsilon, \ell)\)-constrained encoder to obtain \(\sigma' = ENC(\epsilon, \ell)(x) \in \Sigma_4^n\), where \(\sigma'\) is \(\epsilon\)-balanced and \(\ell\)-runlength limited.

(II) Let \(\alpha\) be the last symbol of \(\sigma'\). Let \(\beta\) be arbitrary symbol in \(\Sigma_4 \setminus \{\alpha, f(\alpha)\}\).

(III) Let \(a = \text{Syn}(U_{\sigma'})\) (mod \(n + 1\)) and \(b = \text{Syn}(L_{\sigma'})\) (mod \(n + 1\)), \(e = \sum_{i=1}^n \sigma_i'\) (mod 4)

(IV) Let \(r_1 r_2 \cdots r_{k/2} / \tau_1 r_2 \cdots r_{k/2} f(\tau_{k/2}) \nu_1 f(\nu_1) \nu_2 f(\nu_2) \cdots f(\nu_{k/2})\epsilon f(\epsilon)\)

(V) Set \(p = \beta f(\beta) r_1 f(\tau_1) r_2 f(\tau_2) \cdots r_{k/2} f(\tau_{k/2}) \nu_1 f(\nu_1) \nu_2 f(\nu_2) \cdots f(\nu_{k/2})\epsilon f(\epsilon)\)

(VI) Output \(\sigma = \sigma' p\)

**Theorem 36.** The \((\epsilon, \ell; B^{edit})\)-error-control encoder is correct. In other words, ENC(\(\epsilon, \ell; B^{edit})(x)\) is \(\epsilon\)-balanced, \(\ell\)-runlength limited, and capable of correcting a single edit for all \(x \in \{0, 1\}^m\).

**Proof.** Let \(\sigma = ENC(\epsilon, \ell; B^{edit})(x)\). It is easy to show that \(\sigma\) is \(\epsilon\)-balanced and \(\ell\)-runlength limited (refer to the proof of Theorem 26). It remains to show that \(\sigma\) can correct a single edit. To do so, we provide an efficient decoding algorithm. Suppose the received sequence is \(\sigma'\). The idea is to recover the first \(n\) symbols in \(\sigma\) and then use the \((\epsilon, \ell)\)-constrained decoder to recover the information sequence \(x\). First, the decoder decides whether a deletion, insertion or substitution has occurred. Note that this information can be simply observed by decoding the received sequence. The decoding operates as follows.

(i) If the length of \(\sigma'\) is exactly \(n + 2\log n + 4\), we conclude that at most a single substitution has occurred.

- Let \(p'\) be the suffix of length \(2\log n + 4\) of \(\sigma'\), and \(p' = p'_1 p'_2 \cdots p'_{2k+4}\).
- Let \(\sigma''\) be the prefix of length \(n\) of \(\sigma'\). The decoder computes \(\text{Syn}(U_{\sigma''})\) and \(\text{Syn}(L_{\sigma''})\) (mod \(n + 1\)).
- Let \(a'\) be the integer number whose quaternary representation is \(p'_1 p'_2 \cdots p'_{k+1}\), \(b'\) be the integer number whose quaternary representation is \(p'_{k+3} p'_{k+4} \cdots p'_{2k+1}\) and \(c' = p'_{2k+3}\).
- If \(c'\) is the sum of symbols in \(\sigma''\), then there is no error in \(\sigma''\). The decoder proceeds to obtain \(x = \text{DEC}(\epsilon, \ell)(\sigma'')\).
- Otherwise, if \(a' = \text{Syn}(U_{\sigma''})\) and \(b' = \text{Syn}(L_{\sigma''})\) then there is no error in \(\sigma''\), the decoder proceeds to obtain \(x = \text{DEC}(\epsilon, \ell)(\sigma'')\). On the other hand, if either one statement is false, there is an error in \(\sigma''\). The decoder sets \(y = \text{DEC}_{L_\alpha}(U_{\sigma''})\) and \(z = \text{DEC}_{U_\beta}(L_{\sigma''})\). Finally, \(\sigma = \Psi(y | z)\) and the decoder returns \(x = \text{DEC}(\epsilon, \ell)(\sigma)\).

(ii) If the length of \(\sigma'\) is exactly \(n + 2\log n + 3\), we conclude that a single deletion has occurred (the case of single insertion can be done similarly). The decoder proceeds as follows.

- Let \(p'\) be the suffix of length \(2\log n + 4\) of \(\sigma'\), and \(p' = p'_1 p'_2 \cdots p'_{2k+4}\).
- If \(p'_2 \neq f(p'_1)\), the decoder concludes that there is a deletion in \(p\). The decoder removes the suffix of length \(2k' + 3\) from \(\sigma'\), then use the \((\epsilon, \ell)\)-constrained encoder to obtain \(x = \text{DEC}(\epsilon, \ell)(\sigma')\).
- If \(p'_2 = f(p'_1)\), the decoder concludes that there is no deletion in \(p\) and therefore, \(p' = p\). Let \(\sigma''\) be the sequence obtained by removing the suffix \(p\) from \(\sigma'\). Note that \(\text{Syn}(U_{\sigma''})\) and \(\text{Syn}(L_{\sigma''})\) are known from \(p\). The decoder sets \(y = \text{DEC}_{L_\beta}(U_{\sigma''})\) and \(z = \text{DEC}_{L_\alpha}(L_{\sigma''})\). Finally, \(\sigma = \Psi(y | z)\) and the decoder returns \(x = \text{DEC}(\epsilon, \ell)(\sigma)\).

In conclusion, ENC(\(\epsilon, \ell; B^{edit})(x)\) is \(\epsilon\)-runlength limited, and can correct a single edit for all \(x \in \{0, 1\}^m\).

**Corollary 37.** Let \(M = n + 2\log n + 4\). There exists a linear-time decoding algorithm \(\text{DEC}_{edit} : \Sigma_4^M \rightarrow \mathcal{E}(\epsilon, \ell; B^{edit}) \cap \Sigma_4^M\) such that the following holds. If \(\sigma = \text{ENC}(\epsilon, \ell; B^{edit})(x)\) and \(\sigma' \in B^{edit}(\sigma)\), then \(\text{DEC}_{edit}(\sigma') = \sigma\).

For completeness, we describe the corresponding \((\epsilon, \ell; B^{edit})\)-error-control decoder as follows.

\((\epsilon, \ell; B^{edit})\)-Error-Control Decoder.

**INPUT:** \(\sigma' \in \Sigma_4^{n+2\log n+4}\)

**OUTPUT:** \(x \triangleq \text{DEC}(\epsilon, \ell; B^{edit})(\sigma') \in \{0, 1\}^m\)

(I) Let \(\sigma = \text{DEC}_{edit}(\sigma') \in \Sigma_4^{n+2\log n+4}\)

(II) Use \((\epsilon, \ell)\)-constrained decoder to obtain \(x = \text{DEC}(\epsilon, \ell)(\sigma) \in \{0, 1\}^m\)

(III) Output \(x\)

**Remark 38.** We use \(r_{error}\) to denote the redundancy needed to correct single indel or edit error. When \(B = B^{indel}\), \(r_{error} = \log n + 4\), and when \(B = B^{edit}\), \(r_{error} = 2\log n + 4\). Since \(\frac{\log n}{n} \rightarrow 0\), \(r_{GC} = O(1)\), is a constant, the rate of this encoder...
approaches the rate of the RLL Encoder, and if we use RLL Encoder A then the rate of the $(\epsilon, \ell, B)$-error-control encoder approaches the capacity for sufficient large $n$.

VII. Conclusion

We have presented novel and efficient encoders that translate binary data into strands of nucleotides which satisfy the RLL constraint, the GC-content constraint, and are capable of correcting a single edit and its variants. Our proposed codes achieve higher rates than previous results and approach capacity, have low encoding/decoding complexity and limited error propagation.

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