A Preprint

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June 27, 2019

Abstract

Key to DNA storage is encoding the information to a sequence of nucleotides before it can be synthesised for storage. Definition of such an encoding or mapping must adhere to multiple design restrictions. First, not all possible sequences of nucleotides can be synthesised. Homopolymers, e.g., sequences of the same nucleotide, of a length of more than two, for example, cannot be synthesised without potential errors. Similarly, the G-C content of the resulting sequences should be higher than 50%. Second, given that synthesis is expensive, the encoding must map as many bits as possible to one nucleotide. Third, the synthesis (as well as the sequencing) is error prone, leading to substitutions, deletions and insertions. An encoding must therefore be designed to be resilient to errors through error correction codes or replication. Fourth, for the purpose of computation and selective retrieval, encodings should result in substantially different sequences across all data, even for very similar data. In the following we discuss the history and evolution of encodings.

Keywords DNA Storage · Encoding · Error Detection & Correction

Thanks to the benefits of information density, energy efficiency and a high potential for parallelism, computing information based on DNA using related chemical processes is a promising approach. The additional feature of durability, DNA has a half-life of 521 years \[1\] (without treating it to improve durability), as well as the fact that the materials for synthesizing DNA are abundantly available, makes DNA an interesting approach for data storage alone as well.

In this survey, we study different approaches to encode information in DNA. Although some clearly have only been designed for artistic purposes and not for information storage, we still want to discuss and compare all approaches developed to date. We compare approaches with respect to storage mechanism, information density, error detection & correction mechanisms, biological constraints considered, access mechanism, data stored and the size of the data stored.

We first discuss the criteria for comparison and then discuss the encoding approaches, roughly in chronological order which also reflects their level of sophistication reasonably well.

1 Criteria for Comparison

Particularly early approaches store information in organisms — inserting the DNA into the genetic information of a living organism — whereas later ones store the synthetic DNA on microplates. Storing information in living organisms has the benefit that it can be passed on in highly resistant organisms, e.g., bacteria resistant to adverse conditions (extreme temperatures and similar), over many generations and thus for a very long time. At the same time, however, recombination of the DNA when cells of the organisms divide is an error prone process and so errors may be introduced in the stored information. Using living organisms also limits the amount of information that can be stored because the sequence inserted into the organism cannot be too long without incapacitating the organism. We therefore discuss for each approach the storage mechanism, whether it is inserted into an organism or stored in a microplate.
Given that both synthesis — writing information to DNA — and sequencing — reading from DNA — are error prone, incorporating error detection and correction codes in the encoded information is crucial to correctly recover all information. We analyse the error detection and correction techniques used in each approach, spanning from none to sophisticated Reed-Solomon codes.

The information density assesses how much information (bits) can be stored per nucleotide. Given the high cost of current synthesis technology this is a crucial metric. Several factors affect information density. For example, if a number of nucleotides in a sequence is used to store error detection and correction information, the information density decreases. Information density thus strongly depends on the features of the encoding and it cannot be considered in isolation. We therefore discuss the information density for each approach in the context of its features. We calculate the information density only on the payload encoded — i.e., the actual information carried — and exclude subsequences like primers needed for reading/amplification etc.

We further discuss the access mechanism for each approach. Particularly early encoding approaches required sequential access, i.e., the entire DNA to be sequenced to reconstruct the information to access parts of it. This can be a slow and costly process and later approaches have thus been designed to allow for random access to the data. Enabling random access means that subsets of the information can be selectively read without having to sequence all information. Doing so requires placement of primers such that subset can selectively be amplified.

Further, we discuss whether approaches consider biological constraints, i.e., whether the approaches avoid long homopolymers (repeats of the same nucleotides > 3) and extreme G-C content, both of which affect stability of the sequence and cause errors when synthesising and sequencing.

Finally, we also mention the amount of information stored in the experiments of each approach as well as the data stored.

## 2 Initial Ideas

The first use of DNA as a storage device had primarily artistic purposes and was not meant to provide read and write functionality [2]. The idea was to incorporate artificial (non-biological) information into DNA, and more specifically, into living bacteria (E. coli). The information encoded is the ancient Germanic rune for life and the female earth, bit-mapped to a binary representation. This resulted in a 5×7 or 7×5 figure, totalling 35 bits. To translate the bits to DNA nucleotides, a phase-change model is used. In this model, each nucleotide indicates how many times a bit (0 or 1) is repeated before a change to another bit occurs:

\[ X \rightarrow C \quad XX \rightarrow T \quad XXX \rightarrow A \quad XXXX \rightarrow G \]

With this code, the string 10101 is encoded as CCCC, as each binary digits occurs once before changing, and 0111000 becomes CAA. The entire 35-bit message is therefore encoded with a sequence of 18 nucleotides, i.e., CCCCCCAACGGGCGGCT. An additional sequence CTTAAAGGGG is prepended to indicate the start of the encoded message, for a final length of 28 nucleotides. This DNA is then implanted into a living cell through molecular biology techniques.

The information density of this approach depends on the exact message to be encoded. If, for example, the same bit is repeated multiple times, this approaches only requires very few nucleotides and essentially compresses the information. For the example message, it requires 0.54 nucleotides per bit.

The disadvantages of the encoding approach are the absence of any type of error detection or correction. It neither takes into account biological constraints on the resulting DNA sequence such as long homopolymers or adequate G-C content, making stability, synthesis and sequencing challenging. To retrieve the information, all data has to be sequenced, thus only allowing for sequential access to it. Furthermore, a specific downside of this approach is that DNA sequences are not uniquely decodable. As the nucleotides encode changes, we can translate, for example, a C as either a 0 or 1, and this generalizes to any sequence, e.g., TCA, can be decoded as 001000 or 110111.

Similarly to be understood as primarily art is the Genesis project [3] which has the goal of encoding a sentence from The Book of Genesis. The text used is Let man have dominion over the fish of the sea, and over the fowl of the air, and over every living thing that moves upon the earth. The text is translated to Morse Code which is then again translated to a nucleotide sequence. Both the text and the Morse Code fit the symbolism of “genesis” (the Morse Code being one of the first techniques of the information age).

The Morse code is translated to nucleotides as follows:

\[ \text{Dash} \rightarrow T \quad \text{Dot} \rightarrow C \quad \text{Space (Word)} \rightarrow A \quad \text{Space (Letter)} \rightarrow G \]
Also for this encoding, the length of the DNA sequence depends on the exact message encoded as different letters have a Morse code representation which varies in length. For the message used, 427 nucleotides are needed (using ITU Morse code). Assuming 5 bits are sufficient to encode a character (only adequate for characters), this results in 0.65 nucleotides per bit, i.e., somewhat more than the previous approach.

The resulting encoding addresses one of the issues of the previous encoding, i.e., it encodes information without ambiguity. Still, the resulting DNA sequences may, however, suffer from problems like homopolymer runs and imbalanced G-C content and can only be read through sequential access. Also, due to mutations in the bacteria, it was not possible to recover the original message (undesired modifications occurred) as no error detection or correction means were used in the encoding.

3 First Approaches to Write and Read

The first approach with the goal of storing and also reading information stores information in information DNA (iDNA) and polyprimer key (PPK) sequences. The entire data to be stored is split in chunks and each chunk is stored in a iDNA sequence while the PPK sequences store the metadata (e.g., the order of the chunks) needed to reconstruct the data.

More specifically, the iDNA contains a data chunk in its information segment which is flanked by common forward (F) and reverse (R) primer (approximately 10-20 nucleotides) needed for amplification with PCR. It further contains a sequencing primer (similar length), essentially an identifier for the iDNA sequence, and a common spacer (3-4 nucleotides) that indicates the start of the information segment.

The PPK sequence - the approach currently only uses one such sequence - is flanked by the same forward and reverse primers and, crucially, contains the unique sequencing primers for each iDNA in the order they have to be read. Both type of sequences are illustrated in Figure 1.

For the retrieval process, the PPK is first amplified using PCR and sequenced to know the order in which the iDNA sequences have to be read to reconstruct the initial continuous block of information. All iDNA sequences are then also amplified and sequenced.

For the experiment, extracts from A Tale of Two Cities by Charles Dickens were chosen. The chosen text was “It was the best of times it was the worst of times” and “It was the age of foolishness it was the epoch of belief”. The sentences were picked on the basis that some words were repeated multiple times and thus act as a test for the robustness of the encoding scheme, as repeating data can lead to undesirable effects.

The text is encoded only using the three nucleotides A, C and T, while the sequencing primers are created using all 4 nucleotides, with the additional constraint that each fourth position is a G. Given this encoding approach, information segments cannot be mistaken for sequencing primers as only the latter contain G nucleotides (at least in each fourth position).

The text is processed alphabetically by a ternary code, that starts with A and alternates C and T in the third, second and first positions, e.g., the first letters of the alphabet are encoded as:

\[ A \rightarrow 000 \rightarrow AAA \quad B \rightarrow 001 \rightarrow AAC \quad C \rightarrow 002 \rightarrow AAT \quad \ldots \]

The two sentences were encoded and recovered successfully using the above procedures. The encoding, however, is not scalable as there are only 27 combinations of the three nucleotides, meaning that at most 27 different letters can be
encoded. Further, using only one PPK inherently limits the amount of data that can be stored. However, the authors argue that one PPK should be enough to store the metadata (e.g., order) for all iDNA sequences in a microwell of a microplate.

The method of encoding the information does neither avoid homopolymers of length three or more. A further issue is G-C content: not using the $G$ nucleotide in the information segment also means that encoded sequences cannot reach the ideal range of 45% to 55% G-C content, which is important for stability and for reducing sequencing errors. The approach neither uses any error detection or correction codes.

Although not specifically designed for it, the approach allows for random access to the data. The PPK can be read out to retrieve the primers needed to read a specific iDNA sequence.

iDNA sequences do not strictly have a limit in length but commercial synthesis will probably limit sequences to 200 nucleotides. The forward and reverse primers require a total of 40 nucleotides, the sequencing primer requires a further 20 nucleotides and the spacer ideally only requires 4 nucleotides (as opposed to the experiments where 19 nucleotides were used for the spacer), leaving 136 nucleotides for encoding information which amounts to about 45 letters given the encoding used. Assuming 5 bits are used to encode a letter, this results in 0.89 nucleotides per bit.

For their experiments, two iDNA sequences, one for each sentence encoded, were used with lengths of 232 and 247 nucleotides respectively. The iDNA sequences used are too long for commercial synthesis and were therefore constructed from overlapping short oligonucleotides. Still, for the sake of analysing the information density, we assume iDNA sequences of 232 and 247 nucleotides length. The PPK contains forward and reverse primers of 20 nucleotides each, the two sequencing primers of each iDNA sequence each of 20 nucleotides length and two spacers with 4 nucleotides each, totalling for 88 nucleotides. Factoring in the length of the PPK, this approach encodes results in 1.06 nucleotides per bit.

A further approach [5] studied encoding and storage in extreme conditions. The objective of this project is the development of a solution that can survive under extreme conditions, such as ultraviolet, partial vacuum, oxidation, high temperatures and radiation. For this purpose, the information was stored in the DNA of two well-studied bacteria, 

A similar encoding to [4] is used, but all four nucleotides are used to form the triplets. With this, 81 symbols can be encoded, including letters, digits and punctuation. The first mappings between binary representation and nucleotides are as follows:

$$
0 \rightarrow AAA \quad 1 \rightarrow AAC \quad 2 \rightarrow AAG \quad 3 \rightarrow AAT \quad 4 \rightarrow ACA \quad ...
$$

To avoid interfering with the natural processes of the organism and to find the encoded message in the genome of the host organism, it is flanked by two sentinels, essentially two DNA sequences (see illustration in Figure 2). These two sequences must satisfy two constraints. First, the sentinels must not occur naturally in the host organism such that no DNA sequence of the host will be mistaken for the message. Second, the sentinels need to contain triplets like TAG or TAA that act as markers which tell the bacterium to stop translating the sequence (to proteins). Analyzing the entire genomes of 

For the experiment, fragments from the song "It's a Small World" were used, and the authors successfully stored and retrieved seven artificially synthesized fragments of length between 57 to 99 nucleotides, each flanked by two sentinels picked from the set of 25 sentinels, in seven individual bacteria. Since the flanking sequences are known, they can be used as primers and the retrieval is then performed using PCR.

As discussed for the previous encoding, encoding symbols as triplets does not scale very well and limits the alphabet with no room for improvement. Another scalability issue is that the genome of the host has to be sequenced and then meticulously searched for appropriate locations to insert messages as well as for sentinels. Even for microorganisms the search space is in the realm of billions, so the task is computationally expensive. Finally, storing information in living organisms is subject to mutations and environmental factors. To alleviate these issues, one of the "toughest" microorganisms known was used (Deinococcus), but generally the problem of mutations remains unpredictable and would likely not accommodate large amounts of information. Care must also be taken not to damage
the bacterium by it accidentally sequencing DNA that is meant for information storage and is not part of its genome. Finally, homopolymers and GC content are not considered in the encoding.

In their experiments, the authors encode 182 characters which require 826 nucleotides (including the sentinels). Assuming 7 bits are needed to encode one letter/character (given that the encoding scheme allows for an alphabet of 81 letters), this results in 0.65 nucleotides per bit.

A similar encoding approach \[6\] is used to encode messages and hiding them in a microdot. Alphanumeric values are mapped to sequences of three nucleotides:

\[
\begin{align*}
A & \rightarrow \text{CGA} \\
B & \rightarrow \text{CCA} \\
C & \rightarrow \text{GTT} \\
D & \rightarrow \text{TTG} \\
E & \rightarrow \text{GGT} \\
\ldots
\end{align*}
\]

The mapping also includes special characters in a total of 36 symbols. A total of 64 symbols could be encoded with three nucleotides and so 28 sequences are not used. By picking the sequences carefully, one might avoid homopolymers or also control the GC content, but no such effort is made.

For the experiment, the message "JUNE6 INVASION:NORMANDY" was encoded, resulting in a sequence of 69 nucleotides. The sequences is flanked by two 20 nucleotide primers, resulting in an overall length of 109 nucleotides. Given that the same alphabet could be encoded with 6 bits per symbol, means that 0.79 nucleotides are needed per bit.

Subsequent work \[7\] is the first to use non-trivial encoding and thus offers a considerable improvement in terms of information density. The authors propose three encoding schemes: Huffman codes, comma codes and alternating codes.

The development of the three schemes is driven by efficiency and robustness: the former is achieved by packing more information/bits in the same number of nucleotides as previous approaches and the latter by ensuring that insertions and deletions can be detected (to some degree). A further design goal is that the output of the encoding should be clearly recognisable as artificial, so that it cannot be confused with DNA that occurs naturally. The latter is not a critical feature in practise.

The approaches are theoretical, i.e., have not been tested experimentally, and focus primarily on encoding the information. Aspects such as incorporating primers for amplification and retrieval are not considered - the sole focus lies on encoding.

The Huffman Code: This approach follows the classic, efficient algorithm introduced by Huffman. The input language is encoded such that the most frequent character is encoded with the least number of symbols, and similarly the least frequent input character is encoded with the most symbols (using variable length encodings). For a given alphabet and language, this is the optimal code. For the approach, the Huffman code is used to translate the letters of the Latin alphabet according to English language character frequencies:

\[
\begin{align*}
e & \rightarrow \text{T} & (12.7\% \text{ frequency}) \\
n & \rightarrow \text{GC} & (6.7\% \text{ frequency}) \\
f & \rightarrow \text{ACG} & (2.2\% \text{ frequency}) \\
z & \rightarrow \text{CCCTG} & (0.1\% \text{ frequency})
\end{align*}
\]

The most frequent letter in the English language is e, and thus it is encoded as a single base, T. As the frequency decreases, the codeword grows in size. The average codeword length is 2.2 nucleotides. The size of the codewords ranges between one and five, and the size of the code is 26 (for the letters of the alphabet). While this code is uniquely decodable and optimal in the sense of being the most economical, it also comes with two disadvantages. First, it can only be used for letters, and the frequency of letters depends heavily on the particular language. Second, due to the varying codeword length, it is difficult to observe a pattern in the encoded data, such that it might be confused with naturally occurring data. Third, no error detection or correction codes are incorporated.

Additionally, the encoding scheme does nothing to prevent homopolymers and suboptimal GC content is a considerable challenge for sequencing.

Given that only letters are considered, 5 bits suffice to encode each letter, resulting in 0.44 nucleotides per bit.

The comma code: This code uses one nucleotide, G, as a comma to separate all other codewords with a length of five nucleotides but never uses it elsewhere (i.e., in the other codewords). The proposed code uses G as the comma occurring every six nucleotides:

\[
\text{G} \star \star \star \star \text{G} \star \star \star \star \text{G} \star \star \star \star \text{G} \ldots
\]
The five-nucleotide codewords are limited to use the remaining three nucleotides: A, C, and T with the added constraint that there must be only three A or T nucleotides and only two Cs. Balancing C's and A or T has the benefit that it leads to a more efficient amplification process. The general format of the codewords is CBBC, where B ∈ {A, T}, and the Bs and Cs can occur in any permutation, leading to 80 different possible codewords.

The main advantages of the approach are that it provides simple error-detection capabilities. Insertions and deletions can easily be detected: codewords which are too long or short have clearly been subject to insertion/deletion. Changes, i.e., flipping of one nucleotide, can be detected in 83% of the cases. Given a codeword GCBBBC, three possible point mutations can occur in each position, resulting in 18 single point mutations. Of the single point mutations, only 17% result in valid codons (flipping A to T or vice versa) and the remaining 83% can be detected.

Using one G and two C nucleotides in one codon means that the GC content is exactly 50% and thus well-suited for sequencing. A final advantage is that the occurrence of a G nucleotide in every sixth position means that the sequence can easily be identified as synthetic. While this is not crucial in the context of the data storage, it is a design goal of the authors.

The disadvantages of the encoding are that no mechanism for error correction is provided. Also, DNA sequences produced with this encoding can contain homopolymers of length three.

The encoding uses 80 different codons, each with a length of 7 nucleotides. To encode about the same number (128) of symbols with bits, 7 bits are required. The information density therefore is exactly one nucleotide per bit.

The alternating code: this code is made of 64 codewords of length 6, of the form XYYYY, where X ∈ {A, G} and Y ∈ {C, T} (the X and Y are alternating). The alternating structure is arbitrary and it is argued that other formats, e.g., YYYYY or XXXXY have the same properties.

The advantages of this method are similar to the comma code: it has simple structure and a ratio of 1:1 of the nucleotides, suggesting that it is an artificial code. It also shares the error-detection features of the comma-code, although to a lesser extent (67% of the mutations are not part of the code). Furthermore, given the suggested structure of XYYYY, homopolymers of length three are avoided.

Disadvantages include potentially a suboptimal GC content, although this could be avoided by using a structure such as XXXXY with X ∈ {C, G} and Y ∈ {A, T}, as well as the lack of error correction codes.

The encoding uses 64 different codons. To encode the same number of symbols in a binary representation, 6 bits are needed and thus the information density again is exactly one nucleotide per bit.

A subsequent project [8] avoids explicit error correction codes. Instead, encoded messages are inserted into the genome of the host organisms repeatedly.

The message is first translated to the Keyboard Scan Code Set2 [9]. This hexadecimal code is then converted to binary, and a binary encoding to dinucleotides (pairs of nucleotides) is used to convert the bit sequence into a DNA sequence. The mappings are illustrated in Figure 3. The message encoded in the experiments is "E=mc^2 1905!".

Figure 3: The translation to Keyboard Scan code (left), translation of to binary (middle) and the mapping from binary to dinucleotides (right).

Redundancy is introduced by encoding the message four times. More precisely, the the bit sequence is copied four times, with each copy flanked by different start and end bit sequences of different length. With the help of these bit sequences, the DNA sequences can be identified within the genome of the host organism. At the same time, thanks to the different length of the start and end bit sequence, the resulting DNA sequences are different and, if one will exhibit undesirable
subsequences (e.g., homopolymers) the others will not. More specifically, for the first encoding (C1), the bit sequence is flanked with 0000 and 1111 and hence the DNA sequence is flanked with AA and TT. For the second encoding, the bit sequence is flanked with 111 and 0 and the DNA sequence thus starts with GT and ends with AT. The bit sequence for the third and fourth copy are flanked with 00, 00 and 1 and 111 respectively. As the bit shift is less than four bits for the second, third and fourth copy, the messages are encoded completely different in DNA. Figure 4 illustrates the different encodings.

Message as bit sequence:

| Bit Sequence | DNA Sequence |
|--------------|--------------|
| 000100100010010000100100111 | AA | CA | GA | GA | AC | CA | GA | AC | GT |
| GT | GA | AC | AC | AG | GA | AC | CG | AT |
| AA | AC | AG | CG | AA | AC | CG | TA | AG |
| AG | CG | CA | GA | AA | CG | GA | TC | CA |

Figure 4: Illustration of the encoding of the same bit sequence, with different start and end bit sequences, four times.

These redundant encoded messages are then inserted in different places into the host organism (in this experiment, a strain of Bacillus subtilis). To decode the information, the entire genome is sequenced and then searched for start and end sequences. For this procedure to work, the messages should be above a minimum chosen length. Otherwise, naturally occurring duplicate sequences might be mistaken for the encoded message. For this experiment and particular organism (B.subtilis) it is argued that a minimum length of 20 provides enough specificity to avoid the messages to be mistaken for host DNA.

As with other techniques that store information in an organism, evolution and mutation pose problems, since the message might be altered. This problem is mitigated by using redundant copies placed in different regions of the genome, although this is means the whole genome has to be sequenced, rendering the approach potentially inefficient. The authors predict that a large-scale system is possible, although as explained, the size of the sequences for this method is limited.

The approach does not control homopolymers or the GC content. Error detection and correction are also not taken into account although redundancy helps to remedy errors. In the experiment carried out, however, the data was not completely recovered as only 99% accuracy was achieved.

The encoding uses two nucleotides to encode four bits and thus suggests information density of 0.5 nucleotides per bit. Factoring in start and end sequences (five bit on average, across the four copies), 0.512 nucleotides per bit are needed (using the message length of 120 bit from the experiments). However, when taking into account that every message is copied four times, 2.05 nucleotides per bit are needed.

Subsequent work [10] encodes information entirely different with the goal of avoiding sequencing to read the information back. They accomplish this by taking the binary information and encoding a 0 with a subsequence that has a different weight than the subsequence for 1. By doing so, the content of the encoded information can be decoded based on the weight of the subsequences, making it possible to, for example, use gel electrophoresis instead of sequencing.

In more practical terms, the subsequences representing binary 0’s and 1’s are separated by restriction sites which allow to cut or separate the encoded information precisely. The entirety of encoded information is inserted into the genome of a bacteria, also flanked by restriction sites such that it can be cut out precisely.

The approach uses 4 nucleotides to encode a 1 and 8 nucleotides for a 0. The encoding makes it difficult to assess information density as this will depend on the exact message encoded. In the experiment the message is 'MEMO' which they encode with 3-bit alphabet, thus requiring 60 nucleotides. The restriction sites, which are essential for the encoding, need an additional 50 nucleotides, resulting in a sequence of 110 nucleotides. The information density thus is 9.17 nucleotides per bit. This is comparatively high and is entirely due to the need for restriction sites.

No error detection and correction codes are incorporated in the encoding. No particular reference is made to biological constraints. However, given that only two different codons are needed — one for 1 and one for 0 — the respective subsequence can be chosen to (a) balance GC content and (b) avoid homopolymers. Regarding the former, even though
the distribution of 1’s and 0’s may be uneven, as long as the GC content within the two subsequences is balanced, the GC content of the encoded sequence will be balanced as well.

Having each subsequence representing a bit flanked by restriction sites limits the scalability of the approach as the number of bits that can be stored depends on the number of unique restriction sites available. At the same time, however, using restriction sites enables, albeit rather coincidental, random access to the data.

One of the first works [11] to move beyond a basic proof of concept storing simple text messages, archives text, image and music. The encoding is fundamentally based on an improved Huffman code, building upon previous methods such as [7]. The files stored are not digital information stored in a format such as .mp3, .png, etc. Instead, music is encoded as a series of notes, with additional rhythm information, while for images, it is only possible to encode a series of primitives (circle, ellipse, line, rectangle) along with their position (and orientation).

The approach uses two components, the index plasmid as well as the information plasmid. The index plasmid is responsible for holding metadata such as title, authors, size of library and primer information. Similarly to Bancroft et al [4], the index information is flanked by unique primers, and thus is easy to find, amplify and decode. However, as opposed to Bancroft, the sequencing primers, needed to find the actual data, are not themselves stored in the index plasmid, but in the information section of the library. Thus the index is responsible only for information and structure describing the actual data.

The approach encodes text, music and images. To distinguish between the type of content encoded, it is prepended by tx*, mu* and im* respectively.

One of the main advances proposed by this approach is a more general encoding based on the Huffman code. Previous methods encoded only letters, with an obvious lack of numbers and punctuation. For text encoding, a complete keyboard input set (including shift, space and so on) is encoded by splitting the symbols into three groups of under 25 characters each. Each group has a header, denoted by one or few nucleotides. More specifically, Group 1 → G, Group 2 → TT and Group 3 → TA. The characters in each group are encoded in decreasing order of their frequency, as is common for Huffman codes. For example, the letter e is encoded as GCT, where G denotes the group header and CT is the encoding for e, shift is GTC and g is GAAT and encoding the word Egg thus becomes GTCGCTGAATGAAT.

For music, a single column is used to provide encodings for note values, pitches and meter. For example, a D half-note is encoded as CGTT, where G denotes the D and the TT indicates a half-note. Encodings are provided for all other notes.

For images, the graphic primitives along with their properties, e.g., location, size and orientation are encoded. An excerpt of the encoding for graphic primitives is shown here:

\[
\begin{align*}
; & \rightarrow G \\
. & \rightarrow TT \\
0 & \rightarrow TA \\
1 & \rightarrow AT \\
2 & \rightarrow CT \\
\ldots \\
S(s; x1; y1; a) & \rightarrow AAG \\
R(l; w; x1; y1; a) & \rightarrow AAG \\
L(x1; y1; x2; y2) & \rightarrow CAA \\
\ldots
\end{align*}
\]

A square (S) is defined by the length of its sides (s), the location of its upper right vertex (x1,y1) and the angle of its base (a). A line (L) is defined by its two endpoints (x1,y1) and (x2,y2).

For example, a square in location (0,0) with a side of 1 and angle of 0 will be encoded as AAGATTATATA. Regardless of how many graphic primitives are used, the first one has to be prepended with im* or GCGTAACTACCA to indicate the start of graphic primitives.

In theory, a library of size <10000 nucleotides could be achieved by introducing sequencing primers (of length 20-30nt) every 500nt fragment. The paper provides an example where 409nt of text, 113nt of music, and 238nt of image data, with an additional 16nt for punctuation and 68nt for three primers, for a total of 844nt is used. The information was retrieved with 100% accuracy, although the authors suggest that sequencing with the three primers should be done in a particular order, and sequencing in both orientations might be needed.
This method comes with the common advantages and disadvantages of storing information in organisms capable of independent replication (plasmids). While this is the first work to store considerable amounts data in different forms (text, music and image data), the implementation is only capable of storing simple, structured data (discrete music notes, graphical primitives) and not actual recordings or photographs.

The encoding itself uses Huffman encoding to encode characters and music or graphic primitives. For encoding text, given the distribution/frequency of character/symbols in the English language, the encoding will require on average 3.5 nucleotides for the 71 symbols used. To encode the nearest number of characters (128) in a binary encoding, 7 bits are needed. 0.5 nucleotides per bit are thus required. Assessing the information density of music and graphic is not possible as the distribution of the different primitives and numbers (coordinates, length etc.) is not known.

Generally, the encoding does not take into account biological constraints like GC content or homopolymers. It neither provides any mechanism for error correction and detection. On the positive side, the encoding is very economical using very few nucleotides per bit, at least for text.

A further project [12] uses a very simple mapping where one letter of the alphabet is mapped to three nucleotides, e.g., 0 → ATA. The project has primarily artistic purposes. The encoding is used to map article 1 of the Universal Declaration of Human rights to synthetic DNA. The DNA is then inserted into a bacteria sprayed on apples (to represent the forbidden fruit as well as the tree of knowledge).

With primarily artistic purposes, the project does not take into account error detection/correction or biological constraints. It requires full sequencing to retrieve the information and is stored in an organism. Given that three nucleotides are used to encode a letter, an alphabet of 81 letters can be encoded, which results in approximately 6 bits, thus leading to an information density of exactly 0.5 nucleotides per bit.

### 3.1 Advanced Approaches featuring Error Correction and Random Access

The work [13] by Church et al. is an important milestone in DNA storage, as it is the first to store relatively large amount of information (5.27MBs). This is possible due to the use of "next generation" (at the time) sequencing and synthesis technologies. The goal is long-term storage, i.e., archival. The encoded information is not inserted into living bacteria - but is simply synthesised DNA and store on a microplate. The archived content is composed of a 53.426-word draft of a book, 11 JPG images and one JavaScript program.

The approach has multiple advantages, starting with the encoding: a nucleotide encodes one bit (A or C for zero, G or T for one), instead of two. It is thus possible to encode the same message (as a sequence of bits, i.e., 0s and 1s) in different sequences of nucleotides. A bit sequence of 0000 can, for example, be encoded as GGGT, thus avoiding a homopolymer of length greater than three. The decision whether a zero is encoded as A or C (or a one as G or T) is made at random unless a homopolymer of length four needs to be avoided. The randomness automatically ensures a somewhat balanced GC content (although it could also be enforced).

The information is split into addressable data blocks (which are encoded individually) to avoid long sequences which are generally difficult to synthesise and which may also form secondary structures. Each block has a 19-bit code and thus also a 19 nucleotide subsequence that identifies its position. Each sequence is flanked by primers of 22 nucleotides length for amplification when sequencing.

Synthesis and sequencing errors have a low probability of being coincident, e.g., errors are unlikely to occur in the same location when either synthesising and sequencing. To address error correction and detection, each sequence is consequently replicated multiple times, enabling spotting of errors easily when comparing multiple sequences.

The density achieved in this project is higher than in previous attempts, at 5.5 petabits/mm², reinforcing the idea that DNA is a suitable as a platform for archiving data. The one shortcoming is the lack of a more sophisticated encoding (parity checks, error-correction) and the high cost of synthesis and sequencing compared to traditional, commercial solutions (tape, hard drives). With the simple encoding, a number of small errors (10, mostly caused by homopolymers) occurred, indicating that a more robust technique is needed. The reported long access time (hours to days) is on par with other approaches (due to the slow speed of sequencing) and is acceptable considering this is an approach for archival data which is accessed only very infrequently.

The theoretical information density of this approach is one nucleotide per bit. While this is not particularly good, 0.5 is the best, this encoding approach is the first that avoids homopolymers and also allows to balance the GC content. Taking into account the addressing information (19 nucleotides) and the sequencing primers (twice 22 nucleotides), only 52 nucleotides can be used to store data (given the sequence length of 115 nucleotides). This results in 2.2 nucleotides required per bit.
However, as no error correction or detection is considered, each sequence needs to be replicated multiple times, thereby also adversely affecting the information density.

Work following this encoded substantial amounts of data for the first time. Goldman [14] et al. encoded binary data (text, PDF, MP3, JPEG) totalling to 757'051 Bytes.

Each of the Bytes of the files is represented is mapped to base 3 numbers. A Huffman encoding is used to map each Byte to either five or six base 3 numbers which in turn are translated to nucleotides. More specifically, each base 3 number is then translated to a nucleotide, picked such that it is different from the last one (to avoid homopolymers).

The resulting (long) sequence is partitioned into segments of 100 nucleotides, each overlapping the previous by 75 nucleotides, thereby introducing four fold redundancy as every 25 nucleotide subsequence will be in four sequences as is illustrated in Figure 5. To map each sequence to a file, two base 3 numbers are used, allowing for 9 different files to be stored. To order the sequences within a file, 12 base 3 numbers are used allowing for 531,441 locations per file. One base 3 number is used as parity check and appended at the end (encoded such that no homopolymer is created).

The fourfold redundancy provides effective error correction as each nucleotide is encoded in four of the DNA segments any systematic or random errors in synthesis or sequencing can be corrected by majority vote.

The approach is specifically designed to avoid homopolymers but no specific mechanism is used to balance the GC content. Error detection if first implemented using the parity nucleotide. With it, errors can be detected. The four fold redundancy then also helps to correct errors by majority vote. The approach is based on Huffman encoding and so the information density depends on the data encoded as some bytes are mapped to 5 or 6 base 3 numbers. For the data used in the experiments, 0.63 nucleotides per bit are needed.

In subsequent work [15], Grass et al. propose a novel approach which incorporates error detection and correction. With it, information can be reliably extracted from DNA that is treated to simulate a 2000 year storage period in appropriate conditions. The amount of information stored, 83kB organised into 4991 DNA segments of length 158nt each (with 117 nucleotides use to encode information), is much less than in [13], but the focus is on the novel encoding.

The encoding mechanism is based on Reed-Solomon (RS) codes, a group of well-studied error-correcting codes which have the property of being maximum distance separable (MDS for short - they achieve equality in the Singleton bound). This property is important as a MDS code with parameters \((n, k)\) has the greatest error detection and correction capabilities compared to other codes with the same parameters.
parameters. The set of alphabet symbols of an RS code is a finite field and the number of elements must therefore be a power of a prime number.

Typical input data are files, which can be thought of as sequences of bytes or of a number in base \(2^8 = 256\). The first step of the algorithm is to convert two bytes of the input to three numbers in the finite field \(GF(47)\) (called a Galois Field, hence GF). The number 47 is chosen as it is the closest prime number to 48, the number of 3-base sequences that can be constructed to satisfy biological constraints such as avoiding homopolymers. Once the conversion to \(GF(47)\) is done, the resulting codewords are arranged into a \(594 \times 39\) block. The codewords are shown in Figure 7 in the red box. The dark red box show one line of codewords. A triple of three numbers (in base 47) represents two Bytes. RS-codes are used on the codewords (rows) to add redundancy information of size 119, for a total blocklength of \(594 + 119 = 713\). This is called the outer RS code (on the left). In the next step, an index of size 3 is added to each column (top), for a vector of size 33, followed by the use of a second (inner) RS code (bottom) on said vector of length 6 thus totalling at 39. The index serves to identify each column (one column will be stored in one DNA sequence) and, given the length of 3 (numbers in \(47^3\)), allows to address 103823 columns. The inner RS code is added to correct individual base errors, whereas the outer RS code helps to correct sequences or to recover completely lost sequences.

The columns (yellow rectangle) are uniquely mapped to DNA sequences of length 117, by mapping each element/number to three nucleotides, as described above. Constant primers, referred to as adapters, are added to flank the resulting sequence.

For the decoding process, the DNA is read using the Illumina MiSeq platform. On the sequences read, the inner code is decoded followed by the decoding of the outer code. In the experiments the inner code fixes on average 0.7 nucleotide errors per sequence while the outer code fixes on average the loss of 0.3% of total sequences and corrects about 0.4%. The information was completely recovered, without errors. Furthermore, an experiment where the DNA suffers decay (achieved by thermal treatment) equivalent to one and four half-lifes (about 500, and respectively, 2000 years) shows that the encoding scheme can retrieve the information without errors even in these conditions.

The encoding is the first to properly incorporate error detection and correction codes (without resorting to replication). In this encoding, the RS codes are chosen such that they can fix 3 arbitrary errors per sequence, correct 8% of sequences if they are incorrect and recover 16% of all sequences if they are missing. Homopolymers an GC content are also incorporated through the use of carefully picked subsequences (in the codon wheel Figure 6).

Only 90 nucleotides of the 158 nucleotide sequences carry actual information (20 Bytes, 160 bits) whereas the remainder is used for index, error correction and primers. The nucleotides used per bit for this encoding thus are 0.9875.

The major novelty of the work [16] of Bornholt et al. is the concept of random-access, a feature missing from previous approaches. While the goal is still archival storage, with read-write times similar to other implementations (hours to days), the addition of random-access enables a new level of efficiency, as it is no longer needed to sequence the entire database.

Previous work stored the DNA in a single pool, which comes with several disadvantages. In order to distinguish between different encoded objects, different primers are needed, and this in turn increases the risk of erroneous interactions. In addition, it is unlikely that a random read will contain all the data. On the other hand, a separate pool for each object represents too big of a sacrifice regarding density. As such, the proposed solution is to use a library of pools of a fixed
size, thus balancing the two issues. In theory, the system provides a simple key-value interface, with two basic operations. A "store" operation, put(key, value) that associates the key with the value, and "read" operation get(key) that retrieves the value assigned to key. In practice, this is achieved by mapping a key to a pair of PCR primers. When writing, the primers are added to the data strand. At read time, the primers are used for PCR amplification only of the desired data. As DNA molecules do not have a particular spatial organisation, each encoded strand must contain an address that identifies its position in the original data stream.

As before, to encode a large amount of information, the data is split into blocks, which have the following structure: primers at the ends, a payload of information, two sense nucleotides that aid the decoding and an address (see Figure 8).

![Figure 8: Strand structure containing primer, address and payload.](image)

The payload represents the actual data to be stored. As mentioned, this is a fragment of the entire information that needs to be encoded, and its length can be adjusted depending on the chosen strand length. The two sense nucleotides specify if the strand has been reverse complemented, which is helpful during decoding. The primers are used, as usual, in the PCR amplification process in order to select the desired blocks. The address serves two purposes. First, it associates a key with a block, so that the put and get operations can be implemented. Second, the address also indexes the block within the value associated with the key.

As there is a unique mapping from key to primer sequences, all the strands of a particular object will share a common primer (because an object is associated with a single key). Thus the read operation is simply a PCR amplification using that particular key’s primer. The strands retrieved for a specific object can then be rearranged to recover the original information based on their Address.

The encoding from binary information to nucleotides is similar to previous approaches. Bytes are transformed using a ternary Huffman code to 5 or 6 ternary digits. The ternary strings are then converted to nucleotides using a rotating code that avoids homopolymers (the encoding for a 0, 1 or 2 depends on the previous nucleotide, such that sequences of repeating nucleotides are avoided). The principle of the mapping is illustrated in Figure 9. For example, the binary string 01100001 is mapped to the base-3 string 0112, which can be encoded to DNA as CTCTG. A Huffman code is used as an intermediary step, to map more common characters to 5 ternary digits, while less frequent ones map to 6 digits.

![Figure 9: Mapping of ternary codes to nucleotides.](image)

A novel way to provide error detection and correction through redundancy is introduced as well. The inspiration comes from the encoding used by Goldman et al. Essentially, the Goldman encoding splits the DNA nucleotides into four overlapping fragments, thus providing fourfold redundancy (See Figure 5). This encoding is taken as a baseline to evaluate the results of the current scheme. Bornholt et al. propose a XOR Encoding, in a similar fashion to RAID 5. With this approach, the exclusive-or operation is performed on the payloads A and B of two strands, which produces a new payload A ⊕ B. The address of the newly created block can be used to tell if it is an original strand or the result of the exclusive-or operation. Any two of the three strands A, B and A ⊕ B are sufficient to recover the third. The major advantage of this method is that it offers similar reliability to the Goldman encoding, while being more efficient in terms of density. The Goldman encoding repeats each nucleotide (up to) four times, while for the Bornholt encoding each nucleotide is repeated 1.5 times on average (See Figure 10).
Overall, this design introduces a remarkable feature, random-access, as a proof-of-concept. It incorporates error detection and correction and avoids homopolymers. The information density of this encoding is 1.13 nucleotides per bit. However, the redundancy is provided by repetition with a (tunable) factor of 1.5, meaning that in fact, the density is 1.695 nucleotides per bit.

Other work that implements this feature has been developed concurrently by Yazdi et al. [17]. The approach (or rather experiments) use rather long DNA sequences of 1000 nucleotides length, divided into an address of 16 nucleotides while the remainder is used for encoded information.

The encoding of the information and the design of the addresses follow three goals. First, none of the (distinct) addresses should be part/subsequence of any of the encoded information (weak mutual correlation). Second, the addresses should be as distinguishable as possible. The third goal is to balance GC content and to avoid homopolymers.

The method developed generates two sets $S_1$ and $S_2$ of codewords. $S_1$ is to be used as addresses and the Hamming distance is used to make sure they are distinguishable compared to each other. $S_2$ contains codewords which are to be used to encode information. Properties such as weak mutual correlation, GC content and avoidance of homopolymers are provable with this encoding approach.

In experiments the authors encode the image of a black and white movie poster (Citizen Kane) as well as the color image of a smiley face. The information is first compressed and then encoded in 17 sequences - each with a length of 1000 nucleotides - by picking an address from $S_1$ and mapping the binary content of the images to codewords from $S_2$.

Errors are detected and corrected during post-processing, after sequencing. Using PCR before sequencing means that each sequence will be replicated numerous times. High-quality reads are identified as the ones where the address contains no errors. Following this, the high-quality reads are aligned and a consensus is computed. The alignment uses possible codewords as hint. In the experiments, most errors at this stage are errors of deletions in homopolymers of length at least two. The remaining errors are further corrected by taking into account GC balance which helps to determine which homopolymers are likely.

To sum up this approach, this encoding approach avoids homopolymers and also balances GC content. It does not use any error detection or correction mechanism when encoding. Errors are detected and corrected in post processing. In terms of information density, the images are of size 29064 bits (compressed) and are encoded with 16880 nucleotides ($16 \times 1000$ and one 880 sequences), thus resulting in 1.72 nucleotides per bit.

Subsequent work [18] focused on encoding structured database information and implementing database operations. Two different encodings are discussed, one for storing structured database information, i.e., relational tables and one for implementing database operations.

The first encoding exploits the inherent structure in databases, i.e., that each attribute of a record in a table can be linked to the record using the primary key. Doing so means that attributes of the same record can be distributed across different DNA sequences without the need for addressing. Instead the primary key is used for this purpose, reducing the space needed for the address. Figure 11 illustrates how one record of a table is stored in multiple sequences.

More specifically, dictionary encoding is used to compress the information. The dictionary is encoded in DNA as well. Subsequently, as many attributes as possible are stored in a DNA sequence along with the primary key (to link together attributes of the same record). A parity nucleotide is added to each DNA sequence for error detection. After sequencing,
the parity nucleotide and length of the DNA sequence are used to discard invalid sequences. The remaining sequences are aligned to compute a consensus. In the experiments, based on a subset of the database benchmark TPC-H, multiple tables are encoded, synthesized, sequenced and fully recovered.

The encoding used is based on previous work by Church [13] discussed previously and thus avoids homopolymers and also allows to balance the GC content. Error detection is possible through the parity nucleotide but correction is left to the decoding process (through computing the consensus). The Church approach requires one nucleotide per bit and consequently this approach uses the same.

The second encoding developed in the same work enables processing of data such as selective retrieval of records based on their value as well as database joins, i.e., find pairs records which agree on a particular attribute.

To enable these operations, each attribute is stored in one DNA sequence. To simplify the design, fixed sized hash values are computed for the variable length fields. More particularly, table and attribute name as well as the primary key are hashed for a fixed length and arranged in a DNA sequence with value and error correction codes as shown in Figure 12.

PCR is used to retrieve all DNA sequences encoding a particular value for a specific attribute. Similarly, overlap extension PCR is used to implement a join by annealing matching sequence/attributes together as shown in Figure 13.

In both cases, the encoding of the value must also serve as a primer and must therefore be designed specially. More specifically, to avoid retrieval of similar DNA sequences or joining of similar sequences, similar values must be encoded substantially different. To do so, the encoding outlined before is used but the checksum of the attribute value is computed (using SHA3) and encoded as well. To then make similar attributes encodings substantially different, the encoding of an attribute a as well as the checksum c is separately split into subsets (a1, a2, a3, ... and c1, c2, c3, ...) and one is interleaved with the other (resulting in a1, c1, a2, c2, a3, c3, ...). Thanks to the avalanche effect of SHA3 (and other cryptographic functions) — small differences in input value lead to considerable differences in the checksum — the resulting sequence will be substantially different, even if the attribute values are similar.

Figure 12: Structure of the encoding.
Also here, the encoding used is based on previous work by Church [13] discussed previously and thus avoids homopolymers and also allows to balance the GC content. Error correction and detection is incorporated using reed-solomon codes. The Church approach requires one nucleotide per bit and consequently this approach.

### 3.2 Summary of Comparison

In table below we compare all the approaches discussed previously. We focus on comparing them with respect to their storage mechanism (organism or microplate), information density (nucleotides per bit), error detection and correction mechanisms as well as consideration of biological constraints (avoiding homopolymers and balancing GC content).

| Name/Reference | Storage Mechanism | Information Density | Error Correction and Detection | Biological Constraints | Access Mechanism |
|----------------|-------------------|---------------------|-------------------------------|------------------------|------------------|
| Microvenus [2] | Organism          | 0.54                | -                             | -                      | sequential       |
| Genesis [3]    | Organism          | 0.65                | -                             | -                      | sequential       |
| [4]            | Microplate        | 1.06                | -                             | -                      | random           |
| [5]            | Organism          | 0.65                | -                             | -                      | sequential       |
| Microdot [6]   | Microplate        | 0.79                | -                             | -                      | sequential       |
| Huffman codes [7]| Microplate        | 0.44                | -                             | -                      | sequential       |
| Comma codes [7]| Microplate        | 1                   | detection                     | balanced GC content    | sequential       |
| Alternating codes [7] | Microplate  | 1 | detection | no homopolymers | sequential |
| [8]            | Organism          | 0.512               | through replication           | -                      | sequential       |
| [11]           | Organism          | 0.5                 | through replication           | no homopolymers        | sequential       |
| [13]           | Microplate        | 2.2                 | through replication           | balanced GC content    | sequential       |
| [14]           | Microplate        | 0.63                | error detection and correction | no homopolymers        | sequential       |
| [15]           | Microplate        | 0.9875              | error detection and correction | balanced GC content    | sequential       |
| [16]           | Microplate        | 1.13                | replication                    | no homopolymers        | random           |
| [17]           | Microplate        | 1.72                | error detection and correction | balanced GC content    | sequential       |
| Oligoarchive DB [18] | Microplate | 1 | error detection | no homopolymers | random |
| Oligoarchive Join [18] | Microplate | 1 | error detection and correction | no homopolymers | random |
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