Coding Techniques for Emerging DNA-Based Storage Systems

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Motivation

The Future of Storage

▶ Cost of high-performance parallel storage: \$0.3 per GB per month.



Figure: From Church, Harvard U.

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The Future of Storage

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- ▶ Cost of cloud storage: Google Cloud \$5.47 per 50 GB per month.



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The Future of Storage

- ▶ Cost of high-performance parallel storage: \$0.3 per GB per month.
- ▶ Cost of cloud storage: Google Cloud \$5.47 per 50 GB per month.
- Cost of storage often minor compared to cost of access, processing, and data movement.



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- ▶ DNA sequencing data: 30 50 TB per week.
- ▶ Sloan Digital Sky Survey: 1 2 TB per week.
- Social science (Twitter, Facebook, LinkedIn), NASA weather surveys, consumer and stock market data, Internet sources...



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- DNA write (synthesis) and read (sequencing) costs decrease daily.
- DNA information content of Human cell: 6.4 GB. Mass of a cell: ~ 3 picograms. No. of cells: $15 40 \times 10^{12}$.
- How much information can one store in a gram of DNA?



Implementations

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- Church et al. (Science, 2012) and Goldman et al. (Nature, 2013) stored 739 KB of data in synthetic DNA, mailed it and recreated the original digital files.
- Goal: a digital archival storage system that will safely store the equivalent of one million CDs in a gram of DNA for 10,000 years.



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"Data Storage on DNA Can Keep it Safe for Centuries," NY Times, Dec 2015

Renewed interest in DNA storage (UIUC, MS Research, IARPA Special Program on DNA-Based Storage). Goal: Build a fully operational, cost-efficient, real-time, random access DNA-based memory.





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- Renewed interest in DNA storage (UIUC, MS Research, IARPA Special Program on DNA-Based Storage). Goal: Build a fully operational, cost-efficient, real-time, random access DNA-based memory.
- Yazdi et.al., 2015 First random access, rewritable DNA-based storage system. Encoded Wikipedia entries for six US universities (including MIT).



Our Experiments

Random access achieved via specialized address design.







OE-PCR based method



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Our Experiments

- Random access achieved via specialized address design.
- Context identification and rewriting performed via gBlock or OE-PCR methods.



gBlock based method



OE-PCR based method



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The Write and Read Channels

Biochemistry of synthesis: Adding bases through deprotection & coupling cycles.



 DNA microarray based synthesis (left): Cost effective, large scale. Short strands, higher error rates.



- DNA microarray based synthesis (left): Cost effective, large scale. Short strands, higher error rates.
- Long strand synthesis (right): Synthesize via shorter blocks, assembled. Chemical error-correction.





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- DNA microarray based synthesis (left): Cost effective, large scale. Short strands, higher error rates.
- Long strand synthesis (right): Synthesize via shorter blocks, assembled. Chemical error-correction.
- Types of synthesis errors: predominantly substitutions, much less frequent deletions/insertions.





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The Write and Read Channels

The Read Channel: Illumina and MinIon

 Illumina (MiSeq, left): Best overall performance of modern sequencing technologies in terms of yield and accuracy; large volumes of DNA reads, relatively small error rates (substitutions and context dependent deletions). Drawback short read length.





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The Read Channel: Illumina and MinIon

- Illumina (MiSeq, left): Best overall performance of modern sequencing technologies in terms of yield and accuracy; large volumes of DNA reads, relatively small error rates (substitutions and context dependent deletions). Drawback short read length.
- Oxford Nanopore Minlon (Right): Longer read length, miniaturized architecture. Large coverage errors, excessive number of block deletions.





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The Read Channel: Shotgun Sequencing

Cloning /// Shearing /// Reading of unordered pool /// Computer aided alignment of overlapping fragments /// Consensus



Media Aging

 Breakage - Bursty Deletions - Transpositions/Reversals: No built-in mechanism for correcting damages.



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Media Aging

- Breakage Bursty Deletions Transpositions/Reversals: No built-in mechanism for correcting damages.
- Coupled with synthesis and sequencing errors...



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Wednesday, November 26, 2014

- A formal mathematical theory of error-correction for DNA storage?
 - Microarray Synthesis and Nanopore Sequencing: Asymmetric Lee Distance (ALD) Codes.



 For a positive integer λ, the ALD d_λ((a; b), (c; d)) between pairs of binary sequences (a; b), (c; d) is defined as:

$$d_{\lambda}((\boldsymbol{a};\boldsymbol{b}),(\boldsymbol{c};\boldsymbol{d})) = \sum_{i=1}^{n} (1+\lambda) \left(\mathbb{1}(a_{i},b_{i}) + \mathbb{1}(c_{i},d_{i}) \right) +$$
$$\overset{\text{Wedrystar}}{\mathbb{I}} \left(\overset{\text{Nove}}{d_{i}}, \overset{\text{B}_{i} \in \mathcal{Z}_{i}^{20}}{B_{i}}, \overset{\text{O}_{i}}{d_{i}} \right) - 2(1+\lambda) \mathbb{1}(a_{i},b_{i},c_{i},d_{i}).$$

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A formal mathematical theory of error-correction for DNA storage?

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 - The block DL distance: Extension in which edit units are blocks of limited length.
 - ► Varshamov-Tenengolt's extensions for the DL distance: Uses the derivative of *a*, *a*' = (a₁, a₂ + a₁, a₃ + a₂, ..., a_n + a_{n-1}).

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 - Component codes: $C_H(n,3)$ a single error-correcting code; $C_D(n)$ a single deletion-correcting code.

$$\mathcal{C}_{T \vee D}(n) = \{ \boldsymbol{a} \in \mathbb{F}_2^n : \boldsymbol{a} \in \mathcal{C}_D(n), \boldsymbol{a}' \in \mathcal{C}_H(n,3) \}.$$

The code $C_{T \vee D}(n)$ can correct one single deletion or adjacent transposition.



- Mathematical approaches for enabling random access and rewriting?
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The DNA Storage Channel



Synthesis channel captures the "write" process.



The sequence synthesis process introduces errors (current technologies $\leq 0.1\%$).

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DNA sequencing represents the "read" process. Consists of fragmenting sequence to be read, and "reconstructing" fragments (ℓ -grams).

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Note that strings at the output of the fragmentation block are *not* ordered.

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 Sequencing introduces errors in some l-grams and some l-grams may not be covered.

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- Sequencing introduces errors in some l-grams and some l-grams may not be covered.
- \blacktriangleright Modern Illumina platforms have substitution error rates $\leq 0.5\%.$ Coverage errors context-dependent.

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DNA Storage Channel: Profile Vectors



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DNA Storage Channel: Profile Vectors



The profile vector of a sequence reflects the count of its ℓ -grams;

Example										
Profile of vecto	or x =	10011	001 eq	uals						
	000	001	010	011	100	101	110	111		
	(0,	2,	0,	1,	2,	0,	1,	0).		

Input and Output Profile Vectors



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Profile Vectors: Formal Definition

Fix alphabet size q and fragment (read) length $\ell < n$. The profile vector of some sequence \mathbf{x} , denoted by $\mathbf{p}(\mathbf{x}; q, \ell)$, has length q^{ℓ} and its entry indexed by \mathbf{z} equals the number of occurrences of \mathbf{z} in \mathbf{x} as an ℓ -gram.

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Example									
Profile of \mathbf{x} =	100110	<mark>01</mark> and	d sequ	encing	chanr	nel out	put:		
	000	001	010	011	100	101	110	111	
	(0,	2,	0,	1,	2,	0,	1,	0),	
	(0,	1,	0,	2,	0,	1,	1,	0).	

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Code Design Criteria



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Condition 1

Codewords should have profile vectors that are sufficiently "distinct," i.e., one should be able to correct combination of synthesis substitution (burst), coverage, and ℓ -gram errors.



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The ℓ -gram distance between x and y equals the asymmetric distance (ℓ_1 distance) between $\mathbf{p}(\mathbf{x}; q, \ell)$ and $\mathbf{p}(\mathbf{y}; q, \ell)$.

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Asymmetric Distance

Let $\mathbf{u}, \mathbf{v} \in \mathbb{Z}_{\geq 0}^N$. Define $\Delta(\mathbf{u}, \mathbf{v}) = \sum_{i=1}^N \max(u_i - v_i, 0)$. Asymmetric distance: $d_{asym}(\mathbf{u}, \mathbf{v}) = \max(\Delta(\mathbf{u}, \mathbf{v}), \Delta(\mathbf{v}, \mathbf{u}))$.

		000	001	010	011	100	101	110	111
p(x; 2, 3)	=	(0,	2,	0,	1,	2,	0,	1,	0)
p(y; 2, 3)	=	(0,	0,	3,	0,	0,	3,	0,	0)
$\mathbf{p}(\hat{\mathbf{x}}; 2, 3)$	=	(0,	1,	0,	2,	0,	1,	1,	0).

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Minimum Asymmetric Distance

A DNA storage code with minimum asymmetric distance d can correct s_1 substitution errors due to synthesis, s_2 substitution errors due to sequencing and t coverage errors provided that $d > 2s_1 + 2s_2 + t$.

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Avoid "bad" grams that cause sequencing errors and media instability:

- Weight profiles of ℓ -grams. GC content roughly 50%.
- ▶ Forbidden ℓ-grams. Certain substrings, such as GCG and CGC, are likely to cause coverage errors.



Codewords whose ℓ -grams avoid error-causing substrings.

Avoid "bad" grams that cause sequencing errors and media instability:

- Weight profiles of ℓ -grams. GC content roughly 50%.
- ▶ Forbidden ℓ-grams. Certain substrings, such as GCG and CGC, are likely to cause coverage errors.

For example, may require that $\ell\text{-}\mathsf{grams}$ lie in

 $S = \{001, 010, 011, 100, 101, 110\}.$

Fundamental Questions

Distinct *l*-gram Profile Vectors

Let Q(n; S) be the largest set of q-ary words of length n whose ℓ -grams belong to S, and which have distinct ℓ -gram profile vectors. Determine the size of Q(n; S).

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Fundamental Questions

ℓ-gram Reconstruction Code (GRC)

 $C \subseteq Q(n; S)$ is an (n, d; S)- ℓ -GRC if the ℓ -gram distance between any pair of distinct words is at least d. Construct good (n, d; S)- ℓ -GRC. "Good" means large codebook size, avoidance of bad ℓ -grams.

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Profile Vectors and $\ell\text{-}\mathsf{Gram}$ Codes

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De Bruijn Graphs

Example for q = 2, $\ell = 3$.



De Bruijn Graphs

Nodes are q-ary strings of length $\ell - 1$. $(\mathbf{v}, \mathbf{v}')$ is an arc if $v_2 \quad v_3$

 $v_{\ell-1}$

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Restricted De Bruijn Graphs (Ruskey et al., 2012)

Let $S(\ell; w_1, w_2)$ denote the binary strings of length ℓ with weight between w_1 and w_2 .



Restricted De Bruijn Graphs D(S)

Nodes V are ℓ – 1-prefixes and -suffixes of strings in S. $(\mathbf{v}, \mathbf{v}')$ is an arc if

Profile Vectors and Flows



Representation of profile vectors of words in $\mathcal{Q}(n; S)$ using the digraph D(S).

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Profile Vectors and Flows



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Closed Words

Closed words are words that start and end with the same $(\ell - 1)$ -gram. $\overline{\mathcal{Q}}(n; S)$: largest set of q-ary closed words of length n whose ℓ -grams belong to S and which have distinct ℓ -gram profiles.

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Flows

Paths in D(S) such that sum of incoming arc weights is equal to sum of outgoing arc weights at each vertex. Profile vectors of words in $\overline{Q}(n;S)$ are flow vectors in D(S).

Necessary Conditions

Let ${\bf u}$ be a profile vector (of a closed word). Then ${\bf u}$ satisfies the following conditions.



Let
$$\mathbf{A} = \begin{pmatrix} \mathbf{1} \\ \mathbf{B} \end{pmatrix}$$
 and $\mathbf{b} = (1, 0, \dots, 0)^T$. Rewrite equations as

 $Au = (n - \ell + 1)b$ and $u \ge 0$.

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Sufficient Conditions

Flows are not always profile vectors

Let $\mathbf{u} \geq \mathbf{0}$ be such that

$$\mathbf{A}\mathbf{u} = (n - \ell + 1)\mathbf{b}.$$

This does not imply that \mathbf{u} is a profile vector!



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Sufficient Conditions

If all flows are positive, then the flow vector is indeed a profile vector.



 $Au = (n - \ell + 1)b$ and u > 0.

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Consider the following two sets of lattice points:

$$\mathcal{F}(n;S) = \{ \mathbf{u} \in \mathbb{Z}^{|S|} : \mathbf{A}\mathbf{u} = (n-\ell+1)\mathbf{b}, \ \mathbf{u} \ge \mathbf{0} \},$$
$$\mathcal{E}(n;S) = \{ \mathbf{u} \in \mathbb{Z}^{|S|} : \mathbf{A}\mathbf{u} = (n-\ell+1)\mathbf{b}, \ \mathbf{u} > \mathbf{0} \}.$$

Clearly, one has

 $|\mathcal{E}(n;S)| \le |\overline{\mathcal{Q}}(n;S)| \le |\mathcal{F}(n;S)|.$

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Observations

- $\mathcal{F}(n;S)$ is a polytope. It can be shown to be of dimension |S| |V(S)|.
- $\mathcal{E}(n;S)$ is the interior of $\mathcal{F}(n;S)$ if D(S) is strongly connected.
- May use Ehrhart theory for polytopes to determine $|\mathcal{E}(n;S)|, |\mathcal{F}(n;S)|$.

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$$|\mathcal{E}(n;S)| \le |\overline{\mathcal{Q}}(n;S)| \le |\mathcal{F}(n;S)|.$$

Observations

Define the polytope

$$\mathcal{P}_S = \{ \mathbf{u} \in \mathbb{R}^{|S|} : \mathbf{A}\mathbf{u} = \mathbf{b}, \ \mathbf{u} \ge \mathbf{0} \}.$$

- *F*(n; S) is the set of lattice points in (n − ℓ + 1)*P*_S.
- *E*(n; S) is the set of lattice points in the interior of (n − ℓ + 1)*P*_S.



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Lattice Point Enumeration in Dilated Polytopes



For a polytope $\mathcal{P} \subset \mathbb{R}^N$ and $t \in \mathbb{R}$, the dilation $t\mathcal{P}$ is given by $t\mathcal{P} = \{tx : x \in \mathcal{P}\}.$ The lattice point enumerator for \mathcal{P} is $\mathcal{L}_{\mathcal{P}} : \mathbb{R} \to \mathbb{Z}$ defined by $\mathcal{L}_{\mathcal{P}}(t) = |t\mathcal{P} \cap \mathbb{Z}^N|.$

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Theorem (Ehrhart)

If \mathcal{P} is a rational D-dimensional polytope, then $\mathcal{L}_{\mathcal{P}}(t)$ is a "quasipolynomial" (polynomial with periodic functions as coefficients) in t of degree D.

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Theorem (Ehrhart-Macdonald's Reciprocity)

The number of lattice points in the interior of $t\mathcal{P}$ is given by $(-1)^D \mathcal{L}_{\mathcal{P}}(-t)$, and is thus a "quasipolynomial" of degree D.

Main Enumeration Results

Theorem

Suppose D(S) is strongly connected. Then $|\mathcal{E}(n;S)|$ and $|\mathcal{F}(n;S)|$ are both quasipolynomials in n of the same degree |S| - |V(S)|. In particular, $|\overline{\mathcal{Q}}(n;S)| = \Theta' \left(n^{|S| - |V(S)|}\right)$.

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The Write and Read Cha

The DNA Storage Channel

Corollaries of Main Enumeration Result



Here,
$$|\overline{\mathcal{Q}}(n;S)| = \frac{n^3}{288} + O(n^2)$$
 (Curtesy of Latte).

Theorem (Jacquet, Knessl, Szpankowski, 2012; Ukkonnen, Pevzner 1990's)

Fix q, ℓ and let S be the set of all q-ary strings of length ℓ . Then

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$$\mathcal{E}(n; S| \sim |\mathcal{F}(n; S)| \sim |\overline{\mathcal{Q}}(n; S)| \sim c(S) n^{q^{\ell} - q^{\ell-1}}$$
 where $c(S)$ is a constant.

 $f \sim g$ means that $\lim_{n \to \infty} f(n)/g(n) = 1$.

Corollary

Suppose D(S) is strongly connected and contains loops. Then

 $|\mathcal{E}(n;S| \sim |\mathcal{F}(n;S)| \sim |\overline{\mathcal{Q}}(n;S)| \sim c(S)n^{|S|-|V|}$ where c(S) is a constant.

Sac

Varshamov Codes

Fix d and let p be a prime such that p > d and p > N. Choose N distinct nonzero elements $\alpha_1, \alpha_2, \ldots, \alpha_N$ in $\mathbb{Z}/p\mathbb{Z}$ and consider the matrix

$$\mathbf{H} = \begin{pmatrix} \alpha_1 & \alpha_2 & \cdots & \alpha_N \\ \alpha_1^2 & \alpha_2^2 & \cdots & \alpha_N^2 \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_1^d & \alpha_2^d & \cdots & \alpha_N^d \end{pmatrix}.$$

Pick any vector $\boldsymbol{\beta} \in (\mathbb{Z}/p\mathbb{Z})^N$ and define the code

$$\mathcal{C}(\mathbf{H},\boldsymbol{\beta}) = \{\mathbf{u} \in \mathbb{Z}^N : \mathbf{H}\mathbf{u} \equiv \boldsymbol{\beta} \bmod p\}.$$

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Theorem (Varshamov, 1973)

 $C(\mathbf{H}, \boldsymbol{\beta})$ is a code with minimum asymmetric distance d + 1.

Construction I

Let $\mathbf{p}\mathcal{Q}(n;S)$ be the set of distinct profile vectors of words in S and N = |S|. Then $\mathcal{C}(\mathbf{H}, \boldsymbol{\beta}) \cap \mathbf{p}\mathcal{Q}(n;S)$ is an (n, d+1; S)- ℓ -gram reconstruction code.

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Example

Let q = 2, ℓ = 3, S = $\{001, 010, 011, 100, 101, 110\}$ and so, N = 6. Let d = 3 and pick p = 7, so that

$$\mathbf{H} = \left(\begin{array}{rrrr} 1 & 2 & 3 & 4 & 5 & 6 \\ 1 & 4 & 2 & 2 & 4 & 1 \end{array}\right) \text{ and } \boldsymbol{\beta} = \left(\begin{array}{r} 0 \\ 0 \end{array}\right).$$

Then $C(\mathbf{H}, \boldsymbol{\beta})$ contains the following words. (4, 0, 0, 1, 0, 1) (0, 1, 1, 4, 0, 0) $(2, 2, 0, 2, 0, 0) \leftrightarrow 00100100$ (0, 1, 0, 0, 4, 1) (1, 4, 0, 0, 1, 0) (0, 0, 4, 1, 1, 0) $(1, 1, 1, 1, 1, 1) \leftrightarrow 00101100$ $(0, 0, 2, 0, 2, 2) \leftrightarrow 01101101$ (1, 0, 1, 0, 0, 4)Above, three profile vectors in pQ(8; S).

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Pigeonhole principle: there exists a β such that $|\mathcal{C}(\mathbf{H}, \beta) \cap \mathbf{p}\mathcal{Q}(n; S)|$ is at least $|\mathbf{p}\mathcal{Q}(n; S)|/p^d$. However, the optimal choice of β is not known.

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We fix a certain choice of **H** and β and provide lower bounds on the size of $C(\mathbf{H}, \beta) \cap \mathbf{p}Q(n; S)$ as a function of n.

Ehrhart Theory Continued

Define the $(|V| + 1 + d) \times (|S| + d)$ -matrix

$$\mathbf{A}_{\mathrm{GRC}} = \left(\begin{array}{c|c} \mathbf{A} & \mathbf{0} \\ \hline \mathbf{H} & -p\mathbf{I}_d \end{array} \right).$$

Proposition

If D(S) is strongly connected and $C(\mathbf{H}, \mathbf{0}) \cap \text{Null}_{>0}\mathbf{B}$ is nonempty, then $|C(\mathbf{H}, \mathbf{0}) \cap \mathbf{p}Q(n; S)|$ is at least the number of lattice points in the interior of the polytope

$$\left\{ \mathbf{u} \in \mathbb{R}^{|S|+d} : \mathbf{A}_{\mathrm{GRC}}\mathbf{u} = (n-\ell+1)\mathbf{b}
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▶ Null_{>0}B denotes the set of vectors in the null space of B with strictly positive entries.

Ehrhart Theory Continued

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Theorem

If D(S) is strongly connected and $C(\mathbf{H}, \mathbf{0}) \cap \text{Null}_{>0}\mathbf{B}$ is nonempty, then

$$|\mathcal{C}(\mathbf{H},\mathbf{0}) \cap \mathbf{p}\mathcal{Q}(n;S)| = \Omega'\left(n^{|S|-|V(S)|}\right)$$

• $f(n) = \Omega'(g(n))$ means that for a fixed value of ℓ , there exists an integer λ and a positive constant c so that $f(n) \ge cg(n)$ for sufficiently large n with $\lambda | (n - \ell + 1)$.

Encoding and Decoding?

• Encoding: Systematic encoder that takes profile of input x and converts it into redundant profile.

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Encoding and Decoding?

- Encoding: Systematic encoder that takes profile of input x and converts it into redundant profile.
- Decoding: Receive profile. Correct errors in profile. Assemble profile (say, by using Hierholzer's algorithm).

Literature Overview

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