A fast algorithm for exact sequence search in biological sequences using polyphase decomposition

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ABSTRACT

Motivation: Exact sequence search allows a user to search for a specific DNA subsequence in a larger DNA sequence or database. It serves as a vital block in many areas such as Pharmacogenetics, Phylogenetics and Personal Genomics. As sequencing of genomic data becomes increasingly affordable, the amount of sequence data that must be processed will also increase exponentially. In this context, fast sequence search algorithms will play an important role in exploiting the information contained in the newly sequenced data. Many existing algorithms do not scale up well for large sequences or databases because of their high-computational costs. This article describes an efficient algorithm for performing fast searches on large DNA sequences. It makes use of hash tables of Q-grams that are constructed after downsampling the database, to enable efficient search and memory use. Time complexity for pattern search is reduced using beam pruning techniques. Theoretical complexity calculations and performance figures are presented to indicate the potential of the proposed algorithm.

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1 INTRODUCTION

Decreasing costs of sequencing personal genome have opened up many avenues of research. Several efforts related to Personal Healthcare and Pharmacogenomics are attempting to use the information in an individual’s genomic data towards personalization of healthcare. An important component of these solutions is the search for specific subsequences in a given genome. For example, Cetuximab (Eric et al., 2009)—an Epidermal Growth Factor Receptor (EGFR) inhibitor used to treat various types of cancer is ineffective if certain mutations in the KRAS gene (which lies in Exon 2 of Chromosome 12) exist. Thus, a search for appropriate mutations becomes tedious as the inter-mingling of linked lists is very low-search time complexity. They represent all suffixes of the text as a plurality of inter-mingled linked lists. At times when the knowledge about genomes becomes updated frequently, updating the suffix tree in place becomes tedious as the inter-mingling of linked lists is very sensitive to changes in the text data. Also, as every node in the tree is required to hold tree-related information such as pointers to their parents and children apart from text-based information, even the best implementation of suffix trees require ~15.4 bytes per base (Kurtz et al., 2004), which scales up to 46 GB of memory to store the preprocessed Human Genome.

Deterministic Finite Automaton (DFA)-based methods (Charras and Lecroq, 2004; Gusfield 1997) that yield exact matches have a very low-search time complexity. They represent all suffixes of the text as a plurality of inter-mingled linked lists. At times when the knowledge about genomes gets updated frequently, updating the suffix tree in place becomes tedious as the inter-mingling of linked lists is very sensitive to changes in the text data. Also, as every node in the tree is required to hold tree-related information such as pointers to their parents and children apart from text-based information, even the best implementation of suffix trees require ~15.4 bytes per base (Kurtz et al., 2004), which scales up to 46 GB of memory to store the preprocessed Human Genome.

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We first explain various terminologies we use in the exposition that follows. For this purpose, we use an example sequence, given by:

\[ S = \text{actgcttctact}. \]  

Let the length of the sequence \( S \) be denoted by \( L_S \). Also, \( S[n] \) is used to represent the \( n \)-th base of the sequence \( S \). For example, \( S[0] = \text{a} \) and \( S[1] = \text{c} \).

Downsampling (Vaidyanathan, 1993) a sequence by a factor of \( M \) means that we pick every \( M \)-th base from sequence \( S \) to form a new sequence \( SM \) given by:

\[ SM[n] = S[Mn] , 0 \leq n \leq \left\lfloor \frac{L_S}{M} \right\rfloor \]  

where, \( \lfloor \cdot \rfloor \) indicates the largest integer less than the argument. For example, for the sequence \( S \) and \( M = 3 \), \( S_3 = \text{agta} \).

\( M \)-channel polyphase decomposition (Vaidyanathan, 1993) gives \( M \) possible down-sampled sequences for different integer-phase shifts. The generalized form of polyphase decomposition is given by:

\[ SM[n] = S[Mn + i] , 0 \leq n \leq \left\lfloor \frac{L_S}{M} \right\rfloor , 0 \leq i \leq M - 1. \]  

Note that \( SM = SM0 \). The polyphase decomposition of the sequence \( S \) in Equation (1) for \( M = 3 \) yields:

\[ S_30 = \text{agta}, S_31 = \text{cccc} \]  

\( S_32 = \text{tttt} \)

A \( Q \)-gram of a sequence \( S \) is denoted by \( QS(n) \) and is made up of \( Q \) consecutive bases starting from position \( n \). Thus for sequence \( S \) as in Equation (1) example \( Q \)-grams are:

\[ QS(0) = \text{actg} \]  

\( QS(1) = \text{ctgc} \)

\( QS(2) = \text{tctc} \) \( QS(8) = \text{tact} \)

Contiguous \( Q \)-grams of a sequence \( S \) is the set:

\[ CQS = \{ QS(0)QS(1) ... QS(L_S - Q) \} \]  

where the cardinality of the set \( CQS \) is \( |CQS| = L_S - Q + 1 \). Note that there are \( Q - 1 \) common bases between any two consecutive \( Q \)-grams in \( CQS \). For example, given \( S \) as in Equation (1) and \( Q = 4 \),

\[ CQS = \{ \text{actg}, \text{ctgc}, \text{tctc}, \text{tctg}, \text{cttc}, \text{tctc}, \text{tcte}, \text{cttc}, \text{tact} \} \]

\( NQS \) is the set of non-overlapping \( Q \)-grams of sequence \( S \) given by:

\[ NQS = \{ QS(0)QS(1) ... QS \left( \left\lfloor \frac{L_S}{Q} \right\rfloor \right) \}. \]  

Note that:

\[ \forall QS(i) \in NQS, QS(i) \cap QS(j) = \phi \text{ if } i \neq j \]

where \( \phi \) denotes the null set. That is the \( Q \)-grams in \( NQS \) are pairwise and non-overlapping.

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We now describe the proposed method.

3 PROPOSED METHOD

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We now describe the proposed method which is composed of two stages, namely:

(1) Preprocessing stage.

(2) Pattern-search stage.

The detailed description of each stage is presented in the following subsections.

3.1 Preprocessing stage

A block diagram for the preprocessing stage is shown in Figure 1. In this step, text \( T \) is downsampled and processed into a hash table to support random access into the text. A hash table is a data structure that efficiently links keys to corresponding values called buckets (Cormen et al., 1990). In our case, the key refers to each distinct \( Q \)-gram while bucket refers to the list of locations of that \( Q \)-gram in the text. Here, \( T \) is first downsampled by a factor of \( M \) to give TM and a hash table \( HTMQ \) is then constructed using contiguous \( Q \)-grams of TM. The bucket of a given \( Q \)-gram \( q \) is denoted by \( HTMQ(q) \).

The details of the preprocessing algorithm are given below. This is followed by an example on sample text.

Algorithm–A

(1) Downsampled the text \( T \) by a factor of \( M \) to yield TM.

(2) Generate the set of contiguous \( Q \)-grams for TM, namely, CQTDM.

(3) For each \( Q \)-Gram in CQTDM, consult the key field of the hash table \( HTMQ \).
Fig. 1. Block diagram of the preprocessing stage.

Table 1. A sample Q-gram hash table

| Key: Q(=3) gram | Bucket: Locations’ list |
|-----------------|-------------------------|
| agt             | 0, 3, 6                 |
| gta             | 1, 4, 7                 |
| tag             | 2, 5                    |
| taa             | 8                       |
| aac             | 9                       |
| aca             | 10                      |

(4) If the Q-Gram exists in the key field, append the new position in the bucket \(H_{TMQ}[Q\text{-gram}]\).
(5) Else, add a new Q-gram key and its position in the corresponding bucket in \(H_{TMQ}\).

Example:
Consider the sequence \(T = \text{‘acc gat tag aag ggt tta aga gtc tca acc aga cta agc’}\). For \(M = 3\) and \(Q = 3\), the result of the algorithm is given below.
(1) \(T_3 = \text{agtagtagtacag}\). For \(M = 3\) and \(Q = 3\), the result of the algorithm is given below.
(2) \(CQT_3 = \{\text{agt}(0), \text{gta}(1), \text{tag}(2), \text{agt}(3), \text{gta}(4), \text{tag}(5), \text{agt}(6), \text{gta}(7), \text{taa}(8), \text{aac}(9), \text{aca}(10)\}\). Note that we have also mentioned the indices for each Q-gram in CQT3 in parentheses.
(3) Finally the \(H_{TMQ}\) is as given in Table 1.

3.2 Pattern-search stage
The idea behind the pattern-search algorithm is that given \(T\) and \(P\), if \(P\) occurs in \(T\) at unknown locations, it is necessary that at least one downsampled polyphase \(PM_i\) of \(P\) occurs in \(TM\). Note that the reverse need not be true, that is, a certain \(PM_i\) occurring in \(TM\) does not guarantee that \(P\) occurs in \(T\). Therefore, we first mine for all occurrences of \(PM_i\) in \(TM\) and search around the resulting indices for an exact match in \(T\). Figure 2 presents the block diagram of the procedure.

The definitions of crucial variables are given below:
(1) PPAll: this is the array that holds the locations of exact matches for all polyphases of \(P\). The elements of PPAll denoted by PPAll\((n)\).
(2) PP: this is the array that holds the locations of exact matches of a particular polyphase of \(P\). The elements of PP are denoted by PP\((n)\).

The algorithm breaks each polyphase into non-overlapping Q-grams and bases its search on a successive refinement principle by employing beam pruning technique. That is, matches to the first non-overlapping Q-gram are first found. If these matches extend to the next Q-gram, then these locations are retained. This process is carried out for all the Q-grams in the given polyphase. At the end of this process, those locations where all the Q-grams match represent the locations where the polyphase \(PM_i\) matches \(TM\). These locations are then mapped to the original text \(T\) where the final search takes place. In this manner, the algorithm successively refines the search regions and thus speeds the search process. The algorithm is presented below followed by an example on a sample pattern.

Algorithm—B
(1) Generate \(PM_i\) \(0 \leq i \leq M - 1\) from \(P\) using Polyphase Decomposition.
(2) Initialize PPAll = \{\emptyset\} (an empty array).
(3) For each polyphase \(PM_i\), do (4) and (8).
(4) Generate \(NQPM_i\) (set of non-overlapping Q-grams of polyphase \(PM_i\)).
(5) PP = \(H_{TMQ}[NQPM_i(0)]\) (this represents all positions in \(TM\) where an exact match is found for the first non-overlapping Q-gram of \(PM_i\)).
(6) For all \(NQPM_i(j)\) \(\in NQPM_i\), \(j > 0\) (the rest of the entries in \(NQPM_i\)) do (7).
(7) Delete from PP, PP\((k)\) such that PP\((k) + jQ \notin H_{TMQ}[NQPM_i(j)]\). \(NQPM_i(j)\) should have occurred at location PP\((k) + jQ\) if there was an exact match. But, if that is not the case, there is no chance of an exact match of polyphase \(PM_i\) in \(TM\) at location PP\((k)\). Hence, it must be pruned from the array PP.
(8) Append all PP\((k)\) \(\in PP\) into PPAll. That is, make note of all locations of exact match of \(PM_i\) in \(TM\) in the array PPAll that holds the locations of exact match for all \(PM_i\)s in \(TM\).
(9) Translate PPAll\((n)\) to corresponding location in original text \(T\) and verify exact match of \(P\) in \(T\) at that location.

Note that Steps (4) and (8) deal with extracting exact locations of \(PM_i\) in \(TM\). Step (7) is a beam-pruning method to prune out non-exact-match locations of \(PM_i\) from the PP.

Example:
Consider \(P = \text{‘aag ggt tta aga gtc tca’}\). Also \(M, Q\) and \(T\) as are the same as those used in the previous illustration. We show the steps of the algorithm for one of the polyphases: \(PM_0\). The results of the other two polyphases are presented in Step (8).
We now present the space and time complexity analysis of the solutions in order to avoid this loss is to verify exact match proposed method.

From Algorithm A, because every overlapping 4-gram contributes to an entry in the hash table, the algorithm’s space complexity is $O(L_{TM})$ where the length of TM $L_{TM}=L_{P}/M$ due to downsampling. Also, because constructing the hash table is a sequential process, its time complexity is $O(L_{TM})$.

Note that there are two types of memory in a computer—main memory, which is fast, costly and scarce and the secondary memory, which is slow, cheap and abundant. An efficient design of an algorithm is an optimal balance between its speed and its main memory requirements. In our design, we have retained a smaller, down-sampled version of the text $T$ in the main memory, which we consider for space complexity calculations. For the purposes of exact match verification in Step (9) of Algorithm B, the original text $T$ can reside in the cheaper secondary memory, and relevant sections (with length $<L_F$) can be paged into the main memory when required. Also note that if we set $M=1$, the $H_{TMQ}$ reduces to its naive version and its main memory requirements are then $O(L_F)$.

### 4.2 Time complexity of pattern search

We will now discuss the time complexity for pattern search (Algorithm B). In our analysis, we model the base distribution as an iid process and following uniform distribution. This is reasonable over large databases because it has been shown that DNA sequences at best have weak long-range correlations (Bernaola et al., 2002). The complexity of processing a particular polyphase as described in Steps (4) and (8) is as given below.

Step 4 is the generation of the NQPMi list. This step which generates non overlapping $Q$-grams is computationally simple and its effect on the search complexity can be neglected.

Step 5 is a look up from the hash table. Because this step is only a main memory lookup (Cormen et al., 1990), it contributes $O(1)$ to the search complexity. Also, it follows from our assumption that the distribution of bases is uniform and iid, the probability of the existence of any given $Q$-gram is $1/4^Q$. Thus, the expected number of any $Q$-grams in $TM = L_{TM} \times (1/4^Q)$. That is, the expected number of matches for the first $Q$-gram in any given polyphase is $L_{TM}/4^Q$.

Step 7 is the beam pruning procedure, where entries from the array PP are removed based on the entries in the bucket $H_{TMQ}(NQPMi(j))$. This translates to traversal of both arrays, namely, PP and $H_{TMQ}(NQPMi(j))$. The complexity of this step then depends on the lengths of each array.

- The bucket: following the above explanation, the bucket has an average of $L_{TM}/4^Q$ entries.
- The PP Array: note that for any $j$, the PP Array holds the locations of a string of length $j \times Q$. Therefore, the expected length of the PP Array for any $j$ is $L_{TM}/4^Q$.

As a result, employing binary search, the complexity of the beam pruning procedure for a single polyphase is $O(L_{TM}/4^Q \log(L_{TM}/4^Q))$.

Also, note that Steps (1), (2) and (8) are computationally simple and their contribution to the search complexity can be neglected.

Now, the complexity of the algorithm until Step (9) is the complexity of beam pruning procedure for all $M$ polyphases $= O(M(L_{TM}/4^Q \log(L_{TM}/4^Q))) = O(L_T/4^Q \log(L_{TM}/4^Q))$.

The complexity of Step (9) is negligible as its of order $O(L_F)$. $L_F < L_T$. Thus the overall time complexity for the search procedure:

$$O((L_T/4^Q \log(L_T/M4^Q))).$$

A comparison of complexities of various search algorithms are given in Table 2.

As can be seen from the table, the proposed method has superior complexity as compared to most existing methods. Also, while
Table 2. Comparison of theoretical complexities of various pattern/homology search algorithms

| Search algorithm       | Space complexity | Time complexity |
|------------------------|------------------|-----------------|
| BLAST                  | \(O(L_T + L_P)\) | \(O(L_T + L_P)\) |
| FASTA                  | \(O(L_T + L_P)\) | \(O(L_T + L_P)\) |
| Finite automaton       | \(O(L_T)\)      | \(O(L_T)\)      |
| Knuth Morris Pratt    | \(O(L_T)\)      | \(O(L_T)\)      |
| Suffix tree based      | \(O(L_T)\)      | \(O(L_T)\)      |
| BWA-SW                 | \(O(L_T)\)      | \(O(L_T)^{O(Q)}\) |
| SSAHA                  | \(O(L_T)\)      | \(O(L_T)^{O(Q)}\) |
| Proposed              | \(O(L_T/M)\)    | \(O(L_T/M)^{O(Q)}\) |

*Methods also yield approximate matches.

The bold line corresponds to the complexity of the proposed algorithm.

Table 3. Hash table size for \(M - Q\) combinations (MB)

| \(Q\) | \(M = 7\) | \(M = 15\) | \(M = 23\) | \(M = 31\) |
|-------|-----------|-----------|-----------|-----------|
| 8     | 117.0     | 118.3     | 120.3     | 129.1     |
| 9     | 55.5      | 55.3      | 57.6      | 65.0      |
| 10    | 35.9      | 36.4      | 38.4      | 45.3      |
| 11    | 26.7      | 27.2      | 29.2      | 35.2      |
| 23    | 21.3      | 21.7      | 23.7      | 28.9      |

Table 4. Search times for various \(M - Q\) combinations (in micro seconds)

| \(Q\) | \(M = 7\) | \(M = 15\) | \(M = 23\) | \(M = 31\) |
|-------|-----------|-----------|-----------|-----------|
| 8     | 1850      | 277       | 27         | 30        |
| 9     | 288       | 33        | 7          | 3         |
| 10    | 105       | 9         | 14         | 0.5       |
| 11    | 108       | 8         | –          | –         |
| 39    | –         | –         | –          | –         |

Table 5. Number of matches to be processed versus \(M\)

| \(M\) | Number of matches |
|-------|-------------------|
| 7     | 1                  |
| 15    | 1                  |
| 23    | 2                  |
| 31    | 330                |

Thus, it can be seen from the data presented that a large \(M\) results in a smaller hash table, but also generates larger number of potential matches that must be post processed. Also, a larger \(Q\) speeds up the polyphase search, but demands larger hash table size. Therefore, values \(M\) and \(Q\) must be carefully chosen.

For example, for setting parameters \(M\) and \(Q\) for a pattern of length \(\approx 300\), Table 3 inspires us to use a highest value of \(M = 39\) (because this gives the smallest hash table). However, the numbers in Table 4 suggest that it would be reasonable to select the higher values of \(Q\) and set \(M \approx 23\) (because higher \(M - Q\) combinations are either slow or infeasible) and further consultation with Table 5 indicates that a combination of \(M = 25\) and \(Q = 11\) is practical (because the number of matches that must be post processed are near minimal). Thus an optimal choice of parameters would be \(M = 23\) and \(Q = 11\), which requires 45.3 MB for the hash table (Text size = 250 M bases). Also, with respect to the pattern (Pattern size = 300 bases) related searching time, 0.5 ms are required to generate the list of exact matches of polyphases in the downsampled text. Another 1 ms is required to verify if the exact polyphase match translates to exact match in text. Thus a total of 1.5 ms were required for mining exact matches.

5 CONCLUSION

In this article, we presented a method for fast exact sequence search that relies on downsampling and polyphase representations to expedite the search process. We also computed the complexity of the algorithm and showed it to be better than existing methods. Because the proposed method uses polyphase representations, and because searching for exact matches in multiple polyphases does not have any data or functional inter-dependency, the algorithm can be parallelized. This would further reduce time complexity. Implementation of a parallel version of the algorithm will be a topic of further work.

The proposed algorithm addresses the problem of finding exact matches to a substring. Our future research will extend the utility of this algorithm to finding approximate matches.

Conflict of Interest: none declared.
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