Error-Tolerant Read-Mapping to Burrows-Wheeler data

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Overview

- What have we been doing?
  - Read Mapping with BWT
    - Most methods use exact “seed” segment
  - Inexact matching
    - Simulated traversal of the suffix tree using BWT with FM indexing and suffix arrays
    - adaptive substitution matrix, adaptive gap penalty weights, match rewards, match scoring, mismatch lower bound pruning, index-score pruning
  - Applications:
    - Alignment to reads or references with errors
    - Alignment to reads from another closely related species

Methods: Inexact Matching

- Deliverable: command-line tool for mapping reads, set of scripts for testing
  - Use of recursive program structure to bypass need to explicitly construct tree
  - Gives list of matches, scored, with their positions and suffixes
- Use of FM indexing:
  - Basically, store useful things for backward search
    - rank of each letter in the transform
    - number of lexicographically smaller symbols in the reference
    - Suffix array
- Search by keeping track of the error score on each suffix array interval that gets checked for a match

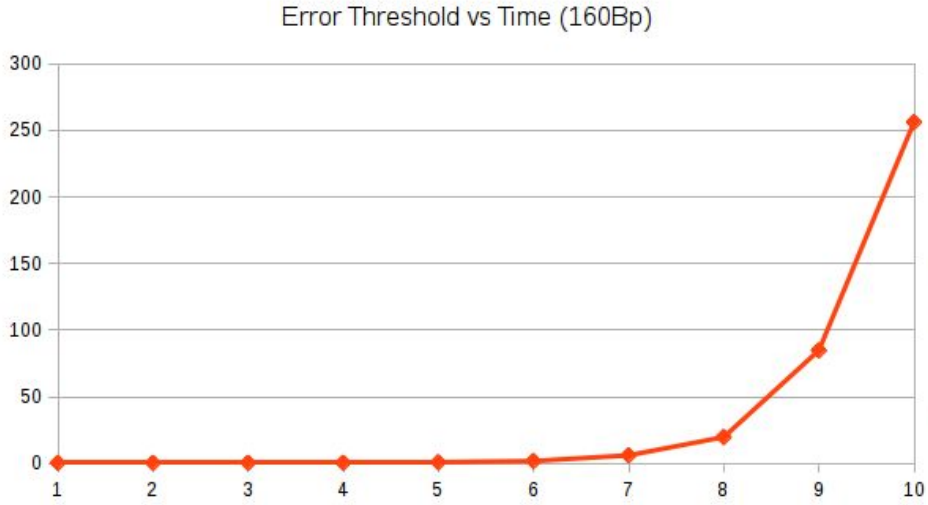
```
def inexact_recursion(s,i,diff,k,l, prev_type):
    '''search bwt recursively and tolerate errors'''

    global num_prunes

    #pruning based on estimated mistakes
    if diff < get_D(i):
        num_prunes += 1
        return set()

    #end of query condition
    temp = set()
    if i < 0:
        for j in range(k,l+1):
            temp.add((j,diff))
        return temp

    #search
    sa_idx = set() #set of suffix array indices at which a match starts

    if not NO_INDELS:
    # Insertion
        if prev_type == Type.INSERTION:
            sa_idx = sa_idx.union(inexact_recursion(s,i-1,diff-gap_ext,k,l,Type.INSERTION))
        else:
            sa_idx = sa_idx.union(inexact_recursion(s,i-1,diff-gap_ext-gap_open,k,l,Type.INSERTION))

    for char in alphabet:
        temp_k = C[char] + get_O(char, k-1) + 1
        temp_l = C[char] + get_O(char, l)

        if temp_k <= temp_l:
            if not NO_INDELS:
            # Deletion
                if prev_type == Type.DELETION:
                    sa_idx = sa_idx.union(inexact_recursion(s,i,diff-gap_ext,temp_k,temp_l,Type.DELETION))
                else:
                    sa_idx = sa_idx.union(inexact_recursion(s,i,diff-gap_ext-gap_open,temp_k,temp_l,Type.DELETION))
            if char == s[i]:
                # Match!
                sa_idx = sa_idx.union(inexact_recursion(s,i-1,diff+match,temp_k,temp_l,Type.MATCH))

            else:
                # Mismatch
                if sub_mat:
                    sa_idx = sa_idx.union(inexact_recursion(s,i-1,diff-mismatch*sub_mat[(s[i],char)],temp_k,temp_l, Type.MISMATCH))
                else:
                    sa_idx = sa_idx.union(inexact_recursion(s,i-1,diff-mismatch,temp_k,temp_l, Type.MISMATCH))
```

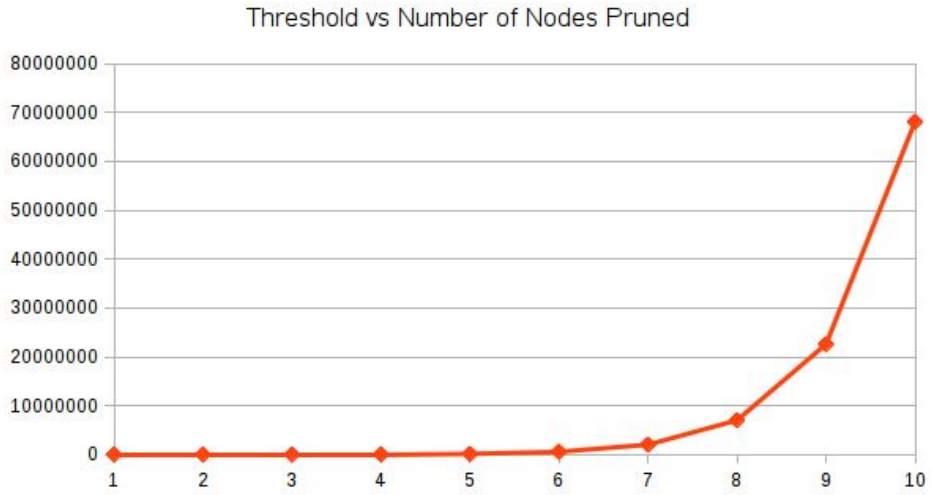
Methods: Scoring and Pruning Matches

- Accept substitutions and indels
- Estimate substitution matrix based on the likelihood of each replacement occurring for each index of the read
- Affine and linear gap penalties based on read and genome length
- Lower bound on number of mismatches of each substring [1:i] of the read
    - Allows pruning when our threshold dips below that level
- Prune examples with the same index and have lower scores

Results: Efficiency

- Algorithmic complexity:
  - $O(2^t)$ for Threshold t in the worst case
  - O(r) time and space for read length r
- Test: Error Threshold Value, Runtime, Number of Nodes Pruned





Results: Accuracy

- Although we only had time to test on a small set, our preliminary results are encouraging:

Program	Error Rate	Time (s)
Our Tool	.2	58
BWA-32	.3	65
BWA-125	.05	88

- 150bp reads mapped to Dengue virus genome with 83% of estimated read positions matching true read positions

```
@SRR1175172.601.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
TGGACCGACAAGAACAGTTTCGAATCGGAAGCTTGCTTAACGTAGTTCTAACAGTTTTTTATTAGAGAGCAGATCTCTGATGAACAACCAACGGAAGAAGACGGGTCGACCGTCTTTCAATATGCTGAAACGCGCGAGAAACCGCGTGTC
+
BCCCCFCCDDDFGGGGGGGGGGGHHGHGGGGHHHHHHHHHHGHHHFHHHHHGHHGHHHGGHHHHGHHHGHHHHHHHHHHGHHHHHHHHHGGHFGGGGFHHHHGEGGEGG?D?CGFHGHHHBGHHHHGHFHDFFGCA@-@CGFFGCC--<C:
@SRR1175172.664.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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+
CCCCCFCCCCCFGGGGGGGGGGGHHGHGGGGHHHHHHHHHHGHHHGHHHHHHHHHHGHHGGHHHHHHHGGHHHHFHHHHHHHHFHHHHHGGHGGGFGGHHHHHGGGEGGGGGGGGAGHHHF@FGGBGF2FGHFC<CCCC@<0<C?CF:;::
@SRR1175172.1242.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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+
BCCBCFCCCCCFGGGGGGGGGGGGFGFHGGGGHHGHHHHGHHGHGHGHHHHHHHHHHHHGGGGHHHHHHHGHGHHHGHHHHFFHHHHHHHGGHFGG?FEFFFGBFCG?<?EBCGFGFEHFHEHGHF2FGFGBDFC<CG?@D?GGF@FD:AD:
@SRR1175172.442.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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+
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@SRR1175172.983.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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+
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+
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+
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@SRR1175172.433.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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@SRR1175172.553.A3KR1.1/2 primary ref=gi|9626685|ref|NC_001477.1| pos=16 mapq=29
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+
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```

Conclusions

- Promising results so far
  - Method seems to be viable for the ascribed problem
- Prospective future work
  - Use heap-like data structure to prioritize best partial alignments
  - Max differences change as a function of read length
  - Reduce memory needs by storing small amount of O array and suffix array; calculate remaining parts as the algorithm progresses